MEDIC

TAF - Lựa chọn mới cho điều trị viêm gan siêu vi B mạn.

PGS.TS. BS. Phạm Thị Thu Thủy
Trung tâm Y Khoa MEDIC TP HCM

NỘI DUNG

I, Tổng quan về HBV.

II, Chẩn đoán viêm gan siêu vi B.

III, Điều trị viêm gan siêu vi B.

IV, Vai trò của TAF trong điều trị viêm gan siêu vi B.

V, Kết luận.

I, Tổng quan về HBV.

International Agency for Research on Cancer
World Health Organization

1, Tình hình ung thư tại Việt Nam.

Viet Nam
Source: Globocan 2018

Viet Nam
Source: Globocan 2018

GCO

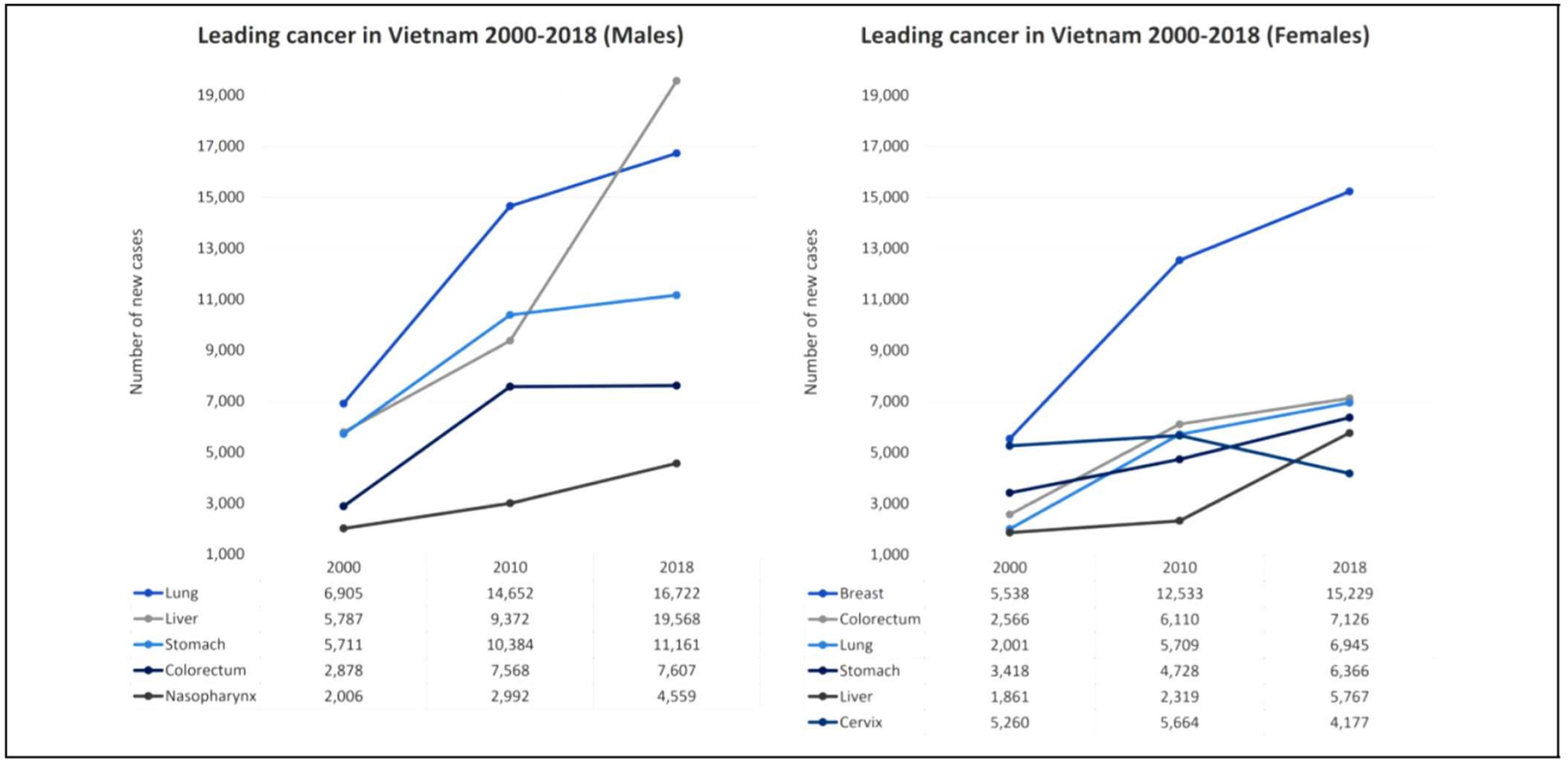
Incidence, Mortality and Prevalence by cancer site

	New cases				Deaths				5-year prevalence (all ages)	
Cancer	Number	Rank	(%)	Cum.risk	Number	Rank	(%)	Cum.risk	Number	Prop.
Liver	25 335	1	16.45	2.59	25 404	1	23.48	2.59	21 055	21.82
Lung	23 667	2	15.37	2.57	20 710	2	19.14	2.27	22 564	23.38
Stomach	17 527	3	11.38	1.86	15 065	3	13.92	1.52	21 839	22.63
Breast	15 229	4	9.89	2.93	6 103	4	5.64	1.24	42 188	86.56
Rectum	8 815	5	5.72	0.93	4 673	6	4.32	0.44	20 184	20.92
Nasopharynx	6 212	6	4.03	0.64	4 232	7	3.91	0.47	16 290	16.88
Leukaemia	6 144	7	3.99	0.52	4 923	5	4.55	0.43	16 565	17.17
Colon	5 457	8	3.54	0.60	3 183	8	2.94	0.31	11 662	12.09
Thyroid	5 418	9	3.52	0.45	528	22	0.49	0.05	16 897	17.51

Tỉ lệ mắc và tử vong do ung thư gan là gần tương đương
Cho thấy mức độ nguy hiểm của ung thư gan.

https://gco.iarc.fr/today/data/factsheets/populations/704-viet-nam-fact-sheets.pdf

Trend of leading cancer incidence in Vietnam, 2000 to 2018.



Pham et al . Cancer Control Volume 26 - 2019: 1-14

TÌNH HÌNH HBV & HCC Ở BỆNH NHÂN VIỆT NAM.

- HBV LÀ NGUYÊN NHÂN CHỦ YẾU GÂY HCC.

- ĐA SỐ PHÁT HIỆN BIẾN CHỨNG HCC RẤT TRỄ.

Nhóm bệnh nhân HCC mới phát hiện : 80.52% có liên quan đến nhiễm virus viêm gan.

KIỂM SOÁT TỐT BỆNH VIÊM GAN SIÊU VI B SẼ GIÚP GIẢM CÁC BIẾN CHỨNG CHẾT NGƯỜI DO BỆNH GAN GÂY RA.

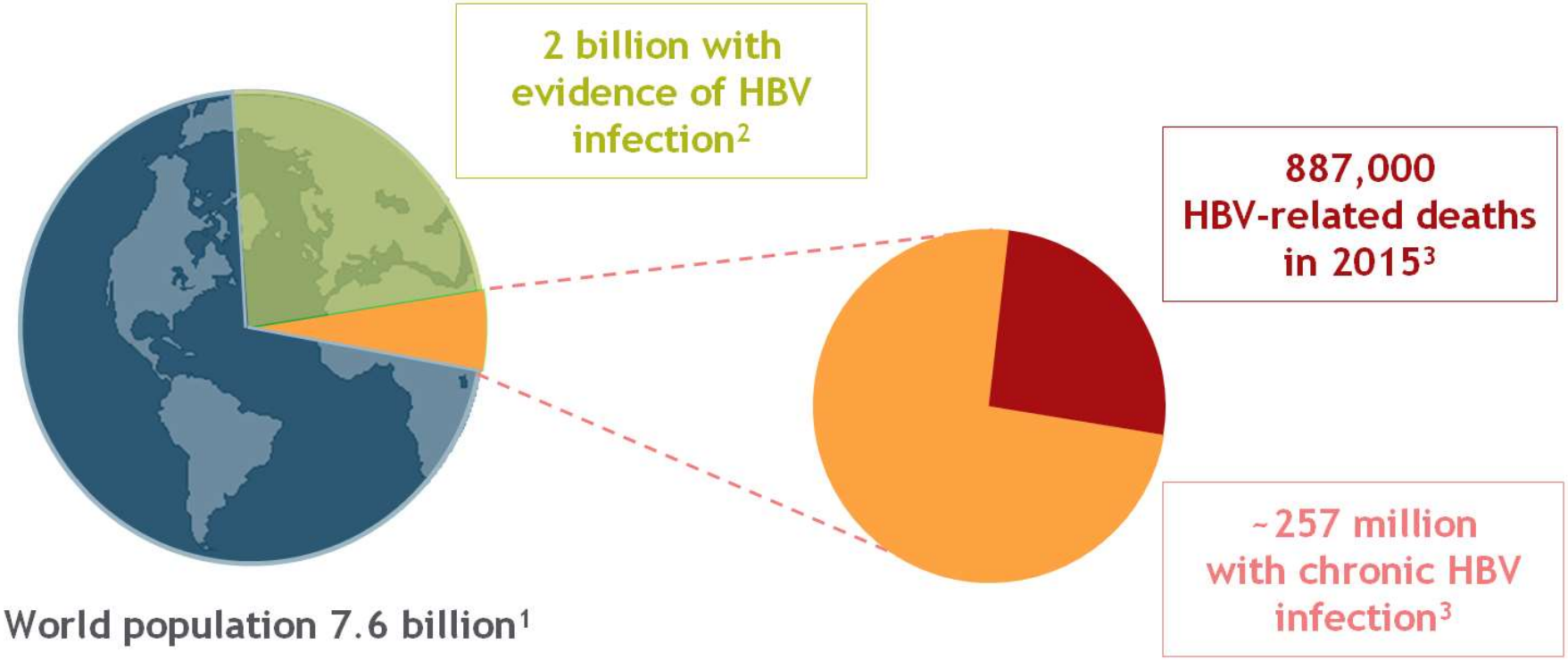
15371 bệnh nhân HCC mới phát hiện.
43.09 % đã quá chỉ định điều trị.

Nhóm bệnh nhân HCC mới phát hiện nhưng đã quá chỉ định điều trị: 75.57% có liên quan đến nhiễm virus viêm gan.

HBV:	57.06%.
HCV:	16.58%.
HBV & HCV:	1.93%.

Nguyễn Đình Song Huy – BV Chợ Rẫy.

2, Global Impact of HBV

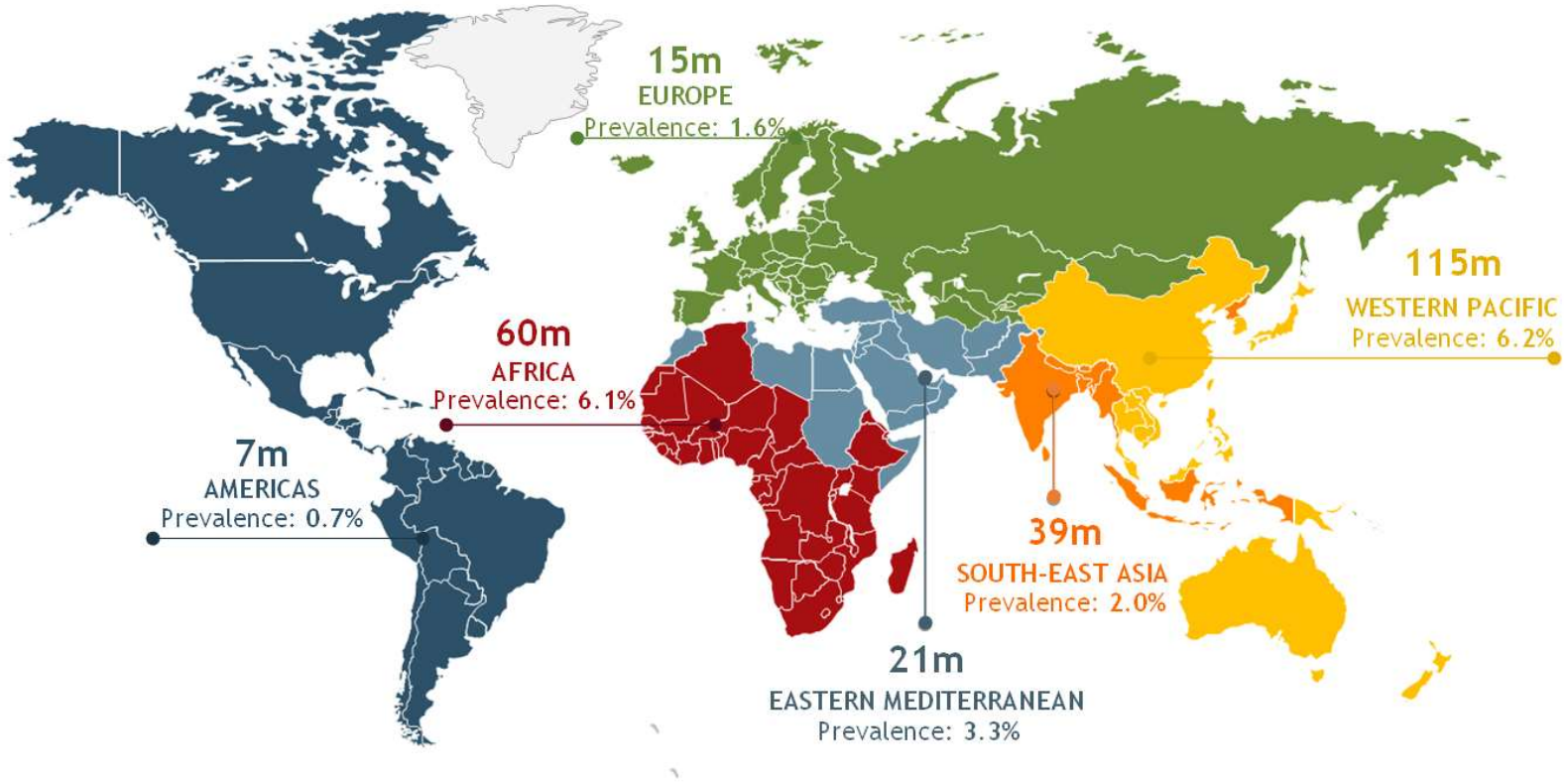


CHB, chronic hepatitis B.

1. U.S. and World Population Clock. *Population Clock*. Web. 5 March 2020.
2. World Health Organization. Guidelines for the Prevention, Care and Treatment of Persons with Chronic Hepatitis B Infection, March 2015 http://apps.who.int/iris/bitstream/handle/10665/154590/9789241549059_eng.pdf;jsessionid=A5C1D0DE1BAC8E2B053E139071630B01?sequence=1
3. World Health Organization. Hepatitis B. Fact Sheet http://www.who.int/news-room/fact-sheets/detail/hepatitis-b. Accessed May, 18 2018.

