The impact of HBV therapy on public health

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Outline: Impact HBV treatment

- Delineating the problem: global burden hepatitis B
- Treatment prospects and gaps
- Improving outcomes in the absence of cure
- Preventing hepatocellular carcinoma

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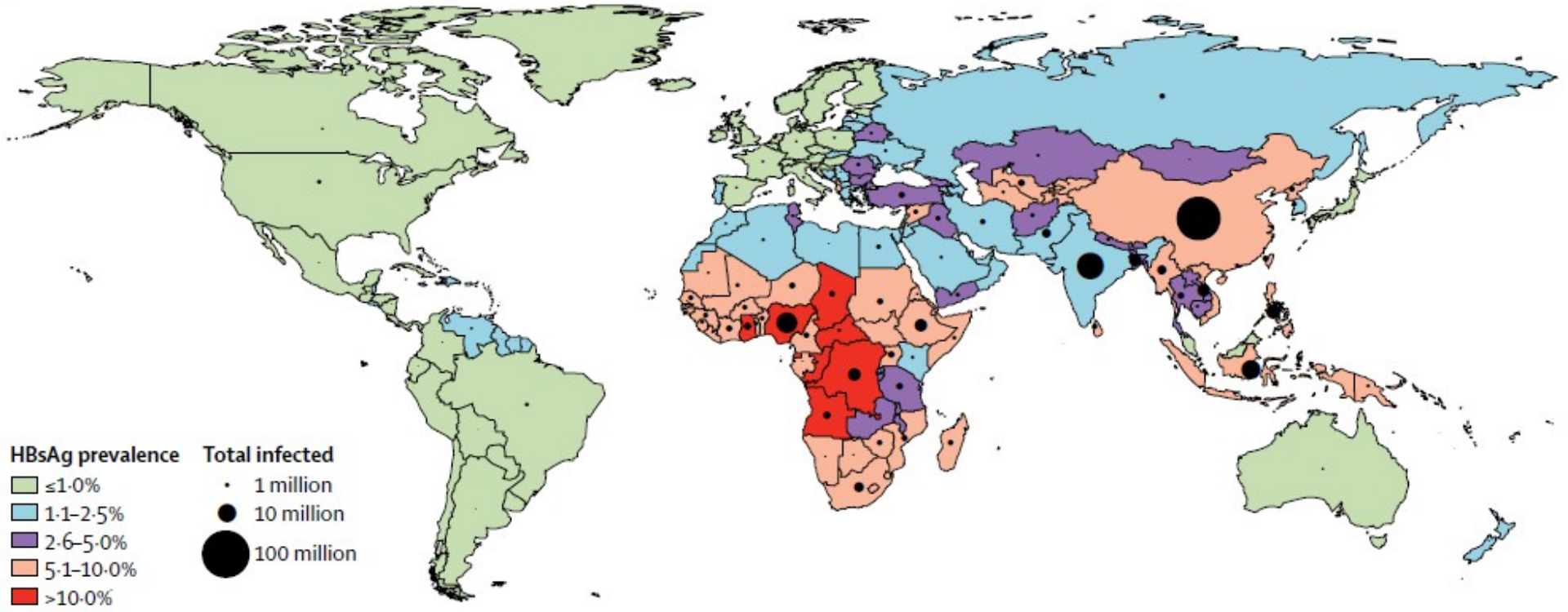
Introduction: Burden of hepatitis B

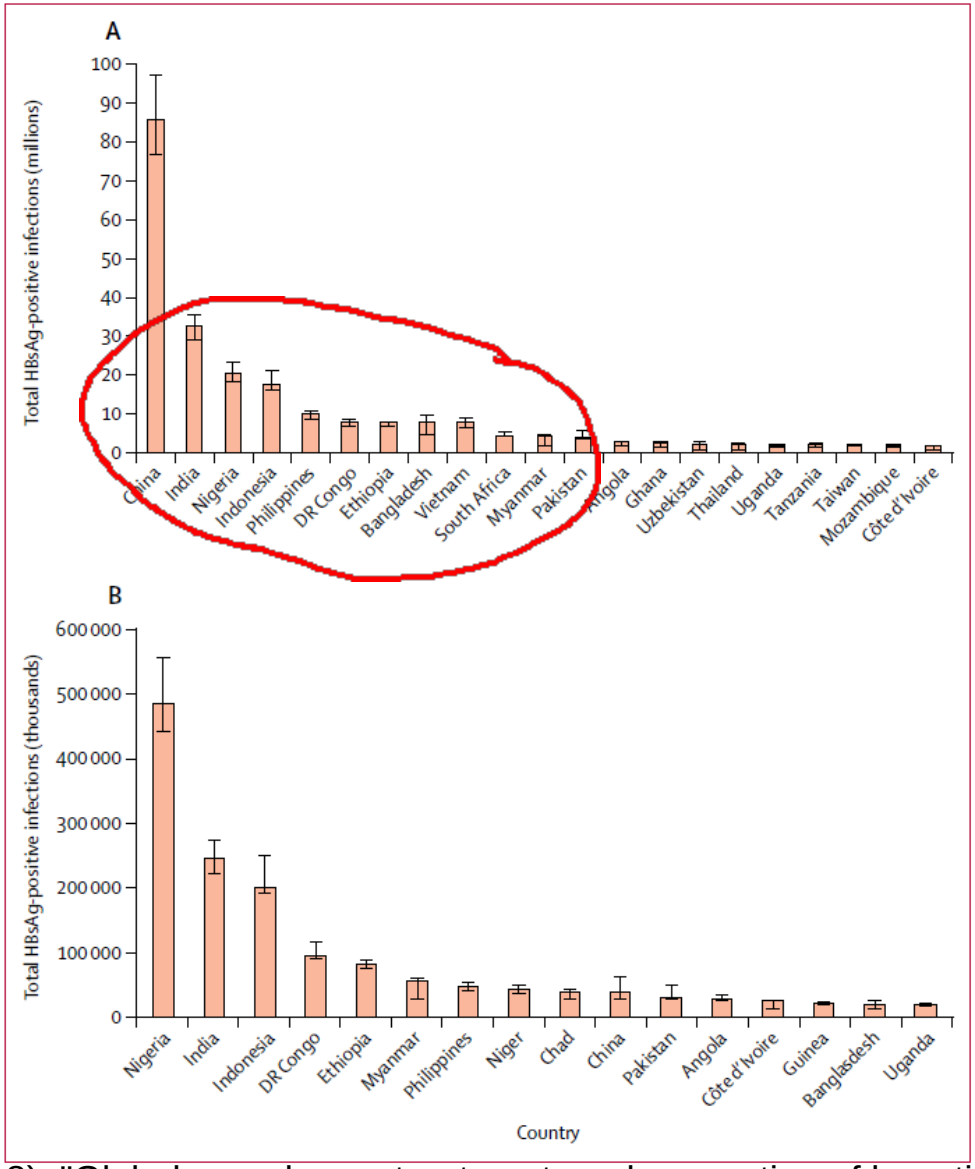
- 257 million people infected globally
- Infection in childhood and neonatal period: chronic infection
- Effective and safe vaccines prevent HBV infection
- Different replicative phases of the disease recognised
- Perhaps 100 million persons with a low replicative state do not qualify for treatment

HBsAg prevalence estimates for 2016



Polaris laboratory, P. (2018). "Global prevalence, treatment, and prevention of hepatitis B virus infection in 2016: a modelling study." The Lancet Gastroenterology & Hepatology.

