The Effect of Plasma Human Immunodeficiency Virus RNA and CD4+ T Lymphocytes on Growth Measurements of Hemophilic Boys and Adolescents

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ABSTRACT. *Objective.* **The investigation examined the associations of plasma human immunodeficiency virus (HIV) RNA and CD4+ T lymphocytes with height, weight, skeletal maturation, testosterone levels, and height velocity for hemophilic children and adolescents with HIV infection in the Hemophilia Growth and Development Study.**

Study Design. **Two hundred seven participants were evaluated over 7 years.**

Results. **A threefold increment in baseline plasma HIV RNA was associated with a 0.98-cm decrease in height and a 1.67-kg decrease in weight; 100-cells/μL decrements in baseline CD4+ were associated with a 2.51-cm decrease in height and a 3.83-kg decrease in weight. Participants with high plasma HIV RNA (>3125 copies/mL) experienced significant delay in achieving maximum height velocity and lower maximum velocity compared with those with low viral load. The high CD4+ (>243)/low plasma HIV RNA group had earlier age at maximum height velocity compared with the other 3 groups and higher maximum height velocity compared with the low CD4+/high plasma HIV RNA and low CD4+/low plasma HIV RNA groups. Decrements in CD4+ were associated with decreases in bone age and testosterone level.**

Conclusions. **CD4+ and HIV RNA were important in predicting growth outcomes.** *Pediatrics* **2001;107(4). URL: http://www.pediatrics.org/cgi/content/full/107/4/e56;** ***hemophilia, physical growth, human immunodeficiency virus, immune function, human immunodeficiency virus RNA.***

ABBREVIATIONS. HGDS, Hemophilia Growth and Development Study; HIV, human immunodeficiency virus; HAART, highly active antiretroviral therapy.

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The Hemophilia Growth and Development Study (HGDS) is a longitudinal, multicenter investigation of the effect of human immunodeficiency virus (HIV) infection on physical growth and sexual maturation, immune function, and neurologic and neuropsychological functioning in children and adolescents with hemophilia. Fourteen collaborating hemophilia treatment centers in the United States enrolled 333 eligible participants from March 1989 through May 1990. Sixty-two percent of the cohort was infected with HIV in the late 1970s and early 1980s through exposure to contaminated clotting factor concentrates.[1] At the baseline examination conducted between 1989 and 1990, the age of the HIV-positive cohort ($n = 207$) ranged from 6 to 19 years (mean: 13.2 ± 3.1). It was estimated that participants had been infected for a mean of 6.7 ± 0.9 years at the time of entry.

Earlier reports from the HGDS documented significant reductions in height-for-age as well as mean age-adjusted bone age for HIV-infected children and adolescents compared with HIV-uninfected participants. HIV-uninfected children and adolescents showed patterns of statural growth similar to those of males without hemophilia. Reductions in linear growth velocity over the first year of follow-up and delays in sexual maturation over the first 4 years of follow-up have also been shown.[2,3] Investigators concluded that the delays in bone age and pubertal maturation strongly suggest that part of the growth failure seen in HIV-infected children can be attributed to pubertal delay,[3] unaffected by thyroid function, inadequate caloric intake, or severe illness.[4] Furthermore, monitoring physical growth and maturation is important because delays might predict HIV-related symptom development.[5]

The purpose of the current investigation was to extend previous analyses of physical growth data from the HIV-infected cohort of the HGDS by examining the effect of plasma HIV RNA and CD4+ T lymphocytes on height, weight, skeletal maturation, testosterone levels, and height velocity for children and adolescents with hemophilia and HIV infection followed prospectively over 7 years.

