Clinical spectrum of paediatric HIV in Nnewi, Nigeria

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Summary
Background: HIV/AIDS is increasingly becoming a predominant cause of childhood morbidity and mortality in this part of the world.
Study Design: A descriptive, prospective study was carried out at the Nnamdi Azikiwe University Teaching Hospital, Nnewi, Southeast Nigeria, to ascertain the clinical features and probable modes of transmission of HIV infection in Children.
Results: Out of 128 HIV-infected children, 53.1% were males and 46.9% females, giving a male:female ratio 1.1:1. They were aged from 3 months to 16 years, with a mean of 4.78 (± 3.97) years. Those in the 1-5 year age bracket made up 47.7%. The presumed route of infection was mother-to-child in 79.7% and blood transfusion in 16.4%. Majority (82.0%) presented with WHO clinical stage 3 disease and 55.7% were severely immunosuppressed. The most frequent clinical features were recurrent/persistent fever, persistent cough, weight loss/failure to thrive and generalized lymphadenopathy. There was co-infection with tuberculosis in 15.6% of patients. Eighteen patients (14.0%) were lost to follow-up. Six children (4.7%) died during the period under review. They all presented in WHO stage 3 and 4. A hundred percent of the dead children had severe weight loss, 83.3% had generalized lymphadenopathy and recurrent or persistent fever respectively. Fifty percent presented with diarrhea and oral thrush. There was no gender difference in mortality. Mortality was highest among infants.
Conclusion: The high rate of vertical transmission of HIV reinforces the need for effective PMTCT interventions in reducing the incidence of HIV in children. A high index of suspicion and awareness of modes of presentation of HIV infection in children is needed for early diagnosis of those infected with HIV.

Key-words: HIV, AIDS, Childhood, Nigeria.

Résultats: Parmi un nombre total de 128 enfants infectés de VIH, 53,1% étaient du sexe masculin et 46,9% du sexe féminin; c'est-à-dire une proportion sexe masculin: sexe féminin de 1:1. Ils étaient dans la tranche d'âge de 3 mois au 16 ans, avec moyen de 4,78 (± 3.97) ans. Ceux dans la tranche d'âge de 1-5 ans constitue 47,7%. La cause présumée de l'infection était mère-à-enfant en 79,7%, et transfusion sanguine en 16,4%. La majorité (82,0%) se sont présentés avec l'OMS 3 étape de la maladie clinique et 55,7% étaient gravement d'immunodépression. Les traits cliniques les plus ordinaires étaient la fièvre chronique, la toux chronique, perte du poids/impuissance de se bien porter et lymphadénopathie générale. Il y avait eu une co-infection avec la tuberculose chez 15,6% des patients. Dix huit patients soit 14,0% étaient perdus sans soins post-hospitaliers. Six enfants sont 4,7% étaient mort au cours de la période en cours de révision. Ils se sont tous présentés dans le cadre de OM3 étapes et 4. Cent pourcent des enfants qui sont mort avaient eu la perte du poids 83,3% avaient eu la lymphadénopathie générale et la fièvre chronique respectivement. Cinquante pourcent se sont présentes atteints de la diarrhée et le muque buccal. Il n’y avait aucune différence du genre en ce qui concerne la mortalité. Mortalité était la plus élevée chez des enfants.

Conclusion: Le taux élevé de la transmission verticale de VIH viole de renforcer le besoin de l’intervention PMTCT efficace afin de réduire la fréquence du VIH chez des enfants. Un taux élevé d’indice de souçon et la prise de conscience des moyens de présentation de l’infection du VIH chez des enfants est nécessaire pour un diagnostic précoce de ceux révélés infectés du VIH.

Introduction
HIV/AIDS is a major cause of infant and childhood mortality and morbidity in Sub-Saharan Africa, and is a threat to recent gains in infant and child survival and health 1. This is a sad situation, considering the fact that HIV infection in children is preventable. In most of Sub-Saharan Africa (Nigeria inclusive) there are limited paediatric HIV diagnostic facilities and most HIV-infected children are diagnosed very late in the course of illness, or not at all. Until January 2004, when Ranbaxy pharmaceuticals commenced local production of antiretroviral (ARV) drugs in Nigeria, paediatric formulations had been inaccessible to the masses of children ravaged by HIV. This study was, therefore, embarked on to determine the clinical features and modes of transmission of HIV infection in children presenting to the Nnamdi Azikiwe
University Teaching Hospital, (NAUTH) Nnewi since commencement of an organized paediatric HIV Care. NAUTH is supported by the U.S. Centers for Disease Control and Prevention (CDC) and is one of the Federal Government primary ARV (Antiretroviral Therapy) Centers.

