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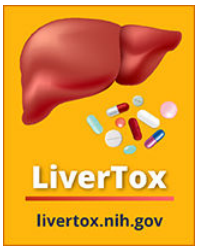


Lamivudine

Updated: April 18, 2019.

OVERVIEW

Introduction

Lamivudine is a nucleoside analogue and reverse transcriptase inhibitor used in the therapy of human immunodeficiency virus (HIV) and hepatitis B virus (HBV) infection. Lamivudine is a very rare cause of clinically apparent drug induced liver injury, but is associated with flares of underlying hepatitis B during therapy or with abrupt withdrawal.

Background

Lamivudine (la miv' ue deen) is an L-enantiomer and substituted analogue of cytidine (2',3'-dideoxy-3'-3-thiacytidine: 3TC) and is active against both HIV and HBV in vitro and in vivo. Lamivudine is phosphorylated intracellularly to the triphosphate which competes with the naturally occurring cytidine triphosphate for incorporation into the growing HIV or HBV DNA chain by the viral polymerase, thereby inhibiting polymerase (or reverse transcriptase) activity and causing chain termination. Lamivudine is indicated for the treatment of HBV infection as a single agent and for HIV infection in combination with other HIV medications. For HIV infection, lamivudine is available as 150 and 300 mg tablets and as oral solutions under the trade name Epivir. Lamivudine is also available in multiple fixed combinations with other antiretroviral agents such as zidovudine, abacavir, tenofovir, efavirenz, nevirapine, dolutegravir and others. The recommended dose of lamivudine for HIV infection in adults is 150 mg twice daily or 300 mg once daily. For HBV infection the recommended dose of lamivudine in adults is 100 mg orally once daily, the drug being available in this dose under the trade name Epivir-HBV. Lamivudine was approved by the FDA for HIV infection in 1995 and for HBV infection in 1998. Lamivudine is currently used in many HAART regimens but is now rarely used to treat hepatitis B because of a high rate of antiviral resistance when it is used as monotherapy as well as the availability of more potent agents with a higher barrier to resistance. Side effects of lamivudine are uncommon but may include headache, nausea, fatigue diarrhea and cough. Severe adverse events occur largely when it is withdrawn in patients with chronic hepatitis B or with the development of antiviral resistance.

Hepatotoxicity

Elevations in serum ALT levels occur in a proportion of patients with chronic hepatitis B treated with lamivudine. These elevations appear to be due to a transient flare in the underlying chronic hepatitis B and occur in three situations during and after therapy: upon initiation of therapy (treatment flares), upon development of antiviral resistance (breakthrough flares), and shortly after stopping therapy (withdrawal flares). Treatment flares typically occur during the first few months of therapy and are marked by asymptomatic elevations in serum aminotransferase levels and rarely with jaundice or symptoms (Case 1). These flares occur during the rapid

decrease in HBV DNA levels with initiation of therapy. An exacerbation of hepatitis also typically occurs after development of lamivudine resistance, a few weeks or months after the initial appearance of the mutant HBV strain and rise in HBV DNA levels (Case 2). Finally, withdrawal flares occur between 4 and 12 weeks after stopping lamivudine and can be severe, symptomatic and even lead to clinical decompensation, acute liver failure and either death or need for emergency liver transplantation. Resistance and withdrawal flares typically occur as HBV DNA levels are high or rising.

Other forms of hepatotoxicity from lamivudine are extremely rare if they occur at all. Lamivudine is a rare cause of liver test abnormalities or clinically apparent liver injury in patients with HIV infection without hepatitis B. Although several instances of lactic acidosis with hepatic steatosis and liver failure have been reported in patients receiving lamivudine, in all instances other nucleoside analogues more clearly associated with mitochondrial injury [didanosine, stavudine, zalcitrabine, zidovudine] were also being taken. No convincing instances of lactic acidosis with microvesicular fat have been reported in patients with hepatitis B who typically receive lamivudine alone or in combination with adefovir or tenofovir.

Likelihood score: E (unlikely cause of clinically apparent liver injury although flares of hepatitis B can occur during or following therapy).

Mechanism of Injury

The safety of lamivudine may relate to its minimal hepatic metabolism. In addition, lamivudine is an L-enantiomer as well as being blocked at the 3' position of the deoxyribose, thus insuring that it is not used by either nuclear or mitochondrial host polymerases. Flares during or following therapy of HBV infection probably represent immune-mediated exacerbation of hepatitis B. Finally, in vitro lamivudine has little activity against mitochondrial polymerase gamma.

