Current Therapy of Hepatitis B
Planning for 2013 and Beyond

"Where East Meets West"
Search for a "cure"

Cebu, The Philippines APASL 2013

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Achieving Heights for an Optimum Management of Hepatitis B Virus Infection

Nov 22, 2013
12:00 nn
3rd APASL Single Topic Conference HCC in 3D
Radisson Blu Hotel Cebu City Philippines

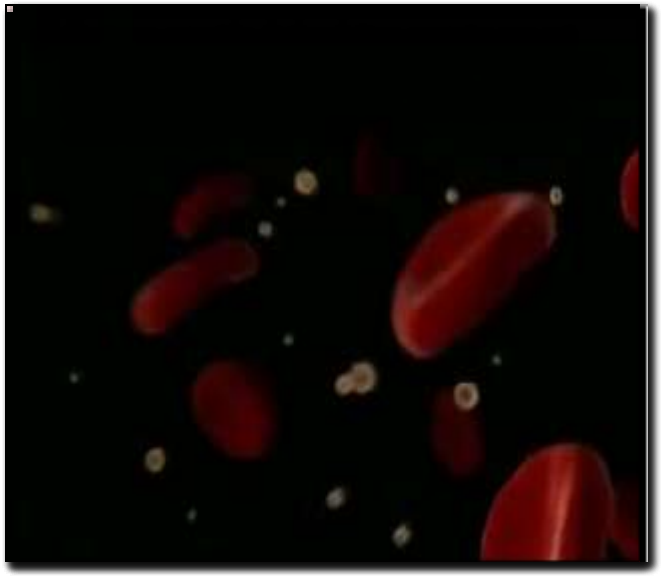
Disclosures

- Advisory Board
  - BMS, Gilead, Genentech, Arrowhead
- Honorarium, speakers bureau
  - BMS, Gilead, Genentech
- Investment (stock options)
  - Arrowhead

My honorarium for this meeting will be donated to recovery efforts in the Philippines via Dr Fajardo and his Sagip Kapamilya ABS CBN Foundation International and the fund raising event in Las Vegas with Martin Nievera on Dec 16th

Hepatitis B: The Facts

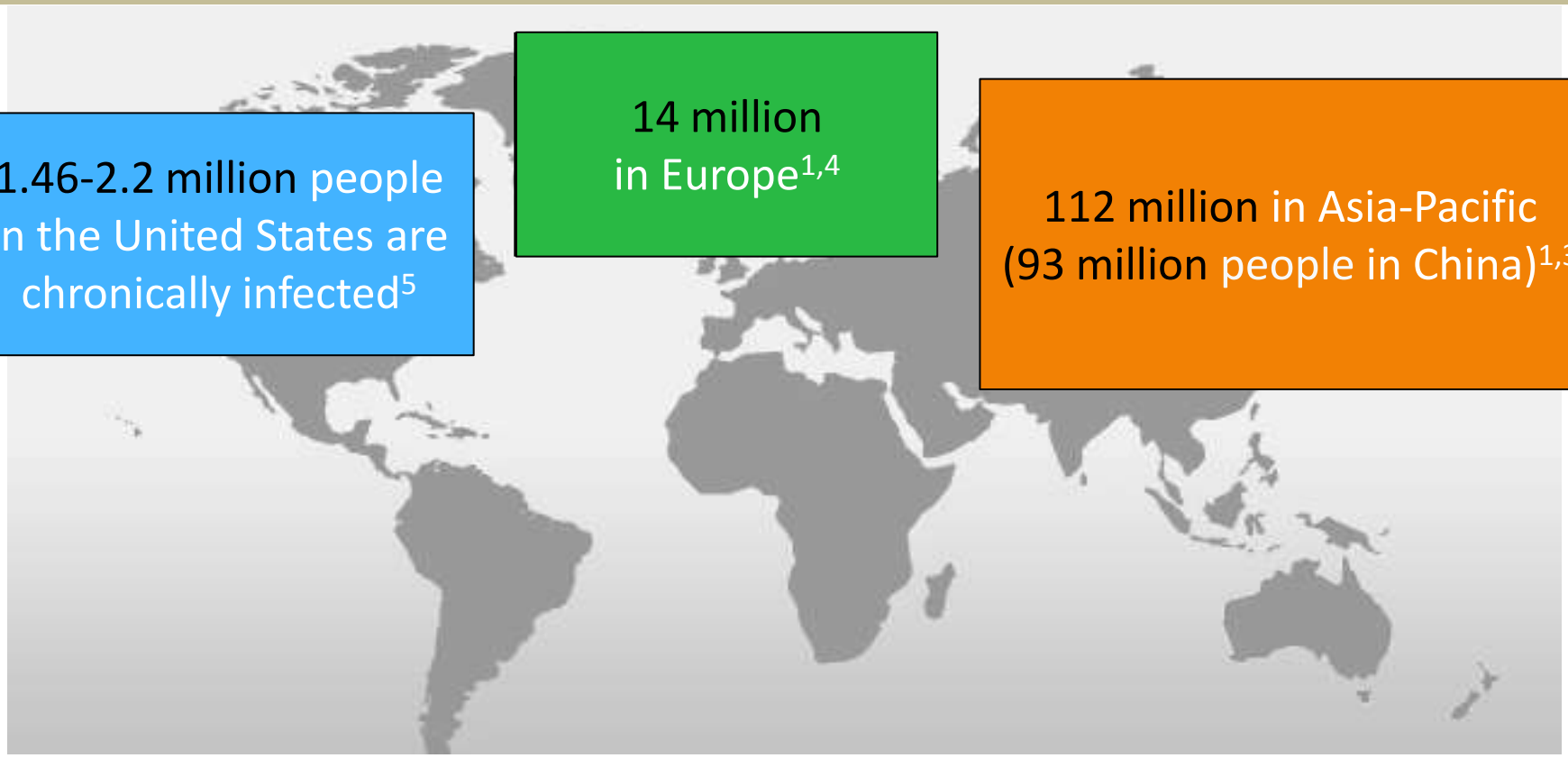
- Hepatitis B is the world's most common serious liver infection[1] and is a widespread global health issue
  - HBV is not curable but controllable and suppressible
  - HBV is 100 times more infectious than HIV (human immunodeficiency virus)[2]
  - 10 times more infectious than hepatitis C[3]
- The virus is transmitted via the blood and bodily fluids[1]
  - Hepatitis B progresses slowly over time
  - Complications generally involve vague symptoms or none at all, and are often undetected for many years



1. Hepatitis Australia. Available at http://www.hepatitisaustralia.com/about_hepatitis/hep_b.html. Accessed April 2009;
2. World Health Organization. Hepatitis B Fact Sheet. Available at http://www.who.int/mediacentre/factsheets/fs204/en/. Accessed April 2009;
3. Ulmer T, et al.(2007) European orientation towards the Better Management of Hepatitis B in Europe .

Hepatitis B: By The Numbers

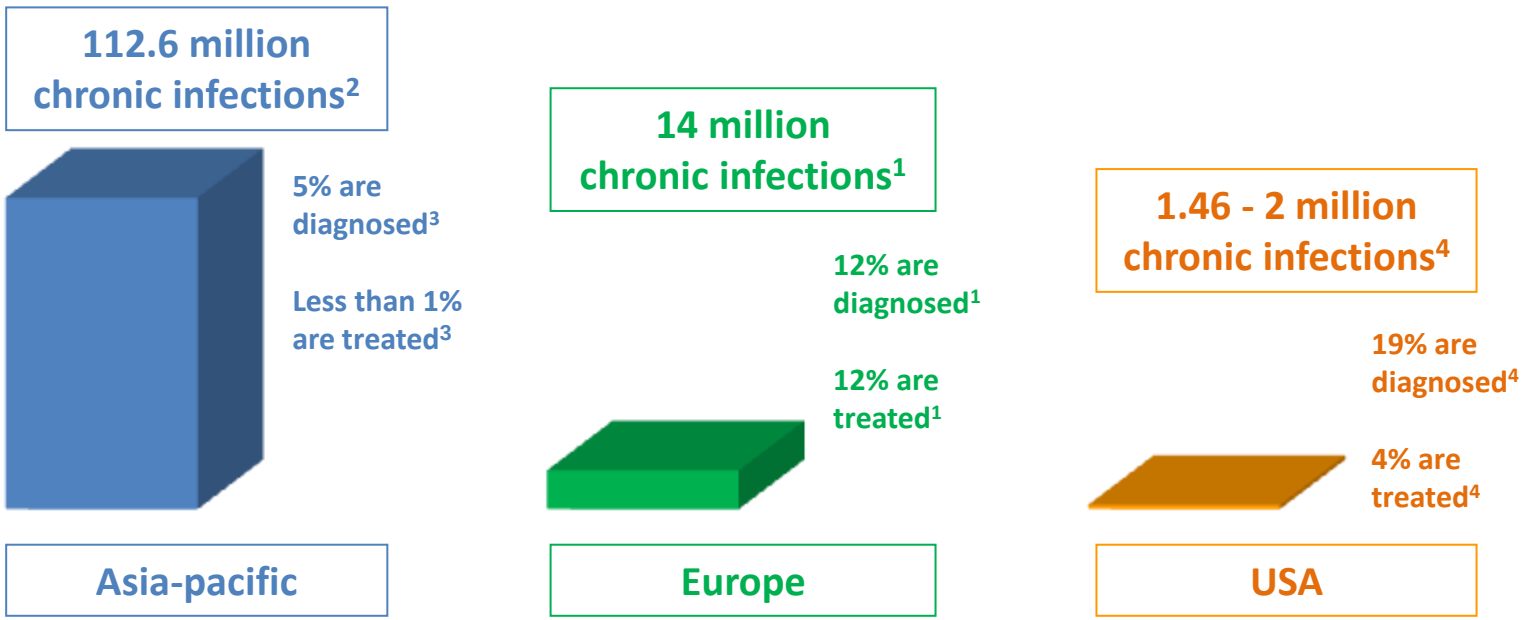
More than 350 million or 1 in 20 people worldwide have chronic hepatitis B infection[1]
(Compared with the 33 million living with HIV[2])



1. WHO. Available at: www.who.int/csr/disease/hepatitis/en/;
2. Ferlay, et al. Globocan 2002, Cancer incidence, mortality and prevalence worldwide, IARC Press, Lyon 2004;
3. Records of the thematic press conference of the Ministry of Health of the PRC at April 21, 2008, from the website of the Ministry of Health of the People's Republic of China;
4. Ulmer T, et al. (2007). European orientation towards the better management of hepatitis B in Europe;
5. CDC. Hepatitis B FAQs for Health Professionals. Available at http://www.cdc.gov/hepatitis/HBV/HBVfaq.htm#overview.

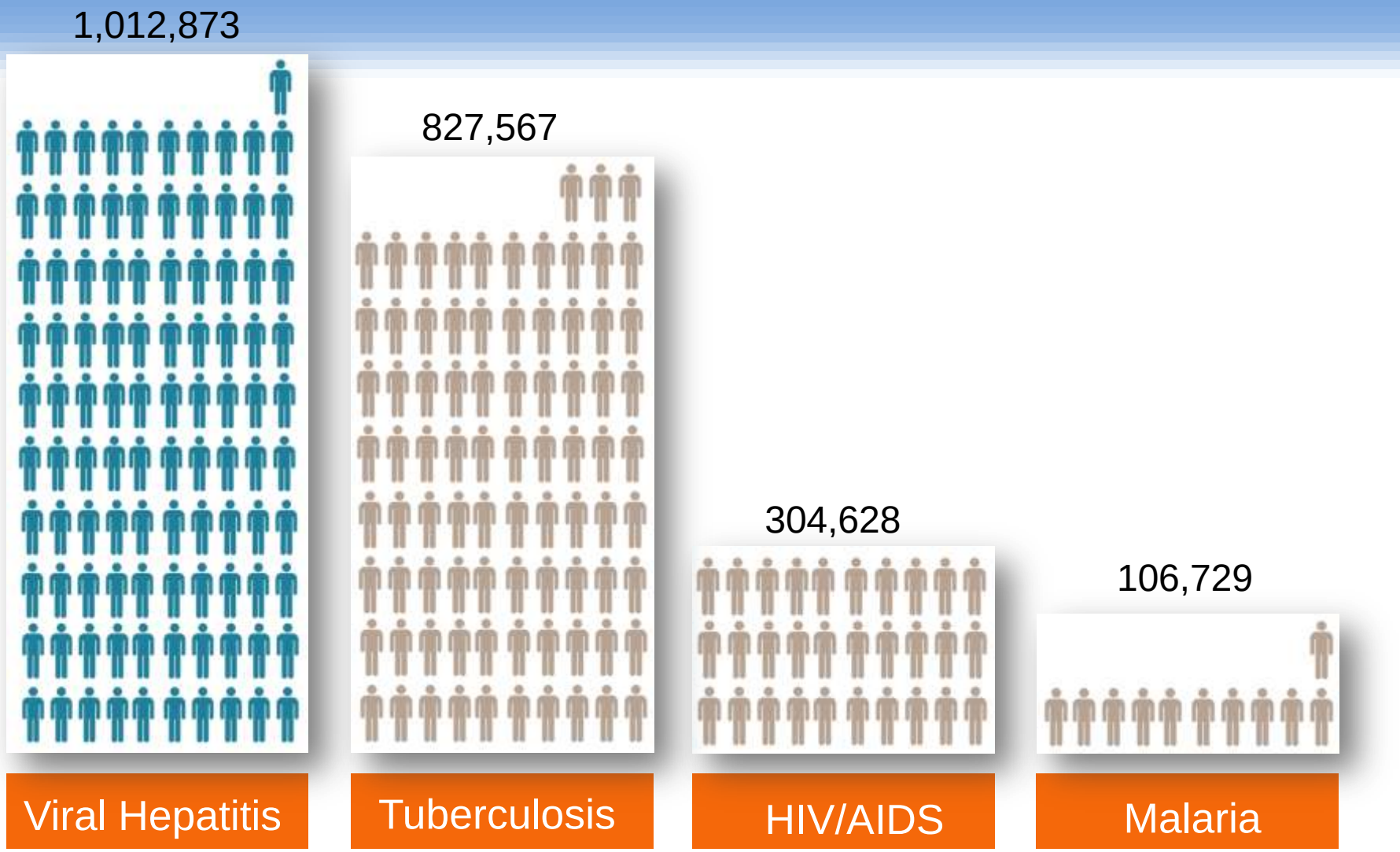
An Unmet Medical Need

- Worldwide, hepatitis B is significantly
  - Under-diagnosed
  - Under-treated[1]



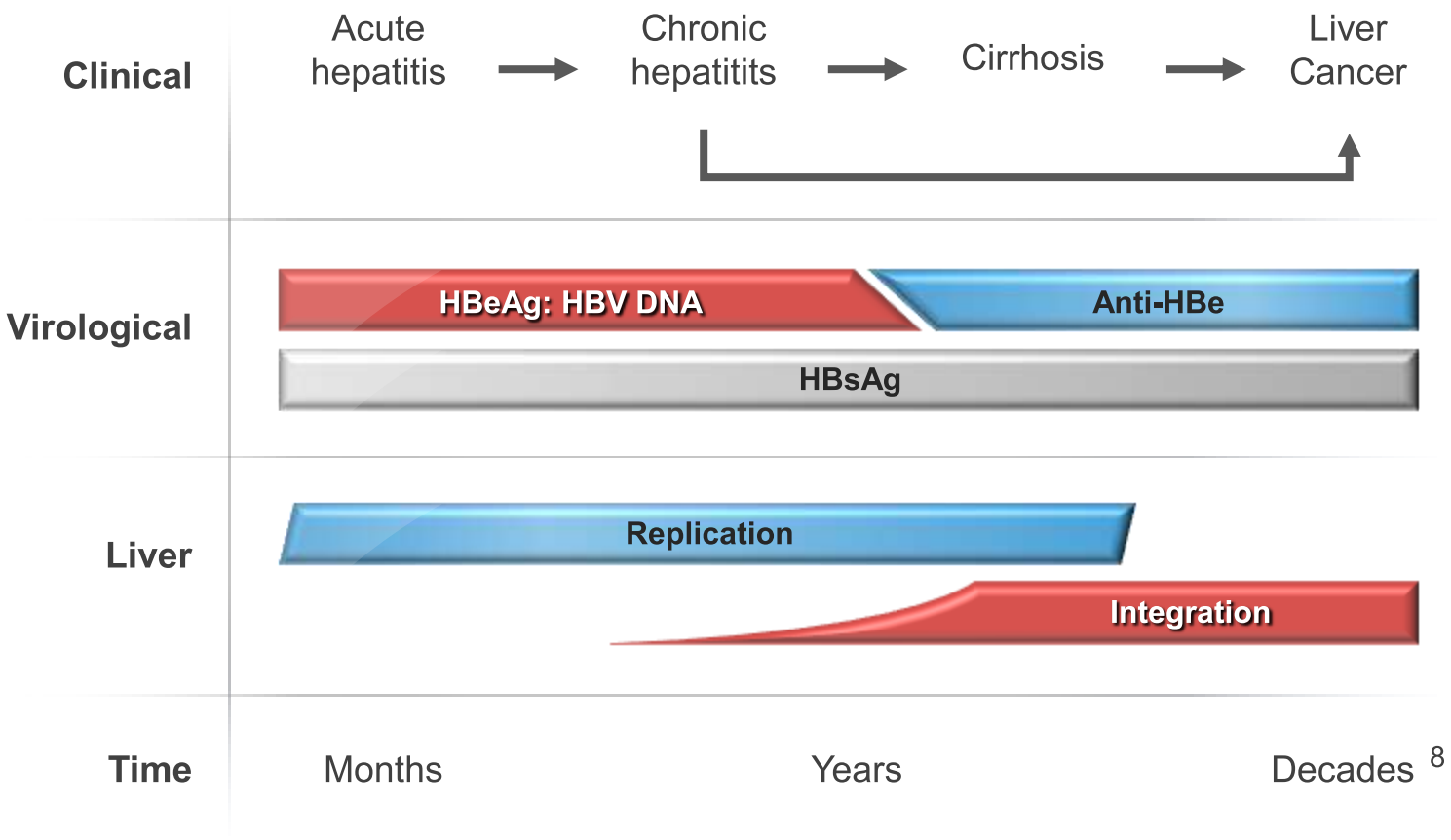
1. BMS Market Research. Information available upon request from Bristol-Myers Squibb;
2. Mohamed R, et al. J Gastroenterol Hepatol 2004;19:958-69;
3. Decision Resources. Hepatitis B virus in China – Emerging markets study #5; 4. BMS Market Research.

