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Predictors of resolution and persistence of renal laboratory abnormalities in Pediatric HIV infection

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Abstract

Background—Among HIV infected youth, the role of renal disease (RD) and its management has become more important as children/adolescents age into young adulthood. Identification of predictors of abnormal renal laboratory events (RLE) may be helpful in the management of their HIV infection and its associated renal complications."

Methods—Data collected from HIV-infected children and youth followed for ≥48 months was analyzed to identify predictors of resolution versus persistence of RLE and determine the utility of RLE to predict the onset of RD. Analysis included descriptive and inferential methods using a multivariable extended Cox proportional hazards model.

Results—428 of 1874 at risk children (23%) developed RLE, which persisted in 229 of 428(54%). CD4<25% (hazard ratio[HR] 0.63, p<0.002) and HIV viral load>100,000 copies/ml (HR 0.31, p<0.01) were associated with reduced rates of resolution. Exposure to HAART/ nephrotoxic HAART prior to or subsequent to RLE in most cases were not. Persistence of RLE was 88% sensitive for identifying new RD. Negative predictive values for RD were >95% for both the at risk cohort and in those with RLE.

Conclusions—Advanced HIV disease predicted persistence of RLE in HIV-infected youth. Persistent RLE were useful for identifying RD.

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Keywords

HIV; HIV renal disease; HAART

Introduction

Among HIV-1 infected children and adolescents, renal disease may occur as a result of the complications of HIV-1 infection and as well as from highly active antiretroviral therapy (HAART) [1–6]. Treatment-dosing guidelines and new drug development have evolved over the years, resulting in exposure to antiretroviral agents from an increasing number of different classes for prolonged periods of time. Indeed, children and adolescents who acquired HIV infection perinatally or early in life as a result of parenteral or sexual exposure have started HAART earlier in the course of their disease and have been maintained on HAART for most of their lives [7]. HIV-associated nephropathy (HIVAN) was recognized previously as the leading cause of chronic kidney disease (CKD) in adults and children with HIV in the United States [8–10]. In 2004 nearly half of the cases of CKD in HIV-infected patients were reported as being due to HIVAN. Since then, however, the spectrum of CKD in HIV-infected patients has been changing with less HIVAN and more comorbid kidney disease, such as that caused by hypertension and diabetes being reported (11–14). Recently, the CDC's Medical Monitoring Project (15) reported an association between renal disease with longer duration of HIV infection. Given the number of recent reports linking nephrotoxicity with certain antiretroviral agents and the length of such therapy in children, it is possible that among HIV-infected youth HAART may increasingly contribute to the development of CKD.

The data reported here are from a retrospective analysis of HIV-1 infected children in the United States enrolled in the Pediatric AIDS Clinical Trials Group (PACTG) Protocol 219/219C. In our initial report from this cohort, Andiman et al [6] described the incidence of renal laboratory abnormalities or renal laboratory events (RLE), which were defined as the last sequence of at least three abnormal values in at least one category; serum creatinine (Cr), urine persistent proteinuria (PP), or estimated glomerular filtration rate (eGFR). Twenty-two percent of the PACTG 219/219C cohort had at least one persistent RLE which was associated with older age, black race, Hispanic ethnicity, use of nephrotoxic antiretroviral drugs (tenofovir and indinavir) and other nephrotoxic antimicrobial agents previously known to be associated with these RLE's. Subsequently, Purswani et al [16] reported kidney biopsy findings in the same cohort, and described both demographic and clinical risk factors for children with HIV associated CKD. The present report extends these previous findings by determining the sensitivity and specificity of RLE's for new renal disease diagnoses as markers of new onset renal disease. We also attempted to identify predictors of resolution versus persistence of RLE's in children with HIV infection followed in P219/219C.

Methods

Study Population

PACTG 219/219C was a multicenter prospective cohort whose main objective was to determine the consequences of HIV-1 infection and its treatment from infancy through childhood into adolescence. The study opened to enrollment in May 1993 and spanned what is now accepted as the pre-HAART era from 1993 to 1997, and the HAART era, from 1998 to May of 2007 [7], when it ended. Details of Protocol 219/219C have been previously described [6, 16]. Children enrolling at or after January 1, 1998 were considered to have enrolled during the HAART era.

Participants in this study were a subset of the 2,102 subjects reported by Andiman et al. [6] who had no abnormal labs or renal diagnosis at study entry. Abnormal renal lab events (RLE) were defined for this study as the first in the sequence of at least three abnormal values in at least one category; serum creatinine (Cr), urine persistent proteinuria (PP), or estimated glomerular filtration rate (eGFR). The date of onset of the abnormal renal lab event was the date of the earliest abnormal lab value, across categories. The timing definition used here contrasts with that used in Andiman et al [6], where the timing of the renal lab event was also the earliest date across categories but within a category the third rather than first sequential lab abnormality defined onset. Cutoff for increased urine protein excretion was trace or greater, while cutoffs for increased serum creatinine (Cr) were age-adjusted [14], and that for reduced eGFR was < 60 mL/min/1.73 m^2. The Modified Schwartz-CKID formula was used to compute eGFR for those less than 18 years of age [17–18] and the Modification of Diet in Renal Disease (MDRD) formula for those over 18 years of age [19].

Study Outcome definitions

Renal Laboratory outcomes

Resolution of RLE: Study participants who were identified with RLE and for whom there were subsequently at least three sequential normal lab values in the given category. If abnormalities occurred in more than one domain, each had to resolve to meet this definition. The date of resolution was the latest of the three normal values, across categories.

Persistence of RLE: Study participants who were identified with RLE and in whom there was no resolution of abnormal measures were considered to have persistent RLE.

New onset renal diagnosis: Any subject with RLE in whom there was no renal diagnosis at P219C study entry, but who subsequently received a specific renal diagnosis was considered as having a new onset renal diagnosis.

Renal-related death: A participant death in which renal disease was either a primary cause or co-existing contributing cause of death.

