Liver disease in individuals with HIV-HBV co-infection is now a major cause of mortality worldwide, including Asia. The pathogenesis of liver disease in this setting is multifactorial, but includes drug toxicity and immunological factors, such as immune restoration disease. Staging of chronic hepatitis B is important prior to commencement of anti-retroviral therapy and should include quantification of HBV DNA, and, where possible, an assessment of liver fibrosis, either by liver biopsy or non-invasive measurement. Earlier treatment of both HIV and HBV is now generally advocated, and treatment is usually life-long.

**Keywords:** Hepatitis, HIV-HBV co-infection, liver fibrosis.

Approximately 370 million people globally are infected with hepatitis B (HBV), nearly 36 million people are infected with human immunodeficiency virus (HIV) and an estimated 2-4 million people have co-infection with HIV and HBV [1]. The prevalence of chronic HBV (CHB) infection in people with HIV is 5-20%, with particularly high levels in many Asian countries [2]. In the TREAT Asia Observational Database, approximately 10% of HIV-positive individuals were co-infected with HBV [3]. Similar rates were found in Singapore and India, but the rate of HBV co-infection was higher in Taiwan at 17% [4-6]. Since the widespread use of highly active antiretroviral therapy (HAART), liver disease has emerged as one of the most important causes of morbidity and mortality among HIV-positive individuals, particularly those co-infected with viral hepatitis [7, 8].

**Natural history and pathogenesis of liver disease**

Without treatment, HIV-HBV co-infection is characterised by higher HBV viral loads than HBV mono-infection [9], less HBeAg seroconversion [10], and more common progression from acute hepatitis B to chronic hepatitis B (CHB) [11]. Lower alanine aminotransferase (ALT) levels and less necro-inflammatory activity on liver biopsies in co-infected individuals, suggest less hepatic inflammation than in mono-infection, and yet progression of fibrosis is more rapid and development of cirrhosis more common [12].

Multiple factors may contribute to increased fibrosis in HIV-HBV co-infection compared to either infection alone. HIV infects different liver cells, including Kupffer cells, portal mononuclear inflammatory cells, endothelial cells and hepatocytes (reviewed in [13]), and may potentially interact with HBV directly. HIV can also infect hepatic stellate cells in vitro [14]. Hepatic stellate cells are the main effector cell leading to hepatic fibrosis, however, HIV infection of these cells has not yet been demonstrated in vivo. In HIV-HBV co-infected individuals receiving HAART, unique mutations in HBV have been defined which may directly alter pathogenesis [15], and high rates of HBV mutations conferring drug resistance have also been demonstrated [16].

Impaired HBV-specific immune responses in HIV-HBV co-infection may also contribute to the increase in liver disease. The HBV-specific CD4
T-cell response is diminished in HIV-HBV co-infection compared to HBV mono-infection [17], and HBV-specific CD8 T-cell responses are reduced following clearance of HBV in HIV infected individuals compared to uninfected individuals [18]. Generalised immune activation may also potentially contribute to liver damage [19]. HIV infection leads to extensive and largely irreversible loss of gut mucosal immune cells, including CD4 T-cells [20]. This may potentially lead to an alteration in gastrointestinal integrity and to microbial translocation, as recently demonstrated by increased lipopolysaccharide (LPS) from bacterial cell walls detected in the circulation of HIV-infected individuals [19]. Impaired portal venous function can also lead to an increase in LPS levels, and elevated concentrations of LPS have been demonstrated in the setting of alcohol use, cirrhosis, chronic HCV infection and HIV-HCV co-infection. However, LPS levels have not been examined in acute or chronic HBV infection or HIV-HBV co-infection [21, 22].

### Assessment of HIV-HBV co-infection prior to treatment

In addition to assessing HIV status with CD4 T-cell count and HIV viral load, specific tests are required in the evaluation and follow up of an individual's co-infected with HBV (Table 1) [23].

#### Aminotransferase levels

Elevated serum ALT levels are associated with increased risk of liver damage, as well as greater likelihood of response to therapy in HBV mono-infection [24]. However, significant fibrosis can occur in individuals with normal ALT levels. In a recent long term prospective study of 3653 Taiwanese participants with chronic HBV mono-infection, called the REVEAL-HBV study, nearly all participants (94%) had a normal baseline ALT. Despite this, a high risk of hepatocellular carcinoma (HCC) and cirrhosis was observed over the median 11-year follow-up. HBV DNA levels greater than 2000 IU/mL (10⁴ copies/mL) was associated with increased risk of HCC or cirrhosis, independent of ALT [25].

