Published in final edited form as:
*Dev Med Child Neurol*. 2009 December ; 51(12): 968–973. doi:10.1111/j.1469-8749.2009.03333.x.

# The role of weight for age and disease stage in poor psychomotor outcome of HIV-infected children in Kilifi, Kenya

**AMINA ABUBAKAR, Phd**[1], **PENNY HOLDING, Phd**[2], **CHARLES R J C NEWTON, Md**[3], **ANNELOES VAN BAAR, Phd**[4], and **FONS J R VAN DE VIJVER, Phd**[4]

[1]Department of Psychology and Developmental Medicine, Centre for Geographic Medicine Research (Coast), Kenya Medical Research Institute, Kilifi, Kenya [2]Coast Programmes, Africa Mental Health Foundation, Nairobi, Kenya [3]Neurosciences Unit, Institute of Child Health, University College London, UK [4]Department of Developmental, Clinical and Cross-Cultural Psychology, Faculty of Social and Behavioural Sciences, Tilburg University, The Netherlands

## Abstract

**AIM—**We aimed to investigate the contribution of disease stage and weight for age to the variability in psychomotor outcome observed among children with human immunodeficiency virus (HIV) infection.

**METHOD—**This cross-sectional study involved 48 Kenyan children (20 females, 28 males) aged 6 to 35 months (mean 19.9mo SD 8.9) exposed prenatally to HIV. Two subgroups of HIV-exposed children were seen: those who were HIV-infected and those who were uninfected. The reference population was composed of 319 children (159 females, 160 males) aged 6–35 months, (mean age = 19 months, SD=8.43) randomly selected from the community. Disease stage varied from stage 1 to stage 3, reflecting progression from primary HIV infection to advanced HIV infection and acquired immune deficiency syndrome. A locally developed and validated measure, the Kilifi Developmental Inventory, was used to assess psychomotor development.

**RESULT—**Using age-corrected psychomotor scores, a significant main effect of HIV status was observed ($F_{(2,38.01)}$=7.89, $p$<0.001). Children in the HIV-infected group had lower mean psychomotor scores than the HIV-exposed children and the reference group. In the HIV-infected group, disease stage was a negative predictor and weight for age a positive predictor of psychomotor outcome.

**INTERPRETATION—**Weight for age and disease stage provide viable, easily measurable benchmarks to specify when frequent developmental monitoring and psychomotor rehabilitation are required. Nutritional intervention and other measures aimed at slowing disease progression may delay the onset and severity of psychomotor impairment in the paediatric HIV population in Africa.

Adverse effects of human immunodeficiency virus (HIV) on psychomotor functioning of children have been widely reported.[1] Given the influence of early psychomotor functioning on later cognitive development,[2] there is need for early intervention to protect against psychomotor deficits in the paediatric HIV population. However, a significant proportion of children infected with HIV show normal psychomotor development,[3] implying that not all children with HIV-infection are in need of intervention to improve psychomotor outcomes.



Correspondence to Dr Amina Abubakar at Kenya Medical Research Institute (KEMRI)/Wellcome Trust Research Programme, Centre for Geographic Medicine Research (Coast), Kilifi, Kenya. AAbubakar@kilifi.kemri-wellcome.org..


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Identifying simple and relatively easy-to-measure indicators for recognizing children at risk of poor psychomotor outcomes may ensure that this high-risk group receives the most appropriate care.

In children from the USA and the Europe,[4] biomedical factors such as nutritional status and disease stage have been implicated as sources of variability in outcome in HIV infection. In the absence of established neuropsychological services in sub-Saharan Africa, documenting the relationship between psychomotor development and factors such as disease stage and weight for age in the HIV population could be useful in identifying children in need of psychomotor rehabilitation. Furthermore, the relationship observed between these indicators and outcome in this population may suggest useful points of intervention, such as a potential role for nutritional intervention in improving psychomotor outcomes. Using a locally developed and validated measure of psychomotor development, we aimed to examine the contribution of weight for age and disease stage to the variability in outcome observed among HIV-infected children.

