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CD4/CD8 T-cell ratio predicts HIV infection in infants: The National Heart, Lung, and Blood Institute P²C² Study

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Abstract

Background—In resource-poor regions of the world, HIV virologic testing is not available.

Objective—We sought to evaluate the diagnostic usefulness of the CD4/CD8 T-cell ratio in predicting HIV infection in infants.

Methods—Data from the 3- and 9-month visits for non-breastfed infants born to HIV-infected mothers enrolled (1990–1994) in the Pediatric Pulmonary and Cardiac Complications of Vertically Transmitted HIV Infection Study (mother-to-child transmission of HIV, 17%) were analyzed. Data from the 3-month visit for infants enrolled (1985–1996) in the Perinatal AIDS Collaborative Transmission Study (mother-to-child transmission of HIV, 18%) were used for validation.

Results—At 3 months of age, data were available on 79 HIV-infected and 409 uninfected non-breast-fed infants in the Pediatric Pulmonary and Cardiac Complications of Vertically Transmitted HIV Infection Study. The area under the curve (AUC) of the receiver operating characteristic curve at 3 months was higher for the CD4/CD8 ratio compared with the CD4⁺ T-cell count (AUC, 0.83 and 0.75; $P = .03$). The mean CD4/CD8 ratio at the 3-month visit was 1.7 for HIV-infected infants and 3.0 for uninfected infants. A CD4/CD8 ratio of 2.4 at 3 months of age was almost 2.5 times more likely to occur in an HIV-infected infant compared with an uninfected infant (test

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sensitivity, 81%; posttest probability of HIV, 33%). Model performance in the Centers for Disease Control and Prevention Perinatal AIDS Collaborative Transmission Study validation test (224 HIV-infected and 1015 uninfected 3-month-old infants) was equally good (AUC, 0.78 for CD4/CD8 ratio).

Conclusion—The CD4/CD8 T-cell ratio is a more sensitive predictor of HIV infection in infants than the CD4⁺ T-cell count.

Clinical implications—The CD4/CD8 T-cell ratio can be used with caution to predict HIV infection in children.

Keywords

CD4/CD8 T-cell ratio; mother-to-child transmission of HIV; HIV infection

Because early treatment intervention can dramatically alter the course of disease in HIV-infected infants, early diagnosis of HIV infection is critically important for infants born to HIV-infected women.^{1,2} Although specific diagnosis of HIV infection requires virologic assays, such as DNA PCR,³ these tests are not available in many parts of the world, and simpler alternative surrogate tests are being investigated. Immunologic assessment of CD4⁺ T cells often is more readily available than virologic assays. CD4⁺ T-cell depletion is a hallmark of HIV infection, and a significant difference in CD4⁺ T-cell counts between infected and uninfected infants has been reported in early infancy.^{4,5} However, infants normally have high CD4⁺ T-cell counts at birth, and because most mother-to-child transmission (MTCT) of HIV occurs around the time of birth, the CD4⁺T-cell counts of HIV-infected infants are equivalent to those of HIV-uninfected infants.⁶ HIV also influences CD8⁺ T cells, causing immune activation and expansion of this cell population.⁷ Establishing the diagnosis of HIV infection by using a surrogate assay, such as CD4/CD8 T-cell ratio, could allow early identification of HIV-infected infants, prompting timely treatment and thus a favorable modification of the disease course. A prior study conducted in sub-Saharan Africa evaluated CD4/CD8 T-cell ratios in infants in whom virologic diagnosis of infection was established by means of PCR and found a concordance between the two.⁸ Also, an analysis of the CD4/CD8 ratio as a predictor of HIV infection in North American infants has been suggested.⁹ Our objectives were to confirm these observations by using the National Institutes of Health's National Heart, Lung, and Blood Institute Pediatric Pulmonary and Cardiac Complications of Vertically Transmitted HIV (P²C²) Study database to evaluate the utility of CD4/CD8 T-cell ratio for the diagnosis of HIV infection among HIV-exposed infants. In addition, we validated our methods of analysis by testing them in the Centers for Disease Control and Prevention Perinatal AIDS Collaborative Transmission Study (PACTS). A preliminary report of our findings has been presented at the Federation of Clinical Immunology Societies meeting on June 8, 2007.¹⁰

METHODS

Study populations

The P²C² Study collected clinical and laboratory data from a birth cohort of 600 children born to HIV-infected women who were enrolled at birth or by 28 days of life beginning in

1990 and followed prospectively for up to 6 years in 5 centers located in Boston, Houston, New York (2 centers), and Los Angeles.¹¹ Breast-feeding was not recommended, and study visits occurred at birth and at 3, 9, 15, 21, and 30 months of life. HIV infection was determined by means of HIV culture. Overall, there were 93 HIV-infected children, 463 HIV-uninfected children, and 44 children of indeterminate HIV infection status, and the rate of MTCT of HIV was 17%. The final assessment of the 600 patients was made at 30 months after the last infant was born. None of the 44 indeterminate children had remained in the study, 9 had died, and the remaining 35 were lost to follow-up.¹² The PACTS database used for validation purposes was derived from 1454 children born to HIV-infected women from 1985 through 1996 in 4 centers located in New York City; Newark, New Jersey; Baltimore, Maryland; and Atlanta, Georgia. The rate of MTCT of HIV was 18%.¹³ Both P²C² and PACTS protocols for human study were approved by local and central institutional review boards, and informed consent was obtained from parents.

