Non AIDS complications and treatment optimizations for HIV-1 infected Thai adult patients with and without TB or hepatitis
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A randomised trial of combination hepatitis B therapy in HIV/HBV coinfected antiretroviral naïve individuals in Thailand

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A Randomized Trial of Combination Hepatitis B Therapy in HIV/HBV Coinfected Antiretroviral Naïve Individuals in Thailand

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Coinfection with human immunodeficiency virus (HIV) and hepatitis B virus (HBV) is associated with considerable liver disease morbidity and mortality. Emerging HIV epidemics in areas of high HBV endemicity such as Asia are expanding the population with HIV/HBV coinfection. Limited randomized trial data exist to support current guidelines for HBV combination therapy in HIV/HBV coinfection. The objective of this prospective randomized clinical trial was to compare the strategy of HBV monotherapy with lamivudine (LAM) or tenofovir disoproxil fumarate (TDF) versus HBV combination therapy with LAM/TDF in antiretroviral-naïve HIV/HBV-coinfected subjects in Thailand. Thirty-six HIV/HBV-coinfected subjects initiating highly active antiretroviral therapy (HAART) were randomized to either LAM (arm 1), TDF (arm 2), or LAM/TDF (arm 3) as HBV-active drugs within HAART. At week 48, time-weighted area under the curve analysis revealed that the median HBV DNA reduction from baseline was 4.07 log10 c/mL in arm 1, 4.57 log10 c/mL in arm 2, and 4.73 log10 c/mL in arm 3 (P = 0.70). HBV DNA suppressed to <3 log10 c/mL in 46% in arm 1, 92% in arm 2, and 91% in arm 3 (P = 0.013, intent-to-treat analysis). HBV-resistant changes were detected in two subjects, both in arm 1. Hepatitis B e antigen (HBeAg) loss was observed in 33% of HBeAg-positive subjects, and 8% experienced hepatitis B surface antigen loss. Hepatic flare was observed in 25% of subjects. Conclusion: LAM monotherapy resulted in a greater proportion of subjects with HBV DNA >3 log10 c/mL at week 48 and in early resistance development. This study confirms current treatment guidelines that recommend a TDF-based regimen as the treatment of choice for HIV/HBV coinfection, but does not demonstrate any advantage of HBV combination therapy in this short-term setting. (HEPATOLOGY 2008;48:1062-1069.)

Abbreviations: ALT, alanine aminotransferase; AZT, zidovudine; EFV, efavirenz; HAART, highly active antiretroviral therapy; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HIV, human immunodeficiency virus; LAM, lamivudine; rt, reverse transcriptase; TDF, tenofovir disoproxil fumarate; ULN, upper limit of normal.

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The presence of chronic hepatitis B infection in HIV-infected individuals has been associated with accelerated liver disease progression and aggressive hepatocellular carcinoma, as well as with high rates of antiretroviral-related toxicity and the phenomenon of hepatitis B–related immune reconstitution flare. In Asian countries such as Thailand, where hepatitis B virus (HBV) infection is known to be highly endemic within the general population, the prevalence of human immunodeficiency virus (HIV)/HBV coinfection is high and may lead to substantial increases in future morbidity and mortality within this population.

Current HIV treatment guidelines recommend the use of combination therapy, including two HBV-active nucleoside analogues, for any HIV/HBV-coinfected patient initiating highly active antiretroviral therapy (HAART). These recommendations are based on observations of widespread lamivudine (LAM) resistance when this drug is used as monotherapy for HBV and clinical experience with the potency of tenofovir disoproxil fumarate (TDF)-based regimens in both LAM-naïve and LAM-experienced individuals. However, randomized clinical trial data to support these recommendations have been lacking. This randomized clinical trial performed among HIV/HBV-coinfected individuals in Thailand was designed to examine the HBV therapeutic strategy of LAM versus TDF versus combination LAM/TDF in antiretroviral-naïve individuals initiating HAART.