## METHOD

### Study site

The study was carried out in Kilifi, a largely rural district on the Kenyan coast. Approximately two-thirds (66.8%) of the population in Kilifi lives below the poverty line.[5] Medical facilities in the district are centred on one district hospital. The HIV prevalence rates are estimated at 11% in the general population and 9% among pregnant women.[6] Comprehensive care for HIV or acquired immune deficiency syndrome (AIDS), which includes monthly follow-ups, treatment for opportunistic infections, and nutritional counselling, is provided through a family health clinic based at the hospital. Antiretroviral treatment was not available at the time of the study.

### Participants

Children were eligible for recruitment if they were aged 6 to 35 months, their parents spoke Kiswahili or one of the local Mijikenda dialects as their primary language, and informed consent was given. The following three groups of were identified: children of HIV-positive mothers who were themselves infected (HIV-infected group), children of HIV-positive mothers who were not infected (HIV-exposed group), and a group of children representative of the community (reference population).

The attending physician identified and approached all women who were HIV-positive with eligible children visiting the family health clinic during the period between September 2005 and June 2006. A total of 52 families were approached; 49 were recruited into the study, and three families declined. Data from one child were not included in the analysis since she was older than 35 months at the time of assessment. Children were considered ‘HIV infected’ if they had a positive HIV antibody test when they were older than 18 months or a polymerase chain reaction test if they were younger than 18 months. They were considered ‘HIV exposed’ if they were born to mothers who were HIV-positive but tested negative.

A reference group of children was recruited to form a representative sample of children in Kilifi, Kenya. The reference group was composed of 319 children (159 females, 160 males) randomly selected from the community aged 6 to 35 months (Mean age = 19 months, SD=8.43). The children were recruited as part of a larger study to develop appropriate reference data for measures of early development appropriate for use in East Africa.[7]

We did not test for the HIV status of children in the reference population for logistical reasons and lack of acceptability of ad-hoc testing. As a consequence, the reference group

may have included HIV-positive children. However, taking into account the prevalence rates of infection (infection rate in mothers of 9%, expected mother–child transmission rate of 25–40%, high mortality of up to 50% by the age of 2y in the infected group, and exclusion of children from the community sample with a reported chronic disease or infection), we estimated that fewer than 10 children (4%) in the community sample are likely to be HIV positive. The community sample probably comprised so few HIV-infected children that their impact on test results would be negligible.

## Measures

A locally developed and validated measure, the Kilifi Developmental Inventory,[7,8] was used to assess psychomotor development. The checklist measures locomotor skills and eye–hand coordination. The two skills are strongly correlated so that their scores can be added in a single overall score for psychomotor skills. An assessor interacted with the children to complete the activities included in the scale. Items were scored on a dichotomous scale (0=child cannot perform the task, 1=child can perform the task). In the reference population the inventory showed excellent internal consistency ($\alpha$=0.96), interobserver agreement (intraclass correlation coefficient=0.98), test–retest reliability (intraclass correlation coefficient=0.96), and sensitivity to age ($r_{(319)}$=0.93, $p$<0.001). Earlier studies had indicated that socioeconomic status is not directly related to performance on this scale.[7,9] Consequently, that variable was not included or controlled for in the analysis.

The World Health Organization (WHO) 1990 clinical staging and case definition of HIV in resource-constrained settings was used. WHO clinical stages 1 to 3 reflect progression from primary HIV infection to advanced HIV or AIDS. Each stage is defined by specific clinical conditions or symptoms. In stage 1, HIV disease is asymptomatic, with generalized lymphadenopathy (i.e. two or more distinct anatomic sites having lymph nodes that are abnormal in size, consistency, or number);[10] this stage is not characterized as AIDS, and no functional impairment is seen. Stage 2 is characterized by mild symptomatic disease, including unexplained chronic diarrhoea, persistent candidiasis, failure to thrive, persistent fever and recurrent bacterial infections, minor mucocutaneous manifestations, and recurrent upper respiratory tract infections. Stage 3 has the severe symptoms of AIDS, characterized by opportunistic infection, severe failure to thrive, progressive encephalopathy, malignancy, recurrent septicaemia, and recurrent meningitis.

