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HIV infection and persistent diarrhoea: a comparative study of HIV positive and HIV negative children.

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Summary

Persistent diarrhoea contributes 20% of diarrhoeal disease burden and 30-50% of its 17% contribution to under-five deaths in developing countries. HIV infection increases the incidence and severity of all childhood diseases, including diarrhoea, and persistent/chronic diarrhoea is one of its presenting features. This study sought to determine the role of HIV seropositivity in persistent diarrhoeal disease morbidity in children managed at the University of Port Harcourt Teaching Hospital (UPTH) from January 1997 to March 2003. This was a retrospective study of all paediatric persistent diarrhoeal cases with known HIV serostatus who were managed at UPTH. Data extracted from their case records included the bio data, presentation, management and outcome of the index episode. EPI Info version 6.04 was used for data entry and analysis. Ninety-nine children, comprising 44.4% HIV positive and 55.6% negative; 57.6% males and 42.4% females, were studied out of which 87.9% were aged 0-23 months. HIV seropositivity was significantly associated with increased duration of diarrhoea, ($p < 0.007$ and the presence of severe wasting, tuberculosis, chronic cough, lymphadenopathy and higher mortality. Persistent diarrhoea-related morbidity and mortality were significantly increased by the co-existence of HIV seropositivity. It is therefore needful not to only scale-up control programmes for both conditions but also to improve their management.

Keywords: *Persistent diarrhoea, HIV infection, child survival*

Résumé

La diarrhée persistante contribue à 20% des cas de diarrhée et 30-50% des 17% de contributions de décès des moins de 5 ans dans les pays développés. L'infection du VIH accroît l'incidence et la sévérité de toutes les maladies de l'enfance inclus la diarrhée

persistante et chronique. Cette étude cherche à déterminer le rôle de la séropositivité au VIH sur la diarrhée persistante sur les enfants suivis au centre universitaire hospitalier de port Harcourt de janvier 1997 à Mars 2003. C'était une rétrospective des cas de diarrhée persistante en pédiatrie avec le statut de VIH vu à UPTH. Les données personnelles, à la présentation et les résultats des examens étaient extraites des registres de l'épisode indexé. Quarante-neuf enfants compris 44.4% des VIH positif et 55.6% négatif. Il y avait 57.6% des males et 42.4% des femelles étaient étudiés sur lesquels 87.9% étaient âgés de 0-23 ans. Les séropositifs avaient significativement une association avec une augmentation de la durée de la diarrhée ($P < 0.05$), la présence de perte sévère, de la tuberculose, de la toux chronique, lymphadénopathie et de plus de décès. La diarrhée persistante liée à la souffrance et la mortalité était augmentée par la co-existence du VIH séropositif. Il est donc nécessaire non seulement d'accroître les programmes de contrôle pour ces conditions mais aussi d'améliorer leurs soins.

Introduction

In spite of the reduction in annual paediatric diarrhoeal deaths from 4.5 million (1979) to 1.6 million (2002), acute diarrhoea continues to exact a high toll on under-fives in developing countries, including Nigeria [1-3]. Furthermore, sub-Saharan Africa was the only region which experienced 3% decline in diarrhoeal deaths compared to the 30-50% reduction documented for the decade 1990 and 2000. Consequently, it was estimated that approximately 40% of childhood deaths from diarrhoeal diseases worldwide by the year 2000 would occur in sub-Saharan Africa, a region that is home to only 19% of the world's under-fives [4-5]. In 1991, diarrhoea was estimated to be responsible for 25-75% of all childhood illnesses in Africa and to contribute to about 14% outpatient visits, 16% hospital admissions, and an average of 35 days of illness per year in under-fives [5].

In Nigeria, 25% of under-fives studied during the 2003 National Demographic and Health Survey had diarrhoea within the preceding 2 weeks with children aged 6-11 months and 12-23 months being the worse affected [6].

Of the 3 known types of diarrhoeal diseases in children, acute diarrhoea is estimated to be responsible for about 80% of the episodes and 50% of its related deaths while persistent diarrhoea contributes to about 10% of episodes and 35% of deaths [7]. In sub-Saharan Africa however, persistent diarrhoea accounts for 2.4-11.4% of all diarrhoea episodes and 22% of the total diarrhoea-related illness days [5]. Persistent diarrhoea is a diarrhoeal episode that has lasted at least 14 days, without a diarrhoea-free period of 3 or more days [7]. Causes of under-five deaths change from region to region and period to period in the same region. Thus, infection by the Human Immunodeficiency Virus (HIV), previously unknown as a cause of under-five deaths by 1999, has emerged as an important contributor. In some African countries, HIV infection was estimated to contribute over 30% of under-five deaths [5,8-10]. In Nigeria, it was estimated that 5-10% under-five deaths recorded in 1999 was HIV-related [10]. In deed the sub-Saharan African region has borne the largest proportional burden of the HIV epidemic since its start with over 60% affected persons being sub-Saharan Africans [11].

