

# HIV drug stavudine (Zerit, d4T) and symptoms mimicking Guillain-Barré syndrome

**Reason for posting:** In a warning letter to physicians Bristol-Myers Squibb has reported 22 cases (including 7 deaths) worldwide of a stavudine-associated rapidly ascending neuromuscular weakness and respiratory failure mimicking Guillain-Barré syndrome (GBS)<sup>1,2</sup> (see box for summary about GBS). All 22 cases occurred in the context of hyperlactatemia,<sup>2</sup> a recognized stavudine effect. Preliminary analysis of 15 of the cases showed symptom onset 12 months on average (range 4–30 months) after the start of treatment and that most of the patients had only modestly elevated lactate levels (Bristol-Myers Squibb: unpublished data).

**The drug:** Stavudine (d4T), a thymidine analogue and nucleoside analogue reverse transcriptase inhibitor (NRTI), is often used in combination with other HIV drugs. A known side effect of the drug is a peripheral neuropathy (numbness, tingling or pain in the hands or feet).<sup>3</sup> Stavudine is also associated with a spectrum of lactic acid abnormalities, from asymptomatic, mild hyperlactatemia to a potentially fatal lactic acidosis syndrome (LAS). NRTI-related lactic acidosis can be associated with myopathy (causing muscle wasting, myalgia, fatigue, weakness and elevated creatinine kinase levels), lipodystrophy, hepatic steatosis, liver dysfunction and possible fulminant liver failure, and pancreati-

tis.<sup>4-6</sup> The toxic effects appear to result from mitochondria damage as a result of DNA polymerase  $\gamma$  inhibition, but it is unknown whether the new GBS-like symptoms are mediated similarly.

Hyperlactatemia (and LAS) is often associated with symptoms of generalized fatigue, nausea, vomiting, sudden weight loss, abdominal pain and distension. Tachypnea and dyspnea are not reliable early signs of LAS and may signal a preterminal state. Similarly, although serum transaminase levels can eventually rise in patients with LAS, they are often normal at presentation.<sup>4</sup> An elevated plasma lactate level is diagnostic of hyperlactatemia (mild 2–5 mmol/L, severe > 5 mmol/L),<sup>7</sup> and patients with LAS often have an additional anion gap metabolic acidosis.

The prevalence of moderate or severe hyperlactatemia (plasma lactate level > 2.2 times the normal limit) was determined to be 1% (9 of 880 patients) in a cross-sectional study of HIV-infected patients, with stavudine predisposing to high lactate levels more than other drugs.<sup>5</sup> The incidence of hyperlactatemia in stavudine-treated patients has been estimated to be 1.2% per year.<sup>6</sup> In most patients in whom lactate levels rise, the levels tend to remain only slightly elevated; however, LAS can develop in these patients, and sudden onset is possible in those with initially normal lactate levels.<sup>7,8</sup> Obesity,

prolonged drug exposure, and female sex and pregnancy may be risk factors for hyperlactatemia.<sup>3</sup> The role of riboflavin and other agents in treating hyperlactatemia<sup>7</sup> is evolving.

**What to do:** Patients should be warned of stavudine-associated LAS and the possibility of potentially lethal neuromuscular failure. If severe hyperlactatemia or motor weakness develops, the drug should be stopped immediately and appropriate supportive care (e.g., ventilation) introduced as needed. Physicians should consider monitoring the lactate levels of patients taking stavudine (recognizing that asymptomatic, mild hyperlactatemia poorly predicts progression to LAS)<sup>7</sup> particularly if symptoms such as fatigue, weight loss, abdominal pain, nausea, vomiting or dyspnea develop.

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## References

1. *Symptoms mimicking the clinical presentation of Guillain-Barré syndrome associated with Zerit (stavudine, d4T)*. Ottawa: Health Canada. 2002 Mar 6. Available: [www.hc-sc.gc.ca/hpb-dggs/therapeut/zfiles/english/advisory/industry/zerit\\_stavudine\\_e.html](http://www.hc-sc.gc.ca/hpb-dggs/therapeut/zfiles/english/advisory/industry/zerit_stavudine_e.html) (accessed 2002 Mar 20).
2. Marcus K, Truffa M, Boxwell D, Toerner J. Recently identified adverse events secondary to NRTI therapy in HIV-infected individuals: cases from the FDA's Adverse Event Reporting System [abstract LB14]. 9th Conference on Retroviruses and Opportunistic Infections; Seattle; 2002.
3. *Zerit (Stavudine) antiretroviral agent* [product monograph]. Montreal (QC): Bristol-Myers Squibb Pharmaceutical Group; 2001 Mar 27.
4. Coghlan ME, Sommadossi JP, Jhala NC, Many WJ, Saag MS, Johnson VA. Symptomatic lactic acidosis in hospitalized antiretroviral-treated patients with human immunodeficiency virus infection: a report of 12 cases. *Clin Infect Dis* 2001;33:1914-21.
5. Boubaker K, Flepp M, Sudre P, Furrer H, Haensel A, Hirschel B, et al. Hyperlactatemia and antiretroviral therapy: the Swiss HIV Cohort Study. *Clin Infect Dis* 2001;33:1931-7.
6. Gérard Y, Maulin L, Yazdanpanah Y, De La Tribonnière X, Amiel C, Maurage CA, et al. Symptomatic hyperlactatemia: an emerging complication of antiretroviral therapy. *AIDS* 2000;14:2723-30.
7. Brinkman K. Management of hyperlactatemia: no need for routine lactate measurements. *AIDS* 2001;15:795-7.
8. John M, Moore CB, James IR, Nolan D, Upton RP, McKinnon EJ, Mallal SA. Chronic hyperlactatemia in HIV-infected patients taking antiretroviral therapy. *AIDS* 2001;15:717-23.

## Guillain-Barré syndrome

Symptoms of Guillain-Barré syndrome (GBS) include rapidly evolving (over days to weeks) symmetrical limb weakness and flaccid paralysis, areflexia, mild (usually absent) sensory disturbances and autonomic dysfunctions.

Often self-limited, GBS involves immune-mediated demyelination of peripheral nerves and occasional axonal degeneration. It often occurs in the wake of specific infections (*Campylobacter jejuni*, cytomegalovirus, Epstein-Barr virus or HIV infection) and some vaccinations (contaminated rabies vaccine or swine influenza vaccine) and may arise because of shared antigens in the peripheral nerves and organisms in question.

Treatment is primarily supportive, and assisted ventilation is needed in one-third of cases. Plasma exchange and IgG infusion may shorten the course of GBS.