Lack of Long-term Effects of In Utero Exposure to Zidovudine Among Uninfected Children Born to HIV-Infected Women

Mary Culnane, MS, CRNP
MaryGlenn Fowler, MD, MPH
Sophia S. Lee, MS
George McSherry, MD
Michael Brady, MD
Karen O’Donnell, PhD
Lynne Mofenson, MD
Steven L. Gortmaker, PhD
David E. Shapiro, PhD
Gwendolyn Scott, MD
Eleanor Jimenez, MD
Ellen C. Moore, MD
Clemente Diaz, MD
Patricia M. Flynn, MD
Bethann Cunningham, MS
James Oleske, MD, MPH
for the Pediatric AIDS Clinical Trials Group Protocol 219/076 Teams

Since the results of the successful perinatal human immunodeficiency virus (HIV) prevention trial, the Pediatric AIDS Clinical Trials Group Protocol 076 (PACTG 076), which included an intensive regimen of zidovudine, were reported in February 1994, use of zidovudine for prevention of mother-to-infant transmission of HIV has become widespread in the United States. However, the late effects of perinatal exposure to antiretroviral drugs on the subsequent health of uninfected children are unknown and can be determined only by the long-term follow-up of children exposed in utero.

Zidovudine is a nucleoside analog reverse transcriptase inhibitor that has been extensively studied in adults and children infected with HIV and shown to...
have moderate antiviral effects for the treatment of persons with HIV infection at all stages of disease. Short-term reversible adverse effects associated with use in adults and children are well documented and include anemia, neutropenia, and elevation of liver enzyme levels. In preclinical lifetime animal carcinogenicity studies, high dosages of zidovudine administered to adult rodents have been associated with the development of vaginal epithelial neoplasms in female rodents receiving the highest dosage, a finding that may be explained by the presence of high concentrations of unmetabolized zidovudine in the rodent urine and reflux from the bladder into the vagina.

Although no significant short-term toxic effects were observed in PACTG 076 for those mothers and infants who received zidovudine, the late effects of in utero zidovudine exposure for growing children and adults are unknown. Based on theoretical concerns about the unknown long-term consequences in utero, PACTG 076 infant participants were prospectively monitored for late effects of therapy in an ongoing long-term follow-up study, the Pediatric AIDS Clinical Trials Group Protocol 219 (PACTG 219).

The purpose of the present study was to describe the safety of perinatal zidovudine for prevention of mother-to-child HIV transmission among HIV-uninfected children with in utero zidovudine exposure. Prospective comparative evaluations were made of the growth, immunologic, cognitive/developmental, cardiac, ophthalmologic, neoplasm, and mortality data available to date for the uninfected children from PACTG 076 coenrolled in PACTG 219 who were randomized to zidovudine or placebo prenatally, intrapartum, and during the immediate postnatal period.

**METHODS**

**Patients and Study Design**

The Pediatric AIDS Clinical Trials Group Protocol 076 was a multicenter, randomized, double-blind, placebo-controlled trial of zidovudine for prevention of perinatal HIV-1 transmission conducted in the United States and France. Asymptomatic pregnant women who were infected with HIV and their newborns were randomized to receive either zidovudine or placebo. Women were treated with oral zidovudine perpartum and intravenous zidovudine during the intrapartum period. Infants received the same randomized treatment assignment as their mothers for the first 6 weeks of life. The first subject enrolled in April 1991. The study was closed to new enrollment and unblinded in February 1994, after an interim analysis demonstrated a significant effect of zidovudine in reducing the risk of perinatal HIV transmission.

All caregivers of infants enrolled in PACTG 076 centers in the United States were offered long-term follow-up for their children in PACTG 219, a long-term, prospective, observational study designed to assess late effects of in utero and neonatal exposure to antiretroviral drugs in perinatal HIV clinical trials as well as late effects of antiretroviral treatment in infected children. All children participating in PACTG perinatal prevention or treatment trials are eligible for enrollment. Comprehensive history taking and physical examinations, including growth, cognitive/developmental function, and quality-of-life data, are performed at least annually. Children are scheduled to be followed up until age 21 years. Since 1993, more than 2200 children initially enrolled in PACTG trials have been followed up in PACTG 219, and one quarter of these children had participated in perinatal prevention trials. The study was approved by the review boards for human subject research at each participating institution. Written informed consent was obtained from each child’s parent or legal guardian.

