Long-Term Follow-Up of Infants Exposed to Antiretroviral Drugs (Last updated January 17, 2020; last reviewed January 17, 2020)

Panel's Recommendation
• Children with *in utero* or neonatal exposure to antiretroviral (ARV) drugs who develop significant organ system abnormalities of unknown etiology, particularly of the nervous system or heart, should be evaluated for potential mitochondrial dysfunction **(CIII)**. • It is important that the long-term medical record of a child without HIV includes information about *in utero* and neonatal ARV exposure **(BIII)**.
Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*
Rating of Evidence: *I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Beginning in the 1990s, evolving long-term monitoring studies, outcomes studies, and other types of surveillance and research have been conducted to assess whether *in utero* exposure to antiretroviral (ARV) drugs may pose later risks to children's health. These include studies of children without HIV infection born to women with HIV (e.g., the Pediatric AIDS Clinical Trial Group [PACTG] Late Outcomes Study and the Surveillance Monitoring for ART Toxicities [SMARTT] study from the Pediatric HIV/AIDS Cohort Study [PHACS]). Participation of children and their parents in observational studies provides an essential contribution to the research needed to monitor and identify long-term health outcomes from *in utero* HIV and ARV exposure. Available evidence does not permit definitive conclusions about whether *in utero* exposure to HIV and ARV agents might affect immunity, infectious morbidity, growth, cardiometabolic, neurodevelopmental, mitochondrial toxicity, or cancer outcomes from infancy through adulthood. Further, long-term investigation of potential HIV- and/or ARV-related toxicities is required, especially as new antiretroviral therapy (ART) for pregnant women with HIV evolves. It is important to include information about perinatal exposure to HIV and ARV agents in the long-term medical record of a child without HIV in the event that the child develops unusual symptoms later in life, or if adverse late effects of HIV or ARV exposure in children without HIV are identified in the future.[1-3]

Potential Increased Morbidity and Mortality

In general, the risks for increased morbidity and mortality are greater in infants who are HIV exposed but uninfected (HEU) than in infants who were HIV unexposed and uninfected (HUU). These differences are more pronounced in infants from low-middle income countries with fewer reports of similar findings in infants from high-income countries.[4] Data from Botswana show higher rates of morbidity and mortality in infants and children who were HEU than in those who were HUU.[5-7] A meta-analysis assessing the difference in all-cause mortality between infants and children who were HEU and those who were HUU, observed increased risk in those who were HEU.[8] Further research is needed to reproduce these results and to determine an immunological basis for the increased susceptibility of infants and children who were HEU to invasive infections.[9]

Potential Immunologic Dysfunction and Infectious Morbidity

The potential long-term impact of HIV/ARV exposure on the immune system of an infant without HIV is unclear. A recent meta-analysis reported that, compared to infants who were HUU, infants who were HEU had a 50% and 70% increased risk for diarrhea and pneumonia, respectively, in the first 6 months of life.[10] The French Perinatal Cohort Group has observed an increased risk of serious bacterial infections with encapsulated organisms in HEU infants born to women with HIV with low CD4 T lymphocyte (CD4) cell counts near the time of delivery.[11] Another study of HEU infants reported that those born to mothers whose viral load at delivery was >1,000 copies/mL had lower CD4 counts than those born to mothers whose viral load was <50 copies/mL at delivery.[12] Other data suggest that exposure to HIV *in utero* may be associated with disturbances in infant CD4 and CD8 cell-mediated immune responses resulting in T-cell dysfunction, altered vaccine responses, and non-specific antigens in infants.[13,14] More recent data indicate immune

activation and proinflammatory responses are greater in infants who were HIV exposed than in those who were unexposed.[15-21]

