PRESENCE OF rtA194T AT BASELINE DOES NOT REDUCE EFFICACY TO TENOFOVIR (TDF) IN PATIENTS WITH LAMIVUDINE (LAM)-RESISTANT CHRONIC HEPATITIS B

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1. Background

- Tenofovir (TDF) is a potent oral nucleotide analogue of adenosine.
- TDF has demonstrated safety and efficacy in pivotal studies for the treatment of chronic hepatitis B.[1,2]
- Antiviral-resistant mutations associated with virologic breakthrough on TDF therapy have not been fully characterized.
- 2/43 (5%) HIV-HBV coinfected patients treated with TDF plus lamivudine after 48-77 weeks were found to have a novel HBV pol mutation, rtA194T (alanine to threonine) in association with L180M + M204V.
- *In vitro* phenotypic analysis of clones harboring A194T+L180M+M204V revealed 2 to 10 fold increase in IC_{50} to TDF compared to wild type virus. [3,4]
- *In vitro* susceptibility of A914T substitution was examined in a separate study.
- A194T alone did not cause significant reduction in the TDF susceptibility.
- Combination of A194T/L180M/M204V unlikely to cause clinical resistance to TDF in HBV patients.
- However, no polymerase mutations associated with tenofovir resistance have been described to date in HBV monoinfected patients.
- Clinical significance of rtA194T substitution is unknown in chronic hepatitis B patients.

2. Aim

To determine the effect of rtA194T on treatment response to TDF 300 mg daily in patients with LAM-resistant HBV.

3. Patients and Methods

- Adult HBV patients receiving oral antiviral therapy at University Health Network Liver Clinics (Toronto, Canada) were monitored for genotypic antiviral resistance.
- Routine bloodwork, HBV serology and HBV DNA levels were measured every 3 months on treatment.
- Resistance testing was performed on all patients who developed virologic breakthrough.
  - *confirmed rise in HBV DNA by > 1 log IU/mL compared to nadir*
  - *in those who failed to achieve undetectable HBV DNA 6 months after starting antiviral therapy.*
- Genotyping and detection of resistance mutations were performed using a line probe assay.
  - *InnoLiPA HBV DR v3 (InnoGenetics, Ghent, Belgium)*
- HBV DNA was measured using real-time PCR (Roche, TaqMan 48, LLQ 12 IU/mL).

1. Marcellin P, Jacobson I, Habersetzer F, *et. al.* Tenofovir disoproxil fumarate (TDF) for the treatment of HBeAg-negative chronic hepatitis B: week 72 TDF data and week 24 adefovir dipivoxil switch data (Study102). 43rd Annual *Meeting of the European Association for the Study of the Liver (EASL)*, Milan Italy, April 23-27, 2008, Oral presentation #1602.
2. Heathcoate J, George J, Gordon S, *et. al.* Tenofovir disoproxil fumarate (TDF) for the treatment of HBeAg-positive chronic hepatitis B: week 72 TDF data and week 24 adefovir dipivoxil switch data (Study 103). *43rd Annual Meeting of the European Association for the Study of the Liver (EASL)*, Milan Italy, April 23-27, 2008, Oral presentation #1593.
3. Delaney W, Ray A, Yang H, *et. al.* Intracellular metabolism and in vitro activity of tenofovir against hepatitis B virus. *Antimicrobial Agents and Chemotherapy*, July 2006 50(7): 2471–2477.
4. Sheldon J, Camino N, Rodés B, et. al. Selection of hepatitis B virus polymerase mutations in HIV-coinfected patients treated with tenofovir. Antiviral Therapy 2005 10:727–734.

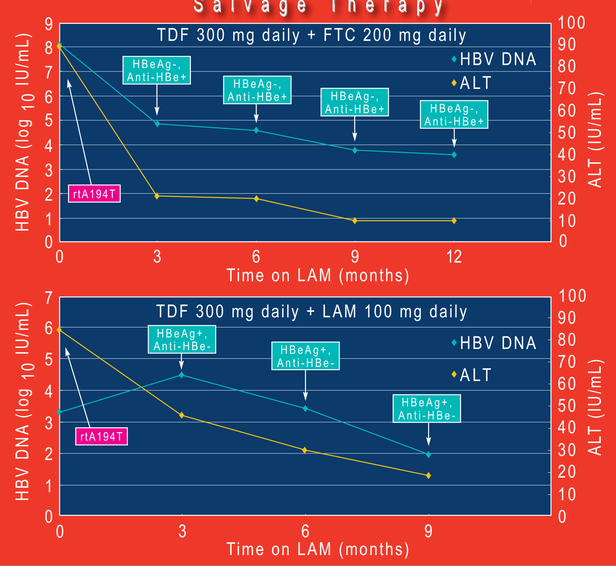
4. Results

Patient Characteristics (N = 10)	
Mean Age (years)	48 ± 17
Male : Female	7:3
% HBeAg-positive	40
Mean ALT (U/L)	52 ± 34
Mean HBV DNA (IU/mL)	5.5 ± 2.5
Mean Platelets (Bil/L)	207
% Cirrhosis (on ultrasound or liver biopsy)	70
HBV genotype (A/B/C/D)	2/3/3/2
Mean duration of lamivudine (months)	43 ± 22

Patient	Genotype	L80V	V173	L180M	M204V/I	A194T
1	C	+	-	+	+	Present
2	B	+	-	+	+	Mixed
3	D	-	+	+	+	Present
4	D	+	-	+	+	Present
5	A	+	-	+	+	Mixed
6	B	-	-	+	+	Present
7	B	-	-	+	+	Present
8	C	-	-	+	+	Present
9	C	-	-	+	+	Mixed
10	A	-	-	+	+	Present

- Of the 283 consecutive treatment-esperienced adult patients with chronic hepatitis B tested for antiviral resistance, 10 (3.5 %) were found to harbour rtA194T.
- rtA194T was found in association with rtL180M + rtM204V/I in all 10 patients.

Salvage Therapy



Patient	Treatment	Mean Duration (months)	Last ALT (IU/mL)	Baseline HBV DNA (log 10 IU/mL	Last HBV DNA (log 10 IU/mL
3	LAM + ADV	15	31	3.6	1.6
4	LAM + TDF	9	28	6.1	1.3
5	LAM + TDF	6	37	6.4	1.1
6	TDF alone	10	24	4.3	<1.0
8	FTC + TDF	12	51	5.9	<1.0
9	TDF alone	6	73	4.5	2.4
10	TDF alone	9	24	5.3	<1.0

LAM: lamivudine 100 mg daily
ADV: adefovir 10 mg daily
TDF: tenofovir 300 mg daily
FTC: emtricitabine 200 mg daily

5. Summary

- rtA194T detected in 10 TDF-naïve HBV patients with lamivudine-resistant CHB.
  - *Always in association with L180M + M204V/I*
  - *Usually as pure viral species or mixed population*
- TDF alone or in combination used as salvage therapy in 7 patients.
  - *Mean treatment of 9.6 months*
  - *HBV DNA undetectable in 4 patients*
  - *ALT normalized in 5 patients*

6. Conclusions

- rtA194T does not appear to be associated with reduced viral suppression or efficacy among LAM-resistant HBV patients salvaged with TDF in short term follow-up.
- These findings suggest rtA194T may represent a viral plymorphism or a LAM compensatory mutation rather than a signature TDF mutation.
- Further clinical studies are required to fully characterize antiviral substitutions associated with TDF resistance.

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