

# **Impact of Current Treatment on Incidence of HCC**

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# Case

- 47-year old asymptomatic man referred for thrombocytopenia, platelets 112 K/mm<sup>3</sup>.
- Known to have HBV infection for many years. No treatment needed for being 'inactive carrier.' No family history of HCC.
- No stigmata. Spleen not palpable.
- Lab: ALT 42 U/L, HBV DNA 72K iu/ml, HBeAg-negative  
Normal synthetic function, Elastography 21 kPa  
US: Cirrhotic appearing liver, Spleen 13 cm

*Question: Should this patient be treated?*

# Case

Patient started on entecavir (ETV) therapy.

- 1 year later: HBV DNA < 10 iu/ml, ALT 29 U/L
- 6 years later:

US: No mass, cirrhotic-appearing liver with surface nodularity

Elastography: 6.5 kPa, Platelets 153 K/mm<sup>3</sup>

*Question: What to expect of the risk of HCC (compared to pre-ETV)?*

- A. No change
- B. Approx 30% reduced
- C. Approx 50% reduced
- D. >90% reduced

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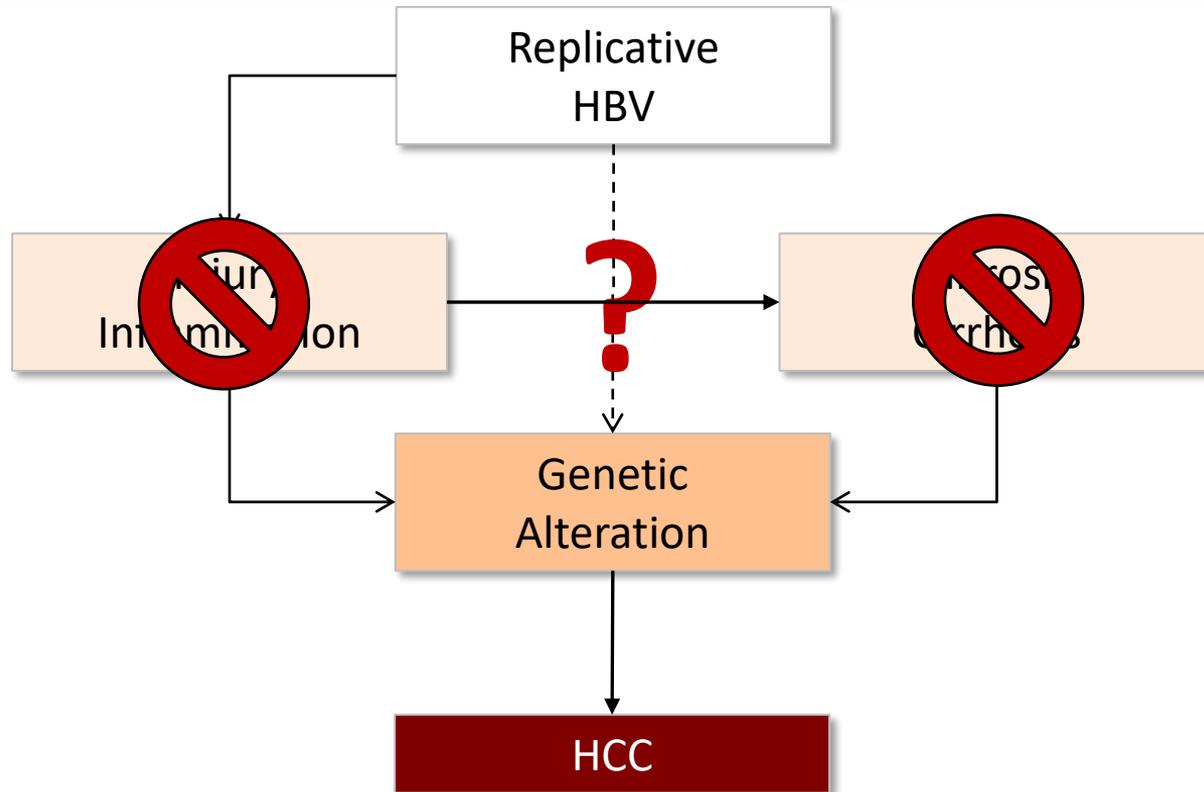
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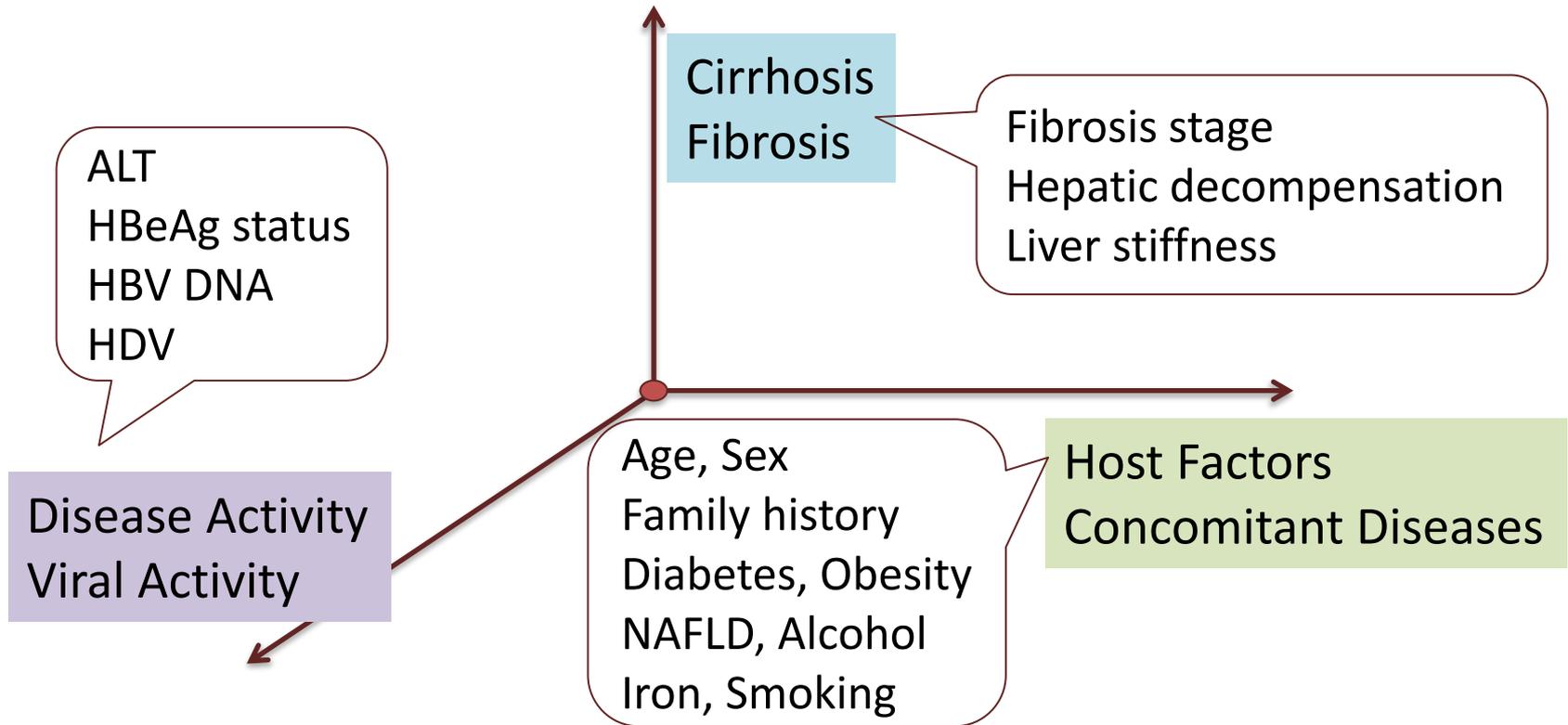
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# HBV and HCC Risk