**Patients and Methods**

**Patients.** Subjects were recruited through the HIV-Netherlands Australia Thailand network located in Bangkok, Thailand, and screened at the HIV outpatient clinic at Chulalongkorn Hospital, Bangkok. All subjects were HIV-1 antibody–positive with detectable HIV RNA and naive to antiretroviral therapy. Further inclusion criteria were documented hepatitis B surface antigen (HBsAg)-positive status for more than 6 months or HBsAg-positive with absence of immunoglobulin M antibodies to HBV core at screening. HBV DNA greater than 100,000 copies/mL (>20,000 IU/mL), no prior HIV antiviral therapy (including LAM, adefovir, or TDF), age 18-70 years, creatinine ≤2 mg/dL, and platelet count ≥50,000 mm$^3$. Exclusion criteria were positive hepatitis C virus RNA, positive immunoglobulin M antibodies to hepatitis A virus, serum alanine aminotransferase (ALT) level > 1,000 IU/L, active opportunistic infection within 6 weeks of entry, other causes of chronic liver disease, concurrent malignancy requiring cytotoxic chemotherapy, Child-Pugh class C or decompensated cirrhosis, and alpha-fetoprotein more than three times the upper limit of normal (ULN) (unless computerized tomography or magnetic resonance imaging scans for hepatoma were negative within 3 months of screening date). Subjects were not required to undergo liver biopsy prior to enrollment, although this was recommended as part of optimal clinical care.

**Study Design.** The study was designed as a prospective three-arm nonblinded randomized clinical trial to compare HBV- and HIV-related outcomes in antiretroviral-naïve HIV/HBV-coinfected individuals initiating HAART with one of three HBV-active regimens. A total of 36 subjects were randomized on a 1:1:1 basis to one of the following arms:

- Arm 1: zidovudine (AZT) plus LAM plus efavirenz (EFV)
- Arm 2: AZT plus TDF plus EFV
- Arm 3: TDF plus LAM plus EFV

Lamivudine was dosed at 150 mg twice daily, TDF at 300 mg/day, and AZT at 250 mg twice daily. Subjects on combination LAM/AZT therapy could take Combidir twice daily. EFV was dosed at 600 mg/day. Subjects were allowed to switch or dose modify the AZT and EFV components of their regimen to other suitable non-HBV active antiretrovirals for reasons of toxicity or inadequate plasma concentrations. All subjects gave informed written consent, and the study was approved by the relevant Human Research Ethics Committees in Thailand and Australia.

**Statistical Methods.** The primary efficacy endpoint of the study was median log$_{10}$ change in HBV DNA from baseline to week 48 estimated using the time-weighted area under the curve. The study was powered to detect a 1.8-log or greater reduction in HBV DNA in the TDF-containing arms compared to LAM-containing arms at a significance level of 0.05 and with 80% power. This figure was based on an anticipated reduction in HBV DNA of approximately 2.7 log$_{10}$ in the LAM arm and 4.5 log$_{10}$ in the TDF arms. The sample size was calculated as 36 subjects. Secondary endpoints included proportion of subjects with undetectable HBV DNA at weeks 12, 24, and 48, hepatitis B e antigen (HBeAg) and HBsAg loss/sorconversion rates, median change from baseline in HIV RNA and CD4 count (cells/mm$^3$), median change in ALT and time to ALT normalization over 48 weeks, development of HBV resistance mutations at week 48, and rate of hepatic flare. In addition, a level of >1,000 c/mL at week 48 was examined based on data published during the conduct of the study, suggesting that this threshold may be associated with future resistance development. All analyses were performed on an intent-to-treat basis where missing = failure. Hepatic flare was defined as an increase in ALT or aspartate aminotransfer-
ase level from baseline of >5 times the ULN or >100 IU/L from baseline if abnormal at entry. In addition, for those subjects with liver biopsies at baseline and week 48, histological changes were determined. Histological scoring was performed initially by a Thai pathologist and then subsequently by an independent pathologist in Australia blinded to the results. Where histological scores differed between the two pathologists by more than two fibrosis stages, the biopsies were scored again by a third independent Australian pathologist. Treatment arms were compared using the Kruskal-Wallis test for continuous variables and Fisher’s exact test for dichotomous variables. All tests were two-sided, and \( \alpha < 0.05 \) was considered statistically significant.