The study population chosen for these analyses included children who participated in PACTG 076 and subsequently enrolled in PACTG 219. Data available as of February 28, 1997, from PACTG 076 children who were born on or before January 4, 1994, were included in this analysis. Children born after January 4, 1994, were excluded because they could not have completed 6 weeks of blinded treatment before the PACTG 076 study was unblinded. All analyses are based on the randomized assignment in PACTG 076 and are intent-to-treat analyses. Findings from uninfected children randomized to zidovudine in utero and for 6 weeks postpartum were compared with uninfected children randomized to placebo.

**Clinical and Laboratory Monitoring**

History, physical examination, growth measurements, and quality-of-life assessments were collected at baseline and every 6 months for children younger than 2 years and every 12 months after age 2 years. Lymphocyte subsets were collected on the same schedule until age 2 years but only as clinically indicated thereafter. Percentages of lymphocyte subsets vary less with age and were used for these analyses. Growth and lymphocyte subset data from PACTG 219 were combined with data collected during the initial 18-month follow-up period of the PACTG 076 protocol.

Cognitive/developmental function tests consisted of the Bayley Scales of Infant Development for children 30 months of age or younger and the McCarthy Scales of Children’s Ability for children aged 30 months to 6 years. Tests were performed at baseline and every 6 months through 24 months of age and then at age 3 years. Raw data from the tests were individually reviewed by the protocol psychologist (K.O.) to ensure that tests seen as invalid by the site examiner and the protocol psychologist were not included in the analyses and questionable data (eg, widely variable scores from one test to the next) could be verified by a query to the site.

Echocardiograms and ophthalmologic examinations (including visual acuity assessment and funduscopic examination) were required for all children by 36 months of age. Sites were asked to enter all echocardiographic and funduscopic results into the database regardless of whether the examination was performed as part of PACTG 219. Examining cardiologists and ophthalmologists were asked to report the clinical rel-
Evidence of any abnormal echocardiogram or funduscopic findings, other related clinical findings (if any), and the child’s current diagnosis, management plan, and health status.

All data, including deaths, echocardiogram results, funduscopic examination results, and cognitive/developmental function test results, were reviewed by members of the study team who were blinded to PACTG 076 treatment assignment.

**Statistical Methods**

Comparisons were based on PACTG 076 randomized treatment assignments and performed using t tests or Wilcoxon tests for continuous outcomes, the likelihood ratio χ² test or Fisher exact test for categorical outcomes, and the Wei-Johnson method on repeated measures CIs.

CIs were calculated assuming a constant difference over time.⁰ All P values are 2-sided.

Infant length/height, weight, and head circumference measurements were converted to age- and sex-adjusted z scores using the Centers for Disease Control and Prevention/World Health Organization standard international growth standard based on the National Center for Health Statistics and Fels reference databases.¹¹ Group mean scores were calculated for specified nominal ages and expressed as the corresponding percentile.

The statistical power of this follow-up study for each outcome measure is indicated below the width of the 95% confidence interval (CI) for the difference from the placebo group mean, based on the sample sizes available. These CIs were calculated assuming a constant difference over time, based on the Wei-Johnson test.¹⁰ Confidence intervals were also translated into more meaningful metrics, eg, the CI for the difference in z scores of weight for age was translated into a difference in SD units (SDU, expressed as a proportion of the SD of the outcome variable) as well as a difference in weight in kilograms.

The 95% CI for a difference between treatment groups over 36 months in weight-for-age z scores was ±0.25 z scores or ±0.18 SDU (corresponding to a difference of ±0.50 kg from the placebo group mean). The 95% CI for a difference in height-for-age z scores over 36 months was ±0.24 z scores or ±0.22 SDU (corresponding to a difference of ±1.0 cm from the placebo group mean). The 95% CI for a difference in head circumference-for-age z scores over 24 months was ±0.25 z scores, or ±0.21 SDU. Similarly, the 95% CI for a difference in CD4+ T lymphocyte percentage over 24 months was ±1.8% (0.25 SDU), and for CD8+ T lymphocyte percentage was ±1.5% (0.27 SDU). The 95% CI for a difference in Bayley scores over 24 months was ±5.0 points (0.28 SDU). With only 1 follow-up at 36 months, the 95% CI for a difference in McCarthy scores was ±8.9 points (0.54 SDU).

