HHS Public Access

Author manuscript

Bone. Author manuscript; available in PMC 2021 October 01.

Published in final edited form as:

Bone. 2020 October ; 139: 115515. doi:10.1016/j.bone.2020.115515.

Fractures in Children and Adolescents Living with Perinatally Acquired HIV

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Conflict of interest:
Denise L. Jacobson, No conflict;
Wendy Yu, No conflict;
Rohan Hazra, No conflict;
Sean Brummel, No conflict;
Mitchell E. Geffner, No conflict;
Kunjal Patel, No conflict;
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Abstract

Background: Across numerous settings, bone mineral density for age and sex is lower in children/adolescents living with perinatally-acquired HIV (PHIV) compared to uninfected peers. We assessed incidences of any fracture/any long bone fracture, and osteoporosis prevalence in PHIV and HIV-exposed uninfected (PHEU) participants in the Pediatric HIV/AIDS Cohort Study (PHACS).

Methodology: Lifetime history of fracture events from birth up to age 20 years was obtained by chart review and/or interview, including age at fracture, mechanism, and bone(s) fractured. Poisson regression models were fit comparing fracture incidence by HIV status adjusted for age, sex, and race, with effect modification by age (<6, ≥6 yr).

Results: PHIV (N=412) were older (median 17.5 vs 16.7 yr) and more frequently reported black race (72% vs 61%) than PHEU children/adolescents (N=206). 17% of PHIV and 12% of PHEU ever reported a fracture. Among children <6 yr, the adjusted incidence rate ratio of ≥1 fracture was higher (7.23; 95% CI 0.98, 53.51) in PHIV than PHEU, but similar among children/adolescents ≥6 years (1.20; 95% CI: 0.77, 1.87). Results were similar for long bone fracture. The most common fracture mechanisms were falling to the ground from a standing height (23.6% PHIV vs 8.8% PHEU) and sports injuries (21.3% vs 32.4%), and the most commonly fractured sites were the forearm and small bones of the wrist/hands. None of the children had osteoporosis.

Conclusions: Among children/adolescents ≥6 yr of age, fractures were similar by perinatal HIV status. Prospective, targeted collection of fracture history will be necessary to determine rates of fracture as PHIV and PHEU age into adulthood.

Summary:

Lifetime fracture history was collected in children/adolescents living with perinatally-acquired HIV (PHIV) and HIV-exposed uninfected (PHEU) children from birth up to age 20 years. Fracture incidence was higher in PHIV compared to PHEU among children <6 years old, but not among older children/adolescents.

Keywords

HIV; children; fracture; tenofovir; perinatal infection

Introduction

Low bone mineral density (BMD) is a frequent complication of HIV disease. In adults living with HIV, the odds of osteoporosis is over three times greater than in uninfected peers; this risk is highest in persons treated with antiretroviral therapy [1]. Globally, children/adolescents living with perinatally-acquired HIV (PHIV) often have lower BMD for age and sex compared to HIV-uninfected peers [2-7], although differences are attenuated after adjusting for height, a surrogate for bone size, as PHIV children often have growth delays [2].

The etiology of low BMD in persons with HIV is multifactorial. In adults, BMD decreases during the first year after antiretroviral therapy (ART) initiation with greater decreases in women than men and with tenofovir disoproxil fumarate (TDF) use compared to other HIV medications [8-10]. Other factors associated with low BMD include low body weight [11], pro-inflammatory state [12], circulating HIV viral proteins [13], and low 25-hydroxy vitamin D [14].

Fracture rates are higher in adults living with HIV than in the general population [15-18] and may differ by type of antiretroviral (ARV) exposure [18-20]. There are few studies evaluating fracture incidence in PHIV children/adolescents [21, 22]. These children have long-term exposures to HIV, ART, and inflammation during critical periods of bone development. In one study of adolescents and young adults living with HIV, fracture rates increased over time in those who were PHIV [22]. In another report, PHIV had similar rates of fracture between the age of 5 and 20 years as perinatally HIV-exposed uninfected (PHEU) children/adolescents [21]. The latter study relied on passive clinical event collection, possibly resulting in underreporting of fracture events in both groups.

To obtain more complete retrospective and prospective fracture data, we developed a questionnaire to collect fracture events from interviews and clinical records of PHIV and PHEU children/adolescents in the longitudinal Pediatric HIV/AIDS Cohort Study (PHACS). The objectives were to compare lifetime fracture rates by HIV status and evaluate the association of ARV use with fractures in PHIV children/adolescents.

Methods

Study Population

The PHACS Adolescent Master Protocol (AMP) is an ongoing prospective cohort study that enrolled 451 PHIV and 227 PHEU children/adolescents aged 7 to <16 yr of age across 15 U.S. sites, including Puerto Rico, between 2007 and 2009 [23]. Institutional review boards (IRB) at each site and at the Harvard T.H. Chan School of Public Health approved the protocol. Informed consent was obtained from each child/adolescent's parent or legal guardian. Assent was obtained from child/adolescent participants per local IRB guidelines.

Fracture questionnaire, BMD, and osteoporosis

In 2011, a bone fracture questionnaire was developed to collect medical history about each incident in which one or more fractures had occurred (fracture event) through participant/caregiver interview and/or from medical charts. Data included: age at fracture event, how the fracture occurred (mechanism), fractured site(s), body part(s), specific bone(s), side of the body when relevant, and facility where the fracture was treated. Under mechanism of fracture, fracture sustained when doing "sports" – including soccer, rugby, netball, hockey etc, were classified as sports injuries and fractures sustained by doing other athletic activities – e.g. skiing, snowboarding, skateboarding were classified as recreational activity injuries.

A **long bone fracture** was defined as any fracture described as being in the humerus or arm; radius, ulna, or forearm; femur, thigh bone, or leg; or tibia, fibula, or lower leg. Lifetime history of fractures was requested when the form was initially administered and intercurrent fracture(s) were recorded at each subsequent annual visit.

Total body (TB)-BMD and lumbar spine (LS)-BMD were measured by dual energy x-ray absorptiometry (DXA) and scans were sent to the Body Composition Analysis Center at Tufts University School of Medicine for central analysis and standardization, and TB- and LS-BMD Z-scores for age and sex were calculated as previously described by DiMeglio et al. [2, 14, 24]. Forty-one percent of scans were performed on Hologic scanners (Hologic Inc., Bedford, Massachusetts, USA) and 59% on Lunar scanners (General Electric Healthcare, UK). DXA scans were obtained at the baseline AMP visit in PHIV and PHEU, and two years later in PHIV children/adolescents. PHIV and PHEU DXA data were used only if we had a DXA obtained before or up to a month after the first fracture questionnaire.

