

# Childhood HIV and Tuberculosis Co-Infection in a Nigerian Tertiary Hospital

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**Abstract— Background:** Tuberculosis and HIV are significant contributors to morbidity and mortality in children living in developing countries. Factors associated with morbidity in Tuberculosis and HIV co-infections have not been sufficiently exhaustively studied. **Aim:** To study the pattern of presentation and outcome of tuberculosis in HIV infected children with a view to identify factor associated with outcome of management. **Methods:** Consecutive children diagnosed with tuberculosis and HIV co-infections seen at the paediatric clinics or wards of LAUTECH teaching hospitals were studied over 10 years. Necessary data were extracted from their case notes and analysed using SPSS version 18. **Results:** A total of 28 children with HIV and tuberculosis co-infection were studied, with age ranging from 3months to 17year. Thirteen (46.4%) children were boys and 15(53.6%) girls. The forms of Tuberculosis diagnosed were pulmonary 18(64.3%), disseminated disease 5(7.9%), abdominal 3(10.7), meningitis 1(3.7%) and miliary 1(3.7%). Sixteen (57.1%) of the 28 children, had complications, while the remaining 12(42.9%) did not. Congestive cardiac failure secondary to pulmonary disease and hypoxemia requiring oxygen therapy were the common complications recorded. Eight (28.6%) children exhibited treatment failure to category I anti-tuberculous (Anti-Tb) drugs and one of these patients eventually exhibited treatment failure to category II Anti-Tb and Multi-drug resistance. Treatment failure with category I Anti-Tb therapy was significantly associated with severe immunosuppression ( $CD4 < 200$ cells/ul, poor viral load suppression (viral load  $> 1000$ ucells/L and disseminated disease ( $p < 0.01$ ). Four mortalities 4(14.3%) were recorded in the course of the study while 24 (85.7%) survived. **Conclusion:** Tuberculosis is a significant cause of morbidity in HIV infected children. Treatment failure is a significant outcome associated with category I Anti-Tb therapy in patients with significant immunological suppression, unsuppressed viral load and those with disseminated and miliary tuberculosis. There is a need to revise Anti-Tb medication regimen in order to prevent treatment failure and resistance among these susceptible groups of children.

**Keywords—** Paediatrics, Co-infections, HIV and Tuberculosis.

## I. INTRODUCTION

Tuberculosis is the most common opportunistic infection in HIV infected individuals.<sup>1</sup> Tuberculosis and HIV co-infections are common and are a significant contributor to morbidity and mortality in the developing countries.<sup>2,3</sup> Nigeria has one of the highest HIV associated TB burdens in the world and in 2015, an estimated 6000 children aged less than 15years were notified to have tuberculosis, which represented 6% of the estimated incident childhood tuberculosis cases.<sup>4</sup>

Institution of timely and appropriate management is imperative for good outcomes, because tuberculosis hastens the progression of HIV infection, while on the hand tuberculosis is more severe and disease progression to death is faster in co-infected individuals.<sup>5</sup> Choice of anti-retroviral and anti-tuberculous drugs is also very important in individuals with co-infections because response to the standard short course therapy is associated with lower cure and higher mortality rates compared with children with only tuberculous disease.<sup>1</sup> The current national guidelines for tuberculosis in both HIV positive and negative individuals however recommends, the standard treatment and course with category I anti-tuberculosis(Anti-TB) for all new cases of tuberculosis, irrespective of disease progression and use of category II Anti-TB drugs for those who return after default, relapse or failed treatment to category I anti-tuberculous course of drugs.<sup>6</sup>

The aim of this study is to examine the response of tuberculosis infected HIV infected children to the standard

recommended Anti-TB regimens. Hopefully the results from this study will provide information that will assist physicians working in resource constrained settings manage tuberculosis better.

## II. METHODOLOGY

The case notes of all the children aged 3months to 17years diagnosed with HIV/TB co-infections and managed in Ladoke Akintola University of Technology Teaching Hospital, Osogbo, Nigeria between January 2008 and December 2018 were obtained and retrospectively analysed for various data. The study protocol was approved by the Ethics and Research Committee of the LAUTECH Teaching Hospital, Osogbo [Protocol number LTH/EC/2019/02/425].

Human immunodeficiency infection (HIV-1) infection was established in the studied children according to international standards, endorsed by the Nigerian Ministry of Health.<sup>7</sup> The data included ages and sexes of the patients, the system and anatomical region affected by the tuberculous infection and the details of the medication such as category I or II Anti-Tb and use of high active anti-retroviral therapy (HAART) and outcome.

