Poster Number
1365

61st Annual Meeting of the American Association for the Study of Liver Diseases
October 29 - November 2, 2010
Boston, Massachusetts, USA

No Resistance to Tenofovir Disoproxil Fumarate (TDF) Detected Following up to 192 Weeks of Treatment in Subjects Mono-Infected with Chronic Hepatitis B Virus

A Snow-Lampart[1], K Kitrinos[1], B Chappell[1], F Myrick[1], J Schawalder[1], E J Heathcote[2], P Marcellin[3], and K Borroto-Esoda[1]

[1]Gilead Sciences, NC, USA; [2]Toronto General Hospital, Ontario, Canada; [3]Hospital Beaujon, Clichy, France

GILEAD
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
Tel: (650)574-3000
Fax: (650)578-9264

Introduction

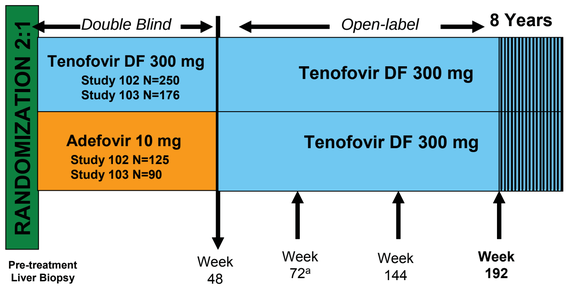
- Tenofovir disoproxil fumarate (tenofovir DF, TDF) is a nucleotide analog with potent antiviral activity in patients mono-infected with HBV and co-infected with HIV-1 and HBV
- HBV pol/RT resistance mutations have been identified following administration of other oral anti-HBV agents (lamivudine, adefovir dipivoxil, entecavir, and telbivudine)
- No amino acid substitutions associated with resistance to tenofovir DF were detected in the HBV pol/RT during the first 144 weeks of TDF treatment of HBeAg- and HBeAg+ patients in Studies 102 and 103[1]

Objectives

- To identify amino acid substitutions in the HBV pol/RT following up to 192 weeks of therapy with TDF 300 mg once daily
- To evaluate the effects of these substitutions on the clinical response to TDF monotherapy in chronic hepatitis B
- To determine whether these substitutions alter susceptibility to tenofovir using *in vitro* HBV replication assays and to evaluate the cross-resistance profile of these substitutions

Methods

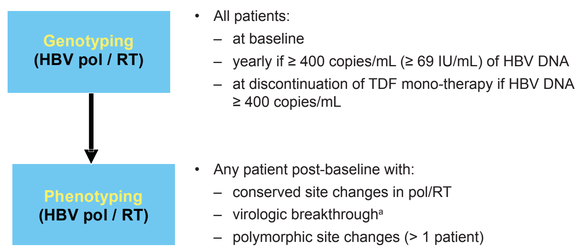
Figure 1. Design of HBeAg- Study 102 and HBeAg+ Study 103 of TDF in Chronic Hepatitis B Patients



a. Patients had the option at the discretion of the investigator to add emtricitabine (FTC) 200 mg to TDF 300 mg if confirmed to be viremic at week 72 or beyond. Of the 51eligible patients, 38 added FTC (4 in study 102, 34 in study 103) while 13 maintained TDF monotherapy

- Patients were enrolled in one of two double-blind, randomized studies of TDF [Study 102 (HBeAg-) or Study 103 (HBeAg+)]
- Genotypic analysis by population di-deoxy sequencing of serum HBV pol/RT
  - Covers AA 1-344 of pol/RT (AA 1-266 of HBsAg)
  - Able to detect AA substitutions present at ≥ 25% of viral quasispecies population
- Phenotypic analyses were conducted in HepG2 cells transiently transfected with:
  - A pool of recombinant HBV plasmid DNA derived from patient serum HBV pol/RT
- Plasma HBV DNA levels were determined by Roche COBAS TaqMan assay (LLOQ = 169 copies/mL; 29 IU/mL)

Figure 2. Virology Analysis Plan for Studies 102 and 103



a. Defined as a confirmed 1log_{10} increase in HBV DNA and/or confirmed HBV DNA ≥ 400cp/ml after having <400 cp/mL

Results

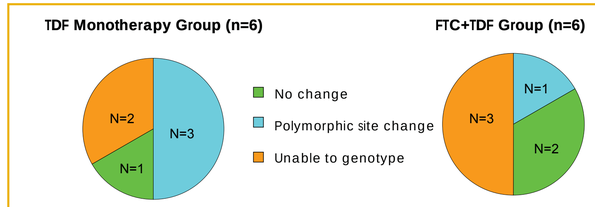
Table 1. HBeAg- and HBeAg+ Patients Evaluated During Year 4

