Current Status of CHRONIC HEPATITIS B in Thailand

Epidemiology, Prevention, Treatment, and Challenges

NCGM
National Center for Global Health and Medicine

Chula
Chulalongkorn University

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OUTline of the PRESENTATION

Current Status of CHRONIC HEPATITIS B in Thailand
Epidemiology, Treatment, and Challenges

- √ Epidemiology of HBV and HCC in Thailand
- √ Prevention & Treatment of chronic HBV infection
- √ Unmet needs for HBV elimination
- √ Summary and Perspective

QA

1

Current Status

Epidemiology

HEPATITIS B VIRUS

HEPATOCELLULAR CARCINOMA in THAILAND

Liver Cancers in Thailand

Thailand
Source: Globocan 2020

GLOBAL CANCER OBSERVATORY

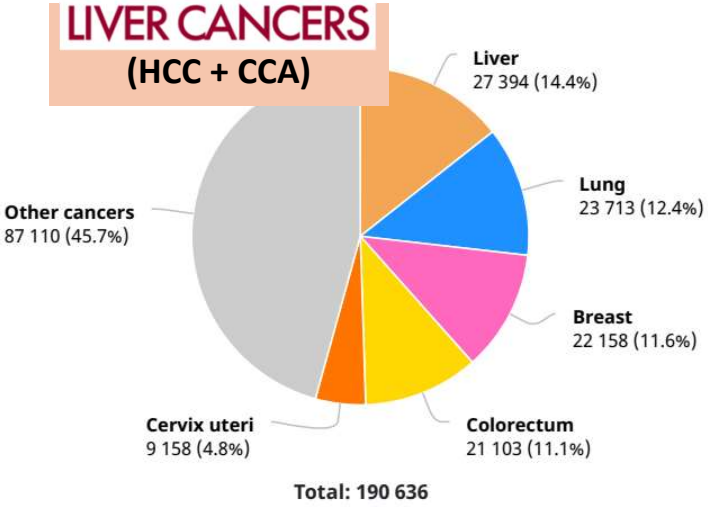
Numbers at a glance

Total population
69 799 978

Number of new cases
190 636

Number of deaths
124 866

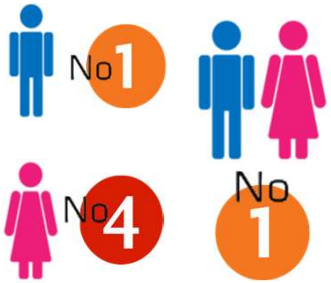
Number of prevalent cases (5-year)
426 366



Number of new cases in 2020, both sexes, all ages

Summary statistic 2020

	Males	Females	Both sexes
Population	33 966 060	35 833 918	69 799 978
Number of new cancer cases	93 425	97 211	190 636
Age-standardized incidence rate (World)	173.1	159.0	164.0
Risk of developing cancer before the age of 75 years (%)	17.2	15.7	16.4
Number of cancer deaths	68 087	56 779	124 866
Age-standardized mortality rate (World)	122.0	83.6	100.5
Risk of dying from cancer before the age of 75 years (%)	12.1	8.6	10.2
5-year prevalent cases	182 412	243 954	426 366
Top 5 most frequent cancers excluding non-melanoma skin cancer (ranked by cases)	Liver Lung Colorectum Prostate Non-Hodgkin lymphoma	Breast Colorectum Cervix uteri Liver Lung	Liver Lung Breast Colorectum Cervix uteri



Etiology and Risk Factors

VIRAL HEPATITIS

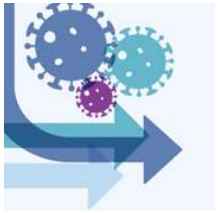
HBV > 60%

HCV

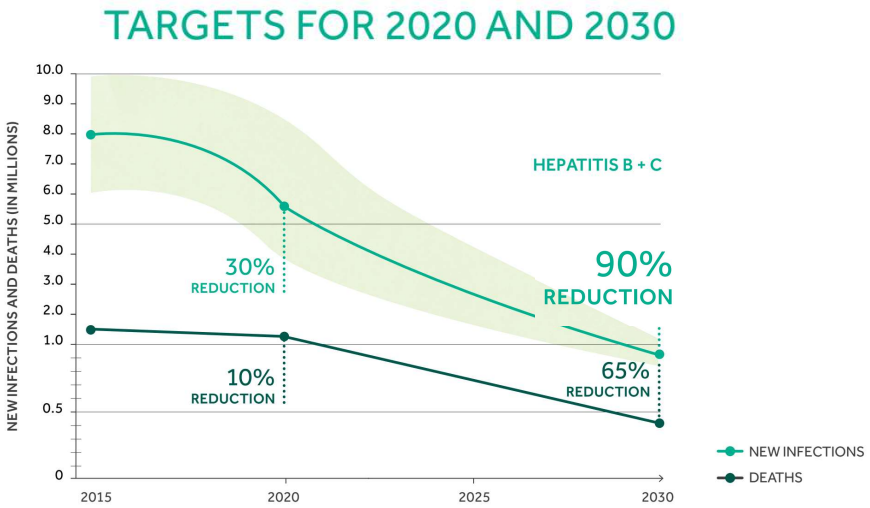
ALCOHOLIC LIVER DISEASE

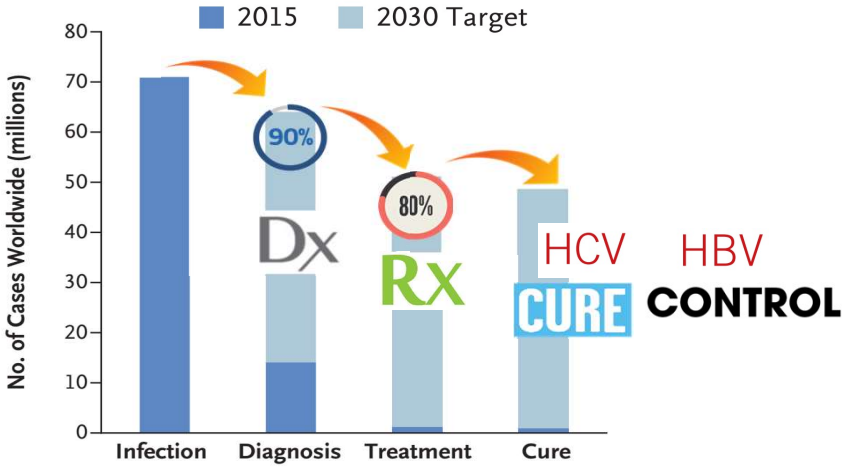
2030 WHO Elimination Targets for Viral Hepatitis

