Poster Number

976

59th Annual Meeting of the American Association for the Study of Liver Diseases
October 31 - November 4, 2008
San Francisco, California, USA

Cost Effectiveness Simulation Analysis of Tenofovir Disoproxil Fumarate (TDF), Lamivudine (LAM), Adefovir Dipivoxil (ADV) and Entecavir (ETV) in HBeAg Negative Patients with Chronic Hepatitis B (CHB) in the USA

B Deniz[1] and F Everhard[2]

[1]United BioSource Corporation, Lexington, MA, USA; [2]Gilead Sciences, Inc., Foster City, CA, USA

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

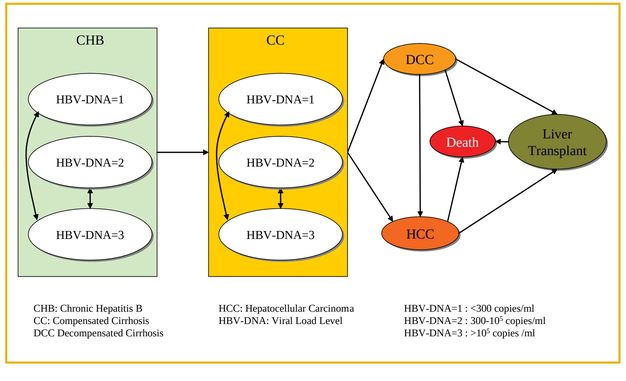
Objective

- To estimate costs and health outcomes of initiating treatment with tenofovir disoproxil fumarate, lamivudine, adefovir dipivoxil or entecavir as 1st line therapy in patients with HBeAg negative CHB in the US

Methods

- A Markov Model was developed to estimate incidence and costs of CHB-related complications according to HBV-DNA viral levels achieved with different hepatitis B (HBV) treatments over time (Figure 1)
- Four cohorts of 1,000 patients with chronic hepatitis B infection are defined based on the following initial HBV treatment:
  1) tenofovir disoproxil fumarate (TDF) cohort
  2) adefovir dipivoxil (ADV) cohort
  3) entecavir (ETV) cohort
  4) lamivudine (LAM) cohort
- Patients in each cohort are associated with a level of HBV-DNA and risk of developing resistance specific to their initial treatment. Patients who develop resistance are assumed to switch to specific mono and combination 2nd line HBV therapies reflecting recommendations from the 2008 Treatment Algorithm for the Management of Chronic Hepatitis B Virus Infection in the United States[1]
- During the analysis, incidence of compensated cirrhosis (CC), decompensated cirrhosis (DCC) and hepatocellular carcinoma (HCC) are estimated for each cohort based on proportion of patients exposed to different HBV-DNA viral levels every year
- Costs of complications are calculated based on the predicted number and type of complications that occurred every year in each cohort. Costs of HBV treatments are calculated based on different HBV treatments used as initial and 2nd line treatment every year in each cohort
- Clinical information on HBV-DNA viral levels and resistance rates for TDF and ADV are based on the Gilead-sponsored study GS-US-174-0102 in HBeAg negative patients with CHB, and on published literature for ETV, LAM and 2nd line therapies. Risk of CHB-related complications and mortality are based on published literature, including EURO HEP study, EASL guidelines REVEAL study, and NICE health technologic assessment reports
- All HBV treatment costs are based on wholesaler acquisition costs. Utility scores and costs associated with CHB-related complications are obtained from published literature and are reflective of 3rd party payers. Both health outcomes and costs are discounted at 3% per year
- A cost-effectiveness analysis was performed by comparing the 4 cohorts of patients based on total cumulated complications, HBV treatment costs and cumulated quality adjusted life years (QALYs)
- A probabilistic sensitivity analysis was conducted to identify which initial HBV treatment option which is cost-saving and cost-effective compared to LAM

Figure 1. Schematic Diagram of Markov CHB Model



Methods (cont'd)

Table 1. Viral Suppression Rates by HBV Treatment

HBV-DNA levels at 48 weeks	TDF[1]	ADV[1]	ETV[2]	LAM[2]
< 300 copies/mL	92%	59%	91%	72%
< 10^5 copies/mL	95%	85%	96%	87%

