Elizabeth Glaser Pediatric AIDS Foundation

Until no child has AIDS.

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Director
National Institute of Allergy and Infectious Diseases
Office of Communications and Government Relations
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Diana Bianchi, MD
Director
National Institute of Child Health and Development
National Institutes of Health
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Dear Dr. Fauci and Dr. Bianchi,

On behalf of the Elizabeth Glaser Pediatric AIDS Foundation, I am writing to urge that NIAID and NICHD maintain a clinical trial network dedicated to addressing the unique research needs of pediatric, adolescent and maternal HIV-affected populations during the upcoming re-competition and reorganization of the NIH HIV/AIDS clinical trial networks.

There remain critical high-priority scientific questions in pediatric and maternal HIV infection that cross all of the scientific areas that have been deemed a priority by NIH – HIV prevention, therapeutics, and vaccine. The Foundation is deeply concerned that the proposed model of separate therapeutic, prevention and vaccine networks, with pediatric and maternal research integrated into each of these networks alongside non-pregnant adults, will significantly diminish the ability to ensure coordination of the global pediatric/obstetric HIV scientific research agenda, will weaken the ability of the pediatric/obstetric HIV experts to conduct the research needed for the next decade, and dilute the contribution of pediatric and obstetric expertise within each of these separate areas.

Without the IMPAACT network and its predecessors, research on and implementation of prevention and treatment interventions for pediatric and maternal HIV and AIDS would be years behind where it is today. As we have seen in previous network structures, without a dedicated focus on maternal and pediatric research, women, infants and children are often overlooked in the development of research agendas and allocation of research resources.

Children and pregnant women are different from non-pregnant adults in ways that require special pediatric, obstetric and maternal-fetal medicine expertise. For example, there are significant differences from non-pregnant adults in the pharmacokinetics, pharmacodynamics and safety issues related to drugs in children and pregnant women, and penetration of drugs into breast milk is an important concern in breastfeeding infants. The developing immune system in infants and children and the immunologic changes during pregnancy need to be considered when developing biomedical interventions, as these differences may result in different responses or safety profiles than observed in non-pregnant adults. Additionally, the developing central nervous system in children is a specific target of HIV infection and requires distinct expertise in pediatrics to evaluate the effects of HIV and its treatment. The manifestations of HIV-related co-infections such as tuberculosis differ between children and adults. Even the microbiome during pregnancy and breastfeeding and within infants and children is different than that in non-pregnant individuals.

It has been noted that the success in prevention of mother-to-child transmission, largely due to interventions developed by the IMPAACT Network and its predecessor the Pediatric AIDS Clinical Trials Group, has resulted in a welcome significant decline in new pediatric HIV infections. However, this success does not mean that all the pressing questions in this area have been answered. Incident infection in women during pregnancy and breastfeeding in sub-Saharan Africa is as high as 3-5%. One and a half million HIV-positive women continue to become pregnant each year and often do not present for care until the third trimester of pregnancy, diminishing the effectiveness of current antiretroviral interventions. The reappearance of active virus replication during the postpartum period in women despite initiation of antiretroviral therapy during pregnancy is not uncommon and there has been a recently observed alarming increase in antiretroviral drug resistance among newly infected infants. The optimal intervention for infants at high risk of HIV infection due to no or short duration maternal antiretroviral therapy, acute infection, persistent detectable viral load, or drug resistance is not defined. Even among women receiving optimal therapy, residual HIV transmission occurs, with rates ranging from 1.5% in the PROMISE clinical trial setting to 4-5% in on-the-ground programs. Even in the best-case scenario of complete implementation of treatment in all HIV-positive pregnant women, this results in 23,000 to 60,000 new pediatric infections annually. In fact, even the ambitious Start Free, Stay Free, AIDS Free targets for the elimination of pediatric AIDS by 2020 still estimates 20,000 new pediatric HIV infections annually. These children will need to be treated.