**Laboratory Methods.** HBV viral load testing was performed at a central laboratory (the Victorian Infectious Diseases Laboratory, Melbourne, Australia). HBV DNA measurement was performed on all samples using the Versant HBV DNA 3.0 bDNA assay (Bayer HealthCare, Tarrytown, NY). The linear dynamic range of the assay is from \( 2 \times 10^3 \) to \( 1 \times 10^7 \) copies/mL or \( 3.6 \times 10^2 \) – \( 1.8 \times 10^7 \) IU/mL. For samples below the lower limit of detection on the bDNA assay, repeat testing was performed using the COBAS TaqMan HBV Test (Roche Diagnostics, Branchburg, NJ). The lower limit of quantification of this assay is approximately \( 1.7 \times 10^2 \) copies/mL or \( 3 \times 10^1 \) IU/mL.

Sequencing of the polymerase gene was undertaken at baseline and in all subjects with viral load rebound (\( >1 \) log HBV DNA increase from nadir). Polymerase chain reaction amplification, sequencing, and sequence analysis were performed as described by Ayres et al.\(^{19}\) HBV consensus sequences were constructed using the ABI Prism SeqScape DNA sequence analysis program Version 2.1 (Applied Biosystems, Foster City, CA). HBV genotype and unique HBV mutations were identified using the Web-based program SeqHepB.\(^{20}\) Safety blood sampling and analysis (hematology, biochemistry, clotting), HBV serology, T cell subsets, and HIV-1 RNA were performed at the local laboratory in Bangkok.

**Results**

Subject disposition throughout the study is given in Figure 1, and baseline characteristics of enrolled subjects are described in Table 1. The study group was predominantly male (64%), and the majority of subjects identified heterosexual exposure as the most likely route of HIV infection. Despite a median duration since diagnosis of HIV infection of only 1.5 years (interquartile range, 11 months to 7 years), this group had advanced HIV disease with a median baseline CD4 at screening of 36 cells/mm\(^3\) and a median HIV RNA of \( 4.7 \log_{10} \) c/mL. Nineteen percent of the cohort had a prior, reflecting advanced levels of immunodeficiency, with 66% and 58% of the group on cotrimoxazole and fluconazole, respectively. Seventeen percent (6/36) were on isoniazid/rifampicin-containing regimens for the treatment of mycobacterial infection. Baseline HBV DNA levels were high at a median of \( 8.4 \log_{10} \) c/mL, and 22 (61%) subjects were HBeAg-positive. There was no significant difference in baseline HBV DNA levels between HBeAg-positive and HBeAg-negative subjects (8.5 \( \log_{10} \) c/mL versus 8.3 \( \log_{10} \) c/mL). Despite highly elevated HBV DNA levels at baseline, the median ALT was only 48 IU/L, and almost half the subjects (47%) had normal ALT at baseline. Liver biopsy was not mandated by the study protocol but was recommended for HBV disease assessment. Twenty-three subjects (64%) underwent this procedure at study entry, and 21 biopsies were suitable for histological assessment. Consistent with the finding of normal transaminases in a high proportion of subjects, 15/21 (71%) biopsies demonstrated stage 0 or 1 Metavir fibrosis. Similarly, 16/21 (76%) biopsies showed Metavir activity A0 or A1, with only five biopsies demonstrating A2, and none A3. Cirrhosis was observed histologically in three subjects, with a further two subjects diagnosed as cirrhotic on clinical/radiological grounds. The prevalence of cirrhosis in this
Table 1. Baseline Characteristics of Study Population in Total and by Randomization

