EDITORIAL

DIAGNOSIS OF PAEDIATRIC HIV/AIDS

The human immunodeficiency virus (HIV) pandemic in sub-Saharan Africa continues to disproportionately affect women. Women comprise 55% of the HIV-infected population in sub-Saharan Africa; twelve to thirteen African women are currently infected for every ten African men(1). Because most cases of paediatric HIV-infection are the result of mother-to-child-transmission, HIV prevalence among children may also be on the rise. The rate of HIV transmission from mother to infant is estimated at 14-42% in the absence of antiretrovirals(2). Over two-thirds of the nearly 600,000 HIV-infected infants born each year reside in sub-Saharan Africa(2). Early diagnosis of HIV infection in paediatric populations is crucial in providing preventive services, effective medical diagnosis and treatment, and improving quality of life. This editorial will discuss the challenges of diagnosing paediatric HIV and acquired immunodeficiency syndrome (AIDS) in the context of determining a pregnant woman's HIV status for prevention of mother-to-child HIV transmission (PMTCT), diagnosing HIV infection in infants less than 18 months of age, the difficulty of developing a clinical case definition to diagnose HIV-infected children, and diagnosing paediatric AIDS through clinical criteria.

How can health care providers identify children who are HIV-infected before they become symptomatic? Ideally, healthcare providers in East Africa can identify HIV- infected mothers antenatally, enroll them in programmes to receive nevirapine or zidovudine to prevent transmission, and closely follow their children after birth. Nevirapine is increasingly available in East Africa and has been proven to be a safe and relatively effective intervention to prevent mother-to-child transmission of HIV(3). These programmes vary in their overall effectiveness in part due to pregnant women choosing not to get HIV-tested. If mothers know their status, health care providers can be alerted to potential HIV-infection in their children.

Many factors influence why pregnant women remain unaware of their HIV status in the current era of increasing availability of voluntary counselling and testing and increasing accessibility to intrapartum nevirapine. Fear of stigma (perceived or real), cultural influences, the role of women in society, fear of domestic violence and other untoward repercussions, blame and shame among others, influence a woman's decision-making process regarding HIV-testing and nevirapine. By treating HIV as a "special disease," health care workers greatly influence a woman's decision as well. There is an urgent need to examine the feasibility and acceptability of routine antenatal testing for all pregnant women, as is currently the standard practice for syphilis.

Effectively implementing perinatal HIV transmission prevention interventions to the target population of pregnant women should begin with routine HIV testing of pregnant women, HIV testing during labour if necessary, and consideration of universal nevirapine for those who remain untested. Normalising HIV disease can initiate the process of destigmatisation and potentially increase the support and involvement of the woman's husband as well as her family. Primary prevention of HIV infection in children remains of utmost importance as well as the development of less expensive diagnostic tests and more accurate clinical criteria for diagnosing paediatric HIV disease and AIDS.

Unfortunately, the accuracy of inexpensive early diagnostic HIV tests suitable for field conditions in resource-poor settings is limited, particularly before the age of 18 months(4). In HIV-infected infants younger than 18 months, HIV antibodies detected are both maternal and infant in origin. In HIV-uninfected infants younger than 18 months and born to an HIV-infected mother, however, all HIV antibodies present are maternal. Therefore, testing for HIV antibodies in infants older than 18 months of age after maternal antibodies have waned, is the standard diagnostic procedure in the absence of polymerase chain reaction (PCR). PCR, an expensive and technically difficult test available only in research facilities, is the only accurate tool currently available for diagnosing HIV-infection in infants younger than 18 months(5,6). Sub-Saharan Africa and the rest of the developing world are in dire need of a simple, inexpensive, and sensitive HIV diagnostic test for infants. Definitive laboratory evidence of infection in children under 18 months generally requires positive tests for HIV DNA or RNA on two separate specimens. The US Centre for Disease Control and Prevention (CDC) and other groups are currently assessing some less expensive laboratory approaches such as a boosted p24 antigen assay.

