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Protease Inhibitors (HIV)

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OVERVIEW

The human immunodeficiency virus (HIV) protease inhibitors are a broad class of agents that are widely used in the therapy and prevention of HIV infection and the acquired immunodeficiency syndrome (AIDS). All of the currently available protease inhibitors have been associated with transient and usually asymptomatic elevations in serum aminotransferase levels, and several (atazanavir, indinavir) with mild-to-moderate elevations in indirect and total bilirubin concentration. The protease inhibitors are rare causes of clinically apparent, acute liver injury. In HBV or HCV coinfected patients, antiretroviral therapy with highly active antiretroviral therapy (HAART) including protease inhibitors may result in an exacerbation of the underlying chronic hepatitis B or C.

The antiretroviral protease inhibitors act by binding to the catalytic site of the HIV protease, thereby preventing the cleavage of viral polyprotein precursors into mature, functional proteins that are necessary for viral replication. Most of these agents were developed by rational drug design based upon chemical structures that would interact with the catalytic site of the HIV protease, based upon x-ray crystallographic studies defining the three-dimensional molecular structure of the protease. For these reasons, the protease inhibitors are heterogeneous molecules with little structural similarity, most of which are peptide-like and resemble the short peptide that is cleaved by the viral protease (usually the N terminal side of the middle proline residue is phenylalanine-proline-proline).

The initial HIV protease approved for use in the United States was ritonavir (1996), followed in short order by indinavir (1996), nelfinavir (1997), saquinavir (1997), amprenavir (1999), lopinavir/ritonavir (2000), atazanavir (2003), fosamprenavir (2003), tipranavir (2005), and darunivir (2006). The potencies of these agents are similar and the major reason for using one or the other relates to pharmacokinetics (whether they are taken once vs multiple times daily), tolerance and presence of antiviral resistance.

Most of the HIV protease inhibitors are metabolized by the liver, via the cytochrome P450 drug metabolizing enzymes. Importantly, all of the approved HIV protease inhibitors have the potential for significant drug-drug interactions because of their potential in inhibiting drug metabolizing enzymes, most commonly CYP 3A4. Ritonavir is the most potent CYP 3A4 inhibitor and, for this reason, is often combined in low doses (100 to 200 mg daily) with other protease inhibitors to produce a "booster" effect, increasing the plasma levels and half-life of the protease inhibitor without significantly increasing side effects. Cobicistat is a more recently introduced pharmacological enhancer which has inhibitory activity against several drug metabolizing enzymes besides CYP 3A4, including CYP 2D6 and the P-glycoprotein transporter, which makes it a potent means of increasing drug levels of agents metabolized by the cytochrome P450 system. Several fixed combinations of cobicistat with antiretroviral agents have been approved for use in the United States, including combinations with atazanavir (Evotaz), elvitegravir (Genvoya and Stribild), and darunavir (Prezcobix). Cobicistat is also available as a separate oral tablet of 150 mg (Tybos).

As with other antiretroviral agents, therapy with the protease inhibitors is limited by the development of antiviral resistance. For this reason, the protease inhibitors are given in combination with other antiretroviral agents, belonging to other drug classes, such as the nucleoside analogues, the nonnucleoside reverse transcriptase inhibitors and the miscellaneous agents. Introduction of the HIV protease inhibitors into clinical practice was followed by a dramatic increase in survival in HIV-infected populations, a major accomplishment towards the goal of decreasing the burden of HIV infection.

The protease inhibitors are associated with four main forms of hepatotoxicity. First, are the mild-to-moderate elevations in serum aminotransferase and alkaline phosphatase levels that occur in a high proportion of patients taking protease inhibitor-containing antiretroviral regimens. Moderate-to-severe elevations in serum aminotransferase levels (above 5 times the upper limit of normal) are found in 2% to 18% of patients depending upon the agent, the frequency of monitoring and, most importantly, the presence of HBV or HCV coinfection. In patients with HIV without HCV or HBV infection ("mono-infection"), ALT and AST elevations are less frequent and levels above 5 times the upper limit of normal are reported in only 1% to 4% of recipients. These elevations are usually asymptomatic and self-limited and can resolve even with continuation of the medication. Outside of carefully monitored clinical trials, serum enzyme elevations are an uncommon reason for discontinuing therapy.

A second liver related reaction to protease inihibitor therapy is hyperbilirubinemia without other evidence of liver injury. Therapy with two protease inhibitors–indinavir and atazanavir–is associated with elevations in unconjugated (indirect) and total serum bilirubin, and can cause clinically apparent jaundice in up to 10% of patients. These elevations are due to the inhibition of UDP glucuronyl transferase, the hepatic enzyme responsible for conjugation of bilirubin that is deficient in Gilbert syndrome. The hyperbilirubinemia is usually mild, averaging 0.9-1.5 mg/dL, but can be more marked in patients with Gilbert syndrome with increases of 2.5 mg/dL or more and clinical jaundice. The jaundice, however, is not indicative of hepatic injury. Nevertheless, the jaundice caused by these agents can be distressing to the patient and is an occasional reason for discontinuation.

A third pattern of hepatotoxicity attributed to protease inhibitors is idiosyncratic, clinically apparent acute liver injury which has been reported with most agents but is decidedly rare. The few cases that have been reported have usually arisen within 1 to 12 weeks of starting therapy and the pattern of serum enzyme elevations has varied from hepatocellular to mixed to cholestatic. Signs of allergy or hypersensitivity (fever, rash, eosinophilia) can occur but are rare, as is autoantibody formation. The acute liver injury due to the protease inhibitors is usually self-limited, but it can be severe, and isolated cases of acute liver failure have been reported particularly in patients with preexisting, underlying liver disease.

Finally, the fourth pattern of hepatotoxicity that occurs during protease inhibitor therapy is the exacerbation of an underlying chronic hepatitis B or C in coinfected individuals started on highly active antiretroviral therapy. The flare of hepatitis typically arises 2 to 12 months after starting therapy and is associated with a hepatocellular pattern of serum enzyme elevations and increases (followed by falls) in serum levels of hepatitis B virus (HBV) DNA or hepatitis C virus (HCV) RNA. These flares can be severe and fatal instances have been reported with many of the protease inhibitors.

The protease inhibitors have not been linked to lactic acidosis and acute fatty liver that are associated with several nucleoside analogue reverse transcriptase inhibitors such as stavudine, didanosine and zidovudine, and rare cases of acute hypersensitivity associated hepatotoxicity as occurs with nevirapine, efaverenz and abacavir. However, because the protease inhibitors are usually given in combination with several other antiretroviral medications, identification of the drug causing the hepatic injury can be difficult.

Each of the following HIV protease inhibitors are discussed individually, but the references are combined and given below.

- Amprenavir

- Atazanavir
- Darunavir
- Fosamprenavir
- Indinavir
- Lopinavir
- Nelfinavir
- Ritonavir
- Saquinavir
- Tipranavir

ANNOTATED BIBLIOGRAPHY

References updated: 01 September 2017

Abbreviations used: HIV, human immunodeficiency virus; HCV, hepatitis C virus; HBV, hepatitis B virus; ULN, upper limit of normal; /r, agent boosted with ritonavir; /c, agent boosted with cobicistat.

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 mentions that risk of liver injury with different protease inhibitors is controversial, but that tipranavir, darunavir, lopinarivr and ritonavir are the leading causes in most case reports and reviews on the topic).

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).

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

(8 patients with HIV who developed severe hepatomegaly and marked steatosis which was associated with hepatic failure and lactic acidosis, 6 being fatal and 2 with recovery; all had received zidovudine, but for varying periods and often stopped well before onset of symptoms from hepatotoxicity).

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

(Review of liver toxicity of antiviral agents, before availability of protease inhibitors).

Bräu N, Leaf HL, Wieczorek RL, Margolis DM. Severe hepatitis in three AIDS patients treated with indinavir. Lancet 1997; 349: 924-5. PubMed PMID: 9093260.

(2 men and 1 woman, ages 37-52 years, developed abdominal pain followed by jaundice 4-10 days after adding indinavir to an antiretroviral regimen [peak bilirubin 17.5, 6.1 and 2.5 mg/dL, ALT 690, 1602 and 1875 U/L, Alk P 145, 49 and 159 U/L]; 1 patient with HBsAg died, the 2 others [one with HCV] resolved on stopping indinavir).

Matsuda J, Gohchi K. Severe hepatitis in patients with AIDS and haemophilia B treated with indinavir. Lancet 1997; 350: 364. PubMed PMID: 9251655.

(27 year old man with hemophilia B and HCV [maximal ALT 94 U/L] had worsening ALT levels [60 rising to 807 U/L] and eosinophilia 6 months after adding indinavir to an antiretroviral regimen, and was maintained on indinavir with persistence of ALT elevations [187 U/L]).

Carr A, Cooper DA. Restoration of immunity to chronic hepatitis B infection in HIV-infected patient on protease inhibitor. Lancet 1997; 349: 995-6. PubMed PMID: 9100629.

(34 year old with HIV-HBV coinfection developed rise in ALT levels [80 to 310 to 680 U/L] 5 weeks after starting ritonavir, with subsequent worsening before clearance of both HBeAg and HBV DNA followed by fall of ALT into the normal range; interpreted as HBeAg seroconversion possibly triggered by immune constitution).

Carr A, Brown D, Cooper DA. Portal vein thrombosis in patients receiving indinavir, an HIV protease inhibitor. AIDS 1997; 11: 165-8. PubMed PMID: 9365776.

(Two patients presenting with portal hypertension without cirrhosis while on antiretroviral therapy with indinavir and stavudine, found to have evidence of portal vein thrombosis, but other possibility was nodular regenerative hyperplasia).

Hammer SM, Squires KE, Hughes MD, Grimes JM, Demeter LM, Currier JS, Eron JJ Jr, et al. A controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infection and CD4 cell counts of 200 per cubic millimeter or less. AIDS Clinical Trials Group 320 Study Team. N Engl J Med 1997; 337: 725-33. PubMed PMID: 9287227.

(Controlled trial of indinavir with 2 nucleoside analogues or the 2 nucleosides alone in 1156 patients with HIV infection; no mention of hepatotoxicity or ALT elevations).

Vandercam B, Moreau M, Horsmans C, Gala JL. Acute hepatitis in a patient treated with saquinavir and ritonavir: absence of cross-toxicity with indinavir. Infection 1998; 26: 313. PubMed PMID: 9795794.

(46 year old man with HIV infection developed nausea within hours of starting stavudine, saquinavir and ritonavir, recurring on restarting [bilirubin normal, ALT 1833 U/L, GGT 175 U/L, no eosinophilia], resolving rapidly and not recurring on starting stavudine, lamivudine and indinavir).

Vergis E, Paterson DL, Singh N. Indinavir-associated hepatitis in patients with advanced HIV infection. Int J STD AIDS 1998; 9: 53. PubMed PMID: 9518018.

(46 year old man with HIV infection developed pain and jaundice 46 days after adding indinavir to antiretroviral regimen [bilirubin 3.7 rising to 12.2 mg/dL, ALT 123 U/L, Alk P 136 U/L], followed by ascites and coagulopathy; biopsy showed fat and necrosis, ultimately resolving: Case 1, indinavir).

Vento S, Garofano T, Renzini C, Casali F, Ferraro T, Concia E. Enhancement of hepatitis C virus replication and liver damage in HIV-coinfected patients on antiretroviral combination therapy. AIDS 1998; 12: 116-7. PubMed PMID: 9456265.

(Among 51 patients with HIV-HCV coinfection started on highly active antiretroviral therapy, rises in HCV RNA levels at one month with worsening of ALT, falls in HIV RNA levels and rises in CD4 count were common; while liver biopsy in 31 patients showed worsening and 7 had clinical decompensation).

Arribas JR, Ibanez C, Ruiz-Antoran B, Pena JM, Esteban-Calvo C, Frias J, Vazquez JJ, et al. Acute hepatitis in HIV-infected patients during ritonavir treatment. AIDS 1998; 12: 1722-4. PubMed PMID: 9764797.

(Among 141 patients treated with full dose ritonavir, 10 developed hepatitis [9 with HCV coinfection] arising within 2 months of starting, 7 with symptoms and 6 with jaundice [bilirubin 0.8 to 16 mg/dL, ALT 418 to 1206 U/L], all resolving, two without dose modification).

Rodiguez-Rosado R, Garcia-Samaniego J, Soriano V. Hepatotoxicity after introduction of highly active antiretroviral therapy. AIDS 1998; 12: 1256. PubMed PMID: 9677182.

(Analysis of first 187 patients starting highly active antiretroviral therapy; rise in ALT >2 times baseline occurred in 14%, bilirubin >2.5 mg/dL in 4%; 4 patients developed hepatic decompensation and one died).

Mina J, Flexman J, French MA. Hepatitis C virus-associated hepatitis following treatment of HIV-infected patients with HIV protease inhibitors: an immune restoration disease? AIDS 1998; 12: 2289-93. PubMed PMID: 9863871.

(Analysis of course of 3 of 133 patients on antiretroviral therapy who developed acute liver injury; all had HCV infection and hepatitis appeared with immune restoration, often with development of anti-HCV in a patient with long standing HCV RNA positivity).