Outcome and Management

Initial on-treatment flares of hepatitis B due to lamivudine are usually mild, asymptomatic and self-limited, not requiring modification of dose or discontinuation. In contrast, flares developing in association with antiviral resistance and withdrawal flares can be severe, accompanied by clinical symptoms and lead to liver decompensation and death or need for liver transplantation. For these reasons, patients who develop viral breakthrough should be followed carefully, and therapy should be replaced by or combined with an agent with a different profile of antiviral resistance. Patients who discontinue lamivudine therapy should be followed carefully and therapy reinitiated promptly if clinical symptoms or signs of severe relapse arise.

[Agents used in therapy of HBV infection include adefovir, emtricitabine, entecavir, lamivudine, telbivudine, tenofovir, interferon alfa and peginterferon.]

Drug Class: Antiviral Agents, Antiretroviral Agents, Hepatitis B Agents

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

CASE REPORTS

Case 1. On treatment flare of hepatitis B shortly after starting lamivudine therapy.

[NIH Case: Lamivudine D6]

A 43 year old man with HBeAg-positive chronic hepatitis B was started on lamivudine (100 mg daily) and developed a mild flare in serum aminotransferase levels within a few weeks of starting therapy. He felt well and

had no symptoms. He was taking no other medications or herbal products and did not drink alcohol. Physical examination was unchanged and unremarkable. Serum aminotransferase levels rose, but total bilirubin levels remained normal. A liver biopsy done before therapy had shown moderate activity and an incomplete cirrhosis (fibrosis score 5+ of a possible 6+). Lamivudine was continued at the same dose. Serum aminotransferase levels remained high for 6 weeks, but subsequently fell to near normal values. HBV DNA levels also decreased. In follow up, he remained HBeAg-positive and by 48 weeks of therapy developed antiviral resistance. He was later treated with the combination of lamivudine and adefovir with success, with loss of HBeAg and fall of HBV DNA levels to undetectable and ALT levels to normal.

Key Points

Medication:	Lamivudine 100 mg daily
Pattern:	Hepatocellular
Severity:	1+
Latency:	4 weeks
Recovery:	12 weeks
Other medications:	None

Laboratory Values

Time After Starting	ALT (U/L)	AST (U/L)	Bilirubin (mg/dL)	HBV DNA (copies/mL)	Other
0	140	90	1.1	2,360,000,000	
2 weeks	168	130	0.7	63,300,000	
4 weeks	248	166	1.1	4,900,000	
8 weeks	307	235	1.3	170,000	Alk P normal
12 weeks	202	111	0.8		
16 weeks	79	59	0.8		
20 weeks	53	46	0.8	20,000	
24 weeks	62	50	0.8	9,000	
Normal	**<42**	**<35**	**<1.2**	**<100**	

Comment

Serum ALT and AST levels doubled and rose to greater than 8 times the upper limit of the normal range during the first 3 months of antiviral therapy. However, these changes occurred while HBV DNA levels were falling, and the patient remained asymptomatic and without jaundice. Transient and asymptomatic elevations of ALT and AST above baseline are common during the first 2-12 weeks of therapy of chronic hepatitis B with virtually all nucleoside analogues. The flare is suspected to indicate a renewed immunological response to HBV, triggered by the sudden fall in HBV DNA levels and inhibition of intracellular replication. These flares may be more prominent or more significant in patients with preexisting cirrhosis, but generally do not require dose modifications or discontinuation of therapy.

Case 2. On treatment flare of hepatitis B upon development of lamivudine resistance.

[NIH Case: Lamivudine D1]

A 32 year old man was found to have abnormal liver tests when he applied for disability insurance. He was positive for hepatitis B surface and e antigen and had high serum aminotransferase and HBV DNA levels. He was minimally if at all symptomatic of liver disease, and physical examination was normal. A liver biopsy showed marked necroinflammatory activity and bridging hepatic fibrosis. He received a course of alpha interferon without a lasting response. He was then started on lamivudine (100 mg/day), whereupon serum ALT and HBV DNA levels fell promptly (Table). After 18 months, he was HBeAg-negative, but anti-HBe was not detected. After 4 years of lamivudine therapy, ALT levels were normal and repeat liver biopsy showed marked improvement. Six months later, however, while still on lamivudine, serum ALT levels began to rise and HBV DNA was again detectable in high levels. Molecular testing revealed lamivudine-resistant mutant (rtM204I) virus. He was later treated with tenofovir with prompt improvement in HBV DNA and ALT levels.

