

# GUIDELINE

## MANAGEMENT OF HIV-HEPATITIS B CO-INFECTION

SOUTHERN AFRICAN HIV CLINICIANS SOCIETY

HIV-hepatitis B virus (HBV) co-infected patients are at risk of increased morbidity and mortality. Early recognition of dual infection is a critical factor in directing appropriate therapy, and HBV screening should therefore be undertaken at the time of HIV diagnosis. Vaccination against HBV should be considered for all HIV patients who are not yet infected with HBV. Antiretroviral therapy containing two antiretrovirals active against HBV should be started if the patient either has symptomatic liver disease or is asymptomatic with a CD4 count of <350 cells/ $\mu$ l.

Hepatitis B virus infection is a global health problem with an estimated 350 million people chronically infected.<sup>1</sup> Routes of transmission differ between geographical regions, with acquisition in developed-world settings characteristically occurring in adulthood, predominantly in high-risk groups through parenteral or sexual exposure. In contrast, perinatal or horizontal transmission during childhood is the norm in most sub-Saharan African regions that do not routinely vaccinate children in the first year of life. Age at HBV infection determines the risk of chronicity of disease, with the highest rates developing in perinatally acquired HBV from mothers who are HBeAg positive (90%). In contrast, 25 - 30% of children infected with HBV develop chronic infection, whereas this figure drops to <5% in adults.<sup>2-5</sup>

Chronic HBV is endemic in sub-Saharan Africa, where HBsAg prevalence varies between 0.3% and 15%<sup>6</sup> and rates of exposure as determined by HBcIgG are between 5% and 80% depending on socio-economic groups and geographical location.<sup>7</sup> HIV infection adversely affects the course of HBV in co-infected patients (Table I). Few studies of HIV-HBV co-infection rates have been conducted in southern Africa and no community-based data are available. However, two studies from urban clinics in Johannesburg documented HBsAg positivity rates in HIV patients of 5%<sup>8</sup> and 4.8%,<sup>9</sup> with a higher rate of 17% reported from an industrial clinic setting.<sup>10</sup>

This guideline is intended to update and expand on those included in the 'Antiretroviral therapy in adults' guideline published in the *Southern African Journal of HIV Medicine* of January 2008 (Vol. 9, No. 1 (Summer issue), pp. 18-31). The exclusion of HBsAg screening at entry into the ART treatment programme adopted by the National Department of Health (NDOH) in 2010<sup>11</sup>

**Convenor:** Marc Mendelson  
**Expert Committee (alphabetical order):** Michael Kew, Gary Maartens, Adam Mahomed, James Nuttall, Regina Osih, Mark Sonderup, Wendy Spearman, Jantjie Taljaard, Gert van Zyl

### DEFINITION OF TERMS

**Chronic hepatitis B:** Persistence of hepatitis B surface antigen positivity for >6 months. There may be evidence of necro-inflammatory change on histological examination of the liver. Alanine transaminase and the HBV DNA level in blood may fluctuate over time.

**Occult hepatitis B:** HBsAg negative but hepatitis B core IgG antibody positive, with low-level HBV DNA in blood, usually <200 IU/ml.

**Hepatitis B viral flare:** An intermittent elevation of aminotransferase activity, often to >10 times the upper limit of normal, or a change of more than twice the baseline value.

is at odds with the guidelines that we present in this document. It is the belief of the authors that further discussion with the NDOH is needed to reconcile the programmatic approach to HIV-HBV management with the recognition that HBV-related liver disease in HIV-infected patients may be prevented by early screening and treatment, thereby positively affecting quality of life, morbidity and mortality.

### 1. SCREENING FOR HEPATITIS B INFECTION IN HIV-INFECTED PATIENTS

The current Southern African HIV Clinicians Society guideline on screening for HBV in HIV-infected patients indicates that all patients should be tested for HBV using blood HBsAg as the marker of infection, although no direction is given as to when screening should take place. The consensus from international guidelines is that screening should be undertaken at the time of diagnosis of HIV to allow for early decisions on specific treatments for HBV and HIV, as well as vaccination of HBV-uninfected individuals.<sup>12-15</sup> These guidelines were produced to direct management in developed, resource-rich nations with higher rates of HBV acquisition in adulthood. In southern Africa, HBV is predominantly acquired between the age of 6 months and 5 years.

