B型肝炎篩檢與治療的臨床實務

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內容

- 國人B型肝炎的篩檢與治療
  - 目前國內篩檢B型肝炎的策略
  - 各種B型肝炎治療的優缺點與限制
  - 最新口服抗病毒藥物介紹
- 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

國人106年因肝病而死亡者

- 肝癌：約八千四百人
- 慢性肝病及肝硬化：約四千六百人

合計：一萬三千人

如何知道自己有無肝病？

- 肝功能檢查
- B型肝炎檢驗
- C型肝炎檢驗
- 甲種胎兒蛋白檢查
- 腹部超音波檢查

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

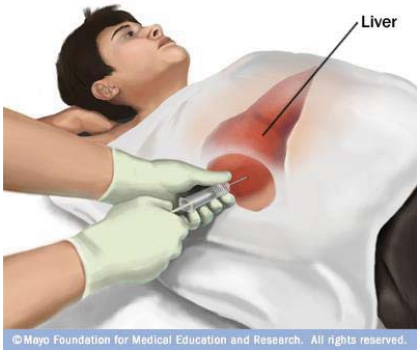
B型肝炎誰需要接受治療?

- 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

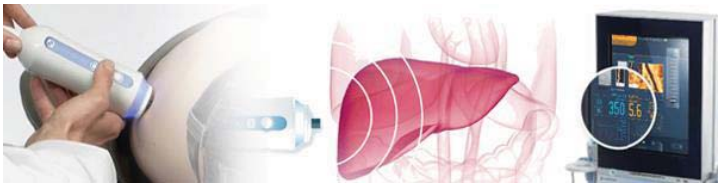
評估肝臟纖維化



- 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

慢性B型肝炎之治療目標

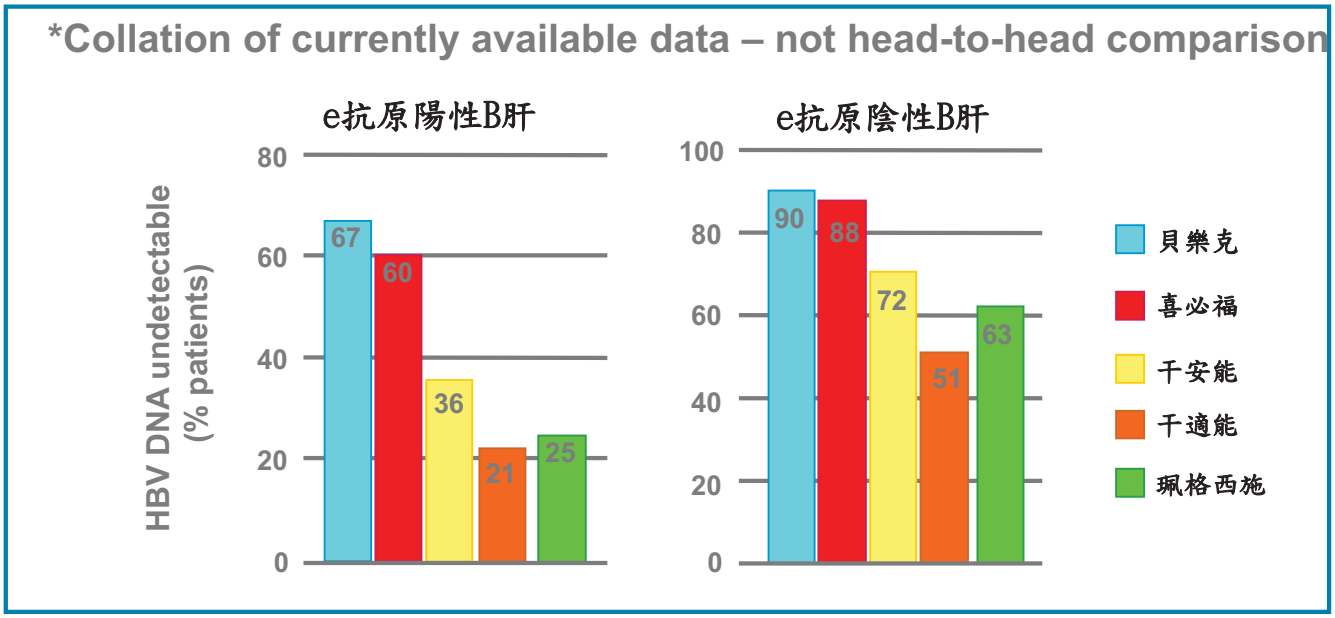
- 清除/壓抑病毒
  - * 減少致病原
  - * 減少傳染性
- 減少肝發炎壞死
  - * 肝炎緩解（逆轉肝纖維化）
  - * 預防肝衰竭
- 遏止病程進展
  - * 減少急性發作，肝硬化和肝細胞癌
- 改善存活率

慢性B型肝炎之治療選擇

- 傳統型干擾素
- 長效型干擾素
  - 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)
- 韋立得 (Tenofovir alafenamide, TAF)

