Current Therapy of Hepatitis B Planning for 2014 and beyond

SOTA 2014

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HBV Relevant Disclosures

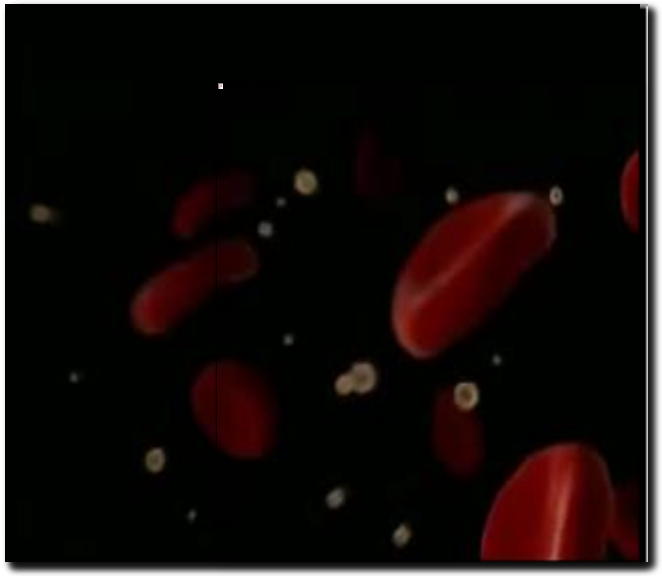
- Advisory Board
  - BMS, Gilead, Genentech, Arrowhead, ISIS
- Honorarium, speakers bureau
  - BMS, Gilead,
- Investment (stock options)
  - Arrowhead

HEV Relevant Disclosures

- Advisory Board
  - None
- Honorarium, speakers bureau
  - None

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
  - HBsAg clearance is a "functional cure"
  - 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

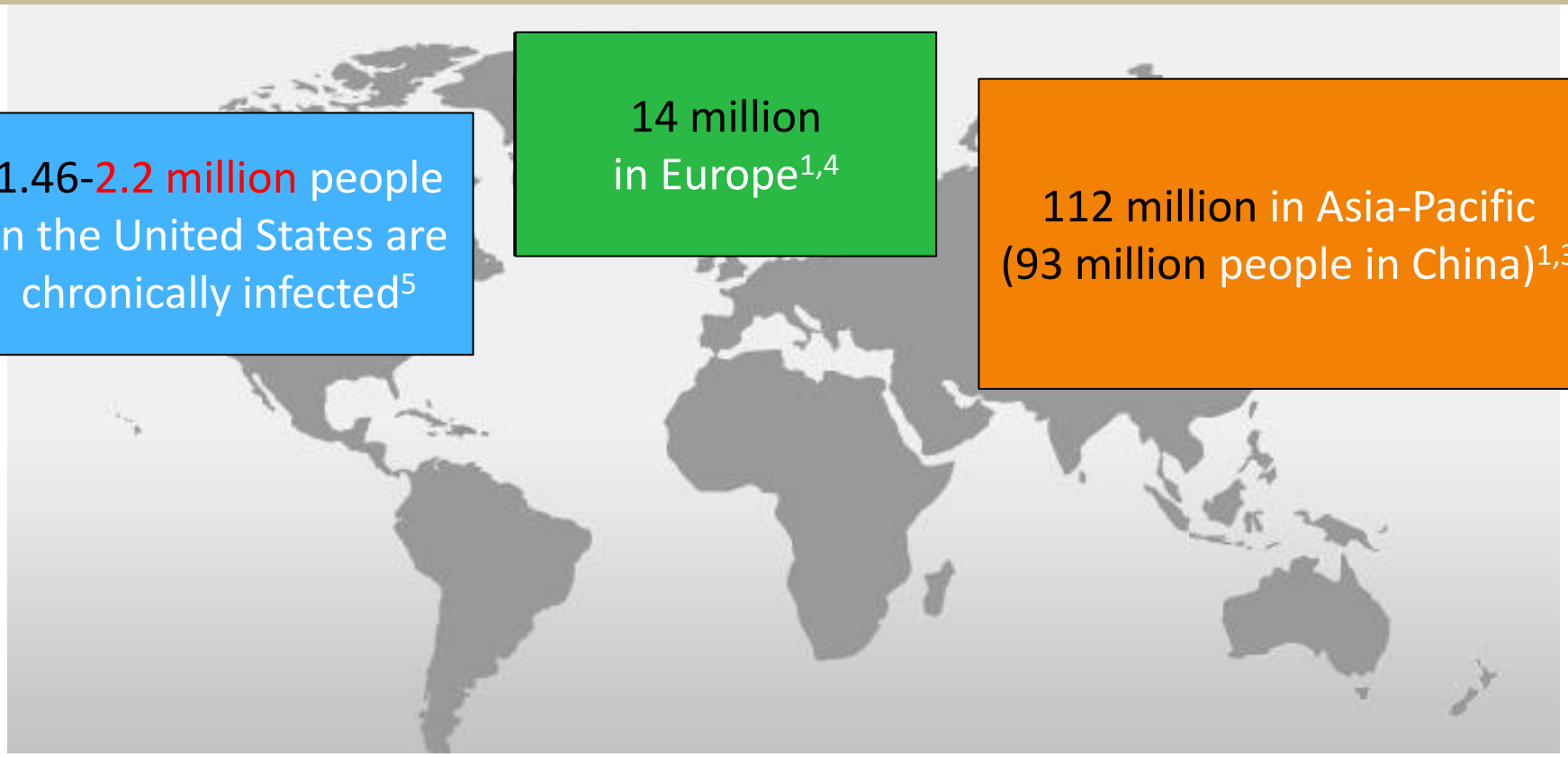


1. Hepatitis Australia. Available at http://www.hepatitisaustralia.com/about_hepatitis/hep_b.html. Accessed April 2009;
2. World Health Organization. Hepatitis B Fact Sheet. Available at http://www.who.int/mediacentre/factsheets/fs204/en/. Accessed April 2009;
3. Ulmer T, et al.(2007) European orientation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

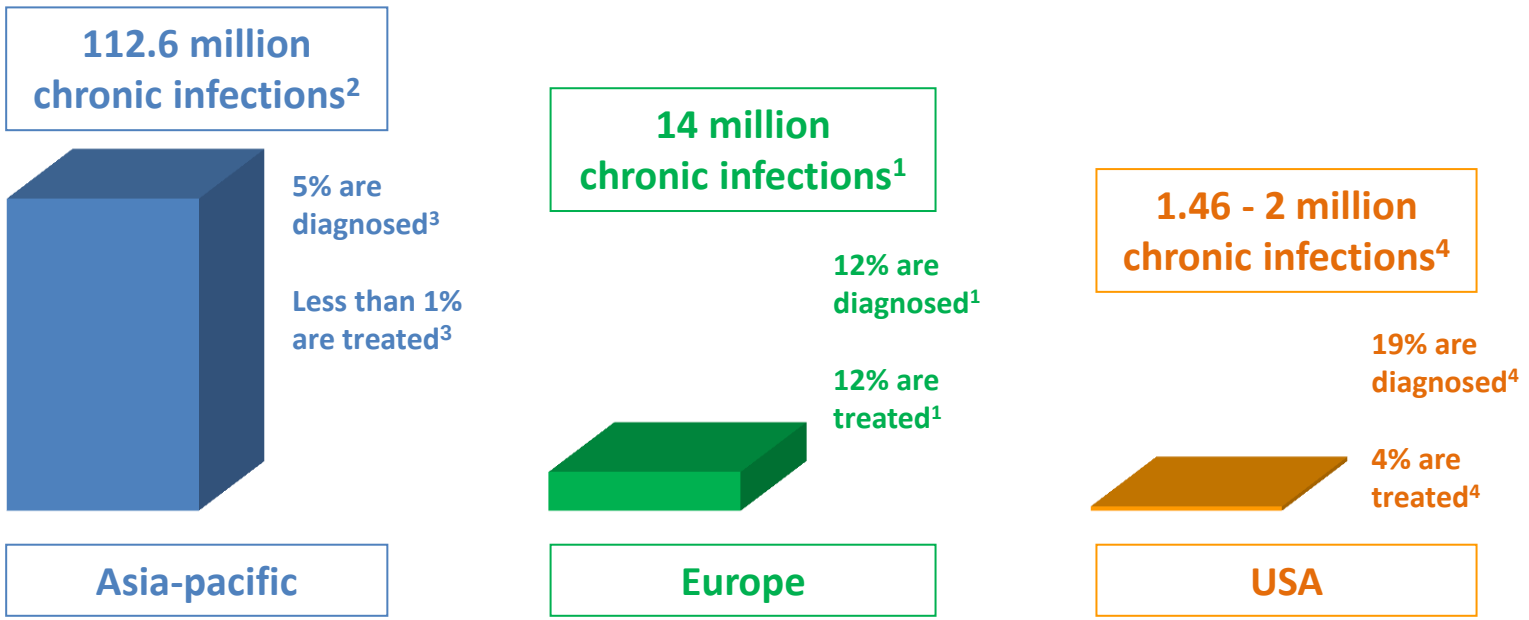
(Compared with the 33 million living with HIV[2])



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.

