Table 17j. Antiretroviral Therapy–Associated Adverse Effects and Management Recommendations—Osteopenia and Osteoporosis

Updated: September 30, 2025
Reviewed: September 30, 2025

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Osteopenia and Osteoporosis	Any ARV regimen **Specific Agents of Concern** • TDF, especially when used in a regimen that includes a boosting agent (i.e., RTV, COBI) • PIs (LPV, ATV>DRV) • EFV	**Onset** • Any age; decrease in BMD is usually seen soon after initiating ART. **Presentation** • Usually asymptomatic • Rarely presents as osteoporosis, a clinical diagnosis defined by evidence of bone fragility (e.g., a fracture with minimal trauma).	**BMD Z-score Less than −2.0** • <10% in U.S. cohorts • Approximately 10% to 20% in international cohorts	Longer duration and greater severity of HIV disease Detectable viral load Vitamin D insufficiency/deficiency Delayed growth or pubertal delay Low BMI Lipodystrophy 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 RPV or an unboosted INSTI. • When using TDF or EFV in a regimen, consider measuring vitamin D levels and supplementing with vitamin D3 if deficiency is identified. **Monitoring** • Assess nutritional intake (i.e., calcium, vitamin D, and total calories).	Same options as for prevention Consider changing the ARV regimen (e.g., switching from TDF to TAF and/or from LPV/r to RPV or an unboosted INSTI whenever possible). Supplement with vitamin D3 to raise serum 25-OH-vitamin D concentrations to >30 ng/mL. There is no clear benefit to administering daily supplemental vitamin D3 doses that are >4,000 IU. If patients are receiving a daily dose of vitamin D3 that is >4,000 IU, consider monitoring levels of 25-OH-vitamin D.

Table 17j. Antiretroviral Therapy–Associated Adverse Effects and Management Recommendations—Osteopenia and Osteoporosis

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
					• Consider measuring serum 25-OH-vitamin D levels, particularly in patients who are taking ARV drugs of concern.[a] • DXA is rarely indicated.[b]	While an overall effect was not seen in a large trial of vitamin D supplementation in adolescents with HIV, an increase in BMD was seen in those adolescents with vitamin D deficiency. An increase in BMD was seen in one trial that evaluated the use of alendronate in youth with HIV and low BMD. However, the role of bisphosphonates in managing osteopenia and osteoporosis in children with HIV has not been established.

[a] Drugs of greatest concern are TDF and EFV. Some experts measure 25-OH-vitamin D in children with HIV with additional risk factors, including living at high latitudes, sun avoidance, low dietary intake, and obesity.

[b] DXA scanning is not routinely recommended for children and youth who are being treated with TDF. DXA scanning can be considered for children and youth who are receiving additional medications that also affect bone density or have non-HIV-related conditions for which DXA scans may be indicated (e.g., cerebral palsy).

Key: 25-OH-vitamin D = 25-hydroxy vitamin D; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; BMD = bone mineral density; BMI = body mass index; COBI = cobicistat; DRV = darunavir; DXA = dual-energy X-ray absorptiometry; EFV = efavirenz; INSTI = integrase strand transfer inhibitor; IU = international unit; LPV = lopinavir; LPV/r = lopinavir/ritonavir; PI = protease inhibitor; RPV = rilpivirine; 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://pubmed.ncbi.nlm.nih.gov/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: https://pubmed.ncbi.nlm.nih.gov/25760566.

3. Bachrach LK, Gordon CM, Section on Endocrinology. Bone densitometry in children and adolescents. *Pediatrics*. 2016;138(4). Available at: https://pubmed.ncbi.nlm.nih.gov/27669735.

4. Baranek B, Wang S, Cheung AM, Mishra S, Tan DH. The effect of tenofovir disoproxil fumarate on bone mineral density: a systematic review and meta-analysis. *Antivir Ther*. 2020;25(1):21-32. Available at: https://pubmed.ncbi.nlm.nih.gov/32077867.

5. Bi X, Liu F, Zhang X, et al. Vitamin D and calcium supplementation reverses tenofovir-caused bone mineral density loss in people taking ART or PrEP: a systematic review and meta-analysis. *Front Nutr*. 2022;9:749948. Available at: https://pubmed.ncbi.nlm.nih.gov/35433788.

6. Braithwaite K, McPherson TD, Shen Y, et al. Bone outcomes in virally suppressed youth with HIV switching to tenofovir disoproxil fumarate. *South Afr J HIV Med*. 2021;22(1):1243. Available at: https://pubmed.ncbi.nlm.nih.gov/34522425.

