

**Title: Human Immunodeficiency Virus Status in Malnourished Children seen at Lagos.**

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## **Abstract**

### **Introduction**

Human immunodeficiency virus and protein energy malnutrition are still prevalent in Nigeria and the occurrence of the two conditions together confers a poor prognosis. The aim of this study was to determine the current categories of malnutrition amongst under 5 children in Lagos, document their HIV status and determine any peculiarities in the clinical features, haematological and some biochemical profile in these children.

### **Methods**

The study was a prospective crosssectional study conducted at the Paediatric department of the Lagos University Teaching Hospital and the Massey Street Children's Hospital over a 6 month period. All the subjects had anthropometry, HIV testing, full blood count and serum proteins done. The factors associated with HIV status were determined with the logistic regression analysis.

### **Results**

Two hundred and fourteen (214) malnourished children  $\leq 5$  years were recruited into the study and 25(11.7%) were HIV positive. One hundred and five (49.1%) of the participants had moderate malnutrition while 25.2% had severe forms of malnutrition. Fever, cough and diarrhea were the commonest symptoms. Severe wasting, oral thrush, dermatoses and splenomegaly were seen more commonly in the HIV positive subjects. The haematological indices were comparable in the two groups, however, the total protein was significantly higher in the HIV positive subjects compared to the negative group ( $p=0.042$ ). Multivariate analysis showed that the total protein ( $p=0.001$ ) and platelet count ( $p=0.016$ ) could significantly predict the occurrence of HIV in the malnourished children

### **Conclusion**

The presence of severe wasting, oral thrush, diarrhea, splenomegaly, thrombocytopenia and high total proteins in malnourished children should heighten the suspicion of possible underlying associated HIV infection. This study reinforces the recommendation by the World Health Organisation (WHO) that all malnourished children should have mandatory HIV screening.

## Introduction

The Human Immunodeficiency Virus (HIV) infection and its attendant problems remain a threat to global health, more so in the sub Saharan continent where malnutrition is also prevalent<sup>1</sup> and the paediatric age group remain the most affected vulnerable group.<sup>1</sup> In developing countries, malnutrition contributes significantly to 50% of childhood mortality either directly or indirectly.<sup>2</sup> The mortality that occurs from the malnourished state is significantly related to the body growth parameters, namely the weight for age, weight for height and height for age.<sup>2,3</sup> Severely malnourished children with z scores of the weight for height less than 3-standard deviation from the mean values (-3SD) are at a 10 fold risk of a higher mortality compared to children with a z-score higher or equal to 1.<sup>2,3,4</sup>

Malnutrition and HIV infection are believed to be intertwined in a vicious cycle as HIV increases the vulnerability to malnutrition while the latter lowers immunity and enhances vulnerability to HIV transmission risk and disease progression in HIV infected children.<sup>5-7</sup> The clinical features of severe malnutrition and HIV/AIDS are known to overlap in young children. This may affect the accurate diagnosis of presumptive HIV infection in resource poor settings where HIV testing facilities are still inadequate and the two conditions often coexist. Malnutrition, although mainly attributed to nutritional deficiency, may be multifactorial in origin and the malnourished state which is usually accompanied by some degree of immunocompromise predisposes to infections generally and this does not exclude the HIV infection. The World Health Organization(WHO) actually classifies wasting as a Stage 3 AIDS condition and thus distinguishing malnutrition from the former clinically sometimes can be difficult,<sup>7-8</sup> thus, the recommendations remains that all malnourished children should have HIV testing done.<sup>8</sup>

