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Incidence of Persistent Renal Dysfunction in Human Immunodeficiency Virus-Infected Children:

Associations With the Use of Antiretrovirals, and Other Nephrotoxic Medications and Risk Factors

Warren A. Andiman, MD[*,†], **Miriam C. Chernoff, PhD**[‡], **Charles Mitchell, MD**[§], **Murli Purswani, MD**[¶], **James Oleske, MD**[‖], **Paige L. Williams, PhD**[‡], **Hans Spiegel, MD**[**], **Phil Gona, PhD**[††], and **George R. Seage III, DSc, MPH**[‡‡] **the PACTG iDACS 617 Study Team**

[*]Department of Pediatrics, Yale University School of Medicine, New Haven, CT

[†]Department of Public Health, Yale University School of Medicine, New Haven, CT

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

[§]University of Miami Medical School, Miami, FL

[¶]Division of Pediatric Infectious Diseases, Bronx-Lebanon Hospital Center, Albert Einstein College of Medicine, Bronx, NY

[‖]University of Medicine and Dentistry of New Jersey, Newark, NJ

[**]Children's National Medical Center, Washington, DC

[††]Statistical Consulting Unit, Department of Mathematics and Statistics, Boston University, Boston, MA

[‡‡]Department of Epidemiology, Harvard School of Public Health, Boston, MA

Abstract

Background—Survival of HIV-infected children continues to increase and the use of antiretrovirals (ARVs) is expanding; however there are few data regarding the incidence of renal dysfunction and associated risk factors among HIV-infected children and youth.

Methods—A total of 2102 children enrolled in Pediatric AIDS Clinical Trials Group Study 219/219C, were followed and assessed prospectively for >30 months. Occurrence of clinical events and laboratory abnormalities were recorded using standardized criteria and forms. Therapeutic decisions were made by clinicians at each site. Occurrence of persistent renal laboratory abnormalities was the main outcome measure.

Address for correspondence: Warren A. Andiman, MD, Department of Pediatrics, Yale University School of Medicine, 333 Cedar Street, 418 LSOG, PO Box 208064, New Haven, CT 06520-8064, warren.andiman@yale.edu.

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Results—Four hundred forty-six (22%) enrollees exhibited at least one persistent renal laboratory abnormality. Elevated serum creatinine (Cr) was more common than persistent proteinuria (15% vs. 8%). The incidence of new renal laboratory abnormalities was 3.7 events per 100 person-years with rates increasing between 1993 and 2005. Older age (≥6 years vs. <6 years), Hispanic ethnicity, and Black non-Hispanic race were associated with increased risk of renal dysfunction, but CDC clinical class and plasma HIV RNA levels were not. Subjects exposed to ARV regimens containing tenofovir and/or indinavir had approximately twice the risk of developing renal dysfunction compared with persons exposed to other ARVs. The risk of renal dysfunction was also elevated for other antivirals (hazard ratio = 5.4) and amphotericin B (hazard ratio = 28).

Conclusions—Persistent renal function abnormalities occur frequently in HIV-infected children. Improved survival, Black race and Hispanic ethnicity, and exposure to tenofovir, indinavir, and other antimicrobial agents increase the risk for renal dysfunction. All HIV-infected children should be monitored closely for evidence of renal disease.

Keywords

pediatric HIV/AIDS; renal disease; complications of antiretroviral therapy; nephrotoxic medications

A dramatic decline has been reported in both mortality and incidence of opportunistic and other related infections among HIV infected children in the United States[1]; however, noninfectious complications of HIV infection, including renal disease, still occur.[2] A number of renal disorders associated with childhood HIV infection have been reported, but because most of these reports are based on retrospective, cross-sectional and geographically localized analyses, the incidence of renal dysfunction in HIV-infected children and youth has not previously been calculated, and demographic and clinical risk factors have not been fully assessed. [3-5]

Among the several types of HIV-associated renal disorders, HIV-1-associated nephropathy (HIVAN) has been well-studied.[6-8] HIVAN, triggered by invasion of the kidney by HIV-1, usually begins with subclinical proteinuria and is often accompanied by an elevated serum Cr and renal tubular acidosis. Large, echogenic kidneys, nephrotic-range proteinuria, and renal insufficiency may occur later. Both the glomerulus and the tubular epithelium develop injury. It is not clear how often manifestations of this and related diseases (eg, immune-mediated glomerulonephritis, focal glomerulosclerosis) occur in HIV-infected children and the extent to which persistent renal function abnormalities signal their onset.

