Published in final edited form as:

J Dev Behav Pediatr. 2009 October ; 30(5): 403–412.

Impact of Medications Prescribed for Treatment of Attention-Deficit Hyperactivity Disorder on Physical Growth in Children and Adolescents With HIV

Patricia A. Sirois, PhD^{*}, Grace Montepiedra, PhD[†], Suad Kapetanovic, MD[‡], Paige L. Williams, PhD[†], Deborah A. Pearson, PhD[§], Kathleen Malee, PhD^{||}, Patricia A. Garvie, PhD[¶], Betsy L. Kammerer, PhD^{**}, Sharon L. Nichols, PhD^{††}, Molly L. Nozyce, PhD^{‡‡}, Mark Mintz, MD^{§§}, Wendy G. Mitchell, MD^{|||}, and James M. Oleske, MD [on behalf of the IMPAACT/PACTG 219C Team]^{¶¶}

^{*}Department of Pediatrics, Tulane University School of Medicine, New Orleans, LA

[†]Department of Biostatistics and Center for Biostatistics in AIDS Research, Harvard School of Public Health, Boston, MA

[‡]Department of Psychiatry and Behavioral Sciences, University of Southern California Keck School of Medicine, Los Angeles, CA

[§]Department of Psychiatry and Behavioral Sciences, University of Texas Medical School, Houston, TX

^{||}Department of Child and Adolescent Psychiatry, Children's Memorial Hospital, Chicago, IL

[¶]Behavioral Medicine Division, St. Jude Children's Research Hospital, Memphis, TN

^{**}Department of Psychiatry, Children's Hospital, Boston, MA

^{††}Department of Neurosciences, University of California at San Diego, La Jolla, CA

^{‡‡}Department of Pediatrics, Jacobi Medical Center, Albert Einstein College of Medicine, Bronx, NY

^{§§}The Center for Neurological and Neurodevelopmental Health and the Clinical Research Center of New Jersey, Voorhees, NJ

^{|||}Department of Neurology, Keck School of Medicine, University of Southern California School of Medicine, and Childrens Hospital Los Angeles, Los Angeles, CA

^{¶¶}Department of Pediatrics, New Jersey Medical School, Newark, NJ

Abstract

Objective—To examine the relationships between physical growth and medications prescribed for symptoms of attention-deficit hyperactivity disorder in children with HIV.

Copyright © 2009 Lippincott Williams & Wilkins

Address for reprints: Patricia A. Sirois, PhD, Department of Pediatrics, Tulane University Medical Center, 1430 Tulane Avenue, TW-41, New Orleans, LA 70112; psirois@tulane.edu.

Dr. Mark Mintz discloses that in the last 2 years, he has functioned in the capacity as an invited consultant or as a member of a Speakers Bureau for the following pharmaceutical companies: UCB Pharma, Eli Lilly, and Novartis. In addition, in the last 5 years, he is participating or has participated in pharmaceutical sponsored clinical drug trials for the following companies: Eli Lilly, Glaxo-Smith-Kline, UCB Pharma, UCB Schwarz/Pharma, Johnson and Johnson Pharmaceutical Research and Development, LLC, Sanofi-Aventis, Pfizer, Amiral Prodesfarma, Addrenex Pharmaceuticals, Eisai Inc., Cephalon Inc., Ovation Pharmaceuticals Inc., King Pharmaceuticals, Neuropharm Ltd.

Methods—Analysis of data from children with perinatally acquired HIV (N = 2251; age 3–19 years), with and without prescriptions for stimulant and nonstimulant medications used to treat attention-deficit hyperactivity disorder, in a long-term observational study. Height and weight measurements were transformed to z scores and compared across medication groups. Changes in z scores during a 2-year interval were compared using multiple linear regression models adjusting for selected covariates.

Results—Participants with (n = 215) and without (n = 2036) prescriptions were shorter than expected based on US age and gender norms ($p < .001$). Children without prescriptions weighed less at baseline than children in the general population ($p < .001$) but gained height and weight at a faster rate ($p < .001$). Children prescribed stimulants were similar to population norms in baseline weight; their height and weight growth velocities were comparable with the general population and children without prescriptions (for weight, $p = .511$ and $.100$, respectively). Children prescribed nonstimulants had the lowest baseline height but were similar to population norms in baseline weight. Their height and weight growth velocities were comparable with the general population but significantly slower than children without prescriptions ($p = .01$ and $.02$, respectively).

Conclusion—The use of stimulants to treat symptoms of attention-deficit hyperactivity disorder does not significantly exacerbate the potential for growth delay in children with HIV and may afford opportunities for interventions that promote physical growth. Prospective studies are needed to confirm these findings.

Index terms

HIV/AIDS; children and adolescents; height; weight; ADHD medication side effects

HIV infection has been reclassified as a chronic medical condition, leading to increased study of the long-term mental health care needs of people with HIV. Children and adolescents with HIV experience significant, multiple risks to mental health and quality of life, including viral infection of the central nervous system, viral and drug exposure in utero, developmental delays, poverty, inadequate support networks, unstable housing, and parental mental illness.¹ These factors place children and adolescents with HIV at risk for adverse behavioral outcomes, including symptoms of attention-deficit hyperactivity disorder (ADHD).¹ With an estimated prevalence of 5 to 7% among school-aged children, ADHD is one of the most common pediatric neurobehavioral disorders.² The prevalence is higher in children who have comorbid developmental conditions such as intellectual disability and autism spectrum disorders.^{3,4} Clinical concerns specific to the presence of comorbid HIV and untreated ADHD are that inattentiveness might impair a child's or adolescent's ability to adhere to antiretroviral treatment, whereas impulsivity might impair an adolescent's ability to practice health-promoting behaviors (e.g., safe sex).

