何鴻燊博士醫療拓展基金會
2017醫學研討會

Recent advances in antiviral therapy for viral hepatitis

病毒性肝炎治療最新進展

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Disclosures

- Advisory committee member: AbbVie, Gilead, Otsuka
- Speaker: AbbVie, Bristol-Myers Squibb, Echosens & Furui, Gilead, Janssen, Otsuka, Roche

WHAT'S NEW IN ANTIVIRAL THERAPY FOR HBV IN 2016?

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New developments for anti-HBV therapy in 2016

1. Prevention of vertical transmission of HBV
2. New nucleos(t)ide analog (NA) approved by FDA in Nov 2016
3. Safety of NA

PREVENTION OF VERTICAL TRANSMISSION OF HBV

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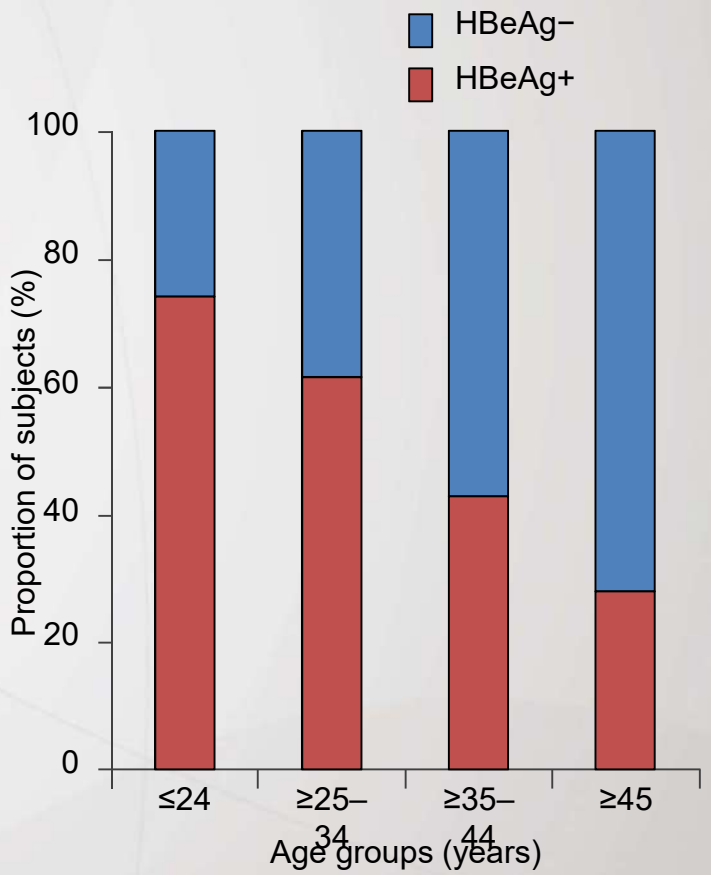
Women of childbearing age have higher levels of HBV DNA and are more likely to be HBeAg+

- Younger vs older women (≤44 vs vs ≥45 years) were more likely to:
  - Be HBeAg+: 57.2% vs 27.5% (P<0.0001)
    - Declined with increasing age
  - Have high viral load (HBV DNA >10^8 copies mL): 46.0% vs 25.5% (P<0.0001)
    - Declined with increasing age
- HBeAg positivity was slightly higher in Asian women
  - Associated with a higher % of HBV genotypes B and C in this population

HBeAg status by age cohorts



Tran TT, et al. PLoS ONE 2015;10:e0121632.

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What's the relevance in Hong Kong?

Free blood tests offered by AsiaHep from 25 Jun to 15 Nov, 2015

2,970 subjects

Age Group	HBsAg test	HBsAg+	Rate
All	2940	352	11.97%
</= 27	**159**	**10**	**6.29%**
28 - 40	**509**	**98**	**19.25%**
41 - 60	1598	189	11.83%
>/= 61	674	55	8.16%

- In 2014, HK population was 7.241M ; crude birth rate is 8.6/1,000.
- No. of birth was 62,278.
- Supposed 5-8% of child-bearing ladies are HBsAg+ve, ~ 3,000-5,000 babies are born by HBsAg+ mothers; **~1,500-2,500** by mothers with high HBV DNA.

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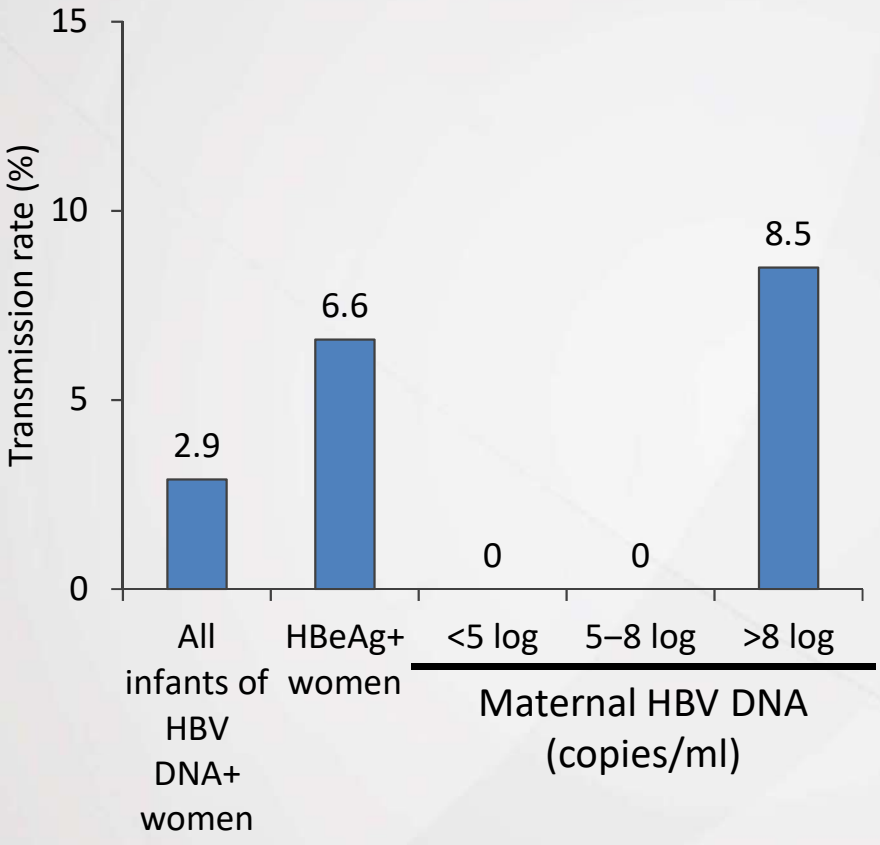
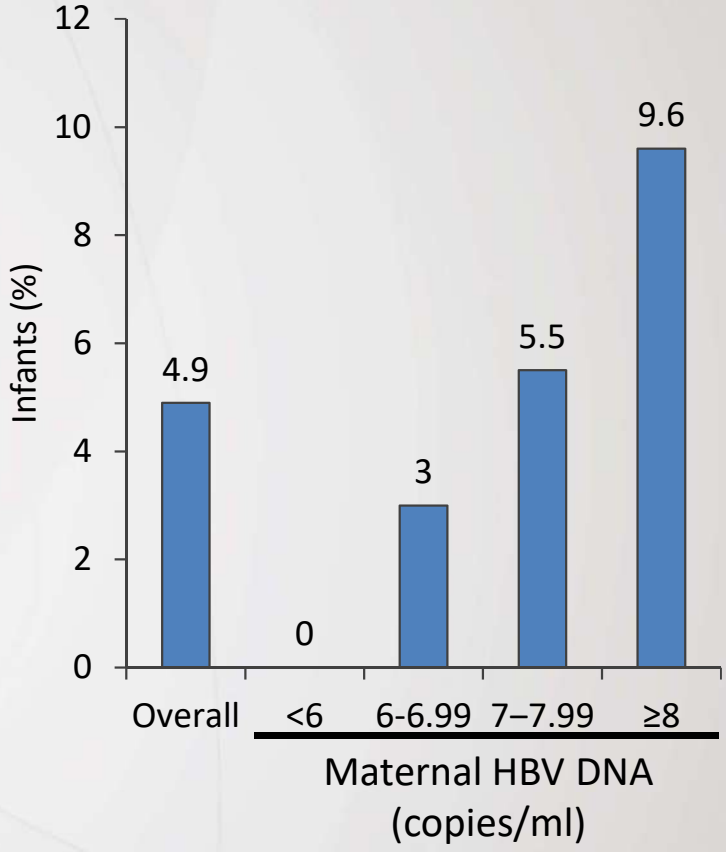
HBV DNA level and perinatal transmission of HBV





Wiseman E, et al. Med J Aust 2009;190:489–92.
Han G, et al. Hepatology 2011;54(Suppl):444A (abstract 170).

Antiviral options for HBV: Pregnancy category

- **Category B**
  - Telbivudine
  - Tenofovir disoproxil fumarate (TDF)
- **Category C**
  - IFNα
  - PEG-IFNα-2a
  - PEG-IFNα-2b
  - Lamivudine
  - Adefovir
  - Entecavir

Pregnancy category B: Animal studies do not indicate a risk to the foetus and there are no controlled human studies, or animal studies do show an adverse effect on the foetus but well-controlled studies in pregnant women have failed to demonstrate a risk to the foetus

Pregnancy category C: Studies have shown that the drug exerts animal teratogenic or embryocidal effects, but there are no controlled studies in women, or no studies are available in either animals or women

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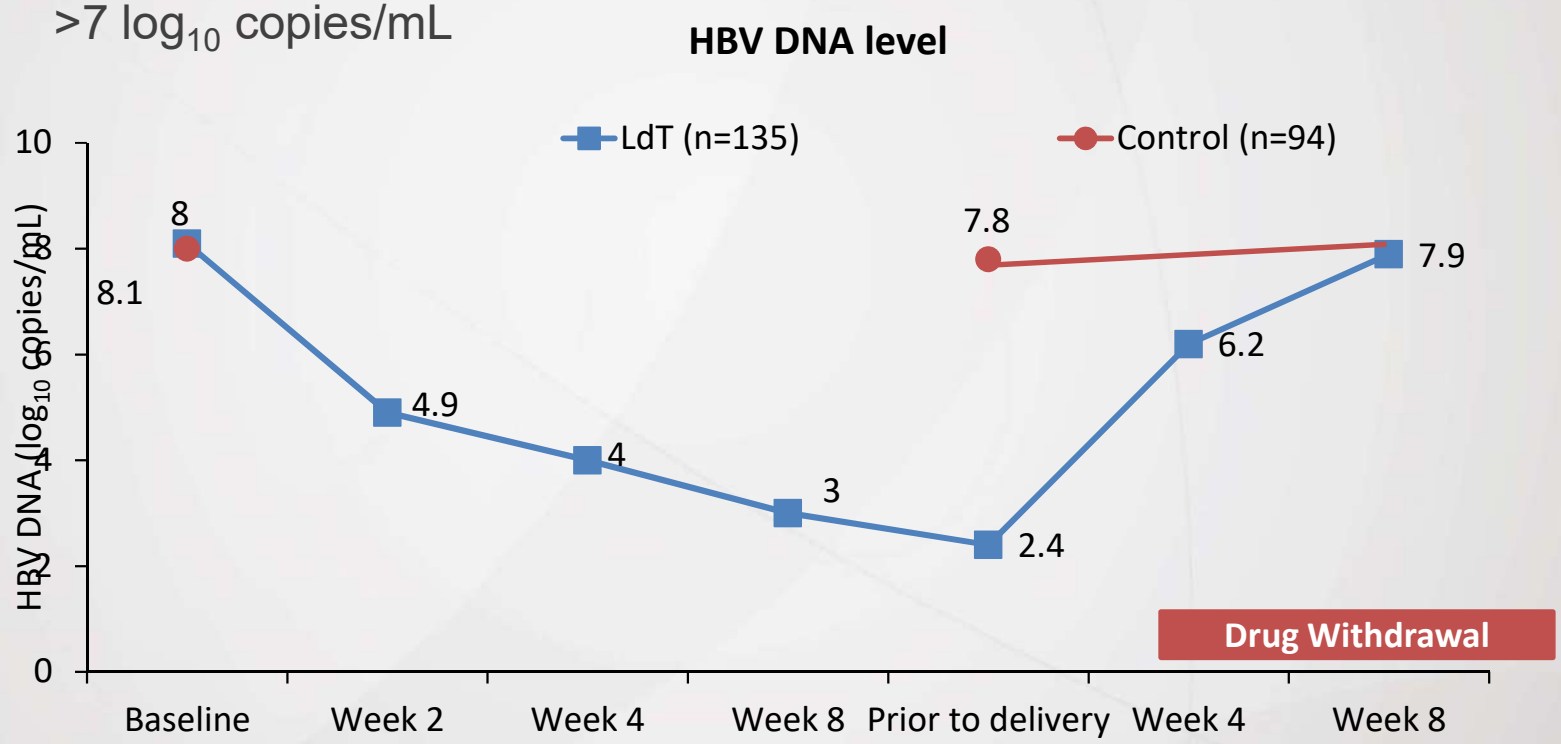
Prescribing information for: Tyzeka®, Viread®, Intron A, Pegasys®, PegIntron®, Epivir®, Hepsera®, Baraclude®.

IFN: interferon; PEG-IFN: pegylated interferon; TDF: tenofovir disoproxil fumarate

NA treatment during pregnancy

- Non-randomised case-controlled study by woman's decision for treatment
- 229 pregnant Asian women with HBeAg+ CHB and HBV DNA >7 $\log_{10}$ copies/mL

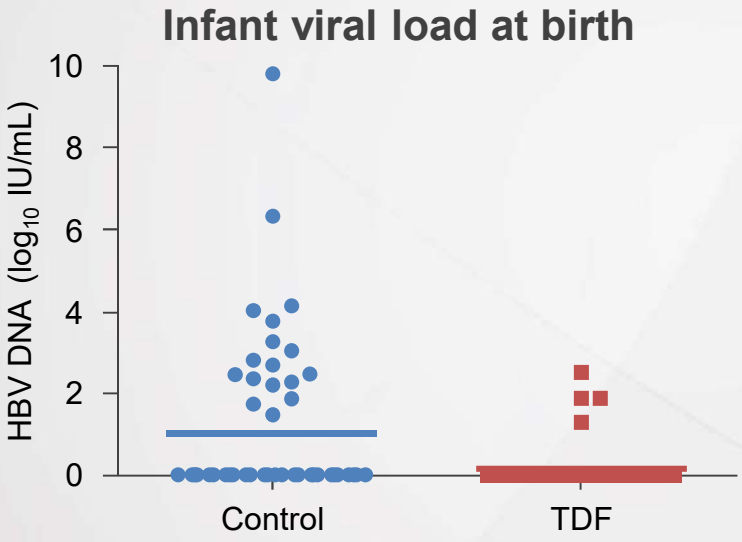


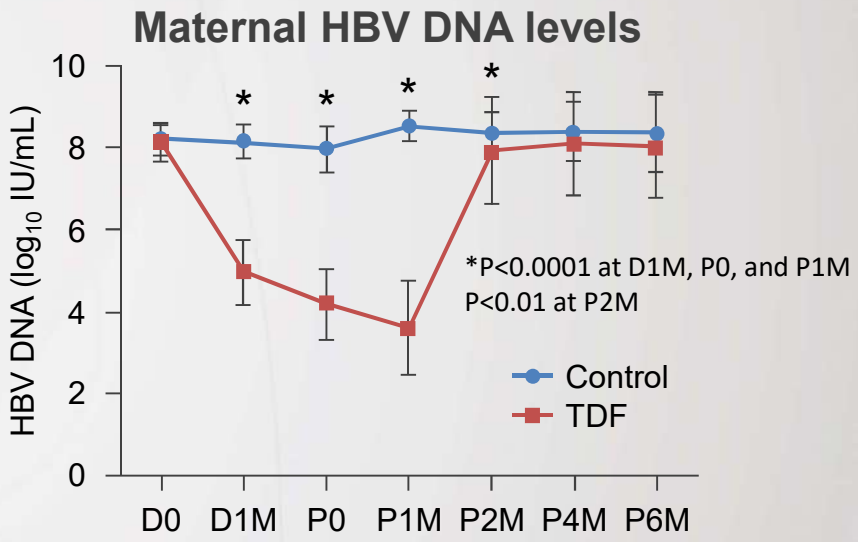
f/u: follow-up; ITT: intention-to-treat;
LdT: telbivudine; NA: nucleos(t)ide analogue

Han GR, et al. J Hepatol 2011;55:1215–21.

Maternal TDF in interrupting MTCT of HBV: Prospective, multicentre trial in Taiwan

- 118 HBsAg– and HBeAg+ pregnant women with HBV DNA ≥7.5 $\log_{10}$ IU/mL
- TDF 300 mg daily (n=62, HBV DNA 8.18±0.47 $\log_{10}$ IU/mL) vs no medication (controls; n=56, HBV DNA 8.22±0.39 $\log_{10}$ IU/mL) from 30–32 weeks GA to 1 month post-partum
- Primary outcome: infant HBsAg status at 6 months





TDF group vs controls:

HBV DNA+ at birth: 6.14% vs 31.48% (P=0.0003)

HBsAg+ at 6 months: 1.54% vs 10.71% (P=0.0481)

Chen HL, et al. Hepatology 2015;62:375–86.

