# Background document: HIV and hepatitis B co-infection*

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## BACKGROUND

### Epidemiology of HIV and hepatitis B co infections.

Co infection with human immunodeficiency virus (HIV) and hepatitis B virus (HBV) is common due to shared routes of transmission. In areas of low endemicity, such as North America, Australia and Europe, HBV and HIV infection are usually acquired in adulthood through sexual or percutaneous transmission. In areas of low endemicity, the prevalence of chronic co infection is around 5-7% among HIV-infected individuals (Alter, 2006). In countries with intermediate and high HBV endemicity, the main routes of transmission of HBV are perinatal or in early childhood; in these countries HBV co infection rates are 10-20% (Lee, 2008;Nyirenda, 2008;Diop-Ndiaye, 2008).

### Impact of co infection on the natural history of HBV and HIV

The rate of progression and complications from viral hepatitis are accelerated in patients with HIV co infection (Puoti, 2006; Thio, 2009). After acquiring HBV infection, HIV infected individuals are 6 times more likely to develop chronic hepatitis B than HIV negative individuals (Bodsworth, 1991;Hadler, 1991,Gatanaga, 2000). This was more likely to occur in HIV infected men with lower CD4 cells (Bodsworth, 1991). Decreased rates of clearance of HBeAg and increased HBV replication are also seen, with higher HBV DNA viral load (Colin, 1999;Gilson, 1997, Krogsgaard, 1987). In addition, HIV infected individuals are more likely to lose previously developed protective anti-HBs antibody and develop acute hepatitis B infection; this risk is also associated with lower CD4 counts (Biggar, 1987;Laukamm-Josten, 1988).

Following initiation of antiretroviral therapy (ART), immune reconstitution inflammatory syndrome (IRIS) may occur which can lead to worsening liver disease including hepatic decompensation (Drake, 2004). In addition, after discontinuation of an ART regimen containing anti-HBV agents, reactivation of hepatitis B can occur: ALT elevations occurred in 29% of 147 patients within 6 months of withdrawal (Bellini, 2009). If reactivation occurs, resuming an agent that is active against HBV is required.

HIV also hastens the progression of HBV related liver disease. Cirrhosis is more common despite lower ALT levels than in HBV mono-infection and is also more common with lower CD4 counts (Colin, 1999;DiMartino, 2002). HIV-HBV co-infected men are greater than 17 times more likely to die of liver related causes compared to those mono-infected with HBV (Thio, 2002). The impact of co infection is especially important in regions with widespread use of ART (Hoffman, 2007). As the use of ART becomes more prevalent in parts of the world with high HBV endemicity and long term survival increases, it is likely that liver disease from chronic hepatitis B in HIV-infected population may emerge as a greater public health problem than before (Hoffman, 2007). It is unclear at present if the risk of hepatocellular carcinoma (HCC) is increased, but there is some evidence that HIV infected individuals with lower CD4 counts are at greater risk of developing HCC (Clifford, 2008).

For individuals on ART, co infection with chronic hepatitis B increases the risk of hepatotoxicity from ART three-fold to five-fold (Puoti, 2003;Sulkowski, 2000;Livry, 2003).

**Assessing for HBV and its sequelae in HIV co infection**

Accurate assessment of HBV infection in HIV co-infected individuals is necessary in order to base therapeutic decisions (Thio, 2009). WHO advocates HBsAg testing especially in areas of high HBV prevalence (WHO, 2006) but additional testing for HBV markers such as HBeAg and HBV DNA and to assess stage of liver disease (e.g. liver enzymes, liver biopsy, etc) may not be widely available in many resource limited countries. For HIV infected individuals with chronic HBV, additional screening for co infection with HCV is recommended; hepatocellular carcinoma screening with alpha fetoprotein and imaging of liver every 6 months is being suggested by some but the cost benefit of one or both tests as well as the frequency of monitoring in various health economies remain to be assessed. (Thio, 2009).

Liver biopsy remains the gold standard for assessing disease severity in HIV-HBV co infection (Thio, 2009). Non-invasive markers are also available but none have been widely studied in co-infected patients (Thio, 2009).

Hoffman and Thio provide management recommendations for use in areas with limited resources (Hoffman, 2007). They recommend that HBsAg and liver enzymes be tested before ART, with liver enzymes being repeated once or twice during the first 3 months after commencing ART. Detection of HBV DNA is helpful but may not be available. Chronic HBV carriers with HBeAg positivity may benefit from starting anti-HBV therapy early.

**Treatment of HBV in HIV-HBV co infection**

**Goals of treatment**

**HIV:** Treatment for HIV has resulted in a marked reduction in AIDS-related mortality. As a result, liver disease from HBV and HCV is now becoming a major cause of morbidity and mortality in HIV infected patients (Puoti, 2000). Therefore the goal of treatment is to optimize anti-HIV therapy in HIV/HBV co-infected patients to improve and/or preserve immune function and reduce HIV associated morbidity and mortality.

**HBV:** In mono-infected patients, HBV therapy can reduce the risk of developing complications of liver disease (Niederau, 1996;Yao, 2001). Natural history studies of chronically infected individuals have linked the risk of progression to cirrhosis and HCC to ongoing HBV replication (Chen, JAMA 2006;Iloeje, 2006;Chen, 2006). In addition, treatment for HBV has been directed at reducing replicating virus. It has been demonstrated that the degree of HBV viral suppression achieved during treatment appears to be the most important determinant of treatment outcomes (Liaw,2006), but HBV DNA levels as low as 2000 IU/mL is still associated with disease progression (Yuen, 2005;Yuan,2005). Recent recommendations have advocated for undetectable HBV DNA as the therapeutic goal with the overall goal of therapy being to reduce

progression to cirrhosis, liver failure, HCC and need for liver transplantation (Keefe, 2007;Keefe, 2008).

**Overview of treatment**

Treatment is most beneficial for those in the immunoactive phase of chronic hepatitis B (characterized by liver enzyme elevations, fluctuating HBV DNA levels and pronounced hepatic necro-inflammation) (Hoffman, 2007). Patient characteristics that favour treatment success are low HBV DNA levels, HBeAg positivity or evidence of liver inflammation based on liver biopsy findings or liver enzyme elevations (Soriano, 2005). In Africa and Asia, it is estimated that large numbers of young people are in the immunotolerant phase with high HBV DNA levels and minimum hepatic inflammation and are unlikely to receive substantial benefit from HBV treatment (Hoffman, 2007). It is unknown if this applies to HIV co-infected individuals who have higher HBV DNA and lower liver enzyme elevations but more cirrhosis and therefore the optimum time to commence treatment in HIV-HBV co-infected individuals is unclear at present.

The treatment and management of co-infected individuals requires modification in resource poor countries due to limited availability of some HBV tests as well as therapeutic agents for treatment of HIV and HBV. 3TC is widely available and tenofovir and adefovir have limited availability (Hoffman, 2007).

There are several agents presently used for the treatment of HBV and HIV co infection including interferon and nucleoside or nucleotide analogs (Soriano, 2006). Decisions regarding when to initiate anti-HBV therapy require assessment of HIV status prior to initiation of treatment as several of these agents (tenofovir, lamivudine, emtricitabine, adefovir and entecavir) have activity against both HIV and HBV. Telbivudine, a newer agent used to treat HBV, has not been shown to have activity against HIV. Treatment decisions should be based on a combination of factors including 1) which virus needs treatment, 2) the type of antiviral agents used in the concurrent anti-HIV regimen, the presence of 3TC-resistant HBV and the potential effect of drug resistance on the long term management of HIV and HBV infection (Hoffman, 2007).

***If ART is to be initiated,*** then first line therapy should include TDF and 3TC/FTC as the nucleoside backbone.

Current WHO criteria (WHO, 2006) for commencing ART in HIV infected individuals are based on a combination of WHO Clinical Stage and CD4 count *(see Appendix A, Recommendations for initiating ART in adults and adolescents in accordance with clinical stages and the availability of immunological markers).*

*Lamivudine/emtricitabine (3TC/FTC)*
Dore et al (Dore, 1999) demonstrated the efficacy of 3TC in persons co infected with HIV and hepatitis B virus in the CAESAR study, a randomized placebo-controlled trial assessing the addition of 3TC or 3TC (150 mg 2x/day) plus loviride (100 mg 3x/day) to

zidovudine-containing background antiretroviral treatment. Baseline HBsAg was positive in 122 (6.8%) of 1790 subjects. At weeks 12 and 52, median $\log_{10}$ HBV DNA change was -2.0 and -2.7, respectively, in the lamivudine arms, compared with no reduction among placebo recipients (P<.001). A trend to lower ALT level, and delayed progression of HIV disease (relative hazard, 0.26; 95% confidence interval, 0.08-0.80) were also seen in the 3TC arms, compared with the placebo group. 3TC used as monotherapy however, results in the development of resistance at rates of 14-32% annually, exceeding 70% after 49 months of treatment and plateauing at > 90% in HIV-co-infected patients at 4-5 years (Benhamou, 199;Matthews, 2006). Since 3TC has been widely used as part of ARV regimens in co infected persons, with HBV Pol mutations observed in 94% of viremic patients who have been on treatment for at least four years (Matthews, 2006).
FTC possesses similar characteristics to 3TC, although FTC has a longer half-life and is more potent in monotherapy in treatment naive patients (Rousseau, 2003). 3TC/FTC are interchangeable agents according to current treatment guidelines.

