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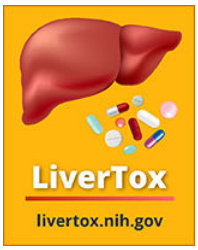


Stavudine

Updated: June 25, 2020.

OVERVIEW

Introduction

Stavudine is a first generation nucleoside analogue and reverse transcriptase inhibitor used in combination with other agents in the therapy of human immunodeficiency virus (HIV) infection and the acquired immunodeficiency syndrome (AIDS). Stavudine is an uncommon, but well established cause of clinically apparent acute and chronic liver injury.

Background

Stavudine (stav' ue deen) is a synthetic thymidine analogue (2',3'-didehydro-2'3'- dideoxydeoxythymidine: d4T) that inhibits HIV replication by competing with naturally occurring thymidine for incorporation into the growing viral DNA chain, causing inhibition of the viral polymerase (reverse transcriptase) and chain termination. Stavudine was approved for use in the treatment of HIV infection in the United States in 1994 and was widely used in many antiretroviral regimens for many years. Recently, stavudine has been replaced by other better tolerated second generation nucleoside analogues and is no longer commonly used in developed countries. It is, however, still used in resource limited settings. Stavudine is available in multiple generic forms and formerly under the brand name Zerit in 15, 20, 30, and 40 mg capsules. Oral solutions of stavudine (1 mg/mL) are also available. The recommended dose of stavudine is 30 to 40 mg orally every 12 hours in adults and in children greater than 30 kg. Common side effects include diarrhea, headache, macrocytosis, nausea and vomiting, peripheral neuropathy and rash. Less common but potentially severe adverse reactions include hepatotoxicity, peripheral neuropathy, lipoatrophy, pancreatitis and immune reconstitution syndrome.

Hepatotoxicity

Stavudine is a well known cause of liver injury and is regularly listed in case series of drug induced liver injury and acute liver failure. Mild and transient elevations in liver enzymes occur in up to half of patients on stavudine, but elevations above 5 times normal occur in only 5% to 13% of treated patients. Clinically apparent hepatotoxicity due to stavudine is well described and is usually marked by lactic acidosis, marked hepatic steatosis (microvesicular fat), and progressive hepatic synthetic dysfunction (LASH). This form of liver injury typically arises only after 2 to 6 months of therapy and is preceded by nonspecific prodromal symptoms of anorexia, nausea, vomiting, diarrhea, and weakness which is followed by dyspnea, jaundice and confusion. Lactic acidosis often accompanies the hepatic injury and may be the predominant clinical feature. Jaundice arises late and serum enzymes are unusually only mildly or moderated elevated, the pattern being mixed or actually cholestatic. Pancreatitis, myopathy and neuropathy may also occur. Lipodystrophy is frequently present. Liver histology during the early course of injury demonstrates marked microvesicular fat with little hepatocyte

injury. Subsequently, cholestasis arises and the fatty change may evolve to a macrovesicular pattern. Late changes include ballooning cell degeneration, Mallory bodies and fibrosis. The hepatotoxicity associated with stavudine can be rapidly fatal, but is potentially reversable with intensive support and early withdrawal of therapy (Case 1). Monitoring of patients on stavudine demonstrates that asymptomatic elevations of serum lactate (hyperlactatemia) usually precedes the appearance of clinical symptoms and acidosis. Once lactic acidosis is present, however, the mortality rate is high (33% to 50%) (Case 2). Preexisting liver injury, female sex, older age, obesity, alcohol use and concurrent therapy with didanosine, ribavirin and tenofovir appear to increase the risk of this syndrome in patients taking stavudine.

Stavudine and other first generation nucleoside analogues used to treat HIV infection have also been linked to cases of chronic liver injury, marked by appearance of signs and symptoms of portal hypertension and liver nodularity without significant fibrosis or cirrhosis after long term use. Nodular regenerative hyperplasia or "noncirrhotic portal hypertension" arise after long term therapy with antiretroviral therapies most typically with didanosine. In some cases, the first complications of portal hypertension arise months or years after the implicated agent is stopped and while other, less hepatotoxic agents are being used. Nodular regenerative hyperplasia is typically characterized by the appearance of signs and symptoms of portal hypertension and advanced liver disease, such as ascites or variceal hemorrhage, with no obvious cause (absence of hepatitis B or C and no history of alcohol abuse or nonalcoholic steatohepatitis). Serum enzymes are only modestly elevated and bilirubin levels can be normal. Liver biopsy can look deceptively benign, with little or no fibrosis and nodularity that is only obvious with reticulum stains that highlight the altered architecture. These patients have typically been receiving multiple antiretroviral agents and the attribution to stavudine alone cannot always be made. Didanosine is most frequently implicated in causing nodular regenerative hyperplasia but isolated instances have also been linked to stavudine, zidovudine and in rare instances tenofovir. The signs and symptoms of portal hypertension tend to improve once the nucleoside analogues are stopped and medical therapy of ascites and portal hypertension is begun.

Likelihood score: A (uncommon well established cause of acute and chronic forms of liver disease).

Mechanism of Injury

Acute, clinically apparent hepatotoxicity from stavudine is typically associated with lactic acidosis and is probably mediated by widespread depletion or dysfunction of mitochondria. In vitro, stavudine has been found to inhibit the gamma polymerase responsible for replication of mitochondria and maintenance of mitochondrial function and numbers. The mitochondrial failure in hepatocytes leads to inability to metabolize lactic acid and free fatty acids and to support usual hepatic synthetic and excretory function. Mitochondrial injury to other tissue can lead to pancreatitis, myopathy and neuropathy. The chronic liver injury from stavudine is probably due to vascular damage to small arterioles and venules that causes a regenerative hyperplasia. The mechanism of the injury is not known, but may also be due to chronic mitochondrial injury.

Outcome and Management

The severity of the liver injury associated with stavudine ranges from mild and transient enzyme elevations to rapidly progressive liver failure with steatosis leading to death. Stavudine is usually listed as one of the most frequent causes of drug induced acute liver failure. Most patients, however, recover from injury particularly if lactic acidosis is not advanced when therapy is stopped. Typically, improvement starts within 2 weeks of stopping stavudine, but may be slow to completely resolve. Rechallenge may lead to recurrence and should be avoided. Persons who develop stavudine hepatotoxicity should avoid use of other dideoxynucleosides such as didanosine and zalcitabine, and caution should be used in use of zidovudine (although it is usually well tolerated without recurrence of lactic acidosis). Various interventions have been used in attempts to treat the severe lactic acidosis and hepatic steatosis induced by nucleoside analogues. These interventions have included bicarbonate infusions, thiamine, riboflavin, l-carnitidine, as well as renal dialysis and mechanical ventilation. Intravenous 20% glucose

decreases lactic acid levels in some patients, probably by providing intracellular ATP from anaerobic glycolysis. Liver transplantation has reversed lactic acidosis in the rare patient that has undergone emergency transplantation, but this option is rarely feasible. Stavudine has not been associated with chronic cholestasis or the vanishing bile duct syndrome.

Nodular regenerative hyperplasia from long term therapy with stavudine, didanosine or zidovudine should be treated conservatively with management of the signs and symptoms of portal hypertension. Stavudine (and all first generation nucleoside analogues) should be discontinued and the patient switched to other antiretroviral agents. Typically, nodular regenerative hyperplasia improves after drug withdrawal, and symptoms, signs and abnormal liver tests may ultimately resolve. The long term consequences of nodular regenerative hyperplasia after drug withdrawal is uncertain and not well defined. Unrelated acute severe medical conditions such as pneumonia or sepsis can cause reappearance of signs and symptoms of portal hypertension (ascites, variceal hemorrhage) and evidence of hepatic decompensation (weakness, jaundice, and hepatic encephalopathy).

Drug Class: Antiviral Agents, Antiretroviral Agents

Other Drugs in the Subclass, Nucleoside Analogues: Abacavir, Adefovir, Didanosine, Emtricitabine, Entecavir, Lamivudine, Telbivudine, Tenofovir, Zidovudine

CASE REPORTS

Case 1. Liver injury, hyperlactatemia and pancreatitis induced by stavudine.(1)

A 45 year old man with HIV infection developed nausea, vomiting and abdominal pain 3 months after starting stavudine (400 mg twice daily). He had been on didanosine (400 mg daily) and prednisone (5 mg daily) for more than 2 years and had previously received zidovudine. On physical examination, he was jaundiced and had right upper quadrant abdominal tenderness. Serum bilirubin was 14 mg/dL, alkaline phosphatase 400 U/L and ALT 300 U/L. Serum amylase levels were mildly elevated. Lactate levels were not measured. Abdominal ultrasound showed changes compatible with fatty liver and percutaneous liver biopsy revealed macrovesicular steatosis and cholestatic hepatitis. Both didanosine and stavudine were stopped. The patient improved, and all tests were normal 3 weeks later. After recovery, stavudine was restarted in the same dose and, within a week, serum lactate levels increased from normal to 9.1 mmol/L, but serum aminotransferase levels did not change. Stavudine was stopped again and the patient remained well off of all antiretroviral therapy and had normal serum enzymes over the next year.

Key Points

Medication:	Stavudine (40 mg twice daily)
Pattern:	Cholestatic (R=1.9)
Severity:	3+ (jaundice, hospitalization)
Latency:	3 months
Recovery:	3 weeks
Other medications:	Prednisone 5 mg daily, didanosine 400 mg daily

Comment

Stavudine was considered to be the most likely cause of the liver injury and hyperlactatemia, although didanosine may have contributed or increased the risk. He had received didanosine without problems for the previous two years, the liver injury arising only with the addition of stavudine. This syndrome appears to be

rapidly reversible with withdrawal of nucleoside analogue therapy in the early stages of hyperlactatemia and liver injury.

Case 2. Fatal lactic acidosis and hepatic steatosis after stavudine therapy. (2)

A 45 year old woman with HIV infection developed worsening peripheral neuropathy followed by jaundice and severe abdominal pain 5 months after changing her antiretroviral regimen from zidovudine and didanosine to nevirapine, stavudine, lamivudine and hydroxyurea. On admission, physical examination showed dehydration, jaundice and abdominal tenderness with tachypnea and tachycardia. Serum bilirubin was 14.3 mg/dL, ALT 45 IU/L, alkaline phosphatase 835 IU/L, amylase 968 U/L, lactate 14.3 mmol/ L and arterial pH 7.26. Tests for hepatitis B and C were negative. Abdominal ultrasound showed pancreatic edema and echogenicity of the liver suggestive of steatosis. Liver biopsy showed steatosis and cholestasis. Despite intensive medical support, she developed intractable lactic acidosis and multiorgan failure, dying within 48 hours of admission.