Recent reports describe potential or actual nephrotoxicities associated with the use of antiretrovirals (ARVs). Indinavir (IDV) is known to cause nephrolithiasis[9] and tenofovir (TDF) is associated with other forms of renal injury and bone mineral toxicity.[10-13] Further, there is concern regarding possible nephrotoxic effects of protease inhibitors, such as ritonavir, and atazanavir, particularly when used in conjunction with tenofovir.[14-16] There are still limited data regarding the incidence of renal dysfunction associated with the use of ARVs in children in the course of routine clinical care, particularly when administered with other classes of drugs that are potentially nephrotoxic, eg, antimicrobials (aminoglycosides, amphotericin), antivirals (acyclovir, adefovir, cidofovir), and nonsteroidal anti-inflammatory drugs (ibuprofen, naproxen).

We report on the occurrence and predictors of renal dysfunction as defined by persistent renal laboratory abnormalities in HIV-infected children enrolled in a large prospective cohort study, Pediatric AIDS Clinical Trials Group (PACTG) study 219/219C. We focus on

the effects of ARVs and other anti-infectives, HIV-1 viral load and demographic factors, including ethnicity.

MATERIALS AND METHODS

Study Design and Population

PACTG 219/219C was a multicenter prospective cohort study designed to examine the long-term consequences of HIV infection and its treatment in US infants, children, and adolescents. PACTG 219 opened in May 1993 to children who participated in other PACTG perinatal or treatment trials. A revised version, PACTG 219C, which opened in September 2000 and closed to follow-up in May 2007, enrolled PACTG 219 participants as well as perinatally or behaviorally HIV-exposed children <21 years of age. Both studies required individual consent/assent for enrollment and Institutional Review Board approval was obtained at each site.

A total of 3451 HIV-infected individuals <21 years of age were enrolled in PACTG 219/219C at sites throughout the United States and Puerto Rico from 1993 through 2004. We limited the current analysis to 2102 HIV-infected participants followed at least 30 months with at least 3 visits during which urine was analyzed and serum Cr was measured. Data obtained through May 3, 2005 were included in our analysis.

Clinical and Laboratory Data

PACTG 219C study visits were scheduled every 3 months. Urine samples were collected at least once a year and urine protein content was assessed by dipstick. Blood was subjected to routine chemical analyses, including measures of blood urea nitrogen and Cr. T-cell subsets and plasma HIV-RNA levels (in more recent years) were measured at each study visit. Occurrences of HIV-related clinical complications and adverse events associated with ARV and other therapies were collected at each scheduled visit, using standardized criteria and structured forms. Self-reported race and ethnicity information, provided by the parent, guardian, or subject, was collected.

Medication Use

Information regarding use of ARV and other medications, including start and stop dates, was collected by study nurses, using a standardized chart abstraction form. For data collected before August 2000, ARV start and stop dates were estimated as the midpoint between study visit dates. HAART was defined as a regimen that comprised at least 3 different ARVs from at least 2 drug classes (NRTI, NNRTI, PI, and FI). ARV use was divided into 3 mutually exclusive categories: (1) nephrotoxic HAART, (2) non-nephrotoxic HAART, and (3) no HAART. Nephrotoxic HAART was defined as any HAART regimen that included TDF and/or IDV. No HAART was defined as any ARV regimen that did not fulfill the criteria for HAART (but that, on rare occasions, may have included TDF or IDV) or infrequent drug regimens that did not include any ARVs.

The effects of exposure of other nephrotoxic medications were also studied: antibiotics (gentamicin, tobramycin, amikacin, rifampicin, sulfadiazine, sulfamethoxazole), antifungals (amphotericin B, pentamidine), non-ARV antivirals (acyclovir, cidofovir, adefovir), and nonsteroidal anti-inflammatory drugs (NSAIDs) (ibuprofen, naproxen); both chronic and occasional use were included.

Outcome Measures

The outcome of persistent renal dysfunction required at least 3 sequentially abnormal renal laboratory values in at least 1 of 3 measures: urine protein content, serum Cr, or estimated

glomerular filtration rate (eGFR). The event time was the earliest date of occurrence for any of the 3 types of abnormalities. Cutoff for increased urine protein was trace or greater. Cutoffs for increased serum Cr were age-adjusted (≥1.0 mg/dL for newborns ≤30 days; ≥0.4 mg/dL for infants >30 days to ≤52 weeks; ≥0.7 for children >52 weeks–12 years; ≥1.0 mg/dL for adolescents ≥13 years–19 years; and ≥1.3 mg/dL for adults 20 years or older).[17] eGFR was computed using the Schwartz formula for those less than 18 years of age with height available[18] or the Modification of Diet in Renal Disease algorithm.[19] The cutoff for decreased eGFR was <60 mL/min/1.73 m^2 for the age and height-adjusted value.

