

Neurodevelopmental Outcomes of Ugandan Infants With Human Immunodeficiency Virus Type 1 Infection

Dennis Drotar, PhD*; Karen Olness, MD*; Max Wiznitzer, MD*; Laura Guay, MD‡; Lawrence Marum, MD, MPH‡; Grace Svilar, MS*; David Hom, MS*; Joseph F. Fagan, PhD*; Christopher Ndugwa, MB, CHB, MMed§; and Rebecca Kiziri-Mayengo, MA§

ABSTRACT. *Background.* The neurodevelopmental outcomes of human immunodeficiency virus type 1 (HIV-1)-infected Ugandan infants of nondrug-using mothers were studied using controlled, prospective methodology.

Method. The sample of 436 full-term infants included 79 HIV-infected infants of HIV-1-infected mothers, 241 uninfected infants of HIV-1-infected mothers (seroreverters), and 116 uninfected infants born to HIV-negative mothers. Neurologic status, information processing ability, and motor and mental development were assessed from 6 to 24 months of age. Observations of caretaker-child interaction and home environments were made at 6 and 12 months. All evaluators were blinded to the HIV status of the child and family.

Results. Compared with seroreverters and uninfected infants, HIV-infected infants demonstrated greater deficits in motor development and neurologic status, and more frequent and earlier onset of motor and neurologic abnormalities. Compared with controls, HIV-infected infants had more abnormalities in mental development at 6 and 18 months and an earlier onset of abnormalities. By 12 months, 30% of HIV-infected infants demonstrated motor abnormalities and 26% cognitive abnormalities as compared with 11% and 6% among seroreverters and 5% and 6% among seronegative infants. HIV-infected infants (62%) demonstrated a higher probability of developing an abnormal neurologic examination by 12 months, compared with seroreverters (17%) or seronegative infants (15%). Information-processing abilities did not differ as a function of HIV infection. Home environments and infants' interactions with caretakers were similar across groups.

Conclusion. We conclude that HIV infection results in more frequent and earlier abnormalities in infants' neurologic status and motor development that are not attributable to other biological and environmental risk factors. More frequent mental developmental abnormalities were evident at several ages. However, information-processing abilities, such as recognition memory, may be spared from HIV-related deficits. *Pediatrics* 1997;100(1). URL: <http://www.pediatrics.org/cgi/content/full/100/1/e5>; HIV infection, neurodevelopment, mental development, motor development, neurological status, information processing ability.

From the *Departments of Pediatrics, Epidemiology, and Psychology, Case Western Reserve University, Cleveland, Ohio; †Johns Hopkins University, Baltimore, Maryland; and the ‡Departments of Pediatrics, Child Health, and Psychology, Makerere University, Kampala, Uganda.

Received for publication Sep 3, 1996; accepted Jan 14, 1997. Reprint requests to (D.D.) Rainbow Babies and Children's Hospital, 11100 Euclid Ave, Cleveland, OH 44106.

PEDIATRICS (ISSN 0031 4005). Copyright © 1997 by the American Academy of Pediatrics.

ABBREVIATION. HIV, human immunodeficiency virus.

The prevalence of human immunodeficiency virus type 1 (HIV-1) in infants and young children in the United States and in the world has dramatically increased.¹⁻⁴ Prevalence rates of HIV infection, which are now more than one million children worldwide, indicate that HIV-1-related central nervous system disease will become a significant cause of mental deficiency and developmental disabilities in the United States and worldwide.⁵ Generalized cognitive deficiencies,⁶⁻¹⁴ language¹⁵ and motor⁹ deficits, and variation in the type and severity of developmental and neurologic deficits have been consistently reported.⁸⁻¹⁶ For this reason, there is a continuing need for controlled studies of neurodevelopmental outcomes among young children with HIV-1, not only in the United States, but also in developing countries where HIV has high prevalence. Although such studies are important in their own right, they also provide an opportunity to assess the impact of HIV infection on children's development unconfounded by the effects of risk factors such as maternal drug addiction.

However, most studies of the developmental outcomes of HIV-infected children have been conducted in the United States. The outcomes obtained in such studies are not directly comparable to those that have been conducted in developing countries because children in the United States are now receiving antiretroviral treatments that may lessen the severity of cognitive and motor deficits.¹⁷ To our knowledge, only three such studies have been reported. The study of Boivan et al¹¹ on Zairian infants from birth to 18 months identified deficits (with the exception of language) on the Denver Developmental Screening Test among HIV-infected (n = 14) versus uninfected (n = 20) children. A second group (n = 11) of HIV-infected children (mean age of 54 months) demonstrated sequential motor and visual spatial memory deficits on the Kaufman Assessment Battery for Children compared with uninfected children.