The NEW ENGLAND JOURNAL of MEDICINE

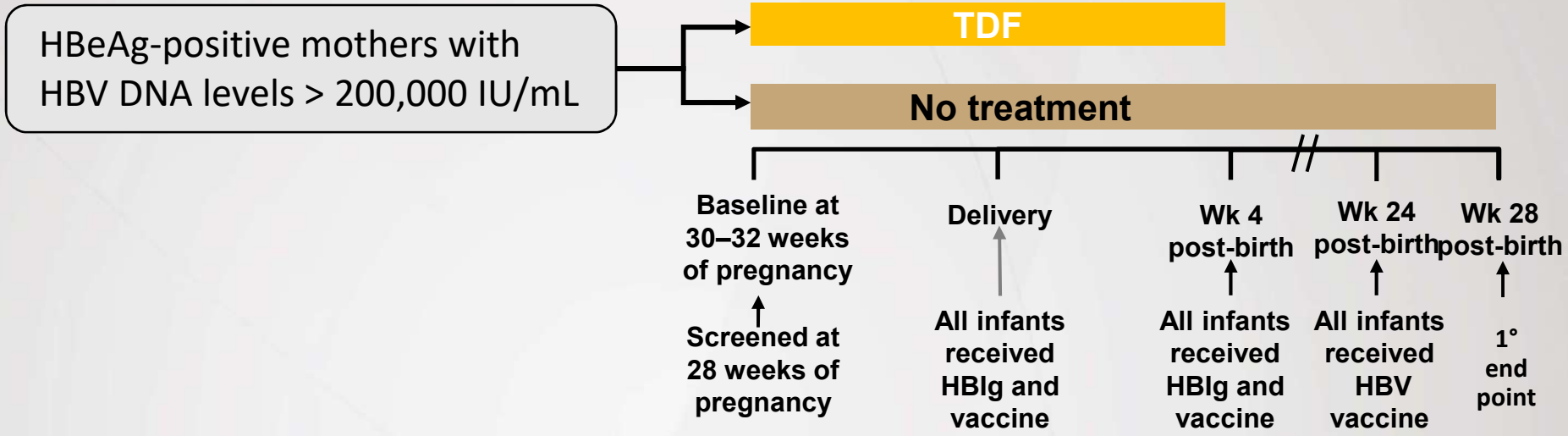
ORIGINAL ARTICLE

Tenofovir to Prevent Hepatitis B Transmission in Mothers with High Viral Load

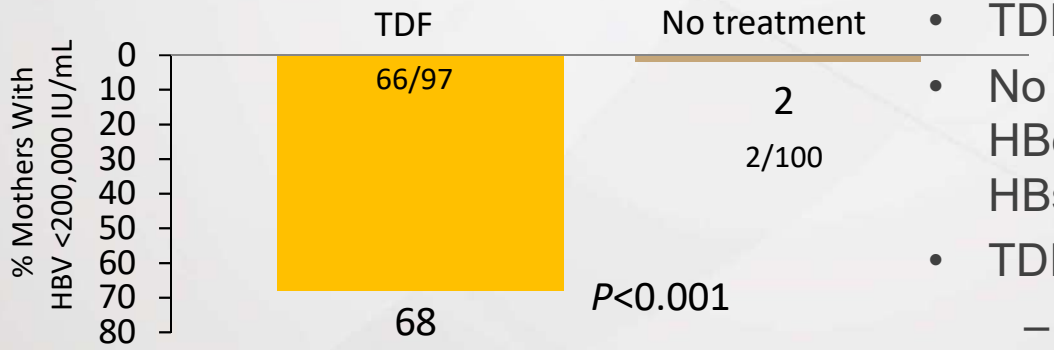
Calvin Q. Pan, M.D., Zhongping Duan, M.D., Erhei Dai, M.D., Shuqin Zhang, M.D., Guorong Han, M.D., Yuming Wang, M.D., Huaihong Zhang, M.D., Huaibin Zou, M.D., Baoshen Zhu, M.D., Wenjing Zhao, M.D., and Hongxiu Jiang, M.D., for the China Study Group for the Mother-to-Child Transmission of Hepatitis B*

N Engl J Med. 2016 Jun 16;374(24):2324-34.

TDF during pregnancy: randomized study



Maternal HBV DNA levels <200,000 IU/mL prior to delivery (ITT)



- Mean duration of TDF therapy: 8.57±0.53 weeks before delivery
- TDF: HBeAg seroconversion loss (n=1)
- No treatment: HBeAg loss (n=4); HBeAg seroconversion (n=3) and HBsAg seroconversion (p=NS)
- TDF therapy was well tolerated
  - Only one mother voluntarily W/D due to nausea (Grade II)
  - No patients D/C due to lack of efficacy

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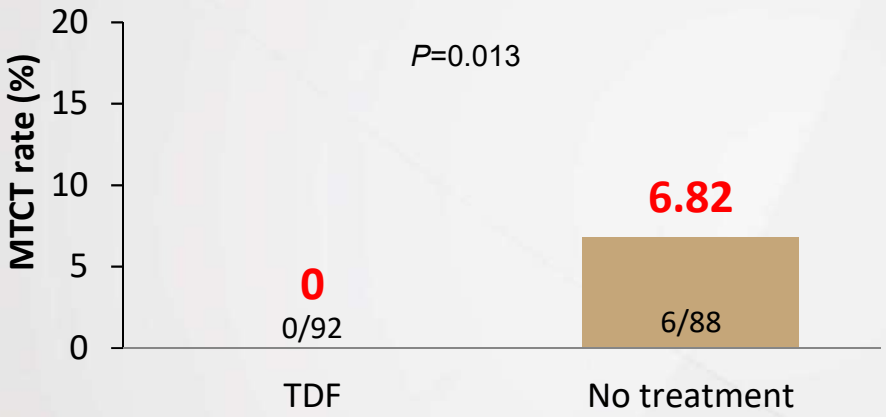
Pan C, et al. N Engl J Med. 2016 Jun 16;374(24):2324-34.

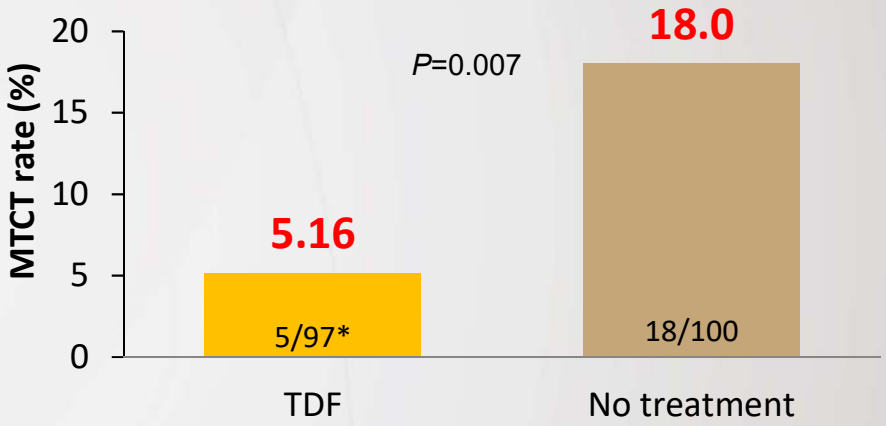
Primary endpoint: MTCT at post-partum Week 28

- MTCT = infants with serum HBV DNA >20 IU/mL or HBsAg positivity at 28 weeks of age

MTCT Rate at Postpartum Week 28 (PP)



MTCT Rate at Postpartum Week 28 (ITT)



*1 mother W/D consent prior to delivery, 1 mother lost fetus prior to delivery, 2 mothers LTFU, and 1 newborn death due to trauma

- Similar safety profile between groups
- No difference in birth defect rates
  - 2.11% (n=2) with TDF, 1.14% (n=1) with no treatment, *P*=1.00

Pan C, et al. N Engl J Med. 2016 Jun 16;374(24):2324-34.

Prevention of HBV perinatal transmission:
EASL / AASLD guideline recommendations

- HBIG and HBV vaccination for the newborn (B1)

- Mothers (HBeAg+) with HBV DNA >10^6 IU/mL (EASL) or 200,000 IU/ml (AASLD):
  - Oral antiviral treatment during the last trimester (B1) plus HBIG and HBV vaccination for the newborn

- If antiviral therapy only for prevention of perinatal transmission: may be discontinued within the firs 3 months after delivery (C1)

EASL. J Hepatol 2012;57:167–85.
Terrault NA, et al. Hepatology. 2016;63:261-83,

HBV drugs in pregnancy and breastfeeding

	Lamivudine	Adefovir	Entecavir	Tenofovir	Telbivudine	PEG-IFN
FDA pregnancy category	C	C	C	B	B	C
Crosses the placenta	Yes	Unknown	Unknown	Yes	Yes (rats and rabbits)	Minimal
Excretion in breast milk	Yes	Unknown	Unknown (yes in animals)	Unknown (yes in animals)	Unknown (yes in animals)	Minimal
Animal studies	Embryonic loss in rabbits at clinical doses	Embryo toxicity and malformation in rats >38 times maximum human exposure	Fetal malformations and retarded development at >250 times human value	Subcutaneous treatment of pregnant monkeys at 30 mg/kg/day reduced fetal serum $PO4^{3-}$	Early deliveries and abortions in rabbits at plasma levels 37 times higher than human dose	Abortifacient activity in Rhesus monkeys

Visvanathan et al. Gut 2016;65:340

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Visvanathan et al. Gut 2016;65:340

After delivery: EASL / AASLD guidelines

- Safety of oral antiviral therapy during lactation is uncertain[1]
- Tenofovir concentrations have been reported in breast milk, but its oral bioavailability is limited and, therefore, infants are only exposed to low levels[2]
- AASLD: Breastfeeding is not contraindicated; insufficient long-term safety data.[3]
- Mother needs to be followed even if not treated[1]
- Re-evaluate the need for treatment, if stopped or delayed[1]

1. EASL. J Hepatol 2012;57:167–85;
2. Benaboud SB, et al. Antimicrob Agents Chemother 2011;55:1315–7.
3. Terrault NA, et al. Hepatology. 2016;63:261-83,

A NEW NUC – TENOFOVIR ALAFENAMIDE (TAF)

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Approved HBV Treatments

- Interferon alpha 2b (Intron)
- Pegylated interferon alpha 2a (Pegasys)

- Lamivudine (Epivir)
- Adefovir (Hepsera)
- Entecavir (Baraclude)
- Telbivudine (Tyzeka)
- Tenofovir (Viread)

Treatments approved for HIV with activity against HBV

- Emtricitabine (Emtriva)
- Tenofovir + Emtricitabine (Truvada)

When to Start Treatment?

- Evidence of liver disease – abnormal ALT (>2x ULN) in the presence of high serum HBV DNA (>20,000 IU/mL)
  - Lower threshold if
    - Older age (>40 years)
    - Active inflammation or advanced fibrosis on biopsy
    - Clinical evidence of cirrhosis
- Borderline ALT or HBV DNA – monitor, if persistent, consider biopsy
- Others – monitor, treat later when indication arises or more effective treatment available

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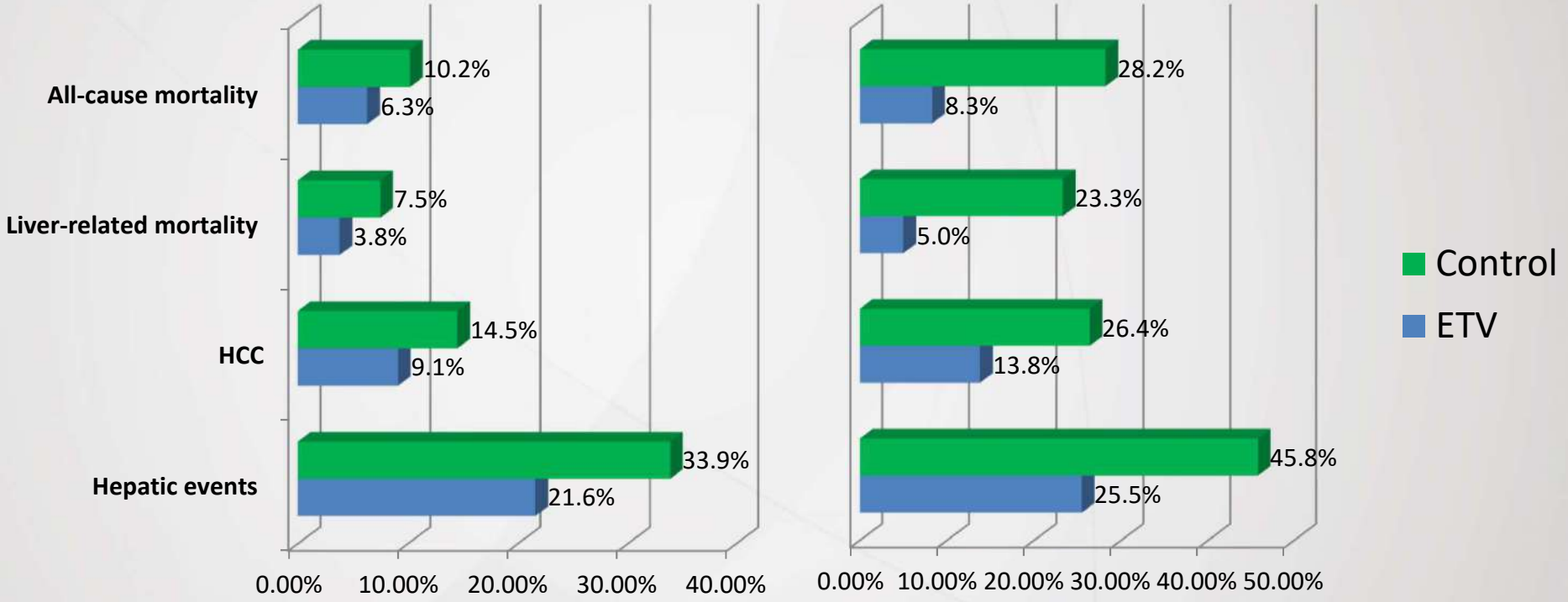
Lok & McMahon, Hepatology 2009

Cumulative probabilities of hepatic events in cirrhotic patients

All $P<0.05$



3 years

5 years

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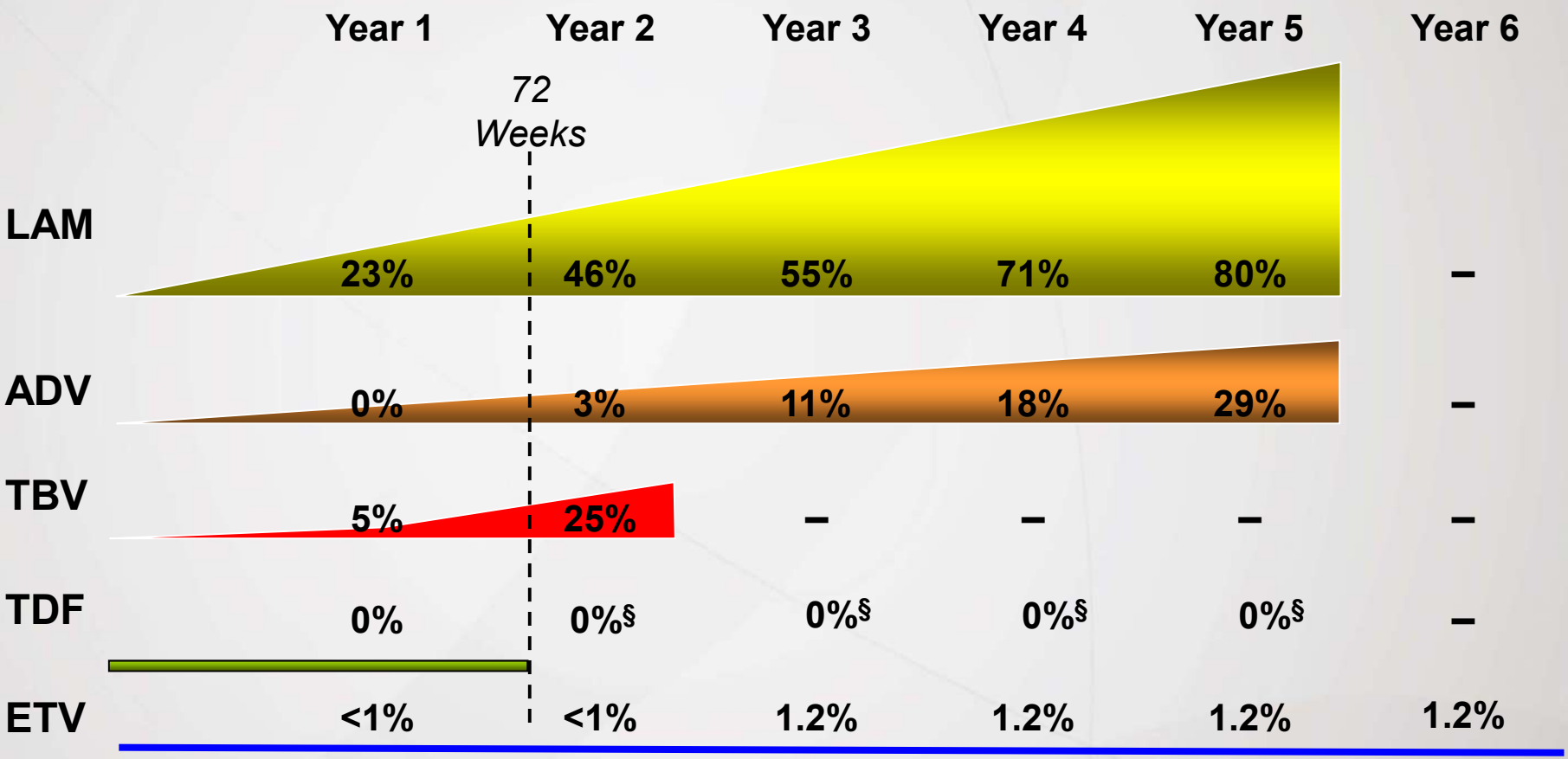
Wong GL, et al. Hepatology 2013;58:1537–1547.