METHODS

Clinical and Laboratory Data

HGDS participants are a population-based group of hemophiliacs enrolled without regard to survivorship potential and repre-

sent children and adolescents who had survived with HIV infection for a period of ~7 years. Although enrolled participants necessarily excluded those who died before study inception, there is little evidence of bias introduced into the study because of selection or loss to follow-up of cohort participants. Analyses were conducted with data on height, weight, skeletal maturation, testosterone, $CD4^+$ counts, and plasma HIV RNA. Height was measured every 6 months using a wall-mounted stadiometer, and weight was recorded every 6 months. Plasma HIV RNA measurements were available annually for 205 participants, and, therefore, a total of 205 participants with 1 to 7 annual height and weight measurements were included in the height and weight analyses. The height velocity analyses, however, used all available semiannual and annual height measurements. Skeletal maturation (bone age) was assessed annually up to year 4 from films of the left hand and wrist. Films were read centrally at the Fels Institute, Wright State University, by the Fels method.[6] One hundred seventy-nine participants with 1 to 5 bone age measurements were included in the bone age analysis. For testosterone, 1 sample from each participant was collected during the first 4 years of study; 169 individuals were included in the analysis.

HIV status was determined by an enzyme immunoassay, with confirmation by Western blot analysis. Testosterone was measured centrally (New York Presbyterian Hospital-Cornell Medical Center) by a specific radioimmunoassay using OP/08 antibody (Pantex, Division of BioAnalysis Inc, Santa Monica, CA). Lymphocyte subpopulations were quantitated centrally, using commercial monoclonal antibodies and direct 2-color immunofluorescence flow cytometry. Heparinized plasma stored at −70°C was used for HIV RNA measurements using a branched DNA assay, Version 2.0 (Chiron Corporation, Emeryville, CA). The assay has a lower quantification limit of 500 copies/mL and is linear to concentrations as high as 1.6×10^6 copies/mL (1 copy of HIV RNA = 1 molecule of HIV RNA).[7,8]

Statistical Methods

Linear mixed effects regression models were fitted to examine the individual effects of plasma HIV RNA and also the joint effects of $CD4^+$ and plasma HIV RNA on height, weight, and bone age, while adjusting for the effects of age and ethnicity. Plasma HIV RNA measurements were log-transformed, while $CD4^+$ levels were square root transformed to better comply with the normality assumptions of the models. Empirical spatial exponential covariance structures were used to model the correlation between the repeated height, weight, and bone age measurements. The longitudinal $CD4^+$ and plasma HIV RNA measurements were partitioned into a baseline component and a change-from-baseline component to quantify both the cross-sectional effect at baseline and the longitudinal effect. Both components were then entered as predictors for each of the 3 mixed effects regression models.[9]

For analyzing the relationship between immune function and height velocity, each individual's repeated $CD4^+$ and plasma HIV RNA values were first averaged over time. The resulting mean values were then dichotomized into low and high groups according to the median values of 243 cells/μL and 3125 copies/mL to provide a clinically straightforward interpretation of average $CD4^+$ and plasma HIV RNA effects on height velocity. For each of the low/high $CD4^+$ and plasma HIV RNA categories, a 4-parameter logistic growth curve[10] was fitted using the SAS NLINMIX Macro (SAS, Cary, NC)[11] with age as the predictor. The height velocity function was then obtained by taking the derivative of the estimated logistic growth function. Comparisons of the maximum velocities and the corresponding ages were performed using asymptotic Wald tests.

For the analysis of testosterone, $CD4^+$ and plasma HIV RNA measurements taken at the corresponding visit when testosterone levels were measured were used as predictors. Linear regression was then used to model the relationship between $CD4^+$ and plasma HIV RNA and the square root transformed testosterone levels, while adjusting for the effects of age and ethnicity.

RESULTS

Height

Before controlling for $CD4^+$, a threefold increment in baseline plasma HIV RNA was associated with a 1.65-cm decrease in height ($P < .001$). With $CD4^+$ included in the model, threefold increments in baseline plasma HIV RNA were associated with a 0.98-cm decrease in height ($P = .036$), whereas 100-cells/μL decrements in $CD4^+$ were associated with a 2.49-cm decrease in height ($P < .001$). Plasma HIV RNA and $CD4^+$ changes from baseline, however, did not contribute to predicting height ($P = .09$ and $P = .44$, respectively).

