

Viral Hepatitis and HIV in Africa

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Abstract

With increasing access to antiretroviral therapy across sub-Saharan Africa, progress is finally being made in combating the devastating HIV epidemic. As HIV-infected individuals live longer, the effects of coinfection with chronic hepatitis B and C will likely become an increasingly relevant issue. Indeed, HIV adversely affects the natural history of HBV and HCV, both of which are endemic across the African continent. Issues ranging from appropriate diagnostic testing to prevention and treatment are affected by HIV coinfection, particularly in resource-limited settings. In addition, some of the more complex problems such as occult infection, immune reconstitution, and antiretroviral hepatotoxicity are becoming increasingly important considerations. In this review, we present the available data on coinfection in Africa with a major emphasis on prevalence, routes of transmission, prevention and treatment strategies. (AIDS Reviews 2007;9:25-39)

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Key words

Hepatitis B. Hepatitis C. HIV. Africa. Coinfection.

Introduction

In addition to the growing pandemic of HIV, there is an enormous burden of infection with chronic viral hepatitis in Africa leading to very high rates of coinfection with HIV, hepatitis C virus (HCV) and/or hepatitis B virus (HBV). Indeed, HIV accelerates the progression of HBV and HCV related chronic liver disease. With the advent of HAART and the resultant decline in AIDS-related opportunistic infections, liver disease will likely emerge as a significant cause of morbidity and mortality in Africa, similar to the trend seen worldwide. Unfortunately, to date, data on coinfection from Africa is very limited and consequently the scope and impact of the problem as well as priorities for intervention are poorly understood.

In this review, the emerging issues of chronic hepatitis in HIV-infected patients are discussed, with a particular emphasis on current and future developments in Africa.

HBV/HIV coinfection

Africa carries the major burden of HIV infection and, along with Asia, is the largest reservoir of chronic HBV. A staggering 25.8 million of the 40.3 million people worldwide infected with HIV reside in sub-Saharan Africa. The adult HIV prevalence in Africa is estimated at 8.8% compared to 0.6 and 0.3% in North America and Europe, respectively¹. Additionally, HBV is the most common cause of chronic liver disease worldwide with 400 million chronic carriers, of whom 50 million are estimated to reside in sub-Saharan Africa^{2,3}. Although HBV prevalence varies widely across the continent, hepatitis B surface antigen (HBsAg) positivity is estimated at 8-20%, while 70-95% have previously been exposed to infection (anti-hepatitis B core antigen [anti-HBc] ± anti-hepatitis B surface antigen [anti-HBs] positive) (Fig. 1)⁴. Most (> 95%) immunocompetent older children and adults are able to mount a strong, broad-based immune response to HBV, leading to viral clearance from blood with the development

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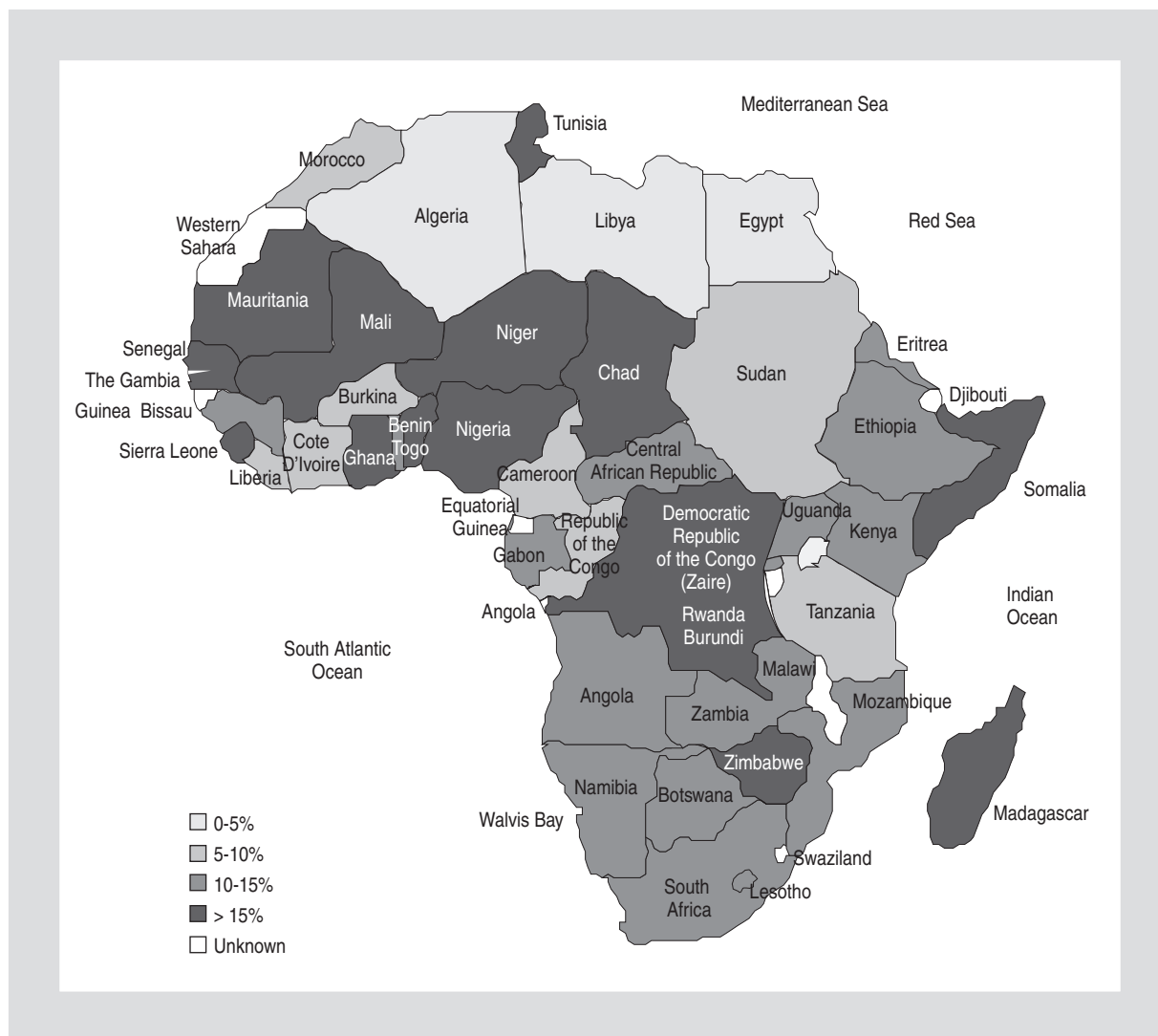


Figure 1. HBV prevalence in Africa¹⁴⁹.

of protective, neutralizing antibodies (anti-HBs). Nevertheless, all those infected at anytime with HBV retain the viral genome in hepatic nuclei in the form of closed covalent circular or cccDNA. Viral replication is controlled by immune surveillance; however, reactivation of HBV may occur at any point if severe immunosuppression develops. In contrast, the majority of young children (> 90%) and immunocompromised individuals are unable to control viral replication and develop chronic HBV infection with circulating HBsAg and hepatitis B e antigen (HBeAg). Although most chronically infected patients will eventually seroconvert HBeAg to anti-HBe and a minority will clear HBsAg and develop anti-HBs, this process may take years to decades to evolve. The repeated attempts by the immune system to control viral replication result in sub-clinical or symptomatic flares of hepatitis and may lead

to progressive fibrosis, cirrhosis, and ultimately hepatocellular carcinoma (HCC).

Prevalence of HIV/HBV coinfection

Although a number of prevalence studies of HIV/HBV coinfection have been performed in Africa, conflicting results have been observed with both higher and lower rates of HBV being reported in HIV-positive patients. However, early studies were limited by small sample size and poorly generalizable populations⁵⁻¹⁴. Numerous disease-prevalence studies have been performed in antenatal clinics in various countries with somewhat discrepant results. In Côte d'Ivoire, HBV serology was performed in 429 pregnant women and no increase in markers of current or past HBV infection was observed in the HIV-positive group^{15,16}. Similarly,

in a three-year study from South Africa involving 864 pregnant women, no increase in HBV prevalence was seen among HIV-positive women¹⁷. More recently, the ANRS 1236 study from Côte d'Ivoire was conducted to estimate the prevalence of HBV and HCV in 1002 pregnant women, 50% of whom were HIV positive. Positivity for HBsAg was found in a similar proportion of HIV-positive (45/499, 9%) and HIV-negative (40/498, 8%) women. On the other hand, a higher proportion of HIV-positive women were viremic based on HBV-DNA testing, (26.7 vs. 9.4%)¹⁸. In contrast, in a study of 1861 pregnant women in Zimbabwe, a non-significant increase in HBsAg prevalence was seen in 340 HIV-positive women. In addition, they noted a higher prevalence of HBeAg positivity in the coinfecting women compared to those with HBV alone (25% HBV/HIV vs. 8.5% HBV alone)¹⁹. Two studies from Nigeria also showed an increased prevalence of HBsAg in HIV-infected patients (25.9% in 490 HIV-positive patients versus 14.9% in 175 HIV-negative blood donors)^{20,21}. However, the importance of sample size is critical, as highlighted by two studies from Tanzania. In an initial cohort of 300 blood donors, a fourfold increase in HBsAg prevalence was reported among HIV-positive compared to HIV-negative individuals. In a subsequent study performed by the same authors, but including 1599 blood donors, no difference in rates of HBsAg positivity was seen, regardless of HIV serostatus^{22,23}.

In summary, although there are somewhat conflicting results, the majority of evidence from the largest studies shows that the prevalence of chronic HBV infection is similar among HIV positive and negative patients. This is in clear contrast to studies from North America and Europe and highlights the differing modes of transmission of the two viruses in Africa. While HIV is typically spread in Africa sexually or through unsterilized needles in adulthood, HBV is largely acquired very early in life through vertical or early horizontal transmission²⁴. In contrast, in low-prevalence countries, the predominant modes of transmission of both HBV and HIV are injection drug use and sexual contact, and therefore coinfection is much more common in high-risk populations. Although HBV is transmitted efficiently through sexual contact, a high percentage of the African population is protected due to previous exposure and clearance, as demonstrated by the very high prevalence of anti-HBc ranging from 70 to 95% across the continent. While the presence of HBsAg may be no more common in HIV-infected populations in Africa, the disease course and consequences of the disease dif-

fer significantly based on HIV status. To date, studies have focused on HBsAg prevalence without looking at HBV-DNA, HBeAg, or severity of liver disease. Coinfection with HIV impacts on rates of HBeAg seroconversion and is associated with higher levels of HBV-DNA as well as occult HBV (HBV-DNA positivity in the absence of HBsAg)²⁵. Future studies of prevalence should also look at markers of active HBV infection in HIV positive versus negative individuals. In addition, the majority of studies have examined low-risk populations, pregnant women, and blood donors, which may underestimate the prevalence of coinfection.