Resistance Rates Through 6 Years of Treatment in Nucleos(t)ide-Naïve Patients



§ Patients with HBV DNA ≥400 copies/mL at Week 72 could add FTC to TDF;
* Cumulative probabilities of resistance, ETV 1.0 mg dose used from year 3 onward

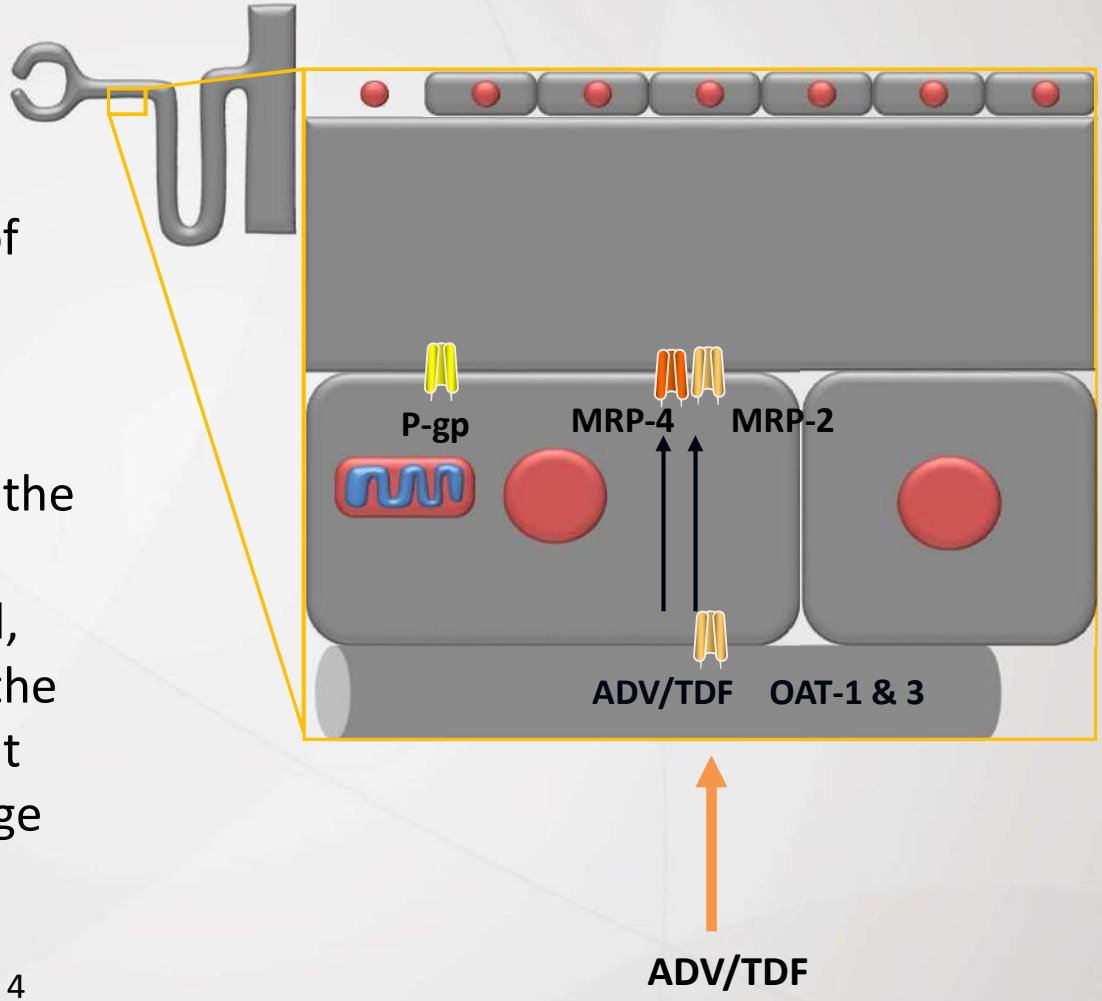
Adverse events described with all NAs

	Approved oral antiviral agents for HBV				
	LAM	ADV	ETV	LdT	TDF
Clearance	Renal	Renal	Renal	Renal	Renal
Adverse events in licensing trials at 1 year	Similar to placebo	Similar to placebo	Similar to LAM	Grade 3/4 CPK 7% 1 year 12% 2 years	Similar to ADV
Post-marketing adverse events	Rare myopathy, neuropathy, pancreatitis	Nephrotoxicity in 3–8% at 5 years	Negligible	Myopathy	Nephrotoxicity

Fontana RJ. *Hepatology* 2009;49:S185–S195.

ADV/TDF accumulates in the proximal tubule

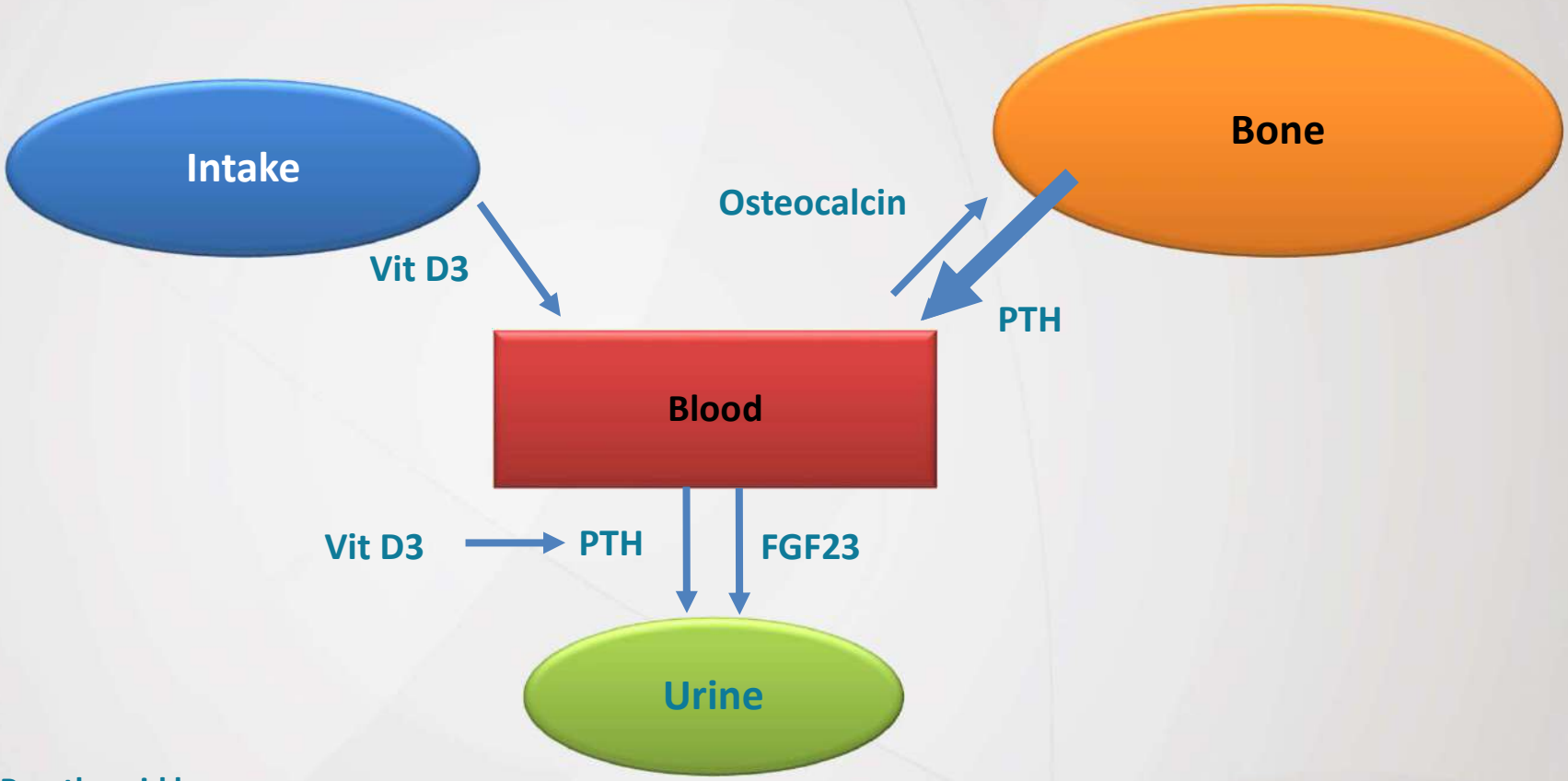
- ADV/TDF is a substrate of OAT1 and OAT3 and is excreted by MRP4
- ADV/TDF is actively transported by MRP4 to the proximal tubule
- When MRP4 is saturated, TDF may accumulate in the intracellular environment leading to tubular damage



OAT =Organic anion transporter
MRP4 = Multidrug resistance protein 4

1. Rodriguez-Novoa S, et al. *CID*; 2009;48: 108-16. 2.Ray AS, et al. *Antimicrob Agents Chemother* 2006;50(10):3297–304.
3. Viread® (tenofovir) SmPC January 2012.

Renal proximal tubular lesions can be associated with phosphaturia and bone loss



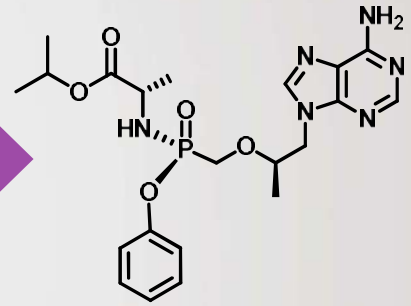
PTH=Parathyroid hormone
FGF=Fibroblast growth factor

Adapted from: Essig M, et al. *J Acquir Immune Defi Syndr*. 2007;46:256–8.

A safer tenofovir is now available

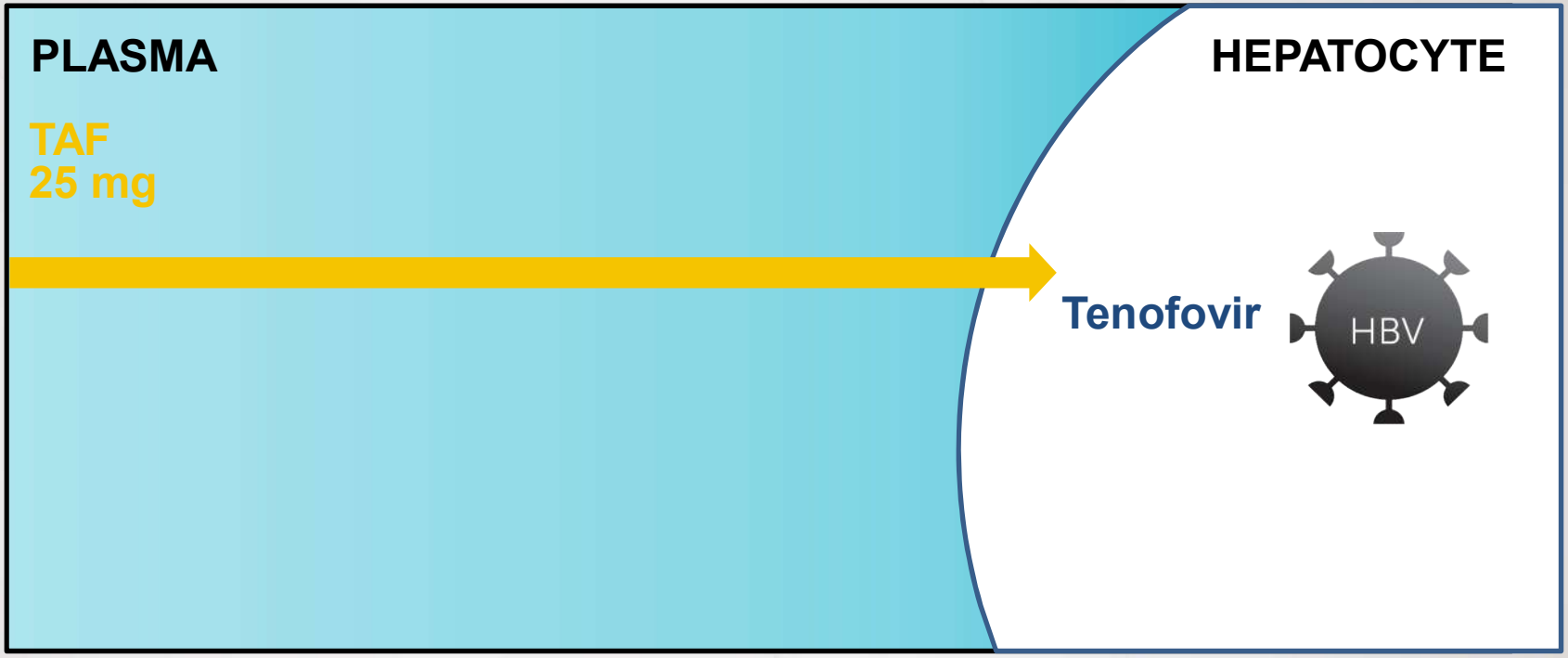
- **Tenofovir alafenamide (TAF)**
  - New tenofovir (TFV) prodrug; greater plasma stability than TDF[1–3]
  - Enhances delivery of active drug (TFV-DP) to hepatocytes[1–3]
  - Reduces circulating levels of TFV relative to TDF[4,5]
  - Improved bone and renal safety demonstrated in HIV patients[5,6]

TAF
Nucleotide reverse transcriptase inhibitor



1. Lee WA, et al. Antimicrob Agents Chemother 2005;49:1898-1906; 2. Murakami E, et al. Antimicrob Agents Chemother 2015;59:3563-69; 3. Babusis D, et al. Mol Pharm 2013;10:459-66; 4. Agarwal K, et al. J Hepatol 2015;62:533-40; 5. Sax P, et al. Lancet 2015;385:2606-15; 6. Mills A, et al. Lancet Infect Dis 2016;16:43-52.

Mechanism of Action

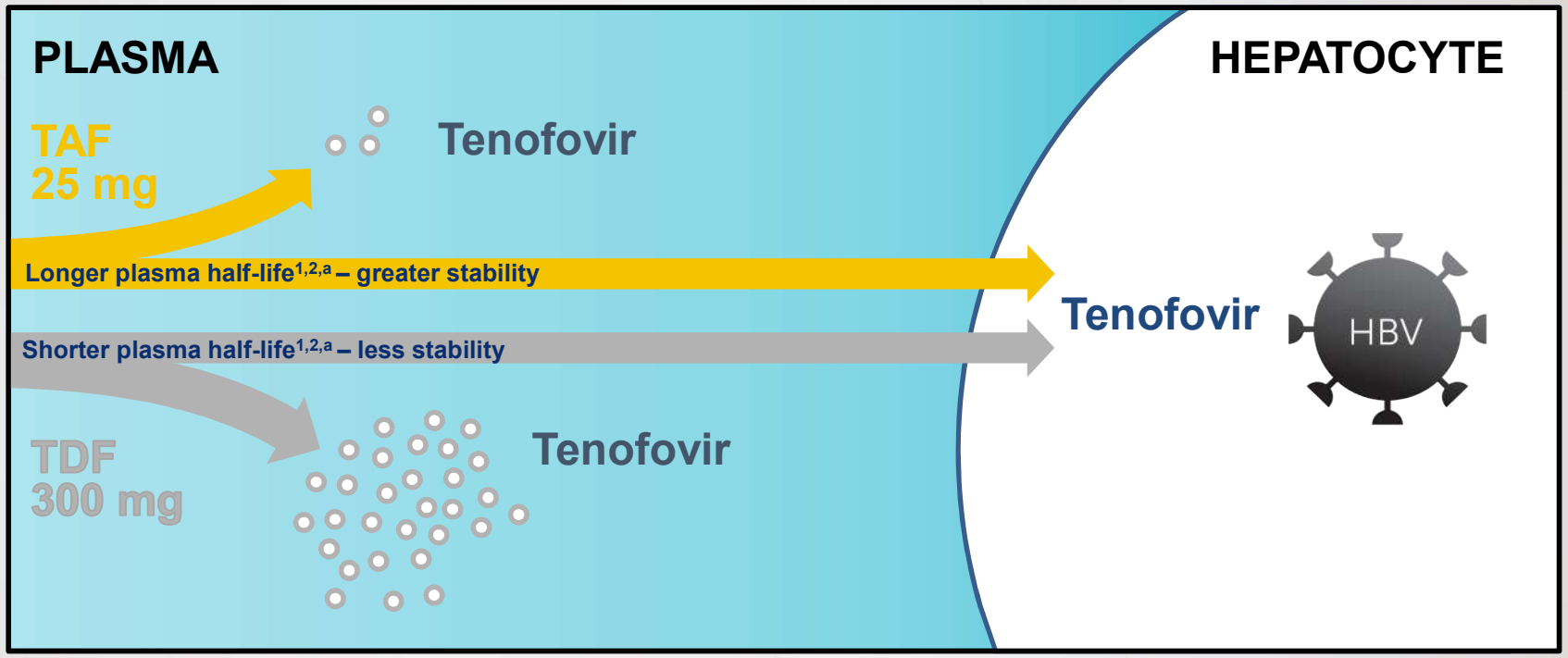


- TAF is a novel, targeted phosphonamidate prodrug of tenofovir[1,2]
- TAF enters primary hepatocytes by passive diffusion and by the hepatic uptake transporters OATP1B1 and OATP1B3[1]
- TAF is converted to tenofovir through hydrolysis primarily by carboxylesterase 1 in primary hepatocytes[1]

OATP1B1 / OATP1B3=organic anion transporting polypeptide 1B1 / 1B3; TAF=tenofovir alafenamide.

