

Human immunodeficiency virus infection in Saudi Arabian children: transmission, clinical manifestations and outcome

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BACKGROUND: Vertical transmission from mother to infant is the most common mode of transmission of HIV infection in children. Data on pediatric HIV in the Middle East and Gulf region are scarce. We describe the spectrum, characteristics and outcome of HIV infection in Saudi children.

METHODS: We collected descriptive data on HIV-infected or exposed children seen at the King Faisal Hospital and Research Centre (KFSH&RC) between 1986 and 2003.

RESULTS: Sixty-three children had proven HIV infection. The source of infection was perinatal transmission in 63.5% of cases and contaminated blood or blood products transfusion in 34.5%. Median age at diagnosis was 6 years. In 42 patients for whom complete records were available, 90% were delivered by spontaneous vaginal delivery and 10% by cesarean delivery. Ninety-three percent of infected infants were breastfed throughout infancy. The complete medical records were available for 66% of children; for the remainder, part of the records could not be retrieved. Thirteen percent had an AIDS-defining opportunistic infection, with disseminated cytomegalovirus (CMV) infection being the most common (37.5%). All cases received antiretroviral therapy starting in 1997. Of those who received highly active antiretroviral therapy, 79% were compliant with treatment and had a sustained virologic response below the detectable level. Seventy-five percent of those diagnosed before 1995 died compared with 7.7% diagnosed later.

CONCLUSION: Effective preventive measures, such as antiretroviral prophylaxis, cesarean delivery, and abstention from breastfeeding are not being applied. This could be largely due to lack of knowledge among patients and healthcare providers. Physicians must recognize the signs and symptoms of HIV infection, and have a high index of suspicion so that infected children are diagnosed early and referred to a specialized center for treatment and follow-up.

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Human immunodeficiency virus (HIV) is the etiologic agent of acquired immunodeficiency syndrome (AIDS) in humans. It is estimated to have infected 60 million people worldwide so far. Women of child-bearing age constitute almost half of adults living with HIV worldwide.¹ Mother-to-child transmission is the dominant mode of acquisition of HIV type 1 infection in children, resulting in approximately 1600 new infections each day, mostly in sub-Saharan Africa.¹ A three-part zidovudine regimen given to the mother prenatally and intrapartum, and to the infant postnatally for 6 weeks as re-

ported by the AIDS Clinical Trial Group Study 076 (ACTG 076) reduced the risk of HIV infection from mother to offspring by 70%.² Elective cesarean delivery before onset of labor combined with zidovudine prophylaxis further decreased perinatal transmission of HIV to less than 1%.³ With improvement in diagnosis and medical treatment, children with HIV infection are living longer.

Saudi Arabia has recorded 872 cases of AIDS with another 1768 Saudi nationals testing HIV positive since 1984 when the Kingdom began monitoring the disease. Males accounted for 77% of HIV infection with a male-to-female ratio of about 3:1. Children under 15 years of age constituted about 9%. Forty-six percent of adult patients contracted the virus through the sexual route. The mother-to-child transmission rate was 5%.^{4,5}

Data on pediatric HIV infection in the Middle East and Gulf region are scarce. King Faisal Specialist Hospital (KFSH&RC) in Riyadh, Saudi Arabia, a tertiary care facility, is considered the major HIV referral and care center for the country. HIV-infected patients are referred for counseling, assessment, and management. In this study we outline the scope of HIV infection in Saudi Arabian children, including mode of transmission, clinical manifestations, and outcome.

Methods

The KFSH&RC AIDS Care Program was established in 1984 with the opening of the combined adult and pediatric HIV clinic. The program has subsequently grown in numbers of patients and providers. The clinic has been developed to provide specialized services tailored to the idiosyncratic needs of patients with HIV infection. Services available within the clinic include counseling, clinical pharmacy, a social work service, pulse oximetry, and provision of aerosolized pentamidine. The clinic has approximately 1200 visits per year and is supervised by eight consultants in adult and pediatric infectious diseases. An important inclusion to hospital AIDS services is access to an advanced diagnostics laboratory and multiple specialists who provide the expertise of their discipline to patients with HIV infection.

