B型肝炎篩檢與治療的臨床實務

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WHO 希望全球消滅 HBV & HCV（2030）

WHO. Global health sector strategy on viral hepatitis 2016–2021.
Available at: http://apps.who.int/iris/bitstream/10665/246177/1/WHO-HIV-2016.06-eng.pdf?ua=1 (accessed April 2018)

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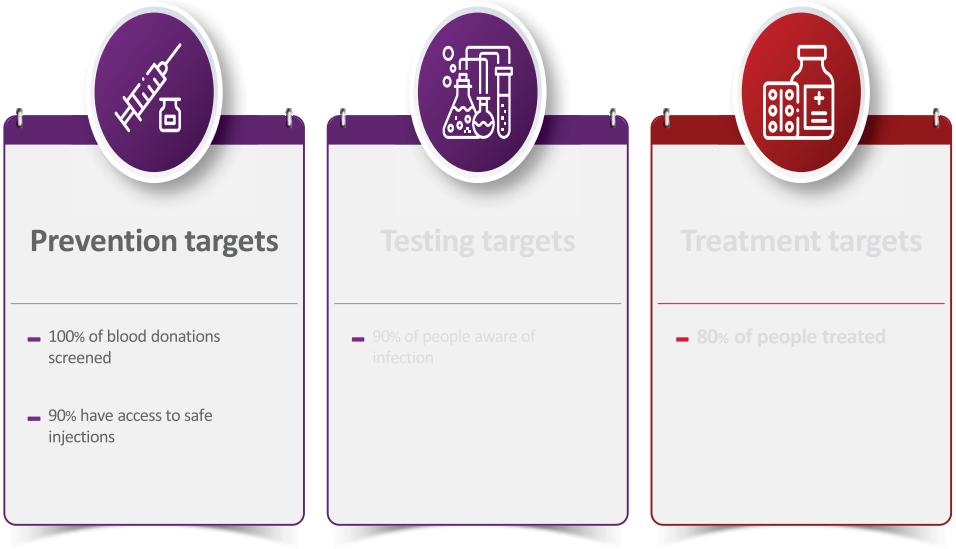
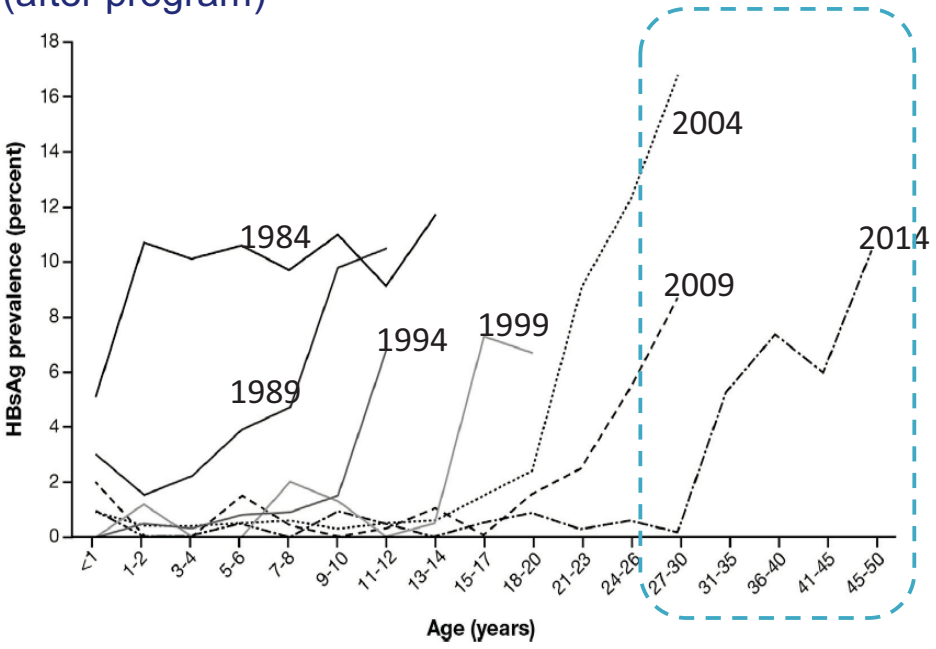


Eliminate viral hepatitis as a public health issue by 2030

WHO. Global health sector strategy on viral hepatitis 2016–2021.
Available at: http://apps.who.int/iris/bitstream/10665/246177/1/WHO-HIV-2016.06-eng.pdf?ua=1 (accessed April 2018)

Taiwan – First Country to Implement Universal Vaccination: Successfully Decrease in HBsAg Prevalence; Elderly Population is Rising Among CHB Patients After 30 Years of Vaccination

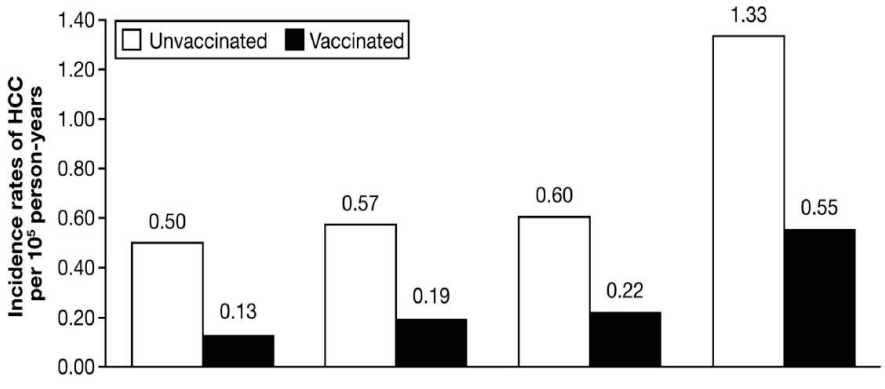
- Vaccination coverage rate is 97.7%
- HBsAg prevalence rate declined from 6.7% (born before program) to 0.5% (after program)



YH Ni et al. Clin Gastroenterol Hepatol. 2016 Sep;14(9):1324-30.

Vaccination Prevents HBV-HCC

Incidence for HCC by age for birth cohorts born before vs. after universal HBV vaccination program



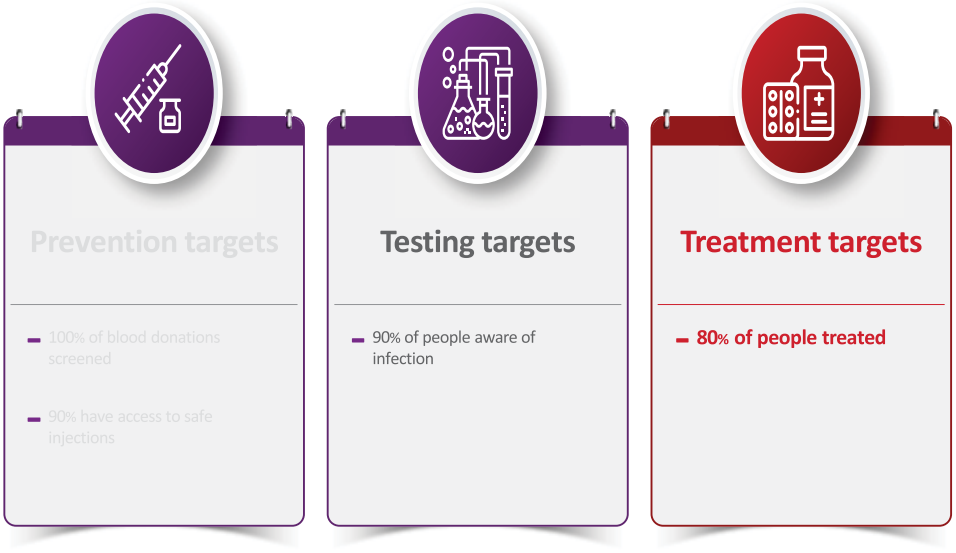
	6-9 yrs	10-14 yrs	15-19 yrs	20-26 yrs
Rate ratio*	0.26 (0.17-0.40)	0.34 (0.25-0.48)	0.37 (0.25-0.51)	0.42 (0.32-0.56)
P-value	<.001	<.001	<.001	<.001

*Rate ratio of vaccinated/unvaccinated birth cohort

* Significant reduction in the incidence of HCC in vaccinated birth cohorts in all age groups between 6 and 26 years old.

Chang et al., NEJM 1997; Chang et al., JAMA 2000; Chang et al., JNCI 2009; Chang et a. Gastroenterology 2016.

