Children with Chronic HBV infection Past , Present and Future

Dr Seema Alam
Prof Pediatric Hepatology
Department of Pediatric Hepatology
Institute of Liver and Biliary Sciences

Universal Immunization Program

- **Hepatitis B vaccine was universalised nationwide in 2011. The UIP schedule recommends hepatitis B birth dose to all infants within 24 hours, followed by three doses at 6, 10 and 14 weeks**

- Hepatitis-B birth dose coverage was
  - 45% in 2015 and 60% in 2016.

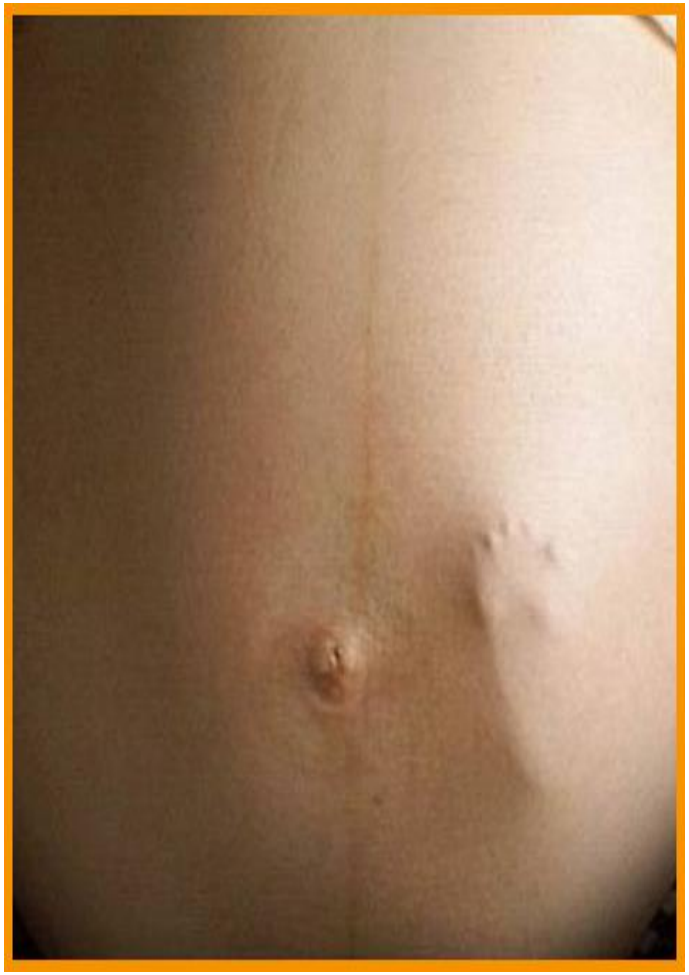
- Missed opportunity 40%

- Coverage amongst institutional deliveries for Hepatitis -B birth dose reported to be 76.36% as of December 2017.

India's target for Hepatitis B immunization

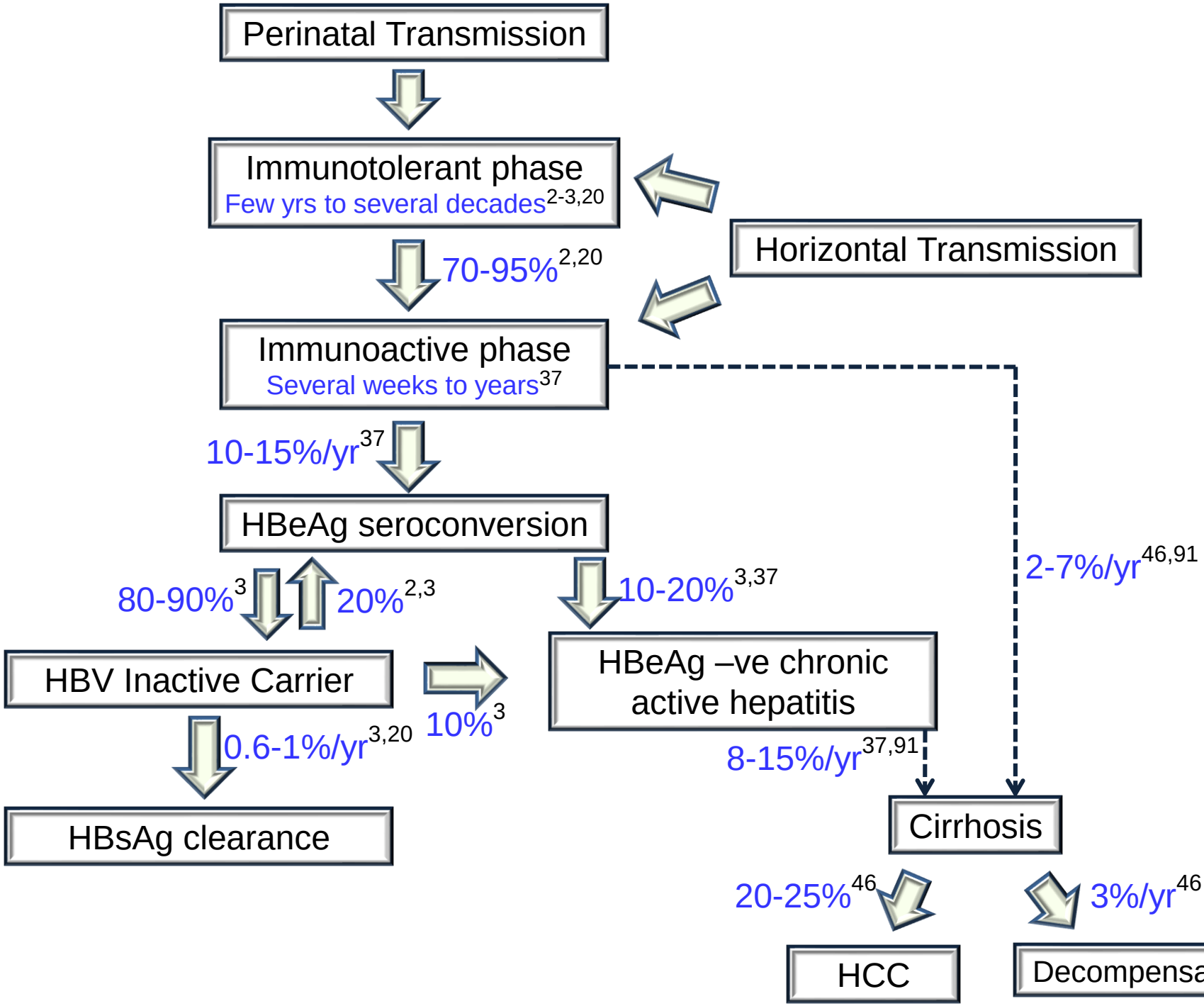
S.No.	Country Targets (to be provided by UIP)	Baseline (2016-17)	2019-20
1.	Coverage of Birth Dose of Hepatitis B (All deliveries)		90%
2.	Coverage with three doses of Hepatitis B vaccine in infants (B3).		95%
3.	Routine Hepatitis B vaccination among health-care workers.	N/A	Will be made Available

Chronic HBV infection in children



Majority have

- infancy-acquired infection (Mother to child transmission, Household contacts, Multitransfused, infected syringes)
- normal transaminases
- high HBV DNA
- minimal histological changes
- ‘immunotolerance’ to HBV


Perinatal Transmission
Immunotolerant phase
Few yrs to several decades[2-3,20]
Horizontal Transmission
70-95%[2,20]
Immunoactive phase
Several weeks to years[37]
2-7%/yr[46,91]
10-15%/yr[37]
HBeAg seroconversion
80-90%[3]
20%[2,3]
10-20%[3,37]
HBV Inactive Carrier
10%[3]
HBeAg –ve chronic active hepatitis
0.6-1%/yr[3,20]
8-15%/yr[37,91]
HBsAg clearance
Cirrhosis
20-25%[46]
3%/yr[46]
HCC
Decompensation