Osteoporosis was defined per International Society for Clinical Densitometry guidelines as having either "one or more vertebral compression (crush) fractures in the absence of local disease or high-energy trauma," or "a clinically significant fracture history" and BMDZ ≤ −2.0 [25, 26]. A clinically significant fracture history was defined as one or more of the following: (1) two or more long bone fractures by age 10 yr or (2) three or more long bone fractures at any age up to 19 yr [25, 26].

Sociodemographics, anthropometrics, and clinical history

Sociodemographic information was collected by interview (sex, race, ethnicity). At each annual visit in AMP, Tanner pubertal stage was assessed [27], height and weight were

measured and expressed as Z-scores for age and sex, and diagnosis of attention deficit hyperactivity disorder was collected by self-report or from clinical records [27]. Among PHIV children/adolescents, lifetime history of ARV use and specifically TDF, protease inhibitors (PI) and ritonavir (RTV), and CD4 T-cell counts were obtained by chart review. We did not have lifetime history of height, weight, diet, physical activity.

Renal function data were collected in AMP and during prior participation in Pediatric Aids Clinical Trials Group (PACTG) 219C [28]. An abnormal glomerular filtration rate (GFR) was defined as <60 mL/min per 1.73 m^2 and abnormal urinary protein as trace or greater. To meet criteria for abnormal renal function, a participant had to have three consecutive abnormal values (at three separate visits) on one or more tests.

Outcomes

The primary outcomes were: (1) any fracture event, (2) any long bone fracture event, and (3) prevalence of osteoporosis.

Analysis

The analysis dataset included all participants with at least one fracture questionnaire completed. Characteristics of PHIV and PHEU children/adolescents at their most recent visit were compared using a t-test or Wilcoxon rank sum test for continuous variables and Chi-square or Fisher's exact test for categorical variables. Fracture events were shown graphically for fracture mechanisms and parts of body fractured, and for probability of having a fracture event using the Kaplan-Meier method, by HIV status. Incidence rates were calculated as total number of fracture events until last follow-up visit divided by age (yr) at last follow-up.

We performed Cox proportional hazards regressions to estimate hazard ratios (HR) to compare PHIV to PHEU children/adolescents for first lifetime occurrence of a) any fracture and b) any long bone fracture, unadjusted (HR) and adjusted (aHR) for sex and race (black vs. non-black). Poisson regression models using the robust variance estimator with a time offset to account for overdispersion were fit to estimate incidence rate ratios (IRRs) of a) any fracture or b) any long bone fracture in PHIV compared to PHEU, unadjusted (IRR) and adjusted (aIRR) for age categories, sex, and race. We did not adjust for variables that could be on the causal pathway. After noticing a pattern by age on survival curves, we tested for effect modification of age group by HIV status on fracture rate because fracture mechanisms can differ before and after school age. The time-varying age categories for any fracture were <6 vs ≥6 yr based on population studies [29, 30], and for long bone fracture were <8 vs ≥8 yr because too few children <6 yr had long bone fractures. We retained effect modification terms at $p < 0.10$.

Separate Poisson regression models were fit to assess incidence (95% confidence interval, 95% CI) of first fracture and recurrent (multiple) fractures. When assessing first fracture event, we censored participants at the first fracture event or at the last visit if they did not have a fracture event. In contrast, the recurrent fracture analysis included all data through the last visit.

We evaluated the association of ARV (i.e., TDF, PIs as a class, and then specifically RTV) use with fracture risk among PHIV children/adolescents. We restricted data to the first date of use, which was 2002 onward for TDF and 1996 onward for PIs and RTV. At the participant level, ARV exposure was considered to have begun at the first date of ARV exposure and was carried forward even if ARV was discontinued. For the TDF analyses, children/adolescents with a reported renal abnormality before 2002 were excluded because we were only interested in renal abnormalities during the TDF era, which may have precluded prescribing TDF and thus be confounding. Using the above described method for Poisson regression, we estimated the IRR of a) any fracture event and b) any long bone fracture by history of ARV use when unadjusted and adjusted for time-updated CD4 count (<25%) and/or renal abnormality.

To characterize most common ARV use during follow-up from 2002 onward for TDF and from 1996 onward for RTV and PI, we calculated person-time. For instance, "TDF person-time was defined as the total time after an individual initiated TDF, and "non-TDF person-time" was defined as the time prior to initiating TDF for those who eventually started TDF added to the total person-time for participants who never initiated TDF. We then calculated the percent of person-time within each of the above time periods in which specific ARV agents were used (e.g. PI, nucleotide reverse transcriptase inhibitor (NRTI), and non-NRTI (NNRTI)).

Results

Characteristics of PHIV and PHEU children

Out of 678 AMP participants (451 PHIV, 227 PHEU), 618 (412 PHIV, 206 PHEU) had at least one fracture questionnaire completed between 2011 and 2016 and were included in the analysis (Table 1). The proportion of males and proportion in each Tanner stage were similar by HIV status. PHIV children/adolescents were more likely to be older, black, and non-Hispanic and, on average, have lower mean Z-scores for height, weight, and BMI. There were no differences in other characteristics by HIV status that have been associated with risk of fracture, including smoking and diagnosis of ADHD. Fifty-nine percent of the non-TDF person-time was covered by use of a PI-based regimen without NNRTI. Of this time on PI without NNRTI, 65% included lamivudine (3TC) use, the majority of which included zidovudine (48%) or stavudine (32%). Fifty-two percent of TDF person-time was covered by use of a PI-based regimen without NNRTI. Of this time, 61% included emtricitabine, the majority of which included atazanavir (43%) or lopinavir/ritonavir (30%). During thirty-six percent of the non-RTV person-time, children with PHIV were on an NRTI without PI, and half of the time this regimen incorporated 3TC use. Thirteen percent of RTV person-time was covered by use of an NRTI without another PI, 35% of this time included 3TC use.

