Comparison of HBV-active HAART regimens in an HIV-HBV multinational cohort: outcomes through 144 weeks

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Abstract

Objectives—To explore factors associated with short and long-term HBV DNA suppression in a multinational cohort of HIV-HBV co-infected subjects receiving HBV-active antiretrovirals.

Methods—115 HIV-HBV co-infected subjects participating in one of two global ACTG randomized clinical trials of different antiretroviral regimens received either HBV-monotherapy with either lamivudine or emtricitabine (N=56) or HBV-dual therapy with TDF plus lamivudine or emtricitabine (N=59). Associations of pre-treatment characteristics with the primary (HBV DNA <200 IU/ml at 24 weeks) and longitudinal outcomes through 144 weeks were explored using logistic regression. HBV drug-resistance mutations were determined by *pol* sequencing in those with viral rebound.

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Results—The proportion with HBV DNA<200 IU/ml was 60% (95% CI 50%–69%) at 24 weeks and 79% (95% CI 69%–88%) at 144 weeks. Pre-treatment factors associated with the primary outcome were HBV DNA, CD4 T-cell count, and AST, but only pre-treatment HBV DNA remained associated with long-term suppression (*P*<0.0001). HBV therapy group was not significantly associated with the primary outcome at 24 weeks; however, longitudinally, a greater proportion in the dual therapy group achieved HBV DNA<200 IU/mL (*P*=0.007). A higher proportion of hepatitis B e antigen negative subjects (n=57) achieved HBV DNA <200 IU/ml at any point, regardless of therapy group. All 12 subjects with emergence of lamivudine-resistant mutants were in the monotherapy group.

Conclusions—TDF-based dual HBV-active antiretroviral therapy is preferred to treat HIV-HBV co-infected patients. In resource-limited settings where TDF may not be universally available, lamivudine or emtricitabine HBV-monotherapy is a reasonable option in patients with low HBV replication.

Keywords

hepatitis B; HIV; lamivudine; tenofovir; HBV treatment; emtricitabine

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Introduction

Chronic hepatitis B, which is the leading cause of end stage liver disease worldwide, is common in human immunodeficiency virus type-1 (HIV)-infected individuals.[1–5] There are limited data on hepatitis B virus (HBV) treatment in HIV-infected patients from resource-limited settings where HBV endemicity is high. In most studies of HBV treatment from resource-rich settings, HIV-HBV co-infected individuals are usually positive for hepatitis B e antigen (HBeAg) and have high HBV DNA, characteristics associated with nearly all of these individuals having lamivudine-resistant HBV after 4 years of lamivudine. [6, 7] For these reasons and because tenofovir disoproxil fumarate (TDF) is widely available, TDF-based antiretroviral therapy (ART) regimens are recommended for HIV-HBV co-infected patients in these locations. However, in many resource-limited settings, TDF, even though recommended by World Health Organization (WHO) for first-line treatment, is still not affordable and not universally recommended for HIV-HBV co-infected patients.[8] In fact, 13 of 58 (22%) low- or medium-income focus countries have not adopted TDF with lamivudine or emtricitabine as the preferred first-line antiretroviral regimen.[8] Thus, ART regimens where lamivudine is the only drug active against HBV continue to be used.

HIV-HBV co-infection in resource-limited settings differs from that in resource-rich settings because there is a higher prevalence of HBeAg-negative disease and of individuals with HBV DNA levels <20,000 IU/ml.[9–12] Thus, the long-term efficacy of lamivudine-based ART in resource-limited settings may be different than in resource-rich settings. A Thai study of 11 HBeAg-negative and 19 HBeAg-positive HIV-HBV co-infected subjects taking lamivudine-based ART for up to 5 years found that all the HBeAg-negative subjects maintained suppression (HBV DNA <150 IU/ml) and none developed lamivudine-resistant HBV.[13] In contrast, of the HBeAg-positive subjects, only 7/19 (37%) maintained suppression, and 50% of those not suppressed developed lamivudine-resistant HBV.

To date, a comparison of lamivudine- or emtricitabine-based ART versus TDF-based ART in HIV-HBV co-infected subjects that includes resource-limited countries has not been performed. Previously, we reported on pre-ART characteristics of a subgroup of HIV-HBV co-infected subjects from two randomized clinical trials (RCT) conducted by the Adult AIDS Clinical Trials Group (ACTG) in diverse resource-limited settings. The first, ACTG A5175 (PEARLS), enrolled HIV-infected men and women in nine countries to compare three initial ART regimens.[14] The second, A5208 (OCTANE), compared the response to first-line ART in women who had and had not received single-dose nevirapine for prevention of mother-to-child transmission of HIV in 7 African countries.[15] Using this pre-defined subgroup of HIV-HBV co-infected individuals from these two trials, we compared outcomes between those who received only one agent with anti-HBV activity (lamivudine or emtricitabine) to those who received two anti-HBV agents (TDF plus lamivudine or emtricitabine) to test whether HBV outcomes differed between these groups and also within subgroups defined on baseline HBV DNA.