WHO 希望全球消滅 HBV & HCV（2030）



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內容

- 國人B型肝炎的篩檢與治療
  - 目前國內外篩檢防治B型肝炎的策略
  - 各種B型肝炎治療的優缺點與限制
  - 停藥後的追蹤與再次治療
- 國內防治慢性病毒性肝炎的成效
  - 減少肝硬化和肝細胞癌
  - 改善存活
- 結論與展望

免費健康檢查

- 成人健康檢查:

(1)年滿六十五歲以上者，每年檢查一次。

(2)年滿四十歲以上，未滿六十五歲者每三年檢查一次。

自2011年起,當年45歲者(1966年(含)以後出生):
終生可免費檢測一次 HBsAg + anti-HCV

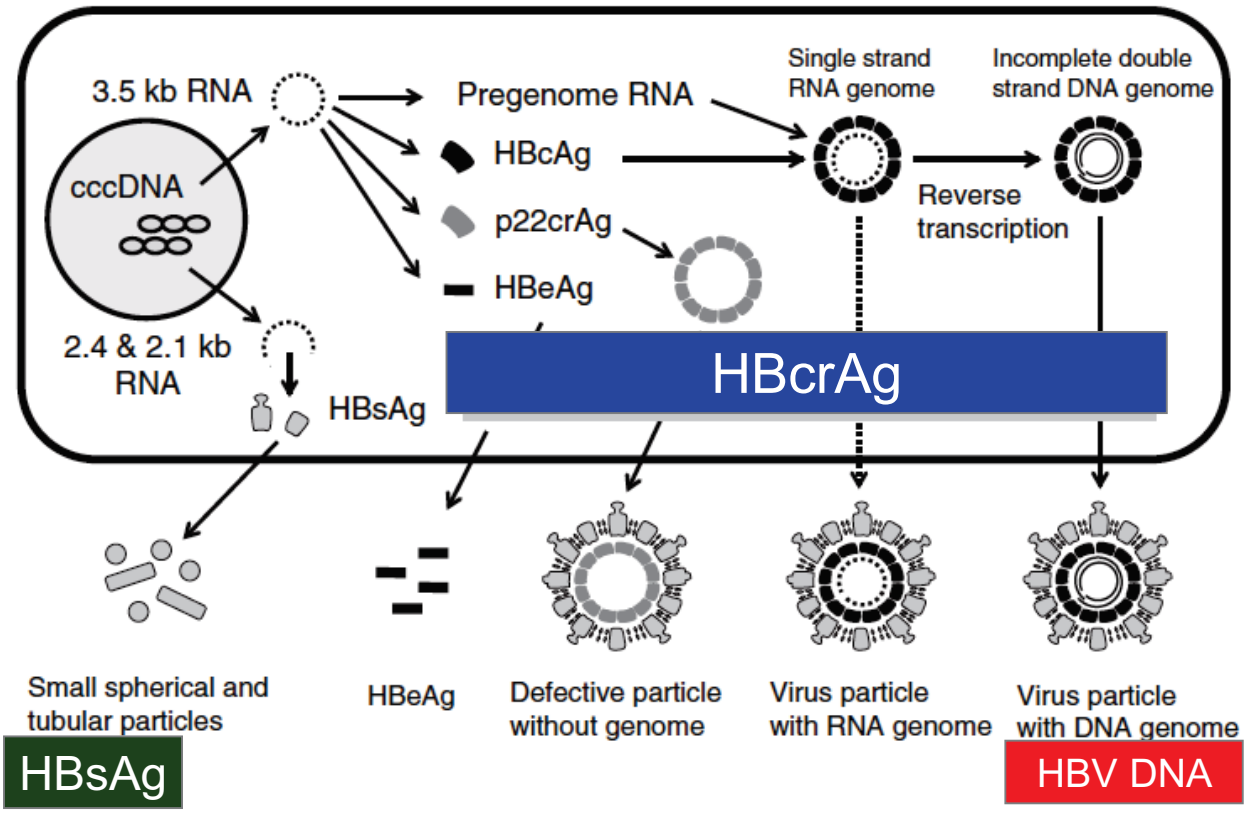
B型肝炎誰需要接受治療?

- 病毒蛋白質(抗原)：血清病毒濃度高
- 反覆發炎與修復：血清ALT異常
- 發炎越久，病程越嚴重：肝臟纖維化較嚴重
- 有機會自我免疫控制改善：觀察3~6個月

病毒量(HBV DNA)

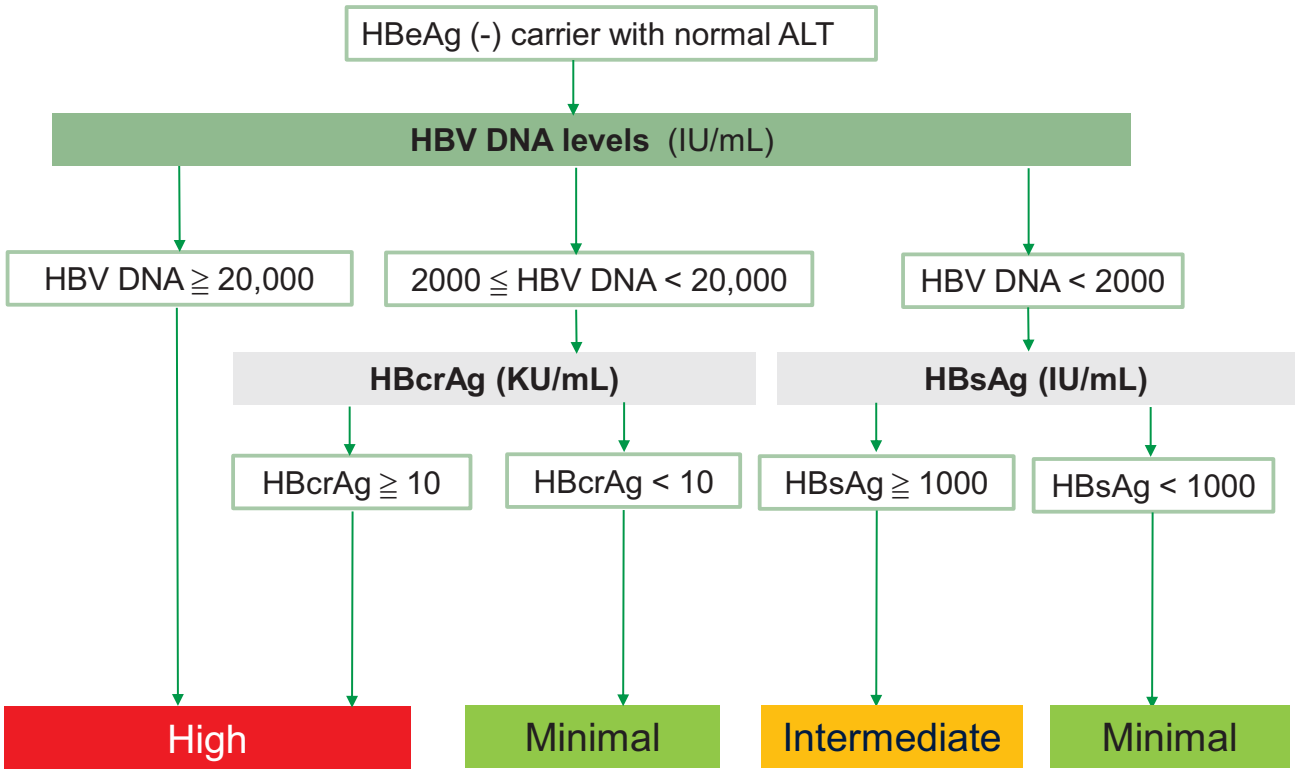
- 直接代表病毒複製的情形
- 隨著感染的時間，會有自然的變化
  - 免疫耐受期、免疫清除期、不活動期、再活化期
- 高病毒量：長期肝硬化、肝癌的風險較高
- 目前高病毒量的定義
  - e抗原陽性： > 20,000 IU/mL
  - e抗原陰性：> 2,000 IU/mL
- 藥物治療的短期目標：病毒量消失

HBV血清生物標誌



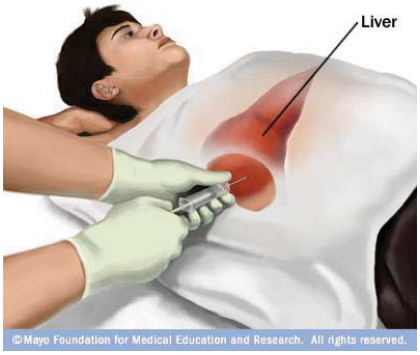
Modified from Tanaka et al. Hepatol Res 2013.