Laboratory methods

The P²C² Study and the PACTS clinical sites used virologic tests and lymphocyte subset analysis recommended by the Pediatric AIDS Clinical Trial Group Quality Control Program.^{14,15} During study visits for the P²C² Study, anticoagulated blood specimens were obtained, and lymphocyte subset analysis was performed within 24 hours by using whole-blood lysis and commercially available antihuman CD-specific antibody conjugated to fluorescein isothiocyanate or phycoerythrin. For PACTS, CD4⁺ T-cell counts were obtained at birth and every 2 to 3 months of life throughout the study.

Statistical methods

Rates of decrease of CD4⁺ T-lymphocyte cell counts in the first year of life were obtained by using a mixed-effects model specifying that CD4⁺ T-lymphocyte counts follow a linear regression over time, with random intercept and slope for each infant. The same model was fit for the CD4/CD8 ratio.

Longitudinal profiles of CD4/CD8 ratio (Box-Cox transformation of ratios) up to 14 months of age for HIV-infected and HIV-uninfected infants were generated. The second-degree fractional polynomials¹⁶ were applied to obtain the best-fitting models with respect to age and CD4/CD8 ratio. Based on the methods of Royston,¹⁷ smoothed percentile curves of the CD4/CD8 ratio for age were estimated by using random-effects modeling.

Two approaches were used to evaluate the CD4/CD8 ratio and the CD4⁺ T-cell count as markers of HIV infection. First, the risk of HIV infection was modeled as a function of the CD4/CD8 ratio (and separately using the CD4⁺ cell count) by using logistic regression performed separately for the 3- and 9-month visit data. Second, marker performance was summarized with classification performance measures, such as sensitivity, specificity, predictive values, receiver operating characteristic (ROC) curves, and likelihood ratios and the corresponding posttest probabilities. Interpretation of likelihood ratios followed the guidelines provided by Jaeschke et al.¹⁸ ROC curves were constructed for each marker at 3 study visits: birth (0–44 days), 3 months (45–150 days), and 9 months (151–365 days). The areas under the curve (AUCs) for the 2 correlated ROC curves were compared at each age

interval by using a nonparametric approach described by DeLong et al.¹⁹ The validation data set included data from the 3-month visit for infants enrolled in the PACTS cohort (45–150 days).

The same statistical methods described in the previous paragraph were used for the validation data set to compare the AUCs for the 2 markers and to summarize the diagnostic accuracy of the CD4/CD8 ratio as a predictor of HIV infection. Calibration evaluates the degree of correspondence between the model's estimated probabilities of HIV infection risk for the P²C² data compared with the PACTS validation data set. To assess model calibration after initial review, the CD4/CD8 ratio data from the P²C² Study were divided into 7 equivalent categories (<0.5, 0.5–1.0, 1.0–1.5, 1.5–2.0, 2.0–2.5, 2.5–3.0, and >3.0), and the logistic regression refit provided HIV risk estimates and 95% CIs for each of the 7 categories. The observed risk estimate from the validation data for each CD4/CD8 category was compared with the P²C² estimates to determine whether the observed results fell within the CIs of the values predicted from the P²C² HIV group.

RESULTS

Derivation of the study populations

Of 600 P²C² subjects, data from 79 HIV-infected infants and 409 HIV-uninfected non-breast-fed infants at the 3-month visit were available for analysis. Similarly, data from 78 HIV-infected infants and 372 HIV-uninfected infants at the 9-month visit were available. Of the 1454 PACTS subjects, data from 224 HIV-infected infants and 1015 HIV-uninfected infants at the 3-month visit were available.

Performance of CD4/CD8 ratio in predicting HIV infection

The mean CD4/CD8 ratios at the 3- and 9-month visits were 1.7 and 1.1 for HIV-infected infants and 3.0 and 2.6 for HIV-uninfected infants, respectively. Diagnostic accuracy statistics for the CD4/CD8 ratio at the 3- and 9-month visits can be found in Tables I and II. At the 3-month visit, a CD4/CD8 ratio of 2.4 was almost 2.5 times (95% CI for the likelihood ratio of a positive test, 2.1–2.9) more likely to occur in an HIV-infected infant compared with an HIV-uninfected infant (test sensitivity, 81%; post-test probability of HIV, 33%; Table I). At the 9-month visit, a CD4/CD8 ratio of 1.8 was almost 3.5 times (95% CI for the likelihood ratio, 2.9–4.3) more likely to occur in an HIV-infected infant compared with an HIV-uninfected infant (test sensitivity, 83%; posttest probability of HIV, 42%; Table II). According to the guidelines reported by Jaeschke et al,¹⁸ a likelihood ratio of 2 to 5 is suggestive of a small but sometimes important change from pretest to posttest probability. For an infant 3 months of age with a CD4/CD8 ratio of 2.4 (1 SD greater than the mean of 1.7 for P²C² HIV-infected infants) whose risk of HIV infection is in the equivocal range, a likelihood ratio of 2.5 is suggestive of a potentially important increase in the probability of HIV infection.

Clinical decision criteria are also formulated in terms of risk. We defined the risk of HIV infection between 10% and 30% (CD4/CD8, >1.70 and <2.62) as being in the indeterminate range. Based on this rule, 18% of infants at the 3-month visit were HIV infected (risk,

30%; CD4/CD8, 1.70), 50% of infants were HIV uninfected (risk, 10%; CD4/CD8, 2.62), and 32% of infants were indeterminate. By the 9-month visit, 21% of infants were HIV infected (risk, 30%; CD4/CD8, 1.40), 62% of infants were HIV uninfected (risk, 10%; CD4/CD8, 1.94), and 17% of infants were indeterminate.