Lifetime fracture history and prevalence of osteoporosis

Sixty-nine (17%) PHIV children/adolescents experienced at least one lifetime fracture (60 had one fracture, nine had two fracture events) compared to 25 (12%) PHEU (21 had one fracture, 4 had two fracture events). Thirteen PHIV and 1 PHEU had a fracture <6 years of age. Eighty-nine total fractures were sustained among the 69 PHIV; most were due to falling

from a standing height (21 [23.6%]), followed by sports injuries (19 [21.3%]), falling from 1.5 to 9 feet (10 [11.2%]), or recreational activity injuries (9 [10.1%]) (Figure 1). In comparison, the 34 total fractures among the 25 PHEU were mainly sustained during sporting activities (11 [32.4%]) and, to a lower extent, from falling to the ground from a standing height (3 [8.8%]) (Figure 1).

The forearm and small bones of the wrist/hands were the most commonly fractured sites in both cohorts (Figure 2), and in males and females (not shown). The radius, hand phalanx (finger), and ulna were the most fractured (Supplemental Figure 1). Fractures of the small bones of the ankle/feet occurred in 10.1% of PHIV and 5.9% of PHEU, while lower extremity fractures occurred in 6.7% of PHIV and 14.7% of PHEU children/adolescents (Figure 2). Among PHIV children, 30% of fractures were due to falls from standing level before age 6 yr, while only one PHEU child had a fracture before age 6 yr due to a fall from under 1.5 feet. In both PHIV and PHEU ≥6 yr, fractures were mostly due to sports injuries (25% and 33.3%, respectively), while fractures due to falls from standing at the same level occurred in 22.4% of PHIV and 9.1% of PHEU. Fracture mechanisms by age category and HIV status are shown in Supplemental Figures 2 and 3. Among the two children with a fracture <1 year of age, the one PHIV child had an orbital fracture at 4 months of age and the one PHEU had a fracture from a fall from <1.5 feet very soon after birth (age listed as 0).

A similar percentage of PHIV and PHEU children/adolescents/parents/guardians knew the body part where the fracture was sustained, but could not recall or did not know the specific bone(s) broken (9 [10.1%] vs 3 [8.8%]). Of note, 32.5% of the fractures identified were by chart review only, 22% by interview only, and 45.5% by interview and chart review. Of the 12 with unknown fracture types, 5 were collected by interview only, 1 by chart review only, and 6 by both interview and chart.

None of the children/adolescents had osteoporosis. One PHEU participant had a vertebral fracture due to high-energy trauma, and with a TB-BMDZ of 1.14 and LS-BMDZ of 1.83. One PHIV participant had a clinically significant fracture history (two long bone fractures by age 10 yr), but no DXA scan performed.

Models of fracture risk/incidence by HIV status

The cumulative probability of first fracture across age and by HIV status is shown in Figure 3. The median age at first fracture was 11 yr in both groups (range 0-20 among PHIV, 0-15 among PHEU). The probability of fracture overall was similar by HIV status (log rank test p=0.17), but the plot suggests differences before 6 years of age. The percent of PHIV and PHEU participants with at least one fracture event before age 6 was 20.2% and 2.9%, respectively; one in PHEU listed at age 0 and one in PHIV at 4 mo.

The incidence rate of first fracture from 0 to 20 yr, the oldest age at reported fracture, was 1.05/100 person-yr in PHIV and 0.78/100 person-yr in PHEU children/adolescents. Table 2 shows the HR and RR of fracture from the Cox and Poisson models, respectively, between PHIV and PHEU children/adolescents. The adjusted risk of having at least one fracture of any type was 1.54 times higher (aHR=1.54; 95% CI: 0.97, 2.44) in PHIV children/adolescents than PHEU. The Poisson model results are stratified by age reflecting effect

modification of age by HIV status. Among children <6 yr, the aIRR of ≥1 fracture was 7.23 times higher (aIRR=7.23; 95% CI 0.98, 53.51) in PHIV than PHEU. In contrast, rates were similar by HIV status among children/adolescents ≥6 yr (aIRR=1.20; 95% CI: 0.77, 1.87). Findings were similar when just one fracture event per person was considered.

The long bone fracture incidence rate was 0.65/100 person-yr in PHIV and 0.43/100 person-yr in PHEU. PHIV had a 1.72 times higher aHR of long bone fracture than PHEU children/adolescents. Among those <8 yr, PHIV children/adolescents had a higher aIRR of having at least one long bone fracture (aIRR=7.46; 95% CI: 0.98, 56.78), but no difference between PHIV and PHEU was observed among those ≥8 yr (aIRR=1. 18; 95% CI 0.65, 2.15). We observed similar results when we excluded older children (15+ yr) and assessed different age groups.

Fracture incidence rate by TDF exposure in PHIV children/adolescents

TDF-exposed children were more likely to experience at least one fracture event since 2002 both when unadjusted (IRR=2.10; 95% CI: 1.27, 3.48) and adjusted (aIRR=1.80; 95% CI: 1.05, 3.09) for age (categorized as 0-5, 6-11, 12-14, and 15+ yr), sex, and race (data not shown). Table 3 shows IRRs among PHIV children/adolescents adjusted for CD4% for a) any type of fracture and b) any long bone fracture since 2002 between TDF-exposed and -unexposed. After adjustment for CD4%, results did not change (aIRR=1.75; 95% CI: 1.03, 2.98). Incidence of any long bone fracture did not differ in TDF-exposed versus unexposed. Renal function abnormality (14.2% of HIV cohort) after 2001 and prior to TDF initiation was not a confounder and not included in TDF-related models.

Fracture incidence rate by PI/RTV exposure in PHIV children/adolescents

Fracture rates were similar for those exposed versus not exposed to PIs. However, RTV-exposed children were more likely to experience at least one fracture event since 1996 both when unadjusted (IRR=2.01; 95% CI: 1.29, 3.14) and adjusted (aIRR=1.66; 95% CI: 1.05, 2.60) for age (categorized as 0-5, 6-11, 12-14, and 15+ yr), sex, and race (data not shown). Table 3 shows IRRs among PHIV children/adolescents adjusted for CD4% for a) any type of fracture and b) any long bone fracture since 1996 between RTV-exposed and -unexposed. After adjustment for CD4%, results did not change for incidence of any type of fracture (aIRR=1.62; 95% CI: 1.03, 2.55) and any long bone fracture (aIRR=1.70; 95% CI: 0.94, 3.09).

Discussion

Exposure to HIV, ART, inflammation, and associated growth delays affect bone accrual during critical periods of bone development both prenatally [31] and postnatally [3-5], and may increase fracture risk during childhood and later in life. Herein, we present results from a large fracture study in PHIV and PHEU children/adolescents. We used a comprehensive system to collect fracture events, including fracture mechanisms and bones affected. We observed a slightly higher lifetime risk of fractures in PHIV compared to PHEU children/adolescents overall. When stratified by age, the fracture incidence rate was significantly

higher in PHIV compared to PHEU children/adolescents <6 yr, but not different in those ≥6 yr. Fracture rates were significantly higher in PHIV children/adolescents exposed to TDF.