Chronic HBV infection

Long term outcome

Before adulthood

- 3-5% develop cirrhosis
- 1-3/10000 have HCC

Whole lifetime

- Risk of cirrhosis - 2-3% / yr

Natural History in children

- Perinatal + HorizontalTransmision

Risk of Chronicity as per age of acquistion

1. Infancy- >90%
2. 1-5 Years- 25-50%
3. > 5 Years- 5-10 %

Seroconversion Rates

Perinatal Transmission- Asians

1. < 3 Yr Age- 2%/Year
2. > 3 Yr Age- 4-5%/Year

Horizontal Transmission- Europeans

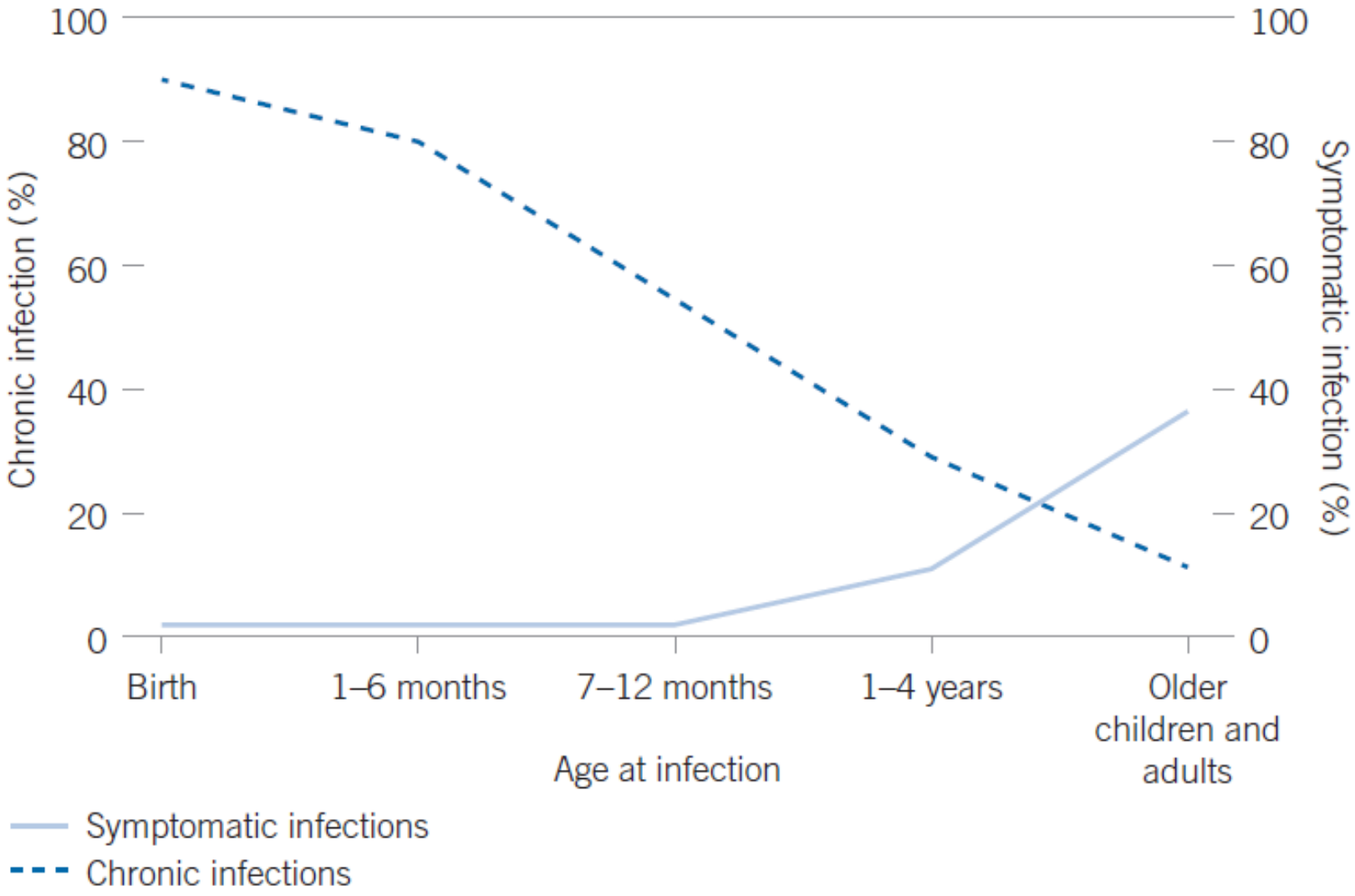
70-80% over 20 Years

Perinatally Acq. HBV: Natural History

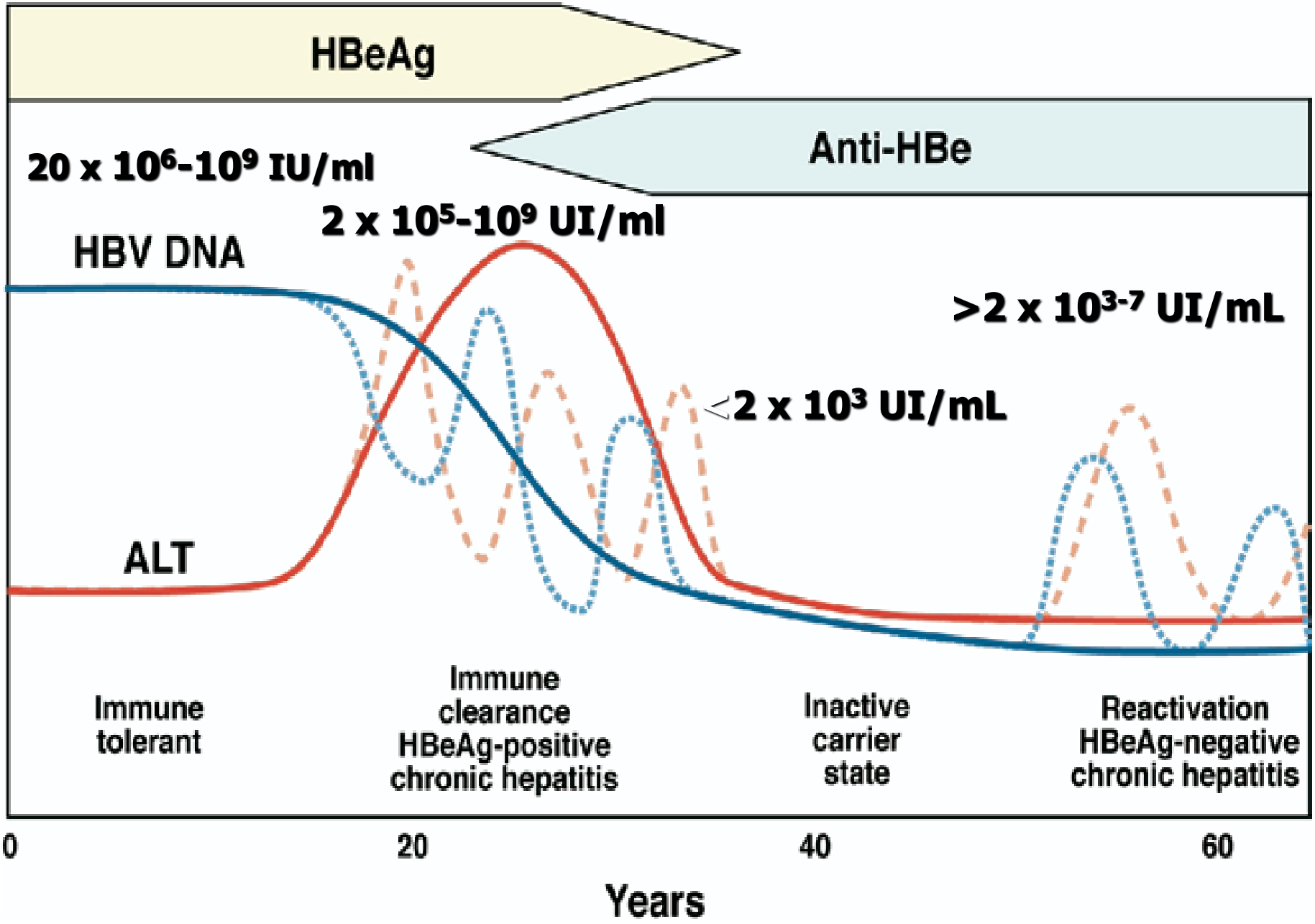
- Loss of tolerance at a median age of 30y
- Two-third: Inactive carrier
- One-third: Chronic hepatitis with subsequent risk of cirrhosis, liver failure, HCC
- Risk of HCC: Higher than in horizontally acquired HBV
- Asymptomatic but highly infectious

Andreani T et al. Clin Gastroenterol Hepatol 2007; 5; 636-41

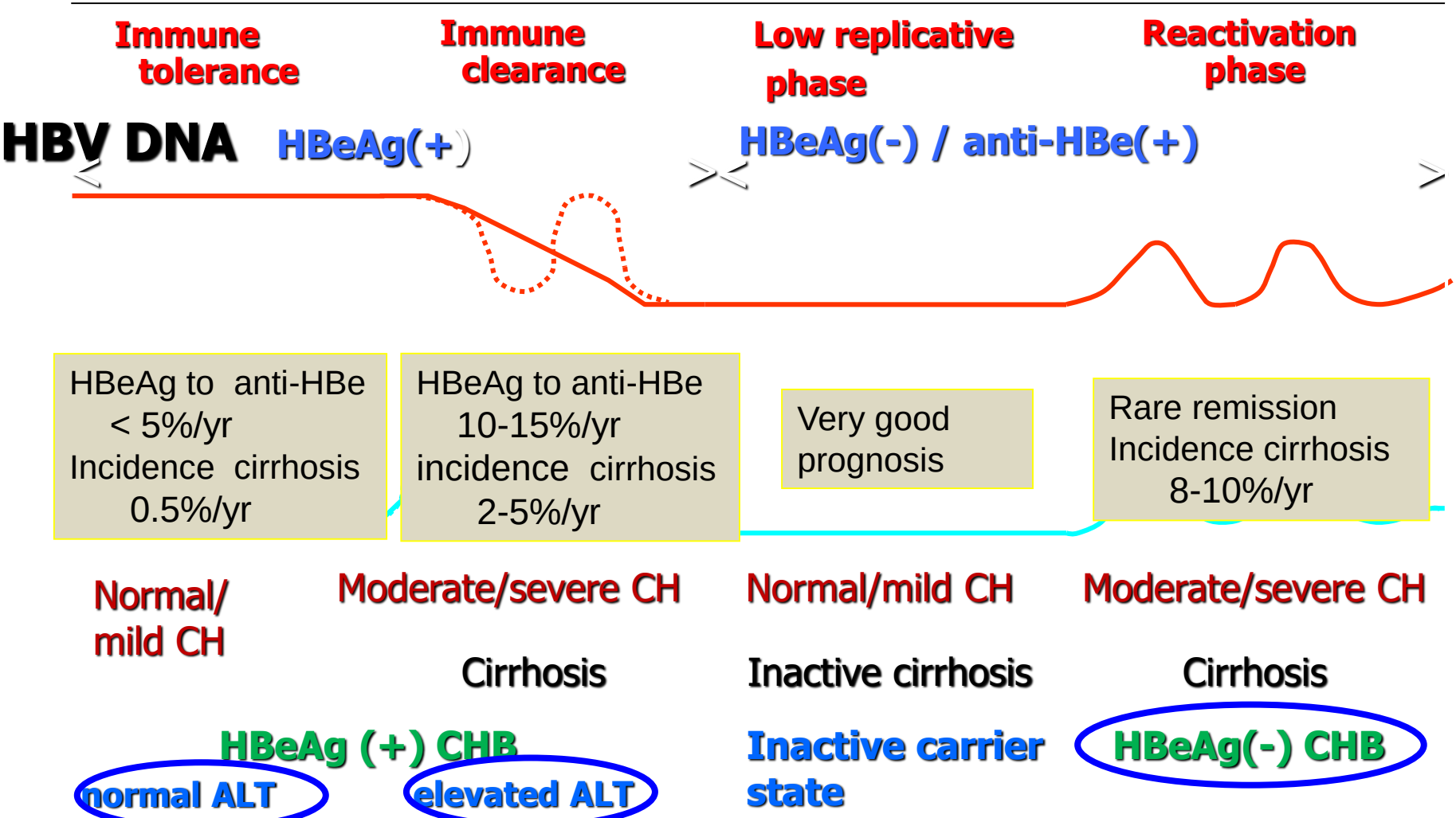
Outcome of HBV infection by age at infection



Stages of HBV infection



Stages of chronic HBV infection

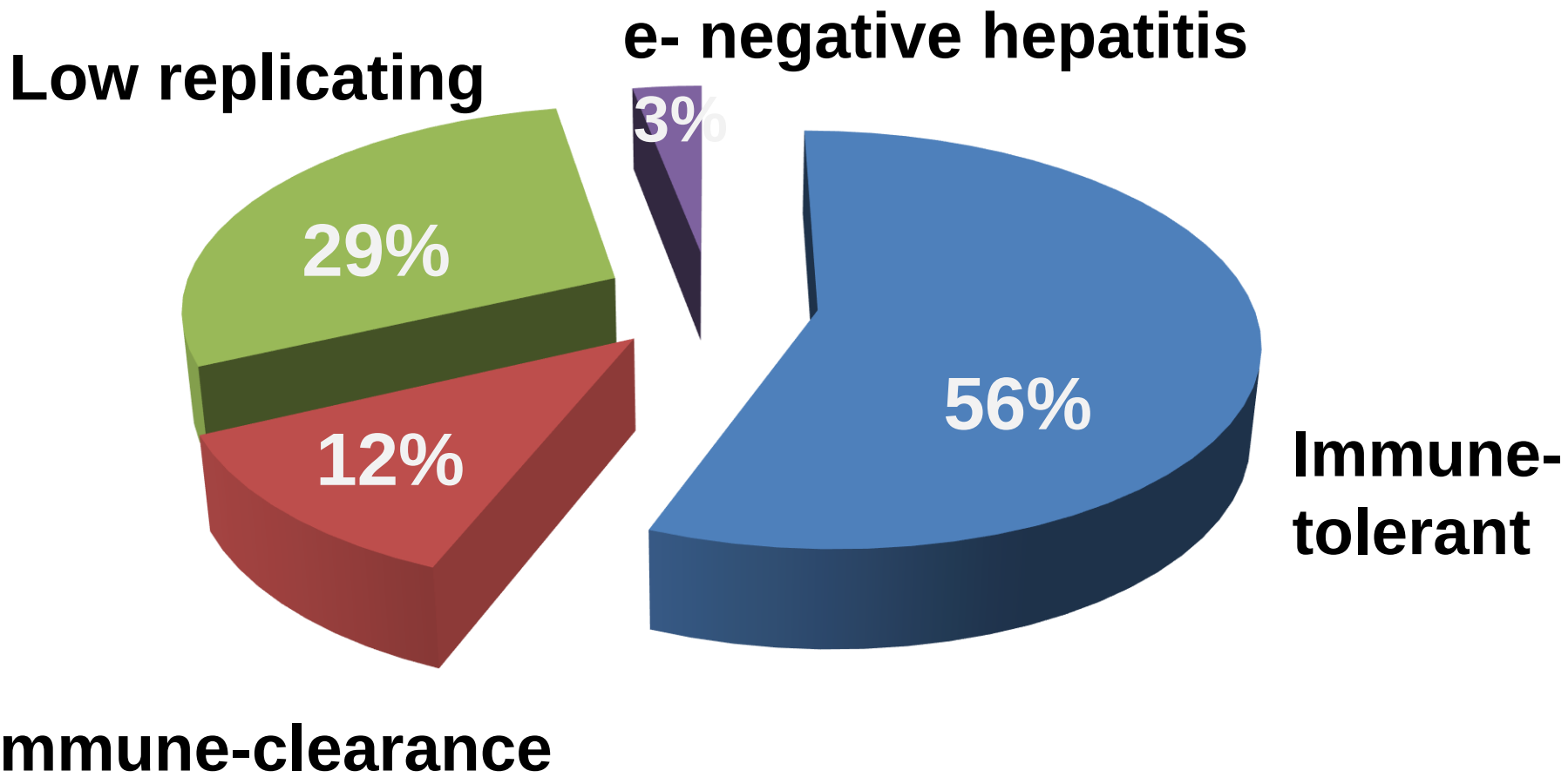


Adapted from Fattovich G. Sem Liver Dis. 2003;23:47-58

Phases of Chronic Hepatitis B in Children

Phase	Labs and Histology
Immunotolerant	➢ HBsAg & HBeAg +ve ➢ HBV DNA > 20,000 IU/ ml (> 10^5 Copies / ml) ➢ ALT Normal ➢ Absent or Minimal Liver Inflammation and Fibrosis
Immunoactive/ Immunoclearance	➢ HBsAg & HBeAg +ve ➢ HBV DNA > 20,000 IU/ ml (> 10^5 Copies / ml) ➢ ALT persistently elevated ➢ Liver inflammation and Fibrosis may develop
Incative Chronic Hepatitis	➢ HBsAg +ve ➢ HBeAg –ve/ Anti HBe +ve ➢ HBV DNA < 2000 IU/ml (< 10^4 Copies/ ml) or Undetectable ➢ ALT Normal ➢ Absent or Minimal Liver Inflammation or Fibrosis
HBeAg Negative Chronic Active Hepatitis (Immune Escape)	➢ HBsAg +ve ➢ HBeAg –ve/ Anti HBe +ve ➢ HBV DNA > 2000 IU/ml (> 10^4 Copies/ml) ➢ ALT Raised ➢ Active Liver Inflammation + Fibrosis

Spectrum of Chr. HBV in Children (n=203)



Am J Gastroenterology 2011; 106: S552-553

Immune-tolerant phase in young patients: evidence for treating earlier

Preserved T-Cell Function in Children and Young Adults With Immune-Tolerant Chronic Hepatitis B

PATRICK T. F. KENNEDY,* ELENA SANDALOVA,‡ JUANDY JO,‡ UPKAR GILL,* INES USHIRO-LUMB,* ANTHONY T. TAN,‡ SANDHIA NAIK,* GRAHAM R. FOSTER,* and ANTONIO BERTOLETTI‡,§,‖

GASTROENTEROLOGY 2012;143:637–645

HBV infection in younger patients is not associated with an immune profile of T-cell tolerance. On the contrary, children and young adults with chronic HBV infection have an HBV-specific immune profile that is less compromised than that observed in older patients.