Comparison of CD4⁺ T-cell count versus CD4/CD8 ratio as a predictor of HIV infection

The average rate of decrease of CD4⁺ T-cell counts during the first year of life (mean \pm SE) was 144 ± 19 cells/ μ L per month in the HIV-infected group versus 55 ± 9 cells/ μ L per month in the HIV-uninfected group ($P < .001$; Fig 1, A). Similarly, the average rate of decrease of the CD4/CD8 ratio in the first year of life was greater in HIV-infected infants (0.134 ± 0.016) compared with that seen in the HIV-uninfected infants (0.052 ± 0.007 , $P < .001$; Fig 1, B). The P value between HIV-positive and HIV-negative infants' values at all time points (1 week and 1, 3, 6, 9, and 12 months) is less than .001 for CD4 T-cell count and CD4/CD8 ratio (Fig 1).

Fig 2 provides longitudinal profiles of the CD4/CD8 ratio up to 14 months of age for HIV-infected and HIV-uninfected infants. From birth to the 3-month visit, the CD4/CD8 ratio decreased to about 1.5 (50th percentile) for the HIV-infected infants. However, the decrease was much less for HIV-uninfected infants (50th percentile = 2.8). By the 9-month visit, the CD4/CD8 ratio decreased to about 1.1 for the HIV-infected infants (50th percentile; ie, less than the 50th percentile for the HIV-uninfected infants).

The CD4/CD8 ratio performed better than the CD4⁺ T-cell count as an early diagnostic marker of HIV infection (data not shown). The AUC estimate at the 3-month visit was higher for the CD4/CD8 ratio compared with the CD4⁺ T-cell count (AUC, 0.83 and 0.75, $P = .03$; Fig 3, A). By the 9-month visit, the AUC estimate of 0.91 for the CD4/CD8 ratio exceeded the AUC estimate of 0.83 for the CD4⁺ T-cell count ($P < .0001$; Fig 3, B). The AUC estimate at the 3-month visit for the CD4/CD8 ratio reflects the proportion (0.83) of infant pairs for which the logistic regression model assigned a higher probability to an infant who will be HIV infected than to an infant who will not be HIV infected.²⁰ The estimate of the AUC increased to 0.87 after adjusting for weight (weight z score at the 3-month visit) and hemoglobin value (at the 6-month visit) in addition to the CD4/CD8 ratio.

Validation of method analysis with PACTS data

Table III and Fig 4 contain the validation-of-method data by the PACTS database. Diagnostic accuracy statistics were similar for the P²C² Study and PACTS (Table III). For PACTS, the AUC estimate for the CD4/CD8 ratio was 0.78 (95% CI, 0.74–0.81; data not shown). Fig 4 indicates that the observed risk of HIV infection based on the PACTS validation data tracks closely to the predicted HIV risk based on the P²C² Study data.

DISCUSSION

In resource-replete countries the diagnosis of HIV infection in infants is rapid, accurate, and definitive, thus enabling the clinician to have confidence in relating infants' HIV infection status to their parents. The authoritative pronouncements of HIV infection in very young children have been brought about by the application of molecular virology to clinical

medicine, which has produced the HIV DNA PCR or similar assays. Such assays, however, are not immediately available in many parts of the resource-limited countries, thus leading to a search for alternative technologies. In some settings access to determination of peripheral blood CD4⁺ T-cell and CD8⁺ T-cell counts/percentages is available, thus prompting a reinvestigation of the use of these lymphocyte subset values to assess HIV infection in children. Indeed, low-cost methodology can be used in small laboratories and rural villages to assess CD4⁺ and CD8⁺ T-cell counts.²¹ Previously, analysis of the CD4⁺ or CD3⁺ T-cell counts has been proposed either as an alternate measure of diagnosis or prediction of HIV disease progression. Although it is possible to wait until maternal anti-HIV antibodies (basis for immunoassay and Western blotting) disappear in infants (ie, 12–18 months of age), an earlier diagnosis of HIV infection is much preferred. Mofenson et al²² have proposed using total lymphocyte cell count and serum albumin concentration to predict mortality in children in resource-poor settings.

Our analysis of the CD4/CD8 T-cell ratio as a surrogate method of determining HIV infection in a large US cohort of prospectively followed HIV-infected children (P²C² Study) has led to some interesting results. The confirmation of these findings with a second large US cohort of HIV-infected children (PACTS) has suggested this alternative method of assessing HIV infection in children as a reliable and simple diagnostic tool. As early as 3 months of age, it is possible to assess with some certainty the state of HIV infection in the P²C² Study cohort by using the CD4/CD8 ratio. This assessment can be expressed based on the strong association of the CD4/CD8 T-cell ratio with the risk of HIV infection and by summarizing the CD4/CD8 T-cell performance with classification performance measures, such as sensitivity, specificity, likelihood ratios, and ROC curves. Setting the indeterminate HIV risk range at a modest level actually observed with P²C² patients (ie, 10% to 30%) results in the ability to diagnose HIV infection in 18% of infants and rule out infection at 3 months of age in 50% of infants, leaving 32% of infants in the indeterminate category. By 9 months of age, this cohort would have 21% HIV-infected, 62% uninfected, and 17% indeterminate infants. Thus a treatment decision (ie, treat vs no treatment) for a population with approximately 20% HIV prevalence (treat or not treat) for 3-month old infants born to HIV-infected women could be made reasonably in two thirds of cases.

Because the prevalence of HIV is approximately 17% in the population studied, a treatment decision is straightforward if the calculated risk of HIV infection is close to 0 or 1. We are assuming that greater than 30% risk of HIV infection is sufficiently high to recommend treatment and that a risk of less than 10% is sufficiently low to decide against treatment. If the calculated risk is in the equivocal or indeterminate range, it is not helpful. Treatment recommendations are most difficult for infants whose risks are calculated in the range of 10% to 30%. A risk model will be most useful for individual decision making if calculated risks of HIV tend to exceed 30% or are less than 10%. Other thresholds might be chosen for defining low and high risk of HIV infection.