Our observation of no overall difference in fracture rates between PHIV and PHEU children/adolescents ≥6 yr is reassuring. However, the higher rate observed in children <6 yr is concerning and not well understood. While not known in our subjects, it seems unlikely that differences in *in utero* ARV exposures would entirely explain observed differences between PHIV and PHEU as average birth years were similar, and our PHIV children were born prior to TDF being widely prescribed to pregnant women. The elevated rate in young children could reflect adverse effects of inflammation due to uncontrolled HIV *in utero* or in early life in PHIV. It could also be a consequence of growth delays and poorer weight gain in young PHIV children thereby negatively impacting early bone acquisition [32]. There may be differences in socioeconomic or neighborhood characteristics between these two populations [33]. Finally, the large 95% CI for children <6 yr suggests considerable uncertainty around the estimate and indicates the need to replicate the study in a prospective manner in another cohort of PHIV children. Due to lack of published recent US pediatric fracture incidence data, we do not know how the fracture rate in our PHIV cohort from birth to 20 years of age compares to that in the general US population. In Swedish children, the reported risk of fracture from birth to age 16 years was 42%-64% in boys and 27%-40% in girls [34]. While we report lower percentages than this for both PHIV and PHEU who ever experienced a fracture, we believe that for our cohort reporting incidence rate based on person-time is a better measure than percentage as not all participants reached the age of 20.

Although TDF may have detrimental effects on bone, as noted in children with HIV who were highly ARV-experienced [35], evidence that TDF increases fracture rates in children is still sparse. In a European pharmacovigilance report, the osteoporotic fractures were more prevalent in those exposed to TDF compared to other ARV medications [36]. Observational data showed a higher rate of fractures with TDF exposure and greater rates when TDF was combined with ritonavir-boosted protease inhibitors (PI) compared to TDF or boosted PIs alone [37]. In a clinical trial of adults, fracture rates were similar in those randomized to TDF compared to other regimens over 96 wk of follow-up [9]. A case-control study found no difference in fracture rates by TDF exposure in adults [38]. At the time of analysis, none of the children/adolescents in our cohort were receiving tenofovir alefenamide (TAF) which has less effect on BMD than TDF in adults [39, 40] and adolescents [41]. We observed significantly higher fractures rates in PHIV children/adolescents exposed to TDF and those exposed to RTV. In our cohort, PHIV who ever received RTV had a higher rate of fracture. While RTV-boosted PI is associated with fracture in adults [19], RTV has not been well-studied in relation to fractures in children.

The mechanism of fracture events and bones fractured in our PHIV and PHEU children/adolescents were similar to those reported in other studies [42, 43]. In one large European study in children/adolescents 0-19 yr the most common mechanisms were falling on the same plane, colliding with or being struck by an object, person, or animal, and falling from greater than 0.5 feet, mostly due to sports and play [42]. Fracture mechanism varied by age in the European study, with 50% of fractures due to falls from greater than 0.5 feet in the

first year of life decreasing to 6% of fractures at 17 yr. The most common bones fractured were the distal forearm followed by the clavicle and fingers.

No cases of osteoporosis were observed in our children/adolescents. One PHEU child had a vertebral fracture, but normal BMDZ. The one PHIV child with two long bone fractures before age 10 yr did not have a DXA scan available and could not be classified. These data are reassuring overall as to severity of any potential bone disease in this population of young PHIV children.

In addition to HIV-specific risks, HIV+ children and adults experience the same traditional risk factors for low BMD and fracture as those without HIV, including poor nutrition, chronic inflammation, and low physical activity [44]. One limitation of our study is that we did not have anthropometric measurements, diet, and exercise history throughout childhood, and, therefore, could not adjust for these factors. Another limitation is that 22% of fracture events were self-reported without medical chart confirmation. While fracture data may be affected by recall bias related to the severity and time since the event, we do not expect this bias to differ by HIV status. While PHEU were on average 3 years younger than PHIV at the DXA scan due to differences in age distribution at enrollment in PHACS, the pediatric definition of osteoporosis is based on a low BMD Z-score for age and sex and, therefore, the age difference between cohorts is unlikely to create much bias in our results. Finally, we evaluated the association of ever-receiving TDF on fractures and ever use of RTV on fractures at each age, but the effect of these agents may vary depending on concurrent use of other ARVs.

In conclusion, we report a comprehensive study of fracture events in PHIV and PHEU children/adolescents. While we must wait to determine the impact of HIV and ART on bone health and later rates of fracture in PHIV, our data so far are overall reassuring in that there were no cases of osteoporosis and the fracture rate was low. Mechanisms of fracture were similar to the general population. Studies of determinants of bone health in young adults with PHIV, particularly at the time of peak bone mass are needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments:

We thank the children and families for their participation in PHACS, and the individuals and institutions involved in the conduct of PHACS. The study was supported by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development with co-funding from the National Institute on Drug Abuse, the National Institute of Allergy and Infectious Diseases, the Office of AIDS Research, the National Institute of Mental Health, the National Institute of Neurological Disorders and Stroke, the National Institute on Deafness and Other Communication Disorders, the National Heart Lung and Blood Institute, the National Institute of Dental and Craniofacial Research, and the National Institute on Alcohol Abuse and Alcoholism, through cooperative agreements with the Harvard T.H. Chan School of Public Health (HD052102) (Principal Investigator: George Seage; Project Director: Julie Alperen) and the Tulane University School of Medicine (HD052104) (Principal Investigator: Russell Van Dyke; Co-Principal Investigator: Ellen Chadwick; Project Director: Patrick Davis). Data management services were provided by Frontier Science and Technology Research Foundation (PI: Suzanne Siminski), and regulatory services and logistical support were provided by Westat, Inc (PI: Julie Davidson).