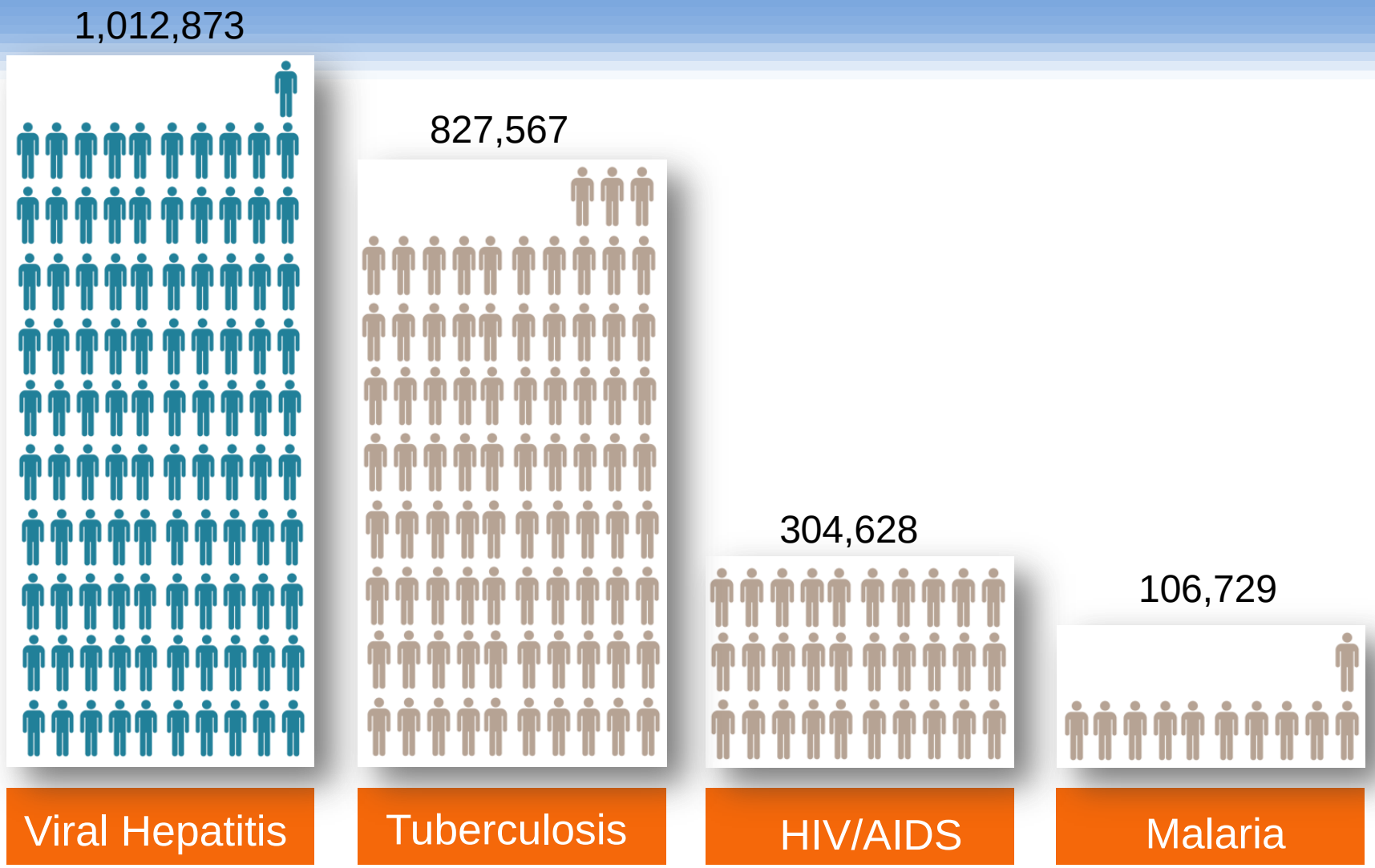
An Unmet Medical Need

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



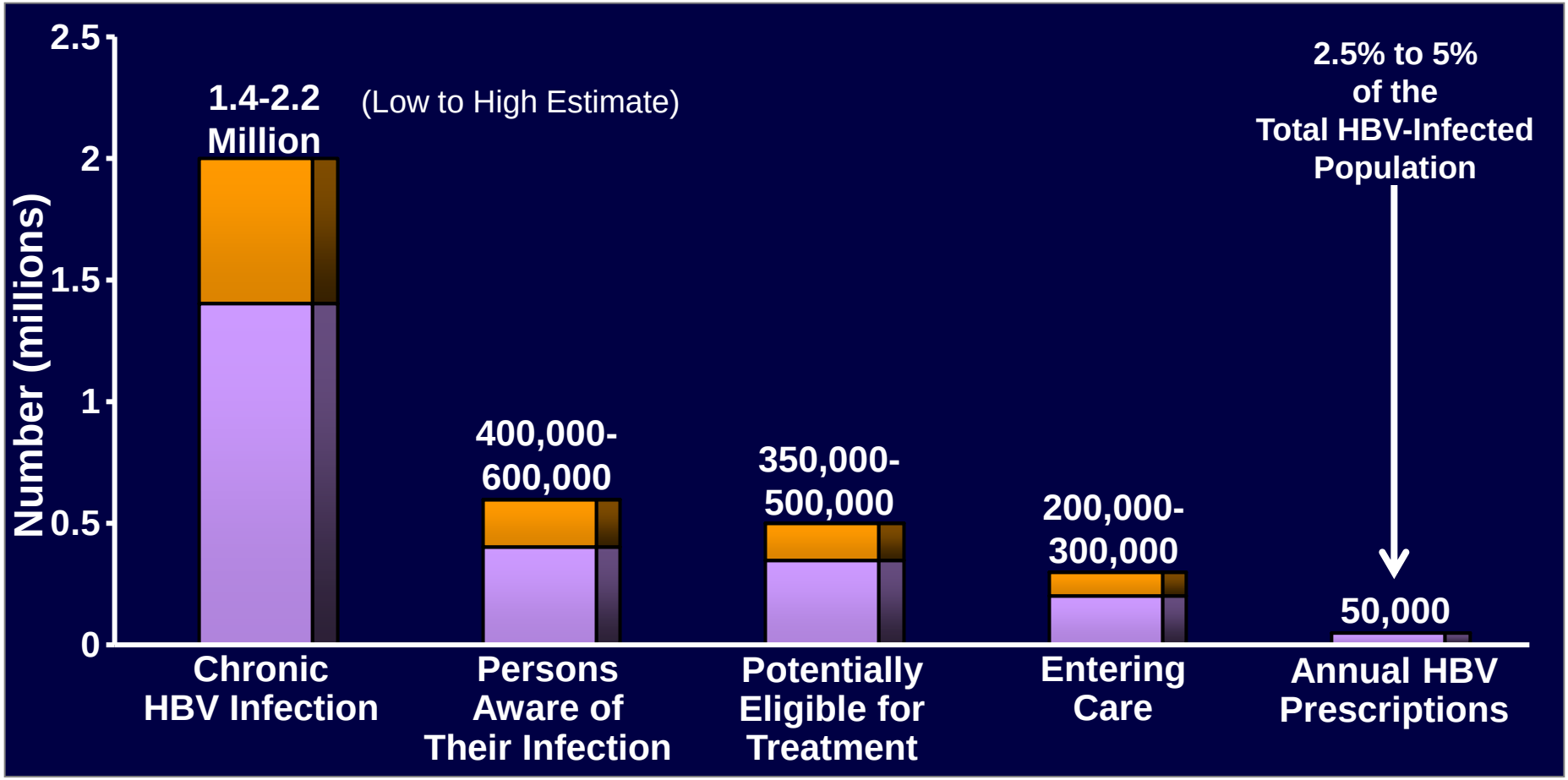
1. BMS Market Research. Information available upon request from Bristol-Myers Squibb;
2. Mohamed R, et al. J Gastroenterol Hepatol 2004;19:958-69;
3. Decision Resources. Hepatitis B virus in China – Emerging markets study #5; 4. BMS Market Research.

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



Attribution: Seng Gee Lim AASLD 2013

HBV Infection, Diagnosis, and Care in the United States



Modified and updated from : Cohen C, et al. *J Viral Hepat.* 2010

Historical/ Current

CDC Recommendations for Routine HBV Testing

	Populations
Increased HBsAg Prevalence	• Persons born in regions with high or intermediate prevalence of HBV infection (HBsAg prevalence ≥2%) • U.S.-born persons not vaccinated as infants whose parents were born in regions with high prevalence of HBV infection (HBsAg prevalence ≥8%)
Manage Exposures	• All pregnant women • Infants born to HBsAg+ women • Injection drug users • Men who have sex with men • Household, needle-sharing, or sex contacts of persons known to be HBsAg+ persons • Source of blood/body fluid exposures (e.g., needlestick, sexual assault)
Prevent Nosocomial Infection	• Donors of blood, plasma, organs, tissue, or semen • Hemodialysis patients
Increased Risk of Medical Consequences	• HIV+ persons • Persons with immunosuppressive therapy • Persons with elevated ALT or AST of unknown etiology

Centers for Disease Control and Prevention. *Morb Mortal Wkly Rep.* 2008;57(RR-8):1-16.

2014

What has the USPHSTF changed and going to recommend?

Foreign Born: from endemic regions

MSM

IVDU

High risk behavior

HBV: Phase I Tests

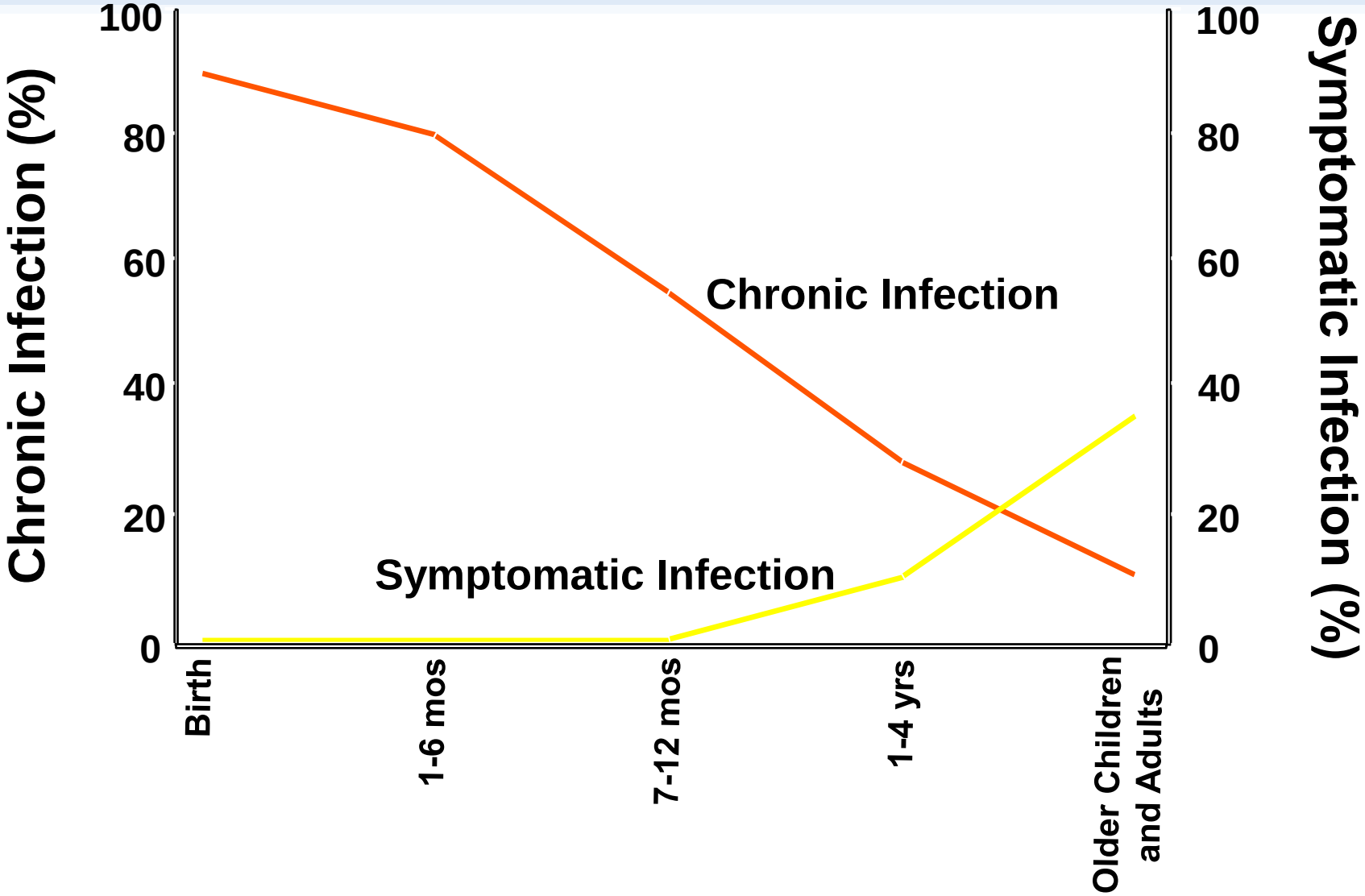
- HBsAg = infection
- Anti-HBs = immunity
  - –if anti-HBc is negative
- Anti-HBc = exposure