Methods

Study subjects

This study included HIV-HBV co-infected individuals followed in either A5175 or A5208, as previously described (Table 1).[14, 15] In brief, HIV-HBV co-infected participants in this study were hepatitis B surface antigen (HBsAg) positive at screening, negative for chronic hepatitis C, and met one of the following three criteria at the study entry visit: positive for HBeAg or hepatitis B e antibody (anti-HBe), or HBV DNA >200 IU/mL. For the 85 (74%) participants from A5175, the anti-HBV agent(s) included either once-daily lamivudine, emtricitabine, or TDF plus emtricitabine (often co-formulated). To complete their anti-HIV ART regimen, they also received either atazanavir or efavirenz, and if not assigned TDF plus emtricitabine, then another NRTI (either zidovudine, stavudine or ddI). Randomization to the ART regimen did not account for HBV infection status. However, sites could add a second anti-HBV agent if a co-infected subject were randomized to a regimen that included only emtricitabine or lamivudine (one subject added adefovir). Participants from A5208 received once-daily TDF plus emtricitabine with either nevirapine or lopinavir/ritonavir. The pre-ART characteristics of the subjects included in this study were described previously.[9]

Informed consent for the parent RCTs was obtained from the study subjects in their native language. This study was approved by the local IRBs and Johns Hopkins University IRB.

The following study entry variables were used in the current analysis: age, sex, race, body-mass index (BMI), history of liver disease, hemoglobin, HIV disease stage, plasma HIV RNA, CD4+ T-cell count, ALT, and AST. At 24-week intervals during follow-up, plasma HIV RNA and CD4+ T-cell count, and ALT/AST (only available from A5175) were extracted from the parent study database. During the same follow-up intervals, stored serum samples were tested for HBeAg, anti-HBe, and HBV DNA. HBV *pol* sequencing was performed on samples from the following scenarios: 1) visits exhibiting evidence of rebound, defined as >1 $\log_{10}$ IU/ml HBV DNA increase from nadir level or HBV DNA >1000 IU/ml after being undetectable (<200 IU/mL), 2) week 48 visit if HBV DNA decline from baseline 1 $\log_{10}$ IU/ml.

Laboratory testing

All serum specimens were stored at −80°C. Serological testing for HBeAg (ETI-EBK Plus, Diasorin, Stillwater MN) and anti-HBe (ETI-AB-EBK Plus, Diasorin) were performed according to manufacturer's instructions. HBV DNA was determined with real-time PCR using either RealART™ HBV LC PCR v 3.0 (Qiagen, Valencia, CA) or Abbott RealTime HBV DNA (Abbott Molecular, Des Plains, IL). The highest common lower limit of detection of these assays was 200 IU/ml, which is the value used as undetectable in the analyses. HBV genotype and drug-resistance mutations were determined by HBV *pol* sequencing, performed as previously described.[6]

Statistical analysis

Comparison groups were defined as those who started two anti-HBV medications (primarily emtricitabine plus TDF—dual therapy group) versus those who started only one anti-HBV medication (emtricitabine or lamivudine—monotherapy group). The primary outcome was HBV DNA <200 IU/ml at 24 weeks following treatment initiation and was compared in an intent-to-treat analysis between groups using Fisher's exact test. Associations between pre-treatment characteristics and the primary outcome were tested using Chi-square or Fisher's Exact Tests for discrete covariates and Wilcoxon Rank-Sum Test for continuous covariates, and fit to logistic regression models one at a time (univariable). To adjust for possible confounding, multivariable logistic regression modeling included variables having $P<0.10$ in univariable models, treatment comparison group, and covariates associated with treatment group. For significantly associated continuous covariates, linearity in the logit was graphically examined, and if rejected, categories were formulated as suggested by the data (e.g. quartiles).

Secondary outcomes included HBV DNA <200 IU/ml at each 24-week follow-up time through week 144, ALT and AST normalization or elevations, HBeAg seroconversion, and durability of HBV DNA suppression. Longitudinal analyses of HBV DNA <200 IU/mL over time used marginal longitudinal modeling estimated via generalized estimating equations, with a logit link, and an exchangeable log odds ratio structure for within participant correlation. ALT and AST levels were graded according to standard ACTG definitions.[16] Among the subgroup of HBeAg-positive subjects at entry, the outcome of HBeAg seroconversion was defined as negative HBeAg and positive anti-HBe. Durability of HBV DNA suppression was formulated in two ways. First, for the subset who achieved HBV DNA <200 IU/ml, it was examined as time to loss of HBV DNA < 200 IU/mL grouped in 24-week intervals. Second, durability was examined as time to loss of a 1 $\log_{10}$ IU/mL HBV DNA decline or time to loss of HBV DNA <200 IU/ml (among those whose low HBV DNA at baseline did not permit a 1 $\log_{10}$ decline) grouped in 24-week intervals.