The prevalence of HIV in malnourished children has varied over the years, depending on the characteristics of the group of children studied. In 1990, Fischer et al<sup>9</sup> documented a prevalence of 3% in south West Nigeria. However, other reports gave a higher prevalence in this group of children, ranging from 8.6% in Niger Republic<sup>10</sup> to 12% in Central African Republic.<sup>11</sup> Most of these reports were in severely malnourished children. In 2014, some authors from Northern Nigeria, i.e., Kano, documented a prevalence of 7.8% across the various degrees of malnutrition. These variations were largely attributable to differences in degree of malnutrition and maternal HIV prevalences in the different groups. However, in south western Nigeria there are no current studies to reflect prevalence of HIV status across the spectrum of malnourished children i.e., mild to severe malnutrition. Thus, this study aimed to determine the prevalence and categories of malnutrition amongst children attending two health facilities in Lagos, the Lagos University Teaching Hospital (LUTH) and the Massey Children's Hospital, and document the HIV status of these malnourished children. In addition, the study aimed to describe any peculiarity in the clinical features, haematological indices and some biochemical indices in these children.

## **Materials and Methods**

The study was a prospective cross-sectional study conducted at the Paediatric Department of the Lagos University Teaching Hospital and the Massey Street Children's Hospital over a 6 months period. All children aged 5 months- 5 years diagnosed with malnutrition were consecutively recruited from the emergency room and paediatric wards during the study period. Details of the study and its relevance were explained to parents and caregivers of affected children following which a written, informed consent was obtained.

Known patient with HIV/AIDS on anti-retroviral therapy were excluded from the study.

The sample size was determined with the cochrane formula for prevalence studies.<sup>12</sup>

The severity of the malnutrition was determined using the using the Weight for Height or z scores (A z-score is the number of standard deviations (SD) below or above the reference median value.) The severity of the Malnutrition was graded as follows:<sup>13</sup>

1. Moderate malnutrition is weight for height of 70%- 80% of expected or z score of between - 2SD to < -3SD.
2. Severe malnutrition refers to any of the following:
  - a) Weight for height <70% or z score of <-3SD, or
  - b) Mid upper arm circumference <115mm, or
  - c) Any form of malnutrition with edema

## **Data Collection**

All the subjects had anthropometry done. The infants were weighed on the bassinet weighing scale (Docbel Braun Model, Doebil Industries, India) while children above 1 year were weighed on a regularly calibrated scale in light clothing. Weight was documented to the nearest Kg. The length of the infants was determined with a standard measuring board (Rolla meter mat 100cm by 1mm) while the height of the older participants was determined to the nearest cm with the stadiometer. The mid upper arm circumference and the Body mass index (BMI) in the children were also determined.  $BMI (Kg/m^2) = \text{Weight in Kg} / \text{height in meters}^2$ .

Pre- and Post- HIV counselling was done by the researchers for all the subjects recruited into the study and all results were treated with confidentiality.

## **Laboratory tests**

HIV testing was performed using the standard HIV algorithm of two enzyme-linked immunoassays (EIA) in parallel in children above 18 months of age. Real-time polymerase chain reaction (RT-PCR) was performed for children below 18 months of age and those with indeterminate results on EIA. Each subject also had a Full blood count and Serum proteins done.

The following parameters were recorded in a standard proforma for all the subjects:

Age, sex, weight, height/length, presence of oedema, diarrhoea and other significant clinical features, haematological tests (packed cell volume, white blood cell (WBC) count, and differentials, platelet count ), HIV tests (ELISA and DNA PCR), Serum Proteins were all documented.

## **Statistical Analysis**

Data were entered into the SPSS version 21 statistical package and basic descriptive statistics were done. Continuous data and categorical data were compared using the student t test and chi-square test respectively. The factors associated with HIV status were determined with the logistic regression analysis.

## **Ethical Considerations**

Ethical approval was obtained for the study from the Health Research and Ethics committee of the Lagos University Teaching Hospital. Participants' privacy and confidentiality of data management was ensured during and after the study.

## Results

### General characteristics of the study population

A total of 214 malnourished children  $\leq 5$  years were recruited into the study. 25 of these children were positive for HIV while 189 were HIV negative. Thus, the prevalence of HIV was 11.7% amongst the study participants.

Table 1 shows the general characteristics of the study population in relation to their HIV status. About half of the study participants belonged to the middle socioeconomic class (50.3%) and were Muslims (53.3%).