1. VEMLIDY Prescribing Information, Foster City, CA: Gilead Sciences, Inc; November 2016; 2. Murakami E, et al. *Antimicrob Agents Chemother.* 2015;59:3563-3569.

Mechanism of Action



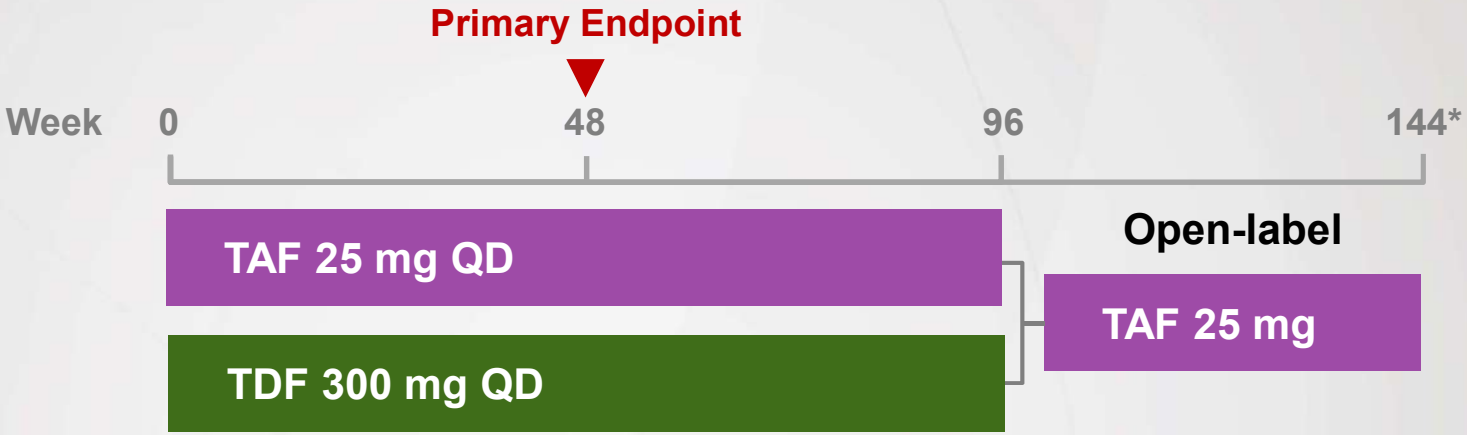
- In a clinical study in subjects with CHB, a 25-mg oral dose of TAF resulted in 89% lower concentrations of tenofovir in plasma, as compared with a 300-mg oral dose of TDF, thereby reducing systemic exposure[1,3,4]
- TAF more efficiently delivers tenofovir to hepatocytes than TDF[4,5]

[a]Plasma half-life: TDF=0.41 minutes[1]; TAF=0.51 hour.[2] CHB=chronic hepatitis B; TDF=tenofovir disoproxil fumarate.

1. Lee WA, et al. *Antimicrob Agents Chemother.* 2005;49:1898-1906; 2. VEMLIDY Prescribing Information, Foster City, CA: Gilead Sciences, Inc; November 2016; 3. Chan HLY, et al. *Lancet Gastroenterol Hepatol.* 2016;1:185-195; 4. Agarwal K, et al. *J Hepatol.* 2015;62:533-540; 5. Murakami E, et al. *Antimicrob Agents Chemother.* 2015;59:3563-3569.

TAF vs TDF

0110 (HBeAg+) / 0108 (HBeAg-)



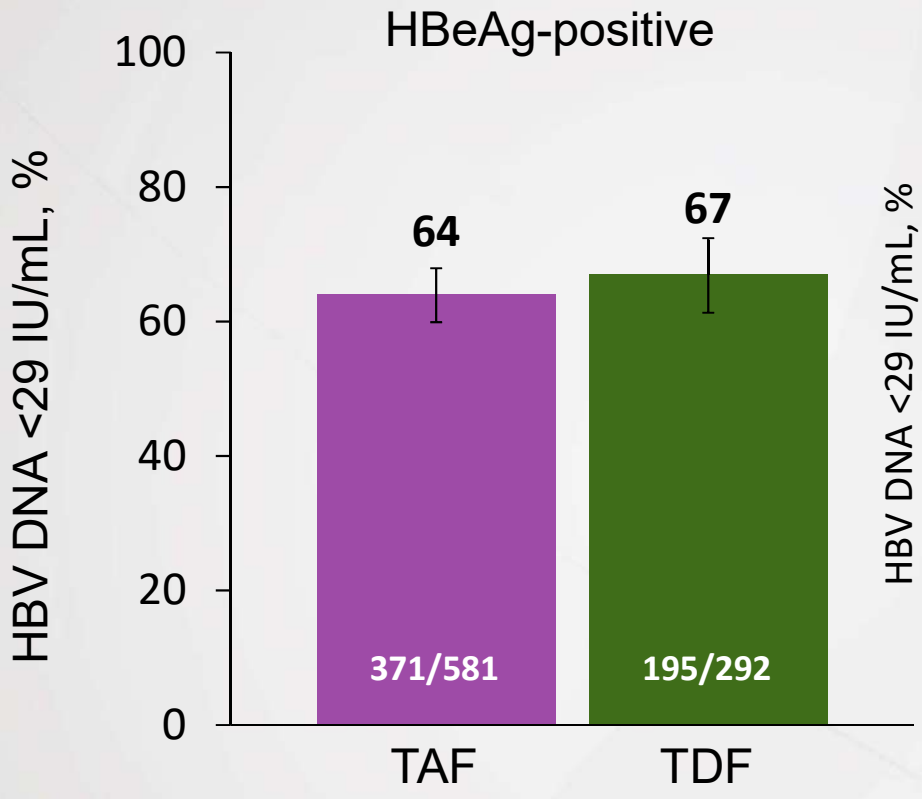
- Double-blind, active-controlled, Phase 3 study
- Key inclusion criteria
  - HBeAg-positive or HBeAg-negative at screening
  - HBV DNA ≥20,000 IU/mL; ALT >60 U/L (males), >38 U/L (females)
- 2:1 randomization
  - Stratified by HBV DNA level and treatment status (naïve vs experienced)

*Amendment to extend double blind to Week 144 and open-label to Week 384 (Year 8) is currently underway

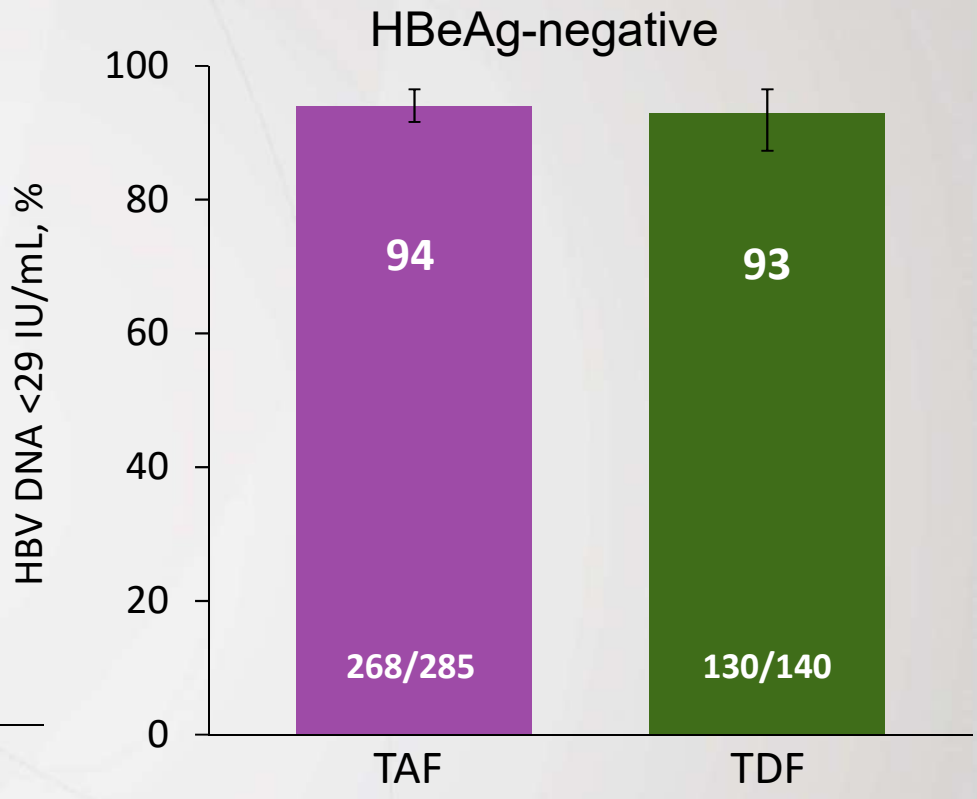
Chan HL, et al. Lancet Gastroenterol Hepatol 2016;1:185-195
Buti M, et al. Lancet Gastroenterol Hepatol 2016;1:196-206

Primary Endpoint

HBV DNA <29 IU/mL at 48 weeks



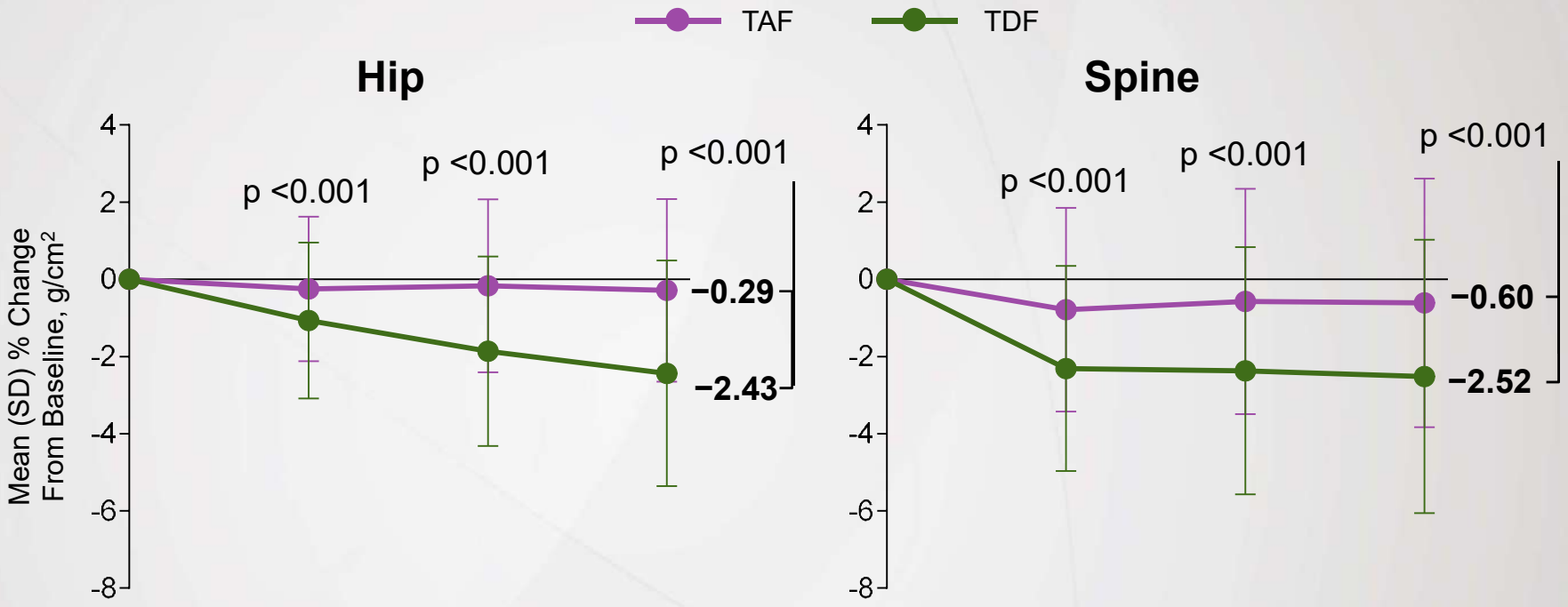
Treatment difference (95% CI):
-3.6% (-9.8%, +2.6%); p=0.25



Treatment difference (95% CI):
+1.8% (-3.6%, +7.2%); p=0.47

Chan HL, et al. Lancet Gastroenterol Hepatol 2016;1:185-195
Buti M, et al. Lancet Gastroenterol Hepatol 2016;1:196-206

Mean Changes in BMD Through Week 72

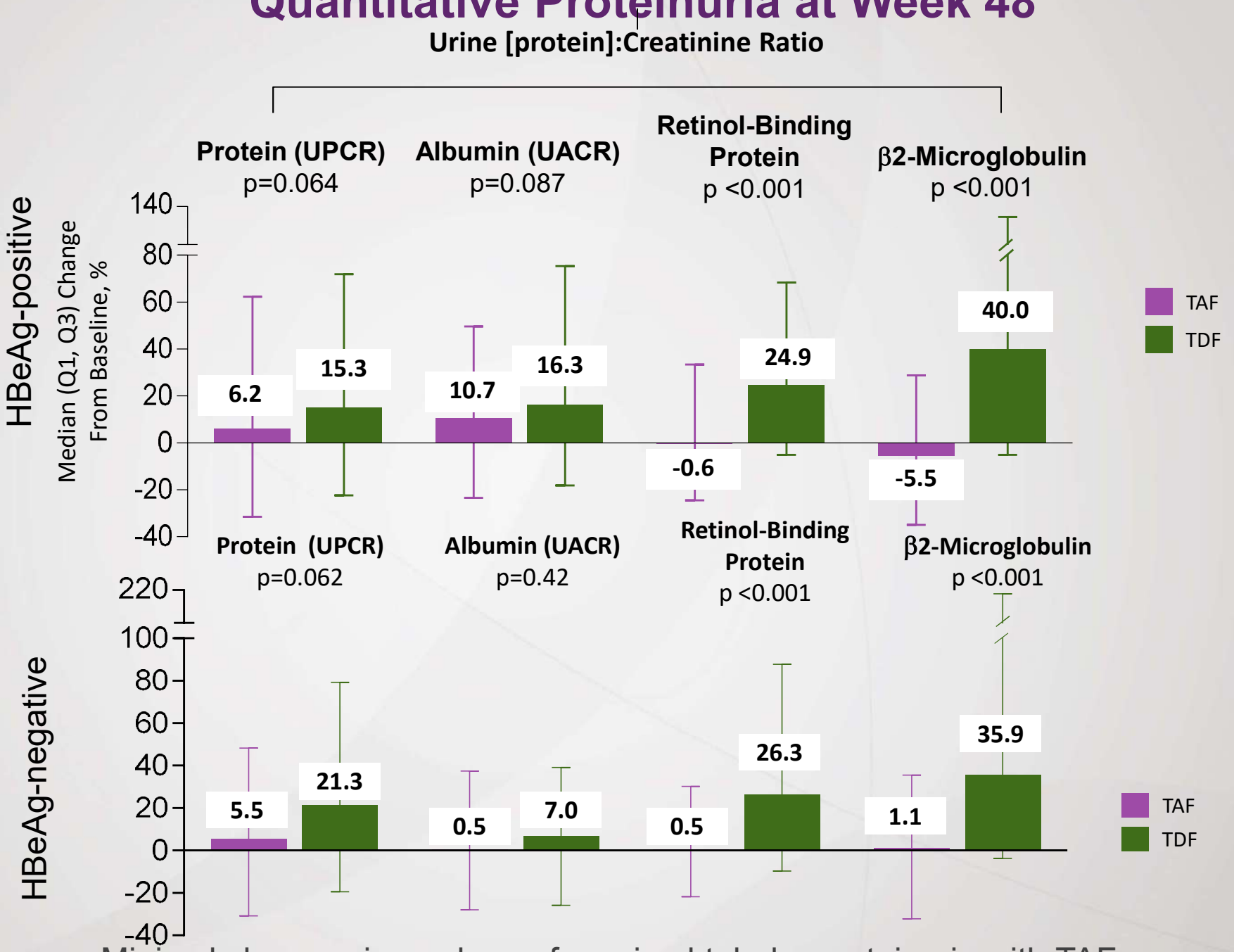


Week	0	24	48	72	0	24	48	72
TAF, N	856	830	814	753	851	822	807	757
TDF, N	426	410	407	373	426	405	404	374

TAF treatment resulted in smaller decline in Hip and Spine BMD compared to TDF

Seto WK, et al. AASLD 2016 Oral 67

Quantitative Proteinuria at Week 48



- Minimal changes in markers of proximal tubular proteinuria with TAF

Tenofovir alafenamide (TAF)

Study 110

- In treatment-naïve and -experienced patients with chronic hepatitis B, treatment with TAF for 48 weeks demonstrated:
  - Noninferior efficacy to TDF for the proportion with HBV DNA <29 IU/mL
  - Higher rates of ALT normalization
  - Rates of HBeAg loss and seroconversion similar to TDF
  - No resistance development to either treatment group
- TAF was safe and well tolerated:
  - Treatment-emergent AEs similar to TDF
  - Significantly less declines in hip and spine BMD compared to TDF, with improved bone biomarkers
  - Significantly smaller increases in sCr and decreases in $eGFR_{CG}$ compared to TDF, with improved markers of renal tubular function

Chan HL, et al. Lancet Gastroenterol Hepatol 2016;1:185-195
Buti M, et al. Lancet Gastroenterol Hepatol 2016;1:196-206

BRIEF

Gilead's Vemlidy approved for hep B in US, EU

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Nov. 11, 2016

Dive Brief:

- The Food and Drug Administration approved Gilead's Vemlidy (tenofovir alafenamide or TAF) for the treatment of hepatitis B in patients with compensated liver disease, the company reported Thursday. The company also got a positive opinion from the Committee for Medical Products for Human Use (CHMP) in Europe.