Countries accounting for 80% or more of the total HBsAg positive infections 2016

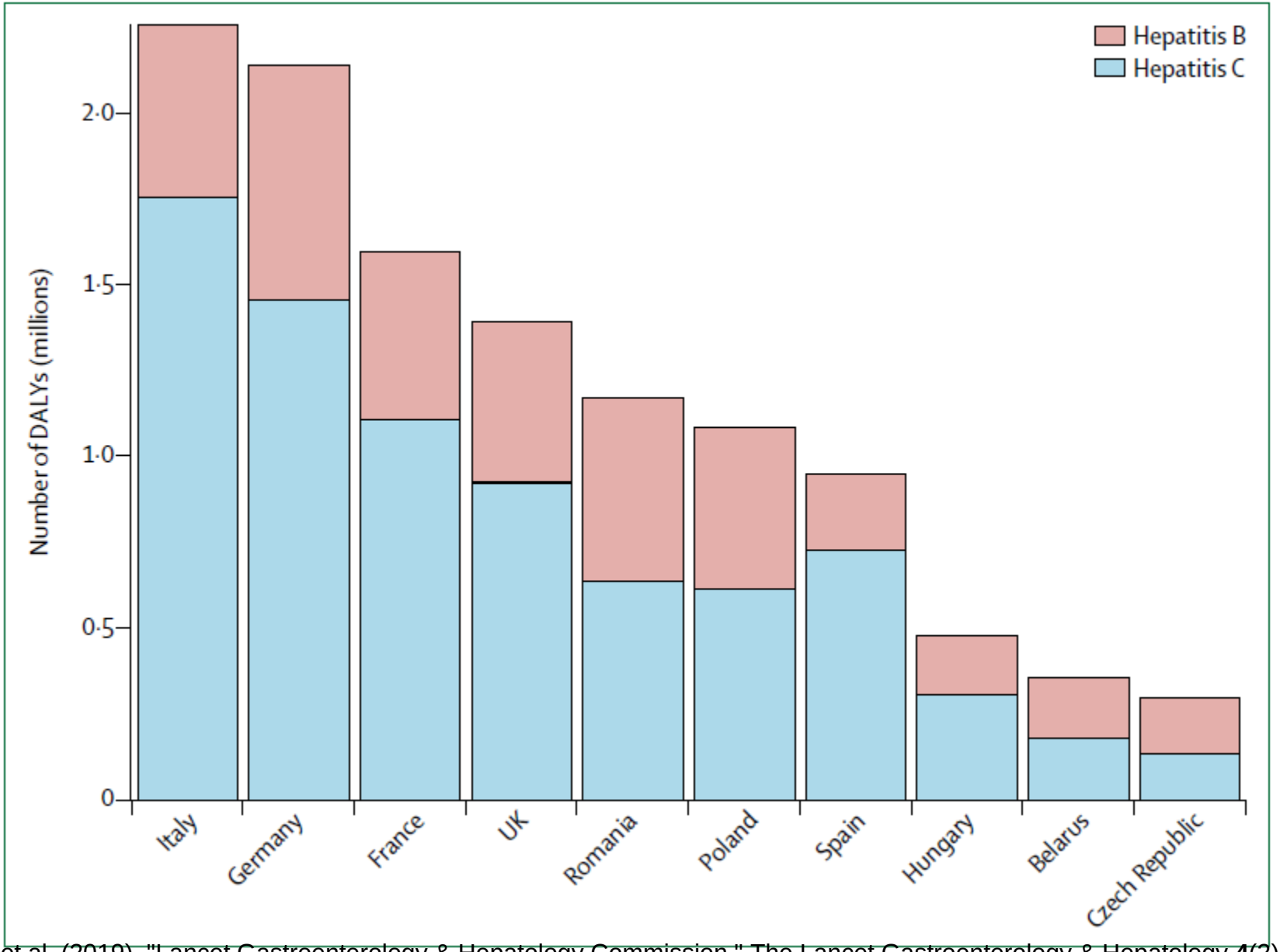


General population

Population aged 5 years

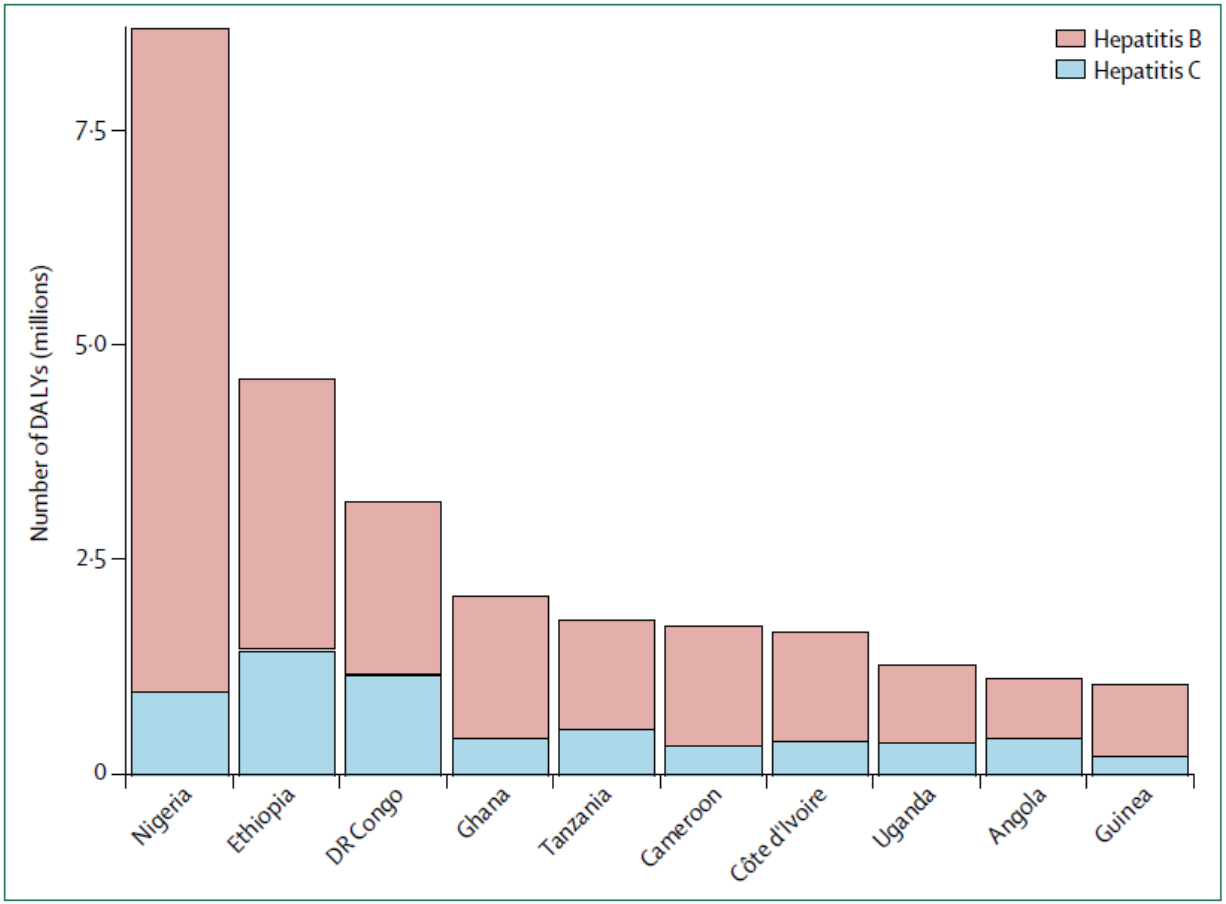
Polaris laboratory, P. (2018). "Global prevalence, treatment, and prevention of hepatitis B virus infection in 2016: a modelling study." The Lancet Gastroenterology & Hepatology.