Table 2. Resistance Rates by HBV Treatment

Annual Resistance Rate	TDF[2]	ADV[3]	ETV[4]	LAM[5]
Year 1	0.0%	0.0%	0.1%	23.0%
Year 2	0.0%	3.0%	0.3%	23.0%
Year 3	*	5.0%	0.7%	9.0%
Year 4	*	6.0%	0.1%	16.0%

* Assume similar resistance rate to entecavir

Table 3. Utility Scores by Disease Stage[6]

Disease Stage	Utility Score
Chronic HBV	0.81
Compensated Cirrhosis	0.82
Decompensated Cirrhosis	0.36
HCC	0.41
Seroconversion	0.99
Liver Transplantation	0.72

Table 4. Mortality Rates by Disease Stage

Mortality Rate	Annual Risk
Chronic Hepatitis B	Age-dependant
Compensated Cirrhosis[8]	5%
Decompensated Cirrhosis[9]	22%
Hepatocellular Carcinoma[10]	54%
Following Liver Transplantation[11]	13%

Table 5. HBV Treatment and Complication Costs

HBV Treatments	Cost	Unit
TDF	$18.41	per day
ADV	$21.46	per day
ETV	$22.73	per day
LAM	$9.44	per day
Complications		
Chronic HBV	$1,019	state/year
Compensated Cirrhosis	$1,148	state/year
Decompensated Cirrhosis	$23,900	state/year
Liver Cancer	$33,260	state/year
Liver Transplantation		
- Procedure 1st year	$182,268	procedure
- Year follow-up	$84,082	year
Death	$6,486	occurence

Table 6. Parameters Used in Probabilistic Sensitivity Analysis

	Distribution type	Parameters
Transition probabilities from one health state to another	Beta	Standard Error: 10% of the mean value
Utility scores by health state	Beta	Standard Error: 5% of the mean value
Mortality Risks by health state	Beta	Standard Error: 10% of the mean value
All costs (except HBV treatments)	Log Normal	Standard Error: 20% of the mean value
Cost of 2nd line HBV therapies for		Average (Min – Max) in US$ per day
Patients with LAM resistance	Uniform	28.9 (27.8 – 30.9)
Patients with ADV resistance	Uniform	30.7 (22.7 – 44.2)
Patients with ETV resistance	Uniform	30.6 (18.4 – 44.2)
Patients with TDF resistance	Uniform	25.4 (22.7 – 28.0)

Results

- Complication rates by patient cohorts over 20-years are presented in Figure 2
- Overall cost per patient (separated as pharmacy and complication management costs) and QALYs over 20 years by patient cohorts are displayed in Table 7
- Cost-effectiveness (Cost/QALY) results comparing TDF cohort versus other treatment cohorts are presented in Table 8. TDF is associated with lower cost and higher QALYs compared to LAM and ADF. Compared to ENT, TDF provides similar QALYs for lower cost
- Probabilistic sensitivity analysis shows that, in comparison to LAM, patients who receive TDF as their 1st line treatment have a higher likelihood to have better Quality Adjusted Life Years and lower costs than patients who initiate treatment with ETV and ADV (Figure 4)

Figure 2. Complication Rates by Patient Cohort over 20 years

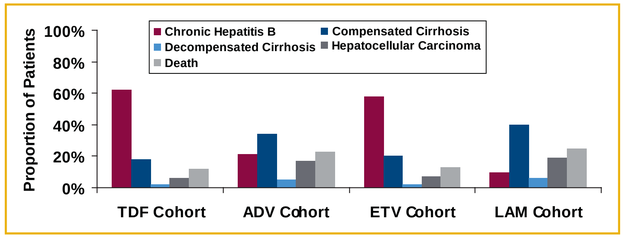


Table 7. Cost and Quality Adjusted Life Years Results over 20 Years

	TDF Cohort	ADV Cohort	ETV Cohort	LAM Cohort
Total HBV Treatments and Complications Costs:	$ 117,794	$ 138,950	$ 141,409	$ 152,336
HBV Treatments Costs (1st and 2nd lines)	$94,781	$105,449	$117,648	$101,990
Complications Costs	$23,013	$33,501	$23,761	$50,346
Quality Adjusted Life Years	10.28	9.72	10.28	8.93

