

Zidovudine

Newborn use only

2020

Alert	Also known as azidothymidine (AZT). No Australian registered intravenous (IV) products are currently available. Retrovir IV ampoules are only available via the Special Access Scheme (SAS) in Australia.												
Indication	Monotherapy or part of a combination therapy for prevention of maternal-foetal HIV transmission.												
Action	Nucleoside analogue that inhibits HIV replication by interfering with viral reverse transcriptase.												
Drug type	Antiretroviral medication												
Trade name	Retrovir												
Presentation	Oral: syrup 10 mg/mL IV: 10 mg/mL in a 20mL single-use vial (SAS) Note: Retrovir is also available in oral capsules, however only the syrup is used in neonates.												
Dose	<p>Oral Start therapy within 4 hours of birth.</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="text-align: center;">Gestation at birth</th> <th style="text-align: center;">Dose</th> <th style="text-align: center;">Interval</th> </tr> </thead> <tbody> <tr> <td style="text-align: center;"><30 weeks</td> <td style="text-align: center;">2 mg/kg</td> <td style="text-align: center;">12 hourly</td> </tr> <tr> <td style="text-align: center;">30⁺-33⁺6 weeks</td> <td style="text-align: center;">2 mg/kg</td> <td style="text-align: center;">12 hourly for 2 weeks and then 8 hourly</td> </tr> <tr> <td style="text-align: center;">≥34 weeks</td> <td style="text-align: center;">4 mg/kg</td> <td style="text-align: center;">12 hourly*</td> </tr> </tbody> </table> <p>*Dose can be rounded up to the nearest 0.5 mg to assist administration.</p> <p>Intravenous (If neonates are unable to take oral zidovudine) ≥34 weeks gestation – 1.5 mg/kg/dose 6 hourly <34 weeks gestation – 1.5 mg/kg/dose 12 hourly, change to 6 hourly at 34 weeks gestation. Switch to oral once the neonate is tolerating oral feeds.</p> <p>Total duration IV and / or oral dosing</p> <ul style="list-style-type: none"> • Very low risk monotherapy – 2 weeks • Low risk monotherapy – 4 weeks • High risk / combination therapy – 4 weeks 	Gestation at birth	Dose	Interval	<30 weeks	2 mg/kg	12 hourly	30 ⁺ -33 ⁺ 6 weeks	2 mg/kg	12 hourly for 2 weeks and then 8 hourly	≥34 weeks	4 mg/kg	12 hourly*
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Dose adjustment	Therapeutic hypothermia: no information. ECMO: no information. Renal: see monitoring and interactions. Hepatic: see monitoring and adverse reactions.												
Maximum dose													
Total cumulative dose													
Route	PO and IV												
Preparation	Oral: Syrup IV: Dilute in 5% glucose before IV administration to a concentration not exceeding 4 mg/mL. [1] A dilution of 4 mg/mL may be prepared by adding 4 mL of the 10 mg/mL concentration to 6 mL of 5% glucose.												
Administration	PO: Can be given without regard to food. IV: Administer IV infusion over 30 minutes - 1 hour.												
Monitoring	At base line and with modification of therapy full blood count, blood sugar level, liver function, renal function tests, viral load, CD4 counts should be obtained. The panel should be repeated within 2-4 weeks of commencement of therapy and then every 3-4 months. [2-4]												
Contraindications	Life-threatening hypersensitivity reactions (e.g., anaphylaxis, Stevens-Johnson syndrome) to zidovudine or any components of the formulations. [5] Zidovudine infusions should not be given to patients with abnormally low neutrophils or haemoglobin levels. [5]												
Precautions	Zidovudine injection vial stopper contains rubber latex which could cause hypersensitivity reaction in latex-allergic patients. There have been reports of pancytopenia associated with the use of zidovudine, which was reversible in most instances after discontinuance of the drug.												