Although most HIV infected children present with the same common diseases found in the uninfected, theirs tend to be recurrent or more severe [12]. For example, diarrhoeal-related deaths increased from 12.0 per 1000 live births in the HIV-negative cohort to 132/1000 live births in HIV-positive infants largely due to persistent diarrhea [5]. Consequently some common disease conditions in children e.g. oral thrush, persistent diarrhoea and presumed bacterial pneumonia, are now considered indicators of the progression of HIV infection to Acquired Immunodeficiency Syndrome (AIDS) [13]. Thus, with increasing HIV infection burden, there will be a commensurate increase in paediatric disease burden. Therefore, for improved case management, it is important to determine the HIV infection status of all children with recurrent or severe forms of these common disease conditions. This retrospective study was therefore conducted to determine the possible role of HIV infection in persistent diarrhoea among children treated at the University of Port Harcourt Teaching Hospital.

Materials and methods

The University of Port Harcourt Teaching Hospital (UPTH) has a Diarrhoea Training Unit (DTU), Children's Wards, Special Care Baby Unit and the Children's Emergency Ward where all paediatric diarrhoeal cases are managed using recommended guidelines [3,14,15]. All cases are entered into each unit's register. This retrospective study involved the retrieval of data from the registers of these units. Data extracted were on children aged 0 – 15 years who presented with persistent diarrhoea between January 1997 and March 2003. The folders of children who were screened for HIV infection using the double ELISA technique were used for this study

Data extracted for each child included the biodata and medical records including the management and outcome of the index diarrhoeal episode. The WHO statistical package, EPI Info Version 6.04 was used to enter and analyse the data. Chi square statistics and Fisher's Exact Test (FET) were used to compare the results for HIV seropositive and seronegative children. A p value of 0.05 or less was considered statistically significant.

The Ethical Committee of the University of Port Harcourt Teaching Hospital approved the study.

Results

General features

Ninety nine children, comprising 57(57.6%) males and 42(42.4%) females met the inclusion criteria, out of whom 44 (44.4%) tested HIV -positive (+ve) and 55(55.6%) -negative (-ve). Among the HIV +ve children were 26(59.1%) males and 18(40.9%) females compared to 31(56.4%) males and 24(43.6%) females who were HIV-ve. This difference was not statistically significant ($P=0.84$ FET). There was a yearly increase in the number of children who had persistent diarrhoea or HIV seropositivity or both (Fig. 1). The ages of the children in both groups were similar, with 87(87.9%) being less than 2 years and 96% being under-fives (Fig. 2). The children were also similar in their family, social, pregnancy, birth, immunisation and nutritional histories (Table 1).

Clinical features of the children

Diarrhoeal disease

The duration of index diarrhoeal disease ranged from 14-2558 days (mode 14 days). Among the HIV +ve children, the duration ranged from 14 to 365 days (mean 69.7 ± 80.7 days, median 30 days and 75 percentile 90 days) while among the HIV-ve children it ranged from 14-2558 days (mean 88.5 ± 396.0 days,

