Table 15h. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Lipodystrophies and Weight Gain (Last updated April 7, 2021; last reviewed April 7, 2021) (page 1 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Lipodystrophy (Fat Maldistribution) General Information	See below for specific associations.	**Onset:** • Increase in trunk and limb fat are the first sign; peripheral fat wasting may not appear for 12–24 months after ART initiation.	Frequency is low (<5%) with current regimens.	Genetic predisposition Puberty HIV-associated inflammation Older age Longer duration of ART Body habitus	**Prevention:** • Initiate a calorically appropriate low-fat diet and an exercise regimen. **Monitoring:** • BMI measurement • Waist circumference and waist-hip ratio	Physicians should perform a regimen review and consider changing the regimen when lipodystrophy occurs. Improvement in fat maldistribution can vary following a regimen change. Improvement may occur after several months or years, or it may not occur at all.
Central Lipohypertrophy **or** **Lipo-accumulation**	Can occur in the absence of ART, but these conditions are most often associated with the use of PIs and EFV.	**Presentation:** • Central fat accumulation with increased abdominal girth, which may include a dorsocervical fat pad (buffalo hump). Gynecomastia may occur in males or breast hypertrophy may occur in females, particularly with the use of EFV.	Frequency is low (<5%) with current regimens.	Obesity before initiation of therapy Sedentary lifestyle	**Prevention:** • Initiate a calorically appropriate low-fat diet and an exercise regimen. **Monitoring:** • BMI measurement • Waist circumference and waist-hip ratio measurements.	Counsel patient on lifestyle modification and dietary interventions (e.g., maintaining a calorically appropriate diet that is low in saturated fats and simple carbohydrates, and starting an exercise regimen, especially strength training). Recommend smoking cessation (if applicable) to decrease future CVD risk. Consider using an INSTI instead of a PI or EFV, although some INSTIs may be associated with generalized weight gain (see below). **Data are Insufficient to Allow the Panel to Safely Recommend Use of Any of the Following Modalities in Children:** • Recombinant human growth hormone • Growth hormone-releasing hormone • Metformin • Thiazolidinediones • Recombinant human leptin • Anabolic steroids • Liposuction

Table 15h. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Lipodystrophies and Weight Gain (Last updated April 7, 2021; last reviewed April 7, 2021) (page 2 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Facial/Peripheral Lipoatrophy	Most cases are associated with the use of ZDV, a thymidine analogue NRTI.	**Presentation:** • Thinning of subcutaneous fat in the face, buttocks, and extremities, measured as a decrease in trunk/limb fat by DXA or triceps skinfold thickness. Preservation of lean body mass distinguishes lipoatrophy from HIV-associated wasting.	Frequency is low (<5%) with current regimens.	Underweight before ART initiation	**Prevention:** • Limit the use of ZDV. **Monitoring:** • Patient self-report and physical examination are the most sensitive methods of monitoring lipoatrophy.	Replace ZDV with another NRTI when possible. **Data are Insufficient to Allow the Panel to Safely Recommend Use of Any of the Following Modalities in Children:** • Injections of poly-L-lactic acid • Recombinant human leptin • Autologous fat transplantation • Thiazolidinediones
Weight Gain	Significant weight gain may occur with all ARV regimens, but it appears to be more pronounced with DTG, BIC, and TAF.	Gradual weight gain after initiating ARV drugs is common with all currently used regimens. The mechanism for weight gain is unclear and is under investigation.	Rate of development of obesity is unclear.	**In Adults:** • Low pre-treatment BMI • Older age • Female sex • Black race Risk factors for weight gain have not been evaluated in infants and children.	**Prevention:** • Initiate a calorically appropriate, low-fat diet and an exercise regimen. **Monitoring:** • BMI measurement • Waist circumference and waist-hip ratio	Counsel patient on lifestyle modification and dietary interventions (e.g., maintaining a calorically appropriate, healthy diet that is low in saturated fats and simple carbohydrates, and starting an exercise regimen, especially strength training).