Msellati et al's follow-up¹³ of Rwandan infants (birth to 24 months) identified higher rates of neurologic impairments (15% to 40%) in HIV-infected children (n = 20 to 43) compared with those (5% or less) of controls (uninfected children born to seropositive mothers, n = 113 to 133, and uninfected children born to seronegative mothers, n = 156 to 193). HIV-

infected children also had more deficits on a developmental screening test.

A recent prospective study¹⁸ assessed the outcomes of infants born to nondrug-using HIV-seropositive Haitian women from 3 to 24 months of age. By 3 months, the mean mental and motor scores of HIV-infected infants (n = 28) were lower than those of uninfected infants (n = 98).

Taken together, these findings have documented significant HIV-related developmental and neurologic deficits that are not attributable to associated risk factors such as maternal drug addiction, and family instability. However, the conclusions that can be drawn from the above studies are limited by several methodological issues that are addressed in the present study. In two of the above studies,^{10,12} developmental outcome data were based entirely on unvalidated screening instruments. In the third, sensorimotor development was assessed using a standardized instrument.

However, no previous study has measured infants' information processing abilities, which have been shown to be more robust predictors of children's cognitive development at school age than measures of sensorimotor development.¹⁹ In addition, previous studies have not determined whether the obtained developmental outcomes were attributable to differences in the quality of home environments and caretaking in families of HIV-infected children. Finally, prior studies have not provided detailed information concerning the time to onset of neurodevelopmental impairments.

To address these needs, our research employed a prospective assessment of Ugandan infants' cognitive development, information-processing abilities, and neurologic status using well-validated measures to describe the nature of neurodevelopmental impairments, including time to onset, in this population. Detailed observations of mother-child interactions and home environments were also conducted. Three groups were studied: HIV-1-infected infants of HIV-1-infected mothers, uninfected infants of HIV-1-infected mothers (seroreverters), and uninfected infants born to HIV-negative mothers.

METHODS

Selection Criteria and Patient Recruitment

The study was approved by the institutional review boards at University Hospitals, Cleveland and Makerere University, Kampala, Uganda. Pregnant women presenting during the second trimester of pregnancy to the Makerere University prenatal clinic at New Mulago Hospital in Kampala, Uganda, gave informed consent for blood drawing for themselves before delivery and for their infants after birth. Infection with HIV-1 was determined by initial enzyme-linked immunosorbent assay (Cambridge Bioscience, Worcester, MA, Recombigen) with confirmation of seropositivity by IG Western blotting (Dupont, Geneva, Switzerland). Biorad Novapath (Hercules, CA) Immunoblot assay, a Western blot immunoblot assay, was interpreted as positive if it contained any two of the following bands: gp 120/160, gp41, or p24.

For every three infants born to HIV-positive mothers, one infant born to a HIV-negative mother was selected from a randomized list of mothers enrolled before delivery. Only full-term infants without significant birth complications or neurologic or genetic impairments based on newborn physical examination were enrolled. No infants or mothers received zidovudine or other antiretroviral treatments, which were not available in Uganda.

Clinical Follow-up

Infants were seen in scheduled visits at 6, 10, and 14 weeks and at 6, 9, 12, 15, 18, 21, and 24 months. Cord and birth blood were obtained on each infant, and blood was subsequently drawn at birth, 6 weeks, 6 months, 12 months, and beyond 15 months. HIV-1 status was determined by HIV-1 enzyme immunoassay beyond 15 months in surviving infants with confirmatory Western blot of all seropositives. HIV-1 DNA polymerase chain reaction and immune complex dissociation p24 antigen testing was performed on specimens from children who were lost to follow-up or died before 15 months of age. Anthropometric measures, (height, weight, and head circumference), interim history (intercurrent illnesses, HIV-related symptoms, feeding, development, and maternal health), and physical and neurologic examinations were performed at each visit. Immunizations, medications, and management of acute interim illnesses were provided for all infants. Infants with growth failure were referred to a weekly nutrition clinic.

Definition and Classification of HIV-1 Infection

Laboratory criteria for diagnosis of HIV infection were enzyme immunoassay and Western blot positive 15 months of age or older or positive HIV DNA polymerase chain reaction (excluding cord blood) or positive neutralizable immune complex dissociation p24 antigen (excluding cord blood).²⁰ Children born to mothers with HIV infection were defined as seroreverters if they became HIV-antibody-negative after 9 months of age and had no other laboratory evidence of HIV infection and did not meet the acquired immunodeficiency syndrome surveillance case definition criteria.²¹ Laboratory measures of immune status such as CD4 were not available in this field setting.

Neurodevelopmental Assessment Procedures

Sensorimotor Development

The Bayley Scales of Infant Development²² including mental development (eg, comprehension, imitation, language) and motor development (motor coordination and skills) was determined at 6, 9, 12, 18, and 24 months. Based on a pilot study (n = 65) of healthy Ugandan infants (ages 3 to 30 months), culturally appropriate modifications of these measures were employed (eg, objects and pictures commonly found in the culture and translation of all instructions into the local language, eg, Luganda).

