

GENOTYPE G HEPATITIS B VIRUS (HBV) AND ADVANCED LIVER FIBROSIS IN HIV/HBV CO-INFECTED PATIENTS

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INTRODUCTION AND AIM OF STUDY

RESULTS

- Approximately 10% of HIV patients are co-infected with hepatitis B virus (HBV).
- Clinical observations suggest HIV/HBV co-infection is associated with faster liver disease progression compared to HBV infection alone. However, the basic mechanism in this setting remains unclear.
- Genotype G (HBV/G) is a defective form of HBV that replicates very poorly in most settings. Genotype G is present in <1% of HBV mono-infected persons, has low HBV DNA levels, and is HBeAg-negative.
- Experiments in immunocompromised animals suggest that HBV/G frequently mixes with other HBV genotypes to enhance its replication capacity. As a result, in the mixture form, HBV/G induces cellular steatosis and has direct cytopathic effects to hepatocytes, and thus increases liver fibrosis.
- The prevalence and impact of HBV genotype G (HBV/G) in co-infected HIV/HBV patients is unclear. **We examined the prevalence of HBV genotype and what impact HBV/G, compared to other genotypes, had on liver fibrosis in HIV/HBV co-infected patients.**

Summary of Study Patients and Lab Experiments

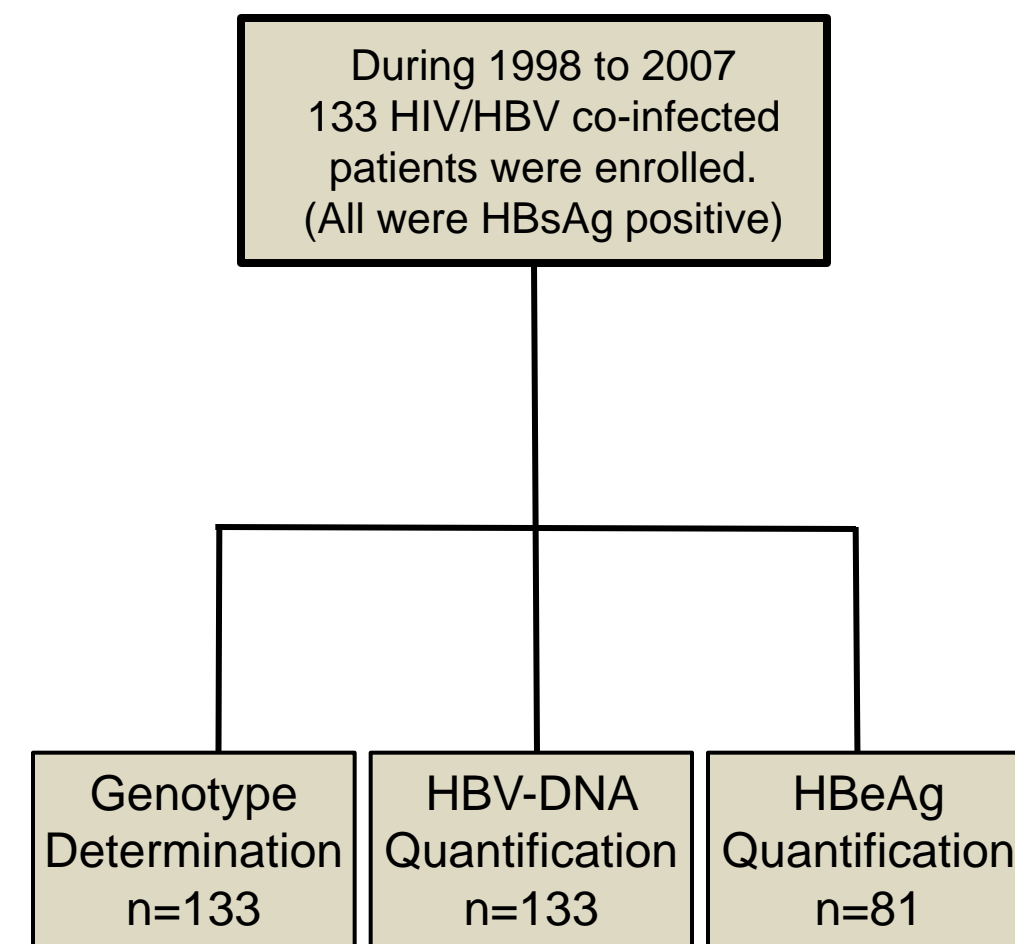


Figure 1: 133 HIV patients who also were HBsAg positive were enrolled in the study. HBV genotype and HBV viral loads were performed on all patients. HBeAg quantification was done on 81/133 (61%).

