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Short Communication: Kidney Dysfunction Among HIV-Infected Children in Latin America and the Caribbean

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Abstract

Renal toxicity is a concern in HIV-infected children receiving antiretrovirals. However, the prevalence [1.7%; 95% confidence interval (CI): 1.0–2.6%] and incidence of kidney dysfunction (0.17 cases/100 person-years; 95% CI: 0.04–0.30) were rare in this multicenter cohort study of 1,032 perinatally HIV-infected Latin American and Caribbean children followed from 2002 to 2011.

Introduction

Combined antiretroviral treatment (cART) for infants during their first year(s) of life provides better clinical, immunological, and virological outcomes when compared to deferred treatment.[1] Consequently children are remaining healthy and living longer. However, certain noninfectious complications, such as kidney diseases, are still common.[2]

The incidence of kidney disease in the HIV-infected pediatric population varies according to the population and endpoint studied. In an earlier cohort study of 2,102 HIV-infected children in the United States (18.2% with HIV RNA < 400 copies/ml), 22% had at least one persistent renal laboratory abnormality during their follow-up; 15% had elevated creatinine and 8% had persistent proteinuria.[3] Persistent renal dysfunction was commonly reported among patients of Hispanic/Latino ethnicity in this study. In another earlier cohort study in Miami, the frequency of proteinuria was 33% among 286 HIV-infected children and 11.2% had nephrotic range proteinuria; the mortality rate was higher among patients with proteinuria.[4] In contrast, the rate of proteinuria was lower in a more recent cohort study of HIV-infected youth in the United States.[5]

Drug-associated nephropathy is also common among HIV-infected children using antiretrovirals, such as tenofovir disoproxil fumarate (TDF) and indinavir. However, the impact of these drugs on HIV-related nephropathy is uncertain, since most studies are underpowered to investigate drug-related adverse events.[3,4] In a study of 448 children, more than 3 years of TDF use was independently associated with proteinuria.[5] Yet, TDF is being widely used, and is considered one of the first line nucleoside reverse transcriptase inhibitors (NRTIs) for use in children globally.[6]

The aim of this study was to examine the prevalence and incidence of kidney dysfunction in a cohort of HIV-infected children from Latin American and Caribbean countries, and to evaluate whether renal function declined over time in this cohort.

Materials and Methods

Data were extracted from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) International Site Development Initiative (NISDI) Pediatric/PLACES (Pediatric Latin American Countries Epidemiologic Study) prospective cohort study.[7] HIV-infected children were systematically followed at 6 month intervals from 2002 to 2011, with medical history (including diagnoses, hospitalizations, medications, and vaccinations), physical examination, laboratory evaluations (including hematology, flow cytometry, and standard biochemical assays), growth parameters, HIV viral load, morbidity evaluation, and mortality status collected. Self-report of antiretroviral adherence was collected only from those subjects enrolled to

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the PLACES protocol, which contributed less than half of the eligible study population. The NISDI protocols were approved by the ethical review board at each clinical site, the institutional review boards at the sponsoring institution (NICHD), and the data management center (Westat), as well as the Brazilian National Ethics Committee (CONEP). Parents/guardians provided written informed consent for participation in the study.

In this protocol, 1,032 perinatally infected children were enrolled; the average length of follow-up was 37 months, with a retention rate of over 90%. At enrollment, the children ranged in age from <1 to 21 years; 55% were female, 70% were from Brazil, and 30% had experienced at least one CDC class C category event. [7]

Patients who did not have serum creatinine measured during study follow-up were excluded from this analysis.

Kidney dysfunction was defined on the basis of an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2, computed using the Schwartz formula.[8] Nephrotoxicity was defined as a Grade 1 or higher creatinine level [creatinine ≥ 1.1 times the upper limit of normal (ULN)], based on the DAIDS toxicity table (http://rsc.tech-res.com/Document/safetyandpharmacovigilance/Table_for_Grading_Severity_of_Adult_Pediatric_Adverse_Events.pdf). For purposes of analysis, the onset of kidney dysfunction or creatinine toxicity was defined by the first occurrence, with the prevalence determined on the basis of the first available eGFR or creatinine measure. Incident cases were defined among nonprevalent cases on the basis of a single measure meeting the outcome definitions; persistence of kidney dysfunction was also examined.