# Determinants of HCC Risk



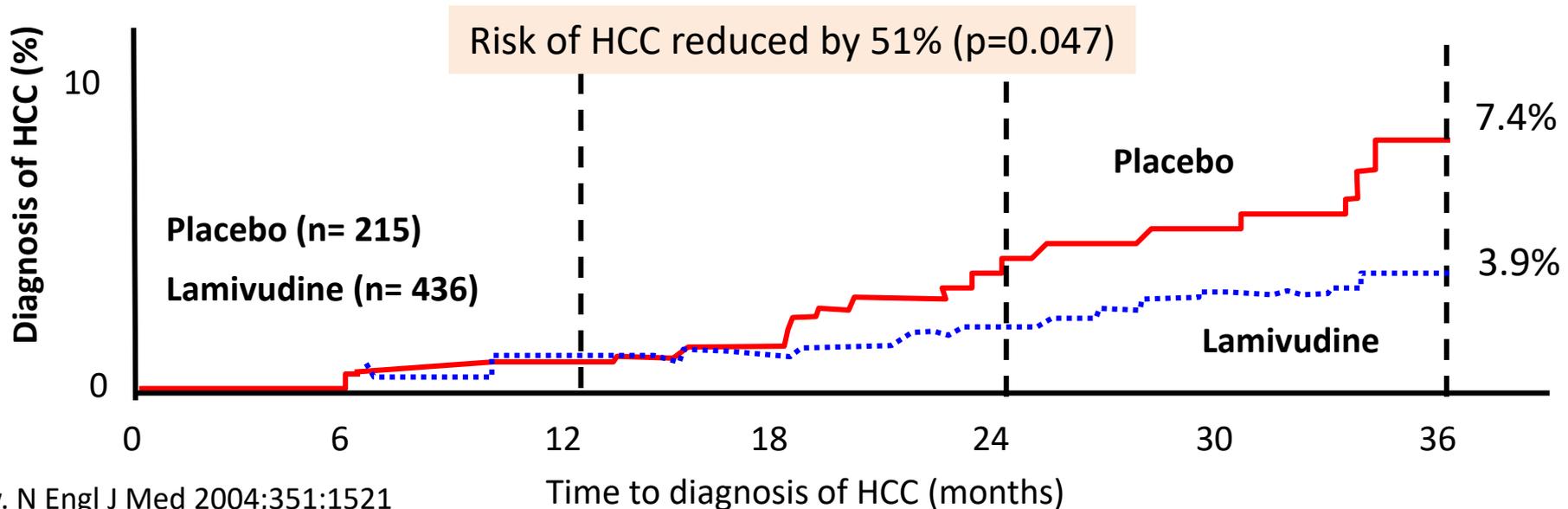
# Predictors of HCC in Untreated HBV Patients

Risk score	GAG-HCC	CU-HCC	LSM-HCC	LS Model	RWS-HCC	REACH-B	REACH-B II	LSPS	AGED	D <sup>2</sup> AS
n (deriv/valid)	820 / 0	1055 / 428	1035 / 520	1250 / 0	583/3353	3584/1505	2227/1113	227 / 0	628/1663	971 / 507
Country/Area	HK	HK	HK	Korea	Singapore	TW, HK, KR	Taiwan	Korea	China	Korea
Variables										
Sex	*			*	*	*	*		*	
Age	*	*	*	*	*	*	*		*	
FHx							*			
DNA	*	*	*	*		*			*	*
HBeAg						*			*	
qHBsAg							*			
Genotype							*			
ALT						*	*			
AFP					*					
Cirrhosis	*	*			*					
LSM			*	*				*		
Albumin		*	*							
Bilirubin		*								
Spleen size								*		
Platelets								*		