The following institutions, clinical site investigators and staff participated in conducting PHACS AMP and AMP Up in 2016, in alphabetical order: **Ann & Robert H. Lurie Children's Hospital of Chicago**: Ram Yogev, Margaret Ann Sanders, Kathleen Malee, Scott Hunter; **Baylor College of Medicine**: William Shearer, Mary Paul, Norma Cooper, Lynnette Harris; **Bronx Lebanon Hospital Center:** Murli Purswani, Mahboobullah Mirza Baig, Alma Villegas; **Children's Diagnostic & Treatment Center**: Ana Puga, Sandra Navarro, Patricia A. Garvie, James Blood; **Boston Children's Hospital:** Sandra K. Burchett, Nancy Karthas, Betsy Kammerer; **Jacobi Medical Center**: Andrew Wiznia, Marlene Burey, Ray Shaw, Raphaelle Auguste; **Rutgers - New Jersey Medical School:** Arry Dieudonne, Linda Bettica, Juliette Johnson; **St. Christopher's Hospital for Children:** Janet S. Chen, Maria Garcia Bulkley, Latreaca Ivey, Mitzie Grant; **St. Jude Children's Research Hospital**: Katherine Knapp, Kim Allison, Megan Wilkins, Jamie Russell-Bell; **San Juan Hospital/Department of Pediatrics:** Midnela Acevedo-Flores, Heida Rios, Vivian Olivera; **Tulane University School of Medicine**: Margarita Silio, Medea Gabriel, Patricia Sirois; **University of California, San Diego**: Stephen A. Spector, Kim Norris, Sharon Nichols; **University of Colorado Denver Health Sciences Center**: Elizabeth McFarland, Eric Cagwin, Emily Barr, Alisa Katai; **University of Miami:** Gwendolyn Scott, Grace Alvarez, Gabriel Fernandez, Anai Cuadra.

Source of Funding:

This work was supported by the *Eunice Kennedy Shriver* National Institute Of Child Health & Human Development (NICHD) with co-funding from the National Institute of Dental & Craniofacial Research (NIDCR); the National Institute of Allergy and Infectious Diseases (NIAID); the National Institute of Neurological Disorders and Stroke (NINDS); the National Institute on Deafness and Other Communication Disorders (NIDCD); Office of AIDS Research (OAR); the National Institute of Mental Health (NIMH); the National Institute on Drug Abuse (NIDA); and the National Institute on Alcohol Abuse and Alcoholism (NIAAA), through cooperative agreements with the Harvard T.H. Chan School of Public Health [HD052102] and the Tulane University School of Medicine [HD052104].

Note: The conclusions and opinions expressed in this article are those of the authors and do not necessarily reflect those of the National Institutes of Health or U.S. Department of Health and Human Services.

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Highlights

- Children with HIV <6 years of age had higher rates of fracture than HIV-exposed uninfected children; in older children the fracture rates were similar.
- The most common fracture mechanisms in children with HIV and HIV-exposed children were falling to the ground from a standing height and sports injuries. The most often fractured sites were the forearm and small bones of the wrist/hands.
- None of the children with HIV or who were HIV exposed uninfected had osteoporosis.

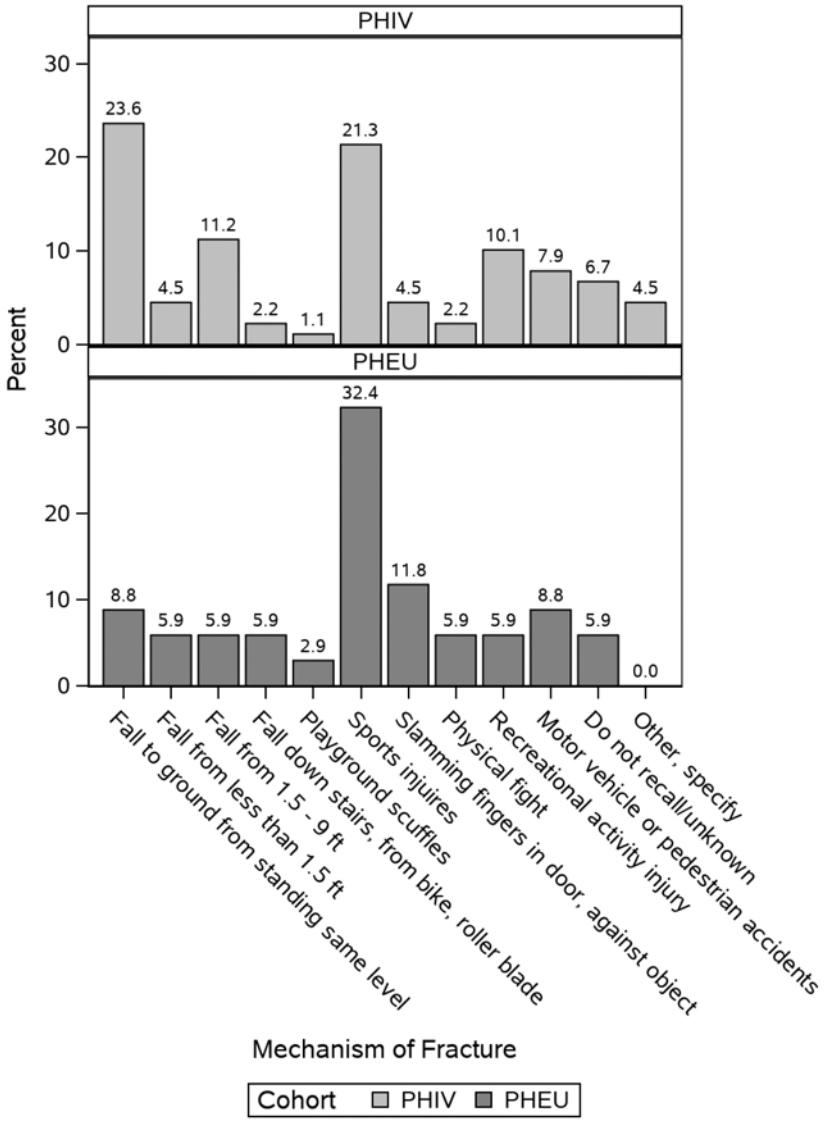


Figure 1: Distribution of Mechanism of Fracture in each Cohort.

Abbreviations: PHIV, children/adolescents living with perinatally acquired HIV; PHEU, perinatally HIV-exposed uninfected. Numbers represent the percentage of all reported fractures sustained through each mechanism.

