

## Hepatitis B infection in Patients Undergoing Chemotherapy- Prevention and management guidelines

### 1. Management Strategy

#### 1.1 Pre-treatment screening

All patients with haematological malignancy, and all solid tumour patients unless assessed as very low risk, should be screened for HBsAg (Hep B surface antigen) and anti-HBc Ab (anti-Hep B core antibody)<sup>1</sup>

#### 1.2 HBsAg<sup>+</sup> patients

-Test for HBeAg, anti-HBe Ab, anti-HBc IgM, HBV DNA, and anti-HDV (Hepatitis delta virus) Ab. Patients with anti-HDV should be tested for HDV RNA.

-Request U&E, Bone profile, LFT's and Serum creatinine, FBC, AFP, PT and abdominal ultrasound scan, and refer to the Hepatology Services for review. Do not delay the management of the malignant condition.

**-Start antiviral therapy, managed by a hepatologist, preferably 2-3 weeks prior to starting chemotherapy or at the latest on the same day.**

#### **If HBV DNA <2000IU/ml and chemotherapy duration expected to last <6months:**

- Lamivudine 100mg once daily can be used<sup>1</sup>.
- Monitor HBV DNA monthly and switch to tenofovir or entecavir 1mg daily if DNA remains detectable after 3 months<sup>1</sup>.
- Continue for minimum of 6 months after chemotherapy.

#### **If HBV DNA <2000IU/ml and chemotherapy duration expected to last >6months:**

- Entecavir 500micrograms once daily (increased to 1mg if previously treated or lamivudine resistance) or tenofovir 245mg once daily should be used<sup>1</sup>. Continue for a minimum of 6 months after HBeAg seroconversion and HBV DNA is undetectable<sup>1</sup>.

#### **If HBV DNA ≥2000 IU/ml:**

- Entecavir 500micrograms once daily (increased to 1mg if previously treated or lamivudine resistance) or tenofovir 245mg once daily should be used<sup>1</sup>.  
*Lamivudine monotherapy is not indicated for patients with high levels of HBV replication.*
- Continue for a minimum of 6 months after HBeAg seroconversion and HBV DNA is undetectable.

#### **Further Monitoring Guidance**

- Monitor ALT regularly at approximately monthly intervals. It is likely that given the greater viral suppression with entecavir and tenofovir that HBV DNA could be measured at 4 weekly intervals until viral suppression is achieved the then at 12 weekly intervals thereafter.
- Monitor HBsAg, HBeAg and anti-HBe Ab every 12 weeks.

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- Therapy may be required indefinitely for some HBsAg+ patients, ask the Hepatitis Services to review before stopping.
- Once the antiviral therapy is discontinued monitor ALT and HBV DNA every 2-4 weeks for 12 weeks.

### **MHRA Alert Rituximab: Screen for hepatitis B virus before treatment (December 2013)**

- Screening for hepatitis B virus is now recommended in all patients (not only those at risk of this infection) before starting treatment for all indications
- Patients with active hepatitis B disease should not be treated with rituximab
- A patient with positive serology for hepatitis B virus should be referred to a specialist in liver disease before starting treatment with rituximab. During treatment, these patients should be monitored and managed to prevent reactivation of the virus.

### **1.3 HBsAg<sup>-</sup>/anti-HBc IgG Ab<sup>+</sup> patients**

#### **For patients who are having rituximab and other B cell depleting chemotherapy e.g. ofatumumab:**

- Use lamivudine 100 mg once daily 2-3 days before starting chemotherapy or at the latest on the same day.<sup>1</sup>
- Monitor ALT at 4 weekly intervals and HBsAg every 4-8 weeks during chemotherapy and every 8-12 weeks subsequently
- Continue therapy for at least 6 months after completion of chemotherapy, or for as long as presumed immune compromised
- Once antiviral therapy is discontinued monitor ALT and HBsAg every 4 weeks for 3 months

#### **All other patients having chemotherapy:**

Two approaches are possible but the second is the preferred option:

1. Measure HBV DNA at monthly intervals during chemotherapy to detect reactivation, and institute antiviral therapy with tenofovir 245mg once daily or entecavir 500micrograms once daily if HBV DNA becomes detectable.