Statistical Analysis

We calculated crude incidence rates for targeted renal abnormalities and exact 95% confidence intervals under a Poisson distribution, overall and for various subgroups, and compared incidence rates across subgroups, using Poisson regression models. Subgroups were based on gender; age group at study entry; race/ethnicity; CDC clinical class; entry $CD4^+$ T-cell %, plasma HIV RNA levels; and nephrotoxic medication exposure prior to entry. Subject-specific person-time was calculated from study entry until the event or, for those without events, censored at the last clinic visit. Participants assigned new renal diagnoses but without corresponding abnormal renal laboratory values (n = 45) and those carrying renal diagnoses at study entry (n = 34) were excluded from our analysis.

We first fit multivariate Cox proportional hazards regression models to estimate hazard ratios and corresponding confidence intervals for risk of new renal laboratory abnormalities adjusting for entry demographic, clinical, and pharmacological characteristics.[20] We next fit extended Cox models with time-varying covariates to assess the association between the risk of a laboratory event and changing levels of exposures to HIV-viral load, to nephrotoxic medications and ART regimen during the course of the study (carrying last values forward), controlling for baseline factors.[21]

In the final set of analyses, we attempted to compare risk of renal toxicities for subjects taking nephrotoxic-HAART and other nephrotoxic medications concurrently, as compared with either alone, but too few subjects received both during any interval to allow this evaluation. Combinations of ARVs and other medications were thus evaluated hierarchically in the following order: (1) nephrotoxic-HAART regimens (with or without other medications); (2) other nephrotoxic-medications including non-HAART, TDF, or IDV; and (3) no nephrotoxic medications. We also assessed the influence of specific classes of non-ARV nephrotoxic medications, the separate impact of TDF and IDV-based HAART regimens, and the effect of TDF regardless of whether it formed part of a HAART regimen.

All analyses were restricted to participants with >1 HIV RNA measurement. Baseline viral load was defined as the greater of the most recent pre-entry HIV RNA value or the estimated area under the curve (AUC) for viral load prior to study entry using a trapezoidal rule with time-averaging.[22] Viral load during follow-up was the cumulative time-adjusted AUC. All analyses were conducted using the SAS Statistical Software version 9.1.[23] $P < 0.05$ was used to determine statistical significance.

RESULTS

The 2102 HIV-infected study subjects who met the entry criteria were followed for a median of 72.5 months (range: 30–142 months). Over half were 6 years of age or older and the great majority were ethnic minorities (Table 1). About 25% were CDC clinical class C, 17% had $CD4^+$ T-cell percentages <15% and 47% had HIV RNA >10,000 copies/mL. At entry, 37% of subjects had received HAART and 3% had received IDV; none had received tenofovir. By the end of the study, 21% had received either IDV or TDF as part of a HAART regimen.

Young children were not given TDF; only 2 of 255 participants exposed to TDF (<1%) were <6 years old when TDF was begun. Cumulatively, 9% started TDF prior to 9 years and 27% prior to 12 years of age. In contrast, 64 received IDV prior to study entry. Cumulatively, 10% of the 255 exposed to IDV started IDV prior to 6 years, 34% prior to 9 years, and 67% prior to 12 years of age.

Of the 2102 children, 34 carried at least one primary renal diagnosis at study entry; thus 2068 were at risk for new events. Of these 2068 participants, 446 (22%) exhibited at least one persistent renal laboratory abnormality among which elevated serum Cr and proteinuria were the most common (Table 2). Persistently elevated serum Cr and/or diminished eGFR were seen more often than persistent proteinuria (15% vs. 8%). Persistent proteinuria alone occurred in 7% of subjects. Only 8 participants had diminished eGFRs and all 8 also had elevated serum Cr.

After excluding subjects who carried diagnoses at study entry and those with discordant clinical diagnoses and laboratory values, there were 2023 participants available for further analysis. Of these, the incidence of new renal laboratory abnormalities (either elevated serum Cr or proteinuria) was 3.7 events per 100 person-years (95% CI: 3.4–4.1), with rates increasing over time (2.4 in 1995–5.6 in 2005; $P < 0.001$).

Among 21 patients with evidence of more than one persistent renal laboratory abnormality, persistent proteinuria occurred more than 90 days before the other laboratory abnormalities in 14 of 21 subjects (67%) (Table 2). In the remaining 7 participants (33%), persistent proteinuria occurred either within 90 days prior to the other laboratory abnormality (n = 3) or afterward (n = 4). The average duration of the first abnormal sequence was 38.8 months (SD: 22.2) for proteinuria, 28.5 months (SD: 21.5) for increased Cr, and 22.2 months (SD: 19.3) for decreased eGFR.

