CHILDHOOD HIV-1 INFECTION IN CENTRAL AFRICA

Introduction

Heterosexual contacts are the major mode for the spreading of the human immunodeficiency virus type 1 (HIV-1) infection in sub-Saharan Africa and in the Caribbean (Piot et al., 1988). In these regions not only the male-to-female ratio among adult acquired immunodeficiency syndrome (AIDS) patients approaches unity, but also the prevalence of HIV-1 infection is often high in the urban general populations.

Indeed, in large cities of central and east Africa, the prevalence of HIV-1 infection in women of childbearing age attending prenatal clinics may reach 30% (Rwandan HIV Seroprevalence Study Group, 1989; Allen et al., 1991). Consequently, the number of children exposed to HIV-1 is much higher in some African countries than in the Western World and paediatric AIDS may make up as much as 15 to 20% of AIDS cases (Lepage and Hitimana, 1991). As an example, it has been estimated that the total numbers of infants infected by HIV-1 during the year 1990 in Kigali (400,000 inhabitants) and in the United States (250 million inhabitants) are very similar (Van de Perre et al., 1992). The WHO estimates that at least 3 million women and children will be killed by the AIDS virus in the 1990s and that over 80% of all children infected perinatally with HIV-1 during the next decade will be born in Africa. In addition, more than a million non-infected children will be orphaned because of HIV-1 infection in their parents (Chin, 1990).

1. Transmission

1.1. *Mother-to-child transmission of HIV*

In Africa as in other parts of the world, HIV is principally transmitted to children by perinatal exposure (Ryder and Temmerman, 1991). Mother-to-child transmission of HIV may occur during pregnancy, at delivery or in the post-partum period by breast-feeding (Van de Perre et al., 1992). However, the proportion of infants who become infected *in utero*, during delivery or postnatally is not well established. Maternal factors have been identified as determinants for mother-to-child transmission of HIV-1: breast-feeding (see below), impaired maternal immunological status (European Collaborative Study, 1992; Lepage et al., 1993) and chorioamnionitis (St Louis et al., 1993). Other possible maternal risk factors for mother-to-child transmission include HIV seroconversion during pregnancy, mode of delivery and prolonged labour (Dabis et al., 1993). The role of other factors such as viral characteristics and protective maternal antibodies is not yet clear.

In recent published prospective cohort studies from Africa, the rate of mother-to-child transmission of HIV-1 was estimated to vary from 25% in Kigali to 48% in Brazzaville (Hira et al., 1989; Lallemant et al., 1989; Ryder et al., 1989; Lepage et al., 1993). By contrast, most perinatal studies carried out in Europe have found much lower transmission rates (Newell et al., 1991). For instance, the mother-to-child transmission rate was 14.4% in the ECS (European Collaborative Study, 1992). When using a common methodology for the calculation of the perinatal transmission of HIV-1, the rate of transmission was still lower in Europe than in Africa: 12% in the ECS versus 24% in Uganda and 25% in Rwanda (Dabis et al., 1993).

The reasons for the discrepancy in transmission rates between the African and European studies are not completely understood but might involve the following:

- first, it is conceivable that immunological impairment is more prevalent among HIV-1-infected women in Africa due to their nutritional status and to the high prevalence of infectious diseases and that they might therefore transmit HIV more efficiently to their offspring;
- secondly, breast-feeding is universal and prolonged in Africa whereas only 5% of women from the ECS are breast-feeding their children;
- thirdly, chorioamnionitis might also be more frequent in Africa.

In contrast to HIV-1, the mother-to-child transmission of HIV-2 appears to be rare (Andreasson et al., 1993).

1.2. *Postnatal transmission of HIV-1 by breast-feeding*

1.2.1. *Risk of transmission of HIV-1 attributable to breast-feeding*

Numerous case-reports strongly suggesting transmission of HIV-1 by breast-feeding have been published (Ziegler et al., 1987; Lepage et al., 1987; Van de Perre et al., 1992). However, these case-reports do not give any information on the rate of postnatal transmission. In Kigali, Van de Perre et al.,

(1991) demonstrated that breast milk may be an efficient channel to transmit the HIV-1 virus from recently infected mothers to their infant.