Routes of transmission

Although childhood infection with HBV is common, epidemiologic studies from Africa have suggested that horizontal (from other infected children or family members) rather than vertical transmission is the major route of HBV acquisition in childhood²⁶⁻²⁹. A study from southern Tanzania in 1999 found that 21% of children born to HBV-negative women were HBsAg(+) by 18 months of age, identical to the rate in a matched cohort born to HBsAg(+) mothers, suggesting horizontal is at least as important as vertical transmission⁸. Vertical transmission clearly occurs, but the rate has been reported to be lower in Africa than in Asia and other high-prevalence regions. This likely relates to earlier HBeAg seroconversion in the HBV genotypes found in Africa. The risk of vertical transmission is strongly correlated with the HBeAg status of the mother, occurring in 90% of cases from HBeAg(+) mothers compared to just 10-30% in HBeAg(-) mothers. Coinfection with HIV may have significant impact on the rates of vertical transmission because HIV-coinfecting women are more likely to be HBeAg(+) and to have higher HBV-DNA levels³⁰. Improving access to the HBV vaccine and possibly hepatitis B immune globulin (HBIG) for post-exposure prophylaxis will be critical to avoid an increase in vertical transmission as HIV rates increase. It will also be important to understand the reasons for horizontal transmission of HBV to see if behavioral modification may reduce the risk.

Nosocomial transmission due to the use of unhygienic practices and unsafe equipment poses a risk for transmission of both HBV and HIV. In addition to injection medical therapy^{34,38,40-44}, occupational exposure in healthcare workers is also a major concern due to inadequate availability of materials and equipment needed for safe practice^{27,31-36}. This highlights the importance of requiring HBV vaccination in all healthcare

workers and medical and nursing students. Blood transfusion is also an important mode of transmission of both HIV and HBV because many centers in Africa lack adequate financial resources to perform appropriate screening tests^{6,23,37}. In most countries, blood is screened for HBsAg; however the techniques used vary widely. A study from Ghana showed that using the cheaper particle agglutination or dipstick tests, 46 and 29% of viremic patients were missed, respectively, whereas enzyme immunoassay (EIA) identified 97% of infectious donors³⁸. They found only 0.5% of HBsAg(-), anti-HBc(+) donors were viremic, suggesting that the additional cost of anti-HBc testing is not warranted, and the focus should remain on ensuring widespread access to accurate (EIA) HBsAg testing prior to all transfusions.

Outcome of HBV/HIV coinfection

The course and outcome of HBV infection is largely affected by the immune status of the individual, and consequently HIV coinfection impacts on almost all aspects of HBV infection, from rates of chronicity to progression of liver disease. Studies from non-African countries have shown that HIV-infected patients have a higher chance of developing chronic HBV infection after exposure than HIV-negative patients³⁹. However, this may be less relevant in Africa where HBV generally predates HIV infection. Little data is available from Africa documenting the course of HIV/HBV coinfection, but data from elsewhere demonstrate that HIV/HBV-coinfected patients have higher HBV-DNA levels and lower rates of spontaneous HBeAg and HBsAg clearance rates than HBV-monoinfected patients⁴⁰⁻⁴². Coinfected patients also have an increased risk of cirrhosis and liver-related mortality than those with HBV alone⁴³⁻⁴⁵. A recent study from Kenya comparing HIV/HBV-coinfected patients with HBV-monoinfected patients found lower CD4+ counts and alanine aminotransferase (ALT) levels in coinfecting patients, suggesting a decreased immune response in these patients⁴⁶, a finding reported in other studies. This highlights the fact that lower ALT values in coinfecting patients do not necessarily reflect less-active liver disease. Unfortunately, this means that serum transaminases may not be an adequate surrogate for liver biopsy to evaluate hepatic inflammation and fibrosis in this setting. Lower CD4+ counts were also associated with higher liver-related mortality in coinfecting patients⁴⁷. In contrast, studies have shown no effect of HBV infection on progression of HIV to AIDS^{48,49}.

Clinical scenarios in HBV/HIV coinfection

HBV reactivation/reverse seroconversion

In the usual course of HBV infection, patients clear HBeAg and develop anti-HBe antibody and may ultimately lose HBsAg with the development of anti-HBs. The development of antibody implies immune control of viral replication as opposed to true clearance of infection. With impaired immune function, "immune control" may be lost and reverse seroconversion may occur. First described in the setting of immunosuppression from chemotherapy, reappearance of HBeAg, and less commonly HBsAg, has been described in HIV infection. Surprisingly, reverse seroconversion has been reported even with normal CD4+ counts and can occur at any time during the course of HIV infection⁵⁰; however this has not been rigorously studied. Reappearance of HBeAg may be associated with a flare of hepatitis. Although reappearance of HBsAg in anti-HBc(+) patients is quite uncommon, with the high prevalence of anti-HBc (75-90% in some countries) and HIV in Africa, this may still constitute a significant burden of disease. An improved understanding of the predictors and consequences of reverse seroconversion will be important for the future management of coinfection in Africa.

Immune reconstitution

Immune reconstitution inflammatory syndrome (IRIS) is defined as a paradoxical exacerbation of preexisting infectious processes, secondary to an exuberant inflammatory response, following the initiation of HAART in HIV-infected patients^{51,52}. Usually, IRIS develops within the first two to three months of HAART initiation^{53,54}. In the setting of HIV/HBV coinfection, initiation of HAART may lead to HBV reactivation and worsening hepatitis in previously diagnosed or undiagnosed healthy HBV carriers⁵⁵⁻⁵⁷. In some patients with good hepatic functional reserve, hepatitis flares associated with IRIS can lead to HBeAg seroconversion⁵⁵. Liver biopsy in such patients shows profound liver cell necrosis and inflammation, and this is thought to be secondary to the recovery of CD4+ and CD8+ cytotoxic T-cells in the face of a high antigenic load from previously unchecked HBV replication^{45,55,58}. Differentiating IRIS from HAART hepatotoxicity may be difficult as both occur shortly after institution of therapy. Levels of HBV-DNA can be helpful, but they are not widely available. Hepatotoxicity has been reported with all classes of

HAART, but is most common with nevirapine and ritonavir^{59,60}. Although hepatotoxicity is reported to be more common in patients with HBV infection, it should not preclude patients with HBV coinfection from receiving therapy. Most patients with liver-enzyme elevation remain asymptomatic. However, if jaundice or even nonspecific symptoms develop, therapy should be discontinued as this may herald the onset of liver failure. Also, IRIS has been seen in patients with HCV/HIV coinfection who are started on HAART therapy. As HAART becomes more widely available across Africa, hopefully a better understanding of IRIS and HAART hepatotoxicity will develop.

HBV genotype

The three HBV genotypes prevalent in Africa are A (subtype A1 or Aa), D, and E. While genotype A1 is found in Southern African countries, genotype D prevails in Northern Africa and genotype E (a variant seen only in sub-Saharan Africa) is found in Western and Central Africa⁶¹. The African subtype of genotype A (A1 or Aa) is associated with HBeAg seroconversion at a younger age and lower HBV-DNA levels compared to the European subtype (A2 or Ae)⁶². Genotype D is also associated with early HBeAg seroconversion due to the predilection to develop mutations in the precore gene that abrogate HBeAg production. In Mediterranean countries, this had led to high rates of HBeAg(-) active hepatitis B. Consequently reliance on HBeAg as a traditional marker of active viral replication may be unreliable. There are, however, no studies from Africa looking at the effect of HBV genotype on disease progression in coinfecting patients.

Management of HIV/HBV coinfection in Africa

Principles for treatment in North America and Europe are based upon studies done in HBV-monoinfected patients and smaller studies in HIV/HBV-coinfecting patients. In general, the decision to institute treatment of HBV in coinfecting patients is similar to that in HBV-monoinfected patients and is based on viral load, biochemical abnormalities, and severity of liver pathology. A number of the HIV reverse transcriptase inhibitors have potent activity against HBV polymerase, leading to marked suppression of HBV replication. These include lamivudine, emtricitabine and tenofovir. Adefovir, which has modest anti-HIV activity at the licensed dose of 10 mg daily, is very active against HBV⁶³⁻⁷². Although the bulk

of experience in coinfecting patients is with lamivudine, the use of this agent is limited by the rapid development of resistance. Lamivudine-resistant HBV emerges at a rate of 15-20% in coinfecting patients⁷³.

Prior to the institution of HAART, hepatitis B serology (ideally HBsAg and anti-HBc) should be performed in all patients as this may impact the choice of HAART and affect long-term management. In coinfecting patients who are newly initiated on HAART therapy for HIV, agents with HBV activity (tenofovir, lamivudine, emtricitabine) should be considered along with a non-nucleoside reverse transcriptase inhibitor (NNRTI) or protease inhibitor (PI). Whether all anti-HBc(+) patients require effective anti-HBV therapy as part of HAART is unknown, but this may have major relevance in Africa. If available, tenofovir or emtricitabine are preferable to lamivudine because of their better resistance profiles. Lamivudine resistance usually leads to an asymptomatic rise in transaminases; however, severe flares in the setting of HIV coinfection have been documented⁷⁴. If lamivudine resistance develops, a second HBV-active agent should be added. If no other options exist, lamivudine should be continued as severe and even fatal withdrawal flares have been reported⁷⁵. It is also important to consider lamivudine-resistant HIV. If HBV serology has not previously been performed, it should be done prior to changing the HAART regimen. Before lamivudine is discontinued in favor of another anti-HIV agent, the HBV infection must also be considered. Unless the replacement agent also has HBV activity, lamivudine should be continued to avoid a withdrawal flare of hepatitis. If there is a need to treat HBV in patients without indications for HAART, agents with no HIV activity are preferable to avoid the development of drug-resistant HIV. Entecavir would be the optimal choice, but its high cost may limit its availability. Adefovir may be a reasonable alternative; however, this agent does have some activity against HIV and there may be cross-resistance with tenofovir, given their structural similarities. If HBeAg seroconversion occurs, it may be reasonable to discontinue HBV therapy after six months; however, there is a significant risk of relapse and patients still require close follow-up. Interferon has not proven very effective in HIV/HBV coinfection and its utility is further limited by cost and side effects⁷⁶.

