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Chronic Kidney Disease Associated with Perinatal HIV infection in Children and Adolescents

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Abstract

Background—This study describes the incidence, clinical and demographic characteristics, and spectrum of chronic kidney disease (CKD) in youths with perinatal HIV-1 infection.

Methods—Retrospective analysis between May 1993 and December 2006 of subjects with renal disease followed in the Pediatric AIDS Clinical Trials Group 219/219C multicenter study examining long-term consequences of perinatal HIV infection. Diagnosis confirmation was made utilizing a questionnaire mailed to research sites. Participants with CKD of other etiology than HIV were excluded. Outcome measures were biopsy-diagnosed CKD and, in absence of biopsy, HIV-associated nephropathy (HIVAN) using established clinical criteria.

Results—Questionnaires on 191 of 2,102 participants identified 27 cases of CKD: 14 biopsy-diagnosed and six clinical cases of HIVAN, and seven biopsy-diagnosed cases of immune complex-mediated kidney disease (lupus-like nephritis, three; IgA nephropathy, two; membranous nephropathy, two). Incidence rates for CKD associated with HIV in pre-HAART (1993–1997) and HAART (1998–2002, 2003–2006) eras were 0.43, 2.84 and 2.79 events per 1000 person years, respectively. In multivariable analysis, Black race and viral load > 100,000 copies/ml (rate ratios 3.28 and 5.05, $p = 0.02$) were associated with CKD.

Conclusions—A variety of immune complex-mediated glomerulonephritides and HIVAN occurs in this population. Black race and uncontrolled viral replication are risk factors for CKD associated with HIV.

Keywords

HIVAN; HIV immune complex kidney disease; FSGS; renal; youth; proteinuria; biopsy

INTRODUCTION

Use of highly active antiretroviral therapy (HAART) in the United States (US), Europe, and increasingly worldwide, has contributed to a decline in mortality in HIV-1-infected adults and children (1–5). Now a chronic disease, there is increased attention to the complications associated with HIV infection and its treatment over time (6–8). Renal disorders are among the ten most common noninfectious conditions occurring in perinatally HIV-infected children and adolescents in the HAART era with an incidence rate of 2.6 per 1000 patient years (7). Chronic kidney disease (CKD) associated with HIV may be a primary consequence of HIV infection, a result of antiretroviral therapy (ARV) and other concurrently administered nephrotoxic medications (8), or due to non-HIV related diseases such as hypertension and diabetes (9). HIV-associated nephropathy (HIVAN) is a well-known cause of CKD in this population (10–12). Kimmel et al subsequently described other groups of HIV-1 virus-specific glomerular diseases in adults, which included immune complex glomerulonephritis and the thrombotic microangiopathies (10, 13). Thus a variety of renal syndromes can occur, generally described in the literature as HIV-associated renal disease. In this paper we use the term CKD associated with HIV (CKD-HIV) to refer to intrinsic disorders of the renal parenchyma in the HIV infected children we studied.

Few published studies have provided detailed descriptions of the spectrum of CKD in HIV-infected children and adolescents. Early descriptions of acquired immunodeficiency syndrome associated-renal disease in children noted a slower progression of disease compared to adults, and histological findings which included focal glomerulosclerosis, mesangial proliferative glomerulonephritis, segmental necrotizing glomerulonephritis and minimal change disease (14–17). In the pre-HAART era, the reported prevalence of pediatric HIVAN ranged from 10%–15% in populations with a majority of HIV-infected African American children (12). One study noted a prevalence of 33% of baseline proteinuria in a large cohort of infected children (18). The true incidence of CKD-HIV is not known, as most pediatric centers do not regularly perform biopsies for children with persistent proteinuria (12, 19). A recently published report (20) showed that 22% of a large cohort of HIV-infected children followed in the Pediatric AIDS Clinical Trials Group (PACTG) exhibited at least one persistent renal laboratory abnormality, and described its association with children of older age, Black race and Hispanic ethnicity, use of nephrotoxic antiretroviral drugs (tenofovir and indinavir) and other nephrotoxic antimicrobial agents. This study reports on kidney biopsy findings in the same cohort and describes demographic and clinical risk factors for children with CKD-HIV.

