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T-cell activation and neurodevelopmental outcomes in perinatally HIV-infected children

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Abstract

Objective—To evaluate baseline T-cell activation and neurodevelopmental outcomes over time in a cohort of perinatally HIV-infected (PHIV-infected) children with severe disease.

Design—Pediatric AIDS Clinical Trials Group protocol 366 (PACTG 366) was a partially randomized, open-label, multicenter 96-week antiretroviral treatment-algorithm study. Neurodevelopmental status, measured by age-dependent evaluations (Bayley scales of infant development-II; Wechsler preschool and primary scale of intelligence-revised; Wechsler intelligence scale for children-III), was a secondary outcome.

Methods—Linear mixed models were used to assess the baseline and follow-up neurodevelopmental outcomes in relation to immune activation, measured by CD38 and human leukocyte antigen (HLA) DR expression on peripheral $CD4^+$ and $CD8^+$ T cells at study baseline. Models were adjusted for age, sex, race/ethnicity, baseline viral load, baseline CD4%, cytomegalovirus (CMV) infection status at entry, study treatment arms, central nervous system penetrance score of antiretroviral regimen at entry, and viral load response 16 weeks postentry.

Results—Among 126 PACTG 366 enrollees who were at least 1 year old and had both immune activation and age-appropriate neurodevelopmental assessments at baseline, 80 (63%) were black non-Hispanic, 71 (56%) males, 122 (97%) were on antiretrovirals, and 45 (36%) were in Centers for Disease Control and Prevention (CDC) disease category C at entry. $CD4^+CD38^+HLADR^+$%, $CD4^+CD38^-HLADR^+$%, and $CD8^+CD38^+HLADR^+$% were positively associated with full-scale Intelligence Quotient scores (FSIQ) (slope =0.18, 0.70, and 0.15, respectively; P=0.02, 0.03, and 0.04, respectively). $CD4^+CD38^+HLADR^-$% was negatively associated with FSIQ (slope =−0.16, P=0.01).

Conclusion—Contrary to HIV-infected adults, in PHIV-infected children higher $CD4^+CD38^+HLADR^+$% may be associated with a neuroprotective effect and higher percentage of $CD4^+CD38^+$ but $HLADR^-$ T cells may be deleterious.

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Conflicts of interest

There are no conflicts of interest.

Keywords

HIV-associated central nervous system disease; immune activation; neurodevelopmental outcomes; pediatric neuro-AIDS; perinatally HIV-infected children

Introduction

With widespread use of HAART, severe forms of central nervous system (CNS) disease, such as dementia or encephalopathy [1–3], have become rare in perinatally HIV-infected (PHIV-infected) children in the United States. Yet, cognitive impairment, developmental delays, motor deficits, behavioral problems, and psychiatric diagnoses remain highly prevalent in PHIV-infected children and adolescents [4–9]. This suggests that factors other than HIV neurotoxicity, including host-related factors, may be involved in the pathogenesis of CNS disease [10,11]. Studies suggest significant relationships between HIV-associated CNS disease and systemic immune parameters including activation of T cells [12,13], excessive production of TNFα, and increased activation-induced lymphocyte apoptosis [1,2,14–17]. Mekmullica *et al.* [18] reported favorable association between $CD8^+HLADR^+$ less than 5% within the first 2 months and Bayley scales of infant development (BSID) scores within 30 months of age in a sample of PHIV-infected infants. Whereas frank encephalopathy with gait disturbances, spasticity, paresis, microcephaly, or ataxia are seen with severe immunosuppression, subtle neurodevelopmental abnormalities do occur at higher $CD4^+$ cell counts [2,14,19].

Given the continued clinical relevance of CNS-related outcomes, further examination of the role of immune activation in neurodevelopment of PHIV-infected children is needed, especially in the contemporary context of increasingly accessible HAART. We evaluated baseline T-cell activation and neurodevelopmental outcomes over time in a cohort of PHIV-infected children with severe disease. We hypothesized that T-cell activation will be inversely associated with neurodevelopmental outcomes.

Methods

Study design

Pediatric AIDS Clinical Trials Group Protocol 366 (PACTG 366) was a partially randomized, open-label, multicenter 96-week treatment algorithm study. Extensively pretreated children were required to be naive to at least two drugs, of which one was nevirapine (NVP), nelfinavir (NFV), or ritonavir (RTV). On the basis of prior antiretroviral class experience, they were assigned a four-drug antiretroviral regimen in which at least two agents were new and at least one of the new agents was NVP, NFV, or RTV. Enrollment occurred between May 1998 and January 2000 at 50 sites, after institutional review board approval and informed consent were obtained. The participants were cross-classified according to nonnucleoside reverse transcriptase inhibitor (NNRTI) and protease inhibitor exposure histories leading to four groups: group 1 was subdivided into group 1a and 1b in which participants were randomized to be switched to either two NNRTIs different from current therapy with NVP/NFV combination (group 1a) or two new NNRTIs with NVP/RTV combination (group 1b). Group 2 patients were switched to one new NNRTI with NVP with NFV and RTV. Groups 3 and 4 were switched to two new NNRTIs with NFV and RTV. More detail on the treatment algorithm and the participant antiretroviral treatment histories is available in the original publication [20]. The primary aim of PACTG 366 was to determine the proportion of participants in the study treatment arms that had a reduction in viral load following the switch and determine duration of the reduction. PACTG 366 enrolled PHIV-infected participants 6 months to 21 years old who, after receiving at least 8

weeks of unchanged continuous antiretroviral therapy, had on two consecutive clinical visits at least one of the following features of severe disease: plasma viral load more than 50 000 copies/ml; $CD4^+$ lymphocyte count less than 200 cells/μl, CD4% less than 15, or a 50% reduction in CD4% within 24 weeks of the start of the current antiretroviral therapy; growth failure (defined as weight for age <5th percentile and a history of failing to grow parallel to the 5th percentile, or 6-month weight-growth-velocity for age measurements below the 3rd percentile for two consecutive 6-month intervals); or CNS disease [defined as a head circumference <5th percentile, intelligence quotient (IQ) or developmental quotient <70, neuroimaging showing atrophy, calcifications, diffuse white matter lesions, ventriculomegaly, or a neurologic examination with abnormalities in tone, reflexes, or neurologic function].