Karras A, Rabian C, Zylberberg H, Hermine O, Duchatelle V, Durand F, Valla D, et al. Severe anoxic necrosis in an HIV-1-hepatitis C virus-co-infected patient starting antiretroviral triple combination therapy. AIDS 1998; 12: 827-9. PubMed PMID: 9619823.

(30 year old man with HIV-HCV coinfection developed red cell aplasia and severe anemia [hemoglobin 3 g/dL] 2 months after starting lamivudine, zidovudine and indinavir, with acute abdominal pain [bilirubin 12.7 mg/dL, ALT 35 times ULN, Alk P normal], recovering in 2 weeks of stopping and tolerating restarting lamivudine, zalcitabine and indinavir without recurrence; biopsy showed ischemic hepatitis).

Picard O, Rosmorduc O, Cabane J. Hepatotoxicity associated with ritonavir. Ann Intern Med 1998; 129: 670-2. PubMed PMID: 9786823.

(28 year old woman with HIV infection developed elevated ALT [133 U/L] 5 weeks after adding ritonavir and stavudine to lamivudine with rapid resolution, but recurrence 5 weeks after restarting with abdominal pain, jaundice, hepatic failure and lactic acidosis [bilirubin 19.4 mg/dL, ALT 254 U/L, prothrombin index 22%], resolving slowly within 8 weeks of stopping; later tolerated lamivudine and stavudine alone).

Havlir DV, Lange JM. New antiretrovirals and new combinations. AIDS 1998; 12 Suppl A: S165-74. PubMed PMID: 9632999.

(Review of new agents for HIV infection, including nelfinavir, nevirapine, delaviridine, efavirenz and abacavir; most significant toxicities discussed include diarrhea for nelfinavir, rash and hepatitis for nevirapine, rash for delavirdine; little information available on toxicities of other agents).

Rutschmann OT, Negro F, Hirschel B, Hadengue A, Anwar D, Perrin LH. Impact of treatment with human immunodeficiency virus (HIV) protease inhibitors on hepatitis C viremia in patients coinfected with HIV. J Infect Dis 1998; 177: 783-5. PubMed PMID: 9498464.

(Analysis of HCV RNA levels in 19 patients with HIV-HCV coinfection; after 6 weeks of highly active antiretroviral therapy, HCV RNA levels increased slightly [mean = +0.4 log IU/mL], returning to baseline by 4 months with little or no change in ALT levels).

Zylberberg H, Chaix ML, Rabian C, Rouzioux C, Aulong B, Bréchot C, Viard JP, et al. Tritherapy for human immunodeficiency virus does not modify replication of hepatitis C virus in coinfected subjects. Clin Infect Dis 1998; 26:1104-6. PubMed PMID: 9597236.

(Among 22 patients with HIV-HCV coinfection started on various regimens of highly active antiretroviral therapy, HIV levels decreased and CD4 counts increased, but ALT and HCV RNA levels did not change significantly).

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

Rockstroh JK, Theisen A, Kaiser R, Sauerbruch T, Spengler U. Antiretroviral triple therapy decreases HIV viral load but does not alter hepatitis C virus (HCV) serum levels in HIV-HCV-co-infected haemophiliacs. AIDS 1998; 12: 829-30. PubMed PMID: 9619824.

(Prospective study of 26 patients with hemophilia and HIV-HCV coinfection started on saquinavir or indinavir on top of chronic therapy with two nucleoside analogues; despite improvements in CD4 counts and HIV RNA levels at 3 months, HCV RNA and ALT levels did not change).

Mastroianni C, Trinhieri V, Santopadre P, Lichtner M, Forcina G, D'Agostino C, Corpolongo A, et al. Acute clinical hepatitis in an HIV-seropositive hepatitis B carrier receiving protease inhibitor therapy. AIDS 1998; 12: 1939-40. PubMed PMID: 9792403.

(62 year old man with HIV-HBV coinfection with normal ALT and no HBeAg developed abdominal pain 12 weeks after starting lamivudine, stavudine and ritonavir [ALT 1340 U/L and presence of HBeAg, HBV DNA and IgM anti-HBc indicative of reactivation], resolving in 8 weeks of stopping despite persistence of HBeAg).

Pai V, Nahata M. Nelfinavir mesylate: a protease inhibitor. Ann Pharmacother 1999; 33: 325-39. PubMed PMID: 10200859.

(Review of the structure, activity, pharmacology, safety and tolerance of nelfinavir, an antiretroviral agent developed using rational drug design as an agent that binds to active site of HIV-1 protease blocking its activity; most common side effects are diarrhea [14-32%], nausea [2-7%] and skin rash [3-4%]; ALT elevations in 1-3%, and lipodystrophy with long term use; also a competitive inhibitor of CYP 3A4 and has major drug-drug interactions).

Orenstein R, LeGall-Salmon E. HIV treatment-associated hepatitis. AIDS Read 1999; 9: 339-46. PubMed PMID: 12737123.

(Review of antiretrovirals and liver injury; by 1998, 80% of antiretroviral regimens included a protease inhibitor; ritonavir most commonly associated with liver injury, with several instances of acute hepatitis arising within 12-82 days, resolving in 1-2 months, 2 positive rechallenges; cases also reported with indinavir, less know about saquinavir and amprenavir).

Velasco M, Moran A, Teliez MJ. Resolution of chronic hepatitis B after ritonavir treatment in an HIV-infected patient. N Engl J Med 1999; 340: 1765-6. PubMed PMID: 10357637.

(35 year old with HIV-HBV coinfection developed nausea 9 weeks after adding ritonavir to didanosine and zidovudine [ALT 503 U/L], resolving despite continuing antiretrovirals, ultimately clearing HBV DNA and HBsAg).

Nigro I, Romano F, Tosto S, Zagami A, Bruno S, Nunnari A. Severe hepatitis in an HIV-positive subject under treatment with a protease inhibitor. Ital J Gastroenterol 1999; 31: 85-6. *(37 year old man with HIV-HBV coinfection, developed jaundice 20 days after adding indinavir to zidovudine and zalcitabine [bilirubin 11.2 mg/dL, ALT 1608 U/L, borderline IgM anti-HBc, CD4 cells having risen from 4 to 97], resolving within 7* PubMed PMID: 10091111.

weeks of stopping with clearance of HBsAg; anti-HCV was also present, but HCV RNA testing was not done).

Ragni MV, Bontempo FA. Increase in hepatitis C virus load in haemophiliacs during treatment with highly active antiretroviral therapy. J Infect Dis 1999; 180: 2027-9. PubMed PMID: 10558963.

(Analysis of 21 patients with hemophilia and HIV-HCV coinfection starting highly active antiretroviral therapy; HCV RNA levels tended to increase with prolonged therapy [48 weeks], one developed decompensation).

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 presented with lactic acidosis and jaundice [bilirubin 10.2 mg/dL, ALT 234 U/L, CPK 3074 U/L], resolving with stopping; unclear which agent[s] were responsible for second episode).

Savès M, Raffi F, Clevenbergh P, Marchou B, Waldner-Combernoux A, Morlat P, Le Moing V, et al., The APROCO Study Group. Hepatitis B or C virus infection is a risk factor for severe hepatic cytolysis after initiation of a protease inhibitor-containing antiretroviral regimen in human immunodeficiency virus-infected patients. Antimicrob Agents Chemother 2000; 44: 3451-5. PubMed PMID: 11083658.

(Among 1047 patients with HIV infection who were started on protease inhibitors, ALT elevations >5 times ULN occurred in 5 per patient-year, HCV infection raised the risk 8-fold and HBsAg 6.7-fold, but rate did not differ by specific protease inhibitor used).

Pai V, Koranyi K, Nahata M. Acute hepatitis and bleeding possibly induced by zidovudine and ritonavir in an infant with HIV infection. Pharmacotherapy 2000; 20: 1135-40. PubMed PMID: 10999509.

(9 year old boy with HIV infection and multiple complications developed fever, thrombocytopenia and hepatitis 2 months after starting zidovudine, lamivudine and ritonavir with progressive liver failure and severe bleeding after liver biopsy; difficult to assign specific causality).

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; 18: F25-32. PubMed PMID: 10716495.

(Description of 14 patients with lipodystrophy and liver dysfunction who were never treated with protease inhibitors, most having received stavudine [86%] or didanosine [71%] for more than 6 months and most developing hyperlactatemia, ALT elevations and symptoms of weight loss, nausea and fatigue; most recovered slowly upon withdrawal).

Puoti M, Gargiulo F, Roldan EQ, Chiodera A, Palvarini L, Spinetti A, Zaltron S, et al. Liver damage and kinetics of hepatitis C virus and human immunodeficiency virus replication during the early phases of combination antiretroviral treatment. J Infect Dis 2000; 181: 2033-6. PubMed PMID: 10837187.

(Monitoring viral levels during initiation of antiretroviral therapy with either nevirapine or indinavir with lamivudine and stavudine in 12 patients with HIV and HCV coinfection found slight rise in HCV RNA during weeks 1-3 of therapy, with no consistent change in ALT).

Puoti M, Spinetti A, Ghezzi A, Donato F, Zaltron S, Putzolu V, Quiros-Roldan E, et al., Hepatitis-HIV Study Group. Mortality for liver disease in patients with HIV infection: a cohort study. J Acquir Immune Defic Syndr 2000; 24: 211-7. PubMed PMID: 10969344.

(Analysis of 308 in hospital deaths in patients with AIDS between 1987-1995, found 35 who died of liver failure [12%]; risk factors were hepatitis B and alcohol abuse; HCV and HDV were significant in univariate analysis, but antiretroviral use was not).

Gisolf E, 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; 3: 1234-9. PubMed PMID: 11073757.

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

den Brinker M, Wit FW, Wertheim-van Dillen PM, Jurriaans S, Weel J, van Leeuwen R, Pakker NG, et al. Hepatitis B and C virus co-infection and the risk for hepatotoxicity of highly active antiretroviral therapy in HIV-1 infection. AIDS 2000; 14: 2895-902. PubMed PMID: 11153671.

(Retrospective analysis of 394 HIV infected patients starting antiretroviral therapy; liver enzyme elevations occurred in 45% with HBV, 33% with HCV, and 12% with neither, onset averaging 25 weeks after starting; HBeAg loss in 7 patients).

Reijers MH, Weigel HM, Hart AA, Ten Kate RW, Mulder JW, Reiss P, Schultemaker H, et al. Toxicity and drug exposure in a quadruple drug regimen in HIV-1 infected patients participating in the ADAM study. AIDS 2000; 14: 59-68. 10714568. PubMed PMID: 10714568.

(Among 65 treatment-naïve patients starting stavudine, lamivudine, nelfinavir or saquinavir, 12 had liver enzyme elevations that required discontinuation, but this did not correlate with excessively high drug levels).

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 >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 out that the majority of the ALT elevations described could not be attributed to immune reconstitution).

Melvin DC, Lee JK, Belsey E, Arnold J, Murphy RL. The impact of co-infection with hepatitis C virus and HIV on the tolerability of antiretroviral therapy. AIDS 2000; 14: 463. PubMed PMID: 10770552.

(The rate of discontinuation of antiretroviral therapy for hepatotoxicity was 17% among 45 HIV-HCV coinfected patients compared to only 6.8% of 50 matched HIV monoinfected patients).

Gavazzi G, Bouchard O, Leclercq P, Morel-Baccard C, Bosseray A, Dutertre N, Micoud M, et al. Change in transaminases in hepatitis C virus- and HIV-coinfected patients after highly active antiretroviral therapy: differences between complete and partial virologic responders? AIDS Res Hum Retroviruses 2000 20; 16: 1021-3. PubMed PMID: 10933615.

(Prospective study of 22 patients with HIV-HCV coinfection starting highly active antiretroviral therapy; levels of HIV fell, CD4 counts rose, but HCV RNA levels did not change between baseline and month 12 both in responders and nonresponders to antiretroviral therapy).

Zucker SD, Qin X, Rouster SD, Yu F, Green RM, Keshavan P, Feinberg J, et al. Mechanism of indinavir-induced hyperbilirubinemia. Proc Natl Acad Sci U S A 2001; 98: 12671-6. PubMed PMID: 11606755.

(Analysis of effects of indinavir on UDP glucuronyltransferase activity in vitro and in vivo, showing competitive inhibition by indinavir, but not saquinavir at therapeutic levels; in 15 patients, rise in bilirubin occurred in 13 and was more marked in those with Gilbert's TATA box variants [0.8 rising to 2.3 mg/dL] than without [0.5 rising to 0.8 mg/dL]).

Riddle TM, Kuhel DG, Woollett LA, Fichtenbaum CJ, Hui DY. HIV protease inhibitor induces fatty acid and sterol biosynthesis in liver and adipose tissues due to the accumulation of activated sterol regulatory element-binding proteins in the nucleus. J Biol Chem 2001; 276: 37514-9. PubMed PMID: 11546771.

(In mice, ritonavir results in increase in plasma triglyceride and cholesterol levels via increase in hydrolysis of precursor sterol regulatory element-binding protein, which causes its release from endoplasmic reticulum and translocation to the nucleus where it induces lipid metabolism enzymes).

Hill JB, Sheffield JS, Zeeman GG, Wendel GD Jr. Hepatotoxicity with antiretroviral treatment of pregnant women. Obstet Gynecol 2001; 98: 909-11. PubMed PMID: 11704198.