METHODS

Study population and design

PACTG protocol 219 was a large prospective cohort study designed to examine the long-term consequences of perinatal HIV-1 infection and its treatment in children and adolescents. It commenced in May 1993 at 78 clinical sites in the US and Puerto Rico and continued as a revised version (219C) in September 2000, eventually closing in May 31, 2007 as described in previous publications (7, 20). HIV infected and uninfected children

whose mothers participated in PACTG clinical trials, or who themselves participated in such trials, were offered enrollment into PACTG 219. Participation in 219C was extended to all HIV infected children 21 years of age in care at study sites, as well as those previously followed in 219. Institutional Review Board approval was obtained at each site conducting the study. Guardians and/or participants signed informed consent prior to participation in 219/219C.

Screening subjects with renal disease and data collection

Of the 3,451 subjects with perinatal HIV infection who enrolled in PACTG 219/219C between 4 May 1993 and 31 December 2004, 2,102 were followed for at least 30 months with at least three visits during which a urinalysis was performed and serum creatinine measured, (data entered through 3 May 2005). Persistent renal dysfunction required at least three sequential abnormal laboratory values in at least one of the following three measures: random urine protein content on dipstick of trace or greater, increased serum creatinine or reduced estimated glomerular filtration rate, as previously described (20). Data and diagnoses were coded utilizing version 6.0 of MedDRA®, the Medical Dictionary for Regulatory Activities by professional medical coders (21). Using MedDRA®'s preferred terms, clinical events captured within the "renal and urinary disorders" system organ class were classified as a primary renal diagnosis, urinary diagnosis, or hypertension event. Of the 480 participants identified in our previous report (20) that met the above criteria, 191 who had either a primary renal diagnosis, or persistent renal dysfunction that did not subsequently resolve, or that resolved and recurred, were included in the final group of subjects that had clinical sites queried for additional information. For these 191 participants, this was done using a questionnaire mailed to sites that had participated in PACTG 219/219C, through December 2006 (ESM 1). The information solicited ensured consistency of data collection and included specific renal diagnoses, results of further investigations such as random urine protein/creatinine (U P/C) ratios, results of renal ultrasounds, renal scintigraphies and kidney biopsies, if performed. Outcomes, such as progression to dialysis, and/or death were collected. Four authors (MP, CM, KK and JO) reviewed the responses and cases were categorized using the case definitions below, with input from the other authors and two consulting pediatric nephrologists.

Case definitions

Histological diagnosis of kidney disease was based on the interpretation of a kidney biopsy by the site pathologist and cases of CKD-HIV were identified. Biopsies with parenchymal renal disease secondary to other etiologies (such as malignancy) were excluded, as were renal disorders not affecting the renal parenchyma or secondary to other factors such as pyelonephritis and antiretroviral drug therapy. Findings such as hematuria and/or nephrolithiasis and interstitial nephritis secondary to antiretroviral therapy were considered to constitute ARV toxicity. As nephrotic-range proteinuria is indicative of glomerular pathology, a diagnosis of clinical HIVAN was applied when: i) proteinuria was present (described as either nephrotic-range by site physicians, or established by at least one random U P/C ratio ≥ 1.0 g/g); and ii) the participant had either enlarged and echogenic kidneys on renal ultrasound, or documented deterioration of renal function by serial serum creatinine measurements, by renal scintigraphy or by the need for dialysis (12, 22). A similar clinical case definition was shown by Post et al to have a sensitivity and specificity of 87% and 94% respectively in patients with biopsy-confirmed kidney disease (22). A preceding history of hypertension, diabetes mellitus, pregnancy or organ transplant excluded this diagnosis. HIV immune complex kidney disease (HIVICK) was applied when glomerular immune deposits were present on renal biopsy consistent with previous reports (10, 13).

CD4+ T cell measures, HIV viral load, ARV and concomitant medications

Clinical and CD4+ T cell age-specific immunologic categories were based on the CDC's revised classification system for HIV infection in children < 13 years of age (23), with adult guidelines followed for participants ≥ 13 years. Quantitative HIV viral loads (HIV VL) and cumulative HIV viral exposure over an interval of time, computed as area under the curve using a trapezoidal rule with time-averaging (AUC HIV VL) were used (20, 24). Lymphocyte subsets and HIV VL measurements were performed locally in laboratories used by the clinical sites. HAART was defined as an antiretroviral regimen that consisted of three ARVs from two different classes of drugs. Renal-toxic HAART was any HAART regimen that included tenofovir or indinavir. Renal-toxic concomitant medications comprised antibiotics, antifungals, non-ARV antiviral agents and nonsteroidal anti-inflammatory drugs as previously described (20).