Key: ART = antiretroviral therapy; ARV = antiretroviral; BIC = bictegravir; BMI = body mass index; CVD = cardiovascular disease; DTG = dolutegravir; DXA = dual energy x-ray absorptiometry; EFV = efavirenz; INSTI = integrase strand transfer inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; TAF = tenofovir alafenamide; ZDV = zidovudine

References

See the archived version of Supplement III, February 23, 2009, Pediatric Guidelines on the HIVinfo website for a more complete discussion and reference list.

General Reviews

1. Fernandez JR, Redden DT, Pietrobelli A, Allison DB. Waist circumference percentiles in nationally representative samples of African-American, European-American, and Mexican-American children and adolescents. *J Pediatr.* 2004;145(4):439-444. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15480363.

2. Alves Junior CAS, de Lima LRA, de Souza MC, Silva DAS. Anthropometric measures associated with fat mass estimation in children and adolescents with HIV. *Appl Physiol Nutr Metab*. 2019;44(5):493-498. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30286302.

3. Kumar S, Samaras K. The impact of weight gain during HIV treatment on risk of pre-diabetes, diabetes mellitus, cardiovascular disease, and mortality. *Front Endocrinol (Lausanne).* 2018;9:705. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30542325.

4. Innes S, Cotton MF, Haubrich R, et al. High prevalence of lipoatrophy in pre-pubertal South African children on antiretroviral therapy: a cross-sectional study. *BMC Pediatr.* 2012;12:183. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23176441.

5. Prendergast AJ. Complications of long-term antiretroviral therapy in HIV-infected children. *Arch Dis Child.* 2013;98(4):245-246. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23413313.

6. Arbeitman LE, O'Brien RC, Somarriba G, et al. Body mass index and waist circumference of HIV-infected youth in a Miami cohort: comparison to local and national cohorts. *J Pediatr Gastroenterol Nutr.* 2014;59(4):449-454. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24709829.

7. Nduka CU, Uthman OA, Kimani PK, Stranges S. Body fat changes in people living with HIV on antiretroviral therapy. *AIDS Rev.* 2016;18(4):198-211. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27438580.

8. Kenny J, Doerholt K, Gibb DM, Judd A, Collaborative HIVPSSC. Who gets severe gynecomastia among HIV-infected children in the United Kingdom and Ireland? *Pediatr Infect Dis J.* 2017;36(3):307-310. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27879556.

9. Ramteke SM, Shiau S, Foca M, et al. Patterns of growth, body composition, and lipid profiles in a South African cohort of human immunodeficiency virus-infected and uninfected children: a cross-sectional study. *J Pediatric Infect Dis Soc.* 2017. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28481997.

10. Sharma TS, Somarriba G, Arheart KL, et al. Longitudinal changes in body composition by dual-energy radiograph absorptiometry among perinatally HIV-infected and HIV-uninfected youth: increased risk of adiposity among HIV-infected female youth. *Pediatr Infect Dis J.* 2018;37(10):1002-1007. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29474262.

11. de Castro JAC, de Lima LRA, Silva DAS. Accuracy of octa-polar bioelectrical impedance analysis for the assessment of total and appendicular body composition in children and adolescents with HIV: comparison with dual energy X-ray absorptiometry and air displacement plethysmography. *J Hum Nutr Diet.* 2018;31(2):276-285. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28799180.

12. Hill A, Waters L, Pozniak A. Are new antiretroviral treatments increasing the risks of clinical obesity? *J Virus Erad.* 2019;5(1):41-43. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30800425.

13. Taramasso L, Ricci E, Menzaghi B, et al. Weight gain: a possible side effect of all antiretrovirals. *Open Forum Infect Dis.* 2017;4(4):ofx239. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29255735.