**RESULTS**

**Baseline Patient Characteristics**

Three hundred thirty-two PACTG 076 uninfected infants (177 in the zidovudine group and 155 in the placebo group) were born at US centers on or before January 4, 1994, and were alive at the time PACTG 219 opened to enrollment in May 1993. Two hundred thirty-four (122 in the zidovudine group and 112 in the placebo group) enrolled in PACTG 219 and met the defined criteria for inclusion in these analyses. One PACTG 076 infant who enrolled at 12 months of age into PACTG 219 was lost to follow-up before infection status was determined. This infant has been excluded from the analyses.

Two hundred thirty-four uninfected children randomized to zidovudine or placebo were born to 230 mothers (1.7% twin births). Characteristics of these mothers and uninfected children were similar to those of the original PACTG 076 study population and did not differ significantly when compared with the mothers and uninfected children who did not enroll in PACTG 219 (Table 1). As of February 28, 1997, the median age of the children at the time of the last follow-up visit was 4.2 years (range, 3.2-5.6 years) and 86% of the uninfected children enrolled in PACTG 219 were still participating in the study; 26 children...
were lost to follow-up or their caregivers refused further contact.

Safety Results

Deaths and Malignancies. There were no deaths or malignancies among the uninfected children.

Growth. Mean age percentiles for weight and height are shown in Figure 1. The uninfected zidovudine group and placebo group followed similar curves, with normal mean weight and height. There were no observed differences between the groups through 208 weeks.

Likewise, no treatment differences in head circumference were noted (Figure 1).

Cognitive/Developmental Function. Five hundred ten Bayley and McCarthy assessments were available from 209 uninfected children (108 in the zidovudine group and 101 in the placebo group). A total of 466 evaluable tests (91%) were included in the analysis.

Overall, both the zidovudine and placebo uninfected children demonstrated normal cognitive/developmental function. Table 2 shows the means for the mental development index (MDI) and psychomotor development index (PDI) on the Bayley Scales of Infant Development. There were no significant differences between groups for the Bayley MDI or PDI scores (Wei-Johnson P value for MDI scores = .24; for PDI scores, P = .84).

Among the oldest children studied in the cohort, McCarthy scores were available from 108 uninfected children: 55 children from the zidovudine group and 53 from the placebo group. The General Cognitive Index (from the McCarthy Scales of Children’s Ability) means for the zidovudine and placebo groups were 85.2 and 85.3, respectively; there was no significant difference between the groups (Wilcoxon P value = .78). The proportion of children with scores lower than 70 (2 SDs below test mean) for both the Bayley and McCarthy tests were equivalent in the zidovudine and placebo groups.

Immunologic Function. Among the uninfected PACTG 076/219 children, mean CD4+ and CD8+ lymphocyte percentages did not differ between treatment groups over time (Figure 2). There were no statistically significant differences between zidovudine and placebo groups either at each point or when analyzed on an overall basis (Wei-Johnson P value = .53 for CD4+; P = .38 for CD8+).

Cardiac Observations. One hundred eighty-six uninfected children (80%) had at least 1 echocardiogram result recorded in the database; 97 (80%) were in the zidovudine group and 89 (80%) were in the placebo group. Sixty-six (28%) of 234 children were missing baseline examinations (ie, >36 months of age without baseline echocardiogram results reported).

