East African Medical Journal Vol. 90 No. 11 November 2013
ASSOCIATION BETWEEN FINGER CLUBBING AND CHRONIC LUNG DISEASE IN HIV INFECTED CHILDREN AT KENYATTA NATIONAL HOSPITAL
J. J. Odionyi, MBChB, MMed (Paeds), C. A. Yuko-Jowi, MBChB, MMed (Paeds, Paediatric Cardiology), Senior Lecturer, D. Wamalwa, MBChB, MMed (Paeds), MPH, Senior Lecturer, N. Bwibo, MBChB, MPH, FAAP, MRCP, Professor, Department of Paediatrics and Child Health, University of Nairobi, Nairobi and E. Amukoye, MBChB, MMed (Paed), Critical Care, Paediatric Bronchoscopy / Respiratory, Senior Research Officer, Centre for Respiratory Disease Research, Kenya Medical Research Institute, P. O. Box 54840-00202, Nairobi, Kenya

Request for reprints to: Dr. J.J. Odionyi, P. O. Box 102299-00101, Nairobi, Kenya

ASSOCIATION BETWEEN FINGER CLUBBING AND CHRONIC LUNG DISEASE IN HIV INFECTED CHILDREN AT KENYATTA NATIONAL HOSPITAL

J. J. ODIONYI, C. A. YUKO-JOWI, D. WAMALWA, N. BWIBO and E. AMUKOYE

ABSTRACT

***Background*: Finger clubbing in HIV infected children is associated with pulmonary diseases. Respiratory diseases cause great morbidity and mortality in HIV infected children.**
***Objective*: To determine association between finger clubbing and chronic lung diseases in HIV infected children and their clinical correlates (in terms of WHO clinical staging, CD4 counts/ percentage, anti-retroviral therapy duration and pulmonary hypertension).**
***Design*: Hospital based case control study.**
***Setting*: The Kenyatta National Hospital (KNH) comprehensive care clinic (CCC) for HIV infected children and Paediatric General Wards.**
***Subjects*: The study population comprised of HIV infected children and adolescents aged eighteen years and below.**
***Results*: Chronic lung disease was more common among finger clubbed (55%) than non finger clubbed patients (16.7%). Finger clubbed patients had higher risk of hypoxemia (46.7%), pulmonary hypertension (46.7%) and advanced disease in WHO stage III/ IV (91.7%) compared to non-finger clubbed patients. Finger clubbed patients had lower CD4 cells count and percentage (median 369cells, 13%) compared to non-clubbed patients (median 861cells, 28%). Duration of ART use was shorter in finger clubbed patients (median 5.5 months) compared to non-finger clubbed patients (median 40 months).**
***Conclusion*: Presence of finger clubbing in HIV infected children was associated with chronic lung disease, advanced WHO stage, lower CD4 counts/ percentage, shorter duration of ART use and higher likelihood of developing pulmonary hypertension.**

INTRODUCTION

Finger clubbing is sometimes referred to as Hippocratic fingers or drumstick fingers (1).It is the enlargement of the distal segments of the fingers and / or toes that result from the proliferation of the connective tissue between the nail matrix and the distal phalanx (2).

Finger clubbing in general has been associated to pulmonary or nonpulmonary conditions like cyanotic heart diseases, infective endocarditis, inflammatory bowel disease, liver cirrhosis and malignancies (2, 3). Finger clubbing has been noted to occur in several pulmonary diseases like cystic fibrosis, bronchiectasis, tuberculosis, lung abscess and lymphoid interstitial pneumonitis (2, 3).

