Early Cognitive and Motor Development Among Infants Born to Women Infected With Human Immunodeficiency Virus

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ABSTRACT. *Objective.* **To examine the frequency, timing, and factors associated with abnormal cognitive and motor development during the first 30 months of life in infants born to women infected with human immunodeficiency virus type 1 (HIV-1).**

Methods. **Serial neurodevelopmental assessment was performed with 595 infants born to women infected with HIV-1 in a multicenter, prospective, natural history cohort study. Survival analysis methods were used to evaluate 6 outcome events related to abnormal cognitive and motor growth (time to confirmed drop of 1 SD, time to first score <69, and time to confirmed drop of 2 SD) in Bayley Scales of Infant Development Mental Developmental Index (MDI) and Psychomotor Developmental Index (PDI) scores among infected (n = 114) and uninfected (n = 481) infants. Proportional hazards modeling was used to evaluate the effects of HIV infection status, prematurity, prenatal exposure to illicit drugs, maternal educational attainment, and primary language.**

Results. **HIV-1 infection was significantly associated with increased risk for all outcome events related to abnormal mental and motor growth. Differences between infected and uninfected infants were apparent by 4 months of age. Prematurity was associated with increased risk for MDI <69 and PDI <69. Maternal education of <9 completed years was associated with increased risk for MDI <69. Neither prenatal exposure to illicit drugs nor primary language other than English was associated with abnormal development.**

Conclusion. **A significant proportion of infants with HIV-1 infection show early and marked cognitive and motor delays or declines that may be important early indicators of HIV disease progression. These abnormalities are independent of other risk factors for developmental delay.** *Pediatrics* **2000;106(2). URL: http://www.pediatrics.org/cgi/content/full/106/2/e25;** ***human immunodeficiency virus, child development.***

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Received for publication Dec 8, 1998; accepted Feb 22, 2000.

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PEDIATRICS (ISSN 0031 4005).

ABBREVIATIONS. HIV-1, human immunodeficiency virus type 1; AIDS, acquired immunodeficiency syndrome; WITS, Women and Infants Transmission Study; MDI, Mental Developmental Index; PDI, Psychomotor Developmental Index; BSID, Bayley Scales of Infant Development; SD, standard deviation; RR, risk ratio; CI, confidence interval.

Neurological and developmental signs are often early markers of human immunodeficiency virus type 1 (HIV-1) disease in infants that may precede other signs of disease progression.[1] Numerous observational data describe the frequency of severe neurodevelopmental abnormalities in pediatric HIV disease. A prospective study of French children with congenital or perinatal HIV-1 infection reported a 19% rate of significant central nervous system impairment.[2] The European Collaborative Study reported a 13% rate of serious neurological signs and symptoms in infected children and a much higher rate (31%) in children with acquired immunodeficiency syndrome (AIDS) or AIDS-related complex.[3] A recent multicenter epidemiologic study in the United States showed HIV-1 encephalopathy diagnosed in 23% of children with perinatally acquired AIDS.[4] HIV encephalopathy was present in 15% of US pediatric AIDS cases reported in 1994[5] and 18% in 1995.[6] However, the frequency and timing of early and less severe neurodevelopmental effects of HIV infection, and the interaction with other known risk factors for developmental impairment, are not well-characterized.

Previous published analyses of neurodevelopmental abnormality in children with HIV-1 disease have been cross-sectional in design or had small sample size, reporting differences between HIV-infected and HIV-exposed but HIV-uninfected infants in mean scores on neurodevelopmental measures at specific ages.[7–9] These studies generally have not adjusted for other important risk factors related to neurodevelopmental abnormality besides HIV status. The Women and Infants Transmission Study (WITS) is an ongoing observational study of maternal–infant HIV transmission and outcome in women infected with HIV-1 and their children. Accrual began in 1989, and

the first infant to be enrolled in WITS was born in 1990. The prospective, systematically collected neurodevelopmental data now available from this study provide an opportunity to examine longitudinal patterns of growth in a multivariate context. The study objectives were to examine the frequency and timing of abnormality in cognitive and motor development in infants born to HIV-infected women and to identify risk factors other than HIV infection that are associated with markers of neurodevelopmental abnormality in these children during the first 30 months of life.

METHODS

Population Studied

Eligible subjects were all singleton infants born to women with HIV-1 infection 15 to 44 years old who entered WITS, a prospective natural history cohort study of maternal–infant HIV infection conducted at 6 clinical centers in the mainland United States and Puerto Rico. Maternal HIV infection was documented by repeated positive results in the US Food and Drug Administration-licensed serologic enzyme immunoassay for HIV-1 antibody with independent supplemental confirmatory test or diagnosis of AIDS as defined by the Centers for Disease Control and Prevention. Analyses were restricted to data collected through the 30-month visit for the 595 such infants in whom the presence or absence of HIV-1 infection had been established by study protocol and who completed at least 1 neurodevelopmental assessment. HIV-1 infection was defined by the presence of 2 or more cultures of peripheral blood mononuclear cells positive for HIV-1 ($n = 114$). Absence of HIV infection ($n = 481$) was defined by 2 or more cultures negative for HIV-1 at 1 month of age or older, with 1 or more cultures negative for HIV at 6 months of age or older, and no positive culture results. Products of multiple births and infants born to mothers already enrolled were excluded. Only subjects with 3 or more neurodevelopmental assessments were included in analyses of confirmed drops in mental or motor scores (infected, $n = 77$ and uninfected, $n = 344$). Thirteen subjects died before 30 months old. All 13 of these infants were HIV-infected. Of these 13 infants, 6 had Metal Developmental Index (MDI) scores <3, and 7 had Psychomotor Developmental Index (PDI) scores <3.