Geographical Distribution

Prevalence of HBV infection (HBsAg) in the general population, by WHO region, 2015



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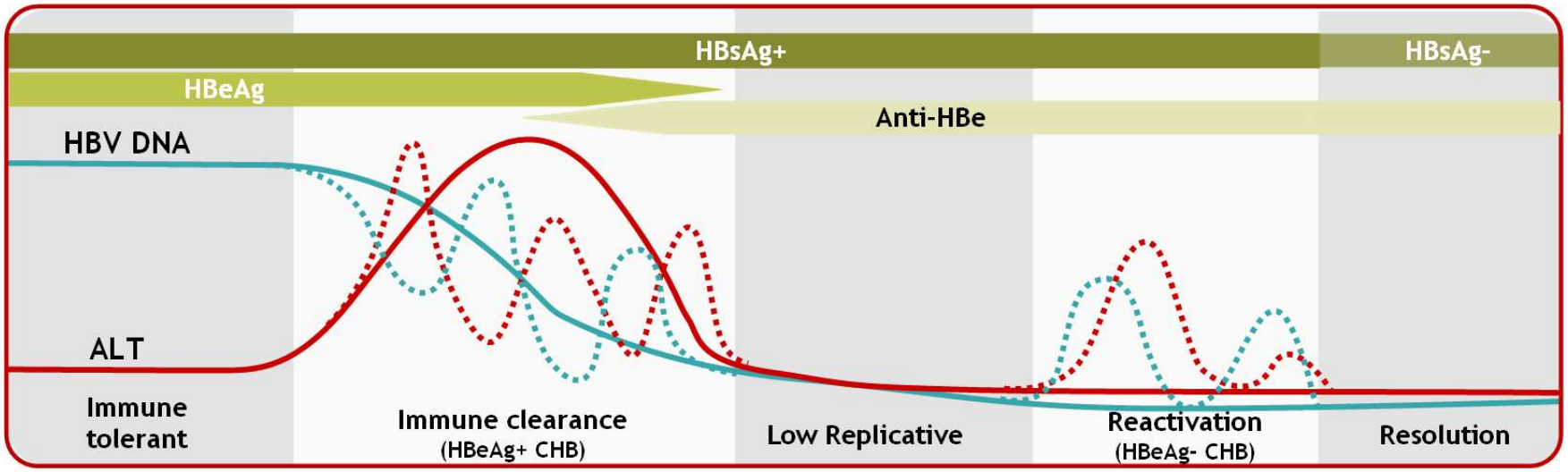
MILLION PERSONS WORLDWIDE ARE LIVING WITH CHRONIC HBV INFECTION

Global Hepatitis Report 2017. Geneva: World Health Organization, 2017.

3, Course of Chronic Hepatitis B Infection



- This phase occurs in patients with perinatally acquired infection
- Minimal or no inflammation
- May last 1 to 4 decades

- High or fluctuating HBV DNA levels
- Persistent or intermittent fluctuation in ALT levels
- Active inflammation and liver damage

- Low or undetectable HBV DNA levels
- Normal ALT levels
- Mild hepatitis, minimal fibrosis, but cirrhosis may be present from previous liver damage

- Some patients may have reactivation of HBV replication
- Usually older patients with more advanced liver disease
- Fluctuating levels of ALT and HBV DNA

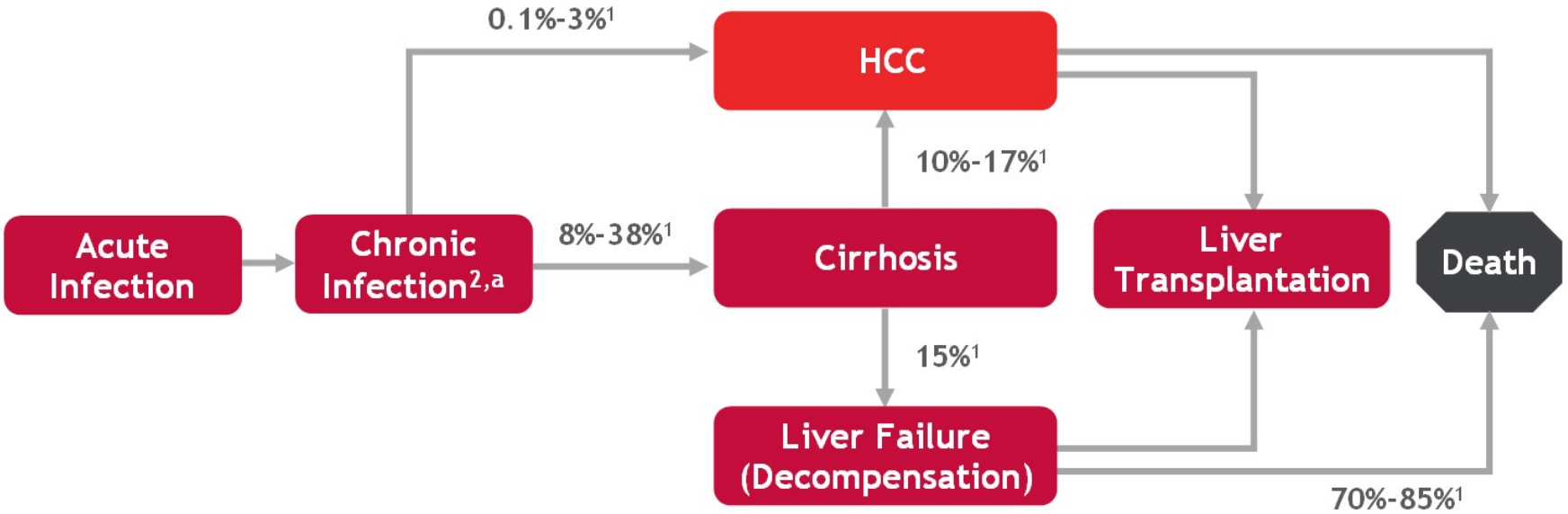
- After many years, some patients may enter a resolution phase
- Not considered a "cure" as intra-cellular HBV DNA is still present

CHB follows a nonlinear clinical course; not all patients will go through each phase

Keeffe EB et al. *Gastroenterol Hepatol*. 2008;6:1315-1341.
Yim HJ, Lok ASF. *Hepatology*. 2006;43:S173-S181.
Martin P, et al. *Clin Gastroenterol Hepatol*. 2015 July 15.

CHB Is Associated With Severe Burden of Disease

Five Year Cumulative Incident Rates of Development of CHB Complications



[a]Patient is chronically infected if HBsAg+ for ≥ 6 months.

Figure adapted with permission from Fattovich G, et al. In: Marcellin P, ed. *Management of Patients With Viral Hepatitis*. Paris: APMAHB; 2004.

1. Fattovich G, et al. *J Hepatol*. 2008;48:335-352.
2. Lok ASF, McMahon BJ. *Hepatology*. 2009;50:1-36.

II, Chẩn đoán viêm gan siêu vi B.

Các dấu ấn (Marker) chẩn đoán siêu vi viêm gan B.

- Có nhiều nhất các dấu ấn chẩn đoán trong các tác nhân gây bệnh.
- Kinh điển & hiện tại ở vài nơi: 5 HBV.
- Nhiều dấu ấn khác nhau giúp cho chẩn đoán chính xác có bệnh; giai đoạn bệnh; theo dõi điều trị bệnh & tiên lượng được bệnh.
- Các xét nghiệm cụ thể hơn: Định tính, định lượng.
- Người Thầy thuốc phải nắm rõ ý nghĩa

của các dấu ấn và sử dụng hợp lý, đúng

trong thực hành hàng ngày.

Xét nghiệm siêu vi B giữ vai trò then chốt trong chẩn đoán, điều trị và tiên lượng bệnh

CÁC XN MIỄN DỊCH.

1, HBsAg: Định tính, định lượng.

2, AntiHBs: Định tính, định lượng.

3, HBeAg: Định tính, định lượng.

4, Anti HBe: Định tính.

5, AntiHBc IgG: Định tính.

6, AntiHBc IgM: Định tính.

7, HBcrAg: Định lượng.

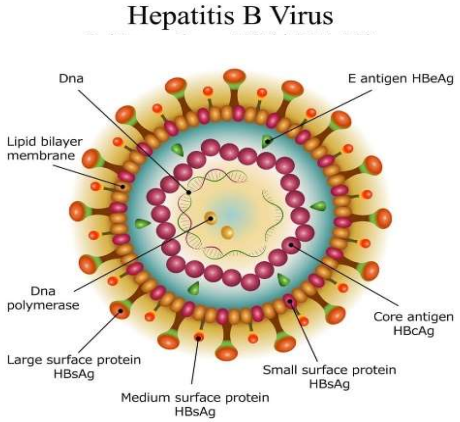
CÁC XN SINH HỌC PHÂN TỬ

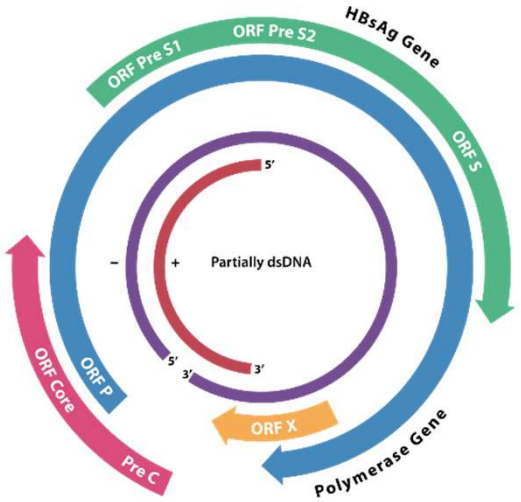
1, HBVDNA: Định tính, định lượng.

2, HBV Genotype.

3, Phát hiện đột biến gene kháng thuốc điều trị, đột biến PC(precore); BCP(basal core promoter)…

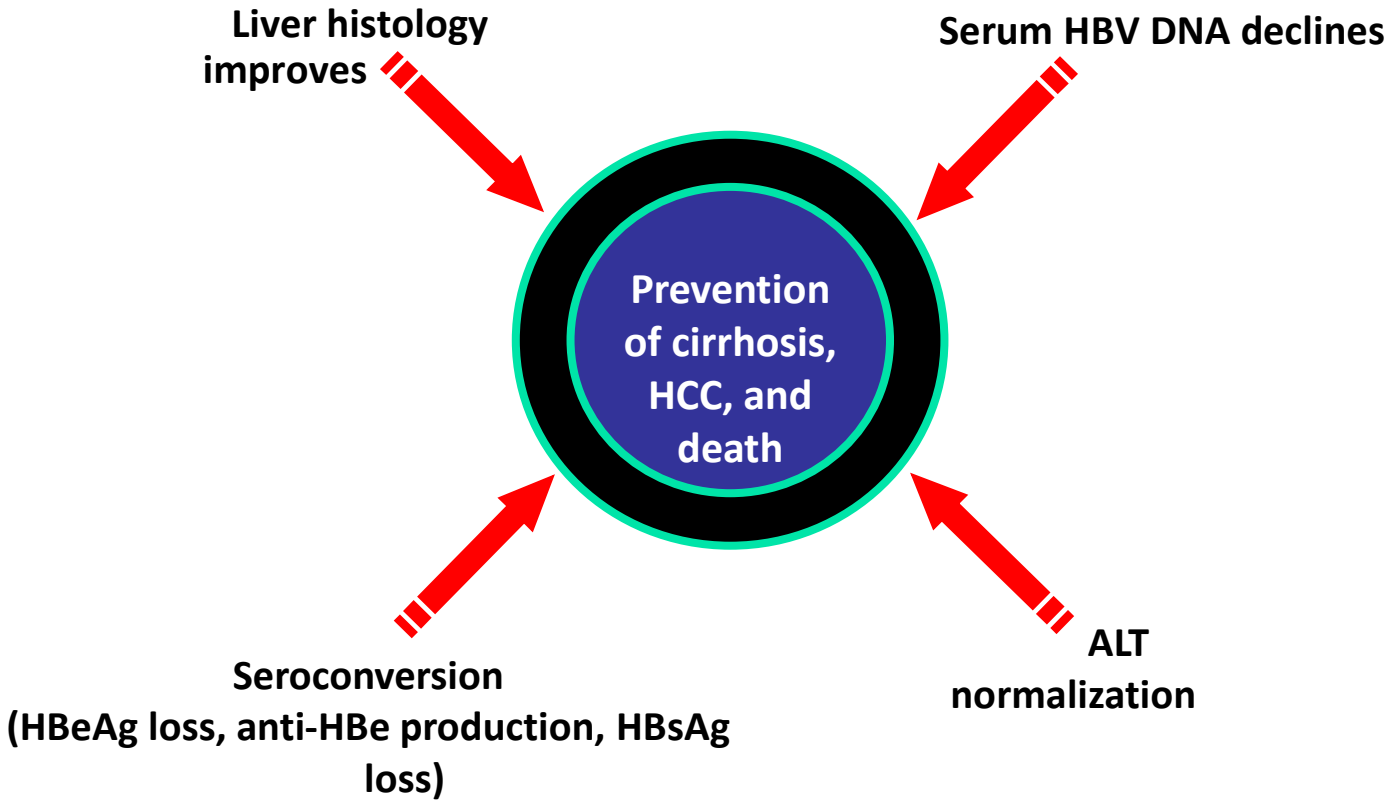
4, HBVRNA: Định lượng.





III, Điều trị viêm gan siêu vi B.

Goals of Therapy for HBV.