Psychopharmacologic treatments for ADHD include stimulants and nonstimulants, both commonly prescribed for children with HIV and ADHD. Stimulant efficacy in children and adolescents is well established.^{2,5,6} For a variety of reasons, including stimulant failure or intolerance, stigma, and potential for abuse, clinicians often prescribe nonstimulants to treat ADHD. One of the most disputed adverse side effects of stimulant medication is growth attenuation in children.² Although some evidence suggests that age-related increases in height and weight may be diminished in children treated with stimulants,^{7,8} the clinical relevance of the growth delay remains controversial.^{9,10} Clinical trials have not demonstrated significant growth attenuation in children treated with nonstimulants.^{11,12}

Children and adolescents with HIV are at risk for growth failure as a complication of their disease.^{13,14} For children with comorbid HIV and ADHD, the use of stimulants to treat ADHD may exacerbate the risk of growth failure related to HIV. There has been little empirical

investigation into growth rates in children with HIV taking stimulants or nonstimulants for ADHD. The primary objective of this study was to examine the relationship between physical growth, as measured by height and weight, in children and adolescents with HIV and the use of commonly prescribed medications for treatment of ADHD. We hypothesized that children with prescriptions for stimulants would be smaller for age and would gain height and weight more slowly than their peers with HIV who were not prescribed stimulant medications.

METHODS

This study evaluated data from the Pediatric AIDS Clinical Trials Group 219C cohort study (P219C), a multicenter, longitudinal observational study of HIV-infected and uninfected, perinatally exposed children and adolescents conducted from September 2000 until May 2007. P219C was a revision of Pediatric AIDS Clinical Trials Group protocol 219 initiated in 1993 to study long-term effects of in utero exposure to antiretroviral medications and complications of HIV infection. P219C was approved by local institutional review boards at more than 80 participating sites in the United States and Puerto Rico. Informed consent and assent were obtained according to local institutional guidelines. On enrollment, study nurses abstracted participants' medical records to obtain medical and treatment histories, including diagnoses and antiretroviral and concomitant medications. Follow-up visits included physical examinations (including Tanner staging for children aged 8 years and older), laboratory studies, and self-reports from children and parents or caregivers to provide updated demographic information, medical history (including psychiatric and neurologic diagnoses), and quality of life information.

Participants

This study included children and adolescents enrolled in P219C with perinatally acquired HIV infection, with and without prescriptions for one or more of the stimulant or nonstimulant medications commonly prescribed to treat symptoms of attention-deficit hyperactivity disorder (ADHD) (Table 1). Among children prescribed at least one of the medications, we included those who started their first medication between the ages of 3 and 19 years, continued that medication for at least 1 month, and had at least 2 growth measurements (height or weight) within 2 years after the start of their first medication. For participants who never received any of the medications, we included children between the ages of 3 and 19 years who had at least 2 growth measurements (height or weight) within 2 years after enrollment into P219C or after the age of 3 years for those who enrolled before the age of 3 years. We considered the perinatally exposed but uninfected cohort in P219C ($n = 1778$), but too few ($n = 31$) had prescriptions for any of the selected medications to make meaningful comparisons; thus, this group was not considered further.

Measures of Physical Growth

Height and weight measurements were obtained every 3 months (± 1 month) from evaluations performed in routine clinical care or during scheduled study visits, according to the standardized protocol in P219C. Children had standing heights measured to the nearest 0.1 cm using a stadiometer; weights were taken without shoes. One height and weight measurements were recorded at each visit. For participants with prescriptions for at least one of the medications in Table 1, baseline height and weight measurements were defined as the earliest measurements available after the start of medication. For participants with no history of treatment with the selected medications, baseline height and weight measurements were defined as the first measurements taken either at enrollment or after enrollment into P219C or the first measurements taken after the age of 3 years for those younger than 3 years at enrollment. The second height and weight measurements were defined as the latest measurements available within 2 years of baseline. Study nurses recorded medication dates as

reported by parents or older participants or as documented in the medical records available to the study.

Baseline Tanner stage, for children aged 8 years and older, was obtained from the latest record available in P219C, either before or at the time of the baseline height or weight measurement. Tanner staging was classified into 2 categories, Stage 1 and Stage 2 or higher, to capture the onset of puberty (and expected growth spurt) and to minimize the potential for misclassification errors across Stages 2 and higher. Children were classified as Tanner Stage 1 if they were younger than 8 years at baseline or if they were older than 8 years, with no Tanner assessment before or at baseline, but with an assessment subsequent to baseline indicating Tanner Stage 1. Children who did not meet these criteria were recorded as having missing Tanner stage data.

Statistical Analysis

Height-for-age and weight-for-age z scores were calculated with reference to national norms for US children and adolescents¹⁵ using the earliest and latest height and weight measurements within the 2-year interval. This metric was used to control for age-related differences in developmental trajectories of height and weight gains. Baseline height and weight z scores were compared across groups defined by medication class (stimulant versus none; nonstimulant vs. none) using pairwise t tests and compared with population norms within each subgroup using a one-sample t test of mean z score equal to 0. Changes in z scores were calculated by subtracting the z score obtained at baseline from the latest z score within the 2-year interval after baseline, divided by the time between measurements (in years). Changes in z scores were compared between participants with and without prescriptions using multiple linear regression models that adjusted for selected covariates. Separate univariate linear regression models for the change in z scores on each of the potential covariates were fit as well as a full multiple linear regression model that included medication class and all covariates. Forward and backward selection approaches were used to select the final model, with medication class forced into the model.

Covariates

Baseline characteristics of participants and primary caregivers were selected as potential covariates of physical growth. For participants, these characteristics included age, sex, race or ethnicity, Tanner stage, antiretroviral medication class (and switching antiretroviral regimens during the 2-year observation period), diagnoses of neurologic or psychiatric disorders, stressful life events, serious academic difficulties (repeated a grade or receiving special educational services), and limitations on school attendance or daily activities because of illness. Indicators of the child's disease status (CD4 count and percent, HIV RNA, and Centers for Disease Control and Prevention Class C classification) were collected closest to and within 6 months of baseline and considered as potential covariates. For parents and caregivers, the potential covariates included educational level and familial relationship to the child (biological parent, other relative, and foster/adoptive parent).

