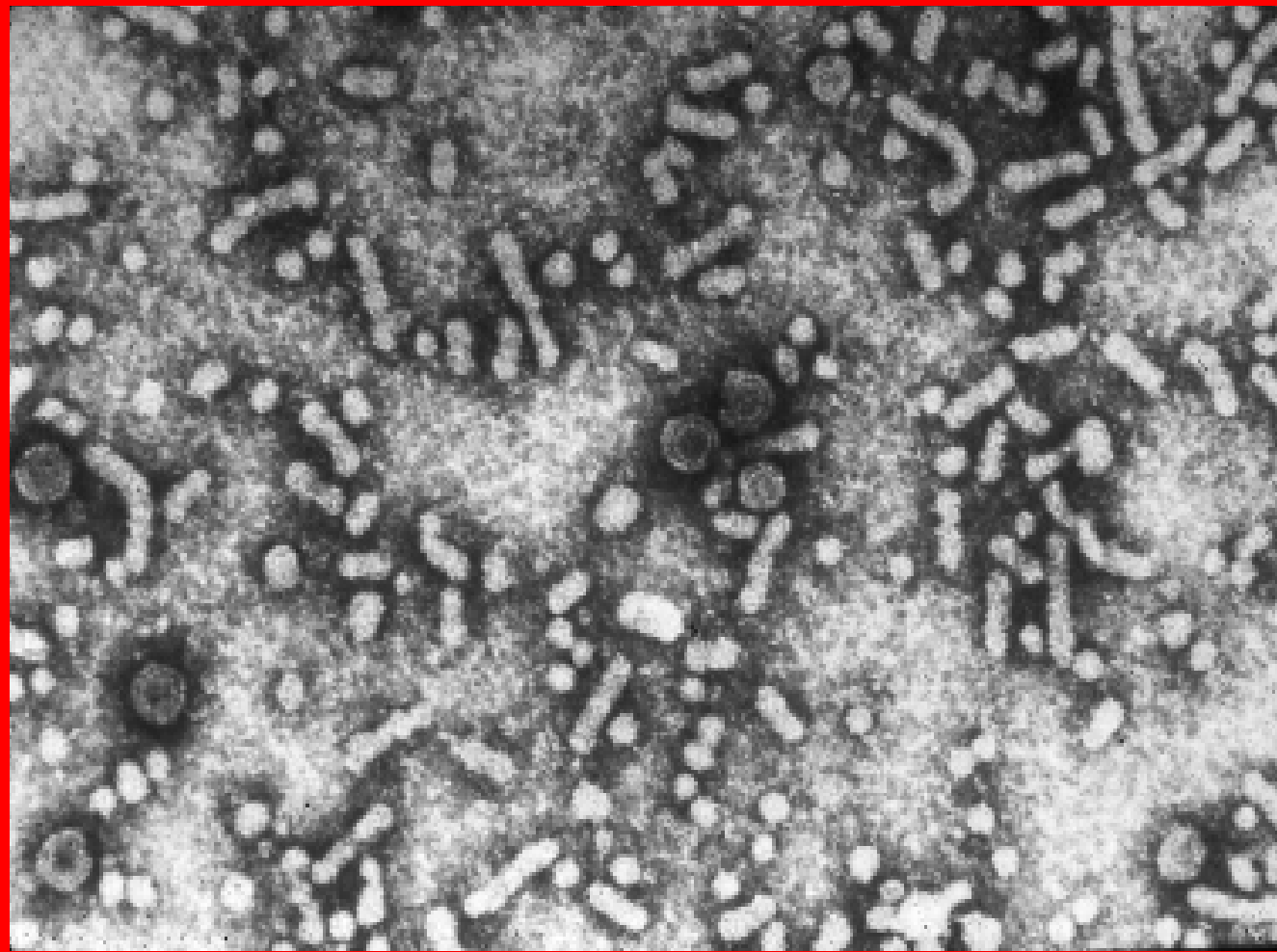


A photograph of the Golden Gate Bridge in San Francisco, California, viewed from a high angle. The bridge's red-orange towers and suspension cables are prominent against a clear blue sky. The water of the bay is visible below, and the city skyline is faintly visible in the distance. The text is overlaid on the image.