World Health Organization



Goal
Eradication
Elimination of transmission
Elimination as a public health problem





Thomas DL. N Engl J Med 2019

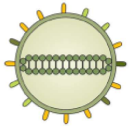
World Health Organization

Hepatitis B Vaccine + HBIG

Prevent MTCT

mother-to-child transmission

≤0.1% HBsAg prevalence in ≤5 year olds



HBV Prevalence in Thailand

Hepatitis B Vaccine

EPI Expanded Program On Immunization

1992

HBsAg Positive

Born before EPI 4.3%

Born after EPI 0.3%

2014

0.1% Prevalence of HBsAg in children ≤5 years of age (2014)

2022 WHO IMPACT TARGET

Thailand has a strong HBV PMTCT programme with coverage surpassing the 2030 global targets.

2022 HBV DIAGNOSIS TREATMENT

Not Adequate

THAILAND

WHO target	Brazil	Egypt	Georgia	Mongolia	Rwanda	Thailand	United Kingdom (England)
Impact targets							
WHO-preferred measurement ≤6 HCV- & HBV-related deaths/100 000 population/year ≤4 HBV-related deaths/100 000 population/year ≤2 HCV-related deaths/100 000 population/year							
Alternative measurements/ available data		NA	NA				NA
Programme targets							
≥90% of persons with chronic HBV infection diagnosed							
≥90% of persons with chronic HCV infection diagnosed							
≥80% of persons with chronic HBV infection treated							
≥80% of persons with chronic							

Measurement system available

Measurement system available with limitation

Measurement system not available

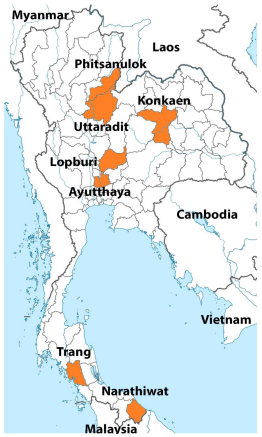
NA=not applicable

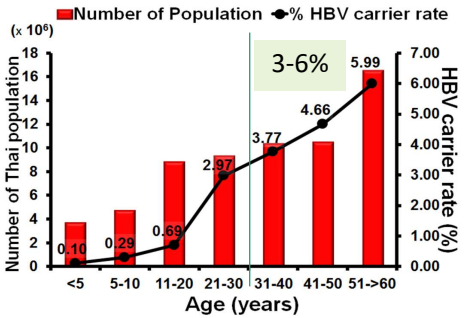
HBV Current Prevalence

THAILAND 2014

HBV = 2.2 million

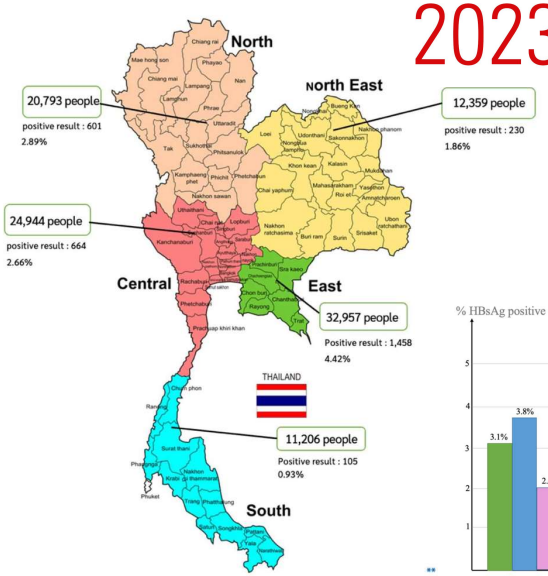
The Success of a Universal Hepatitis B Immunization Program as Part of Thailand's EPI after 22 Years' Implementation