New figures from Global Burden of Disease Survey 2010: number of people infected



Attribution: Seng Gee Lim AASLD 2013

Natural History of Chronic HBV Infection



[8]

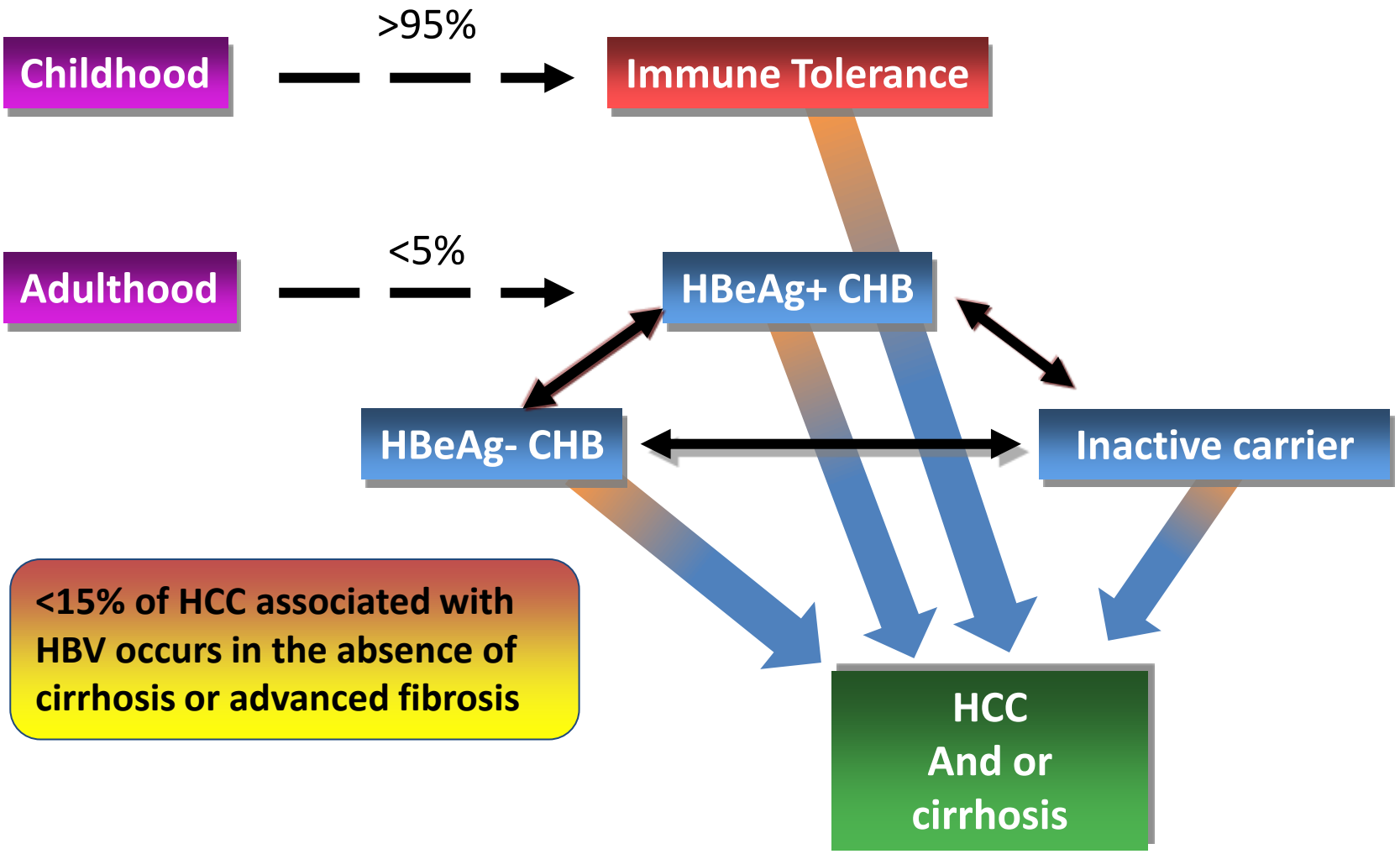
Yim HJ and Lok AS. Hepatology 2006;43:S173-81.

Hepatitis B: By The Numbers

- If it is not treated, in 1/3 of patients, hepatitis B can cause liver damage leading to cirrhosis and liver cancer[1]
- Hepatitis B is responsible for 80% of primary liver cancer globally, which is almost always fatal[2]
  - Liver cancer is the 3rd highest cause of death by cancer in men[3]
  - Without appropriate treatment or monitoring, 1 in 4 persons with chronic hepatitis B will die of liver cancer or liver disease

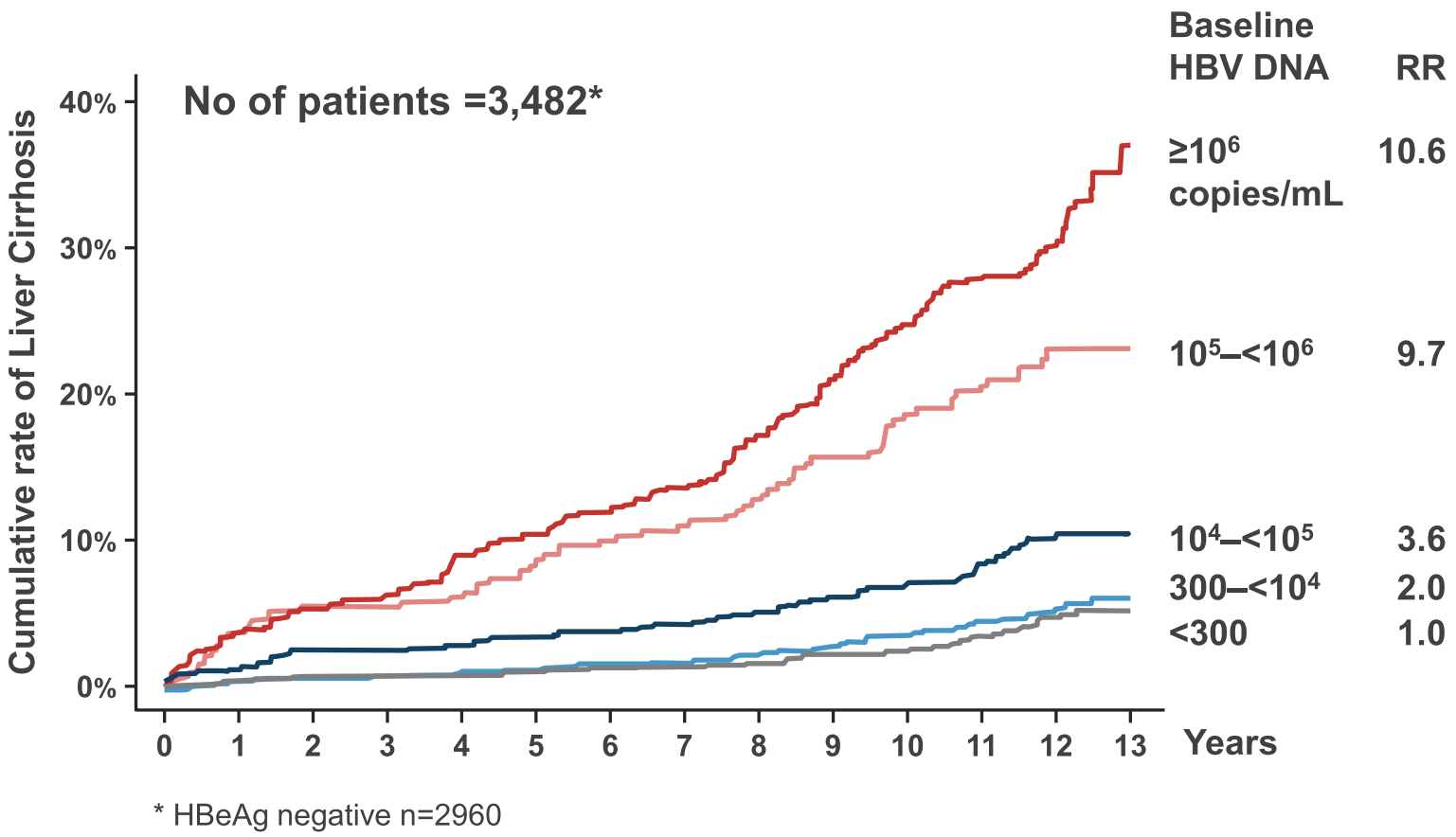
1. WHO. Available at: www.who.int/csr/disease/hepatitis/en/;
2. Hepatitis B Foundation. Hepatitis B and Primary Liver Cancer.
Available at http://www.hepb.org/professionals/hepb_and_liver_cancer.htm. Accessed 4 February 2010;
3. WHO. Cancer Fact Sheet. Available at http://www.who.int/mediacentre/factsheets/fs297/en/index.html.

Natural History of Chronic HBV Infection



Pungpapong S, et al. Mayo Clin Proc. 2007;82:967-5; Chen DS. J Gastroenterol Hepatol. 1993;8:470-5; Seeff LB, et al. N Engl J Med. 1987;316:965-70; Lok ASF, McMahon BJ. Hepatology. 2009;50:1-36.

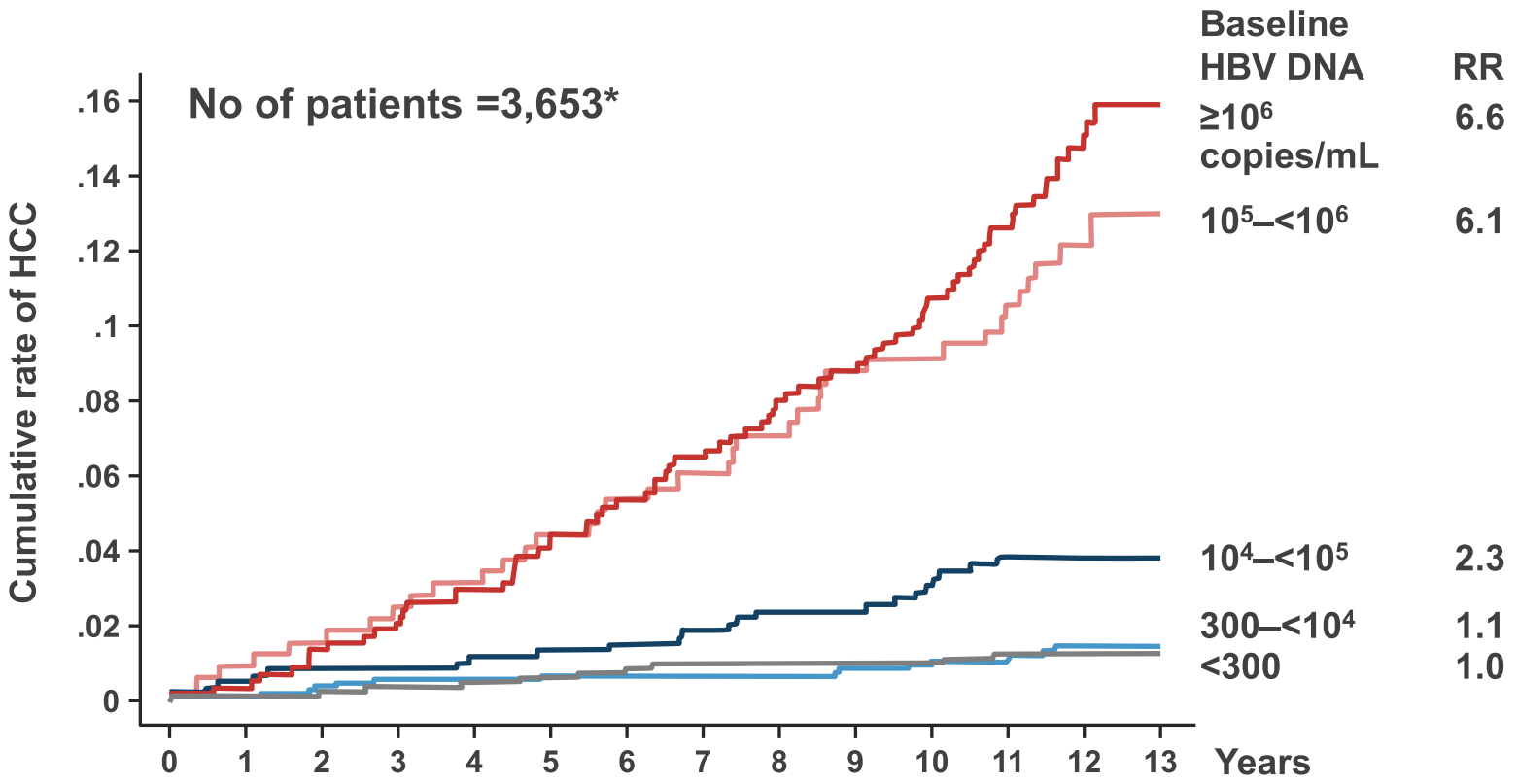
HBV DNA vs. Liver Cirrhosis : REVEAL data



* HBeAg negative n=2960

Iloeje UH, et al. Gastroenterology 2006;130:678-86.

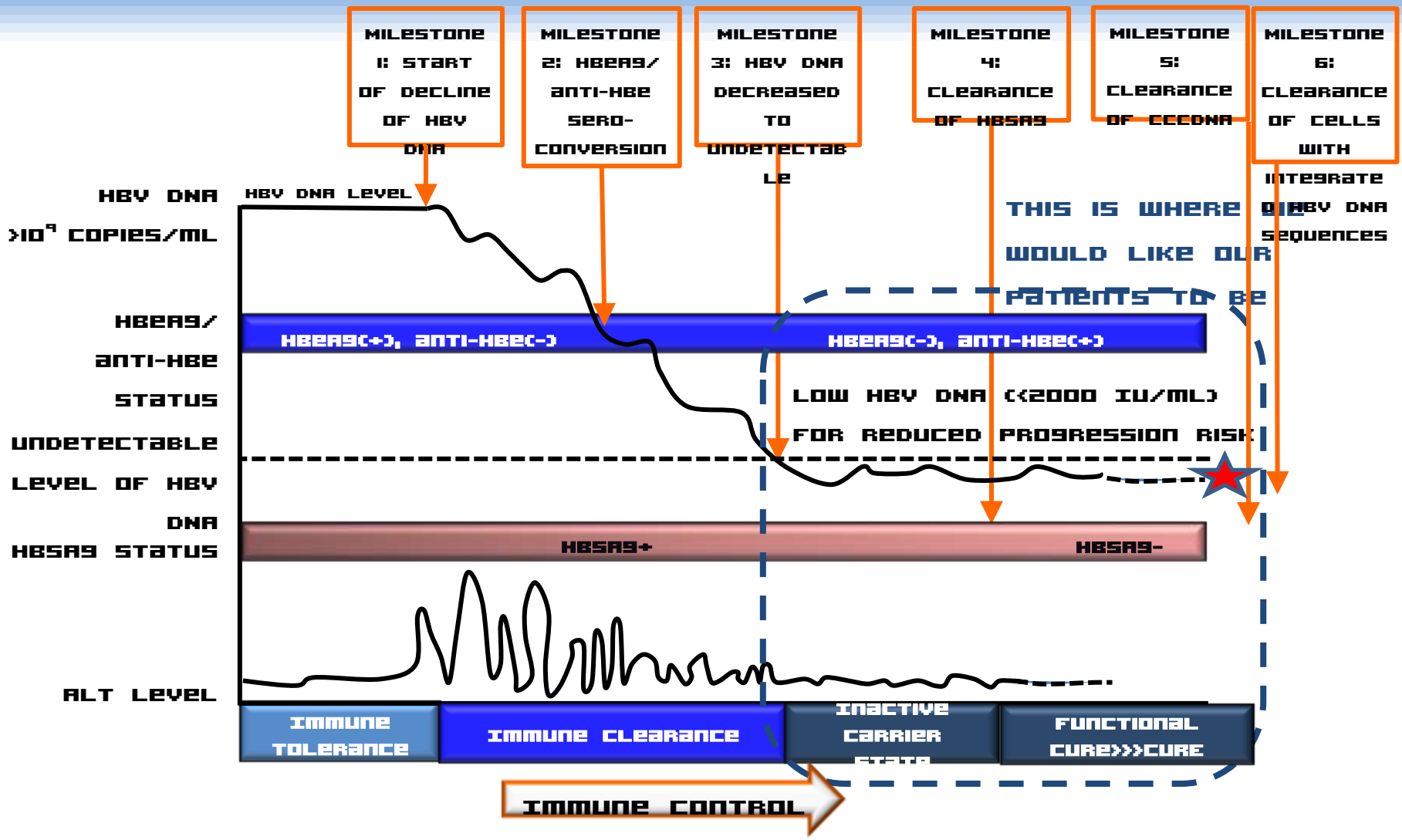
HBV DNA vs. HCC : REVEAL Data



*HBeAg negative n=3088

Chen CJ, et al. JAMA 2006;295:65-73.

