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Short Communication: Fracture Risk by HIV Infection Status in Perinatally HIV-Exposed Children

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Abstract

The objective of this study was to examine the incidence of fractures in HIV-infected children and comparable HIV-exposed, uninfected (HEU) children in a multicenter, prospective cohort study (PACTG 219/219C) in the United States. The main outcome was first fracture during the risk period. Nine fractures occurred in 7 of 1326 HIV-infected and 2 of 649 HEU children, corresponding to incidence rates of 1.2 per 1000 person-years and 1.1 per 1000 person-years, respectively. The incidence rate ratio was 1.1 (95% CI 0.2, 5.5). There was no evidence of a substantially increased risk of fracture in HIV-infected compared to HEU children.

Introduction

Effective therapies have transformed HIV infection in children from a progressive, fatal illness into a chronic disease.[1–3] Most perinatally infected children in the United States are in adolescence and are expected to survive into adulthood and even old age. However, long-term survival in the face of chronic HIV infection, lifelong antiretroviral therapy (ART), and a persistent inflammatory state may also be accompanied by the development of new complications, including cardiovascular, neurocognitive, renal, and bone disease.[4]

Low bone mineral density (BMD) occurs at higher than expected rates in HIV-infected children and adults.[5–7] In addition to general risk factors for low BMD (low body mass, increasing age, menopause, smoking, alcohol use, corticosteroid use, low calcium intake, vitamin D deficiency, limited physical activity), HIV infection and its treatment may contribute to low BMD.[8–11] Specific drug classes or agents, such as protease inhibitors (PIs), stavudine and tenofovir disoproxil fumarate (TDF), have been implicated in some, but not all studies.[5,6,8,10–14] There has been much interest in understanding whether HIV infection confers not only an increased risk of low BMD but also an increased risk of fracture. In the SMART (Strategies for Management of Antiretroviral Therapy) study, HIV-infected adults assigned to continuous ART had a higher incidence of serious fractures than adults assigned to intermittent ART.[15] Increased risk of fractures attributable to HIV infection was also demonstrated in a population-based study.[16] In a study of mostly premenopausal women, on the other hand, there was no significantly increased risk in fracture attributable to HIV infection.[17] Similar data are not available for HIV-infected children and youth.

Since children, in general, are at lower risk of fracture than older adults, have bones that are still accruing mineral mass, and represent a group for whom the risk of fracture associated with low BMD is less well established, it is critical to assess the potential contribution of HIV infection to fracture risk in children directly. The current study aims to characterize the fracture rate in a prospective cohort study of HIV-infected and HIV-exposed but uninfected (HEU) children.

Materials and Methods

Study population

The Pediatric AIDS Clinical Trials Group (PACTG) 219 and 219C studies of Pediatric Late Outcomes enrolled HIV-infected and HEU children. The original 219 study began enrollment in 1993; the 219C study enrolled children between 2000 and 2006 from clinics across the United States. The study closed to follow-up in 2007. Demographic and clinical data were collected prospectively using standardized clinical report forms (CRFs); fracture events were not specifically ascertained but were reported through a standardized CRF for reporting diagnoses. Children were followed until (1) age 24, (2) study closure in May 2007, (3) withdrawal or lost-to follow-up, or (4) death. Study details have been described elsewhere.[3]

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Outcome

The outcome in this analysis is the first fracture event within the risk period (defined below). If a child had multiple fractures, only the first one was counted. Traumatic and atraumatic fractures (excluding skull fracture) were included, because bone fragility may contribute to both fracture types.[18]

Analytic dataset

Our main goal in these analyses was to examine incidence rates of fractures in HIV-infected and HEU children of comparable age. As HIV-infected children were much older than HEU at 219/219C study entry, we excluded visits when a child in either group was less than 5 years of age. We also excluded children who entered 219/219C after age 10 years. We limited follow-up until a maximum of 20 years of age. The final dataset included 1326 HIV-infected and 649 HEU children.