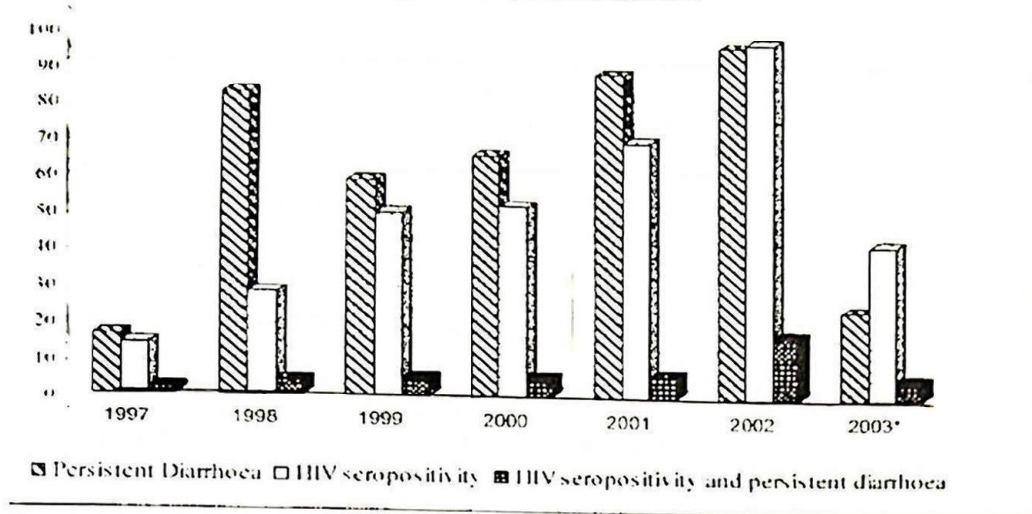


Fig. 1: The yearly distribution of persistent diarrhoea, HIV seropositivity and both conditions combined. (*In 2003, data collection was for January-March)

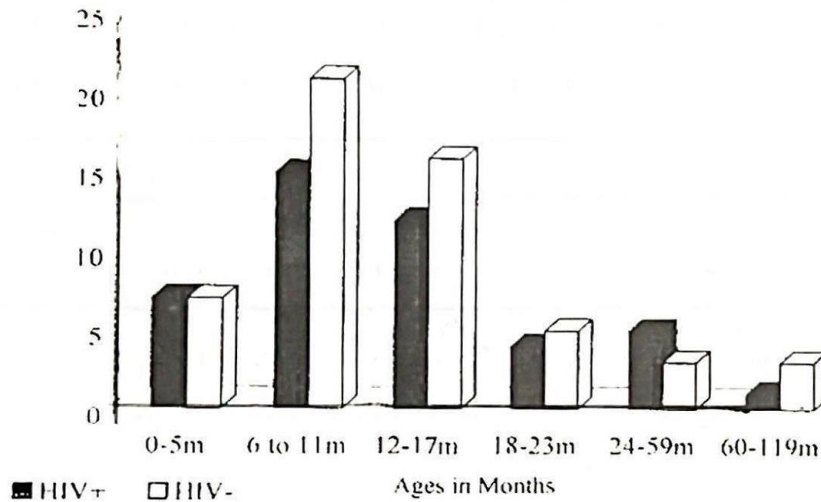


Fig. 2: The age distribution of the HIV+ and HIV- persistent diarrhoea cases

median 21 days, and 75 percentile 30 days). (One HIV -ve child aged over 7 years had diarrhoea for over 7 years before being brought for medical attention). Of the 35 HIV +ve and 41 HIV -ve children whose final durations of the diarrhoeal episodes were decided, 17 (48.6%) HIV +ve compared to 7 (17.1%) HIV -ve children had diarrhoeal episodes lasting longer than 14-30 days ($\chi^2 = 7.27$, $p < 0.007$ with Yates' correction). Additionally, 6 HIV+ ve and 10 HIV- ve children had bloody stools during the index episode.

Other symptoms and signs

Other symptoms reported for the children included fever, cough, catarrh, rashes, oral thrush, and lymph node enlargement (Table 2). A statistically significant number of HIV+ ve children also had cough, chronic

cough, lymphadenopathy and fever compared to the HIV negative children (Table 2). Although the HIV +ve and -ve children were similar in their clinical signs, the HIV+ ve children were significantly more ill and had severe pallor, wasting, dyspnoea, splenomegaly and chest signs such as subcostal recession (chest in-drawing) and crepitations (Table 2).

The nutritional status of the patients

The weights of the HIV+ ve children ranged from 3.80 to 19.00 kg (mean 7.24 ± 3.92 kg, median 5.70 kg, and 75 percentile 8.20 kg) compared to a weight range of 3.40 to 9.00 kg (mean 6.94 ± 1.79 kg, median 5.70 kg, 75 percentile 8.20 kg) among the HIV- ve children. The Weight- for- Age Z (WAZ) scores for the HIV+ ve children ranged from -6.70 to 1.86 (mean -2.784 ± 1.81 , median -3.02 and 75 percentile -1.80)

Table 1: Socio-demographic characteristics of the children

Socio-demographic characteristics	HIV- Frequency (N=55)	Percent	HIV+ Frequency N=44	Percent (100)	χ^2 / Fisher's Exact Test	P value
Parental marital status (Married /single mothers)	22/4	40/7.3	15/0	34.1/0	FET	>0.278
Parental Socio-economic class (high/middle/low)	4/3/15	7.3/5.5/27.3	1/6/11	2.3/13.6/25.0	3.05(df=2)	>0.218
Place of residence for the family (high density/low density)	23/5	41.8/9.1	20/3	45.5/6.8	FET*	>0.715
Child's birth position in the family (last/others)	17/4	30.9/7.3	18/2	40.9/4.5	FET	<0.663
Immunisation status of the child (full/partial or unimmunised)	17/12	30.9/21.8	18/9	40.9/20.5	0.12(YC*)	<0.73
Developmental mile stones (normal/abnormal)	9/11	16.4/ 20.0	13/3	29.5/6.8	3.51(YC)	>0.061
Breastfeeding at all	23/2	41.8/3.6	18/3	40.7/6.8	FET	<0.648
Normality of pregnancy (uneventful / complicated)	15/7	27.3/12.7	15/3	34.1/6.8	FET	>0.464
Places of birth of the child (outside/Inside health facilities)	3/17	5.5/30.9	6/8	13.6/18.2	FET	<0.116

