HEPATOLOGY SOCIETY
DHAKA, BANGLADESH
4th International Hepatology Conference
DHAKA 2016

Cornerstones of Hepatitis B: Past, Present and Future

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Outline

- Past
  - Natural history studies
    - Development of HBV-related complications
    - Treatment Endpoints
  - Therapeutic options
- Present
  - Effects of long-term treatment
- Future
  - Treatment goals
  - New treatment options

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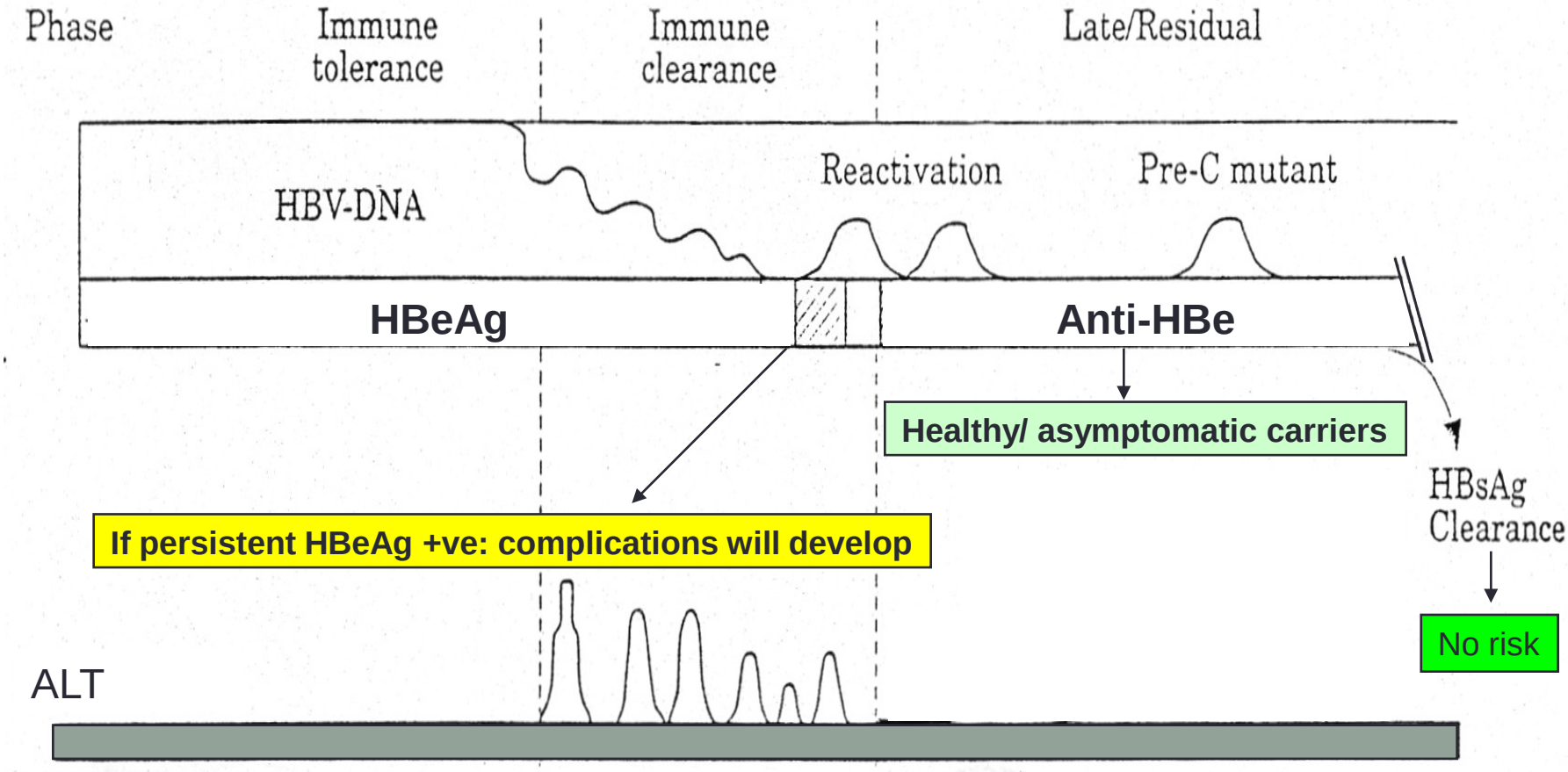
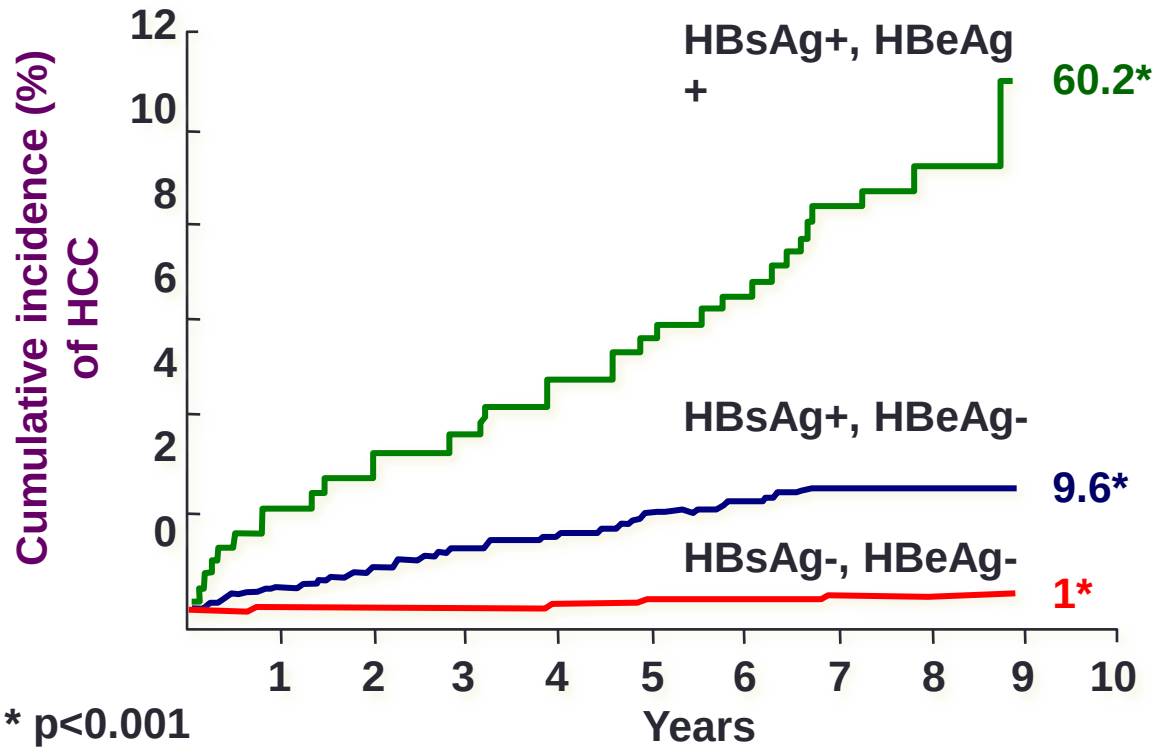
Difference Phases Of CHB: Development Of Complications



HBeAg Seroconversion To Anti-HBe

- 11,893 Taiwan males; FU 92,359 person-years

Relative risk of developing HCC



- HBeAg / anti-HBe status only on entry to study, NOT at time of HCC development.