Potential Adverse Growth and Metabolic Outcomes

Similar to data on overall morbidity and mortality in infants who were HEU, observations on the effect of *in utero* HIV/ARV exposure on infant and child growth have largely differed between low- and high-income settings.[22-24] Among studies that compared growth in children who were HEU and those who were HUU, a recent Nigerian study reported compromised growth in children who were HEU, and a South African study found persistently lower weight-for-age z-scores (WAZ) over the first year of life, as well as higher rates of stunting, in those who were HEU.[25,26] However, in a large Danish study of postnatal growth through 5 years of life, no significant differences in WAZ after 2 weeks of life or length-for-age z-scores after 6 months of life were noted between children who were HEU and a matched comparator group of children who were HUU.[27] In addition, the PHACS SMARTT study in the United States has demonstrated above-average growth in children who were HEU compared to children in the general pediatric population.[23] This positive relationship may carry potential long-term cardiometabolic risk for children from high-income settings who were HEU. PHACS SMARTT has found high rates of obesity in children and adolescents who were HEU,[28] and obese children and adolescents who were HEU have a greater risk for systolic and diastolic hypertension than obese children and adolescents in the general pediatric population.[29] In addition, although data have revealed early derangements in fuel utilization and intermediary metabolism in infants who were HEU in the United States and Africa, the significance of these findings on the long-term metabolic health of this population is still undetermined.[30,31]

Potential Neurodevelopmental Outcomes

Studies investigating whether the risk for poor neurodevelopmental outcomes is higher in children who were HEU than in those who were HUU have not been conclusive.[32] In addition, the heterogeneity of study populations and study designs may further complicate interpretation of cumulative data. Several studies found no differences in early neurodevelopment between children who were HEU and those who were HUU, although some studies reported an increased risk for poorer neurodevelopmental outcomes in children who were HEU.[33-35] Some studies evaluated whether maternal factors or *in utero* ARV drug exposure contribute to adverse neurodevelopmental outcomes among children who were HEU. Although worse infant neurodevelopment was observed with maternal viremia in one study[36] and with *in utero* efavirenz exposure in another,[37] several studies have not identified associations between maternal ARV use and infant neurodevelopment.[35,36,38-40] Recently, the PHACS SMARTT study evaluated the risk of microcephaly associated with *in utero* ARV exposure in children who were HEU and found that those with *in utero* exposure to efavirenz had a greater risk of microcephaly than those without *in utero* efavirenz exposure (see Teratogenicity). Neurodevelopmental assessments at ages 1 and 5 years demonstrated that HEU children with microcephaly had lower mean scores and a higher prevalence of neurodevelopmental impairment than HEU children without microcephaly.[41,42] At present, there is no definitive evidence showing an association between *in utero* exposure to specific ARV drugs and poorer neurodevelopmental outcomes, although recent studies[37,41] provide data suggesting a possible association with EFV.

Potential Mitochondrial Toxicity

Nucleoside reverse transcriptase inhibitor (NRTI) drugs induce some degree of mitochondrial dysfunction reflecting varying affinity for mitochondrial gamma DNA polymerase. This affinity can interfere with mitochondrial replication, resulting in mitochondrial DNA (mtDNA) depletion and dysfunction.[43-45] Aberrant histological morphology of mitochondria, mtDNA mutations, alterations in mtDNA levels in cord blood mononuclear cells, and even aneuploidy in cord blood cells have all been described in both non-human primates and neonates exposed *in utero* to NRTI drugs.[2,46-50] The degree to which these documented mitochondrial abnormalities are clinically relevant is unknown, but they are significantly outweighed by the robust, proven efficacy of maternal and infant ARV prophylaxis in preventing perinatal HIV transmission.[2,51]

Evidence of clinically apparent effects of mitochondrial toxicity are also conflicting. Though earlier studies from the French Perinatal Study Group cohort noted a significantly increased incidence of clinical effects possibly reflecting mitochondrial dysfunction including seizures, cognitive and motor delays, abnormal neuroimaging, hyperlactatemia, cardiac dysfunction, and two deaths (12 of 2,644 infants vs. 0 of 1,748 infants with and without exposure to *in utero* ARV drugs, respectively, $P = 0.002$),[52,53] low rates of hyperlactatemia (3.4%) have been documented among infants who were HEU born to women with HIV in the United States who were receiving ART during pregnancy.[54] In addition, further clinical studies from the United States and Europe have not duplicated findings from the French studies.[55-61] Some small alterations in mtDNA and oxidative phosphorylation enzyme activities were documented in stored specimens from children who were HEU in the United States. PACTG 219/219C trial, but the clinical significance of these observations is unknown.[62,63]

Given the above data, mitochondrial dysfunction should be considered in children without HIV, but with perinatal exposure to ARV drugs who present with severe clinical findings of unknown etiology, particularly neurologic findings.