Procedures

Informed consent was obtained from each mother during pregnancy for herself and the fetus and again after the child's birth for enrollment of the child. Neurodevelopmental assessment was performed at 4, 9, 12, 15, 18, 24, and 30 months of age. The Bayley Scales of Infant Development (BSID),[10] was administered in strict accordance with published test instructions and standard test procedures by trained examiners uninformed of subject protocol-defined infection status.

The BSID was selected as a widely used and accepted, well-standardized, dependable multipart instrument for evaluation of developmental status in the first 2½ years of life. The instrument has 163 items on the Mental Scale and 81 items on the Motor Scale. The Mental Scale is designed to assess sensory-perceptual acuities, discriminations, and the ability to respond to these; early acquisition of object constancy and memory, learning, and problem-solving ability; vocalizations and beginnings of verbal communications; and early evidence of ability to form generalizations and classifications. Results are expressed as a standard score, the MDI. The Motor Scale is designed to provide a measure of the degree of control of the body, coordination of the large muscles, and finer manipulative skills of the hands and fingers. It is specifically directed toward behaviors reflecting motor coordination and skills. Results are expressed as a standard score, the PDI. The standard scores are normalized for each of 14 age groups to have a mean value of 100 and a standard deviation (SD) of 16. The standard score range of 50 to 150 covers >3 SD on either side of the average MDI or PDI for each age.

Intertester reliability was maintained by centralized training for WITS examiners and supervisors, periodic review and clarification of scoring criteria, and selected review of videotapes of the assessments. Neurodevelopmental assessments were uniformly scheduled to precede any invasive or painful procedures, such as phlebotomy, and postponed in instances of acute illness. Assessments were conducted in the primary language used in the subject's home, by an examiner fluent in the primary language or through an interpreter who assisted with the assessment. The raw and standard scores of the BSID Mental and Psychomotor Scales were recorded at each assessment for each subject. Any examination limiting factors, such as poor cooperation or poor intelligibility on the child's part, were noted and recorded.

For MDI and PDI scores <50, an extrapolated score was obtained using tables by Naglieri[11] of statistically derived expected scores for the BSID. The minimum score using these extrapolated scores is 28 rather than 50. For premature infants (<37 completed weeks of gestation), actual chronologic ages without adjustment were used in calculating MDI and PDI. Prematurity was incorporated as a covariate in the modeling process as a dichotomous variable. Gestational age was determined by a combination of prenatal ultrasonography, physical examination of uterine fundal height, and menstrual history. Prenatal drug exposure was defined by maternal prenatal use of illicit drugs (opiates, cocaine, or other injectables) or methadone, as assessed by a combination of interview and urine toxicologic studies. The measure of maternal disease progression was the average of all maternal CD4 measures available during pregnancy. Other covariates and sociodemographic characteristics, including primary language and maternal education, were assessed by trained interviewers using uniform questionnaires and interview techniques.[12] Informed consent was obtained for all women and infant subject participants according to local institutional review board and federal guidelines[13] and regulations.[14] Consent for infant enrollment was obtained from the legal guardian within 7 days after birth.

Statistical Methods

Mean MDI and PDI scores were calculated for each visit by HIV status. Survival analysis and proportional hazards modeling techniques were used to evaluate 3 different types of abnormal cognitive (measured by MDI) or motor (measured by PDI) developmental outcome events in order of increasing severity: a 16-point (1 SD) confirmed drop in scaled score, first occurrence of a scaled score <69 (2 SD or more below mean), and a 32-point (2 SD) confirmed drop in scaled score. The BSID was constructed psychometrically with a mean of 100 and SD of 16, thus defining a score of ≤69 as below the normal range. To ensure that our results were not driven by arbitrary choices in the endpoint definitions, we considered both drops of 1 and 2 SDs, with the requirement of confirmation at a subsequent visit. In recently published and ongoing trials by the Pediatric AIDS Clinical Trials Group, a drop in MDI or PDI of 2 SD of 1 occasion or 1 SD confirmed on a second test are used as neuropsychologic endpoints to define treatment failure.[15–17] Confirmed drops were defined as declines of at least the specified magnitude (16 or 32 points) below any previous score for a given subject, with the next consecutive score for that subject also being at least the specified magnitude (16 or 32 points) below any score previous to the 1 representing the initial drop. Subjects whose maximum MDI or PDI scores precluded the possibility of dropping a full 16 or 32 points were excluded from analyses of drops in those specific scores but were included in the analyses of scores <69. There were 6 such exclusions from 3 infected children.

Kaplan-Meier estimates of the cumulative probability of each 1 of the 3 outcome events across time for each of the 2 developmental indexes (MDI and PDI) were generated for each of the covariates (HIV infection, prematurity, prenatal drug exposure, maternal educational attainment <9 completed years, and primary language other than English) and its complement and were compared using the log-rank test. The simultaneous effects of all 5 covariates on the risk of reaching an outcome event were assessed using a multivariable Cox proportional hazards regression model. Additional analyses were performed excluding all children whose gestational age was <34 weeks and adding maternal CD4% as a covariate in the regression model.

RESULTS

Description of Sample

Sociodemographic and maternal characteristics of infant subjects were similar for the overall sample

(n = 595) and for the subgroup with 3 or more assessments (n = 421) and are summarized in Table 1 by infection status. HIV-infected subjects more frequently experienced premature birth, prenatal drug exposure, and lower maternal educational attainment. A higher proportion of biological mothers of HIV-infected subjects were white and a higher proportion of families of HIV-infected subjects spoke English as the primary language, compared with those of HIV-uninfected subjects. Not unexpectedly, immune function, as measured by the maternal CD4%, was lower for mothers of HIV-infected subjects, compared with mothers of HIV-uninfected subjects.

By the closing date for data analysis, 534 of the study children (90%) had reached their first birthday. Of these, an MDI and/or PDI score was obtained for 390 (73%). A total of 410 had reached their second birthday. Of these, 277 (68%) provided a developmental score.