	Study 102 (HBeAg−)		Study 103 (HBeAg+)	
	TDF-TDF	ADV-TDF	TDF-TDF	ADV-TDF
Patients Entering Year 4	218/250	109/125	130/176	71/90
Patients with HBV DNA ≥ 400 copies/mL	4	0	6	2
TDF Monotherapy	3	0	2	1[a]
FTC/TDF Combination Therapy	1	0	4	1
Completed Year 4	3	0	5	2
Discontinued During Year 4	1	0	1	0
Virologic Breakthrough	3[b]	0	0	0

Virologic Breakthrough defined as a confirmed 1 log_{10} increase in HBV DNA from nadir or confirmed HBV DNA >400 copies/mL after having been <400 copies/mL

a. Patient added FTC during Year 4; HBV DNA was <169 at Week 192
b. Two of the 3 patients with virologic breakthrough had documented history of non-adherence

Figure 3. No Patient Developed a Conserved Site Change Following up to 4 Years of TDF Therapy



The median HBV DNA level at Week 192/last on-treatment visit was 3.0log_{10} copies/mL among the 5 patients who were unable to be genotyped, the median baseline HBV DNA viral load was 9.4log_{10} copies/mL.

Figure 4. HBV DNA Profiles for the TDF Treated Patients Experiencing Virologic Breakthrough

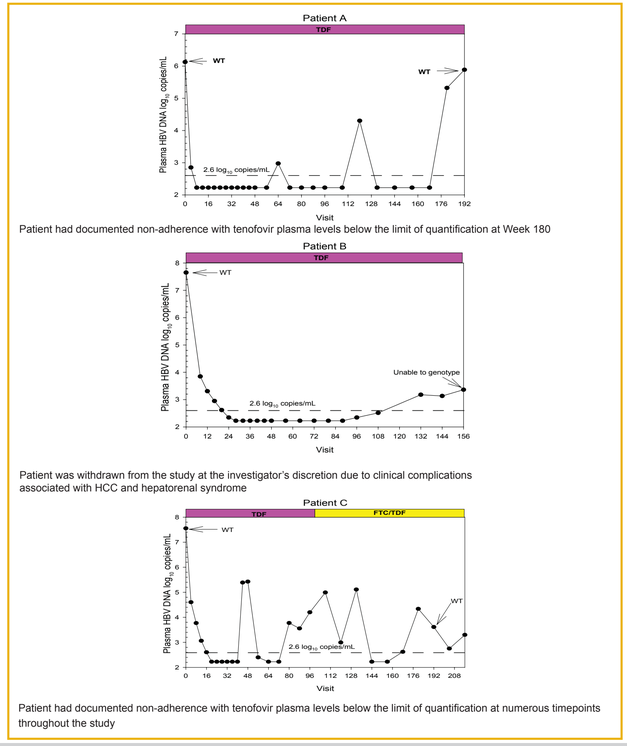


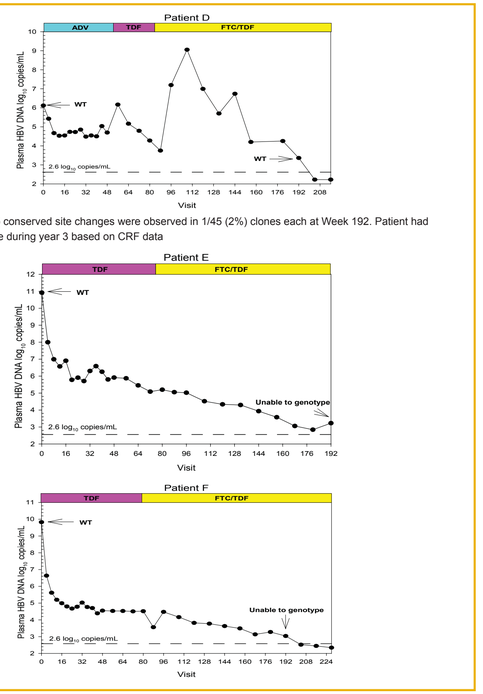
Table 2. Three HBeAg+ Patients Exhibited Persistent Viremia Through Year 4