As-treated analyses, which excluded subjects once they were no longer taking the same number of anti-HBV medications as assigned at entry (e.g. persons adding TDF when assigned to emtricitabine alone), were performed as sensitivity analyses to the primary, intent-to-treat comparisons, which did not consider treatment information after ART initiation. Subgroup analyses were performed according to baseline HBeAg status and HBV DNA. Additionally, a post-hoc subgroup analysis was performed to further explore the

hypothesis that monotherapy with lamivudine or emtricitabine may be effective in people with low baseline HBV DNA (<20,000 IU/ml), a level chosen because there is a greater risk for poor liver outcomes above this level [17]. We estimated the proportion of participants with baseline HBV DNA <20,000 IU/ml who achieved HBV DNA <200 IU/ml at 24-week intervals stratified by therapy group.

For all analyses, missing data were ignored and significance was set at 0.05 without adjustment for multiple comparisons.

Results

Of the 115 HIV-HBV co-infected subjects, 56 (49%) received either lamivudine (n=25) or emtricitabine (n=31) as the only anti-HBV drug (monotherapy) and 59 (51%) received dual therapy with 58/59 subjects receiving TDF and emtricitabine and one receiving adefovir and emtricitabine. At least 88% of the expected HBV DNA results were available among participants in follow-up through week 144 (N=89).

All the subjects in the monotherapy group and 28 (47%) in the dual therapy group were from A5175. Of the demographic and HIV pre-treatment characteristics, the two comparison groups differed by sex (P=0.001), country of origin (P=0.001), CD4+ T-cell count distribution (P=0.06), plasma HIV RNA (P=0.02), and hemoglobin (P=0.009) (Table 1). The differences in sex and country of origin were expected due to the distribution of the subjects from the two RCTs. None of the HBV characteristics were significantly different between monotherapy and dual therapy groups with 50% being HBeAg negative (Table 1). The median HBV DNA in the mono and dual therapy groups was 5.2 and 4.9 $\log_{10}$ IU/ml, respectively. Forty-eight (41.8%) subjects had HBV DNA <20,000 IU/ml prior to ART while 46 (45.2%) were $>2.0 \times 10^7$ IU/ml. Genotype A HBV was the most common (60%) followed by genotype D (15%); the genotype distributions in the two comparison groups were similar.

HBV DNA <200 IU/ml

The proportion of subjects achieving HBV DNA <200 IU/ml was 60% (66/100; 95% CI 50–69%) for the primary outcome at week 24 and 79% at week 144 (62/78; 95% CI 69–88%) (Figure 1). In the comparison groups at week 24, 57% (30/53; 95% CI 42–70%) in the monotherapy and 63% (36/57; 95% CI 49 to 76%) in the dual therapy group (exact P = 0.56) achieved HBV DNA <200 IU/ml. However, the estimated proportion with HBV DNA <200 IU/mL increased more over time in the dual than in the monotherapy group (p=0.007) (Figure 1). This between group difference over time remained statistically significant (P=0.02) when adjusted for baseline HBV DNA and HBeAg. The as-treated analysis, which included 98.5% of the expected visits, was similar to the ITT analysis.

Initial multivariable models included pre-treatment characteristics associated with HBV comparison groups or with the primary outcome. Sex, HIV-1 RNA, hemoglobin, CD4 cell count, and HDV status were all associated with HBV DNA comparison groups (Table 1), while AST, HBeAg, and HBV DNA were associated with the primary outcome. Hemoglobin was removed from the multivariable model due to co-linearity with sex and

CD4 count. The linearity in the logit was rejected for CD4 cell count and AST; therefore, these variables were grouped in quartiles. In the multivariable model for the primary outcome, HBV therapy group was not associated (OR 1.8, 95% CI: 0.5–7.9, Table 2). Participants with baseline CD4 cell count <70 cells/mm^3 were 14.8-fold (95% CI: 1.9–201.7) more likely to achieve HBV DNA <200 IU/mL at week 24 compared to those with >140 cells/mm^3. However, change in CD4+ T-cell count from baseline to 24 weeks was not associated. Higher AST (>44 IU/mL) compared to lower levels (< 33 U/L) were associated with HBV DNA <200 IU/mL at 24 weeks (OR 14.1, 95% CI: 1.9 – 228.6) as was lower baseline HBV DNA (OR 4.6/$\log_{10}$ HBV DNA decrease, 95% CI: 2.7 – 10.9). Lower baseline HBV DNA was the only variable that remained significantly associated longitudinally (P<0.0001).

A subgroup analysis to determine if achieving HBV DNA <200 IU/ml differed based on pre-treatment HBeAg status demonstrated that a greater proportion of HBeAg-negative subjects achieved HBV DNA <200 IU/mL at week 24 (47 of 53, 89%) than HBeAg-positive subjects (18 of 56, 32%). This finding was true over both HBV therapy groups, and this difference significantly increased over time (P=0.04).

