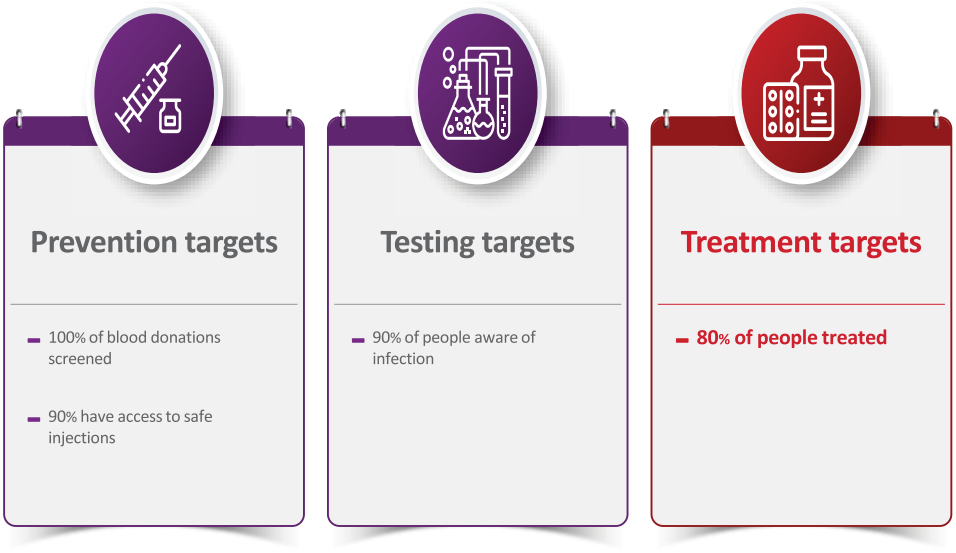
B型肝炎篩檢與治療的臨床實務

劉俊人

台大醫學院內科暨臨床醫學研究所、
台大醫院內科部暨肝炎研究中心

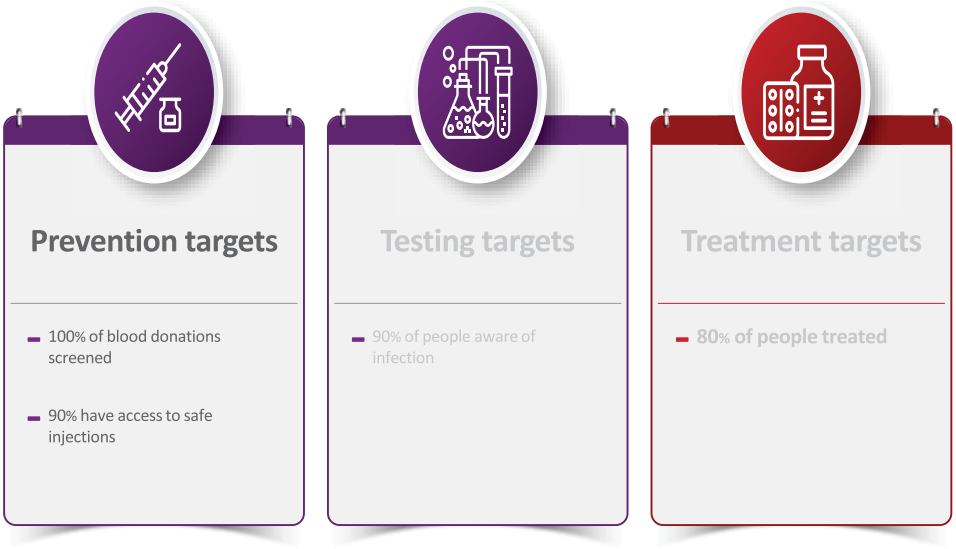
WHO 希望全球消滅 HBV & HCV（2030）



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)

WHO 希望全球消滅 HBV & HCV（2030）

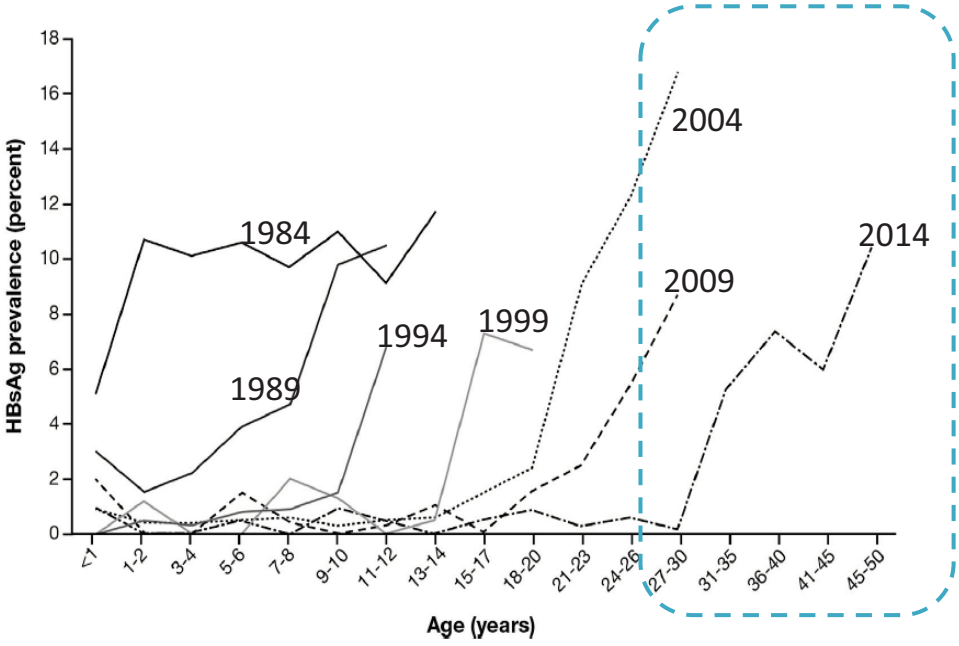


Eliminate viral hepatitis as a public health issue by 2030

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)

臺灣經驗:30年疫苗注射計畫有效減少新世代B肝帶原者

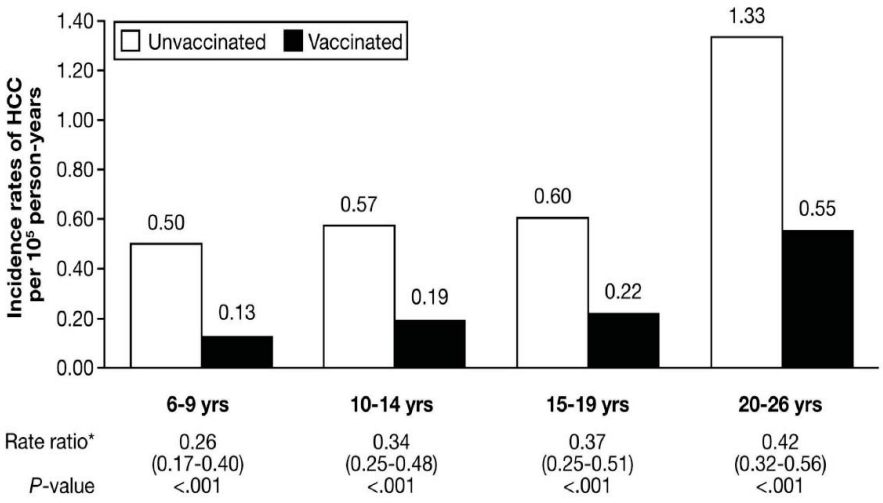
- 疫苗注射涵蓋率:97.7%
- B肝帶原率: 6.7% → 0.5%



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

臺灣經驗:30年疫苗注射計畫有效減少B肝相關肝細胞癌發生

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



*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.

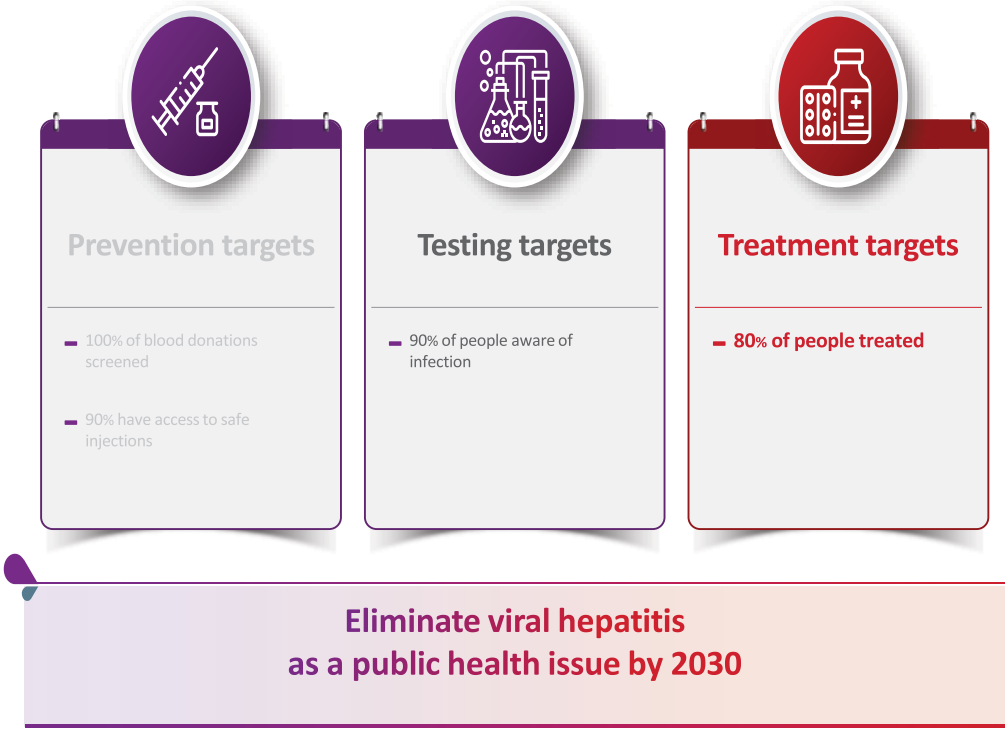
Chang et al., NEJM 1997; Chang et al., JAMA 2000; Chang et al., JNCI 2009; Chang et a. Gastroenterology 2016.

