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Combination HBV therapy is linked to greater HBV DNA suppression in a cohort of lamivudine-experienced HIV/HBV co-infected individuals

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Introduction

Approximately 10% of HIV-infected individuals worldwide are chronically infected with hepatitis B virus (HBV). HIV co-infection increases the risk of developing liver disease related (LDR)- complications including end stage liver disease (ESLD) and hepatocellular carcinoma [1–3]. The introduction of effective HIV therapy has resulted in a marked reduction in AIDS-related mortality and consequently, liver disease from HBV and hepatitis C virus (HCV) has emerged as a leading cause of morbidity and mortality in HIV-infected patients [4]. Thus, it is important to optimize anti-HBV therapy in HIV-HBV co-infected patients especially as HIV therapy is being escalated in areas of the world with the greatest HBV endemicity, such as Africa and Asia.

In HBV monoinfected patients, successful HBV therapy can reduce the risk of developing LDR-complications [5,6]. Since these complications are difficult to monitor during therapy, recent recommendations have advocated for an undetectable HBV DNA as a treatment goal [7]. With the recent expansion of anti-HBV therapeutic options, this goal is attainable in a majority of patients; however, in both HBV monoinfected and HIV-HBV co-infected patients, little is known regarding the choice of agent(s) that maximizes the chance for reaching undetectable HBV DNA and minimizes the risk for developing drug-resistant HBV. Current guidelines recommend the use of tenofovir (TDF) and emtricitabine (FTC), or TDF and lamivudine (LAM), as the nucleos(t)ide reverse transcriptase inhibitor (NRTI) backbone of antiretroviral regimens in HIV-HBV coinfecting individuals i.e. combination anti-HBV therapy [8–11]. However, the superiority of TDF-containing combination therapy to TDF monotherapy for HBV has not been definitively demonstrated in any patient population. Indeed a multicentre European study in 2006 suggested HBV virological responses to be similar in antiretroviral naïve subjects treated with combination LAM/TDF to those treated with sequential TDF monotherapy [12].

In order to test the hypothesis that combination anti-HBV therapy is more likely to suppress HBV DNA, we studied an international HIV-HBV co-infected cohort that was designed to prospectively study liver disease in the era of highly active antiretroviral therapy (HAART). Since the majority of the subjects were on an anti-HIV regimen that was active against HBV (HBV active HAART) at study entry, we performed a cross-sectional study to determine whether combination HBVactive HAART regimens were superior to others in terms of HBV DNA suppression.

Patients and Methods

Study subjects

HIV-HBV co-infected individuals from three established cohorts, one in the United States and two in Australia, were enrolled from October 2004 to October 2006, with plans for prospective follow-up. Eligibility criteria included i) documented HIV infection as determined by the presence of HIV antibody, ii) documented positive hepatitis B surface antigen (HBsAg) on two occasions separated by a minimum of 6 months with at least one of these occasions prior to initiation of HAART, iii) on HAART or expected to start HAART within one year of enrollment, iv) known date of HAART initiation if taking HAART at enrollment, and v) documented HIV and HBV treatment history prior to enrollment. The only exclusion criterion was having chronic hepatitis C, which was defined as HCV antibody and HCV RNA positive.

Overall 122 HIV-HBV co-infected subjects were available for this study as follows:

- i. The United States subjects were participants in the Multicenter AIDS Cohort Study (MACS), which is an ongoing observational cohort study of HIV infection in men

who have sex with men (MSM) and has been fully described elsewhere [13,14]. Participants were recruited into MACS in three phases (1984–1985, 1987–1991, and 2001–2003) at four sites in the U.S (Baltimore, Chicago, Pittsburgh, and Los Angeles). 63 of the MACS men met the inclusion criteria, nine of whom were not included in this analysis since they had died prior to October 2004 leaving 54 men from the MACS.

