Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

Table 15j. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Osteopenia and Osteoporosis (Last updated April 16, 2019; last reviewed April 16, 2019)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Osteopenia and **Osteoporosis**	Any ART regimen Specific Agents of Concern: • TDF, especially when used in a regimen that includes a boosting agent (i.e., RTV, COBI) • PIs, especially LPV/r	Onset: • Any age; decrease in BMD is usually seen soon after initiation of ART. Presentation: • Usually asymptomatic • Rarely presents as osteoporosis, a clinical diagnosis defined by evidence of bone fragility (e.g., fracture with minimal trauma)	BMD *z* Score Less Than -2.0: • <10% in U.S. cohorts • Approximately 20% to 30% in international cohorts	Longer duration and greater severity of HIV disease Vitamin D insufficiency/ deficiency Delayed growth or pubertal delay Low BMI Lipodystrophy Non-black race Smoking Prolonged systemic corticosteroid use Medroxyprogesterone use Lack of weight-bearing exercise	Prevention: • Ensure that the patient has sufficient intake and levels of both calcium and vitamin D • Encourage weight-bearing exercise. • Minimize modifiable risk factors (e.g., smoking, low BMI, use of steroids or medroxyprogesterone). • Use TAF instead of TDF whenever possible. • Use TDF with EFV or an unboosted INSTI. • When using TDF in a regimen, consider supplementing with vitamin D3 at a daily dose of 1,000–4,000 IU Monitoring: • Assess nutritional intake (calcium, vitamin D, and total calories). • Strongly consider measuring serum 25-OH-vitamin D levels, particulary in patients who are taking ARV drugs of concern.[a] • Obtain a DXA.[b]	Same options as for prevention. Consider changing the ARV regimen (e.g., switching from TDF to TAF, and/or from LPV/r to EFV or an un-boosted INSTI whenever possible). Treat patient with vitamin D3 to raise serum 25-OH-vitamin D concentrations to >30 ng/mL. Vitamin D3 levels should be monitored in patients who are receiving a daily dose of vitamin D3 >4,000 IU. The role of bisphosphonates in managing osteopenia and osteoporosis in children with HIV has not been established.

[a] Some experts periodically measure 25-OH-vitamin D. This is especially important in children and adolescents with HIV who live in urban areas; the prevalence of vitamin D insufficiency is high in that population.

[b] Until more data are available on the long-term effects of TDF on bone mineral acquisition in childhood, DXA scanning is not usually recommended for children who are being treated with TDF. Obtaining a DXA could be considered for adolescent women who are receiving TDF and medroxyprogesterone and for children with indications that are not uniquely related to HIV infection (such as cerebral palsy).

Key to Acronyms: ART = antiretroviral therapy; ARV = antiretroviral; BMD = bone mineral density; BMI = body mass index; COBI = cobicistat; DXA = dual-energy x-ray absorptiometry; EFV = efavirenz; INSTI = integrase strand transfer inhibitor; IU = international unit; LPV/r = lopinavir/ritonavir; PI = protease inhibitor; RTV = ritonavir; TAF= tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

References

1. Arpadi SM, Shiau S, Strehlau R, et al. Efavirenz is associated with higher bone mass in South African children with HIV. *AIDS*. 2016;30(16):2459-2467. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27427876.
2. Aurpibul L, Cressey TR, Sricharoenchai S, et al. Efficacy, safety and pharmacokinetics of tenofovir disoproxil fumarate in virologic-suppressed HIV-infected children using weight-band dosing. *Pediatr Infect Dis J*. 2015;34(4):392-397. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25760566.
3. Bachrach LK, Gordon CM, Section On Endocrinology. Bone densitometry in children and adolescents. *Pediatrics*. 2016;138(4). Available at: https://www.ncbi.nlm.nih.gov/pubmed/27669735.
4. Bunders MJ, Frinking O, Scherpbier HJ, et al. Bone mineral density increases in HIV-infected children treated with long-term combination antiretroviral therapy. *Clin Infect Dis*. 2013;56(4):583-586. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23097583.
5. DiMeglio LA, Wang J, Siberry GK, et al. Bone mineral density in children and adolescents with perinatal HIV infection. *AIDS*. 2013;27(2):211-220. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23032412.
6. Eckard AR, Mora S. Bone health in HIV-infected children and adolescents. *Curr Opin HIV AIDS*. 2016;11(3):294-300. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26890208.
7. Eckard AR, O'Riordan MA, Rosebush JC, et al. Effects of vitamin D supplementation on bone mineral density and bone markers in HIV-infected youth. *J Acquir Immune Defic Syndr*. 2017;76(5):539-546. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28902705.
8. Gafni RI, Hazra R, Reynolds JC, et al. Tenofovir disoproxil fumarate and an optimized background regimen of antiretroviral agents as salvage therapy: impact on bone mineral density in HIV-infected children. *Pediatrics*. 2006;118(3):e711-718. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16923923.
9. Havens PL, Stephensen CB, Van Loan MD, et al. Vitamin D3 supplementation increases spine bone mineral density in adolescents and young adults with human immunodeficiency virus infection being treated with tenofovir disoproxil fumarate: a randomized, placebo-controlled trial. *Clin Infect Dis*. 2018;66(2):220-228. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29020329.
10. Huang JS, Hughes MD, Riddler SA, Haubrich RH, AIDS Clinical Trials Group A5142 Study Team. Bone mineral density effects of randomized regimen and nucleoside reverse transcriptase inhibitor selection from ACTG A5142. *HIV Clin Trials*. 2013;14(5):224-234. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24144899.
11. Jacobson DL, Lindsey JC, Gordon CM, et al. Total body and spinal bone mineral density across Tanner stage in perinatally HIV-infected and uninfected children and youth in PACTG 1045. *AIDS*. 2010;24(5):687-696. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20168204.
12. Jacobson DL, Spiegelman D, Duggan C, et al. Predictors of bone mineral density in human immunodeficiency virus-1 infected children. *J Ped Gastroenterol Nutr*. 2005;41(3):339-346. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16131991.
13. Kalkwarf HJ, Zemel BS, Gilsanz V, et al. The bone mineral density in childhood study: bone mineral content and density according to age, sex, and race. *J Clin Endocrinol Metab*. 2007;92(6):2087-2099. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17311856.
14. Kizito H, Gaur A, Prasitsuebsai W, et al. Changes in renal laboratory parameters and bone mineral density in treatment-naive HIV-1-infected adolescents initiating therapy with INSTI-based single-tablet regimens containing tenofovir alafenamide (TAF) or tenofovir disoproxil fumarate (TDF). Presented at: The 21st International AIDS Conference. 2016. Durban, South Africa.
15. LaFleur J, Bress AP, Myers J, et al. Tenofovir-associated bone adverse outcomes among a U.S. national historical cohort of HIV-infected veterans: risk modification by concomitant antiretrovirals. *Infect Dis Ther*. 2018;7(2):293-308. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29492905.
16. Lima LR, Silva RC, Giuliano Ide C, Sakuno T, Brincas SM, Carvalho AP. Bone mass in children and adolescents infected with human immunodeficiency virus. *J*