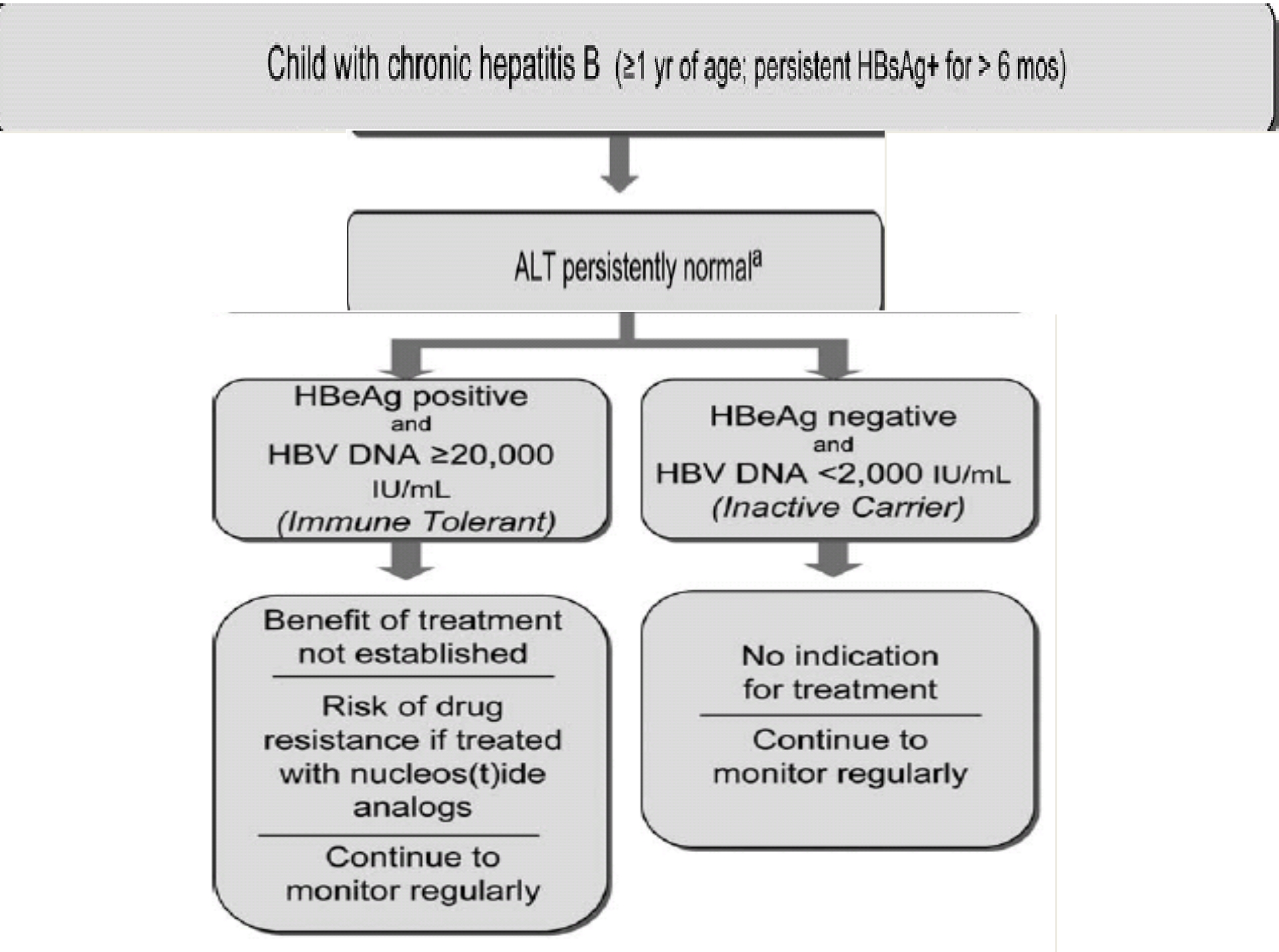
Do we need to treat these patients?

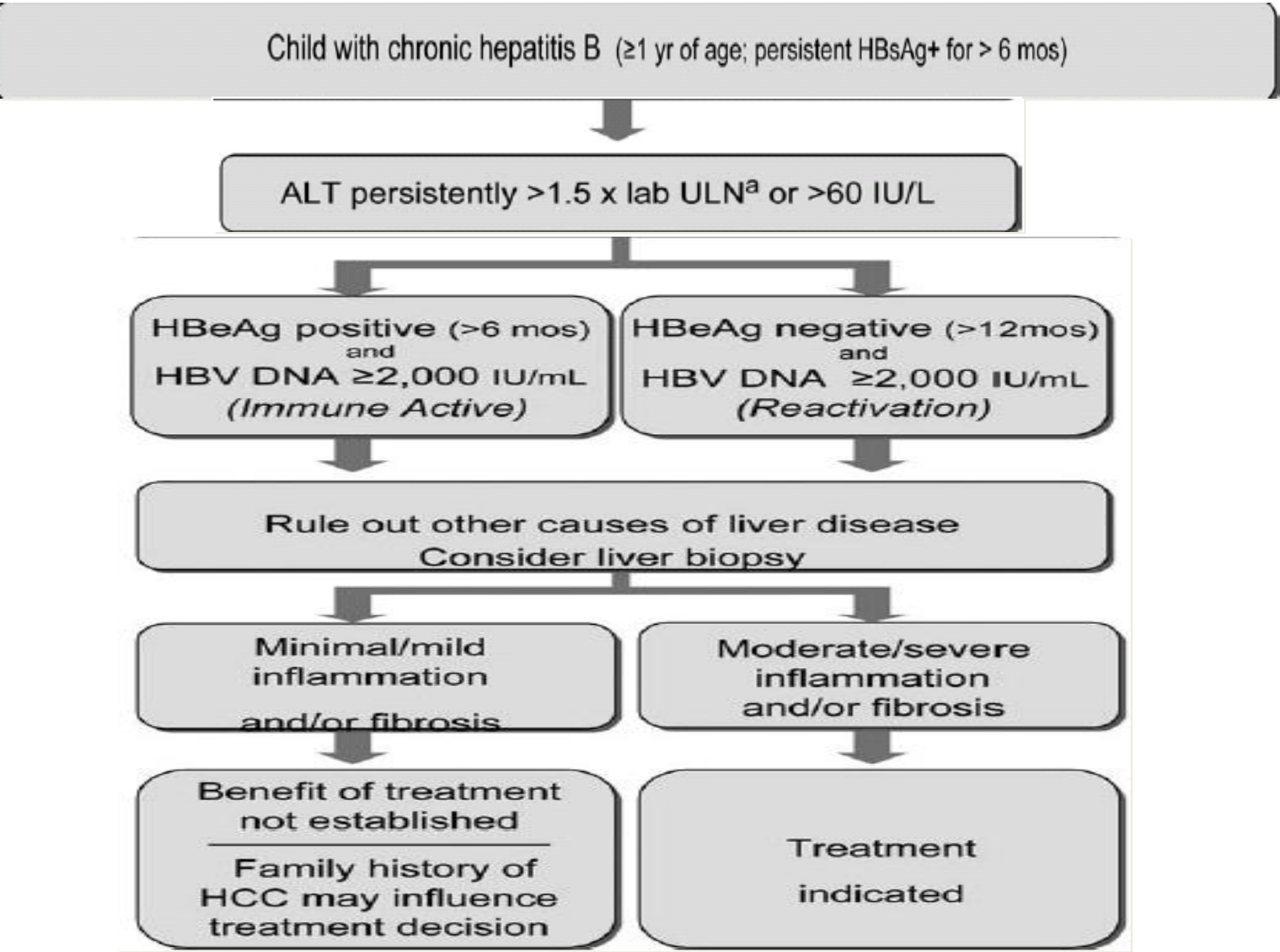
Pros

- Asians with Perinatal Transmission- Long I-T Phase- Higher risk of Cx
- High Viral Load- Decrease makes sense to prevent risk of HCC and Cirrhosis
- Prevent the **spread of infection**
- Psychological trauma/social stigma

Cons

- Why treat when liver Disease is minimal?
- Risk of antiviral resistance- Lack of future options


Child with chronic hepatitis B (≥1 yr of age; persistent HBsAg+ for > 6 mos)
ALT persistently normal[a]
HBeAg positive
and
HBV DNA ≥20,000 IU/mL
(Immune Tolerant)
HBeAg negative
and
HBV DNA <2,000 IU/mL
(Inactive Carrier)
Benefit of treatment not established
Risk of drug resistance if treated with nucleos(t)ide analogs
Continue to monitor regularly
No indication for treatment
Continue to monitor regularly


Child with chronic hepatitis B (≥1 yr of age; persistent HBsAg+ for > 6 mos)
ALT persistently >1.5 x lab ULN[a] or >60 IU/L
HBeAg positive (>6 mos) and HBV DNA ≥2,000 IU/mL (Immune Active)
HBeAg negative (>12mos) and HBV DNA ≥2,000 IU/mL (Reactivation)
Rule out other causes of liver disease Consider liver biopsy
Minimal/mild inflammation and/or fibrosis
Moderate/severe inflammation and/or fibrosis
Benefit of treatment not established
Family history of HCC may influence treatment decision
Treatment indicated

Scenario 1

- 8yrs/ Male
- Resident of Delhi
- Born FTND to 2nd para mother
- Birth weight 3 kg
- Antenatal & Perinatal periods uneventful

History

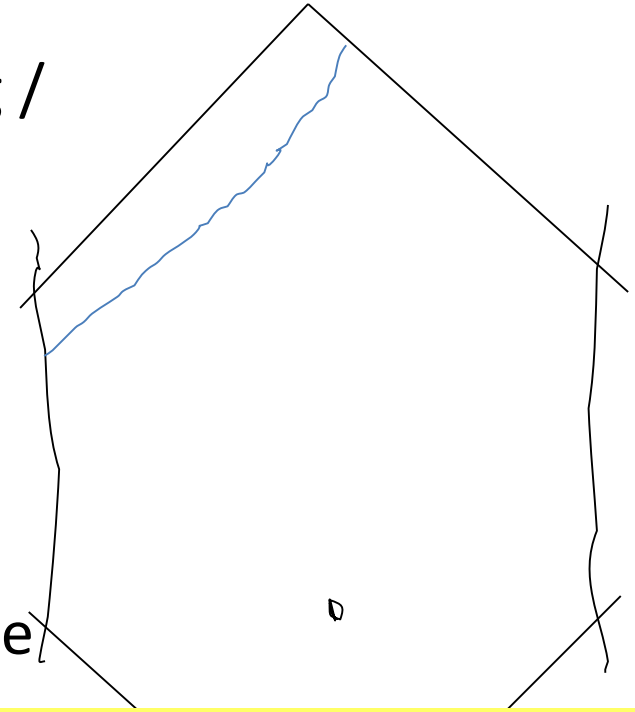
- Mother HBeAg+ on family screening

- Father – HBsAg +ve
- Elder sibling – HBsAg -ve

No maternal H/O jaundice, blood transfusion, body piercing, tattooing, dental extraction, operative procedure

Examination

- Vitals stable
- No pallor / icterus / edema / clubbing / LNs
- No stigmata of CLD



- P/A – soft, non distended
  Liver 2 cm BCM (span 6 cm)
  soft, rounded margins, smooth surface
  Spleen not palpable, no [illegible]

- Rest systems: NAD

Child with Incidentally detected
Asymptomatic HBsAg+
?Vertically transmitted
No peripheral stigmata of CLD

Investigations

	6 mo	7 mo	10 mo
INR		1.0	
Bil/D (mg/dL)	0.4/0.1	0.3/0.0	0.4/0.1
AST (IU/L)	56	59	35
ALT (IU/L)	**35**	**35**	**27**
Alb (g/dL)	3.8	3.4	3.7
HBsAg		+	
HBeAg		+	
Anti Hbe		**Negative**	
HBV DNA(IU/mL)		**>1.1X10^8**	

Immunotolerant phase of chronic hepatitis-B

USG abdomen: Normal

Fibroscan = 6.3 kPa

Role of Fibroscan as a non-invasive tool for liver fibrosis

Is Liver Bx indicated at this stage?