Aiming for True Inactive Carrier Status



Next Steps in HBV Management

- Use the right NUC to control HBV for the right patient
  - Personalized medicine
- Stop oral (NUC) therapy, current Rx is indefinite
- Choose the correct Nuc for your patient
  - Pregnancy, Drug resistance, Management
- Safe use of each medicine
- Use combination therapy when appropriate
- Permanent clearance of HBV
  - HBsAg clearance: 10% rate now reported with TDF at 5 years of follow up
    - cccDNA clearance and integrated HBV DNA clearance or preventation
      - CURE?

Endpoints of Antiviral Therapy Compensated Cirrhosis

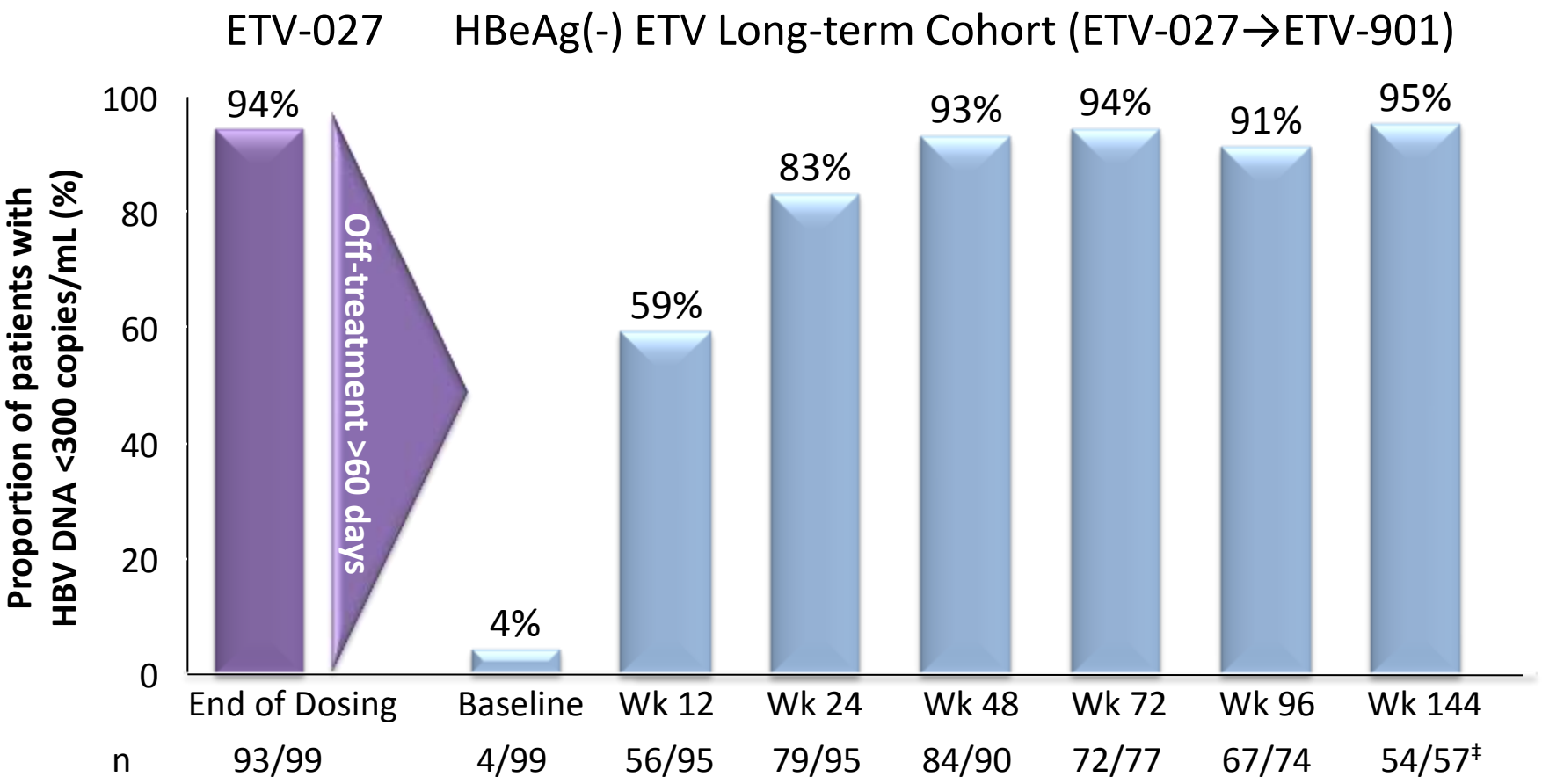
- Clinical endpoints similar to those for HBeAg-positive and HBeAg-negative CHB patients
- No liver failure
  - Now
    - Decreased rate of HCC
    - Falling rates of liver transplant
    - Lower death rates due to HBV
  - Future
    - Clear sAg in all patients
    - No ccc DNA remaining in liver cells
    - Cure- Functional >>>> real cure

US FDA dates of Approved Therapies for CHB

Nucleosides/Nucleotides			
Tenofovir	VIREAD®	Gilead Sciences	2008
Telbivudine	TYZEKA™	Idenix / Novartis	2006
Entecavir	BARACLUDE™	Bristol-Myers Squibb	2005
Adefovir dipivoxil	HEPSERA™	Gilead Sciences	2002
Lamivudine	EPIVIR-HBV®	GlaxoSmithKline	1998
Interferons			
Peginterferon alfa-2a	PEGASYS®	Roche Laboratories	2005
Interferon alfa-2b, recombinant	INTRON® A	Schering / Merck	1992

Preferred therapies – AASLD Guidelines

ETV 3-year Clinical Trial HBV DNA Suppression HBeAg-negative Patients



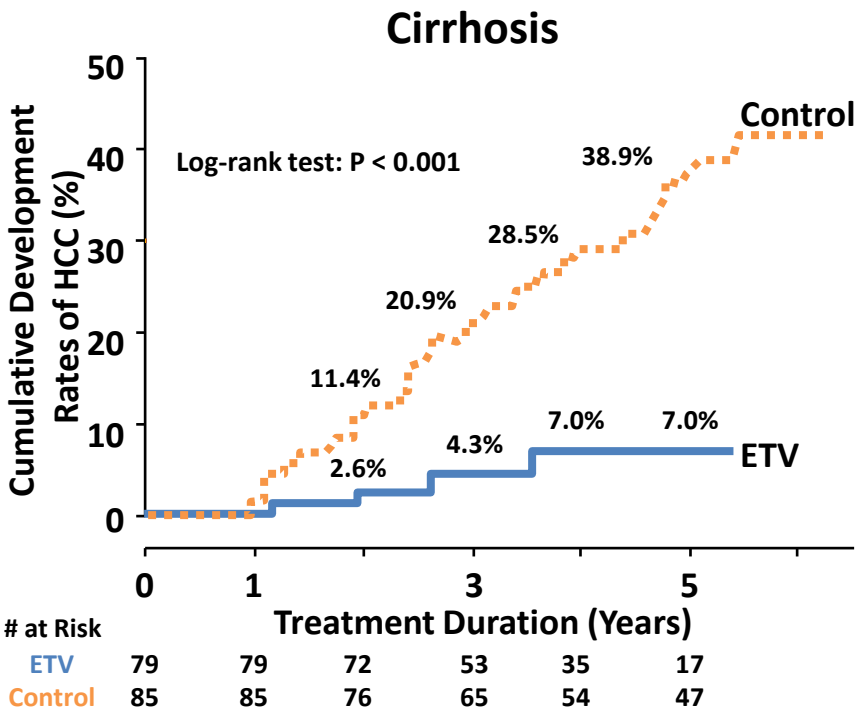
†In the randomised controlled study (ETV-027), patients received 0.5mg ETV. In the 901 rollover study, patients received 1mg ETV

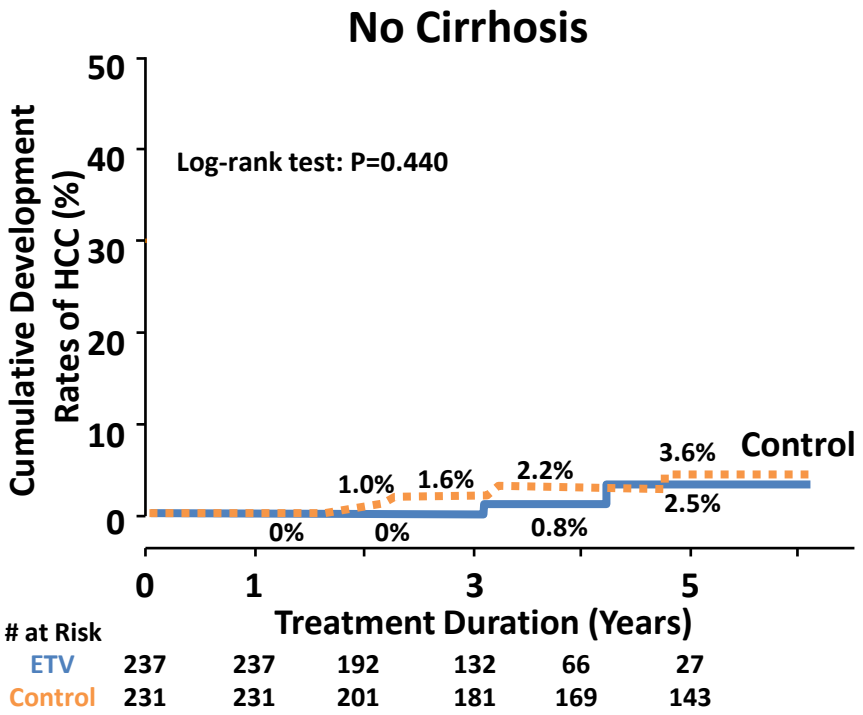
‡ 10 patients who remained on treatment at Week 144 of ETV-901 visit had missing PCR samples

Shouval D, et al. AASLD 2008; poster 927.

HCC Incidence in Patients Treated with Long-term ETV

After propensity score matching, significant difference of treatment effect between groups was seen in patients with cirrhosis (*P*<0.001), but not in patients without cirrhosis (*P*=0.440)





- In comparison to a historical untreated control group, long-term ETV treatment reduces the incidence of HCC, especially in cirrhotic CHB patients

Hosaka T, et al. Hepatology, 2013;58:98-107.

Studies 102/103: Virologic Suppression With TDF at Year 6

Response	HBeAg- Patients (Study 102)		HBeAg+ Patients (Study 103)	
	Year 5	Year 6	Year 5	Year 6
HBV DNA < 400 copies/mL Intent-to-treat*, % (n/N)	**83** (291/350)	**81** (281/345)	**65** (160/248)	**63** (157/251)
HBV DNA < 400 copies/mL On treatment†, % (n/N)	**99** (292/295)	**99.6** (283/284)	**97** (170/175)	**99** (167/169)

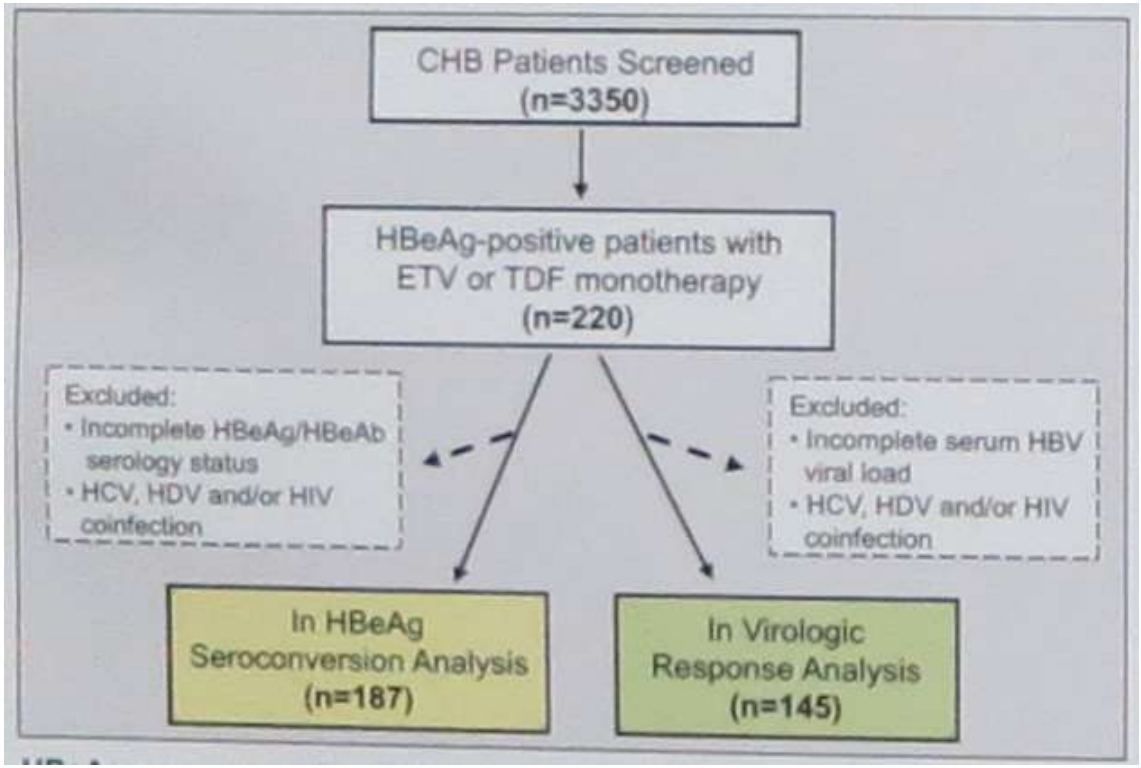
* LTE-TDF (missing = failure/addition of FTC = failure)
† Observed (missing = excluded/addition of FTC = included)

- 80% of 585 patients entering the open-label phase remained on study at Year 6; 73% of enrolled patients remained on study
- HBeAg loss/seroconversion rates of 50% and 37%, respectively, through 6 years
- 11% of HBeAg+ patients had confirmed HBsAg loss (8% with seroconversion)
- No resistance to TDF was detected through 6 years

Marcellin P, et al. AASLD 2012; abstract 374.

