MAJOR ARTICLE

CD4 Cell Response to Antiretroviral Therapy in Children with Vertically Acquired HIV Infection: Is It Associated with Age at Initiation?

European Collaborative Study[a]

Background. Considerable uncertainty remains as to whether early initiation of antiretroviral therapy (ART) in children with vertically acquired human immunodeficiency virus (HIV) infection increases the benefit in terms of immunological response.

Methods. The association between immunological outcome and early initiation of and/or more-potent ART was investigated, using age-standardized *z* scores for CD4 cell counts (hereafter, "CD4 *z* scores"), in 131 HIV-infected children enrolled in the European Collaborative Study, a birth cohort study.

Results. Median age at initiation of the most-potent ART was 4 years (range, 0.1–15.5 years). Initiation of treatment after 5 months of age resulted in nonsignificantly lower CD4 *z* scores 6 months after initiation. Time to a 20% increase in CD4 *z* score was associated with age at initiation of the most-potent ART (adjusted hazard ratios [AHRs], 0.37 [$P < .01$] and 0.43 [$P = .05$] for 5 months–5 years of age and >5 years of age, respectively, compared with <5 months of age), ethnicity (AHR, 0.48 [$P = .01$], for black vs. white), and highly active ART (HAART) with or without prior ART (AHRs, 3.16 [$P < .01$] and 3.95 [$P < .001$], vs. mono or dual ART, respectively). The risk of subsequent deterioration of CD4 *z* score was similar for children who initiated ART in different age groups ($\chi^2 = 0.824$; $P = .82$).

Conclusions. We confirm the effectiveness of HAART with respect to the recovery of CD4 cell count and suggest a benefit of initiating ART before the age of 5 months. Age at initiation of the most-potent ART was not associated with the likelihood of sustaining the recovery of CD4 cell count.

Vertically acquired HIV infection has become a chronic disease, and growing numbers of perinatally infected children are surviving into adolescence and beyond [1–4]. Results from birth cohort studies of vertically infected children suggest that 70%–80% of untreated children survive to 5 years of age [3, 5, 6]; with increasing and earlier use of highly active antiretroviral therapy (HAART), survival is improving.

However, despite nearly 15 years of experience in the treatment of HIV-infected children [7], considerable uncertainty remains as to when to start ART. The benefits of early initiation (prevention of disease progression) need to be balanced against the costs and drawbacks (quality of life, lifelong therapy, the need for good adherence, resistance, adverse effects, and limited therapeutic options), because a complex relationship exists among ART regimen, duration, and adherence.

Although policies regarding the initiation of ART in children vary across Europe, clinical outcomes do not significantly differ by center policy [7]. However, the effect of age at initiation of ART on clinical outcome is difficult to assess, given that disease progression is slow in children receiving ART [5, 8]. Alternative approaches include the use of virological or immunological endpoints, but in young children the considerable age-related variation in HIV RNA load and CD4 cell count complicates such assessments [9, 10]. To avoid this problem, CD4 cell count can be adjusted for age.

Received 2 August 2005; accepted 27 October 2005; electronically published 23 February 2006.

Potential conflicts of interest: none reported.

Financial support: European Commission (concerted action grant QLK2-CT-2000-00002); United Kingdom Medical Research Council Sexual Health and HIV Strategy Committee (support to the European Collaborative Study Coordinating Centre). The views expressed here are those of the authors.

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The Journal of Infectious Diseases 2006; 193:954–62

0022-1899/2006/19307-0008$15.00

Here, we investigate whether early initiation and/or more-intense ART among HIV-infected children enrolled in the prospective European Collaborative Study (ECS) was associated with immunological or clinical outcome by use of *z* scores for CD4 cell counts (hereafter, "CD4 *z* scores"), which standardize the counts in relation to age.

METHODS

Since 1986 [5, 11], data on infected children born to HIV-1–infected women at 11 pediatric centers in 9 European countries have been prospectively collected from birth, using a standard clinical and laboratory protocol. Follow-up was frequent during the first 2 years of life and subsequently was done at least every 6 months. Parental consent was obtained, and the ECS was approved by local ethics committees.

