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Prevalence and Characteristics of Hepatitis B Virus Mutations in Chronic Hepatitis B Patients on Oral Antiviral Therapy: The CHARM Study

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for the CHARM Study Group

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Introduction

- The advent of newer, more potent oral antiviral therapies (AVT) has been a significant advance in the treatment of chronic hepatitis B (CHB)
- However, long-term management of CHB may be compromised by the emergence of drug-resistant mutations (genotypic resistance) that may lead to virologic breakthrough and progressive liver disease
- Detection of genotypic resistance:
  - Facilitates treatment modification before viral or clinical rebound
  - prevents the initiation of inappropriate, cross-resistant AVT
- However, resistance testing is not routine

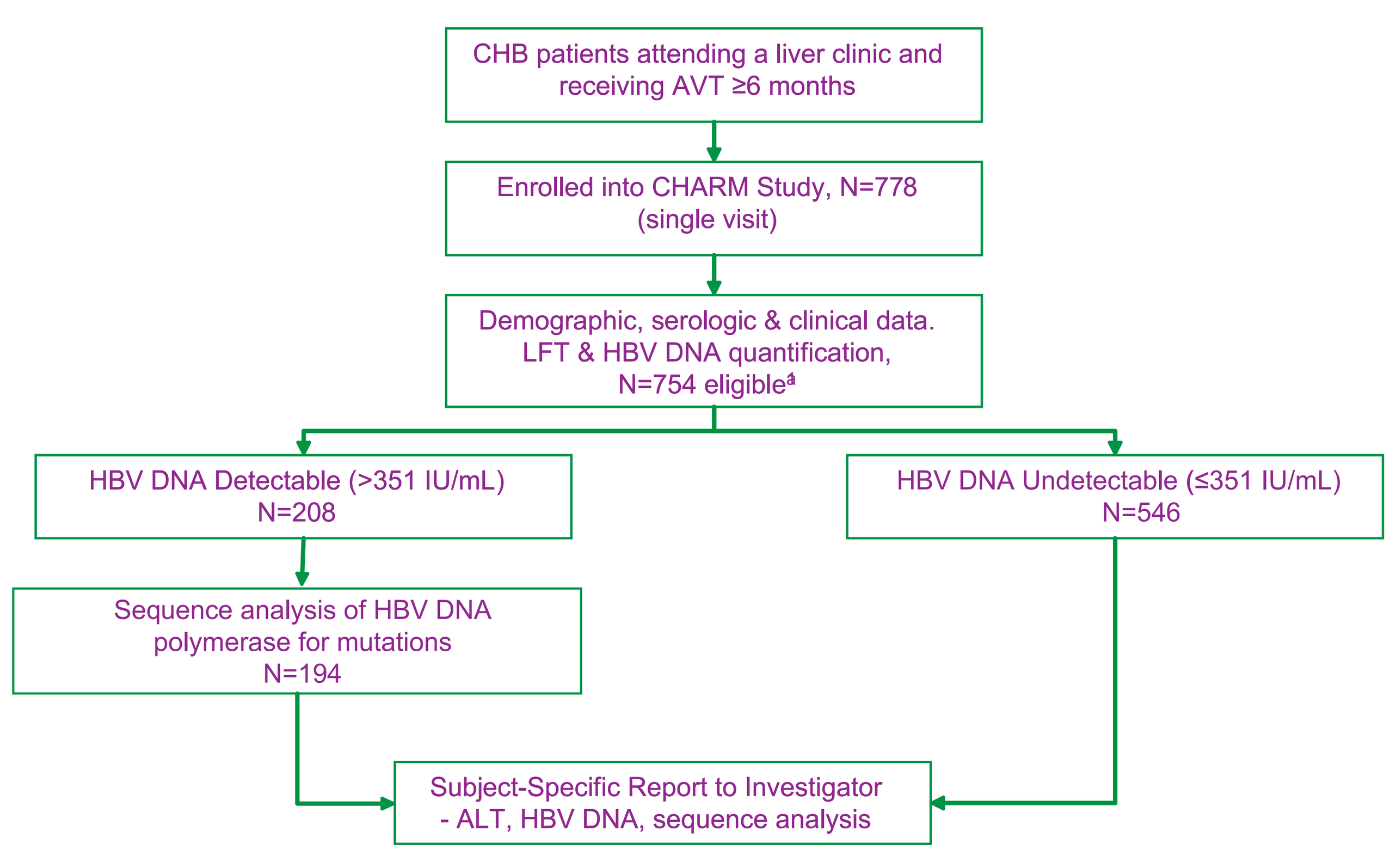
Objective

- The aim of the study was to describe the prevalence and nature of hepatitis B virus (HBV) mutations that confer drug resistance in patients receiving AVT in a tertiary clinic outpatient setting in Australia