Occult HBV in coinfecting patients

Occult HBV is defined as the presence of HBV-DNA in the absence of HBsAg. It has been detected with

increasing prevalence in HIV-coinfected patients⁷⁷⁻⁷⁹, with one study reporting that 85% of coinfected patients with anti-HBc alone were HBV-DNA positive⁸⁰. Although many studies have documented this phenomenon in coinfected patients in the Northern hemisphere, very limited data is available from Africa. In a recent study from South Africa, occult hepatitis B was found in 22.1% of HIV-positive individuals compared to 2.4% of HIV-negative individuals. In the same study it was found that HBsAg was more frequently positive in HIV-negative individuals as compared to HIV-positive individuals (35.2 vs. 16.2%), suggesting that HIV infection might be a risk factor for occult hepatitis B (false-negative HBsAg test)⁸¹. The scope of this problem is not well understood in HIV/HBV-endemic regions of Africa where PCR-based HBV-detection methods are not commonly available. The clinical significance of this syndrome is also unclear. While most patients with occult HBV are asymptomatic with normal liver enzymes, there is concern that these patients may be at risk for progressive liver damage and/or the development of HCC, particularly in the setting of immunosuppression from HIV. A better understanding of the scope and consequences of this problem will be important because testing all anti-HBc(+) patients for HBV-DNA is very costly.

Postexposure prophylaxis

The World Health Organization (WHO) through the Safe Injection Global Network (SIGN) organization is striving to make postexposure prophylaxis (PEP) available to babies of known HBV carriers and healthcare workers who have been exposed to HBsAg(+) blood. Although recommended PEP for infants consists of both HBIG and vaccination, a recent study from Thailand shows that vaccine alone may be equally effective, especially in HBeAg(-) mothers⁸². This may be particularly relevant in Africa where HBeAg seroconversion occurs earlier and HBIG is expensive and not widely available. For exposed healthcare workers, HBIG and vaccination are recommended, or a booster dose of HBV vaccine alone for those previously vaccinated. Many countries provide antiretroviral therapy for HIV-infected mothers to prevent vertical transmission. Whether a similar strategy would work for HBV remains unclear. Preliminary data suggest that lamivudine decreases the risk of HBV transmission, particularly from mothers with high levels of HBV-DNA⁸³. Because of the high prevalence of HIV/HBV coinfection and the ability to use HBV active agents that also po-

tentially would prevent HIV transmission, Africa is the ideal place to study vertical-transmission prevention strategies for both infections.

Hepatocellular carcinoma

The most devastating complication of HBV infection is the development of HCC. Although cirrhosis greatly increases the risk of HCC, integration of HBV into the host genome puts infected individuals at risk even in the absence of significant fibrosis. Little is known about the effect of HIV on the risk of HCC, but reports showing an association with HBeAg positivity and higher HBV-DNA levels (both features of HBV-HIV coinfection) are concerning⁸⁴. As the availability of HAART is increasing and people are living longer, HCC may emerge as a major problem. This may be of particular concern in parts of East Africa where contamination of staple foods with aflatoxin, a major promoter of HCC, is common⁸⁵. Moreover, genotype A subtype A1, the predominant genotype in south East Africa, is also associated with an increased risk of HCC at a younger age⁸⁶.

HCV/HIV coinfection

Over 170 million people (3% of the world's population) are chronically infected with HCV^{87,88}. With the decreasing mortality from AIDS-related opportunistic infections after the introduction of HAART⁸⁹, liver disease has emerged as an important cause of morbidity and mortality in the coinfected population^{90,91}. Similar to HIV, Africa has the highest prevalence rates for HCV (Figs. 2 and 3)⁹². Hence, it becomes very important to understand the interaction of HIV and HCV in coinfected patients and their effect on each other on the progression of disease in Africa.

Prevalence of coinfection

Although the prevalence of HCV mono-infection across Africa is estimated at 5.3%, there is wide variation across the continent, with the highest rates reported in the Nile River basin of Egypt (7.4-18%) followed by central sub-Saharan Africa (6%), West Africa (2.4%), and Southern and Eastern Africa (1.6%)^{92,93}. There are very scarce data on the prevalence of HCV/HIV coinfection in Africa. The ANRS 1262 study from Cameroon looking at the risk of mother-to-child transmission of HCV estimated the HCV/HIV coinfection rate to be 0.001% (6/5008 pregnant women screened)⁹⁴. Simi-

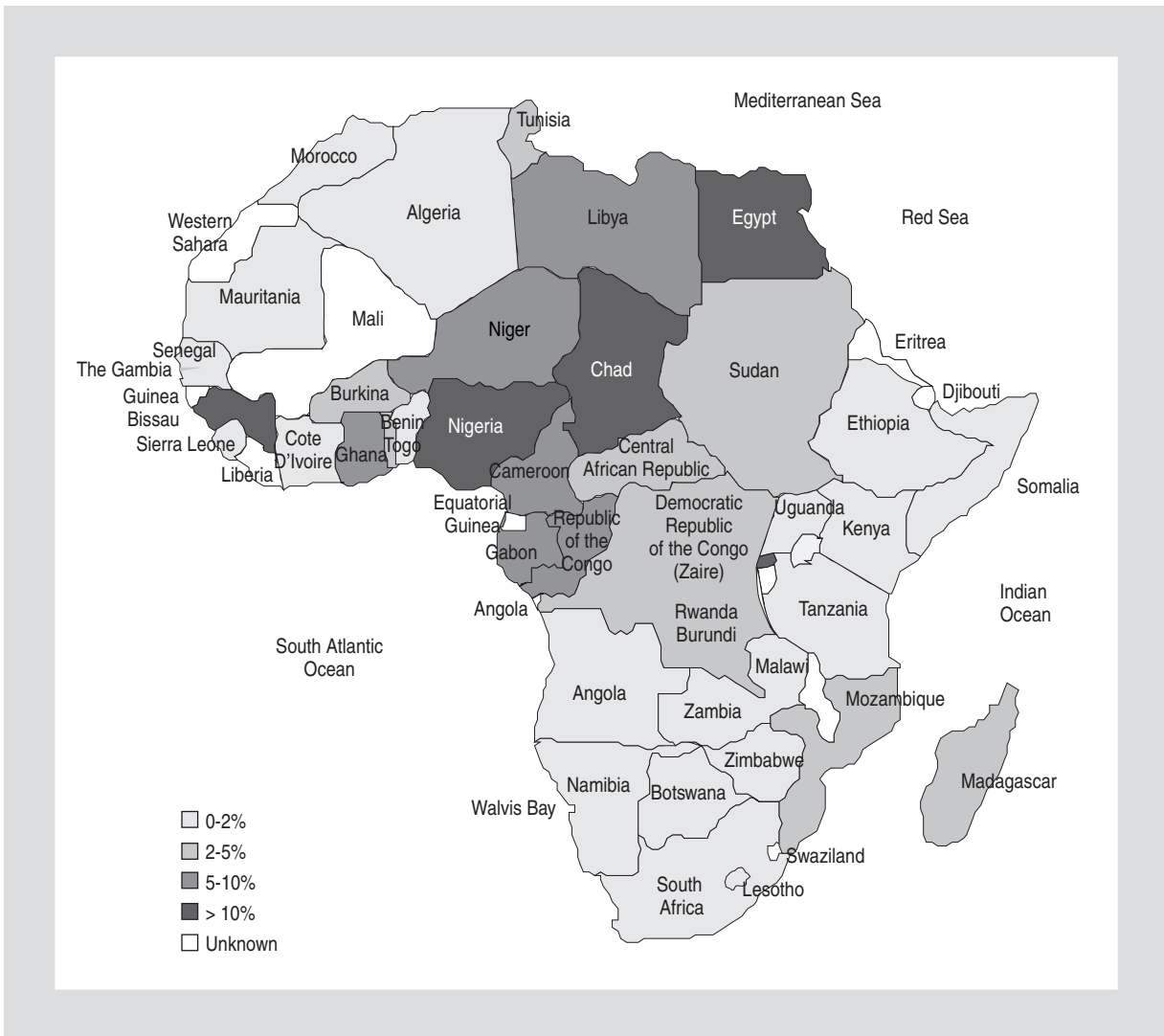


Figure 2. HCV prevalence in Africa¹⁴⁹.

larly, a study from a rural area of Zimbabwe on 124 HIV-positive patients showed a low HCV prevalence rate of 0.8% (1/124 patients)⁹⁵. The prevalence rates of coinfection from studies conducted in various parts of Africa are shown in table 1⁹⁶. From the data available, it appears that the prevalence of HIV/HCV coinfection is low in most parts of Africa.