Accurately diagnosing early, asymptomatic HIV infection in children remains of utmost importance and is impossible to do clinically. Diagnosing early HIV disease is also challenging in a paediatric population, and definitive criteria are necessary to guide prophylaxis for opportunistic infections (OIs) and use of antiretrovial drugs as their availability in sub-Saharan Africa moves closer toward reality. For the time being, HIV serology combined with clinical judgment remain the basis for diagnosing HIV disease in children under 18 months of age in Africa. Clinicians must recognise that, first, the likelihood of a severely ill, seropositive child being truly infected with HIV is high. Second, however, even in symptomatic children, positive serology will reflect the passive transfer of maternal antibodies. It is desirable in all seropositive children to repeat HIV testing after 18 months of age when maternal antibodies will have definitely disappeared; in most cases, they do so at a much younger age.

In the absence of a simple, inexpensive laboratory test to diagnose HIV-infection in children less than 18 months of age, health care providers in Africa must rely on clinical

criteria for diagnosing HIV disease and AIDS in this age group. Because the signs and symptoms of HIV disease in children usually resemble common clinical problems found in HIV-uninfected children, clinical criteria are limited in diagnosing HIV disease in children. Unfortunately, current paediatric AIDS clinical case definitions are also limited in their capacity to identify children with AIDS.

The term AIDS was introduced as a case definition for epidemiologic investigation and surveillance in the early 1980s, initially in adults(7-9) but later also in children(10,11). Because of limited laboratory facilities in Africa, clinical case definitions were proposed, also for surveillance purposes. These clinical AIDS surveillance case definitions were not designed for diagnosing HIV infection in individual patients in Africa(12), yet they are often used that way today. Using a case definition, created for surveillance purposes, for determining HIV status will result in a necessarily imperfect evaluation. Multiple evaluations of the World Health Organisation (WHO) criteria have shown a sensitivity of only 35-58%, specificity of 87-92%, and a positive predictive value of 25-74% for HIV seropositivity(13-16). Sensitivity is the probability that the case will identify a child as being HIV-infected when the child actually is infected with HIV. Specificity is the probability that the case definition will identify a child as not being HIV-infected when he child actually is not infected with HIV. Positive predictive value is the probability that a child who is identified by the screening test as HIV-infected will actually be HIV-infected. Other paediatric AIDS clinical case definitions, such as the one presented in this issue, are being proposed and evaluated. Perhaps a better term for clinical use is "HIV disease," and what is needed for clinical work, along with a simple and reliable diagnostic test, is a classification system similar to that from the CDC(11) rather than a case definition.

Even with a sensitive, specific, universally applicable clinical case definition for paediatric AIDS, prevention of progression from HIV-infection to AIDS should be the overriding goal. Waiting until the development of symptomatic, clinical disease in order to make the diagnosis is not conducive to providing quality care and prophylaxis for OIs in children. Early diagnosis of HIV infection is required for delivering quality preventive services and vigilant supportive care to children to improve their quality of life. Outpatient or asymptomatic diagnosis is preferable to diagnoses made in hospitalised children where AIDS has clearly manifested. OI prophylaxis and early treatment of OIs could then be more effectively offered based on knowledge of a child's infection status.

As we struggle with diagnosing HIV infection, HIV disease, and AIDS in children, we must remember this clinical picture represents five separate levels of failure of prevention: (i) failure to prevent HIV infection in women of reproductive age; (ii) failure to have adequate HIV counseling and testing services for pregnant women; (iii) failure to prevent HIV transmission from mother-to-child; (iv) failure to develop an inexpensive laboratory alternative to PCR for diagnosing early HIV infection in children younger than 18 months and, (v) failure to prevent OIs in HIV-infected children. It is appropriate that much attention and effort is currently being concentrated on prevention of mother-to-child HIV transmission in the African region. It is equally important, however, that the same attention be given to these other essential prevention activities. OI prophylaxis and appropriate HIV/AIDS care have been relatively neglected in Africa, and paediatricians as well as adult physicians must play their roles in striving to optimise care in resource-limited settings.

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