Yang et al. N Engl J Med 2002; 347

Natural History Of CHB

- A study with 3,233 CHB patients in Hong Kong
  - All were asymptomatic without complications on presentation
  - Median age: 38 yrs
  - HBeAg: anti-HBe ratio 1: 1.5
  - Mean follow up: 46.9 months
    - 307 (10%) had FU > 10 yrs

Yuen MF, et al. Gut 2005; 54:1610

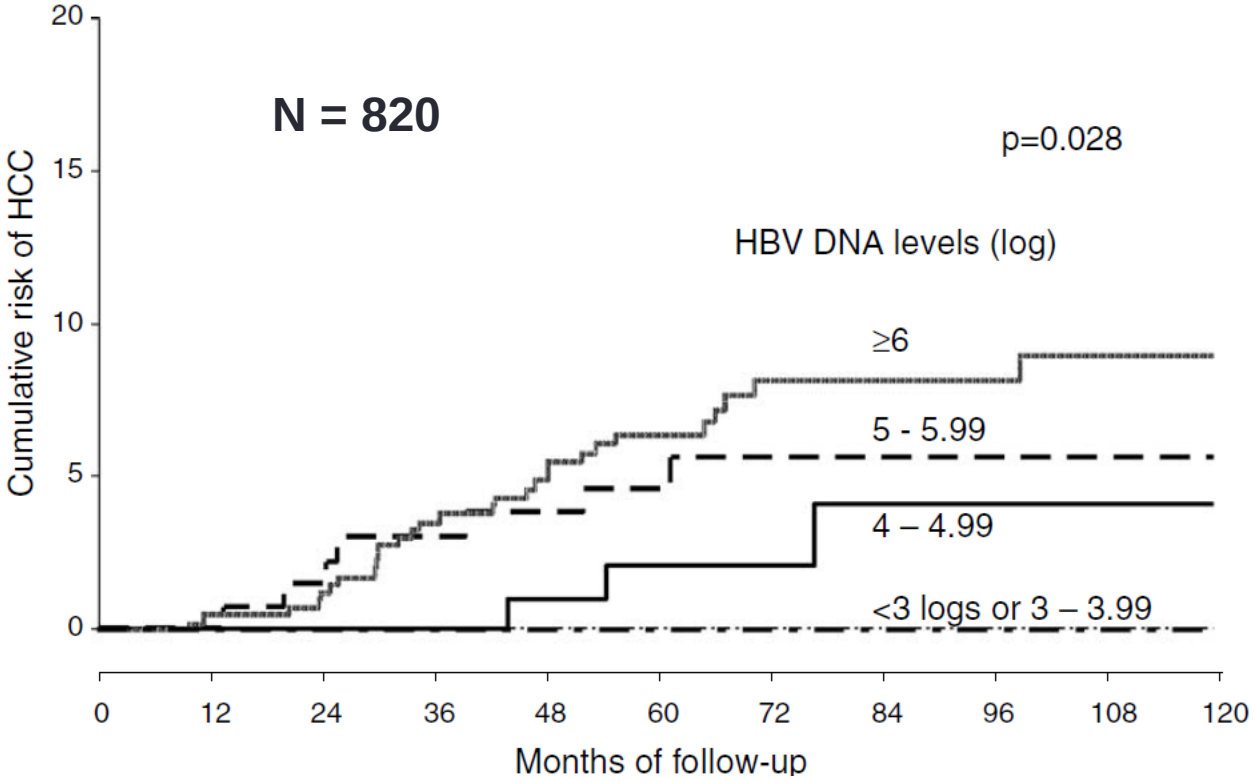
HBeAg Seroconversion To Anti-HBe

- Development of cirrhosis complications and HCC
  - 3,233 Chinese patients
  - Mean follow-up 46.9 months

	Median age in yrs	% anti-HBe
HBeAg seroconversion	35	-
All complications	57.2	73.5%
Ascites	57.7	68.8%
SBP	60.0	76.7%
Varices	54.3	76.3%
Encephalopathy	58.5	65.0%
HCC	59.0	81.1%

Yuen MF, et al. Gut 2005; 54:1610

HBV DNA Level And HCC



Yuen MF et al., J Hepatol 2009;50:80-8

Natural History Of Chronic Hepatitis B: Update

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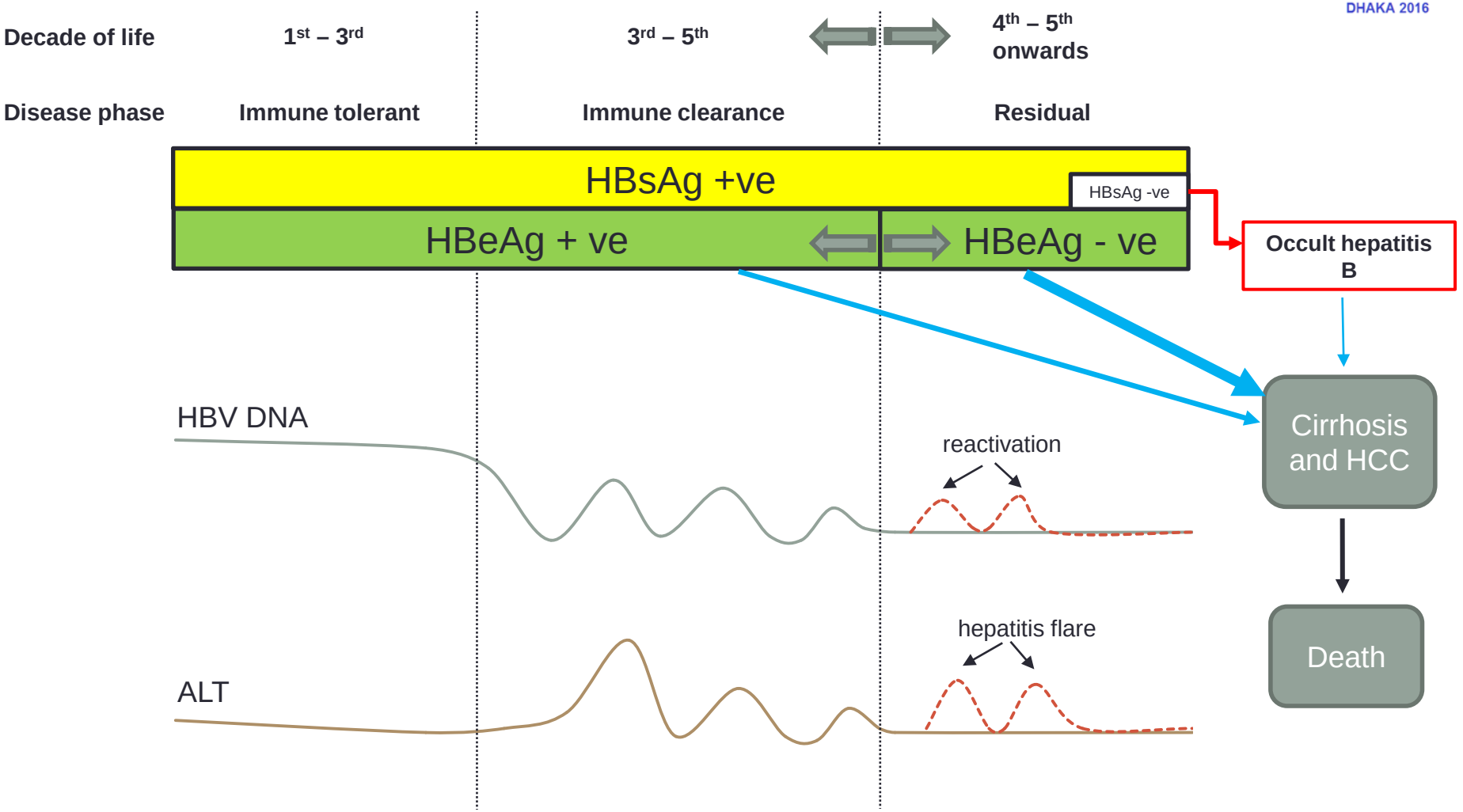

Modified from Yuen MF, occult hepatitis B infection, Hepatitis B Virus and Liver Disease

Endpoints In Chronic Hepatitis B Treatment

Virologic response

1) ↓ HBV DNA to undetectable

2) ↓ cccDNA

Biochemical and liver synthetic test improvement

ALT, bilirubin, albumin

Aims:

Prevent progression to cirrhosis, HCC and death

Histologic improvement

Serologic responses

HBeAg loss/ seroconversion
HBsAg loss/seroconversion

Adapted from EASL guidelines. J Hepatol 2012;57:167–185.