HBeAg seroconversion

Overall, 16 of the 53 (30%) HBeAg-positive subjects had HBeAg seroconversion, with 10 occurring in the first 48 weeks. These seroconversions were maintained throughout follow-up in 11 (69%). A significant difference was not observed between the mono and dual therapy groups with 27% and 33% seroconversions, respectively. Seroconversion was associated with higher baseline AST (median 47 versus 33 U/L)(P< 0.001), a lower baseline HBV DNA (median 2.30 versus 3.26 $\log_{10}$ IU/ml)(P< 0.001), and trended towards a lower baseline CD4+ T-cell count (median 63 versus 139 cells/uL)(P=0.07). Multivariable models were not informative due to the small number of outcomes.

ALT and AST outcomes

Of the 23 subjects from A5175 with grade 1–4 ALT or AST at baseline, only three did not experience normalization (one died at week 9 from bacterial pneumonia and two were lost to follow-up after weeks 4 and 16). Normalization occurred between weeks 2 and 34. Of the 74 participants from A5175 with grade 0 ALT or AST at baseline, 45 (61%) experienced an elevation to grades 1–4 during follow-up. Only two experienced a severe elevation (grade 3) and one was life-threatening (grade 4). All three subjects normalized after the elevation. The life-threatening elevation required temporary discontinuation of ART but was later successfully restarted.

Durability of HBV DNA suppression or of 1 $\log_{10}$ HBV DNA decline

Of the 105 subjects with 48 weeks of follow-up, 85 (81%) achieved HBV DNA <200 IU/ml and were followed for durability of this outcome. Nineteen (22.4%) of them did not maintain an HBV DNA <200 IU/mL and the time to rebound was similar between the monotherapy and dual therapy groups (logrank P=0.8). In particular, nine of 36 (25%) in the monotherapy group compared to 10 of 49 (20%) in the dual therapy group did not have a durable HBV DNA <200 IU/ml response. Of the 19 individuals, only four had HIV RNA

>400 copies/ml at the same time as the HBV DNA rebound, and these individuals came from both the monotherapy and dual therapy groups. Of the 66 subjects who maintained HBV DNA <200 IU/ml throughout their follow-up, 53 (80%) did so for 24 months.

101 subjects met criteria for inclusion into the analysis for durability of $1 \log_{10}$ IU/ml HBV DNA decline from baseline. In subjects whose baseline HBV DNA was <2000 IU/ml, achieving HBV DNA <200 IU/mL was considered a $1 \log_{10}$ decline. Of the 101 subjects, 21 (20.8%) did not have a durable $1 \log_{10}$ decline with the majority of failures (n=16) occurring within 18 months of having an initial response. In the monotherapy group, 17/47 (36.2%) individuals failed to maintain this outcome compared to 4/54 (7.4%) in the dual therapy group. Interestingly, the failures in the monotherapy group were primarily in those with HBV DNA >20,000 IU/ml (Figure 2).

HBV resistance

For 22 subjects, HBV *pol* sequencing was performed with 12 having emergence of known lamivudine-resistance mutations including one rtM204V/I, eight rtM204V/I+ rtL180M, two rtV173+rtL180M+ rtM204V/I, and one rtM204V/I+ rtM250L. These mutants all emerged in subjects in the monotherapy group (seven on lamivudine, four on emtricitabine, and one changed from lamivudine to emtricitabine).

Post-hoc subgroup analysis

Since most of the subjects who did not maintain a 1 log decline in HBV DNA over time were in the monotherapy group with HBV DNA >20,000 IU/ml, a post-hoc analysis was designed to test the hypothesis that when pre-therapy HBV DNA levels are <20,000 IU/ml, lamivudine or emtricitabine monotherapy can achieve and maintain HBV DNA <200 IU/ml. Among the 21 subjects in the monotherapy group and 25 in the dual therapy group with baseline HBV DNA <20,000 IU/ml, all were <200 IU/mL at week 24 and they were likely (>89%) to have HBV DNA <200 IU/mL at all follow-up time points regardless of whether they received mono or dual HBV therapy.

Discussion

This is the largest multinational HIV-HBV co-infected study to compare HBV outcomes between lamivudine/emtricitabine monotherapy versus TDF-based dual therapy as part of ART through 144 weeks of treatment. Another unique aspect is that ~40% of the subjects had HBV DNA <20,000 IU/ml, a group that is not included in clinical trials of anti-HBV therapies since they do not meet treatment criteria [18]. Overall, we found no difference in becoming undetectable at 24 weeks between treatment groups, but a higher proportion on TDF-based dual therapy achieved an undetectable HBV DNA over time, a finding driven primarily by those with higher baseline HBV replication. In the subgroup analysis, individuals with HBV DNA <20,000 IU/ml responded well regardless of treatment regimen through 144 weeks of therapy. In addition, the subjects in the monotherapy group who failed to maintain a response to therapy over time had HBV DNA 20,000 IU/ml. Taken together, our data support that when possible, TDF-based dual ART should be used to treat HIV-HBV co-infected patients, but in resource-limited settings where TDF may not be universally

available, baseline HBV replication status, as measured by HBV DNA or HBeAg, may help determine whether lamivudine or emtricitabine monotherapy for HBV is a therapeutic option.

