Need for long-term evaluation of therapy in Chronic Hepatitis B

VHPB meeting Budapest 18/03/2010

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Licensed Therapy Chronic hepatitis B

Drug	Date of licence	Efficacy marker	Disease marker	Clinical outcome	Mortality
Interferon peginterferon	1991 2005	HBeAg loss	ALT normal Histology	CC: reduced cirrhosis	reduced
Lamivudine	1998	HBeAg loss	ALT normal Histology	RCT: reduction liverfailure/HCC	unchanged
Adefovir	2002	HBeAg loss	ALT normal Histology		
Entecavir	2005	HBVDNA HBeAg loss	ALT normal Histology		
Tenofovir	2008	HBVDNA HBeAg loss			

Antiviral Therapy Chronic Hepatitis B: A Systematic Review Ann Int Med 2009

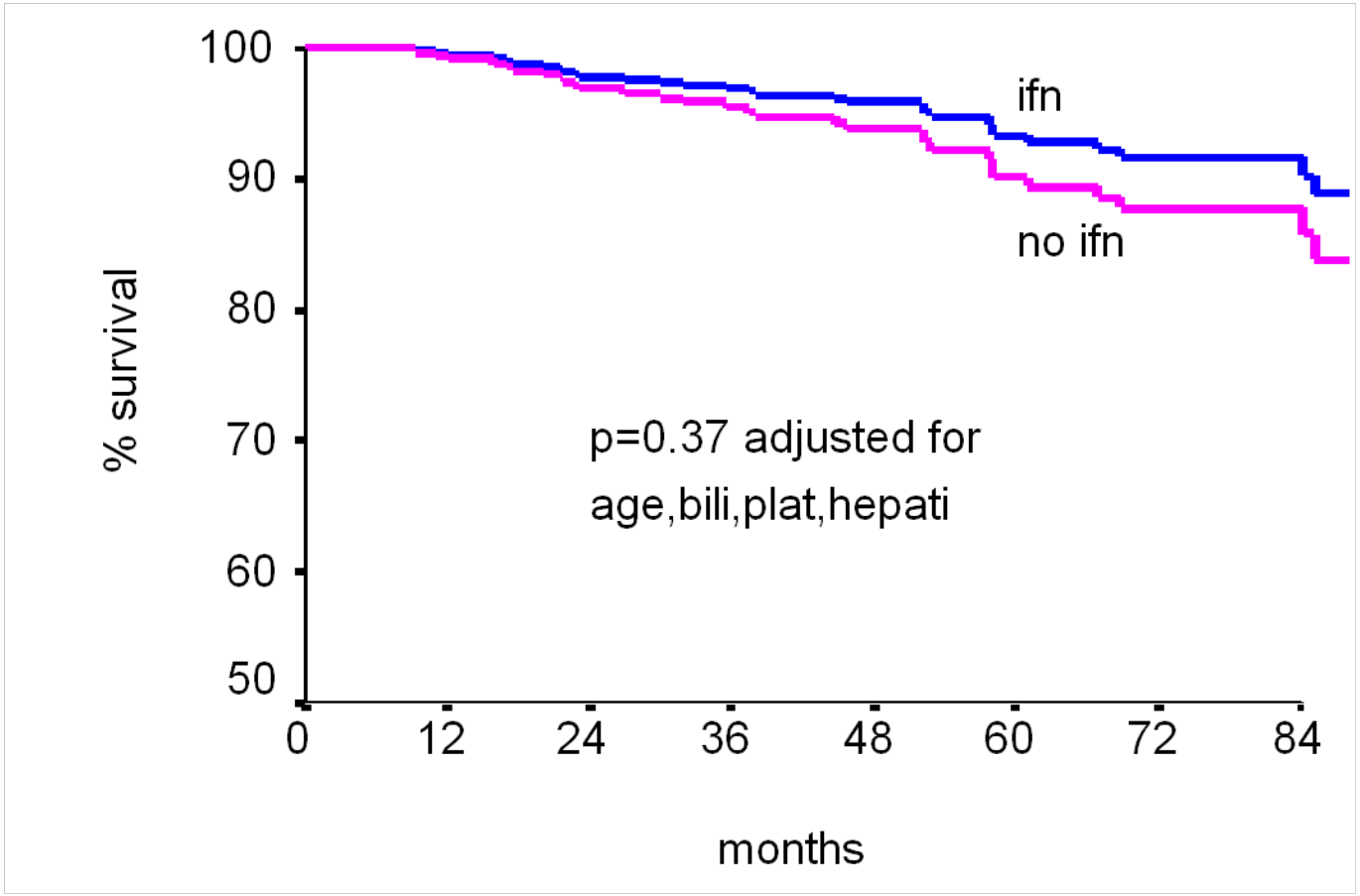
National Institutes of Health Consensus Development Conference:

- **Purpose:** To evaluate the effectiveness of antiviral therapy for adults with chronic hepatitis B infection
- **Conclusion:** Evidence was insufficient to assess treatment effect on clinical outcomes or determine whether improvements in selected intermediate measures are reliable surrogates. Future research is needed to provide evidence-based recommendations about optimal antiviral therapy in adults with chronic hepatitis B infection

Comments:

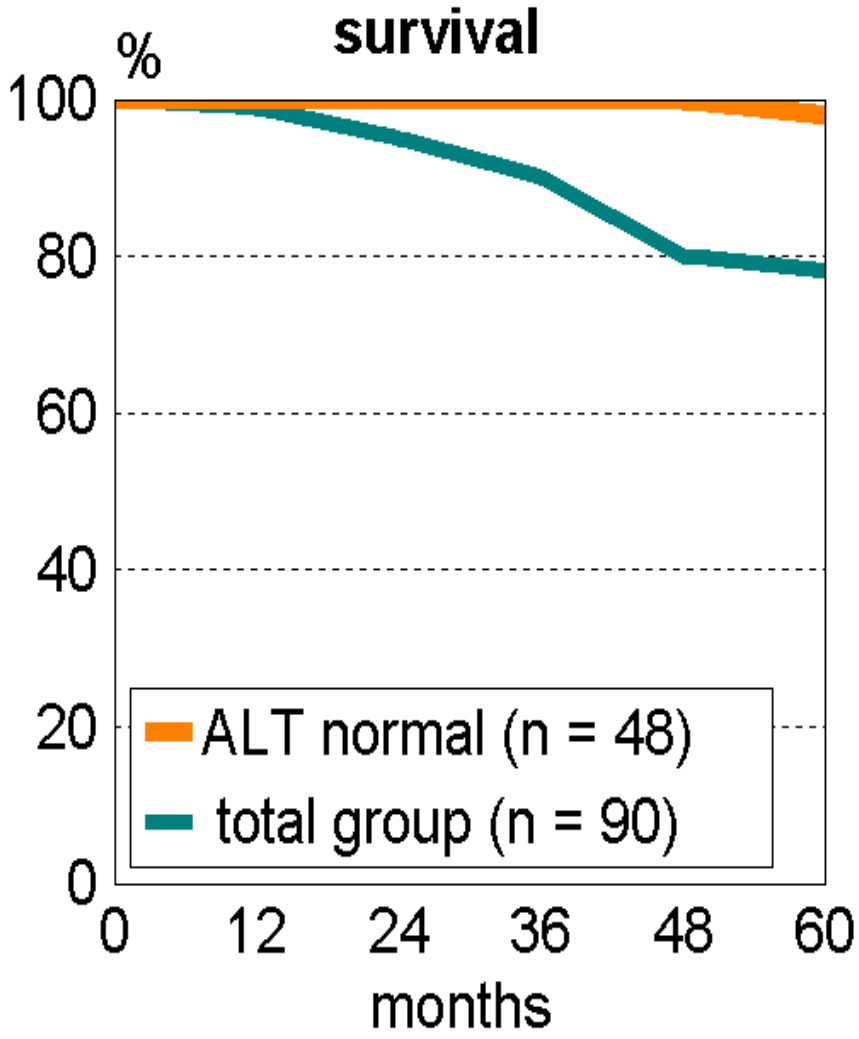
All studies: non-USA and <1000 patients were excluded

Cirrhosis & IFN



Fattovitch G Hepatology 1997

Long-term Outcome in Cirrhosis Type B prognostic factors



determinants of survival by Cox regression

age :	+
ALT normalization :	+
loss of HBeAg :	--
IFN treatment :	--

Fattovich , Hepatology 1997

Cirrhosis type B & Lamivudine
3-year outcome

Outcome measure	Lamivudine %	Placebo %	P-value
Any clinical endpoint	8	18	0,001
HCC	4	7	0,047
Child-Pugh score up > 2	3	9	0,023
Mortality (%)	**3**	**2**	**n.s**