A child was considered to be infected after the detection of virus in at least 2 separate blood samples or after the persistence of antibody beyond 18 months of age. Laboratory tests, including HIV RNA polymerase chain reaction (PCR) and assays for CD4 cell count, and were done locally, with the assays used recorded. HIV RNA copy number was usually assessed by either nucleic acid sequence–based amplification (Nuclisens; Organon Teknika) or the Roche Amplicor Monitor Test (versions 1.0 and 1.5; Roche Diagnostic Systems). CD4 cell counts were based on flow cytometry.

We assigned Centers for Disease Control and Prevention (CDC) clinical and immunological categories at each follow-up visit on the basis of information on current status, which enabled reclassification in light of changing clinical status, such that children could be moved to a less-serious clinical category if their clinical or immunological status improved [5]. Clinical categories were as follows: asymptomatic (CDC clinical stage N), mildly symptomatic (stage A), moderately severe symptoms (stage B), and severe symptoms (stage C) [5, 12]. Immunological categories were as follows: normal (CDC immunological stage 1), moderate immune suppression (stage 2), and severe immune suppression (stage 3) [5, 12]. To be included in the analyses, children had to have had a CD4 cell count measured within 2 months of either side of the initiation of ART. CD4 cell counts were measured before the initiation of ART in 122 children and after the initiation of ART in 9 children; the characteristics of these 9 children were similar to those of the remaining 122. At each follow-up visit, information was collected on ART; the date of first report of the most-potent ART was considered to be the date of initiation, which in most cases would be close to the actual initiation date, especially for young children with frequent follow-up. The type of most-potent ART was classified as mono or dual ART, HAART with prior ART, and HAART without prior ART.

For statistical analyses, SD scores (*z* scores) were obtained after modeling $\log_{10}$-transformed CD4 cell counts by use of the LMS method [13], using 10,330 measurements from 2106 uninfected children in the ECS cohort as the reference population [14]. By use of this method, *z* scores are no longer age dependent, because each measurement is compared with the standard for that age. The standardized normal distribution was used to convert CD4 *z* scores to percentiles.

Time to an event was calculated from the date of initiation of the most-potent ART to the date of reaching a 20% increase in CD4 *z* score and was assessed using Kaplan-Meier and Cox regression analysis (with log-rank tests) as well as unadjusted and adjusted hazard ratios (HRs) [15, 16]. A 20% increase was deemed to be evidence of successful treatment on the basis of the percentage decrease in median CD4 *z* score between initiation and 6 months later. Event-free children were right censored at the time of their last visit. This analysis used an intention-to-treat approach, with all children included from the time of initiation of their most-potent ART, regardless of subsequent modifications. Recursive partitioning and regression-tree methods were used to assess which age categories had the highest degree of association with the probability of immunological response [17]; the optimal cutoffs derived from this data-driven process were included in subsequent analyses. The assumption of proportional hazards in Cox regression models was formally assessed using Therneau and Grambsch's *zph* test [18].

An ordinary least-squares regression model was used to investigate the effect of neonatal characteristics and type and timing of treatment on CD4 *z* scores 6 months after initiation of the most-potent ART, using data from 120 vertically infected children for whom data on all variables were available. Univariable and multivariable logistic regression was used to investigate risk factors associated with deterioration of CDC clinical stage after initiation of the most-potent ART and to obtain unadjusted and adjusted odds ratios, respectively. After the multivariable model was adjusted for CDC clinical stage at initiation of the most-potent ART, the addition of subsequent variables and any improvements to the model were assessed by analysis of the deviance of the 2 models.

Data entry and management were done using Microsoft Access XP (2002) and SAS (version 9.1; SAS Institute). Statistical analyses were done using R (version 2.1.0) [19].

RESULTS

Study Population

ART was initiated in 131 HIV-infected children (table 1), of whom 42 (32%) were born before 1990, 83 (63%) were born from 1990 to 1999, and only 6 (5%) were born after 1999 (reflecting the decreasing vertical-transmission rate over time [20]). Of the 131 children, 39 (30%) began receiving and only ever received mono or dual ART (median age at initiation, 21 months; range, 0.75–97 months); 55 (42%) began receiving mono or dual ART (median age at initiation, 30 months; range,

Table 1. Characteristics of children with vertically acquired HIV infection at the time of initiation of the most-potent antiretroviral therapy (ART) (n = 131).