Table IV indicates that HIV risk decreases as the positive diagnostic likelihood ratio (DLR⁺) decreases and as sensitivity increases. Treatment of a 3-month-old infant with a CD4/CD8 T-cell ratio of 1.0 has a very high HIV risk (0.54) and DLR⁺ (32.3). However, because the sensitivity (0.32) is low, many HIV-positive infants would not be treated. Not treating

infants with a CD4/CD8 ratio of 3.00 is appealing for both risk (0.06) and sensitivity (0.92). However, the DLR^+ is somewhat low ($1.7 < 2$).

Treatment decisions based solely on risk (10% and 30% are the threshold values) and DLR^+ suggest treatment when the CD4/CD8 T-cell ratio is 1.8 or less. However, because the sensitivity (<0.61) is low, many HIV-infected infants would not be treated. If the sensitivity is increased to at least 80%, then treating a 3-month infant with a CD4/CD8 ratio of 2.4 to 2.6 or less might be reasonable. Even though the risk (10% to 13%) is in the indecisive region, it, at least, is not suggestive against treatment. If the CD4/CD8 T-cell ratio is as high as 2.80, the risk is low ($<8\%$) and therefore suggestive against treatment. Appendix E1 in the Online Repository (available at www.jacionline.org) contains additional illustrations of the calculations of risk of infection by using a CD4/CD8 ratio of 1.00, 2.00, and 3.00.

These methods of calculating the risk of infection are obviously much less accurate than using the HIV DNA PCR assay, in which sensitivity and specificity are near 100%. Nevertheless, in circumstances in which testing such as DNA PCR assays cannot be performed and $CD4^+$ and $CD8^+$ T-cell measurements are available, decisions to treat or not treat high-risk infants on the basis of the CD4/CD8 ratio reasonably can be made in 68% of infants at 3 months and 83% of infants at 9 months of age. Of course this calculation assumes the infant will not be breast-fed, which adds a risk factor of infection of up to 15%.²³ Although we did not study HIV infection through breast milk in the P²C² Study, it is possible that our findings would be applicable to children infected through that route of transmission. Another caveat to our findings is that CD4/CD8 ratios might be altered in other congenital infections, such as cytomegalovirus (CMV) infection, although the incidence of congenital CMV infection in the newborn population in resource-poor countries (estimated at 1%) would be low compared with that of perinatal HIV infection.²⁴

We conclude that in circumstances in which HIV DNA PCR testing is not available, assessment of $CD4^+$ and $CD8^+$ T-cell values will permit the calculation of CD4/CD8 ratios that are helpful in making treatment decisions in a majority of infants at 3 to 9 months of age.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations used

AUC	Area under the curve
DLR	Diagnostic likelihood ratio
MTCT	Mother-to-child transmission
PACTS	Perinatal AIDS Collaborative Transmission Study
P²C² Study	Pediatric Pulmonary and Cardiac Complications of Vertically Transmitted HIV Infection Study
ROC	Receiver operating characteristic

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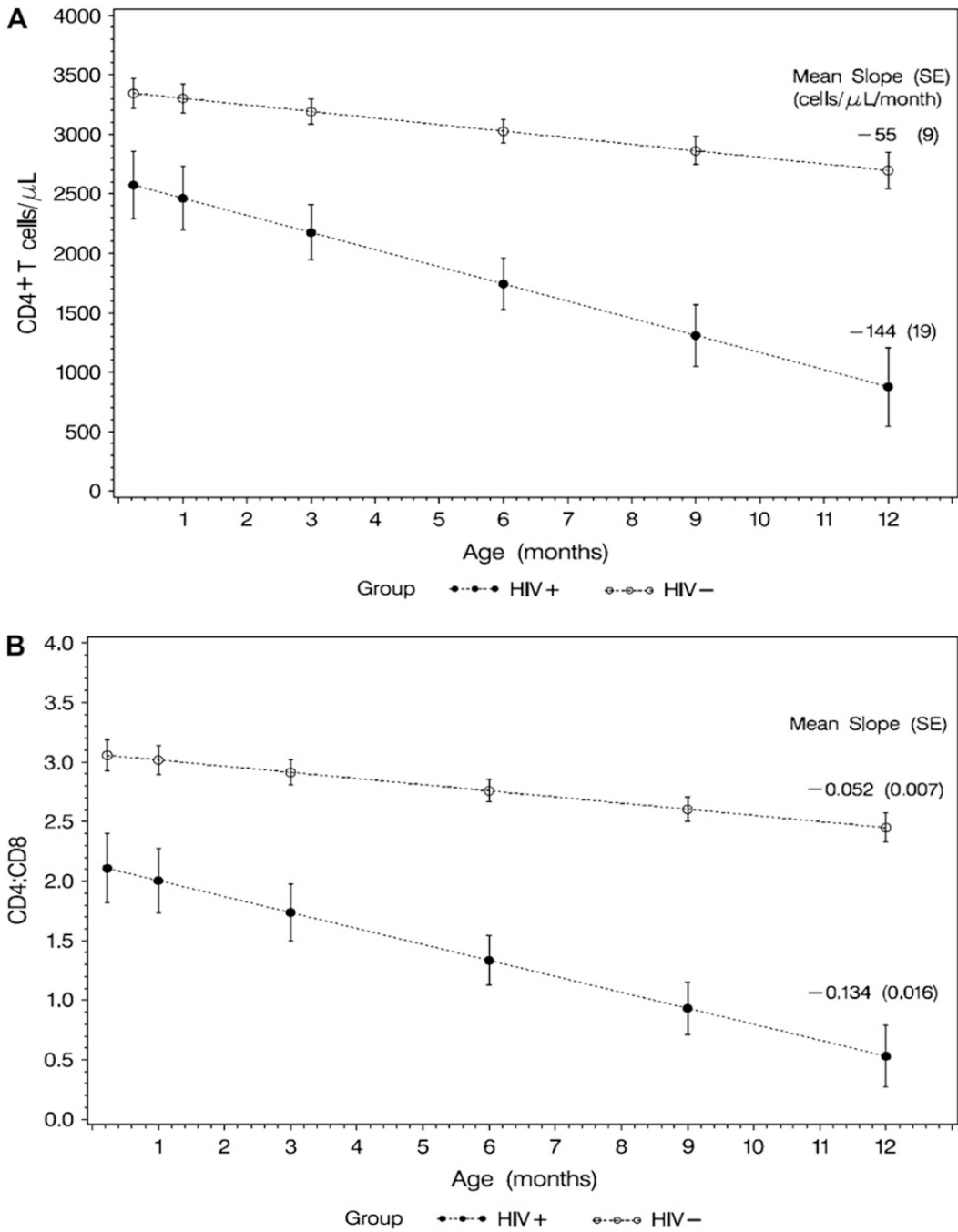


