Taking stock: triumphs and challenges in the field of pediatric HIV infection

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'Unprecedented efforts in the laboratory and in the field have elucidated our understanding of the etiology and pathogenesis of this disease and identified highly successful ways to both prevent and treat pediatric HIV infection.'

Over the last two decades, enormous advances have been made in the scientific arena of pediatric HIV infection. Since the first reports of children with a fatal unexplained immunodeficiency in the early 1980s, unprecedented efforts in the laboratory and in the field have elucidated our understanding of the etiology and pathogenesis of this disease and identified highly successful ways to both prevent and treat pediatric HIV infection [1,2]. A woman with HIV can now decide to have a child and, for the most part assure, through a variety of preventive measures, that her baby will not acquire HIV. For children living with HIV infection, what was once considered a rapidly fatal disease of childhood has been transformed into a chronic disease with excellent prospects for survival into adulthood.

A vast body of research has been accumulated in the area of mother-to-child transmission (MTCT). We increasingly understand the mechanisms of transmission and have identified the critical factors that enhance or diminish the risks of MTCT. Most importantly, we know that effectively treating maternal HIV disease, providing antiretroviral prophylaxis to the baby, minimizing the risks of delivery (particularly with elective cesarean section) and providing replacement feeds in lieu of breast feeding can reduce the likelihood of transmission to 1–2% [3,4,101]. In resource-rich settings and increasingly in moderately resourced countries, such as Brazil and Thailand, the scientific gains and advances of the last decades have had an unusually positive impact on health policy and financing. In general, HIV testing has become a routine part of antenatal care, antiretroviral medications are available for treatment and prophylaxis of the pregnant woman and her newborn; cesarean section is part of the prevention armamentarium and formula feeding is both publicly financed and safe. In this context, each new pediatric HIV infection is considered a missed opportunity for prevention. At the same time, research efforts are exploring issues relevant to populations of women and families where antiretroviral treatment is widely available and MTCT rates are low, such as long-term consequences to the mother and child of antiretroviral use during pregnancy, optimal prevention for women with multidrug-resistant HIV, pharmacologic properties of antiretroviral medications during pregnancy and treatment of coinfections such as hepatitis B and C.

Parallel advances have been made for pediatric HIV disease. As investigators described the pathogenesis, natural history and correlates of pediatric disease progression, others defined efficacious ways to diagnose HIV infection in infants, prevent opportunistic infections and successfully treat HIV-infected infants, children and adolescents. Many lessons, particularly regarding antiretroviral treatment, have been gleaned from studies in adults. However, the changes over time that are the hallmark of the passage from infancy through adolescence – physical, physiologic, neurological and emotional growth and development – have provided particular scientific challenges and required special study in children. For example, primary infection of infants occurs against the backdrop of a naive, developing immune system, resulting in high levels of viremia during the first months of life and subsequent high rates of rapid disease progression [5,6]. Defining optimal timing and regimens for initiating treatment of these vulnerable babies remains an area of active investigation. Similarly, proper antiretroviral dosing across the pediatric age spectrum has not been fully determined for many medications, whether old or new. Unlike the 'one-size-fits-all' approach that generally appears suitable for adults, dosing in children varies with age secondary to changes in size, body composition and hepatic and renal function. Unfortunately, new agents are often widely used for pediatric treatment before proper dosing can be fully defined [7,8]. In addition, both short- and

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long-term toxicities associated with antiretroviral medications are still uncertain for a variety of drugs currently in use.

Despite these and other equally pressing unanswered questions, children living with HIV infection in well-resourced settings are doing well, the beneficiaries of two decades of highly successful scientific inquiry, the accumulated expertise of pediatric HIV clinicians and good access to the required therapies. A recent analysis of the cohort of children followed in the UK and Ireland reported that 40% of the 1441 children in care were aged 10 years or older at their most recent visit and that antiretroviral treatment continues to be associated with improved immune function and low rates of hospitalization and death [9]. In New York City, NY, USA, (one of the epicenters of the pediatric HIV epidemic in the USA), of 2474 children diagnosed with HIV infection before the age of 13 years and believed to have been infected perinatally, 62% are aged 13 years or older [102]. This includes more than 300 young adults now in their twenties. Overall, only 17 deaths were reported in 2005.

