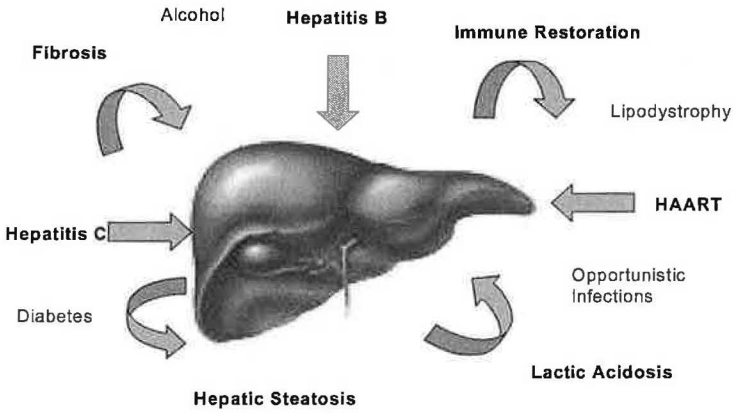
Liver Disease in the HAART Era



Mamta K. Jain, M.D., M.P.H.

Internal Medicine Grand Rounds
University of Texas Southwestern Medical Center at Dallas
February 9, 2007

This is to acknowledge that Mamta Jain, M.D. has disclosed financial interests and other relationships with commercial concerns related directly or indirectly to this program.
Dr. Jain will be discussing off-label uses in this presentation.

Mamta K. Jain, M.D, M.P.H.
Assistant Professor of Medicine
Division of Infectious Diseases

Dr. Jain's research interest focuses on HIV and coinfection with viral hepatitis. Dr. Jain has conducted research to examine the influence of viral factors in response to therapy in HIV/HBV and HIV/HCV coinfected patients. Her NIH-K23 career development award focuses on determining clinical and molecular factors that may lead to lower response rates in HIV/HCV coinfected patients treated with pegylated interferon and ribavirin. In addition, Dr. Jain is also interested in examining co-morbid illnesses that may impact mortality in HIV-infected persons.

Dr. Jain acknowledges a potential conflict of interest from her participation as a member of the Speaker's Bureaus for Gilead Sciences and Abbott Virology. She also receives research support from Gilead Sciences.

Introduction

We are now 25 years into the HIV epidemic. The first reported case of acquired immunodeficiency syndrome (AIDS) was reported in 1981 in a young "healthy" male [1]. During the earlier days of HIV, the epidemic was marked by deaths due to opportunistic infections (OIs) and AIDS related cancers. In 1996, highly active antiretroviral therapy (HAART) become available and changed the course of HIV disease. A dramatic improvement in HIV/AIDS related mortality [2-4] has occurred with HAART and immune restoration. Over the past ten years, however, new diseases have emerged as a cause of significant morbidity and mortality as OIs have become less common [2]. These emerging comorbid conditions include liver, cardiovascular, and oncological diseases.

As HIV has become a chronic disease with the use of HAART, other co-morbid illnesses such as chronic viral hepatitis due to hepatitis B (HBV) or C (HCV) are impacting the course and quality of life in HIV-infected persons. HIV therapy itself also affects the liver due to drug induced hepatotoxicity and mitochondrial toxicity. In addition, immune restoration due to HAART may also impact viral hepatitis leading to hepatic flares. Thus, liver disease has grown to play an important role in HIV-infected persons. This protocol will review the impact of viral hepatitis and HAART on liver disease in HIV-infected persons.

Liver Disease in the Pre-HAART Era

In the earlier years of the HIV/AIDS epidemic, a person often was diagnosed when he presented with his first OI. Over time, prophylactic medications were used to prevent or at least diminish the occurrence of certain OIs such as pneumocystis pneumonia (PCP) and toxoplasmosis with trimethoprim/sulfamethoxazole or mycobacteria avium intracellulare (MAI) with azithromycin.

Liver disease during this time was often related to hepatitis due to systemic OIs or neoplastic diseases. An estimated 75% of patients with AIDS were reported to have liver function abnormalities and hepatomegaly [5]. Early reports frequently found unexplained histologic findings including granulomas, steatosis, and focal hepatic necrosis. Over 75% of AIDS patients, most of whom had injection drug use (IDU) or were men who have sex with men (MSM), had serologic evidence of HBV exposure. The impact of HCV on liver disease was not known at the time. Other viral infections, were seen on liver biopsies/autopsies. For example, cytomegalovirus (CMV) that often causes retinitis, esophagitis, or colitis can also cause hepatitis. Herpes simplex virus (HSV) has been reported to cause fulminant hepatitis in AIDS patients [6].

Mycobacterial diseases were also commonly seen on liver biopsy specimens and again reflected systemic disease. Liver biopsy specimens typically revealed noncaseating granulomas with a paucity of lymphocytes[5]. Mycobacterium tuberculosis (MTB), often seen in AIDS patients, could be seen on liver biopsies but often with few to rare acid-fast bacilli (AFB). Mycobacterium avium-intracellular (MAI) was seen in those patients with CD4 counts <50 cells/μL and liver biopsies would often reveal larger numbers of AFB than seen in MTB.

Bacillary angiomatosis, due to *Bartonella quintana*, a gram-negative bacillus associated with skin lesions and in the immunocompromised host can be associated with disseminated disease, including the liver. Several cases of bacillary angiomatosis associated with peliosis hepatitis have been described [7].

Fungal infections due to *Cryptococcus neoformans, Histoplasmosis capsulatum Candida albicans, and Coccidioides imitis* can all involve the liver. Although primary hepatic involvement is uncommon, disseminated disease can often involve the liver and cause granulomas [5].

Protozoal infections, most commonly, PCP have been reported to cause infections in the liver [8]. AIDS -related OIs can also affect the biliary system. AIDS cholangiopathy is characterized by chronic abdominal pain, low-grade fever, and cholestasis with biliary dilation and irregular bile duct wall. It has been estimated that 60% of these cases were due to cryptosporidium or CMV and the other 40% were related to enterocytozoon bieneusi (E.bieneusi) [9].

Opportunistic neoplasms such Kaposi's sarcoma (KS), non-Hodgkin's lymphoma (NHL), and Hodgkin's disease can all affect the liver, but often these are secondary manifestations instead of primary disease. Up to one-third of patients with cutaneous KS have hepatic involvement [10, 11]. Both NHL and Hodgkin's disease often present with extranodal and diffuse disease in AIDS patients, but primary hepatic involvement has been reported [11-13].

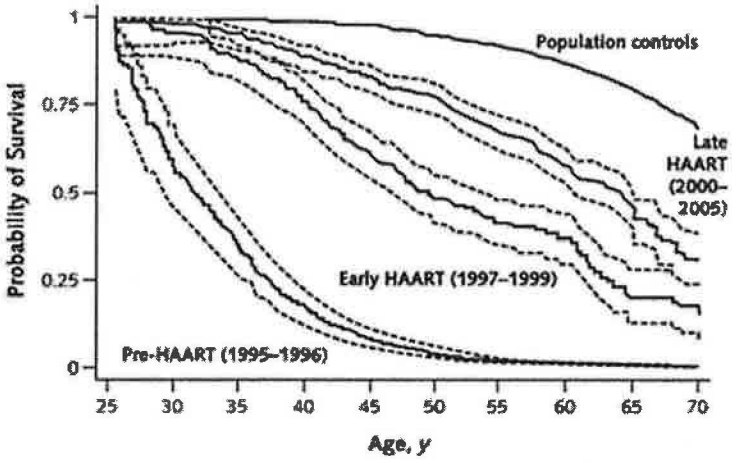


Figure 1: Survival from age 25 years. Cumulative survival curve for HIV-infected persons (without hepatitis C coinfection) and persons from the general population. Persons with HIV infection are divided into 3 calendar periods of observation. Dashed lines indicate 95% CIs.

In 1996, HAART became available leading to a subsequent decrease in AIDS mortality [3]. Furthermore, a decrease in OIs and mortality due to OIs also occurred [2, 14]. The impact of HAART was measured recently in a study from Denmark that examined survival in all HIV-infected persons (n=3990) compared to the general population (n=379,872) from 1995-2005. The median survival in HIV-infected persons, estimated from age 25 was 19.9 years (95% CI, 18.5-21.3) compared to 51.1 years (95% CI, 50.9-51.5) for those without HIV (Figure 1). However the overall survival increased to 32.5 years (95% CI, 29.4-34.7) in those with HIV during 2000-2005 period. In a subgroup analysis of those without HCV, the survival was 38.9 years (95% CI, 35-40.1) compared to 19.6 years (95% CI, 16.1-21.9) for those with HCV/HIV 2000-2005 [15]. Over the past ten years, patients are living longer due to HAART, but experiencing

increased morbidity and mortality from other diseases such as HCV, which shortens life expectancy.

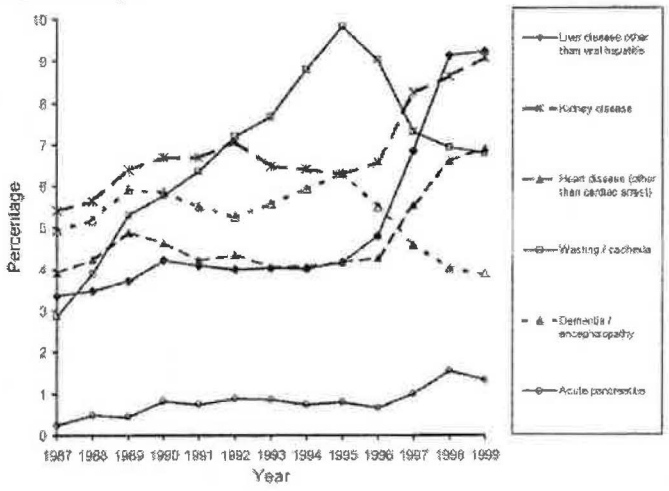


Figure 2: Trends in the demographically adjusted annual proportions of deaths reported with conditions other than cancers or infections among deaths reported with HIV during 1987-1999 (standardized to mean distribution of deaths by sex, race, and age).

Between 1995-1999 in the US, mortality from CMV, cachexia/wasting, and dementia decreased, but increased from septicemia, diseases of the liver, kidney, and heart [16] (Figure 2). Liver disease related deaths increased from 4.9% to 11.6% during this time period. Thus, liver diseases in HIV-infected persons are of increasing importance in the post-HAART era, defined as the period after 1996.

Hepatitis C

Epidemiology and Prevalence

HCV is the most common viral hepatitis in HIV-infected persons because of the common route of transmission through IDU. The prevalence of HCV varies depending on the risk factors of the population. For example, in cohorts composed primarily MSMs, the prevalence of HCV is only 10%. However, in populations with a high proportion of IDU, the prevalence may be as high as 60-70%. In most HIV clinics, the prevalence is approximately 30%. At the Parkland HIV clinic, 25% of HIV-infected persons are coinfected with HCV.

Six distinct genotypes of HCV have been described. Genotype 1 is the dominate genotype in the US and accounts for 75-80% of infections. Genotypes 2 and 3 are more commonly seen in Europe. The prevalence of HCV genotypes in coinfected patients is similar in those with HCV alone.

Recently, reports of acute HCV occurring in MSM have been published. In one retrospective study of 12 HIV-positive MSM, 10 of the patients had asymptomatic acute infection with seroconversion of anti-HCV and detection of serum HCV RNA. HCV genotype 4d was found and on phylogenetic analysis clustered separately suggesting a common source infection. The only risk factor in these patients was unprotected sexual intercourse with men [17]. Another study from Paris identified 29 cases of acute HCV in HIV+ MSM who had no other risk factors for HCV acquisition except unprotected anal sex, fisting, and concomitant sexually transmitted infections. Thus, unprotected sexual

intercourse with bleeding/trauma and perhaps mucosal lesions due to other sexually transmitted diseases may facilitate the sexual transmission of HCV[18, 19].

Spontaneous clearance of HCV is estimated to occur between 15% to 38% in those with HCV alone [20]. In HIV/HCV patients, spontaneous clearance of HCV appears to be reduced. A longitudinal study following injection drug users found the spontaneous clearance of HCV to be 7.4% in those with HIV. In those with CD4 cell count >500 cells/μL, the rate was 8.3% compared to 5% in those with CD4<200 cells/μL [21]. However a recent prospective study of 50 HIV-infected persons with acute HCV found spontaneous clearance of HCV RNA in 12/50 (24%) at 12 weeks. Spontaneous clearance was associated with higher baseline CD4 count and lower HCV RNA levels [22].