Potential Cancer Risk and Exposure to Nucleoside Reverse Transcriptase Inhibitor Drugs

Animal studies have reported potential transplacental genotoxicity of nucleoside analogue therapy in monkeys, and micro-nucleated erythrocytes have been identified in infants with *in utero* nucleoside analogue exposure.[64,65] An updated report from the French Perinatal Cohort described 21 cancers among 15,163 children without HIV (median age 9.9 years) exposed *in utero* to HIV and ≥1 NRTI drug.[66,67] Among the NRTIs studied, didanosine (which **is no longer recommended**) was potentially associated with risk of cancer. In a study in the United States, there were four cancer diagnoses among 3,087 children exposed to HIV; the number of cancer cases did not differ significantly from the number of cases expected based on national reference rates.[68] Continued follow-up of children who were HIV- and ARV-exposed but uninfected is needed to evaluate the potential risk of cancer as these children age into adulthood.

Conclusion

In the United States, ongoing evaluation of the early and late effects of *in utero* exposure to ARV drugs and of infant feeding approaches include the Pediatric HIV/AIDS Cohort Study Surveillance Monitoring of Antiretroviral Toxicity study, natural history studies, and HIV/AIDS surveillance conducted by state health departments and the Centers for Disease Control and Prevention. It is critical that studies to evaluate potential adverse effects of *in utero* drug exposure continue to be supported given the fast pace at which newly developed ARV drugs are being made available to pregnant women living with HIV. HIV surveillance databases from states that require HIV reporting provide an opportunity to collect population-based information concerning *in utero* exposure to ARV drugs. To the extent permitted by federal law and regulations, data from these confidential registries can be compared with information from birth defects and cancer registries to identify potential adverse outcomes of *in utero* ARV drug exposure.

References

1. Mofenson LM, Watts DH. Safety of pediatric HIV elimination: the growing population of HIV- and antiretroviral-exposed but uninfected infants. *PLoS Med*. 2014;11(4):e1001636. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24781352.

2. Jao J, Abrams EJ. Metabolic complications of *in utero* maternal HIV and antiretroviral exposure in HIV-exposed Infants. *Pediatr Infect Dis J*. 2014;33(7):734-740. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24378947.

3. Hazra R, Siberry GK, Mofenson LM. Growing up with HIV: children, adolescents, and young adults with perinatally acquired HIV infection. *Ann Rev Med*. 2010;61:169-185. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19622036.

4. Yeganeh N, Watts DH, Xu J, et al. Infectious morbidity, mortality and nutrition in HIV-exposed, uninfected, formula-fed infants: results from the HPTN 040/PACTG 1043 trial. *Pediatr Infect Dis J*. 2018;37(12):1271-1278. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29750766.

5. Zash R, Leidner J, Souda S, et al. HIV-exposed children account for more than half of 24-month mortality in Botswana. Presented at: Conference on Retroviruses and Opportunistic Infections. 2016. Boston, MA.

6. Dryden-Peterson S, Ramos T, Shapiro R, Lockman S. Maternal ART and hospitalization or death among HIV-exposed uninfected infants. Presented at: Conference on Retroviruses and Opportunistic Infections. 2016. Seattle, WA.

7. Ajibola G, Mayondi G, Leidner J, et al. Higher mortality in HIV-exposed/uninfected vs HIV-unexposed infants, Botswana. The 23rd Conference on Retroviruses and Opportunistic Infections. 2016. Seattle, WA.

8. Brennan AT, Bonawitz R, Gill CJ, et al. A meta-analysis assessing all-cause mortality in HIV-exposed uninfected compared with HIV-unexposed uninfected infants and children. *AIDS.* 2016;30(15):2351-2360. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27456985.