The systems affected were classified as pulmonary, abdominal, meningitis or miliary tuberculosis and the details recorded were used to calculate the tuberculosis score/index.<sup>6</sup> A score of 7 and above was interpreted as having a tuberculous disease while scores less than 7 was interpreted as not having tuberculosis.

The results of the investigations extracted include the Gene expert, Mantoux, Erythrocyte Sedimentation Rate, CD4 counts and viral load. Information on whether HAART was initiated before commencing the Anti-TB drugs and the Anti-TB drugs regimen administered to the patient whether category I or II were also obtained. Anti-Tuberculous drug classification into category I and II with the duration of the medications was based on the guidelines provided by the Nigerian Federal ministry of Health.<sup>6</sup>

Outcome on completing the Anti-Tb medication was also obtained, in terms of whether patient was cured or experienced treatment failure. Cure was regarded as resolution of presenting symptoms and recovery changes in the investigations such as plain chest radiographs where applicable or no more detection of acid fast bacilli in those originally acid fast bacilli positive. Failure was regarded as either deterioration in clinical state or failure to revert to normal findings in investigative processes such as radiographs showing active or sputum examination still showing presence of acid fast bacilli (Aafb).

Information obtained on the morbidity arising from the co-infection includes, the system affected by tuberculosis and presence or absence of complications. Additional details on whether or not the patient was hospitalised for in-patient care as part of management was also extracted and recorded. The outcome of the whole management in terms of whether the patient died or survived the disease was also extracted and recorded.

All the information obtained was inputted on to a personal computer and the results were analyzed using the statistical package for Social sciences version 18 (SPSS version 18). Categorical variables were expressed in proportions, ratios and percentages. Categorical variables were compared using the Chi-square ( $\chi^2$ ) test and Odds ratio where appropriate. Statistical significance was set at 'p' value less than 0.05.

### III. RESULTS

A total of 28 patients were studied. Of the 28, five (17.9%) were managed as outpatients through the paediatric anti-retroviral clinic, while the remaining 23 (82.1%) were admitted for initial phase of treatment or as a result of needs such as development of complications which required admission for appropriate care delivery.

#### Age and sex distribution of children studied

Thirteen (46.4%) boys and 15 (53.6%) girls were studied giving a male: female ratio of 1.0: 1.4. The ages of the children studied ranged from 3 months to 17 years with a mean age of 6.7 +/- 4.3 years. Most of the children were aged below 5 years and the minority aged above 11 years. Details of the age groups studied and the gender distribution are shown Table 1.

#### The history elicited

The symptoms were chronic cough 17 (60.7%), Prolonged fever lasting more than two weeks in 9 (32.1%), weight loss in 12 (42.9%), fever for less than two weeks in 7 (25%), breathlessness in 6 (21.4%), abdominal swelling in 6 (21.4%),

failure to thrive in 3 (10.7%) and night sweats in 2 (7.1%) patients. None of the children or caregivers gave a history suggestive of contact with patients having tuberculosis.

TABLE 1. Age and sex distribution

Age	Number (%)
1 - 5	12 (41.4%)
6 - 10	11 (37.9%)
11 - 15	2 (6.9%)
15 - 17	2 (6.9%)
Sex	
Male	13 (44.8%)
Female	15 (51.7%)

#### Clinical findings

Hepatomegaly, generalised lymph node enlargement, tachypnoea, splenomegaly, lung crepitation's, digital clubbing, reduced breath sounds and chest recession were found in 17 (60.7%), 14 (50%), 11 (39.3%), 10 (35.7%), 8 (26.3%), 4 (14.3%), 4 (14.3%), 3 (10.7%) children respectively

#### Anthropometric findings

Nine of the children had (normal weights with a) weight of 80% and above for the expected age while 13 were underweight with weights between 60-80% and 6 were marasmic. Mid upper Arm Circumference measurements were taken in the 10 children aged between 6 months and 5 years, 2 (20%) had normal measurement while 3 (30%) and 5 (50%) had measurements indicating moderate and severe malnutrition respectively.

#### Routine childhood vaccinations

Of the 28 children studied, 14 (50%) had BCG vaccination, while the remaining 14 (50%) were not vaccinated with BCG. Of the total 28 children studied 8 (27.6%) were up to date with their vaccinations based on the Nigerian Program on Immunization. The details given by the other caregivers were not reliable because their wards either presented as adolescents or consultations were with the child and caregivers who were not their parents. These caregivers did not have the details of immunization for the child under review.