Liaw Y-F, Sung JJY, Chow WC, Farrell G NEJM 2004

Cirrhosis type B & Lamivudine
3-year outcome

Outcome measure	Lamivudine YMDD neg	Lamivudine YMDD pos	Placebo
Number	221	209	214
HCC (%)	4	4	8
Child-Pugh score up > 2 (%)	<1	7	10
LR-Mortality (%)	1	4	2

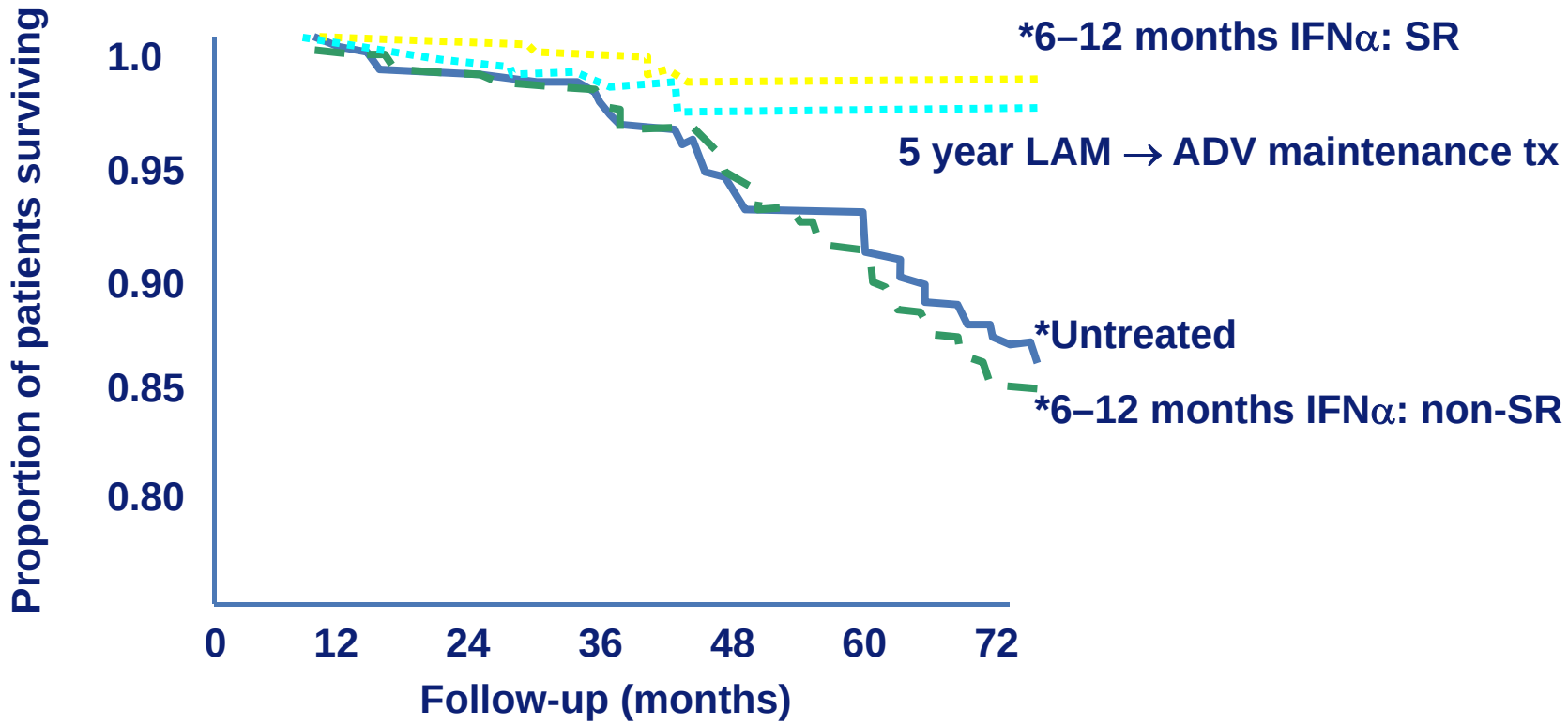
Liaw Y-F, Sung JJY, Chow WC, Farrell G NEJM 2004

HBeAg-negative cirrhosis & Lamivudine
5-year outcome

Outcome	Lamivudine response n=21	Lamivudine resistance n=22	
Decompensation	0%	32%	p<0,01
HCC	28%	43%	n.s.
Total complications	28%	64%	p<0,01
Survival	74%	74%	n.s