*Tenofovir (TDF) with or without 3TC/FTC*
There is now significant data supporting the use of TDF in co-infected patients. TDF is highly effective in suppressing HBV replication in HBV mono-infected patients with 3TC resistant HBV (van Bommel, 2006;van Bommel, 2004). TDF has also demonstrated potent anti-HBV efficacy in the setting of HIV co infection (van Bommel, 2004;Dore, 2004;Nunez M, Ristig 2002;Nelson 2003;Stephan 2005). Appendix B summarizes the studies listed below *(Appendix B: Summary of 3TC/TDF studies since 2004 in patients co infected with HIV and HBV).*

Dore (Dore, 2004) did a substudy analysis of two phase 3 randomized, double-blind, placebo-controlled trials recently examined the safety and efficacy of tenofovir DF among antiretroviral therapy-experienced (.study 907) and -naive (study
903) HIV-1-infected patients. Substudies of study 907 and study 903 were undertaken to examine the safety and efficacy of tenofovir DF among antiretroviral therapy-experienced and -naive HIV-HBV-co infected individuals. Individuals in study 907 were randomized to receive TDF or placebo, and individuals in study 903 were randomized to receive antiretroviral therapy regimens that included lamivudine plus tenofovir. Among individuals co infected with HIV and HBV in these 2 randomized controlled trials, therapy with TDF demonstrated anti-HBV virologic efficacy. During 48 weeks of therapy with TDF, a mean reduction of 4 -5 log, copies/mL in the HBV DNA level was seen in antiretroviral therapy-experienced HIV-HBV-co infected individuals with or without resistance to lamivudine. During the 48 weeks of the study, a similar reduction in the HBV DNA level was seen in antiretroviral therapy-naive HIV-HBV-co infected individuals who received combination therapy with lamivudine and TDF as a component of their initial 3-drug HAART regimen. A trend toward greater suppression of HBV DNA as well as reduced YMDD resistance in HIV-HBV-co infected individuals who were receiving lamivudine and TDF, compared with lamivudine alone.

Van Bommel et al (van Bommel, 2004) evaluated 52 patients with HBV infection, 21 co-infected with HIV and compared TDF with adefovir (ADV) in 3TC resistant HBV. All TDF treated patients (n=35) showed a strong and early suppression of HBV DNA within

a few weeks as compared to ADV. At week 48, TDF treated individuals had a higher reduction in viral load (5.5 log10 copies/ml for TDF vs 2.8 log10 copies/ml with ADV) and 100% TDF were undetectable vs 44% with ADV. There was no resistance in TDF treated patients at 130 weeks.

Benhamou (Benhamou, 2006) evaluated the efficacy and tolerability of TDF in 3TC naïve and 3TC refractory co-infected patients in a retrospective study. Of 65 co-infected patients (54 HBeAg positive and 11 HBeAg negative) with serum HBV DNA > 2.3 copies/ml were started on TDF therapy. 68% were 3TC refractory. Over 12 months, the median reduction in HBV DNA as 4.56 log10 copies/ml in HBeAg positive patients and 2.53 log10 copies/ml in HBeAg negative individuals. At the end of the study (median follow up of 12 months), 30% of HBeAg positive and 82% of HBeAg negative had undetectable HBV DNA. No TDF mutations were detected in this study.

Jain (Jain, 2007) retrospectively examined 45 HIV/HBV co-infected patients: Group 1 - 15 treated with only 3TC (27% ARV experienced), Group 2- 10 treated with 3TC and TDF (20% ARV experienced) and Group 3 - 20 with 3TC alone x 6 months then 3TC and TDF (100% ARV experienced). A similar proportion were on PI or NNRTI regimens (not specified). Group 1 and 2 showed equivalent HBV DNA declines over a year of therapy but Group 3 showed lower HBV decline than other cohorts. Of note, genotype A (predominant in US and representing 78% in this cohort) showed higher treatment responses than on genotype A. Small sample size in each arm so insufficient power to note difference between treatment groups.

Lacombe (Lacombe,2008) evaluated 85 HIV-HBV co infected patients in an open label study initiating an ARV regimen including either TDF or ADV. The decline in HBV DNA was more pronounced in patients treated with TDF than with ADV at 12 months (66% versus 53%, p=00001). Patients receiving TDF had a steeper rate of decline and mean time to undetectable HBV DNA was 19 months with TDF compared to 26 months with ADV.

The combination of TDF and 3TC has also been evaluated in a multi centre European study (Schmutz,2006). Schmutz et al (Schmutz, 2006) compared the efficacy of TDF plus 3TC with that of sequential therapy with TDF in HIV infected individuals with 3TC resistant HBV. In this study, 50 patients received TDF as the only active HBV agent subsequent to 3TC therapy and 25 received ART containing TDF plus 3TC. At 116 weeks, 84% treated with TDF had undetectable HBV DNA < 1000 copies/ml compared to 76% receiving TDF plus 3TC; this was not a statistically significant difference (p=0.53). The rates of loss of HBeAg and HBsAg were similar in both arms. This study indicates that TDF plus 3TC are no more efficacious than TDF alone. Sheldon (Sheldon, 2005) reported the development of resistance to TDF in 2 of 43 HIV-HBV co infected patients treated for longer than 12 months.

Matthews et al (Matthews, 2008) evaluated 36 HIV-HBV co-infected patients in Thailand; subjects were randomized to receive either 3TC, TDF or both. At the end of 48 weeks, the average decline in HBV DNA was similar in all three arms, ranging from

4.07-4.73 log10 copies/ml. However, suppression of HBV DNA levels to < 1000 copies/ml was more frequent in subjects receiving TDF (92% and 91% compared to 46% in 3TC arm). Again, adding 3TC to TDF is no more efficacious than TDF alone. Drug resistance developed in 2 subjects both in 3TC only arm.

In a study in Australia, Matthews (Matthews, 2009) evaluated a cross sectional cohort of 3TC experienced HIV-HBV co infected patients. Individuals receiving TDF plus either 3TC or FTC were more likely to have undetectable HBV DNA (<100IU/ML) than those receiving either TDF or 3TC monotherapy. The combination group was also less likely to have high HBV DNA levels (>200,000 IU/ML). Despite the limitations of a cross sectional study, this study does provide some evidence that TDF-3TC/FTC combination therapy is superior to TDF or 3TC monotherapy in HIV-HBV co infected individuals with 3TC resistant HBV. However, confounders were not controlled for.

Alvarez-Uria (Alvarez-Uria,2009) reported on their experience in the UK in a retrospective observational study to investigate the long term efficacy of TDF against HBV in a cohort of HIV co infected patients. Median duration of follow up was 34 months and 41 (79%) were HBeAg positive and 35 had received previous 3TC therapy for a median duration of 32 months. Nadir CD4 cell count was 110 cells/mm3 in individuals experiencing virologic breakthrough. At the end of the follow up period, HBV DNA was < 1000 copies/ml in 42 (81%) patients and < 200 copies/ml in 31 (60%) patients. In the 3TC experienced group, longer duration of 3TC was associated with failure to achieve HBV DNA < 200 copies/ml (p=0.036). Adding 3TC or FTC did not improve virologic suppression. Of 39 patients who achieved HBV DNA of < 200 copies/ml during TDF treatment, virologic breakthrough was seen in 2 (5% patients) after a median follow up of 40 months.

*Entecavir (ETV)*

Entecavir (ETV) has been shown to be superior to 3TC with superior histological improvement, greater mean reduction in HBV DNA and normalization of serum ALT levels and large RCT have demonstrated efficacy up to 96 weeks (Chang,2006). Entecavir is associated with lower rates of development of resistance as compared with 3TC (Colonno, 2006). Entecavir monotherapy is now considered contra-indicated as anti-HIV activity has been described and monotherapy has led to the development of HIV resistance mutation (M184V0 which are relevant for HIV therapy (McMahon,2007). There is one RCT of ETV in 68 HIV/HBV co infected patients comparing ETV to placebo while continuing 3TC containing ART for 24 weeks followed by ETV open-label (Pessoa, 2008). ETV was given at 1.0mg dose. At 24 weeks, 6% of 51 patients had HBV DNA < 300 copies/ml and at 48 weeks, 8% had HBV DNA < 300 copies/ml. Mean decline in HBV DNA was 3.65 log10 copies/ml.