Risk Factors for the Development of Renal Laboratory Abnormalities

The results of the Cox proportional hazards model that evaluated baseline medication exposure and the extended Cox model evaluating the independent study-time-varying exposures of nephrotoxic-HAART and non-ARV nephrotoxic medications yielded similar results; thus we report only the latter (Tables, Supplemental Digital Content 1, http://links.lww.com/A1125 and Supplemental Digital Content 2, http://links.lww.com/A1126). After adjusting for baseline and time-varying factors in the Cox model, participants receiving nephrotoxic HAART had a significantly elevated risk of renal laboratory abnormalities, whether exposure occurred prior to study entry (hazard ratio [HR] = 1.9; 95% CI: 1.1, 3.4) or during the course of the study (HR = 1.8; 95% CI: 1.3, 2.5). Those who had never been on HAART during the course of the study experienced less risk (HR = 0.7; 95% CI: 0.6, 0.9) than those who had been on non-nephrotoxic-HAART regimens. There was no association between cumulative plasma HIV-RNA levels and renal dysfunction (Table, Supplemental Digital Content 1, http://links.lww.com/A1125).

Among baseline covariates, older age (6 years or greater vs.<6 years; HR = 1.6; 95% CI: 1.2, 1.9), Hispanic ethnicity, (HR = 1.9; 95% CI: 1.3, 2.7), and Black, non-Hispanic race (HR = 1.4; 95% CI: 1.0, 2.0) were associated with greater risk for development of renal dysfunction in the course of follow-up. There was also a slightly increased risk among males (HR = 1.2; 95% CI: 1.0, 1.5). CDC clinical class and exposure to other non-ARV nephrotoxic medications prior to study entry were not associated with later renal abnormalities. Children with low or moderate levels of immune suppression ($CD4^+$ T-cells: 0%-14.9%, 15%-24.9%) had slightly lower rates of renal laboratory abnormalities compared with those with $CD4^+$ T-cell percentages ≥25% (HR = 0.8; 95% CI: 0.6,1.0 and HR = 0.7; 95% CI: 0.6, 1.0, respectively).

We also evaluated the combined effect of nephrotoxic HAART and other nephrotoxic medications controlling for changing viral load during the study as well as baseline characteristics. Subjects who received nephrotoxic HAART with or without exposure to other nephrotoxic drugs had about twice the risk of renal dysfunction when compared with those who had no exposure to a nephrotoxic medication, whether we combined TDF-based and IDV-based HAART exposure into 1 category (HR = 2.0; analysis 1 of Table, Supplemental Digital Content 2, http://links.lww.com/A1126) or looked at them separately. TDF posed the greatest risk (HR = 2.3); the risk associated with IDV was somewhat less (HR = 1.7; analysis 2 of Table, Supplemental Digital Content 2, http://links.lww.com/A1126). The risk of use of other nephrotoxic medications in the absence of nephrotoxic HAART was elevated but not statistically significant in both analyses (HR = 1.5, HR = 1.6; analysis 1 and 2, respectively; Table, Supplemental Digital Content 2, http://links.lww.com/A1126). TDF was associated with about the same 2-fold risk, whether or not it formed part of a HAART regimen (analysis 3, Table, Supplemental Digital Content 2, http://links.lww.com/A1126).

We next attempted to ascertain the risk posed to subjects who had received non-ARV nephrotoxic drugs of specific types (eg, antibiotics, other antivirals, amphotericin B, NSAIDs, etc.). Although the number exposed was small, there was a greater risk of persistent renal dysfunction among those exposed to non-ARV antivirals used alone (HR = 5.4) and those exposed to amphotericin B alone (HR = 28.0; analyses 5 and 7, respectively, Table, Supplemental Digital Content 2, http://links.lww.com/A1126).

DISCUSSION

As survival of perinatally infected HIV-positive children has continually increased, there has been interest in the expression of noninfectious late events, particularly those that affect the central nervous and cardiovascular systems, the skeleton and the kidneys.[2,24] With the advent of HAART, there has been controversy as to whether one or more components of the therapy reduces or increases the frequency of renal disease.[25-28] Children have substantially lower rates of the multiple comorbidities that influence the occurrence of renal dysfunction in adults, eg, illicit drug use, infectious hepatitis, atherosclerosis, hypertension, diabetes, and prolonged treatment with multiple ARV agents. Nevertheless, among the 2102 HIV-infected children who met entry criteria for this study, nearly 22% developed persistent abnormalities of renal function over a period of 30 months or more.

There are now about 2 dozen drugs in 6 different classes that are approved by the FDA to treat HIV infection. Although most have not been formally studied in children, many are used regularly as part of routine clinical practice. Children are prone to many of the same adverse effects, such as renal dysfunction, that are seen in adults. In our study, those who received HAART regimens that included TDF or IDV were nearly twice as likely as those who had received no nephrotoxic medication to develop persistent renal laboratory abnormalities. Those treated with non-ARV antivirals and amphotericin B had a still greater risk of acquiring kidney disease. In addition, the age at which certain ARVs are first prescribed may play a role in causing renal disease. We performed a sensitivity analysis which showed that younger children initiating TDF (<12 years) had almost 3 times the risk of developing renal dysfunction as those who started TDF at older ages (≥12 years).