<table>
<thead>
<tr>
<th></th>
<th>Arm 1 (n = 13)</th>
<th>Arm 2 (n = 12)</th>
<th>Arm 3 (n = 11)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years [mean (SD)]</td>
<td>37.5 (7.0)</td>
<td>32.1 (8.0)</td>
<td>36.9 (9.9)</td>
<td>35.5 (8.4)</td>
</tr>
<tr>
<td>Female sex</td>
<td>23%</td>
<td>33%</td>
<td>45%</td>
<td>36%</td>
</tr>
<tr>
<td>Body mass index, kg/m² [mean (SD)]</td>
<td>20.0 (3.0)</td>
<td>20.4 (3.2)</td>
<td>20.8 (2.7)</td>
<td>20.4 (2.9)</td>
</tr>
<tr>
<td>HIV risk factor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterosexual</td>
<td>77%</td>
<td>75%</td>
<td>82%</td>
<td>78%</td>
</tr>
<tr>
<td>Men who have sex with men</td>
<td>23%</td>
<td>25%</td>
<td>18%</td>
<td>22%</td>
</tr>
<tr>
<td>Prior AIDS (CDC group C)</td>
<td>15%</td>
<td>16%</td>
<td>27%</td>
<td>19%</td>
</tr>
<tr>
<td>Median baseline CD4, cells/mm² [median (IQ range)]</td>
<td>44 (18-204)</td>
<td>25 (12-250)</td>
<td>39 (28-216)</td>
<td>36 (19-208)</td>
</tr>
<tr>
<td>Median baseline HIV RNA, log₁₀ c/mL (IQ range)</td>
<td>4.8 (4.4-4.8)</td>
<td>5.0 (4.2-5.3)</td>
<td>4.7 (4.3-4.9)</td>
<td>4.7 (4.3-5.1)</td>
</tr>
<tr>
<td>HBV DNA, log₁₀ c/mL (IQ range)</td>
<td>8.4 (8.3-9.5)</td>
<td>8.6 (7.2-9.4)</td>
<td>8.4 (6.6-9.4)</td>
<td>8.4 (8.1-9.5)</td>
</tr>
<tr>
<td>Alcohol consumption &gt;3 L/day</td>
<td>23%</td>
<td>50%</td>
<td>9%</td>
<td>28%</td>
</tr>
<tr>
<td>HBV genotype*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>15%</td>
<td>8%</td>
<td>18%</td>
<td>14%</td>
</tr>
<tr>
<td>C</td>
<td>85%</td>
<td>75%</td>
<td>82%</td>
<td>81%</td>
</tr>
<tr>
<td>G</td>
<td>0</td>
<td>8%</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>ALT, IU/mL [median (IQ range)]</td>
<td>54 (44-104)</td>
<td>46 (30-85)</td>
<td>40 (27-66)</td>
<td>48 (29-85)</td>
</tr>
<tr>
<td>HBsAg-positive</td>
<td>69%</td>
<td>50%</td>
<td>64%</td>
<td>61%</td>
</tr>
<tr>
<td>Fibrosis score†</td>
<td>(n = 7)</td>
<td>(n = 8)</td>
<td>(n = 6)</td>
<td></td>
</tr>
<tr>
<td>0/1</td>
<td>4</td>
<td>6</td>
<td>5</td>
<td>15 (71%)</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>3 (14%)</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

Abbreviations: CDC, Centers for Disease Control and Prevention; IQ, interquartile; SD, standard deviation.
*Unable to obtain genotype in one subject at baseline.
†In 21 subjects undergoing liver biopsy with interpretable histology.