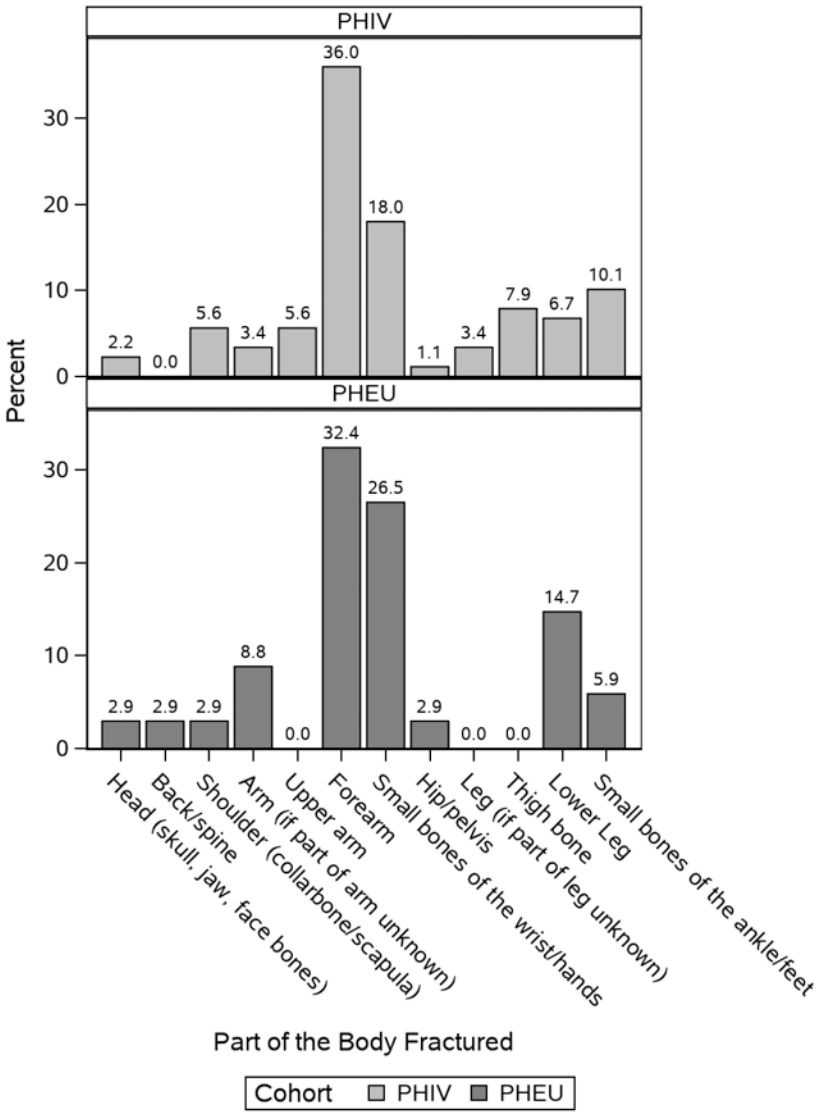
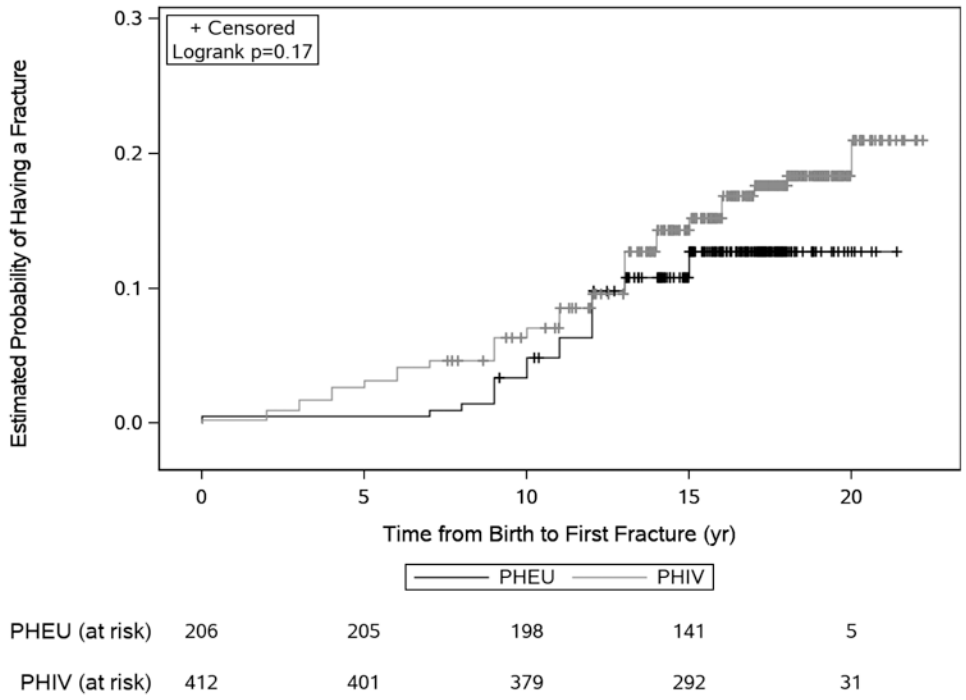


Figure 2: Distribution of Body Part Fractured in each Cohort.

Abbreviations: PHIV, children/adolescents living with perinatally acquired HIV; PHEU, perinatally HIV-exposed uninfected. Numbers represent the percentage of all reported fractures sustained through each mechanism.



PHEU (at risk)	206	205	198	141	5
PHIV (at risk)	412	401	379	292	31

Figure 3: Cumulative Incidence Plot for Estimated Fracture Probability by Age for PHIV and PHEU.

Abbreviations: PHIV, children/adolescents living with perinatally acquired HIV; PHEU, perinatally HIV-exposed uninfected.

Table 1:

Characteristics of PHIV and PHEU children/adolescents at most recent visit with a fracture assessment

