Selected Properties of Stavudine

Other names	d4T, Zerit®, Zerit XR® (in US only)
Manufacturer	Bristol-Myers Squibb Canada
Pharmacology/Mechanism of Action	• thymidine analogue, intracellular triphosphorylation to active form with preferential activity in active cell • competes with natural nucleoside substrate for binding to active site of reverse transcriptase • causes viral DNA chain termination via absence of 3'-hydroxyl group to inhibit HIV reverse transcription inhibits cellular DNA polymerase beta and gamma and reduces the synthesis of mitochondrial DNA
Activity	The concentration of drug necessary to inhibit HIV-1 replication by 50% (IC50) ranged from 0.009 to 4 µM against laboratory and clinical isolates of HIV-1.
Resistance - genotypic	Mutations in the reverse transcriptase gene associated with resistance to reverse transcriptase inhibitors (IAS-USA Fall 2005 Resistance Mutations): • M41L, *E44D*,* K65R, 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: 1.6-fold ↑ (intermediate resistance) M41L/210W/T215Y: 2.6-fold ↑ (intermediate resistance) D67N +K70R +K219Q: 1.5-fold ↑ (intermediate resistance) K70R: 1.1 fold ↑ (low resistance) M184V + TAMS: ↑ susceptibility to stavudine T215Y: 1.5 fold ↑ (intermediate resistance)
Cross-Resistance	Potential cross-resistance to ddI, ddC, (?AZT)
Oral Bioavailability	86.4 ± 18.2 (adults), 76.9 ± 31.7% (pediatrics)
Effect of Food	Can take with or without food. Food delays rate but not extent of absorption.
Protein Binding	negligible
Vd	46 ± 21 L
Tmax	0.5-0.7h

<table>
<tr><td>Serum T ½</td><td>1-2.5h</td></tr>
<tr><td>Intracellular T½</td><td>3.5h</td></tr>
<tr><td>Drug Concentrations</td><td>With 40 mg BID dosing (n=8 adults):
AUC 2568 ± 454 ng.h/mL
Cmax 536 ± 146 ng/mL
Cmin 8 ± 9 ng/mL</td></tr>
<tr><td>CSF (% of serum)</td><td>59 +/-35% (in pediatric patients)
2010 CNS Penetration Effectiveness (CPE) Score: 2
[Letendre S et al. 2010]</td></tr>
<tr><td>Metabolism</td><td>not metabolized</td></tr>
<tr><td>Excretion</td><td>Renal clearance is approximately 40% of total clearance. Renal clearance includes active tubular secretion as well as glomerular filtration; remaining 60% of drug eliminated by endogenous pathways.

Clearance decreases with renal impairment.</td></tr>
<tr><td>Dosing – Adult</td><td>Regular capsules:
≥60kg: 40mg po bid
<60kg: 30mg po bid

Zerit XR®:
≥60kg: 100 mg po once daily
<60kg: 75 mg po once daily</td></tr>
<tr><td>Dosing – Pediatric</td><td>Birth to 13 days old: 0.5 mg/kg/dose q12h
Pediatric (at least 14 days old): 1mg/kg/dose q12h (up to weight of 30 kg).
Pediatric patients weighing 30 kg or greater should receive the recommended adult dosage.</td></tr>
<tr><td>Special instructions for pediatric patients</td><td>If d4T upsets the stomach, take with food. May open capsule & give in small portion of food or 5-10 mL cool tap water.
1 mg/mL fruit-flavoured suspension available via SAP (613-941-2108). Shake well, refrigerate, 30 day expiry.</td></tr>
<tr><td>Adjust in Liver Dysfunction</td><td>No adjustment in hepatic impairment; single-dose stavudine kinetics not different in patients with cirrhosis (Child-Pugh classification B or C).</td></tr>
<tr><td>Adjust in Renal Failure/ Dialysis
[a] CrCl (mL/min) for men:
(140 - age) (wt) x 60
(Scr) (50)

*CrCl (mL/min) for women:
as above multiplied by 0.85</td><td>Stavudine terminal half life increases as creatinine clearance decreases. Reduce dose based on CrCl[a] and body weight (BW):