10 countries with the greatest burden from viral hepatitis in the EU



ke, G. S., et al. (2019). "Lancet Gastroenterology & Hepatology Commission." The Lancet Gastroenterology & Hepatology **4**(2): 135-184.

The 10 countries with the greatest burden from viral hepatitis in sub-Saharan Africa



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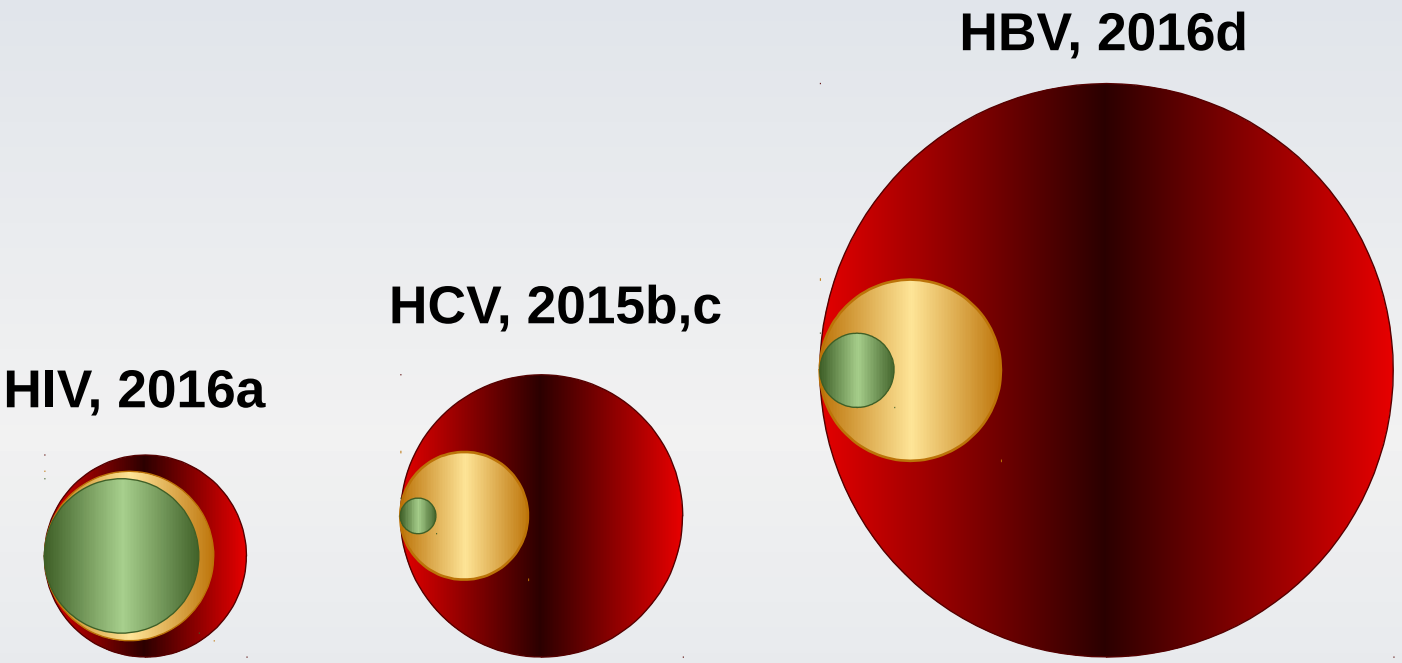
Gaps – HIV, HCV, HBV

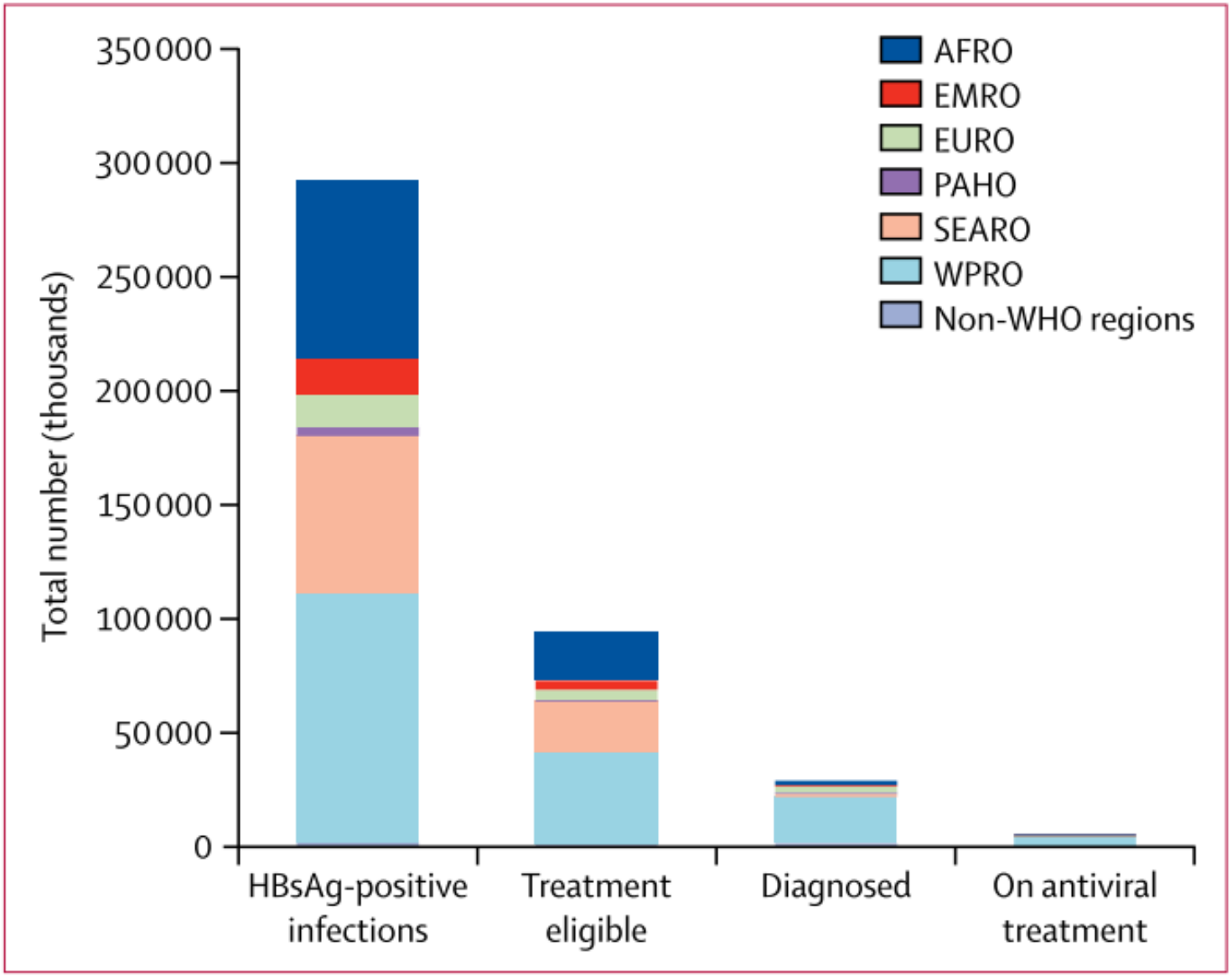


Global Estimates in Million of Patients			
Prevalence	36.7	71.1	292.0
Diagnosed	25.7	14.2	28.8
Treated	20.9[e]	1.1	4.8

a. UNAIDS Fact Sheet, World AIDS Day 2017. http://www.unaids.org/en/resources/fact-sheet; b. Blach et al., *Lancet Gastroenterol. Hepatol.*, 2017.
c. WHO Global Hepatitis Report, 2017. http://www.who.int/hepatitis/publications/global-hepatitis-report2017-executive-summary/en/;
d. Razavi et al., *Lancet Gastroenterol. Hepatol.*, 2018; e. 2017 data.