Lampertico P AASLD 2003

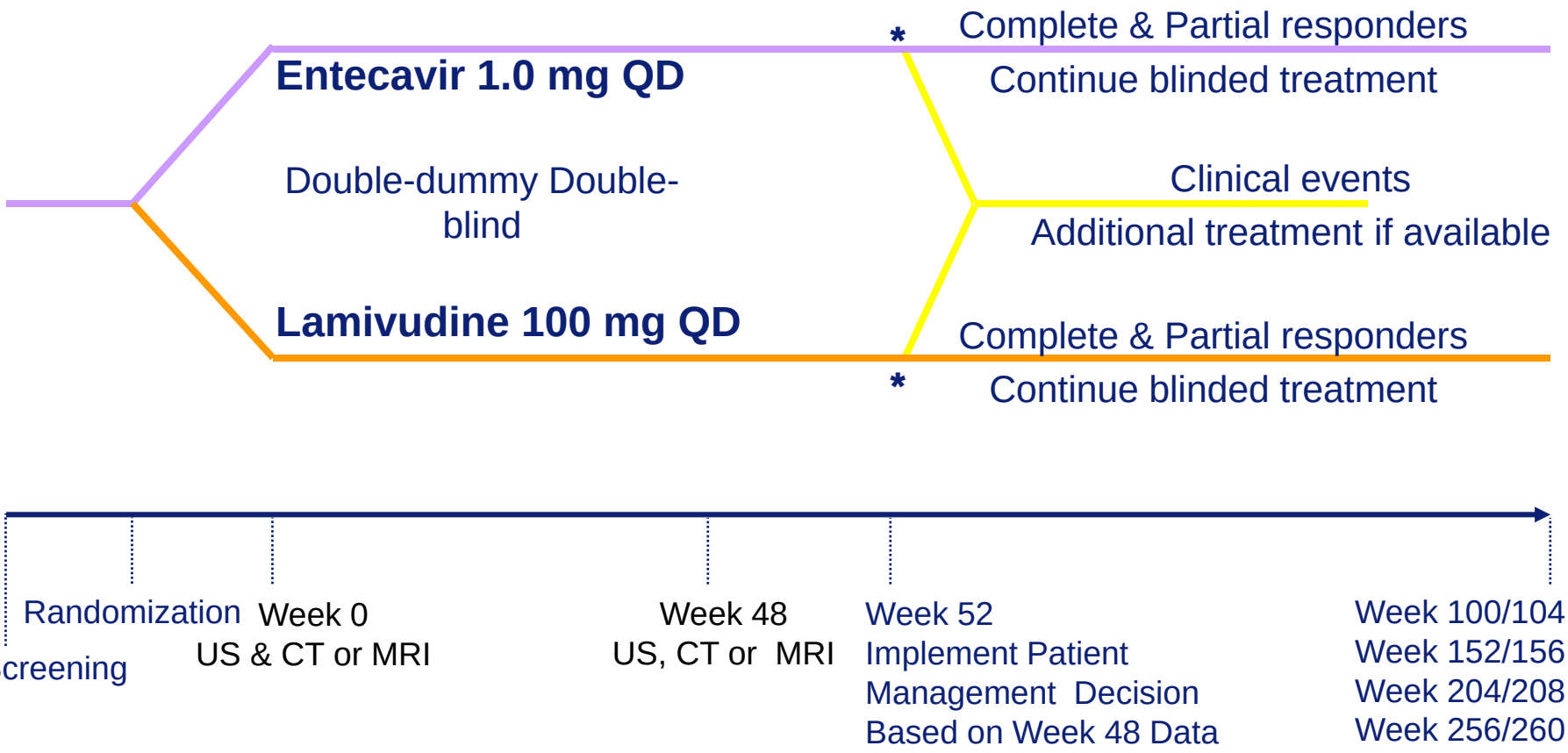
Long-term Outcome Chronic hepatitis B
Lam-ADV Treatment Compared with Historical* IFNα Data



- follow-up for a relatively short time
- comparison with historical IFNα data – not a head-to-head comparison

Papatheodoridis *Hepatology* 2005

Design Cirrhosis type B & Entecavir Prospective RCT



Design Cirrhosis type B & Entecavir RCT: power analysis

Data source	Estimated 5-year mortality	Estimated 5-year decompensation rate
Lamivudine	7 %	10%
Entecavir	2 %	5%
Number needed per arm	290	475

Project killer: academic opinion that RCT with lamivudine as comparator ethically unacceptable is in view of availability of HBVDNA monitoring and effective drugs for lamivudine resistance.

