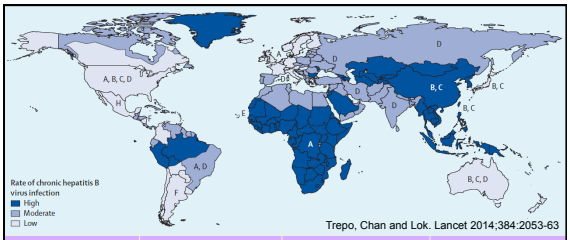
Challenges of Hepatitis B in Asia

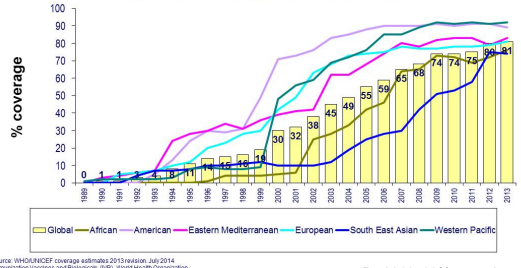
Prof. Henry LY Chan
MBChB, MD, FRCP (Edin, Lond), FAASLD, FHKCP, FHKAM (Med)
Head, Division of Gastroenterology and Hepatology
Director, Institute of Digestive Disease
Director, Center for Liver Health
Assistant Dean, Faculty of Medicine
The Chinese University of Hong Kong
香港中文大學醫學院
Faculty of Medicine
The Chinese University of Hong Kong



Trepo, Chan and Lok. Lancet 2014;384:2053-63

Prevalence	High (>7%)	Intermediate (2%-7%)	Low (<2%)
Transmission	Perinatal Percutaneous	Percutaneous Sexual	Sexual Percutaneous
Age of infection	Perinatal & early childhood	Early childhood	Adult

Global Immunization 1989-2013, 3rd dose of Hepatitis B coverage in infants global coverage at 81% in 2013

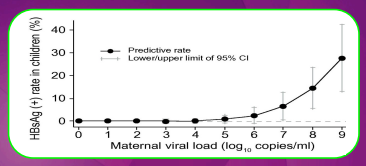


Source: WHO/UNICEF coverage estimates 2013 revision, July 2014
Immunization Vaccines and Biologicals, (IVB), World Health Organization.
194 WHO Member States. Date of slide: 29 July 2014.

World Health Organization

By 2013, 99% countries has universal vaccination programme

HBV vaccine cannot protect all babies from high viral load carrier mothers

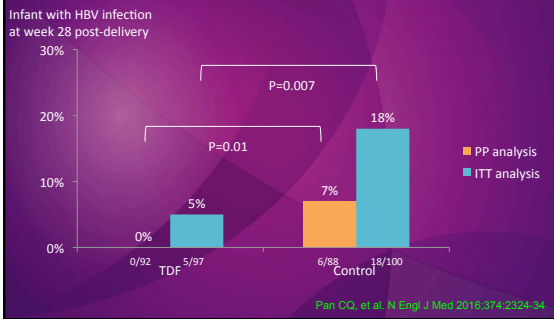


HBV DNA (log cp/ml)	Adjusted odds ratio	P value
5	0.9%	0.334
6	2.6%	0.165
7	6.6%	0.033
8	14.6%	0.001
9	27.7%	<0.001

- 10 of 303 babies borne to HBV carrier mothers had HBV infection despite HBV vaccination
- All mothers of infected babies had positive HBeAg
- All infected babies had 3 doses vaccine with HBIG at birth

Wen WH, et al. J Hepatol 2013;59:24-30

Randomized controlled trial of TDF at week 30-32 for mothers with HBV DNA >200,000 IU/ml



Pan CQ, et al. N Engl J Med 2016;374:2324-34

Post-partum ALT flare

ALT increase post-partum (ULN = 40 U/L)	TDF (N=97)	Control (N=100)	P
ALT 1.1-5x ULN	56%	32%	0.001
ALT 5.1-10x ULN	5%	6%	NS
ALT >10x ULN	1%	3%	NS
Any time during trial	62%	41%	0.004
BL to post-partum wk 4	16%	22%	NS
Post-partum wk 5-28	46%	30%	0.03

