HBV-TAG

2021 CONFERENCE

Pharmacoeconomic Considerations in Hepatitis B Drug Development

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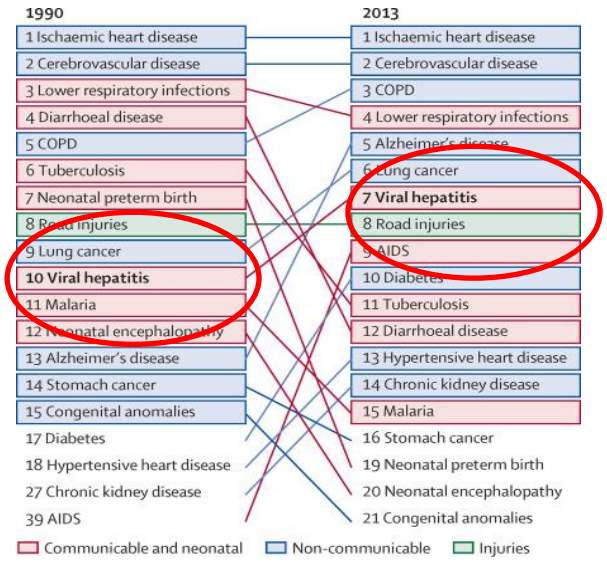
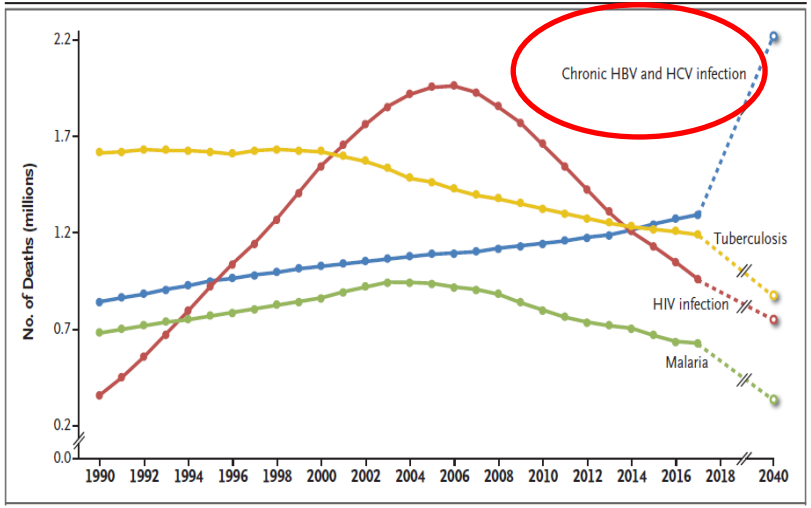
Aims

- Highlight the urgency of finding a cure for hepatitis B
- Discuss the strengths and limitations of cost-effectiveness models
- Preliminary results of cost effectiveness model for an ideal hepatitis B curative therapy

Increasing Importance of Viral Hepatitis as a Cause of Mortality





Stanaway J, et al. Lancet. 2016; Thomas D. *N Engl J Med*. 2019

Summary of Treatment Criteria for Chronic Hepatitis B

Guideline	HBeAg+		HBeAg-	
	HBV DNA IU/mL	ALT U/L	HBV DNA IU/mL	ALT U/L
AASLD 2018	>20,000	>2 x ULN or significant histological disease	>2,000	>2 x ULN or significant histological disease
EASL 2017	≥2,000	>ULN and/or at least moderate liver necroinflammation or fibrosis	≥2,000	>ULN and/or at least moderate liver necroinflammation or fibrosis
	≥20,000	>2 x ULN irrespective of fibrosis	≥20,000	>2 x ULN irrespective of fibrosis
JSH 2017	≥2,000	>ULN	≥2,000	>ULN
APASL 2015	≥20,000	Varies	≥2,000	Varies

Terrault NB et al. *Hepatology* 2018. EASL. *J Hepatol* 2017. JSH. 2017. Sarin SK, et al. *Hepatol Int* 2015.