- ii. The Melbourne, Australia cohort recruited subjects from HIV clinics in two tertiary care centres, the Alfred and Royal Melbourne Hospitals, between 1995 and 2005. Patients are seen in the outpatient clinic every three months, and clinical and laboratory data are recorded on database/clinical records. Between February 2005 and August 2006, 27 HIV-HBV coinfecting individuals met the cohort eligibility criteria and were enrolled.
- iii. The Sydney, Australia cohort recruited individuals from two locations. Subjects were recruited from the HIV, Immunology, Infectious Disease Unit at St Vincent's Hospital, one of the largest HIV tertiary care centres in Australia, where patients are followed every 3–6 months and all clinical/demographic and laboratory data are stored on the clinic-specific database. Subjects were also recruited from the Taylor Square Clinic, a high HIV caseload primary care practice located in close proximity to the hospital. Between February 2005 and August 2006, 41 HIV-HBV co-infected individuals meeting the eligibility criteria were enrolled from these two sites.

All subjects gave informed written consent at entry to the cohort, and the study was approved by the relevant Human Research Ethics Committees in the United States and Australia.

Cohort data collection and specimen retrieval

Baseline data collection included details on demographics, prior and current antiretroviral or other HBV-active therapy, HIV and HBV related clinical events, Child-Pugh stage, and previous liver biopsy data. Laboratory measurements at study entry included ALT, AST, INR or prothrombin time, hemoglobin, white blood cell count, platelets, hepatitis B e antigen (HBeAg), hepatitis B e antibody, HBsAg, and HCV antibody using commercially available assays. HCV RNA was determined in HCV antibody positive subjects using the standard available PCR test at each site. HBV DNA testing was also obtained using the method described below. Liver biopsy was not mandated but was performed during the first year of study enrollment in 21 subjects. One pathologist scored all of the biopsy specimens. Two methods of non-invasive fibrosis assessment using serum biochemical algorithms, the APRI score [15] and FIB4 score [16], were calculated on all subjects.

Virological testing

HBV DNA quantification—HBV DNA was determined using the RealART™ HBV LC PCR (QIAGEN) according to the manufacturer's instructions, as previously described[17]. The linear dynamic range of this assay is approximately 20 IU/ml to 4×10^9 IU/ml. In the MACS cohort HBV DNA quantification was undertaken using the methods outlined above or, in some instances, the COBAS Amplicor HBV assay, which was performed according to the manufacturer's instructions. The dynamic range of this assay is 5×10^2 to 2×10^5 c/ml (approximately 100 – 40,000 IU/ml). For this analysis, we used 100 IU/ml as the lower limit of detection, which was the lower limit of the COBAS.

PCR Amplification and Sequencing—Full genomic length HBV DNA was amplified from the extracted DNA according to the method of Gunther et al [18]. The amplified product was purified using PCR purification columns from MO BIO Laboratories Inc.

(Carlsbad, CA, USA). The HBV polymerase (Pol) gene was sequenced using the full length HBV amplicon as template with Big Dye terminator Cycle sequencing Ready Reaction Kit Version 3.1 (Applied Biosystems, Foster City, CA, USA).

Sequence Analysis—HBV consensus sequences were constructed using the ABI Prism SeqScape DNA sequence analysis program Version 2.1 (Applied Biosystems). HBV genotype and unique HBV mutations are identified using the web based program, SeqHepB [19].

Statistical Analysis—Analyses were performed using graphical displays of the data and descriptive statistics (e.g., mean, standard deviation, median, inter-quartile range (IQR)), and univariate statistical associations were assessed using the Pearson Chi-square, Wilcoxon Rank Sum and Kruskal-Wallis tests, as dictated by the data. Ordinal logistic regression (OLR) methods were used to assess the association between HBV DNA level and HBV therapy regimens adjusted for the following study entry cofactors: age, current HAART use, HIV RNA, CD4 cell count, duration of HIV infection, ALT, HBV genotype, and HBeAg positivity. The HBV DNA level outcome variable was stratified into three levels for the OLR analyses: undetectable ($<2.0 \log_{10}$ IU/ml), low to moderate (between $2.0 \log_{10}$ and $6.3 \log_{10}$ IU/ml). We fit a series of univariate, bivariate, and multivariate OLR models to identify the cofactors that were consistently associated with HBV DNA level while simultaneously satisfying the proportional odds assumption. The final model includes cofactors found to be independently associated with HBV DNA level and satisfies the proportional odds assumption. All statistical analyses were performed using SAS 9.1 (SAS Institute, Cary, NC, USA). P-values < 0.05 were interpreted as indicating statistical significance.

