

STAVUDINE CAPSULES, USP

30 mg and 40 mg

R only

(Patient Information Leaflet Included)

WARNING: LACTIC ACIDOSIS and SEVERE HEPATOMEGALY with STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGUES ALONE or in COMBINATION, INCLUDING STAVUDINE and OTHER ANTIRETROVIRALS. FATAL LACTIC ACIDOSIS HAS BEEN REPORTED in PREGNANT WOMEN who RECEIVED the COMBINATION of STAVUDINE and DIDANOSINE with OTHER ANTIRETROVIRAL AGENTS. THE COMBINATION of STAVUDINE and DIDANOSINE SHOULD be USED with CAUTION DURING PREGNANCY and IS RECOMMENDED ONLY if the POTENTIAL BENEFIT CLEARLY OUTWEIGHS the POTENTIAL RISK (SEE WARNINGS and PRECAUTIONS: PREGNANCY). FATAL and NONFATAL PANCREATITIS HAVE OCCURRED DURING THERAPY when STAVUDINE WAS PART of a COMBINATION REGIMEN that IN-CLUDED DIDANOSINE, WITH or WITHOUT HYDROXYUREA, in BOTH TREATMENT-NAIVE and TREATMENT-EXPERIENCED PATIENTS, REGARDLESS of DEGREE of IMMUNOSUPPRESSION (SEE WARNINGS).

DESCRIPTION: Stavudine (d4T), a synthetic thymidine nucleoside analogue, active against the human immunodeficiency virus (HIV).

Stavudine Capsules, USP are supplied for oral administration in strengths of 30 mg and 40 mg of stavudine. Each capsule also contains inactive ingredients microcrystalline cellulose, sodium starch glycolate, lactose anhydrous, and magnesium stearate. The hard gelatin shell consists of D&C Yellow No.10, FD&C Yellow No.6, gelatin and titanium dioxide. The capsules are printed with edible inks containing black iron oxide (E172).



Stavudine is a white to off-white crystalline solid with the molecular formula C₁₀H₁₁N₃O₄ and a molecular weight of 224.21. The solubility of stavudine at 23°C is approximately 83 mg/mL in water and 30 mg/mL in propylene glycol. The n-octanol/water partition coefficient of stavudine at 23°C is 0.144.

MICROBIOLOGY: Mechanism of Action: Stavudine, a nucleoside analogue of thymidine, is phosphorylated by cellular kinases to the active metabolite stavudine triphosphate. Stavudine triphosphate inhibits the activity of HIV-1 reverse transcriptase (RT) by competing with the natural substrate thymidine triphosphate (K_i = 0.0083 to 0.032 μM) and by causing DNA chain termination following its incorporation into viral DNA. Stavudine triphosphate inhibits cellular DNA polymerases β and γ and markedly reduces the synthesis of mitochondrial DNA.

Antiviral Activity: The cell culture antiviral activity of stavudine was measured in peripheral blood mononuclear cells, monocytic cells, and lymphoblastoid cell lines. The concentration of drug necessary to inhibit HIV-1 replication by 50% (EC50) ranged from 0.009 to 4 μm against laboratory and clinical isolates of HIV-1. In cell culture, stavudine exhibited additive to antagonistic activity in combination with zidovudine. Stavudine in combination with either abacavir, didanosine, tenofovir, or zalcitabine exhibited additive to synergistic anti-HIV-1 activity. Ribavirin, at the 9 to 45 μm concentrations tested, reduced the anti-HIV-1 activity of stavudine by 2.5 to 5 fold. The relationship between cell culture susceptibility of HIV-1 to stavudine and the inhibition of HIV-1 replication in humans has not been established.

Drug Resistance: HIV-1 isolates with reduced susceptibility to stavudine have been selected *in vitro* (strain-specific) and were also obtained from patients treated with stavudine. Phenotypic analysis of HIV-1 isolates from 61 patients receiving prolonged (6 to 29 months) stavudine monotherapy showed that post-treatment isolates from four patients exhibited EC₅₀ values more than 4-fold (range 7- to 16-fold) higher than the average pretreatment susceptibility of baseline isolates. Of these, HIV-1 isolates from one patient contained the zidovudine-resistance-associated mutations T215Y and K219E, and isolates from another patient contained the multiple-nucleoside-resistance-associated mutation Q151M. Mutations in the RT gene of HIV-1 isolates from the other two patients were not detected. The genetic basis for stavudine susceptibility changes has not been identified.