### KEY SUMMARY POINTS

- To reduce the burden of hepatitis B virus (HBV) infection in sub-Saharan Africa; countries within the region that have not already instigated a programme of HBV vaccination in children should be encouraged to incorporate the vaccine as part of their extended programme of immunisation (EPI).
- HIV-infected patients should be screened for HBV infection using the hepatitis B surface antigen (HBsAg) test at the time of HIV diagnosis.
- HIV-HBV co-infected patients should have a CD4 T-cell count performed after diagnosis. If the CD4 count is  $<350$  cells/ $\mu$ l, the patient should be entered into the highly active antiretroviral therapy (HAART) programme. HAART must include two agents with anti-HBV activity, namely tenofovir plus lamivudine or emtricitabine, in addition to a non-nucleoside reverse transcriptase inhibitor or protease inhibitor (PI).
- Owing to the propensity of nevirapine to cause hepatitis, its use should be avoided in HIV-HBV co-infected patients whenever possible.
- To prevent HBV 'flares', co-infected patients taking tenofovir plus lamivudine or emtricitabine who require a change in antiretroviral regimen should continue tenofovir plus lamivudine or emtricitabine in addition to the new antiretrovirals, unless severe adverse effects from these drugs preclude their use.
- Co-infected patients whose CD4 count is  $\geq 350$  cells/ $\mu$ l should be assessed for symptomatic liver disease and have the secretory protein hepatitis B envelope antigen (HBeAg) and alanine transaminase (ALT) tested. If HBeAg is positive, and/or ALT is more than twice the upper limit of normal, the patient should be referred for tenofovir plus lamivudine or emtricitabine-based antiretroviral therapy (ART), as above. Similarly, any co-infected patient with symptomatic liver disease or chronic liver disease should be referred for ART, irrespective of the CD4 count.
- Co-infected patients whose CD4 count is  $\geq 350$  cells/ $\mu$ l but who test HBeAg negative and whose ALT level is less than twice the upper limit of normal should have their ALT re-checked every 6 months, or before if clinical events dictate. If ALT increases to more than twice the upper limit of normal, the patient should be referred for tenofovir plus lamivudine or emtricitabine-based ART.
- Co-infected children should be referred to/discussed with a specialist paediatrician for further management.
- HIV-infected patients who are HBsAg negative on screening, but are at high risk of acquiring HBV infection, should be tested for the presence of hepatitis B core IgG antibody (HBcIgG) and if negative, should be offered vaccination against HBV.
- Vaccination should not be attempted in patients with CD4 counts  $<200$  cells/ $\mu$ l as protective efficacy is poor. Rather, withhold vaccination until immune reconstitution has been achieved on ART.
- Vaccination should include a total of 3 doses administered at 0, 1 and 6 months. Double-dose vaccination should be considered in patients with CD4 counts of  $\geq 350$  cells/ $\mu$ l. If using the rapid schedule, for example for post-exposure prophylaxis or for babies born to infected mothers, a 4-dose schedule is used, administered at 0, 1, 2 and 12 months.
- All HIV-infected pregnant women must be tested for HBsAg and may require ART.
- Although not directly related to HIV-HBV co-infection, this guideline strongly supports the testing of *all* pregnant women for HBsAg to identify at-risk babies, irrespective of their HIV status.
- Babies born to mothers who are HIV-HBV co-infected must receive hepatitis B immunoglobulin (HBIG) and the first dose of HBV vaccine at two distinct sites within 12 hours of birth. A 4-dose vaccination course should be completed and the baby tested for presence of HBsAg and hepatitis B surface antibodies (HBsAb) at 6 months of age. HBIG should be repeated at 1 month if the mother is HBeAg positive. If the baby is HBsAb negative at 6 months of age, a repeat vaccination course is required.
- Co-infected babies should be referred to a specialist paediatrician for further management.
- All co-infected patients should be counselled with regard to lifestyle modifications to reduce hepatotoxicity, including alcohol, substance abuse, and co-prescription of herbal and traditional medicines.
- All co-infected patients should be tested for hepatitis C virus (HCV) infection, and those who are co-infected should be discussed with a specialist for advice on management.
- All HIV-HBV co-infected patients with evidence of chronic liver disease should be tested for hepatitis A immunity and immunised if non-immune. Resource constraints and the high level of hepatitis A infection in the South African population as a whole do not support routine testing for all HIV-HBV co-infected patients.

TABLE I. INFLUENCE OF HIV ON THE COURSE OF HEPATITIS B VIRUS INFECTION

- Higher rates of chronicity after acute HBV infection
- Decreased rates of spontaneous HBsAg and HBeAg seroconversion
- Increased rates of HBV DNA replication
- More severe liver disease, with increased rates of cirrhosis and hepatocellular carcinoma
- Increased rates of liver-related mortality
- Increased rates of occult HBV infection
- Increased rate of reactivation and seroreversion with decreasing CD4 counts
- Increase risk of HBV flare after starting HAART due to HBV-immune reconstitution inflammatory syndrome (HBV-IRIS)

However, no studies have been conducted on the rate of acquisition of new HBV infection in HIV-infected adults, so the applicability of developed-world guidelines to the southern African setting remains unknown. Despite this, screening for HBV at the time of diagnosis of HIV has considerable potential benefits, both for the individual and for public health programmes.

