The NEW ENGLAND JOURNAL of MEDICINE

Perspective

AUGUST 18, 2011

GLOBAL HEALTH

Pediatric HIV — A Neglected Disease?

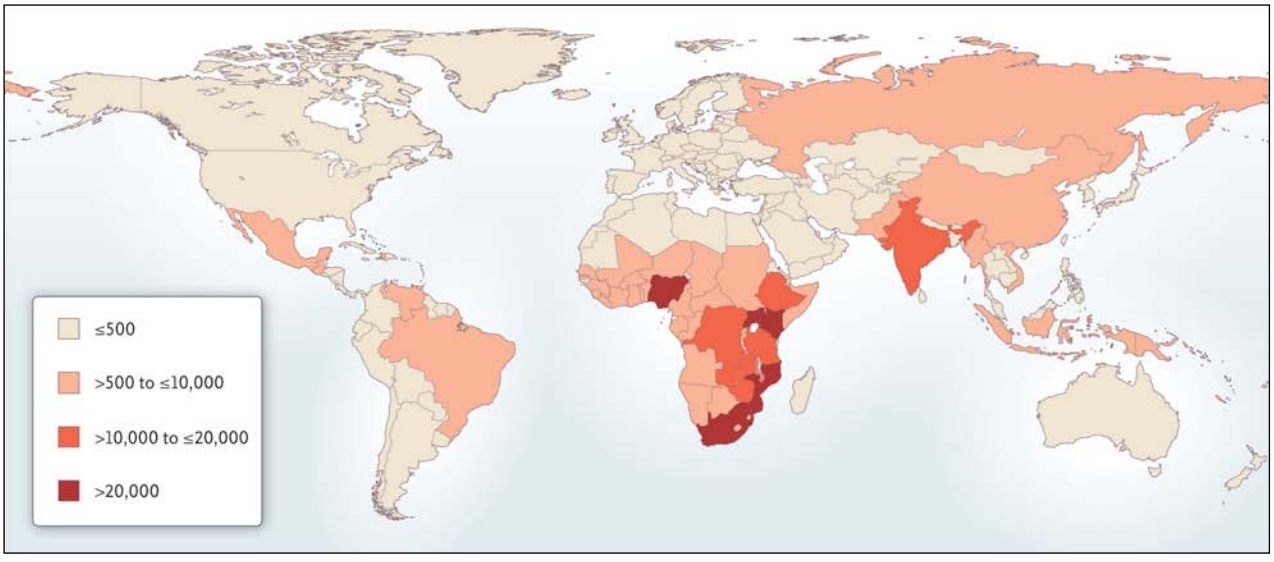
Marc Lallemant, M.D., Shing Chang, Ph.D., Rachel Cohen, M.P.P., and Bernard Pecoul, M.D., M.P.H.

The results of the HIV Prevention Trials Network 052 (ClinicalTrials.gov number, NCT00074581) study were released this past May, 30 years after the first publication about U.S. cases of what would come to be called AIDS. The new study's stunning results — earlier treatment of human immunodeficiency virus (HIV) infection leads to a 96% reduction in the risk of HIV transmission within sero-discordant couples — will influence guidelines in the direction of even earlier initiation of antiretroviral therapy.[1] The notions of "test and treat" and "treatment as prevention" come as no surprise to anyone who has been involved in the fields of prevention of mother-to-child transmission of HIV and pediatric HIV care.

Fifteen years after the first study demonstrated the remarkable efficacy of zidovudine in reducing mother-to-child transmission of HIV, perinatal HIV has been virtually eliminated in high-income countries. In the countries most affected by HIV, however, particularly those in sub-Saharan Africa and Asia, prevention coverage remains appalling. The failure to implement prevention programs for mother-to-child transmission on an appropriate scale has resulted in hundreds of thousands of preventable HIV infections among newborns. Each day, more than 1000 children are newly infected with HIV (see map), and an alarming 700 die from AIDS-related complications.

In pediatric HIV care, "test and treat" strategies have been on the research and implementation agenda for more than 10 years. The Children with HIV Early Antiretroviral Therapy (CHER) trial in South Africa, which compared immediate treatment of HIV-infected newborns with treatment initiated on the basis of immunologic decline or clinical symptoms, demonstrated the survival benefit of immediate initiation of antiretroviral therapy, which reduced early mortality by 76%.[2] Yet as of the end of 2010, less than one third of children who needed antiretroviral therapy were receiving it. Without treatment, one third of children born with HIV die before their first birthday; 50% die before they turn two.

There are many reasons for this unacceptable state of affairs. One of the most glaring — and yet often overlooked — is that treatment options for children, particularly the youngest and most vulnerable, are insufficient. Pharmaceutical companies have invested little in ensuring the safety and efficacy of antiretro-



Number of New HIV Infections among Children, 2009.
Data are from UNAIDS.

viral use in children or in developing child-appropriate drug formulations. Children with HIV–AIDS in low- or middle-income countries are a largely neglected population.

Vertical transmission of HIV is preventable, and in wealthy countries effective interventions for preventing mother-to-child transmission have virtually eliminated HIV infections in newborns. In low- and middle-income countries, however, there are numerous barriers to prevention: antenatal care attendance is low, particularly in rural areas; too few pregnant women have access to HIV testing; access to optimal antiretroviral prophylaxis or therapy is insufficient; and alternatives to breast-feeding are uncommon. In its 2010 progress report, the World Health Organization (WHO) indicated that only one quarter of pregnant women had received an HIV test, and among those identified as HIV-infected, only half received any antiretroviral prophylaxis during pregnancy or at delivery.