HBV

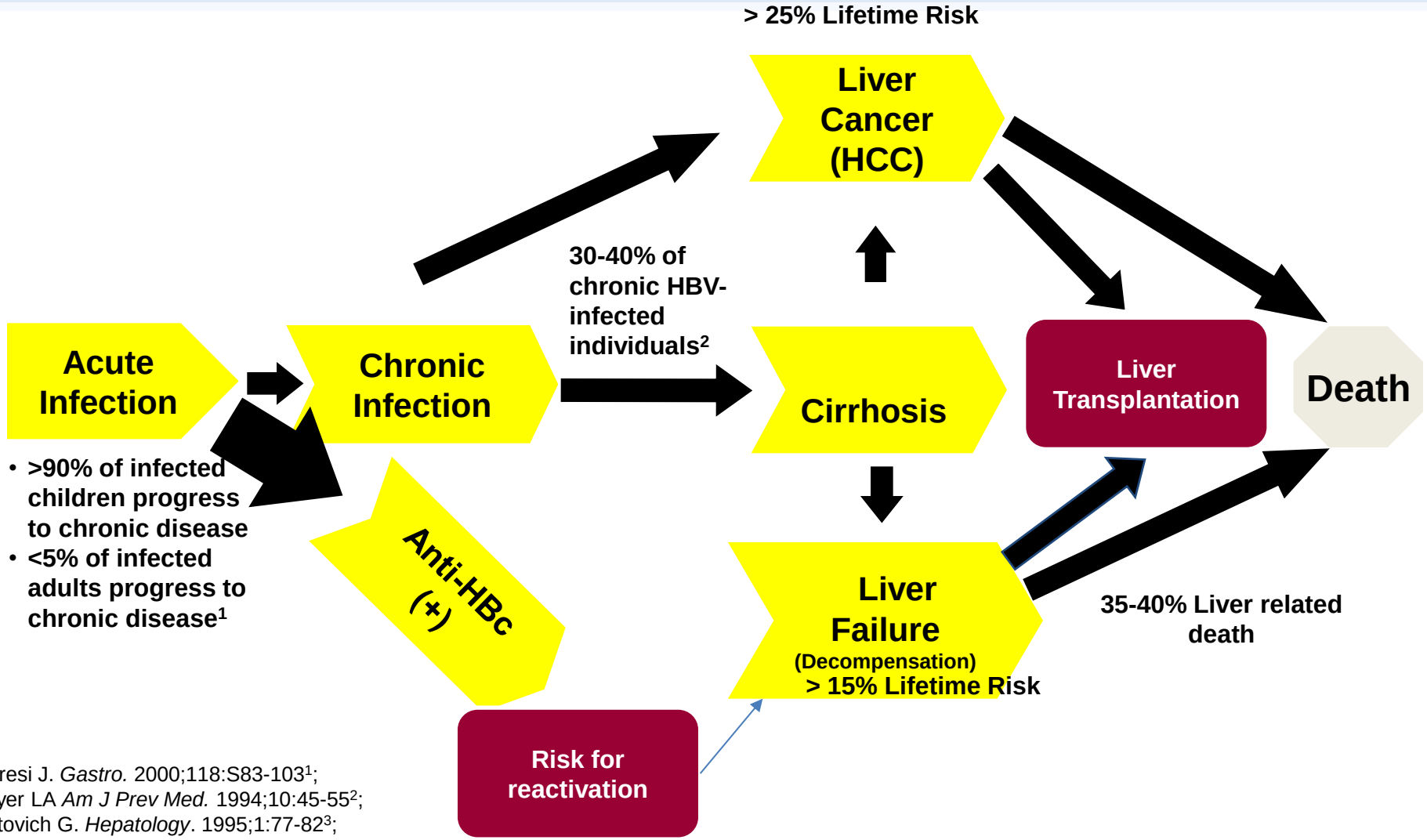
- Is not curable

- New term: (oxymoron) “functional cure”
  - When HBsAg becomes negative

Outcome of Hepatitis B Virus Infection by Age at Infection



Hepatitis B Disease Progression



Torresi J. *Gastro.* 2000;118:S83-103[1];
Moyer LA *Am J Prev Med.* 1994;10:45-55[2];
Fattovich G. *Hepatology*. 1995;1:77-82[3];
Perrillo RP. *Hepatology.* 2001;33:424-432.[4]

HBV Diagnostic Markers

Serologic Marker Results				
HBsAg	Total Anti-HBc	IgM Anti-HBc	Anti-HBs	Interpretation
-	-	-	-	Never infected and no evidence of immunization
+	+	+	-	Acute infection
+	+	-	-	Chronic infection
-	+	-	+	"Recovered" from past infection and not immune, low level carrier
-	-	-	+	Immune (immunization)

HBeAg- High infectivity

HBeAb- Low infectivity

Weinbaum CM, et al. *MMWR Recomm Rep.* 2008;57(RR-8):1-20.

Testing Paradigm

- Always test: anti-HBc

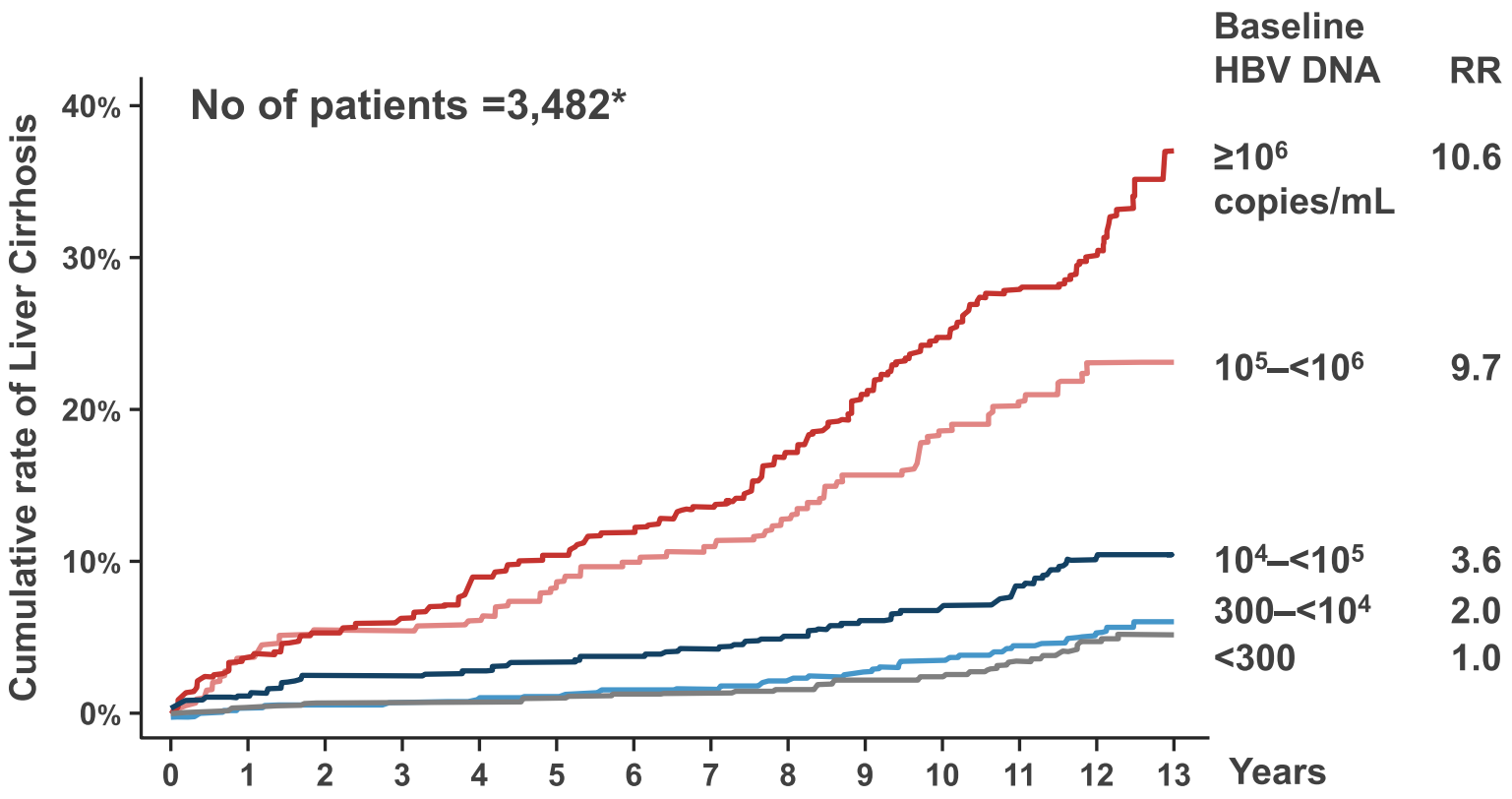
- If anti-HBc + > does not need vaccination
  - >>> risk for reactivation

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]
  - Historically: Liver cancer was the 3rd highest cause of death by cancer in men[3]
  - Now 2014: Liver cancer is the 2rd highest cause of caner death worldwide[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.

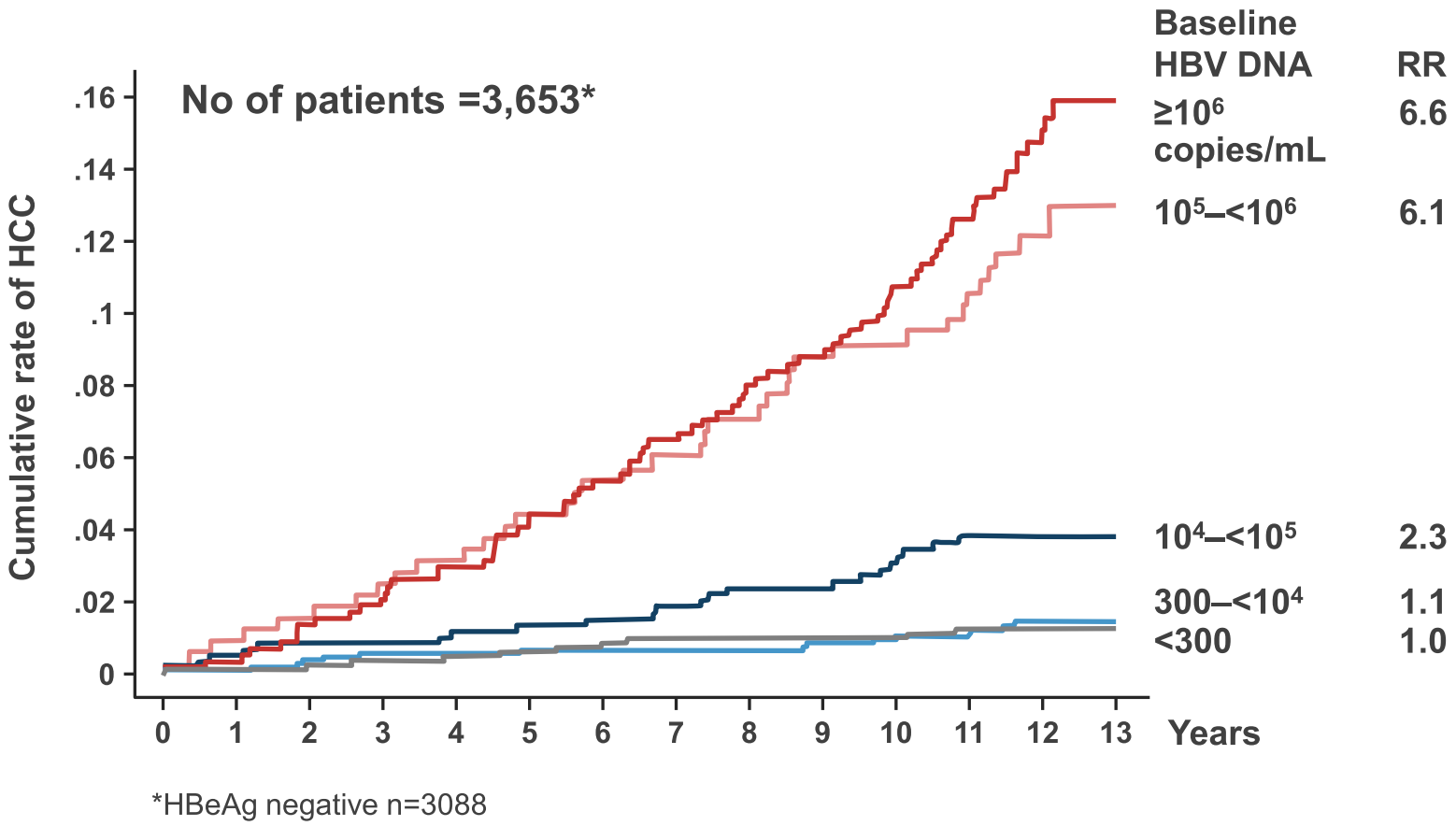
HBV DNA vs. Liver Cirrhosis : REVEAL data