- **Early diagnosis of co-infection allows assessment of the requirement for specific anti-HBV treatment.** This applies to co-infected patients who qualify for ART because of CD4 count or stage of disease, as well as those who, despite not qualifying for ART on those grounds, have signs of active liver disease. This is in line with regional advice such as South African national policy, which advises early ART (to include specific anti-HBV drugs) irrespective of CD4 count in these patients.
- **Early instigation of specific anti-HBV therapy to reduce viral replication will decrease infectivity of the patient to others.**
- **Early identification of co-infected women and appropriate counselling will alert them to the need for targeted HBV intervention for their babies, should they be chronically infected.**
- **Early identification of HIV-HBV co-infection allows intervention in terms of counselling to affect lifestyle modifications that may reduce liver damage:**
  - alcohol
  - substance abuse
  - traditional or herbal medicines
  - screening and intervention for patients who are co-infected with hepatitis C.
- **Hepatitis A vaccination in patients with chronic liver disease, if non-immune.**
- **Identification of HBV seronegative HIV-infected individuals will allow for the option of vaccination against HBV.**

#### 1.1 OCCULT HEPATITIS B INFECTION

Screening for chronic hepatitis B using HBsAg will fail to detect a small proportion of patients who have occult HBV, i.e. HBsAg negative, HBcIgG positive and low level of HBV DNA in blood, typically <200 IU/ml. Data on the prevalence and significance of occult HBV infection in HIV-infected patients are limited, particularly in the southern African setting. A prospective observational cohort of patients attending an urban ART-preparedness clinic in Johannesburg found that 10.6% of clinic attendees were positive for anti-HBc alone, 88% of whom had evidence of HBV DNA in blood.<sup>9</sup> In a second study looking retrospectively at 192 stored sera from HIV-infected patients initiating ART, 23% were HBsAg positive and a further 23% had occult HBV.<sup>16</sup> Whether occult HBV infection poses a significant clinical problem to co-infected patients remains undetermined and needs to be the focus of longitudinal studies in the southern African setting. Of note, 81% of patients with occult HBV in the prospective cohort study had blood HBV DNA levels of <10<sup>4</sup> copies/ml.<sup>9</sup> Such low levels of DNA replication are less likely to cause significant liver damage, although the long-term natural history remains unknown. Both prospective and retrospective studies suggest that the

true rate of chronic HBV infection in HIV co-infected patients is higher than our current understanding based on HBsAg screening alone. However, with the limited amount of evidence and the major cost implications that additional screening tests would impose (see appendix), we are unable to advocate extension of screening tests to include HBcIgG and HBV DNA until further studies clarify the significance of occult HBV infection in our setting.

#### 1.2 HEPATOCELLULAR CARCINOMA

Hepatitis B is a recognised risk factor for development of hepatocellular carcinoma (HCC). HCC screening requires measurement of alpha-fetoprotein (AFP) and specialist ultrasonography, which are not practical in the southern African setting, where resources should be directed towards preventing infection and treating infected persons with effective antiviral therapy.

In summary, these guidelines advocate the continued use of HBsAg as the screening test for HIV-HBV co-infection. However, screening should be brought forward from entry into the ART programme to the time of HIV diagnosis so as to identify co-infected patients early in the course of their disease, allowing the option of early ART to include anti-HBV drugs in those who qualify for treatment.

## 2. VACCINATION OF HIV-INFECTED PATIENTS WHO SCREEN NEGATIVE FOR HBV

As indicated previously, it is currently not known how common HBV acquisition is in adulthood in southern Africa. However, we do know that acquisition of HBV infection by HIV-infected persons adversely affects morbidity and causes appreciable mortality. Hence, there is a rationale for advocating for HBV vaccination in all HIV-infected persons who are not already infected with HBV. HBV vaccination responses depend on CD4 counts; vaccination during the early stages of HIV disease when CD4 counts are preserved will result in improved protection. Patients who are eligible for HBV vaccination but who have CD4 counts <200 cells/ml mount poor antibody responses to HBV vaccine. It is therefore generally recommended, that vaccination in these individuals be delayed until immune reconstitution is achieved by ART. The exception to this rule is in the event of occupational or non-occupational exposure to blood or potentially infectious material from an HBV-infected source. In that case, if the recipient is HIV-infected and non-immune to HBV, hepatitis B immunoglobulin and vaccination should be offered regardless of CD4 count.