Patient ID[a]	Treatment Arm	Viral Genotype	Baseline HBV DNA[b]	HBV DNA[b] (@ Week)	Change from Baseline in HBV pol/RT[c]
D	ADV-TDF-TVD	D	6.1	3.4 (Wk 192)	Wild-type
E	TDF-TVD	D	10.9	3.2 (Wk 192)	Unable to Genotype
F	TDF-TVD	D	9.8	3.0 (Wk 192)	Unable to Genotype

a. All patients were enrolled in study 103
b. HBV DNA is expressed in log_{10} copies/mL
c. Change from baseline in HBV pol/RT reflects genotypic changes observed at week 192/last on-study using population based di-deoxy sequencing

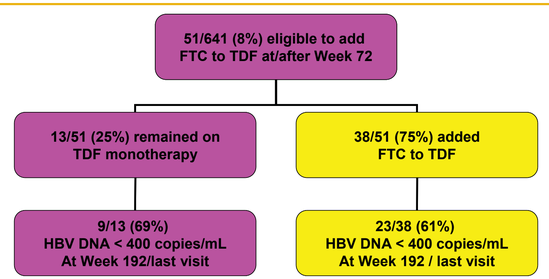
The median decline from baseline in HBV DNA among the 3 patients with persistent viremia was 6.8 log_{10} copies/mL

Figure 5. HBV DNA Profiles for the Patients Exhibiting Persistent Viremia Through Year 4



The (rtR114C and rtC188Y) conserved site changes were observed in 1/45 (2%) clones each at Week 192. Patient had documented non-adherence during year 3 based on CRF data

Figure 6. Evaluation of Adding FTC to TDF Between Weeks 72-192 and the Impact on Subsequent HBV DNA Decline



The week 192 visit is out of window or missing HBV DNA values for 2 additional patients who added FTC; both patients have undetectable HBV DNA levels at Week 180 and Week 204

Table 3. Clinical Isolates from Patients Experiencing Virologic Breakthrough Remained Sensitive to Tenofovir *in vitro*

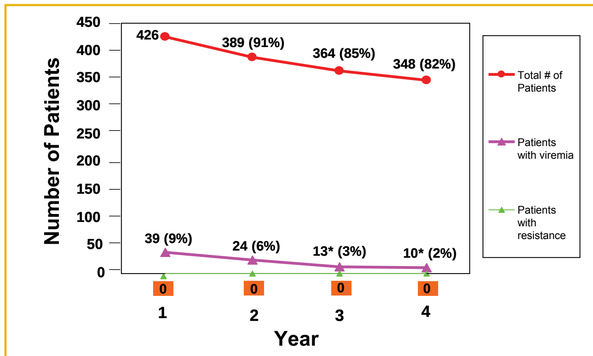
Treatment Group	Viral Isolate	Fold Change from BL[b]
TDF	Patient A	
	Week 192_pool	0.9
TDF-FTC/TDF	Patient C	
	Last on-TDF_pool	0.9
	Week 192_pool	1.3
TDF-FTC/TDF	Patient G[a]	
	Last on-TDF_pool	1.0
	Week 156_pool	1.5

Only patients with a genotypic result could be evaluated for phenotypic susceptibility, therefore patient B was not evaluated using *in vitro* analyses
a. Patient experienced unconfirmed virologic breakthrough at the time of study discontinuation, Week 156
b. Values ≤ 2-fold are not statistically significant

Results Summary

- Conserved site changes in HBV pol/RT were not observed among the 528 patients across both arms of Studies 102 and 103 during Year 4
- Polymorphic site changes observed in 4 patients
  - Represent natural polymorphic changes as observed historically among placebo-treated patients
  - The presence of these substitutions at baseline did not impact clinical response to TDF
- Virologic breakthrough observed in 3 patients
  - Associated with non-adherence in 2 cases
  - Not associated with *in vitro* resistance to tenofovir
- Persistent viremia observed in 3 patients
  - Conserved site changes were not observed in more than one clone

Figure 7. Summary of Resistance Analyses of TDF-Treated Patients Through Year 4



*Includes 7 and 5 patients on FTC+TDF at Year 3 and Year 4, respectively.

Conclusions

- **No resistance to TDF developed following up to 4 years of TDF monotherapy in 348 patients**
- **No resistance to TDF developed among 180 ADV-treated patients following up to 3 years of subsequent TDF monotherapy**
- **Virologic breakthrough was rare (<1%) and attributed to documented non-adherence in the majority of cases**
- **Persistent viremia was rare (<1%) and not associated with virologic resistance to tenofovir**
- **Patient retention remained high, 82.4% (528/641) across both arms of Studies 102 and 103**

References & Acknowledgements

1. Snow-Lampart et. al. AASLD 2009, Poster #480