Cross-resistance: Cross-resistance among HIV-1 reverse transcriptase inhibitors has been observed. Several studies have demonstrated that prolonged stavudine treatment can select and/or maintain mutations associated with zidovudine resistance. HIV-1 isolates with one or more zidovudine-resistance-associated mutations (M41L, D67N, K70R, L210W, T215Y/F, K219Q/E) exhibited reduced susceptibility to stavudine in cell culture.

CLINICAL PHARMACOLOGY: Pharmacokinetics: The pharmacokinetics of stavudine have been evaluated in HIV-infected adult and pediatric patients (Tables 1 to 3). Peak plasma concentrations (C_{max}) and area under the plasma concentration-time curve (AUC) increased in proportion to dose after both single and multiple doses ranging from 0.03 to 4 mg/kg. There was no significant accumulation of stavudine with repeated administration every 6, 8, or 12 hours.

Absorption:Following oral administration, stavudine is rapidly absorbed, with peak plasma concentrations occurring within 1 hour after dosing. The systemic exposure to stavudine is the same following administration as capsules or solution. Steady-state pharmacokinetic parameters of stavudine in HIV-infected adults are shown in Table 1.

Parameter	Stavudine 40 mg BID Mean ± SD (n = 8)
AUC (ng•h/mL) ^a	2568 ± 454
C _{max} (ng/mL)	536 ± 146
C _{min} (ng/mL)	8 ± 9
^a from 0 to 24 hours AUC = area under the curve over 24 hours C _{max} = maximum plasma concentration C _{min} = trough or minimum plasma concentration	

Distribution: Binding of stavudine to serum proteins was negligible over the concentration range of 0.01 to 11.4 mcg/mL. Stavudine distributes equally between red blood cells and plasma. Volume of distribution is shown in Table 2.

Metabolism: The metabolism of stavudine has not been elucidated in humans.

Elimination: In humans, renal elimination accounts for about 40% of the overall clearance regardless of the route of administration (Table 2). The mean renal clearance was about twice the average endogenous creatinine clearance, indicating active tubular secretion in addition to glomerular filtration. The remaining 60% of the drug is presumably eliminated by endogenous pathways.

Parameter	Mean ± SD	n
Oral bioavailability (%)	86.4 ± 18.2	25
Volume of distribution (L) ^a	46 ± 21	44
Total body clearance (mL/min) ^a	594 ± 164	44
Apparent oral clearance (mL/min) ^b	560 ± 182 ^c	113
Renal clearance (mL/min) ^a	237 ± 98	39
Elimination half-life, IV dose (h) ^a	1.15 ± 0.35	44
Elimination half-life, oral dose (h) ^b	1.6 ± 0.23	8
Urinary recovery of Stavudine (% of dose) ^{a,d}	42 ± 14	39
^a following 1-hour IV infusion ^b following single oral dose ^c assuming a body weight of 70 kg ^d over 12 to 24 hours		

Special Populations: Pediatric: For pharmacokinetic properties of stavudine in pediatric patients, see Table 3.

Parameter	Ages 5 weeks to 15 years	n	Ages 14 to 28 days	n	Day of Birth	n
Oral bioavailability (%)	76.9 ± 31.7	20	ND		ND	
Volume of distribution (L/kg) ^a	0.73 ± 0.32	21	ND		ND	
Ratio of CSF-plasma concentrations (as %) ^b	59 ± 35	8	ND		ND	
Total body clearance (mL/min/kg) ^a	9.75 ± 3.76	21	ND		ND	
Apparent oral clearance (mL/min/kg) ^c	13.75 ± 4.29	20	11.52 ± 5.93	30	5.08 ± 2.80	17
Elimination half-life, IV dose (h) ^a	1.11 ± 0.28	21	ND		ND	
Elimination half-life, oral dose (h) ^c	0.96 ± 0.26	20	1.59 ± 0.29	30	5.27 ± 2.01	17
Urinary recovery of Stavudine (% of dose) ^{a,d}	34 ± 16	19	ND		ND	
^a following 1-hour IV infusion. ^b at median time of 2.5 hours (range 2 to 3 hours) following multiple oral doses. ^c following single oral dose. ^d over 8 hours. ND = not determined.						

