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TLALELETSO

HIV & Hepatitis B

Hepatitis B Virus is the leading cause of liver disease worldwide and HIV infection is associated with increased risk of chronic hepatitis B after HBV exposure. In this issue we review the epidemiology, presentation and treatment of HBV/HIV co-infected patients

INTRODUCTION

The epidemics of hepatitis B and HIV have led to new understanding of the complicated interactions between these two viruses. Both are important health concerns in Botswana, especially given that chronic hepatitis B infection is frequently unrecognized by clinicians.

Co-infection with HIV has a major impact on the natural history, diagnosis, progression, and morbidity and mortality related to hepatitis B virus (HBV) infection. The presence of chronic hepatitis B can also lead to an increased risk of hepatotoxicity related to the administration of potent antiretroviral therapy (ART).

The epidemiology, clinical manifestations, and diagnosis of hepatitis B in the HIV-infected patient will be reviewed in this issue of Tlaleletso.

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Notes from the Editor….

Tlaleletso is a monthly publication produced by the Botswana UPenn Partnership, in response to your expressed need for accessible, digestible clinical information.

This issue of Tlaleletso looks at HBV/HIV co-infection and the clinical challenges associated with their management

DID YOU KNOW?

HBV was detected in a mummified body found in South Korea in 1985. The body was 500 years old. The earliest confirmed case of hepatitis B.

HBV & HIV - EPIDEMIOLOGY

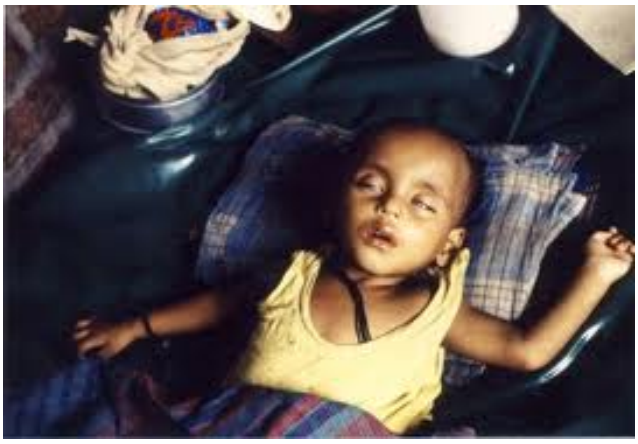
Hepatitis B infection represents a significant epidemiologic problem worldwide. Over 500 million people are infected and approximately 1 million people die from HBV related liver disease each year. Available data suggests that approximately 8% of the general population across southern Africa have been infected with the virus.

In Botswana recent research suggests that up to 58% of HIV-infected adults have been exposed to HBV (confirmed by hepatitis B core antibody test), while 10.6% of HIV infected adults demonstrated serologic evidence of chronic active HBV infection (confirmed by Hepatitis B surface antigen test)[1]. A study performed in the Baylor clinic recently reported that 5.6% of HIV-infected adults had evidence of chronic active hepatitis B co-infection[2].

Clinical Signs

When someone first becomes infected with the hepatitis B virus, they may develop jaundice, loss of appetite, pain in the abdomen, malaise, nausea, vomiting, fever, or muscle and joint aches. In some cases, people can develop a form of acute liver failure called fulminant hepatitis, which can be very serious or even fatal. However, many people do not notice any symptoms at all when they become infected. In fact, most infections in Africa happen in young children and infants and signs and symptoms are often very non-specific.

Active chronic hepatitis B virus infection may also cause ongoing or intermittent symptoms of hepatitis. However, it is often asymptomatic until the disease if well advanced.



Chronic Hepatitis

In some people, the hepatitis B virus continues to reproduce in the body long after initial infection. They are sometimes called 'chronic carriers', meaning that they are infectious for life, although they may not experience any symptoms themselves.