The trend in eGFR measures during study follow-up was examined using a generalized estimating equations (GEE) model.[9] This approach enabled fitting regression models to the eGFR data that account for possible correlations among the repeated measures obtained for study participants, yet does not require that there be equal numbers of eGFR measures obtained for each participant. The trend was modeled as a linear association, as well as a polynomial association (inclusion of quadratic and cubic terms) to allow for a possible curvilinear relationship for the change in eGFR over time. The best fit to the data was determined by the QIC (Quasilikelihood under the Independence model Criterion),[10] analogous to the AIC (Akaike's Information Criterion) statistic used for comparing model fit.

Table 1. Demographic Characteristics of the Study Population

Characteristic at study enrollment	N *(%)*	*Mean (SD)*
Country		
Argentina	71 (6.9)	
Brazil	712 (69.1)	
Mexico	148 (14.4)	
Peru	78 (7.6)	
Jamaica	22 (2.1)	
Age (years)		5.9 (3.7)
Gender		
Female	550 (53.3)	
Male	481 (46.7)	
HIV viral load (copies/ml)		
>400	661 (64.4)	
≤400	365 (35.6)	
CD4 count (cells/mm^3)		
<200	35 (3.4)	
200–499	168 (16.5)	
≥500	815 (80.1)	
CD4 percent		
<15%	88 (9.5)	
15–24%	256 (27.7)	
≥25%	579 (62.7)	
ARV regimen		
No ARVs	206 (20.0)	
NNRTI-containing regimen, no PIs	178 (17.3)	
PI-containing regimen[a]	542 (52.6)	
Other ARV regimen	105 (10.2)	
CDC disease classification		
N	115 (11.2)	
A	245 (23.8)	
B	316 (30.7)	
C	352 (34.2)	
Duration of ARV use (years)		3.5 (2.9)
HIV RNA (log_{10} transformed)		3.5 (1.4)

[a]Of the 542 chlidren receiving combination therapy containing a PI, 265 (48.9%) were receiving a regimen containing lopinavir/ritonavir, seven (1.3%) were receiving indinavir and none atazanavir; two patients received TDF with lopinavir/ritonavir.

SD, standard deviation; ARV, antiretroviral; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; TDF, tenofovir disoproxil fumarate.

Results

The study population consisted of 1,032 perinatally HIV-infected children; one patient did not have any creatinine measurements, leaving 1,031 children for this investigation.

At enrollment, the mean (±standard deviation) age of participants was 5.9 (±3.7) years and 53% were female. Other characteristics of the study population at enrollment are given in Table 1.

During the study, 17 (1.6%) participants died. The primary cause of death and underlying cause/contributing factors were abstracted from medical records for 16 of the subjects who died; renal disease was not indicated as a primary or underlying cause of death for any of them.

There were 17 of 1,028 participants [1.7%; 95% confidence interval (CI): 1.0–2.6%] with prevalent kidney dysfunction; height was not measured at the baseline visit for three participants preventing their eGFR from being calculated. Only one patient persisted with kidney dysfunction at the next available measure. Three of 1,000 participants (only one also had prevalent kidney dysfunction) with laboratory standards available for defining the ULN, required for applying the DAIDS toxicity criteria, presented with prevalent Grade ≥1 nephrotoxicity (0.3%; 95% CI: 0.1–0.9%): two patients presented with Grade 2 toxicity and one with Grade 4. None of these toxicities persisted with the next available creatinine measure.

Excluding subjects with prevalent kidney dysfunction based on eGFR ($n=17$), seven of the remaining 1,011 subjects had incident dysfunction (0.7%; 95% CI: 0.3–1.4%). The incidence of kidney dysfunction was 0.17 cases/100

person-years of follow-up (95% CI: 0.04–0.30). None of the incident cases had an eGFR value below 60 for the next available measure.

Excluding the three cases with prevalent nephrotoxicity, there were only seven Grade ≥ 1 toxicities among the remaining 997 participants (0.7%; 95% CI: 0.3–1.4%): two children had Grade 1 toxicity, four had Grade 3 toxicity, and one had Grade 4 toxicity. There were 0.17 cases/100 person-years of follow-up (95% CI: 0.04–0.30). None of the toxicities persisted with the next available creatinine measure. There was little overlap between those with incident kidney dysfunction and those with incident nephrotoxicity with only one participant having both.