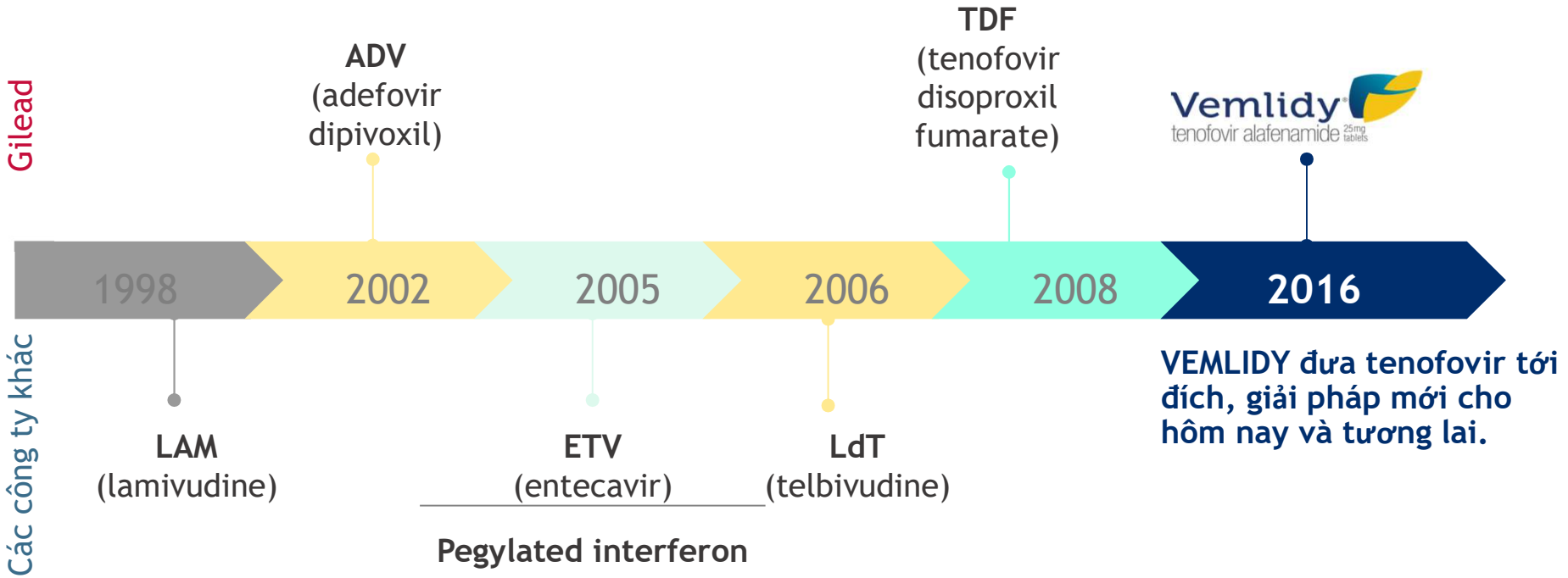
ĐỊNH NGHĨA ĐIỀU TRỊ KHỎI HBV

- 1. Điều trị khỏi virus hoàn toàn:không phát hiện HBsAg và HBV DNA/ huyết thanh và cccDNA trong gan.
- 2. Điều trị khỏi về mặt chức năng: HBsAg và HBV DNA không phát hiện trong huyết thanh kéo dài, giảm tổn thương gan , có thể kết thúc sự phiên mã cccDNA.
- 3. Điều trị khỏi một phần: HBsAg vẫn phát hiện và HBV DNA không phát hiện trong huyết thanh kéo dài.

EASL 2018

Điều trị viêm gan B đang thay đổi hằng ngày.

Theo thời gian, điều trị HBV đã phát triển để đáp ứng nhu cầu thay đổi của bệnh nhân.



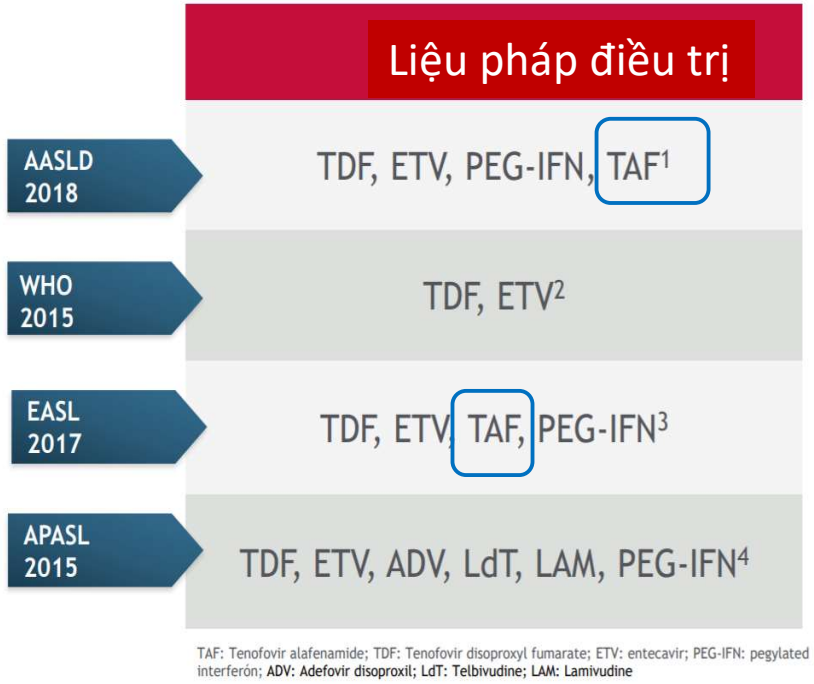
Dates provided are based on US approval dates.
Vietnam/VEM/072020/001.

FDA Approved Therapies for CHB

Generic Name	Trade Name	Manufacturer	Date Approved for CHB
Interferons			
Interferon alfa-2b, recombinant	Intron® A	Schering Corporation	1992
Peginterferon alfa-2a	Pegasys®	Roche Laboratories	2005
Nucleosides/Nucleotides			
Lamivudine	Epivir-HBV®	GlaxoSmithKline	1998
Adefovir dipivoxil	Hepsera®	Gilead Sciences	2002
Entecavir	Baraclude®	Bristol-Myers Squibb	2005
Telbivudine	Tyzeka®	Idenix and Novartis	2006
Tenofovir DF	Viread®	Gilead Sciences	2008
Tenofovir alafenamide	Vemlidy®	Gilead Sciences	2016

U.S. Food and Drug Administration (FDA)
https://www.fda.gov/forpatients/illness/hepatitisbc/ucm408658.htm Accessed May 18, 2018

TAF là liệu pháp điều trị đầu tay được khuyến cáo bởi các hướng dẫn quốc tế & Bộ Y Tế Việt Nam.



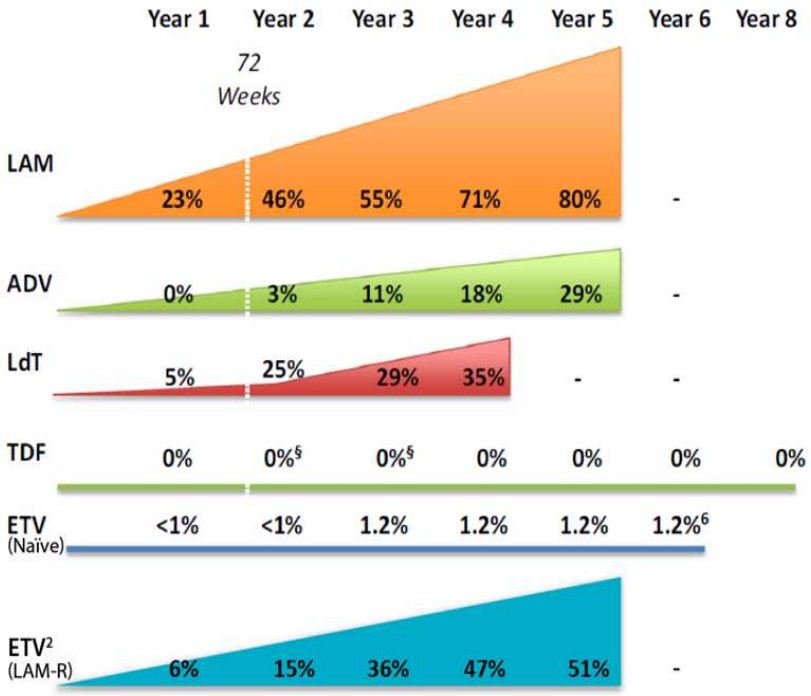
TAF: Tenofovir alafenamide; TDF: Tenofovir disoproxyl fumarate; ETV: entecavir; PEG-IFN: pegylated interferón; ADV: Adefovir disoproxil; LdT: Telbivudine; LAM: Lamivudine

Hướng dẫn điều trị viêm gan B Bộ Y Tế VN. *3310/QĐ-BYT – 7/2019*

Tên thuốc	Liều người lớn	Liều trẻ em	Tác dụng phụ
Tenofovir disoproxil fumarate* (TDF)	- 300 mg/ngày - Đối với người có suy thận: điều chỉnh liều theo mức lọc cầu thận (Phụ lục 4)	≥ 12 tuổi và cân nặng ≥ 35 kg: liều lượng như người lớn	Bệnh thận, hội chứng Fanconi, hội chứng loãng xương, nhiễm toan lactic
Entecavir (ETV)	- 0,5 mg/ngày (1 mg/ngày nếu người bệnh từng sử dụng lamivudine hoặc có xơ gan mất bù) - Đối với người có suy thận: điều chỉnh liều theo mức lọc cầu thận (Phụ lục 4)	Trẻ ≥ 2 tuổi: tính liều theo cân nặng: - 10-11 kg: 0,15 mg (3 mL) - > 11-14 kg: 0,2 mg (4 mL) - > 14-17 kg: 0,25 mg (5 mL) - > 17-20 kg: 0,3 mg (6 mL) - > 20-23 kg: 0,35 mg (7 mL) - > 23-26 kg: 0,4 mg (8 mL) - > 26-30 kg: 0,45 mg (9 mL) - > 30kg: 0,5 mg (10 mL dung dịch uống hoặc 1 viên 0,5 mg)	Nhiễm toan lactic
Tenofovir alafenamide (TAF)**	- 25 mg/ngày - Không cần giảm liều đối với các trường hợp suy thận nhẹ, vừa và nặng, hoặc chạy thận.	Trẻ ≥ 12 tuổi: liều như người lớn*	Nhiễm toan lactic, không chỉ định cho trường hợp xơ gan mất bù
Peg-IFN-α-2a (người lớn)* IFN-α-2b (trẻ em)**	180 µg/tuần	Trẻ ≥ 1 tuổi: 6 triệu đơn vị/m² x 3 lần/tuần	Các triệu chứng giả cúm, mệt mỏi, rối loạn tâm thần, giảm bạch cầu, rối loạn miễn dịch ở người lớn, chán ăn và sụt cân

Key Points of the APASL Guidelines

- Cumulative incidence of antiviral resistance in long-term studies of NA therapy[1]:

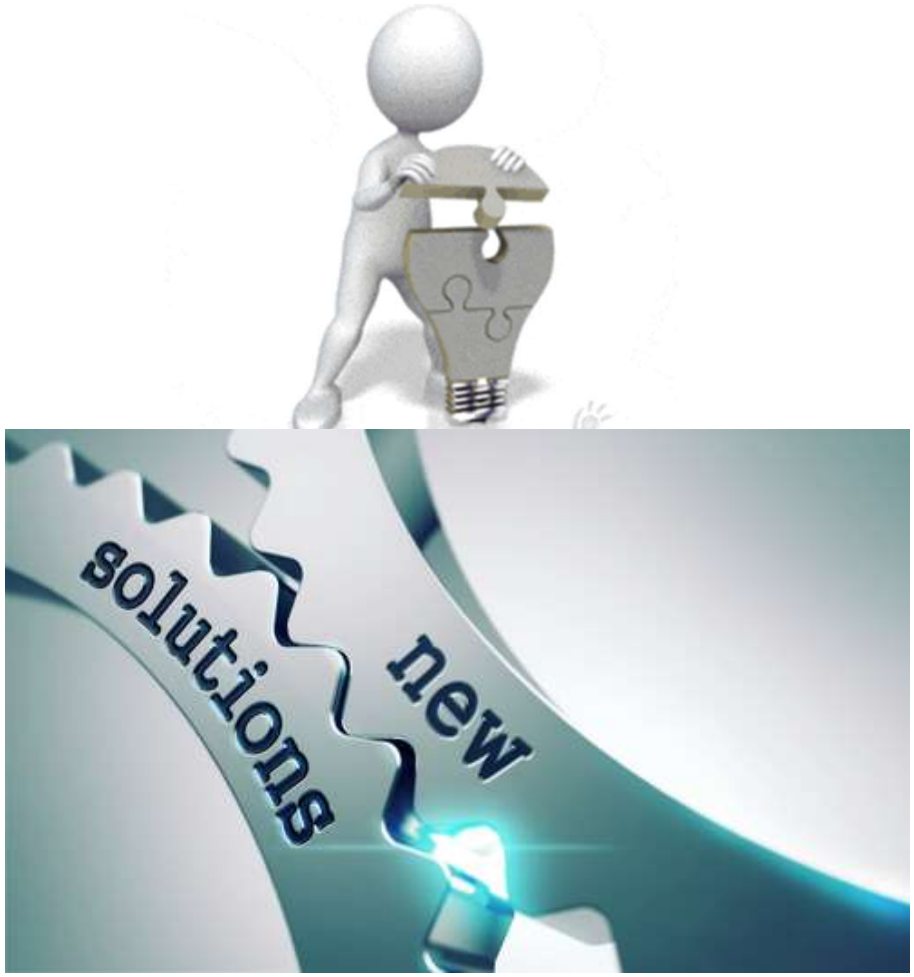


- Recommendations: **treatment failure to therapy** and its management in chronic HBV infection (Only A1)[1]:
- The best strategy for drug resistance is prevention through patient education on compliance and selection of an agent with high potency and high barrier to resistance (entecavir and tenofovir) (A1).
- Regular monitoring for viral breakthrough should be performed in patients receiving an agent with low barrier to resistance (lamivudine, telbivudine and adefovir) (A1).
- For patients who develop drug resistance while on LAM or LdT, switching to TDF is indicated (A1).
- For patients who develop drug resistance while on ADV therapy, without prior lamivudine exposure, switching to either ETV or TDF monotherapy is indicated (A1).