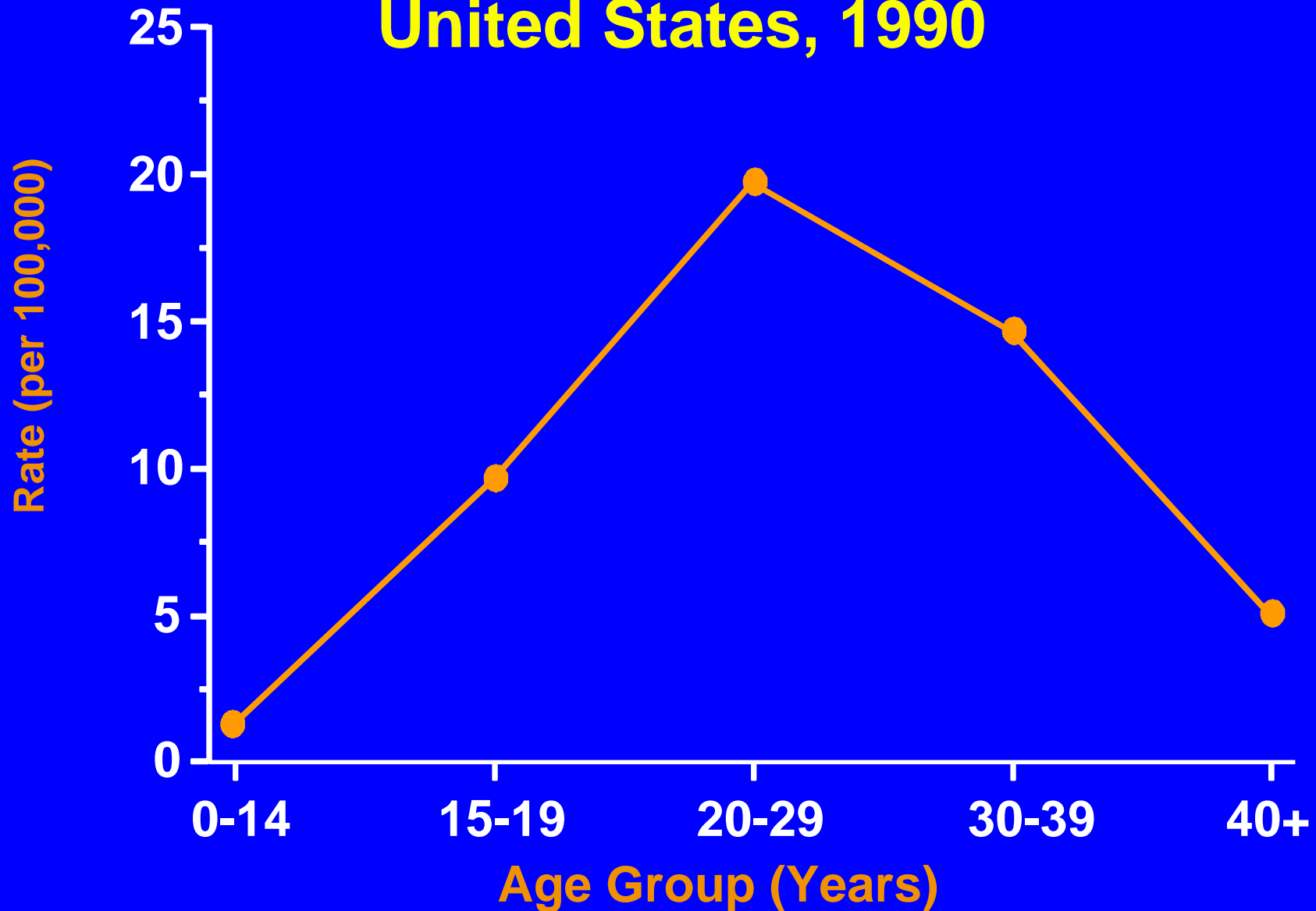
Hepatitis B Treatment in Children Today

Philip Rosenthal, M.D.
Professor of Pediatrics & Surgery
University of California,
San Francisco

Hepatitis B Virus



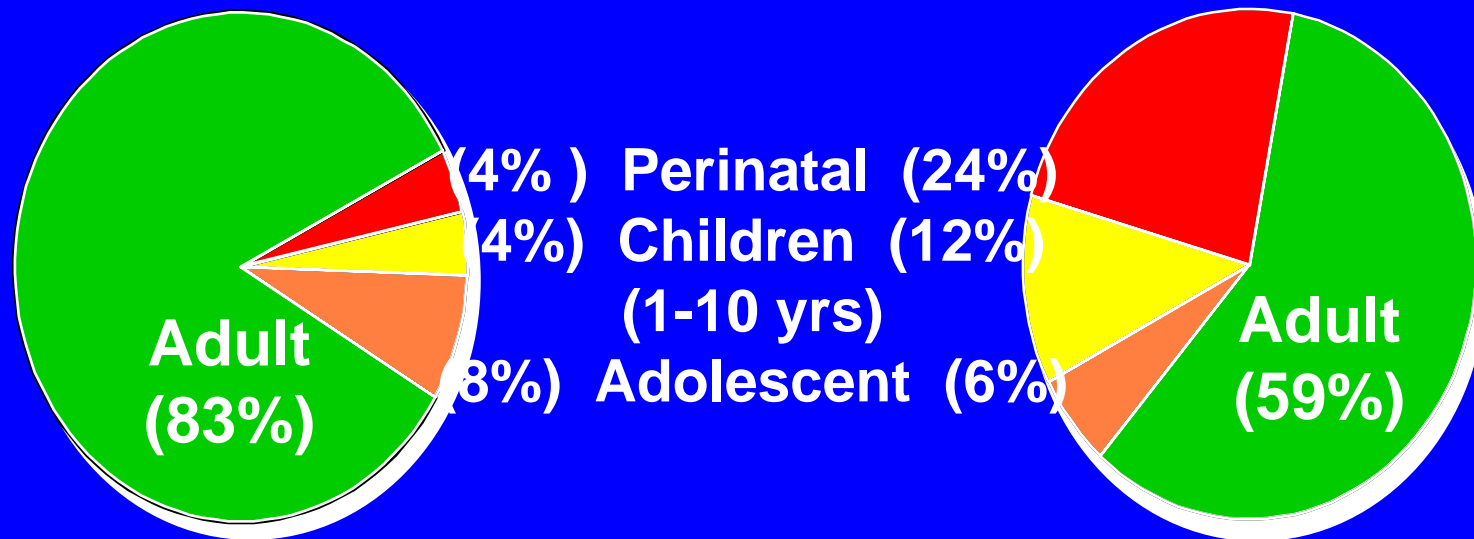
Rate of Reported Hepatitis B by Age Group United States, 1990