Diagnosing HIV infection in infants is also a major challenge in resource-limited settings. WHO guidelines recommend HIV testing of exposed infants as part of routine care, as early as 6 weeks of age. But in most HIV-exposed children in resource-limited settings, the infection can be diagnosed with serologic testing only after 15 to 18 months of age, when maternal antibodies have disappeared from the child's blood. Waiting until a child is 18 months old means that as many as half of infected children will die before their HIV status is even known.

In high-income countries, kits for HIV DNA or RNA polymerase chain reaction (PCR), considered to be the gold standard for diagnosis of HIV in infants, are commonly used. In resource-poor areas of Africa and Asia, their availability is largely limited to clinical research settings because of prohibitive costs and the need for laboratory infrastructure and trained personnel.

Researchers have developed alternative virologic tests using real-time PCR and dried blood spots on filter paper for sample collection, which can be transported from remote areas to central laboratories. Early diagnosis of HIV in infants is therefore within reach, although it has yet to be widely implemented. Still, better-adapted diagnostic tests that can be used at the point of care are needed to ensure that diagnosis is possible in early infancy even in the most remote and rural settings.

The WHO recommends immediate antiretroviral therapy for all HIV-infected children less than 2 years of age.[3] But the safety and appropriate dosing of many of the key antiretroviral agents used in adults have not yet been established in children, particularly in younger age groups, and appropriate formulations simply do not exist for children.

The most commonly used regimen in children in resource-limited settings is a fixed-dose combination of stavudine, lamivudine, and nevirapine. But stavudine is no longer preferred be-

cause of toxicity concerns, and nevirapine is not recommended for children who have been exposed to nevirapine for the prevention of mother-to-child transmission, since the virus may have developed resistance.

The results of two recent studies[4,5] generated strong evidence that protease-inhibitor–based therapies — such as zidovudine, lamivudine, and lopinavir boosted with ritonavir — should be used extensively in HIV-infected infants. However, this combination of three separate liquid formulations is impractical for caregivers, is unpalatable for children, requires refrigeration, and owing to drug interactions, is difficult to manage in cases of coinfection with tuberculosis. Improved first-line therapies for children are urgently needed.

In 2010, our organization, the Drugs for Neglected Diseases initiative (DNDi), a not-for-profit research and development organization that develops new drugs for neglected diseases such as human African trypanosomiasis, visceral leishmaniasis, Chagas' disease, and malaria, was called on by various organizations, including Doctors Without Borders (Médecins sans Frontières) and the international drug-purchase organization UNITAID, to apply its expertise to the development of pediatric HIV drugs. In consultation with experts from countries where HIV is endemic (including South Africa, Ivory Coast, and Thailand), major research institutions, and international and nongovernmental organizations, DNDi developed "ideal" and "acceptable" specifications for desired formulations or combinations of pediatric antiretroviral drugs and identified priorities for acceleration of clinical studies in infants.

There was consensus around the need to develop an improved first-line regimen for infants, irrespective of prior exposure to antiretrovirals. Ideally, this new first-line pediatric therapy needs to be easy to administer and better tolerated by children than current drugs. The ideal formulation would be palatable, heat-stable, easily dispersible, and administered once daily or less. It must also carry minimal risk for the development of resistance and be suitable for infants and young children (<2 months to 3 years of age), with minimum requirements for weight adjustments. Finally, any new drug must be compatible with tuberculosis drugs and, especially, affordable.

When it comes to research and development, it is difficult to see HIV therapeutics as a neglected field. Since HIV was first discovered, more than 20 antiretroviral drugs and several additional antiretroviral combinations have been approved for the treatment of HIV, and today there remains a robust pipeline of new products in development.

Yet there is no such pipeline for pediatric HIV. Because it has been virtually eliminated in wealthy countries, pharmaceutical companies have little incentive to develop child-appropriate formulations. Children with HIV–AIDS in low- and middle-income countries are not considered in the HIV research and development agenda because they are poor and voiceless and do not represent a lucrative market in the traditional sense. Although every effort should certainly be made to eliminate new HIV infections in children in low- and middle-income countries, we must not forget the millions of children already living with HIV–AIDS — and those who will become infected in the coming years — who urgently need improved, affordable, and appropriate treatment.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

From the Drugs for Neglected Diseases initiative, Geneva (M.L., S.C., B.P.) and New York (R.C.); and the Institut de Recherche pour le Développement Programs for HIV Prevention and Treatment, Chiang Mai, Thailand (M.L.).

1. Treating HIV-infected people with antiretrovirals protects partners from infection: findings result from NIH-funded international study. Bethesda, MD: National Institute of Allergy and Infectious Disease, May 12, 2011. (http://www.niaid.nih.gov/news/newsreleases/2011/Pages/HPTN052.aspx.)

2. Violari A, Cotton MF, Gibb DM, et al. Early antiretroviral therapy and mortality among HIV-infected infants. N Engl J Med 2008;359:2233-44.

3. Antiretroviral therapy of HIV infection in infants and children: towards universal access: recommendations for a public health approach — 2010 revision. Geneva: World Health Organization, 2010.

4. Palumbo P, Violari A, Lindsey J, et al. NVP-vs LPV/r-basedART among HIV+ infants in resource-limited settings: the IMPAACT P1060 Trial. Presented at the 18th Conference on Retroviruses and Opportunistic Infections, Boston, February 27–March 2, 2011. abstract.

5. Coovadia A, Abrams EJ, Stehlau R, et al. Reuse of nevirapine in exposed HIV-infected children after protease inhibitor-based viral suppression: a randomized controlled trial. JAMA 2010;304:1082-90.