TABLE 1. Description of Sample of Children With More Than or Equal to One and More Than or Equal to Three Examinations by HIV Status

	≥1 Examination		≥3 Examinations	
	HIV-Negative n = 481	HIV-Positive n = 114	HIV-Negative n = 344	HIV-Positive n = 77
Gender				
Male	236 (49.1)	56 (49.1)	173 (50.3)	41 (53.3)
Prematurity				
<37 wk	83 (17.3)	29 (25.4)	61 (17.7)	17 (22.1)
Hard drug exposure*				
Unexposed	292 (60.7)	53 (46.5)	206 (59.9)	34 (44.2)
Exposed	186 (38.7)	61 (53.5)	135 (39.2)	43 (55.8)
Unknown	3 (.6)	0 (.0)	3 (.9)	0 (.0)
Maternal education				
0–8 y	57 (11.9)	20 (17.5)	39 (11.3)	13 (16.9)
9+ y	415 (86.3)	94 (82.5)	298 (86.6)	64 (83.1)
Unknown	9 (1.9)	0 (.0)	7 (2.0)	0 (.0)
Primary language†				
Spanish	148 (30.8)	25 (21.9)	108 (31.4)	20 (26.0)
English	330 (68.6)	88 (77.2)	236 (68.6)	57 (74.0)
Unknown	3 (.6)	1 (.9)		
Maternal race				
White	67 (13.9)	22 (19.3)	50 (14.5)	15 (19.5)
Black	203 (42.2)	43 (37.7)	142 (41.3)	27 (35.1)
Hispanic	182 (37.8)	42 (36.8)	131 (38.1)	32 (41.6)
Other	21 (4.4)	7 (6.1)	15 (4.4)	3 (3.9)
Unknown	8 (1.7)	0 (.0)	6 (1.7)	0 (.0)
Household income				
<$10 000	319 (66.3)	79 (69.3)	229 (66.6)	54 (70.1)
≥$10 000	117 (24.3)	25 (21.9)	87 (25.3)	17 (22.1)
Unknown	45 (9.4)	10 (8.8)	28 (8.1)	6 (7.8)
Maternal CD4%				
<14%	34 (7.1)	11 (9.7)	23 (6.7)	9 (11.7)
14%–28%	189 (39.3)	64 (56.1)	134 (39.0)	44 (57.1)
>28%	247 (51.4)	38 (33.3)	178 (51.7)	23 (29.9)
Unknown	11 (2.3)	1 (.9)	9 (2.6)	1 (1.3)

* Positive maternal report or positive prenatal or perinatal urine toxicology for cocaine, heroin, methadone, or injection drugs.
† Primary language spoken in home.

Table 2 displays the mean MDI and PDI scores by visit for HIV-infected and HIV-negative children. Unadjusted mean scores were significantly lower in the HIV-negative group at every visit up to and including the 24-month visit.

Multivariate Analysis of Neurodevelopmental Indices

HIV-1 infection was a significant predictor for all 6 neurodevelopmental outcome events when considered alone or adjusted for the other covariates. Of the other 4 covariates, prematurity and maternal education showed significant association with the occurrence of any of the outcome events related to mental or motor growth. Neither prenatal exposure to hard drugs nor primary language in the home showed significant associations with the declines or deficits in the mental or motor scores examined. Interactions among covariates were not significant.

Confirmed Drops of 1 SD in Mental/Motor Scores

Results of the proportional hazards analysis considering the simultaneous effects of all covariates on risk for 16-point (1 SD) confirmed drops in MDI or PDI are shown in Table 3. HIV-1 infection was associated with elevated risk both for mental (MDI, risk ratio [RR]: 1.50; 95% CI [confidence interval]: 1.03–2.18; $P = .034$) or motor (PDI, RR: 1.66; 95% CI: 1.12–2.45; $P = .011$) outcome events of this type. Thus, given 2 subjects of the same age who have not yet experienced a 16-point (1 SD) confirmed drop in cognitive or motor performance as measured by the BSID, the HIV-infected subject is one half to two thirds again more likely to experience such a drop in the next time interval, compared with the HIV-uninfected subject, all other things being equal. Unexpectedly, premature infants were less likely to experience abnormal motor (PDI) outcome events of this type (RR: .51; 95% CI: .31–.85; $P = .009$), compared with term infants. No increased risk for reaching a 16-point confirmed drop in MDI or PDI was associated with prenatal drug exposure, low maternal educational attainment, or non-English primary language.

Figures 1 and 2 depict the cumulative probability of experiencing a 16-point confirmed drop in MDI or PDI from 4 to 30 months of age in HIV-infected, compared with HIV-uninfected subjects. HIV-infected subjects were more likely than uninfected subjects to experience either of these 2 outcome events indicating deceleration of developmental growth after 9 months of age. However, these outcomes were not specific to the HIV-infected group. The 2-year incidence of a16-point confirmed drop in MDI was 53.8% in HIV-infected subjects, compared with 39.5% among HIV-uninfected subjects (log-rank $P = .01$) by 24 months of age. Similarly, for PDI, the 2-year incidence of a 16-point confirmed drop was 49.5% among HIV-infected subjects, compared with 36.8% among HIV-uninfected subjects (log-rank $P = .06$). Consistent with multivariate analysis, full-term infants exhibited a 41.7% probability by 24 months old of a confirmed drop in PDI, compared with 27.9% among the premature subjects (log-rank $P = .01$).