We analyzed prospectively collected data from the PACTG 366 enrollees who were at least 1 year of age and had both age-appropriate neurodevelopmental evaluations and immune activation data at baseline.

Study procedures

All participants were examined monthly for the first 6 months and then every 2 months for the next 6 months. All had routine hematology, chemistry, urinalyses, T-cell subsets, and plasma viral load evaluations at preentry, entry, and at every study visit. The Pediatric ACTG Core Immunology and Core Virology Laboratories followed consensus protocols and participated in the ACTG quality assurance certification program.

Assessment of viral load and viral load response

Plasma viral load was measured as copies/milliliter from acid citrate dextrose-treated whole blood by the Roche Diagnostics Amplicor 1.0 PCR test kit (Roche Laboratories, Inc., Nutley, New Jersey, USA) with a lower limit of detection of 400 copies/ml in laboratories approved by the Division of AIDS (DAIDS) of the National Institute of Allergy and Infectious Diseases (NIAID). Data from preentry and entry and weeks 48 and 52 were averaged and represented as baseline and week 48 viral load, respectively. The viral load assessments were batched and run at the 16-week visit and were done in real-time thereafter. Early viral load response was assessed by averaging the $\log_{10}$ copies per milliliter at 12 and 16 weeks and comparing this value to the average of the preentry and baseline $\log_{10}$ viral load. Participants whose viral loads decreased to less than 400 copies/ml from baseline to average week 12/16 were considered to be viral load responders (VLRs); those who had viral load at least 400 copies/ml but who had a reduction in viral load of at least 0.75 $\log_{10}$ copies/ml were considered to be partial VLRs; and all others were considered to be non-VLRs and were taken off study after completing end-of-study evaluations within 8 weeks unless, after discussion with study chairs, were considered to show clinical benefits. VLRs and partial VLRs remained in the study to week 96/100.

After 16 weeks on study, participants who had viral load rebound, defined as an increase of at least 0.75 $\log_{10}$ above the viral load nadir and more than 10 000 copies/ml, were also taken off study after completing end-of-study evaluations unless clinical benefits were confirmed.

Assessment of $CD4^+$ and $CD8^+$ T-cell activation

Immunophenotyping of $CD4^+$ and $CD8^+$ T cells was performed at study weeks 0 (baseline), 12, 20, and 48 using three-color flow cytometry in laboratories that participated in the National Institutes of Health, NIAIDs, DAIDS Quality Assurance Program. Samples were shipped at room temperature by priority overnight express mail to the designated special immunology laboratory. The current analysis focuses on eight phenotypes:

$CD4^+CD38^+HLADR^-$, $CD4^+CD38^+$ $HLADR^+$, $CD4^+CD38^-HLADR^-$, $CD4^+CD38^-$ $HLADR^+$, $CD8^+CD38^+HLADR^-$, $CD8^+CD38^+$ $HLADR^+$, $CD8^+CD38^-HLADR^-$, and $CD8^+CD38^-HLADR^+$.

Assessment of neurodevelopmental status

Protocol neuropsychologists administered BSID-second edition (BSID-II) [21] to participants who were 6–36 months old, at preentry or entry, and at study weeks 8, 24, 48, and 96; Wechsler preschool and primary scale of intelligence-revised (WPPSI-R) [22] to participants older than 36 months, and up to 6 years of age; and Wechsler intelligence scale for children-third edition (WISC-III) [23] to participants between 6 and 18 years of age. Both Wechsler scales were administered at preentry or entry and at study weeks 24, 48 and 96.

Similar to the method previously used by Malee *et al.* [24], we combined BSID-II Mental Developmental Index and the composite scores of the WPPSI-R and WISC-III to measure general cognitive ability; we labeled this combined variable as full-scale IQ (FSIQ). For those participants who had been assessed with the Wechsler scales, we also included the Wechsler verbal IQ (VIQ) and performance IQ (PIQ) scores. These are age-adjusted standard scores with mean of 100 and SDs of 15 computed using normative data provided by the test publishers [21–23]. Assessments judged invalid by the neuropsychologist administering the test were not included.

