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TENOFOVIR (TDF) IS EFFECTIVE IN LAMIVUDINE (LAM)-RESISTANT CHRONIC HEPATITIS B PATIENTS WHO HARBOUR rtA194T AT BASELINE

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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]
- No signature resistance mutations have been identified in patients receiving 3 years of continuous TDF therapy.[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 rtA194T (alanine to threonine) in association with L180M + M204V.[3]
- An *in vitro* study of HBV constructs harbouring A194T+L180M+M204V showed reduced viral replication efficacy and increase in fold-resistance to tenofovir.[4]
- However, *in vitro* susceptibility of A914T examined in other studies yielded contradictory results.[5]
- The clinical significance of rtA194T substitution in chronic hepatitis B patients is unknown.

1. Marcellin P. *et. al.* Tenofovir Disoproxil Fumarate versus Adefovir Dipivoxil for Chronic Hepatitis B. *NEJM* 2008; 359(23): 2442 - 2455.
2. Heathcote E. J. *et. al.* Two Year TDF Treatment and ADV Switch Data in HBeAg-Positive Patients With Chronic Hepatitis B (Study 103). *AASLD* 2008, Abstract # 157.
3. Sheldon J. *et. al.* Selection of hepatitis B virus polymerase mutations in HIV-coinfected patients treated with tenofovir. *Antivir. Ther.* 2005 (10): 727–734.
4. Amini-Bavil-Olyaee S. et. al. The rtA194T polymerase mutation impacts viral replication and susceptibility to tenofovir in hepatitis B e-antigen-positive and hepatitis B e-antigen-negative hepatitis B virus strains. *Hepatology* 2009 (49):1158-1165.
5. Qi et al, *Int Molec HBV*, Sept 2005, Germany.

2. Aim

To determine the effect of rtA194T on treatment response to TDF 300 mg daily alone or in combination with other antiviral agents in patients with lamivudine-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).

4. Results

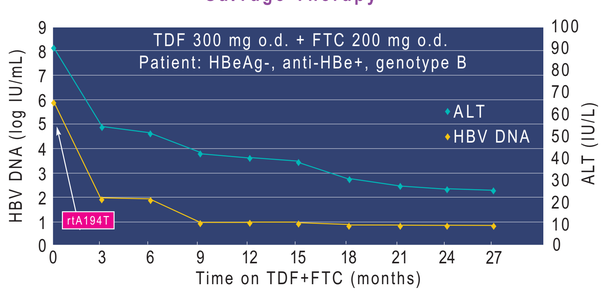
Patient Characteristics (N = 12)

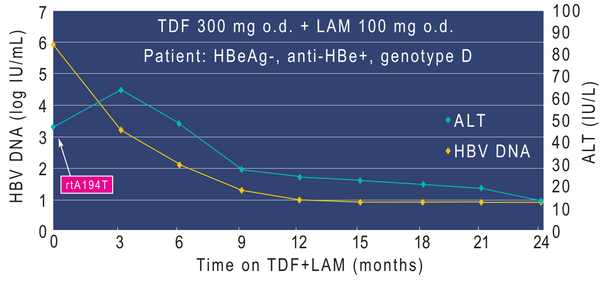
Mean Age ± SD (years)	49 ± 20
Male : Female	8:4
% HBeAg-positive	42
Mean ALT ± SD (U/L)	52 ± 34
Mean HBV DNA ± SD (IU/mL)	5.5 ± 2.3
Mean Platelet Count ± SD (bil/L)	214 ± 68
% Cirrhosis (on US or liver biopsy)	42
% HBV genotype (A/B/C/D)	17/33/33/17
Mean duration of LAM (months) ± SD prior to salvage	36 ± 26

SD: standard deviation; US: ultrasound

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
11	B	-	-	-	-	Mixed
12	C	+	-	-	-	Present

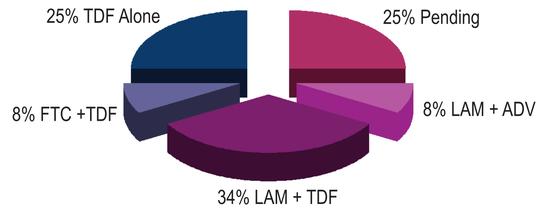
Salvage Therapy





Patient	Treatment	Duration (Months)	Baseline HBV DNA (log IU/mL)	Last HBV DNA (IU/mL)	Last ALT (IU/L)
3	LAM + ADV	30	3.6	<12	30
4	LAM + TDF	26	6.1	UND	13
5	LAM + TDF	21	6.4	UND	35
6	TDF alone	13	4.3	<12	55
8	FTC + TDF	27	5.9	UND	24
9	TDF alone	18	4.5	3.4 $\log_{10}$	277
10	LAM + TDF	24	4.3	UND	27
11	TDF alone	8	4.5	<12	24
12	LAM + TDF	9	7.3	<12	21

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



- Of the 950 consecutive treatment-experienced adult patients with chronic hepatitis B tested for antiviral resistance, 12 (1.2 %) were found to harbour rtA194T.
- rtA194T was found in association with rtL180M + rtM204V/I in all 10/12 (83%) patients.
- After detection of LAM-resistant mutation, salvage therapy was started in 9/12 (75%) patients.

5. Summary

- rtA194T detected in 12 TDF-naïve HBV patients with lamivudine-resistant CHB.
  - *Amost 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 10 patients.
  - *Mean treatment of 19.5 months*
  - *HBV DNA <12 IU/mL or undetectable in 7 (88%) patients*
  - *1 patient underwent treatment for hepatocellular carcinoma and was admittedly non-compliant with TDF*
  - *ALT normalized in 6 (75%) patients*

6. Conclusions

- Contrary to *in vitro* studies, rtA194T was not associated with reduced viral suppression among LAM-resistant HBV patients salvaged with TDF alone or in combination with LAM, ADV or FTC with > 1.5 year follow-up.
- These findings suggest rtA194T may represent a viral polymorphism 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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