Courtesy John Martin

Global and regional HBV care cascade 2016



Polaris laboratory, P. (2018). The Lancet Gastroenterology & Hepatology.

Cooke et al The Lancet Gastroenterology & Hepatology **4**(2): 135-

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Therapeutic goals in hepatitis B

To prevent disease related mortality: Continued high levels of HBV replication together with hepatic inflammation increases the risk of cirrhosis and HCC

Prevention of HCC

Prevention of disease-related mortality

Prevention of decompensated cirrhosis

HBeAg Clearance
HBsAg clearance

Reversal of fibrosis/cirrhosis

Control of viral replication

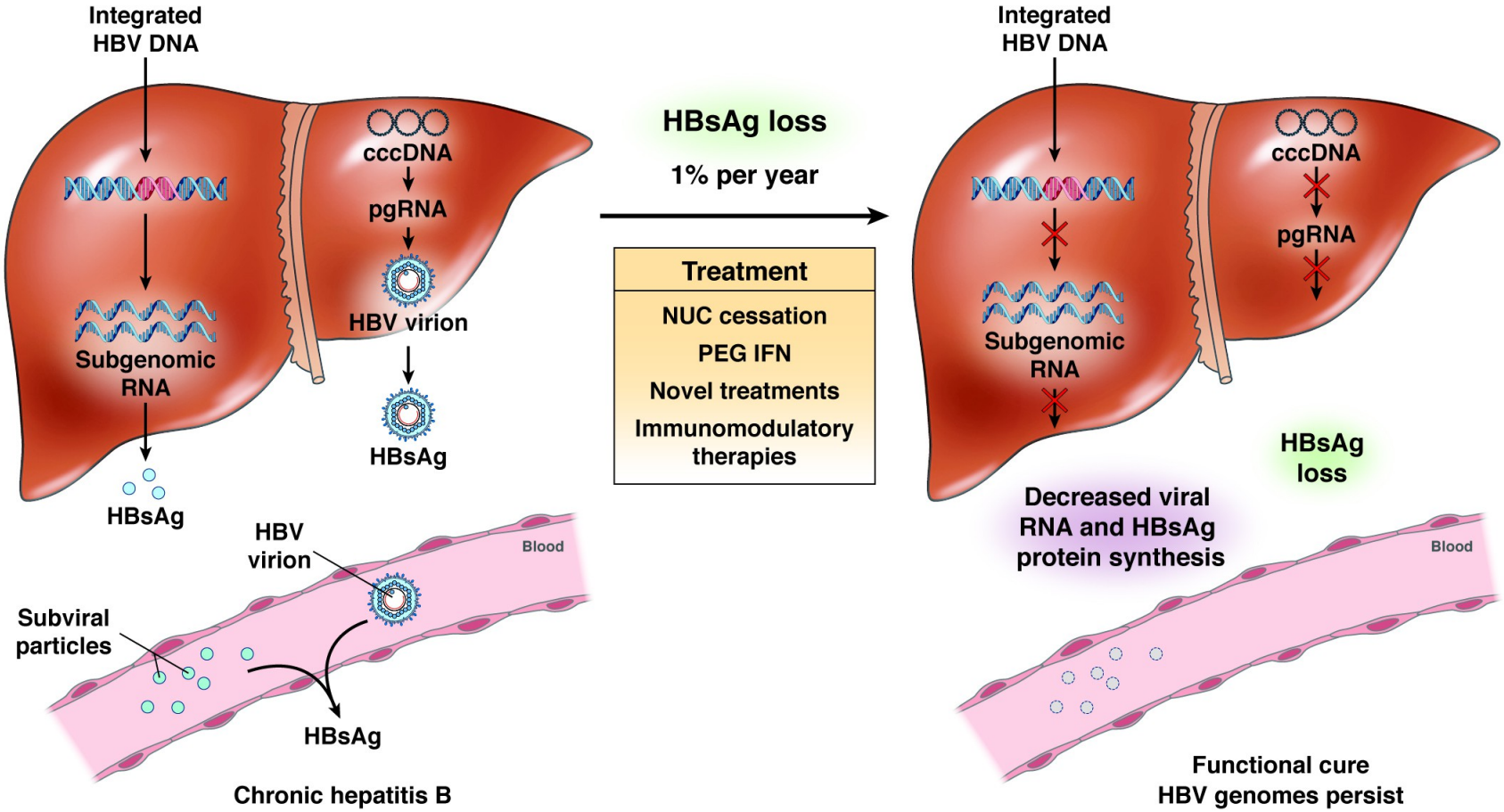
Primary aim

Risk of progression

HBV DNA (HBeAg) HBsAg Stage of disease
HBV genotype
Age, gender, family history
HDV, HCV and HIV
Environmental (alcohol, smoking, aflatoxin)
Diabetes mellitus

1. EASL Clinical Practice Guidelines. J Hepatol 2012;57:167–85;
2. Liaw YF, et al. Hepatol Int 2012;6:809–10; Marcellin Lancet 2103: 381, 468
3. Lok A, McMahon B. Hepatology 2009;50:661–2,1–36.; Wong G Hepatology 2013: 58:1537; Kim Hepatology 2017: 66:335

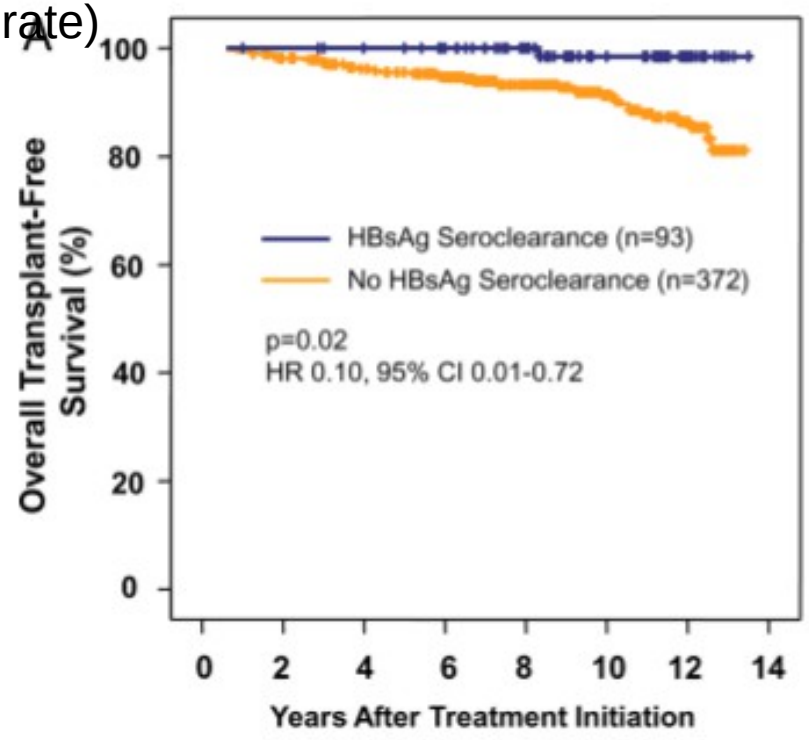
Low rates of HBsAg loss either spontaneously or with antiviral treatment