Respiratory complications in HIV-infected children are common and responsible for substantial morbidity and mortality (4 -7). Chronic lung disease is common in HIV positive children as their age advances (8, 9). The spectrum of chronic lung disease in HIV infected children includes pulmonary tuberculosis, lymphoid interstitial pneumonitis, and bronchiectasis, persistent and atypical pneumonias (4, 10). The presence of clubbing in HIV-infected patients is attributed to concomitant pulmonary infections which result in hypoxia. An earlier study by Graham *et al* (11) reported that digital clubbing in Malawian children aged between four months to 12 years was associated with chronic lung disease and HIV infection. Another South African study by Zar *et al* (12) reported that finger clubbing occurred in 20% of HIV-infected

children compared with 1% HIV-negative control patients. It is hypothesised that presence of finger clubbing in HIV infection may indicate underlying lung pathology. Finger clubbing is a clinical sign that is easy and quick to detect without sophisticated equipment and very feasible to diagnose. Therefore, finger clubbing could provide simple screening tool to identify children for further evaluation for chronic lung disease and hence timely intervention which may result in lower morbidity and mortality. However, the association and clinical correlates of finger clubbing in HIV infected children in relationship to chronic lung conditions and WHO clinical staging, CD4 counts/percentage, anti-retroviral use and pulmonary hypertension have not been studied in our set up. We undertook a hospital based case control study of HIV infected children presenting to Kenyatta National Hospital, Nairobi, and the largest public teaching hospital in Kenya.

MATERIALS AND METHODS

This was a hospital based case control study. The cases were defined as HIV-positive children with finger clubbing present while controls were HIV-positive children without finger clubbing who presented to Kenyatta National Hospital between February 2012 and January 2013. Written informed consent was obtained from all study participants who were below eighteen years of age. Patients were ineligible if they had a congenital heart disease or rheumatic heart disease, liver pathology or elevated liver enzymes, any form of malignancy and chronic diarrhea or/and inflammatory bowel diseases, all known to be associated with clubbing. The study was undertaken after obtaining a written approval from the Department of Paediatrics and Child Health, University of Nairobi, and the Ethical Review Committee, Kenyatta National Hospital. We recruited 60 Cases (HIV infected children who had finger clubbing) and 60 Controls (HIV infected children without finger clubbing.

In this study, finger clubbing was defined as finger clubbing that was obvious to the investigators eye without need of any measurements and the presence of schamroth's sign. In this study, schamroth's sign was said to be present if the dorsal surfaces of the terminal phalanges of the opposite fingers were placed together and there was disappearance of the normal diamond shaped window at the bases of the nail beds. The controls had no obvious finger clubbing as observed by the investigator and schamroth's sign was absent.

Then, information on demographic characteristics, previous respiratory illness and current chest symptoms and their duration were obtained through interviewing the parents or guardians of all recruited children (both cases and controls). History on the duration of the current illness and other serious intercurrent illness other than the lungs were also recorded. History of anti-retroviral use and duration was elicited and these were recorded in a pretested questionnaire.

Physical examination including pulse oximetry and World Health Organization HIV clinical staging at recruitment were done on each child recruited as a case or control.

Hypoxia was defined as oxygen saturations less than 92% on pulse oximetry (13).

All the recruited patients had blood samples drawn for CD4 counts and percent and full blood counts and erythrocyte sedimentation rate done. Chest radiograph and echocardiogram were done to all study patients within one week of enrolment to the study. Chest radiographs obtained from all participants were reported by first radiologist, and then a second independent radiologist also reported on it. The diagnosis of chronic lung disease if present was made on both cases and controls based on clinical examination and radiological findings of the patients. Chronic lung disease was defined as:

1. Presence of chronic cough for more than a month together with
2. Chest radiological abnormalities plus
3. Presence any of the following signs:
    - Fever of more than 37.5 C
    - Chest deformity which included pes carinatum, pes excavatum, hyperinflated chest.
    - Abnormal breath sounds like wheeze, crackles or bronchial breathing

The diagnosis of chronic lung disease included the following conditions: tuberculosis, lymphocytic interstitial pneumonia, bronchiectasis, interstitial pneumonitis and chronic chest infections