短期治療的療效指標與比較

治療1年後病毒量下降之比率

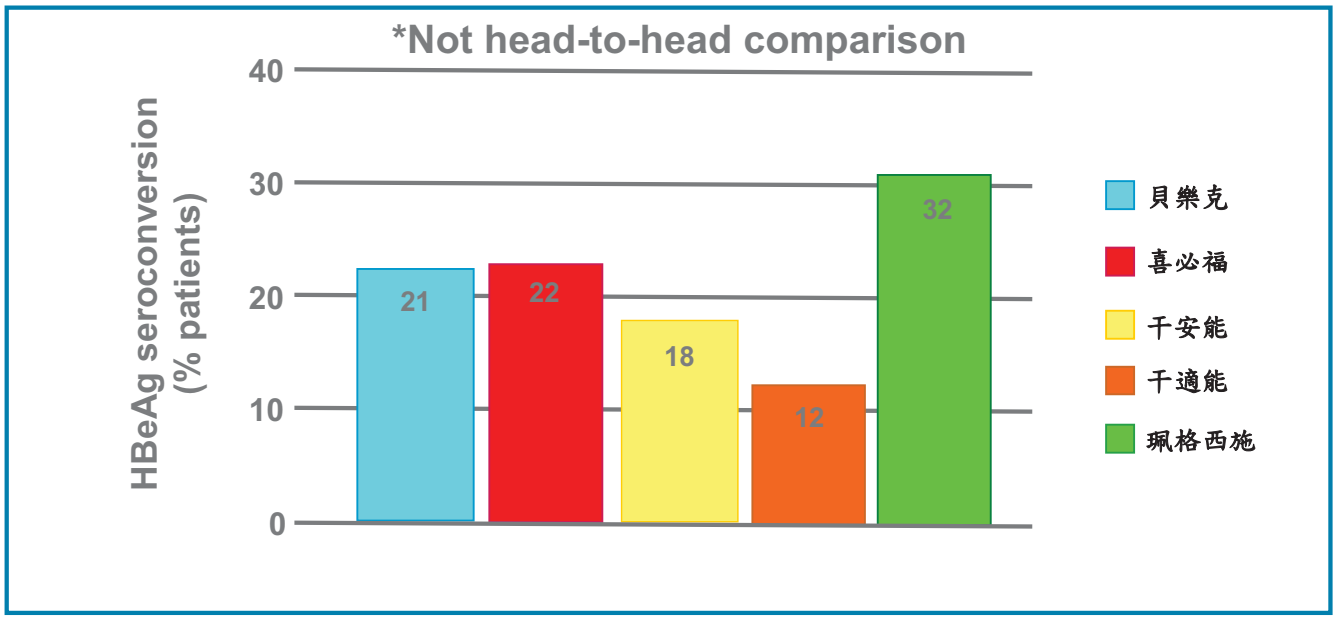


*Undetectable <300 copies/mL
#Undetectable <400 copies/mL

Lai CL, et al. Hepatology 2005; 42(Suppl 1):748A (abstract LB01); Lau G, et al. NEJM 2005; 352:2882–2695; Chang T-T, et al. NEJM 2006; 354:1000–1010; Lai CL, et al. NEJM 2006; 354:1011–1020; Marcellin P, et al. NEJM 2003;348:808–816; Marcellin P, et al. NEJM 2004;348:1206–1217; Hadziyannis SJ, et al. NEJM 2003;348:800–807

治療一年後之HBe抗原轉換率

HBe抗原轉換 = HBe抗原轉陰和HBe抗體轉陽



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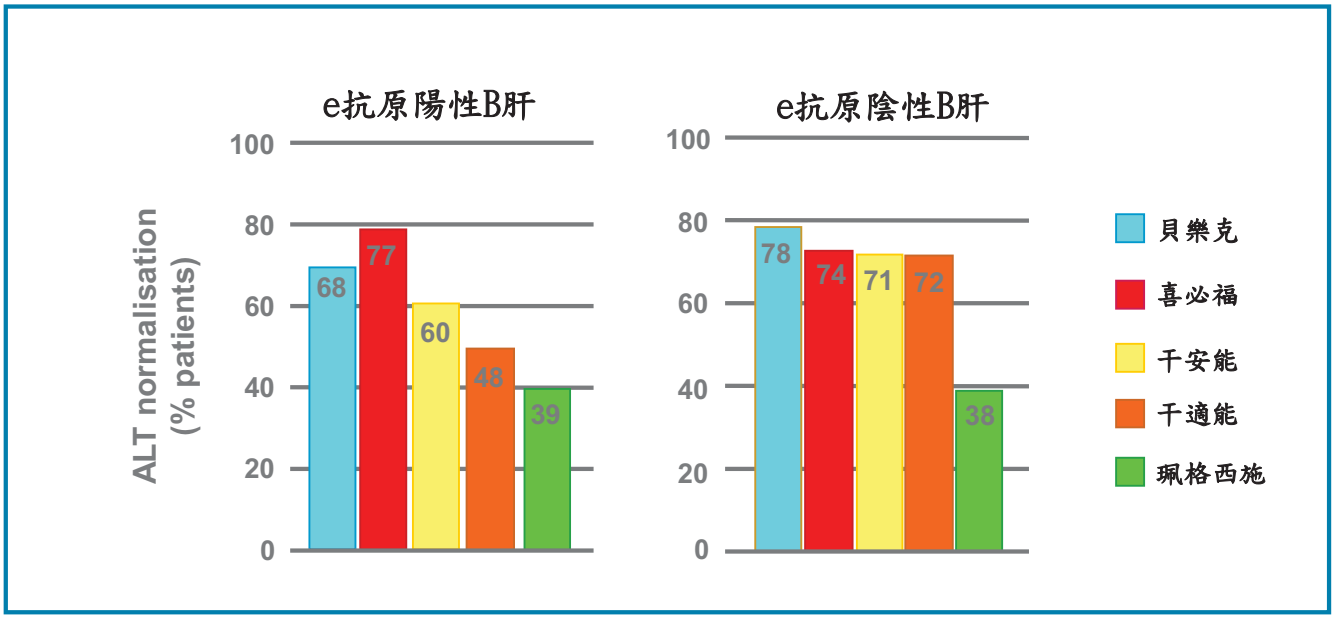
Chang T-T, et al. NEJM 2006; 354:1000–1010.
Marcellin P, et al. NEJM 2003;348:808–816.

治療1年後ALT正常之比率



Lai CL, et al. Hepatology 2005; 42(Suppl 1):748A (abstract LB01); Lau G, et al. NEJM 2005; 352:2882–2695; Chang T-T, et al. NEJM 2006; 354:1000–1010; Lai CL, et al. NEJM 2006; 354:1011–1020; Marcellin P, et al. NEJM 2003;348:808–816; Marcellin P, et al. NEJM 2004;348:1206–1217; Hadziyannis SJ, et al. NEJM 2003;348:800–807;

Efficacy of first-line anti-HBV

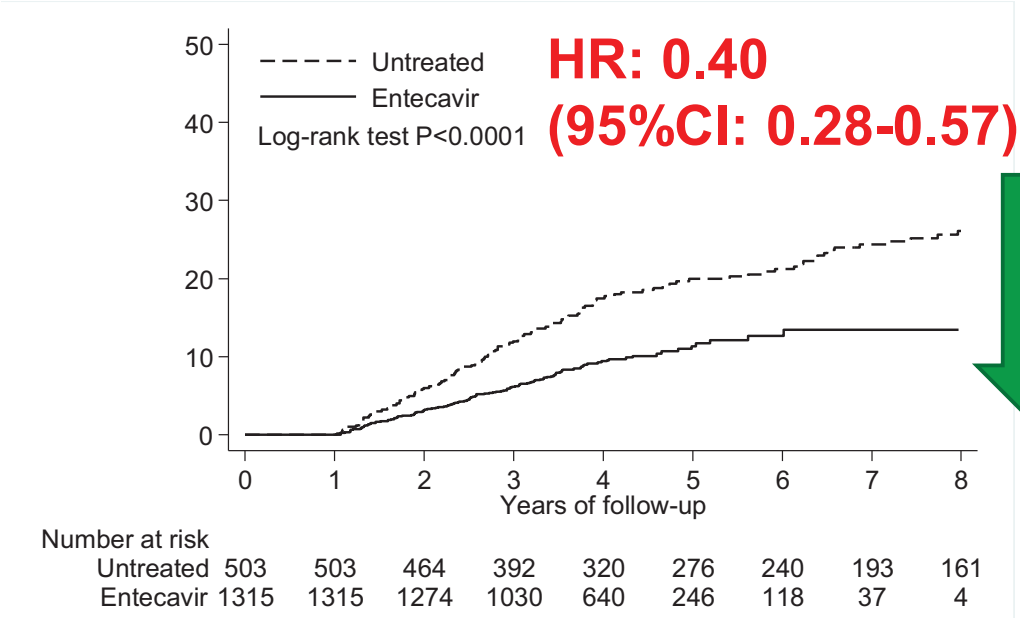
HBeAg Positive	Peg-IFN*	Entecavir†	Tenofovir Disoproxil Fumarate†	Tenofovir Alafenamide‡
% HBV-DNA suppression (cutoff to define HBV-DNA suppression)§	30-42 (<2,000-40,000 IU/mL) 8-14 (<80 IU/mL)	61 (<50-60 IU/mL)	76 (<60 IU/mL)	73 (<29 IU/mL)
% HBeAg loss	32-36	22-25	—	22
% HBeAg seroconversion	29-36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