Key Points

Medication:	Stavudine (400 mg twice daily)
Pattern:	Cholestatic (R<1)
Severity:	5+ (fatal)
Latency:	5 months
Recovery:	None
Other medications:	Nevirapine, lamivudine, hydroxyurea; previously zidovudine, didanosine

Comment

Five months after stavudine was added to a chronic antiretroviral regimen, this patient developed severe liver injury and lactic acidosis that was rapidly fatal. Symptoms of neuropathy had been present for several weeks and diagnosis was delayed until severe lactic acidosis was present. The mitochondrial injury from nucleoside analogues can affect liver, pancreas, muscle and peripheral nerves singly or in combination.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Stavudine – Generic, Zerit®

DRUG CLASS

Antiviral Agents

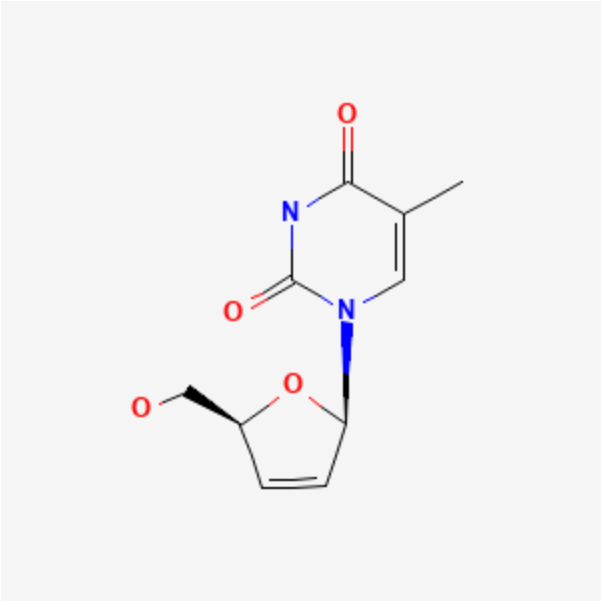
COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE

Table continued from previous page.

Stavudine	3056-17-5	C10-H12-N2-O4	

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1. Bleeker-Rovers CP, Kadir S, van Leusen R, Richter C. Hepatic steatosis and lactic acidosis caused by stavudine in an HIV-infected patient. Neth J Med. 2000;57:190–3. PubMed PMID: 11063865.
2. Cornejo-Juárez P, Sierra-Madero J, Volkow-Fernández P. Metabolic acidosis and hepatic steatosis in two HIV-infected patients of stavudine (d4T) treatment. Arch Med Res. 2003;34:64–9. PubMed PMID: 12604378.

ANNOTATED BIBLIOGRAPHY

References updated: 25 June 2020

Abbreviations used: AIDS, acquired immune deficiency syndrome; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HPA, hepatoportal sclerosis; HVPG, hepatic venous pressure gradient; mt, mitochondrial; NASH, nonalcoholic steatohepatitis; NCPH, noncirrhotic portal hypertension; NRH, nodular regenerative hyperplasia; TE, transient elastography.

Núñez M. Hepatic toxicity of antiviral agents. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 505-18.

(Review of hepatotoxicity of antiviral agents including stavudine).

Flexner C. Antiretroviral agents and treatment of HIV infection. In, Brunton LL, Hilal-Dandan R, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 13th ed. New York: McGraw-Hill, 2018, pp. 1137-58.

(Textbook of pharmacology and therapeutics).

National Institutes of Health. http://aidsinfo.nih.gov/guidelines.

(Clinical guidelines on the use of antiretroviral agents in HIV-1 infected adults, adolescents and children).

Freiman JP, Helfert KE, Hamrell MR, Stein DS. Hepatomegaly with severe steatosis in HIV-seropositive patients. AIDS. 1993;7:379–85. PubMed PMID: 8471200.

(Reports of 6 fatal and 2 nonfatal cases of hepatomegaly and steatosis in patients with HIV on zidovudine for 3-12 months).

Chattha G, Arieff AI, Cumings G, Tierney LM Jr. Lactic acidosis complicating the acquired immunodeficiency syndrome. Ann Intern Med. 1993;118:37–9. PubMed PMID: 8416156.

(Report of 7 patients with HIV infection who developed lactic acidosis of unknown cause, presenting with nausea, anorexia and weight loss followed by dyspnea, stupor and death [in 4]; 4 on zidovudine, 1 ganciclovir and 1 clofazimine; initial arterial pH 7.09-7.27, lactate 10.4-17.4 mmol/L).

McKenzie R, Fried MW, Sallie R, Conjeevaram H, Di Bisceglie AM, Park Y, Savarese B, et al. Hepatic failure and lactic acidosis due to fialuridine(FIAU), an investigational nucleoside analogue for chronic hepatitis B. N Engl J Med. 1995;333:1099–105. PubMed PMID: 7565947.

(Description of syndrome of lactic acidosis, hepatic failure and pancreatitis arising after 8-11 weeks of fialuridine treatment in 15 patients with chronic hepatitis B; among 7 patients affected, 5 died of intractable lactic acidosis and 2 survived, but required emergency liver transplantation).

Lewis W, Dalakas MC. Mitochondrial toxicity of antiviral drugs. Nat Med. 1995;1:417–22. PubMed PMID: 7585087.

(Review of mechanisms for mitochondrial injury by nucleoside analogues, including inhibition of mitochondrial DNA polymerase gamma).

Styrt B, Freiman JP. Hepatotoxicity of antiviral agents. Gastroenterol Clin North Am. 1995;24:839–52. PubMed PMID: 8749901.

(Early review of liver toxicity of antiviral agents, covering the first four nucleoside analogues used for HIV infection: zidovudine, didanosine, zalcitabine and stavudine).

Lenzo NP., Garas BA, French MA. Hepatic steatosis and lactic acidosis associated with stavudine treatment in an HIV patient: a case report. AIDS. 1997;11:1294–6. PubMed PMID: 9256950.

(32 year old woman with HIV infection developed lactic acidosis and hepatic steatosis 6 months after starting stavudine with zidovudine and lamivudine [bilirubin 1.6 mg/dL, ALT 67 U/L], resolving rapidly upon stopping stavudine).

Schiano TD, Lissoos T, Ahmed A, Siano C, Zaitman D, Cohn G, Ehrenpreis E. Lamivudine-stavudine-induced liver failure in hepatitis B cirrhosis. Am J Gastroenterol. 1997;92:1563–4. PubMed PMID: 9317091.

(69 year old man with HIV-HBV coinfection and cirrhosis developed flare of hepatitis beginning 2 weeks after adding lamivudine to long term stavudine [peak bilirubin 20.7 mg/dL, ALT 2414 U/L, ascites and pruritus], improving slowly once lamivudine was stopped; HBV DNA level was high, but timing and serial results were not given).

Zylberberg H, Pialoux G, Carnot F, Landau A, Bréchot C, Pol S. Rapidly evolving hepatitis C virus-related cirrhosis in a human immunodeficiency virus-infected patient receiving triple antiretroviral therapy. Clin Infect Dis. 1998;27:1255–8. PubMed PMID: 9827279.

(36 year old woman with HIV-HCV coinfection developed ascites 9 months after starting lamivudine, indinavir and stavudine [bilirubin 2.1 mg/dL, ALT 60 U/L, Alk P 107 U/L], with subsequent liver failure; biopsy showed nodularity and "cirrhosis").

Brinkman K, ter Hofstede HJ, Burger DM, Smeitink JAM, Koopmans PP. Adverse effects of reverse transcriptase inhibitors: mitochondrial toxicity as a common pathway. AIDS. 1998;12:1735–44. PubMed PMID: 9792373.

(Review of mitochondrial function and role of mitochondrial toxicity or depletion in the adverse side effects of nucleoside analogues).

Finkle HI. Hepatic mitochondrial toxicity from nucleoside analog therapy. Arch Pathol Lab Med. 1999;123:189. PubMed PMID: 10086505.

(42 year old man with HIV infection developed lactic acidosis on combination therapy with stavudine and didanosine, with ALT 73 U/L, autopsy showing microvesicular steatosis).

Benveniste O, Longuet P, Duval X, Le Moing V, Leport C, Vildé JL. Two episodes of acute renal failure, rhabdomyolysis, and severe hepatitis in an AIDS patient successively treated with ritonavir and indinavir. Clin Infect Dis. 1999;28:1180–1. PubMed PMID: 10452668.

(34 year old man with HIV-HCV coinfection developed fever and jaundice 6 days after starting ritonavir [bilirubin 12.3 mg/dL, ALT 491 U/L, creatinine 4.1 mg/dL], resolving with stopping and then tolerating indinavir, stavudine and lamivudine for 1 year when she presented with lactic acidosis and jaundice [bilirubin 10.2 mg/dL, ALT 234 U/L, CPK 3074 U/L], resolving again with stopping; unclear which agent[s] were responsible for second episode).

Allaouchiche B, Duflo F, Cotte L, Mathon L, Chassard D. Acute pancreatitis with severe lactic acidosis in an HIV-infected patient on didanosine therapy. J Antimicrob Chemother. 1999;44:137–8. PubMed PMID: 10459826.

(58 year old man with HIV infection developed abdominal pain and elevated amylase [1059 U/L] after treatment with didanosine, stavudine and indinavir [bilirubin 7.3 mg/dL, ALT 75 U/L, Alk P 107 U/L, lactate 13 mmol/L], resolving within 3 weeks of stopping).

Frippiat F, Derue G, Heller F, Honore P, Moreau M, Vandercam B. Acute pancreatitis associated with severe lactic acidosis in human immunodeficiency virus-infected patients receiving triple therapy. J Antimicrob Chemother. 2000;45:411–2. PubMed PMID: 10702573.

(Letter in response to Allaouchiche et al. suggesting that stavudine may have been the cause or contributed to the mitochondrial toxicity and pancreatitis).

Bleeker-Rovers CP, Kadir S, van Leusen R, Richter C. Hepatic steatosis and lactic acidosis caused by stavudine in an HIV-infected patient. Neth J Med. 2000;57:190–3. PubMed PMID: 11063865.

(45 year old man with HIV developed nausea and abdominal pain after 2 years of didanosine and 3 months of stavudine therapy [bilirubin 14.0 mg/dL, ALT 300 U/L, Alk P 400 U/L, no obvious acidosis], resolving slowly after stopping; rechallenge with stavudine resulted in rise in lactate levels within one week [9.1 mmol/L] and stavudine was stopped again: Case 1).

ter Hofstede HJ, de Marie S, Foudraine NA, Danner SA, Brinkman K. Clinical features and risk factors of lactic acidosis following long-term antiretroviral therapy: 4 fatal cases. Int J STD AIDS. 2000;11:611–6. PubMed PMID: 10997508.

(Four patients on stavudine [3 on didanosine as well] for 6-18 months developed fatal lactic acidosis, presenting with nausea, abdominal pain and weight loss [pH 7.04-7.17]; autopsies in 2 showed severe hepatomegaly, micro- and macro-steatosis, and cholestasis).

Gérard Y, Maulin L, Yazdanpanah Y, De La Tribonnière X, Amiel C, Maurage CA, Robin S, et al. Symptomatic hyperlactataemia: an emerging complication of antiretroviral therapy. AIDS. 2000;14:2723–30. PubMed PMID: 11125891.

(Identified 14 patients with symptoms of elevated lactate [levels 0.9 to 9.4 mmol/L] with fatigue, abdominal pain, weight loss, neuropathy and dyspnea on exertion, all on stavudine [9 also on didanosine] for 2-29 months).

Brivet FG, Nion I, Mégarbane B, Slama A, Brivet M, Rustin P, Munnich A. Fatal lactic acidosis and liver steatosis associated with didanosine and stavudine treatment: a respiratory chain dysfunction? J Hepatol. 2000;32:364–5. PubMed PMID: 10707883.