Characteristic	Value
Ethnicity	
White	84 (66)
Black	34 (26)
Other	10 (8)
Sex	
Female	69 (53)
Male	62 (47)
Type of most-potent ART	
Mono or dual ART	39 (30)
HAART with prior ART	55 (42)
HAART without prior ART	37 (28)
Age at initiation	
<5 months	17 (13)
5 months–5 years	56 (43)
>5 years	58 (44)
Median (range), years	4 (0.1–15.5)
CD4 cell count at initiation, median (range), 10^6 cells/L	580 (8–4028)
HIV-1 RNA load at initiation, median (range), $\log_{10}$ copies/mL[a]	4.43 (2.04–6.09)
CDC clinical stage at initiation	
N (no symptoms)	84 (64)
A (mild symptoms)	20 (15)
B (moderate symptoms)	20 (15)
C (severe symptoms)	7 (6)
CDC immunological stage at initiation	
1 (immunologically normal)	52 (40)
2 (moderate suppression)	36 (27)
3 (severe suppression)	43 (33)

NOTE. Data are no. (%) of children, unless otherwise noted. CDC, Centers for Disease Control and Prevention; HAART, highly active ART.

[a] n = 51 with detectable viral load.

0.25–141 months) and subsequently changed to HAART (median age at initiation, 90 months; range, 17–185 months); and 37 (28%) first began receiving HAART without any prior ART (median age at initiation, 6 months; range, 1–175 months).

Immunological and Virological Status

Nearly half of the children were classified as CDC immunological stage 1 at initiation of their most-potent ART (table 1). However, at initiation, 47 children (36%) had CD4 z scores below the first percentile, 41 (31%) had CD4 z scores between the first and 15th percentiles, and 37 (28%) had CD4 z scores above the 15th percentile; 85% (40/47), 66% (27/41), and 68% (25/37), respectively, showed subsequent immunological improvement. The median CD4 z score was −2.01 (approximately the second percentile) at initiation, which improved by almost 20% to −1.64 (approximately the fifth percentile) after 6 months of ART.

In children with a detectable viral load at initiation of their most-potent ART, the median HIV RNA load was 4.43 $\log_{10}$ copies/mL (range, 2.04–6.09 $\log_{10}$ copies/mL) (n = 51; data were not available for 67 children, and 13 had an undetectable viral load, of whom 4 were naive and 9 had received dual ART). At 6 months after initiation, the median viral load was reduced to 3.89 $\log_{10}$ copies/mL (range, 1.75–6.70 $\log_{10}$ copies/mL) (n = 50; data were not available for 54 children, and 27 had an undetectable viral load). Of the 55 children with data on viral loads available at initiation and 6 months later, 32 (58%) had a decreased viral load (median decrease, 4.40 $\log_{10}$ copies/mL; range, 2.18–6.09 $\log_{10}$ copies/mL), 10 (18%) remained stable (with undetectable loads at both measurements), and 13 (24%) had an increased viral load (median increase, 3.63 $\log_{10}$ copies/mL; range, 2.06–5.86 $\log_{10}$ copies/mL). Achievement of an undetectable viral load was not significantly associated with the type of most-potent ART (P = .32) (although there were only 2 children receiving dual ART and all others were receiving HAART), with ethnicity (P = .48), or with age at initiation of the most-potent ART (P = 1), but statistical power was limited. Viral load at initiation and CD4 z score 6 months after initiation were inversely but not highly correlated (correlation coefficient, −0.32; P < .05); similarly, the correlation coefficients for both were −0.29 (P < .05) at initiation and −0.35 (P < .01) at 6 months after initiation for the 55 children and was −0.41 for

all children with both data on viral load and CD4 cell count available at 6 months after initiation.

Most children were asymptomatic at initiation of the most-potent ART (table 1); 28 had improved clinical status 12 months after initiation (14 from CDC clinical stage A to N, 9 from B to N, 1 from C to A, 2 from C to B, and 2 from B to A), 20 deteriorated clinically (5 from N to A, 8 from N to B, 3 from N to C, 2 from A to B, and 2 from B to C), and 5 died (1 of whom was classified as A at initiation, 2 of whom were classified as B, and 2 of whom were classified as C). The clinical status of the remaining children was unchanged.