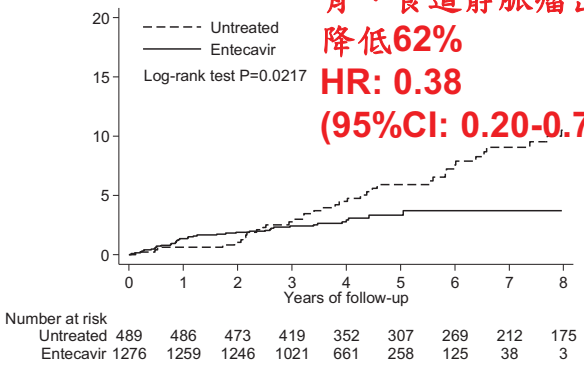
長期治療的好處

長期抗病毒藥物治療降低6成肝硬化患者之肝癌發生率

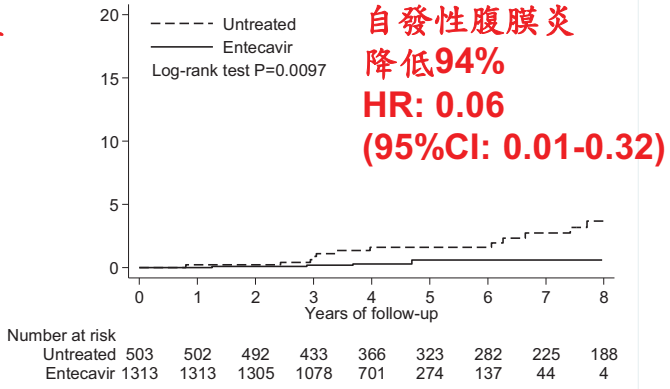


Su and Kao et al., Liver Int. 2016 Dec;36(12):1755-1764

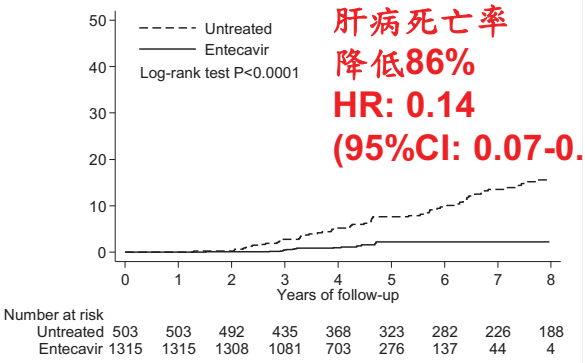
長期抗病毒藥物治療降低肝硬化併發症及死亡率



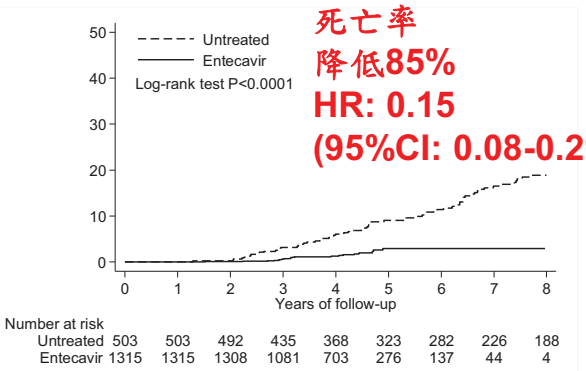
胃、食道靜脈瘤出血
降低62%
HR: 0.38
(95%CI: 0.20-0.74)



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



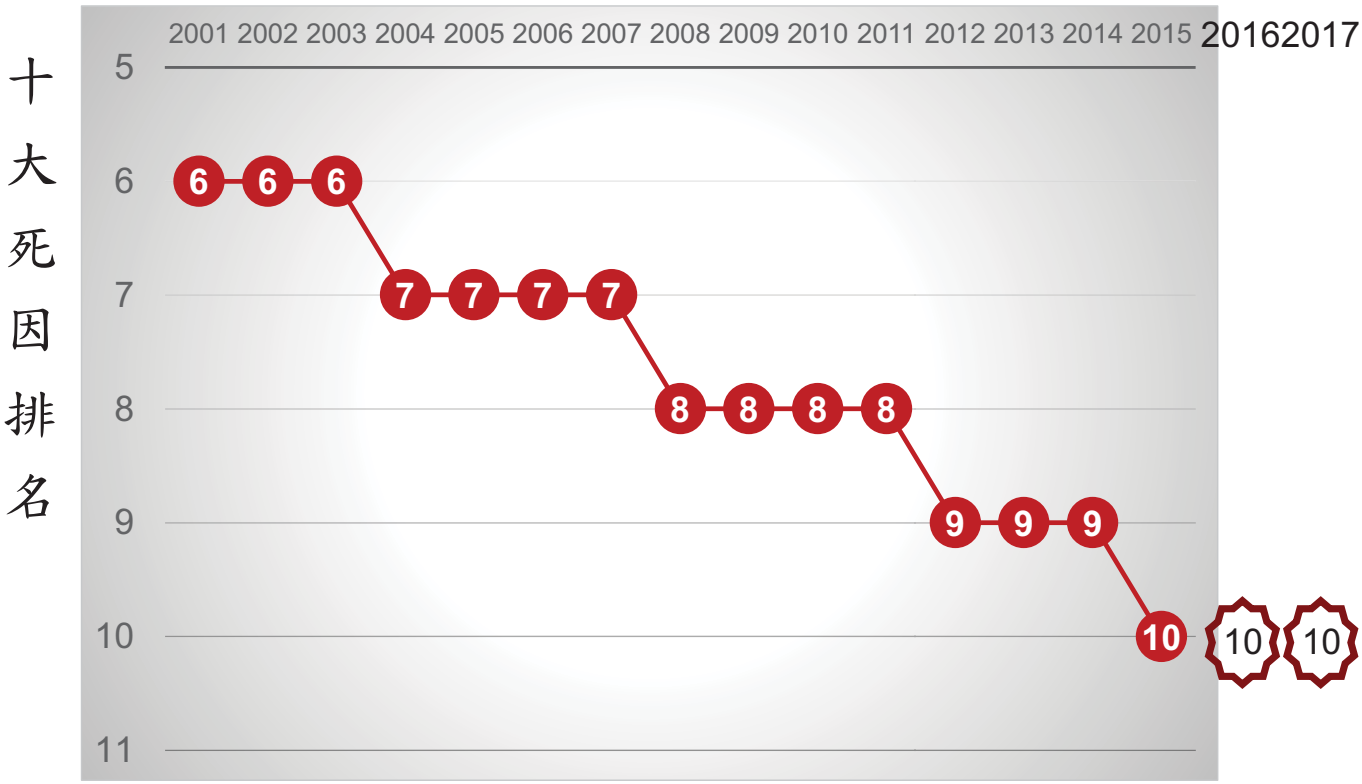
肝病死亡率
降低86%
HR: 0.14
(95%CI: 0.07-0.30)