Prospective Cirrhosis B Cohort Study methodology

Design: prospective ***multi center*** cohort study

Study population: patients with viral hepatitis B associated *compensated* cirrhosis

HBVDNA > 10e3 irrespective of e-status or HDV coinfection

no signs of HCC; HIV or serious disease with high risk predicted mortality

Treatments: ***entecavir 1 mg daily***

No of patients to be included: ***500***

Outcomes:

a. treatment failure (Ltx or liver-related death, decompensation, HCC);

b. non-liver related mortality

Prospective Cirrhosis B Cohort Study statistics

This cohort study can be set up as a:

SURVIVAL-study:
Endpoint = disease progression (yes or no) and time of progression

Or

Logistic regression analysis:
Endpoint = disease progression at 3 years (yes or no)

Project killer: FDA requirement that company making entecavir conducts a 10,000 patient cohort study for 10 years to exclude drug oncogenicity

The potential impact of long-term nucleoside therapy on the mortality and morbidity of active chronic hepatitis B

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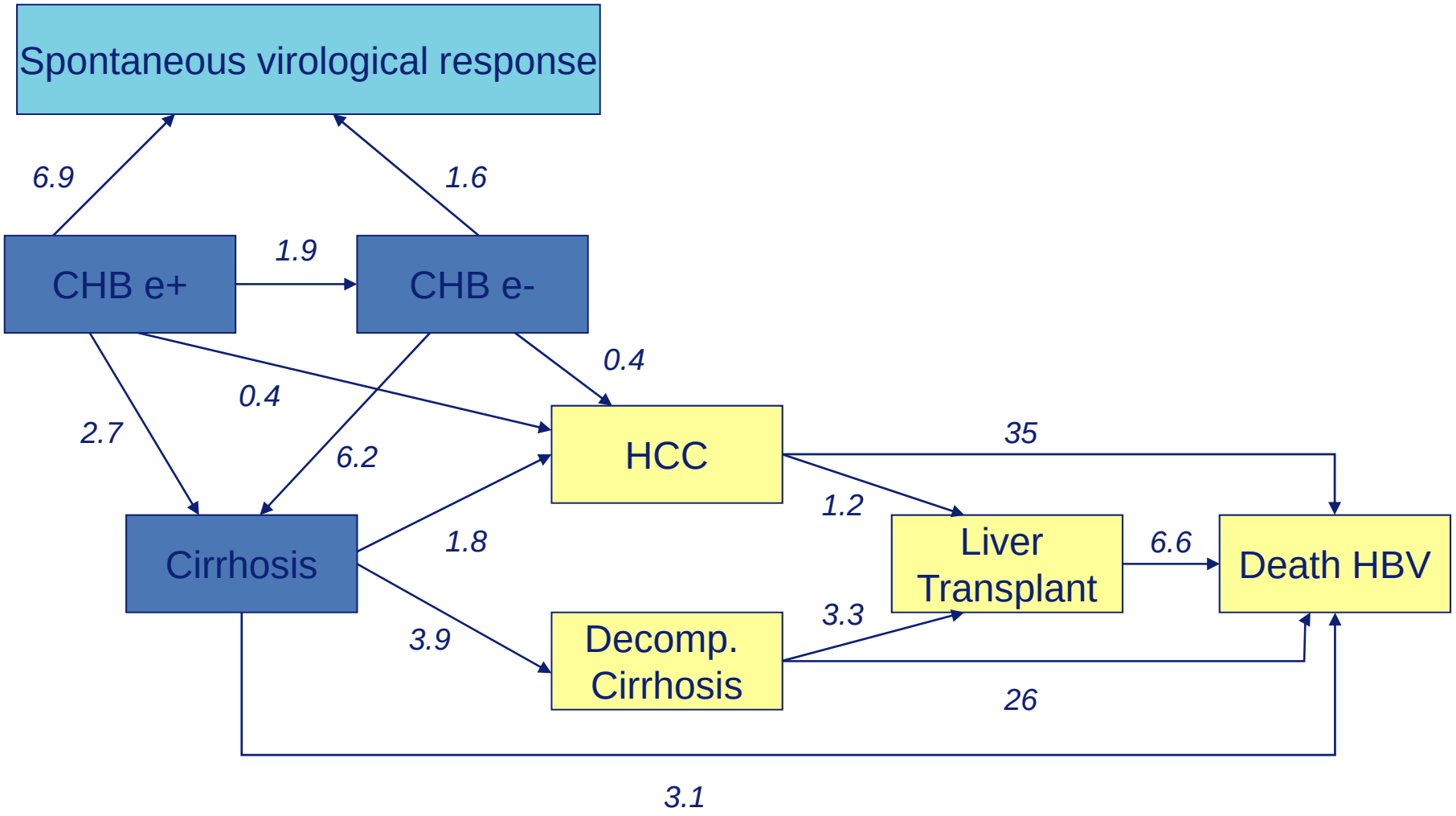
Methods