Time to Improvement in CD4 *z* Score after ART

Kaplan-Meier analysis. An estimated 59% (95% confidence interval [CI], 49%–67%) of children overall would have achieved a 20% increase in CD4 *z* score 12 months after initiation of the most-potent ART, with white European children having a substantially and significantly increased likelihood of attaining a 20% relative increase in CD4 *z* score than black children ($\chi^2 = 4.7$; 1 *df*; $P = .03$). Differences by ethnicity only became apparent after ~8 months of ART: at 8 months after initiation, ~40% of both white and black children would have achieved a 20% increase in CD4 *z* score, but, at 24 months after initiation, the percentages would be 83% (95% CI, 71%–83%) for white children and 57% (95% CI, 33%–72%) for black children; at 36 months, the percentages would be 88% (95% CI, 75%–95%) and 68% (95% CI, 41%–83%), respectively.

Time to a 20% increase in CD4 *z* score was not significantly associated with CDC clinical stage at the time of initiation of the most-potent ART ($\chi^2 = 4.8$; 1 *df*; $P = .19$), and there was only a marginally statistically significant association with CD4 *z* score percentile category at the time of initiation ($\chi^2 = 5.0$; 2 *df*; $P = .08$); children in the lowest percentile category were more likely to achieve a 20% increase.

However, significant differences did exist by type of most-potent ART ($\chi^2 = 19.9$; 2 *df*; $P < .0001$) and age at initiation of most-potent ART ($\chi^2 = 12.1$; 2 *df*; $P < .01$) (figure 1*A* and 1*B*). Children who received mono or dual ART but never received HAART were considerably less likely to achieve a 20% increase in CD4 *z* score than were children who had received HAART with or without prior ART. Estimated, data-driven, optimal age cutoffs reflecting the changing associations between the type of most-potent ART and CD4 *z* score after initiation were <5 months, 5 months–5 years, and >5 years; in these age groups, 15 (79%), 13 (23%), and 9 (16%) children, respectively, received HAART as their first treatment regimen. There was some evidence that children who initiated ART between 5 months and 5 years of age were less likely to attain a 20% increase in CD4 *z* score than were those who initiated ART before 5 months or after 5 years of age. The estimated median time from initiation of ART to a 20% increase in CD4 *z* score