Current Hepatitis B Antiviral Therapy

Current first line treatment:

- Entecavir
- Tenofovir DF
- Tenofovir alafenamide

Strengths:

- Tolerable and safe
- Effective in viral suppression
- Increase overall and liver-specific survival

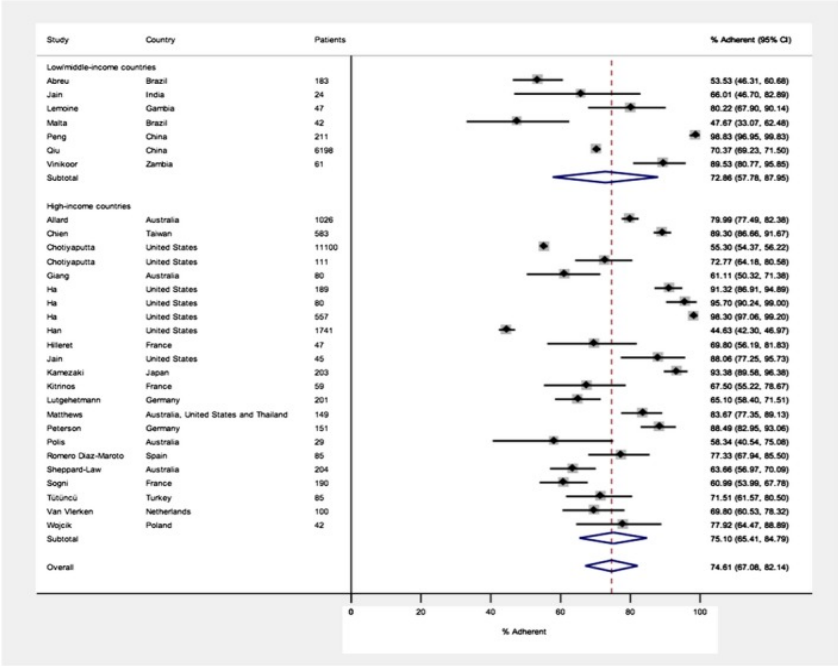
Limitations:

- Serological clearance uncommon
- No temporal endpoints
- Adherence issues with long term treatment
- Long term safety data missing

Adherence with Hepatitis B Oral Antiviral Therapy

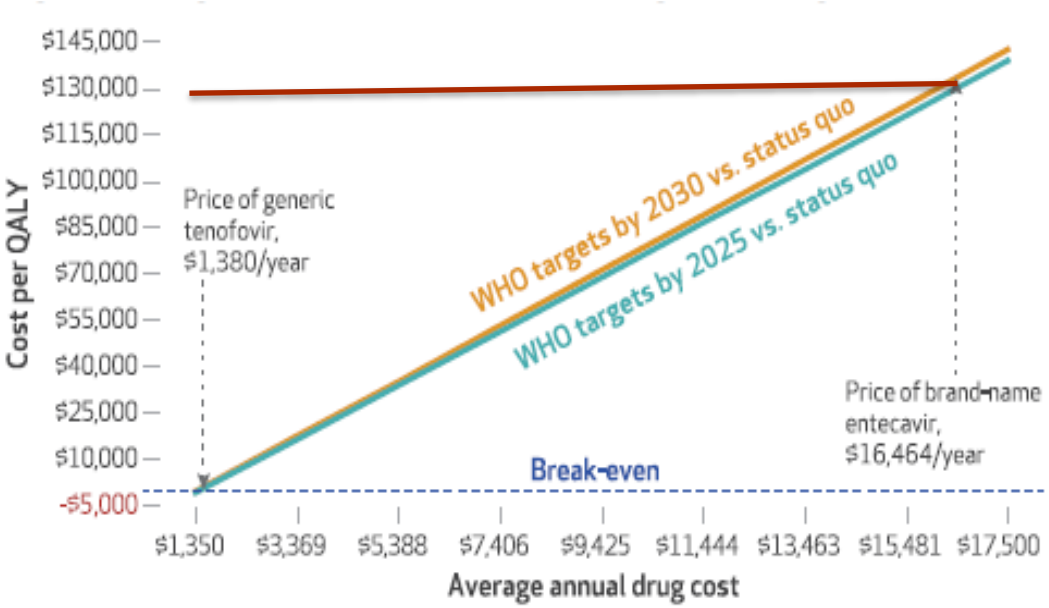
- 30 studies
- N = 23,823 patients.
- Overall treatment adherence was 74.6% (95% confidence interval [CI] 67.1%-82.1%).
- Adherence similar in high-income (75.1%; 95% CI, 65.4%-85.0%) and in low-income and middle-income settings (72.9%; 95% CI, 57.8%-88.0%).
- Barriers to adherence included forgetting, limited understanding of the importance of adherence, and change to routine.

Pooled proportion of patients adherent to HBV medication. Data points represent percentage adherence and 95% CI. Diamonds represent pooled proportions. Dotted line indicates the overall pooled proportion.