(Patient with HIV infection on didanosine and stavudine for 9 months developed nausea and anorexia [bilirubin 1.2 mg/dL, ALT 206 U/L and progressive lactic acidosis] leading to death 5 days later; autopsy showed pancreatitis and hepatomegaly with severe macrovesicular steatosis).

Carr A, Miller J, Law M, Cooper DA. A syndrome of lipoatrophy, lactic acidemia and liver dysfunction associated with HIV nucleoside analogue therapy: contribution to protease inhibitor related syndrome. AIDS. 2000;14:F25–32. PubMed PMID: 10716495.

(Description of 14 patients who developed lipodystrophy on antiretroviral therapy, who never received protease inhibitors, but had received stavudine [86%] or didanosine [71%] for >6 months and most had hyperlactatemia, ALT elevations and weight loss, nausea and fatigue and resolved slowly upon withdrawal).

Gisolf EH, Dreezen C, Danner S, Weel JL, Weverling GJ; Prometheus Study Group. Risk factors for hepatotoxicity in HIV-1 infected patients receiving ritonavir and saquinavir with or without stavudine. Clin Infect Dis. 2000;31:1234–9. PubMed PMID: 11073757.

(Among 218 patients with HIV infection starting antiretroviral therapy, 18 [9%] developed liver enzyme elevations after an average of 12 weeks [ALT 150 to 1890 U/L]; risk factors were HBV coinfection and stavudine use).

Sulkowski MS, Thomas DL, Chaisson RE, Moore RD. Hepatotoxicity associated with antiretroviral therapy in adults infected with human immunodeficiency virus and the role of hepatitis C or B virus infection. JAMA. 2000;283:74–80. PubMed PMID: 10632283.

(Among 298 patients with HIV infection, ALT elevations above 5 times ULN occurred in 10.4% per year during antiretroviral treatment; factors associated with ALT elevations included ritonavir [27.3%] and coinfection with either HCV or HBV; ALT with bilirubin elevations occurred in 3 patients; 2 on indinavir and all 3 with coinfection).

Velasco M, Guijarro C. Elevated liver enzymes following initiation of antiretroviral therapy. JAMA. 2000;283:2526–7. PubMed PMID: 10815112.

(Letter in response to Sulkowski et al. [JAMA 2000] pointing out that antiretroviral therapy can cause immune reconstitution and flares of hepatitis B or C, which may be misdiagnosed as hepatotoxicity).

Sulkowski MS, Thomas DL, Chaisson RE, Moore RD. Elevated liver enzymes following initiation of antiretroviral therapy. JAMA. 2000;283:2526–7. PubMed PMID: 10815113.

(Reply to Velasco and Guijarro pointing at that the majority of the ALT elevations described could not be attributed to immune reconstitution).

Johri S, Alkhuja S, Siviglia G, Soni A. Steatosis-lactic acidosis syndrome associated with stavudine and lamivudine therapy. AIDS. 2000;14:1286. PubMed PMID: 10894300.

(Three women, ages 36 to 40 years, with HIV infection developed lactic acidosis and hepatic steatosis 1-8 months after starting stavudine and lamivudine [AST 291, 48 and 119 U/L, severe acidosis, and fatty liver by imaging]; two died, one of whom had massive hepatomegaly and steatosis on autopsy).

Lonergan JT, Behling C, Pfander H, Hassanein TI, Mathews WC. Hyperlactatemia and hepatic abnormalities in 10 human immunodeficiency virus-infected patients receiving nucleoside analogue combination regimens. Clin Infect Dis. 2000;31:162–6. PubMed PMID: 10913415.

(Over a 6 month period, authors identified 10 HIV-positive patients with high lactate levels [2.9-6.2 mmol/L]; all 10 were taking stavudine, 5 didanosine and 7 lamivudine for 4-20 months; 8 had symptoms of abdominal pain, nausea or distension; all 20 had ALT elevations [2-10.7 times ULN], 3 with HBV or HCV; imaging showed fatty liver in 5; all resolved with stopping, lactate levels falling to normal after 16-111 days).

Miller KD, Cameron M, Wood LV, Dalakas MC, Kovacs JA. Lactic acidosis and hepatic steatosis associated with use of stavudine: report of four cases. Ann Intern Med. 2000;133:192–6. PubMed PMID: 10906833.

(2 women and 2 men with HIV infection, ages 15 months to 63 years, developed hepatic steatosis and lactic acidosis 3, 6, 15 and 15 months after starting stavudine [bilirubin not mentioned, ALT 43-356 U/L, elevated lactates 4.3-13.6 mmol/L, fatty liver on imaging], two had liver biopsies showing severe steatosis, all resolved with medical support and stopping stavudine).

Mokrzycki MH, Harris C, May H, Laut J, Palmisano J. Lactic acidosis associated with stavudine administration: a report of five cases. Clin Infect Dis. 2000;30:198–200. PubMed PMID: 10619755.

(4 women and one man with HIV infection developed lactic acidosis and hepatic steatosis 1-12 months after starting stavudine;1 died of pancreatitis, 4 recovered in 4-60 weeks; 2 cases described in detail [bilirubin 0.7 and 2.0 mg/dL, ALT 43 and 41 U/L, Alk P 46 and 41 U/L]).

Claessens Y-E, Cariou A, Chiche J-D, Dauriat G, Dhainaut J-F. L-carnitine as a treatment of life-threatening lactic acidosis induced by nucleoside analogues. AIDS. 2000;14:472–3. PubMed PMID: 10770558.

(34 year old man developed abdominal pain and nausea 11 months after starting stavudine, didanosine and saquinavir with severe lactic acidosis, cholestasis and fatty liver; given intravenous l-carnitine and slowly recovered).

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. PubMed PMID: 11371686.

(349 patients with HIV infection were screened for lactate levels on multiple occasions; 2 on stavudine had symptomatic lactic acidosis, estimated incidence of 3.9 per 1000 person years).

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. PubMed PMID: 11692304.

(Experience with 12 cases of lactic acidosis in patients with HIV infection seen over 6 years, typically with anorexia, nausea and weight loss for several weeks, AST variably elevated, 11 on stavudine, 9 didanosine, 1 zidovudine alone; 6 with pancreatitis, 6 having liver biopsies all showed macro- and micro-steatosis; five died).

Boubaker K, Flepp M, Sudre P, Furrer H, Haensel A, Hirschel B, Boggian K, et al. Hyperlactatemia and antiretroviral therapy: the Swiss HIV Cohort Study. Clin Infect Dis. 2001;33:1931–7. PubMed PMID: 11692306.

(Cross sectional analysis of lactate testing on 880 Swiss patients with HIV receiving antiretroviral therapy; elevated levels were associated with stavudine and didanosine use and with lipodystrophy [and high glucose and triglycerides] but not with age, sex, CD4 counts or HIV RNA levels).

Carr A, Morey A, Mallon P, Williams D, Thorburn DR. Fatal portal hypertension, liver failure, and mitochondrial dysfunction after HIV-1 nucleoside analogue-induced hepatitis and lactic acidaemia. Lancet. 2001;357:1412–4. PubMed PMID: 11356442.

(65 year old man developed hyperlactatemia and ascites 14 months after starting didanosine and stavudine [lactate 7 mmol/L, no acidosis, ALT 181 U/L], recovering slowly after stopping, but presenting 1 year later with signs of portal hypertension, ascites, encephalopathy and varices; biopsy did not show cirrhosis; possibly nodular regenerative hyperplasia).

Côté HC, Brumme ZL, Craib KJ, Alexander CS, Wynhoven B, Ting L, Wong H, et al. Changes in mitochondrial DNA as a marker of nucleoside toxicity in HIV-infected patients. N Engl J Med. 2002;346:811–20. PubMed PMID: 11893792.

(High serum lactate levels were associated with low ratio of mitochondrial to nuclear DNA in peripheral blood mononuclear cells from patients with HIV on stavudine and other agents).

Moyle GJ, Datta D, Mandalia S, Morlese J, Asboe D, Gazzard BG. Hyperlactataemia and lactic acidosis during antiretroviral therapy: relevance, reproducibility and possible risk factors. AIDS. 2002;16:1341–9. PubMed PMID: 12131210.

(Retrospective analysis of results of testing for lactate levels in 1239 patients with HIV infection, 108 [9%] had elevated levels >2.5 mmol/L and 9 [1%] >5 mmol/L of whom 4 had lactic acidosis and 2 died; in multivariate analysis, elevations were associated with didanosine use and female sex).

Hillaire S, Bonte E, Denninger MH, Casadevall N, Cadranel JF, Lebrec D, Valla D, et al. Idiopathic non-cirrhotic intrahepatic portal hypertension in the West: a re-evaluation in 28 patients. Gut. 2002;51:275–80. PubMed PMID: 12117894.

(Among 28 cases of NCPH diagnosed between 1994 and 1998, none were diagnosed with HIV infection and no discussion of drug relatedness; 12 had a prothrombotic disorder).

Dybul M, Fauci AS, Bartlett JG, Kaplan JE, Pau AK; Panel on Clinical Practices for the Treatment of HIV. Guidelines for using antiretroviral agents among HIV-infected adults and adolescents. Recommendations of the Panel on Clinical Practices for Treatment of HIV. MMWR Recomm Rep. 2002;51(RR-7):1–55. PubMed PMID: 12027060.

(Recommendations on use of antiretroviral agents for HIV infection including indications, efficacy, need for monitoring and side effects including hepatotoxicity).

Lemberg DA, Palasanthiran P, Goode M, Ziegler JB. Tolerabilities of antiretrovirals in paediatric HIV infection. Drug Saf. 2002;25:973–91. PubMed PMID: 12408730.

(Review of adverse events for the antiretrovirals in children; rates of hepatotoxicity appear to be similar in children as adults, mitochondrial toxicity is rare, but deaths due to pancreatitis and liver failure have been reported in children on didanosine).

Cihlar T, Birkus G, Greenwalt DE, Hitchcock MJM. Tenofovir exhibits low cytotoxicity in various human cell types: comparison with other nucleotide reverse transcriptase inhibitors. Antiviral Research. 2002;54:37–45. PubMed PMID: 11888656.

(Study to evaluate the in vitro effects of nucleoside analogues in various human cell types; tenofovir was less cytotoxic towards erythroid progenitor cells than zidovudine, stavudine, and zalcitabine).

Falcó V, Rodríguez D, Ribera E, Martínez E, Miró JM, Domingo P, Diazaraque R, et al. Severe nucleoside-associated lactic acidosis in human immunodeficiency virus-infected patients: report of 12 cases and review of the literature. Clin Infect Dis. 2002;34:838–46. PubMed PMID: 11850865.

(Between 1997-2000, 12 cases of lactic acidosis were reported in HIV-infected patients at 4 hospitals in Spain; ~1:1000 patient-years of treatment; all receiving nucleoside analogues for 1-36 months, 1 attributed to zidovudine, 11 to stavudine [1 also on didanosine] with ALT 30-524 U/L, 33% fatality rate).