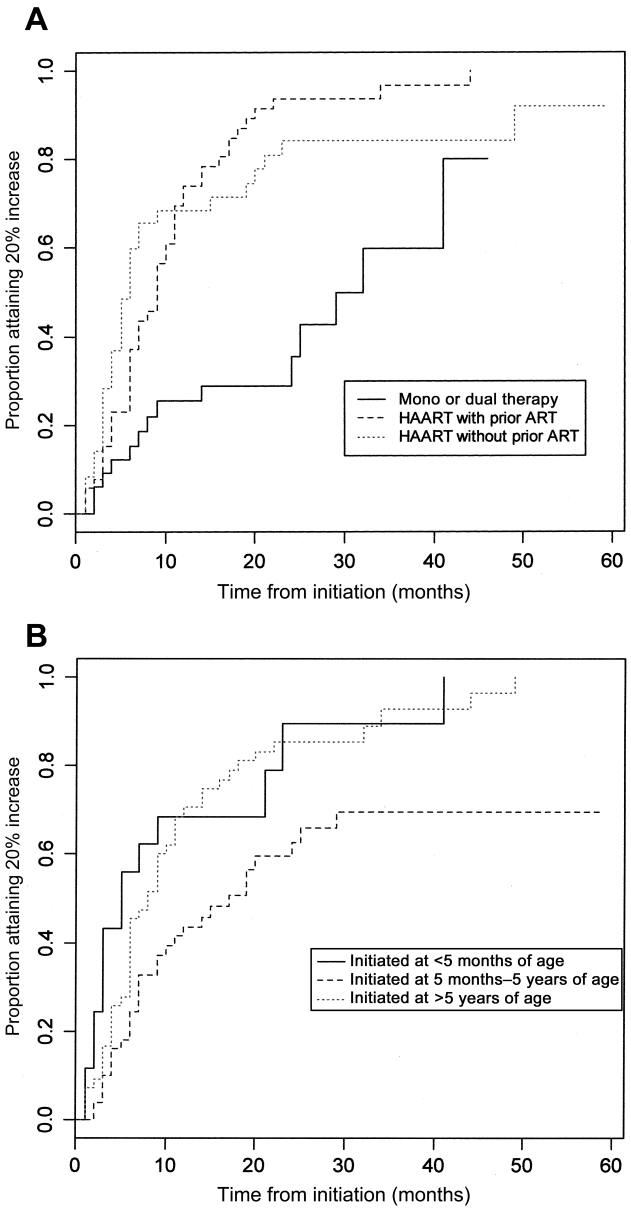

Figure 1. *A,* Time to attaining a 20% increase in *z* score for CD4 cell count from the time of initiation of the most-potent antiretroviral therapy (ART). *B,* Time to attaining a 20% increase in *z* score for CD4 cell count from the time of initiation of most-potent ART. HAART, highly active ART.

was 5 months (95% CI, 2–21 months) for children who initiated ART before 5 months of age, was 17 months (95% CI, 10–29 months) for children who initiated ART between 5 months and 5 years of age, and was 8 months (95% CI, 6–11 months) for those who initiated ART after 5 years of age.

Cox proportional-hazards analysis. These findings were confirmed in univariable Cox regression analyses (table 2): children who initiated their most-potent ART between 5 months and 5 years of age were almost 60% less likely to attain a 20% increase in CD4 *z* score at any time, compared with children

Table 2. Factors associated with improved immunological response (20% increase in *z* score for CD4 cell count) after initiation of the most-potent antiretroviral therapy (ART) ($n = 123$).

Factor	Immunological improvement, no. (%) of children		Univariable[a]		Multivariable[b]	
	No	Yes	HR	*P*	HR	*P*
Ethnicity						
White (and other)	24	71 (77)				
Black	11	20 (65)	0.58	.03	0.48	.01
Sex						
Female	17	46 (73)				
Male	15	45 (75)	1.22	.35	…	…
Type of most-potent ART						
Mono or dual ART	21	14 (40)				
HAART with prior ART	5	47 (90)	3.58	<.001	3.16	<.01
HAART without prior ART	6	30 (83)	3.13	<.001	3.95	<.001
Age at initiation						
<5 months	3	14 (82)				
5 months–5 years	21	30 (59)	0.41	<.01	0.37	<.01
>5 years	8	47 (85)	0.84	.58	0.43	.05
CD4 *z* score percentile at initiation						
Below the first percentile[b]	7	39 (85)				
Between the first and 15th percentiles	14	27 (66)	0.65	.08	0.995	.99
Above the 15th percentile	11	25 (69)	0.61	.06	0.50	.04
CDC clinical stage at initiation						
N (no symptoms)	19	60 (46)				
A (mild symptoms)	4	16 (80)	1.39	.26	1.05	.87
B (moderate symptoms)	5	13 (72)	1.20	.56	1.17	.65
C (severe symptoms)	4	2 (0.33)	0.32	.11	0.16	.02

NOTE. HAART, highly active ART; HR, hazard ratio.

[a] *z* score for CD4 cell count below −2.5.

[b] Adjusted for ethnicity, type of most-potent ART, and *z* score for CD4 cell count, age, and Centers for Disease Control and Prevention (CDC) clinical stage at initiation of the most-potent ART.

who initiated their most-potent ART before 5 months of age. Children who initiated their most-potent ART after 5 years of age were 16% less likely to attain this increase than were children who initiated their most-potent ART before 5 months of age, but this difference was not statistically significant. However, in multivariable analysis controlling for ethnicity, type of most-potent ART, and CD4 *z* score, age, and CDC clinical stage at initiation, the association with age at initiation was statistically significant for both age categories, with a 20% increase in CD4 *z* score being ~60% less likely in children who initiated ART after 5 months of age than in those who initiated ART before that age. Furthermore, a 20% increase in CD4 *z* score was approximately half as likely in black children than in white children; was 3 to nearly 4 times more likely in children receiving HAART than in those receiving mono or dual ART (regardless of history of previous ART); and was half as likely in children whose CD4 *z* scores were above the 15th percentile at initiation of the most-potent ART than were those whose scores were below the first percentile or between the first and 15th percentiles. Children who initiated their most-potent ART at a clinical stage of C (AIDS) were 84% less likely to achieve a 20% increase in CD4 *z* score than were those who initiated at a clinical stage of B, A, or N (no or mild/moderate symptoms).