The median (range) age for the study participants was 15(5-60) months and the median age which was comparable in the HIV positive and negative children. There was no statistical difference in the maternal age ( $p=0.982$ ), subject's weight ( $p=0.052$ ) and length ( $p=0.086$ ) in the HIV positive and Negative children.

**Table 1: General characteristics of the study participants**

<b>Parameter</b>	<b>HIV positive</b>	<b>HIV negative</b>	<b>P value</b>
<b>Age(months)</b>			
Median(range)	12(9-36)	12(5-60)	
<b>Gender (n(%))</b>			
Male	11(44.0)	83(43.9)	0.000
Female	14(56.0)	106(56.1)	
<b>Weight</b>			
Median(IQR)	7.75(6.55-8.55)	7.72(6.00-8.10)	0.520
<b>Length/Height</b>			
Median(IQR)	69.75(64.37-75.00)	70.20(65.00-76.00)	0.086
<b>Z score</b>			
WHZ	-2.51(-3.50 to -1.37)	-2.50 (-3.83 to -1.50)	0.224
LHZ	-2.85(-3.45 to -0.95)	-2.85 (-3.63 to -0.460)	0.606
<b>Maternal age</b>			
Median(IQR)	29.00(26.00-34.00)	30.00 (25.00-33.00)	0.982
<b>Socioeconomic status N (%)</b>			
High	1(4)	36(19.0)	0.162
Middle	14(56)	95(50.3)	
Low	10(40)	58(30.7)	
<b>Religion N (%)</b>			
Christianity	12(48)	(37.6)	0.563
Islam	12(48)	112(59.2)	
Others	1(4)	16(3.2)	

**Median (IQR)= Median(Interquartile range), WHZ-Weight for height z score, LHZ-Length/Height for age z score, n(%)= number(percentage)**

## HIV seropositivity

The prevalence of HIV in the subjects with malnutrition was 11.7%. Most of the HIV positive children were in the age bracket 12 -24 months (60%). However, the highest percentage seropositivity (25.0%) was seen in the age group 25-36 months. The lowest seropositivity was seen in the infants (8.2%) as shown in Table 2.

**Table 2: Seropositivity of HIV amongst the age categories**

Variable	HIV Status		Seropositivity in each age group
	Positive N (%)	Negative N (%)	
Age category (months)			Percentage (%)
<12 months	5 (20)	56 (29.6)	8.2
12-24	15 (60)	109 (57.7)	12.1
25-36	3 (12)	9 (4.8)	25.0
>36	2 (8)	15 (7.9)	11.7
Total	25 (100)	189(100)	11.7

HIV-Human immunodeficiency virus

With the use of the WHO classification about three quarters of the study participants, had moderate malnutrition (74.8%) while about a quarter (25.2%) had severe forms of malnutrition. (see table 3). 64% of the HIV positive subjects also had moderate malnutrition and almost a

quarter of the HIV positive subjects had severe malnutrition. Amongst the HIV positive subjects 16% of the children had severe wasting and 8% had edematous malnutrition.

**Table 3: Severity of malnutrition and HIV status**

<b>Severity Classification Z score</b>	<b>Total N (%)</b>	<b>Positive N (%)</b>	<b>Negative N (%)</b>	<b>P value</b>
	214(100)	25(100)	189(100)	
-2SD to -3SD	160(74.8)	19(76.0)	141(.74.6)	0.892
>-3SD	54(25.2)	6(24.0)	48(25.4)	0.835
Severe wasting	46(21.5)	4(16.0)	42(22.2)	0.476
Edematous malnutrition	8(3.7)	2(8)	6(3.2)	0.557

**Moderate= z score: between -2SD and -3SD, Severe=z score: >-3SD; p<0.05 is significant, Chisquare (X<sup>2</sup>=3.371), p=0.815**

## **Clinical features**

Fever, cough and diarrhea were the commonest symptoms seen amongst the study participants while oral thrush, dermatoses and splenomegaly were the commonest signs. (see Table 4)