Routes of transmission

Unlike in industrialized nations where HCV rates are much higher in HIV-infected individuals, this does not appear to be the case in Africa. This suggests that the predominant modes of HCV and HIV transmission likely differ. Data from North America have shown increased rates of both vertical and sexual transmission of HCV in HIV-positive individuals by as much as

3.8-fold^{97,98}. However, studies from numerous African countries have shown low rates of HCV in sex-worker cohorts despite a high prevalence of HIV infection. In addition, low rates of vertical HCV transmission have been reported. In a study from Tanzania among 980 pregnant women, the HCV vertical-transmission rate was found to be 5% and the ANRS 1262 study from Cameroon and a study from Burkina Faso showed similarly low rates of vertical transmission^{94,98}. A history of exposure to injection medical/dental therapy and blood transfusion has also been reported to be a significant risk factor for HCV in various African countries. However, many patients have no identifiable risk factor^{6,99}. At this point, although nosocomial spread is clearly important, whether this is the predominant mode of HCV transmission in Africa remains unclear. This is particularly important, given that no vaccine

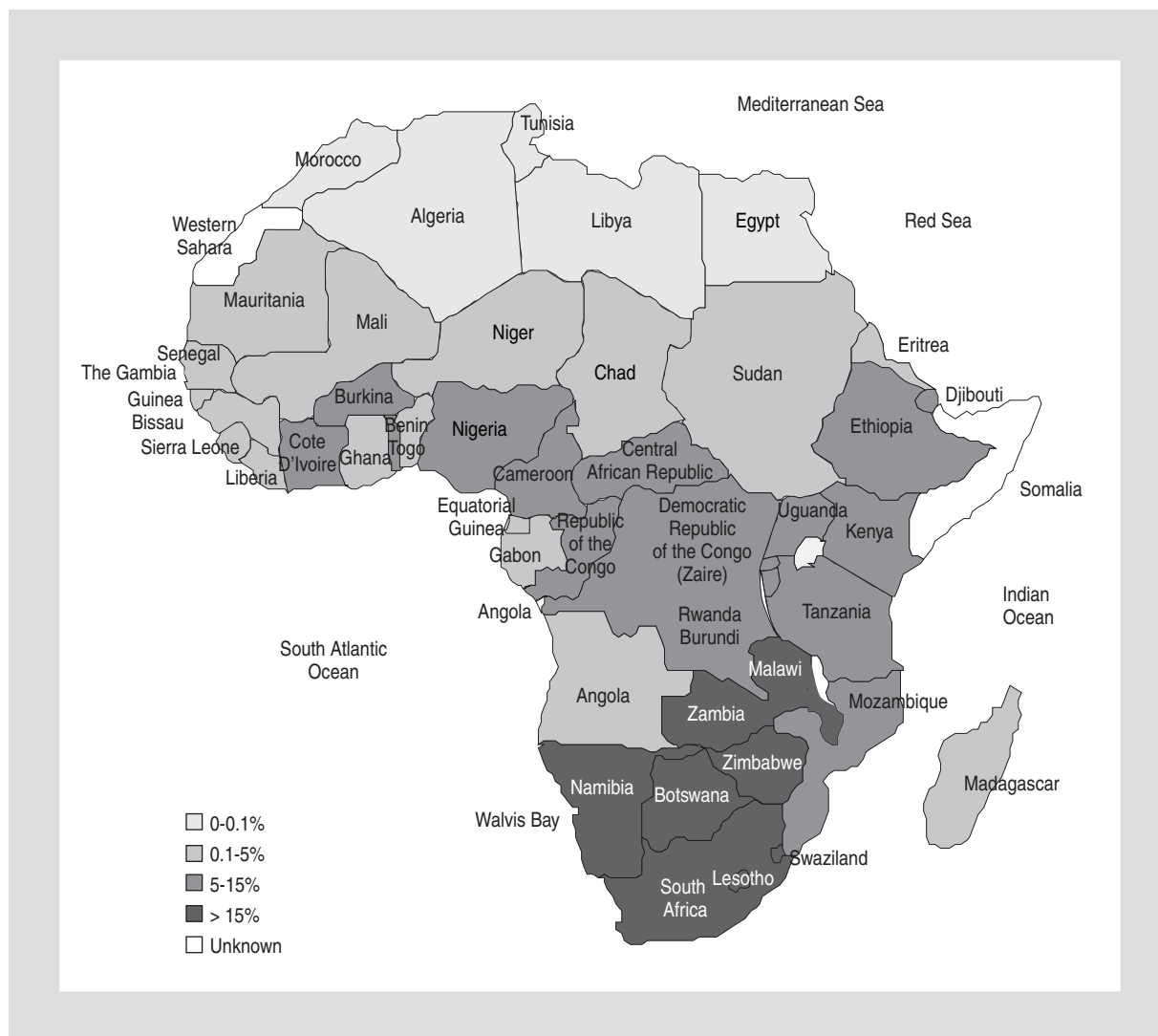


Figure 3. HIV prevalence in Africa (adapted from UNAIDS, 2000).

exists and treatment is generally unavailable due to financial constraints. Consequently, identification of the major sources of HCV transmission will be critical to prevent further spread across the continent.

Severity and outcome of coinfection

Studies from the northern hemisphere have shown that HIV-infected patients are less likely to spontaneously clear HCV after an exposure than those without HIV¹⁰⁰. Coinfected patients progress to cirrhosis faster than HCV-monoinfected patients^{101,102}. A meta-analysis found that the risk of decompensated liver disease increased sixfold in coinfecting patients, and they were at increased risk for morbidity and mortality secondary to end-stage liver disease¹⁰³. The converse is less clear. There is conflicting data about the effect of HCV

on HIV disease progression and mortality. While some studies predict increased risk of developing AIDS-related opportunistic infections and mortality in HCV-coinfected patients, others do not¹⁰⁴⁻¹⁰⁶. A study looking at the effect of HCV genotype on disease progression found that genotype 1 was associated with higher HCV viral loads, lower CD4+ counts, and increased AIDS related mortality in 207 HIV/HCV-coinfecting patients¹⁰⁷. Although most reports have identified genotype 4 as the predominant genotype in Africa, recent data suggest that the prevalence of genotype 1 infection is increasing¹⁰⁸. This may portend worse progression of liver disease in the setting of HIV coinfection, but perhaps more importantly, it will impact on treatment outcome if and when therapy becomes more readily available. To date there are no studies from Africa looking into the outcome and progression of

Table 1. Rates of HCV/HIV coinfection in African countries

Country	Year	Total pts. screened	Prevalence of HCV in HIV(+) population	Cohort Studied
West Africa				
Burkina Faso ⁹⁸	2005	547	1.3% (7/547)	AN
Cote d'Ivoire	1995-96	429	3.1% (7/223)	OP
Niger	1990	1163	22.2% (2/9)	BD
Niger	1990	250	24.7% (18/73)	SW
Togo	1993-94	478	6.8% (6/87)	BD, IP, STD
East Africa				
Eritrea	1995	323	9.6% (3/31)	SW
Ethiopia	1994	5936	4.0% (25/623)	GP, AN, SW
Kenya ¹⁴⁵	2005	976	3.7%	IP
Kenya ¹⁴⁶	2005	6154	0.02%	BD
Somalia	1990	438	0% (0/5)	SW
Tanzania	1989-90	497	4.5% (1/22)	GP
Tanzania	1993	192	0% (0/44)	IP
Tanzania	1995	980	1.5% (1/66)	GP
Tanzania ²²	2006	1559	0%	BD
Southern Africa				
South Africa	1992	833	0% (0/19)	STD, FP, GP
South Africa	1992	263	3.3% (1/30)	GP
South Africa ¹⁴⁷	2003	1649	1.9%	OP
Zambia	1995	343	0.6% (1/182)	IP
Zimbabwe ⁹⁵	2003	269	0.8% (1/124)	GP
Central Africa				
Burundi	1991	685	9.9% (15/151)	OP
Cameroon	1991-92	380	9.1% (1/11)	AN
Cameroon	1998	482	12.9% (16/124)	OP, STD
Cameroon	2005	5008	6.7% (6/89)	AN
CAR	1995	157	3.3% (1/30)	STD
DR Congo	1988	1138	7.4% (29/390)	SW
DR Congo	1990	1089	6.5% (2/31)	AN
Nigeria ¹⁴⁸	2004		8.2% (12/146)	OP

AN: antenatal; OP: outpatient; IP: inpatient; SW: sex worker; GP: general population; BD: blood donors, STD: patients attending sexually transmitted disease clinics; FP: patients attending family planning clinic; CAR: Central African Republic.

Table 2. Main causes of elevated liver enzymes in HBV/HIV, HCV/HIV coinfecting patients

	Comments
Viral hepatitis	
Acute hepatitis A & E	Usually asymptomatic but can cause acute hepatitis and rarely liver failure
Delta hepatitis	Rapid progression of liver disease
GBV-C	May slow HIV progression
Drug Hepatotoxicity	
NNRTI	Nevirapine hypersensitivity reaction can cause fulminant liver failure
PI	Ritonavir-dose related toxicity, not severe
NRTI	Mitochondrial toxicity causing lactic acidosis
INH	Asymptomatic increase in AST/ALT; if jaundice/symptoms develop, high risk of liver failure
Rifampin	Drug interaction with NNRTI
Immune reconstitution	
	Reactivation of HBV or HCV

NNRTI: nonnucleoside reverse transcriptase inhibitors; PI: protease inhibitors; INH: Isoniazid; NRTI: nucleoside reverse transcriptase inhibitors.

disease in patients with coinfection. As HAART becomes more widely available, HCV-related liver disease may become a much more significant problem.

Management of HIV/HCV coinfection

Treatment of HCV in coinfecting patients with pegylated interferon and ribavirin has slightly lower response rates than in HIV-negative patients, particularly in patients with genotype 1 infection and high HCV viral loads^{109,110}. If treatment of coinfecting patients is to be undertaken, a few issues must be considered. Coadministration of ribavirin and didanosine can lead to lactic acidosis secondary to mitochondrial toxicity and should be avoided^{57,111}. Similarly, coadministration of ribavirin and zidovudine increases the risk of anemia and should be avoided¹¹². Patients coinfecting with HCV are at increased risk of HAART hepatotoxicity. While the diagnosis of HCV should certainly not preclude patients from receiving HAART, it may help guide therapeutic options to minimize the risk of liver toxicity by avoiding agents such as nevirapine and ritonavir, if possible. Other causes of liver enzyme elevation in the setting of coinfection must also be considered (Table 2). In most of Africa, HCV infection in coinfecting individuals remains undiagnosed and untreated because of the high costs of diagnostic testing and treatment. Although it is unlikely that HCV will be commonly treated in most resource-poor countries until more affordable options become available, it would still be very useful to better understand the epidemiology and burden of HCV-related disease across the continent. To achieve these goals, increased funding for diagnosis will be necessary.

Prevention programs

Almost all prevention programs in Africa are directed towards the burgeoning HIV epidemic. However, due to similar routes of transmission among HIV, HBV, and HCV, the same general prevention principles apply to coinfection. Table 3 outlines the current prevention programs utilized in Africa to combat HIV, HBV, and HCV.