9. Ruck C, Reikie BA, Marchant A, Kollmann TR, Kakkar F. Linking susceptibility to infectious diseases to immune system abnormalities among HIV-exposed uninfected infants. *Front Immunol.* 2016;7:310. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27594857.

10. Brennan AT, Bonawitz R, Gill CJ, et al. A meta-analysis assessing diarrhea and pneumonia in HIV-exposed uninfected compared with HIV-unexposed uninfected infants and children. *J Acquir Immune Defic Syndr.* 2019;82(1):1-8. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31408450.

11. Taron-Brocard C, Le Chenadec J, Faye A, et al. Increased risk of serious bacterial infections due to maternal immunosuppression in HIV-exposed uninfected infants in a European country. *Clin Infect Dis.* 2014;59(9):1332-1345. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25053719.

12. Kakkar F, Lamarre V, Ducruet T, et al. Impact of maternal HIV-1 viremia on lymphocyte subsets among HIV-exposed uninfected infants: protective mechanism or immunodeficiency. *BMC Infect Dis.* 2014;14:236. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24885498.

13. Kidzeru EB, Hesseling AC, Passmore JA, et al. In-utero exposure to maternal HIV infection alters T-cell immune responses to vaccination in HIV-uninfected infants. *AIDS.* 2014;28(10):1421-1430. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24785950.

14. Jalbert E, Williamson KM, Kroehl ME, et al. HIV-exposed uninfected infants have increased regulatory T cells that correlate with decreased T cell function. *Front Immunol.* 2019;10:595. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30972079.

15. Schoeman JC, Moutloatse GP, Harms AC, et al. Fetal metabolic stress disrupts immune homeostasis and induces proinflammatory responses in human immunodeficiency virus type 1- and combination antiretroviral therapy-exposed infants. *J Infect Dis.* 2017;216(4):436-446. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28633455.

16. Evans C, Chasekwa B, Rukobo S, et al. Inflammation, CMV and the growth hormone axis in HIV-exposed uninfected infants. Abstract 873. Presented at: Conference on Retroviruses and Opportunistic Infections. 2018. Boston, Massachusetts. Available at: http://www.croiconference.org/sessions/inflammation-cmv-and-growth-hormone-axis-hiv-exposed-uninfected-infants.

17. Mussi-Pinhata MM, Weinberg A, Yu Q, et al. Increased inflammation and monocyte activation in HIV-exposed uninfected infants. Presented at: Conference Retroviruses and Opportunistic Infections. 2018. Boston, Massachusetts. Available at: http://www.croiconference.org/sessions/increased-inflammation-and-monocyte-activation-hiv-exposed-uninfected-infants-0.

18. Broncano PG, Kgole SW, Masasa G, et al. Innate immune activation among HIV-1 exposed uninfected infants from Botwswana. Abstract 881. Presented at: Conference on Retroviruses Opportunistic Infections. 2018. Boston, Massachusetts. Available at: http://www.croiconference.org/sessions/innate-immune-activation-among-hiv-1-exposed-uninfected-infants-botswana.

19. Mitchell C, Dominguez S, George V, et al. Microbial Translocation, immune activation, and gut dysbiosis in HIV-exposed infants. Abstract 882. Presented at: Conferences on Retroviruses and Opportunistic Infections. 2018. Boston, Massachusetts. Available at: http://www.croiconference.org/sessions/microbial-translocation-immune-activation-and-gut-dysbiosis-hiv-exposed-infants-0.

20. Dirajlal-Fargo S, Mussi-Pinhata MM, Weinberg A, et al. HIV-exposed-uninfected infants have increased inflammation and monocyte activation. *AIDS.* 2019;33(5):845-853. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30649056.

21. Gabriel B, Medin C, Alves J, et al. Analysis of the TCR Repertoire in HIV-exposed but uninfected infants. *Sci Rep.* 2019;9(1):11954. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31420576.

22. Neri D, Somarriba GA, Schaefer NN, et al. Growth and body composition of uninfected children exposed to human immunodeficiency virus: comparison with a contemporary cohort and United States national standards. *J Pediatr.* 2013;163(1):249-254 e241-242. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23360565.