Figure 1. Mean CD4 cell count versus age (A) and mean CD4/CD8 ratio versus age (B) in infants born to HIV-infected mothers. In Fig 1, A, the mean CD4 cell count (in cells per microliter) at 1 week and 1, 3, 6, 9, and 12 months of age and the average rate of decrease of CD4 T-cell counts in the first year of life for HIV-infected infants and HIV-uninfected infants is shown. In Fig 1, B, similar data for CD4/CD8 ratio by HIV infection status are shown. Rates of CD4 T-cell count decrease and CD4/CD8 ratio decrease were significantly greater in

HIV-infected infants compared with those seen in HIV-uninfected infants. *Vertical bars, 95% CI.*

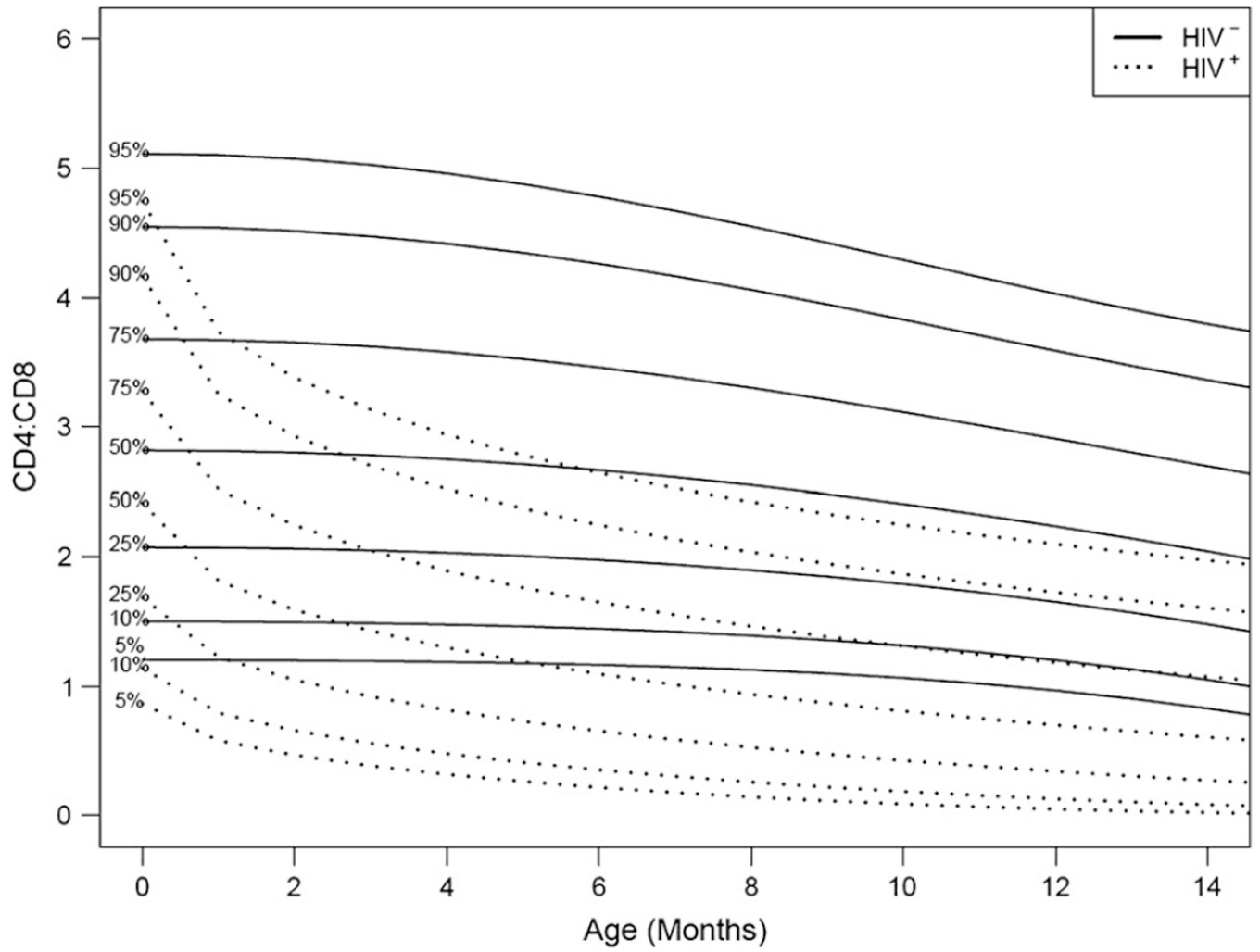


Figure 2. Reference percentile curves for CD4/CD8 ratio by HIV status in the first 14 months of life.