- In a Nov. 11 statement, Gilead pointed to clinical data that showed its new

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AASLD: AbbVie reports positive 8-week data in HCV
Nov. 14

SAFETY OF NA

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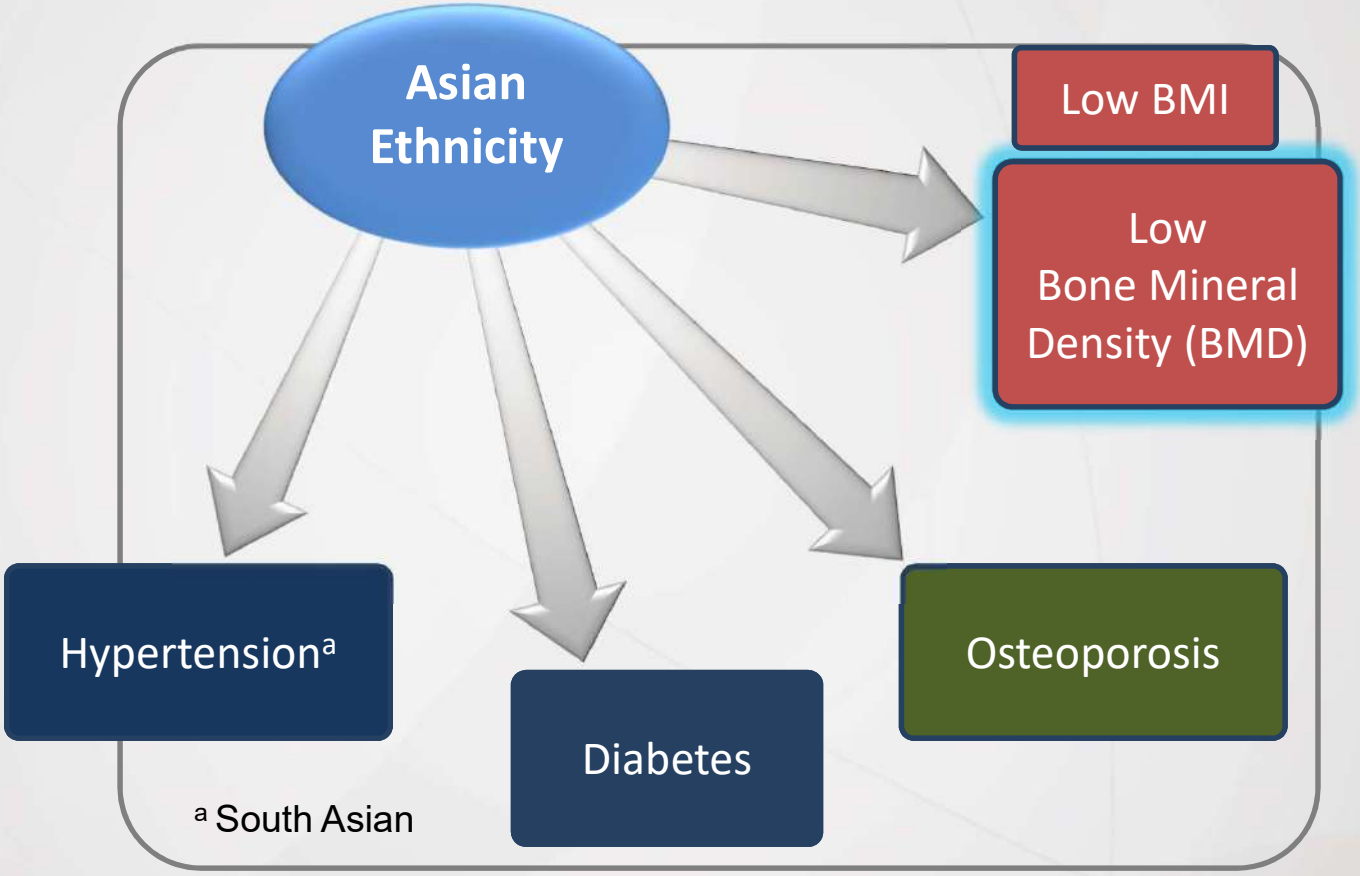
Faculty of Medicine
The Chinese University of Hong Kong

Asian patients are at risks of renal and bone problems

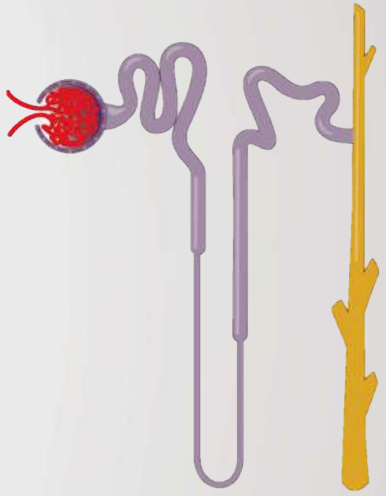
Presence of common comorbidities



American Heart Association. http://www.americanheart.org/. (Sep 2010). Dixon AN, *et al. Diabetes and Vascular Dis Res* 2006; 3:22–25. Li-Ng M, *et al. Digest Liver Dis* 2007;6:549–556. National Digestive Diseases Information Clearinghouse.http://digestive.niddk.nih.gov/ddiseases/pubs/lactoseintolerance/. (Sep 2010). National Osteoporosis Foundation. http://www.nof.org/osteoporosis/diseasefacts.htm. (Sep 2010).

Important clinical questions

- Does long-term NA treatment increase renal and bone toxicities in real-world setting?



- Any difference between various NAs?
  - nucleotide analogs vs. nucleoside analogs

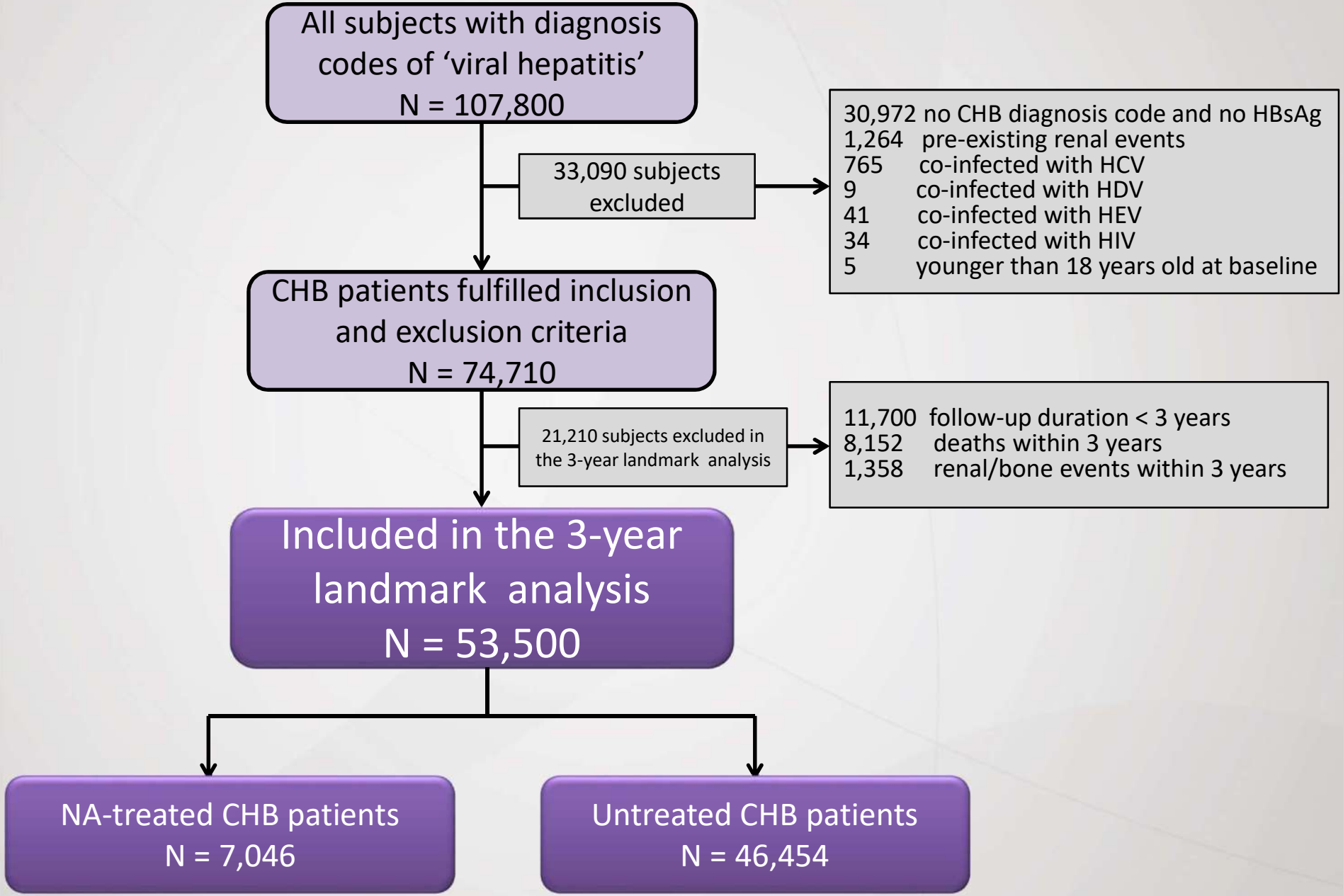
HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases

Long-Term Safety of Oral Nucleos(t)ide Analogs for Patients With Chronic Hepatitis B: A Cohort Study of 53,500 Subjects

Grace Lai-Hung Wong,[1,2,3] Yee-Kit Tse,[1,2] Vincent Wai-Sun Wong,[1,2,3] Terry Cheuk-Fung Yip,[4] Kelvin Kam-Fai Tsoi,[5] and Henry Lik-Yuen Chan[1,2,3]

Widespread and long-term use of oral nucleos(t)ide analogs (NAs) to treat chronic hepatitis B (CHB) brings about safety data in a real-life setting. We aimed to determine the risks of renal and bone side effects in patients receiving or who have received NAs as CHB treatment. A territory-wide cohort study using the database from Hospital Authority, the major provider of medical services in Hong Kong, was conducted. We identified CHB patients by International Classification of Diseases, Ninth Revision, Clinical Modification diagnosis codes, diagnosed between 2000 and 2012. The primary events were renal (incident renal failure and renal replacement therapy [RRT]) and bone events (incident hip, vertebral, and all fractures). A 3-year landmark analysis was used to evaluate the relative risk of primary outcome in patients with or without NA treatment. A total of 53,500 CHB patients (46,454 untreated and 7,046 treated), who were event free for 3 years, were included in the analysis. At a median follow-up of 4.9 years, chronic renal failure, RRT,

Patient inclusion



Incidence rates and weighted hazard ratios of renal and bone events

NA-treated vs. untreated (N=53,500)

	NA-treated	Untreated	HR[#] (95% CI)	*P* value
Renal failure	100, 4.1 (3.3-5.0)	270, 1.3 (1.1-1.4)	0.91 (0.69-1.21)	0.517
RRT	49, 2.0 (1.5-2.7)	96, 0.5 (0.4-0.6)	1.31 (0.85-2.03)	0.225
Hip fracture	17, 0.7 (0.4-1.1)	48, 0.2 (0.2-0.3)	0.95 (0.46-1.97)	0.887
Spine fracture	15, 0.6 (0.3-1.0)	53, 0.3 (0.2-0.3)	0.79 (0.42-1.49)	0.469
All fractures	95, 3.9 (3.2-4.8)	318, 1.5 (1.3-1.7)	0.87 (0.66-1.15)	0.338

[#]Based on Rubin's rule after propensity score weighting.
CI = confidence intervals, HR = hazard ratios, NAs = nucleos(t)ide analogues, RRT = renal replacement therapy.

Incidence rates and weighted hazard ratios of renal and bone events

Nucleotide-treated vs. Nucleoside-treated (N=7,046)

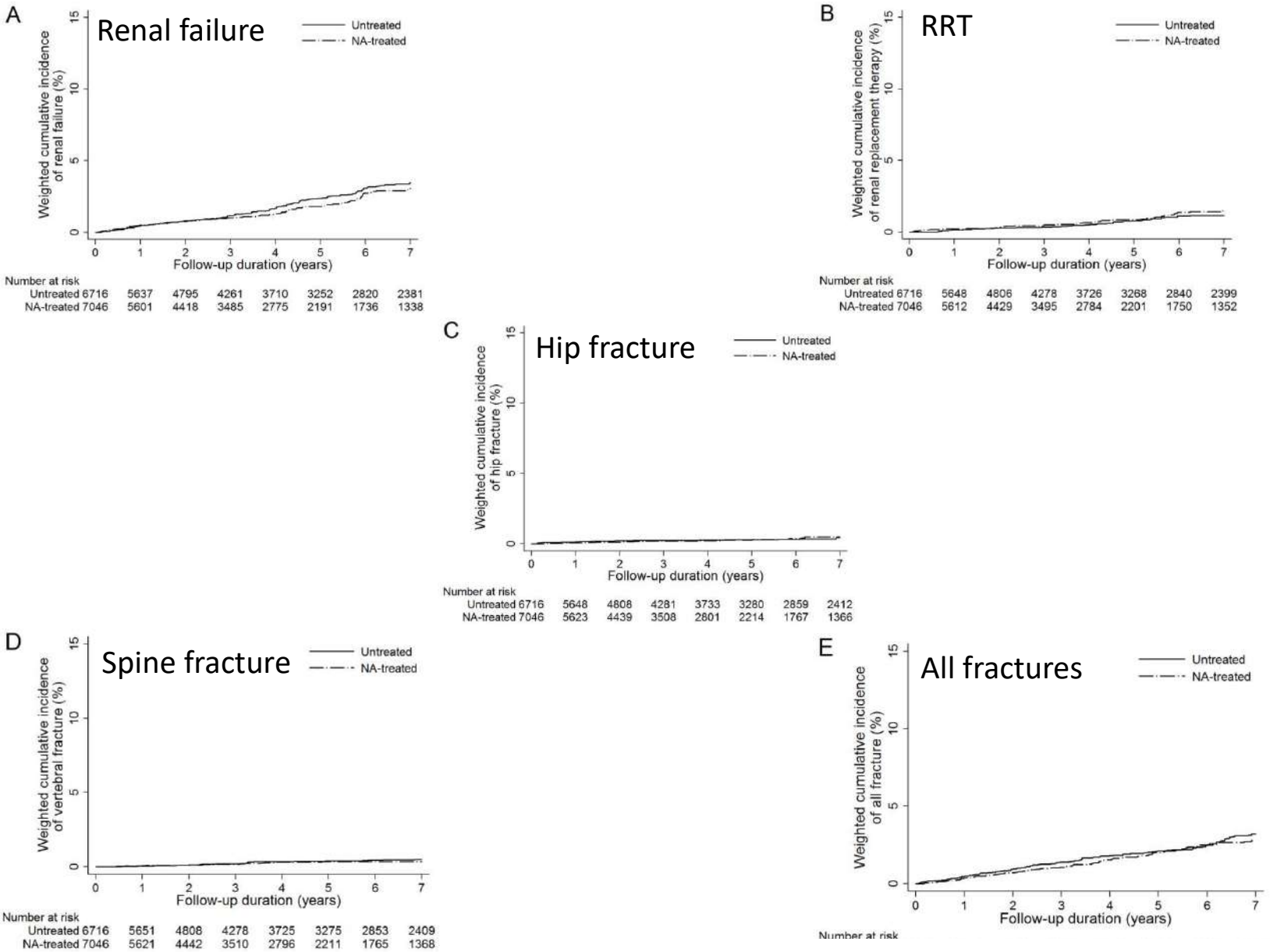
	Nucleotide-treated	Nucleoside-treated	HR[#] (95% CI)	*P* value
Renal failure			34)	0.202
RRT			)	0.433
Hip fracture			9)	***0.001***
Spine fracture			)	0.823
All fractures	14, 5.2 (2.8-8.6)	81, 3.8 (3.0-4.7)	1.44 (0.81-2.58)	0.217

All hip fractures occurred in patients took adefovir but not tenofovir.