Statistical Analysis

Baseline demographic and clinical characteristics of children with CKD-HIV (cases) were compared to those without renal disease using Fisher's Exact Test, Chi-square tests, Wilcoxon rank sum tests, and t-tests as appropriate. Race and ethnicity was classified as Hispanic, non-Hispanic Black or non-Hispanic White (including Asian, Native American and other races), and self-reported. We considered CD4+ T cell % closest to study entry and nadir values prior to entry (allowing for a 90-day window after entry), as well as exposure to ARVs and nephrotoxic concomitant medications. At study entry, we chose the higher of either the entry AUC HIV VL, or the closest HIV VL to entry. For cases, only values prior to event time points were included in the computations. In analyses, we defined "no-HAART" to include participants with no exposure to ARVs as well as exposure to non-HAART ARV regimens.

Incidence rates (IR) for CKD-HIV were computed with exact 95% confidence intervals (CI) by calendar year, grouped into 3 categories: the pre-HAART era (1993–1997) and two HAART eras (1998–2002 and 2003–2006), based on pediatric guidelines described by Brogly et al (25). IRs were expressed as number of cases per 1000 person years. Comparisons were carried out using Poisson regression, with the pre-HAART era as the referent, and also testing for linear trend. IRs were also computed for each explanatory factor and the univariate association with incidence of renal disease was tested using regular and exact Poisson regression. For all univariate and multivariable incidence rate analyses, we censored HIV VL, CD4 T cell % and medication exposure for non-cases at the median time for new cases. Values for clinical cases were censored at the last value prior to the clinical event. To maximize our sample, we included missing as an indicator in analyses of viral load.

For the exact tests, because of the small number of incident cases, we dichotomized classification of Black race and Hispanic ethnicity, any HAART, renal-toxic HAART, and nadir CD4 T cell %. For HIV VL, in addition to the missing indicator level, we dichotomized VL at ≥ 100,000 copies/ml. We incorporated all personal, medication and HIV disease variables with $p < 0.20$ in the exact Poisson regression into a multivariable exact Poisson regression model to test the association with incidence of CKD-HIV. All analyses considered $p < 0.05$ as statistically significant and were performed using SAS version 9.1 and Log Exact version 8.

RESULTS

Of 2,102 HIV-infected children in PACTG 219/219C followed for a median of 72.5 months (range 30–142 months) between 4 May 1993 and 31 December 2004, 191 participants met

the inclusion criteria for further data collection using the questionnaire developed for this purpose. A renal diagnosis was confirmed in 86 (4.1%) subjects with 27 cases of CKD-HIV (1.3% of subjects; 4 prevalent, with an entry diagnosis, and 23 incident; figure shown in ESM 2). There were 1,577 HIV-infected children with no evidence of renal disease, laboratory or otherwise, that served as the comparison group. Non-Hispanic Blacks comprised the largest ethnic group in the cohort (57.6%); the median age at study entry of the cohort was 6.3 years (Table 1). Children without renal disease had a lower median HIV VL at study entry (3.85 versus 4.80 logs, $p = 0.002$) and higher median nadir CD4+ T cell % to study event (18 versus 10.5, $p = 0.005$) compared to those with CKD-HIV. Those without renal disease also had significantly greater survival by the end of the study period (96.9% compared to 70.4%, $p < 0.001$). A kidney biopsy had been performed in 21 children (Table 2), of which three had been performed in the pre-HAART era. HIVAN was the pathologic diagnosis in fourteen subjects, and HIVICK in seven. Only two of fourteen renal biopsies with HIVAN exhibited collapsing glomerulopathy in the setting of focal segmental glomerular sclerosis (FSGS). Of those with HIVICK, three had lupus-like nephritis (one white, one Black and one Hispanic) with no clinical evidence of systemic lupus erythematosus (SLE), two had IgA nephropathy (one Black and one Hispanic) and two had membranous glomerulonephritis (both of Black race), neither with concomitant hepatitis B or C infection.