Statistical methods

Neurodevelopmental status, measured by FSIQ, PIQ, and VIQ scores from BSID-II and Wechsler tests, was the primary outcome of interest in this study. Distributions of FSIQ, PIQ, and VIQ scores at weeks 0, 24, 48, and 96 were described using means, standard SDs, medians, and interquartile ranges. Neurodevelopmental scores were also available at weeks 8 and 16 for a very small number of participants, and thus excluded from the analyses. Linear mixed models were used to assess the trend in neurodevelopmental status over time and associations between neurodevelopmental status and baseline individual characteristics. Univariate models were adjusted for week of neurodevelopmental assessment. In addition to adjusting for week of neurodevelopmental assessment, multivariate linear mixed models adjusted for age, sex, race, CNS penetrance score of baseline antiretroviral regimen (prior to randomization to study treatment arms), baseline CMV infection status, viral load response at week 16 (VLR, partial VLR, non-VLR, or missing), and treatment arm. The immune activation markers, the primary exposures of interest, were analyzed primarily as percentages and secondarily as absolute counts. The distributions of the markers in terms of both percentages and counts were described using means, SDs, medians, and ranges. Associations between neurodevelopmental outcomes and each of the eight markers were assessed using separate models. Additional models assessed effects of adjusting for baseline viral load, baseline CD4%, or both. Neurodevelopmental test version was not explicitly adjusted for, as age was considered to be a proxy for test version. Age at baseline was categorized according to the Centers for Disease Control and Prevention (CDC) guidelines for immune status maturity (1–12 months, 1–5, 6–12, and >12 years). The youngest age group was excluded due to small sample size. CNS-penetrance effectiveness (CPE) score, which measures the ability of antiretrovirals to penetrate the CNS, was developed and improved by Letendre *et al.* [25]. CPE score of the baseline antiretroviral regimen was calculated by summing the individual scores of each antiretroviral in the regimen. Participants not taking antiretroviral drugs at baseline were assigned a CPE score of 0. CPE score was dichotomized at the median value with scores less than 5 considered low and at least 6 considered high. The effect of treatment arm was explored by adding an interaction term between time and treatment to the models. As treatment arm was randomized at entry,

the effect of treatment arm was explored by adding an interaction term between time and treatment to the models. Additionally, the effect of immune activation on neurodevelopmental outcomes over time was tested using interaction terms between time and immune activation marker. Associations are declared significant for *P*-values less than 0.05 and marginally significant if less than 0.10.

Results

Participant characteristics

Of 200 children enrolled into PACTG 366, 126 (63%) were at least 1 year old and had both immune activation and appropriate neurodevelopmental assessments at baseline (week 0). Baseline demographic and disease characteristics of these 126 participants are shown in Table 1; most were black non-Hispanic (63%), males (57%), and on some type of antiretroviral therapy (97%) at entry (prior to randomization to study treatment arm). At entry, 36% were in CDC disease category C [26], and 43% were CMV-infected. At week 16, there were 40% VLRs, 16% partial responders, 29% nonresponders, and 15% were missing viral load response data.

Description of neurodevelopmental scores and trends over time

The 200 PACTG 366 participants completed a total of 604 neurodevelopmental evaluations during the study: 192 at week 0, 37 at week 8, 30 at week 16, 140 at week 24, 123 at week 48, and 82 at week 96. Of these 604 evaluations, 40 were excluded as invalid. Table 2 shows distributions of FSIQ, PIQ, and VIQ scores and the neurodevelopmental test versions taken by the 126 participants for this analysis by week. PIQ and VIQ scores were only available for participants who took WPPSI-R or WISC-III tests. Baseline mean FSIQ, PIQ, and VIQ scores were 80.4, 85.4, and 82.9 respectively. Mean and median IQ scores increased over time. Of the 126 FSIQ assessments conducted at baseline, 26 (21%) were BSID-II, 32 (25%) were WPPSI-R, and 68 (54%) were WISC-III. Twelve participants (10.4%) converted from WPPSI to WISC-III and three (1.6%) converted from BSID-II to WPPSI-R from baseline to week 96.

The trend in test scores over time was highly significant in models without covariates for all three outcomes of interest and models adjusted for covariates for FSIQ and PIQ. Adjusted for covariates, every 3-month increase in time was associated with an estimated average increase of 0.7 in the FSIQ score ($P<0.01$) and 1.3 in the PIQ score ($P<0.001$) (Table 3).

Baseline predictors of neurodevelopmental scores

Table 3 shows univariate and multivariate model estimates and *P*-values for FSIQ, PIQ, and VIQ vs. baseline participant characteristics and covariates. Age was a significant predictor of FSIQ scores ($P=0.01$), with participants aged 1–5 years having FSIQ scores on average 10.4 points lower than those aged 6–12 ($P=0.004$). Participants on antiretroviral regimens with high baseline CPE scores had VIQ scores that were on average 7.4 points higher ($P=0.02$) than in those on regimens with low CPE scores. Differences in FSIQ scores with respect to CPE scores were only marginally significant. Treatment arm was a significant predictor of VIQ unadjusted for other covariates ($P=0.03$), but was only marginally significant after adjustment ($P=0.07$). Sex, race/ethnicity, CD4% at entry, log viral load at entry, CMV infection status at entry, and viral load response at week 16 were not associated with FSIQ, PIQ, or VIQ.

Relationship between immune activation and neurodevelopmental outcomes

The results of the primary analysis that evaluated associations between neurodevelopmental status and immune activation markers are shown in Table 4. Of the eight activation markers

analyzed, four were found to be significant predictors of FSIQ. Higher $CD4^+CD38^+HLADR^+$%, $CD4^+CD38^-HLADR^+$%, and $CD8^+CD38^+HLADR^+$% were significantly associated with higher FSIQ (slope =0.18, 0.70, and 0.15, respectively; P =0.02, 0.03, and 0.04, respectively) and marginally associated with higher VIQ (slope =0.15, 0.52, and 0.12, respectively; P =0.05, 0.06, and 0.08, respectively). Higher $CD4^+CD38^+HLADR^-$% were significantly associated with lower FSIQ scores (slope = −0.16, P =0.01) and marginally associated with lower VIQ scores (slope =−0.11, P =0.09). Adding baseline viral load to the models had no substantial effect, whereas adding baseline CD4% had a minimal effect on the associations between the $CD8^+$ activation markers and FSIQ, PIQ, and VIQ and the associations between the $CD4^+$ activation markers and FSIQ. When baseline CD4% was added to the models for PIQ and VIQ vs. the $CD4^+$ activation markers, in general, the effect estimates had a marked increase in magnitude and the corresponding P-values decreased. No significant interactions between time and immune activation marker were observed.