Diagnosis

The diagnosis of HCV is made by an enzyme-linked immunosorbent assay (EIA). However, false negative HCV antibodies have been reported in those with severe immune suppression. A recent study examined 1175 HIV-infected patients from three different cohorts in which HCV EIA 2.0 had been used and found 3.2% of the anti-HCV negative patients had HCV by HCV RNA. However, in a subset of injection drug users who had either an elevated ALT or a CD4 cell count <200 cells/μL, the prevalence of a false negative anti-HCV was 24% [23]. Of course, it is possible that some of the seronegative patients were acute infections. However, we found an increased risk of seronegative antibodies in those with a CD4<100 [24]. In longitudinal samples, we demonstrated the appearance of anti-HCV with immune restoration in patients who were initially seronegative while being HCV RNA+. More compelling, however, may be the cases in which anti-HCV was seen and HCV RNA was positive, then with immune failure subsequent tests found anti-HCV to be negative while HCV RNA persisted. Although the newer generation EIAs are more sensitive than the previous ones, the diagnosis of HCV infection may be complicated due to the impact of immune suppression. All HIV-infected patients with abnormal ALT or history of IDU and immune suppression should have a confirmatory HCV RNA if HCV EIA is negative. Both qualitative and quantitative HCV RNA assays are available and can be used to confirm the diagnosis of active HCV.

Impact of HIV disease on HCV

HCV viral load (VL)

HCV VL appears to be elevated in HIV-infected patients in most studies [25-32] but not all [33, 34]. A longitudinal study of injection drug users with HCV found a dramatic increase in HCV RNA levels in those who subsequently became anti-HIV+. HCV VL may also be associated with CD4 cell count. Several studies have indicated an inverse correlation of CD4 count and HCV RNA. Thus, more severe immune suppression was associated with higher HCV RNA levels [26, 31-34].

The impact of HAART and immune restoration on HCV RNA remains controversial. Several case reports have shown HCV viral suppression following the use of HAART [35, 36]. Chung and colleagues examined 60 HIV/HCV coinfected patients enrolled in AIDS Clinical Trial Group (ACTG) study for at least 16 weeks of HAART. Immune recovery was associated with persistent increases in HCV RNA especially in

those with baseline CD4 cell counts <350 cells/μL [37]. Others have reported similar findings [38-41]. HCV RNA was noted to increase initially and then return to baseline after 17 and 32 weeks of therapy [42] in one study. Others have reported a modest decrease in HCV RNA at 12 months [43] or no change at all [44, 45]. Thus, several studies appear to suggest that an increase in HCV RNA; however this increase in HCV RNA $\log_{10}$ is 0.2-0.8, which may not be clinically significant. The effect of immune suppression on HCV viral replication and clearance needs to be studied further. In addition, improvement in CD4 count may not correlate with restoration of immune function, which may explain the discrepant findings.

HCV disease progression

Numerous studies show HCV disease progression to cirrhosis or end stage liver disease (ESLD) is faster in those with coinfection than those with HCV alone. The prevalence of cirrhosis in HIV/HCV co-infected patients appears to be inversely correlated with CD4 cell count [46]. Factors associated with increased progression to cirrhosis include CD4 count <200 cells/μL and alcohol consumption >50 g/day [47]. Even after controlling for confounders such as alcohol, duration of HCV infection, and age, an accelerated progression to cirrhosis appears to occur in those with HIV/HCV [48-50] especially with CD4 <200 cells/μL [47-49]. In hemophiliacs, using the endpoint of ESLD, a faster progression was also seen in those with HIV/HCV compared to HCV alone [51-54] especially with lower CD4 cell counts. A meta-analysis using studies in both injection drug users and hemophiliacs found an adjusted relative risk of 2.92 (95% CI, 1.7-5.01) for the combined end point of decompensated liver disease or histologic cirrhosis [55]. Thus, HIV/HCV coinfected patients were three times more likely to develop cirrhosis and decompensated liver disease than those with HCV alone.

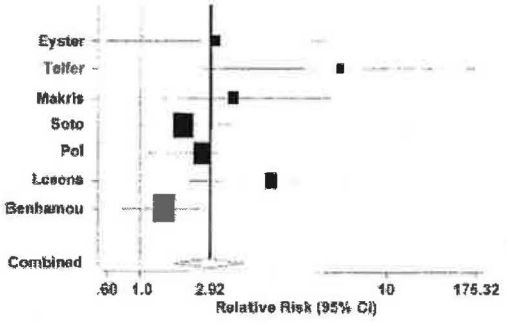


Figure 3: Meta-analysis of studies which examined the relative risk of decompensated liver disease or histologic cirrhosis in patients with HIV/HCV compared to those with HCV alone. HIV/HCV coinfected patients are almost 3 times more likely to have cirrhosis or decompensated liver disease

Hepatocellular cancer

Hepatocellular cancer (HCC) also seems to occur at a younger age in coinfected compared to monoinfected persons. In one study, coinfected (n=7) developed HCC on average at age of 42 compared to 69 in those with HCV ($p<0.001$). Estimated duration of HCV was on average 18 years for coinfected compared to 28 years in those with HCV alone, ($p<0.05$)[56]. An Italian-Spanish study found shorter survival in 41 HIV-infected compared to 384 HIV negative patients with HCC [57]. However, a recent study, evaluating 62 HIV+ patients with HCC with 226 HIV negative controls, found age of diagnosis was significantly younger (52 vs. 64 years, $p=<0.01$) and patients were more likely to be symptomatic at presentation, (51% vs. 38%, $p=0.048$). HCC developed on

average faster in HIV/HCV compared to those with HCV alone (26 vs. 34 years, p=0.002. HIV-infected persons were more likely to receive HCC therapy (48% vs. 31%, p=0.017), but median survivals were similar. HIV-infection was not an independent risk factor for survival. In HIV-infected persons who did not receive HCC therapy, median survival was longer in those with suppressed HIV RNA (<400 copies/mL) than those with viremia (6.5 vs. 2.6 months, p=0.013) [58]. Thus, in HIV-infected persons with HCC if given and able to receive HCC therapy, survival does not appear to be decreased due to HIV status.

Mortality

HCV has been associated with increased mortality in coinfected patients in the post-HAART era [59]. Monga et al found 47% of deaths in HIV/HCV coinfected patients were due to liver disease [60]. Among hemophiliacs the rate of liver mortality was 16 time higher than the general population and 5.6 times higher for liver cancer [61]. In a study with 25,178 HIV-infected persons, with 265 deaths in 2001, 49% (n=129) were due to AIDS, 14% (n=38) were due to ESLD and 37% (n=98) attributable to other causes. Furthermore, an increased prevalence of ESLD-related mortality occurred from 1995-2001 [62]. Although population based studies are finding more evidence for increasing liver-related death rates [63], local trends may not always reflect national changes. We examined the causes of death in 1995 (pre-HAART) compared to 1999-2000 (post-HAART) and found that there was a decrease in the number of deaths per year. However, the leading cause of death in the post-HAART era remained PCP similar to the pre-HAART era. Fifty percent of the patients who died in the post-HAART era were not on HIV medications, some due to non-adherence and others who were recently diagnosed but had not returned for continued HIV care as an outpatient [64]. We did see a significantly higher rate of deaths due to ESLD in those with a CD4 >200 cells/μL. Thus, our study reflects the importance of HAART in reducing mortality and the impact of not receiving HAART, which leads to continued risk of deaths due to OIs.

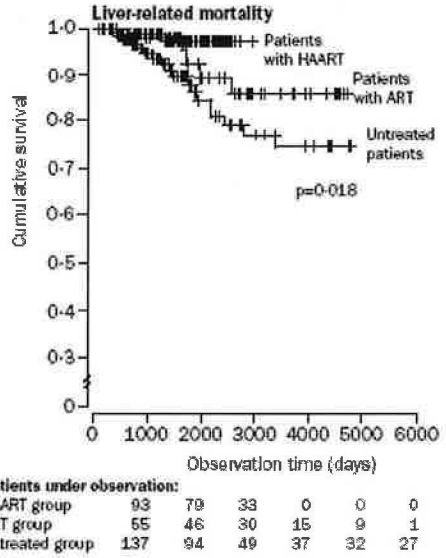


Figure 4. Kaplan-Meier analysis of liver related mortality. Deaths due to non-hepatic causes were censored.

HAART is also associated with a decrease in liver-related mortality (Figure 4). In one study the rate of liver-related mortality was 0.45 vs. 1.70 per 100 person years of follow-up in those on HAART compared to untreated group, p=0.018 [65] others have found similar findings [66]. Even among patients who presented with decompensated liver disease, survival was higher if the patients were on HAART [67].

A recently published study, which combined 11 HIV cohorts with over 23,000 patients, found that the risk of death due to liver disease increased with immune suppression (Table 1).

Table 1: Predictors of Liver –Related Mortality

Risk Factors	Adjusted Relative Risk	95% CI
CD4 <50 cells/μL vs. >500 cells/ μL	16.1	8.1-31.7
HCV	6.7	4.0-11.2
HBV	3.7	2.4-5.9
IDU	2.0	1.2-3.4
Age per 5 years	1.3	1.2-1.4

Univariate analysis did not show a relationship between years on HAART and liver related mortality. However, adjustment for CD4 count and patient characteristics did show a modest increased risk of liver-related mortality per year of HAART (RR 1.11, 95% CI 1.02-1.21, p=0.02) [68]. Although there may be some excess risk of liver-related mortality with HAART, there seems to be evidence that the risk of death without HAART is significantly higher.

Impact of HAART on HCV Related Liver Disease

Hepatic fibrosis progression may be slower in those who have suppressed HIV RNA due to HAART. Those with suppressed HIV RNA progressed at a rate similar to those with HCV alone [69]. Others have found that HAART was not associated with more severe fibrosis [70, 71]. However, one study did show HIV/HCV coinfected patients with more severe stage 3 or 4 fibrosis had a higher incidence of hepatotoxicity due to HAART[72].

It does appear that immune suppression enhances hepatic fibrosis, or allows HCV liver disease to progress faster to cirrhosis. Thus, for both the improvement in HIV long-term survival and perhaps in slowing down HCV related liver disease, HAART should be administered in all HIV/HCV coinfected patients especially those with AIDS and increasingly some experts suggests that perhaps administrating HAART at higher CD4 cell counts may improve liver –related mortality.

Impact of HCV on HIV disease

The impact of HCV on HIV disease progression is controversial. Some studies suggest clinical disease progression [73] while others do not [74]. Sulkowski and colleagues found that in the Hopkins cohort there was no difference in progression to AIDS/death in HIV/HCV coinfected after adjusting for HAART exposure and HIV immune suppression [75]. Others have found a slower increase in CD4 count in those with HIV/HCV when HAART is initiated [76, 77] but over time this did not persist [78] or appeared to have similar levels of immune restoration [37, 75, 79]. The EuroSIDA cohort included 5957 patients with 33% HCV-positive. Among the 2260 in which HCV

status was known who initiated HAART, after adjusting for baseline characteristics; they found no significant difference between HCV-seropositive compared to HCV – seronegative patients with respect to virologic response (relative hazards (RH) 1.13; 95% CI, 0.84-1.51) and immunologic response as measured by ≥ 50% increase (RH 0.94; 95% CI, 0.77-1.16) or a ≥50 cells/μL increase (RH 0.92; 95% CI, 0.77-1.11) [80]. A recent meta-analysis using 8 studies reported patients with HIV/HCV coinfection did suggest a blunted immune response after 12 months of HAART [81]. However, the analysis was limited because the authors were unable to stratify results based on baseline CD4 cell count. Clinically, patients with CD4 <100 cells/μL may have a lower CD4 rise than those who have a CD4 at baseline of >300 cells/ μL.

However, immune response to HAART, as measured by CD4 count, may not be the only outcome to measure the impact on HIV disease course. A study comparing the risk of OIs, death, and hospitalizations in the pre-HAART to post-HAART era found that HCV+ patients did not appear to experience clear benefit from HAART as the risk of OIs, death, and hospitalizations did not change between the pre- and post-HAART era. In the HCV-negative group, a significant reduction was experienced for OIs, hospitalizations, and deaths [82].

Another provocative study that may challenge the notion that HIV response is impaired in HIV/HCV patients, examined CD4 cell counts in 60 HIV-negative patients with cirrhosis. A total of 65% (n=39) had low CD4 cell counts with 43% (n=26) having CD4 cell count<350 cells/μL and 7% (n=4) with <200 cells/μL. The CD4%, however, was normal in 95% of patients. They compared their findings to CD4 cell counts reported in the literature in healthy non-HIV patients without known liver disease and found that cirrhotic patients had significantly lower CD4 cell counts. The authors postulate that portal hypertension and splenic sequestration is the mechanism for these findings [83]. However, these findings have significant implications in interpreting CD4 counts in HIV/HCV coinfected patients. The concern about poor response to HAART may not be due a poor immunologic response, but may be related more to the severity of liver disease.

HCV treatment

In order to reduce liver-related morbidity and mortality; the NIH, in the last consensus conference, stated that HIV coinfected patients need to be treated for HCV. Since that time, several pivotal trials have been published.

