## Table 17f. Antiretroviral Therapy–Associated Adverse Effects and Management Recommendations—Insulin Resistance, Asymptomatic Hyperglycemia, and Diabetes Mellitus

Updated: April 11, 2022
Reviewed: April 11, 2023

| Adverse Effects | Associated ARVs | Onset/Clinical Manifestations | Estimated Frequency | Risk Factors | Prevention/ Monitoring | Management |
|---|---|---|---|---|---|---|
| Insulin Resistance, Asymptomatic Hyperglycemia, and Diabetes Mellitus[a] | ZDV, LPV/r and, possibly, other PIs and INSTIs | Onset<br>• Weeks to months after beginning therapy<br><br>Presentation<br>• Asymptomatic fasting hyperglycemia (which sometimes occurs in the setting of lipodystrophy), metabolic syndrome, or growth delay<br>• Symptomatic DM (rare) | Children<br>• IR, 6% to 12% (incidence is higher during puberty, 20% to 30%)<br>• IFPG, 0% to 7%<br>• IGT, 3% to 4%<br>• DM, 0.2 per 100 child-years | Risk Factors for Type 2 DM<br>• Lipodystrophy<br>• Metabolic syndrome<br>• Family history of DM<br>• High BMI (obesity) | Prevention<br>• Lifestyle modification<br><br>Monitoring<br>• Monitor for signs of DM, change in body habitus, and acanthosis nigricans.<br>• Obtain RPG levels at initiation of ART, 3–6 months after ART initiation, and yearly thereafter.<br>• In patients with an RPG ≥140 mg/dL, obtain FPG after an 8-hour fast and consider referring the patient to an endocrinologist. | Counsel patient on lifestyle modification (e.g., implementing a diet low in saturated fat, cholesterol, trans fat, and refined sugars; increasing physical activity; ceasing smoking).<br><br>Recommend that the patient consult with a dietician.<br><br>If the patient is receiving ZDV, switch to TAF, TDF, or ABC.<br><br>For Patients With Either an **RPG ≥200** mg/dL Plus Symptoms of DM or an **FPG ≥126** mg/dL<br>• These patients meet diagnostic criteria for DM; consult an endocrinologist.<br><br>For Patients With an FPG **of 100**–125 mg/dL<br>• Impaired FPG suggests insulin resistance; consult an endocrinologist. |

**Table 17f. Antiretroviral Therapy–Associated Adverse Effects and Management Recommendations—Insulin Resistance, Asymptomatic Hyperglycemia, and Diabetes Mellitus**

| Adverse Effects | Associated ARVs | Onset/Clinical Manifestations | Estimated Frequency | Risk Factors | Prevention/ Monitoring | Management |
|---|---|---|---|---|---|---|
| | | | | | | For Patients With an FPG **<100** mg/dL<br>• This FPG is normal, but a normal FPG does not exclude IR. Recheck FPG in 6–12 months. |

[a] IR, asymptomatic hyperglycemia, IFPG, IGT, and DM form a spectrum of increasing severity.

*IR:* Often defined as elevated insulin levels for the level of glucose observed.

*IFPG:* Often defined as an FPG of 100–125 mg/dL.

*IGT:* Often defined as an elevated 2-hour plasma glucose (PG) of 140–199 mg/dL in a 75-g oral glucose tolerance test (OGTT) (or, if the patient weighs <43 kg, 1.75 g per kg of glucose up to a maximum of 75 g).

*DM:* Often defined as either an FPG ≥126 mg/dL, an RPG ≥200 mg/dL in a patient with hyperglycemia symptoms, a glycosylated hemoglobin (HgbA1c) of ≥6.5%, or a 2-hour PG ≥200 mg/dL in an OGTT.

However, the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV does not recommend performing routine measurements of insulin levels, HgbA1c, or glucose tolerance without consulting an endocrinologist. These guidelines are instead based on the readily available RPG and FPG levels. The HgbA1c test may underestimate glycemia in people with HIV; it is not recommended for diagnosis and may present challenges for monitoring.

Key: ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; BMI = body mass index; DM = diabetes mellitus; FPG = fasting plasma glucose; IFPG = impaired fasting plasma glucose; IGT = impaired glucose tolerance; INSTI = integrase strand transfer inhibitor; IR = insulin resistance; LPV/r = lopinavir/ritonavir; mg/dL = milligrams per deciliter; PI = protease inhibitor; RPG = random plasma glucose; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine

## References[1-24]


1. Aldrovandi GM, Lindsey JC, Jacobson DL, et al. Morphologic and metabolic abnormalities in vertically HIV-infected children and youth. *AIDS*. 2009;23(6):661-672. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19279441.

2. American Diabetes Association. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes-2022. *Diabetes Care*. 2022;45(Suppl 1):S17-S38. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34964875.

3. Chantry CJ, Hughes MD, Alvero C, et al. Lipid and glucose alterations in HIV-infected children beginning or changing antiretroviral therapy. *Pediatrics*. 2008;122(1):e129-138. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18519448.