Renal-toxic HAART: Medications recorded in the P219/219C database were considered in this analysis if they met the definition of renal-toxic medications as defined in Andiman

(2009). HAART regimens which included either TDF or IDV were considered to be renal-toxic.

Only participants who had been on study for at least 48 months were included in the analysis in order to allow sufficient additional time (18 months) for a patient who previously had an RLE during the first 30 months on study to experience a resolution (three sequential normal lab values).

Renal Diagnoses

Clinical renal diagnoses were coded using the Medical Dictionary for Regulatory Activities (MedDRA®) v14.1, a hierarchical and multiaxial medical coding terminology for clinical events. Queries for renal events were done broadly using Preferred Terms associated with the renal and urinary system organ class (SOC). We also identified conditions via the Standardized MedDRA Queries (SMQ), the acute renal failure SMQ, the hypertension SMQ and the renovascular disorders SMQ. SMQs are predefined sets of related Preferred Terms.

Diagnoses were classified into broad types of renal problems (primary renal, other renal, urinary tract infections, hypertension, renal laboratory abnormalities, edema, hematuria). The earliest occurring episode was selected for further analysis. Information on participant deaths was identified in the source P219/219C database via the death case report form which collected death dates and major and contributing causes, among other information.

Statistical Analysis

Selected sensitivity and specificity analyses included the full study population (n=2102). The remaining analyses considered only those participants who experienced RLEs. Medication exposures were classified according to whether they occurred at or prior to the date of the RLE or after this time. Medication exposures after RLE resolution were not considered in the analysis. We classified children by their exposure status before and after RLE.

We compared personal and HIV disease laboratory markers for participants who enrolled in P219/219C in the pre-HAART to the HAART eras using standard statistical tests as appropriate: Fisher’s exact test, Pearson chi square, and the Wilcoxon rank sum test. We next explored the association between each medication exposure and RLE resolution with a Pearson chi square test, classifying outcomes according to whether participants with exposure to medication at or prior to their RLE were switched off medication after the event. We also computed the sensitivity, specificity, positive and negative predictive values for the RLE and its persistence in predicting primary renal diagnoses.

Finally, we fit multivariable extended Cox proportional hazards models to explore the associations between the resolution of the RLE and changing medication exposure during the course of the study, adjusting for personal (age at renal event, race, ethnicity, sex) and clinical characteristics (e.g., CDC HIV stage at P219/219C study entry, HIV viral load and CD4 percent). Study time began at the RLE and ended at either its resolution or censor (last study visit). HIV disease markers were considered in these models separately as they changed over time and as they were measured at the RLE (defined as the closest value at or

before the time of the RLE). In addition to considering the continuous values of CD4 percent and HIV RNA viral load, we also used categorical values by classifying CD4 percent using a cutoff of 25% and HIV RNA viral load using a cutoff of 100,000 copies/ml.

We used a two-step modeling process. In the first step, we explored the univariable associations between covariates and RLE resolution. We then built a core multivariable model by including univariable covariates with a $p < 0.20$, retaining only those factors with adjusted $p < 0.15$. In the second step, we explored the associations between changing medication use and RLE resolution after adjusting for the core model variables. Each model included a separate medication exposure. Time-dependent HIV markers(viral load and CD4 percent) were the most recent values prior to the start of the interval for which changes in medication were reported. We performed secondary sensitivity analyses, focusing only on the association between these markers and RLE resolution. Finally, analyses were performed on the subset of participants who enrolled into P219/219C during the HAART era. SAS v9.2 was used for the analyses and values with two-sided $p < 0.05$ were considered to be statistically significant.

Results

Study population

Figure 1 depicts a flow chart showing the breakdown of the 1874 participants who met study criteria and the subsequent distribution of those children who developed new renal lab abnormality or event (RLE) or new renal diagnoses. The majority of these children (1734, or 93%) were perinatally infected. Four hundred twenty-eight (428) of the 1874 subsequently had a new RLE either in serum creatinine (Cr), urine persistent proteinuria (PP) or estimated glomerular filtration rate (eGFR). All but 15 of these children were perinatally infected (96%).

Of the 428 subjects with new RLE, 199 resolved their RLE while 229 did not. Among those 229 who had persistent RLE, 35 (15.3%) developed a new renal diagnosis. There were 8 deaths in this later group; 4 of whom died of renal-related causes. There were an additional 8 deaths in the group without new renal diagnoses. None of these latter deaths were renal-related Among the 199 who resolved their abnormalities and the 1446 children who did not develop any new RLE, there was a much smaller percentage of children (2.5%[5/199] and 2.7%[39/1446] respectively) who developed a new renal diagnosis. Among the 1446 children, six of the 39 children with new renal diagnoses died; 3 of renal related causes. Forty-two of the other 1407 children died, only one being renal-related. That one renal-related death was counted as a “new renal diagnosis” for the purposes of the sensitivity/specificity analysis. There was one non-renal-related death in the group of 199 who resolved their RLE.

The frequency and severity of the new renal diagnoses were more pronounced among those children who had persistent abnormalities. While the frequency of renal tubular disorders was only minimally increased (1/199 (0.5%) among children who resolved their RLE versus 4/229 (1.7%) among children with persistent RLE), the frequency of proteinuria, renal parenchymal disease and renal failure were all markedly higher among children who had

persistent RLE. In each of these three categories, the percentage among children who had persistent RLE was at least five times higher than that among children who experienced resolution of their RLE. Seventeen (7.4%) of the children with persistent RLE developed one of the following renal parenchymal diseases (nephrosis [11], focal segmental glomerulosclerosis [2], glomerulonephritis [2], and lupus nephritis[2]).