Drug interactions	<p>Stavudine - zidovudine should not be administered in combination with stavudine because of in vitro virologic antagonism.</p> <p>Coadministration of zidovudine with drugs that are nephrotoxic, cytotoxic, or which interfere with red blood cell and white blood cell number or function (e.g. ganciclovir, amphotericin B or interferon) may increase the risk of toxicity. If concomitant therapy with any of these drugs is necessary then extra care should be taken in monitoring renal function and haematological parameters.</p> <p>Ribavirin antagonizes in vitro antiviral activity of zidovudine and so concomitant use should be avoided.</p> <p>Doxorubicin - simultaneous use of doxorubicin and zidovudine should be avoided. Doxorubicin may inhibit the phosphorylation of zidovudine to its active form.</p> <p>Phenytoin - phenytoin blood levels have been reported to be low in some patients receiving zidovudine. Monitor phenytoin levels if neonate is receiving both medications. [5]</p> <p>Clarithromycin - oral clarithromycin reduces the absorption of zidovudine. This can be avoided by separating the doses by at least 2 hours. [5]</p>
Adverse reactions	<p>Anaemia and neutropenia are common. Transient lactic acidemia, vomiting, headache, insomnia, hepatomegaly with hepatic steatosis, lipodystrophy, lipoatrophy, myopathy, cardiomyopathy and myositis. [6, 7] In most cases the adverse events are mild and self-limiting. Prolonged use increases the risk of adverse events.</p>
Compatibility	<p>Fluids: glucose 5%, sodium chloride 0.9%</p> <p>Y site: aciclovir, amikacin, amphotericin B, aztreonam, cefepime, ceftazidime, ceftriaxone, cimetidine, clindamycin, dexamethasone, dobutamine, dopamine, erythromycin lactobionate, fluconazole, gentamicin, heparin, imipenem, linezolid, lorazepam, metoclopramide, morphine, nafcillin, oxacillin, piperacillin, piperacillin-tazobactam, potassium chloride, ranitidine, remifentanyl, rocuronium, tobramycin, trimethoprim-sulfamethoxazole, and vancomycin.</p> <p>Note: This is not an exhaustive list. Please refer to the relevant resources eg. Micromedex, Australian Injectable Drugs Handbook for detailed information.</p>
Incompatibility	<p>Fluids: no information</p> <p>Y site: lansoprazole, meropenem</p>
Stability	<p>Vial: store below 30°C</p> <p>After dilution, the drug solution is stable for 24 hours if stored below 25°C or in refrigerator. Protect from light. [5]</p>
Storage	<p>Oral syrup and any unused vials are to be stored at room temperature and protected from light. Any remaining unused infusion preparations should be discarded. [5]</p>
Excipients	<p>Retrovir Oral Syrup: Each 5 mL contains zidovudine 50 mg, and glycerol, citric acid, sodium benzoate, saccharin sodium, maltitol solution, Flavour Strawberry 500286E, Flavour White Sugar 3112044, and water-purified.</p> <p>Retrovir IV vials: hydrochloric acid, sodium hydroxide, water for injection.</p>
Special comments	<p>Dosage adjustment is required in renal and hepatic impairment. Fixed drug combinations should be avoided in infants with renal and hepatic insufficiency.</p>
Evidence	<p>Efficacy</p> <p>The risk of mother to child transmission of HIV can be significantly reduced by postnatal antiretroviral therapy in addition to antenatal management. [8] The Pediatric AIDS Clinical Trials Group Protocol 076 Study Group showed 67.5% reduction in the relative risk of perinatal HIV transmission by administering Zidovudine during antenatal, intrapartum period and to neonates for 6 weeks. [LOE II] [9] Petra et al reported significant reduction in perinatal HIV transmission (8.9 vs 14.2%) if ART prophylaxis was administered to neonates in addition to intrapartum maternal ART in a group of women who did not receive antenatal ART. [LOE II] [10] A retrospective analysis using data from the New York State Department of Health showed a transmission 9.3% if postnatal zidovudine prophylaxis was commenced within 48 hours compared with 26.6% in the absence of ZDV prophylaxis. [LOE III-1] [11] In a resource-rich setting with use of standard antenatal ART in mother, 4 weeks postnatal neonatal zidovudine prophylaxis was comparable to 6 weeks regimen. [LOE III-3] [12] In pregnant</p>