Investigations

	6 mo	7 mo	10 mo	18 mo
INR		1.0		1.1
Bil/D (mg/dL)	0.4/0.1	0.3/0.0	0.4/0.1	0.4/0.1
AST (IU/L)	56	59	35	56
ALT (IU/L)	**35**	**35**	**27**	**65**
Alb (g/dL)	3.8	3.4	3.7	3.8
HBsAg		+	+	+
HBeAg		+		+
Anti Hbe		**Negative**		
HBV DNA(IU/mL)		**>1.1X10^8**		**>1.1X10^8**

Liver Biopsy- Chronic Hepatitis with Minimal Activity

Ishak's Modified HAI-3

Fibrosis- 0

Indication of Liver Bx at this stage

Diagnosis – Scenario 1

- **Chronic Hepatitis B infection**
  - **Immunotolerant → Immunoclearance phase**

    e+, Anti e-, HBV DNA >1.1X10^8 IU/mL, ALT-65

- Perinatal transmission

- Liver Biopsy - Chronic Hepatitis with Minimal Activity Ishak's Modified HAI-3, Fibrosis- 0
- Fibroscan – 6.3 kPa

Family screening

- HBsAg
- Anti-HBs titre
- Total Anti-HBc

	HBsAg	Total Anti-HBc	Anti-HBs	Status	Remarks
1.	-	+	<10 mIU/mL	Exposed	Offer vaccination
2.	-	-	<10 mIU/mL	Unexposed Unimmunized	Offer vaccination
3.	-	-	>10 mIU/mL	Unexposed Immunized	No vaccination
4.	+	+	<10 mIU/mL	Infected	Further testing HBeAg, Anti-HBe, DNA

Chronic HBV infection : Who to treat

Better Response to treatment

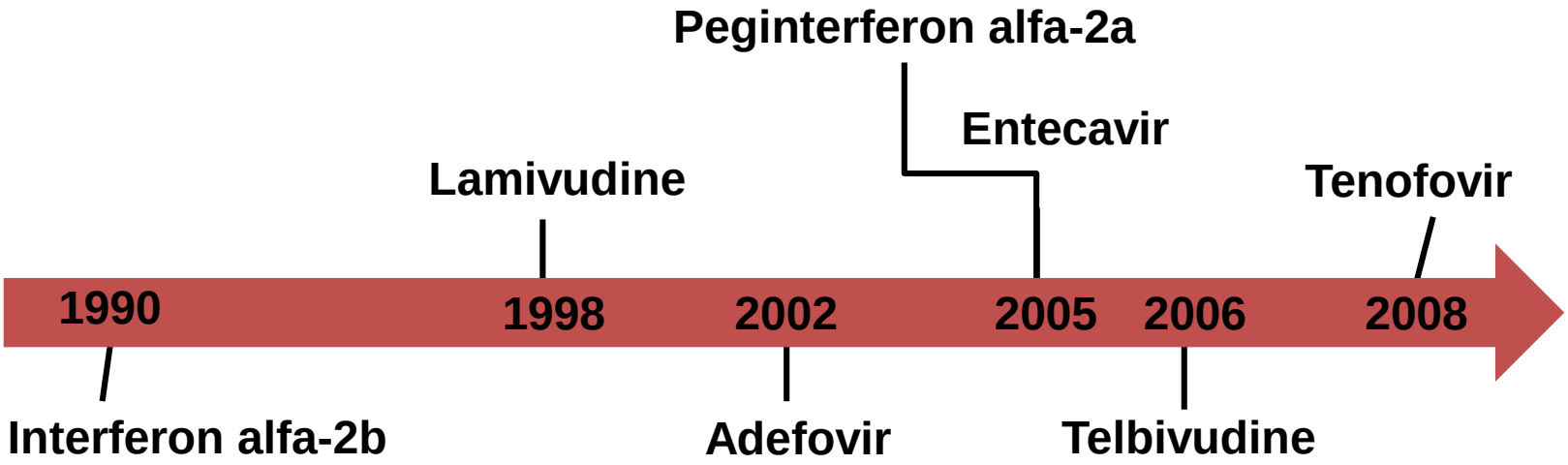
- **High ALT**
- **Inflammation in biopsy**
- **Low HBV DNA**
- **Late acquisition of infection**

Mei-Hwei Chang. Pediatric Gastroint Dis. 2004

Table 2. Special Circumstances in Which Either Temporary or Long-Term Treatment of Children With Chronic HBV Infection Should be Strongly Considered

Rapid deterioration of liver synthetic function
Cirrhosis (compensated or decompensated)
Glomerulonephritis due to HBV infection
Prevention or treatment of recurrent HBV infection after liver transplantation
Recipient of a liver graft from an anti-hepatitis B core antigen (anti-HBc)-positive donor
Need for immunosuppression or chemotherapy
Presence of coinfections (HBV/HIV, HBV/HCV, HBV/HDV)
Children with a strong family history of HCC who are in the immune active phase
Pregnant females with high viral load (>20 million IU/mL) in the third trimester, especially those who have had a previous infant with failed perinatal immunoprophylaxis

Evolution of Chronic HBV Therapy



Approved HBV treatments

Immunomodulator :

- **Interferon alfa 2a & 2b**

Oral Antiviral (Nuc's)

- **Lamivudine**
- **Adefovir**
- **Entecavir**
- **Tenofovir**

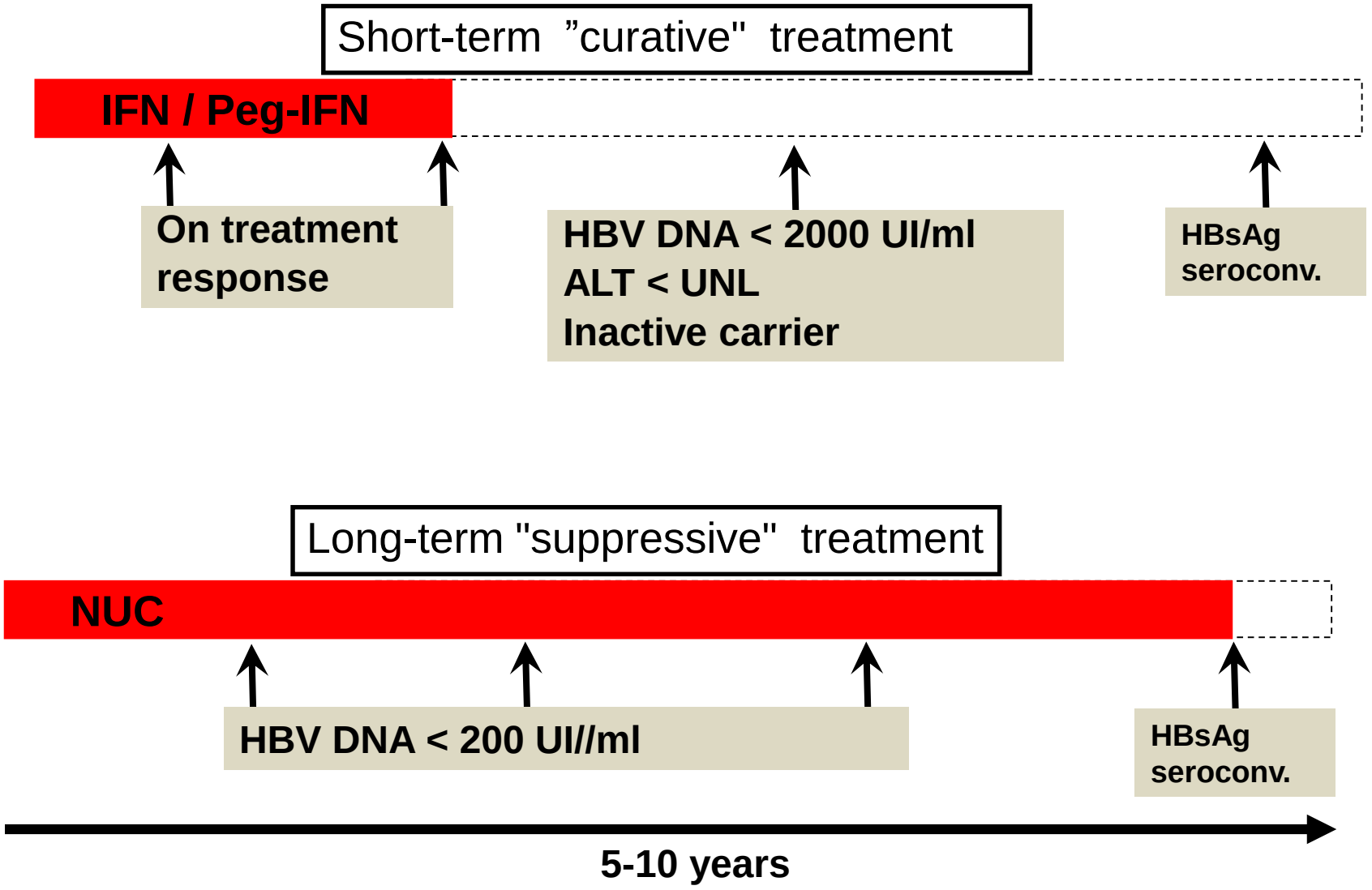
PLACEBO-CONTROLLED TRIAL OF RECOMBINANT α_2-INTERFERON IN CHINESE HBsAg-CARRIER CHILDREN

CHING-LUNG LAI
ANNA SUK-FONG LOK
HSIANG-JU LIN
PUI-CHEE WU
ENG-KIONG YEOH
CHAP-YUNG YEUNG

Departments of Medicine and Paediatrics, University of Hong Kong, Queen Mary Hospital, Hong Kong

r-IFN was safe but had no long-term beneficial effects on HBsAg carriage in Chinese children.

Therapeutic strategy for CHB



Which route to take ?