死亡率
降低85%
HR: 0.15
(95%CI: 0.08-0.29)

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

國人十大死因中慢性肝病排名逐年下降



2017

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

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

2017-01-01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)，Tenofovir，Telbivudine，Lamivudine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)，Tenofovir，Lamivudine，Telbivudine 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

2017-01-01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、Tenofovir、Telbivudine、Lamivudine長期給予	•Entecavir 0.5mg、Tenofovir、Telbivudine、Lamivudine 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Tenofovir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Tenofovir或合併Tenofovir/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

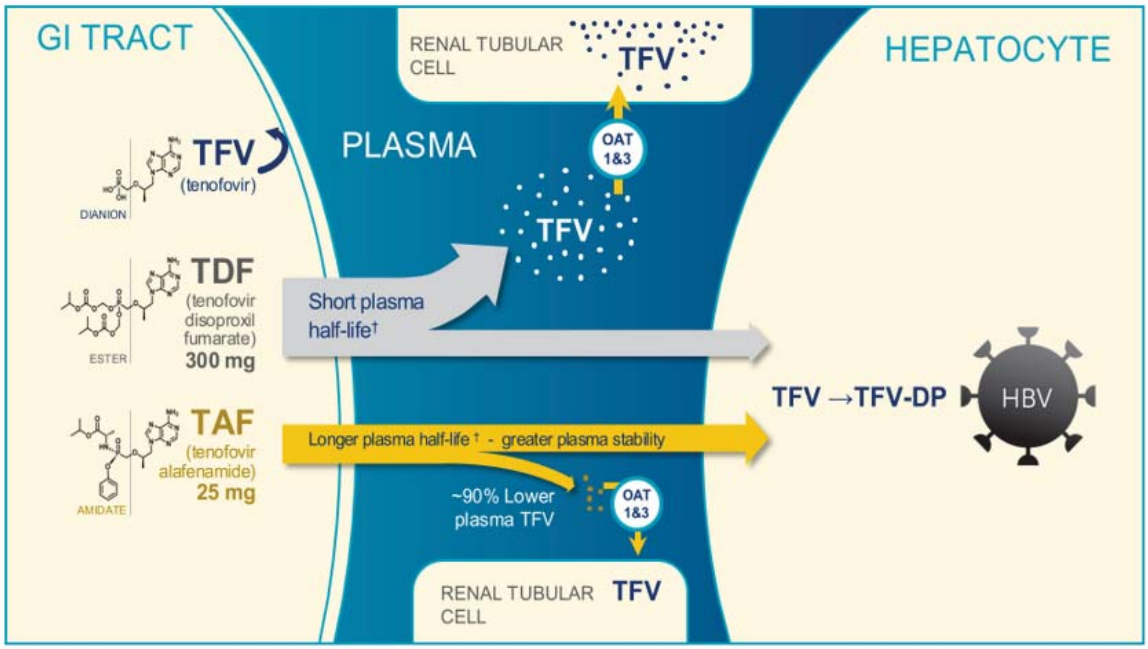
初次治療　可再次治療　不限次數 再治療

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

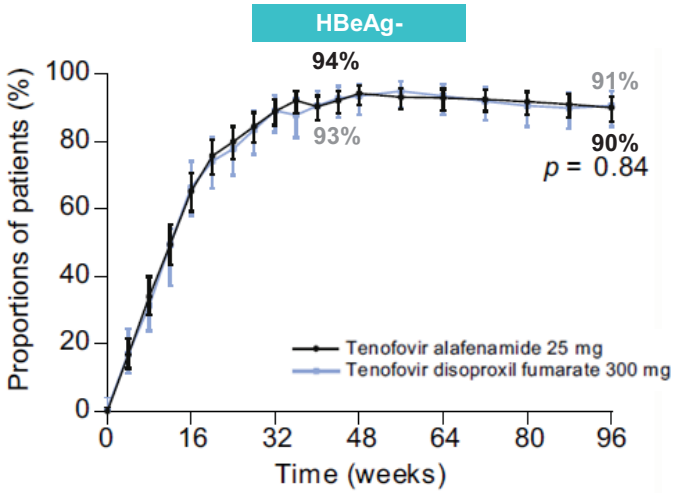
新一代治療慢性B肝口服藥物

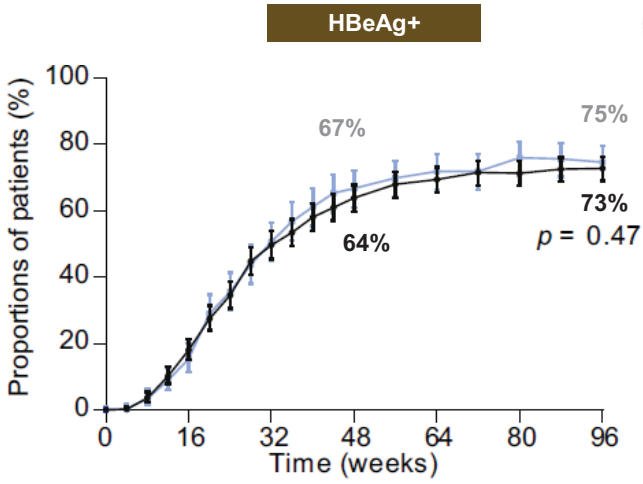
Tenofovir alafenamide (TAF)