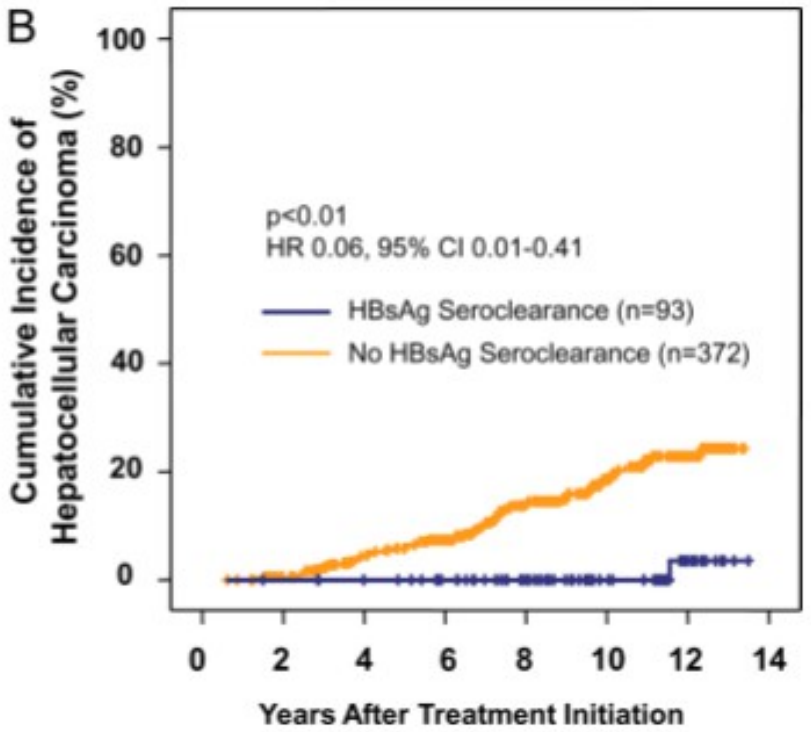


Dusheiko and Wang Gastroenterology 2019 in press

Clinical outcomes after nucleotide analogue therapy with or without HBsAg clearance

Median follow-up period 6 years (33,567 patient-years) of 5409 CHB patients treated w
lamivudine or entecavir, 110 achieved HBsAg seroclearance (0.33% annual seroclearan
rate)





Predictors of HBsAg loss: Baseline ALT level >5 times > probability HBsAg clearance
HBeAg positivity, high HBV DNA level, cirrhosis: inversely associated HBsAg loss

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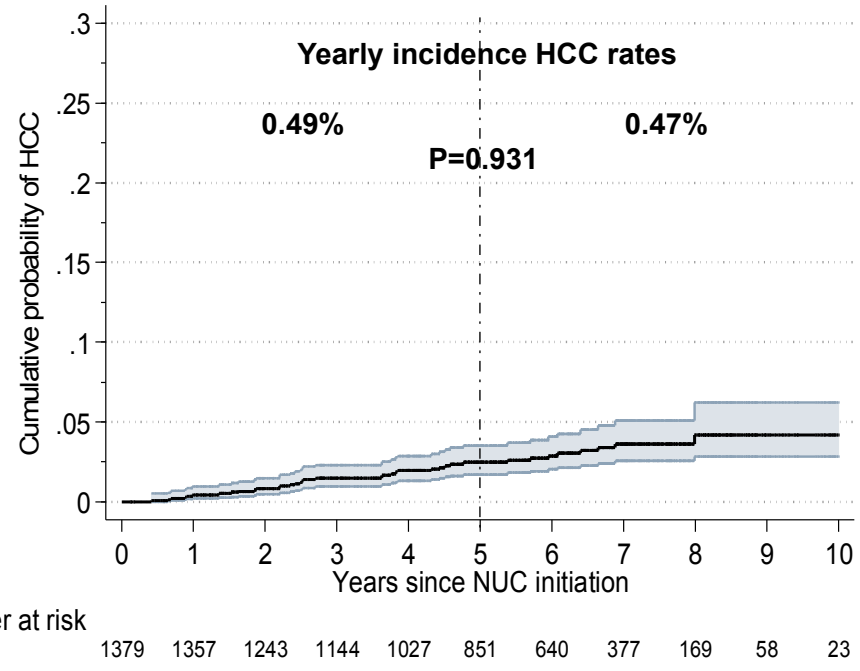
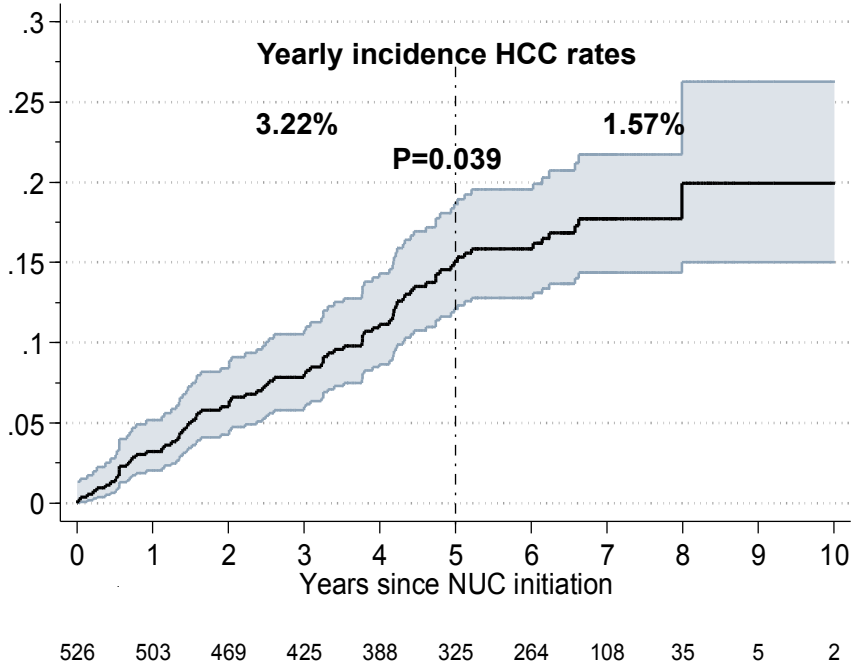
The PAGE-B study
HCC in ETV/TDF treated pts beyond year 5

1951 patients on ETV/TDF for 72 months

Chronic hepatitis



Compensated cirrhosis



- **The HCC risk decreases after the first 5 yrs of ETV/TDF therapy in patients with compensated cirrhosis at baseline but not in those with CH.**
- **Older age, especially ≥50 yrs, and lower platelets represent the main risk factors for late HCC development.**

Papatheodoridis et al (HEPATOLOGY 2017;66:1444-1453).