23. Jacobson DL, Patel K, Williams PL, et al. Growth at 2 years of age in HIV-exposed uninfected children in the United States by trimester of maternal antiretroviral initiation. *Pediatr Infect Dis J.* 2017;36(2):189-197. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27798548.

24. Sudfeld CR, Lei Q, Chinyanga Y, et al. Linear growth faltering among HIV-exposed uninfected children. *J Acquir Immune Defic Syndr.* 2016;73(2):182-189. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27116046.

25. Jumare J, Datong P, Osawe S, et al. Compromised growth among HIV-exposed uninfected compared with unexposed children in Nigeria. *Pediatr Infect Dis J.* 2019;38(3):280-286. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30418356.

26. le Roux SM, Abrams EJ, Donald KA, et al. Growth trajectories of breastfed HIV-exposed uninfected and HIV-unexposed children under conditions of universal maternal antiretroviral therapy: a prospective study. *Lancet Child Adolesc Health.* 2019;3(4):234-244. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30773459.

27. Moseholm E, Helleberg M, Sandholdt H, et al. Children exposed or unexposed to HIV: weight, height and BMI during the first five years of life. A Danish nationwide cohort study. *Clin Infect Dis.* 2019. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31271208.

28. Jacobson DL, Patel K, Siberry GK, et al. Body fat distribution in perinatally HIV-infected and HIV-exposed but uninfected children in the era of highly active antiretroviral therapy: outcomes from the Pediatric HIV/AIDS Cohort Study. *Am J Clin Nutr.* 2011;94(6):1485-1495. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22049166.

29. Jao J, Jacobson DL, Yu W, et al. A comparison of metabolic outcomes between obese HIV-exposed uninfected youth from the PHACS SMARTT study and HIV-unexposed youth from the NHANES study in the United States. *J Acquir Immune Defic Syndr.* 2019;81(3):319-327. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30844997.

30. Kirmse B, Hobbs CV, Peter I, et al. Abnormal newborn screens and acylcarnitines in HIV-exposed and ARV-exposed infants. *Pediatr Infect Dis J.* 2013;32(2):146-150. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22935866.

31. Jao J, Kirmse B, Yu C, et al. Lower preprandial insulin and altered fuel use in HIV/antiretroviral-exposed infants in Cameroon. *J Clin Endocrinol Metab.* 2015;100(9):3260-3269. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26133363.

32. McHenry MS, McAteer CI, Oyungu E, et al. Neurodevelopment in young children born to HIV-infected mothers: a meta-analysis. *Pediatrics.* 2018;141(2). Available at: https://www.ncbi.nlm.nih.gov/pubmed/29374109.

33. Wedderburn CJ, Yeung S, Rehman AM, et al. Neurodevelopment of HIV-exposed uninfected children in South Africa: outcomes from an observational birth cohort study. *Lancet Child Adolesc Health.* 2019;3(11):803-813. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31515160.

34. Kerr SJ, Puthanakit T, Vibol U, et al. Neurodevelopmental outcomes in HIV-exposed-uninfected children versus those not exposed to HIV. *AIDS Care.* 2014;26(11):1327-1335. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24878112.

35. Piske M, Budd MA, Qiu AQ, et al. Neurodevelopmental outcomes and in-utero antiretroviral exposure in HIV-exposed uninfected children. *AIDS.* 2018;32(17):2583-2592. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30134292.

36. le Roux SM, Donald KA, Kroon M, et al. HIV viremia during pregnancy and neurodevelopment of HIV-exposed uninfected children in the context of universal antiretroviral therapy and breastfeeding: a prospective study. *Pediatr Infect Dis J.* 2019;38(1):70-75. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30234792.

37. Cassidy AR, Williams PL, Leidner J, et al. *In utero* efavirenz exposure and neurodevelopmental outcomes in HIV-exposed uninfected children in Botswana. *Pediatr Infect Dis J.* 2019;38(8):828-834. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30985518.