Mental/Motor Scores Less Than 69

Table 4 shows the results of proportional hazards analysis for occurrence of mental (MDI) and motor (PDI) scores 2 or more SDs below the mean (MDI or PDI <69). Both HIV-1 infection and prematurity were strongly associated with elevated risk of reaching these abnormal cognitive or motor outcomes. RRs for MDI <69 were 4.88 (95% CI: 2.94–8.12; $P = .0001$) for HIV-infected compared with HIV-uninfected subjects, and 4.03 (95% CI: 2.44–6.66; $P = .0001$) for premature compared with term infants. Similarly, RRs for PDI <69 were 4.75 (95% CI: 2.79–8.06; $P = .0001$) and 3.37 (95% CI: 1.98–5.73; $P = .0001$) for HIV-infected subjects and for infants born prematurely, respectively. Higher maternal educational attainment showed an association with reduced risk of developing MDI <69 (RR: .52; 95% CI:

TABLE 2. Mean MDI and PDI Scores at Each Visit by HIV Status, With *P* Value for Statistical Significance of the Difference in Mean Scores

Age (Months)	MDI Score				*P* Value
	HIV-Negative		HIV-Infected		
	n	Mean (SD)	*n*	Mean (SD)	
4	362	105.0 (15.2)	80	96.8 (19.2)	<.001
9	337	105.7 (18.3)	74	91.5 (25.2)	<.001
12	322	104.8 (16.1)	68	87.9 (30.3)	<.001
15	162	103.2 (14.8)	35	93.5 (21.0)	.01
18	256	97.3 (15.6)	63	81.9 (26.2)	<.001
24	220	94.4 (16.1)	57	83.1 (23.0)	<.001
30	84	97.8 (14.4)	27	96.0 (20.9)	.69
Age (Months)	PDI Score				*P* Value
	HIV-Negative		HIV-Infected		
	n	Mean (SD)	*n*	Mean (SD)	
4	359	108.3 (15.8)	78	97.7 (19.9)	<.001
9	335	103.7 (17.0)	74	84.1 (25.5)	<.001
12	318	100.1 (15.4)	66	78.2 (25.3)	<.001
15	161	101.2 (13.7)	35	87.6 (20.9)	<.001
18	252	96.2 (13.6)	60	83.8 (24.5)	<.001
24	213	101.2 (16.8)	57	83.5 (23.8)	<.001
30	78	99.8 (19.0)	27	91.0 (21.3)	.07

TABLE 3. Multivariable Cox Proportional Hazards Models Conditional RR and 95% Confidence Limits for One SD Confirmed Drops‡ in MDI and PDI Scores

Outcome	Covariate	RR (95% Confidence Limits)	*P* Value
MDI 1 SD drop	HIV-positive	1.50 (1.03, 2.18)	.034
n = 414	Prematurity (<37 wk)	.63 (.39, 1.00)	.052
151 events	Hard drug exposure*	1.01 (.72, 1.42)	.946
263 censored	Education (<9 y)	.69 (.45, 1.07)	.096
	Language (Spanish)†	1.27 (.87, 1.85)	.223
PDI 1 SD drop	HIV-positive	1.66 (1.12, 2.45)	.011
n = 406	Prematurity (<37 wk)	.51 (.31, .85)	.009
144 events	Hard drug exposure*	.95 (.66, 1.35)	.757
262 censored	Education (<9 y)	.65 (.41, 1.02)	.062
	Language (Spanish)†	.87 (.60, 1.26)	.455

* Positive maternal report or positive prenatal or perinatal urine toxicology for cocaine, heroin, methadone, or injection drugs.
† Primary language spoken in home.
‡ A decline of 1 SD from any previous assessment with the score at the next consecutive assessment also being 1 SD below any previous score.

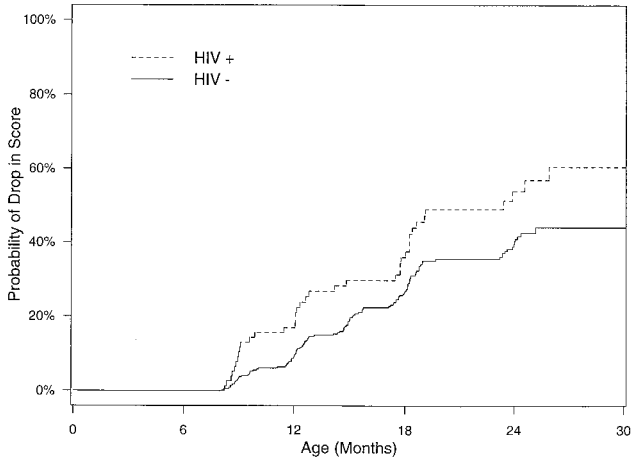

Fig 1. Cumulative incidence of 1 SD confirmed drop in MDI × HIV status.

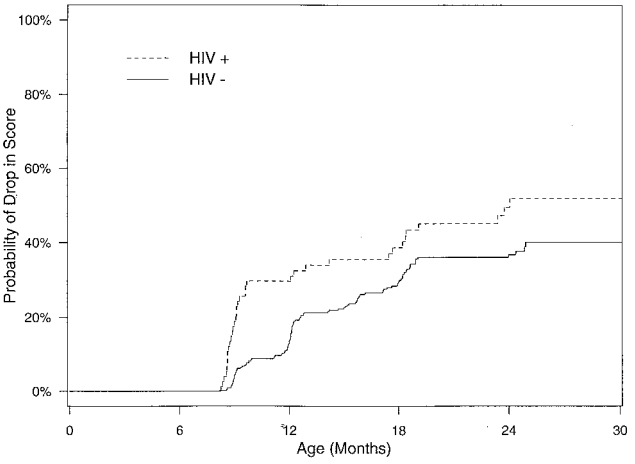

Fig 2. Cumulative incidence of 1 SD confirmed drop in PDI × HIV status.

.28–.99; P = .032). No increase in risk of reaching abnormal cognitive or motor outcome events of this type was associated with prenatal drug exposure or with non-English primary language.

HIV-infected subjects were more likely than uninfected subjects to exhibit MDI or PDI scores <69 (2 SD below the mean) at all ages examined. Figures 3 and 4 depict the cumulative probability of occurrence of this type of abnormal cognitive (MDI) or motor (PDI) outcome event from 4 to 30 months of age in HIV-infected subjects, compared with HIV-uninfected subjects. Early, sustained, and increasing differences between the HIV-infected and HIV-uninfected subjects were observed at the earliest time point examined and all subsequent time points. The incidence of MDI <69 was 16.5% by 12 months and 35.6% by 24 months for HIV-infected infants, compared with 3.2% by 12 months and 8.2% by 24 months among HIV-uninfected infants (log-rank P = .001).