	IFN / PEG-IFN	ANTIVIRALS
Advantages	• Finite duration • No resistance • Sustained response (30% HBeAg+, 20% HBeAg -) • HBsAg clearance	• New NUCs (ETV,TDF) might inhibit viral replication as monotherapy in most pts for at least 5 yrs • Well tolerated • oral
Disadvantages	• Side effects • Injections • Contraindicated for decompensated pts	• Long/indefinite therapy • drug resistance • Expensive if long term • Long term toxicity unknown

Treatment goal

Ideal end point :

Loss of HBsAg , anti-HBs seroconversion and loss of cccDNA

Functional Cure :

Sustained viral suppression along with Hbe seroconversion (HBeAg-ve, anti HBeAb+ve)

Options in Immunotolerant phase

- No treatment recommendation
- Sequential treatment

Lam X 8 wks → LAM + IFN X 44 wks (2 studies)

	D'Antiga (n=23)	**Poddar (n=28)**
Age (years)	10 (3-17)	6 (2-13)
End treatment seroconversion	5 (22%)	10 (36%)
Sustained seroconversion	5 (22%)	11 (39.3%)
HBsAg loss	4 (17%)	6 (21.5%)
Durability of response	100%	91%
YMDD mutation	Nil	Not done

Options in Immunoclearance phase in children

Drug	Duration	HBeAg loss	DNA loss	ALT N	HBsAg loss
IFN-alpha	24 wks	33-48%	26%	-	8-10%
Lamivudine	1-2 yrs	26-51%	23-28%	-	2%
Adefovir	1-2 yrs	17-58%	11-39%	-	2%
Entecavir	24 wks to ≥1 yr	38%	88% in e- 23% in e+	88%	-
Tenofovir	72 wks	21%	-	74%	2%

Sequential treatment	Duration	Seroconversion
IFN + LAM → LAM	6mo → 6 mo	49-60%
LAM X 2 mo → LAM + IFN X 6 mo → LAM X 4 mo	2 mo → 6 mo → 4 mo	34%

Bikrant et al 2017….ILBS

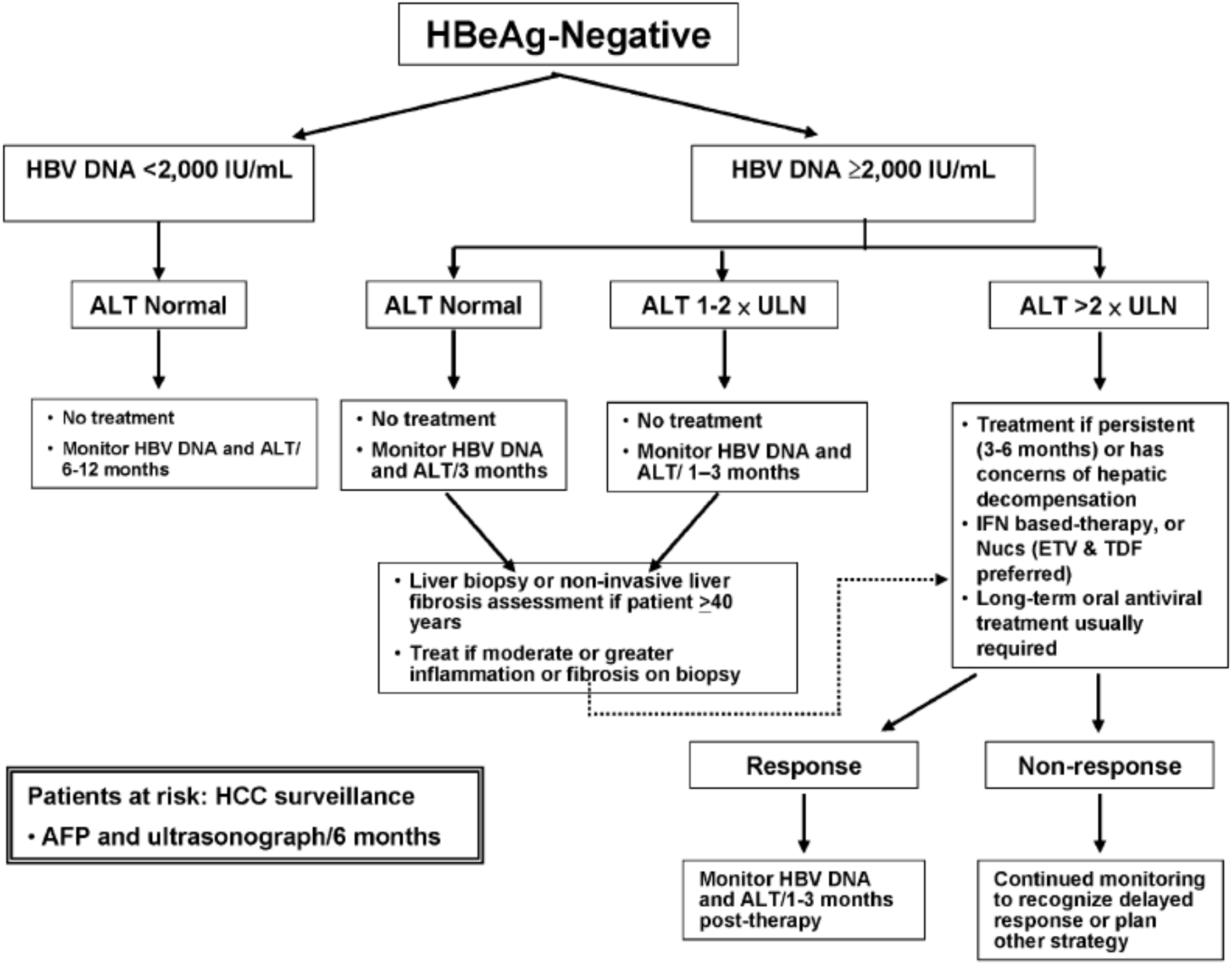
- Sequential therapy
- Effective in IC phase with ALT more than 100
- Not effective in IT

Pegylated interferon-based sequential therapy for treatment of HBeAg reactive pediatric chronic **hepatitis B**-First study in children.
Lal BB, Sood V, Khanna R, Rawat D, Verma S, Alam S.

Conclusion

- Universal immunization HB vaccine
- Immunotolerant children may not be treated unless family history of Cirrhosis and HCC
- Immunoactive patients with high ALT may be treated ……60-70% may seroconvert
- Hbe Ag negative and those with higher levels of activity and fibrosis can be treated
- Need for more studies on treatment indications and stopping rule of the therapy
- Family screening and vaccination


Thank You!


HBeAg-Negative
HBV DNA <2,000 IU/mL
HBV DNA ≥2,000 IU/mL
ALT Normal
ALT Normal
ALT 1-2 x ULN
ALT >2 x ULN
• No treatment
• Monitor HBV DNA and ALT/ 6-12 months
• No treatment
• Monitor HBV DNA and ALT/3 months
• No treatment
• Monitor HBV DNA and ALT/ 1–3 months
• Treatment if persistent (3-6 months) or has concerns of hepatic decompensation
• IFN based-therapy, or Nucs (ETV & TDF preferred)
• Long-term oral antiviral treatment usually required
• Liver biopsy or non-invasive liver fibrosis assessment if patient ≥40 years
• Treat if moderate or greater inflammation or fibrosis on biopsy
Response
Non-response
Monitor HBV DNA and ALT/1-3 months post-therapy
Continued monitoring to recognize delayed response or plan other strategy
Patients at risk: HCC surveillance
• AFP and ultrasonograph/6 months

Determinants of outcome

HBeAg seroconversion

Older age*
Higher ALT levels at presentation*
Acute exacerbations*
HBV genotype (B > C)
Ethnicity (other than Asian)

Cirrhosis

Host Factors	Virus Factors	Environmental Factors
Older age* (longer duration)	High levels of HBV replication*	Concurrent infection (HCV*, HDV, HIV)
Male*	Genotype (C > B)*	Alcohol consumption*
Immune status	HBV variant (core promoter)	Diabetes mellitus†
		Obesity†

HCC

Host Factors	Virus Factors	Environmental Factors
Older age (longer duration)*	High levels of HBV replication*	Concurrent infection (HCV*, HDV)
Male*	Genotype (C>B)	Alcohol consumption*
Presence of cirrhosis*	HBV variant (core promoter)	Aflatoxin
		Smoking†
Family history of HCC*	X gene transactivation	Diabetes mellitus†
Race (Asian, African)		Obesity†

Interferon / Peg - Interferon

Gastroenterology. 1998 May;114(5):988-95.

Interferon alfa therapy for chronic hepatitis B in children: a multinational randomized controlled trial.

Sokal EM, Conjeevaram HS, Roberts EA, Alvarez F, Bern EM, Goyens P, Rosenthal P, Lachaux A, Shelton M, Sarles J, Hoofnagle J.

Cliniques St. Luc, Pediatric Hepatology, Université Catholique de Louvain, Brussels, Belgium. sokal@pedilucl.ac.be

	Treated 70	Untreated 74	*p*
HBeAg/HBVDNA neg			
at 24 weeks	18 (26%)	8 (11%)	<0.05
at 48 weeks	23 (33%)	8 (11%)	<0.05
HBsAg neg	7 (10%)	1 (1.2%)	<0.05

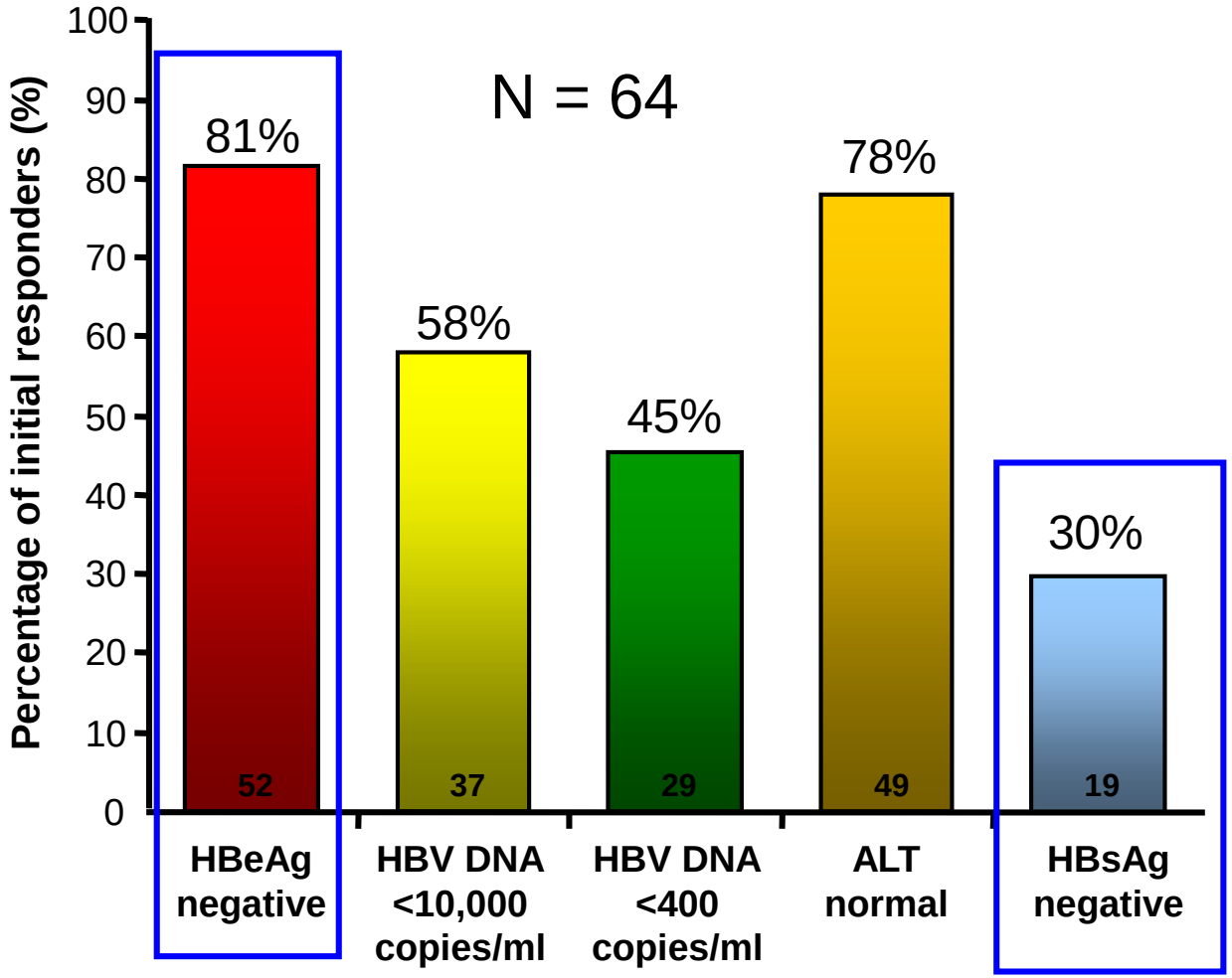
Long term effect of alpha interferon in children with chronic hepatitis B

F Bortolotti, P Jara, C Barbera, G V Gregorio, A Vegnente, L Zancan, L Hierro, C Crivellaro, G Mieli Vergani, R Iorio, M Pace, P Con, A Gatta

After 5 yr observation :

- HBeAg clearance : 60% of treated patients
  65% of controls
  But
- HBsAg clearance : 25 % in early IFN responders
  0 % in controls