	<p>women who did not receive antenatal prophylaxis, two and three drug anti-retroviral regimens are more effective than Zidovudine alone in reducing risk of HIV transmission. [LOE II] [13]</p> <p>Safety Zidovudine is generally well tolerated in neonates including preterm infants. In a cohort of 112 neonates with mean GA 37 weeks, Smith et al reported anaemia in 39%, neutropenia in 39% and thrombocytopenia in 3% of the infants. Hyperbilirubinemia occurred in 42% and elevated ALT and AST in 3 and 1% infants respectively. [7] In a cohort of 76 preterm neonates (24-34 weeks) who received Zidovudine for 6 weeks, Capparelli reported that risk of severe anaemia requiring transfusion (45%) which is similar to rates in infants of similar gestation. The incidence of other haematological abnormalities was low (neutropenia 11%; thrombocytopenia 13%) and no death attributable to zidovudine was reported. [14] In a cohort of 374 HIV-exposed, uninfected infants, there was no association between in utero exposure to ARV regimens at any time during pregnancy and any Bayley-III outcome at 9-15 months. [15]</p> <p>Pharmacokinetics Metabolized primarily in the liver to zidovudine glucuronide and renally excreted. Boucher et al. studied the pharmacokinetics of ZDV in full-term infants during the first months of life and found reduced ZDV elimination in those younger than 14 days, with CL averaging 10.9 mL/min/kg and t_{1/2} averaging 3.12 hours. In full-term infants, ZDV elimination increases rapidly during the first weeks of life. [16] In 15 preterm neonates (GA 26-31 weeks), Mirochnick et al found lower ZDV clearance (2.5 ml/kg/min) and longer half-life (7 hours) compared to term infants. The clearance of ZDV increases and the half-life decreases with postnatal age. [17] Postnatal age was the best predictor of Zidovudine clearance with other factors being gestational at birth, and serum creatinine. Protein binding is approximately 25%. Zidovudine distributes into cells by passive diffusion and is relatively lipophilic. The CSF: plasma ratio was 0.24. The relationship between serum concentration and clinical efficacy is unclear. The oral syrup is well-absorbed, but only 65% bioavailable due to significant first-pass metabolism. The serum half-life in term newborns is 3 hours, declining to 2 hours after 2 weeks of age (half-life of intracellular zidovudine triphosphate in 9 hours). In preterm infants less than 33 weeks gestation, plasma half-life during the first two weeks of life ranges from 5 to 10 hours, decreasing to 2 to 6 hours afterward. [14, 17]</p>
<p>Practice points</p>	<p>Zidovudine is the recommended antiretroviral agent as either monotherapy or combination therapy for prevention of perinatal HIV transmission to neonates. The ANMF has adapted the 2018 British HIV Association guidelines for the management of HIV in pregnancy and postpartum 2018 and the categories used to determine the duration of therapy are defined as follows. [18, 19]</p> <p>Very low risk: 2 weeks of zidovudine monotherapy is recommended if (1) the woman has been on cART for longer than 10 weeks, AND (2) two documented maternal HIV viral loads <50 HIV RNA copies/mL during pregnancy at least 4 weeks apart, AND (3) Maternal HIV viral load <50 HIV RNA copies/mL at or after 36 weeks.</p> <p>Low risk: 4 weeks of zidovudine monotherapy if (1) the “very low risk criteria” are not all fulfilled but maternal HIV viral load is <50 HIV RNA copies/mL at or after 36 weeks, (2) if the infant is born prematurely (<34 weeks) but most recent maternal HIV viral load is <50 HIV RNA copies/mL.</p> <p>High risk: Combination therapy if maternal birth HIV viral load is known to be or likely to be >50 HIV RNA copies/mL on day of birth, if uncertainty about recent maternal adherence or if viral load is not known.</p>
<p>References</p>	<ol style="list-style-type: none"> 1. Murray KL, Wright D, Laxton B, Miller KM, Meyers J, Englebright J. Implementation of standardized pediatric i.v. medication concentrations. <i>Am J Health Syst Pharm.</i> 2014;71:1500-8. 2. AIDSinfo and Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children: Guidelines for the use of antiretroviral agents in Pediatric HIV infection.