Demographic and clinical characteristics

Table 1 shows the demographic and clinical characteristics for the 428 participants in the analysis who had three consecutive RLE comparing those enrolled pre-HAART to those enrolled during the HAART era. Participants enrolled during the HAART era were slightly older at the time of the RLE and were followed (to resolution/last visit date) for less time compared to those enrolled during the pre-HAART era. As expected, there were fewer deaths among those enrolled during the HAART era. Overall, about 46% of the participants' RLEs resolved. The number of participants who resolved their RLE was similar in both subgroups. Both CD4% and HIV RNA viral load values indicate that HAART-era participants were healthier at the time of the RLE than were those enrolled prior to the HAART era (all $p < 0.05$). Note that 84 participants, primarily among those enrolled during the pre-HAART era, had no HIV RNA viral load measured at the renal lab event time.

Sensitivity and Specificity of Renal Lab Events for New Renal Diagnoses

Panel A in Figure 2 depicts the respective values for sensitivity, specificity, and positive and negative predictive values for an abnormal RLE for predicting a new renal diagnosis in children in the source population (1874). Panel B in Figure 2 depicts these same values but in this case for persistent abnormal RLE for predicting a new renal diagnosis among children who developed a new RLE (428). The sensitivity of RLE for predicting a new renal diagnosis for all children in the source population was only 50%, while the specificity for ruling out renal disease was high (78%). In contrast, the sensitivity of persistent RLE for predicting a new renal diagnosis among the 428 children with new onset of RLE was high (88%) while the specificity of persistent RLE was low (50%); absence of persistent RLE only identified half of those without renal diagnoses. In both groups, the positive predictive values of RLE and persistent RLE for a new renal diagnosis were low (about 10–15%) while the negative predictive values for both were greater than 95%. There was no marked difference in the figures for sensitivity, specificity, or negative predictive values when these values were determined for separate groups of children enrolled during the pre-HAART versus the HAART era. Though somewhat different, positive predictive values were low for both subgroups (<40%, data not shown). Hence, as a screening test for clinically significant renal disease, among those children with RLE, persistence of RLE captures almost 90% of those with renal diagnoses while, among all children in the source population, presence of an RLE identifies about half of those with renal diagnoses.

Medication Exposures

In the total group of 428 participants, 88% of the children enrolled during the HAART era were exposed to HAART prior to the onset of their first renal lab event as opposed 61.5% of those enrolled during the pre-HAART era ($p<.001$, Fisher's Exact Test) but this was likely due to the ready availability of HAART during the latter time period. There was no

statistical difference relative to timing of exposure to renal-toxic HAART between children who enrolled during the two eras; 20% of HAART-era participants received renal-toxic HAART prior to the renal lab event compared to 14% of pre-HAART-era participants (p=0.11). Similarly, for the other classes of medications, exposure timing for HAART-era and pre-HAART-era participants did not differ. When we analyzed the timing of medication exposure and resolution outcome, the statistical results were heavily weighted by the number of subjects never exposed to the medications (Table 2). We then focused on those study participants receiving medications prior to the time of the abnormal renal lab event, cross classifying outcomes according to whether or not they were still exposed after the RLE. While 46% of those participants on HAART continuously did resolve their RLE, 55% of patients never treated with HAART also experienced resolution (Table 2, p=0.05). There is no evidence for increased rates of resolution when renal-toxic regimens were stopped. For example, of those participants who no longer had exposure to renal-toxic HAART after the RLE, 30% resolved the RLE as compared to 29.8% of those subjects who still remained on that class of medication. When this analysis was performed using hierarchical and mutually exclusive classification of medication exposure prior to the RLE (if they had any exposure to renal-toxic HAART and, if not, another HAART regimen, a non-HAART antiretroviral regimen, or no exposure to any antiretroviral agent), there was a suggestion that a lower resolution rate was associated with early renal-toxic HAART exposure (30%) as compared to the rate for those exposed to other antiretroviral regimens, (50%; p=0.03).

Time to Resolution of Abnormal Renal Lab Events

Table 3 shows, for the youths with renal laboratory abnormalities, the association between medication exposures and resolution, adjusting for time-varying CD4 percent, CDC stage C and Black race. (HIV RNA viral load measurements as they changed over time did not meet core model inclusion criteria). None of the medication exposures (renal toxic HAART, TDF, IDV, or non-antiretroviral renal toxic concomitant medications) were significantly associated with RLE resolution ($p \geq 0.53$; results repeated as analysis set 1 of Table 4). We repeated the modeling process to adjust for CD4% (< 25), and HIV RNA viral load (> 100,000 copies) at the time of the first RLE (Table 4, analysis set 2). In addition to Black race and CDC Stage C, only HIV RNA viral load met model inclusion criteria. There were no significant associations between medication exposures and resolution ($p>0.35$). Since many participants were missing viral load data, we next developed a core model adjusting only for CD4 percent measured at the renal lab event. No other core model covariates met the inclusion criterion. There were no significant associations with medication exposure ($p>0.63$, Table 4, analysis set 3). Results for core model covariates suggested reduced rates of resolution for youths with CDC Stage C disease classification ($p< 0.10$), low time-varying CD4 percents (p=0.06), higher HIV RNA viral loads at RLE($p = 0.01$), and low CD4 percent at RLE(p=0.002) (Table 5). There were also no significant associations with medication exposure, when we analyzed only the participants enrolled during the HAART era ($p > 0.24$, data not shown). For these participants, older age at renal lab events was associated with a longer time to RLE resolution (p=0.02; data not shown).

Results of a sensitivity analysis focused solely on the relation between resolution and each CD4% and HIV RNA viral load measures (Supplemental Table 1) confirmed the reduced

resolution rates for youths with low CD4 percentage and high HIV RNA viral loads. Additional analyses also confirmed the association between CDC Stage C disease classification and reduced resolution ($p < 0.10$; data not shown). In the sensitivity analysis of the HAART era-enrolled participants, the only significant findings were the association between older age at first RLE and reduced resolution rates ($p=0.01$; data not shown).