Methods

Figure 1: Study Design



- **HBeAg seroconversion (SC):** a positive HBeAb qualitative test with HBeAg loss
- **Virologic response (VR):** a serum HBV load <1000 IU/mL

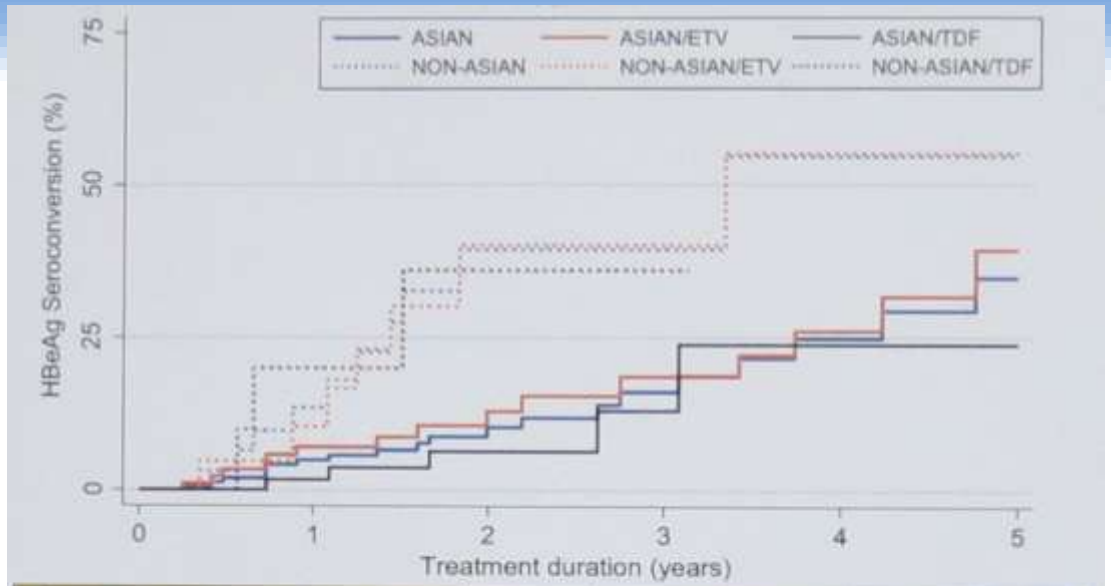
- Jo KJ, et al. AASLD 2013, Washington, DC. Poster 961.

Table 1: Baseline Characteristics

Baseline Characteristics	HBeAg Seroconversion Analysis (n=187)				Virologic Response Analysis (n=145)			
	N	Asian (n=155)	Non-Asian (n=32)	*P*	N	Asian (n=113)	Non-Asian (n=32)	*P*
ETV	114	93 (60%)	21 (66%)	0.55	98	77 (68%)	21 (66%)	0.79
TDF	73	62 (40%)	11 (34%)		47	36 (32%)	11 (34%)	
Age (Years)	187	39 ± 12	50 ± 13	<0.001	145	40 ± 13	51 ± 13	<0.001
Gender (Male)	187	76 (49%)	26 (81%)	<0.001	145	55 (49%)	25 (78%)	0.004
BMI (kg/m^2)	162	24 ± 5	28 ± 5	0.002	131	25 ± 5	28 ± 5	0.006
Creatinine (mg/dl)	142	0.8 (0.7-0.9)	0.9 (0.8-1.1)	0.02	117	0.8 (0.7-0.9)	1.0 (0.9-1.1)	0.002
ALT (IU/ml)	163	46 (33-84)	57 (46-141)	0.02	128	49 (34-81)	62 (45-147)	0.02
Albumin (g/dl)	157	4.1 ± 0.6	3.9 ± 0.5	0.11	127	4.0 ± 0.6	3.8 ± 0.6	0.09
Platelets (K/ml)	148	210 ± 68	197 ± 86	0.35	120	214 ± 67	196 ± 86	0.25
Cirrhosis	185	20 (13%)	4 (12%)	1	143	15 (14%)	6 (19%)	0.57
HBV viral load (log10 IU/ml)	168	6 ± 2	7 ± 2	0.21	132	7 ± 1	7 ± 1	0.6
HBV genotype	187				145			
B		39 (25%)	0 (0%)	<0.001		28 (25%)	0 (0%)	<0.001
C		60 (39%)	1 (3%)	<0.001		48 (42%)	2 (6%)	<0.001
Other		16 (10%)	21 (66%)	<0.001		15 (13%)	20 (63%)	<0.001
Unknown		40 (26%)	10 (31%)	0.52		22 (19%)	10 (31%)	0.22
Previous treatment	187				145			
Naïve		73 (47%)	20 (62%)	0.12		67 (59%)	23 (72%)	0.22
INF		14 (9%)	3 (9%)	1		10 (9%)	2 (6%)	1
LAM		45 (29%)	8 (25%)	0.83		28 (25%)	6 (19%)	0.64
Other NUC		80 (52%)	10 (31%)	0.05		44 (39%)	8 (25%)	0.21
LAM resistance	187	28 (18%)	5 (16%)	1	145	17 (15%)	5 (16%)	1

- Values expressed as mean ± SD, meadian (IQR), or frequency (%) patients.
- Non-Asians (n=32) in SC analysis: Caucasian (23); Black (4); Hispanic (4); Pacific Islander (1).
- Non-Asians (n=32) in VR analysis: Caucasian (24); Black (4); Hispanic (3); Pacific Islander (1).
- Jo KJ, et al. AASLD 2013, Washington, DC. Poster 961.

Figure 2: Cumulative Incidence of HBeAg Seroconversion Among Asians Versus Non-Asians Treated with ETV or TDF Monotherapy

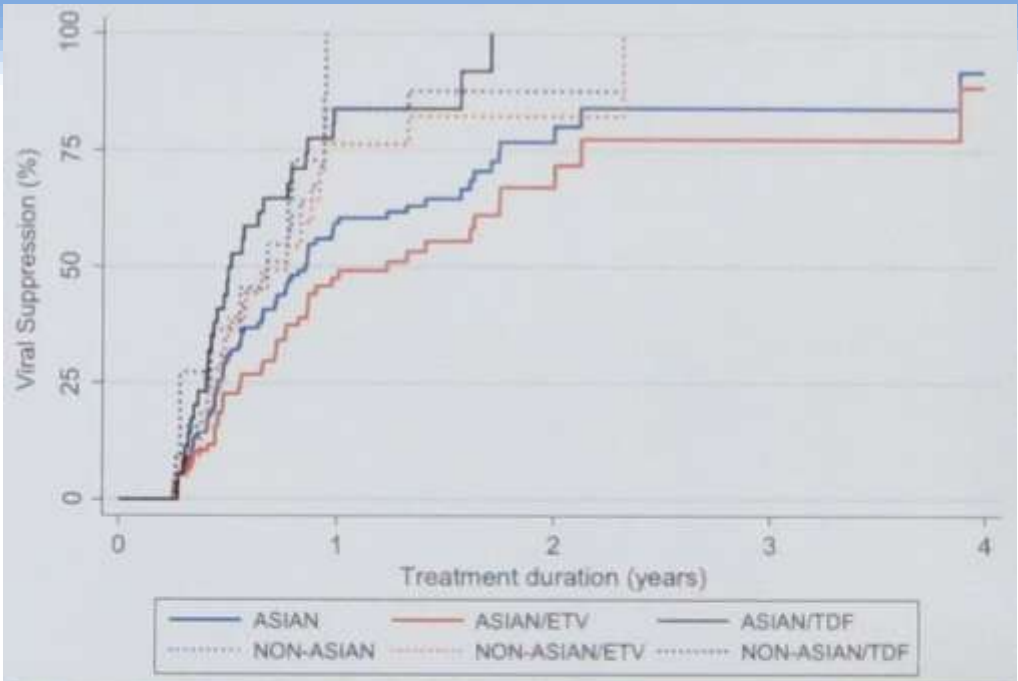


Cumulative incidence of seroconversion on ETV or TDF monotherapy	Year 1	Year 2	Year 3	Year 4	Year 5
Asian (n=155)	5%	10%	16%	25%	35%
non-Asian (n=32)	14%	39%	39%	55%	55%
p-value	0.07	<0.001	0.001	0.001	0.002

Cumulative incidence of seroconversion by drug type		Year 1	Year 2	Year 3	Year 4	Year 5
ETV	**Asian** (n=93)	7%	13%	19%	26%	39%
	non-Asian (n=21)	10%	40%	40%	55%	55%
	p-value	0.63	0.02	0.04	0.02	0.04
TDF	**Asian** (n=62)	2%	6%	13%	24%	
	non-Asian (n=11)	20%	36%	36%		
	p-value	0.005	0.002	0.005		

- Jo KJ, et al. AASLD 2013, Washington, DC. Poster 961.

Figure 3: Cumulative Incidence of Virologic Response Among Asians Versus Non-Asians Treated with ETV or TDF Monotherapy



Cumulative incidence of virologic response on ETV or TDF monotherapy	Year 1	Year 2	Year 3	Year 4
Asian (n=113)	59%	77%	84%	92%
non-Asian (n=32)	84%	88%	100%	
p-value	0.046	0.05	0.04	

Cumulative incidence of virologic response in Asians by drug type	Year 1	Year 2
Asian on ETV (n=77)	47%	67%
Asian on TDF (n=36)	84%	100%
p-value	<0.001	<0.001

* Kaplan-Meier method was used to determined the cumulative incidence of SC and VR.

- Jo KJ, et al. AASLD 2013, Washington, DC. Poster 961.

Table 3: Multivariate Analysis: Factors Associated with HBeAg Seroconversion and Virologic Response

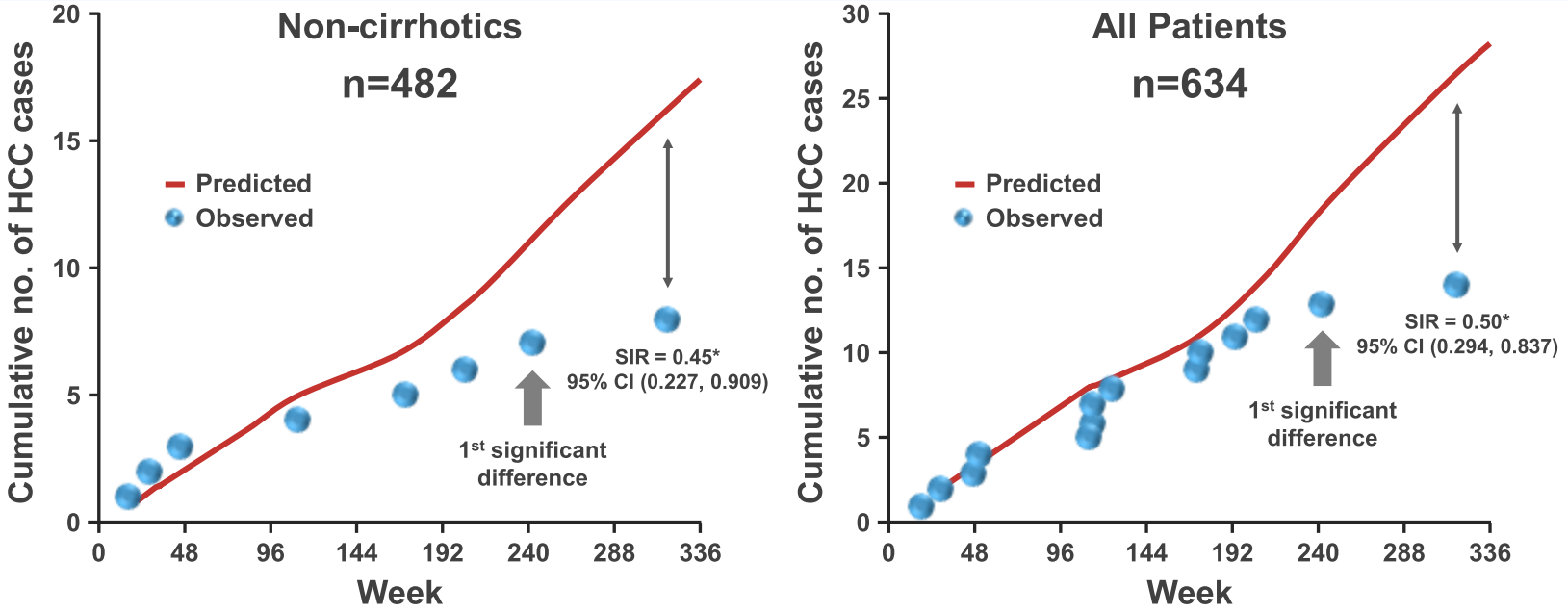
Parameter	HBeAg Seroconversion		Virologic Response	
	HR (95% CI)	P	HR (95% CI)	P
Drug type (ETV)			0.33 (0.21-0.53)	<0.001
Asian	0.33 (0.16-0.71)	0.004	1.11 (0.67-1.83)	0.69
ALT[§] <40 IU/ml 40-100 IU/ml >100 IU/ml			 1 1.73 (0.99-3.01) 4.31 (2.23-8.32)	 0.05 <0.001
HBV viral load[§] (per log10 increase)			0.64 (0.55-0.75)	<0.001
Previous treatment LAM			 0.48 (0.27-0.87)	 0.01

- Cox proportional hazards regression was used for multivariate analysis. Parameters with p<0.1 in the univariate analysis were evaluated in the multivariate analysis using backward elimination with p>0.05 for removal from the final models
- Factors relevant to the study hypotheses, including race, remained in the final multivaraite analysis to assess the independent association with each outcome

- [§]Baseline values.
- Jo KJ,

- Jo KJ, et al. AASLD 2013, Washington, DC. Poster 961.

Studies TDF 102/103: Observed vs. Predicted HCC Cases

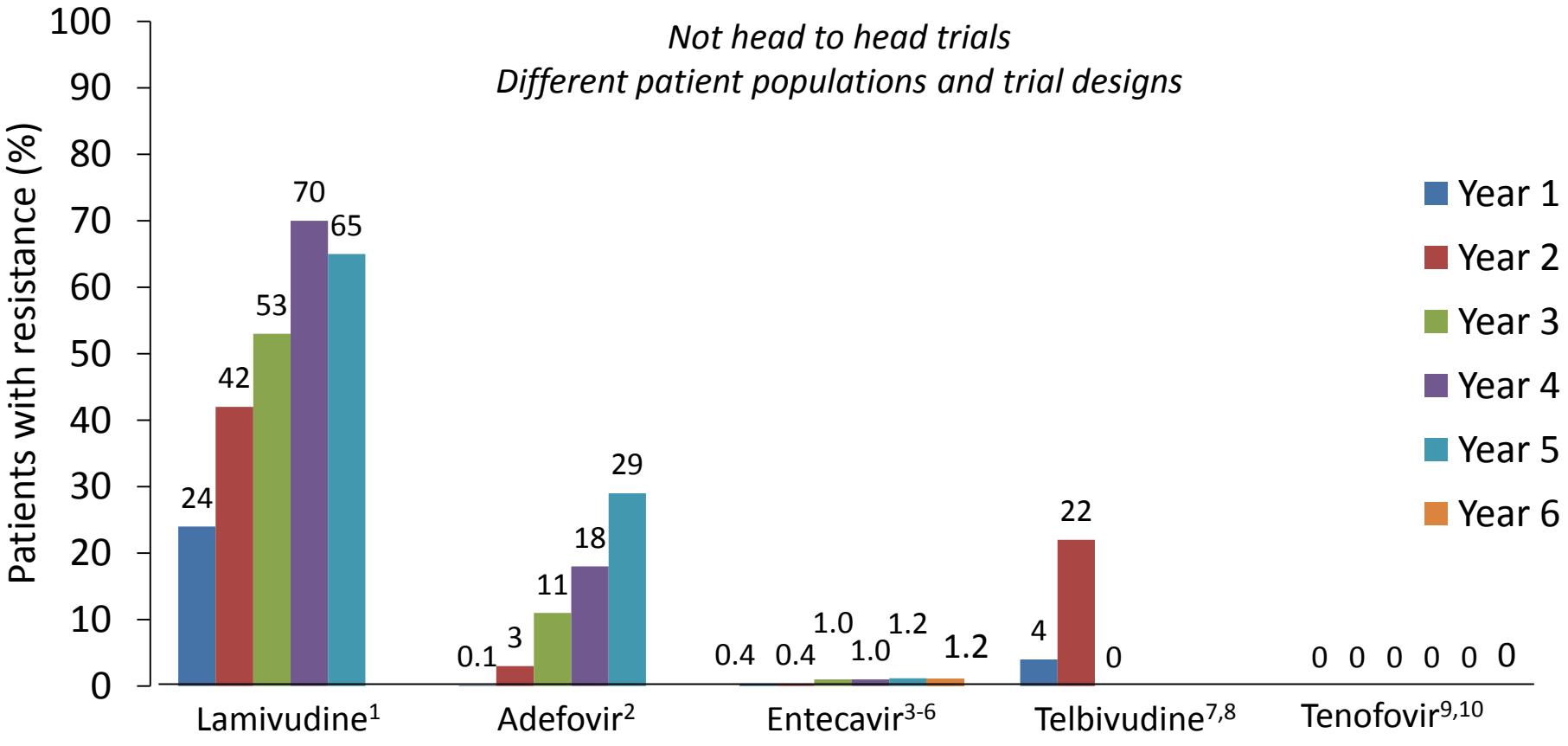


- Incidence of HCC in patients on TDF in studies 102/103 was lower than predicted by the REACH-B model
- In non-cirrhotic patients, the effect of TDF becomes noticeable between 2-3 years of therapy and became statistically (55% reduction) at 6 years of therapy

*Statistically significant at nominal α-level of 0.05.

