Recommendation on the Management of Human Immunodeficiency Virus and Hepatitis B Coinfection
(adopted from SCAS, CHP, DH Guidelines, Oct 2008)

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Background

1. Chronic hepatitis B virus (HBV) infection is the leading cause of liver-related complications and death worldwide. Over 2 billion of people are estimated to have been infected worldwide and more than 400 million are chronic carriers of HBV.[1] The majority of these cases are found in Asian & African countries and many of these areas are also hit hard by the HIV epidemic.

2. The main routes of transmission of HBV, namely sexual contacts, percutaneous exposure to blood and blood products, and vertical transmissions, are shared by HIV infections. Therefore, co-infection of these viruses is not uncommon. The prevalence of HBV infections among HIV infected individuals from western studies varies from 6-14% overall, including 4-6% of HIV-positive heterosexuals, 9-17% of HIV-positive homosexual men, and 7-10% of injection drug users.[2-4] Surveillance report in Hong Kong indicated that the prevalence of HBV infections in HIV/AIDS patients from 2000-2006 ranged from 4.9 to 16.4%, which was substantially higher than that of HIV-uninfected clients (2-10%).[5]

3. After the introduction of highly active anti-retroviral therapy (HAART), the rate of HIV associated mortality and morbidity have dropped significantly. Unfortunately liver diseases have emerged as the leading cause of death in the HIV population.[2,6,7]

Objective

4. The objective of this paper is to make recommendations for the diagnosis, treatment and monitoring of HIV/HBV co-infected individuals.

Significance of HIV/HBV co-infection

5. In HBV/HIV co-infected patients, higher HBV DNA and lower average liver enzyme levels with a higher rate of progression to cirrhosis, end-stage liver disease and death are noted, as compared to those of HBV mono-infected patients.[2,8,9] A multicentre, prospective cohort study involving 5293 men who had sex with men has demonstrated that the liver-related mortality rate was 14.2/1000 person years in HIV/HBV co-infected men, which was much higher than those with HIV mono-infections (1.7/1000 person years) and those with HBV mono-infections (0·8/1000 person-years).[2] These results have been confirmed by another cohort study which showed a high liver related mortality in 72 HIV infected individuals with chronic hepatitis B.[10]

6. HBV DNA level correlates positively with the development of cirrhosis and hepatocellular carcinoma (HCC) in HBV mono-infected patients.[11,12] A prospective cohort study of 3653 HBV mono-infected Taiwanese (aged 30-65 years) revealed that,

the incidence of HCC increased with serum HBV DNA level at study entry in a dose-response relationship ranging from 108 per 100 000 person-years for an HBV DNA level of less than 300 copies/mL to 1152 per 100 000 person-years for an HBV DNA level of 1 million copies/mL or greater.[11] However, similar studies have not been performed for patients with co-infections.

7. Successful viral suppression is suggested by the presence of hepatitis B e antigen (HBeAg) seroconversion and undetectable HBV DNA by Real-time Polymerase Chain Reaction. HBeAg seroconversion occurs at a rate of 8-15% per year in HIV-uninfected patients. However, HBV/HIV co-infected individuals are less likely than HBV-mono-infected individuals to clear HBV DNA spontaneously or to lose HBeAg.[8,13]

8. The effects of HBV infection on the natural history of HIV have been shown to be minimal. In a European study involving 9802 HIV patients, chronic HBV infection was not associated with the progression to AIDS & did not affect the viral or immunological response to HAART.[14] In another Thai cohort study of 692 HIV patients receiving HAART, HIV RNA decline was equivalent at weeks 4 and 12 for HIV mono-infected and HBV/HIV co-infected patients initiating HAART. Early (weeks 4 and 8) increases in CD4+ Cells were significantly greater in the HIV mono-infected patients than in the co-infected group, but by week 12, CD4+ cell counts were equivalent in the two groups.[15]

9. However, chronic HBV infections may complicate the administration of ART by increasing the risk of liver toxicities. Co-infections can actually increase the risk of hepatotoxicity from ART by a factor of 3 to 5 folds.[16-18] Superimposed with the risk of liver derangement for the management of opportunistic infections (e.g. anti-tuberculosis therapy) in many countries where chronic HBV is also endemic, liver function should be closely monitored. In patients on HAART and anti-tuberculosis therapy, chronic hepatitis B increases the risk for severe liver enzyme elevations by three folds.[19]

Initial evaluation

10. All newly diagnosed HIV infected individuals should be screened for hepatitis B surface antigen (HBsAg) and Anti-HBs. Diagnosis of HBV co-infection is based on positive HBsAg.