利用血清生物標誌預測預後



Tseng, Liu and Kao et al, Gastroenterology 2012 & 2019

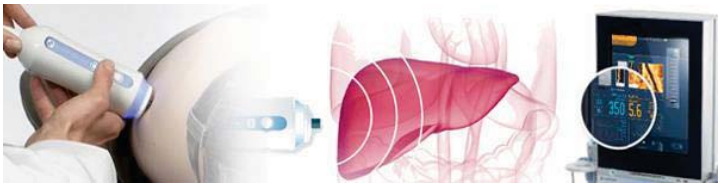
評估肝臟纖維化



- 肝穿刺 (Liver biopsy)
- 抽血檢驗 (Noninvasive tests)
  - APRI
  - FIB-4
  - Fibrotest
  - BioFibroScore
- 纖維檢測儀 (Elastography)
  - Transient elastography
  - MR elastography
- ARFI

$$\text{APRI} = \frac{\frac{\text{AST Level}}{\text{AST (Upper Limit of Normal)}}}{\text{Platelet Count } (10^9/\text{L})} \times 100$$

$$\text{FIB-4} = \frac{\text{Age (years)} \times \text{AST (U/L)}}{\text{Platelet Count } (10^9/\text{L}) \times \sqrt{\text{ALT (U/L)}}}$$



肝癌風險計算機 (HCC Risk calculator)

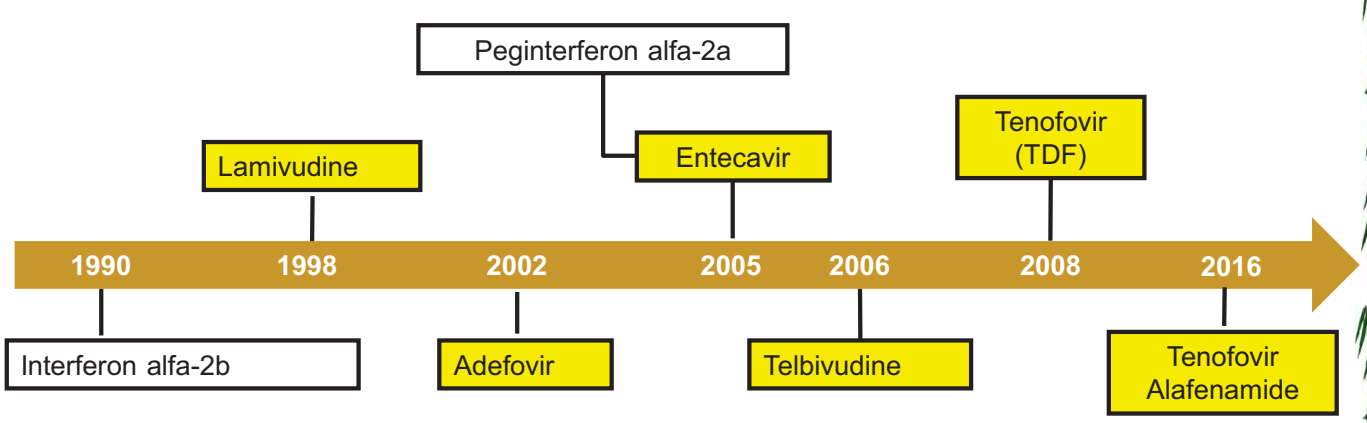
REACH-B HCC risk score developed using REVEAL cohort (n=3,584)

Risk predictor	Risk score
Gender	
Female	0
Male	2
Age	
30-34	0
35-39	1
40-44	2
45-49	3
50-54	4
55-59	5
60-65	6
ALT, U/L	
<15	0
15-44	1
≥45	2
HBeAg	
Negative	0
Positive	2
HBV DNA level, copies/mL	
<300 (Undetectable)	0
300-9999	0
10000-99999	3
100000-999999	5
≥10^6	4

Cumulative risk score	HCC risk		
	At 3rd year	At 5th year	At 10th year
0	0.0%	0.0%	0.0%
1	0.0%	0.0%	0.1%
2	0.0%	0.0%	0.1%
3	0.0%	0.1%	0.2%
4	0.0%	0.1%	0.3%
5	0.1%	0.2%	0.5%
6	0.1%	0.3%	0.7%
7	0.2%	0.5%	1.2%
8	0.3%	0.8%	2.0%
9	0.5%	1.2%	3.2%
10	0.9%	2.0%	5.2%
11	1.4%	3.3%	8.4%
12	2.3%	5.3%	13.4%
13	3.7%	8.5%	21.0%
14	6.0%	13.6%	32.0%
15	9.6%	21.3%	46.8%
16	15.2%	32.4%	64.4%
17	23.6%	47.4%	81.6%

Yang HI et al. *Lancet Oncol* 2011;12:568-574

抗病毒藥物的演進



IFN has mainly immune modulatory effects and weak direct antiviral effects.

Nucleos(t)ide analogues (NUCs) have direct antiviral effects only.

慢性B型肝炎之治療選擇

- 傳統型干擾素
- 長效型干擾素(Peginterferon alfa-2a)
  - 佩格西施(Pegasys)
- 干安能 (lamivudine)
- 干適能 (adefovir dipivoxil)
- 貝樂克 (entecavir)
- 喜必福 (telbivudine)
- 惠立妥 (Tenofovir disoproxil fumarate, TDF)
- 韋立得 (Tenofovir alafenamide, TAF)

抗病毒藥物的特性比較(1)

Treatment	Preferred	Notes
Entecavir	Yes	High potency, high genetic barrier to resistance
Tenofovir Alafenamide (TAF)	Yes	High potency, high genetic barrier to resistance, lower risk of kidney and bone adverse effects
Tenofovir (TDF)	Yes	High potency, high genetic barrier to resistance
PegIFN	Yes	Less safe in patients with cirrhosis, contraindicated in patients with decompensated cirrhosis
Adefovir	No	Low genetic barrier to resistance
Lamivudine	No	Low genetic barrier to resistance
Telbivudine	No	Low genetic barrier to resistance

Terrault. Hepatology. 2018;67:1560. www.aasld.org.
EASL. J Hepatol. 2017;67:370.

抗病毒藥物的特性比較(2)

Comparative Measure	ETV	TAF	TDF
Dose	0.5 mg/day	25 mg/day	300 mg/day
Presence of LAM resistance	Increase dose	Active	Active
Anticipated pregnancy	Pregnancy Category C	No human data in pregnancy	Pregnancy Category B
Renal disease	Decrease dose if CrCl < 50 mL/min	Decrease dose is not require	Decrease dose if CrCl < 50 mL/min
Bone disease	Recommended	Recommended	Recommended

Terrault. Hepatology. 2018;67:1560.

慢性B型肝炎之治療目標

- 清除/壓抑病毒
  - ＊ 減少致病原
  - ＊ 減少傳染性
- 減少肝發炎壞死
  - ＊ 肝炎緩解（逆轉肝纖維化）
  - ＊ 預防肝衰竭
- 遏止病程進展
  - ＊ 減少急性發作，肝硬化和肝細胞癌
- 改善存活率