* HBeAg negative n=2960

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

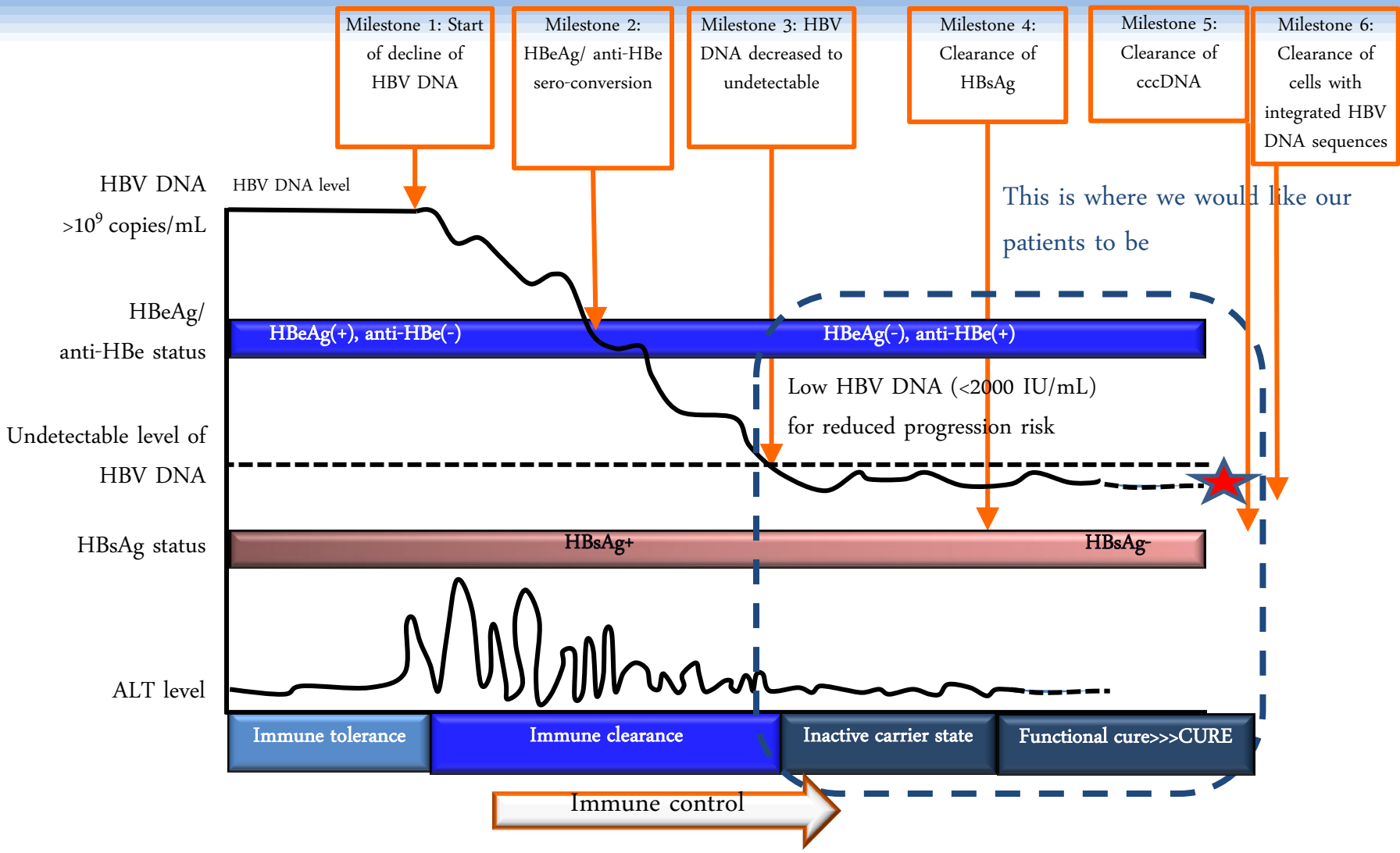
HBV DNA vs. HCC : REVEAL Data



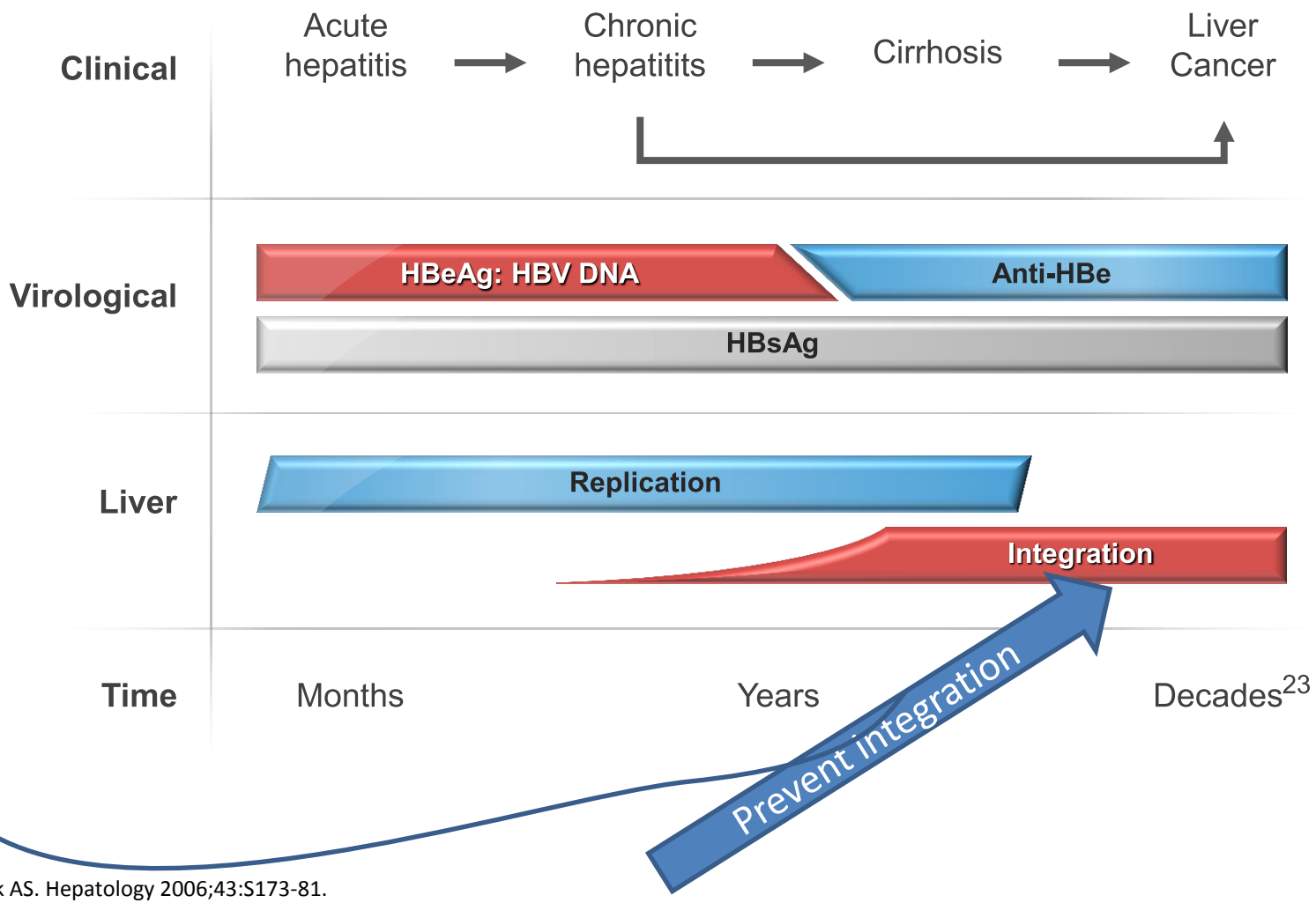
*HBeAg negative n=3088

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

Aiming for True Inactive Carrier Status and CURE



Why treat early ?
Natural History of Chronic HBV Infection



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

Next Steps in HBV Management

- Use the right NUC to control HBV for the right patient
  - Personalized medicine
- Help Stop oral (NUC) therapy, current Rx is indefinite
- Choose the correct Nuc for your patient
  - Pregnancy, Drug resistance, Management, Lactic Acidosis
- 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