2. Initiate pre-emptive therapy to prevent reactivation:

- a) Use lamivudine 100 mg once daily 2-3 days before starting chemotherapy or at the latest on the same day
- b) Monitor ALT at 4 weekly intervals and HBsAg every 4-8 weeks during chemotherapy and every 8-12 weeks subsequently
- c) Continue therapy for at least 6 months after completion of chemotherapy, or for as long as presumed immune compromised
- d) Once antiviral therapy is discontinued monitor ALT and HBsAg every 4 weeks for 3 months

### **1.4 Breakthrough during antiviral therapy**

- This is signalled by reappearance of HBsAg in persons who were HBsAg<sup>-</sup> at baseline, or  $\geq 1$  log increase in HBV DNA in persons who were HBsAg<sup>+</sup> at baseline

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- Request a HBV resistance test and ask for an urgent opinion from the Hepatitis Services
- For patients with ALT increases, measure the PT to determine the severity of the liver injury.

# Management Algorithm

Based upon guidance in NICE CG165 June 2013

Baseline screening  
HBsAg and anti-HBc Ab  
(All patients with haematological malignancy, and all solid tumour patients unless assessed as very low risk)

**HBsAg<sup>+</sup>**

**HBsAg<sup>-</sup>/anti-HBc IgG or Total Ab<sup>+</sup>**

**HBV DNA**

**MUST BE** Referred to Hepatology Services

LFT, Renal profile, FBC, AFP, PT, Abdominal US scan

Is the patient having B cell depleting therapies e.g. rituximab, ofatumumab

Discuss with Hepatology Services

HBV DNA >2000 IU/ml

HBV DNA ≤2000 IU/ml

**YES**

**NO**

Liver biopsy may be considered

Use:

- Entecavir 500micrograms once daily(increase to 1mg if previously treated),
- OR**
- Tenofovir 245mg once daily

Use:

- Lamivudine 100mg once daily if chemotherapy is **<6months**
- Entecavir 500micrograms (increase to 1mg if previously treated) once daily if chemotherapy duration is expected to be **>6months**
- OR**
- Tenofovir 245mg once daily if chemotherapy duration chemotherapy is **>6months**

Lamivudine monotherapy 100mg once daily

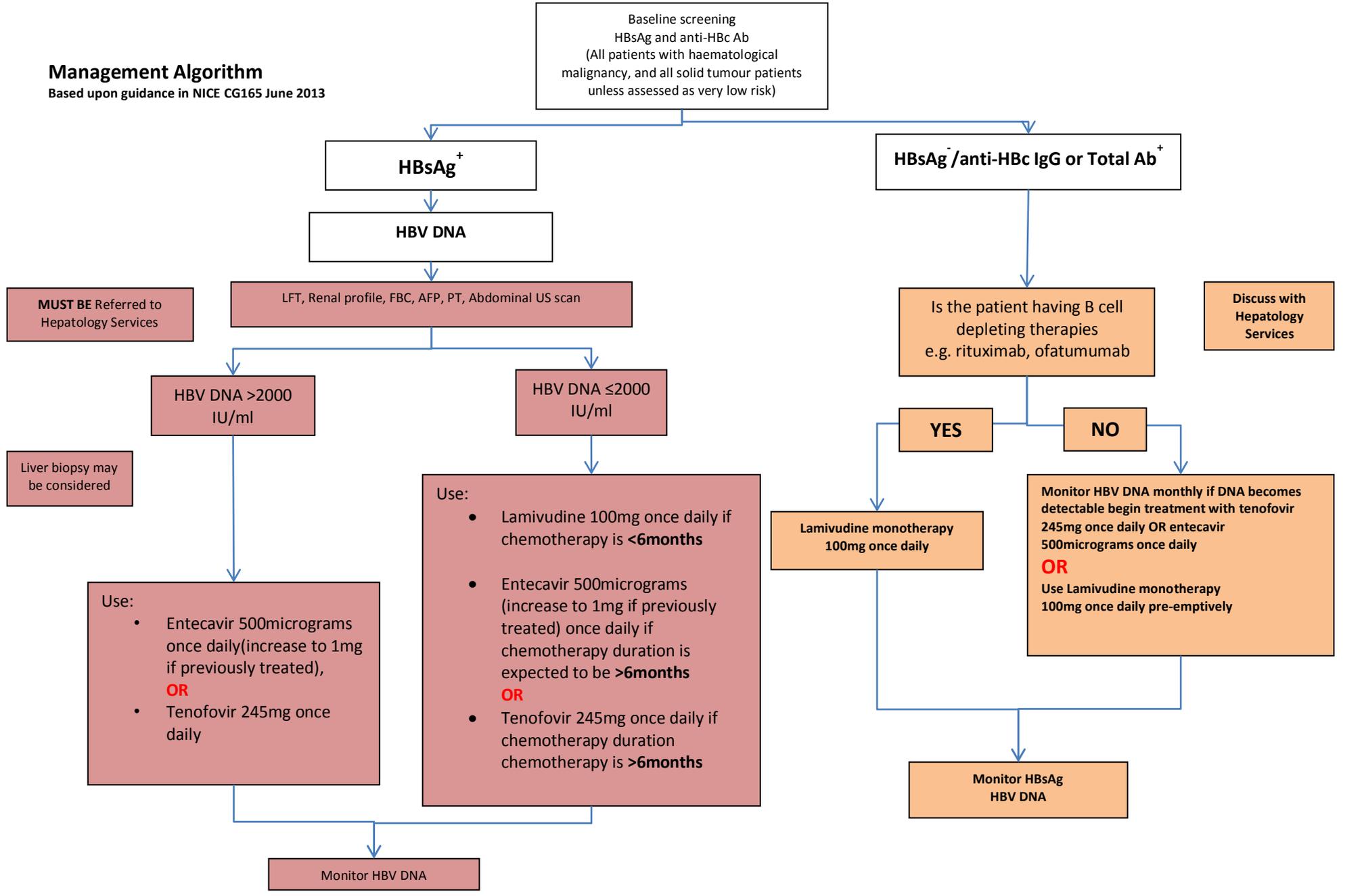
Monitor HBV DNA monthly if DNA becomes detectable begin treatment with tenofovir 245mg once daily OR entecavir 500micrograms once daily