Weight

Without adjusting for $CD4^+$, a threefold increment in baseline plasma HIV RNA was associated with a 2.67-kg decrease in weight ($P < .001$). With $CD4^+$ included in the model, threefold increments in baseline plasma HIV RNA were associated with a 1.67-kg decrease in weight ($P = .012$), whereas 100-cells/μL decrements in baseline $CD4^+$ were associated with a 3.83-kg decrease in weight ($P < .001$). One hundred-cells/μL decreases in $CD4^+$ changes from baseline were also associated with a 1.04-kg decrease in weight ($P < .019$), but plasma HIV RNA changes from baseline were not predictive of weight changes ($P = .27$).

Height Velocity

Participants with high plasma HIV RNA (>3125 copies/mL) experienced a significant delay in achieving their maximum velocity (age = 13.2 years; $P < .001$) and also a lower maximum velocity (5.79 cm/year; $P = .005$) compared with those with low viral load (age = 12.5 years; maximum velocity = 7.11 cm/year; Fig 1). When the $CD4^+$ effect was also considered, the high $CD4^+$ (>243)/low plasma HIV RNA group had an earlier age at maximum velocity compared with the other 3 groups and also higher maximum velocity compared with the low $CD4^+$/high plasma HIV RNA and low $CD4^+$/low plasma HIV RNA groups (Table 1; Fig 2).

Bone Age

Without $CD4^+$, a threefold increment in baseline plasma HIV RNA was associated with a 0.22-year decrease in bone age ($P = .004$). However, after controlling for $CD4^+$, both the baseline plasma HIV RNA effect ($P = .128$) and the longitudinal plasma HIV RNA effect ($P = .386$) were not significant. In contrast, 100-cells/μL decrements in baseline $CD4^+$ were associated with a 0.39-year decrease in bone age ($P = .002$), whereas 100-cells/uL decreases over time were associated with a 0.21-year decrease in bone age ($P = .018$). Ethnicity was also an important covariate for bone age, where on average, the bone age of whites was 0.67 years lower ($P = .001$) than of nonwhites.

Testosterone

Before controlling for $CD4^+$, a threefold increment in baseline plasma HIV RNA was associated with a 1.55-ng/dL decrease in testosterone level ($P = .002$). But after controlling for $CD4^+$, plasma HIV RNA no longer had an effect, although 100-cells/μL decrements in $CD4^+$ were associated with a 4.61-ng/dL decrease in testosterone level ($P = .008$).