Prodrug Pharmacology of TDF and TAF



Proportion of Patients With HBV DNA <29 IU/mL Through Week 96



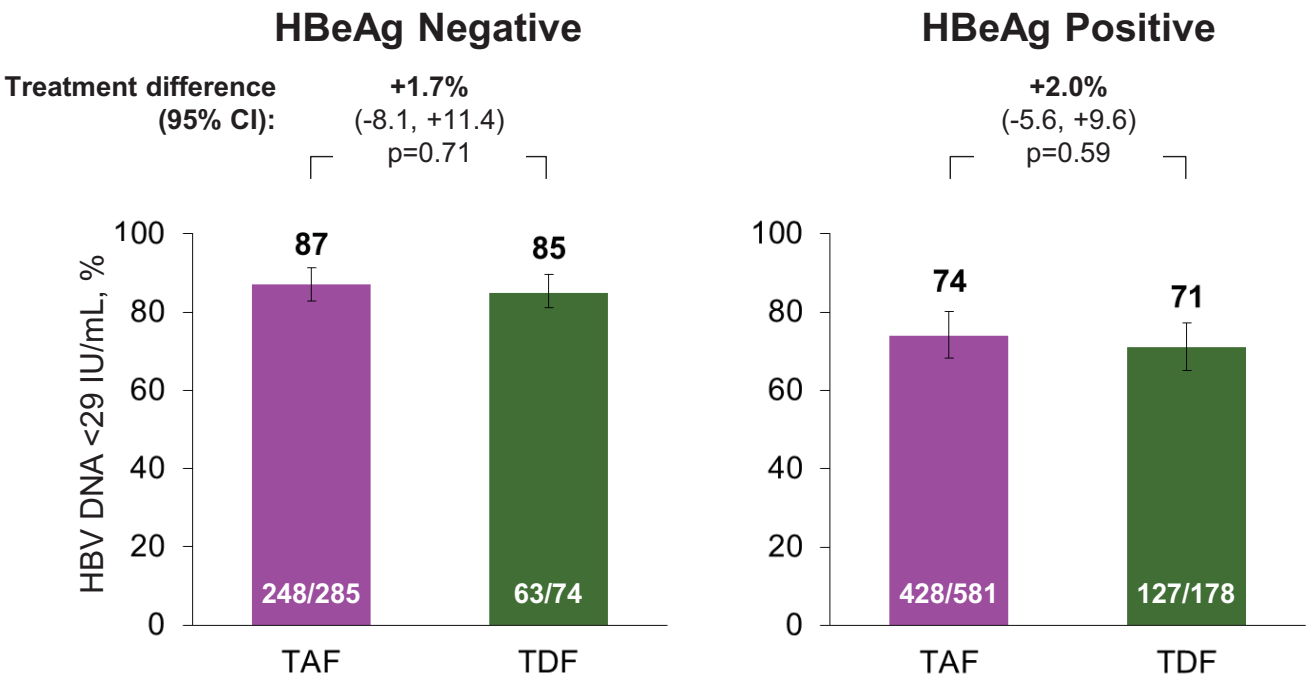


	TAF	TDF
HBsAg loss	<1%	0

	TAF	TDF
HBeAg seroconversion	18%	12%
HBsAg loss	1%	1%

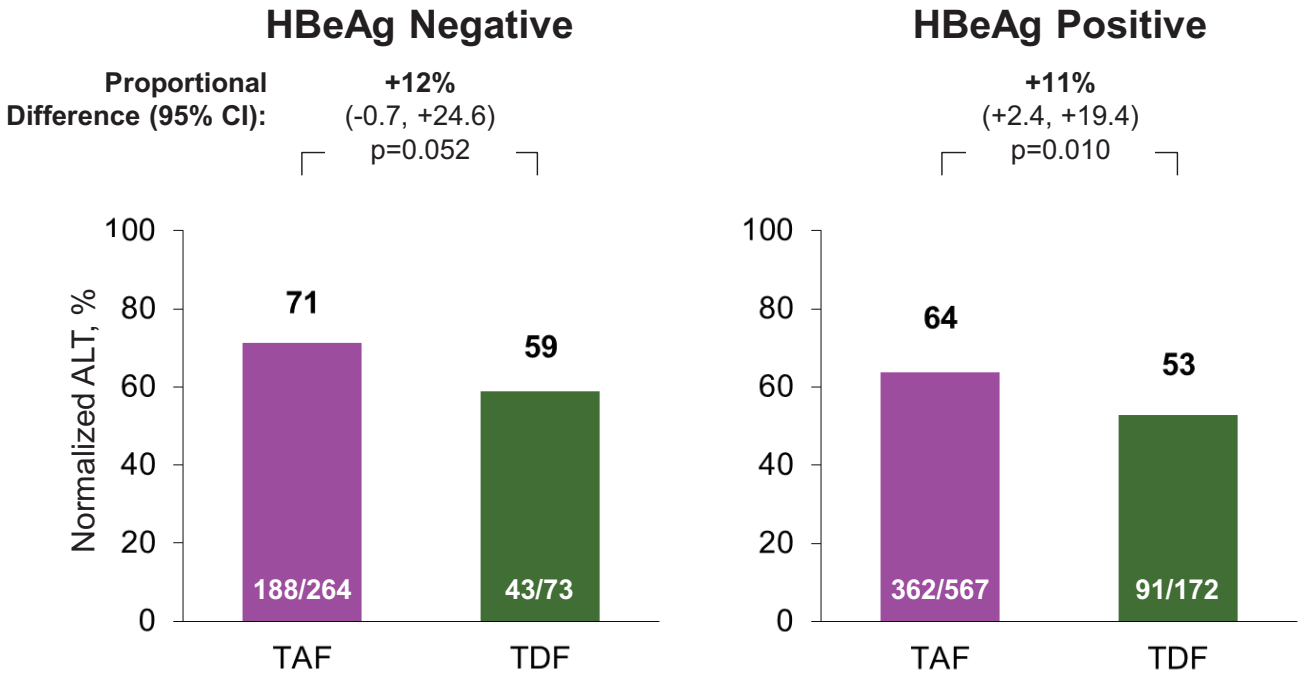
Agarwal et al. J Hepatol. 2018; 68:672

Week 144 Virology in Patients Receiving 144 Weeks of TAF or TDF



Chan HY et al. Poster #381 The Liver Meeting 2018

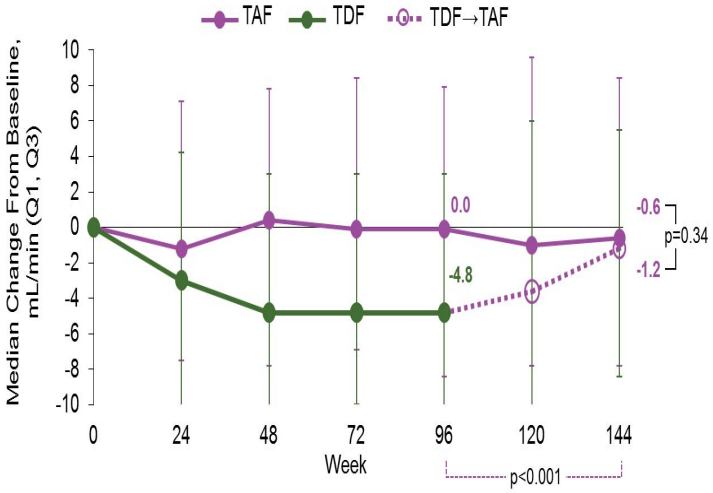
ALT Normalization at Week 144 in Patients Receiving TAF or TDF