In HIV-HBV co-infection, ALT levels tend to be lower overall, due to either impaired HBV-specific immune response, or reduced hepatic necro-inflammation, and yet significant fibrosis may still be present [12]. Normal ALT levels should therefore be viewed with caution in HIV-HBV co-infection, especially in the presence of high HBV DNA levels.

Elevated ALT levels in HIV-HBV co-infection may be multifactorial (summarized in Table 2) [23].

A recent study of HAART in 537 HIV-infected individuals in South Africa, of whom 106 (20%) were HBsAg-positive, showed low rates of hepatotoxicity.

### Table 1. Tests for the evaluation and follow-up of HIV-HBV co-infected individuals.

<table>
<thead>
<tr>
<th>Evaluating HBV in HIV-HBV co-infected individuals</th>
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<tbody>
<tr>
<td>ALT</td>
</tr>
<tr>
<td>HBeAg and anti-HBe</td>
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<tr>
<td>HBV DNA</td>
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</tbody>
</table>

Testing for other hepatitis viruses: HAV, HCV, HDV (formerly known as Delta virus)

### Additional evaluation of HBV (where available)

- Liver fibrosis staging
  - Liver biopsy
    - Non-invasive tools such as FibroScan®
    - Algorithms such as Fibrotest®, Hepascore or APRI
  - HBV genotype
  - HBV polymerase sequencing (if prior exposure to anti-HBV drugs)

### Monitoring (6 monthly, depending on resources)

- Clinical assessment
- ALT
- HBeAg and anti-HBe
- HBV DNA
- HCC monitoring (cirrhosis or >45 years old): 6 monthly AFP and liver ultra-sound

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HBV=hepatitis B virus; ALT=alanine aminotransferase; HBeAg=hepatitis B virus e antigen; HAV=hepatitis A virus; HCV=hepatitis C virus; HDV=hepatitis D virus; APRI=aspartate aminotransferase (AST) to platelet ratio index; HCC=hepatocellular carcinoma; AFP=alpha-fetoprotein.
The rate of elevated ALT in those with a low HBV DNA level (<2000 IU/mL, n=60) was similar to the rate in HBsAg-negative individuals, although in the group with high HBV DNA level (n=46) elevated ALT was 4.4 times more likely and occurred more commonly within 12 weeks of commencing HAART.

A very common cause of elevated ALT is HAART [23]. Possible mechanisms for HAART-related hepatic flare (HF) include cumulative dose-related liver injury with drugs such as nevirapine [27], hypersensitivity reactions to nevirapine or abacavir [28], or mitochondrial damage from didanosine, zidovudine or stavudine [29]. Several protease inhibitors, including the recently licensed darunavir are associated with increased hepatotoxicity in co-infected patients via an unclear mechanism [30]. Other newer agents such as the non-nucleoside reverse transcriptase (NRTI), etravirine, the integrase-inhibitor raltegravir, and CCR5-antagonist maraviroc have not been associated with increased hepatotoxicity in HIV-hepatitis co-infected individuals to date [31-33].

HBeAg and HBeAb

HBeAg is a soluble derivative of the precore protein of HBV secreted into the serum. It is required for the establishment of persistent infection [34], and is thought to induce immunological T-cell tolerance [35]. Mutations can occur in the precore (PC) or basal core promoter (BCP) region of the HBV genome, reducing the amount of HBeAg secreted. The commonest BCP variants involve the double mutation of A1762T plus G1764A [36]. In genotypes B and C, more common in Asia, the BCP mutations usually occur in conjunction with the PC mutation G1896A, which leads to a stop codon and loss of HBeAg [37]. Seroconversion from HBeAg to anti-HBe leads to a significant drop in HBV DNA to undetectable levels, normalisation of ALT, and an improvement in disease outcome. Instead, the mutations described above may lead to lower levels of HBV DNA but continued disease activity. HBeAg seroconversion is less common in HIV-HBV co-infection than HBV mono-infection [10, 38]. However, HBeAg loss in a recent prospective study following initiation of HBV-active HAART was relatively high at 33% over 48 weeks of treatment [39]. Recently, quantitative measurement of HBeAg has become possible and studies have explored the use of HBeAg levels as a predictor of response to therapy [40, 41].