38. Chaudhury S, Mayondi GK, Williams PL, et al. *In-utero* exposure to antiretrovirals and neurodevelopment among HIV-exposed-uninfected children in Botswana. *AIDS.* 2018;32(9):1173-1183. Available at: https://www.ncbi.nlm.nih.gov/

pubmed/29547434.

39. Kacanek D, Williams PL, Mayondi G, et al. Pediatric neurodevelopmental functioning after *in utero* exposure to triple-NRTI vs. dual-NRTI + PI ART in a randomized trial, Botswana. *J Acquir Immune Defic Syndr.* 2018;79(3):e93-e100. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30015793.

40. Williams PL, Marino M, Malee K, et al. Neurodevelopment and *in utero* antiretroviral exposure of HIV-exposed uninfected infants. *Pediatrics.* 2010;125(2):e250-260. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20083530.

41. Williams PL, Yildirim C, Chadwick EG, et al. Association of maternal antiretroviral use with microcephaly in children who are HIV-exposed but uninfected (SMARTT): a prospective cohort study. *Lancet HIV.* 2019;S2352-3018(19)30340-6. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31740351.

42. le Roux SM, Abrams EJ. Efavirenz in pregnancy. *Lancet HIV.* 2019;S2352-3018(19)30330-3. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31740349.

43. Brinkman K, Ter Hofstede HJ, Burger DM, et al. Adverse effects of reverse transcriptase inhibitors: mitochondrial toxicity as common pathway. *AIDS.* 1998;12(14):1735-1744. Available at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9792373&dopt=Abstract.

44. Birkus G, Hitchcock MJ, Cihlar T. Assessment of mitochondrial toxicity in human cells treated with tenofovir: comparison with other nucleoside reverse transcriptase inhibitors. *Antimicrob Agents Chemother.* 2002;46(3):716-723. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11850253.

45. Saitoh A, Haas RH, Naviaux RK, Salva NG, Wong JK, Spector SA. Impact of nucleoside reverse transcriptase inhibitors on mitochondrial DNA and RNA in human skeletal muscle cells. *Antimicrob Agents Chemother.* 2008;52(8):2825-2830. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18541728.

46. Divi RL, Leonard SL, Kuo MM, et al. Transplacentally exposed human and monkey newborn infants show similar evidence of nucleoside reverse transcriptase inhibitor-induced mitochondrial toxicity. *Environ Mol Mutagen.* 2007;48(3-4):201-209. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16538687.

47. Poirier MC, Divi RL, Al-Harthi L, et al. Long-term mitochondrial toxicity in HIV-uninfected infants born to HIV-infected mothers. *J Acquir Immune Defic Syndr.* 2003;33(2):175-183. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12794551.

48. Martin F, Taylor GP. The safety of highly active antiretroviral therapy for the HIV-positive pregnant mother and her baby: is 'the more the merrier'? *J Antimicrob Chemother.* 2009;64(5):895-900. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19706669.

49. Jao J, Powis KM, Kirmse B, et al. Lower mitochondrial DNA and altered mitochondrial fuel metabolism in hiv-exposed uninfected infants in cameroon. *AIDS.* 2017. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28926411.

50. Budd MA, Calli K, Samson L, et al. Blood mitochondrial DNA content in HIV-exposed uninfected children with autism spectrum disorder. *Viruses.* 2018;10(2). Available at: https://www.ncbi.nlm.nih.gov/pubmed/29439467.

51. Newell ML, Bunders MJ. Safety of antiretroviral drugs in pregnancy and breastfeeding for mother and child. *Curr Opin HIV AIDS.* 2013;8(5):504-510. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23743789.

52. Blanche S, Tardieu M, Rustin P, et al. Persistent mitochondrial dysfunction and perinatal exposure to antiretroviral nucleoside analogues. *Lancet.* 1999;354(9184):1084-1089. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10509500.

53. Barret B, Tardieu M, Rustin P, et al. Persistent mitochondrial dysfunction in HIV-1-exposed but uninfected infants: clinical screening in a large prospective cohort. *AIDS.* 2003;17(12):1769-1785. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12891063.