Confirmed Drops of 2 SD in Mental or Motor Scores

Results of the proportional hazards analysis considering the simultaneous effects of all covariates on risk for 32-point (2 SD) confirmed drops in MDI or PDI are shown in Table 5. HIV-1 infection was strongly associated with elevated risk for abnormal cognitive (MDI, RR: 2.40; 95% CI: 1.27–4.56; P = .007) and motor (PDI, RR: 3.81; 95% CI: 1.93–7.54; P = .0001) outcome events of this type. Thus, given 2 subjects of the same age who have not yet experienced a 32-point (2 SD) confirmed drop in cognitive or motor performance as measured by the BSID, a subject with HIV-1 infection is more than twice as likely to experience it in the next time interval than an uninfected subject, all other things being equal. None of the other covariates examined (gestational age, prenatal drug exposure, maternal educational attainment, or primary language) were significantly related to risk for reaching a 32-point confirmed drop in MDI or PDI.

Figures 5 and 6 depict the cumulative probability of experiencing a 32-point confirmed drop in MDI or PDI from 4 to 30 months of age in HIV-infected subjects, compared with HIV-uninfected subjects. Differences were apparent beginning at 9 months old. HIV-infected subjects were more likely than HIV-uninfected subjects to experience this type of outcome event at all subsequent ages examined. The proportions of HIV-infected subjects compared with HIV-uninfected subjects experiencing a 32-point confirmed drop in cognitive (MDI) were 6.6% versus 1.5% by 12 months and 20.7% versus 10.4% by 24 months (log-rank P = .01).

TABLE 4. Multivariable Cox Proportional Hazards Models Conditional RR and 95% Confidence Limits for MDI and PDI Scores Less Than 69

Outcome	Covariate	RR (95% Confidence Limits)	*P* Value
MDI <69	HIV-positive	4.88 (2.94, 8.12)	.0001
n = 582	Prematurity (<37 wk)	4.03 (2.44, 6.66)	.0001
62 events	Hard drug exposure*	.70 (.42, 1.19)	.190
520 censored	Education (<9 y)	.52 (.28, .99)	.032
	Language (Spanish)†	1.56 (.82, 2.96)	.171
PDI <69	HIV-positive	4.75 (2.79, 8.06)	.0001
n = 581	Prematurity (<37 wk)	3.37 (1.98, 5.73)	.0001
57 events	Hard drug exposure*	.92 (.53, 1.59)	.767
524 censored	Education (<9 y)	.94 (.44, 1.99)	.864
	Language (Spanish)†	1.07 (.56, 2.01)	.844

* Positive maternal report or positive prenatal or perinatal urine toxicology for cocaine, heroin, methadone, or injection drugs.
† Primary language spoken in home.

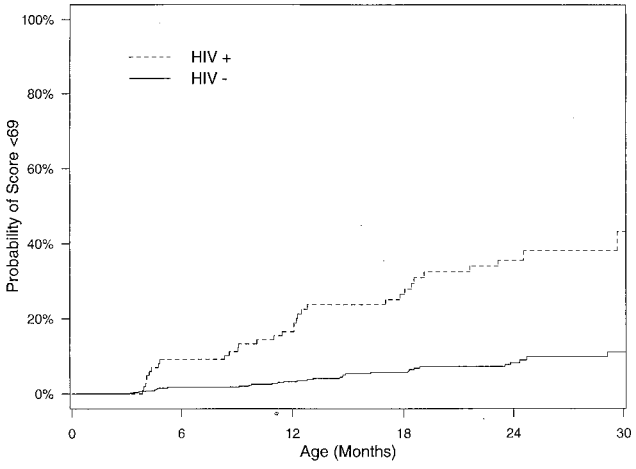

Fig 3. Cumulative incidence of MDI <69 × HIV status.

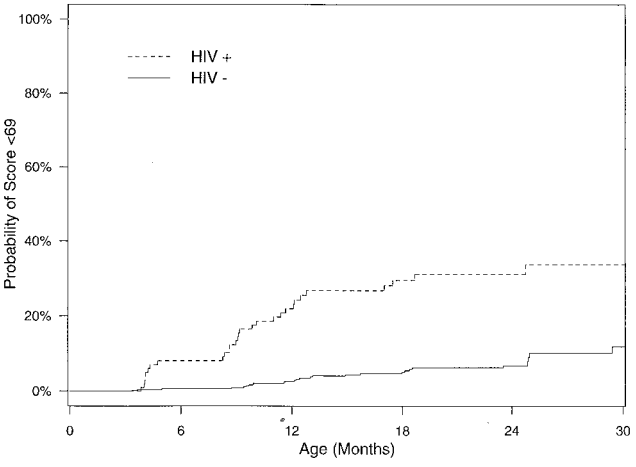

Fig 4. Cumulative incidence of PDI <69 × HIV status.

Table 6 shows the gestational age distribution by HIV status. The number of infants with gestational age <34 weeks was 19 (23%) and 9 (31%), for HIV-infected and HIV-uninfected infants, respectively. We repeated the multivariate analyses after excluding the infants with gestational age <34 weeks. The associations between HIV status and developmental outcomes changed only slightly when the premature infants were excluded. Excluding infants with gestational age <34 weeks did not substantively alter the results.

When prenatal maternal CD4% was added to the multivariate model, the results changed slightly. Table 7 shows the result of the proportion hazards models containing all covariates and maternal CD4% for all 6 outcome events. After adjusting for maternal CD4%, HIV status was still significantly associated with all PDI outcomes and MDI scores of <69. HIV status was associated with an MDI 1 SD drop (P = .09) and an MDI 2 SD drop (P = .11), but the association was no longer statistically significant.