Figure 1 shows the plots of neurodevelopmental scores over time by $CD4^+$ activation marker percentage in which the markers values represent the 5th, 25th, 50th, 75th, and 95th percentiles. The parallel nature of the lines indicates that the effect of immune activation on FSIQ does not change over time (i.e., no longitudinal effect). However, the separation between the lines for the plots $CD4^+CD38^+HLADR^-$%, $CD4^+CD38^+HLADR^+$%, and $CD4^+CD38^-HLADR^+$% reflects a significant main effect (i.e., cross-sectional effect) of the marker on FSIQ.

Separate models were run with absolute counts of the eight T-cell subsets of interest (instead of their percentages). There were no significant associations between absolute counts of any of the eight subsets of interest with the neurodevelopmental outcomes (data not shown). Baseline distributions of the absolute counts and the percentages of $CD4^+$ and $CD8^+$ T-cell subsets are shown in Table 5.

Discussion

Contrary to our hypothesis, we observed beneficial associations between selected T-cell activation markers in the peripheral blood at baseline and neurodevelopmental outcomes over time in a cohort of extensively pretreated PHIV-infected children with severe disease enrolled in a controlled trial of a four-drug antiretrovirals regimen. Demographic characteristics of the 126 children included were representative of the PHIV-infected children in the United States.

The positive association between the percentage of $CD4^+$ T cells expressing HLADR (both with and without co-expressed CD38) and FSIQ scores suggests favorable neurodevelopmental prognostic meaning for this $CD4^+$ T-cell activation marker in PHIV-infected children. The expression of CD38 molecule on $CD4^+$ T cells does not depend upon cell activation, as this molecule is also a marker of immaturity and is normally highly expressed in circulating $CD4^+$ T cells in children (approximately 75% in healthy and 50% in PHIV-infected children) [27,28]. Thus, the favorable associations between both $CD4^+CD38^+HLADR^+$% and $CD4^+$ $CD38^-HLADR^+$% and FSIQ as well as the unfavorable one between $CD4^+CD38^+HLADR^-$% and FSIQ suggest key role of $CD4^+$ activation.

The percentages of $CD8^+CD38^+HLADR^+$ T cells, which include HIV-specific cytotoxic T cells if these are present [29], were positively associated with FSIQ scores. This contradicts negative prognostic implications of this marker in HIV-positive adults [29], but supports the assertion made by de Martino *et al.* [27] that the cytotoxic effect of these activated $CD8^+$ T cells may have positive prognostic implications in young children. Our finding suggests that

such protective association may extend to the CNS of PHIV-infected children. Furthermore, $CD8^+CD38^+HLADR^-$%, $CD8^+CD38^-HLADR^-$%, and $CD8^+CD38^-HLADR^+$% were not significantly associated with the neurodevelopmental outcomes, suggesting that this beneficial association is restricted only to $CD8^+CD38^+HLADR^+$ T cells. Other studies have offered clues as to why this may be the case. Schlesinger *et al.* [30] reported significant correlations between both $CD8^+$% and $CD8^+CD38^+$% and survival of PHIV-infected children under 2 years of age, leading to their hypothesis that the relative resistance of PHIV-infected children to disease progression may be partially due to physiologically high numbers of circulating $CD8^+CD38^+$ cells. de Martino *et al.* [27] reported favorable prognostic implication of $CD8^+CD38^+$% in young PHIV-infected children, coupled with a strong correlation between $CD8^+CD38^+$ and $CD8^+HLADR^+$, suggesting an activation-dependent mechanism. In the present study, $CD8^+CD38^+HLADR^+$% was favorably associated with the neurodevelopmental outcomes but $CD8^+CD38^+$ $HLADR^-$% was not, again suggesting key role of activation. Importantly, the Schlesinger *et al.* [30] study also evaluated the concentrations (i.e. absolute numbers) in addition to percentages of T-cell subsets, and observed that mortality of HIV-positive infants under 2 years of age was predicted by $CD8^+$ cell count less than 750 cells/μl and by $CD8^+CD38^+$ less than 600 cells/μl at study baseline. In the present study, both the mean and median values of $CD8^+$ and $CD8^+CD38^+$ concentrations were well above these two respective thresholds (Table 5). Given that $CD8^+CD38^+$ alone is also a marker of immaturity, it could be that the beneficial effect associated with immune activation in young PHIV-infected children is possible only when the following two conditions are met: their physiologically high levels of circulating immature $CD8^+$ T cells are preserved; and their physiologically high thymic output is preserved. In HIV-infected adults, however, this same mechanism may be detrimental because of the inability to renew the depleted $CD4^+$ pool following the physiological involution of the thymus, and the lack of readily available circulating $CD8^+$ T cells that would help suppress viral replication [27–29,31].