APRICOT, the largest study in HIV-infected persons, randomized 868 HIV/HCV coinfected patients into three arms: interferon alfa-2a three times weekly with ribavirin 800 mg (n=285), pegylated interferon alfa-2a alone (n=286), and pegylated interferon alfa-2a with 800 mg of ribavirin (n=289). Pegylated interferon plus ribavirin was superior with an overall sustained virologic response (SVR) rate of 40%. In genotype 1 the SVR was 29% and was 62% in genotypes 2 and 3 [84]. Premature discontinuation occurred overall in 32% of patients. Approximately 1/3 of patients experienced leukopenia, anemia, or thrombocytopenia. The incidence of pancreatitis, symptomatic hyperlactatemia, and lactic acidosis was low. Hepatic decompensation occurred in 1.6% (n=14) all of whom had cirrhosis and 6 of the 14 died.

ACTG 5071 treated 133 HIV/HCV coinfected patients with 180 mcg of pegylated interferon alfa-2a compared to interferon alfa-2a (6 million units three times weekly for

12 weeks than 3 million units until week 48) with both arms receiving dose escalation of ribavirin starting at 600 mg. Overall SVR was 27% in the pegylated interferon arm with 14% and 73% in genotype 1 compared to genotype 2/3, respectively [85]. Premature discontinuation occurred in 12% (n=8). Grade 2 or 3 level cytopenias, flu-like symptoms, and depression were the most common adverse effects. One patient developed pancreatitis, and one patient died of Hodgkin's disease, which was not related to study medications. Episodes of hepatic failure or lactic acidosis were not seen.

The RIBAVIC trial randomized 412 HIV/HCV coinfected patients to pegylated interferon alfa-2b (1.5 ug/kg) with 800 mg ribavirin compared to interferon alfa-2b (3 million units three times weekly) with 800 mg of ribavirin. The overall SVR was 27% in the pegylated interferon with 17% achieving an SVR in genotype 1 and 44% in genotypes 2 and 3 [86]. Treatment discontinuation occurred 39% and clinical adverse events occurred in 17%. Cytopenias were seen in up to 14% of patients. HIV-related adverse events included increase in lipodystrophy and oral candidiasis. Pneumonia, liver failure, and mitochondrial toxicity was seen in 3-5% of patients. Deaths occurred in 1.7% (n=7).

These studies have established that pegylated interferon can be safely used in coinfected persons. However, drug interactions have emerged. Namely, the interaction of ribavirin and didanosine which has led to fatal hyperlactatemia leading to an FDA black box warning to not use these drugs concomitantly. Data is now emerging that zidovudine may increase risk of anemia during HCV treatment [87]. Other cytopenias, which can complicate treatment, include leukopenia/neutropenia. Growth factors such as darbepoetin alfa, epoetin alfa, and filgrastim are often used and needed to manage the cytopenias in coinfected patients.

Another side effect, which has become well established, is the drop in CD4 cell count during interferon therapy due to bone marrow suppression. Although the %CD4 remains stable and may actually go up, we routinely monitor CD4 counts and administer PCP prophylaxis if the CD4 count drops below 200 cells/μL.

The response rates, however, are lower than what is seen in HCV monoinfected patients. Relapse after treatment discontinuation is common. This has led to the idea of prolonging therapy to reduce relapse. An ACTG study currently underway is examining the impact of prolonged therapy of 72 weeks in this population.

Interest has also developed in using maintenance therapy to improve fibrosis. The data is not available as to whether maintenance therapy will improve clinical outcomes. HALT-C is a 5-year study examining this question in HCV monoinfected patients. SLAM-C, an ACTG study, is an ongoing study evaluating maintenance therapy in coinfected patients.

Transplantation

There will be many patients who fail HCV treatment or have clinical progression. Liver transplantation in these patients is being performed in many centers throughout the country and is increasing in many centers worldwide. Concerns about transplantation in immunosuppressed patients exist including survival, risk of OIs, drug-interactions, and safety. The University of Pittsburgh has published data on 15 liver-transplants in HIV-infected persons, most of whom became positive during the peri-operative period with contaminated blood products. Among those initial 15, 7 were alive 2.75 years later. After 12.7 years of follow-up, only 2 remain alive [88] but these transplants occurred in the

pre-HAART era. One study, using the UNOS database, identified 19 HIV-infected patients who had received liver transplants. The overall patient survival was 79% with median follow –up of 314 days, which is similar to non-HIV patients who have a 1 year survival of 88% [89]. Another study in HIV/HBV patients found a survival rate of 69% at 1 year with no re-infection of graft when HBIG was administered with lamivudine or adefovir/tenofovir [90]. One problem in HIV/HBV coinfected patients was a high level of lamivudine resistance. On the other hand, transplantation in HIV/HCV has been plagued with high numbers of re-infection after transplantation. Another issue includes the dosing of antiretrovirals in which the pharmacokinetics may be skewed due to decompensated liver disease. There may also be significant drug interactions with HAART especially ritonavir-based regimens and immunosuppressive medications requiring lowering doses of immunosuppressive drugs. An interesting finding but still not clinically proven is the inadvertent improvement that cyclosporine may have on HIV. Cyclosporine interferes with cellular cyclophilin, which is used by HIV for structural protein processing. Studies from patients who acquired HIV during the peri-operative period in the pre-HAART era seemed to have a lower risk of HIV disease progression if on cyclosporine [91]. Much remains unknown about transplantation in this population. The NIH has sponsored a large multi-center trial to assess safety and efficacy for kidney and liver transplantations in HIV-infected individuals. Over time we will see if HIV-infected patients can experience similar survival benefits as their HIV-negative counterparts.

Hepatitis B

HBV is a non-cytopathic virus which causes liver damage through immune-mediated mechanisms [92, 93]. Cytotoxic CD8 T cells, in the context of HLA class I molecules, recognize HBV antigen on the surface of infected hepatocytes and destroy the cell leading to elevation of aminotransferases. Chronic hepatic inflammation is thought to lead to cirrhosis. HBV establishes a persistent infection as a covalently closed circular DNA (cccDNA) within the nucleus of the hepatocyte. Clinical disease of HBV in HIV infected persons is mediated by both the immunosuppression of HIV and also to the treatment of HIV with restoration of the immune system.

Prevalence and Epidemiology

The prevalence of HBV is reported to be from 6-10% in the HIV-infected cohorts. In the Parkland HIV clinic, approximately 8% of HIV infected patients are HBsAg-positive. Although HBV is the leading cause of liver disease world-wide, in the US population the prevalence is <0.5% [94].Thus, the burden of HBV is larger in the HIV population.

The most common mode of transmission is sexual, mostly occurring in MSM. The incidence of acute HBV has declined since the late 1980s mostly attributable to vaccination among children and adolescents. Since 1999, the incidence of HBV has increased 5% among men 20-39 years and males and females ≥ 40 years of age [95]. The most common risk factors is multiple sex partners, MSM, and IDU[94]. There has been increases in sexually transmitted diseases among MSM including syphilis and HIV [96, 97]. The changing pattern of sexual behavior in this population may be responsible for the increasing transmission of HBV in MSM.

Eight HBV genotypes exist each with >8% sequence diversity. The distribution of HBV genotypes varies globally. In the US, the most common genotype is A. Among Asians in the US and in China, the most common genotype is B and C. Genotype D is more often seen in Europe, and genotype F in South America. In a small study of HIV/HBV patients at Parkland, we found as expected 78% with genotype A. In addition, we had 2 with genotype F, 2 with genotype D, 4 with genotype G, and 1 with genotype A/G mix [98]. The high number of genotype G in the HIV population is unusual but the few cases reports of genotype G have been reported in MSM [99]. It remains to be determined if there is a different distribution of HBV genotypes among HIV-infected persons.

HBV Vaccination in HIV-infected patients

Hepatitis B is a vaccine preventable disease. However, the vaccine is ineffective in HIV patients with CD4<200 cells/μL and should be deferred until HAART can be given to improve CD4 cell counts. In those with CD4>500 cells/μL, the response to vaccine is 87%. However, in those with CD4 between 200-500, the response to HBV vaccination is 33%. Thus, the majority of patients will not have protective antibodies despite having received the full course. It has been recommended, that a more intense vaccination schedule be performed at 0, 1, 2, and 12 months. Those who do not respond to the first cycle should be given booster dose or given a new cycle with 40 μg. Those with CD4 >500 cells/μL can receive the routine vaccine series at 20 μg at 0,1, and 6-12 months [100]. Unfortunately, cases of acute HBV continue to be seen in HIV-infected patients despite these patients receiving routine medical care.

Impact of HIV on HBV disease

The natural history of HBV appears to be altered in the setting of HIV-infection. A person with HIV who acquires HBV is much less likely to be able to clear the infection spontaneously compared to those without HIV [101-103]. Hepatitis B e antigen (HBeAg) seroconversion is also less likely to occur in those with HIV/HBV compared to HBV alone. Serum aminotransferase elevations may be milder than those with HBV alone [102-104], this is often in the setting of severe immune suppression. However, serum HBV DNA levels are often elevated compared to those with HBV alone [102-105]. Furthermore, histologic studies in the pre-HAART era showed that liver disease was often milder in HIV/HBV coinfected persons [106, 107] but others found no difference [104, 106, 107]. Colin et al. examined the risk for cirrhosis in HIV/HBV compared to HBV alone and found in a multivariate analysis that HIV-infection was an independent risk factor for cirrhosis [104]. Overall, it appears that HBV in HIV-infected patients may have lower liver function tests, higher HBV DNA levels, milder histopathology, but still be associated with higher prevalence of cirrhosis.

Mortality

Liver-related mortality appears to be significantly higher compared to those with HIV alone or HBV alone. In one of the largest cohort studies, to date, composed of 5293 MSM of whom 6% (n=326) were hepatitis B surface antigen (HBsAg)-positive with 65% having HIV-infections (n=213) and 4967 HBsAg-negative with 47% having HIV-infection (n=2346). Liver related mortality was 14.2/1000 person years in those with

HIV/HBsAg-positive compared to 1.7/1000 person years in those with HIV-infection and 0.8/1000 person years in those with HBsAg-positive alone. The risk was 8 times higher of liver related mortality in those with HIV/HBV compared to HIV alone and 17 times higher than those with HBV alone[108]. Another disturbing finding in Thio's study was that in those who enrolled in the cohort during the period 1996-2000, the risk of liver-related mortality was higher (RR 11.4; 95% CI, 2.4-38.0) compared to those prior to 1996 (RR 7.6; 95% CI, 4.0-14.1)[108]. Other factors such as alcohol may contribute to mortality. In one study examining in-hospital liver-related deaths, HBsAg -reactivity and alcohol abuse to be independent predictors of liver-related mortality in HIV-infected persons [109]. A recent study from France examining deaths of 964 HIV-infected persons in 2000 found AIDS as the leading cause of death (47%) followed by liver disease (11%), cancers (11%), and cardiovascular deaths (7%). Although AIDS remained the most frequent cause of death in HIV/HBV patients, liver-related mortality was seen in 20%. In those who were HBeAg-positive, the mortality rate was 27% [110]. In the subpopulation with HIV/HBV/HCV, liver-related mortality was significantly higher at 44% than other groups, $p<0.001$) [110]. Thus, during the post-HAART era, HIV/HBV patients appear to have increased risk of liver-related mortality.

Treatment of HBV in HIV infected persons

Nucleoside therapies used for HIV suppression and to restore immune function may also lead to increasing liver enzyme elevations in the post-HAART era. Drug hepatotoxicity has lead to liver failure and death in a few cases, but these cases were using HIV medications which had no activity for HBV [111]. Now, several nucleosides are available which have dual activity for both HIV and HBV including lamivudine, tenofovir disoproxil fumarate, and emtricitabine. Only lamivudine is FDA approved for both HIV and HBV indications. However, these nucleosides can be an important component of HAART and provide viral suppression of HBV.

Lamivudine has shown at 2.7 log reduction of HBV in HIV/HBV treated with HAART with lamivudine compared to non-lamivudine based HAART regimen [112]. HBV virologic suppression occurs from 40-87% and HBeAg seroconversion from 22-29% [112-114]. Comparisons between studies is difficult as the assays used to determine HBV DNA suppression have differing thresholds. However, these response rates appear to be similar to those seen in HBV monoinfected persons [115].

One of the problems, which has emerged with lamivudine use as a single agent for HBV, is the emergence of lamivudine resistance for HBV (YMDD). An estimated 32-38% of patients on lamivudine develop YMDD mutation at 1 year [116, 117]. In HIV/HBV coinfected patients, YMDD mutations have been detected in 14% at 1 year and 50% at 2 years [114, 118, 119]. Over time the prevalence of HBV resistance has been observed and may be 100% after 5 years of therapy [114]. Thus, the need for drugs that can treat lamivudine-resistant mutations has emerged.