Subjects and methods

A prospective twenty-eight month review spanning from May 1, 2003 to August 31, 2005, yielded 128 HIV-infected children seen in the paediatric HIV clinic. These children were recruited from four sources:

- Patients receiving treatment at the Children’s outpatient clinics and Children Emergency room of NAUTH, who were screened on suspicion by the attending physicians;
- Referrals of HIV-positive children from private clinics, primary and secondary level health facilities, and HIV/AIDS Support groups and Non-Governmental Organisations within Anambra state and beyond;
- Referrals of HIV-positive progeny of patients attending the Adult HIV clinic of NAUTH;
- Symptomatic babies of HIV-positive mothers on follow-up in the PMTCT (Prevention of Mother to Child Transmission of HIV) programme in NAUTH.

On enrollment, a pre-coded proforma was completed. Presenting features, demographic data, family history, maternal perinatal history, HIV status of parents and siblings and immunization status of each child, among other data were filled in. A complete physical examination and base line laboratory investigations were carried out. These included an HIV screening test, Confirmatory test (Western Blot or Double Ellisa), CD4 lymphocyte count, complete blood count, liver function tests, urine analysis and chest x-ray when indicated. Child-Parent/guardian pairs had post-test counselling (since they usually came with a positive test result). All referred patients had a repeat HIV screening test done after an informed consent was obtained from the parent/guardian. At follow-up visits, new complaints, findings on physical examination, adherence issues to ARV and other drugs were addressed. Searching for opportunistic infections were also made. In the absence of definitive virologic diagnosis, seropositive children below 18 months of age were assumed infected when they became symptomatic (World Health Organisation (WHO) criteria for symptomatic HIV infection) and showed evidence of immunosuppression (low CD4 count for age). Age is an important determinant of the rate of disease progression in HIV, the disease progressing much faster in infants and children than in adults, therefore there is a provision for diagnosis of probable HIV infection in those with clinical features and positive antibody results where virologic tests are not available.42 The result should be confirmed by repeat antibody testing after the child is more than 18 months of age.4 The WHO clinical case definition for paediatric AIDS4 and the U.S. Centers for Disease Control and Prevention (CDC) immunological classification5 were applied for all patients.

Initial Screening was done with Genscreen Plus (Bioread laboratories) for antibodies to HIV 1 and 2. Confirmation was done initially with New-Lay Blot 1 (Bioread lab) until September 2004, when the U.S. PEPFAR (President Emergency Program for AIDS Relief) program supplied rapid test screening kits (Capillus and Genie II) for confirmation. A sample was considered HIV antibody-positive if the serum was reactive in both tests. Where discordance occurred Determine test kit was used as a tie breaker. CD4 lymphocyte counts were carried out with the Dynal CD4 kit, Manual Counter counter CD 4 kit (in March 2005), and from April 2005, Partec Cyflow machine. Strict compliance with manufacturer's instructions on usage and storage of reagents was adhered to. The presenting features were categorized as recurrent or chronic diarrhea (>1 month), chronic or recurrent otitis media, recurrent or persistent fever (>1 month), persistent cough, weight loss or failure to thrive, oral thrush (beyond the neonatal period), persistent generalised lymph node enlargement, hepatosplenomegaly, parotid enlargement, anaemia (unexplained and especially recurrent), papuloma and dermatitis of varying types.

The presumed mode of transmission of HIV was arrived at after obtaining a history of blood transfusion in the child and serology status of the parents. The transmission was attributed to blood transfusion in those children who had a history of transfusion more than three months prior to presentation and whose parents were HIV negative. Plausible reasons for arriving at such conclusions include:

a) A screened HIV-seronegative donor may possibly be recently infected and be in the ‘window period’ with a high viral load undetectable by antibody serological screening tests.

b) Insensitive and unstandardized, poor quality screening reagents may give false negative results. These could occur in the numerous privately operated laboratories in the country, since there is at present no strict monitoring of blood transfusion services.

c) Some blood transfusion carried in private hospitals with blood donated by parents were hitherto unscreened.

