

Selected Properties of Zidovudine

Other names	Retrovir®, AZT, ZDV Combination formulations: <ul style="list-style-type: none"> • Combivir®: 3TC + zidovudine • Trizivir®: zidovudine + 3TC + abacavir;
Manufacturer	ViiV Healthcare Shire Canada
Pharmacology/Mechanism of Action	<ul style="list-style-type: none"> • Thymidine analogue, intracellular triphosphorylation to active form with preferential activity in active cells • Causes viral DNA chain termination via absence of 3'-hydroxyl group (replaced by azido group) to inhibit HIV reverse transcription • Competes with natural nucleoside substrate for binding to active site of reverse transcriptase • Inhibits cellular DNA polymerase β and γ to a minor extent
Activity	In vitro activity in laboratory and clinical isolates of HIV: IC ₅₀ and IC ₉₀ values of 0.003 to 0.013 and 0.03 to 0.13 mcg/mL, respectively (1 nM = 0.27 ng/mL). The IC ₅₀ and IC ₉₀ values of HIV isolates recovered from 18 untreated AIDS/ARC patients were in the range of 0.003 to 0.013 mcg/mL and 0.03 to 0.3 mcg/mL, respectively
Resistance - genotypic	<p>Mutations in the reverse transcriptase gene associated with resistance to reverse transcriptase inhibitors (IAS-USA Fall 2005 Resistance Mutations):</p> <ul style="list-style-type: none"> • M41L, E44D*, D67N, K70R, V118I*, L210W, T215Y/F, K219Q/E <p><i>*increased level of resistance to stavudine & zidovudine in the setting of TAMS</i></p> <ul style="list-style-type: none"> • <i>Presence of TAMS confers cross-resistance: M41L, D67N, K70R, L210W, T215Y/F, K219Q/E</i> • <i>69 Insertion Complex is associated with resistance to all approved NRTIs when present with ≥ 1 TAM at codons 41, 210 or 215.</i> • <i>Q151M complex (with A62V, V75I, F77L, F116Y) is associated with resistance to all approved NRTIs except for tenofovir.</i>
Resistance - phenotypic	<p>Phenotypic data on clinical virus isolates associated with various mutations using ViroLogic PhenoSense™ (http://hivdb.stanford.edu/):</p> <p><i>M41L/T215Y: 19-fold ↑ (high resistance)</i></p> <p><i>M41L/L210W/T215Y: 64-fold ↑ (high resistance)</i></p> <p><i>D67N +K70R +K219Q: 10-fold ↑ (high resistance)</i></p> <p><i>K70R: 4 fold ↑ (low resistance)</i></p> <p><i>M184V + TAMS: ↑ susceptibility to zidovudine</i></p> <p><i>T215Y: 10-fold ↑ (high resistance)</i></p>
Cross-Resistance	Potential for cross-resistance to other NRTIs depending upon what mutations develop.

Oral Bioavailability	65%; fatty meal delays rate (3x) and extent of absorption up to 50%
Effect of Food	Best on empty stomach. Can take with non-fatty meal to minimize nausea.
Protein Binding	<38 %
Vd	1.6+/- 0.6 L/kg
Tmax	0.5-1.5h (fasting)
Serum T_{1/2}	0.9-1.4h
Intracellular T_{1/2}	3-4h
Drug Concentrations	AUC 1,400 +/- 200 ng.hr/mL
CSF (% of serum)	60% (4-262%) 2010 CNS Penetration Effectiveness (CPE) Score: 4 [Letendre S et al. 2010]
Metabolism	first pass effect; glucuronidation to GZDV (GAZT) and AMT
Excretion	<ul style="list-style-type: none"> renal excretion of parent (14%) and glucuronide (75%) via tubular secretion renal clearance is 0.34 L/hr/kg parent clearance decreases to 18ml/min in uremia
Dosing – Adult	<p>po: 600 mg/day in 2-3 divided doses IV: 1-2mg/kg IV over 1hr q4h (1mg/kg IV q4h = 100mg po q4h) HIV dementia: 500-1200mg/d po ITP: 500-900mg/d, dose-related response Prevention of Vertical Transmission (based on ACTG076 protocol):</p> <ul style="list-style-type: none"> During pregnancy: 14-34 wks pregnancy, 100mg po 5x/day until start of labor (in clinical practice dose is 600 mg/day in 2-3 divided doses to increase compliance; in addition, at least 2 other antiretrovirals are prescribed). Intrapartum (maternal): 2mg/kg (actual body weight) IV over 1h followed by infusion of 1mg/kg/hr until clamping of umbilical cord. Postpartum (newborn): 2mg/kg po q6h beginning within 12h of birth, until 6 wks, or 1.5mg/kg IV over 30 min q6h <p>Post-Exposure Prophylaxis: For high risk exposure, 300mg po bid + 3TC 150mg bid +/- protease inhibitor x 4wks (see guidelines)</p> <p>Combination tablets Combivir®: 300 mg zidovudine/150 mg lamivudine po BID Trizivir®: zidovudine 300 mg/lamivudine 150 mg/abacavir 300 mg po BID</p>

