Pattern of respiratory diseases among human immunodeficiency virus-infected children in Enugu, Nigeria

Adaeze C Ayuk[1,2], Agozie C Ubesie[1,2], Kenechukwu K Iloh[1,2], Ijeoma N Obumneme-Anyim[3], Ifeoma J Emodi[4], Ngozi S Ibeziako[4], Chukwuemeka J Anikene[5], Eziamaka J Enemuo[5], Ogochukwu Iloh[6], Uloma Nwogu[7]

From [1]Senior Lecturer, [2]Consultant Pediatrician, [4]Professor, [6]Lecturer, Department of Pediatrics, College of Medicine, University of Nigeria Enugu Campus, [3]Consultant Pediatrician, [5]Fellow, Department of Pediatrics, University of Nigeria Teaching Hospital Enugu, Nigeria, [7]Lecturer, Department of Radiography, College of Medicine University of Nigeria Enugu Campus, Enugu, Nigeria

Correspondence to: Ayuk C Adaeze, Department of Paediatrics, College of Medicine, University of Nigeria Enugu Campus, University of Nigeria Teaching Hospital Enugu, Enugu, Nigeria. E-mail: adaraymond@yahoo.com

Received - 01 May 2019 Initial Review - 25 May 2019 Accepted - 06 June 2019

ABSTRACT

Introduction: The lung is a major target for infectious and non-infectious complications of human immunodeficiency virus (HIV) infection. **Objective:** This study sought to assess the prevalence and pattern of respiratory diseases among HIV-infected children attending our pediatric HIV specialist clinic. **Methods:** A 10-year retrospective review of data on HIV-infected children seen at the Paediatric HIV clinic of the University of Nigeria Teaching Hospital, Ituku/Ozalla, Enugu. HIV diagnosis was made by HIV-DNA polymerase chain reaction testing and antibody testing depending on the age of the child. Diagnosis of pneumonia was made using the WHO pneumonia clinical algorithm while pulmonary tuberculosis (PTB) was diagnosed using clinical and radiological criteria. Data analyses were done with Statistical Package for the Social Sciences version 19 (Chicago, IL). **Results:** A total of 555 HIV-infected children were analyzed. There were 277 males (49.9%) with male to female ratio of 0.9–1. The cough was the most common complaint in 51.9% of the children. There were 327 respiratory cases observed in 181 of 555 (34.7%) of the children. Using clinical symptoms, 65 of 327 (9.9%) of study participants had upper airway-related diseases with otitis media being most predominant (27/65; 41.5%); pneumonia was reported in 146 of 327 (45%) and PTB in 115 of 327 (35%). Total 124 of 181 children (72.5%) with respiratory infections compared to 18 of 287 (6.3%) without infections had an abnormal chest X-ray (CXR) ($p<0.001$). Identified risk factors for developing respiratory disease were low socio-economic status, being on second-line highly active antiretroviral therapy and having an abnormal CXR finding. **Conclusions:** Pneumonia and PTB are common in children with HIV. Chronic radiological change is more common among HIV-infected children with clinical features of respiratory pathology. The need for close lung function monitoring in children with HIV is recommended for early detection of morbidity associated with these infections.

Key words: *Children, Human immunodeficiency virus, Nigeria, Respiratory infection*

The respiratory system is majorly susceptible for infectious and non-infectious complications associated with human immunodeficiency virus (HIV) [1-4]. Respiratory illnesses of both acute and chronic nature are the most common presenting complaints and causes of morbidity among HIV-infected children [4-7]. In a study in Kenya [6], the major reasons for hospital admission in children with HIV/AIDS were malnutrition (40.8%) and pulmonary tuberculosis (PTB) (20.9%), while in another study in Zambia [7], upper respiratory tract infection (URTI) was a major cause of morbidity among HIV-infected children on antiretroviral (ARV) therapy with an incidence rate of 100.6/100 children/years. HIV associated lung function decline is also well documented [8].