Tenofovir disoproxil fumarate is an effective drug for the treatment of both HIV [120] and HBV [121, 122]. Tenofovir is active against lamivudine resistant mutations [122]. Studies have shown a 3 to 5 log drop in HBV DNA in lamivudine-resistant patients at 12-71 weeks [121, 123, 124]. Approximately 25% of patients on tenofovir underwent HBeAg seroconversion at 52 weeks [125]. To date, only one case of tenofovir

resistance has been reported [126]. However, like most drugs, resistance will probably emerge over time.

Emtricitabine, a nucleoside analogue, has also been shown to be a potent selective inhibitor of HIV [127] and HBV [128]. Emtricitabine 200 mg per day for 48 week showed HBV DNA suppression (<400 copies/mL) in 54% of patients compared 2% in placebo ($p<.001$). HBe Ag loss and HBe Ag seroconversion occurred 12% [129]. In a two year study, 53% of patients on emtricitabine had HBV DNA <4700 copies/mL, 33% anti-HBe seroconversion and 85% had normal alanine aminotransferase (ALT) [130]. However, like lamivudine, emtricitabine has already shown emergence of YMDD (rt M2041; rtL180M+rtM204I/V) mutations in 9% and 18% at weeks 48 and 96, respectively [130].

The question of dual therapy for HBV is a controversial strategy in the HBV monoinfected patients. No data to date has shown a synergistic improvement in HBV suppression with dual therapy. However, in the world of HIV it has become accepted that dual therapy should be given for HBV. Experts in HIV therapy postulate that dual therapy is beneficial to prevent the emergence of viral resistant strains and guidelines on HIV/HBV coinfection recommend the use of combination therapy for HBV [100].

Impact of Immune Restoration

As previously described, the impact of HBV on liver disease is due the immune response to HBV. Thus, in HIV/HBV coinfected patients in whom immune function is restored due to HAART, HBeAg seroconversion and HBV flares can be seen. Case reports of spontaneous HBsAg seroconversion have been reported after the initiation of HAART [131, 132]. Often these cases of seroconversion, however, occur in the setting of HBV flares. However, because of concerns of drug-induced hepatotoxicity sometimes HBV flares are mistaken for drug-induced liver injury. HIV/HBV co-infected patients have a higher incidence of severe (grade 4) aminotransferase elevations while on HAART [133]. Several studies indicate HAART in co-infected patients is associated with higher rates of HIV treatment discontinuation and fatal liver disease [59, 134]. Acute flares in disease activity may occur in chronic HBV infection in association with spontaneous reactivation, antiviral therapy, HBV genotypic variation, superimposed hepatotropic infections, and other opportunistic infections [111, 135]. Acute hepatitis flares may occasionally lead to clearance of HBV DNA due to immune reconstitution [132] and decreased HIV viremia [135] in co-infected patients. We examined three HIV/HBV co-infected patients (Figure 5) who developed acute flares that were unlikely to represent HAART toxicity and were most compatible with re-activation of HBV in the setting of two active drugs against HBV. All patients received lamivudine and tenofovir as part of HAART. The degree of liver enzyme elevation varied with each patient in proportion to the degree of $CD4^+$ cell count recovery.

Each patient had a different CD4 rise with HAART and experienced different magnitude of HBV flares. The patient with a rapid increase in CD4 cell count developed severe hepatitis. However, after the hepatitis resolved, the patient had cleared HBV. The second patient had a moderate increase in CD4 with milder elevation of liver enzymes. Although this patient subsequently had HBV DNA suppression, she was not able to achieve HBeAg seroconversion. The last patient had a mild increase in CD4 count in response to HAART. His liver enzymes increased, but not as significantly. His HBV

DNA was suppressed, but he was not able to resolve the infection and remained HBeAg-positive [136]. Acute HBV reactivation is thought to result from stimulated cytotoxic T-cells directed toward HBV viral epitopes on the surface of hepatocytes [135]. Restoration of both $CD4^+$ and $CD8^+$ cell function through HIV suppression can also lead to flare of HBV[137]. Varying degrees of HBV-specific CD8 T-cell expansion [138] as well as decline of serum HBV DNA load due to nucleoside therapy [135] may have led to the HBV flares observed.

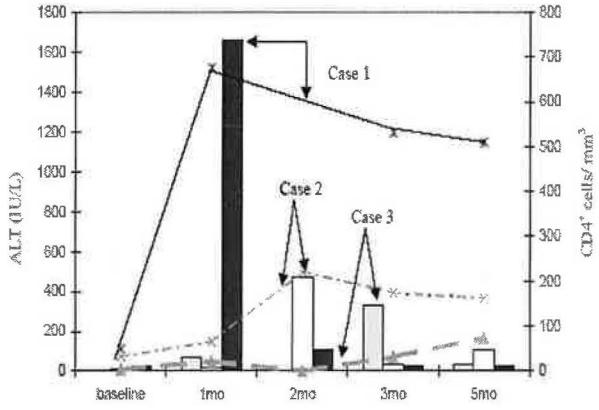


Figure 5: Relationship of $CD4^+$ Cell Count Increase and ALT° Elevation. The lines depict rise in $CD4^+$ cell count (measured on the right Y-axis). The bars reflect elevation of ALT (measured on the left Y-axis). X-axis reflects months after initiation of HIV therapy. Case 1: Patient with brisk increase in $CD4^+$ cell count with severe elevation of ALT. Case 2: Patient with modest increase in $CD4^+$ cell count with moderate increase in ALT. Case 3: Patient with minimal increase in $CD4^+$ cell count with mild elevation of ALT.

Monitoring of HBV Response in HIV-infected persons

Over the last 10 years, HBV therapeutic options have grown. Suppression of HBV replication using nucleos(t)ide analogues results in histologic improvement, slower disease progression, and increased long-term survival [139]. Effective management of patients on HBV-active drugs requires following HBV disease markers such as ALT, HBeAg status, and, particularly, HBV DNA to determine if therapy is needed and to assess response to treatment [140-142]. The goal of HBV therapy continues to be suppression of HBV replication and, if possible, HBeAg clearance [141, 143]. In addition, HBV management guidelines recommend screening for cirrhosis with imaging, alpha-fetoprotein (AFP), and liver biopsy where appropriate [141]. Previous HIV treatment guidelines [144] have outlined both when HIV therapy should be initiated and HIV VL measured and currently [145] recommend agents for HIV/HBV coinfected patients, but they do not suggest how to monitor HBV response. No studies, thus far, have focused on how HIV providers evaluate and monitor HIV/HBV coinfected patients. Thus, the goal of our study was to determine what level of care for HBV infection that was being provided to HIV patients by their providers. We identified 357 HIV and HBsAg-positive patients tested between 1999-2003; 155 patients new to our clinic who initiated HIV and/or HBV therapy were considered for study. The frequency of HIV tests (HIV VL and CD4 cell count) performed during the first year of therapy was compared to HBV measurements (HBe antigen/antibody, HBV DNA), abdominal ultrasound, and serum levels of AFP. HBV DNA was obtained in only 16% of patients prior HAART initiation whereas 99% of the same patients had HIV VL obtained prior to HAART. The total number of HIV VLs obtained during the first year after HAART initiation was 497 (median per patient 3.0) compared to 85 (median per patient <1) for

HBV DNAs ($p<0.001$). The proportion of patients who received any level of HBV monitoring (HBV DNA, HBe antigen/antibody) after ART initiation increased from 7% in 1999 to 52% in 2001 ($p<0.001$), while HIV VL testing in the same patients remained at 80-90% during the same time period [146]. This study demonstrates how the field of HIV has changed such that among the drugs we use to treat HIV, we are able to treat HBV. However, a gap appears to exist in the level of training and awareness of how to manage HBV disease. In fact, the Department of Health and Human Services [145] which periodically published guidelines on the management of HIV, only recently added a section which reflected the importance of using drugs like lamivudine, tenofovir, and emtricitabine in HIV/HBV coinfected patients. The guidelines failed, however, to provide recommendations on serologic and virologic tests to guide clinicians.

Hepatotoxicity

Although HAART has clearly prolonged survival in HIV-infected persons, the trade-off may be in drug-induced toxicities including the development of diabetes, lipodystrophy, peripheral neuropathy, to name a few. Drug-induce liver injury is also one of the important toxicities that has emerged in the post-HAART era.

Prevalence and Natural History

The prevalence of HIV medication related liver toxicity is reported between 2% [147] to 38% [148]. The incidence of liver enzyme elevation after HAART initiation may vary from 0.54/100 person-years to 17.7/100 person years [149, 150]. The reason for the variation in the prevalence and incidence of disease is in part due to the variation in defining "hepatotoxicity." The definition of drug induced liver injury varies with some studies reporting hepatotoxicity as doubling of ALT or ALT>200 IU/mL. However, most studies have adapted the ACTG scale for liver toxicity. According to the scale, severe hepatotoxicity is defined as grade 3, defined as > 5X upper limit of normal (ULN) or grade 4, >10X ULN, change in AST and /or ALT levels during antiretroviral therapy. Other have used ALT/AST $\geq$ 5X the ULN or 3.5X the abnormal baseline, to adjust for those who have abnormal baseline liver function tests.

Another factor, which may affect the reporting of prevalence of "hepatotoxicity", is the type of population studied. In studies using clinical trials data to evaluate drug-induce liver injury, the population entering into the study may not be representative of the clinic population. Thus, the prevalence of those with hepatitis B and C co-infection are limited. Furthermore, both the number of patients and person-year follow-up is limited. However, the data collected from clinical trials is more comprehensive and is not limited by ascertainment bias like cohort studies.

Sulkowski and colleagues have reported severe liver enzyme elevations were seen in 10% of patients but found no severe or irreversible outcomes were seen in patients with severe hepatotoxicity [151]. Others have found that liver enzymes, especially in coinfected patients actually may decrease over time [152, 153].

However, a number of fulminant liver failures in HIV/HCV co-infected patients in the HAART era were seen in one study after excluding advanced liver disease and adjusting for alcohol intake [154]. Because of the risk of fulminant hepatitis, HIV providers often will discontinue HAART due to perceived hepatotoxicity. In one study HAART discontinuation due to hepatotoxicity increased from 6% in 1996 to 32% in

1998-1999 [59], despite the fact that most cases of liver enzyme elevations do not lead to fulminant hepatic failure.

Risk factors for toxicity

Multiple studies have found an association with chronic HCV and HBV and severe hepatotoxicity (SH) (usually grade 3 or 4 liver enzyme elevation) [152, 155-164]. One study found an increased risk of SH was more likely in those with HCV genotype 3, and another study found SH more common in those with grade 3-4 fibrosis [72]. Mehta and colleagues, however, did not find that HAART lead to serious liver injury in their cohort. In fact increased fibrosis was noted among those who had persistently elevated liver enzymes and was not correlated with duration of type of antiretroviral therapy [71]. The mechanism of why HCV may be related to higher risk of liver enzyme elevation is unclear. Studies have found an increase in HCV viral load in those after the initiation of HAART [37]. However, no association with increased HCV RNA levels and liver enzyme elevation or hepatic fibrosis has been established. However, Puoti did show that in those who did develop SH, treatment of HCV with interferon lead to improvement in transaminases [165]. Although mechanism that leads to higher risk of toxicity from antiretroviral therapy in HIV/HCV co-infected patients is unclear, the treatment of HCV may need to be considered in the management of this type of toxicity.

Alcohol abuse and drug addiction may also play an important role when evaluating liver enzyme elevations in an HIV-infected person. In cohort studies in which SH was based on liver enzyme elevations only, concomitant risks such as alcohol and illicit drug use may be overlooked. Furthermore, concomitant medications used to treat OIs in severely immunosuppressed patients may also play a role in contributing liver enzyme elevations. Some studies have suggested abnormal baseline liver function tests maybe a risk for future elevation of liver function tests [163, 164]. Determining what specific antiretrovirals may cause drug injury is difficult as many cohort studies do not represent all drugs, and since these drugs are used in combination attributing drug toxicity to one drug is difficult. However, certain drugs have emerged in which the mechanism of toxicity is known.

Risk of Toxicity by Drug Class

Protease Inhibitors

Protease inhibitors (PI)s have been implicated in liver enzyme elevations in patients with HAART. Ritonavir, when used at full dose, was associated with the highest risk of toxicity [151]. Drugs such as indinavir, saquinavir, and nelfinavir are associated with a low risk for liver enzyme elevations [151, 166, 167]. Ritonavir, a potent inhibitor of the cytochrome P450, enzyme system, can be used to increase the serum concentrations of other PIs. Studies comparing HAART regimens with ritonavir-sparing to ritonavir –boosted therapy found no differences in rates of liver enzyme elevations [168-171]. Risk of toxicity with ALT>5 X ULN was seen in 5% of patients but was associated with HCV or HBV coinfection [162]. Tipranavir, recently approved by the FDA, has a black box label warning stating that tipranavir, when co-administered with 200 mg of ritonavir, has been associated with clinical hepatitis and some fatalities. Increased vigilance is warranted in patients with HBV or HCV coinfection as these

patients are at increased risk of hepatotoxicity[172]. The package insert for darunavir, also metabolized by Cyp3A, cautions on the use of this drug in patients with hepatic impairment but no specific toxicity is associated with HCV or HBV coinfections [173].