Estimates toward the targets of the Global Health Sector Strategy: WHO goals and the 2019 status in Taiwan

Target Areas	WHO Goal		2019 Status (Taiwan, 2019)
	2020	2030	
1. Impact targets			
Incidence: New HBV infection	30%↓	90%↓	>90%↓
Mortality: Viral hepatitis B and C deaths	10%↓	65%↓	CLDs and Cirrhosis 38%↓ HCC: 44%↓
2. Service coverage targets			
HBV Vaccination Coverage (3rd dose of childhood vaccine)	90%	90%	98%
HBV birth-dose vaccination coverage	50%	90%	99%
Blood Safety (donation screened)	95%	100%	100%
Safe Injection	95%	100%	100%
Harm reduction: # sterile needles & syringes per PWID	200/py	300/py	165/py (200/py in 2020)
HBV-infected diagnosed	30%	90%	54.7%
HBV patients on treatment	--	80%	33%

Wu & Pwu, Taiwan Viral Hepatitis Flagship Program, 2019 (unpublished)

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)

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
  - 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
- 待解決的臨床議題
  - 停藥後的追蹤與再次治療
  - 臨床預測指標
- 結論與展望

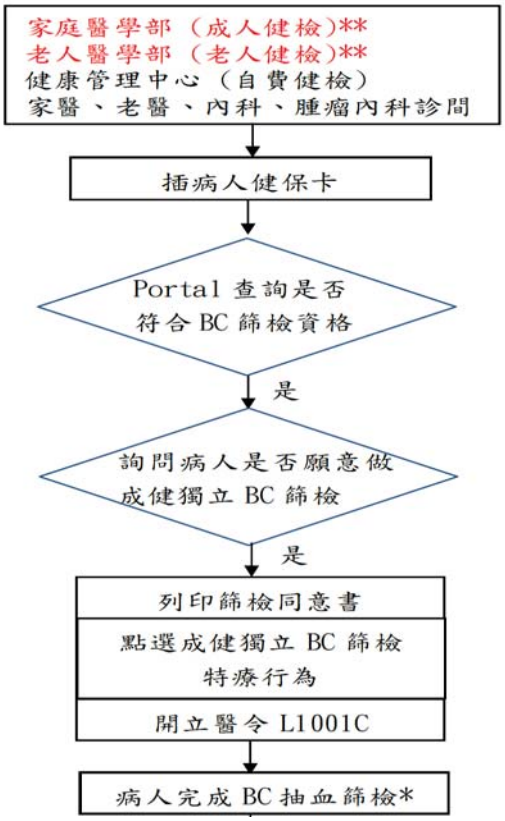
免費健康檢查

年滿45-79歲民眾，終身1次B、C肝篩檢
別讓您的權益睡著

2020/9/28

- 國民健康署目前提供民國55年次或以後出生且滿45歲及年滿40至60歲具原住民身分的民眾，搭配成人預防保健終身可接受1次B、C型肝炎篩檢服務。
- 為配合國家消除C肝政策，業核定擴大放寬年滿45至79民眾，都可接受終身一次的B、C型肝炎篩檢服務，以早期發現、提供適當治療，避免演變為慢性肝病及肝硬化。

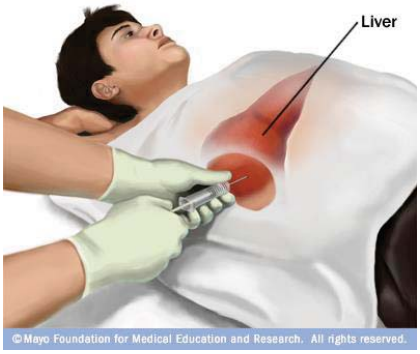
台大醫院成人預防保健擴大ＢＣ肝篩檢 (20220101)



B型肝炎誰需要接受治療?

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

評估肝臟纖維化

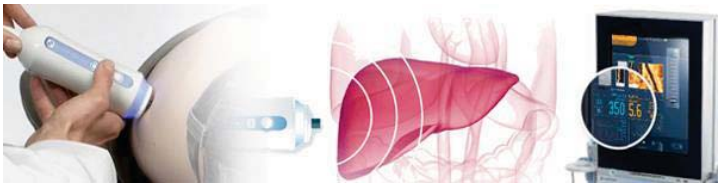


- 肝穿刺 (Liver biopsy)
- 抽血檢驗 (Noninvasive tests)
  - APRI
  - FIB-4
  - Fibrotest
  - BioFibroScore

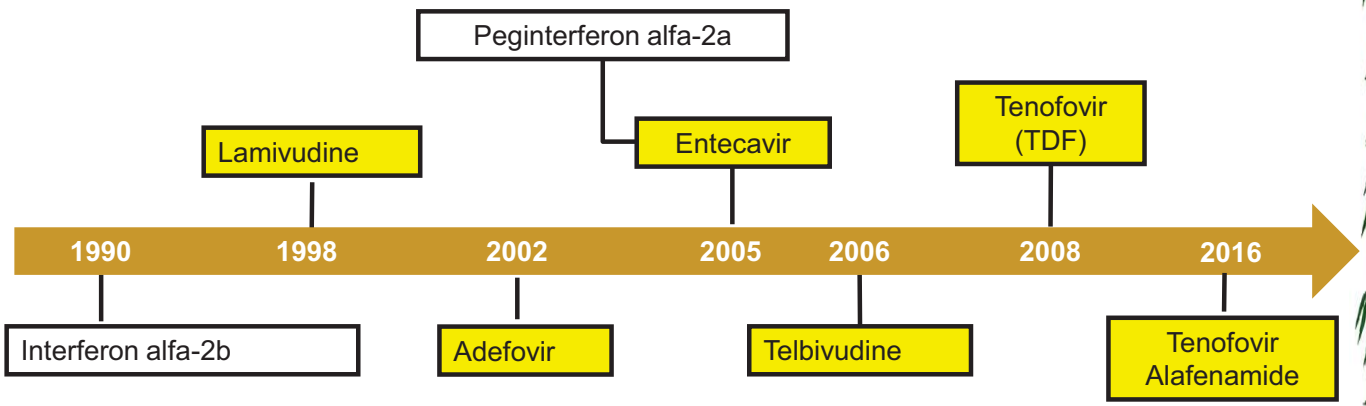
$$\text{APRI} = \frac{\frac{\text{AST Level}}{\text{AST (Upper Limit of Normal)}}}{\text{Platelet Count } (10^9/\text{L})} \times 100$$

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

- 纖維檢測儀 (Elastography)
  - Transient elastography (Fibroscan®)
  - MR elastography
- ARFI



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

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.

短期治療的療效指標與比較

第一線抗病毒藥物療效比較

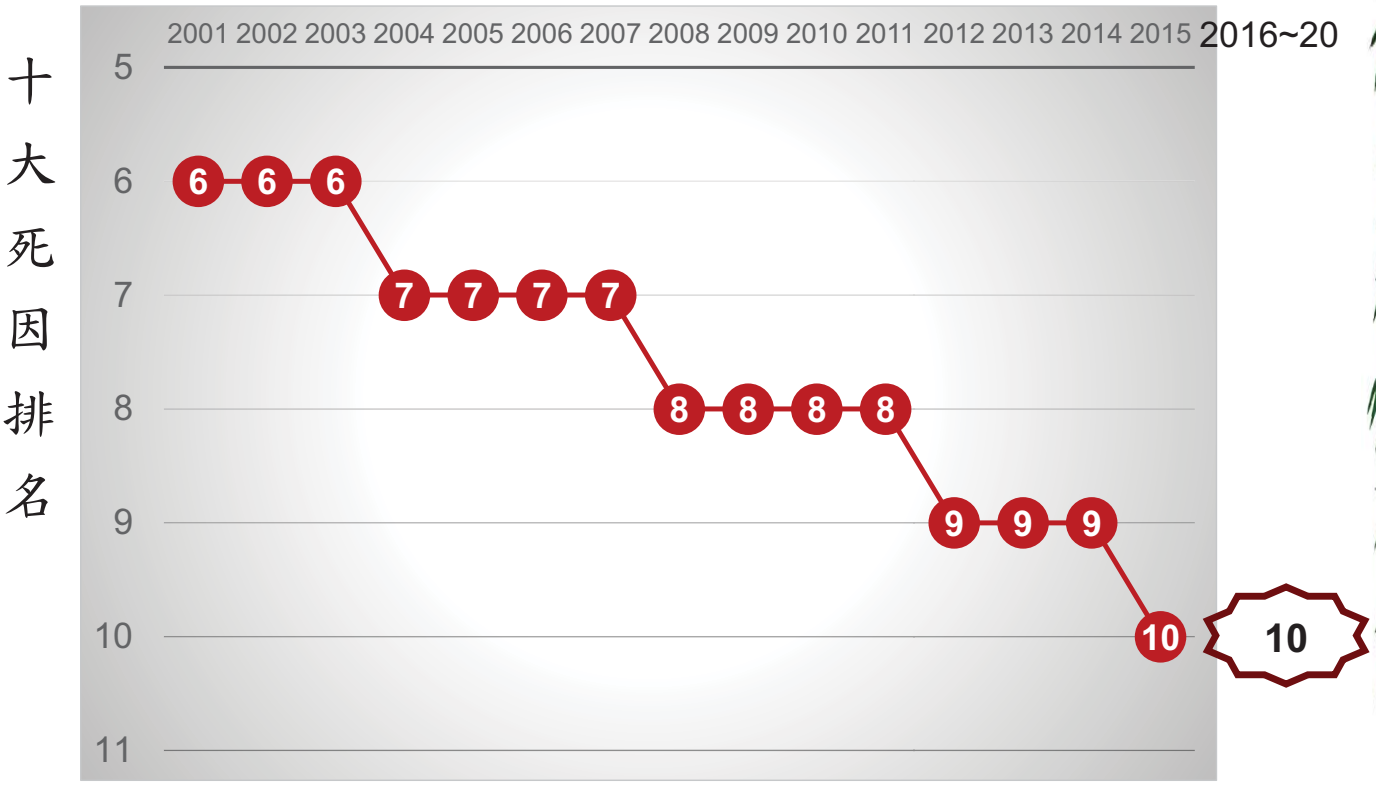
HBeAg Positive	Peg-IFN*	Entecavir†	Tenofovir Disoproxil Fumarate†	Tenofovir Alafenamide‡
% HBV-DNA suppression (cutoff to define HBV-DNA suppression)§	30-42 (<2,000-40,000 IU/mL) 8-14 (<80 IU/mL)	61 (<50-60 IU/mL)	76 (<60 IU/mL)	73 (<29 IU/mL)
% HBeAg loss	32-36	22-25	—	22
% HBeAg seroconversion	29-36	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