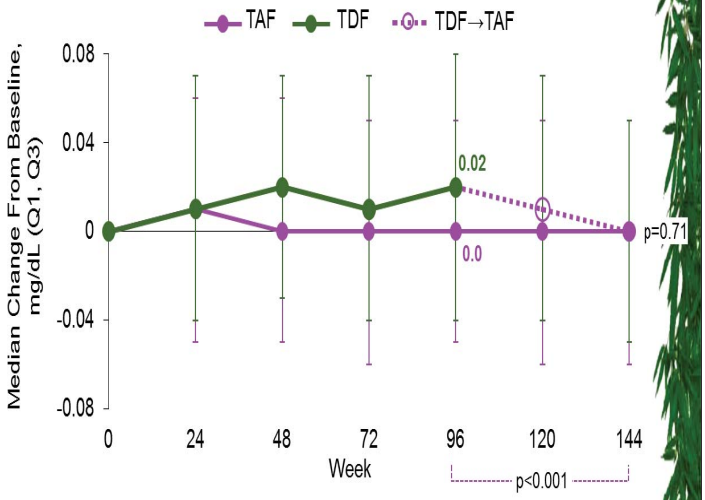


2018 AASLD ALT cutoffs: <25 U/L females and <35 U/L males

Chan HY et al. Poster #381 The Liver Meeting 2018

Renal Function After Switching From TDF to TAF

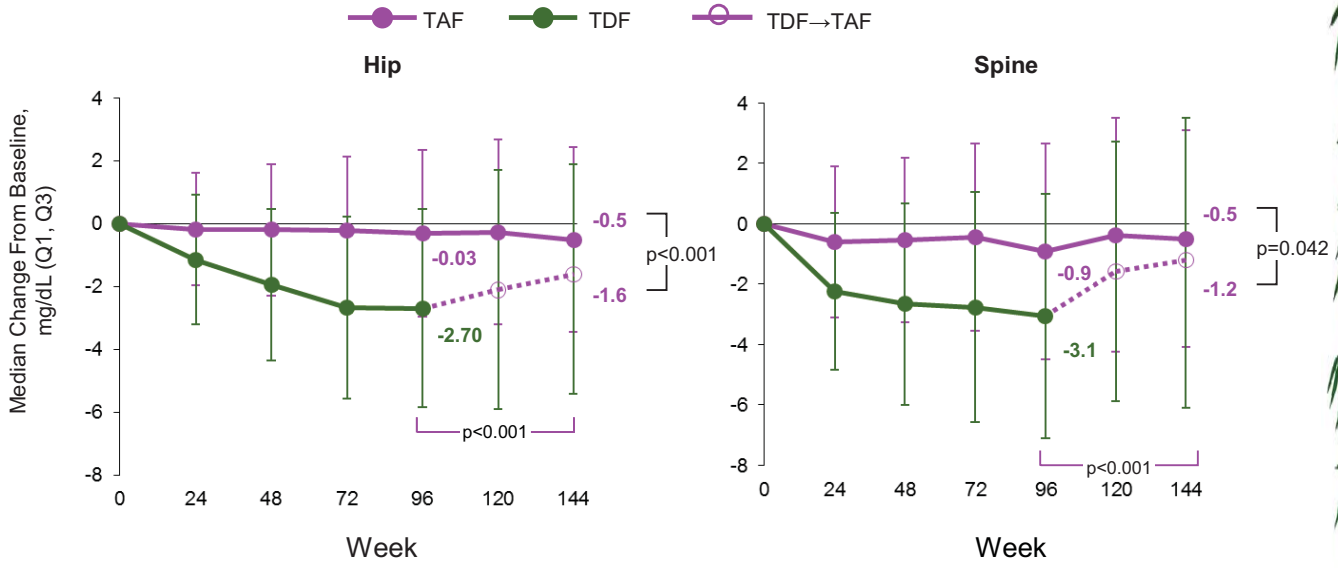




- **Median change from baseline in creatinine clearance decreased significantly at 144wk in patients who switched from TDF to TAF at week 96**
- **Median change from baseline in serum creatinine decreased at week 144 in patients who switched from TDF to TAF at week 96**

Shalimar, APASL, 2018, Oral O-HBV-13

BMD After Switching From TDF to TAF



- **A significant improvement in hip and spine BMD were observed at week 144 in patients who switched from TDF to TAF at 96wks**

Shalimar, APASL, 2018, Oral O-HBV-13

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

Prospective, non-randomized trial in 118 HBeAg+ pregnant women in Taiwan with CHB, who either took TDF (n=62) from 30–32 weeks of gestation until post-

200 HBeAg+ mothers with HBV DNA >200,000 IU/mL randomised (1:1) to usual care or to TDF from 30–32 weeks of

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。

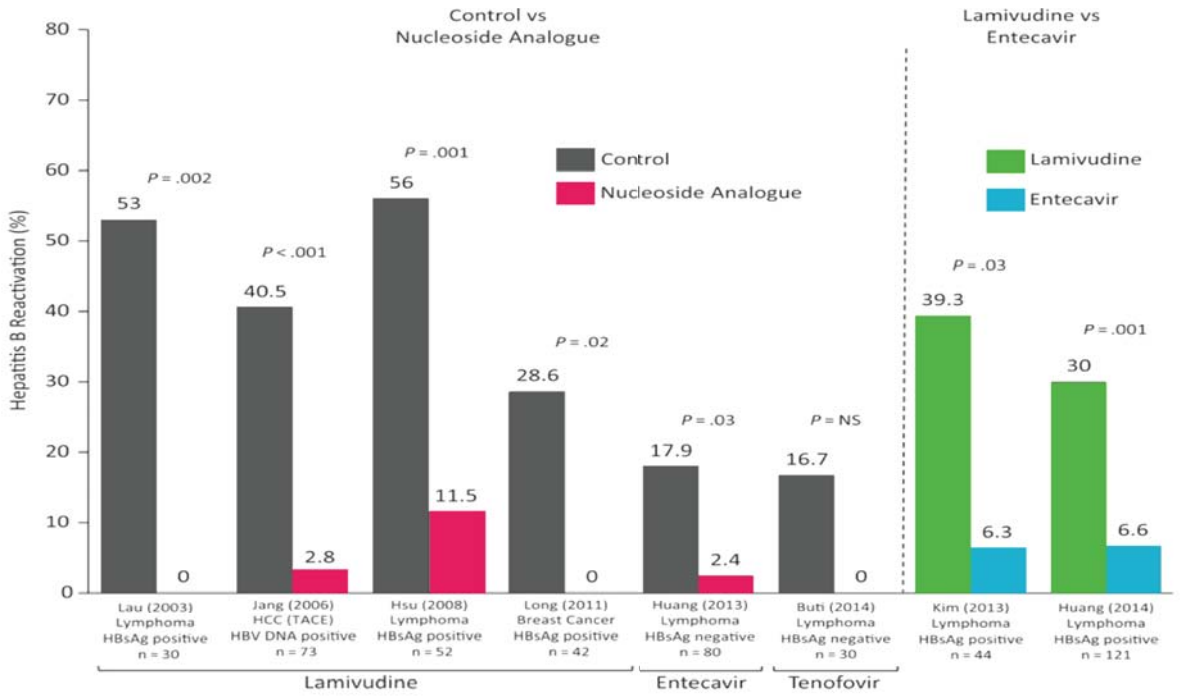
Change in HBV DNA, log_{10} IU/mL from baseline	-3.89±0.87	-0.11±0.51	
Infant Outcomes, n/N (%)			
HBsAg-positive at Month 6	1/65 (1.54%)	6/56 (10.71%)	0.0481