# Effects of Lamivudine on HCC Incidence

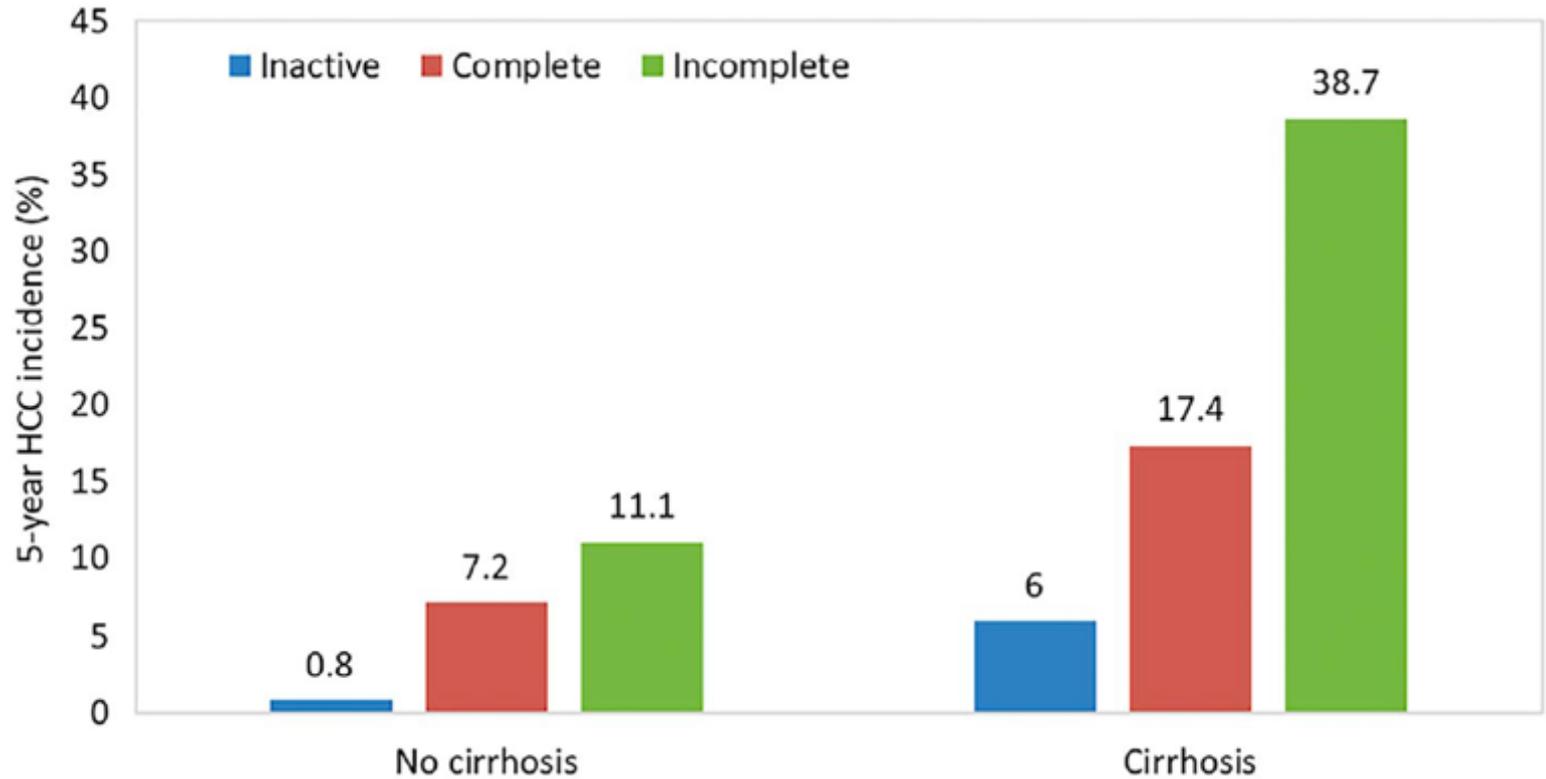
(Proof of Concept)

- Randomized controlled trial comparing lamivudine versus placebo
  - Patients with advanced fibrosis or cirrhosis
  - HBV-DNA ( $>10^5$  copies/mL) or HBeAg+