The study group was thus 14%. The HBV genotype was C in over 80% of subjects, consistent with the HBV genotypic distribution in Thailand.²¹

**HBV Virological Response.** HBV DNA levels fell rapidly in all treatment arms, with a median reduction in log₁₀ c/mL of 2.0 by week 2, 4.0 at week 12, 5.3 at week 24, and 5.9 at week 48. The curve of median HBV DNA decline was comparable across randomized arms (Figure 2). The primary endpoint of the study, median time-weighted change in HBV DNA (log₁₀ c/mL) from baseline to week 48, was calculated as 4.07 log₁₀ c/mL in arm 1 (LAM), 4.57 log₁₀ c/mL in arm 2 (TDF), and 4.73 log₁₀ c/mL in arm 3 (LAM/TDF). Although HBV DNA suppression was greater in the TDF-containing arms, this finding was not significant (P = 0.70). The proportion of subjects with HBV DNA below the most sensitive level of detection 170 c/mL (equivalent to 30 IU/mL) at 48 weeks by intent-to-treat analysis was higher in the TDF-containing groups (75% TDF and 64% LAM/TDF) than in the LAM group (46%), though these findings also were not significant (P = 0.65). However, when a cut-off for HBV DNA suppression of 1,000 c/mL was used, a significant difference was observed. Only 46% of subjects in the LAM group achieved this level compared with 92% in the TDF group and 91% in the LAM/TDF group (P = 0.013). In fact, all subjects in the LAM/TDF group who were still in follow-up at week 48 had suppressed HBV DNA to <1000 c/mL and 70% to <170 c/mL (Figure 3). In the TDF group, only one subject failed to suppress to <1,000 c/mL. HBV DNA in this subject fell from a baseline HBV DNA of 8,35 log₁₀ c/mL to a nadir of 950 c/mL at week 24, and then rose again to 2,000 c/mL by week 48. HIV viral load also became detectable at week 48, having been previously suppressed; poor adherence or inadequate drug levels due to malabsorption may have been responsible in this case. Sequence analysis failed in this subject at week 48 due to the relatively low HBV DNA level. In the LAM group, five subjects still under follow-up at week 48 failed to suppress HBV DNA to <1,000 c/mL. Week 48 HBV DNA level in these subjects varied from 3.0 log₁₀ c/mL to 7.1 log₁₀ c/mL. In all but one case, this represented a continued reduction from baseline of 3 logs or greater (Table 2). Virological rebound (defined as an increase in HBV DNA of >1 log...
HBV genotype* 1 (LAM), 4.57 log 10 c/mL in arm 2 (TDF), and 4.73 log 10 line to week 48, was calculated as 4.07 log 10 c/mL in arm rapidly in all treatment arms, with a median reduction in Fibrosis score† (n HBeAg-positive 69% 50% 64% 61%

Body mass index, kg/m 2 [mean (SD)] 20.0 (3.0) 20.4 (3.2) 20.8 (2.7) 20.4 (2.9)

Fibrosis score was seen in three subjects, all of whom were cirrhotic at baseline. Metavir activity score improved by one stage in five subjects and was unchanged in 10 subjects.

Hepatic Flare and Other Adverse Events. Hepatic flare, as defined by an increase in ALT to >5 × ULN, or a rise in ALT of >100 IU/L from baseline at entry, was observed in nine (25%) subjects. In eight of nine subjects, hepatic flare occurred during the first 12 weeks of study participation (early flare) and in one subject at week 24. Median time to flare was 56 days (range 21-86 days), and median ALT at flare was 391 IU/L (range 178-2560 IU/L). Four of the eight cases of early flare were HBeAg-positive at baseline; three (75%) of these subjects subsequently lost HBeAg, and two also experienced anti-HBe seroconversion and subsequent HBSAg loss. The case of late flare, occurring at 6 months of therapy, was also followed by anti-HBe seroconversion and HBSAg loss. One subject with hepatic flare shortly after initiating HAART (arm 3: LAM/TDF/EFV) developed rapid hepatic decompensation. This subject was a 56-year-old male with a baseline CD4 count of 102 cells/mm³, baseline ALT of 80 IU/L, and baseline HBV DNA

from nadir) occurred in one subject only and was associated with the development of known LAM-resistant mutations in the reverse transcriptase (rt) domain of the viral polymerase, rtL180M + rtM204V at week 48. One other subject in the LAM group with detectable HBV DNA >1,000 c/mL at week 48 had a polymerase mutation at rtM204I, also associated with LAM resistance. Polymerase sequencing demonstrated no resistance mutations (wild-type) in two subjects and was not possible due to the low HBV DNA level in the fifth subject (Table 2).