Posuwan N, et al. PLoS ONE 2016

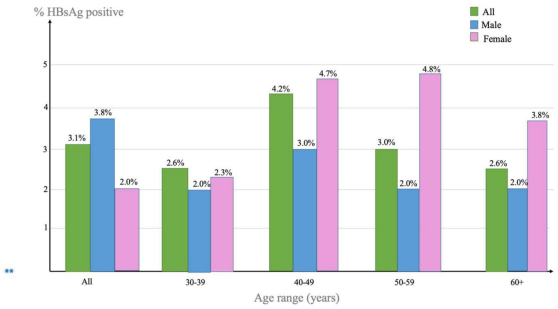
2023



Age 30 YEARS

ตรวจคัดกรองไวรัสตับอักเสบบี 99,259 ราย

HBsAg positive=3.1%



Risk factors assessment of HBV infection

2023 NEW DATA QUESTIONNAIRE

RISK FACTOR

✓ Persons living with HIV and

PWID

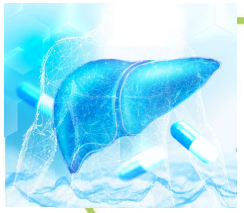
MSM

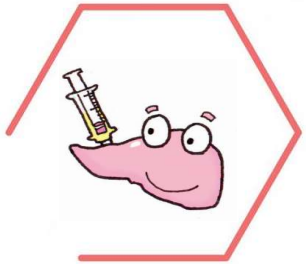
✓ Family

2

Current

STRATEGY





Prevent
MTCT

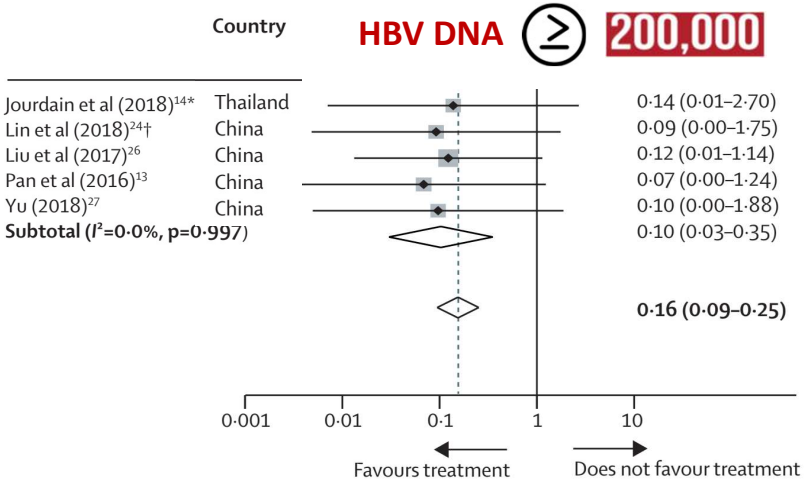
HBV Treatment

PREVENT mother-to-child transmission

BEYOND VACCINATION

TDF tenofovir disoproxil fumarate 300mg Tablet

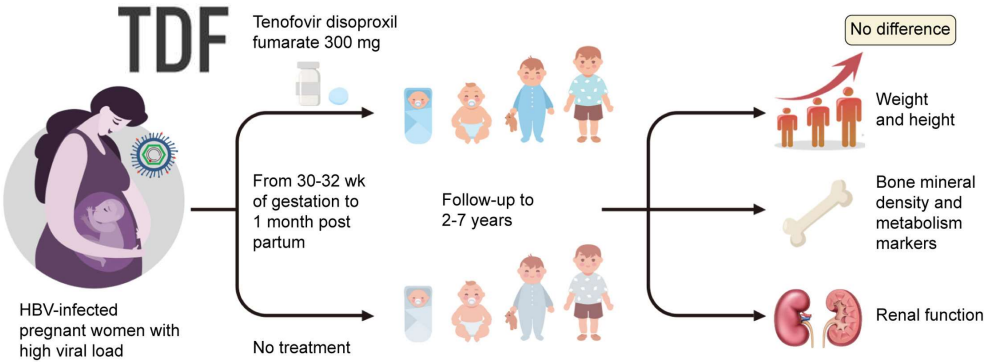
Efficacy and safety of antiviral prophylaxis during pregnancy to prevent mother-to-child transmission of hepatitis B virus: a systematic review and meta-analysis



Interpretation

Peripartum antiviral prophylaxis is highly effective at reducing the risk of HBV MTCT (from 10% to nearly zero)

FunK AL, et al. Lancet Infect Dis 2020



Wen WH, et al. J Hepatol 2020

GUIDELINE

HBsAg Positive

HBeAg Positive

HBV DNA ≥ 200,000

Rx TENOFOVIR (TDF)

Weeks 28-32 pregnancy

↓

Week 4 postpartum

Hepatitis B Vaccine + HBIG → SET ZERO

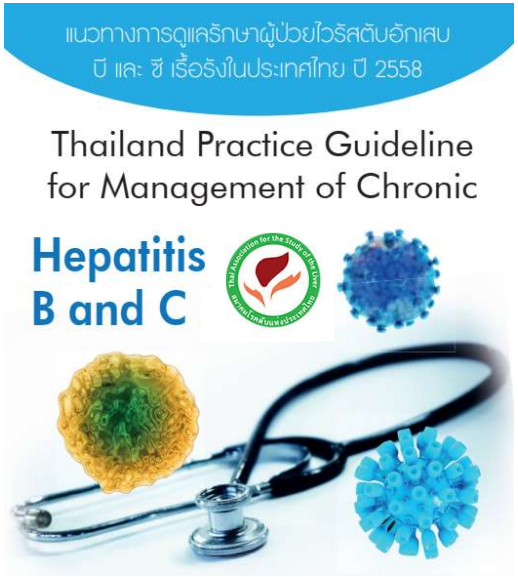
Clinical Guidelines on the treatment of chronic HBV infection

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

EASL
The Home of Hepatology

Asian Pacific Association for the Study of the Liver

NUC
Antiviral Drugs
Suppressive Therapy



International and Thai guidelines recommend initiating antiviral treatment for HBV based on viral replication with inflammation or fibrosis.

The goal of HBV therapy is to improve quality of life and survival by preventing progression to cirrhosis, end-stage liver disease, and HCC

HBV Antiviral Drugs

TAF

tenofovir alafenamide 25mg tablets

FIRSTLINE drug

NLEM บัญชียาหลักแห่งชาติ National List of Essential Medicines 2022

Effective drug

- -High potency
- -Low drug resistance
- -Low side effects

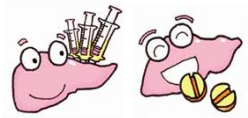
COST SAVINGS

Health Economic Point of VIEW

Dilokthornsakul P, et al. AHEHP 2022

Approved Therapy

Interferon-based therapy
Nucleos(t)ide analogues (NUCs)



2024

- 1991 Interferon-α
- 1998 Lamivudine
- 2002 Adefovir
- 2005 Peg-Interferon-α, Entecavir
- 2006 Telbivudine
- 2008 TDF
- 2016 TAF

Preferred Drugs

- Entecavir
- Tenofovir

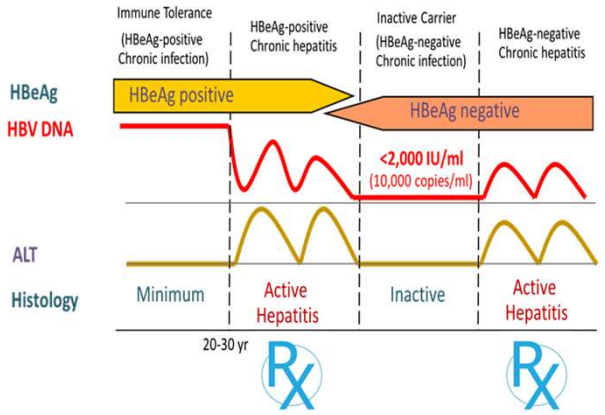
Tenofovir Disoproxil Fumarate (TDF)
Tenofovir Alafenamide (TAF)