Results

Demographics, HIV-related parameters, and antiretroviral use

The 122 subjects from the two continents were similar in age, BMI, gender, HIV risk factor, and time since HIV diagnosis (Table 1). Although the majority of subjects were Caucasian (70%), the MACS were nearly half (46%) African-American, whereas the Australian cohorts were 10% Asian. At study entry, 60% of subjects had a history of significant immunodeficiency, defined as an AIDS defining illness or a nadir CD4 count <200 cells/mm³. The median HIV RNA level was <400 copies (c)/ml, and the median CD4 count was 438 cells/mm³ (range 19–1080 cells/mm³). 102 subjects were on HAART at baseline with a mean duration of 6.8 years (range 1.1 – 10.3 years) and nearly all (98%) were LAM experienced. The majority (89%) were currently on HBV-active HAART (i.e. therapy including one or more of LAM, FTC or TDF), 11 subjects were on HAART that did not include any HBV active drug and 20 subjects were on no HAART at all. Of subjects not on HAART, 8 were antiretroviral naïve, 11 had previous ART experience but were not currently taking therapy, and 1 was on a dual nucleoside only regimen.

In the 91 subjects on HBV active HAART, the HBV component included 49 (54%) receiving combination therapy of TDF with FTC or LAM (92% on TDF/LAM combination), 31 (34%) receiving LAM or FTC as monotherapy, and 11 (12%) taking TDF monotherapy. Baseline differences between subjects by HBV-active therapy are given in Table 2. Not surprisingly, the group on no HBV-active HAART had a higher median nadir CD4, higher median HIV RNA and less previous LAM experience than the groups on HBV active HAART. Generally the three HBV-active groups were comparable with regards to demographics and HIV related parameters.

The total median cumulative exposure to LAM or FTC was similar in subjects currently taking either of these drugs, irrespective of whether in combination with TDF or as monotherapy. Likewise, both median cumulative TDF exposure and median duration on current regimen were almost identical between subjects on TDF monotherapy and subjects on TDF in combination with LAM or FTC, suggesting no major inequalities between these two groups in length of time on treatment.

HBV DNA

The majority of participants (57%) had HBV DNA <100 IU/ml ($2 \log_{10}$ IU/ml) at study entry while 25% of the participants had HBV DNA $>20,000$ IU/ml (Figure 1). As expected, the median HBV DNA in the 20 subjects not receiving HAART ($7.2 \log_{10}$ IU/ml) was significantly higher than in those subjects receiving HAART (median HBV DNA $<2 \log_{10}$ IU/ml, $p=0.0006$). However, median HBV DNA in the 8 subjects on non-HBV active HAART did not differ significantly from those on HBV active HAART ($2.1 \log_{10}$ IU/ml vs $<2 \log_{10}$ IU/ml, $p=0.18$).

In both the combination therapy group and the FTC/LAM monotherapy group, the median HBV DNA was $<2 \log_{10}$ IU/ml whereas the median HBV DNA in the TDF monotherapy group was also low but detectable at $2.9 \log_{10}$ IU/ml (range $<2 \log_{10}$ – $9.2 \log_{10}$ IU/ml), despite the similar durations on current therapy (Table 2). The proportion of subjects with HBV DNA $<2 \log$ IU/ml was also higher in the combination group (77%) compared to the LAM/FTC monotherapy group (55%) ($p=0.08$) and the TDF monotherapy group (30%) ($p=0.006$) (Table 3). Importantly, the proportion of subjects with HBV DNA in the highest strata ($>20,000$ IU/ml) was significantly lower in the combination group (4%) compared to the non-HBV active group (54%), the LAM/FTC monotherapy group (31%), and the TDF monotherapy group (30%) ($p<0.0001$) (Figure 1). In an OLR model, monotherapy with either TDF or LAM remained independently associated with higher HBV DNA, as did HBeAg positivity and detectable HIV RNA (Table 4).

HBV sequencing

HBV Pol sequencing was possible in 37 subjects with detectable HBV DNA. Mutations were identified in 15 (41%) with 10 having the classic mutation rtL180M+rtM204V, 4 having the triple mutation rtV173L + rtL180M + rtM204V, and one having the rtL180M +rtM204V + rtT184A, a mutation associated with entecavir (ETV) resistance. No patient had mutations known to be associated with resistance to TDF. As expected the majority of these mutations were identified in the LAM/FTC monotherapy group (data not shown), but the cross sectional nature of the data and the small numbers involved means that further interpretation of the data at this stage is limited. Ongoing longitudinal follow-up of these subjects will allow more detailed exploration of the significance of these mutations and their relationship to therapeutic response.