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

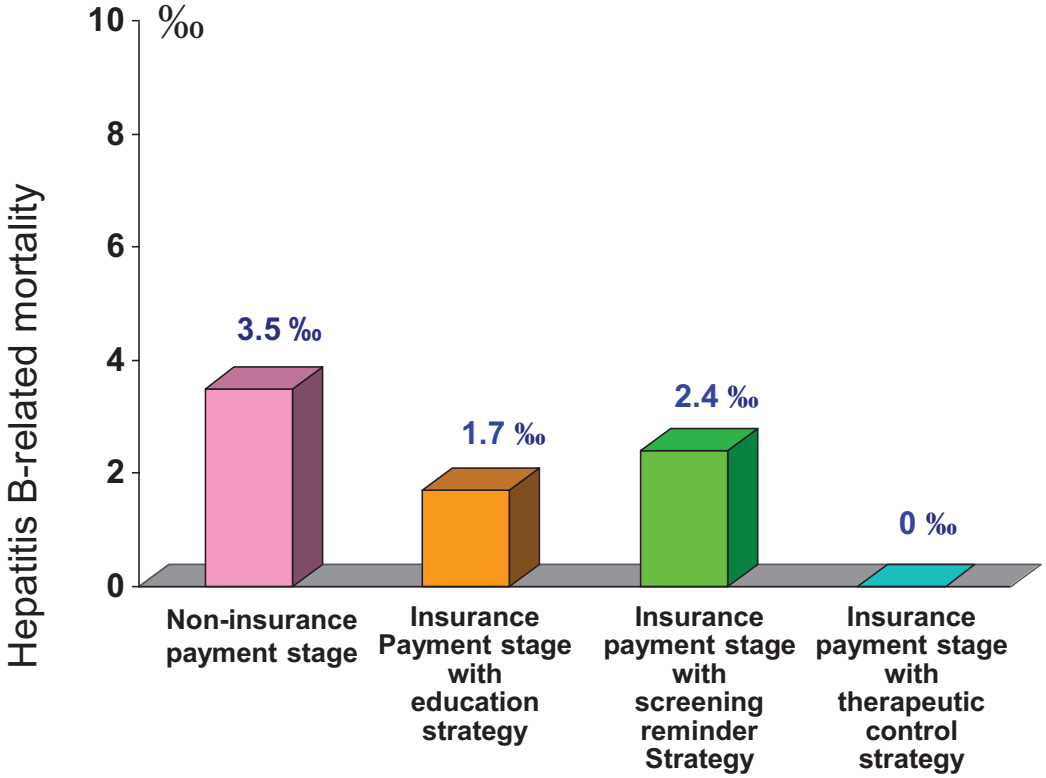
ITT analysis included infants born to all enrolled participants except for those who withdrew consent before the initiation of treatment.
PP analysis excluded infants born to women who withdrew consent, were lost to follow-up, or discontinued treatment for any reason. MTCT: mother-to-child transmission;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

HBVr 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, AASLD 2017 (Washington DC)

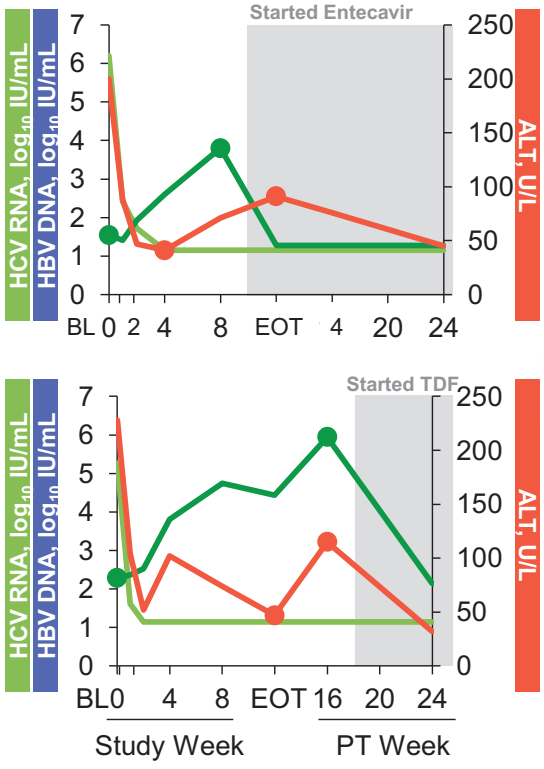
Two asymptomatic patients started HBV therapy

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

- HBV DNA increased from 1.54$\log_{10}$ IU/mL (BL) to 3.8$\log_{10}$ 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 2.28$\log_{10}$ IU/mL (BL) to 5.95$\log_{10}$ 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



Updated EASL recommendations HCV/HBV co-infection

- Treated with the same anti-HCV regimens, following the same rules as HCV monoinfected patients (B1).
- Patients fulfilling the standard criteria for HBV treatment should receive NUC treatment according to the EASL 2017 Guidelines on HBV (A1).
- Patients who are HBsAg+ve should receive NUC prophylaxis at least until wk 12 post anti-HCV therapy and be monitored monthly if HBV treatment is stopped (B1).