Although the current programs are making an impact, other areas will require attention in the future. Education is a critical issue. Significant strides have been made in educating young people about HIV transmission, but little mention is made of viral hepatitis. Because many programs to address the spread of HIV are already in place, minor adjustments to include discussion of hepatitis, including vaccination, would be very useful. Furthermore, healthcare workers must receive formal training in the handling of blood products and safe surgical techniques and procedures. They should also all receive HBV vaccination.

Although largely hampered by cost, improved screening of transfused blood is another important issue. Development of cheap, reliable serologic testing will be critical if testing is to become widespread, particularly in rural areas. Another issue that needs urgent attention is the common practice of reusing needles after a modest sterilization technique has been performed. This is almost entirely a financial issue due to the costs of syringes, needles, and disposable equipment. To tackle this problem, the WHO organizes the secretariat of the SIGN conference to provide auto-disable syringes for all immunization injections and safety boxes for used syringes and needles collection⁴. In its

Table 3. Prevention programs for HIV and viral hepatitis

Current prevention and treatment programs implemented to combat HIV, HBV, and HCV in Africa

- GAVI: The Global Alliance for Vaccines and Immunization assists African countries to include HBV vaccination into their Expanded Programs on Immunization (EPI).
- SIGN: Secretariat of the Safe Injection Global Network conference organized by WHO provides auto-disable syringes for all immunization injections and safety boxes for used syringes and needles collection.
- MIMS: Making Medical Injections Safer program trains healthcare workers in methods of safe sharps disposal.
- WHO: Working towards increasing availability of antiretrovirals.
- Intensive prevention programs aimed at increasing the distribution of condoms and treatment of sexually transmitted infections.

Making Medical Injections Safer (MIMS) program, it aims to train healthcare workers in methods of safe sharps disposal using small, locally built incinerators, and decreasing the need for unnecessary injections by spreading awareness among healthcare workers and patients⁴. While these programs are helpful, greater implementation of existing programs and novel approaches are required.

Management of HBV transmission would be greatly improved by more widespread use of vaccination. This has had profound effects on the incidence of HBV infection worldwide, particularly in Taiwan and other parts of Asia¹¹³. The Global Alliance for Vaccines and Immunization (GAVI) endeavors to assist African countries to include HBV vaccination in their Expanded Programs on Immunization (EPI) by providing information and financial assistance⁴. Many African countries have already introduced the vaccine in their EPI and many more are in the process of finalizing their plans.

Other hepatitis virus/HIV coinfection

Hepatitis A virus (HAV) and to a lesser extent hepatitis E virus (HEV) are both endemic in Africa and cause only acute hepatitis with no chronic phase. The course of both infections does not appear to be significantly altered by HIV coinfection, but there is minimal data on this subject.

Delta hepatitis (HDV) is a defective RNA virus that requires the simultaneous presence of HBV for virion assembly and secretion. Coinfection of HBV and HDV is usually transient and self-limited and has a very low rate of progression to chronic disease¹¹⁴. In contrast, HDV superinfection in HBV-infected patients usually presents as severe or even fulminant hepatitis and has a high rate of progression to chronic disease and cirrhosis. In general, HDV inhibits HBV replication in hepatocytes. Triple-infection with HIV has been shown to counter the inhibitory effect of HDV on HBV replication,

without affecting HDV replication or the severity of liver histology¹¹⁵. The prevalence of HDV in HBsAg(+) individuals varies considerably across Africa. While Tunisia, Cameroon, Senegal, and Uganda have high rates of HDV prevalence in HBV-infected populations (27-47%)¹¹⁶⁻¹²⁰, Nigeria has reported low prevalence of HDV (4-6%)^{121,122}. There is very limited data on the prevalence of triple infection with HIV/HBV/HDV in Africa, but in certain regions it is likely substantial. In a study from West Africa, it was observed that HIV-positive patients were more frequently coinfecting with HBV and HDV compared to HIV-negative individuals¹²³. This likely represents increased parenteral exposures rather than increased susceptibility to HDV infection due to HIV. All three viruses share common routes of transmission; however, which mode is most predominant differs significantly between, and possibly within, countries. To date, treatment with HBV-active agents (nucleos(t)ide analogs and interferon) has proven disappointing in both HIV positive and negative patients with HDV^{124,125}. Therefore efforts need to focus on prevention of HBV, and therefore HDV, through vaccination.

Hepatitis G virus, now known as GBV-C virus, is an RNA virus that is mainly transmitted parenterally. Various routes of infection including blood transfusion^{126,127}, injection drug use¹²⁸, and vertical^{129,130} and sexual transmission^{131,132} have been documented from studies in Western countries. A study from Egypt observed that direct percutaneous exposure from reusing syringes, dental treatment, surgery, and invasive medical maneuvers including hemodialysis was responsible for more cases of GBV-C than blood transfusion. The overall prevalence of GBV-C in this Egyptian cohort of 354 patients was 16%. Coinfection was very common with HCV (65%), but also seen with HBV (7.6%)¹³³. The prevalence of GBV-C in Congo and Morocco has been found to be similar to or higher than that of HCV^{134,135}. Despite initially being called hepatitis G virus, infection

with GBV-C generally does not cause liver disease¹³⁶⁻¹³⁸. There have been reports of GBV-C-related acute and chronic hepatitis as well as fulminant hepatic failure; however, clear causation has been hard to establish¹³⁹⁻¹⁴¹. More importantly, growing evidence has shown that GBV-C/HIV-coinfected patients have much improved outcomes compared to HIV-monoinfected individuals. Coinfected patients have been shown to have a better response to HAART, slower progression to AIDS, and decreased mortality¹⁴²⁻¹⁴⁴. No data from Africa exist on the prevalence and outcome HIV/GBV-C coinfection. Given the apparent beneficial effect of GBV-C, this certainly warrants further study.

Future directions

Major initiatives are underway to control the growing HIV epidemic in Africa. As progress is made, coinfection with HBV and HCV will become an increasing problem. Research on coinfection has begun in a number of African countries. Larger epidemiologic studies aimed at identifying the prevalence, routes of transmission, and severity of disease in coinfection need to be initiated so that appropriate prevention strategies can be implemented. Some issues unique to Africa such as the risk of HBV reactivation in anti-HBc(+) individuals with HIV will be critical to better assess the potential burden of disease. Understanding the effect of HIV on the risk of HCC will also be crucial, particularly as people begin living longer with the introduction of HAART. Better ability to predict and manage HAART-induced hepatotoxicity in the setting of coinfection will also be important. Determining the natural history of disease and particularly how it may differ from that in Western populations will be critical to make most efficient use of limited resources for prevention and treatment. Promotion of knowledge and awareness among the general population of how HIV, HBV, and HCV are transmitted will be vital for the success of prevention strategies. Healthcare professionals need to be made aware of the severity of coinfection to ensure that it is identified in vulnerable populations. Finally, more financial resources will be required, not only for treatment, but to provide the educational tools, safer medical equipment, and greater access to vaccination that will prevent further coinfection.

Financial support

This work was supported by the Intramural Research Program of NIDDK.

References

- UNAIDS. AIDS epidemic update: December 2005. In; 2005; Geneva; 2005.
- Lok A, McMahon B. Chronic hepatitis B. *Hepatology* 2001;34:1225-41.
- CDC Website. Geographic Distribution of Hepatitis B. http://www.cdc.gov/ncidod/diseases/hepatitis/slideset/hep_b/slide_9.htm. September 10, 2006.
- WHO Hepatitis B Fact-sheet. <http://www.who.int/mediacentre/factsheets/fs204/en/> September 10, 2006.
- Ahmed S, Cuevas L, Brabin B, et al. Seroprevalence of hepatitis B and C and HIV in Malawian pregnant women. *J Infect* 1998;37:248-51.
- Candotti D, Mundy C, Kadewele G, Nkhoma W, Bates I, Allain J. Serological and molecular screening for viruses in blood donors from Ntcheu, Malawi: high prevalence of HIV-1 subtype C and of markers of hepatitis B and C viruses. *J Med Virol* 2001;65:1-5.
- Lodenyo H, Schoub B, Ally R, Kairu S, Segal I. Hepatitis B and C virus infections and liver function in AIDS patients at Chris Hani Baragwanath Hospital, Johannesburg. *East Afr Med J* 2000;77:13-5.
- Menendez C, Sanchez-Tapias J, Kahigwa E, et al. Prevalence and mother-to-infant transmission of hepatitis viruses B, C, and E in Southern Tanzania. *J Med Virol* 1999;58:215-20.
- Nacro B, Dao B, Dahourou H. HBs antigen in children with suspicion of HIV infection. *J Trop Pediatr* 2001;47:303-4.
- Nakwagala F, Kagimu M. Hepatitis B virus and HIV infections among patients in Mulago hospital. *East Afr Med J* 2002;79:68-72.
- Ogutu E, Amayo E, Okoth F, Lule G. The prevalence of hepatitis B surface antigen (HBsAg), anti-hepatitis B surface (anti-HBs) and anti-hepatitis B core (anti-HBc) in patients with AIDS. *East Afr Med J* 1990;67:355-8.
- Pawlotsky J, Belec L, Gresenguet G, et al. High prevalence of hepatitis B, C, and E markers in young sexually active adults from the Central African Republic. *J Med Virol* 1995;46:269-72.
- Shao J, Haukenes G, Yangi E, Vollset S. Association of hepatitis B and HIV infections in Tanzanian population groups. *Eur J Clin Microbiol Infect Dis* 1993;12:62-4.
- Ter Meulen J, Wittkowski K, Kidenya J, et al. Evaluation of sero-epidemiological associations between HIV-infection, hepatitis B and other sexually transmitted diseases in African patients. *Eur J Epidemiol* 1989;5:158-63.
- Combe P, La Ruche G, Bonard D, et al. Hepatitis B and C infections, HIV and other sexually transmitted infections among women of childbearing age in Cote d'Ivoire, West Africa. *Trans R Soc Trop Med Hyg* 2001;95:493-6.
- Sutcliffe S, Taha T, Kumwenda N, Taylor E, Liomba G. HIV-1 prevalence and herpes simplex virus 2, hepatitis C virus, and hepatitis B virus infections among male workers at a sugar estate in Malawi. *J Acquir Immune Defic Syndr* 2002;31:90-7.
- Burnett R, Francois G, Hoosen A, et al. Three-year analysis of HBV infection in HIV-infected antenatal women from national HIV surveys in South Africa. Proceedings of the 11th International Symposium on Viral Hepatitis and liver disease, Sydney, Australia, April 2003 [abstract WC4-01].
- Rouet F, Chaix M, Inwoley A, et al. HBV and HCV prevalence and viremia in HIV-positive and HIV-negative pregnant women in Abidjan, Cote d'Ivoire: the ANRS 1236 study. *J Med Virol* 2004;74:34-40.
- Oshitani H, Kasolo F, Mpabalwani M, et al. Prevalence of hepatitis B antigens in HIV-1 seropositive and seronegative pregnant women in Zambia. *Trans R Soc Trop Med Hyg* 1996;90:235-6.
- Ejele O, Nwauche C, Erhabor O. The prevalence of hepatitis B surface antigenemia in HIV-positive patients in the Niger Delta Nigeria. *Niger J Med* 2004;13:175-9.
- Uneke C, Ogbu O, Inyama P, Anyanwu G, Njoku M, Idoko J. Prevalence of hepatitis-B surface antigen among blood donors and HIV-infected patients in Jos, Nigeria. *Mem Inst Oswaldo Cruz* 2005;100:13-6.