The indications for treatment are based on HCC risk

Advanced disease
✓ CIRRHOSIS

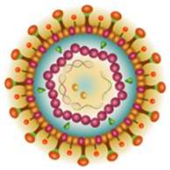
IMMUNE ACTIVE PHASES — Active disease

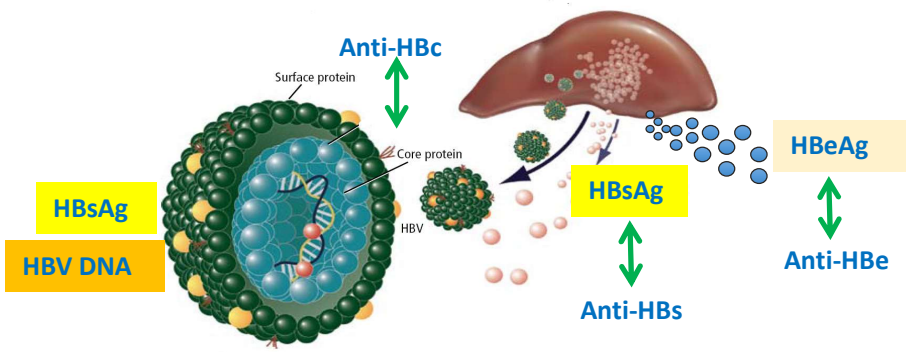
Elevated HBV DNA level
Elevated ALT level



High risk of HCC (e.g., first-degree family of cirrhosis/HCC)

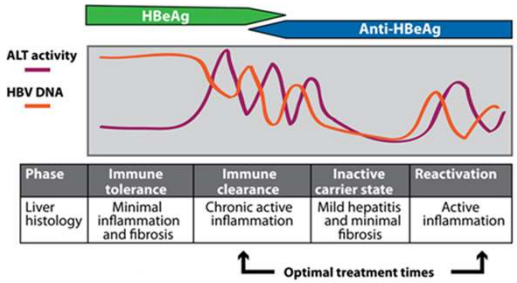
CONVENTIONAL HBV Biomarkers





HBsAg Quantification

Low HBV DNA levels (<2000 IU per milliliter), plus low HBsAg levels (<100 IU per milliliter) and normal serum aminotransferase levels



GOOD PROGNOSIS

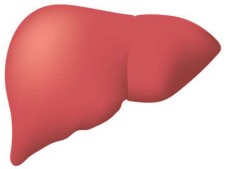
Dusheiko G, et al. NEJM 2023

Inactive Carriers

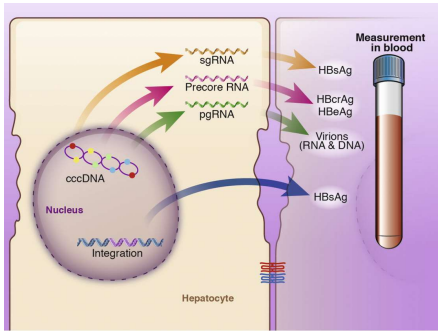
NEW HBV Biomarkers

- Newer non-invasive HBV tests, used only in research settings so far, aim to quantify levels of intrahepatic HBV replication (esp. cccDNA)

Covalently closed circular DNA **cccDNA**



Liver Biopsy

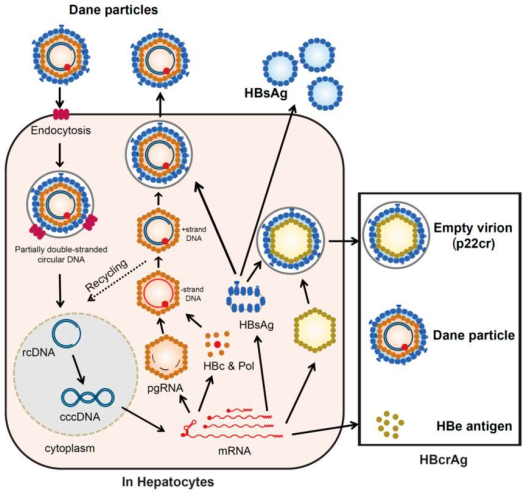


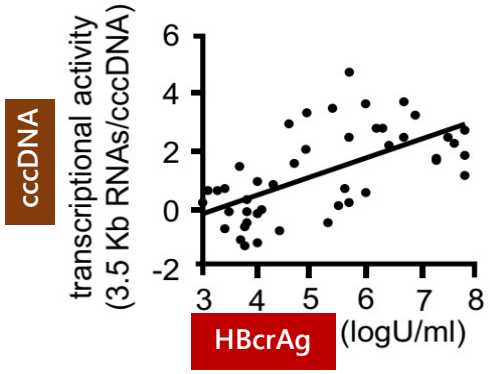
HBcrAg

Serum Hepatitis B core-related antigen (HBcrAg)

HBV RNA Serum HBV RNA (pgRNA)

Serum Hepatitis B core-related antigen (HBcrAg)





predict RX RESPONSE

Pegylated Interferon
Pegylated Interferon alpha -2a

HBeAg Positive

VIRAL HEPATITIS

Serum hepatitis B core-related antigen as a treatment predictor of pegylated interferon in patients with HBeAg-positive chronic hepatitis B

Natthaya Chuaypen[1], Nawarat Posuwan[2], Sunchai Payungporn[1], Yasuhito Tanaka[3], Noboru Shinkai[3], Yong Poovorawan[2] and Pisit Tangkijvanich[1]

1 Research Unit of Hepatitis and Liver Cancer, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand
2 Center of Excellence in Clinical Virology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand
3 Department of Virology and Liver Unit, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan

Liver Int. 2016; 36: 827–836. DOI: 10.1111/liv.13046

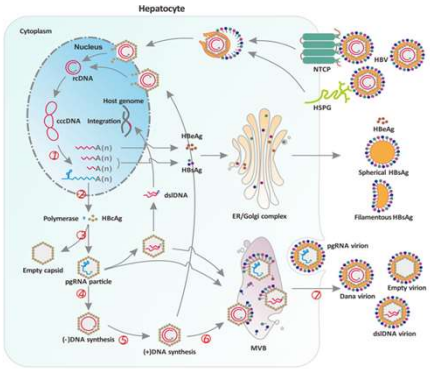
HBeAg Negative

Predictive role of serum HBsAg and HBcrAg kinetics in patients with HBeAg-negative chronic hepatitis B receiving pegylated interferon–based therapy