Key Points

Medication:	Lamivudine 100 mg daily
Pattern:	Hepatocellular
Severity:	1+ (aminotransferase elevations without jaundice)
Latency:	4 years
Recovery:	After switching to tenofovir therapy
Other medications:	None

Laboratory Values

Time After Starting	ALT (U/L)	Bilirubin (mg/dL)	HBV DNA (copies/mL)	Other
0	524	0.9	94,500,000	Liver biopsy
1 month	210	1.1	2,430,000	
2 month	32	1.1	2,000	
12 months	27	1.1	100	
2 years	20	0.9	<100	HBeAg negative
4 years	20	0.6	200	Biopsy
5 years	259	1.1	157,800,000	HBeAg positive
5.5 years	1657	1.2	59,800,000	rtM201I mutant
5.8 years	81	1.0	37,120,000	
6.5 years	101	0.6	6,670,000	
	Lamivudine stopped and tenofovir (300 mg daily) started			
7.5 years	56	1.0	None detected	Still HBeAg positive
Normal	**<42**	**<1.2**	**<100**	

Comment

Long term therapy of hepatitis B with lamivudine is associated with a high rate of antiviral resistance, particularly in patients with HBeAg and high levels of serum HBV DNA. Resistance usually arises in the first 2 years of therapy, but can arise at any time with long term treatment. Generally, HBV DNA levels begin to rise first, followed by increases in serum aminotransferase levels. Molecular testing shows the presence of mutations in the polymerase gene that are associated with resistance to the nucleoside analogue being used. The flare of hepatitis that accompanies development of antiviral resistance is often referred to as “breakthrough” and can be severe and even fatal, particularly in patients with preexisting, underlying cirrhosis. These features make

monotherapy with lamivudine problematic in chronic hepatitis B and underscore the need to monitor patients on long term therapy carefully.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Lamivudine – Epivir®

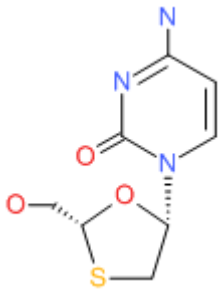
DRUG CLASS

Antiviral Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Lamivudine	134678-17-4	C8-H11-N3-O3-S	

ANNOTATED BIBLIOGRAPHY

References updated: 18 April 2019

Nunez M. Hepatotoxicity 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).

Flexner C. Antiretroviral agents and treatment of HIV infection. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1623-63.

(Textbook of pharmacology and therapeutics).

Acosta EP. Antiviral agents (nonretroviral). 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. 1105-18.

(Textbook of pharmacology and therapeutics).

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. Nature Med 1995; 1: 417-23. 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).

Honkoop P, de Man RA, Heijtink RA, Schalm SW. Hepatitis B reactivation after lamivudine. Lancet 1995; 346: 1156-7. PubMed PMID: 7475613.

(29 year old with chronic hepatitis B developed flare of hepatitis starting 4 weeks after 6 month course of lamivudine, with jaundice [peak bilirubin 7 mg/dL, ALT 3290 U/L] and high levels of HBV DNA, having rebounded after therapy).

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 with HIV developed lactic acidosis and hepatic steatosis 6 months after starting stavudine [plus zidovudine and lamivudine] with bilirubin 1.6 mg/dL and ALT 67 U/L, rapid resolution with stopping stavudine).

Schiano T, 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.

(Patient with HIV-HBV coinfection and cirrhosis developed flare of hepatitis beginning 2 weeks after adding lamivudine to long term stavudine; bilirubin rising to 20.7 mg/dL, ALT 2414 U/L, ascites and pruritus; slowly improving 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, Bréot 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 with HIV-HCV coinfection developed ascites 9 months after starting lamivudine, indinavir and stavudine with bilirubin 2.1 mg/dL, ALT 60 U/L, and 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).

Bessesen M, Ives D, Condreay L, Lawrence S, Sherman KE. Chronic active hepatitis B exacerbations in human immunodeficiency virus-infected patients following development of resistance to or withdrawal of lamivudine. Clin Infect Dis 1999; 28: 1032-5. PubMed PMID: 10452630.

(Five patients with HIV-HBV coinfection had clinically apparent flares of hepatitis [ALT 163-1408 U/L, bilirubin 0.8-9.5 mg/dL] either on lamivudine [n=3; all 3 with lamivudine resistance] or upon withdrawal [n=2; when switched to other antiretrovirals without activity against HBV]; one died).

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 with HIV infection developed lactic acidosis and hepatic steatosis 1-8 months after starting stavudine and lamivudine with 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 6 months, authors identified 10 HIV-infected patients with high lactate levels [2.9-6.2 mmol/L]; all were taking stavudine, 5 didanosine and 7 lamivudine for 4-20 months; 8 with symptoms of abdominal pain, nausea or distension; all with 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).