When trying to measure the additional risk of mother-to-child transmission of HIV-1 which is attributable to breast-feeding, one should clearly distinguish between two very different situations:

- the risk for the child of mothers who acquire HIV-1 infection during the lactation period;
- and the risk for the child of mothers with a stable HIV infection acquired during or before pregnancy (Van de Perre et al., 1992a).

One of the first cohort studies appraising the risk of postnatal transmission of HIV from women who acquired HIV-1 infection during the breast-feeding period was performed in Kigali, Rwanda, from 1988 to 1991 (Van de Perre et al., 1991). Out of 9 women seroconverting for HIV-1 after the first trimester postpartum, 4 transmitted the virus to their child within a three-month period. All 4 children had repeated negative serological and Polymerase Chain Reaction (PCR) tests before seroconverting, confirming the postnatal acquisition of the infection. At least 4 prospective studies of the same type have been performed so far. A meta analysis, including the results of these five studies, gave an estimated rate of transmission of 26 % (at the 95% Confidence Interval, it means from 13 to 39%) in these circumstances (Dunn et al., 1992). This dramatically high rate of transmission has to be linked with the high viral burden observed in the early phase of HIV infection (Clarck et al., 1991). The association of the time at which mothers and their children acquire an HIV infection is evidently in favour of this hypothesis.

The estimation of the additional risk of mother-to-child transmission of HIV-1 attributable to breast-feeding from mothers with a stable HIV-1 infection is much more problematic. *David Dunn* and colleagues performed a meta analysis on 5 observational studies from industrialized countries and one case-control study from Zaire by comparing the mother-to-child transmission rates in breast-fed versus artificially fed infants (Dunn et al., 1992), giving an additional risk of transmission attributable to breast-feeding of 14%, with a 95% CI of 7 to 22%. However, this meta analytic approach is probably weakened by the observational and retrospective nature of the pooled studies and by the fact that studies with negative results may have been potentially omitted.

A more direct methodological approach to estimate this risk has been recently proposed (Simonon et al., 1993). By using such a sensitive diagnostic technique as PCR on repeated blood samples in a cohort of children born to HIV-1 infected mothers, it is indeed possible to estimate the relative contribution of *in utero*, intra-partum and postnatal transmission of the virus. Following the Kaplan Meier method (Simonon et al., 1993), the probability, of having, at a certain moment, a positive PCR test, has been calculated in 47 children known to be HIV-infected at 24 months of age from our cohort study in Kigali, Rwanda.

All children from this cohort had been partially breast-fed for a median time of 580 days. For the paediatric HIV infection the definition used was the one proposed by an International Working Group in Ghent, Belgium, in 1992, (Dabis et al., 1992): it takes into account, in presence or absence of clinical signs and symptoms suggesting HIV infection, the serological result obtained at 15 months of age or at the child's death. The general aspect of this curve was not different when using a non-parametric method to express the probabilities. A positive PCR test had only a 30% probability at birth and 68 % at 3 months of age. It gradually reached 100 % at 24 months. From these data, it was possible to approximate directly the relative contribution of each of the transmission mechanisms. The overall transmission rate in our cohort was 25 % (Lepage et al., 1993).

Due to the uncertainty as how to interpret PCR results obtained during the first three months of life, two extreme estimates of the additional risk of transmission by breast-feeding could be calculated. If one considers that all HIV-1 infected children with a negative PCR test on cord blood, acquired the infection intra-partum or in the postnatal period, then intra-partum plus postnatal transmission rate is 18 % or only two-thirds of the mother-to-child transmission rate. On the other hand, if only children having obtained a positive PCR after 3 months of age were considered infected in the postnatal period, late postnatal transmission rate is 8 % or grossly one-third of the global transmission rate. These estimates are fitting very well into David Dunn's estimations obtained by meta analysis. When comparing mother-to-child transmission rates calculated following the standardized Ghent definition of paediatric HIV infection, the rates calculated in industrialized countries, where most mothers had not been breast-feeding, are generally higher than the rates drawn from the studies performed in Africa where breast-feeding is the rule (Dabis et al., 1992). The difference between these rates of transmission is of the same magnitude as the additional risk of transmission by breast-feeding. However, it remains to be demonstrated that these differences are due to breast-feeding only.

