HIV/TB Co-infection Among HIV Positive Children Attending Clinics In Imo State University Teaching Hospital Orlu, Imo State, Nigeria

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ABSTRACT

Background: ***Human Immunodeficiency Syndrome and tuberculosis are among the leading causes of death from infectious diseases worldwide. The resurgence of tuberculosis in children is partly attributed to the co-existing burden of human immunodeficiency virus infection, which is most pronounced in sub Saharan Africa.***

Aim: ***To determine the prevalence and pattern of HIV/TB co-infection among HIV positive children attending clinics at Imo State University Teaching Hospital.***

Method: ***This is a retrospective review of HIV/AIDS children attending HIV clinics at Imo State University Teaching Hospital, Orlu, Imo State, Nigeria from January, 2011- December, 2012.***

Results: ***Of the total of 128 HIV infected children reviewed during the 24 months period, 16(12.5%) were co-infected with tuberculosis, (95% CI, 10.7% - 14.3%). Among these 16 patients, TB co-infection was diagnosed before commencement of ART in 93.7% of them. Majority of the TB cases (87.5%) presented with pulmonary TB amongst whom only 25.0% were sputum positive. The factors found to affect TB development significantly were stage of HIV disease (p=0.000) and CD4 count level (P=0.021) of patients. The factor with the highest influence on TB development was the clinical stage of HIV disease (Odds ratio =6.013) and that of least influence was sex of patient (Odds ratio= 0.8319).***

Conclusion: ***The study revealed a moderately high TB/HIV co-infection rate. Low CD4 count level below 200cell/ml and late clinical stages of HIV disease contribute significantly to the development of TB disease.***

Key Words: ***HIV/AIDS, tuberculosis, co-infection, children.***

INTRODUCTION

Worldwide, the human immunodeficiency virus/ acquired immunodeficiency syndrome (HIV/AIDS) epidemic has been accompanied by a severe epidemic of tuberculosis (TB)[1]. HIV infection is the leading risk factor for TB. HIV promotes progression of latent or recent infections of mycobacterium tuberculosis to active disease and also increases the rate of occurrence of TB[2]. People living with HIV may also be more susceptible to TB infection[3]. HIV is the first and TB is the second leading cause of death from infectious disease Worldwide[4]. Globally 2 billion people are estimated to be latently infected with tuberculosis[5]; whilst, there are an estimated 35.3 million people living with HIV, 70% of who live in sub-Saharan Africa[6]. Annually, there are an estimated 8.7 million (range 8.3-9.0 million) new cases of TB, and 2.5 million new HIV infections[5,6]. Of the 8.7 million new cases of TB in 2011, 1.1 million (13%) were among people living with HIV[6].

There are well established epidemiological and biological synergies between HIV and TB, influencing the distribution, progression and outcomes of both infections. The HIV epidemic is a key factor behind the resurgence of TB incidence worldwide and HIV is the pre-incident risk factor for the development of TB[4]. One in eight incident cases of TB occur in HIV positive individuals, with a quarter of all TB deaths in people with HIV, while around a fifth of HIV related deaths occur in new TB cases[6, 7]. Much of the burden of TB and HIV co-infection is in Africa, where one-third of the approximately 2.3 million people who developed TB in 2010 were HIV positive[5]. Other regions strongly affected by TB and HIV dual epidemics are India and Eastern Europe[8,9].

There are scarce data on the incidence of TB among HIV positive children diagnosed with TB, and the information that is available is difficult to interpret due to problems with diagnosis, under-reporting and selection of study populations (i.e. most are recruited from hospitals or referral hospitals rather than the community)[4]. Worldwide, over one million children are infected with tuberculosis and 630,000 by HIV annually[10, 11]. While TB alone is responsible for over 250,000 deaths in children every year, HIV is projected to cause more than 56,000 deaths worldwide annually [12,13]. The World Health Organization (WHO) estimates that HIV prevalence among children with TB, in countries with moderate to high prevalence, ranges from 10-60%[14]. Prevalence varies depending on background rates of HIV infection[15].