In many resource-limited settings the transition from stavudine-based to TDF-based ART has been slow. One challenge in phasing out stavudine is uncertainty about how to prioritize the phase-out. In resource-limited settings, studies demonstrate that HIV-HBV co-infected patients who have HBeAg-negative disease are likely to have low HBV DNA [9, 19]. This fact taken together with our current findings demonstrating that the subjects with HBV DNA <20,000 IU/ml on lamivudine-based therapy were able to maintain HBV DNA suppression through nearly three years of therapy suggests that one potential strategy is to phase out stavudine in the HIV-HBV co-infected patients who are HBeAg-positive since they will derive the most benefit. Also, our data support that for patients with known renal insufficiency where TDF is not an option, lamivudine or emtricitabine as the only HBV-active drug may be a reasonable alternative if they are HBeAg-negative or have a pre-treatment HBV DNA <20,000 IU/ml.

Lower baseline HBV DNA was the only factor in multivariable analysis that was associated with achieving HBV DNA <200 IU/ml throughout follow-up, which is consistent with other studies [20–22]. In the ALLRT cohort, 68 treatment-naïve HIV-HBV co-infected subjects received either lamivudine or TDF-based HAART, and baseline HBV DNA was the only factor associated with HBV DNA suppression at 48 weeks [21]. Interestingly, that study did not find a difference in HBV DNA suppression between the 21 subjects on TDF-based dual therapy and the 47 subjects on lamivudine monotherapy (OR 1.42, p=0.63). Similar to our study, but different from other clinical trials, the ALLRT cohort included subjects with low HBV DNA. Due to the smaller number of subjects, they could not stratify response by baseline HBV DNA.

The difference between the therapy groups in the durability of HBV DNA suppression outcome was only observed with the >1 $\log_{10}$ decline in HBV DNA and not with the HBV DNA <200 IU/ml outcome. This discrepancy is likely due to including more subjects with higher HBV DNA levels in the >1 $\log_{10}$ decline outcome compared to the HBV DNA <200 IU/ml durability outcome.

It is also important to note that at 48 weeks only 69% had undetectable HBV DNA and that even amongst those receiving TDF-based dual therapy, only 76% were undetectable, a proportion that is comparable to studies of HBV monoinfected subjects on entecavir or TDF [23–26]. Even at 144 weeks, 11% of those on TDF-based dual therapy still had a detectable HBV DNA, which is consistent with long-term data of HIV-HBV co-infected subjects from resource-rich settings[27]. Notably, those who did not suppress had baseline HBV DNA 20,000 IU/ml.

We observed unexpectedly that those with the lowest baseline CD4+ T-cell count were more likely to achieve an undetectable HBV DNA at 24 weeks but not at later time points. This may be due to differences in the robustness of the immune reconstitution in the period immediately after ART initiation. However, change in the CD4 T-cell count in the first 24

weeks was not associated with HBV DNA suppression. Since CD4+ T-cell count increase is a crude measure of immune reconstitution with ART, it is possible that those with a lower baseline CD4+ T-cell count had greater change in a different arm of the immune response in the first 24 weeks or in a specific subset of CD4+ T cells. Further studies of immune reconstitution with ART are needed to explore these hypotheses.

The rates of HBeAg seroconversion and ALT normalization did not differ between therapy groups, as is consistent with prior studies [18]. We also found that drug-resistant HBV only emerged in those on lamivudine or emtricitabine monotherapy, which is consistent with data showing no resistance with TDF-based therapy [22, 28, 29].

There are several limitations to this study. First, this was not a RCT in terms of HBV therapy, so there were differences in baseline characteristics between the groups; however, none of these differences were in HBV parameters. Second, subjects were only followed through 144 weeks, so whether other differences occur between therapy groups with longer follow-up is not known. Third, we did not have data on adherence; however, as stated in the Results, few subjects who did not have a durable HBV DNA response also lost HIV RNA suppression. Thus, adherence did not explain a large proportion of the HBV relapse.

In summary, for HIV-HBV co-infected subjects in a multinational setting, TDF/ emtricitabine dual therapy for HBV as part of ART should be the first-line therapy if available and cost-effective especially in patients with HBV DNA levels 20,000 IU/ml or with HBeAg-positivity. For subjects with lower levels of replication, lamivudine or emtricitabine-based monotherapy is a possible alternative at least through 144 weeks of therapy. In resource-limited settings, these data may inform strategic plans regarding which patients to transition to or to initiate on TDF-based ART.