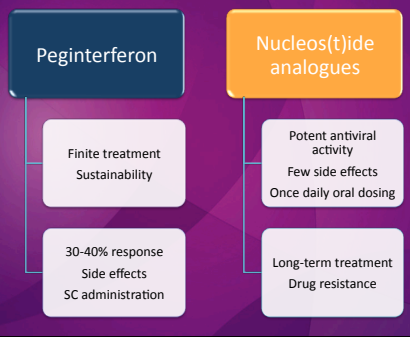
Pan CQ, et al. N Engl J Med 2016;374:2324-34

Uncertainty in stopping antiviral treatment in pregnant women on antiviral treatment

AASLD 2016	EASL 2012	APASL 2016
Antiviral therapy was discontinued at birth to 3 months postpartum in most of the studies. With discontinuation of treatment, women should be monitored for ALT flares every 3 months for 6 months. (C1)	May be discontinued within the first 3 months after delivery Close monitoring is necessary as there is a risk of hepatic flare, especially after delivery (B1)	The NAs could be stopped at birth and when breastfeeding starts, if there is no contraindication to stopping NAs (B2)

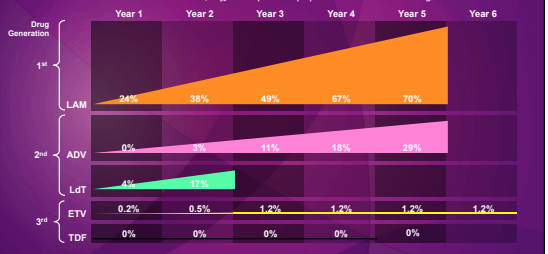
Terrault N, et al. Hepatology 2016;63:261-83
EASL. J Hepatol 2012;57:167-85;
Sarin S, et al. Hepatol Int 2016;10:1-98

Current Landscape of HBV Treatment



Entecavir and Tenofovir are the first line NA treatment for CHB

Not head-to-head trials; different patient populations and trial designs



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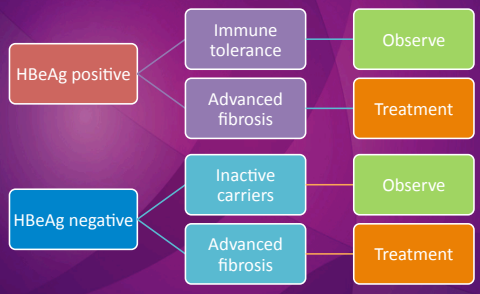
Adapted from 1. EASL. J Hepatol 2009;50:227-42. 2. Tenney DJ, *et al. EASL* 2009. Oral presentation #20. 3. Marcellin P, *et al.* Hepatology 2009;50(4, Suppl.):532A-3A. 4. Heathcote EJ, *et al.* Hepatology 2009;50(4, Suppl.):533A-4A. 5. Marcellin P, *et al. Lancet* 2013;381:468-75.

Key indications of liver fibrosis assessment in patients with normal or mildly elevated ALT



Chan HLY, et al. Antivir Ther 2009;14:489-99

Histology series in Asian-Americans with positive HBeAg, normal ALT (AASLD criteria) and high HBV DNA (mean 7.7 logs copies/ml)

e+

27 patients
Age 37±12 years

Nguyen MH, et al. Am J Gastroenterol 2009;104:2206-13

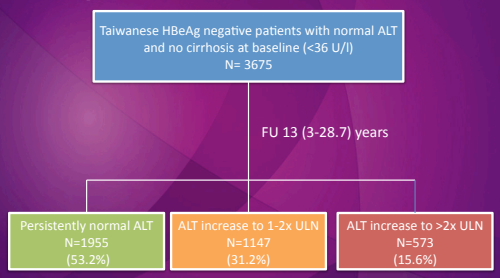
Liver biopsy considered to detect advanced liver fibrosis for antiviral therapy in HBeAg positive patients

e+

AASLD 2009/2016	APASL 2016	EASL 2012
ALT 1-2x ULN Age > 40 HBV DNA > 6 logs IU/ml	ALT 1-2x ULN Age > 35 FH of HCC/cirrhosis	ALT normal Age > 30 FH of HCC/cirrhosis