[#]Based on Rubin's rule after propensity score weighting.

CI = confidence intervals, HR = hazard ratios, NAs = nucleos(t)ide analogues, RRT = renal replacement therapy.

Kaplan-Meier analysis of the weighted cumulative incidence of events in NA-treated versus untreated patients



Wong GL et al. Hepatology 2015;62:684-93.

Renal and bone safety of NA

- This large-scaled population-based study does not suggest an increased risk of renal and bone complications from NA treatment in CHB patients.

- Special attention to patients receiving nucleotide analogues (e.g. adefovir) is still necessary as they may have increased risk of hip fracture, although the overall event rate remains low.

- Treatment guidelines recommend monitoring renal function in patients receiving nucleotide analogs.

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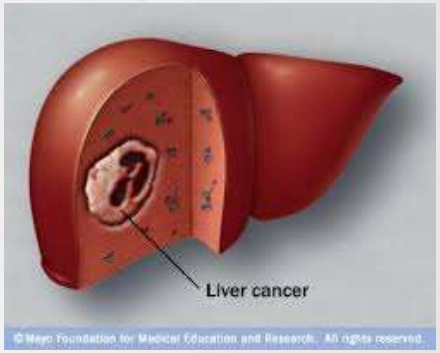
Wong GL et al. Hepatology 2015;62:684-93.

Are NAs carcinogens or anti-carcinogens?

Mice

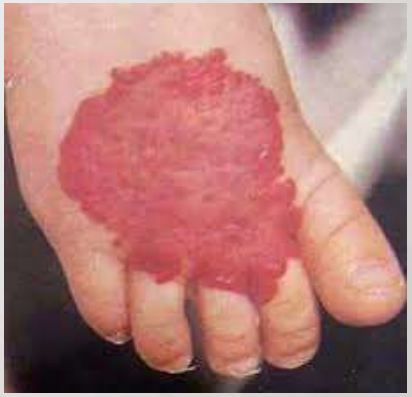
Entecavir
4mg daily

Lung adenomas and carcinomas



HCC

Vascular tumors



http://www.bmscanada.ca/static/products/en/pm_pdf/Baraclude_EN_PM.pdf

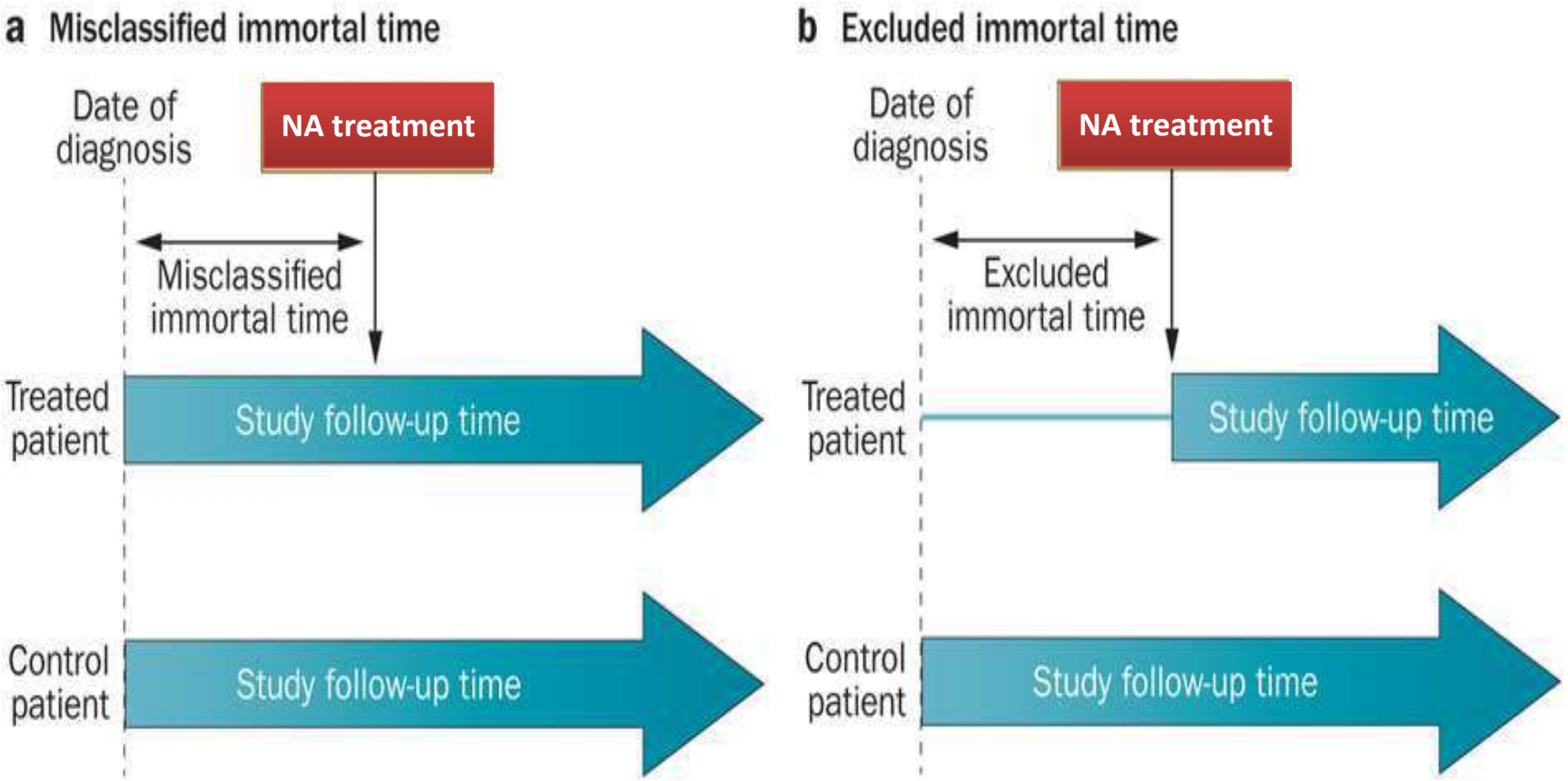
Are NAs carcinogens or anti-carcinogens?

A Korean Nationwide Cohort Study:
25,651 NA-treated *vs.* 145,870 NA-naïve

	HR(95% CI)	*p* value
Thyroid gland	0.650(0.497-0.849)	0.0016
Stomach	0.610(0.445-0.836)	0.0021
Colorectal	0.797(0.646-0.981)	0.0326
Lung	0.717(0.527-0.974)	0.0336
Prostate	0.633(0.503-0.796)	<0.0001

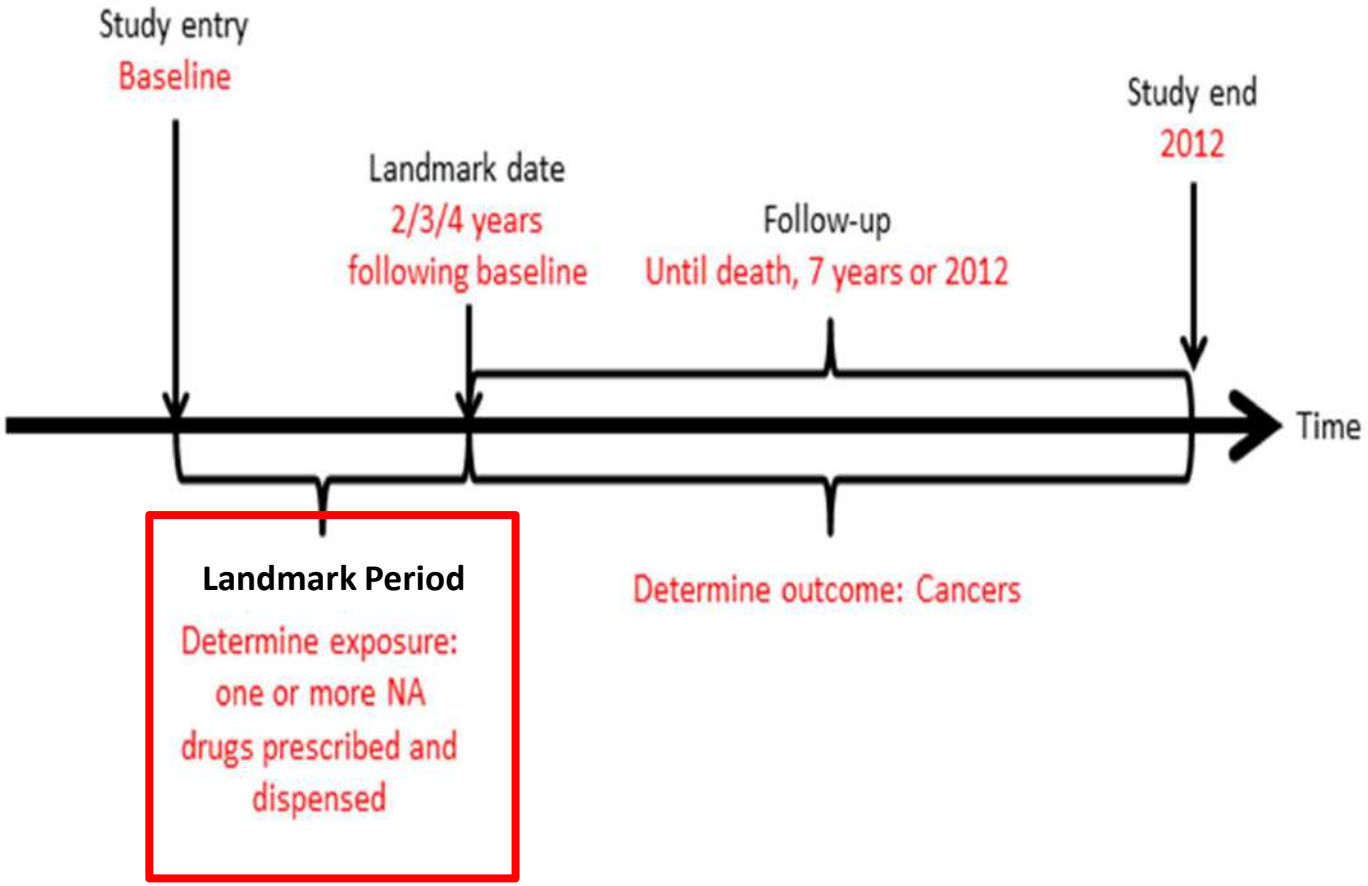
Lee DH, et al. 2015;62(Supp 1):116A.

Immortal time bias



Palma, D. A. *et al.* Nat. Rev. Clin. Oncol. 2014

Landmark analysis



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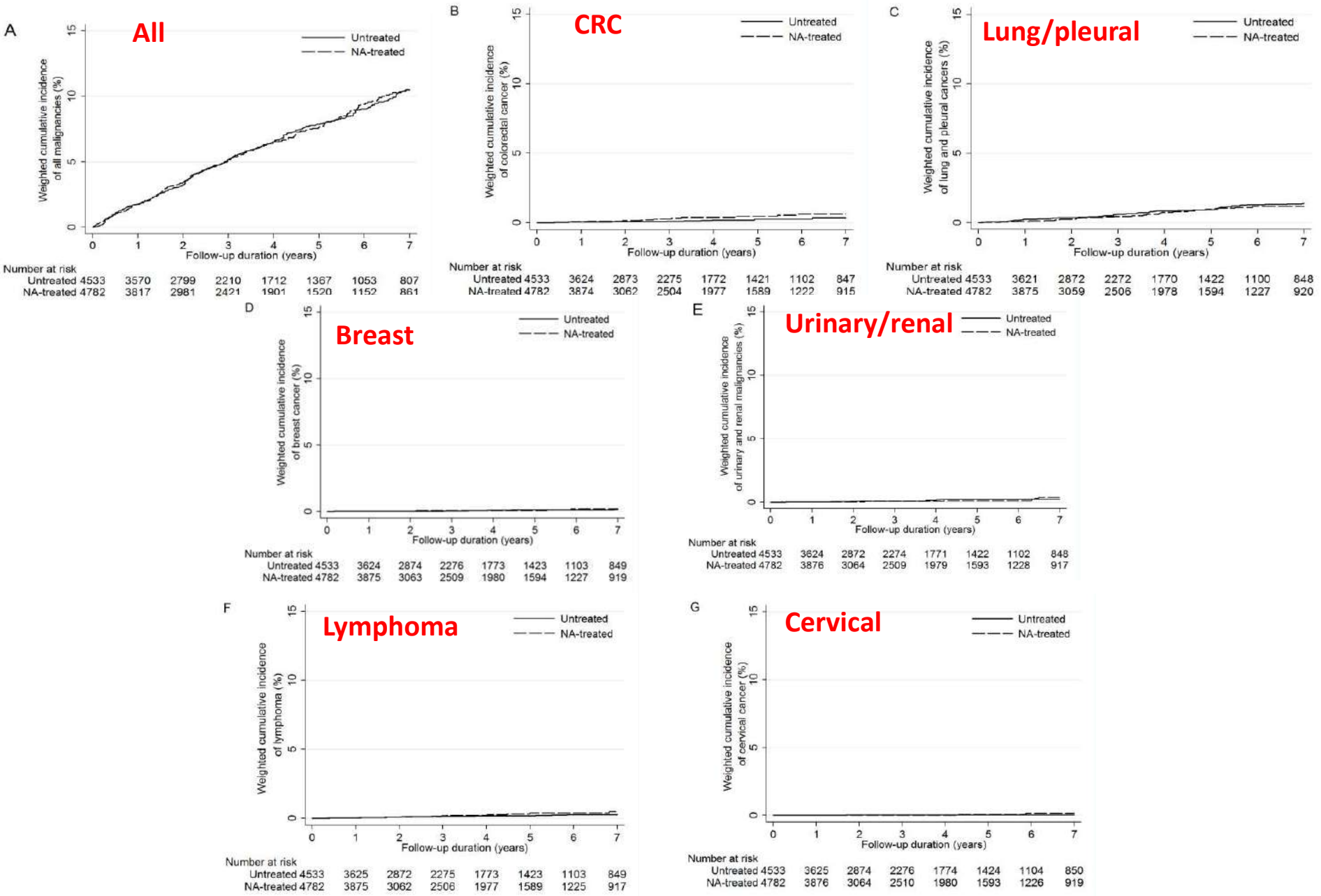
Wong GL, et al. J Hepatol 2016;54(Suppl 1):S163.

Kaplan-Meier analysis of the weighted cumulative incidence of malignancies in NA-treated versus untreated patients



New developments for anti-HBV therapy in 2016

- Oral antiviral treatment during the last trimester reduces the risk of vertical transmission of HBV in mothers with high viral load.
- Tenofovir alafenamide (TAF) has similar efficacy yet better safer profile than TDF.
- No significant increased risk of renal and bone complications from NA treatment in CHB patients.
  - For patients receiving nucleotide analogues (e.g. adefovir): increased risk of hip fracture, although the overall event rate remains low.
- NA therapy does not increase the risk of various malignancies in CHB patients.