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Long Term Effects Of Interferon Treatment

Prevention Of HCC By IFN In CHB

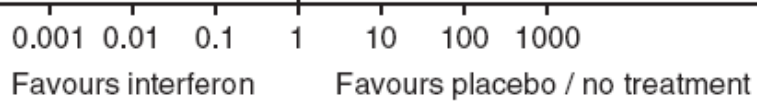
- 208 IFN-treated vs. 203 controls
- Median follow up 107 vs. 108 months
  - HCC in 7 IFN-treated patients and none in controls (p=NS)

Yuen MF, et al. Hepatology 2001;34:139–45.

Prevention Of HCC By IFN In CHB

Study, Year (Reference)	Interferon *n/N*	Placebo / no treatment *n/N*	RR (fixed) 95% CI	Years of follow-up
Fattovich, 1997 (17)	4/40	6/50	0.83 [0.25, 2.75]	7.2
Benvegnu, 1998 (18)	1/13	7/24	0.26 [0.04, 1.92]	6.0
Brunetto, 1998 (19)	8/49	18/97	0.88 [0.41, 1.88]	5.8
Ikeda, 1998 (20)	10/94	51/219	0.46 [0.24, 0.86]	7.0
Krogsgaard, 1998 (21)	2/210	1/98	0.93 [0.09, 10.17]	4.7
DiMarco, 1999 (22)	2/109	6/193	0.59 [0.12, 2.87]	7.8
Mazzella, 1999 (23)	1/33	2/31	0.47 [0.04, 4.92]	7.2
Papatheodoridis, 2001 (24)	17/209	15/195	1.06 [0.54, 2.06]	6.0
Tangkijvanich, 2001 (25)	2/67	9/72	0.24 [0.05, 1.07]	5.0
Yuen, 2001 (26)	6/208	0/203	12.69 [0.72, 223.79]	8.9
Truong, 2005 (27)	1/27	0/35	3.86 [0.16, 91.12]	6.5
Lin, 2007 (28)	5/233	16/233	0.31 [0.12, 0.84]	6.5
Total (95% CI)	1292	1450	0.66 [0.48, 0.89]	

Total events: 59 (Interferon), 131 (Placebo/no treatment)
Test for heterogeneity: χ^2= 14.16, df= 11 (P = 0.22), I^2= 22.3%
Test for overall effect: Z = 2.75 (P = 0.006)



Sung JJ, et al. Aliment Pharmacol Ther 2008;28:1067–77.

Prevention Of HCC By IFN In CHB

- Prevention of HBV-related HCC
  - Interferon vs. no treatment
    - 10 studies: only 3 showed some improvement; 7 showed NO difference
    - Conclusion: inconsistent results; beneficial effect of IFN possibly in responders (ie, ~30%) with pre-existing cirrhosis

Lai CL, Yuen MF. Hepatology 2013;57:399–408.

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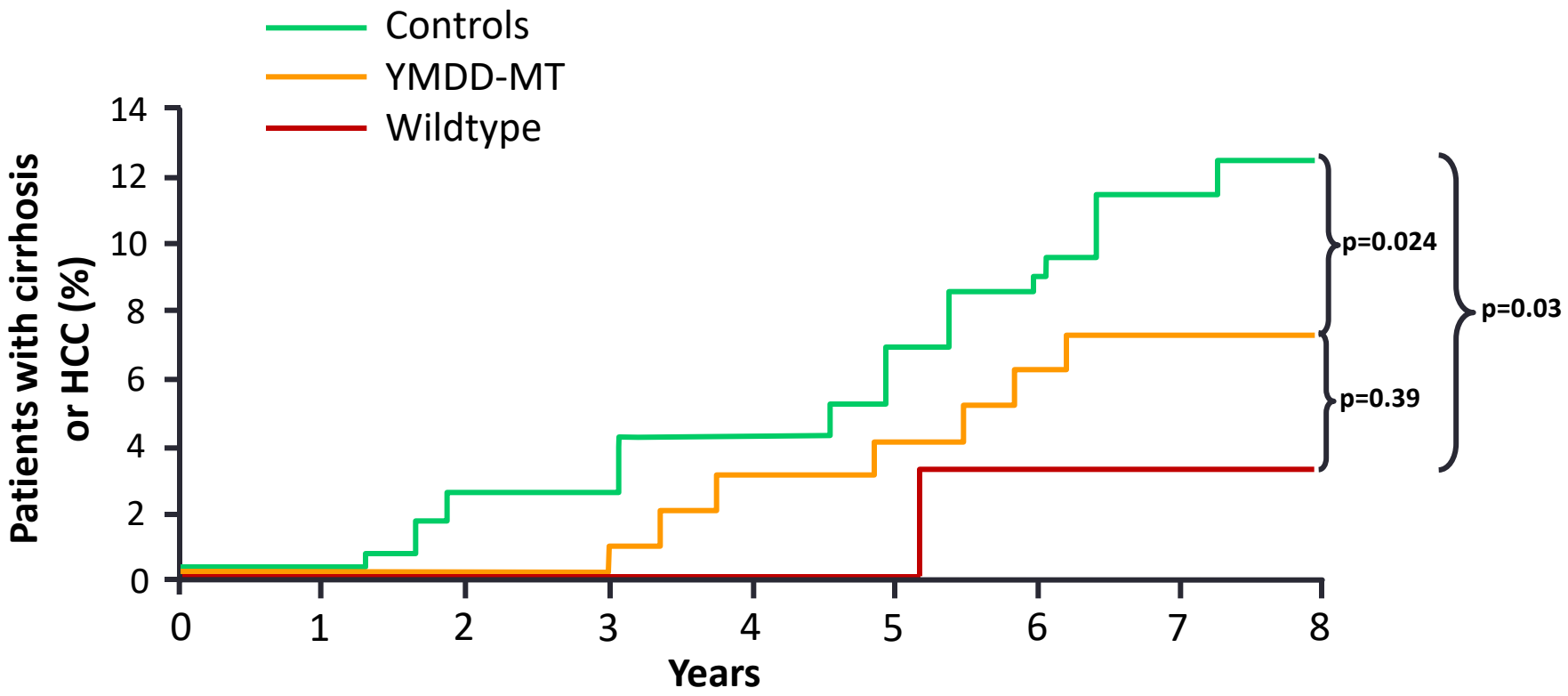
Long Term Effects Of First Generation Of Nucleoside Analog Treatment