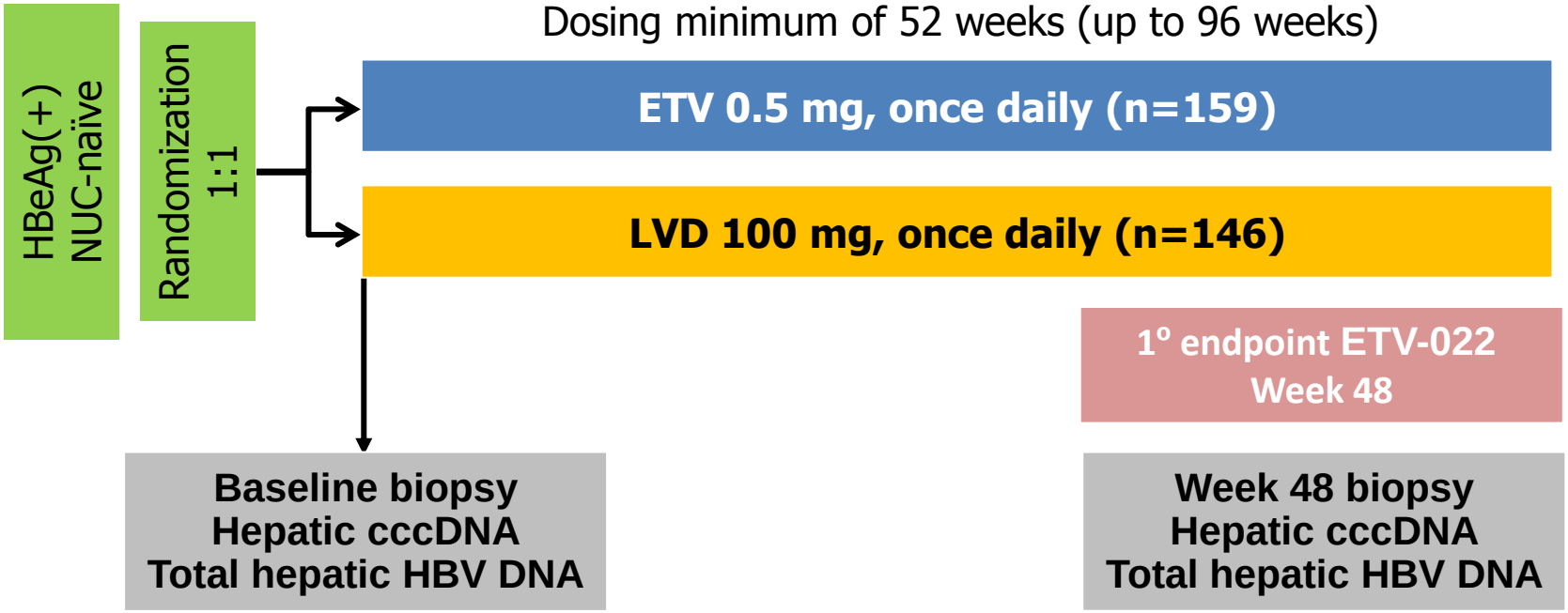
Kim WR, et al. EASL 2013. Oral 43.

Differences in Development of Resistance with Long-term Treatment in Nuc-naïve Patients



1. Lok ASF, et al. Gastroenterology 2003;125:1714-22; 2. Hadziyannis SJ, et al. Gastroenterology 2006;131:1743-1752; 3. Colonno RJ, et al. Hepatology 2006;44:1656-65;
4. Colonno RJ, et al, Hepatology 2006, 44 (Suppl 1):229; 5. Colonno RJ, et al. J Hepatol. 2007;46(Suppl 1):S294; 6. Tenney DJ et al. Gastroenterology 2009;136(Suppl 1):A-865;
7. Telbivudine (Tyzeka®) prescribing information; May 2009; Novartis Pharmaceuticals, East Hanover, NJ; 8. Lai CL, Hepatology 2006;44(Suppl 1):222A.
9. Tenofovir (Viread®) prescribing information; May. 2009; Gilead Sciences, Foster City, CA; 10. Snow-Lampart A et al. Hepatology 2008;48(Suppl 1):745A.

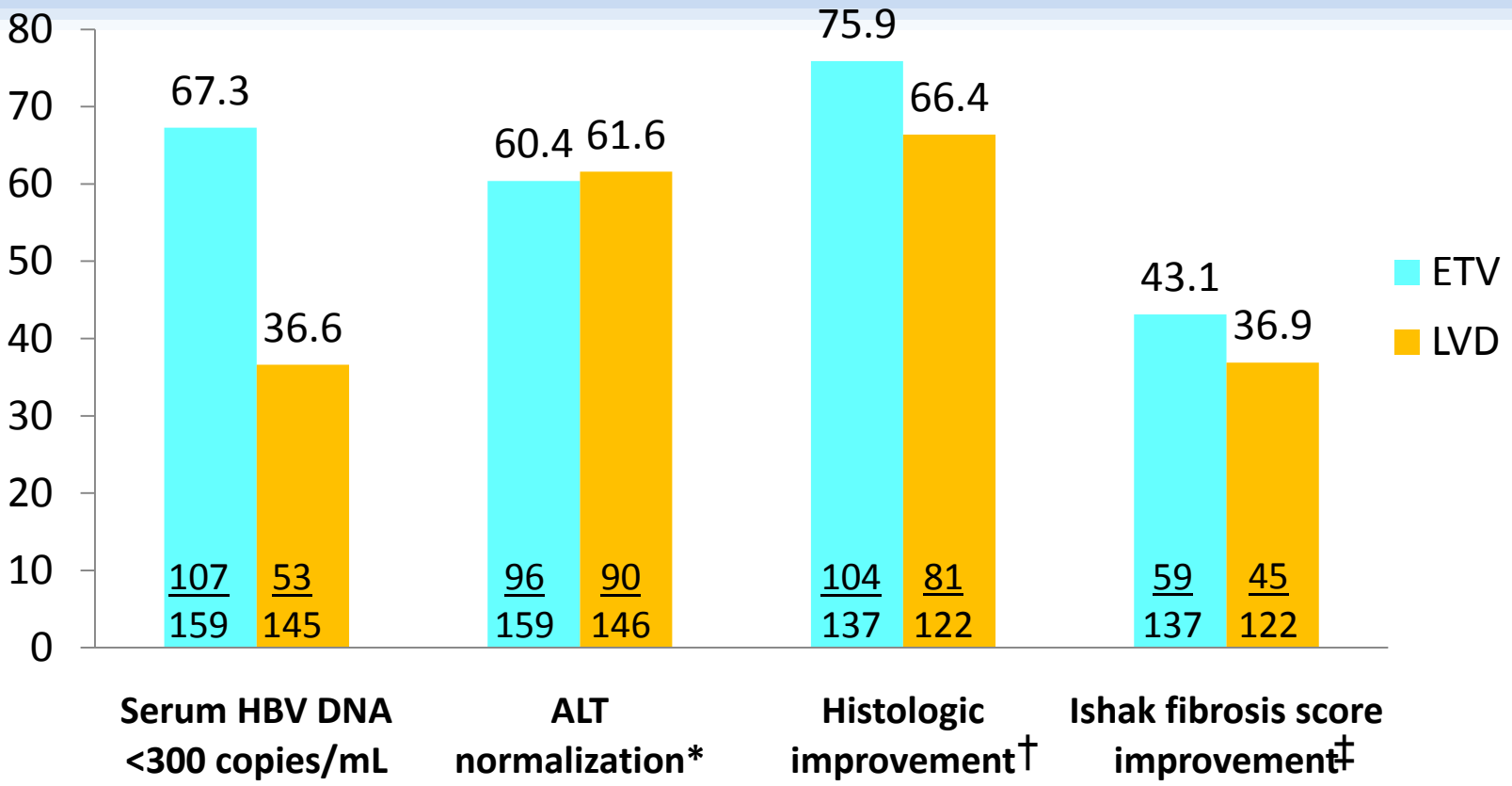
cccDNA in Patients Treated with ETV: Study Design



- Post-hoc analysis of phase 3, double-blind, randomized, comparative trial of ETV versus LVD (ETV-022)[1]
- Patients with baseline and Week 48 measurements of total hepatic HBV DNA and hepatic cccDNA were included

1. Chang TT, *et al. N Engl J Med* 2006;354:1001-10.

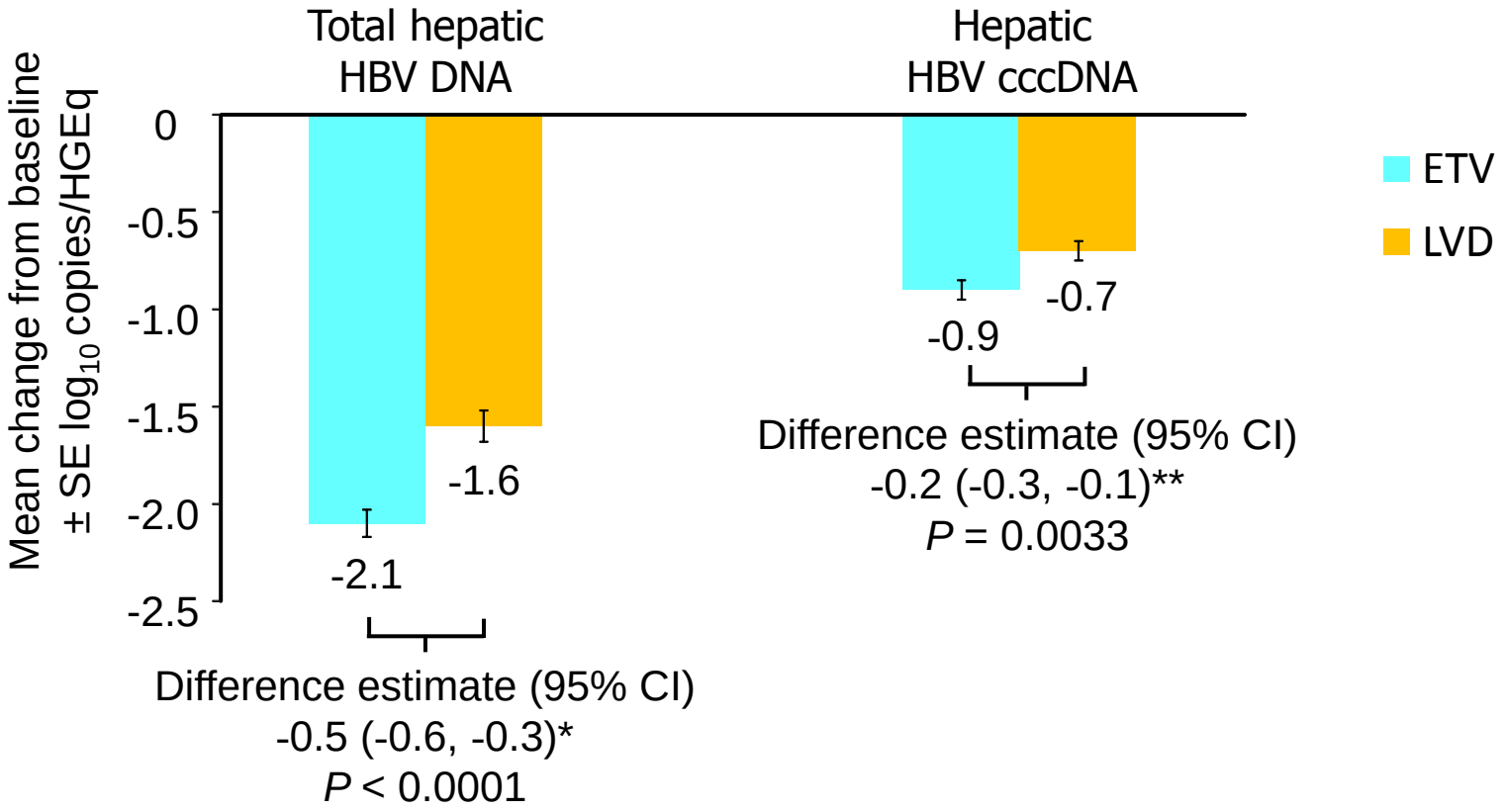
Virologic, Biochemical, and Histologic Efficacy at Week 48



Among patients with paired hepatic HBV DNA measurements. Non-completer = missing analysis

*ALT < 1.25 × ULN. † ≥ 2-point decrease in Knodell necroinflammatory score with no worsening (≥ 1-point increase from baseline) of Knodell fibrosis score. ‡ ≥ 1-point decrease in Ishak fibrosis score from baseline.

Change from Baseline at Week 48 in Total Hepatic HBV DNA and cccDNA



HGEq, human genome equivalent; SE, standard error.

*Difference estimated using linear regression analysis adjusted for baseline total hepatic HBV DNA level.
**Difference estimated using linear regression analysis adjusted for baseline hepatic cccDNA level.

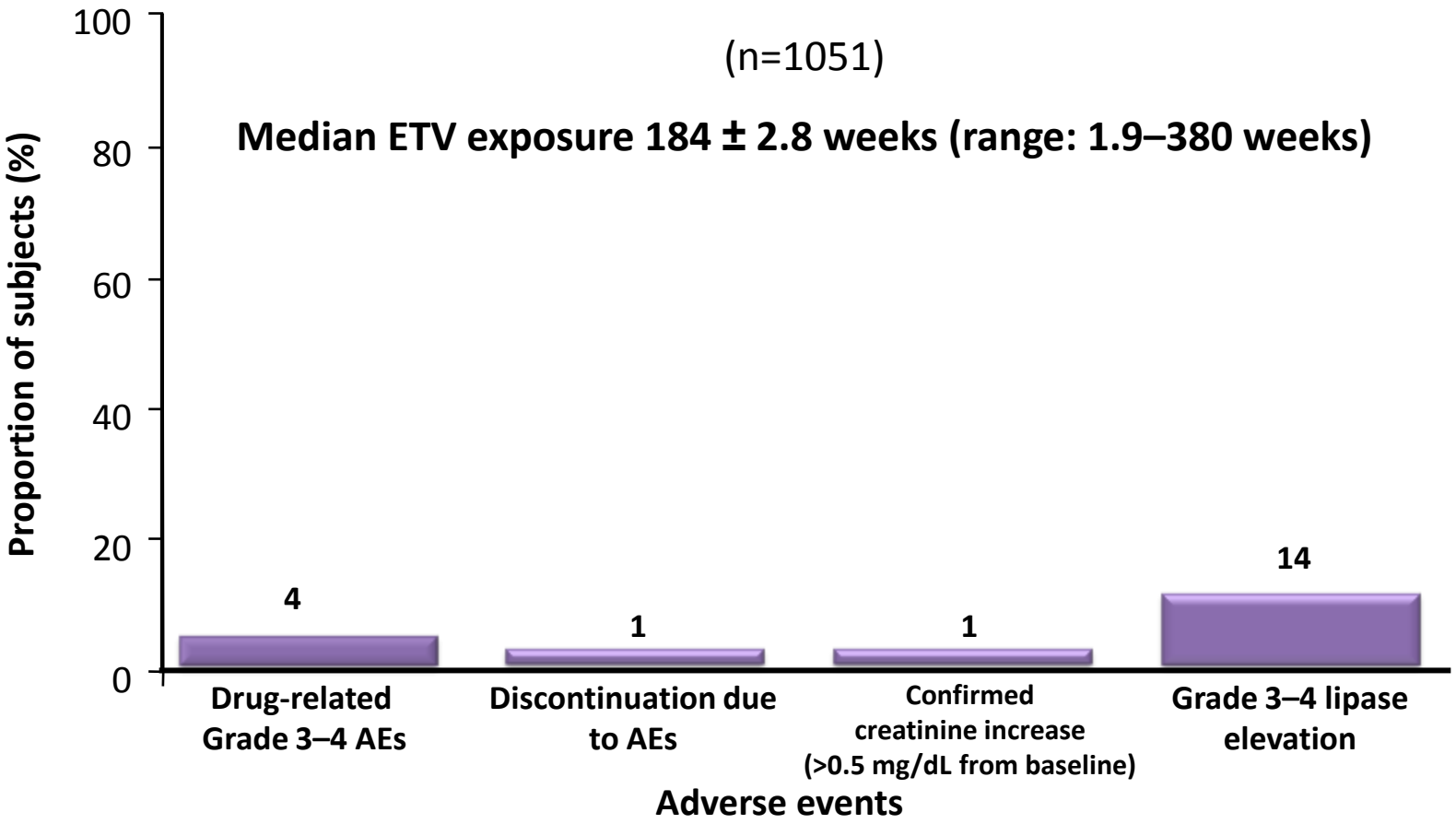
Scott Bowden, DDW 2013

Conclusions

- At Week 48, treatment with ETV was superior to LVD in reducing hepatic HBV cccDNA and total hepatic HBV DNA from baseline
- Lower baseline HBV cccDNA was associated with lower baseline serum HBV DNA, lower baseline total hepatic HBV DNA, and HBV genotype F
- HBV cccDNA reduction at Week 48 was associated with
    1) Lower baseline serum HBV DNA
    2) Lower baseline ALT
    3) Greater on-treatment decrease in serum HBV DNA
    4) Greater decline in total hepatic HBV DNA on therapy
    5) Improvement in Knodell necroinflammatory score
    6) Reduction in ALT
    7) HBeAg loss
- Absolute reductions in serum and tissue HBV DNA was associated with an "amplified" cccDNA reduction