There was a trend towards increased incidence rates for CKD-HIV in the era of HAART between 1998 to 2002 (2.84 events per 1000 person years, 95% CI 1.59–4.68, $p = 0.07$) and 2003 to 2006 (2.79 events per 1000 person years, 95% CI 1.12–5.76, $p = 0.08$) in comparison to the baseline pre-HAART period from 1993 to 1997 (0.43 events per 1000 person years respectively, 95% CI 0.01–2.38). Exact univariate Poisson regression analysis (complete data shown in ESM 3) identified nadir CD4+ T cell $< 15\%$ ($p = 0.02$) and HIV VL $> 100,000$ copies/ml ($p = 0.002$) as being associated with a higher risk for renal disease, with a trend for renal-toxic HAART, renal-toxic concomitant medications as well as Black race (all with $p = 0.12$). After adjusting for variables with $p < 0.20$, exact multivariable Poisson regression modeling (Table 3) showed that non-Hispanic African Americans, with an incidence rate ratio of 3.28 (95% CI 1.2–11.4, $p = 0.02$) and HIV VL $> 100,000$ copies/ml, rate ratio of 5.05 (95% CI 1.5–15.3, $p = 0.01$) were significant clinical characteristics associated with the development of CKD-HIV.

DISCUSSION

Clinical review of cases of CKD-HIV in children in this series is similar to that described in the adult HIV-infected population by Kimmel et al (10, 13). HIVAN comprised approximately two-thirds, and HIVICK the remaining one-third of biopsy diagnoses.

Subsequent to its first description in adults in 1984 (26), and then in children in 1987 (15–17), HIVAN is now the third leading cause of end stage renal disease (ESRD) in African Americans between the ages of 20 and 64 years (27). It is the commonest kidney disease in HIV-infected adults (27) and children (12). The diagnosis can be established by kidney biopsy with histology demonstrating collapsing glomerular capillary tufts in the setting of FSGS and microcystic tubular changes in adults. Collapsing glomerulopathy (CG) has been described in adults and children without HIV infection, and its presence is not a requirement for the biopsy diagnosis of HIVAN in children (16, 28). In our report only two of the fourteen biopsy diagnoses exhibited this feature, consistent with the observation by Singh et al that CG is uncommon in children (29). It is thought to be a variant of FSGS, as it is characterized by pseudocrescentic capillary collapse and podocyte proliferation, as opposed to the segmental sclerosis and podocytopenia of FSGS (30). Similarly, mesangial glomerulonephritis with accompanying tubular changes without FSGS has also been

reported in children (16, 17). A review on the pathogenesis of HIVICK (31) suggests that circulating immune complexes composed of HIV peptides and antibodies directed against these antigens are either trapped in glomerular cells, or may form there in situ, eliciting an immune response that eventually develops into glomerulonephritis. Lupus nephritis, complicating a clinical diagnosis of SLE and “lupus-like nephritis”, occurring in the absence of serologic and clinical evidence of SLE, along with IgA nephropathy and membranous glomerulonephritis, have all also been reported with HIV infection in adults and children (17, 32–38). The proportion of adult biopsies with a diagnosis of HIVICK ranged from 21% in a series from South Africa (39) to 55% in another from Italy (38). In two pediatric biopsy series, one in Cape Town and the second in Johannesburg, the proportion with histology consistent with HIVICK was 7 and 51% respectively (11), compared to 33% in our series. Use of kidney biopsy illustrates the different histopathologic manifestations of immune complex mediated CKD complicating HIV infection. While some series have described these various entities separately (39), recent reports (13, 31, 38) have grouped them together under the umbrella of HIVICK, as was done in this study.

It now appears that HIV productively infects renal tubular and glomerular cells in vivo (28, 40, 41). There are several studies, predominantly in adults, showing that virologic and immunologic factors are predictors of HIVAN, and are associated with poorer outcome in HIVICK (42, 43). Our data show that increased viral burden is associated with increased incidence of CKD-HIV in children and adolescents, and a contributing factor in both HIVAN and the immune-complex manifestations of glomerular renal disease. Lifetime nadir CD4 T cells < 15%, a marker for the development of complications with HIV infection, was associated with CKD-HIV disease by univariate, but not multivariable analysis, possibly due to the small number of cases in this study.

African Americans suffer from higher rates of kidney disease than European Americans and the increased risk for HIVAN in this population is well documented in the adult literature. We observed an increased risk for CKD-HIV in children of Black race in this pediatric cohort as well. Genetic variation at a locus in the *MYH9* gene on chromosome 22 has been proposed as an explanation for the increased risk for HIVAN, as well as for non HIV-associated FSGS and hypertension-attributed end-stage kidney disease (44, 45). However, Genovese et al and Tzur et al, described two independent sequence variants in the *APOL1* gene on the same chromosome that are even more highly associated with end-stage kidney disease in African Americans than *MYH9* (46, 47). In contrast, HIVICK has been reported more often in White and Asian patients (48).