Chronic lung diseases in children with HIV include obliterative bronchiolitis, bronchiectasis, recurrent/persistent pneumonia of varied etiology, lymphocytic interstitial pneumonia (LIP), lung malignancies, pulmonary hypertension, interstitial pneumonitis, and immune reconstitution inflammatory syndrome among others [6-10]. These diagnoses sometimes require both a high index of suspicion and expertise to detect, and in resource-limited countries, there is more dependence on clinical features to make the diagnosis. There is inadequate data within the sub-region on lung pathologies affecting HIV-infected children and adolescents. This study thus assesses the prevalence and risk factors for respiratory disease among HIV-infected children attending our specialist clinic. This will highlight the burden of respiratory illness among HIV-infected children and possibly highlight the need for regular respiratory reviews and research for improved health outcomes in children with HIV.

MATERIALS AND METHODS

Pediatric HIV clinic is a referral clinic located at the University of Nigeria Teaching Hospital (UNTH) Enugu, Southeast Nigeria. It was established in March 2004. The clinic attends to patient's twice-weekly providing care and treatment for HIV-infected children, which includes nutritional check, tuberculosis (TB) screening, and laboratory services where blood parameters are monitored. The clinic receives referrals from health facilities within and outside Enugu metropolis and parts of the Southeast of Nigeria and attends to an average of 20 patients/week. Ethical approval was obtained from the Health Research and Ethics Committee of UNTH Enugu.

This was a retrospective study. The electronic medical records at enrolment of HIV-infected children seen between December 2004 and November 2015 were extracted and critically reviewed. Inclusion criteria enlisted participants whose HIV results were clearly documented as positive in the folder, for whom standard methods of HIV testing were used. Participants with inconclusive HIV result, those with only HIV exposure but not confirmed disease and those with missing data on respiratory and demographic variables were excluded from the study. HIV diagnosis was based on positive HIV DNA polymerase chain reaction (PCR) testing for children younger than 18 months and antibody testing for children ≥18 months.

Diagnosis of pneumonia was made using the WHO pneumonia clinical algorithm [9,10]. Furthermore, chest X-ray (CXR) was used to confirm "pneumonic" changes such as bronchovascular markings or reticular densities, parenchymal consolidation, nodular densities, hyperinflation, fibrosis, cavities, and interstitial. Diagnosis of PTB was done using clinical and radiological criteria (fever, cough of >1-month duration, weight loss, history of contact with an adult with chronic cough, night sweats, positive smear/Gene Xpert test of sputum or gastric aspirate where available). Radiological signs that were used as "suggestive of TB" were miliary nodules, airway narrowing, and tracheal deviation to the left, presence of hilar, paratracheal, subcarinal, or another lymphadenopathy, evidence of calcification, cavitation, pleural effusion, or thickening.

Using the case notes, these were analyzed with the clinical evidence by the researchers and the CXR interpretation was done by an independent consultant radiologist who was blinded to case note of patient. Socio-economic status (SES) was determined by modified validated methods described by Ogunlesi *et al.* Using the parenteral level of education and type of vocation of parents and these were further categorized into lower Class 3 (socio-economic class [SEC] 4 and 5), middle Class 2 (SEC 2 and 3), and upper Class 1 (SEC 1) [11].

Risk factors for the presence of respiratory pathologies that were also sought for included age, gender, SES, and markers of disease severity such as the presence of digital clubbing, HIV stage, and highly active ARV therapy (HAART) status.

Retrieved data that were available for the various parameters were analyzed using the Statistical Package for the Social Sciences version 19.0 (Chicago IL). Individual variables were analyzed in isolation using univariate analysis. Student t-test and Analysis of Variance (ANOVA) were used to compare means of continuous variables while the Chi-square test was used to test the significant association of categorical variables. Regression analyses of risk factors for respiratory disease were also done. $p<0.05$ was regarded as statistically significant and 95% confidence interval was reported where indicated.