## Procedure

Children were seen at home accompanied by their primary caregivers. Teams of two experienced assessors, who were trained before the data collection, carried out the assessment of developmental outcome and took anthropometric measurements. One of the assessors interacted with the child to collect data on psychomotor development, while the second assessor interviewed the mother to collect data on other aspects of functioning, such as language development and home environment. In assessing psychomotor skills, an assessor provides instructions and demonstrations for the child to model in a range of relevant activities. Children were weighed on a SECA digital scale (Seca GmbH & Co., Hamburg, Germany). Weights were taken three times and recorded when a consistent result within one decimal point was achieved. For technical reasons no data on height are available.

Recruitment was carried out by a team not involved in the assessment, and the assessment team was not informed of the families' HIV status. However, because of the physical conditions of some children and family members, the child's HIV status may have been apparent. Children from the HIV-exposed and reference groups were seen during the same study period to minimize interviewer effects.

### Data management and analysis

Data were double entered in FoxPro (Microsoft Corp., Redmond, WA, USA) and verified before being transferred to SPSS version 12 (SPSS Inc., Chicago, IL, USA) for analysis. Mean and frequencies were used to compute descriptive statistics. Analysis of variance was used to compute group differences. However, if data violated the assumption of homogeneity of variance, we used the Brown–Forsythe *F*-ratio and the Games–Howell approach to evaluate whether there were any differences between groups.[11] Cohen's *d*, the standardized difference between two mean, was computed to estimate the magnitude of impairment. Levels of impairment are described as small, moderate, and severe, defined by cut-offs at 0.20, 0.50, and 0.80 respectively.[12] Weight for age was computed using the WHO Anthro 2005 software (World Health Organization, Geneva, Switzerland) and reference population.[13] Being underweight was defined as having a weight for age score less than–2SD of the reference population score distribution.

Age-corrected scores were used in all analyses. Age correction was carried out using linear regression methods, where the test scores were entered as a dependent variable and age as an independent variable; individual standardized residuals arising from the regression analysis were saved and used in all further analyses.

The Kenya Medical Research Institute National Scientific and Ethical Committees approved the study. Written informed consent was obtained from all families of study participants. The consent form was read out to parents in the language with which they were most familiar. Before individual consent was sought, we held a series of meetings with elders and community leaders, to inform them of the study aims and to obtain permission to work in their communities.

## RESULTS

### Sample descriptive

The characteristics of the children in each group are presented in Table I. The distribution of disease stage in the HIV-infected group was as follows: four children were at stage 1, 21 were at stage 2, and six were at stage 3. No significant difference was found in the ages of the children in the three groups ($F_{(2,366)}$=1.20, $p$<0.30).

### Psychomotor development

Table I also shows the results of the psychomotor assessments. The scores for the HIV-infected group were consistently lower than for the HIV-exposed and reference groups. We found a significant effect of HIV status on psychomotor scores ($F_{(2,38.01)}$=7.81, $p$<0.001). Post-hoc analyses indicated that children in the HIV-infected group performed significantly more poorly than either the HIV-exposed group or the reference group (Table II). A similar pattern of scores was found in the subscales (locomotor scale: $F_{(2,39.19)}$=5.01, $p$<0.05; eye–hand coordination: $F_{(2,43.57)}$=10.80, $p$<0.001).

The HIV-infected group was characterized by a wider variability in outcome (SD 1.86 vs 0.84 and 0.60 for the reference group and HIV-exposed group respectively). It was also characterized by a greater proportion of children with severe degrees of impairment in psychomotor, locomotor, and eye–hand coordination skills: psychomotor total score Cohen's $d$=0.86; locomotor=0.70 and eye–hand coordination=0.84.