The assessments of the risk of mother-to-child transmission of HIV-1 by breast-feeding have many drawbacks. They have been drawn from observational studies. To date no intervention trials, randomized or not, have been reported on this subject. Also, many of these estimates have been based on studies with a limited sample size.

1.2.2. *Factors influencing the risk for breast-feeding transmission of HIV-1*

Of equal importance is the identification of risk factors for breast-feeding transmission of HIV-1. At least three cohort studies performed in Rwanda, Haiti and the US have suggested that the presence of cells infected by HIV-1 identified by PCR in the milk of HIV-infected mother is predictive of mother-to-child transmission of the virus (Van de Perre et al., 1993, Bulterijs et al., 1992, Ruff et al., 1992). In the Rwandan study, when integrating various potential risk factors for mother-to-child transmission of HIV-1 in a multivariate model, both a positive PCR test on the breast milk sample collected at 15 days post-partum and the existence of a profound immune deficiency in the mother at the time of delivery were the factors most predictive of transmission of HIV by breast-feeding. Other factors are theoretically plausible such as nipple cracks during breast-feeding, mucosal surface of the infant interrupted by oral ulcerations or thrush, and achlorhydria of the neonate. Finally, breast abscess as been recently suggested to be associated with postnatal transmission, in a case-report (Van de Perre et al, 1992b).

In 1988 an attempt to detect HIV antibodies in the milk of four women seropositive for HIV was described (Van de Perre et al, 1988). Two women had no detectable HIV-1-specific secretory IgA and IgM antibodies in their milk. However, the two others had both anti-HIV-1-IgA and IgM. Interestingly, in neither of these two women were anti-HIV-1-IgA and IgM antibodies detected in serum samples collected at the same time as milk samples. This suggests that, although the presence of IgG in milk could be the consequence of transudation from the extracellular compartment, the secretion of Immunoglobulin A and IgM takes place into the mammary gland in response to the presence of the virus in periductal tissue (Van de Perre et al, 1988). More recent observations from Rwanda suggest that specific secretory IgA and IgM in breast milk of HIV-1 infected mothers may be protective against transmission (Van de Perre et al., 1993). Also, *Newburg* and colleagues described in breast milk samples from HIV-infected mothers the existence of a factor able to inhibit the binding of HIV-1 gp120 on the CD4 receptor and then impair viral entry into susceptible cells (Newburg et al., 1992).

In the already mentionned cohort study performed in Kigali, Rwanda, milk samples were collected in 218 HIV-1 infected mothers at 15 days, 6 months and 18 months postpartum for the detection of specific HIV antibodies. Specific IgG were the most frequently detected antibody class, followed by specific IgM. Surprisingly, a secretory IgA response directed to HIV-1 was frequently defective: only 23% of the 15 days samples, 28% of 6 months samples and 41% of the 18 months samples had detectable levels of anti-HIV-1 secretory IgA (Van de Perre et al., 1993).

However, when present in the early milk samples, secretory IgA were associated with the absence of transmission of HIV-1 from mother-to-child. In a multivariate model, the persistence of a specific IgM during the whole lactation period was inversely related to HIV-1 transmission from mother to child, suggesting that specific IgM could play an important protective role against transmission (Van de Perre et al., 1993). This hypothesis seems to be confirmed by a bimodal model combining PCR and IgM detection results from the same cohort. The least favourable combination for protection is the presence of infected cells and the absence of an IgM immune response where the likelihood of transmission is 47%. The possible protective roles of IgM in breast milk are multiple. Although more susceptible to digestive hydrolase than secretory IgA, secretory IgM may similarly protect the infant mucosal surfaces by providing an antiseptic cover whereby viral attachement and entry in the submucosal tissue is prevented.