Source: CDC Viral Hepatitis Surveillance Program

Age at Acquisition of Acute and Chronic HBV Infection

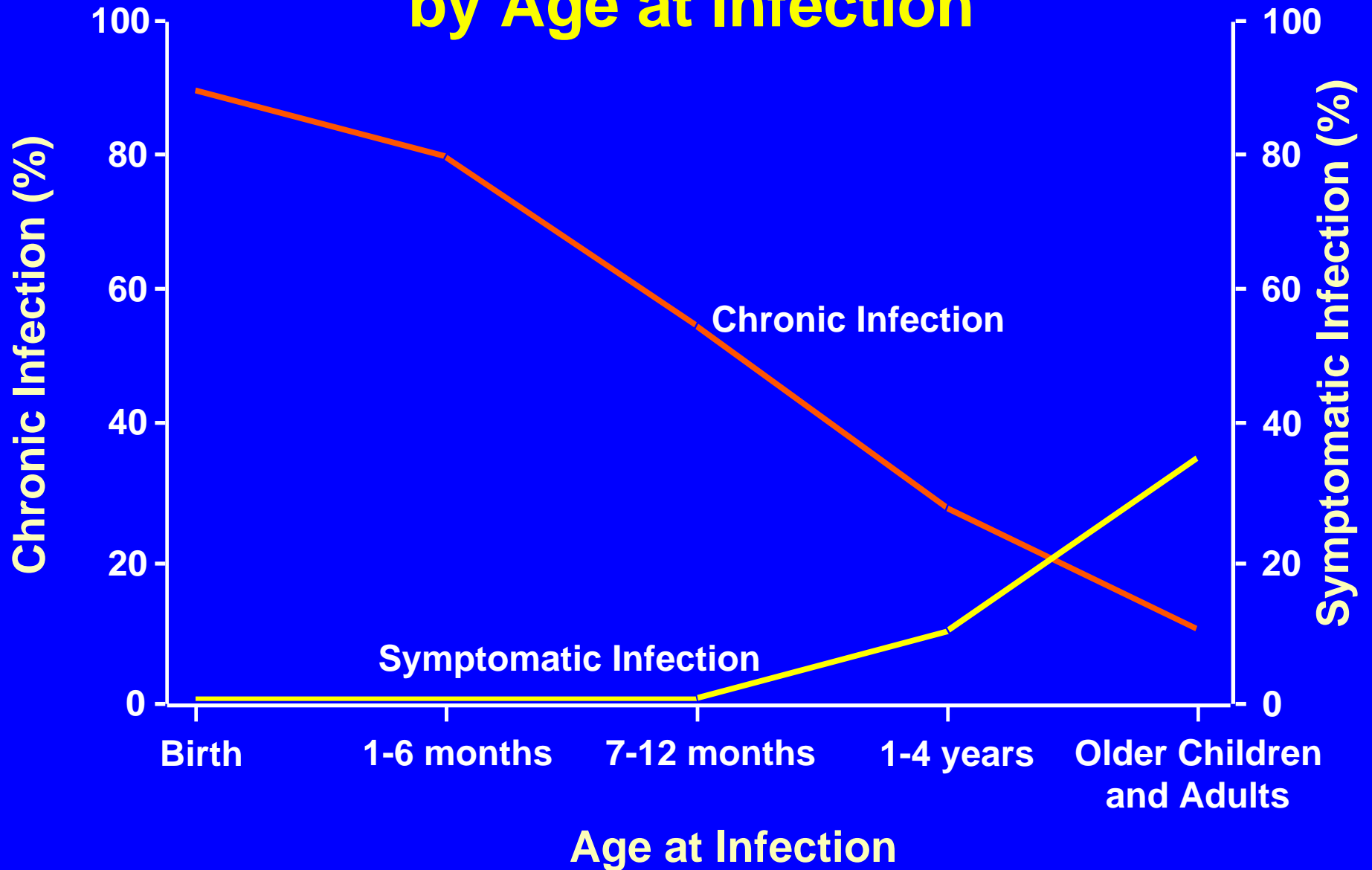
United States, 1989 Estimates



Acute HBV Infections

Chronic HBV Infections

Outcome of Hepatitis B Virus Infection by Age at Infection



Concentration of Hepatitis B Virus in Various Body Fluids

<u>High</u>	<u>Moderate</u>	<u>Low/Not Detectable</u>
blood	semen	urine
serum	vaginal fluid	feces
wound exudates	saliva	sweat
		tears
		breastmilk