14. Sax PE, Erlandson KM, Lake JE, et al. Weight gain following initiation of antiretroviral therapy: risk factors in randomized comparative clinical trials. *Clin Infect Dis.* 2020;71(6):1379-1389. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31606734.

Associated ARVs/Etiology

15. Haubrich RH, Riddler SA, DiRienzo AG, et al. Metabolic outcomes in a randomized trial of nucleoside, nonnucleoside and protease inhibitor-sparing regimens for initial HIV treatment. *AIDS.* 2009;23(9):1109-1118. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19417580.

16. Hulgan T, Tebas P, Canter JA, et al. Hemochromatosis gene polymorphisms, mitochondrial haplogroups, and peripheral lipoatrophy during antiretroviral therapy. *J Infect Dis.* 2008;197(6):858-866. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18419350.

17. McComsey GA, Libutti DE, O'Riordan M, et al. Mitochondrial RNA and DNA alterations in HIV lipoatrophy are linked to antiretroviral therapy and not to HIV infection. *Antivir Ther.* 2008;13(5):715-722. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18771055.

18. Arrive E, Viard JP, Salanave B, et al. Metabolic risk factors in young adults infected with HIV since childhood compared with the general population. *PLoS One.* 2018;13(11):e0206745. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30408056.

19. Arpadi S, Shiau S, Strehlau R, et al. Metabolic abnormalities and body composition of HIV-infected children on lopinavir or nevirapine-based antiretroviral therapy. *Arch Dis Child.* 2013;98(4):258-264. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23220209.

20. Cohen S, Innes S, Geelen SP, et al. Long-term changes of subcutaneous fat mass in HIV-infected children on antiretroviral therapy: a retrospective analysis of longitudinal data from two pediatric HIV-cohorts. *PLoS One.* 2015;10(7):e0120927. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26148119.

21. Dos Reis LC, de Carvalho Rondo PH, de Sousa Marques HH, Jose Segri N. Anthropometry and body composition of vertically HIV-infected children and adolescents under therapy with and without protease inhibitors. *Public Health Nutr.* 2015;18(7):1255-1261. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25115797.

22. McComsey GA, Moser C, Currier J, et al. Body composition changes after initiation of raltegravir or protease inhibitors: ACTG A5260s. *Clin Infect Dis.* 2016;62(7):853-862. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26797215.

23. Moure R, Domingo P, Gallego-Escuredo JM, et al. Impact of elvitegravir on human adipocytes: Alterations in differentiation, gene expression and release of adipokines and cytokines. *Antiviral Res.* 2016;132:59-65. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27216995.

24. Innes S, Harvey J, Collins IJ, Cotton MF, Judd A. Lipoatrophy/lipohypertrophy outcomes after antiretroviral therapy switch in children in the UK/Ireland. *PLoS One.* 2018;13(4):e0194132. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29617438.

25. Bhagwat P, Ofotokun I, McComsey GA, et al. Changes in waist circumference in HIV-infected individuals initiating a raltegravir or protease inhibitor regimen: effects of sex and race. *Open Forum Infect Dis.* 2018;5(11):ofy201. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30465010.

26. Norwood J, Turner M, Bofill C, et al. Brief Report: Weight gain in persons with HIV switched from efavirenz-based to integrase strand transfer inhibitor-based regimens. *J Acquir Immune Defic Syndr.* 2017;76(5):527-531. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28825943.

27. Bourgi K, Rebeiro PF, Turner M, et al. Greater weight gain in treatment naive persons starting dolutegravir-based antiretroviral therapy. *Clin Infect Dis.* 2019. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31100116.

28. Gomez M, Seybold U, Roider J, Harter G, Bogner JR. A retrospective analysis of weight changes in HIV-positive patients switching from a tenofovir disoproxil fumarate (TDF)- to a tenofovir alafenamide fumarate (TAF)-containing treatment regimen in one German university hospital in 2015–2017. *Infection*. 2019;47(1):95-102. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30269210.