Terrault N, et al. Hepatology 2016;63:261-83;
Lok ASF and McMahon BJ. Hepatology 2009
Sarin S, et al. Hepatol Int 2016;10:1-98
EASL. J Hepatol 2012;57:167-85

Significant proportion of HBeAg-negative patient with normal ALT develops ALT elevation on FU

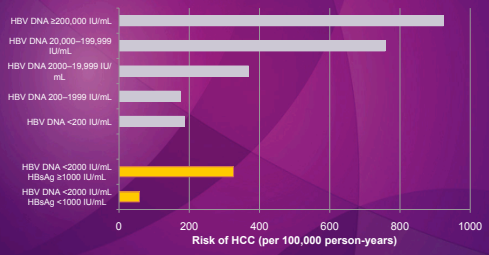


Tai DI, et al. Hepatology 2009;49:1859-67

HBsAg <1000 IU/ml and HBV DNA <2000 IU/ml : Very low risk of HCC

ERADICATE-B Study

2,688 Taiwanese chronic hepatitis B patients followed for a mean of 14.7 years



Tseng et al. Gastroenterology 2012; Chan HL. Gastroenterology 2012

Liver biopsy considered to detect advanced liver fibrosis for antiviral therapy in HBeAg negative patients

AASLD 2009/2016	APASL 2016	EASL 2012
ALT 1-2x ULN HBV DNA >2000 IU/ml	ALT 1-2x ULN Age > 35 FH of HCC/cirrhosis	ALT > 1x ULN HBV DNA > 2000 IU/ml

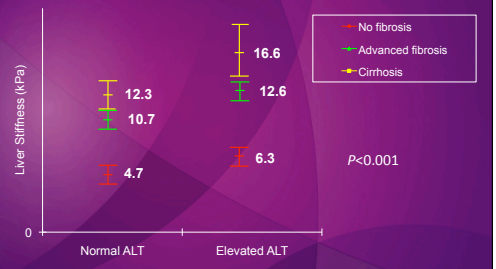
Terrault N, et al. Hepatology 2016;63:261-83;
Lok ASF and McMahon BJ. Hepatology 2009
Sarin S, et al. Hepatol Int 2016;10:1-98
EASL. J Hepatol 2012;57:167-85

Indication of non-invasive measurement of liver fibrosis in CHB

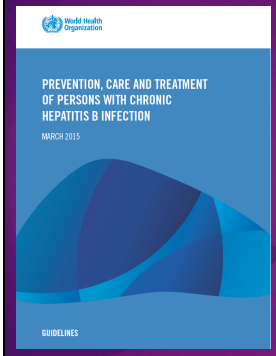
- Transient elastography has better prediction for advanced liver fibrosis and cirrhosis than serum biomarkers in chronic hepatitis B (**B1**).
- Transient elastography can be used to exclude severe fibrosis-cirrhosis in inactive carriers (HBeAg negative, low viral load (HBV DNA <2000 IU/ml) and normal ALT). Liver biopsy should only be considered in doubtful cases after transient elastography (**A1**).

EASL. J Hepatol 2015;63:237-64

Liver stiffness is least affected if serum ALT is normal



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

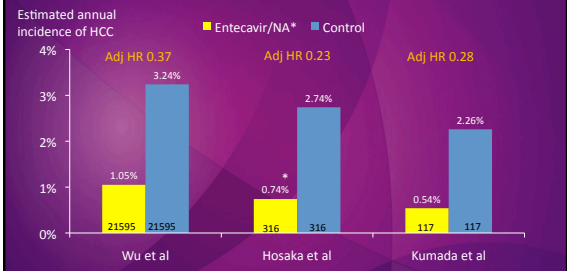


APRI as the preferred non-invasive test to assess cirrhosis (APRI >2) in resource limited settings