Limiting the analysis to the 97 children who were below the 25th CD4 *z* score percentile at initiation of most-potent ART, we examined the time to a favorable immunological response (defined as crossing the 25th CD4 *z* score percentile) by use of a Kaplan-Meier analysis, censoring those children who had not reached this point at 24 months after initiation or at the time of death. An estimated 25% (95% CI, 15%–33%) of children would have crossed the 25th CD4 *z* score percentile 12 months after initiation.

Because the actual date of initiation of the most-potent ART could have occurred before the date of first report, the analysis was repeated, taking the date of initiation as the midpoint between the date of first report of the most-potent ART and the previous follow-up visit. There were no substantial differences in the association with the type of most-potent ART ($\chi^2 = 17.2$; $P < .0001$) or with age at initiation of the most-potent ART ($\chi^2 = 8.2$; $P = .01$), and the size and direction of

the adjusted HRs from Cox regression analyses were similar (data not shown).

CD4 Cell Response to ART 6 Months after Initiation

A linear regression of CD4 *z* scores 6 months after initiation of the most-potent ART was used to clarify the association between immunological status and ART and to quantify the associated changes in CD4 cell count. CD4 *z* score percentile category and CDC clinical stages B and C at initiation of the most-potent ART and HAART without prior ART were the only factors significantly associated with immunological response to treatment (table 3). HAART without prior ART was associated with a significant increase of 1.08 in *z* score 6 months after initiation, whereas HAART with prior ART was associated with a nonsignificant increase of 0.23 in CD4 *z* score 6 months after initiation, compared with mono or dual ART. Initiation of ART in children 5 months–5 years of age and those >5 years of age was associated with nonsignificant decreases of 0.60 and 0.10 in CD4 *z* score 6 months after initiation, respectively, compared with children who initiated ART before 5 months of age. Ethnicity was not significantly associated with CD4 *z* score 6 months after initiation. With CD4 *z* score at initiation of the most-potent ART as a continuous rather than a categorical variable, a 1 U increase in *z* score at initiation was associated with a highly significant increase of 0.41 in CD4 *z* score 6 months later.

ART-Associated Immunological Response and Clinical Status

To assess whether age at initiation of the most-potent ART was associated with immunological outcome, as measured by CD4 *z* score 6 months after initiation, in children whose HIV disease was not advanced, the multivariable analysis was repeated excluding children classified as CDC clinical stage C at the time when ART was initiated. The correlation coefficients for age were only marginally different and remained not statistically significantly associated with CD4 *z* score; children who were <5 months of age at the initiation of most-potent ART did better in terms of subsequent CD4 *z* score.

To assess risk factors for the deterioration in CDC clinical stage or death 12 months after initiation, a univariable and multivariable logistic regression was performed on 112 children, with data on all variables included (data not shown). Neither

Table 3. Factors associated with *z* score for CD4 cell count 6 months after initiation of the most-potent antiretroviral therapy (ART) (*n* = 120; all variables are included).

Factor	Children, no. (%)	Coefficient[a]	*P*	Coefficient[b]	*P*
Ethnicity					
White (and other)	90 (75)				
Black	30 (25)	−0.50	.20	−0.49	.20
Sex					
Female	61 (51)				
Male	59 (49)	−0.0047	.99	…	…
Type of most-potent ART					
Mono or dual ART	33 (28)				
HAART with prior ART	52 (43)	0.94	.02	0.23	.62
HAART without prior ART	35 (29)	1.45	<.01	1.08	.02
Age at initiation					
<5 months	16 (13)				
5 months–5 years	50 (42)	−0.91	.55	−0.60	.28
>5 years	54 (45)	−0.16	.57	−0.10	.87
CD4 *z* score percentile at initiation					
Below the first percentile	44 (37)				
Between the first and 15th percentiles	41 (34)	1.66	<.0001	1.63	<.001
Above the 15th percentile	35 (29)	3.24	<.0001	2.68	<.001
CDC clinical stage at initiation					
N (no symptoms)	78 (65)				
A (mild symptoms)	20 (17)	0.58	.18	0.62	.15
B (moderate symptoms)	17 (14)	−1.37	<.01	−1.23	<.01
C (severe symptoms)	5 (4)	−2.03	.01	−1.96	.02

NOTE. HAART, highly active ART.