Also, specific IgM may contribute to decrease the viral load in milk by its potential lytic action on free virion, by direct neutralization or by antibody dependent cellular Cytotoxicity.

1.2.3. *The recommendations dilemma*

Out of the three mechanisms of transmission of HIV-1 from mother to child, *in utero,* intra-partum and postnatal, the latter one seems the most prone to public health interventions. Indeed, avoidance of breast-feeding may be seen as a simple way to reduce at least partly the risk of transmission. However, this simplicity is only apparent and, due to the impressive benefits of breast-feeding, making this strategy certainly not applicable worldwide.

Breast-feeding provides protection to babies by many ways. It provides the ideal nutrition to the infant at no cost, an immunological protection

against agents responsible for diarrhoeal and respiratory diseases as well as other infections. Breast-feeding plays also an important role in birth spacing, mainly in the developing world. Finally, breast-feeding is important as favouring mother-child interactions and the psychosocial development of the child (see the chapter Mother and Child Health, pp. 759, 763 and 765-768).

In terms of morbidity, it is now evident that the breast-fed child is effectively protected against diarrhoeal diseases and respiratory tract infections. Below six months of age, this benefit is most apparent in children exclusively breast-fed as compared with those partially breast-fed or artificially fed. A relative protection may also be conferred by breast-feeding against other infections such as otitis media, bacteraemia and meningitis and also against allergy and some childhood cancer.

However, quantifying the benefit of breast-feeding in terms of infant and children morbidity is a very difficult task. Data generated by a pooled analysis of many different studies performed in various parts of the world at different times clearly suggests that the higher impact of breast-feeding on diarrhoeal morbidity is on infants younger than 6 months with relative risks for diarrhoea varying from 2 to 3 (Feache m et al., 1984). It is equally difficult to quantify the risk of mortality attributable to artificial feeding. Table 1 summarizes some examples of observations made in various parts of the world.

Table 1: Risk of mortality attributable to artificial feeding (from Cunningham et al., 1991)

	Risk difference	Relative Risk
In industrialized countries		
England , 1986	< 5.1/1000	-
USA, 1989	4 / 1000	-
In developing countries		
Rwanda, 1981	135 / 1000	2.0
Egypt, 1981	130 - 290 / 1000	2.0 - 50
Malaysia, 1988	28 - 153/1000	2.5 - 52
Bangladesh, 1988	-	3.0

While the mortality attributable to artificial feeding in industrialized countries is somewhat limited although not negligible — around 5 per thousand — this risk is impressive in developing countries with figures of the difference in risk higher than 10 percent and a relative risk for death of 2 to 5. As shown in urban Brazil, most part of this mortality is due to diarrhoeal diseases and respiratory tract infections (Victora et al., 1987). When comparing infant mortality in exclusively breast-fed infants versus artificially fed infants and partially breast-fed infants, the relative risk for death due to diarrheoal diseases and respiratory tract infections was strickingly higher in completely weaned infants — 14.2 and 3.6 respectivelly — and in partially weaned infants — 4.2 and 1.6, respectively (Victora et al., 1987).

Evidence is thus strong that breast-feeding protects babies against morbidity and mortality from infectious diseases. However, one should keep in mind that the available data quantifying this benefit are not ideal. Most of the available data are quite old, some of them originating from the first decade of this century. Most of them have been drawn from retrospective and observational studies, due to the difficulty of designing a trial truly randomized on feeding practices. In addition, little assessment of confounding have been attempted in most of these observational studies and it remains possible that a part of the difference in morbidity and mortality observed in the groups of children is not exclusively due to the feeding and the outcome of nutrition or health may be not those of causality but rather of association.