Scott Bowden, DDW 2013

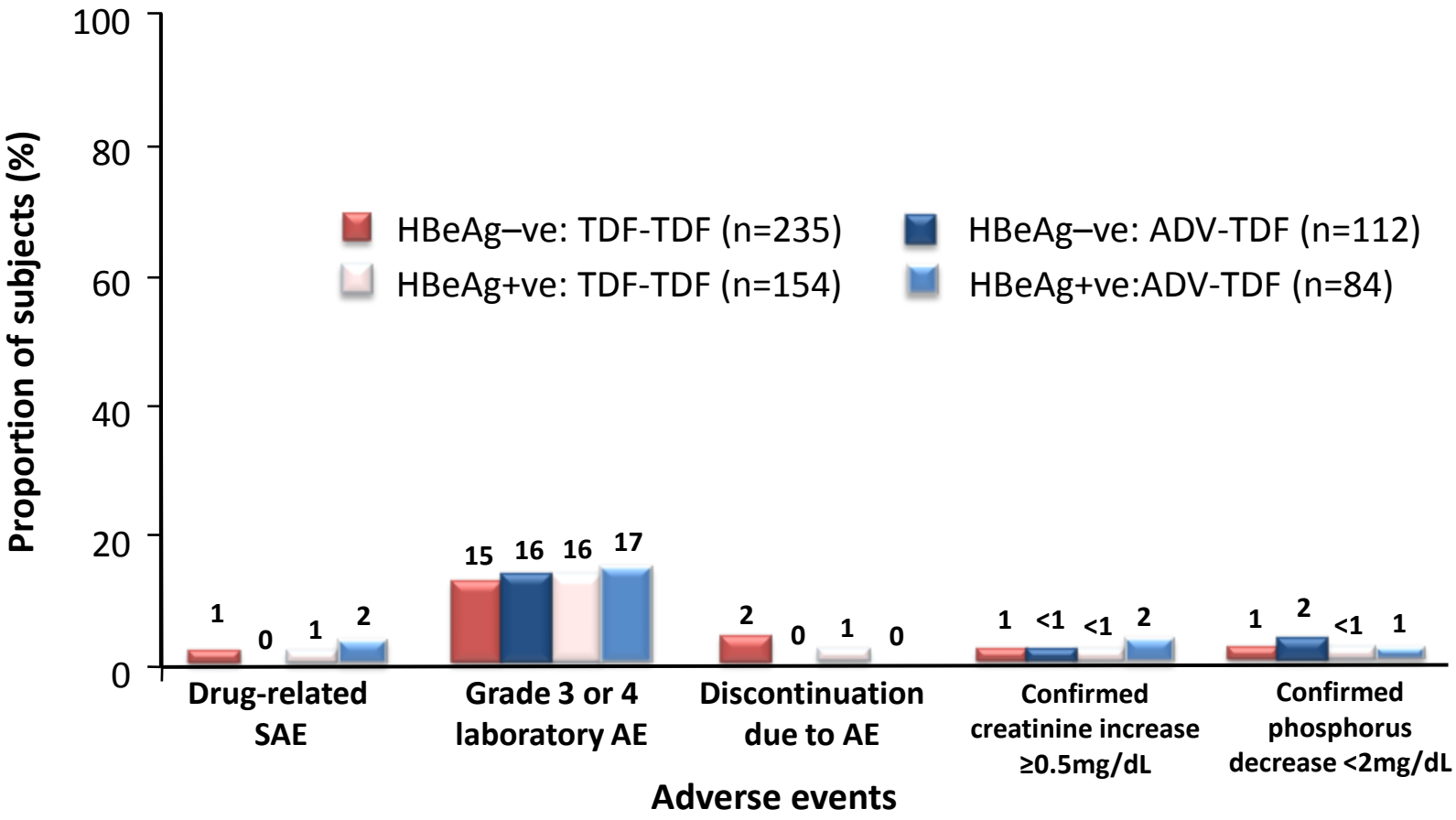
ETV has a Generally Favourable Open-label Safety Profile up to 380 Weeks*



*49% patients enrolled in ETV-901 had >5 years total ETV treatment (including treatment time in parent protocols). Patients in the ETV-901 rollover study received 1-mg ETV.

Manns M, et al. Expert Opin Drug Saf 2012;11:361-8.

TDF has a favourable clinical trial safety profile up to and beyond 192 Weeks*



*On/After week 72, patients with confirmed HBV DNA ≥400 copies/mL were eligible to add FTC in a fixed dose combination tablet

Marcellin P et al. AASLD 2010; poster 476; Heathcote EJ, et al. AASLD 2010; poster 477.

Renal considerations with NUC treatment

- NUCs are cleared by the kidneys, and appropriate dosing adjustments are recommended for patients with reduced creatinine clearance[1–5]
- Renal dysfunction has been reported with nucleotide usage, including TDF[1,6–8]
- Licensing clinical trials have not shown significant signs of TDF impacting on creatinine clearance in HBV treatment at Week 192[9,10]
- Case series have shown delta in GFR with ADF and TDF use
- There was no difference in renal events with TDF and ETV in a case controlled study[12]
- However, creatinine clearance rates and 0.5 thresholds may not provide an accurate assessment of early renal damage[11]

1. Viread® (tenofovir) SmPC September 2010; 2. Hepsera® (adefovir) SmPC June 2009; 3. Baraclude® (entecavir) SmPC February 2011;
4. Zeffix® (lamivudine) SmPC July 2010; 5. EASL Clinical Practice Guidelines: Management of chronic hepatitis B. J Hepatol 2009;50:227–42;
6. Hepsera® (adefovir) SmPC June 2009; 7. Karras A, et al. Clinical Infect Dis. 2003;36:1070–3; 8. Woodward CL, et al. HIV Med 2009;10(8):482–7;
9. Marcellin P et al. AASLD, 2010; poster 476; 10. Heathcote EJ, et al. AASLD, 2010; poster 477;
11. Johnson R, et al. Comprehensive Clinical Nephrology; 2000: 4.15.1-4.15.15; St. Louis, Mosby. 12.Gish JCGH 2012

Protocol for Dose Reductions for Oral HBV Medications if Changes in Renal Function

- Recommended GFR >>> dose adjustments, although each hepatologist was free to use their own interpretation of the guidelines in the package insert
  - >70 mL 7 tablets per week
  - 60-69 mL 6 tablets per week
  - 50-59 mL 5 tablets per week
  - 40-49 mL 4 tablets per week
  - 30-39 mL 3 tablets per week
  - 20-29 mL 2 tablets per week
  - 10-19 mL 1 tablet per week

Gish R, et al. J Clin Gastro Hep 2012

Methods

- Analyst tracked
  - Serum creatinine levels at baseline and during treatment and scored as an event
    - Any SCr increase of 0.2 mg per dL
    - SCr increase of 0.2 mg/dL confirmed with a second blood test
    - Any patients who reached a new SCr value at >1.5, > 2.0, or > 2.5
  - eGFR measured using Cockcroft-Gault and MDRD equations
    - Also scored:
      - If eGFR was < 60ml/min
      - > 20% decrease in eGFR from baseline
  - History of diabetes, HTN, P-HTN, and transplant
  - Baseline HBV DNA (real-time PCR)

Gish R, et al. J Clin Gastro Hep 2012

Comorbidities

TDF Arm		ETV Arm	
DM	17	DM	14
HTN	7	HTN	15
P-HTN	17	P-HTN	11
Liver TX	14	Liver TX	12
Renal TX	2	Renal TX	0
DM + HTN	3	DM + HTN	4
DM + P-HTN	6	DM + P-HTN	6
DM + Liver Tx	5	DM + Liver Tx	5
DM + Renal Tx	0	DM + Renal Tx	0
DM + Liver Tx + Renal Tx	0	DM + Liver Tx + Renal Tx	0
HTN + Liver Tx	2	HTN + Liver Tx	1
HTN + Renal Tx	1	HTN + Renal Tx	0
HTN + Liver Tx + Renal Tx	0	HTN + Liver Tx + Renal Tx	0
P-HTN + Liver Tx	4	P-HTN + Liver Tx	5
P-HTN + Renal Tx	1	P-HTN + Renal Tx	0
P-HTN + Liver Tx + Renal Tx	1	P-HTN + Liver Tx + Renal Tx	0
Liver Tx + Renal Tx	1	Liver Tx + Renal Tx	0

Gish R, et al. J Clin Gastro Hep 2012

Renal Function Changes of TDF Arm vs. ETV Monotherapy

On-treatment Renal Changes	TDF, n (%)	ETV, n (%)	*P*-value
Scr increase of 0.2	39 (48)	30 (40)	0.345
0.2 confirmed	2 (2)	9 (11)	0.029
Scr of 1.5	15 (18)	15 (18)	0.999
Scr of 2.0	3 (4)	6 (7)	0.304
Scr of 2.5	0 (0)	7 (9)	0.007
eGFR <60 ml/min on Tx (C-G)	14 (17)	7 (9)	0.068
eGFR decrease of >20% (C-G)	27 (32)	36 (43)	0.343
eGFR <60 ml/min on Tx (MDRD)	13 (15)	13 (15)	0.368
eGFR decrease of >20% (MDRD)	36 (43)	38 (45)	0.756
Dose Change*	14 (17)	4 (5)	0.004

Gish R, et al. J Clin Gastro Hep 2012

7 ETV Patients who Developed SCr over 2.5

- 3 DM
- 1 HTN
- 4 portal HTN
- 3 had preexisting Renal Dx confirmed by Chart Review
- 2 had liver transplants

Ethnicity	DM	HTN	Portal HTN	Renal Hx	Post OLT
API	Y	N	Y	Y	N
Caucasian	Y	Y	N	N	N
API	N	N	N	N	Y
Caucasian	N	N	Y	Y	N
API	N	N	N	Y	N
API	Y	N	Y	N	Y
Caucasian	N	N	Y	N	N

Gish R, et al. J Clin Gastro Hep 2012

Logistic Regression to Determine Factors Associated with SCr Increases of 0.2

Factor	Adjusted OR	95% CI	*P* value
Gender	0.643	0.298 - 1.391	0.262
Age	1.008	0.981 - 1.036	0.546
Ethnicity	0.638	0.291 - 1.398	0.261
Diabetes	4.138	1.585 - 10.804	0.004
Hypertension (all)	1.192	0.551 - 2.579	0.656
Transplant	5.122	1.820 - 14.411	0.002
TDF Therapy	1.279	0.639 - 2.558	0.487

Gish R, et al. J Clin Gastro Hep 2012

Conclusions

- Changes in renal function were common in both (TDF and ETV) patient treatment groups
- Since ETV has no renal toxicity, the frequent changes in renal function were attributed to underlying comorbidities which probably resulted in fewer dose adjustments in the ETV arm (5% ETV vs 17% TDF, p= 0.004)
- TDF was shown to be well tolerated when multiple parameters were evaluated in terms of renal events:
  - SCr increases of 0.2 were found to be common in both arms, however, confirmed increases of 0.2 were more common in patients on ETV therapy than TDF therapy (11% vs 2%, p-value = 0.029)
- There were more dose adjustments in the TDF arm compared to the ETV arm (p- 0.004), which may explain the less frequent confirmed renal events (0.2 mg/dL SCr increase confirmed) seen in the TDF therapy group (p=0.029)

Gish R, et al. J Clin Gastro Hep 2012

Interferon

- Short fixed duration therapy
- No Renal toxicity
- Ideal for patients with high ALT and medium to low DNA
- Has stopping rules and “continuation” rules

Biomarker for Hepatitis B

Natural Course

Different phases[1,2,3]
Inactive HBsAg Carrier[3,4,5]
Risk for HCC[6]
HIV co-infection[7]

HBsAg

NUCs:

Prediction of HBsAg loss[8-10]

PEG-IFN:

Personalisation of treatment[11-15]

Adapted from: Chan et al., J Hepatol 2011;55:1121-31.

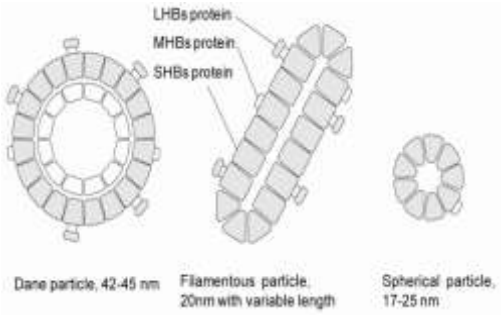
1. Jaroszewicz J, et al., J Heaptol 2010;52:514-22; 2. Nguyen T, et al., J Hepatol 2010;52:508-13; 3. Brunetto MR, et al., Gastroenterology 2010;139:48-90; 4. Manesis EK, et al., AASLD 2010; abstract 483; 5. Martinot-Peignoux M, et al., AASLD 2010; abstract 992; 6. Lee JH, et al., AASLD 2011; abstract 1095; 7. Jaroszewicz J, et al., Plos One 2012;7: e43143; 8. Wursthorn et al., Hepatology 2010;52:1611-20; 9. Jaroszewicz J, et al., Antiviral Ther 2011;16:915-24; 10. Zoutendijk R, et al., JID 2011;204:415-8 & 2012;206:974-80; 11. Moucari R, et al., Hepatology 2009;49:1151-7; 12. Brunetto MR, et al., Hepatology 2009;49:1141-50; 13. Sonneveld et al., Hepatology 2010;52:1251-7; 14. Rijckborst V, et al., Hepatology 2010;52:454-61; 15. Rijckborst V, et al., J Hepatol 2012;56:1006-11.

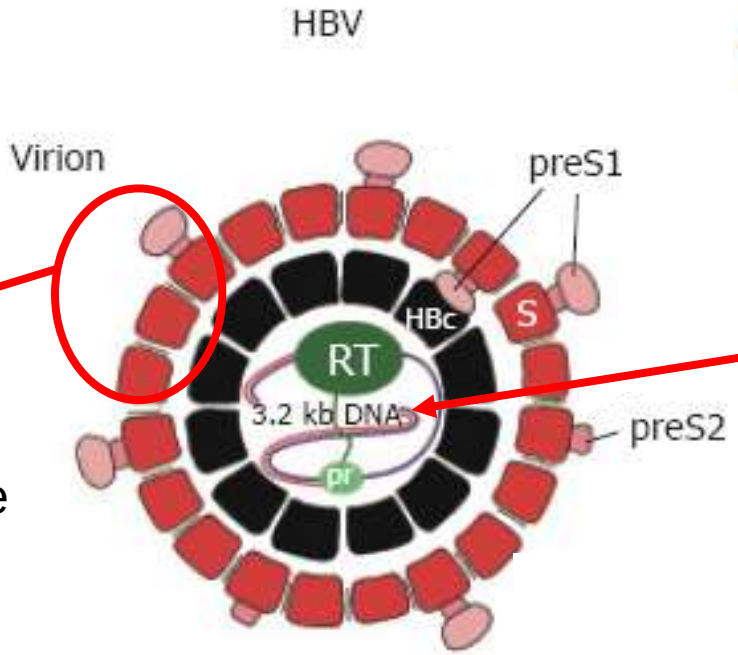
HBsAg Quantification/HBV DNA Quantification

HBsAg quantification and HBV DNA quantification provide complementary information

Peg-interferon

HBsAg
=
marker of
Immunological response





Oral antiviral agents (NAs)

HBV DNA
=
marker of
Virus replication

HBsAg quantification is an additional information to HBV DNA quantification!

Brunetto MR. Editorial. J Hepatol 2010;52:475-7.