If ART is not to be initiated then the decision to treat HBV infection need to take into consideration of replication status of HBV as well as stage of liver disease. If HIV treatment is not to be started, peginterferon alfa-2a or alfa 2b, telbivudine and possibly adefovir are options.

*Telbivudine*

Telbivudine is not known to be active against HIV but one drawback is that HBV resistance may develop if this drug is used a single agent; in the GLOBE trial comparing 3TC vs telbivudine for mono-infected patients, resistance developed in 25% patients receiving telbivudine vs 40% those treated with 3TC (Liaw,2009).

*Adefovir (ADV)*

Of agents with activity against HBV, adefovir is the least potent. In addition, adefovir at low doses (10mg) does not have activity against HIV but higher doses do have activity against HIV (Keefe, 2008). Adefovir has been studied in 35 co-infected patients continuing on 3TC and after 144 weeks of therapy, 45% achieved HBV DNA < 1000 copies/ml (vs 56% in HBV mono-infection) (Marcellin, 2003;Benhamou, 2006). Resistance also develops less frequently than with 3TC in HBV mono-infected patients with HBeAg negative CHB: 2% after 2 years, 11% after 3 years, 18% after 4 years and 29% after 5 years (Hadziyannis,2005).

*Interferon*

Pegylated interferon-alpha has not been studied as HBV treatment in HIV co infected individuals and as such its efficacy in this setting is unknown (Thio, 2007). However, in HIV-uninfected individuals, it has been demonstrated to be more effective than short-acting interferon. One small study of 18 co-infected patients who were HBeAg positive, with documented 3TC resistance to HBV and on ART containing 3TC evaluated the use of ADV and pegylated interferon alpha2a for 48 weeks and achieved a median decline in HBV DNA of 3.6 $\log_{10}$ copies/ml at 48 weeks and 1.4 $\log_{10}$ copies./ml at 72 weeks. None of the patients became HBeAg negative. On treatment response was not maintained off therapy.

**SYSTEMATIC REVIEW (Summary)**

**Objectives**

Systematic review of literature on treatment options for HIV-HBV co-infected patients in response to specific questions

**Questions**

***1) When to start ART in HIV/HBV co infected adult patients***

***Question: should cART be initiated earlier in HIV infected patients with active chronic hepatitis B co infection?***

Population: HIV infected adults, adolescents and children > 5 years old with chronic active hepatitis B co infection

Interventions:

1) cART for patients with CD4 cell count < 350 or WHO HIV clinical stage 3 irrespective of CD4 cell count)
2) cART for patients with CD4 cell count < 500, irrespective of WHO HIV clinical stage
3) cART for all patients, irrespective of CD4 cell count

Comparator:

cART for patients with CD4 cell count < 200 or WHO clinical stage 4

Outcomes:

Critical:

1. Mortality 1, 2 and 5 years
2. HIV disease progression
3. HBV disease progression (cirrhosis, hepatocarcinoma)
4. Severe treatment associated adverse events

Non-critical:

1. CD4 recovery
2. Other non-AIDS morbidities
3. Other HBV related morbidities
4. HIV viral load response
5. HBV viral load response
6. HBV drug resistance
7. HIV drug resistance
8. Adherence

***2) What ART to start in HIV/HBV co-infected adult patients***

***Question: Should 1st line (or initial) ART regimens used for HIV+ patients with chronic active hepatitis B contain more than one anti-HBV drug in their NRTI component?***

Population: HIV infected adults, adolescents and children > 5 years old with chronic active hepatitis B co infection

Interventions:
1) 1st line or initial EFV based ART regimens containing TDF and 3TC (or FTC)
2) 1st line or initial triple nuke ART regimens containing TDF and 3TC (or FTC)
3) 1st line or initial PI based ART regimens containing TDF and 3TC (or FTC)

Comparator:
1st line or initial cART regimens containing 3TC (or FTC) as the only HBV active drug

Outcomes:
Critical:
1. Mortality 1, 2 and 5 years
2. HIV disease progression
3. HBV disease progression (cirrhosis, hepatocarcinoma)
4. Severe treatment associated adverse events

Non-critical:
1. CD4 recovery
2. Other non-AIDS morbidities
3. Other HBV related morbidities
4. HIV viral load response
5. HBV viral load response
6. HBV drug resistance
7. HIV drug resistance
8. Adherence

***3) What ART to switch to in HIV/HBV co-infected adult patients***

***Question; Should 2nd line ART regimens (or subsequent regimen after HIV treatment failure) for HIV+ patients with chronic active hepatitis B c-infection maintain more than one anti HBV drug in their NRTI component?***

Interventions:
2nd line or subsequent cART regimens containing TDF and 3TC (or FTC)

Comparator:
2nd line or subsequent cART regimens containing 3TC or FTC or TDF as the only HBV drug.

Outcomes:
Critical:
1. Mortality 1, 2 and 5 years
2. HIV disease progression
3. HBV disease progression (cirrhosis, hepatocarcinoma)
4. Severe treatment associated adverse events

Non-critical:
1. CD4 recovery
2. Other non-AIDS morbidities
3. Other HBV related morbidities
4. HIV viral load response
5. HBV viral load response
6. HBV drug resistance
7. HIV drug resistance
8. Adherence

**Data Sources:**
PubMed, review articles, trial articles, commentaries and treatment guidelines on HIV and HBV

**Study eligibility criteria:**
Randomized or observational studies providing sufficient information to report on the outcomes as posed by questions
Studies containing small numbers ($\leq$ 10 per treatment arm) excluded

**Summary of articles reviewed**
Articles identified by PubMed Search (search terms HIV, Hepatitis B and treatment, restricted to English language and human trials, 1990-current) = 298

- 92 articles identified on treatment of HIV-HBV co-infected patients
    - 32 articles reviewed on treatment including TDF, LAM/FTC

Additional 25 articles identified by expanded search (non PubMed- see above)

- 9 articles reviewed on treatment including TDF, LAM/FTC (See Appendix B for summary of studies since 2004 with TDF/3TC and reasons for inclusion/exclusion)

10 articles (including 1 abstract) included in final responses to questions.

**RESPONSES TO QUESTIONS (See Appendix B and Appendix C)**

***1) When to start ART in HIV/HBV co infected adult patients***
***Question: should cART be initiated earlier in HIV infected patients with active chronic hepatitis B co infection?***

Population: HIV infected adults, adolescents and children > 5 years old with chronic active hepatitis B co infection

Interventions:
1) cART for patients with CD4 cell count < 350 or WHO HIV clinical stage 3 irrespective of CD4 cell count)
2) cART for patients with CD4 cell count < 500, irrespective of WHO HIV clinical stage
3) cART for all patients, irrespective of CD4 cell count

Comparator:
cART for patients with CD4 cell count < 200 or WHO clinical stage 4

Outcomes:
Critical:
1. Mortality 1, 2 and 5 years
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Non-critical:
1. CD4 recovery
2. Other non-AIDS morbidities
3. Other HBV related morbidities
4. HIV viral load response
5. HBV viral load response
6. HBV drug resistance
7. HIV drug resistance
8. Adherence

***Response:***
WHO guidelines currently recommend starting ART in individuals with CD4 counts < 200 cells/mm3 and to consider treatment in 1) WHO Clinical Stage 3 with CD4 count of 200-350 cells/mm3 and 2) WHO Clinical Stage 4, irrespective of CD4 count (WHO, 2006).

There are no trials comparing early initiation of ART (based on either CD4 or WHO Clinical stage) compared with late (CD4<200 or WHO Stage 4) initiation of ART.

The recommendations to initiate ART early are based on theoretical considerations and indirect data:

1) Observation of faster progression to liver disease in HIV-HBV co-infected individuals than mono-infected persons (Thio, 2002)

2) Hoffman and colleagues observed that ART initiation in co-infected persons did not affect treatment response for HIV but individuals remained at high risk for LRD, possibly due to incomplete HBV suppression. (Hoffman, 2009). This led these authors and Jain (Jain, 2009) to postulate that with earlier and more effective (combination) anti-HBV therapy, liver mortality would decrease.

3) Recent data suggests the importance of HIV in the fibrogenic process through the binding of gp120 to CCR5 receptors of hepatic stellate cells thus triggering an increased expression of collagen and inflammatory chemokines (Marra, 2007). This could imply a need for early combined therapy to produce rapid suppression of HBV replication and abate liver disease progression.

**In conclusion,** there are no direct data to support early initiation of ART in HIV-HBV co-infected individuals but early ART should be considered in HIV-HBV co-infected individuals with:

- CD4 < 500 OR
- WHO Clinical Stage $\geq$ Stage 3 OR
- Patients with active hepatitis, regardless of CD4 count or WHO Clinical Stage

The definition of active hepatitis is variable but may be based on of HBV DNA levels > 2000 copies/ml (where available) and/or persistent elevation of transaminases. In patients with CD4 cell counts of > 500, it may be more appropriate to use drugs with activity only against HBV (where available), e.g. IFN, Entecavir. It is unclear at present if adefovir, the least potent of the drugs can be used. When it is used at a dose of 10mg daily, it has no activity against HIV and although it has theoretical risk of developing HIV resistance mutations, recent data suggest this risk is very low (Locarnini, 2005).