Hepatitis B Virus

Modes of Transmission

- Sexual
- Parenteral
- Perinatal

Elimination of Hepatitis B Virus Transmission United States - Immunization

Objectives

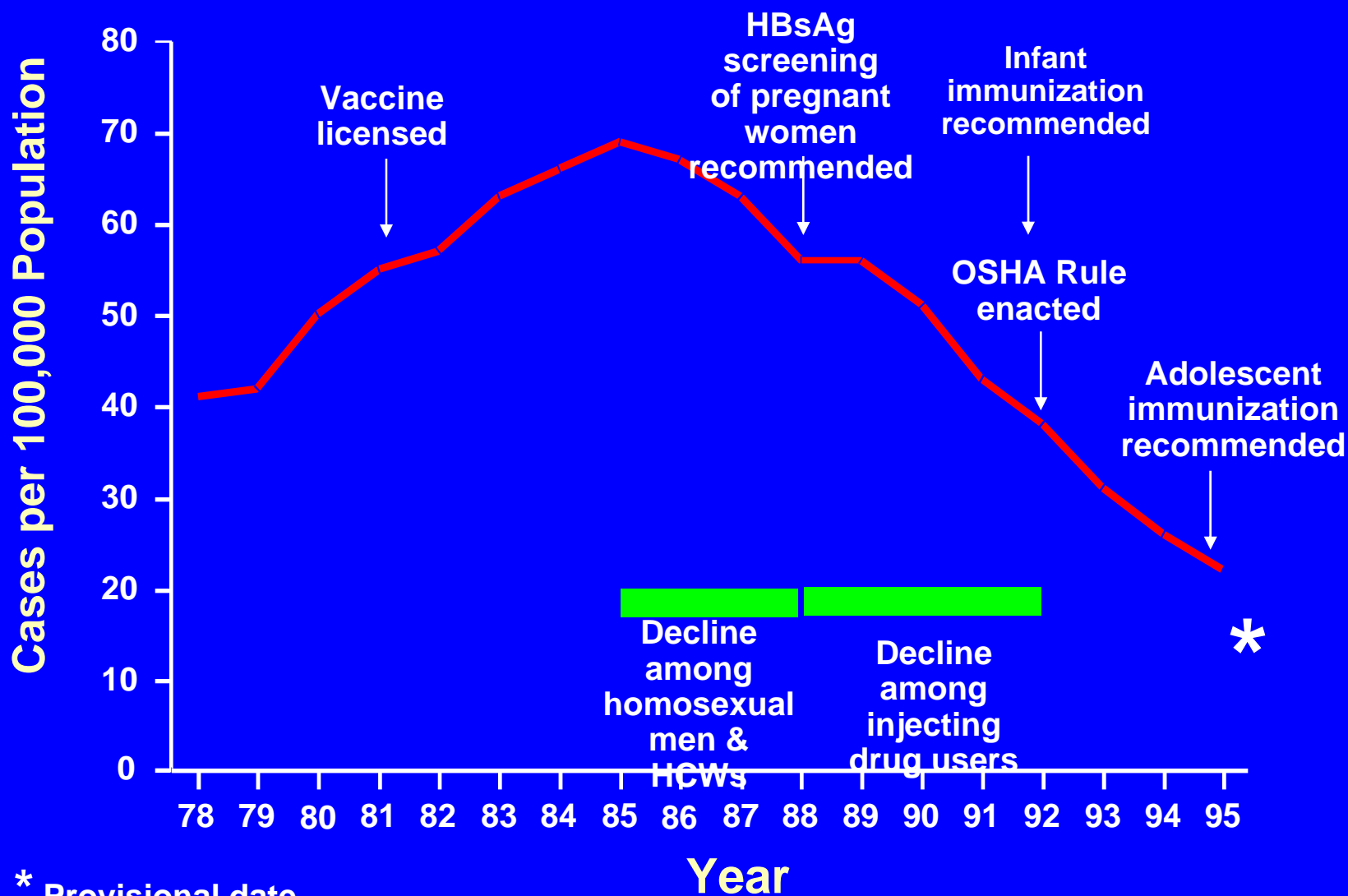
- Prevent chronic HBV Infection
- Prevent chronic liver disease
- Prevent primary hepatocellular carcinoma
- Prevent acute symptomatic HBV infection

Elimination of Hepatitis B Virus Transmission United States -Immunization

Strategy

- Prevent perinatal HBV transmission
- Routine vaccination of all infants
- Vaccination of children in high-risk groups
- Vaccination of adolescents
 - all unvaccinated children at 11-12 years of age
 - “high-risk” adolescents at all ages
- Vaccination of adults in high-risk groups

Estimated Incidence of Acute Hepatitis B United States, 1978-1995



Hepatitis B Immunization Rates

- Many At-Risk Adults Not Being Vaccinated Against Hepatitis B
- The incidence of acute HBV infections fell from 8.5 to 2.1 per 100,000 population between 1990 and 2004, due primarily to high vaccination rates among children and adolescents
- Of the estimated 60,000 new infections in 2004, 95% occurred among adults
- Vaccine coverage in 2004 was highest -- 48.1% -- among individuals age 18 to 20, and lowest -- 25.6% -- among those 41 to 49 years old.
- The highest proportion of vaccinees was health-care workers (80.5%) and police or firefighters (63.6%)

Evaluation of Patients with Chronic HBV- Initial Evaluation

- History & physical examination
- Laboratory tests to assess liver disease- CBC with platelets, hepatic panel & PT
- Tests for HBV replication- HBeAg, anti-HBe, HBV DNA
- Tests to rule out other causes of liver disease- anti-HCV, anti-HDV
- Tests to screen for HCC- AFP, ultrasound
- Liver biopsy to grade and stage liver disease

Follow-up of Patients with Chronic HBV- Not for Treatment

- HBeAg + with HBV DNA $>10^5$ copies/ml and normal ALT
 - ALT q 3-6 months
- If ALT $>1-2X$ ULN recheck ALT q 1-3 months
- If ALT $>2X$ ULN for 3-6 months & HBeAg+, HBV DNA $>10^5$ copies/ml, consider liver biopsy & Rx
- Consider HCC screen
- Inactive HBsAg carrier state
- ALT q 6-12 months
- If ALT $>1-2X$ ULN, serum HBV DNA & exclude other causes of liver disease
- Consider HCC screen

FDA Approved Hepatitis B Treatment in Children

- Interferon α 2b
- Subcutaneous
- HBeAg+ 3X /week for 4-6 months
- HBeAg- 3X/week for 1 year
- Side effects-many
- Drug resistance - none
- Lamivudine
- Oral
- HBeAg+ Daily for ≥ 1 year
- HBeAg- Daily for >1 year
- Side effects-negligible
- Drug resistance - $\sim 20\%$, year 1, $\sim 70\%$ year 5

Chronic Hepatitis B Treatment (Gastroenterology 114:988-995, 1998)

- Interferon alfa-2b, recombinant
- FDA approved treatment for children 1 to 17 years of age with chronic hepatitis B
- Approval based upon a multi-center, randomized, controlled international trial in children