ADV: Adefovir disoproxil; ETV: entecavir; IFN: Interferon; LAM: Lamivudine; LdT: Telbivudine; NA: nucleos(t)ide analogues; TDF: Tenofovir disoproxyl fumarate

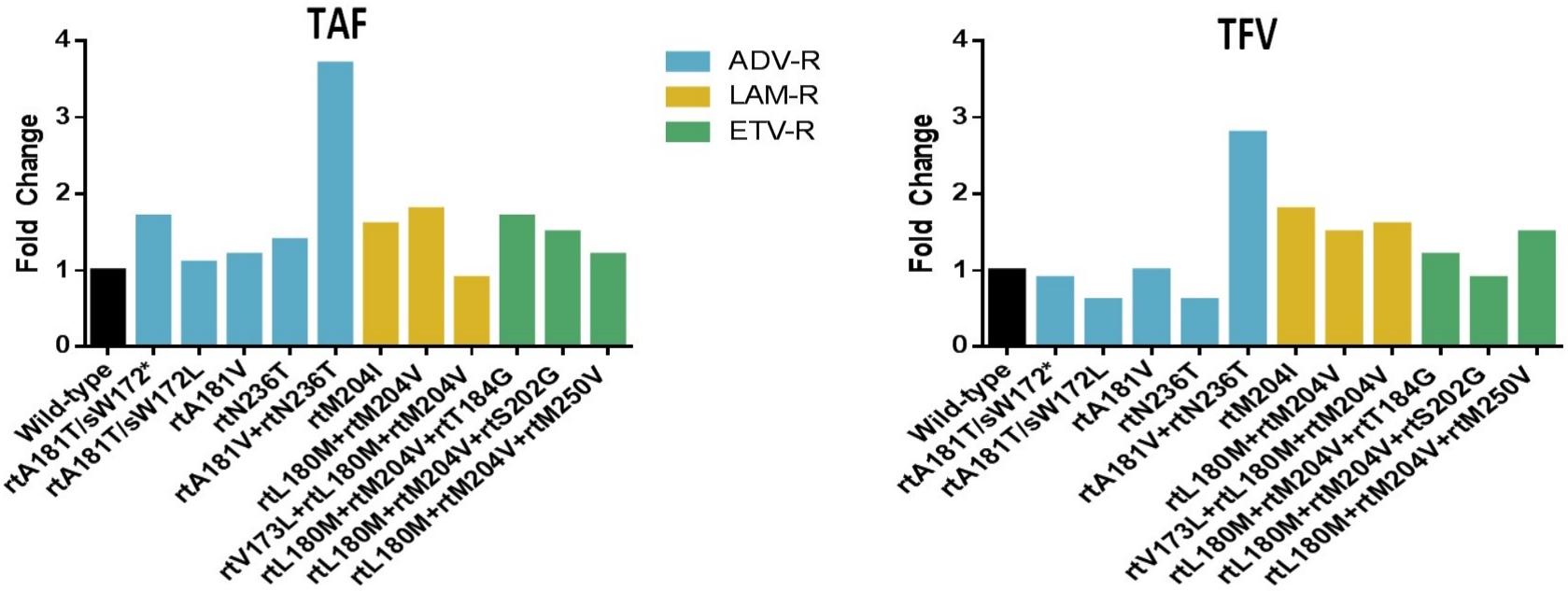
1, Sarin SK et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. *Hepatol Int* (2016) 10:1–98.
2, Tenney DJ et al. Long-Term Monitoring Shows Hepatitis B Virus Resistance to Entecavir in Nucleoside-Naïve Patients Is Rare Through 5 Years of Therapy. *Hepatology* 2009;49:1503-1514.

IV, Vai trò của TAF trong điều trị viêm gan siêu vi B.



1, Antiviral Activity of Tenofovir Alafenamide Against Drug-Resistant HBV Isolates

In vitro activity of TAF against ADV-R, LAM-R, and ETV-R HBV isolates



- The majority of drug resistant isolates remain sensitive to TAF (FC < 2)
  - rtA181V+rtN236T demonstrated reduced susceptibility (FC = 3.7).
- Drug susceptibility fold change values observed with TAF are similar to those previously observed with TFV

*Indicates stop codon in HBsAg.

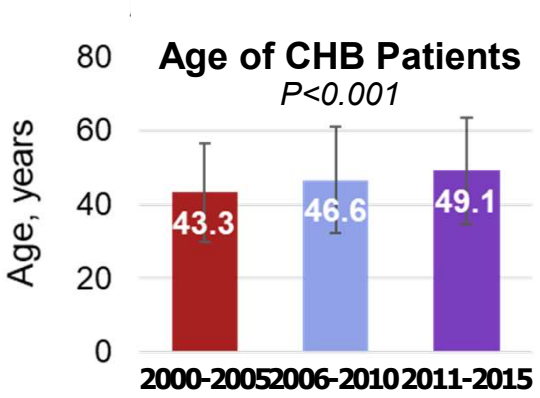
Liu Y, et al. Antiviral Res. 2017; 139:25-31.

2, THE CHB POPULATION IS AGING

Multicenter, retrospective cohort study of comorbidities in 2734 CHB patients over 15 years in the United States (San Francisco Bay Area Cohort)[1]

	2000–2005 N=885	2006–2010 n=888		*P*-value
HBeAg+, %	26.4	20.9	15.8	<0.001
HBV DNA (log_{10} IU/mL)	4.2±2.6	3.7±2.4	3.3±2.3	<0.001

- *HBeAg positivity and viral load declined over time*

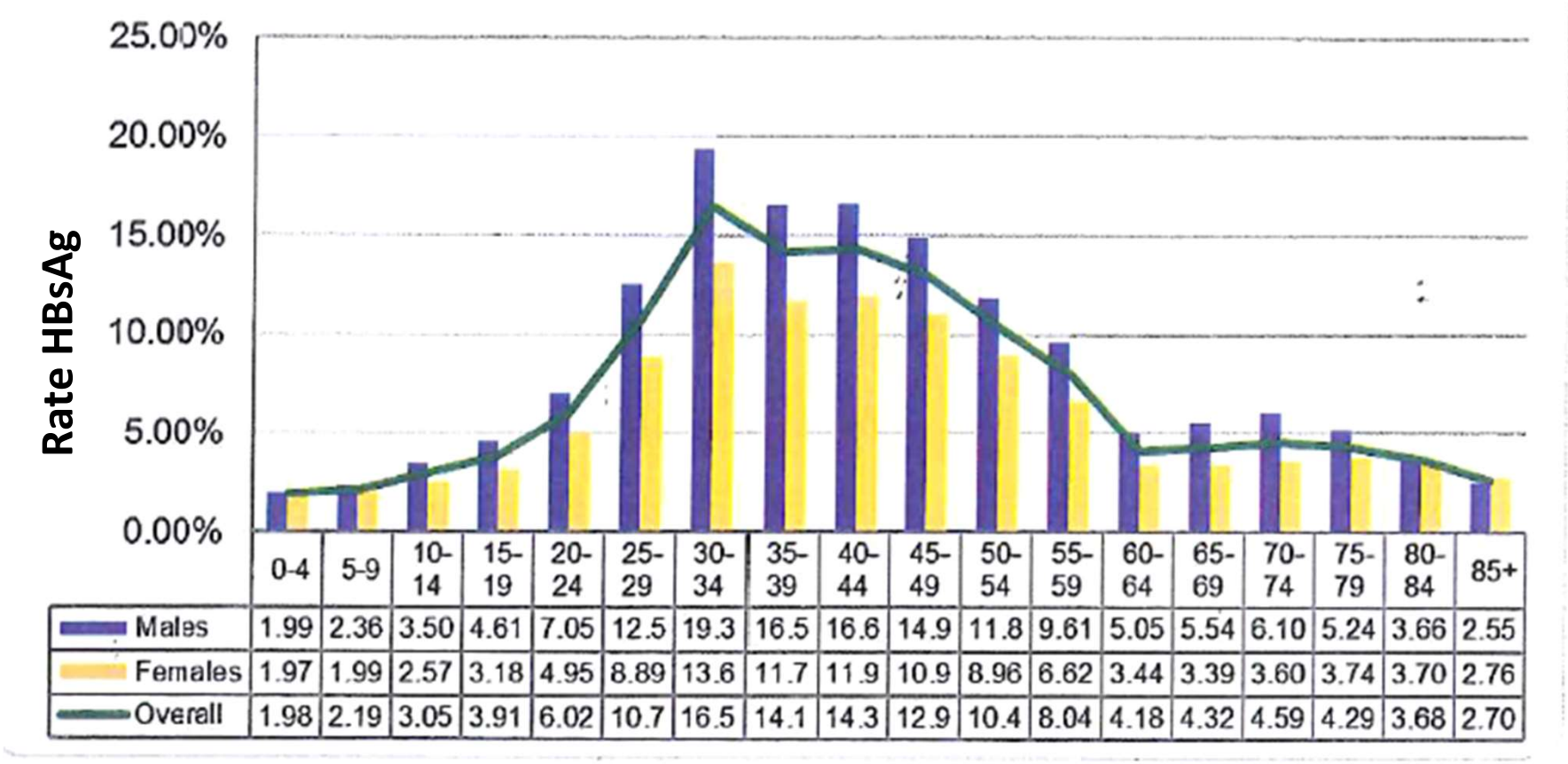


- *Patients presented at increasingly older ages*

- **A study of >44,000 US CHB patients also reported that median age increased significantly from 2006-2015; by 2015, >50% of all commercial- and Medicaid-insured patients were >50 years old[2]**

1. Liu A, et al. *Clin Transl Gastroenterol*. 2018;9(3):141. doi: 10.1038/s41424-018-0007-6.
2. Nguyen, EASL 2017, Poster SAT-132.

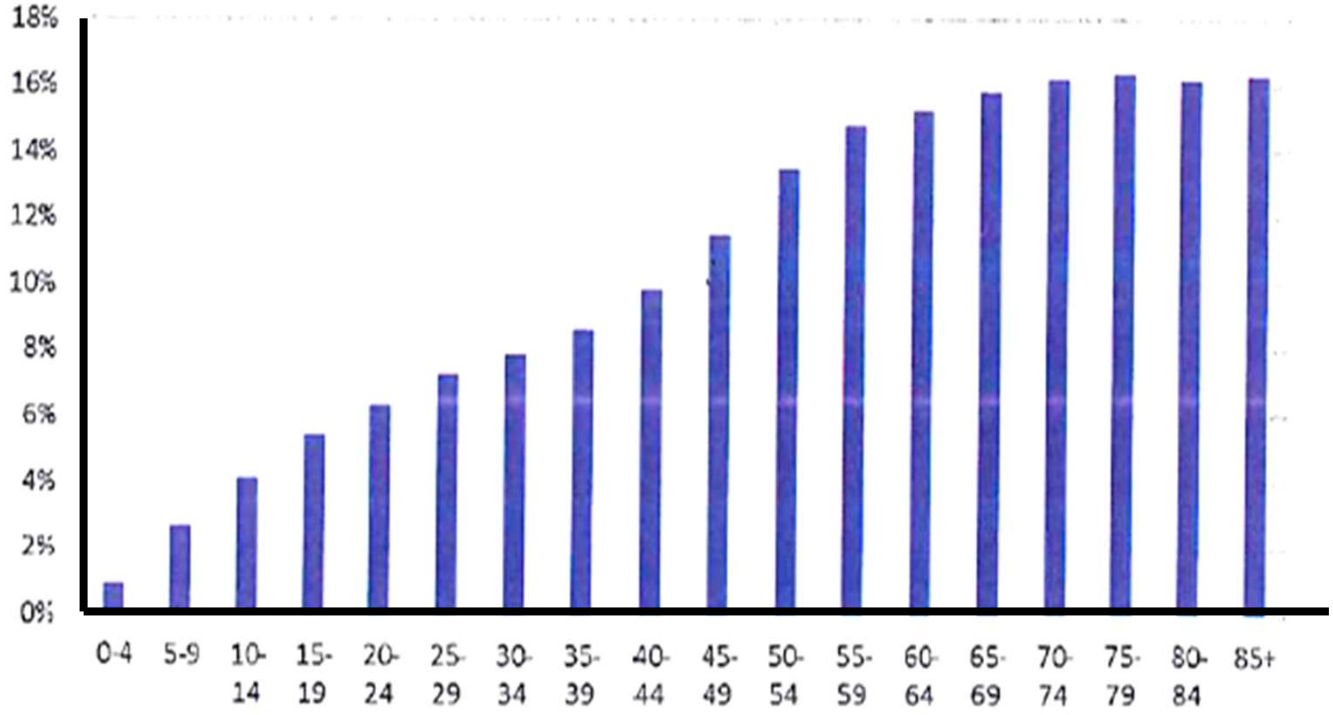
Tỉ lệ nhiễm HBV theo tuổi và giới



	0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
Males	1.99	2.36	3.50	4.61	7.05	12.5	19.3	16.5	16.6	14.9	11.8	9.61	5.05	5.54	6.10	5.24	3.66	2.55
Females	1.97	1.99	2.57	3.18	4.95	8.89	13.6	11.7	11.9	10.9	8.96	6.62	3.44	3.39	3.60	3.74	3.70	2.76
Overall	1.98	2.19	3.05	3.91	6.02	10.7	16.5	14.1	14.3	12.9	10.4	8.04	4.18	4.32	4.59	4.29	3.68	2.70

Nguyễn Thu Anh- Vietnam Viral Hepatitis Alliance- July 2017.

Tỉ lệ nhiễm HBV có xơ gan tăng theo tuổi

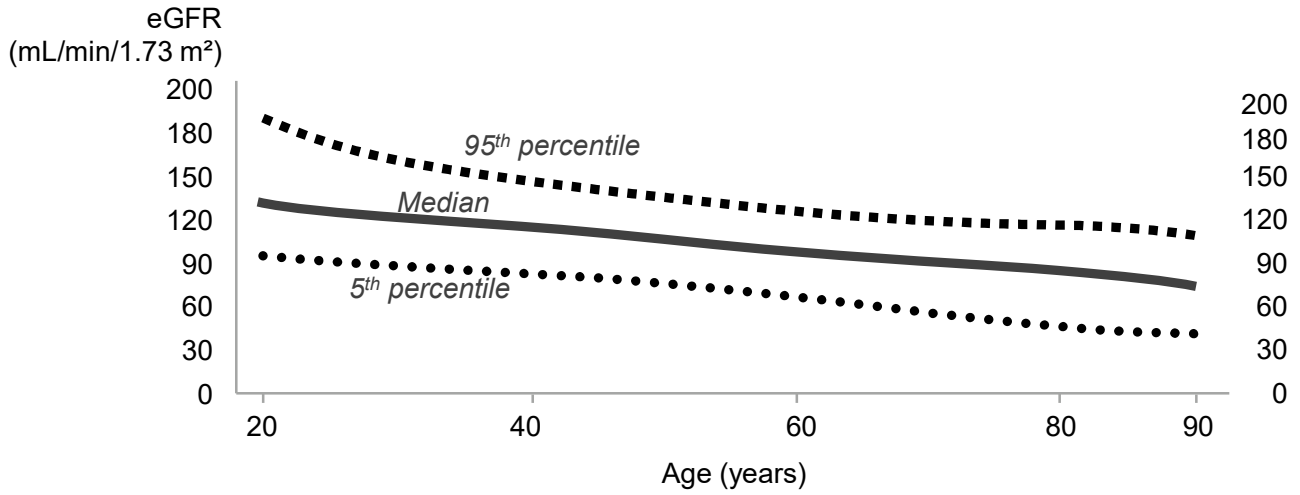


Nguyễn Thu Anh- Vietnam Viral Hepatitis Alliance- July 2017.

GFR GENERALLY DECLINES WITH AGE

- The estimated rate of decline in eGFR is **1 mL/min/1.73 m^2 per year** in both men and women after 20 to 30 years of age; this decline is accelerated in older adults

Percentiles of eGFR Regressed on Age (NHANES III)



GFR, glomerular filtration rate.

National Kidney Foundation. *Am J Kidney Dis.* 2002;39:S1-S266.