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QUICK UPDATE FOR ANTIVIRAL TREATMENT FOR HCV

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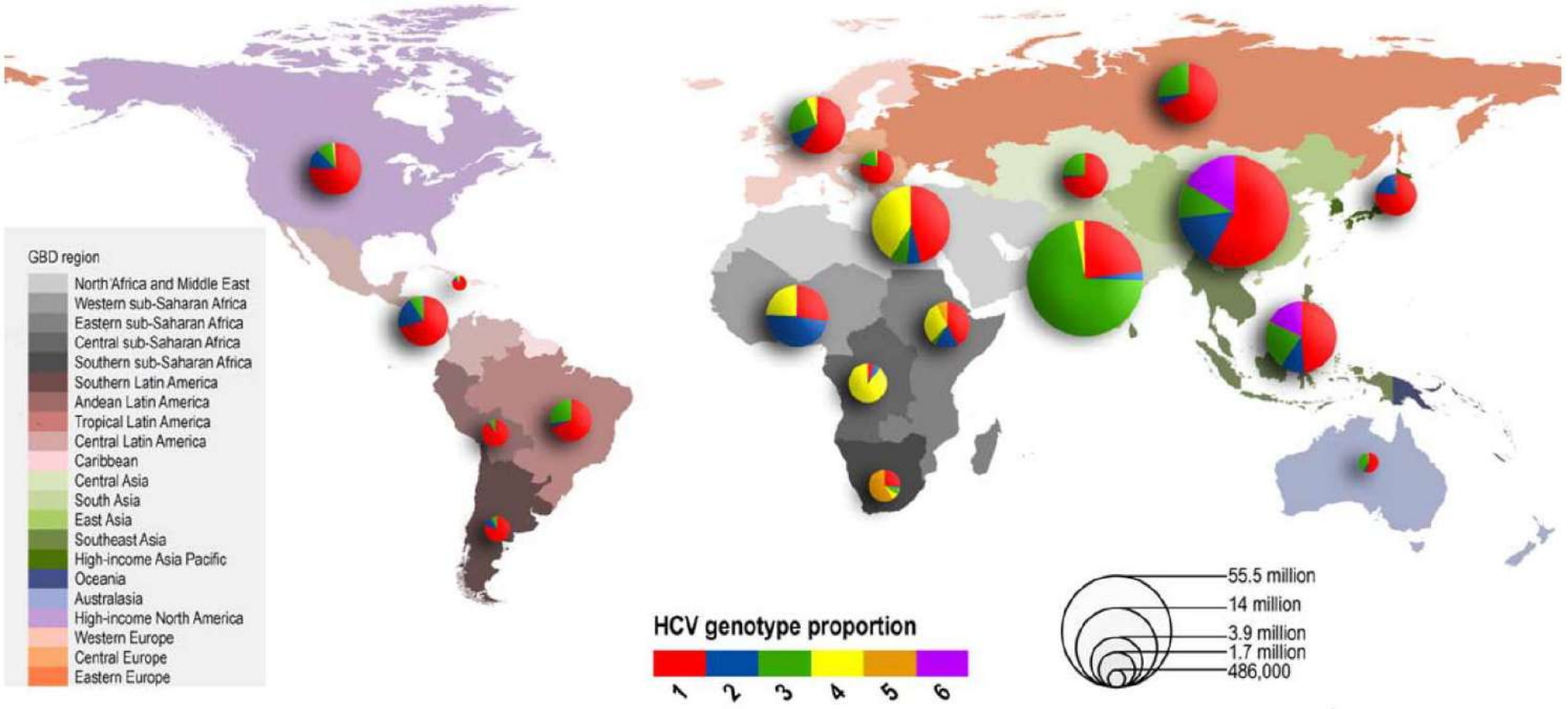
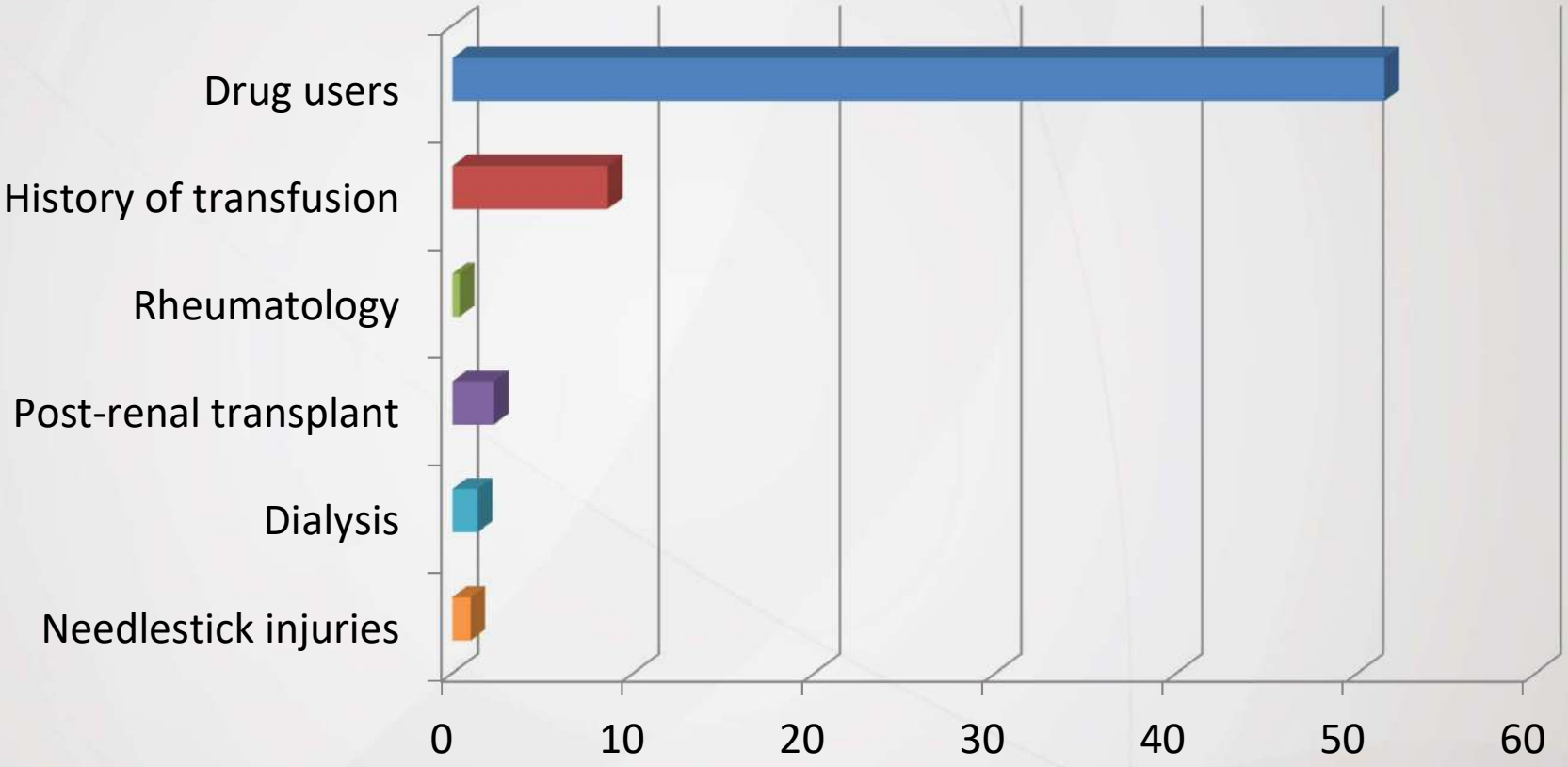
Global HCV genotype distribution



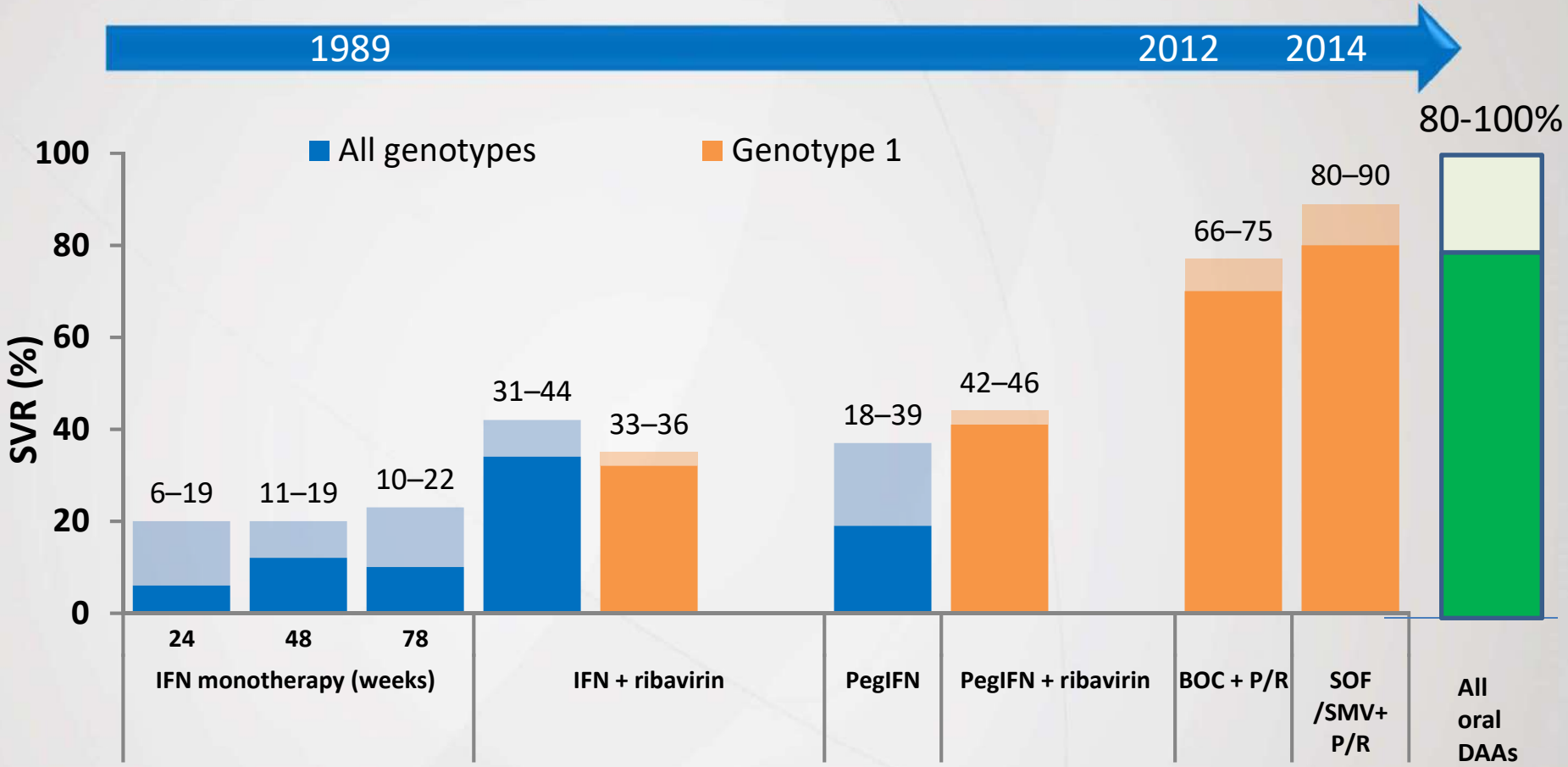
Messina JP, et al. Hepatology 2014

Anti-HCV prevalence in specific groups



Centre for Health Protection – 2012 Update Report

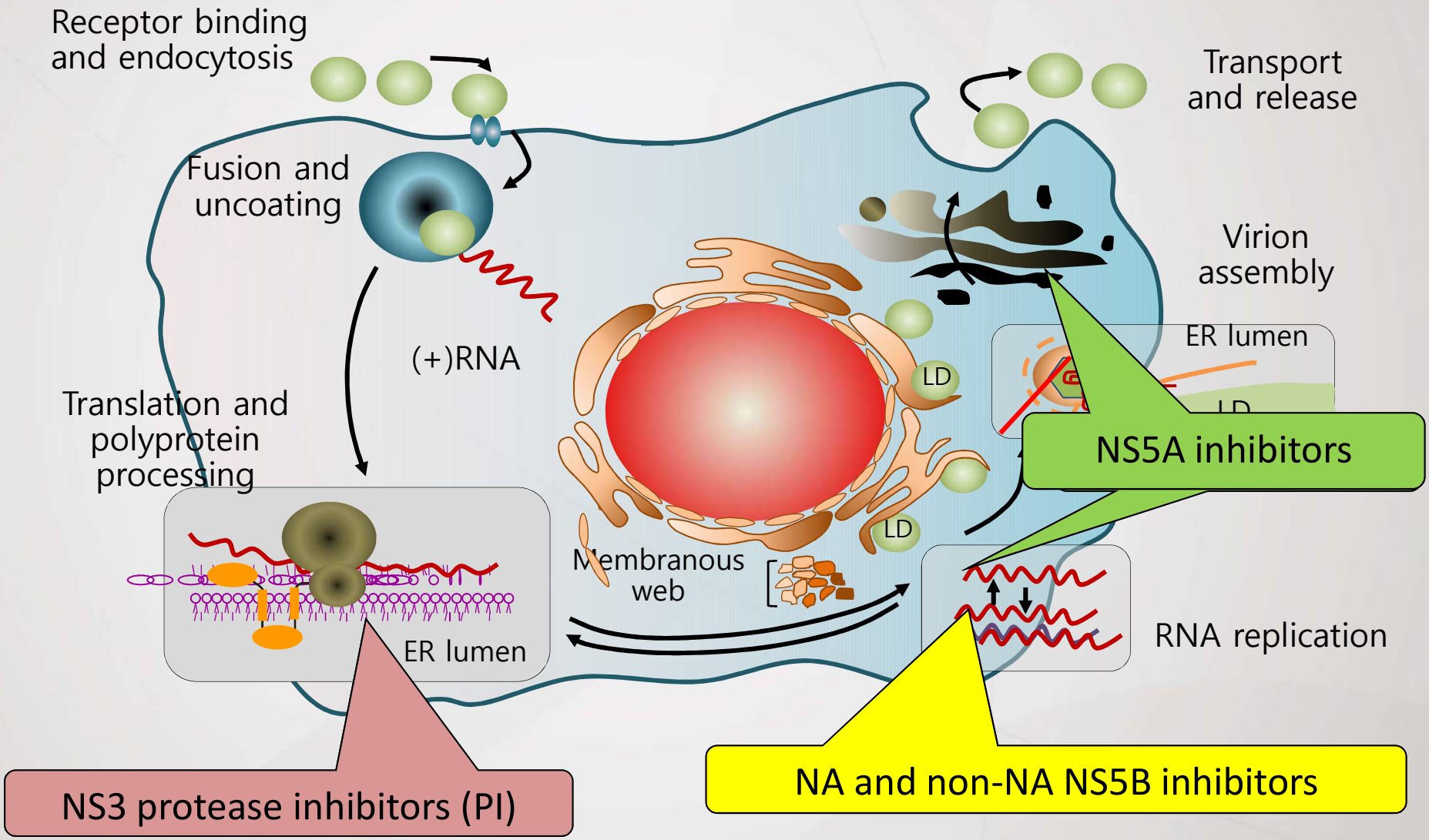
Treatment paradigm will change with all oral DAAs



BOC, BOCEPREVIR;
SMV, SIMEPREVIR;
SOF, SOFOSBUVIR;
P/R, PEGIFN + RIBAVIRIN
DAA, DIRECT ACTING ANTIVIRALS

Davis GL, et al. N Engl J Med. 1989;321:1501–1506; Poynard T, et al. N Engl J Med. 1995;332:1457–1462; McHutchison JG, et al. N Engl J Med. 1998;339:1485–1492; Poynard T, et al. Lancet. 1998;352:1426–1432; Zeuzem S, et al. N Engl J Med. 2000; 343:1666–1672; Linsay KL, et al. Hepatology. 2001;34:395–403; Pockros PJ, et al. Am J Gastroenterol. 2004;99:1298–1305; Manns MP, et al. Lancet. 2001;358:958–965; Fried MW, et al. N Engl J Med. 2002;347:975–982; Poordad F, et al. N Engl J Med. 2011; 364:1195–1206; Jacobson IM, et al. N Engl J Med. 2011;364:2405–2416; Simeprevir prescribing information, November 2013; Lawitz E, et al. N Engl J Med. 2013;368:1878–1887; Zeuzem S, et al. Hepatology. 2013;58(suppl 1):733A; AbbVie press release 2014 [Accessed 25-02-14]; Gilead press release 2013 [Accessed 25-02-14]; Sulkowski MS, et al. N Engl J Med. 2014;370:211–221.

Targets in the HCV life cycle for direct-acting antiviral agents



Manns M, et al. Nat Rev Drug Discov 2007;6:991–1000.