22. Matee M, Magesa P, Lyamuya E. Seroprevalence of HIV, hepatitis B and C viruses and syphilis infections among blood donors at the Muhimbili National Hospital in Dar es Salaam, Tanzania. *BMC Public Health* 2006;6:21.
23. Matee M, Lyamuya E, Mbeni E, et al. Prevalence of transfusion-associated viral infections and syphilis among blood donors in Muhimbili Medical Centre, Dar es Salaam, Tanzania. *East Afr Med J* 1999;76:167-71.
24. Davis L, Weber D, Lemon S. Horizontal transmission of HBV. *Lancet* 1989;1:889-93.
25. Vento S, Di Perri G, Garofano T, Concia E, Bassetti D. Reactivation of hepatitis B in AIDS. *Lancet* 1989;2:108-9.
26. Kew M. Progress towards the comprehensive control of hepatitis B in Africa: a view from South Africa. *Gut* 1996;38(Suppl 2):S31-6.
27. Kiire C. The epidemiology and prophylaxis of hepatitis B in sub-Saharan Africa: a view from tropical and subtropical Africa. *Gut* 1996;38(Suppl 2):S5-12.
28. Mphahlele M, Francois G, Kew M, Van Damme P, Hoosen A, Meheus A. Epidemiology and control of hepatitis B: implications for eastern and southern Africa. *S Afr J epidemiol Infect* 2002;17:12-7.
29. Nur Y, Groen J, Elmi A, Ott A, Osterhaus A. Prevalence of serum antibodies against bloodborne and sexually transmitted agents in selected groups in Somalia. *Epidemiol Infect* 2000;124:137-41.
30. Herrero Martinez E. Hepatitis B and hepatitis C coinfection in patients with HIV. *Rev Med Virol* 2001;11:253-70.
31. Ansa V, Udoma E, Umoh M, Anah M. Occupational risk of infection by HIV and HBV among health workers in southeastern Nigeria. *East Afr Med J* 2002;79:254-6.
32. Drucker E, Alcabes P, Marx P. The injection century: massive unsterile injections and the emergence of human pathogens. *Lancet* 2001;358:1989-92.
33. Hauri A, Armstrong G, Hutin Y. The global burden of disease attributable to contaminated injections given in health care settings. *Int J STD AIDS* 2004;15:7-16.
34. Mayans M, Hall A, Inskip H, et al. Do bedbugs transmit hepatitis B? *Lancet* 1994;343:761-3.
35. Simonsen L, Kane A, Lloyd J, Zaffran M, Kane M. Unsafe injections in the developing world and transmission of blood-borne pathogens: a review. *Bull World Health Organ* 1999;77:789-800.
36. Vall Mayans M, Hall A, Inskip H, et al. Risk factors for transmission of HBV to Gambian children. *Lancet* 1990;336:1107-9.
37. Chikwem J, Mohammed I, Okara G, Ukwandu N, Ola T. Prevalence of transmissible blood infections among blood donors at the University of Maiduguri Teaching Hospital, Maiduguri, Nigeria. *East Afr Med J* 1997;74:213-6.
38. Allain J, Candotti D, Soldan K, et al. The risk of HBV infection by transfusion in Kumasi, Ghana. *Blood* 2003;101:2419-25.
39. Hadler S, Judson F, O'Malley P, et al. Outcome of HBV infection in homosexual men and its relation to prior HIV infection. *J Infect Dis* 1991;163:454-9.
40. Bodsworth N, Donovan B, Nightingale B. The effect of concurrent HIV infection on chronic hepatitis B: a study of 150 homosexual men. *J Infect Dis* 1989;160:577-82.
41. Colin J, Cazals-Hatem D, Liorit M, et al. Influence of HIV infection on chronic hepatitis B in homosexual men. *Hepatology* 1999;29:1306-10.
42. Gilson R, Hawkins A, Beecham M, et al. Interactions between HIV and HBV in homosexual men: effects on the natural history of infection. *Aids* 1997;11:597-606.
43. Konopnicki D, Mocroft A, de Wit S, et al. Hepatitis B and HIV: prevalence, AIDS progression, response to HAART and increased mortality in the EuroSIDA cohort. *Aids* 2005;19:593-601.
44. 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.
45. Thio C, Seaberg E, Skolasky R, et al. HIV-1, HBV, and risk of liver-related mortality in the Multicenter Cohort Study (MACS). *Lancet* 2002;360:1921-6.
46. Otedo A. HBV, HIV coinfection at Kisumu District Hospital, Kenya. *East Afr Med J* 2004;81:626-30.
47. Di Martino V, Thevenot T, Colin J, et al. Influence of HIV infection on the response to interferon therapy and the long-term outcome of chronic hepatitis B. *Gastroenterology* 2002;123:1812-22.
48. Scharschmidt B, Held M, Hollander H, et al. Hepatitis B in patients with HIV infection: relationship to AIDS and patient survival. *Ann Intern Med* 1992;117:837-8.
49. Sinicco A, Raiteri R, Sciandra M, et al. Coinfection and superinfection of HBV in patients infected with HIV: no evidence of faster progression to AIDS. *Scand J Infect Dis* 1997;29:111-5.
50. Chamorro A, Casado J, Bellido D, Moreno S. Reactivation of hepatitis B in an HIV-infected patient with antibodies against hepatitis B core antigen as the only serological marker. *Eur J Clin Microbiol Infect Dis* 2005;24:492-4.
51. DeSimone J, Pomerantz R, Babinchak T. Inflammatory reactions in HIV-1-infected persons after initiation of HAART. *Ann Intern Med* 2000;133:447-54.
52. Shelburne S, Hamill R, Rodriguez-Barradas M, et al. Immune reconstitution inflammatory syndrome: emergence of a unique syndrome during HAART. *Medicine (Baltimore)* 2002;81:213-27.
53. French M, Lenzo N, John M, et al. Immune restoration disease after the treatment of immunodeficient HIV-infected patients with HAART. *HIV Med* 2000;1:107-15.
54. Michelet C, Arvieux C, Francois C, et al. Opportunistic infections occurring during HAART. *Aids* 1998;12:1815-22.
55. Carr A, Cooper D. Restoration of immunity to chronic hepatitis B infection in HIV-infected patient on protease inhibitor. *Lancet* 1997;349:995-6.
56. Drake A, Mijch A, Sasadeusz J. Immune reconstitution hepatitis in HIV and HBV coinfection, despite lamivudine therapy as part of HAART. *Clin Infect Dis* 2004;39:129-32.
57. Sulkowski M, Thomas D, Mehta S, Chaisson R, Moore R. Hepatotoxicity associated with nevirapine or efavirenz-containing antiretroviral therapy: role of hepatitis C and B infections. *Hepatology* 2002;35:182-9.
58. Velasco M, Moran A, Tellez M. Resolution of chronic hepatitis B after ritonavir treatment in an HIV-infected patient. *N Engl J Med* 1999;340:1765-6.
59. Nunez M, Lana R, Mendoza J, Martin-Carbonero L, Soriano V. Risk factors for severe hepatic injury after introduction of HAART. *J Acquir Immune Defic Syndr* 2001;27:426-31.
60. Abrescia N, D'Abbraccio M, Figoni M, et al. Fulminant hepatic failure after the start of an efavirenz-based HAART regimen in a treatment-naive female AIDS patient without hepatitis virus coinfection. *J Antimicrob Chemother* 2002;50:763-5.
61. Kramvis A, Restorp K, Norder H, Botha J, Magnus L, Kew M. Full genome analysis of HBV genotype E strains from Southwestern Africa and Madagascar reveals low genetic variability. *J Med Virol* 2005;77:47-52.
62. Tanaka Y, Hasegawa I, Kato T, et al. A case-control study for differences among HBV infections of genotypes A (subtypes Aa and Ae) and D. *Hepatology* 2004;40:747-55.
63. Benhamou Y, Bochet M, Thibault V, et al. Safety and efficacy of adefovir dipivoxil in patients coinfecting with HIV-1 and lamivudine-resistant HBV: an open-label pilot study. *Lancet* 2001;358:718-23.
64. Benhamou Y, Katlama C, Lunel F, et al. Effects of lamivudine on replication of HBV in HIV-infected men. *Ann Intern Med* 1996;125:705-12.
65. Benhamou Y, Thibault V, Vig P, et al. Safety and efficacy of adefovir dipivoxil in patients infected with lamivudine-resistant hepatitis B and HIV-1. *J Hepatol* 2006;44:62-7.
66. Benhamou Y, Tubiana R, Thibault V. Tenofovir disoproxil fumarate in patients with HIV and lamivudine-resistant HBV. *N Engl J Med* 2003;348:177-8.
67. Dore G, Cooper D, Barrett C, Goh L, Thakrar B, Atkins M. Dual efficacy of lamivudine treatment in HIV/HBV-coinfecting persons in a randomized, controlled study (CAESAR). The CAESAR Coordinating Committee. *J Infect Dis* 1999;180:607-13.
68. Dore G, Cooper D, Pozniak A, et al. Efficacy of tenofovir disoproxil fumarate in antiretroviral therapy-naive and -experienced patients coinfecting with HIV-1 and HBV. *J Infect Dis* 2004;189:1185-92.