Echocardiography to determine the pulmonary pressures was performed on all recruited study patients by a paediatric cardiologist. Standard two dimension and colour flow Doppler was done to asses and rule out congenital and rheumatic heart disease. Trans-thoracic echocardiography was performed in all patients using of a portable Vivid i Echo colour ultrasound System® echocardiogram machine. Cardiac measurements were performed according to the guidelines of The American Society of Echocardiography. Colour codes guided spectral Doppler was sampled at the tricuspid valve in the short axis and apical four chamber view. A minimum of five sequential complexes were recorded. Continuous wave Doppler sampling of the peak tricuspid regurgitant jet velocity was used to estimate the pressure gradient between the right ventricular and the right atrium using the modified Bernoulli's equation (Gradient $=4\times (TRV^2)$) where TRV means tricuspid regurgitation velocity.

The pulmonary arterial systolic pressure was

calculated as the sum of the pressure gradient (Gradient =4× (TRV²)) and a constant assumed right atrial pressure of 10mmHg. This calculation was pre-programmed in the echocardiography machine used in the study.

Trace or absence of tricuspid regurgitation was indicative of normal pressure.

Pulmonary arterial hypertension was defined as tricuspid regurgitation velocity (TRV) of 2.5m/s and above equivalent to right ventricular to right atrial pressure gradient of 25mmHg (as derived using the modified Bernoulli's equation) and pulmonary arterial systolic pressure of 35mmHg. For the purpose of this study, pulmonary arterial hypertension was graded as mild if pulmonary arterial systolic pressure of 35-49mmHg, moderate if pulmonary arterial systolic pressure of 50-70mmHg, and severe if pulmonary arterial systolic pressure was greater than 70mmHg. Both cases and controls were recruited by consecutive sampling whereby every patient who satisfied the inclusion criteria was serially recruited until the desired sample size was achieved. There was no matching of the cases to the controls.

RESULTS

The total number of participants recruited into the study was 120 HIV infected children at KNH pediatric wards and comprehensive care clinic during the period of February 2012 to January 2013. The study participants comprised of 60 children with finger clubbing (cases) and 60 children without finger clubbing (controls).

There were 68 (56.7%) males and 52(43.3%) females in the study yielding a male-to-female ratio of 1: 1.3. Among the cases, there were 35 (58.3%) males and 25 (41.7%) females compared to controls where males were 33 (55%) and females 27(45%) (Table 2).The median age of children who participated in the study was 7.5 years (Interquartile Ratio, IQR 3.0 to 11.0). The cases were younger with a median age of 6.5 years (IQR 2.0-10.5) compared to 9.0 years (IQR 4.5-13.5) for the controls (Table 1).

Table 1
Baseline characteristics

Characteristics	Overall (n=120)	Case (n=60)	Control (n=60)	OR (95% CI)	P value
Median age in years (IQR)	7.5(3.0-11.0)	6.5 (2.0-10.5)	9.0 (4.5-13.5)	-	0.083
Age group					
0-11 months	11 (9.2)	6 (10.0)	5 (8.3)		0.377
1-5 years	32 (26.7)	19 (31.7)	13 (21.7)		0.099
6-10 years	39 (32.5)	20 (33.3)	19 (31.7)		0.299
11-18 years	38 (31.7)	15 (25.0)	23 (38.3)		
Residence					
Nairobi	98(81.7)	46(76.7)	52(86.7)	0.5(0.2-1.3)	0.157
Outside Nairobi	22(18.3)	14(23.3)	8(13.3)		
Sex					
Male	68 (56.7)	35 (58.3)	33 (55.0)	1.1 (0.6-2.4)	0.713
Female	52 (43.3)	25 (41.7)	27 (45.0)	1.0	
Site					
CCC	75 (62.5)	22 (36.7)	53 (88.3)	0.1 (0.0-0.2)	<0.001
Ward	45 (37.5)	38 (63.3)	7 (11.7)	1.0	
Previous treatment of lung disease					
Yes	68 (56.7)	34 (56.7)	33 (55.9)	1.0 (0.5-2.1)	0.936
No	52 (43.3)	26 (43.3)	26 (44.1)	1.0	

Cases and controls were not significantly different in relation to their age, sex and previous treatment of lung disease. However, significantly less cases, 22 (36.7%) were recruited from the comprehensive care clinic as compared to controls whose majority, 53 (88.3%) were recruited from the comprehensive care clinic, OR 0.1 (95% CI 0.0-0.2), p<0.001(Table 1).