BONE-RELATED MORBIDITY IS COMMON AND INCREASES WITH AGE

- **Worldwide, 1/3 women and 1/5 men aged >50 years will experience osteoporotic fractures[1,2,3]**
  - **≈40% lifetime risk** of hip, forearm, and vertebral fracture (equivalent to the lifetime risk of cardiovascular disease)[4]
- **The 44 million people in the US with osteoporosis or low bone mass represent 55% of all people aged ≥50 years[5]**

Normal age-related changes in BMD[6]

- Slow loss of cortical bone mass (**0.3%–0.5% per year**) begins around age 40 in both genders
- In addition, women generally experience accelerated bone loss around menopause **(~5% to 6% per year, for up to 10 years)**

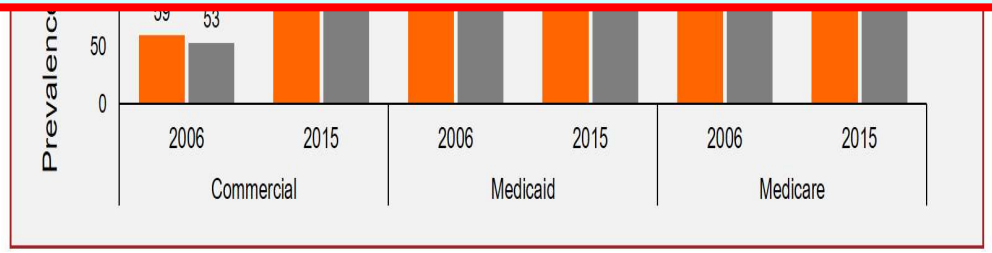
1. Melton LJ, et al. *J Bone Miner Res.* 1998;13:1915. 2. Melton LJ, et al. *J Bone Miner Res.* 1992;7:1005. 3. Kanis JA, et al. *Osteoporos Int.* 2000;11:669. 4. Kanis JA. *Lancet.* 2002;359:1929. 5. www.nof.org. 2011. 6. Germain-Lee EL. *Geriatric Rehabilitation Manual*. London, England: Churchill Livingstone; 2007.

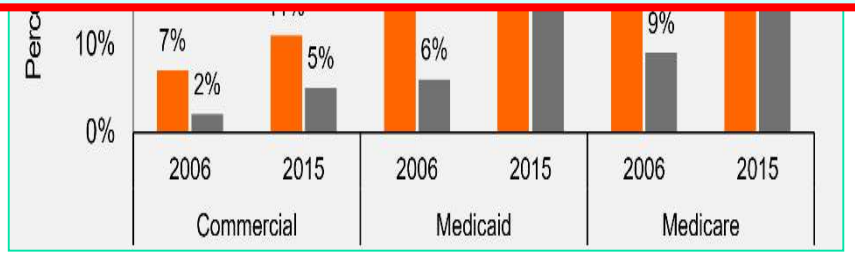
PREVALENCE OF BONE AND RENAL COMORBIDITIES IS HIGHER AMONG US CHB PATIENTS VS NON-CHB MATCHED CONTROLS

NHU CẦU THỰC SỰ CẦN THIẾT CỦA THUỐC

ĐIỀU TRỊ HBV LÂU DÀI

KHÔNG CÓ ẢNH HƯỞNG LÊN THẬN & XƯƠNG.





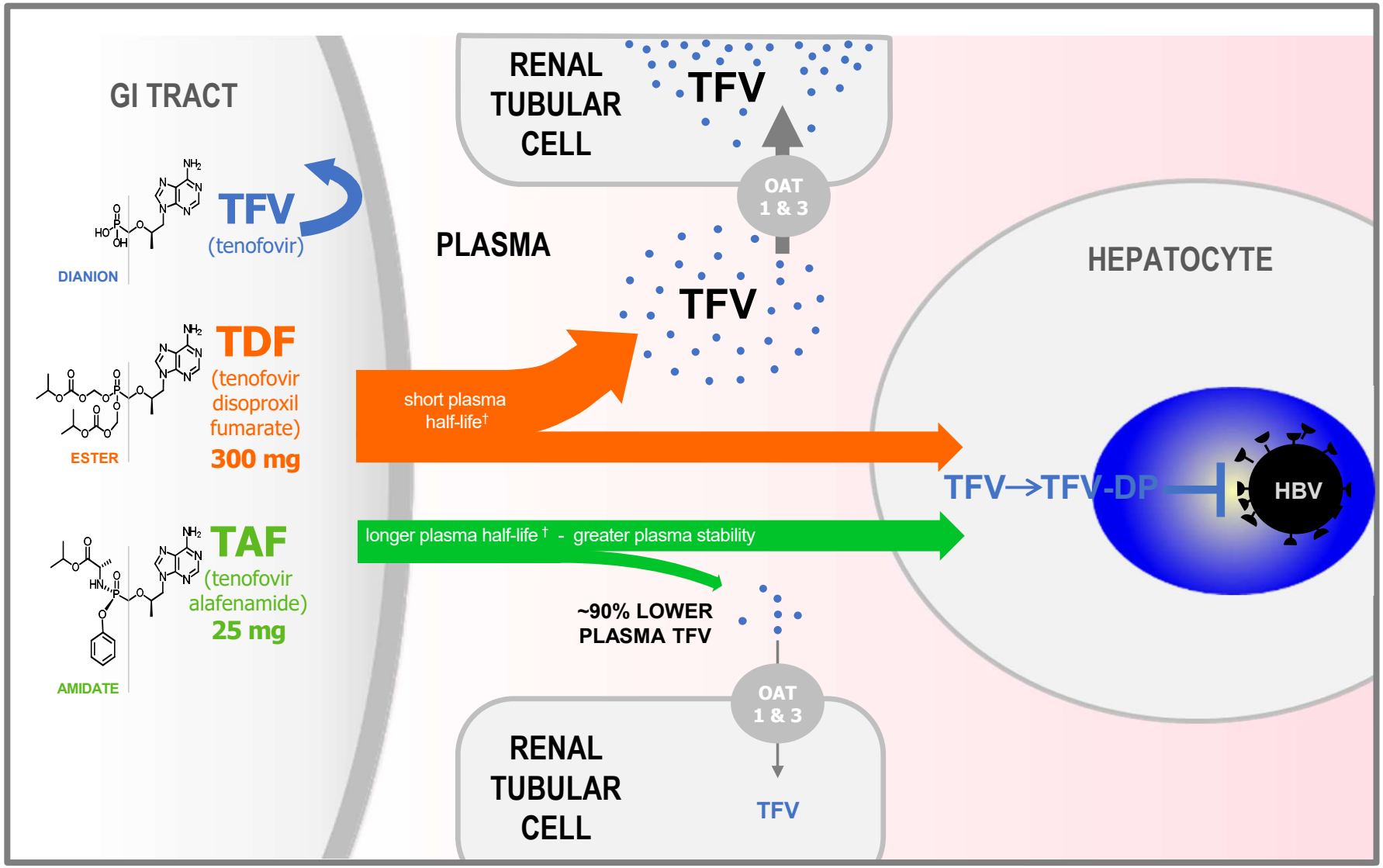
- The prevalence of osteoporosis, fracture, and renal impairment[a] among CHB patients increased from 2006 to 2015, and was significantly higher than matched non-CHB controls across all time periods and all types of insurance.

[a]Renal impairment: CKD stages I-IV, unspecified CKD, ESRD, chronic pyelonephritis, glomerulonephritis, nephrolithiasis, nephropathy, renal osteodystrophy, or proteinuria.

Nguyen, EASL 2017, SAT-132.

Mechanism of Action

TAF – A Novel Prodrug of Tenofovir



† $T_{1/2}$ based on *in vitro* plasma data - TDF = 0.4 minutes, TAF = 90 minutes.

Lee W et. *Antimicr Agents Chemo* 2005;49(5):1898-1906. Birkus G et al. *Antimicr Agents Chemo* 2007;51(2):543-550. Babusis D, et al. *Mol Pharm* 2013;10(2):459-66.
Ruane P, et al. *J Acquir Immune Defic Syndr* 2013; 63:449-5. Sax P, et al. *JAIDS* 2014. 2014 Sep 1;67(1):52-8. Sax P, et al. *Lancet* 2015. Jun 27;385(9987):2606-15. Agarwal K et al. *J Hepatology* 2015; 62: 533-540;
Buti EASL 2016, Oral GS06; Chan, EASL 2016, Oral GS12

U.S. Food and Drug Administration Approves Gilead's Vemlidy® (Tenofovir Alafenamide) for the Treatment of Chronic Hepatitis B Virus Infection

November 10, 2016 1:07 PM ET

-- Vemlidy is a Once-Daily Treatment that Demonstrated Similar Efficacy with Improved Renal and Bone Laboratory Safety Parameters Compared to Viread --

FOSTER CITY, Calif.--(BUSINESS WIRE)--Nov. 10, 2016-- Gilead Sciences, Inc. (Nasdaq: GILD) today announced that the U.S. Food and Drug Administration (FDA) has approved Vemlidy® (tenofovir alafenamide, TAF) 25mg, a once-daily treatment for adults with chronic hepatitis B virus (HBV) infection with compensated liver disease.

Vemlidy has a boxed warning in its product label regarding the risks of lactic acidosis/severe hepatomegaly with steatosis and post-treatment severe acute exacerbation of hepatitis B. See below for important safety information.

http://www.gilead.com/news/press-releases/2016/11/us-food-and-drug-administration-approves-gileads-vemlidy-tenofovir-alafenamide-for-the-treatment-of-chronic-hepatitis-b-virus-infection

JOURNAL OF HEPATOLOGY

EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection☆

European Association for the Study of the Liver*

Clinical Practice Guidelines

Table 5. Indications for selecting ETV or TAF over TDF.*

1. Age >60 years
2. Bone disease
Chronic steroid use or use of other medications that worsen bone density
History of fragility fracture
Osteoporosis
3. Renal alteration**
eGFR <60 ml/min/1.73 m^2
Albuminuria >30 mg/24 h or moderate dipstick proteinuria
Low phosphate (<2.5 mg/dl)
Hemodialysis

* TAF should be preferred to ETV in patients with previous exposure to nucleoside analogues.

** ETV dose needs to be adjusted if eGFR <50 ml/min; no dose adjustment of TAF is required in adults or adolescents (aged at least 12 years and of at least 35 kg body weight) with estimated creatinine clearance (CrCl) ⩾15 ml/min or in patients with CrCl <15 ml/min who are receiving haemodialysis.

Dialysis and renal transplant patients

Recommendations

- All dialysis and renal transplant recipients should be screened for HBV markers (Evidence level II-2, grade of recommendation 1).
- HBsAg-positive dialysis patients who require treatment should receive ETV or TAF (Evidence level II-2, grade of recommendation 1).
- All HBsAg-positive renal transplant recipients should receive ETV or TAF as prophylaxis or treatment (Evidence level II-2, grade of recommendation 1).
- HBsAg-negative, anti-HBc positive subjects should be monitored for HBV infection after renal transplantation (Evidence level III, grade of recommendation 1).

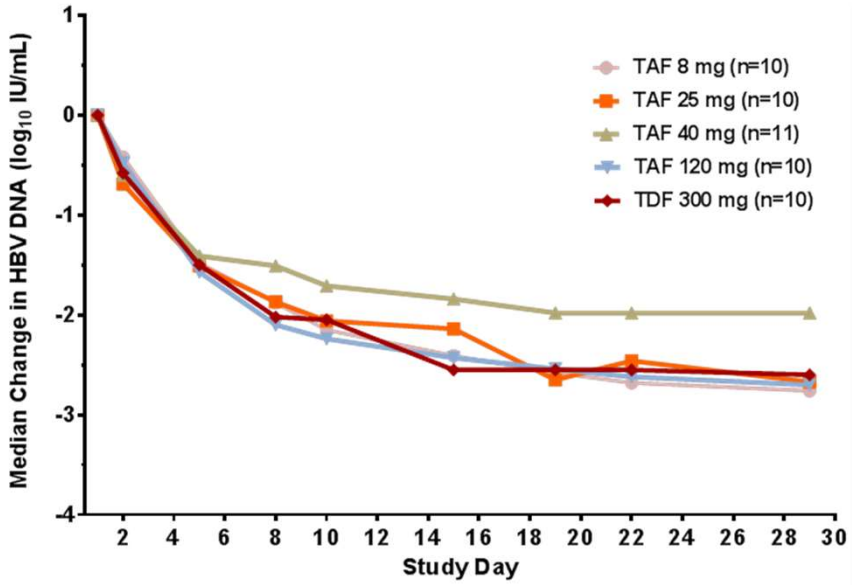
EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infectionq

Journal of Hepatology 2017 vol. 67 j 370–398

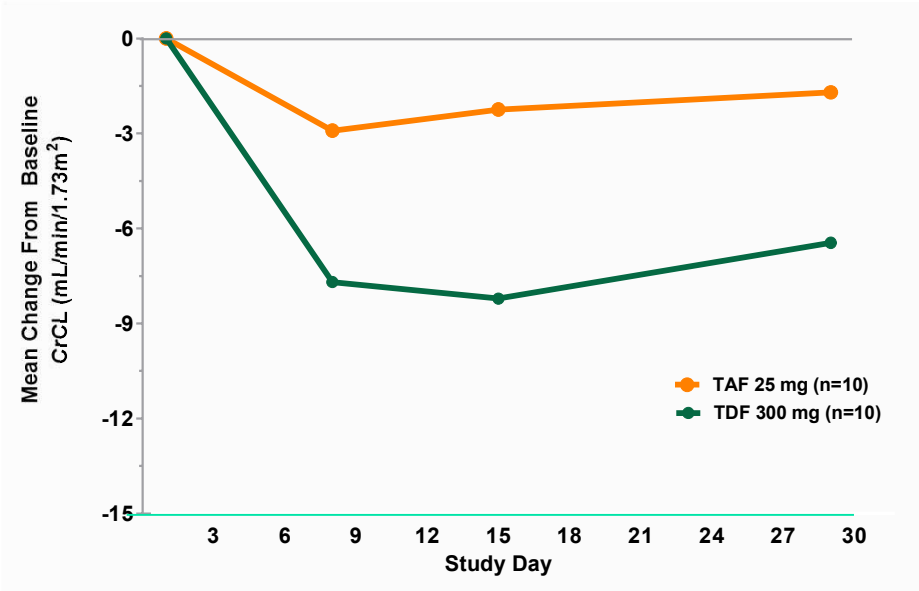
TAF Phase 1b in CHB.

28 day safety, and antiviral activity of tenofovir alafenamide for treatment of chronic hepatitis B

Viral Suppression



Creatinine Clearance



- TAF 25mg antiviral activity was similar to TDF 300mg.
- eGFR (CL_{Cr}) declined less with TAF vs TDF.