A higher proportion of the HIV positive subjects compared to the negative subjects had oral thrush, dermatoses and edema but this was not statistically significant. Hepatosplenomegaly was the least presenting signs in both groups. None of the subjects with HIV had otitis media or Jaundice. Splenomegaly was the only significantly different sign among the 2 groups of malnourished children (p=0.0001)

**Table 4: Clinical characteristics of the malnourished children: HIV positive and HIV negative children.**

Clinical features	HIV Positive N=25	HIV Negative N=189	P value
Fever	16(64)	119(62.9)	0.919
Cough	13(52)	92(48.7)	0.754
Oral Thrush	3(12)	8(4.2)	0.984
Diarrhea	5((20)	56(29.6)	0.316
Jaundice	0	2(1.1)	0.605
Edema	2(8)	6(3.2)	0.232
Dermatoses	3(12)	17(8.9)	0.627
Hepatomegaly	2(8)	12(6.3)	0.753
<b>Splenomegaly</b>	<b>2(8)</b>	<b>0(0)</b>	<b>0.0001</b>

HIV-Human immunodeficiency virus

Table 5 shows the laboratory investigations in the study participants. The PCV ranged between 14.1% - 52.5% with a median (IQR) of 35.2 % (28.77-38.10) in the study participants

The median PCV was comparable in both groups. 30(14%) of the study participants had anaemia of which only 2 (0.9%) of the subjects had severe anaemia.

Total WBC ranged from 1,630-56,600cells/mm<sup>3</sup> with a median of 11,600/mm<sup>3</sup>. The WBC and platelets were lower in the HIV positive subjects than the HIV negative subjects but this did not reach statistically significant levels. The proportion of the neutrophil and lymphocytes were also comparable in the two groups.

However, the total protein and serum globulin levels (figure 1) were significantly higher in the HIV positive group (p=0.042, p= 0.015). The serum albumin though lower in the HIV positive group did not reach statistically significant levels. (p= 0.477) CD4 count and CD4% in the HIV group were 645.00 (293.00-1,060) and 12.25 % (10.00-14.25) respectively.

**Table 5: The laboratory investigations in the study participants.**

<b>Parameter</b>	<b>HIV positive Median(IQR)</b>	<b>HIV negative Median(IQR)</b>	<b>P value</b>
PCV(%)	34.75 (28.77-38.10)	35.40 (32.00-33.00)	0.391
Total WBC(x10 <sup>9</sup> /L)	11.10 (9.4750-15.950)	11.80 (9.0250-16.175)	0.603
Neutrophils (%)	47.40(28.30-62.00)	47.8 (34.80-59.90)	0.749
Lymphocytes (%)	41.40(27.60-57.30)	41.65 (29.72-54.77)	0.847
Platelets(x10 <sup>9</sup> /L)	431,000(294,000-494,000)	445,000 (333,000-586,000)	0.153
<b>Total protein(g/dl)</b>	<b>66.42 (63.11-73.58)</b>	<b>63.48 (58.49-68.31)</b>	<b>0.042</b>
Serum Albumin(g/dl)	36.15(28.62-40.82)	37.15(31.35-41.00)	0.535
<b>Serum Globulin</b>	<b>30.53(24.61-39.73)</b>	<b>27.50 (23.28-31.23)</b>	<b>0.015</b>

HIV-Human immunodeficiency virus, PCV-Packed cell volume, WBC- White blood cell count.  
IQR-Interquartile range

The risk factors for HIV evaluated in the study participants are shown in table 7. Multivariate analysis showed that the total protein (p=0.001) and platelet count (p=0.016) were the only factors that could significantly predict the occurrence of HIV in the study population.

