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EXECUTIVE SUMMARY

The Pediatric, Adolescent, and Maternal AIDS Branch (PAMAB), within the Center for Research for Mothers and Children of the National Institute of Child Health and Human Development (NICHD), was established in 1988. Its mission is to support and conduct domestic and international research into the epidemiology, clinical manifestations, pathogenesis, transmission, treatment, and prevention of HIV infection and its complications in infants, children, adolescents, and both pregnant and non-pregnant women.

In the last decade, researchers have made substantial advances in understanding the pathogenesis of HIV infection, treating and monitoring HIV disease, and developing potent combination antiretroviral therapeutic regimens, which have led to significant reductions in HIV-related morbidity and mortality. However, as with research on many other diseases, studies of children have often lagged behind those of adults, and gender differences often go unappreciated.

An important component of the PAMAB mission is to ensure that adequate research is focused on HIV infection in women, children, and adolescents. To that end, the PAMAB and PAMAB-funded researchers have made substantial contributions to domestic and international research efforts in pediatric and maternal HIV/AIDS. PAMAB has a long history of establishing effective collaborations and promoting collaborative research in pediatric, adolescent, and maternal HIV infection, including collaborations with other National Institutes of Health (NIH) Institutes and U.S. Department of Health and Human Services (DHHS) agencies, including the Centers for Disease Control and Prevention (CDC) and Health Resources and Services Administration (HRSA), the President's Emergency Plan for AIDS Relief (PEPFAR), as well as international organizations, such as the Pediatric European Network for Treatment of AIDS (PENTA) and the World Health Organization (WHO).

This report is the fourth update on Branch activities for the National Advisory Child Health and Human Development (NACHHD) Council. This report outlines the major initiatives of the Branch, highlights recent scientific advances from PAMAB-supported research, describes the PAMAB planning process, and defines the Branch's future research directions.

CHANGING HIV RESEARCH NEEDS: AN OVERVIEW OF THE PAMAB RESEARCH PORTFOLIO

Since its last report to the NACHHD Council in 2003, the Branch has enhanced funding for international research and adolescent issues, in accordance with changes in the epidemiology of HIV infection in the Unites States and globally (see Figure 2). In addition, the PAMAB portfolio was recently expanded to include microbicide-related clinical trials.

Research into the prevention of mother-to-child transmission (MTCT) of HIV and the treatment of children and their mothers in resource-limited countries are critical components of the PAMAB research portfolio. Although the United States has experienced success in preventing MTCT, approximately 1,500 children still become infected with HIV every day, the majority of whom reside in resource-limited countries. An estimated 2.3 million children are living with HIV worldwide, and most of them acquired the virus from their mothers. Without treatment, progression of HIV disease in children is particularly aggressive. For instance, in sub-Saharan Africa, the median survival of perinatally infected children is to 1.6 years of age, and 60 percent of children die before the age of three years.

The number of grants supported by PAMAB related to international HIV issues in children and women has dramatically expanded. Of the investigator-initiated research grants funded by the Branch between 2003 and 2006, more than 80 percent supported an international research agenda in countries including Botswana, Brazil, Cote d'Ivoire, India, Kenya, Malawi, Romania, South Africa, Tanzania, Thailand, Uganda, Vietnam, Zambia, and Zimbabwe. Additionally, to address the global nature of HIV, PAMAB began funding international clinical trial sites in Latin America in 1999 as part of its NICHD International and Domestic Pediatric and Perinatal HIV Clinical Trials Network (hereafter, the NICHD Network). In 2006, nearly 40 percent of the NICHD International and Domestic Pediatric and Maternal HIV Studies Coordinating Center contract funding was directed toward international activities.

While PAMAB has made progress in international research, its support of domestic research has not waned. Maintaining domestic capacity for clinical trials is critical to ensuring that therapies become available to treat HIV and its complications in the vulnerable populations of children, adolescents, and women in the United States. Despite dramatic decreases in HIV MTCT in the United States, approximately 200 HIV-infected infants are born in the United States annually, in addition to the 10,000 to 15,000 children currently living with HIV infection in this country. All of these infants and children will eventually need treatment. Additionally, with the decrease in MTCT, the number of HIV-exposed but uninfected children with *in utero* antiretroviral exposure is dramatically increasing. However, there is a lack of information on the long-term effects of such exposures for these children. Finally, the proportion of HIV/AIDS cases in females, currently 27 percent, continues to increase, and nearly 6,000 HIV-infected women become pregnant and give birth each year in the United States. Drugs and treatments need to be evaluated to assess appropriate dosing and safety of use in pregnancy.

The PAMAB continues to support the NICHD Network, which consists of domestic and international clinical trials sites that conduct pediatric and perinatal clinical trials in collaboration

with the National Institute of Allergy and Infectious Diseases (NIAID) International Maternal, Pediatric, and Adolescent AIDS Trials (IMPAACT) Network and other clinical trials networks in the United States and Europe. The new PAMAB-led Pediatric HIV/AIDS Cohort Study (PHACS), initiated in late 2005, was designed to stimulate research to address the issue of long-term effects of *in utero* antiretroviral drug exposure in uninfected children in the Surveillance Monitoring for Antiretroviral Treatment Toxicities (SMARTT) study.

With treatment, HIV has become a chronic disease for many children in the United States. A recent study found that 90 percent of HIV-infected children treated with current triple-therapy regimens are alive at age 14 years; thus, many children with perinatal infection are now surviving into adolescence. However, the treatments that are prolonging life may also be associated with long-term adverse effects. Thus, a portion of PAMAB-supported research has shifted to evaluate the impact of HIV infection and its treatments on growth, sexual maturation, metabolism, including bone development, and neurodevelopment and neurological function as infected children age into adolescence. The PHACS Adolescent Master Protocol (AMP) study was designed to stimulate research in this area.

Individuals between the ages of 13 and 24 years of age in the United States, particularly minority youth, comprise a group at great risk for acquisition of HIV infection. An estimated 25 percent of new infections in the United States occur in adolescents ages 13 to 19 years, and half of all new infections occur in youth younger than age 24 years. New infections among adolescent females, primarily acquired through heterosexual contact, now equal or surpass new infections in young men, and a resurgence in transmission among young men who have sex with men is particularly worrisome. Preventive interventions are needed, including behavioral interventions (both with HIV-infected and uninfected youth) and studies of HIV vaccines and microbicides in youth. Also, treatment of adolescents infected with HIV is complicated by unique challenges and management demands. Particularly needed are trials to study newer drug schedules that allow simpler regimens, evaluation of programs to promote antiretroviral treatment adherence in youth, and clinical trials to evaluate therapies that may exploit the immunologic resilience of recently infected youth.

PAMAB has a long record in addressing HIV infection in adolescents, beginning in 1988 with the Hemophilia Growth and Development Study, an observational study of the effects of HIV on pubertal growth and sexual development that was discussed at the 2003 Council meeting. Branch efforts continued from 1994 through 2001 with its funding of the Adolescent Medicine HIV/AIDS Research Network (AMHARN). In 2001, PAMAB created the Adolescent Trials Network for HIV/AIDS Interventions (ATN) in response to specific recommendations of the AMHARN External Scientific Advisory Panel. The ATN is in its second five-year funding cycle; its research agenda includes primary prevention of new infections in youth, as well as therapeutic and behavioral research in infected youth.

In resource-limited countries, youth and particularly young women are at the forefront of the HIV epidemic. Biological, social, cultural, and economic factors contribute to the disparate vulnerability of young women to HIV. HIV infection rates among adolescent women in some countries are up to six times higher than among adolescent males. These statistics underscore the need for prevention strategies, such as microbicides, that are controlled by women. The

PAMAB has funded research on women's health since its establishment; these efforts include gender-specific HIV clinical trials conducted through the NICHD Network, and co-funding for the Women's Interagency HIV Study (WIHS).

In addition, the PAMAB recently assumed primary responsibility for the NICHD's collaboration with the NIAID's Microbicide Trials Network (MTN), and for investigator-initiated grants related to microbicides for HIV prevention. PAMAB work related to the MTN will focus on: microbicide studies in youth, in collaboration with the ATN; and microbicide use during pregnancy.

Thus, as the HIV epidemic continues to evolve both domestically and globally, the PAMAB has endeavored to ensure that research funded by the Branch reflects the changes in the field, and to secure sufficient flexibility in funding so that researchers can address important, unanticipated research opportunities and important research gaps as they arise.

MAJOR PROGRAM INITIATIVES

NICHD DOMESTIC AND INTERNATIONAL PEDIATRIC AND PERINATAL HIV STUDIES COORDINATING CENTER

Background and History

The PAMAB has funded the NICHD Domestic and International Pediatric and Perinatal HIV Studies Coordinating Center since 1987. Initially, funding was applied to the conduct of a single multi-center clinical trial to evaluate the use of intravenous immunoglobulin (IVIG) prophylaxis for bacterial infections in HIV-infected children; this study was the first clinical trial conducted in HIV-infected children in the United States. The NICHD Domestic and International Pediatric and Perinatal HIV Clinical Trials Network (hereafter, the NICHD Network) enrolled 376 children from 28 clinical centers into this trial, which subsequently demonstrated the efficacy of IVIG for the stated purpose, was published in the *New England Journal of Medicine* in 1991, and resulted in approval of IVIG use in children for this indication by the Food and Drug Administration.

In 1989 and 1990, the clinical trials sites funded by the Coordinating Center for the NICHD IVIG Clinical Trial became the NICHD Pediatric HIV Clinical Trials Network and began collaboration with the NIAID-funded Pediatric AIDS Clinical Trials Group (PACTG) to develop and conduct clinical trials, a successful effort that continues today. The NICHD Network, which now includes domestic and international clinical trials sites, will continue this collaboration with the new NIAID-funded IMPAACT Network, which represents the combination of two predecessor networks: the PACTG and the perinatal portion of the HIV Prevention Trials Network (HPTN). The NICHD Network also collaboratively conducts trials with other networks, such as the ATN or PENTA. Clinical studies of special relevance to the NICHD mission are conducted solely at sites under the Coordinating Center contract.

The Coordinating Center contract, which was recompeted in 1992, 1997, and 2002, will be recompeted again in 2007. The Coordinating Center includes subcontracts for clinical sites to conduct studies using performance-based and adjustable funding. As the demographics of pediatric and maternal HIV infection have changed over time, the flexibility and responsiveness of the contract mechanism has allowed the PAMAB to rapidly adjust to emerging opportunities by modifying the number and type of clinical trials sites in the NICHD Network, as well as the types of studies performed within the Coordinating Center contract. Such flexibility is critical in the rapidly changing arena of HIV research to allow timely initiation of targeted, high-priority initiatives in response to unanticipated needs. Special projects are often initiated with start-up funds from the National Institutes of Health (NIH) Office of AIDS Research (OAR) for research deemed of high priority by the OAR and the NICHD.

PAMAB recognizes increasing international needs for pediatric and maternal HIV research, the evolution of critical research questions over time, and the need for increased attention to developing research collaborations with resource-limited countries for HIV prevention and treatment. The PAMAB has diversified the activities of the Coordinating Center to encompass new international research issues and infrastructure development, as well as the conduct of clinical trials at domestic and international NICHD Network sites.

The Coordinating Center contract encompasses several inter-related projects, which are described separately in the following sections. (See Figure 9 for details on funding for the NICHD Network Coordinating Center contract projects.)

- NICHD Domestic and International Pediatric and Perinatal HIV Clinical Trials Network (NICHD Network)
- Latin American/Caribbean NICHD International Site Development Initiative (NISDI)
- International Clinical Trial of Post-Exposure Prophylaxis of HIV-Exposed Infants (NICHD/HPTN 040 Trial)
- India Perinatal Project
- Breastfeeding and HIV International Transmission Study (BHITS) Meta-analysis

NICHD Domestic and International Pediatric and Perinatal HIV Clinical Trials Network (NICHD Network)

The NICHD Network, which has been funded through the NICHD Coordinating Center contract since 1987, consists of domestic and international clinical sites that enroll study subjects in trials related to preventing and treating HIV infection and its complications in neonates, infants, children, adolescents, and pregnant women. Domestically, the Network includes 20 centers, located in 18 cities, in 10 states/territories (including Puerto Rico); internationally, the NICHD Network includes six clinical trials sites: five sites in different areas of Brazil, and one in the Bahamas. (See Appendix D for a list of the domestic and international sites.)

PAMAB uses a centralized specimen repository to store coded biologic specimens specifically related to the NICHD Network. An extensive repository policy, developed in concert with the DHHS Office for Human Research Protections, includes non-disclosure forms and specimen-use agreements to establish a privacy "firewall," which renders the stored coded specimens

anonymous. This process greatly facilitates future studies on repository samples. Because the studies are conducted under contract, the government has ownership of and specific responsibility for the storage and use of the specimens. These stored specimens are a valuable resource. Outside investigators can request use of the samples for evaluating pathogenesis questions related to pediatric HIV infection within the context of clinical trials or other studies conducted by the NICHD Network.

Descriptions of the NICHD Network's collaborations with other networks and projects appear below.

Collaboration with the Pediatric AIDS Clinical Trials Group (PACTG) and the International Maternal Pediatric and Adolescent AIDS Trials (IMPAACT) Network

Since 1990, the NICHD Network has collaborated in scientific design and joint conduct of clinical trials within the PACTG; this collaboration will continue with the newly funded IMPAACT Network. As mentioned earlier, the IMPAACT Network is the combination of two predecessor networks: the PACTG, and the perinatal portion of the HPTN. The PACTG/NICHD Network collaboration has been the principal entity for conducting clinical trials of HIV treatment in children worldwide. Similarly, the HPTN has been the premier entity for conducting clinical trials of interventions to prevent HIV MTCT in international settings. Taken together, the activities of these two networks have represented a major component of cross-Institute collaboration between NICHD and NIAID, and clinical trials conducted by both networks have materially advanced PAMAB and NICHD research goals.

NICHD Network sites enroll approximately 700 to 1,000 subjects each year into various trials and contribute 35 percent to 40 percent of overall enrollments into PACTG studies. Investigators in the NICHD Network participate as full scientific partners in the PACTG, serving on all major scientific committees and on the executive committee, which sets the scientific agenda for therapeutic research on HIV-infected children and pregnant women. These investigators also serve as protocol team members and chairs. The PAMAB supports NICHD Network site investigators who have relevant laboratory expertise in conducting specialized pathogenesis-based substudies within the context of PACTG trials. Selected NICHD Network sites also participate in the NIAID-funded quality assurance/certification for standard virology and immunology laboratories; these programs provide better centralization of laboratory testing and quality assurance for the NICHD Network sites.

Through collaboration with IMPAACT, the PAMAB will continue its long-standing collaboration with NIAID on pediatric studies by funding non-overlapping domestic and international clinical trials sites. Investigators in the NICHD Network will continue to participate in the scientific activities of the new IMPAACT Network by enrolling patients into jointly developed pediatric, adolescent, and perinatal clinical trials. The NICHD will also continue to support a Core Laboratory for the IMPAACT Network and provide certification for selected NICHD Network sites working on standard virology and immunology assays.

Collaboration with the Adult AIDS Clinical Trials Group (ACTG)

For more than 15 years, PAMAB has collaborated with women's health investigators in the ACTG to support enrollment of women identified at NICHD Network sites into ACTG protocols designed to answer questions related to gender-specific manifestations of HIV infection and treatment. NICHD Network sites have enrolled nearly one-fourth of the women cumulatively enrolled in ACTG studies on women-specific topics, such as optimal management of cervical dysplasia, interactions of antiretroviral therapies with contraceptive hormones, and metabolic complications of antiretroviral therapy during pregnancy. This collaboration will continue with the recently re-funded NIAID ACTG.

Collaboration with the Adolescent Trials Network for HIV/AIDS Interventions (ATN)

The ATN is funded primarily by the NICHD, but also receives co-funding from the National Institute of Mental Health (NIMH) and the National Institute on Drug Abuse (NIDA). The mission of the ATN is to conduct research, both independently and in collaboration with other research networks, on: treatment and clinical management of HIV and related conditions in infected youth; and primary prevention of HIV transmission in at-risk youth. NICHD Network collaboration with the ATN began in 2004 with the ATN 015 trial—a study of short-cycle therapy in adolescents who had established viral suppression on continuous therapy—at NICHD Network domestic sites. Since 2005, three additional ATN studies have opened at NICHD Network sites. As protocols relevant to the population seen at NICHD Network sites are developed within the ATN, such protocols will be made available for co-enrollment at NICHD Network sites.

Collaboration with the Pediatric European Network for Treatment of AIDS (PENTA)

The NICHD Network began collaborating with PENTA in late 2004 on protocol PACTG 390—a strategy trial evaluating two different antiretroviral drug regimens in treatment-naïve children who require therapy (initial therapy with a protease inhibitor-based regimen versus a non-nucleoside analogue reverse transcriptase inhibitor-based regimen). The study also compares two different strategies for determining when to change therapy (i.e., a "low" and "higher" viral-load threshold). The PACTG and NICHD Network site investigators jointly developed the study in collaboration with investigators from PENTA. Patients from all three networks are enrolled in the study.

More generally, PENTA and the NICHD Network Coordinating Center have done extensive work on harmonizing data submission, management, and adverse event reporting; these efforts give NICHD Network investigators access to PENTA studies of interest so they can enroll patients at NICHD Network sites. As a result, in 2006, the protocol PENTA 11—a CD4-guided treatment-interruption study in children—opened enrollment at NICHD Network sites.

Joint development of new protocols—including a study of a "simplification" strategy for children with virologic suppression (PENTA 17)—between the NICHD Network and PENTA is under discussion.

Collaboration with Other Institutes or Agencies

On issues of importance to the NICHD mission, PAMAB has also fostered collaborations between the NICHD Network and other NIH Institutes, such as the National Heart, Lung, and Blood Institute (NHLBI) and NIMH, and with other agencies, such as the HRSA, to create specific studies conducted within the context of the NICHD Network. For example, NHLBI collaborated with the NICHD Network on a clinical trial of HIV hyperimmune globulin to prevent MTCT; NIMH collaborated with the NICHD Network on a study to define optimal neurodevelopmental assessment tools for evaluating infected children in clinical trials.

LATIN AMERICAN/CARIBBEAN NICHD INTERNATIONAL SITE DEVELOPMENT INITIATIVE (NISDI)

Following the NICHD Network's experience with opening antiretroviral drug treatment trials in Brazil and the Bahamas in 1998 and 1999, PAMAB identified a need for further training and development to increase Latin American and Caribbean capacity for conducting clinical trials, particularly those involving experimental drugs. The NISDI, funded through the NICHD Coordinating Center contract, was designed to provide capacity-building and training for international sites through the conduct of two observational studies.

The goal of the NISDI is to train investigators and develop sites that will be able to fully participate in future international prevention and treatment trials in collaboration with IMPAACT, the ACTG, the ATN, and other relevant domestic or international HIV prevention and treatment networks. By conducting these observational studies, the NISDI will also provide important data about the demographic, clinical, immunologic, and virologic characteristics of HIV-infected women and children in Latin America and the Caribbean. This information will assist in developing an international research agenda and creating specific clinical trials relevant to these countries, while also providing critical information on the safety of antiretroviral drugs and other therapies for infected pregnant women and children in these areas.

The NISDI perinatal protocol is a prospective study that will describe the characteristics of HIV-infected pregnant women and their infants who receive care at participating clinical sites, where formula and antiretroviral prophylaxis are available to prevent MTCT of HIV. HIV-infected women are evaluated antepartum, intrapartum, and six months postpartum; infants are evaluated through six months of age. The study will provide information on the type, safety, and efficacy of interventions used to prevent MTCT of HIV in Latin America, including use of antiretroviral drugs and cesarean section before labor and membrane rupture, and track short-term infant outcomes potentially related to *in utero* and neonatal exposure to antiretroviral medications.

The NISDI pediatric protocol seeks to describe the demographic, clinical, immunologic, and virologic characteristics of HIV-infected children and adolescents and to follow HIV-exposed but uninfected children. Prospective data collection includes medical history, physical examination, laboratory evaluations (including hematology, flow cytometry, biochemical and HIV-specific viral assays), growth parameters, morbidity, and mortality. The study will provide critical information on the long-term safety of *in utero* and postnatal antiretroviral drug exposure

for uninfected infants, as well as information related to the long-term outcomes of therapy in HIV-infected children.

Currently, 25 sites in six countries are participating in the protocols; the NISDI includes patients from Mexico, Argentina, Brazil, Bahamas, Jamaica, and Peru (see Appendix E for a list of the NISDI sites). As of April 30, 2007, sites had enrolled 1,229 pregnant women and 1,627 pediatric patients into their respective protocols.

CLINICAL TRIAL OF POST-EXPOSURE ANTIRETROVIRAL PROPHYLAXIS FOR HIV-EXPOSED INFANTS (NICHD/HPTN 040)

Using supplemental start-up funding from the NIH OAR, PAMAB is providing funding and leadership for a clinical trial on the efficacy and safety of neonatal antiretroviral prophylaxis for infants born to HIV-infected women who did not receive antiretroviral therapy during pregnancy. The study is managed by the NICHD Network Coordinating Center. It includes women who were first identified as HIV-infected during labor, and who were therefore unable to receive antepartum prophylaxis. This situation is common in many countries, even in the United States, where up to 15 percent of HIV-infected women lack prenatal care.

The study opened to enrollment in Brazil and the United States in the summer of 2004, and it currently has eight participating sites in Brazil and six in the United States (see Appendix F for a listing of these sites). An additional site in Johannesburg, South Africa, began accrual in September 2005; a NISDI site in Buenos Aires, Argentina, began enrolling patients in March 2006; and a site in Cape Town, South Africa, began enrolling in late 2006. As of March 2007, more than 900 infants had been enrolled; accrual is expected to be completed in 2008.

Participants in the trial are randomized to one of three therapy arms: zidovudine (ZDV) for six weeks—the standard of care to prevent transmission in this situation in Brazil, the United States, and many other countries; ZDV for six weeks, plus three doses of nevirapine (NVP) during the first week after birth; or ZDV for six weeks, plus daily lamivudine (3TC) and nelfinavir, a protease inhibitor, for two weeks. Women may receive ZDV therapy during labor if HIV infection is diagnosed in time to permit its administration, and women in the trial are counseled not to breastfeed.

Current observational data suggest that neonatal ZDV may reduce perinatally acquired HIV infection by about two-thirds compared to no treatment; thus, ZDV is the control arm of the trial. The combination therapy arms were included based on the enhanced efficacy of combination therapy for treating established HIV infection, and based on the hypothesis that combination therapy may have enhanced efficacy for preventing MTCT without having undue toxicity for infants. Research on the pharmacokinetics of NVP and nelfinavir in infants is also included in the study. The results of this study will have broad global applicability, providing crucial data on the optimal regimen for neonatal prophylaxis that balances efficacy, safety, and cost for women whose HIV infection is diagnosed at the time of delivery. The NVP pharmacokinetic study is complete and results have been submitted for publication.

THE PERINATAL HIV TRANSMISSION PREVENTION PROJECT IN INDIA

While resource-rich countries with a relatively low burden of HIV infection among women and children have achieved major successes in preventing MTCT of HIV, significant challenges remain with regard to preventing such transmission in countries where resources are more limited and a greater population burden of HIV infection exists. India is a prime example of this situation. Approximately 20 million births occur each year in India, where the HIV seroprevalence rate among pregnant women is estimated at 1 percent to 2 percent; thus, 200,000 to 400,000 HIV-infected Indian women deliver babies annually. Assuming a minimal estimate of a 25-percent transmission rate without any intervention, 50,000 to 100,000 HIV-infected infants are likely born each year. Implementation of efficacious interventions in India to prevent perinatal transmission has been hampered due, in large part, to the expense and infrastructure requirements of such interventions.