Non-nucleoside reverse transcriptase inhibitors

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) such as efavirenz and nevirapine have been associated with hepatotoxicity. In one study 15.6% of patients on nevirapine and 8% on efavirenz developed severe liver enzyme elevations. Only 50% of efavirenz and 32% of nevirapine related liver enzyme elevation occurred in the first 12 weeks of starting medications. This risk was highest in those with viral hepatitis and those also given concurrent PIs [155]. One study, which measured plasma levels of nevirapine, found that those on nevirapine and PI or coinfected with HBV were at increased risk of liver enzyme elevation; however, the risk of liver toxicity was not associated with plasma concentration of nevirapine [157]. Others have found the risk of liver toxicity to be associated with HCV, >40 g of alcohol, and nevirapine-and efavirenz-containing regimens [158]. Gender may also play a role in drug-induced liver injury. Women with CD4 count >250 have especially been found to be at risk for nevirapine – related fulminant hepatic failure [174]. Whereas, a study of men who were on NNRTIs found no increased risk for liver toxicity [147]. Two cases of fulminant hepatic failure and 12 cases of severe liver injury in healthy subjects receiving nevirapine as part of post-exposure prophylaxis has lead to the recommendation to avoid this drug [175, 176].

Nucleoside reverse transcriptase inhibitors

Nucleoside reverse transcriptase inhibitors (NRTIs) have been associated with liver injury through mitochondrial dysfunction, lactic acidosis, and subsequent hepatic steatosis. However, in the ICONA cohort stavudine was associated with a lower risk of ALT>200 IU/L compared to zidovudine-containing regimens which is different from most studies[159]. NRTIs have been associated with mitochondrial toxicity that will be discussed later.

Mechanisms of toxicity

Direct toxicity

Direct toxicity of antiretrovirals or any other drug to the liver can occur as many drugs are metabolized through the cytochrome pathways. Polymorphisms in these pathways have been linked to hepatotoxicity [177]. For example, hyperbilirubinemia may be seen with atazanavir. A recent study evaluating atazanavir found a direct correlation between plasma concentrations of atazanavir and risk of hyperbilirubinemia. Polymorphisms at MDR1-3435 influence atazanavir plasma levels, which is directly correlated with risk of hyperbilirubinemia. Furthermore, the risk of severe hyperbilirubinemia is further increased in the presence of UGT1A1-TA7 allele [178]. The mechanism of hyperbilirubinemia for atazanavir appears to be similar to Gilbert's syndrome.

Drug hypersensitivity reaction

Hypersensitivity reaction is an idiosyncratic reaction of the host and is not related to dose of the drug. Most often these reactions occur within 4-6 weeks of drug initiation. Nevirapine has been found to have this mechanism of toxicity and is often associated with onset of fever and rash. Warning issued by the company marketing nevirapine on the risk of severe toxicity linked to women with CD4>250 within 6 weeks of initiation of HAART. Furthermore, low body mass index is another independent risk factor for nevirapine hypersensitivity reaction [179]. Abacavir also has been associated with a drug-induced hypersensitivity reaction which may occurs 5-6% of the time. The clinical presentation, often within 6 weeks of drug initiation, is rash, abdominal pain, fever, and sometime hepatitis. Once this reaction has occurred, re-challenge can be fatal.

Genetic polymorphisms in the host can now identify those who may be at risk for these types of reactions. Individuals with HLA-DRB*0101 especially those with <25% CD4 may be at greater risk of developing NVP-induced hypersensitivity reaction [180]. Abacavir which can cause drug-induced hypersensitivity reaction in 4% of those treated also has been associated with genetic polymorphism at HLA-B*5701. Fever, rash, nausea, vomiting, abdominal pain, and lethargy characterize the hypersensitivity reaction, which usually occurs within 6 weeks of initiating medications. Less commonly renal or hepatic failure, anaphylaxis, and paresthesias can be seen [181]. Because of the fatal outcome of this reaction, a person may be evaluated for this polymorphism and if present, the drug should be avoided.

Immune reconstitution

Liver enzyme elevation as a consequence of immune restoration has been reported in HBV. We have shown that the degree of immune restoration correlates with the degree of liver enzyme elevation [136]. Several studies have also shown changes in HCV VL due to immune restoration [37, 42, 182-184]. Others have associated increase in CD4 count to be a risk factor for liver enzyme elevations [151]. However one study did find HCV –specific immune responses, T-cell activation and inflammation correlated with hepatotoxicity [185]. A study in which liver biopsies were performed in those with had >10X ULN elevation of liver enzyme or >5 X the abnormal baseline found a direct correlation with increase in ALT and increase in CD4 count. Of the 26 patients with severe elevation of liver enzymes, 96% were coinfected with HCV and 19% with HBV. The authors felt that immune reconstitution was playing an important role in severe liver enzyme elevation because most patients were coinfected with viral hepatitis; correlation of increasing CD4 and ALT; liver histology showed exacerbation of chronic hepatitis; absence of relapse of most patients when rechallenged and/or treated with interferon [165]. However, it remains controversial if immune reconstitution could be the mechanism for liver toxicity.

Mitochondrial toxicity/lactic acidosis

Although mitochondrial toxicity is infrequent it can lead to acute liver failure. Lactic acidosis has been described as a complication of nucleoside analogue therapy, specifically with zidovudine, stavudine [186-189], and didanosine [186, 187]. In one study the most common regimen associated with NRTI associated symptomatic lactic acidosis was stavudine plus didanosine [186].

Subclinical hyperlactatemia is associated with elevated venous lactate levels and no clinical symptoms, and has been reported to be 8-18% [190]. However, the association with NRTIs with subclinical hyperlactatemia is poor and prognosis is excellent. Symptomatic hyperlactatemia is thought to occur 8-14.5 cases/1000 patient-years and is highly associated with NRTI use. Serum lactate levels are usually <5.0 mmol/L but metabolic acidosis is not seen. Symptomatic hyperlactatemia may be associated with hepatic injury and hepatic steatosis. The prognosis is usually good as long as NRTIs are stopped. Lactic acidosis syndrome (LAS), reported to occur 1.3-3.9 cases/1000 patient-years is associated with multiorgan failure and mortality has been reported to be from 30% to 100%. Co-administration of hydroxyurea or ribavirin with didanosine has also been associated with in increased risk of LAS. Stavudine and hydroxyurea has also been associated with this syndrome. It is thought the hydroxyurea and ribavirin increases intracellular concentrations of triphosphate. By October 2002, 24 cases of ribavirin and didanosine combination leading to fatal and non-fatal lactic acidosis had been reported to the FDA, which lead to the subsequent black box label warning against the use of these two drugs together.

Neither HIV VL or CD4 count is associated with NRTI-related hyperlactatemia (NRH), however both female gender and obesity have been associated. The time to presentation of NRH is reported to be 3-20 months, median time 9 months. Many patients have a 2-4 week prodrome with the most common symptoms including nausea, vomiting, vague abdominal pain, and abdominal distension. Some reports have found antecedent weight loss. Patients with LAS often present with hepatic injury and at times liver failure. Carr et al reported one case of NRTI associated hyperlactatemia and acute hepatitis with no evidence of viral hepatitis. Liver biopsy showed hepatic steatosis and electron microscopy showed abnormal mitochondria. Although the hepatitis and lactatemia resolved with discontinuation of HAART, the patient went on to develop non-cirrhotic portal hypertension and died from variceal hemorrhage [191].

Hepatic Steatosis

Fat accumulation in hepatocytes initially leads to microvesicular changes then may lead to macrovesicular changes on histopathology. Steatohepatitis is fatty liver with inflammation and can lead to cirrhosis. Hepatic steatosis is commonly associated by obesity, alcoholism, and diabetes mellitus. However, this may not be the mechanism through which hepatic steatosis occurs in HIV-infected persons. The prevalence rates of hepatic steatosis has been reported from 38%-72% based on liver biopsies in HIV/HCV co-infected patients [11, 192-195]. However, case reports of hepatic steatosis in HIV-infected patients without HCV have been reported [196].

Fat redistribution due to lipodystrophy maybe a cause of hepatic steatosis in HIV infected persons [197]. Another mechanism of hepatic fat accumulation may be through NRH. Mitochondrial toxicity is associated with accumulation of microvesicular steatosis and this may evolve to macrovesicular steatosis. The clinical picture may resemble alcohol induced liver injury, acute fatty liver of pregnancy, or Reyes syndrome [177]. However the causal mechanism remains unknown. Reduced ß-oxidation of fatty acids is thought to be a possible mechanism since mitochondrial enzymes are needed for this process.

Several studies have evaluated hepatic steatosis in the HIV/HCV coinfected population. Most studies have found an association with more severe steatosis and increased fibrosis [192-195]. One prospective study did find a linear correlation between the amount of steatosis and degree of fibrosis thus implying a possible causal relationship [198]. Some studies found an association with certain nucleoside analogues such as stavudine and didanosine [193, 194] but others did not [195]. Another study found an association with >4 years of HAART and hepatic steatosis but not with any specific component [198]. HCV genotype 3 has also associated with steatosis in some studies [193, 195]. Interestingly, BMI was a potential risk factor in a few studies [194, 195] but not in others [198, 199]. The pathologic findings of steatosis appears to be mixed steatosis or microvesicular [193, 198] which is unlike the macrovesicular steatosis seen in monoinfected patients. Perhaps a different mechanism or multiple mechanisms could be accounting for the steatosis seen in HIV-infected patients.

Conclusions

The HIV epidemic has evolved over the last 25 years. Although we continue to see patients with severe immunosuppression and OIs, combination antiretroviral therapy has lead to a diminished occurrence of OIs. However, increased survival in these patients has led to the emergence of new problems and morbidities. Because of the high rates of coinfection with HBV and HCV, liver disease has become an important factor in the quality and quantity of life in HIV patients. Complications of end stage liver disease continue occur. Furthermore, the very drugs which help prolong life also bring with it adverse side effects from direct injury to the liver or through immune restoration.

In the future, we hope to have more HIV medications, which have less liver toxicity and can be safe and effective in HIV coinfected patients. Patients will continue to progress to end stage liver disease and the need for transplantation will grow. The results from the NIH study will help us determine how well HIV-infected patients can tolerate and survive from liver and kidney transplants. Furthermore, we need to focus on developing collaborations with our colleagues in other divisions such as hepatology, cardiology, oncology, and endocrinology as the HIV-infected person will have complicated diseases requiring expertise from those trained in HIV and experts from other sub-specialties. Ultimately, the care of HIV-infected persons will require a collaborative effort between the HIV provider and sub-specialists.

References:

1. Pneumocystis pneumonia--Los Angeles. MMWR Morb Mortal Wkly Rep **1981**;30:250-2.
2. Brodt HR, Kamps BS, Gute P, Knupp B, Staszewski S and Helm EB. Changing incidence of AIDS-defining illnesses in the era of antiretroviral combination therapy. AIDS **1997**;11:1731-8.
3. Palella FJ, Jr., Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. N Engl J Med **1998**;338:853-60.
4. Hogg RS, O'Shaughnessy MV, Gataric N, et al. Decline in deaths from AIDS due to new antiretrovirals. Lancet **1997**;349:1294.
5. Bach N, Theise ND and Schaffner F. Hepatic histopathology in the acquired immunodeficiency syndrome. Semin Liver Dis **1992**;12:205-12.
6. Kaufman B, Gandhi SA, Louie E, Rizzi R and Illei P. Herpes simplex virus hepatitis: case report and review. Clin Infect Dis **1997**;24:334-8.
7. Perkocha LA, Geaghan SM, Yen TS, et al. Clinical and pathological features of bacillary peliosis hepatis in association with human immunodeficiency virus infection. N Engl J Med **1990**;323:1581-6.
8. Merkel IS, Good CB, Nalesnik M and Roseman SR. Chronic Pneumocystis carinii infection of the liver. A case report and review of the literature. J Clin Gastroenterol **1992**;15:55-8.
9. Pol S, Romana CA, Richard S, et al. Microsporidia infection in patients with the human immunodeficiency virus and unexplained cholangitis. N Engl J Med **1993**;328:95-9.
10. Glasgow BJ, Anders K, Layfield LJ, Steinsapir KD, Gitnick GL and Lewin KJ. Clinical and pathologic findings of the liver in the acquired immune deficiency syndrome (AIDS). Am J Clin Pathol **1985**;83:582-8.
11. Schneiderman DJ, Arenson DM, Cello JP, Margaretten W and Weber TE. Hepatic disease in patients with the acquired immune deficiency syndrome (AIDS). Hepatology **1987**;7:925-30.
12. Ziegler JL, Beckstead JA, Volberding PA, et al. Non-Hodgkin's lymphoma in 90 homosexual men. Relation to generalized lymphadenopathy and the acquired immunodeficiency syndrome. N Engl J Med **1984**;311:565-70.
13. Welch K, Finkbeiner W, Alpers CE, et al. Autopsy findings in the acquired immune deficiency syndrome. JAMA **1984**;252:1152-9.
14. Ko WF, Cello JP, Rogers SJ and Lecours A. Prognostic factors for the survival of patients with AIDS cholangiopathy. Am J Gastroenterol **2003**;98:2176-81.
15. Lohse N, Hansen AB, Pedersen G, et al. Survival of persons with and without HIV infection in Denmark, 1995-2005. Ann Intern Med **2007**;146:87-95.
16. Selik RM, Byers RH, Jr. and Dworkin MS. Trends in diseases reported on U.S. death certificates that mentioned HIV infection, 1987-1999. J Acquir Immune Defic Syndr **2002**;29:378-87.
17. Serpaggi J, Chaix ML, Batisse D, et al. Sexually transmitted acute infection with a clustered genotype 4 hepatitis C virus in HIV-1-infected men and inefficacy of early antiviral therapy. AIDS **2006**;20:233-40.
18. Gotz HM, van Doornum G, Niesters HG, den Hollander JG, Thio HB and de Zwart O. A cluster of acute hepatitis C virus infection among men who have sex with men--results from contact tracing and public health implications. AIDS **2005**;19:969-74.
19. Gambotti L, Batisse D, Colin-de-Verdiere N, et al. Acute hepatitis C infection in HIV positive men who have sex with men in Paris, France, 2001-2004. Euro Surveill **2005**;10:115-7.
20. McKiernan SM, Hagan R, Curry M, et al. Distinct MHC class I and II alleles are associated with hepatitis C viral clearance, originating from a single source. Hepatology **2004**;40:108-14.
21. Thomas DL, Astemborski J, Rai RM, et al. The natural history of hepatitis C virus infection: host, viral, and environmental factors. JAMA **2000**;284:450-6.
22. Gilleece YC, Browne RE, Asboe D, et al. Transmission of hepatitis C virus among HIV-positive homosexual men and response to a 24-week course of pegylated interferon and ribavirin. J Acquir Immune Defic Syndr **2005**;40:41-6.
23. Chamie G, Bonacini M, Bangsberg DR, et al. Factors Associated with Seronegative Chronic Hepatitis C Virus Infection in HIV Infection. Clin Infect Dis **2007**;44:577-83.
24. Berggren R, Jain MK, Hester J, Vinson G, Dawson B and Keiser P. False-Negative Hepatitis C Antibody Is Associated with Low CD4 Cell Counts in HIV/HCV-Coinfected Patients [abstract]. In: 8th Conference on Retroviruses and Opportunisitic Infections. Chicago,IL **2001.**
25. Bonacini M, Govindarajan S, Blatt LM, Schmid P, Conrad A and Lindsay KL. Patients co-infected with human immunodeficiency virus and hepatitis C virus demonstrate higher levels of hepatic HCV RNA. J Viral Hepat **1999**;6:203-8.
26. Beld M, Penning M, Lukashov V, et al. Evidence that both HIV and HIV-induced immunodeficiency enhance HCV replication among HCV seroconverters. Virology **1998**;244:504-12.
27. Cribier B, Rey D, Schmitt C, Lang JM, Kirn A and Stoll-Keller F. High hepatitis C viraemia and impaired antibody response in patients coinfected with HIV. AIDS **1995**;9:1131-6.

28. Simmonds P. Variation in HIV virus load of individuals at different stages in infection: possible relationship with risk of transmission. AIDS **1990**;4 Suppl 1:S77-83.
29. Sherman KE. Implications of peginterferon use in special populations infected with HCV. Semin Liver Dis **2003**;23 Suppl 1:47-52.
30. Telfer PT, Brown D, Devereux H, Lee CA and DuSheiko GM. HCV RNA levels and HIV infection: evidence for a viral interaction in haemophilic patients. Br J Haematol **1994**;88:397-9.
31. Thomas DL, Shih JW, Alter HJ, et al. Effect of human immunodeficiency virus on hepatitis C virus infection among injecting drug users. J Infect Dis **1996**;174:690-5.
32. Eyster ME, Fried MW, Di Bisceglie AM and Goedert JJ. Increasing hepatitis C virus RNA levels in hemophiliacs: relationship to human immunodeficiency virus infection and liver disease. Multicenter Hemophilia Cohort Study. Blood **1994**;84:1020-3.
33. Soto B, Sanchez-Quijano A, Rodrigo L, et al. Human immunodeficiency virus infection modifies the natural history of chronic parenterally-acquired hepatitis C with an unusually rapid progression to cirrhosis. J Hepatol **1997**;26:1-5.
34. Ghany MG, Leissinger C, Lagier R, Sanchez-Pescador R and Lok AS. Effect of human immunodeficiency virus infection on hepatitis C virus infection in hemophiliacs. Dig Dis Sci **1996**;41:1265-72.
35. Ranieri R, Santambrogio C, Veronelli A and Pontiroli AE. Hepatitis C viremia persistently suppressed by HAART. Clin Infect Dis **2003**;36:1086-7.
36. De Rosa FG, Audagnotto S, Bargiacchi O, et al. Resolution of HCV infection after highly active antiretroviral therapy in a HIV-HCV coinfected patient. J Infect **2006**;53:e215-8.
37. Chung RT, Evans SR, Yang Y, et al. 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.
38. Matsiota-Bernard P, Vrioni G, Onody C, Bernard L, de Truchis P and Peronne C. Human immunodeficiency virus (HIV) protease inhibitors have no effect on hepatitis C virus (HCV) serum levels of HIV-HCV co-infected patients. Int J Antimicrob Agents **2001**;17:155-7.
39. Puoti M, Gargiulo F, Roldan EQ, 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.
40. Ragni MV, Bontempo FA. Increase in hepatitis C virus load in hemophiliacs during treatment with highly active antiretroviral therapy. J Infect Dis **1999**;180:2027-9.
41. Bower WA, Culver DH, Castor D, et al. Changes in hepatitis C virus (HCV) viral load and interferon-alpha levels in HIV/HCV-coinfected patients treated with highly active antiretroviral therapy. J Acquir Immune Defic Syndr **2006**;42:293-7.
42. Rutschmann OT, Negro F, Hirschel B, Hadengue A, Anwar D and 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.
43. Tedaldi EM, Chen L, Markowitz N, Kelly L and Abrams D. Effect of IL-2 on hepatitis C virus RNA levels in patients co-infected with human immunodeficiency virus receiving HAART. J Viral Hepat **2005**;12:414-20.
44. Torre D, Tambini R, Cadario F, Barbarini G, Moroni M and Basilico C. Evolution of coinfection with human immunodeficiency virus and hepatitis C virus in patients treated with highly active antiretroviral therapy. Clin Infect Dis **2001**;33:1579-85.
45. Zylberberg H, Chaix ML, Rabian C, et al. Tritherapy for human immunodeficiency virus infection does not modify replication of hepatitis C virus in coinfected subjects. Clin Infect Dis **1998**;26:1104-6.
46. Bonacini M, Puoti M. Hepatitis C in patients with human immunodeficiency virus infection: diagnosis, natural history, meta-analysis of sexual and vertical transmission, and therapeutic issues. Arch Intern Med **2000**;160:3365-73.
47. Benhamou Y, Bochet M, Di Martino V, et al. Liver fibrosis progression in human immunodeficiency virus and hepatitis C virus coinfected patients. The Multivirc Group. Hepatology **1999**;30:1054-8.
48. Puoti M, Bonacini M, Spinetti A, et al. Liver fibrosis progression is related to CD4 cell depletion in patients coinfected with hepatitis C virus and human immunodeficiency virus. J Infect Dis **2001**;183:134-7.
49. Allory Y, Charlotte F, Benhamou Y, Opolon P, Le Charpentier Y and Poynard T. Impact of human immunodeficiency virus infection on the histological features of chronic hepatitis C: a case-control study. The MULTIVIRC group. Hum Pathol **2000**;31:69-74.
50. Pol S, Lamorthe B, Thi NT, et al. Retrospective analysis of the impact of HIV infection and alcohol use on chronic hepatitis C in a large cohort of drug users. J Hepatol **1998**;28:945-50.
51. Ragni MV, Belle SH. Impact of human immunodeficiency virus infection on progression to end-stage liver disease in individuals with hemophilia and hepatitis C virus infection. J Infect Dis **2001**;183:1112-5.
52. Eyster ME, Diamondstone LS, Lien JM, Ehmann WC, Quan S and Goedert JJ. Natural history of hepatitis C virus infection in multitransfused hemophiliacs: effect of coinfection with human immunodeficiency virus. The Multicenter Hemophilia Cohort Study. J Acquir Immune Defic Syndr **1993**;6:602-10.

53. Rockstroh JK. Influence of viral hepatitis on HIV infection. J Hepatol **2006**;44:S25-7.
54. Lesens O, Deschenes M, Steben M, Belanger G and Tsoukas CM. Hepatitis C virus is related to progressive liver disease in human immunodeficiency virus-positive hemophiliacs and should be treated as an opportunistic infection. J Infect Dis **1999**;179:1254-8.
55. Graham CS, Baden LR, Yu E, et al. Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: a meta-analysis. Clin Infect Dis **2001**;33:562-9.
56. Garcia-Samaniego J, Rodriguez M, Berenguer J, et al. Hepatocellular carcinoma in HIV-infected patients with chronic hepatitis C. Am J Gastroenterol **2001**;96:179-83.
57. Puoti M, Bruno R, Soriano V, et al. Hepatocellular carcinoma in HIV-infected patients: epidemiological features, clinical presentation and outcome. AIDS **2004**;18:2285-93.
58. Brau N, R.K. F, Marks KM, et al. Hepatocellular Carcinoma (HCC) in HIV-infected vs. Uninfected Patients and the Influence of HIV Viral Load on Survival. Final Results of a U.S.-Canadian Multicenter Study [abstract]. Hepatology **2006**;44:499A.
59. Bica I, McGovern B, Dhar R, et al. Increasing mortality due to end-stage liver disease in patients with human immunodeficiency virus infection. Clin Infect Dis **2001**;32:492-7.
60. Monga HK, Rodriguez-Barradas MC, Breaux K, et al. Hepatitis C virus infection-related morbidity and mortality among patients with human immunodeficiency virus infection. Clin Infect Dis **2001**;33:240-7.
61. Darby SC, Ewart DW, Giangrande PL, et al. Mortality from liver cancer and liver disease in haemophilic men and boys in UK given blood products contaminated with hepatitis C. UK Haemophilia Centre Directors' Organisation. Lancet **1997**;350:1425-31.
62. Rosenthal E, Poiree M, Pradier C, et al. Mortality due to hepatitis C-related liver disease in HIV-infected patients in France (Mortavic 2001 study). AIDS **2003**;17:1803-9.
63. Mocroft A, Soriano V, Rockstroh J, et al. Is there evidence for an increase in the death rate from liver-related disease in patients with HIV? AIDS **2005**;19:2117-25.
64. Jain MK, Skiest DJ, Cloud JW, Jain CL, Burns D and Berggren RE. Changes in mortality related to human immunodeficiency virus infection: comparative analysis of inpatient deaths in 1995 and in 1999-2000. Clin Infect Dis **2003**;36:1030-8.
65. Qurishi N, Kreuzberg C, Luchters G, et al. Effect of antiretroviral therapy on liver-related mortality in patients with HIV and hepatitis C virus coinfection. Lancet **2003**;362:1708-13.
66. Tedaldi EM, Baker RK, Moorman AC, et al. Influence of coinfection with hepatitis C virus on morbidity and mortality due to human immunodeficiency virus infection in the era of highly active antiretroviral therapy. Clin Infect Dis **2003**;36:363-7.
67. Merchante N, Giron-Gonzalez JA, Gonzalez-Serrano M, et al. Survival and prognostic factors of HIV-infected patients with HCV-related end-stage liver disease. AIDS **2006**;20:49-57.
68. Weber R, Sabin CA, Friis-Moller N, et al. Liver-related deaths in persons infected with the human immunodeficiency virus: the D:A:D study. Arch Intern Med **2006**;166:1632-41.
69. Brau N, Salvatore M, Rios-Bedoya CF, et al. Slower fibrosis progression in HIV/HCV-coinfected patients with successful HIV suppression using antiretroviral therapy. J Hepatol **2006**;44:47-55.
70. Martin-Carbonero L, Benhamou Y, Puoti M, et al. Incidence and predictors of severe liver fibrosis in human immunodeficiency virus-infected patients with chronic hepatitis C: a European collaborative study. Clin Infect Dis **2004**;38:128-33.
71. Mehta SH, Thomas DL, Torbenson M, et al. The effect of antiretroviral therapy on liver disease among adults with HIV and hepatitis C coinfection. Hepatology **2005**;41:123-31.
72. Aranzabal L, Casado JL, Moya J, 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.
73. Piroth L, Duong M, Quantin C, et al. Does hepatitis C virus co-infection accelerate clinical and immunological evolution of HIV-infected patients? AIDS **1998**;12:381-8.
74. Dorrucci M, Pezzotti P, Phillips AN, Lepri AC and Rezza G. Coinfection of hepatitis C virus with human immunodeficiency virus and progression to AIDS. Italian Seroconversion Study. J Infect Dis **1995**;172:1503-8.
75. Sulkowski MS, Moore RD, Mehta SH, Chaisson RE and Thomas DL. Hepatitis C and progression of HIV disease. JAMA **2002**;288:199-206.
76. De Luca A, Bugarini R, Lepri AC, et al. Coinfection with hepatitis viruses and outcome of initial antiretroviral regimens in previously naive HIV-infected subjects. Arch Intern Med **2002**;162:2125-32.
77. Greub G, Ledergerber B, Battegay M, et al. Clinical progression, survival, and immune recovery during antiretroviral therapy in patients with HIV-1 and hepatitis C virus coinfection: the Swiss HIV Cohort Study. Lancet **2000**;356:1800-5.