	<p>AIDSinfo, Rockville, MD, Mar01, 2016. Available at: https://aidsinfo.nih.gov/contentfiles/lvguidelines/pediatricguidelines.pdf.</p> <ol style="list-style-type: none"> 3. Palasanthiran P, Starr M, Jones C, Giles M. Management of Perinatal Infections. Australian society for infectious diseases 2014. https://www.asid.net.au/documents/item/368 Downloaded 29/05/2020. 4. AIDS info: Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States. Accessed on 1st April 2019. Available at: https://aidsinfo.nih.gov/guidelines/html/3/perinatal-guidelines/0. 5. Product Information: RETROVIR(R) oral capsules, oral syrup, intravenous injection, zidovudine oral capsules, oral syrup, intravenous injection. Viv Healthcare (per FDA), Research Triangle Park, NC, Feb 2017. 6. Alimenti A, Burdge DR, Ogilvie GS, Money DM, Forbes JC. Lactic acidemia in human immunodeficiency virus-uninfected infants exposed to perinatal antiretroviral therapy. <i>Pediatr Infect Dis J</i>. 2003;22:782-9. 7. Smith C, Forster JE, Levin MJ, Davies J, Pappas J, Kinzie K, Barr E, Paul S, McFarland EJ, Weinberg A. Serious adverse events are uncommon with combination neonatal antiretroviral prophylaxis: a retrospective case review. <i>PLoS One</i>. 2015;10:e0127062. 8. Hurst SA, Appelgren KE, Kourtis AP. Prevention of mother-to-child transmission of HIV type 1: the role of neonatal and infant prophylaxis. <i>Expert Rev Anti Infect Ther</i>. 2015;13:169-81. 9. Connor EM, Sperling RS, Gelber R, Kiselev P, Scott G, O'Sullivan MJ, VanDyke R, Bey M, Shearer W, Jacobson RL, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. <i>N Engl J Med</i>. 1994;331:1173-80. 10. Petra Study T. Efficacy of three short-course regimens of zidovudine and lamivudine in preventing early and late transmission of HIV-1 from mother to child in Tanzania, South Africa, and Uganda (Petra study): a randomised, double-blind, placebo-controlled trial. <i>Lancet</i>. 2002;359:1178-86. 11. Wade NA, Birkhead GS, Warren BL, Charbonneau TT, French PT, Wang L, Baum JB, Tesoriero JM, Savicki R. Abbreviated regimens of zidovudine prophylaxis and perinatal transmission of the human immunodeficiency virus. <i>N Engl J Med</i>. 1998;339:1409-14. 12. Ferguson W, Goode M, Walsh A, Gavin P, Butler K. Evaluation of 4 weeks' neonatal antiretroviral prophylaxis as a component of a prevention of mother-to-child transmission program in a resource-rich setting. <i>Pediatr Infect Dis J</i>. 2011;30:408-12. 13. Nielsen-Saines K, Watts DH, Veloso VG, Bryson YJ, Joao EC, Pilotto JH, Gray G, Theron G, Santos B, Fonseca R, Kreitchmann R, Pinto J, Mussi-Pinhata MM, Ceriotta M, Machado D, Bethel J, Morgado MG, Dickover R, Camarca M, Mirochnick M, Siberry G, Grinsztejn B, Moreira RI, Bastos FI, Xu J, Moye J, Mofenson LM, Team NHPP. Three postpartum antiretroviral regimens to prevent intrapartum HIV infection. <i>N Engl J Med</i>. 2012;366:2368-79. 14. Capparelli EV, Mirochnick M, Dankner WM, Blanchard S, Mofenson L, McSherry GD, Gay H, Ciupak G, Smith B, Connor JD, Pediatric ACTGI. Pharmacokinetics and tolerance of zidovudine in preterm infants. <i>J Pediatr</i>. 2003;142:47-52. 15. Sirois PA, Huo Y, Williams PL, Malee K, Garvie PA, Kammerer B, Rich K, Van Dyke RB, Nozyce ML, Pediatric HCS. Safety of perinatal exposure to antiretroviral medications: developmental outcomes in infants. <i>Pediatr Infect Dis J</i>. 2013;32:648-55. 16. Boucher FD, Modlin JF, Weller S, Ruff A, Mirochnick M, Pelton S, Wilfert C, McKinney R, Jr., Crain MJ, Elkins MM, et al. Phase I evaluation of zidovudine administered to infants exposed at birth to the human immunodeficiency virus. <i>Journal of Pediatrics</i>. 1993;122:137-44. 17. Mirochnick M, Capparelli E, Dankner W, Sperling RS, van Dyke R, Spector SA. Zidovudine pharmacokinetics in premature infants exposed to human immunodeficiency virus. <i>Antimicrob Agents Chemother</i>. 1998;42:808-12.
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	<p>18. British HIV Association guidelines for the management of HIV in pregnancy and postpartum 2018 (2019 second interim update). https://www.bhiva.org/file/5bfd30be95deb/BHIVA-guidelines-for-the-management-of-HIV-in-pregnancy.pdf Accessed on 19 May 2020.</p> <p>19. Gilleece DY, Tariq DS, Bamford DA, Bhagani DS, Byrne DL, Clarke DE, Clayden MP, Lyall DH, Metcalfe DR, Palfreeman DA, Rubinstein DL, Sonecha MS, Thorley DL, Tookey DP, Tosswill MJ, Utting MD, Welch DS, Wright MA. British HIV Association guidelines for the management of HIV in pregnancy and postpartum 2018. HIV Med. 2019;20 Suppl 3:s2-s85.</p>
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VERSION/NUMBER	DATE
Original	29/05/2020
REVIEW (5 years)	29/05/2025

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