Clark SJ, Creighton S, Portmann B, Taylor C, Wendon JA, Cramp ME. Acute liver failure associated with antiretroviral treatment for HIV: a report of six cases. J Hepatol. 2002;36:295–301. PubMed PMID: 11830344.

(6 patients with HIV infection who developed acute liver failure on stavudine [n=5], lamivudine [n=3], didanosine [n=2], saquinavir [n=2], efavirenz [n=2], nevirapine [n=2], or nelfinavir, delavirdine or zidovudine [n=1] for 1-3 months [peak bilirubin 2.7-32 mg/dL, AST 240-8650 U/L, Alk P 122-191 U/L]; 2 with signs of hypersensitivity; 2 with hepatitis B; 5 died, autopsies showing massive necrosis, one with massive steatosis, likely multiple causes).

Spengler U, Lichterfeld M, Rockstroh JK. Antiretroviral drug toxicity—a challenge for the hepatologist? J Hepatol. 2002;36:283–94. PubMed PMID: 11830343.

(Review of the diagnosis of drug induced liver disease in patients with HIV on antiretroviral agents, with discussion of mechanisms including mitochondrial toxicity and hypersensitivity reactions).

Cornejo-Juárez P, Sierra-Madero J, Volkow-Fernández P. Metabolic acidosis and hepatic steatosis in two HIV-infected patients of stavudine (d4T) treatment. Arch Med Res. 2003;34:64–9. PubMed PMID: 12604378.

(1 woman and 1 man developed fatigue and jaundice 5 and 1 months after switching to an antiretroviral regimen that included stavudine [bilirubin 14.3 and 27.0 mg/dL, ALT 45 and 62 U/L, Alk P 835 and 296 U/L] with lactic acidosis, hepatic steatosis and fatal outcome: Case 2).

Koch RO, Graziadel IW, Zangerle R, Romani N, Maier H, Vogel W. Acute hepatic failure and lactic acidosis associated with antiretroviral treatment for HIV. Wien Klin Wochenschr. 2003;115:135–40. PubMed PMID: 12674693.

(36 year old woman with HIV infection developed nausea and abdominal pain 18 months after starting didanosine and stavudine [bilirubin 1.2 rising to 12.0 mg/dL, ALT 40 to 177 U/L], developing pancreatitis, lactic acidosis, hepatic encephalopathy and ascites, recovering slowly upon stopping drugs, liver biopsy showed microvesicular fat and cholestasis with little inflammation).

Lonergan JT, Barber RE, Mathews WC. Safety and efficacy of switching to alternative nucleoside analogues following symptomatic hyperlactatemia and lactic acidosis. AIDS. 2003;17:2495–9. PubMed PMID: 14600521.

(Description of 12 patients with HIV infection on antiretrovirals who developed hyperlactatemia >5 mmol/L [2 with acidosis; all on stavudine], improving upon stopping therapy, and restarting nucleosides without stavudine was tolerated in all but one case [on zidovudine] who later tolerated lamivudine and abacavir).

Manfredi R, Motta R, Patrono D, Calza L, Chiodo F, Boni P. Frequency, risk factors and features of hyperlactatemia in a large number of patients undergoing antiretroviral therapy. AIDS. 2003;17:2131–3. PubMed PMID: 14502021.

(High lactate level found at least once in 36% of 743 HIV infected patients on antiretroviral therapy; few distinguishing characteristics from those who did not develop high lactates, longer duration of therapy and concurrent lipodystrophy or myopathy).

Kontorinis N, Dieterich D. Hepatotoxicity of antiretroviral therapy. AIDS Rev. 2003;5:36–43. PubMed PMID: 12875106.

(Review of hepatotoxicity of antiretroviral drugs; definition of hepatotoxicity in antiretroviral studies; grade 1=1.25-2.5 times, grade 2=2.6-5 times, grade 3=5.1-10 times and grade 4=>10 times normal or baseline ALT values; abacavir and lamivudine are least likely to cause hepatotoxicity).

Ogedegbe AE, Thomas DL, Diehl AM. Hyperlactataemia syndromes associated with HIV therapy. Lancet Infect Dis. 2003;3:329–37. PubMed PMID: 12781504.

(Review of mechanisms of hyperlactatemia with antiretroviral therapy, occurs mostly with use of nucleoside analogues, stavudine, didanosine and zidovudine, attributed to mitochondrial depletion, but other mechanisms may be involved).

Rivas P, Polo J, de Górgolas M, Fernández-Guerrero ML. Drug points: Fatal lactic acidosis associated with tenofovir. BMJ. 2003;327:711. PubMed PMID: 14512477.

(45 year old woman with HIV-HCV coinfection on didanosine, stavudine, and nevirapine developed jaundice and hepatomegaly after switching from nevirapine to tenofovir [bilirubin 12.6 mg/dL, ALT 157 U/L, CT showing fatty liver] and had worsening lactic acidosis despite medical support, and she died 36 hours after presentation).

Gérard Y, Viget N, Yazdanpanah Y, Ajana F, de La Tribonnière X, Bocket L, Deuffic-Burban S, et al. Hyperlactataemia during antiretroviral therapy: incidences, clinical data and treatment. Therapie. 2003;58:153–8. PubMed PMID: 12942856.

(Prospective study identified 64 patients with high lactate levels [18/1000 person-years], 10 with lactic acidosis [lactate 5.0-16 mmol/L, ALT 25-122 U/L], all receiving stavudine, one died).

Verucchi G, Calza L, Manfredi R, Chiodo F. Incidence of liver toxicity in HIV-infected patients receiving isolated dual nucleoside analogue antiretroviral therapy. J Acquir Immune Defic Syndr. 2003;33:546–8. PubMed PMID: 12869847.

(Retrospective analysis of 132 patients with HIV infection treated with two nucleoside analogues for at least 24 months; 52% developed ALT elevation, 6% >5 times ULN, only 1 with jaundice requiring discontinuation; higher rates in patients with HIV-HCV coinfection and with stavudine).

Lichterfeld M, Fischer HP, Spengler U, Rockstroh JK. Dtsch Med Wochenschr. 2003;128:81–4. [Fatty liver and increased serum lactate in a woman with HIV]. PubMed PMID: 12529837.

(50 year old developed abdominal pain and hepatomegaly 7 months after starting stavudine, lamivudine, indinavir and low dose ritonavir [ALT 434 U/L, GGT 58 U/L, lactate 9.2 mmol/L, pH 7.2], liver biopsy showing micro- and macro-steatosis, resolving a few weeks after stopping antivirals; most likely due to stavudine).

Ofotokun I, Pomeroy C. Sex differences in adverse reactions to antiretroviral drugs. Top HIV Med. 2003;11:55–9. PubMed PMID: 12717043.

(Review of sex differences in adverse events; higher frequency of mitochondrial toxicity and hypersensitivity in women than men).

Ogedegbe AO, Sulkowski MS. Antiretroviral-associated liver injury. Clin Liver Dis. 2003;7:475–99. PubMed PMID: 12879995.

(Review of hepatotoxicity of antiretrovirals; ALT elevations above 5 times ULN reported in 7% with zidovudine, 16% didanosine, 9-13% stavudine, <1% lamivudine, tenofovir and abacavir, 3-10% protease inhibitors, 10% nevirapine and 8% efavirenz; recommend monitoring at 4 weeks and then every 12 weeks, stopping if ALT levels are >10 times ULN or if symptoms of liver injury are present, monitoring more closely if ALT levels are elevated).

Bonnet F, Bonarek M, Morlat P, Mercie P, Dupon M, Gemain MC, Malvy D, et al. Risk factors for lactic acidosis in HIV-1-infected patients treated with nucleoside reverse-transcriptase inhibitors: a case-control study. Clin Infect Dis. 2003;36:1324–8. PubMed PMID: 12746780.

(Case control study of 9 patients [5 women] with HIV infection and lactic acidosis, 6 with hepatomegaly and 5 with jaundice, 8 on stavudine, 7 on didanosine, 6 on zidovudine; 6 died; risk factors were renal insufficiency and low CD4 counts, but numbers of cases were few).

Arenas-Pinto A, Grant AD, Edwards S, Weller IVD. Lactic acidosis in HIV-1 infected patients: a systematic review of published cases. Sex Transm Infect. 2003;79:340–3. PubMed PMID: 12902594.

(Review of 217 published cases of lactic acidosis; 53% female, all taking at least one nucleoside for 1-36 months, 61% on stavudine, 33% didanosine, 31% zidovudine, 30% lamivudine; 92% had hepatic steatosis on biopsy or autopsy; 48% died).

Lonergan JT, McComsey GA, Fisher RL, Shalit P, File TM Jr, Ward DJ, Williams VC, et al; ESS40010 (TARHEEL) Study Team. Lack of recurrence of hyperlactatemia in HIV-infected patients switched from stavudine to abacavir or zidovudine. J Acquir Immune Defic Syndr. 2004;36:935–42. PubMed PMID: 15220700.

(Prospective study of 118 patients with HIV infection on stavudine switched to abacavir or zidovudine, lactate levels fell with stopping stavudine and despite starting other agents; few were markedly hyperlactatemic).

Gallant JE, Staszewski S, Pozniak AL, DeJesus E, Suleiman JM, Miller MD, Coakley DF, et al. for the 903 Study Group. Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naïve patients: a 3-year randomized trial. JAMA. 2004;292:191–201. PubMed PMID: 15249568.

(Controlled trial of 3 years of tenofovir vs stavudine added to lamivudine and efavirenz in 600 treatment-naïve patients with HIV infection; ALT rises above 5 times normal in 4% of tenofovir- vs 5% of stavudine-treated; lactic acidosis in no tenofovir- vs 3 [1%] stavudine-treated subjects).

Montaner JS, Côté HC, Harris M, Hogg RS, Yip B, Harrigan PR, O'Shaughnessy MV. Nucleoside-related mitochondrial toxicity among HIV-infected patients receiving antiretroviral therapy: insights from the evaluation of venous lactic acid and peripheral blood mitochondrial DNA. Clin Infect Dis. 2004;38 Suppl 2:S73–9. PubMed PMID: 14986278.

(Review of issue of mitochondrial [mt] toxicity of nucleoside analogues in antiretroviral therapy; random testing for venous lactate levels identifies some patients with symptoms of mt toxicity, but does not predict severe lactic acidosis; mtDNA to nuclear DNA ratios in peripheral blood mononuclear cells correlates with hyperlactaemia and mt toxicity; ratios were lower in HIV-infected and in stavudine-treated subjects).

Walker UA, Bäuerle J, Laguno M, Murillas J, Mauss S, Schmutz G, Setzer B, et al. Depletion of mitochondrial DNA in liver under antiretroviral therapy with didanosine, stavudine, or zalcitabine. Hepatology. 2004;39:311–7. PubMed PMID: 14767983.

(Liver biopsies from 94 patients with chronic HCV [80 with concurrent HIV] were assessed for mitochondrial DNA content, which were 50% lower in patients on zalcitabine, didanosine, or stavudine compared to other nucleoside analogues; the decrease required 6 months or more of therapy).

Pujari SN, Patel AK, Naik E, Patel KK, Dravid A, Patel JK, Mane AA, et al. Effectiveness of generic fixed-dose combinations of highly active antiretroviral therapy for treatment of HIV infection in India. J Acquir Immune Defic Syndr. 2004;37:1566–9. PubMed PMID: 15577409.

