Table 15d. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Hematologic Effects (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
Anemia[a]	ZDV	**Onset:** • Variable; weeks to months after starting therapy **Presentation** *More Common:* • Asymptomatic • Mild fatigue • Pallor • Tachypnea *Rare:* • Congestive heart failure	**Newborns Exposed to HIV:** • Severe anemia is uncommon, but might be coincident with physiologic Hgb nadir. **Children with HIV Who Are Taking ARV Drugs:** • Anemia is two to three times more common with ZDV-containing regimens than with all other regimens.	**Newborns Exposed to HIV:** • Premature birth is the most common risk factor • *In utero* exposure to ZDV-containing regimens • Advanced maternal HIV • Neonatal blood loss • Combination ARV prophylaxis or presumptive HIV therapy, particularly ZDV plus 3TC and NVP **Children with HIV Who Are Taking ARV Drugs:** • Underlying hemoglobinopathy (e.g., sickle cell disease, G6PD deficiency) • Myelosuppressive drugs (e.g., TMP-SMX, rifabutin) • Iron deficiency • Advanced or poorly controlled HIV disease • OIs of the bone marrow • Malnutrition	**Newborns Exposed to HIV:** • Obtain CBC at birth. • Consider repeating CBC at 4 weeks for neonates who are at higher risk (e.g., those born prematurely or who are known to have low birth Hgb) and for neonates who receive ZDV beyond 4 weeks. **Children with HIV Who Are Taking ARV Drugs:** • Avoid using ZDV in children with severe anemia when alternative agents are available. • Obtain CBC as part of routine care (see Clinical and Laboratory Monitoring of Pediatric HIV Infection).	**Newborns Exposed to HIV:** • Anemia rarely requires intervention unless it is symptomatic or Hgb <7.0 g/dL. • ZDV administration can be limited to 4 weeks in low-risk neonates (see Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection). **Children with HIV Who Are Taking ARV Drugs:** • Discontinue non-ARV, marrow-toxic drugs, if feasible. • Treat coexisting iron deficiency, OIs, and malignancies. • For persistent, severe anemia that is thought to be associated with ARV drugs (typically macrocytic anemia), switch to a regimen that does not contain ZDV.
Macrocytosis	ZDV	**Onset:** • Within days or weeks of starting therapy **Presentation:** • Asymptomatic, but MCV often is >100 fL • Sometimes associated with anemia	>90% to 95% for all ages	None	No monitoring required—macrocytosis can be detected if CBC is obtained as part of routine care (see Clinical and Laboratory Monitoring of Pediatric HIV Infection).	No management required.

Table 15d. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Hematologic Effects (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
Neutropenia[a]	ZDV	**Onset:** • Variable **Presentation:** • Asymptomatic	**Newborns Exposed to HIV:** • Rare **Children with HIV Who Are Taking ARV Drugs:** • 2% to 4% of children on ARV drugs • Highest rates occur in children on ZDV-containing regimens	**Newborns Exposed to HIV:** • *In utero* exposure to ARV drugs • Combination ARV prophylaxis, particularly ZDV plus 3TC and NVP **Children with HIV Who Are Taking ARV Drugs:** • Advanced or poorly controlled HIV infection • Myelosuppressive drugs (e.g., TMP-SMX, ganciclovir, hydroxyurea, rifabutin)	**Children with HIV Who Are Taking ARV Drugs:** • Obtain CBC as part of routine care.	**Newborns Exposed to HIV:** • No established threshold for intervention; some experts would consider using an alternative NRTI for prophylaxis if ANC reaches <500 cells/mm^3. ZDV administration can be limited to 4 weeks in low-risk neonates (see Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection). **Children with HIV Who Are Taking ARV Drugs:** • Discontinue non-ARV, marrow-toxic drugs, if feasible. • Treat coexisting OIs and malignancies. • In cases of persistent, severe neutropenia that is thought to be associated with ARV drugs, switch to a regimen that does not contain ZDV.

[a] HIV infection itself, OIs, and medications that are used to prevent OIs (e.g., TMP-SMX) can all contribute to anemia and neutropenia. Prolonged use of NVP with ZDV in three drug regimens for the prevention of perinatal HIV transmission has been associated with increased rates of anemia and neutropenia in some, but not all, studies. The effects are of uncertain clinical significance and appear to be transient.

Key: 3TC = lamivudine; ANC = absolute neutrophil count; ARV = antiretroviral; CBC = complete blood count; fL = femtoliter; G6PD = glucose-6-phosphate dehydrogenase; g/dL - grams per deciliter; Hgb = hemoglobin; MCV = mean cell volume; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; OI = opportunistic infection; TMP-SMX = trimethoprim-sulfamethoxazole; ZDV = zidovudine

References

1. Arrow Trial team, Kekitiinwa A, Cook A, et al. Routine versus clinically driven laboratory monitoring and first-line antiretroviral therapy strategies in African children with HIV (ARROW): a 5-year open-label randomised factorial trial. *Lancet*. 2013;381(9875):1391-1403. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23473847.

2. Bunupuradah T, Kariminia A, Chan KC, et al. Incidence and predictors of severe anemia in Asian HIV-infected children using first-line antiretroviral therapy. *Int J Infect Dis*. 2013;17(10):e806-810. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23764352.