HBeAg-positive CHB: 3-year follow-up of HBeAg responders to PEG-IFN

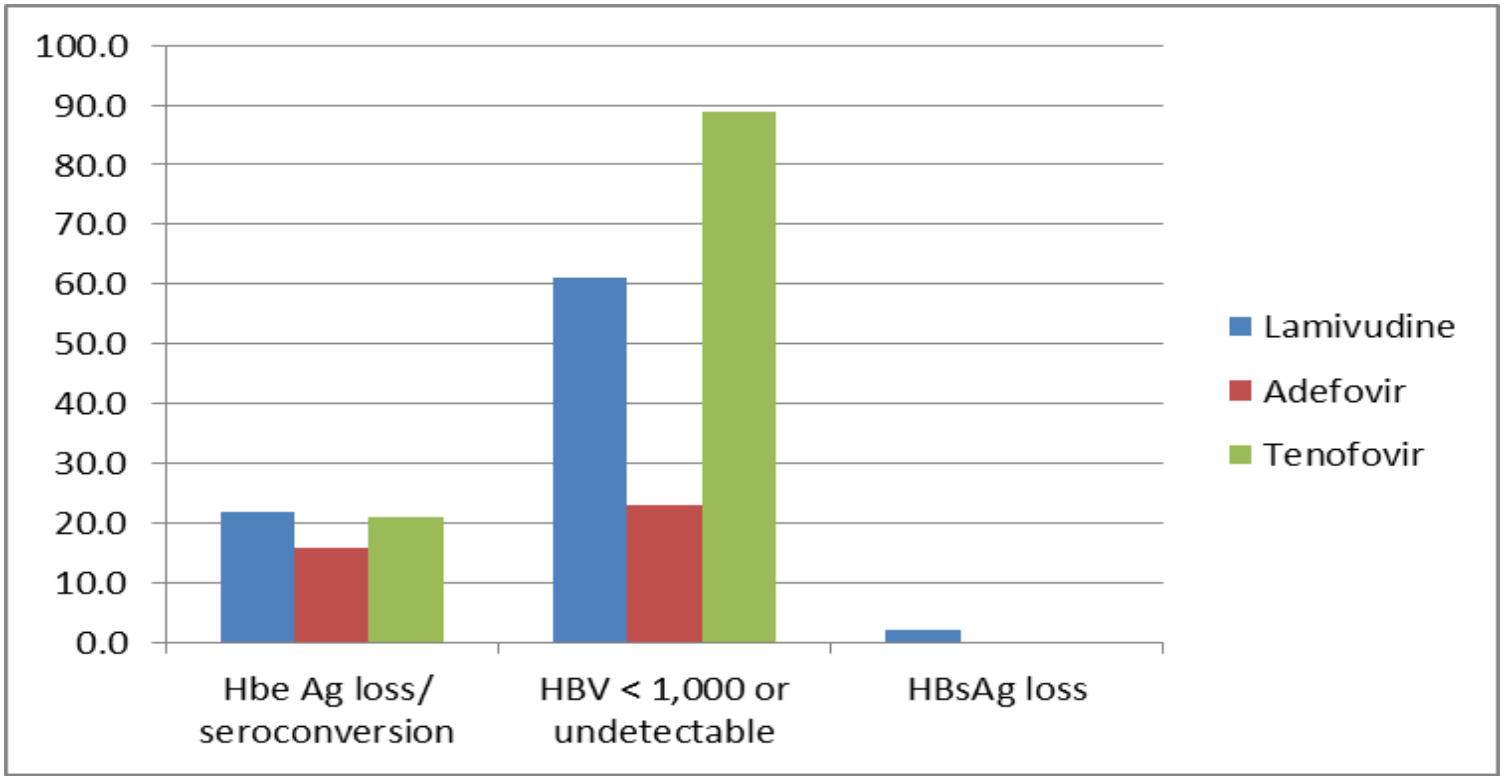


Buster et al, Gastroenterology 2008 in press

NUC’s

Lamivudine, Entecavir, Adefovir, Tenofovir

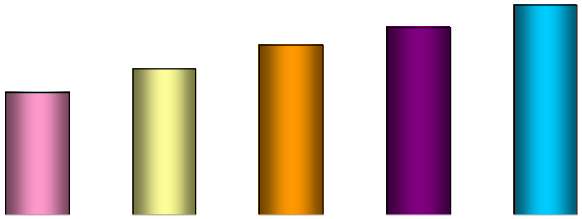
NUC's in children with chronic HBV



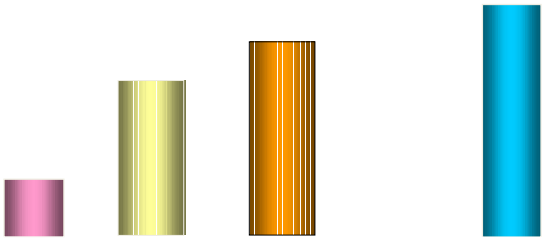
Jonas et al – 2002 NEJM – Lamivudine
Jonas et al – 2008 Hepatology – Adefovir
Murray et al – 2013 Hepatology – Tenofovir

HBeAg seroconversion during continued treatment

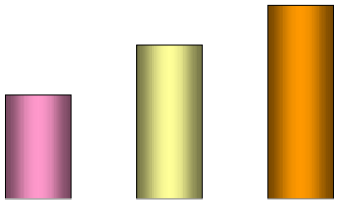
Lamivudine



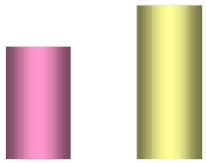
Adefovir



Entecavir



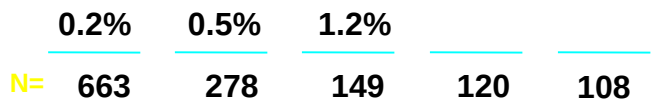
Telbivudine



Resistance Rates in Nucleoside-Naive Patients

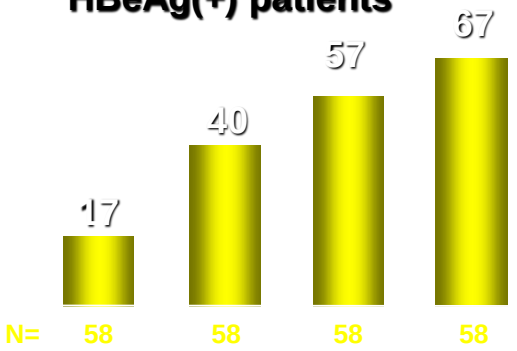
Genotypic resistance to ENTECAVIR

HBeAg(+) and (-) patients



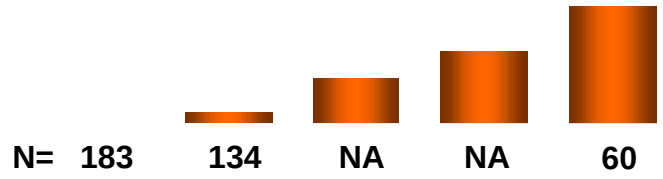
Genotypic resistance to LAMIVUDINE[1]

HBeAg(+) patients

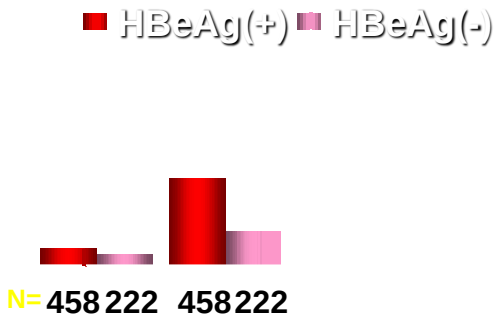


Genotypic resistance to ADEFOVIR[2]

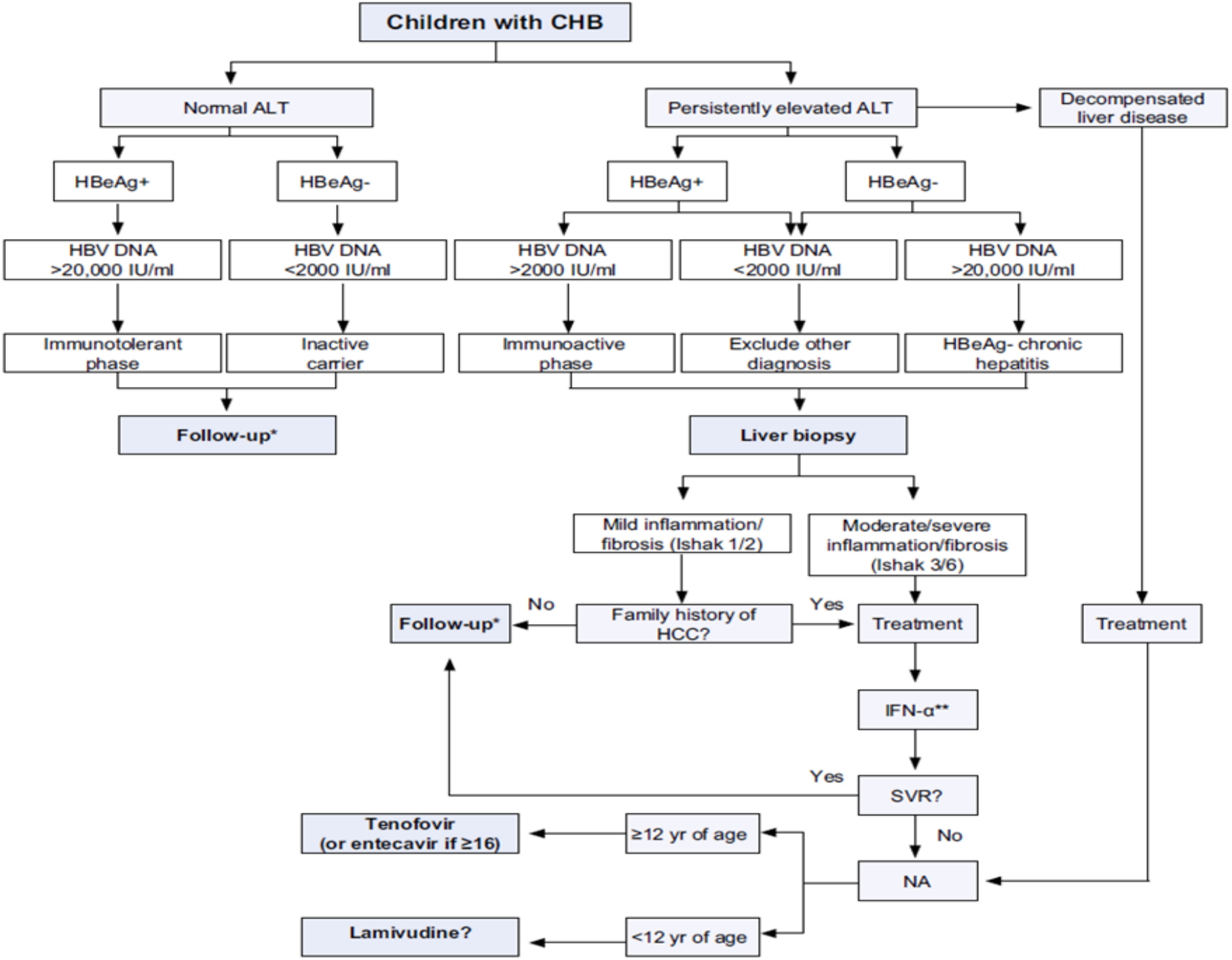
HBeAg(-) patients



Viral breakthrough with genotypic resistance to TELBIVUDINE[3,4]



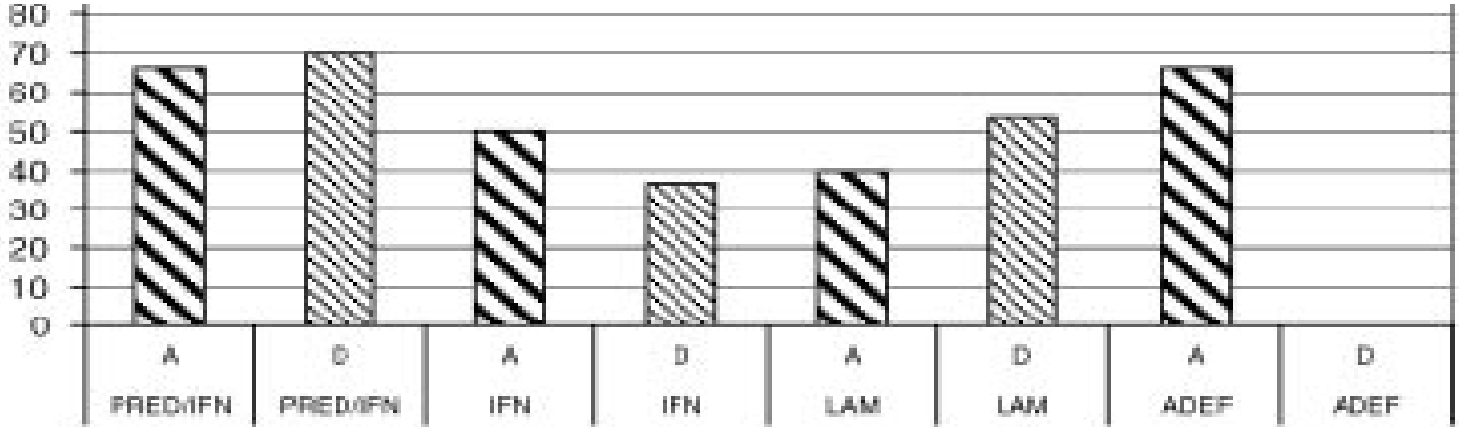
1. Chang TT, et al. *J Gastroenterol Hepatol* 2004; 19:1276-1282; 2. Hadziyannis S, et al. Gastroenterology 2006;131:1743-1751;
3. Standring DN, et al. J Hepatol. 2006;44(Suppl 2):S191 (Poster 514); 4. Lai CL, et al. Hepatology. 2006;44(Suppl 1):222A (Oral 91).