PATIENT INFORMATION

STAVUDINE CAPSULES, USP

(stavudine, also known as d4T)

R only

What is Stavudine?

Stavudine is a prescription medicine used in combination with other drugs to treat adults and children who are infected with HIV (the human immunodeficiency virus), the virus that causes AIDS. Stavudine belongs to a class of drugs called nucleoside reverse transcriptase inhibitors (NRTIs). By reducing the growth of HIV, stavudine helps your body maintain its supply of CD4 cells, which are important for fighting HIV and other infections.

Stavudine will not cure your HIV infection. At present there is no cure for HIV infection. Even while taking stavudine you may continue to have HIV-related illnesses, including infections caused by other disease-producing organisms. Continue to see your doctor regularly and report any medical problems that occur.

Stavudine does not prevent a person infected with HIV from passing the virus to other people. To protect others, you must continue to practice safe sex and take precautions to prevent others from coming in contact with your blood and other body fluids.

There is limited information on the long-term use of stavudine.

Who should not take stavudine?

Do not take stavudine if you are allergic to any of its ingredients, including its active ingredient, stavudine, and the inactive ingredients. (See **Inactive Ingredients** at the end of this leaflet.) Tell your doctor if you think you have had an allergic reaction to any of these ingredients.

How should I take stavudine?

How should I store it?

Your doctor will determine your dose (the amount in each capsule) based on your body weight, kidney and liver function, and any side effects that you may have had with other medicines. Take stavudine exactly as instructed. Try not to miss a dose, but if you do, take it as soon as possible. If it is almost time for the next dose, skip the missed dose and continue your regular dosing schedule. Stavudine may be taken with food or an empty stomach.

- Stavudine capsules are usually taken twice a day (every 12 hours). Store stavudine capsules in a tightly closed container at room temperature away from heat and out of the reach of children and pets. Do NOT store this medicine in a damp place such as a bathroom medicine cabinet or near the kitchen sink.

If you have a kidney problem: If your kidneys are not working properly, your doctor may monitor your kidney function while you take stavudine. Also, your dosage of stavudine may be adjusted.

What should I do if someone takes an overdose of stavudine?

If you suspect that you or someone else has taken an overdose of stavudine, get medical help right away. Contact a doctor or a poison control center.

What important information should I know about taking stavudine with other medicines?

- Do not take zidovudine (AZT) while taking stavudine, because AZT may interfere with the actions of stavudine. Products containing AZT include Combivir®, Retrovir®, and Trizivir®.
- If you are taking ribavirin or interferon, your doctor may need to monitor your therapy more closely or may consider a change in your therapy.
- Tell your doctor or pharmacist about any other medicine, vitamin, supplement, or herbal preparation you are taking.

What about pregnancy and nursing (breast-feeding)?

- It is not known if stavudine can harm a human fetus. Pregnant women have experienced serious side effects when taking stavudine (the active ingredient in stavudine capsules) in combination with didanosine and other HIV medicines. Stavudine should be used during pregnancy only after discussion with your doctor. **Tell your doctor if you become pregnant or plan to become pregnant while taking stavudine.**

- Because studies have shown stavudine is in the breast milk of animals receiving the drug, it may be present in human breast milk. The Centers for Disease Control and Prevention (CDC) recommends that HIV-infected mothers not breast-feed to reduce the risk of passing HIV infection to their babies and the potential for serious adverse reactions in nursing infants. Therefore, do not nurse a baby while taking stavudine.

What are the possible side effects of stavudine?

- Lactic acidosis, severe increase of lactic acid in the blood, severe liver enlargement, including inflammation (pain and swelling) of the liver, and liver failure, which can cause death, have been reported among patients taking stavudine. **Symptoms of lactic acidosis may include:**

- nausea, vomiting, or unusual or unexpected stomach discomfort;
- feeling very weak and tired;
- shortness of breath;
- weakness in arms and legs.

If you notice these symptoms or if your medical condition has suddenly changed, stop taking stavudine and call your doctor right away. Lactic acidosis is a medical emergency that must be treated in a hospital. Women (including pregnant women), overweight patients, and those who have had lengthy treatment with nucleoside medicines are more likely to develop lactic acidosis. The combination of stavudine, didanosine, and

Renal Impairment:Data from two studies in adults indicated that the apparent oral clearance of stavudine decreased and the terminal elimination half-life increased as creatinine clearance decreased (see Table 4). C_{max} and T_{max} were not significantly altered by renal impairment. 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, timed to occur between 2 to 6 hours post-dose, was 31 ± 5%. Based on these observations, it is recommended that stavudine dosage be modified in patients with reduced creatinine clearance and in patients receiving maintenance hemodialysis (see DOSAGE AND ADMINISTRATION).