3. Dryden-Peterson S, Shapiro RL, Hughes MD, et al. Increased risk of severe infant anemia after exposure to maternal HAART, Botswana. *J Acquir Immune Defic Syndr*. 2011;56(5):428-436. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21266910.

4. Esan MO, Jonker FA, Hensbroek MB, Calis JC, Phiri KS. Iron deficiency in children with HIV-associated anaemia: a systematic review and meta-analysis. *Trans R Soc Trop Med Hyg*. 2012;106(10):579-587. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22846115.

5. European Pregnancy and Pediatric HIV Cohort Collaboration (EPPICC) Study Group in EuroCoord. Severe haematologic toxicity is rare in high risk HIV-exposed infants receiving combination neonatal prophylaxis. *HIV Med*. 2019;20(5):291-307. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30844150.

6. Greiter BM, Kahlert CR, Eberhard N, Sultan-Beyer L, Berger C, Paioni P. Lymphocyte subsets in HIV-exposed uninfected infants: the impact of neonatal postexposure prophylaxis with zidovudine. *Open Forum Infect Dis*. 2020;7(4):ofaa108. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32368562.

7. Kibaru EG, Nduati R, Wamalwa D, Kariuki N. Impact of highly active antiretroviral therapy on hematological indices among HIV-1 infected children at Kenyatta National Hospital-Kenya: retrospective study. *AIDS Res Ther*. 2015;12:26. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26279668.

8. Lahoz R, Noguera A, Rovira N, et al. Antiretroviral-related hematologic short-term toxicity in healthy infants: implications of the new neonatal 4-week zidovudine regimen. *Pediatr Infect Dis J*. 2010;29(4):376-379. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19949355.

9. Lau E, Brophy J, Samson L, et al. Nevirapine pharmacokinetics and safety in neonates receiving combination antiretroviral therapy for prevention of vertical HIV transmission. *J Acquir Immune Defic Syndr*. 2017;74(5):493-498. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28114187.

10. Melvin AJ, Warshaw M, Compagnucci A, et al. Hepatic, renal, hematologic, and inflammatory markers in HIV-infected children on long-term suppressive antiretroviral therapy. *J Pediatric Infect Dis Soc*. 2017;6(3):e109-e115. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28903520.

11. Mocroft A, Lifson AR, Touloumi G, et al. Haemoglobin and anaemia in the SMART study. *Antivir Ther.* 2011;16(3):329-337. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21555815.

12. Mulenga V, Musiime V, Kekitiinwa A, et al. Abacavir, zidovudine, or stavudine as paediatric tablets for African HIV-infected children (CHAPAS-3): an open-label, parallel-group, randomised controlled trial. *Lancet Infect Dis*. 2016;16(2):169-179. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26481928.

13. Nguyen TTT, Kobbe R, Schulze-Sturm U, et al. Reducing hematologic toxicity with short course postexposure prophylaxis with zidovudine for HIV-1 exposed infants with low transmission risk. *Pediatr Infect Dis J*. 2019;38(7):727-730. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31033907.

14. Nielsen-Saines K, Watts DH, Veloso VG, et al. Three postpartum antiretroviral regimens to prevent intrapartum HIV infection. *N Engl J Med*. 2012;366(25):2368-2379. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22716975.

15. Nyesigire Ruhinda E, Bajunirwe F, Kiwanuka J. Anaemia in HIV-infected children: severity, types and effect on response to HAART. *BMC Pediatr*. 2012;12:170. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23114115.

16. Renner LA, Dicko F, Koueta F, et al. Anaemia and zidovudine-containing antiretroviral therapy in paediatric antiretroviral programmes in the IeDEA Paediatric West African Database to evaluate AIDS. *J Int AIDS Soc*. 2013;16(1):18024. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24047928.

17. Shet A, Bhavani PK, Kumarasamy N, et al. Anemia, diet and therapeutic iron among children living with HIV: a prospective cohort study. *BMC Pediatr*. 2015;15:164. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26482352.

18. Smith C, Forster JE, Levin MJ, et al. Serious adverse events are uncommon with combination neonatal antiretroviral prophylaxis: a retrospective case review. *PLoS One*. 2015;10(5):e0127062. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26000984.

19. Smith C, Weinberg A, Forster JE, et al. Maternal lopinavir/ritonavir is associated with fewer adverse events in infants than nelfinavir or atazanavir. *Infect Dis Obstet Gynecol*. 2016;2016:9848041. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27127401.

20. The European Pregnancy and Paediatric HIV Cohort Collaboration, ,(EPPICC) study Group in EuroCoord. Safety of zidovudine/lamivudine scored tablets in children with HIV infection in Europe and Thailand. *Eur J of Clin Pharmacol*. 2017;73(4):463-468. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5350228/.

21. Van Dyke RB, Wang L, Williams PL, Pediatric AIDS Clinical Trials Group C. Team. Toxicities associated with dual nucleoside reverse-transcriptase inhibitor regimens in HIV-infected children. *J Infect Dis*. 2008;198(11):1599-1608.. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19000014.