78. Macias J, Pineda JA, Lozano F, et al. Impaired recovery of CD4+ cell counts following highly active antiretroviral therapy in drug-naive patients coinfected with human immunodeficiency virus and hepatitis C virus. Eur J Clin Microbiol Infect Dis **2003**;22:675-80.
79. Rancinan C, Neau D, Saves M, et al. Is hepatitis C virus co-infection associated with survival in HIV-infected patients treated by combination antiretroviral therapy? AIDS **2002**;16:1357-62.
80. Rockstroh JK, Mocroft A, Soriano V, et al. Influence of hepatitis C virus infection on HIV-1 disease progression and response to highly active antiretroviral therapy. J Infect Dis **2005**;192:992-1002.
81. Miller MF, Haley C, Koziel MJ and Rowley CF. Impact of hepatitis C virus on immune restoration in HIV-infected patients who start highly active antiretroviral therapy: a meta-analysis. Clin Infect Dis **2005**;41:713-20.
82. Klein MB, Lalonde RG and Suissa S. The impact of hepatitis C virus coinfection on HIV progression before and after highly active antiretroviral therapy. J Acquir Immune Defic Syndr **2003**;33:365-72.
83. McGovern BH, Golan Y, Lopez M, et al. The impact of cirrhosis on CD4+ T cell counts in HIV-seronegative patients. Clin Infect Dis **2007**;44:431-7.
84. Torriani FJ, Rodriguez-Torres M, Rockstroh JK, et al. Peginterferon Alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients. N Engl J Med **2004**;351:438-50.
85. Chung RT, Andersen J, Volberding P, et al. Peginterferon Alfa-2a plus ribavirin versus interferon alfa-2a plus ribavirin for chronic hepatitis C in HIV-coinfected persons. N Engl J Med **2004**;351:451-9.
86. Carrat F, Bani-Sadr F, Pol S, et al. Pegylated interferon alfa-2b vs standard interferon alfa-2b, plus ribavirin, for chronic hepatitis C in HIV-infected patients: a randomized controlled trial. JAMA **2004**;292:2839-48.
87. Alvarez D, Dieterich DT, Brau N, Moorehead L, Ball L and Sulkowski MS. Zidovudine use but not weight-based ribavirin dosing impacts anaemia during HCV treatment in HIV-infected persons. J Viral Hepat **2006**;13:683-9.
88. Fung J, Eghtesad B, Patel-Tom K, DeVera M, Chapman H and Ragni M. Liver transplantation in patients with HIV infection. Liver Transpl **2004**;10:S39-53.
89. Roland ME, Stock PG. Review of solid-organ transplantation in HIV-infected patients. Transplantation **2003**;75:425-9.
90. Terrault NA, Carter JT, Carlson L, Roland ME and Stock PG. Outcome of patients with hepatitis B virus and human immunodeficiency virus infections referred for liver transplantation. Liver Transpl **2006**;12:801-7.
91. Bouscarat F, Samuel D, Simon F, Debat P, Bismuth H and Saimot AG. An observational study of 11 French liver transplant recipients infected with human immunodeficiency virus type 1. Clin Infect Dis **1994**;19:854-9.
92. Bertoletti A, Ferrari C. Kinetics of the immune response during HBV and HCV infection. Hepatology **2003**;38:4-13.
93. Rehermann B. Immune responses in hepatitis B virus infection. Semin Liver Dis **2003**;23:21-38.
94. Goldstein ST, Alter MJ, Williams IT, et al. Incidence and risk factors for acute hepatitis B in the United States, 1982-1998: implications for vaccination programs. J Infect Dis **2002**;185:713-9.
95. Incidence of acute hepatitis B--United States, 1990-2002. MMWR Morb Mortal Wkly Rep **2004**;52:1252-4.
96. Wolitski RJ, Valdiserri RO, Denning PH and Levine WC. Are we headed for a resurgence of the HIV epidemic among men who have sex with men? Am J Public Health **2001**;91:883-8.
97. Primary and secondary syphilis among men who have sex with men--New York City, 2001. MMWR Morb Mortal Wkly Rep **2002**;51:853-6.
98. Jain MK, Comanor L, White C, et al. Treatment of hepatitis B with lamivudine and tenofovir in HIV/HBV-coinfected patients: factors associated with response. Journal of Viral Hepatitis (OnlineEarly Articles) **2006**. (in press).
99. Kato H, Orito E, Gish RG, et al. Hepatitis B e antigen in sera from individuals infected with hepatitis B virus of genotype G. Hepatology **2002**;35:922-9.
100. Soriano V, Puoti M, Bonacini M, et al. Care of patients with chronic hepatitis B and HIV co-infection: recommendations from an HIV-HBV International Panel. AIDS **2005**;19:221-40.
101. Bodsworth NJ, Cooper DA and Donovan B. The influence of human immunodeficiency virus type 1 infection on the development of the hepatitis B virus carrier state. J Infect Dis **1991**;163:1138-40.
102. Arendrup M, Lindhardt BO, Krogsgaard K, Gaub J and Nielsen JO. Antibody to HIV in patients with acute hepatitis B in the period 1975-1984. Scand J Infect Dis **1987**;19:167-72.
103. Gilson RJ, Hawkins AE, Beecham MR, et al. Interactions between HIV and hepatitis B virus in homosexual men: effects on the natural history of infection. AIDS **1997**;11:597-606.
104. Colin JF, Cazals-Hatem D, Loriot MA, et al. Influence of human immunodeficiency virus infection on chronic hepatitis B in homosexual men. Hepatology **1999**;29:1306-10.
105. Scharschmidt BF, Held MJ, Hollander HH, et al. Hepatitis B in patients with HIV infection: relationship to AIDS and patient survival. Ann Intern Med **1992**;117:837-8.
106. Goldin RD, Fish DE, Hay A, et al. Histological and immunohistochemical study of hepatitis B virus in human immunodeficiency virus infection. J Clin Pathol **1990**;43:203-5.

107. Rustgi VK, Hoofnagle JH, Gerin JL, et al. Hepatitis B virus infection in the acquired immunodeficiency syndrome. Ann Intern Med **1984**;101:795-7.
108. Thio CL, Seaberg EC, Skolasky R, Jr., et al. HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS). Lancet **2002**;360:1921-6.
109. Puoti M, Spinetti A, Ghezzi A, et al. Mortality for liver disease in patients with HIV infection: a cohort study. J Acquir Immune Defic Syndr **2000**;24:211-7.
110. Salmon-Ceron D, Lewden C, Morlat P, et al. 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.
111. Bessesen M, Ives D, Condreay L, Lawrence S and Sherman KE. Chronic active hepatitis B exacerbations in human immunodeficiency virus-infected patients following development of resistance to or withdrawal of lamivudine. Clin Infect Dis **1999**;28:1032-5.
112. Dore GJ, Cooper DA, Barrett C, Goh LE, Thakrar B and Atkins M. Dual efficacy of lamivudine treatment in human immunodeficiency virus/hepatitis B virus-coinfected persons in a randomized, controlled study (CAESAR). The CAESAR Coordinating Committee. J Infect Dis **1999**;180:607-13.
113. Hoff J, Bani-Sadr F, Gassin M and Raffi F. Evaluation of chronic hepatitis B virus (HBV) infection in coinfected patients receiving lamivudine as a component of anti-human immunodeficiency virus regimens. Clin Infect Dis **2001**;32:963-9.
114. Benhamou Y, Bochet M, Thibault V, et al. Long-term incidence of hepatitis B virus resistance to lamivudine in human immunodeficiency virus-infected patients. Hepatology **1999**;30:1302-6.
115. Lai CL, Chien RN, Leung NW, et al. A one-year trial of lamivudine for chronic hepatitis B. Asia Hepatitis Lamivudine Study Group. N Engl J Med **1998**;339:61-8.
116. Seta T, Yokosuka O, Imazeki F, Tagawa M and Saisho H. Emergence of YMDD motif mutants of hepatitis B virus during lamivudine treatment of immunocompetent type B hepatitis patients. J Med Virol **2000**;60:8-16.
117. Dienstag JL, Schiff ER, Mitchell M, et al. Extended lamivudine retreatment for chronic hepatitis B: maintenance of viral suppression after discontinuation of therapy. Hepatology **1999**;30:1082-7.
118. Wolters LM, Niesters HG, Hansen BE, et al. Development of hepatitis B virus resistance for lamivudine in chronic hepatitis B patients co-infected with the human immunodeficiency virus in a Dutch cohort. J Clin Virol **2002**;24:173-81.
119. Pillay D, Cane PA, Ratcliffe D, Atkins M and Cooper D. Evolution of lamivudine-resistant hepatitis B virus and HIV-1 in co-infected individuals: an analysis of the CAESAR study. CAESAR co-ordinating committee. AIDS **2000**;14:1111-6.
120. Squires K, Pozniak AL, Pierone G, Jr., et al. Tenofovir disoproxil fumarate in nucleoside-resistant HIV-1 infection: a randomized trial. Ann Intern Med **2003**;139:313-20.
121. Nunez M, Perez-Olmeda M, Diaz B, Rios P, Gonzalez-Lahoz J and Soriano V. Activity of tenofovir on hepatitis B virus replication in HIV-co-infected patients failing or partially responding to lamivudine. AIDS **2002**;16:2352-4.
122. Benhamou Y, Tubiana R and Thibault V. Tenofovir disoproxil fumarate in patients with HIV and lamivudine-resistant hepatitis B virus. N Engl J Med **2003**;348:177-8.
123. Ristig MB, Crippin J, Aberg JA, et al. Tenofovir disoproxil fumarate therapy for chronic hepatitis B in human immunodeficiency virus/hepatitis B virus-coinfected individuals for whom interferon-alpha and lamivudine therapy have failed. J Infect Dis **2002**;186:1844-7.
124. Lacombe K, Gozlan J, Boelle PY, et al. Long-term hepatitis B virus dynamics in HIV-hepatitis B virus-co-infected patients treated with tenofovir disoproxil fumarate. AIDS **2005**;19:907-15.
125. Nelson M, Portsmouth S, Stebbing J, et al. An open-label study of tenofovir in HIV-1 and Hepatitis B virus co-infected individuals. AIDS **2003**;17:F7-10.
126. Sheldon J, Camino N, Rodes B, et al. Selection of hepatitis B virus polymerase mutations in HIV-coinfected patients treated with tenofovir. Antivir Ther **2005**;10:727-34.
127. Wang LH, Begley J, St Claire RL, 3rd, Harris J, Wakeford C and Rousseau FS. Pharmacokinetic and pharmacodynamic characteristics of emtricitabine support its once daily dosing for the treatment of HIV infection. AIDS Res Hum Retroviruses **2004**;20:1173-82.
128. Gish RG, Leung NW, Wright TL, et al. Dose range study of pharmacokinetics, safety, and preliminary antiviral activity of emtricitabine in adults with hepatitis B virus infection. Antimicrob Agents Chemother **2002**;46:1734-40.
129. Lim SG, Ng TM, Kung N, et al. A double-blind placebo-controlled study of emtricitabine in chronic hepatitis B. Arch Intern Med **2006**;166:49-56.
130. Gish RG, Trinh H, Leung N, et al. Safety and antiviral activity of emtricitabine (FTC) for the treatment of chronic hepatitis B infection: a two-year study. J Hepatol **2005**;43:60-6.
131. Proia LA, Ngui SL, Kaur S, Kessler HA and Trenholme GM. Reactivation of hepatitis B in patients with human immunodeficiency virus infection treated with combination antiretroviral therapy. Am J Med **2000**;108:249-51.

