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Tenofovir

Updated: December 3, 2013.

OVERVIEW

Introduction

Tenofovir disoproxil fumarate is an acyclic nucleotide analogue of adenosine used in combination with other agents in the therapy of the human immunodeficiency virus (HIV) and as single agent in hepatitis B virus (HBV) infection. Tenofovir does not appear to be a significant cause of drug induced liver injury.

Background

Tenofovir (ten of' oh vir) is an acyclic nucleotide analogue of adenosine, but is poorly absorbed orally. For this reason, the prodrug–tenofovir disoproxil fumarate–is used, which is well absorbed from the intestines, rapidly hydrolyzed to tenofovir intracellularly and then phosphorylated to the active form, tenofovir diphosphate. Tenofovir diphosphate is a competitive inhibitor of the HIV reverse transcriptase (and the HBV polymerase) and is also incorporated into the nascent DNA strand causing chain termination. Tenofovir was approved for use in HIV infection in the United States in 2001 and for use in hepatitis B in 2008. Clinical indications include treatment and prevention of HIV infection, usually in combination with other reverse transcriptase or protease inhibitors. Tenofovir is also approved for use in chronic hepatitis B as a single agent. Tenofovir is available under the brand name Viread in 300 mg oral tablets. Tenofovir is also available in various fixed combinations with other antiviral agents for use in treatment of HIV infection, usually in a single oral daily dose: with emtricitabine as Truvada in 300/200 mg oral tablets; with emtricitabine and efavirenz as Atripla in 300/200/600 mg oral tablets; with emtricitabine and rilpivirine as Complera in 300/200/25 mg oral tablets; and, with emtricitabine, elvitegravir and cobicistat as Stribild in 300/200/150/150 mg oral tablets. The recommended dose of tenofovir in adults is 300 mg once daily. Side effects are uncommon; they include asthenia, diarrhea, flatulence, nausea and vomiting, renal dysfunction and rash.

Hepatotoxicity

Like all nucleoside analogues used as therapy of hepatitis B, tenofovir can cause transient increases in serum aminotransferases during or after therapy. These abnormalities appear to be due to an exacerbation or flare of the underlying hepatitis B. Three types of flares due to nucleoside analogue therapy have been described: transient flares during initiation of therapy (treatment flares), flares occurring in association with development of antiviral resistance (breakthrough flares) and flares occurring in the few months after stopping therapy (withdrawal flares). Treatment flares generally arise during the first few months of starting therapy, are usually mild, asymptomatic and self-limited and do not require dose modification or interruption of therapy. Breakthrough flares generally follow the development of antiviral resistance and subsequent rise in HBV DNA levels during nucleoside analogue therapy. Breakthrough flares can be symptomatic and severe. Because

tenofovir is associated with a very low rate of antiviral resistance (<1% after 4 years), no convincing cases of breakthrough hepatitis have been linked to its use. Finally, sudden discontinuation of antiviral therapy is capable of causing a hepatitis B withdrawal flare. Withdrawal flares can be severe and several instances of acute liver failure resulting in death or the need for liver transplantation have been reported after stopping nucleoside analogue therapy. The rate of such flares after withdrawal of tenofovir therapy has not been clearly defined.

Tenofovir appears to have little or no direct hepatotoxicity. There have been no convincing reports of acute, clinically apparent liver injury attributable to tenofovir, although the combination of tenofovir and didanosine appears to lead to liver injury, with microvesicular fatty liver disease and lactic acidosis more commonly than didanosine with other antiretrovirals, perhaps because of drug-drug interactions. Tenofovir may also predispose to serum aminotransferase elevations during efavirenz therapy, again possibly because of drug-drug interactions.

Mechanism of Injury

The majority of cases of lactic acidosis and hepatic failure in patients receiving tenofovir appear to be due to didanosine, stavudine or zidovudine coadministration. Addition of tenofovir to an antiretroviral regimen including didanosine concurrently can increase didanosine concentrations by up to 60%, thus amplifying its potential to cause mitochondrial injury. Tenofovir by itself appears to have little hepatotoxic potential.

Outcome and Management

The minor ALT elevations associated with initiation of tenofovir therapy in chronic hepatitis B are usually asymptomatic and transient. Care should be taken in stopping tenofovir therapy in patients with chronic HBV infection. If administered concurrently with tenofovir, didanosine should be reduced in dosage and patients monitored carefully.