(Two cases, 28 year old woman on zidovudine, lamivudine and efavirenz developed jaundice at 18 weeks gestation [bilirubin 20.3 mg/dL, ALT 421 U/L], remaining jaundiced until delivered at 27 weeks, resolving in 5 months after delivery; 22 year old started on lamivudine, zidovudine and nelfinavir at 14 weeks gestation and developed jaundice 10 weeks later [bilirubin 8.9 mg/dL, ALT 1598 U/L], progressing to acute liver failure and death).

Trapé M, Barnosky S. Nelfinavir in expanded postexposure prophylaxis causing acute hepatitis with cholestatic features: two case reports. Infect Control Hosp Epidemiol 2001; 22: 2-3. PubMed PMID: 11519908.

(Among 15 subjects treated prophylactically with zidovudine, lamivudine and nelfinavir after accidental exposure to HIV, 2 developed symptomatic liver disease; 54 year old physician developed fatigue, nausea, fever and abdominal pain 15 days after starting therapy; 32 year old surgical resident developed fever and nausea at 15 and jaundice after 17 days of therapy. Both resolved within weeks of stopping nelfinavir, continuing others [no laboratory results given]).

Núñez M, Lana R, Mendoza JL, Martin-Carbonero L, Soriano V. Risk factors for severe hepatic injury after introduction of highly active antiretroviral therapy. J AIDS 2001; 27: 426-31. PubMed PMID: 11511818.

(Retrospective review of 222 patients started on highly active antiretroviral therapy, 96 with protease inhibitors; 10% had ALT elevations >5 times ULN, risk factors were HCV infection, alcohol use and older age, but not type of agent; transient in all except HCV infected).

Hernandez LV, Gilson I, Jacobson J, Affi A, Puetz TR, Dindzans VJ. Antiretroviral hepatotoxicity in human immunodeficiency virus-infected patients. Aliment Pharmacol Ther 2001; 15: 1627-32. PubMed PMID: 11564003.

(Retrospective analysis identified 24 of 65 patients on antiretroviral therapy with suspected hepatotoxicity [ALT twice normal 5 to 90 days after starting or rapid ALT decline with stopping]; risk factors were hepatitis C, older age and low CD4 counts, but not any specific agent or duration of therapy).

Manegold C, Hannoun C, Wywiol A, Dietrich M, Polywka S, Chiwakata CB, Gunther S. Reactivation of hepatitis B virus replication accompanied by acute hepatitis in patients receiving highly active antiretroviral therapy. Clin Infect Dis 2001; 32: 144-8. PubMed PMID: 11118394.

(Two cases of reactivation with reappearance of HBsAg in HIV-positive patients with subsequent flare of hepatitis B on antiretroviral therapy; 65 year old man with anti-HBs and anti-HBc without HBsAg, developed HBsAg 4 months after starting antiretroviral therapy [without lamivudine], with transient increase in HBV DNA and ALT followed by resolution; 35 year old man with flare of hepatitis B after withdrawal of lamivudine and subsequent recovery).

Bonfanti P, Landonio S, Ricci E, Martinelli C, Fortuna P, Faggion I, Quirino T, CISAI Study Group. Risk factors for hepatotoxicity in patients treated with highly active antiretroviral therapy. J Acquir Immune Defic Syndr 2001; 27: 316-8. PubMed PMID: 11464155.

(Analysis of 1477 Italian patients with HIV infection starting therapy with at least one protease inhibitor; ALT elevations occurred in 5.8 per 100 patient years; ALT levels above 5 times ULN in 2.7 per 100 patient years; risk factors were HCV coinfection and preexisting ALT elevations).

Monforte AD, Bugarini R, Pezzotti P, De Luca A, Antionori A, Mussini C, Vigevani GM, et al., ICONA Study Group. Low frequency of severe hepatotoxicity and association with HCV coinfection in HIV-positive patients treated with HAART. J Acquir Immune Defic Syndr 2001; 28: 114-23. PubMed PMID: 11588504.

(Among 1255 patients with HIV infection starting antiretroviral therapy, mean ALT levels did not change and only 4.5% developed ALT above 200 U/L during median follow up of 18 months; the only independent risk factor for ALT elevations was baseline ALT levels).

Bica I, McGovern B, Char R, Stone D, McGowan K, Scheib R, Snydman DR. Increasing mortality due to end-stage liver disease in patients with HIV infection. Clin Infect Dis 2001; 32: 492-7. PubMed PMID: 11170959.

(While the mortality rate of HIV infection fell with development of effective antiretroviral therapies, the proportion of deaths due to liver disease has increased from 11.5% in 1991 to 50% in 1999, mostly due to hepatitis C).

Reisler K. High hepatotoxicity rate seen among HAART patients. AIDS Alert 2001; 16: 118-9. PubMed PMID: 11547496.

(News report on abstract: study of 10,011 patients in 21 clinical trials with HIV infection, showing that ALT elevations >5 times normal occur in 6.2% of highly active antiretroviral therapy treated patients; 10.8% with efavirenz, 8.9% with nevirapine and 3.6% with delavirdine in short term studies).

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 had signs of hypersensitivity, two had hepatitis B; 5 died, autopsies showing massive necrosis, one with massive steatosis; likely multiple causes).

Cooper CL, Parbhakar MA, Angel JB. Hepatotoxicity associated with antiretroviral therapy containing dual versus single protease inhibitors in individuals coinfected with hepatitis C virus and human immunodeficiency virus. Clin Infect Dis 2002; 34: 1259-63. PubMed PMID: 11941553.

(Retrospective analysis of 66 HIV-HCV coinfected patients initiating antiretroviral therapy with protease inhibitors; ALT elevations >5 times ULN occurred in 24% of ritonavir containing vs 22% of ritonavir sparing regimens).

Stone SF, Lee S, Keane NM, Price P, French MA. Association of increased hepatitis C virus (HCV)-specific IgG and soluble CD26 dipeptidyl peptidase IV enzyme activity with hepatotoxicity after highly active antiretroviral therapy in human immunodeficiency virus-HCV-coinfected patients. J Infect Dis 2002; 186: 1498-502. PubMed PMID: 12404169.

(Serial testing for levels of anti-HCV [core specific, IgG] and DPP IV enzyme activity in 16 patients with HIV-HCV coinfection on antiretroviral therapy found rises in these markers occurred concurrent with or shortly after ALT elevations thought be suggestive of role of immune reconstitution).

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).

Chung R, Evans S, Yang Y, Theodore D, Valdez H, Clark R, Shikuma C, et al., AIDS Clinical Trial Group 383 Study Team. Immune recovery is associated with persistent rise in hepatitis C virus RNA, infrequent liver test flares, and is not impaired by hepatitis C virus in co-infected subjects. AIDS 2002; 16: 1915-23. PubMed PMID: 12351951.

(Analysis of 60 patients with HIV-HCV coinfection starting highly active antiretroviral therapy, HCV RNA levels increased by ~0.4 log IU/mL which persisted to week 48, ALT levels rose early and then fell to baseline, only 2 patients had ALT elevations >5 times ULN, no decompensation).

Thio CL, Seaberg EC, Skolasky R Jr, Phair J, Visscher B, Muñoz A, Thomas DL; Multicenter AIDS Cohort Study. HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS). Lancet 2002; 360: 1921-6. PubMed PMID: 12493258.

(Risk of liver related death was increased in patients with HIV infection and particularly high in those with HIV-HBV coinfection).

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 in children for each of the antiretrovirals; 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).

Martín-Carbonero L, Núñez M, Ríos P, Pérez-Olmeda M, González-Lahoz J, Soriano V. Liver injury after beginning antiretroviral therapy in HIV/hepatitis C virus co-infected patients is not related to immune reconstitution. AIDS 2002; 16: 1423-5. PubMed PMID: 12131221.

(Analysis of changes in ALT, CD4 counts, HIV RNA and HCV RNA in 42 HIV/HCV coinfected patients started on antiretroviral therapy; 72% developed ALT elevations, 14% >5 times ULN, but no correlation between amount of HIV decrease or CD4 increase and frequency of ALT elevation, but those with severe injury all had improvements in CD4 counts and slight increase in HCV RNA levels).

Murcia JM, Boix V, Merino E, Manso MI, Portilla J. Drug toxicity or syndrome of immune restoration causing fulminant cirrhosis after HAART-induced immune recovery. Eur J Clin Microbiol Infect Dis 2002; 21: 153-5. PubMed PMID: 11939401.

(25 year old man with HIV-HCV-HBV coinfections developed rising ALT levels 1 year after starting stavudine, nelfinavir and nevirapine [peak bilirubin 17.6 mg/dL, ALT 1502 U/L, HCV RNA 786,000 copies/mL, no detectable HBV DNA on several determinations] and acute-on-chronic hepatitis by liver biopsy which progressed to liver failure, despite stopping antivirals and fall of HCV RNA to undetectable; authors attributed acute severe flare to immune reconstitution).

Shahmanesh M, Cartledge J, Miller R. Lactic acidosis and abnormal liver function in advanced HIV disease. Sex Transm Infect 2002; 78: 139-42. PubMed PMID: 12081178.

(Case report and discussion: 48 year old man with HIV infection on zidovudine, didanosine and indinavir developed ascites, mild lactemia and abnormal liver tests [ALT 116 U/L, Alk P 324 U/L] and subsequent variceal hemorrhage, multiorgan failure and death, possibly nodular regenerative hyperplasia and not nucleoside analogue related hepatotoxicity).

Selik R, Byers R, Dworkin M. Trends in diseases reported on US death certificates that mentioned HIV infection. 1987-99. J Acquir Immune Defic Syndr 2002; 29: 378-87. PubMed PMID: 11917243.

(Analysis of US vital statistics; deaths from AIDS rose from 15,331 in 1987 to 47,977 in 1995 then falling to 16,061 in 1999, with increases in the proportion of deaths due to liver disease from 4.9% in 1987 to 11.6% in 1999).

Aceti A, Pasquazzi C, Zechini B, De Bac C, LIVERHAART Group. Hepatotoxicity development during antiretroviral therapy containing protease inhibitors in patients with HIV. The role of hepatitis B and C virus infection. J Acquir Immune Defic Syndr 2002; 29: 41-8. PubMed PMID: 11782588.

(Among 1325 patients starting highly active antiretroviral therapy, 11% developed ALT elevations, 3.2% >5 times ULN, often remaining high at 12 and 24 months; elevations were more common with ritonavir [17.5%], saquinavir [12.6%], and indinavir [8.5%]).

Núñez M, Rios P, Martin-Carbonero L, Perez-Olmeda M, González-Lahoz J, Soriano V. Role of hepatitis C virus genotype in the development of severe transaminase elevation after the introduction of antiretroviral therapy. J Acquir Immune Defic Syndr 2002; 30: 65-8. PubMed PMID: 12048364.

(Among 70 patients with HIV-HCV coinfection, 37 [53%] developed ALT elevations after starting antiretroviral therapy, 12 [17%] >5 times ULN, and higher rate in patients with HCV genotype 3 [71% for any elevation; 33% for >5 times ULN]).

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).

Wit FW, Weverling GJ, Weel J, Jurriaans S, Lange JM. Incidence of and risk factors for severe hepatotoxicity associated with antiretroviral combination therapy. J Infect Dis 2002; 186: 23-31. PubMed PMID: 12089658.

(Retrospective analysis found 6.3% incidence of liver enzyme elevations >5 times ULN among 560 Dutch patients on highly active antiretroviral therapy; 71% had either HBV or HCV infection; risk factors included recent introduction of nevirapine or high dose ritonavir or stopping lamivudine).

Qurishi N, Kreuzberg C, Luchters G, Effenberger W, Kupfer B, Sauerbruch T, Rockstroh JK, et al. Effect of antiretroviral therapy on liver-related mortality in patients with HIV and hepatitis C virus coinfections. Lancet 2003; 362: 1708-13. PubMed PMID: 14643119.

(Analysis of liver related mortality in cohort of largely hemophilic patients with HIV infection; 0.45/100,000 in those on highly active antiretroviral therapy vs 0.69 in those on nucleoside analogues only vs 1.70 among antiretroviral untreated patients).

Carter M. ART and liver-related mortality in HIV/HCV. IAPAC Mon 2003; 9: 315. PubMed PMID: 15055165.

(News report on the rising proportion of deaths due to liver disease among HIV-infected persons as reported by Qurishi [2003]).

Dore G. Antiretroviral therapy-related hepatotoxicity: predictors and clinical management. J HIV Ther 2003; 8: 96-100. PubMed PMID: 14671507.

(Review with suggested algorithm for management of ALT elevations on HAART therapy).

Weissbrich B, Langmann P, Schubert J, Jassoy C, Klinker H. Resolution of HCV infection in a HIV-infected patient under HAART after several hepatitis flare-ups. Eur J Med Res 2003; 8: 495-8. PubMed PMID: 14644704.

(Patient with HIV and severe hepatitis C became HCV RNA negative after complications of cirrhosis on long term nevirapine and indinavir therapy).

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, grade 2=2.6-5, grade 3=5.1-10, and grade 4=>10 times ULN or baseline ALT values; abacavir and lamivudine are least likely to cause hepatotoxicity).

Lichterfeld M, Fischer HP, Spengler U, Rockstroh JK. [Fatty liver and increased serum lactate in a woman with HIV] Dtsch Med Wochenschr 2003; 128: 81-4. 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 showed micro- and macro-steatosis, resolving a few weeks after stopping antivirals; most likely due to stavudine).