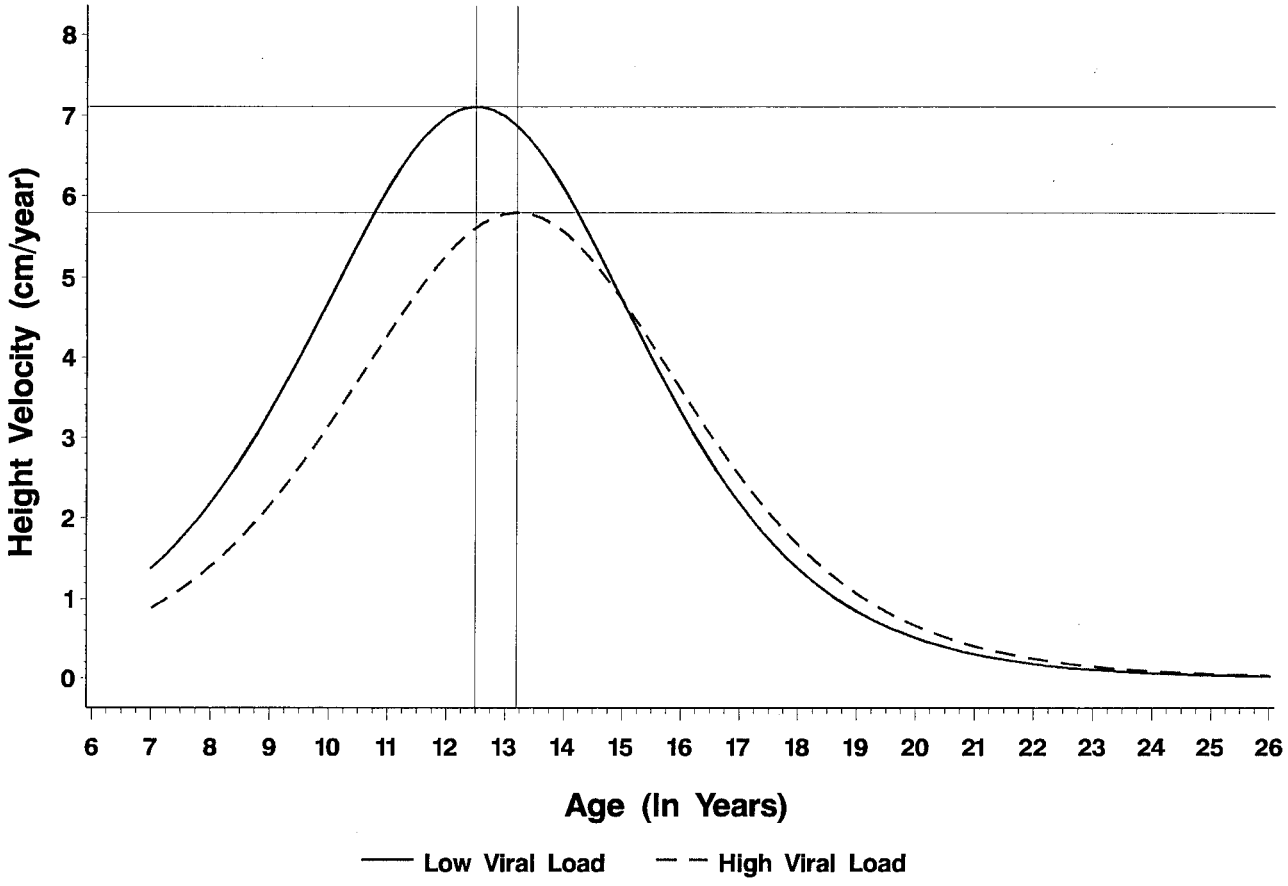

Fig 1. Plot of height velocity curves by plasma HIV RNA category. Plasma HIV RNA values were dichotomized into low and high groups according to the median value of 3125 copies/mL. The solid line represents participants with low plasma HIV RNA; dashed line, participants with high plasma HIV RNA.

TABLE 1. Maximum Height Velocity and Age at Maximum Height Velocity for $CD4^+$ and Plasma HIV RNA Category

Category	Maximum Velocity (cm)	Age at Maximum Velocity
High $CD4^+$/low plasma HIV RNA	7.38	12.47
High $CD4^+$/high plasma HIV RNA	6.89	13.13
Low $CD4^+$/low plasma HIV RNA	5.65	14.45
Low $CD4^+$/high plasma HIV RNA	5.28	13.32
Comparison With High $CD4^+$ Low Plasma HIV RNA	**Maximum Velocity Difference**	**Age Difference**
High $CD4^+$/high plasma HIV RNA	−0.49 ($P = .3660$)	0.66 ($P = .0418$)
Low $CD4^+$/low plasma HIV RNA	−1.73 ($P = .0020$)	1.98 ($P < .0001$)
Low $CD4^+$/high plasma HIV RNA	−2.10 ($P < .0001$)	0.85 ($P = .0065$)

Antiretroviral Therapy

Antiretroviral therapy was not a significant covariate for any of the 3 outcomes. Although 86% of study participants received antiretroviral therapy at some time during follow-up, there was minimal use of highly active antiretroviral therapy (HAART). Only 9 participants were treated with protease inhibitor-containing 3 drug regimens during the 7 years of the current investigation, 5 of the 9 having treatment onset <6 months before the final follow-up point.