Regular capsules:
<table>
<tr><th rowspan="2">Creatinine Clearance (mL/min)</th><th colspan="2">Recommended ZERIT Dose by Patient Weight</th></tr>
<tr><th>≥ 60 kg</th><th>< 60 kg</th></tr>
<tr><td>> 50 *</td><td>40 mg every 12 hours*</td><td>30 mg every 12 hours *</td></tr>
<tr><td>26 - 50</td><td>20 mg every 12 hours</td><td>15 mg every 12 hours</td></tr>
<tr><td><25 †</td><td>20 mg every 24 hours</td><td>15 mg every 24 hours</td></tr>
</table>
* Normal dose, no adjustment necessary.</td></tr>
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<table>
<tr><td></td><td>Extended release capsules (Zerit XR®):
<table>
<tr><th rowspan="2">Creatinine Clearance (mL/min)</th><th colspan="2">Recommended ZERIT XR Dose by Patient Weight</th></tr>
<tr><th>≥60 kg</th><th><60 kg</th></tr>
<tr><td>>50</td><td>100 mg once daily</td><td>75 mg once daily</td></tr>
<tr><td>26–50</td><td>50 mg once daily</td><td>37.5 mg once daily</td></tr>
<tr><td>10–25</td><td>50 mg every 48 hours</td><td>37.5 mg every 48 hours</td></tr>
<tr><td>Hemodialysis patients*</td><td>50 mg every 48 hours</td><td>37.5 mg every 48 hours</td></tr>
</table>
<u>Hemodialysis:</u>
The mean ± SD hemodialysis clearance value of stavudine was 120 ± 18 mL/min (n=12); the mean ± SD percentage of the stavudine dose recovered in the dialysate, was 31 ± 5%.
• Regular capsules: Reduce stavudine dose to 20 mg every 24 hours (≥60 kg) or 15 mg every 24 hours (<60 kg), administered after the completion of hemodialysis and at the same time of day on non-dialysis days.
• Extended-release capsules (Zerit XR®): 50 mg every 48 hours (≥60 kg) or 37.5 mg every 48 hours (<60 kg), administered after the completion of hemodialysis and at the same time of day on nondialysis days.</td></tr>
<tr><td>Toxicity</td><td>• diarrhea, abdominal pain, nausea, vomiting, headache, rash, increased LFTs
• peripheral neuropathy related to cumulative dose (52%)
• hypertriglyceridemia (mainly, but may also increase LDL and total cholesterol)

• pancreatitis when used with ddI (use with caution or avoid use in alcoholics, hx of pancreatitis; avoid with ddI, ddC, and other pancreatoxins)

• Mitochondrial toxicity: lactic acidosis ± severe hepatomegaly with steatosis ± pancreatitis, including fatalities. May also have rapidly progressing ascending neuromuscular weakness that may mimic Guillain-Barré Syndrome; some patients develop ventilator-dependent respiratory failure. D/C all AVRs; partial or complete recovery may take months.

• Lipoatrophy- peripheral fat loss (thinning face, arms, legs and buttocks)</td></tr>
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Pregnancy & Lactation	Pregnancy risk category C. ~76% placental transfer. No evidence of teratogenicity, Use standard adult dose. Cases of fatal lactic acidosis have been reported in pregnancy women on ddI with d4T- avoid combination. Use d4T only as alternate agent. Avoid use with zidovudine due to potential antagonism. - d4T is secreted into breast milk of lactating rats.
Drug Interactions	**Potential for additive/synergistic toxicity when coadministered with neurotoxins or pancreatoxins.** **AZT** intracellular phosphorylation inhibited in vitro by D4T (both thymidine analogues) thus avoid combination See separate Drug Interaction chart.
Baseline Assessment	CBC/diff, electrolytes, anion gap, serum bicarbonate, amylase, cholesterol profile, LFTs, neurological status
Routine Labs	CBC/diff, electrolytes, anion gap, serum bicarbonate, amylase/lipase, LFTs q3-6mos. Cholesterol profile at 3-6 months, then annually. Monitor for evidence of lipoatrophy. 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, amylase >200 (asymptomatic), pancreatitis, LFTs >5xULN, ANC< 0.5, painful neuropathy
Dosage Forms	**Capsules:** 15 mg, DIN 02216086 20 mg, DIN 02216094 30 mg, DIN 02216108 40 mg (beige), DIN 02216116 **Zerit XR® sustained release capsules:** 37.5 mg, DIN 02247912 50 mg, DIN 02247913 75 mg, DIN 02247914 100 mg, DIN 02247915 **Oral solution**: 1 mg/mL fruit-flavoured solution (200 mL bottle); stable for 30 days in fridge. Shake well.
Storage	Refrigerate oral suspension; capsules stable at room temperature.

References:

Bristol-Myers Squibb Canada. Zerit® Product monograph. Montreal, QC. August 5th, 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.