[a] Estimated coefficients from univariable ordinary least-squares regression model, adjusted for *z* score for CD4 cell count at initiation.

[b] Coefficients adjusted for multivariable linear regression model, which included ethnicity, type of most-potent ART, and *z* score for CD4 cell count, age, and Centers for Disease Control and Prevention (CDC) clinical stage at initiation.

type nor age at initiation of most-potent ART was significantly associated with the likelihood of clinical deterioration, but the number of events was small.

Sustainability of CD4 Cell Response to ART

Treating infants with HAART before 5 months of age (which is like treating primary infection) was thus associated with a better response in terms of CD4 *z* score than starting treatment later, but it remained unclear whether this response was sustained. In a subanalysis of 84 children who attained at least a 20% increase in CD4 *z* score and with data on subsequent CD4 cell counts available, 38 (45%) experienced a reduction in their CD4 *z* scores to below the initial 20% increase. Kaplan-Meier analysis showed that the risk of subsequent deterioration of CD4 *z* score was similar for children who initiated treatment in different age groups ($\chi^2 = 0.824$; 2 *df*; $P = .82$) (figure 2). There was also no significant difference in risk between black and white children ($\chi^2 = 0.1$; 1 *df*; $P = .72$) or between children who initiated ART at different CD4 *z* score percentile categories ($\chi^2 = 4.7$; 2 *df*; $P = .10$).

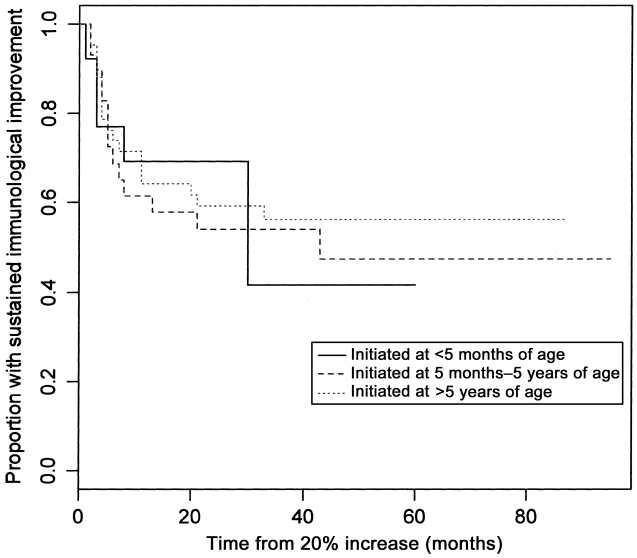

Figure 2. Time to a decrease in *z* score for CD4 cell count to less than the initial 20% increase after initiation of the most-potent antiretroviral therapy.

DISCUSSION

The timing of the initiation of ART in HIV-infected children, particularly in those followed from birth and, thus, identified during primary infection, has been found to be key to their clinical management, but it remains a contentious issue [21–23]. In the present European cohort, many children were clinically and immunologically well at the time they were reported to have initiated their most-potent ART (HAART, in 70% of cases). Because of the substantial natural variation in CD4 cell count in children of different ages [24], we used age-adjusted CD4 *z* scores [14]. We found that both early initiation (before 5 months of age) and starting with HAART were strongly associated with a more-rapid improvement in CD4 cell count, independent of immunological and clinical status at initiation.

The benefits of HAART with respect to immunological and clinical disease progression in infected children has been well described [5, 25–27]. We have confirmed that HAART is effective in terms of the recovery of CD4 cell count: HAART with or without prior ART was associated with a 3–4-fold increased likelihood of a 20% increase in CD4 *z* score, compared with mono or dual ART. Six months after initiation of the most-potent ART, children with prior mono or dual ART had a substantially lower (although nonsignificant) CD4 *z* score than did those who initiated HAART with or without prior ART, implying that the latter group responded faster to therapy.