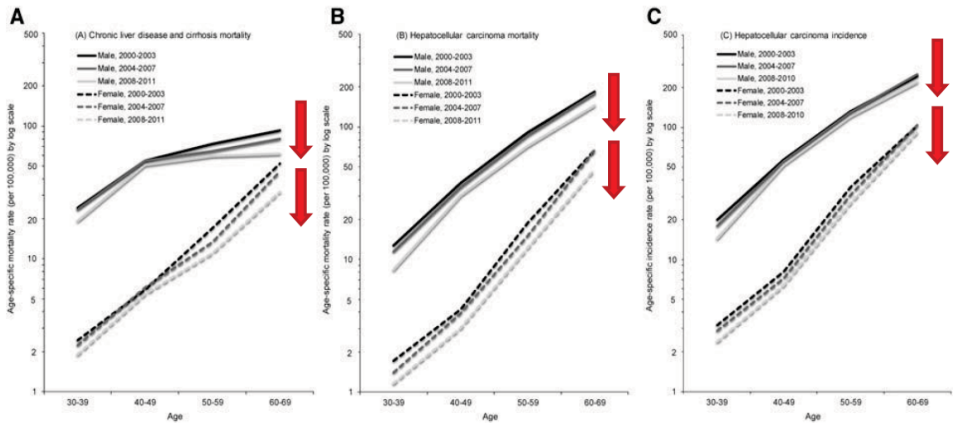
國人十大死因：慢性肝病排名逐年下降



衛福部統計處

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

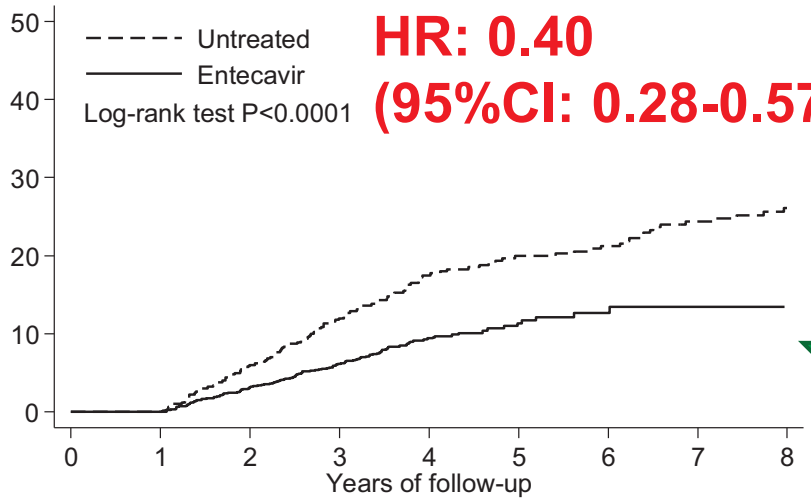


Year	CLD Mortality	HCC Mortality	HCC Incidence
2000-2003	1.00 (referent)	1.00 (referent)	1.00 (referent)
2004-2007	0.92 (0.90-0.94)	0.95 (0.93-0.97)	0.98 (0.96-0.99)
2008-2011	0.78 (0.76-0.80)	0.76 (0.75-0.78)	0.86 (0.85-0.88)

Chiang et al. Hepatology 2015

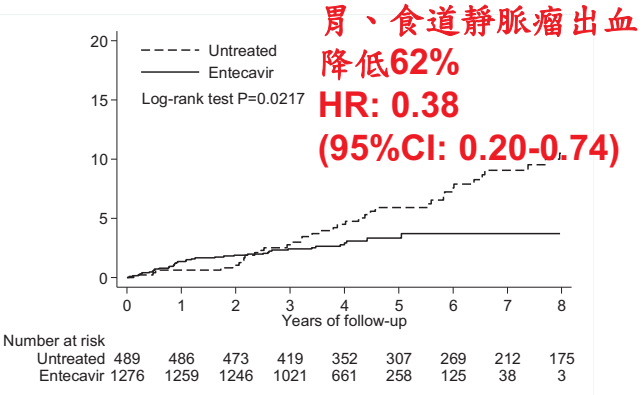
Chiang CJ et al.
Hepatology 2015

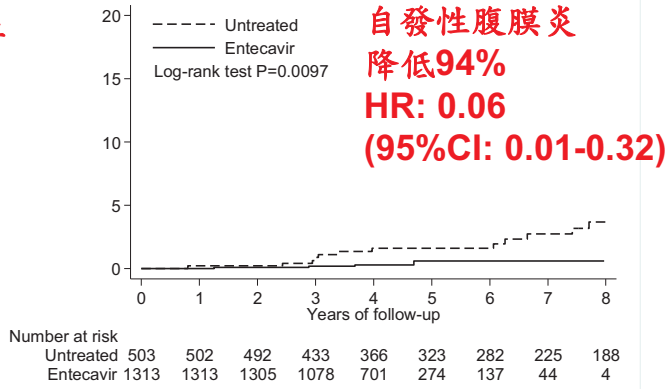
長期抗病毒藥物治療降低6成肝硬化患者之肝癌發生率：多中心觀察

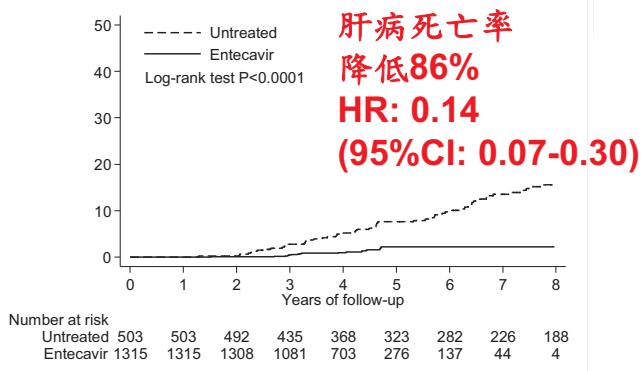


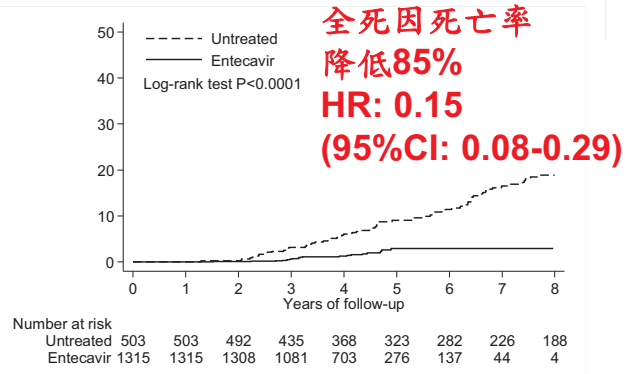
Su and Kao et al., Liver Int. 2016 Dec;36(12):1755-1764

長期抗病毒藥物治療降低肝硬化併發症及死亡率









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

2003~2022

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

- 肝硬化B肝患者終生給付口服藥物
- 非肝硬化B肝患者停藥復發可給付再治療一次

2017.01

- 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

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

Reimbursement of CHB treatment in Taiwan (2021)

e抗原陽性 HBeAg(+)

- HBsAg(+)>6個月 或 IgM anti-HBc(-)
- HBeAg(+)>3個月
- ALT ≥5倍ULN或2倍 ≤ALT ≤5倍ULN且HBVDNA ≥20,000IU/mL 或肝組織切片 HBcAg(+)*
- ALT≥ 1倍ULN(>3個月),且纖維化=F3, 且 HBV DNA > 20,000 IU/mL 或肝組織切片 HBcAg(+)

e抗原陰性 HBeAg(-)

- HBsAg(+)>6個月或
- IgM anti-HBc(-)
- HBeAg(-)>3個月
- ALT >2倍ULN(半年有兩次以上，每次間隔三個月)且HBVDNA >2,000IU/mL 或肝組織切片 HBcAg(+)*
- ALT≥ 1倍ULN(>3個月),且纖維化=F3, 且 HBV DNA > 20,000 IU/mL 或肝組織切片 HBcAg(+)

長期用藥

1. 肝硬化併門脈高壓, 測得到HBV DNA
2. 非肝臟之器官移植後，B型肝炎發作者
3. 接受癌症化學療法中，B型肝炎發作者
4. 肝癌病患並接受根除性治療病患且測得到HBV DNA