DISCUSSION

Previous reports from the HGDS have documented reductions in height, height velocity, bone age, and sexual maturation for HIV-infected compared with HIV-uninfected study participants.[2–3] The delays in bone age and pubertal maturation suggest that part of the growth failure seen in HIV-infected children can be attributed to pubertal delay.[3] Earlier studies of children with hemophilia and HIV reported poor growth in children before the

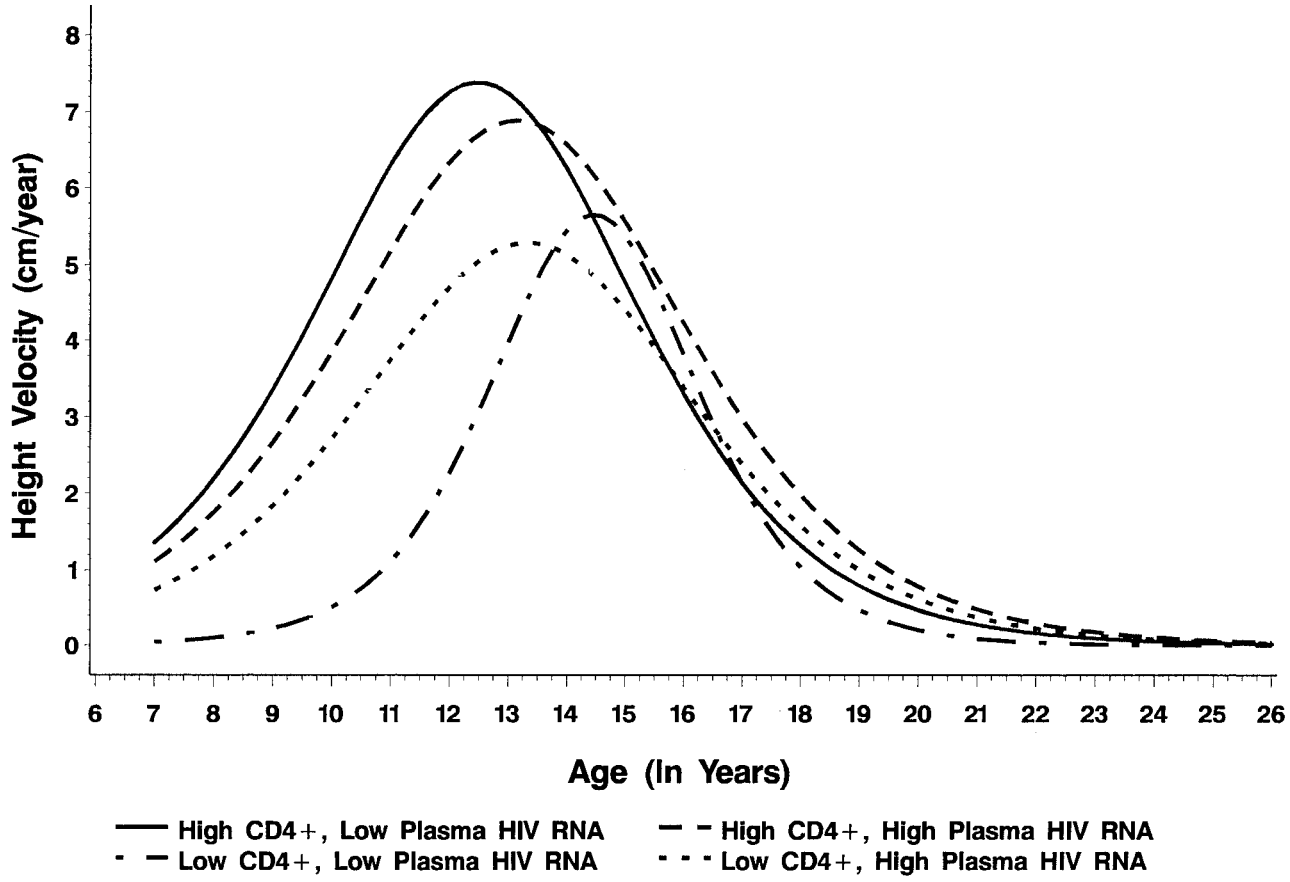

Fig 2. Plot of height velocity curves by $CD4^+$ and plasma HIV RNA category. $CD4^+$ and plasma HIV RNA values were dichotomized into low and high groups according to the median values of 243 cells/μL and 3125 copies/mL. The solid line represents the high $CD4^+$/low plasma HIV RNA group; dashed line, high $CD4^+$/high plasma HIV RNA group; dotted line, low $CD4^+$/high plasma HIV RNA group; dotted and dashed line, low $CD4^+$/low plasma HIV RNA group.