The total numbers of items passed on the Bayley Scales were utilized as indices of developmental status for several reasons: pilot data indicated that standardized mental and motor developmental scores (equivalent to IQ) based on United States test norms were not equivalent for Ugandan infants. Second, derived standardized scores (as opposed to the number of items passed) cannot distinguish between a child who does not acquire developmental milestones at a normal rate and a child who loses developmental skills.¹⁴ Finally, the developmental status of children with very low standardized scores cannot be accurately described because they are all grouped into a single score (50 or less).¹⁴

Information Processing Ability

The Fagan Test of Infant Intelligence was administered at 6, 9, and 12 months of age because it measures information-processing ability, does not require any motoric responses,²³ has established predictive validity for detection of mental retardation,^{19,24} and is feasible in field settings with infants from different cultures.²⁵ The Fagan test assesses recognition memory by measuring an infant's differential visual attention to a novel stimulus (a picture of a novel human face) relative to a familiar stimulus (human face) that was previously presented. The average percentage of total time that infants looked at novel versus familiar faces across 10 such pairings was calculated.

Neurologic Status

During each well-child visit, physical examinations included neurodevelopmental assessments that identified focal deficits and abnormalities in strength, tone, and coordination based on the Amiel-Tison scoring system.²⁶ An on-site developmental pediatrician (L.M.) supervised clinical assessments. All clinicians were blinded to HIV status of mothers and infants. Abnormal neuro-

logic examinations were checked by a second clinician. An experienced pediatric neurologist (M.W.) trained all physicians and reviewed cumulative neurologic examination results to derive a rating of normal versus abnormal. To be classified as abnormal, a child had to demonstrate a persistent (rather than transient) neurologic examination as documented by abnormalities on two or more consecutive examination.

Family Characteristics, Mother-Child Interaction, and Quality of Home Environment

Based on measures developed in African field research,²⁷ family caretaker-child interactions were assessed in home visits at 6 and 12 months of age. Each 30-minute visit yielded objective data concerning the frequency of mother-child and caretaker-child (eg, extended family, siblings) interactions, including touch, vocalization, and physical care. Observers also rated the quality of home environments, such as caretaker responsiveness and organization, based on reliable and valid procedures^{28,29} that were modified for Uganda based on pilot work. Interrater reliabilities ranged from .75 to .88.

Procedures to Enhance Reliability and Validity of Data

All staff, including physicians and research assistants who conducted psychologic and home assessments, were blind to maternal and child HIV status. Data were reviewed regularly by the investigators to enhance quality control and interobserver reliability. Infants were not assessed when acutely ill.

Data Analyses

Analyses of variance compared group means. Post-hoc pairwise comparisons were adjusted using a Bonferroni corrected *P* value (*P* < .015). χ^2 tests for contingency tables and Fisher's exact tests compared categorical and event frequency data. Kaplan-Meier right-censored product-limit life-table analysis estimated the probability of an abnormal neurologic (Amiel-Tison) or psychologic examination (Bayley or Fagan) and infant infection status while also adjusting for time to abnormal examination and/or censoring attributable to early death or loss to follow-up. Unweighted Wilcoxon log-rank and Breslow (weighted for early events) statistics were used to identify differences (two-sided nominal *P* values) in pair-wise survival curve comparisons. All analyses and data management were conducted using SPSS/PC + V6.0 and EPI-INFO V5.01B.

RESULTS

Description of Completed Follow-up Assessments

The number and percentages of living children who completed developmental assessments (Bayley Scales) from 6 to 24 months are shown in Table 1. Forty-four (56%) of the HIV-infected children, 14 (6%) of the seroreverters, and only 1 (.09%) of the uninfected children died. Maternal mortality was comparable in the HIV-infected (13.6%) and seroreverter (11.5%) groups, but was 0% for seronegative mothers.

The percentage of living children who missed assessments varied across ages but was comparable

across the three groups. Moreover, at 24 months only 7% of the sample was lost to follow-up for reasons other than mortality. Families of children with complete versus incomplete follow-up data had comparable demographic characteristics, including parental education and occupation, marital status, number of adults and children in the home, housing type, and changes in family structure.

Mental and Motor Development

Bayley Motor and Mental Development scores (number of items passed) are shown in Table 2. Analyses of variance indicated that HIV-infected children's motor development scores were lower than that of noninfected infants at all ages (*P* < .002 or greater). HIV-infected infants had lower mental development scores than the other groups at 6, 18, and 24 months (*P* < .001 or greater). Seroreverters and uninfected children had comparable scores on these measures at all time points.

To describe clinical significance, Bayley scores were converted to either a normal score (within two standard deviations of the mean) or abnormal score (defined as more than two standard deviations below the mean of uninfected children born to seronegative mothers). Group differences in frequencies of children with normal versus abnormal motor and mental test scores were tested by χ^2 . As shown in Table 3, a greater percentage of HIV-infected children demonstrated motor abnormalities at every age compared with the other groups, which did not differ (*P* < .02 or greater). A greater percentage of HIV-infected infants also had more abnormal Bayley Mental Development scores than uninfected infants at 6 and 18 months (*P* < .01).