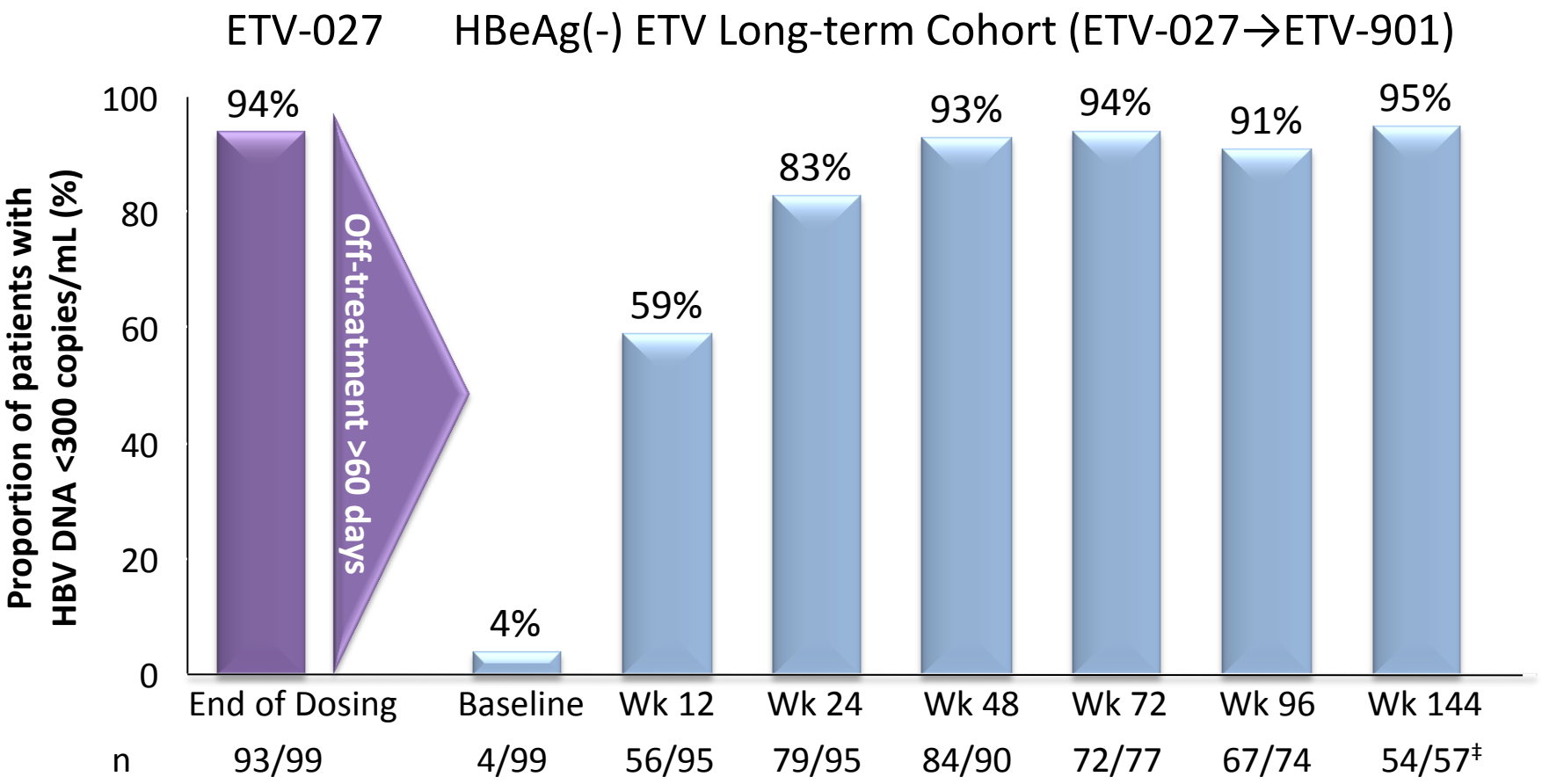
- Clinical endpoints similar to those for HBeAg-positive and HBeAg-negative CHB patients
- No liver failure
  - Now
    - Decreased rate of HCC
    - Falling rates of liver transplant
    - Lower death rates due to HBV
  - Future
    - Clear sAg in all patients
    - No ccc DNA remaining in liver cells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



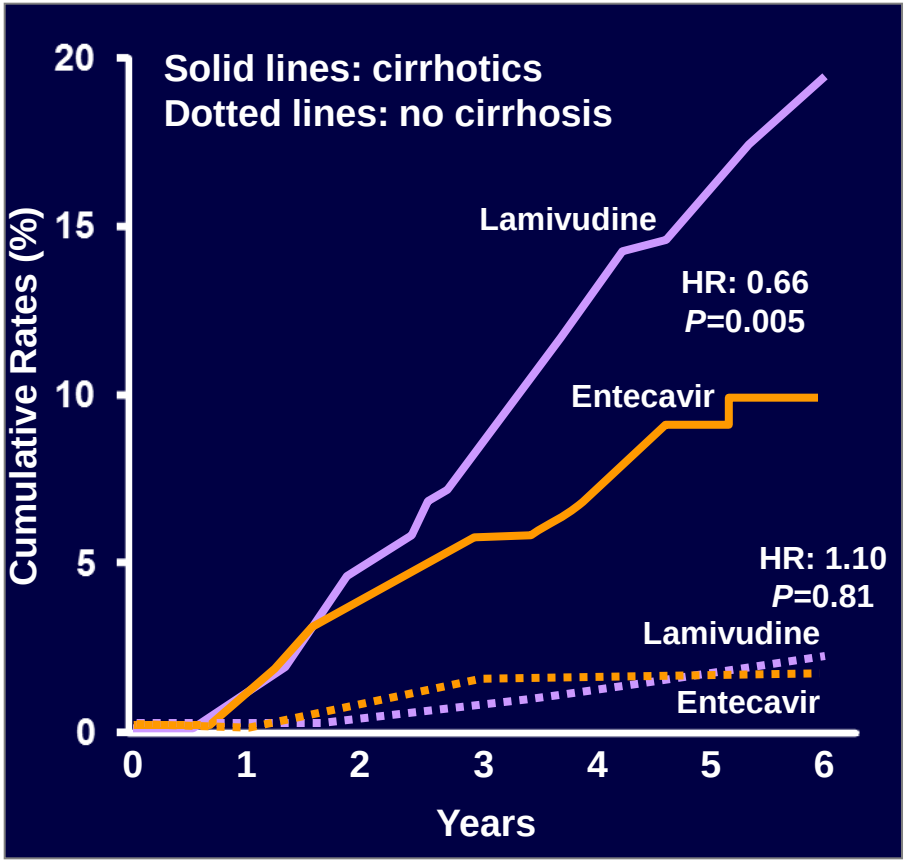
†In the randomised controlled study (ETV-027), patients received 0.5mg ETV. In the 901 rollover study, patients received 1mg ETV

‡ 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.

Korean Cohort: Impact of Entecavir and Lamivudine on Survival in HBV (1999-2011)

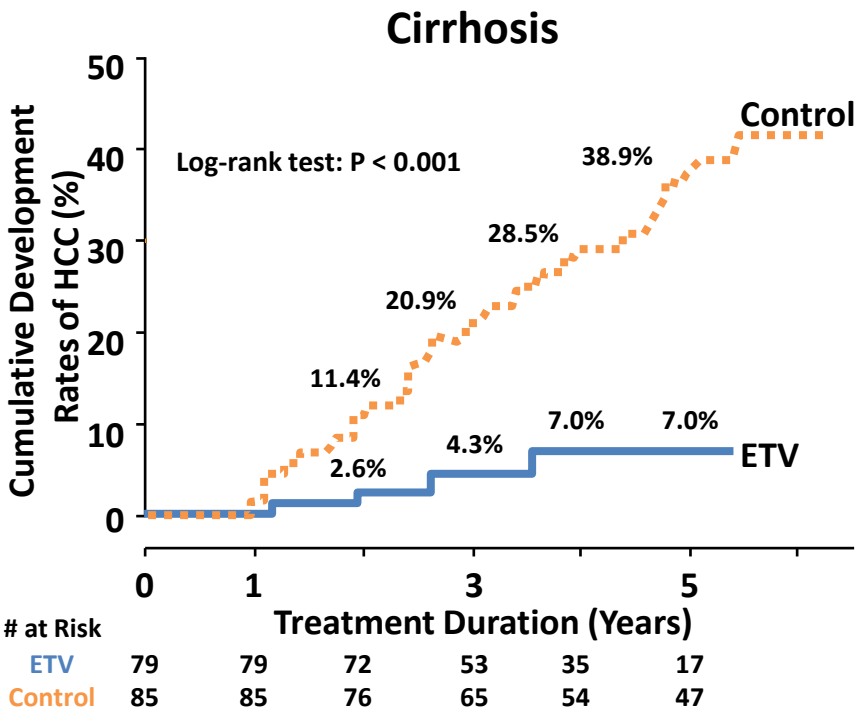
- Single-center cohort of chronic HBV (n=9615 treatment-naïve)
  - Entecavir 0.5 mg/day or lamivudine 100 mg/day
  - ≥20 years of age; no prior HCC, transplant, HCV, HDV, or HIV; HBV DNA ≥2000 IU/mL
- Treatment with entecavir was associated with
  - Minimal risk of drug resistance 1.5% verus 50.8%; *P*<0.001)
  - Minimal need for rescue therapy (1.8% verus 39.3%; *P*<0.001)
  - Significantly lower risk of death or transplantation (adjusted hazard ratio 0.42; *P*<0.001)

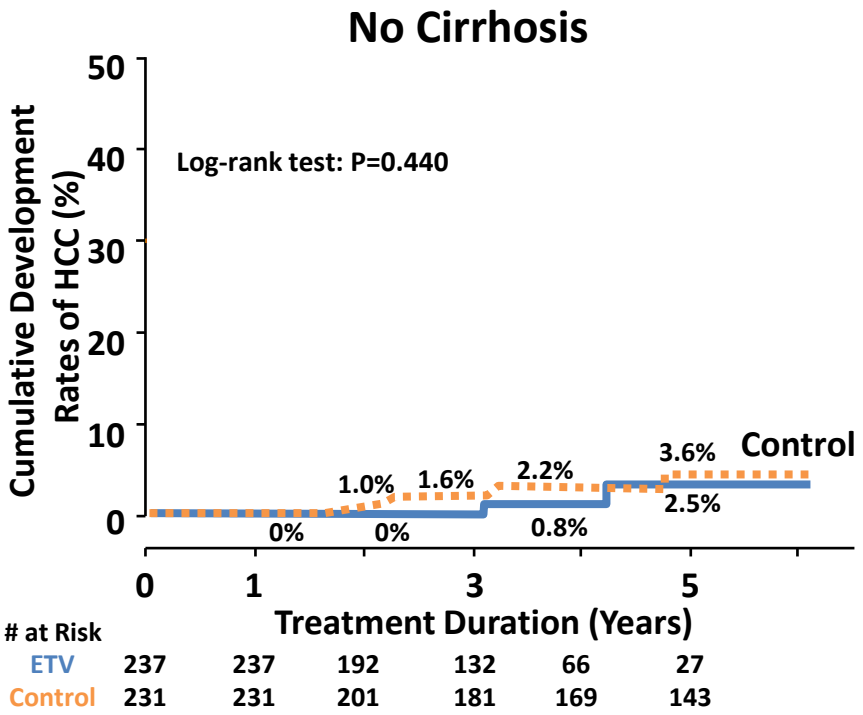


Lim Y, et al. *Hepatology.* 2013;58(suppl 1):223A. Abstract 32.