(Analysis of 1291 patients started on nevirapine based combination regimens in India; rash in 6.6% and hepatitis in 3.2%, but no deaths from liver injury except 4 with lactic acidosis on stavudine).

Te HS. Cholestasis in HIV-infected patients. Clin Liver Dis. 2004;8:213–28. viii-ix. PubMed PMID: 15062202.

(Review of causes of cholestasis in HIV-infected patients including antiretrovirals).

Verucchi G, Calza L, Biagetti C, Attard L, Costigliola P, Manfredi R, Pasquinelli G, et al. Ultrastructural liver mitochondrial abnormalities in HIV/HCV-coinfected patients receiving antiretroviral therapy. J Acquir Immune Defic Syndr. 2004;35:326–8. PubMed PMID: 15076252.

(Electron microscopy of 34 liver biopsies done on HIV-HCV coinfected patients on long term antiretroviral therapy [2-14 years] and in 4 on no therapy found mitochondrial abnormalities in all except 1, but not associated with a specific agent and unclear whether due to therapy, HCV, HIV or other factors).

Abrescia N, D'Abbraccio M, Figoni M, Busto A, Maddaloni A, De Marco M. Hepatotoxicity of antiretroviral drugs. Curr Pharm Des. 2005;11:3697–710. PubMed PMID: 16305505.

(Review of hepatotoxicity of antiretrovirals; major syndrome is mitochondrial injury with lactic acidosis and severe hepatomegaly and steatosis).

Torti C, Lapadula G, Casari S, Puoti M, Nelson M, Quiros-Roldan E, Bella D, et al; EPOKA-MASTER Study Group. Incidence and risk factors for liver enzyme elevation during highly active antiretroviral therapy in HIV-HCV co-infected patients: results from the Italian EPOKA-MASTER Cohort. BMC Infect Dis. 2005;5:58. PubMed PMID: 16018804.

(Among 1038 HIV-HCV coinfected patients starting antiretroviral therapy, the risk of ALT elevations above 5 times ULN was 17.1/100 patient years in treatment-naïve and 8.2 in treatment-experienced group; risk factors being baseline ALT levels and use of nonnucleoside reverse transcriptase inhibitors).

Sulkowski MS, Mehta SH, Torbenson M, Afdhal NH, Mirel L, Moore RD, Thomas DL. Hepatic steatosis and antiretroviral drug use among adults coinfected with HIV and hepatitis C virus. AIDS. 2005;19:585–92. PubMed PMID: 15802977.

(Analysis of liver histology from 112 patients with HIV-HCV coinfection; 40% had some degree of steatosis [>5% of hepatocytes with fat] which was independently associated with white race, body weight, high blood sugar and ever having used stavudine).

Hofman P, Nelson AM. The pathology induced by highly active antiretroviral therapy against human immunodeficiency virus: an update. Curr Med Chem. 2006;13:3121–32. PubMed PMID: 17168701.

(Review of pathology of adverse effects of antiretroviral agents with examples of mitochondrial liver injury and cholestasis).

Núñez M. Hepatotoxicity of antiretrovirals: incidence, mechanisms and management. J Hepatol. 2006;44(1 Suppl):S132–9. PubMed PMID: 16364487.

(Review of hepatotoxicity of antiretrovirals; elevations in ALT or AST above 5 times ULN occurs in 2-18% of HIV-positive patients starting therapy, more frequent with HCV or HBV coinfection; combination of protease inhibitors with low dose ritonavir does not seem to increase risk; agents with highest risk are nevirapine and the nonnucleoside reverse transcriptase inhibitors).

Björnsson E, Olsson R. Suspected drug-induced liver fatalities reported to the WHO database. Dig Liver Dis. 2006;38:33–8. PubMed PMID: 16054882.

(In WHO database of fatal adverse drug reactions from 1968-2003, there were 4690 reports of fatal drug induced injury: stavudine was ranked the 4th most common cause [~120 cases]).

Labarga P, Soriano V, Vispo ME, Pinilla J, Martin-Carbonero L, Castellares C, Casado R, et al. Hepatotoxicity of antiretroviral drugs is reduced after successful treatment of chronic hepatitis C in HIV-infected patients. J Infect Dis. 2007;196:670–6. PubMed PMID: 17674307.

(Among 133 patients with HIV-HCV coinfection who were treated with interferon or peginterferon, 33% had a sustained response and subsequent yearly rate of hepatic events was higher among nonresponders [12.9%] than responders [3.1%]; also more common with receipt of di-deoxynucleosides).

Lapadula G, Izzo I, Costarelli S, Cologni G, Bercich L, Casari S, Gambarotti M, et al. Dideoxynucleoside HIV reverse transcriptase inhibitors and drug-related hepatotoxicity: a case report. J Med Case Rep. 2007;1:19. PubMed PMID: 17488516.

(43 year old woman with HIV and AIDS had elevations in ALT [222 U/L] while on stavudine and tenofovir for 2.8 years and indinavir and ritonavir for 5 months; worsening [ALT 353 U/L] despite stopping indinavir; liver biopsy showed micro- and macrovesicular fat and fibrosis; ALT improved after stopping stavudine despite remaining on tenofovir, lamivudine and nelfinavir).

Bourlière M, Duclos-Vallée JC, Pol S. Gastroenterol Clin Biol. 2007;31:895–905. [Liver and antiretrovirals: hepatotoxicity, steatosis and monitoring of patients with liver disease]. French. PubMed PMID: 18166875.

(Review of hepatotoxicity of antiretrovirals in French discussing patterns of toxic idiosyncrasy, hypersensitivity [nevirapine and abacavir], mitochondrial toxicity [zalcitabine, didanosine, stavudine and zidovudine], steatohepatitis [protease inhibitors with lipodystrophy], immune restoration [in patients with HIV-HBV or -HCV coinfection]; recommendations for management focusing on prevention and monitoring).

Esser S, Helbig D, Hillen U, Dissemond J, Grabbe S. Side effects of HIV therapy. J Dtsch Dermatol Ges. 2007;5:745–54. PubMed PMID: 17760894.

(Review of side effects of antiretroviral agents focusing on immune reconstitution syndrome, lipodystrophy, cutaneous skin reactions, hypersensitivity reactions [abacavir, nevirapine], hyperbilirubinemia [indinavir, atazanavir], local reactions [enfuvirtide], and hyperpigmentation [zidovudine, emtricitabine]).

Gil ACM, Lorenzetti R, Mendes GB, Marcillo AM, Toro AADC, da Silva MTN, dos Santos Vilela MM. Hepatotoxicity in HIV-infected children and adolescents on antiretroviral therapy. Sao Paulo Med J. 2007;125:205–9. PubMed PMID: 17992389.

(Retrospective analysis in 152 children [ages 1 to 18 years] with HIV infection on antiretroviral therapy; only 14 [10%] had ALT elevations and all were less than 5 times ULN; 4 on antituberculosis therapy; rarely used nonnucleoside reverse transcriptase inhibitors).

Jain MK. Drug-induced liver injury associated with HIV medications. Clin Liver Dis. 2007;11:615–39. vii-viii. PubMed PMID: 17723923.

(Review of hepatotoxicity of antiretroviral medications; ALT elevations occur in 2-18% of patients, but often resolve spontaneously even without dose modification; classes of injury include hypersensitivity [nevirapine, efavirenz, abacavir], mitochondrial injury [stavudine, didanosine, zidovudine], flares of hepatitis B [lamivudine, emtricitabine, tenofovir], flares of hepatitis C [any potent regimen], idiosyncratic injury [ritonavir, nevirapine, efavirenz], cholestatic hepatitis [many agents]).

Wester CW, Okezie OA, Thomas AM, Bussmann H, Moyo S, Muzenda T, Makhema J, et al. Higher-than-expected rates of lactic acidosis among highly active antiretroviral therapy-treated women in Botswana: preliminary results from a large randomized clinical trial. J Acquir Immune Defic Syndr. 2007;46:318–22. PubMed PMID: 18090299.

(Among 650 patients starting antiretroviral therapy, 2% developed hyperlactaemia [>4.4 mmol/L] and 1% lactic acidosis [all female, trend towards older age and higher body mass index] all on stavudine, didanosine, and/or zidovudine; 6 died, 4 of pancreatitis).

Songa PM, Castelnuovo B, Birabwa E, Ocama P, Kambugu A. Symptomatic hyperlactatemia associated with nucleoside analogue reverse-transcriptase inhibitor use in HIV-infected patients: a report of 24 cases in a resource-limited setting (Uganda). Clin Infect Dis. 2007;45:514–7. PubMed PMID: 17638205.

(Identified 24 patients with symptomatic hyperlactatemia, all on combination therapy including stavudine for 7 to 36 months, 83% women, 83% had neuropathy, weight loss common–2 to 18 kilograms; lactate 3.3 to 21.8 mmol/L, ALT and AST minimally elevated, 5 died).

Bolhaar MG, Karstaedt AS. A high incidence of lactic acidosis and symptomatic hyperlactatemia in women receiving highly active antiretroviral therapy in Soweto, South Africa. Clin Infect Dis. 2007;45:254–60. PubMed PMID: 17578788.

(Among 1735 adults with HIV infection started on antiretroviral therapy, 3% developed hyperlactatemia; 23 [1%] with lactic acidosis [22 women and 22 on stavudine, 1 on didanosine and zidovudine], 30% mortality; 44 had symptomatic hyperlactatemia [37 women, all 44 on stavudine, 3 also with didanosine], able to switch to zidovudine without recurrence, 2 of 3 relapsed on restarting stavudine).

Lactic Acidosis International Study Group. Risk factors for lactic acidosis and severe hyperlactataemia in HIV-1-infected adults exposed to antiretroviral therapy. AIDS. 2007;21:2455–64. PubMed PMID: 18025882.

(Retrospective case control study of 110 cases of patients with HIV and hyperlactataemia and 220 controls, identified risk factors of older age, female gender, low CD4 counts, and use of stavudine, didanosine or both).

Mussi-Pinhata MM, Rego MA, Freimanis L, Kakehasi FM, Machado DM, Cardoso EM, Read JS; NISDI Perinatal Protocol Study Group. Maternal antiretrovirals and hepatic enzyme, hematologic abnormalities among human immunodeficiency virus type 1-uninfected infants: the NISDI perinatal study. Pediatr Infect Dis J. 2007;26:1032–7. PubMed PMID: 17984811.

(Liver enzyme elevations in newborns of HIV infected mothers on various antiretroviral regimens; infants whose mothers received protease inhibitors were more likely to have ALT elevations [odds ratio 1.9] similarly for nonnucleoside reverse transcriptase inhibitors [odds ratio 2.4], most elevations were mild and self-limited).

Mallet V, Blanchard P, Verkarre V, Vallet-Pichard A, Fontaine H, Lascoux-Combe C, Pol S. Nodular regenerative hyperplasia is a new cause of chronic liver disease in HIV-infected patients. AIDS. 2007;21:187–92. PubMed PMID: 17197809.