Kaplan-Meier life table analyses indicated that HIV-infected infants demonstrated higher probabilities of having motor and mental impairments by 12 months than infants in the other groups (see Figs 1 and 2). By 12 months, 30% of HIV-infected infants had motor abnormalities and 26% mental abnormalities, compared with 11% and 6% among seroreverters, and 5% and 6% among seronegative infants (*P* < .0001, pair-wise comparison to infected infants). These differences persisted beyond 12 months and were even more pronounced by 24 months, with 44% and 35% of infected infants demonstrating motor and mental deficits, respectively, compared with their uninfected counterparts, who on average had only 10% motor and 10% mental abnormalities.

TABLE 1. Summary of Completed Developmental Assessments Over Two Years of Follow-up*

	Birth	6 Months	9 Months	12 Months	18 Months	24 Months
HIV-infected children	79	59/66 89%	46/56 81%	47/51 92%	41/46 89%	31/32 97%
Uninfected children born to seropositive mothers	241	211/239 88%	161/235 68%	211/232 91%	203/222 89%	210/214 93%
Uninfected children born to seronegative mothers	116	107/116 92%	89/116 77%	109/115 94%	103/114 90%	110/111 96%
Total	436	377/421 91%	296/407 72%	367/398 92%	347/382 89.4%	351/357 93%

* The denominator is the number of children in each age group who were living at the time of the assessment and hence eligible to participate. The numerator is the number of children who were tested, which is also expressed as percentage.

TABLE 2. Means and Standard Deviations of Raw Scores on Bayley Scale for Children Ages 6 to 24 Months According to HIV Infection Status

Group	6 Months	9 Months	12 Months	18 Months	24 Months
<i>Motor Development</i>					
HIV infected children	31.20 (5.43) (n = 59)	40.89 (3.57) (n = 46)	44.98 (4.13) (n = 47)	48.17 (7.08) (n = 41)	52.84 (5.99) (n = 31)
Uninfected children born to seropositive mothers	32.67 (2.82) (n = 211)	42.27 (3.26) (n = 161)	46.41 (4.26) (n = 211)	53.12 (4.30) (n = 203)	57.44 (4.96) (n = 210)
Uninfected children born to seronegative mothers	33.34 (2.03) (n = 107)	42.79 (2.53) (n = 89)	47.43 (3.50) (n = 109)	53.09 (3.52) (n = 103)	58.01 (5.99) (n = 110)
<i>P Value*</i>	<.0002	<.004	<.002	<.0002	.00007
<i>Mental Development</i>					
HIV infected children	74.72 (12.02) (n = 59)	92.42 (5.92) (n = 46)	102.66 (9.10) (n = 47)	113.32 (10.53) (n = 41)	128.90 (10.24) (n = 31)
Uninfected children born to seropositive mothers	78.96 (7.22) (n = 211)	93.37 (6.17) (n = 161)	105.01 (10.14) (n = 211)	119.08 (10.47) (n = 203)	134.46 (8.58) (n = 210)
Uninfected children born to seronegative mothers	79.23 (6.18) (n = 107)	93.94 (6.01) (n = 89)	105.40 (7.17) (n = 109)	120.17 (6.92) (n = 103)	135.11 (13.42) (n = 110)
<i>P Value^a</i>	<.0009	NS†	NS	<.0007	<.001

* *P* values refer to differences between HIV-infected children and the other two groups.

† NS, not significant.

TABLE 3. Frequency and Percentage of Children With Normal Versus Abnormal Scores on Bayley Scales*

Group	Motor Development									
	6 Months		9 Months		12 Months		18 Months		24 Months	
	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal
HIV-infected	49 (84)	9 (16)	36 (80)	9 (20)	40 (87)	6 (13)	33 (82)	7 (18)	23 (77)	7 (23)
Seroreverter	195 (92)	16 (8)	152 (94)	9 (6)	202 (96)	9 (4)	195 (96)	8 (4)	208 (99)	2 (1)
Uninfected children born to HIV-negative mothers	103 (96)	4 (4)	86 (97)	3 (3)	106 (97)	3 (3)	101 (98)	2 (2)	107 (97)	3 (3)
<i>P Value†</i>	<.02		<.001		<.02		<.0001		<.0001	
Group	Mental Development									
	6 Months		9 Months		12 Months		18 Months		24 Months	
	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal
HIV-infected	49 (84)	9 (16)	43 (96)	2 (4)	41 (89)	5 (11)	33 (82)	7 (18)	29 (97)	1 (3)
Seroreverter	199 (94)	12 (6)	159 (99)	2 (1)	200 (95)	11 (5)	195 (96)	8 (4)	208 (99)	2 (1)
Uninfected children born to HIV-negative mothers	102 (98)	5 (5)	88 (99)	1 (1)	106 (97)	16 (3)	101 (98)	2 (2)	109 (99)	1 (1)
<i>P value†</i>	<.01		NS		NS		<.0003		NS	

* Percentages are in parentheses.