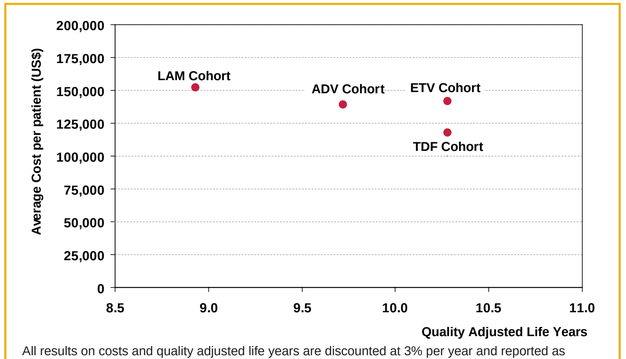
All results on costs and quality adjusted life years are discounted at 3% per year and reported as an average per patients over 20 year simulation

Table 8. Incremental Cost and Cost Per Quality Adjusted Life Year Gained

	TDF Cohort vs. ETV Cohort	TDF Cohort vs. ADV Cohort	TDF Cohort vs. LAM Cohort
Incremental Total HBV Treatment and Complication Costs	-$23,615	-$21,156	-$34,542
Incremental Quality Adjusted Life Years	0.001	0.562	1.351
Incremental cost per Quality Adjusted Life Year gained	Dominant[a]	Dominant[a]	Dominant[a]

a. Dominant means TDF cohort is expected to have higher Quality Adjusted Life Year gained at lower cost than alternative treatment cohort

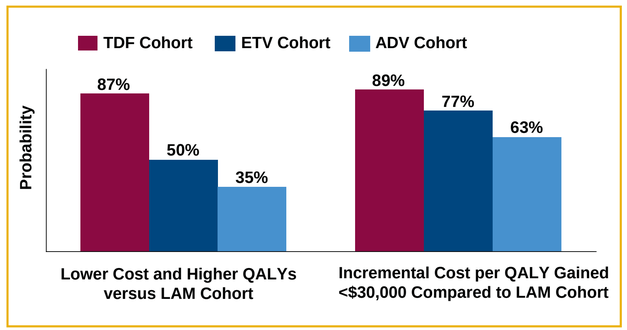
Figure 3. Cost-Effectiveness Results by Patient Cohort Over 20 Years



All results on costs and quality adjusted life years are discounted at 3% per year and reported as an average per patients over 20 year simulation

Figure 4. Probabilistic Sensitivity Analyses

- Probabilities are derived from the number of model replications which meet the defined criteria for Quality Adjusted Life Year and Cost changes
- Probabilities are based on comparisons against LAM Cohort



Conclusions

- **Initiating HBV treatment with TDF is predicted to provide better health outcomes at a lower cost than with ETV, ADV and LAM in patients with HBeAg negative chronic hepatitis B**
- **These findings are in line with the recent recommendation from the 2008 Treatment Algorithm for the Management of Chronic Hepatitis B Virus Infection that TDF be used as first-line initial treatment for CHB**

References

1. Keeffe EB et al, Clin Gastroenterol Hepatol. 2008 Aug 23
2. Marcellin P et al, AASLD 2007
3. Data On File, Gilead Sciences
4. Lai CL et al, NEJM 2006,9,354(10):1011-20
5. Hadziyannis SJ et al, Gastroenterol 2006,131(6) :1746-51
6. Colonno RJ et al. EASL 2007
7. Lai CL et al, Clin Infect Dis 2003,15,35(6):687-96
8. Gines P et al, Hepatology 1987,7(1) :122-128
9. Fattovich G et al, Am J Gastroenterol 2002,Nov,97(11) :2886-2895
10. Llovet JM et al, Lancet 2003,6,362(9399):1907-1917
11. Bismuth H et al, Semin Lever Dis 1999,19(3):311-322
12. Levy AR et al, Value Health 2008,11(3):527-38

Acknowledgements

This study is sponsored by Gilead Sciences