Bruno R, Sacchi P, Malfitano A, Filice G. YMDD-mutant HBV strain as a cause of liver failure in an HIV-infected patient. Gastroenterology 2001; 121: 1027-8. PubMed PMID: 11665695.

(38 year old man with HIV-HBV coinfection on long term antiretroviral therapy including lamivudine [~4 years] developed jaundice with bilirubin 7.4 mg/dL, ALT 1658 U/L, normal lactate, INR 4 and HBV DNA of 270,000 copies/mL with lamivudine resistant mutations [rtM201I and rtL180M], progressive liver failure and death).

Mina J, 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 had lactic acidosis and were both symptomatic and on stavudine: 3.9 per 1000 person-years).

Ormseth EJ, Holtzmuller KC, Goodman ZD, Colonna JO, Batty DS, Sjogren MH. Hepatic decompensation associated with lamivudine: a case report and review of lamivudine-induced hepatotoxicity. Am J Gastroenterol 2001; 96: 1619-22. PubMed PMID: 11374710.

(62 year old with HBV related cirrhosis developed severe flare starting 8 weeks after starting lamivudine [ALT rising from 171 to 1500 U/L, bilirubin 3.1 to 11 mg/dL while HBV DNA became undetectable]; variceal hemorrhage and progressive encephalopathy led to emergency liver transplant, after which lamivudine was continued and he remained HBsAg negative).

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.

(In vitro study of nucleoside analogues found that tenofovir and lamivudine were less cytotoxic to several human cell types than zidovudine, stavudine, didanosine and zalcitabine).

Clark S, Creighton S, Portmann B, Taylor C, Wendon J, Cramp M. 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, delaviridine 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; two 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).

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: 340-4. 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).

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).

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).

Lok AS, Lai CL, Leung N, Yao GB, Cui ZY, Schiff ER, Dienstag JL, et al. Long-term safety of lamivudine treatment in patients with chronic hepatitis B. Gastroenterology 2004; 126:1932-3. PubMed PMID: 14724824.

(Analysis of hepatitis flares in 998 patients treated with lamivudine for up to 6 years; during the first year, flares [ALT >3 times normal] were less common during lamivudine [10%] than placebo [19%] therapy, but increased thereafter usually in association with antiviral resistance; 8 patients developed hepatic decompensation and 2 with antiviral resistance died).

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 with nucleoside analogues is mitochondrial injury with lactic acidosis and severe hepatomegaly and steatosis).

Chang TT, Gish RG, de Man R, Gadano A, Sollano J, Chao YC, Lok AS, et al.; BEHoLD AI463022 Study Group. A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B. N Engl J Med 2006; 354: 1001-10. PubMed PMID: 16525137.

(Controlled trial comparing entecavir [n=354] to lamivudine [n=355] in patients with HBeAg-positive chronic hepatitis B; on-treatment ALT elevations >5 times normal in 10% of entecavir- vs 17% of lamivudine-treated subjects [entecavir therapy stopped in one patient]; posttreatment elevations in 2% vs 12%).

Lai CL, Shouval D, Lok AS, Chang TT, Cheinquer H, Goodman Z, DeHertogh D, et al.; BEHoLD AI463027 Study Group. Entecavir versus lamivudine for patients with HBeAg-negative chronic hepatitis B. N Engl J Med 2006; 354: 1011-20. PubMed PMID: 16525138.

(Controlled trial comparing entecavir [n=325] to lamivudine [n=313] in patients with HBeAg-negative chronic hepatitis B; on-treatment ALT elevations >5 times normal in 2% of entecavir- vs 3% of lamivudine-treated; posttreatment elevations in 12% vs 29%, no deaths from flares).

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

(Among 4690 reports of fatal acute liver failure due to medications reported to a WHO data, 80 were attributed to lamivudine which ranked 6th, even though the lamivudine was probably being given for the acute liver failure rather than causing it).

Lai CL, Gane E, Liaw YF, Hsu CW, Thongsawat S, Wang Y, Chen Y, et al.; Globe Study Group. Telbivudine versus lamivudine in patients with chronic hepatitis B. N Engl J Med 2007; 357: 2576-88. PubMed PMID: 18094378.

(Trial of telbivudine [600 mg/day] vs lamivudine [100 mg/day] for 52 weeks in 1370 patients with chronic hepatitis B; ALT >3 times ULN in 3.7% of telbivudine, 6.3% of lamivudine; 1 on lamivudine developed antiviral resistance and liver failure requiring liver transplant).