Covariates with $p < .25$ in either the univariate models or the full multiple linear regression models were initially considered as candidates in model selection. Each neurologic and psychiatric diagnosis was considered, one at a time, after selection of a multivariate model to evaluate any potential effect on medication class estimates. Variables retained in the final model were considered significant when $p < .05$ and marginally significant when $p < .10$.¹⁶ All analyses used data submitted to the P219C data management center by May 2007 and were conducted using SAS 9.1 software (SAS Institute, Cary, NC).

RESULTS

Participants

Of the 2589 children with perinatal HIV infection enrolled in P219C, 367 had a prescription for one or more of the medications shown in Table 1 and met inclusion criteria for this study. Of these, 204 (56%) entered P219C with one or more prescriptions for the selected medications: 4 received their first prescription within 1 month before study entry, 16 within 1 to 3 months, 11 within 3 to 6 months, and 173 more than 6 months before study entry. As an adjunctive measure, we had planned to examine premedication and post-medication growth rates in the sample but were unable to do so because of the large proportion (200 of 367; 55%) of children with prescriptions who entered P219C with medication history greater than 1 month.

Of the 367 who met inclusion criteria, 265 had at least 2 height measurements and 268 had at least 2 weight measurements within 2 years of starting their first medication. At some point during the 2-year interval, 50 children either switched from one medication class to the other or held prescriptions for medications in both classes. Because it would not be possible to determine the relative effect of each regimen on the child's height and weight trajectories, these 50 were excluded from the analyses, resulting in 215 participants with 2 height measurements and 218 with 2 weight measurements collected within 2 years after starting their first medication. Of the 2180 participants in P219C who did not have prescriptions for the selected medications, 2036 had at least 2 height measurements within 2 years after enrollment and 2047 had at least 2 weight measurements.

Table 2 presents the distribution of demographic characteristics of participants included in the height analysis; the distribution was almost identical for those included in the weight analysis. The significant difference in age distribution between participants with prescriptions and those without ($p < .001$) was due to the smaller percentage among those with prescriptions who were 3 to 6 years (3%) and the larger percentage who were 9 to 12 years (42%). The percentage of boys among those with prescriptions was significantly higher than among those without (64 vs. 46%, $p < .001$). Among children with prescriptions, 51% lived with their biological parents or other relatives; among those without prescriptions, 75% lived with biological relatives ($p < .001$). There was no significant difference in racial or ethnic distribution or baseline Tanner stage between participants with and without prescriptions. Of the 2251 children included in this study, 99 (4.4%) had no recorded Tanner assessment available; their data were excluded from subsequent analyses using Tanner staging.

Timing of Measurements

The baseline measurements were defined as the first measurements in P219C obtained after the medication start date; however, the majority of eligible study participants with prescriptions for either a stimulant or non-stimulant entered P219C having held the prescription for at least 1 month. At baseline, the median interval between medication start date and the first available height and weight measurements was 2.0 months (interquartile range = 0.9–5.7 months). The median interval between the first and second assessments, used to assess height growth rates, was 21.6 months (interquartile range = 19.3–23.2 months) for those with prescriptions and 17.5 months (interquartile range = 9.0–20.8 months) for those without prescriptions; these distributions were similar for weight.

Medication Class and Neurologic or Psychiatric Diagnoses

Stimulants were the first medicines prescribed for the majority (83%) of participants with prescriptions (Table 1), and the majority (63%) of these children had one or more reported neurologic or psychiatric diagnoses (Table 3). Except for 2 diagnostic categories (hypotonia/hypertonia and microcephaly/failure to thrive), the prevalence of reported diagnoses was

significantly higher for children with prescriptions than for those without (Fisher's exact test, Table 3). The observed percentages in Table 3 might suggest that the nonstimulant class was driving the results of the comparisons between those on medications versus those not on medications; however, additional exploration using Pearson's χ^2 test and logistic regression analyses comparing the children in each medication class to the group without medications revealed that both medication classes were contributing to the significant differences observed across all diagnostic categories except encephalopathy/cerebral palsy (results available on request). It is important to note that there were relatively high numbers of children in each medication class with no recorded diagnosis: 40% of children with prescriptions for stimulants and 19% of those with prescriptions for nonstimulants (Table 3). For this reason, our findings with respect to medication class and diagnostic category should be interpreted with caution.

Medication Class and Changes in Height

Baseline Height z Scores—Participants with and without prescriptions were shorter on average than the general population of US children of the same age and sex ($p < .001$; Table 4). Children with prescriptions for nonstimulants had the lowest mean height z score at baseline and were significantly shorter than those who did not have prescriptions for either medication class ($p = .008$). Children without prescriptions were marginally shorter than children with prescriptions for stimulants ($p = .06$).

Height Growth Rate—The mean change in height z score was significantly different from 0 for children without prescriptions (mean change = 0.03 standard deviation (SD) per year, $p < .001$; Table 4), indicating they were gaining height at a faster rate than children of the same age and sex in the general population. The mean change in height z score was marginally different from 0 for children with prescriptions for nonstimulants (mean change = -0.14 SD per year, $p = .06$), indicating they were growing more slowly than their peers in the general population. Children with prescriptions for stimulants grew at a rate comparable with their peers in the general population (mean change = 0.01 SD per year, $p = .75$).