With 2.1 million children living with HIV worldwide, more than 400 new pediatric infections every day, and tens of thousands of children becoming infected annually even with optimal program implementation, there is still more work that needs to be done in providing better first, second and third line drug options for those children living with HIV, approved and formulated all the way down to the neonatal period (including preterm and low birth weight infants). The limited availability of antiretroviral drugs also continues to limit the pediatric cure agenda. In an era of universal treatment, all pregnant and breastfeeding women require treatment – and it is critical to have studies to define optimal dosing of new drugs and safety of drug regimens in these populations and their infants.

The IMPAACT Network, with its pediatric, neonatal and obstetric pharmacology expertise, has successfully assisted with the approval of new drugs for use in pediatrics, helping to save the lives of HIV-positive children. For example, the P1093 study has enabled approval of dolutegravir in children to age 6 years, and is currently studying the drug down to age 4 weeks. Similarly, IMPAACT P1026s study was critical in demonstrating significantly diminished (>50%) elvitegravir/cobicistat drug levels in the second and third trimester of pregnancy, with recurrent active virus in about 25% of women.

If a preventive vaccine for HIV is developed, the first population that should be vaccinated is children prior to their sexual debut – allowing a new generation to live HIV-free, providing a lifetime of protection. Some of the most promising cure research is in pediatrics given their naïve immune systems, as seen through the most recent example of the South African child whose HIV has remained in remission for years without drugs after very early treatment initiation soon after birth. Immunotherapeutic approaches (monoclonal antibodies, therapeutic HIV vaccines) for cure/remission in children may be particularly important to study and could yield different results than observed in adults. Without ensuring a coordinated and strong pediatric research agenda these populations will not be prioritized in cure and vaccine research and may not benefit from progress made. How the NIH chooses to restructure the HIV/AIDS clinical trials networks will shape the course of pediatric HIV and AIDS prevention and treatment for years to come.

A pediatric/obstetric-focused research agenda facilitates the development and testing of new drugs, treatment modalities, and prevention interventions in pregnant women, infants and adolescents, which pharmaceutical companies may otherwise avoid conducting. The clinical trials networks provide crucial support to maintain the specialized clinical, laboratory, and regulatory infrastructure needed to conduct vital, high quality, scientifically sound research in children and pregnant and breastfeeding women, particularly in countries with limited resources and health infrastructures. Furthermore, diffusing the pediatric and maternal research expertise across the proposed new network structure (therapeutics, vaccines, and prevention) would weaken each network's capacity to develop and implement the needed pediatric and maternal research agenda. Finally, it is often the case in pediatrics that therapeutics, vaccines and prevention research are closely linked and close coordination is imperative – this would be lost should these populations be separated under individual networks.

The Foundation believes that a dedicated network of pediatric and obstetric experts, focusing on a coordinated and broad scientific agenda in HIV research in maternal, pediatric and adolescent populations is the most effective way to ensuring the priority research areas for these populations are addressed in a strategic and thoughtful way. In our view, eliminating a pediatric-obstetric-focused network will compromise global efforts to end pediatric AIDS once and for all through HIV prevention, treatment, and eventually cure. The specialized, collective expertise that the IMPAACT Network nurtures and coordinates will be sharply diminished if spread across the adult-focused networks, and NIH will be viewed as potentially deprioritizing the remaining critical scientific agenda among these highly vulnerable populations.

Any changes to the existing network structure must consider the expertise and attention required for pediatric and maternal research and put in place significant safeguards to ensure that pediatric research does not "fall through the cracks" in the broader HIV/AIDS research agenda. If we truly hope to eliminate pediatric HIV and AIDS in this country and around the world, we cannot allow research and innovation for maternal and pediatric populations to be diluted and to stall.

The Foundation intends to send more detailed formal comments to the Division of AIDS but wanted to weigh in with both NIAID and NICHD given your specific interest in this area.

Thank you for your time and consideration of this matter. Please reach out with any questions or if there is anything the Foundation or I can assist with during this process.

Sincerely,

Charles Lyons
President and CEO

CC: Dr. Carl Dieffenbach, Director, Division of AIDS
Dr. Maureen Goodenow, Director, Office of AIDS Research