In countries such as South Africa where a universal childhood HBV vaccination programme has been adopted, vaccination will have a long-term positive impact in reducing HIV-HBV co-infection. However, there has been no catch-up vaccination programme, and until this impact is felt, unvaccinated HIV-infected adolescents and adults remain at risk of a preventable disease. Three approaches could be adopted:

- Do not offer HBV vaccine to HBV-uninfected persons.
- Target HBV vaccine to high-risk groups – acquisition of

HBV infection is increased in intravenous drug users (IVDUs), men who have sex with men (MSM) and partners of HBsAg-positive patients. Other high-risk groups that might be targeted include sex workers, patients with chronic liver disease, home-based caregivers of HBV patients, travellers, prisoners, police, traditional healers, and people involved in high-risk contact sports such as boxing.

- Universal HBV vaccination for all HIV-infected persons who have not yet been infected by HBV.

Adoption of a particular policy will be country-specific, depending on current vaccination policy, HBV seroprevalence profile and resources. However, it is the opinion of the authors that all HIV mono-infected persons should be offered HBV vaccination, as the impact of this simple intervention could radically alter the course of HIV disease if the person was to be infected with HBV. The vaccination schedule should comprise 3 doses at 0, 1 and 6 months. Results of a randomised controlled trial of single- versus double-dose recombinant HBV vaccine in HIV-infected persons showed an increased seroconversion rate (anti-HBsAb titre  $\geq 10$  mIU/ml) in the double-dose arm in the group whose CD4 count was  $\geq 350$  cells/ $\mu$ l (64% for the double dose v. 39% for the single dose).<sup>17</sup> At CD4 counts  $< 350$  cells/ $\mu$ l, although there was a trend towards increased seroconversion in the double-dose arm, it was not statistically significant. Follow-up testing for seroconversion is generally not advocated due to resource limitations. However, certain high-risk groups with anticipated repeat exposure, such as health care workers and IVDUs, should have their antibody titres checked as a once-off. If anti-HBs

antibody titres are  $< 10$  mIU/ml, consult an infectious diseases specialist for further advice. Guidelines for the management of health care workers exposed to an HBsAg-positive or unknown source are detailed in Table II.

### 3. MANAGEMENT OF HIV-HBV CO-INFECTED PATIENTS

#### 3.1 LIFESTYLE MODIFICATION

HIV-HBV co-infected patients will require additional counselling and support over and above that given to patients diagnosed with HIV mono-infection. There is a need to concentrate on lifestyle modifications that will reduce the risk of further liver injury, as well as for explanation of why a more tailored ART regimen to include ARVs active against both viruses is necessary. All HIV-HBV co-infected patients, irrespective of whether they qualify for ART or not, must be counselled on the lifestyle modifications outlined in Table III.

#### 3.2 ANTIRETROVIRAL THERAPY

The CD4 count after diagnosis will dictate the initial management of co-infected patients (Fig. 1). South African national guidelines on treatment of HIV infection have recently been updated, with a move to earlier initiation of ART in pregnant women and patients with tuberculosis. Overwhelming evidence from multiple studies shows that delaying ART initiation once the CD4 count has dropped below 350 cells/ $\mu$ l is associated with increased mortality and the number of new AIDS-defining events.<sup>18</sup> Accordingly, we advocate the inclusion of HIV-HBV co-infected patients as a third group to receive ART at CD4 counts  $< 350$  cells/ $\mu$ l.

TABLE II. MANAGEMENT OF HEALTH CARE WORKER EXPOSED TO HBsAg-POSITIVE OR UNKNOWN SOURCE

Vaccinated status of exposed worker	Anti-HBs	HBIG (0.06 ml/kg)	HBV vaccine	Comment
Previous vaccination and known responder	None	None	None	
Not vaccinated	If anti-HBs $> 10$ mIU/ml, no treatment	If anti-HBs $< 10$ mIU/ml, give stat HBIG and repeat at 1 month	1st dose stat and proceed to accelerated schedule 1 - 2 - 12 months	HBIG and HBV vaccine can be administered concomitantly at different sites
Incomplete vaccination or unsure	As above	Single dose stat	Complete depending on documentation or restart 0 - 1 - 2 - 12 months	As above
Vaccinated, but unknown response	As above	As above	Single booster stat	As above
Non-responder to primary vaccination	No	1 dose stat repeated after 1 month	1st dose stat and proceed to accelerated schedule 1 - 2 - 12 months	As above
Previously vaccinated with 4 doses or 2 completed vaccine series but non-responder		As above	Consider alternative vaccine	