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Estimated rates of TB among children with HIV vary widely across the globe, partly depending on whether the study is taking place in a TB endemic area or not, and on highly active antiretroviral treatment (HAART) coverage in that area, but also due to problems of reaching a definitive diagnosis of TB in children with HIV and under-reporting[4]. In London, United Kingdom, the proportion of co-infection among HIV infected paediatric patients was 5.5%[16]. Three percent was reported in a US cohort of nearly 1500 HIV infected children[17], 17.0% reported among hospitalized children in peru[3], and 48.0% reported from a study in South Africa[18]. In Nigeria, the true prevalence and magnitude of HIV/TB co-infection in children has remained under-reported[19]. Reports from few studies done showed that the prevalence of 15.2% was reported among children from Nnewi[20], 19.5% reported from among HIV positive children in Abuja[19], and 48.8% found among HIV positive children in Benin[30]. About 10% prevalence rate has been reported from another West African country[21].

Those children with co-infection also have a higher case fatality rate[2]. In resource–limited settings, mortality rates among HIV-infected children diagnosed with TB range from 20-35%[22-24]. HIV infection has been known to weaken the immune system by depleting the CD4 cell counts and in turn giving room for opportunistic infections[19], while TB itself accelerates the progression of HIV disease by increasing viral replication and reducing CD4 counts still further[25-28]. Children infected with HIV have 50 times greater risk of developing primary progressive TB in a year from severe immune suppression of young age and HIV infection[21]. Thus, the aim of this study is to determine the prevalence and pattern of HIV/TB co-infection among HIV positive children attending HIV clinics in Imo State University Teaching Hospital, Orlu, Imo State Nigeria.

METHODOLOGY

Imo State University Teaching Hospital is situated in Orlu, the 2nd largest town in Imo State. It is the only teaching hospital in the state that has a population of about 4.2 million people[29]. The hospital operates a specialist clinic for HIV/AIDS patients including that for children. Similarly, a chest clinic has been established in the hospital which provides anti-tuberculosis treatment for all TB patients. The study population comprised all HIV/AIDS patients below the age of 18 years who attended the paediatric HIV clinic from January 2011 to December 2012.

Medical records of all patients that attended HIV clinic within the stipulated period were reviewed. Data was extracted using a standardized form including; socio-demographic data, socioeconomic status of parents/guardians, clinical features, mode of diagnosis, treatment and outcome. In addition, base line CD4 count level and WHO clinic stage at presentation were noted. Ethical clearance was obtained from the ethics committee of Imo State University Teaching Hospital Orlu, Imo State.

At the study centre HIV infection was diagnosed based on suggestive clinical symptoms and positive spot test for HIV antibodies (STAT PAK by Chemobio Diagnostic System Inc, New York and DETERMINE by Abbott Laboratory, Japan) or a positive HIV DNA-PCR in six weeks and a repeat using dry blood spot (DBS) sample in those less than 18 months of age. The diagnosis of tuberculosis was made using a combination of the following; history of cough greater than three weeks, contact with adult with chronic cough/confirmed TB, weight loss, fever greater than one month, and abnormal chest radiograph, positive mantoux test of > 5mm in diameter, identification of acid fast bacilli (AFB) in sputum,gastric or body fluids, and non-response to conventional antibiotics.

The data was analysed using Epi-info version 7.1 software. Quantitative variables were summarized using the appropriate summary indices while categorical variables were tabulated using frequencies and percentages. The chi-square test was used for testing the significance of differences between categorical variables. Odd ratios were generated to assess the level of influence of associated factors. A p-value of less than 0.05 was considered as statistically significant.