In light of the situation in India, the NICHD established a collaboration with Indian investigators to support infrastructure development and operational research capacity in India, following consultation with the Indian Council on Medical Research, the National AIDS Control Organization, and the AIDS Society of India. The project's initial activity was to select a pilot site for operational research on preventing MTCT of HIV in a rural setting in India. This project is managed by the NICHD Network Coordinating Center.

During Stage I of the study, all pregnant women registered in the antenatal clinics were offered the opportunity to participate in an educational session about HIV infection and transmission. Pre- and post-session assessments of knowledge, attitudes, and beliefs were administered to a random sample of women. Voluntary counseling and HIV testing were offered to all women, and researchers estimated HIV seroprevalence from these samples. Enrollment into this first part of the protocol took place between December 2003 and December 2004.

During the second stage of the protocol, enrollment in a prospective cohort study was opened to those women identified as HIV-infected. These women were initially offered standard short-course ZDV prophylaxis for the prevention of HIV MTCT beginning at 28 weeks' gestation (or as soon as possible thereafter, if late presentation for antenatal care), as well as intrapartum ZDV; in addition, the study provided six weeks of ZDV prophylaxis to the infant. Subsequently, the protocol was revised to incorporate the addition of a single-dose of NVP for the mother and one dose for the infant to the ZDV regimen. All women in the study received education and counseling regarding infant feeding.

Researchers conducted follow-up of the mothers and children to assess rates of HIV MTCT, according to the history of antiretroviral prophylaxis received and the child's feeding modality, and to assess 12-month infant morbidity and mortality. Enrollment into the second part of the protocol began in early 2004, and the final subject study visits were completed in May 2006. Researchers have presented results of this study in abstract form at national and international meetings; they are currently preparing manuscripts for journal submission.

THE BREASTFEEDING AND HIV INTERNATIONAL TRANSMISSION STUDY (BHITS) META-ANALYSIS

Although research has conclusively demonstrated that HIV can be transmitted through breastfeeding, knowledge about the variation in breastfeeding transmission risk over time is needed to appropriately inform infant-feeding policies in regions of the world where complete avoidance of breastfeeding is generally not feasible. Therefore, PAMAB initiated an international collaborative effort to further characterize HIV transmission through breastfeeding. This project was managed by the NICHD Network Coordinating Center. Researchers pooled individual patient data from 3,442 HIV-infected women and their children who participated in nine randomized clinical trials conducted in sub-Saharan Africa to assemble a study population of sufficient size to achieve adequate statistical power for the planned analyses. The database was compiled prior to 2003, but multiple analyses have occurred since the last report to the NACHHD Council. The analysis has resulted in three manuscripts to date.

The primary analysis goals were to: estimate the contribution of late, postnatal HIV transmission through breastfeeding to overall perinatal infection; identify times of higher and lower risk of transmission; and identify determinants of late postnatal transmission. A child who had a negative HIV diagnostic test result at or after four weeks of age, but who then had a positive test result was classified as a late postnatal transmission case. The results of this analysis indicated that: late postnatal transmission contributes substantially to overall MTCT of HIV; the risk of late postnatal transmission is generally constant throughout breastfeeding; and risk of late postnatal HIV acquisition is associated with a lower maternal CD4-cell count and male sex.

Earlier studies reported conflicting results regarding maternal mortality among HIV-infected breastfeeding women in Africa; one study suggested an increased risk of mortality compared to formula-feeding women, while another showed no differences in maternal mortality by infant feeding modality. Following the completion of the analysis of late postnatal transmission of HIV described above, researchers used the BHITS database to develop a more reliable estimate of the overall mortality risk and timing of mortality, in relation to duration of breastfeeding, among HIV-infected women who breastfed during a 12- to 18-month period after delivery, and to identify factors associated with mortality in these women. This analysis revealed that: HIV-infected women with lower CD4-cell counts were less likely to initiate breastfeeding; mothers' mortality during the 18-month period after delivery did not differ significantly according to children's feeding modality (ever breastfed versus never breastfed); and among women who initiated breastfeeding, the lower mortality risk among those still breastfeeding compared with those no longer breastfeeding likely represents better overall maternal health (i.e., healthier women are able to breastfeed longer).

In another secondary analysis using the BHITS database, the Ghent International AIDS Society Working Group on HIV Infection in Women and Children evaluated the mortality of HIV-exposed infants in Africa. Mortality in HIV-infected infants was very high, with 35-percent mortality by age one year, and 53-percent mortality by age two years. Mortality in HIV-exposed but uninfected children was much lower, with 5-percent mortality at age one year, and 8-percent mortality at age five years. Mortality varied by geographic location; maternal death was associated with an increased risk of infant mortality regardless of infant HIV-infection status.

CDC/NICHD Collaboration on Clinical Trials to Prevent Postnatal Breast-Milk HIV Transmission

During fiscal year 2003, PAMAB entered a unique collaboration with the CDC by co-funding a cooperative agreement to support two clinical trials that would assess interventions for reducing breast-milk HIV transmission and improve infant survival in resource-limited countries with high HIV seroprevalence. Within the context of these trials, nested research studies are also assessing mechanisms of transmission during lactation and issues related to the effectiveness of interventions, including assessment of factors affecting mode of feeding or weaning decisions, evaluation of toxicity and survival among HIV-infected women and their children, and tests of simplified tools for monitoring drug toxicity in community-based health care facilities in resource-limited settings. After the CDC issued a request for proposals, an external expert panel reviewed the submitted applications and selected two clinical trials to be jointly supported by the CDC and PAMAB.

The first of the two studies—the Kesho Bora study—has an overall goal of optimizing the use of antiretroviral drugs during the antepartum, intrapartum, and postpartum periods to prevent HIV MTCT and to preserve the health of the mother and infant in settings where the majority of HIV-infected women breastfeed. Specifically, the study is evaluating the safety and efficacy of potent combination antiretroviral therapy (specifically ZDV, 3TC, and a protease inhibitor, Kaletra®) given to HIV-infected women whose CD4-cell count was between 200 cells/uL and 500 cells/uL, and who did not require therapy for their own health during late pregnancy and lactation, compared to the standard short-course antiretroviral prophylaxis recommended by the WHO (specifically, short course antepartum ZDV plus single-dose intrapartum/newborn NVP). This work is being conducted as part of a multi-site collaborative trial with the WHO and is open to enrollment; PAMAB/CDC funds support a site in Nairobi, Kenya. A total of 1,000 HIV-infected women will be enrolled from multiple sites. As of February 2007, 344 women were enrolled in the randomized clinical trial.

The *Extended Infant Post-Exposure Prophylaxis with Antiretrovirals to Reduce Postnatal HIV Transmission*, or PEPI-Malawi Study, is the second trial supported by PAMAB/CDC. The trial is being conducted in Blantyre, Malawi, in collaboration with the College of Medicine at University of Malawi and Johns Hopkins University Bloomberg School of Public Health. The study, which focuses on infants born to HIV-infected breastfeeding women, is a three-arm open-label randomized efficacy trial to evaluate the safety and efficacy of extended antiretroviral drug administration to the infant during early breastfeeding, and the effect on HIV-free survival through age two years. All infants receive the short-course control regimen of single-dose NVP plus ZDV for one week and are randomized immediately after birth to: the control short regimen alone; the control short-course regimen plus extended daily NVP alone for 14 weeks; or the control short regimen plus extended daily NVP plus ZDV for 14 weeks. Mothers are counseled to exclusively breastfeed during the first six months and to wean their infants thereafter.

The study began recruiting in April 2004 and, as of February 2007, 2,853 of the needed 3,500 infants were enrolled; enrollment should be complete by mid to late 2007. The independent Data and Safety Monitoring Board has already conducted one efficacy review, noting no safety concerns and recommending that the study continue.

HIV PREVENTION TRIALS NETWORK (HPTN)

The HPTN was an international prevention trials collaborative group funded primarily by NIAID, with co-funding by NICHD, NIMH, NIDA, and the Fogarty International Center. Co-funding from NICHD was focused on HPTN studies that evaluated prevention of perinatal HIV transmission, and examined the safety and efficacy of microbicides for prevention of sexual HIV transmission. In 2006, NIAID recompeted all NIAID-funded clinical trials networks, and, as a result, perinatal investigators in the HPTN combined their activities with pediatric researchers in the PACTG to form the newly funded IMPAACT Network. The microbicide research activities of the HPTN were re-competed separately and are now funded as the MTN. The NICHD will continue to provide staff participation and co-funding for the MTN and IMPAACT Leadership Groups; the MTN and IMPAACT Network will collaborate on clinical trials with investigators and sites supported through the NICHD-funded clinical trial networks, including the NICHD Network and the ATN.

During the period of HTPN funding by the NICHD, a number of perinatal HPTN protocols were completed or initiated; see the *Research Advances* section of this report for more information. Two of these studies are continuing enrollment as part of the new IMPAACT Network:

- HIVNET/HPTN 027 is a phase I, randomized, double-blind, placebo-controlled study that began enrollment in Uganda in late 2006. The study will evaluate the safety and immunogenicity of a live, recombinant canarypox-vector HIV vaccine (ALVAC-HIV vCP1521) in infants born to HIV-infected women whose CD4-cell counts are greater than 500 cells/μL. In all, 60 infants will be randomized to receive ALVAC-HIV vCP1521 or saline on or before day three post birth, and at four, eight, and 12 weeks; a prior neonatal vaccine study, PACTG 326, done in the United States, showed that this vaccination schedule optimized neonatal immune response. The study will follow infants intensively through 24 months of age.
- HIVNET/HPTN 046 is a randomized, double-blind, phase III trial that began enrollment in Uganda in late 2006 and in Zimbabwe in early 2007; additional sites are expected to open in Tanzania and South Africa later in 2007. The study will assess whether antiretroviral prophylaxis given to the breastfeeding infant of HIV-infected women will reduce breast-milk HIV transmission. The study will evaluate the efficacy of daily infant NVP provided for six months or through cessation of breastfeeding, whichever is earliest, compared to placebo. An earlier study, HIVNET 023, established safety and tolerability of this six-month daily regimen. This study will enroll approximately 1,500 HIV-infected women and their infants.

ADOLESCENT TRIALS NETWORK FOR HIV/AIDS INTERVENTIONS (ATN)

Initially funded in 2001, the ATN is a domestic, multi-center research network that conducts both independent and collaborative research through a cooperative agreement mechanism; the NICHD provides primary funding for the ATN, and NIDA and NIMH provide co-funding. During the first project period, the ATN established its organizational structure and scientific committees and began developing clinical trials and enrolling patients. The first funding cycle, which ended in February 2006, produced 11 scientific papers (at the writing of this report), nine papers currently in review, and 17 scientific abstracts. The ATN was re-competed in 2005 and was funded in 2006 for a second five-year period.

The primary mission of the ATN is to conduct research that explores promising behavioral, microbicidal, prophylactic, therapeutic, and vaccine modalities in HIV-infected and HIV at-risk adolescents ages 12 through 24 years. ATN research is done both independently and in collaboration with existing research networks, such as the MTN, HIV Vaccine Trials Network (HVTN), IMPAACT, ACTG, and others. The ATN includes: a Leadership Group, which defines and develops the research agenda; a data and operations center; and 15 sites across the United States and Puerto Rico (see Appendix G for a list of the sites). The research agenda of the ATN includes three broad areas: therapeutics, behavior, and community prevention. The range of studies includes primary prevention in uninfected youth, including preparation for HIV-preventive vaccine trials and microbicide studies, and the clinical management of HIV-infected youth, including treatment regimens and management strategies, medication adherence, and risk reduction.

The ATN has established collaborations with the major treatment networks:

- In the first funding cycle, the ATN and PACTG each co-endorsed a number of the other group's protocols that were of joint scientific interest for co-enrollment. The ATN and IMPAACT will continue this collaboration.
- The NICHD Network clinical trial sites have enrolled patients into selected ATN studies since 2004.
- The ATN is collaborating with the MTN; the two networks completed development of their first collaborative protocol, MTN 004. This trial will enroll 30 adolescent/young adult minority females at two ATN sites to test the safety and acceptability of a dendrimer-based microbicide product in the form of a vaginal gel.
- The ATN is collaborating with the ACTG on a treatment protocol that will allow generation of data on novel antiretroviral regimens in adolescents.
- In 2002, the ATN leadership joined the HVTN Pediatric Vaccine Liaison Group, which evolved into the HVTN Adolescent Working Group. At a consultation with representatives from the South African AIDS Vaccine Initiative, who are also members of the HVTN Adolescent Working Group, ATN researchers presented the Connect-to-Protect® (C2P) Program (see the *Community Prevention Research Agenda of the ATN* section for a description of the program). The ATN, HVTN, and IMPAACT Network are now collaborating on the development of a phase I safety study of the prime-boost strategy utilizing a multi-clade HIV-1 DNA plasmid/adenovirus vector (Ad5), a product from the NIH Vaccine Research Center, in adolescents; the study will be conducted domestically, at a limited number of sites from all three networks.

Therapeutic Research Agenda of the ATN

The therapeutic agenda of the ATN seeks to optimize diagnosis and management, and to improve HIV-related co-morbidities in HIV-infected youth. Currently 12 protocols are open or in follow-up, including a range of studies, such as:

- Evaluation of a short-cycle treatment strategy and a pharmacokinetic study of a new protease inhibitor, atazanavir, in infected youth;
- Intensive evaluation of the pathogenesis of metabolic disorders in HIV-infected youth compared to uninfected controls;
- A study of several Hepatitis B virus (HBV) vaccine strategies in infected youth, based on data from the Reaching for Excellence in Adolescent Care and Health (REACH) Project of AMHARN that indicated poor immune response of infected youth to standard HBV immunization schedule;
- A study of HBV vaccine strategies in uninfected at-risk youth, including an evaluation of tools proposed for future HIV-preventive vaccine trials (e.g., risk assessment tools, risk-reduction interventions, and consent issues);
- Examination of the correlates of HBV-specific immune response to HBV vaccine in infected and uninfected youth;
- Use of the detuned Orasure® oral HIV-antibody assay to determine recent HIV infection in youth screened in community settings, and evaluation of primary antiretroviral drug resistance in recently infected youth;
- Evaluation of HIV-specific CD8-cell response and escape mutations to explain specific human leukocyte antigen (HLA) class I allele-associated differences in HIV disease progression observed in REACH; and
- A study of vitamin D levels in infected youth.

Several new studies are in final stages of protocol development, including: evaluation of a novel management strategy (e.g., early initiation of therapy in recently infected youth, followed by de-intensification to maintenance therapy with atazanavir/ritonavir) and its effect on preservation of the immune system; usefulness of vitamin D supplementation in reversing adverse effects of the drug tenofovir on bone metabolism; evaluation of the safety and immunogenicity of human papillomavirus (HPV) vaccine (Gardasil®) in HIV-infected adolescent females; MTN 004, a phase I microbicide study in female youth (discussed earlier); and a phase I HIV vaccine study in collaboration with the HVTN and IMPAACT (discussed earlier).

Behavioral Research Agenda of the ATN

The behavioral research agenda of the ATN is broadly defined to include the development, adaptation, implementation, and/or evaluation of culturally appropriate, theory-driven behavioral preventive interventions for HIV and other sexually transmitted disease in at-risk youth. In addition to prevention studies, the behavioral research agenda aims to examine interventions that preserve and improve the well-being of HIV-infected adolescents and young people.

Currently, 14 protocols are open or in follow-up, representing a robust and varied agenda that was, in part, generated within ATN working groups and, in part, proposed by external investigators through established and accessible ATN procedures. The Network's behavioral

research agenda includes randomized controlled studies of individual-level or social network-level interventions to reduce sexual risk, and evaluations of engagement in HIV care and its relationship to substance use or mental health disorders. Pilot studies include an intervention to improve risk-behavior communication between mothers and at-risk adolescent girls. Formative research includes: evaluating gender identity among gay youth, to inform development of a risk-reduction intervention; and evaluating the health needs of transgender youth to generate a survey instrument focused on their health needs, and then administering the survey to transgender youth. Focus group studies include: evaluating ways to simplify HIV vaccine trial concepts to inform a controlled trial to assess whether there is improved comprehension with simplified consent forms and developing a survey instrument to determine relative influence of different factors on antiretroviral drug adherence; a qualitative study to interview HIV-positive female adolescents who have experienced physical and/or sexual abuse; and similar work to explore support needed when one receives an HIV diagnosis to inform the development of a psychosocial intervention aimed at improving adjustment to HIV diagnosis. The ATN is supporting a behavioral substudy to the collaborative MTN/ATN trial (MTN 004) that will assess adherence and acceptability of the microbicide product under study.

In addition to the major focus on adolescents at risk of sexual HIV acquisition, other ATN protocols target perinatally infected youth to address important gaps in information needed to care for this population and to handle issues, such as status disclosure and risk reduction.

New behavioral protocols are also being developed to examine issues, such as validity of screening tools, an intervention for youth newly diagnosed with HIV infection, an intervention for substance-abusing HIV-infected youth, and a study examining psychosocial development and risk behaviors among young men who have sex with men.

Community Prevention Research Agenda of the ATN

PAMAB conducted a community consultation in 2001 to ascertain how racial and ethnic minorities would respond to clinical HIV vaccine trials for youth. Responses were clear: decision-making must reside within the communities themselves. Respondents also felt that the researchers were obliged to give them all necessary information to make informed decisions, and that participation in vaccine trials should not be the only prevention option offered to youth.

Based on this information, the ATN developed Connect-to-Protect® (C2P), an ambitious seven-year program to build community trust and engagement, establish a primary prevention research infrastructure, and test a model of community mobilization that uses structural change to produce measurable improved-health outcomes in community youth. C2P builds a solid framework and infrastructure for future HIV vaccine and microbicide studies in youth. All ATN sites participate in C2P.

The C2P portfolio includes four interrelated studies that evaluate specific key components of the overall community engagement strategy. In the first phase of C2P, researchers strategically assessed the community at the ATN site location for both youth risk and service resources. They then collected extant data related to public health, criminality, scholastic outcomes, and other issues that were used in computer mapping to identify census tracts of enhanced risk. Researchers then identified community stakeholders, interviewed them, and invited them to a

town hall meeting to discuss the needs of community youth. C2P also produced service directories for each ATN city.

In the second phase, researchers conducted further evaluation of areas of enhanced risk using ethnographic assessment and brief venue surveys to determine high-risk venues. They engaged community representatives as partners in evaluating venue data, in choosing the target population (e.g., young women or gay youth) and in setting specific goals. Importantly, the investigators formally evaluated the quality of community partnerships through the conduct of specific evaluation measurements at multiple time points throughout the project; these evaluations assessed the formation and maintenance of the community-researcher partnerships and measured the activities and output of the partnerships, along with changes in the community partner's attitudes and perceptions about research/researchers over time. Investigators also conducted anonymous audio-computer assisted surveys (ACASI) in youth at high-risk venues to evaluate sexual and drug use risk practices, and conducted anonymous HIV serosurveys in youth at these venues. All ATN sites have completed the first two phases of C2P.

In the third, ongoing phase of C2P, ATN site staff, community partners, and newly invited community sector representatives formed local coalitions to strategically develop and implement a local action plan for achieving the C2P goals identified in phase two. The intervention consists of community mobilization activities that are expected to lead to structural change and to the adoption of an HIV-prevention program developed with the CDC. An evaluation of the overall process occurs both within the site and across ATN sites to assess the overall efficacy of the community mobilization intervention. The evaluation involves annual collection of anonymous data from ACASI surveys from two cohorts that represent the target population or "population of focus" for each participating ATN site. The data collected allows researchers to track venues at which the risk population congregates and to assess of HIV-related risk behaviors. In the final year of the study, researchers will conduct a second anonymous HIV serosurvey to evaluate trends in HIV seroprevalence in high-risk youth over time. They will use these collective data to evaluate the overall efficacy of the community mobilization intervention and to assess changes in HIV-related risks over time.

In addition, selected ATN-C2P sites will conduct two community-level prevention programs developed by the CDC for HIV/sexually transmitted diseases. In one study, selected sites will participate in the adaptation and implementation of the CDC Community Peers Reaching Out and Modeling Intervention Strategies for HIV/AIDS Risk Reduction in their Community (PROMISE) program, which relies on role model stories and peer advocates from the community. Additionally, selected sites will adapt and implement the CDC MPowerment program, a community prevention program that relies on peer advocates from the community to lead outreach activities including discussion groups ("M-groups"), venue-based outreach, social events, and a publicity campaign. The objective of both protocols is to effect community change through diffusion of health-promoting information via naturally occurring social networks.

The ATN also has two new community protocols in development. One will evaluate linkage to care and components of care-seeking behavior in youth who were recently diagnosed with HIV infection. The other will examine the feasibility and acceptability of identifying and recruiting

HIV-infected and HIV at-risk young women to serve as index recruiters for two or more members of their friendship network to undergo HIV testing.

WOMEN AND INFANTS TRANSMISSION STUDY (WITS)

PAMAB co-sponsors WITS, the United States' longest continuously enrolling, prospective cohort study of HIV-infected pregnant women and their children. The study was initiated in 1988 through a cooperative agreement co-funded by the NICHD, NIAID, and NIDA. In 2006, WITS ended its fourth and final funding cycle, and the study is currently in its final analysis phase.

The original objectives of WITS were to: identify and characterize factors that influence maternal-infant transmission of HIV; develop and evaluate methods for early diagnosis of HIV in perinatally exposed infants; and identify and characterize factors that influence HIV disease progression in HIV-infected pregnant and postpartum women and children.

As of December 2005, the six clinical sites in the United States and Puerto Rico had enrolled 3,297 HIV-infected pregnant women and 2,842 infants born to them. In addition to collecting clinical and laboratory information on participants at regular intervals, WITS maintains a valuable repository of biological samples for current and future research.

Specific aims of the final WITS cycle focused on: understanding the pathogenesis and course of pediatric HIV disease in an era of antiretroviral treatment; monitoring the long-term effects of fetal and neonatal exposure to antiretroviral agents in uninfected children; describing the course of maternal HIV disease in an era of antiretroviral treatment; identifying and characterizing factors that influence the development of viral drug resistance; identifying and characterizing factors that influence adherence to medication regimens; and understanding the pathogenesis and natural history of hepatitis C virus (HCV) co-infection in HIV disease.

Between 1989 and 2005, WITS established numerous landmark research advances that improved understanding of perinatal HIV transmission, pediatric HIV diagnosis, and pediatric HIV disease. As of March 2006, WITS investigators had authored more than 150 primary or related publications. Additionally, a significant number of secondary research projects using the WITS database or specimen repository were funded through R01 or other grant mechanisms, significantly adding to the value of the investment in WITS.

WITS data analyses will continue into 2007 and beyond. The rich database and repository will remain available for research by WITS and other interested investigators. WITS follow-up, which closed in 2006, has been succeeded by the Pediatric HIV/AIDS Cohort Study (PHACS); see below for a description of PHACS. PHACS will allow continued follow-up of many of the children enrolled in WITS after the WITS funding period ends.