短期用藥

1. 免疫抑制藥物治療中B肝發作(HBsAg+, 或HBsAg-/anti-HBc(+)), 開始給付使用至免疫抑制劑停用後6個月

預防用藥

1. 接受肝臟移植者或非肝臟之器官移植者, 異體造血幹細胞移植者(HBsAg+或HBsAg-/anti-HBc+)可預防性使用
2. 接受癌症化學療法，可於化學療法前1週開始給付使用，直至化學療法結束後6個月(HBsAg+或HBsAg-/anti-HBc+)
3. 使用免疫抑制藥物(Rituximab, Anthracycline, prednisolone≥ 20mg/day > 4wks), 前一週開始使用, 直至治療結束後6個月(HBsAg+)

產生抗藥株的病患

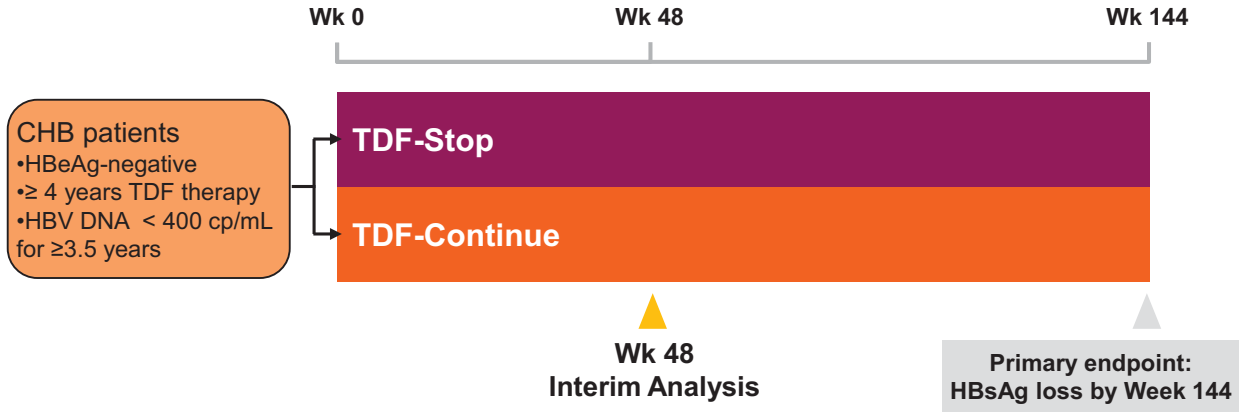
經使用經使用lamivudine 100mg、entecavir 0.5mg或1.0mg、telbivudine治療或預防B型肝炎發作出現抗藥株(指於治療中一旦HBV DNA從治療期間之最低值上升超過一個對數值（1 log IU/mL）

B型肝炎患者達成治療目標時，可以考慮停止藥物治療

TDF FINITE CHB

停止藥物治療的臨床試驗(1)：HBeAg-Negative CHB

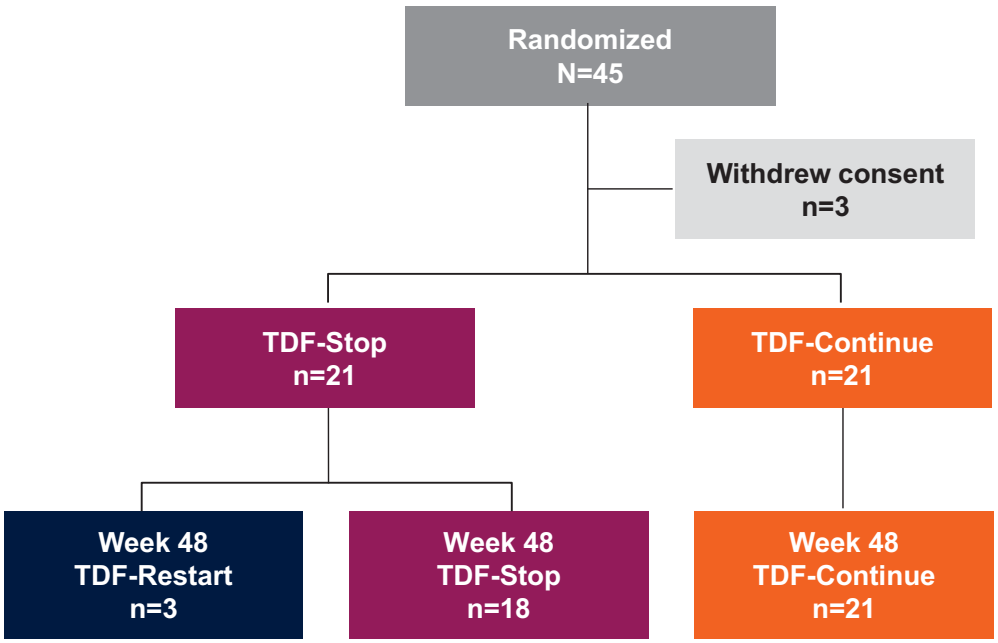
Open-label, multicenter, randomized, controlled trial



Berg T et al. J Hepatol 2017;67:918-924

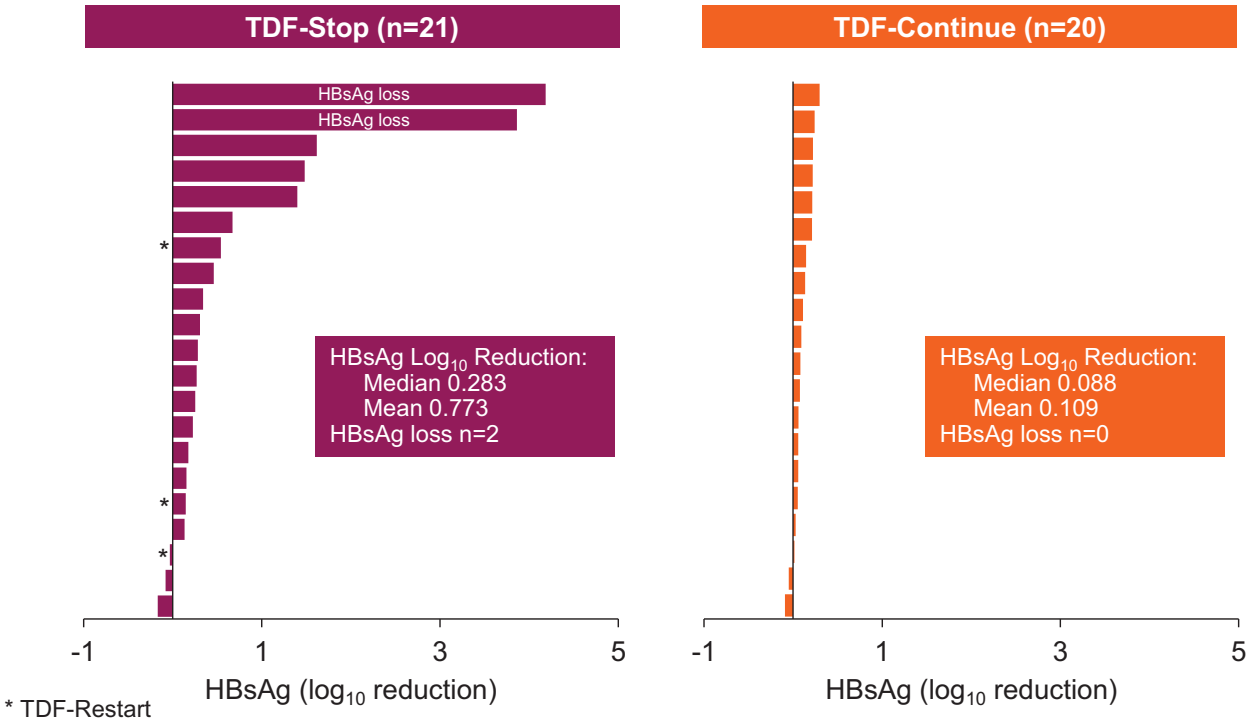
FINITE CHB

停止藥物治療的臨床試驗(1)：HBeAg-Negative CHB



Berg T et al. J Hepatol 2017;67:918-924

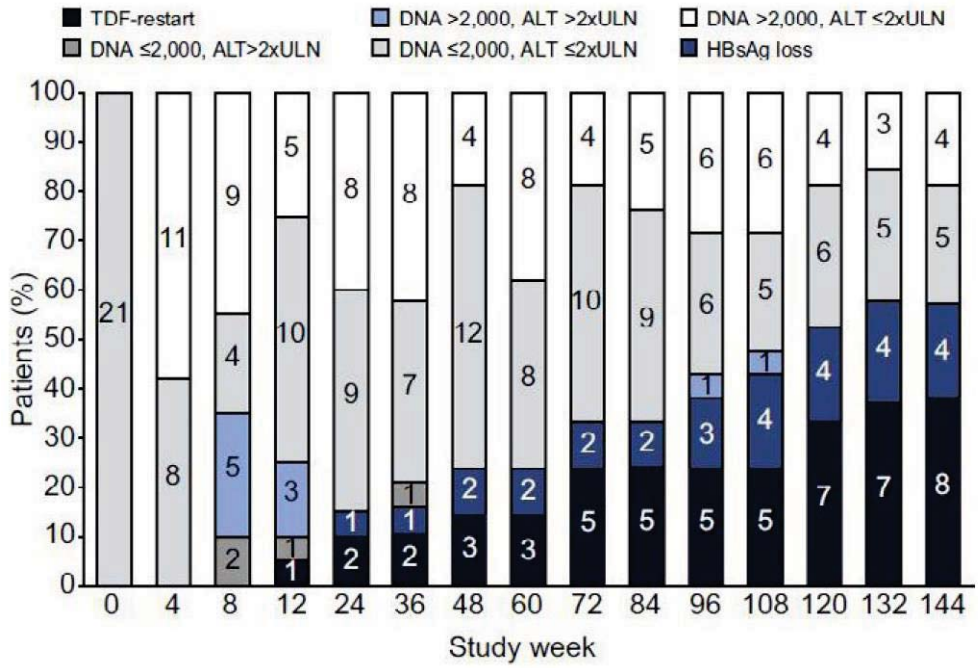
Week 48 HBsAg log_{10} Reduction (Individual Patients)