11. If patients are HBsAg positive, HBeAg, anti-HBe and HBV DNA should be tested. If patients are HBsAg negative, they should be recommended to receive HBV vaccination.

12. Besides having thorough history and physical examinations, all newly diagnosed HIV infected individuals should have blood screening for complete blood pictures, tests on liver and renal functions, clotting profiles including prothrombin time, international normalized ratio (INR) and alpha-fetoprotein (AFP).

13. A baseline hepatic ultrasound should be performed.

14. An assessment of fibrosis by liver biopsy has been recommended by international panels for all HIV/HBV co-infected individuals.[1] However, sampling variations, inter-observers' variability and the risk of complications are the major limitations of liver biopsy. Although non-invasive diagnostic tools like transient elastography (Fibroscan®) is a promising technique for monitoring fibrosis progression and regression in individual

cases of mono-infected patients, [20] more data are awaited for broader usage of this application, especially for HIV/HBV co-infection.

15. Patients should also be screened for hepatitis A virus (HAV) and C virus (HCV). Vaccination for hepatitis A should be recommended if anti-HAV is non-reactive. Screening for hepatitis D virus should be offered to patients coming from endemic areas or having a history of injection drug uses.

16. Household and sexual partners should be screened for HBV and vaccinated if they are uninfected.

17. Occult HBV infection is defined as the presence of HBV DNA without detectable HBsAg. In mono-infected patients with occult HBV, often the only serum marker is antibodies to hepatitis B core antigen (anti-HBc). Therefore, in cases with high risk of acquiring hepatitis B but was HBsAg negative, anti-HBc level may need to be checked. However, the presence of anti-HBc alone is rarely associated with occult infection in HIV-uninfected patients.[21] Therefore, HBV DNA should be measured. Based on current evidence, routine surveillance for HBV DNA in the absence of detectable HBsAg is not indicated.

Treatment options for HIV/HBV co-infection

18. Treatment for HBV infection aims to control inflammatory responses (normalization of liver enzymes), reduce viral replication (rendering HBV DNA undetectable), improve immune control (HBe and HBs seroconversions) and prevent liver related complications like cirrhosis and hepatocellular carcinoma.

19. Medications listed in Table 1, including standard interferon alfa-2b, pegylated interferon (PEG-IFN) alfa-2a, lamivudine (3TC), adefovir (ADV), entecavir (ETV), telbivudine (TBV), have been approved for the treatment of mono-infected chronic hepatitis B in Hong Kong. Two additional drugs approved for HIV treatment, tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC), also have anti-HBV activity. [22]

20. Generally, 3TC, FTC and TDF are active against both HBV and HIV. Monotherapy of these agents for the treatment of HBV infection should absolutely be avoided since resistance to HIV will rapidly develop, which precludes their future use as HAART.

21. 3TC-resistance YMDD mutation occurs at a rate of 20% per year in HIV/HBV co-infected patients taking lamivudine as part of the HAART.[23] The efficacy in suppressing HBV DNA and resistance pattern of FTC are similar to that of 3TC in HBV mono-infected patients.[24,25] It is therefore considered interchangeable with 3TC for the treatment of HIV. [26] The resistance profile of TBV is also similar to that of 3TC but with enhanced potency in suppressing HBV replication.[27]

22. Since nucleotide analogues ADV and TDF do not exhibit cross-resistance with 3TC, they can be used in YMDD mutated co-infected subjects. TDF has been noted to have greater activities than ADV, probably because it can be administered in much higher doses. [28] The resistance patterns of the 2 anti-virals are also different. ADV resistance has been reported in 30% of HBV mono-infected subjects after 5 years of treatment,[29] while only sporadic cases of TDF resistance are found.[30] Together with its potent anti-retroviral activities, the combination of TDF with either FTC or 3TC, has emerged

as the preferred treatment of HBV in co-infected patients requiring concomitant therapy for HIV infection.