PEDIATRIC HIV/AIDS COHORT STUDY (PHACS)

Looking at future research needs and with guidance from the NACHHD Council, PAMAB, in collaboration with NIAID, NIDA, NIMH, the National Institute on Deafness and Other Communication Disorders, and the NHLBI, invited investigators in 2005 to plan for and address two critical pediatric HIV research issues: the long-term safety of fetal and infant exposure to prophylactic antiretroviral chemotherapy, and the effects of perinatally acquired HIV infection in adolescents. This project, funded through a cooperative agreement, refocused WITS and planned for a data merger from other U.S.-based pediatric HIV cohort studies, including the "Late Outcomes Protocol" 219C of the former PACTG.

The PHACS has two primary objectives: create a body of data that helps investigators to more fully understand the effect of HIV on sexual maturation, pubertal development, growth and bone development, and socialization of perinatally HIV-infected pre-adolescents and adolescents; and acquire more definitive information regarding long-term safety of antiretroviral agents when used during pregnancy and in newborns.

There is substantial urgency in addressing both questions. The number of perinatally infected children born domestically (where a study of this intensity is feasible) has dropped sharply since 1998. Studying a closed cohort of these children remains possible because the timing of the pediatric HIV epidemic in the United States is such that children with perinatal HIV infection are just now reaching adolescence. At the same time, ever-increasing numbers of children worldwide sustain fetal or neonatal exposure to a growing variety of antiretroviral chemotherapeutic drugs, even though little information on long-term safety exists; it has only been a decade since the effectiveness of antiretroviral chemoprophylaxis for MTCT was first demonstrated in PACTG 076. Thus, study of an open cohort of HIV-uninfected children who were fetally and neonatally exposed to antiretrovirals to identify potential consequences is a critical need.

The existing research agendas for the WITS and other cohorts have thus been refocused and prioritized to address emerging scientific issues in the pediatric population. The NICHD and its co-sponsor Institutes are working with PHACS investigators to further the HIV research agenda for American children in two major ways: by developing a mechanism to identify long-term safety issues arising as a consequence of exposure to antiretroviral chemotherapy; and by developing research protocols that address specific questions regarding the effects of perinatal HIV infection in adolescents.

The PHACS study consists of two protocols: the Adolescent Master Protocol (AMP), which will address the impact of HIV disease on sexual maturation, pubertal development, and socialization of perinatally HIV-infected preadolescents and adolescents; and the Surveillance Monitoring for Antiretroviral Treatment Toxicities (SMARTT) Study, which will address the consequences of *in utero*/neonatal antiretroviral exposure. Both the base protocol and the surveillance system are structured to accommodate focused substudies in future years. Specific focus areas in PHACS include:

- Neurodevelopmental, language and hearing, cognitive, academic, vocational, and behavioral outcomes

- Growth, endocrinologic, and bone development issues (including nutritional effects)
- Sexual maturation and reproductive capacity
- Body composition changes and tissue redistribution syndromes
- Cardiovascular complications and cardiovascular disease risk
- Mitochondrial effects of exposure to antiretroviral drugs
- Effects of maternal drug use on outcomes in infants and children

With fiscal year 2005 funding from PAMAB, the NICHD and the co-sponsoring partners formed a multidisciplinary Leadership Group to identify critical research questions and define the best scientific methodology to address them. A Data and Operations Center was funded to determine common elements that may be shared among existing datasets, develop the database structure for the prospective base, and compete subcontract applications from clinical sites. In 2006, clinical sites were competitively selected and a total of 25 institutional subcontract awards were made to 22 sites for the SMARTT Study and to 12 sites for the AMP. Subject enrollment and follow-up began in 2007.

INTERNATIONAL EPIDEMIOLOGIC DATABASES TO EVALUATE AIDS (IEDEA): PEDIATRIC COMPONENT

The IeDEA project is funded by the NIAID; since 2006, PAMAB has provided co-funding to IeDEA to allow the inclusion of children in the project studies.

IeDEA is a collaborative group of seven international regional data centers—four in Africa (West, Central, East and South) and one each in Asia, Central/South America/Caribbean, and North America—that allow the compilation of data on a global basis to address HIV research questions existing individual cohorts are unable to address, including: better characterization of HIV natural history in resource-rich and resource-limited countries; identification of factors associated with disease progression, including co-infections, particularly in resource-limited countries, where co-infections differ from those in the United States and Europe; and evaluation of the effectiveness of therapy and other interventions, including adverse effects. IeDEA will compile regional, generalizable datasets that represent study populations based on data from different settings and populations, and create procedures and approaches to allow regions to more accurately address and monitor the HIV epidemic within their populations. In an era in which antiretroviral therapy is becoming available in resource-limited countries, these databases will allow evaluation of the effectiveness these interventions.

In its initial funding of IeDEA, NIAID focused on data collected from HIV-infected adults. However, it is estimated that, globally, 2.3 million children are living with HIV infection, and an additional 700,000 are born each year. The vast burden of pediatric HIV infection resides in resource-limited countries. While there are cohort studies to address the morbidity and mortality of HIV infection in children in the United States and Europe, there are few cohorts and only limited data available related to the nature of HIV infection in children in resource-limited countries. Available data indicate rapid progression of HIV in children in Africa. Antiretroviral therapy is now becoming available for children in resource-limited countries through the Global Fund, PEPFAR, the Clinton Foundation, and other organizations. A mechanism for evaluating

the effectiveness of therapy in children, the changes in the natural history of HIV disease that may occur with such therapy, and the complications and potential toxicities of such therapy in these settings is critically needed.

By co-funding IeDEA, the PAMAB secures the addition of pediatric data collection to the project's regional networks to allow: definition of the prognosis of HIV-infected children treated with antiretroviral therapy in resource-limited settings; comparison of experiences, ways of delivering therapy, and types of monitoring of therapy and complications of therapy among different settings; and comparison of prognosis of treated children in resource-limited settings with that observed in industrialized nations. PAMAB funding will ensure inclusion of pediatric data in the four African and the Asian regional networks. (PAMAB will not co-fund the North or South American networks because the Branch already funds extensive pediatric data collection in these regions through the PHACS and NISDI projects.) The collaboration between PAMAB, NIAID, and the IeDEA investigators will facilitate compatible approaches to data collection so that data from PHACS and NISDI can contribute to the overall IeDEA database for analyses that require large datasets.

WOMEN'S INTERAGENCY HIV STUDY (WIHS)

WIHS is the largest and longest ongoing cohort study of HIV-infected women in the United States. This multi-center study of the natural history of HIV infection in women is co-funded by the NICHD, NIAID, NIDA, and the National Center Institute. Of the six clinical sites and data center in WIHS, PAMAB has funded the University of California clinical site since the study began in 1993.

The primary goal of WIHS is to describe the natural history of HIV infection in women, including risk factors, use of and response to therapy, and complications of HIV infection and therapy. With the development of potent combination therapy, HIV has become a treatable, chronic disease; therefore, WIHS is now describing the impact of therapy on HIV infection in women, including the benefits in slowing disease progression and improving survival, the complications of therapy, the interactions with other chronic infections, such as HCV, and the impact on concomitant conditions, such as genital neoplasia. The median age of the original cohort is now 47 years, meaning investigators can study the interaction of menopause and changes related to aging on HIV infection and complications of therapy.

The initial cohort enrolled 2,059 HIV-infected and 569 HIV-uninfected women. Changes in the epidemic that resulted from availability of more effective antiretroviral therapy, and from the aging of the cohort, led study sponsors to expand WIHS in 2001 to enroll additional women, especially younger women and women naïve to antiretroviral therapy, to better delineate complications of therapy versus those of HIV and aging. The expansion added 744 HIV-infected women and 408 HIV-uninfected women who had characteristics similar to the infected women. Because 85 percent of the enrollees are women of color, WIHS reflects the demographics of HIV infection in women in the United States.

The study also includes a similar control group of HIV-uninfected women to allow differentiation of complications from HIV infection and its therapy and from prevalent conditions related to poverty and aging. To learn about the WIHS key findings, see the *Research Advances* section of this report; to learn about the WIHS plans, read the *Future Directions for the Branch* section of the report.

As of January 2007, WIHS investigators had authored more than 300 peer-reviewed publications. The investigators have also used the WIHS platform of data and specimen collection to leverage additional funding, primarily through the NIH R01 grant mechanism. Currently, more than $8 million per year is in place in collaborative R01 and P01 funding for researchers to use the WIHS data and specimens to answer additional scientific questions. As an example, researchers used or are using R01 funding to: test for multiple HPV types in genital specimens from each visit; conduct detailed studies of HCV infection, including effects on the immune system and detection of HCV at extrahepatic sites; use HLA testing to evaluate the role of variations in host genetics on the immune response to HIV; conduct carotid intimal thickening testing and define other measures of cardiovascular disease; study the rate and effects of renal disease in the WIHS cohort; explore population pharmacokinetic testing of different antiretroviral drugs; and conduct viral resistance studies. Researchers are seeking additional grant funding to: assess non-invasive markers of progression of liver disease among HCV-infected women; evaluate genetic markers of susceptibility for metabolic complications of HIV infection and therapy; and supplement current standardized assessments of the effects of HIV, menopause, and aging on neurocognitive function using neuroimaging. The WIHS investigators will continue to maximize the use of data and specimens by seeking additional funding and by expanding collaborations with investigators not currently working with the WIHS.

MICROBICIDE STUDIES

The PAMAB recently assumed primary responsibility for the NICHD's biomedical microbicide research agenda. The Institute will implement much of this agenda through its co-funding of the recently established MTN and its collaboration with the ATN. The MTN, funded by NIAID, NICHD, and NIMH, seeks to develop and implement a full array of clinical trials in hopes of identifying one or more effective microbicides for the prevention of HIV transmission. Ancillary studies within the clinical trials are designed to identify surrogate markers of efficacy and toxicity, and to understand factors that affect acceptability of microbicidal products. Of special interest to the NICHD are studies in adolescents and issues of including pregnant women in microbicide studies.

Adolescent women in the United States and internationally are at higher risk than other age groups for acquisition of HIV and other sexually transmitted infections. Through collaboration between the MTN and ATN, investigators will do early phase studies of MTN products at ATN sites to assess the safety and acceptability of microbicides among adolescent and young adult women.

Pregnant women seem to be at increased risk for seroconversion to HIV, possibly related to hormonal effects on the susceptibility of the female genital tract. When an effective microbicide

becomes available, pregnant women will want to use the product to limit their risk of HIV infection; women may also conceive while using microbicides. The safety of microbicide use during pregnancy must be assessed during the product's development to assure wide availability and applicability once efficacy is demonstrated. PAMAB staff are leading the effort to ensure that appropriate studies, including animal reproduction studies and appropriate phase I studies in non-pregnant women, are done to adequately evaluate the use of candidate microbicides during pregnancy. Investigators are creating templates for a progression of studies in pregnant women to be performed once preliminary studies outside of pregnancy indicate safety; the ultimate goal of the studies is to allow participation of pregnant women in phase III microbicide studies. Ultimately, microbicides may even be applicable for use during labor to reduce the risk of vertical HIV transmission.

The MTN has a wide array of studies in progress or under development, including: an ongoing phase II/IIb study of the safety and effectiveness of the vaginal microbicides BufferGel™ and 0.5% PRO2000/5 Gel (P) to prevent HIV infection in women (target enrollment = 3,220); a phase II expanded safety and acceptability study of the antiretroviral vaginal microbicide 1% tenofovir gel (target enrollment = 200). As discussed earlier in this report, the MTN-ATN collaborative study, MTN 004, is also ongoing. Additional studies in active development include a protocol to follow women who seroconvert while participating in microbicide trials, a pharmacokinetic study of oral and topical tenofovir, a study of the absorption of tenofovir gel in labor, and a multi-arm phase III trial of oral compared to topical tenofovir to prevent HIV transmission.

Additional PAMAB activities related to microbicides include participation in collaborative groups working to advance the microbicide research agenda and management of relevant grant portfolios. The collaborative groups include a working group to develop standardized toxicity grading tables for vaginal and rectal microbicide trials, the International Working Group on Microbicides, and the NIH OAR Microbicide Working Group. In addition, researchers are working on several grants to evaluate the mechanisms of heterosexual transmission using cellular and tissue culture models; this work should yield important information on possible targets for microbicide development.

PAMAB INVESTIGATOR-INITIATED GRANT PORTFOLIO

The Branch supports a growing portfolio of investigator-initiated research grants, many of which have an international focus (see Figure 3 for more details). More than 80 percent of investigator-initiated research grants funded by PAMAB between 2003 and 2006 supported an international research agenda. A general description of some of these grants appears below.

Animal Model Research

The Branch supports research on the following aspects of this topic:

- Researchers are using a rat model to evaluate the neurodevelopmental consequences of perinatal exposure to HIV proteins Tat and gp120. Study goals are to determine the types of adverse events secondary to HIV infection that are observed in the developing central

nervous system, examine the associated dose-response relationships, and identify critical time points during development when the risk is greatest.

- Another investigator is using proprietary technology to formulate sustained-release suspensions of NVP. Formulations with adequate *in vitro* release characteristics will then be evaluated for their *in vivo* release properties in rats. These studies are expected to provide the basis for more detailed animal testing of product pharmacokinetics and safety, leading in turn to an investigational new drug application for human testing. The resulting products could contribute very significantly to the armamentarium of antiretrovirals available for HIV treatment and prevention, particularly prevention of breastfeeding transmission.
- Researchers are using a macaque oral simian-human immunodeficiency virus (SHIV) challenge model to dissect the protective effects of maternally acquired neutralizing antibody (NAbs). Study goals are to determine whether antibody can affect the establishment or severity of SHIV infection, and whether maternal immune globulin G can synergize with monoclonal antibodies to produce enhanced protection.

Studies of the Biology of HIV Infection in Children

PAMAB supports several observational and laboratory studies, which enroll participants from other research or treatment programs, or that use stored biological specimens from cohort studies or clinical trials. These projects help to leverage NIH investments by acquiring important new information with a moderate commitment of new costs.

- One investigator is using stored samples from a previous PAMAB-funded cohort study of youth with hemophilia to evaluate immune responses that might control or potentiate disease from HIV and HCV.
- Another investigator is using stored specimens from HIV-infected infants who received antiretroviral therapy, and who experienced immune reconstitution despite persisting high viral loads to examine whether alterations in HIV-cell tropism favor replication in macrophage-related cells, thereby reducing replication in thymic tissue and in lymphocytes, contributing to immune reconstitution.
- A study using longitudinal specimens obtained from Zambian infants infected with HIV-clade C viruses examined viral replication and tropism, patterns of viral diversity and sequence evolution, and integrated the longitudinal analyses of viral sequences with clinical disease manifestations.
- Specimens from a trial of Tanzanian HIV-infected women who were randomized to receive vitamin A supplementation or placebo are being used to determine the biological basis for the observed increase in breastfeeding transmission risk associated with vitamin A supplementation.
- The central nervous system is a major target of HIV infection in children. One investigator will enroll HIV-infected children from the Democratic Republic of Congo immediately before they enter into the national antiretroviral program. This study will sample HIV present in cerebrospinal fluid to characterize virus variants present in the central nervous system compartment, assess the impact of antiretroviral treatment on virus variation, and assess the impact of viral variation on encephalopathy.

Studies of Factors that Influence Perinatal HIV Transmission

PAMAB supports investigators who conduct laboratory or cohort studies to illuminate the biological basis for perinatal HIV transmission:

- Preliminary studies suggest an association between maternal HLA-G mutation and reduced risk of HIV MTCT. Current studies are looking at mutations in a specific HLA-G exon to determine which polymorphisms might be protective.
- Another investigator is dissecting HIV immune responses by examining South African infants born to HIV-infected mothers who received no antiretroviral drugs during pregnancy. This effort looks at antigen-specific cytokine production by cord blood cells and the association with infant infection status. The study is also examining the occurrence and immunologic relevance of interactions between maternal and infant HLA genes.

Studies Examining the Clinical Significance of Nevirapine Resistance Elicited by Single-Dose Administration to Prevent MTCT

Previous studies have proven that administration of a single dose of NVP to mothers shortly before delivery, and a single dose to the newborn in the first 72 hours after birth is safe and effective for reducing the incidence of perinatal HIV transmission; however, even this brief exposure to NVP can elicit NVP-resistant variants of HIV. The clinical consequences of such resistant variants are not known. Investigating this question is a very high research priority, and several PAMAB-supported investigators are approaching the question in different ways:

- One investigator is examining the HIV nucleotide sequences in women exposed to a single-dose NVP regimen and correlating resistance mutations in different HIV-1 clades with levels of drug sensitivity and with viral replication fitness.
- Another investigator is evaluating a cohort of women who received single-dose NVP compared to placebo in the context of a randomized clinical trial assessing efficacy of short-course ZDV with and without NVP. The study is also examining therapeutic outcomes in such women when they later require therapy, which is usually non-nucleoside reverse transcriptase inhibitor-based, during the postpartum period.
- A third investigator is conducting an observational study to compare therapeutic outcomes of NVP-containing treatment regimens for postpartum women who received single-dose NVP 12 months or more prior to requiring therapy compared those who did not receive NVP prophylaxis.
- A fourth study is examining the therapeutic consequences of single-dose NVP for infants who were exposed to NVP, but who still became HIV infected, by comparing treatment outcomes of NVP-containing versus NVP-sparing regimens.

Studies of the Biology of Breast-Milk HIV Transmission

Because breastfeeding comprises a major component of overall risk for MTCT, the research field has experienced an increased research focus on HIV transmission risk associated with breastfeeding. The PAMAB supports several research projects to illuminate the biological factors involved in breastfeeding transmission:

- An observational study in Botswana is evaluating the impact of breastfeeding itself on morbidity and mortality in HIV-infected mothers. This work will provide important information needed to evaluate strategies for reducing HIV transmission from breastfeeding.

- Another investigator is conducting *in vitro* analyses of breast milk specimens from HIV-infected mothers to determine viral content, and to test the functional activity of antibodies and innate immune factors present in milk to inactivate autologous HIV.
- Children enrolled in a trial to examine chemoprevention of breastfeeding transmission will also be enrolled in a study to examine immune responses to determine if oral exposure to HIV elicits specific immune responses in the absence of established HIV infection.
- Another investigator is studying HIV variation and cellular immune responses in the breast-milk compartment and evaluating the impact of mastitis on HIV variation.
- In a separate study, the same investigator is examining the effects of prolonged breastfeeding on T-cell production and plasma viremia and exploring a possible connection between estrogen or other mediators of lactation and thymic output.

Clinical Trials

In addition to clinical trials carried out through PAMAB-sponsored networks, the Branch also supports several international clinical trials through the R01 grant mechanism. This research is conducted mainly in international settings and deals with the unique questions posed by the populations in those areas:

- In Zambia, a randomized trial is comparing abrupt weaning following four months of exclusive breastfeeding to exclusive breastfeeding with standard, gradual weaning for safety and efficacy in reducing breast-milk HIV transmission. This grant also serves as a conduit for PEPFAR funds to provide wider access to antiretroviral drugs to the Lusaka area, and to evaluate unique ways of providing prophylaxis to prevent HIV MTCT.
- A novel pharmacokinetic study is evaluating antiretroviral drug (administered to the mother) penetration into breast milk to estimate milk-borne drug dosages acquired by infants. This study will provide important insights on the potential good or bad effects for infants of such maternally acquired drugs.
- One study is examining the utility of tracking height and weight velocity as indicators of response to pediatric antiretroviral treatment, in addition to a number of standard laboratory evaluations, in order to develop a simple clinical and laboratory algorithm for evaluating therapeutic response for use in resource-limited countries.
- Another study, in Thailand, is comparing management of HIV treatment by monitoring viral load versus by monitoring CD4-cell levels. If successful, this study could provide a less expensive means for therapeutic management in resource-limited countries.
- A study in Kenya is examining whether very early treatment of infected infants can promote immune reconstitution, resulting in a reduced viral set point at which drugs are stopped.
- In Tanzania, a clinical trial is assessing micronutrient supplementation to reduce mortality and morbidity in children born to HIV-infected mothers.
- Based on prior research that showed multivitamin supplementation slowed the decline of CD4-cell count and clinical progression in HIV-infected women who received supplementation during pregnancy and postpartum, investigators are conducting another study in Tanzania to evaluate the safety and efficacy of multivitamin supplement use in infected individuals who are starting antiretroviral treatment.

Training and Career Development

PAMAB continues to expand its career training awards with a mix of K08 (Mentored Clinical Scientist Development Award), K23 (Mentored Patient-Oriented Research Career Development Award), K24 (Mid-Career Investigator Award in Patient-Oriented Research), F31 (Minority Pre-Doctoral Fellowship Program), and F32 (Individual National Research Service Award) grants (see Figure 6 for more details). Most of these career awards support research conducted in international settings that is linked to other grants funded by the NICHD or NIAID.

RESEARCH ADVANCES

This section of the report highlights some of the research advances from PAMAB-supported scientists and Branch staff since the last report to the NACHHD Council in 2003. These advances are organized into four major topic groups based on populations of interest: HIV-infected pregnant women and their infants (includes studies on the prevention of MTCT); pediatric HIV infection; adolescents and HIV infection; and HIV infection in women.

RESEARCH ADVANCES IN HIV-INFECTED PREGNANT WOMEN AND THEIR INFANTS

A significant portion of research funded by the PAMAB with regard to HIV-infected pregnant women and their infants is focused on interventions to prevent MTCT of HIV and on studies of HIV transmission through breast milk.

Interventions for the Prevention of MTCT of HIV

PAMAB has supported a number of important large clinical trials on prevention of MTCT in the developing world. Analysis of data generated from investigator-initiated grants, as well as studies conducted within the NISDI, WITS, PACTG, and the HPTN have provided important insights into the efficacy and effectiveness of such interventions.

ANTIRETROVIRAL INTERVENTIONS FOR THE PREVENTION OF HIV MTCT

In 1994, results from the PACTG 076 study in the United States showed that ZDV given after the first trimester, intravenously during delivery, and to the infant for six weeks following birth reduced MTCT by nearly 70 percent. Based on PAMAB-supported studies, such as WITS, that demonstrated the independent effect of maternal viral load and complexity of antiretroviral prophylaxis on risk of MTCT, use of three-drug combination antiretroviral prophylaxis is now standard and has reduced MTCT in the United States to less than 2 percent.

In resource-limited countries, studies show that shorter antiretroviral regimens can also reduce MTCT by approximately 40 to 50 percent. Based on studies supported by PAMAB and other Institutes and organizations, several regimens are known to be effective in reducing MTCT, including: a short-course ZDV regimen given in the third trimester and given to the infant for one week; and a single-dose NVP regimen, with one dose given to the mother during labor and one given to the newborn. While antiretroviral drug treatment is becoming more available to

individuals with symptomatic HIV disease in resource-limited countries (including pregnant women), use of combination drug regimens for prophylaxis of MTCT in women who don't require therapy suffers from complexity, cost, and lack of data on safety, particularly among breastfeeding populations. However, it is clear that regimens with greater efficacy than the available short-course regimens need to be identified.

Through an R01 grant, PAMAB supported a critical clinical trial of non-breastfeeding women in Thailand. This placebo-controlled randomized trial compared short-course ZDV alone to short-course ZDV plus maternal and infant single-dose NVP, or maternal single-dose NVP alone, to see if the addition of single-dose NVP would improve efficacy. The investigators found a dramatic 83-percent reduction in transmission with the combination regimen: MTCT was 1.1 percent with short-course ZDV combined with maternal/infant NVP compared to 6.2 percent with ZDV alone. No significant difference occurred in transmission when combining ZDV with maternal/infant NVP compared to ZDV plus maternal NVP alone (1.1 percent versus 2.0 percent, respectively). Efficacy of the combination regimens was greatest in women who had high viral loads and low CD4-cell counts near the time of delivery. This regimen has now become the standard regimen recommended by the WHO for prevention of MTCT in resource-limited countries for women who do not require therapy for their own health.