### Disease stage

A significant effect of disease stage on psychomotor scores was observed ($F_{(4,366)}$=10.24, $p$<0.001, $\eta^2$=0.10). A considerable drop in the mean psychomotor scores was observed in

each progressive disease stage for the full scale and the subscales (stage 1 mean 0.40, SD 1.68; stage 2 mean −1.01, SD 1.93; stage 3 mean −1.46, SD 1.57). Children at stage 3 showed scores almost 1.5 SD below those at stage 1. A contrast analysis indicated that the scores of children in stage 2 or 3 differed significantly from those of the reference population. A similar pattern of results was seen with the subscale scores (locomotor scores: $F_{(4,362)}=7.58$, $p<0.001$, $\eta^2=0.08$; eye–hand coordination: $F_{(4,362)}=9.47$, $p<0.001$, $\eta^2=0.10$). These partial $\eta^2$ values indicate moderate effects for all scores.

### Weight for age

A significant main effect of HIV status on weight for age scores was found ($F_{(2,364)}=9.06$, $p<0.001$, $\eta^2=0.05$). A post-hoc analysis indicated that the HIV-infected children had significantly lower mean weights than the HIV-exposed and reference populations. In the HIV-exposed group only three children were underweight, making adequate statistical testing of the effect on outcome impossible. The available data suggests that the prevalence of underweight children and the effects of being underweight on psychomotor scores may be close to that seen in the reference population. In the reference and HIV-exposed groups the percentages of underweight children (23% and 18% respectively) were much lower than in the HIV-infected group where 45% of children were underweight.

A significant effect of being underweight on psychomotor function was observed in the reference population ($F_{(1,317)}=9.85$, $p<0.002$, $\eta^2=0.05$) and in the HIV-infected group. The standardized mean (SD) scores of underweight children (−2.05 [2.11]) were lower than the scores of children with normal weight (0.03 [0.90]; $F_{(1,29)}=13.59$, $p<0.001$, $\eta^2=0.32$). A similar pattern of results was seen on the subscales (locomotor: −1.99 [2.13] for underweight; 0.26 [0.98] for normal weight; $F_{(1,29)}=15.05$, $p=0.001$, $\eta^2=0.34$; eye–hand coordination:−0.24 [0.81] for underweight; 1.71 [1.78] for normal weight; $F_{(1,29)}=9.33$, $p=0.005$, $\eta^2=0.24$).

### Combination of weight for age and disease stage

We investigated whether weight for age and disease stage showed independent or combined effects on psychomotor functioning (Table III). Children in HIV stage 2 or 3 were grouped together (symptomatic cases), and all of the other groups (reference population, HIV-exposed but uninfected, and HIV-infected stage 1) were combined in a single group. The influence of disease progression, being underweight, and psychomotor outcome were tested in a multivariate analysis of variance. Disease progression and being underweight were independent variables, and the psychomotor scores, eye–hand coordination, and locomotor scores were dependent variables. The Wilks' lambda value indicated a significant multivariate effect; univariate analyses pointed to the influence of both variables on outcome in addition to an interactive effect in all scores (disease progression: $F_{(2,362)}=17.42$, $p<0.001$, $\eta^2=0.09$; underweight: $F_{(2,362)}=22.72$, $p<0.001$, $\eta^2=0.11$; their interaction: $F_{(2,362)}=13.04$, $p<0.001$, $\eta^2=0.07$). Subsequent univariate analyses indicated that disease stage and weight for age are both independent predictors of outcome for all scores. In combination an interaction effect is observed; the adverse effect of advanced disease stage on psychomotor performance is most salient for children who are underweight. Figure 1 indicates that the combination of disease progression and being underweight contributes to the worst psychomotor outcome.

## DISCUSSION

Consistent with other studies, we observed large variability in outcomes of children with HIV-infection. The remarkable score heterogeneity in the HIV-infected group is in line with the common finding that the group includes both children with normal development and

those with impaired development, and it points to the need to evaluate sources of variability in outcome on the psychomotor scores. Part of the variability among children with HIV-infection may be explained by disease progression. As the disease progresses beyond the first stage, a difference from the reference population emerges; this is consistent with reports from developed countries.[14-16] Poor weight for age was associated with motor impairment across all the groups. Our study suggests that weight for age and disease progression reinforce each other's influence on psychomotor outcome of children infected with HIV.

