Zidovudine
Newborn use only

2020

<table>
<tr><td>Alert</td><td>No Australian registered intravenous products are available. Retrovir IV ampoules are only available via the Special Access Scheme (SAS) in Australia.
Also known as azidothymidine (AZT).</td></tr>
<tr><td>Indication</td><td>Monotherapy or part of a combination therapy for prevention of maternal-foetal HIV transmission.</td></tr>
<tr><td>Action</td><td>Nucleoside analogue that inhibits HIV replication by interfering with viral reverse transcriptase.</td></tr>
<tr><td>Drug type</td><td>Antiretroviral medication</td></tr>
<tr><td>Trade name</td><td>Retrovir</td></tr>
<tr><td>Presentation</td><td>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.</td></tr>
<tr><td>Dose</td><td>Oral
Start therapy within 4 hours of birth.
<table>
<tr><th>Gestation at birth</th><th>Dose</th><th>Interval</th></tr>
<tr><td><30 weeks</td><td>2 mg/kg</td><td>12 hourly</td></tr>
<tr><td>30^{+0}-33^{+6} weeks</td><td>2 mg/kg</td><td>12 hourly for 2 weeks and then 8 hourly</td></tr>
<tr><td>≥34 weeks</td><td>4 mg/kg</td><td>12 hourly*</td></tr>
</table>
*Dose can be rounded up to the nearest 0.5 mg to assist administration.

IV
If neonates are unable to take oral zidovudine
<table>
<tr><th>Gestation at birth</th><th>Dose</th><th>Interval</th></tr>
<tr><td>≤33^{+6} weeks gestation*</td><td>1.5 mg/kg/dose</td><td>12 hourly</td></tr>
<tr><td>≥34 weeks gestation</td><td>1.5 mg/kg/dose</td><td>6 hourly</td></tr>
</table>
∗ Change interval to 6 hourly at 34 weeks gestation.
Switch to oral once the neonate is tolerating oral feeds.

Total duration IV/oral dosing
• Very low risk monotherapy – 2 weeks
• Low risk monotherapy – 4 weeks
• High risk / combination therapy – 4 weeks</td></tr>
<tr><td>Dose adjustment</td><td>Therapeutic hypothermia: no information.
ECMO: no information.
Renal: see monitoring and interactions.
Hepatic: see monitoring and adverse reactions.</td></tr>
<tr><td>Maximum dose</td><td></td></tr>
<tr><td>Total cumulative dose</td><td></td></tr>
<tr><td>Route</td><td>Oral
IV</td></tr>
<tr><td>Preparation</td><td>Oral: Syrup
IV: Draw up 1mL (10mg of ziduvodine) and add 9mL of glucose 5% to make a final volume of 10mL with a final concentration of 1mg/mL. [1]</td></tr>
<tr><td>Administration</td><td>Oral: Can be given without food.
IV: infusion over 30 minutes - 1 hour.</td></tr>
<tr><td>Monitoring</td><td>Full blood count, blood sugar level, liver function, renal functions, 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]</td></tr>
<tr><td>Contraindications</td><td>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]</td></tr>
</table>

Precautions	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	Stavudine - zidovudine should not be administered in combination with stavudine because of in vitro virologic antagonism. Co-administration 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. Ribavirin antagonizes in vitro antiviral activity of zidovudine and so concomitant use should be avoided. Doxorubicin - simultaneous use of doxorubicin and zidovudine should be avoided. Doxorubicin may inhibit the phosphorylation of zidovudine to its active form. 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] Clarithromycin - oral clarithromycin reduces the absorption of zidovudine. This can be avoided by separating the doses by at least 2 hours. [5]
Adverse reactions	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.
Compatibility	Fluids: glucose 5%, sodium chloride 0.9% 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, remifentanil, rocuronium, tobramycin, trimethoprim-sulfamethoxazole, and vancomycin. Note: This is not an exhaustive list. Please refer to the relevant resources eg. Micromedex, Australian Injectable Drugs Handbook for detailed information.
Incompatibility	Fluids: no information Y site: lansoprazole, meropenem
Stability	Vial: store below 30°C After dilution, the drug solution is stable for 24 hours if stored below 25°C or in refrigerator. Protect from light. [5]
Storage	Oral syrup and any unused vials are to be stored at room temperature and protected from light. [5]
Excipients	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. Retrovir IV vials: hydrochloric acid, sodium hydroxide, water for injection.
Special comments	Dose adjustment is required in renal and hepatic impairment. Fixed drug combinations should be avoided in infants with renal and hepatic insufficiency.
Evidence	**Efficacy** 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 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] **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] **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 t1/2 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]
Practice points	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] **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. **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. **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.
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Authors Contribution

Original author/s	Nilkant Phad, Srinivas Bolisetty
Evidence Review	David Osborn
Expert review	Pamela Palasanthiran
Nursing Review	Eszter Jozsa, Kirsty Minter
Pharmacy Review	Carmen Burman, Cindy Chen, Michelle Jenkins
ANMF Group contributors	Himanshu Popat, Carmen Burman, Thao Tran, John Sinn, Emily Do, Wendy Huynh, Bhavesh Mehta
Final editing and review of the original	David Osborn, Michelle Jenkins, Srinivas Bolisetty
Electronic version	Ian Callander, Cindy Chen
Facilitator	Dr Srinivas Bolisetty