DISCUSSION

Analysis of prospective neurodevelopmental data from the WITS cohort of infants born to women infected with HIV-1 suggests that, with or without accounting for other factors known or suspected to have adverse influence on developmental growth, several types of abnormal cognitive and motor neurodevelopmental outcome events occur earlier and at significantly increased frequency throughout the first 2½ years of life among HIV-infected infants, compared with HIV-exposed but HIV-uninfected infants. These findings are in essential agreement with previous studies.[2–4,7,8] Using a cross-sectional or externally defined measure of abnormality (standard scores 2 SD or more below age-specific normative mean) significant cognitive and motor deficits already were evident among an increased proportion of HIV-infected infants, compared with HIV-uninfected infants, by 4 months of age—the earliest time point examined in this study. Using individual growth curve measures of abnormality (16-point/1 SD or 32-point/2 SD confirmed drops within a given subject's scores compared with previous scores), HIV infection likewise was strongly associated with increased frequency of abnormal cognitive or motor neurodevelopment outcome events beginning at 9 months of age—the earliest time point at which such an event could occur in the study.

Overall, the data indicate that significant proportions of HIV-infected infants experience delays or declines in cognitive and/or motor development, which may be important early indicators of HIV disease progression.

Our investigation of the impact of HIV disease on early neurodevelopmental growth represents an advance in terms of its assessment of outcomes based

TABLE 5. Multivariable Cox Proportional Hazards Models Conditional RR and 95% Confidence Limits for Two SD Confirmed Drops‡ in MDI and PDI Scores

Outcome	Covariate	RR (95% Confidence Limits)	*P* Value
MDI 2 SD drop	HIV-positive	2.40 (1.27, 4.56)	.007
n = 413	Prematurity (<37 wk)	.43 (.15, 1.19)	.104
45 events	Hard drug exposure*	.93 (.48, 1.78)	.820
368 censored	Education (<9 y)	1.52 (.54, 4.28)	.429
	Language (Spanish)†	.84 (.43, 1.65)	.614
PDI 2 SD drop	HIV-positive	3.81 (1.93, 7.54)	.0001
n = 405	Prematurity (<37 wk)	.82 (.34, 1.97)	.649
36 events	Hard drug exposure*	.79 (.38, 1.65)	.528
369 censored	Education (<9 y)	.96 (.37, 2.49)	.928
	Language (Spanish)†	.55 (.27, 1.13)	.106

* Positive maternal report or positive prenatal or perinatal urine toxicology for cocaine, heroin, methadone, or injection drugs.
† Primary language spoken in home.
‡ A decline of 2 SD from any previous assessment with the score at the next consecutive assessment also being 2 SD below any previous score.

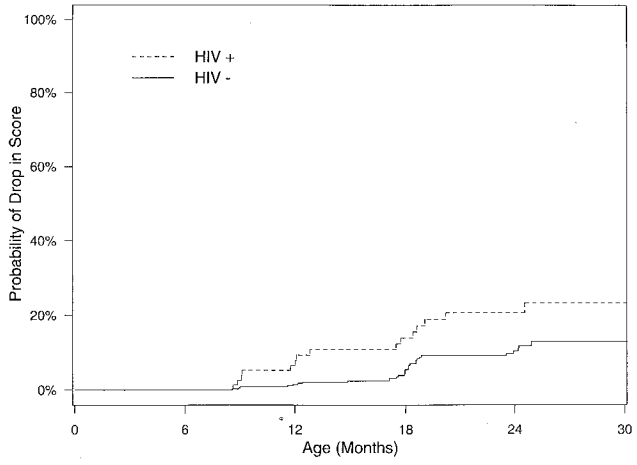

Fig 5. Cumulative incidence of 2 SD confirmed drop in MDI × HIV status.

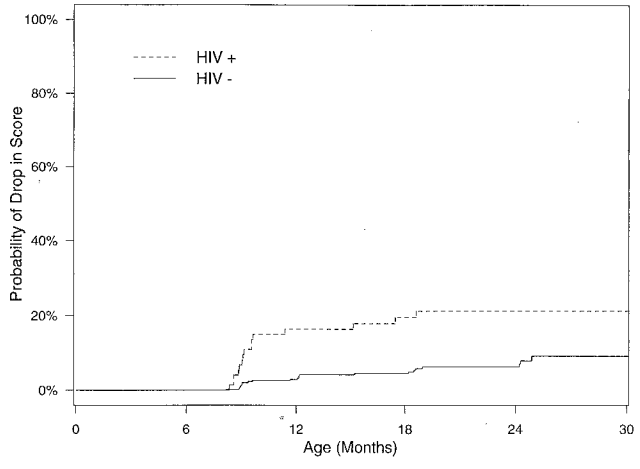

Fig 6. Cumulative incidence of 2 SD confirmed drop in PDI × HIV status.

on individual performance over time, rather than cross-sectional analysis. The variable course of HIV disease suggests that analysis of individual growth and change is called for, with prompt identification of critical signs of deceleration in developmental growth, rather than cross-sectional analysis. Use of an extrapolation method for calculating MDI and PDI scores <50 allowed inclusion of >98% of the sample of children with 3 or more assessments, thus more accurately reflecting the full spectrum of neurodevelopmental status. Standardized training of examiners, large sample size, use of a well-matched comparison group, and multiple assessments within subjects over time are additional important strengths of the study.

