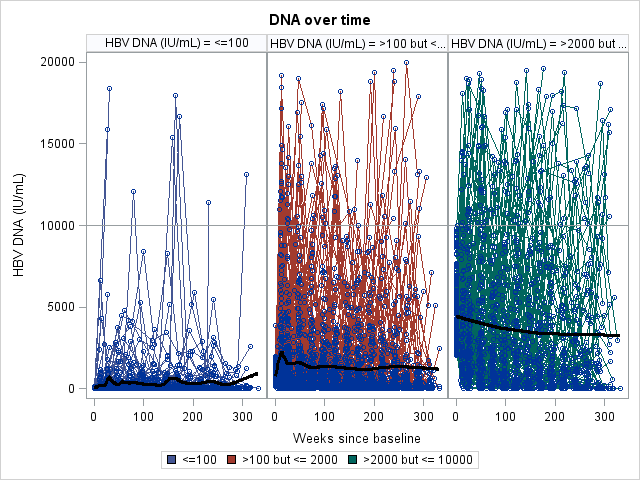
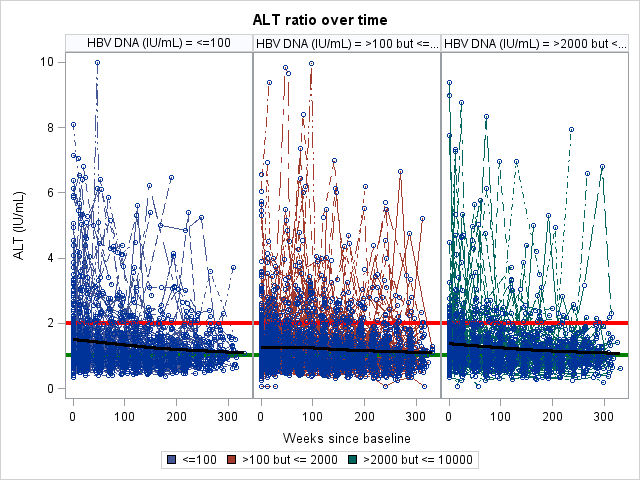
**Supplementary Figure 1**: Individual excursions of a) HBV DNA >10,000 IU/mL and b) ALT ratio >2\* by category of HBV DNA level over duration of follow-up