In a Botswana study of a breastfeeding population (called the Mashi Study), short-course ZDV prophylaxis was combined with single-dose intrapartum maternal NVP or placebo. All infants received single-dose NVP at birth and ZDV for four weeks if formula fed, or for six months if breastfed. In this study, transmission was similar regardless of whether women received single-dose NVP or placebo; MTCT at age one month was 4.3 percent versus 3.7 percent with and without maternal single-dose NVP, respectively. These findings suggest that maternal NVP is not necessary when sufficient antepartum ZDV is received and infant single-dose NVP is provided at birth with ZDV. These data are important because avoiding the maternal intrapartum NVP dose would eliminate the risk of maternal NVP resistance.

In the United States and Europe, where longer and more complex regimens are standard for preventing MTCT, PACTG 316 studied the addition of single-dose maternal/infant NVP to standard combination antiretroviral prophylaxis regimens; this placebo-controlled clinical trial was supported by the NICHD and NIAID. In this study, 77 percent of women were receiving combination regimens during pregnancy, and most had undetectable viral load at delivery. Women were randomized to receive single-dose maternal/infant NVP or placebo, in addition to their standard regimens. The study found remarkably low transmission rates and virtually no difference between study arms (1.4 percent and 1.6 percent, respectively). Based on this study, researchers do not recommend this regimen in the United States, where women receive combination antiretroviral therapy as standard of care, because the addition of single-dose NVP showed no significant benefit in combination and was associated with a potential risk of NVP resistance.

Antiretroviral drugs are needed during pregnancy for both prevention of MTCT and for the treatment of pregnant women who have symptomatic HIV disease. However, studies of new drugs for use in pregnancy are often lacking, and health care professionals end up administering the drugs to pregnant women without knowledge of appropriate dosing and safety. Through the

networks funded by PAMAB and NIAID, researchers are beginning to evaluate the pharmacokinetics and safety of new antiretroviral drugs in pregnant women and their neonates. These studies have already demonstrated that the recommended doses of nucleoside reverse transcriptase inhibitor and non-nucleoside reverse transcriptase inhibitor drugs are safe and effective during pregnancy and have provided short-term safety data for use in mother and infant. However, studies indicate that the levels of protease inhibitor drugs are decreased in pregnant women in the third trimester; therefore studies evaluating higher doses and/or boosting the drugs with low dose-ritonavir are in progress.

ANTIRETROVIRAL DRUG RESISTANCE, PREVENTION OF MTCT, AND RESPONSE TO LATER THERAPY

Resistance to antiretroviral drugs can limit the efficacy and effectiveness of regimens for prevention of HIV MTCT. Many studies have assessed antiretroviral resistance in subtype B HIV infections, the most common HIV subtype in the United States. However, less is known about drug resistance to other subtypes, even though non-B subtypes account for the overwhelming majority of HIV infections worldwide. Research on drug resistance in non-subtype B HIV is becoming increasingly important for two reasons: the prevalence of non-subtype B HIV is increasing in the United States and other countries where antiretroviral drugs are widely used; and the availability and use of antiretroviral drugs is growing in developing countries where non-subtype B HIV-1 is prevalent. PAMAB-supported research has provided important insights into the effect of viral subtype on development of NVP resistance.

Single-dose intrapartum maternal/infant NVP, a regimen widely used in low-resource settings around the world to prevent HIV MTCT, is also associated with the development of NVP resistance. The half-life of NVP is prolonged; that is, NVP levels are detectable for 14 to 21 days following single-dose intrapartum NVP in both mother and infant. These persistent drug levels may provide significant benefit in terms of prevention of MTCT. Researchers have shown that maternal viral load is reduced in plasma and in breast milk for two weeks or more postpartum following single-dose NVP, which explains why NVP is so effective in reducing intrapartum transmission, and why NVP appears to reduce early breast-milk HIV transmission as well. However, persistent drug levels also result in a prolonged period of functional monotherapy, and PAMAB-supported studies have shown that even when single-dose NVP is combined with ZDV, NVP resistance can develop in a significant proportion of women and in infants who become infected despite NVP prophylaxis.

Branch-supported researchers have conducted a number of studies on NVP resistance to evaluate the effect of viral subtype on development of resistance. After administration of single-dose NVP, a highly sensitive resistance assay detected the *K103N* mutation associated with NVP resistance more frequently and at quantitatively higher levels in women infected with HIV subtypes C and D than in those infected with subtype A. Evaluation of the dynamics of fading NVP resistance demonstrated that HIV subtype influences not only the selection, but also the fading of specific drug resistance mutations. These data suggest that NVP resistance may persist for longer periods after single-dose NVP in individuals with certain subtypes of HIV.

A separate study examined the persistence of NVP-resistance mutations in detail. Data indicated that NVP resistance in circulating free virus (HIV RNA) was detectable after six weeks, but then declined rapidly over time; the frequency of resistance mutation decreased from 87 percent at six

weeks after NVP exposure, to 65 percent, 39 percent, and 11 percent at three, seven, and 12 months postpartum, respectively. The actual frequency of resistant variants in the HIV quasispecies was limited—the median *K103N* resistance mutation frequency was 11 percent at six weeks, 6 percent at three months, 1 percent at 12 months, and 0.7 percent at 18 months. Persistence of resistance mutations in cellular HIV DNA was unusual, observed in only 4 percent of women one year after exposure.

Infants who become infected despite single-dose NVP prophylaxis are also at high risk for developing NVP-resistant viral variants. Researchers in Malawi showed that the risk of resistance was lower when the infants received a short course of ZDV in addition to NVP, and when the mother did not receive NVP. The rate of resistance with standard maternal/infant NVP was 87 percent at age six to eight weeks compared to 27 percent when infants received ZDV and no maternal NVP was given. Using sensitive resistance assays, investigators showed that resistant HIV variants persisted in some infants for one year or more after the administration of single-dose NVP.

Initial studies suggested that exposure to single-dose NVP for prevention of MTCT may compromise its use in the mother if she later requires treatment for her own health. A recent landmark study sponsored by PAMAB and published in the *New England Journal of Medicine* in 2007 (Lockman S et al., *NEJM, Jan 11; 356*, 235-247) examined the response to NVP-based combination antiretroviral treatment among Botswanan women in the Mashi Study (described earlier) who had previously been randomly assigned to a single intrapartum dose of NVP or to placebo. The time following exposure to single-dose NVP was critical in terms of virologic response to NVP-based therapy. When treatment was initiated less than six months after receipt of intrapartum NVP, results showed higher rates of virologic failure; however, if treatment was initiated more than six months after single-dose NVP, the results showed similar rates of virologic failure in women who had and did not have prior single-dose NVP exposure. A second PAMAB-sponsored study in South Africa has shown similar results; in this study, researchers observed no significant difference in virologic response to NVP-based therapy in women who had single-dose NVP exposure a median of 18 months before to starting therapy compared to women without such exposure.

The effect of single-dose NVP exposure on response to NVP-based treatment among infants who become infected despite single-dose NVP prophylaxis is under study. The IMPAACT Network, sponsored by the NICHD and NIAID, is conducting a clinical trial in African HIV-infected infants who had/did not have single-dose NVP exposure to evaluate response to subsequent treatment regimens that include NVP or a protease inhibitor. Additionally, PAMAB is sponsoring two investigator-initiated grants that will examine different approaches to treatment in NVP-exposed infected infants.

Safety of Elective Cesarean Section (ECS) for the Prevention of MTCT

In the late 1990s, PAMAB-sponsored research demonstrated that cesarean delivery before labor and before membranes ruptured, called elective cesarean section (ECS), was efficacious and effective in preventing MTCT of HIV. Subsequently, concerns were raised whether the risk of postpartum morbidity or HIV disease progression following ECS outweighed its benefit for preventing MTCT.

A recent analysis from WITS found no difference in postpartum disease progression among women who underwent cesarean delivery either before labor or after the onset of labor compared to those who delivered vaginally. Investigators from the NISDI Perinatal Study evaluated the relationship between mode of delivery and postpartum morbidity among HIV-infected women in mid-developed countries of Latin America and the Caribbean. The observed rate of postpartum morbidity was low (5 percent), and women with ECS did not have a statistically significant increase in the risk of postpartum morbidity compared with those who delivered vaginally. The lack of association between ECS and postpartum morbidity, along with the very low overall rate of postpartum morbidity observed in this study, support the conclusions of the U.S. Public Health Service Perinatal Guidelines Working Group and other groups: the benefits associated with ECS for prevention of MTCT of HIV outweigh the risks of postpartum morbidity.

PASSIVE AND ACTIVE IMMUNIZATION FOR THE PREVENTION OF MTCT

Research suggests that maternal neutralizing antibodies (NAbs) may play a role in HIV MTCT; specifically, higher levels of both autologous and heterologous NAbs are associated with non-transmission. Although use of NVP has dramatically limited transmission, concern regarding development of NVP-resistant viruses has raised interest in testing vaccines or immunotherapies during the early breastfeeding period, when postnatal transmission risk is highest. In previous PAMAB-supported research, investigators established a perinatal SHIV transmission model using *M. nemestrina*, in which there is evidence for extraordinary virus control in infected and exposed newborn macaques. This model allowed a detailed analysis of transmitted variants, passive transfer of maternal IgG and NAbs, and the development of autologous *de novo* responses in newborns. Subsequently, the investigators developed a SHIV/macaque model of transmission from infected dams to their infants. This model then provided the basis for passive immunization studies to dissect the protective effects of maternally acquired NAbs. Researchers transplacentally transferred varying levels of binding antibodies and NAbs to infants and detected passive antibodies in plasma on the day of birth that persisted for five weeks. Infants infected at or after birth controlled acute and post-acute viremia. Exposure to maternal SHIV during birth and suckling in the presence of autologous maternal NAbs may have affected transmission or pathogenesis in the infants. This important transmission model will allow investigation of key parameters involved in HIV MTCT.

Active immunization of newborns, coupled with antiretroviral prophylaxis or passive immunization, is a potential intervention to prevent MTCT of HIV through breastfeeding. Investigators have evaluated several recombinant canarypox-HIV vaccine vectors (ALVAC) and recombinant envelope subunit vaccines as candidate HIV vaccines for adults; candidates tested both safe and immunogenic. The first study of an ALVAC HIV-1 vaccine in HIV-exposed infants evaluated the vCP205 vaccine, which was well-tolerated; many infants developed long-lived HIV-specific proliferative and cytotoxic T lymphocyte responses. Infants had no significant serum (IgG) or mucosal (IgA) antibody responses to the vCP205 vaccine. In a subsequent study, infants born to HIV-infected women were immunized with the next generation ALVAC vaccine—vCP1452 paired with a subunit HIV-envelope vaccine, rgp120. Infants were randomized to receive vP1452 alone, vCP1452 with rgp120, or corresponding placebos. Vaccine administration was well tolerated, and researchers observed vaccine-induced immune responses, supporting further study of HIV vaccination as a strategy to reduce postnatal HIV

MTCT. Through an IMPAACT Network study of neonates in Uganda, researchers are now learning about responses to an ALVAC vaccine more specific to the clades of HIV found in Africa.

Breast-Milk HIV Transmission

RATES, RISK FACTORS, AND PATHOGENESIS OF BREAST-MILK HIV TRANSMISSION

As discussed earlier, PAMAB staff directed the largest individual patient-data meta-analysis of breast-milk HIV transmission to date; the analysis provided important information regarding the rate and timing of such transmission, including that late postnatal transmission through breastfeeding (from four weeks of age onwards) contributes substantially to overall HIV MTCT. The risk of late postnatal transmission is generally constant throughout breastfeeding, and late postnatal transmission is associated with a lower maternal CD4-cell count and male sex. The cumulative probability of late postnatal transmission at 18 months was 9.3 percent, or approximately 0.5 percent/month. These results are informing the development of appropriate interventions to prevent breast-milk transmission in areas of the world where complete avoidance of breastfeeding is generally not feasible. The researchers used the same database to assess mortality among 4,237 HIV-infected women based on their children's feeding modality. Mothers' mortality during the 18-month period after delivery did not differ significantly according to children's feeding modality (ever breastfed versus never breastfed).

Several investigator-initiated grants have provided important data regarding the mechanisms of breast-milk transmission. Researchers showed that the risk of infant infection from breastfeeding is influenced by breast-milk virus load, which is highest early after delivery. Higher maternal plasma virus load, lower maternal CD4 T-cell count, and detection of HIV-1 DNA in maternal genital secretions were significantly associated with elevated breast-milk HIV-1 RNA. Among women who do not transmit virus, levels of HIV RNA in breast milk remain low over time; levels among those who do transmit the virus increased by eight- to 16-fold between day eight and day 90 post-delivery. Among women who received ZDV prophylaxis for MTCT prevention, levels of HIV RNA in breast milk increase from day eight to day 45 post-delivery; this increase was associated with discontinuation of maternal ZDV prophylaxis. These results suggest maternal antiretroviral prophylaxis may need to continue throughout the entire breastfeeding period to optimally reduce MTCT.

Increased levels of HIV-infected breast-milk cells are associated with increased risk of transmission via breastfeeding after adjusting for cell-free virus in plasma and breast milk, a finding that suggests the cellular virus may play a more important role in breast-milk HIV transmission than does cell-free virus. The probability of breast-milk HIV-1 transmission was quantified by PAMAB researchers to be 0.00064 per liter of milk ingested, a figure similar in magnitude to the probability of heterosexual transmission per unprotected sex act in adults, and 0.00028 per day of breastfeeding. Infectivity is significantly higher for mothers whose disease was more advanced, as measured by prenatal HIV-1 RNA plasma levels and CD4-cell counts. Breast-milk viral load is substantially higher after rapid weaning, which suggests an increased risk of HIV transmission if breastfeeding resumes after a period of cessation.

With regard to host defense, researchers have shown that CD8 lymphocytes present in breast milk have the capacity to recognize HIV-infected cells and may be selectively transported to reduce either viral replication or transmission via breast milk. Researchers identified a population of extra-lymphoid CD8 cells with an effector memory phenotype in breast milk that contributes to understanding the potential for local virologic control. HIV-specific cell-mediated immunity of breast milk may influence the likelihood of breast-milk HIV MTCT. Research has shown that the HLA class I allele B*18 may protect breastfed infants against both early and late HIV acquisition; a trend toward early HIV acquisition was observed for infants who had HLA A*29 and increased late breast-milk HIV acquisition was observed for infants who had both Cw*07 and Cw*08. These findings could have implications for the design and monitoring of HIV vaccines that target cellular immune responses against HIV.

In an observational, longitudinal cohort study done in Nairobi, researchers demonstrated a complex interplay among virus levels, breast-milk chemokines, and postnatal MTCT. The study showed that increased levels of the chemokines MIP-1beta and SDF-1 were associated with reduced risk of infant infection, while increased levels of the chemokine RANTES was associated with higher transmission risk. The chemokines MIP-1alpha, MIP-1beta, RANTES, and SDF-1 were all positively correlated with breast-milk HIVmRNA. Women with clinical mastitis had 50-percent higher MIP-1alpha and MIP-1beta levels, while women with subclinical mastitis had approximately 70-percent higher MIP-1alpha, MIP-1beta, and RANTES compared to women who did not have mastitis.

INTERVENTIONS TO PREVENT BREAST-MILK HIV TRANSMISSION

A number of PAMAB-sponsored studies are evaluating antiretroviral interventions provided to either the lactating mother or to the breastfeeding infant, for varying periods of time, followed by early weaning to reduce postnatal HIV transmission. One study is evaluating the safety and efficacy of six months of daily infant NVP administration compared to six months of daily placebo administration during breastfeeding; another is comparing 14 weeks of infant NVP, or NVP and ZDV, to standard single-dose NVP and one week of ZDV; and a third study is evaluating the efficacy of highly active antiretroviral therapy (HAART) given to the mother during lactation compared to a standard short-course regimen.

Substudies conducted as part of the Mashi Study have provided valuable information regarding maternal use of antiretroviral drugs during lactation. Researchers found that giving maternal HAART decreased cell-free HIV RNA in breast milk, but not the level of cell-associated HIV DNA; this finding is important because some studies suggest that cell-associated HIV DNA load in breast milk is a more important risk factor than RNA levels in breast milk for postnatal transmission during the early months of breastfeeding. Additionally, antiretroviral drug levels in the breast milk of women who received HAART varied by drug; levels of ZDV and 3TC were more than three times those observed in maternal serum, while NVP levels were only slightly more than half that of maternal serum. Among breastfeeding mothers who received HAART during lactation, the antiretroviral drug levels of their infants were much higher than anticipated; infant serum NVP levels were close to those observed following receipt of a single-dose NVP. While the drug levels in the infant blood could provide some prophylaxis against breast-milk HIV transmission, they also expose the infant to potential toxicity.

In a PAMAB-sponsored randomized study, the Zambia Exclusive Breastfeeding Study (ZEBS), investigators compared the efficacy of exclusive breastfeeding with abrupt weaning at age four months to continued breastfeeding for the duration of the mother's choice with standard gradual weaning for reducing breast-milk HIV transmission risk. The main outcomes were HIV MTCT and two-year mortality. Despite the finding that early weaning prevented breast-milk HIV transmission compared to continued breastfeeding, overall HIV-free survival at age two years did not differ between groups, as a result of increased risk of infant death due to gastrointestinal and other infections among infants who underwent early weaning compared to those who continued to be breastfed. In children who became HIV infected, early weaning was particularly deleterious. Findings from this study resulted in modification of WHO recommendations regarding breastfeeding by HIV-infected mothers.

The Mashi study in Botswana had results similar to ZEBS. The Mashi study had a factorial design; one aspect of the study compared rates of MTCT among infants randomized to: breastfeed while receiving six months of ZDV prophylaxis, followed by early weaning; or to formula feed from birth. HIV-free survival at 18 months did not differ between the study arms. Even though formula feeding reduced postnatal HIV transmission, diarrheal and respiratory infections in the formula-fed group led to a higher rate of infant mortality.

Thus, ZEBS, the Mashi Study, and several other studies indicate that early weaning to prevent breast-milk HIV transmission may not be an appropriate strategy in low-resource settings because of increased infant mortality in uninfected infants due to non-HIV-related infections and growth failure in areas where safe formula feeding is not available. The MTCT postnatal prevention strategies that rely on using antiretroviral drugs for the infant or mother for four to six months followed by early weaning may not be optimal strategies for some low-resource settings. Therefore, efforts to make continued breastfeeding safer are critically needed.

Additionally, researchers in the Mashi study found that adherence to formula feeding was problematic in the study; more than 20 percent of women in the formula-feeding arm were determined to breastfeed their infants, suggesting that infant-feeding strategies different from the local norm may have low adherence and reduced effectiveness. Additionally, a number of studies have demonstrated that infants who receive breast milk and other liquids or foods during the first six months after birth have significantly higher risk of postnatal infection than infants who are exclusively breastfed. Further analyses of the rich database from Mashi study and ZEBS are underway and will likely make a major contribution to preventing MTCT in resource-limited settings.

RESEARCH ADVANCES IN PEDIATRIC HIV INFECTION

Results of research conducted with PAMAB funding or co-funding continue to advance scientific understanding of HIV pathogenesis, disease course, comorbidities, and the short- and long-term effects of treatments, domestically and internationally. Recent work placed a major emphasis on advances in the development and evaluation of new therapies.

Pathogenesis of HIV Infection in Children and Predictors of Disease Progression

PAMAB-supported investigators have advanced the understanding of viral pathogenesis by developing a comprehensive classification schema for viral envelope-glycoprotein phenotypes that identify both target-cell tropism and chemokine co-receptor usage. These parameters are important factors in viral transmission, in developing drugs that inhibit viral entry, and in the rational development of HIV preventative vaccines.

Since 2003, PAMAB-funded researchers have studied maternal factors that may predict the disease course of infants born to HIV-infected mothers. Data from Lusaka, Zambia, showed that advanced maternal HIV disease profoundly impacts exposed infants, regardless of infant infection status; uninfected infants born to mothers with advanced disease were at high risk of morbidity and mortality within the first six months after birth. Among infants who were HIV-infected, maternal anemia, delivery complications, formula feeding, early growth failure, and low infant CD4-cell count were predictors of early mortality; this knowledge may be useful for early identification and treatment of high-risk infants. Researchers also learned that higher maternal HIV RNA at or close to delivery strongly predicts early disease progression for infected infants and correlates with the early peak of viremia in the infected child. High maternal HIV RNA, high infant HIV RNA, and infant CD4-cell levels were independent predictors of disease progression during the first six months after birth in this study. Investigators also showed that high maternal HIV-1 viral load during the last trimester may impair maternal-fetal immunoglobulin transfer, which increases the risk of measles and other serious infections among HIV-exposed infants because they lack protective maternal antibodies.

PAMAB researchers, in collaboration with PENTA, conducted a meta-analysis of individual longitudinal data for 3,941 children from eight cohort studies and nine randomized trials in Europe and the United States as part of the HIV Paediatric Prognostic Markers Collaborative Study (HPPMCS). In initial analyses, the investigators evaluated the predictive value of CD4-cell count/percentage and HIV viral load for short-term risk of progression to AIDS and of mortality. The CD4 or viral-load thresholds associated with a given risk of AIDS or death varied significantly by age. Additionally, while both CD4-cell count/percentage and viral load were independent predictors of progression and death in children older than one year of age, the predictive value for young infants was poor, and the risk of progression or death was higher among younger children for any given CD4-cell level or viral load. Researchers used these data as the basis for age-related treatment recommendations in United States, Europe, and, most recently, for the WHO pediatric treatment recommendations.

Identifying new clinical and laboratory markers to predict disease progression in pediatric HIV infection and to evaluate response to antiretroviral treatment remain important areas of research. In addition to its work in determining the normal distribution of lymphocyte subsets in healthy infants, children, and adolescents in the United States, the PAMAB supported investigation of less expensive, less complex alternatives to CD4-lymphocyte count and HIV viral measurement for HIV prognosis and response to treatment in resource-limited settings. Data from a study of HIV-infected children in the United States who were predominantly African American, reflecting the epidemiology of the HIV epidemic in the United States, showed that low total lymphocyte count and serum albumin independently predicted the risk of death. Subsequently, further analyses from the HPPMCS meta-analysis showed that total lymphocyte count was a

strong predictor of 12-month disease progression for children older than two years of age, but was less so in younger children, suggesting that total lymphocyte count can serve as an alternative to CD4-cell percentage as an indicator of when to start antiretroviral therapy in children older than age two in resource-limited settings.

PAMAB-supported researchers have also studied somatic growth in children as a predictive marker of HIV disease progression; they determined that height-growth velocity predicts survival independent of age, viral load, and CD4-cell count in symptomatic HIV-infected children who are taking nucleoside reverse transcriptase inhibitor therapy. Increases in height-for-age z-score, but not weight-for-age z-score, were associated with subsequent immune reconstitution and reduced risk of subsequent clinical progression, suggesting that researchers include its use as part of composite endpoints for phase II and III clinical trials. In other studies, researchers demonstrated that potent combination antiretroviral therapy can restore weight growth to normal and can improve height growth.