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Programs caring for children with perinatal HIV infection throughout the USA and Europe are examining optimal ways to transition aging adolescents to adult-care settings. At the same time, clinicians, HIV-infected youth and their families are grappling with the challenges of living with a chronic, stigmatized disease that requires good adherence to often-complex medication regimens. High rates of poverty, social disenfranchisement, family instability, mental illness and behavioral problems, as well as the stigma of HIV infection juxtaposed against the natural inclination of youth to want to be like their peers, have contributed to inadequate adherence to treatment and subsequent therapeutic failure. The availability of several new classes of antiretroviral agents for the treatment of multidrug-resistant virus should further extend longevity for many children and youths who have exhausted currently available drugs. However, there are few models of successful treatment of chronic diseases during adolescence to provide insight into the best ways to support these youths to take their drugs and remain in regular care as they prepare for the transition to adulthood.

Given this remarkable array of scientific accomplishments, one might wonder why each day more than 1400 children acquire HIV infection, 90% via MTCT. In 2006, it was estimated that 530,000 children were newly infected with HIV and 380,000 pediatric deaths worldwide were attributed to HIV/AIDS. More than 2.3 million children are living with this infection worldwide, and of the 780,000 believed to be in urgent need of antiretroviral treatment, it is estimated that only 11% are receiving therapy [103]. Few of the benefits of the past two decades of successful scientific inquiry and implementation experience have been extended to high-burden, low-resource settings where the vast majority of HIV-infected women and children live.

Multiple factors have contributed to this situation, but none more outstanding than the failure to implement adequate prevention of mother to child transmission (PMTCT) programs in high HIV prevalence settings. In 1999, the results of the HIVNET-012 trial, which demonstrated that a single dose of nevirapine (sd-NVP) to a laboring woman and to her newborn child could reduce the rate of early MTCT by 40%, galvanized the establishment of PMTCT programs throughout the world [10]. Coupled with the availability of rapid HIV-antibody testing, the sd-NVP regimen was viewed as a safe, feasible and affordable means to reduce MTCT in settings with limited healthcare infrastructure, late attendance in antenatal care and few dedicated financial resources. In fact, many programs have implemented this regimen, and many pediatric infections have been averted over the last decade [11]. However, only 10% of pregnant women worldwide were tested for HIV in 2005, and only 11% of those estimated to be infected received any antiretroviral therapy for PMTCT [103]. Even fewer HIV-exposed children, 8%, received antiretroviral prophylaxis.

A multitude of reasons can be offered to explain the chasm between what we know and what we do to prevent pediatric infections. First, it appears that the initial enthusiasm for PMTCT implementation has been eclipsed by the global scale-up of HIV care and treatment services. The unprecedented availability of billions of dollars for antiretroviral treatment in low-resource settings, particularly sub-Saharan

Africa, has resulted in a rapid and highly successful rollout of treatment. By the end of 2006, more than 2 million individuals living in low- and middle-income countries had initiated antiretroviral therapy [104]. At the same time, however, the emphasis on treatment has overshadowed efforts to prevent pediatric infections. PMTCT has remained a discrete program and has not been effectively integrated into the scale-up process in the field, in local health ministries, or in the eyes of donors. In this context, programs have not expanded to reach the large numbers of women in need of services, particularly women in rural communities and those who do not routinely access health services during pregnancy.