Adapted from the European recommendations for the management of health care workers occupationally exposed to hepatitis B virus and hepatitis C virus.<sup>24</sup>

TABLE III. LIFESTYLE MODIFICATION TO LIMIT LIVER INJURY IN HIV-HBV CO-INFECTED PERSONS

Alcohol	Abstinence from alcohol should be encouraged. Heavy alcohol intake (>20 g/day in women and >30 g/day in men) is a risk factor for developing cirrhosis
Substance abuse	Intravenous drug use should be discouraged to reduce risk of new infection or re-infection with HBV and/or HCV
Safe sex	Although this will already be stressed as part of preventing HIV transmission to others, safe sex practices are to be strongly advocated to reduce transmission of HBV. Mucosal traumatic sexual practices associated with high-risk blood contact should be discouraged
Other measures to reduce risk of transmission	Attention to prompt clean-up of blood spills with detergent or bleach and avoid sharing razors

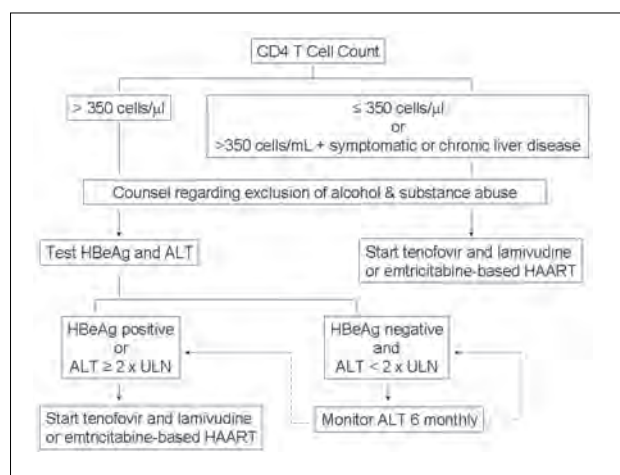


Fig. 1. Algorithm for management of HIV-HBV co-infected patients.

The choice of ART in co-infected patients must take into account the need for drugs active against both HIV and HBV, and the need to limit the emergence of drug-resistant HBV strains; 14 - 32% of patients at 1 year of lamivudine monotherapy and 50 - 90% at 5 years have developed a mutation in the YMDD motif of HBV DNA polymerase that confers resistance to the lamivudine.<sup>19</sup> Emergence of lamivudine resistance in patients on ART regimens containing lamivudine as the only drug active against HBV is associated with viral breakthrough and hepatitis flares. Hence, to limit the emergence of HBV resistant strains and optimise control of HBV replication, HIV-HBV co-infected patients should be started on an ART regimen that includes 2 drugs active against HBV, tenofovir plus either lamivudine or emtricitabine. Tenofovir is contraindicated in patients with significant renal impairment (creatinine clearance <50 ml/min), and the choice of ART in such patients should be discussed with an HIV specialist.

In order to limit the incidence of hepatitis flares, once started, anti-HBV drugs in the ART regimen of co-infected patients should not be stopped, even when changes to ARVs are required due to HIV virological failure or intolerance to other antiretrovirals. Hence, other than severe clinical adverse events or grade 3 or 4 laboratory abnormalities ascribed to tenofovir or lamivudine/emtricitabine, co-infected patients should remain on these drugs lifelong.

### 3.3 MANAGEMENT OF CO-INFECTED PATIENTS WITH A CD4 COUNT >350 CELLS/μl

Although there is increasing evidence of a reduction in disease progression (including non-AIDS-related events) when HIV-infected patients are started on ART at CD4 counts >350 cells/μl, owing to resource constraints throughout southern Africa we cannot advocate starting ART in all co-infected patients with higher CD4 counts at this time. Most international guidelines use the HBV DNA level in blood to guide the use of ART in co-infected patients with higher CD4 counts. Again, resource limitations put this expensive test (see appendix) outside our reach as a decision-making tool. However, for ARV-naïve patients with CD4 counts >500 cells/μl and chronic hepatitis B, where resources allow, the clinician is encouraged to refer/discuss the case with a hepatologist with regard to pegylated interferon.

HIV-HBV co-infected patients with ALT ≥2 times the upper limit of normal are at increased risk of HBV disease progression. Hence, in line with international guidelines, we advocate starting tenofovir + lamivudine or emtricitabine-containing ART in patients with CD4 counts > 350 cells/μl if either HBeAg is positive or ALT is 2 times the upper limit of normal. Furthermore, in line with current national policy, ART is recommended for any co-infected patient with CD4 counts >350 cells/μl who has symptomatic liver disease.