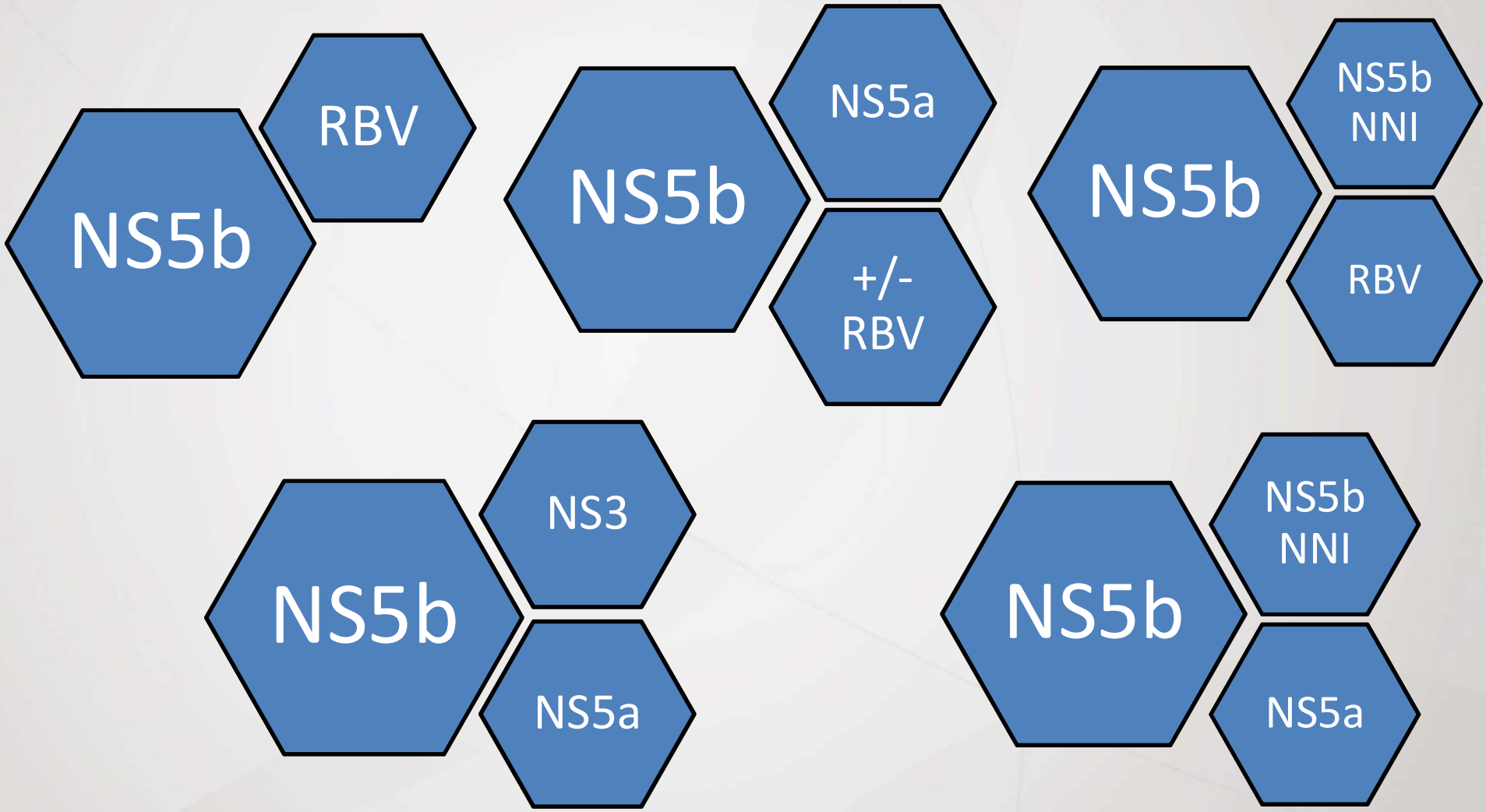
Different classes of direct acting antivirals (DAAs)

NS3	NS5a	NS5b (N)	NS5b (NN)	Cyclophilin
Telaprevir	Daclatasvir	Sofosbuvir	Dasabuvir (ABT-333)	Alisporivir
Boceprevir	Ledipasvir	VX-135	Deleobuvir	
Simeprevir	Ombitasvir (ABT-267)	IDX20963	BMS-791325	
Asunaprevir	Elbasvir (MK-8742)	ACH-3422	PPI-383	
Paritaprevir (ABT-450)	GS-5885		GS-9669	
Grazoprevir (MK-5172)	GS-5816		TMC647055	
Faldaprevir	ACH-3102			
Sovaprevir	PPI-668			
ACH-2684	GSK2336805			
	Samatasvir			

DAA class profile

	NS3 1st gen	NS3 2nd gen	NS5a 1st gen	NS5a 2nd gen	NS5b (NN)	NS5b (N)
Efficacy						
Resistance						
Pangenotypic activity						
Adverse events						
Drug-drug interation						

Components for Achieving SVR in HCV: 2016 and beyond



DAA strategies available for adults with chronic HCV

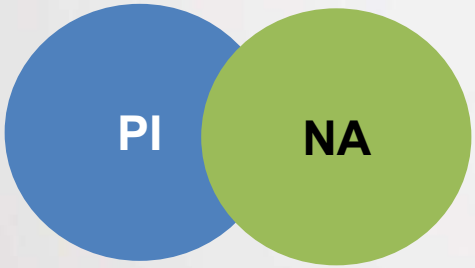
In combination with PEG-IFN + RBV or as IFN-free therapy combinations

SMV
GT 1, 4

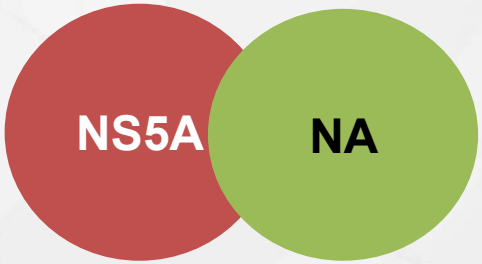
DCV
GT 1–4

SOF
All GTs

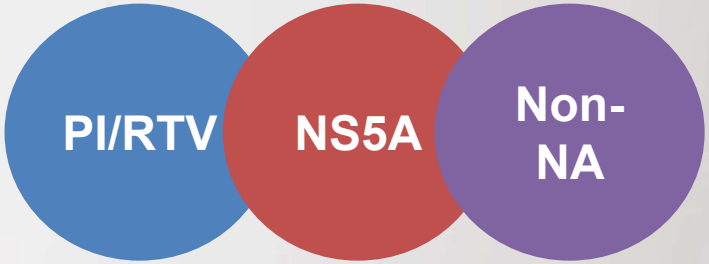
IFN-free therapy only



SMV + SOF



LDV/SOF
DCV + SOF



OMV/PTV/RTV
+ DSV

- Janssen-Cilag Ltd. OLYSIO▼ (simeprevir), SmPC, May 2014; Bristol-Myers Squibb Pharma EEIG. DAKLINZA▼ (daclatasvir), SmPC, September 2014; Gilead Sciences Europe Ltd. SOVALDI▼ (sofosbuvir), SmPC, July 2015; Gilead Sciences Europe Ltd. HARVONI▼ (ledipasvir/sofosbuvir), SmPC, October 2015; AbbVie Ltd. VIEKIRAX▼ (ombitasvir/paritaprevir/ritonavir), SmPC, January 2015; AbbVie Ltd. EXVIERA▼ (dasabuvir SmPC, January 2015.

DAA: direct-acting antiviral agent; DCV: daclatasvir; DSV: dasabuvir; GT: genotype; LDV: ledipasvir; IFN: interferon; NA: nucleos(t)ide inhibitor; NS: non-structural protein; OMV: ombitasvir; PTV: paritaprevir; PEG-IFN: pegylated interferon; PI: protease inhibitor; RBV: ribavirin; RTV: ritonavir; SmPC: summary of product characteristics; SMV: simeprevir; SOF: sofosbuvir

All-oral DAA regimens in non-cirrhotic GT 1 patients

Regimen	Duration (weeks)	SVR (treatment-naïve)	SVR (treatment-experienced)
SOF + SMV	12–24	100%[1,2†]	100%[1,2†]
SOF + DCV	12–24	100%[3‡]	100%[3‡]
LDV SOF	8–24	94–100%[4–6‡]	94–100%[6–8‡]
OMV PTV/RTV + DSV ± RBV*	12	96%[9‡]	96%[10‡]

*RBV is not required in GT 1b patients;

†Phase 2 studies; ‡Phase 3 studies

1. Lawitz E, et al. Lancet 2014;384:1756–65;
2. Janssen-Cilag Ltd. OLYSIO (simeprevir), SmPC, February 2015;
3. Sulkowski MS, et al. N Engl J Med 2014;370:211–21;
4. Kowdley KV, et al. N Engl J Med 2014;370:1879–88;
5. Afdhal N, et al. N Engl J Med 2014;370:1889–98;
6. Mizokami M, et al. Lancet Infect Dis 2015;15:645–53;
7. Afdhal N, et al. N Engl J Med 2014;370:1483–93;
8. Lawitz E, et al. Lancet 2014;383:515–23;
9. Feld JJ, et al. N Engl J Med 2014;370:1594–603;
10. Zeuzem S, et al. N Engl J Med 2014;370:1604–14.

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Potential antiHCV regimes

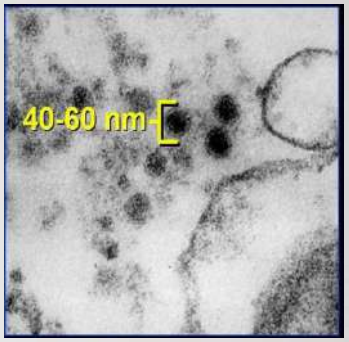
Genotype	Naïve or TE	Cirrhosis	Regimes
1	Naïve	No	PEG+RBV PEG+RBV+SOF SOF+LDV DCV+ASV (1b) ABT-450/r + ABT-267 + ABT-333 + RBV (3D regime)
1b	TE	No	SOF+LDV+/-RBV ABT-450/r + ABT-267 + ABT-333 + RBV (3D regime) DCV+ASV
1b	Naïve	Yes	SOF+LDV+RBV DCV+ASV ABT-450/r + ABT-267 + ABT-333 + RBV (3D regime)
2	Naïve	No	PEG+RBV SOF+RBV
3	Naïve	No	PEG+RBV SOF+DCV
2/3	Naïve or TE	Yes	PEG+RBV+SOF SOF+RBV SOF+DCV

Hepatitis C Therapy Will Parallel Helicobacter pylori Therapy

H pylori

Treatment regimen	Duration	Eradication rate (%)
Omeprazole (Prilosec) 20mg daily, plus amoxicillin (Biaxin), 500mg daily	14 days	80 to 86
Lansoprazole (Prevacid), 30mg twice daily, plus amoxicillin, 1g twice daily, 500mg twice daily	10 to 14 days	86
Bismuth subsalicylate (Pepto-Bismol) 525mg four time daily, plus metronidazole (Flagyl), 250mg four times daily, plus tetracycline, 500mg four time daily, plus histamine H_2 blocker	14 days (H_2 blocker alone for an additional 14 days taken once or twice daily	80

HCV



All Oral Therapy

Duration 8-24 weeks

Polymerase Inhibitor

±

±

Protease Inhibitor

NS5a

±

Non-nucleoside Inhibitor

±

All Oral Therapy, single tablet

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AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C

IDSA
Infectious Diseases Society of America

What's New and Updates/Changes:

This version of the Guidance has been updated to reflect several important developments, including the recent approval of elbasvir/grazoprevir, together with new information regarding the use of testing for HCV resistance associated variants. Click here for list of all updated sections.

Background of the Hepatitis C Guidance

New direct-acting oral agents capable of curing hepatitis C virus (HCV) infection have been approved for use in the United States. The initial direct-acting agents were approved in 2011, and many more oral drugs are expected to be approved in the next few years. As new information is presented at scientific conferences and published in peer-reviewed journals, health care practitioners have ...o provide ... the Infectious ...n of evidence-

New sections will be added, and the recommendations will be updated on a regular basis as new information becomes available. An ongoing summary of "recent changes" will also be available for readers who want to be directed to updates and changes.

About Hepatitis C

An estimated 3 million to 4 million persons in the United States are chronically infected with HCV, and approximately half are unaware of their status. These individuals may ultimately progress to advanced liver disease and/or hepatocellular cancer. However, those outcomes can be prevented by treatment, which is rapidly improving and offers the potential of a cure to more patients than has been previously possible.

Access the Full Report

Search the Guidance

Enter your keywords

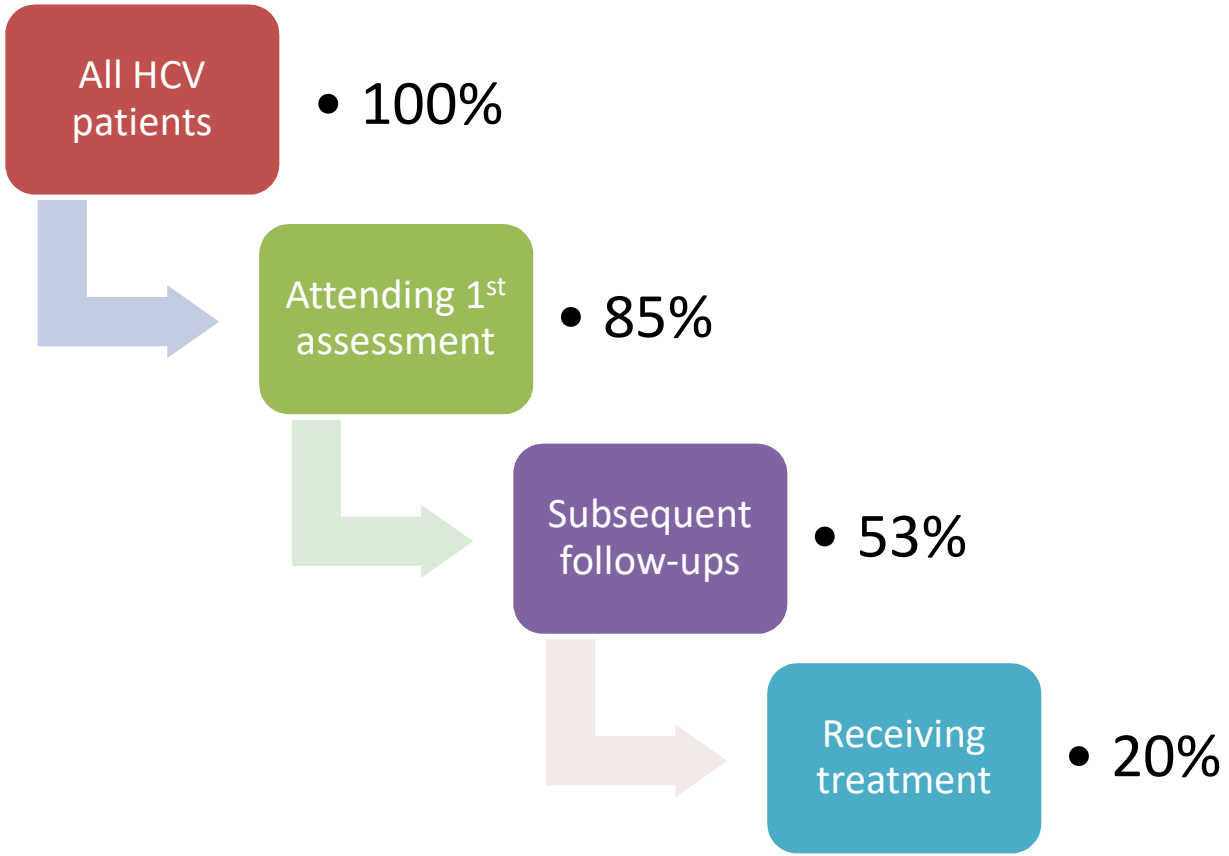
What's New and Updates/Changes

Wednesday, February 24, 2016

This version of the Guidance has been updated to reflect several important developments, including the recent approval of elbasvir/grazoprevir, together with new information regarding the use of testing for HCV resistance associated variants.... Read more >

http://www.hcvguidelines.org/

Diagnosis does not guarantee treatment



Wong VW et al. J Gastroenterol Hepatol 2014;29:116

Barriers to medical follow-up

- Doctor’s knowledge
- Patient’s knowledge
- Long waiting time

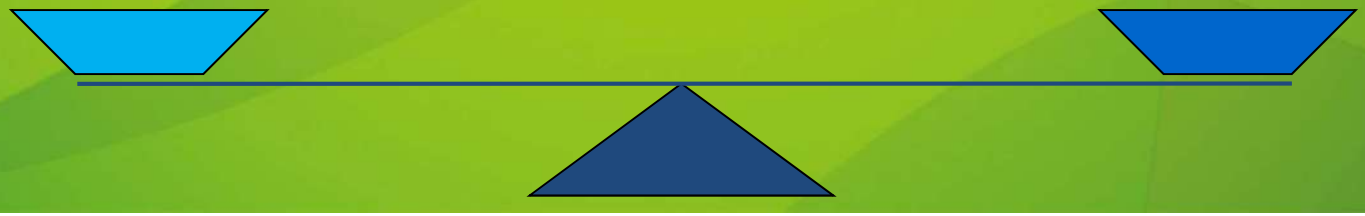
HCV Treatment Based on Individualized Risk-Benefit Analysis

Treat now

- Triple therapy substantially increases SVR rates
- Successful treatment may arrest progression of liver disease
- Earlier treatment has higher success rates
- Uncertainty about timelines for approval and reimbursement

Defer

- Current PIs are imperfect
  - Complex regimens (TID, lead-in)
  - Challenging adverse events
  - Unsuccessful treatment may reduce subsequent treatment success
- Next-wave DAAs may achieve
  - Higher cure rates
  - Shorter treatment duration
  - Improved safety and tolerability
  - IFN-free treatment
  - Better resistance profile
  - Activity in non-GT1



Era of tickling a scientifically cured virus
Meet the unmet needs

	SOF/LVD+/-RBV	Abbvie 3D-regi…RBV
TE + cirrhotic	12-24 weeks	
DAA-relapsers /NR	12-24 weeks inde…	
Gen 3/…		
Decom …		
Renal insu…	…indicated	OK
HIV/HCV	12-24 weeks	12-24 weeks

Increase access of efficacious HCV treatment to improve its effectiveness!!!

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Thank you for your attention!

Liver team, The Chinese University of Hong Kong

Grace Lai-Hung Wong
Institute of Digestive Disease
The Chinese University of Hong Kong
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