[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, Lamivudine, Stavudine, Telbivudine, Zidovudine

CASE REPORTS

Case 1. Lactic acidosis arising during therapy with didanosine after addition of tenofovir.

[Modified from: Rivas P, Polo J, de Górgolas M, Fernández-Guerrero ML. Drug Points: Fatal lactic acidosis associated with tenofovir. BMJ 2003; 327: 711. PubMed Citation]

A 45 year old woman with HIV infection and chronic hepatitis C developed vomiting, abdominal pain, and obtundation 8 weeks after the addition of tenofovir to her long term antiretroviral regimen of stavudine and didanosine. Tenofovir was used to replace nevirapine, which was discontinued because of minor serum enzymes elevations which then returned to initial values. On admission, she was jaundiced and disoriented and had tender hepatomegaly. Serum bilirubin was 12.6 mg/dL, ALT 157 U/L, and an international normalized ratio (INR) was 2.1. She had lactic acidosis with blood pH of 7.24 and lactate levels of 16.4 mmol/L. Imaging of the liver suggested fatty infiltration. Antiretrovirals were discontinued, but the lactic acidosis and hepatic failure worsened and she died two days after admission.

Key Points

Medication:	Didanosine, stavudine, and tenofovir
Pattern:	Mild serum ALT elevations
Severity:	5 (fatal)
Latency:	8 weeks
Recovery:	None
Other medications:	Nevirapine, 8 weeks previously

Comment

Acute microvesicular hepatic steatosis with liver failure and lactic acidosis is a syndrome associated with several medications including the nucleoside analogues, particularly didanosine, stavudine and zidovudine. A similar syndrome occurs with intravenous tetracycline, aspirin (Reyes syndrome) and valproate, but the timing and course is different for those agents (shorter latency period), probably because they directly affect function of mitochondria rather than by causing functional failure by inhibition of mitochondrial replication and mitochondrial depletion. Mitochondria have a half-life of several weeks, so that inhibition of mitochondrial replication would be expected to lead to severe dysfunction (mitochondrial failure) after 2 to 3 months. Both didanosine and stavudine have been linked to many cases of hepatic steatosis and lactic acidosis and the addition of tenofovir appears to increase the risk of this complication. This syndrome has not been reported with the use of tenofovir alone. Other risk factors for hepatic steatosis with lactic acidosis include presence of underlying liver disease (such as hepatitis C), obesity and alcohol use.

Case 2. Transient flare of hepatitis B with initiation of tenofovir therapy.

[NIH Case: Tenofovir A2]

A 29 year old Asian-American woman was started on the combination of tenofovir and emtricitabine (Truvada) in a clinical trial of therapy of HBeAg-positive hepatitis B and developed a doubling of serum ALT levels to ~14 times the upper limit of normal within two weeks of starting therapy. At the same time, HBV DNA levels had fallen by four log10 IU (352 million to 36,160 IU/mL), but she remained HBsAg and HBeAg positive. Serum direct and total bilirubin levels increased slightly, but remained in the normal range. She had no symptoms of hepatitis and reported no other side effects. Tests for hepatitis A, C and D showed no evidence of de novo infection with these viruses. She was taking no other medications or herbal products. The dose of tenofovir and emtricitabine was not changed and, subsequently, her serum aminotransferase levels fell into the normal range and HBV DNA to undetectable. After 36 weeks of treatment, she became HBeAg-negative but did not develop anti-HBe. At one year, histologic evidence of inflammation and fibrosis had improved, but she remained HBsAg-positive and was continued on therapy.

Key Points

Medication:	Tenofovir (300 mg) and emtricitabine (200 mg) daily
Pattern:	Hepatocellular (ALT elevations only; R=14)
Severity:	1+ (aminotransferase elevations without jaundice)
Latency:	1 month
Recovery:	2 weeks
Other medications:	None

Laboratory Values

Weeks After Starting	ALT (U/L)	Alk P (U/L)	Direct and Total Bilirubin (mg/dL)		HBV DNA (IU/mL)	Other
Pre	261	67	0.2	0.8	76,000,000	
0	272	69	0.2	0.6	352,000,000	HBeAg +ve
2	569	95	0.3	1.0	36,100	INR=1.06
4	26	59	0.1	0.7	91	
8	30	45	0.0	0.7	28	
12	43	43	0.1	0.5	<10	
24	23	52	0.2	0.6	<10	
36	23	82	0.1	0.5	<10	HBeAg -ve
48	22	62	0.2	0.6	<10	
Normal	**<40**	**<115**	**<0.3**	**<1.2**	**<10**	

Comment

A minor flare in hepatitis is not uncommon with initiation of antiviral therapy of hepatitis B and should not lead to dose modification, if HBV DNA levels are decreasing and no other cause for acute liver injury can be found. The flare of hepatitis probably represents an immunological reaction to the sudden decrease in HBV replication and may actually be a favorable sign, predictive of a serological and virological response (loss of HBeAg during treatment which occurred at 36 weeks).