RESULTS

A total of 128 HIV positive children attended the HIV clinics of Imo State University Teaching Hospital within the period under review. The mean and median ages of respondents were 7.6 $\pm$ 0.8 and 9.5 years respectively, with age group 0-5 years having the highest frequency, 59(46.1%). These were more males, 77(60.2%), than females, 51(39.8%). Other socio-demographic data are as in table I. A greater proportion of the respondents had CD4 count levels greater than 200 cells/ml, 88 (60.7%). The mean and median CD4 count levels are 279.3 $\pm$ 96.5 cells/ml and 281.5cells/ml respectively. Majority of them, 87(67.0%), presented at stage I and II of HIV disease (see table I).

Of the total 128 HIV-infected children reviewed, 16 (12.5%) were co-infected with TB. Among these 16 patients, TB co-infection has been diagnosed before the commencement of ART in 15 (93.7%) of them. In those with co-infection, majority of them, 14(87.5%), had

pulmonary tuberculosis (PTB), among whom only 4 (25.0%) were sputum positive. Most of the diagnosis of TB, 10 (62.5%), were made by Chest X-ray suggestive of PTB. All the cases of extra pulmonary tuberculosis diagnosed were abdominal TB. The commonest symptoms at presentation were cough greater than 3 weeks, (68.8%), followed by low grade fever, 62.5%, and weight loss, 31.3% (see table II).

Co-infection rate was slightly higher in females, 7 (13.7%) than males, 9 (11.6%). The reverse was the case when the burden of the disease was assessed, (56.3% versus 43.7%); this difference was not statistically significant. Co-infection rate and burden of co-infection was higher in children greater than 5 years of age, 13.0% and 56.2%. This difference was not statistically significant. Patients with CD4 counts below 200 cells/ml, had a higher co-infection rate (22.5%) and burden of co-infection (56.2%) than those with CD4 counts greater than 200 cells/ml (p=0.021). Also, HIV patients co-infected with TB had a median CD4 lymphocyte count of 198 cells/ml when compared to 282 cells/ml found in those without co-infection (p>0.05). With respect to WHO clinical stage, patients at stages III and IV of HIV disease had higher prevalence (14.3%) and burden (68.7%) of the disease (see table III) than their counterparts at stages I and II of HIV disease (P=0.000).

The factor with the highest influence on co-infection using odds ratio was the clinical stage of the disease, (OR=6.013, 95% CI, 1.9292-18.7434) followed by level of CD4 count of patients, (OR=3.3594, 95% CI, 1.1512-9.8036), while the factor with the least influence among the accessed ones was sex of patient (OR, 0.8319, 95% CI, 0.2888-2.3966).

Table I: Socio-Demographic Characteristic, CD4count and Staging of HIV Disease among HIV Positive Children Attending Clinics in IMSUTH.

Socio-demographic characteristic	Frequency	Percentage
Sex		
Male	77	60.2
Female	51	39.8
Total	128	100.0
Age (Years)		
0-5	59	46.1
6-10	36	28.1
11-18	33	25.8
Total	128	100.0
Care giver		
Parents	80	66.0
Grand parents	8	6.3
Others relatives	40	27.7
Total	128	100.0
Occupation of care givers		
Traders	56	
Artisan	32	43.8
Teachers	24	25.0
Farmers	8	18.8
Civil servants	8	6.2
Total	128	6.2 100.0
Educational status of care givers		
None	16	12.5
Primary	24	18.7
Secondary	56	43.8
Tertiary	32	25.0
Total	128	100.0
CD4 count levels		
1-200	40	31.3
201-300	30	23.4
>301	58	45.3
Total	128	100.0
Stage of disease		
I and II	87	67.0
III and IV	41	32.0
Total	**128**	**100.0**

Table II: Tuberculosis Presentation in HIV/TB co-infected Patients Attending Paediatric HIV Clinics in Imo State University Teaching Hospital, Orlu.