HBV DNA

In HBV mono-infected individuals, the relationship between HBV DNA and clinical disease (cirrhosis and HCC) is based on strong evidence including data from the REVEAL-HBV study [42]. In this study, individuals with a baseline HBV DNA level greater than 20 000 IU/mL or 200 000 IU/mL were six and ten times more likely respectively to develop cirrhosis than those with undetectable HBV DNA at baseline.

Similar long term natural history studies for HIV-HBV co-infected individuals have not been performed. Previously, experts have recommended using similar thresholds for treatment of HBV mono-infection for HIV-HBV co-infection [43, 44]. However, more recent HIV-HBV co-infection guidelines recommend a lower threshold of 2 000 IU/mL for treating patients with CHB due to its accelerated course in HIV-infected individuals [11, 23, 45]. In patients with cirrhosis, HBV should be suppressed to the lowest possible level [46].

HBV Genotype

HBV genotype can help predict response to therapy and risk of progression to cirrhosis and HCC. Genotypes B and C are more common in Asia, whereas genotype A is more common in the United States, Northern Europe and Africa. Genotype D is found in Southern Europe, Middle East and India [47]. In Asian studies, genotype B appears to have a more benign course than genotype C, with more common spontaneous HBeAg seroconversion, less rapid progression to cirrhosis, and lower rates of HCC [48]. However, subtypes of genotype B, B1 (or Bj) and B2 (or Ba), found more commonly in Japan and Taiwan, respectively may have different profiles [47].

Table 2. Possible causes for raised ALT in HIV-HBV co-infected individuals.

<table>
<thead>
<tr>
<th>Direct drug toxicity</th>
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<tr>
<td>Immune restoration disease (IRD)</td>
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<tr>
<td>HBsAg or HBeAg seroconversion or reversion</td>
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<tr>
<td>Selection of drug resistance</td>
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Genotypes also vary in their response to pegylated interferon (pegIFN) in terms of HBeAg and HBsAg clearance (A>B>C>D) [49, 50]. Where HBV genotype testing is available, it offers a useful tool that may help predict response to pegIFN.

**HBV polymerase sequencing**

The HBV genome contains four overlapping open reading frames (ORFs), the largest of which is the Pol ORF which encodes the polymerase protein. This protein is made up of four regions (Fig. 1), including the DNA polymerase/reverse transcriptase (Pol/RT) [51]. This enzyme reverse transcribes the minus DNA strand from an RNA intermediate during the viral replication cycle, but lacks a proof-reading capacity and is therefore error-prone. A four codon sequence of the polymerase gene encoding amino acid positions 551-554 of the polymerase protein (also denoted rt203-206 because the Pol/RT region begins at amino acid 349) is the so-called YMDD motif (tyrosine-methionine-aspartate-aspartate) [52]. Mutations within this motif at position rt204 are typical of LMV and telbivudine resistance but are also important contributors to resistance to other nucleos(t)ide analogues [52].

Sequencing of the polymerase gene can be performed using a variety of polymerase chain reaction (PCR) techniques. The detected sequence of dominant strains of HBV present in an individual can then be compared with published sequences to determine significant mutations.

**Staging liver fibrosis**

Although liver biopsy remains the “gold standard” for assessing hepatic fibrosis, non-invasive measures of elastic stiffness, such as FibroScan® are now more widely available. Algorithms based on a range of biochemical and haematological indices such as FibroTest®, Hepascore, or aspartate aminotransferase (AST) to platelet ratio index (APRI) are also available. FibroScan® and the available algorithms have not yet been studied extensively in HIV-HBV co-infection.

Fibrosis staging offers important prognostic value, as well as guiding the timing of therapy and the role of intensive hepatocellular carcinoma (HCC) screening, or screening for oesophageal varices. The detection of advanced fibrosis also predicts those individuals at greatest risk of significant hepatic flare due to drug toxicity, drug resistance or seroconversion/reversion. Liver biopsy or non-invasive measures of liver stiffness are recommended, but if unavailable then treatment decisions need to be made without fibrosis staging.