HBV characteristics

HBeAg—Just over half (56%) of the participants were HBeAg positive. As expected, the HBeAg negative subjects were older (median: 49 vs 44 years, $p=0.01$) with lower median ALT (30 IU/L vs 45 IU/L, $p=0.0005$) and lower median HBV DNA ($<2 \log$ vs $3.4 \log$, $P<0.0001$) than the HBeAg positive group. However, HIV-related characteristics (nadir CD4, baseline CD4, HAART duration) were similar between the groups. There was a trend for more subjects in the HBeAg positive group to have had exposure to TDF (66% vs 47%, $p=0.04$) with only 33% of the LAM/FTC monotherapy group documented HBeAg positive compared to 78% and 62% of the TDF monotherapy and combination therapy groups respectively.

HBV genotype—Assessment of HBV genotype was possible in 55 subjects with detectable HBV DNA. Genotype A was the most common (80%) followed by genotype G (7%), genotype D (7%), mixed population (4%), and genotype F (2%).

Liver disease characteristics—The median baseline ALT in the cohort was 37 IU/L (IQ range 26–55 IU/L) with a normal ALT (< 40 IU/L) recorded in 54% of the cohort. Of the 21 subjects with a liver biopsy at enrollment, only 2 (10%) had severe fibrosis (F3/4 on the Metavir scale), neither of whom had stage F4 or cirrhosis, with the majority, 15/21 (71%), having F0/1. Similarly the majority (76%) had mild METAVIR inflammatory scores of A0 or A1. Fibrosis scores as calculated using either APRI or FIB4 similarly identified only 9% of the cohort with significant fibrosis and 52% with no or mild fibrosis.

Discussion

In this cross-sectional study of 122 HIV-HBV co-infected subjects with prior LAM exposure, we demonstrate that individuals receiving combination HBV therapy within HAART, comprising TDF with either FTC or LAM, were significantly more likely to have undetectable HBV DNA than those receiving monotherapy with either TDF or FTC/LAM. Furthermore, those on combination therapy were significantly less likely to have high levels of HBV DNA (>20,000 IU/ml), compared to those in the FTC/LAM and TDF monotherapy groups. This advantage of TDF/FTC or LAM combination remained evident in a multivariate analysis adjusting for other factors associated with HBV DNA levels. Additionally, since the median duration of TDF was similar in the TDF monotherapy and the combination therapy group, we do not believe that difference in duration of TDF can explain these findings. These data suggest that, particularly in patients with prior LAM therapy, there may be an advantage to using TDF in combination with LAM/FTC.

These findings raise several interesting hypotheses that may explain our observations. First, combination therapy for HBV may simply be more potent than monotherapy, as has been clearly demonstrated for HIV therapy. However, although clinical trial data indicate that TDF/LAM combination is superior to LAM alone in this setting [20], we are not aware of any evidence suggesting that TDF monotherapy is less potent than TDF/LAM combination [21]. In the randomized clinical trial TICO, conducted amongst ARV-naïve subjects in Thailand, no benefit for TDF/LAM combination was observed over TDF monotherapy [21]. Importantly, 85% of subjects in TICO were genotype C and thus it is possible that this trial did not show an advantage due to the different distribution in HBV genotypes in Thailand. It is also the case that 90% of the subjects in our study were LAM experienced, not ARV naïve, and are therefore likely to have had LAM-resistant mutations prior to starting TDF, thus representing a different patient population. Data in treatment experienced patients comes from a multicentre matched pair analysis from Europe [12]. This European study reported reductions in HBV viraemia and serological change to be similar in TDF monotherapy (prescribed in the setting of LAM resistance), to those in combination TDF plus LAM (prescribed in antiretroviral naïve subjects). Although this study found no difference in efficacy of TDF against HBV between treatment experienced and treatment naïve individuals, it was unable to examine whether there is an advantage to continuing LAM with TDF in the setting of LAM-resistant HBV. This is an important issue since an alternative hypothesis to our observation is that having the M204V mutation may actually hypersensitize HBV to TDF. This is a well-described phenomenon in HIV therapy with the identical mutation, M184V, hypersensitizing HIV to TDF [22] [23]. Thus, it is plausible that HBV hypersensitivity could occur with TDF. To date, however, the only *in vitro* testing that has correlated TDF susceptibility with resistance mutations suggested that the rtA194T mutation in conjunction with LAM resistance mutations (rtM204V and rtL180M) may actually reduce TDF susceptibility [24].