Law WP, Dore GJ, Duncombe CJ, Mahanontharit A, Boyd MA, Ruxrungtham K, Lange JM, et al. Risk of severe hepatotoxicity associated with antiretroviral therapy in the HIV-NAT Cohort, Thailand, 1996-2001. AIDS 2003; 17: 2191-9. PubMed PMID: 14523276.

(Among 692 patients in 8 controlled trials in Thailand, rate of ALT elevations >5 times ULN was 6.1/100 patient years overall; in multivariate analysis, risk factors were HBV [RR=3.9], HCV [3.0], and use of nonnucleoside reverse transcriptase inhibitors [6.8], rate with nevirapine [18.6/100 person years] higher than efavirenz [2.4]).

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 >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).

Livry C, Binquet C, Sgro C, Froidure M, Duong M, Buisson M, Grappin M, et al. Acute liver enzyme elevations in HIV-1-infected patients. HIV Clin Trials 2003; 4: 400-10. PubMed PMID: 14628283.

(Retrospective analysis of 239 patients with HIV on antiretroviral therapy found ALT or Alk P elevations >2.5 times ULN in 10.7 per 100 patient years in treated and 7.4 per 100 patient years in untreated patients; associated with HCV or HBV co infection, antiretroviral therapy and AIDS severity, but not specific agents).

Pialoux G, Bonnard P, Rozenbaum W. [Liver toxicity of antiretroviral treatments] Gastroenterol Clin Biol 2003; 27: 155-8. French. PubMed PMID: 12658125.

(Review of hepatotoxicity of antiretrovirals; elevations in ALT or AST levels above 5 times ULN occur in 5.7% to 18% of patients on combination antiviral therapies).

Sulkowski MS. Hepatotoxicity associated with antiretroviral therapy containing HIV-1 protease inhibitors. Semin Liver Dis 2003; 23: 183-94. PubMed PMID: 12800071.

(All 6 protease inhibitors used for HIV infection have been associated with hepatotoxicity, all are extensively metabolized by the hepatic CYP450 system; overall range of ALT elevations above 5 times ULN is 3% to 18%, but symptomatic liver injury occurs in only 1.5 to 5% of patients; risk factors ALT elevations are HCV, HBV and full dose ritonavir).

Puoti M, Torti C, Ripamonti D, Castelli F, Zaltron S, Zanini B, Spinetti A, et al.; HIV-HCV Co-Infection Study Group. Severe hepatotoxicity during combination antiretroviral treatment: incidence, liver histology, and outcome. J Acquir Immune Defic Syndr 2003; 32; 259-67. PubMed PMID: 12626885.

(Among 755 HIV-positive patients starting antiretroviral therapy, 26 [4.2/100 person-years] developed ALT elevations above 10 times ULN, but only in patients with HCV [n=25], HBV [n=4] or HDV [n=4] coinfection; 7 died).

Vennarecci G, Ettorre GM, Antonini M, Maritti M, Moricca P, D'Offizzi G, Narciso P, et al. [Acute liver toxicity of antiretroviral therapy(HAART) after liver transplantation in a patient with HIV-HCV coinfection and associated hepatocarcinoma (HCC)]. Tumori 2003; 89 (4 Suppl): 159-61. Italian. PubMed PMID: 12903579.

(46 year old man with HIV-HCV coinfection and hepatocellular carcinoma developed severe graft dysfunction immediately after transplant, possibly related to alteration in antiretroviral drug levels).

Zell SC. Clinical vignette in antiretroviral therapy: jaundice. J Int Assoc Physicians AIDS Care (Chic Ill) 2003; 2: 133-9. PubMed PMID: 14986514.

(35 year old man with AIDS developed jaundice 17 months after starting lopinavir, stavudine and lamivudine [bilirubin 12.5 mg/dL, ALT 200 U/L, Alk P 435 rising to 958 U/L], resolving in 2 months after substituting nelfinavir for lopinavir).

Uberti-Foppa C, De Bona A, Morsica G, Galli L, Gallotta G, Boeri E, Lazzarin A. Pretreatment of chronic active hepatitis C in patients coinfected with HIV and hepatitis C virus reduces the hepatotoxicity associated with subsequent antiretroviral therapy. J Acquir Immune Defic Syndr 2003; 33: 146-52. PubMed PMID: 12794546.

(Rates of ALT elevations >5 times ULN or 3.5 times baseline were less among 66 patients who were pretreated for hepatitis C [interferon with or without ribavirin] compared to 39 who were not treated [6% vs 15%, p=NS]).

French AL, Benning L, Anastos K, Augenbraun M, Nowicki M, Sathasivam K, Terrault NA. Longitudinal effect of antiretroviral therapy on markers of hepatic toxicity: impact of hepatitis C coinfection. Clin Infect Dis 2004; 39: 402-10. PubMed PMID: 15307009.

(Statistical analysis of ALT and AST levels in 1106 HIV infected women who initiated highly active antiretroviral therapy; proportion with elevations was higher in HIV coinfected, but did not increase in either group or by agent class used after starting therapy).

Sulkowski MS, Mehta SH, Chaisson RE, Thomas DL, Moore RD. Hepatotoxicity associated with protease inhibitor-based antiretroviral regimens with or without concurrent ritonavir. AIDS. 2004; 18: 2277-84. PubMed PMID: 15577540.

(Prospective analysis of 1161 patients [1996-2003] started on protease inhibitors, ALT >5 times ULN occurred in 12.7%, with slightly higher rates for saquinavir/ritonavir [17.2%] and with HCV coinfection; multivariate analysis identified HCV infection and use of saquinavir or indinavir associated with ALT >5 times ULN).

Meraviglia P, Schiavini M, Castagna A, Viganò P, Bini T, Landonio S, Danise A, et al. Lopinavir/ritonavir treatment in HIV antiretroviral-experienced patients: evaluation of risk factors for liver enzyme elevation. HIV Med 2004; 5: 334-43. PubMed PMID: 15369508.

(Among 782 HIV-positive patients treated with lopinavir and low dose ritonavir, 71 [9%] developed abnormal liver tests, mostly mild, asymptomatic and self-limited, but 4 had symptomatic hepatitis, 3 were jaundiced and one died; multivariate analysis showed HCV and HBV coinfection, younger age, high ALT values and use of efavirenz were risk factors for abnormal liver tests).

Gathe JC Jr, Ive P, Wood R, Schümann D, Bellos NC, DeJesus E, Gladysz A, et al. SOLO: 48-week efficacy and safety comparison of once-daily fosamprenavir /ritonavir versus twice-daily nelfinavir in naive HIV-1-infected patients. AIDS 2004; 18: 1529-37. PubMed PMID: 15238771.

(In a controlled trial of fosamprenavir with low dose ritonavir versus nelfinavir, both combined with abacavir and lamivudine, ALT elevations above 5 times ULN occurred in 8% of both treatment arms).

Eholié SP, Lacombe K, Serfaty L, Wendum D, Girard PM. Acute hepatic cytolysis in an HIV-infected patient taking atazanavir. AIDS 2004; 18: 1610-1. PubMed PMID: 15238786.

(56 year old woman developed fatigue and ALT elevations 7 months after being switched from lopavir/r and stavudine to atazanavir and tenofovir while remaining on didanosine [bilirubin normal, ALT 405 U/L, Alk P 158 U/L], resolving 8 weeks after stopping atazanavir, subsequently tolerating didanosine, tenofovir and nelfinavir).

González de Requena D, Núñez M, Jiménez-Nácher I, González-Lahoz J, Soriano V. Liver toxicity of lopinavir-containing regimens in HIV-infected patients with or without hepatitis C coinfection. AIDS Res Hum Retroviruses 2004; 20: 698-700. PubMed PMID: 15307912.

(Among 120 patients started on lopinavir-containing regimens for HIV, ALT elevations above 5 times ULN or above 3.5 times baseline arose in 6 [5%], all cases occurring in HCV infected [n=4] or patients abusing alcohol [n=2]).

Kottilil S, Polis MA, Kovacs JA. HIV Infection, hepatitis C infection, and HAART: hard clinical choices. JAMA 2004; 292: 243-50. PubMed PMID: 15249574.

(Case report of patient with HIV and HCV coinfection on antiretrovirals; nonresponse to a course of peginterferon and ribavirin).

Hicks C, King MS, Gulick R, Clinton White A, Eron JJ, Kessler HA, Benson C, et al. Long-term safety and durable antiretroviral activity of lopinavir/ritonavir in treatment-naï patients: 4-year follow up study. AIDS 2004; 18: 775-9. PubMed PMID: 15075512.

(Among 100 treatment-naïve patients treated with lopinavir with low dose ritonavir in differing doses, ALT elevations >5 times ULN occurred in 11% by 4 years; rates were higher in those with HBV or HCV coinfection).

Sulkowski MS. Drug-induced liver injury associated with antiretroviral therapy that includes HIV-1 protease inhibitors. Clin Infect Dis 2004; 38 Suppl 2: S90-7. PubMed PMID: 14986280.

(Review focusing upon protease inhibitors; forms of injury include indirect hyperbilirubinema caused by indinavir and atazanavir and ALT elevations that occur in 3% to 11% of patients treated with combinations including protease inhibitors, higher rates of ALT elevations are associated with HBV and HCV coinfection, full dose ritonavir, alcohol abuse and during initial therapy accompanied by marked rises in CD4 counts).

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).

Havlir DV, O'Marro SD. Atazanavir: new option for treatment of HIV infection. Clin Infect Dis 2004; 38: 1599-1604. PubMed PMID: 15156449.

(Atazanavir was the 7th protease inhibitor approved for use and given with ritonavir boost [300/100 mg] once daily, metabolized by and inhibits CYP 3A and UGT1A1, bilirubin levels >2.6 times ULN occur in 1/3 of patients, ALT elevations >5 times ULN in 9% to 15% of patients with HBV or HCV co-infection, rates of enzyme elevations were similar to comparative agents).

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 antiviral agent and unclear whether due to therapy, HCV, HIV or other factors).

Sherman KE, Shire NJ, Cernohous P, Rouster SD, Omachi JH, Brun S, Da Silva B. Liver injury and changes in hepatitis C Virus (HCV) RNA load associated with protease inhibitor-based antiretroviral therapy for treatment-naive HCV-HIV-coinfected patients: lopinavir-ritonavir versus nelfinavir. Clin Infect Dis 2005; 41: 1186-95. PubMed PMID: 16163639.

(Among 70 patients with HIV-HCV coinfection treated with lopinavir/ritonavir [r] vs nelfinavir for 48 weeks, slight increase in HCV RNA levels, particularly in those with low initial CD4 counts occurred and were associated with ALT flares above 5 times ULN in 19.5% of nelfinavir vs 7% of lopinavir/r treated patients).

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; recommended approach to managing patients with elevations in ALT levels during therapy).

Anon. Drug-induced hepatitis with saquinavir/ritonavir + rifampin. AIDS Clin Care 2005; 17: 32. PubMed PMID: 15828118.

(News report that Roche sent an alert letter reporting that 11 of 28 healthy controls developed ALT elevations in a phase 1 study of saquinavir/ ritonavir with rifampin [Schmitt, 2009]).

Kramer J, Giordano T, Soucheck J, El-Serag H. Hepatitis C coinfection increases the risk of fulminant hepatic failure in patients with HIV in the HAART era. J Hepatol 2005; 42: 309-14. PubMed PMID: 15710213.

(Analysis of US Veterans Administration hospital database, including 16,439 HIV-positive patients, identified 92 patients with acute liver failure [0.5 per 1000 patient-years], risk factors were HCV coinfection, but casees occurred only during the highly active antiretroviral therapy era).

Salmon-Ceron D, Lewden C, Morlat P, Bevilacqua S, Jougla E, Bonnet F, Heripret L, et al., the Morality 2000 Study Group. Liver disease as a major cause of death among HIV infected patients; role of hepatitis C and B viruses and alcohol. J Hepatol 2005; 42: 799-805. PubMed PMID: 15973779.

(In analysis of 924 deaths during 2000 among HIV infected patients in France; liver disease accounted for 11% of all deathsl, 31% among HCV coinfected, 20% HBV coinfected, but only 2% in patients without HBV or HCV; 88% of liver deaths were from end stage liver disease and 15% had hepatocellular carcinoma; the authors estimated that only 9% of liver disease deaths were attributable to drug hepatotoxicity).

Bonfanti P, Ricci E, Penco G, Orofino G, Bini T, Sfara C, Miccolis S, et al., CISAI Study Group. Low incidence of hepatotoxicity in a cohort of HIV patients treated with lopinavir/ritonavir. AIDS 2005; 19: 1433-4. PubMed PMID: 16103779.

(Among 755 patients with HIV receiving lopinavir/ritonavir followed in an Italian surveillance program, 0.59% per year had ALT elevations >5 times ULN, a lower rate than in most studies).

Mocroft A, Soriano V, Rockstroh J, Reiss P, Kirk O, de Wit S, Gatell J, et al.; EuroSIDA Study Group. Is there evidence for an increase in the death rate from liver-related disease in patients with HIV? AIDS 2005; 19: 2117-25. PubMed PMID: 16284461.