Mekmullica *et al.* study [18], cited in the introduction of this article, had categorized immune activation as ‘high’ vs. ‘low’ in which either $CD8^+HLADR^+$ 5% or less or $CD8^+CD38^+$ 25% or less were considered a marker of low activation, based on a study that compared long-term immunological nonprogressors vs. progressors [32]. The PHIV-infected children in the present study had been aggressively switched to a four-drug HAART regimen, whereas the Mekmullica *et al.* data were from the pre-HAART era. These methodological and treatment differences make it difficult to reconcile the findings from the two studies.

Study participants included in the present analysis who were on antiretroviral regimens with high CPE scores prior to study treatment initiation had significantly better VIQ scores than those on antiretroviral regimens with low CPE scores prior to study treatment initiation. This remained true even after adjusting for study treatment arm effect. However, CPE scores were not the primary exposure of interest in the present analysis, so caution is advised in interpreting this data. We agree with the conclusion from recent literature review that randomized, controlled trials should be conducted in order to evaluate the potential neuroprotective role of antiretroviral regimens with high CPE scores [33].

This study has limitations. The HAART regimens provided in the PACTG 366 were not as potent as the ones available today. The children had severe disease prior to receiving a four-drug regimen. The potency of HAART regimens available in the contemporary clinical care and the corresponding improvements in viremia control and the overall disease severity may critically influence the relationship between lymphocyte activation and neurodevelopmental outcomes. The present study evaluated a small number of T-cell markers. However, the unanticipated findings could potentially have significant clinical implications and will

hopefully lead to more mechanistic studies interrogating T-cell subsets within the $CD4^+$ and $CD8^+$ T-cell populations and their relationship with clinical outcomes in PHIV-positive youth.

In conclusion, contrary to the starting hypothesis, our findings suggest that $CD4^+$ activation and, under certain circumstances, $CD8^+$ activation may have favorable neurodevelopmental implications in young PHIV-infected children. We propose that factors salient to the young children's immune system, such as high numbers of circulating T cells and preserved thymic output play a key role in this association.

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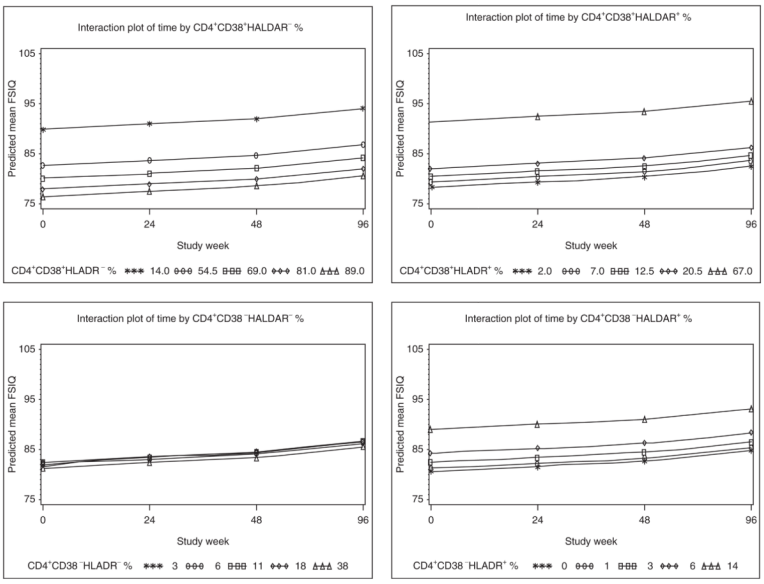

Fig. 1. Plots of predicted mean Intelligence Quetient (IQ) scores over time by CD4 immune activation markers

Plots of neurodevelopmental scores over time by $CD4^+$ activation marker percentage; the markers values represent the 5th, 25th, 50th, 75th, and 95th percentiles. HLADR, human leukocyte antigen DR.

Table 1

Participant characteristics.

Characteristic	Total (*N* =126)
Growth failure, *n* (%)[a]	14 (11%)
CNS abnormality, *n* (%)[a]	29 (23%)
HIV-1 RNA >50 000 copies/ml, *n* (%)[a]	91 (72%)
CD4% <15 or 50% decrease in CD4 percentage or count within 6 months, *n* (%)[a]	48 (38%)
Age (years), median (range)	7 (4, 10)
Age (years), *n* (%)	
1–5	42 (33%)
6–12	66 (52%)
>12	18 (14%)
Sex, *n* (%)	
Male	71 (56%)
Female	55 (44%)
Race/ethnicity, *n* (%)	
White non-Hispanic	11 (9%)
Black non-Hispanic	80 (63%)
Hispanic (regardless of race)	33 (26%)
Other/unknown	2 (2%)
CDC[b] disease category at entry 1, *n* (%)	
A	28 (22%)
B	42 (33%)
C	45 (36%)
N	11 (9%)
Baseline HIV-1 RNA level at entry 1 (copies/ml), median (Q1, Q3)[c]	60 274 (24 972, 130 305)
Baseline HIV-1 RNA level at entry 1 (copies/ml), *n* (%)[b]	
<50 000	49 (39%)
>50 000–100 000	32 (26%)
>100 000	44 (35%)
CD4 percentage at entry 1, median (Q1, Q3)[d]	19 (12, 27)
CD4 percentage at entry 1, *n* (%)[d]	
0 to <15	45 (37%)
15–25	43 (35%)
>25	35 (28%)
Antiretroviral (ARV) regimen, *n* (%)[e]	
HAART with PI	45 (36%)
HAART without PI	12 (10%)
Non-HAART ARV regimen	65 (52%)
Not on ARV drugs	4 (3%)