Approximately 90% of babies exposed to the hepatitis B virus before the age of one year become chronic carriers, compared to 20 to 50% of children aged one to five years at the time of exposure. In contrast, only 5 to 10% of HBV-infected adults go on to develop chronic infection, even though about half develop symptoms of acute infection. People co-infected with HIV are less likely to clear the hepatitis B virus without treatment.

Several factors affect progression to chronic liver inflammation, cirrhosis and liver cancer. These include the state of the immune system, gender, HIV co-infection, the age of the patient at time of infection, the stage of infection and other genetic and viral factors. Hepatitis B viral genotype C (found mostly in south-east Asia) has been associated with greater risk of liver inflammation, cirrhosis and liver cancer than genotype B.

HIV WORSENS HBV OUTCOMES

When an HIV negative adult is infected with HBV, the virus is eliminated in 95% of cases. However, HIV infected adults have 3-6 times increased risk of progressing to chronic hepatitis. Furthermore, there is a higher risk of HBV reactivation in HIV infected adults. Co-infected patients also have a significantly increased risk of liver fibrosis, cirrhosis and hepatocellular carcinoma. HIV-infected adults with chronic HBV infection are 17 times more likely to die than HIV negative HBV infected adults. Hepatocellular carcinoma also occurs at an earlier age among patients who are HIV-infected compared with HIV-seronegative patients.

In addition, HIV-associated immunosuppression has an adverse effect on HBV-related disease; in co-infected individuals, the risk of liver-related mortality and HCC increases as the CD4 cell count.

HBV: IMPACT ON HIV OUTCOMES?

Existing data does not suggest that HBV affects the course of HIV disease significantly. In one recent study, HBV had no impact on HIV viral suppression OR increases in CD4 counts after 6 to 12 months of HAART. In a study from Taiwan, co-infected patients had similar risks of new HIV related opportunistic illnesses, similar increases in CD4 counts after 6-12 months of HAART, and similar risk for virologic failure and death. A meta-analysis of all reported

DID YOU KNOW?
In 1883, in Germany, 15% of 1289 shipyard workers inoculated with a smallpox vaccine fell ill with jaundice. It is possible that they were infected by HBV

DIAGNOSING HBV

Blood tests can detect the presence of hepatitis B virus antigen and antibodies, which show whether an individual has been exposed to the virus. People who have successfully cleared the virus are left with antibodies against it. If fragments of the virus itself, called hepatitis B surface antigen (HBsAg), are found in the blood for more than six months, the person is a chronic carrier and capable of infecting others.

People with chronic infection are sometimes also positive for hepatitis B e antigen (HBeAg), which indicates that the virus is actively replicating. However, some people are infected by a mutant precore form of the virus known as HBeAg-negative that does not produce this antigen, and appears to be harder to treat. Some people with chronic hepatitis C may be co-infected with hepatitis B but lack detectable hepatitis B virus surface antigen. In addition, some HIV-positive people, especially if they also have hepatitis C, may not show either HBV surface antigen or surface antibodies, but may still have hepatitis B virus core antibodies, which the immune system produces to fight the virus. This is called an occult infection, and its clinical significance is not known.

There are also tests that measure hepatitis B virus's genetic material, or DNA, in the blood. These viral load tests may detect DNA even if antibodies and antigens are not detectable. These tests are used to tell how well anti-hepatitis B treatment is working. In a patient with confirmed chronic hepatitis B (defined as having a persistently elevated HBsAg) it is important to quantify HBV viral load and test for HBeAg. These tests can be ordered through Diagnofirm.

DIAGNOSIS (cont.d)

After a diagnosis of chronic infection, regular monitoring of the liver is also advised. Blood tests including liver function tests should be conducted at least every six to 12 months. Liver enzymes, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) can be measured to determine how well the liver is working. If a patient already has cirrhosis, a liver ultrasound should be conducted regularly to screen for signs of liver cancer. A liver biopsy may also be performed to determine the extent of liver damage.