From 1986 to 2003, 66 children who were either exposed or infected with HIV were seen at the HIV clinic. These cases were either referred from other hospitals in the Kingdom for diagnosis and/or management, or diagnosed at the facility. The complete medical records of 42 children were available for review. For the remaining patients, parts of the records

were archived and could not be retrieved for review. Patients were diagnosed with HIV by using enzyme immunoassay and confirmed by immunoblot assay until 1996. Since 1997, HIV polymerase chain reaction (PCR) has been used to confirm the diagnosis in patients with reactive serologic tests. HIV viral load assay was introduced in 1998 for monitoring response to treatment.

Serologic tests included the AxSYM HIV 1/2 gO, a microparticle enzyme immunoassay (MEIA) (Abbott Laboratories, Abbott Park, USA) for the qualitative detection of antibodies to HIV type 1 and 2, and the Chiron RIBA HIV-1/HIV-2 strip immunoblot assay, a qualitative enzyme immunoassay for the detection of antibodies to HIV types 1 and 2. If the qualitative detection by MEIA was reactive, the specimens were retested. If still reactive, specimens were tested for confirmation using the strip immunoblot assay, which is intended for use in the confirmation of specimens found to be repeatedly reactive using a MEIA. Anti-HIV reactivity in a specimen was determined by comparing the intensity of each antigen band to the intensity of the human immunoglobulin G.

Molecular tests included HIV PCR, which used three sets of four primers from envelope, polymerase, reverse transcriptase and core protein genes. The initial test was followed by a nested PCR. The PCR product was run using agarose gel electrophoresis. If only one band appeared after duplicate testing, the test was reported as indeterminate. Two bands are required for the test to be reported as positive. Viral load was measured by the branched DNA method (VERSANT HIV-1 RNA 3.0 Assay, [bDNA], Bayer Diagnostics, Berkeley, CA, USA). Results were reported as positive from 50 to >500 000 copies/mL. Virologic responders were defined as those who either reached an undetectable viral load (<50 copies/mL) or had a more than 1.5 log reduction in viral load compared with baseline at 12 weeks after the initiation of highly active antiretroviral therapy (HAART), which was maintained during the follow-up period.⁶ CD4+ count was obtained by standard flow cytometric methods.

All patients who were 14 years of age or younger at the time of HIV diagnosis were included in the study. The data collected on a customized data abstraction sheet included demographic data, referring hospital, age at presentation, mode of delivery, type of feeding, mother's and father's HIV status, symptoms and signs associated with HIV, vaccinations, method of HIV testing, antiretroviral therapy and