After adjusting for all potential covariates, the final multiple linear regression model for change in height z scores (Table 5) showed medication class was a significant predictor of height growth ($p = .02$). Children with prescriptions for nonstimulants had a smaller mean change in height z score than children without prescriptions (slope = -0.159 , 95% confidence interval: -0.271 to -0.048 , $p = .005$). In contrast, children with prescriptions for stimulants were similar in height growth rate to children without prescriptions (slope = -0.007 , $p = .80$). Thus, children with HIV who were prescribed stimulant medications were found to have similar growth in height to children with HIV who were not prescribed any of the medications used to treat attention-deficit hyperactivity disorder (ADHD). Children with HIV who had prescriptions for nonstimulants were found to have made fewer gains in height than either their peers with prescriptions for stimulants or those with no prescriptions for ADHD medications. The final model also showed that the mean change in height z scores was significantly smaller (slower growth rate) for children with higher viral load (slope = -0.028 , $p = .001$) and lower baseline height (slope = -0.059 , $p < .001$). It was significantly larger (faster growth rate) for girls (slope = 0.030 , $p = .04$), adolescents aged 15 to 18 years (slope = 0.077 , $p = .04$), and children with illness-related limitations in daily activities (slope = 0.050 , $p = .03$). In univariate analyses, baseline Tanner stage had a marginally significant association with change in height z scores (slope = -0.030 , $p = .054$); however, it was not significant when included in the multiple linear regression analyses and thus excluded from the final model for height growth rate.

Medication Class and Changes in Weight

Baseline Weight z Scores—Children who did not have prescriptions were significantly below average in weight compared with their peers in the general population (mean weight z

score = -0.11 , $p < .001$; Table 4). There were no significant differences in mean weights at baseline between the children with prescriptions for stimulants or nonstimulants compared with children in the general population ($p = .66$ and $.16$, respectively) and to those without prescriptions ($p = .45$ and $.30$, respectively).

Weight Growth Rate—The mean change in weight z score was significantly different from 0 for children without prescriptions (mean change = 0.03 SD per year, $p < .001$; Table 4), indicating they were gaining weight at a faster rate than children in the general population. The mean change in weight z score was marginally significant for children with prescriptions for nonstimulants (mean change = -0.17 SD per year, $p = .07$), indicating they were gaining weight more slowly than their peers. Children with prescriptions for stimulants grew at a rate comparable with their peers in the general population (mean change = -0.02 , $p = .51$).

After adjusting for all potential covariates, the final multiple linear regression model for change in weight z scores (Table 6) showed medication class was a significant predictor of weight gain ($p = .02$). Children prescribed nonstimulants had a significantly smaller mean change in weight z score than children who did not have prescriptions for either medication class (slope = -0.182 , 95% confidence interval: -0.329 to -0.036 , $p = .02$). The mean change in weight z score for children prescribed stimulants was marginally smaller than the mean change for children without prescriptions (slope = -0.052 , 95% confidence interval: -0.115 to 0.010 , $p = .10$). These findings suggest that the stimulant medications had a subtle, though not statistically significant, adverse influence on weight gain in children with HIV who had prescriptions for medicines used to treat ADHD, relative to children with HIV who were not prescribed any of these medicines. In contrast, nonstimulants were associated with significantly smaller weight gains in children with HIV who were prescribed this form of medication for ADHD, relative to children with HIV who were not prescribed medications for ADHD. The final model also showed the mean change in weight z score was significantly smaller for children with higher viral load (slope = -0.052 , $p < .001$), lower baseline weight (slope = -0.042 , $p < .001$), those aged older than 12 to 15 years (slope = -0.091 , $p = .02$), and those aged older than 15 to 18 years (slope = -0.193 , $p < .001$). In univariate analyses, baseline Tanner stage was not significantly associated with change in weight z scores (slope = 0.017 , $p = .36$); however, it was significant in the multiple linear regression analyses and thus included as a correlate in the final model. Participants at Tanner Stage 2 and higher demonstrated significantly greater weight gain (slope = 0.122 , $p < .001$) than those at Tanner Stage 1.

DISCUSSION

The children and adolescents in this study were shorter on average than their peers in the general population, whether or not they held prescriptions for stimulant or nonstimulant medications, and the children who did not have prescriptions for either medication class were significantly below average in weight compared with population norms. These findings are consistent with previous studies of physical growth in children and adolescents with HIV.^{13,14} Children with prescriptions for either stimulants or nonstimulants were similar in weight to their peers in the general population; these findings are not consistent with previous research showing significantly lower weight in children with HIV.^{13,14} For children with HIV who were prescribed stimulants, we found no significant difference in height growth rate and a marginally significant difference in weight growth relative to children with HIV who were not prescribed medications used to treat attention-deficit hyperactivity disorder (ADHD). Interestingly, in contrast, children prescribed nonstimulants were found to have significantly slower rates of growth in both height and weight relative to children with HIV who were not prescribed any medications for ADHD. Thus, our findings indicate that stimulants exert a subtle, adverse influence on weight gain, whereas nonstimulants are associated with significantly increased risks for growth delays in both height and weight, beyond that attributable to HIV alone. It

should be noted that with the sample sizes used, the minimal stimulant effect size that the analysis could detect using 5% significance level and with 80% power is 0.10. Hence, a marginally significant result may signal the plausible presence of a smaller effect not detectable with the sample size used but which may be clinically interesting.

The interval between height and weight measurements was shorter for children with prescriptions than for those without, reflecting the need for frequent monitoring of children with prescriptions for medicines used to treat ADHD. For the children prescribed stimulants, it is possible that these more frequent clinic visits provided additional opportunities for clinicians to initiate interventions that directly or indirectly improved the children's physical growth. Alternatively, the children's prescribing physicians may have been inclined to prescribe the stimulants to those youth with HIV who were not significantly undernourished at their premedication baseline, but limitations in the pretreatment growth data precluded us from examining this possibility.

Children prescribed nonstimulants had the lowest mean height z score at the time of the first measurement and were significantly shorter than those without prescriptions. Their height growth rate was marginally slower than expected based on population norms and significantly slower (after adjusting for important covariates) than children with no prescriptions. They gained weight more slowly (marginally) than peers in the general population and showed significantly smaller weight gain than children in this study who did not have prescriptions. This group also had the largest diversity of neurologic and psychiatric diagnoses, including cerebral palsy, anxiety and affective disorders, and failure to thrive. This pattern, combined with the diversity of pharmacodynamic properties and side-effect profiles of the 5 nonstimulants in this study, precludes attribution of the study findings to any particular pharmacological mechanism.