Figure 1
Presence of Chronic lung disease

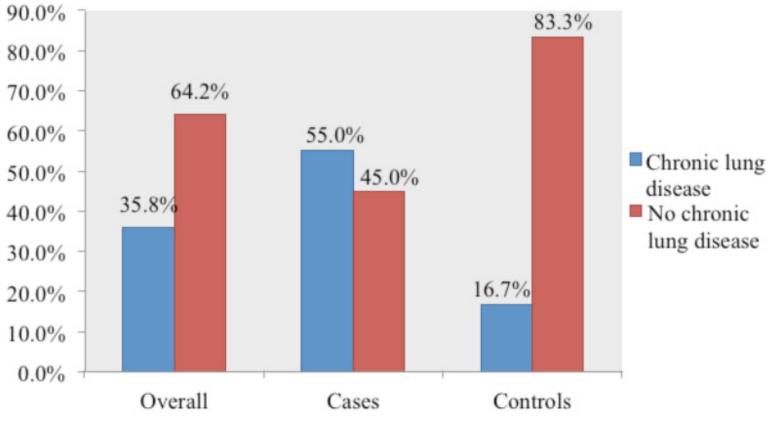

Table 2
Chronic lung disease and Chest radiography report.

Variable	Overall n = 120	Case n = 60	Control n = 60	OR (95% CI)	P value
Chest x-ray report					
Abnormal	90 (75.0)	54 (90.0)	36 (60.0)	6.0 (2.2-16.1)	<0.001
Normal	30 (25.0)	6 (10.0)	24 (40.0)	1.0	
Presence of chronic Lung Disease					
Yes	43 (35.8)	33 (55.0)	10 (16.7)	6.1 (2.6-14.3)	<0.001
No	77 (64.2)	27 (45.0)	50 (83.3)	1.0	

Overall, 43 (35.8%) of the patients had chronic lung disease as defined by the presence of chronic cough for more than a month and any of the following: fever, chest deformity, wheeze, crackles and/or bronchial breathing together with radiological changes. Diagnosis of chronic lung disease was more common among the cases, 33 (55%) than the controls, 10 (16.7%), OR 6.1 (95% CI 2.6-14.3), p<0.001 as shown in Figure 1 and Table 2.

The observed abnormal radiographic findings included patchy infiltrates, opacities, hilar adenopathy, lung consolidaton, cavitations, pleural effusion, and lung collapse, reticulonodular shadowing and military nodules typical of tuberculosis. Abnormalities of the chest radiographs were reported in 90 (75%) of all study participants. In patients with finger clubbing, 54 (90%) had abnormal radiographs compared to 36 (60%) of those without finger clubbing as shown in Table 2.

Pulmonary tuberculosis was the commonest diagnosed chronic lung disease in both cases, 18 out of 33, (54.5%) and controls five out of ten, (50%). The cases had more incidences of atypical pneumonia (five patients) than the controls who were three patients. Bronchiectasis was found in four patients with finger clubbing who had previously been treated for pulmonary tuberculosis. Two cases and one control that were on continuation phase of pulmonary tuberculosis treatment were diagnosed with pneumocystis jirovecii pneumonia. Co-existence of pulmonary tuberculosis and lymphoid interstitial pneumonitis was also diagnosed in one patient with finger clubbing (Table 3).