Two Concepts for Response-guided Therapy Approach Based on HBsAg Levels

Identify responders (PPV)

✓

Continue therapy

Motivate the patient

Track success

Identify non-responders (NPV)

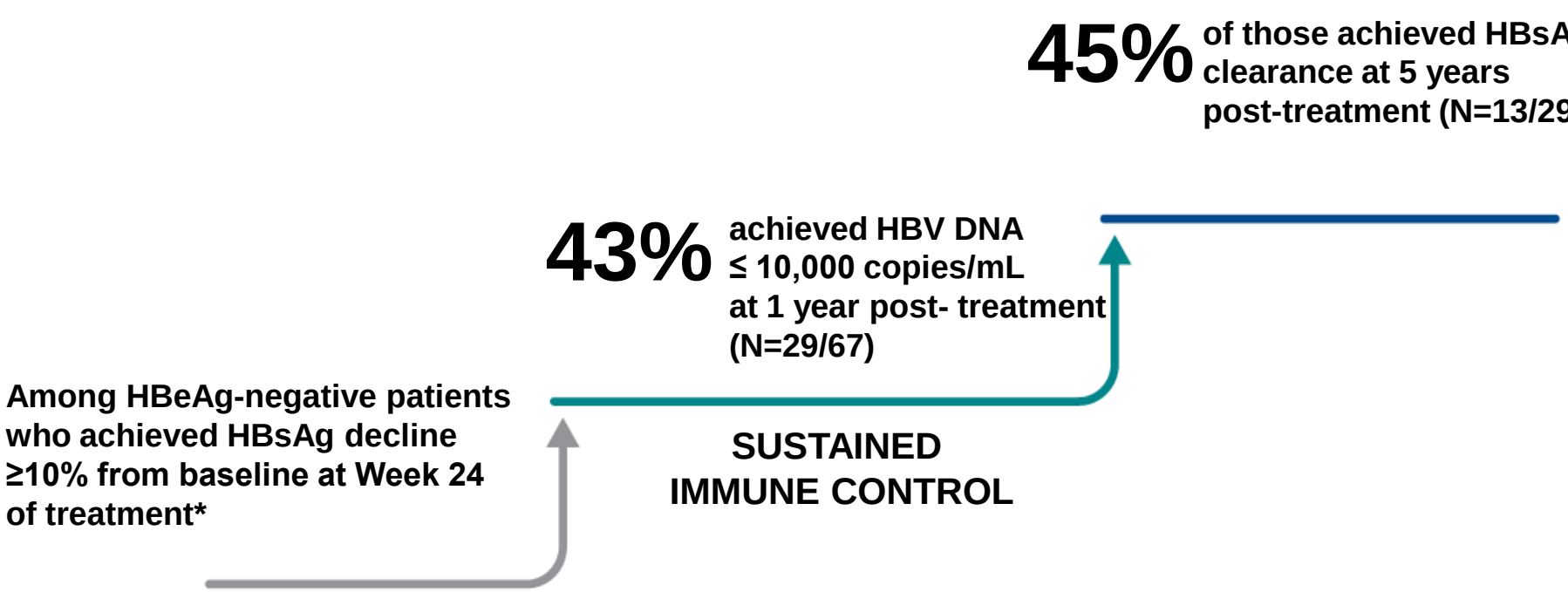
✗

Change strategy

Stop PEG-IFN
(or add on an NA?)

The earlier the better

HBsAg Reduction at Week 24 of PEG INF can Predict of Future HBsAg Clearance

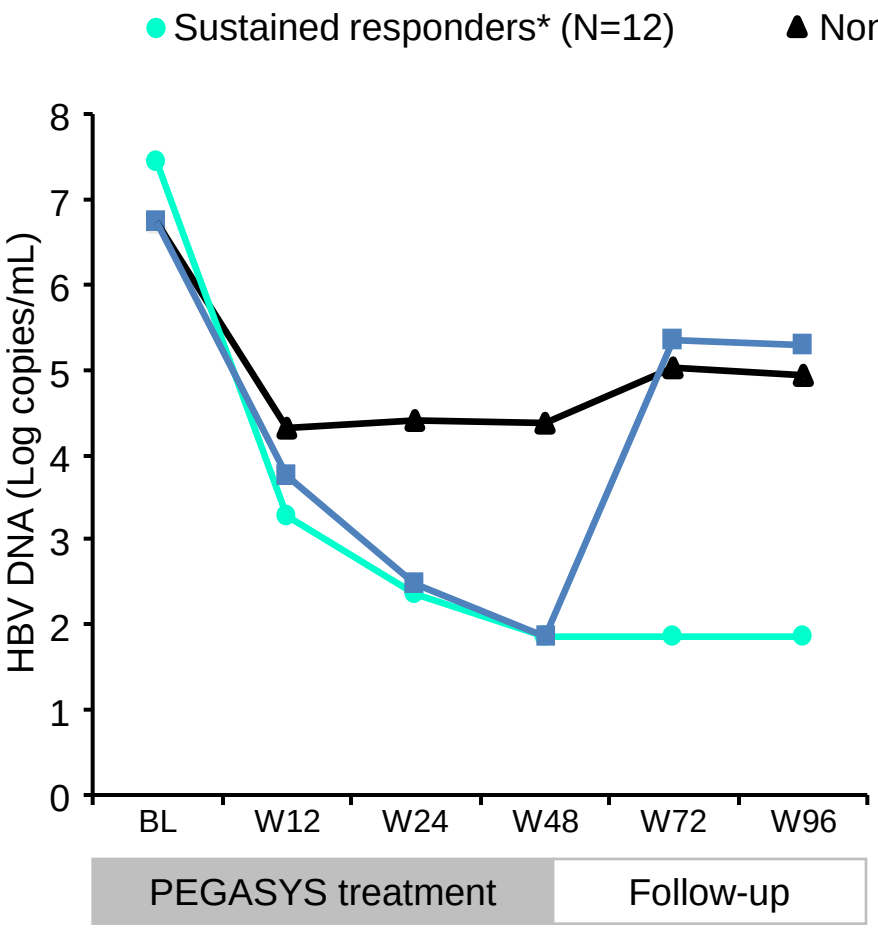


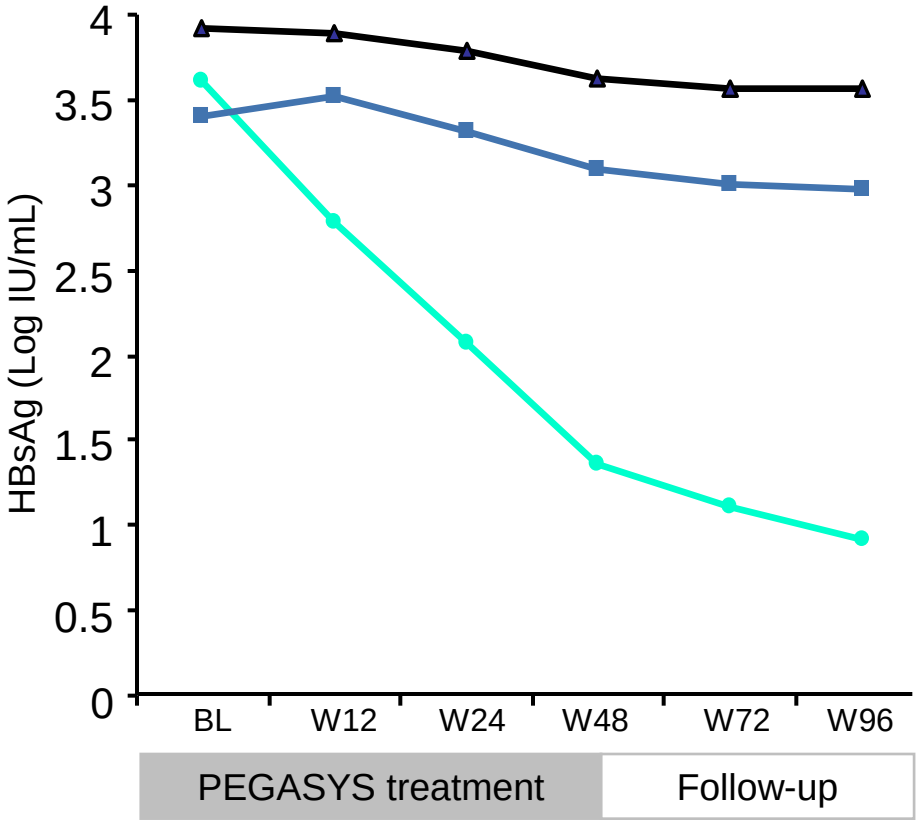
*56% of patients achieved HBsAg decline ≥10% at week 24

Marcellin P, et al. APASL 2010.

On-treatment HBsAg Decline can Distinguish Between Relapsers and Responders

In HBeAg-negative patients

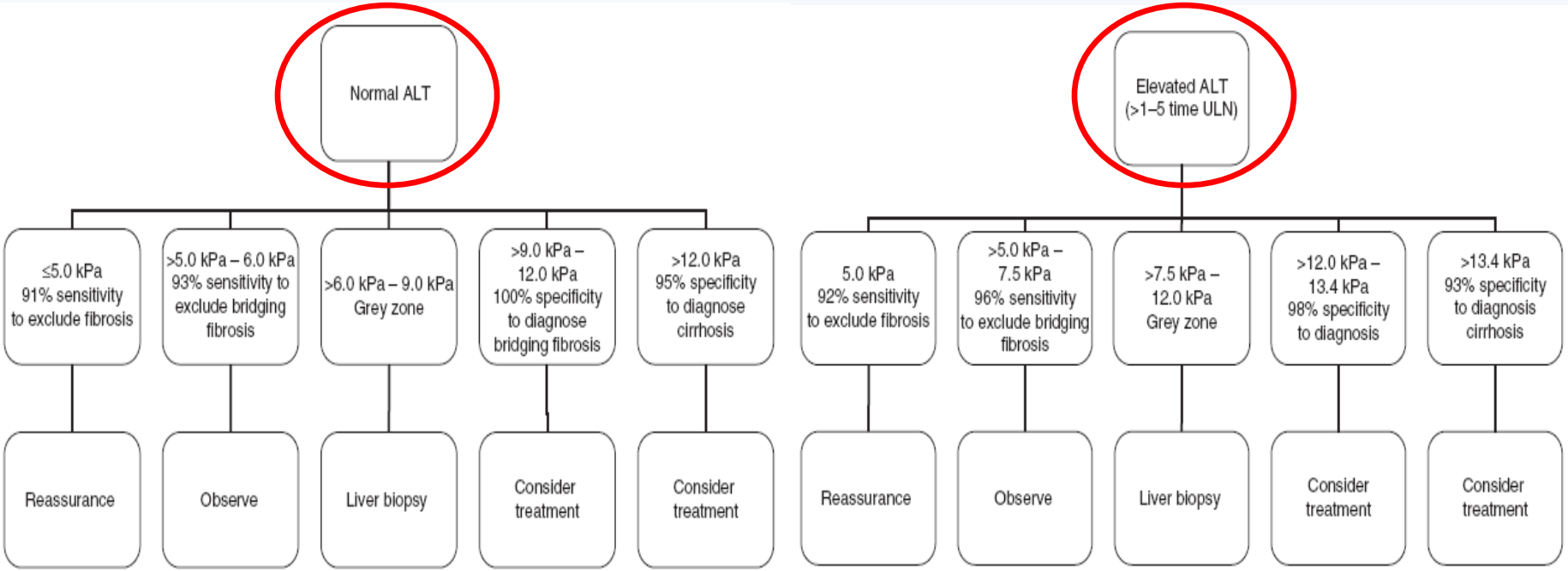




*HBV DNA undetectable by PCR 1 year post-treatment

Moucarir R, et al. Hepatology 2009;49:1151-7.

FibroSCan: Enhancing Performance to Predict Cirrhosis using Different Cut-off Values



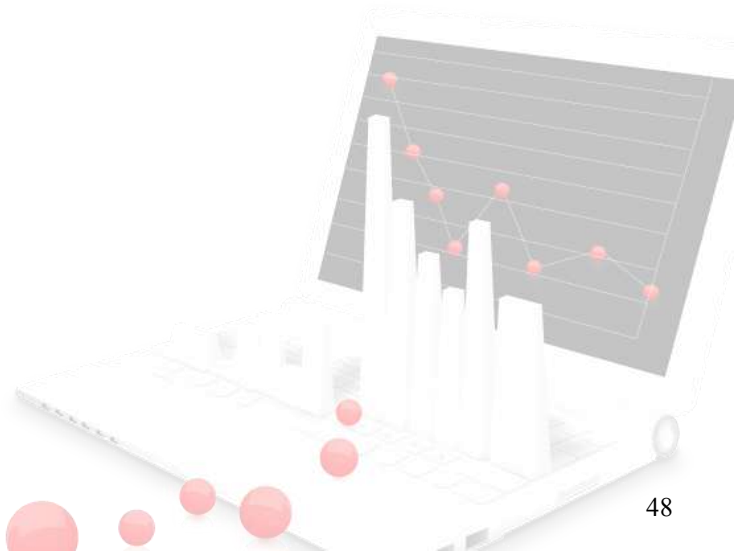
In this way, liver biopsy can be avoided in approximately 62% of patients with normal ALT and 58% of patients with elevated ALT

Chan HL, et al. J Viral Hepat 2009;16:36-44.

REACH B
Risk Calculator for HCC Risk Estimation

Generation of risk calculator

- **Database of REVEAL study**
  - population-based cohort
  - 3,584 patients, age 30-65 years
  - HBsAg (+), anti-HCV (-)
  - No cirrhosis
  - HBV DNA measured at study entry
  - No antiviral therapy
  - Median follow-up of 12 years
  - 131 HCC developed



Yang HI, et al. Lancet Oncol 2011;12:568-74.

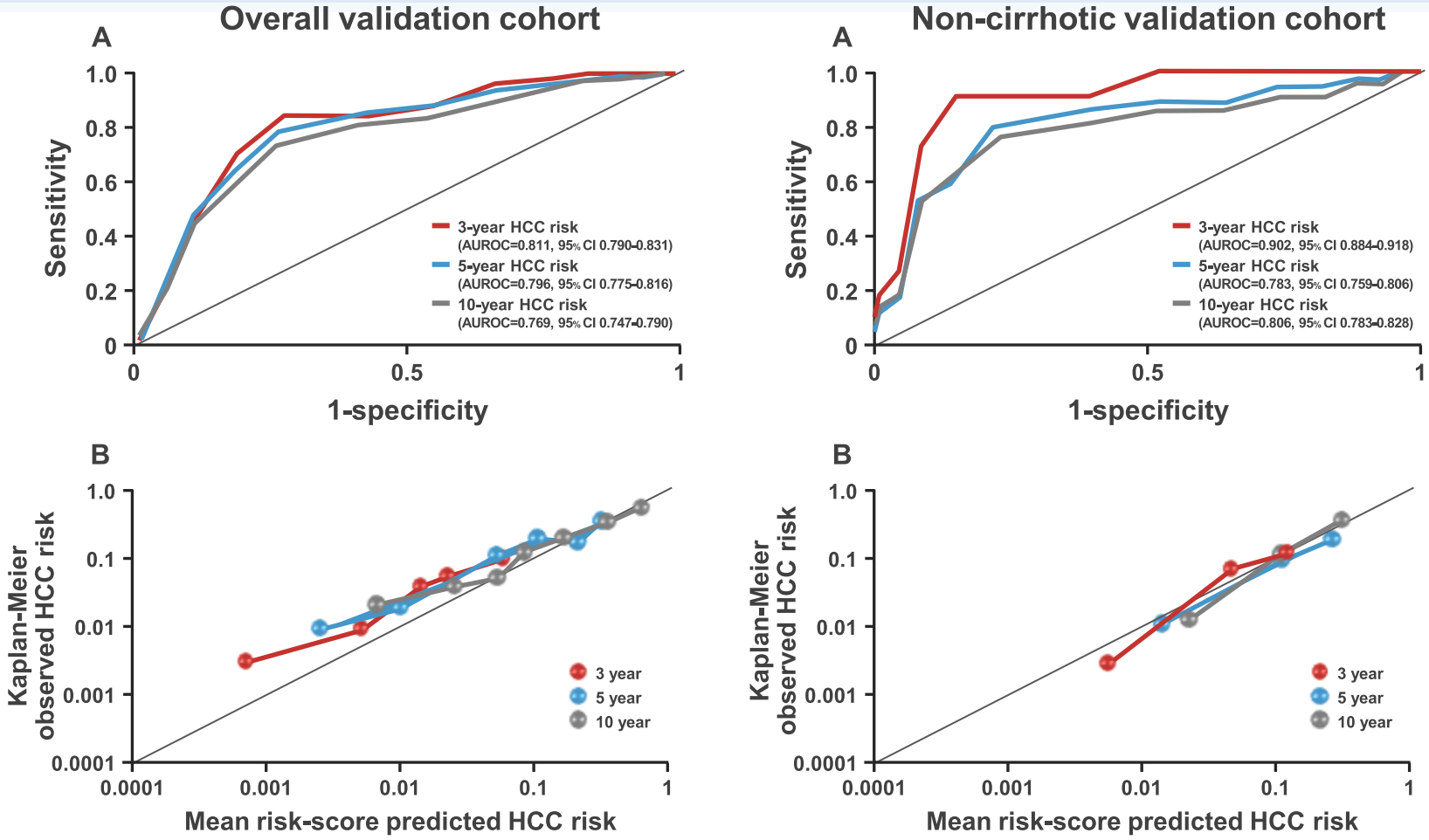
Development Cohort: Multivariate Cox Proportional Hazards Model

	Hazard ratio (95% CI)	β coefficient	p value	Risk score
Sex				
Female	1.00	1.00	..	0
Male	2.2 (1.4-3.4)	0.78798	0.0004	2
Age (years)				
Per 5 years	1.64 (1.48-1.87)	0.49295	<0.0001	1
33-34	..	..	..	0
33-39	..	..	..	1
40-44	..	..	..	2
45-49	..	..	..	3
50-54	..	..	..	4
55-59	..	..	..	5
60-65	..	..	..	6
ALT (U/L)				
<15	1.00	1.00	..	0
15-44	1.5 (1.0-2.2)	0.38823	0.0559	1
≥45	2.6 (1.5-4.4)	0.96311	0.0003	2
HBeAg				
Negative	1.00	1.00		0
Positive	2.3 (1.3-3.8)	0.81308		2
HBV DNA level (copies per mL)				
<300 (undetectable)	1.00	1.00	..	0
300-9999	1.1 (0.4-2.9)	0.11648	0.8063	0
10000-99999	3.7 (1.6-8.5)	1.31467	0.0017	3
100000-999999	9.7 (4.4-21.3)	2.27028	<0.0001	5
≥10^6	8.1 (3.5-19.0)	2.09258	<0.0001	4*

ALT=alanine aminotransferase. HBV=hepatitis B virus. *The risk score attributed to HBV DNA ≥10^6 copies per mL was less than that for HBV DNA of 100000-999999 copies per mL because most patients with HBV DNA ≥10^6 copies per mL were also HBeAg positive, thus sharing the associated higher score for this category.