Evaluating Methods for Diagnosing of Infant HIV Infection

Given the high risk of disease progression in infected infants, improving options for early diagnosis is essential, particularly in resource-limited settings. PAMAB investigators demonstrated that a plasma HIV-RNA assay matched or exceeded the diagnostic performance of quantitative peripheral blood mononuclear cell microculture or HIV-DNA assay. RNA assays are less expensive, have reduced sample requirements, and have more rapid turnaround than other assays. In addition, researchers demonstrated that dried blood and dried plasma spots for HIV-RNA assays are an easy and inexpensive means for collecting and storing specimens for both diagnosis and monitoring of disease in resource-limited countries, under field conditions.

Understanding the Natural History and Complications of Pediatric HIV Disease

HIV infection has a profound impact on the growth and maturation of perinatally infected children. Researchers have identified multiple endocrine abnormalities in HIV-infected children compared to their uninfected counterparts, including significantly reduced insulin growth factor binding protein 3 (IGFBP-3) concentration and delayed onset of puberty. Onset of puberty was associated with the degree of immune suppression; girls and boys with severe immune suppression were half as likely as children with intact immune responses to enter adrenarche.

The impact of HIV infection on the brain continues to be one of the disease's most devastating consequences. In Tanzania, HIV-infected infants performed worse on tests of neurodevelopment and were significantly more likely than uninfected children to be identified as developmentally delayed during the first 18 months after birth. The risk of developmental delay was highest among children whose infection occurred *in utero*. Researchers also found that, even in the context of antiretroviral therapy, HIV-infected school-aged children in the United States were at nearly four times the risk for psychiatric hospitalization during childhood and early adolescence as was the general pediatric population.

Researchers have shown that maximum and "set point" viral loads are significantly higher in infants than in adults, a finding that perhaps explains why children do not always reach undetectable viral loads as rapidly as adults do. The HIV-RNA viral load set-point was significantly higher among infants whose infection was acquired *in utero*, intrapartum, or

through early breast-milk transmission before age two months than for infants who were infected through late breast-milk transmission (after age two months) or for adults who were infected through heterosexual transmission. Researchers also demonstrated gender differences in HIV-RNA levels in children that were similar to those described in adults: girls had lower plasma viral load than boys, but had paradoxically higher mortality compared to boys.

PAMAB-funded research has achieved much progress toward eliminating the devastating sequelae of opportunistic infections associated with HIV-induced immunosuppression:

- Researchers demonstrated that antibiotic prophylaxis for *Pneumocystis jiroveci* pneumonia can be safely withdrawn without great risk of disease occurrence in children who are on stable antiretroviral therapy and who have CD4-cell recovery.
- Researchers found that, while opportunistic infections and other related infections are less common among children in the HAART era, opportunistic infections still occur in children who have persistently severe immunosuppression. Lack of sustained immune response to treatment, rather than age at or duration of treatment predicted the risk of developing an opportunistic infection.
- A study of perinatally infected children in the United States found the prevalence of HCV co-infection was 1.5 percent, a figure eight- to 10-times higher than for the general pediatric population.
- Researchers observed a greatly increased incidence of cancer in HIV-infected children, 1.56/1,000 child-years, which was markedly higher than that of HIV-uninfected children, but lower than European cohorts with perinatal HIV infection. The cancers were predominantly lymphomas, contrasting with types of cancer seen in HIV-uninfected children, who primarily have leukemia; of the less common soft tissue tumors, all were leiomyosarcomas. Cancer incidence was highest in children who were severely immunosuppressed, and in children who had received less than two years of treatment.

Researchers have also conducted clinical trials to determine the safety, immunogenicity, and effectiveness of routine pediatric immunizations for HIV-infected children. Vaccines that have been evaluated in infected children include pneumococcal conjugate and polysaccharide vaccine, live attenuated varicella vaccine, and hepatitis A virus (HAV) vaccine. Each vaccine was found to be safe and immunogenic in children who received treatment. However, the HAV vaccine generated low antibody titers of limited durability; therefore, an additional dose of the vaccine may be warranted for HIV-infected children.

Antiretroviral Agents and Regimens for the Treatment of Pediatric HIV Infection

Effective treatment of pediatric HIV disease remains challenging due, in part, to a lack of appropriate formulations for children and insufficient pharmacokinetic data to guide drug dosing. Investigators funded by the PAMAB through investigator-initiated grants and the NICHD Network, working in collaboration with IMPAACT Network investigators, are conducting pharmacokinetic and therapeutic drug trials to achieve accelerated domestic and international approval of antiretroviral drugs for pediatric indications. Since 2003, PAMAB-funded investigators have conducted trials to evaluate a variety of new drugs, new combinations of existing drugs, and different types of therapeutic strategies in infants and children:

- Data generated by PAMAB-supported researchers has contributed to the labeling and licensure of new antiretroviral drugs in children:
  - Researchers studied the pharmacokinetics and long-term safety of T-20 (enfuvirtide), an HIV fusion inhibitor and the first of a new class of drugs targeted at inhibiting entry of HIV into cells. The drug was found to be safe, well tolerated, and efficacious in treatment-experienced children, and the study contributed to the labeling and licensure of this drug for use in pediatric patients.
  - A trial of the protease inhibitor atazanavir, in a pediatric powder formulation and an adult capsule formulation, is nearing completion. Findings from the research will provide critical data to help guide dosing for infants, children, and adolescents. Preliminary data showed that adequate atazanavir drug levels in young children are only attainable with the addition of low doses of ritonavir, a potent inhibitor of the hepatic enzyme that metabolizes atazanavir. In this case, ritonavir acts as a "pharmacologic booster," increasing drug exposure by prolonging atazanavir half-life.
- Establishing doses of protease inhibitors in very young children is difficult due to lack of appropriate formulations, developmental differences in drug metabolism, and high levels of intra- and inter-patient variability of the drugs themselves.
  - Studies showed sub-optimal exposure of the protease inhibitor nelfinavir in very young infants (younger than six weeks of age), making its use for this age group problematic.
  - More recently, a study of the protease inhibitor lopinavir/ritonavir demonstrated significantly lower exposures in very young children.
- Researchers have conducted trials evaluating the efficacy and pharmacology of several antiretroviral treatment regimens, providing valuable insights into the use of combination therapies.
  - In a seminal study of early treatment of infants published in the *New England Journal of Medicine* in 2004 (Luzuriaga K et al., *NEJM, June 10;350,* 2471-2480), researchers demonstrated that initiating treatment as early as two weeks of age, using three- or four-drug combination therapy, resulted in sustained long-term viral suppression. These findings influenced recommendations for early initiation of therapy in young HIV-infected infants.
  - An open-label pharmacokinetic, safety, and therapeutic strategy trial of didanosine, emtricitabine, and efavirenz examined whether a once-daily treatment regimen improved adherence and was efficacious in pediatric subjects who had limited treatment experience. The data suggest that the regimen is safe, effective, and durable. However, efavirenz concentrations in children who received the oral solution were lower than anticipated and required dose escalation.

Although research has made remarkable advances in the treatment of children with HIV infection during the last several years, the process continues to identify new adverse effects associated with short- and long-term use of antiretroviral therapy. For example, researchers found a 13-percent prevalence of hypercholesterolemia in children with perinatal HIV infection; current use of a protease inhibitor-containing antiretroviral regimen was noted as the strongest risk factor for hypercholesterolemia. Researchers are now planning an interventional study to address this issue.

RESEARCH ADVANCES IN ADOLESCENTS AND HIV INFECTION

PAMAB-supported research has contributed significantly to filling the gaps in knowledge about the natural history of HIV disease in adolescents and young adults, including but not limited to defining response to therapy, characterizing immunologic and virologic parameters, and identifying important co-morbidities in this population. Work in the behavioral arena has also achieved scientific advances, including: providing insights into psychosocial factors that may affect risk behaviors of at-risk youth subpopulations; and, in terms of a community scientific agenda, progress in building extensive infrastructure to promote community capacity to mobilize partners and in creating structural changes that will ultimately lead to decreased HIV-acquisition risk and will enable researchers to conduct HIV vaccine and microbicide trials in this population.

Early Detection of HIV Infection in Youth and Primary Drug Resistance

Two ATN studies assessed the prevalence of recent HIV infection among youth who presented for care and evaluated the prevalence of drug resistance in these youth. ATN 022 enrolled 358 adolescents, between the ages of 12 and 24 years, who recently entered into care for their HIV infection at ATN sites, and who were antiretroviral naïve. Using a serologic "detuned" assay to identify those youth whose infection was acquired within 180 days prior to the testing, researchers identified 25 percent of youth as recently infected. These data suggest the need to develop further interventions that provide HIV testing to at-risk youth, and to optimize management strategies, both behavioral and biomedical, that will capitalize on the immunologic resilience of this cohort.

ATN 029 evaluated the prevalence of genotypic and phenotypic drug resistance in these recently infected youth; 18 percent had major mutations that conferred drug resistance on genotypic resistance testing, while 22 percent had phenotypic drug resistance. Triple drug-class resistance was uncommon (2 percent of youth). The presence of drug resistance in 18 percent to 22 percent of newly infected youth is a cause for concern and suggests that drug-resistant virus was transmitted to these youth. The finding of major primary resistance mutations in almost one-fifth of this group of recently infected youth has significant implications for the implementation of routine viral genotyping upon initial clinical presentation of these patients.

HLA-Related Differences in HIV Disease Progression in Adolescents

Previous studies by PAMAB-funded researchers identified differences in HIV disease progression between youth with different HLA class I alleles. For example, ATN 026 evaluated HIV-specific CD8+ cell responses and escape mutations as explanations for observed HLA class I allele-associated differences in HIV disease progression. Subjects who were identified as HLA Class I HLA-B*27, B*35, B*53, and/or B*57+ were enrolled into this protocol. Researchers determined that the epitope-specific responses that exhibited the most efficient cross-recognition of amino acid-substituted variants were those strongly associated with delayed progression of disease. Also, not all epitopes restricted by the same HLA class I allele showed similar variant cross-recognition efficiency, a finding consistent with the hypothesis that the reported associations between certain HLA class I alleles and the rate of disease progression may stem from the quality of the responses to particular epitopes. This effort also showed that flexibility in cross-recognition is not conferred by the overall clonal breadth of the response, but results from the properties of the dominant T-cell receptors used for epitope recognition. These findings

support the rationale of pursuing improved understanding of T-cell responses associated with long-term control of viral replication to exploit these responses in the design of novel HIV-vaccine candidates.

Investigators also evaluated the relative contributions of HLA alleles and T-cell receptors to the prevention of mutational viral escape by examining HIV-specific CD8 T-cell responses restricted by two closely related HLA class I alleles, B*5701 and B*5703. These alleles differ by only two amino acids, but are both associated with a dominant response to the same HIV epitope, KF11. They found that, when this epitope is presented by HLA-B*5701, it induced a T-cell receptor repertoire that is highly conserved among individuals, is cross-recognized viral epitope variants, and is rarely associated with mutational escape. In contrast, the KF11 epitope presented by HLA-B*5703 induced an entirely different, more heterogeneous T-cell receptor repertoire that failed to recognize specific KF11-escape variants, which frequently arise in clade-C infected HLA-B*5703+ individuals. These data demonstrated the influence of HLA-allele subtypes on T-cell receptor selection and indicated that extensive T-cell receptor diversity is not a prerequisite for preventing allowable viral mutations.

Co-Morbidities in HIV-Infected Adolescents and Young Adults

ATN 049 investigators measured and correlated plasma 25-OH vitamin D levels in samples from the REACH cohort, for whom other micronutrient, vitamin, antioxidant, and biochemical and dietary intake data were available; they then correlated these levels with measures of HIV-disease states and immune activation. Investigators found an 87-percent prevalence of vitamin-D deficiency among this cohort of both HIV-infected and uninfected youth that did not depend on HIV status. Further, they concluded that the high prevalence of this insufficiency was likely due to the high proportion of African American youth (72 percent) in this study who likely reside in urban areas and, consequently, may have limited sun exposure. The findings in this representative ATN cohort have implications for further investigations of HIV-related co-morbid conditions, such as osteopenia.

In an investigation of the relationships among dietary quality, weight, and HIV infection in youth, more than half (52 percent) were overweight or obese. Obesity was positively correlated with being female, living independently, watching more than three hours of television per day, previous dieting, and being from the northeastern or southern United States. However, the rates of obesity among HIV-infected youth were similar to those of uninfected youth; therefore the rates are more reflective of the general obesity epidemic in the United States that is more significant among minority populations (as is HIV infection). Given the metabolic consequences associated with HIV infection and its management, these findings have important implications for nutritional interventions for HIV-infected youth.

Community Prevention and Vaccine Preparedness—Community Partners

To improve acceptability of the research infrastructure through which domestic adolescents and young adults will be offered HIV-vaccine trial participation, the ATN Connect-To-Protect (C2P) Project (described earlier in this report) has undertaken tremendous efforts to build community trust and engagement, establish a primary prevention research infrastructure, and test a model of community mobilization using structural change to produce measurable improved health

outcomes in community youth. (See the *Community Prevention Research Agenda for the ATN* section of this report for a description of C2P.)

RESEARCH ADVANCES IN WOMEN AND HIV INFECTION

Natural History/Disease Progression

Research funded by the PAMAB has contributed greatly to understanding the natural history of HIV disease in women, including response to therapy, differences in disease parameters between men and women, and causes of death among HIV-infected women. For instance, WIHS researchers demonstrated that, in the pre-HAART era, survival time and time to AIDS development were similar during three years of follow-up among women whose CD4-lymphocyte counts were between 200 cells/uL and 349 cells/uL, and greater than 350 cells/uL. Subsequent data showed that the rate of AIDS development and death was similar between these two groups up to four years after initiation of HAART, a result that has helped inform the debate about when to initiate therapy. Analysis of causes of death among women enrolled in WIHS indicated that 20 percent of deaths among HIV-infected women were not directly related to HIV, but rather resulted from non HIV-related events, such as liver failure, drug overdose, malignancies not associated with HIV, cardiac events, and trauma. These findings suggest important additional areas for intervention.

WIHS also demonstrated that HIV RNA levels in women compared to men, and in non-whites compared to Caucasians, were lower at a given CD4-cell count until that count dropped to less than 200 cells/uL. In women and men whose CD4-cell count was less than 200 cells/uL, HIV RNA levels were high, but were similar between groups. Researchers evaluated additional markers of disease progression that are more easily determined, such as total lymphocyte count, hemoglobin, serum albumin, C-reactive protein, and anergy; these markers proved to be independent predictors of disease progression and may be useful as inexpensive and less complex tests for determining when to start therapy in resource-limited settings.

Investigators in both WITS and WIHS have also evaluated the effects of substance abuse on disease progression. Women in the WITS cohort who used “hard” drugs (e.g., cocaine, heroin, or any injected drug) showed no differences from non-drug using women in terms of their CD4-cell or HIV RNA trajectories or risk of death; however drug users were more likely to develop AIDS-defining illnesses, including recurrent herpes, pulmonary tuberculosis (TB), and recurrent pneumonia. Recently, researchers evaluating the WIHS cohort found an increased risk of disease progression and death among smokers and among persistent non-injection drug users.

Impact of Pregnancy and Therapy for Preventing MTCT on HIV Disease Progression

Because the majority of HIV-infected women in the United States and worldwide are of reproductive age, it is important to evaluate whether pregnancy might affect HIV disease progression or response to antiretroviral therapy. The changes in CD4-lymphocyte count, HIV RNA levels, and time to AIDS-defining illness were similar among women in the WITS who had either one pregnancy or two pregnancies while in the study, suggesting that repeated pregnancies did not accelerate disease progression. An evaluation of antiretroviral therapy use by women who became pregnant during WIHS demonstrated that, over time, the patterns of therapy use for

pregnant women become similar to those for non-pregnant women, with similar proportions of both groups receiving HAART. Researchers are analyzing data from women who continued HAART after pregnancy to determine whether the rebound in HIV RNA levels that was reported after delivery among women who were not treated or who received ZDV monotherapy also occurs in women who received HAART and, if so, what factors are associated with this rebound. In a study from Tanzania, multivitamin supplementation during pregnancy reduced the risk of WHO Stage-4 disease (AIDS) or death, with a median follow-up of 71 months after enrollment during pregnancy.

Recent reports of increased HIV disease progression and adverse events among subjects enrolled in trials with scheduled treatment interruption arms compared to continuous therapy have raised questions about whether short-term antiretroviral therapy for MTCT prevention during pregnancy may have a negative impact on the woman's long-term health. An analysis of the WITS cohort compared changes in CD4-lymphocyte counts, HIV RNA levels, and clinical progression between women whose CD4-lymphocyte counts were greater than 350 cells/uL and who either stopped treatment or continued therapy postpartum. None of the women in either group progressed to AIDS, and changes in CD4-cell counts and HIV RNA were similar between groups during one year postpartum, suggesting that stopping therapy after delivery is safe if the woman has no other indications for therapy.

Use and Response to Highly Active Antiretroviral Therapy (HAART)

WIHS has provided population-based data that documents a decreased rate of new AIDS diagnoses and deaths as the rate of HAART use increased among a predominantly minority and disadvantaged group of women. An analysis of WITS data also documented decreasing rate of AIDS-defining illnesses with the availability of HAART and a 70-percent reduction in progression to death among women who had an AIDS-defining illness. In addition, WIHS researchers documented the large number of treatment regimens used (more than 200 unique regimens among 1,056 women on HAART) and found a high frequency of switching or discontinuing therapy, with a median time of only eight months from initiation of HAART until regimen change. Among women who did not respond to their initial HAART regimen (i.e., their HIV RNA levels did not decrease to less than 80 copies/mL within one year), those with new protease inhibitor or non-nucleoside genotypic resistance mutations showed better CD4-lymphocyte response than those who had no genotypic resistance, suggesting decreased fitness of the resistant virus.

An evaluation of cancers among women in the WIHS demonstrated a significant reduction in AIDS-associated non-Hodgkin's lymphoma during the HAART era compared to the pre-HAART period. There were fewer cases of Kaposi's sarcoma, but the decrease was not significant, although the number of cases in both eras was low. Lung cancer cases increased similarly in both HIV-infected and HIV-uninfected women in the WIHS compared to age- and race-matched populations, a situation related to the high rate of smoking among women in the WIHS cohort. Other non-AIDS cancers did not seem to be increased among these women.

Hormonal Influences and HIV

WIHS investigators have independently and in collaboration with other studies, such as the CDC-funded HIV Epidemiologic Research Study, evaluated the effects of HIV on the menstrual cycle, the impact of hormonal changes during the cycle on systemic and genital HIV and cytokines, and the interaction of the genital milieu and HIV detection. They found that HIV-infected women had somewhat increased rates of amenorrhea and oligomenorrhea, and that the rate of abnormalities increased with decreased CD4-lymphocyte counts. Of note, more than half of the cases of amenorrhea were not related to menopause or ovarian failure, but were associated with low gonadotropin levels. Further study of ovarian reserve and causes of menstrual abnormalities are now in progress.

Researchers also developed and validated methods for detecting HIV-1 infection in the female genital tract. Even though plasma HIV levels were the key predictors of HIV detection in the genital tract, HIV was detected in the genital tracts of some women who had undetectable plasma HIV RNA. Among women who had plasma HIV RNA levels of less than 500 copies/mL, factors associated with detection of genital tract HIV RNA included use of non-nucleoside reverse transcriptase inhibitor-based regimens (compared to protease inhibitor-based regimens), having multiple sexual partners, and ongoing illicit drug use. In another study, genital HIV RNA levels were lower among women in whom active genital antibody-dependent cytotoxicity was present. Several studies have suggested increased detection and levels of HIV in the genital tracts of women who have bacterial vaginosis, and findings suggest that this increase is specifically associated with decreased levels of lactobacilli and increased levels of *Mycoplasma hominis*.

The potential effects of the pharmacologic levels of estrogen and progesterone in hormonal contraceptives on both HIV progression and the metabolism of antiretroviral agents is an important issue for the care of HIV-infected women. Researchers found no differences in plasma HIV RNA levels between women using or not using hormonal contraceptives. Likewise, the response to HAART did not differ between women on hormonal contraceptives and those not using hormonal agents. In studies evaluating interactions between hormonal contraceptives and antiretroviral drugs, intracellular and plasma ZDV levels were not affected by concomitant use of combined oral contraceptives or depot medroxyprogesterone acetate (DMPA); plasma and genital HIV RNA levels did not change after initiation of hormonal contraception. Similarly, initiation of DMPA did not cause clinically significant changes in levels of nelfinavir, efavirenz, or NVP, and DMPA levels remained in the therapeutic range throughout the 12-week study period. Investigators observed no changes in CD4-lymphocyte counts or HIV RNA levels with DMPA use, nor did they note increased toxicities among HIV-infected women. A current study is evaluating potential interactions between the contraceptive patch and lopinavir.

Human Papillomavirus (HPV) Infection and Genital Neoplasia

WIHS results have played a key role in understanding the interaction between HIV and HPV infection. It is known that HPV is the primary risk factor for development of genital and anal neoplasia in individuals without HIV infection. Important findings to date include: the increased prevalence and incidence of genital, oral, and anal HPV infection, warts, and cervical cytologic abnormalities among HIV-infected women who have decreased CD4-lymphocyte counts and increased HIV RNA levels; the relatively uncommon occurrence of high-grade

cervical dysplasia among HIV-infected women; and the potential for HAART to induce regression of HPV-related cervical abnormalities. Of note, HPV16, the virus type associated with more than 50 percent of cervical cancers in all women, was less associated with CD4-lymphocyte count and HIV RNA levels, suggesting relative resistance to immune surveillance, a finding consistent with its frequent detection in dysplasia and cancer in HIV-uninfected women. New detection of HPV among 22 percent of HIV-infected women whose CD4-lymphocyte counts were less than 200 cells/uL and who denied any sexual activity for over two years suggests the potential for reactivation of latent HPV with declining immunity. Low-grade cervical dysplasia, although less likely to regress among HIV-infected women than among HIV-uninfected women, progressed infrequently, suggesting that observation rather than ablative therapy is safe for use in HIV-infected women.

A combined analysis of data from WIHS and WITS demonstrated that the incidence of new HPV infections during pregnancy was lower than during the postpartum period, but was similar to the pre-pregnancy rate. The overall prevalence of HPV did not differ between pregnancy and the period before and after pregnancy. The large sample size and continuing follow-up from these studies enables researchers to assess responses to specific types of HPV among HIV-infected and HIV-uninfected women and will allow evaluation of the effects of the HPV vaccine on acquisition and persistence of infection in HIV-infected women. In addition, this work has delineated other factors that affect the natural history of HPV, such as smoking and bacterial vaginosis.

Hepatitis C Virus (HCV) Co-Infection

Rates of HCV co-infection (HCV is a chronic viral infection of the liver) are high among women in both WIHS and WITS. In the WIHS cohort, researchers noted an increasing proportion of deaths related to liver disease. In the WITS cohort, investigators observed no difference in HIV disease progression between those with and without HCV. Further evaluation of WIHS data showed that HCV had no effect on response to HAART, and that women with HCV had higher levels of memory CD4 and CD8 T-lymphocytes compared to those without HCV infection. In WIHS, 42 percent of HIV/HCV co-infected women had HCV replication in the peripheral blood mononuclear cells compared to none of the HIV-uninfected/HCV-infected women. Extrahepatic replication of HCV was associated with higher plasma HIV RNA levels and high alcohol consumption. Investigators detected HCV in 28 percent of genital specimens from HIV/HCV co-infected women compared to none of the HIV-uninfected/HCV-infected women. Genital detection of HCV was associated with the level of HCV viremia and detection of genital HIV, but not with CD4-lymphocyte counts or plasma HIV RNA levels. Among HIV-infected women, HCV co-infection was associated with decreased cytokine production and decreased performance on neuropsychological tests.