#### Complications of tuberculosis

Of the 28 children 16 (57.1%) had complications, while the remaining 12 (42.9%) did not have complications. The complications encountered were congestive cardiac failure secondary to pulmonary disease in 6 (21.4%), hypoxemia requiring oxygen therapy in 4 (14.3%), meningitis in 3 (10.7%). Severe anaemia requiring transfusion, miliary dissemination of tuberculosis, pleural effusion, kyphosis, chronic secretory otitis media and pneumothorax were seen in 1 patient each. Some patients had more than 1 complication.

#### Laboratory indicators for diagnosis

Erythrocyte sedimentation rate was markedly elevated in nine of the patients studied but was not done in the remaining 19. The values in the 9 were in the range between 96 - 150 mm/hr in those in whom it was done. Mantoux was

positive in 1(3.6%) while none of the 10 children who had Gene expert investigation had a positive result.

*Plain Chest radiograph findings*

Chest radiograph was suggestive of tuberculosis in 16 of the patients, with reticulonodular shadows in 6(21.4%), hilar shadows in 4(14.3%), lung cavities in 3(10.7%), miliary shadows in 2(7.1%) and bronchopneumonia with effusion in 1 (3.6%).

*NTB score index*

NTB score ranged from 2-12, with 4 children having a score less than 7 and the remaining 24 children having a score of 7 and above.

*Basis for making diagnosis of tuberculosis*

Fourteen of the children had chest radiograph features suggestive of tuberculosis and NTB score above 7. Diagnosis of tuberculosis was based on the NTB score only in 7(25.0), therapeutic trial in 1(3.6%). NTB, suggestive chest radiograph and cerebrospinal fluid findings in 2, and a positive Mantoux test in 1. A high ESR was recorded in 9(32%)

*Duration of admissions*

Twenty three (82.1%) patients were admitted, while 5(17.9%) were treated on out-patient basis. Concerning those admitted the duration of stay ranged from 2 – 63days, while the mean duration of stay was 16.8 +/-2.0 days

*HAART initiation and anti-tuberculous treatment*

Of the 28 children studied 7 had initiated HAART before diagnosis of TB was made, while 21 were yet to initiate HAART therapy. Seven (25%) of the children had treatment failure with category I Anti-Tb drugs, while 21(75%) had resolution of their Tuberculosis with category I Anti-Tb drugs. One of the seven children treated with category II Anti-Tb drugs still had treatment failure with his medications and this patient on further investigation was found to have developed Anti-TB multidrug resistance. This patient was transferred out to a multi-drug resistance (MDR) treatment unit. The details for the association between response to category I Anti-Tb medications and viral load, CD4 counts and disease dissemination can be found in Table 2.

TABLE 2. Types of tuberculosis

Type of tuberculosis	Number (%)
Pulmonary	18(64.3)
Disseminated tuberculosis	5(17.9)
Abdominal Tuberculosis	3(10.7)
Meningitis	1(3.6)
Miliary	1(3.6)
Total	28(100.0)

*Outcome of admission*

Of the 28 children studied 24(85.7%) survived, while 4(14.3%) died. One of the 24 children classified as survival was transferred to the Anti-TB, multi-drug treatment unit. The details for the association between outcome of admission and viral load, CD4 counts and disease dissemination can be found in Table 3.

TABLE 3. Association between disease dissemination, CD4 count, viral load and response to category I anti-tuberculous therapy

	Good response to category I anti-Tb drug	Treatment failure with Category I anti-Tb drugs	X <sup>2</sup>	P value
Disseminated & Miliary Tb	3	5	6.32	0.01
Non-disseminated or Miliary Tb	17	3		
CD4 count > 200	16	3	4.73	0.01
CD4 count between 1-200	4	5		
Virological Suppression VL<1000 copies/ml	16	2	7.53	<0.01
Virological Failure VL>1000 copies/ml	4	6		

TABLE 4. Association between disease dissemination, CD4 count, viral load and Outcome

	Good outcome Discharged alive and well	Death	X <sup>2</sup>	P value
Disseminated & Miliary Tb	6	2	1.05	0.31
Non-disseminated or Miliary Tb	18	2		
CD4 count > 200	17	2	0.68	0.41
CD4 count between 1-200	7	2		
Virological Suppression VL<1000 copies/ml	16	2	0.42	0.52
Virological Failure VL> 1000copies/ml	8	2		

IV. DISCUSSION

Tuberculosis remains a common opportunistic infection in HIV infected children, as seen in the present study in which an incidence rate of 28% has been recorded for TB/HIV co-infection. The findings in the present study compare favourably with other studies from Nigeria and India.<sup>8,9,10</sup>

The similarities in the presentation of tuberculosis and HIV underscore the need to routinely screen cases diagnosed with either tuberculosis or HIV for the converse infection. The pattern and presentation of tuberculosis in the present case series with pulmonary tuberculosis being the most common presentation is similar to findings from other reports.<sup>8,9,10</sup> The fact that most children acquire tuberculosis by inhalation from droplets released to the environment by an infected adult may explain why the lungs are the most common focus of infection.