Fibroscan or Fibrotest as preferred non-invasive test in settings where they are available and cost is not a major constraint

(conditional recommendation; low quality of evidence)

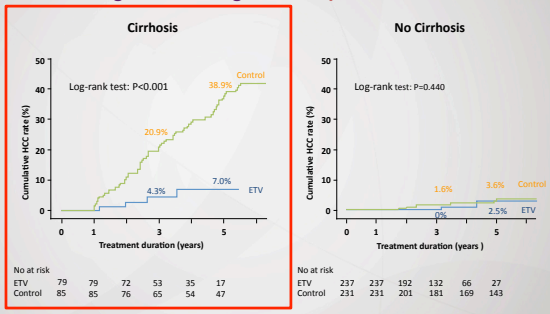
Estimated annual incidence of HCC in patients based on 5 year FU



Propensity score matched

Wu CY, et al. Gastroenterology 2014;147:143-51;
Hosaka T, et al. Hepatology 2013;58:98-107;
Kumada T, et al. J Hepatol 2013;58:427-33.

Toranomon Hospital cohort: reduction in HCC incidence with ETV greater among cirrhotic patients



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

Annual risk of HCC in cirrhotic patients Asian vs Caucasian

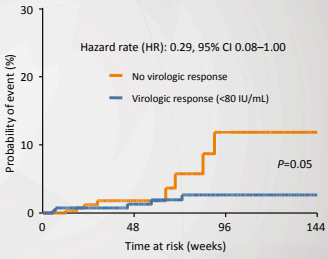
Papatheodoridis G, Chan HL, et al. J Hepatol 2015;62:956-67

VIRGIL ETV study
Virologic response is associated with a lower probability of disease progression

Retrospective cohort study in 10 large European centers
Study population (N=372)

Median follow-up 20 (3–51) months

98 patients have liver cirrhosis



*** Composite endpoint: Hepatic decompensation, jaundice, variceal bleeding, ascites or encephalopathy, HCC, death.**

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Zoutendijk R, et al. Gut 2013;62:760-5

Virologic remission is an independent factors preventing HCC development in cirrhotic patients under ETV treatment

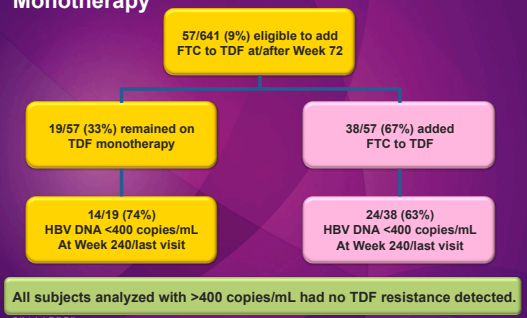
1531 CHB patients (69% treatment naïve) on ETV for 42±13 months
332 (22%) had liver cirrhosis

Cirrhotic patients	Adjusted HR	95% CI	P value
Albumin <35 g/L	7.1	1.8-28.7	0.02
Total bilirubin ≥18 umol/l	5.9	0.5-59.5	0.48
Duration of virologic remission ≥24 months	0.3	0.2-0.7	0.003

Adjusted for age, gender, albumin, bilirubin, ALT, HBeAg, baseline HBV DNA and HBsAg

Wong GL, et al. Gastroenterology 2013;144:933-44

Studies 102/103: Adding FTC does not improve viral suppression vs Maintaining TDF Monotherapy



All subjects analyzed with >400 copies/mL had no TDF resistance detected.

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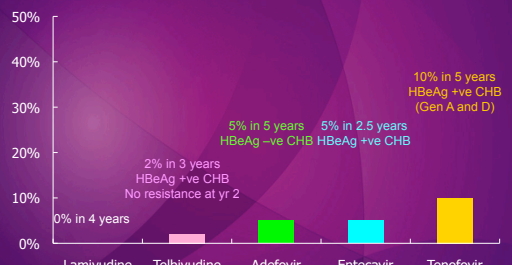
Marcellin P, et al. AASLD 2011. Oral 238.