Twenty-nine uninfected children (16%) had an abnormal echocardiogram result: 16 (16%) in the zidovudine group and 13 (15%) in the placebo group. There was no significant difference between treatment groups in terms of the abnormal echocardiogram results (Fisher exact P value = .84). None of these children had required an echocardiogram on the basis of symptoms. All echocardiograms were performed to meet PACTG 219 requirements or because the

Figure 1. Mean Age Percentiles for Growth Parameters With 95% Confidence Intervals for Uninfected Infants Who Received Zidovudine or Placebo in the Pediatric AIDS Clinical Trials Group Protocol 076

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Zidovudine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head Circumference</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
child was participating in a natural history study that also required at least 1 echocardiogram. Only 1 echocardiogram abnormality was considered significant. The echocardiogram of an uninfected child aged 48 months randomized to zidovudine revealed borderline left ventricular function and mild dilatation. The child was reported to have a mild cardiomyopathy of unknown etiology; no previous echocardiograms were performed. The child’s mother had received 20 weeks of zidovudine during the antepartum period and the child had received the full 6 weeks of zidovudine during the first 6 weeks of life while enrolled in PACTG 076. The site cardiologist has reported that the child is asymptomatic and healthy; however, repeated attempts to schedule a follow-up echocardiogram have been unsuccessful. In all other cases, follow-up with the site cardiologists revealed that echocardiogram findings reported as abnormal were considered insignificant. All children with abnormal echocardiogram results, other than the child just described, have reported normal cardiac status and are not being followed up in specialty clinics.

**Ophthalmologic Observations.** One hundred thirty-seven uninfected children (59%) had at least 1 ophthalmologic examination (including funduscopic results) recorded in the database; 72 (59%) were in the zidovudine group and 65 (58%) were in the placebo group. Thirteen children (9%) had results from more than 1 examination in the database. Eighty-eight (38%) of the 234 children were missing baseline examinations (ie, >36 months without baseline results reported). The majority of children with missing examinations had missed their scheduled appointment and will be rescheduled for the evaluation.

The following findings based on general examination were reported: astigmatism (2 children, both from zidovudine group), ptosis (1 child from zidovudine group) and epicanthal folds (1 child from placebo group).

Two children had other abnormal findings recorded on funduscopic examination. A funduscopic examination performed at 51 months of age for 1 child from the zidovudine group revealed bilateral “thinned vessels; discs look slightly pale”; vision was reported as normal. The examining ophthalmologist reported that this was not a significant finding and a 6-month follow-up is planned. Another child from the zidovudine group, aged 33 months, had a reported “copper beaten look” noted on the fundus. The child’s mother had received 6 weeks of zidovudine during the antepartum period and the child had received the full 6 weeks of zidovudine during the first 6 weeks of life while enrolled in PACTG 076. The examining ophthalmologist was queried and reported that this was not related to a metabolic disease. The child is scheduled for a follow-up visit. Overall, there was no significant difference between groups in terms of the abnormal ophthalmologic findings (Fisher exact P value > .99).

**COMMENT**

This article presents reassuring data regarding longitudinal follow-up through the preschool years of uninfected children exposed to in utero and neonatal zidovudine for the prevention of mother-to-child transmission of HIV. With average follow-up to age 4.2 years (range, 3.2–5.6 years), results so far reveal no adverse outcomes with respect to growth, cognitive/developmental function, immune function, cancers, or mortality for uninfected PACTG 076 children randomized to zidovudine in utero when compared with uninfected PACTG 076 children randomized to placebo. One uninfected, asymptomatic, healthy child randomized to zidovudine was reported to have a mild cardiomyopathy (no previous echocardiograms) of unknown etiology. These are crucial data because zidovudine is now used extensively in the United States and other developed countries for the prevention of mother-to-child HIV transmission. Likewise, programs to expand perinatal interventions in developing countries are undergoing consideration.

The findings of this study complement the original PACTG 076 results, in which the infants were followed up through 18 months of age, and are consistent with the limited human data addressing potential effects of perinatal ex-