(Among ~11,000 patients followed in European studies of HIV infected subjects, 184 [1.7%] had liver related death, decreasing by 7% between 1995 and 2004; controlling for CD4 count and patient characteristics [but not age or duration of infection], however, liver related death rate has increased).

Mehta SH, Thomas DL, Torbenson M, Brinkley S, Mirel L, Chaisson RE, Moore RD, et al. The effect of antiretroviral therapy on liver disease among adults with HIV and hepatitis C coinfection. Hepatology 2005; 41: 123-31. PubMed PMID: 15619237.

(Analysis of liver biopsy histology from 210 patients with HIV-HCV coinfection; neither fibrosis nor necroinflammatory activity correlated with episodes of liver enzyme elevations due to antiretroviral therapy; predictors of fibrosis included persistent ALT elevations, age and alcohol use).

Núñez M, Soriano V. Hepatotoxicity of antiretrovirals: incidence, mechanisms and management. Drug Saf 2005; 28: 53-66. PubMed PMID: 15649105.

(Review of liver toxicity of antiretrovirals).

Flexner C, Bate G, Kirkpatrick P. Tipranavir. Nat Rev Drug Discov 2005; 4: 955-6. PubMed PMID: 16370086.

(Review of discovery, structure, activity, clinical efficacy, indications and "market analysis" of tipranavir).

Aranzabal L, Casado JL, Moya J, Quereda C, Diz S, Moreno A, Moreno L, et al. Influence of liver fibrosis on highly active antiretroviral therapy-associated hepatotoxicity in patients with HIV and hepatitis C virus coinfection. Clin Infect Dis 2005; 40: 588-93. PubMed PMID: 15712082.

(Among 107 patients with HIV-HCV coinfection with liver histology, 27 [25%: 5 events per 100 patient years] had ALT elevations >5 times ULN or >3.5 times baseline; more frequent in patients with higher levels of fibrosis [38% vs 15%], also higher in patients receiving nonnucleoside reverse transcriptase inhibitors).

Servin-Abad L, Molina E, Baracco G, Arosemena L, Regev A, Jeffers L, Schiff E. Liver enzyme elevation after HAART in HIV-HCV co-infection. J Viral Hepat 2005; 12: 429-34. PubMed PMID: 15985015.

(Among 85 patients with HIV-HCV coinfection who started antiretroviral therapy and were followed for at least 1 year, 4% per year developed ALT or AST elevations >5 times ULN, more frequent with higher baseline levels; all asymptomatic and no association with a specific agent).

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, risk of ALT elevations >5 times ULN was 17.1 per 100 patient years in treatment-naïve and 8.2 in treatment-experienced patients; risk factors for elevations were baseline ALT levels and nonnucleoside reverse transcriptase inhibitor use).

Rotger M, Taffe P, Bleiber G, Gunthard HF, Furrer H, Vernazza P, Drechsler H, et al.; Swiss HIV Cohort Study. Gilbert syndrome and the development of antiretroviral therapy-associated hyperbilirubinemia. J Infect Dis 2005; 192: 1381-6. PubMed PMID: 16170755.

*(Retrospective analysis of 96 Swiss patients with HIV infection genotyped for UGT1A1 and assessed for bilirubin elevations during antiretroviral therapy; total bilirubin increased by 0.43 on atazanavir and 0.28 on indinavir, and higher levels with hetero- or homo-zygosity for UGT1A1 *28).*

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, which was independently associated with white race, body weight, high blood sugar and ever having used stavudine).

Verma S, Bhakta H, Nowain A, Pais S, Kanel G, Squires K, Squires K. Severe cholestatic liver injury days after initiating antiretroviral therapy in a patient with AIDS: drug toxicity or immune reconstitution inflammatory syndrome? Dig Dis Sci 2005; 50: 1813-7. PubMed PMID: 16187179.

(37 year old man with AIDS developed rash and fever one week after starting efavirenz and lopinavir/ritonavir and one day after restarting azithromycin, trimethoprim/sulfamethoxazole [TMP/SMS], one week later became jaundiced [bilirubin 0.4 rising to 9.9 mg/dL, ALT 103 U/L and Alk P 700 U/L], values normalizing in a few weeks, and jaundice recurring after 2 rechallenges using same antiretroviral regimen without TMP/SMS).

Canta F, Marrone R, Bonora S, D'Avolio A, Sciandra M, Sinicco A, De Rosa FG, et al. Pharmacokinetics and hepatotoxicity of lopinavir/ritonavir in non-cirrhotic HIV and hepatitis C virus (HCV) co-infected patients. J Antimicrob Chemother 2005; 55: 280-1. PubMed PMID: 15650005.

(Among 149 HIV infected patients started on lopinavir with low dose ritonavir, 78 were HCV coinfected and cumulative rates of ALT elevations above 2 times ULN were 12.5% in monoinfected vs 61% in coinfected patients and degree of elevations were lower in those without HCV infection; those with and without ALT elevations had similar peak drug levels).

Aceti A, Pasquazzi C, Zechini B, De Bac C; the LIVERHAART Group. Development of hepatotoxicity in HIV patients switching at least one protease inhibitor. Int J STD AIDS 2005; 16: 148-52. PubMed PMID: 15825250.

(Among 182 patients with HIV infection on at least one protease inhibitor for at least 24 months and who then switched to another agent, ALT levels above 5 times ULN occurred in 40% on ritonavir, 18% nelfinavir, 12% indinavir, 11% saquinavir; thus, switching protease inhibitors was not always followed by similar ALT increases on new agent).

Rabaud C, Burty C, Grandidier M, Christian B, Penalba C, Béinot I, Jeanmaire H, et al. Tolerability of postexposure prophylaxis with the combination of zidovudine-lamivudine and lopinavir-ritonavir for HIV infection. Clin Infect Dis 2005; 40: 303-5. PubMed PMID: 15655751.

(Among 121 persons given zidovudine, lamivudine, lopinavir/ritonavir for prevention of HIV after acute exposure, nausea occurred in 67%, fatigue 47%, rash 11%, ALT elevations >3 times ULN in 4%).

Bruno R, Sacchi P, Maiocchi L, Zocchetti C, Filice G. Hepatotoxicity and nelfinavir: a meta-analysis. Clin Gastroenterol Hepatol 2005; 3: 482-8. PubMed PMID: 15880318.

(Pooled analysis of 4268 patients in 4 clinical trials, combined estimates of liver related enzyme level increases were 2.9% for nelfinavir, 3.1% indinavir, 5.4% saquinavir, 9.6% ritonavir, and 12% for saquinavir/r based regimens).

Mira JA, Macias J, Giron-Gonzalez JA, Merino D, Gonzales-Serrano M, Jimenez-Mejias ME, Caballero-Granado FJ, et al. Incidence of and risk factors for severe hepatotoxicity of nelfinavir-containing regimens among HIV-infected patients with chronic hepatitis C. J Antimicrob Chemother 2006; 58: 140-6. PubMed PMID: 16720565.

(Among 80 patients with HIV-HCV coinfection treated with nelfinavir, 9 had an episode of hepatotoxicity, 8 with ALT levels above 5 times ULN and one had hepatic decompensation; nevirapine use was associated with a higher risk of hepatic side effects [8.9]).

Manfredi R, Sabbatani S. Serious, multi-organ hypersensitivity to lopinavir alone, involving cutaneous-mucous rash, and myeloid, liver, and kidney function. AIDS 2006; 20: 2399-400. PubMed PMID: 17117031.

(38 year old woman developed Stevens Johnson syndrome 5 days after reintroduction of antiretroviral therapy using lamivudine, stavudine and lopinavir/ritonavir, lopinavir being the only new agent; with pancytopenia, renal dysfunction and increase in liver tests which resolved within 15 days of stopping and did not recur on atazanavir/ritonavir based regimen).

Julg B, Bogner JR, Goebel FD. Severe hepatotoxicity associated with the combination of enfuvirtide and tipranavir/ritonavir: case report. AIDS 2006; 20: 1563. PubMed PMID: 16847416.

(52 year old man with HIV-HBV co-infection developed marked increase in ALT [538 U/L] without jaundice, 2 weeks after adding tipranavir and ritonavir to a regimen of zidovudine, lamivudine and enfuvirtide, resolving within 4 weeks of stopping; possibly related to effects of enfuvirtide on drug levels, no analysis of HBV reactivation or lamivudine resistance).

Pineda JA, Palacios R, Rivero A, Abdel-Kader L, Márquez M, Cano P, Mira JA, et al. Low incidence of severe liver toxicity in patients receiving antiretroviral combinations including atazanavir. J Antimicrob Chemother 2006; 57: 1016-7. PubMed PMID: 16556636.

(Among 99 patients with HIV started on atazanavir, 3 developed a severe liver event, 2 with decompensation and one with ALT elevations above 5 times ULN, all 3 were either HBV or HCV coinfected).

Shelton MJ, Wire MB, Lou Y, Adamkiewicz B, Min SS. Pharmacokinetic and safety evaluation of high-dose combinations of fosamprenavir and ritonavir. Antimicrob Agents Chemother 2006; 50: 928-34. PubMed PMID: 16495253.

(Pharmacokinetic studies of fosamprenavir, a prodrug of amprenavir, combined with low dose ritonavir; increased rates of ALT elevations with higher doses [32% vs 4% and 12% with lower doses in a 14 day trial]).

Servoss JC, Kitch DW, Andersen JW, Reisler RB, Chung RT, Robbins GK. Predictors of antiretroviral-related hepatotoxicity in the adult AIDS Clinical Trial Group (1989-1999). J Acquir Immune Defic Syndr 2006; 43: 320-3. PubMed PMID: 16967041.

(In an analysis of factors predicting "serious hepatotoxicity" that arose in 9% of 8851 patients with HIV infection enrolled in trials of antiretroviral therapy, factors identified included baseline liver test abnormalities, HCV infection, and in subgroups, didanosine, nevirapine and 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 mentions that elevations of ALT or AST levels above 5 times ULN occur in 2-18% of HIV-positive patients starting therapy, elevations being 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 other nonnucleoside reverse transcriptase inhibitors).

Palacios R, Vergara S, Rivero A, Aguilar I, Mací J, Camacho A, Lozano F, et al. Low incidence of severe liver events in HIV patients with and without hepatitis C or B coinfection receiving lopinavir/ritonavir. HIV Clin Trials 2006; 7: 319-23. PubMed PMID: 17197379.

(Retrospective analysis of 388 patients with HIV infection starting antiretroviral regimens, that included lopinavir with low dose ritonavir, identified 6 cases of severe liver injury, all in HCV coinfected patients and arising within first 6 months of treatment for a rate of ~1% per year).

Torti C, Lapadula G, Puoti M, Casari S, Uccelli MC, Cristini G, Bella D, et al. Influence of genotype 3 hepatitis C coinfection on liver enzyme elevation in HIV-1-positive patients after commencement of a new highly active antiretroviral regimen: results from the EPOKA-MASTER Cohort. J Acquir Immune Defic Syndr 2006; 41: 180-5. PubMed PMID: 16394850.

(Analysis of 492 HIV-HCV coinfected patients treated with highly active antiretroviral therapy found ALT elevations >5 times ULN in 14 per 100 patient years, higher in those with genotype 3 [25] compared to other genotypes [11]; patients with genotype 3 also had higher ALT levels).

Jain MK, Parekh NK, Hester J, Lee WM. Aminotransferase elevation in HIV/hepatitis B virus co-infected patients treated with two active hepatitis B virus drugs. AIDS Patient Care STDS 2006; 20: 817-22. PubMed PMID: 17192146.

(3 cases of transient flare of hepatitis B and loss of HBeAg after initiation of tenofovir, lamivudine and protease inhibitor in HIV-HBV coinfected patients with preexisting HBeAg and high levels of HBV DNA; ALT 892, 691 and 328 U/L and bilirubin 3.5, 5.8 and normal; 2 were IgM anti-HBc positive; all resolved on continuing therapy).

Sauleda S, Martorell M, Esteban JI, Tural C, Ruiz I, Puig L, Esteban R, et al. Hepatotoxicity of antiretroviral drugs in HIV HCV patients with congenital coagulopathies followed at a Haemophilia Unit during a decade. Haemophilia 2006; 12: 228-36. PubMed PMID: 16643206.

(Retrospective analysis of 246 courses of antiretroviral therapy in 47 patients with hemophilia and HIV infection; ALT elevations >5 times ULN occurred during 28 treatment courses [11%]; most were asymptomatic; one death from liver failure in patient with cirrhosis).

Hicks CB, Cahn P, Cooper DA, Walmsley SL, Katlama C, Clotet B, Lazzarin A, et al.; RESIST investigator group. Durable efficacy of tipranavir-ritonavir in combination with an optimized background regimen of antiretroviral drugs for treatment-experienced HIV-1-infected patients at 48 weeks in the Randomized Evaluation of Strategic Intervention in multi-drug resistant patients with Tipranavir (RESIST) studies: an analysis of combined data from two randomized open-label trials. Lancet 2006; 368: 466-75. PubMed PMID: 16890833.

(Trial of tipranavir/ritonavir versus comparator protease inhibitors for 48 weeks in 1483 patients with HIV infection; overall rates of side effects were similar in two arms; rates of ALT elevations >5 times ULN were 10.2% in tipranavir/ritonavir and 3.3% in comparator arms; no mention of clinically apparent liver injury, hepatitis or deaths from liver disease).