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

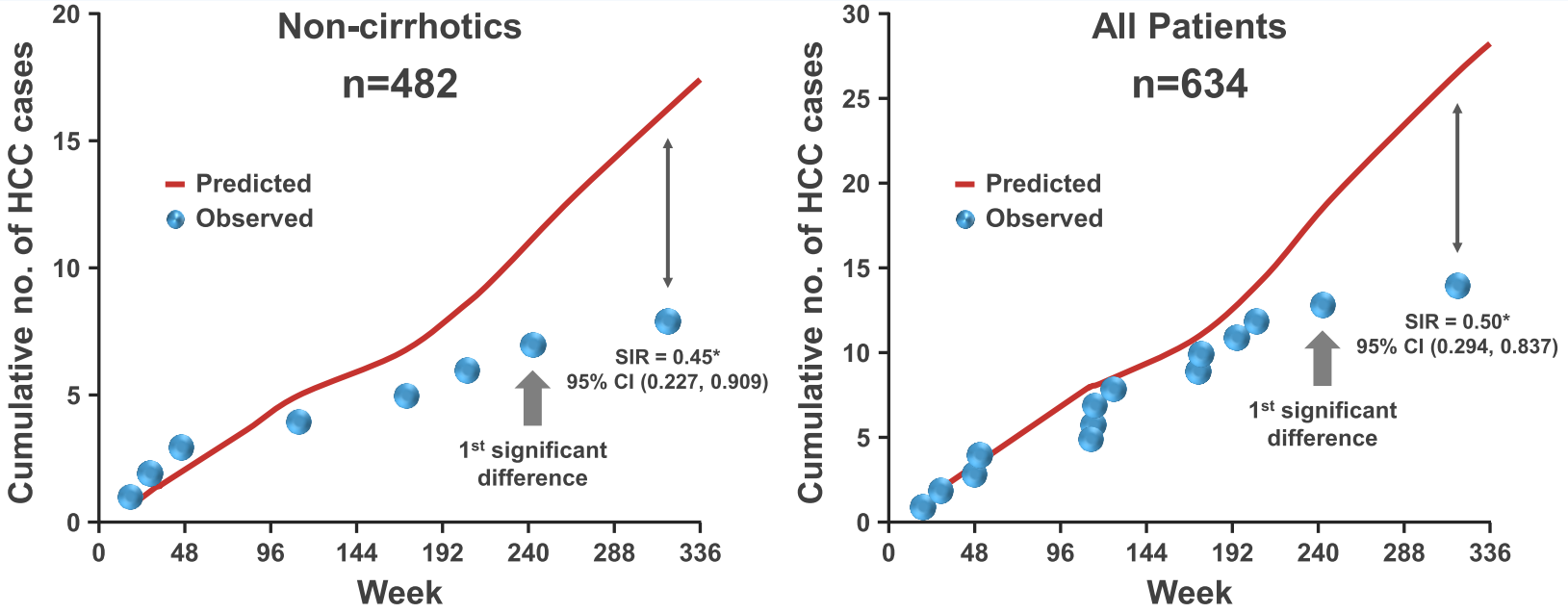
Response	HBeAg- Patients (Study 102)		HBeAg+ Patients (Study 103)	
	Year 5	Year 6	Year 5	Year 6
HBV DNA < 400 copies/mL Intent-to-treat*, % (n/N)	**83** (291/350)	**81** (281/345)	**65** (160/248)	**63** (157/251)
HBV DNA < 400 copies/mL On treatment†, % (n/N)	**99** (292/295)	**99.6** (283/284)	**97**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

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

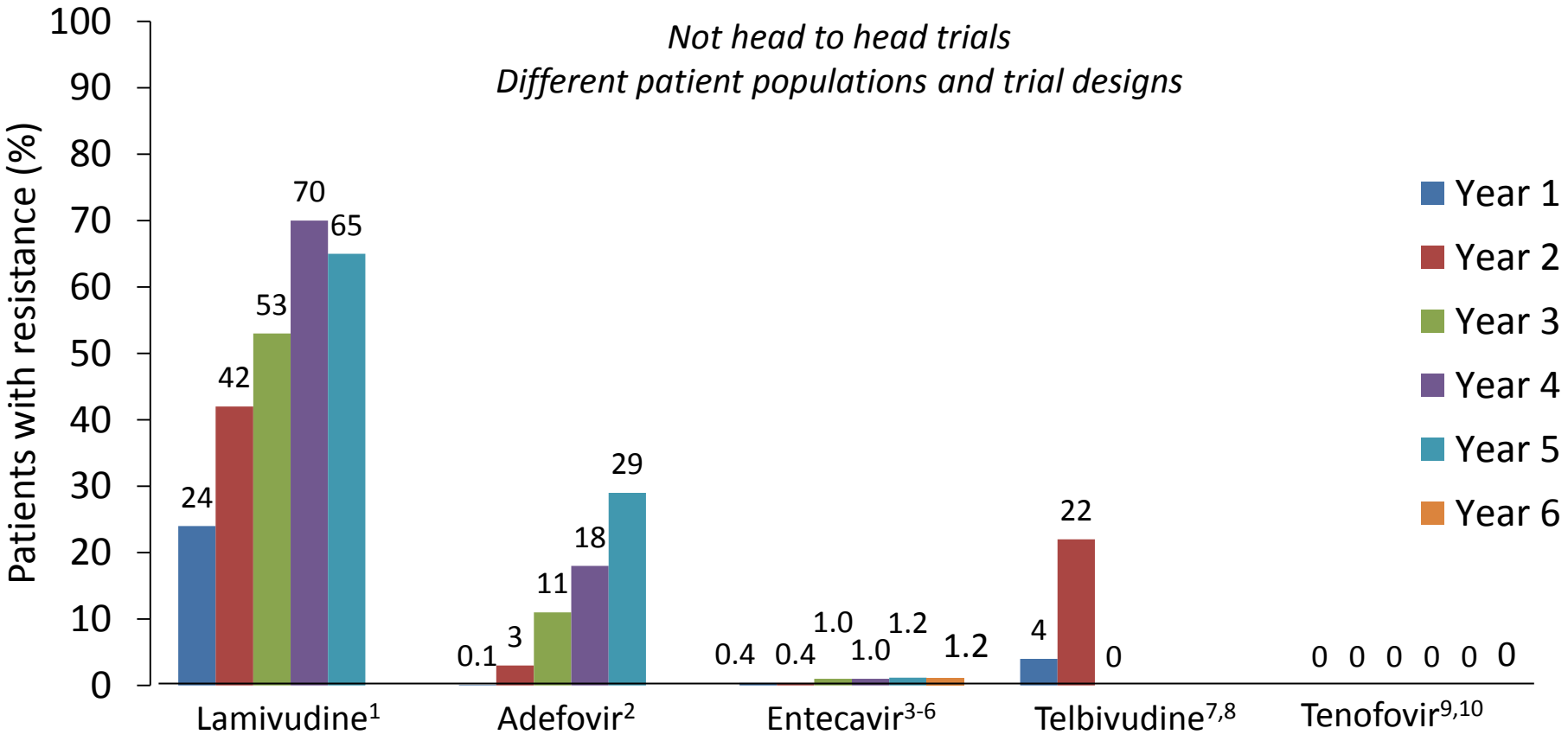


- Incidence of HCC in patients on TDF in studies 102/103 was lower than predicted by the REACH-B model
- In non-cirrhotic patients, the effect of TDF becomes noticeable between 2-3 years of therapy and became statistically (55% reduction) at 6 years of therapy

*Statistically significant at nominal α-level of 0.05.

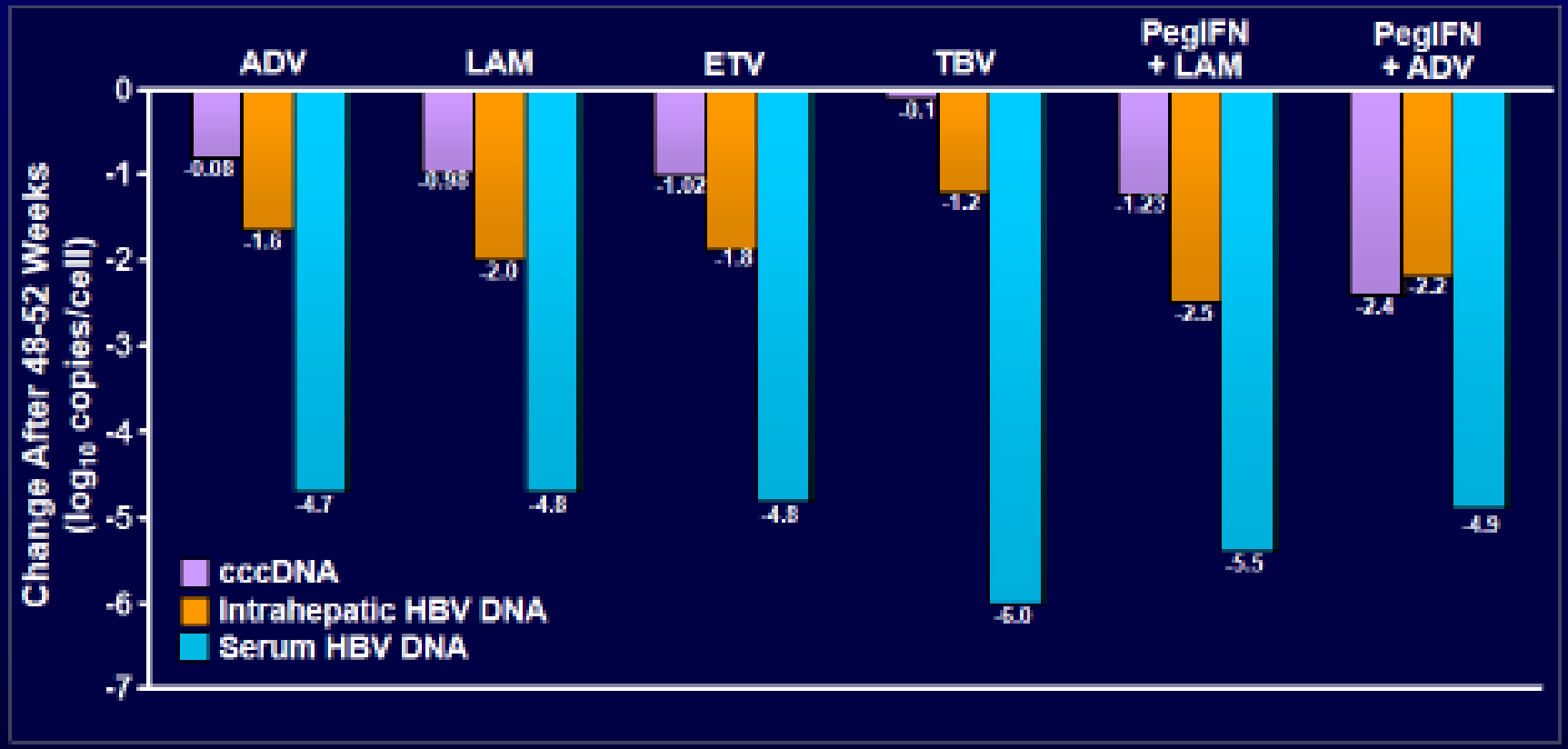
Kim WR, et al. EASL 2013. Oral 43.