7. Burt LA, Billington EO, Rose MS, Raymond DA, Hanley DA, Boyd SK. Effect of high-dose vitamin D supplementation on volumetric bone density and bone strength: a randomized clinical trial. *JAMA*. 2019;322(8):736-745. Available at: https://pubmed.ncbi.nlm.nih.gov/31454046.

8. Dave JA, Cohen K, Micklesfield LK, Maartens G, Levitt NS. Antiretroviral therapy, especially efavirenz, is associated with low bone mineral density in HIV-infected South Africans. *PLoS One*. 2015;10(12):e0144286. Available at: https://pubmed.ncbi.nlm.nih.gov/26633015.

9. Eckard AR, Mora S. Bone health in HIV-infected children and adolescents. *Curr Opin HIV AIDS*. 2016;11(3):294-300. Available at: https://pubmed.ncbi.nlm.nih.gov/26890208.

10. 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://pubmed.ncbi.nlm.nih.gov/28902705.

11. Ferrand R, Dzavakwa L, Kasonka J, Group VT. Randomised placebo-controlled trial of high-dose vitamin D and low-dose calcium supplementation to improve bone density in adolescents with perinatally-acquired HIV in Southern Africa. Presented at: 25th International AIDS Conference; 2024. Munich, Germany. Available at: https://www.natap.org/2024/IAS/IAS_32.htm.

12. Golden NH, Abrams SA, Committee on Nutrition. Optimizing bone health in children and adolescents. *Pediatrics*. 2014;134(4):e1229-1243. Available at: https://pubmed.ncbi.nlm.nih.gov/25266429.

13. Gregson CL, Hartley A, Majonga E, et al. Older age at initiation of antiretroviral therapy predicts low bone mineral density in children with perinatally-infected HIV in Zimbabwe. *Bone*. 2019;125:96-102. Available at: https://pubmed.ncbi.nlm.nih.gov/31082498.

14. Havens PL, Long D, Schuster GU, et al. Tenofovir disoproxil fumarate appears to disrupt the relationship of vitamin D and parathyroid hormone. *Antivir Ther*. 2018;23(7):623-628. Available at: https://pubmed.ncbi.nlm.nih.gov/30260797.

15. 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://pubmed.ncbi.nlm.nih.gov/29020329.

16. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2011;96(7):1911-1930. Available at: https://pubmed.ncbi.nlm.nih.gov/21646368.

17. Jacobson DL, Lindsey JC, Gordon C, et al. Alendronate improves bone mineral density in children and adolescents perinatally infected with human immunodeficiency virus with low bone mineral density for age. *Clin Infect Dis*. 2020;71(5):1281-1288. Available at: https://pubmed.ncbi.nlm.nih.gov/31573608.

18. Jacobson DL, Yu W, Hazra R, et al. Fractures in children and adolescents living with perinatally acquired HIV. *Bone*. 2020;139:115515. Available at: https://pubmed.ncbi.nlm.nih.gov/32619695.

19. LaFleur J, Bress AP, Myers J, et al. Tenofovir-associated bone adverse outcomes among a US national historical cohort of HIV-infected veterans: risk modification by concomitant antiretrovirals. *Infect Dis Ther*. 2018;7(2):293-308. Available at: https://pubmed.ncbi.nlm.nih.gov/29492905.

20. 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: https://pubmed.ncbi.nlm.nih.gov/23544816.

21. Lindsey JC, Jacobson DL, Spiegel HM, Gordon CM, Hazra R, Siberry GK. Safety and efficacy of 48 and 96 weeks of alendronate in children and adolescents with perinatal human immunodeficiency virus infection and low bone mineral density for age. *Clin Infect Dis*. 2021;72(6):1059-1063. Available at: https://pubmed.ncbi.nlm.nih.gov/32584996.

22. Mahtab S, Scott C, Asafu-Agyei NAA, et al. Prevalence and predictors of bone health among perinatally HIV-infected adolescents. *AIDS*. 2020;34(14):2061-2070. Available at: https://pubmed.ncbi.nlm.nih.gov/32910060.

23. McComsey GA, Lupo S, Parks D, et al. Switch from tenofovir disoproxil fumarate combination to dolutegravir with rilpivirine improves parameters of bone health. *AIDS*. 2018;32(4):477-485. Available at: https://pubmed.ncbi.nlm.nih.gov/29239893.

24. 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: https://pubmed.ncbi.nlm.nih.gov/26538525.