Ford N et al. *Hepatology Communications*. 2018

Cost per quality-adjusted life-year of treatment by various average annual drug costs per patient



Treatment	AWP (year)
Entecavir	$15,984
Tenofovir DF	$13,824
Tenofovir alafenamide	$17,700

QALY ~ quality-adjusted life-year; AWP ~ Average wholesale price. Accessed 5/21/2021.

Toy M, et al. *Health Affairs* 2018

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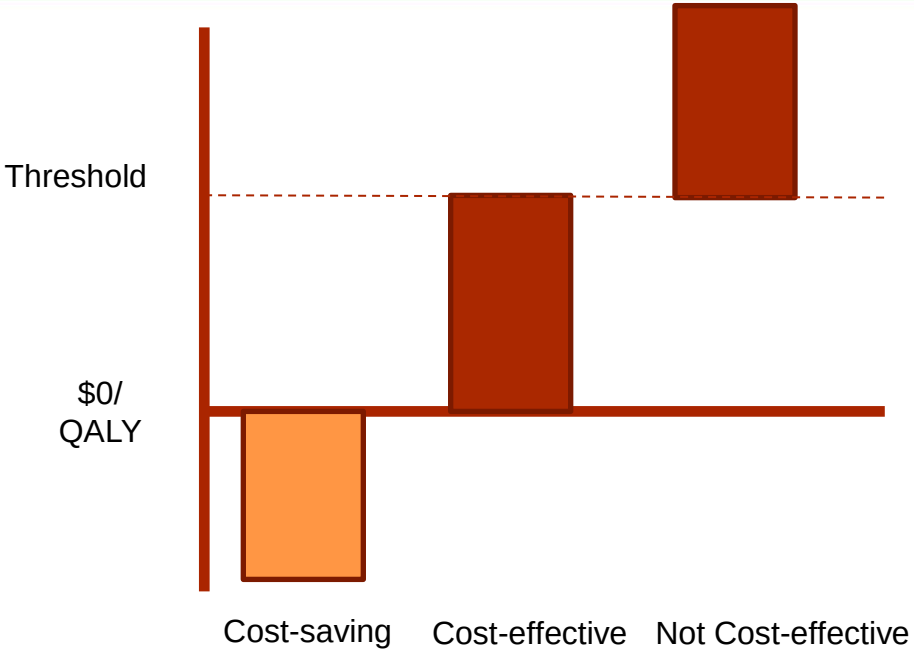
Cost-effectiveness Modeling

- Cost-effectiveness analysis is a way to examine both the costs and health outcomes of one or more interventions.
- It compares an intervention to another intervention (or status quo) by estimating how much it costs to gain a unit of a health outcome, like a life year gained or a death prevented.
- Cost-effectiveness is expressed as a ratio
  - numerator is cost associated with the health gain improved
  - denominator is a gain in health from a measure

$$\frac{\text{Costs (new – old)}}{\text{Effectiveness (new – old)}}$$

https://www.cdc.gov/policy/polaris/economics/cost-effectiveness/index.html. Accessed 5/22/21

Incremental Cost-Effective Ratio



Value (US)	ICER
High	<$50,000/QALY
Intermediate	~ $50,000 – 150,000/QALY
Low	~ $150,000/QALY

- WHO benchmark based upon a country's GDP per capita

- US GDP (2019): $65, 298 per capita
- China GDP (2019): $10,262 per capita

Abbreviations: US ~ United States; ICER ~ incremental cost-effective ratio; QALY~ quality adjust life year; WHO ~ world health organization; GDP ~ gross domestic product.

Steps in a Cost-Effectiveness Analysis

- State the problem
- Describe the conceptual model
- Define the perspective ~ society, individual, health insurance
- Identify costs and gather data to value costs
  - Quality of life years (multiply the utility value associated with a given state of health by the years lived in that state.
- Discounting
  - USD1 today is worth more than USD 1 in 10 years time
- Identify outcomes and gather data to value outcomes
- Estimate cost-effectiveness
- Do sensitivity analysis