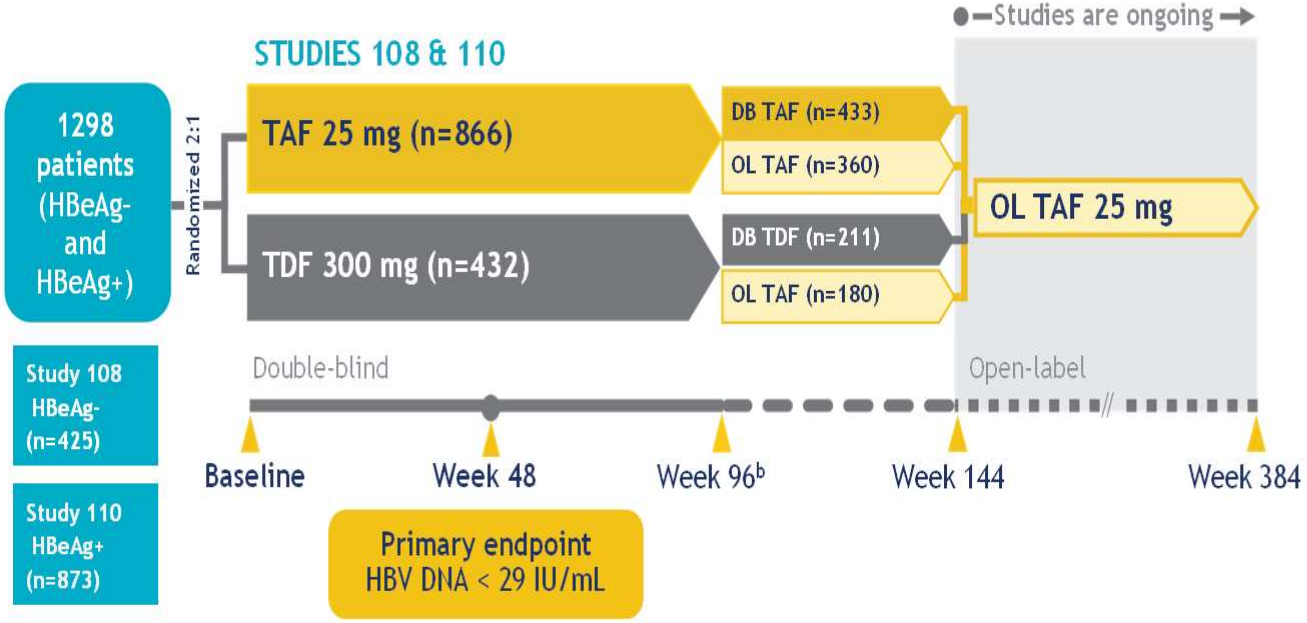
Agarwal K et al. J Hepatology 2015;62:533-40

Study 108 and 110: Phase 3 CHB Studies: TAF vs TDF

TAF HBV Phase 3 Studies

Two phase 3, randomized, double-blind studies[1-8,a]

– The efficacy and safety of VEMLIDY in the treatment of adults with chronic HBV infection with compensated liver disease are based on data from 2 randomized, double-blind, active-controlled, noninferiority studies.



Efficacy endpoints evaluated at Week 48, Week 96, and Week 144 for both studies include the proportion of patients with HBV DNA < 29 IU/mL, ALT normalization, and HBsAg loss and seroconversion. HBeAg loss and seroconversion were also assessed in Study 110.

Key inclusion criteria: HBV DNA ≥ 20,000 IU/mL; ALT > 60 U/L (males), > 38 U/L (females) and ≤ 10x ULN by central laboratory range.

[a] The original study design for Studies 108 and 110 was amended to extend the double-blind phase from 96 to 144 weeks and the open-label phase to Week 384. Prior to the amendment to the double-blind phase, 540 patients had already entered the open-label phase at Week 96; 360 patients remained on TAF and 180 patients switched from TDF to TAF at Week 96.

[b] The numbers of patients listed after Week 96 refer to those who entered the open-label phase or remained in the double-blind phase, and exclude patients who prematurely discontinued double-blind study treatment by Week 96.

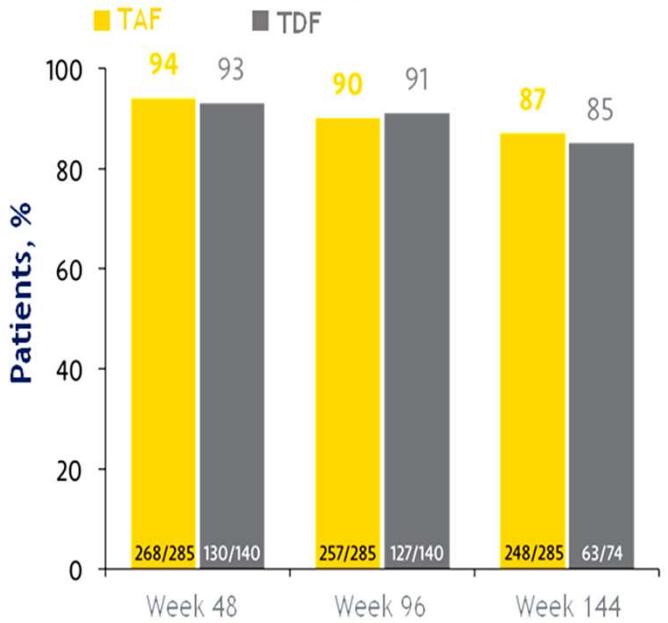
1. Vemlidy EU SmPC, Gilead Inc, April 2018; 2. Buti M et al. *Lancet G&H* 2016; doi: 10.1016/S2468-1253(16)30107-8; 3.Chan HLY et al. *Lancet G&H 2016*; doi: /10.1016/S2468-1253(16)30024-3; 4. Agarwal K, et al. *J Hepatol*. 2018;68:672-681. 5. Chan HLY, et al. AASLD 2018; November 9-13, 2018; San Francisco, CA. Poster 381.; 6. Seto WK, et al., AASLD 2018; November 9-13, 2018; San Francisco, CA. Poster 404. 7. AASLD. Posters (Abstracts 301-2389). *Hepatology*. 2018;68:S184-S1353; 8. Data on file. Gilead Sciences, Inc.

Study 108 and 110: Phase 3 CHB Studies: TAF vs TDF

Antiviral Efficacy of TAF and TDF Through Week 144

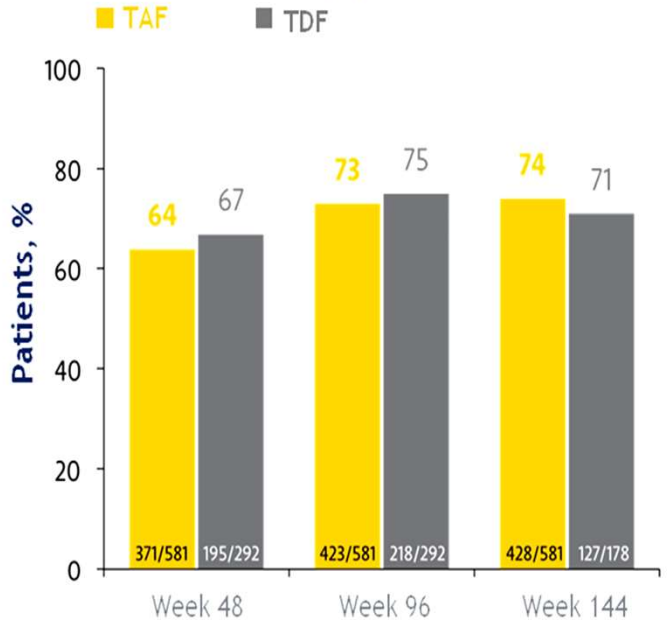
Viral Suppression (ITT; M=F) HBV DNA < 29 IU/mL[a, 1-8]

Study 108 (HBeAg- patients)[b]



Week 48 treatment difference: +1.8% (95% CI: -3.6%, +7.2%)
Week 96 treatment difference: -0.6% (95% CI: -7.0%, +5.8%)
Week 144 treatment difference: +1.7% (95% CI: -8.1%, +11.4%)

Study 110 (HBeAg+ patients)[b]



Week 48 treatment difference: -3.6% (95% CI: -9.8%, +2.6%)
Week 96 treatment difference: -2.2% (95% CI: -8.3%, +3.9%)
Week 144 treatment difference: +2.0% (95% CI: -5.6%, +9.6%)

No resistance was detected through Week 144

Similar HBV DNA suppression rates for TAF compared to TDF through Week 144

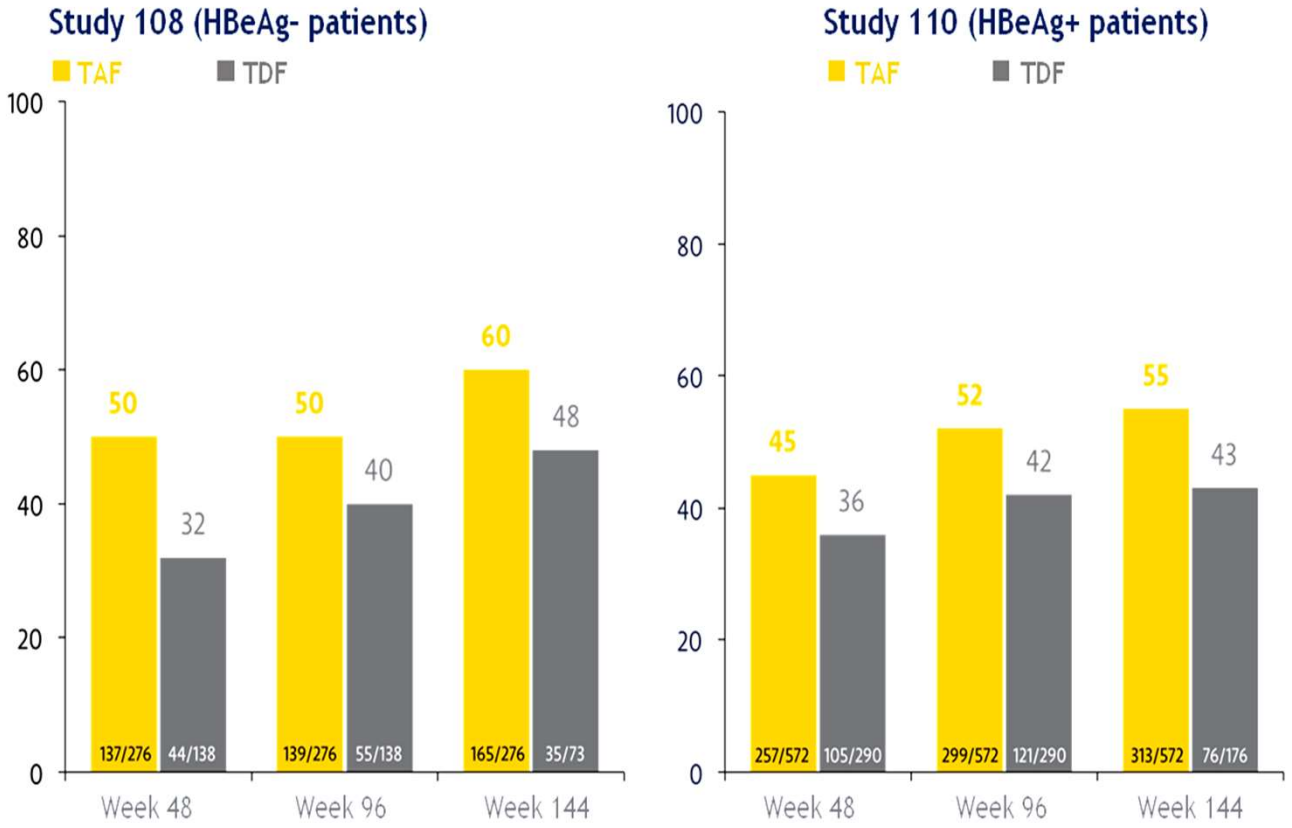
[a] Patient populations analyzed included all patients who were randomized into the study and received at least 1 dose of study drug; a missing=failure approach was used. The Week 144 analysis did not include the 180 patients (HBeAg-: 66 patients; HBeAg+: 114 patients) who had rolled over from double-blind TDF to open-label VEMLIDY at Week 96 prior to the study amendment.[7]
[b] Mean baseline plasma HBV DNA: 5.8 $\log_{10}$ IU/mL in Study 108 (HBeAg−); 7.6 $\log_{10}$ IU/mL in Study 110 (HBeAg+).[1]

1, Vemlidy EU SmPC, Gilead Inc, April 2018; 2. Buti M et al. *Lancet G&H* 2016; doi: 10.1016/S2468-1253(16)30107-8; 3.Chan HLY et al. *Lancet G&H 2016*; doi: /10.1016/S2468-1253(16)30024-3; 4. Agarwal K, et al. *J Hepatol*. 2018;68:672-681. 5. Chan HLY, et al. AASLD 2018; November 9-13, 2018; San Francisco, CA. Poster 381; 6. AASLD. Posters (Abstracts 301-2389). *Hepatology*. 2018;68:S184-S1353; 7. Gilead, Data on File; 8. Chan HLY, et al. Poster presented at: AASLD 2018; November 9-13, 2018; San Francisco, CA. Poster 386.

Study 108 and 110: Phase 3 CHB Studies: TAF vs TDF

ALT Normalization of TAF and TDF Through Week 144

ALT normalization (2016 AASLD criteria)[a,b, 1-7]



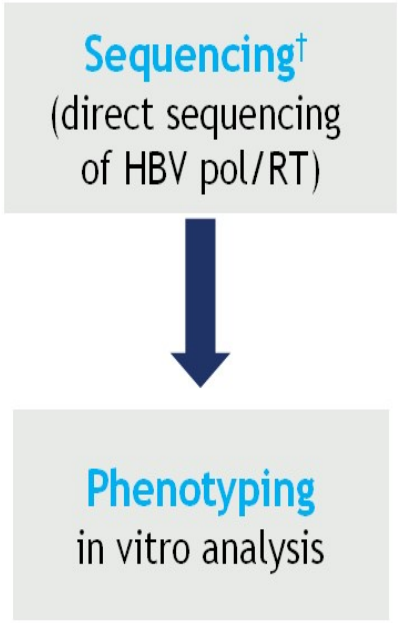
Improved rates of ALT normalization in treatment-naïve and treatment-experienced patients with compensated liver disease

[a] The population used for analysis of ALT normalization included only patients with ALT > ULN per the 2016 AASLD criteria (> 30 U/L for males and > 19 U/L for females) at baseline.
[b] Patient populations analyzed included all patients who were randomized into the study and received at least 1 dose of study drug; a missing=failure approach was used. The Week 144 analysis did not include the 180 patients (HBeAg-: 66 patients; HBeAg+: 114 patients) who had rolled over from double-blind TDF to open-label VEMLIDY at Week 96 prior to the study amendment.[7]

1, Vemlidy EU SmPC, Gilead Inc, April 2018; 2. Buti M et al. *Lancet G&H* 2016; doi: 10.1016/S2468-1253(16)30107-8; 3.Chan HLY et al. *Lancet G&H 2016*; doi: /10.1016/S2468-1253(16)30024-3; 4. Agarwal K, et al. *J Hepatol*. 2018;68:672-681. 5. Chan HLY, et al. AASLD 2018; November 9-13, 2018; San Francisco, CA. Poster 381; 6. AASLD. Posters (Abstracts 301-2389). *Hepatology*. 2018;68:S184-S1353; 7. Gilead, Data on File

Study 108 and 110: Phase 3 CHB Studies: TAF vs TDF.