短期治療的療效指標與比較

第一線抗病毒藥物療效比較

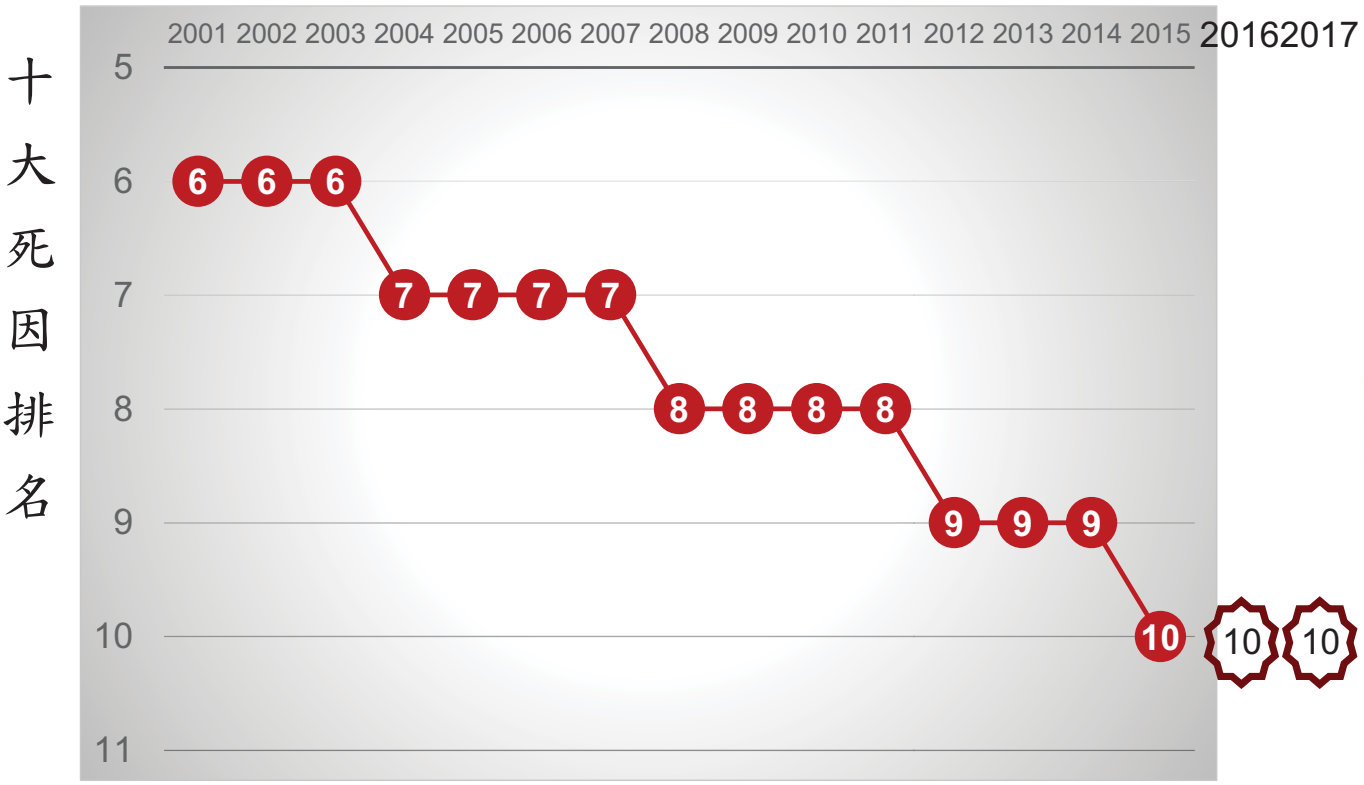
HBeAg Positive	Peg-IFN*	Entecavir†	Tenofovir Disoproxil Fumarate†	Tenofovir Alafenamide‡
% HBV-DNA suppression (cutoff to define HBV-DNA suppression)§	30-42 (<2,000-40,000 IU/mL) 8-14 (<80 IU/mL)	61 (<50-60 IU/mL)	76 (<60 IU/mL)	73 (<29 IU/mL)
% HBeAg loss	32-36	22-25	—	22
% HBeAg seroconversion	29-36	21-22	21	18
% Normalization ALT	34-52	68-81	68	—
% HBsAg loss	2-7 11 (at 3 years posttreatment)	4-5	8	1

HBeAg Negative	Peg-IFN	Entecavir	Tenofovir Disoproxil Fumarate†	Tenofovir Alafenamide‡
% HBV-DNA suppression (cutoff to define HBV-DNA suppression)‖	43 (<4,000 IU/mL) 19 (<80 IU/mL)	90-91 (<50-60 IU/mL)	93 (<60 U/mL)	90 (<29 IU/mL)
% Normalization ALT¶	59	78-88	76	81
% HBsAg loss	4 6 (at 3 years posttreatment)	0-1	0	<1

Terrault NA et al. Hepatology 2018

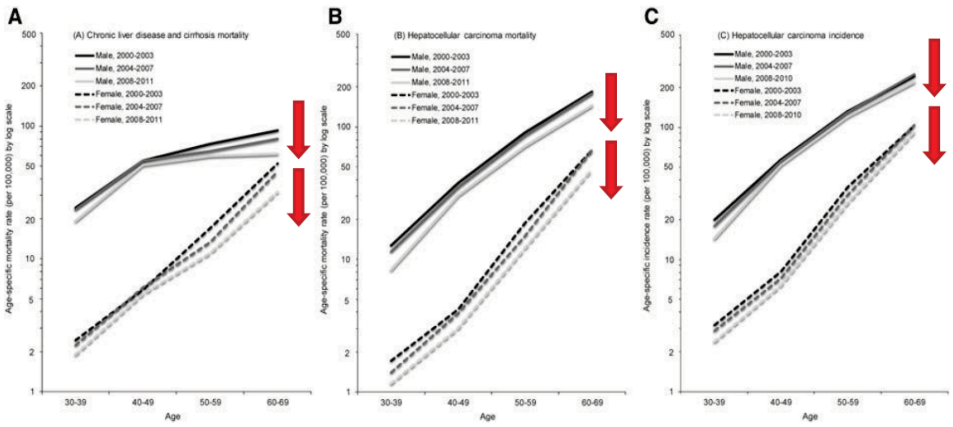
長期治療的好處

國人十大死因中慢性肝病排名逐年下降



國內健保給付治療B肝之長期療效:全國資料

Age-sex-specific mortality and incidence rates before and after the launch of chronic viral hepatitis therapy program since October 2003 in Taiwan

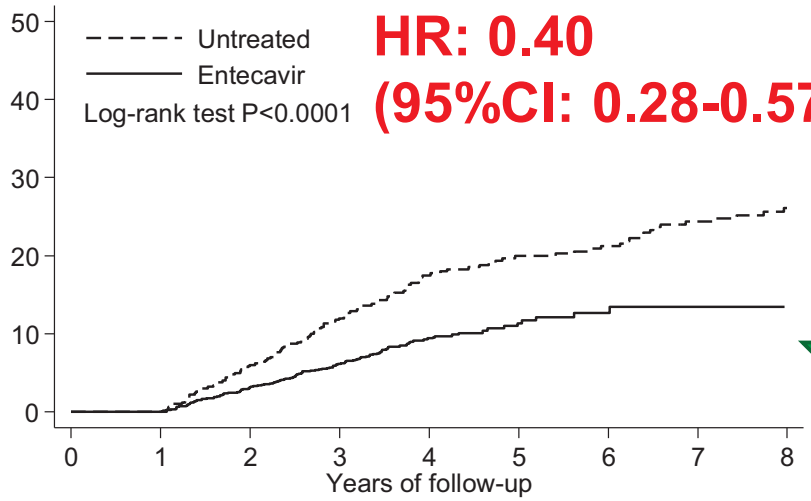


Year	CLD Mortality	HCC Mortality	HCC Incidence
2000-2003	1.00 (referent)	1.00 (referent)	1.00 (referent)
2004-2007	0.92 (0.90-0.94)	0.95 (0.93-0.97)	0.98 (0.96-0.99)
2008-2011	0.78 (0.76-0.80)	0.76 (0.75-0.78)	0.86 (0.85-0.88)

Chiang et al. Hepatology 2015

Chiang CJ et al.
Hepatology 2015

長期抗病毒藥物治療降低6成肝硬化患者之肝癌發生率：多中心觀察



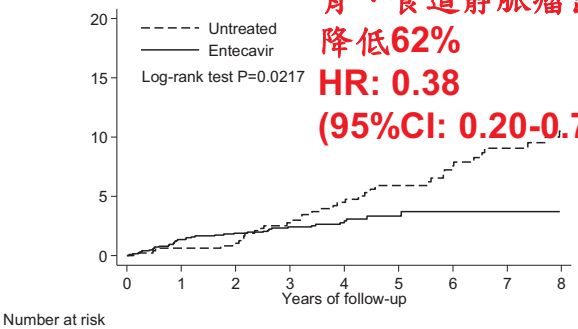
Number at risk

Untreated	503	503	464	392	320	276	240	193	161
Entecavir	1315	1315	1274	1030	640	246	118	37	4

Su and Kao et al., Liver Int. 2016 Dec;36(12):1755-1764

長期抗病毒藥物治療降低肝硬化併發症及死亡率

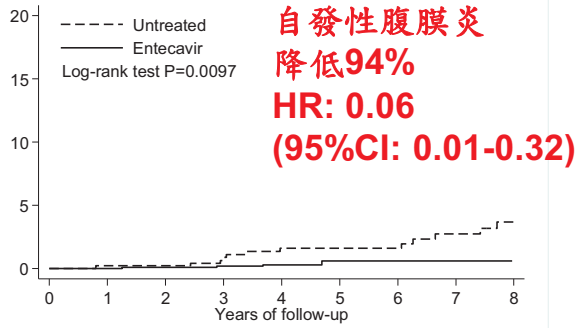
胃、食道靜脈瘤出血
降低62%
HR: 0.38
(95%CI: 0.20-0.74)



Number at risk

Untreated	489	486	473	419	352	307	269	212	175
Entecavir	1276	1259	1246	1021	661	258	125	38	3

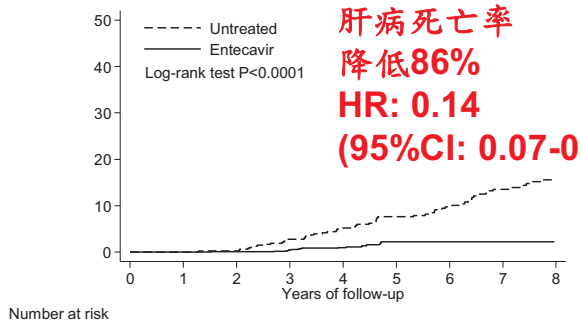
自發性腹膜炎
降低94%
HR: 0.06
(95%CI: 0.01-0.32)