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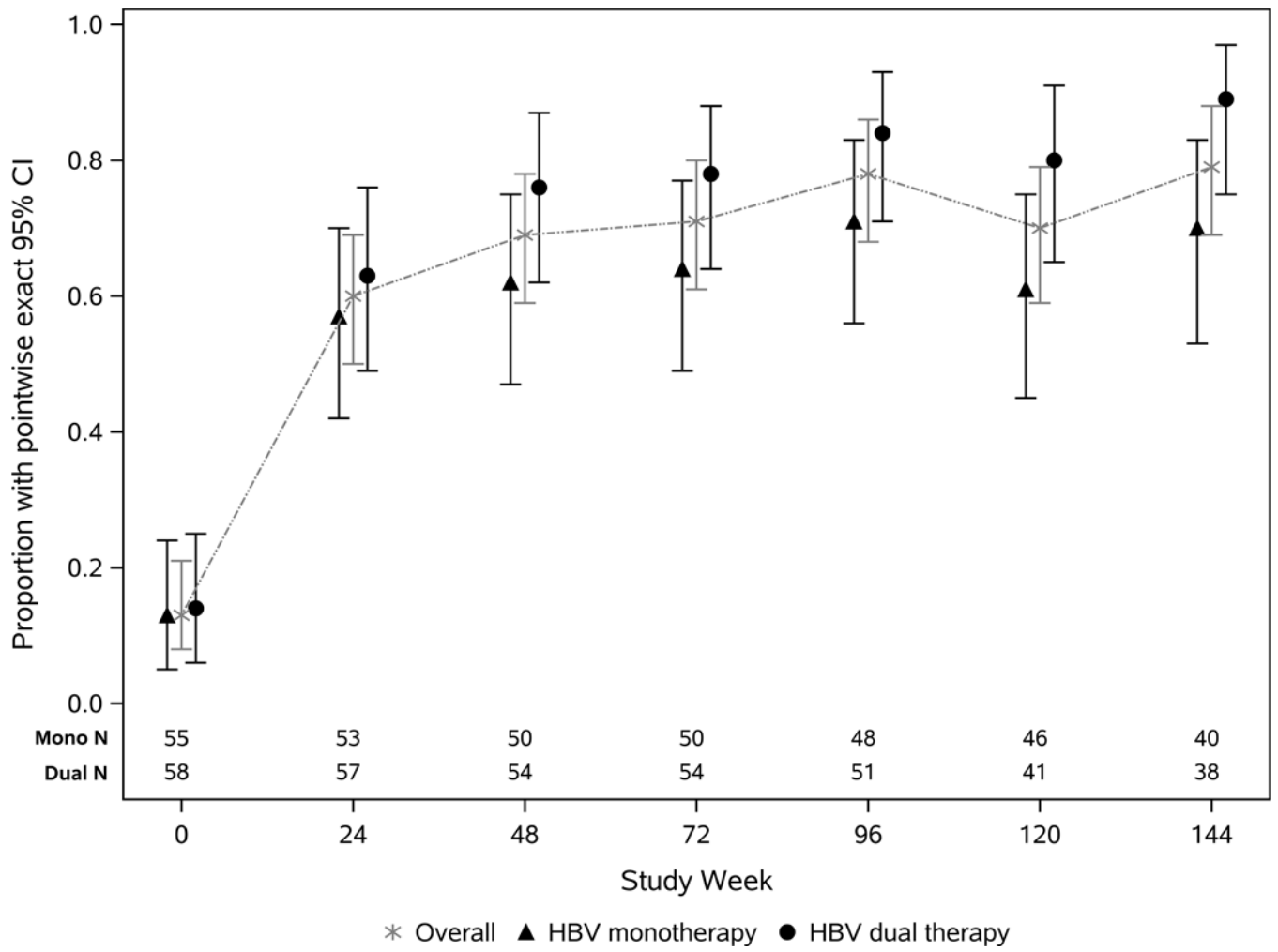
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Figure 1.
Estimated proportion of HBV DNA < 200 IU/mL (y-axis) through 144 weeks stratified by HBV treatment group.
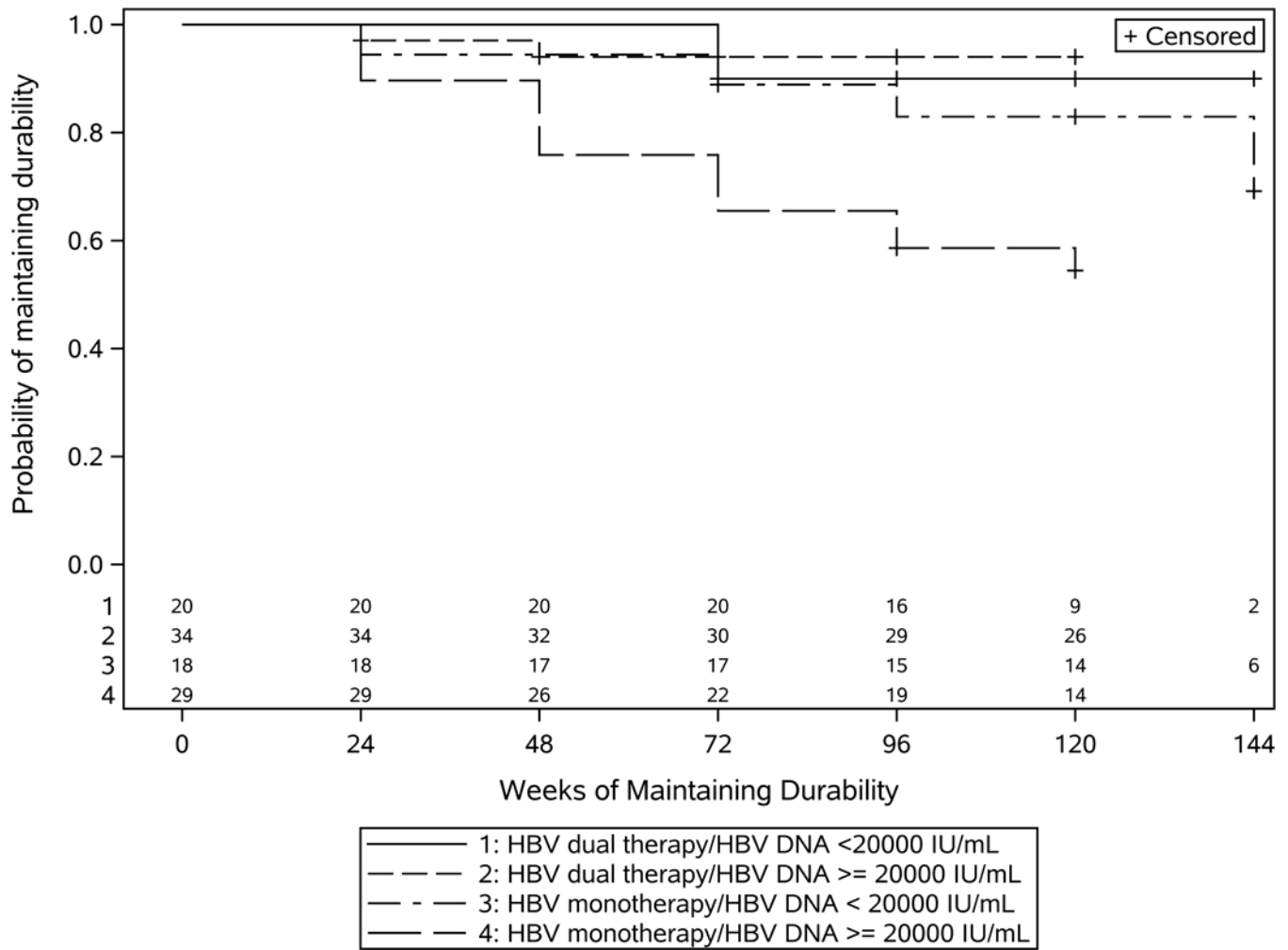
Figure 2.