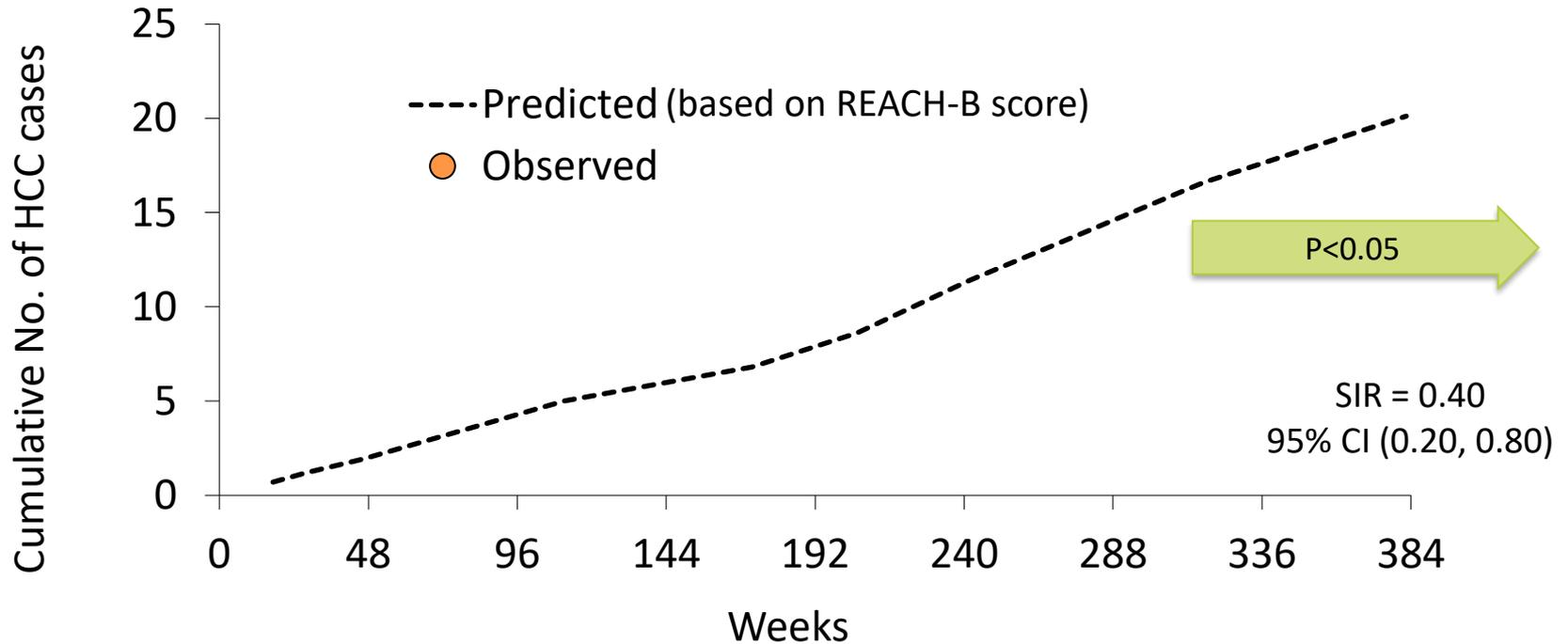
# Antiviral Response and HCC Risk Reduction

1,378 treatment-naïve patients starting NUC therapy versus 1,014 inactive carriers



# HCC Risk Reduction in Non-cirrhotic Patients

TDF global registration trial data (n=482, HBeAg+/-)