Other Co-Infections

Analyses determined that HIV-infected women in WIHS were more likely to have genital ulcerations, warts, and candidiasis compared to HIV-uninfected women, who were more likely to have bacterial vaginosis and *Trichomonas* infections. The incidence of tuberculosis was similar between HIV-infected and HIV-uninfected women; although the incidence has decreased over time, the adjusted hazard of death was 3.7 among HIV-infected women with tuberculosis compared to those without tuberculosis, and this hazard did not decrease with the availability of

HAART. Herpes zoster rates increased as HIV RNA levels increased. Detection of Kaposi sarcoma-associated herpes virus (HHV8) in saliva increased with higher CD4-lymphocyte counts, which suggests a higher transmission risk for HHV8 early in HIV infection.

Psychosocial/Behavioral Issues

Several analyses have explored psychosocial issues among women enrolled in WIHS and the impact of these issues on medication adherence and study retention. Two-thirds of women enrolled in WIHS had a history of domestic violence and more than one-quarter had a history of childhood sexual abuse; proportions were of both were similar among HIV-infected and HIV-uninfected women. Both domestic violence and childhood sexual abuse were associated with an increased risk of illicit drug use, increased risk of sexually transmitted infections other than HIV, and decreased HAART utilization.

Assessment for depression revealed similarly high rates in both HIV-infected and uninfected women; less education, lower income, drug or alcohol use, domestic abuse, and fewer social supports were associated with depression in both groups. Treatment of depression with counseling with or without antidepressant medication increased HAART use and adherence, while treatment with antidepressants alone did not improve HAART use. Among HIV-infected women, self-reported adherence to antiretroviral therapy was associated with increased age, lack of cocaine or heroin use, health perception score, and having undetectable HIV RNA levels. Assessment of sexual behavior revealed that HIV-infected women were more likely than HIV-uninfected women to use condoms (63 percent versus 28 percent), but risky sexual behavior remained common in both groups and increased for some women after HAART initiation.

Metabolic Effects of HIV and HAART

A number of studies have evaluated the effects of HIV and HAART on metabolic parameters and body composition. Over time, researchers observed decreased trunk and extremity measurements among HIV-infected women, and the effect was most pronounced among women on stavudine regimens; trunk and extremity measurements increased over time in HIV-uninfected women. Dual Energy X-Ray Absorptiometry/Densitometry (DEXA) scanning done in a subset of women confirmed loss of body fat in HIV-infected women. Diabetes, pre-diabetes, and insulin resistance were not associated with the HIV serostatus of women in the WIHS; impaired glucose metabolism was associated only with increased body mass index in both HIV-infected and HIV-uninfected women.

FUTURE DIRECTIONS FOR THE PAMAB

As funding for biomedical research becomes more limited, it is ever more important to ensure that limited resources are used in the most efficient and effective manner possible to answer the highest priority scientific questions. In accordance with the NICHD leadership model of a transparent planning process that includes external scientific and public input, the PAMAB solicited recommendations from a panel of multidisciplinary experts. This panel, 11 individuals with domestic and international research expertise in pediatric, adolescent, and adult HIV research, included members from the NACHHD Council and advocate representatives from the American Academy of Pediatrics and the Elizabeth Glaser Pediatric AIDS Foundation (see Appendix H for list of panel members). The panel was charged with strategically assessing the Branch's portfolio of research and suggesting future research directions and priorities. As a springboard for discussion, the PAMAB expert panel was asked to address three overarching questions, including:

- Given the mission of the PAMAB and its collaborations with other Institutes, what are the most important scientific opportunities, domestic and international, that the Branch should try to pursue in the next four years?
- Given the mission of the PAMAB, what are the most important public health issues, domestic and international, that need to be addressed by the Branch in the next four years?
- What areas of the current PAMAB portfolio deserve less emphasis because progress has been made or will continue to be made without further stimulation from the NICHD in general or the PAMAB in particular?

The expert panel received extensive information about research projects supported by the Branch as well as related fiscal information to assist in the review (see Figure 1, Figure 4, Figure 5, and Figure 10 for more information). The expert panel had a conference call in March 2006, and then a full-day in-person meeting on September 15, 2006, to discuss the Branch's performance and make recommendations concerning scientific opportunities and public health issues PAMAB might pursue in the next four years. Branch staff carefully considered discussions from the September meeting in developing the goals outlined in the following pages. The first section provides a summary of the expert panel discussion and recommendations; the second section lists the Branch's proposed activities for the next four years.

PANEL DISCUSSION

Expert panel members noted the exceptionally productive efforts of the PAMAB in working with multiple organizations within and outside of the government to address the pediatric and maternal HIV research agenda. They similarly noted the successful track record of the PAMAB in leveraging relatively limited amounts of money through these multiple collaborations to ensure that the most important research in children, adolescents, and women is funded. Panel members commented that the PAMAB serves as a model for other NIH Institutes for fostering collaborative research.

The panel members noted that the scientific and public health priorities in the field of HIV research in women and children overlap extensively. The panel also stated that the research supported by the PAMAB is appropriately focused on the major critical scientific and public health research issues in the area of pediatric, adolescent, and maternal HIV infection, and that, consequently, it saw no areas for which effort should be significantly reduced. However, panel members noted that PAMAB funding should continue to target research specifically in the domain of the Branch mission (i.e., infants, children, adolescents, and women) and not to address more generic issues related to HIV infection, such as basic science questions not closely related to these populations. The panel noted the importance of monitoring the productivity of the various research projects that the Branch funds, and of adjusting funding appropriately.

In terms of domestic research, the panel felt that research on HIV infection in adolescents (both in perinatally infected children aging into adolescence, as well as incident cases in horizontally infected adolescents) and efforts related to preventing HIV infection in uninfected adolescents should remain important focuses of PAMAB activities. The panel also emphasized long-term follow-up of HIV-exposed uninfected children for potential early and late effects of *in utero* antiretroviral exposure to HIV and to antiretroviral drugs as another critical focus. Panel members viewed long-term follow-up as an important way to better define and evaluate the potential long-term effects of prolonged therapy among HIV-infected children who now survive on treatment into adolescence and beyond. Maintenance of domestic capacity for the conduct of pharmacokinetics research and ensuring the safety of both new and existing drugs for treating HIV infection and its complications in infants, children, adolescents, and pregnant women was also identified as a critical need. The panel suggested that the PAMAB consider increasing its efforts in behavioral research, particularly those targeting adolescent behavior and adherence to treatment. Incorporating new technologies and genomics into ongoing and new research projects was also encouraged. The panel noted the productivity of using PAMAB's repository-stored samples from cohort studies to answer basic science and pathogenesis questions and indicated the importance of continuing this emphasis. Additionally, panel members stressed the importance of collaborations between cohort studies. For example, researchers from adult cohort studies should try to enlist infected children who are currently enrolled in pediatric studies into their cohorts, to ensure follow-up of these patients as they age into adulthood. Further, researchers in different countries could collaborate on analyzing data of mutual interest, as was the case, for example, in the successful collaboration of researchers involved in the HPPMCS. These investigators combined data from United States and European cohorts to evaluate prognostic value of CD4-cell count and RNA levels in infected children.

The panel also commented on the critical need to continue and enhance international studies on preventing breast-milk HIV transmission, including research on the basic science of the pathogenesis of and risk factors for such transmission and on different interventions to prevent transmission, such as: antiretroviral prophylaxis for the mother, the infant, or both; early weaning; and HIV vaccines. Additionally, members explained the need for better understanding of the effect of early weaning on morbidity and mortality in uninfected and infected infants.

They added that mechanisms to provide long-term follow-up for study participants in resource-limited settings should also be explored. As antiretroviral therapy and prophylaxis to prevent MTCT become available in such settings, an increasing number of uninfected children will have

in utero antiretroviral drug exposure, and infected children will be surviving longer. Thus, questions similar to those currently being addressed in PHACS in the United States should also be evaluated internationally, although panel members acknowledged that the tasks would be more difficult to accomplish in resource-limited settings. Panel members also suggested expanding the PAMAB research portfolio to include more research on co-infections, such as tuberculosis or malaria, common among HIV-infected children and pregnant women in resource-limited settings. Training international investigators, particularly pediatricians and obstetricians/gynecologists, in the conduct of research was also an area of emphasis for the panel, which encouraged continued support for new young investigators, both domestically and internationally.

Although the experts recognized that HIV vaccine research is primarily funded by NIAID, they also noted that collaboration between PAMAB/NICHD and NIAID on HIV vaccine studies was an important way to ensure that children, adolescents, and women are included in this research. Evaluation of a vaccine to prevent or reduce MTCT, members explained, should also be a focus of this research in the near future. The panel also discussed the advantages and disadvantages of possibly broadening the PAMAB mission to include other perinatally acquired infections, such as cytomegalovirus, HBV, and HCV infections.

Panel members had strong favorable comments about the expansion of the PAMAB mission to HIV-related research in the area of microbicides. They noted that the Branch staff's extensive experience in conducting clinical trials lends itself well to collaboration with the NIAID-funded MTN, both on issues related to prevention of HIV transmission in adolescents and related to the safety of product use during pregnancy.

FUTURE RESEARCH DIRECTIONS FOR THE BRANCH

Since the Branch's last report to NACHHD Council, it has continued to update its portfolio of HIV research to strengthen the focus on international issues related to perinatal HIV transmission prevention and pediatric HIV treatment, as well as on infrastructure development and training of international investigators. The Branch has also increased efforts on interventional research in youth, including primary prevention research, such as HIV vaccine and microbicide trials, and clinical management of HIV-infected youth, such as evaluation of novel drug regimens, treatment adherence, behavioral studies, and risk reduction. The Branch has also expanded its portfolio to include a major new focus on long-term follow-up and toxicity issues for uninfected children who were exposed to HIV and antiretroviral drugs *in utero*, and for perinatally infected children who received long-term antiretroviral treatment and are now entering adolescence. The PAMAB portfolio also includes microbicide research, such as collaborative efforts conducted in HIV-infected women and continued work with the MTN, especially focusing on microbicide studies in adolescents and pregnant women. The Branch will continue funding projects in these areas of emphasis during the next four years.

PAMAB staff benefited from the expert panel's thoughtful, interesting, and broad discussion. In general, panel members felt that the Branch's research portfolio reflected the most important HIV-related research areas for the populations of interest and recommended continuing all

ongoing programs. The panel also recommended continued expansion of Branch activities in the area of co-infections, microbicides, international research, and adolescent research.

Based on internal portfolio analysis and on the expert panel's recommendations, the PAMAB will consider:

- Continuing to support the infrastructure for and conduct of clinical trials on prevention and treatment of HIV infection and its complications in infants, children, adolescents, and pregnant and non-pregnant women through the:
  - NICHD Network
  - ATN
  - IMPAACT Leadership Group
  - MTN Leadership Group
  - Clinical trials of the prevention of HIV MTCT in resource-limited settings (e.g., NICHD/HPTN 040 and CDC/NICHD co-sponsored studies to prevent breast-milk transmission)
  - Investigator-initiated studies
- Continuing to support longitudinal epidemiologic studies that evaluate the natural history of HIV in the antiretroviral era in infants, children, adolescents, and women through:
  - PHACS
  - WIHS
  - NISDI
  - IeDEA
  - Investigator-initiated studies

The following examples describe specific scientific issues that will be prominent in the Branch portfolio during the next four years.

Perinatal HIV Research

Examples of specific topics the PAMAB may address include:

- Research to prevent breast-milk HIV transmission:
  - Evaluate the biological mechanisms and risk variation over time for postnatal breast-milk HIV transmission.
  - Evaluate the role of maternal virologic and maternal and infant cellular and humoral aspects, as well as genetic factors in transmission, using investigator-initiated grants and pathogenesis studies conducted in the context of clinical trials.
  - Support and encourage the development of studies to evaluate the safety and efficacy of different interventions for preventing postnatal transmission, including infant antiretroviral drug use during the breastfeeding period, maternal antiretroviral drug use during lactation, and infant immunization.
- Research on the effects of *in utero* exposure to antiretroviral drugs for MTCT prevention on the fetus and infant:
  - Continue support of the PHACS SMARTT protocol to conduct surveillance for toxicity signals in approximately 3,000 HIV-exposed uninfected infants who have a history of *in utero* and/or neonatal exposure to antiretroviral drugs.

  - Modify the NISDI perinatal protocol to mirror the SMARTT protocol, with a focus on surveillance for toxicity in HIV-exposed uninfected infants who had antiretroviral drug exposure and conduct collaborative analyses with PHACS.
  - Design studies to address toxicity in resource-limited settings, through a request for applications (RFA) or by otherwise encouraging R01 submissions that address the topic.
  - Continue to have PAMAB staff represent NICHD on the Antiretroviral Pregnancy Registry.

- Research on the effect of interventions for the prevention of MTCT on the mother and infected infants:
  - Continue to support studies on the safety and pharmacokinetics of antiretroviral drugs in HIV-infected women and their neonates.
  - Support existing and encourage the development of new R01 studies and clinical trials to assess the risk factors for, and ways to prevent development of, NVP resistance after single-dose NVP exposure, and to evaluate alternatives to single-dose NVP.
  - Support existing and encourage the development of new R01 studies and clinical trials to assess the effect of prior exposure to single-dose NVP on subsequent response to therapy in women and infants who were infected despite NVP prophylaxis.
  - Study the effect of stopping combination drug therapy that is used solely to prevent MTCT on subsequent maternal HIV disease progression and response to therapy.

- Research on obstacles to implementing perinatal prevention programs in resource-limited settings:
  - Continue to provide guidance to PEPFAR-related MTCT prevention programs.
  - Encourage collaboration among PAMAB grantees, who have developed perinatal research programs and infrastructure in resource-limited countries, and PEPFAR to implement projects related to the prevention of MTCT and maternal treatment.
  - Encourage investigator-initiated research and develop operational research studies on implementing perinatal interventions in resource-limited countries.

Pediatric HIV Research

One area that is currently receiving little research funding, but is of critical importance is the intersection between HIV infection and TB in children. PAMAB staff are working to collaborate with other NIH Institutes and with the global Stop TB Partnership on efforts related to this topic. PAMAB staff are proposing a new initiative for fiscal year 2008 that would stimulate research in this area.

Other examples of specific pediatric topics the PAMAB may address include:

- Research on management and treatment of HIV and its complications in children:
  - Maintain domestic capacity to study pharmacokinetics and safety of both new and existing drugs for the treatment of HIV and its complications in infants, children, and adolescents to ensure that pediatric drug approval occurs at or near the same time as for adults; this work can be accomplished through the NICHD Network, the ATN, IMPAACT, and other collaborations with Networks such as PENTA and the ACTG.
  - Develop and conduct clinical trials of new integrase inhibitor and CCR5-antagonist drugs for use in HIV-infected children.

  - Continue to support ongoing and develop and conduct new therapeutic studies to evaluate when to start treatment, what type of treatment to start, when to switch regimens, and what regimen to switch for treating HIV-infected children in the United States and internationally.

- Research evaluating the impact of HIV and the effects of chronic therapy in HIV-infected children as they age:
  - Continue to support the PHACS AMP protocol, which examines the impact of perinatal HIV infection on children who are entering adolescence and the long-term consequences of HIV and its treatment on organ systems, neurodevelopment, and behavior in these children.
  - Modify the NISDI pediatric protocol to mirror the AMP, with a focus on the effect of HIV and its treatment on Latin American children who were infected perinatally and who survive into adolescence conduct collaborative analyses with PHACS and IeDEA.
  - Continue to support the pediatric component of the IeDEA project to evaluate the early and late effects of pediatric treatment in infected children in resource-limited settings.

- Research on improving diagnosis and management of co-infections prevalent in resource-limited settings in HIV-infected children:
  - Promote research on pediatric HIV and TB through an RFA that focuses on improving the diagnosis of TB in children, and through research on the pharmacokinetic interactions between TB and HIV treatments.
  - Encourage investigator-initiated projects on pediatric HIV co-infections, including TB, malaria, and other co-infections.

Adolescent HIV Research

Examples of specific topics the PAMAB may address include:

- Research on optimizing treatment of HIV in adolescents, including interventions to improve treatment adherence, care, and management:
  - Encourage case-finding efforts in collaboration with other Institutes and the CDC to improve the identification and engagement in care of hard to reach, infected, and/or at-risk youth, including young African American females outside of the perinatal setting, and minority HIV-infected men who have sex with men who often come to care very late in their disease course.
  - Support the broadened availability of rapid HIV testing through community prevention campaigns, such as the ATN's C2P Program.
  - Continue to support the ATN in conducting clinical trials of treatment and management of HIV and its complications in HIV-infected youth, both in the ATN alone and in collaboration with other Networks, such as IMPAACT, ACTG, and PENTA.
  - Evaluate prevention and treatment of co-infections of importance to adolescents, such as HBV and HPV.

- Behavioral research on the prevention of HIV infection in at-risk adolescents and modifying risk behaviors in HIV-infected youth:
  - Support existing behavioral research and encourage a more rigorous behavioral research effort, in collaboration with other Institutes and NICHD Branches, to decrease domestic HIV infections among disenfranchised communities, such as young African American

women and men who have sex with men, with a particular focus on research targeting adolescent risk behavior, substance use, and mood disorders.
- Evaluate interventions to improve therapy adherence in infected youth.
- Continue to build and expand community infrastructure through community prevention efforts, such as the C2P Program, that allow the safe and expedient conduct of HIV vaccine and microbicide studies in adolescents and young adults in the United States.
- Share the C2P Program model with other Networks, such as IMPAACT, HVTN, and MTN for adaptation to international settings.
- Collaborate with NIAID, NIMH, NIDA, and other Institutes to support and expand HIV-prevention efforts in adolescents and young adults through combined efforts with IMPAACT, HVTN, and MTN, and to identify and test promising novel HIV vaccines and microbicide candidates, both domestically and internationally.

Women's HIV Research

Examples of specific topics the PAMAB may address include:

- Research to evaluate the natural history of HIV disease in women in the antiretroviral era:
  - Continue to support studies of factors that affect HIV disease in women, including response to therapy after interventions to prevent MTCT.
  - Support existing and design new studies to evaluate simple and robust methodologies for monitoring treatment of women in resource-limited settings.
  - Evaluate whether multivitamin supplements, which showed benefit in delaying disease progression in HIV-infected women who weren't on antiretroviral therapy, have added benefit when combined with antiretroviral therapy compared to antiretroviral therapy alone.
  - Continue support of WIHS with specific attention to studies on the rate of development of HIV-drug resistance mutations and on their impact on response to therapy, response to antiretroviral therapy, evolution of HPV and dysplasia, and metabolic effects of HIV and its treatment; expand the WIHS to include:

    Ongoing HPV evaluation and collection of information regarding vaccination to allow determination of the effects of HPV vaccination in HIV-infected women on acquisition and clearance of vaccine types.

    Establishment of a DNA repository using state-of-the-art molecular techniques to allow continued access to genomic material for planned studies of genetic influences on HIV disease progression, drug metabolism and response to HAART, metabolic complications of HAART, response to viral co-infections, such as HCV and HPV, and other topics.

    More detailed metabolic studies and measurement of carotid intima-media thickening to allow a better understanding of metabolic changes, such as decreased bone mineralization and insulin resistance, related to HIV infection, antiretroviral therapy, and aging and their impact on risk of complications, such as cardiovascular disease.

    More detailed assessments of ovarian reserve and menstrual function, including measurement of inhibin-B and Mullerian inhibiting substance, to allow assessment of the effects of aging, menopause, and HIV on multiple processes including neurocognitive function, metabolic complications, and immune function.

- Research on treatment of HIV and its complications in women, including gender-specific aspects of HIV infection and of its co-infections:
  - Continue to support the collaboration between the NICHD Network and the ACTG on gender-related HIV studies in women.
  - Promote development of a collaborative agenda for research in women's health and develop guidelines to facilitate co-endorsement and joint conduct of protocols among the NICHD Network, IMPAACT, ACTG, and ATN through PAMAB participation on the new Inter-Network Women's Health Committee.
  - Promote research within existing clinical trials networks or through investigator-initiated research to evaluate interactions between existing/new antiretroviral agents and hormonal contraceptives, optimization of antiretroviral prophylaxis regimens during pregnancy to preserve future therapy options, management of opportunistic infections in HIV-infected women during pregnancy, and effects and management of immune reconstitution inflammatory syndrome during pregnancy.
- Microbicide research to evaluate efficacy and safety of microbicides in women:
  - Continue the collaboration with the MTN, with a focus on safety evaluation of new microbicide agents for vaginal use in adolescents.
  - Ensure that strategies are developed to evaluate the safety of topical microbicides for pregnant women as the products are developed.

FIGURES AND TABLES

FIGURE 1: PAMAB FUNDING, FISCAL YEAR 1999 THROUGH FISCAL YEAR 2006

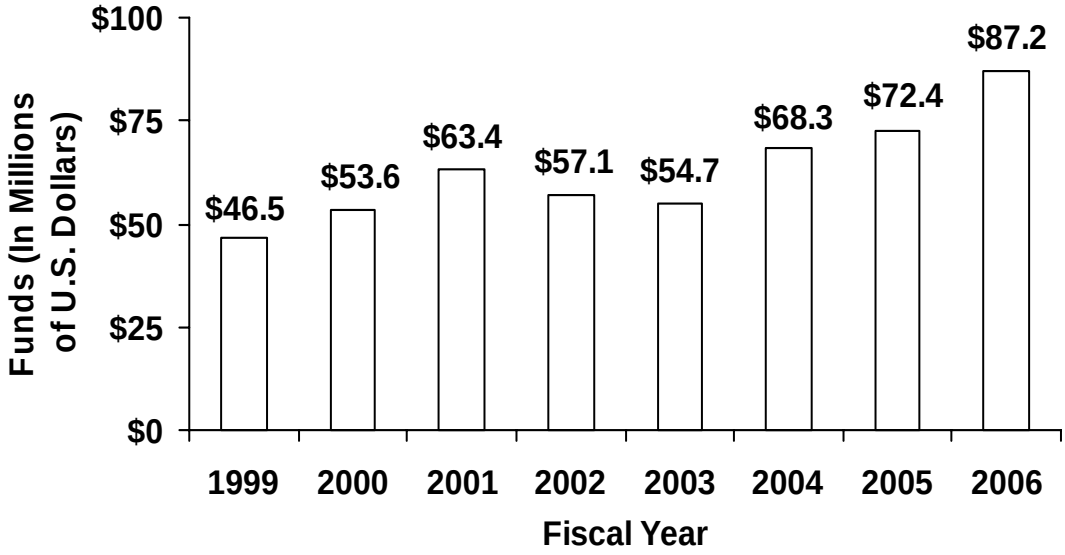
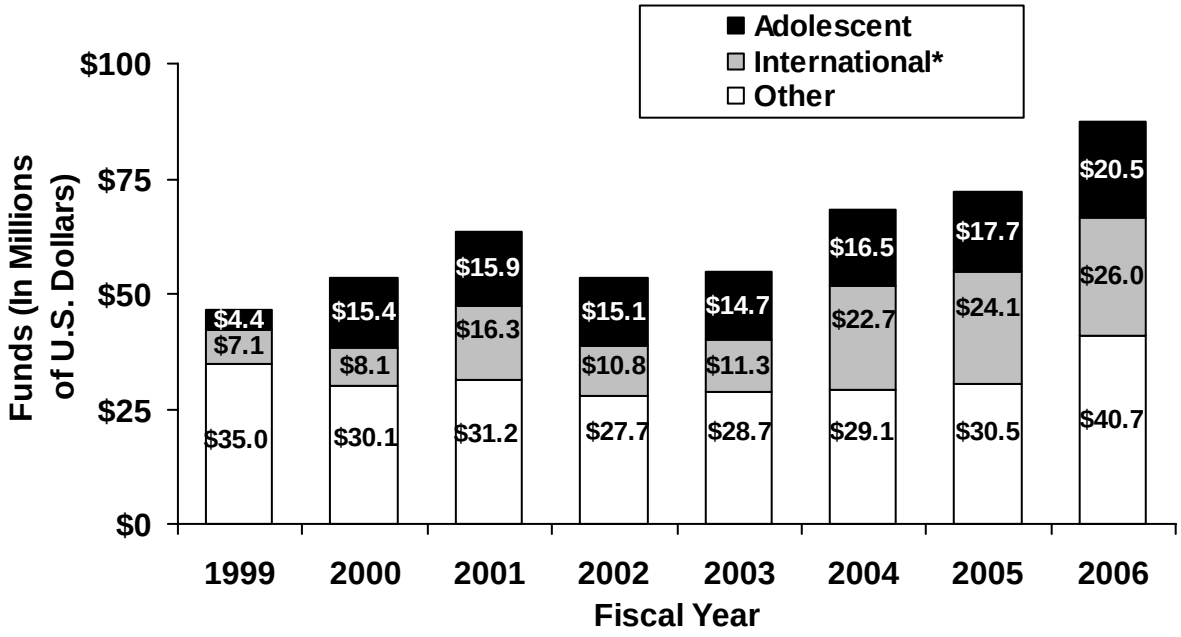


FIGURE 2: PAMAB FUNDING, BY FOCUS, FISCAL YEAR 1999 THROUGH FISCAL YEAR 2006



* The "International" category includes: international sites in the NICHD Network, the NISDI, the India Perinatal Project, NICHD/HPTN 040, international investigator-initiated grants, and co-funding of the HPTN, IeDEA, CDC breastfeeding studies, and the IMPAACT Network.