Analysis

Baseline is defined as the beginning of the risk period, the first visit in the analytic database. Baseline characteristics by HIV status are described by mean (SD) and range for continuous variables and by frequency and percentage for categorical variables. We described demographic and clinical characteristics of the children with fractures. The calendar year and age were at the time of fracture. Antiretroviral therapy, CD4% and viral load, as well as height, weight, and BMI *z*-scores were obtained at the time of fracture or at the study visit immediately preceding the fracture. Follow-up time in the cases was time (years) until the first episode of fracture during the risk period. Follow-up time (years) in the noncases was until age 20 years, loss-to-follow-up/withdrawal from 219/219C, or death. The incidence of fractures (incidence density) was calculated as the number of fracture cases divided by the person-years of follow-up for the HIV-infected and HEU children, separately. The incidence rate ratio is the incidence among the HIV-infected children divided by the incidence in the HEU children. The 95% confidence intervals (95% CI) around the rate ratio were computed by the method of Rosner.[19] In addition, we calculated the minimum detectable rate ratio based on person-years of follow-up in each group and fracture events in the HEU children, assuming an alpha of 0.05 and 80% power.

SAS version 9.13 was used for all analyses.

Results

In total, there were 1326 HIV-infected children and 649 HEU children in the analytic dataset. The median follow-up time was 4.97 years for the HIV-infected children and 2.26 years for HEU children. HIV-infected children, compared to HEU children, were older, were more likely black and non-Hispanic, and had significantly smaller height, weight, and BMI *z*-scores at baseline (Table 1). At baseline, HIV-infected children more often received PIs (70.6%) than nonnucleoside reverse transcriptase inhibitors (NNRTIs) (34.6%); most commonly used nucleoside reverse transcriptase inhibitors (NRTIs) were stavudine (59.7%), lamivudine (48.8%), zidovudine (24.5%), and abacavir (9.2%).

There were nine fractures that occurred in seven HIV-infected children and two HEU children. The total follow-up time was 5640 person-years in HIV-infected children and 1845 person-years in HEU children. The incidence rates were 1.2 per 1000 person-years and 1.1 per 1000 person-years for HIV-infected and HEU children, respectively. The incidence rate ratio was 1.1 (95% CI 0.2, 5.5). Based on prior calculations we had 83% power to detect an incidence rate ratio of 8.0 in HIV-infected compared to HEU children.

Characteristics of the HIV-infected and HEU children around the time of the fracture are shown in Table 2. Both HEU children but only three (43%) HIV-infected children with fractures were girls, despite similar (51% for both) proportions of overall HEU and HIV-infected children being girls. Fractures occurred in the lower extremity in all but one (6/7) of the HIV-infected children and one of the two HEU children. The majority of HIV-infected children with fractures were taking a PI (4/7) and/or stavudine (5/7), but none was taking TDF. No children were on steroids or depot medroxyprogesterone at the time of the fracture.

Table 1. Baseline Demographics for All Children by HIV Status

Category	*HIV$^+$ children (N = 1326)*	*HEU children (N = 649)*	p *value*
Mean age (min, max) (years)	7.1 (5.0, 10.0)	5.8 (5.0, 10.0)	<0.001
Sex			0.97
Female	679 (51%)	333 (51%)	
Male	647 (49%)	316 (49%)	
Race/ethnicity			<0.001
White non-Hispanic	152 (11%)	71 (11%)	
Black non-Hispanic	824 (62%)	341 (53%)	
Hispanic (regardless of race)	324 (24%)	226 (35%)	
Other	26 (2%)	11 (2%)	
Mean height *z*-score (min, max)	−0.40 (−5.45, 3.28)	0.32 (−2.70, 4.38)	<0.001
Mean weight *z*-score (min, max)	−0.03 (−4.75, 3.48)	0.63 (−2.60, 4.41)	<0.001
Mean BMI *z*-score (min, max)	0.34 (−3.86, 3.06)	0.69 (−8.82, 5.16)	<0.001
Steroid use			0.47
Ever	21 (2.0%)	7 (1%)	
Never	1305 (98%)	642 (99%)	

Baseline is defined as the first visit of the risk period. HEU, HIV exposed but uninfected.