We found an unexpected temporal trend in the incidence of CKD-HIV, ranging from 0.43 events per 1000 person-years (py) in the referent pre-HAART era (1993–1997) to 2.84 and 2.79 events per 1000 py in two subsequent HAART eras (1998–2002 and 2003–2006, respectively). Because of increased mortality from infectious etiologies and other AIDS-defining conditions in the pre-HAART era, many subjects may not have survived long enough to develop renal disease. In fact, there was only one incident case in this period. Patients in the subsequent HAART eras had access to early ARV regimens with incomplete viral suppression, followed by much better control of their disease as more effective combination ARV regimens became available. In both instances this resulted in improved survival, with more patients being screened for renal disease and undergoing biopsies, and therefore a higher observed incidence of CKD-HIV. Further, the increased mortality in the group of children with CKD-HIV compared to those without (29.6% versus 3.1%, $p < 0.001$, table 1) is striking. The fact that renal disease was the primary cause in only two of the eight deaths suggests that it serves as a marker for more severe and advanced HIV disease.

There are limitations to this study. Our study was a retrospective analysis of the data collected in PACTG 219/219C. Given the need to increase specificity, a stringent set of criteria was used to define clinical cases of HIVAN. Some of the cases in which a clinical diagnosis of nephropathy did not meet study criteria for clinical HIVAN were not included in the analysis, but may still constitute cases. It is possible that some of them might represent cases of HIVICK that could not be distinguished in the absence of a biopsy. Of 43 children presenting with signs of disease that would prompt consideration of a kidney biopsy, only 21 (approximately 50%) received one. As a consequence, incidence rates of CKD-HIV reported here are likely to be underestimations of the true values. In conclusion, a wide spectrum of CKD is associated with HIV infection in children and adolescents, with Black race and uncontrolled viral replication identified as risk factors. HIVAN is the most common, with different types of immune-complex glomerulonephritis constituting approximately one-third of cases.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline characteristics of children with and without chronic kidney disease associated with HIV, PACTG 219/219C cohort, 1993–2004.

	Total (N = 1604)	Children without renal disease (N = 1577)	Children with renal disease (N = 27)	P-Value
Male gender (N, %)	772 (48.1%)	757 (48.0%)	15 (55.6%)	0.45 <i>(a)</i>
Race/Ethnicity (N, %)				
White (non-Hispanic), Other	253 (15.8%)	252 (16.0%)	1 (3.7%)	0.19 <i>(b)</i>
Black (non-Hispanic)	924 (57.6%)	905 (57.4%)	19 (70.4%)	
Hispanic (any race)	427 (26.6%)	420 (26.6%)	7 (25.9%)	
Median age at study entry, (interquartile range), years	6.26 (3.54, 9.47)	6.23 (3.52, 9.41)	7.83 (4.30, 12.32)	0.07 <i>(c)</i>
0–5.9 (N, %)	762 (47.5%)	752 (47.7%)	10 (37.0%)	0.47 <i>(a)</i>
6–12.9	682 (42.5%)	668 (42.4%)	14 (51.9%)	
13 or more	160 (10.0%)	157 (10.0%)	3 (11.1%)	
Age at event/median time to new case diagnosis **, (median, interquartile range), years	12.84 (10.12, 16.22)	12.83 (10.11, 16.21)	12.88 (10.54, 16.25)	0.73 <i>(c)</i>
0–5.9 (N, %)	66 (4.1%)	63 (4.0%)	3 (11.1%)	0.18 <i>(a)</i>
6–12.9	754 (47.0%)	742 (47.1%)	12 (44.4%)	
13 or more	784 (48.9%)	772 (49.0%)	12 (44.4%)	
Death during study (N, %)	57 (3.6%)	49 (3.1%)	8 (29.6%)	< 0.001 * <i>(a)</i>
Log ₁₀ HIV viral load at study entry [§] , (Median, interquartile range)	3.86 (2.78, 4.68)	3.85 (2.77, 4.66)	4.80 (4.34, 5.38)	0.002 * <i>(c)</i>
HIV viral load at study entry [§] , copies/ml (N, %)				
0 to 400	280 (18.9%)	278 (19.0%)	2 (11.1%)	0.01 * <i>(a)</i>
401 to < 10,000	540 (36.5%)	538 (36.8%)	2 (11.1%)	
10,000 to < 100,000	427 (28.9%)	420 (28.7%)	7 (38.9%)	
100,000 or more	233 (15.7%)	226 (15.5%)	7 (38.9%)	
Missing	124	115	9	
CD4% at study entry [§] , (median, interquartile range)	27 (19, 36)	27 (20, 36)	25.5 (14.5, 31.5)	0.21 <i>(c)</i>
CD4% at study entry, (N, %) ^{†§}				
0–14.9 %	249 (15.6%)	243 (15.4%)	6 (25.0%)	0.45 <i>(a)</i>
15–24.9 %	390 (24.4%)	385 (24.4%)	5 (20.8%)	
25% or more	962 (60.1%)	949 (60.2%)	13 (54.2%)	
CDC class C at study entry	382 (23.8%)	372 (23.6%)	10 (37.0%)	0.11 <i>(a)</i>
Nadir CD4% to event/median time to new case diagnosis **, (median, interquartile range) [†]	18 (10, 26)	18 (10, 26)	10.50 (1.00, 18.50)	0.005 * <i>(c)</i>
Nadir CD4% to event/median time to new case diagnosis **, (N, %) [†]				
0–14.9 %	582 (36.4%)	567 (36.0%)	15 (62.5%)	0.03 * <i>(a)</i>
15–24.9 %	564 (35.2%)	560 (35.5%)	4 (16.7%)	
25% or more	455 (28.4%)	450 (28.5%)	5 (20.8%)	