Prediction and need for HCC surveillance after first 5 years of ETV/TDF therapy in Caucasian CHB patients of PAGE-B cohort

Hypothesis/Aim/Objective:
To assess predictors and need for HCC surveillance beyond year 5 of ETV/TDF in CHB patients

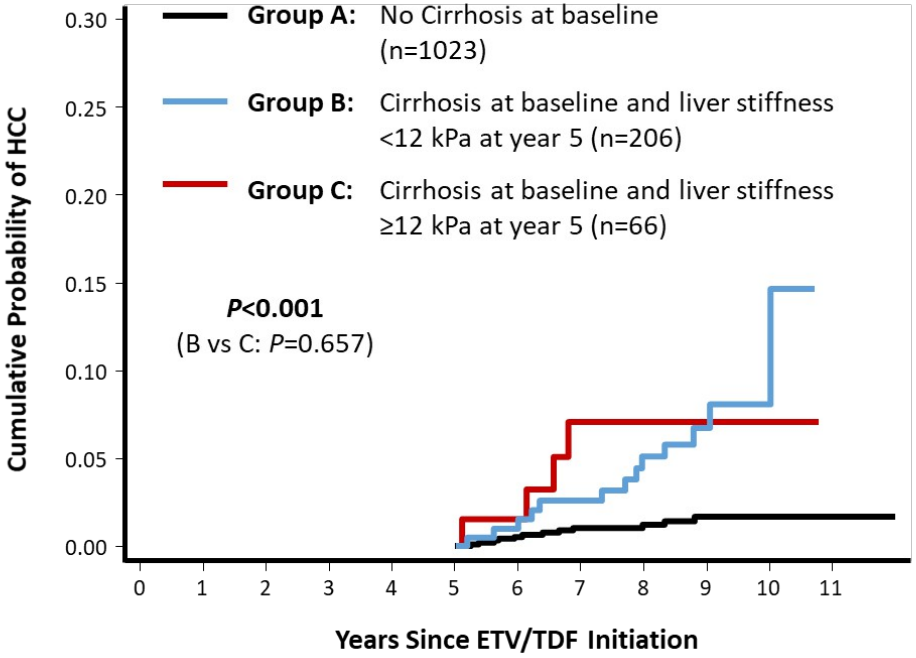
Methods:

- Patient population: 1427 (73%) of the 1951 adult Caucasians with CHB ± compensated cirrhosis included in the PAGE-B cohort who have completed follow-up >5 years without HCC until year 5
- Age at year 5: 57 ± 13 years, males: 70%, baseline cirrhosis: 26%
- Mean follow-up: 8.1 ± 1.6 (median: 8.3) years from ETV/TDF onset

Conclusions:
HCC after the first 5 years of ETV/TDF therapy seems to develop exclusively in patients older than 50 years, while elastographic reversion of cirrhosis at year 5 does not appear to decrease the HCC risk.

Papatheodoridis GV, et al., Abstract 17

Cumulative probability of HCC beyond year 5 of ETV/TDF therapy in CHB patients without HCC within the first 5 years



Predictive factors associated with HCC and mortality after HBsAg seroclearance in patients with CHB

Aim:

We examined the predictive factors associated with HCC incidence and mortality after HBsAg seroclearance in patients with chronic hepatitis B.

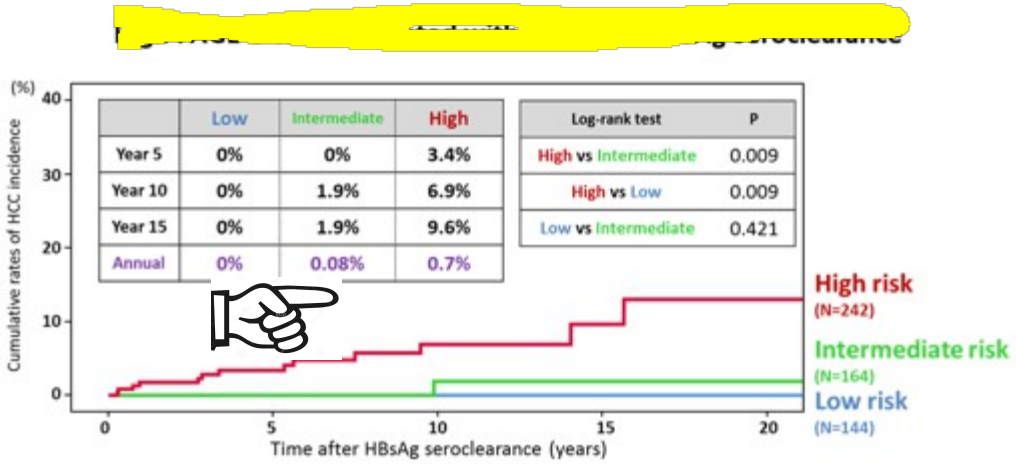
Methods:

We conducted a retrospective cohort study of 550 adult patients who had chronical HBV mono-infection and subsequently achieved HBsAg seroclearance with or without antiviral treatment in the single center.

Conclusions:

PAGE-B score may have a potential to predict HCC incidence and be useful to HCC surveillance after HBsAg seroclearance, and all-cause mortality after HBsAg seroclearance was similar to general population.

Hosaka T, et al., Abstract 213



	Low	Intermediate	High
Year 5	0%	0%	3.4%
Year 10	0%	1.9%	6.9%
Year 15	0%	1.9%	9.6%
Annual	0%	0.08%	0.7%

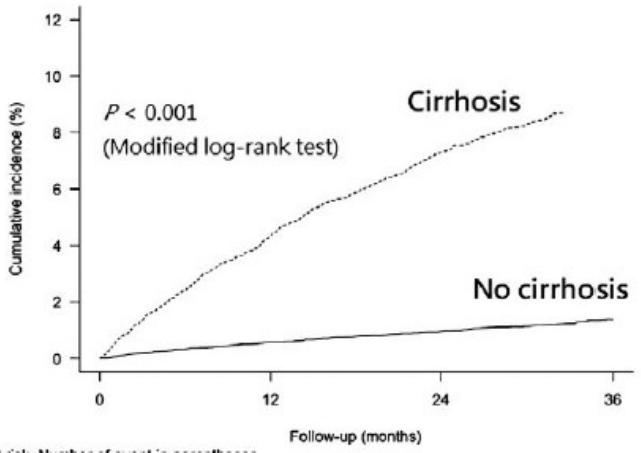
Log-rank test	P
High vs Intermediate	0.009
High vs Low	0.009
Low vs Intermediate	0.421

Variable	No. Pts N=550	HCC Cases N=14	Total Pt-Years	Incidence Rate Per 1000 PY	*Multivariate Adjusted HR (95% CI)	*P*
PAGE-B (High Risk)	242	13	1795.4	7.2	11.8 (1.53–90.5)	0.018
Pre-Existing Cirrhosis Before HBsAg Seroclearance	87	10	675.5	14.8	9.62 (3.00–30.8)	<0.001

550 patients who subsequently achieved HBsAg seroclearance

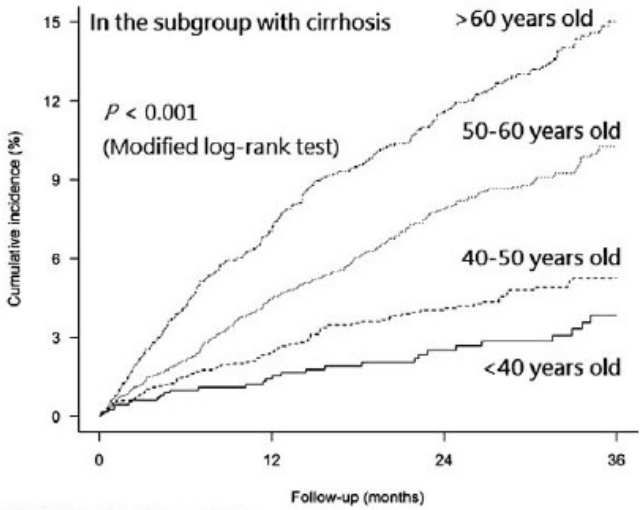
The risk of HCC based on pretreatment factors HBV on entecavir or tenofovir

(A)



