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*ORIGINAL ARTICLE*

# Clinical Staging of HIV Infection as a Surrogate for CD4 Count in HIV-Infected Children

## *Classification clinique de l'infection à VIH en tant que substitut pour CD4 chez les enfants infectés par le VIH*

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**ABSTRACT**

BACKGROUND: **Human immunodeficiency virus (HIV) infection is a major cause of infant and childhood mortality and morbidity; without treatment about 50% of them will succumb to HIV/AIDS before the age of two years.**

OBJECTIVE: **To evaluate the usefulness of clinical manifestations of HIV infection as a surrogate for CD4 counts in antiretroviral-naive HIV-infected children.**

METHODS: **Newly diagnosed HIV-infected children, antiretroviral-naïve attending a paediatric infectious diseases unit were enrolled. The clinical manifesta-tions, age, sex, and WHO clinical stage of each patient were determined. CD4 count and CD4% were estimated at presentation and correlated with various clinical manifestations of HIV disease.**

RESULTS: **The study population consisted of 126 children, aged four months to 14 years with a mean of 3.2 ± 2.7 years and a male to female ratio of 1.2:1. Eighty-one percent of the children acquired HIV infection through mother-to-child transmission (MTCT). The CD4% was higher in infants (p<0.000) and lower in children over five years of age. Eighty-six percent of them in stage 4 were children less than 24 months of age. CD4% showed a modest correlation with WHO paediatric clinical staging (r=0.62, p=0.002). Patients with lymphadenopathy (stage 1) had a high absolute CD4 count whereas patients with failure to thrive had a relatively low absolute CD4 count.**

CONCLUSION: **WHO Paediatric clinical staging for HIV infection correlates with CD4% and can be used as a surrogate to CD4. CD4 count and CD4% vary with age and complications of the disease. WAJM 2010; 29(5): 299–302.**

Keywords: **WHO clinical staging, HIV, CD4 count, CD4%, Surrogate, Paediatrics.**

*RÉSUMÉ*

*CONTEXTE: Le virus de l'immunodéficience humaine (VIH) est une cause majeure de mortalité infantile et la mortalité infantile et la morbidité; sans traitement d'environ 50% d'entre eux succombent au VIH / SIDA avant l'âge de deux ans.*

*OBJECTIF: évaluer l'utilité des manifestations cliniques de l'infection par le VIH comme un substitut à la numération des CD4 dans les naïfs de traitement antirétroviral des enfants infectés par le VIH.*

*MÉTHODES: les enfants nouvellement diagnostiqués infectés par le VIH, naïfs de traitement antirétroviral pédiatrique assister à une unité de maladies infectieuses ont été inscrits. Les manifestations cliniques-tions, l'âge, le sexe, et de l'OMS au stade clinique de chaque patient ont été déterminées. numération des CD4 et CD4% ont été estimés à la présentation et la corrélation avec diverses manifesta-tions cliniques de la maladie.*

*RÉSULTATS: La population étudiée comprenait 126 enfants, âgés de quatre mois à 14 ans avec une moyenne de 3,2 ± 2,7 ans et un ratio hommes / femmes de 1.2:1. Quatre-vingt-un pour cent des enfants ont contracté l'infection à VIH par transmission mère-enfant (TME). Le% de CD4 était plus élevé chez les nourrissons (p <0,000) et plus faible chez les enfants de plus de cinq ans. Quatre-vingt-six pour cent d'entre eux à l'étape 4 étaient des enfants de moins de 24 mois d'âge. CD4% ont montré une faible corrélation avec l'OMS stade clinique pédiatrique (r = 0,62, p = 0,002). Les patients atteints de lymphadénopathie (étape 1) avaient un taux de CD4 élevé absolue alors que les patients avec un retard de croissance ont un taux de CD4 relativement faible absolue.*

*CONCLUSION: l'OMS stade clinique pédiatrique de l'infection par le VIH est en corrélation avec CD4% et peut être utilisé comme substitut au CD4. numération des CD4 et CD4% varient avec l'âge et les complications de la maladie. WAJM 2010; 29 (5): 299–302.*