23. Recently ETV has become the first line therapy in the treatment of HIV/HBV co-infected individuals not requiring HAART, because of its high efficacy, high genetic barrier to resistance and its apparent lack of anti-retroviral activity.[27] However, it is now contraindicated since the anti-HIV activity of ETV was demonstrated, which led to the emergence of resistance mutations relevant for HIV therapy (M184V).[31]

24. Both standard and pegylated forms have been approved for the treatment of HBV infection, but with the more convenient dosing schedule and the superiority of the pegylated form, the standard form becomes less widely used. The potency of PEG-IFNs in terms of HBV viral suppression, HBeAg & HBsAg seroconversion are superior to that of 3TC in HBV mono-infected patients.[32,33] However, no evidence is available so far for co-infection.

Recommendations on treatment of HIV/HBV co-infection

25. Since there have not been any studies performed to investigate the clinical significance of HBV DNA and liver enzyme levels in HIV/HBV co-infected patients, indication for anit-HBV therapy is largely based on recommendations on the management of HBV mono-infected individuals. Figure 1 outlines the possible management and therapeutic recommendation in HIV/HBV co-infected patients. Special consideration has to be taken for the treatment of this special group of people as regards:

    (a) Whether the patient is indicated for HAART.
    (b) Whether there is 3TC resistance.

26. If HAART is not indicated, anti-virals with HIV activity (3TC, FTC, TDF, ETV) should be avoided to prevent the emergence of resistance HIV toward these agents. [1,27,34-36] In general, if the HBV DNA level is high ($\geq$ 20,000 IU/ml in HBeAg-positive patients or $\geq$ 2,000 IU/ml in HBeAg-negative patients), and alanine transaminase (ALT) is elevated, treatment should be considered. [27,37] Otherwise, a watchful monitoring at an interval of 3-6 months is needed. Liver biopsy may also be considered for those with normal ALT but high HBV DNA and treatment should be offered in cases of significant activities. [1,27,34-37]

27. The medications of choice for these conditions in HBeAg positive patients are PEG-IFN alpha 2a or ADV. [1,27,34-36] Newer drugs that have no anti-HIV activity (TBV [34], clevudine[38]) may also be useful in these situations. Dose and duration of PEG-IFN remain unknown, but the same regime for HBV mono-infected patients is applied.

28. In patients indicated for HAART or have already been on HAART, a regime containing TDF plus either 3TC or FTC is favoured so as to prevent the development of resistance to 3TC or FTC. [1,27,34-36]

29. 3TC or FTC resistance should be suspected during treatment in patients who experience virological breakthrough, that is, more than 1 log10 copies/ml increase from HBV DNA nadir. [1] Once the resistance HBV to 3TC or FTC is confirmed by molecular studies, TDF should be included in the anti-retroviral regime and 3TC or FTC should be maintained. ETV or ADV may be added to the HAART as an alternative. [34]

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Table 1: Anti-virals for hepatitis B virus infection in HIV/HBV co-infected patients*

Drugs	Lamivudine	Adefovir	Emtricitabine	Telbivudine	Tenofovir	Conventional interferon	Pegylated interferon	Entecavir
ALT normalization	50% at 48 weeks	25% at 48 weeks			36% at 48 weeks			
Undetectable HBV DNA	40% <400 copies/ml at 52 weeks	6% <200 copies/ml at 48 weeks			20% <200 copies/ml at 48 weeks; 29.6% of HBeAg + & 81.6% of HBeAg - have <200 copies/ml at 12 months	27% < 2 pg/ml 6 months after treatment		8% (<300 copies/mL at 48 weeks (Lamivudine - refractory)
HBe Seroconversion	11%	7%			4%	9%		
Potency for HBV infection	++	++	++	+++	+++	++	++	+++
Dosage	150mg twice daily (for HIV infection)	10mg daily	200mg daily	600mg daily	300mg daily	5MU daily or 10MU 3 x / week for 6-12 months	180 mcg / week for 48 weeks	Lamivudine refractory: 1mg daily; lamivudine naive: 0.5mg daily
Anti-HIV activities	+++	None	+++	None	+++	+	+	+
Used in YMDD mutation	No	Yes	No	No	Yes	?	?	Yes
Major side effect	Minimal	Renal impairment	Minimal	Minimal	Renal impairment	Flu-like symptoms, cytopenia, autoimmune activation, thyroid dysfunction, mood change	Flu-like symptoms, cytopenia, autoimmune activation, thyroid dysfunction, mood change	Headache, fatigue, dizziness, gastrointestinal upset
Reference	39	28,40			28,40	41		42