Number at risk

Untreated	503	502	492	433	366	323	282	225	188
Entecavir	1313	1313	1305	1078	701	274	137	44	4

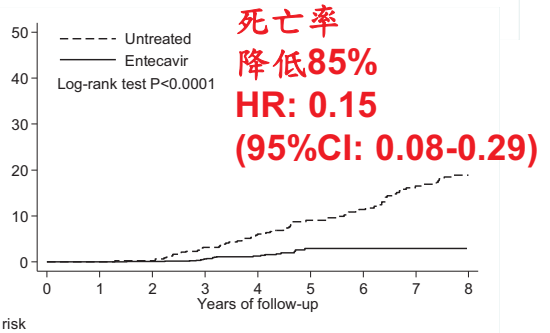
肝病死亡率
降低86%
HR: 0.14
(95%CI: 0.07-0.30)



Number at risk

Untreated	503	503	492	435	368	323	282	226	188
Entecavir	1315	1315	1308	1081	703	276	137	44	4

死亡率
降低85%
HR: 0.15
(95%CI: 0.08-0.29)



Number at risk

Untreated	503	503	492	435	368	323	282	226	188
Entecavir	1315	1315	1308	1081	703	276	137	44	4

Su and Kao et al., Liver Int. 2016 Dec;36(12):1755-1764

2003~2019

肝炎健保給付大躍進

台灣B肝健保給付里程碑

2008.08

- 給付新一代B肝口服抗病毒藥物

2009.11

- 口服藥物給付18個月改為36個月
- DNA取代biopsy

台灣B肝健保給付里程碑

2010.07

Jan. 2019: NUC for HBV post HCC curative treatment
May 2019: TAF (tenofovir alafenamide) for CHB

- e抗原陽性病患取消口服藥物3年限制,治療至e抗原轉陰
- 針劑干擾素治療由6個月延長為12個月
- 非肝硬化B肝患者停藥復發不限制再治療次數

全民健康保險慢性B型肝炎治療試辦計畫
口服藥給付規定及流程

2019修訂

HBeAg 陽性病患	HBeAg 陰性病患	肝代償不全病患
• HBsAg (+) > 6 個月 • HBeAg (+) > 3個月 • ALT ≥ 5倍 ULN 或 • 2倍 ≦ALT <5倍 ULN 且HBV DNA ≥ 20,000 IU/mL 或肝組織切片 HBcAg (+)（血友病患及類血友病患得不做切片）	• HBsAg (+) > 6 個月 • HBeAg (-) > 3個月 • ALT ≥ 2倍 ULN (半年有兩次以上,每次間隔3個月)且HBV DNA ≥ 2,000 IU/mL，或肝組織切片 HBcAg (+)（血友病患及類血友病患得不做切片）	HBsAg (+)且已發生肝代償不全 *已發生肝代償不全 1. PT延長≥3秒 或 2. T-Bil. ≥ 2 mg/dL

Entecavir (0.5 mg)，TDF，Telbivudine，Lamivudine ，TAF擇一 給付
HBeAg(-)病患治療至少2年，每次療程至多給付36個月
HBeAg (+)患者治療至e抗原轉陰並再多給付最多12個月

(肝代償不全者Entecavir使用1mg)

治療完成後，觀察3 - 6個月 ，復發且符合治療條件

Entecavir (0.5 mg)，TDF，Lamivudine，Telbivudine ，TAF 再次給付

全民健康保險慢性B型肝炎治療試辦計畫
口服藥給付規定及流程

2019修訂

長期給予	預防性使用	B型肝炎發作出現抗藥株 (指於治療中一旦HBV DNA從治療期間之最低值上升超過一個對數值 1 log IU/mL)
•HBsAg (+) •肝硬化病患* •接受非肝臟器官移植後或接受癌症化學治療法中B型肝炎發作者 •接受肝臟器官移植後，持續接受免疫抑制劑者	•HBsAg (+) •接受肝臟器官移植或接受癌症化學療法的病患預防性使用 •異體造血幹細胞移植，捐贈者可接受預防性投藥至HBV DNA偵測不到，受贈者移植前一週開始給付，至免疫抑制劑停用後6個月	• 原藥物加上Adefovir 3年 • Entecavir 1mg (限Lamivudine抗藥) 3年 • Tenofovir 3年 • Interferon, pegylated interferon 1年
•Entecavir 0.5mg、TDF、Telbivudine、Lamivudine、TAF長期給予	•Entecavir 0.5mg、TDF、Telbivudine、Lamivudine、TAF化療前一週至結束後6個月	• 若停藥後復發，得以合併療法或TDF或TAF治療3年或干擾素再治療1年 • 再復發時得再治療，不限治療次數 • 多重抗藥性時，可用TDF或TAF或合併Entecavir 1mg治療3年

* 肝硬化條件為需同時符合下列二項條件：

(一) HBsAg (+)且血清HBV DNA ≥ 2,000 IU/mL者。

(二) 診斷標準：1. 肝組織切片 (Metavir F4或Ishak F5以上，血友病患及類血友病患經照會消化系專科醫師同意後，得不作切片) 或 2. 超音波診斷為肝硬化併食道或胃靜脈曲張，或肝硬化併脾臟腫大。

B肝健保給付大躍進
---與亞太治療指引接軌

給付時間

一年　三年　不以時間為限

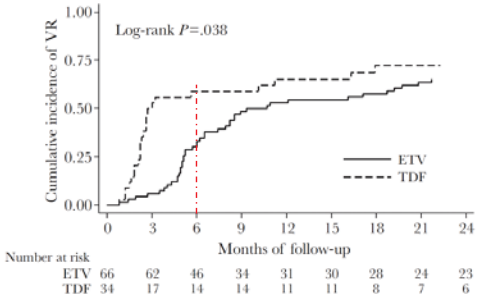
給付次數

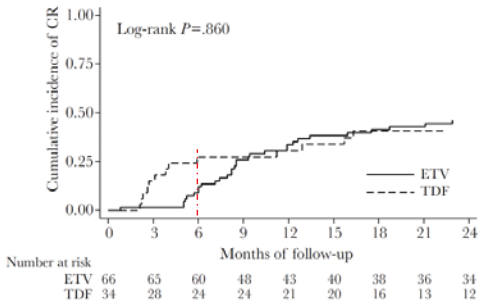
初次治療　可再次治療　不限次數 再治療

呼籲目前未在治療的B肝帶原者，主動回診詢問是否可進入治療，建議病毒量檢測以幫助評估

B型肝炎患者完成治療後，須監測與治療B型肝炎復發

停止口服藥物後, 須監測B型肝炎復發





Relapse type, Time after EOT	ETV, % (95% CI)	TDF, % (95% CI)	P
VR			
3 mo	6.1 (2.3-15.4%)	52.9 (37.5-70.2)	<0.001
6 mo	33.3 (23.4-46.1)	58.8 (43.1-75.2)	0.014
12 mo	53.0 (41.6-65.4)	65.2 (49.3-80.5)	0.248
CR			
3 mo	1.5 (0.2-10.3)	15.2 (6.6-32.6)	0.007
6 mo	12.1 (6.3-22.8)	27.3 (15.2-45.9)	0.060
12 mo	33.7 (23.6-46.5)	30.6 (17.8-49.4)	0.877

Su TH et al JID 2018

B肝高病毒濃度孕婦使用抗病毒藥物預防母嬰B型肝炎傳染

Antiviral Therapy During the Third Trimester can Reduce MTCT of HBV

- **TDF is Reimbursed in Pregnant Women in Taiwan Since Feb. 1, 2018:**

血清**HBV DNA ≧10^6 IU/mL** 之懷孕者，可於懷孕滿**27** 週後開始給付使用**telbivudine** 或**tenofovir**，直至產後**4** 週。