TABLE 6. Distribution of Gestational Ages for Premature Infants by HIV Status

Gestational Age (Weeks)	HIV-Negative (%)	HIV-Infected (%)
26	3 (3.6)	1 (3.4)
27	1 (1.2)	1 (3.4)
28	1 (1.2)	0
29	0	2 (6.9)
30	3 (3.6)	3 (10.3)
31	2 (2.4)	1 (3.4)
32	3 (3.6)	0
33	6 (7.2)	1 (3.4)
34	10 (12.0)	4 (13.8)
35	12 (14.5)	6 (20.7)
36	42 (50.6)	10 (34.5)

Ideally this study would have included a second control group of HIV-unexposed children to control for the effects of maternal illness. Other limitations include those imposed by the study design, including the inability to control for use of antiretroviral treatment in HIV-infected subjects and the low frequency of 2 SD drops in motor or mental score as outcome events, which may have limited our ability to detect small or subtle effects of other covariates. The assessment instrument used was not designed as a measure of longitudinal growth for individual children and may not adequately target specific aspects of development that may be subtly impaired in HIV-1 infection. Expanding the analysis beyond that of age-adjusted scores to include analysis of individual children's raw scores on the BSID would have allowed identification of children who lost previously acquired skills, or who failed to gain any new skills over time, or who experienced an insidious developmental decline that was not steep enough to be identified in this study, but, nevertheless, may have represented central nervous system disease

TABLE 7. Proportion Hazards Models Containing All Covariates and Maternal CD4 Percent

Outcome	Covariate	RR (95% CI)	*P* Value
MDI—1 SD drop	HIV-positive	1.40 (.095, 2.05)	.09
	Prematurity (<37 wk)	.60 (.37, .97)	.04
n = 405	Hard drugs	1.07 (.75, 1.51)	.71
Events = 145	Education (<9 y)	.68 (.44, 1.06)	.09
Censored = 259	Language (Spanish)	1.23 (.83, 1.81)	.30
	Maternal CD4% ≤28	1.41 (1.01, 1.97)	.04
MDI—2 SD drop	HIV-positive	1.73 (.89, 3.35)	.11
	Prematurity (<37 wk)	.42 (.15, 1.17)	.10
n = 404	Hard drugs	1.11 (.58, 2.13)	.76
Events = 43	Education (<9 y)	1.80 (.55, 5.86)	.33
Censored = 361	Language (Spanish)	.72 (.36, 1.44)	.35
	Maternal CD4% ≤28	3.25 (1.61, 6.57)	.001
MDI <69	HIV-positive	4.05 (2.43, 6.74)	<.001
	Prematurity (<37 wk)	4.15 (2.50, 6.88)	<.001
n = 571	Hard drugs	.80 (.48, 1.34)	.40
Events = 61	Education (<9 y)	.45 (.24, .84)	.02
Censored = 510	Language (Spanish)	1.60 (.83, 3.07)	.16
	Maternal CD4% ≤28	2.77 (1.54, 4.99)	<.001
PDI—1 SD drop	HIV-positive	1.52 (1.02, 2.27)	.04
	Prematurity (<37 wk)	.48 (.28, .81)	.006
n = 398	Hard drugs	1.03 (.72, 1.47)	.89
Events = 140	Education (<9 y)	.66 (.42, 1.05)	.08
Censored = 258	Language (Spanish)	.85 (.58, 1.23)	.38
	Maternal CD4% ≤28	1.34 (.96, 1.89)	.10
PDI—2 SD drop	HIV-positive	3.60 (1.79, 7.26)	<.001
	Prematurity (<37 wk)	.80 (.33, 1.93)	.61
n = 397	Hard drugs	.79 (.38, 1.67)	.54
Events = 36	Education (<9 y)	.87 (.33, 2.28)	.78
Censored = 361	Language (Spanish)	.54 (.26, 1.10)	.09
	Maternal CD4% ≤28	1.29 (.65, 2.56)	.47
PDI <69	HIV-positive	4.32 (2.53, 7.38)	<.001
	Prematurity (<37 wk)	3.33 (1.96, 5.67)	<.001
n = 570	Hard drugs	.95 (.56, 1.64)	.85
Events = 57	Education (<9 y)	.84 (.39, 1.80)	.65
Censored = 513	Language (Spanish)	1.03 (.55, 1.94)	.92
	Maternal CD4% ≤28	1.60 (.91, 2.80)	.10

progression. In addition, there may be other covariates beyond those considered in our analysis, including maternal smoking, severity of maternal illness, household income, and developmental intervention services that contribute to early neurodevelopmental growth or deficit in infants born to HIV-infected women. However, taken together, these factors suggest that the observed results may represent a minimum estimate of the size and timing of the effect of HIV on early development.

The fact that exclusion of children with gestational age <34 weeks did not substantially change the results is notable. Prematurity was significantly associated with increased risk for MDI and PDI scores >2 SD below the mean (<69). However, prematurity seemed to have a protective effect when confirmed drops of 1 SD were examined, indicating the continued need to view carefully premature infants as a subgroup in the selection and analysis of neurodevelopmental outcome events. We chose to use prematurity as a covariate rather than using developmental scores corrected for prematurity to evaluate the relative contributions of HIV status and prematurity to neurodevelopmental performance. However, the use of developmental index scores that were uncorrected for prematurity may have increased the probability that premature infants would achieve an MDI or PDI <69 and may have decreased the probability that premature infants would achieve a confirmed drop in developmental index scores as defined in this study.

Although correcting for prematurity (subtracting the number of weeks to term from the premature infant's postbirth chronologic age) is common practice in scoring developmental tests for clinical use, for research purposes, such practice hinders accurate assessment of the relative effect of prematurity as an independent variable on dependent variables of interest in multivariate analysis. Because the scaled scores of premature infants were not corrected for prematurity (thereby preventing over adjustment for this condition in multivariate analysis) but scored according to the norms for actual chronologic age, substantially lower MDI and PDI values were observed than if age had been adjusted for prematurity.