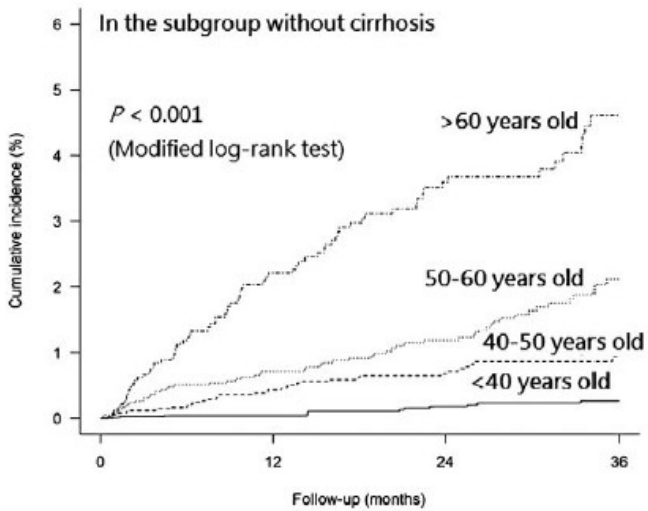
Number at risk, Number of event in parentheses							
Non-cirrhosis	18585	(96)	14360	(48)	10053	(33)	4193
Cirrhosis	9235	(361)	6598	(178)	4400	(86)	1967

(B)



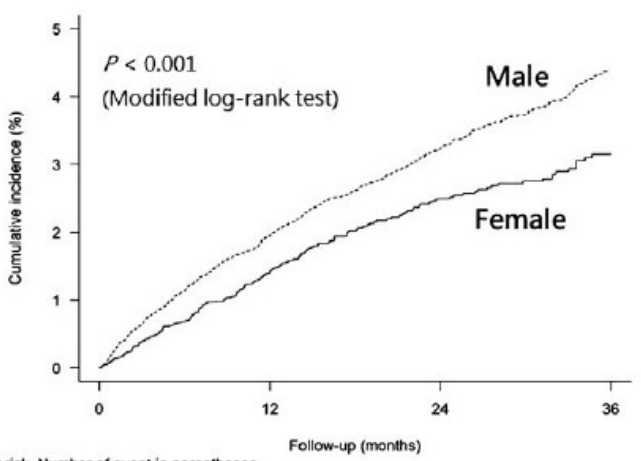
Number at risk, Number of event in parentheses							
<40	1155	(15)	844	(8)	579	(6)	276
40-50	2337	(52)	1731	(27)	1157	(12)	532
50-60	3064	(123)	2250	(69)	1524	(32)	683
>60	2679	(171)	1773	(74)	1140	(36)	476

(C)



Number at risk, Number of event in parentheses							
<40	6797	(3)	5417	(6)	3868	(3)	1732
40-50	5158	(20)	4028	(9)	2818	(6)	1130
50-60	4293	(28)	3247	(13)	2239	(16)	904
>60	2337	(45)	1668	(20)	1128	(8)	427

(D)

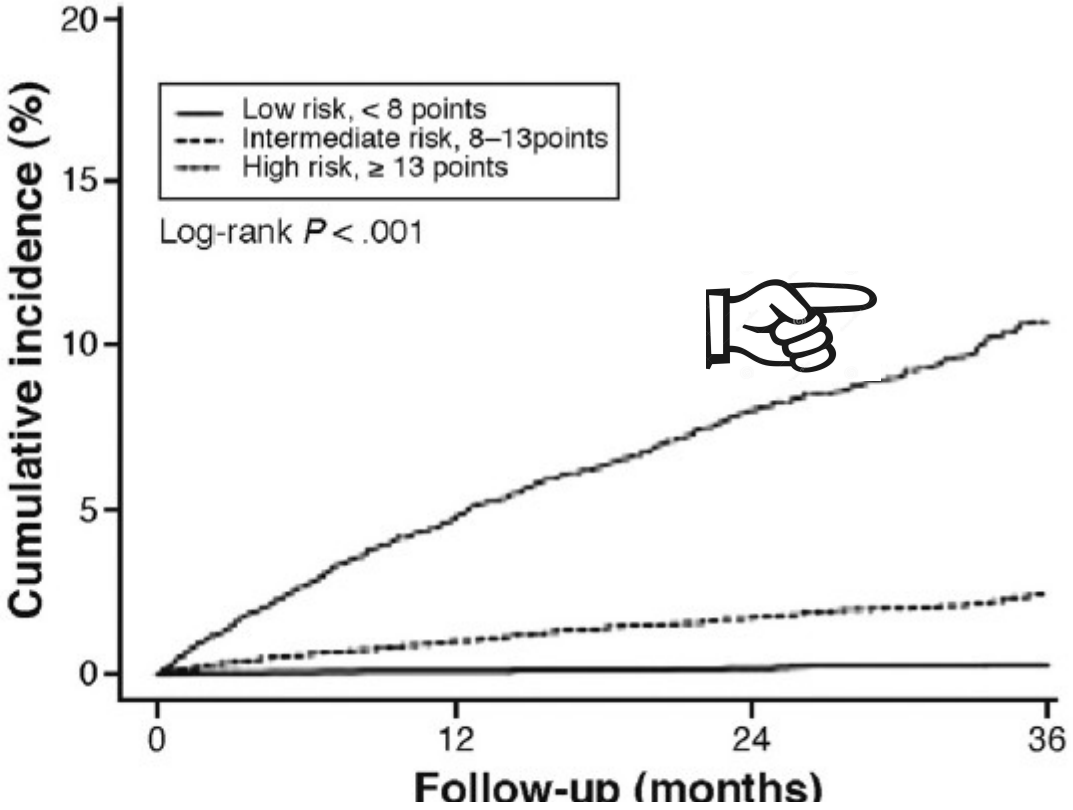


Number at risk, Number of event in parentheses							
Female	7222	(92)	5414	(50)	3704	(19)	1551
Male	20598	(365)	15544	(176)	10749	(100)	4609

Hsu, Ho et al. 2018)Hsu, Y. C., et al. (2018). J Viral Hepat **25**(5):