	Creatinine Clearance			Hemodialysis Patients ^b (n = 11)
	> 50 mL/min (n = 10)	26 to 50 mL/min (n = 5)	9 to 25 mL/min (n = 5)	
Creatinine clearance (mL/min)	104 ± 28	41 ± 5	17 ± 3	NA
Apparent oral clearance (mL/min)	335 ± 57	191 ± 39	116 ± 25	105 ± 17
Renal clearance (mL/min)	167 ± 65	73 ± 18	17 ± 3	NA
T _{1/2} (h)	1.7 ± 0.4	3.5 ± 2.5	4.6 ± 0.9	5.4 ± 1.4
^a Single 40 mg oral dose ^b Determined while patients were off dialysis T _{1/2} = terminal elimination half-life NA = not applicable				

Hepatic Impairment: Stavudine pharmacokinetics were not altered in five non-HIV-infected patients with hepatic impairment secondary to cirrhosis (Child-Pugh classification B or C) following the administration of a single 40 mg dose.

Geriatric: Stavudine pharmacokinetics have not been studied in patients > 65 years of age. (See PRECAUTIONS: Geriatric Use.)

Gender: A population pharmacokinetic analysis of data collected during a controlled clinical study in HIV-infected patients showed no clinically important differences between males (n = 291) and females (n = 27).

Race: A population pharmacokinetic analysis of data collected during a controlled clinical study in HIV-infected patients showed no clinically important differences between races (n = 233 Caucasian, 39 African-American, 41 Hispanic, 1 Asian, and 4 other).

Drug Interactions: (See PRECAUTIONS: Drug Interactions.)

Zidovudine: Zidovudine competitively inhibits the intracellular phosphorylation of stavudine. Therefore, use of zidovudine in combination with stavudine should be avoided.

Doxorubicin: *In vitro* data indicate that the phosphorylation of stavudine is inhibited at relevant concentrations by doxorubicin.

Ribavirin: *In vitro* data indicate ribavirin reduces phosphorylation of lamivudine, stavudine, and zidovudine. However, no pharmacokinetic (e.g., plasma concentrations or intracellular triphosphorylated active metabolite concentrations) or pharmacodynamic (e.g., loss of HIV/HCV virologic suppression) interaction was observed when ribavirin and lamivudine (n = 18), stavudine (n = 10), or zidovudine (n = 6) were coadministered as part of a multi-drug regimen to HIV/HCV co-infected patients (see WARNINGS).

Stavudine does not inhibit the major cytochrome P450 isoforms CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4; therefore, it is unlikely that clinically significant drug interactions will occur with drugs metabolized through these pathways.

Because stavudine is not protein-bound, it is not expected to affect the pharmacokinetics of protein-bound drugs.

Tables 5 and 6 summarize the effects on AUC and C_{max} with a 95% confidence interval (CI) when available, following coadministration of stavudine with didanosine, lamivudine, and neftinavir. No clinically significant pharmacokinetic interactions were observed.

Drug	Stavudine Dosage	n ^a	AUC of Stavudine (95% CI)	C _{max} of Stavudine (95% CI)
Didanosine, 100 mg q12h for 4 days	40 mg q12h for 4 days	10	↔↔	↑17%
Lamivudine, 150 mg single dose	40 mg single dose	18	↔↔ (92.7% to 100.6%)	↑12% (100.3% to 126.1%)
Nelfinavir, 750 mg q8h for 56 days	30 to 40 mg q12h for 56 days	8	↔↔	↔↔
↑ indicates increase. ↔↔ indicates no change, or mean increase or decrease of < 10% ^a HIV-infected patients				

Drug	Stavudine Dosage	n ^a	AUC of Coadministered Drug (95% CI)	Cmax of Coadministered Drug (95% CI)
Didanosine, 100 mg q12h for 4 days	40 mg q12h for 4 days	10	↔↔	↔↔
Lamivudine, 150 mg single dose	40 mg single dose	18	↔↔ (90.5% to 107.6%)	↔↔ (87.1% to 110.6%)
Nelfinavir, 750 mg q8h for 56 days	30 to 40 mg q12h for 56 days	8	↔↔	↔↔
↔↔ indicates no change, or mean increase or decrease of < 10%. ^a HIV-infected patients				

INDICATIONS AND USAGE: Stavudine capsules, in combination with other antiretroviral agents, is indicated for the treatment of HIV-1 infection (see Clinical Studies).