Patients with CD4 counts of >350 cells/μl who are asymptomatic, HBeAg negative and have an ALT <2 times the upper limit of normal should be closely monitored with repeat ALT recordings 6-monthly. If there are signs of liver dysfunction without evidence of a cause other than HBV disease progression, the patient should start tenofovir + lamivudine or emtricitabine-based ART.

### 3.4 CHOICE OF THE THIRD DRUG IN AN ART REGIMEN FOR CO-INFECTED PATIENTS

In constructing an ART regimen for co-infected patients, apart from needing to choose drugs with dual activity against HIV and HBV, it is also of paramount importance to try to limit further hepatotoxicity. Given this, we advise avoiding the use of nevirapine in co-infected patients. We recommend efavirenz for first-line ART whenever possible. In women of childbearing age, a boosted PI regimen should be considered if injectable contraception and condom use are not adhered to.

### 3.5 HEPATITIS FLARES IN HIV-INFECTED PERSONS WHO DO NOT KNOW THAT THEY ARE HBV INFECTED

There is no current policy in place for 'catch-up' HBV testing in HIV-infected patients who started ART before the onset of HBV screening. Furthermore, if current national policy is adhered to, there will be an increasing number of HIV-HBV co-infected patients who do not know that they are infected with HBV. These patients may be on ART regimens that include lamivudine as the sole active drug against HBV. Lamivudine resistance will develop in up to 90% at 5 years, at which time a viral breakthrough and hepatitis flare may develop. Since there is a wide range of possible causes for sudden deterioration in liver function during ART, a clinical approach to the co-infected patient on ART who develops liver dysfunction is required. One such approach is depicted in Fig. 2.

## 4. SPECIAL GROUPS

### 4.1 PREGNANT WOMEN

Screening for HBV infection in pregnant women to prevent mother-to-child transmission is a well-established, evidence-based standard of care in developed countries. Furthermore, a systematic review of randomised controlled trials in 2006 found that prophylaxis (vaccination and/or immunoglobulin) given to newborns of mothers infected with HBV reduced perinatal transmission of the virus.<sup>20</sup> This is the critical reason why screening for HBV infection in pregnant women is so important, be it in women who turn out to be co-infected or HBV mono-infected.

Although there are theoretical concerns about the use of tenofovir in pregnancy in relation to bone mineral density and skeletal development of the newborn, the benefit of dual therapy, which includes tenofovir for pregnant co-infected women, outweighs the risk. Similarly, in order to avoid nevirapine, we advocate for the use of efavirenz after 20 weeks' gestation. Boosted lopinavir is an alternative third drug in the co-infected pregnant woman.

### 4.2 NEWBORNS

The risk of developing chronic HBV infection is greatest in newborns who are infected perinatally (90%). Hence any intervention that prevents transmission will have a major impact on long-term morbidity and mortality as well as reducing transmission of HBV to others during childhood and once the person becomes sexually active. If the mother is known to be HBV infected, post-exposure prophylaxis becomes an option.

All newborn babies of mothers infected with HBV, be they mono-infected or co-infected with HIV, should receive HBIG plus the first dose of the hepatitis B vaccine within the first 12 hours after delivery. HBIG and vaccine should be administered at different sites and the 4-dose vaccination schedule completed. If the mother is known to be HBeAg positive, with evidence of high-level viral replication and infectivity, HBIG should be repeated at 1 month. Babies should be tested for the presence of HBsAg at 6 months to determine whether post-exposure prophylaxis was successful.

### 4.3 CHILDREN

Perinatal and horizontal transmission during childhood is the predominant mode of HBV acquisition in southern Africa. Although the principles underlying treatment of adults and children with HIV-HBV co-infection are similar, there are important differences. Only pegylated interferon-alpha, adefovir and lamivudine are licensed for use in children with HBV. Although the efficacy of interferon-alpha in children is similar to that in adults if they are in the immune clearance phase of HBV infection, most children, particularly those in the immune tolerant phase, have normal ALT with high HBV DNA levels, and <10% of these children will clear HBeAg with interferon-alpha.<sup>21</sup>

Tenofovir is not licensed for use in children <18 years of age, although it has been used off-label as part of salvage therapy. Tenofovir is available as an un-scored 300 mg tablet and the suggested childhood dose is 8 mg/kg/day. This means that it is effectively contraindicated in any child weighing <37 kg. A recent study of the use of tenofovir in children in the UK and Ireland as part of ART found evidence of considerable under- and over-dosing.<sup>22</sup> There are also theoretical concerns regarding the use of tenofovir in respect of depletion of bone mineral density. As tenofovir is therefore limited in many infants and children, this effectively leaves lamivudine monotherapy to treat HBV in the face of HIV co-infection. Perinatally and childhood-acquired infection is associated with a high HBV viral load, which increases the risk of acquiring lamivudine resistance if the patient is on monotherapy. The options for management include the use of ART with lamivudine or withholding lamivudine in the regimen until tenofovir can be used. This will depend on the age of the child and the activity/stage of the liver disease, and should be discussed with a specialist paediatrician and hepatologist.