We have previously shown in the ECS cohort immunological differences between white European children and black children, regardless of infection status [28]. We describe here ethnic differences in immunological improvement after initiation of the most-potent ART, with black children (predominantly born to sub-Saharan African mothers) following a trajectory similar to that of white children during the first 8 months of therapy, with the former showing reduced improvement over time in unadjusted analyses. However, black children were more likely than white children to initiate HAART without prior receipt of ART and to do so before 5 months of age, and, in adjusted analyses, CD4 *z* score 6 months after initiation was not significantly lower in black children than in white children. Similarly, black children were not more likely to show serious clinical deterioration than were white children 12 months after initiation, although statistical power was limited.

HAART has brought enormous benefits in terms of improved survival, health, and quality of life [29]—albeit with drawbacks, including adverse effects, the need for good adherence to avoid treatment failure, and the development of resistance. In this cohort of vertically infected children, immunological response to treatment was more rapid when ART was initiated early. In unadjusted analyses, white children who initiated ART before 5 months of age were equally likely to attain a 20% increase in CD4 *z* score as were children who initiated ART at >5 years of age, although this was likely to be due to different reasons. Children <5 months of age have a primary infection, and thymic productivity and, hence, immunological response is greater in this group than in older children [8, 30, 31]. Children ⩾5 months of age had more-severe HIV disease at the time of initiation and were also more likely to initially receive less-effective regimens. Lower CD4 cell count at initiation was associated with an increased likelihood of a 20% increase in CD4 *z* score. In adjusted analyses, immunological response in children initiating ART at >5 years of age became similar to that

in children initiating ART between 5 months and 5 years of age. The age-related response pattern was different for black children; those who started before 5 months of age responded more rapidly than did either of the 2 older groups, and the oldest category did worst.

Our results suggest that there is benefit in initiating ART early, soon after HIV diagnosis, although without treatment only about a fifth of infected children would be expected to progress rapidly to AIDS [5, 32]; our findings also suggest that the likelihood of sustaining an immunological response was not dependent on age at initiation. Predicting on clinical grounds which children would benefit from early initiation is, and is likely to remain, problematic [7, 33]. Our conclusions are based on data from a prospective observational cohort, which raises the problems of potential selection bias and temporal changes in the therapeutic management of HIV disease. For example, the youngest children were not only more likely to receive HAART but were also more likely to receive it as their first regimen. Although we adjusted for the timing of therapy and prior ART use, our findings are limited by the relatively small numbers of children in the youngest age group. However, in the absence of randomized trials to evaluate the effectiveness of earlier versus later initiation of ART, our findings contribute to the evidence base.

EUROPEAN COLLABORATIVE STUDY COLLABORATORS

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Acknowledgments

We thank all of the mothers and their children for their participation in the European Collaborative Study and L. Chieco-Bianchi, F. Zacchello, E. Ruga, A. M. Laverda, S. Cozzani, C. Cattelan, A. Mazza, B. Grella, A. R. Del Mistro, and S. Oletto (Padua, Italy); C. Feiterna and R. Weigel (Berlin, Germany); S. Burns, N. Hallam, P. L. Yap, and J. Whitelaw (Edinburgh, Scotland); B. Sancho and G. Fontan-Casanego (Madrid, Spain); A. Gonzalez Molina, M. Gobernado, J. L. Lopez, and J. Cordoba (Valencia, Spain); A. van der Plas (Amsterdam, The Netherlands); P. Bolme and U. Ewald (Sweden); G. Di Siena, E. Pontali, M. F. Pantarotto, G. Mantero, P. Dignetti, A. Nuzzolese, R. Rosso, S. Ferrando, and J. Nicoletti (Genoa, Italy); A. Hottard, M. Poncin, S. Sprecher, B. Lejeune, G. Zissis, and N. Clumeck (Belgium); and M. Guxens and P. Martinez (Barcelona, Spain). We also gratefully acknowledge the support of Colin Newell in the development and maintenance of the database.

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