Transmission of HIV by breast-feeding has evoked a great deal of anxiety and questionning. It is therefore our duty to provide women, couples and families with recommendations based on our present knowledge of both mother-to-child transmission of HIV and of the best feeding modes available for their children. Several mathematical models have been proposed in order to guide decisions on the way to feed the child in case of HIV infection of the mother. One of the most comprehensive one has been designed by *Dale Hu* and colleagues and takes into account the prevalence of HIV infection in the population of pregnant women, the estimated risk of transmission of HIV-1 by breast-feeding and the estimated risk of mortality due to artificial feeding in a given environment (Hu et al., 1992). In 1992, the World Health Organization and the United Nations Children Fund produced a consensus statement which recommends to continue the protection, promotion and support of breast-feeding worldwide (World Health Organization, 1992). It also recommends to continue breast-feeding for all women living in settings where infectious diseases and malnutrition are the primary causes of infant deaths. However, women living in this environment but who could safely apply an alternative to breast-feeding should be offered, if available and affordable, a voluntary and confidential HIV testing accompanied by pre- and post-test counselling and make a decision according to the test results. In settings where infectious diseases and malnutrition are not the primary causes of infant deaths, pregnant women known to be infected should be advised not to breast-fed and to use a safe alternative.

Like any public health recommendations, the WHO/UNICEF consensus statement on HIV transmission and breast-feeding is based on available scientific data. One should keep in mind that both pans of the scale — the risk of transmission of HIV to the child by breast-feeding and the risk of mortality if the child is deprived from breast milk — are based on data that are far from being satisfactory. Consequently and inevitably health professionals in the field, particularly if practicing in developing countries or in pockets of poverty in industrialized countries, are left alone with their own arbitrary estimation of risks in order to give women, couples and families advice of potential tremendous consequences.

1.2.4. *Research priorities*

Many dark areas remain in our understanding of postnatal mother-to-child transmission of HIV-1. From the biological point of view, one of the most urgent informations to gain is the timing of transmission of HIV by breast-feeding. Indeed, due to the high cellular content of colostrum and of early breast milk, it is conceivable that transmission can occur preferentially in early phases of lactation. However, biological plausibility does not preclude demonstration and this hypothesis remains to be validated.

Also unknown is the portal of entry for HIV in newborns and infants. The relationship between specific humoral response and viral load in milk deserves also careful studies. Well-designed epidemiological studies still need to be performed in order to assess precisely the transmission rates of HIV according to different feeding modes. Due to the immunological cover on the intestinal mucosa conferred by exclusive breast-feeding, it is plausible that this feeding mode is associated with a lower transmission rate than partial breast-feeding. The impact of breast-feeding on the course of paediatric HIV infection has been incompletely studied. From the prevention angle, it will be essential to evaluate if protective milk factors such as IgM and IgA can be triggered by active immunization or, in case of impairement, can be compensated by immuno-prophylaxis.

In conclusion, the potential impact of postnatal transmission on child health should stimulate us to consider designing and testing the effectiveness, feasibility and acceptability of innovative preventive interventions other than artificial feeding, such as colostrum withdrawal, wet-nursing, and milk banking plus pasteurization. The time has come to realize that we still need to learn a great deal not only on milk transmission of HIV but also on remote nutritional, immunological and public health aspects of breast-feeding in general. Let us just consider postnatal transmission of HIV by breast-feeding for what it really is: an exceptional situation requiring exceptional investigations and adapted solutions.

1.3. *Transmission by blood transfusions and by medical injections*

Other modes of HIV-1 transmission than perinatal exposure and breast-feeding exist. Blood transfusions contaminated with HIV-1 are an effective way to transmit HIV infection in Africa (Van de Perre et al., 1985) as in other parts of the world.

Among hospitalized HIV seropositive children born to seronegative mothers 31% in Kinshasa (Mann et al., 1986) and 39% in Kigali (Lepage et al., 1986) had been transfused. A strong dose-response association between blood transfusion and HIV seropositivity was observed in hospitalized children in Kinshasa (Greenberg et al., 1988).