FIGURE 3: PAMAB FUNDING FOR INVESTIGATOR-INITIATED GRANTS, DOMESTIC AND INTERNATIONAL FOCUS, FISCAL YEAR 2003 THROUGH FISCAL YEAR 2006

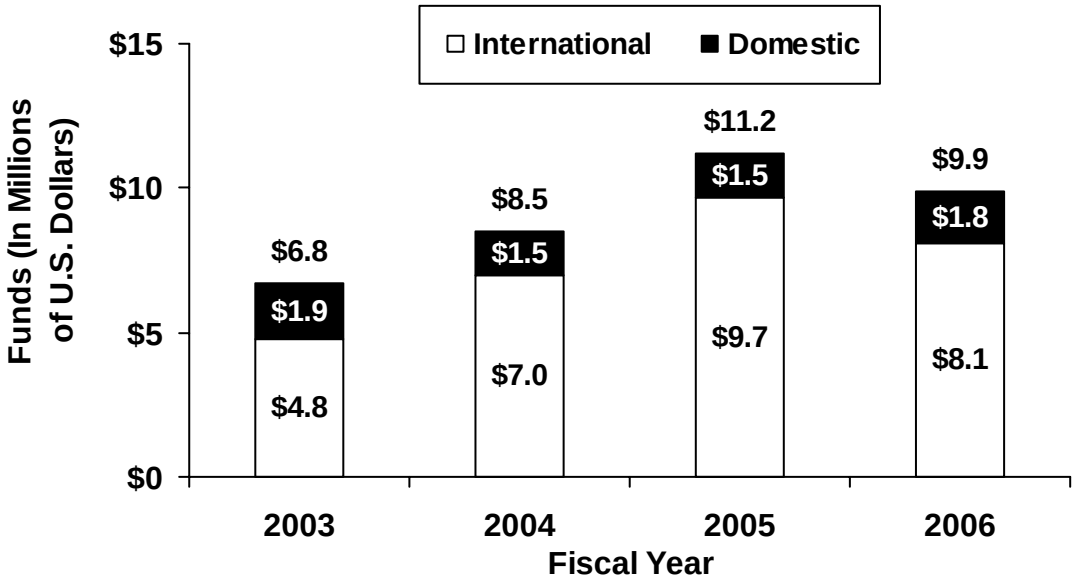


FIGURE 4: PAMAB FUNDING FOR INVESTIGATOR-INITIATED GRANTS, RESEARCH AND TRAINING GRANTS, FISCAL YEAR 2003 THROUGH FISCAL YEAR 2006

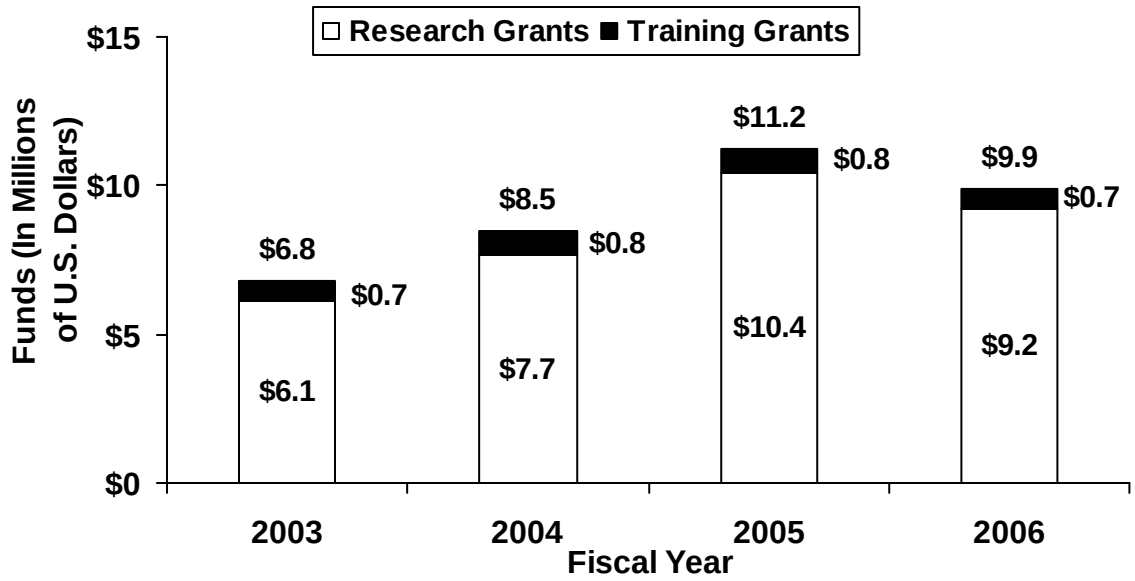


FIGURE 5: PAMAB PORTFOLIO, BY GRANT TYPE, FISCAL YEAR 2003 THROUGH FISCAL YEAR 2006

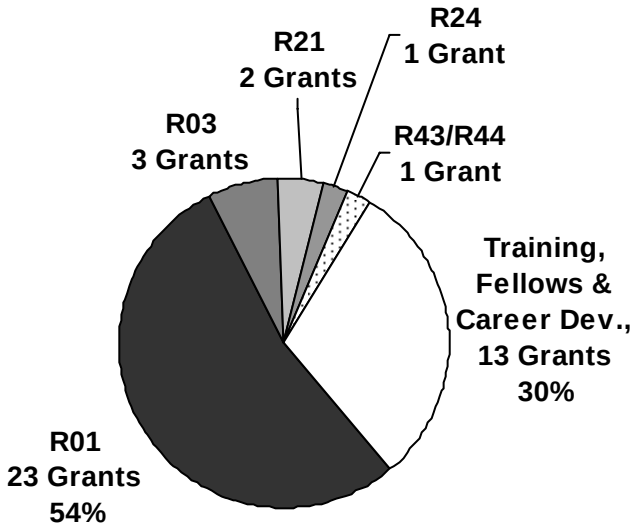


FIGURE 6: PAMAB TRAINING PORTFOLIO, BY GRANT TYPE, FISCAL YEAR 2003 THROUGH FISCAL YEAR 2006

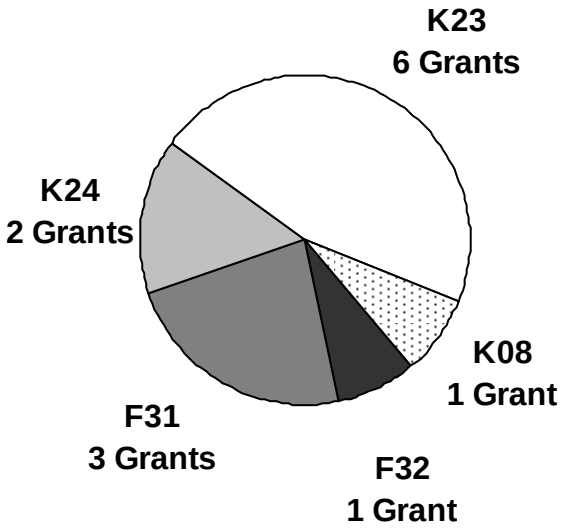


FIGURE 7: ADOLESCENT TRIALS NETWORK FOR HIV/AIDS INTERVENTIONS (ATN) FUNDING, FISCAL YEAR 2003 THROUGH FISCAL YEAR 2006

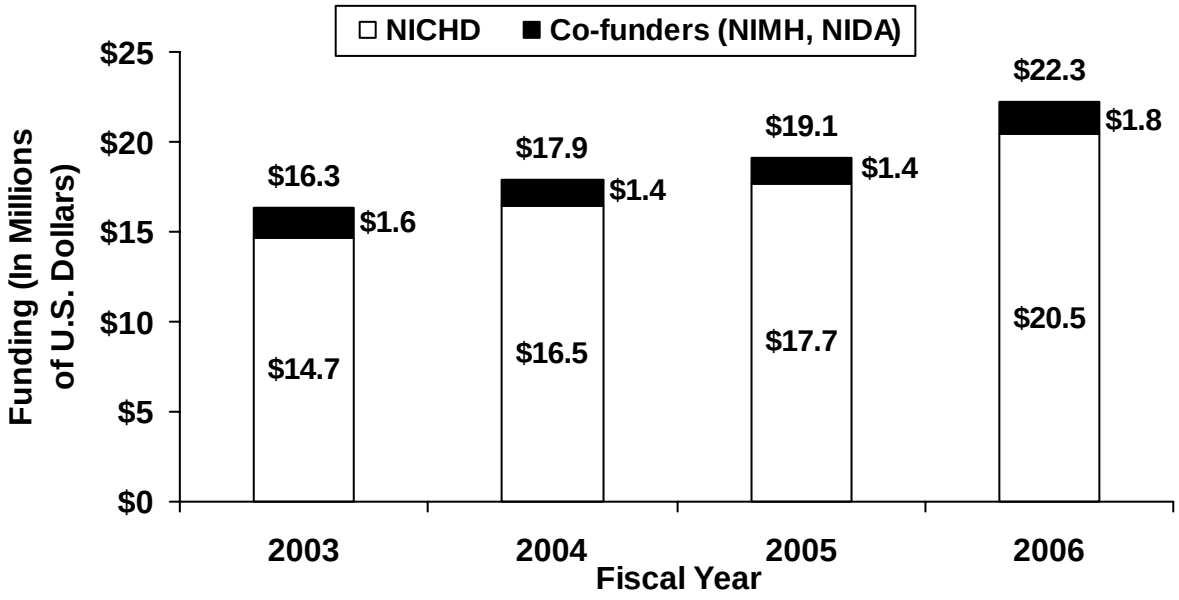
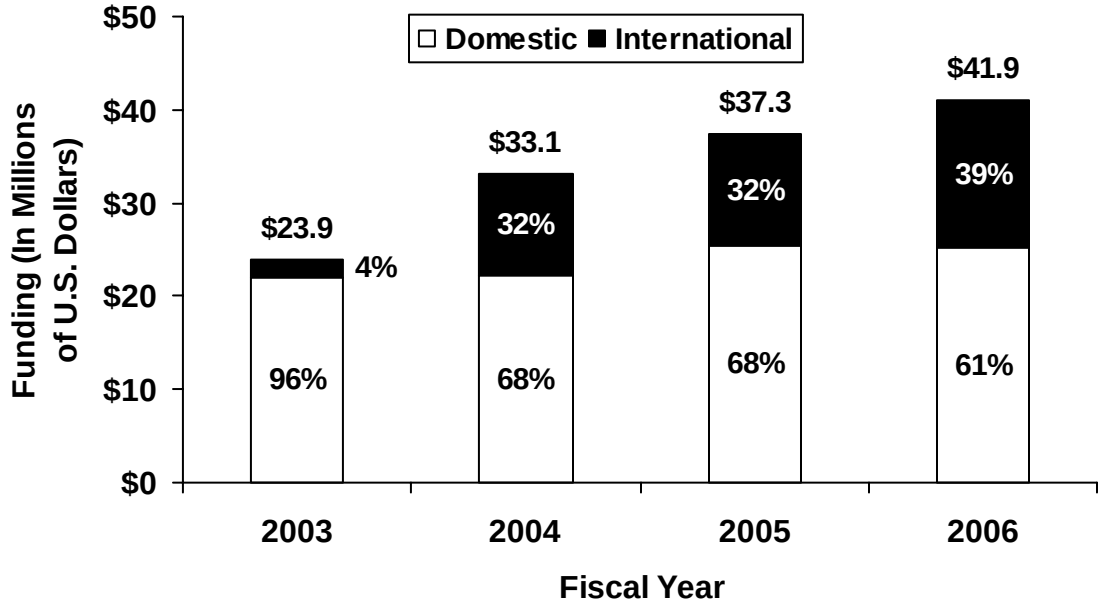


FIGURE 8: NICHD NETWORK COORDINATING CENTER CONTRACT, FISCAL YEAR 2003 THROUGH FISCAL YEAR 2006



* Based on actual expenses by contract year

FIGURE 9: NICHD NETWORK COORDINATING CENTER CONTRACT, BY PROJECT, FISCAL YEAR 2003 THROUGH FISCAL YEAR 2006

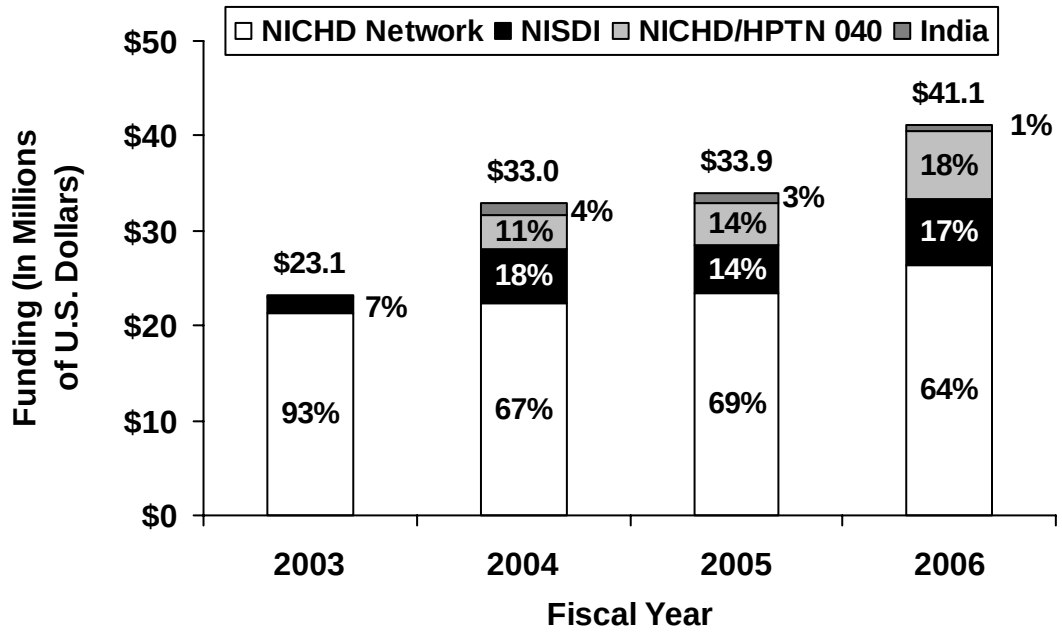
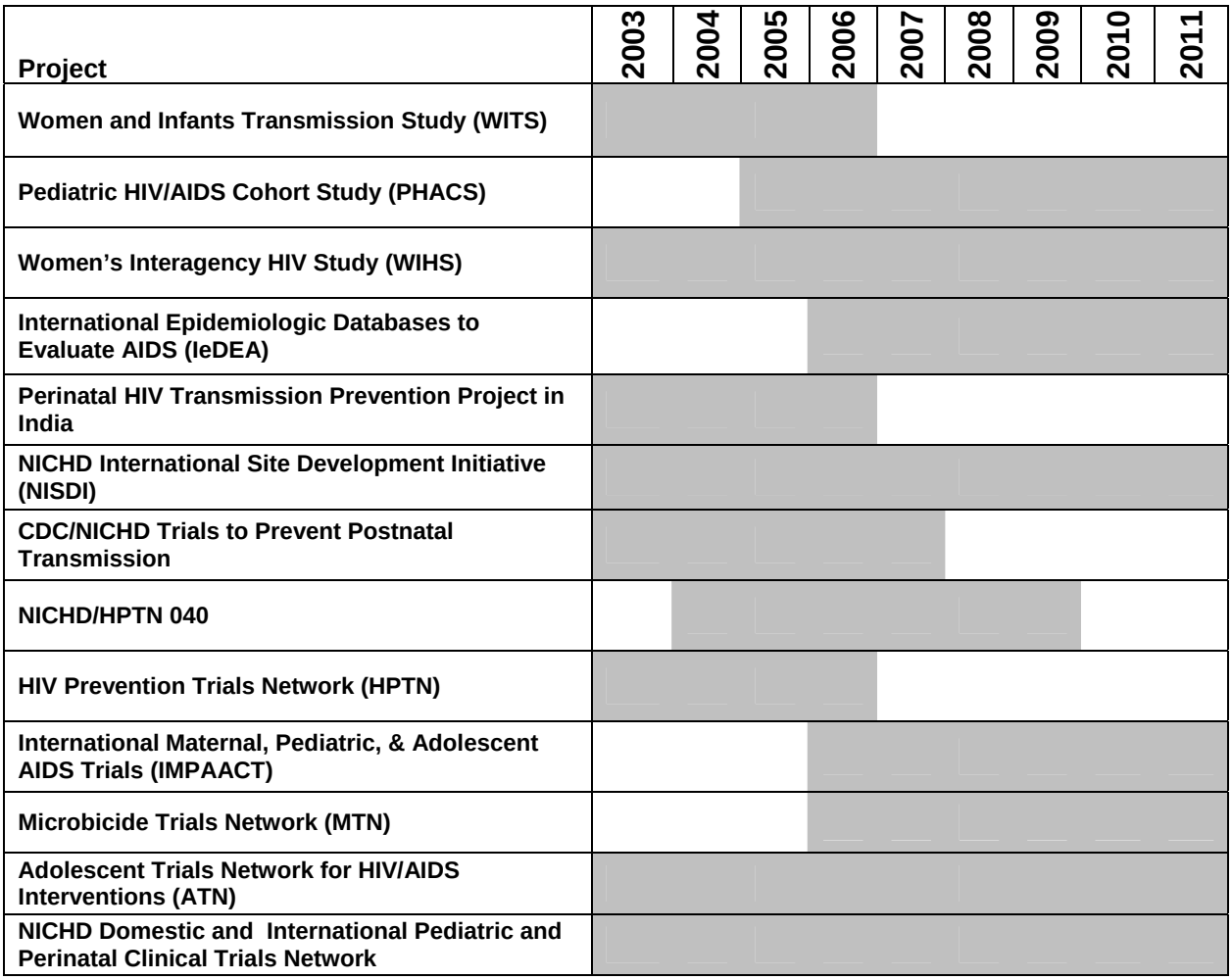


FIGURE 10: MAJOR PAMAB PROJECTS TIMELINE, FISCAL YEAR 2003 PROJECTED THROUGH FISCAL YEAR 2011



APPENDIX A: PAMAB STAFF

Lynne M. Mofenson, M.D., chief of the PAMAB, is an infectious disease specialist and board-certified pediatrician. Dr. Mofenson received her medical degree with honors (Alpha Omega Alpha) from Albert Einstein College of Medicine in 1977. She then completed a pediatric residency at Boston Children's Hospital and finished a pediatric chief residency and joint adult/pediatric infectious disease fellowship at the University of Massachusetts Medical School. Prior to coming to the NIH, she spent five years as Assistant Commissioner for Public Health in Massachusetts, where she directed the Communicable Disease Program for the Massachusetts Department of Public Health. Before that position, she spent three years in the private practice of adult and pediatric infectious diseases and pediatrics in Massachusetts. Dr. Mofenson came to the NIH in 1989, as associate Branch chief for clinical research in PAMAB and became chief of PAMAB in December 2001. Dr. Mofenson is responsible for program planning and for the development and scientific direction of research studies and clinical trials in domestic and international pediatric, adolescent, and maternal HIV infection, disease, and AIDS. She is project officer for the multi-site NICHD International and Domestic Pediatric and Perinatal NIH Clinical Trials Network (NICHD Network) and for the NICHD portion of the International Maternal, Pediatric, and Adolescent AIDS Trials (IMPAACT) Leadership Group. Dr. Mofenson has published extensively on treatment of HIV infection in children and women, and on prevention of mother-to-child transmission (MTCT) of HIV. She is involved in many national and international policy and guideline groups related to HIV infection in children and women and serves as a consultant to the World Health Organization on issues related to antiretroviral treatment and care of HIV-infected women and their children. Dr. Mofenson received the inaugural NIH AIDS Day Award in December 2006.

Kevin Ryan, Ph.D., joined the PAMAB in June 2005 as deputy Branch chief. He earned his B.S. in microbiology from the University of Iowa in 1978, and his Ph.D. in cellular and molecular biology from the University of Michigan in 1984. After postdoctoral training in molecular virology in the NIAID Intramural program, Dr. Ryan joined St. Jude Children's Research Hospital in Memphis as a trainee in 1986 and joined the faculty there in 1989. Dr. Ryan was recruited to the NIAID Scientific Review Program in 1998, where he was responsible for peer review of grants and contracts related to HIV/AIDS in the areas of preclinical research, vaccine research and development, and clinical trials networks. In 2000, Dr. Ryan joined the NIAID Division of AIDS, Prevention Sciences Branch, as a program officer with primary responsibility for laboratory and administrative oversight of the HIV Prevention Trials Network (HPTN). Dr. Ryan became branch chief in 2002 and held that position until moving to PAMAB. At PAMAB, Dr. Ryan is responsible, along with the branch chief, for providing administrative, fiscal, and safety oversight of all PAMAB grant and cooperative agreements.

Bill G. Kapogiannis, M.D., joined PAMAB in July 2005. He is a board-certified infectious-disease specialist in both pediatrics and internal medicine. He received his M.D. from the University of Illinois at Chicago College of Medicine and completed a four-year internal medicine/pediatrics residency program at the University of Illinois at Chicago before finishing a combined fellowship training in infectious diseases within the departments of Internal Medicine and Pediatrics at Emory University, Atlanta, Georgia. Part of Dr. Kapogiannis' research

involved assembling, collecting, and analyzing immunologic data on an HIV-positive adolescent cohort from Atlanta. Within the PAMAB, Dr. Kapogiannis' research is also focused on HIV in adolescents; he is the scientific director of the Adolescent Trials Network for HIV/AIDS Interventions (ATN), which is evaluating biomedical, behavioral, and community level interventions for treatment and management of HIV infection and its complications among youth, as well as the prevention of HIV transmission in the adolescent population, including HIV vaccine and microbicide studies.