**HBV DNA over time**

**A**

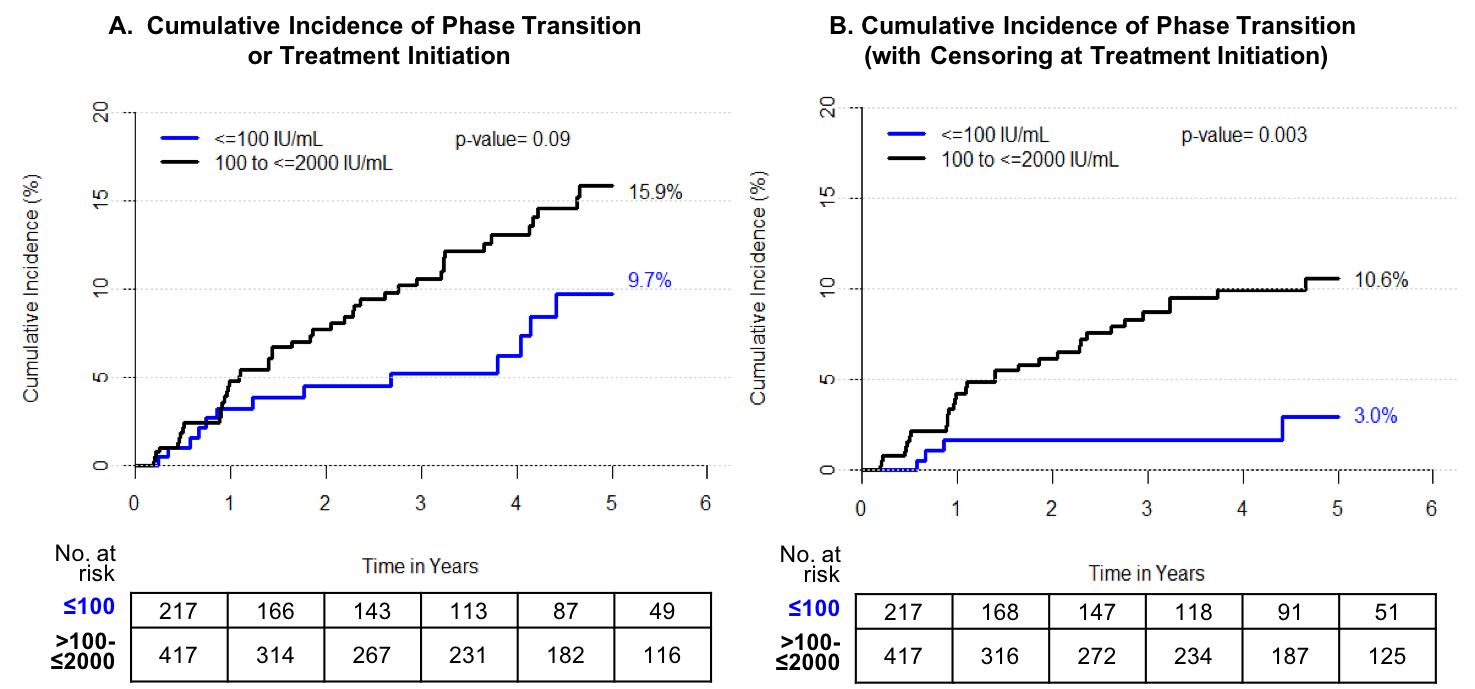


**B**

\*ALT ratio calculated as ALT/ALT [ULN]; ULN = 20 U/L in males and 30 U/L in females.

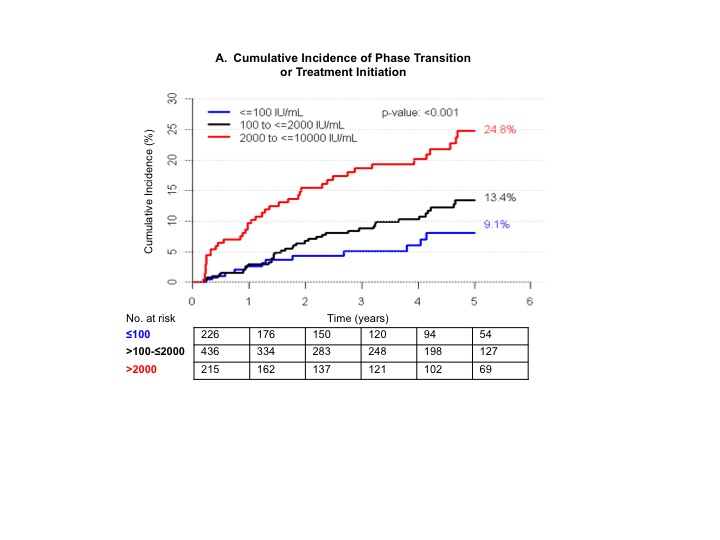
Red line represents a) HBV DNA level of 10,000 IU/mL and b) ALT ratio of 2. Black line represents overall trend for all participants over 300 weeks of follow-up time.

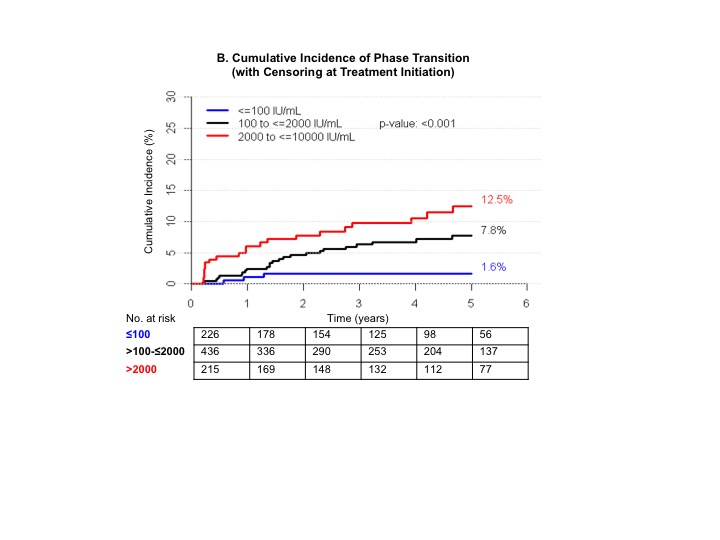
**Supplementary Figure 2**. Cumulative incidence for participants with HBV DNA≤2000 IU/mL with A) phase transition with treatment initiation and B) phase transition with censoring of treatment initiation over 5 years of follow-up



The Kaplan-Meier plots show up to five-years of follow-up, when a reasonable number of participants were still at risk of outcome (n=165 in Panel A and n=176 in Panel B).