![Fig. 1 HBV polymerase and common drug-resistant mutations (adapted from [52]). HBV=hepatitis B virus; RT, rt=reverse transcriptase;Pol/RT=polymerase/RT region; LMV=lamivudine; ADV=adefovir; TDF=tenofovir.](image)
Treatment

**Therapeutic Goals**

In HBeAg-positive CHB mono-infection, HBeAg seroconversion combined with undetectable HBV DNA is usually the goal of therapy. If this is sustained for greater than six months then therapy is frequently ceased. In HBeAg-negative CHB, treatment is usually life-long, and aimed at sustained viral suppression to the lowest possible level (undetectable HBV DNA by sensitive PCR assay), to prevent the long-term complications of cirrhosis and HCC.

In HIV-HBV co-infection, the therapeutic goal is also the prevention of the same long-term sequelae of CHB, by suppressing HBV DNA below detection by the most sensitive available assay [43]. An additional aim is to minimise HAART-associated hepatotoxicity. Treatment is usually lifelong, and cessation of HBV-active HAART following HBeAg seroconversion is not usually recommended [43, 44, 53]. The timing and choice of treatment depends upon the need for HAART, primarily according to CD4 criteria, although commencement at any CD4 count has recently been recommended for those with HIV-HBV co-infection, on an individualised basis [54]. If HAART is required, the regimen usually includes two agents with complementary anti-HBV activity. If HAART is not required, agents with exclusive HBV and no HIV activity are used to avoid inducing HIV resistance (see Fig. 2).

**Monitoring treatment response and for drug resistance**

Recommended monitoring of HIV-HBV co-infected patients on treatment is summarised in Table 1. The risk of developing HCC is higher in individuals with HIV-HBV co-infection than HBV mono-infection [55]. Screening for early HCC, with liver ultrasound and serum α-fetoprotein (AFP) measurement every 6-12 months is frequently recommended, although evidence for this is still limited [56]. However, screening is usually practiced in the hope of detecting early HCC for which potentially curative hepatic resection or orthotopic liver transplantation (OLT) may be offered [57]. Screening for oesophageal varices by gastroscopy is also recommended in patients with cirrhosis, and referral to a liver transplant or gastroenterology unit is recommended for the management of patients with decompensated cirrhosis. OLT in HIV-positive individuals is complex, although cumulative survival is similar to HIV-negative controls when performed in transplant centres by experienced surgeons, hepatologists and infectious diseases physicians [23, 58].

**Concurrent treatment of HBV and HIV**

When HAART is required in HIV-HBV co-infected individuals, it is preferable to include two HBV-active agents, regardless of the HBV DNA level or fibrosis stage [23]. An NRTI backbone with HBV

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**Fig. 2** When to treat HBV in HIV-HBV co-infected individuals. HAART=highly active anti-retroviral therapy; HBV=hepatitis B virus.
combination therapy can be delivered using the co-formulation of tenofovir (TDF) and emtricitabine, Truvada®. If LMV has been used previously as part of HAART, and HBV replication is not controlled, then LMV-resistant HBV is invariably present [59]. HBV treatment should therefore be based on rescue therapy with TDF, entecavir (ETV) or adefovir (ADV). If TDF cannot be tolerated, other options would include either ADV or ETV in combination with either emtricitabine or LMV. If emtricitabine/ LMV cannot be tolerated, then TDF alone or in combination with ETV is another option.

Lamivudine

Lamivudine (LMV) shares cross-resistance with emtricitabine and telbivudine, as they are all L-nucleoside analogues. LMV has been extensively studied against HBV (at 100 mg per day), and has good anti-HIV activity (at 300 mg per day). Although it is well tolerated and is highly potent against HBV [60], the barrier to resistance is low and the rate of drug resistance high. Resistance rates of up to 20% per year are reported in HBV mono-infection [61], and 50% after two years, and 90% after four years in co-infected patients [16].