Three types of interventions can be implemented to diminish the spread of HIV via blood transfusions:
- First, physicians working in areas of high HIV infection prevalence should try to reduce the frequency of transfusions;
- Secondly, as routine practice in Rwanda since 1985, all blood donors should be tested for HIV antibodies;
- Thirdly, because the risk of HIV infection from transfusion of a screened unit of blood in high prevalence areas remains substantial, blood donors should be selected from population groups with the lowest HIV seroprevalence, such as rural populations and adolescents (Lepage and Van de Perre, 1988).

In contrast, medical injections do not appear to be an important mode of HIV transmission in most African countries (Lepage and Van de Perre, 1988). However, in spite of the low risk of transmission from infected patients to hospital workers and from medical injections, precautions to prevent acquisition of HIV infection in health care must be taken.

2. Impact of HIV-1 infection on pregnancy outcome

A history of spontaneous abortion was more commonly reported among HIV-infected mothers than among non-infected ones in Kenya and Rwanda (Temmerman et al., 1990 and 1993; Lepage et al., 1991).

A prospective cohort study in the Congo and Rwanda found that the impact of maternal HIV infection was limited during the neonatal period (Lallemant et al., 1989; Lepage et al., 1991). In these studies, the rates of prematurity, of low birthweight and of neonatal mortality were not different among newborns of HIV-infected and of non-infected mothers. In contrast, in Zaire (Ryder et al., 1989) and in Kenya (Temmerman et al., 1990 and 1993), the rate of prematurity was higher among newborns of seropositive mothers. This discrepancy may be related to the stage of immunodeficiency of these mothers: women in Zaire and Kenya frequently presented signs of HIV-related disease whereas mothers in the Congo and Rwanda were asymptomatic at the time of enrolment.

In Rwanda, the mean birthweight, body length and head circumference was lower in infected newborns of seropositive mothers than in newborns of seronegative mothers. On the other hand, non-infected children born to seropositve mothers had comparable neonatal characteristics to children born to seronegative mothers (Lepage et al., 1992).

3. Evolution

In central Africa, the mortality among children born to HIV seropositive mothers is high in the first 2 years of life, occurs early and is mainly due to diarrhoeal diseases and pulmonary infections (Lallemant et al., 1989; Ryder et al., 1989; Lepage et al., 1993; Thea et al., 1993). The mortality associated with HIV is 2 to 10 times higher among African children born to HIV-infected mothers than among European ones.

The different factors that may play a role as well in the higher morbidity as in the mortalities among African HIV-infected children are not only the higher rates of mother-to-child transmission, but also the increased risk of infection from the environment, the poor nutritional status of children, the difficult access to standard medical care and the lack of specific therapy in Africa (Lepage and Hitimana, 1991). In Kinshasa, HIV-infected children with persistent diarrhoea had a 80-fold higher risk of mortality than non-infected ones (Thea et al., 1993).

A bimodal pattern of HIV-1-related disease has been described in HIV-1 infected children from industrialized countries (Scott et al., 1989; Blanche et al., 1991): a proportion of perinatally-infected infants develop severe signs in the first year of life and have a poor survival prognosis, while the others become symptomatic later, show milder complications and may survive for many years. This bimodal expression of HIV disease also exists in African children. A group of 16 perinatally HIV-infected children surviving over 5 years of age has been described in Kigali (Lepage et al., 1991). Their major clinical manifestations were of a short stature, pulmonary involvement, chronic parotitis and persistent generalized lymphadenopathy. Severe infections and neurological involvement were uncommon. After a mean follow-up of 40 months, only 2 children had died (Lepage et al., 1991). Although the proportion of perinatally HIV-1-infected children who remain pauci-symptomatic for a prolonged period is low, the pool of infected mothers and infants is growing. In the near future, children of school age and even adolescents with HIV-1 infection will become an important public health problem in some African areas.

4. Clinical aspects of HIV-1 infection in children

4.1. *Signs and symptoms*

Symptoms most commonly described in Africa include a persistent cough, chronic diarrhoea and prolonged fever. Signs frequently described are failure to

thrive, persistent generalized lymphadenopathy, oral candidiasis, chronic otitis media, pulmonary infection and pruritic dermatitis (Lepage and Hitimana, 1991). These signs and symptoms have been incorporated in the WHO clinical case definition of AIDS (Colebunders et al., 1987; Lepage et al., 1989).