Table 2. Characteristics of the HIV-Infected and HIV-Exposed But Uninfected Children at or Near the Time of Fracture

HIV status	*Fracture location*	*Year of fracture*	*Sex*	*Age at fracture (years)*	*HTZ*	*WTZ*	*BMI z*	*Any NRTI*	*TDF*	*d4T*	*Any PI*	*CD4%*	*VL (copies/ml)*
Infected	Femoral condyle	2001	M	6.1	−2.4	1.0	2.7	Yes	No	Yes	Yes	31	37,111
Infected	Leg	2003	F	7.1	1.1	2.1	2.0	Yes	No	No	Yes	32	212
Infected	Tibia	2006	M	5.9	−1.2	−0.8	0.1	Yes	No	Yes	Yes	21	42,100
Infected	Ankle	2006	M	11.6	1.2	1.6	1.5	Yes	No	Yes	No	33	75
Infected	Femur	2002	F	8.6	0.7	2.7	2.6	No	No	No	No	20	5,080
Infected	Ankle	2006	M	12.3	−0.7	−0.4	0.1	Yes	No	Yes	Yes	28	8,630
Infected	Wrist	2006	F	9.9	−1.5	−1.5	−0.8	Yes	No	Yes	No	35	1,480
HEU	Humerus	2006	F	6.2	2.6	2.3	1.6	—	—	—	—	—	—
HEU	Leg	2005	F	9.9	0.3	0.0	0.0	—	—	—	—	—	—

HEU, HIV exposed but uninfected. Fracture location, year of fracture, sex, and age were at the time of fracture. Height *z* (HTZ), weight *z* (WTZ), and BMI *z* reflect values obtained at the time of fracture or at the last 219/219C visit before the fracture. Exception is for HEU subject with 2005 leg fracture for whom values from the first 219/219C visit after the fracture were used, since values at the prefracture visit were missing. Antiretroviral therapy, CD4%, and viral load were at the visit prior to the fracture. NRTI, nucleoside analogue reverse transcriptase inhibitor; TDF, tenofovir disoproxil fumarate; D4T, stavudine; PI, protease inhibitor; CD4%, last $CD4^+$ T-lymphocyte percentage; VL, viral load (copies/ml); M, male; F, female.

Discussion

We evaluated the risk of fracture in HIV-infected and HEU school-aged children who were enrolled in the prospective cohort study, PACTG219/219C. The reported rates of fracture were very low in both groups and there was no evidence of a substantially increased risk of fracture in HIV-infected children compared to HEU children. In addition, there were no large differences in fracture risk by traditional bone fragility risk factors, such as low BMI or steroid use, in both cohorts combined or within the HIV^+ group only. Due to the small numbers of cases, it is difficult to interpret the observation that the majority of fractures in HIV-infected, but not HEU children, occurred in boys. However, evidence from previous studies suggesting greater risk of lower bone mineral density in HIV-infected boys than girls[11] highlights the importance of exploring the effect of sex on bone outcomes in future studies. We acknowledge that this study was underpowered to detect small differences in fracture risk by HIV status or by other known risk factors. In addition, the rate of fractures may be an underestimate of the true rate of fractures in HIV-infected and HEU children because this was not a primary outcome of the 219/219C study.

Large studies of HIV-infected children and comparable controls that include active ascertainment of fracture through childhood and adolescence are sorely needed to address the concern that HIV-infected children may experience premature and high rates of bone mineral loss and fracture as they age into adulthood.

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Author Disclosure Statement

No competing financial interests exist.

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