Serological and Biochemical Response. The serological response rate over 48 weeks is given in Table 3. Sixty-one percent (22/36) of the study group were HBeAg-positive at baseline, and in this group 33% (7/22) lost HBeAg and 27% (5/22) underwent anti-HBe seroconversion. No significant differences in HBeAg seroconversion rates were seen between randomized groups. Three subjects (8%), one from each arm, lost HBsAg. The CD4 count at week 12 in subjects with HBeAg loss (197 cells/mm³) was similar to that in subjects with no HBeAg loss (148 cells/mm³; P = 0.97). In addition, the change in CD4 count between baseline and week 12 was not significantly different in subjects with and without HBeAg loss (168 cells/mm³ versus 112 cells/mm³; P = 0.48). Median ALT was unchanged from 48 IU/L at baseline to 43 IU/L at week 48. Among subjects with an elevated ALT at baseline (19/36), normalization occurred in 32% (6/19), with all these subjects having complete HBV DNA suppression to <170 c/mL at week 48.

HIV-Related Outcomes. The median CD4 cell count rose from 36 cells/mm³ at baseline to 133 cells/mm³ at week 24, and to 202 cells/mm³ at week 48, indicating marked immune recovery in the overall study group. The median CD4 count improved in all groups, though a significantly greater increase in CD4 cell count was observed in subjects in arm 3 (LAM/TDF/EFV) compared with arm 1 (AZT/LAM/EFV) and arm 2 (AZT/TDF/EFV): arm 1, +141 cells/mm³; arm 2, +118 cells/mm³; arm 3, +195 cells/mm³ (P = 0.048). HIV RNA suppression <50 c/mL was achieved in the majority of subjects in all treatment arms by week 48 (intent-to-treat: arm 1, 85%; arm 2, 75%; arm 3, 91%; P = 0.75).

Histological Response. Sixteen of 23 subjects who underwent liver biopsy at the start of the study underwent a subsequent liver biopsy at study completion (week 48), and paired liver biopsies were available for analysis in 15 subjects. In eight subjects, no change in fibrosis score was observed (all stage 0/1 at baseline). Fibrosis score worsened by 1 stage in five subjects. An improvement in fibrosis score was seen in three subjects, all of whom were cirrhotic at baseline. Metavir activity score improved by one stage in five subjects and was unchanged in 10 subjects.

Table 2. HBV DNA at Baseline and Week 48 in 6 Subjects with HBV DNA >1,000 c/mL at Week 48

<table>
<thead>
<tr>
<th>Subject</th>
<th>Baseline HBV DNA (c/mL)</th>
<th>Week 48 HBV DNA (c/mL)</th>
<th>Polymersase Sequencing Analysis at Week 48</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject 1 (Arm 2)</td>
<td>2.65 × 10⁷</td>
<td>2000</td>
<td>Wild-type</td>
</tr>
<tr>
<td>Subject 2 (Arm 1)</td>
<td>3.38 × 10⁷</td>
<td>1.14 × 10⁷</td>
<td>L180M/M204V</td>
</tr>
<tr>
<td>Subject 3 (Arm 1)</td>
<td>492 × 10⁷</td>
<td>8.87 × 10⁷</td>
<td>Wild-type</td>
</tr>
<tr>
<td>Subject 4 (Arm 1)</td>
<td>1.90 × 10⁷</td>
<td>1110</td>
<td>Wild-type</td>
</tr>
<tr>
<td>Subject 5 (Arm 1)</td>
<td>5.70 × 10⁷</td>
<td>1.77 × 10⁷</td>
<td>Wild-type</td>
</tr>
<tr>
<td>Subject 6 (Arm 1)</td>
<td>2.65 × 10⁷</td>
<td>2.68 × 10⁵</td>
<td>Wild-type</td>
</tr>
</tbody>
</table>

