

Providing ART to Infants and Children

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The explosive spread of HIV/AIDS in Eurasia has led to increased numbers of people suffering from the disease, including women and children. UNAIDS estimates indicate that HIV-infected individuals in this region numbered 1.8 million by the end of 2003. Newborns are mainly infected vertically, with the infant contracting the virus in utero, during labor or delivery, or through breast milk. When steps are not taken to prevent mother-to-child transmission (MTCT) of HIV, there is a 20-45 percent risk that the newborn will be infected, depending on a number of factors, including the stage of the mother's disease.

Prophylactic measures can reduce the risk of infection to 2 percent. These measures mainly come down to the use of antiretroviral (ARV) medications, planned Cesarean sections, and/or discouragement of breastfeeding. However, MTCT prophylaxis is a complex problem; solving it requires a comprehensive approach that encompasses a wide range of social and bioethical issues. This is confirmed by the following fact: 30-70 percent of HIV-infected pregnant women in the region—many of whom lead a chaotic lifestyle and are slow to seek medical assistance—use illicit injected drugs. Because it is very difficult to reach this population with preventive measures, it is logical to assume that very soon the number of HIV-infected children in Eurasia will increase and healthcare workers possessing the specialized knowledge and skills required to manage this patient group will be required.

The course of HIV infection in children differs from that seen in adults. AIDS symptoms appear in 15-20 percent of children as early as the first year of life; a marked immune deficiency develops in 30 percent by the time they reach 5-7 years of age; AIDS symptoms appear in most of the remaining children when they are 9 or 10. Symptoms are absent until adolescence only in a fairly small group of children. The rate of progression of HIV infection is related to both the child's immune status and the stage of the disease in the mother. Predicting the timing of AIDS development is of considerable practical significance. Knowing with a certain degree of probability when AIDS will threaten a child, care providers can institute treatment capable of preventing the onset of the disease.

So-called disease progression markers are used to assess prognosis. The more sensitive and specific the marker, the greater its prognostic value. The plasma CD4 lymphocyte ratio and the viral load are generally accepted, and are the best studied markers of progression of HIV infection. A meta-analysis focused on elucidating the relationship between the risk of progression of HIV infection in children in the coming 12 months and the CD4 lymphocyte ratio, viral load, and age has shown that the risk of death in children older than two years increases markedly with a CD4 lymphocyte ratio below 10 percent, and the risk of AIDS, with a CD4 lymphocyte ratio below 15 percent, while there is a relatively low and stable risk of an unfavorable outcome of HIV infection with a CD4 lymphocyte ratio greater than 25 percent. The risk of AIDS developing and death occurring is higher in children younger than two years of age with the same CD4 lymphocyte ratios. This risk is also increased with a viral load greater than 100,000 copies/mL. However, it should be noted that the prognostic value of the viral load is less than the CD4 lymphocyte ratio.

Unfortunately, determination of these markers is not available in all Eurasian countries. The use of other, so-called indirect, markers of immune deficiency is permissible in this situation. These are less specific, although their sensitivity is fairly high. Among these are the absolute lymphocyte count, as well as the presence of some syndromes and conditions, including anemia and thrombocytopenia. It has been established that HIV infection progresses more rapidly in premature infants, as well as in children whose mothers have suffered from immune deficiency during pregnancy. Accelerated disease progression has also been noted in children infected *in utero*. Moreover, the risk of progression of HIV infection rises in children who are observed to have hepatosplenomegaly and lymphadenopathy in the first months of life. Studies have not confirmed the data previously obtained on increased frequency of congenital anomalies in children born to HIV-positive women.