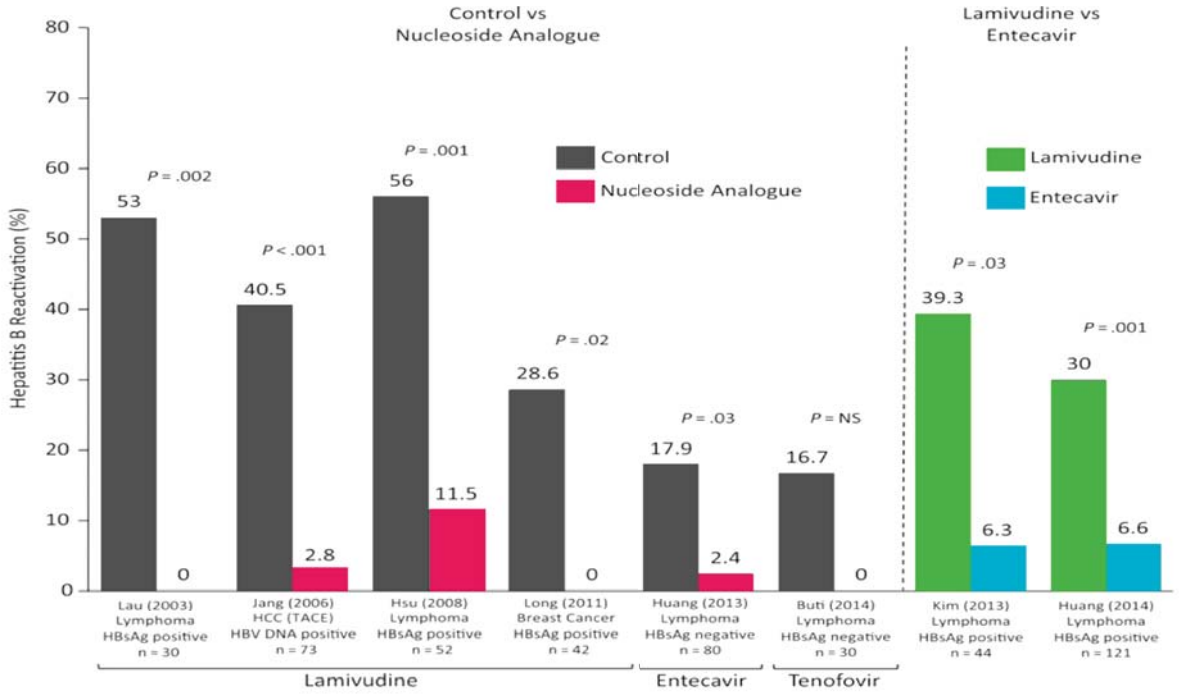
- **HBIG can be Applied to all Pregnant Women with HBsAg Carriage in Taiwan Since July 2019**
- 母親**HBsAg**陽性幼兒滿**12**個月可抽血檢驗，若**anti-HBs(-) and HBsAg (-)**，可以免費追加一劑疫苗

1. Chen, AASLD, 2014, Poster #1632
2. Pan CQ, et al. *N Engl J Med.* 2016;374:2324–34

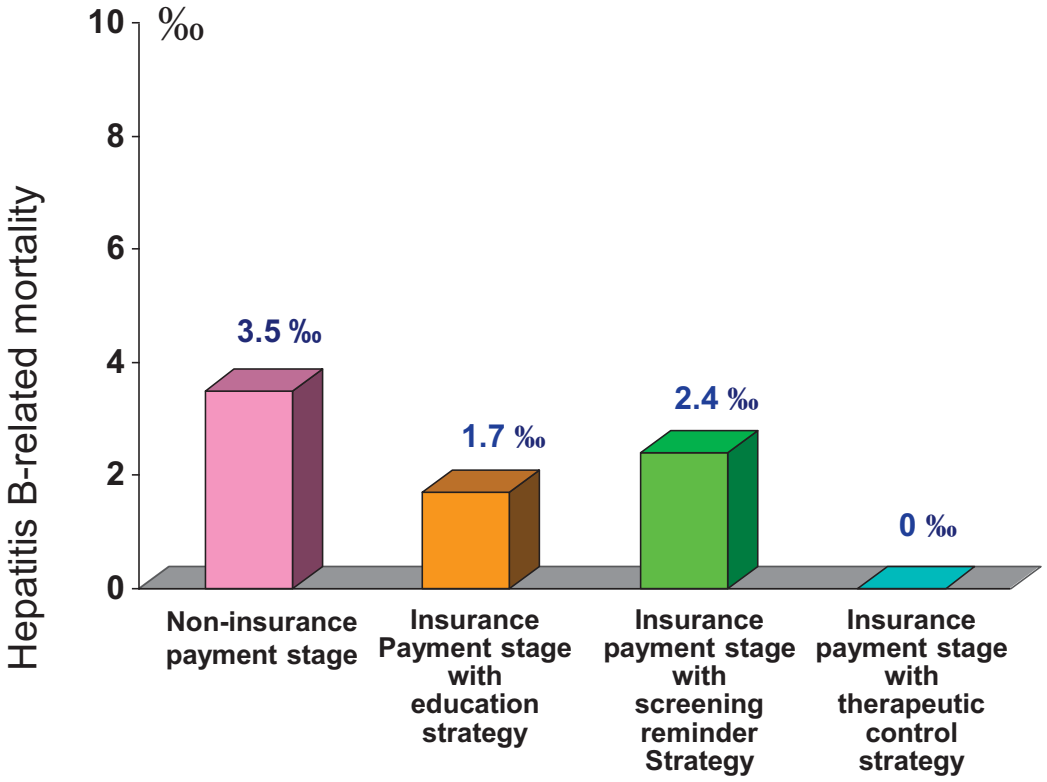
ITT analysis included infants born to all enrolled participants except for those who withdrew consent before the initiation of treatment.
PP analysis excluded infants born to women who withdrew consent, were lost to follow-up, or discontinued treatment for any reason. MTCT: mother-to-child transmission; PP: per protocol

癌症患者接受化學治療中預防B型肝炎復發

Prospective RCTs evaluating antiviral prophylaxis for HBVr



Gonzalez SA, Perrillo RP. *Clin Infect Dis* 2016;**62** Suppl 4:S306-13.



Hepatitis B-related mortality rate in cancer patients receiving chemotherapy

Hsu PI et al. Hepatology 2015

C型肝炎患者接受DAA治療中監測與預防B型肝炎復發

Comparison between IFN- & DAA-based therapy for dual B+C patients

	IFN-based	DAA-based
Treatment target(s)	HCV and potentially HBV	HCV only
HCV SVR	Satisfactory	Very high
HBsAg seroclearance	Occurs in a proportion	Unlikely
Risk of HBV reactivation	Exists	Higher & earlier
Special populations	Not applicable	Applicable

HBV reactivation through post treatment week 48

- Overall, 79/111 patients (71%) experienced HBV DNA reactivation
  - **61%** (48/79) for the first time during treatment period
  - **28%** (22/79) between EOT and FU-12
  - **5%** (4/79) between FU-12 and FU-24
  - **6%** (5/79) between FU-24 and FU-48
  - 77% (61/79) had HBV reactivation at multiple time points
  - **11% (9/79) had concomitant ALT elevation >2x ULN**
- Closely monitor and prompt anti-HBV treatment: No patient had AEs of jaundice, liver decompensation, liver failure or liver transplant

Liu CJ et al, Gastroenterology 2018

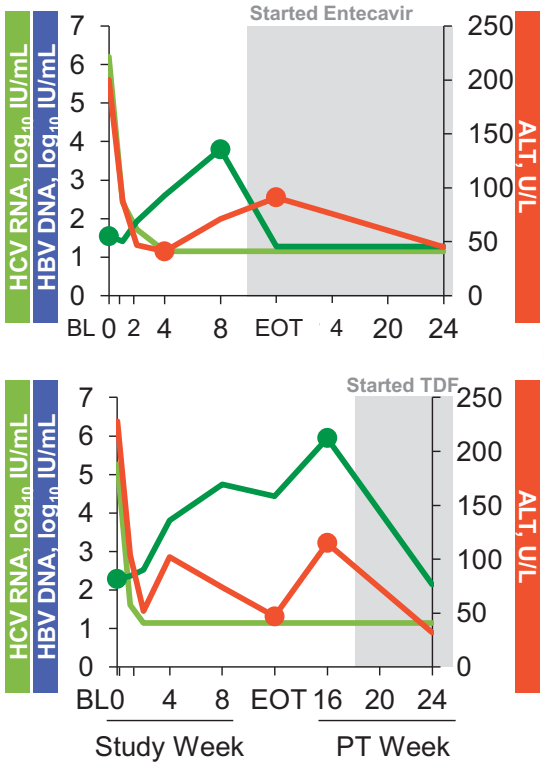
Two asymptomatic patients started HBV therapy

60-year-old female, HCV GT1b, HBeAg negative, with cirrhosis

- HBV DNA increased from 1.54log_{10} IU/mL (BL) to 3.8log_{10} IU/mL at Day 57 (Week 8)
- Associated with ALT increase from nadir value of 41 to 71 IU/mL
- Started HBV treatment on study Day 71

61-year-old male, HCV GT2, HBeAg negative, without cirrhosis

- HBV DNA increased from 2.28log_{10} IU/mL (BL) to 5.95log_{10} IU/mL 30 days post last dose (post-treatment Week 4)
- Associated with ALT increase from nadir value of 47 to 115 IU/mL
- Started HBV treatment during post-treatment follow-up Week 5



AASLD 2018 HBV guidance on HCV and HBV coinfected subjects

- HBsAg-positive patients: Monitoring of HBV DNA levels every 4 to 8 weeks during treatment and for 3 months post-treatment is indicated in those who do not meet treatment criteria for monoinfected patients.
- HBV treatment is determined by HBV DNA and ALT levels as per the AASLD HBV guidelines for monoinfected patients.