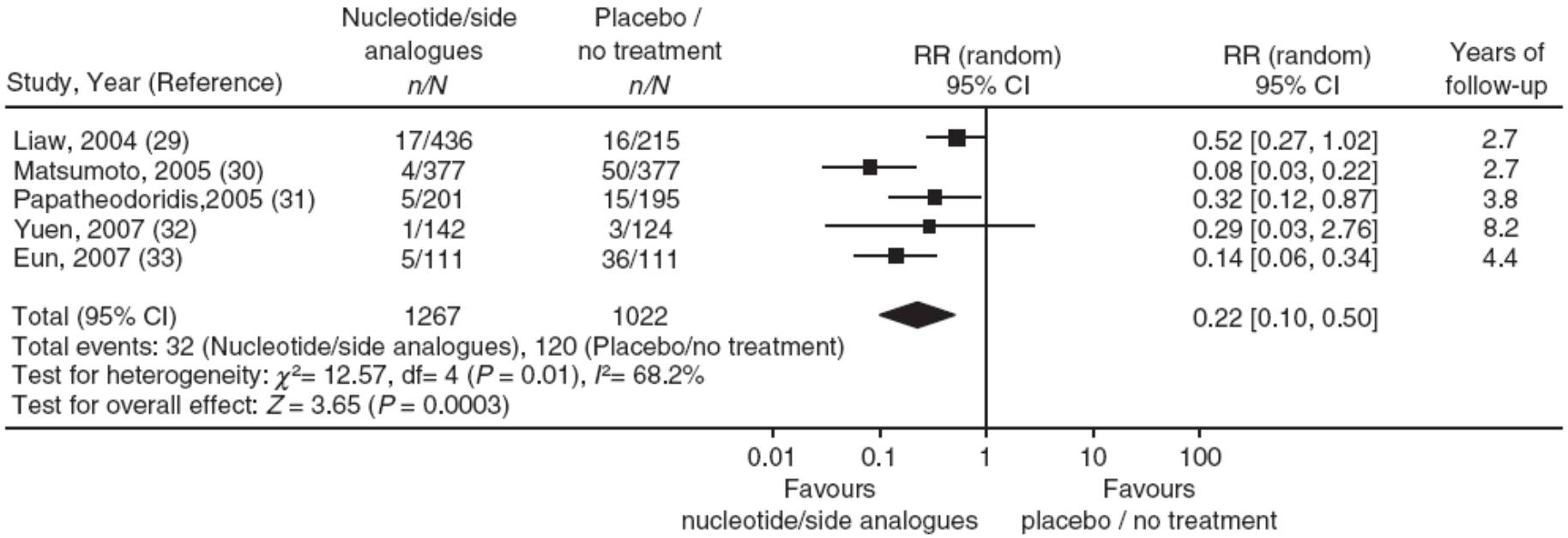
Prevention Of HCC By Lamivudine In CHB



No. of patients									
Lamivudine	142	142	142	140	136	133	125	112	58
Control	124	124	121	120	117	115	108	95	73

Yuen MF, et al. Antivir Ther 2007;12:1295–303.

Prevention Of HCC By Lamivudine In CHB



Sung JJ, et al. Aliment Pharmacol Ther 2008;28:1067–77.

Nucleos(t)ide Analogs

- Prevention of HBV-related HCC
  - Lamivudine/adefovir vs. no treatment:
    - 5 studies: ALL showed beneficial effects
    - Conclusion: consistent reduction of HCC in patients with and without cirrhosis (effect blunted but still present with resistance development)

Lai CL, Yuen MF. Hepatology 2013;57:399–408.

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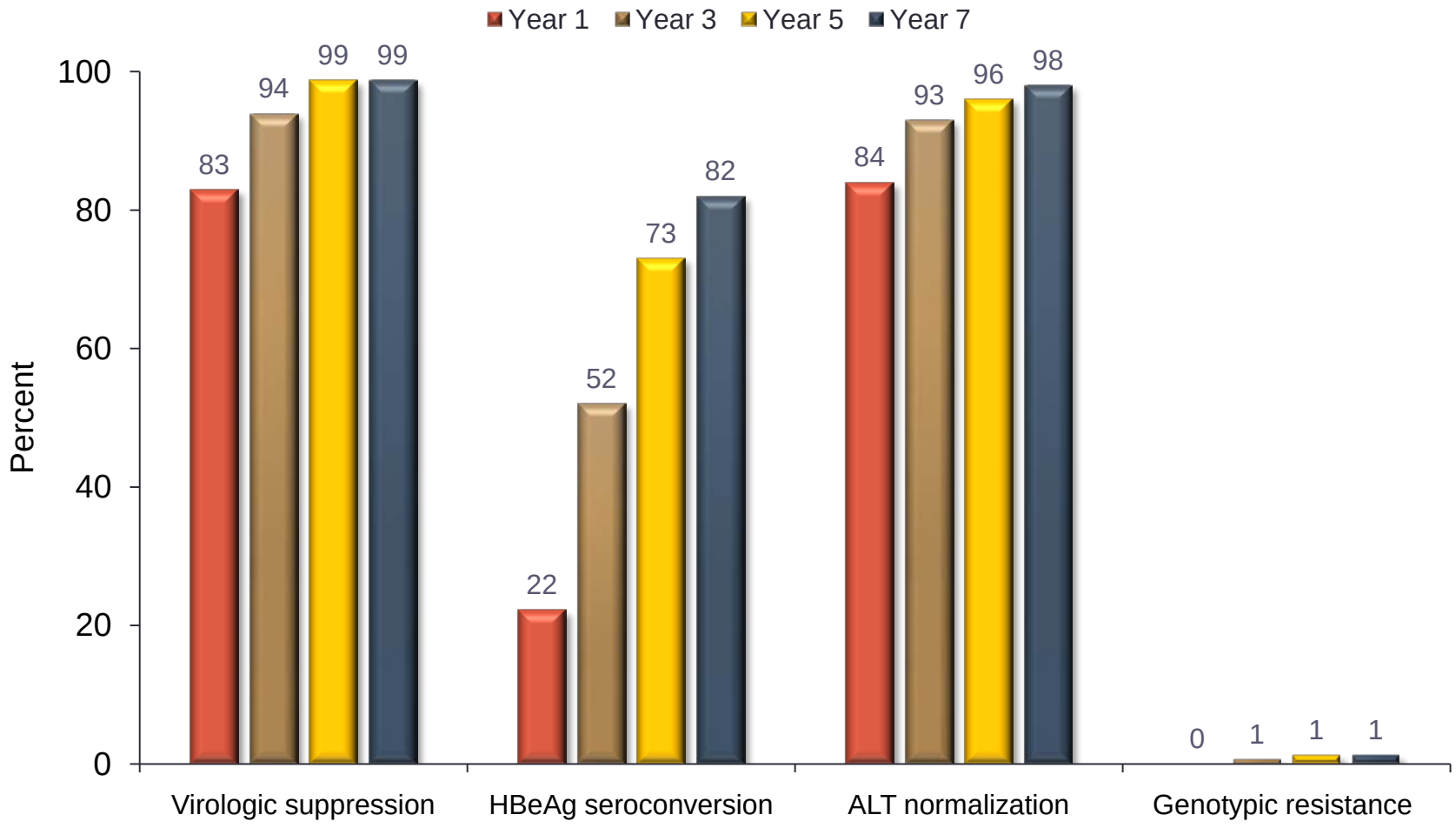
Long Term Effects Of More Potent Nucleoside Analogs

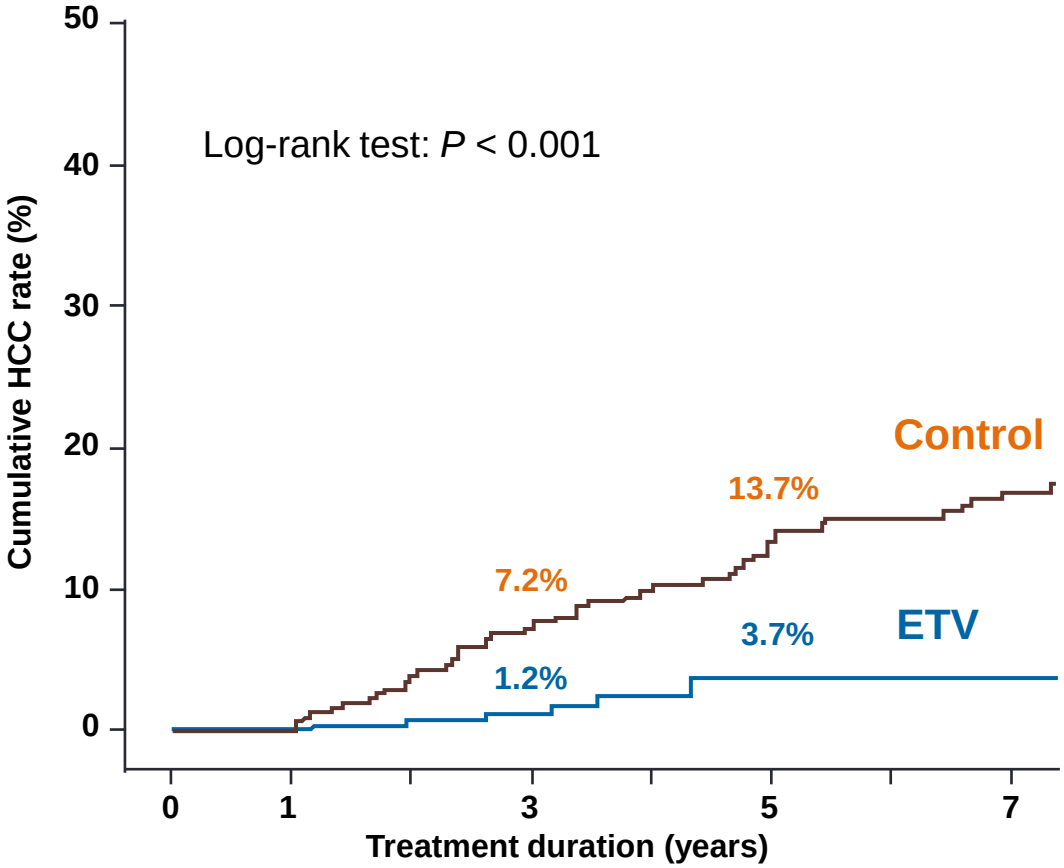
Rates Of Virologic Suppression, HBeag Seroconversion, ALT Normalization And Genotypic Resistance – 7-year Entecavir Data