Clinical Studies: *Combination Therapy:* The combination use of stavudine is based on the results of clinical studies in HIV-infected patients in double- and triple-combination regimens with other antiretroviral agents.

One of these studies (START 1) was a multicenter, randomized, open-label study comparing stavudine (40 mg twice daily) plus lamivudine plus indinavir to zidovudine plus lamivudine plus indinavir in 202 treatment-naïve patients. Both regimens resulted in a similar magnitude of inhibition of HIV RNA levels and increases in CD4 cell counts through 48 weeks.

Monotherapy: The efficacy of stavudine was demonstrated in a randomized, double-blind study (AI455-019, conducted 1992 to 1994) comparing stavudine with zidovudine in 822 patients with a spectrum of HIV-related symptoms. The outcome in terms of progression of HIV disease and death was similar for both drugs.

CONTRAINDICATIONS: Stavudine capsules are contraindicated in patients with clinically significant hypersensitivity to stavudine or to any of the components contained in the formulation.

WARNINGS:

1. Lactic Acidosis/Severe Hepatomegaly with Steatosis: Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including stavudine and other antiretroviral.

Although relative rates of lactic acidosis have not been assessed in prospective well controlled trials, longitudinal cohort and retrospective studies suggest that this infrequent event may be more often associated with antiretroviral combinations containing stavudine. Female gender, obesity, and prolonged nucleoside exposure may be risk factors. Fatal lactic acidosis has been reported in pregnant women who received the combination of stavudine and didanosine with other antiretroviral agents. The combination of stavudine and didanosine should be used with caution during pregnancy and is recommended only if the potential benefit clearly outweighs the potential risk (see PRECAUTIONS: Pregnancy).

Particular caution should be exercised when administering stavudine to any patient with known risk factors for liver disease; however, cases of lactic acidosis have also been reported in patients with no known risk factors. Generalized fatigue, digestive symptoms (nausea, vomiting, abdominal pain, and unexplained weight loss); respiratory symptoms (tachypnea and dyspnea); or neurologic symptoms (including motor weakness, see **3. Neurologic Symptoms**) might be indicative of the development of symptomatic hyperlactatemia or lactic acidosis syndrome.

Treatment with stavudine should be suspended in any patient who develops clinical or laboratory findings suggestive of symptomatic hyperlactatemia, lactic acidosis, or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

2. Hepatic Impairment and Toxicity: The safety and efficacy of stavudine have not been established in HIV-infected patients with significant underlying liver disease. During combination antiretroviral therapy, patients with preexisting liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities, including severe and potentially fatal hepatic adverse events, and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

Use with Didanosine and Hydroxyurea-Based Regimens: An increased risk of hepatotoxicity may occur in patients treated with stavudine in combination with didanosine and hydroxyurea compared to when stavudine is used alone. Deaths attributed to hepatotoxicity have occurred in patients receiving this combination. This combination should be avoided.

Use with Interferon and Ribavirin-Based Regimens: *In vitro* studies have shown ribavirin can reduce the phosphorylation of pyrimidine nucleoside analogues such as stavudine. Although no evidence of a pharmacokinetic or pharmacodynamic (e.g., loss of HIV/HCV virologic suppression) interaction was seen when ribavirin was coadministered with stavudine in HIV/HCV co-infected patients (see CLINICAL PHARMACOLOGY: Drug Interactions), **hepatic decompensation (some fatal) has occurred in HIV/HCV co-infected patients receiving combination antiretroviral therapy for HIV and interferon and ribavirin.** Patients receiving interferon with or without ribavirin and stavudine should be closely monitored for

treatment-associated toxicities, especially hepatic decompensation. Discontinuation of stavudine should be considered as medically appropriate. Dose reduction or discontinuation of interferon, ribavirin, or both should also be considered if worsening clinical toxicities are observed, including hepatic decompensation (e.g., Child-Pugh > 6) (see **the complete prescribing information for interferon and ribavirin**).