Terrault NA et al. Hepatology 2018

需積極接受治療的患者

- 慢性B型肝炎：
  - ALT 數值超過正常值上限2倍
- 代償良好之活動性肝硬化
- 代償失調之活動性肝硬化
- 40歲以上且肝切片顯示有顯著肝纖維化
- 器官 (肝臟) 移植前後
- 接受免疫抑制劑或化學藥物治療
  - 接受rituximab治療

Met and unmet needs in the management of CHB

Met

- Potent antiviral agent to suppress HBV replication
- Improved clinical outcomes after antiviral therapy
  - Halt progression of liver disease
  - Reduce risk of HCC development

Unmet

- Rate of HBV cure: Low
  - New anti-HBV agent, combination therapy
- We can identify responders only in some
  - We need reliable biomarkers
- Individualization of therapy?
  - Special populations
- Prevention of HCC development: not complete

Reimbursement and restrictions of CHB treatment in Taiwan

Reimbursement

- HBeAg-positive CHB
- HBeAg-negative CHB
- Liver cirrhosis with active viral replication
- Prevention of MTIT of HBV
- Prevention of HCC recurrence in patients receiving curative treatment of HCC

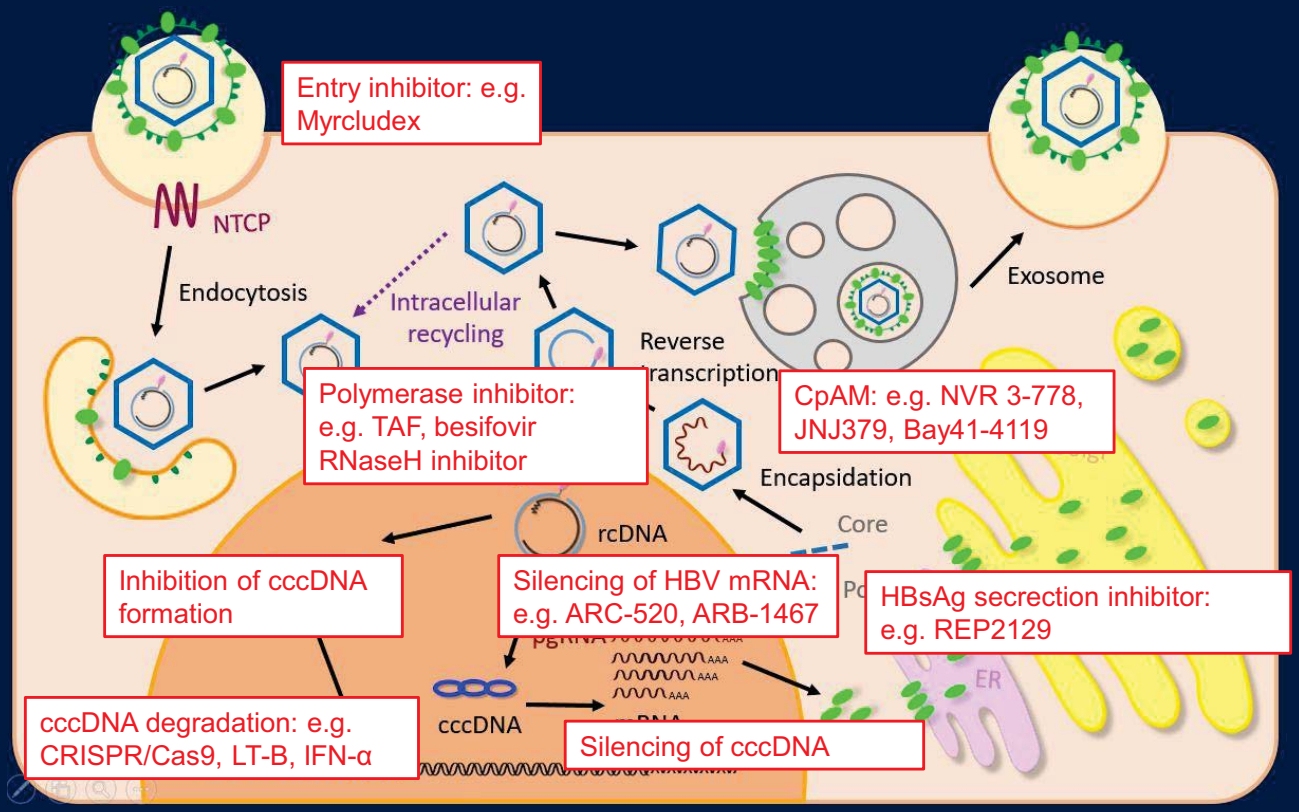
Restrictions

- 3-year duration (HBeAg-ve)
- Risk of relapse and cumulative liver injury
- Risk of decompensation if baseline limited liver reserve
- Mild/evident liver injury?
- Immunosuppression other than cancer chemotherapy

結論及未來方向

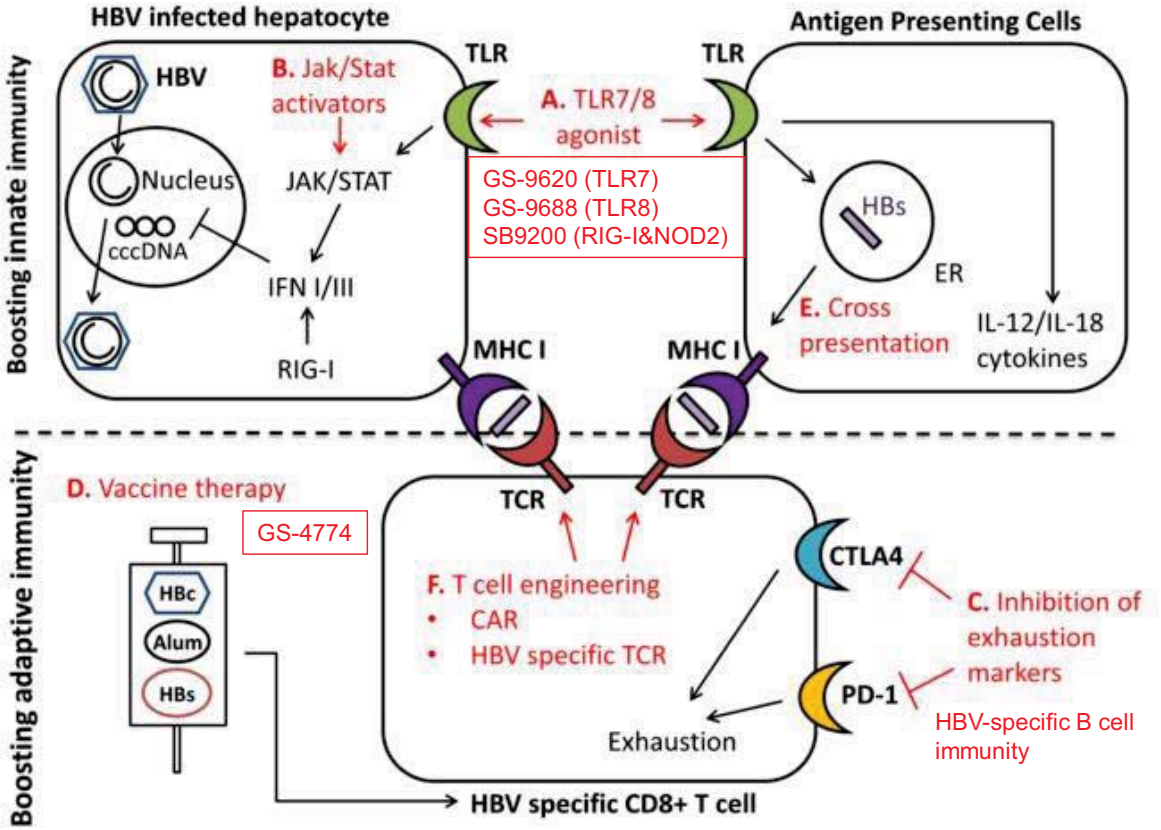
- 慢性B型肝炎之治療仍有努力的空間
- 發展更有效的口服抗病毒藥物和免疫調節劑
- 合併療法是未來努力的方向，但最佳之處方尚待發掘
- 依宿主、病毒和肝病狀況訂做個人化療法