(Among 8 patients with HIV infection referred for evaluation of liver disease of unknown cause, all had nodular regenerative hyperplasia and had received didanosine [and many received stavudine or zidovudine] for 1-2 years [bilirubin 0.2-2.0 mg/dL, ALT 0.4-2.0 times ULN, Alk P 0.9-19.1 times ULN, platelets 71-149,000/μL], all had varices and 5 had ascites).

Rosenthal E, Pialoux G, Bernard N, Pradler C, Rey D, Bentata M, Michelet C, et al; GERMIVIC Joint Study Group. Liver-related mortality in human-immunodeficiency-virus-infected patients between 1995 and 2003 in the French GERMIVIC Joint Study Group Network (MORTAVIC 2003 Study). J Viral Hepat. 2007;14:183–8. PubMed PMID: 17305884.

(A rising proportion of deaths among HIV infected patients in France were due to end stage liver disease: 1.5% in 1995, 6.6% in 1997, 14.3% in 2001, and 12.6% in 2003, HCV being the major cause [93%] and high alcohol intake [26%]).

Bae WH, Wester C, Smeaton LM, Shapiro RL, Lockman S, Onyait K, Thior I, et al. Hematologic and hepatic toxicities associated with antenatal and postnatal exposure to maternal highly active antiretroviral therapy among infants. AIDS. 2008;22:1633–40. PubMed PMID: 18670224.

(Prospective monitoring found that only 1 of 69 infants born to antiretroviral-treated mothers and none of 109 infants born to drug therapy unexposed mothers with HIV infection developed ALT elevations >5 times ULN during the first 7 months of life).

Hammer SM, Eron JJ Jr, Reiss P, Schooley RT, Thompson MA, Walmsley S, Cahn P, et al; International AIDS Society-USA. Antiretroviral treatment of adult HIV infection: 2008 recommendations of the International AIDS Society-USA panel. JAMA. 2008;300:555–70. PubMed PMID: 18677028.

(Recommendations on use of antiviral therapy in adults with HIV infection including use of recently approved agents: raltegravir, maraviroc and etravirine).

Inductivo-Yu I, Bonacini M. Highly active antiretroviral therapy-induced liver injury. Current Drug Safety. 2008;3:4–13. PubMed PMID: 18690975.

(Review of drug induced liver injury due to antiretroviral agents).

Saifee S, Joelson D, Braude J, Shrestha R, Johnson M, Sellers M, Galambos MR, et al. Noncirrhotic portal hypertension in patients with human immunodeficiency virus-1 infection. Clin Gastroenterol Hepatol. 2008;6:1167–9. PubMed PMID: 18639498.

(Among 11 patients with HIV presenting with NCPH [mean bilirubin 1.2 mg/dL, ALT 53 U/L, ALK P 226 U/L, Platelet count 177,000/μL], 6 had protein S deficiency, all had received didanosine, all had NRH, 3 had portal venopathy, all had esophageal varices, 3 with bleeding, 6 with ascites and 2 requiring porto-systemic stent shunts).

Jevtović Dj, Ranin J, Salemović D, Pesić I, Dragović G, Zerjav S, Djurković-Djaković O. The prevalence and risk of hepatitis flares in a Serbian cohort of HIV and HCV co-infected patients treated with HAART. Biomed Pharmacother. 2008;62:21–5. PubMed PMID: 17223307.

(Among 364 HIV-infected patients treated with antiretrovirals in Belgrade between 1998-2006, 24 [7%] developed ALT elevations >5 times ULN [mostly asymptomatic], risk factors being HCV [21%] and use of stavudine and saquinavir/ritonavir).

Akhtar MA, Mathieson K, Arey B, Post J, Prevette R, Hillier A, Patel P, et al. Hepatic histopathology and clinical characteristics associated with antiretroviral therapy in HIV patients without viral hepatitis. Eur J Gastroenterol Hepatol. 2008;20:1194–204. PubMed PMID: 18989143.

(23 patients with HIV infection without HBV or HCV coinfection with abnormal liver tests; attributed to antiretroviral agents in 17 [74%]; fatty liver was common).

Thoden J, Lebrecht D, Venhoff N, Neumann J, Muller K, Walker UA. Highly active antiretroviral HIV therapy-associated fatal lactic acidosis: quantitative and qualitative mitochondrial DNA lesions with mitochondrial dysfunction in multiple organs. AIDS. 2008;22:1093–4. PubMed PMID: 18520357.

(62 year old man developed hyperlactatemia [3.7 mmol/L] without acidosis or symptoms 16 months after starting didanosine-stavudine-efavirenz, 2 months later developed fatal lactic acidosis and multiorgan failure; mitochondrial copy numbers assessed in multiple organs being reduced to 7% of normal levels in liver, 20% in kidney, 28% in muscle and 72% in heart).

Castelnuovo B, Nanyonjo A, Kamya M, Ocama P. Is it safe to switch from stavudine to zidovudine after developing symptomatic hyperlactatemia? Afr Health Sci. 2008;8:133–4. PubMed PMID: 19357764.

(60 year old woman developed symptomatic lactatemia 19 months after starting stavudine, lamivudine and nevirapine; switching to zidovudine was followed by fall of lactate levels to normal [5.2→1.6 mmol/L], but 10 months later levels rose again [3.7 mmol/L]).

Fabian J, Venter WD, Mkhabela L, Levin JB, Baker L, Naicker S. Symptomatic hyperlactataemia in adults on antiretroviral therapy: a single-centre experience. S Afr Med J. 2008;98:795–800. PubMed PMID: 19115757.

(Retrospective analysis of 2587 adults with HIV infection started on antiretroviral therapy; 35 developed serum lactate levels >5 mmol/L, all of whom were on stavudine for 2-13 months, 86% females, 37% had neuropathy, most had weight loss, 7 died).

Stead D, Osler M, Boulle A, Rebe K, Meintjes G. Severe hyperlactataemia complicating stavudine first-line antiretroviral therapy in South Africa. Antivir Ther. 2008;13:937–43. PubMed PMID: 19043928.

(Retrospective analysis of 75 patients with HIV infection and symptomatic hyperlactatemia; 95% were women, all on stavudine [1.7 per 100 patient-years], 71% with lactic acidosis, 12 died; 30 switched to zidovudine without recurrence).

Nelson M, Azwa A, Sokwala A, Harania RS, Stebbing J. Fanconi syndrome and lactic acidosis associated with stavudine and lamivudine therapy. AIDS. 2008;22:1374–6. PubMed PMID: 18580619.

(42 year old woman developed lactic acidosis 9 months after starting stavudine, lamivudine and nevirapine [serum enzymes normal, pH 7.15, lactate 5.3, glucosuria, phosphaturia], improving stopping therapy).

van Griensven J, Atté EF, Reid T. Symptomatic hyperlactatemia: lessons learned using a point-of-care device in a health care center- and nurse-based antiretroviral program in Rwanda. Clin Infect Dis. 2008;46:320–2. PubMed PMID: 18171270.

(Attempt at standardized approach for early recognition of symptoms and signs of hyperlactatemia with limited testing resources).

Soriano V, Puoti M, Garcia-Gascó P, Rockstroh JK, Benhamou Y, Barreiro P, McGovern B. Antiretroviral drugs and liver injury. AIDS. 2008;22:1–13. PubMed PMID: 18090386.

(Review of hepatotoxicity of antiretroviral drugs with recommendations on management, stopping therapy if symptoms arise, with overt jaundice [direct bilirubin], evidence of mitochondrial toxicity, ALT >10 times ULN, ALT at lower levels if newly marketed agent; important to rule out other causes, problematic agents include didanosine, stavudine and zidovudine; nevirapine and efavirenz, full dose ritonavir and tipranavir).

Kumarasamy N, Venkatesh KK, Cecelia AJ, Devaleenal B, Lai AR, Saghayam S, Balakrishnan P, Yepthomi T, Poongulali S, Flanigan TP, Solomon S, Mayer KH. Spectrum of adverse events after generic HAART in southern Indian HIV-infected patients. AIDS Patient Care STDS. 2008;22:337–44. PubMed PMID: 18422462.

(Among 3154 patients with HIV infection treated with antiretroviral agents over a 4 year period at a single center in Southern India, hepatitis occurred in 3.5% usually within the first 3 months; lactic acidosis was more common in women and was associated with stavudine use).

Chalasani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, Yang H, Rochon J; Drug Induced Liver Injury Network (DILIN). Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. Gastroenterology. 2008;135:1924–34. PubMed PMID: 18955056.

(Among 300 cases of drug induced liver disease in the US collected between 2004 and 2008, 7 were attributed to antiretroviral agents, 2 nevirapine, 1 efavirenz and 4 miscellaneous combinations).

Ingiliz P, Benhamou Y. Elevated liver enzymes in HIV monoinfected patients on HIV therapy: what are the implications? J HIV Ther. 2009;14:3–7. PubMed PMID: 19731558.

(Review of the causes of serum enzyme elevations during antiretroviral therapy; nucleoside analogues can cause lactic acidosis but vary considerably in risk).

Ferrajolo C, Capuano A, Verhamme KM, Schuemie M, Rossi F, Stricker BH, Sturkenboom MC. Drug-induced hepatic injury in children: a case/non-case study of suspected adverse drug reactions in VigiBase. Br J Clin Pharmacol. 2010;70:721–8. PubMed PMID: 21039766.

(Worldwide pharmacovigilance database contained 9036 hepatic adverse drug reactions in children, 3 antiretroviral agents were among the top 40 cases, including zidovudine [8th, 106 cases], lamivudine [26th, 45 cases] and nevirapine [36th, 37 cases]).

Reuben A, Koch DG, Lee WM; Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology. 2010;52:2065–76. PubMed PMID: 20949552.

(Among 1198 patients with acute liver failure enrolled in a US prospective study between 1998 and 2007, 133 were attributed to drug induced liver injury and 4 to antiretroviral agents, including 3 to combinations with stavudine and 1 to abacavir).

Moses M, Zachariah R, Tayler-Smith K, Misinde D, Foncha C, Manzi M, Bauerfeind A, et al. Outcomes and safety of concomitant nevirapine and rifampicin treatment under programme conditions in Malawi. Int J Tuberc Lung Dis. 2010;14:197–202. PubMed PMID: 20074411.

(Among 156 African patients with HIV infection and tuberculosis starting treatment with stavudine, lamivudine and nevirapine and given isoniazid, rifampin and pyrazinamide for tuberculosis, ALT elevations >5 times ULN developed in only one patient and none had clinically apparent liver injury).

van Griensven J, Zachariah R, Rasschaert F, Mugabo J, Atté EF, Reid T. Stavudine- and nevirapine-related drug toxicity while on generic fixed-dose antiretroviral treatment: incidence, timing and risk factors in a three-year cohort in Kigali, Rwanda. Trans R Soc Trop Med Hyg. 2010;104:148–53. PubMed PMID: 19732926.

(In a cohort study of 2190 adults receiving antiretroviral therapy, hepatotoxicity arose in 1.3% of patients taking nevirapine, but in none of those on stavudine).

Kovari H, Ledergerber B, Battegay M, Rauch A, Hirschel B, Foguena AK, Vernazza P, et al. Incidence and risk factors for chronic elevation of alanine aminotransferase levels in HIV-infected persons without hepatitis b or c virus co-infection. Clin Infect Dis. 2010;50:502–11. PubMed PMID: 20085465.