Although too few renal laboratory events occurred during concurrent use of nephrotoxic-HAART and other nephrotoxic-medications for analysis, we also hypothesized that exposure to different classes of nephrotoxic drugs might produce kidney damage that would accrue and, perhaps, even compound over time. To test this hypothesis we performed 2 sensitivity analyses in which the sequential or concurrent effects of drug exposures were carried

forward in time (data not shown). We continued to observe nearly a doubling of risk with exposure to nephrotoxic HAART when compared with lack of exposure to any nephrotoxic drugs. In addition we found a substantial risk for concurrent or sequential use of nephrotoxic HAART and NSAIDs (HR: 4.5) and for nephrotoxic HAART and antibiotics (HR: 5.6). Finally, we found increased risk associated with exposure to NSAIDs (HR: 2.1), certain antivirals (HR: 1.5), potentially nephrotoxic antibiotics (HR: 1.9), and amphotericin B (HR: 3.6) alone.

Hispanic children were somewhat more likely than African-American children and much more likely than Whites to develop signs of renal dysfunction. This finding was initially surprising because HIV-infected Blacks have almost always been cited as having the greatest risk of developing renal disease when compared with other ethnicities.[29-32] Although classic HIVAN is found most often in African-American adults, other forms of HIV-associated renal pathology have been reported more often in persons of European descent.[33,34] In one survey, the prevalence of chronic kidney disease was nearly identical in American non-Hispanic Blacks and Mexican-Americans (19%-20%) and was greater in both groups than the prevalence in non-Hispanic Whites (16%).[35] Therefore, the greater occurrence of signs of renal disease in self-described Hispanic children in the United States is consistent with observations by others. Based on data from other PACTG studies for co-enrolled participants, about 20% of self-described HIV+ Hispanics are racially Black. As greater numbers of HIV+ children live longer as a result of improved care and treatment options, clinicians should expect to see renal dysfunction develop in a significant proportion of children of all racial and ethnic groups; those with Hispanic ethnicity may be at greatest risk, for unknown reasons.

It has been shown that HIV invades the kidney and replicates in both the glomerulus and renal tubular epithelium.[36,37] Viral messenger RNA, gene products, and structural proteins can be found in human renal tissue.[38] Therefore, we hypothesized that the cumulative load of HIV in plasma, as derived from an AUC model, would be a predictor of subsequent renal disease.[39] This could not be confirmed; there were no significant differences in risk of renal disease among those with cumulative viral load AUCs ranging from 0–400 RNA copies per mL compared with those with more than 100,000 RNA copies per mL. These results are comparable with those reported by others and suggest several possibilities: either the titer of virus in blood does not predict the load of infectious virus in kidney tissue or factors other than viral load alone predict the occurrence of renal functional abnormality.[40] Inflammatory or immunologic responses to the virus in kidney tissue may play a role in determining the type and the extent of renal cell dysfunction. This hypothesis is supported by our having found lower rates of renal laboratory abnormalities in children with moderately decreased versus better preserved $CD4^+$ T-cell percentages.

We were fortunate to be able to assess several thousand children who represent the entire spectrum of HIV-infection that can be found in a diverse US population. Our study comprised almost 12,000 person-years of follow-up. Nonetheless, the study was subject to limitations. Because ours was a substudy of a much larger longitudinal, prospective cohort study that had been accruing data since 1993, many questions about the incidence and the risk factors for renal disease could not have been anticipated when the study was designed more than 15 years ago. Also, the clinical care that was provided by the P219/219C investigators was not constrained by the limits of the study protocol; multiple caregivers at 93 study sites rendered care, prescribed drugs, and assigned clinical diagnoses according to their best judgments. Although all study subjects had routine urinalyses and measures of serum blood urea nitrogen and Cr at each visit (usually 2–4 times per year), measurements of urine protein/Cr ratios and 24-hour urine protein concentrations, and formal calculation of Cr clearances were not required for continued study participation. Also, by using trace

proteinuria as the cutoff for identifying some study subjects with renal impairment, we may have overestimated its frequency. Nevertheless, about twice as many subjects had increased serum Cr as had persistent proteinuria, suggesting that most of those with elevated Cr did not have glomerular disease and that proteinuria is not the earliest or sole signal of renal dysfunction in HIV+ pediatric subjects. For children with increasing evidence of renal disease, renal ultrasounds and kidney biopsies were not done uniformly. Future studies that more fully evaluate the natural history and pathophysiology of renal disease and that include the results of ultrasonographic studies, histologic evaluations, dialysis, and other treatments will strengthen our understanding of the renal abnormalities associated with pediatric HIV infection.