69. Hoff J, Bani-Sadr F, Gassin M, Raffi F. Evaluation of chronic HBV infection in coinfecting patients receiving lamivudine as a component of anti-HIV regimens. *Clin Infect Dis* 2001;32:963-9.
70. Nelson M, Portsmouth S, Stebbing J, et al. An open-label study of tenofovir in HIV-1 and HBV coinfecting individuals. *Aids* 2003;17:F7-10.
71. Nunez M, Perez-Olmeda M, Diaz B, Rios P, Gonzalez-Lahoz J, Soriano V. Activity of tenofovir on HBV replication in HIV-coinfecting patients failing or partially responding to lamivudine. *Aids* 2002;16:2352-4.
72. Snow A, Harris J, Borroto-Esoda K, et al. Emtricitabine therapy for hepatitis infection in HIV+ patients coinfecting with HBV: efficacy and genotypic findings in antiretroviral treatment-naive patients. Presented at the 11th CROI, Boston, MA.
73. Benhamou Y, Bochet M, Thibault V, et al. Long-term incidence of HBV resistance to lamivudine in HIV-infected patients. *Hepatology* 1999;30:1302-6.
74. Bessesen M, Ives D, Condreay L, Lawrence S, Sherman K. Chronic active hepatitis B exacerbations in HIV-infected patients following development of resistance to or withdrawal of lamivudine. *Clin Infect Dis* 1999;28:1032-5.
75. Lim S, Wai C, Rajnakova A, Kajiji T, Guan R. Fatal hepatitis B reactivation following discontinuation of nucleoside analogs for chronic hepatitis B. *Gut* 2002;51:597-9.
76. Wong D, Yim C, Naylor C, et al. Interferon- α treatment of chronic hepatitis B: randomized trial in a predominantly homosexual male population. *Gastroenterology* 1995;108:165-71.
77. Hofer M, Joller-Jemelka H, Grob P, Luthy R, Opravil M. Frequent chronic HBV infection in HIV-infected patients positive for antibody to hepatitis B core antigen only. Swiss HIV Cohort Study. *Eur J Clin Microbiol Infect Dis* 1998;17:6-13.
78. Laure F, Zagury D, Saimot A, Gallo R, Hahn B, Brechot C. HBV-DNA sequences in lymphoid cells from patients with AIDS and AIDS-related complex. *Science* 1985;229:561-3.
79. Piroth L, Binquet C, Vergne M, et al. The evolution of HBV serological patterns and the clinical relevance of isolated antibodies to hepatitis B core antigen in HIV-infected patients. *J Hepatol* 2002;36:681-6.
80. Grob P, Jilg W, Bornhak H, et al. Serological pattern "anti-HBc alone": report on a workshop. *J Med Virol* 2000;62:450-5.
81. Mphahlele M, Lukhwani A, Burnett R, Moropeng L, Ngobeni J. High risk of occult hepatitis B virus infection in HIV-positive patients from South Africa. *J Clin Virol* 2006;35:14-20.
82. Poovorawan Y, Sanpavat S, Pongpunlert W, Chumdermpadetsuk S, Sentrakul P, Safary A. Protective efficacy of a recombinant DNA hepatitis B vaccine in neonates of HBe antigen-positive mothers. *Jama* 1989;261:3278-81.
83. Van Zonneveld M, van Nunen A, Niesters H, de Man R, Schalm S, Janssen H. Lamivudine treatment during pregnancy to prevent perinatal transmission of HBV infection. *J Viral Hepat* 2003;10:294-7.
84. Yang H, Lu S, Liaw Y, et al. Hepatitis B e antigen and the risk of hepatocellular carcinoma. *N Engl J Med* 2002;347:168-74.
85. Turner P, Sylla A, Diallo M, Castegnaro J, Hall A, Wild C. The role of aflatoxin and hepatitis viruses in the etiopathogenesis of hepatocellular carcinoma: A basis for primary prevention in Guinea-Conakry, West Africa. *J Gastroenterol Hepatol* 2002;17(Suppl):S441-8.
86. Kew M, Kramvis A, Yu M, Arakawa K, Hodgkinson J. Increased hepatocarcinogenic potential of hbv genotype A in Bantu-speaking sub-Saharan Africans. *J Med Virol* 2005;75:513-21.
87. Global surveillance and control of hepatitis C. Report of a WHO Consultation organized in collaboration with the Viral Hepatitis Prevention Board, Antwerp, Belgium. *J Viral Hepat* 1999;6:35-47.
88. Boyer N, Marcellin P. Pathogenesis, diagnosis and management of hepatitis C. *J Hepatol* 2000;32(Suppl 1):98-112.
89. Furrer H, Fux C. Opportunistic infections: an update. *J HIV Ther* 2002;7:2-7.
90. Bica I, McGovern B, Dhar R, et al. Increasing mortality due to end-stage liver disease in patients with HIV infection. *Clin Infect Dis* 2001;32:492-7.
91. Soriano V, Garcia-Samaniego J, Valencia E, Rodriguez-Rosado R, Munoz F, Gonzalez-Lahoz J. Impact of chronic liver disease due to hepatitis viruses as cause of hospital admission and death in HIV-infected drug users. *Eur J Epidemiol* 1999;15:1-4.
92. Madhava V, Burgess C, Drucker E. Epidemiology of chronic HCV infection in sub-Saharan Africa. *Lancet Infect Dis* 2002;2:293-302.
93. el-Sayed N, Gomatos P, Rodier G, et al. Seroprevalence survey of Egyptian tourism workers for HBV, HCV, HIV, and *Treponema pallidum* infections: association of HCV infections with specific regions of Egypt. *Am J Trop Med Hyg* 1996;55:179-84.
94. Njouom R, Pasquier C, Ayoub A, et al. Low risk of mother-to-child transmission of HCV in Yaounde, Cameroon: ANRS 1262 study. *Am J Trop Med Hyg* 2005;73:460-6.
95. Kallestrup P, Zinyama R, Gomo E, et al. Low prevalence of HCV antibodies in HIV-endemic area of Zimbabwe support sexual transmission as the major route of HIV transmission in Africa. *Aids* 2003;17:1400-2.
96. Gisselquist D, Perrin L, Minkin S. Parallel and overlapping HIV and bloodborne hepatitis epidemics in Africa. *Int J STD AIDS* 2004;15:145-52.
97. Memon M, Memon M. Hepatitis C: an epidemiologic review. *J Viral Hepat* 2002;9:84-100.
98. Simpore J, Ilboudo D, Samandoulougou A, Guardo P, Castronovo P, Musumeci S. HCV and HIV coinfection in pregnant women attending St. Camille Medical Centre in Ouagadougou (Burkina Faso). *J Med Virol* 2005;75:209-12.
99. Kitundu J, Msengi A, Matee M, et al. Posttransfusion hepatitis C seroprevalence in Tanzanian children. *Ann Trop Paediatr* 2001;21:343-8.
100. Sherman K, Rouster S, Chung R, Rajcic N. HCV prevalence among patients infected with HIV: a cross-sectional analysis of the US adult AIDS Clinical Trials Group. *Clin Infect Dis* 2002;34:831-7.
101. Benhamou Y, Bochet M, Di Martino V, et al. Liver fibrosis progression in HIV and HCV coinfecting patients. The Multivirc Group. *Hepatology* 1999;30:1054-8.
102. Puoti M, Bonacini M, Spinetti A, et al. Liver fibrosis progression is related to CD4 cell depletion in patients coinfecting with HCV and HIV. *J Infect Dis* 2001;183:134-7.
103. Graham C, Baden L, Yu E, et al. Influence of HIV infection on the course of HCV infection: a meta-analysis. *Clin Infect Dis* 2001;33:562-9.
104. El-Serag H, Giordano T, Kramer J, Richardson P, Soucek J. Survival in HCV and HIV coinfection: a cohort study of hospitalized veterans. *Clin Gastroenterol Hepatol* 2005;3:175-83.
105. Greub G, Ledergerber B, Battegay M, et al. Clinical progression, survival, and immune recovery during antiretroviral therapy in patients with HIV-1 and HCV coinfection: the Swiss HIV Cohort Study. *Lancet* 2000;356:1800-5.
106. Sulkowski M, Moore R, Mehta S, Chaisson R, Thomas D. Hepatitis C and progression of HIV disease. *Jama* 2002;288:199-206.
107. Yoo T, Donfield S, Lail A, Lynn H, Daar E. Effect of HCV genotype on HCV and HIV-1 disease. *J Infect Dis* 2005;191:4-10.
108. Pasquier C, Njouom R, Ayoub A, et al. Distribution and heterogeneity of hepatitis C genotypes in hepatitis patients in Cameroon. *J Med Virol* 2005;77:390-8.
109. Chung R, Andersen J, Volberding P, et al. PEG-IFN α -2a plus ribavirin versus IFN α -2a plus ribavirin for chronic hepatitis C in HIV-coinfecting persons. *N Engl J Med* 2004;351:451-9.
110. Torriani F, Rodriguez-Torres M, Rockstroh J, et al. PEG-IFN α -2a plus ribavirin for chronic HCV infection in HIV-infected patients. *N Engl J Med* 2004;351:438-50.
111. Balzarini J, Lee C, Herdewijn P, De Clercq E. Mechanism of the potentiating effect of ribavirin on the activity of 2',3'-dideoxyinosine against HIV. *J Biol Chem* 1991;266:21509-14.
112. Fuster D, Huertas J, Gomez G, et al. Short communication. Baseline factors associated with hematologic toxicity that leads to a dosage reduction of PEG-IFN α -2a and ribavirin in HIV/HCV-coinfecting patients on HCV antiviral therapy. *Antivir Ther* 2005;10:841-7.
113. Chang M. Impact of hepatitis B vaccination on hepatitis B disease and nucleic acid testing in high-prevalence populations. *J Clin Virol* 2006;36(Suppl 1):S45-50.