N. Chuaypen [1], N. Posuwan [2], S. Chittmittraprap [1], N. Hirankarn [3], S. Treeprasertsuk [4], Y. Tanaka [5], N. Shinkai [5], Y. Poovorawan [2], P. Tangkijvanich [1,*]

Clin Microbiol Infect 2018;24:306.e7–306.e13

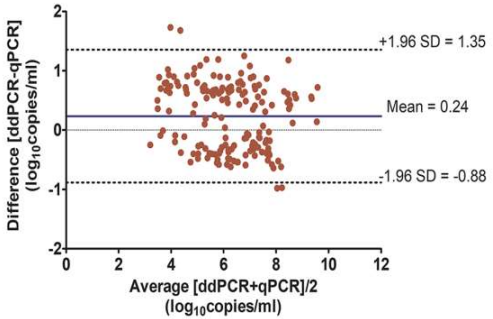
Serum HBV RNA (pgRNA)

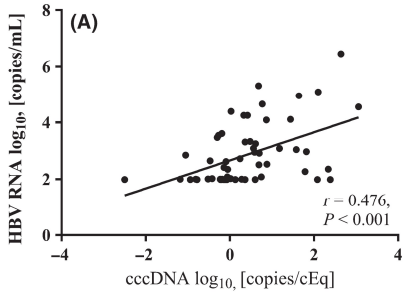


Reverse transcriptase droplet digital PCR vs reverse transcriptase quantitative real-time PCR for serum HBV RNA quantification

Umaporn Limothai[1] | Natthaya Chuaypen[1] | Kittiyod Poovorawan[2] | Watcharasak Chotiyaputta[3] | Tawesak Tanwandee[3] | Yong Poovorawan[4] | Pisit Tangkijvanich[1]

J Med Virol. 2020;92:3365–3372.





predict RX RESPONSE

HBeAg Negative

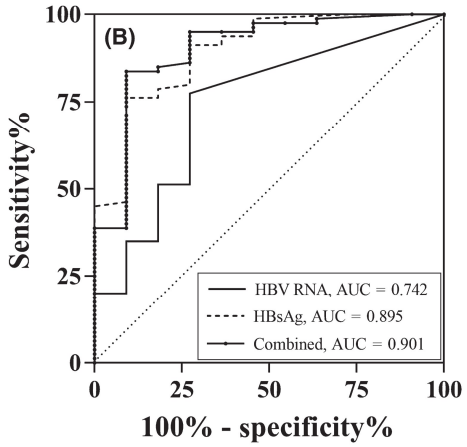
Pegylated Interferon

Pegylated interferon alpha -2a

Baseline and kinetics of serum hepatitis B virus RNA predict response to pegylated interferon-based therapy in patients with hepatitis B e antigen-negative chronic hepatitis B

Umaporn Limothai[1] | Natthaya Chuaypen[1] | Kittiyod Poovorawan[2] | Watcharasak Chotiyaputta[3] | Tawesak Tanwandee[3] | Yong Poovorawan[4] | Pisit Tangkijvanich[1]

J Viral Hepat. 2019;26:1481–1488.



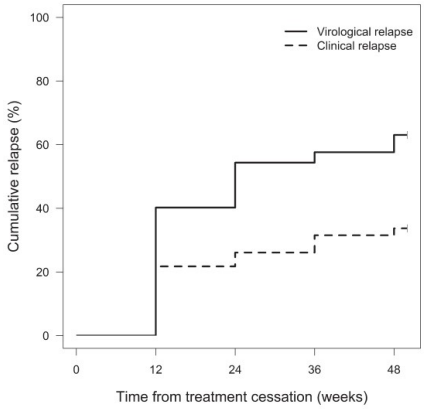
ROC in predicting HBsAg clearance

Hepatitis B surface antigen, core-related antigen and HBV RNA: Predicting clinical relapse after NA therapy discontinuation

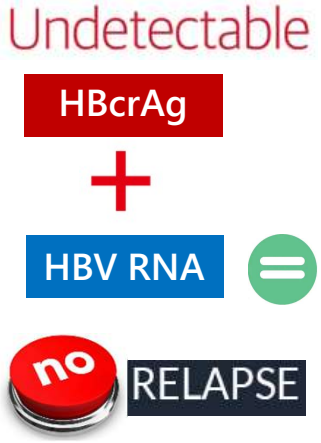
Liver International. 2020

Apichat Kaewdech[1] | Pisit Tangkijvanich[2] | Pimsiri Sripongpun[1] | Teepawit Witeerungrot[3] | Sawangpong Jandee[1] | Yasuhito Tanaka[4] | Teerha Piratvisuth[1,3]

- 92 patients treated with long-term NAs who fulfilled the stopping criteria of the APASL guideline were enrolled.
- Virological relapse was defined as HBV DNA level greater than 2000 IU/mL, and clinical relapse was defined as virological relapse plus ALT > 2 ULN



Characteristics	Clinical relapse (n = 31)	No clinical relapse (n = 61)	*P* value
Age, years	58.0 (52.0-63.5)	54.0 (49.0-62.0)	.264
Male gender, n (%)	23.0 (74.2)	36.0 (59.0)	.228
End-of-treatment levels			
HBV DNA, IU/mL	<20.0	<20.0	Not applicable
qHBsAg, $\log_{10}$ IU/mL	3.14 (2.76-3.57)	2.82 (2.30-3.41)	.089
HBcrAg, $\log_{10}$ U/mL	3.70 (3.20-4.40)	3.00 (<3.00-3.40)	<.001
HBV RNA, $\log_{10}$ copies/mL	2.55 (<2.00-3.24)	2.00 (<2.00-2.66)	.012



- Multivariate analysis revealed that EOT HBcrAg and HBV RNA were independently associated with clinical relapse.
- During follow-up, no patients with undetectable HBcrAg (<3.0 $\log_{10}$ U/mL) and HBV RNA (<2.0 $\log_{10}$ copies/mL) at EOT developed clinical relapse, in comparison with 22.9% and 62.5% patients with detectable levels of one or both biomarkers respectively

Conclusions: The combined EOT HBcrAg and HBV RNA were highly predictive of subsequent clinical relapse