- A population cohort of CHB was constructed, by age specific prevalence of HBsAg in the Dutch population.
- HBsAg-positive cohort was divided based on HBeAg positivity, HBV DNA and ALT levels, and was further classified to the stage of liver disease (non-cirrhosis and cirrhosis).
- Markov mathematical simulation was used to model the outcome.

Methods: transition estimates for Markov model

- The model uses annual probabilities of progression from chronic hepatitis to cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, and finally death, obtained from systematic reviews published in the literature.

Basic cohort model



Methods: transition estimates for Markov model

- Different probability estimates for younger patients (age 0-24) and adults (age 25-65+).

- Analyses by mathematically simulating the cohort segments separately based on age and HBe-antigen status, for each strategy:

  - Natural history (no treatment)
  - Lamivudine (high resistance profile drug)
  - Adefovir (salvage therapy)
  - Entecavir (low resistance profile drug)

Methods: assumptions

- The disease stops progressing in patients who achieve sustained virological response.
- The progression rates during antiviral therapy are reduced with:
  - for the liver failure pathway: 80% for lamivudine & adevofir, and 90% for entecavir
  - for the HCC pathway: 50% for all three scenarios
- The probability of developing resistance with a low resistant profile drug for the coming 20 years will stay 1% per year.

Results: Cohort (1)

Age-specific view of the Dutch population, by HBsAg prevalence

Age years	Population in millions	HBsAg+ Prevalence %	HBsAg+ cases
<15	3.0	0.1	2.708
15-24	1.9	0.7	14.415
25-34	2.2	0.4	10.051
35-44	2.6	0.6	16.519
45-54	2.3	0.7	16.437
55-64	1.9	0.1	2.713
65+	2.3	0.1	1.005
Total	16.3 million	0.4 %	63.848

Results: Cohort (2)

Age (yr)	HBsAg+ cases	HBeAg+ cases	HBeAg- cases	HBV DNA > 10e5 cp/ml and ALT>2 ULN: HBeAg+ cases	HBV DNA > 10e5 cp/ml and ALT>2 ULN: HBeAg- cases
<15	2,708	812	1,896	211	133
15-24	14,415	4,325	10,091	1,124	706
25-34	10,051	2,010	8,041	523	563
35-44	16,519	2,643	13,876	687	971
45-54	16,437	822	15,615	214	1,093
55-64	2,713	190	2,523	49	177
65+	1,005	0	1,005	0	70
Total	63,848	10,802	53,046	2,808	3,713