***Mots-clés:*** *stade clinique OMS, le VIH, la numération des CD4, CD4%, des successions, de la pédiatrie.*

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**Abbreviations: AIDS,** Acquired Immunodeficiency syndrome; **ART,** Antiretroviral Therapy; **CMs,** Clinical manifestations; **ELISA,** Enzyme linked Immunosorbent Assay; **FTT,** Failure to thrive; HIV, Human Immunodeficiency Virus; **LIP,** Lymphoid interstitial pneumonia; **MTCT,** Mother-to-Child Transmission; **OIs,** Opportunistic Infections; **PCP,** Pneumocytis carinii pneumonia; **PCR,** Polymerase chain reaction; PENTA, Paediatric European Network for treatment of AIDS; **PEPFAR,** President Emergency Programme for AIDS Relief; PGL, Persistent generalized lymphadenopathy; **PMTCT,** Prevention of Mother-to-Child Transmission; **UMTH,** University of Maiduguri Teaching Hospital; **UNAIDS,** Joint United Nation Programme on HIV/ AIDS; **WHO,** World Health Organisation.

## INTRODUCTION

Human immunodeficiency virus (HIV) infection is a major cause of infant and childhood mortality and morbidity. An estimated 2.3 million children were reported to be living with HIV/AIDS as at the end of 2006; two million of these children were in sub-Saharan Africa.[1] The World Health Organization (WHO) and the Joint United Nations Programme on HIV/AIDS (UNAIDS) reported that only 40,000 of the more than 660,000 HIV positive children requiring antiretroviral therapy (ART) were receiving it in 2005 and without treatment about 50% of them will succumb to HIV/AIDS before the age of two years.[2]

The absolute CD4+ lymphocyte count and percentage, and plasma viral load have been considered the most reliable markers of disease progression in HIV-infected patients[3–4] and have been the basis for indicating ART as well as prophylaxis against opportunistic infections (OIs). However, these tests require resources and technical expertise, neither of which is routinely available in resource-poor settings such as Nigeria. Opportunistic infections in HIV-infected children are generally seen in the setting of severe depression of the CD4 count.[5] It is therefore reasonable to assume that concomitant manifestations of opportunistic infections may reflect a severe drop in CD4 count thereby making clinical manifestations (CMs) a possible surrogate for CD4 cell count. In an effort to scale-up ARV therapy in developing countries the WHO has recommended the use of Paediatric HIV clinical staging system in initiating antiretroviral therapy in children where CD4 count is unavailable.[2] For effective patient management in resource limited settings, there is the need to assess the usefulness of alternative markers such as the CMs. This study aimed to evaluate CMs as surrogate for CD4 count in HIV-infected children in Africa.

## SUBJECTS, MATERIALS, AND METHODS

### Subjects

One hundred and twenty-six newly diagnosed HIV-infected and antiretroviral-naïve children attending the paediatric infectious diseases unit at the University of Maiduguri Teaching Hospital (UMTH), Maiduguri, north-east Nigeria, from July 2006 to June 2007 were enrolled. The UMTH serves as a tertiary referral centre for infectious diseases from the neighbouring states and from the Cameroon, Niger and Chad republics.

Their HIV status was confirmed by Western blot test after an initial reactive ELISA test (Orgenic, Israel). Polymerase chain reaction (PCR) for HIV-1 DNA was used to confirm HIV status in children less than 18 months.

Ethical approval was obtained from the ethical committee of UMTH. Written consent for participation in the study was obtained from children's parents/ caregivers at the time of enrolment. Following consent, further analysis of absolute CD4 count and CD% was done.

On enrolment, a fill-in protocol detailing biodata, clinical history and physical examination was conducted for each of the patient with special emphasis on clinical features of HIV. Information obtained was entered into a data sheet and analysed for correlation of CD4 count and CD% with various clinical features. Using the WHO paediatric HIV clinical staging system,[6] patients were allocated to stages 1, 2, 3 or 4.

### Mode of Transmission

History of blood transfusion, use of non-sterilized body piercing instruments, traditional surgery, sexual exposure/abuse and maternal HIV status in order to establish the likely source of infection was also sought. In children in whom the aforementioned sources could not be determined are considered to be unknown.