Variable	Frequency	Percentage
Type of TB	n=16	
PTB	14	87.5
EPTB	2	12.5
Total	16	100.0
Diagnosis		
AFB positive	4	25.0
C-Xray suggestive of TB	10	62.5
Mantoux positive	2	12.5
Total	16	100.0
Symptoms at presentation (multiple response applicable)		
Cough	11	68.8
Fever	10	62.5
Weight loss	8	50.0
Distended abdomen	5	31.3
Others	2	12.5
Others (night sweats, stunted growth)		
ART status prior to diagnosis		
On HAART	1	6.3
Not on HAART	15	93.7
Total	**16**	**100.0**

Table III: HIV/TB co-infection

Variable	Co-infected (%)	Not Co-infected (%)	Total (%)	Co-infection Burden (n/Nx100)	χ2	p-value
Sex						
Male	9(11.6)	68(88.3)	77(100.0)	56.3		
Female	7(13.7)	44(86.3)	51(100.0)	43.7	0.116	0.733
Total	16(12.5)	112(87.5)	128(100.0)	100.0		
Age						
0-5	7(11.9)	52(88.1)	59(100.0)	43.8		
6-10	4(11.1)	32(88.9)	36(100.0)	25.0	0.065	0.7981
11-18	5(15.2)	28(84.8)	33(100.0)	31.2		
Total	16(12.5)	112(87.5)	128(100.0)	100.0		
CD4 count						
1-200	9(22.5)	31(77.5)	40(100.0)	56.2		
> 201	7(8.0)	81(92.0)	88(100.0)	43.8	5.319	0.021*
Total	16(12.5)	112(87.5)	128(100.0)	100.0		
Stage of disease						
I and II	5(5.7)	82(94.3)	87(100.0)	43.7		
III and IV	11(26.8)	32(73.2)	41(100.0)	55.3	11.32	0.000*
Total	**16(12.5)**	**112(87.5)**	**128(100.0)**	**100.0**		

Table IV: Level of influence of some factors in development of HIV/TB co-infection using odd ratio.

Factors	Co-infection (%)	Odd ratio	95 CI
Sex			
Male	9(11.6)		
Female	7(13.7)	0.8319	0.2888-2.3966
Age			
0-5	7(11.9)		
>5	9(13.0)	0.8974	0.3124-2.5781
Level of CD4 count			
1-200	9(22.5)		
>201	7(8.0)	3.3594	1.1512-9.8036
Stage of disease			
I and II	7(8.1)		
III and IV	9(22.0)	6.013	1.9292-18.7434

DISCUSSION

The HIV/TB co-infection rate found in our study environment was moderately high (12.5%). This is within the limits (10-60%) reported by WHO among HIV children, in countries with moderate to high TB burden[14]. This is also comparable to 15.2% reported from HIV children at Nnewi, Nigeria[20] and 10.0% reported from studies in another West African Country[2]. It is however lower than 19.5% reported from Abuja, Nigeria[19],17.0% reported among HIV hospitalized children in Peru[12], and even much lower than 48.8% found among HIV positive children in Benin, Nigeria[30]and 48.0% reported from a study in South Africa[18] . It is higher than 3.0% and 5.5% reported from US and UK respectively[16,17]. These wide variations in the co-infection rates of HIV/TB in children across the globe, as reported, can partly be accounted for by the following reasons: level of TB endemicity, coverage level of highly active antiretroviral treatment (HAART), unique challenges of TB diagnosis in children with HIV, under-reporting, diagnostic procedures used and study methodology applied. These high prevalence reported from studies in African countries, including Nigeria, re-affirm earlier reports from United Nations Programme on HIV/AIDS (UNAIDS) and WHO that over 90% of 2.3 million world children living with HIV reside in the sub-Saharan Africa alone[11,31]. Nigeria is one of the countries of the sub region that have continued to bear the greatest burden of paediatric HIV/AIDS[20]. Studies have shown that more than 80% of people living with TB reside in the sub-region, and that those with HIV have fifty times more risk of developing TB in a year than those not affected[31].

Most of the patients (87.5%) presented with pulmonary tuberculosis and diagnosis was made by a combination of signs, symptoms and laboratory investigation. Generally, tuberculosis is an air borne infection that manifest in its pulmonary form in up to 70.0% of cases and rarely in extrapulmonary form, especially when the immune system is compromised as in late stages of HIV disease[33]. Only 25.0% of the cases had AFB test positive while majority of the cases had chest x-ray suggestive of TB (62.5%). This low AFB test positive is comparable to finding in Abuja[19] which was 22.0% and that by Cohen et al[16] which was 20.0%.