Total treatment eligible cohort 6,521

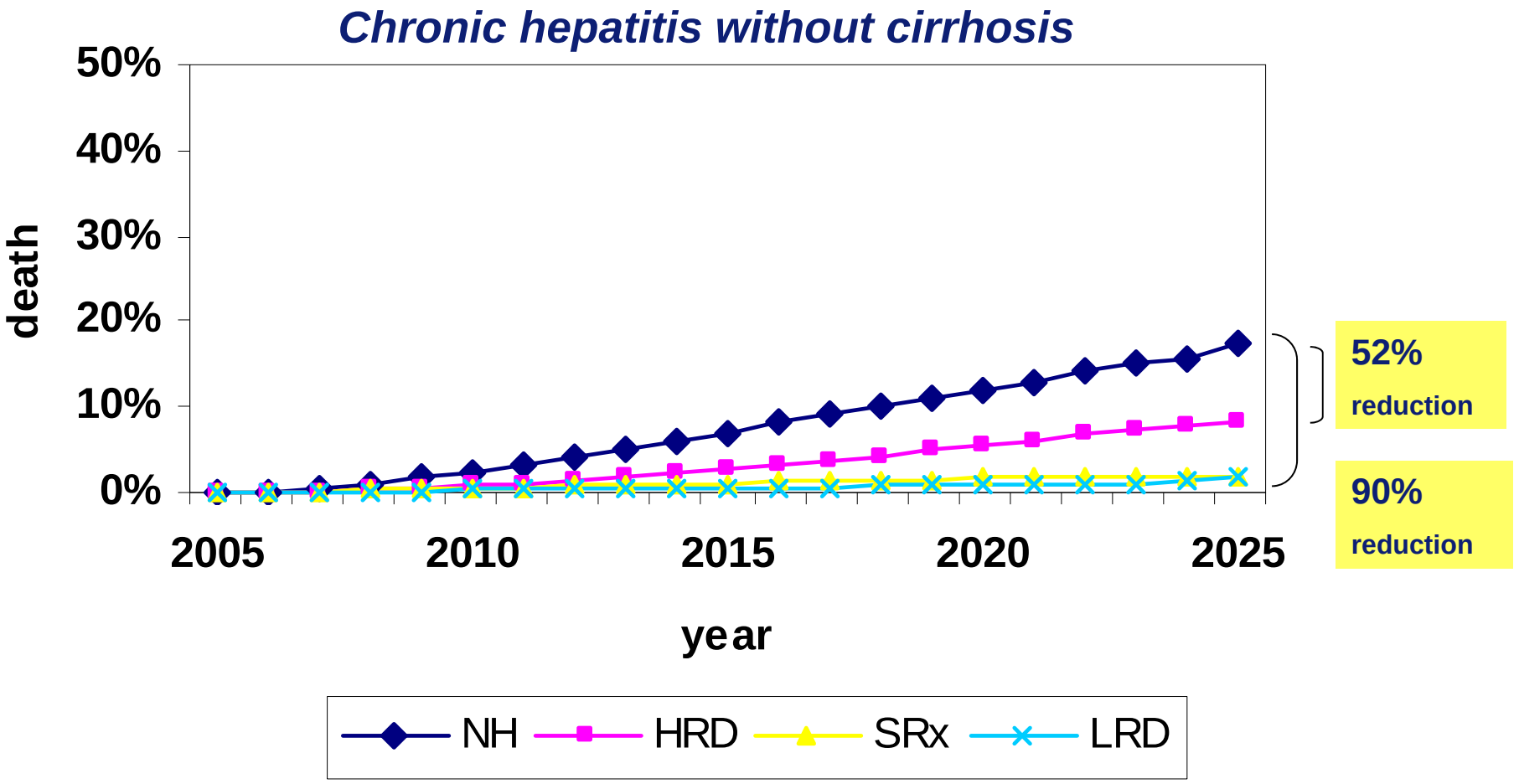
Results: Natural history Outcomes

Morbidity and mortality of active chronic hepatitis B cohort by HBeAg status, and stage of liver disease

Stage at entry	Outcome n (%)					
	N	Cirrhosis	Decomp. Cirrhosis	HCC	LT	Death
Total*	**6521**	**2507 (38)**	**575 (9)**	**670 (10)**	**38 (0,6)**	**1725 (26)**
Chronic hepatitis no cirrhosis	**5685**	**1671 (29)**	**360 (6)**	**481 (8)**	**30 (0,5)**	**1106 (20)**
HBeAg+	2634	*317 (12)*	*94 (3)*	*93 (3)*	*8 (0,3)*	*248 (10)*
HBeAg-	3051	*1354 (44)*	*266 (9)*	*388 (13)*	*22 (0,7)*	*858 (28)*
Cirrhosis	**836**	**836 (100)**	**215 (26)**	**189 (23)**	**8 (1)**	**619 (74)**
HBeAg+	174	*174 (100)*	*55 (31)*	*17 (10)*	*2 (1)*	*127 (73)*
HBeAg-	662	*662 (100)*	*160 (24)*	*172 (26)*	*6 (1)*	*492 (74)*