Pediatr (Rio J). 2013;89(1):91-99. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23544816.

17. Mills A, Arribas JR, Andrade-Villanueva J, et al. Switching from tenofovir disoproxil fumarate to tenofovir alafenamide in antiretroviral regimens for virologically suppressed adults with HIV-1 infection: a randomised, active-controlled, multicentre, open-label, Phase 3, non-inferiority study. *Lancet Infect Dis*. 2016;16(1):43-52. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26538525.
18. Mirani G, Williams PL, Chernoff M, et al. Changing trends in complications and mortality rates among US youth and young adults with HIV infection in the era of combination antiretroviral therapy. *Clin Infect Dis*. 2015;61(12):1850-1861. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26270680.
19. Okonkwo RI, Weidmann AE, Effa EE. Renal and bone adverse effects of a tenofovir-based regimen in the treatment of HIV-infected children: a systematic review. *Drug Saf*. 2016;39(3):209-218. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26692394.
20. Overton ET, Chan ES, Brown TT, et al. Vitamin D and calcium attenuate bone loss With antiretroviral therapy initiation: a randomized trial. *Ann Intern Med*. 2015;162(12):815-824. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26075752.
21. Palchetti CZ, Szejnfeld VL, de Menezes Succi RC, et al. Impaired bone mineral accrual in prepubertal HIV-infected children: a cohort study. *Braz J Infect Dis*. 2015;19(6):623-630. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26477385.
22. Puthanakit T, Saksawad R, Bunupuradah T, et al. Prevalence and risk factors of low bone mineral density among perinatally HIV-infected Thai adolescents receiving antiretroviral therapy. *J Acquir Immune Defic Syndr*. 2012;61(4):477-483. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22918157.
23. Puthanakit T, Siberry GK. Bone health in children and adolescents with perinatal HIV infection. *J Int AIDS Soc*. 2013;16:18575. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23782476.
24. Puthanakit T, Wittawatmongkol O, Poomlek V, et al. Effect of calcium and vitamin D supplementation on bone mineral accrual among HIV-infected Thai adolescents with low bone mineral density. *J Virus Erad*. 2018;4(1):6-11. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29568546.
25. Ross AC. The 2011 report on dietary reference intakes for calcium and vitamin D. *Public Health Nutr*. 2011;14(5):938-939. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21492489.
26. Siberry GK, Li H, Jacobson D, Pediatric ACTGCS. Fracture risk by HIV infection status in perinatally HIV-exposed children. *AIDS Res Hum Retroviruses*. 2012;28(3):247-250. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22471877.
27. Tebas P, Kumar P, Hicks C, et al. Greater change in bone turnover markers for efavirenz/emtricitabine/tenofovir disoproxil fumarate versus dolutegravir + abacavir/lamivudine in antiretroviral therapy-naive adults over 144 weeks. *AIDS*. 2015;29(18):2459-2464. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26355674.
28. Schall JI, Hediger ML, Zemel BS, Rutstein RM, Stallings VA. Comprehensive safety monitoring of 12-month daily 7000-IU vitamin D3 supplementation in human immunodeficiency virus-infected children and young adults. *JPEN J Parenter Enteral Nutr*. 2016;40(7):1057-1063. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26160254.
29. Dougherty KA, Schall JI, Zemel BS, et al. Safety and efficacy of high-dose daily vitamin D3 supplementation in children and young adults infected with human immunodeficiency virus. *J Pediatric Infect Dis Soc*. 2014;3(4):294-303. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26625449.
30. Pramyothin P, Holick MF. Vitamin D supplementation: guidelines and evidence for subclinical deficiency. *Curr Opin Gastroenterol*. 2012;28(2):139-150. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22274617.