(Among 2365 HIV-infected patients followed longitudinally, 26% of those on stavudine had liver test abnormalities, which also correlated with zidovudine use, increased BMI, and elevated HIV RNA levels).

Fielder J, Rambiki K. Occurrence of stavudine-induced lactic acidosis in 3 members of an African family. J Int Assoc Physicians AIDS Care (Chic). 2010;9:236–9. PubMed PMID: 20798404.

(A 35 year old father, 29 year old mother and 5 year old child all developed high lactate levels and gastrointestinal symptoms 1-2 years after starting stavudine with nevirapine and lamivudine [ALT 89, 231 U/L and not given, lactate 4.4, 7.9 and 5.3 µmol/L, arterial pH not given], resolving slowly over 3-6 months).

Menezes CN, Maskew M, Sanne I, Crowther NJ, Raal FJ. A longitudinal study of stavudine-associated toxicities in a large cohort of South African HIV infected subjects. BMC Infect Dis. 2011;11:244. PubMed PMID: 21923929.

(Analysis of cohort of 8497 adults started on stavudine based antiretroviral therapy followed for median of 19 months found incidence of lactic acidosis to be 1.6 and symptomatic hyperlactataemia 3.6 per 100 person years, risk factors being higher BMI and female sex).

Hartleb M, Gutkowski K, Milkiewicz P. Nodular regenerative hyperplasia: evolving concepts on underdiagnosed cause of portal hypertension. World J Gastroenterol. 2011;17:1400–9. PubMed PMID: 21472097.

(Review of etiology, course and management of nodular regenerative hyperplasia; mentions its association with azathioprine, mercaptopurine, thioguanine, oxaliplatin and antiretroviral agents).

Dlamini J, Ledwaba L, Mokwena N, Mokhathi T, Orsega S, Tsoku M, Kowo H, et al. Lactic acidosis and symptomatic hyperlactataemia in a randomized trial of first-line therapy in HIV-infected adults in South Africa. Antivir Ther. 2011;16:605–9. PubMed PMID: 21685549.

(Among 1771 patients with HIV infection treated with one of 4 antiviral regimens with didanosine or stavudine, 13 developed lactic acidosis [3.5/1000 patient-years]; lactic acidosis cases were more likely female, with higher BMI and exposure to stavudine).

Feeney ER, Chazallon C, O'Brien N, Meiffrédy V, Goodall RL, Aboulker JP, Cooper DA, et al; INITIO Trial International Co-ordinating Committee. Hyperlactataemia in HIV-infected subjects initiating antiretroviral therapy in a large randomized study (a substudy of the INITIO trial). HIV Med. 2011;12:602–9. PubMed PMID: 21599820.

(Among 911 patients with HIV infection started on antiretroviral therapy with didanosine and stavudine, 24 developed elevated lactate levels; abnormalities were more frequent in women than men and those with higher BMI; not predicted by or accompanied by peripheral lymphocyte mitochondrial DNA levels).

Schiano TD, Uriel A, Dieterich DT, Fiel MI. The development of hepatoportal sclerosis and portal hypertension due to didanosine use in HIV. Virchows Arch. 2011;458:231–5. PubMed PMID: 21057809.

(45 year old man with HIV infection developed nodular regenerative hyperplasia 5 years after starting a regimen of didanosine, stavudine and protease inhibitors that progressed despite switching to zidovudine, lamivudine, abacavir and tenofovir, with biopsy 5 years later showing hepatoportal sclerosis).

Cotte L, Bénet T, Billioud C, Miailhes P, Scoazec JY, Ferry T, Brochier C, et al. The role of nucleoside and nucleotide analogues in nodular regenerative hyperplasia in HIV-infected patients: a case control study. J Hepatol. 2011;54:489–96. PubMed PMID: 21056493.

(Case controlled study of 13 patients with HIV infection and nodular regenerative hyperplasia [NRH] and 78 HIV infected controls found that age, duration of didanosine and stavudine therapy were independently associated with NRH).

Blanco F, Barreiro P, Ryan P, Vispo E, Martín-Carbonero L, Tuma P, Labarga P, et al. Risk factors for advanced liver fibrosis in HIV-infected individuals: role of antiretroviral drugs and insulin resistance. J Viral Hepat. 2011;18:11–6. PubMed PMID: 20088890.

(Among 681 unselected patients with HIV infection undergoing ultrasound elastography, 215 had elevated values [>9.5 kPa] which were independently associated with HCV coinfection, ALT elevations, history of alcohol abuse, abnormal HOMA values and exposure to didanosine or stavudine).

Kalyesubula R, Kagimu M, Opio KC, Kiguba R, Semitala CF, Schlech WF, Katabira ET. Hepatotoxicity from first line antiretroviral therapy: an experience from a resource limited setting. Afr Health Sci. 2011;11:16–23. PubMed PMID: 21572852.

(Among 240 adults starting one of 3 antiretroviral regimens, 66 [27%] had new onset of ALT or AST elevations during first 3 months of therapy, but only 10 [4.2%] with ALT >2.5 times ULN, 5 with jaundice, no deaths).

Domingo P, Cabeza MC, Pruvost A, Torres F, Salazar J, del Mar Gutierrez M, Mateo MG, et al. Association of thymidylate synthase gene polymorphisms with stavudine triphosphate intracellular levels and lipodystrophy. Antimicrob Agents Chemother. 2011;55:1428–35. PubMed PMID: 21282454.

(Analysis of polymorphisms in the thymidylate synthase [TS] gene in patients with and without lipodystrophy found an association of higher intracellular stavudine TP levels in white cells, "low expression" TS variants and lipodystrophy).

Castelnuovo B, Kiragga A, Kamya MR, Manabe Y. Stavudine toxicity in women is the main reason for treatment change in a 3-year prospective cohort of adult patients started on first-line antiretroviral treatment in Uganda. J Acquir Immune Defic Syndr. 2011;56:59–63. PubMed PMID: 20861741.

(Among 704 adults started on antiretroviral therapy with stavudine or zidovudine and followed for a median of 33 months, 91 had a drug treatment change because of toxicity, 87 [84%] were for stavudine).

Palmer M, Chersich M, Moultrie H, Kuhn L, Fairlie L, Meyers T. Frequency of stavudine substitution due to toxicity in children receiving antiretroviral treatment in Soweto, South Africa. AIDS. 2013;27:781–5. PubMed PMID: 23169331.

(Among 2222 children starting antiretroviral therapy for HIV infection between 2004 and 2008 followed for an average of 18 months, 96 developed stavudine toxicity including 87 cases of lipodystrophy and 3 of lactic acidosis).

Menezes CN, Duarte R, Dickens C, Dix-Peek T, Van Amsterdam D, John MA, Ive P, et al. The early effects of stavudine compared with tenofovir on adipocyte gene expression, mitochondrial DNA copy number and metabolic parameters in South African HIV-infected patients: a randomized trial. HIV Med. 2013;14:217–25. PubMed PMID: 23036096.

(Among 60 adults started on antiretroviral therapy, at 4 weeks adipocyte mitochondrial DNA decreased by 22-35% in stavudine treated vs 4% in tenofovir treated patients).

van Oosterhout JJ, Mallewa J, Kaunda S, Chagoma N, Njalale Y, Kampira E, Mukaka M, et al. Stavudine toxicity in adult longer-term ART patients in Blantyre, Malawi. PLoS One. 2012;7(7):e42029. PubMed PMID: 22848696.

(Monitoring of 253 adults enrolling in an antiretroviral program for HIV infection in Malawi found incident rates for any adverse event as 27 per 100 person-years, including peripheral neuropathy [20 per 100 person years], lipodystrophy [11], high lactate [2.1]).

Morén C, Noguera-Julian A, Garrabou G, Catalán M, Rovira N, Tobías E, Cardellach F, et al. Mitochondrial evolution in HIV-infected children receiving first- or second-generation nucleoside analogues. J Acquir Immune Defic Syndr. 2012;60:111–6. PubMed PMID: 22362155.

(Among 28 children with HIV infection, lactate levels rose and cytochrome c oxidase activity in white cells fell in those treated with first generation nucleoside analogues for up to 2 years [including stavudine: n=15], but not in those on second generation agents [n=13]).

Schouten JN, Van der Ende ME, Koëter T, Rossing HH, Komuta M, Verheij J, van der Valk M, et al. Risk factors and outcome of HIV-associated idiopathic noncirrhotic portal hypertension. Aliment Pharmacol Ther. 2012;36:875–85. PubMed PMID: 22971050.

(Comparison of 16 patients with HIV infection and NCPH vs 64 controls identified in the Netherlands, cases were younger [44 vs 52 years], had lower CD4 counts, higher ALT and Alk P, and more likely to have received didanosine [16] or stavudine [11] or both).

Phan V, Thai S, Choun K, Lynen L, van Griensven J. Incidence of treatment-limiting toxicity with stavudine-based antiretroviral therapy in Cambodia: a retrospective cohort study. PLoS One. 2012;7:e30647. PubMed PMID: 22303447.

(Retrospective analysis of cohort of 2581 adults initiating stavudine based regimens for HIV infection found rates of discontinuation of stavudine to be 11% for neuropathy, 37% lipodystrophy and 0.5% [n=14] for lactic acidosis; risk factors for lactic acidosis being female sex, higher BMI and concurrent therapy for tuberculosis).

Mateo MG, del Mar Gutierrez M, Vidal F, Domingo P. Drug safety evaluation profile of stavudine plus lamivudine for HIV-1/AIDS infection. Expert Opin Drug Saf. 2012;11:473–85. PubMed PMID: 22468613.

(Review of the safety of stavudine and lamivudine as an antiretroviral regimen in resource limited settings; while no longer recommended in the developed world, stavudine may have a role, "if there is no other chance" for antiretroviral therapy).

Dragovic G, Jevtovic D. The role of nucleoside reverse transcriptase inhibitors usage in the incidence of hyperlactatemia and lactic acidosis in HIV/AIDS patients. Biomed Pharmacother. 2012;66:308–11. PubMed PMID: 22658063.

(Among 396 patients with HIV infection started on antiretroviral therapy, hyperlactemia developed in 19 [none died] and lactic acidosis in 15 [4 died]; risk factors for lactic acidosis were exposure to didanosine [n=3], stavudine [n=4] or both [n=8]).

Arenas-Pinto A, Weller I, Ekong R, Grant A, Karstaedt A, Reiss P, Telisinghe L, Weber R, Bolhaar M, Bradman N, Ingram C. Common inherited mitochondrial DNA mutations and nucleoside reverse transcriptase inhibitor-induced severe hyperlactataemia in HIV-infected adults: an exploratory study. Antivir Ther. 2012;17:275–82. PubMed PMID: 22293466.

(Among 40 South African patients with HIV infection who developed hyperlactemia on stavudine based therapy, distribution of mitochondrial DNA haplotypes was the same as in controls).

Barlow-Mosha L, Eckard AR, McComsey GA, Musoke PM. Metabolic complications and treatment of perinatally HIV-infected children and adolescents. J Int AIDS Soc. 2013;16:18600. PubMed PMID: 23782481.