* TDF-Restart

Berg T et al. J Hepatol 2017;67:918-924

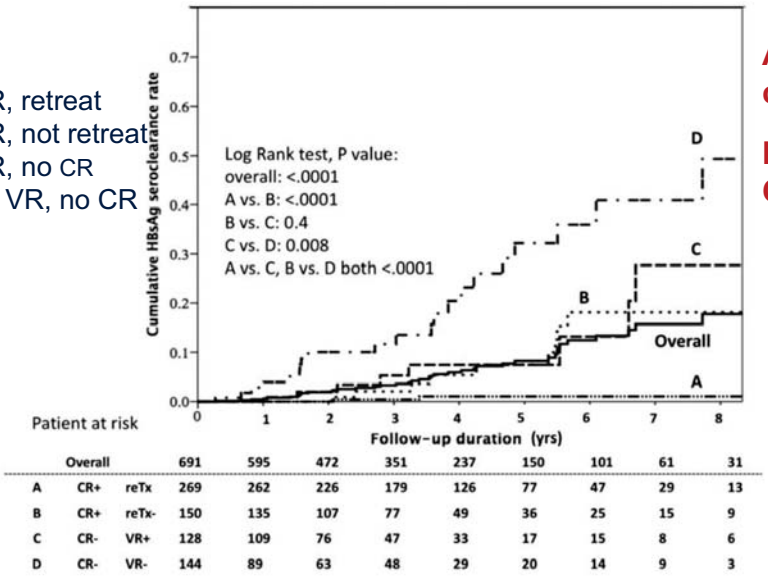
血清HBV DNA, ALT, 和HBsAg變化以及TDF再治療：停藥後144週觀察



Berg T et al. J Hepatol 2017;67:918-924

停止藥物治療的臨床觀察：
HBeAg-Negative CHB

A: CR, retreat
B: CR, not retreat
C: VR, no CR
D: no VR, no CR



Patient at risk

Overall			691	595	472	351	237	150	101	61	31
A	CR+	reTx	269	262	226	179	126	77	47	29	13
B	CR+	reTx-	150	135	107	77	49	36	25	15	9
C	CR-	VR+	128	109	76	47	33	17	15	8	6
D	CR-	VR-	144	89	63	48	29	20	14	9	3

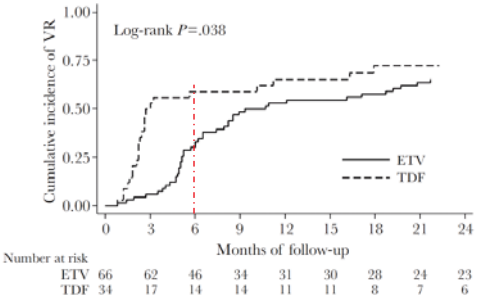
Annual HBsAg loss cumulative incidence:

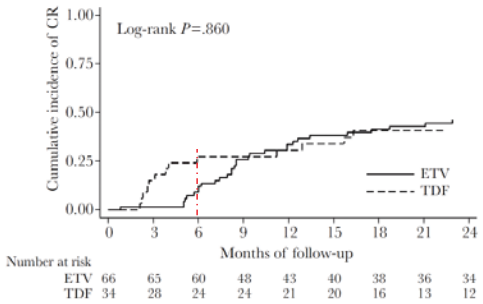
DC group: 1.78%.
Continue group: 0.15%

- **The incidence of HBsAg seroclearance after stopping NUC was much higher than that during therapy**
- **Higher incidence of HBsAg clearance in patients with clinical relapse who remained untreated than those who received retreatment**

Jeng WJ, et al. Hepatology. 2018;68:425-434

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

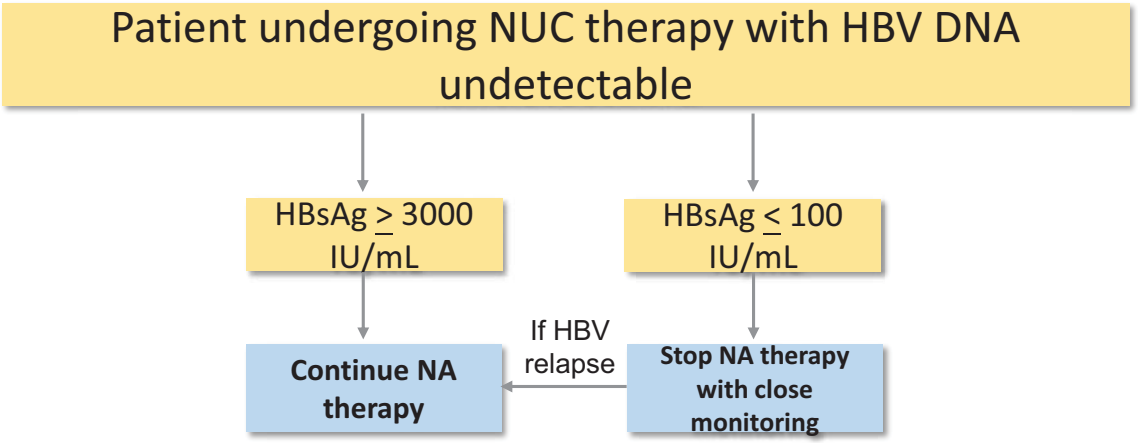
Su TH et al JID 2018

HBeAg-Negative CHB患者經口服藥物治，依照APASL指南停藥後復發的風險

Study	Number	Viral Relapse	Clinical Relapse
Ha et al 48	145	95 (65.5%)	93 (64.1%)
Jeng et al 24	95	55 (57.9%)	43 (45.3%)
kim et al 49	45	33 (73.3%)	24 (53.3%)
Chen et al 22	169	108 (64.3%)	87 (51.6%)
Jiang et al 50	39	25 (64.1%)	19 (48.7%)
Lee et al 51	64	50 (77.7%)	26 (41.9%)
Seto et al 31	184	168 (91.4%)	42 (22.8%)
Jung et al 52	68	37 (54.4%)	19 (28.9%)
Overall (total)	809	571	353
Overall (%)		70.5%	43.6%

B型肝炎患者完成治療後，須監測與治療B型肝炎復發

Stopping rules for CHB patients base on EOT HBsAg level



Patients considered to have a lower risk of virologic and biochemical relapses:
1) HBsAg levels at the time of stopping treatment, e.g., < 100–150 IU/mL
2) Longer consolidated treatment duration
3) Lower HBV DNA at the time of treatment initiation

Kao JH, Jeng WJ and et al. Hepatology International
https://doi.org/10.1007/s12072-021-10223-5

Close Monitoring for Non-cirrhosis HBeAg-Negative Patients is Highly Recommended

Monitoring Plan for HBeAg(-)

Under NUCs, HBeAg(-) undetectable HBV DNA, ALT≤ULN

Consolidation therapy

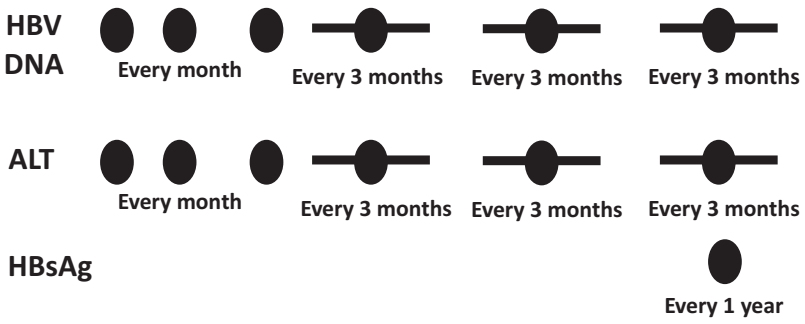
ALT & HBV DNA monthly for 3 months, Every 3 months until month 12*

**Type of NA could affect monitoring intervals*

Harmful Relapse: Re-treatment See indication for retreatment

Durable Relapse: ALT & HBV DNA every 3-6 months, HBsAg every 12 months, HCC surveillance

Routine Testing and Monitoring Frequency



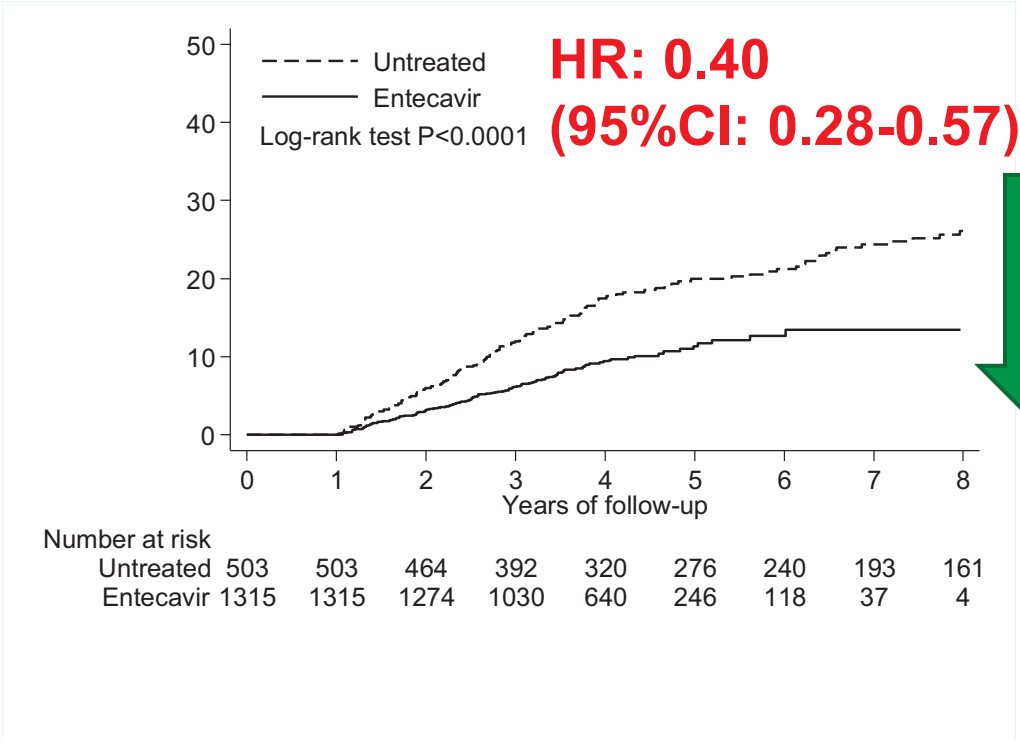
Kao JH, Jeng WJ and et al. Hepatology International https://doi.org/10.1007/s12072-021-10223-5
Anderson KA, et al. Hepatology. 2009 May ; 49(5 Suppl): S166–S173.