Chronic Hepatitis B Treatment

- IFN trial
- **Subjects-** 72 treated vs. 77 untreated children
- **Results-** 24% of the treatment group lost HBV DNA and HBeAg vs. 10% of the control group at 24 weeks follow-up (P=0.05)

Chronic Hepatitis B Treatment

- IFN trial
- **Results**-95% of treated responders decreased or normalized their serum ALT levels
- 90% of overall responders remained HBV DNA & HBeAg negative 12-24 months posttreatment
- 30% of responders lost HBsAg

Chronic Hepatitis B Treatment

- IFN trial
- Results-in addition
- Of 28 untreated patients who then received IFN:
- 32% were overall responders
- All remained HBV DNA and HBeAg negative 9-24 months posttreatment

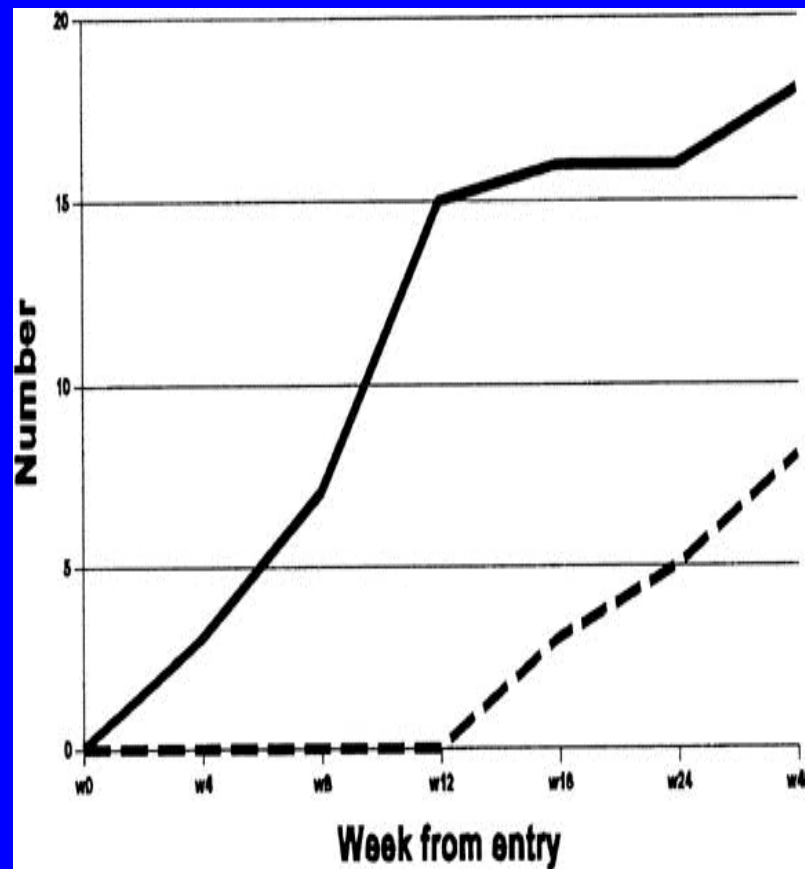
Chronic Hepatitis B Treatment

- **IFN Rx**
- For children 1 year of age or older with chronic HBV with compensated liver disease and positive serum HBeAg
- Side effects: flu-like symptoms, GI disorders, infections (17% viral), central and peripheral nervous system disorders, nausea and vomiting, and neutropenia

Chronic Hepatitis B Treatment

- IFN Rx
- Bedtime Rx, antipyretics and good hydration can lessen flu-like symptoms
- Pediatric dosing: for 16-24 weeks
- Starting dose: 3 million IU/m² TIW for 1st week
- Then, 6 million IU/m² TIW (max. 10 million IU TIW)

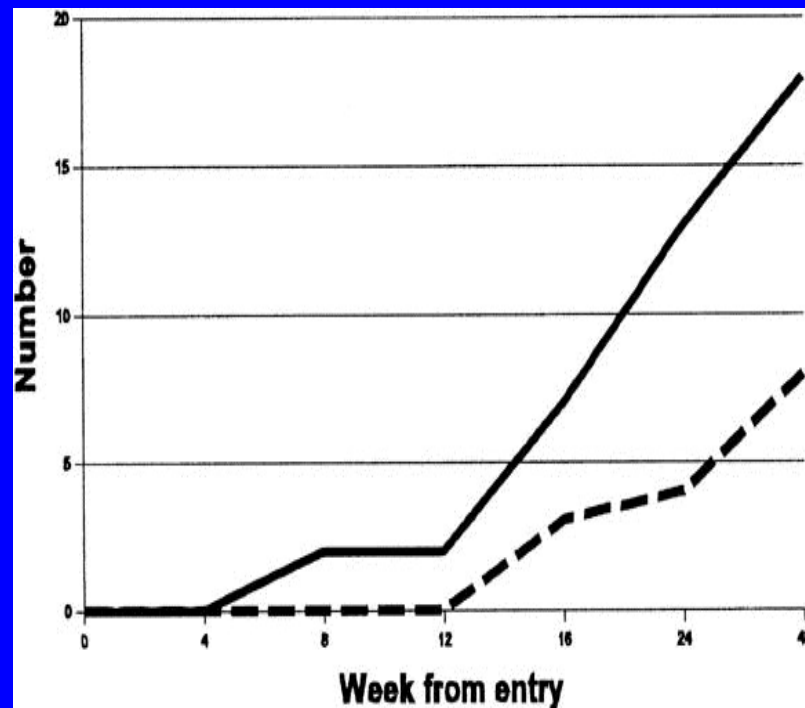
RESULTS



- Cumulative number of children who became HBV DNA negative by time from entry in the 70 treated (*solid line*) and 74 control (*dotted line*) patients.