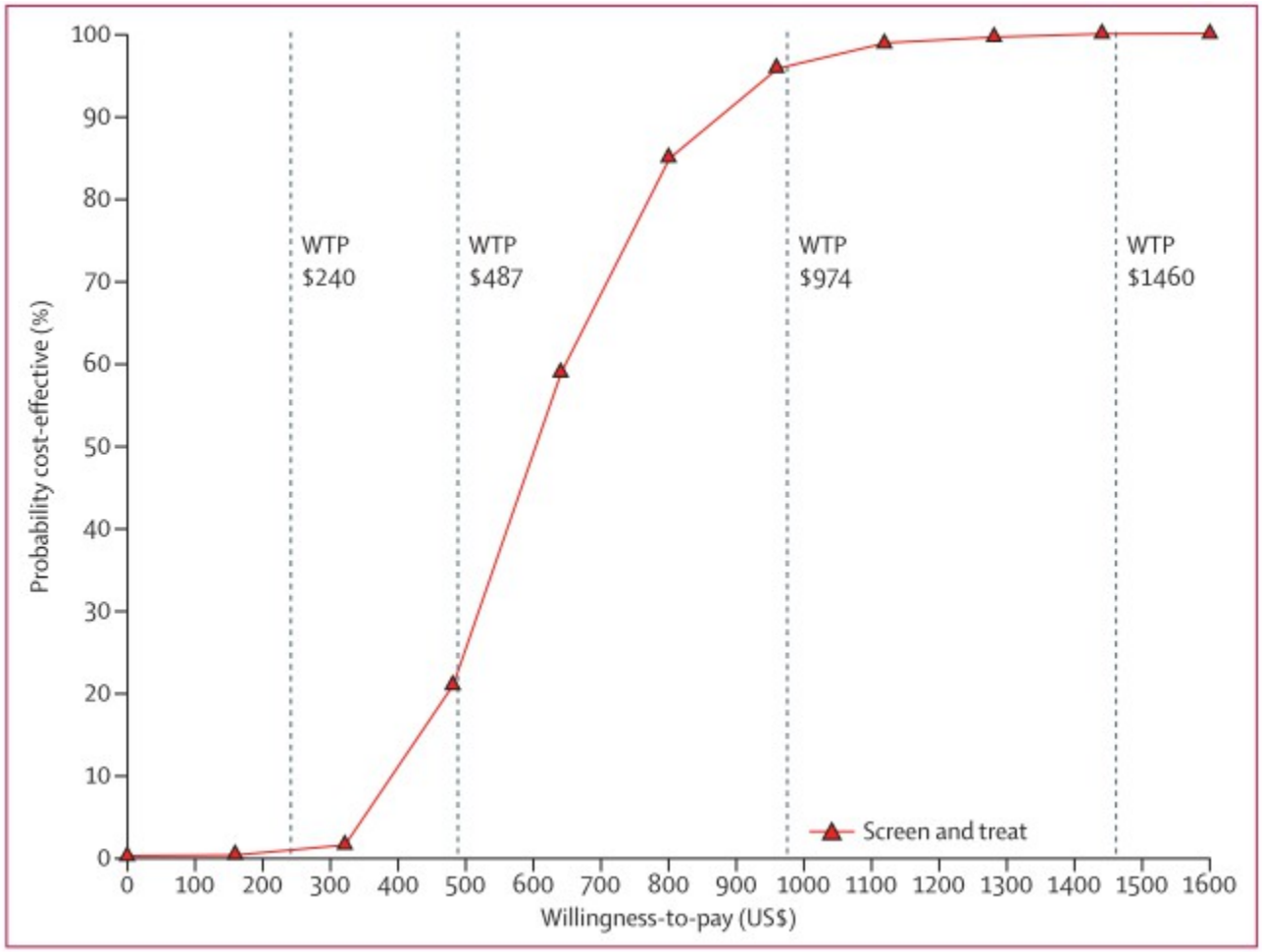
Risk of HCC in patients with hepatitis B receiving antiviral treatment Cirrhosis, Age, Male sex, Diabetes CAMD score)

Variable	Risk score
Cirrhosis	
No cirrhosis	0
Cirrhosis with age < 40 yr	10
Cirrhosis with age ≥ 40 yr	6
Age	
Age < 40 yr	0
Age 40–49 yr	5
Age 50–59 yr	8
Age 50 yr or older	10
Gender	
Female sex	0
Male sex	2
Diabetes mellitus	
Not diabetic	0
Diabetic	1



ulik and El-Serag Gastroenterology 2018) 10.1053/j.gastro.2018.08.065; Hsu, Ho et al. 201
u, Y. C., et al. (2018). J Viral Hepat **25**(5): 543-551.

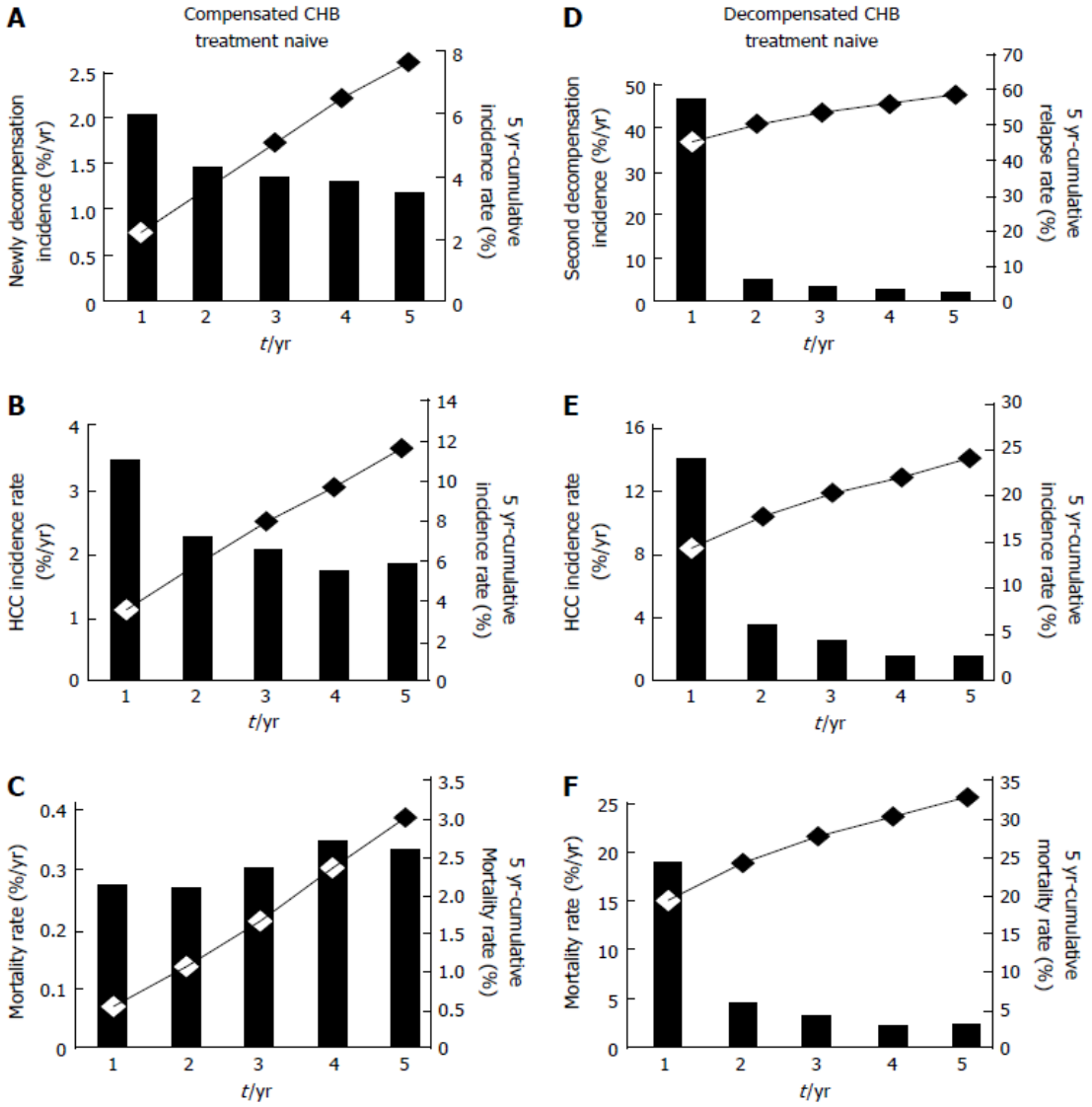
Probability of screen and treat intervention cost effectiveness over range of willingness to pay/DALY's



Nayagam et al Lancet Global Health 4:e568-78 201

Clinical course CHB on antiviral therapy

48365 antiviral treatment-naive patients treated between 2008 and 2009 Korean Health Insurance: each follow-up period >/= 5 years.



cidence of hepatocellular carcinoma and mortality sharply decreased after one year treatme

Ju, Y. C., et al. (2018). "World J Gastroenterol **24**(40): 4606-4614

The global challenge of hepatitis B infection

- A good understanding of the prevalence of the disease and disease burden
- Awareness of the disease (populace) lower than that for HIV
- Treatment forms part of control of this disease
- Only 30 million individuals (10%) diagnosed and of these perhaps approximately 5 million are currently receiving antiviral treatment
- Drug costs are not the limiting factor for HBV
- Unsatisfactory progress in some parts of the world in implementing treatment: vaccination accepted
- Overlooked the larger picture: screening diagnos,is and treatment to prevent progression