ALT=alanine aminotransferase; HBeAg=hepatitis B envelop antigen.

Lam FY…Yuen MF. manuscript submitted.

ETV Reduced HCC Incidence



No. at risk

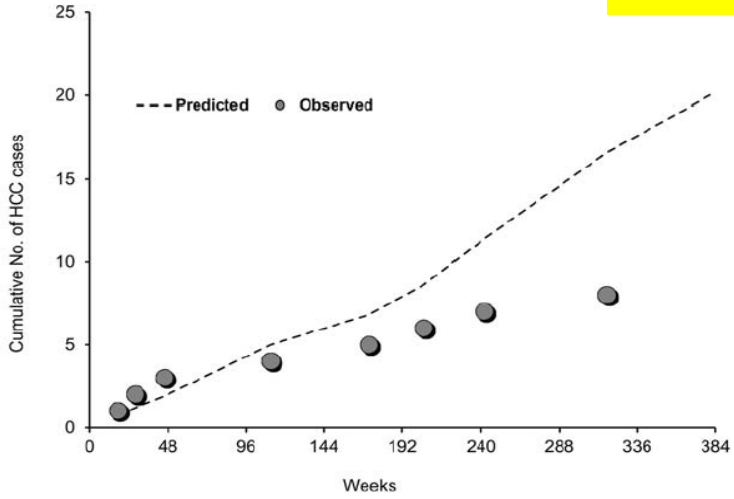
ETV	316	316	264	185	101	44	2	2
Control	316	316	277	246	223	200	187	170

- ETV therapy reduced the 5-year HCC risk by > 60% compared with control group
- Multivariate Cox regression analysis:*
  HR 0.37 (95% CI 0.15–0.91);
  P = 0.030

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

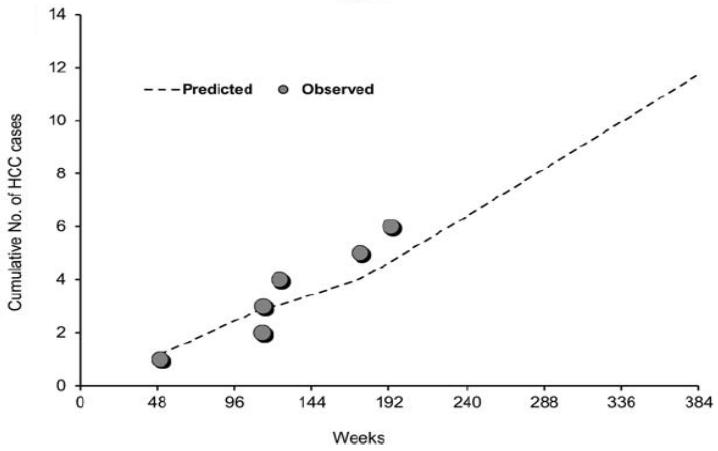
Risk Of HCC Is Predicted To Be Decreased With Long-term TDF

Patients without cirrhosis



Time of Incident	Cumulative HCC Cases			
Week (Year)	Predicted	Observed	SIR	95% CI
17.3 (0.33)	0.74	1	1.36	0.191–9.622
28.1 (0.54)	1.19	2	1.68	0.421–6.727
46.1 (0.88)	1.92	3	1.56	0.503–4.835
111.7 (2.14)	5.03	4	0.80	0.299–2.120
172.3 (3.30)	6.79	5	0.74	0.307–1.769
206.0 (3.95)	8.63	6	0.70	0.312–1.548
242.4 (4.65)	11.45	7	0.61	0.292–1.283
318.1 (6.10)	16.62	8	0.48	0.241–0.963
End of week 384[b]	20.11	8	0.40[c]	0.199–0.795

Patients with cirrhosis



Time of Incident	Cumulative HCC Cases			
Week (Year)	Predicted	Observed	SIR	95% CI
50.0 (0.96)	1.17	1	0.85	0.120–6.060
113.9 (2.18)	2.91	2	0.69	0.172–2.745
114.1 (2.19)	2.92	3	1.03	0.332–3.189
124.6 (2.39)	3.04	4	1.32	0.494–3.508
174.6 (3.35)	4.02	5	1.24	0.518–2.988
194.1 (3.72)	4.67	6	1.28	0.577–2.859
End of week 384[b]	11.67	6	0.51	0.231–1.144

Kim WR et al., Cancer 2015;121:3631-8.

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Treatment Goals

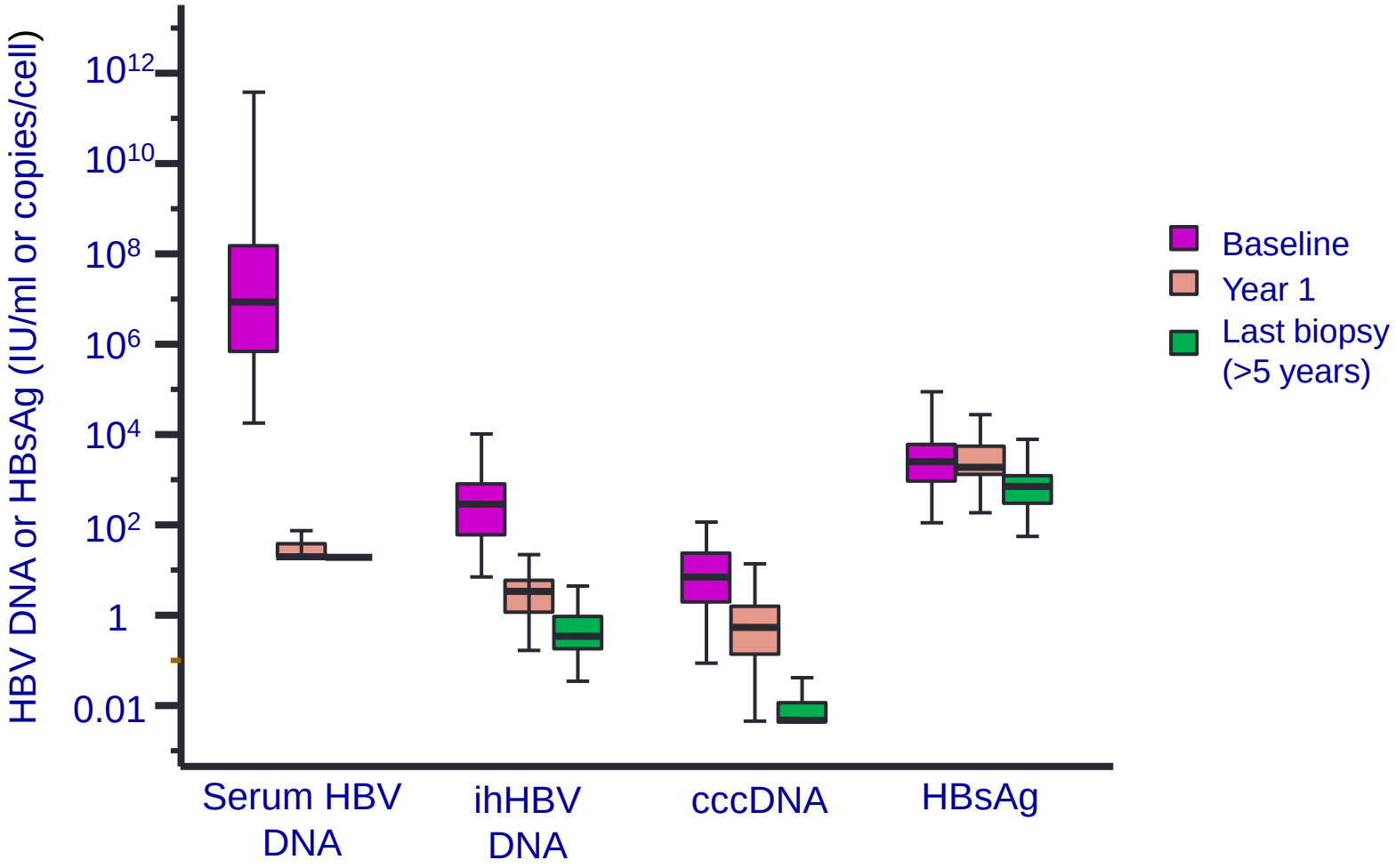
1) Entering disease residual phase ⟶ HBeAg seroconversion