Table 3
Spectrum of chronic lung disease

The spectrum of chronic lung disease	Cases n = 33	Controls n = 10	P-value
Pulmonary tuberculosis	18 (54.5%)	5 (50.0%)	0.801
Atypical pneumonia	5 (15.2%)	3 (30.0%)	0.290
Bronchiectasis	3 (9.1%)	0 (0.0%)	0.323
Bronchiectasis with cor pulmonale	1 (3.0%)	0 (0.0%)	0.578
Persistent pneumonia	0 (0.0%)	1 (10.0%)	0.066
Persistent pneumonia with cor pulmonale	3 (9.1%)	0 (0.0%)	0.323
Pneumocystis jirovencii pneumonia with underlying PTB	2 (6.1%)	1 (10.0%)	0.668
PTB with lymphoid interstitial pneumonitis co-infection	1 (3.0%)	0 (0.0%)	0.578

Table 4
Complications of chronic lung disease

Variable	Overall n = 120	Case n = 60	Control n=60	OR (95% CI)	P value
Oxygen saturations					
80-92% Mild/ Moderate	43 (35.8)	28 (46.7)	15 (25.0)	2.6 (1.2-5.7)	0.013
93-100% Normal	77 (64.2)	32 (53.3)	45 (75.0)	1.0	
Pulmonary pressure					
Normal	82 (68.3)	32 (53.3)	50 (83.3)	1.0	
Mild/Moderate/ Severe	38 (31.7)	28 (46.7)	10 (16.7)	4.4 (1.9-10.2)	0.001

Figure 2
WHO clinical staging

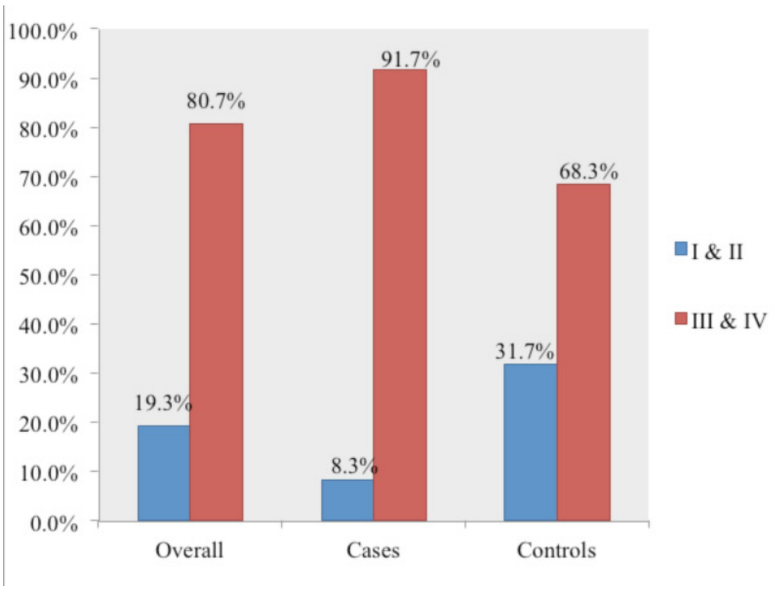

Table 5
CD4 cells count and Anti-retroviral therapy treatment

Variable	Overall n = 120	Case n = 60	Control n = 60	OR (95% CI)	P value
Median CD4 count (IQR)	567(290-1057)	369 (103-708)	861(505-1165)	-	<0.001
Median CD4 % (IQR)	21 (11-31)	13 (5-23)	28 (19-35)	-	<0.001
Anti-retroviral therapy					
Yes	94 (78.3)	43 (71.7)	51 (85.0)	0.4 (0.2-1.1)	0.076
No	26 (21.7)	17 (28.3)	9 (15.0)	1.0	
Anti-retroviral therapy duration	24 (1-48)	5.5 (0.0-33.5)	40 (10.5-60)	-	<0.001

Of all the patients studied, 43 (35.8%) and 38 (31.7%) had abnormal oxygen saturations and pulmonary pressure respectively. The cases were at a higher risk of being diagnosed with mild to moderate hypoxemia, 28 (46.7%), OR 2.6 (95% CI 1.2-5.7), p = 0.013, and mild to severe pulmonary hypertension, 28 (46.7%), OR 4.4 (95% CI 1.9-10.2), p = 0.001 as compared to the controls (Table 4).