Time to loss of maintaining durability by HBV therapy group and baseline HBV DNA level stratified at 20,000 IU/ml. Durability is defined as a composite of: i) Maintaining a ≥ 1 log IU/mL HBV DNA decline from baseline or ii) maintaining HBV DNA < 200 IU/mL if baseline HBV DNA was < 2000 IU/mL. The numbers at each week describe the number of participants who were at risk of not maintaining durability. There were only a limited number of participants who were at risk for not maintaining durability at week 144.

Table 1

Baseline characteristics by therapy group

Characteristic	Monotherapy N=56	Dual therapy[a] N=59	Overall N=115	P^g
Age, years (IQR)[b]	35 (30, 39.5)	34 (29, 40)	34 (30, 40)	0.15
Country of origin (N, %)[c,d]				0.001
Botswana (M)	0 (0)	4 (6.8)	4 (3.5)	
Haiti (L)	4 (7.1)	2 (3.4)	6 (5.2)	
India (L)	9 (16.1)	4 (6.8)	13 (11.3)	
Kenya (L)	0 (0)	3 (5.1)	3 (2.6)	
Malawi (L)	16 (28.6)	8 (13.6)	24 (20.9)	
Peru (M)	4 (7.1)	2 (3.4)	6 (5.2)	
South Africa (M)	3 (5.3)	14 (23.7)	17 (14.8)	
Thailand (M)	4 (7.1)	4 (6.8)	8 (7.0)	
United States (H)	8 (14.3)	2 (3.4)	10 (8.7)	
Zimbabwe (L)	8 (14.)	16 (27.1)	24 (20.9)	
Male (N, %)[e]	35 (62.5)	19 (32.2)	54 (47.0)	0.001
Race (N, %)[c]				
Asian	13 (23.2)	8 (13.6)	21 (18.3)	0.30
African American	37 (66.1)	48 (81.4)	85 (73.9)	
White	2 (3.6)	1 (1.7)	3 (2.6)	
Other	4 (7.1)	2 (3.4)	6 (5.2)	
CD4 count groups (cells/mm³) (N,%)[c]				
< 50	11 (19.6)	7 (11.9)	18 (15.7)	0.06
50 – 99	10 (17.9)	13 (22.0)	23 (20.0)	
100 – 149	7 (12.5)	18 (30.5)	25 (21.7)	
150 – 199	7 (12.5)	10 (16.9)	17 (14.8)	
200 – 249	13 (23.2)	5 (8.5)	18 (15.7)	
250 – 299	8 (14.3)	6 (10.2)	14 (12.2)	
HIV RNA, log cp/ml[b] (IQR)	4.9 (4.5, 5.4)	5.3 (4.7, 5.8)	5.1 (4.6.5.6)	0.02
Hemoglobin, g/dL[b] (IQR)	12.4 (11.2, 13.8)	11.5 (10.2, 13.3)	11.9 (10.9, 13.7)	0.009
ALT, U/L[b] (IQR)	28 (20.5, 37.5)	25 (18, 44)	25.5 (19, 38)	0.64
AST U/L[b] (IQR)	35.1 (24.5, 49.5)	33 (27.2, 42)	34 (27, 44)	0.88
HBeAg+ (N, %)[f]	27 (48.2)	29 (49.1)	57 (49.6)	0.92
HBV DNA >200 IU/ml (N, %)[c,f]	49 (87.5)	54 (91.5)	103 (89.6)	0.52
HBV DNA, $\log_{10}$ IU/ml[b] (IQR)	5.2 (2.8, 8.2)	4.9 (2.6,7.52)	5.1 (2.7, 8.1)	0.58
HBV DNA categories				
< 2,000 IU/mL	19 (33.9)	21 (35.6)	40 (34.8)	
2,000 – 20,000 IU/mL	3 (5.4)	5 (8.5)	8 (7.0)	
> 20,000 IU/mL	33 (58.9)	32 (54.2)	65 (56.5)	