onset of HIV-related symptoms,[12,13] and a subsequent prospective study reported growth failure as a strong prognostic variable for HIV disease progression in HIV-infected children with hemophilia.[5] Previous investigations of HIV-infected cohorts have examined basal metabolic rate or resting energy expenditure in detail.[14–18] Although resting energy expenditure was not measured in the HGDS, extensive endocrine evaluations were performed that showed normal thyroid function and insulin-like growth factor-1 levels suggesting that secondary or inadequate caloric intake or the malnutrition of severe illness were not the cause of growth abnormalities and pubertal development.[4]

Plasma HIV RNA and $CD4^+$ T lymphocytes have been established as independent predictors of progression to acquired immunodeficiency syndrome and death in many studies including the HGDS.[19–23] Data from infants and children enrolled in AIDS Clinical Trials Group 152 also suggested that plasma HIV RNA and $CD4^+$ had independent effects for predicting growth failure.[24] In the current report, plasma HIV RNA had a significant impact on height and weight but not on height velocity, bone age, or testosterone, after controlling for $CD4^+$. Furthermore, baseline immune function was more important in predicting outcome than were changes from baseline. Such results may be influenced by the fact that the children and adolescents in the HGDS had already been infected with HIV for ~7 years at the time of the first viral load measurement, a duration that is several years longer than the cohorts investigated in some other studies.[25,19] In addition, analytical and biological variability in the plasma HIV RNA and $CD4^+$ measurements may impact the conclusions of the analysis.[26] Had the HGDS been designed to quantify the measurement variability in plasma HIV RNA and $CD4^+$ T lymphocytes, these estimates of variability then could be incorporated in an analysis controlling for the effects of measurement error.[27]

The results from analyses of height velocity suggest that the effects of $CD4^+$ and plasma HIV RNA on growth were evident throughout childhood and adolescence. In addition, the data indicate that, in general, $CD4^+$ count was a more precise predictor of growth outcome in this group of HIV-infected hemophiliac children and adolescents than was plasma HIV RNA. Because so few participants were treated with HAART, it is not likely that the extreme diminution in HIV RNA levels associated with HAART could explain this finding. Rather, the observation is consistent with the explanation that $CD4^+$ may serve as a composite reflection of all antecedent plasma HIV RNA levels in the period of infection; and in the current study, $CD4^+$ may be more reflective of the

pathophysiology of both the host and his organ system functions than plasma HIV RNA.

APPENDIX

The following individuals are the Center Directors, Study Coordinators or Committee Chairs of the study: Childrens Hospital Los Angeles, E. Gomperts, W.-Y. Wong, F. Kaufman, M. Nelson, S. Pearson; New York Presbyterian Hospital-Cornell Medical Center, M. Hilgartner, S. Cunningham-Rundles, I. Goldberg; University of Texas Medical School, Houston, W. K. Hoots, K. Loveland, M. Cantini; The National Institutes of Health, National Institute of Child Health and Human Development, A. Willoughby, Robert Nugent; New England Research Institutes, Inc, S. McKinlay; Rho, Inc, S. Donfield; Baylor College of Medicine, C. Contant, Jr; University of Iowa Hospitals and Clinics, C. T. Kisker, J. Stehbens, S. O'Conner, J. McKillip; Tulane University, P. Sirois; Children's Hospital of Oklahoma, C. Sexauer, H. Huszti, F. Kiplinger, S. Hawk; Mount Sinai Medical Center, S. Arkin, A. Forster; University of Nebraska Medical Center, S. Swindells, S. Richard; University of Texas Health Science Center, San Antonio, J. Mangos, A. Scott, R. Davis; Children's Hospital of Michigan, J. Lusher, I. Warrier, K. Baird-Cox; Milton S. Hershey Medical Center, M. E. Eyster, D. Ungar, S. Neagley; Indiana Hemophilia and Thrombosis Center, A. Shapiro, J. Morris; University of California-San Diego Medical Center, G. Davignon, P. Mollen; and Kansas City School of Medicine, Children's Mercy Hospital, B. Wicklund, A. Mehrhof.

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