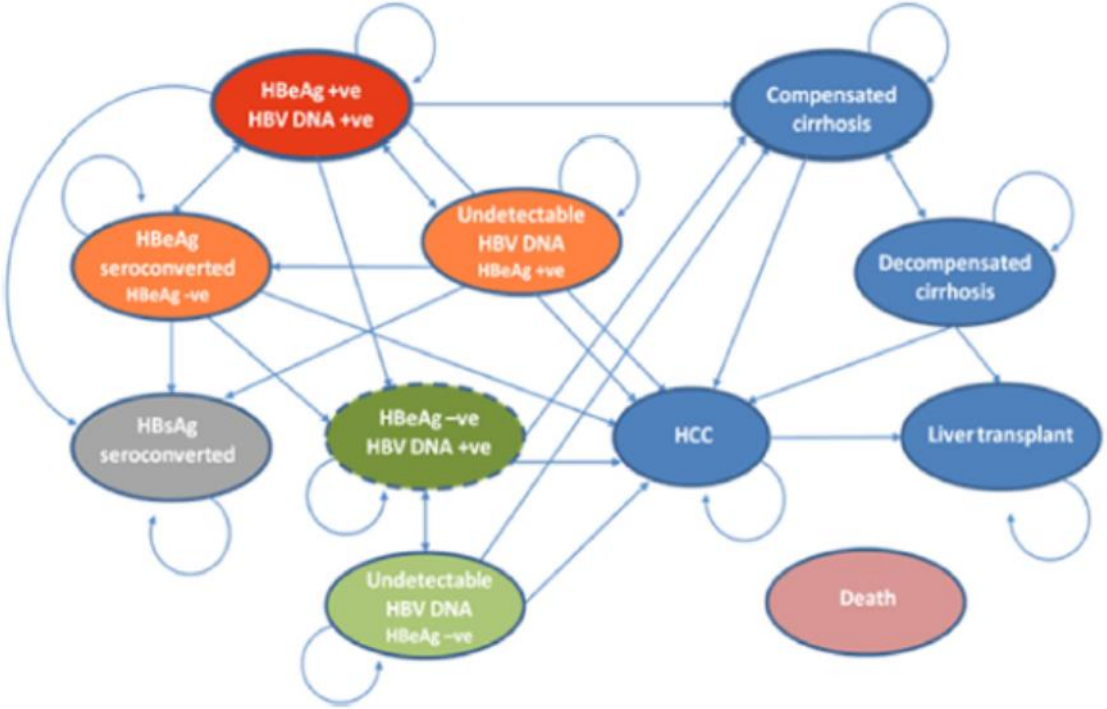
Components of Direct Costs for Hepatitis B

On/off Antiviral Therapy

- Cost of treatment
  - Antiviral therapy
  - Treatment complication
  - Monitoring
    - Laboratory/Imaging
    - Clinic visit

- Cost of disease complication
  - HCC treatment
  - Decompensated cirrhosis
  - Liver transplantation
  - Post-liver transplant care
  - Death

Natural history of Chronic Hepatitis B



Bermingham S, et al. *Value Health* 2015

Abusing “Cost-Effectiveness”

- In the absence of data on both cost
- In the absence of effectiveness ~ short and long term
- Extra-hepatic manifestations not considered
  - Stigmata of infection

Can we improve natural history estimates to tailor antiviral therapy

Demographic

- Family History of liver complications
- Hepatitis B Genotype
- Co-morbidities: alcohol
- Stigmatization

Laboratory

- HBsAg titers
- Estimates of fibrosis (ELF, APRI)

Imaging

- MRE
- Transient elastrography

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Format of Hepatitis B model

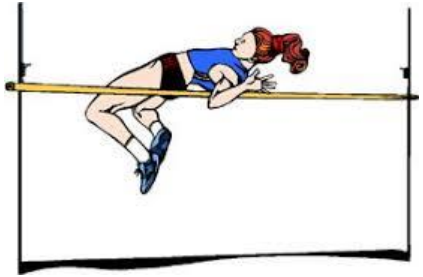
Assumptions	Bias
20 year horizon model	Unclear bias
N = 100 non-cirrhotic patients	Unclear bias
Natural history transition rates obtained from literature	Bias against new treatment
Competing causes of death not considered	Bias against new treatment
End point was lives saved (not adjusted)	Unclear bias
No discounting	Bias against new treatment
Comparative group was no treatment	Unclear bias
No adverse effect with therapy	Bias for new treatment

Incremental Cost Effective Model and NNT with Ideal Hepatitis B Curative Therapy

Base	Efficacy of New Treatment	Alive after 20 years	Routine Care Costs	Tx Costs	Cost Difference	Survival Difference	CE Ratio	NNT
Wild		71	$7,271,667					
Tx1	50% curative	78	$5,474,815	$22,000	$403,148	7	$57,593	14
	50% curative	78	$5,474,815	$25,000	$703,148	7	$100,450	14
Tx2	75% curative	83	$4,410,252	$35,000	$638,585	12	$53,215	8
	75% curative	83	$4,410,525	$41,000	$1,238,585	12	$103,215	8
Tx3	100% curative	87	$3,291,815	$48,000	$820,148	16	$51,259	6
	100% curative	87	$3,291,815	$56,000	$,1620,148	16	$101,259	6