Liver-related mortality of active CHB

Impact of resistance on the reduction of mortality by antiviral therapy



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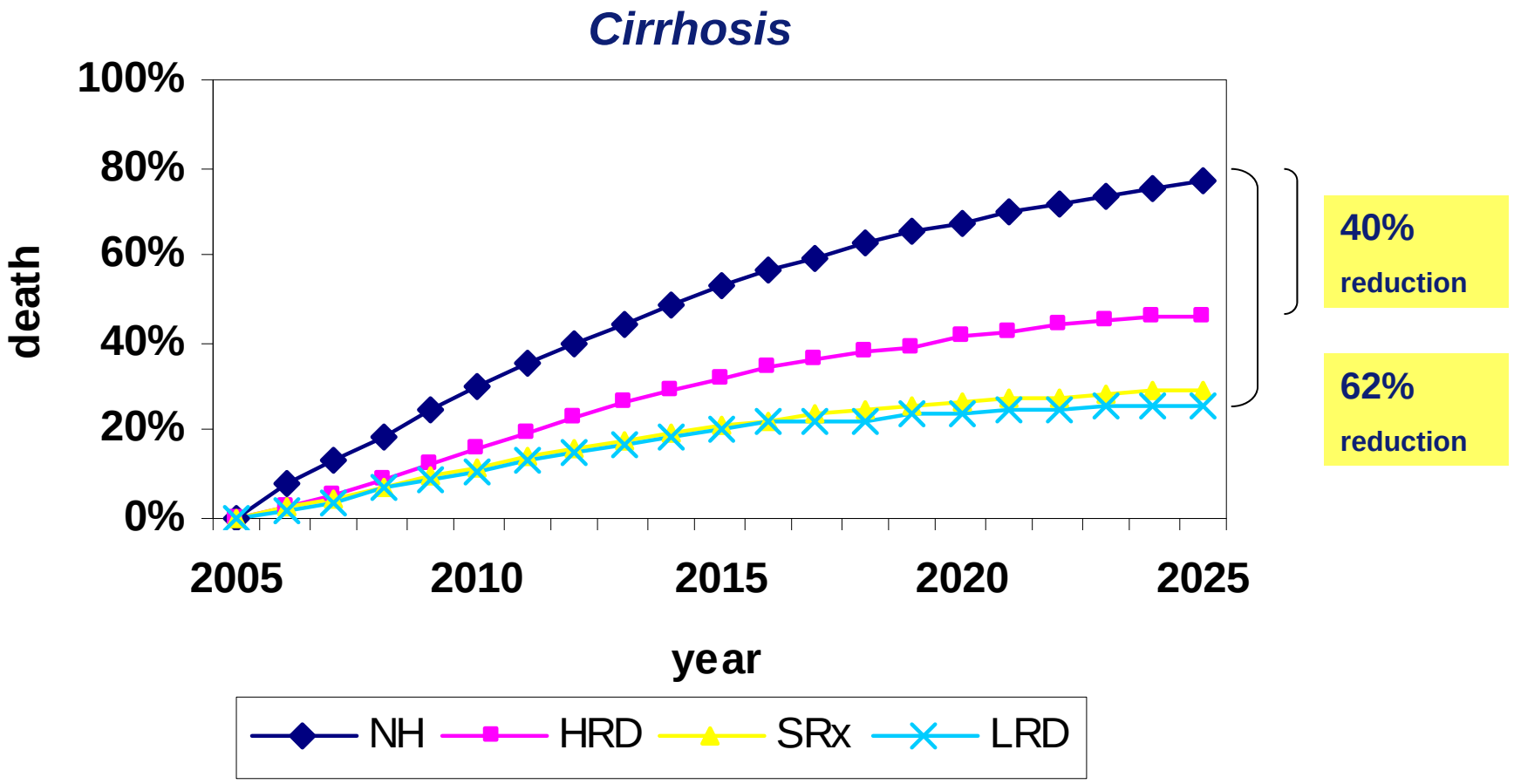

Discussion

- If all patients from the active CHB cohort are fully treated, liver-related mortality can be reduced by almost 80% if a low-resistance profile drug is chosen from the start.

- The beneficial effect of antiviral therapy is due to both the reduction in complications of cirrhosis and to the prevention of the development of cirrhosis.

- Clinical benefits of antiviral therapy may be strongly reduced when high resistance profile drugs are used and antiviral resistance remains unaddressed.

Conclusion

- This cohort-based model provides a realistic tool to estimate country-specific HBV-related mortality and morbidity and the potential impact of antiviral therapy.

- Long-term antiviral therapy with a strategy that minimizes or controls resistance will have a major preventive effect on liver-related mortality and morbidity of chronic hepatitis B.

- Antiviral resistance when unaddressed may reduce the clinical benefits of antiviral therapy with almost 50%

Need for Long-term Evaluation of Therapy Conclusions

- European studies of small size point to clinical benefit of antiviral therapy in chronic hepatitis B in case of persistent viral suppression.
- Model study indicates impressive reduction of mortality if on a country scale all active chronic hepatitis B cases are detected and long-term antiviral therapy with minimal antiviral resistance is initiated.
- Field studies to confirm model findings are should be performed in view of paralyzing effect of treatment uncertainty on public health action
  - Cohort with therapy: outcome comparison with model.
  - Case control study: outcome comparison compliant vs non-compliant