4. Dirajlal-Fargo S, Musiime V, Cook A, et al. Insulin resistance and markers of inflammation in HIV-infected Ugandan children in the CHAPAS-3 Trial. *Pediatr Infect Dis J*. 2017;36(8):761-767. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28067719.

5. Espiau M, Yeste D, Noguera-Julian A, et al. Metabolic syndrome in children and adolescents living with HIV. *Pediatr Infect Dis J*. 2016;35(6):e171-176. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26910591.

6. Fitch KV. Contemporary lifestyle modification interventions to improve metabolic comorbidities in HIV. *Curr HIV/AIDS Rep*. 2019;16(6):482-491. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31776973.

7. Fortuny C, Deya-Martinez A, Chiappini E, Galli L, de Martino M, Noguera-Julian A. Metabolic and renal adverse effects of antiretroviral therapy in HIV-infected children and adolescents. *Pediatr Infect Dis J*. 2015;34(5 Suppl 1):S36-43. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25629891.

8. Geffner ME, Patel K, Jacobson DL, et al. Changes in insulin sensitivity over time and associated factors in HIV-infected adolescents. *AIDS*. 2018;32(5):613-622. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29280758.

9. Geffner ME, Patel K, Miller TL, et al. Factors associated with insulin resistance among children and adolescents perinatally infected with HIV-1 in the Pediatric HIV/AIDS Cohort Study. *Horm Res Paediatr*. 2011;76(6):386-391. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22042056.

10. Gojanovich GS, Jacobson DL, Jao J, et al. Mitochondrial dysfunction and insulin resistance in pubertal youth living with perinatally acquired HIV. *AIDS Res Hum Retroviruses*. 2020;36(9):703-711. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32586116.

11. Hadigan C, Kattakuzhy S. Diabetes mellitus type 2 and abnormal glucose metabolism in the setting of human immunodeficiency virus. *Endocrinol Metab Clin North Am*. 2014;43(3):685-696. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25169561.

12. Hazra R, Hance LF, Monteiro JP, et al. Insulin resistance and glucose and lipid concentrations in a cohort of perinatally HIV-infected Latin American children. *Pediatr Infect Dis J*. 2013;32(7):757-759. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23360832.

13. Innes S, Abdullah KL, Haubrich R, Cotton MF, Browne SH. High prevalence of dyslipidemia and insulin resistance in HIV-infected pre-pubertal African children on antiretroviral therapy. *Pediatr Infect Dis J*. 2015;35(1):e1-7. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26421804.

14. Loomba-Albrecht LA, Bregman T, Chantry CJ. Endocrinopathies in children infected with human immunodeficiency virus. *Endocrinol Metab Clin North Am*. 2014;43(3):807-828. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25169569.

15. Mirani G, Williams PL, Chernoff M, et al. Changing trends in complications and mortality rates among U.S. youth and young adults with HIV infection in the era of combination antiretroviral therapy. *Clin Infect Dis*. 2015;61(12):1850-1861. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26270680.

16. Non LR, Escota GV, Powderly WG. HIV and its relationship to insulin resistance and lipid abnormalities. *Transl Res*. 2017;183:41-56. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28068521.

17. Paengsai N, Jourdain G, Salvadori N, et al. Recommended first-line antiretroviral therapy regimens and risk of diabetes mellitus in HIV-infected adults in resource-limited settings. *Open Forum Infect Dis*. 2019;6(10):ofz298. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31660327.

18. Paganella MP, Cohen RA, Harris DR, et al. Association of dyslipidemia and glucose abnormalities with antiretroviral treatment in a cohort of HIV-infected Latin American children. *J Acquir Immune Defic Syndr*. 2017;74(1):e1-e8. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27570910.

19. Patel K, Wang J, Jacobson DL, et al. Aggregate risk of cardiovascular disease among adolescents perinatally infected with the human immunodeficiency virus. *Circulation*. 2014;129(11):1204-1212. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24366631.

20. Rebeiro PF, Jenkins CA, Bian A, et al. Risk of incident diabetes mellitus, weight gain, and their relationships with integrase inhibitor-based initial antiretroviral therapy among persons with human immunodeficiency virus in the United States and Canada. *Clin Infect Dis*. 2021;73(7):e2234-e2242. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32936919.

21. Samaras K. Prevalence and pathogenesis of diabetes mellitus in HIV-1 infection treated with combined antiretroviral therapy. *J Acquir Immune Defic Syndr*. 2009;50(5):499-505. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19223782.

22. Shah S, Hill A. Risks of metabolic syndrome and diabetes with integrase inhibitor-based therapy: Republication. *Curr Opin HIV AIDS*. 2021;16(2):106-114. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33625041.

23. Summers NA, Lahiri CD, Angert CD, et al. Metabolic changes associated with the use of integrase strand transfer inhibitors among virally controlled women. *J Acquir Immune Defic Syndr*. 2020;85(3):355-362. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33060420.

24. Takemoto JK, Miller TL, Wang J, et al. Insulin resistance in HIV-infected youth is associated with decreased mitochondrial respiration. *AIDS*. 2017;31(1):15-23. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27755108.