132. Carr A, Cooper DA. Restoration of immunity to chronic hepatitis B infection in HIV-infected patient on protease inhibitor. Lancet **1997**;349:995-6.
133. Reisler RB, Han C, Burman WJ, Tedaldi EM and Neaton JD. Grade 4 events are as important as AIDS events in the era of HAART. J Acquir Immune Defic Syndr **2003**;34:379-86.
134. Lewden C, Raffi F, Cuzin L, et al. Factors associated with mortality in human immunodeficiency virus type 1-infected adults initiating protease inhibitor-containing therapy: role of education level and of early transaminase level elevation (APROCO-ANRS EP11 study). The Antiproteases Cohorte Agence Nationale de Recherches sur le SIDA EP 11 study. J Infect Dis **2002**;186:710-4.
135. Perrillo RP. Acute flares in chronic hepatitis B: the natural and unnatural history of an immunologically mediated liver disease. Gastroenterology **2001**;120:1009-22.
136. Jain MK, Parekh NK, Hester J and 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.
137. Lederman MM, Connick E, Landay A, et al. Immunologic responses associated with 12 weeks of combination antiretroviral therapy consisting of zidovudine, lamivudine, and ritonavir: results of AIDS Clinical Trials Group Protocol 315. J Infect Dis **1998**;178:70-9.
138. Shimada N, Yamamoto K, Kuroda MJ, et al. HBcAg-specific CD8 T cells play an important role in virus suppression, and acute flare-up is associated with the expansion of activated memory T cells. J Clin Immunol **2003**;23:223-32.
139. Mommeja-Marin H, Mondou E, Blum MR and Rousseau F. Serum HBV DNA as a marker of efficacy during therapy for chronic HBV infection: analysis and review of the literature. Hepatology **2003**;37:1309-19.
140. Liaw YF. Treatment of chronic hepatitis B virus infection: who, when, what for and how. J Gastroenterol Hepatol **2000**;15 Suppl:E31-3.
141. Lok AS, McMahon BJ. Chronic hepatitis B. Hepatology **2001**;34:1225-41.
142. Lau GK, Carman WF, Locarnini SA, et al. Treatment of chronic hepatitis B virus infection: an Asia-Pacific perspective. J Gastroenterol Hepatol **1999**;14:3-12.
143. Lok AS, McMahon BJ. Chronic hepatitis B: update of recommendations. Hepatology **2004**;39:857-61.
144. Fauci AS, Bartlett JG. Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents: Panel on Clinical Practices for Treatment of HIV Infection convened by the Department of Health and Human Services (DHHS) and the Henry J.Kaiser Family Foundation, **1999.** Available at :hhtp://*AIDSinfo*.nih.gov. Accessed 28 November 2006.
145. Bartlett JG, Lane HC. Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents: Department of Health and Human Services (DHHS) Panel on Antiretroviral Guidelines for Adults and Adolescents (a Working Group of the Office of AIDS Reserach Advisory Council, **2006.** Available at :hhtp://*AIDSinfo*.nih.gov. Accessed 26 June 2006.
146. Jain MK, Osuagwu C, Opio C, Pillai R, Keiser P and Lee WM. HIV Providers Neglect to Monitor for Hepatitis B Therapy Responses in HIV/HBV Patients Treated with HAART [abstract]. In: 13th Conference on Retroviruses and Opportunistic Infections. Denver, CO, **2006.**
147. Palmon R, Koo BC, Shoultz DA and Dieterich DT. Lack of hepatotoxicity associated with nonnucleoside reverse transcriptase inhibitors. J Acquir Immune Defic Syndr **2002**;29:340-5.
148. Hernandez LV, Gilson I, Jacobson J, Affi A, Puetz TR and Dindzans VJ. Antiretroviral hepatotoxicity in human immunodeficiency virus-infected patients. Aliment Pharmacol Ther **2001**;15:1627-32.
149. Bonfanti P, Landonio S, Ricci E, et al. Risk factors for hepatotoxicity in patients treated with highly active antiretroviral therapy. J Acquir Immune Defic Syndr **2001**;27:316-8.
150. Torti C, Lapadula G, Casari S, et al. 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.
151. Sulkowski MS, Thomas DL, Chaisson RE and 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.
152. den Brinker M, Wit FW, Wertheim-van Dillen PM, 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.
153. French AL, Benning L, Anastos K, et al. Longitudinal effect of antiretroviral therapy on markers of hepatic toxicity: impact of hepatitis C coinfection. Clin Infect Dis **2004**;39:402-10.
154. Kramer JR, Giordano TP, Souchek J and El-Serag HB. Hepatitis C coinfection increases the risk of fulminant hepatic failure in patients with HIV in the HAART era. J Hepatol **2005**;42:309-14.
155. Sulkowski MS, Thomas DL, Mehta SH, Chaisson RE and Moore RD. Hepatotoxicity associated with nevirapine or efavirenz-containing antiretroviral therapy: role of hepatitis C and B infections. Hepatology **2002**;35:182-9.

156. Aceti A, Pasquazzi C, Zechini B and De Bac C. 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.
157. De Maat MM, Mathot RA, Veldkamp AI, et al. Hepatotoxicity following nevirapine-containing regimens in HIV-1-infected individuals. Pharmacol Res **2002**;46:295-300.
158. Ena J, Amador C, Benito C, Fenoll V and Pasquau F. Risk and determinants of developing severe liver toxicity during therapy with nevirapine-and efavirenz-containing regimens in HIV-infected patients. Int J STD AIDS **2003**;14:776-81.
159. Monforte Ade A, Bugarini R, Pezzotti P, et al. 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.
160. Nunez M, Lana R, Mendoza JL, Martin-Carbonero L and Soriano V. Risk factors for severe hepatic injury after introduction of highly active antiretroviral therapy. J Acquir Immune Defic Syndr **2001**;27:426-31.
161. Saves M, Vandentorren S, Daucourt V, et al. Severe hepatic cytolysis: incidence and risk factors in patients treated by antiretroviral combinations. Aquitaine Cohort, France, 1996-1998. Groupe dEpidemiologie Clinique de Sida en Aquitaine (GECSA). AIDS **1999**;13:F115-21.
162. Saves M, Raffi F, Clevenbergh P, et al. Hepatitis B or hepatitis 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. The APROCO Study Group. Antimicrob Agents Chemother **2000**;44:3451-5.
163. Servoss JC, Kitch DW, Andersen JW, Reisler RB, Chung RT and 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.
164. Wit FW, Weverling GJ, Weel J, Jurriaans S and Lange JM. Incidence of and risk factors for severe hepatotoxicity associated with antiretroviral combination therapy. J Infect Dis **2002**;186:23-31.
165. Puoti M, Torti C, Ripamonti D, et al. Severe hepatotoxicity during combination antiretroviral treatment: incidence, liver histology, and outcome. J Acquir Immune Defic Syndr **2003**;32:259-67.
166. Hammer SM, Squires KE, Hughes MD, 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.
167. Gulick RM, Mellors JW, Havlir D, et al. Treatment with indinavir, zidovudine, and lamivudine in adults with human immunodeficiency virus infection and prior antiretroviral therapy. N Engl J Med **1997**;337:734-9.
168. Cooper CL, Parbhakar MA and 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.
169. Bonfanti P, Ricci E, Penco G, et al. Low incidence of hepatotoxicity in a cohort of HIV patients treated with lopinavir/ritonavir. AIDS **2005**;19:1433-4.
170. Sherman KE, Shire NJ, Cernohous P, et al. 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.
171. Sulkowski MS, Mehta SH, Chaisson RE, Thomas DL and Moore RD. Hepatotoxicity associated with protease inhibitor-based antiretroviral regimens with or without concurrent ritonavir. AIDS **2004**;18:2277-84.
172. Tipranavir (Aptivus)[package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, **2006**
173. Darunavir (Prezista) [package insert]. Gurabo, Puerto Rico: Tibotec, Inc, **2006**
174. Lyons F, Hopkins S, Kelleher B, et al. Maternal hepatotoxicity with nevirapine as part of combination antiretroviral therapy in pregnancy. HIV Med **2006**;7:255-60.
175. Serious adverse events attributed to nevirapine regimens for postexposure prophylaxis after HIV exposures--worldwide, 1997-2000. MMWR Morb Mortal Wkly Rep **2001**;49:1153-6.
176. Benn PD, Mercey DE, Brink N, Scott G and Williams IG. Prophylaxis with a nevirapine-containing triple regimen after exposure to HIV-1. Lancet **2001**;357:687-8.
177. Bissell DM, Gores GJ, Laskin DL and Hoofnagle JH. Drug-induced liver injury: mechanisms and test systems. Hepatology **2001**;33:1009-13.
178. Rodriguez-Novoa S, Martin-Carbonero L, Barreiro P, et al. Genetic factors influencing atazanavir plasma concentrations and the risk of severe hyperbilirubinemia. AIDS **2007**;21:41-6.
179. Sanne I, Mommeja-Marin H, Hinkle J, et al. Severe hepatotoxicity associated with nevirapine use in HIV-infected subjects. J Infect Dis **2005**;191:825-9.
180. Martin AM, Nolan D, James I, et al. Predisposition to nevirapine hypersensitivity associated with HLA-DRB1*0101 and abrogated by low CD4 T-cell counts. AIDS **2005**;19:97-9.
181. Mallal S, Nolan D, Witt C, et al. Association between presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir. Lancet **2002**;359:727-32.

182. Gavazzi G, Bouchard O, Leclercq P, 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**;16:1021-3.
183. John M, Flexman J and 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.
184. Vento S, Garofano T, Renzini C, Casali F, Ferraro T and Concia E. Enhancement of hepatitis C virus replication and liver damage in HIV-coinfected patients on antiretroviral combination therapy. AIDS **1998**;12:116-7.
185. Stone SF, Lee S, Keane NM, Price P and 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.
186. Coghlan ME, Sommadossi JP, Jhala NC, Many WJ, Saag MS and Johnson VA. Symptomatic lactic acidosis in hospitalized antiretroviral-treated patients with human immunodeficiency virus infection: a report of 12 cases. Clin Infect Dis **2001**;33:1914-21.
187. Gerard Y, Viget N, Yazdanpanah Y, et al. Hyperlactataemia during antiretroviral therapy: incidences, clinical data and treatment. Therapie **2003**;58:153-8.
188. Miller KD, Cameron M, Wood LV, Dalakas MC and Kovacs JA. Lactic acidosis and hepatic steatosis associated with use of stavudine: report of four cases. Ann Intern Med **2000**;133:192-6.
189. Mokrzycki MH, Harris C, May H, Laut J and Palmisano J. Lactic acidosis associated with stavudine administration: a report of five cases. Clin Infect Dis **2000**;30:198-200.
190. Ogedegbe AO, Sulkowski MS. Antiretroviral-associated liver injury. Clin Liver Dis **2003**;7:475-99.
191. Carr A, Morey A, Mallon P, Williams D and Thorburn DR. Fatal portal hypertension, liver failure, and mitochondrial dysfunction after HIV-1 nucleoside analogue-induced hepatitis and lactic acidaemia. Lancet **2001**;357:1412-4.
192. Marks KM, Petrovic LM, Talal AH, Murray MP, Gulick RM and Glesby MJ. Histological findings and clinical characteristics associated with hepatic steatosis in patients coinfected with HIV and hepatitis C virus. J Infect Dis **2005**;192:1943-9.
193. McGovern BH, Ditelberg JS, Taylor LE, et al. Hepatic steatosis is associated with fibrosis, nucleoside analogue use, and hepatitis C virus genotype 3 infection in HIV-seropositive patients. Clin Infect Dis **2006**;43:365-72.
194. Sulkowski MS, Mehta SH, Torbenson M, et al. Hepatic steatosis and antiretroviral drug use among adults coinfected with HIV and hepatitis C virus. AIDS **2005**;19:585-92.
195. Bani-Sadr F, Carrat F, Bedossa P, et al. Hepatic steatosis in HIV-HCV coinfected patients: analysis of risk factors. AIDS **2006**;20:525-31.
196. Kahraman A, Miller M, Gieseler RK, Gerken G, Scolaro MJ and Canbay A. Non-alcoholic fatty liver disease in HIV-positive patients predisposes for acute-on-chronic liver failure: two cases. Eur J Gastroenterol Hepatol **2006**;18:101-5.
197. Merriman RB. Nonalcoholic fatty liver disease and HIV infection. Curr HIV/AIDS Rep **2006**;3:113-7.
198. Gaslightwala I, Bini EJ. Impact of human immunodeficiency virus infection on the prevalence and severity of steatosis in patients with chronic hepatitis C virus infection. J Hepatol **2006**;44:1026-32.
199. Monto A, Dove LM, Bostrom A, Kakar S, Tien PC and Wright TL. Hepatic steatosis in HIV/hepatitis C coinfection: prevalence and significance compared with hepatitis C monoinfection. Hepatology **2005**;42:310-6.