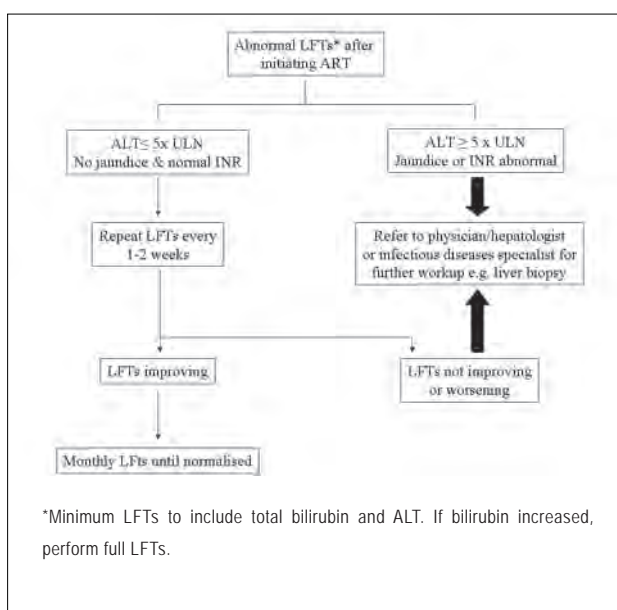


Fig. 2. Clinical approach to management of HIV-HBV co-infected patients who develop liver dysfunction on ART.

#### 4.4 ALTERNATIVE TREATMENT OPTIONS FOR CO-INFECTED PATIENTS WITH HIGH CD4 COUNTS

Alternative therapy for HBV co-infected patients with high CD4 counts is limited primarily by cost (see appendix). The efficacy of pegylated interferon-alpha depends on viral load, ALT level, genotype and the degree of necro-inflammation on liver biopsy. Although good trial evidence is lacking for its use in HIV-HBV co-infection, expert opinion suggests that patients who are HBeAg positive, have elevated transaminases and high CD4 counts, and are found to have necro-inflammation on liver biopsy are most likely to benefit from pegylated interferon-alpha.<sup>23</sup>

#### REFERENCES

- Lavanchy D. Hepatitis B virus epidemiology, disease burden, treatment and current and emerging prevention and control measures. *J Viral Hepat* 2004;11:97-107.
- Beasley RP, Hwang LY, Lin CC, Leu ML, et al. Incidence of hepatitis B virus infections in preschool children in Taiwan. *J Infect Dis* 1982;146:198-204.
- Beasley RP, Hwang LY, Lee GC, et al. Prevention of perinatally transmitted hepatitis B virus infections with hepatitis B virus infections with hepatitis B immune globulin and hepatitis B vaccine. *Lancet* 1983;2:1099-1102.
- Coursaget P, Yvonne B, Chotard J, et al. Age- and sex-related study of hepatitis B virus chronic carrier state in infants from an endemic area (Senegal). *J Med Virol* 1987;22:1-5.
- McMahon BJ, Alward WL, Hall DB, Heyward WL, Bender TR, Francis DP, et al. Acute hepatitis B virus infection: relation of age to the clinical expression of disease and subsequent development of the carrier state. *J Infect Dis* 1985;151:599-603.
- Vardas E, Mathai M, Blaauw D, McAnerney J, Coppin A, Sim J. Preimmunization epidemiology of hepatitis B virus infection in South African children. *J Med Virol* 1999;58(2):111-115.
- Burnett RJ, Francois G, Kew MC, et al. Hepatitis B virus and human immunodeficiency virus coinfection in sub-Saharan Africa: a call for further investigation. *Liver Int* 2005;25:201-213.
- Firnhaber C, Reyneke A, Schulze D, et al. The prevalence of hepatitis B coinfection in a South African urban government HIV clinic. *S Afr Med J* 2008;98(7):541-544.
- Firnhaber C, Viana R, Reyneke A, et al. Occult hepatitis B virus infection in patients with isolated core antibody and HIV coinfection in an urban clinic in Johannesburg, South Africa. *Int J Infect Dis* 2009;13(4):488-492.
- Hoffmann CJ, Charalambous S, Thio CL, et al. Hepatotoxicity in an African antiretroviral therapy cohort: the effect of tuberculosis and hepatitis B. *AIDS* 2007;21(10):1301-1308.
- National Department of Health, South Africa. Clinical Guidelines for the Management of HIV & AIDS in Adults and Adolescents. NDOH, 2010. [http://www.doh.gov.za/docs/factsheets/guidelines/adult\\_art.pdf](http://www.doh.gov.za/docs/factsheets/guidelines/adult_art.pdf) (accessed 25 March 2011).
- BHIVA Guidelines – HIV and Chronic Hepatitis: Coinfection with HIV and Hepatitis B virus infection. Updated October 2004. <http://www.bhiva.org> (accessed 25 March 2011).