29. Eckard AR, McComsey GA. Weight gain and integrase inhibitors. *Curr Opin Infect Dis*. 2020;33(1):10-19. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31789693.

Management

30. Hadigan C. Peroxisome proliferator-activated receptor gamma agonists and the treatment of HIV-associated lipoatrophy: unraveling the molecular mechanism of their shortcomings. *J Infect Dis.* 2008;198(12):1729-1731. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18954262.

31. Lindegaard B, Hansen T, Hvid T, et al. The effect of strength and endurance training on insulin sensitivity and fat distribution in human immunodeficiency virus-infected patients with lipodystrophy. *J Clin Endocrinol Metab.* 2008;93(10):3860-3869. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18628529.

32. Lo J, You SM, Canavan B, et al. Low-dose physiological growth hormone in patients with HIV and abdominal fat accumulation: a randomized controlled trial. *JAMA*. 2008;300(5):509-519. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18677023.

33. Tebas P, Zhang J, Hafner R, et al. Peripheral and visceral fat changes following a treatment switch to a non-thymidine analogue or a nucleoside-sparing regimen in HIV-infected subjects with peripheral lipoatrophy: results of ACTG A5110. *J Antimicrob Chemother.* 2009;63(5):998-1005. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19299471.

34. Falutz J, Mamputu JC, Potvin D, et al. Effects of tesamorelin (TH9507), a growth hormone-releasing factor analog, in human immunodeficiency virus-infected patients with excess abdominal fat: a pooled analysis of two multicenter, double-blind placebo-controlled phase 3 trials with safety extension data. *J Clin Endocrinol Metab.* 2010;95(9):4291-4304. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20554713.

35. Ferrer E, del Rio L, Martinez E, et al. Impact of switching from lopinavir/ritonavir to atazanavir/ritonavir on body fat redistribution in virologically suppressed HIV-infected adults. *AIDS Res Hum Retroviruses*. 2011;27(10):1061-1065. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21166602.

36. Negredo E, Miro O, Rodriguez-Santiago B, et al. Improvement of mitochondrial toxicity in patients receiving a nucleoside reverse-transcriptase inhibitor-sparing strategy: results from the Multicenter Study with Nevirapine and Kaletra (MULTINEKA). *Clin Infect Dis.* 2009;49(6):892-900. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19663689.

37. Raboud JM, Diong C, Carr A, et al. A meta-analysis of six placebo-controlled trials of thiazolidinedione therapy for HIV lipoatrophy. *HIV Clin Trials*. 2010;11(1):39-50. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20400410.

38. Sheth SH, Larson RJ. The efficacy and safety of insulin-sensitizing drugs in HIV-associated lipodystrophy syndrome: a meta-analysis of randomized trials. *BMC Infect Dis*. 2010;10:183. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20573187.

39. Tungsiripat M, Bejjani DE, Rizk N, et al. Rosiglitazone improves lipoatrophy in patients receiving thymidine-sparing regimens. *AIDS.* 2010;24(9):1291-1298. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20453626.

40. Spoulou V, Kanaka-Gantenbein C, Bathrellou I, et al. Monitoring of lipodystrophic and metabolic abnormalities in HIV-1 infected children on antiretroviral therapy. *Hormones (Athens)*. 2011;10(2):149-155. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21724540.

41. Young L, Wohl DA, Hyslop WB, Lee YZ, Napravnik S, Wilkin A. Effects of raltegravir combined with tenofovir/emtricitabine on body shape, bone density, and lipids in African-Americans initiating HIV therapy. *HIV Clin Trials*. 2015;16(5):163-169. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26249671.

42. Taramasso L, Di Biagio A, Bovis F, et al. Switching to integrase inhibitors unlinked to weight increase in perinatally HIV-infected young adults and adolescents: a 10-year observational study. *Microorganisms*. 2020;8(6). Available at: https://www.ncbi.nlm.nih.gov/pubmed/32521616.