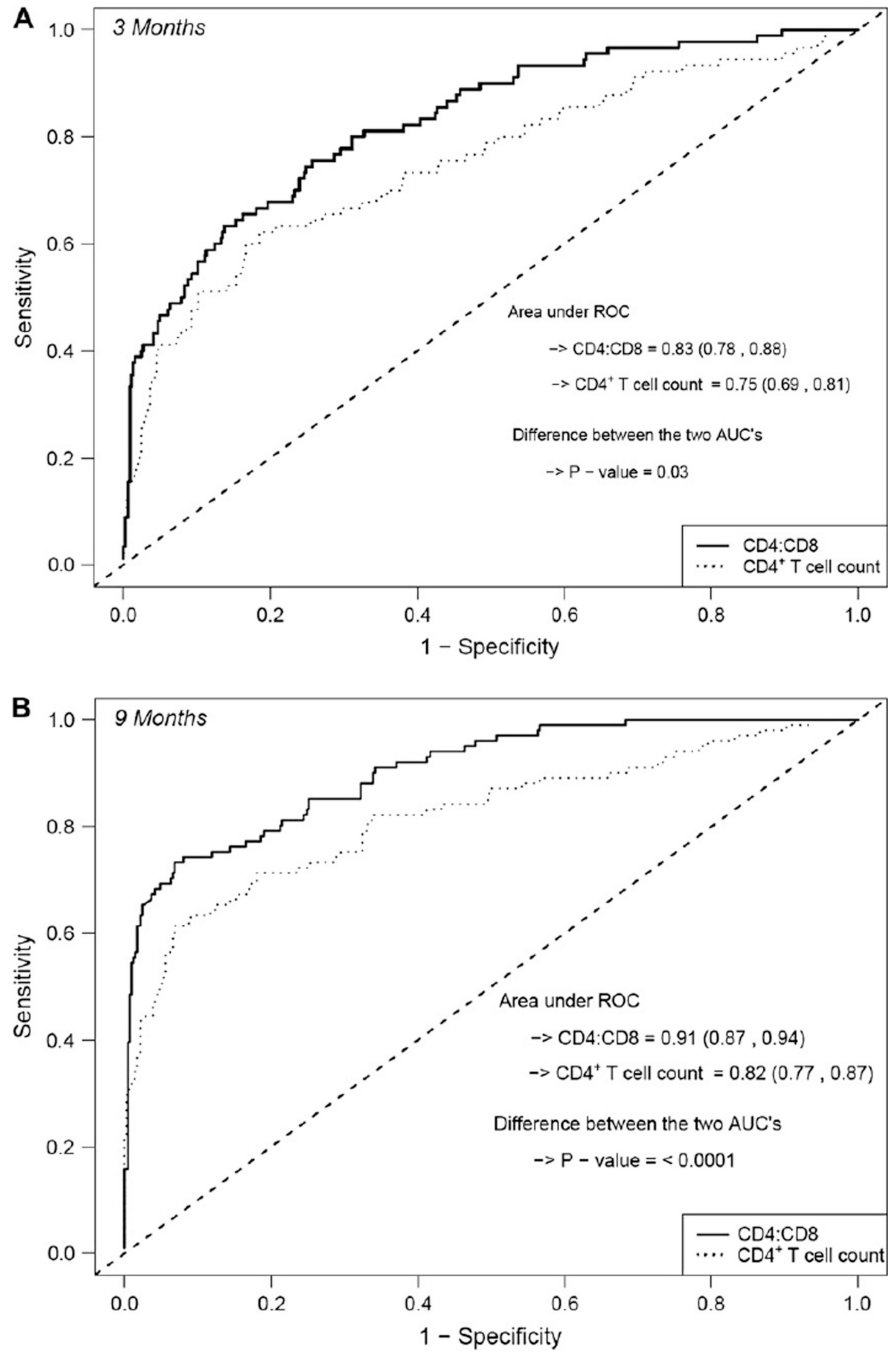


Figure 3. ROC curves based on the P²C² data for CD4 T-cell count and CD4/CD8 ratio. **A**, Three-month study visit. **B**, Nine-month study visit.