Clinical efficacy of a novel, high-sensitivity HBcrAg assay in the management of chronic hepatitis B and HBV reactivation

Takako Inoue[1], Shigeru Kusumoto[2], Etsuko Iio[3], Shintaro Ogawa[3], Takanori Suzuki[4], Shintaro Yagi[5], Atsushi Kaneko[6], Kentaro Matsuura[4], Katsumi Aoyagi[5,6], Yasuhito Tanaka[1,3,7,*]

Journal of Hepatology **2021** vol. 75 | 302–310

Assay	Pretreatment process: Procedure	Main denaturants	Incubation	TAT (include pretreatment)	LOQ
G-HBcrAg	Manual	Detergents	60°C for 30 min	>60 min	2.8 Log U/ml*
iTACT -HBcrAg	Automatic (on-board)	Acid, detergents, reducing agent	37°C for 6.5 min	35 min	2.1 Log U/ml

*LOQ used in this study

HBsAg-HQ
LLOQ is 0.005 IU/mL,

Role of iTACT-HBcrAg and HBsAg-HQ for predicting treatment outcome in HCC patients with occult HBV infection (OBI)

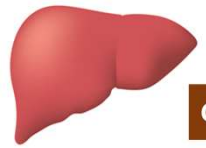
OnGoing Project

OBJECTIVES

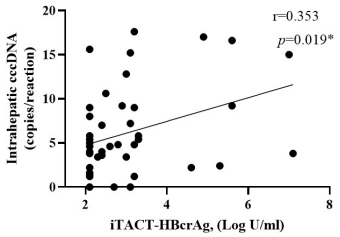
1. To examine the clinical utility of serum iTACT-HBcrAg and HBsAg-HQ as surrogate markers of cccDNA.
2. To assess whether serum iTACT-HBcrAg/HBsAg-HQ could predict the prognosis of HCC patients with OBI undergoing HCC treatment.

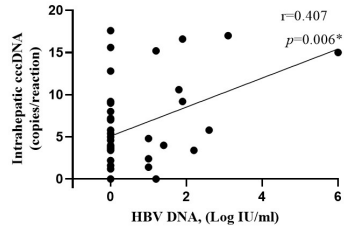
PRELIMINARY results

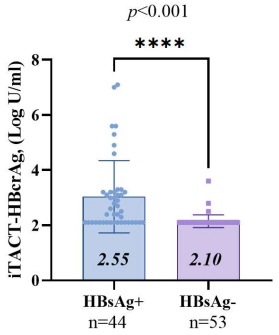
1 Surgery

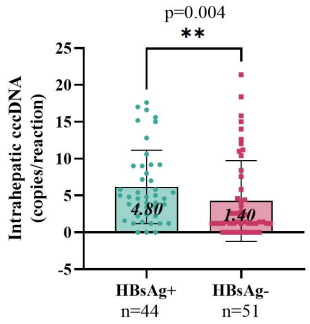


cccDNA

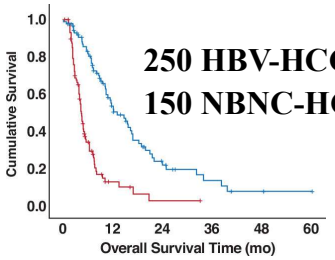








2 iTACT-HBcrAg HBsAg-HQ Predict PROGNOSIS



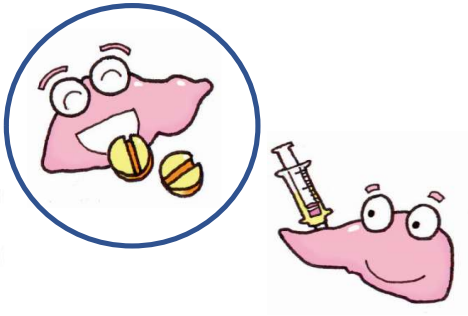
250 HBV-HCC
150 NBNC-HCC

ONGOING ANALYSIS

Unmet Needs

1

HBV Treatment



A finite-duration antiviral therapy with NUCs is not clear

STOP ?

LONG-TERM TREATMENT

HBV Antiviral Drugs

NUC nucleoside or nucleotide analogues

LONG-TERM TREATMENT

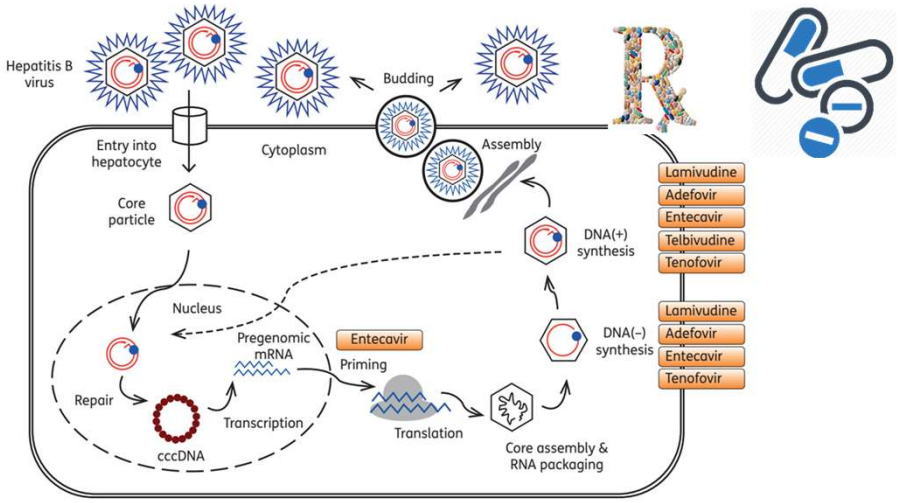
Suppressive Therapy

HBV Cure Uncommon

-10%

Benefit	Limitations
Long-term suppression of HBV DNA	1. No direct effect of NA on cccDNA 2. High relapse after NA discontinuation
Fibrosis regression and cirrhosis reversal	Low rate of HBsAg loss/seroconversion (functional cure)
Reduced risk of HCC and complication of cirrhosis	Long term therapy 1. Risk of HCC remains 2. Resistance issue 3. Safety concern