Yang HI, et al. Lancet Oncol 2011;12:568-74.

Validation Cohort: ROC Curves for Risk of Developing HCC and Predicted vs Observed HCC



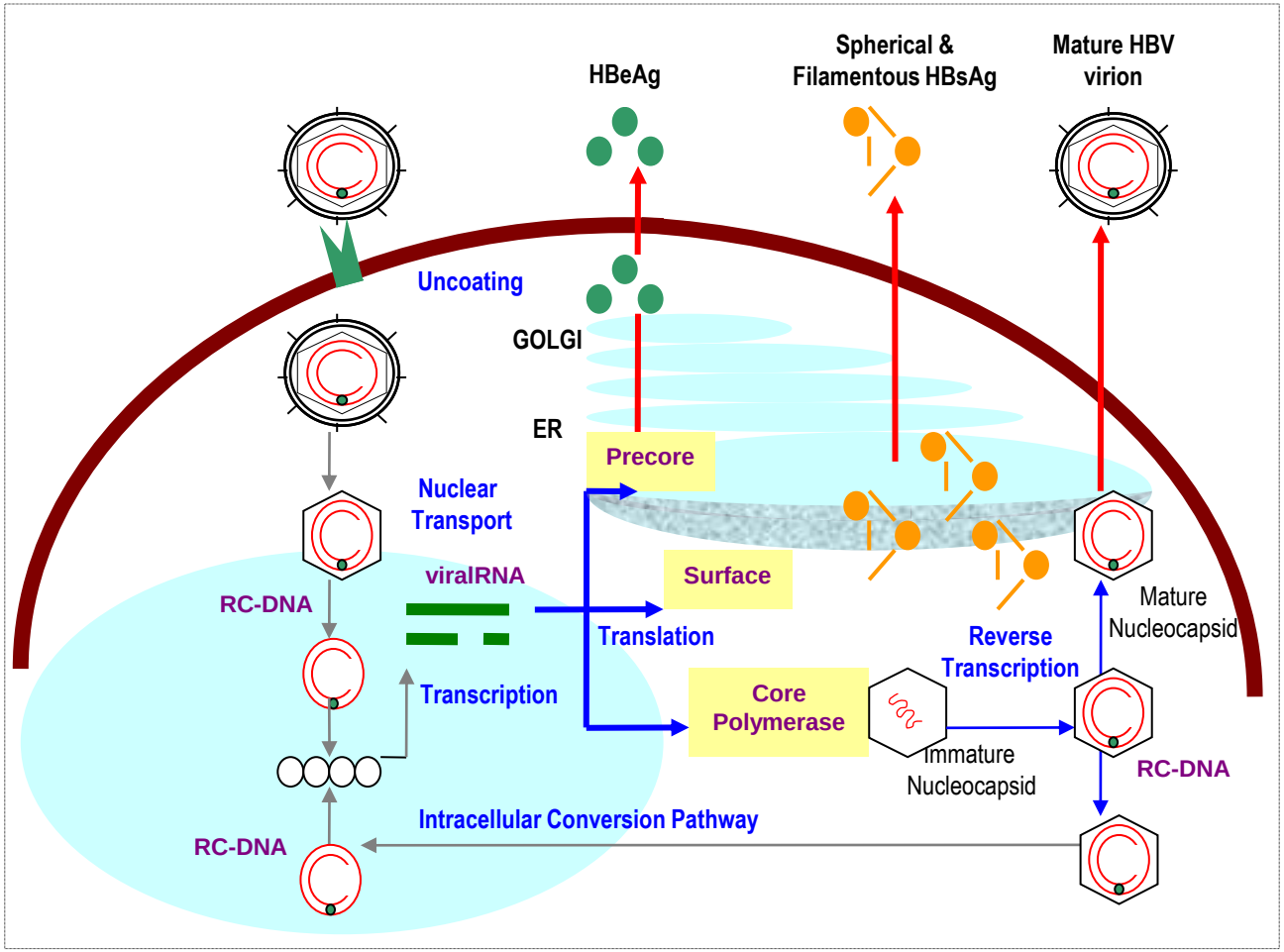
ROC=receiver operating characteristics. HCC=hepatocellular carcinoma. **AUROC**=area under receiver operating characteristic curve.

Yang HI, et al. Lancet Oncol 2011;12:568-74.

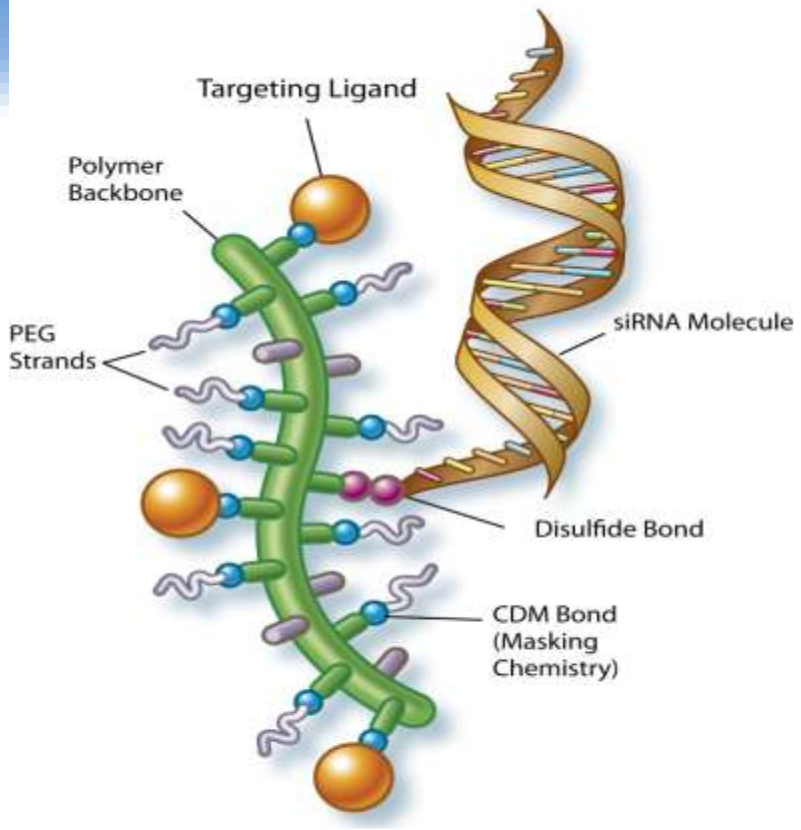
Specific Populations

- Immune tolerant patients: NNT is too high with current data to justify treatment
- Occult HBV (defined as anti-HBc (+) and HBsAg(-)
  - Risk of cancer: no intervention yet justified
  - Risk of reactivation: high risk demanding prophylaxis
    - Rituximab, StCTx, BMTx, ablative therapies
- Children
  - Use of INF and approved nucleos(t)ides to treat selected patients
- Pregnancy
  - Use first line, category B drugs (TDF) during 3rd trimester if HBV DNA >10^6
- FHF or AoC: treat HBV with oral therapies while waiting for HBV DNA
- Test all “at risk” patients for delta hepatitis
  - Advanced liver disease
  - IVDU or sexual transmission as risk for HBV

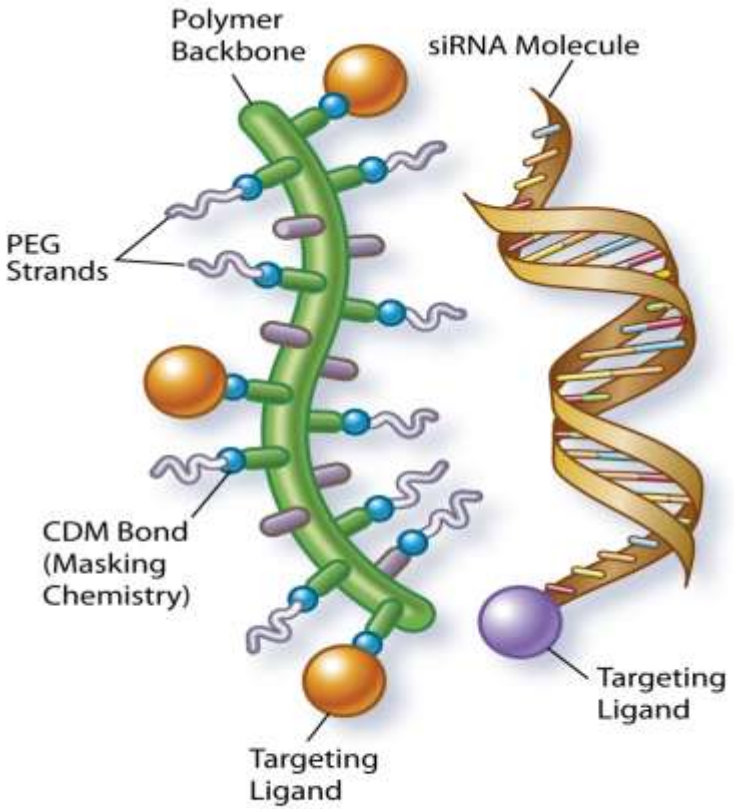
We Need New Herbal or Western Therapies to Attack: HBV Replication: @ cccDNA Pathway



siRNA: new clinical trial in HK Jan 2014

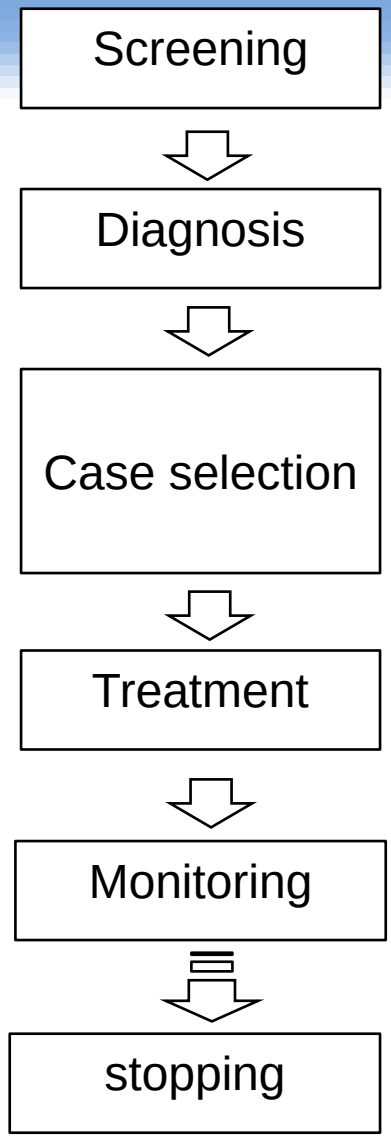


Prototypical DPC
Covalent attachment of siRNA to masked endosomolytic polymer



DPC + targeted siRNA
CDM-masked endosomolytic polymer and siRNA are NOT attached and do NOT interact. Targeted independently to the same cell after co-injection

Chronic Hepatitis B APASL guidelines

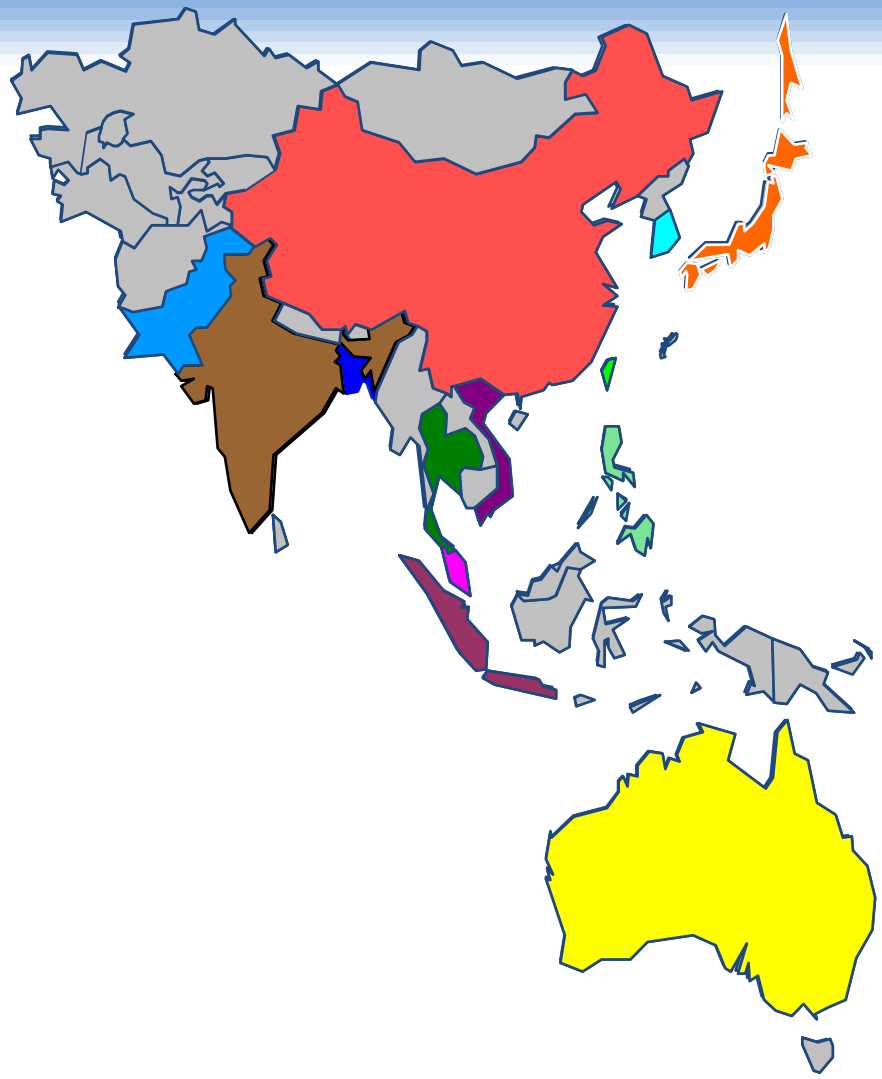


Principle	Recommendation
• Identify patients	• Nil
• Confirm HBsAg+	• Nil
• Select those at risk of disease progression	• ALT≥2xULN, HBV DNA≥2x10^{3-4}(eAg), after >3-6m monitoring
• Decide on therapy	• IFN 4-6m/pegIFN 1y • high genetic barrier NA • Every 3m
• Monitor those on treatment	• HBeAg SC, can stop NA after 2y if DNA neg x3

VACCINATE !

Regional and Country Specific Polices action plans, peer review publications, technical working groups, white papers, buy in from NGO, patients and patients advocates

Asia: Specific Challenges in CHB



- Large burden of undiagnosed infection
- Vaccination: availability, quality, cold chain
- Disparity in health care costs
  - Reimbursement confined to developed countries
  - Cost effectiveness is country specific
- Disparity in infrastructure
  - Laboratories, equipment, trained medical staff
- Large burden of viral resistance
- Rate of non-adherence?
- Optimal treatment strategy for different resourced countries
- Disparity in education of healthcare workers
  - Poor access to guidelines and educational material

Attribution: Seng Gee Lim AASLD 2013

Concluding Points

- There are currently 7 approved therapies for CHB and determination of which therapy to use includes careful consideration of duration of treatment, stopping rules, drug efficacy, side effects, and potential for antiviral resistance with the nucleos(t)ide analogs

- There is no cure: so what is next ?
  - Functional “cure” ? S Ag clearance
  - New treatments: clear capsid and cccDNA
    - iRNA
    - Capsid inhibitors
    - Anti-Sense
    - Entry inhibitors
    - RNAase H target

Thank you

- Congress chairs, APASL, Diana Payawal and my other kind hosts AP organizations and attendees who contributed so much to this meeting
  - All of my HBV global gurus: Seng Gee Lim, the REVEAL team, Robert Brown, Tram Tran, Sammy Saab and many more

- Slides ?: List Serv?: Advise ?
  - See my website for downloads: robertgish.com
  - Or send me an Email: rgish@robertgish.com
  - Liver List Serv? Send me an email: rgish@robertgish.com
  - Twitter: @rgish1