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]).

Hou J, Yin YK, Xu D, Tan D, Niu J, Zhou X, Wang Y, et al. Telbivudine versus lamivudine in Chinese patients with chronic hepatitis B: Results at 1 year of a randomized, double-blind trial. Hepatology 2008; 47: 447-54. PubMed PMID: 18080339.

(Trial of telbivudine vs lamivudine for 52 weeks in 332 patients with hepatitis B; ALT elevations >3 times normal occurred in 9.1% of lamivudine vs 5.4% of telbivudine treated subjects, usually associated with viral breakthrough; none fatal).

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(Analysis of 245 patients with advanced chronic hepatitis B in 3 clinical trials; on-treatment flares [ALT >10 times normal] occurred in 1 of 120 entecavir- vs 4 of 125 lamivudine-treated patients).

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).

Soriano V, Puoti M, Garcia-Gascó 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).

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 efavirez and 4 miscellaneous combinations but none to lamivudine).

Fontana RJ. Side effects of long-term oral antiviral therapy for hepatitis B. Hepatology 2009; 49 (5 Suppl): S185-95. PubMed PMID: 19399802.

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(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, but none were attributed to lamivudine).

Björnsson ES, Bergmann OM, Björnsson HK, Kvaran RB, Olafsson S. Incidence, presentation and outcomes in patients with drug-induced liver injury in the general population of Iceland. Gastroenterology 2013 ; 144: 1419-25. PubMed PMID: 23419359.

(In a population based study of drug induced liver injury from Iceland, 96 cases were identified over a 2 year period, but none were attributed to lamivudine or other antivral agents used to treat hepatitis B).

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, two of which were attributed to lamivudine but both in combination with zidovudine to treat HIV infection).

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 [1.3%] were attributed to antiretroviral agents but none were due to lamivudine or agents being used to treat hepatitis B).

Lee KS, Kweon YO, Um SH, Kim BH, Lim YS, Paik SW, Heo J, et al. Efficacy and safety of entecavir versus lamivudine over 5 years of treatment: A randomized controlled trial in Korean patients with hepatitis B e antigen-negative chronic hepatitis B. Clin Mol Hepatol 2017; 23: 331-9. PubMed PMID: 28946736.

(Among 120 Korean patients with chronic hepatitis B treated with lamivudine or entecavir for at least 2 years, virologic responses were less common with lamivudine [48% vs 95%] while breakthough was more frequent [43% vs 1%]; serious adverse events were rare and were unrelated to therapy).

Pan CQ, Yi W, Liu M, Wan G, Hu YH, Zhou MF. Lamivudine therapy during the second vs the third trimester for preventing transmission of chronic hepatitis B. J Viral Hepat 2017; 24: 246-52. PubMed PMID: 28025872.

(Among 160 HBsAg positive expectant mothers with high levels of HBV DNA who were treated with lamivudine starting in the 2nd or 3rd trimester of pregnancy, none had evidence of transmission of hepatitis B to their newborns, while ALT flares occurred in 3% during pregnancy and 9% postpartum when lamivudine was stopped, but none had severe hepatitis or acute liver failure).

Triumeq--a 3 drug combination for HIV. Med Lett Drugs Ther 2015; 57 (1459): 7-8. PubMed PMID: 25555073.

(Concise review of the clinical effiacy, safety and costs of the fixed dose combination of lamivudine, abacavir and dolutegravir as a single tablet regimen for HIV infection; mentions common adverse events of insomnia, headahce and fatigue and that ALT and AST elevations can occur in patients with HBV or HCV coinfection).

Cahn P, Madero JS, Arribas JR, Antinori A, Ortiz R, Clarke AE, Hung CC, Et al.; GEMINI Study Team. Dolutegravir plus lamivudine versus dolutegravir plus tenofovir disoproxil fumarate and emtricitabine in antiretroviral-naive adults with HIV-1 infection (GEMINI-1 and GEMINI-2): week 48 results from two multicentre, double-blind, randomised, non-inferiority, phase 3 trials. Lancet 2019; 393 (10167): 143-55. PubMed PMID: 30420123.

(Among 1441 patients with HIV infection enrolled in two controlled trials comparing 2-drug [dolutegravir and lamivudine] to 3-drug [dolutegravir, tenofovir, emtricitabine] regimens, virologic response rates were similar [91% vs 93%] while drug related adverse events were less frequent with the 2-drug regimen [18% vs 24%], but serious events were similar in frequency [1% vs 1%].