Children with CHB
Normal ALT
Persistently elevated ALT
Decompensated liver disease
HBeAg+
HBeAg-
HBeAg+
HBeAg-
HBV DNA >20,000 IU/ml
HBV DNA <2000 IU/ml
HBV DNA >2000 IU/ml
HBV DNA <2000 IU/ml
HBV DNA >20,000 IU/ml
Immunotolerant phase
Inactive carrier
Immunoactive phase
Exclude other diagnosis
HBeAg- chronic hepatitis
Follow-up*
Liver biopsy
Mild inflammation/ fibrosis (Ishak 1/2)
Moderate/severe inflammation/fibrosis (Ishak 3/6)
No
Follow-up*
Family history of HCC?
Yes
Treatment
Treatment
IFN-α**
Yes
SVR?
No
Tenofovir (or entecavir if ≥16)
≥12 yr of age
NA
Lamivudine?
<12 yr of age

Does Genotype Predict Response to Treatment in Children Infected With Hepatitis B Perinatally?

TABLE II. Genotype and HBeAg to Anti-HBe Seroconversion

Genotype	Interferon alone HBeAg seroconversion/total treated	Interferon + prednisolone HBeAg seroconversion/total treated	Lamivudine	Adefovir	Genotype total
A	2/4 (50%)	4/6 (66.7%)	2/5 (40%)	2/3 (66.7%)	10/18 (55.5%)
B	0/5	0/2	0/1	0	1/8 (12.5%)
C	0/0	0/1	0/1	0/1	0/3
D	4/11 (36%)	7/10 (70%)	8/15 (53.3%)	0/3	19/39 (48.7%)
Total	6/20	11/19	10/22	2/7	68



J. Med. Virol. DOI 10.1002/jmv

Antibody Levels and Protection after Hepatitis B Vaccination: Results of a 15-Year Follow-up

Table 1. **The Predicted Geometric Mean Concentrations of Antibody to Hepatitis B Surface Antigen 15 Years after Initial Hepatitis B Vaccination from Linear Mixed Model***

Sex and Age Class	Predicted Anti-HBs Level, *mIU/mL*		
	Initial Anti-HBs Level		
	100 mIU/mL	1000 mIU/mL	10 000 mIU/mL
Female			
0–4 y	1.8	11.6	72.9
5–19 y	4.3	27.0	169.9
≥20 y	8.4	52.9	332.9
Male			
0–4 y	2.6	16.6	104.1
5–19 y	6.1	38.6	242.8
≥20 y	12.0	75.6	475.5

* Anti-HBs = antibody to hepatitis B surface antigen.

Antibody Levels and Protection after Hepatitis B Vaccination: Results of a 15-Year Follow-up

Table 2. **Antibody Concentrations and Markers of Hepatitis B Virus Infection in 24 Study Participants with Evidence of Breakthrough Hepatitis B during 15 Years after Hepatitis B Immunization***

Age at First Vaccine Dose, *y*	Sex	Time from First Dose to Anti-HBc Positivity, *y*	Anti-HBs Level, *mIU/mL*			HBV DNA Status	HBV Conversion Status†
			Highest before Infection	1 y before Infection	At Time of First Anti-HBc–Positive Result		
22	Female	1	22	NA	214‡	Positive	Definite
54	Female	2	5	5	604	Positive	Definite
44	Female	4	505	173	176	Negative	Definite
45	Female	4	8	1	3026	Positive	Definite
11	Female	5	518	30	21	Positive	Definite
1 8/12	Male	5	608	54	183	Negative	Definite
47	Male	5	37	0	209§	Positive	Definite
25	Male	5	181	18	16	Negative	Definite
46	Female	6	44	0	1424	Negative	Definite
46	Female	7	2	NA	229	Negative	Definite
1 4/12	Female	7	1011	11	540	Negative	Definite
16	Male	8	23	NA	132	Negative	Definite
1 11/12	Female	8	456	2	333	Negative	Definite
6	Female	8	1817	142	210	Negative	Definite
42	Female	9	0	0	0‖	Negative	Definite
1 2/12	Male	11	12	0	29¶	Positive	Definite
17	Male	5	86	9	5809	Negative	Possible
59	Male	5	7	NA	406	Negative	Possible
4	Female	6	4474	292	1692	Negative	Possible
1 5/12	Female	6	11	4	3	Negative	Possible
49	Female	7	6284	NA	3939**	Negative	Possible
1 8/12	Male	9	4850	4850	1417	Negative	Possible
9	Male	11	18 456	951	889	Negative	Possible
65	Female	15	2	0	0	Negative	Possible

HBV - NEW MARKER

HBsAg levels

- Serum levels of HBsAg correlates with intrahepatic cccDNA concentration
- Decline in HBsAg level on treatment may herald induction of immune control
- HBsAg levels during treatment can indentify patients with very high or very low probability of response.

Response-Guided Peginterferon Therapy in Hepatitis B e Antigen-Positive Chronic Hepatitis B Using Serum Hepatitis B Surface Antigen Levels

Milan J. Sonneveld,[1] Bettina E. Hansen,[1,2] Teerha Piratvisuth,[3] Ji-Dong Jia,[4] Stefan Zeuzem,[5] Edward Gane,[6] Yun-Fan Liaw,[7] Qing Xie,[8] E. Jenny Heathcote,[9] Henry L.-Y. Chan,[10] and Harry L.A. Janssen[1,9]

- 803 adults (3 global studies)
- Stopping rule –
  - Wk 12 - No decline of HBsAg titre for genotype A,D
    HBsAg titre >20,000 IU/ml in genotype B, C
  - Wk 24 - No decline from baseline at wk 24
- Prediction rule –
  - High probability of response – HBsAg <1500 IU/ml
  - Low probability of response – HBsAg >20,000 IU/ml

Hepatology : 8, Issue3 2013,

Definitions

Inactive HBsAg carrier state

1. HBsAg+ > 6 months
2. HBeAg-, anti-HBe+
3. Serum HBV DNA <2,000 IU/ml
4. Persistently normal ALT/AST levels
5. Liver biopsy confirms absence of significant hepatitis

Resolved hepatitis B

1. Previous known history of acute or chronic hepatitis B or the presence of anti-HBc ± anti-HBs
2. HBsAg–
3. Undetectable serum HBV DNA#
4. Normal ALT levels

Lok ASF, et al. *Hepatology*. 2007;45:507.

CAN WE DO BETTER WITH EXISTING TREATMENTS?

Chronic HBV infection
Who should be treated?

- Those with active disease who are more likely to clear the virus spontaneously

- Those with tolerant disease who are less likely to clear the virus spontaneously

COMBINED LAMIVUDINE/INTERFERON-α TREATMENT IN 'IMMUNOTOLERANT' CHILDREN PERINATALLY INFECTED WITH HEPATITIS B: A PILOT STUDY

LORENZO D'ANTIGA, MD, MARION AW, MD, MARK ATKINS, FRCPATH, ALISON MOORAT, BSC, DIEGO VERGANI, MD, AND GIORGINA MIELI-VERGANI, MD

Harnessing the innate and adaptive immune system: rationale for combining IFN and NUCs in HBV treatment

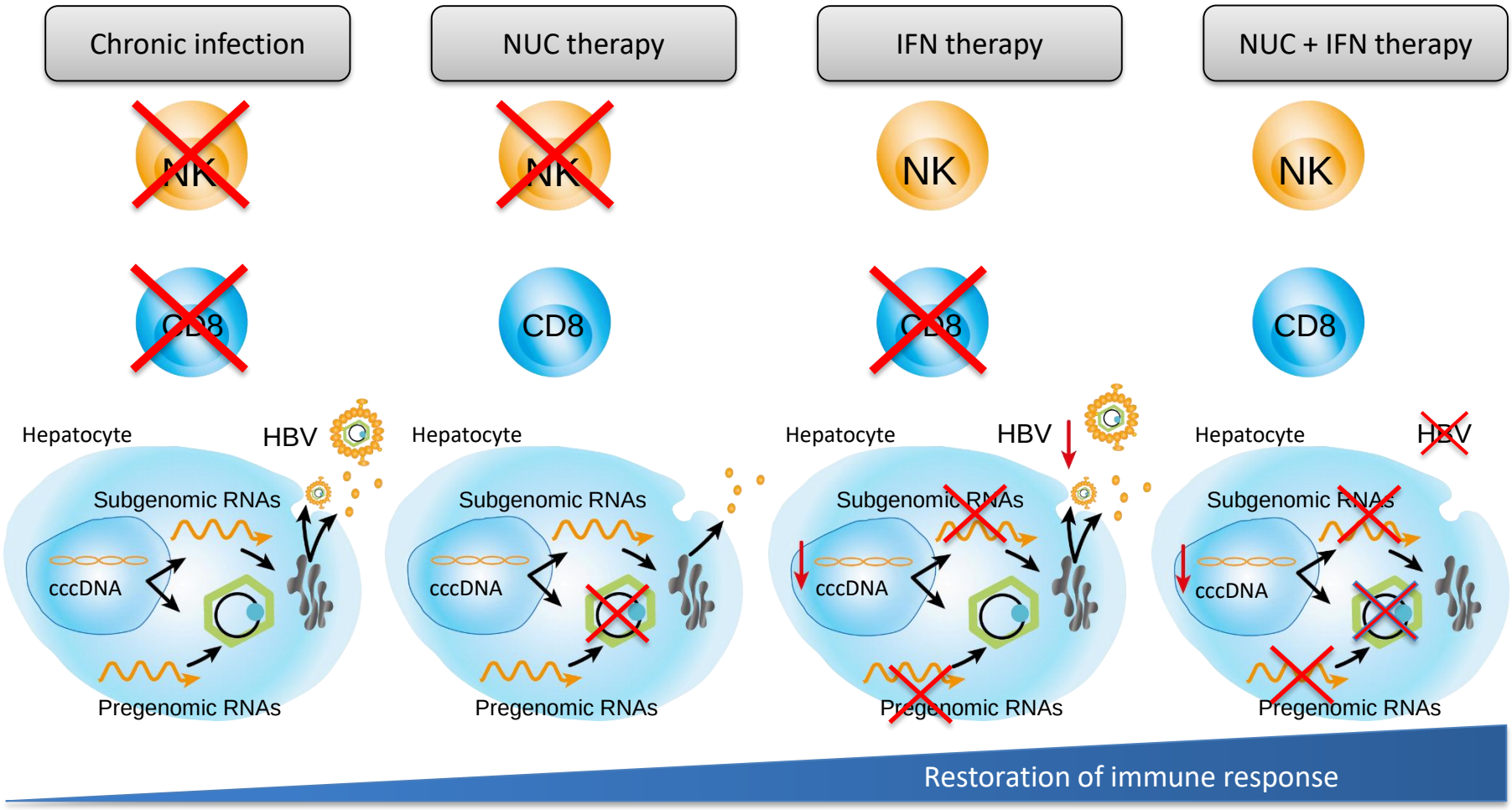


Figure adapted from Thimme R, et al. J Hepatol 2013;58:205–9. Micco L, et al. J Hepatol. 2013;58:225–33.