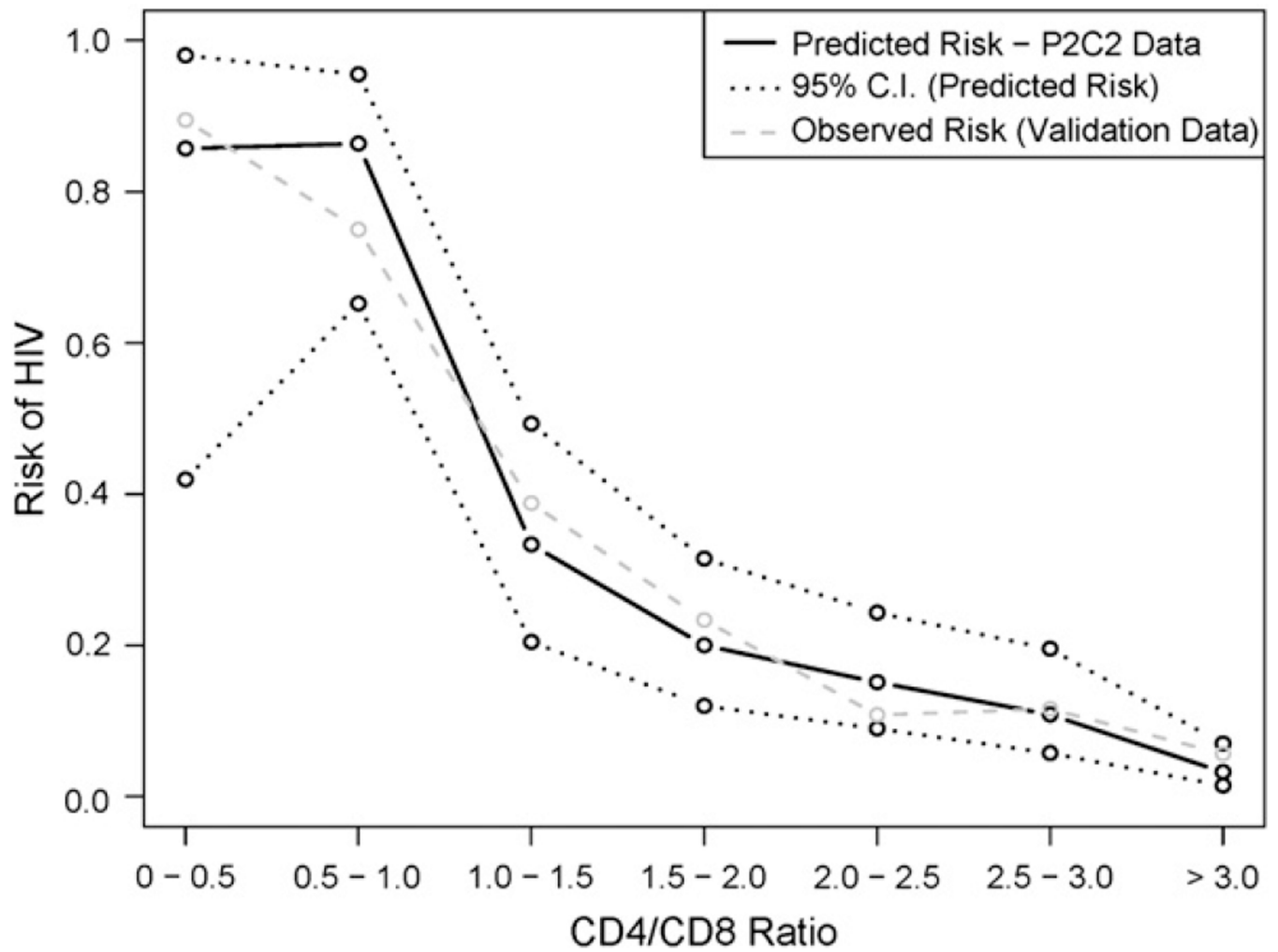


Figure 4.
 Predicted risk of HIV infection by CD4/CD8 ratio: P²C² Study data versus validation (PACTS) data.

TABLE I

Diagnostic accuracy of the CD4/CD8 ratio in the P²C² HIV cohort at the 3-month study visit (45–150 days; n = 79 HIV-infected and n = 409 HIV-uninfected subjects)

CD4/CD8 ratio	HIV-positive group No.*	HIV-negative group No.*	Diagnostic accuracy measures							Posttest probability (% [95% CI])
			SE	SP	PPV	NPV	DLR ⁺ (95% CI)	DLR ⁻ (95% CI)		
1.00	25	4	0.32	0.99	0.86	0.88	32.3 (11.6–90.2)	0.7 (0.6–0.8)	87 (84–89)	
1.20	30	8	0.38	0.98	0.79	0.89	19.4 (9.2–40.7)	0.6 (0.5–0.8)	80 (76–83)	
1.40	36	21	0.46	0.95	0.63	0.90	8.9 (5.5–14.4)	0.6 (0.5–0.7)	65 (59–69)	
1.60	41	37	0.52	0.91	0.53	0.91	5.7 (4.0–8.3)	0.5 (0.4–0.7)	54 (48–59)	
1.80	48	57	0.61	0.86	0.46	0.92	4.4 (3.2–5.9)	0.5 (0.4–0.6)	47 (42–52)	
2.00	51	82	0.65	0.80	0.38	0.92	3.2 (2.5–4.2)	0.4 (0.3–0.6)	40 (34–45)	
2.20	58	105	0.73	0.74	0.36	0.94	2.9 (2.3–3.5)	0.4 (0.3–0.5)	37 (32–42)	
2.40	64	135	0.81	0.67	0.32	0.95	2.5 (2.1–2.9)	0.3 (0.2–0.5)	33 (29–38)	
2.60	65	163	0.82	0.60	0.29	0.95	2.1 (1.8–2.4)	0.3 (0.2–0.5)	30 (25–34)	
2.80	71	202	0.90	0.51	0.26	0.96	1.8 (1.6–2.1)	0.2 (0.1–0.4)	27 (23–31)	
3.00	73	229	0.92	0.44	0.24	0.97	1.7 (1.5–1.8)	0.2 (0.1–0.4)	25 (21–29)	
Total [†]	79	409								

The pretest probability is 17% (95% CI, 14% to 20%).

SE, Sensitivity; SP, specificity; PPV, positive predictive value; NPV, negative predictive value; DLR⁺, diagnostic positive likelihood ratio; DLR⁻, diagnostic negative likelihood ratio.

* Number of infants having a CD4/CD8 ratio of less than the cutoff point within each HIV group.

[†] Total, Number of infants in this age interval within each HIV group.