Characteristic	Total (*N* =126)
On PIs at entry 1, *n* (%)[e]	48 (38%)
On NNRTIs at entry 1, *n* (%)[e]	24 (19%)
CNS penetrance score, *n* (%)	
0–5	55 (44%)
>5	71 (56%)
Cytomegalovirus-infected at study entry 1	54 (43%)
Viral load response at week 16	
Response	50 (40%)
Partial response	20 (16%)
Nonresponse	36 (29%)
Missing	20 (16%)
Treatment arm[f]	
1A	29 (23%)
1B	24 (19%)
2	35 (28%)
3 and 4	38 (30%)

CNS, central nervous system; NNRTIs, non-nucleoside reverse transcriptase inhibitors; NRTIs, nucleoside reverse transcriptase inhibitors; PI, protease inhibitor.

[a]Based on screening data.

[b]Centers for Disease Control and Prevention.

[c]Two missing observations.

[d]Three missing observations.

[e]Most recent set of antiretroviral drugs taken within 30 days prior to randomization was assumed to comprise the baseline antiretroviral regimen.

[f]Treatment arm 1A: 2NRTIs +nevirapine +nelfinavir; arm 1B: 2NRTIs + nevirapine +ritonavir; arm 2: 1NRTI +nevirapine +nelfinavir +ritonavir; arm 3: 2NRTIs +nelfinavir +ritonavir; arm 4: 2NRTIs +nelfinavir +ritonavir.

Table 2

Test characteristics by week.

NP test/test version	Week 0 (*N* =126)	Week 24 (*N* =84)	Week 48 (*N* =76)	Week 96 (*N* =48)
Wechsler test version				
BSID-II	26 (21%)	16 (19%)	10 (13%)	2 (4%)
WPPSI-R	32 (25%)	17 (20%)	17 (22%)	9 (19%)
WISC-III	68 (54%)	51 (61%)	49 (64%)	37 (77%)
Full scale IQ				
Mean (SD)	80.4 (15.9)	83.3 (15.3)	85.7 (14.2)	90.0 (14.7)
Median (Q1, Q3)	82.5 (71.0, 92.0)	85.0 (75.0, 92.5)	86.0 (77.5, 96.0)	89.0 (81.0, 103.0)
Performance IQ[a]				
Mean (SD)	85.4 (15.5)	89.9 (16.4)	93.7 (13.8)	95.5 (15.8)
Median (Q1, Q3)	87.0 (77.0, 96.5)	90 (81.0, 102.0)	94.0 (87.0, 103.0)	96.0 (82.0, 106.0)
Verbal IQ[a]				
Mean (SD)	82.9 (13.1)	84.0 (12.0)	86.0 (12.0)	87.3 (14.5)
Median (Q1, Q3)	83.0 (75.0, 91.5)	84.0 (78.0, 91.0)	85.0 (78.0, 94.0)	86.0 (78.0, 99.0)

[a]Performance and verbal IQ scores not available for children who had BSID-II evaluations.

Table 3

Univariate and multivariate associations between patient characteristics and neurodevelopmental outcomes.

	FSIQ		PIQ		VIQ	
	Univariate[a] estimate (*P*)	**Multivariate[b] estimate (*P*)**	**Univariate[a] estimate (*P*)**	**Multivariate[b] estimate (*P*)**	**Univariate[a] estimate (*P*)**	**Multivariate[b] estimate (*P*)**
Week of neurodevelopmental evaluation (from study entry)	0.07 (<0.001)	0.05 (0.01)	0.10 (<0.001)	0.10 (<0.001)	0.03 (0.01)	0.01 (0.66)
Age (years)	(0.01)	(0.01)	(0.16)	(0.08)	(0.79)	(0.67)
6–12 vs .1–5	8.95 (0.003)	10.35 (0.004)	6.34 (0.09)	10.37 (0.03)	−0.74 (0.83)	1.53 (0.70)
>12 vs. 1–5	8.83 (0.04)	8.26 (0.11)	8.52 (0.08)	9.32 (0.07)	−2.79 (0.51)	−1.86 (0.68)
Sex (male vs. female)	−2.73 (0.32)	−2.49 (0.43)	−0.90 (0.76)	−1.34 (0.71)	−2.07 (0.42)	−0.22 (0.94)
Race/ethnicity	(0.87)	(0.28)	(0.52)	(0.45)	(0.29)	(0.53)
Black non-Hispanic vs. white/other	−2.37 (0.61)	−7.34 (0.13)	−5.66 (0.31)	−7.55 (0.21)	−2.83 (0.56)	−1.85 (0.72)
Hispanic (regardless of race) vs. white/Other	−1.71 (0.73)	−8.33 (0.13)	−3.45 (0.56)	−6.26 (0.33)	−6.66 (0.20)	−4.98 (0.38)
CD4% at entry	−0.18 (0.15)	−0.17 (0.27)	−0.05 (0.73)	−0.072 (0.68)	0.11 (0.39)	0.011 (0.94)
Baseline log HIV-1 RNA level at entry	−4.59 (0.06)	−3.99 (0.16)	−2.61 (0.34)	−1.40 (0.65)	−2.02 (0.41)	−2.11 (0.44)
High CNS penetrance score	4.32 (0.11)	6.11 (0.055)	5.29 (0.07)	4.45 (0.20)	6.56 (0.01)	7.36 (0.02)
Cytomegalovirus-infected at study entry	0.60 (0.83)	1.73 (0.55)	0.29 (0.92)	0.50 (0.88)	1.16 (0.66)	2.02 (0.47)
Viral load response at week 16	(0.74)	(0.54)	(0.31)	(0.24)	(0.23)	(0.77)
Response vs. nonresponse	1.81 (0.59)	3.93 (0.29)	0.37 (0.92)	3.78 (0.36)	1.20 (0.70)	0.92 (0.80)
Partial response vs. nonresponse	−2.54 (0.55)	−2.46 (0.59)	−5.43 (0.23)	−4.78 (0.34)	−5.05 (0.20)	−2.50 (0.57)
Missing vs. nonresponse	−0.66 (0.88)	0.18 (0.97)	−6.06 (0.21)	−4.51 (0.40)	−4.74 (0.25)	−2.93 (0.52)
Treatment arm[c]	(0.29)	(0.32)	(0.77)	(0.73)	(0.03)	(0.07)
1A vs. 3 and 4	0.016 (0.51)	0.016 (0.52)	−0.014 (0.68)	−0.010 (0.77)	0.046 (0.06)	0.043 (0.08)
1B vs. 3 and 4	0.054 (0.08)	0.050 (0.10)	−0.022 (0.60)	−0.020 (0.65)	0.088 (0.004)	0.075 (0.01)
2 vs. 3 and 4	0.037 (0.19)	0.041 (0.16)	0.021 (0.59)	0.028 (0.47)	0.031 (0.26)	0.031 (0.25)