YC= Yates Correction

FET= Fisher's Exact Test

Table 2: The Clinical Symptoms and signs that differed between HIV+ and HIV- children with persistent diarrhoea

Symptoms or signs	HIV- Frequency (N=55)	Percent (100)	HIV+ Frequency (N=44)	Percent (100)	χ^2	P value
<i>Symptoms</i>						
Cough	4	7.2	22	50	16.25	<0.000
Lymphadenopathy	1	1.8	8	18.2	FET	<0.01
Chronic Cough	5	9.1	13	29.5	5.57	>0.018
Fever	24	43.6	30	68.2	4.99	>0.025
<i>Signs</i>						
Pallor	11	20	20	45.5	6.23	<0.013
Wasting	6	10.9	15	34.1	6.53	<0.011
Severe wasting	4	7.3	11	25	4.68	<0.031
Lymphadenopathy	3	5.5	12	27.3	7.43	<0.006
Dyspnoea	3	5.5	11	25	6.17	<0.010
Creptitations	2	3.6	11	25	8.0	<0.005
Hepatomegaly	7	12.7	16	36.4	6.39	<0.011
Splenomegaly	0	0	6	13.6	FET	<0.006

compared to -5.01 to -0.19, (mean -2.785 ± -1.33 , median -2.97 and 75 percentile -2.33) for the HIV - ve children. Although 74.1% HIV+ ve children compared to 80% HIV-ve children had WAZ score ≤ -2 or less, the difference was not statistically significant ($P=1.000$, FET). Although there was also no statistically significant difference in the number of HIV +ve (11) and HIV -ve (5) children who had

poor nutritional status ($P<0.228$; FET), the HIV + ve children (15(34.1%)) were significantly more wasted than the HIV -ve ones (6(10.9%)) ($\chi^2= 6.53$, $P<0.011$ with Yates correction). Oedema of both feet was detected in 2 HIV + ve and 6 HIV -ve children ($P> 0.294$, FET); and sunken eyes in 11 HIV + ve and 8 HIV - ve and children ($\chi^2= 1.11$, $P>0.291$).

The clinical diagnoses

In addition to the index persistent diarrhoea episode, other diagnoses made in the children were septicaemia, pneumonia, malaria, tuberculosis, anaemia and dysentery (Table 3). Although the children in both groups were similar in their additional diagnoses, tuberculosis was more frequently diagnosed in the HIV +ve children $\chi^2 = 19.1$, $p=0.000$ for TB).

with follow-up appointments ($\chi^2 = 0.09$, $df=2$, $p<0.956$). Of the 8 children in either group that kept at least a follow-up appointment or represented for other reasons, all the HIV+ ve children compared to one HIV- ve child were still ill. This difference was statistically significant ($p<0.002$, FET).

Discussion

This study has demonstrated the continued role of diarrhoeal diseases in paediatric morbidity and

Table 3: Additional diagnoses made in the children with persistent diarrhoea

Diagnoses	HIV- cases		HIV+ Cases		P value
	Frequency N=55	%	Frequency (N=44)	Percentage (100)	
AIDS	5	9.1	26	59.1	26.14 >0.000
Tuberculosis	4	7.3	21	47.7	19.10 >0.000
Pneumonia	3	5.5	8	18.2	FET* <0.058
Anaemia	2	3.6	4	9.1	FET* <0.066
Malaria	2	3.6	4	9.1	FET* <0.066
Dysentery	7	12.7	4	9.1	FET* >0.750
Malnutrition	15	27.3	11	25.0	0.00(YC)** <0.98
Others***	17	30.9	10	22.7	0.46 <1.00

* FET= Fisher's Exact Test

** YC= Yates' Correction applied

*** Other diagnoses made included: Oral thrush, chronic suppurative otitis media, persistent fever, failure to thrive, fever, scabies skin sepsis, etc.