Diagnosing tuberculosis in HIV infected children and older individuals is a challenge because of the overlapping clinical and radiologic features with other opportunistic diseases associated with HIV disease.<sup>1,3</sup> Chest radiography was the most helpful investigation suggestive of tuberculosis in the present case series. Previous studies have documented that findings such as hilar shadows, mediastinal widening, cavities and diffuse nodular shadows or pleural effusions should be

viewed as highly suggestive of tuberculosis.<sup>11, 12,13</sup> Most of the previous studies also supported the conventional practice of the use of the chest radiograph in making a diagnosis of tuberculosis. The gene expert and Mantoux test had very low yields and their usefulness in paediatric practice in our setting is doubtful. Previous studies also regard the sensitivity of both the gene expert and mantoux tests as sub-optimal and not to be relied upon for making a diagnosis of tuberculosis.<sup>14, 15</sup> However a positive result for gene expert may be confirmatory while it could be a false positive for the mantoux.<sup>14, 15</sup>

The Erythrocyte Sedimentation Rate also gave a high positive yield, however its sensitivity and specificity in diagnosis of tuberculosis has been also documented to be sub-optimal.<sup>16</sup> The score chart designed by the National Tuberculosis and Leprosy Control Program (NTBLCP) for diagnosing tuberculosis in children was found to be most useful in making a diagnosis in the present study. The score chart incorporates parameters such as duration of illness, weight loss, failure to thrive and history of contact with a person with tuberculosis into its clinical component parameters.<sup>6</sup> Radiologic findings in the disease and the results of the mantoux are the only parameters incorporated to this score.<sup>6</sup> In using the NTBLCP scoring, a score more than 7 is accepted as highly suggestive of tuberculosis.<sup>6</sup> The strengths of this scoring system as a diagnostic tool include the fact that it is based on many parameters and not just one single test. This scoring system can however be improved upon by incorporating the Gene expert and the ESR test into the system.

The relationship between HAART administration and outcome in children with tuberculosis and HIV infection is multi-phased. Tuberculosis may be the pointer to the underlying HIV infection as it was the case for the 25% of the subjects in this study and thus would be the indication to initiate HAART. On the other hand, it could be a pointer to treatment failure in an infected child, who develops tuberculous disease while on treatment. The National guidelines recommends HIV screening tests for children with tuberculosis and apparently healthy individuals who desire screening.<sup>6</sup> Furthermore the guideline recommends initiation of HAART for anybody found to be HIV infected irrespective of whether the individuals is symptomatic of opportunistic diseases or not.<sup>6</sup>

Treatment recommendations for tuberculosis in both HIV infected and non-infected new cases suggest or advocate the administration of category I Anti-Tb drugs for 6months, while cases of relapse and treatment failure in return after default should be managed with category 2 anti-TB drugs for 8 months.<sup>6,17</sup> Anti-tuberculosis drugs should be commenced as soon as the diagnosis is established in patient that will undergo either category I or II treatment. Treatment failure and need for category two Anti-Tb treatment was significantly associated with high viral load, immunological treatment failure and disseminated tuberculosis in the present case series. This is a reasonable and expected finding, however, this finding has not been sufficiently researched from the point of view of effective Anti-Tb regimen and duration of therapy.<sup>17,18,19,20</sup> However, some studies have identified a need

to extend the duration of Anti-Tb to at least 8 months for all cases in order to attain a better cure rate.<sup>19,20</sup>

The morbidity associated with tuberculosis in HIV infected children is evidenced by the clinical features of the illness with which the disease presented and the complications suffered by the patients. Other indications of the morbidity were the number of days spent on hospitalization in this present case series and eventual mortality outcome in four children.

It is concluded that tuberculosis is a significant cause of morbidity and mortality in the HIV infected children studied in the present series. Treatment failure is a significant complication associated with treatment with category I Anti-Tb drug in the significantly immunosuppressed with unsuppressed viral load and those with disseminated and miliary tuberculosis. Treatment failure to category II drugs, though not as common as to category I Anti-Tb drugs also exist. An alternative anti-tb regimen medication should be considered for new cases with significant immunosuppression, unsuppressed viral load and disseminated and miliary tuberculosis.

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