Overall, 96 (80.7%) of the study patients had WHO clinical stage III and IV. The number of patients with WHO stage III and IV disease was significantly higher among the cases, 55 (91.7%) than the controls, 41(68.3%), OR 6.4 (95% CI 2.0-20.2), p<0.001 (Figure 2).

The cases had a significantly lower CD4 cells count (median 369 cells) compared to the controls (median 861 cells), p<0.001. Similarly, the CD4% for the cases was lower (median 13%) than that of the controls (median 28%), p<0.001 (Table 5).

Majority, 94 (78.3%) of the patients were using anti-retroviral therapy and there was a trend towards higher percentage of anti-retroviral use among the controls, 51(85%) compared to the cases 43(71.7%), p=0.076. However, duration of anti-retroviral therapy was significantly different between cases and controls (p<0.001). The cases had a shorter duration of anti-retroviral use (median 5.5 months) compared to the controls (median 40 months) (Table 5).

DISCUSSION

This study has demonstrated that finger clubbing in children is associated with HIV infection and chronic lung disease accompanied by higher likelihood of pulmonary hypertension and hypoxemia.

This study reveals that, HIV infected children with finger clubbing are more likely to have chronic lung disease as compared to those without finger clubbing (OR 6.1 (95% CI 2.6-14.3), p<0.001). This is similarly reported by Ferrand *et al* (14) from Harare where 10% of HIV infected adolescents with chronic lung disease had finger clubbing and in Nigeria, 15% of HIV infected adults with pulmonary complications had finger clubbing (15). However, these two studies were observational without comparison of the non finger clubbed group.

Tuberculosis was the most common diagnosed chronic lung diseases in both finger clubbed and non finger clubbed patients in this study. This was similar to the Ugandan adult study by Ddungu *et al* (16). This may be due to the fact that Kenya is a high TB prevalence area and this trend is similar in other sub-Saharan African countries where HIV and TB co-infection is high (14,17). However, in a South African study, the commonest chronic lung disease associated with finger clubbing was reported to be lymphocytic interstitial pneumonia (12). The reason for the difference could not be ascertained.

The other chronic HIV-associated lung disease associated with finger clubbing found in this study included lymphocytic interstitial pneumonia, persistent and atypical pneumonia, bronchiectasis, and pneumocystis jirovecii pneumonia. The spectrum of chronic lung diseases in HIV in this study is similarly reflected by another study by Jeena *et al* (18).

In this study, 56% of all participants had been treated previously for a lung disease. This applied to both finger clubbed and non finger clubbed patients. This is due to the fact that in children with HIV infection, lung disease appears to be common as has been reported in other studies (9, 19, 20).

It was also noted from this study that 90% of finger clubbed patients had abnormal chest radiological findings compared to 60% of non clubbed patients. Many other studies have reported similar findings. Norton *et al* (21) for instance reported the cumulative incidence of chronic radiographic lung changes in HIV-1–infected children to be 32.8% by four years old. Ferrand *et al* (14) also reported that

47% of long time survivors of vertically acquired HIV had subtle chest radiographic abnormalities. In another study by Desai *et al* (22), chest radiographic abnormalities were highly prevalent in adolescents with vertically-acquired HIV infection. However, these studies did not compare the chest abnormalities in regard to presence or absence of finger clubbing.

In this study, patients with finger clubbing were younger with a median age of 6.5 years compared to 9.0 years for those without finger clubbing. The youngest patient with finger clubbing in this study was nine months. Graham *et al* (11) too reported that finger clubbing in HIV infected children may occur as early as infancy.