† *P* values refer to differences between HIV-infected children and the other two groups.

‡ NS, not significant.

Neurologic Examination

As shown in Table 4, at each age HIV-infected infants demonstrated higher percentages of abnormal neurologic examinations (ranging from 40% at 6 months to 56% at 18 months) than seroreverters and uninfected children who did not differ. By life table analysis (see Fig 3), HIV-infected infants (62%) demonstrated a higher probability of developing an abnormal neurologic examination by 12 months, compared with seroreverter (17%) or seronegative (15%) children ($P < .0001$, pair-wise comparison to infected infants).

Information Processing

The groups did not differ on information processing based on Fagan test scores. HIV-infected infants' mean percentages of differential response to novel stimuli of .58 (6 months), .60 (9 months), and .60 (12 months) were comparable to those of seroreverters (.57 [6 months], .59 [9 months], and .60 [12 months])

and to those of uninfected children born to seropositive mothers (.58 [6 months], .59 [9 months] and .59 [12 months]).

The three groups also had comparable frequencies of abnormal information-processing scores (a score of 53 or less on the Fagan test) at all ages. Survival curve analyses also revealed no group differences in the probabilities of developing an abnormal information-processing score at various ages.

Assessment of Quality of Home Environment and Mother-Child Interaction

To determine whether the neurodevelopmental deficits associated with HIV infection could be attributed to group differences in the quality of caretaking, the frequency of positive interactions (summary of vocalizations, touches, and holds) with all caregivers and total home environment scores were compared at 6 and 12 months. Higher scores indicated more positive interactions and home environments.

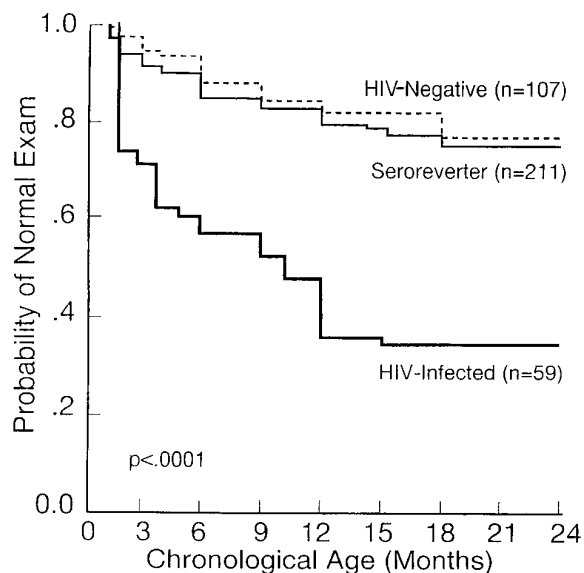


Fig 1. Cumulative probability of normal Bayley motor score.

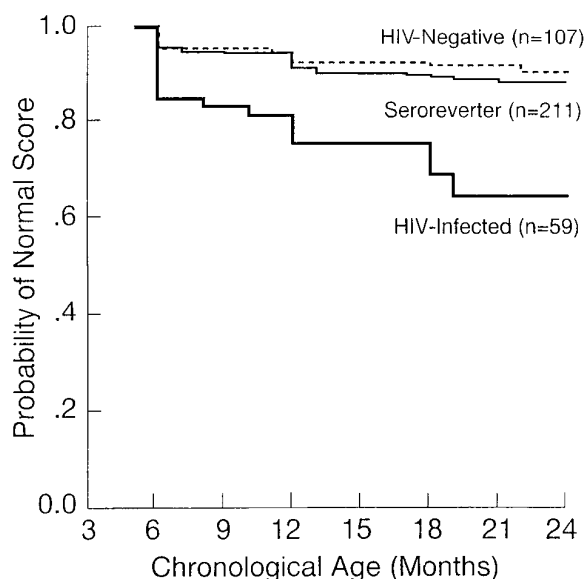


Fig 2. Cumulative probability of normal Bayley mental score.

HIV-infected children had comparable positive interaction scores at 6 (Mean [M] = 40.13) and 12 (M = 45.83) months compared with seroreverters at 6 (M = 38.50) and 12 months (M = 44.48) and seronegative children at 6 (M = 40.06) and 12 (M = 45.14) months. HIV-infected infants' home environment scores at 6 (M = 13.04) and 12 (M = 12.29) months were also similar to that of seroreverters at 6 (M = 11.38) and 12 (M = 12.08) months and seronegative children at 6 (M = 11.04) and 12 (M = 12.21) months.