*Adapted from Cheruvu S, Marks K, Talal AH. Understanding the pathogenesis and management of hepatitis B/HIV and hepatitis B/hepatitis C virus coinfection. *Clin Liver*

Dis. 2007;11:917-43

Figure 1: Algorithm for the management of HIV/HBV co-infection
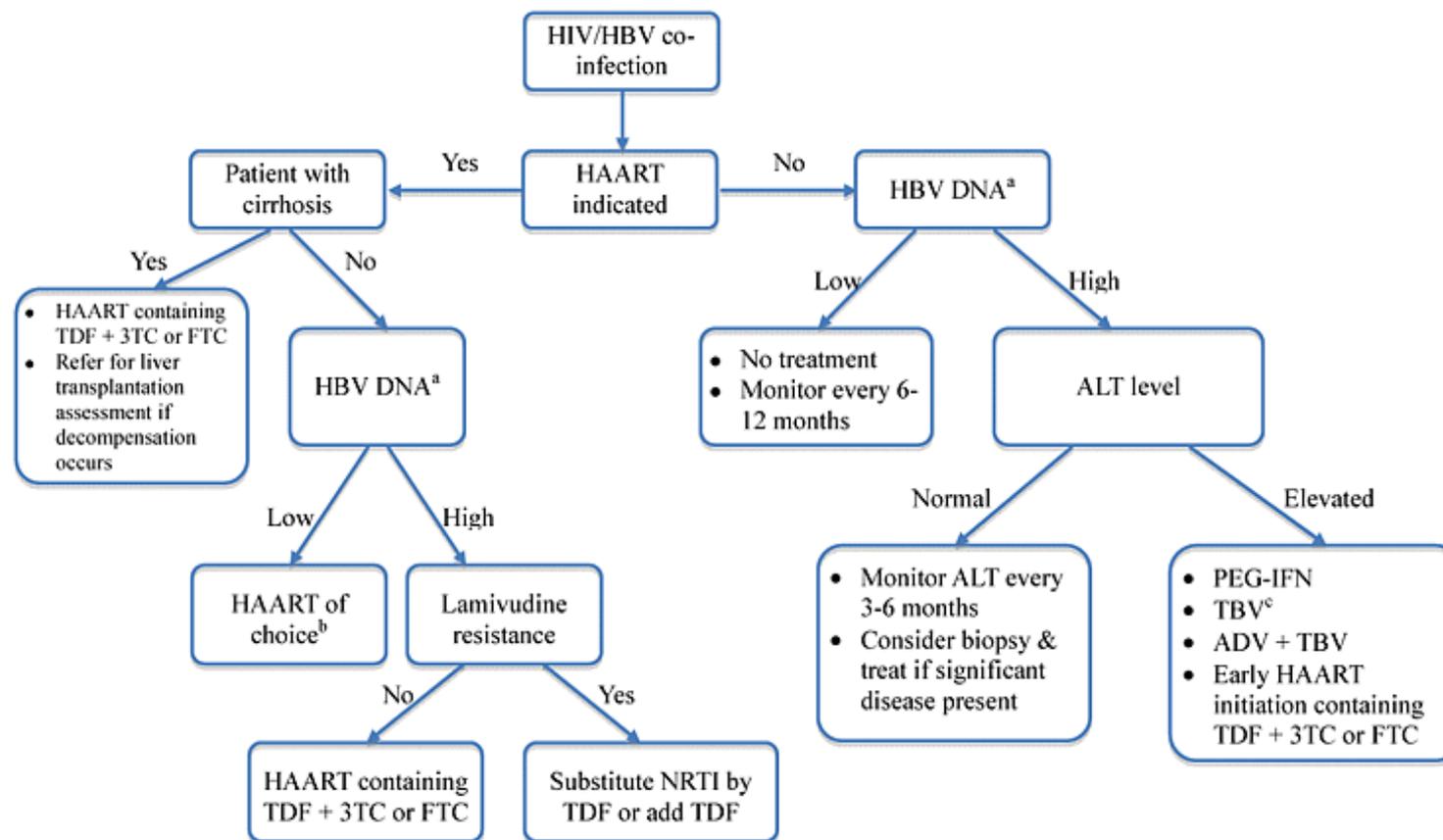
a High HBV DNA level (≥ 20,000 IU/ml in HBeAg-positive patients or ≥ 2,000 IU/ml in HBeAg-negative patients)

b Some experts assert that any HBV-infected patients requiring HAART should receive TDF + 3TC/FTC unless they cannot tolerate TDF.

c If HBV-DNA remains detectable at week 24, adefovir should be added to minimize risk of resistance development.