During study follow-up, 7.9% ($n = 81$) of the participants ever used TDF. Of those that did, 70% received it for more than 100 days; the median duration of use was 329 days (maximum = 1,596 days). At least 80% of the participants were reported to be taking the recommended or higher than recommended dose of TDF. Among the participants aged 12 years or older, one of 30 participants was reported to be taking a lower than recommended dose of TDF; among 44 participants younger than 12 years of age at the time of initial TDF, nine (20.5%) were reported to be receiving less than the recommended dose. In seven patients the TDF dosage was not available in the medical record. No participant on TDF developed kidney dysfunction or nephrotoxicity.

Figure 1 reports the trend in eGFR measures over time, including the means of the raw data, as well as model-based estimates. Due to the substantial drop-off in the sample size after 4 years of follow-up, the modeling was restricted to the baseline and first eight 6-month follow-up visits. The raw data and all of the models demonstrate that eGFR increased over time. Among the different models fit to the data, the linear model was judged the preferred model based on the QIC fit statistic. For this model the predicted increase in mean eGFR per 6-month visit was 3.0 ml/min/1.73 m^2 and differed significantly from zero ($p < 0.0001$).

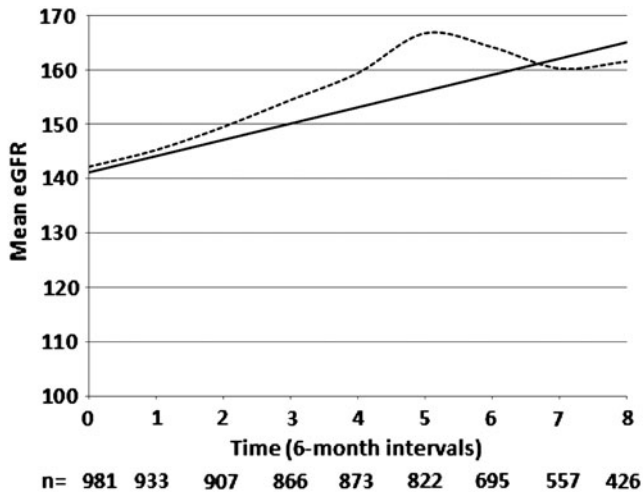

FIG. 1. Trends in mean estimated glomerular filtration rate (eGFR) over time for observed data and linear model-based estimates. – – – –, raw data; ———, linear model.

Discussion

In this prospective cohort study of 1,032 perinatally HIV-infected children, predominantly of Latino ethnicity, the prevalence and cumulative incidence of kidney dysfunction were very low (1.7% and 0.7%, respectively), with almost none persisting over time. These rates are much lower than those seen in two American cohort studies: 15% of elevated creatinine level in one study and 33% of proteinuria in the other.[3,4] However, both of those studies spanned the years before and after cART became available, with higher rates of kidney disease, as expected, with less well controlled HIV disease. In addition, both of these cohorts included older children and a large percentage of African Americans who are at increased risk of kidney dysfunction.

Another important factor associated with nephropathy in HIV-infected children is the specific drug used. Among HIV-infected children, TDF use is important to consider. Although the most commonly reported TDF nephropathy is proximal tubulopathy, consistent with increased renal phosphate and calcium losses, decreasing eGFR has also been cited.[3–5] In our study, where 8% of the children were exposed to TDF, there was no association between TDF use and kidney dysfunction.

In a cohort study of 615 adults, although eGFR improved after cART initiation, it declined in most patients including those with viral suppression, suggesting an effect of cART.[10] In our study, we found that eGFR increased over time, although the majority of children did not have viral suppression.

The main limitation of our study is that proteinuria, phosphaturia, and calciuria measurements were not performed. Therefore, nephrotoxicity, including TDF-related nephrotoxicity, could be underestimated. It is important to consider these measures in deciding on the clinical use and monitoring of this drug. Although we do not have accurate adherence data, at least 50% of the patients on cART had a viral load < 400 copies/ml, consistent with a good compliance.

In conclusion, this study of a large Latin American cohort of perinatally HIV-infected children demonstrated that kidney dysfunction based on eGFR or nephrotoxicity based on creatinine level was rare and was not seen in the 8% of children who were treated with TDF. Further longitudinal follow-up, including screening for albuminuria and/or proteinuria, is necessary to assess whether dysfunction increases as children enter adolescence and young adulthood with increased cumulative exposure to ARVs, particularly those with a potential for nephrotoxicity such as TDF.

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Author Disclosure Statement

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