HBV TREATMENT

The aim of treatment for hepatitis B is to reduce liver inflammation, lower hepatitis B viral load and, ideally, to eradicate the virus and produce antibodies. Determining a patient's HIV status is also important – since the threshold for intiaiting antiviral therapy is different if a patient is co-infected with HIV.

There are currently several treatments for chronic hepatitis B. These include pegylated interferon alfa 2a, conventional interferon alfa, adefovir and entecavir. However, several HIV drugs – including 3TC, FTC and TDF also have anti-HBV activity. Consequently in Botswana a combination of these drugs is used as first line therapy – the most combination is TDF and FTC (truvada).

TREATMENT FOR HIV-UNINFECTED ADULTS

Treatment for these patients should involve combining two or more drugs to treat hepatitis B. In Botswana, the drug of choice for treating HBV+/HIV- patients is truvada. Dr Haverkamp can manage these patients at the IDCC clinic at Princess Marina.

Dr Haverkamp recommends sending a HBV viral load and HB e antigen blood test, *in advance* of referring patients to her. HBV viral load level is useful in monitoring response to therapy (a 2 log decline in HBV viral load is expected after 6 months of therapy).

Several international expert committees recommend HBV treatment for all HBV+/HIV- patients with abnormal ALT values or HBV DNA levels >2000 IU/ml. If the patient's HBV viral load is less than 2000 IU/ml and the ALT is normal, a liver biopsy may be considered as those with no or limited evidence of cirrhosis may not require treatment.

TREATMENT FOR HIV-INFECTED ADULTS

WHO recommends that HIV/HBV co-infected individuals with evidence of active chronic hepatitis should be initiated on HBV and HIV treatment, regardless of CD4 count. For patients requiring antiretroviral therapy, the suggested first-line regimen is tenofovir plus 3TC or FTC, plus another anti-HIV drug. In Botswana it would be appropriate to prescribe atripla for patients with HBV co-infection.

Importantly, clinicians managing patients with HIV / hepatitis B virus co-infection who are taking or considering 3TC or FTC should be aware that HBV can quickly develop resistance to either of these drugs if they are given as HBV monotherapy. Furthermore, patients with chronic HBV are at risk of having a hepatitis flare if any of the HIV drugs that have anti-HBV activity are discontinued.

TREATMENT (cont.d)

One recent clinical trial found that around 20% of co-infected people who stopped 3TC experienced a rebound in hepatitis B viral load, and 2 to 4% had increased ALT and bilirubin levels, a sign of impaired liver function.

If a co-infected patient needs to switch from truvada for treatment of their HIV (ie, because of virological vailure), it may be necessary to continue a combination of antiretrovirals that ensures that they remain on two drugs with anti-HBV activity. If a patient cannot tolerate TDF, because of kidney disease, it is vital to determine the cause of the kidney disease and try and reverse it where possible. Patients with a creatinine clearance that is less than 40 ml/min should be referred to a Hepatitis/HIV specialist for further management.

DIFFERENTIAL DIAGNOSIS

There are many other causes of abnormal LFTs – a non-exhaustive list is included on the last page.

When evaluating any patient with abnormal LFTs, it is essential to take a complete history. Causes of hepatocellular injury (characterized by elevated aminotransferases +/- elevated alkaline phosphatase and bilurbin) include paracetamol, alcohol, ischemia, other viral infections, and inherited conditions such as Wilsons disease and hemochromatosis.

SEROLOGICAL EVIDENCE OF HBV

Test	Acute Hepatitis B	Immunity through Infection	Immunity through Vaccination	Chronic Hepatitis B	Healthy Carrier
HBsAg	+	--	--	+	+
Anti-HBs	--	+	+	--	--
HBeAg	+	--	--	+/--	--
Anti-HBe	--	+/--	--	+/--	+
Anti-HBc	+	+	--	+	+
IgM anti-HBc	+	--	--	--	--
HBV DNA	+	--	--	+	+ (low)
ALT	Elevated	Normal	Normal	Elevated	Normal

SUMMARY

Hepatitis B virus (HBV) infection and HIV are often diagnosed in the same patient because they share similar routes of transmission. HBV is a frequently unrecognized problem in HIV infected adults.