Discussion

Recent data have suggested that highly active antiretroviral therapy can change the natural history of HIVAN, not only by preventing its development but also by halting its progression once developed [11, 12]. While the time to–event analysis did not directly address the impact of non-renal toxic HAART on resolution of RLE, in descriptive analyses there appeared to be little impact of HAART on RLE resolution. We attempted to determine whether there was any association between persistent RLE and the use of renal-toxic HAART (as suggested recently by Leal et al, 2010 [20]). We once again found little evidence for a relationship between medication exposure and resolution of abnormal renal laboratory events. What this study did show, however, was that low CD4 percent values, higher HIV RNA viral load values, and older age at the time of the renal lab event were all associated with reduced rates of RLE resolution. A possible explanation is that patients with advanced HIV disease might have severe renal disease that does not respond to HAART. Since our analysis encompassed both the pre-HAART and HAART eras, data from the sicker pre-HAART era children is likely driving these findings. Nevertheless, some individual findings from our unadjusted, descriptive analyses suggest that continued exposure to renal toxic HAART may be associated with persistent RLE. The sensitivity and specificity analyses showed that three sequential abnormal renal labs are only modestly effective in predicting the occurrence of new primary renal diagnoses in HIV infected children and adolescents. It is noteworthy that for those participants with an existing RLE, finding persistence of these renal lab abnormalities was a good screening measure for these same outcomes. Overall, the negative predictive values of these two assessments were high. Therefore absence of RLE was a good indicator to rule out renal diagnoses, as would intuitively be expected. This suggests that when screening HIV-infected children and adolescents for renal disease, persistence of any of these three renal laboratory abnormalities should prompt referral to a nephrologist for a more thorough evaluation.

One limitation of our analyses was that PACTG 219/219C was not designed specifically to study HIV-renal related disease; consequently all renal related data collection was done as part of the child's continuing care and not mandated prospectively as part of the study design. Nor did it include screening for microalbuminuria, or determining the microalbumin/Cr ratio. Despite these limitations, we have previously published two papers describing the nature of HIV-related renal disease using this same dataset (6, 5). A second limitation was that some of our retrospective analyses divided the total number of study subjects into two subgroups: those children enrolled in P219/219c during the pre-HAART era (1993–1997) versus those enrolled during the HAART era (1998–2007). The children enrolled during the pre-HAART era continued to be followed and had data collected during the latter time period when they were being treated with HAART. Hence, the results from this group may have been biased by the effects of untreated HIV infection prior to the time

they started HAART. One additional limitation of our analysis was that we did not specifically assess for the potential nephrotoxic effects of either ritonavir-boosted atazanavir or lopinavir as suggested recently in a report by Ryom et al [21] based upon data from adult patients enrolled in the D:A:D study (Data Collection on Adverse events of Anti-HIV Drugs Study).

Based upon recent data from adults, it is probable that the nature of HIV-associated renal disease is changing. The frequency of HIVAN may be decreasing as a result of the widespread availability of HAART which may be preventing the development of the early stages of HIVAN. At the same time there is a greater recognition of the potential nephrotoxicity of various antiretroviral agents which may be a concern among younger HIV-infected children whose renal function is still maturing. The difficulty here relates to how to distinguish the effects of the virus from the effects of the drugs. While proteinuria, especially persistent proteinuria, is a laboratory hallmark of HIVAN; additional laboratory abnormalities including alterations in serum Cr, eGFR, or other electrolyte abnormalities may be secondary to the effects of HIV or the medications (22). The ability to discern the etiology of renal lab abnormalities may be especially difficult in those patients who have more advanced HIV disease, and are being treated with HAART (especially if they are on nephrotoxic HAART). This may have influenced our results. Approximately 25% of the total group of children had AIDS (CDC Class C) at entry while 39% had a CD4% of less than 25% at or prior to the first RLE. The median age of the entire group at the first abnormal laboratory was 10.5 years; hence many of these children had been infected for at least a decade.

In summary, we analyzed 14 years of prospectively collected data from 1874 HIV-1 infected youth enrolled in PACTG 219/219C. We were able to document that persistent renal lab abnormalities are associated with an increased frequency and severity of primary renal diagnoses, and that advanced HIV renal disease is more likely to result in a lack of resolution of RLEs with HAART. Although the sensitivity and specificity analyses show that three sequential abnormal renal labs alone are only modestly effective in predicting primary renal diagnoses, in those participants with RLE, the persistence of these RLEs was a good predictor of these same outcomes. The negative predictive values of these same two assessments were also high.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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APPENDIX I

Participating institutions in the U.S.-based multisite cohort study, PACTG 219/219C, between 1993–2007.

The following institutions and clinical site investigators participated in PACTG 219/219C:

University of New Jersey Medical and Dental School - Department of Pediatrics, Division of Allergy, Immunology & Infectious Diseases: *Dr. James Oleske, Dr. Arlene Bardeguez, Dr. Arry Dieudonne, Linda Bettica, Juliette Johnson,* Boston Medical Center, Division of Pediatric Infectious Diseases: *Dr. Stephen I. Pelton, Dr. Ellen R. Cooper, Lauren Kay, Ann Marie Regan,* Med, Children's Hospital LA - Department of Pediatrics, Division of Clinical Immunology & Allergy: *Dr. Joseph A. Church, Theresa Dunaway,* Long Beach Memorial Medical Center, Miller Children's Hospital: *Dr. Audra Deveikis, Dr. Jagmohan Batra, Susan Marks, Ilaisanee Fineanganofo,* Harbor - UCLA Medical Center - Department of Pediatrics, Division of Infectious Diseases: *Dr. Margaret A. Keller, Dr. Nasser Redjal, Spring Wettgen, Sheryl Sullivan,* Johns Hopkins Hospital & Health System - Department of Pediatrics, Division of Infectious Diseases: *Dr. Nancy Hutton, Beth Griffith, Mary Joyner, Carolyn Keifer,* University of Maryland Medical Center, Division of Pediatric Immunology & Rheumatology: *Dr. Douglas Watson, Dr. John Farley,* Texas Children's Hospital, Allergy & Immunology Clinic: *Dr. Mary E. Paul, Chivon D. Jackson, Faith Minglana, Dr. Heidi Schwarzwald,* Cook County Hospital: *Dr. Kenneth M. Boyer, Dr. Jamie Martinez, Dr. James B. McAuley, Maureen Haak,* Children's Hospital of Columbus, Ohio: *Dr. Michael Brady, Dr. Katalin Koranyi, Jane Hunkler, Charon Callaway,* University of Miami Miller School of Medicine, Division of Pediatric Immunology & Infectious Disease: *Dr. Gwendolyn B. Scott, Dr. Charles D. Mitchell, Dr. Claudia Florez, Joan Gamber,* University of California San Francisco School of Medicine, Department of Pediatrics: *Dr. Diane W. Wara, Dr. Ann Petru, Nicole Tilton, Mica Muscat,* Children's Hospital & Research Center Oakland, Pediatric Clinical Research Center & Research Lab: *Dr. Ann Petru, Teresa Courville, Karen Gold, Katherine Eng,* University of California San Diego Mother, Child & Adolescent HIV Program: *Dr. Stephen A. Spector, Dr. Rolando M. Viani, Mary Caffery, Kimberly Norris,* Duke University School of Medicine - Department of Pediatrics, Children's Health Center: *Margaret Donnelly, Dr. Kathleen McGann, Carole Mathison, John Swetnam,* University of North Carolina at Chapel Hill School of Medicine - Department of Pediatrics, Division of Immunology and Infectious Diseases: *Dr. Tom Belhorn, Jean Eddleman, Betsy Pitkin,* Schneider Children's Hospital: *Dr. Vincent R. Bonagura, Dr. Susan Schuval, Dr. Blanka Kaplan, Dr. Constance Colter,* Harlem Hospital Center: *Dr. Elaine J. Abrams, Maxine Frere, Delia Calo,* New York University School of Medicine, Division of Pediatric Infectious Diseases: *Dr. William Borkowsky, Nagamah Deygoo, Maryam Minter, Seham Akleh,* Children's National Medical Center, George Washington University: *Diana Dobbins, Deidre Wimbley, Dr. Lawrence D'Angelo, Hans Spiegel,* University of Washington School of Medicine - Children's Hospital and Regional Medical Center: *Dr. Ann J. Melvin, Kathleen M. Mohan, Michele Acker, Suzanne Phelps,* University of Illinois College of Medicine at Chicago, Department of Pediatrics: *Dr. Kenneth C. Rich, Dr. Karen Hayani, Julia Camacho,* Yale University School of Medicine - Department of Pediatrics, Division of Infectious Disease: *Dr. Warren A. Andiman, Leslie Hurst, Dr. Janette de Jesus, Donna Schroeder,* SUNY at Stony Brook School of Medicine, Division of Pediatric Infectious Diseases: *Denise Ferraro, Jane Perillo, Michele Kelly,* Howard University Hospital, Department of Pediatrics & Child Health: *Dr. Sohail Rana, Dr. Helga Finke, Patricia Yu, Dr. Jhoanna Roa,* LA County/University of Southern California Medical Center: *Dr. Andrea Kovacs, Dr. James Homans, Dr. Michael Neely, Dr. La Shonda Spencer,* University of Florida Health Science Center Jacksonville, Division of Pediatric