LMV-resistant mutations occur at a number of sites in the HBV polymerase, such as rtM204V/I, which is often accompanied by the compensatory mutation rtL180M. (Fig. 1) The rtM204V/I mutation confers cross-resistance to other L-nucleosides (emtricitabine, telbivudine and clevudine) [62]. The addition of just one of rtS184G, rtS202I or rtM250V to the two common LMV-resistant mutations, rtL180M and rtM204V, results in ETV resistance [63]. When rtL173V is added to these two common LMV-resistant mutations, the resulting triple mutant has impaired binding to HBsAb in vitro. Therefore, this mutant could act as a “vaccine escape mutant” and could potentially infect individuals vaccinated to HBV. This triple mutant occurs at great frequency in HIV-HBV co-infected individuals and has been reported in up to 17% of patients on long-term lamivudine [16]. Another common LMV-resistant mutant, rtA181T/V confers cross-resistance to adefovir [52]. This low barrier to resistance and wide cross-resistance makes LMV monotherapy inappropriate in individuals with HBV, with or without HIV.

Emtricitabine

Emtricitabine (FTC) is structurally similar to LMV and therefore shares a common resistance profile and efficacy against HIV and HBV [64, 65]. Emtricitabine and LMV should be considered interchangeable, and emtricitabine offers no advantage in the setting of lamivudine resistance.

Tenofovir

Tenofovir disoproxil fumarate (TDF) is an adenosine nucleotide analogue like adefovir, but with better efficacy and safety profiles for treating HIV. An anti-HBV effect in both treatment-naive and LMV-resistant HBV has been demonstrated in subgroup analyses of HBV-infected individuals within HIV trials [66]. TDF is more potent than adefovir at suppressing HBV (91% versus 56% with undetectable HBV DNA after 48 weeks (p<0.001)) among HBeAg-negative HBV mono-infected individuals [67]. Similar results have been reported in retrospective analyses and one small prospective study in co-infected individuals [68].

No virological resistance has been reported to TDF, although complete virological suppression is not achieved in all patients, even after 72 weeks [69]. The reasons for this are unclear as in many cases the persistent virus is wild-type. A novel HBV polymerase mutation (rtA194T) has been reported in individuals taking TDF, which conferred reduced susceptibility in vitro, when combined with LMV-resistance mutations, rtL180M and rtM204V [70]. This mutation has not yet been associated with clinical or virological treatment failure. Long-term prospective data for TDF in co-infection are lacking. However, the dual antiviral activities of TDF, favourable side-effect profile, and high genetic barrier to resistance make it a popular agent in treating HIV-HBV co-infection.

Treatment of HBV when HAART not yet required

Anti-HBV agents shown not to significantly affect HIV are the alpha interferons (standard interferon (IFN) and pegIFN), adefovir (ADV) and telbivudine (LDT). ETV was previously thought not to have anti-HIV activity but reduction in HIV viral load and the development of resistance mutations have since been linked to ETV. ETV still has a role in the treatment of HIV-HBV co-infection, but must be used in conjunction with HAART.
Interferons

The use of interferons to treat HBV in HIV-HBV co-infection has not been extensively studied. Small open-label studies of IFN found poor response rates in HIV-HBV co-infection, probably due to immune deficiency [71, 72]. Only one small study of pegIFN in HIV-HBV co-infection has been reported (n=10), in which a pegIFN monotherapy was compared to pegIFN and delayed TDF [73]. The safety profile of pegIFN has been demonstrated in HIV-HCV co-infection, and evidence of increased efficacy in HBV mono-infection supports the role of pegIFN in treating HIV-HBV co-infected individuals with preserved CD4 T-cell counts without decompensated cirrhosis.

In HBV mono-infected individuals, the HBeAg seroconversion and viral suppression rate is approximately 24-32% [74, 75]. Factors favouring virological response in HBV mono-infection are HBeAg-positive CHB, low HBV DNA levels, raised ALT levels and HBV genotype A or B. PegIFN remains an option for the treatment of HBV where HIV does not yet require treatment, due to the finite duration of treatment (48 weeks) and the lack of potential for drug resistant HIV, particularly for those with favourable HBV characteristics. However, data in HIV-HBV co-infection are lacking, and the unfavourable side-effect profile is a significant disadvantage.