### Definition of Terms

Persistent generalized lymphadenopathy (PGL) was diagnosed as the presence of enlarged lymph nodes (one cm) in two or more sites, excluding other causes. Hepatomegaly was defined as liver size greater than two cm palpable below the costal margin at right mid-clavicular line and splenomegaly as spleen enlargement palpable per abdomen.[7] Clinical oral candidiasis was registered if pseudomembranous oral lesion was observed.[8] Persistent diarrhoea was diagnosed as diarrhoea lasting more than 14 days associated with weight loss. Failure to thrive (FTT) was defined by weight of less than 80% of expected weight for age and height of less than 90% of expected height for age.[9] Tuberculosis was diagnosed on the basis of symptomatology, history of adult contact with open tuberculosis, radiology, Mantoux test, sputum or gastric lavage for acid-fast bacilli, lymph node biopsy, poor response to antibiotic therapy and response to antituberculous treatment.[10] Pneumocytis carinii pneumonia (PCP) was diagnosed on the basis of dyspnoea, fever and radiological evidence of bilateral diffuse alveolar infiltrates.[10] Lymphoid interstitial pneumonia (LIP) was diagnosed on the basis of chronic respiratory symptoms, hypoxia and radiology showing interstitial pulmonary infiltration that responded poorly to antibiotic therapy with at least two of the following: bilateral parotid swelling, generalized lymphadenopathy, digital clubbing or response to corticosteroids.[10] HIV nephropathy was determined by the presence of significant proteinuria with or without other deranged renal function tests and excluding other causes of renal dysfunction.[11]

### Laboratory Evaluation

Dynal beads technique (Dynal Biotech, Oslo, Norway) for CD4 counting was used. This technique uses paramagnetic polymer beads coated with anti-CD4 monoclonal antibodies to capture and isolate the CD4 from the blood. Other investigations done were dictated by the clinical condition of the patients.

### Data Analysis

Data was analyzed using SPSS statistical software version 10. Statistical analysis included one way ANOVA and paired t-test for comparison. A p-value of $<0.05$ was considered significant for all statistical comparisons. Average values are presented as mean ±SD.

## RESULTS

### Study Population

The study group consisted of 126 children aged four months to 14 years with a mean of 3.2 ± 2.7 years. Of the 126 children, 69 (54.8%) were male and 57 (45.2%) were female with a male to female ratio of 1.2:1.

### Mode of Transmission

The predominant mode of transmission was mother-to-child transmission (MTCT) in 102 (81%) patients, sexual exposure in three (2.4%), through blood transfusion in two (1.6%) and unknown in 19 (15%).

### Correlation between CD4 count and Clinical Manifestations

CD4 count was estimated in 121 patients and CD4 % in 96. The mean CD4 count and CD4% showed an inverse relationship with age, with children less than one year having the higher values and those over five year having lower values (Table 1).Using the WHO paediatric clinical staging system, 22 (17.5%) patients were in stage 1, 31 (24.6%) in stage 2, 59 (46.8%) in stage 3 and 14 (11.1%) in stage 4. Twelve patients in stage 4 (86%) are less than 24 months of age. The CD4% in each of the stages is shown in Fig. 1. The correlation between CD4% and clinical 'stage showed a decreasing trend with transition from stage 1 to 4, ($r = 0.62$, $p = 0.002$).

**Table 1: Pattern of CD4 Count and CD% among Different Age Groups**

| Age in years | Mean absolute CD4 (±SD) | Mean CD4% (±SD) |
|---|---|---|
| <1 | 420 ± 11 | 15 ± 3 |
| 1 – 5 | 678 ± 9 | 23 ± 2 |
| >5 | 854 ± 17 | 40 ± 6 |