No Resistance to TAF and TDF detected Through Week 144



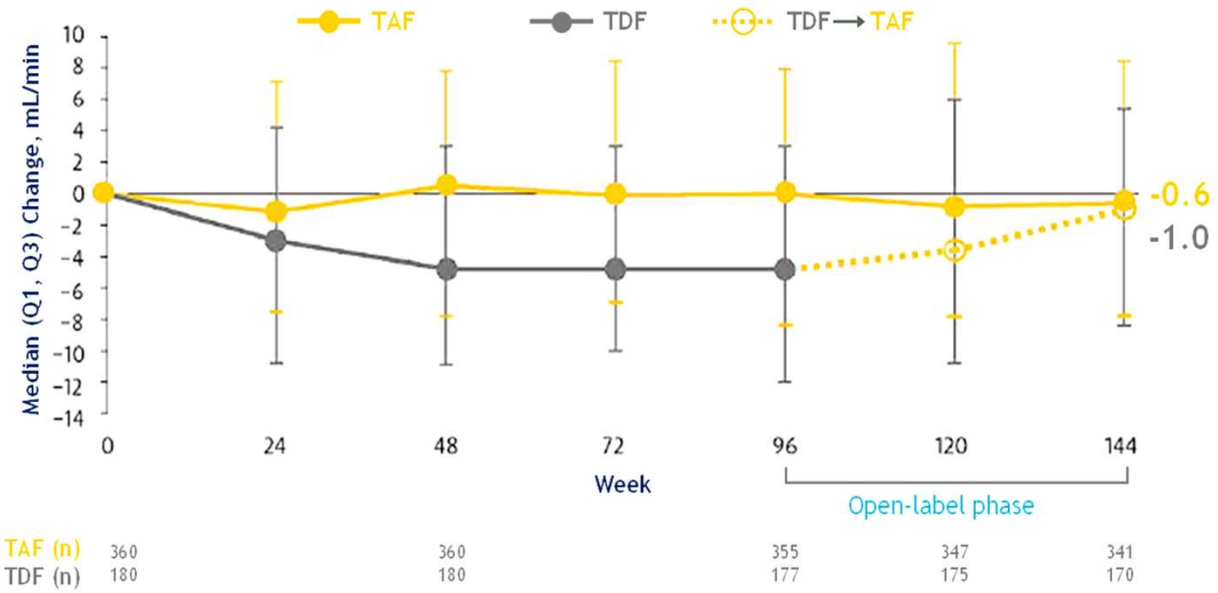
- Week 144 virology resistance surveillance[1]:
  - HBV polymerase/reverse transcriptase (pol/RT) sequencing conducted for patients with HBV DNA ≥ 69 IU/mL at Week 144 and at early discontinuation if HBV DNA ≥ 69 IU/mL
- In vitro phenotyping performed for patients with[1]:
  - Changes at conserved sites in HBV pol/RT
  - Changes at polymorphic sites if seen in > 1 patient
  - Virologic breakthrough while on study drug‡

No resistance to TAF and TDF was detected through Week 144[1]

†Limit of sequencing assay = 69 IU/mL, consensus level results are reported (15% cutoff)
‡ Virologic breakthrough: HBV DNA increase 1 $\log_{10}$ IU/mL above nadir or DNA ≥ 69 IU/mL after being < 69 IU/mL for 2 consecutive visits.
1, Natap. Chan HLY, et al. http://www.natap.org/2018/AASLD/AASLD_235.htm. Accessed in May 2019.

Renal Laboratory Parameters in CHB Patients Treated with TAF or TDF

Change in $eGFR_{CG}$ from Baseline[1,a]



Median change in $eGFR_{CG}$ from Week 96 to Week 120[2]

- Patients who remained on TAF: -0.6 mL/min
- Patients who switched from TDF to TAF: +1.8 mL/min

[a] The graph shows changes in $eGFR_{CG}$ from baseline for the subset population of patients who entered the open-label phase at Week 96.

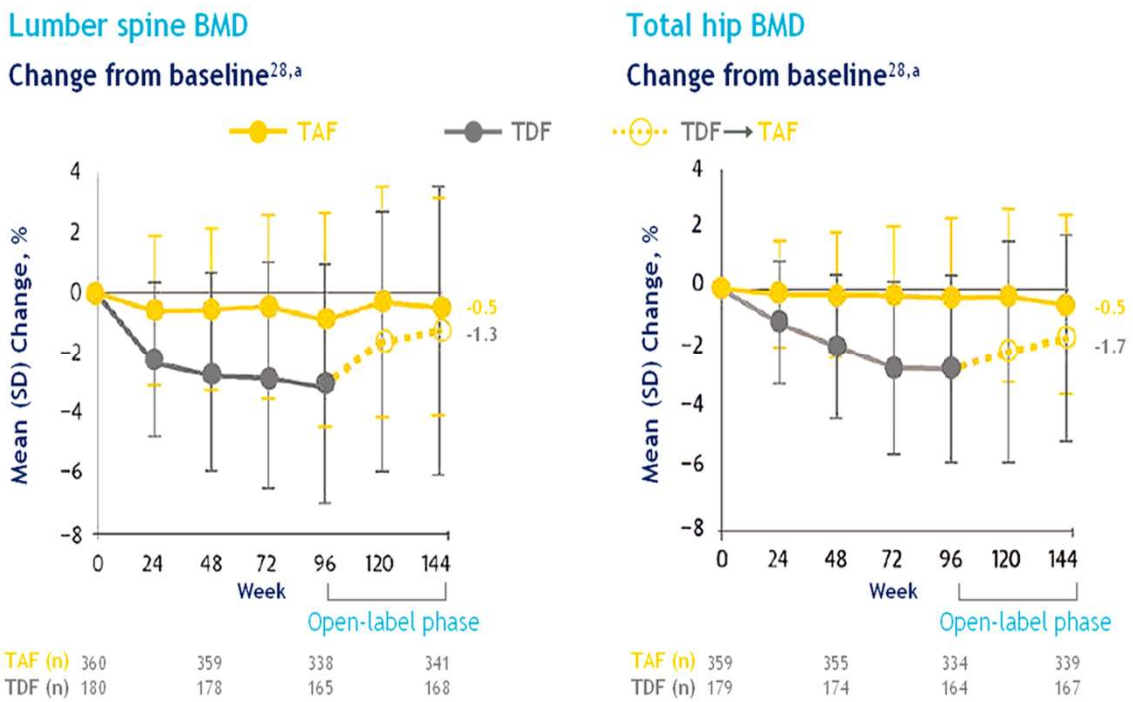
Improvement in $eGFR_{CG}$ at Week 144 in patients who switched from TDF to TAF at Week 96[1]

$eGFR_{CG}$, estimated glomerular filtration rate as measured by the Cockcroft-Gault equation

1. Gilead, Data on File; 2. Vemlidy EU SmPC, Gilead Inc, April 2018.

Changes in BMD in CHB Patients Treated with TAF or TDF

Change in BMD from Baseline[1]



Improvement in spine and hip BMD at week 144 in patients who switched from TDF to TAF at Week 96[1]

Mean percentage change in lumbar spine BMD from Week 96 to Week 120[2]

- Patients who remained on TAF: +0.6%
- Patients who switched from TDF to TAF: +1.7%

Mean percentage change in total hip BMD from Week 96 to Week 120[2]

- Patients who remained on TAF: 0%
- Patients who switched from TDF to TAF: +0.6%

[a] The graph shows changes in $eGFR_{CG}$ from baseline for the subset population of patients who entered the open-label phase at Week 96.

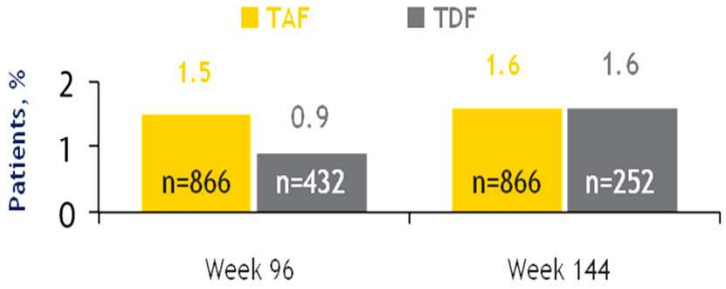
1. Gilead, Data on File; 2. Vemlidy EU SmPC, Gilead Inc, April 2018.

Study 108 and 110
Phase 3 CHB Studies: Week 96 to Week 144 Open-label Safety Data

Adverse Reactions in CHB Patients Treated with TAF or TDF

Adverse Event Profile[1]

- The proportion of patients who discontinued treatment due to adverse reactions of any severity is shown in the graph below:



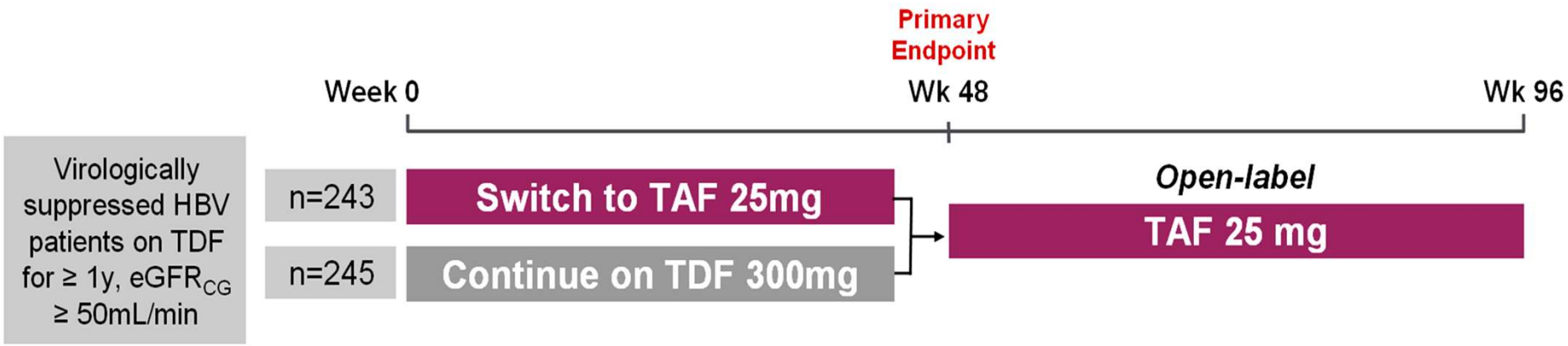
- Based on the Week 96 and 144 analyses, the most common adverse reactions (all grades) reported in at least 5% of patients in the TAF group were:
  - **Week 96:** Headache, abdominal pain, cough, back pain, fatigue, nausea, arthralgia, diarrhea, and dyspepsia
  - **Week 144:** Headache, upper respiratory tract infection, cough, back pain, arthralgia, fatigue, nausea, diarrhea, dyspepsia, abdominal pain, and pyrexia
- The safety profile of TAF in patients who remained on TAF in the open-label phase through Week 144 was similar to that in patients who switched from TDF to TAF at Week 96
- **Differences were observed between TAF and TDF in certain lipid parameters**
  - Mean changes in fasting LDL-C and triglycerides from baseline to Week 96 were +7 mg/dL and +13 mg/dL, respectively, for TAF vs −10 mg/dL and −7 mg/dL for TDF
    - **At Week 144:** +8 mg/dL and +18 mg/dL for TAF and −8 mg/dL and −2 mg/dL for TDF
  - Fasting LDL-C > 190 mg/dL was observed at Week 96 in 6% of patients receiving TAF vs 1% with TDF
    - **At Week 144:** 7% of patients receiving TAF vs 1% with TDF
  - The mean change in total cholesterol to HDL-C ratio at Weeks 96 and 144 from baseline was 0 for both TAF and TDF
- In the open-label phase, lipid parameters at Week 144 in patients who remained on TAF were similar to those at Week 96
- In patients who switched from TDF to TAF, the mean change from Week 96 to Week 144 in total cholesterol was 23 mg/dL, HDL-C was 3 mg/dL, LDL-C was 16 mg/dL, triglycerides was 28 mg/dL, and total cholesterol to HDL-C ratio was 0 mg/dL

1. Data on File, Gilead Sciences;

Study 4018: Phase 3 CHB TDF to TAF Switch Study: 48 Week Analysis

Study Design

Phase 3, randomized, double-blind, active-controlled study



Study Objective:

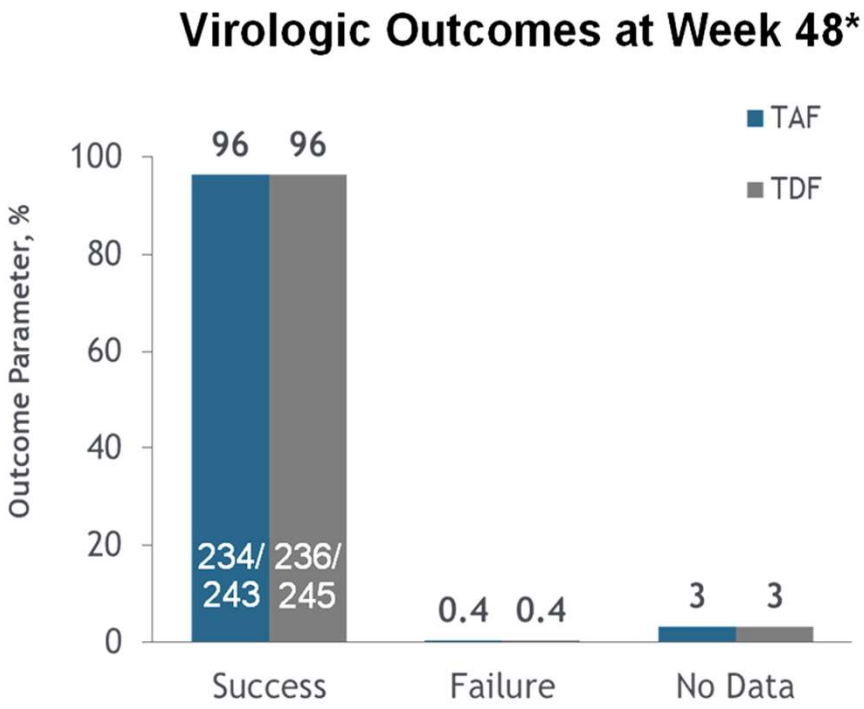
- To evaluate the efficacy and safety of switching to TAF from TDF compared with continued TDF treatment in virologically suppressed patients with chronic HBV