114. Caredda A, d'Arminio Monforte A, Rossi E, et al. Prospective study of epidemic delta infection in drug addicts. *Prog Clin Biol Res* 1983;143:245.
115. Pol S, Wesenfelder L, Dubois F, et al. Influence of HIV infection on hepatitis delta virus superinfection in chronic HBsAg carriers. *J Viral Hepat* 1994;1:131-7.
116. Jenhani F, Ayed K, Gorgi Y, Zoulim F, Pichoud C, Trepo C. Delta infection in chronic HBsAg carriers in Tunisia: high prevalence in chronic asymptomatic HBsAg carriers and in HBsAg positive cirrhosis. *Ann Trop Med Parasitol* 1990;84:349-53.
117. Ndumbe P. Hepatitis D in Yaounde, Cameroon. *Apms* 1991;99:196-8.
118. Roingear P, Sankale J, Dubois F, et al. Infection due to hepatitis delta virus in Africa: report from Senegal and review. *Clin Infect Dis* 1992;14:510-4.
119. Triki H, Said N, Ben Salah A, et al. Seroepidemiology of hepatitis B, C and delta viruses in Tunisia. *Trans R Soc Trop Med Hyg* 1997;91:11-4.
120. De Lalla F, Rizzardini G, Rinaldi E, Santoro D, Zeli P, Verga G. HIV, HBV, delta-agent and *Treponema pallidum* infections in two rural African areas. *Trans R Soc Trop Med Hyg* 1990;84:144-7.
121. Ojo O, Akonai A, Thursz M, et al. HDV antigen in HBsAg positive chronic liver disease in Nigeria. *East Afr Med J* 1998;75:329-31.
122. Ojo O, Thursz M, Thomas H, et al. HBV markers, HDV antigen and HCV antibodies in Nigerian patients with chronic liver disease. *East Afr Med J* 1995;72:719-21.
123. Soubeyrand J, Niamkey E, Ouattara S, Diallo D, Leleu J, Beda B. HIV-1 seropositivity and B and D viruses in West Africa. *Pathol Biol (Paris)* 1990;38:899-902.
124. Puoti M, Rossi S, Forleo M, et al. Treatment of chronic hepatitis D with IFN α -2b in patients with HIV infection. *J Hepatol* 1998;29:45-52.
125. Wolters L, van Nunen A, Honkoop P, et al. Lamivudine-high dose interferon combination therapy for chronic hepatitis B patients co-infected with the hepatitis D virus. *J Viral Hepat* 2000;7:428-34.
126. Halasz R, Barkholt L, Lara C, et al. Relation between GB virus C/hepatitis G virus and fulminant hepatic failure may be secondary to treatment with contaminated blood and/or blood products. *Gut* 1999;44:274-8.
127. Jarvis L, Davidson F, Hanley J, Yap P, Ludlam C, Simmonds P. Infection with hepatitis G virus among recipients of plasma products. *Lancet* 1996;348:1352-5.
128. Anastassopoulou C, Paraskevis D, Sypsa V, et al. Prevalence patterns and genotypes of GB virus C/hepatitis G virus among imprisoned intravenous drug users. *J Med Virol* 1998;56:246-52.
129. de Martino M, Azzari C, Resti M, et al. Hepatitis G virus infection in HIV-1-infected mothers and their children. *J Infect Dis* 1998;178:862-5.
130. Wejstal R, Manson A, Widell A, Norkrans G. Perinatal transmission of hepatitis G virus (GB virus type C) and HCV infections—a comparison. *Clin Infect Dis* 1999;28:816-21.
131. Sarrazin C, Roth W, Zeuzem S. Heterosexual transmission of GB virus-C/hepatitis G virus infection. *Eur J Gastroenterol Hepatol* 1997;9:1117-20.
132. Scallan M, Clutterbuck D, Jarvis L, Scott G, Simmonds P. Sexual transmission of GB virus C/hepatitis G virus. *J Med Virol* 1998;55:203-8.
133. El-Zayadi A, Abe K, Selim O, Naito H, Hess G, Ahdy A. Prevalence of GBV-C/hepatitis G virus viremia among blood donors, health care personnel, chronic non-B non-C hepatitis, chronic hepatitis C and hemodialysis patients in Egypt. *J Virol Methods* 1999;80:53-8.
134. Cacoub P, Ohayon V, Sekkat S, et al. Epidemiologic and virologic study of HCV infections in Morocco. *Gastroenterol Clin Biol* 2000;24:169-73.
135. Liu H, Muyembe-Tamfum J, Dahan K, Desmyter J, Goubau P. High prevalence of GB virus C/hepatitis G virus in Kinshasa, Democratic Republic of Congo: a phylogenetic analysis. *J Med Virol* 2000;60:159-65.
136. Alter H, Nakatsuji Y, Melpolder J, et al. The incidence of transfusion-associated hepatitis G virus infection and its relation to liver disease. *N Engl J Med* 1997;336:747-54.
137. Chen M, Fischler B, Hultgren C, Halasz R, Nemeth A, Sallberg M. Analysis of GB virus C markers in families over three generations. *J Clin Microbiol* 1999;37:4153-5.
138. Di S, Ferraro D, Bonura C, et al. Are hepatitis G virus and TT virus involved in cryptogenic chronic liver disease? *Dig Liver Dis* 2002;34:53-8.
139. Linnen J, Wages J, Zhang-Keck Z, et al. Molecular cloning and disease association of hepatitis G virus: a transfusion-transmissible agent. *Science* 1996;271:505-8.
140. Tameda Y, Kosaka Y, Tagawa S, et al. Infection with GB virus C (GBV-C) in patients with fulminant hepatitis. *J Hepatol* 1996;25:842-7.
141. Yoshiba M, Okamoto H, Mishiro S. Detection of the GBV-C hepatitis virus genome in serum from patients with fulminant hepatitis of unknown etiology. *Lancet* 1995;346:1131-2.
142. Lefrere J, Roudot-Thoraval F, Morand-Joubert L, et al. Carriage of GB virus C/hepatitis G virus RNA is associated with a slower immunologic, virologic, and clinical progression of HIV disease in coinfecting persons. *J Infect Dis* 1999;179:783-9.
143. Tillmann H, Heiken H, Knapik-Botor A, et al. Infection with GB virus C and reduced mortality among HIV-infected patients. *N Engl J Med* 2001;345:715-24.
144. Yeo A, Matsumoto A, Hisada M, Shih J, Alter H, Goedert J. Effect of hepatitis G virus infection on progression of HIV infection in patients with hemophilia. Multicenter Hemophilia Cohort Study. *Ann Intern Med* 2000;132:959-63.
145. Karuru J, Lule G, Joshi M, Anzala O. Prevalence of HCV and HCV/HIV coinfection among in-patients at the Kenyatta National Hospital. *East Afr Med J* 2005;82:170-2.
146. Karuru J, Lule G, Joshi M, Anzala O. Prevalence of HCV and HIV/HCV coinfection among volunteer blood donors and VCT clients. *East Afr Med J* 2005;82:166-9.
147. Amin J, Kaye M, Skidmore S, Pillay D, Cooper D, Dore G. HIV and hepatitis C coinfection within the CAESAR study. *HIV Med* 2004;5:174-9.
148. Agwale S, Tanimoto L, Womack C, et al. Prevalence of HCV coinfection in HIV-infected individuals in Nigeria and characterization of HCV genotypes. *J Clin Virol* 2004;31(Suppl 1):S3-6.
149. Feld J, Ocama P, Ronald A. The liver in HIV in Africa. *Antivir Ther* 2005;10:953-65.

Treatment of HIV/HBV Coinfection: Clinical and Virologic Issues

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Abstract

Chronic hepatitis B affects nearly 10% of HIV-infected patients. Thus, approximately four million people worldwide are HBV/HIV coinfecting. Hepatitis B virus (HBV) infection is a dynamic disease and coinfection with HIV impacts directly on the outcome of HBV infection, considerably complicating its natural history, diagnosis, and management. Hepatic necroinflammation is lower in HBV/HIV coinfection, yet liver damage, especially fibrosis, progresses at a faster rate than in HBV mono-infection. With improved control of HIV disease with HAART, liver disease has emerged as one of the leading causes of death in patients with HIV. Anti-HBV therapy should be considered for all HIV/HBV-coinfecting patients with evidence of liver disease, irrespective of the CD4 cell count. In coinfecting patients not requiring HAART, HBV therapy should be based on agents with no HIV activity such as adefovir. In contrast, in patients with CD4 counts less than 350 cells/ μ l, the use of agents with dual anti-HIV and anti-HBV activity should be considered. Combination therapy should ideally be used to avoid or delay the development of antiviral resistance. Regular monitoring of patients is imperative to recognize reactivation and subsequent need for treatment, and to identify drug resistance and viral breakthrough early. Similar close monitoring is required for patients presenting with advanced HIV infection and reduced functional hepatic reserve due to HBV-related cirrhosis. Effective antiviral treatment can precipitate immune reconstitution disease resulting in serious hepatic flare and precipitating liver decompensation. Clearly, more data are needed to more effectively treat HIV/HBV coinfection. (AIDS Reviews 2007;9:40-53)

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Key words

HIV. Hepatitis B. Liver. Adefovir. Tenofovir. Entecavir. Lamivudine. Drug resistance.

Introduction: effect of HIV infection on chronic hepatitis B

Serological evidence of hepatitis B virus (HBV) infection is found in up to 90% of HIV-infected individuals worldwide, and 10% of HIV-infected patients are chronically infected with HBV. There is considerable variation in prevalence according to geographic region and expo-

sure risk. Under normal circumstances, HBV replication in hepatocytes is not generally cytopathic¹; rather, it is the host's immune response, which is either inadequate or inappropriate, that is responsible for the liver disease of chronic hepatitis B (CHB). Coinfection with HIV results in considerable modification of the natural history of HBV infection and is associated with increased hepatitis B e antigen (HBeAg) carriage, higher rates of chronic infection as well as higher HBV-DNA levels, lower serum alanine aminotransferase (ALT) levels and decreased HBeAg seroconversion. Also, milder histologic necroinflammatory scores have been recorded, but despite this, progression to cirrhosis is more common. Most importantly, HIV coinfection leads to increased liver-related mortality from CHB². However, the exact mechanism(s) by which HIV interacts with HBV in this process is presently unknown. This observed increase in liver-disease pro-

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