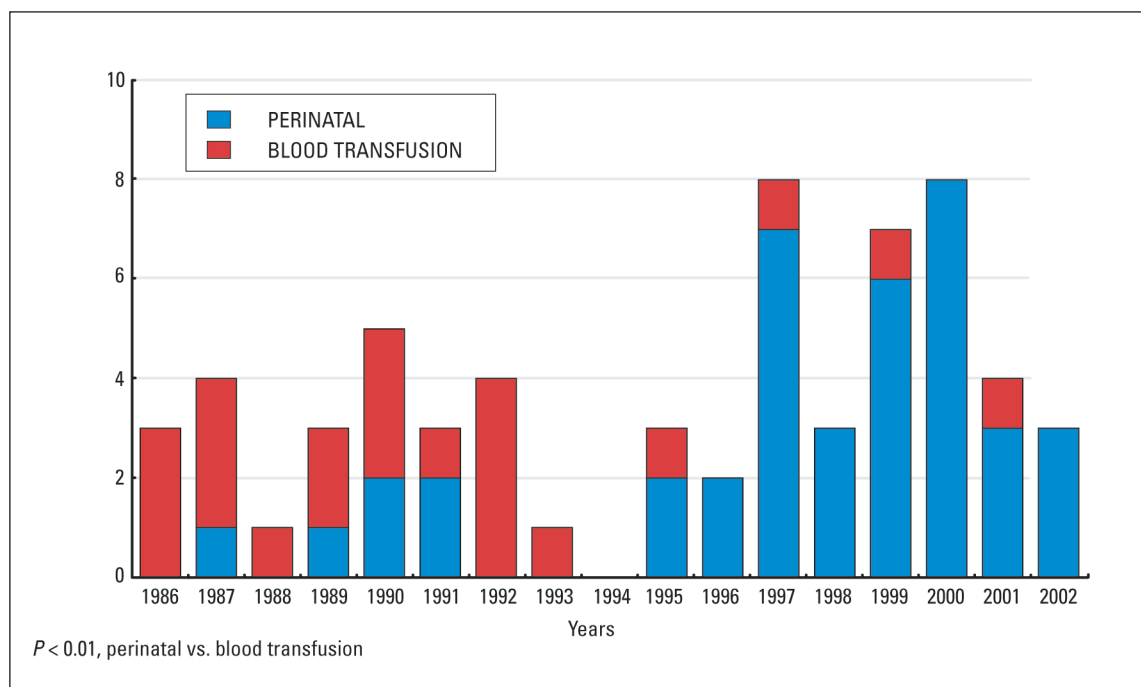


Figure 1. Mode of HIV transmission in 63 infected children.

opportunistic infections. On admission and at each visit, the clinic evaluated growth and development, treatment compliance, history of intercurrent and opportunistic infections, CD4 count and percentage, neutrophil count, hemoglobin, platelet count, HIV viral load, liver and renal function tests, lipid profile and lipase. This data was included in the collection. Also recorded for each patient was the disease classification based on the clinical and immunologic categories according to the Centers for Disease Control and Prevention (CDC) 1994-revised classification system for HIV infection in children less than 13 years of age.⁷

Data was entered using the Epiinfo 2002 program. Analysis of data was performed using the SPSS statistical analysis software program (SPSS Inc, Chicago, IL, version 10.0.5 for Windows). A two-tailed statistical test was used with a P value of <0.05 as the cut-off for significance.

Results

Sixty-six children with possible HIV infection were seen in the pediatric HIV clinic between 1986 and June 2003. Of these, 63 cases were confirmed to have HIV infection (Table 1). Three children who had been exposed to maternal infection during gestation were subsequently proven not to have the infection. Thirteen children were diagnosed at KFSH&RC;

the remaining children were initially diagnosed at the referring hospital, but the diagnosis was confirmed at KFSH&RC. The reasons for referral from other facilities were the lack of confirmatory tests and unavailability of antiretroviral medications at the referring hospitals.

The overall median age at presentation was 6 years. The median age at presentation of perinatally infected children was 3.8 years compared to 8 years for those who were infected through contaminated blood/blood products. Among the transfusion-related HIV infection cases, 19 of 22 (86.4%) had hemophilia or hemoglobinopathies. In children who were diagnosed before 1995, the commonest mode of transmission was contaminated blood/blood products transfusion, whereas the majority of children diagnosed after that period acquired their infection through perinatal transmission (odds ratio=0.04, 95%CI 0.01-0.18, $P<0.01$) (Figure 1). Nineteen patients received transfusions before 1985 and 3 patients after 1985. In one child the mode of transmission could not be determined.

Thirty-six of 40 children (90%) were delivered via spontaneous vaginal delivery and were breastfed; of 4 cases delivered by cesarean section, 2 were breastfed. None of the mothers delivered by cesarean section had received zidovudine during pregnancy or labor. On the other hand, three women who delivered by

Table 1. Characteristics of HIV-infected children.

Characteristics	Number of Patients	%
Median age (years)		
Overall: 6	63	100
Perinatal: 3.8	40	63
Other: 8	23	37
Gender (n=63)		
Male	39	62
Female	24	38
Region (n=42)		
South	15	35.7
West	10	23.8
Middle	7	16.7
East	6	14.3
North	4	6.5
HIV diagnosis (n=63)		
ELISA/WB and PCR	31	49.2
ELISA/WB	30	47.6
ELISA/WB and P24	2	3.2
Route of acquisition (n=63)		
Perinatal	40	63.5
Blood/blood products	22	34.9
Unknown	1	1.6
Parents HIV status (n=63)		
Both parents positive	28	44.5
Mother positive	12	19
Both parents negative	23	36.5
Delivery mode (perinatally transmitted infection, n=40)		
Vaginal	36	90
Cesarean section	4	10
Feeding type (perinatally transmitted infection, n=40)		
Breast	37	92.5
Bottle	3	7.5

Table 2. Clinical data and outcome in HIV-infected children.