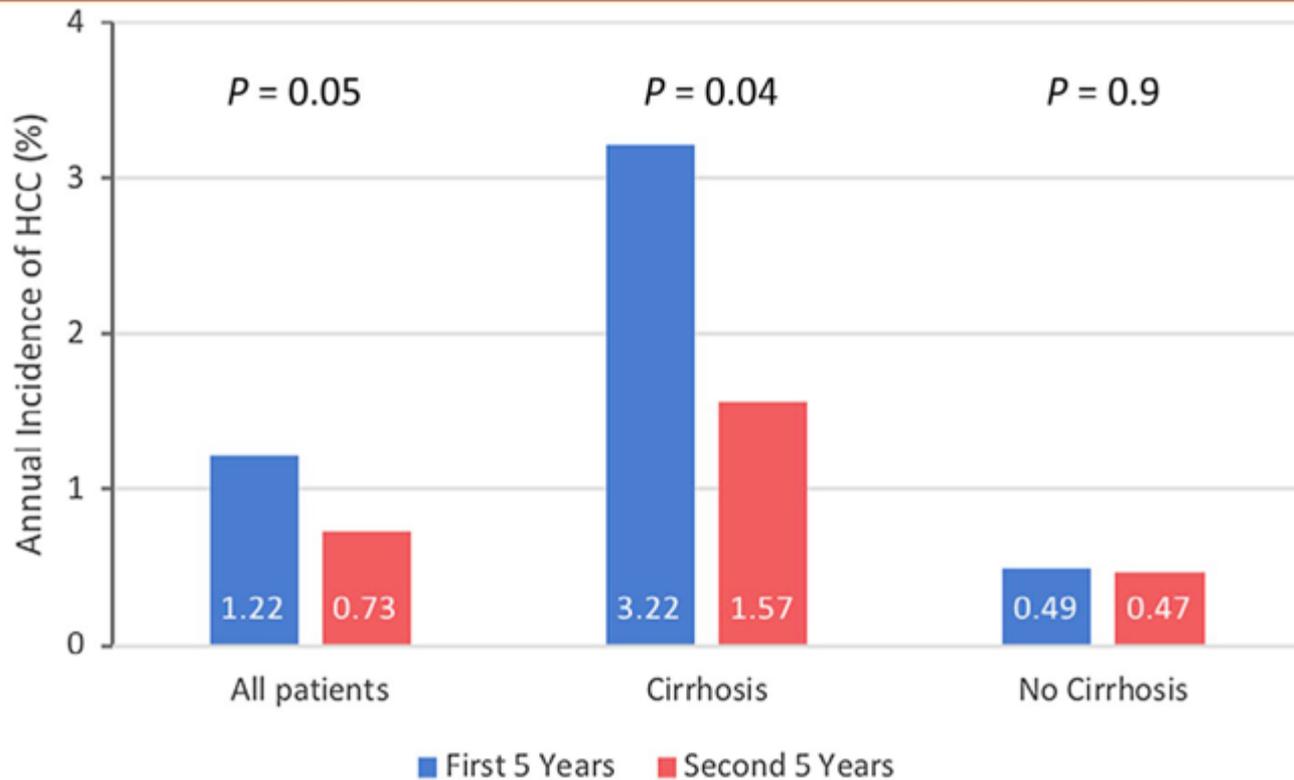


# Predictors of HCC in Antiviral-Treated Patients

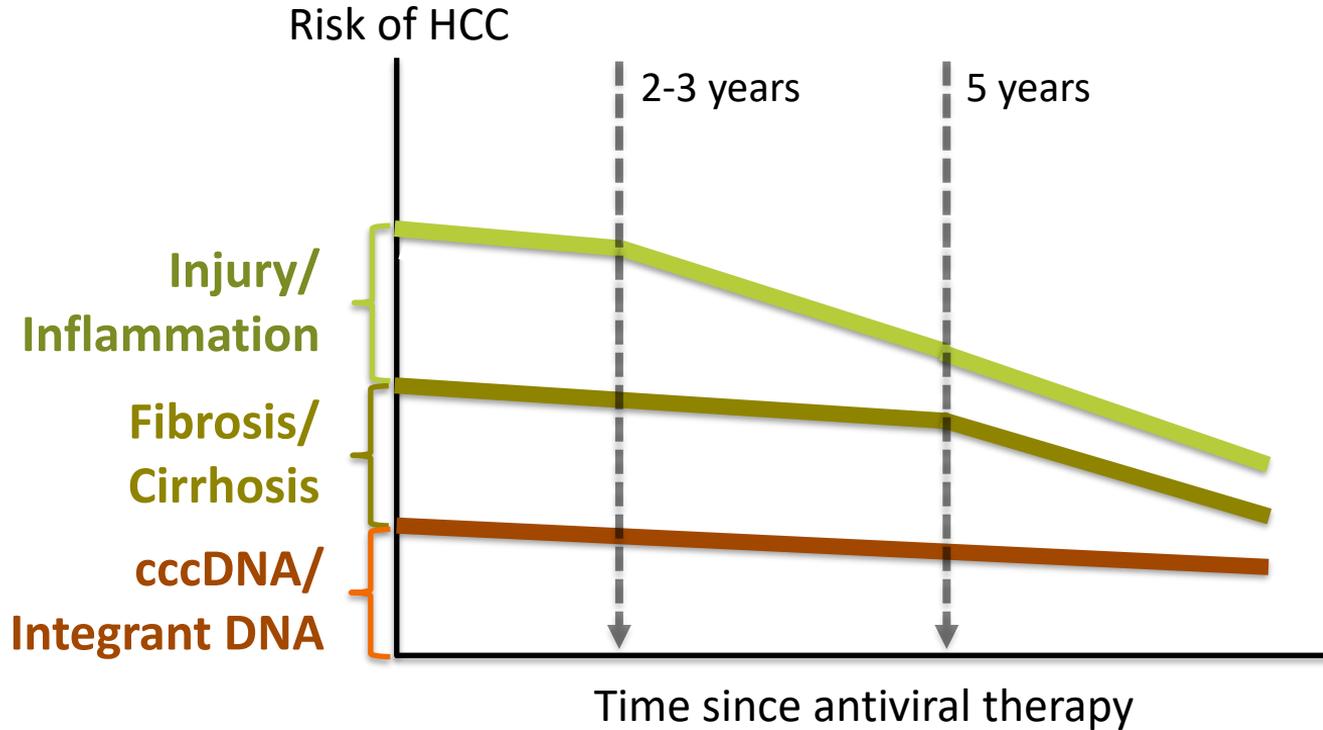
Risk score	REACH-Bm	PAGE-B	HCC-RESCUE	APA-B	CAMD	mPAGE-B	AASL
n (deriv/valid)	192/0	1325/490	990/1071	883/442	23851 / 19321	2001/1000	944/298
Country/Area	Korea	Europe	Korea	Taiwan	Taiwan, HK	Korea	Korea
Variables							
Sex	*	*	*		*	*	*
Age	*	*	*	*	*	*	*
Diabetes					*		
HBV DNA							
HBeAg	*						
ALT	*						
AFP				*			
Cirrhosis			*		*		*
LSM	*						
Albumin						*	*
Platelets		*		*		*	

# Fibrosis Regression and HCC

European multicenter study of adult Caucasians receiving ETV/TDF (n=1,951)