4.2. *Bacterial infections*

Severe and recurrent bacterial infections are often reported in HIV-1-infected children in central Africa (Lepage and Van de Perre, 1988, Lepage et al., 1989). These infections include sepsis, pneumonia, meningitis, urinary tract infections, chronic otitis media, chronic sinusitis, abscesses and pyomyositis. Commonly isolated organisms from blood cultures include *Pneumococci, Haemophilus influenzae, Staphylococci* and *Salmonellae*. In Rwanda, non-typhoid Salmonellae are cultured in a high proportion of affected children, probably due to an increased risk of contamination from the environment (Lepage and Van de Perre, 1988, Lepage et al., 1989).

4.3. *Opportunistic infections*

The opportunistic infections described in children – mainly *Pneumocystis carinii* pneumonia (PCP), *Candida oesophagitis, Mycobacterium avium-intracellulare* infection, disseminated cytomegalovirus infection, chronic herpes simplex infection and cryptosporidiosis — are very similar to those described in adults with AIDS (see p. 665). PCP is the most common opportunistic infection both among children and adults in developed nations (Falloon et al., 1989). Preliminary studies seem to indicate that PCP is less prevalent in African AIDS children than in European patients.

Given the limited diagnostic technology available in most African countries, the relative importance of the different opportunistic agents has not been established. It remains to be understood why so few African HIV-1 infected children develop cryptococcal meningitis while it is one of the leading causes of opportunistic infection among adults in many African countries.

4.4. *Other infections*

The interaction between HIV-1 infection and infections that are more prevalent and/or more severe in Africa than in industrialized countries, such as measles and tuberculosis, deserves further studies. HIV-1-infected subjects with measles carry a high fatality rate and do not always manifest typical measles rash. Infected children should be vaccinated early in life, if possible before severe immunodeficiency has developed (Lepage et al., 1992).

Until now, tuberculosis in central African children infected with HIV has been given little attention. Tuberculosis seems to be a less prevalent complication in children than in adults, perhaps due to frequent reactivation occurring in adults.

Varicella is often severe and sometimes fatal. As in adults, herpes zoster infection may occur in an otherwise pauci-symptomatic child and may be a diagnostic sign.

In a study from Kinshasa, *Plasmodium falciparum* malaria was no more common or more severe in HIV-infected children than in non-infected subjects (Greenberg et al., 1991).

4.5. *Neurological involvement*

HIV-1 is known to invade the central nervous system. Studies from North America have shown very pessimistic results with between 77% to 90% of the children with symptomatic HIV-1 infection showing to have a severe neurologic impairment (Falloon et al., 1989). The results from the ECS (Cogo et al., 1990) and from the study in Rwanda (Msellati et al., 1993) where the intravenous drug use is not a confounding factor but has less negative conclusions. Among HIV-1-infected children in Kigali, 30% of those aged 12 months and 41% of those aged 18 months, respectively, were considered as neurodevelopmentally delayed (versus 6% among non-infected controls). In Kigali, neurodevelopmental delay was principally due to gross motor retardation (Msellati et al., 1993).

4.6. *Malignancies*

Kaposi's sarcoma is very rare in HIV-1 infected children. When it occurs in young children, Kaposi's sarcoma is often localized in the lymph nodes in contrast to adults where the dermatological forms predominate.

4.7. *Clinical features that are more frequent in children than in adults:*

4.7.1. *Lymphoid Interstitial Pneumonitis (LIP)*

LIP is frequently found among children, both in Western countries and in Africa. It was described in 22% of 107 symptomatic children in Kigali (Lepage and Hitimana, 1991). Subjects with LIP are affected with progressive diffuse bilateral micronodular infiltrates, sometimes with hilar and mediastinal adenopathy on chest roentgenogram. On biopsy, LIP is characterized by infiltration of the alveolar septa

and pulmonary interstitium by small lymphocytes, plasma cells and immunoblasts. The true pathogenesis of LIP is unknown but may result from the interaction between HIV-1 and Epstein-Barr virus in the lungs. Clinical expression is mild with sometimes moderate hypoxaemia. LIP usually develops in children older than one year of age with generalized lymphadenopathy, chronic parotitis and hypergammaglobulinaemia.