RESULTS

A total of 555 HIV-infected children were included in the data analysis with a mean age of 9.9±4.6 years (range 2 months–22 years). There were 277 (49.9%) males with a male to female ratio of 0.9–1. Of all the study participants, 341 (61.4%) were from the lower social class, as shown in Table 1. Mother-to-child transmission of HIV accounted for 481 (92.5%) of cases. The mean age at HIV diagnosis was 5.3±3.9 years. The mean CD4 count was 681.52 (609.626) and RNA viral load of 394,043.36 (log 5.6). There were 217 (39%) and 206 (37%) children who were at HIV Stages II and III, respectively. Sixty-one children had failed first-line ARVs medications and were on the second line (Table 1).

There were 327 respiratory related disease cases diagnosed in all study participants and occurred either alone or in combination with other respiratory diagnosis (Fig. 1).

Number Key to Respiratory Diseases

1=Otitis media 8.2%; 2=Upper airway obstruction (adenoidal hypertrophy, enlarged TB lymph node) 1.5%; 3=Parotitis 2.8%; 4=Sinusitis 0.3%; 5=Other URTI 6.7%; 6=PTB 35.2%; 7=Bronchopneumonia/lobar pneumonia 44.7%; 8=Pneumocystis Carinii Pneumonia (PCP) pneumonia 0.3%; 9=LIP pneumonia 0.3%

Table 1: Basic profile of the study participants with HIV

Characteristics	HIV-positive n (%)
Gender	
Male	277 (49.9)
Female	278 (50.1)
Socio-economic class	
Upper class	24 (4.8)
Middle class	138 (27.4)
Lower class	341 (67.8)
HIV staging	
1	103 (18.6)
2	217 (39.1)
3	206 (37.1)
4	29 (5.2)
HAART status	
First line	346 (71.2)
Second line	61 (12.6)
Yet to commence HAART	79 (16.3)

HAART: Highly active antiretroviral therapy, HIV: Human immunodeficiency virus

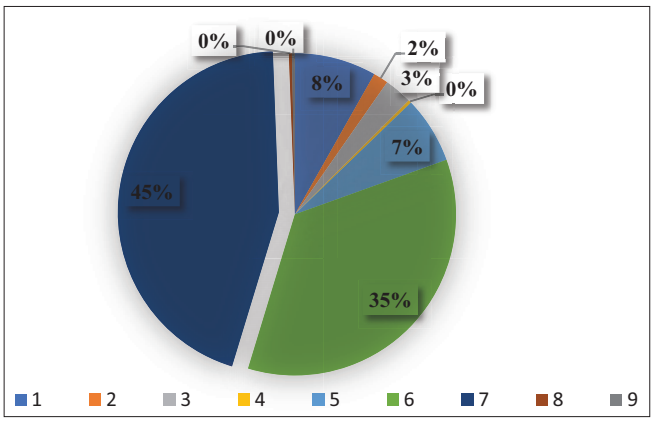

Figure 1: Pattern of respiratory infections in children with human immunodeficiency virus

Cough as a symptom was the most common respiratory complaint and occurred in 271 of 555 (48.8%) of participants. Using clinical symptom analyses, 65 of 327 (19.9%) of all cases were upper airway-related diseases and otitis media were the most predominant (27/65; 41.5%), while pneumonia cases were 146 of 327 (45%) and PTB reported in 115 of 327 (35%), both representing the predominant lower airway diseases. None of the children was previously hospitalized for PTB as at the time of recruitment. Only one child had digital clubbing. All children were fully immunized for age and as most were above 6 years, breastfeeding data were not included in analyses.

The mean age at HIV diagnosis among children with respiratory-related complaints was 4.9±3.3 years compared to 5.4±4.1 years among those without respiratory pathologies (p=0.14). Out of 277 males, 110 (39.7%) compared to 84 of 278 females (30.2%) with HIV, had associated respiratory pathology (p=0.019), as depicted in Table 2.

Chest radiographs were requested in 458 children who required further evaluation of their respiratory symptoms. One hundred and forty-two (32%) of these children whose chest radiographs were studied, had an abnormal CXR, suggestive of possible bronchopneumonia, lobar pneumonia, PCP pneumonia, LIP, TB, and bronchiectasis. Finding an abnormality on CXR was positively associated with the presence of respiratory clinical symptoms. Of those who had clinical symptoms related to the respiratory system, 124 of 171 (72.5%) had abnormal CXR, while among the 287 of 555 who did not have respiratory-related symptoms only 18 of 287 (6.3%) had any CXR abnormalities (p<0.001).