長期治療可以減少但無法完全避免肝細胞癌發生

⇩

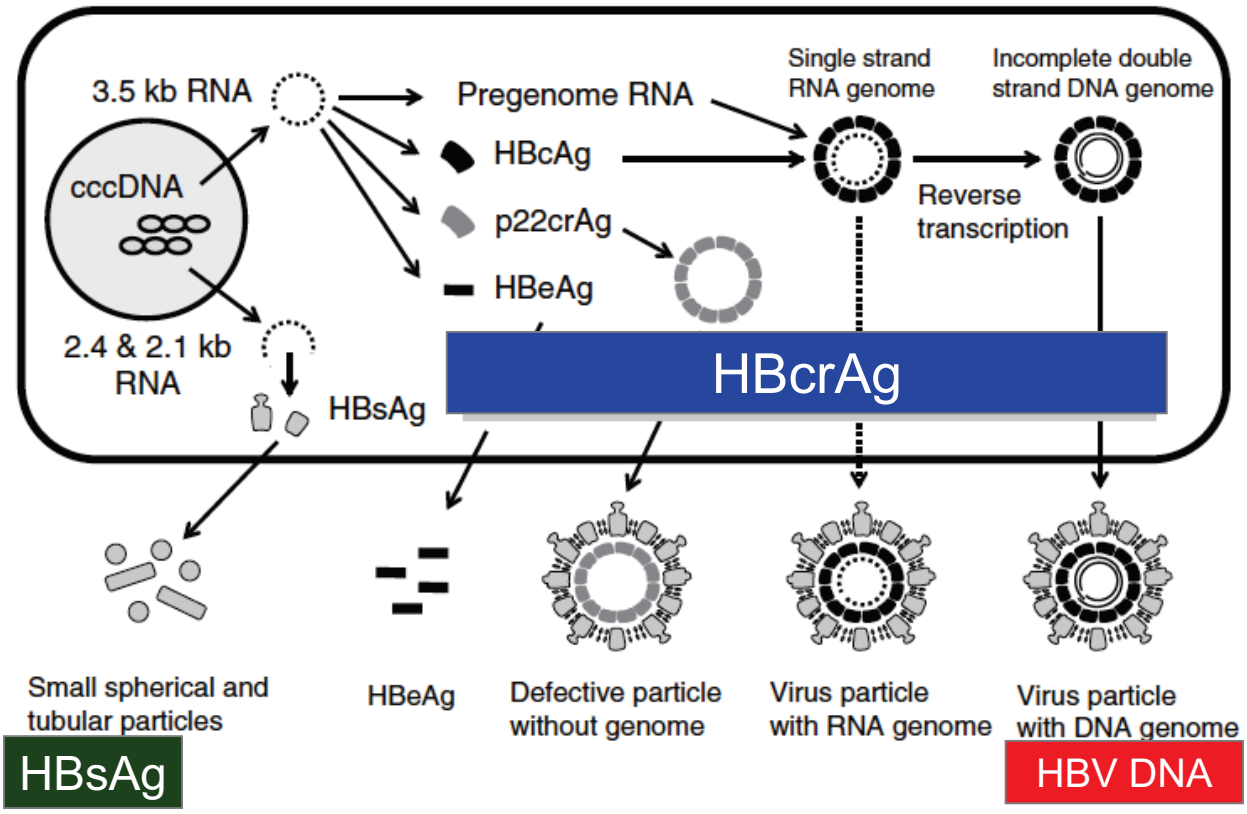
接受治療患者需持續監測B型肝炎患者發生肝細胞癌風險之預測標誌

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



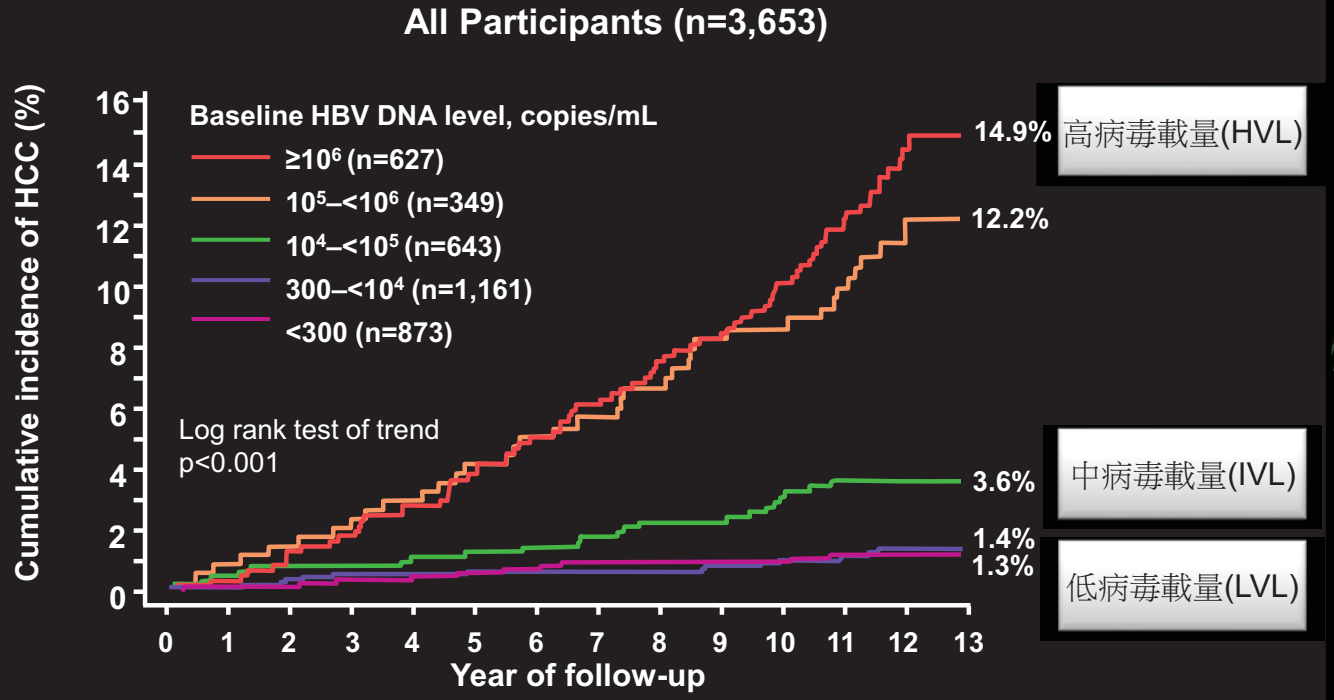
Su and Kao et al., Liver Int. 2016 Dec;36(12):1755-1764

HBV血清生物標誌



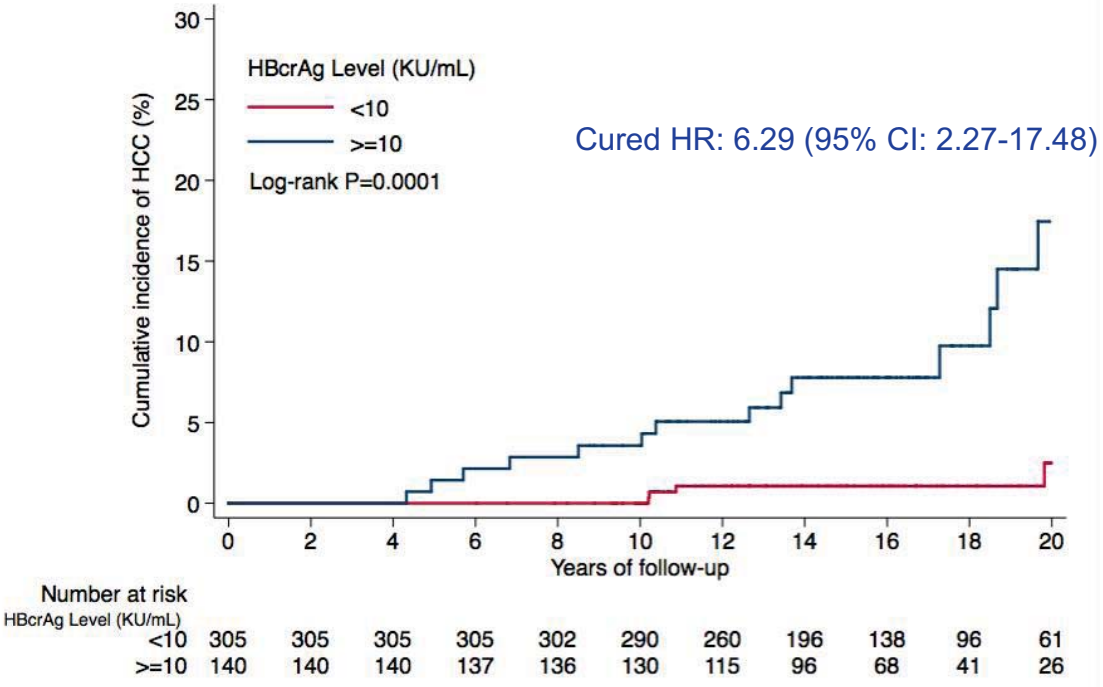
Modified from Tanaka et al. Hepatol Res 2013.