2) Total elimination of HBV ⟶ no covalently closed circular (ccc) DNA

3) Functional cure ⟶ loss of HBsAg

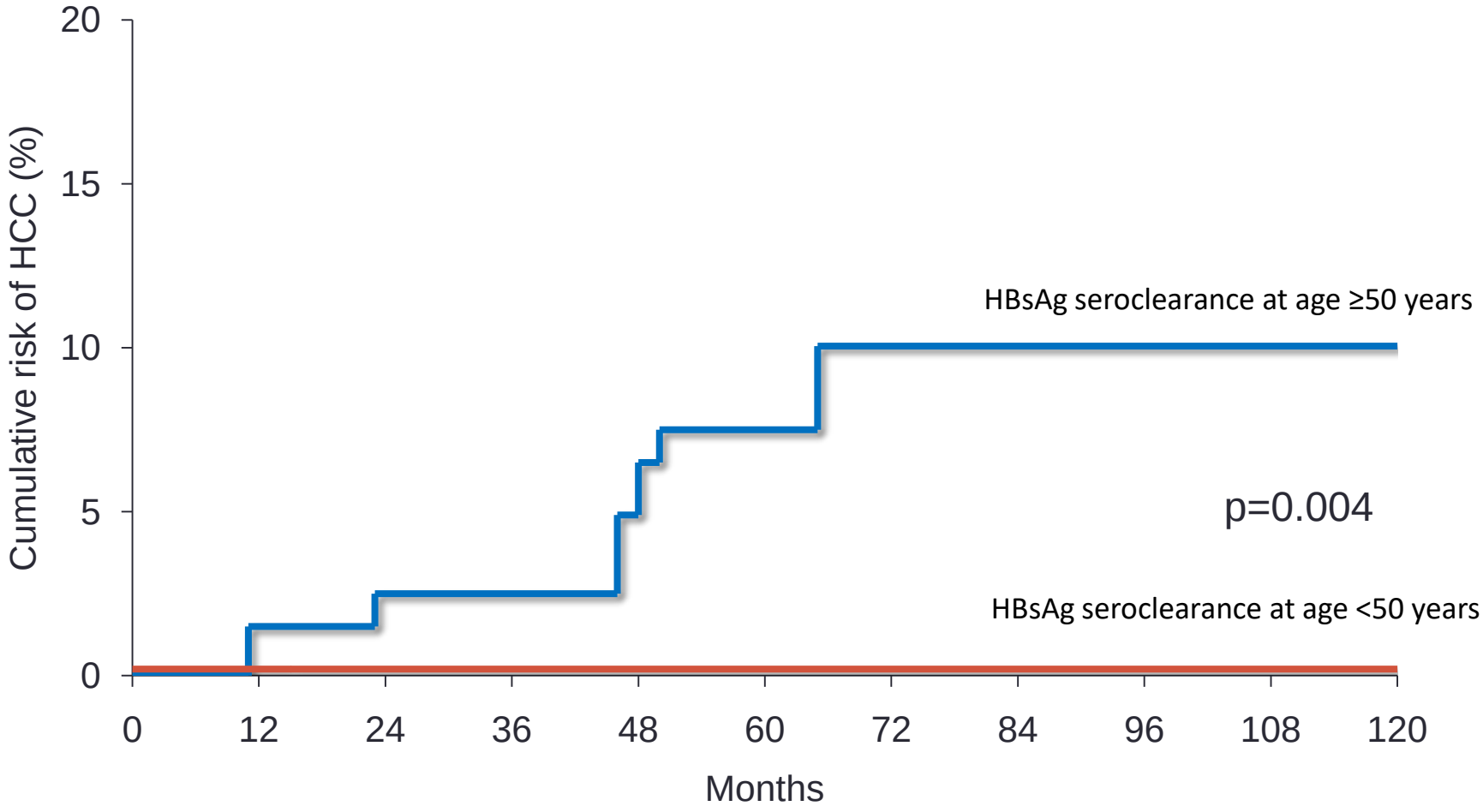
cccDNA reduction/ elimination

cccdna Reduction On Long Term Nucleoside Treatment



Lai CL…Yuen MF. J Hepatol 2016 (in press).

Hbsag Seroclearance: Development Of Complications



Yuen MF. et al. Gastroenterology 2008;135:1192-1199.

HBsag Seroclearance As Endpoint

- Treatment guidelines from APASL, EASL and AASLD all agree that this is the optimal endpoint

The new treatment paradigm is to continue CHB treatment until HBsAg seroclearance is achieved for both HBeAg-positive and HBeAg-negative CHB patients.