Infectious Disease & Immunology: *Dr. Mobeen H. Rathore, Dr. Ayesha Mirza, Kathy Thoma, Almer Mendoza,* North Broward Hospital District, Children's Diagnostic & Treatment Center: *Dr. Ana M. Puga, Dr. Guillermo Talero, James Blood, Stefanie Juliano,* University of Rochester Medical Center, Golisano Children's Hospital: *Dr. Geoffrey A. Weinberg, Barbra Murante, Susan Laverty, Dr. Francis Gigliotti*, Medical College of Virginia: *Dr. Suzanne R. Lavoie, Tima Y. Smith,* St. Jude Children's Research Hospital, Department of Infectious Diseases*: Dr. Aditya Gaur, Dr. Katherine Knapp, Dr. Nehali Patel, Marion Donohoe,* University of Puerto Rico, U. Children's Hospital AIDS: *Dr. Irma L. Febo, Dr. Licette Lugo, Ruth Santos, Ibet Heyer,* Children's Hospital of Philadelphia, Center for Pediatric & Adolescent AIDS: *Dr. Steven D. Douglas, Dr. Richard M. Rutstein, Carol A. Vincent, Patricia C. Coburn,* St. Christopher's Hospital for Children/Drexel University College of Medicine*: Dr. Jill Foster, Dr. Janet Chen, Dr. Daniel Conway, Dr. Roberta Laguerre,* Bronx-Lebanon Hospital Center, Infectious Diseases: *Dr. Emma Stuard, Caroline Nubel, Dr. Stefan Hagmann, Dr. Murli Purswani,* New York Medical College/ Metropolitan Hospital Center: *Dr. Mahrukh Bamji, Dr. Indu Pathak, Dr. Savita Manwani, Dr. Ekta Patel*, University of Massachusetts Memorial Children's Medical School, Department of Pediatrics: *Dr. Katherine Luzuriaga, Dr. Richard Moriarty,* Baystate Health, Baystate Medical Center: *Dr. Barbara W. Stechenberg, Dr. Donna J. Fisher, Dr. Alicia M. Johnston, Maripat Toye,* Connecticut Children's Medical Center: *Dr. Juan C. Salazar, Kirsten Fullerton, Gail Karas,* Medical College of Georgia School of Medicine, Department of Pediatrics, Division of Infectious Disease: *Dr. Stuart Foshee, Dr. Chitra S. Mani, Dr. Deniis L. Murray, Dr. Christopher White,* University of South Alabama College of Medicine, Southeast Pediatric ACTU: *Dr. Mary Y. Mancao, Dr. Benjamin Estrada,* LSU Health Sciences Center: *Dr. Ronald D. Wilcox,* Tulane University Health Sciences Center: *Dr. Margarita Silio, Dr. Thomas Alchediak, Cheryl Borne, Shelia Bradford,* St. Josephs Hospital and Medical Center, Cooper University Hospital - 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 - 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 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, 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, Children’s Hospital, Washington, D.C., Children’s Hospital of the King’s Daughters, University of Alabama 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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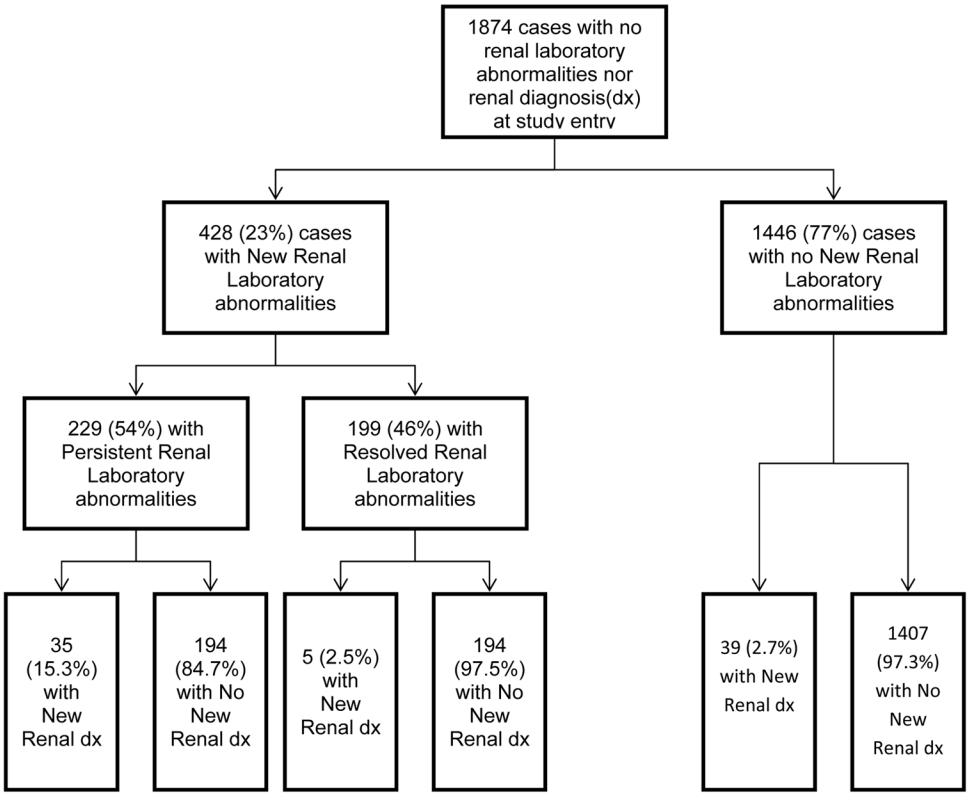

Figure 1. Impact of persistent or resolved renal laboratory abnormalities on development of new renal disease diagnoses

The Flow chart depicts the outcome in developing new renal diagnosis based on renal laboratory screening tests that persist or resolve. There were 1874 children in the study cohort with no renal laboratory abnormalities nor renal diagnosis at study entry. During follow-up, 428 (23%) developed new renal laboratory abnormalities while 1446 (77%) did not. Of those cases with new renal laboratory abnormalities, 229 (54%) had persistence of abnormal laboratory renal studies with 35 (15.3%) developing a new renal diagnosis. In contrast, 199 (46%) had resolution of their abnormal renal studies with only 5 (2.5%) developing a new renal diagnosis. In the 1446 (77%) cases that never developed new renal laboratory abnormalities, there were 39 (2.7%) who developed renal diagnosis.

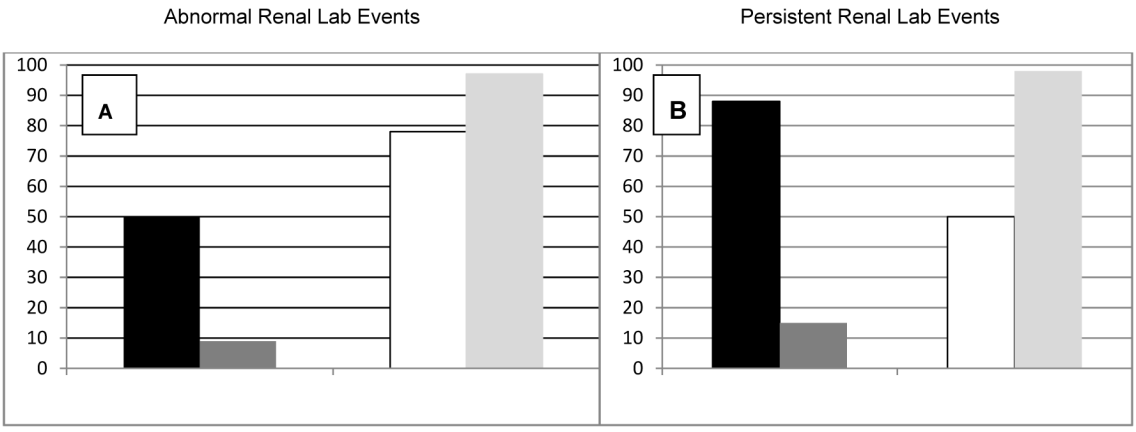

Figure 2.

Sensitivity (Black bar), Specificity(White bar), Positive(Dark Gray bar) and Negative(Light Gray bar) Predictive Values of Abnormal Renal Lab Events(Panel A) in the source population(1874) and Persistent Renal Lab Events (Panel B) in the group with RLE (428) for New Renal Diagnoses.

Table 1

Characteristics of Patients who Developed New Renal Lab Events (RLE) during the Pre-HAART versus the HAART Eras.