Abbreviations: Tx ~ treatment; CE ~ cost-effective; NNT ~ number needed to treat

The Bar for Hepatitis B Modeling



- No data on efficacy, adverse, and tolerability
  - Differ for different liver disease severity or other liver disease factor
  - Natural history after HBsAg loss
- Who is the target population ~ active infection, immune tolerant
  - Tailored therapy vs treating all (Covid lesson)
- Costs of comparative drug will depend on local availability
- Can results be generalizable to across the globe

Diagnostic Criteria and Definitions for Chronic Hepatitis B

	ALT	HBV DNA	HBeAg	Liver Histology
Immune-tolerant CHB	Normal or minimally elevated ALT and/or AST	Elevated, typically > 1 million IU/mL	Positive	No fibrosis and minimal inflammation
Immune-Active CHB	Intermittently or persistently elevated ALT and/or AST	Elevated ≥ 20,000 IU/mL	Positive	Moderate-to-severe necroinflammation and with or without fibrosis
		Elevated ≥ 2,000 IU/mL	Negative	
Inactive CHB phase	Persistently normal ALT and/or AST levels	< 2,000 IU/mL	Negative	Absence of significant necroinflammation and variable levels of fibrosis

Terrault NB et al. *Hepatology* 2018.

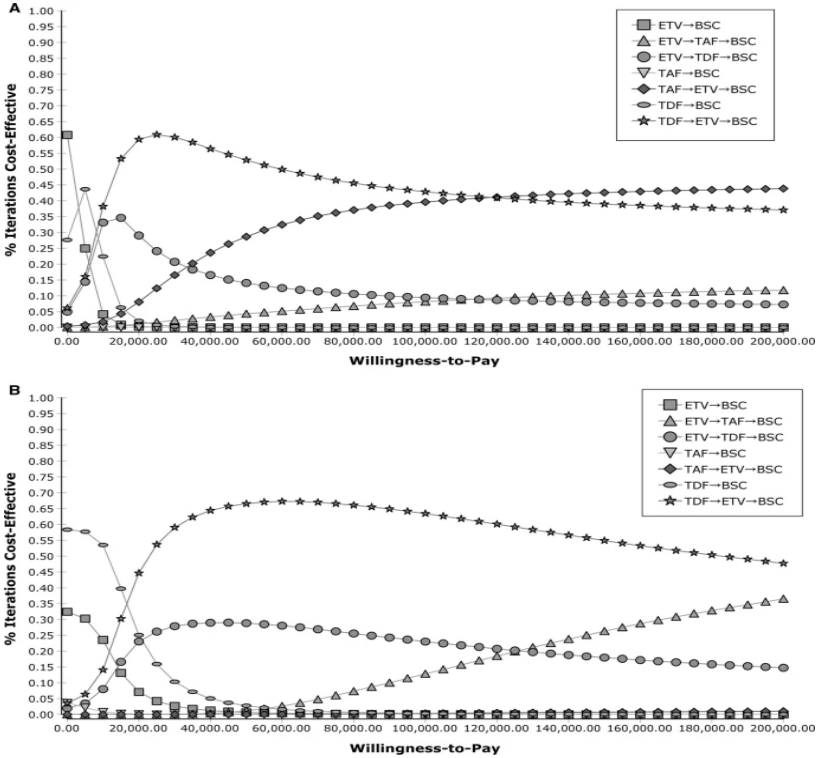
Generic Pharmacy Costs

Medications	Actual Costs/month	Acquisition Wholesale Price
Generic entecavir	$20-50	$1,333
Generic tenofovir	$15-30	$1,219

Cost-effectiveness of Hepatitis B Antiviral Agents

"..TAF is not cost effective at its current cost. A 33.4% reduction in price would be required to make it cost effective for HBeAg-positive patients with a Can$50,000 willingness-to-pay threshold."

Probabilistic sensitivity analysis



Tian F, et al. *PharmacoEconomics* 2020

Conclusions

- If curative hepatitis B therapy becomes available, the elimination of hepatitis B may more efficient than that of hepatitis C because a multi-pronged approach would be possible.

- Cost effective studies important to provide a frame of reference for major stake holders