In this study, new techniques for TB diagnosis were not available; most of the diagnosis (75%) was based on presumptive basis, with therapeutic trial of anti-TB therapy. This is because ours is a low resource setting where these newer methods and well trained man power are scarce. The culture of respiratory specimen often considered as gold standard for diagnosis of TB in adult population performs poorly in children with rapid confirmation by smear achieved in less than 15.0%, with a positive culture generally in only 30-40% of cases after a delay of 4-8 weeks. Hence there is yet no established gold standard for children[19]. Even in resources rich setting with newer diagnostic facilities, majority of TB Co-infected children were treated on presumptive basis[16]. However, in context of emergence of drug resistant TB, the presumptive or therapeutic trial becomes questionable.

The demographic features of the study revealed a slightly higher co-infection rate in females (13.7%) than males (11.6%). The male to female ratio was 1.3:1. Generally the male to female ratio of TB in children is approximately unity, but the ratio increases in disfavour of the female child in adolescence [30]. The ratio of co-infection was slightly higher among the adolescent age group (15.2%), $p>0.05$; though, there was a higher burden of the disease in those less than 5 years of age (43.8%). Tuberculosis is commoner among children who are under-five years of age because of their vulnerable immune status. Ages between 5 and14years is considered the favoured age, but the prevalence of TB

begins to increase steadily in adolescence, especially for girls[30]. This seems to explain the reason for a higher prevalence in the adolescent age group found in this study. The high burden in the lower age group is likely due to high burden of HIV which reduces as the child gets older. Before most HIV children get to adolescent age in a resource poor environment like ours, most of them might have died of complications related to HIV/AIDS.

The association of lower CD4 cell counts and late stages of HIV/AIDS (III and IV) with TB co-infection observed in our study is expected as this has been consistently reported in several studies[2,4,12,17,19,20,25,27,28]. Cohen and co-workers[16], however made no such observation in their report, in fact they noted that many cases of TB in their co-infected children have relatively preserved T-cell function and found no association between CD4 cells count and TB manifestation. They attributed such observation to the small number of their study population. In most literature there is no clear cut-off for CD4 count above which the risk for TB development is diminished but research has however revealed a clear inverse correlation between CD4 count above which the risk of TB development is diminished[34,35]. It is well recognized that the risk of opportunistic infections, including TB, in persons with HIV increases markedly when CD4 count cell drops below 200 cells/mm^3 [36-38]. Depletion of $CD4^+$T cells seen in advanced HIV disease impairs host response to mycobacterium tuberculosis, particularly granuloma formation, hence facilitating progression of recent infection as well as reactivation of latent TB to active disease[39].

CONCLUSION

Our study revealed a moderately high prevalence of tuberculosis among HIV positive children. This is of great concern in that HIV/TB, both represent major threats to public health worldwide, especially in resource low setting like ours. This is a hospital based study; hence, the prevalence observed may not accurately reflect that of all HIV children not attending clinics in the environment due to iceberg phenomenon. Also to note is the difficulty in diagnosis of HIV/TB in children which is a major draw-back and can lead to missed diagnosis. Therefore there is need to adhere strictly to HIV preventive measures in pregnancy and child birth so as to reduce transmission of HIV. It is important to strengthen existing facilities using appropriate technology and personnel, this might be lacking in our environment. There is also need to create the necessary awareness so that communities will be involved in early active HIV/TB case finding and reporting to appropriate authorities.

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Conflict of Interest

The authors hereby declare that there is no competing interest.

Authors' contributions

Authors DCB, UKA, DKC designed the study, wrote the first draft, and contributed to the literature review and data analysis while CHN, NCC, OS and AC contributed to the literature review and data analysis. All authors read, reviewed, and approved the final draft.

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