TABLE II

Diagnostic accuracy of the CD4/CD8 ratio in the P²C² HIV cohort at the 9-month age interval (151–365 days; n = 78 HIV-positive and n = 372 HIV-negative patients)

CD4/CD8 ratio	HIV-positive group No.*	HIV-negative group No.*	SE	SP	PPV	NPV	Diagnostic accuracy measures			Posttest probability (% [95% CI])
							DLR ⁺ (95% CI)	DLR ⁻ (95% CI)	DLR ⁻ (95% CI)	
1.00	50	10	0.64	0.97	0.83	0.93	23.8 (12.7–44.9)	0.4 (0.3–0.5)	0.4 (0.3–0.5)	83 (80–86)
1.20	55	22	0.71	0.94	0.71	0.94	11.9 (7.8–18.3)	0.3 (0.2–0.4)	0.3 (0.2–0.4)	71 (66–75)
1.40	56	37	0.72	0.90	0.60	0.94	7.2 (5.2–10.1)	0.3 (0.2–0.5)	0.3 (0.2–0.5)	60 (54–64)
1.60	58	56	0.74	0.85	0.51	0.94	4.9 (3.8–6.5)	0.3 (0.2–0.4)	0.3 (0.2–0.4)	50 (45–55)
1.80	65	88	0.83	0.76	0.42	0.96	3.5 (2.9–4.3)	0.2 (0.1–0.4)	0.2 (0.1–0.4)	42 (36–47)
2.00	68	115	0.87	0.69	0.37	0.96	2.8 (2.4–3.4)	0.2 (0.1–0.3)	0.2 (0.1–0.3)	37 (31–41)
2.20	71	145	0.91	0.61	0.33	0.97	2.3 (2.0–2.7)	0.2 (0.1–0.3)	0.2 (0.1–0.3)	32 (28–37)
2.40	74	175	0.95	0.53	0.30	0.98	2.0 (1.8–2.3)	0.1 (0.0–0.3)	0.1 (0.0–0.3)	29 (25–34)
2.60	77	207	0.99	0.44	0.27	0.99	1.8 (1.6–2.0)	0.03 (0.0–0.2)	0.03 (0.0–0.2)	27 (22–31)
Total [†]	78	372								

The pretest probability is 17% (95% CI, 14% to 20%).

SE, Sensitivity; SP, specificity; PPV, positive predictive value; NPV, negative predictive value; DLR⁺, diagnostic positive likelihood ratio; DLR⁻, diagnostic negative likelihood ratio.

* Number of infants having a CD4/CD8 ratio of less than the cutoff point within each HIV group.

[†]Total, Number of infants in this age interval within each HIV group.

TABLE III

Diagnostic accuracy of the CD4/CD8 ratio in the P²C² HIV and PACTS (validation data) cohorts at 3 months of age

CD4/CD8 ratio	Percentage of HIV-positive subjects below cutoff point	Percentage of HIV-negative subjects below cutoff point	Sensitivity (%)	Specificity (%)	DLR ⁺	DLR ⁻	Posttest probability* (%)	Posttest probability [†] (%)
1.00	86 (79)	14 (21)	32 (26)	99 (98)	32.3 (16.7)	0.7 (0.8)	87 (79)	12 (14)
1.20	79 (68)	21 (32)	38 (33)	98 (97)	19.4 (9.4)	0.6 (0.7)	80 (68)	11 (13)
1.40	63 (57)	37 (43)	46 (41)	95 (93)	8.9 (6.1)	0.6 (0.6)	65 (57)	11 (12)
1.60	53 (51)	47 (49)	52 (51)	91 (89)	5.7 (4.7)	0.5 (0.6)	54 (51)	10 (11)
1.80	46 (42)	54 (58)	61 (57)	86 (83)	4.4 (3.4)	0.5 (0.5)	47 (42)	9 (10)
2.00	38 (38)	62 (62)	65 (68)	80 (76)	3.2 (2.8)	0.4 (0.4)	40 (38)	8 (8)
2.20	36 (33)	64 (67)	73 (74)	74 (67)	2.9 (2.2)	0.4 (0.4)	37 (33)	7 (8)
2.40	32 (29)	68 (71)	81 (79)	67 (58)	2.5 (1.9)	0.3 (0.4)	33 (30)	5 (7)
2.60	29 (27)	71 (73)	82 (82)	60 (51)	2.1 (1.6)	0.3 (0.4)	30 (27)	6 (7)
2.80	26 (25)	74 (75)	90 (86)	51 (44)	1.8 (1.5)	0.2 (0.3)	27 (25)	4 (7)
3.00	24 (24)	76 (76)	92 (90)	44 (38)	1.7 (1.4)	0.2 (0.3)	25 (24)	3 (6)

The pretest probabilities for P²C² data and validation data sets are 17% and 18%, respectively. For each column, the first number is based on the P²C² data set, and the number within parentheses is calculated from the validation data set (PACTS).

* Posttest probability for a positive test result.

[†] Posttest probability for a negative test result.

TABLE IV

Linking risk estimates and performance measures

CD4/CD8 ratio	Risk (%)	DLR ⁺	Sensitivity	Specificity
Summary of P ² C ² data (3 mo):				
1.00	54	32.3	0.32	0.99
1.20	46	19.4	0.38	0.98
1.40	39	8.9	0.46	0.95
1.60	33	5.7	0.52	0.91
1.80	27	4.4	0.61	0.86
2.00	21	3.2	0.65	0.80
2.20	17	2.9	0.73	0.74
2.40	13	2.5	0.81	0.67
2.60	10	2.1	0.82	0.60
2.80	8	1.8	0.90	0.51
3.00	6	1.7	0.92	0.44
For 3-mo age window:				
<1.80	>30% (approx.)	>4.4	<0.61	>0.86
1.80–2.60	10% to 30%	2.1–4.4	0.61–0.82	0.60–0.86
2.60	<10%	<2.1	>0.82	<0.60