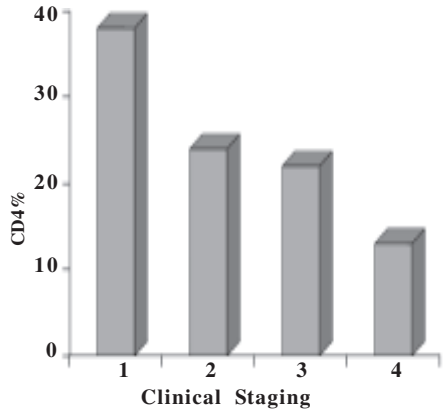


**Fig. 1: Relationship between CD4% and WHO Clinical Stage (r = 0.62, p = 0.002).**

**Table 2: Absolute CD4 Count by Clinical Features**

| Clinical Feature | No. of Patients (%) | Mean(±SD) Absolute CD4 cell/m² |
|---|---|---|
| Lymph nodes | 60 (47.6) | 932 ± 511 |
| Hepatospenomegaly | 52 (42.3) | 627 ± 375 |
| Skin lesion | 47 (37.3) | 676 ± 401 |
| Recurrent pneumonia | 32 (25.4) | 787 ± 463 |
| Chronic Diarrheoa | 41 (32.5) | 702 ± 611 |
| Oral thrush | 29 (23.0) | 540 ± 377 |
| Tuberculosis | 59 (46.8) | 496 ± 294 |
| Failure to thrive | 38 (30.2) | 322 ± 167 |

The common clinical presentations and variation of CD4% and CD4 count in each clinical presentation as shown in Table 2. Absolute CD4 count was relatively high in patients with stage 1 disease (lymphadenopathy and hepato-splenomegaly), compared with low count in patients with FTT and oral thrush (stage 3).

## DISCUSSION

Plasma HIV Type 1 (HIV-1) viral load, the number of CD4 cells and CD% are still the useful markers for predicting the clinical course and response to ART as well as starting prophylaxis for opportunistic infections in HIV-infected adults and children.[3,4] However, the infrastructure of clinical laboratories located in many resource-constrained countries can't afford to perform these tests required for implementation of HIV therapy.[11] In this study, we have evaluated the clinical presentations of HIV infection as a surrogate for CD4 count/CD4% in determining the optimal time to initiate antiretroviral therapy in HIV-infected African children.

### Mode of HIV Transmission

The predominant mode of transmission was MTCT in 102 (81%) patients in the present study. Several other reports[12–15] showed that MTCT accounted for 80% or more of HIV transmission. Research findings provide a strong rationale for implementation of prevention of mother-to-child transmission (PMTCT) interventions in resource-poor countries, especially in Africa. [16-17]

### Correlation between CD4 count and Clinical Manifestations

In this study, the CD4 count and CD4% were higher in infants with subsequent decline in children over five years of age. This finding is in consonance with that of HIV Pediatric Prognostic Markers Collaborative Study Group[18] and the Paediatric European Network for treatment of AIDS (PENTA)[19] that CD4 count/CD4% varied with age. Analysis of age-related clinical staging showed that, the younger children aged one year and below were all in the advanced and severe stages. This is in agreement with other studies from Nigeria[12–14] and from other developing countries.[20–21] This severe manifestation of HIV infection in most developing countries may be responsible for the 45–50% of HIV infected children in Africa dying from the disease before their second birthday without treatment.

In this study we observed a decreasing trend in CD4% with transition from stage 1 to 4, with an overall modest correlation between paired CD4% and WHO paediatric HIV clinical stages in 126 HIV-infected African children. The result of our study supports the WHO recommendation for initiating anti-retroviral therapy in children using clinical staging alone where viral load and CD4 count estimation are not available. The WHO recommends the initiation of antiretroviral drugs in children in stages 3 and 4 irrespective of the CD4 count, especially in younger children.[2]

In conclusion, this study has provided additional information with regard to the use of clinical manifestations of HIV infection as a surrogate to CD4 count in initiating antiretroviral therapy in Africa children. It is also necessary to take into account the relationship of CD4 count with age. It is important, too, to remember that inter-current infection might artificially reduce the CD4 count and therefore, in the presence of infection, CD4% correlates better. Prevention of mother-to-child transmission is the most cost-effective antiretroviral programme and one of the most attractive interventions for prevention of HIV. It is hoped the result will help in scaling-up antiretroviral treatment to over 660,000 HIV-infected children who presently need care.

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**Duality of Interest**

We (authors) declare that we have no competing/duality of interests.