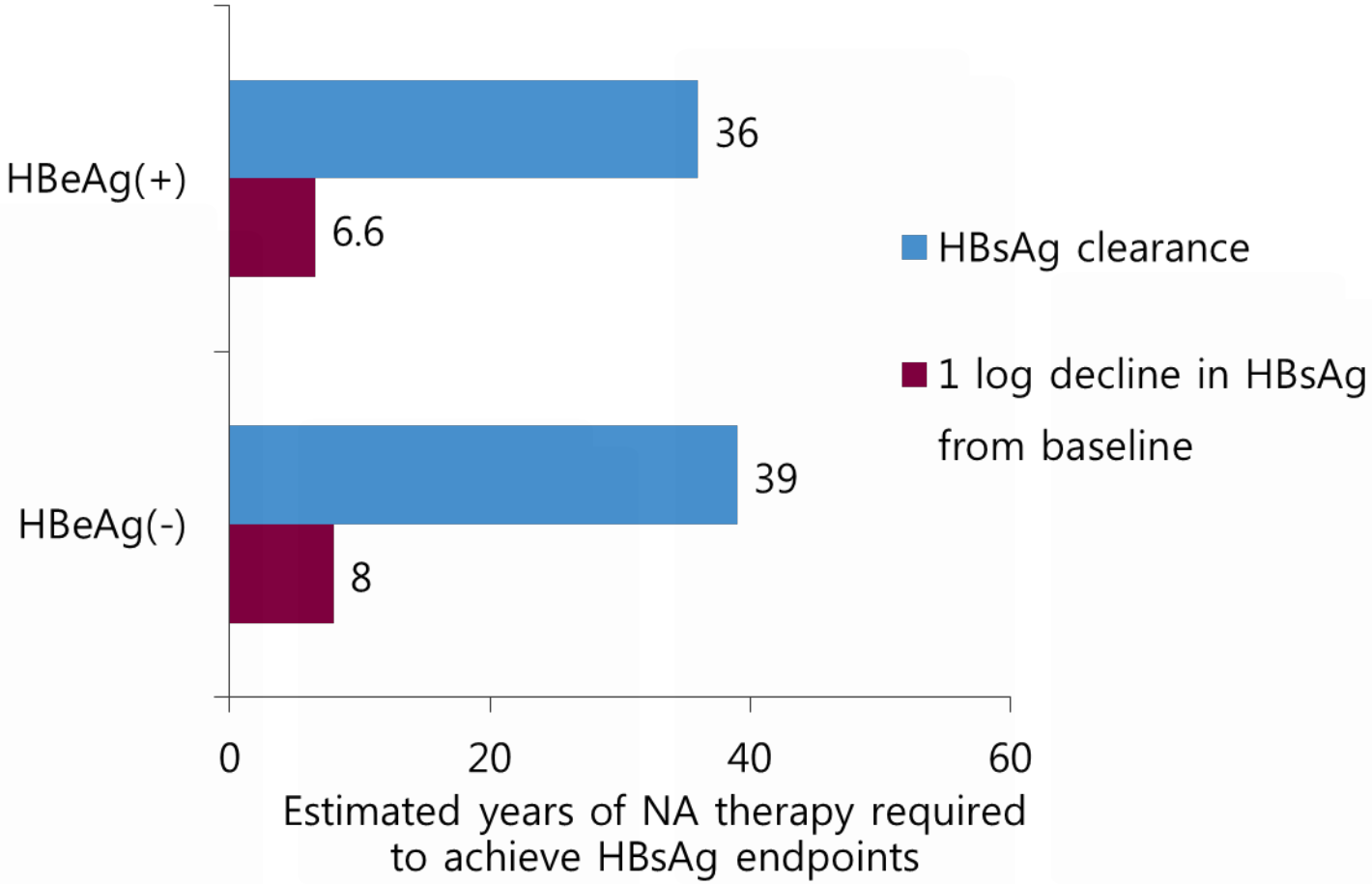
Yuen MF, et al. J Clin Gastroenterol 2016;50:286–294.

HBsAg Loss With Current Therapies

Drug	At 1 Year	At 2 Years	At 3-10Years
Lamivudine	0%	2.8%	10% (10 years)
Entecavir	0%	5.1% *	
Telbivudine	-	-	6% (3 years)
Tenofovir	3%	6%	12% (7 years)
Peginterferon	3-7%	-	8% (3 years)
Teno + PegIFN	9.1%	-	

* Continuous treatment stopped at year 2

Decades Of NA Treatment Are Required Before Patients Achieve HBsAg Loss…



Zoutendijk R, et al. J Infect Dis 2012;206:974–80.

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Investigational Drugs Enhancing HBsAg Seroclearance

HBV Life Cycle And Therapeutics Currently Undergoing Clinical Trials In Humans

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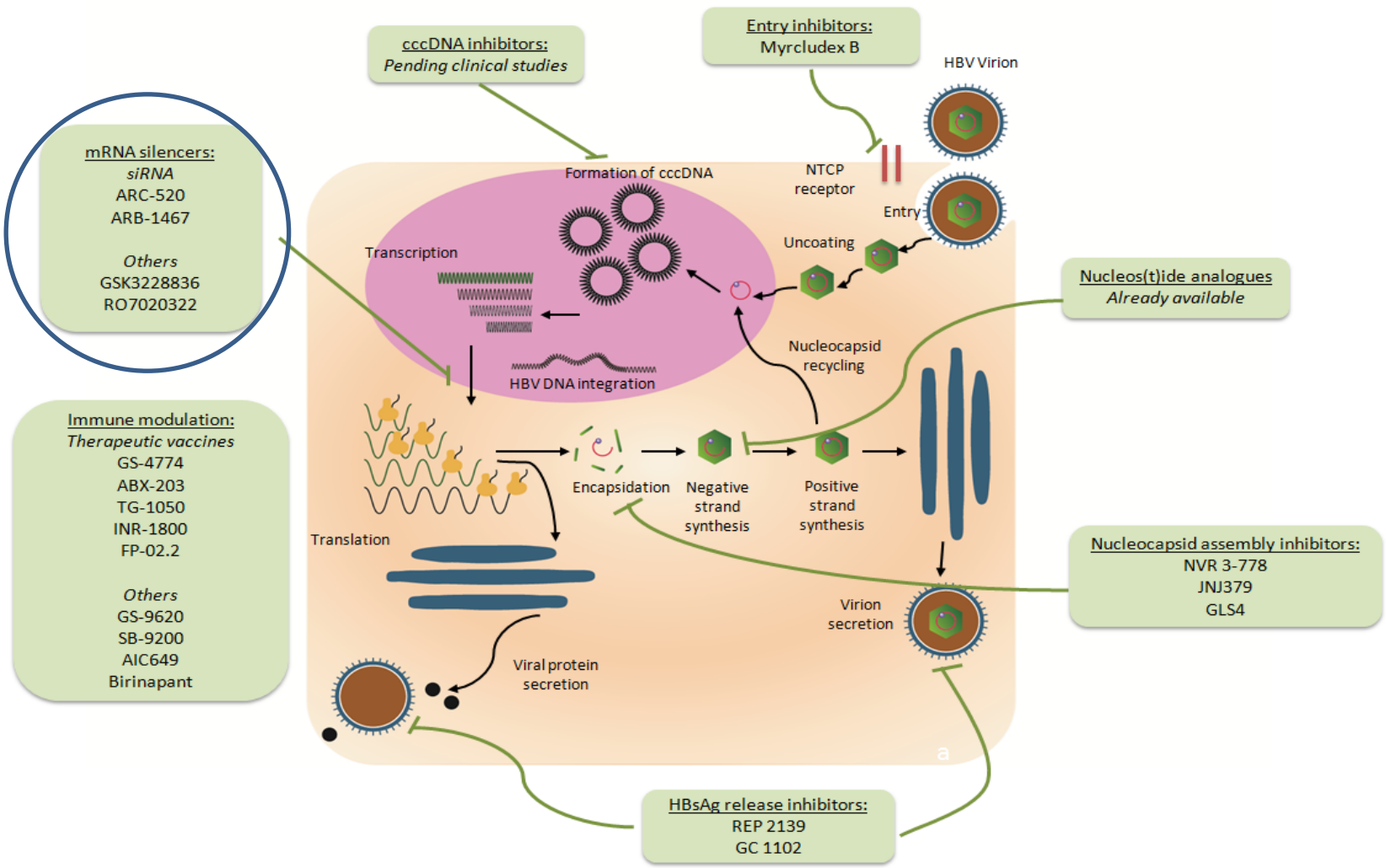
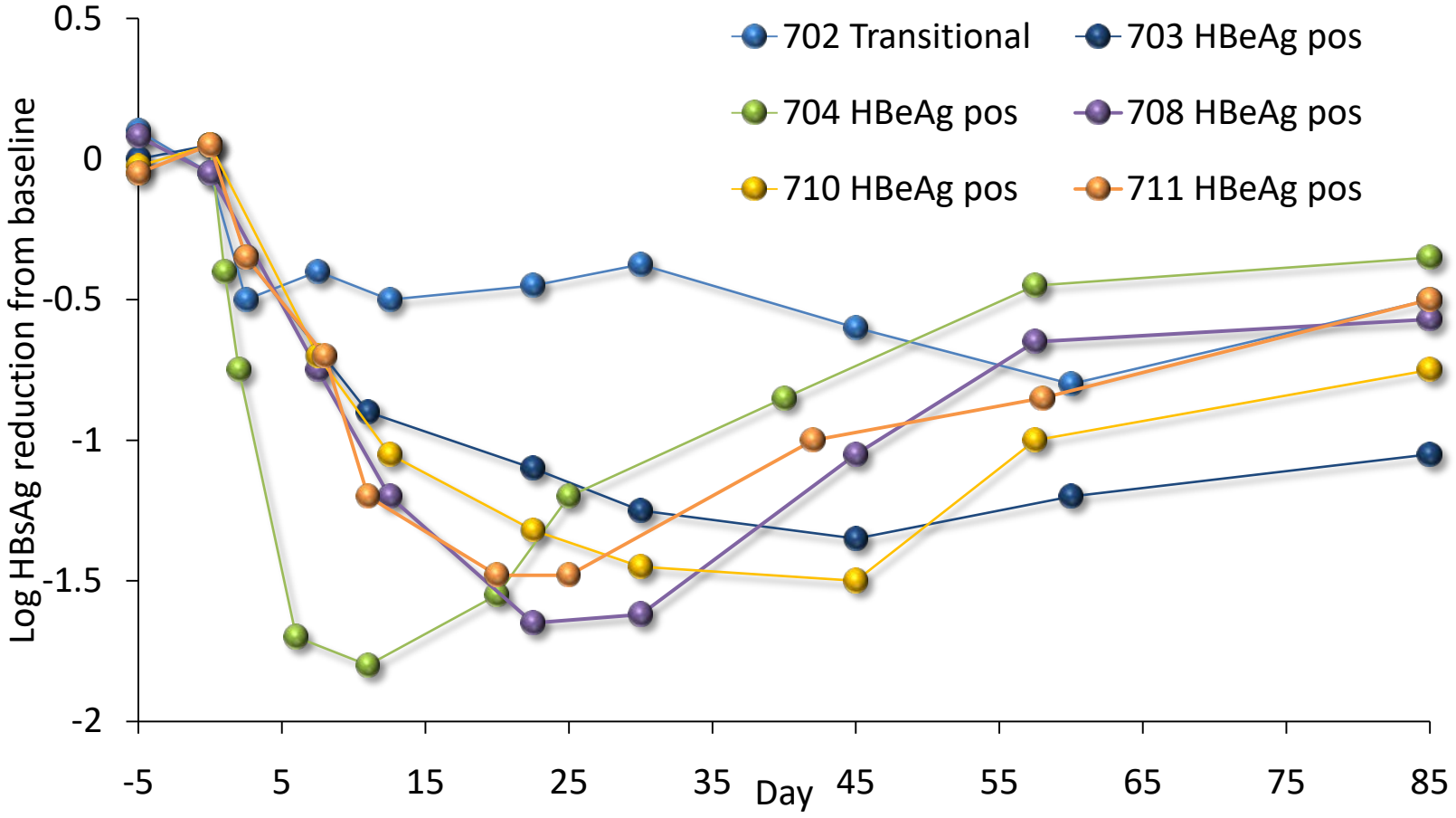