DISCUSSION

Our primary finding was that HIV infection was associated with higher rates of abnormalities in motor development and neurologic status from 6 to 24 months of age, as well as with earlier onset of these deficits. In general, mental development was less powerfully affected, although HIV-infected infants demonstrated an earlier onset of significant impair-

ment in mental development than uninfected infants, more abnormalities at 6 and 18 months, and lower mental development scores at 18 and 24 months.

Our findings coincide with the results of several previous studies of non-United States samples of HIV-infected children^{11,13,18} but advance knowledge in three important respects. First, these data describe the probabilities to onset of neurodevelopmental impairments from 6 to 24 months among HIV-infected infants who were followed from birth. Second, the neurodevelopmental deficits that were identified cannot be attributed to group differences in the quality of home environments or caretaking. Third, our comprehensive assessment revealed that the impact of HIV infection varied as a function of the specific outcome parameter that was assessed. Young children's motor development and coordination (eg, Bayley Motor Scale) and muscle tone and reflexes (eg, neurologic examination) were most consistently and strongly affected by HIV infection. Cognitive developmental skills, eg, vocalization, comprehension, and puzzle performance, as measured by the Bayley Mental Scale were less powerfully affected, showing effects only at certain ages.

A unique and surprising finding was that among the outcomes assessed, infant visual recognition memory, which does not involve any motor response whatsoever and hence is closest to a pure measure of information processing,²³ was not affected by HIV infection. Given the extensive predictive validity and cross-cultural data that supports the Fagan test,^{24,30} we believe it is unlikely that this finding reflects measurement insensitivity. Moreover, others have recently found that compared with motor development, information-processing abilities are spared among other populations of young infants who are at neurologic risk.³¹

Taken together, our findings suggest that HIV infection is associated with multiple focal motor abnormalities but not necessarily with mental or information-processing deficits. As a group, HIV-infected infants in this sample were capable of processing visually presented information in an age-appropriate manner, despite evidence of clinically significant motor and neurologic impairments.

These findings should be replicated. However, insofar as they document areas of intact cognitive processing among survivors of HIV infection, they may have salient implications for developmental rehabilitation of HIV-infected children,³² most especially in developing countries, where zidovudine treatment is not available. For example, our findings underscore the need for caregivers to recognize that their HIV-infected children retain their capacities to learn via visual information and social interchange, despite their impairments in motor and mental development. The findings suggest that these infants would continue to benefit from age-appropriate visual and social stimulation.

Several issues should be considered in interpreting our findings. The similarity of findings based on neurologic examination and the Bayley Motor Scale is not at all surprising given the overlap of the functions that are assessed on each of these measures. It

TABLE 4. Numbers and Percentages of Children With Normal Versus Abnormal Neurological Exams*

Group	6 Months		9 Months		12 Months		18 Months		24 Months	
	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal
HIV-infected	34 (60)	23 (40)	28 (64)	16 (36)	23 (51)	22 (49)	17 (44)	22 (56)	14 (47)	16 (53)
Uninfected children born to seropositive mothers	179 (85)	31 (15)	136 (85)	24 (15)	175 (83)	35 (17)	162 (80)	40 (20)	165 (79)	44 (21)
Uninfected children born to seronegative mothers	94 (8)	13 (12)	76 (85)	13 (15)	91 (83)	18 (17)	80 (78)	23 (22)	85 (77)	25 (23)
P Value†	<.00001		<.003		<.00001		<.0001		<.0005	

* Percentages are in parentheses

† P values refer to differences between HIV-infected children and each of the other two groups.

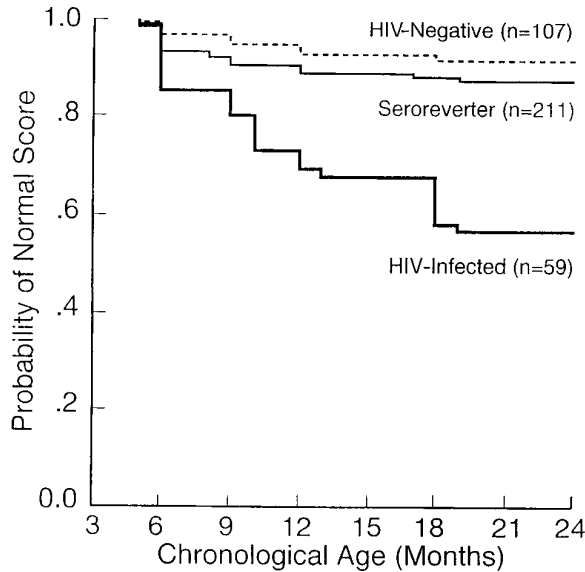


Fig 3. Cumulative probability of normal neurological examination.