	Enrollment during HAART era (1998 or after)			
	Total (N=428)	**No (N=299)**	**Yes (N=129)**	**P-Value**
Male, N (%)	224 (52.3%)	157 (52.5%)	67 (51.9%)	0.92 *(a)*
Race/Ethnicity, N (%)				0.11 *(a)*
White, non-Hispanic	47 (11.0%)	37 (12.4%)	10 (7.8%)	
Black, non-Hispanic	222 (51.9%)	144 (48.2%)	78 (60.5%)	
Hispanic (any race)	152 (35.5%)	113 (37.8%)	39 (30.2%)	
Other/Unknown	7 (1.6%)	5 (1.7%)	2 (1.6%)	
CDC stage C at 219/219C study entry, N (%)	109 (25.5%)	69 (23.1%)	40 (31.0%)	0.09 *(a)*
Age, y at RLE, Median (Q1, Q3)	10.53 (8.51, 12.18)	10.33 (8.02, 12.08)	11.22 (9.51, 12.84)	<.001 *(b)*
Months on study from RLE to resolution/or last patient contact, Median (Q1, Q3)	38.27 (24.10, 58.52)	42.40 (29.24, 61.64)	28.88 (20.23, 44.08)	<.001 *(b)*
All lab abnormal sequences resolve, N (%)	199 (46.5%)	141 (47.2%)	58 (45.0%)	0.75 *(a)*
Death, N (%)	17 (4.0%)	16 (5.4%)	1 (0.8%)	0.03*(a)*
Renal-related primary or secondary cause of death, N(%)	4 (23.5%)	4 (25.0%)	0 (0.0%)	1.00 *(a)*
CD4 % at/prior to RLE				
Median (Q1, Q3)	28 (20, 35)	27 (19, 34)	30 (22, 35)	0.03 *(b)*
CD4 pct < 25, at/prior to RLE, N (%)	167 (39.0%)	128 (42.8%)	39 (30.2%)	0.02 *(a)*
Log RNA VL at/prior to RLE				
N	344	218	126	
Median (Q1, Q3)	3.11 (2.60, 4.18)	3.33 (2.60, 4.36)	2.83 (2.60, 3.64)	0.003 *(b)*
HIV RNA at/prior to RLE >100,000 copies, N (%)	27 (7.8%)	23 (10.6%)	4 (3.2%)	0.01 *(a)*

(a) Fisher's Exact Test

(b) Wilcoxon Test

Table 2

Timing of Medication Exposure for all Participants Relative to the Renal Lab Event

		All lab abnormal sequences resolve		
		No (N=229)	**Yes (N=199)**	**P-Value** *(a)*
HAART, Exposure summary	Switched off	7 (100.0%)	0 (0.0%)	0.05
	Switch on	44 (52.4%)	40 (47.6%)	
	Always Exposed	157 (54.1%)	133 (45.9%)	
	Never Exposed	21 (44.7%)	26 (55.3%)	
Renal toxic HAART, Exposure summary	Switched off	7 (70.0%)	3 (30.0%)	0.01
	Switched on	36 (58.1%)	26 (41.9%)	
	Always Exposed	40 (70.2%)	17 (29.8%)	
	Never Exposed	146 (48.8%)	153 (51.2%)	
Renal toxic HAART/IDV, Exposure summary	Switched off	15 (75.0%)	5 (25.0%)	0.27
	Switched on	12 (54.5%)	10 (45.5%)	
	Always Exposed	15 (53.6%)	13 (46.4%)	
	Never Exposed	187 (52.2%)	171 (47.8%)	
Renal toxic HAART/TDF, Exposure summary	Switched off	2 (100.0%)	0 (0.0%)	<.001
	Switched on	35 (64.8%)	19 (35.2%)	
	Always Exposed	20 (87.0%)	3 (13.0%)	
	Never Exposed	172 (49.3%)	177 (50.7%)	
IDV, Exposure summary	Switched off	17 (77.3%)	5 (22.7%)	0.11
	Switched on	9 (45.0%)	11 (55.0%)	
	Always Exposed	18 (58.1%)	13 (41.9%)	
	Never Exposed	185 (52.1%)	170 (47.9%)	
TDF, Exposure summary	Switched off	2 (100.0%)	0 (0.0%)	<.001
	Switched on	36 (64.3%)	20 (35.7%)	
	Always Exposed	20 (87.0%)	3 (13.0%)	
	Never Exposed	171 (49.3%)	176 (50.7%)	

(a) Chi-Square Test

“Switched off” indicates medication exposure before RLE but not after.

“Switched on” indicates medication exposure after RLE but not before.

“Always exposed” indicates medication exposure both prior to and after RLE.

“Never exposed” indicates no medication exposure prior to end of followup or RLE resolution.

Exposure status considered until resolution, in cases where RLE resolved, or end of follow-up,

Table 3

The association between personal and HIV disease characteristics and medication exposure with time to resolution of renal laboratory events.(RLE)[†]