**OR**

Use Lamivudine monotherapy 100mg once daily pre-emptively

Monitor HBsAg  
HBV DNA

Monitor HBV DNA



## 2. Explanation behind recommended guidance above.

### **1. Background**

- Infection with the hepatitis B virus (HBV) can be associated with significant morbidity and has the potential to cause mortality in patients receiving cytotoxic or immunosuppressive chemotherapy for malignancies, particularly lymphoma<sup>2-7</sup>. One study reported a 37% risk of mortality among lymphoma patients who experienced HBV reactivation<sup>3</sup>
- In patients who do not experience severe HBV-related disease or are able to recover from HBV-related disease, cancer survival may be impaired because of the alterations or cessation of chemotherapy that may be required in the presence of HBV infection and hepatic impairment<sup>8,9</sup>
- Disease pathogenesis is related to an increase in HBV replication during immunosuppression, with a resultant hepatocyte destruction and inflammation upon immune reconstitution
- The likelihood of HBV reactivation is highest in HBsAg positive patients and lowest in HBsAb patients with a high anti-HBs titre. (See 3. for interpretation of HBV virological markers)

### **2. Conditions that enhance the risk for HBV-reactivation**

- Risk factors for HBV-related reactivation, subsequent hepatitis and mortality have been proposed, but it is difficult to reliably define the level of risk in individual patients. Identified risk factors include:
- Host: Male gender and young age
- Disease: High-intensity cytotoxic or immunosuppressive chemotherapy, continuous immune suppressive therapy, use of steroids, anthracyclines, or rituximab<sup>9-15</sup>
  - Steroids directly promote HBV replication by acting on a responsive element on the HBV genome
  - The reported risk of reactivation following use of rituximab alone or rituximab+chemotherapy is ~20% and ~15% respectively<sup>9</sup>. The highest risk is reported in patients treated with both steroids and rituximab
  - Some authors have also reported a risk following use of alemtuzumab or infliximab

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### 3. Interpretation of HBV virological markers

HBsAg	Anti-HBc Total Ab	Anti-HBc IgM	Anti-HBs Ab	HBeAg	Anti-HBe Ab	HBV DNA (IU/ml)	Interpretation
+	+	usually negative	usually negative	+	-	$>10^4$	Chronic hepatitis B <sup>1</sup>
+	+	-	usually negative	-	+	$<10^3$	Inactive phase <sup>2</sup>
+	+	-	usually negative	-	+	$>10^{3-4}$	Chronic HBeAg negative hepatitis B
-	+	-	+/-	-	+/-	-	Past HBV infection <sup>4</sup>
-	+	-	-/+	-	+/-	+	Occult HBV infection <sup>5</sup>
-	-	-	+	-	-	-	Vaccination