There are no clinical data on whether LAM requires continuation once TDF is commenced in the presence of LAM resistance. In the setting of HBV monoinfection, adefovir dipivoxil resistance is considerably lower when LAM is continued compared to switching to adefovir dipivoxil monotherapy [25]. Although TDF is a far more potent drug than adefovir dipivoxil, our data suggest that there may indeed be an advantage to combination therapy with FTC/LAM in this setting. It should be noted however that this finding is based on a cross-sectional analysis performed when subjects were first recruited into the cohort and further prospective study is warranted to determine if combination TDF/FTC or LAM therapy continues to have a longer-term advantage in terms of HBV DNA suppression.

The liver biopsy data in this cohort are encouraging as the majority of those who were biopsied did not have evidence of severe liver disease. Only 20% of the participants were biopsied, but the subjects who were excluded from biopsy in the MACS cohort were those with both normal ALT/AST and undetectable HBV DNA; thus biopsies were biased toward detecting significant liver disease. These mild liver biopsy findings were surprising since it is well-documented that HIV co-infection increases liver disease progression [1,4], so it is plausible that anti-HBV active HAART has improved the liver disease of this cohort. These data are consistent with findings from a Spanish study examining liver disease using transient elastography which found minimal or no fibrosis in 57% of 38 extensively treated HIV-HBV coinfecting subjects [26]. On the other hand, it is also conceivable that there is a survivor bias so that those who survived long enough to be included in this study have milder liver disease. The agreement between the biopsy findings and those of the non-invasive biochemical algorithms is interesting and requires further exploration and validation using longitudinal follow-up.

It was surprising that 10% of those on HAART were not on any HBV active drugs. There are data to support that HBV treatment in HIV-infected patients has been suboptimal [27], and these data would reinforce that hypothesis as well. Further support for this is that 22% of subjects on HAART containing HBV active drugs had significant HBV viraemia ($>3.4 \log_{10}$ IU/ml) indicating inadequate HBV control, and 12% had levels of HBV $> 5.4 \log_{10}$ IU/ml. Thus, increased awareness of HBV disease in the HIV-infected population is needed.

The major limitation of this study is its cross-sectional design. Since all subjects were evaluated only at the baseline visit for this report, HAART status was assessed at a single timepoint and HBV and HIV characteristics prior to HAART initiation were not uniformly ascertained. The pre-treatment baseline values and treatment induced changes in variables prior to cohort entry were not universally available, thus placing limitations on the level of certainty with which our conclusions can be drawn.

For example, many of these subjects were on LAM as HBV monotherapy prior to study entry, and we were not able to determine mutations existing prior to HAART initiation or at the time of TDF addition/substitution. Thus, we cannot determine if the mutations we found emerged on the current therapy or on prior therapy. We are also not aware of considerations that were taken into account by the provider when the study entry HAART regimen was chosen. Lastly, since we did not find any TDF-resistance mutations, this study does not address whether combination therapy delays the emergence of TDF resistance. Follow-up of this cohort will be needed to determine factors associated with the development of TDF resistance.

In summary, in this large HIV-HBV co-infected cohort on HAART, one-quarter of subjects had HBV DNA levels $>20,000$ IU/ml underscoring the need to consider HBV when choosing anti-HIV regimens. Furthermore, the combination of TDF and FTC or LAM was

associated with a higher rate of undetectable HBV DNA levels compared to monotherapy with either LAM/FTC or TDF.

Further work is needed to determine whether this combination appears favorable because of its increased potency or because maintaining certain resistance mutations leads to hypersensitivity to TDF. Regardless of the mechanism, these data support using TDF with LAM or FTC especially in patients with prior LAM experience.