	Total (N = 1604)	Children without renal disease (N = 1577)	Children with renal disease (N = 27)	P-Value
Nadir CD4% at study entry [‡] (Median, interquartile range)	22 (14, 30)	22 (14, 30)	22.00 (13.00, 27.50)	0.41 ^(c)
Nadir CD4% at study entry [‡] (N, %)				
0–14.9 %	402 (25.3%)	395 (25.2%)	7 (29.2%)	0.90 ^(a)
15–24.9 %	510 (32.1%)	503 (32.1%)	7 (29.2%)	
25% or more	678 (42.6%)	668 (42.7%)	10 (41.7%)	
Missing	14	11	3	

*
p < 0.05;

**
Event refers to a new case of chronic kidney disease associated with HIV during follow-up in study, and the median time for this to occur;

[‡] N = 3 youths with renal disease have missing CD4% data;

[§] Allows values after study entry according to algorithm whereby values within 31 days before, then within 31 days after entry were prioritized. The higher of either the HIV VL or AUV HIV VL was used;

[‡] Allows values within 90 days after study entry;

^(a) Fisher's Exact Test;

^(b) Chi-Square Test;

^(c) Wilcoxon Test.

Table 2

Incident and prevalent cases of chronic kidney disease associated with HIV, PACTG 219/219C Cohort, 1993–2006.