HBV Genotype G Comprises 17% (23/133) of the Co-infected Patients

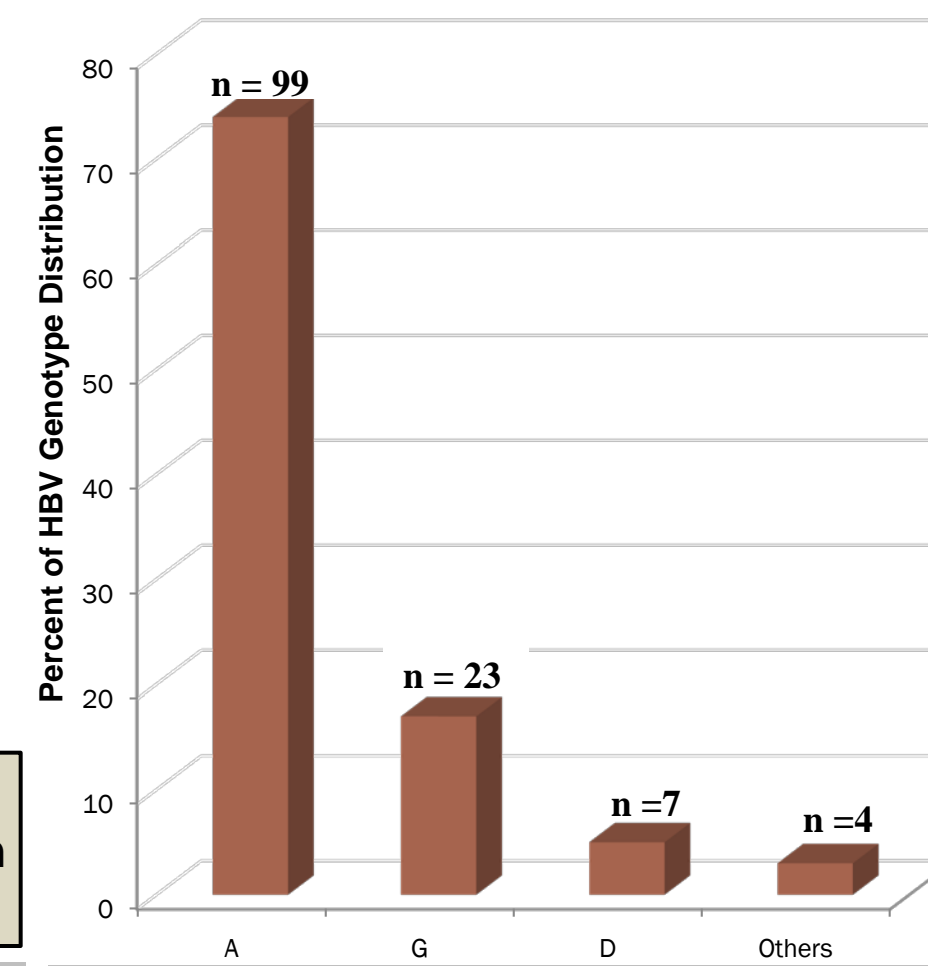


Figure 2: Distribution of HBV genotypes in the co-infected patients. Genotype G was present in 23/133 (17%) and genotype A in 99/133 (74%) followed by genotypes D 7/133 (5%) and others 4/133 (3%).