Almost one half of the children with prescriptions for stimulants and more than one third of those prescribed nonstimulants had a reported diagnosis of ADHD or other behavior disorder, but there were no reported psychiatric diagnoses for a relatively large proportion of the sample: 40% of children with prescriptions for stimulants and 19% with prescriptions for nonstimulants. The availability of data concerning neurologic and psychiatric diagnoses varied across sites in P219C because of differences in the sites' access to medical and psychiatric records, and the results reported here probably underestimate the true frequency of psychiatric diagnoses in the P219C cohort. Similarly, the fact that ADHD and behavior problems were only reported for 38% of children on nonstimulants suggests that these medications were prescribed for other reasons, for example, for depression or anxiety disorders. Nevertheless, given the present study's focus on ADHD medication side effects on physical growth, the availability of data central to the analyses was not affected by this limitation.

The study was limited by lack of control over the interval between medication start date and the first height and weight measurements. The median interval of 2 months was longer than anticipated because of the large proportion of children who entered P219C with prescriptions for stimulants or nonstimulants. Although we do not believe this longer interval at baseline significantly affected our ability to capture changes in height growth rate during the 2-year period, it is possible that it affected capture of the earliest effects of stimulant medication on appetite and weight gain. The study was also limited by lack of data concerning the children's adherence to stimulants and nonstimulants and concomitant use of antipsychotic medications. An increase in weight as a side effect of antipsychotic medications¹⁷ could offset a decrease in weight as a side effect of stimulant medications. Knowledge of the children's access to nutritionists and use of dietary supplements would have assisted in the interpretation of results but was unavailable. Finally, a longer period of follow-up, in conjunction with information about the children's adherence to stimulant and nonstimulant medications, would have allowed

a more detailed examination of changes in physical growth as a function of medication use and advancing HIV disease.

The findings of this study indicate that the use of stimulant medications to treat symptoms of ADHD in children and adolescents with HIV does not significantly exacerbate the potential for growth delay beyond the risk attributable to HIV alone. Nevertheless, given the importance of weight maintenance in children with HIV disease, the subtle effects observed in this sample warrant clinical consideration and indicate the need for additional research to replicate the findings. Furthermore, the results suggest that children and adolescents with HIV who receive treatment for problem behaviors might experience unexpected benefits in physical growth, possibly because of increased contact with clinical personnel or because the children and/or their caregivers become more reliable and responsible for their health care regimen and general well-being. Future research should include prospective studies designed to evaluate the effect of medical treatment for ADHD on the physical growth of children and adolescents with HIV and examine the cost of the side effects relative to the benefits of treatment.

APPENDIX

The following institutions, by order of enrollment, were involved in the design, data collection, and conduct of P219C but not involved in the present analysis, interpretation of data, writing of the manuscript, or decision to submit for publication: Baylor Texas Children's Hospital: Minglana F, Paul ME, Jackson CD; University of Florida, Jacksonville: Rathore MH, Khayat A, Champion K, Cusic S; Chicago Children's Memorial Hospital: Yogev R, Chadwick E; University of Puerto Rico, University Children's Hospital AIDS Program: Febo-Rodriguez I, Nieves S; Bronx Lebanon Hospital Center: Purswani M, Baksi S, Stuard E, Dummit M; San Juan Hospital: Acevedo M, Gonzalez M, Fabregas L, Texidor ME; University of Miami: Scott GB, Mitchell CD, Taybo L, Willumsen S; University of Medicine & Dentistry of New Jersey: Bettica L, Amour J, Dashefsky B, Dieudonne A; Charity Hospital of New Orleans & Earl K. Long Early Intervention Clinic: Van Dyke R, Silio M, Alchediak T, Borne C, Cowie M; UCSD Mother, Child & Adolescent HIV Program: Spector SA, Viani R, Caffery M, Proctor L; Howard University: Rana S, Darbari D, Roa JC, Yu PH; Jacobi Medical Center: Donovan M, Serrano R, Burey M, Auguste R; St. Christopher's Hospital for Children, Philadelphia: Chen J, Foster J; Baystate Medical Center Children's Hospital: Stechenberg BW, Fisher DJ, Johnston AM, Toye M; Los Angeles County Medical Center/USC: Homans J, Neely M, Spencer LS, Kovacs A; Children's Hospital Boston: Burchett S, Karthas N; Children's Hospital of Michigan: Moore E, Cromer C; St. Jude Children's Research Hospital, Memphis: Flynn PM, Patel N, Donohoe M, Jones S; New York University School of Medicine/Bellevue Hospital: Borkowsky W, Chandwani S, Deygoo N, Akleh S; The Children's Hospital at Downstate: Handelsman E, Moallem HJ, Swindell DM, Kaye JM; The Columbia Presbyterian Medical Center & Cornell University New York Presbyterian Hospital: Higgins A, Foca M, LaRussa P, Gershon A; The Children's Hospital of Philadelphia: Rutstein RM, Vincent CA, Douglas SD, Koutsoubis GA; Children's Hospital of Oakland: Petru A, Courville T; UCSF, Moffitt Hospital: Wara D, Trevithick D; Children's Hospital, University of Colorado, Denver: McFarland E, Salbenblatt C; Johns Hopkins University Pediatrics: Hutton N, Griffith B, Joyner M, Kiefner C; Children's Hospital and Regional Medical Center, Washington: Acker M, Croteau R, McLellan C, Mohan K; Metropolitan Hospital Center: Bamji M, Pathak I, Manwani S, Patel E; Children's National Medical Center: Spiegel H, Amos V; University of Massachusetts Medical School: Luzuriaga K; University of Alabama at Birmingham: Pass R, Crain M; University of Maryland Medical Center: Farley J, Klipner K; Schneider Children's Hospital: Bonagura VR, Schuval SJ, Colter C, Campbell L; Boston Medical Center: Pelton SI, Reagan AM; University of Illinois: Rich KC, Hayani K, Bicchinella M; SUNY Stony Brook: Nachman S, Ferraro D, Madjar S; North Broward Hospital District: Puga A; Duke University: Wiley F, Whitfield K, Johnson O, Dizney R; Harlem Hospital: Champion S, Frere M, DiGrado