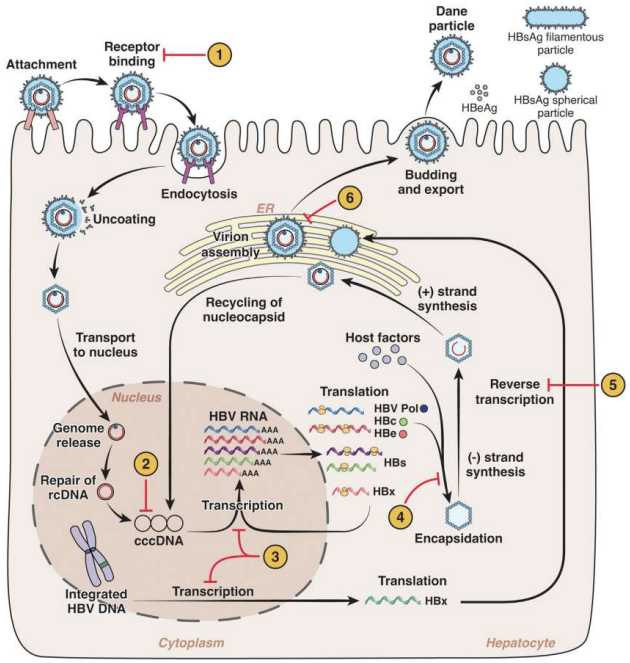
Lin CL, et al. Aliment Pharmacol Ther 2016



cccDNA=covalently closed circular DNA

HEPATITIS B Future Therapy

DAA DIRECT ACTING ANTIVIRALS (DAA)



Yardeni D, et al. Gastroenterology 2023

(1) Targeting viral entry
(2) targeting cccDNA via elimination or silencing
(3) targeting viral transcription
(4) targeting the HBV core (HBc) protein
(5) targeting the HBV polymerase (HB Pol)
(6) targeting HBsAg secretion

(3) Small interfering RNA (siRNA)

(4) **capsid assembly modulator**

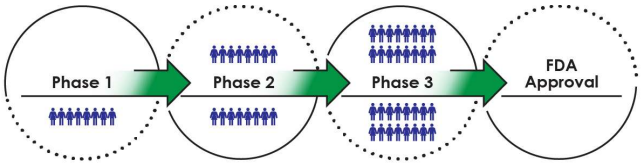
HTA HOST TARGETING AGENTS (HTA)

Targeting cell intrinsic and innate immune responses			
RO7020531	TLR7 agonist	Oral	I
Vesatolimod, GS-9620	TLR7 agonist	Oral	II
Selgantolimod, GS-9688	TLR8 agonist	Oral	I
AIC649	TLR9 agonist	Oral	I
Targeting adaptive immune responses			
Checkpoint inhibitors			
Nivolumab	Anti-PD1	Intravenous infusion	I
Cemiplimab, REGN2810	Anti-PD1	Intravenous infusion	I/II
Therapeutic vaccines			
TG1050/T101	Non-replicative adenovirus serotype 5 encoding three HBV proteins	Subcutaneous injection	I
ChAdOx1 HBV	Adjuvanted ChAd and MVA vectored	Intramuscular injection	I
HepTcell	HBV peptide therapeutic vaccine with TLR9 adjuvant IC31	Intramuscular injection	I
JNJ-64300535	Electroporation of DNA vaccine	Electroporation-mediated intramuscular injection	I
INO-1800	DNA plasmids encoding HBsAg and HBcAg plus INO-9112 (DNA plasmid encoding human interleukin 12)	Electroporation-mediated intramuscular injection	I

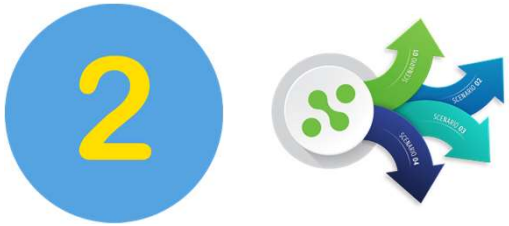
The future of the HBV cure possibly depends on **combination therapies** such as (1) replication inhibition, (2) antigen reduction, and (3) immune stimulation

Lim SG, et al. Nat Rev GH 2023

PHASES of a CLINICAL TRIAL



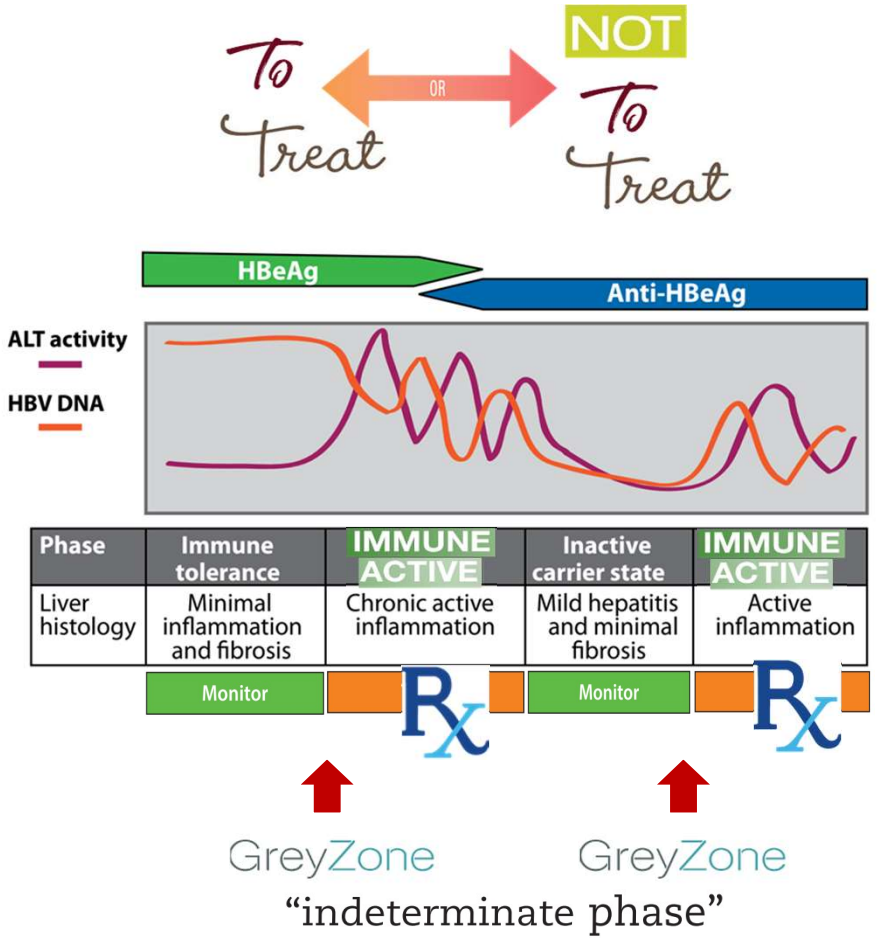
Unmet Needs



- HCV or HIV guidelines have promoted the early treatment of all infected patients regardless of disease severity