**REFERENCES**

1. UNAIDS/WHO. AIDS epidemic update – Executive susmmary. Geneva: *Joint United Nation Programmes on HIV/ AIDS,* 2006: 1–36.
2. WHO. Scaling Up Antiretroviral Therapy in Resource-Limited Settings. Available at: http://www.who.int
3. Mellors JW, Munoz A, Giorgi JV, Margolick JB, Tassoni CJ, Gupta P., *et al*. Plasma viral load and CD4z lymphocytes as prognostic markers of HIV-1 infection. *Ann Intern Med* 1997; **126:** 946–54.
4. Chattopadhya D, Baveja UK, Bose M, Kumar A. Disease progression markers during asymptomatic phase of HIV-1 infected children with unimpaired CD4z cell values: evaluation of repeat CD4z cell evaluation vs other immunological parameters. *J Trop Pediatr* 2002; **48:** 340–7.
5. Yogev R, Chadwick EG. Acquired immunodeficiency syndrome. In: Behrman RE, Kleigman RM and Jenson HB (Eds). Nelson Text book of Pediatrics. WB Saunders co. 2001: 1022–1032.
6. Wikipedia Contributors. WHO Disease Staging System for HIV Infection and Disease in Children [Internet]. Wikipedia, The Free Encyclopedia; January 18, 2007, 07: 48UTC (cited 2007 July 15).
7. William FB: Manifestation of liver disease In: Behrman RE, Kleigman RM, Jenson HB (eds). *Nelson Text Book of Pediatrics,* Saunders co. 2001. Pp 1198–1203.
8. GM Ashir, MG Mustapha, AI Rabasa, F Bashir, IU Halima. HIV-related oral candidiasis in Nigerian children: A marker of HIV disease progression. *SAJCH* 2008; **2:** 152–54.
9. Waterlow JC. Some aspects of childhood malnutrition as a public health problem. *BMJ* 1974; **4:** 88–90.
10. Graham SM, Coulter JBS, Gilks CF. Pulmonary disease in HIV-infected African Children. *International Journal of Tuberculosis and Lung Disease* 2001; **5:** 12–23.
11. Berggren R, Batuman V. HIV-associated renal disorders: recent insights into pathogenesis and treatment. *Curr HIV/ AIDS Rep*. 2005; **2:** 109–15.
12. Erhabor O, Uko E.K, Adias T. Absolute lymphocyte count as a marker for CD4 T-lymphocyte count: Criterion for initiating antiretroviral therapy in HIV-infected Nigerians. *Nig J Med* 2006; **15:** 56–59.
13. Osinusi K, Brown BJ. Clinical presentation of HIV infection in children at the University College Hospital, Ibadan: A one-year review. Proceedings of the 35th Annual General meeting and Science Conference of the Paediatric Association of Nigeria. Zaria, Nigeria: *PANCONF,* 2004: 6.
14. Ojukwu JU, Ogbu CN. Paediatric HIV/ AIDS in Abakaliki. *Nig J Paediatr* 2003; **30:** 128–133.
15. Angyo IS, Okpe ES, Onah J. Paediatric AIDS in Jos, Nigeria. *West Afr J Med* 1998; **17:** 268–272.
16. Hira SK, Kamanya J, Bhat GJ, Mwale G, Tembo N, Luo PL. Perinatal transmission of HIV-1 in Zambia. *BMJ* 1989; **299:** 1250–2 X
17. WHO. Child health research: a foundation for improving child health (WHO/FCH/CAH/02.3). Geneva: WHO.2002.
18. Dabis F, Newell ML, Fransen L, Saba J, Lepage P, Leroy V, *et al.* Prevention of mother-to-child HIV transmission of HIV in developing countries: recommendations for practice. *Health Policy Plann* 2000; **15:** 34-42. X
19. Dunn D. HIV Paediatric Prognostic Markers Collaborative Study Group. Short-term risk of disease progression in HIV-1-infected children receiving no antiretroviral therapy or zidovudine monotherapy: a meta-analysis. *Lancet* 2003; **362:** 1605–11.
20. Paediatric European Network for treatment of AIDS (PENTA). HIV-1 viral load and CD4 cell count in untreated children with vertically acquired asymptomatic or mild disease. *AIDS* 1998; **12:** F1–8.
21. Tudor-Williiams G. HIV infection in developing countries. *Trans Roy Soc Trop Med Hyg* 2000; **94:** 3–4.
22. UNAIDS. Pediatric HIV infection and SIDS-UNAIDS point of view. Geneva, Switzerland: *Joint United Nation Programs on HIV/AIDS,* 2002: 1–7.