M, Abrams EJ; Cook County Hospital: Martinez J; University of South Alabama: Mancao M; Connecticut Children's Medical Center: Salazar J, Karas G; University of North Carolina at Chapel Hill: Belho T, Pitkin B, Eddleman J; Ruiz Arnau University Hospital: Figueroa W, Reyes E; SUNY Upstate Medical University: Weiner LB, Contello KA, Holz WA, Famiglietti MJ; Children's Medical Center of Dallas; University of Florida at Gainesville: Lawrence R, Lew J, Delany C, Duff C; Children's Hospital at Albany Medical Center: Fernandez AD, Hughes PA, Wade N, Adams ME; Lincoln Medical & Mental Health Center; Phoenix Children's Hospital: Piatt JP, Foti J, Clarke-Steffen L; Public Health Unit of Palm Beach County: Sleasman J, Delaney C; Medical College of Georgia: Mani CS; Yale University School of Medicine: Andiman WA, Romano S, Hurst L, de Jesus J; Vanderbilt University Medical Center: Wilson G; University of Rochester Medical Center: Weinberg GA, Gigliotti F, Murante B, Lavery S; St. Josephs Hospital and Medical Center, New Jersey: Hutchcon N, Townley A; Emory University Hospital: Nesheim S, Dennis R; University of South Florida: Emmanuel P, Lujan-Zilberman J, Graisberry C, Moore S; Children's Hospital of the King's Daughters: Fisher RG, Cunnion KM, Rubio TT, Sandifer D; Medical University of South Carolina: Johnson GM; University of Mississippi Medical Center: Gay H, Sadler S; Harbor-UCLA Medical Center: Keller M, Hayes J, Gagajena A, Mink C; Mount Sinai Medical Center: Johnson D; Children's Hospital of Los Angeles: Church J, Dunaway T, Salata C; Long Beach Memorial: Deveikis A, Melton L; Robert Wood Johnson Medical School: Gaur S, Whitley-Williams P, Malhotra A, Cerracchio L; Sinai Children's Hospital: Dolan M, D'Agostino J, Posada R; The Medical Center, Pediatric Columbus, Georgia: Mani C, Cobb S; Medical College of Virginia: Lavoie SR, Smith TY; Cooper Hospital—University Medical Center: Feingold A, Burrows-Clark S; University of Cincinnati: Mrus J, Beiting R; Columbus Children's Hospital: Brady M, Hunkler J, Koranyi K; Sacred Heart Children's CMS of Florida: Albritton W; St. Luke's/Roosevelt Hospital Center: Warford R, Arpadi S; Incarnation Children's Center, New York: Gershon A, Miller P; Montefiore Medical—AECOM: Rubinstein A, Krienik G; Children's Hospital of Los Angeles: Kovacs A, Operskalski E; San Francisco General Hospital: Wara D, Kamrin A, Farrales S; Cornell University New York Presbyterian: Johan-Liang R, O'Keefe K; St. Louis Children's Hospital: McGann KA, Pickering L, Storch GA; North Shore University Hospital: Pahwa S, Rodriguez L; Oregon Health and Science University: Lewis P, Croteau R.

Acknowledgments

We thank the children and their families, the P219C study team, and the individuals and institutions involved in the conduct of P219C for contributing to this research. The study was supported by the National Institute of Allergy and Infectious Diseases (grant numbers U01AI068632 and 1U01AI068616), the National Institute of Child Health and Human Development, and the Statistical and Data Analysis Center (SDAC) of the Pediatric AIDS Clinical Trials Group at Harvard School of Public Health, under the National Institute of Allergy and Infectious Diseases cooperative agreement No. 5U01AI41110. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Allergy and Infectious Diseases or the National Institutes of Health. The institutions shown in the Appendix, by order of enrollment, were involved in the design, data collection, and conduct of P219C but not involved in the present analysis, interpretation of data, writing of the manuscript, or decision to submit for publication.

References

1. Donenberg GR, Pao M. Youths and HIV/AIDS: psychiatry's role in a changing epidemic. *J Am Acad Child Adolesc Psychiatry* 2005;44:728–747. [PubMed: 16034275]
2. American Academy of Child and Adolescent Psychiatry. Practice parameter for the assessment and treatment of children and adolescents with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 2007;46:894–921. [PubMed: 17581453]
3. Pearson DA, Santos CW, Roache JD, et al. Treatment effects of methylphenidate on behavioral adjustment in children with mental retardation and ADHD. *J Am Acad Child Adolesc Psychiatry* 2003;42:209–216. [PubMed: 12544181]