However, HIV/HBV co-infected patients have an increased risk of liver-related mortality compared with patients with HBV infection alone. It is important to consider HBV in any HIV-infected adult with abnormal LFTs.

Chronic HBV infection is an indication for initiating ART. Several of the drugs used to treat HIV have activity against HBV. Clinicians need to be aware of the fact that HBV monotherapy quickly leads to HBV drug resistance.

In some patients, immune recovery after initiation of AR can lead to spontaneous clearance of HBV, while in others with advanced liver disease, immune reconstitution can lead to liver failure. Close monitoring with input from HIV/HBV specialists is therefore essential.

References

1. Wester WC et al. Serological Evidence of HIV-Associated Infection among HIV-1–Infected Adults in Botswana. Clinical Infectious Diseases 2006; 43:1612–5.
2. Patel, P et al. Hepatitis B Surface Antigen Prevalence in the Outpatient Adult HIV Population in Gaborone, Botswana. AIDS 2010, abstract # WEPDB205.
3. Nikolopoulos GK et al. Impact of hepatitis B virus infection on the progression of AIDS and mortality in HIV-infected individuals: a cohort study and meta-analysis. Clin Infect Dis 48(12):1763-71, 2009
4. AASLD Practice Guidelines, Hepatology, Sept 2009.
5. Soriano V. Care of HIV patients with chronic hepatitis B: updated recommendations from the HIV-Hepatitis B Virus International Panel. AIDS 2008, 22:1399–1410
6. WHO HIV treatment guidelines for Adults, 2010.

Upcoming Lectures

NOVEMBER
HIV & IRIS

DECEMBER
Christmas Special

Got a clinical question about a complicated medical patient or a patient with HIV?

Mike Reid
267 724 78 777
OR
Miriam Haverkamp
267 76516520

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Differential Diagnosis for Elevated LFTs

Cholestatic **(increased alkaline phosphatase, direct bilirubin, mild increases in AST and ALT)**		**Hepatic** **(nearly isolated elevation of AST and ALT)**
Intrahepatic	**Extrahepatic**	
Chlorpromazine	Acalculous cholecystitis, calculous cholecystitis (gallstones), choledocholithiasis	Viral hepatitis, including immune reconstitution from Hep B in HIV + patient initiating truvada or 3TC (Hep A, B, C, and rarely Herpes Simplex)
Cholestasis of pregancy	AIDS Cholangiopathy (usually in conjunction with cryptosporidium, microsporidium, CMV and cyclospora, although in 20-40% of cases no etiology found	Autoimmune Hepatitis
Primary biliary cirhosis	Cholangiocarcinoma	Drugs: EtOH, rifampin, INH, PZA, nevirapine, efavirenz, phenytoin, valproate, carbemazapine, methotrexate, ***paracetamol,*** brufen, co-trimoxazole, fluconazole
amyloidosis	Clonochis sinensis (chinese liver fluke, endemic to Asia, find eggs in stool, tx with praziquantel)	Aflatoxin ingestion*
Tuberculosis	Fasciola hepatica (sheep fluke, humans incidental hosts. Found where cattle/sheep raised in Asia, case reports from Africa.)	Ischemia (cardiac failure, prolonged hypotension, acute hepatic vein thrombosis)
sarcoidosis	Ascaris lumbricoides	Metabolic diseases (primary hemochromatosis, Wilson's disease both of which are extremely rare, increased incidence in those of Western European descent), Secondary hemochromatosis
Drugs (Beta lactams chlorpromazine, cimetidine, erythromycin, trimethoprim-sulfamethoxazole)	Schistosomiasis	Non-alcoholic steatohepatitis
Cholestasis of sepsis	Malignancy: hepatoma, pancreatic carcinoma	Adrenal Insufficiency, thyroid disease