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Test paper - Recommendation on the Management of Human Immunodeficiency Virus and Hepatitis B Coinfection

Expiration Date: Jan 2010

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◦   Please indicate one answer to each question.

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1. What is true about the prevalence of HBV/HIV coinfection from available data?
    (a) The prevalence of HBV/HIV coinfection is substantially higher than HBV mono-infection in the population
    (b) Prevalence of HBV infection in HIV-infected individuals is not affected by the background HBV prevalence
    (c) Prevalence of HBV in HIV infected patients in Hong Kong is lower than in western countries
    (d) Prevalence of HBV/HIV coinfection does not reach the high level of HCV/HIV coinfection in any risk populations
    (e) None of the above

2. What are the observations of effects of HIV on chronic HBV?
    (a) Greater progression to cirrhosis
    (b) Higher HBV DNA level
    (c) Less transaminitis
    (d) Greater risk of liver-death
    (e) All of the above

3. Which of the following is incorrect regarding HBV viral replication and suppression?
    (a) HBV/HIV coinfected patients are less likely to have spontaneous clearance of HBeAg
    (b) Undetectable HBV DNA in blood implies successful viral suppression
    (c) HBeAg seroconversion occurs at 8-15% per year in HBV mono-infected subjects
    (d) HBV DNA level could be associated with the likelihood of development of liver cirrhosis and carcinoma
    (e) None of the above

4. Which of the following statements is not true concerning the impact of HBV on HIV disease course and treatment?
    (a) HBV leads to faster HIV disease progression
    (b) HIV suppression from highly active antiretroviral therapy (HAART) is not worse in HBV/HIV coinfected patients
    (c) CD4 response is similar in HBV/HIV coinfected patients after HAART albeit it could be slower
    (d) The risk of hepatotoxicity from HAART can be elevated
    (e) The risk of liver toxicity can be compounded by drugs used to treat opportunistic infections

5. Which of the following does not form part of baseline work up for HBV/HIV coinfection?
    (a) HBeAg, anti-HBe
    (b) HBV DNA
    (c) Liver function test

(d) Ultrasound liver
(e) None of the above

6. Which of the following is not true about assessment for liver fibrosis?
   (a) Liver biopsy is the standard investigation
   (b) Transient elastography (Fibroscan®) is an noninvasive alternative procedure
   (c) Much data is available on the application of Transient elastography in HBV/HIV coinfected patients to warrant its standard recommendation
   (d) Sampling variation and risk of complications are drawbacks of liver biopsy
   (e) None of the above

7. Which of the following is correct about the objectives of HBV treatment?
   (a) Reduce viral replication
   (b) Control liver inflammation
   (c) Improve immune control of the virus
   (d) Prevent chronic liver complications
   (e) All of the above

8. Which of the following drugs does not have both anti-HIV and anti-HBV effects?
   (a) Lamivudine (3TC)
   (b) Tenofovir disoproxil fumarate (TDF)
   (c) Emtricitabine (FTC)
   (d) Telbivudine (TBV)
   (e) Entecavir (ETV)

9. Which of the following is not true regarding treatment for HBV/HIV coinfection?
   (a) Monotherapy with agents active against both HBV and HIV must be avoided
   (b) 3TC is more potent than telbivudine in HBV suppression and has similar resistance pattern
   (c) 3TC resistance to HBV can develop more rapidly in coinfected than HBV mono-infected patients
   (d) 3TC and FTC are interchangeable in treatment of HBV and HIV
   (e) resistance pattern of adefovir is different from that of 3TC

10. Which of the following is not true regarding treatment for HBV/HIV coinfection?
    (a) Combination of tenofovir and 3TC is now the recommended treatment in HBV/HIV coinfected patients, together with a third anti-HIV drug as recommended
    (b) Entecavir alone is an alternative agent
    (c) Data of standard and pegylated interferon efficacy in comparison to antiviral agents is not available
    (d) Tenofovir is more efficacious than adefovir
    (e) None of the above