should also be noted that the higher frequency of neurologic abnormalities identified in our overall sample compared with previous studies may be attributed in part to the numbers of infants with abnormalities such as hypotonia. It is possible that some of the deficits in motor and mental development that were obtained may reflect the impact of the child's systemic illness on test performance, rather than the specific effects of HIV infection on cognitive functioning. To minimize such effects, children were not tested when their illness was judged to interfere with optimal test performance. However, we recognize that this strategy reduces, but does not eliminate, the impact of the child's acute illness on their test performance. Finally, the fact that this was a field study in a developing country limited our ability to correlate neurodevelopmental data with findings from computed tomographic scans.³³

Consistent with previous research,^{8-18,34} we found wide variation in the levels of cognitive and motor development among individual children with HIV infection. Factors that contribute to such variation should be identified in future research. Description of the neurodevelopmental course of children with HIV infection using detailed statistical analyses of individual patterns of change is another necessary next step in research.³⁵ Longer term follow-up is also needed to document the developmental outcomes and educational attainments of an increasing number

of preschool and school-age survivors who have acquired HIV infection through vertical transmission.^{36,37}

ACKNOWLEDGMENTS

This study was supported by National Institutes of Health grant NS28631, World Health Organization, Rotary International, and the Catholic Agency for Overseas Development.

REFERENCES

1. Quinn TC, Ruff A, Halsey N. Pediatric acquired immunodeficiency syndrome: special considerations for developing nations. *Pediatr Infect Dis J.* 1991;11:558-568
2. Pizzo P, Wilfert C. *Pediatric Aids: the Challenge of HIV Infection in Infants, Children, and Adolescents.* Baltimore, MD: William & Wilkins; 1991
3. Goodgame RW. AIDS in Uganda. Clinical and social features. *N Engl J Med.* 1990;323:383-389
4. Crocker AC, Cohen HJ, Kastner TA. *HIV Infection and Developmental Disabilities.* Baltimore, MD: Paul H. Brookes Publishing Co; 1992
5. World Health Organization. AIDS-global data. The current global situation of the HIV-1 AIDS pandemic. *Weekly Epidemiol Rec.* 1994;6:189-192
6. Ulmann MH, Belman AI, Ruff HA. Developmental abnormalities in infants and children with acquired immune deficiency syndrome (AIDS) and AIDS related complex. *Dev Med Child Neurol.* 1985;27:563-571
7. Epstein LG, Charer LR, Oleske JM. Neurologic manifestations of human immunodeficiency virus in children. *Pediatrics.* 1986;78:678-687
8. Belman AL. AIDS and pediatric neurology. *Pediatr Neurol.* 1990;8:571-603
9. Aylward EH, Butz AM, Hutton N, Joyner ML, Vogelhut JW. Cognitive and motor development in infants at risk for human immunodeficiency virus. *Am J Dis Child.* 1992;146:218-222
10. Levinson RL, Mellins CA, Zawadzki L, Kairan R, Stein Z. Cognitive assessment in HIV exposed children. *Am J Dis Child.* 1992;146:1479-1483
11. Boivan MJ, Green DRS, Davies AG, Giordani B, Mokili JKL, Cutting WAM. A preliminary evaluation of the cognitive and motor effects of pediatric HIV-infection on African children. *Health Psychol.* 1995;14:13-21
12. Mellins CA, Levenson RL, Zawadzki R, Kairan R, Weston M. Effects of pediatric HIV infection and prenatal drug exposure on mental and motor development. *J Pediatr Psychol.* 1994;19:617-628
13. Msellati P, Lepage P, Hitmana D, VanGoethem C, Vande Perre P, Dabis F. Neurodevelopmental testing of children born to human immunodeficiency virus type 1 seropositive and seronegative mothers: a prospective cohort study in Kigali, Rwanda. *Pediatrics.* 1993;92:843-848
14. Nozyce M, Hittelman J, Muenz L, Durako SJ, Fisher ML, Willoughby A. Effect of perinatally acquired human immunodeficiency virus infection and neurodevelopment in children during the first two years of life. *Pediatrics.* 1994;94:883-891
15. Condini A, Axia G, Cattelan C, et al. Development of language in 18-30 month-old HIV-1 infected but ill children. *AIDS.* 1991;5:735-739
16. Diamond GW. Developmental problems in children with HIV infection. *Ment Retard.* 1989;27:213-217
17. Falloon J, Eddy J, Wiener L. Human immunodeficiency virus infection in children. *J Pediatr.* 1989;114:1-30
18. Gay CL, Armstrong D, Cohen D, et al. The effects of HIV on cognitive and motor development in children born to HIV seropositive women with no reported drug use: birth to 24 months. *Pediatrics.* 1995;95:1078-1082
19. Fagan JF, Singer LT, Montie J, Shepherd PA. Selective screening device for the early detection of normal or delayed cognitive development in