Clinicians should be mindful of the incidence of renal disease in this population and, other than the use of HAART, studies should be designed to test the utility of a number of other interventions to ameliorate renal dysfunction. We have shown that TDF and IDV, when used to treat children who are exposed to other nephrotoxic drugs, may increase significantly the risk of renal functional abnormalities. Use of TDF is expanding throughout the world and IDV, although used less frequently in the United States, is still prescribed in other countries. Tenofovir is sometimes used as part of ARV regimens that are given to HIV-infected pregnant women for treatment and to prevent vertical transmission. It is also used increasingly as part of salvage regimens in older children and youth. Therefore, its potential impact on interrupting transmission and on boosting treatment efficacy will need to be carefully balanced with long-term safety concerns. Clinicians should also consider the ethnic predisposition to renal dysfunction and should monitor renal function accordingly, paying special attention to children of Hispanic and African American ancestry.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Appendix

The following institutions and individuals participated in PACTG Protocol 219C: UMDNJ New Jersey Medical School-Department of Pediatrics, Division of Allergy, Immunology and Infectious Diseases, Arlene Bardeguez, MD, Arry Dieudonne, MD, Linda Bettica, Juliette Johnson; Boston Medical Center (BMC), Division of Pediatric Infectious Diseases, Stephen I. Pelton, MD, Ellen R. Cooper, MD, Lauren Kay, RN, Ann Marie Regan, PNP, Med; Children's Hospital LA - Department of Pediatrics, Division of Clinical Immunology and Allergy, Joseph A. Church, MD, Theresa Dunaway, RN; Long Beach Memorial Medical Center, Miller Children's Hospital, Audra Deveikis, MD, Jagmohan Batra, MD, Susan Marks, RN, Ilaisanee Fineanganofo, BA; Harbor - UCLA Medical Center - Department of Pediatrics, Division of Infectious Diseases, Margaret A. Keller, MD, Nasser Redjal, MD, Spring Wettgen, RN, PNP, Sheryl Sullivan, LVN; Johns Hopkins Hospital & Health System - Department of Pediatrics, Division of Infectious Diseases, Nancy Hutton, MD, Beth Griffith, RN, Mary Joyner, MSN, CPNP, Carolyn Keifer, RN, BSN; University of Maryland Medical Center, Division of Pediatric Immunology & Rheumatology, Douglas Watson, MD, John Farley, MD, MPH; Texas Children's Hospital, Allergy & Immunology Clinic, Mary E. Paul, MD, Chivon D. Jackson, RN, BSN, AND, Faith Minglana, RN, BSN, Heidi Schwarzwald, MD, Cook County Hospital, Kenneth M. Boyer, MD, Jamie Martinez, MD, James B. McAuley, MD, Maureen Haak, RN, MSN; Children's Hospital of Columbus, Ohio, Michael Brady, MD, Katalin Koranyi, MD, Jane Hunkler, RN, Charon Callaway, RN; University of Miami Miller School of Medicine, Division of Pediatric Immunology & Infectious Disease, Gwendolyn B. Scott, MD, Charles D. Mitchell, MD, Claudia Florez, MD, Joan Gamber; University of California San Francisco (UCSF) School of Medicine,