Stopping rules with NUCs for HBV therapy

CHB Treatment Guidelines	AASLD (Jan 2016)	EASL (April 2012)	APASL (Jan 2016)
HBeAg+ve	HBeAg seroconversion + undetectable DNA + normal ALT for ≥12 months	HBeAg seroconversion with 12 months of consolidation	HBeAg seroconversion + undetectable DNA + normal ALT for ≥12 months, preferably 3 years
HBeAg-ve	(HBsAg clearance)	(HBsAg clearance)	HBsAg clearance for 12 months OR Treatment for at least 2 years + DNA undetectable 3 times 6 months apart

Terrault N. et al. Hepatology 2016. [Epub ahead of print]; EASL. J Hepatol 2012;57:167-85; Sarin S. et al. Hepatol Int. 2016;10:1-98.

HBsAg clearance is the ideal treatment endpoint for NA, but it is difficult to achieve



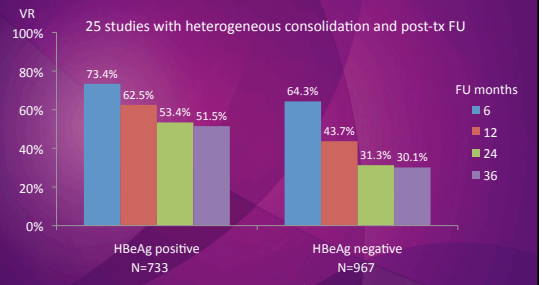
Chang et al., JGH 2004; Hsu et al., APASL 2009; Hadziyannis et al., Gastroenterol 2006; Han et al., AASLD 2008; Marcellin et al., Lancet 2013

Estimation to HBsAg loss by qHBsAg kinetics

	Chevaliez S et al	Chan HL et al	Li et al.
Patients	Active disease, mixed wild type and drug resistant mutants	Immune tolerance, treatment naive	Active disease, responders to NA
N	18	126	102
Asians	20%	89%	100%
HBeAg positive	22%	99%	76%
Antiviral therapy	Various	TDF or TDF+FTC	ETV or ADV
Estimated time to HBsAg loss	52 years	26-33 years	25-30 years

Chevaliez S, et al. J Hepatol 2013;58:676-873
Chan HL, et al. Gastroenterology 2014;146:1240-8
Li MR, et al. PLOS One 2014;9:e98476

Systemic review on virological response after stopping NA

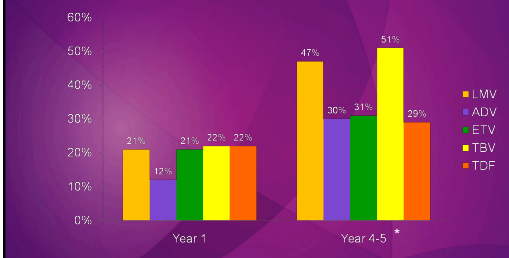


Virological response (VR) = HBV DNA <200 - <20000 IU/ml

Papatheodoridis G, et al. Hepatology 2016;63:1481-92.

On-treatment HBeAg seroconversion by different antiviral drugs is low

e+



*Year 4-5 are not full ITT dataset

Chang et al., J Gastroenterol Hepatol 2004, Marcellin et al, Hepatology 2008
Han et al, AASLD 2008, Wang et al, AASLD 2009, Heathcote AASLD 2010

Very low HBeAg seroconversion rate in immune tolerance patients

e+

HBeAg +ve pts with high HBV DNA and normal ALT (n=126)

1:1 Randomization

- TDF 300 mg (n=64)
- TDF 300mg + FTC 200mg (n=62)

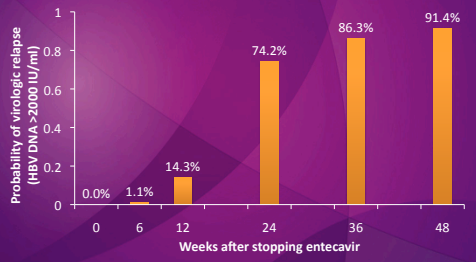
Response = HBV DNA < 69 IU/ml at week 192