Characteristics		Cohort		
		PHIV (N=412)	PHEU (N=206)	P-value
Age (yr) at Visit	Median (Min, Max)	17.5 (7.6, 22.2)	16.7 (9.1, 21.4)	<0.001
	Q1, Q3	16.0, 18.6	15.0, 17.5	
Sex	M	192 (47%)	105 (51%)	0.31
	F	220 (53%)	101 (49%)	
Race	White/Other/Unknown	116 (28%)	80 (39%)	0.007
	Black	296 (72%)	126 (61%)	
Ethnicity	Hispanic or Latino	101 (25%)	75 (36%)	0.001
	Not Hispanic or Latino	311 (75%)	128 (62%)	
	Missing	0 (0%)	3 (1%)	
Region	Northeast	152 (37%)	56 (27%)	<0.001
	Midwest	74 (18%)	22 (11%)	
	Puerto Rico and South	148 (36%)	92 (45%)	
	West	38 (9%)	36 (17%)	
Tanner Stage	Stage 1	5 (1%)	1 (0%)	0.15
	Stage 2	14 (3%)	3 (1%)	
	Stage 3	19 (5%)	7 (3%)	
	Stage 4	48 (12%)	37 (18%)	
	Stage 5	315 (76%)	154 (75%)	
	Missing	11 (3%)	4 (2%)	
Ever reported a fracture	Yes	69 (17%)	25 (12%)	0.13
	No	343 (83%)	181 (88%)	
Number of lifetime fracture	0	343 (83%)	181 (88%)	0.30
Events				
	1	60 (15%)	21 (10%)	
	2	9 (2%)	4 (2%)	
Age (yr) at first fracture	Median (Min, Max)	11 (0, 20)	11 (0, 15)	0.79
	Q1, Q3	7, 14	9, 12	
	N	69	25	
Height Z-scores	Median (Min, Max)	−0.48 (−4.73, 3.20)	−0.09 (−3.62, 2.50)	<0.001
	Mean (s.d.)	−0.50 (1.18)	−0.01 (1.00)	
	Q1, Q3	−1.19, 0.25	−0.69, 0.66	
	# missing	13	1	
Weight Z-scores	Median (Min, Max)	0.14 (−7.41, 3.46)	0.70 (−2.67, 3.52)	<0.001
	Mean (s.d.)	0.09 (1.48)	0.77 (1.33)	
	Q1, Q3	−0.72, 1.12	−0.13, 1.85	
	# missing	13	1	
BMI Z-scores	Median (Min, Max)	0.31 (−5.21, 2.91)	0.76 (−2.80, 2.99)	<0.001
	Mean (s.d.)	0.31 (1.29)	0.74 (1.30)	

Characteristics		Cohort PHIV (N=412)	PHEU (N=206)	P-value
	Q1, Q3	−0.51, 1.21	−0.19, 1.86	
	# missing	13	1	
Total body BMD Z-score[a]	Median (Min, Max)	−0.07 (−3.81, 4.12)	0.02 (−2.98, 4.08)	0.40
	Mean (s.d.)	−0.09 (1.29)	0.00 (1.23)	
	Q1, Q3	−0.89, 0.70	−0.84, 0.78	
	# missing	38	9	
Spine BMD Z-score[a]	Median (Min, Max)	−0.04 (−3.10, 5.30)	0.12 (−2.50, 5.18)	0.17
	Mean (s.d.)	0.05 (1.21)	0.20 (1.28)	
	Q1, Q3	−0.82, 0.77	−0.68, 0.82	
	# missing	34	9	
Low BMD Z-score[a]	Yes	41 (10%)	9 (4%)	0.011
	No	338 (82%)	189 (92%)	
	Unknown	33 (8%)	8 (4%)	
Ever smoked	Yes	143 (35%)	65 (32%)	0.11
	No	222 (54%)	136 (66%)	
	Unknown	47 (11%)	5 (2%)	
Age (yr) at first cigarette use[b]	Median (Min, Max)	13 (3, 19)	13 (4, 20)	0.78
	Q1, Q3	12, 15	11, 15	
Ever diagnosed with ADHD	Yes	111 (27%)	61 (30%)	0.49
	No	301 (73%)	145 (70%)	
Time on cART up to current visit (yr)	Median (Min, Max)	13.2 (0.0, 17.9)	-	
	Q1, Q3	9.2, 15.2	-	
	# missing	0	-	
CD4 T-cell count categories	≥ 500 cells/μl	251 (61%)	-	
	200 - 499 cells/μl	105 (25%)	-	
	< 200 cells/μl	34 (8%)	-	
	Missing	22 (5%)	-	

Abbreviations: PHIV, children/adolescents living with perinatally acquired HIV; PHEU, perinatally HIV-exposed uninfected; ADHD, attention deficit hypersensitivity disorder.cART, combination anti-retroviral therapy; P-values from T-test, Wilcoxon, Fisher's exact, or Chi Square test as appropriate.

[a]DXA scans prior to or up to 1 month after first fracture questionnaire are described. For children at Tanner stage 1-4, bone mineral density (BMD) was adjusted for bone age (BA) and sex. For children at Tanner 5, BMD was adjusted for chronologic age (CA) and sex.

[b]Among those that ever smoked, 5 PHIV and 1 PHEU are missing data on age at first cigarette use.

Table 2:

Summary table of models for fracture events in PHIV compared to PHEU children/adolescents

Model #	Model Type	Follow-up Time	Adjustments	Age (yr) Group[a]	Unadjusted HR or IRR (95% CI) of PHIV vs PHEU	P-value	Wald P-value	Adjusted HR or IRR (95% CI of PHIV vs PHEU	P-value	Wald P-value
Any Type of Fracture										
A1	Cox	Until first event or last visit if no event	Sex and race		HR=1.37 (0.87, 2.17)	0.17		HR=1.54 (0.97, 2.44)	0.068	
A2	Poisson[b]	Until first event or last visit if no event	Sex, race, and interaction between age and HIV status	A,B	<6 IRR=6.64 (0.87, 50.94)	0.068	0.095	IRR=7.48 (0.98, 57.04)	0.052	0.093
					6+ IRR=1.12 (0.69, 1.80)	0.65		IRR=1.25 (0.77, 2.02)	0.37	
A3	Poisson[b]	Recurrent events until last visit	Sex, race, and interaction between age and HIV status	A, B	<6 IRR=6.49 (0.85, 49.72)	0.072	0.083	IRR=7.23 (0.98, 53.51)	0.053	0.081
					6+ IRR=1.07 (0.68, 1.70)	0.76		IRR=1.20 (0.77, 1.87)	0.42	
Any Long Bone Fracture										
B1	Cox	Until first event or last visit if no event	Sex and race		HR=1.52 (0.83, 2.78)	0.17		HR=1.72 (0.93, 3.15)	0.081	
B2	Poisson[c]	Until first event or last visit if no event	Sex, race, and interaction between age and HIV status	C, D	<8 IRR=6.62 (0.88, 49.90)	0.067	0.091	IRR=7.56 (1.01, 56.83)	0.049	0.089
					8+ IRR=1.07 (0.57, 2.01)	0.084		IRR=1.21 (0.65, 2.25)	0.56	
B3	Poisson[c]	Recurrent events until last visit	Sex, race, and interaction between age and HIV status	C, D	<8 IRR=6.51 (0.86, 49.35)	0.070	0.090	IRR=7.46 (0.98, 56.78)	0.052	0.093
					8+ IRR=1.03 (0.55, 1.91)	0.093		IRR=1.18 (0.65, 2.15)	0.58	

Abbreviations: HR, hazard ratio; IRR, incidence rate ratio; CI, confidence interval; PHIV, children/adolescents living with perinatally acquired HIV; PHEU, perinatally HIV-exposed uninfected; TDF, tenofovir disoproxil fumarate.

