Selected Properties of Zidovudine

Other names	Retrovir®, AZT, ZDV Generic: Apo-Zidovudine (Apotex), Novo-AZT (Novopharm) Combination formulations: • **Combivir**®: lamivudine + zidovudine • **Generic**: Apo-Lamivudine-Zidovudine • **Trizivir®:** zidovudine + lamivudine + abacavir
Manufacturer	ViiV Healthcare ULC
Pharmacology/Mechanism of Action	• 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 b and g to a minor extent
Activity	In vitro activity in laboratory and clinical isolates of HIV: IC50 and IC90 values of 0.003 to 0.013 and 0.03 to 0.13 mcg/mL, respectively (1 nM = 0.27 ng/mL). The IC50 and IC90 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	Mutations in the reverse transcriptase gene associated with resistance to reverse transcriptase inhibitors (IAS-USA Fall 2005 Resistance Mutations): • M41L, *E44D**, D67N, K70R, *V118I*,* L210W, T215Y/F, K219Q/E **increased level of resistance to stavudine & zidovudine in the setting of TAMS* • *Presence of TAMS confers cross-resistance: M41L, D67N, K70R, L210W, T215Y/F, K219Q/E* • *69 Insertion Complex is associated with resistance to all approved NRTIs when present with ≥1 TAM at codons 41, 210 or 215.* • *Q151M complex (with A62V, V75I, F77L, F116Y) is associated with resistance to all approved NRTIs except for tenofovir.*
Resistance - phenotypic	Phenotypic data on clinical virus isolates associated with various mutations using ViroLogic PhenoSense™ (http://hivdb.stanford.edu/): *M41L/T215Y: 19-fold ↑ (high resistance)* *M41L/210W/T215Y: 64-fold ↑ (high resistance)* *D67N +K70R +K219Q: 10-fold ↑ (high resistance)* *K70R: 4 fold ↑ (low resistance)* *M184V + TAMS: ↑ susceptibility to zidovudine* *T215Y: 10-fold ↑ (high resistance)*

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 ½	0.9-1.4h
Intracellular T½	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	• 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	**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)**:** • <u>During pregnancy:</u> 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). • <u>Intrapartum (maternal):</u> 2mg/kg (actual body weight) IV over 1h followed by infusion of 1mg/kg/hr until clamping of umbilical cord. • <u>Postpartum (newborn):</u> 2mg/kg po q6h beginning within 12h of birth, until 6 wks, or 1.5mg/kg IV over 30 min q6h; see Pediatric Dosing for more detailed information ***NB: Note: more current dosing strategies for prevention of vertical transmission are available (see DHHS Perinatal Guidelines)** **Post-Exposure Prophylaxis:** For high risk exposure, 300mg po bid + 3TC 150mg bid +/- protease inhibitor x 4wks (see current DHHS guidelines) **Combination tablets** **Combivir®:** 300 mg zidovudine/150 mg lamivudine po BID **Trizivir®:** zidovudine 300 mg/lamivudine150 mg/abacavir 300 mg po BID