PMTCT programming has also not evolved to reflect a more nuanced, evidence-based approach that takes into consideration the scientific knowledge accumulated over the past decade. Multiple studies have demonstrated that maternal health status during pregnancy and lactation is a major determinant of the health outcome of her child. Women with advanced HIV disease are more likely to transmit infection to their infants, and those babies lucky enough to escape perinatally acquired infection appear to be at increased risk of early morbidity and mortality compared with infants born to healthier mothers [6,12–15]. Despite this knowledge, programs continue to rely on sd-NVP as the mainstay for perinatal prevention. There has been a general reluctance to recognize pregnancy – a time when most women seek healthcare – as an opportune time to evaluate the health status of HIV-infected women, identify those with advanced disease and initiate more complex antiretroviral regimens to prevent maternal disease progression as well as reduce the risk of infant infection [16]. In high-resource settings, the success of PMTCT programs has relied heavily on the understanding that pregnancy provides a unique entry point for the woman and her family into chronic HIV care and treatment services, with emphasis on maximizing maternal health status during gestation, and continuing care and long-term follow-up of the mother and child. These principles have been noticeably absent in the philosophy and implementation of PMTCT programs in settings where large numbers of HIV-infected women reside.

Similar to the contradictions we see in the implementation of PMTCT programs, few of the scientific advances and little of the accumulated clinical and treatment expertise has reached the large number of children living with HIV in high-prevalence, poor countries. More than 1000 pediatric deaths daily are attributed to HIV infection, and despite decades of efforts to improve child health, child mortality rates are once again on the rise, particularly in the countries with the highest HIV burden. Without antiretroviral treatment, it is expected that approximately 50% of children with perinatal infection will die before age 2 years [6]. And while multiple investigators have demonstrated that children in low-resource settings respond well to antiretroviral therapy, not unlike children in rich countries, most remain undiagnosed, untreated and at high risk for an early death [17–19].

Despite increasing access to antiretroviral treatment and HIV care services, children remain under-represented. While multiple barriers have been successfully overcome to initiate care for adults, several issues distinct to children have impeded efforts to scale-up pediatric services [20]. For example, pediatric formulations, particularly liquids, are generally more expensive and complex to transport and store in comparison with adult tablet formulations. Fixed-dose combination tablets of antiretroviral agents suitable for children have only recently become available. Similarly, the need to adjust medication doses by weight or body surface area at treatment initiation and regularly as the child grows and ages can be viewed as prohibitively time consuming to busy clinicians with long lines of patients waiting for care. The development of a simplified approach to determining pediatric dosing using weight bands in place of calculating precise doses at each visit should extend antiretroviral treatment to more children [103]. Another complex issue particular to children is early infant diagnosis, distinguishing the infected from the uninfected infant born to a woman with HIV. The need to use specialized virologic tests, not routinely available in low-resource settings, to diagnose infant infection has delayed treatment for many sick infants when their infection status could not be confirmed.

It seems unlikely that the achievements we have witnessed in rich countries are within easy reach for most HIV-infected children worldwide. However, even the simplest interventions are not routinely available for most HIV-exposed and infected children. Few babies born to mothers enrolled in PMTCT programs are engaged in ongoing care to monitor their health. Weight is routinely measured in child health programs, but

growth monitoring using growth charts, a highly informative tool to measure a child's health status, is rarely performed. Many children do not receive a complete set of childhood immunizations, leaving them at risk for a variety of preventable diseases. Insecticide-treated bednets are only intermittently available for families with young children and, if available, only intermittently put to use. And few children, only 4% of those in need, receive cotrimoxazole, a cheap and effective intervention that has been demonstrated to decrease morbidity and mortality for children with HIV infection [21,103]. In general, health systems where HIV-exposed and -infected children receive care appear ill-prepared to provide even the most basic interventions for these children.

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There are multiple challenges and barriers to a transformation of PMTCT and pediatric services from a model built upon an acute, episodic care approach (where the intervention is limited to a single healthcare visit) to one that requires repeated encounters with the healthcare system over time. Many of these challenges have already been met and successfully addressed in the care and treatment arena. The same ingenuity, enthusiasm and commitment that have resulted in the initiation of antiretroviral treatment for hundreds of thousands of individuals throughout the world need to be applied more broadly to address the needs of pregnant women and their children. While many important scientific questions still require study, the application of what we already know is likely to spare the lives of many women and children.

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