R.E.V.E.A.L.: 高病毒載量增加肝細胞癌風險



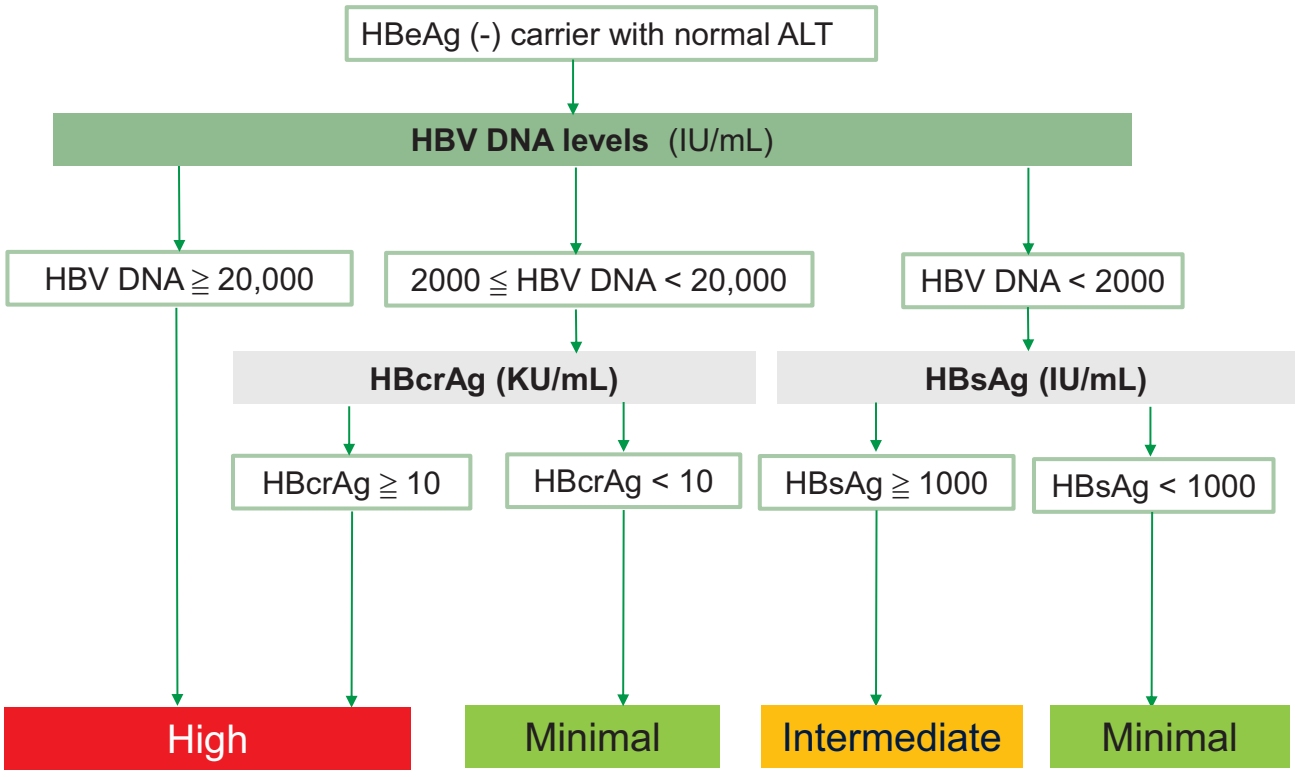
Chen et al. JAMA 2006; 2006;295:65.

針對445 eAg^{neg} 患者屬於IVL+ALT<40 U/L時，HBcrAg可以分辨HCC之風險



Tseng TC et al, Gastroenterology. 2019 ;157:1518-1529

利用血清生物標誌預測預後



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

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。

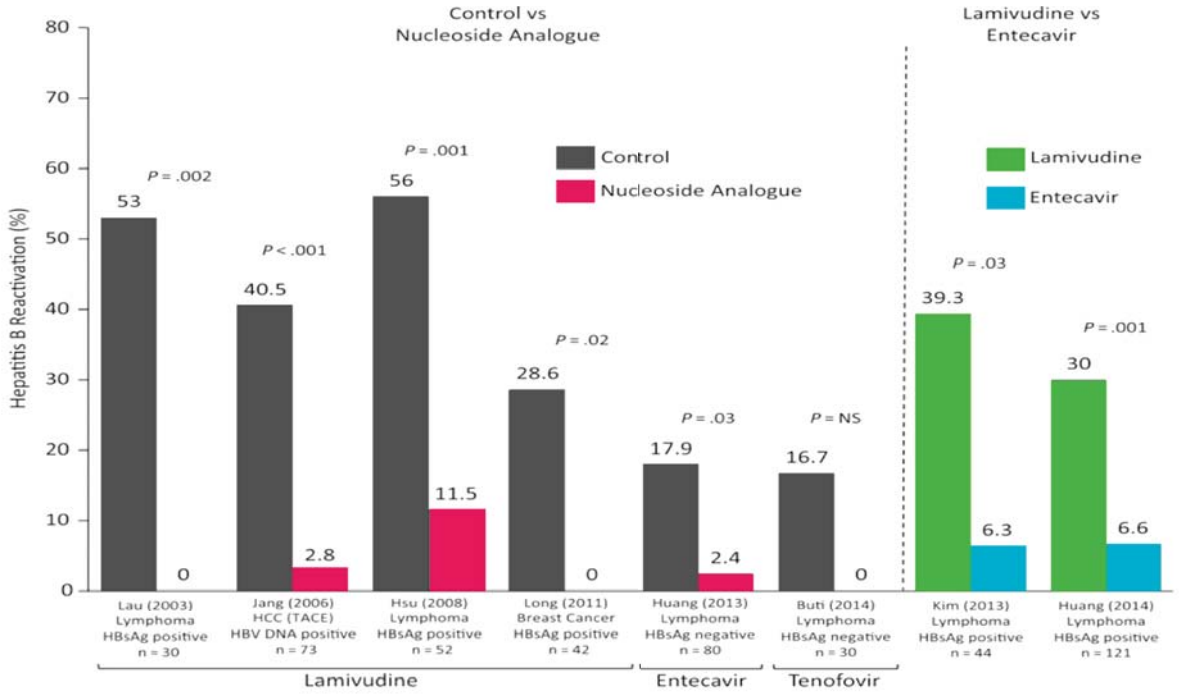
- **HBIG can be Applied to all Pregnant Women with HBsAg Carriage in Taiwan Since July 2019**
- 母親**HBsAg**陽性幼兒滿**12**個月可抽血檢驗，若**anti-HBs(-) and HBsAg (-)**，可以免費追加一劑疫苗

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

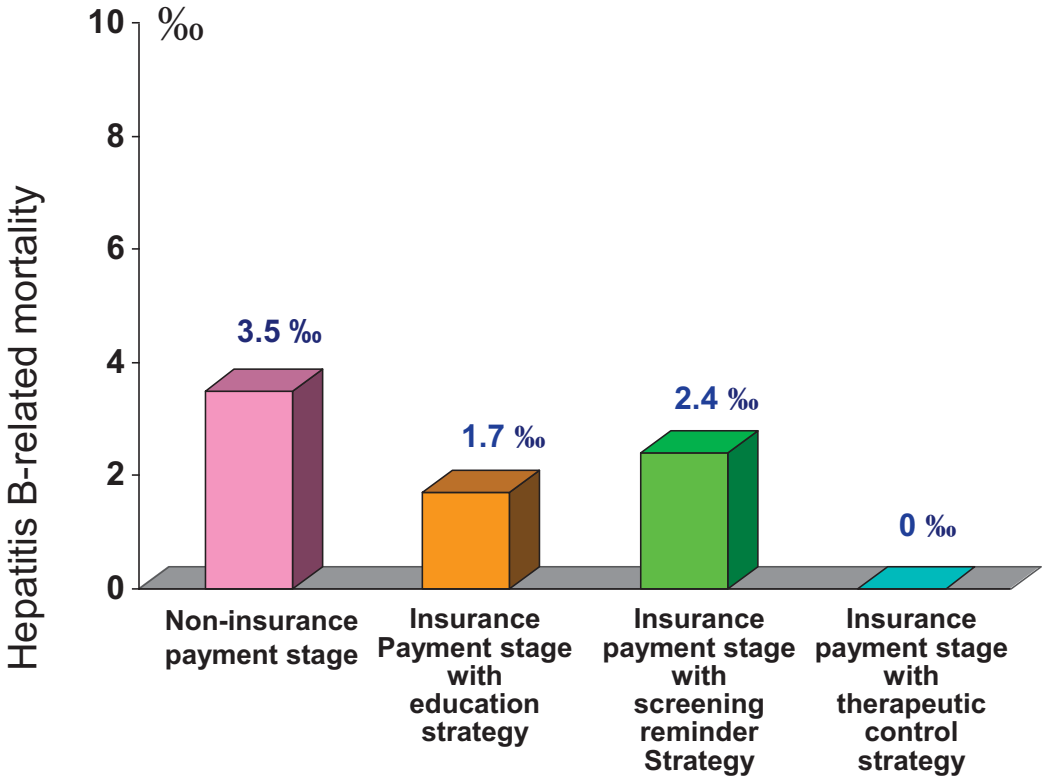
ITT analysis included infants born to all enrolled participants except for those who withdrew consent before the initiation of treatment.
PP analysis excluded infants born to women who withdrew consent, were lost to follow-up, or discontinued treatment for any reason. MTCT: mother-to-child transmission;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