After adjusting for confounding variables, the SES (p=0.04), children on second-line HAART (p=0.03), and those with abnormal CXR (p=0.02) remained significant risk factors for respiratory infection in children with HIV (Table 3).

Table 2: Prevalence of respiratory illnesses among gender and SES

Characteristics	Respiratory diseases		p value
	Yes (%)	No (%)	
Gender			
Male	110 (39.7)	167 (60.3)	0.019
Female	84 (30.2)	194 (69.8)	
SES			
Upper class	5 (2.9)	19 (5.8)	0.212
Middle class	44 (25.3)	94 (28.6)	
Lower class	125 (71.8)	216 (65.6)	

SES: Socio-economic class

Table 3: Risk factors for respiratory disease in children with HIV

Possible risk factors	Wald	df	p value
Gender	0.165	1	0.685
Age at HIV diagnosis	0.366	1	0.545
Duration of HAART treatment	0.525	5	0.991
Socioeconomic status	11.430	5	0.043
Vertical transmission	4.620	3	0.202
On first-line HAART	1.667	2	0.435
On second-line HAART	4.576	1	0.032
Abnormality in chest X-ray	7.342	2	0.025

HAART: Highly active antiretroviral therapy, HIV: Human immunodeficiency virus

DISCUSSION

In consonance with previously conducted studies, it was observed that otitis media were the most prevalent upper respiratory pathology while cough was the most commonly reported symptom. Mehta *et al.* [12], in India, reported that 96% of their study participants presented with cough. URTI have in some reports occurred as frequently irrespective of HIV status [13]; however, the high incidence reported among children with HIV may be related to their immune deficiency status with a predisposition for organs such as the lungs. The incidence was as high as 33% in a study by Wallace *et al.* [14], who also noted chronic sinusitis to be common.

In another cohort study among adults with HIV, self-reported acute sinusitis, acute bronchitis, pulmonary Kaposi sarcoma, asthma, and chronic obstructive pulmonary disease were documented [15]. High incidence of pneumonia and TB in HIV-infected individuals is reported as observed also in our series. Similar to our study, Mehta *et al.* [12] also reported that PTB was the most common respiratory infection in 72% of their study group far and above bacterial pneumonia reported in 22% of their study population. The high prevalence of pneumonia and TB as respiratory infections in people with HIV reinforces the immune dysfunction, especially for PTB when HIV has caused CD4 depletion when the two diseases coexist.

When making a diagnosis of TB in children, the use of clinical and radiologic criteria remains pertinent especially in resource-poor countries where there is limited access to advanced techniques for TB diagnosis in children such as sputum gene Xpert. This is more so when the "gold standard," which is sputum culture may take as long as 6 weeks before obtaining results.

Furthermore, the diagnosis of TB in children infected with HIV is even more difficult [8], as the clinical and radiographic features are shared with other opportunistic diseases that occur in HIV [14]. This may have possibly contributed to the high prevalence in our study and that in India [12]. Controversies abound on inter and intra-observer discordance in CXR interpretation [16,17]. It is thus important to be cautious and not place more emphasis than required

on CXR findings, but rather combine clinical, radiological, and other diagnostic tools where available.

However, in areas where TB is endemic, there should still be a call to action to make available the current and more reliable diagnostic tools and for proper contact tracing to be done for children in households with adults who have open TB. This would reduce transmission and eventually impact on high TB prevalence. Social status had a significant effect on the respiratory outcome. This emphasizes the need for proper education about TB and other respiratory illness at the grassroots, where poverty, ignorance, and disease will affect the outcome in children with HIV whose parents belong to the low social class.