Parameter	Unadjusted Results[1]		Adjusted Results[2]	
	Hazard Ratio (95% CI)	P-value	Hazard Ratio (95% CI)	P-Value
Core models: Personal characteristics and HIV disease markers				
Male	0.96 (0.7,1.3)	0.78	--	
Age, at RLE	1.01 (1.0,1.1)	0.51	--	
Race, Black	0.82 (0.6,1.1)	0.15	0.80 (0.6,1.1)	0.15
Ethnicity, Hispanic	1.18 (0.9,1.6)	0.26	--	
CDC Stage C	0.73 (0.5,1.0)	0.08	0.72 (0.5,1.1)	0.09
HIV RNA copies (Log10) at RLE	0.74 (0.6,0.9)	<.001 *	--	
CD4 % at RLE	1.02 (1.0,1.0)	<.001 *	--	
HIV RNA copies > 100,000 at RLE	0.30 (0.1,0.7)	0.004 *	--	
CD4 % < 25 at RLE	0.63 (0.5,0.8)	0.002 *	--	
CD4 % (time-varying)	1.01 (1.0,1.0)	0.03 *	--	
CD4 % < 25 (time-varying)	0.71 (0.5,1.0)	0.03 *	0.75 (0.6,1.0)	0.06
HIV RNA copies (Log10)(time-varying)	0.95 (0.8,1.1)	0.48	--	
HIV RNA, copies > 100K (time-varying)	0.83 (0.5,1.3)	0.38	--	
Antiretroviral medication exposures[3]				
Renal toxic HAART (time-varying)	0.89 (0.6,1.3)	0.58	0.94 (0.6,1.4)	0.79
TDF Exposure (time-varying)	0.93 (0.6,1.5)	0.78	1.06 (0.6,1.8)	0.82
IDV Exposure (time-varying)	0.86 (0.5,1.6)	0.63	0.83 (0.5,1.5)	0.53
Renal toxic concomitant meds (time-varying)	0.88 (0.3,2.4)	0.81	1.06 (0.4,2.9)	0.92

[1] Unadjusted analyses include all potential confounders and antiretroviral medications. Each row represents a separate analysis.

[2] Adjusted results include the time varying HIV disease markers and personal characteristics which made it through the core-model building process with $p < 0.20$ to include and $p < 0.15$ to remain.

[3] For adjusted analyses, each row represents a separate analysis of a medication exposure, adjusting for core model covariates.

* $p < 0.05$

[†] This analysis was carried out on the primary derived dataset, formed using medication exposure observations as the framework, adding in CD4 and RNA viral load values.

Table 4

The association between medication exposure and time to abnormal renal lab event (RLE) resolution for three separate analyses, considering time-varying HIV disease markers and HIV disease markers at the first RLE.

Analysis set	Parameter	Unadjusted Results		Adjusted Results[1]	
		Hazard Ratio (95% CI)	P-value	Hazard Ratio (95% CI)	P-Value
Analysis set 1: time varying CD4, RNA[2]	Renal toxic HAART (time-varying)	0.89 (0.6,1.3)	0.58	0.94 (0.6,1.4)	0.79
	TDF Exposure (time-varying)	0.93 (0.6,1.5)	0.78	1.06 (0.6,1.8)	0.82
	IDV Exposure (time-varying)	0.86 (0.5,1.6)	0.63	0.83 (0.5,1.5)	0.53
	Renal toxic concomitant meds (time-varying)	0.88 (0.3,2.4)	0.81	1.06 (0.4,2.9)	0.92
Analysis set 2: CD4, RNA @ RLE[3]	Renal toxic HAART (time-varying)	0.89 (0.6,1.3)	0.58	0.83 (0.5,1.3)	0.42
	TDF Exposure (time-varying)	0.93 (0.6,1.5)	0.78	0.77 (0.5,1.3)	0.35
	IDV Exposure (time-varying)	0.86 (0.5,1.6)	0.63	0.88 (0.4,1.7)	0.71
	Renal toxic concomitant meds (time-varying)	0.88 (0.3,2.4)	0.81	1.34 (0.4,4.3)	0.62
Analysis set 3: CD4 @ RLE[4]	Renal toxic HAART (time-varying)	0.89 (0.6,1.3)	0.58	0.92 (0.6,1.4)	0.68
	TDF Exposure (time-varying)	0.93 (0.6,1.5)	0.78	0.98 (0.6,1.6)	0.94
	IDV Exposure (time-varying)	0.86 (0.5,1.6)	0.63	0.87 (0.5,1.6)	0.64
	Renal toxic concomitant meds (time-varying)	0.88 (0.3,2.4)	0.81	1.04 (0.4,2.8)	0.95

†These analyses were carried out on the primary derived dataset, formed using medication exposure observations as the framework, adding in CD4 and RNA viral load values.

[1]Results adjust for the final core models, which were developed with $p < 0.20$ to include and $p < 0.15$ to remain. Each row represents a separate time to event multivariate regression analysis.

[2]The core model for analysis 1 included Black race, CDC Stage C, CD4% < 25 (time varying)

[3]The core model for analysis 2 included Black race, CDC Stage C, HIV RNA at 1st ARL > 100,000

[4]The core model for analysis 3 included CD4% at 1st ARL< 25

Table 5

The association between personal characteristics and HIV disease markers and time to abnormal renal lab (RLE) resolution for three separate analyses, considering time-varying HIV disease markers and HIV disease markers at the first RLE[†].

Analysis set	Parameter	Unadjusted Results		Adjusted Results	
		Hazard Ratio (95% CI)	P-value	Hazard Ratio (95% CI)	P-Value
Analysis 1:, time varying CD4, RNA	Race, Black	0.82 (0.6,1.1)	0.15	0.80 (0.6,1.1)	0.15
	CDC Stage C	0.73 (0.5,1.0)	0.08	0.72 (0.5,1.1)	0.09
	CD4 pct < 25 (time-varying)	0.71 (0.5,1.0)	0.03 *	0.75 (0.6,1.0)	0.06
Analysis 2: CD4, RNA @ RLE	Race, Black	0.82 (0.6,1.1)	0.15	0.78 (0.6,1.1)	0.13
	CDC Stage C	0.73 (0.5,1.0)	0.08	0.71 (0.5,1.0)	0.08
	HIV RNA copies > 100,000 at RLE	0.30 (0.1,0.7)	0.004 *	0.31 (0.1,0.7)	0.01 *
Analysis 3: CD4 @ RLE	CD4 pct < 25 at RLE	0.63 (0.5,0.8)	0.002 *	0.63 (0.5,0.8)	0.002 *

Note: These results only show core variable models. Core models were built with $p < 0.20$ to include and $p < 0.15$ to retain.

* $p < 0.05$

† These analyses were carried out on the primary derived dataset, formed using medication exposure observations as the framework, adding in CD4 and RNA viral load values.