25. Negredo E, Langohr K, Bonjoch A, et al. High risk and probability of progression to osteoporosis at 10 years in HIV-infected individuals: the role of PIs. *J Antimicrob Chemother*. 2018;73(9):2452-2459. Available at: https://pubmed.ncbi.nlm.nih.gov/29860519.

26. 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: https://pubmed.ncbi.nlm.nih.gov/26692394.

27. 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: https://pubmed.ncbi.nlm.nih.gov/26075752.

28. 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: https://pubmed.ncbi.nlm.nih.gov/26477385.

29. Penner J, Ferrand RA, Richards C, Ward KA, Burns JE, Gregson CL. The impact of vitamin D supplementation on musculoskeletal health outcomes in children, adolescents, and young adults living with HIV: a systematic review. *PLoS One*. 2018;13(11):e0207022. Available at: https://pubmed.ncbi.nlm.nih.gov/30439968.

30. Pornpaisalsakul K, Songtaweesin WN, Tepmongkol S, et al. Effects of vitamin D and calcium supplementation on bone mineral density among Thai youth using daily HIV pre-exposure prophylaxis. *J Int AIDS Soc*. 2020;23(10):e25624. Available at: https://pubmed.ncbi.nlm.nih.gov/33040465.

31. Ross AC, Manson JE, Abrams SA, et al. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. *J Clin Endocrinol Metab*. 2011;96(1):53-58. Available at: https://pubmed.ncbi.nlm.nih.gov/21118827.

32. Rukuni R, Rehman AM, Mukwasi-Kahari C, et al. Effect of HIV infection on growth and bone density in peripubertal children in the era of antiretroviral therapy: a cross-sectional study in Zimbabwe. *Lancet Child Adolesc Health*. 2021;5(8):569-581. Available at: https://pubmed.ncbi.nlm.nih.gov/34139202.

33. Shen Y, Shiau S, Strehlau R, et al. Persistently lower bone mass and bone turnover among South African children living with well-controlled HIV. *AIDS*. 2021. Available at: https://pubmed.ncbi.nlm.nih.gov/34127577.

34. Starup-Linde J, Rosendahl SB, Storgaard M, Langdahl B. Management of osteoporosis in patients living with HIV-a systematic review and meta-analysis. *J Acquir Immune Defic Syndr*. 2020;83(1):1-8. Available at: https://pubmed.ncbi.nlm.nih.gov/31809356.

35. Sudjaritruk T, Bunupuradah T, Aurpibul L, et al. Impact of vitamin D and calcium supplementation on bone mineral density and bone metabolism among Thai adolescents with perinatally acquired human immunodeficiency virus (HIV) infection: a randomized clinical trial. *Clin Infect Dis*. 2021;73(9):1555-1564. Available at: https://pubmed.ncbi.nlm.nih.gov/34125899.

36. Sudjaritruk T, Bunupuradah T, Aurpibul L, et al. Adverse bone health and abnormal bone turnover among perinatally HIV-infected Asian adolescents with virological suppression. *HIV Med*. 2017;18(4):235-244. Available at: https://pubmed.ncbi.nlm.nih.gov/27477214.

37. 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: https://pubmed.ncbi.nlm.nih.gov/26355674.

38. Torrejon C, Galaz MI, Vizueta E, et al. Evaluation of bone mineral density in children with vertical infection by HIV. *Rev Chilena Infectol*. 2018;35(6):634-641. Available at: https://pubmed.ncbi.nlm.nih.gov/31095183.

39. Van Welzen BJ, Thielen MAJ, Mudrikova T, Arends JE, Hoepelman AIM. Switching tenofovir disoproxil fumarate to tenofovir alafenamide results in a significant decline in parathyroid hormone levels: uncovering the mechanism of tenofovir disoproxil fumarate-related bone loss? *AIDS*. 2019. Available at: https://pubmed.ncbi.nlm.nih.gov/31021851.

40. Wohl DA, Orkin C, Doroana M, et al. Change in vitamin D levels and risk of severe vitamin D deficiency over 48 weeks among HIV-1-infected, treatment-naive adults receiving rilpivirine or efavirenz in a Phase III trial (ECHO). *Antivir Ther*. 2014;19(2):191-200. Available at: https://pubmed.ncbi.nlm.nih.gov/24430534.

41. Zemel BS, Kalkwarf HJ, Gilsanz V, et al. Revised reference curves for bone mineral content and areal bone mineral density according to age and sex for black and non-black children: results of the bone mineral density in childhood study. *J Clin Endocrinol Metab*. 2011;96(10):3160-3169. Available at: https://pubmed.ncbi.nlm.nih.gov/21917867.