A normal CD4+ count is from 500 to 1400 cells/mm^3. This is affected by non-initiation or non-adherence to ARV therapy. With counts below 200 cells/mm^3, susceptibility to opportunistic infections is made worse [13-15,18,19]. Our patients had a mean count above 600 cells/mm^3. It is, however, important to note that when HIV is not diagnosed early, the patients are predisposed to several chest infections even at relatively high CD4+ counts [19] and if not managed properly, could be prone to chronic lung infections, poor lung function, [18] with the worse outcome due to advanced immunosuppression. In our study population, cases were diagnosed at about 5 years, though not yet immune suppressed.

The early initiation of ARV therapy, when CD4+ count is still expectedly high, is known to have a modulating effect on respiratory outcome in children with HIV [19]. In a study by Kitahata *et al.* [19], initiation of HAART before the CD4+ count reached below certain thresholds, significantly improved survival, when compared with those whose therapy had been deferred for one reason or another. Children who commenced second-line HAART may have thus been more likely to have been diagnosed late, among other possible reasons and thus explaining why it is a risk factor, as seen in our study.

Although CXR and its interpretation may be controversial in the diagnosis of respiratory infection, it is still a veritable screening tool and a good adjunct to clinical examination in detecting respiratory pathology even though not usually recommended in straight forward Community-Acquired Pneumonia [10,16,20]. Radiological findings in HIV infection may, however, be atypical and possibly difficult to distinguish between various respiratory diagnoses. However, when combined with other clinical parameters, it is still a very sensitive screening tool especially in resource-poor settings where access to the chest ultrasound, sputum induction techniques, and spirometry may be lacking.

In our study, abnormalities detected on CXR gave credence to clinical diagnoses earlier made such as pneumonia, TB, and bronchiectasis. Our study further supported the need for an initial request for CXR in HIV infected children with respiratory complaints as there was a significant finding of respiratory disease whenever abnormality on CXR was detected. Given the burden of respiratory disease in this population, having a sensitive and objective measure of lung function would be helpful for early detection of disease and longitudinal follow-up to optimize management and improve respiratory health outcomes. When following up children with HIV, serial measurement of lung function is thus imperative. Other chronic lung diseases like bronchiectasis were not prevalent in this study. It is possible that they were present but missed as information from spirometry and computed tomography (CT) scan would have been invaluable to support these diagnoses.

The present study had some limitations from our retrospective analyses. Core reliance on the clinical/X-ray diagnosis of pneumonia and TB may have led to over-diagnosis of these diseases. Bronchoalveolar lavage and sputum culture/PCR were not done; thus, the specific spectrum of microbiological organisms was not available as this would have been informative on the organism prevalent in HIV respiratory diseases in this region. CT scan of the chest was not done due to the cost, and thus, the prevalence of diseases like bronchiectasis may be wrongly misrepresented. The retrospective nature of the data used also limits inferences made from the study.

CONCLUSIONS

There was a significant finding of respiratory diseases among HIV-infected children; with pneumonia and TB ranking the highest. Low SES, being on second-line HAART and having abnormal CXR are significant risk factors for respiratory infection among children with HIV. The need for full respiratory review, including lung function testing in children with HIV in the sub-region is recommended.