***2) What ART to start in HIV/HBV co-infected adult patients***

***Question: Should 1st line (or initial) ART regimens used for HIV+ patients with chronic active hepatitis B contain more than one anti-HBV drug in their NRTI component?***

Population: HIV infected adults, adolescents and children > 5 years old with chronic active hepatitis B co infection

Interventions:
1) 1st line or initial EFV based ART regimens containing TDF and 3TC (or FTC)
2) 1st line or initial triple nuke ART regimens containing TDF and 3TC (or FTC)
3) 1st line or initial PI based ART regimens containing TDF and 3TC (or FTC)

Comparator:

1st line or initial cART regimens containing 3TC (or FTC) as the only HBV active drug

Outcomes:
Critical:
1. Mortality 1, 2 and 5 years
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Non-critical:
1. CD4 recovery
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4. HIV viral load response
5. HBV viral load response
6. HBV drug resistance
7. HIV drug resistance
8. Adherence

***Response:***

There are several reasons for recommending combination therapy at initiation of ART: 1) 3TC resistance develops rapidly if used as mono-therapy in HIV-HBV co-infected patients – 50% after two years of monotherapy and 90% after 4 years of monotherapy (Matthews, 2006); 2) HBV treatment response is better with combination therapy. In an RCT from Thailand , co-infected ART naïve patients randomized to receive TDF and 3TC had more frequent suppression of HBV DNA to < 1000 copies/ml as compared to those receiving 3TC alone (Matthews, 2008). Drug resistance developed in 2 of the 36 study patients, both of whom were on 3TC monotherapy.

In a cross sectional study done in the U.S and Australia demonstrated that 3TC experienced individuals receiving TDF and 3TC were more likely to achieve HBV DNA levels < 100 copies/ml than those receiving monotherapy with either TDF or 3TC (Matthews, 2009). In addition, this combination may reduce the rate of development of TDF-resistant HBV (Thio,2007).

In the study by Alvarez-Uria [see details in Background above], ART containing TDF was able to control HBV replication in most co-infected patients with nadir CD4 count of 110 cells/mm3 after a median follow up of 34 months, regardless of prior 3TC treatment (Alvarez-Uria, 2009). TDF treatment allowed low levels of HBV viremia to be maintained in 80% of patients. However, virologic breakthrough was seen in 9 (17%) cases. This study is the first to demonstrate high rates of virologic breakthrough not reported in other studies where the duration of follow up was shorter (Bani-Sadr, 2004;Benhamou,2006;Dore, 2004;Nelson 2003;Nunez,2002;Ristig, 2002;Schmutz,2006). In the study by Alvarez-Uria, 35 (67%) of patients had received 3TC with a median

duration of 32 months. Other studies have demonstrated that previous 3TC monotherapy produces an accumulation of 3TC mutations in mono-infected as well as co infected individuals (Fung, 2004;Matthews, 2006). It is therefore likely that this study population had 3TC resistant virus. Also the duration of previous 3TC monotherapy predicted failure to achieve undetectable HBV DNA at the end of the study period but the sample size was small and therefore limited the ability to detect a statistical difference. This suggests that mutations against 3TC could compromise optimal treatment response with TDF. In vitro studies also show reduced TDF activity in 3TC resistant HBV (Lada, 2004;Villet, 2008;Sheldon, 2005). In the study by Alvarez-Uria as well there was no additional benefit to adding 3TC or FTC. The limitations of this study are that baseline HBV DNA levels before TDF were not measured, HBV resistance testing was not performed, sample size was small and the study design was retrospective.

The selection of 3TC resistant HBV must be avoided for at least 4 reasons: 1) the benefit of slowing progression of LRD disappears; 2) selection of 3TC resistance results in cross resistance to other anti-HBV agents, 3) selection of HBV vaccine escape mutants may be favored and 4) transmission of drug resistant HBV may increase (Soriano, 2008).

**In conclusion,** initial ART regimens in HIV-HBV co-infected individuals should include TDF plus either 3TC or FTC in patients receiving EFV. Limited data are available but theoretical considerations as discussed above support the use of combination therapy in those receiving PI based regimens. No data are available for triple NRTIs but theoretical considerations support the use of combination therapy.

***3) What ART to switch to in HIV/HBV co-infected adult patients***
***Question; Should 2nd line ART regimens (or subsequent regimen after HIV treatment failure) for HIV+ patients with chronic active hepatitis B c-infection maintain more than one anti HBV drug in their NRTI component?***

Interventions:
2nd line or subsequent cART regimens containing TDF and 3TC (or FTC)

Comparator:
2nd line or subsequent cART regimens containing 3TC or FTC or TDF as the only HBV drug.

Outcomes:
Critical:
1. Mortality 1, 2 and 5 years
2. HIV disease progression
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Non-critical:
1. CD4 recovery

2. Other non-AIDS morbidities
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4. HIV viral load response
5. HBV viral load response
6. HBV drug resistance
7. HIV drug resistance
8. Adherence

***Response:***

4 studies were included in the response to this question (Benhamou, 2006; Schmutz, 2006, Matthews, 2009, Alvarez-Uria, 2009). All are observational studies (see summaries in section on Treatment of HBV) with incomplete reporting of outcomes as posed in the question above.

To reduce the development of resistance to both HBV and HIV (as discussed in Response to Question 2 above), at least 2 agents with activity against HBV should be used in the 2nd line regimen. In the case of 3TC resistance, TDF plus either 3TC/FTC may be used but in individuals with longer prior exposure to 3TC, HBV resistance to TDF is likely to develop more rapidly (Alvarez-Uria, 2009).

# Abbreviations

| | |
|---|---|
| 3TC | lamivudine |
| ADV | adefovir |
| ALT | alanine transaminase |
| Anti-HBs | antibody to hepatitis B surface antigen |
| ARV | antiretroviral therapy |
| cART | combination antiretroviral therapy |
| CHB | chronic hepatitis B |
| ETV | entecavir |
| FTC | emtricitabine |
| HAART | highly active antiretroviral therapy |
| HBV | hepatitis B |
| HBV DNA | hepatitis B deoxyribonucleic acid |
| HBeAg | hepatitis B e antigen |
| HBsAg | hepatitis B surface antigen |
| LRD | liver related disease |
| RCT | randomised controlled trial |
| TDF | tenofovir |

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# Appendix A:

**Recommendations for initiating ART in adults and adolescents in accordance with clinical stages and the availability of immunological markers (taken from WHO, 2006)**

| WHO clinical staging | CD4 testing not available | CD4 testing available |
|---|---|---|
| 1 | Do not treat **[A-III]** | Treat if CD4 count is below 200 cells/mm$^3$ [a] **[A-III]** |
| 2 | Do not treat [b] **[B-III]** | |
| 3 | Treat **[A-III]** | Consider treatment if CD4 count is below 350 cells/ mm$^3$ [a c d] and initiate ART before CD4 count drops below 200 cells/mm$^3$ [e] **[B-III]** |
| 4 | Treat **[A-III]** | Treat irrespective of CD4 cell count **[A-III]** |

[a] CD4 cell count advisable to assist with determining need for immediate therapy for situations such as pulmonary TB and severe bacterial infections, which may occur at any CD4 level.

[b] A total lymphocyte count of 1200/mm3 or less can be substituted for the CD4 count when the latter is unavailable and mild HIV disease exists. It is not useful in asymptomatic patients. Thus, in the absence of CD4 cell counts and TLCs, patients with WHO adult clinical stage 2 should not be treated.

[c] The initiation of ART is recommended in all HIV-infected pregnant women with WHO clinical stage 3 disease and CD4 counts below 350 cells/mm3 (see Section 11.2).

[d] The initiation of ART is recommended for all HIV-infected patients with CD4 counts below 350 cells/mm3 and pulmonary TB (see Section 12.1) or severe bacterial infection.

[e] The precise CD4 cell level above 200/mm3 at which ARV treatment should be started has not been established.