**Table 6: Predictors of the Risk of occurrence of HIV in the malnourished children: Logistic Regression**

Parameter	B	S.E	Wald	P value	Ex(B) Odd's ratio	95% Confidence Interval
Age	0.327	0.318	1.055	0.304	1.386	0.743-2.586
Gender	-0.062	0.657	0.009	0.925	0.940	0.260-3.406
Socioeconomic status	2.113	1.339	2.491	0.114	8.276	0.600-114.170
Nutritional status	1.169	0.856	1.865	0.172	3.220	0.601-17.242
Edema	-1.575	1.324	1.416	0.234	0.207	0.015-2.771
Diarrhea	2.250	1.203	3.495	0.062	9.483	0.897-100.282
Oral thrush	-0.926	1.395	0.440	0.507	0.396	0.026-6.107
Fever	-0.193	0.635	0.093	0.761	0.824	0.237-2.861
<b>Total Protein</b>	-0.140	0.064	4.754	<b>0.029</b>	0.870	0.767-0.986
Globulin	0.036	0.062	0.347	0.556	0.964	0.854-1.088
PCV	0.057	0.056	1.049	0.306	1.059	0.949-1.180
Total WBC	0.041	0.046	0.799	0.377	1.041	0.952-1.140
<b>Platelet count</b>	0.005	0.002	5.094	<b>0.024</b>	1.005	1.001-1.009

P< 0.05 is considered significant, PCV- Packed cell volume, WBC- White blood cell count

## Discussion

In this study, the prevalence of HIV infection amongst malnourished children aged 5 years and below attending two health facilities in Lagos was 11.7%. This prevalence is much higher than the national prevalence for HIV in Nigeria (4.4%) and from other reports in malnourished children in Ogbomosho (3%),<sup>14</sup> South Western Nigeria and Kano (7.8%)<sup>14</sup> in northern Nigeria. Reports from apparently well children by Ogunbosi et al (10%)<sup>15</sup> and Motayo et al (6.7%) have also been observed to be lower.<sup>16</sup> The possible reasons for the high prevalence observed in this present study may be due to the fact that this was a hospital based study. Other possible explanations may be due to ignorance, weak maternal to child transmission services and failure of early infant diagnosis in the country.

Majority of the subjects in our study were in the age bracket 12-24 months, however the subjects within the age bracket 25-36 months had the highest seropositivity (25%) This age bracket was the peak age of presentation of the infection and probably represented the second phase in HIV infection. It has also been observed that the children who did not receive treatment at this time are likely to die from the illness.<sup>17</sup> Currently, most children who receive treatment and are compliant now survive into adolescent period and beyond. In terms of sex predilection, there were more females than males in this study which is similar to the findings of Sudawa<sup>17</sup> and Ogunbosi et al.<sup>15</sup> Reports from India however document a male preponderance. A female preponderance has also been described in adolescents and adults and this has been attributed to heterosexual transmission. This is not applicable in the paediatric age group and gender differences thus may be a chance finding.<sup>15</sup>

The use of the WHO classification for malnutrition actually reflects the severity of the malnourished state. According to this classification majority of the subjects in this present study

had moderate malnutrition and the severe forms was seen in a quarter of the subjects.

Edematous malnutrition was present in minority(3.7%) of the subjects. Other reports from south western Nigeria <sup>18</sup>have also observed that the less severe forms of malnutrition are no longer prevalent in south western Nigeria.<sup>18</sup> This may be a reflection of the global effort and efforts at the national level which has resulted in the effective reduction in the severe forms of malnutrition especially in many countries in the sub-Saharan continent.

Majority of the HIV positive subjects in this present study also had moderate malnutrition since this was commonest form of malnutrition seen in the subjects. In contrast, Sudawa et al<sup>17</sup> in 2013 in Kano state observed that marasmus (48.3%) was the commonest type of malnutrition seen in under fives with HIV infection and only minority (6.5%) had edematous malnutrition. Severe wasting without edema is a common finding in severe malnutrition with concomitant HIV infection.<sup>18-22</sup> Presently, WHO has corroborated this fact by classifying wasting as seen in Marasmus as a stage 3 AIDS defining illness. Thus, the need arises to always screen children with severe wasting for retroviral disease.