# Change in HCC Risk with Anti-HBV Therapy

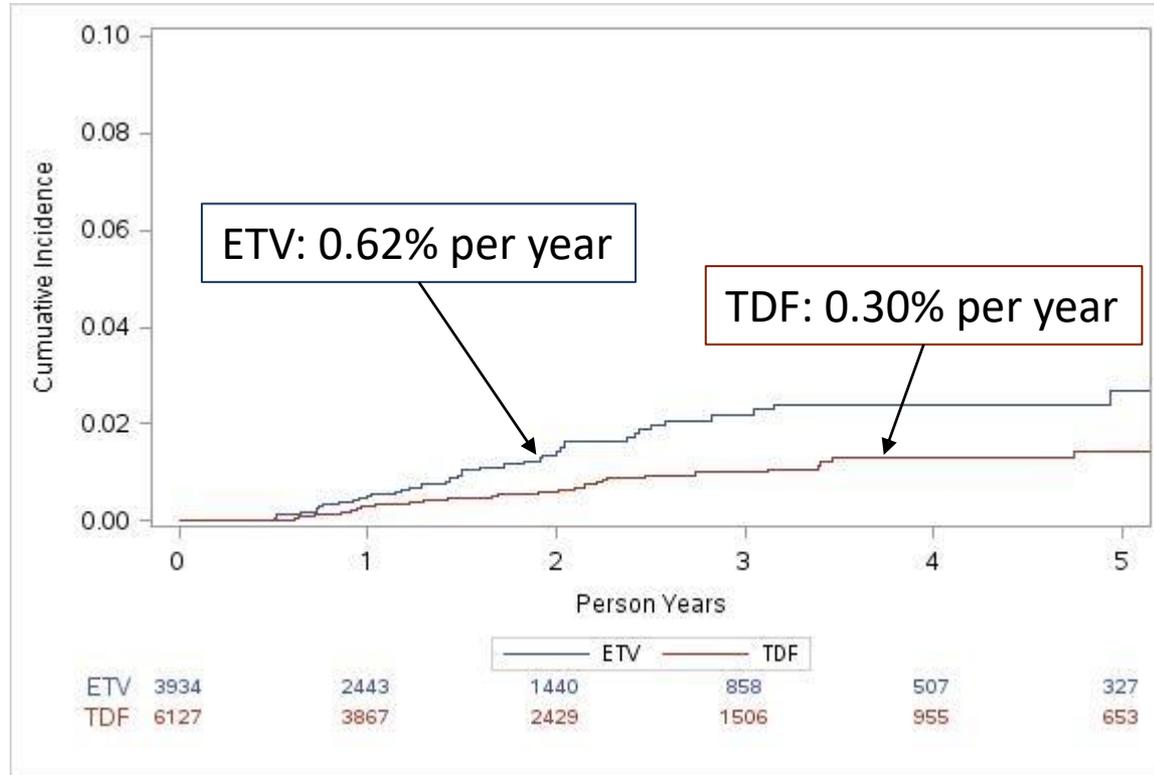


# ETV versus TDF

## US claims data

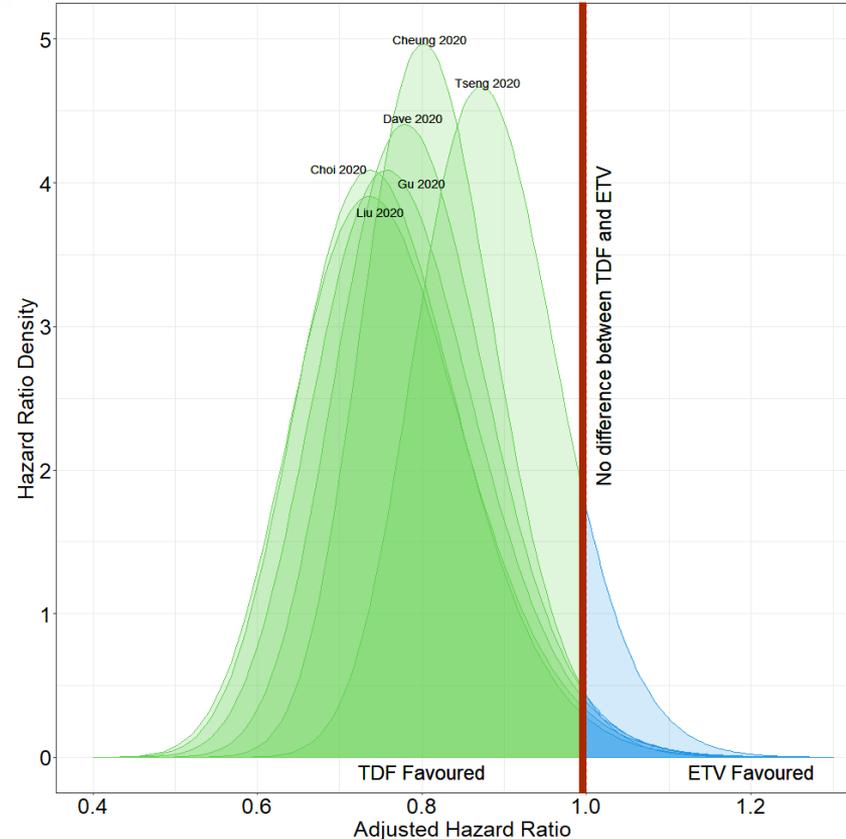
- Tx-naïve HBV patients
  - TDF (n=6,127)
  - ETV (n=3,934)
- 91% without cirrhosis

PS-weighted adjusted HR:  
0.57 (95% CI: 0.38-0.88)



# The Controversy

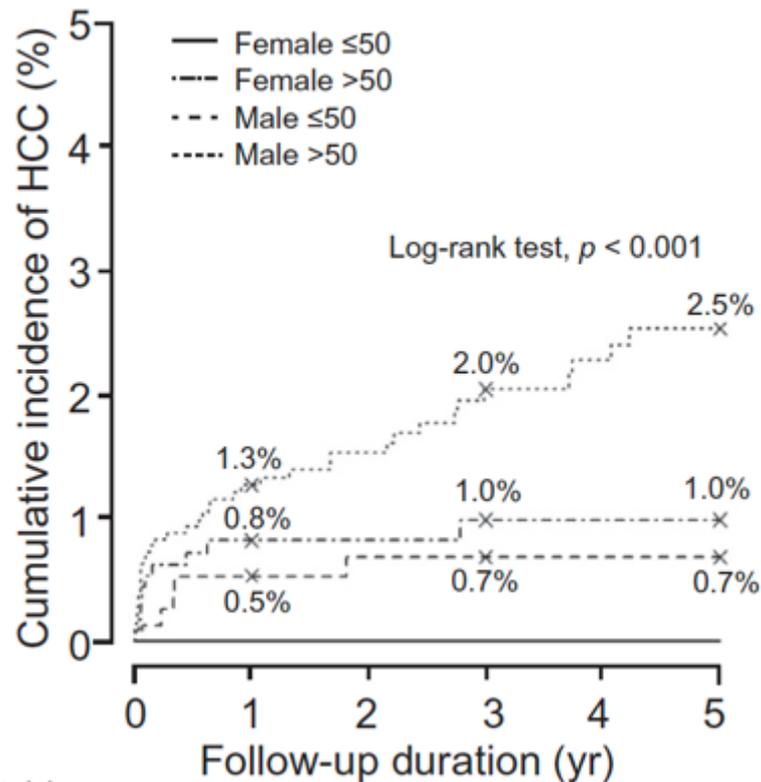
- > 5 meta-analysis since 2019:
  - 1 analysis concluding no difference
  - Others: Risk reduction TDF > ETV
  - Summary HR: ~0.8 (~20% better reduction with TDF)
- Effect likely driven by patients without cirrhosis
- The difference may be meaningful in patients at high risk.