<p>Dosing – Pediatric</p>	<p>Pediatric (4 weeks to <18 years of age):</p> <p>The recommended oral dosage in pediatric patients 4 weeks of age and older and weighing >4 kg is provided in Table 1. Zidovudine syrup should be used to provide accurate dosage when whole tablets or capsules are not appropriate.</p> <table border="1" data-bbox="669 380 1417 646"> <thead> <tr> <th colspan="4">Table 1: Recommended Pediatric Dosage of Retrovir</th> </tr> <tr> <th rowspan="2">Body Weight (KG)</th> <th rowspan="2">Total Daily Dose</th> <th colspan="2">Dose Regimen and Dose</th> </tr> <tr> <th>b.i.d.</th> <th>t.i.d.</th> </tr> </thead> <tbody> <tr> <td>4 to <9</td> <td>24 mg/kg/day</td> <td>12 mg/kg</td> <td>8 mg/kg</td> </tr> <tr> <td>≥9 to <30</td> <td>18 mg/kg/day</td> <td>9 mg/kg</td> <td>6 mg/kg</td> </tr> <tr> <td>≥30</td> <td>600 mg/day</td> <td>300 mg</td> <td>200 mg</td> </tr> </tbody> </table> <p>Alternatively, zidovudine dosing can be based on body surface area (BSA) for each child. The recommended oral dose of zidovudine is 480 mg/m²/day in divided doses (240 mg/m² twice daily or 160 mg/m² three times daily). In some cases the dose calculated by mg/kg will not be the same as that calculated by BSA.</p> <p>IV: 120 mg/m²/dose q6h or 20 mg/m²/hour</p> <p>Perinatal exposure/prevention: start dose within 8-12 hours after birth (if mother received full AZT regimen) OR start ≤6-12 hours after birth (if mother did not receive full AZT regimen) for 6 weeks as follows:</p> <p>Neonate/Infant dose (Term to 6 weeks old) (ACTG 076): Oral: 2 mg/kg/dose po q6h IV: 1.5 mg/kg/dose IV q6h</p> <p>Premature (< 35 weeks): 1.5 mg/kg/dose IV or 2 mg/kg/dose po q12h advancing to q 8 h intervals at 2 weeks of age if > 30 weeks gestation at birth, or at 4 weeks of age if < 30 weeks gestation at birth.</p>	Table 1: Recommended Pediatric Dosage of Retrovir				Body Weight (KG)	Total Daily Dose	Dose Regimen and Dose		b.i.d.	t.i.d.	4 to <9	24 mg/kg/day	12 mg/kg	8 mg/kg	≥9 to <30	18 mg/kg/day	9 mg/kg	6 mg/kg	≥30	600 mg/day	300 mg	200 mg
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<p>Special instructions for pediatric patients</p>	<ul style="list-style-type: none"> - manufacturer recommends 30 minutes before meals or 1 hour after, but OK to take with food - if ZDV upsets the stomach, take with food - may open capsule & give in small portion of food or 5-10 mL cool tap water - 10mg/mL syrup is also available 																						
<p>Adjust in Liver Dysfunction</p>	<p>60-400% ↑ AUC observed in patients with moderate-severe liver disease compared to normal volunteers; reduction in daily dose may be necessary.</p>																						

