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Mechanisms of drug induced hepatotoxicity

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M Peters

University of California San Francisco, San Francisco, CA, USA

Hepatotoxicity is often seen in patients with HIV: this may be mild or severe hepatitis, or uncommonly, fulminant liver disease. All HIV patients should have serum aminotransferases performed prior to therapy and any abnormalities should be evaluated as many have pre-existing underlying liver disease. Drug induced hepatotoxicity in HIV subjects has become of increasing importance in the era of HAART, especially with the high incidence of viral hepatitis and non-alcoholic steatohepatitis in these subjects. Hepatotoxicity may be intrinsic in etiology, reproducible and dose dependent (acetaminophen); or idiosyncratic, with a low incidence due to drug allergy (for example, sulfas) or a toxic metabolite (for example, isoniazid). Toxins can be classified based on presumed mechanism (direct injury or idiosyncratic, hypersensitivity or allergic reaction); on type of liver injury (cholestatic or hepatocellular or mixed); or by intrinsic toxicity versus host idiosyncrasy. Understanding in which category various drugs belong, is of importance in evaluating the relative risk of certain agents and possible drug interactions. Fulminant hepatic failure has resulted from multiple drugs, including NSAIDs, lipid lowering agents, antibiotics (cephalexin, clindamycin), nevirapine, fluconazole, anti-tuberculous drugs, psychotropic medications and niacin. In addition, ecstasy, Chinese herbs and mushrooms have caused liver failure in some patients.

Antiretroviral therapies may induce hepatotoxicity: some in a dose dependent manner; others more commonly in patients with viral hepatitis; and still others in an idiosyncratic manner. All classes of HAART have caused liver damage to a certain degree and the incidence is increased in patients with chronic hepatitis B or C. Large retrospective studies and a few prospective studies have evaluated the incidence of hepatotoxicity in patients on various regimens. In patients with pre-existing necroinflammatory liver disease, especially hepatitis B or C, HAART may be very difficult to manage but this talk will not address drug toxicity in viral hepatitis *per se*. It is unclear when ALT rises, if it is

due to the drug, immune reconstitution or underlying liver disease. Careful assessment of liver function should include serum ALT, AST, alkaline phosphatase, bilirubin (if increased, perform conjugated and unconjugated), albumin and prothrombin time. If serum conjugated bilirubin is increased with drug toxicity, this has a more ominous prognosis (Hy's Law), but this should not be confused with unconjugated hyperbilirubinemia of certain ART. Drug toxicity inducing prolonged prothrombin time with hepatic encephalopathy has a very high mortality and immediate intervention even liver transplantation may be required. When multiple drugs are being utilized it may be difficult to determine the culprit. Careful evaluation for type of injury, stopping the likely drug of concern and reporting of all abnormal LFTs and concomitant liver disease is necessary to both early diagnosis and intervention in individual patients as well as to determine the true incidence of specific HAART induced hepatotoxicity.

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