[a]Different age groups used in models: A: 0-5, 6-11, 12-14, 15+ yr; B: <6, 6+ yr; C: 0-7, 8-11, 12-14, 15+ yr; D: <8, 8+ yr

[b]We assessed the unadjusted interaction between binary age (<6, 6+ yr) and HIV status. To further assess the interaction between binary age and HIV status, we adjusted for age group (0-5, 6-11, 12-14, 15+ yr), sex, and race.

[c]We assessed the unadjusted interaction between binary age (<8, 8+ yr) by HIV status. To further assess the interaction between binary age and HIV status, we adjusted for age group (0-7, 8-11, 12-14, 15+ yr), sex, and race.

Bone. Author manuscript; available in PMC 2021 October 01.

Table 3:

Summary table of Poisson models for fracture events by TDF, PI, and RTV ever use in PHIV children/adolescents

Model #	Parameters	Follow-up Time	Unadjusted IRR (95% CI)	P-value	Adjusted for age[a] IRR (95% CI)	P-value	Adjusted for age[a], sex, and race IRR (95% CI)	P-value
Any Type of Fracture								
A1	CD4% <25 TDF ever use	Until first event or last visit if no event	1.03 (0.56, 1.92)	0.91	1.03 (0.56, 1.91)	0.92	1.10 (0.59, 2.04)	0.77
			2.19 (1.31, 3.68)	0.003	1.95 (1.08, 3.55)	0.028	1.93 (1.06, 3.51)	0.031
A2	CD4% <25 TDF ever use	Recurrent events until last visit	0.99 (0.55, 1.80)	0.98	1.00 (0.55, 1.81)	0.99	1.05 (0.59, 1.88)	0.86
			2.03 (1.24, 3.34)	0.005	1.82 (1.04, 3.18)	0.036	1.75 (1.03, 2.98)	0.039
A3	CD4% <25 PI ever use	Until first event or last visit if no event	1.17 (0.65, 2.08)	0.61	1.15 (0.64, 2.06)	0.65	1.19 (0.67, 2.11)	0.56
			1.55 (0.78, 3.10)	0.21	1.28 (0.61, 2.66)	0.52	1.26 (0.59, 2.67)	0.55
A4	CD4% <25 PI ever use	Recurrent events until last visit	1.13 (0.66, 1.94)	0.65	1.09 (0.64, 1.87)	0.75	1.16 (0.69, 1.96)	0.57
			1.75 (0.89, 3.42)	0.10	1.38 (0.69, 2.78)	0.36	1.34 (0.66, 2.71)	0.41
A5	CD4% <25 RTV ever use	Until first event or last visit if no event	1.13 (0.63, 2.01)	0.68	1.12 (0.63, 2.00)	0.70	1.16 (0.65, 2.06)	0.61
			1.71 (1.06, 2.77)	0.028	1.54 (0.94, 2.51)	0.088	1.57 (0.96, 2.55)	0.071
A6	CD4% <25 RTV ever use	Recurrent events until last visit	1.09 (0.64, 1.86)	0.74	1.06 (0.63, 1.81)	0.82	1.14 (0.68, 1.90)	0.62
			1.89 (1.20, 2.97)	0.006	1.64 (1.04, 2.60)	0.034	1.62 (1.03, 2.55)	0.037
Any Long Bone Fracture								
B1	CD4% <25 TDF ever use	Until first event or last visit if no event	1.53 (0.75, 3.12)	0.25	1.51 (0.74, 3.10)	0.26	1.61 (0.79, 3.27)	0.19
			1.43 (0.73, 2.82)	0.30	1.32 (0.58, 3.01)	0.52	1.26 (0.56, 2.83)	0.58
B2	CD4% <25 TDF ever use	Recurrent events until last visit	1.39 (0.69, 2.80)	0.36	1.39 (0.69, 2.80)	0.36	1.47 (0.74, 2.92)	0.27
			1.41 (0.75, 2.66)	0.29	1.39 (0.65, 2.97)	0.40	1.29 (0.62, 2.66)	0.49
B3	CD4% <25 PI ever use	Until first event or last visit if no event	1.73 (0.91, 3.31)	0.097	1.69 (0.88, 3.24)	0.12	1.77 (0.93, 3.36)	0.083
			1.51 (0.63, 3.57)	0.35	1.27 (0.52, 3.05)	0.60	1.28 (0.52, 3.17)	0.59
B4	CD4% <25 PI ever use	Recurrent events until last visit	1.57 (0.83, 2.95)	0.16	1.54 (0.82, 2.90)	0.18	1.63 (0.88, 3.01)	0.12
			1.52 (0.66, 3.50)	0.32	1.28 (0.55, 3.00)	0.57	1.28 (0.53, 3.08)	0.58
B5	CD4% <25 RTV ever use	Until first event or last visit if no event	1.68 (0.88, 3.20)	0.12	1.65 (0.86, 3.15)	0.13	1.73 (0.91, 3.27)	0.093
			1.81 (0.99, 3.32)	0.053	1.64 (0.88, 3.08)	0.12	1.67 (0.90, 3.10)	0.11
B6	CD4% <25 RTV ever use	Recurrent events until last visit	1.51 (0.81, 2.83)	0.20	1.49 (0.79, 2.80)	0.22	1.59 (0.86, 2.93)	0.14
			1.86 (1.05, 3.29)	0.033	1.71 (0.94, 3.10)	0.079	1.70 (0.94, 3.09)	0.080

Abbreviations: IRR, incidence rate ratios; CI, confidence interval; PHIV, children/adolescents living with perinatally acquired HIV; TDF, tenofovir disoproxil fumarate; PI, protease inhibitor; RTV, ritonavir.

[a] For models assessing any type of fracture, age is categorized as 0-5, 6-11, 12-14, 15+ yr. For models assessing any long bone fracture, age is categorized as 0-7, 8-11, 12-14, 15+ yr.

[b] Models were restricted to data from the first date of ARV use, which was 2002 onward for TDF and 1996 onward for PIs as a class and specifically RTV.