**Supplementary Figure 3:** Sensitivity analysis of A) phase transition or treatment initiation and B) phase transition with censoring of treatment initiation over 5 years of follow-up using higher normal ALT (<25 for females, <35 for males)

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**Supplementary Table 1**: Results of univariate Cox regression analysis with primary outcome of phase transition or treatment initiation among HBV DNA≤10,000 IU/mL

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Covariate** | **Hazard Ratio** | **Lower 95%** | **Upper 95%** | **p-value** |
| Gender |  |  |  |  |
| Male | 1.05 | 0.705 | 1.564 | 0.812 |
| Race |  |  |  | 0.474 |
| Asian | 1.362 | 0.722 | 2.57 | 0.340 |
| Black | 0.885 | 0.39 | 2.006 | 0.769 |
| Other | 1.213 | 0.269 | 5.478 | 0.802 |
| Genotype |  |  |  | 0.066 |
| B | 2.092 | 1.101 | 3.978 | 0.024 |
| C | 1.654 | 0.84 | 3.256 | 0.146 |
| D | 0.703 | 0.227 | 2.183 | 0.542 |
| Others | 0.985 | 0.22 | 4.402 | 0.984 |
| G1896 Mutation |  |  |  |  |
| Yes | 1.055 | 0.565 | 1.968 | 0.867 |
| Any BCP mutation |  |  |  |  |
| Yes | 1.867 | 1.004 | 3.472 | 0.048 |
| Marital Status |  |  |  |  |
| In a Marriage or Marriage-Like Relationship | 0.807 | 0.528 | 1.234 | 0.322 |
| Education |  |  |  | 0.005 |
| High school or equivalent (GED) | 0.8 | 0.449 | 1.427 | 0.450 |
| Some college or equivalent | 0.618 | 0.322 | 1.185 | 0.148 |
| Bachelors or above | 0.409 | 0.242 | 0.693 | 0.001 |
| Employment |  |  |  | 0.312 |
| Homemaker, not currently working for pay | 0.4 | 0.098 | 1.628 | 0.201 |
| Not currently employed | 0.783 | 0.463 | 1.323 | 0.361 |
| Med Hx: Diabetes |  |  |  |  |
| Yes | 2.141 | 1.143 | 4.011 | 0.018 |
| Source of Infection |  |  |  |  |
| Horizontal | 0.819 | 0.506 | 1.324 | 0.415 |
| Med Hx: Hyperlipidemia |  | |  |  |
| Yes | 1.91 | 1.188 | 3.073 | 0.008 |
| Metabolic Syndrome |  |  |  |  |
| Yes | 1.5 | 0.858 | 2.625 | 0.155 |
| Prior Treatment |  |  |  |  |
| Non-IFN-based | 0.742 | 0.374 | 1.475 | 0.395 |
| HDV |  |  |  |  |
| Positive | 2.249 | 0.91 | 5.557 | 0.079 |
| ALT |  |  |  | <0.001 |
| ALT (IU/L) > ULN but <=1.5XULN | 2.078 | 1.303 | 3.315 | 0.002 |
| ALT (IU/L) >1.5XULN but <= 2 X ULN | 2.941 | 1.701 | 5.084 | <0.001 |
| HBV DNA |  |  |  | <0.001 |
| HBV DNA (IU/mL) <=2000 | 1.529 | 0.819 | 2.857 | 0.183 |
| HBV DNA (IU/mL) >2000 but <= 10,000 | 3.419 | 1.838 | 6.362 | <0.001 |
| HBsAg Categories |  |  |  |  |
| > 1000 IU/mL | 1.246 | 0.82 | 1.893 | 0.303 |
| APRI |  |  |  |  |
| >0.50 | 3.646 | 2.184 | 6.084 | <0.001 |
| Fib4 |  |  |  | 0.041 |
| FIB-4, categorized 1.45-3.25 | 1.837 | 1.143 | 2.954 | 0.012 |
| FIB-4, categorized >3.25 | 1.54 | 0.212 | 11.161 | 0.670 |
| Age at baseline (per year) | 1.017 | 1.001 | 1.033 | 0.036 |
| Body Mass Index (per kg/m2) | 0.976 | 0.933 | 1.022 | 0.301 |
| HOMA-IR (per 1) | 0.942 | 0.781 | 1.136 | 0.530 |
| log10 HBsAg Quant (Central Lab) per 1 log | 1.25 | 1.022 | 1.527 | 0.029 |
| Time (in years) since HBV diagnosis per year | 0.99 | 0.968 | 1.012 | 0.364 |
| ALT (IU/mL) per 1 IU/mL | 1.042 | 1.024 | 1.061 | <0.001 |
| ALT Ratio per 1 unit | 3.648 | 2.186 | 6.088 | <0.001 |
| HBV DNA per 1 log | 2.139 | 1.597 | 2.865 | <0.001 |
| AST (IU/mL) per 1 IU/mL | 1.031 | 1.013 | 1.051 | 0.001 |
| Platelet (per 10^3 mm^3) | 0.996 | 0.992 | 1.000 | 0.040 |
| APRI per 1 unit | 3.688 | 1.995 | 6.816 | <0.001 |
| FIB-4 per 1 unit | 1.228 | 1.044 | 1.445 | 0.013 |