4. Pearson DA, Loveland KA, Lachar D, et al. A comparison of behavioral and emotional functioning in children and adolescents with autistic disorder and PDD-NOS. *Child Neuropsychol* 2006;12:321–333. [PubMed: 16911976]
5. Pliszka SR, Greenhill LL, Crismon ML, et al. The Texas Children's Medication Algorithm Project: Report of the Texas Consensus Conference Panel on Medication Treatment of Childhood Attention-Deficit/Hyperactivity Disorder. Part I. *J Am Acad Child Adolesc Psychiatry* 2000;39:908–919. [PubMed: 10892234]
6. Pliszka SR, Greenhill LL, Crismon ML, et al. The Texas Children's Medication Algorithm Project: Report of the Texas Consensus Conference Panel on Medication Treatment of Childhood Attention-Deficit/Hyperactivity Disorder. Part II: tactics. *J Am Acad Child Adolesc Psychiatry* 2000;39:920–927. [PubMed: 10892235]
7. Poulton A. Growth and sexual maturation in children and adolescents with attention deficit hyperactivity disorder. *Curr Opin Pediatr* 2006;18:427–434. [PubMed: 16914999]
8. Swanson J, Greenhill L, Wigal T, et al. Stimulant-related reductions of growth rates in the PATS. *J Am Acad Child Adolesc Psychiatry* 2006;45:1304–1313. [PubMed: 17023868]
9. Pliszka SR, Matthews TL, Braslow KJ, et al. Comparative effects of methylphenidate and mixed salts amphetamine on height and weight in children with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 2006;45:520–526. [PubMed: 16670648]
10. Spencer TJ, Faraone SV, Biederman J, et al. Does prolonged therapy with a long-acting stimulant suppress growth in children with ADHD? *J Am Acad Child Adolesc Psychiatry* 2006;45:527–537. [PubMed: 16670649]
11. Banaschewski T, Roessner V, Dittmann RW, et al. Non-stimulant medications in the treatment of ADHD. *Eur Child Adolesc Psychiatry* 2004;13(Suppl 1):I102–I116. [PubMed: 15322961]
12. Kratochvil CJ, Wilens TE, Greenhill LL, et al. Effects of long-term atomoxetine treatment for young children with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 2006;45:919–927. [PubMed: 16865034]
13. Buchacz, K.; Cervia, JS.; Lindsey, JC., et al. Impact of protease inhibitor-containing combination antiretroviral therapies on height and weight growth in HIV-infected children; *Pediatrics*. 2001 [September 1, 2009]. p. e72<http://www.pediatrics.org/cgi/content/full/108/4/e72>
14. Hilgartner, MW.; Donfield, SM.; Lynn, HS., et al. Hemophilia Growth and Development Study. The effect of plasma human immunodeficiency virus RNA and CD4+ T-lymphocytes on growth measurements in hemophilic boys and adolescents; *Pediatrics*. 2001 [September 1, 2009]. p. e56<http://www.pediatrics.org/cgi/content/full/107/4/e56>
15. Centers for Disease Control and Prevention. National Health and Nutrition Examination Survey: Z-score data files. 2000 [November 7, 2008]. Available at: <http://www.cdc.gov/nchs/about/major/nhanes/growthcharts/zscore/zscore.htm>
16. Rosnow RL, Rosenthal R. Statistical procedures and the justification of knowledge in psychological science. *Am Psychol* 1989;44:1276–1284.
17. Kapetanovic S, Simpson GM. Review of antipsychotics in children and adolescents. *Expert Opin Pharmacother* 2006;7:1871–1885. [PubMed: 17020414]

Table 1

Medications Selected for Study and Medication History of Study Participants (N = 367)

Generic Name	First Prescribed, n (%)	Ever Prescribed, n (%)
Stimulants		
Methylphenidate	211 (57)	321 (87)
Mixed amphetamine salts (dextroamphetamine saccharate, amphetamine aspartate, dextroamphetamine sulfate, amphetamine sulfate)	72 (20)	125 (34)
Dextroamphetamine sulfate	16 (4)	27 (7)
Dexmethylphenidate	3 (1)	7 (2)
Magnesium pemoline	1 (<1)	1 (<1)
Nonstimulants		
Clonidine Hcl	31 (8)	69 (19)
Atomoxetine Hcl	8 (2)	43 (12)
Bupropion Hcl	11 (3)	27 (7)
Guanfacine Hcl	6 (2)	21 (6)
Imipramine Hcl, desipramine Hcl	8 (2)	14 (4)

Table 2

Selected Characteristics of Participants at the Time of Baseline Height Measurement

Characteristic	Overall (N = 2251)	With Prescriptions (N = 215)	Without Prescriptions (N = 2036)	<i>p</i>
Age at height measurement (yrs)				<.001 ^a
3–6	470 (21%)	7 (3%)	463 (23%)	
>6–9	548 (24%)	66 (31%)	482 (24%)	
>9–12	636 (28%)	91 (42%)	545 (27%)	
>12–15	406 (18%)	36 (17%)	370 (18%)	
>15–18	191 (8%)	15 (7%)	176 (9%)	
Female gender	1182 (53%)	78 (36%)	1104 (54%)	<.001 ^b
Race/ethnicity				0.141 ^a
White, non-Hispanic	289 (13%)	31 (14%)	258 (13%)	
Black, non-Hispanic	1332 (59%)	130 (60%)	1202 (59%)	
Hispanic	591 (26%)	47 (22%)	544 (27%)	
Others	39 (2%)	7 (3%)	32 (2%)	
Primary caregiver				<.001 ^a
Biological parent	1057 (47%)	54 (25%)	1003 (49%)	
Relative	584 (26%)	55 (26%)	529 (26%)	
Other adults	582 (26%)	95 (44%)	487 (24%)	
Other/unknown	28 (1%)	11 (5%)	17 (1%)	
Tanner stage				.793 ^a
Stage 1	1424 (66%)	140 (67%)	1284 (66%)	
Stage 2 or higher	728 (34%)	69 (33%)	659 (34%)	
Missing	99 (—)	6 (—)	93 (—)	
HIV RNA ^c [in log(copies/mL)]				.568 ^d
Mean (SD)	3.38 (0.91)	3.34 (0.88)	3.38 (0.91)	
Median	2.98	2.89	2.99	
CD4 count ^e				.036 ^d
Mean (SD)	857.6 (535.6)	784.5 (436.9)	865.4 (544.5)	
Median	778.0	738.0	781.0	
CD4 percent ^e				.099 ^d
Mean (SD)	29.5 (10.9)	30.7 (11.1)	29.4 (10.8)	
Median	30.0	32.0	30.0	

^a Pearson's χ^2 test, missing values excluded.^b Fisher's exact test.^c Ten patients had no viral load (HIV RNA) data within 6 months from the date of height measurement (7 without prescriptions, 3 with prescriptions).^d Student's *t* test for 2 independent samples.

^eTwenty-six patients had no CD4 count and CD4 percent data within 6 months from the date of height measurement (24 without prescriptions, 2 with prescriptions). The distribution of characteristics was similar at the time of the baseline weight measurement.