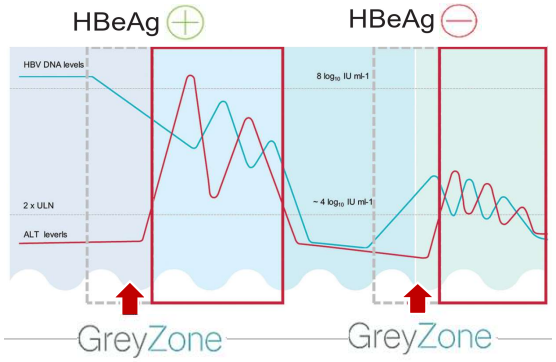
- In contrast, current international HBV guidelines recommend antiviral treatment in subsets of patients based on liver severity, serum HBV DNA, and ALT levels

Rx IMMUNE ACTIVE PHASES



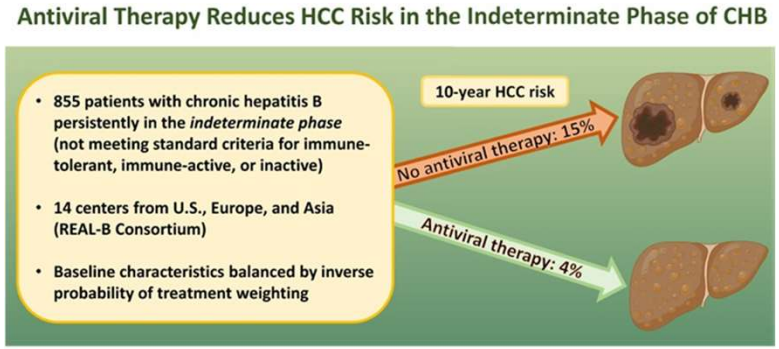
Patients in the gray zone with significant HBV DNA (>2000 IU/mL), regardless of ALT levels, still have a significantly high risk of liver inflammation and fibrosis.

HBV & HCC RISK



℞

"indeterminate phase"



Huang and Tran, et al. *Hepatology.* 2023 HEPATOLOGY

Conclusion:

- Antiviral therapy reduces HCC risk by 70% in the indeterminate phase
- These data have important implications for the potential expansion of CHB treatment criteria

CLOSETHEGAP

World Health Organization 2024

WHO announces the update of hepatitis B guidelines on testing and treatment

Expanding antiviral therapy indications

SCALE UP + Simplified Guideline

Effective drugs

TAF tenofovir alafenamide 25mg tablets

Diagnostic Tests

Point-of-Care Testing POCT

New recommendations

Expanding antiviral therapy indications

Who to treat among people with CHB

Treatment is recommended for all adults and adolescents (aged ≥12 years) with chronic hepatitis B (CHB)[a] (including pregnant women and girls and women of reproductive age) with:

1. Evidence of significant fibrosis (≥F2[b]) based on an APRI score of >0.5 or transient elastography value of >7 kPa or evidence of cirrhosis (F4) based on clinical criteria[c] (or an APRI score of >1 or transient elastography value of >12.5 kPa[b]), regardless of HBV DNA or ALT levels.

Evidence of significant fibrosis (≥F2)
regardless of HBV DNA or ALT levels

OR

2. HBV DNA >2000 IU/mL and an ALT level above the upper limit of normal (ULN) (30 U/L for men and boys and 19 U/L for women and girls). For adolescents, this should be based on ALT>ULN on at least two occasions in a 6- to 12-month period.[d]

HBV DNA >2000 IU/mL and an ALT level >ULN

HBV care cascade

Simplified for **GENERAL DOCTORS**

HEPATITIS CLINIC

GP MEDICAL STAFF

CERTIFIED

ONLINE TRAINING PROGRAM

Community Hospitals

NEW PUBLIC HEALTH GUIDELINES

Treatment Eligibility

EXPANDED CRITERIA

Age≥30 years
HBV DNA ≥2000 IU/ml
Any ALT

Health Economic Modeling
Cost-effectiveness

Dilokthornsakul P, et al. VHRI 2024

genpop

AGE+ 30 YEARS

Born before EPI **1992**

HBsAg RAPID TEST

One-time universal screening

REIMBURSEMENT

POSITIVE

HBV

L.F.T.
HBV DNA
US liver
(if indicated)

CIRRHOSIS

Non-Cirrhosis

YES

NO

Follow up!

First-line

TAF

tenofovir alafenamide 25mg tablets

LONG-TERM

CIRRHOSIS

Clinical RISK SCORE (mPAGE-B)

TELECONSULTATION GP → GI

Referral System

HCC surveillance

US + AFP

every six months is recommended

Toward HBV Elimination in Thailand

SUMMARY

1 แนวทางการดำเนินงานการกำจัดการถ่ายทอดโรคไวรัสตับอักเสบ บี จากแม่สู่ลูก GUIDELINE

Immunize against HBV (HBIG & vaccine)

TDF Preventing MOTHER-TO-CHILD TRANSMISSION

2 Screening HBV genpop AGE+ 30 YEARS

Raising awareness & KNOWLEDGE

Source of Infection → Transmission → Susceptible Persons

Treat HBV-infected persons (Control HBV)

3 TAF first line Rx Health Policy REIMBURSEMENT

4 Simply Effective GP

new Treatment Guideline genpop

5 TELECONSULTATION GP → GI

Online! REGISTRATION

PROBLEM SOLUTION

Referral to Treatment

NATIONWIDE HBV DATA

THANK YOU

for YOUR ATTENTION