Sonia Lee, Ph.D., joined the PAMAB in June 2006. Dr. Lee earned her B.A. in psychology from the University of Pennsylvania, and her M.A. and Ph.D. in clinical psychology from American University in Washington, D.C. Prior to joining PAMAB, she was a psychologist on the special immunology service at Children's National Medical Center in Washington, D.C., dealing with assessment and care HIV-infected children and adolescents; she also served as research associate for an intervention trial promoting adherence to antiretroviral medications in children and adolescents. Her earlier positions include research assistant in the Cognitive Neuroscience Section of the NINDS. Within the PAMAB, Dr. Lee works with investigators in the ATN to design and implement behavioral studies and to develop behavioral components to biomedical studies in HIV-infected or at-risk youth. She is also the PAMAB chair of the Behavioral and Community Leadership Groups, which develop the behavioral agenda of the ATN. In addition, Dr. Lee contributes behavioral science expertise to all activities supported by the Branch.

John H. Moye, M.D., is a pediatrician and former state public health official who joined the PAMAB in 1990 as a physician scientist and medical officer. His background is in clinical and laboratory medicine and public health, with an emphasis on the prevention and control of communicable and chronic diseases, including sexually transmitted diseases and HIV/AIDS. He is a 1982 graduate of the University of Massachusetts Medical School and trained in pediatrics from 1982 to 1986 at the Boston City Hospital, where he then served as chief resident and as senior attending physician in pediatric emergency services from 1986 to 1990. He has been an HIV/AIDS consultant for state departments of social services, corrections, youth services, and education. He has been a member of the Massachusetts Governor's Task Force on AIDS, the New England Governors' Conference Task Force on AIDS and Intravenous Drug Use, and the U.S. Public Health Service Surgeon General's Panel on Women, Adolescents, and Children with HIV Disease and AIDS. His areas of activity for PAMAB include: Pediatric HIV/AIDS Cohort Study (PHACS), for which he is scientific director; the NICHD Network and IMPAACT activities; the NICHD/HPTN 040 study; virology and immunology research; laboratory quality assurance; growth and nutrition; and international research initiatives.

Jennifer S. Read, M.D., M.S., M.P.H., D.T.M. & H., board certified in pediatrics and in pediatric infectious diseases, joined the NICHD in 1990. She received her undergraduate and graduate degrees in biological sciences from Stanford University. Subsequently, she graduated from medical school at the University of Arkansas for Medical Sciences and completed her residency in pediatrics at the University of Michigan. She received clinical fellowship training in pediatric infectious diseases at the Johns Hopkins University and the University of Michigan and received advanced training in tropical medicine at the London School of Hygiene and Tropical Medicine. She began a U.S. Public Health Service Epidemiology Training Program

Fellowship at the NICHD in 1990, received a master's degree in public health from the Harvard University School of Public Health in 1991, and worked as a staff fellow and subsequently a senior staff fellow in the Division of Epidemiology, Statistics, and Prevention Research of the NICHD before joining PAMAB in 1995. Since then, Dr. Read has contributed to the development, execution, and analysis of domestic and international clinical trials and other epidemiological studies related to pediatric HIV infection and prevention of MTCT. Her research has focused on the role of cesarean section in the prevention of MTCT and, more recently, on the prevention of such transmission among mothers who breastfeed; she developed and led two international collaborations that resulted in individual patient-data meta-analyses in these areas. In addition, she has created an operational research project regarding prevention of MTCT of HIV in rural India, and, as the principal investigator for the Latin American/Caribbean NICHD International Site Development Initiative (NISDI) perinatal protocol, is collaborating with in-country investigators on description and analysis of HIV MTCT in Latin America and the Caribbean. She received the Pediatric Infectious Diseases Society Young Investigator Award in 2001.

Leslie K. Serchuck, M.D., M.A., an infectious disease specialist and board-certified pediatrician, joined the PAMAB in 2001. She received her graduate degree in counseling psychology and her medical degree from Boston University School of Medicine. She did her residency and fellowship training in infectious diseases at Boston City Hospital (now Boston Medical Center). Following her fellowship, she worked at the HIV and AIDS Malignancy Intramural Branch at the National Cancer Institute for five years before joining PAMAB as a medical officer in January 2001. Dr. Serchuck is currently responsible for collaboration with the Pediatric AIDS Clinical Trials Group (PACTG) and IMPAACT regarding the design and analysis of clinical trials that evaluate pediatric HIV therapies. She is an active member of the leadership group of the ATN. As the principal investigator for the NISDI pediatric protocol, she is collaborating with in-country investigators on a prospective, observational study of HIV-exposed and infected infants, children, and adolescents at international sites in Latin America. In addition, since 1998, she has played an important and active role on the Clinical Center Bioethics Committee at the NIH.

D. Heather Watts, M.D., joined the PAMAB in July 1998 from the University of Washington, where she was an associate professor of obstetrics and gynecology, adjunct associate professor in health services, and medical director for obstetrics for the Seattle King County Department of Public Health. She graduated from the Pennsylvania State University and Jefferson Medical College, completed her residency in obstetrics and gynecology at Thomas Jefferson University Hospital, and completed her fellowship training in maternal-fetal medicine and infectious diseases at the University of Washington. She is board certified in obstetrics and gynecology and maternal-fetal medicine. Currently, Dr. Watts is participating in many collaborative efforts aimed at improving the health of HIV-infected women and preventing perinatal transmission of HIV. Dr. Watts leads the PAMAB study of neonatal antiretroviral prophylaxis for prevention of transmission among infants born to untreated women in Brazil, also known as NICHD/HPTN 040. She is an active participant on many PACTG/IMPAACT trials aimed at reducing HIV MTCT and providing optimal treatment for HIV-infected pregnant women. In addition, Dr. Watts serves on the Women's Health Committee, advises on several women's health studies in the Adult AIDS Clinical Trials Group (ACTG), and is the PAMAB representative to the

executive committee of the MTN. She has chaired the mucosal/reproductive health working group and serves on the executive committee of WIHS. Dr. Watts serves on many U.S. Public Health Service guideline committees related to HIV and sexually transmitted disease in pregnant women and is the current president of the Infectious Disease Society for Obstetrics and Gynecology. She received an NIH Merit Award in 2003.

Carol Worrell, M.D., joined the PAMAB in October 2006. Dr. Worrell is a pediatric infectious diseases specialist, who spent her undergraduate years at Harvard College, graduated cum laude, and received her M.D. from Columbia University College of Physicians and Surgeons. Residency and infectious disease fellowship were also spent in New York City, at Babies Hospital at Columbia Presbyterian Medical Center and New York University Medical Center, respectively. She spent the next few years at Harlem Hospital Center doing primary care for HIV-infected and exposed children, while also acting as a pediatric infectious diseases consultant and the attending pediatrician at the Felton National Tuberculosis Center. She came to the intramural program at the National Cancer Institute in 2001 as a member of the Pediatric HIV Working Group of the HIV and AIDS Malignancy Branch, where she participated in the design and implementation of phase I/II clinical trials for treatment-experienced, HIV-infected children. In 2005, she joined the Division of AIDS, NIAID, where she served as a medical officer for many HIV-related pediatric clinical trials. At the PAMAB, she continues her work on pediatric and adolescent HIV-related clinical trials. She is involved in implementing the pediatric component that NICHD is funding within International Epidemiologic Databases to Evaluate AIDS (IeDEA) and is working on issues related to pediatric HIV/tuberculosis co-infection.

APPENDIX B: PAMAB STAFF ACTIVITIES

Lynne Mofenson

U.S. PUBLIC HEALTH SERVICE COMMITTEES

- Perinatal Treatment Guidelines Committee (Executive Secretary)
- Pediatric Antiretroviral Treatment Guidelines Committee (Executive Secretary)
- Prevention and Treatment of Opportunistic Infections in HIV-1-Infected Children Guidelines Committee (Executive Secretary)
- Adult Antiretroviral Treatment Guidelines Committee

PRESIDENTS EMERGENCY PLAN FOR AIDS RELIEF (PEPFAR) COMMITTEES

- PEPFAR Prevention of Mother to Child Transmission (MTCT)/Pediatric Working Group
- PEPFAR Scientific Advisory Board
- Public-Private Partnership for Pediatric Antiretroviral Drugs Group

NIH COMMITTEES

- Office of AIDS Research (OAR) Therapeutics Research Planning Committee, International Research Planning Committee, and Vaccine Research Planning Committee

WORLD HEALTH ORGANIZATION COMMITTEES

- Guidelines Committee for Antiretroviral Therapy in HIV-Infected Adults in Resource-Limited Settings (Writing Group)
- Guidelines Committee for Antiretroviral Therapy of HIV-Infected Children in Resource-Limited Countries (Writing Group)
- Guidelines Committee for Treatment of HIV-Infected Pregnant Women and Prevention of MTCT in Resource-Limited Countries (Writing Group)

OTHER ORGANIZATIONS

- Committee on Pediatric AIDS, American Academy of Pediatrics (AAP) (NICHD liaison)
- Elizabeth Glaser Pediatric AIDS Foundation Children's Research Fund Advisory Committee
- *Journal of the Acquired Immune Deficiency Syndromes* Editorial Board
- *Pediatric Infectious Disease Journa*l Editorial Board
- *Public Library of Science Medical Journal (PLosMed)* Editorial Board
- The National Resource Center for AIDS Education and Training Center Faculty Reviewer

Bill Kapogiannis

NIH COMMITTEE

- OAR Vaccine Research Planning Committee
- Clinical Research Monitoring Committee

OTHER ORGANIZATIONS

- HIV Vaccine Trials Network (HVTN) Adolescent Working Group
- Microbicide Trials Network (MTN) Toxicity Table Working Group

Sonia Lee

NIH COMMITTEE

- OAR Racial and Ethnic Minority Committee

Jack Moye

U.S. PUBLIC HEALTH SERVICE COMMITTEE

- Health Resources and Services Administration HIV Guidelines for Nutrition Working Group

NIH COMMITTEE

- OAR Etiology and Pathogenesis Committee

Jennifer Read

U.S. PUBLIC HEALTH SERVICE COMMITTEE

- Prevention and Treatment of Opportunistic Infections in HIV-1-Infected Children Guidelines Committee

NIH COMMITTEE

- NIH Human Microbiome Project Working Group

OTHER ORGANIZATIONS

- Ghent-International AIDS Society Working Group on HIV in Women and Children (Steering Committee)
- Committee on Pediatric AIDS, AAP (Member)
- Pediatric Infectious Disease Society liaison to the HIV Medicine Association of the Infectious Disease Society of America

Leslie Serchuck

U.S. PUBLIC HEALTH SERVICE COMMITTEES

- Pediatric Antiretroviral Treatment Guidelines Committee
- Prevention and Treatment of Opportunistic Infections in HIV-1-Infected Children Guidelines Committee

PRESIDENTS EMERGENCY PLAN FOR AIDS RELIEF (PEPFAR) COMMITTEES

- PEPFAR Tuberculosis (TB) Working Group

NIH COMMITTEES

- OAR Natural History/Epidemiology Committee and International Committee
- Clinical Bioethics Committee (Clinical Center)
- Clinical Research Advisory Committee (NICHD)
- National Eye Institute Institutional Review Board (Adjunct *Ad Hoc* Member)

OTHER ORGANIZATIONS

- STOP-TB Partnership Pediatric Treatment Working Group

Heather Watts

U.S. PUBLIC HEALTH SERVICE COMMITTEES

- Perinatal Treatment Guidelines Committee
- Sexually Transmitted Diseases Treatment Guidelines Committee
- Prevention and Treatment of Opportunistic Infections in HIV-1-Infected Adults Guidelines Committee

NIH COMMITTEES

- Trans-Institute Microbicide Working Group
- OAR Microbicide Research Planning Group

OTHER ORGANIZATIONS

- American College of Obstetricians and Gynecologists Committee on Health Care for Underserved Women
- Infectious Disease Society for Obstetrics and Gynecology (President)
- Antiretroviral Pregnancy Registry (NICHD Liaison)

Carol Worrell

PRESIDENTS EMERGENCY PLAN FOR AIDS RELIEF (PEPFAR) COMMITTEES

- PEPFAR Prevention of MTCT/Pediatric Working Group

OTHER ORGANIZATION

- STOP-TB Partnership Pediatric Treatment Working Group

APPENDIX C: PAMAB STAFF PUBLICATIONS, FISCAL YEAR 2003 THROUGH FISCAL YEAR 2007

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APPENDIX D: NICHD NETWORK CLINICAL SITES

Domestic

- Children's Diagnostic and Treatment Center of South Florida, Fort Lauderdale, Florida
- Children's National Medical Center, Washington, D.C.
- Harlem Hospital Center (subsite at Mount Sinai Hospital), New York City, New York
- Howard University Hospital, Washington, D.C.
- Jacobi Medical Center (subsite at Lincoln Hospital), Bronx, New York
- New York University Hospital, New York City, New York
- San Juan City Hospital, San Juan, Puerto Rico
- State University of New York Health Science Center at Brooklyn, Brooklyn, New York
- State University of New York Health Science Center at Stony Brook, Stony Brook, New York
- State University of New York Health Science Center at Syracuse, Syracuse, New York
- University of Colorado Health Sciences Center, Denver, Colorado
- University of Florida College of Medicine, Gainesville, Florida
- University of Florida Health Science Center, Jacksonville, Florida
- University of Illinois College of Medicine, Chicago, Illinois
- University of Rochester School of Medicine and Dentistry/Strong Memorial Hospital, Rochester, New York
- University of South Florida, Tampa, Florida
- University of Southern California Medical Center/Los Angeles County Hospital, Los Angeles, California
- University of Washington (subsite at University of Oregon, Portland, Oregon), Seattle, Washington
- Wayne State University, Detroit, Michigan
- Yale University of Medicine, New Haven, Connecticut

International

- Hospital das Clinicas da Faculdade de Medicina de Ribeirao Preto da Universidade de Sao Paolo, Ribeirao Preto, Brazil
- Hospital dos Servidores do Estado, Rio de Janeiro, Brazil
- Instituto de Infectologia Emilio Ribas, Sao Paolo, Brazil
- Servico de Doencase Infecciosas-Federal University, Rio de Janeiro, Brazil
- Princess Margaret Hospital, Nassau, Bahamas
- Universidade Federal de Minas Gerais, Belo Horizonte, Brazil

APPENDIX E: NICHD INTERNATIONAL SITE DEVELOPMENT INITIATIVE (NISDI) CLINICAL SITES

Argentina

- Fundacion Huesped (Coordinating Center), Buenos Aires
- Hospital Juan Fernandez, Buenos Aires
- Hospital Diego Paroissien, Buenos Aires
- Hospital de Agudos Cecilia Gierson, Buenos Aires
- Hospital General de Agudos Jose Maria Ramos Mejia, Buenos Aires

Bahamas

- Princess Margaret Hospital, Nassau, Bahamas

Brazil

- Universidade Federal de Minas Gerais, Belo Horizonte
- University of Caxias do Sul Consortium (coordinating center), Caxias do Sul
- Hospital Geral de Caxias do Sul, Caxias do Sul
- STD/HIV Clinic Caxias do Sul, Caxias do Sul
- Hospital Conceicao, Porto Allegre
- Hospital Femina, Porto Allegre
- Hospital das Clinicas da Faculdade de Medicina de Ribeirao Preto da Universidade de Sao Paolo, Ribeirao Preto
- Hospital dos Servidores do Estado, Rio de Janeiro
- Servico de Doencase Infecciosas-HUCFF, Rio de Janeiro
- Instituto da Crianca-HCFM Universidade de San Paolo, Sao Paulo
- Federal University of Sao Paulo, Sao Paulo
- Instituto de Infectologia Emilio Ribas, Sao Paolo

Jamaica

- University Hospital of the West Indies
- Victoria Jubilee Maternity Hospital-Comprehensive Health Center

Mexico

- Hospital Infantil de Mexico Federico Gomez, Mexico City
- Institutio Nacional de Perinatologia, Mexico City
- Institutio Nacional de Ciencias Medicas y Nutricion “Salvador Zubiran”, Mexico City

Peru

- Instituto Especializado de Salud del Nino, Lima
- Instituto Expecializado Materno Perinatal, Lima

APPENDIX F: NICHD/HTPN 040 INFANT PROPHYLAXIS PERINATAL CLINICAL TRIAL SITES

United States

- Baylor College of Medicine, Houston, Texas
- San Juan City Hospital, San Juan, Puerto Rico
- University of California at Los Angeles, Los Angeles, California
- University of Florida Collage of Medicine, Gainesville, Florida
- University of Florida Health Science Center, Jacksonville, Florida
- University of Medicine and Dentistry of New Jersey, Newark, New Jersey

Brazil

RIO DE JANEIRO

- Fiocruz (Fundação Instituto Oswaldo Cruz) (Brazil Central Coordinating Center and Lab)
- Hospital dos Servidores do Estado Saúde/ Pro-Matre
- Hospital Rocha Faria
- Hospital Geral de Nova Iguaçu

PORTO ALEGRE

- Grupo Hospitalar Conceição (Hospital Conceicao e Hospital Femina)
- Complexo Hospitalar da Irmandade Santa Casa da Misericórdia
- Centro de Atendimento em Doenças Sexualmente Tranmissiveis e AIDS da Secretaria Municipal da Saúde

BELO HORIZONTE

- Universidade Federal de Minas Gerais
- Maternidade Odete Valadares

SÃO PAULO

- Maternidade Amparo
- Universidade Federal de São Paulo

Argentina

- Hospital Diego Paroissien, Buenos Aires

South Africa

JOHANNESBURG

- Chris Hani Baragwanath Hospital

CAPETOWN

- Tygerberg Hospital
- Hottentots Holland Hospital
- Macassar Hospital

APPENDIX G: ADOLESCENT TRIALS NETWORK FOR HIV/AIDS INTERVENTIONS (ATN) CLINICAL SITES

- Children's Diagnostic and Treatment Center of South Florida, Fort Lauderdale, Florida
- Children's Hospital of Los Angeles, Los Angeles, California
- Children's Memorial Hospital, Chicago, Illinois
- Children's National Medical Center, Washington, D.C.
- Children's Hospital of Philadelphia, Philadelphia, Pennsylvania
- Hektoen Institute for Medical Research (Cook County Hospital), Chicago, Illinois
- Montifiore Medical Center, Bronx, New York
- Mount Sinai Medical Center, New York City, New York
- St. Jude Children's Research Hospital, Memphis, Tennessee
- Tulane University of Louisiana, New Orleans, Louisiana
- University of California at San Francisco, San Francisco, California
- University of Maryland, Baltimore, Maryland
- University of Miami, Miami, Florida
- University of South Florida, Tampa, Florida
- University of Puerto Rico Health Science Center, San Juan, Puerto Rico
- Data and Coordinating Center: Westat, Inc, Rockville, Maryland
- Scientific Leadership Coordinating Center: University of Alabama at Birmingham, Birmingham, Alabama

APPENDIX H: EXPERT PANEL MEMBERS

- **Coleen Cunningham, M.D.**, chief, Department of Pediatric Infectious Diseases, Duke University Medical Center, Durham, North Carolina
- **Mark Del Monte, J.D.**, assistant director, Department of Federal Affairs, American Academy of Pediatrics, Washington, D.C.
- **Lawrence Deyton, M.S.P.H., M.D.**, director, AIDS Service, U.S. Department Veterans Affairs, Washington, D.C.
- **Patricia Flynn M.D.**, Department of Infectious Diseases, St. Jude Children's Research Hospital, Memphis, Tennessee
- **Diana Gibb, M.D.**, professor of epidemiology, Medical Research Council Clinical Trials Unit, London, United Kingdom
- **Lisa Henry-Reid, M.D.**, chair, Division of Adolescent and Young Adult Medicine, John H. Stronger Jr. Hospital of Cook County, Chicago, Illinois
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APPENDIX J: ACRONYMS AND ABBREVIATIONS USED IN THIS REPORT

Abbreviation/Acronym	Description/Full Term
3TC	Lamivudine
AAP	American Academy of Pediatrics
ACASI	Audio-Computer Assisted Surveys
ACTG	Adult AIDS Clinical Trials Network
AIDS	Acquired Immune Deficiency Syndrome
AMHARN	Adolescent Medicine HIV/AIDS Research Network
AMP	Adolescent Master Protocol (of PHACS)
ATN	Adolescent Trials Network for HIV/AIDS Interventions
BHITS	Breastfeeding and HIV International Transmission Study
C2P	Connect to Protect Program (of ATN)
CDC	Centers for Disease Control and Prevention
DEXA	Dual Energy X-Ray Absorptiometry/Densitometry
DHHS	Department of Health and Human Services
DMPA	Depot Medroxyprogesterone Acetate
ECS	Elective Cesarean Section
HAART	Highly Active Antiretroviral Therapy
HAV	Hepatitis A Virus
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HHV-8	Human Herpes Virus-8
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HPPMCS	HIV Prognostic Pediatric Marker Collaborative Study
HPTN	HIV Prevention Trials Network
HPV	Human Papillomavirus
HRSA	Health Resources and Services Administration
HVTN	HIV Vaccine Trials Network
IeDEA	International Epidemiologic Databases for Evaluation of AIDS
IGFBP	Insulin Growth Factor Binding Protein
IMPAACT	International Maternal Pediatric Adolescent AIDS Clinical Trials
IVIG	Intravenous Immunoglobulin
MTCT	Mother-to-Child Transmission
MTN	Microbicide Trials Network
NAbs	Neutralizing antibodies
NACHHD	National Advisory Child Health and Human Development (Council)
NHLBI	National Heart, Lung, and Blood Institute
NIAID	National Institute of Allergy and Infectious Diseases
NICHD	National Institute of Child Health and Human Development
NICHD Network	NICHD International and Domestic Pediatric and Perinatal HIV Clinical Trials Network
NICHD/HPTN 040 Trial	International Clinical Trial of Post-Exposure Prophylaxis of HIV-Exposed Infants
NIDA	National Institute on Drug Abuse

Abbreviation/Acronym	Description/Full Term
NIDCD	National Institute on Deafness and Other Communication Disorders
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
NISDI	Latin American/Caribbean NICHD International Site Development Initiative
NVP	Nevirapine
OAR	Office of AIDS Research (NIH)
PACTG	Pediatric AIDS Clinical Trials Network
PAMAB	Pediatric, Adolescent, and Maternal AIDS Branch
PENTA	Pediatric European Network for Treatment of AIDS
PEPFAR	President's Emergency Plan for AIDS Relief
PHACS	Pediatric HIV/AIDS Cohort Study
REACH	Reaching for Excellence in Adolescent Care and Health (Study of AMHARN)
RFA	Request for Applications
SHIV	Simian-Human Immunodeficiency Virus
SMART	Surveillance Monitoring for Antiretroviral Treatment Toxicities (Study of PHACS)
TB	Tuberculosis
WHO	World Health Organization
WIHS	Women's Interagency HIV Study
WITS	Women and Infants Transmission Study
ZDV	Zidovudine
ZEBS	Zambian Exclusive Breastfeeding Study