EASL. HCV guidelines. 2018 (online)

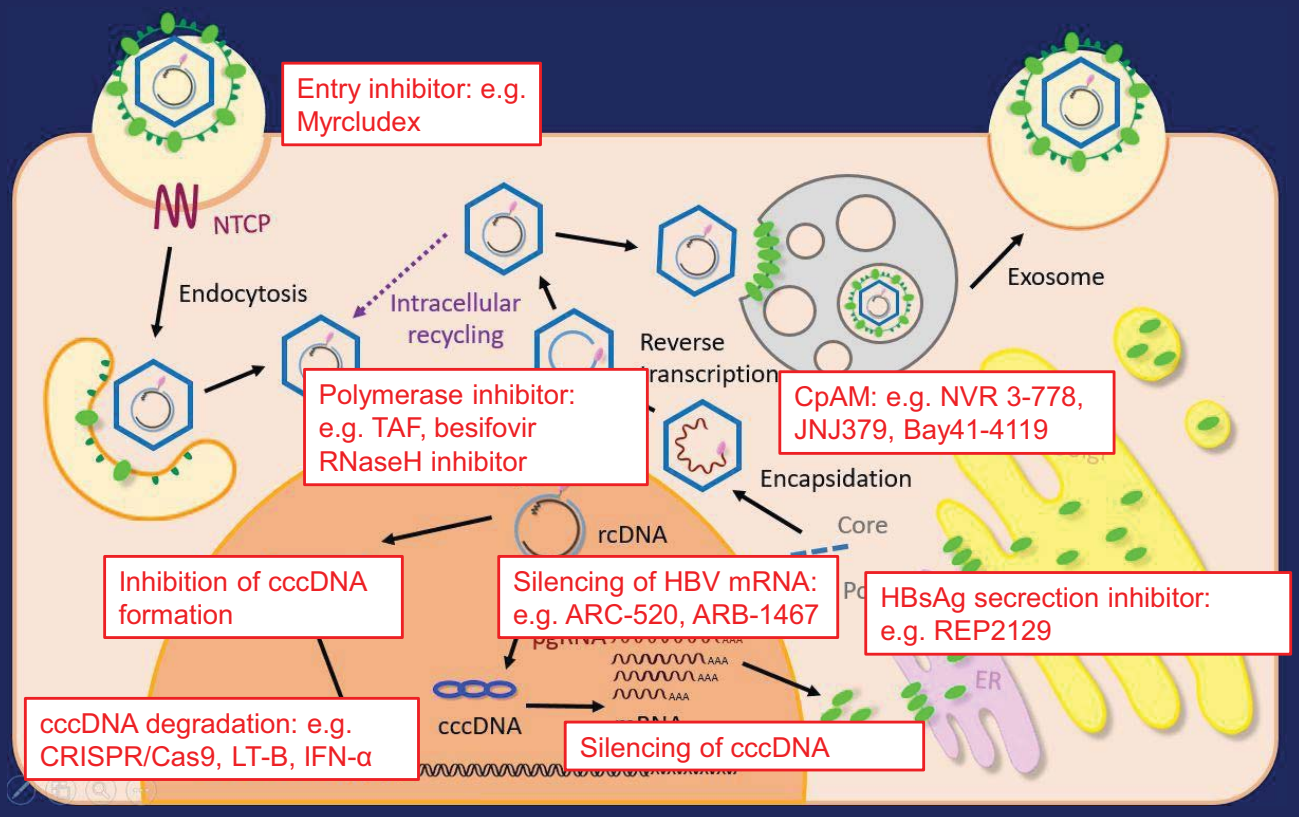
AASLD 2018 HBV guidance on HCV and HBV coinfected subjects

- HBsAg-positive patients: Monitoring of HBV DNA levels every 4 to 8 weeks during treatment and for 3 months posttreatment 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

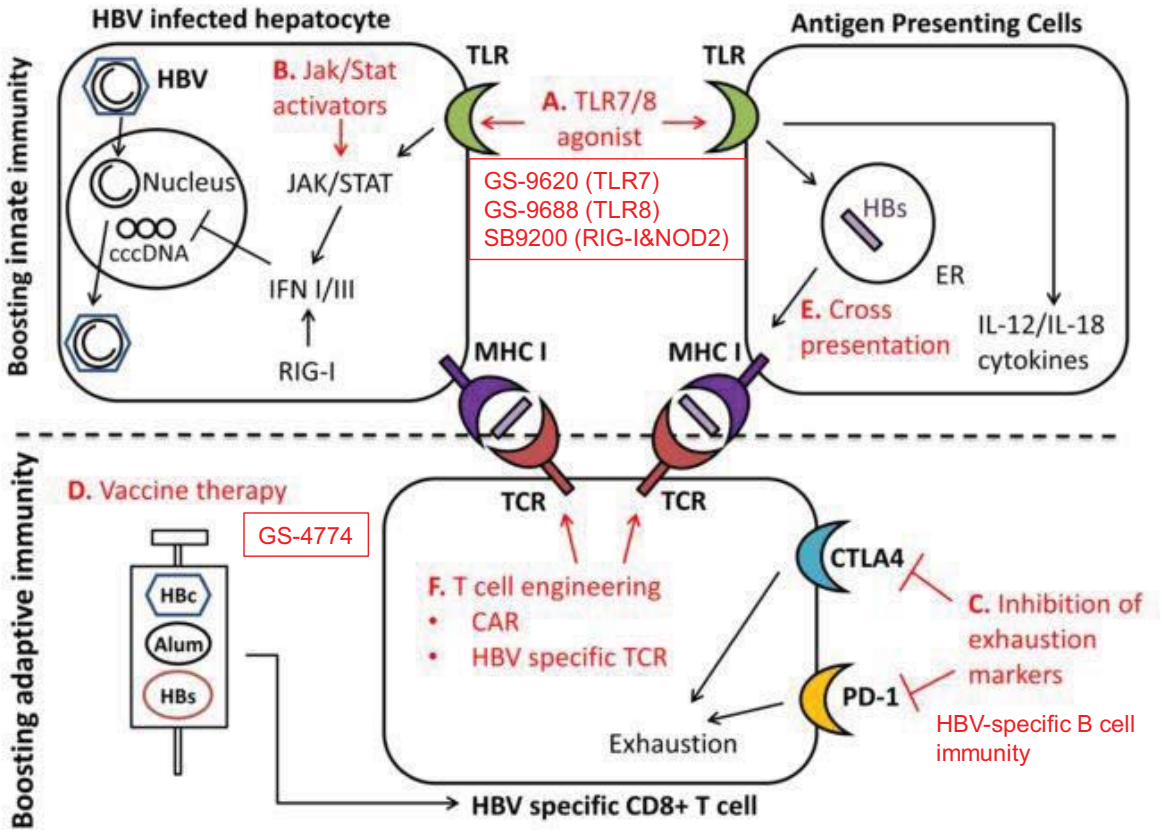
研發中B型肝炎之治療策略

HBV life cycle and antiviral targets



Modified from Yang HC & Chen PJ, Virus, 2017

Potential Immunotherapeutic targets



Yang N & Bertoletti A, Hepatol Int, 2015

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