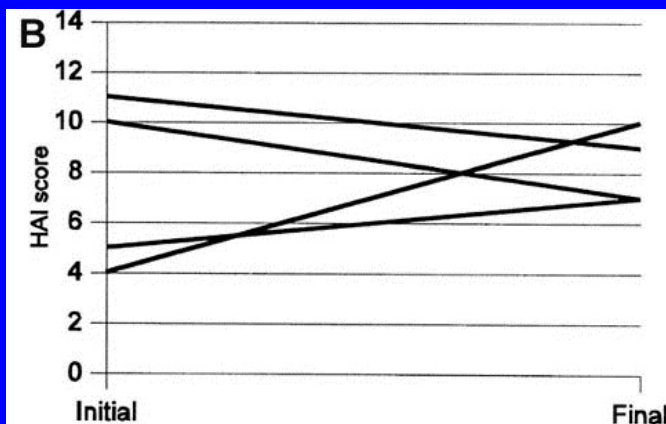
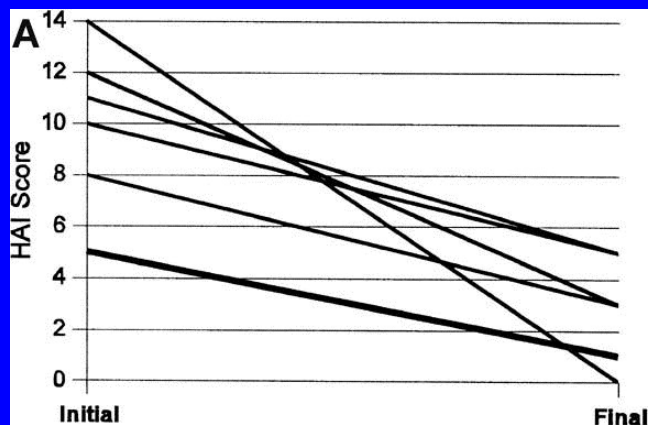
Gastroenterology 114:988-995, 1998

RESULTS



- Cumulative number of children who became HBeAg negative by time from entry in the 70 treated (*solid line*) and 74 control (*dotted line*) patients.

RESULTS



- Initial and follow-up necroinflammatory HAI scores in 10 treated children, (A) 6 of whom responded to therapy with loss of HBV DNA and HBeAg and (B) 4 of whom did not respond.

Clinical Trial of Lamivudine in Children with Chronic Hepatitis B

Maureen M. Jonas, M.D., Deirdre A. Kelley, M.D., Jacek Mizerski, M.D., Isabel B. Badia, M.D., Jorge A. Areias, M.D., Kathleen B. Schwarz, M.D., Nancy R. Little, B.S., Martin J. Greensmith, Ph.D., Stephen D. Gardner, M.S.P.H., M. Steve Bell, B.Sc., Etienne M. Sokal, M.D. and the International Pediatric Lamivudine Investigator Group

N Engl J Med
Volume 346;22:1706-1713
May 30, 2002



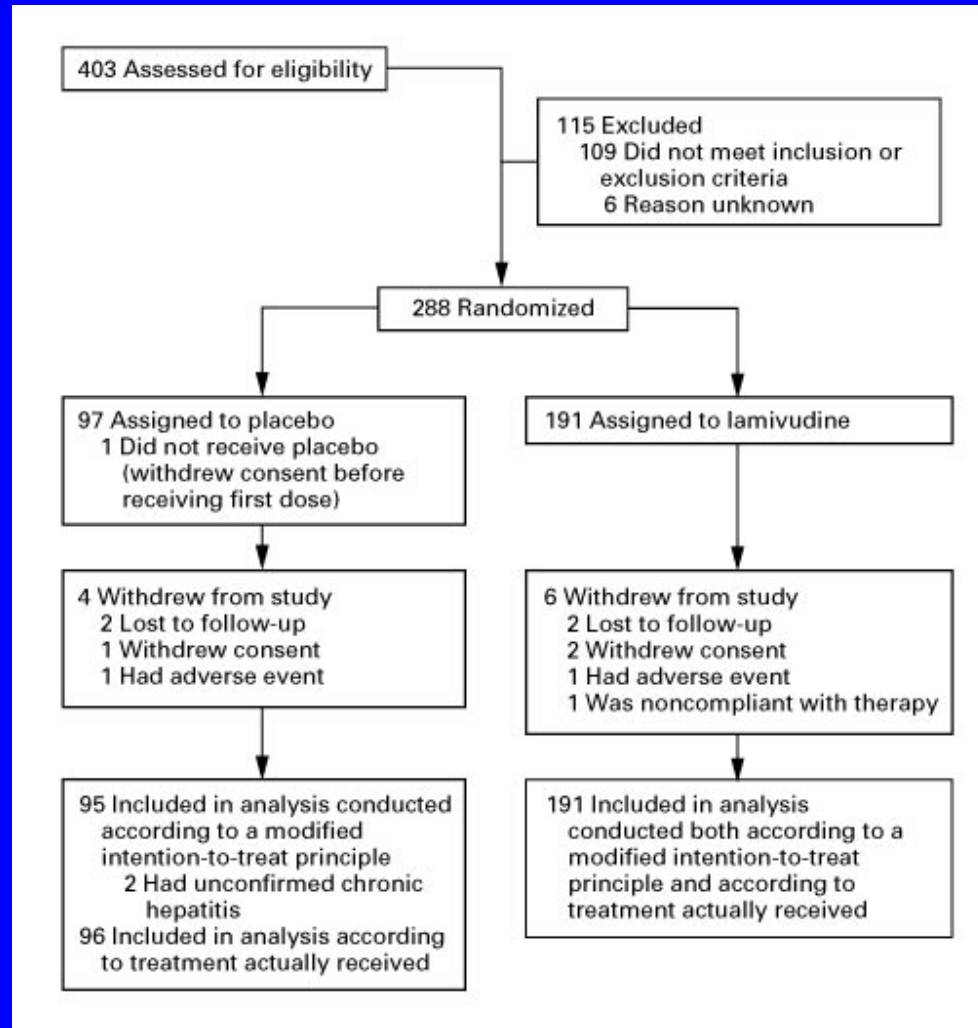
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Study Overview