Fig. 3. Suppression of HBV DNA at 48 weeks by randomization arm. Three subjects were excluded because no week 48 result was available.
of $3.0 \times 10^{11}$ c/mL. The subject was HBeAg-negative and had clinical signs of cirrhosis (Child-Pugh class A) at screening, but declined liver biopsy. At week 3 of therapy the subject’s ALT rose to 233 IU/L and by week 4 to 522 IU/L. Despite EFV cessation and supportive measures, further ALT elevation was seen together with laboratory evidence of hepatic dysfunction. The subject developed rapid hepatic failure and died at week 8 of the study.

No impairment in renal function or sustained elevations in serum creatinine above the ULN were observed in any subject during the study.

**Discussion**

In this randomized clinical study of HBV therapy in antiretroviral-naïve HIV/HBV-coinfected subjects commencing their first HAART regimen in Thailand, we found that HBV DNA suppression to $<170$ c/mL (30 IU/mL) was achievable in the majority of subjects (61%) over the first 48 weeks of treatment, irrespective of their randomized therapy. This finding is encouraging given the advanced level of immunosuppression and the high HBV DNA level at baseline within the group. Greater HBV DNA reduction was observed in the TDF-containing arms ($4.73 \log_{10}$ c/mL TDF/LAM versus $4.57 \log_{10}$ c/mL TDF versus $4.07 \log_{10}$ c/mL LAM) but was not statistically significant. A significant difference was seen between groups in the proportion of subjects able to suppress below 1,000 c/mL by week 48. All subjects under follow-up in the LAM/TDF combination arm were suppressed to below this level, compared with 92% in the TDF arm and 55% of the LAM arm. This has particular relevance because a level of 1,000 c/mL has been suggested as a marker for the development of HBV resistance with continued therapy.18 Indeed, HBV resistance was seen in only two subjects at week 48, and both of these were in the LAM-only arm.

The efficient response to HBV therapy in all three arms was mirrored by the high rate of seroconversion observed, with a third of HBeAg-positive subjects losing HBeAg and seroconverting to anti-HBe, and 8% experiencing HBsAg loss. This 48-week rate of HBeAg seroconversion is higher than observed in HBV monoinfection nucleoside analogue studies22 and more similar to seroconversion rates in HBV monoinfection pegylated interferon studies.23,24 A potential explanation for this finding is that HAART-induced immune reconstitution provides similar HBV-specific immunological control benefits as seen in interferon-based therapy. No association was found in our study between change in CD4 count to week 12 and HBeAg loss, but this may relate to the relatively small study population. Similar high rates of HBeAg seroconversion among HIV/HBV-coinfected subjects on TDF-containing HAART have been shown in other cohorts,25 but only in antiretroviral-naïve individuals, and not when TDF is commenced as a second-line agent.26

The high incidence of hepatic flare in our study and the particularly high rate of HBeAg seroconversion among HBeAg-positive early hepatic flare cases (75%) also suggest a close relationship between immune reconstitution, HBeAg seroconversion, and hepatic inflammation. Causes of hepatic flares in HIV/HBV coinfected patients may be multifactorial, particularly in advanced HIV disease.27 The early onset of hepatic flare events is potentially consistent with deregulated immune restoration of HBV-specific responses driving hepatic inflammation following control of both HIV RNA and HBV DNA.28,29 The potential combined benefits of initiation of HBV-active HAART through immune restoration and HBV DNA control need to be seen in the context of potential harm, particularly in subjects with advanced liver disease. The one death in the study followed rapid hepatic decompensation associated with early hepatic flare in a subject with underlying probable cirrhosis. This case confirms the importance of liver biopsy in the assessment of HIV/HBV-coinfected individuals prior to the initiation of HAART. Decompensation associated with hepatic flare has been described by others30 and is a recognized complication in patients with cirrhosis and HIV/HBV coinfected individuals. Strategies to prevent severe immunomediated flare are unproven but could involve HBV DNA reduction prior to immune restitution in those at highest risk.