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References

1. Konopnicki D, Mocroft A, de Wit S, Antunes F, Ledergerber B, Katlama C, et al. Hepatitis B and HIV: prevalence, AIDS progression, response to highly active antiretroviral therapy and increased mortality in the EuroSIDA cohort. *AIDS* 2005;19:593–601. [PubMed: 15802978]
2. Thio CL, Seaberg EC, Skolasky R Jr, Phair J, Visscher B, Munoz A, Thomas DL. HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS). *Lancet* 2002;360:1921–1926. [PubMed: 12493258]
3. Salmon-Ceron D, Lewden C, Morlat P, Bevilacqua S, Jouglu E, Bonnet F, et al. Liver disease as a major cause of death among HIV infected patients: role of hepatitis C and B viruses and alcohol. *J Hepatol* 2005;42:799–805. [PubMed: 15973779]
4. Puoti M, Spinetti A, Ghezzi A, Donato F, Zaltron S, Putzolu V, et al. Mortality for liver disease in patients with HIV infection: a cohort study. *J Acquir Immune Defic Syndr* 2000;24:211–217. [PubMed: 10969344]
5. Niederau C, Heintges T, Lange S, Goldmann G, Niederau CM, Mohr L, Haussinger D. Long-term follow-up of HBeAg-positive patients treated with interferon alfa for chronic hepatitis B. *N Engl J Med* 1996;334:1422–1427. [PubMed: 8618580]
6. Yao FY, Terrault NA, Freise C, Maslow L, Bass NM. Lamivudine treatment is beneficial in patients with severely decompensated cirrhosis and actively replicating hepatitis B infection awaiting liver transplantation: a comparative study using a matched, untreated cohort. *Hepatology* 2001;34:411–416. [PubMed: 11481627]
7. Keefe EB, Zeuzem S, Koff RS, Dieterich DT, Esteban-Mur R, Gane EJ, et al. Report of an international workshop: Roadmap for management of patients receiving oral therapy for chronic hepatitis B. *Clin Gastroenterol Hepatol* 2007;5:890–897. [PubMed: 17632041]
8. Brook MG, Gilson R, Wilkins E. BHIVA guidelines on HIV and chronic hepatitis: coinfection with HIV and hepatitis B virus infection (2005). *HIV Med* 2005;6 (Suppl 2):84–95. [PubMed: 16011538]
9. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. Department of Health and Human Services; Nov 3, 2008 Available at <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>
10. Soriano V, Puoti M, Bonacini M, Brook G, Cargnel A, Rockstroh J, et al. Care of patients with chronic hepatitis B and HIV co-infection: recommendations from an HIV-HBV International Panel. *AIDS* 2005;19:221–240. [PubMed: 15718833]
11. Lok AS, McMahon BJ. Chronic hepatitis B. *Hepatology* 2007;45:507–539. [PubMed: 17256718]