Our results provide further evidence for the salient role of nutritional status in HIV-related neurocognitive effects.[17-19] The relationship between being underweight and poor psychomotor outcome among children in resource-poor settings is not unique to the HIV population;[20,21] what is striking is that the coexistence of HIV and being underweight amplifies the effects on psychomotor development. Combined with results from Tanzania, which indicated that children of HIV-positive mothers who had received multivitamin supplementation had improved psychomotor outcomes,[22] our results suggest that improvement in nutritional status may improve psychomotor outcomes even among children in advanced disease stages.

The lack of culturally appropriate and standardized measures of childhood outcome has been a major impediment in adequately studying the effects of disease exposure in sub-Saharan Africa. In this study, a locally developed and validated measure of childhood outcome was used. Our results indicate that it is feasible to develop culturally appropriate measures that are sensitive to effects of HIV. These measures can adequately discriminate between the different levels of risk in the paediatric HIV population. Future efforts should be focused on evaluating the sensitivity of this measure for treatment effects, to allow a more definitive statement on its potential use in an HIV management programme.

Poor psychomotor development may result from several factors. Other pre- and postnatal experiences might confound development. However, detailed birth and hospital records are not systematically kept in this area. A prospective longitudinal study that addresses these confounding factors would overcome this limitation.

This study illustrates the possibility of applying a straightforward measure (weight for age) to support the planning of interventions and targeted follow-up for the optimal use of scarce resources in sub-Saharan Africa. Establishing measures to stop disease progression and to provide nutritional support among children with HIV infection in sub-Saharan Africa is recommended as a major public health concern, because improvement in nutrition may reduce the severity and incidence of psychomotor impairment in this population and lead to a better quality of life.

## Acknowledgments

This paper is published with permission of the Director of KEMRI. Amina Abubakar and Penny Holding were supported by NIMH Fogarty R21 award (Grant MH72597-02). CRJC Newton was funded by the Wellcome Trust, UK. The authors would like to thank L. Mbonani, R. Kalu, B. Kabunda, R. Mapenzi, C. Mapenzi, P. Nzai, J. Maitha, M. Mwangome, E. Obiero, K. Rimba and G. Bomu for their role in the data collection, and K. Katana and P. Kadii for data entry. We would also like to thank the staff at the Family Health Clinic for identifying children and providing a framework within which this study could be carried out. Our sincere gratitude goes to the participating families who generously gave of their time to make this work possible.

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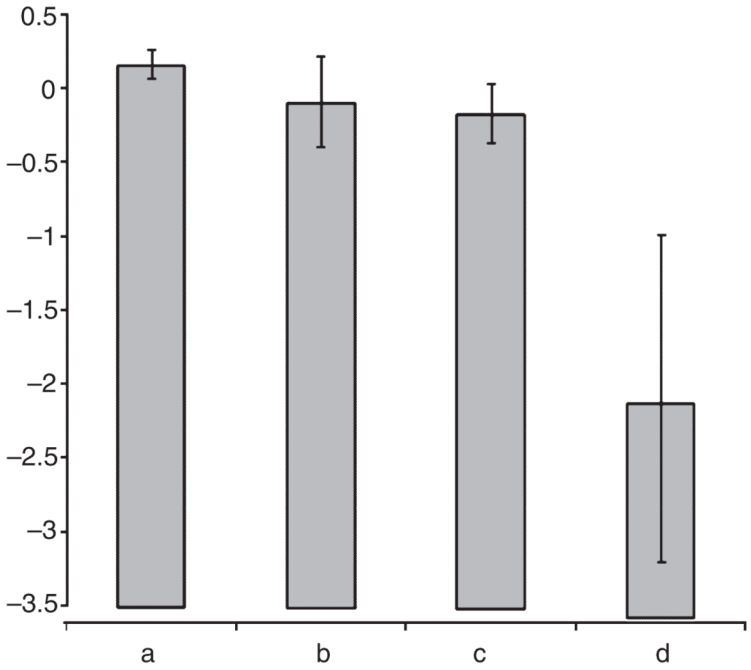


**Figure 1.**
Standardized means for the psychomotor scores of children in the disease progressed and the reference population, grouped by weight (normal or underweight). Bars indicate 95% confidence intervals. (a), children without progressive human immunodeficiency virus (HIV) infection (i.e. those from the community sample, those who were exposed to HIV but were uninfected, and those with HIV stage 1 infection) with normal weight; (b), children with symptomatic HIV infection (stage 2 or 3) with normal weight; (c), children without progressive HIV infection who were underweight; (d), HIV-infected children who were underweight.