Adefovir

Adefovir dipivoxil (ADV) shows anti-HIV activity at 120 mg, but is used at a reduced dose of 10 mg per day due to high rates of nephrotoxicity at higher doses. ADV does not demonstrate anti-HIV activity at this dose, and no HIV mutations have been detected due to ADV monotherapy in the setting of uncontrolled HIV replication [76]. ADV is effective against both wild-type and LMV-resistant HBV, although ADV resistance mutations at rtN236T and rtA181V can be found at rates of up to 29% after almost 5 years of treatment [77]. The rate of resistance is markedly reduced when ADV is added to LMV rather than used as sequential monotherapy in LMV-resistant HBV [78, 79]. Primary resistance to ADV is not uncommon, particularly in the presence of polymorphisms such as rtD233V [23], and HBV DNA reduction of less than 2 log is seen in up to 25% of HBV mono-infected individuals over 48 weeks [80].

Telbivudine

Telbivudine (LdT; b-L-2’-deoxythymidine) is an orally bioavailable L-nucleoside with specific anti-HBV activity. In a recent double-blind phase 3 study of 1370 patients with either HBeAg-positive or HBeAg-negative CHB, participants were randomised to receive 600 mg telbivudine or 100mg LMV once daily [81]. The primary endpoint was a reduction in serum HBV DNA to <5 log copies/ml along with HBeAg loss or normalisation of ALT. A therapeutic response was achieved in 75% following telbivudine compared with 67% following LMV (p=0.005). The antiviral potency was higher and the emergence of drug resistance was lower in telbivudine compared with LMV [81]. Unfortunately, telbivudine and LMV share cross-resistance, so that combination therapy with LMV and telbivudine is actually less effective than telbivudine monotherapy [82].

Experience with telbivudine and HIV is limited. In vitro, telbivudine has no activity against HIV-1 [83]. Telbivudine is currently recommended as the preferred treatment of HBV for HIV-HBV co-infected individuals when treatment of HIV is not required (usually when CD4+ T-cells >350 cells/ml). However, there is in fact very limited experience of telbivudine in HIV-HBV co-infected individuals in vivo [84, 85]. Telbivudine should not be used in HIV-HBV co-infected individuals with previous or current LMV-resistance.

Entecavir

Entecavir (ETV) is a guanosine analogue with high potency against HBV at 0.5 mg per day. Compared to LMV in HBeAg-positive, nucleoside analogue-naive HBV mono-infected individuals, ETV demonstrated more frequent histological improvement (72% versus 62%, p=0.009), ALT normalisation (68% versus 60%, p=0.02), undetectable HBV DNA (67% versus 36%, p<0.001), but no difference in HBeAg over 48 weeks.[86] Similar results were also seen in HBeAg-negative patients [87].

ETV was initially thought not to have anti-HIV activity, but recent studies have demonstrated significant anti-HIV activity with a one log decline in HIV RNA and the emergence of the rtM184V mutation which is associated with reduced susceptibility to lamivudine [88, 89]. Therefore, ETV is now contraindicated for the treatment of HBV in the absence of HAART in HIV-HBV co-infected individuals.
Genotypic HBV-resistance to ETV depends on at least three mutations: rtL180M and rtM204V and either rt184G/S, rtS202I or rtM250V. The first two mutations are common LMV-resistant mutations, while changes at position 184 also occur in patients on LMV [63]. Therefore, ETV resistance is more common in LMV-experienced individuals, where a higher dose of 1mg daily is used. The main role for ETV in individuals with HIV-HBV co-infection is as rescue therapy for LMV or TDF resistance or intolerance, in the presence of suppressed HIV under HAART. Care should be taken when changing from TDF to ETV in individuals with a prior history of LMV-resistance and fully suppressed HBV DNA. A small recent case series showed high rates of viral rebound in this setting [90].

Combination therapy

In HBV mono-infection, combination therapy using nucleos(t)ide analogues can result in the prevention of drug resistance. Combination therapy using adefovir and LMV monotherapy in less virological breakthrough and fewer YMDD mutations (2% versus 20%) than LMV monotherapy over 52 weeks in a prospective randomised study of 115 treatment-naive patients with CHB [91]. In the setting of LMV-resistance, add-on therapy with adefovir results in less adefovir resistance and greater viral suppression than switching to adefovir [78].

A recent prospective randomised study in Thailand called the Tenofovir in Co-infection study (TICO) compared LMV monotherapy (arm 1, n=13) with TDF monotherapy (arm 2, n=12) and combination therapy using LMV and TDF (arm 3, n=11) in treatment-naive HIV-HBV co-infected individuals [39]. HBV DNA suppression below 200 IU/mL was more common TDF-based regimens (92% in arm 2 and 91% in arm 3) compared to LMV monotherapy (46% in arm 1, p=0.013). However, combination therapy did not show any advantage over TDF monotherapy over the first 48 weeks reported to date. Nonetheless, current recommendations favour combination HBV therapy, preferably with TDF and either LMV or emtricitabine for HIV-HBV co-infection whenever possible.