(Review of metabolic complications [including lipodystrophy and lactic acidosis] of long term antiretroviral therapy in children and adolescents).

Vispo E, Cevik M, Rockstroh JK, Barreiro P, Nelson M, Scourfield A, Boesecke C, et al; European Network of Clinical Trials (NEAT). Genetic determinants of idiopathic noncirrhotic portal hypertension in HIV-infected patients. Clin Infect Dis. 2013;56:1117–22. PubMed PMID: 23315321.

(Case control study of 22 HIV infected patients with noncirrhotic portal hypertension [NCPH] and 58 controls for single nucleotide polymorphisms in genes for enzymes involved in purine metabolism identified 2 single nucleotide polymorphisms in the 5-nucleotidase and 2 in the xanthine oxidase genes associated with presence of NCPH).

Verheij J, Schouten JN, Komuta M, Nevens F, Hansen BE, Janssen HL, Roskams T. Histological features in western patients with idiopathic non-cirrhotic portal hypertension. Histopathology. 2013;62:1083–91. PubMed PMID: 23600724.

(Histological analysis of 70 patients with NCPH, 13 with HIV infection who were more likely to have NRH [93% vs 46%] and who had a similar risk for underlying thrombophilic condition [31% vs 40%]).

Wagner TA, Lin CH, Tobin NH, Côté HC, Sloan DD, Jerome KR, Frenkel LM. Quantification of mitochondrial toxicity in HIV-infected individuals by quantitative PCR compared to flow cytometry. Cytometry B Clin Cytom. 2013;84:55–8. PubMed PMID: 23044657.

(Ratios of concentrations of mitochondrial vs nuclear DNA and proteins in peripheral blood mononuclear cells were similar in patients with or without clinical evidence of mitochondrial injury due to antiretroviral therapy).

van Oosterhout JJ, Gardner K, Mallewa J, Kaunda S, Kampira E, Payne B, Heyderman RS, et al. Severe toxicity and polymerase-γ gene abnormalities in Malawian adults on stavudine-based antiretroviral therapy. Pharmacogenet Genomics. 2013;23:624–6. PubMed PMID: 23962909.

(Among 14 patients with severe stavudine toxicity [lactate syndromes, neuropathy, lipodystrophy], none had mutations in the POLG gene, suggesting that heterozygosity for these gene mutations is not a risk factor for mitochondrial toxicity of stavudine).

Chagoma N, Mallewa J, Kaunda S, Njalale Y, Kampira E, Mukaka M, Heyderman RS, et al. Longitudinal lactate levels from routine point-of-care monitoring in adult Malawian antiretroviral therapy patients: associations with stavudine toxicities. Trans R Soc Trop Med Hyg. 2013;107:615–9. PubMed PMID: 23926161.

(Among 253 patients with HIV infection on stavudine based antiretroviral therapy who were monitored for serum lactate levels, 210 [83%] had at least one elevation and 64 [26%] had sustained elevations).

Menezes CN, Crowther NJ, Duarte R, Van Amsterdam D, Evans D, Dickens C, Dix-Peek T, et al. A randomized clinical trial comparing metabolic parameters after 48 weeks of standard- and low-dose stavudine therapy and tenofovir disoproxil fumarate therapy in HIV-infected South African patients. HIV Med. 2014;15:3–12. PubMed PMID: 23980620.

(Among 60 patients with HIV infection treated with either [low or standard dose] stavudine vs tenofovir for 48 weeks, mitochondrial DNA copies decreased by 4% among tenofovir vs 29-32% among stavudine treated patients, and 3 cases of lactic acidosis occurred in stavudine vs none in the tenofovir treated subjects).

Sood A, Castrejón M, Saab S. Human immunodeficiency virus and nodular regenerative hyperplasia of liver: A systematic review. World J Hepatol. 2014;6:55–63. PubMed PMID: 24653794.

(A review of the literature on nodular regenerative hyperplasia in HIV infected patients).

Yajima K, Uehira T, Otera H, Koizumi Y, Watanabe D, Kodama Y, Kuzushita N, et al. A case of non-cirrhotic portal hypertension associated with anti-retroviral therapy in a Japanese patient with human immunodeficiency virus infection. J Infect Chemother. 2014;20:582–5. PubMed PMID: 25034388.

(35 year old Japanese woman with HIV infection presented with ascites and gastrointestinal bleeding 4 years after stopping a 5 year course of didanosine [bilirubin 0.2 mg/dL, ALT 82 U/L, AST 83 U/L, Alk P 268 U/L, platelets 207,000 /μL, TE=9.3 kPa, biopsy showing no cirrhosis], with improvement and resolution of ascites and abnormal liver tests after control of bleeding and avoidance of nucleoside analogs).

Parikh ND, Martel-Laferriere V, Kushner T, Childs K, Vachon ML, Dronamraju D, Taylor C, et al. Clinical factors that predict noncirrhotic portal hypertension in HIV-infected patients: a proposed diagnostic algorithm. J Infect Dis. 2014;209:734–8. PubMed PMID: 23911709.

(Comparison of 35 HIV infected persons with noncirrhotic portal hypertension to 68 controls identified multiple clinical differences; authors propose a diagnostic algorithm that includes exposure to didanosine, splenomegaly, low platelet count or serum enzyme elevations as suggestive of diagnosis and warranting further evaluation).

Hernández N, Bessone F, Sánchez A, di Pace M, Brahm J, Zapata R, A, Chirino R, et al. Profile of idiosyncratic drug induced liver injury in Latin America. An analysis of published reports. Ann Hepatol. 2014;13:231–9. PubMed PMID: 24552865.

(Systematic review of literature of drug induced liver injury in Latin American countries published from 1996 to 2012 identified 176 cases, 5 of which [3%] were attributed to antiretroviral agents [nevirapine, zidovudine and lamivudine], but none to stavudine).

Brescini L, Orsetti E, Gesuita R, Piraccini F, Marchionni E, Staffolani S, Castelli P, et al. Evaluating liver fibrosis by transient elastometry in patients with HIV-HCV coinfection and monoinfection. Hepat Mon. 2014;14:e15426. PubMed PMID: 25337140.

(Among 354 adults undergoing transient elastography (TE), abnormal stiffness was found in 13% with HIV infection alone, 39% with HCV infection alone and 51% with both; treatment with stavudine and didanosine being associated with higher TE scores).

Turon F, Silva-Junior G, Hernandez-Gea V, Garcia-Pagan JC. Hipertensión portal idiopática no cirrótica. Gastroenterol Hepatol. 2015;38:556–62. [Idiopathic non-cirrhotic portal hypertension]. Spanish. PubMed PMID: 26321321.

(Review of noncirrhotic portal hypertension including epidemiology, pathogenesis, clinical presentation and management).

Arora A, Sarin SK. Multimodality imaging of obliterative portal venopathy: what every radiologist should know. Br J Radiol. 2015;88:20140653. PubMed PMID: 25514699.

(Review of the radiologic findings of noncirrhotic portal hypertension that accompanies obliterative portal venopathy; typical findings being increased spleen size and stiffness with normal or shrunken liver, portal vein enlargement and varices).

Ioannou GN, Bryson CL, Weiss NS, Boyko EJ. Associations between lipodystrophy or antiretroviral medications and cirrhosis in patients with HIV infection or HIV/HCV coinfection. Eur J Gastroenterol Hepatol. 2015;27:577–84. PubMed PMID: 25769096.

(In an analysis of the Veterans Administration Healthcare system Clinical Care Registry, long term use of didanosine but not other antiretroviral agents was found to be a risk factor for cirrhosis in patients with HIV monotherapy in contrast to patients with HIV-HCV coinfection, in whom all long term antiretroviral therapies were risk factors for cirrhosis).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology. 2015;148:1340–52.e7. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, 12 cases [1.3%] were attributed to antiretroviral agents, including one to zidovudine and one to didanosine but none to stavudine).

Kovari H, Sabin CA, Ledergerber B, Ryom L, Reiss P, Law M, Pradier C, et al. Antiretroviral drugs and risk of chronic alanine aminotransferase elevation in human immunodeficiency virus (HIV)-monoinfected

persons: the data collection on adverse events of anti-HIV drugs study. Open Forum Infect Dis. 2016;3:ofw009. PubMed PMID: 26925429.

(Among 21,495 persons observed for an average of 4-5 years in a prospective observation study of adverse events among HIV positive patients without HBV or HCV on antiretroviral therapy, 6368 [30%] developed chronically elevated liver tests [6 per 100 patient years] and risk factors included didanosine, stavudine and tenofovir therapy but not lamivudine, abacavir or most protease inhibitors).

Vilarinho S, Sari S, Yilmaz G, Stiegler AL, Boggon TJ, Jain D, Akyol G, et al. Recurrent recessive mutation in deoxyguanosine kinase causes idiopathic noncirrhotic portal hypertension. Hepatology. 2016;63:1977–86. PubMed PMID: 26874653.

(Complete exome sequencing of DNA from 8 children with idiopathic noncirrhotic portal hypertension identified an extremely rare gene variant which was homozygous in all 8 children, the gene being deoxyguanosine kinase, an enzyme required for mitochondrial DNA replication that is also inhibited by didanosine, perhaps explaining its hepatotoxicity).

Ryom L, Lundgren JD, De Wit S, Kovari H, Reiss P, Law M, El-Sadr W, et al. D:A:D Study Group. Use of antiretroviral therapy and risk of end-stage liver disease and hepatocellular carcinoma in HIV-positive persons. AIDS. 2016;30:1731–43. PubMed PMID: 26752282.

(Among 45,544 individuals followed for a median of 8.4 years in a prospective observation study of adverse events in patients with HIV infection on antiretroviral drugs, 209 developed end stage liver disease and 110 hepatocellular carcinoma, the combined rate being 1 per 1000 patient years; increase risk for these outcomes occurred in those with HCV and HBV infection but was also linked to long-term therapy with stavudine, didanosine, and tenofovir).

Ahmad AK, Atzori S, Taylor-Robinson SD, Maurice JB, Cooke GS, Garvey L. Spleen stiffness measurements using point shear wave elastography detects noncirrhotic portal hypertension in human immunodeficiency virus. Medicine (Baltimore). 2019;98:e17961. PubMed PMID: 31764798.

(Among 25 patients with HIV infection undergoing shearwave elastography, spleen stiffness was more reliable than liver stiffness in assessing noncirrhotic portal hypertension, being elevated in 6 of 11 cases of NCPH but in none of 14 controls).

Venter WDF, Kambugu A, Chersich MF, Becker S, Hill A, Arulappan N, Moorhouse M, et al. Efficacy and safety of tenofovir disoproxil fumarate versus low-dose stavudine over 96 weeks: a multicountry randomized, noninferiority trial. J Acquir Immune Defic Syndr. 2019;80:224–33. PubMed PMID: 30640204.

(Among 1072 patients with HIV infection treated with stavudine or tenofovir [both combined with lamivudine and efavirenz], response rates were similar while drug related adverse events were more frequent with stavudine [31% vs 25%], including lipodystrophy [5.6% vs 0.2%], lactic acidosis [0.8% vs none] and discontinuations for adverse events [6.7% vs 1.1%]).