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Tenofovir – Viread®

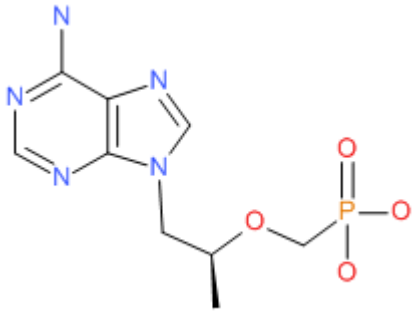
DRUG CLASS

Antiviral Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Tenofovir	147127-20-6	C9-H14-N5-O4-P	

ANNOTATED BIBLIOGRAPHY

References updated: 03 December 2013

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).

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. 1623-64.

(Textbook of pharmacology and therapeutics).

http://aidsinfo.nih.gov/guidelines.

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

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).

Gallant JE, Deresinski S. Tenofovir disoproxil fumarate. Clin Infect Dis 2003; 37: 944-50. PubMed PMID: 13130407.

(Review on the efficacy and safety of tenofovir mentions that it is well tolerated and has little evidence of mitochondrial toxicity).

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 or 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 HIV-positive patients were admitted with acute liver failure over a 25 month period, of whom five died; all had been treated with antiretrovirals and only two had had AIDS-defining illnesses).

Pecora Fulco P, Kirian MA. Effect of tenofovir on didanosine absorption in patients with HIV. Ann Pharmacother 2003; 37: 1325-8. PubMed PMID: 12921517.

(When given together, tenofovir increases plasma concentrations of didanosine).

Blanchard JN, Wohlfeiler M, Canas A, King K, Lonergan JT. Pancreatitis with didanosine and tenofovir disoproxil fumarate. Clin Infect Dis 2003; 37: 57-62. PubMed PMID: 12942419.

(4 patients developed pancreatitis and lactic acidosis arising 2-6 months after adding tenofovir to HIV regimen including didanosine; 1 died, 3 who survived were able to restart tenofovir without didanosine; liver tests mentioned only in fatal case [bilirubin 5.3 mg/dL, ALT 89 U/L]).

Callens S, De Schacht C, Huyst V, Colebunders R. Pancreatitis in an HIV-infected person on a tenofovir, didanosine and stavudine containing highly active antiretroviral treatment. J Infect 2003; 47: 188-9. PubMed PMID: 12860159.

(33 year old woman developed pancreatitis 5 months after starting didanosine and 1 month after addition of tenofovir to HIV regimen [ALT 386 U/L, Alk P 208 UL, amylase 11395 U/L], resolving rapidly when antivirals were stopped).

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 infection treated with diadanosine and stavudine developed jaundice and hepatomegaly 8 weeks after switching from nevirapine to tenofovir [bilirubin 12.6 mg/dL, ALT 157 U/L, CT showed fatty liver], despite stopping antivirals and medical support lactic acidosis worsened and she died 36 hours later: Case 1).

Murphy MD, O'Hearn M, Chou S. Fatal lactic acidosis and acute renal failure after addition of tenofovir to an antiretroviral regimen containing didanosine. CID 2003; 36: 1982-6. PubMed PMID: 12684925.

(49 year old man with HIV infection and renal insufficiency on long term didanosine developed progressive, fatal lactic acidosis 6 weeks after starting tenofovir [lactate 5.5 rising to 16.7 mmol]; no mention of liver injury).

Gallant JE, Staszewski S, Pozniak AL, DeJesus E, Suleiman JM, Miller MD, Coakley DF, et al.; 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; ALT rises above 5 times normal occurred in 4% of tenofovir- vs 5% of stavudine-treated; lactic acidosis arose in no tenofovir- vs 3 [1%] stavudine-treated subjects).

Guo Y, Fung HB. Fatal lactic acidosis associated with coadministration of didanosine and tenofovir disoproxil fumarate. Pharmacotherapy 2004; 24: 1089-94. PubMed PMID: 15338857.