Brau N, Salvatore M, Rios-Bedoya CF, Fernandez-Carbia A, Paronetto F, Rodriguez-Orengo JF, Rodriguez-Torres M. Slower fibrosis progression in HIV/HCV-coinfected patients with successful HIV suppression using antiretroviral therapy. J Hepatol 2006; 44: 47-55. PubMed PMID: 16182404.

(Comparison of liver histology and estimated fibrosis progression rate among 274 patients with HIV-HCV coinfection vs 382 with HCV infection alone; rate was higher in HIV infected, but only if HIV RNA was detectable).

Maida I, Babudieri S, Selvia C, D'Offizi G, Fenu L, Solinas G, Narciso P, et al. Liver enzyme elevation in hepatitis C virus (HCV)-HIV-coinfected patients prior to and after initiating HAART: role of HCV genotypes. AIDS Res Hum Retorviruses 2006; 22: 139-143. PubMed PMID: 16478395.

(Analysis of 306 HIV-positive patients starting antiretroviral therapy [48% with HCV coinfection], only 5 [4%] had ALT elevations above 5 times ULN, all with preexisting ALT elevations; 2 [5.1%] with HCV genotype 3 and 2 [2.3%] with other HCV genotypes).

Cicconi P, Cozzi-Lepri A, Phillips A, Puoti M, Antonucci G, Manconi PE, Tositti G, et al. for the ICoNA Study Group. Is the increased risk of liver enzyme elevation in patients co-infected with HIV and hepatitis virus greater in those taking antiretroviral therapy? AIDS 2007; 21: 599-606. PubMed PMID: 17314522.

(Among 5272 patients in an Italian observational study [47% with HCV or HBV coinfection], 275 developed ALT elevations above 5 times ULN or 3.5 times baseline [15 per 1000 person-years], coinfection increased risk of elevations [relative risk: RR=5.1], but not highly active antiretroviral therapy [RR=1.19]).

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

(Review of hepatotoxicity of antiretrovirals 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]; provides recommendations for management focusing on prevention and monitoring).

Raffi F, Battegay M, Rusconi S, Opravil M, Blick G, Steigbigel RT, Kraft M, et al. Combined tipranavir and enfuvirtide use associated with higher plasma tipranavir concentrations but not with increased hepatotoxicity: sub-analysis from RESIST. AIDS 2007; 21:1 977-80. PubMed PMID: 17721109.

(Analysis of clinical trial of tipranavir/ritonavir [r] vs comparator protease inhibitors/r who received enfuvirtide; tipranavir [+31%], lopinavir [+19%] and saquinavir levels [39%] were higher in enfuvirtide treated, but rates of ALT elevations above 5 times ULN were lower with each agent [6.5% vs 13%; 1% vs 2.5%; 0.9% vs 1.6%]

Rachlis A, Clotet B, Baxter J, Murphy R, Lefebvre E. Safety, tolerability, and efficacy of darunavir (TMC114) with low-dose ritonavir in treatment-experienced, hepatitis B or C co-infected patients in POWER 1 and 3. HIV Clin Trials 2007; 8: 213-20. PubMed PMID: 17720661.

(Pooled analysis of two trials of darunavir with low dose ritonavir in 697 HIV infected patients; rate of ALT elevations similar in darunavir/r treated vs other protease inhibitor treated, any elevation in 23% vs 24% and >5 times ULN in 1.7% vs 2.0% of those without coinfection; higher rates with co-infection 5.1% vs 10%).

de Mendoza C, Morelló J, Garcia-Gascó P, Rodríguez-Novoa S, Soriano V. Tipranavir: a new protease inhibitor for the treatment of antiretroviral-experienced HIV-infected patients. Expert Opin Pharmacother 2007; 8: 839-50. PubMed PMID: 17425479.

(Review of tipranavir; a nonpeptidic protease inhibitor, used in salvage therapy always given in combination with low dose ritonavir [r], ALT elevations above 5 times ULN occur in 10% of tipranavir/r vs 3% in comparator protease inhibitor/r treated patients, and rates with tipranavir alone are similar to tipranavir/r; in addition, cases of clinically apparent liver injury and hepatic decompensation have been reported).

Pavel S, Burty C, Alcaraz I, de la Tribonnière X, Baclet V, Ajana F, Mouton Y, et al. Severe liver toxicity in postexposure prophylaxis for HIV infection with a zidovudine, lamivudine and fosamprenavir/ritonavir regimen. AIDS 2007; 21: 268-9. PubMed PMID: 17197833.

(Among 26 HIV-negative subjects given prophylaxis against HIV infection after acute exposure using zidovudine, lamivudine and fosamprenavir/ritonavir for 4 weeks, 7 developed abdominal pain and nausea, three had rash and two had ALT increases at week 1 [with rash, ALT 958 U/L] and week 2 [with nausea, ALT 517 U/L], resolving rapidly upon stopping).

Chauvel O, Lacombe K, Bonnard P, Lascoux-Combe C, Molina J-M, Miailhes P, Girard P-M, et al. Risk factors for acute liver enzyme abnormalities in HIV-hepatitis B virus-coinfected patients on antiretroviral therapy. Antivir Ther 2007; 12: 1115-26. PubMed PMID: 18018770.

(Analysis of 300 French patients with HIV-HBV coinfection during antiretroviral therapy, rate of ALT or AST elevations above 2 times ULN was 14 per 100 person years; rate of ALT, Alk P and bilirubin elevations above 2 times ULN was 7 per 100 person-years; independent risk factors for ALT elevations were higher HBV DNA and HIV RNA levels and higher CD4 counts, but not specific agents; risk factors for cholestatic injury were duration of HIV infection, protease inhibitor use and recent change in regimen).

Chihrin S, Antoniou T, Raboud J, Shen S, Govan V, Fletcher D, Rachlis A, et al. Risk factors for grade 3-4 liver enzyme elevation in HIV and hepatitis C coinfected patients on combination antiretroviral therapy. AIDS Patient Care STDS 2007; 21: 469-78. PubMed PMID: 17651028.

(Retrospective analysis of risk factors for ALT elevations above 5 times ULN in 23% of 151 HIV-HCV coinfected patients starting new antiretroviral regimen identified lopinavir/r as associated with a higher rate of elevations, but baseline aminotransferase values were often not available).

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.

(In a retrospective analysis of 152 children [ages 1 to 18 years] with HIV on antiretroviral therapy, only 14 [10%] had ALT elevations and all were less than 5 times ULN; 4 were also 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]).

Molina JM, Cohen C, Katlama C, Grinsztejn B, Timerman A, Pedro Rde J, Vangeneugden T, et al.; TMC114-C208 study Group; TMC114-C215 Study Group. Safety and efficacy of darunavir(TMC114) with low-dose ritonavir in treatment-experienced patients: 24-week results of POWER 3. J Acquir Immune Defic Syndr 2007; 46: 24-31. PubMed PMID: 17621237.

(Open labeled study of darunavir/ritonavir [r] in combination with optimized background regimen for 24 weeks in 246 treatment-experienced patients with HIV infection; ALT elevations above 5 times ULN occurred in 8 patients [2%] and there was no clinically apparent hepatotoxicity or deaths from liver disease).

Madruga JV, Berger D, McMurchie M, Suter F, Banhegyi D, Ruxrungtham K, Norris D, Lefebvre E, et al.; TITAN study group. Efficacy and safety of darunavir-ritonavir compared with that of lopinavir-ritonavir at 48 weeks in treatment-experienced, HIV-infected patients in TITAN: a randomised controlled phase III trial. Lancet 2007; 370: 49-58. PubMed PMID: 17617272.

(In a trial of darunavir/ritonavir[r] versus lopinavir/r combined with optimized background regimens for 48 weeks in 595 patients with HIV infection, ALT elevations occurred in 9% of both groups; no mention of clinically apparent hepatitis and no liver related deaths).

Clotet B, Bellos N, Molina JM, Cooper D, Goffard JC, Lazzarin A, Wöhrmann A, et al.; POWER 1 and 2 study groups. Efficacy and safety of darunavir-ritonavir at week 48 in treatment-experienced patients with HIV-1 infection in POWER 1 and 2: a pooled subgroup analysis of data from two randomised trials. Lancet 2007; 369: 1169-78. PubMed PMID: 17416261.

(Trial of darunavir/ritonavir versus comparator protease inhibitors in antiretroviral regimen for 48 weeks in 230 patients with HIV infection; ALT elevations above 5 times ULN occurred in 2% of darunavir/ritonavir vs 3% of comparator treated patients; no mention of clinically apparent liver injury in list of adverse reactions).

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).

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.

(Analysis of liver enzyme elevations in newborns of HIV infected mothers on various antiretroviral regimens, found that 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).

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 frequently present [26%]).

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 several agents that had been recently approved: raltegravir, maraviroc and etravirine).

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.

(Among 69 newborns exposed to antiretrovirals in utero, only 1 had ALT elevations above 10 times ULN, compared to 0 of 109 unexposed newborns).

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).

Jevtovi. DJ, Ranin J, Salemovi. D, Pesic I, Dragovic G, Zerjav S, Djurkovic-Djakovic 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 above 5 times ULN [mostly asymptomatic], risk factors for elevations being HCV coinfection [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.

(Among 23 patients with HIV infection without HBV or HCV coinfection who had with abnormal liver tests, 17 [74%] were attributed to antiretroviral agents [defintely in 6, possibly in 11]; fatty liver was common).

Chan-Tack KM, Struble KA, Birnkrant DB. Intracranial hemorrhage and liver-associated deaths associated with tipranavir/ritonavir: review of cases from the FDA's Adverse Event Reporting System. AIDS Patient Care STDS 2008; 22: 843-50. PubMed PMID: 19025478.

(Analysis of MedWatch reports on tipranavir with low dose ritonavir from 2005-2007 found 14 cases of intracerebral bleeding and 12 cases of liver related death [6 had HCV, 1 HBV coinfection]).

Burty C, Pavel S, Ghomari K, Vermersch A, Christian B, Pouaha J, Yazdanpanah Y, et al. Tolerability of fosamprenavir/ritonavir associated with zidovudine-lamivudine used as postexposure prophylaxis for HIV infection. J Acquir Immune Defic Syndr. 2008; 49: 334-6. PubMed PMID: 18978479.

(54 patients enrolled in a study of 4 weeks of zidovudine, lamivudine and fosamprenavir with low dose ritonavir for postexposure prophylaxis against acute HIV exposure; side effects were frequent, including nausea [73%], diarrhea [58%], fatigue [62%], rash [11%], but no "clinical or biological grade 3 or 4 event"; see Pavel, 2007).

Boffito M, Miralles D, Hill A. Pharmacokinetics, efficacy, and safety of darunavir/ritonavir 800/100 mg once-daily in treatment-naïve and -experienced patients. HIV Clin Trials 2008; 9: 418-27. PubMed PMID: 19203907.

(Review and comparison of efficacy and safety of once- vs twice-daily regimens of darunavir/ritonavir).

DeJesus E, Gottlieb MS, Gathe JC Jr, Greenberg ML, Guittari CJ, Zolopa AR. Safety and efficacy of enfuvirtide in combination with darunavir-ritonavir and an optimized background regimen in treatment-experienced human immunodeficiency virus-infected patients: the below the level of quantification study. Antimicrob Agents Chemother 2008; 52: 4315-9. PubMed PMID: 18809940.

(Among 137 patients with HIV receiving enfuvirtide with darunavir/ritonavir for 24 weeks there were 4 discontinuations and 18 serious adverse events, none were liver related and no mention of ALT elevations).

Vispo E. Warning on hepatotoxicity of darunavir. AIDS Rev 2008; 10: 63. PubMed PMID: 18432296.

(FDA released warning about clinical hepatotoxicity of darunavir boosted with low dose ritonavir in March 2008; during clinical development, hepatitis reported in 0.5% of recipients; several postmarketing reports of decompensation in patients with preexisting liver disease calls for careful monitoring).

Panther E, Thimme R, Blum HE. [Jaundice in an HIV-positive pregnant woman] Dtsch Med Wochenschr 2008; 133: 1560-2. German. PubMed PMID: 18642217.

(32 year old Nigerian woman with HIV infection on nelfinavir, zidovudine and lamivudine in last trimester of pregnancy developed jaundice [bilirubin 2.5 mg/dL, ALT 3126 U/L, Alk P 180 U/L]; further testing demonstrated anti-HEV positivity; antiretrovirals were restarted with resolution of the hepatitis; HEV tends to be severe in pregnant women).

Pineda JA, Pérez-Elí MJ, Peña JM, Luque I, Rodríguez-Alcantara F; Fosamprenavir Expanded Access Program Group. Low rate of adverse hepatic events associated with fosamprenavir/ritonavir-based antiretroviral regimens. HIV Clin Trials 2008; 9: 309-13. PubMed PMID: 18977719.

(Among 635 patients given fosamprenavir/ritonavir in an open access program, 3 developed ALT levels above 5 times ULN for a rate of 1% at 24 weeks; 2 with HCV and 1 with HBV; 4 patients with chronic hepatitis C had clinical decompensation and 1 died).

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 or 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, et al. 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 efavirez and 4 miscellaneous combinations).

Molina JM, Andrade-Villanueva J, Echevarria J, Chetchotisakd P, Corral J, David N, Moyle G, et al.; CASTLE Study Team. Once-daily atazanavir/ritonavir versus twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naive HIV-1-infected patients: 48 week efficacy and safety results of the CASTLE study. Lancet 2008; 372 (9639): 646-55. PubMed PMID: 18722869.