4.7.2. *Chronic Parotitis*

Chronic parotitis is more frequently found in children rather than in adults. It is often seen in combination with generalized lymphadenopathy and LIP.

4.7.3. *Perivasculitis*

Perivasculitis of the retinal vessels has been described in 39% of 162 symptomatic HIV-1-infected children from the Department of Paediatrics of the *Centre Hospitalier de Kigali* (Kestelyn et al., 1985). Ophthalmologic manifestations of AIDS in adults (cotton-wool spots, cytomegalovirus retinitis, toxoplasma choroiditis) are less commonly observed in children (Kestelyn et al., 1985).

5. Clinical case definition

The World Health Organization (WHO) has proposed a clinical case definition for AIDS in adults and children (WHO, 1986) to be used where laboratory facilities are limited. In the WHO definition, paediatric AIDS is suspected in a child having at least 2 major signs, associated with at least 2 minor signs (see the chapter AIDS, pp. 661-662). Indeed, in developing countries, specific definitions such as those of the Centers for Diseases Control are not helpful because the diagnosis of opportunistic infections is seldom possible. The WHO definition, tested in hospitalized children in Kinshasa (Colebunders et al., 1987) and Kigali (Lepage et al., 1989) has a satisfactory specificity, but a low sensitivity and a low positive predictive value. Therefore, its use seems limited for diagnostic purposes. On the other hand, the WHO definition can be a useful tool for epidemiological surveillance. In hospitalized children in Kigali, generalized lymphadenopathy and respiratory distress secondary to pulmonary infection were highly predictive of HIV-1 seropositivity (Lepage et al., 1989; Msellati et al., 1991). Rare signs — such as chronic parotitis, herpes zoster infection — were also very specific of HIV infection in children in Kigali. When possible, HIV testing should be added to the clinical definition (De Cock et al., 1991).

6. Diagnosis

In adults, the detection of anti-HIV IgG antibodies in serum is sufficient to establish the diagnosis of HIV infection.

In young children, the interpretation of HIV serology is difficult for several reasons:

1) In infants born to seropositive mothers, IgG antibodies passively acquired through the placenta may persist for up to 18 months (European Collaborative Study, 1992; Lepage et al., 1993). In these circumstances, it is difficult to discriminate between true infection in the infant and passive transmission of maternal antibodies.
2) False negative serological results are not infrequent in paediatric HIV-1 infection and transient seroreversion has been described in infants born to seropositive mothers in Africa (Lepage et al., 1989 and 1992).

It is, however, essential to diagnose HIV-1 infection as soon as possible, in early infancy, to permit optimal therapeutic intervention before immunodeficiency and HIV-related disease are manifest. In the African context, the most promising tests for early diagnosis of perinatally acquired HIV-1 infection are the polymerase chain reaction (Van de Perre et al., 1991), detection of specific IgA (Quinn et al., 1991) and p24 detection after acid dissociation of immune complexes (Miles et al., 1993). These assays are however still very expensive for developing countries and require considerable laboratory expertise.

7. Further studies

A lot of information has been accumulated through clinical and descriptive epidemiological studies on the natural history and particularly on the clinical features of HIV-1 infection in children during the last decade. However, longer follow-up of a large series of infected children is needed to determine the prognosis of subjects aged more than two years old. The interactions between tropical diseases and HIV-infection, and between malnutrition and HIV-infection, require detailed studies. We also need to better define clinical, immunological and virological factors that are associated with a poor or with a prolonged survival. Moreover, in high prevalence regions, such as in some Central African countries, research should move on in the near future from descriptive epidemiology to intervention studies.

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