REFERENCES

1. Pettit AC, Kaltenbach LA, Maruri F, Cummins J, Smith TR, Warkentin JV, *et al.* Chronic lung disease and HIV infection are risk factors for recurrent tuberculosis in a low-incidence setting. Int J Tuberc Lung Dis 2011;15:906-11.
2. Zar HJ. Chronic lung disease in human immunodeficiency virus (HIV) infected children. Pediatr Pulmonol 2008;43:1-10.
3. Rennert WP, Kilner D, Hale M, Stevens G, Stevens W, Crewe-Brown H, *et al.* Tuberculosis in children dying with HIV-related lung disease: Clinical-pathological correlations. Int J Tuberc Lung Dis 2002;6:806-13.
4. Jeena PM, Coovadia HM, Thula SA, Blythe D, Buckels NJ, Chetty R, *et al.* Persistent and chronic lung disease in HIV-1 infected and uninfected African children. AIDS 1998;12:1185-93.
5. Abrams EJ. Opportunistic infections and other clinical manifestations of HIV disease in children. Pediatr Clin North Am 2000;47:79-108.
6. Wamsele J, Kisenger R. HIV/AIDS and associated morbidity and mortality among hospitalised children in Kilifi, Kenya. Tanzan Health Res 2006;8:90-4.
7. Mubiana-Mbewe M, Bolton-Moore C, Banda Y, Chintu N, Nalubamba-Phiri M, Giganti M, *et al.* Causes of morbidity among HIV-infected children on antiretroviral therapy in primary care facilities in Lusaka, Zambia. Trop Med Int Health 2009;14:1190-8.
8. Githinji LN, Gray DM, Zar HJ. Lung function in HIV-infected children and adolescents. Pneumonia (Nathan) 2018;10:6.
9. World Health Organization and UNICEF. Model Chapter for Text Books IMCI-Integrated Management of Childhood Illness. Geneva: WHO/FCH/CAH, Department of Child and Adolescent Health and Development; 2001.
10. Bradley JS, Byington CL, Shah SS, Alverson B, Carter ER, Harrison C, *et al.* The management of community-acquired pneumonia in infants and children older than 3 months of age: Clinical practice guidelines by the pediatric infectious diseases society and the infectious diseases society of America. Clin Infect Dis 2011;53:e25-76.

11. Ogunlesi AT, Dedeke IO, Kuponiyi OT. Socio-economic classification of children attending specialist paediatric centres in Ogun state, Nigeria. Niger Med Pract 2008;54:21-5.
12. Mehta AA, Anil KV, Vithalani KG, Patel KR. Clinico-epidemiological profile of HIV patients with respiratory infections and tuberculosis in Western India. J Clin Diagn Res 2011;5:206-9.
13. Miller R. HIV-associated respiratory diseases. Lancet 1996;348:307-12.
14. Wallace JM, Rao AV, Glassroth J, Hansen NI, Rosen MJ, Arakaki C, *et al.* Respiratory illness in persons with human immunodeficiency virus infection. The pulmonary complications of HIV infection study group. Am Rev Respir Dis 1993;148:1523-9.
15. Gingo MR, Balasubramani GK, Kingsley L, Rinaldo CR Jr., Alden CB, Detels R, *et al.* The impact of HAART on the respiratory complications of HIV infection: Longitudinal trends in the MACS and WIHS cohorts. PLoS One 2013;8:e58812.
16. Waterer GW. The diagnosis of community-acquired pneumonia. Do we need to take a big step backward? Am J Respir Crit Care Med 2015;192:912-3.
17. Self WH, Courtney DM, McNaughton CD, Wunderink RG, Kline JA. High discordance of chest x-ray and computed tomography for detection of pulmonary opacities in ED patients: Implications for diagnosing pneumonia. Am J Emerg Med 2013;31:401-5.
18. Githinji LN, Gray DM, Hlengwa S, Myer L, Zar HJ. Lung function in South African adolescents infected perinatally with HIV and treated long-term with antiretroviral therapy. Ann Am Thorac Soc 2017;14:722-9.
19. Kitahata MM, Gange SJ, Abraham AG, Merriman B, Saag MS, Justice AC, *et al.* Effect of early versus deferred antiretroviral therapy for HIV on survival. N Engl J Med 2009;360:1815-26.
20. Lim WS, Baudouin SV, George RC, Hill AT, Jamieson C, Le Jeune I, *et al.* BTS guidelines for the management of community acquired pneumonia in adults: Update 2009. Thorax 2009;64 Suppl 3:31-55.

Funding: None; Conflict of Interest: None Stated.

How to cite this article: Ayuk AC, Ubesie AC, Iloh KK, Obumneme-Anyim IN, Emodi IJ, Ibeziako NS, *et al.* Pattern of respiratory diseases among human immunodeficiency virus-infected children in Enugu, Nigeria. Indian J Child Health. 2019; 6(6):287-291.

Doi: 10.32677/IJCH.2019.v06.i06.007