Case #	Sex	Age (yrs)	Ethnicity	Incident	Diagnosis	Biopsy report/clinical criteria	Year of Diagnosis
1	M	1.8	Hispanic	No	HIVAN, biopsy	Sclerotic glomeruli, prominent and hypercellular mesangium and chronic interstitial inflammatory infiltrate	1990
2	M	3.1	Black	Yes	HIVAN, biopsy	Focal segmental glomerulosclerosis with mesangial proliferation and interstitial edema	1994
3	F	15.9	Hispanic	Yes	HIVAN, biopsy	Focal segmental glomerulosclerosis with chronic tubulointerstitial inflammation	1999
4	M	15.1	Black	Yes	HIVAN, biopsy	Mild mesangial glomerulonephritis with slight focal tubular atrophy	1999
5	F	15.2	Black	Yes	HIVAN, biopsy	Collapsing segmental glomerulosclerosis, edematous interstitium with mild lymphocytic infiltrate	2000
6	M	17.1	Black	Yes	HIVAN, biopsy	Focal segmental glomerulosclerosis	2000
7	F	11	Black	Yes	HIVAN, biopsy	Focal segmental glomerulosclerosis with mesangial proliferation and chronic interstitial inflammation	2001
8	M	16.7	Hispanic	No	HIVAN, biopsy	Acute changes consistent with immune mediated glomerulonephritis and chronic tubulointerstitial changes consistent with HIV nephropathy	2001
9	F	10.5	Black	Yes	HIVAN, biopsy	Focal and segmental glomerulosclerosis	2001
10	F	21	Black	Yes	HIVAN, biopsy	Focal glomerulosclerosis, chronic tubulointerstitial injury and arteriolonephrosclerosis	2003
11	M	17.2	Black	Yes	HIVAN, biopsy	Focal segmental glomerulosclerosis, immune complex deposition, chronic tubulointerstitial injury and prominent interstitial nephritis, sickle cell disease	2003
12	M	16.1	Black	Yes	HIVAN, biopsy	Focal segmental glomerulosclerosis, perihilar variant	2004
13	M	11.5	Hispanic	Yes	HIVAN, biopsy	Focal segmental glomerulosclerosis with mesangial hypercellularity and interstitial inflammation	2004
14	M	16.6	Black	Yes	HIVAN, biopsy	Collapsing glomerulopathy with microcystic tubular dilatation consistent with HIV nephropathy	2006
15	M	2	Black	No	HIVICK, biopsy	Membranous glomerulonephritis	1994
16	M	9.9	White	Yes	HIVICK, biopsy	Focal segmental lupus glomerulonephritis	1998
17	F	6.7	Black	Yes	HIVICK, biopsy	Crescentic IgA nephropathy	1998
18	M	10.1	Black	Yes	HIVICK, biopsy	Diffuse proliferative lupus nephritis	1998
19	F	11.7	Black	Yes	HIVICK, biopsy	Membranous glomerulonephritis	2001
20	F	16.9	Hispanic	Yes	HIVICK, biopsy	IgA nephropathy with low grade chronic and active interstitial nephritis	2002
21	F	10.8	Hispanic	Yes	HIVICK, biopsy	Diffuse proliferative lupus nephritis	2004
22	M	12.9	Black	Yes	HIVAN, clinical	Nephrotic syndrome, renal ultrasound revealed enlarged kidneys with mild increased echogenicity	2000
23	M	13.3	Black	Yes	HIVAN, clinical	Nephrotic-range proteinuria with U P/C ratios 6.89 and 21.6 g/g, renal ultrasound revealed echogenic enlarged kidneys	2001
24	F	10.9	Black	No	HIVAN, clinical	Chronic renal failure on hemodialysis, single U P/C ratio of 10.0 g/g. Renal ultrasound noted minimal increased echogenicity	2002
25	F	16.2	Black	Yes	HIVAN, clinical	Persistent proteinuria with U P/C ratios 0.42–1.97 g/g, azotemia and MAG-3 renal scan showing 60% function for left and 50% for right kidney	2002

Case #	Sex	Age (yrs)	Ethnicity	Incident	Diagnosis	Biopsy report/clinical criteria	Year of Diagnosis
26	M	11.7	Black	Yes	HIVAN, clinical	Persistent proteinuria with U P/C ratios 0.24–2.93 g/g, elevated creatinine with renal insufficiency. Renal ultrasound noted as abnormal appearing kidneys	2002
27	F	12.9	Black	Yes	HIVAN, clinical	Chronic renal failure on hemodialysis, U P/C ratios of 1.9 and 12 g/g, renal ultrasound showing enlarged and echogenic kidneys	2003

Table 3

Incidence Rate Ratios for chronic kidney disease associated with HIV from exact multivariate Poisson regression modeling, PACTG 219/219C Cohort, 1993 through 2006.

Characteristic	Contrast	Incidence Rate Ratios (95% CI)	P-value
Race	Black, non-Hispanic (vs. all other)	3.28 (1.16, 11.36)	0.02 [*]
Nadir CD4% [†]	0–14.9% (vs. 15%)	2.0 (0.74, 5.82)	0.20
AUC HIV VL (copies/ml) [†]	100,000 (vs. 0–< 100,000)	5.05 (1.50, 15.32)	0.01 [*]
	Missing (vs. 0–< 100,000)	1.38 (0.38, 4.23)	0.72
Renal-toxic concomitant medication [†]	Yes (vs. no)	1.57 (0.54, 4.21)	0.45
Renal-toxic HAART [†]	Yes (vs. no)	2.2 (0.67, 6.25)	0.20

[†] Prior to event (chronic kidney disease associated with HIV) or median time to new case diagnosis;

^{*} p < 0.05.