Management and its outcome

Out of 24(54.5%) HIV + ve and 18(32.7%) HIV - ve children admitted, 6 in each group died and 4 absconded, or were discharged against medical advice, while 14 HIV +ve and 8 HIV - ve children were discharged. The differences were not statistically significant ($\chi^2 = 0.8$, $p<0.672$).

The management of diarrhoea was similar for both groups and included rehydration with ORS and Intravenous fluids (when needed), feeding, multivitamins, vitamin A supplementation and appropriate antibiotics for those with bloody diarrhoea. Other treatments offered were patient-specific, based on their additional diagnosis (es). They included antibiotics, antifungals, antimalarials, blood transfusions and counselling for HIV in 8 (18.2%) and antiretroviral drugs in 3 (6.8%) HIV +ve children. The discharged patients in both groups failed to keep follow-up appointments ($\chi^2 = 0.31$, $p>0.858$). Eleven HIV + ve children and 8 HIV - ve children were lost to follow-up ($\chi^2 = 0.000$, $p<0.986$). The counselling of caregivers on the child's HIV serostatus did not significantly influence compliance

mortality in our setting. The similarities in the socio-demographic and pre-illness data of the HIV +ve and -ve children highlight their similar exposures to risk factors for persistent diarrhoea. These factors include lack of exclusive breastfeeding, poor sanitation and water supply and poor infant and young child feeding practices [16]. The low socio-economic status of most of the children's caregivers may explain the delay in the presentation for treatment, the high rate of discharge against medical advice and abscondment from treatment. It may also account for the failure to bring the children for follow-up appointments, in spite of their knowledge of the severity of their children's conditions, including their HIV serostatus. Poverty has been identified as an important contributor to increased child morbidity and mortality hence the eradication of extreme poverty was adopted as one of the Millennium Development Goals [17-19]. Poverty may be one of the reasons for failure of a number of cost-effective strategies to reach those who need them most and therefore leaves them with increased morbidity and mortality [9,20]. One of the challenges, therefore, of public health is to ensure universal access of all persons,

irrespective of their social status, to these cost effective interventions which have positively impacted on child survival [21].

This study confirms previous reports that HIV infection increased the susceptibility of children to frequent and severe forms of the common childhood illnesses [13]. The increase in the number of cases of HIV positive children is of great concern since it agrees with reports that as the epidemic worsens, more HIV-related under-five deaths will occur [10-12]. Thus, without expanding the access of women to the Prevention of Mother-to-Child Programme for HIV, the present vertical infection rate of 25-45% in our setting will remain and the threatened loss of the gains of the Child Survival activities of the last two decades may become a reality [5,8-10,13].

The persistent diarrhoea-related morbidity and mortality previously documented has also persisted in our setting [5]. Our results showed that, overall, a large proportion of HIV positive patients had longer duration of diarrhoea compared with HIV negative patients. Additionally, HIV seropositivity significantly increased the morbidity and mortality in children with persistent diarrhoea. These findings support the recommendation that, in high HIV prevalence areas all children presenting with diarrhoea, pneumonia or otitis media should be assessed for HIV infection [16]. This will lead to early detection of HIV infection and improved management of affected children and their families, since most paediatric HIV infections are vertically acquired [11].

The poor compliance with follow-up appointments noted in this study highlights the need for community-based programmes to improve services to ill children and their families, especially those with chronic illnesses such as sickle cell disease, tuberculosis, diabetes mellitus and HIV infection. This is because the poor compliance may be as a result of similar illnesses such as HIV and tuberculosis, in the caregivers. Such programmes may contribute to improved adherence to long term treatment programmes such as those required for HIV and sickle cell disease.

Diarrhoeal disease is preventable and its morbidity and mortality can be reduced by the application of the principles of diarrhoeal case management [1,3,7,14,15]. We therefore have the task of ensuring that these cost effective and high impact strategies are accessible and affordable on a wider scale [21-24]. The successful implementation of these strategies and others related to the attainment

of the MDGs require long term commitment from all stakeholders in all regions [10,17,21-25].

Conclusions

Persistent diarrhoea, irrespective of the child's HIV infection status, is associated with significant morbidity and mortality. It contributes to severe malnutrition. HIV infection, however, significantly increases a child's susceptibility to diarrhoeal diseases and its severity. The existence of other co-morbidities such as tuberculosis and severe wasting significantly worsen the course of diarrhoeal diseases. Children under-five years of age are unfortunately most vulnerable to HIV infection or persistent diarrhoea, probably because of their early acquisition of the infection vertically and their poorly developed immune status. The yearly increase in the prevalence of HIV documented in this series should alert policy makers on the need for more aggressive HIV control measures in the country.

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