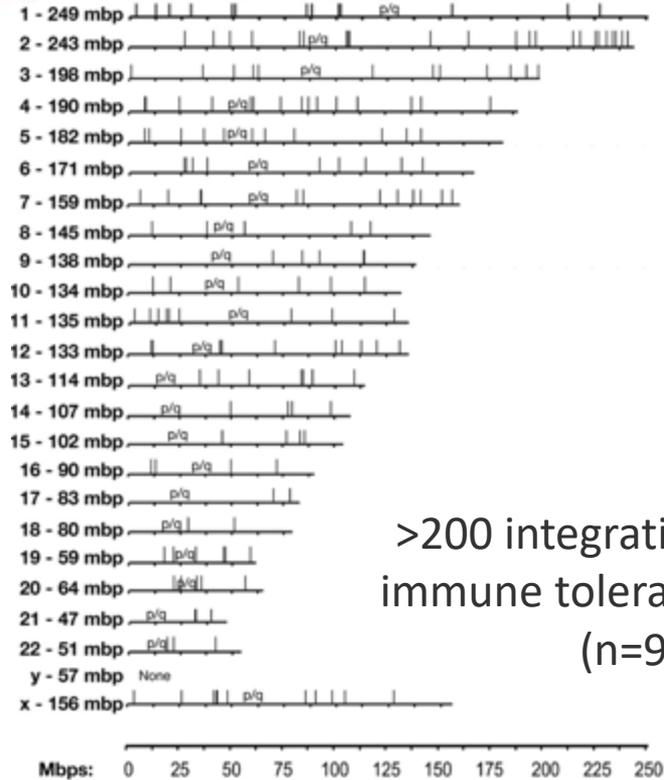
# HCC Incidence after HBsAg Clearance

## HK Population-based study (2000-16)

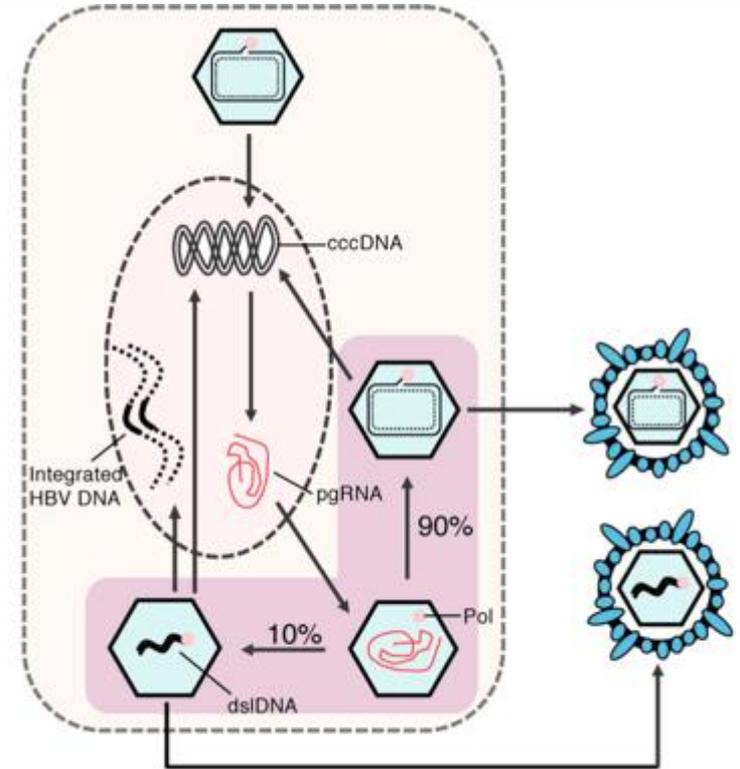
- 4,568 patients with HBsAg seroclearance
- Majority: spontaneous
  - 17% after nuc Tx
  - 1.3% with interferon
- 54 developed HCC (median 3.4 years)
  - Cum. 5-year incidence = 1.5%