<sup>1</sup> Anti-HBc IgM may be detectable during flares of chronic infection

<sup>2</sup> Patients with HBV DNA levels around  $10^3$  require careful assessment as an apparently inactive carrier may prove to have fluctuating levels of HBV DNA and active disease

<sup>3</sup> HBV DNA levels may fluctuate and more than one measurement may be required to identify active disease

<sup>4</sup> A proportion of anti-HBc Total Ab<sup>+</sup> results (in the absence of anti-HBs and/or anti-HBe Ab) may be false positive. There are no reliable strategies for differentiating past infection from false positivity in haematology patients, although weakly reactive results should undergo confirmation in a subsequent sample. Challenge with one dose of the HBV vaccine has been proposed as a strategy, whereby an anti-HBs Ab response  $>10$  IU/L measured one to four weeks after vaccination can be regarded as indicative of a past infection. However, the strategy has not been evaluated in haematology patients who may have suboptimal immune responses to vaccination and be wrongly classified as a result. This strategy is not currently recommended

<sup>5</sup> HBV DNA detection in blood is typically intermittent and negative results do not exclude occult infection.

### 4. HBV-related disease

- Patients who are **HBsAg<sup>+</sup> with high HBV DNA levels (typically  $>10^4$  IU/ml)** are at risk of severe liver disease in the short term and show an increased long-term risk of progressive disease leading to cirrhosis and hepatocellular carcinoma
- Patients who are **HBsAg<sup>+</sup> with low HBV DNA levels ( $<10^3$  IU/ml)** are at risk of reactivation with resumption of high levels of virus replication
- Patients who are **HBsAg<sup>-</sup>/anti-HBc<sup>+</sup>** are at risk of reactivation with reappearance of HBsAg and high levels of virus replication<sup>16</sup>. The risk is highest in persons with anti-HBs  $<10$  IU/L, but HBV may reactivate despite high anti-HBs levels
- Increases in HBV DNA levels  $>10^3$  IU/ml typically precede liver injury and ALT elevation
- Disease severity ranges from mild to fatal. Although spontaneous resolution can occur, severe liver disease and fulminant hepatitis have been reported.
- Responses to antiviral therapy can be poor, and mortality increased if therapy is started after reactivation and the onset of liver damage<sup>6</sup>. In patients with

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progressive liver injury the risk of mortality can be as high as 40% despite lamivudine therapy

- The timing of LFT impairment varies, although it often coincides with the withdrawal of immunosuppression

### **5. "Occult" HBV infection**

- Defined as the detectable HBV DNA in blood or liver, in the absence of HBsAg
- Anti-HBc and/or anti-Hbs Ab are generally (but not universally) present
- HBV DNA levels in blood are generally low ( $<10^2$ )
- Detection of HBV DNA in blood is intermittent in patients followed prospectively. Negative HBV DNA results do not exclude "occult" infection and all patients with anti-HBc Total Ab should be regarded as possible carriers of HBV DNA. Evidence indicates a risk of reactivation and disease in patients who are HBsAg<sup>-</sup>/anti-HBc<sup>+</sup>/HBVDNA<sup>-</sup> in blood but have detectable HBV DNA in the liver<sup>18</sup>