Department of Pediatrics, Diane W. Wara, MD, Ann Petru, MD, Nicole Tilton, PNP, Mica Muscat, PNP; Children's Hospital & Research Center Oakland, Pediatric Clinical Research Center & Research Laboratory, Ann Petru, MD, Teresa Courville, RN, MN, Karen Gold, MA, PNP, Katherine Eng, RN, PNP; University of California San Diego (UCSD) Mother, Child & Adolescent HIV Program, Stephen A. Spector, MD, Rolando M. Viani, MD, MTP, Mary Caffery, RN, MSN, Kimberly Norris, RN; Duke University School of Medicine - Department of Pediatrics, Children's Health Center, Margaret Donnelly, PA, Kathleen McGann, MD, Carole Mathison, MA, John Swetnam; University of North Carolina (UNC) at Chapel Hill School of Medicine - Department of Pediatrics, Division of Immunology and Infectious Diseases, Tom Belhorn, MD, PhD, Jean Eddleman, ACSW, CCSW, Betsy Pitkin, RN; Schneider Children's Hospital, Vincent R. Bonagura, MD, Susan Schuval, MD, Blanka Kaplan, MD, Constance Colter, RN, PNP; Harlem Hospital Center, Elaine J. Abrams, MD, Maxine Frere, RN, Delia Calo; New York University (NYU) School of Medicine, Division of Pediatric Infectious Diseases, William Borkowsky, MD, Nagamah Deygoo, Maryam Minter, RN, Seham Akleh, RN; Children's National Medical Center, ACTU, Diana Dobbins, RN, MSN, Deidre Wimbley, RN, Lawrence D'Angelo, MD, MPH, Hans Spiegel, MD, PhD; University of Washington (UW) School of Medicine - Children's Hospital and Regional Medical Center (CHRMC), Ann J. Melvin, MD, MPH, Kathleen M. Mohan, ARNP, Michele Acker, MN, ARNP, Suzanne Phelps, MS; University of Illinois College of Medicine at Chicago, Department of Pediatrics, Kenneth C. Rich, MD, Karen Hayani, MD, Julia Camacho, RN; Yale University School of Medicine - Department of Pediatrics, Division of Infectious Disease, Warren A. Andiman, MD, Leslie Hurst, MS, Janette de Jesus, MD, Donna Schroeder, BS; SUNY at Stony Brook School of Medicine, Division of Pediatric Infectious Diseases, Denise Ferraro, RN, Jane Perillo, PNP, Michele Kelly, PNP; Howard University Hospital, Department of Pediatrics & Child Health, Sohail Rana, MD, Helga Finke, MD, Patricia Yu, MS, Jhoanna Roa, MD; LA County/University of Southern California (USC) Medical Center, Andrea Kovacs, MD, James Homans, MD, Michael Neely, MD, LaShonda Spencer, MD; University of Florida Health Science Center Jacksonville (HSCJ), Division of Pediatric Infectious Disease & Immunology, Mobeen H. Rathore, MD, Ayesha Mirza, MD, Kathy Thoma, MA, Almer Mendoza; North Broward Hospital District, Children's Diagnostic & Treatment Center, Ana M. Puga, MD, Guillermo Talero, MD, James Blood, MSW, Stefanie Juliano, MSW; University of Rochester Medical Center, Golisano Children's Hospital, Geoffrey A. Weinberg, MD, Barbra Murante, MS, RN, PNP, Susan Laverty, RN, Francis Gigliotti, MD, Medical College of Virginia, Suzanne R. Lavoie, MD, Tima Y. Smith, RN; St. Jude Children's Research Hospital, Department of Infectious Diseases, Aditya Gaur, MD, Katherine Knapp, MD, Nehali Patel, MD, Marion Donohoe, RN, MSN, PNP; University of Puerto Rico, U. Children's Hospital AIDS, Irma L. Febo, MD, Licette Lugo, MD, Ruth Santos, RN, Ibet Heyer, RN; Children's Hospital of Philadelphia, Center for Pediatric & Adolescent AIDS, Steven D. Douglas, MD, Richard M. Rutstein, MD, Carol A. Vincent, CRNP, MSN, Patricia C. Coburn, RN, BSN; St. Christopher's Hospital for Children/Drexel University College of Medicine, Jill Foster, MD, Janet Chen, MD, Daniel Conway, MD, Roberta Laguerre, MD; Bronx-Lebanon Hospital Center, Infectious Diseases, Emma Stuard, MD, Caroline Nubel, Stefan Hagmann, MD, Murli Purswani, MD; New York Medical College/ Metropolitan Hospital Center, Mahrukh Bamji, MD, Indu Pathak, MD, Savita Manwani, MD, Ekta Patel, MD; University of Massachusetts Memorial Children's Medical School, Department of Pediatrics, Katherine Luzuriaga, MD, Richard Moriarty, MD; Baystate Health, Baystate Medical Center, Barbara W. Stechenberg, MD, Donna J. Fisher, MD, Alicia M. Johnston, MD, Maripat Toye, RN, MS; Connecticut Children's Medical Center, Juan C. Salazar, MD, MPH, Kirsten Fullerton, Gail Karas, RN; Medical College of Georgia School of Medicine, Department of Pediatrics, Division of Infectious Disease, Stuart Foshee, MD, Chitra S. Mani, MD, Dennis L. Murray, MD, Christopher White, MD; University of South Alabama College of Medicine, Southeast Pediatric ACTU, Mary Y. Mancao, MD, Benjamin Estrada, MD; LSU Health Sciences