[a]All univariate models are adjusted for week of NP evaluation.

[b] Multivariate models are adjusted for all covariates listed in Table 3.

[c] Estimates and *P*-values correspond to the interaction between treatment and week.

Table 4

Multivariate associations between baseline immune activation (percentage value) and longitudinal cognitive functioning (IQ score).

	Outcome		
	Full-scale IQ[a]	**Performance IQ**	**Verbal IQ**
Immune activation marker, model	Estimate (95% CI) *P*	Estimate (95% CI) *P*	Estimate (95% CI) *P*
$CD4^+CD38^+HLADR^{b-}$			
Model 1	−0.16 (−0.29, −0.04) 0.01	−0.11 (−0.25, 0.03) 0.13	−0.11 (−0.23, 0.01) 0.09
Model 1 with HIV viral load	−0.17 (−0.30, −0.05) 0.01	−0.11 (−0.25, 0.03) 0.12	−0.11 (−0.23, 0.01) 0.08
Model 1 with CD4%	−0.18 (−0.33, −0.03) 0.02	−0.15 (−0.32, 0.02) 0.08	−0.16 (−0.31, −0.02) 0.03
Model 1 with HIV viral load and CD4%	−0.19 (−0.34, −0.04) 0.02	−0.15 (−0.32, 0.02) 0.08	−0.17 (−0.31, −0.02) 0.03
$CD4^+CD38^+HLADR^+$			
Model 1	0.18 (0.03, 0.33) 0.02	0.10 (−0.07, 0.27) 0.24	0.15 (0.00, 0.29) 0.05
Model 1 with HIV viral load	0.20 (0.05, 0.36) 0.01	0.11 (−0.06, 0.29) 0.20	0.16 (0.01, 0.31) 0.04
Model 1 with CD4%	0.18 (0.01, 0.35) 0.04	0.12 (−0.08, 0.32) 0.23	0.21 (0.04, 0.38) 0.02
Model 1 with HIV viral load and CD4%	0.21 (0.03, 0.38) 0.02	0.13 (−0.07, 0.34) 0.20	0.22 (0.05, 0.39) 0.01
$CD4^+CD38^-HLADR^-$			
Model 1	0.00 (−0.25, 0.25) 1.00	0.02 (−0.24, 0.28) 0.88	−0.08 (−0.30, 0.14) 0.49
Model 1 with HIV viral load	−0.00 (−0.25, 0.25) 1.00	0.02 (−0.24, 0.28) 0.88	−0.08 (−0.30, 0.15) 0.50
Model 1 with CD4%	−0.01 (−0.28, 0.25) 0.91	0.03 (−0.23, 0.29) 0.83	−0.07 (−0.30, 0.16) 0.54
Model 1 with HIV viral load and CD4%	−0.02 (−0.28, 0.24) 0.89	0.03 (−0.24, 0.29) 0.84	−0.07 (−0.30, 0.16) 0.55
$CD4^+CD38^-HLADR^+$			
Model 1	0.70 (0.09, 1.32) 0.03	0.51 (−0.12, 1.14) 0.11	0.52 (−0.02, 1.06) 0.06
Model 1 with HIV viral load	0.64 (0.00, 1.27) 0.05	0.51 (−0.14, 1.16) 0.13	0.49 (−0.07, 1.05) 0.09
Model 1 with CD4%	0.69 (0.04, 1.34) 0.04	0.58 (−0.08, 1.24) 0.09	0.58 (0.01, 1.16) 0.05
Model 1 with HIV viral load and CD4%	0.60 (−0.08, 1.29) 0.09	0.58 (−0.11, 1.27) 0.10	0.56 (−0.04, 1.16) 0.07
$CD8^+CD38^+HLADR^-$			
Model 1	−0.12 (−0.30, 0.06) 0.18	0.08 (−0.11, 0.28) 0.40	−0.07 (−0.24, 0.10) 0.42
Model 1 with HIV viral load	−0.13 (−0.30, 0.05) 0.16	0.09 (−0.11, 0.28) 0.39	−0.07 (−0.24, 0.10) 0.44
Model 1 with CD4%	−0.12 (−0.30, 0.06) 0.20	0.07 (−0.12, 0.27) 0.47	−0.07 (−0.24, 0.11) 0.46
Model 1 with HIV viral load and CD4%	−0.13 (−0.31, 0.06) 0.18	0.08 (−0.12, 0.28) 0.46	−0.06 (−0.24, 0.11) 0.47
$CD8^+CD38^+HLADR^+$			
Model 1	0.15 (0.01, 0.30) 0.04	0.02 (−0.14, 0.18) 0.85	0.12 (−0.01, 0.26) 0.08
Model 1 with HIV viral load	0.17 (0.03, 0.32) 0.02	0.02 (−0.14, 0.18) 0.82	0.13 (−0.01, 0.27) 0.07
Model 1 with CD4%	0.15 (−0.00, 0.30) 0.06	0.01 (−0.16, 0.18) 0.91	0.13 (−0.02, 0.27) 0.09
Model 1 with HIV viral load and CD4%	0.16 (0.01, 0.32) 0.04	0.01 (−0.16, 0.18) 0.89	0.13 (−0.01, 0.28) 0.07
$CD8^+CD38^-HLADR^-$			
Model 1	−0.15 (−0.35, 0.04) 0.13	−0.09 (−0.29, 0.12) 0.41	−0.14 (−0.32, 0.03) 0.11
Model 1 with HIV viral load	−0.16 (−0.36, 0.04) 0.11	−0.09 (−0.30, 0.12) 0.40	−0.15 (−0.33, 0.03) 0.11
Model 1 with CD4%	−0.14 (−0.35, 0.06) 0.17	−0.08 (−0.29, 0.14) 0.49	−0.15 (−0.33, 0.04) 0.12
Model 1 with HIV viral load and CD4%	−0.15 (−0.35, 0.05) 0.15	−0.08 (−0.30, 0.14) 0.48	−0.15 (−0.34, 0.04) 0.12
$CD8^+CD38^-HLADR^+$			