12. Schmutz G, Nelson M, Lutz T, Sheldon J, Bruno R, von Boemmel F, et al. Combination of tenofovir and lamivudine versus tenofovir after lamivudine failure for therapy of hepatitis B in HIV-coinfection. *Aids* 2006;20:1951–1954. [PubMed: 16988516]
13. Kaslow RA, Ostrow DG, Detels R, Phair JP, Polk BF, Rinaldo CR Jr. The Multicenter AIDS Cohort Study: rationale, organization, and selected characteristics of the participants. *Am J Epidemiol* 1987;126:310–318. [PubMed: 3300281]
14. Dudley J, Jin S, Hoover D, Metz S, Thackeray R, Chmiel J. The Multicenter AIDS Cohort Study: retention after 9 1/2 years. *Am J Epidemiol* 1995;142:323–330. [PubMed: 7631636]
15. Imbert-Bismut F, Ratziu V, Pieroni L, Charlotte F, Benhamou Y, Poynard T. Biochemical markers of liver fibrosis in patients with hepatitis C virus infection: a prospective study. *Lancet* 2001;357:1069–1075. [PubMed: 11297957]
16. Sterling RK, Lissen E, Clumeck N, Sola R, Correa MC, Montaner J, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. *Hepatology* 2006;43:1317–1325. [PubMed: 16729309]
17. Matthews GV, Bartholomeusz A, Locarnini S, Ayres A, Sasaduesz J, Seaberg E, et al. Characteristics of drug resistant HBV in an international collaborative study of HIV-HBV-infected individuals on extended lamivudine therapy. *AIDS* 2006;20:863–870. [PubMed: 16549970]
18. Gunther S, Li BC, Miska S, Kruger DH, Meisel H, Will H. A novel method for efficient amplification of whole hepatitis B virus genomes permits rapid functional analysis and reveals deletion mutants in immunosuppressed patients. *J Virol* 1995;69:5437–5444. [PubMed: 7636989]
19. Yuen LK, Ayres A, Littlejohn M, Colledge D, Edgely A, Maskill WJ, et al. SeqHepB: a sequence analysis program and relational database system for chronic hepatitis B. *Antiviral Res* 2007;75:64–74. [PubMed: 17215050]
20. Nelson, M.; Bhagani, S.; Fisher, M.; Leen, C.; Brook, G.; Mandalia, S., et al. A 48 week study of Tenofovir DF (TDF) or Lamivudine (LAM) or a combination of Tenofovir and Lamivudine for the treatment of chronic hepatitis B in HIV/hepatitis B co-infected individuals. 13th Conference on Retroviruses and Opportunistic Infections; Denver, U.S.A.. 2006.
21. Matthews GV, Avihingsanon A, Lewin SR, Amin J, Rerknimitr R, Petcharapirat P, et al. A randomized trial of combination hepatitis B therapy in HIV/HBV coinfecting antiretroviral naive individuals in Thailand. *Hepatology* 2008;48:1062–1069. [PubMed: 18697216]
22. White KL, Margot NA, Wrin T, Petropoulos CJ, Miller MD, Naeger LK. Molecular mechanisms of resistance to human immunodeficiency virus type 1 with reverse transcriptase mutations K65R and K65R+M184V and their effects on enzyme function and viral replication capacity. *Antimicrob Agents Chemother* 2002;46:3437–3446. [PubMed: 12384348]
23. Miller MD, Anton KE, Mulato AS, Lamy PD, Cherrington JM. Human immunodeficiency virus type 1 expressing the lamivudine-associated M184V mutation in reverse transcriptase shows increased susceptibility to adefovir and decreased replication capability in vitro. *J Infect Dis* 1999;179:92–100. [PubMed: 9841827]
24. Sheldon J, Camino N, Rodes B, Bartholomeusz A, Kuiper M, Tacke F, et al. Selection of hepatitis B virus polymerase mutations in HIV-coinfected patients treated with tenofovir. *Antivir Ther* 2005;10:727–734. [PubMed: 16218172]
25. Rapti I, Dimou E, Mitsoula P, Hadziyannis SJ. Adding-on versus switching-to adefovir therapy in lamivudine-resistant HBeAg-negative chronic hepatitis B. *Hepatology* 2007;45:307–313. [PubMed: 17256746]
26. Maida I, Soriano V, Castellares C, Ramos B, Sotgiu G, Martin-Carbonero L, et al. Liver fibrosis in HIV-infected patients with chronic hepatitis B extensively exposed to antiretroviral therapy with anti-HBV activity. *HIV Clin Trials* 2006;7:246–250. [PubMed: 17162318]
27. Jain MK, Opio CK, Osuagwu CC, Pillai R, Keiser P, Lee WM. Do HIV care providers appropriately manage hepatitis B in coinfecting patients treated with antiretroviral therapy? *Clin Infect Dis* 2007;44:996–1000. [PubMed: 17342656]

Figure 1.

Level of HBV virological suppression by HBV active HAART therapy

Y axis: Proportion of subjects with HBV viraemia in 4 defined categories of HBV DNA suppression (<100 IU/ml, 100–1,999 IU/ml, 2,000–19,999 IU/ml, > 20,000 IU/ml)

X axis: Study subjects overall and by HBV active therapy (no HBV active therapy, FTC or LAM in HAART, TDF in HAART, TDF plus FTC or LAM in HAART)