Dosing – Pediatric	<u>Neonate/infant (< 6 weeks of age) dose for prevention of transmission or treatment:</u> • For prevention of transmission, start ZDV immediately (preferably within 2 to 6 hours but no longer than 6 - 12 hours after birth) and administer for 6 weeks.[3] • *Less than 30 weeks gestation*: – PO: 2 mg/kg/dose po q12h for 4 weeks, then increase to 3 mg/kg/dose q12h for last 2 weeks – IV: 1.5 mg/kg/dose IV q12h for 4 weeks, then increase to 2.3 mg/kg/dose q12h for last 2 weeks • *≥ 30 to < 35 weeks gestation:* – PO: 2 mg/kg/dose po q12h for 2 weeks, then increase to 3 mg/kg/dose q12h for last 4 weeks – IV: 1.5 mg/kg/dose q12h for 2 weeks, then increase to 2.3 mg/kg/dose q12h for last 4 weeks • *≥ 35 weeks gestation:* – PO: 4 mg/kg/dose po q12h – IV: 3 mg/kg/dose IV q12h <u>Pediatric treatment dose (6 weeks to < 18 years):</u> • PO: 240 mg/m^2/dose po q12h <u>or:</u> • MG/KG DOSING: (6 WEEKS OF AGE AND OLDER) – 4 kg to < 9 kg: 12 mg/kg/dose po BID – 9 kg to < 30 kg: 9 mg/kg/dose po BID – ≥ 30 kg: 300 mg po BID <u>Adult/Adolescent (18 years or older):</u> 300 mg po BID
Special instructions for pediatric patients	Should not be administered with d4T due to poor antiretroviral effect. May open capsule and give in small portion of food or 5 – 10 mL cool tap water. COMBIVIR®: Film-coated immediate release tablet however no studies, but likely acceptable to crush immediately before ingestion. May have a bitter aftertaste. TRIZIVIR®: Film coated immediate release tablet however no studies regarding stability of split or crushed tablets.
Adjust in Liver Dysfunction	60-400% ↑ AUC observed in patients with moderate-severe liver disease compared to normal volunteers; reduction in daily dose may be necessary.
Adjust in Renal Failure/ Dialysis [a] CrCl (mL/min) for men: <u>(140 - age) (wt) x 60</u> (Scr) (50) *CrCl (mL/min) for women: as above multiplied by 0.85	- may require dose reduction or increased dosing interval to 100-200mg q8-12h in renal dysfunction, but unclear -peritoneal or hemodialysis: 100mg q6-8h po, or 1mg/kg q6-8h IV Hemodialysis: minimal effect on AZT elimination, enhances GAZT elimination significantly. Administer dose after dialysis session to avoid potential clinically significant removal of metabolite.

Toxicity	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 erythropoetin; neutropenia: ANC< 0.5 (1.8%), myopathy (10%) related to cumulative dose and ↑ CK, myositis, nail pigmentation (40%). Rare: thrombocytopenia, hepatotoxicity, cardiomyopathy; Mitochodrial 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.
Pregnancy & Lactation	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. 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 Glaxo-Wellcome registry to follow prenatal exposure to antiretrovirals:1-800-387-7374
Drug Interactions	Potential for additive/synergistic toxicity when co-administered with: **bone marrow toxins:** Septra, ampho B, dapsone, flucytosine, pentamidine (CBC weekly, may hold AZT during acute PCP tx with Septra); - 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) **D4T** inhibits AZT intracellular phosphorylation in vitro, both thymidine analogues thus avoid combination **Probenecid** ↑ AZT 80%, monitor closely or avoid combo See separate drug interaction chart.
Baseline Assessment	CBC/diff (incl MCV), CK, electrolytes, anion gap, serum bicarbonate, LFTs
Routine Labs	CBC/diff q 3 months, CK/LFTs, electrolytes, anion gap, serum bicarbonate q3-6mos 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. **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

Dosage Forms	**Retrovir®:** • **Capsule:** 100mg (white & blue); DIN 01902660 • **Syrup:** 50mg/5mL (240mL bottle), strawberry flavour; DIN 01902652 • **IV:** 200mg/20mL vial **Combination tablets** • **Combivir®:** 300 mg zidovudine/150 mg lamivudine tablet; DIN 02239213 • **Apo-Lamivudine-Zidovudine®**: 150/300 mg tablet, DIN 02375540 • **Trizivir®:** zidovudine 300 mg/lamivudine150 mg/abacavir 300 mg tablet; DIN 02244757. **Generic:** • Apo-Zidovudine® (Apotex) 100 mg capsule; DIN 01946323 • Novo-AZT® (Novopharm) 100 mg capsule; DIN 01953877
Storage	Store all dosage forms at room temperature.

References:

ViiV Healthcare ULC. Retrovir Product monograph. Montreal, QC, February 16th, 2010.

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.