- Chronic hepatitis B can be successfully treated in adults with the antiviral agent lamivudine
- In this international, randomized, double-blind, placebo-controlled trial, children with hepatitis B, some of whom had had no response to treatment with interferon, received either lamivudine or placebo for 52 weeks
- The rate of virologic response was 23 percent in the lamivudine group, as compared with 13 percent in the placebo group (P=0.04)
- A two-year open-label extension of the trial is in progress
- Neither interferon nor lamivudine is a wonder drug in this group of patients
- Lamivudine is an alternative treatment with efficacy similar to that of interferon and may be easier for children with chronic hepatitis B to tolerate



Numbers of Patients Included in or Excluded from Randomization and Subsequent Analyses



Jonas, M. et al. N Engl J Med 2002;346:1706-1713



Results of Liver Biopsy Performed before Treatment

TABLE 1. RESULTS OF LIVER BIOPSY PERFORMED BEFORE TREATMENT.*

HISTOLOGIC ACTIVITY INDEX SCORE	PLACEBO GROUP (N=95)	LAMIVUDINE GROUP (N=191)	P VALUE†
Total score			
Median	4	4	
Range	0-13	0-12	
Mean ±SD	5.7±2.7	4.7±2.2	0.002
Necrosis-inflammation score			
Median	3	3	
Range	0-10	0-9	
Mean ±SD	4.3±2.1	3.5±1.7	0.002
Fibrosis score			
Median	1	1	
Range	0-4	0-4	
Mean ±SD	1.4±0.9	1.2±0.8	0.035

*Liver biopsies were performed up to 24 months before enrollment in the study and at least 12 months after the completion of interferon therapy (in patients who had received interferon therapy). Scores for the Histologic Activity Index can range from 0 (normal) to 22 (severely abnormal) and are the sum of four histologic components: the severity of periportal necrosis (range of scores, 0 to 10), intralobular necrosis (range of scores, 0 to 4), portal inflammation (range of scores, 0 to 4), and fibrosis (range of scores, 0 to 4).

†P values were calculated with use of a Wilcoxon rank-sum test.

Jonas, M. et al. *N Engl J Med* 2002;346:1706-1713



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Efficacy of Treatment

TABLE 2. EFFICACY OF TREATMENT.*

RESPONSE AT WEEK 52	PLACEBO GROUP (N=95)	LAMIVUDINE GROUP (N=191)	ODDS RATIO (95% CI)	P VALUE†
	no. (%)			
Virologic response‡	12 (13)	44 (23)	2.1 (1.0–4.1)	0.04
Sustained normalization of alanine aminotransferase level§	11 (12)	100 (55)	8.4 (4.2–16.9)	<0.001
Virologic response and acquisition of anti-HBe	12 (13)	42 (22)	1.9 (1.0–3.9)	0.06
Loss of HBeAg	14 (15)	50 (26)	2.1 (1.1–3.9)	0.03
HBV DNA undetectable¶	15 (16)	117 (61)	8.4 (4.5–15.7)	<0.001
Loss of HBsAg	0	3 (2)	—	—

*CI denotes confidence interval, anti-HBe hepatitis B e antibody, HBeAg hepatitis B e antigen, HBV hepatitis B virus, and HBsAg hepatitis B surface antigen.

†P values were calculated with the use of the chi-square test.

‡A virologic response was defined by the absence of HBeAg and HBV DNA in serum.

§Only patients with base-line alanine aminotransferase levels that exceeded the upper limit of the normal range were included in the analysis (88 in the placebo group and 183 in the lamivudine group).

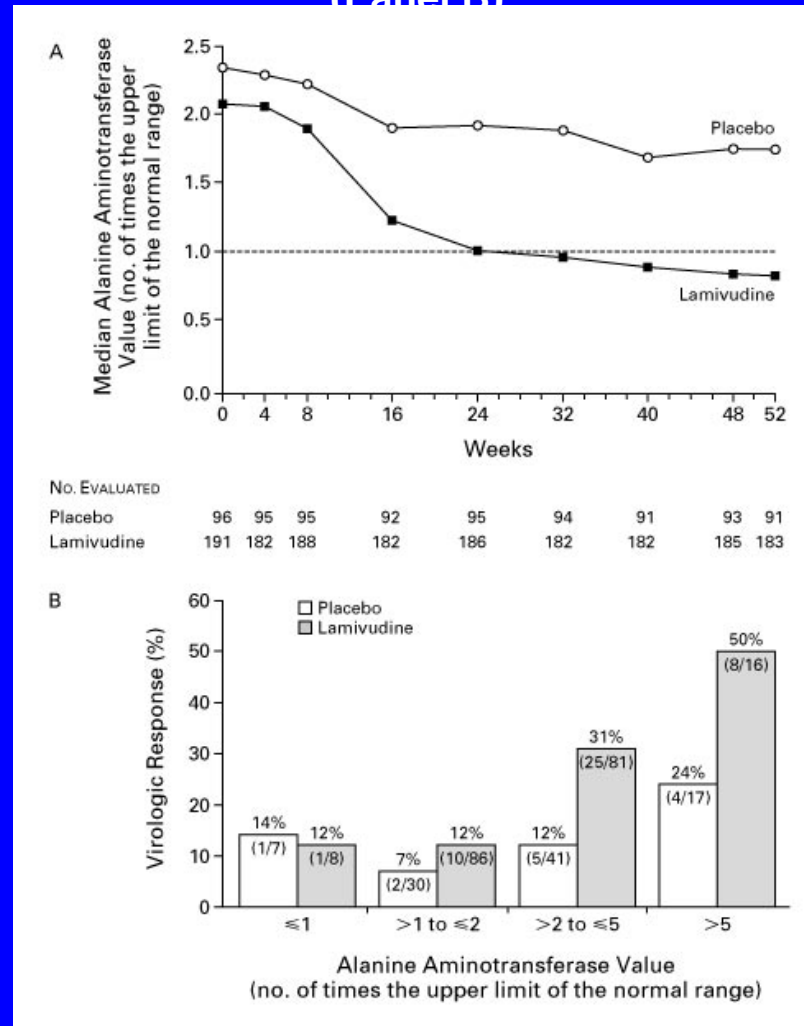
¶Levels were undetectable on branched-chain DNA assay with a lower limit of detection of 0.7 meq per milliliter.