	Outcome		
	Full-scale IQ[a]	**Performance IQ**	**Verbal IQ**
Model 1	0.10 (−0.33, 0.52) 0.65	−0.21 (−0.65, 0.22) 0.34	0.08 (−0.30, 0.46) 0.69
Model 1 with HIV viral load	0.02 (−0.42, 0.47) 0.91	−0.26 (−0.72, 0.20) 0.27	0.04 (−0.36, 0.43) 0.86
Model 1 with CD4%	0.14 (−0.30, 0.58) 0.54	−0.18 (−0.63, 0.27) 0.43	0.07 (−0.32, 0.46) 0.73
Model 1 with HIV viral load and CD4%	0.06 (−0.39, 0.52) 0.79	−0.22 (−0.69, 0.25) 0.36	0.03 (−0.39, 0.44) 0.89

Model 1 includes the following independent variables: immune marker percentage, week from study entry, age category (1–5, 6–12, and >12 years), sex, race category (black non-Hispanic, Hispanic regardless of race, white/other), central nervous system penetrance of baseline antiretroviral regimen (high vs. low), cytomegalovirus infection status, viral load response at week 16 (responder, partial-responder, nonresponder, missing), and treatment arm.

[a] IQ, intelligence quotient.

[b] HLADR, human leukocyte antigen DR.

Table 5

Distribution of $CD4^+$ and $CD8^+$ T-cell subsets among the Pediatric AIDS Clinical Trials Group protocol 366 (PACTG 366) participants included in the analysis.

	Cell counts (cells/mm^3)			Percentages		
T-cell subset	***N***	**Mean (SD)**	**Median (range)**	***N***	**Mean (SD)**	**Median (range)**
$CD4^+CD38^+HLADR^-$	121	422 (444)	251 (0–2061)	124	64 (23)	69 (1–95)
$CD4^+CD38^+HLADR^+$	121	66 (83)	43 (0–550)	124	17 (18)	13 (0–92)
$CD4^+CD38^-HLADR^-$	121	62 (64)	46 (0–371)	124	14 (11)	11 (0–76)
$CD4^+CD38^-HLADR^+$	121	17 (19)	11 (0–126)	124	5 (5)	3 (0–34)
All $CD4^+CD38^+$	121	488 (470)	343 (2–2248)	124	82 (13)	85 (23–98)
All $CD4^+HLADR^+$	121	82 (95)	56 (0–580)	124	22 (21)	15 (0–97)
All $CD4^+$	123	570 (499)	423 (2–2342)	123	20 (11)	19 (1–59)
$CD8^+CD38^+HLADR^-$	122	447 (323)	366 (0–1575)	125	41 (17)	39 (0–80)
$CD8^+CD38^+HLADR^+$	122	497 (550)	345 (0–3922)	125	39 (20)	38 (0–91)
$CD8^+CD38^-HLADR^-$	122	165 (189)	103 (0–974)	125	15 (14)	10 (0–70)
$CD8^+CD38^-HLADR^+$	122	80 (124)	36 (0–736)	125	6 (7)	4 (0–38)
All $CD8^+CD38^+$	122	945 (688)	865 (66–4510)	125	80 (16)	83 (29–102)
All $CD8^+HLADR^+$	122	577 (632)	384 (0–4216)	125	44 (22)	46 (0–99)
All $CD8^+$	123	1191 (811)	1044 (80–4902)	123	46 (14)	44 (14–76)

HLADR, human leukocyte antigen DR.