The clinical picture of the acute febrile stage of HIV infection in children is nonspecific, and resembles that stage in other diseases and conditions. Therefore the early diagnosis of HIV infection in infants is extremely important. It is advisable to use the



qualitative polymerase chain reaction for HIV DNA or RNA for this purpose. If this diagnostic method is not available, a definitive diagnosis can be made at 18 months of age using enzyme immunoassay for HIV antibodies. Other, less sensitive, early diagnostic methods include detection of the HIV p24 antigen and HIV reverse transcriptase. Growth and developmental retardation is one of the most important clinical manifestations of HIV infection in children. If the child is not suffering from an acute illness, has not had one recently, and is receiving satisfactory nutrition, a plateau or dip in the physical development chart (of weight and height) should alert the physician, as it may be evidence of the development of immune deficiency.

The following are the most common AIDS-indicator diseases: pneumocystis pneumonia, recurrent candidiasis, chronic diarrhea, lymphadenopathy, hepatosplenomegaly, parotitis, and dermatitis. Repeated bacterial infections, including sepsis, pneumonia, otitis, and sinusitis, caused by encapsulated bacteria and the blue pus bacillus, are also possible. Pneumocystis pneumonia occurs especially frequently in children younger than one year of age regardless of the CD4 lymphocyte count. The onset of the illness is acute; the mortality rate is high. For that reason the strategy of mandatory prophylaxis of pneumocystis pneumonia in children born to HIV-positive women up to one year of age, using trimethoprim/sulfamethoxazol, is entirely justified. Another condition—interstitial lymphocytic pneumonia—occurs in children much more often than in adults; according to some reports, up to 40 percent of HIV-positive children may experience it.

Nephropathy and cardiomyopathy also occur more frequently in children. Central nervous system impairment, manifested in retarded neuropsychological development and encephalopathy, is an important distinguishing feature of AIDS in children. Unlike adults, Kaposi's sarcoma, esophageal candidiasis, toxoplasma encephalitis, cytomegalovirus chorioretinitis, tuberculosis, and cryptococcal meningitis are rarely found in children.

Tuberculosis must be given separate consideration, however, because it is hard to diagnose in children and HIV infection complicates the effects of tuberculosis even more. As a rule, the diagnosis of tuberculosis is based on the identification of risk factors for mycobacterial infection—these include, in particular, exposure to patients with active tuberculosis—as well as on symptoms of growth and developmental retardation. The sensitivity and specificity of such diagnostic methods as the tuberculin test, microscopic examination for bacteria, and

inoculation of the sputum, are limited and range from 30-70 percent. As in the past, fluoroscopy remains an important diagnostic method for pulmonary tuberculosis in children. As many as 50 percent of children infected with tuberculosis mycobacteria in infancy become ill with the disease within a year. Therefore, all children exposed to patients with active forms of tuberculosis should undergo prophylaxis with isoniazid.

The past seven to eight years have been marked by a significant decline in morbidity and mortality among HIV-positive children in economically developed countries. In many respects this has occurred thanks to the appearance of new ARVs. The same drugs prescribed for adults are used for children. At the same time, small children cannot always take tablets or capsules and not all drugs are supplied in syrup and other pharmaceutical forms for children. Another difficulty of providing antiretroviral therapy (ART) to children is the need to recalculate drug dosages in keeping with the child's growth and development. However, compliance with the ART regimen has the most serious impact on treatment success. It must be borne in mind that small children cannot take tablets by themselves and are entirely dependent on those who take care of and raise them. Adolescents represent another difficult category of patient because their behavior typically has an adverse effect on compliance to treatment regimens. For these reasons, problems associated with ART compliance require special attention.

The indications for initiation of ART in children are a stumbling block in discussions among experts. At this point there is not enough information on the effectiveness of therapy in relation to when to start treatment. Questions and considerations that must be taken into account before treatment begins can be provisionally divided into two categories:

1. Simple questions and considerations

Is the diagnosis of HIV infection reliable?

Do the clinical manifestations of HIV infection correspond to category C or stage 3 according to WHO classifications?

Is the patient prepared to take the drugs? (In most cases, the initiation of ART may be delayed for some time.)