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## Table I

Mean (SD) of the participants' background and outcome variables

| Variables | Reference population | HIV-exposed | HIV-infected | *p* |
|---|---|---|---|---|
| Participants | 319 | 17 | 31 | |
| Sex, male:female | 160:159 | 11:6 | 17:14 | |
| Age, mo | 18.84 (8.43) | 17.72 (8.77) | 21.10 (8.86) | 0.300 |
| Maternal education duration, y[a] | 3.40 (3.50) | 4.35 (4.07) | 4.80 (3.55) | 0.069 |
| Weight for age | −1.24 (1.08) | −1.28 (0.79) | −2.12 (1.36) | 0.001 |
| Psychomotor total score[b] | 0.08 (0.84) | 0.11 (0.60) | −0.91 (1.86) | 0.001 |
| Locomotor subscale[b] | 0.06 (0.84) | 0.27 (0.65) | −0.76 (1.98) | 0.050 |
| Eye–hand coordination subscale[b] | 0.09 (0.90) | −0.10 (0.65) | −0.90 (1.50) | 0.001 |

HIV, human immunodeficiency virus.

[a]Education was determined by recording the number of years a mother had attended formal schooling.

[b]Based on the Kilifi Developmental Inventory.

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## Table II

Differences in the standardized mean for the participating groups

| Variable | Status (*I*) | Status (*J*) | Mean difference (*I*–*J*) |
|---|---|---|---|
| Psychomotor total score[a] | Reference | HIV-exposed | −0.02 |
| | | HIV-infected | 1.00[b] |
| | HIV-exposed | HIV-infected | 1.02[b] |
| Locomotor subscale[a] | Reference | HIV-exposed | −0.21 |
| | | HIV-infected | 0.82 |
| | HIV-exposed | HIV-infected | 1.03[b] |
| Eye–hand coordination subscale[a] | Reference | HIV-exposed | 0.19 |
| | | HIV-infected | 1.00[b] |
| | HIV-exposed | HIV-infected | 0.8 [b] |

HIV, human immunodeficiency virus.

[a]Based on the Kilifi Developmental Inventory.

[b]The mean difference is significant at the 0.05 level.

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## Table III

Standardized psychomotor scores of children in the disease progressed and the reference group

| | Weight [a] | Disease progression [b] | *n* | Mean | SD |
|---|---|---|---|---|---|
| Psychomotor total score [c] | Normal growth | 0 | 263 | 0.16 | 0.81 |
| | | 1 | 13 | −0.09 | 0.57 |
| | Underweight | 0 | 77 | −0.16 | 0.90 |
| | | 1 | 14 | −2.05 | 2.11 |
| Locomotor subscale [c] | Normal growth | 0 | 263 | 0.14 | 0.82 |
| | | 1 | 13 | 0.19 | 0.77 |
| | Underweight | 0 | 77 | −0.15 | 0.89 |
| | | 1 | 14 | −1.99 | 2.14 |
| Eye–hand coordination subscale [c] | Normal growth | 0 | 263 | 0.14 | 0.86 |
| | | 1 | 13 | −0.38 | 0.53 |
| | Underweight | 0 | 77 | −0.13 | 1.00 |
| | | 1 | 14 | −1.71 | 1.78 |

[a] Being underweight was defined as having weight-for-age scores less than −2.00 SD of the reference population score distribution

[b] 0=children from the community sample, those who were exposed to human immunodeficiency virus (HIV) but were uninfected, and those with HIV stage 1 infection; 1=children with symptomatic HIV infection (stage 2 or 3).

[c] Based on the Kilifi Developmental Inventory.