This study showed that approximately half (46.7%) of the HIV infected patients with finger clubbing had mild to moderate hypoxemia compared to a quarter (25%) of non clubbed patients. In the study by Graham et al (19), only 12.5% of the HIV infected children with finger clubbing had hypoxemia (oxygen saturation less than 90% on pulse oximetry). Our study had higher percentage compared to Graham *et al* (19) because our cut off for hypoxemia was oxygen saturations of less than 92%. The study by Graham *et a*l (19) however, did not also have a comparison group of non finger clubbed patients.

In this study, pulmonary hypertension was found to be more common in patients with finger clubbing. About 46.7% of finger clubbed patients had pulmonary hypertension compared to 16.7% of the patients without finger clubbing who had pulmonary hypertension. Two (7%) of patients with finger clubbing had severe pulmonary hypertension (>70mmHg). In both finger clubbed and non finger clubbed patients, mild pulmonary hypertension was predominant. There were no similar studies for comparison in regards to HIV infected children with finger clubbing and development of pulmonary hypertension. However, this is high compared to the Zimbabwe study by Ferrand *et al* (14), which found pulmonary hypertension in 7% of long-term survivors of vertically acquired HIV infection.

It was found that finger clubbing was significantly associated with advanced disease, WHO clinical stage of III and IV. It is also worth noting that all the chronic lung disease in HIV fall in this WHO stages. However, this differed from an adult study by Ddungu e*t al* (16) who reported that finger clubbing was not associated with the stage of HIV infection. There were no other similar studies in the paediatric population for comparison.

The finger clubbed patients were more likely to be hospitalised and had a lower CD4 counts and percentage as found in this study. This, therefore, means that patients with finger clubbing are more likely to be very sick requiring hospitalisation compared to the ones without finger clubbing. Similar findings were reported by Zar *et al* (12) in South Africa that, HIV infected children with finger clubbing had lower CD4 count levels compared to those without finger clubbing.

In our study, the patients with finger clubbing had a shorter duration of anti-retroviral therapy use (median 5.5 months) compared to the patients without finger clubbing (median 40 months). However, there were no other similar studies available for comparison.

The study limitations included a small sample size as a larger control group would have increased the power of the study. Another limitation was lack of specialised and sophisticated investigations like CT scan of the chest, culture of bronchial aspirates, PCR assays which may have assisted with a more definitive aetiological cause of chronic lung disease.

In conclusion, finger clubbing in HIV infected children is a pointer to the existence of chronic lung disease, and the presence of finger clubbing in HIV infected children is associated with advanced WHO stage III or IV, lower CD4 counts and percentage and a shorter duration of anti-retroviral therapy use. HIV infected children with finger clubbing have a higher likelihood of developing pulmonary hypertension. In view of these findings, all HIV infected children must be examined for the presence of finger clubbing. All HIV infected children with finger clubbing should have physical, radiological evaluation and echocardiography to asses for chronic lung disease and its complications.

ACKNOWLEDGEMENTS

To the patients and staff at Kenyatta National Hospital who participated in the study. The echocardiography studies were kindly sponsored by Hurligham Heart Clinic, Nairobi Kenya.

REFERENCES

1. Tosti A, Piraccini BM. Nail disorders. In: Bolognia JL, Jorizzo JL, Rapini RP, editors. Dermatology. London: Mosby; 2003: 1069
2. Myers KA, Farquhar DR. Does this patient have clubbing? *JAMA* 2001; **286**: 341–7
3. Vandemergel X, Renneboog B. Prevalence, aetiologies and significance of clubbing in a department of general internal medicine. *Eur J Int Med* 2008; **19**: 325–9.
4. Graham SM. Impact of HIV on Childhood Respiratory Illness: Differences between Developing and Developed Countries. *Paediatric Pulmonology* 2003; **36**:462–8.
5. Kouakoussui A, Fassinou P, Anaky MF, Elenga N, Laguide R, Wemin ML *et al*. Respiratory manifestations in HIV-infected children pre- and post-HAART in Abidjan, the Ivory Coast. *Paediatr Respir Rev* 2004; **5**:311-5.