In general, HIV-related virological and immunological responses to HAART in this study were excellent. The greater rise in CD4 count in the combination therapy arm likely reflects the inclusion of AZT in the other two arms, rather than any specific immunological benefit associated with the TDF/LAM combination per se. These data indicate that, consistent with findings from others,30 coinfection...
tion with HBV does not appear to impair immunological recovery or virological suppression with HAART.

A majority of our study subjects had mild hepatic activity with limited fibrosis, partly related to the inclusion of subjects with normal ALT levels. The generally early liver disease together with the biochemical and virological profiles of this group of HIV/HBV-coinfected subjects would be consistent with findings from subjects in the immunotolerant phase of chronic hepatitis B (high HBV DNA, predominantly normal aminotransferases, and minimal histological activity). There are little data on the effect of HAART on long-term HBV-related outcomes (hepatic decompensation and hepatoma) in HIV/HBV-coinfected subjects. Although individuals in the immunotolerant phase of chronic hepatitis B are rarely recommended for HBV treatment, the accelerated liver disease progression and high liver disease mortality among HIV/HBV-coinfected patients, particularly among those with advanced HIV disease, suggests that even patients with relatively early liver disease may warrant HBV-specific therapeutic intervention. HAART with HBV-active drugs that are both potent in achieving HBV virological suppression and durable with regard to resistance development is therefore essential to include in regimens for these patients.

Our study confirms that over 48 weeks, levels of HBV DNA that promote resistance are more likely with LAM alone than with either TDF or LAM/TDF combination, and the development of resistance cases only in the LAM arm further supports the use of TDF as an important component of HAART in HIV/HBV-coinfected patients. The potential benefit of LAM/TDF combination therapy in preference to TDF alone needs to be further explored in studies with larger sample size and longer-term follow-up. Following study completion, all subjects in arm 1 substituted TDF for AZT while arms 2 and 3 continued on their original regimens. Further data from ongoing study follow-up will provide additional information.

LAM and emtricitabine have similar anti-HBV activity and are often considered interchangeable in the treatment of chronic hepatitis B. Guidelines for the management of HIV/HBV coinfection in high-income countries recommend the use of combination therapy in initial regimens where there is easy access to Truvada (TDF/emtricitabine) in a single once-daily pill. Access to antiretroviral therapy in low- and middle-income countries is more restricted. Current World Health Organization guidelines recommend the use of LAM and/or TDF as first-line agents in HIV/HBV-coinfected individuals, but TDF may not be widely available or cost-efficient. Thus, decisions on the most appropriate antiretroviral regimens in HIV/HBV-coinfected individuals in resource-limited settings must be carefully considered and based as far as possible on data from within those populations.

Some limitations need to be considered in the TICO study. The small sample size made the study somewhat underpowered, particularly for secondary endpoints. However, combined analyses across randomized arms yielded important findings on HBV disease outcomes, including serological patterns. The relatively early liver disease stage of most subjects and the small number with paired liver biopsies limited histological outcome assessment. Finally, the advanced HIV disease and Asian ethnicity study characteristics make generalizing TICO outcomes problematic, particularly in developed countries where HBV natural history and genotypes differ and HAART initiation is earlier.

In conclusion, LAM monotherapy for HBV/HBV-coinfected patients in Thailand was initially effective in achieving HBV virological suppression in the majority of subjects, but was associated with the development of drug resistance. A TDF-based regimen should be the treatment of choice for all HIV/HBV-coinfected patients whenever possible.

References