Table 1

Baseline characteristics of HIVHBV cohort

	All N=122	Australia N=68	MACS N=54
Age (years)			
Mean (sd)	46.9 (8.9)	47.1 (8.8)	46.3 (9.1)
Sex, number (%)			
Male	120 (98.4)	66 (97.1)	54 (100)
Female	1(0.8)	1(1.5)	
Transgender	1 (0.8)	1(1.5)	
Race, number (%)			
African-American	28 (23)	3 (4)	25 (46)
Caucasian	85 (70)	58 (85)	27 (50)
Other	9 (7)	7 (10)	2 (4)
BMI (kg/m ²)			
mean (sd)	24.5 (4.1)	24.1 (3.3)	25.1 (5.0)
range	17 – 43	17 – 31	19 – 43
HIV Risk Factor [#] , number (%)			
Male homosexual	107 (88)	56 (82)	51 (94)
IDU	13 (11)	7 (10)	6 (11)
Time from HIV diagnosis (yrs)			
mean (sd)	11.3 (7.9)	11.4 (7.0)	11.3 (8.2)
range	0.3 – 21.3	0.3 – 19.3	1.5 – 21.3
Prior AIDS, number (%)	35 (29)	25 (37)	10 (19)
On HAART at enrollment, number (%)	102 (84)	59 (87)	43 (80)
Nadir CD4 (cells/ml)			
median	153	140	200
range	3 – 694	4 – 466	3 – 694
CD4 at enrollment (cells/ml)			
median	438	440	418
range	19 – 1080	31–1008	19 – 1080
HIV RNA level at enrollment (copies/ml)			
median	<400	<400	<400
range	<400 – 440000	<400 – 440000	<400 – 257000

[#] Major risk factors for HIV documented only. Categories are not mutually exclusive.

Table 2

Baseline differences between subjects by HBV active therapy

	No HBV active	HAART	LAM or FTC	monotherapy	TDF	monotherapy	TDF + LAM/FTC	combination	p-value [#]
Number (%)	31 (25.4)		31 (25.4)		11 (9.0)		49 (40.2)		
Age (median, yrs)	43.5		46.5		42.4		47.9		0.32
ALT (median, IU/L)	34.5		38		38		37		0.99
IQR	27-63		26-51		26-47		25-59		
% <40	53.6		56.7		50.0		53.2		
HBV DNA (median, log ₁₀ IU/ml)	5.9		<2		2.9		<2		<0.0001
HBsAg positive (%)	61.3		33.3		77.8		61.7		0.38
CD4 (median, cells/ml)	450		494		384		394		0.23
Nadir CD4 (median cells/ml)	265		157		162		119		0.04
Time since HAART initiation (median, yrs)	5.0		6.7		8.2		8.2		0.053
Duration on current HBV active therapy (median, yrs)									
LAM/FTC	0		3.4		0		2.4		<0.0001
TDF	0		0		2.1		1.9		<0.0001
Cumulative exposure to HBV active therapy (median, yrs)									
LAM/FTC	1.1		5.4		2.1		5.1		<0.0001
TDF	0		0		2.1		2.1		<0.0001
LAM experience ever (%)	74.2		100		90.9		98.0		0.003
HIV RNA (median)	2150		<400		<400		<400		0.0006

[#] p-value reflects the comparison across all 4 groups *except* for the comparison of duration on current active therapy where the p-value reflects the comparison across the HBV-active treatment groups only.

Table 3

HBV DNA at enrollment by ARV therapy groups

	N	Median HBV DNA (log ₁₀ IU/ml)
Number with VL data available/total (% of total subjects)	114/122 (93%)	<=2.0
By HBV active drugs:		
None	28/31 (90%)	5.9
FTC/LAM only	29/31 (94%)	<=2.0
TDF only	10/11 (91%)	2.9
TDF + (FTC or LAM)	47/49 (96%)	<=2.0
p-value		<0.001
Selected 2-way comparisons:		% HBV undetectable
FTC/LAM only	29	55
TDF only	10	30
p-value		0.27
FTC/LAM only	29	55
TDF+(FTC or LAM)	47	77
p-value		0.08
TDF only	10	30
TDF+(FTC or LAM)	47	77
p-value		0.008
FTC/LAM/TDF only	39	49
TDF+(FTC or LAM)	47	77
p-value		0.01

VL viral load; FTC emtricitabine; LAM lamivudine; TDF tenofovir

<= 2.0 representing less than or equal to 2.0

Table 4

Ordinal logistic regression analysis: Association of HBV DNA level with therapy, HIV RNA, and hepatitis B e antigen positivity.

	OR	95% CI
HBV active therapy		
TDF + FTC/LAM*	1	
Not taking TDF, LAM, or FTC	16.8	4.1 – 69.0
LAM or FTC only	36.6	7.2 – 186.0
TDF only	8.4	1.3 – 54.0
Detectable HIV virus	7.4	2.4 – 22.3
HBeAg positive	85.2	18.2 – 398.6

* reference group.