<p>| Table 2. Means, SDs, and Numbers of Children Tested Using Bayley and McCarthy Scales for Uninfected Children by Randomized Treatment Assignment |
| Age, mo (Range) | Bayley Scales of Infant Development* | Test Scores | McCarthy Scales of Children’s Ability (General Cognitive Index)† |</p>
<table>
<thead>
<tr>
<th></th>
<th>Mental Development Index</th>
<th>Psychomotor Development Index</th>
<th>Zidovudine</th>
<th>Placebo</th>
<th>Zidovudine</th>
<th>Placebo</th>
<th>Zidovudine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 (3-9)</td>
<td>Mean (SD)</td>
<td>109.2 (16.9)</td>
<td>104.7 (15.8)</td>
<td>109.8 (15.1)</td>
<td>104.0 (12.7)</td>
<td>No.</td>
<td>19</td>
<td>17</td>
</tr>
<tr>
<td>12 (9-15)</td>
<td>Mean (SD)</td>
<td>103.1 (17.2)</td>
<td>102.4 (20.6)</td>
<td>105.0 (13.5)</td>
<td>102.6 (16.0)</td>
<td>No.</td>
<td>34</td>
<td>31</td>
</tr>
<tr>
<td>18 (15-21)</td>
<td>Mean (SD)</td>
<td>96.2 (14.6)</td>
<td>92.4 (17.9)</td>
<td>97.9 (16.7)</td>
<td>97.4 (14.9)</td>
<td>No.</td>
<td>55</td>
<td>59</td>
</tr>
<tr>
<td>24 (21-30.5)</td>
<td>Mean (SD)</td>
<td>93.6 (17.1)</td>
<td>89.3 (18.3)</td>
<td>101.2 (16.6)</td>
<td>101.0 (21.1)</td>
<td>No.</td>
<td>65</td>
<td>74</td>
</tr>
</tbody>
</table>

*Test mean (SD) = 100 (16). For mental development index, Wir-Johnson P value = .24; for psychomotor development index, Wir-Johnson P value = .84.
†Test mean (SD) = 100 (16). For General Cognitive Index, Wilcox P value = .78.
posure to antiretroviral drugs. Birth registry data from the Antiretroviral Pregnancy Registry found no increased risk in the proportion of congenital birth defects among 301 infants exposed to zidovudine monotherapy\textsuperscript{17} during the antenatal period. One other study evaluated short-term risk for tumors in 734 infants and children with known zidovudine exposure (including 115 children in the current study and 619 infants and children from the Women and Infants Transmission Study, a natural-history study). In this combined cohort, with 1110.6 person-years of follow-up, no neoplasms have occurred.\textsuperscript{18}

There are caveats to the data presented. Only two thirds of the children enrolled in the original PACTG 076 protocol are currently being followed up in this late-effects protocol. Maintaining uninfected children in longitudinal study will be difficult; because of risk factors associated with HIV in their families, many will eventually be placed in foster care or adoptive settings. Loss to follow-up is estimated to be about 10\% per year.

A critical strength of this study is the randomized design and substantial follow-up rates. The primary end points of long-term growth, cognitive/developmental function, cardiac and ophthalmologic toxic effects, and assessment of cancers and mortality provide an ongoing opportunity to address potential late adverse effects. With a sample size of 120 per arm, there is limited power to detect very rare adverse events, but the sample size allows for adequate statistical power to detect any clinically relevant differences between treatment groups for growth, immunologic parameters, and cognitive/developmental function. The study is positioned to clarify whether perinatal zidovudine use is safe in the long-term to early adulthood and may be able to address issues raised by 2 recently published but conflicting animal studies about the potential transplacental carcinogenic effects of zidovudine.\textsuperscript{19,20}

Early initiation of aggressive combination antiretroviral therapy is now the standard of care for treatment of all HIV-infected individuals, including pregnant women. Increasing numbers of uninfected children will have prolonged intrauterine exposure to multiple antiretroviral agents used for treatment of their mother’s HIV infection.\textsuperscript{21} These trends highlight the need for long-term surveillance of perinatally exposed children. Protocol 219 is a surveillance mechanism within the framework of the PACTG trial network for children who have been exposed to antiretroviral drugs in utero. However, there is currently no surveillance in place for long-term tracking of children exposed to antiretroviral drugs perinatally who are not part of the PACTG framework. Approaches that have been proposed in the United States include national or regional passive tracking systems, with registries of those exposed to perinatal interventions being linked in future years to cases from cancer registries. Building innovative approaches to look for late effects will be necessary as these interventions become widely implemented.