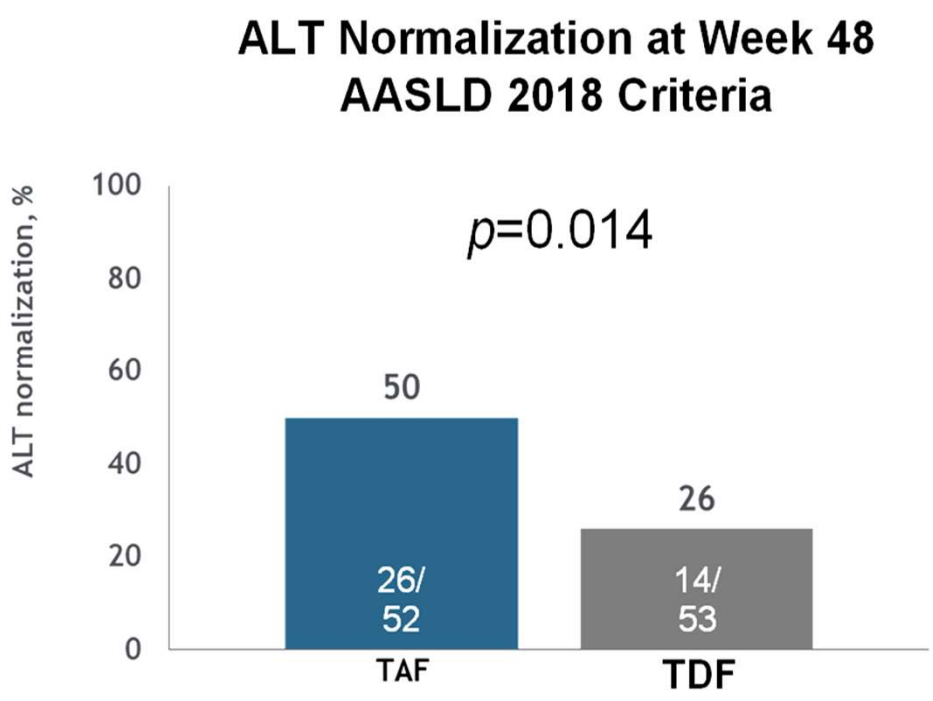
Primary Endpoint:

- HBV DNA ≥20 IU/mL at Week 48

Lampertico, EASL, 2019, FRI-183

Efficacy Analysis at Week 48





Switching to TAF was noninferior to continuing TDF at Week 48
No resistance was detected in either group

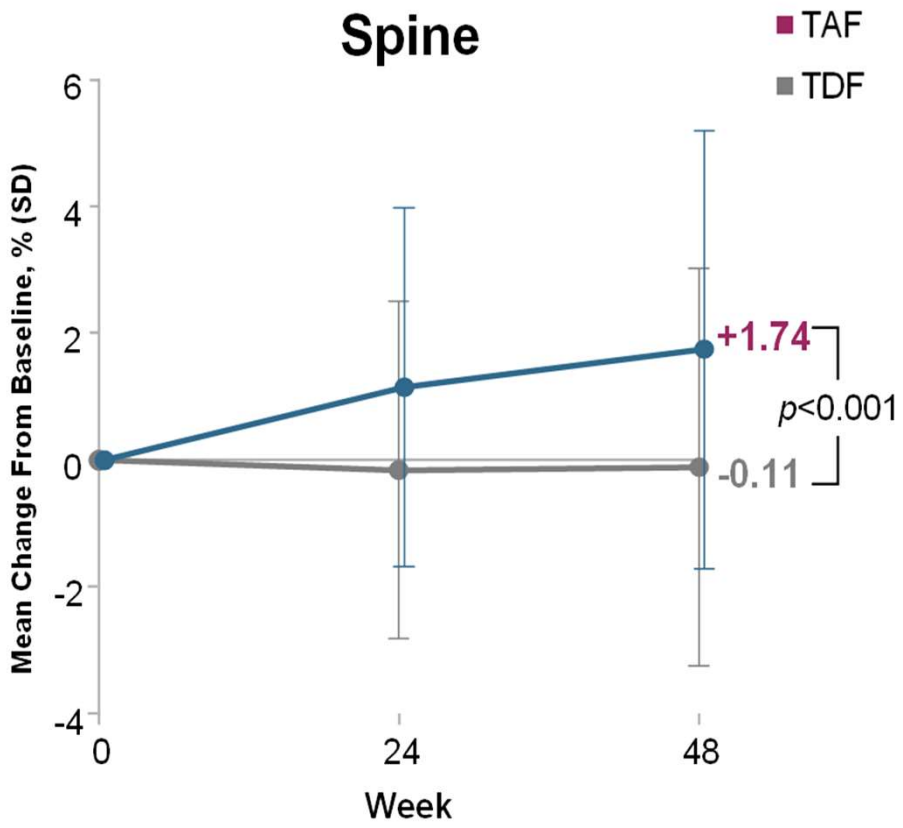
*Noninferiority to TDF (4% margin; 95% confidence interval [CI] approach) by US Food and Drug administration modified snapshot algorithm
ULN for AASLD criteria: 35 and 25 U/L in men and women, respectively; ALT normalization results are missing=failure.

Lampertico, EASL, 2019, FRI-183

Renal and Bone Safety at Week 48

Renal Safety

	TAF n=243	TDF n=245	*p*-value
$eGFR_{CG}$ change, mL/min	0.94 (-4.47, 6.24)	-2.74 (-7.89, 1.88)	<0.001
Grade ≥1 proteinuria, n/n (%)	33/242 (14)	54/243 (22)	0.01
≥1-stage worsening in CKD stage†	15/234 (6)	32/237 (14)	<0.001
≥1-stage improvement in CKD stage†	28/112 (25)	9/116 (8)	



†Chronic kidney disease (CKD) stages: ≥90 mL/min (Stage 1), ≥60–<90 mL/min (Stage 2), ≥30–<60 mL/min (Stage 3), and <30 mL/min (Stage 4); worsening or improvement in CKD stage at Week 48 relative to baseline stage.

Lampertico, EASL, 2019, FRI-183

Study 4018: Phase 3 CHB TDF to TAF Switch Study: 48 Week Analysis

Safety Through Week 48

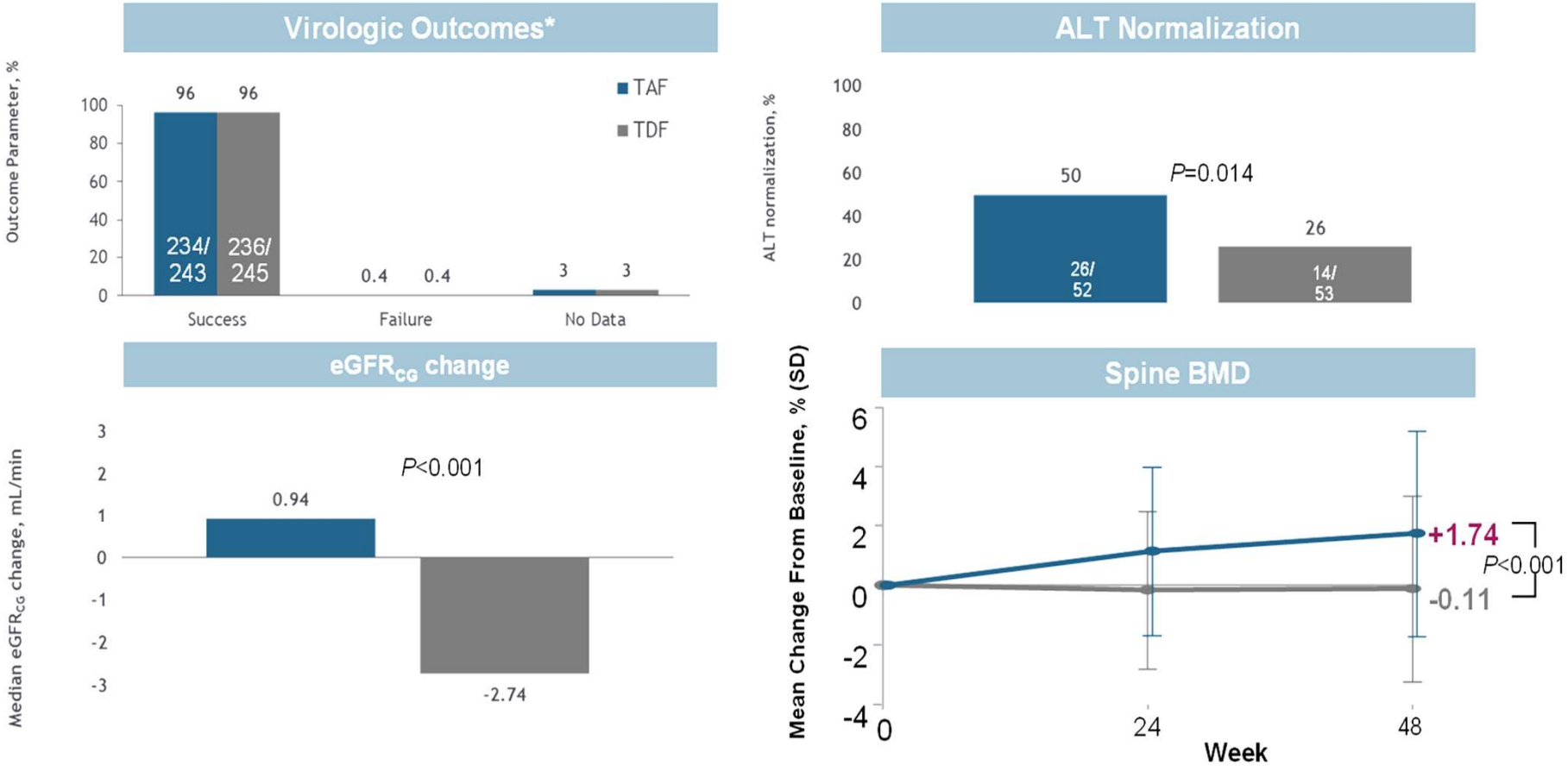
	Patients, n (%)	TAF n=243	TDF n=245
Adverse Events	AE	126 (52)	118 (48)
	Grade 3-4 AE	8 (3)	4 (2)
	Serious AE	11 (5)	3 (1)
	Serious AE related to study drug	0	0
	D/C due to AE	2 (<1)	0
	HCC	1 (<1)	1 (<1)
	Death	0	0
Laboratory Abnormalities, ≥1%	Grade 3-4	23/242 (10)	18/243 (7)
	Creatine kinase	1 (<1)	3 (1)
	Hyperglycemia (fasting)	3 (1)	1 (<1)
	LDL cholesterol	9 (4)	4 (2)
	Urine erythrocytes	2/179 (1)	3/177 (2)
	Urine glucose	3 (1)	5 (2)

Switching to TAF from TDF was safe and well tolerated

Lampertico, EASL, 2019, FRI-183

Study 4018: Phase 3 CHB TDF to TAF Switch Study: 48 Week Analysis

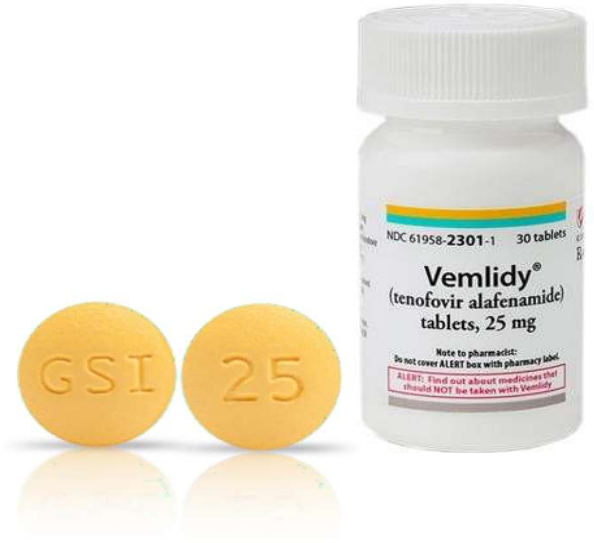
Efficacy and Safety Overview at Week 48



*Noninferiority to TDF (4% margin; 95% confidence interval [CI] approach) by US Food and Drug administration modified snapshot algorithm ULN for AASLD criteria: 35 and 25 U/L in men and women, respectively; ALT normalization results are missing=failure.

Lampertico, EASL, 2019, FRI-183

Thành phần & dạng bào chế.



Vemlidy® PI Việt Nam

Vemlidy® 25 mg viên nén bao phim.

- Mỗi viên nén bao phim chứa: 28,04 mg tenofovir alafenamide fumarate tương đương với **25mg tenofovir alafenamide (TAF).**
- Viên thuốc màu vàng, tròn, dạng viên nén bao phim.
- Một chai gồm 30 viên.

safety first

Thuốc có tính an toàn cao.

Tác dụng phụ thường gặp nhất		
Buồn nôn 6%	Nhức đầu 12%	Mệt mỏi 6%

Liu Y, et al. Antiviral Res. 2017; 139:25-31

Không cần chỉnh liều trên 1 số đối tượng bệnh nhân đặc biệt.

Người cao tuổi.

Không cần điều chỉnh liều dùng cho bệnh nhân từ 65 tuổi trở lên.

Suy Thận.

- Không cần điều chỉnh liều dùng trên bệnh nhân có độ thanh thải creatinine (CrCl) ≥ 15 mL/phút hoặc ở bệnh nhân có CrCl < 15 mL/phút đang điều trị bằng thẩm tách máu.
  - Vào những ngày thẩm tách máu, bệnh nhân nên dùng Vemlidy sau khi hoàn thành điều trị bằng thẩm tách máu.
  - Không có khuyến cáo liều dùng cho các bệnh nhân có CrCl < 15 mL/phút không điều trị bằng thẩm tách máu.

Khuyến cáo cho trẻ em.

Chưa xác định được tính an toàn và hiệu quả của Vemlidy ở trẻ em dưới 12 tuổi hoặc có cân nặng < 35 kg

Suy gan.

Không cần điều chỉnh liều dùng.

Kết luận

- Bệnh viêm gan siêu vi B vẫn còn là một thách thức lớn.

  Nhiều tiến bộ trong chẩn đoán bệnh.

  Nguy cơ biến chứng vẫn còn dù bệnh đã được kiểm soát tốt.
- Điều trị khó khăn, lâu dài, tốn kém và phải chấp nhận các tác dụng phụ của thuốc.

  TAF: Một bước tiến bộ mới trong kiểm soát bệnh hiệu quả và ít tác dụng phụ trong điều trị lâu dài.

  TAF hiện nay là thuốc uống được chọn lựa đầu tay cho điều trị viêm gan B vì khả năng ức chế virus cao, không kháng thuốc, an toàn cho xương và thận, đặc biệt dùng an toàn cho người lớn tuổi, người có tiền sử bệnh xương và người có chức năng thận yếu.

  Trông chờ các thế hệ thuốc mới: Điều trị hết bệnh ???
- Tiêm ngừa: Vẫn là chìa khóa quan trọng trong cuộc chiến chống lại HBV.

CÁM ƠN QUÝ VỊ ĐÃ CHÚ Ý THEO DÕI