HBV life cycle and antiviral targets

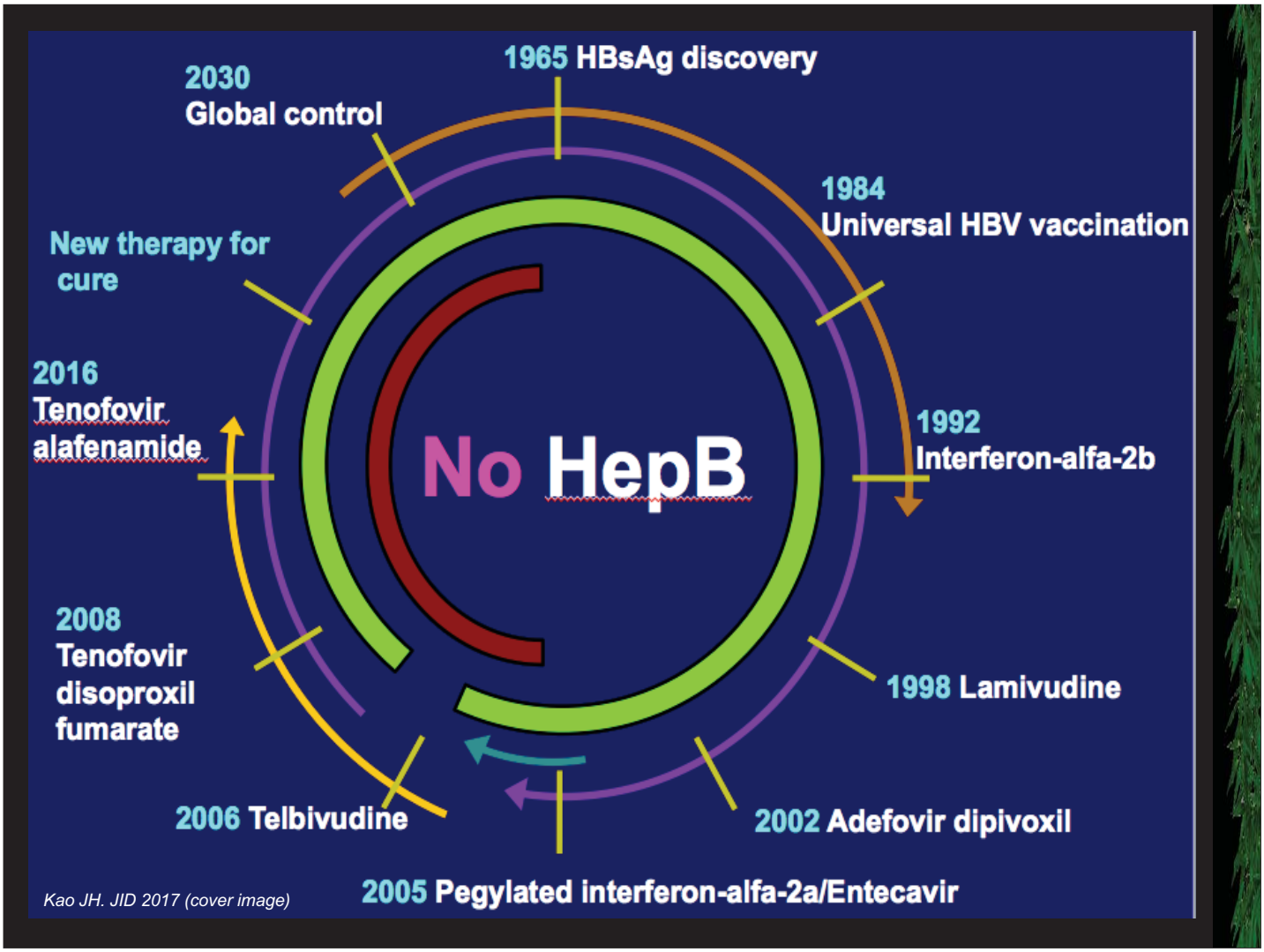


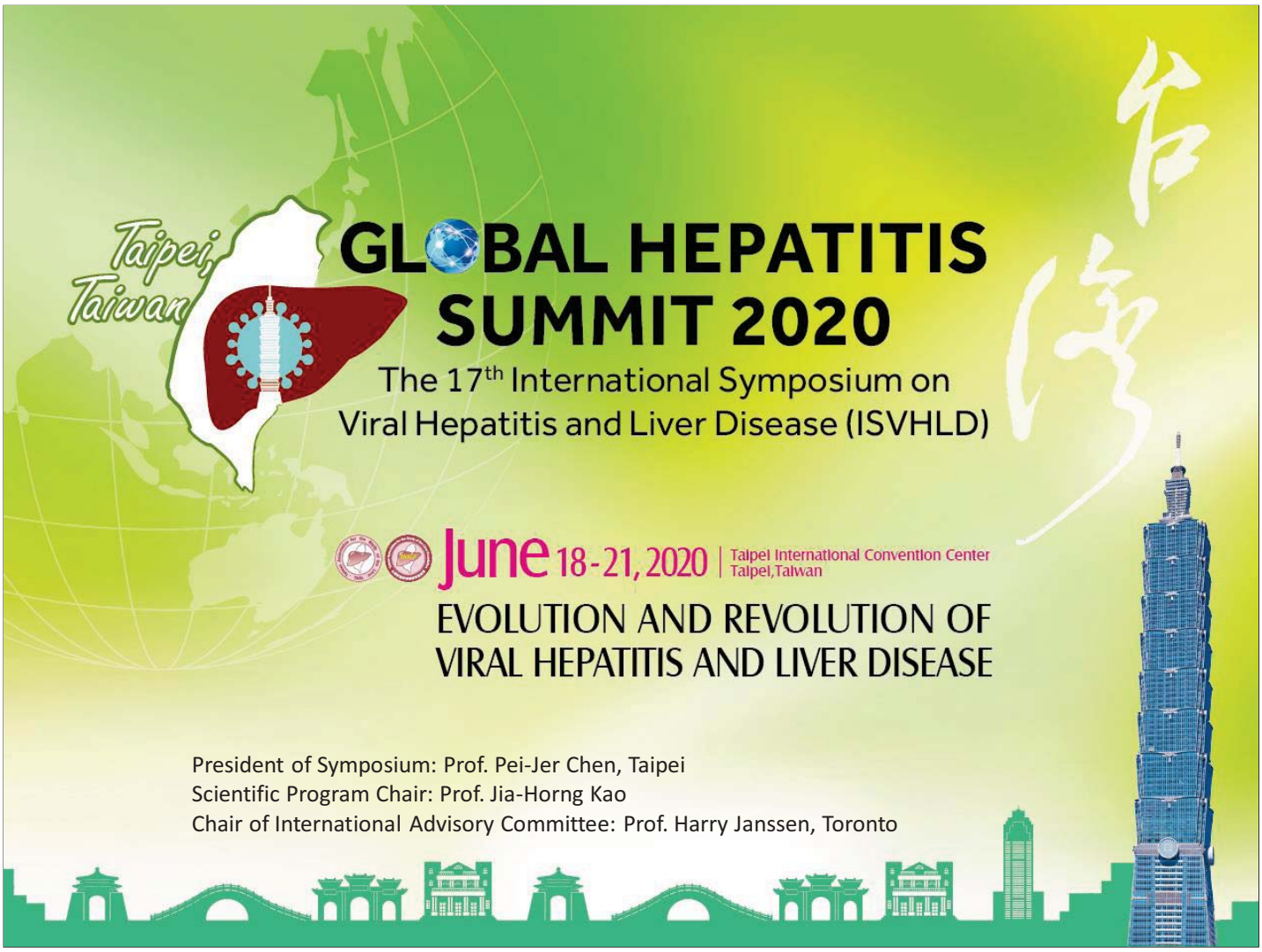
Modified from Yang HC & Chen PJ, Virus, 2017

Potential Immunotherapeutic targets



Yang N & Bertoletti A, Hepatol Int, 2015


1965 HBsAg discovery
2030
Global control
1984
Universal HBV vaccination
New therapy for
cure
2016
Tenofovir
alafenamide
No HepB
1992
Interferon-alfa-2b
2008
Tenofovir
disoproxil
fumarate
1998 Lamivudine
2006 Telbivudine
2002 Adefovir dipivoxil
2005 Pegylated interferon-alfa-2a/Entecavir
Kao JH. JID 2017 (cover image)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