Although theoretical concerns about late effects of in utero/neonatal antiretroviral exposure exist based on animal models, the findings from this comparative follow-up study of uninfected PACTG 076 children exposed to zidovudine vs placebo suggest no evidence of adverse effects through the preschool years. A critical public health goal is the development and implementation of long-term tracking strategies to assess potential late effects of perinatal antiretroviral exposure among the vast majority of children exposed to perinatal antiretroviral

Figure 2. Mean Values for Lymphocyte Subset Parameters for Uninfected Infants Who Received Zidovudine or Placebo in the Pediatric AIDS Clinical Trials Group Protocol 076

<table>
<thead>
<tr>
<th>Age, wk</th>
<th>Zidovudine, n</th>
<th>Placebo, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤18</td>
<td>113</td>
<td>101</td>
</tr>
<tr>
<td>18-36</td>
<td>114</td>
<td>110</td>
</tr>
<tr>
<td>36-61</td>
<td>104</td>
<td>92</td>
</tr>
<tr>
<td>61-91</td>
<td>107</td>
<td>104</td>
</tr>
<tr>
<td>91-117</td>
<td>72</td>
<td>77</td>
</tr>
</tbody>
</table>

The Wei-Johnson P value for CD4\(^+\) cell counts = .52; for CD8\(^+\) cell counts, P = .38.
drugs in clinical care settings but not followed in cohort studies.

Author Affiliations: Pediatric Medicine Branch (Ms Culhane) and Efficacy Trials Branch (Dr Fowler), Division of AIDS, National Institute of Allergy and Infectious Diseases, and the Pediatric, Adolescent and Maternal AIDS Branch, National Institute of Child Health and Human Development (Dr Mofenson), National Institutes of Health, Bethesda, Md, Center for Biostatistics in AIDS Research, Harvard School of Public Health, Public Health, Boston, Mass (Ms Lee and Drs Gortmaker and Shapiro); Department of Pediatrics, University of Medicine and Dentistry of New Jersey, New Jersey Medical School, Newark (Drs McSherry and Oleske); Section of Infectious Diseases, Columbus Children’s Hospital, Ohio State University, Columbus (Dr Brady); Department of Pediatrics, Duke University Medical Center, Durham, NC (Dr O’Donnell); Department of Pediatrics, University of Miami School of Medicine, Miami, Fla (Dr Scott); Departments of Pediatrics, San Juan City Hospital (Dr Jimenes) and School of Infectious Diseases, St Jude Children’s Research Hospital, Memphis, Tenn; Department of Pediatrics, University of Puerto Rico (Dr Diaz), San Juan; Department of Pediatrics, Wayne State University, Detroit, Mich (Dr Moore); Department of Infectious Diseases, St Jude Children’s Research Hospital, Memphis, Tenn (Dr Flynn); and the Frontier Science and Technology Research Foundation, Amherst, NY (Ms Cunningham).

This work was performed under the auspices of the Pediatric AIDS Clinical Trials Group of the National Institute of Allergy and Infectious Diseases and the Pediatric/Perinatal HIV Clinical Trials Network of the National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Md.