Characteristics	Number of Patients	%
CDC classification (n=42)*		
N 1/2/3	1/1/01	
A 1/2/3	7/5/03	
B 1/2/3	1/8/04	
C 1/2/3	1/3/07	
Median HIV-1 RNA copies/mL (n=27)	47 359 (<50->500 000)	
Median CD4 percentage (n=37)	22 (1-54)	
Median hemoglobin (n=39)	101 (65-163)	
Median absolute neutrophil count (n=39)	2190 (240-10 200)	
Median platelet count (n=38)	300 (20-528)	
Outcome (n=63)		
Survived	41	65.1
Died	21	33.3
Unknown	2	1.6

*N, not symptomatic; A, mildly symptomatic; B, moderately symptomatic; C, severely symptomatic

spontaneous vaginal delivery received intrapartum prophylaxis, but breastfed their infants. It was not clear if these mothers were informed about the risk of HIV transmission through breastfeeding.

Twenty-eight of 40 (70 percent) HIV-infected mothers got the infection through sexual contact with infected husbands, and 12 of 40 (30%) got the infection from blood or blood product transfusions before 1985. Nine of 34 (26.5%) children showed no virologic response to treatment. The percentage of CD4 lymphocyte count increased to a median of 22 percent (range, 2-40 percent) after 6 months of therapy (Table 2).

The mortality rate was higher among those who were diagnosed before 1995 compared to those diagnosed after 1995 (75%, 18/24 and 7.7%, 3/39, respectively). The mortality rate was also higher among transfusion-related (63.6%) cases compared with perinatally infected children (17.5%).

Opportunistic infections were found in 10 of 44 (22.7%) children (Table 3). All affected patients were alive at the time of writing. Three patients had disseminated infection with cytomegalovirus (CMV). One patient had retinitis leading to blind-

ness. Another patient had CMV and concomitant *Pneumocystis carinii* pneumonia. Both organisms were recovered from the bronchoalveolar lavage. One patient had CMV hepatitis as evidenced by histopathologic changes and a positive in-situ hybridization test for CMV. Three patients had *P. carinii* pneumonia diagnosed by bronchoalveolar lavage. These patients had severe respiratory symptoms requiring ventilation. None of the three were receiving *P. carinii* chemoprophylaxis at the time of diagnosis. All three responded to treatment with trimethoprim-sulfamethoxazole.

Two patients had disseminated *Mycobacterium avium-intracellulare* complex (MAC). Both presented with prolonged fever and abdominal pain. MAC was recovered from blood and stool. In one patient there was an appendiceal mass that was removed surgically and which grew MAC. One patient also had retinitis. One patient had herpes-zoster infection of the ophthalmic division of the trigeminal nerve bilaterally, with involvement of the right cornea. The lesions healed completely without sequelae.

Discussion

HIV infection in children requires a comprehensive multidisciplinary approach to treatment. In our region, information about the existence of the disease and its epidemiologic pattern is lacking. Thus, diagnosis is often overlooked or delayed leading to inappropriate management of infected patients. There has been an increase in the number of HIV-infected patients referred to our hospital in the last six years. This increase can be attributed to improved awareness, which facilitates early disease recognition and referral. While our results do not reflect the actual magnitude of HIV infection in the Kingdom, they serve to increase awareness about the presence of pediatric HIV infection in this country, highlight the need for early diagnosis and management, and describe the modes of transmission, and clinical manifestations of pediatric HIV infection.

At present, perinatal transmission is the main mode of transmission of HIV infection in children. As the prevalence of HIV infection in the Kingdom is low, screening during pregnancy is not routinely performed. Pregnant women are screened for HIV infection only if there are risk factors, such as an infected husband or child, or a clinical suspicion of infection. Transmission of HIV infection from the mother to her infant can be significantly reduced by using a three-part zidovudine prophylaxis regimen

Table 3. Opportunistic infections in HIV-infected children.

Causative agent	Site	Number of cases
Cytomegalovirus	Pneumonia	1
	Hepatitis	1
	Retinitis	1
<i>Pneumocystis carinii</i>	Pneumonia	3
<i>Mycobacterium avium-intercellularae</i>	Disseminated	2
<i>C. albicans</i>	Esophagitis	1
Varicella-Zoster	Keratitis	1
Total		10

Table 4. Clinical features of HIV-infected children.