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



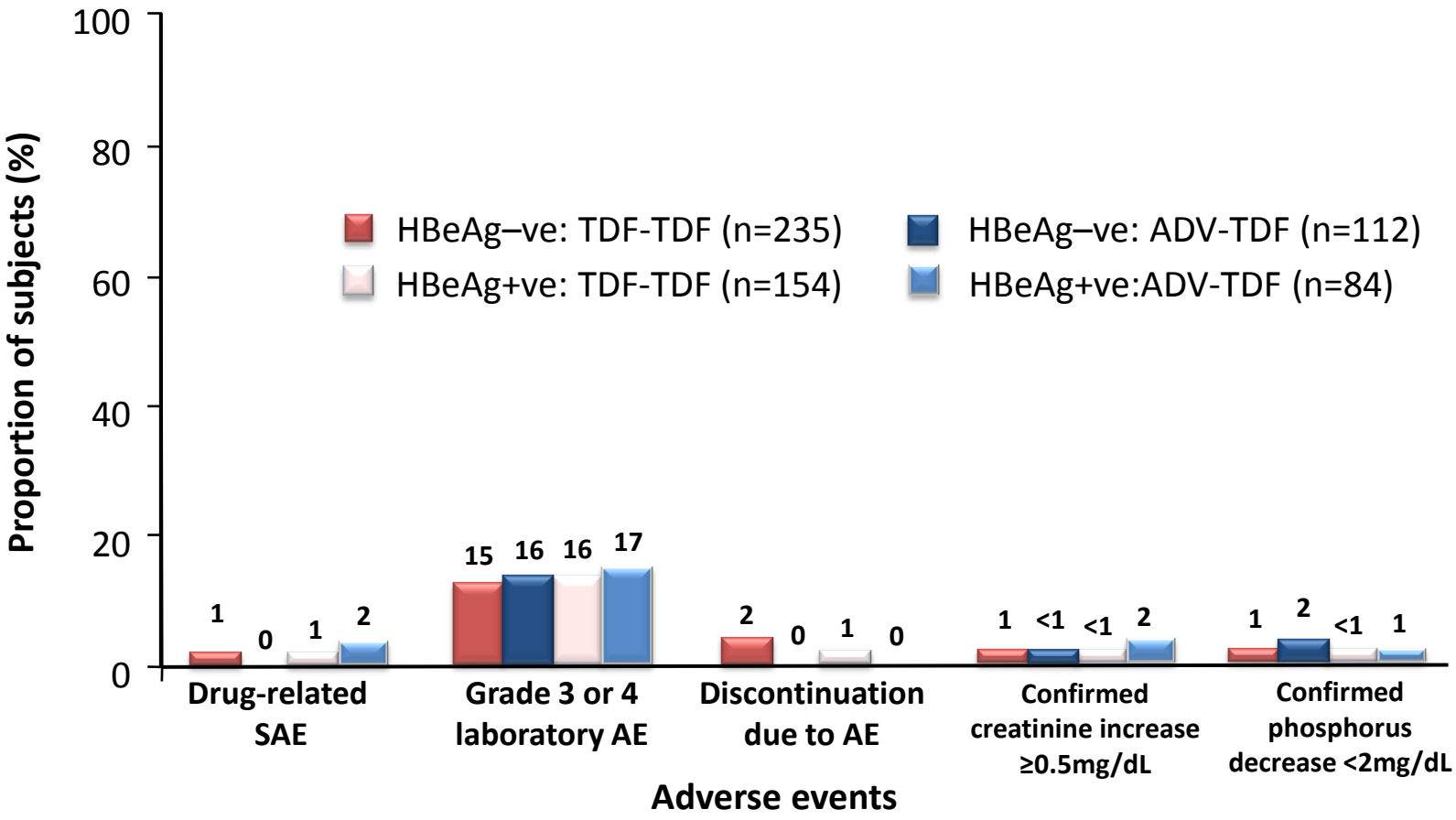
1. Lok ASF, et al. Gastroenterology 2003;125:1714-22; 2. Hadziyannis SJ, et al. Gastroenterology 2006;131:1743-1752; 3. Colonno RJ, et al. Hepatology 2006;44:1656-65;
4. Colonno RJ, et al, Hepatology 2006, 44 (Suppl 1):229; 5. Colonno RJ, et al. J Hepatol. 2007;46(Suppl 1):S294; 6. Tenney DJ et al. Gastroenterology 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.

Change in cccDNA Levels After 48-52 Weeks of Antiviral Therapy



Doo EC, et al. *Clin Liver Dis.* 2010;14:397-408.

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.

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

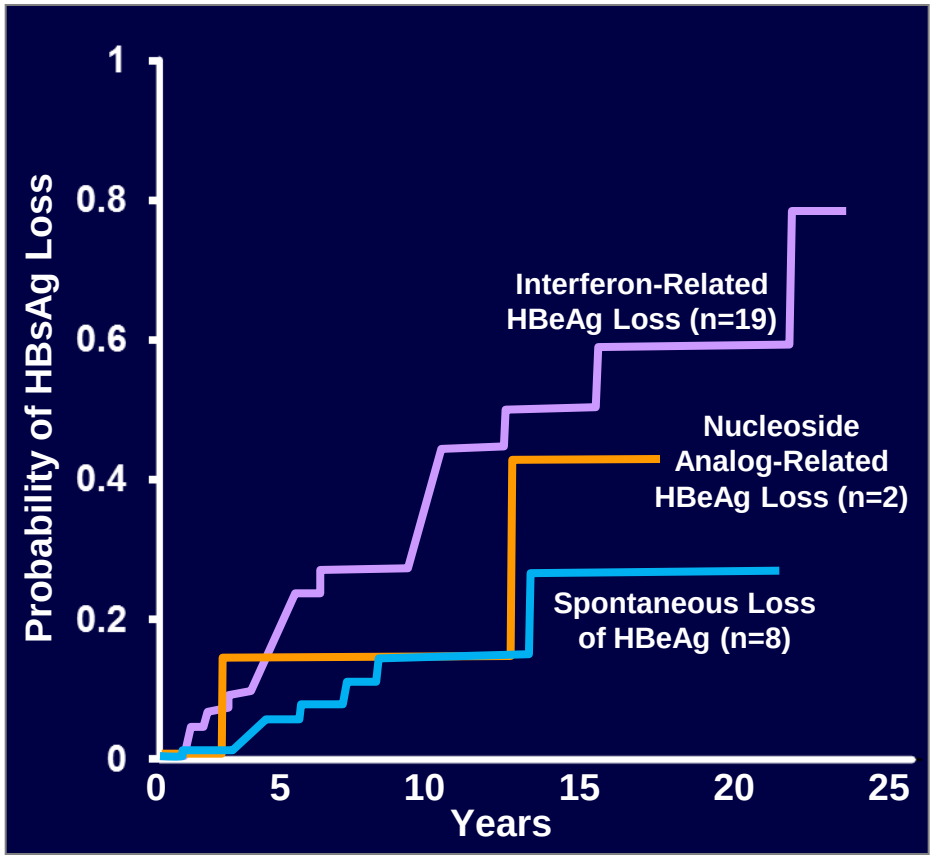
Gish R, et al. J Clin Gastro Hep 2012

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
- Chance of DNA suppression long-term is less than 20%
- HBsAg loss is 10%
  - Same as with Nuc therapy
- HBsAg quant is best stopping (test) rule, but not available in the US

NIDDKD Cohort: HBsAg Loss by Mode of HBeAg Clearance

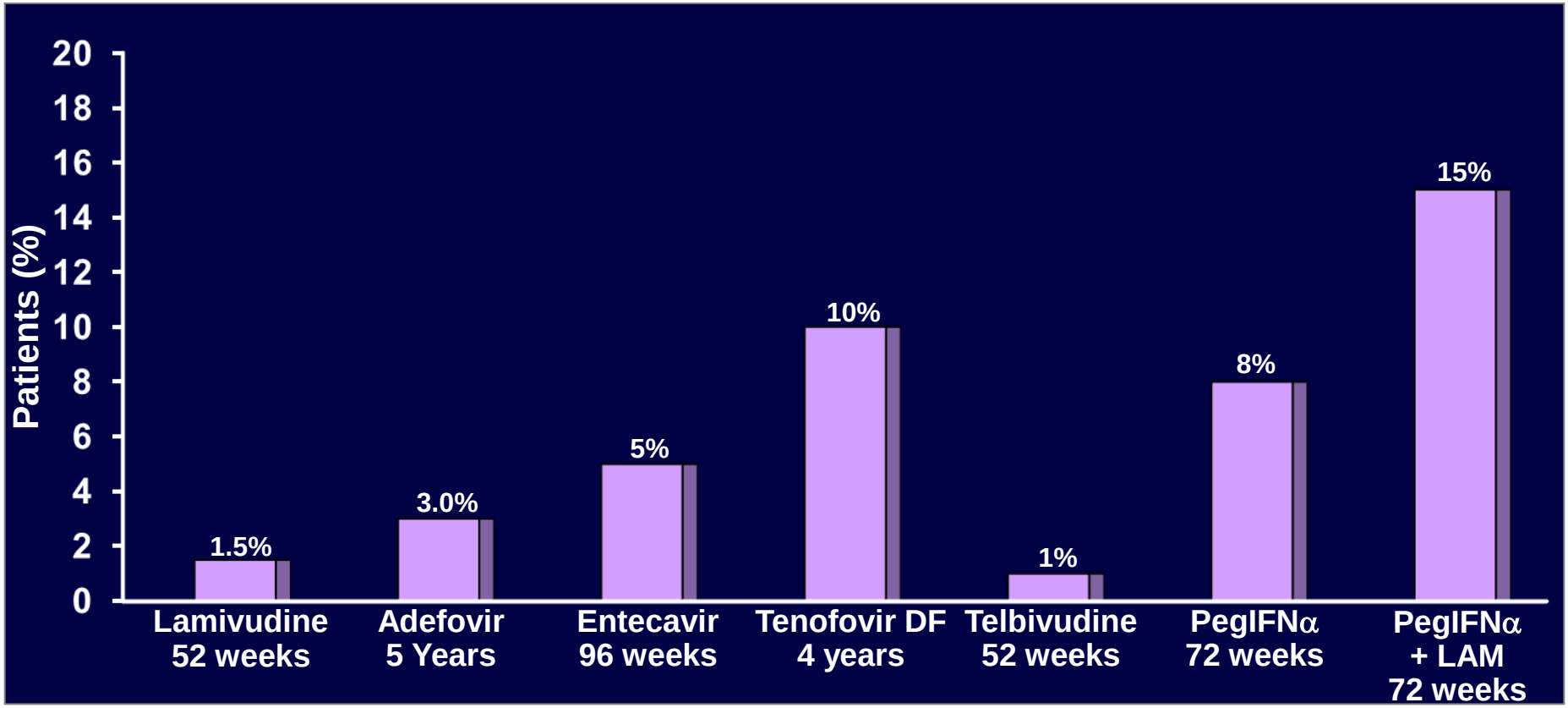
- Treatment-induced HBeAg clearance (n=51)
  - Interferon related: 86%
- Cumulative incidence of HBeAg loss per year (*P*=0.02)
  - Spontaneous: 1.6%
  - Nucleoside analog induced: 4.4%
  - Interferon induced: 6.3%
- Most significant predictors of HBsAg loss
  - Mode of HBeAg loss
  - Race



NIDDKD: National Institute of Diabetes and Digestive and Kidney Diseases.