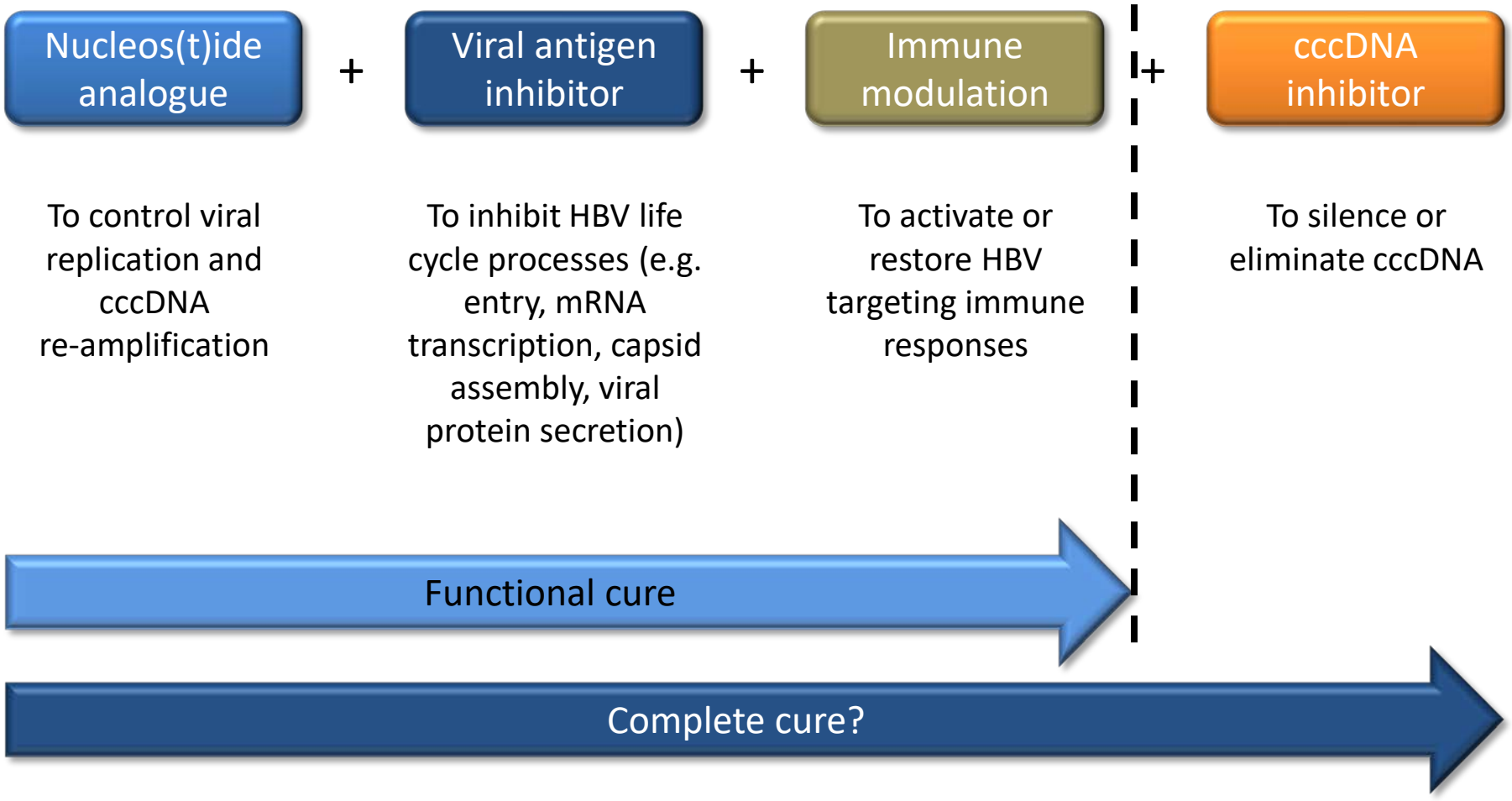
Seto WK & Yuen MF. Clinical Liver Disease 2016 (in press).

siRNA (ARC-502)-Reduction in HBsAg in Treatment Naive CHB Patients: A Single Dose of 4 mg/kg



Adapted from: Yuen MF, et al. EASL 2016. Poster 193.

Final Goal: Possible Future Curative Regimen For CHB



Seto WK & Yuen MF. Clinical Liver Disease 2016 (in press).

Conclusions

- Past:
  - Natural history of chronic hepatitis B was better defined
  - Nucleos(t)ide analog (NA) treatment was a great milestone of drug development for chronic hepatitis B
- Present:
  - Long-term NA treatment is very effective in reducing the risk of development of complications from the disease
- Future:
  - Drug development programs to enhance HBsAg seroclearance are actively underway

Thank you !!