Signs and symptoms	Number of cases	%
Lymphadenopathy	27	64.3
Growth retardation	25	59.5
Hepatomegaly	22	52.4
Fever	17	42.5
Persistent cough	16	38.1
Splenomegaly	16	38.1
Oral thrush	15	35.7
Chronic ear discharge	9	22.5
Microcephaly	7	16.7
Chronic diarrhea	6	12.5
Encephalopathy	6	12.5
Parotid swelling	5	11.9
Seizure	3	7.5
Lymphocytic interstitial pneumonia	2	4.8
Asymptomatic	8	20

consisting of the following: oral zidovudine 100 mg 5 times daily, starting at 14 to 34 weeks gestation, and continued throughout pregnancy; intrapartum zidovudine intravenously in a 1-hour initial dose of 2 mg/kg followed by a continuous infusion of 1 mg/kg /hour until delivery; and oral zidovudine at a dose of 2 mg/kg body weight every 6 hours to the newborn for the first 6 weeks of life, beginning at 8 to 12 hours after birth.⁸

Table 5. Types of antiretroviral drugs used in treatment of HIV-infected children.

Highly active antiretroviral therapy	No. of cases
Zidovudine	3
Zidovudine, didanosie	5
Zidovudine, lamivudine, nelfinavir	16
Zidovudine, didanosine, nelfinavir	14
Didanosine, lamivudine, nelfinavir	4
Total	42

Elective cesarean delivery can further decrease the rate of transmission of HIV infection from mother to infant. In a prospective study, use of a three-part zidovudine prophylaxis regimen and elective cesarean delivery reduced perinatal transmission of HIV infection to less than 1%.^{2,9} Breastfeeding is associated with a 10% to 17% risk of perinatal transmission of HIV infection. Thus, it is recommended that HIV-infected women refrain from breastfeeding when safe formula feedings are available, as is the case in our society.

Many infected pregnant women do not have regular prenatal follow-up, and only come to the hospital for delivery when they are in active labor. Thus, opportunities to use effective measures for prevention of HIV transmission from the mother to the infant are lost. In addition, there seems to be a lack of awareness among patients and healthcare providers about proper measures to prevent perinatal HIV transmission. In our series, zidovudine prophylaxis was used only in few cases, while 90% of HIV-infected children were delivered vaginally and 92.5% were breastfed, suggesting that education targeting patients and healthcare providers caring for HIV-infected women about proper prevention strategies are highly needed.

For prevention strategies to be effective, infected women must be identified early in pregnancy, treated with appropriate antiretroviral therapy to control their infection and to prevent transmission to their infants, and delivered by cesarean section. The need for routine HIV screening of all pregnant women has to be evaluated based on studies that assess the actual prevalence of HIV in this population as well as other logistic and financial considerations.

Three of the children who acquired HIV infection from a blood transfusion were born after 1986, when routine screening of blood donors for HIV came into effect. One of these children received an exchange

blood transfusion in Italy during the neonatal period. The other two received blood transfusions at their local hospitals in the Kingdom. Transmission of HIV by transfusion has become rare since the initiation of routine HIV antibody testing of all donations. In 2003 in the United States, the risk of HIV-1 transmission per unit of blood transfused was estimated to be between 1 in 1.4 million and 1 in 1.8 million units. HIV antibody tests fail to identify HIV-infected blood donated by HIV-infected persons who have not yet seroconverted (window period).

The clinical manifestations and opportunistic infections in children in our series were similar to those usually reported in children with HIV infection (Table 3, 4). The high rate of opportunistic infections was due to the severity of immunosuppression at the time of diagnosis. *P. carinii* pneumonia (PCP) is the most common opportunistic infection in HIV-infected children in the developed countries.¹⁰ In contrast; it is uncommon in HIV-infected children in Africa.¹¹⁻¹⁴ Difficulties in diagnosing PCP are particularly relevant to HIV-infected infants in developing countries because diagnosis requires identification of PCP in lower respiratory tract secretions by specialized staining or immunofluorescence techniques that may not be available in developing countries.¹⁵ PCP infection could be prevented by chemoprophylaxis. The preventive drug of choice is trimethoprim-sulfamethoxazole, but alternative agents such as dapsone, pentamidine, or atovoquone may be used. HIV-infected children should receive prophylaxis against *P. carinii* for the first year of life. The need for subsequent prophylaxis should be determined on the basis of age-specific CD4+ T-lymphocyte count thresholds. The safety of discontinuing prophylaxis in HIV-infected children receiving antiretroviral therapy has not been studied extensively, but appears to be safe in adults. Three of our patients who were diagnosed with *P. carinii* pneumonia were not receiving prophylaxis at the time of diagnosis.