(Among 883 patients with HIV infection treated with atazanavir or lopinavir with ritonavir boost combined with tenofovir/emtricitabine, ALT elevations above 5 times ULN occurred in 1.8% vs 1.4% and bilirubin above 2.5 mg/dL in 34% vs 0.3%).

Macías J, Orihuela F, Rivero A, Viciana P, Márquez M, Portilla J, Ríos MJ, et al.; Hepatip Study Group. Hepatic safety of tipranavir plus ritonavir (TPV/r)-based antiretroviral combinations: effect of hepatitis virus co-infection and pre-existing fibrosis. J Antimicrob Chemother 2009; 63: 178-83. PubMed PMID: 18952618.

(Among 150 patients with HIV infection starting antiretroviral regimens including tipranavir/ritonavir, 12 [8%] developed ALT elevations above 5 times ULN: 7.5 per 100 patient-years).

Torti C, Lapadula G, Antinori A, Quirino T, Maserati R, Castelnuovo F, Maggiolo F, et al. Hyperbilirubinemia during atazanavir treatment in 2,404 patients in the Italian atazanavir expanded access program and MASTER cohorts. Infection 2009; 37: 244-9. PubMed PMID: 19471856.

(Among 2404 patients started on atazanavir [75% with low dose ritonavir boost], 45% developed bilirubin above 2.5 times ULN and 7.2% above 5 times ULN; risk factors being baseline bilirubin and ritonavir boost; bilirubin elevations were not associated with ALT elevations).

Jamois C, Riek M, Schmitt C. Potential hepatotoxicity of efavirenz and saquinavir/ritonavir coadministration in healthy volunteers. Arch Drug Inf 2009; 2: 1-7. PubMed PMID: 19381337.

(In a pharmacokinetic study done in healthy volunteers, one subject given saquinavir/ritonavir for 14 days developed abdominal pain and vomiting within 24 hours of adding efavirenz, with ALT rising to 145 U/L and then falling to normal 10 days after stopping medications; the study was terminated early).

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; nonnucleoside reverse transcriptase inhibitors are capable of causing a hypersensitivity reaction with liver injury arising during the first 6 weeks of therapy, as well as an immunologically mediated injury that arises 6-12 months after starting treatment; all protease inhibitors are metabolized in the liver by CYP 3A and have the potential to cause liver injury, this being most common with tipranavir).

Schmitt C, Riek M, Winters K, Schutz M, Grange S. Unexpected hepatotoxicity of rifampin and saquinavir/ritonavir in healthy male volunteers. Arch Drug Inf 2009; 2: 8-16. PubMed PMID: 19381336.

(In a phase I study of the combination of rifampin with saquinavir and ritonavir, 11 of 17 patients developed ALT elevations and gastrointestinal symptoms within 1-5 days of starting medication, with peak ALT levels of 400-5000 U/L, all resolving within 2 weeks of stopping).

Hughes CA, Robinson L, Tseng A, MacArthur RD. New antiretroviral drugs: a review of the efficacy, safety, pharmacokinetics, and resistance profile of tipranavir, darunavir, etravirine, rilpivirine, maraviroc, and raltegravir. Expert Opin Pharmacother 2009; 10: 2445-66. PubMed PMID: 19678794.

(Review of tipranavir, darunavir, etravirine, rilpivirine, maraviroc and raltegravir; regimens including tipranavir/ritonavir are associated with higher rates of significant ALT elevations [above 5 times ULN] than comparators; darunavir, the newest approved protease inhibitor, is an inhibitor of CYP 3A4, but pooled safety analyses showed no increased risk for adverse events vs comparator arms).

Bentué-Ferrer D, Arvieux C, Tribut O, Ruffault A, Bellissant E. Clinical pharmacology, efficacy and safety of atazanavir: a review. Expert Opin Drug Metab Toxicol 2009; 5: 1455-68. PubMed PMID: 19863454.

(Review of the chemistry, pharmacology, efficacy and safety of atazanavir; the most common "grade 2-4" side effect is dose dependent, reversible increase in indirect bilirubin, occurring in 20-60% of patients and more frequently with ritonavir boost; hyperbilirubinemia can be a reason for drug discontinuation, but largely for cosmetic reasons).

Haas DW, Koletar SL, Laughlin L, Kendall MA, Suckow C, Gerber JG, Zolopa AR, et al; A5213 StudyTeam. Hepatotoxicity and gastrointestinal intolerance when healthy volunteers taking rifampin add twice-daily atazanavir and ritonavir. J Acquir Immune Defic Syndr 2009; 50: 290-3. PubMed PMID: 19194314.

(In a small open label study assessing interactions of rifampin and atazanavir/ritonavir, the first 3 subjects who added protease inhibitors to rifampin developed nausea and ALT elevations within 24 hours [Peak ALT 792, 173 and 154 U/L] and study was stopped, values returning to normal within 1-2 weeks).

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 (2): 81-3. PubMed PMID: 20452889.

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

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.

(World wide 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]).

Devarbhavi H, Dierkhising R, Kremers WK, Sandeep MS, Karanth D, Adarsh CK. Single-center experience with drug-induced liver injury from India: causes, outcome, prognosis, and predictors of mortality. Am J Gastroenterol 2010; 105: 2396-404. PubMed PMID: 20648003.

(313 cases of drug induced liver injury were seen between 1997 and 2008 at a large hospital in Bangalore, India; none were attributed to antiretroviral agents).

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).

Heil EL, Townsend ML, Shipp K, Clarke A, Johnson MD. Incidence of severe hepatotoxicity related to antiretroviral therapy in HIV/HCV coinfected patients. AIDS Res Treat. 2010; 2010: 856542. PubMed PMID: 21490905.

(Among 56 patients with HIV-HCV coinfection who were started on antiretroviral therapy and followed at 2 infectious disesae clinics for an average of 3 years, 6 [11%] developed ALT or AST elevations above 5 times ULN, including 1 on indinavir, 1 saquinavir, 1 nelfinavir, but none on atazanavir or lopinavir).

Balayssac E, Autret-Leca E, Jonville-Béra AP, Diè-Kacou H, Beau-Salinas F. [Adverse reactions of atazanavir, fosamprenavir and tipranavir in "real life"]. Therapie 2010; 65: 121-8. PubMed PMID: 20478244.

(Summary of spontaneous reports of adverse side effects of HIV protease inhibitors to a French Pharmacovigilance Registry between 2004 and 2007, mentions hepatic adverse events from atazanavir [29 cases], fosamprenavir [5 cases] and tipranavir [5 cases], but most were hyperbilirubinemia alone [atazanavir] or serum enzyme elevations, often in patients with HIV-HCV coinfection).

Morsica G, Bianchi G, Bagaglio S, Conte C, Salpietro S, Porrino L, Uberti-Foppa C. Hepatic safety profile of darunavir with low-dose ritonavir (DRV/r) in HIV/HCV coinfected and HIV monoinfected patients. New Microbiol 2011; 34: 317-21. PubMed PMID: 21811753.

(Among 47 patients with HIV infection [18 coinfected with HCV] treated with darunavir/r for 72 weeks, median ALT and AST levels did not increase significantly and were never more than 1.6 times ULN).

Molleston JP, Fontana RJ, Lopez MJ, Kleiner DE, Gu J, Chalasani N: Drug-induced Liver Injury Network. Characteristics of idiosyncratic drug-induced liver injury in children: results from the DILIN prospective study. J Pediatr Gastroenterol Nutr 2011; 53: 182-9. PubMed PMID: 21788760.

(Among 30 children with suspected drug induced liver injury, none were attributed to an antiretroviral agent).

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 patients with HIV treated at a single center in Uganda, ALT elevations occurred in 4.2% by 14 weeks; few predictive features present except for antituberculosus therapy).

Merchante N, López-Cortés LF, Delgado-Fernández M, Ríos-Villegas MJ, Márquez-Solero M, Merino D, Pasquau J, et al; Grupo Andaluz para el Estudio de las Hepatitis Viricas (HEPAVIR) de la Sociedad Andaluza de Enfermedades Infecciosas (SAEI). Liver toxicity of antiretroviral combinations including fosamprenavir plus ritonavir 1400/100mg once daily in HIV/hepatitis C virus-coinfected patients. AIDS Patient Care STDS 2011; 25: 395-402. PubMed PMID: 21688986.

(Among 65 patients with HIV-HCV coinfection treated with an antiretroviral regimen including fosamprenavir/ritonavir for 48 weeks, 9 [14%] developed ALT elevations of above 5 times ULN, but none stopped therapy for this reason; neither cirrhosis nor fibrosis were associated with a higher likelihood of ALT elevations during therapy).

Dejesus E, Mills A, Bhatti L, Conner C, Storfer S. A randomised comparison of safety and efficacy of nevirapine vs. atazanavir/ritonavir combined with tenofovir/ emtricitabine in treatment-naïve patients. Int J Clin Pract 2011; 65: 1240-9. PubMed PMID: 21999631.

(Among 152 patients with HIV infection who were treated with nevirapine vs atazanavir/ritonavir, 1 patient in each group discontinued therapy for liver injury [enzyme elevations and jaundice]).

Daar ES, Tierney C, Fischl MA, Sax PE, Mollan K, Budhathoki C, Godfrey C, et al.; AIDS Clinical Trials Group Study A5202 Team. Atazanavir plus ritonavir or efavirenz as part of a 3-drug regimen for initial treatment of HIV-1. Ann Intern Med 2011; 154: 445-56. PubMed PMID: 21320923.

(Among 1848 patients with HIV infection treated with efavirenz or atazanavir/ritonavir in combination with nucleoside analogues, ALT elevations occurred in 2% and at a similar rate in both groups).

Minniear TD, Zeh C, Polle N, Masaba R, Peters PJ, Oyaro B, Akoth B, et al. Rash, hepatotoxicity and hyperbilirubinemia among Kenyan infants born to HIV-infected women receiving triple-antiretroviral drugs for the prevention of mother-to-child HIV transmission. Pediatr Infect Dis J 2012; 31: 1155-7. PubMed PMID: 22772167.

(Among 464 full term infants born to Kenyan mothers exposed to nevirapine or nelfinavir, there were no significant differences in rates of liver injury [0% vs 1.9%] or hyperbilirubinemia [3.9% vs 5.3%]).

Macías J, Neukam K, Mallolas J, López-Cortés LF, Cartón JA, Domingo P, Moreno S, et al.; COINS Study Team. Liver toxicity of initial antiretroviral drug regimens including two nucleoside analogs plus one non-nucleoside analog or one ritonavir-boosted protease inhibitor in HIV/HCV-coinfected patients. HIV Clin Trials 2012; 13: 61-9. PubMed PMID: 22510353.

(Retrospective analysis of 745 HIV infected patients started on antiviral regimens found ALT elevations above 5 times ULN in 11% starting nevirapine, 6% efavirenz, 10.5% protease inhibitor [PI]-based regimens, while discontinuations for enzyme elevations occurred in 13% on nevirapine, 4% efavirenz and 6% PI based regimens).

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.

(Among 708 ppatients with HIV infection treated with boosted elvitegravir vs atazanavir based regimens for 48 weeks, HIV RNA response were similar and both regimens were "well tolerated", elevations in ALT occurring in 15% vs 22%, bilirubin 3% vs 96% which were severe in 0.5% vs 58%).

McDonald C, Uy J, Hu W, Wirtz V, Juethner S, Butcher D, McGrath D, et al. Clinical significance of hyperbilirubinemia among HIV-1-infected patients treated with atazanavir/ritonavir through 96 weeks in the CASTLE study. AIDS Patient Care STDS 2012; 26: 259-64. PubMed PMID: 22404426.

(Among 441 patients treated with atazanavir/r for 96 weeks in the CASTLE study [Molina 2008], 192 [44%] developed bilirubin elevations, among whom ALT elevations were no more frequent with in those without hyperbilirubinemia [4% vs 3%]; 3 patients discontinued therapy because of bilirubin elevations, but not because of concurrent ALT elevations).

Ha B, Wine B, Rodriguez-Alcantra F, Shaefer M. Hepatic safety profile of fosamprenavir-containing regimens in HIV-1-infected patients with or without hepatitis B or C coinfection. HIV Clin Trials 2012; 13: 171-7. PubMed PMID: 22592097.

(Among 1319 patients with HIV infection enrolled in clinical trials of fosamprenavir for at least 48 weeks, ALT elevations above 5 times ULN occurred in 14% of 205 patients with HBV or HCV coinfection, but only 1% of those with HIV monoinfection).

Surgers L, Lacombe K. Hepatoxicity of new antiretrovirals: a systematic review. Clin Res Hepatol Gastroenterol 2013; 37: 126-33. PubMed PMID: 23522569.

(Review of reports of heaptotoxicity of antiretroviral agents that had been recently approved including darunavir).

Wood R, Gathe JC, Givens N, Sedani S, Cheng K, Sievers J. Long-term safety study of fosamprenavir-containing regimens in HIV-1-infected patients. HIV Clin Trials 2013; 14:183-91. PubMed PMID: 24144895.