<p>Adjust in Renal Failure/ Dialysis</p> <p>^a CrCl (mL/min) for men: $\frac{(140 - \text{age}) (\text{wt}) \times 60}{(\text{Scr}) (50)}$</p> <p>*CrCl (mL/min) for women: as above multiplied by 0.85</p>	<p>- may require dose reduction or increased dosing interval to 100-200mg q8-12h in renal dysfunction, but unclear</p> <p>-peritoneal or hemodialysis: 100mg q6-8h po, or 1mg/kg q6-8h IV</p> <p>Hemodialysis: minimal effect on AZT elimination, enhances GAZT elimination significantly. Administer dose after dialysis session to avoid potential clinically significant removal of metabolite.</p>
<p>Toxicity</p>	<p>Transient headache and insomnia, malaise (53%), nausea (50%), anorexia (20%), vomiting (17%), macrocytosis (90%) unresponsive to B12, anemia: Hgb <80 (1%) may be responsive to erythropoietin if low baseline endogenous erythropoietin; neutropenia: ANC < 0.5 (1.8%), myopathy (10%) related to cumulative dose and ↑ CK, myositis, nail pigmentation (40%).</p> <p>Rare: thrombocytopenia, hepatotoxicity, cardiomyopathy; Mitochondrial toxicity: lactic acidosis ± severe hepatomegaly with steatosis ± pancreatitis, including fatalities. Some patients develop ventilator-dependent respiratory failure. D/C all antiretrovirals; partial or complete recovery may take months.</p>
<p>Pregnancy & Lactation</p>	<p>Pregnancy risk category C. ~ 85% placental transfer. No evidence of human teratogenicity. No fetal malformations in animal studies, but embryotoxic to mouse embryo. Well-tolerated, short-term safety demonstrated for mother and infant. Use regular adult dosing during pregnancy. Preferred NRTI as part of HAART regimen in pregnancy. Avoid use if toxicity found or d4T is used.</p> <p>Unknown whether AZT excreted into human breast milk, however it is secreted into the milk of lactating mice; avoid breast-feeding to avoid postnatal HIV transmission</p> <p>Glaxo-Wellcome registry to follow prenatal exposure to antiretrovirals:1-800-387-7374</p>
<p>Drug Interactions</p>	<p>Potential for additive/synergistic toxicity when co-administered with:</p> <p>bone marrow toxins: Septra, amphi B, dapsone, flucytosine, pentamidine (CBC weekly, may hold AZT during acute PCP tx with Septra);</p> <p>- neutropenia with ganciclovir (hold AZT during induction, restart with caution); sulfadiazine/ pyrimethamine can ↑ anemia, ↓ AZT clearance, AZT may ↓ pyrimethamine effect vs toxo (may hold AZT during toxo tx, or switch antiviral)</p> <p>D4T inhibits AZT intracellular phosphorylation in vitro, both thymidine analogues thus avoid combination</p> <p>Probenecid ↑s AZT 80%, monitor closely or avoid combo</p> <p>See separate drug interaction chart.</p>
<p>Baseline Assessment</p>	<p>CBC/diff (incl MCV), CK, electrolytes, anion gap, serum bicarbonate, LFTs</p>

Routine Labs	<p>CBC/diff monthly, CK/LFTs, electrolytes, anion gap, serum bicarbonate q3-6mos</p> <p>Measure serum lactate if low serum bicarbonate or high anion gap and Sx of lactic acidosis. Prodromal Sx include: nausea, anorexia, abdominal pain, vomiting, weight loss, fatigue. Rapidly progressive Sx: tachycardia, tachypnea, hyperventilation, dyspnea, muscular weakness, jaundice, mental status changes. May also progress to multi-organ failure (hepatic, pancreatitis, encephalopathy, respiratory) and death.</p> <p>D/C drug: Sx of lactic acidosis, serum lactate > 5 mmol/L; sx of myopathy (4-8wk to resolve), Hgb <80 or persistent sx, ANC < 0.5, LFTs ↑ >4-5x ULN</p>
Dosage Forms	<p>Capsule: 100mg (white & blue); DIN 01902660</p> <p>Syrup: 50mg/5mL (240mL bottle), strawberry flavour; DIN 01902652</p> <p>IV: 200mg/20mL vial</p> <p>Combination tablets</p> <p>Combivir®: 300 mg zidovudine/150 mg lamivudine tablet; DIN 02239213</p> <p>Trizivir®: zidovudine 300 mg/lamivudine 150 mg/abacavir 300 mg tablet; DIN 02244757.</p>
Storage	Store all dosage forms at room temperature.

References:

GlaxoSmithKline Inc. Retrovir Product monograph. Mississauga, Ont.: December 10th, 2007.

Letendre S, Ellis RJ, Deutsch R, Clifford DB, Collier AC, Gelman GG, et al. Correlates of time-to-loss-of-viral-response in CSF and plasma in the CHARTER Cohort: CPE score predicts CSF suppression [abstract 430]. 17th Conference on Retroviruses and Opportunistic Infections, San Francisco, CA, February 16-19, 2010.