免疫抑制患者接受治療風險評估與預防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

Risk stratification of HBVr: High

Risk Level	HBV Serology	
	HBsAg(+)	HBsAg(-)/anti-HBc(+)
High (>10 %)	• Anti-CD20 monoclonal antibodies: Rituximab, Ofatumumab, Obinutuzumab • Steroid (high dose) ≥ 20 mg/day for ≥ 4 weeks • Anti-TNF agents with higher potency: Adalimumab, Infliximab, Golimumab, Certolizumab pegol • Anthracyclines • Hematopoietic stem cell transplantation (both allogeneic and autologous) • DAA for HBV/HCV coinfection (high risk in meta-analysis and prospective study), except non-cirrhotics with HBsAg < 10 IU/ml • Immune Checkpoint inhibitors (moderate to high risk): - Anti-PD-1: nivolumab, pembrolizumab - Anti-PD-L1: atezolizumab - Anti-CTLA-4: ipilimumab • Tyrosine kinase inhibitors (moderate-to- high): Imatinib, Nilotinib, Dasatinib, Erlotinib, Gefitinib, Osimertinib, Afatinib	• Anti-CD20 monoclonal antibodies: Rituximab, Ofatumumab, Obinutuzumab • Allogeneic hematopoietic stem cell transplantation

Lau G, et al. Hepatology International (2021) 15:1031–1048

Risk stratification of HBVr: Moderate

Risk Level	HBV Serology: HBsAg(+)	HBV Serology: HBsAg(-)/anti-HBc(+)
Moderate (1–10%)	• Cytotoxic chemotherapy (except anthracyclines) • Anti-TNF agents with lower potency: Etanercept • Steroid (median dose): 10–20 mg/day for ≥ 4 weeks • Proteasome inhibitor: Bortezomib Ustekinumab	• **Anthracyclines** • Autologous hematopoietic stem cell transplantation • Anti-TNF agents with higher potency: Adalimumab, Infliximab, Golimumab, Certolizumab pegol • Proteasome inhibitor: Bortezomib Ustekinumab

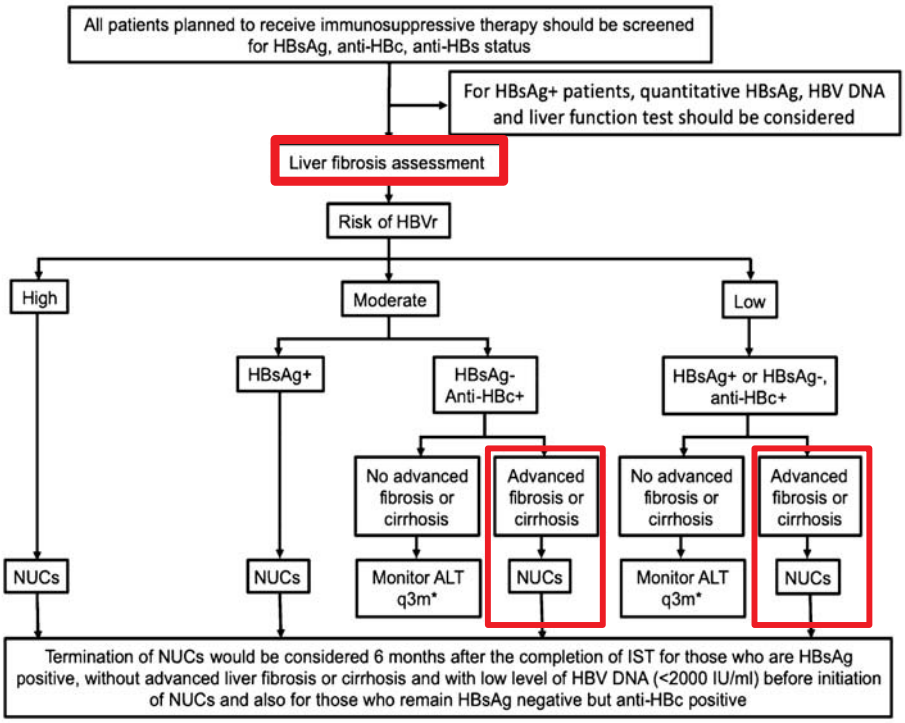
Lau G et al. Hepatology International (2021) 15:1031–1048

Risk stratification of HBVr: Low and Uncertain

Risk Level	HBV Serology: HBsAg(+)	HBV Serology: HBsAg(-)/anti-HBc(+)
Low (<1%)	• Methotrexate • Azathioprine • Steroid (low dose < 10 mg/day) • DAA for HBV/HCV coinfection for non-cirrhotic patients with HBsAg < 10 IU/ml	• Cytotoxic chemotherapy (except anthracyclines) • Steroid (high dose) ≥ 20 mg/day • Anti-TNF agents with lower potency: Etanercept • Tyrosine kinase inhibitors Imatinib, Nilotinib, Dasatinib • DAA for HCV
Uncertain (more studies are needed)	• Abatacept (case reports and small retrospective studies) • Tocilizumab (case reports and small studies) • Ibrutinib (case reports and small retrospective study) • Alemtuzumab (case reports) Natalizumab (case reports) • Ocrelizumab (case reports) Ibritumomab (case reports)	• **Immune Checkpoint inhibitors** - Anti-PD-1: nivolumab, pembrolizumab - Anti-PD-L1: atezolizumab - Anti-CTLA-4: ipilimumab

Lau, Yu ML et al. Hepatology International (2021) 15:1031–1048

APASL practice guideline on HBV treatment upon immunosuppressive therapy



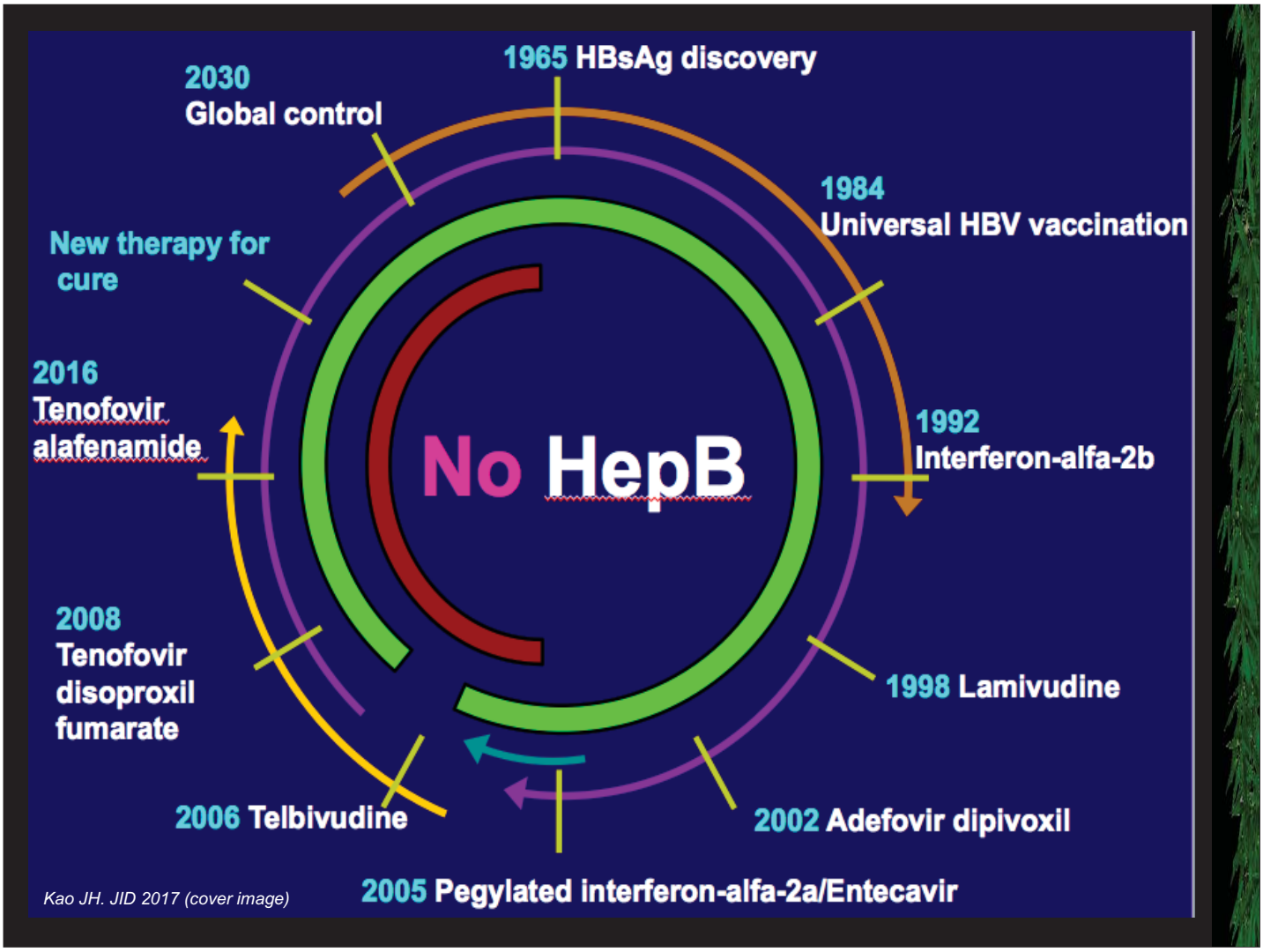
Lau G et al. Hepatology International (2021) 15:1031–1048

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

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



謝謝大家聆聽