# Appendix B:

## Summary of 3TC/TDF studies since 2004 in patients co infected with HIV and HBV

| **Author of study, yr of publication**<br><br>***Included/ excluded in Gradepro summary (reason for exclusion)*** | **Type of study [Settings]** | **# patients, HIV/ HBV status** | **3TC status** | **RX used** | **Rx response (key findings)** | **Comments** |
|---|---|---|---|---|---|---|
| Dore, 2004<br><br>*Excluded (small sample size in each Rx arm, n<10)* | Substudy of RCT, Phase 3 HAART trials [W. Europe, North America, Australia] | Study 907: 23 co infected<br>Study 903: 23 co infected | Some 3TC naïve and some 3TC experienced | Study 907: TDF or placebo<br>Study study 903: TDF &3TC or 3TC alone | 48 wks: reduction in HBV DNA in pts on TDF; trend toward greater reduction in HBV DNA and also reduction in YMDD mutations with both TDF and 3TC | |
| Van Bommel, 2004<br><br>*Excluded (small sample, N=21 co infected and TDF compared with ADV)* | Prospective [Germany] | 52 with HBV<br>- 21 co infected with HIV | 3TC resistant HBV | TDF vs ADV | TDF (n=35)<br>- strong early suppression HBV DNA<br>- wk 48: higher ↓ viral load vs ADV | No resistance to TDF at 130 wks |
| Benhamou, 2006<br><br>*Excluded (outcomes not reported by specific ARV – i.e. PI vs NNRTI vs NRTI)* | Retrospective [France] | 65 co infected (54 eAg + and 11 eAg - ) | 68% 3TC refractory | | 30% HBeAg pos and 82% HBeAg neg had undetectable HBV DNA at end study | No TDF mutations at median follow up of 12 months |
| Schmutz, 2006<br><br>*Included* | Multi-centre, 1:2 matched pair analysis [Germany] | 75 co infected | 3TC resistant HBV | 50 TDF alone<br>25 TDF & 3TC | 116 wks: 84% TDF alone UD HBV DNA (<1000 copies/ml) vs 76% TDF &3TC (p=0.53)<br>Rate of loss of HBeAg and sAg same | |
| Jain, 2007 | Retrospective cohort [US] | 45 co infected | Gp 1: 27% previous HIV Rx; Gp 2 20% | Gp 1 (n= 15): 3TC alone, Gp 2 | HBV DNA < 2000 copies/ml: Gp 1= 60%, Gp 2 = 80%, Gp 3=55%. | Small sample size - insufficient power to notice |

| | | | | | | |
|---|---|---|---|---|---|---|
| *Excluded (outcomes not reported by specific ARV – i.e. PI vs NNRTI vs NRTI)* | | | and Gp 3 100% | (n=10): 3TC and TDF, Gp 3 (n=20), 3TC x 6 mos then 3TC plus TDF | Higher Rx response (HBV DNA < 2000) with HBV genotype A vs non genotype A: 74% vs 20% (odds ratio 11.1, 95% CI 2.04-50) | differences between Rx arms |
| Lacombe, 2008<br><br>*Excluded (TDF compared with ADV)* | Open label [France] | 85 co infected | | TDF or ADV | Decline in HBV DNA more pronounced in TDF vs ADV (66% vs 53%, p=0000.1) | |
| Matthews, 2008<br><br>*Included* | RCT [Thailand] | 36 co infected | | 3TC, TDF or both | 48 wks: av decline in HBV DNA similar in all 3 arms; suppression to < 1000 copies/ml more frequent in TDF arms (92% and 91% vs 46% in 3TC arm) | 3TC resistance in 2 subjects in 3TC only arm |
| Matthews, 2009<br><br>*Included* | Cross sectional cohort [US/Australia] | 122 co infected | 3TC experienced | TDF plus either 3TC or FTC | TDF plus either 3TC or FTC more likely to have undetectable HBV DNA than TDF or 3TC alone. | |
| Alvarez-Uria, 2009<br><br>*Included* | Retrospective observational [UK] | Co infected pts:<br>35 prior 3TC for median 32 months | | 34 prolonged 3TC use | Median FU 34 mos: HBV DNA < 1000 copies/ml in 42 (81%) and < 200 copies/ml in 31 (60%)<br>3TC experienced: longer duration of 3TC associated with failure to achieve HBV DNA < 200 copies/ml. Adding 3TC or FTC did not improve virologic suppression. of 39 achieving HBV DNA < 200 copies/ml, virologic breakthrough in 2 (5%) pts at 40 mos. | Nadir CD4 110 |

## APPENDIX C: GRADE Tables

**Author(s):** Ameeta Singh/Tom Wong
**Date:** 2009-09-11
**Question:** Should Antiretroviral therapy be used early for HIV and Hepatitis B co-infected individuals > 5 years old?
**Settings:** Multiple
**Bibliography:** There are no trials comparing early initiation of HAART (based on either CD4 or WHO Clinical stage) compared with late (CD4<200 or WHO Stage 4) initiation of HAART. The recommendations to initiate HAART early are based on theoretical considerations and indirect data: 1) Observation of faster progression to liver disease in HIV-HBV co-infected individuals than mono-infected persons (Thio CL, Seaberg EC, Skolasky RL et al. HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multi-Center AIDS Cohort Study (MACS). Lancet 2002;360:1921-26) 2) Hoffman and colleagues observed that HAART initiation in co-infected persons did not affect treatment response for HIV but individuals remained at high risk for LRD, possibly due to incomplete HBV suppression. (Hoffman CJ, Charalambous S, Martin DJ et al. Hepatitis B virus infection and response to antiretroviral therapy (ART) in a South African ART Program. Clin Infect Dis 2009;47:1479-85). This led these authors and Jain (Jain M. Mortality in patients co infected with hepatitis B virus and HIV: could antiretroviral therapy make a difference? Clin Infect Dis 2009;48:1772-4) to postulate that with earlier and more effective (combination) antiHBV therapy, liver mortality would decrease. 3) Recent data suggests the importance of HIV in the fibrogenic process through the binding of gp120 to CCR5 receptors of hepatic stellate cells thus triggering an increased expression of collagen and inflammatory chemokines (Marra F, Bruno R, Galastri . gp120 induces directional migration of human hepatic stellate cells: a link between HIV infection and liver fibrogenesis. Hepatology 2007:46:Abstract A125). This could imply a need for early combined therapy to produce rapid suppression of HBV replication and abate liver disease progression.

| Quality assessment | | | | | | | Summary of findings | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | No of patients | | Effect | | Quality | Importance |
| No of studies | Design | Limitations | Inconsistency | Indirectness | Imprecision | Other considerations | Antiretroviral therapy | control | Relative (95% CI) | Absolute | | |
| **Mortality 1, 2 and 5 years** | | | | | | | | | | | | |
| 0 | no evidence available | | | | | none | 0/0 (0%) | 0/0 (0%) | not pooled | not pooled | | |
| | | | | | | | | 0% | | not pooled | | |
| **HIV disease progression** | | | | | | | | | | | | |
| 0 | no evidence available | | | | | none | 0/0 (0%) | 0/0 (0%) | RR 0 (0 to 0) | 0 fewer per 1000 (from 0 fewer to 0 fewer) | | |
| | | | | | | | | 0% | | 0 fewer per 1000 (from 0 fewer to 0 fewer) | | |
| **HBV disease progression (cirrhosis, HCC)** | | | | | | | | | | | | |
| 0 | no evidence available | | | | | none | 0/0 (0%) | 0/0 (0%) | RR 0 (0 to 0) | 0 fewer per 1000 (from 0 fewer to 0 fewer) | | |
| | | | | | | | | 0% | | 0 fewer per 1000 (from 0 fewer to 0 fewer) | | |
| **Severe treatment associated adverse events** | | | | | | | | | | | | |
| 0 | no evidence available | | | | | none | 0/0 (0%) | 0/0 (0%) | RR 0 (0 to 0) | 0 fewer per 1000 (from 0 fewer to 0 fewer) | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | 0% | | 0 fewer per 1000 (from 0 fewer to 0 fewer) | | |
| **CD4 recovery** | | | | | | | | | | | | |
| 0 | no evidence available | | | | | none | 0/0 (0%) | 0/0 (0%)<br>0% | RR 0 (0 to 0) | 0 fewer per 1000 (from 0 fewer to 0 fewer)<br>0 fewer per 1000 (from 0 fewer to 0 fewer) | | |
| **Other non-AIDS morbidities** | | | | | | | | | | | | |
| 0 | no evidence available | | | | | none | 0/0 (0%) | 0/0 (0%)<br>0% | RR 0 (0 to 0) | 0 fewer per 1000 (from 0 fewer to 0 fewer)<br>0 fewer per 1000 (from 0 fewer to 0 fewer) | | |
| **Other HBV related morbidities** | | | | | | | | | | | | |
| 0 | no evidence available | | | | | none | 0/0 (0%) | 0/0 (0%)<br>0% | RR 0 (0 to 0) | 0 fewer per 1000 (from 0 fewer to 0 fewer)<br>0 fewer per 1000 (from 0 fewer to 0 fewer) | | |
| **HIV viral load response** | | | | | | | | | | | | |
| 0 | no evidence available | | | | | none | 0/0 (0%) | 0/0 (0%)<br>0% | RR 0 (0 to 0) | 0 fewer per 1000 (from 0 fewer to 0 fewer)<br>0 fewer per 1000 (from 0 fewer to 0 fewer) | | |
| **HBV viral load response** | | | | | | | | | | | | |
| 0 | no evidence available | | | | | none | 0/0 (0%) | 0/0 (0%)<br>0% | RR 0 (0 to 0) | 0 fewer per 1000 (from 0 fewer to 0 fewer)<br>0 fewer per 1000 (from 0 fewer to 0 fewer) | | |
| **HBV drug resistance** | | | | | | | | | | | | |
| 0 | no evidence available | | | | | none | 0/0 (0%) | 0/0 (0%)<br>0% | RR 0 (0 to 0) | 0 fewer per 1000 (from 0 fewer to 0 fewer)<br>0 fewer per 1000 (from 0 fewer to 0 fewer) | | |
| **HIV drug resistance** | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 0 | no evidence available | | | | | none | 0/0 (0%) | 0/0 (0%)<br>0% | RR 0 (0 to 0) | 0 fewer per 1000 (from 0 fewer to 0 fewer)<br>0 fewer per 1000 (from 0 fewer to 0 fewer) | | |
| **Adherence** | | | | | | | | | | | | |
| 0 | no evidence available | | | | | none | 0/0 (0%) | 0/0 (0%)<br>0% | RR 0 (0 to 0) | 0 fewer per 1000 (from 0 fewer to 0 fewer)<br>0 fewer per 1000 (from 0 fewer to 0 fewer) | | |