#### Declaration of interests and support within the last 3 years (sponsors, managed care and pharmaceutical organisations)

Marc Mendelson receives support from PEPFAR/USAID through ANOVA Healthcare, Wendy Spearman has received travel and conference support from Roche, and Mark Sonderup has received conference support from Hoffman-La Roche.

- Rockstroh JK, Bhagani S, Benhamou Y, et al. European AIDS Clinical Society (EACS) guidelines for the clinical management and treatment of chronic hepatitis B and C coinfection in HIV-infected adults. *HIV Med* 2008;9:82-88.
- World Health Organization. Antiretroviral therapy for HIV infection in adults and adolescents. Recommendations for a public health approach. 2006 revision. <http://www.who.int/hiv/pub/arv/adult/en/> (accessed 25 March 2011).
- Lok ASF, McMahon BJ. Chronic hepatitis B: Update 2009. *Hepatology* 2009;50:661-662.
- Lukhwareni A, Burnett RJ, Selabe SG, Mzileni MO, Mphahlele MJ. Increased detection of HBV DNA in HBsAg-positive and HBsAg-negative South African HIV/AIDS patients enrolling for highly active antiretroviral therapy in a tertiary hospital. *J Med Virol* 2009;81(3):406-412.
- Fonseca MO, Pang LW, de Paula Vacalheiro N, Barone AA, Lopes MH. Randomized trial of recombinant hepatitis B vaccine in HIV-infected adult patients comparing a standard dose to a double dose. *Vaccine* 2005;23:2902-2908.
- Sterne JA, May M, Costagliola D, et al. Timing of initiation of antiretroviral therapy in AIDS-free HIV-1-infected patients: a collaborative analysis of 18 HIV cohort studies. *Lancet* 2009;373:1352-1363.
- 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(5):1302-1306.
- Lee C, Gong Y, Brok J, Boxall EH, Gluud C. Effect of hepatitis B immunisation in newborn infants of mothers positive for hepatitis B surface antigen: systematic review and meta-analysis. *BMJ* 2006;332:328-326.
- Lai CL, Lok AS, Lin AS, et al. Placebo-controlled trial of recombinant alpha 2-interferon in Chinese HBsAg-carrier children. *Lancet* 1987;2:877-880.
- Riordan A, Judd A, Boyd K, et al. Tenofovir use in human immunodeficiency virus-1-infected children in the United Kingdom and Ireland. *Pediatr Infect Dis J* 2009;28:204-209.
- Soriano V, Puoti M, Bonacini M, et al. Care of patients with chronic hepatitis B and HIV coinfection: recommendations from an HIV-HBV international panel. *AIDS* 2005;19:221-240.
- Puro V, De Carli G, Cicalini S, et al. European recommendations for the management of healthcare workers occupationally exposed to hepatitis B virus and hepatitis C virus. *Eurosurveillance* 2005;10(10):260-264.

#### APPENDIX. COST OF LABORATORY TESTS FOR HBV IN THE STATE AND PRIVATE SECTORS, 2010/2011 (PROVIDED BY THE NATIONAL HEALTH LABORATORY SERVICE) AND DRUGS USED IN TREATMENT OF HBV INFECTION (PRICES ARE SUBJECT TO CHANGE – CURRENT PRICES AT THE TIME OF GOING TO PRINT)

Laboratory tests	State sector	Private sector
HBsAg	R 105.89	R171.30
HBeAg	R 105.89	R171.30
Anti-HBc IgG	R 105.89	R171.30
Anti-HBs antibody	R 105.89	R171.30
HBV DNA	R 1 141.22	R1 772.60
<b>Drugs used in the treatment of HBV</b>		
Tenofovir (Aspen)	R210.90 (1 month, incl. of VAT)	
Lamivudine (Adcock)	R96.51 (1 month, incl. of VAT)	
Lamivudine (Sonke)	R44.40 (1 month, incl. of VAT)	
Truvada (tenofovir + emtricitabine) (Aspen)	R313.50 (1 month, incl. of VAT)	
Pegylated interferon-alpha	R11 000/month for adults	