COMBINED LAMIVUDINE/INTERFERON-α TREATMENT IN 'IMMUNOTOLERANT' CHILDREN PERINATALLY INFECTED WITH HEPATITIS B: A PILOT STUDY

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8 weeks lamivudine followed by 44 weeks lamivudine + IFN-α

- 23 children (16 oriental)
- Anti-HBe seroconversion : 5/23 (22%)
- Anti-HBs seroconversion : 4/23 (17%)
- No YMDD mutations

J Paediatr, 2006

J Paediatr, 2006

King's pilot treatment study in children with infancy-acquired CHB

Therapy response results

	End of therapy	Follow-up Week 24	Follow-up Year 1	Follow-up Year 5	Follow-up Year 10
HBeAg clearance	5 patients (22%)	5 patients (22%)	6 patients (26%)	7 patients (30%)	11 patients (48%)
HBsAg clearance	4 patients (17%)	5 patients (22%)	5 patients (22%)	5 patients (22%)	5 patients (22%)
HBV DNA <100 IU/ml	4 patients (17%)	5 patients (22%)	5 patients (22%)	5 patients (22%)	5 patients (22%)
YMDD mutation	0 patients (0%)	0 patients (0%)	0 patients (0%)	0 patients (0%)	0 patients (0%)

Journal of Viral Hepatitis, 2013, **20**, 311–316 doi:10.1111/jvh.12007

Cure for immune-tolerant hepatitis B in children: is it an achievable target with sequential combo therapy with lamivudine and interferon?

U. Poddar,[1] S. K. Yachha,[1] J. Agarwal[1] and N. Krishnani[2] [1]*Department of Pediatric Gastroenterology; and* [2]*Department of Pathology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India*

- 28 children
- Anti HBe seroconversion – 11/28 (39%)
- Anti HBs seroconversion – 6/28 (21%)

JOURNAL OF VIROLOGY, Mar. 2011, p. 2416–2428 Vol. 85, No. 5
0022-538X/11/$12.00 doi:10.1128/JVI.01449-10

Immune and Viral Profile from Tolerance to Hepatitis B Surface Antigen Clearance: a Longitudinal Study of Vertically Hepatitis B Virus-Infected Children on Combined Therapy▽

Ivana Carey,[1] Lorenzo D'Antiga,[1] Sanjay Bansal,[1] Maria Serena Longhi,[1] Yun Ma,[1] Irene Rebollo Mesa,[2] Giorgina Mieli-Vergani,[1] and Diego Vergani[1]*

Institute of Liver Studies and Paediatric Liver Centre, King's College London School of Medicine at King's College Hospital, Denmark Hill, London SE5 9RS, United Kingdom,[1] and MRC Centre for Transplantation, King's College London School of Medicine at Guy's Hospital, St. Thomas Street, London, SE1 9RT, United Kingdom[2]

JOURNAL OF VIRAL HEPATITIS JVH

Journal of Viral Hepatitis, 2014 doi:10.1111/jvh.12316

HBsAg plasma level kinetics: a new role for an old marker as a therapy response predictor in vertically infected children on combination therapy

I. Carey, M. Bruce, M. Horner, Y. Zen, L. D'Antiga, S. Bansal, D. Vergani and G. Mieli-Vergani *Institute of Liver Studies and Paediatric Liver, GI & Nutrition Centre, King's College London School of Medicine at King's College Hospital, London, UK*

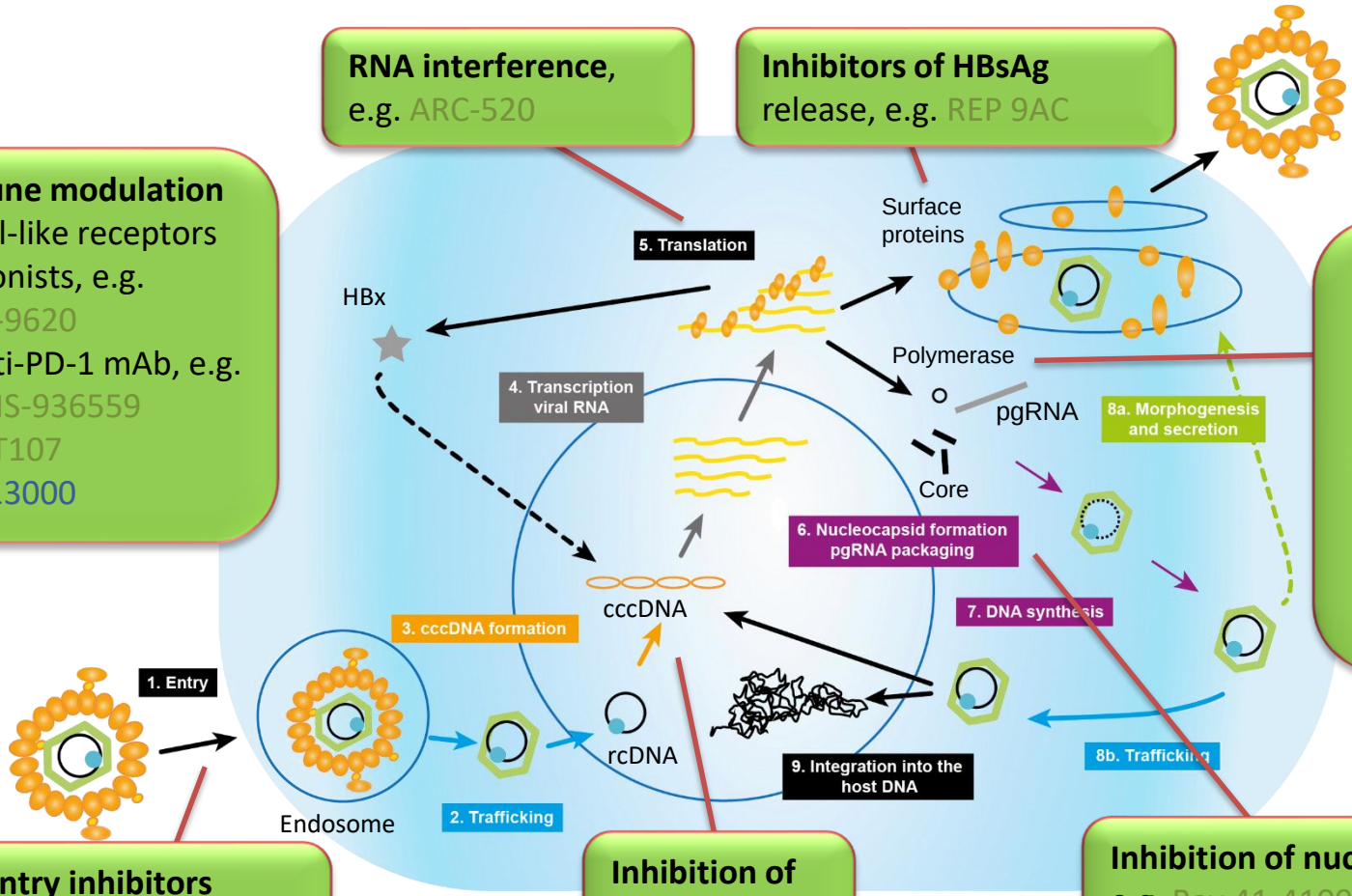
Ongoing treatment trial

1. Pegylated Interferon monotherapy for children with chronic HBV infection with abnormal liver function tests

2. Pegylated Interefron +/- Oral NUCs for immunotolerant children with chronic HBV infection

FUTURE DIRECTIONS FOR HBV TREATMENT - ? CURE

Future directions: drugs in development



Development stage: **preclinical**, **clinical**

Zoulim F, et al. Antiviral Res 2012;96(2):256–9; HBF Drug Watch, Available at: http://www.hepb.org/professionals/hbf_drug_watch.htm. Accessed 15 Aug 2013. Zoulim F, et al. Gastroenterology 2013;144:1342–4.

Table 1. Experimental HBV Therapeutics in Late Preclinical or Clinical Stage*

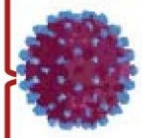
Compound	Mechanism/ Target†	Stage of Development	Sponsor	Reference
Direct-acting antivirals:				
GS-7340 (tenofovir alafenamide fumarate	Polymerase (prodrug of tenofovir)	Phase 2/3	Gilead Sciences	47; NCT0194047, NCT01940341‡
CMX157	Polymerase (prodrug of tenofovir)	Phase 1/2§	Contravir (Chimerix)	146; NCT01080820‡
NVR1221/3778	Capsid	Phase 1/2	Novira	84; NCT02112799‡
Sulfamoylbenzamides	Capsid	Animal	Oncore	147
GLS4	Capsid	Phase 1	HEC Pharm Group, China	148
Bay41-4109	Capsid	Phase 1	AiCuris	83
REP 2139-Ca	Assembly/HBsAg	Phase 1/2	Replicor	NCT02233075‡
ARC-520	RNAi	Phase 1/2	Arrowhead	94; sponsor's website; NCT02065336‡
TKM-HBV	RNAi	Phase 1	Tekmira	Sponsor's website; NCT02041715‡
ALN-HBV	RNAi	Animal	Alnylam	Sponsor's website
DNA-directed RNAi	RNAi	Animal	Benitec	Sponsor's website
ISIS HBV	Antisense	Phase 1	Isis	Sponsor's website
Host targeting agents:				
Myrcludex B	Entry/NTCP	Phase 1/2	Myr-GmbH/Hepatera	75
Birinapant	Apoptosis/second mitochondrial activator of caspases	Phase 1	Tetralogic	Sponsor's website; NCT02288208‡
Flavonoids	STING agonist (pattern recognition receptor)	Animal	Oncore	149
NVP018	Cyclophilins, IRF-9	Animal	Oncore (NeuroVive)	Sponsor's website
Epitope HBV	Glucosidase/therapeutic vaccine	Animal	Blumberg Institute	150

Immune modulatory agents:

GS-9620	TLR-7 agonist	Phase 2	Gilead Sciences	122; NCT02166047‡
Nivolumab	PD-1 blockade	Phase 1‖	BMS	151; Sponsor's website, NCT01658878‡
SB 9200HBV	RIG-I and NOD2 activation	Phase 1/2	INC/Springbank	152; NCT01803308‡
GS-4774	Therapeutic vaccine	Phase 2/3	Gilead Sciences/GlobeImmune	144; NCT02174276‡
ANRS HB02	Therapeutic vaccine	Phase 1/2	French National Agency for Research on AIDS and Viral Hepatitis	141; NCT02166047‡
Heplisav B Dynavax 601	Therapeutic vaccine	Phase 1	Dynavax	153; NCT01023230‡
Nasvac	Therapeutic vaccine	Phase 2/3	CGEB, Cuba	154
TG1050	Therapeutic vaccine	Phase 1/1b	Transgene	NCT02428400
HBIG + GM-CSF + HBV vaccine	Therapeutic vaccine	Phase 1/2	Beijing 302 Hospital	NCT01878565
HBV vaccine + IFN-α2b + IL-2	Therapeutic vaccine	Phase 2/3	Tongji Hospital	NCT02360592 (labeled as Phase 4)
HBV vaccine-activated dendritic cells	Therapeutic vaccine	Phase 1/2	Third Affiliated Hospital, Sun Yat-Sen University	NCT01935635
Euvax + PEG-IFN-α	Therapeutic vaccine	Phase 2/3	Seoul National University	NCT02097004 (labeled as Phase 4)
PD-1 monoclonal antibody	PD1 blockade	Animal	AcadSin	155
Altravax HBV	Therapeutic vaccine	Animal	Altravax	Sponsor's website
INO-1800	Therapeutic vaccine	Animal	Innovio	Sponsor's website

Future curative CHB regime :

Approach	Potential benefit
Entry/release inhibitor	Prevent entry/spread
cccDNA inhibitor	Deplete cccDNA reservoir
Potent polymerase inhibitor	Suppress replication
Immune modulator	Activate or restore antiviral immunity



Thank you

Infancy-acquired chronic HBV infection

Predictors of outcome

-
-
-
-
-

Carey et al, submitted to AASLD 2014

Infancy-acquired chronic HBV infection

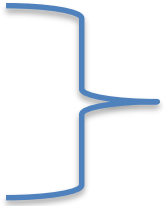
Predictors of outcome

at last follow-up

- **38% HBeAg seroconversion**
-
-

predictors of HBeAg seroconversion

-
-
-



predictors of HBsAg seroconversion

-

Carey et al, submitted to AASLD 2014