**Author(s):** Ameeta Singh, Tom Wong
**Date:** 2009-09-11
**Question:** Should 1st line EFV based ART regimen with TDF and 3TC (or FTC) vs 1st line ART containing 3TC (or FTC) as only HBV drug be used for HIV/HBV co-infected individuals > 5 years old?
**Settings:** Thailand
**Bibliography:** Matthews GV, Avihingsanon A, Lewin SR et al. A randomized trial of combination hepatitis B therapy in HIV/HBV co-infected antiretroviral naïve individuals in Thailand. Hepatol 2008;48:1062-9.

| Quality assessment | | | | | | | Summary of findings | | | | | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | No of patients | | Effect | | Quality | |
| No of studies | Design | Limitations | Inconsistency | Indirectness | Imprecision | Other considerations | 1st line EFV based ART regimen with TDF and 3TC (or FTC) | 1st line ART containing 3TC (or FTC) as only HBV drug | Relative (95% CI) | Absolute | | |
| **Mortality 1,2 and 5 years (follow-up 48 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 1/11 (9.1%) | 0/13 (0%)<br>0% | RR 0 (0 to 0)[2] | 0 fewer per 1000 (from 0 fewer to 0 fewer)<br>0 fewer per 1000 (from 0 fewer to 0 fewer) | ⊕⊕⊕O MODERATE | CRITICAL |
| **HIV disease progression - not measured** | | | | | | | | | | | | |
| 0 | - | - | - | - | - | none | 0/0 (0%) | 0/0 (0%) | - | - | | |
| **HBV disease progression (cirrhosis, HCC) (follow-up 48 weeks; liver biopsy)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 0/11 (0%) | 0/13 (0%) | RR 0 (0 to 0)[3] | 0 fewer per 1000 (from 0 fewer to 0 fewer) | ⊕⊕⊕O MODERATE | CRITICAL |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | 0% | | 0 fewer per 1000 (from 0 fewer to 0 fewer) | | |
| **Severe treatment associated adverse events (follow-up 48 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[4] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 1/11 (9.1%) | 0/13 (0%)<br>0% | RR 0 (0 to 0)[5] | 0 fewer per 1000 (from 0 fewer to 0 fewer)<br>0 fewer per 1000 (from 0 fewer to 0 fewer) | ⊕⊕⊕O MODERATE | CRITICAL |
| **CD4 recovery (follow-up 48 weeks; measured with: CD4 cell count; range of scores: 0-1000; Better indicated by higher values)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 11 | 13 | - | median 54 higher (0 to 0 higher) | ⊕⊕⊕⊕ HIGH | IMPORTANT |
| **Other non-AIDS morbidities - not measured** | | | | | | | | | | | | |
| 0 | - | - | - | - | - | none | 0/0 (0%) | 0/0 (0%) | - | - | | |
| **Other HBV related morbidities - not measured** | | | | | | | | | | | | |
| 0 | - | - | - | - | - | none | 0/0 (0%) | 0/0 (0%) | - | - | | |
| **HIV viral load response (follow-up 48 weeks; undetectable HIV RNA < 50c/ml)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 10/11 (90.9%) | 11/13 (84.6%)<br>90% | RR 1.07 (0.8 to 1.45)[6] | 59 more per 1000 (from 169 fewer to 381 more)<br>63 more per 1000 (from 180 fewer to 405 more) | ⊕⊕⊕⊕ HIGH | IMPORTANT |
| **HBV viral load response (follow-up 48 weeks; undetectable HBV DNA level (log10 c/ml))** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 7/11 (63.6%) | 6/13 (46.2%)<br>0% | RR 1.38 (0.66 to 2.88)[7] | 175 more per 1000 (from 157 fewer to 868 more)<br>0 more per 1000 (from 0 fewer to 0 more) | ⊕⊕⊕⊕ HIGH | IMPORTANT |
| **HBV drug resistance (follow-up 48 weeks; LAM resistance mutations (rtL180M + rtM204V or rtM204I)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 0/11 (0%) | 2/13 (15.4%) | RR 0 (0 to 0)[8] | 154 fewer per 1000 (from 154 fewer to 154 fewer) | ⊕⊕⊕O MODERATE | CRITICAL |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | 0% | | 0 fewer per 1000 (from 0 fewer to 0 fewer) | | |
| **HIV drug resistance - not measured** | | | | | | | | | | | | |
| 0 | - | - | - | - | - | none | 0/0 (0%) | 0/0 (0%) | - | - | | |
| **Adherence - not measured** | | | | | | | | | | | | |
| 0 | - | - | - | - | - | none | 0/0 (0%) | 0/0 (0%) | - | - | | |

[1] Small sample size & short duration of follow-up
[2] RR not reported
[3] RR not reported
[4] small sample size
[5] RR not reported
[6] RR not reported; calculated using Epi Info
[7] RR not reported; calculated using EpiInfo
[8] RR not reported

**Author(s):** Ameeta Singh/Tom Wong
**Date:** 2009-10-08
**Question:** Should 1st line EFV based ART regimen with TDF and 3TC (or FTC) vs 1st line ART containing 3TC (or FTC) as only HBV drug be used for HIV/HBV co-infected individuals > 5 years old?
**Settings:** US/Australia
**Bibliography:** Matthews GV, Seaberg E, Dore GJ et al. Combination HBV therapy is linked to greater HBV DNA suppression in a cohort of lamivudine-experienced HIV/HBV co infected individuals. AIDS 2009;23:1707-15.

| Quality assessment | | | | | | | Summary of findings | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | No of patients | | Effect | | | |
| **No of studies** | **Design** | **Limitations** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **1st line EFV based ART regimen with TDF and 3TC (or FTC)** | **1st line ART containing 3TC (or FTC) as only HBV drug** | **Relative (95% CI)** | **Absolute** | **Quality** | **Importance** |
| **Mortality 1, 2 and 5 years - not measured** | | | | | | | | | | | | |
| 0 | - | - | - | - | - | none | 0/0 (0%) | 0/0 (0%) | - | - | | CRITICAL |
| **HIV disease progression - not measured** | | | | | | | | | | | | |
| 0 | - | - | - | - | - | none | 0/0 (0%) | 0/0 (0%) | - | - | | IMPORTANT |
| **HBV disease progression (cirrhosis, HCC) - not measured** | | | | | | | | | | | | |
| 0 | - | - | - | - | - | none | 0/0 (0%) | 0/0 (0%) | - | - | | CRITICAL |
| **Severe treatment associated adverse events - not measured** | | | | | | | | | | | | |
| 0 | - | - | - | - | - | none | 0/0 (0%) | 0/0 (0%) | - | - | | IMPORTANT |
| **CD4 recovery - not measured** | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 0 | - | - | - | - | - | none | 0/0 (0%) | 0/0 (0%) | - | - | | IMPORTANT |
| **Other non-AIDS morbidities - not measured** | | | | | | | | | | | | |
| 0 | - | - | - | - | - | none | 0/0 (0%) | 0/0 (0%) | - | - | | IMPORTANT |
| **Other HBV related morbidities - not measured** | | | | | | | | | | | | |
| 0 | - | - | - | - | - | none | 0/0 (0%) | 0/0 (0%) | - | - | | IMPORTANT |
| **HIV viral load response - not measured** | | | | | | | | | | | | |
| 0 | - | - | - | - | - | none | 0/0 (0%) | 0/0 (0%) | - | - | | IMPORTANT |
| **HBV viral load response (undetectable HBV DNA level (log10 c/ml))** | | | | | | | | | | | | |
| 1 | observational studies | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 36/47 (76.6%) | 16/29 (55.2%)<br>0% | RR be 1.39 (95%CI = 0.96-2.00)[3] | 552 fewer per 1000 (from 552 fewer to 552 fewer)<br>0 fewer per 1000 (from 0 fewer to 0 fewer) | ⊕OOO VERY LOW | IMPORTANT |
| **HBV drug resistance (HBV Pol sequencing for mutations)** | | | | | | | | | | | | |
| 1 | observational studies | serious[4] | no serious inconsistency | no serious indirectness | serious[5] | none | 0/0 (0%)[6] | 0/0 (0%)<br>0% | RR 0 (0 to 0) | 0 fewer per 1000 (from 0 fewer to 0 fewer)<br>0 fewer per 1000 (from 0 fewer to 0 fewer) | ⊕OOO VERY LOW | CRITICAL |
| **HIV drug resistance - not measured** | | | | | | | | | | | | |
| 0 | - | - | - | - | - | none | 0/0 (0%) | 0/0 (0%) | - | - | | IMPORTANT |
| **Adherence - not measured** | | | | | | | | | | | | |
| 0 | - | - | - | - | - | none | 0/0 (0%) | 0/0 (0%) | - | - | | IMPORTANT |