Management of specific clinical situations

Immune restoration disease (IRD)

Following the initiation of HAART in individuals with low CD4 T-cell counts (<100 cells/mL), approximately 10-30% of individuals present with a new opportunistic infection or worsening clinical symptoms of an already established infection [92], a condition which is often referred to as immune restoration disease (IRD). Hepatotoxicity (Grade 3 (5-20x upper limit of normal (ULN)) or Grade 4 (>20x ULN) transaminitis) after HAART occurs more frequently in HIV-infected individuals with either HBV or HCV co-infection [93]. The aetiology of abnormal ALT, or HF, following the initiation of HAART is often multi-factorial including worsening of underlying liver disease, antiretroviral hepatotoxicity, other medications and opportunistic infections, as well as IRD [94].

A newly regenerated immune response can result in significant hepatic inflammatory activity and marked reductions in HBV viraemia, even occasionally in the absence of active HBV drugs [95]. In individuals with advanced HIV infection, HF is common and is significantly associated with higher HBV DNA and ALT prior to initiation of HAART [39]. Occasionally, HBV IRD is subsequently followed by anti-HBe, and even anti-HBs, seroconversion. In TICO, seroconversion rates were high: 33% lost HBeAg and 8% lost HBsAg [39]. When HBV IRD is followed by seroconversion there is a high chance of long term HBV control providing immunological restoration is maintained [95]. On the other hand HBV IRD with HF can also be potentially serious, even fatal, in some circumstances. Hepatic decompensation following HBV IRD is a recognized complication in patients with underlying cirrhosis and in a few cases this has resulted in death [96]. The relative risk of HBV IRD in individuals who initiate HAART with higher CD4 T-cell counts is currently unknown [94].

A potential strategy to reduce the incidence of HF or HBV-related IRD may be to initially treat HBV alone until there is a significant reduction in HBV DNA and then initiate HAART. This approach has been utilised to reduce the incidence of IRD secondary to other co-infections including Mycobacterium tuberculosis (MTb), Cytomegalovirus (CMV) and Pneumocystis jirovecii pneumonia (PCP) although there are limited prospective studies evaluating the efficacy of this strategy [97]. If this strategy was to be applied to the management of HIV-HBV co-infection, TDF or LMV could not be used as one would need to use an anti-HBV NRTI that has activity only against HBV.
Lamivudine resistance
TDF has good activity against LMV-resistant HBV, but long-term experience with ADV suggests that continuing LMV in this setting may reduce the risk of TDF resistance [78, 98]. ETV at 1mg daily may be used, but is less preferred because LMV resistance predisposes to ETV resistance, as discussed earlier [52, 63]. Telbivudine is not effective in this setting.

Tenofovir intolerance or contra-indication
Although TDF is very well tolerated, toxicities can occur and sometimes treatment needs to be stopped [99]. In the setting of renal toxicity, one can consider dose adjustment according to glomerular filtration rate [100]. However, if TDF cannot be continued and there is a history of prior LMV-resistance, the alternative agents to consider are ADV (in addition to LMV) and ETV at 1 mg daily. Adefovir should be used with caution as nephrotoxicity can occur but this is uncommon with the lower dose of 10 mg/day [101]. If there is no history of LMV-resistance, options include ETV, ADV or telbivudine in addition to HAART.

Conclusions
The diagnosis of HBV must be considered in all individuals with HIV, prior to commencement of HAART. HIV-HBV co-infection is present in roughly 10% of HIV-positive individuals, with higher rates in some parts of Asia. The dual activity against HIV and HBV of lamivudine, emtricitabine and tenofovir mean that effective combination therapy against both viruses is achievable. The optimal management of individuals with HIV-HBV co-infection and a high CD4 count is not yet known although current guidelines recommend earlier initiation of HBV-active HAART in all co-infected individuals. Further clinical trials are needed to address this question as well as to determine the optimal strategy to prevent or treat HBV-IRD.

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