The mode of transmission was assumed vertical, if the mother was HIV-positive and there was no

<table>
<thead>
<tr>
<th>Age of patients</th>
<th>Number of patients</th>
<th>Percent of total patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 12 months</td>
<td>29</td>
<td>15.6</td>
</tr>
<tr>
<td>1-5 years</td>
<td>61</td>
<td>47.7</td>
</tr>
<tr>
<td>5.1-12 years</td>
<td>39</td>
<td>30.4</td>
</tr>
<tr>
<td>&gt;12 years</td>
<td>8</td>
<td>6.3</td>
</tr>
<tr>
<td>Total</td>
<td>128</td>
<td>100.00</td>
</tr>
</tbody>
</table>

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Table 2  Presenting clinical features of the HIV-infected children

<table>
<thead>
<tr>
<th>Feature</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent fever</td>
<td>89</td>
<td>69.5</td>
</tr>
<tr>
<td>Persistent cough</td>
<td>75</td>
<td>58.6</td>
</tr>
<tr>
<td>Persistent generalized</td>
<td>72</td>
<td>56.3</td>
</tr>
<tr>
<td>lymph node enlargement</td>
<td>72</td>
<td>56.3</td>
</tr>
<tr>
<td>Weight loss /failure to thrive</td>
<td>72</td>
<td>56.3</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>49</td>
<td>38.3</td>
</tr>
<tr>
<td>Recurrent or chronic diarrhea</td>
<td>38</td>
<td>29.7</td>
</tr>
<tr>
<td>Hepatosplenomegaly</td>
<td>37</td>
<td>28.9</td>
</tr>
<tr>
<td>Oral thrush</td>
<td>25</td>
<td>19.5</td>
</tr>
<tr>
<td>Chronic otitis meata</td>
<td>14</td>
<td>10.9</td>
</tr>
<tr>
<td>parotid gland enlargement</td>
<td>13</td>
<td>10.2</td>
</tr>
<tr>
<td>Anaemia (unexplained)</td>
<td>5</td>
<td>3.9</td>
</tr>
<tr>
<td>Papillomata</td>
<td>2</td>
<td>1.6</td>
</tr>
</tbody>
</table>

history of blood transfusion or other high risk exposure in the child. When there was no obvious route of infection the mode of transmission was termed indeterminate.

Data was analyzed with the SPSS statistical package.

Results

Out of the 128 HIV-infected children, 68 (53.1%) were males and 60 (46.9%) females giving a male: female ratio of 1.1:1. Their ages ranged from 3 months to 16 years with a mean of 4.78 (± 3.97) years.

The age distribution is given in Table 1. Infants made up 15.6%. Those between 1 and 5 years were 47.7%. The paediatric age group spans up to 16 years, including adolescents. Adolescents and older children may have similar presenting features as adults as the CD4 count approximates the adult count from about 6 years of age (according to the CDC Immunological classification). One hundred and two children (79.7%) were infected by vertical transmission. Another twenty-one (16.4%) were infected via blood transfusion. In four children (3.1%) the mode of transmission could not be ascertained. One teenager (0.8%) got infected by engaging in unprotected sex with multiple partners. Fifty-two children (40.6%) were on ARV drugs and 76 (59.4%) were not. The drugs used were a combination of 2 Nucleoside Reverse Transcriptase Inhibitors (NRTIs) and 1 non Nucleoside reverse Transcriptase Inhibitor (NNRTI)-the Highly Active Anti-Retroviral Therapy (HAART) regimen. The NRTIs included Zidovudine 240 mg/m² body surface area twice daily; Lamivudine 4mg/kg body weight twice daily; Stavudine 1mg/kg body weight twice daily. In the NNRTI group were Nevirapine commenced once daily for the first 14 days, then maintained on 7mg/kg twice daily for age <8 years, and 4mg/kg twice daily for age ≥8 years; Eflavirenz for age > 3 years (especially for those on concomitant anti-tuberculosis therapy) as a single daily dose as follows: 10< 15kg 200mg, 15< 20kg 250mg, 20<25kg 300mg, 25<33kg 350mg and 33<40kg 400mg. Stavudine and Zidovudine were not used together. The number of children receiving ARV drugs have increased since late June and early July 2005 with the supply of free ARVs from the PEPFAR and Government of Nigeria (GON) programs.