54. Crain MJ, Williams PL, Griner R, et al. Point-of-care capillary blood lactate measurements in human immunodeficiency virus-uninfected children with *in utero* exposure to human immunodeficiency virus and antiretroviral medications. *Pediatr Infect Dis J.* 2011;30(12):1069-1074. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22051859.

55. Sperling RS, Shapiro DE, McSherry GD, et al. Safety of the maternal-infant zidovudine regimen utilized in the pediatric AIDS clinical trial group 076 study. *AIDS.* 1998;12(14):1805-1813. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9792381.

56. The Perinatal Safety Review Working Group. Nucleoside exposure in the children of HIV-infected women receiving antiretroviral drugs: absence of clear evidence for mitochondrial disease in children who died before 5 years of age in five United States cohorts. *J Acquir Immune Defic Syndr.* 2000;25(3):261-268. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11115957.

57. Lipshultz SE, Easley KA, Orav EJ, et al. Absence of cardiac toxicity of zidovudine in infants. Pediatric pulmonary and cardiac complications of vertically transmitted HIV infection study group. *N Engl J Med.* 2000;343(11):759-766. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10984563.

58. European Collaborative Study. Exposure to antiretroviral therapy *in utero* or early life: the health of uninfected children born to HIV-infected women. *J Acquir Immune Defic Syndr.* 2003;32(4):380-387. Available at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12640195&dopt=Abstract.

59. Alimenti A, Forbes JC, Oberlander TF, et al. A prospective controlled study of neurodevelopment in HIV-uninfected children exposed to combination antiretroviral drugs in pregnancy. *Pediatrics.* 2006;118(4):e1139-1145. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16940166.

60. Brogly SB, Ylitalo N, Mofenson LM, et al. *In utero* nucleoside reverse transcriptase inhibitor exposure and signs of possible mitochondrial dysfunction in HIV-uninfected children. *AIDS.* 2007;21(8):929-938. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17457086.

61. Hankin C, Lyall H, Peckham C, Tookey P. Monitoring death and cancer in children born to HIV-infected women in England and Wales: use of HIV surveillance and national routine data. *AIDS.* 2007;21(7):867-869. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17415042.

62. Brogly SB, DiMauro S, Van Dyke RB, et al. Short communication: transplacental nucleoside analogue exposure and mitochondrial parameters in HIV-uninfected children. *AIDS Res Hum Retroviruses.* 2011;27(7):777-783. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21142587.

63. Brogly SB, Foca M, Deville JG, et al. Potential confounding of the association between exposure to nucleoside analogues and mitochondrial dysfunction in HIV-uninfected and indeterminate infants. *J Acquir Immune Defic Syndr.* 2010;53(1):154-157. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20035168.

64. Olivero OA, Fernandez JJ, Antiochos BB, Wagner JL, St Claire ME, Poirier MC. Transplacental genotoxicity of combined antiretroviral nucleoside analogue therapy in Erythrocebus patas monkeys. *J Acquir Immune Defic Syndr.* 2002;29(4):323-329. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11917235.

65. Witt KL, Cunningham CK, Patterson KB, et al. Elevated frequencies of micronucleated erythrocytes in infants exposed to zidovudine *in utero* and postpartum to prevent mother-to-child transmission of HIV. *Environ Mol Mutagen.* 2007;48(3-4):322-329. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17358032.

66. Hleyhel M, Goujon S, Delteil C, et al. Risk of cancer in children exposed to didanosine *in utero*. *AIDS.* 2016;30(8):1245-1256. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26854809.

67. Hleyhel M, Goujon S, Sibiude J, et al. Risk of cancer in children exposed to antiretroviral nucleoside analogues *in utero*: The french experience. *Environ Mol Mutagen.* 2019;60(5):404-409. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29206312.

68. Ivy W, 3rd, Nesheim SR, Paul SM, et al. Cancer among children with perinatal exposure to HIV and antiretroviral medications—New Jersey, 1995–2010. *J Acquir Immune Defic Syndr.* 2015;70(1):62-66. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26017660.