6. Madhivanan P, Mothi SN, Kumarasamy N, Yepthomi T, Venkatesan C, Lambert JS *et al*. Clinical manifestations of HIV infected children. *Indian J Pediatr* 2003; **70**:615-20.
7. Perez MS, Van Dyke RB. Pulmonary infections in children with HIV infection. *Semin Respir Infect* 2002; **17**: 33-46.
8. Norton KI, Kattan M, Rao JS, Cleveland R, Trautwein L, Mellins RB et al. Chronic radiographic lung changes in children with vertically transmitted HIV-1 infection. *Am J Roentgenol*. 2001; **176**:1553-8.
9. Berdon WE, Mellins RB, Abramson SJ, Ruzal-Shapiro C. Pediatric HIV infection in its second decade--the changing pattern of lung involvement. Clinical, plain film, and computed tomographic findings. *Radiol Clin North Am*. 1993; **31**:453-63.
10. Zar JH. Chronic Lung Disease in Human Immunodeficiency Virus (HIV) infected children. *Paediatric Pulmonology* 2008; **43**:1-10.
11. Graham SM, Daley HM, Ngwira B. Finger clubbing and HIV infection in Malawian children. *Lancet* 1997; **349**: 31.
12. Zar HJ, Hussey G. Finger clubbing in children with human immunodeficiency virus infection. A*nn Trop Paediatr*. 2001; **21**:15-9.
13. Jubran A. Pulse oximetry. *Crit Care.* 1999; **3**: 11-17.
14. Ferrand RA, Desai SR, Hopkins C, Elston CM, Copley SJ, Nathoo K *et al*. Chronic Lung Disease in Adolescents With Delayed Diagnosis of Vertically Acquired HIV Infection. *Clin Infect Dis* 2012; **55**:145–52
15. Peters EJ, Essien OE, Immananagha KK, Inah GA, Philip-Ephraim EE, Agbulu RE. CD4 count levels and pattern of respiratory complications in HIV seropositive patients in Calabar Nigeria. *Niger J Physiol Sci* 2007; **22**: 93-7.
16. Ddungu H, Johnson JL, Smieja M, Harriet Mayanja-Kizza H. Digital clubbing in tuberculosis – relationship to HIV infection, extent of disease and hypoalbuminemia. BMC Infectious Diseases 2006; 6:1471-2334.
17. Bhat GJ, Diwan VK, and Chintu C, *et al*. HIV, BCG and TB in children: a case control study in Lusaka, Zambia. *J Trop Pediatr.* 1993; **39**:219-23.
18. Jeena PM, Coovadia HM, Thula SA, Blythe D, Buckels NJ, Chetty R. Persistent and chronic lung disease in HIV-1 infected and uninfected African children. *AIDS*. 1998; **12**:1185-93.
19. Mouzinho A. Pulmonary Complications of HIV. *Pediatric Pulmonology, Supplement* 2004; **26**:57–8.
20. Graham SM. Non-tuberculosis opportunistic infections and other lung diseases in HIV-infected infants and children. *Int J Tuberc Lung Dis* 2005; **9**:592–602.
21. Paton JY, Bautista DB, Stabile MW, Waldman AE, Nassar AG, Platzker AC *et al.* Digital clubbing and pulmonary function abnormalities in children with lung disease. *Pediatr Pulmonol* 1991; **10**:25–9.
22. Desai SR, Copley SJ, Barker RD, Elston CM, Miller RF, Wells AU *et al*. Chest radiography patterns in 75 adolescents with vertically-acquired human immunodeficiency virus (HIV) infection. *Clin Radiol* 2011; **66**:257-63.