(63 year old man with HIV-HCV coinfection developed fatal lactic acidosis 1.5 years after starting didanosine-tenofovir-lopinavir-ritonavir regimen with pancreatitis, multiorgan failure and death; liver injury not mentioned).

Giola M, Basilico C, Grossi P. Fatal lactic acidosis associated with tenofovir and abacavir. Int J Infect Dis 2005; 9: 228-9. PubMed PMID: 15916912.

(60 year old man with HIV infection developed fatal lactic acidosis and aminotransferase elevations 5 months after being switched from stavudine to abacavir while continuing tenofovir and nevirapine [ALT 70 U/L, lactate 9.7 mmol], and progressive acidosis).

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 risk factors, epidemiology and pathogenic mechanisms of hepatotoxicity caused by antiretroviral drugs).

Masiá M, Gutiérrez F, Padilla S, Ramos JM, Pascual J. Severe toxicity associated with the combination of tenofovir and didanosine: case report and review. Int J STD AIDS 2005; 16: 646-8. PubMed PMID: 16176639.

(45 year old man with HIV-HCV coinfection developed lactic acidosis and "mild cholestasis" 3 months after adding tenofovir to didanosine, resolving slowly after stopping therapy).

Pozniak AL, Gallant JE, DeJesus E, Arribas JR, Gazzard B, Campo RE, Chen SS, et al. Tenofovir disoproxil fumarate, emtricitabine, and efavirenz versus fixed-dose zidovudine/lamivudine and efavirenz in antiretroviral-naive patients: virologic, immunologic, and morphologic changes—a 96-week analysis. J Acquir Immune Defic Syndr 2006; 43: 535-40. PubMed PMID: 17057609.

(Controlled trial of tenofovir and emtricitabine vs zidovudine and lamivudine combined with efavirenz in 517 patients with HIV infection; elevations in ALT >3 times normal occurred in 8% vs 9% in first 2 years of study).

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], and cholestatic hepatitis [many agents]).

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 with HIV infection on stavudine for 3 years and tenofovir for 6 months developed rise in ALT levels (222 to 392 U/L), which persisted despite stopping indinavir and resolved slowly after stopping stavudine; liver biopsy showed inflammation, fat and Mallory bodies).

Lattuada E, Lanzafame M, Carolo G, Gottardi M, Concia E, Vento S. Does tenofovir increase efavirenz hepatotoxicity? AIDS 2008; 22: 995. PubMed PMID: 18453862.

(Three patients with HIV infection without hepatitis B or C on efavirenz therapy developed ALT elevations 4-6 weeks after starting tenofovir [ALT 144, 186 and 392 U/L] [previously normal], resolving with stopping tenofovir).

Marcellin P, Heathcote EJ, Buti M, Gane E, de Man RA, Krastev Z, Germanidis G, et al. Tenofovir disoproxil fumarate versus adefovir dipivoxil for chronic hepatitis B. N Engl J Med 2008; 359: 2442-55. PubMed PMID: 19052126.

(Two controlled trials of tenofovir vs adefovir in 641 patients with chronic hepatitis B; ALT levels above 5 times the ULN occurred in 6% of tenofovir vs 3% of adefovir recipients, usually within 8 weeks of starting; all self-limited even with continuing drug).

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.

(Recent 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 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).

Nüesch R, Ananworanich J, Srasuebkul P, Chetchotisakd P, Prasithsirikul W, Klinbuayam W, Mahanontharit A, et al. Interruptions of tenofovir/emtricitabine-based antiretroviral therapy in patients with HIV/hepatitis B virus co-infection. AIDS 2008; 22: 152-4. PubMed PMID: 18090405.

(Among 10 patients with HIV-HBV coinfection on tenofovir therapy, 6 had a rise in HBV DNA levels and one had a clinically significant flare of hepatitis within 6 months of tenofovir withdrawal; all responded to restarting).

Sulkowski MS. Management of hepatic complications in HIV-infected persons. J Infect Dis 2008; 197 Suppl 3: S279-93. PubMed PMID: 18447614.

(Review of the complications, natural history and management of hepatitis B in patients with HIV infection).

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

(Review of side effects of nucleoside analogues used to treat chronic hepatitis B).

Ortu F, Weimer LE, Floridia M, Manconi PE. Raltegravir, tenofovir, and emtricitabine in an HIV-infected patient with HCV chronic hepatitis, NNRTI intolerance and protease inhibitors-induced severe liver toxicity. Eur J Med Res 2010; 15: 81-3. PubMed PMID: 20452889.