# HBV DNA Integration

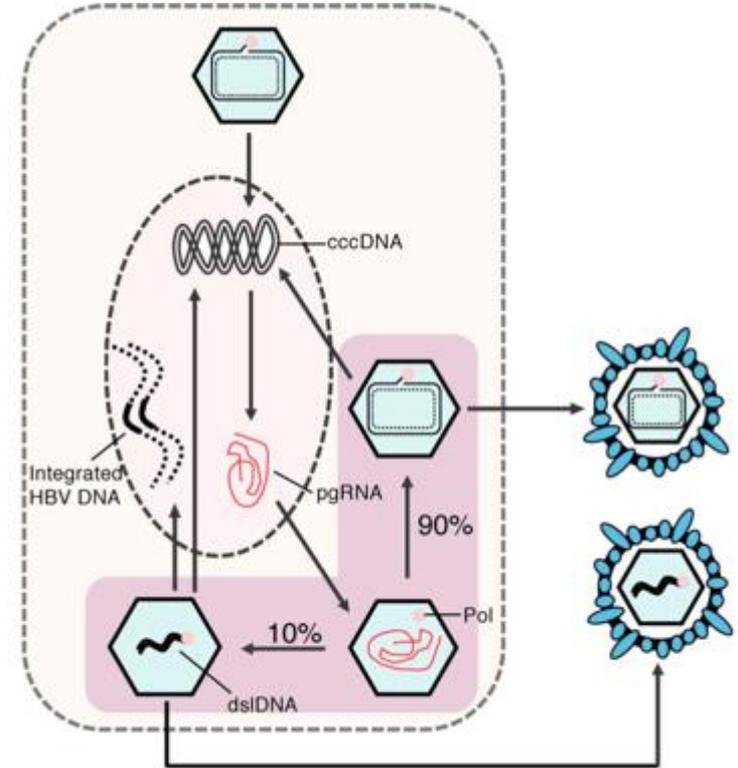
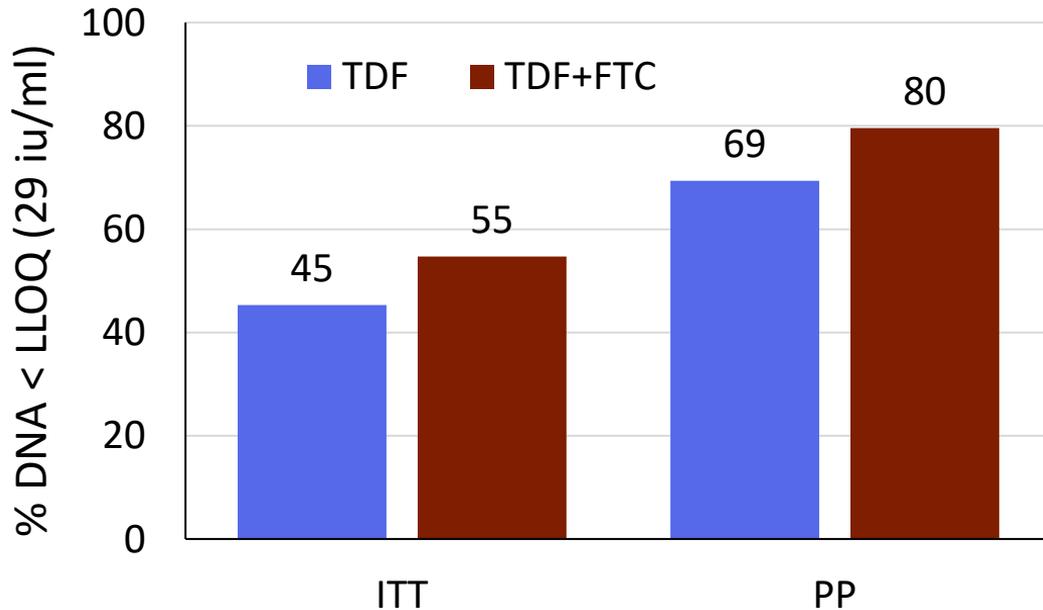


>200 integration sites in  
 immune tolerant patients  
 (n=9)

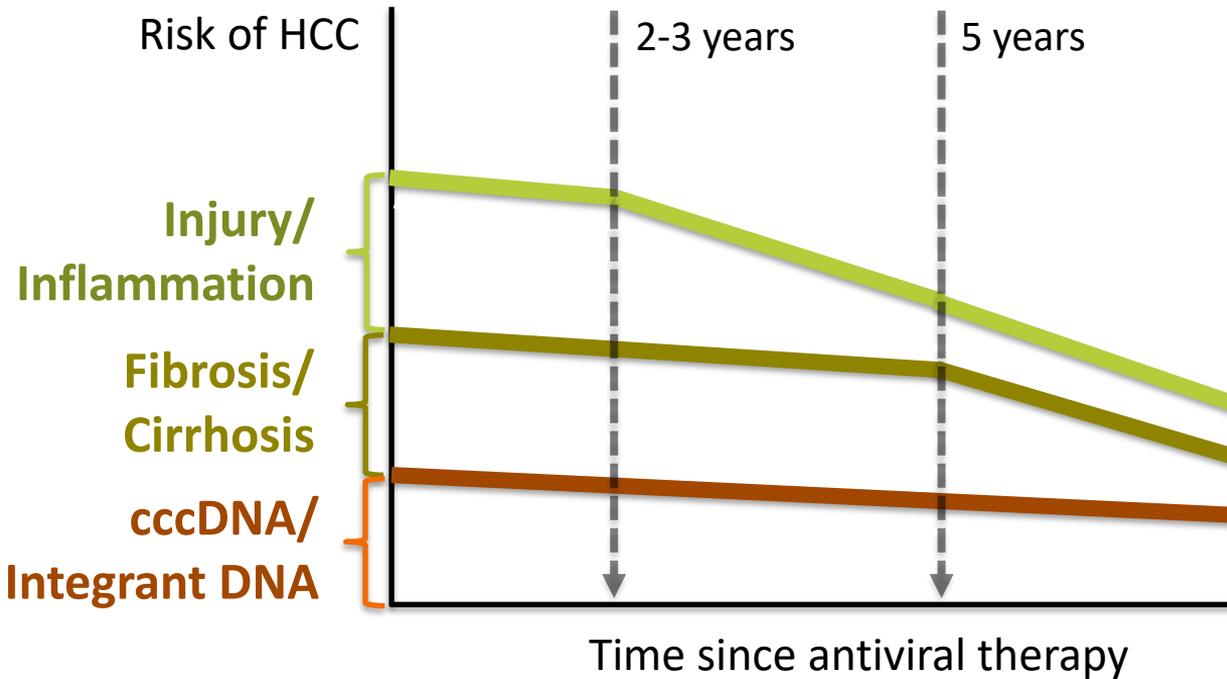


# HBV DNA Integration and Antiviral Therapy

Immune-tolerant (HBV DNA  $\sim 10^8$  iu/mL)



# Take Home



## Active hepatitis

- Nice thing to know (little impact on management decisions)

## 'Grey zone' patients

- Informed decision-making
- Patient preference
- Prediction model