Methods

- Multi-centre, cross-sectional, epidemiology study
- 18 Australian sites
- Entry criteria
  - Adults with CHB attending tertiary outpatient clinics
  - Receiving one or more AVT ≥6 months
  - HIV, HCV, HDV co-infection, and/or concurrent immunomodulatory therapy excluded
- Demographic and clinical data collected:
  - serology, AVT (current and treatment history), histology, patient-assessed compliance, and prior HBV mutations.
- HBV DNA quantification
  - performed on all patients (Versant HBV DNA v3.0 assay; LLOQ = 351 IU/mL)
  - Direct sequence analysis (catalytic region of HBV DNA polymerase, encoding amino acids 1-257) attempted on all patients with detectable HBV DNA

Figure 1. Patient Disposition



a. Laboratory result either missing or invalid for 13/754 patients

Results

Table 1. Demographics

Parameter		N=754
Male		75%
Median age (range)		50 years (20-83)
Ethnicity	Asian	77%
	Caucasian	17%
	Aboriginal/Torres Strait or Pacific islander	3%
	African	2%
	Other	1%
Overseas born (non-Australian born)		93%
Known family history of liver disease		47%
Estimated mode of transmission	Birth/Early childhood	66%
	Horizontal	7%
	Other	27%
AVT	1st regimen	39%
	2nd regimen	27%
	3rd regimen	16%
	≥4th regimen	18%

Table 2. Current AVT Regimen

Current AVT Regimen[a]	% (N=754)	Mean duration of current regimen ± SD (months)
Entecavir 0.5mg	25%	14 ± 5.7
Lamivudine	23%	48 ± 27.2
Adefovir + lamivudine	23%	19 ± 15.7
Entecavir 1.0 mg	10%	23 ± 15.2
Adefovir	8%	38 ± 21.9
Adefovir + entecavir[b]	4%	11 ± 7.6
Tenofovir DF + lamivudine	3%	13 ± 12.9
Tenofovir DF	2%	20 ± 9.3
Telbivudine	1%	29 ± 14.4
Adefovir + telbivudine	<1%	12
Tenofovir DF + entecavir 0.5 mg	<1%	9
Entecavir 1.0 mg + lamivudine	<1%	15 ± 0.4

a. Combinations reported if > 3 months duration
b. 28/30 received entecavir 1.0 mg; 1/30 received 0.5 mg entecavir; 1/30 dose of entecavir not reported

Table 3. Clinical CHB Status of Patients Receiving AVT

Parameter		HBV DNA Detectable (>351 IU/mL)	HBV DNA Undetectable (≤351 IU/mL)
		208/741 (28%)	533/741 (72%)
% with ≥1 drug resistance mutation detected		64%	N/A
Advanced fibrosis/cirrhosis[a]		25%	42%
Mean ALT (IU/L)		42	31
ALT	≤40 IU/L	67%	81%
	≤30 IU/L men/ ≤19IU/L women[b]	38%	51%

a. Biopsy data only available for 506 patients; 132/208 (63%) HBV DNA detectable & 364/533 (68%) HBV DNA undetectable. Most recent biopsy information collected.
b. Using The Royal College of Pathologists, Australia normal range ≤ 40 U/L. Central Lab normal range <50 U/L
c. Prati D et al. Updated Definitions of Healthy Ranges for Alanine Aminotransferase Levels. Ann Intern Med 2002; 137: 1-9

Table 4. Clinical and Virological Characteristics of Patients with and without Drug-resistance Mutation