Table 3

First Medication Prescribed, by Selected Neurologic and Psychiatric Diagnoses, for Participants With Height Growth Measurements (N = 2251)

Diagnostic Category ^a	First Medication Prescribed		
	Stimulant, n (% of 183)	Nonstimulant, n (% of 32)	None, n (% of 2036)
ADHD/behavior disorder ^{***}	85 (46)	12 (38)	69 (3)
Encephalopathy/cerebral palsy [*]	21 (11)	13 (41)	206 (10)
Hypotonia/hypertonia	19 (10)	6 (19)	243 (12)
Intellectual disabilities/developmental disorder ^{**}	19 (10)	5 (16)	105 (5)
Epilepsy/seizure/infantile spasm ^{**}	13 (7)	4 (13)	64 (3)
Depression/anxiety/bipolar disorder ^{b***}	9 (5)	6 (19)	47 (2)
Microcephaly/failure to thrive	9 (5)	4 (13)	99 (5)
At least one of the above ^{***}	109 (60)	26 (81)	542 (27)
None of the above	74 (40)	6 (19)	1494 (73)

ADHD, attention-deficit hyperactivity disorder.

^aIncludes diagnoses recorded until the time of the second height measurement.

^bIncludes dysthymia and suicidal tendencies.

* $p < .05$;

** $p < 0.01$;

*** $p < 0.001$.

The distribution of diagnoses was similar for the group of participants with weight growth measurements. p values based on Fisher's exact test of the difference between the group with prescriptions (stimulants or nonstimulants) vs. the group without prescriptions. Both medication classes contributed to the significant differences across all categories except encephalopathy/cerebral palsy.

Table 4

Height and Weight z Scores and Changes in z Scores by Medication Class

Variable	Medication Class			Between Group Comparison (<i>p</i> Value) ^a	
	Stimulant	Nonstimulant	None	Stimulant vs. None	Nonstimulant vs. None
Baseline height z score (n)	183	32	2036		
Mean (SD)	-0.37 (1.03)	-1.11 (1.29)	-0.54 (1.20)	.06	.008
Median (25th, 75th)	-0.30 (-1.14 to 0.36)	-1.22 (-1.80 to -0.36)	-0.49 (-1.30 to 0.28)		
Within group <i>p</i> value ^b	<.001	<.001	<.001		
Change in height z score, per year (n)	183	32	2036		
Mean (SD)	0.01 (0.36)	-0.14 (0.40)	0.03 (0.34)	.45	.005
Median (25th, 75th)	-0.03 (-0.20 to 0.20)	-0.13 (-0.33 to 0.11)	0.01 (-0.15 to 0.19)		
Within group <i>p</i> value ^b	.754	.063	<.001		
Baseline weight z score (n)	185	33	2047		
Mean (SD)	-0.04 (1.08)	-0.33 (1.32)	-0.11 (1.22)	0.45	.30
Median (25th, 75th)	-0.09 (-0.81 to 0.65)	-0.14 (-1.17 to 0.70)	-0.08 (-0.84 to 0.66)		
Within group <i>p</i> value ^b	.657	.158	<.001		
Change in weight z score, per year (n)	185	33	2047		
Mean (SD)	-0.02 (0.47)	-0.17 (0.53)	0.03 (0.40)	0.11	.005
Median (25th, 75th)	-0.04 (-0.27 to 0.23)	-0.12 (-0.43 to 0.19)	0.02 (-0.14 to 0.22)		
Within group <i>p</i> value ^b	0.511	0.072	<.001		

^a *p* Value based on two-sample *t* test.

^b Within group *p* value based on Student's one-sample *t* test for the mean.

Table 5

Final Multiple Linear Regression Model of Change in Height *z* Scores Among Participants With and Without Prescriptions for Selected Medications (n = 215)

Predictor	Slope	95% Confidence Interval		<i>p</i>
Intercept	−0.040	−0.179	0.100	.571
Medication class	—	—	—	.020
None	0.000	—	—	Ref
Stimulant	−0.007	−0.056	0.043	.796
Nonstimulant	−0.159	−0.271	−0.048	.005
Age group (yrs)	—	—	—	.005
3–6	0.000	—	—	Ref
>6–9	0.061	−0.001	0.123	.056
>9–12	0.004	−0.058	0.066	.904
>12–15	0.024	−0.041	0.089	.468
>15–18	0.077	0.002	0.151	.044
Female	0.030	0.002	0.058	.039
Log(RNA)	−0.028	−0.044	−0.012	.001
Baseline height <i>z</i> score	−0.059	−0.072	−0.047	<.001
Interval between measurements	−0.0002	−0.0003	−0.0001	.001
Limited school attendance	0.040	−0.005	0.085	.083
Limited activities	0.050	0.005	0.096	.029

Table 6

Final Multiple Linear Regression Model of Change in Weight *z* Scores Among Participants With and Without Prescriptions for Selected Medications (n = 218)

Predictor	Slope	95% Confidence Interval		<i>p</i>
Intercept	0.107	0.011	0.202	.029
Medication class	—	—	—	.016
None	0.000	—	—	Ref
Stimulant	−0.052	−0.115	0.010	.100
Nonstimulant	−0.182	−0.329	−0.036	.015
Age group (yrs)	—	—	—	<.001
3–6	0.000	—	—	Ref
>6–9	0.011	−0.039	0.062	.655
>9–12	−0.070	−0.124	−0.016	.011
>12–15	−0.091	−0.168	−0.014	.021
>15–18	−0.193	−0.286	−0.100	<.001
Tanner stage 2 and higher	0.122	0.054	0.171	<.001
Log(RNA)	−0.052	−0.071	−0.033	<.001
Baseline weight <i>z</i> score	−0.042	−0.056	−0.027	<.001
Encephalopathy/cerebral palsy	−0.052	−0.107	0.004	.068
Microcephaly/failure to thrive	−0.070	−0.148	0.009	.081