(Among 753 patients with HIV infection enrolled in long term extension studies of fosamprenavir containing regimens for up to 8 years, ALT elevations above 5 times ULN occurred in 8% overall, 3% of those with monoinfection and 13-35% of those with HBV or HCV coinfection; and among 5 deaths, none were due to liver disease).

Rockstroh JK, DeJesus E, Henry K, Molina JM, Gathe J, Ramanathan S, Wei X, et al; GS-236-0103 Study Team. A randomized, double-blind comparison of coformulated elvitegravir/cobicistat/emtricitabine/tenofovir DF vs ritonavir-boosted atazanavir plus coformulated emtricitabine and tenofovir DF for initial treatment of HIV-1 infection: analysis of week 96 results. J Acquir Immune Defic Syndr 2013; 62: 483-6. PubMed PMID: 23337366.

(Among 708 patients with HIV infection treated with evitegraveir/c vs atazanavir/r based regimens for up to 2 years, virologic response rates were similar while jaundice was reported in <1% vs 21% and led to discontinuation in 0% vs 0.6%; no mention of ALT elevations or clinically apparent liver injury).

Vispo E, Fernández-Montero JV, Labarga P, Barreiro P, Soriano V. Low risk of liver toxicity using the most recently approved antiretroviral agents but still increased in HIV-hepatitis C virus coinfected patients. AIDS 2013; 24; 27: 1187-8. PubMed PMID: 23739226.

(Among 1982 patients with HIV infection starting antiretroviral therapy, liver enzyme elevations occurred in 9% [17% with, 6% without HCV], but only 0.4% were greater than 5 times ULN [0.6% with and 0.2% without HCV]; rates were highest with darunavir and atazanavir and lowest with raltegravir and etravirine).

Samuel M, Bradshaw D, Perry M, Chan SY, Dhairyawan R, Byrne L, Smith K, et al. Antenatal atazanavir: a retrospective analysis of pregnancies exposed to atazanavir. Infect Dis Obstet Gynecol 2014; 2014: 961375. PubMed PMID: 25328370.

(Among 145 pregnancies in women with HIV infection treated with atazanavir, transient self-limited ALT or AST elevations occurred, but none required drug discontinuation, and there was no increase in frequency of neonatal hyperbilirubinemia over expected rates).

Floridia M, Ravizza M, Masuelli G, Giacomet V, Martinelli P, Degli Antoni A, Spinillo A, et al; Italian Group on Surveillance on Antiretroviral Treatment in Pregnancy. Atazanavir and lopinavir profile in pregnant women with HIV: tolerability, activity and pregnancy outcomes in an observational national study. J Antimicrob Chemother 2014; 69: 1377-84. PubMed PMID: 24370933.

(Among pregnancies in HIV positive women treated with lopinavir [n=322] or atazanavir [106] based regimens, there was no diferences in weight gain, glucose intolerance, but were higher median total cholesterol [239 vs 221 mg/dL] and triglycerides [226 vs 181 mg/dL] with lopinavir; no discontinuations for liver test abnormalities).

Di Biagio A, Nicolini LA, Lorenzini P, Puoti M, Antinori A, Cozzi-Lepri A, Gori A, et al, For The Icona Foundation Study Group. Liver enzyme elevation during darunavir-based antiretroviral treatment in HIV-1-infected patients with or without hepatitis C coinfection: data from the ICONA foundation cohort. HIV Clin Trials 2014; 15: 151-60. PubMed PMID: 25143024.

(Among 703 patients with HIV infection enrolled in an Italian multicenter registry who were treated with a darunavir/r based regimen, 101 [11 per 100 patient-years] developed liver test elevations, with a 3 fold higher risk among those with HCV coinfection).

Lapadula G, Costarelli S, Chatenoud L, Castelli F, Astuti N, Di Giambenedetto S, Quiros-Roldan E, et al; Italian MASTER Cohort. Risk of Liver Enzyme Elevation During Treatment With Ritonavir-Boosted Protease Inhibitors Among HIV-Monoinfected and HIV/HCV-Coinfected Patients. J Acquir Immune Defic Syndr 2015; 69: 312-8. PubMed PMID: 25723139.

(Among 6,193 patients with HIV infection who started antiretroviral therapy during follow up in a multicenter Italian registry, 761 [12%] had ALT or AST elevations above 5 times ULN, rates of elevations being higher among those with HIV-HCV coinfection than HIV infection alone [8 vs 1 per 100 patient-years]; multivariant analysis found no association of ALT elevations with specific protease inhibitor used).

Lê MP, Mandelbrot L, Descamps D, Soulié C, Ichou H, Bourgeois-Moine A, Damond F, et al. Pharmacokinetics, safety and efficacy of ritonavir-boosted atazanavir (300/100 mg once daily) in HIV-1-infected pregnant women. Antivir Ther 2015; 20: 507-13. PubMed PMID: 25599649.

(Among 103 women with HIV infection treated with atazanavir/r based regimens during pregnancy, there were no "clinical relevant" adverse events, only 1 woman with bilirubin above 2.5 mg/dL and 5 neonates with values above 5.8 mg/dL).

Rutstein RM, Samson P, Fenton T, Fletcher CV, Kiser JJ, Mofenson LM, Smith E, et al; PACTG 1020A Study Team. Long-term safety and efficacy of atazanavir-based therapy in HIV-infected infants, children and adolescents: the Pediatric AIDS Clinical Trials Group Protocol 1020A. Pediatr Infect Dis J 2015; 34: 162-7. PubMed PMID: 25232777.

(Among 195 children with HIV infection treated with atazanavir based regimens for 48 weeks, 9% developed bilirubin values above 5.1 mg/dL and 3% had ALT elevations above 2.5 times ULN).

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.

(Among 176 reports of drug induced liver injury from Latin America published between 1996 and 2012, 3 were attributed to antiretroviral agents [nevirapine, zidovudine and lamivudine], but none to HIV protease inhibitors).

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: 1340-1352.e7. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, 13 cases [1.5%] were attributed to antiretroviral therapy, including 3 to darunavir, 1 atazanavir and 1 nelfinavir).

Slama L, Landman R, Assoumou L, Benalycherif A, Samri A, Joly V, Pialoux G, et al; IMEA 040 DATA Study Group. Efficacy and safety of once-daily ritonavir-boosted atazanavir or darunavir in combination with a dual nucleos(t)ide analogue backbone in HIV-1-infected combined ART (cART)-naive patients with severe immunosuppression: a 48 week, non-comparative, randomized, multicentre trial (IMEA 040 DATA trial). J Antimicrob Chemother 2016; 71: 2252-61. PubMed PMID: 27068399.

(Among 120 patients with advanced AIDs treated with either atazanavir/r or darunavir/r based therapy for 48 weeks, 1 patient in both groups stopped therapy because of "hepatic cytolysis" and 1 on atazanavir for jaundice, but no details provided).

Cooper DA, Cordery DV, Zajdenverg R, Ruxrungtham K, Arastéh K, Bergmann F, Neto JL; study team. Tipranavir/Ritonavir (500/200 mg and 500/100 mg) was virologically non-iInferior to lopinavir/ritonavir (400/100 mg) at week 48 in trreatment-naïve HIV-1-infected patients: a randomized, multinational, multicenter trial. PLoS One 2016; 11: e0144917. PubMed PMID: 26730818.

(Among 558 treatment-naive patients with HIV infection treated with tipranavir/r [one of 2 dose of ritonavir] or lopinavir/r for 48 weeks, response rates were similar, but ALT elevations were more frequent with tipranavir [7%-22% vs 3.2%] which more frequently led to discontinuation [3%-7% vs 1%]).

Nasta P, Salmon D, d'Arminio Monforte A, Pimenta JM, Cerini C, Giralda M, Winnock M, et al. Fosamprenavir/ritonavir in patients with viral hepatitis coinfection: an observational multicohort study. HIV Clin Trials 2016; 17: 96-108. PubMed PMID: 27125364.

(Among 1096 patients with HIV infection treated with either fosamprenavir/r or lopinavir/r, ALT elevations above 200 U/L occurred in 5.6 per 100 person-years, and rates were similar for the two protease inhibitors).

Teófilo E, Rocha-Pereira N, Kuhlmann B, Antela A, Knechten H, Santos J, Jiménez-Expósito MJ; REMAIN study group. Long-term efficacy, tolerability, and renal safety of atazanavir/ritonavir-based antiretroviral therapy in a cohort of treatment-naïve patients with HIV-1 iInfection: the REMAIN Study. HIV Clin Trials 2016; 17: 17-28. PubMed PMID: 26899539.

(Among 517 patients with HIV infection treated with atazanavir/r based therapy and followed for 3 years, 16% discontinued therapy because of adverse events, 9% for hyperbilirubinemia).

Yunquera-Romero L, Asensi-Díez R, Del Rio-Valencia JC, Muñoz-Castillo I, Castaño-Carracedo MA. [Darunavir/cobicistat monotherapy. Experience in a tertiary hospital]. Rev Esp Quimioter 2016; 29: 308-317. PubMed PMID: 27888600.

(Among 78 patients with HIV infection who were switched from ritonavir to cobicistat to boost darunavir-based therapy, HCV RNA levels remained undetectable in 83% of patients and there were "no signficant differences" in serum ALT or AST levels with the change).

Antinori A, Meraviglia P, Monforte Ad, Castagna A, Mussini C, Bini T, Gianotti N, et al. Effectiveness, durability, and safety of darunavir/ritonavir in HIV-1-infected patients in routine clinical practice in Italy: a postauthorization noninterventional study. Drug Des Devel Ther 2016; 10: 1589-603. PubMed PMID: 27226708.

(Among 875 patients with HIV infection being treated with darunavir/r in an Italian clinical practice registry, darunavir was "effective and well tolerated", 2 patients discontinue therapy because of serum ALT elevations, but overall levels remained stable).

Pernas B, Grandal M, Tabernilla A, Cid P, Pértega S, Castro-Iglesias Á, Mena Á, et al. Long-term clinical experience with darunavir (2007-2015) in a large cohort of HIV-infected patients in Spain. J Med Virol 2016; 88: 2125-2131. PubMed PMID: 27218208.

(Among 173 patients with HIV infection who started antiretroviral therapy with darunavir between 2007 and 2015, 90% of patients had no "relevant" adverse events; no mention of ALT levels or liver related serious adverse events).

Kaspar MB, Sterling RK. Hyperbilirubinaemia in HIV-HCV co-infected patients on antiretroviral therapy: drug effect or liver disease severity? BMJ Open Gastroenterol 2016; 3: e000072. PubMed PMID: 26966552.

(Among 344 patients with HIV-HCV coinfection undergoing liver biopsy, 33% had hyperbilirubinemia; those attributable to indinavir [40%] or atazanavir [46%] did not correlate with hepatic fibrosis, whereas those elevations in patients on other antiretrovirals did correlate with biopsy fibrosis grade).

Fätkenheuer G, Jessen H, Stoehr A, Jung N, Jessen AB, Kümmerle T, Berger M, et al. PEPDar: A randomized prospective noninferiority study of ritonavir-boosted darunavir for HIV post-exposure prophylaxis. HIV Med 2016; 17: 453-9. PubMed PMID: 27166295.

(Among 305 patients with acute exposure to HIV who were treated with darunavir/r vs lopinavir/r based regimens for 28-30 days, none developed HIV infection and none suffered a serious adverse event; no mention of ALT elevations).

Masetti M, Magalotti D, Martino E, Andreone P, Scuteri A, Zoli M. A case of acute liver failure during ritonavir-boosted paritaprevir, ombitasvir and dasabuvir therapy in a patient with HCV genotype 1b cirrhosis. J Gastrointestin Liver Dis 2016; 25: 559-561. PubMed PMID: 27981315.

(84 year old man with HCV-related cirrhosis developed hepatic decompensation 13 days after starting Viekira Pak for HCV infection, with slow and incomplete recovery upon stopping).

Buzas C, Tantau M, Ciobanu L. Fatal acute liver failure during ritonavir-boosted paritaprevir, ombitasvir and dasabuvir plus ribavirin therapy. J Gastrointestin Liver Dis 2017; 26: 93-94. PubMed PMID: 28338122.

(65 year old woman with HCV related cirrhosis developed hepatic decompensation 3 days after starting Veikira Pak therapy for hepaittis C and died of hepatic failure 19 days later).

Fofiu C, Dobru D, Boeriu A. Potential pitfalls of Viekira Pak™ therapy in patients with HCV genotype 1b cirrhosis. J Gastrointestin Liver Dis 2017; 26: 94-95. PubMed PMID: 28338123.

(60 year old woman with HCV related cirrhosis developed decompensation 6 weeks after starting Viekira Pak for HCV infection [bilirubin rising from 2.1 to 6.8 mg/dL, INR 1.4 to 1.8], resolving slowly after discontinuation of the combination antiviral therapy; role of ritonavir unclear).

Menshawy A, Ismail A, Abushouk AI, Ahmed H, Menshawy E, Elmaraezy A, Gadelkarim M, et al. Efficacy and safety of atazanavir/ritonavir-based antiretroviral therapy for HIV-1 infected subjects: a systematic review and meta-analysis. Arch Virol 2017; 162: 2181-2190. PubMed PMID: 28361290.

(Systematic review of literature comparing atazanavir/r based regimens to darunavir/r or lopinavir/r, found rates of bilirubin elevations were markedly higher with atazanavir/r, but rates of ALT and AST elevations were similar).

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