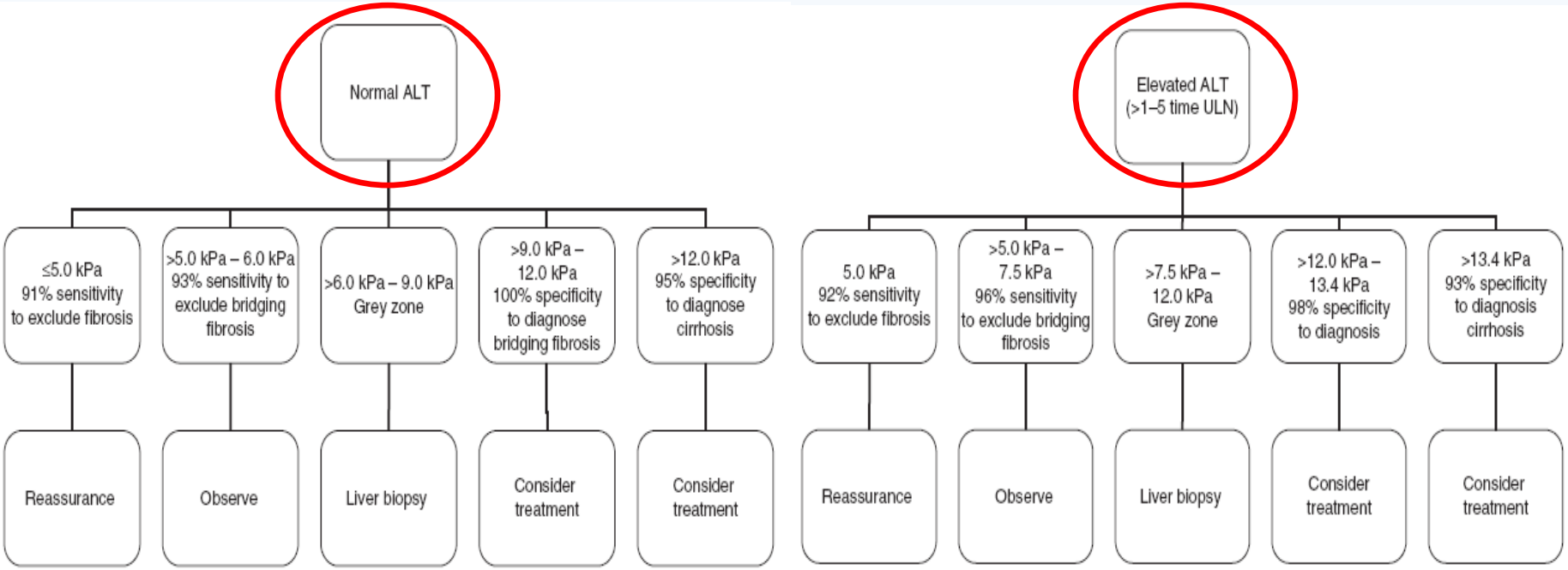
Abdalla A, et al. *Hepatology.* 2013;58(suppl 1):627A. Abstract 883.

HBsAg Loss in HBeAg-Positive and HBeAg-Negative Patients



Lok AS, et al. *Hepatology*. 2009;50:661-662. Available at: http://www.aasld.org.
Heathcote EJ, et al. *Hepatology.* 2010;52(suppl):556A-557A. Abstract 477.
Gish RG, et al. *J Viral Hepatitis.* 2010;17:16-22.

FibroScan: Enhancing Performance to Predict Cirrhosis in HBV Patients using Different Cut-off Values

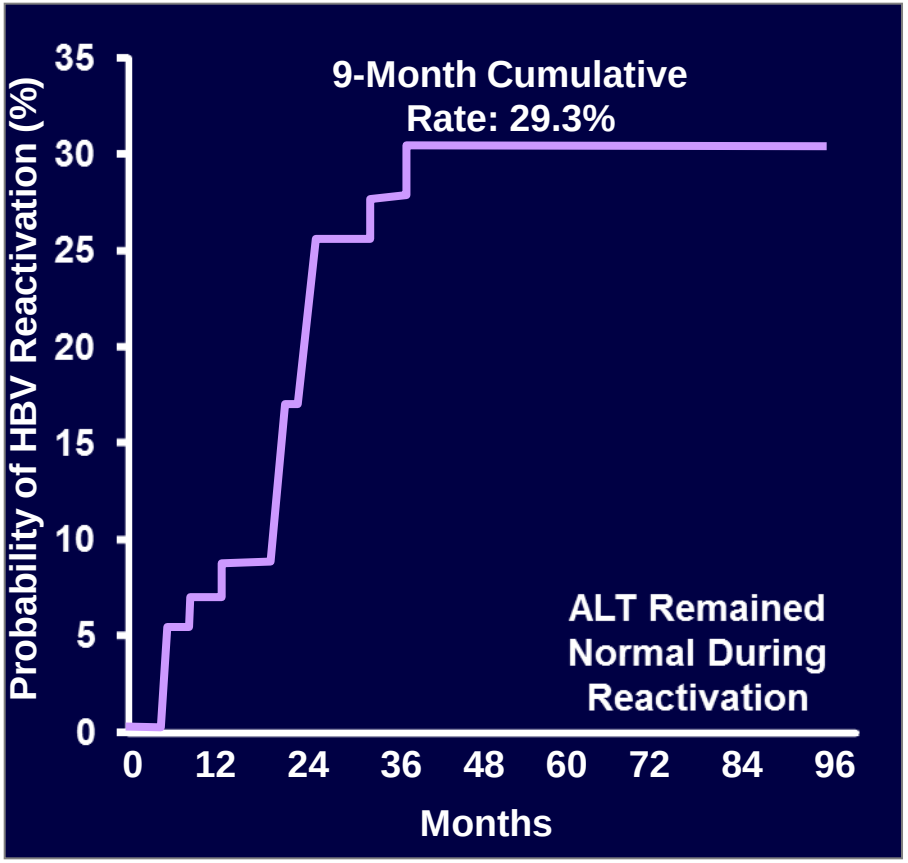


In this way, liver biopsy can be avoided in approximately 62% of patients with normal ALT and 58% of patients with elevated ALT

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

HBV Reactivation Following Rituximab-Containing Chemotherapy

- Single-center cohort with a variety of hematologic diagnoses (n=62) (2011-2013)
  - HBsAg negative, anti-HBc positive
  - HBV DNA <10 IU/mL
  - No concomitant liver disease or prior HBV treatment
  - Reactivation: HBV DNA >10 IU/mL regardless of HBsAg status
  - Follow-up: 36.6 months
- High rate of reactivation
  - Majority occurred within the first 6 months (86.7%)
  - Presence of low anti-HBs levels was not protective against HBV reactivation

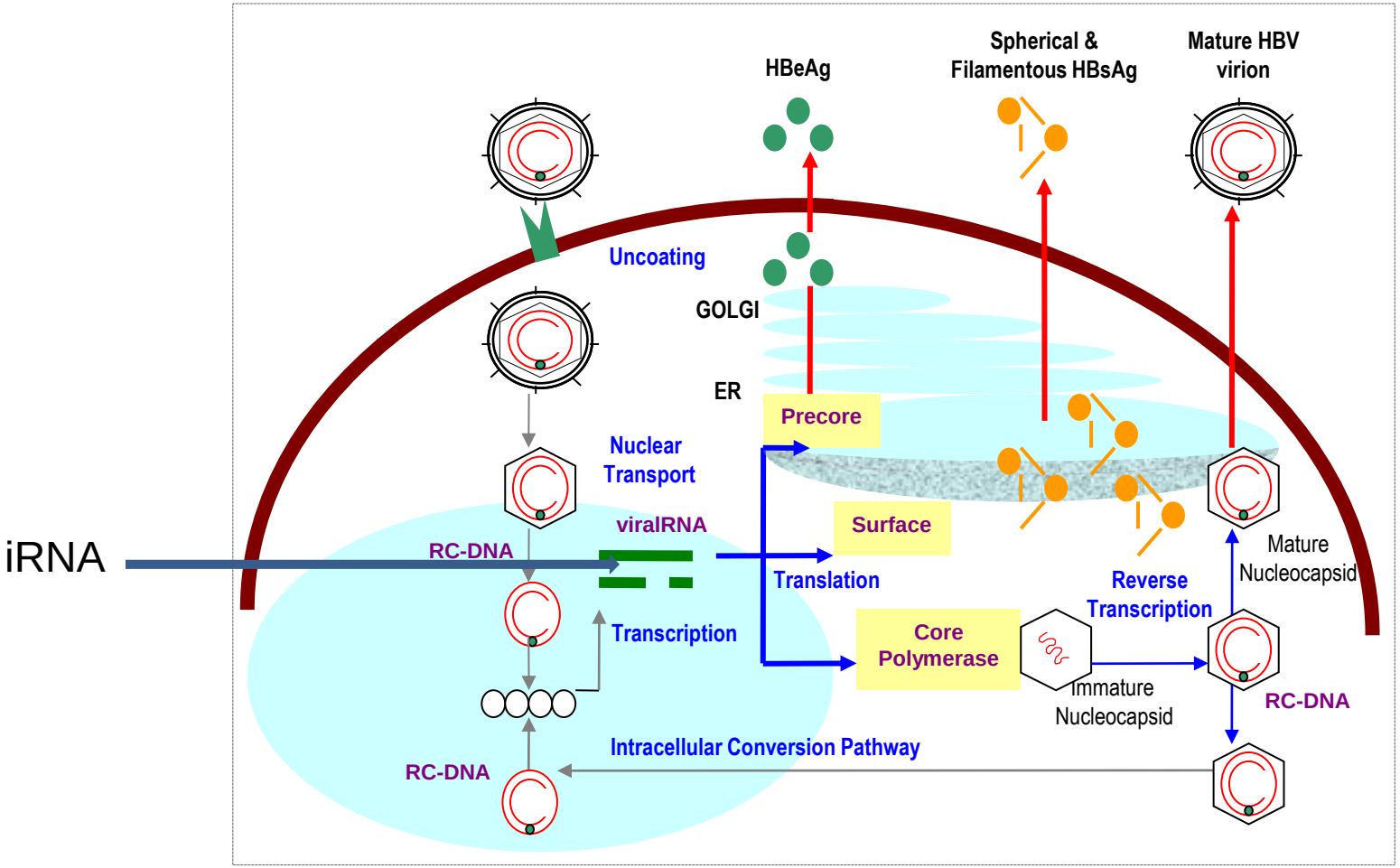


Seto W, et al. *Hepatology.* 2013;58(suppl 1):224A. Abstract 34.

Specific Populations: For the Panel

- 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 Therapies to Attack: HBV Replication: @ cccDNA Pathway



New therapies en-route

- Anti-Sense: DNA like molecules ISIS
- iRNA: Modified RNA Arrowhead
- Uptake inhibitors blocking entry Myclurdex
- Capsid formation inhibitors: block release and cccDNA formation Various
- Block RNAaseH Various
- Block histone modifications Various

VACCINATE !

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

TEST VACCINATE TREAT SURVEILLANCE

Thank you

- Ashley Sandoval
- Drs Paul Pockros and Carrie Frenette
- Our Pharma supporters