	TDF n=64	TDF/FTC n=62	p-value
Primary endpoint			
HBV DNA <69 IU/mL	55%	76%	0.016
Secondary endpoints			
HBeAg loss	6%	2%	0.365
HBeAg seroconversion	5%	0%	0.244
HBsAg loss	0%	0%	

Chan HL, et al. Gastroenterology 2014;146:1240-8

Virologic relapse is common after stopping entecavir in HBeAg-negative patients

184 HBeAg negative CHB patients on ETV on 3.06±0.64 years
Prospectively stopped ETV according to APASL criteria with undetectable HBV DNA >18 months

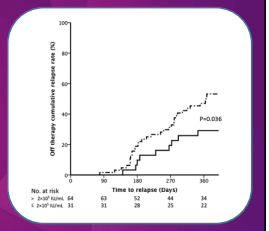


Only 10 patients had HBsAg <100 IU/ml

Seto WK, ... Chan HL. Gut 2015;64:667-72

Clinical relapse (increase of HBV-DNA >2,000 IU/mL and ALT >2 × ULN) after stopping ETV

- 95 HBeAg-negative patients treated with ETV after cessation of ETV therapy by the stopping rule of APASL
- The median duration of consolidation therapy was 448 (345-1,678) days.
- The cumulative off-therapy clinical relapse rate was 45.3% in 1 year with a median duration to relapse of 230 days (79-368 days).



HBV DNA ≤20000 IU/ml at baseline is associated with fewer clinicial relapse

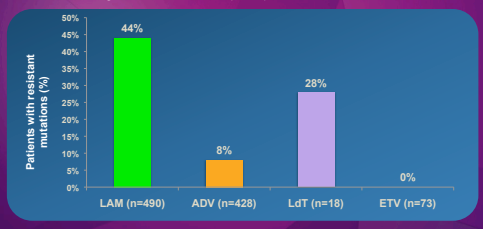
Jeng W.J. et al. Hepatology 2013

Reimbursement policies differ across Asia-Pacific countries

Low reimbursement	Partial reimbursement	High reimbursement
Lamivudine is most commonly used	Drug use according to reimbursement policy	Entecavir & Tenofovir are most commonly used
Drug resistance	?	High cost
Thailand, Indonesia, Philippines, Vietnam	Hong Kong, Taiwan, Korea, China	Japan, Singapore, Australia, New Zealand

The increasing problem of HBV drug resistance in Asia

- 1803 nucleos(t)ide analogue-experienced (NUC) Chinese patients with CHB monitored for genotypic resistance
- 1009 patients receiving NUC monotherapy
  - Classic drug mutations found in 254 (25.2%)

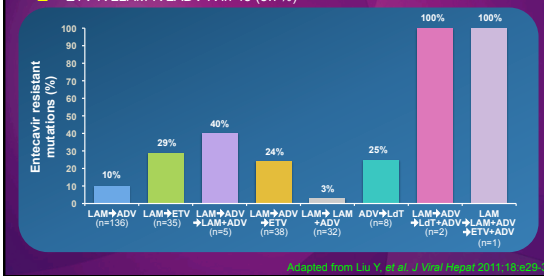


Adapted from Liu Y, *et al. J Viral Hepat* 2011;18:e29-39.

The increasing problem of HBV drug resistance in Asia

794 patients receiving sequential/combination NUCs

- Diverse drug mutations found in 306 (38.5%)
- ETV-R ±LAM-R ±ADV-R in 45 (5.7%)



Adapted from Liu Y, *et al. J Viral Hepat* 2011;18:e29-39.

Challenges of HBV in Asia

- Incomplete vaccination coverage in Southeast Asia
- Incomplete protection by vaccination to high viraemic mothers
- Antiviral prophylaxis for carrier mothers
- Availability of non-invasive assessment of liver fibrosis
- Risk of HCC despite antiviral therapy, especially in cirrhotic patients
- Management incomplete responders to NA
- Relapse after stopping antiviral therapy
- Drug resistance in low reimbursement areas