Premature infants are less mature developmentally, and the use of uncorrected scaled scores would be expected to increase the likelihood of observing MDI or PDI scores <69. In addition, because the magnitude of the effect of such adjustment (or lack of adjustment) is greatest early in infancy, when the proportion of postbirth chronologic age that the weeks to term correction factor represents is greatest, the use of uncorrected scaled scores also would be expected to decrease the probability that premature infants would experience confirmed drops in MDI or PDI (by reducing early scores more than later scores). In the case of 2 SD confirmed drops, however, no

significant effect of prematurity was observed, possibly attributable to the relatively severe nature and smaller number of such events.

Current definitions of encephalopathy in pediatric HIV disease used for epidemiologic surveillance include as one of the criteria for diagnosis "the failure to attain or loss of developmental milestones or loss of intellectual ability, verified by standard developmental scales or neuropsychological tests."[17] A clear working definition of this criterion for clinical and research application has not yet been formulated. Various indices of neurodevelopmental deficit and decline might be selected to study the occurrence and timing of abnormality in the developmental growth of HIV-infected infants and children. These include plateaus or drops in raw scores, frequency of abnormal age-adjusted scores, and drops in age-adjusted scores obtained with standardized neurodevelopmental testing. To be useful, an index of abnormality in neurodevelopmental growth related to HIV infection must minimize the identification of neurodevelopmental deficit attributable to variables other than HIV infection that are associated with risk for deficits in cognitive and motor development, such as prematurity,[18] prenatal drug exposure,[19,20] and poverty.[21]

The present study suggests that in the systematic diagnosis of HIV encephalopathy in infants and children, a 32-point (2 SD) confirmed drop in cognitive (MDI) or motor (PDI) scores on the BSID may be a useful indicator of central nervous system progression. In addition, the occurrence of MDI or PDI scores 2 or more SD below the age-specific mean (<69) may be an even more useful indicator, but has the potential to be confounded by effects of premature birth or maternal educational attainment. Finally, 16-point (1 SD) confirmed drops in MDI or PDI scores, although statistically more frequent in HIV-infected subjects compared with HIV-uninfected subjects, lack specificity for HIV disease and are additionally confounded by the presence of other covariates, so that use of this particular outcome is probably not appropriate in the application of current diagnostic criteria for encephalopathy. The high frequency of 16-point confirmed drops in scores among HIV-exposed but HIV-uninfected infants and children must be viewed in the context of the socioeconomic stressors that characterize the epidemiology of HIV infection in the United States, the multiple demands placed on families caring for 1 or more family members with life-threatening illness, and the frequent separations of child and parent because of illness. In attempting to explain the wide variability in individual developmental patterns in infants born to women with HIV-1 infection, the possibility of early encephalopathy, as evidenced by a deceleration of neurodevelopmental growth, must be weighed in the context of intervening environmental stresses and life events.

In contrast with findings of others who studied children exposed to drugs but not to HIV,[19–21] maternal use of illicit drugs during pregnancy did not seem to play an important role in the genesis of deficits and declines in cognitive or motor performance of infants exposed to drugs and born to mothers with HIV infection.

Although cross-sectional analysis of mean scores at different ages may have revealed differences between infants with and without prenatal drug exposure, the relative severity of the neurodevelopmental outcome events examined in this study and the observed powerful effects of HIV infection and other covariates, such as premature birth, may have diminished the ability to detect the effects of drug exposure.

CONCLUSION

Careful longitudinal monitoring of developmental growth is a necessary component of comprehensive medical care for children with HIV disease.[22] One of the primary challenges in the care of infants and children infected by HIV is the early and accurate diagnosis of encephalopathy. BSID cognitive or motor scores 2 SD or more below the mean (<69) likely are an important early marker of severe HIV-related central nervous system disease. Likewise, 32-point (2 SD) confirmed drops in MDI or PDI seem to be clear indicators of early HIV-related central nervous system compromise. An even greater challenge is the prompt and reliable identification of infants or children at high risk for central nervous system disease progression, before the onset of encephalopathy, to initiate early, aggressive initiation of specific antiretroviral treatment in hopes of preventing devastating effects of HIV on the developing brain. The association of abnormal cognitive and motor developmental outcomes, defined by the present investigation with declines in immune function, quantitative measures of viral load, and progression of disease in other organ systems, including the incidence and timing of deceleration of brain growth and development of cortical atrophy, merits further study. Other quantitative and qualitative measures of developmental status and changes also warrant investigation to assess their utility as early indicators of risk for HIV-related central nervous system impairment in infants with congenital or perinatal HIV infection.

ACKNOWLEDGMENTS

This study was supported by the National Institute of Allergy and Infectious Diseases and the National Institute of Child Health and Human Development, National Institutes of Health. It is also part of the Women and Infants Transmission Study.

Principal investigators, study coordinators, program officers, and funding include: Clemente Diaz, Edna Pacheco-Acosta (University of Puerto Rico, San Juan, PR; Grant U01 AI34858); Ruth Tuomala, Ellen Cooper, Donna Mesthene (Boston/Worcester site, Boston, MA; Grant UO1 AI 34856); Jane Pitt, Alice Higgins (Columbia Presbyterian Hospital, New York, NY; Grant UO1 AI 34842); Sheldon Landesman, Hermann Mendez, Gail Moroso (State University of New York, Brooklyn, NY; Grants HD-8-2913 and R0–1-HD-25714); Kenneth Rich, Delmyra Turpin (University of Illinois at Chicago, Chicago, IL; Grant U01 AI 34841); William Shearer, Celine Hanson, Norma Cooper (Baylor College of Medicine, Houston, TX; Grant UO1 AI 34840); Mary Glenn Fowler (National Institute of Allergy and Infectious Disease, Bethesda, MD); Vincent Smeriglio (National Institute on Drug Abuse, Rockville, MD); and Sonja McKinlay, Leslie Kalish, Susan Ellis (New England Research Institutes, Watertown, MA; Grant N01 AI 35161).

We thank the investigators, study staffs, and especially the

families who have participated in the Women and Infants Transmission Study.

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DOI: 10.1542/peds.106.2.e25

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