Center, Ronald D. Wilcox, MD; Tulane University Health Sciences Center, Margarita Silio, MD, MPH, Thomas Alchediak, MD, Cheryl Borne, RN, Shelia Bradford, RN; St. Josephs Hospital and Medical Center, Cooper University Hospital, HMS - Children's Hospital Boston, Division of Infectious Diseases, David Geffen School of Medicine at UCLA - Department of Pediatrics, Division of Infectious Diseases, Children's Hospital of Orange County, Children's Memorial Hospital - Department of Pediatrics, Division of Infectious Disease, University of Chicago - Department of Pediatrics, Division of Infectious Disease, Mt. Sinai Hospital Medical Center - Chicago, Women's & Children's HIV Program, Columbia University Medical Center, Pediatric ACTU, Incarnation Children's Center, Cornell University, Division of Pediatric Infectious Diseases & Immunology, University of Miami Miller School of Medicine - Jackson Memorial Hospital, Bellevue Hospital (Pediatric), San Francisco General (Pediatric), Phoenix Children's Hospital, Metropolitan Hospital Center (N.Y.), University of Cincinnati, SUNY Downstate Medical Center, Children's Hospital at Downstate, North Shore University Hospital, Jacobi Medical Center, University of South Florida (USF) - Department of Pediatrics, Division of Infectious Diseases, Cornell University, Oregon Health & Science University - Department of Pediatrics, Division of Infectious Diseases, Children's Hospital of the King's Daughters, Infectious Disease, Lincoln Medical & Mental Health Center, Mt. Sinai School of Medicine, Division of Pediatric Infectious Diseases, Emory University Hospital, San Juan City Hospital, UMDNJ - Robert Wood Johnson, Ramon Ruiz Arnau University Hospital, Medical University of South Carolina, SUNY Upstate Medical University, Department of Pediatrics, Wayne State University (WSU) School of Medicine, Children's Hospital of Michigan, Children's Hospital at Albany Medical Center, Children's Medical Center of Dallas, Children's Hospital - University of Colorado at Denver and Health Sciences, Center (UCHSC), Pediatric Infectious Diseases, Columbus Children's Hospital, University of Florida College of Medicine - Department of Pediatrics, Division of Immunology, Infectious Diseases & Allergy, University of Mississippi Medical Center, Palm Beach County Health Department, Children's Hospital LA - Department of Pediatrics, Division of Adolescent Medicine, Vanderbilt University Medical Center, Division of Pediatric Infectious Diseases, Washington University School of Medicine at St. Louis, St. Louis Children's Hospital, Children's Hospital & Medical Center, Seattle ACTU, Oregon Health Sciences University, St. Luke's-Roosevelt Hospital Center, Montefiore Medical Center - Albert Einstein College of Medicine (AECOM), Children's Hospital, Washington, DC, Children's Hospital of the King's Daughters, University of Alabama (UAB) at Birmingham, Department of Pediatrics, Division of Infectious Diseases, Columbus Regional HealthCare System, The Medical Center, Sacred Heart Children's Hospital/CMS of Florida, Bronx Municipal Hospital Center/Jacobi Medical Center.

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TABLE 1

Summary of Baseline Characteristics Among 2102 HIV-Infected Subjects Enrolled in PACTG 219/219C, 1993–2005

	No. HIV Subjects (%) (N = 2102)
Gender	
Male	1040 (49.5%)
Female	1062 (50.5%)
Baseline age (yr)	
Median	6.32 yr
0–5.9 yr	981 (46.7%)
6 yr or more	1121 (53.3%)
Race/Ethnicity	
White, nonhispanic	283 (13.5%)
Black, nonhispanic	1189 (56.6%)
Hispanic (any race)	597 (28.4%)
Other/Unknown	33 (1.6%)
Baseline CDC clinical class*	
N, A, or B	1588 (75.5%)
C	514 (24.5%)
No. HIV-1 RNA copies at study entry†	
Median copies (log_{10})	3.9
0–400 copies	346 (18.2%)
401–10000	669 (35.2%)
10001–100000	578 (30.4%)
100001 or more	306 (16.1%)
Missing	203
$CD4^+$ T-cell % at study entry‡	
Median	27%
0%–14.9%	357 (17.0%)
15%–24.9%	518 (24.6%)
25% or more	1227 (58.4%)
Nadir $CD4^+$ T-cell % prior to third abnormal laboratory result	
Median	17%
0%–14.9%	838 (39.9%)
15%–24.9%	725 (34.5%)
25% or more	539 (25.6%)

*If not recorded at study entry, this designation was based on review of clinical diagnoses and in a subset, also laboratory values.

†Copies per mL plasma; computed as maximum of AUC prior to study entry or closest value to study entry (preferably within 31 d prior).

‡Closest value to study entry (preferably within 31 d prior).

TABLE 2

Occurrence of Renal Disease Laboratory Indicators Among 2068 HIV-Infected PACTG 219/219C Study Subjects and Sequence of Abnormalities Among 446 With at Least One Abnormality

	n	(%)
Occurrence of renal laboratory abnormality (N = 2068)		
Persistently elevated creatinine*	307	(14.9%)
PP (≥ trace)	160	(7.7%)†
Persistent proteinuria and persistently abnormal creatinine and/or eGFR	21	(1.0%)
At least 1 persistent renal laboratory abnormality	446	(21.6%)
Sequence of renal laboratory abnormalities (N = 446)		
Abnormal in only one parameter	425	(95.3%)‡
Abnormal in >1 parameter	21	(4.7%)
PP occurs >90 d before another abnormality	14	(3.1%)
PP occurs within 90 d of another abnormality	3	(0.7%)
Elevated creatinine and/or eGFR occurs before PP	4	(0.9%)

*With or without abnormally low eGFR.

†6.7% of subjects had PP only.

‡32.7% of subjects with at least one lab abnormality had PP only.

PP indicates persistent proteinuria.