Many studies on malnourished children and HIV status have focused on severely malnourished children as the target group for HIV and the possible reason may be related to the apparent overlap between the two conditions. This present study is one of the few reports which documents the retroviral status across the spectrum of malnourished children in Nigeria and from this present study and other reports it is evident that even children with less severe forms of malnutrition and apparently healthy children are also at risk of the infection.<sup>14-15,17</sup>

In terms of clinical findings, fever, cough and diarrhea were the commonest symptoms seen in the subjects in this present study. These findings are similar to that of previous workers.<sup>17,19,15</sup>

Splenomegaly was seen more in the HIV subjects and appeared to be the only discriminatory clinical feature amongst the HIV positive and negative of malnourished children. Severe malnutrition and HIV have clinical features which overlap and it becomes difficult to differentiate between the two group of patients especially in the resource limited countries however some authors have noted that the severely malnourished HIV infected children were more likely to have oral thrush and persistent diarrhea and these may serve as possible discriminating features.<sup>3,18-19,21-23</sup>

The haematologic indices evaluated in the malnourished children were observed to be lower in the HIV positive group compared with the HIV negative group but this was not statistically significant. This is consistent with the findings of Ezeonwu et al<sup>24</sup> in Enugu and Adetifa et al<sup>25</sup> in Lagos. Lower haematologic indices have been reported in severely malnourished HIV positive children and is probably a reflection of the bone marrow suppression state. Malnourished children are predisposed to anaemia for several reasons namely inadequate intake, micronutrient deficiency (iron and folate deficiencies), increased nutrient loss from recurrent diarrhea. These conditions are prevalent in the HIV infected children and these factors may influence the prevalence of anemia in this group of children.<sup>26</sup> The aetiology of haematologic abnormalities in the HIV children has been attributed to the release or production of cytokines which occurs in the condition which is believed to suppress haemopoiesis and cause myelosuppression.<sup>24</sup> In addition, other associated comorbid conditions, the presence of opportunistic infections<sup>27,28</sup> and the use of antiretroviral drugs<sup>26,30</sup> especially zidovudine may contribute to the occurrence of anaemia and other haematological abnormalities.<sup>24, 29-30</sup>

In contrast, the total protein in the HIV group in this present study was significantly higher than the HIV negative group. A higher level of serum proteins in HIV infection has been reported by

other workers<sup>31-33</sup> and this finding has been attributed to hyperglobulinaemia. The increased total protein levels which occurs in HIV infection is believed to occur as a result of increased immunoglobulins seen in the condition. In our study the globulin level was also found to be higher in the HIV positive subjects compared to the HIV negative children. Theories postulated for the hyperglobulinaemia is the polyclonal B cell activation.<sup>34-36</sup> The viral proteins (glycoprotein 41) is said to be responsible for the activation of the polyclonal B cell which occurs as the infection progresses.<sup>34-36</sup> However, the serum albumin was lower in the HIV group compared to the non HIV group which may still be a reflection of the malnutrition state or chronic infection with HIV.

The predictors of the occurrence of HIV in the malnourished subjects were determined with the use of the multivariate analysis and the total protein level and platelet count were able to predict the risk of occurrence of HIV infection in this cohort of malnourished children. Reported predictors/risk factors in malnourished children by Madec et al<sup>10</sup> however includes gender and previous hospitalizations.

## **Limitations**

It would have been desirable to follow up the subjects and monitor any changes in the haematological and biochemical profile but this was difficult due to logistic reasons.

## **Conclusions**

Malnourished children remain a high risk group for HIV infection and the prevalence of the infection obtained in this group of children is still unacceptably high.

The presence of severe wasting or marasmus, oral thrush, diarrhea, splenomegaly, thrombocytopenia and high total proteins in malnourished children should heighten the suspicion of possible underlying associated HIV infection. Continual and mandatory screening of malnourished children for HIV infection is advocated. Further longitudinal studies on malnourished children with HIV is advocated.

## **Acknowledgements**

We acknowledge the contribution of the Central research Committee of the University of Lagos for the support for the study. We are also grateful to Mr Niyi and the resident doctors in the department of Paediatrics Lagos University Teaching Hospital who assisted with the recruitment of the subjects and the collection of the data for the study.

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