Clinical and Virologic Characteristics	HBV DNA detectable			HBV DNA Undetectable (N=533)
	All (N = 208)	Drug-resistance mutation(s) (N=134)	No drug-resistance mutation(s) (N=74)	
HBeAg positive	63%	60%	69%	20%
Mean HBV DNA (IU/mL) ± SD	$5.8 \times 10^5 \pm 3.5 \times 10^6$	$5.4 \times 10^5 \pm 2.4 \times 10^6$	$6.6 \times 10^5 \pm 4.9 \times 10^6$	N/A
Mean ALT (IU/L) ± SD	42 ± 45	44 ± 54	37 ± 22	31 ± 16
1st oral AVT regimen	39%	19%	42%	43%
2 prior AVT regimen	27%	27%	28%	27%
3 prior AVT regimen	16%	21%	20%	15%
≥ 4 prior AVT regimen	18%	34%	9%	14%
Prior oral AVT	61%	81%	58%	57%
Mean duration of current oral AVT (months)	21 ± 22	23 ± 25	16 ± 15	27 ± 22
Mean duration of cumulative oral AVT (months)	54 ± 31	64 ± 26	35 ± 30	50 ± 31
Patient assessed non-compliance (≥1 dose missed in last 28 days)	14%	15%	12%	10%

Table 5. Most Common Drug-Resistance Mutations

Mutations[a]	Prevalence in viraemic patients (N=208)	Proportion of patients receiving active AVT regimen[b]
L180M + M204V/I	32 (15%)	18 (56%)
M204V/I	27 (13%)	12 (44%)
A181V/T	14 (7%)	4 (29%)
E164D + V173L + L180M + M204V/I	10 (5%)	8 (80%)
L80V/I + L180M + M204V/I	9 (4%)	6 (67%)
N236T	8 (4%)	2 (25%)
L180M +T184A/I/L/S + M204V/I	7 (3%)	5 (71%)
L80V/I + M204V/I	5 (2%)	4 (80%)
A181V/T + N236T	5 (2%)	2 (40%)
L180M + S202G + M204V/I	4 (2%)	0 (0%)
P120T + L180M + M204V/I	2 (1%)	1 (50%)
L180M + T184I + S202G + M204V/I	2 (1%)	1 (50%)

49% (60/123) patients with drug resistance mutations receiving inactive/sub-optimal AVT
M204V/I reported in 80% of patients with drug resistance mutations

a. Mutations reported in only 1 patient not presented
b An active regimen is one to which the reported mutations are fully susceptible, i.e. it contains one or more AVT to which the mutations do not confer either resistance or reduced susceptible (ref: VIDRL classifications for HBV mutations).

Table 6. Patients with Genotypic Resistance to Current Regimen

Current AVT	% patients receiving an inactive/ sub-optimal AVT regimen[a]
Entecavir 1.0mg + lamivudine	1/2 (50%)
Entecavir 1.0mg	18/74 (24%)
Adefovir	8/60 (13%)
Telbivudine	1/8 (13%)
Lamivudine	19/170 (11%)
Adefovir + lamivudine	5/165 (3%)
Entecavir 0.5mg	5/190 (3%)
Adefovir + entecavir (0.5 or 1.0mg[2])	0/30 (0%)
Tenofovir + lamivudine	0/26 (0%)
Tenofovir	0/17 (0%)
Adefovir + telbivudine	0/1 (0%)
Tenofovir + entecavir 0.5mg	0/1 (0%)

8% (57/741) of patients are receiving an inactive/sub-optimal AVT

a. Presence of a mutation or combination of mutations that confers reduced susceptibility/resistance to AVT regimen
b. 28/30 received 1.0 mg entecavir; 1/30 received 0.5 mg entecavir; 1/30 dose of entecavir not reported

Conclusions

- **CHB patients receiving AVT in Australia are predominantly**
  - **Overseas born (93%)**
  - **Asian ethnicity (77%)**
  - **HBeAg negative (68%)**
  - **Male (75%)**
- **39% of patients were receiving their first AVT regimen**
- **18% had received ≥4 different regimens**
- **28% of patients had a detectable viral load (>351 IU/mL)**
  - **The majority (64%) of these patients had at least one drug resistance mutation**
- **Of those with drug resistance mutations**
  - **Approximately 49% are not receiving active therapy**
  - **The majority are**
    - **HBeAg positive (60%)**
    - **Treatment experienced, with approximately 1/3 receiving at least 4 regimens**
    - **Cumulative treatment of approximately 5 years.**
- **8% of all patients receiving oral antiviral therapy are receiving sub-optimal or inactive therapy**
  - **29% of patients with detectable HBV DNA**
- **These data support:**
  - **The recommendation that genotypic resistance testing be considered in all patients who are HBV DNA positive**
  - **That resistance testing should form part of the regimen selection process;**
  - **That there is an urgent need for better education or referral advice in the treatment of CHB**

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