3. Neurologic Symptoms: Motor weakness has been reported rarely in patients receiving combination antiretroviral therapy including stavudine. Most of these cases occurred in the setting of lactic acidosis. The evolution of motor weakness may mimic the clinical presentation of Guillain-Barré syndrome (including respiratory failure). Symptoms may continue or worsen following discontinuation of therapy.

Peripheral neuropathy, manifested by numbness, tingling, or pain in the hands or feet, has been reported in patients receiving stavudine therapy. Peripheral neuropathy has occurred more frequently in patients with advanced HIV disease, with a history of neuropathy, or in patients receiving other drugs that have been associated with neuropathy, including didanosine (see ADVERSE REACTIONS).

4. Pancreatitis: Fatal and nonfatal pancreatitis have occurred during therapy when stavudine was part of a combination regimen that included didanosine, with or without hydroxyurea, in both treatment-naïve and treatment-experienced patients, regardless of degree of immunosuppression. The combination of stavudine and didanosine (with or without hydroxyurea) and any other agents that are toxic to the pancreas should be suspended in patients with suspected pancreatitis. Reinstitution of stavudine after a confirmed diagnosis of pancreatitis should be undertaken with particular caution and close patient monitoring. The new regimen should contain neither didanosine nor hydroxyurea.

PRECAUTIONS: Fat Redistribution: Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and “cushingoid appearance” have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Immune Reconstitution Syndrome: Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including stavudine. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jiroveci* pneumonia (PCP), or tuberculosis), which may necessitate further evaluation and treatment.

Information for Patients (See Patient Information Leaflet): Patients should be informed of the importance of early recognition of symptoms of symptomatic hyperlactatemia or lactic acidosis syndrome, which include unexplained weight loss, abdominal discomfort, nausea, vomiting, fatigue, dyspnea, and motor weakness. Patients in whom these symptoms develop should seek medical attention immediately. Discontinuation of stavudine therapy may be required.

Patients should be informed that an important toxicity of stavudine is peripheral neuropathy. Patients should be aware that peripheral neuropathy is manifested by numbness, tingling, or pain in hands or feet, and that these symptoms should be reported to their physicians. Patients should be counseled that peripheral neuropathy occurs with greatest frequency in patients who have advanced HIV disease or a history of peripheral neuropathy, and that dose modification and/or discontinuation of stavudine may be required if toxicity develops.

Caregivers of young children receiving stavudine therapy should be instructed regarding detection and reporting of peripheral neuropathy.

Patients should be informed that when stavudine is used in combination with other agents with similar toxicities, the incidence of adverse events may be higher than when stavudine is used alone. An increased risk of pancreatitis, which may be fatal, may occur in patients treated with the combination of stavudine and didanosine, with or without hydroxyurea. Patients treated with this combination should be closely monitored for symptoms of pancreatitis. An increased risk of hepatotoxicity, which may be fatal, may occur in patients treated with stavudine in combination with didanosine and hydroxyurea. This combination should be avoided.

Patients should be informed that stavudine is not a cure for HIV infection, and that they may continue to acquire illnesses associated with HIV infection, including opportunistic infections. Patients should be advised to remain under the care of a physician when using stavudine. They should be advised that stavudine therapy has not been shown to reduce the risk of transmission of HIV to others through sexual contact or blood contamination. Patients should be informed that the long-term effects of stavudine are unknown at this time.

Patients should be informed that the Centers for Disease Control and Prevention (CDC) recommend that HIV-infected mothers not nurse newborn infants to reduce the risk of postnatal transmission of HIV infection.

Patients should be informed that redistribution or accumulation of body fat may occur in individuals receiving antiretroviral therapy and that the cause and long-term health effects of these conditions are not known at this time.

Patients should be advised of the importance of adherence to any antiretroviral regimen, including those that contain stavudine.

Drug Interactions (see also CLINICAL PHARMACOLOGY): Zidovudine competitively inhibits the intracellular phosphorylation of stavudine. Therefore, use of zidovudine in combination with stavudine should be avoided.

In vitro data indicate that the phosphorylation of stavudine is also inhibited at relevant concentrations by doxorubicin and ribavirin. The clinical significance of these *in vitro* interactions is unknown; therefore, concomitant use of stavudine with either of these drugs should be undertaken with caution. (See WARNINGS.)