Genotype G is Associated with more Advanced Fibrosis Score than those with HBV/A

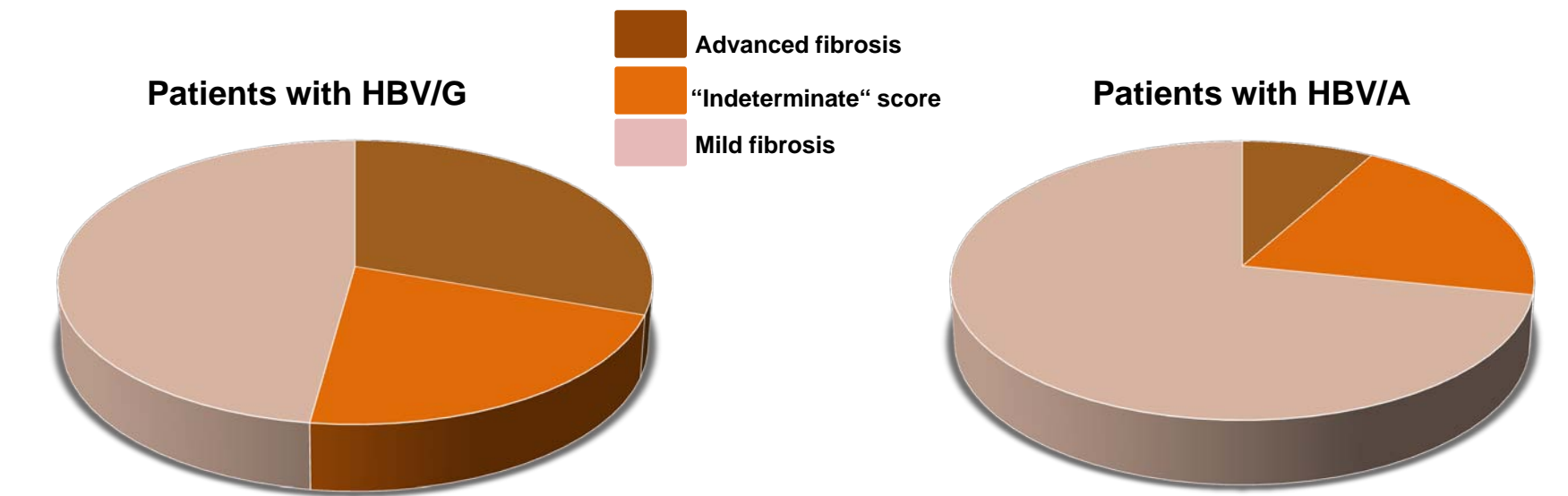


Figure 3: Patients with HBV genotype G (HBV/G) have distribution of fibrosis scores as follows: advanced (>3.25) n=7, "indeterminate" (1.45-3.25) n=8, and mild (<1.45) n=11. Likewise, HBV/A patients are: advanced n=8, "indeterminate" n=20, and mild n=71. Only patients with advanced or mild fibrosis scores were analyzed and those who had HBV/G were more likely to have more advanced fibrosis score [7/18 (39%)] compared to those with HBV/A [8/71 (11%)]. P=0.01.

Genotype A HBV Group versus Genotype G HBV Group by Fib-4 Scores: <1.45 vs. >3.25

Variable	Univariate		Multivariate**	
	O.R (95% CI)	P value	O.R (95% CI)	P value
HBV Genotype G	5.01 (1.5- 16.6)	0.01	4.3 (1.2-16.2)	0.03
AA*	0.19 (0.05-0.72)	0.014	0.17 (0.04-0.71)	0.01

Table 2: Both univariate and multivariate analyses reveal that HBV genotype G and non-AA race are important predictors of advanced liver fibrosis.