2. Complex questions and considerations

Does the expected benefit from ART justify the risk of side effects associated with it?

As many as 40-50 percent of vertically infected children survive up to 8-10 years without ART.

The treatment methods currently available do not make it possible to cure HIV infection completely.

Protracted compliance with the drug regimen is the main obstacle to achieving a positive response.

WHO has recently published recommendations on ART for countries with limited financial resources. Various approaches to the management of children born to HIV-positive women and for children who contracted HIV through other transmission routes are reflected in these recommendations. They also contain information on choice of ART regimens. Several regimens consisting of three ARV drugs are specified, the selection of which depends on the age of the child and his or her tolerance to the treatment.

The most widely studied ART regimens in children at the present time are based on protease inhibitors. They make it possible to achieve a fairly pronounced effect, in particular to restore the state of the immune system and to suppress viral replication in the blood. However, the use of these agents has a number of shortcomings. The use of protease inhibitors may sometimes cause serious metabolic side effects; moreover—and this is very important—their pharmaceutical forms for children are not sufficiently perfected, have an unpleasant taste, and require a large number of tablets or a large volume of syrup be taken at each required dosage time.

Another type of ART regimen is based on non-nucleoside reverse transcriptase inhibitors. These make it possible to reduce the viral load to an undetectable level in 60 percent of children, but experience with their use in pediatrics is still limited. The main side effects of these regimens are rash and hepatotoxicity. Finally, ART regimens of three nucleoside reverse transcriptase inhibitors are quite well tolerated in children. At the same time, experience with these regimens in adults has demonstrated that when there is a high viral load initially they are less effective than other ART regimens. In this connection, the use of these regimens has been reserved for children with concomitant tuberculosis infection, or those who cannot tolerate or take ARV drugs of other groups.

Monitoring the treatment of HIV infection in children is based on an assessment of the aggregate of clinical, laboratory, and social indicators. Those falling in the first category are primarily recovery of appetite, weight gain, and the leveling of the weight and height curves on the percentile charts of physical development. A rise in the CD4 lymphocyte ratio, as well as a

drop in the viral load to an undetectable level, are the most important of the laboratory indices. Rates of compliance with the therapy regimen and how strictly parents or others caring for the child carry out a physician's recommendations are the primary social indicators.

It has not been possible in West European or North American countries to suppress HIV replication and reduce the viral load to an undetectable level in many children; at the same time, however, ART maintains immunological efficiency and clinical progression of the disease is not seen. Sufficient data have not yet been collected at the present stage to come to definitive conclusions as to when therapy should be changed, how to choose the best possible regimen, or the role that tests for HIV drug resistance should play. Many HIV experts prefer not to change virologically ineffective ART—defined as a viral load that has not gone below 50 copies/mL or increased one log above the lowest value reached—in children who are in good clinical condition and who have a stable CD4 count. Obviously, this approach involves the risk that the number of resistance-related mutations found in children will increase over time.

The possibility of modifying an ART regimen is often determined by the availability of new ARVs. A new approach to ART for children will probably evolve over the next several years due to the appearance of drug-resistant strains of HIV, drug side effects, and antecedent ART, as well as the appearance of new ARV drug types or groups. Salvage therapy should only be used in cases of virological, immunological, and clinical failures. In other words, the following are indications for switching to salvage therapy: the development of new AIDS-indicator conditions, progressive weight loss, growth retardation, and a sharp fall in CD4 lymphocyte ratio, combined with an increase in viral load, in the absence of acute illnesses.

In conclusion, it is important to note that in the context of the growing number of HIV-infected children in the countries of Eurasia, it is necessary to work out strategic approaches to the treatment and management of such children. The countries of this region must develop and adopt recommendations for the management of children born to HIV-infected women and for the early diagnosis of HIV infection, as well as develop an approach to the prescription of ARV drugs in relation to the stages of the disease and the age of the child. It is important in limited-resource countries to increase the access of children and adults to ART in equal measure. ■