[1] Small sample size (n=122), cross sectional study design
[2] See 1. above
[3] RR not reported; calculated using EpiInfo
[4] See 1. above
[5] See 1. above
[6] Detailed data not reported except to indicate that mutations identified in 15(41%) of 37 patients with detectable HBV DNA and majority in LAM/FTC monotherapy group

**Author(s):**
**Date:** 2009-09-11
**Question:** Should 1st line initial triple nuke ART regimens containing TDF and 3TC (or FTC) vs 1st line or initial ART regimens containing 3TC (or FTC) as the only HBV active drug be used for HIV/HBV co-infected adults > 5 years?
**Settings:** Multiple
**Bibliography:** No studies available

| Quality assessment | | | | | | | Summary of findings | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | No of patients | | Effect | | Quality | Importance |
| No of studies | Design | Limitations | Inconsistency | Indirectness | Imprecision | Other considerations | 1st line initial triple nuke ART regimens containing TDF and 3TC (or FTC) | 1st line or initial ART regimens containing 3TC (or FTC) as the only HBV active drug | Relative (95% CI) | Absolute | | |
| **Mortality 1,2 and 5 years** | | | | | | | | | | | | |
| 0 | no evidence available | | | | | none | 0/0 (0%) | 0/0 (0%) | RR 0 (0 to 0) | 0 fewer per 1000 (from 0 fewer to 0 fewer) | | |
| | | | | | | | | 0% | | 0 fewer per 1000 (from 0 fewer to 0 fewer) | | |
| **HIV disease progression** | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 0 | no evidence available | | | | | none | 0/0 (0%) | 0/0 (0%)<br>0% | RR 0 (0 to 0) | 0 fewer per 1000 (from 0 fewer to 0 fewer)<br>0 fewer per 1000 (from 0 fewer to 0 fewer) | | |
| **HBV disease progression (cirrhosis,HCC)** | | | | | | | | | | | | |
| 0 | no evidence available | | | | | none | 0/0 (0%) | 0/0 (0%)<br>0% | RR 0 (0 to 0) | 0 fewer per 1000 (from 0 fewer to 0 fewer)<br>0 fewer per 1000 (from 0 fewer to 0 fewer) | | |
| **Severe treatment associated adverse events** | | | | | | | | | | | | |
| 0 | no evidence available | | | | | none | 0/0 (0%) | 0/0 (0%)<br>0% | RR 0 (0 to 0) | 0 fewer per 1000 (from 0 fewer to 0 fewer)<br>0 fewer per 1000 (from 0 fewer to 0 fewer) | | |
| **CD4 recovery** | | | | | | | | | | | | |
| 0 | no evidence available | | | | | none | 0/0 (0%) | 0/0 (0%)<br>0% | RR 0 (0 to 0) | 0 fewer per 1000 (from 0 fewer to 0 fewer)<br>0 fewer per 1000 (from 0 fewer to 0 fewer) | | |
| **Other non-AIDS morbidities** | | | | | | | | | | | | |
| 0 | no evidence available | | | | | none | 0/0 (0%) | 0/0 (0%)<br>0% | RR 0 (0 to 0) | 0 fewer per 1000 (from 0 fewer to 0 fewer)<br>0 fewer per 1000 (from 0 fewer to 0 fewer) | | |
| **Other HBV related morbidities** | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 0 | no evidence available | | | | | none | 0/0 (0%) | 0/0 (0%)<br>0% | RR 0 (0 to 0) | 0 fewer per 1000 (from 0 fewer to 0 fewer)<br>0 fewer per 1000 (from 0 fewer to 0 fewer) | | |
| **HIV viral load response** | | | | | | | | | | | | |
| 0 | no evidence available | | | | | none | 0/0 (0%) | 0/0 (0%)<br>0% | RR 0 (0 to 0) | 0 fewer per 1000 (from 0 fewer to 0 fewer)<br>0 fewer per 1000 (from 0 fewer to 0 fewer) | | |
| **HBV viral load response** | | | | | | | | | | | | |
| 0 | no evidence available | | | | | none | 0/0 (0%) | 0/0 (0%)<br>0% | RR 0 (0 to 0) | 0 fewer per 1000 (from 0 fewer to 0 fewer)<br>0 fewer per 1000 (from 0 fewer to 0 fewer) | | |
| **HIV drug resistance** | | | | | | | | | | | | |
| 0 | no evidence available | | | | | none | 0/0 (0%) | 0/0 (0%)<br>0% | RR 0 (0 to 0) | 0 fewer per 1000 (from 0 fewer to 0 fewer)<br>0 fewer per 1000 (from 0 fewer to 0 fewer) | | |
| **Adherence** | | | | | | | | | | | | |
| 0 | no evidence available | | | | | none | 0/0 (0%) | 0/0 (0%)<br>0% | RR 0 (0 to 0) | 0 fewer per 1000 (from 0 fewer to 0 fewer)<br>0 fewer per 1000 (from 0 fewer to 0 fewer) | | |

**Author(s):**
**Date:** 2009-09-11
**Question:** Should 1st line or initial PI based ART regimens containing TDF and 3TC (or FTC) vs 1st line or initial ART regimens containing 3TC (or FTC) as the only HBV active drug be used for HIV/HBV co-infected individuals > 5 years old?
**Settings:** UK
**Bibliography:** Alvarez-Uria G,Ratcliffe L, Vilar JF. Long term outcome of tenofovir-disproxil fumarate use against hepatitis B in an HIV-infecetd cohort. HIV Med 2009;10:269-73.

| Quality assessment | | | | | | | Summary of findings | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | No of patients | | Effect | | | |
| No of studies | Design | Limitations | Inconsistency | Indirectness | Imprecision | Other considerations | 1st line or initial PI based ART regimens containing TDF and 3TC (or FTC) | 1st line or initial ART regimens containing 3TC (or FTC) as the only HBV active drug | Relative (95% CI) | Absolute | Quality | Importance |
| **Mortality 1,2 and 5 years - not reported[1]** | | | | | | | | | | | | |
| 0 | - | - | - | - | - | none | 0/0 (0%) | 0/0 (0%) | - | - | | CRITICAL |
| **HIV disease progression - not reported[2]** | | | | | | | | | | | | |
| 0 | - | - | - | - | - | none | 0/0 (0%) | 0/0 (0%) | - | - | | |
| **HBV disease progression - not reported[3]** | | | | | | | | | | | | |
| 0 | - | - | - | - | - | none | 0/0 (0%) | 0/0 (0%) | - | - | | |
| **Severe treatment assoicated adverse events** | | | | | | | | | | | | |
| 0 | no evidence available | | | | | none | 0/0 (0%) | 0/0 (0%) | RR 0 (0 to 0) | 0 fewer per 1000 (from 0 fewer to 0 fewer) | | |
| | | | | | | | | 0% | | 0 fewer per | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | 1000 (from 0 fewer to 0 fewer) | | |
| **CD4 recovery - not reported[4]** | | | | | | | | | | | | |
| 0 | - | - | - | - | - | none | 0/0 (0%) | 0/0 (0%) | - | - | | |
| **Other non-AIDS morbidities - not reported[5]** | | | | | | | | | | | | |
| 0 | - | - | - | - | - | none | 0/0 (0%) | 0/0 (0%) | - | - | | |
| **Other HBV related morbidities - not reported[6]** | | | | | | | | | | | | |
| 0 | - | - | - | - | - | none | 0/0 (0%) | 0/0 (0%) | - | - | | |
| **HIV viral load response - not reported[7]** | | | | | | | | | | | | |
| 0 | - | - | - | - | - | none | 0/0 (0%) | 0/0 (0%) | - | - | | |
| **HBV viral load response (follow-up median 34 months; Virological breakthrough: HBV DNA increase in serum by 1log10 (10 fold) above nadir)** | | | | | | | | | | | | |
| 1 | observational studies | serious[8] | no serious inconsistency | no serious indirectness | serious[9] | none | 0/0 (0%) | 0/0 (0%) | OR 7.64 (0.88 to 66.4) | 0 more per 1000 (from 0 fewer to 0 more) | VERY LOW | CRITICAL |
| | | | | | | | | 0% | | 0 more per 1000 (from 0 fewer to 0 more) | | |
| **HIV drug resistance - not reported[10]** | | | | | | | | | | | | |
| 0 | - | - | - | - | - | none | 0/0 (0%) | 0/0 (0%) | - | - | | |
| **Adherence - not reported[11]** | | | | | | | | | | | | |
| 0 | - | - | - | - | - | none | 0/0 (0%) | 0/0 (0%) | - | - | | |