* AA: African American compared to non-AA, ** Adjusted for follow-up time

MATERIALS AND METHODS

- Patient population and Laboratory Experiments (figure 1):**
 - 133 HIV-infected patients who were HBV surface antigen (HBsAg) positive and had an available stored sample of sera for analysis were included.
 - The cohort was composed of patients who received HIV care in Parkland, which is the primary teaching hospital for UT Southwestern Medical Center at Dallas.
 - Sera was collected for routine HIV care and extra sera was stored. Approval to use the stored samples for research purposes was obtained by UT Southwestern IRB. Baseline (at the time of sample) data on demographics were obtained by chart review.
 - We obtained the most recent liver function tests and platelet count to perform non-invasive measurement of fibrosis.
 - Quantification of HBV DNA was performed by Versant® HBV 3.0 [bDNA; Siemens Diagnostics; dynamic range: 3-8 log₁₀ copies/mL (c/mL)]
 - Quantification of HBeAg was done using the ADVIA®Centaur™ HBeAg (dynamic range: 0.1-1,000 index value (signal/noise))
 - HBV genotyping was done by direct sequencing of the surface region of HBV genome.
 - Liver biopsies are infrequently performed and thus could not be used to determine fibrosis.
- Non-invasive biomarker based formula was used to assess fibrosis stage at the last clinical follow-up**
 FIB-4: [Age (yr) * AST] / [(Platelets) * √ALT]
 - Fib-4 < 1.45 => Fibrotic stage ≤ F1
 - Fib-4 > 3.25 => Fibrotic stage ≥ F2
- Statistical analysis:**
 - All statistical tests were performed by SAS
 - Fib-4 scores were dichotomized to examine scores indicating stage 1 fibrosis or ≥ stage 2 fibrosis. Indeterminate values were not assessed.
 - Dichotomized variables were analyzed by chi-square and continuous by Wilcoxon Rank Sum test.
 - Those variables which showed significance in the univariate analysis were included in the multivariate analysis.
 - P value of ≤ 0.05 is considered significant

Demographics of Study Patients

Characteristics	Total (n=133)	Genotype A (n=99)	Genotype G (n=23)	Univariate P value	
Female	21 (16%)	17 (17%)	1 (4%)	0.12	
Race	African American	65 (49%)	53 (54%)	10 (44%)	0.69
	Caucasian	50 (38%)	34 (34%)	10 (44%)	
	Hispanics	14 (11%)	8 (8%)	3 (13%)	
	Other	4 (3%)	4 (4%)	0	
Age (median years (range))	42 (22-64)	42 (22-64)	39 (24-52)	0.42	
Time interval of follow-up (months)	35 (0-110)	37 (0-101)	19 (0-98)	0.02	
HCV antibody positive	No	97 (73%)	71 (72%)	18 (78%)	0.52
	Yes	36 (27%)	28 (28%)	5 (22%)	
Alcohol Use	None or occasional use	35 (61%)	22 (55%)	10 (83%)	0.08
	Moderate/Excessive	22 (39%)	18 (45%)	2 (17%)	
Fibrosis Score	Mild Fibrosis (<1.45)	82 (84%)	63 (89%)	11 (61%)	0.01
	Advanced fibrosis (>3.25)	16 (16%)	8 (11%)	7 (39%)	
Baseline HIV viral load (log ₁₀ copies/mL)	n: 122, Median (range): 4.75 (1.69-6.88)	n: 90, Median (range): 4.81 (1.69-6.88)	n: 21, Median (range): 4.51 (1.69-5.88)	0.85	
Baseline CD4+ Count (cells/μL)	n: 123, Median (range): 190 (1-1132)	n: 91, Median (range): 162 (4-1132)	n: 21, Median (range): 190 (1-657)	0.59	
HBV DNA titers (log ₁₀ copies/mL)	n: 133, Median (range): 8.0 (3.31-8.0)	n: 99, Median (range): 8.0 (3.31-8.0)	n: 23, Median (range): 8.0 (4.05-8.0)	0.32	
HBeAg Quant (Index value)	n: 81, Median (range): 1000 (0-1000)	n: 60, Median (range): 1000 (0-1000)	n: 15, Median (range): 1000 (0-1000)	0.29	
Anti-HBe Quantitation (Index value)	n: 79, Median (range): 0 (0-4.51)	n: 59, Median (range): 0 (0-4.5)	n: 14, Median (range): 0 (0-2.2)	0.73	

Table 1: Demographic characteristics of entire cohort and comparison between patients with Genotype A vs. G

SUMMARY AND CONCLUSIONS

- HBV genotype G was prevalent in the HIV-infected population but likely had gained replicative fitness and HBeAg production by mixing with other genotypes, most likely genotype A.
- HBV genotype G in the mixed form with other HBV genotypes would explain the high HBV DNA and HBeAg levels observed.
- Being African American is associated with milder fibrosis score.
- Despite significantly shorter time of follow-up, patients with HBV genotype G appear have more advanced fibrosis in HIV/HBV co-infected patients. The reason for this more aggressive disease is unclear.
- In HIV/HBV co-infection, HBV genotyping may be an important tool to assess if the patient is at increased risk for liver disease progression.

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