Majority (102, 82.0%) presented in WHO stage 3 disease, 16 (11.0%) in stage 2, 6 (4.7%) in stage 1, and 1 (0.8%) in stage 4. All the patients in stage 1 were asymptomatic (in immune categories 1 [66.7%] and 2 [33.3%]) and were screened following a diagnosed symptomatic family member. Their CD4 counts on presentation ranged from 20-2447 lymphocytes/μl. As regards the immunological status, 55.7% were in category 3 (severe immunosuppression), 22.8% in category 2 (moderate immunosuppression) and 21.5% in category 1 (no immunosuppression). The common presenting features are outlined in Table 2. The most frequent clinical features were fever, cough, weight loss/failure to thrive and generalized lymphadenopathy. Twenty children (15.6%) were co-infected with tuberculosis. Outcome was catalogued into ‘alive and being followed up’ (81.3%), ‘lost to follow up’ (14.0%), and ‘dead’ (4.7%). With progressive immunosuppression clinical symptomaticity increased (p=0.005). Even though the finding was not statistically significant (p=0.09917) those children infected vertically were more symptomatic. There was no gender difference in the presenting features (p=0.99508). Children aged one to five years had more symptoms than their younger and older counterparts (p=0.01777). All the children who died had WHO stages 3 (83.3%) and 4 (16.7%) diseases. Death was from pneumonia and diarrheal disease. A hundred percent of the dead children had severe weight loss, 83.3% had generalized lymphadenopathy and recurrent or persistent fever respectively. Fifty percent presented with diarrheal and oral thrush. There was no gender difference in mortality (p=0.9717). Mortality was highest among infants (p=0.5212).

Discussion

This study serves as an initial audit of clinical cases presenting to the paediatric HIV clinic of NAUTH, Nnewi since its formal inception in May 2002. There was an equal affectation of male and female children in this study. The same was observed by workers in Jos, Northern Nigeria. 6 In Ife, Southwest Nigeria,7 there were more females than males, while in India22 there was a male preponderance. No reason could be advanced for this. The mean age of 4.78 years is at par with the 4.5year average age observed in India.8 The predominant mode of transmission of HIV in this cohort of children was vertical. This concurs with studies in 24 in southwest Nigeria, 25 in Northern Nigeria, and elsewhere in India,8, 11 and Barbados.12 However, Emodi and Okafor 24 in a review in Enugu, Southeast Nigeria, found blood transfusion a major route of infection in children. This was probably in the pre-
PMTCT (Prevention of Mother-to-Child Transmission of HIV) era when few mothers were screened for HIV. Blood transfusion was second to vertical transmission. In this study, a significant proportion of the blood transfused to the children was donated by their fathers and given unscreened on trust in private health facilities. This practice is common in this part of the country and is at variance with the observation by Adejuigbhe et al. of HIV transmission occurring more from blood donated by paid donors. Transfusion of unscreened parent's blood should be discouraged. There was a case of transfusion of screened 'HIV negative' blood subsequently resulting in infection of the recipient. This has been reported in literature as infection during the 'window period'.

Reduction in the prevalence of blood transfusions by good nutrition and micronutrient supplementation is advocated. A National Blood Transfusion Service that regulates blood donation and transfusion and has facilities for viral antigenic testing would obviate transfusion of infected antibody-negative blood. Even though transmission by sexual intercourse was low among the children, it has also been reported in life and cannot be neglected among teenagers in our primary and secondary schools who experiment with sex. Paediatric age group may be exposed to HIV/AIDS from sexual activity through molestation (rape), sexual exploitation and child prostitution for survival. In this study, as in others, prolonged fever, persistent cough, failure to thrive, and generalized lymphadenopathy rank the most frequent presenting features. Prolonged fever and failure to thrive are major signs in the WHO case definition of AIDS in children, and both features appear to be the most consistent in symptomatic HIV in children in the developing world. These features also categorize patients into the WHO clinical stage 3 and hence are late symptoms. Clinical suspicion-based screening even though important provides a relatively under-utilized opportunity for detection of new cases and detects mainly advanced cases. Approximately 16% of patients were co-infected with tuberculosis. Higher figures were recorded in other studies with proportions ranging from 29.47% to 67.5%. HIV infection predisposes to tuberculosis because of the underlying immunosuppression. A mortality of 4.7% is low compared to findings elsewhere. This was probably because of the availability of antiretroviral therapy in this study. The high mortality among infants in this review was corroborated in North eastern Nigeria and in Barbados. This is as a result of an immature immune response to HIV mounted by infants in comparison to adolescents and adults. The clinical progression to AIDS and death is more rapid the younger the patient. Another noteworthy observation was a high loss to follow up. This was consistent in various reviews. All the losses to follow up in this study occurred when patients had to buy their antiretroviral drugs.

Conclusion
The high rate of vertical transmission of HIV reinforces the need for effective PMTCT interventions in reducing the incidence of HIV in children. A high index of suspicion and awareness of modes of presentation of HIV infection in children is needed for early diagnosis of those infected with HIV.

References