(43 year old woman with HIV/HCV coinfection developed symptomatic elevations of serum enzymes on saquinavir, fosamprenavir and again on darunavir, was adequately maintained on tenofovir/emtricitabine and raltegravir).

Garg H, Sarin SK, Kumar M, Garg V, Sharma BC, Kumar A. Tenofovir improves the outcome in patients with spontaneous reactivation of hepatitis B presenting as acute-on-chronic liver failure. Hepatology 2011; 53: 774-80. PubMed PMID: 21294143.

(Randomized trial of tenofovir versus placebo in 90 patients with acute liver failure due to spontaneous reactivation of hepatitis B found improved survival at 3 months with tenofovir therapy and no evidence of renal or liver toxicity from the antiviral).

Dore GJ, Soriano V, Rockstroh J, Kupfer B, Tedaldi E, Peters L, Neuhaus J, et al; SMART INSIGHT study group. Frequent hepatitis B virus rebound among HIV-hepatitis B virus-coinfected patients following antiretroviral therapy interruption. AIDS 2010; 24: 857-65. PubMed PMID: 20216301.

(Among 54 patients with HIV-HBV coinfection who were withdrawn from chronic antiretroviral therapy, 12 [22%] had a >3 log rebound in HBV DNA levels including 7 of 17 [41%] who had been on tenofovir vs 3 of 27 [11%] on lamivudine; ALT flares were uncommon and no patient developed hepatic decompensation).

DeJesus E, Rockstroh JK, Henry K, Molina JM, Gathe J, Ramanathan S, Wei X, et al; GS-236-0103 Study Team. Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate versus ritonavir-boosted atazanavir plus co-formulated emtricitabine and tenofovir disoproxil fumarate for initial treatment of HIV-1 infection: a randomised, double-blind, phase 3, non-inferiority trial. Lancet 2012; 379(9835): 2429-38. PubMed PMID: 22748590.

(Controlled trial of two combination regimens of once daily antivial agents in 708 patients with HIV infection for at least 48 weeks; ALT elevations occurred in 18% vs 22% and bilirubin elevations in 11% vs 96% of patients in the tenofovir/emtricitabine/elvitegravir/cobicistat vs the atazanavir/ritonavir/tenofovir/ emtricitabine combination, the ALT elevations being attributable to underlying liver disease in most cases and the bilirubin elevations largely due to atazanavir).

Vermund SH. Safety and tolerability of tenofovir for preexposure prophylaxis among men who have sex with men. J Acquir Immune Defic Syndr 2013; 64: 3-6. PubMed PMID: 23881239.

(Editorial in response to Grohskopf et al [2013]).

Grohskopf LA, Chillag KL, Gvetadze R, Liu AY, Thompson M, Mayer KH, Collins BM, et al. Randomized trial of clinical safety of daily oral tenofovir disoproxil fumarate among HIV-uninfected men who have sex with men in the United States. J Acquir Immune Defic Syndr 2013; 64: 79-86. PubMed PMID: 23466649.

(Controlled trial of daily oral tenofovir vs placebo for 24 months in 373 HIV negative men who have sex with men found no excess of adverse events in tenofovir- vs placebo-treated subjects and no hepatic severe adverse events; changes in ALT levels were not discussed).

Marcellin P, Gane E, Buti M, Afdhal N, Sievert W, Jacobson IM, Washington MK, et al. Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study. Lancet 2013; 381(9865): 468-75. PubMed PMID: 23234725.

(Among 348 patients with chronic hepatitis B who underwent liver biopsy before and after a 4 year course of tenofovir, liver histology improved in 304 [87%] and fibrosis regressed in 176 [51%], including 74% of those who had cirrhosis on initial biopsy; no antiviral resistance breakthroughs occurred).

Köklü S, Tuna Y, Gülşen MT, Demir M, Köksal AŞ, Koçkar MC, Aygün C, et al. Long-term efficacy and safety of lamivudine, entecavir, and tenofovir for treatment of hepatitis B virus-related cirrhosis. Clin Gastroenterol Hepatol 2013; 11: 88-94. PubMed PMID: 23063679.

(Retrospective analysis of 227 patients with cirrhosis due to hepatitis B who were treated with lamivudine [n=74], entecavir [n=77] or tenofovir [n=72]; viral breakthrough occurred in 32% on lamivudine, 2.5% on entecavir, but none on tenofovir; no discussion of ALT flares).