**Supplementary Table 2**: Key baseline differences in participants with and without clinical diagnosis of hyperlipidemia (HBV DNA ≤10,000 IU/mL)

|  |  |  |  |
| --- | --- | --- | --- |
| **Characteristic** | **No hyperlipidemia N=832** | **Hyperlipidemia N=132** | **p-value** |
| Age at baseline | 41.0 (34.0-51.0) | 54.5 (46.0-63.0) | <0.001 |
| Male | 381 (45.8%) | 82 (62.1%) | 0.001 |
| Estimated Duration of HBV Infection | 33.0 (21.0-42.0) | 43.0 (22.0-56.0) | <0.001 |
| HBV DNA (IU/mL) |  |  | 0.99 |
| <=100 | 234 (28.1%) | 36 (27.3%) |  |
| >100 but <= 2000 | 403 (48.4%) | 65 (49.2%) |  |
| >2000 but <= 10,000 | 195 (23.4%) | 31 (23.5%) |  |
| ALT (IU/L) |  |  | 0.17 |
| <=ULN | 349 (42.7%) | 55 (43.0%) |  |
| >ULN but <= 1.5 X ULN | 274 (33.5%) | 33 (25.8%) |  |
| >1.5XULN but <= 2 X ULN | 97 (11.9%) | 22 (17.2%) |  |
| >2 X ULN | 97 (11.9%) | 18 (14.1%) |  |
| Metabolic Syndrome | N=357 | N=81 | <0.001 |
| No | 302 (84.6%) | 17 (21.0%) |  |
| Yes | 55 (15.4%) | 64 (79.0%) |  |

**Supplementary Table 3**: Results of multivariable Cox regression analysis with secondary outcome of phase transition (with censoring of treatment initiation) among HBV DNA≤10,000 IU/mL

|  |  |
| --- | --- |
| **Covariates** | **Adjusted HR (95% CI)** |
| ALT |  |
| <= ULN | Ref |
| >ULN but <= 1.5 X ULN | 2.1 (1.0-4.4) |
| >1.5XULN but <= 2 X ULN | 4.3 (2.0-9.2) |
| HBV DNA |  |
| <=100 IU/mL | Ref |
| >100 but <= 2000 IU/mL | 3.9 (1.2-12.8) |
| >2000 but <= 10,000 IU/mL | 7.1 (2.1-23.9) |
| Platelet count (per 20000 mm3 decline) | 1.2 (1.1-1.4) |

**Supplementary Table 4**: Results of multivariable Cox regression analysis with primary outcome of phase transition or treatment initiation among participants with baseline HBV DNA ≤2000 IU/mL

|  |  |
| --- | --- |
| **Covariates** | **Adjusted HR (95% CI)** |
| History of diabetes | 4.0 (2.0-7.8) |
| ALT (U/L) ≤ULN | Ref |
| >ULN to ≤1.5x ULN | 1.8 (1.0-3.2) |
| 1.5x ULN to ≤2x ULN | 3.3 (1.7-6.4) |
| HBV DNA (IU/mL) ≤100 | Ref |
| 100 to ≤2000 | 1.5 (0.9-2.8) |

**Supplemental Table 5:** Sensitivity analysis of predictors of primary outcome of phase transition or treatment initiation using higher normal ALT (<25 for females, <35 for males) among HBV DNA≤10,000 IU/mL

|  |  |
| --- | --- |
| **Covariates** | **Adjusted HR (95% CI)** |
| Genotype A | Ref |
| B | 3.6 (1.6-8.1) |
| C | 3.0 (1.4-6.4) |
| D | 1.5 (0.4-4.8) |
| Other | 1.1 (0.2-5.2) |
| No history of hyperlipidemia | Ref |
| History of hyperlipidemia | 2.7 (1.6-4.6) |
| ALT (U/L) ≤ULN | Ref |
| >ULN to ≤1.5x ULN | 3.0 (1.8-5.1) |
| 1.5x ULN to ≤2x ULN | 3.9 (2.0-7.9) |
| HBV DNA (IU/mL) ≤100 | Ref |
| 100 to ≤2000 | 2.7 (0.9-7.6) |
| 2000 to ≤10,000 | 4.1 (1.4-11.6) |
| Platelet count (per 20000 mm3 decline) | 1.1 (1.0-1.3) |
| HBsAg (IU/mL) ≤1000 | Ref |
| HBsAg >1000 | 1.5 (0.9-2.5) |