Two patients in our series had lymphocytic interstitial pneumonia (LIP). LIP may mimic *P. carinii* clinically and radiologically. It is a syndrome of fever, cough, and dyspnea, with bibasilar pulmonary infiltrates consisting of dense interstitial accumulations of lymphocytes and plasma cells. It is associated with HIV type 1 and human T-cell leukemia virus (HTLV) type 1. It is important to confirm the diagnosis of LIP as this has implications for therapy. LIP responds to steroids and antiretroviral therapy, as was the case in our patients.

The pathogenesis of CMV in the setting of HIV infection may vary between adults and children. CMV disease in adults with HIV is probably the result of reactivation of a latent infection that occurred before HIV infection. In one series, it was shown that primary CMV infection in children most likely occurs after infection with HIV.¹⁸ CMV is prevalent in the adult Saudi population. Ninety-two percent of women of child-bearing age are CMV seropositive.¹⁹ All HIV-infected children should be screened for CMV infection at presentation, and those with low CD4 counts should be assessed by indirect ophthalmoscopy to determine if there is retinitis. Children with persistently very low CD4 counts should be monitored regularly to assess the potential for re-activation of CMV infection. Antiviral agents, such as ganciclovir or valganciclovir should be considered for primary prophylaxis against CMV disease in CMV-infected children who are severely immunosuppressed (e.g., CD4+ T lymphocyte count less than 50 cells/ μ L). No data is available to guide decisions concerning discontinuation of secondary prophylaxis in children who have been treated for CMV disease, but it is reasonable to consider stopping when sustained T-cell responses to antiretroviral therapy are present.

Disseminated MAC infections represent a particular risk for children with advanced immunosuppression. Such children should be given azithromycin or clarithromycin prophylaxis according to CD4+ lymphocyte thresholds.

Combination antiretroviral therapy has provided substantial clinical benefit to HIV-infected infants, children, and adolescents with immunologic or clinical symptoms of HIV infection, particularly as more potent therapies have become available (Table 5). Ideally, antiretroviral therapy should maximally suppress viral replication to undetectable levels using HIV RNA assays. This may not always be achievable in HIV-infected children.²⁰

Twenty-six percent of our patients showed no virologic response to therapy. The primary reason for this failure was noncompliance with the antiretroviral drug regimen. Children should be monitored fre-

quently to assess adherence with therapy, and assisted in finding strategies to improve compliance if and when problems arise. Close follow-up and monitoring of patients requires frequent hospital visits. This may be a challenging task for patients who reside outside Riyadh. The Ministry of Health started three clinics in three different provinces in the Kingdom dedicated to management of HIV-infected patients. These clinics will facilitate follow-up and monitoring of patients who reside in those provinces.

The mortality rate in children who were diagnosed after 1995 was much lower than that of children diagnosed earlier (7.7% versus 75%). This dramatic decline can be attributed to multiple factors, including earlier diagnosis and referral for treatment, increasing availability of antiretroviral agents, identification and treatment of opportunistic infections, and use of chemoprophylaxis against opportunistic infections.

Seventy percent of mothers of HIV-infected children in our series acquired infection from their husbands. Measures to identify infected individuals before marriage and proper counseling to prevent transmission are needed. One such measure that was found to be cost-effective was the use of voluntary counseling and testing, which combines confidential provision of information on HIV serostatus, counseling of seropositive individuals, and education on reducing the risks of transmission to sexual contacts.^{21,22}

The clinical manifestations of HIV infection in Saudi children are similar to what has been reported in children elsewhere. The delay in diagnosis and referral for treatment largely accounts for the high rate of opportunistic infections. Physicians should be aware of the clinical manifestations of HIV infection in children and have a high index of suspicion of such infection. Referrals to centers that have facilities for treatment and monitoring response to therapy must be done as soon as the diagnosis is confirmed. Education of patients and healthcare providers about the modes of transmission and prevention must be given due importance. Effective measures for prevention of HIV infection from mother to infant must be applied.

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