- infants at risk for later mental retardation. *Pediatrics*. 1986;78:1021-1026
20. CDC 1994 Revised classification system for human immunodeficiency virus infection for children less than 13 years of age. *MMWR*. 1994;43; No. RR12
 21. CDC revision of the surveillance case definition for acquired immunodeficiency syndrome. *MMWR*. 1987;36(suppl):1-15a
 22. Bayley N. *Bayley Scales of Mental Development*. New York, NY: Psychological Corporation; 1969
 23. Drotar D, Mortimer J, Shepherd A, Fagan JF. Case report: recognition memory as a method to assess intelligence in an infant with quadriplegia. *Dev Med Child Neurol*. 1989;31:391-394
 24. McCall RB, Carriger MS. A meta-analysis of infant habituation and recognition performance as a prediction of later IQ. *Child Dev*. 1992;64: 57-69
 25. Fagan JF, Drotar D, Olness K, et al. *The Fagan Test of Infant Intelligence: Cross-cultural and Racial Differences*. Presented at annual meeting of Society for Behavioral Pediatrics; September 21, 1991; Baltimore, MD
 26. Amiel-Tison C, Grenier A. *Neurologic Assessment During the First Year of Life*. New York, NY: Oxford University Press; 1986
 27. Sigman M, Neumann L, Carter E, Cattle DJD, Souza S, Biwilbo N. Home interactions and the development of Embu toddlers in Kenya. *Child Dev*. 1989;59:1251-1261
 28. Caldwell BM, Bradley RH. *Home Observation for Measurement of the Environment*. Little Rock, AR: University of Arkansas; 1979
 29. Elardo R, Bradley RH. The home observation for the measurement of the environment (HOME) Scale: a review of research. *Dev Rev*. 1981;1: 113-145
 30. Fagan JF, Detterman D. The Fagan Test of infant intelligence: a technical summary. *J Appl Dev Psychol*. 1992;13:173-193
 31. Bellinger DC, Jonas RA, Rappaport LA, et al. Developmental and neurologic status of children after heart surgery with hypothermic circulatory arrest or low flow cardiopulmonary bypass. *N Engl J Med*. 1995; 332:549-555
 32. Johnson CB. Developmental issues: Children infected with the human immunodeficiency virus. *Inf Young Child*. 1993;6:1-10
 33. Browsers P, DeCarli C, Civitello L, Moss H, Wolters P, Pizzo D. Correlation between computed tomographic brain scan abnormalities and neuropsychological function in children with symptomatic human immunodeficiency virus disease. *Arch Neurol*. 1995;52:39-44
 34. Diamond GW, Kaufman J, Belman AL, Cohen L, Cohen HG, Rubinstein R. Characterization of cognitive functioning in a subgroup of children with congenital HIV infection. *Arch Clin Neuropsychol*. 1987;2:245-256
 35. Frances DJ, Fletcher JM, Stuebing KK, Davidson KC, Thompson NM. Analysis of change: modeling individual growth. *J Consult Clin Psychol*. 1991;59:27-37
 36. Cohen HJ, Papola P, Alvarez M. Neurodevelopmental abnormalities in school age children with HIV infection. *J Sch Health*. 1994;54:11-13
 37. Papola P, Alvarez M, Cohen HJ. Developmental and service needs of school-age children with human immunodeficiency virus infection: a descriptive study. *Pediatrics*. 1994;94:914-918

Neurodevelopmental Outcomes of Ugandan Infants With Human Immunodeficiency Virus Type 1 Infection

Dennis Drotar, Karen Olness, Max Wiznitzer, Laura Guay, Lawrence Marum, Grace Svilar, David Hom, Joseph F. Fagan, Christopher Ndugwa and Rebecca

Kiziri-Mayengo

Pediatrics 1997;100:e5

DOI: 10.1542/peds.100.1.e5

Updated Information & Services

including high resolution figures, can be found at:
<http://pediatrics.aappublications.org/content/100/1/e5>

References

This article cites 29 articles, 4 of which you can access for free at:
<http://pediatrics.aappublications.org/content/100/1/e5#BIBL>

Subspecialty Collections

This article, along with others on similar topics, appears in the following collection(s):
Infectious Disease
http://www.aappublications.org/cgi/collection/infectious_diseases_sub

Permissions & Licensing

Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
<http://www.aappublications.org/site/misc/Permissions.xhtml>

Reprints

Information about ordering reprints can be found online:
<http://www.aappublications.org/site/misc/reprints.xhtml>

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN®



PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Neurodevelopmental Outcomes of Ugandan Infants With Human Immunodeficiency Virus Type 1 Infection

Dennis Drotar, Karen Olness, Max Wiznitzer, Laura Guay, Lawrence Marum, Grace Svilar, David Hom, Joseph F. Fagan, Christopher Ndugwa and Rebecca Kiziri-Mayengo

Pediatrics 1997;100:e5

DOI: 10.1542/peds.100.1.e5

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://pediatrics.aappublications.org/content/100/1/e5>

Pediatrics is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. Pediatrics is owned, published, and trademarked by the American Academy of Pediatrics, 345 Park Avenue, Itasca, Illinois, 60143. Copyright © 1997 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 1073-0397.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN®