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Median Alanine Aminotransferase Values during the 52-Week Treatment Period (Panel A) and Rates of Virologic Response According to the Base-Line Alanine Aminotransferase Value (Panel B)



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Adjusted Odds Ratios for Virologic Response to Lamivudine Associated with Potential Prognostic Variables

TABLE 3. ADJUSTED ODDS RATIOS FOR VIROLOGIC RESPONSE TO LAMIVUDINE ASSOCIATED WITH POTENTIAL PROGNOSTIC VARIABLES. *

VARIABLE	LAMIVUDINE GROUP (N=191)	ADJUSTED ODDS RATIO (95% CI)	P VALUE
	no./total no. (%)		
Base-line alanine aminotransferase			<0.001
Twice the upper limit of the normal range or less	11/94 (12)	1.0	
More than twice the upper limit of the normal range	33/97 (34)	3.41 (1.75-6.66)	
Histologic Activity Index score†			0.002
0-4	12/113 (19)	1.0	
5-9	20/53 (38)	1.77 (0.95-3.29)	
10-14	2/7 (29)	2.57 (0.81-8.17)	
Base-line HBV DNA			0.04‡
<800 meq/ml	30/93 (32)	1.0	
≥800 meq/ml	14/98 (14)	0.25 (0.13-0.49)	
Racial or ethnic origin			0.54
White	29/139 (21)	1.0	
Asian	10/33 (30)	1.27 (0.61-2.66)	
Other	5/19 (26)	1.05 (0.40-2.76)	

*Odds ratios were adjusted for base-line alanine aminotransferase values and base-line Histologic Activity Index score and are based on a logistic-regression model that included the treatment assignment and the factor of interest. CI denotes confidence interval, and HBV hepatitis B virus.

†Scores for the Histologic Activity Index can range from 0 (normal) to 22 (severely abnormal) and are the sum of four histologic components: the severity of periportal necrosis (range of scores, 0 to 10), intralobular necrosis (range of scores, 0 to 4), portal inflammation (range of scores, 0 to 4), and fibrosis (range of scores, 0 to 4).

‡Subgroup analyses indicated an interaction between HBV DNA level and treatment, so the P value for this factor should be interpreted with caution.

Jonas, M. et al. *N Engl J Med* 2002;346:1706-1713



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Median Levels of Hepatitis B Virus (HBV) DNA and Alanine Aminotransferase, According to the Presence or Absence of a Mutation in the YMDD Motif

TABLE 4. MEDIAN LEVELS OF HEPATITIS B VIRUS (HBV) DNA AND ALANINE AMINOTRANSFERASE, ACCORDING TO THE PRESENCE OR ABSENCE OF A MUTATION IN THE YMDD MOTIF. *

VARIABLE	No. OF PATIENTS	HBV DNA		ALANINE AMINOTRANSFERASE	
		BASE LINE	WEEK 52	BASE LINE	WEEK 52
		meq/ml		no. of times the upper limit of the normal range	
YMDD variant absent	135				
Median		753.2	0.35	2.0	0.8
Range		2.2–28,300	0.35–2604	0.7–16.9	0.2–3.7
YMDD variant present	31				
Median		1648	6.75	2.2	1.2
Range		158.5–13,018	0.35–1217	1.3–5.5	0.4–5.4

*Analyses for the YMDD (tyrosine, methionine, aspartate, and aspartate) motif were performed at base line and week 52 in 166 patients in the lamivudine group; the variant was found only at week 52.



Conclusions

- In children with chronic hepatitis B, 52 weeks of treatment with lamivudine was associated with a significantly higher rate of virologic response than was placebo



Phase III Lamivudine Trial

- Results
- Response rate (Loss of HBeAg/HBV DNA) at 1 yr. Lamivudine 23% vs. control 13% (P value significant but not different from adults)
- YMDD mutant rate at 1 yr. 18%
- Safety profile excellent

N Engl J Med 2002;346: 1706-1713

Adefovir

- Approved for use in adults only
- Benefit for lamivudine resistant patients, YMDD mutants and liver transplant patients
- Randomized Control trial in children in progress

Other Therapies

Not approved for use in children

- Entecavir
 - Oral
 - Once daily
 - Considered most potent
- Famciclovir
- Tenofovir

Pegylated Interferon

- IFN therapy limited by its limited half-life (4-6 hr.)
- PEG-IFN has a serum half-life of >90 hr. allowing once weekly dosing
- Not currently approved for use in children