Members of the Pediatric AIDS Clinical Trials Group Protocol 219: Charles Mitchell, MD, Brenda Hallowton-Jones, RN, BSN, MBA, ACRN, and Irma Infante, BS, University of Miami, Miami, Fla; Jorge Gandia, MD, Enilda Abreu, PhD, Harbour compliant, MPH, and Miguel Lugo, MD, San Juan City Hospital, San Juan, Puerto Rico; Ricelle Flores, MD, Irma Febo, and Carmen Rivera, RN, MPH, University of Puerto Rico, San Juan; Duanne Harrison, MD, Elizabeth Secondo, MD, Charnell Cromer, RN, MSN, and Mary Moss, RN, Children’s Hospital of Michigan, Detroit; Walter T. Hughes, MD, Jerry L. Shene, MD, Nanette Howlett, RN, FNP, and Michele Roy, RRA, St Jude Children’s Research Hospital, Memphis, Tenn; William T. Shearer, MD, PhD, Mark W. Kline, MD, Nancy Calles, RN, BSN, and Lisa Moreau, RN, BSN, Baylor/Texas Children’s Hospital, Houston; Russell Van Dyke, MD, Dawn Sokol, RN, Margaret Silo, MD, and Tom Alchadiak, MD, Tulane University Charity Hospital, New Orleans, La; Peggy King, RN, Connie McLellan, RN, Ann Melvin, MD, and Kathy Mohan, ARNP, Children’s Hospital and Medical Center, Seattle, Wash; Stephen A. Spector, MD, Wayne M. Dankner, MD, Lisa Stangl, RN, FNP, and Mary Caffery, RN, University of California at San Diego Medical Center; Maria Garcia, MD, Wanda Marrero, RN, Eva J. Reyes, NP, and Francisco Berges, MD, Ramon Ruiz Arzua University Hospital, San Juan, Puerto Rico; William Borkowsky, MD, Mona Rigaud, MD, Saluchni Chandwani, MD, and Henry Pollack, MD, Bellevue Hospital, New York, NY; Rhoda Sperling, MD, David Hodes, MD, Henry Sacks, PhD, MD, and Eileen Chusid, PhD, M ’Sini Medical Center, New York, NY; Nancy Wade, MD, MPH, Martha Lepow, MD, and Patricia Hughes, DO, Albany Medical Center, Albany, NY; Jocelyne Grandchamp, RN, and Deborah Storm, RN, PhD, Children’s Hospital of New Jersey, Newark; Sohail Rana, MD, Srinagesh Baluvi, MD, Margaret Akinsiku, RN, and Patricia Houston, MS, Howard University Hospital, Washington, DC; Ross E. McKinney Jr, MD, Megan Valentine, PA-C, and Lori Ferguson, RN, Duke University, Durham, NC; Andrea Kovacs, MD, and Margaret Kouyou, MD, Los Angeles County Medical Center, Los Angeles, Calif; Anne Grinshon, MD, Jane Pitt, RN, Alice Cragin, RN, and Andrea Jurgens, RN, FNP, Columbia Presbyterian Medical Center, New York, NY; Sandra Burchett, MD, Ellen Cooper, MD, Dawn Jacobs, RN, and Nancy Karthas, RN, MS, CPNP, Children’s Hospital of Boston, Boston, Mass; Yvonne J. Byrson, MD, Maryanne Dillon, RN, NP, Audra Deveks, MD, and Richard Stehm, MD, University of California at Los Angeles Medical Center; Kenneth C. Rich, MD, Karen Hayani, MD, Doris Carroll, RN, BSN, and Pamela Lofton, RN, MSN, University of Illinois at Chicago; Elizabeth J. McFarland, MD, Myron J. Levin, MD, Carol Salbenblatt, RN, and Jane Eddy, RN, CPNP, University of Colorado, Denver; Hermann Mendez, MD, Edward Handelsman, MD, and Helen Bergin, RN, Kings County Hospital Center, New York, NY; Leonard Weiner, MD, Coleen Cunningham, MD, Kathie Contello, CSNP, MSN, and Kim Kirkwood, CPNP, MSN, SUNY Health Science Center, Syracuse, NY; Sharon Nachman, MD, Michel Davi, FNP, Debra Hickey, FNP, and Katie Tarpy, FNP, State University of New York at Stony Brook; Daniel Johnson, MD, Cynthia Sullivan, RN, BSN, Lakshmi Das, MD, and Lynn Heald, RN, Children’s Memorial Hospital, Chicago, IL; Richard Rutstein, MD, Carol Vincent, CRNP, Deborah Schable, PharmD, and Stuart E. Starr, MD, Children’s Hospital of Philadelphia, Philadelphia, Pa; Francis Giglotti, MD, Geoffrey Weinberg, MD, Susan Laverty, RN, and Barbara Murante, FNP, University of Rochester, Rochester, NY; Andrew Wenzia, MD, Joanna Dobrosyński, MD, Wanda Biernick, RN, and Margaret Chin, MD, Bronx Lebanon Hospital Center, New York, NY; Richard Gelber, PhD, PACTG Statistical and Data Analysis Center, Harvard School of Public Health, Boston, Mass; and Kristine Coughlin, Linda Draper, and Lynne Strusa, PACTG Data Management Center, Frontier Science and Technology Research Foundation, Inc, Amherst, NY.

REFERENCES


©1999 American Medical Association. All rights reserved.