[1] Not reported: LAM/FTC plus TDF plus PI vs LAM/FTC alone plus PI
[2] See 1. above
[3] See 1. above
[4] See 1. above
[5] See 1. above
[6] See 1. above
[7] See 1. above
[8] Retrospective observational study
[9] Retrospective observational study
[10] See 1. above
[11] See 1. above

**Author(s):** Ameeta Singh/Tom Wong
**Date:** 2009-09-11
**Question:** Should 2nd line or subsequent ART regimens containing TDF and 3TC (or FTC) vs 2nd line or subsequent ART regimens containing 3TC or FTC or TDF as the only HBV drug be used for HIV/HBV co-infected individuals > 5 years old?
**Settings:** Multiple
**Bibliography:** 1. Benhamou Y, Fleury H, Trimoulet P et al. Anti-hepatitis B virus efficacy of tenofovir disoproxil fumarate in HIV-infected patients. Hepatol 2006;43:548-55. 2. Schmutz G, Nelson M, Lutz T et al. Combination of tenofovir and lamivudine versus tenofovir after lamivudine failure for therapy of hepatitis B in HIV-co infection. AIDS 2006;20:1951-54. 3. Matthews GV, Seaberg E, Dore GJ et al. Combination HBV therapy is linked to greater HBV DNA suppression in a cohort of lamivudine-experienced HIV/HBV co infected individuals. AIDS 2009;23:1707-15. 4. Alvarez-Uria G,Ratcliffe L, Vilar JF. Long term outcome of tenofovir-disproxil fumarate use against hepatitis B in an HIV-infecetd cohort. HIV Med 2009;10:269-73

| Quality assessment | | | | | | | Summary of findings | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | No of patients | | Effect | | | |
| No of studies | Design | Limitations | Inconsistency | Indirectness | Imprecision | Other considerations | 2nd line or subsequent ART regimens containing TDF and 3TC (or FTC) | 2nd line or subsequent ART regimens containing 3TC or FTC or TDF as the only HBV drug | Relative (95% CI) | Absolute | Quality | Importance |
| **Mortality 1, 2 and 5 years (follow-up median 34 months; death during follow up period)** | | | | | | | | | | | | |
| 4 | observational studies | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 0/43 (0%) | 0/16 (0%) | Not estimable | 0 fewer per 1000 (from 0 fewer to 0 fewer) | VERY LOW | CRITICAL |
| **HIV disease progression - not reported** | | | | | | | | | | | | |
| 0 | - | - | - | - | - | none | 0/0 (0%) | 0/0 (0%) | - | - | | |
| **HBV disease progression (cirrhosis, HCC) (follow-up median 12 months)** | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | observational studies | serious[3] | no serious inconsistency | no serious indirectness | serious[4] | none | 0/65 (0%) | 0/0 (0%)<br>0% | RR 0 (0 to 0) | 0 fewer per 1000 (from 0 fewer to 0 fewer)<br>0 fewer per 1000 (from 0 fewer to 0 fewer) | VERY LOW | CRITICAL |
| **Severe treatment associated adverse events (follow-up median 12 months; see note[5])** | | | | | | | | | | | | |
| 1 | observational studies | serious[6] | no serious inconsistency | no serious indirectness | serious[7] | none | 1/65 (1.5%) | 0/0 (0%)<br>0% | RR 0 (0 to 0) | 0 fewer per 1000 (from 0 fewer to 0 fewer)<br>0 fewer per 1000 (from 0 fewer to 0 fewer) | VERY LOW | |
| **CD4 recovery - not measured[8]** | | | | | | | | | | | | |
| 0 | - | - | - | - | - | none | 0/0 (0%) | 0/0 (0%) | - | - | | |
| **Other non-AIDS morbidities - not reported** | | | | | | | | | | | | |
| 0 | - | - | - | - | - | none | 0/0 (0%) | 0/0 (0%) | - | - | | |
| **Other HBV related morbidities - not reported** | | | | | | | | | | | | |
| 0 | - | - | - | - | - | none | 0/0 (0%) | 0/0 (0%) | - | - | | |
| **HIV viral load response (follow-up median 34 months; HIV RNA < 2.6 log 10 copies/ml)** | | | | | | | | | | | | |
| 1 | observational studies | serious[9] | no serious inconsistency | no serious indirectness | serious[10] | none | 43/64 (67.2%) | 29/62 (46.8%)<br>0% | RR 1.44 (1.05 to 1.97)[11] | 206 more per 1000 (from 23 more to 454 more)<br>0 more per 1000 (from 0 more to 0 more) | VERY LOW | IMPORTANT |
| **HBV viral load response (follow-up median 34 months[12]; HBV DNA < 200 copies/ml)** | | | | | | | | | | | | |
| 4 | observational studies | serious[13] | no serious inconsistency | no serious indirectness | serious[14] | none | 31/52 (59.6%)[15] | 0/0 (0%) | RR 0 (0 to 0) | 0 fewer per 1000 (from 0 fewer to 0 fewer) | VERY LOW | IMPORTANT |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | 0% | | 0 fewer per 1000 (from 0 fewer to 0 fewer) | | |
| **HBV drug resistance (follow-up median 34 months; virologic breakthrough[16])** | | | | | | | | | | | | |
| 1 | observational studies | serious[17] | no serious inconsistency | no serious indirectness | serious[18] | none | 9/59 (15.3%) | 0% | RR 0 (0 to 0) | 0 fewer per 1000 (from 0 fewer to 0 fewer) | VERY LOW | CRITICAL |
| **HIV drug resistance (follow-up median 34 months; HIV drug resistance test)** | | | | | | | | | | | | |
| 1[19] | observational studies | serious[20] | no serious inconsistency | no serious indirectness | serious[21] | none | 1/52 (1.9%)[22] | 0% | RR 0 (0 to 0) | 0 fewer per 1000 (from 0 fewer to 0 fewer) | VERY LOW | IMPORTANT |
| **Adherence (follow-up median 34 months; rebound in HIV RNA on treatment)** | | | | | | | | | | | | |
| 1 | observational studies | serious[23] | no serious inconsistency | no serious indirectness | serious[24] | none | 1/52 (1.9%)[25] | 0% | RR 0 (0 to 0) | 0 fewer per 1000 (from 0 fewer to 0 fewer) | VERY LOW | IMPORTANT |

[1] See Footnote 1
[2] Studies varied in duration of follow up - study by Alvarez Uria longest and included here. None specifically reported on mortality but no deaths reported in this study with longest duration of follow up.
[3] See 4 above
[4] See 4. above
[5] Single patient on TDF developed renal tubulopathy (co-existing Castelman disease and non Hodgkin's lymphoma) at month 20. Developed Fanconi type syndrome without renal failure. Recovered few weeks after TDF withdrawal.
[6] Retrospective observational study
[7] See 8. above
[8] ARV treatment experienced patients; CD4 change not reported
[9] See 8. above
[10] See 8. above
[11] RR not reported; p=0.01; RR calculated using Epi Info
[12] Variable median follow up in studies - Alvarez Uria included here (median FU 34 months). Other studies: Schmutz: median 116-129 weeks; Matthews: time since HAART initiation 6.7 months on LAM or FTC alone, 8.2 months on TDF alone and 8.2 months on TDF and LAM/FTC; Benhamou: median duration ARV 6 years
[13] See 1 above re details of studies
[14] See 1 above re details of studies
[15] No significant difference between LAM naive and LAM experienced groups
[16] no signiificant differences in characteristics (gender, age, HBeAg positive,preexisiting cirrhosis, CD4 nadir or end of study CD4, previous duration of LAM, concomitant use of LAM or PI) in patients experiencing virologic breakthrough and those not
[17] Alvarez Uria retrospective observational study design
[18] Alvarez Uria study retrospective observational
[19] Alvarez Uria retrospective observational study design
[20] see 22. above

[21] see 2.. above
[22] Type of resistance in the single patient note reported except to say showed resistance mutations against the HIV ARV regimen the patient was on. Patient's HIV RNA was 3168 copies/ml.
[23] Alvarez Uria retrospective observational study design
[24] Alvarez Uria retrospective observational study design
[25] Adherence indirectly measured and reported based on development of rebound HIV RNA in 1 of 9 patients with HBV virologic breakthrough