### **6. Antiviral therapy**

- Given that reactivation of HBV infection carries a risk of mortality that may not be abolished by prompt institution of antiviral treatment, pre-emptive prophylaxis is considered the preferred option in patients at risk<sup>19-27</sup>
- Little has been published regarding antiviral therapy for HBV in haematology patients. Current options include lamivudine, tenofovir and entecavir. Lamivudine has been used in haematology patients, whereas experience with other antivirals is very limited in this population. Nonetheless, there is sufficient experience from the general HBV infected population to guide the use of the newer and more potent antivirals, i.e. tenofovir or entecavir
- Prophylaxis with lamivudine decreases the incidence of HBV reactivation among HBsAg<sup>+</sup> persons from 21%-80% to 0%-17%<sup>19-27</sup>. Lamivudine prophylaxis has been shown to be cost-effective among HBsAg<sup>+</sup> patients undergoing chemotherapy for lymphoma<sup>2</sup> by reducing the number and severity of HBV reactivations, and the risk of both liver-related and cancer-related deaths
- It should be noted however that:
  - Dosage and duration of antiviral treatment have not been optimised
  - Flares of hepatitis and even fulminant hepatitis have been described following withdrawal of antiviral therapy
  - The long-term use of lamivudine can be complicated by the emergence of resistance
  - Breakthrough reactivation can occur despite lamivudine prophylaxis. The overall risk is estimated to range up to 17%
- Alternative medications for patients that require greater antiviral potency and a higher barrier to the emergence of resistance (typically, patients with high rates of HBV replication) include tenofovir or entecavir. Patients who have already developed lamivudine resistance can be treated with tenofovir alone. Entecavir has reduced activity in the presence of lamivudine resistance and is not routinely recommended as monotherapy in this setting (the licensed dose of entecavir in this setting is 1mg daily)

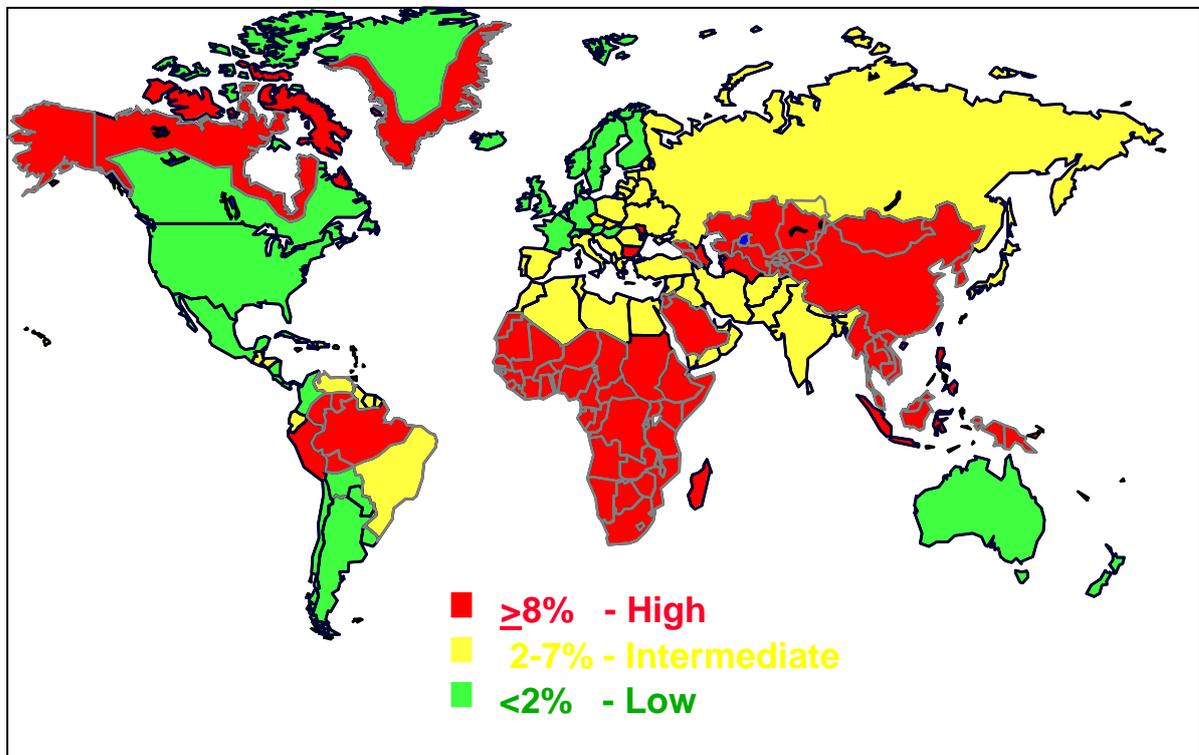
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- Entecavir has a good overall (including renal) safety profile. Both tenofovir and entecavir require dose adjustment in the presence of renal impairment.
- Of the two agents tenofovir and entecavir- tenofovir has more evidence of being used safely used during pregnancy<sup>28</sup>.

#### Prevalence of HBsAg positivity worldwide



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