Characteristic	Monotherapy N=56	Dual therapy[a] N=59	Overall N=115	P[g]
Missing	1 (1.8)	1 (1.8)	2 (1.7)	
HBV DNA genotype (n,%)[f]				0.64
A	29 (51.8)	40 (67.8)	69 (60.0)	
C	3 (5.4)	2 (3.4)	5 (4.3)	
D	9 (16.1)	6 (10.2)	15 (13.0)	
E	2 (3.6)	2 (3.4)	4 (3.5)	
F	2 (3.6)	1 (1.7)	3 (2.6)	
Missing	11 (19.6)	8 (13.6)	19 (16.5)	
HDV antibody negative (N,%)[c]	54 (96.4)	44 (74.6)	98 (85.2)	<0.01

[a] one person received adefovir plus emtricitabine

[b] median values

[c] Fisher's Exact

[d] The L, M, H designation after the country name represent the income level as classified by the World Bank (http://data.worldbank.org/country) with L representing low and low middle, M upper middle, and H high income.

[e] Chi-Square

[f] HBV characteristics determined among 113 of the 115 subjects. Two subjects did not have serum available at baseline.

[g] P-values represent difference between the monotherapy and dual therapy groups

Table 2

Multivariable logistic regression model primary outcome of HBV DNA <200 IU/ml at 24 weeks

	Univariate OR (95% CI)	Multivariate OR (95% CI)
Dual vs. monotherapy [i]	1.4 (0.6–3.0)	1.8 (0.5–7.9)
Baseline CD4+ T-cell count [ii]		
<70 cells/mm^3 (lowest observed quartile)	1.5 (0.6–4.0)	14.8 (1.9–201.7)
70–140 cells/mm^3 (observed second quartile)	1.0 (0.4–2.6)	1.7 (0.3–9.6)
>140 cells/mm^3 (above observed median)	1.0 (ref)	1.0 (ref)
Baseline AST Value [iii]		
< 33 (U/L) (below observed median)	1.0 (ref)	1.0 (ref)
33–44 (U/L) (observed third quartile)	0.7 (0.3–1.9)	3.1 (0.5 – 25.0)
>44 (U/L) (highest observed quartile)	0.5 (0.2–1.3)	14.1 (1.9 – 228.6)
Baseline HBV DNA (per 1 log$_{10}$ IU/ml decrease) [iv]	2.7 (2.0–4.0)	4.6 (2.7–10.9)

[i] Forced into all models – tests for interaction terms between this comparison group and CD4 group, AST group, and HBV DNA (in separate models) were not significant.

[ii] Actual CD4 cell count entered into initial multivariable model due to association with HBV comparison group, retained by stepwise selection, and groups formed due to linearity in the logit being rejected

[iii] Actual AST value entered into initial multivariable model due to association with primary outcome, retained by stepwise selection, and groups formed due to linearity in the logit being rejected

[iv] Actual HBV DNA levels entered into initial multivariable model due to association with primary outcome, retained by stepwise selection, and linearity in the logit not rejected.

• Other baseline covariates entered into initial multivariable model due to association with HBV comparison group included the following: sex, plasma HIV-1 RNA, hemoglobin, and HDV antibody. Hemoglobin removed due to collinearity.

• HBeAg at baseline entered into initial multivariable model due to association with primary outcome, but was not retained in stepwise selection process.