HBV Update from EASL 2017

Ahmed Elsharkawy
Consultant Hepatologist QE Birmingham
Chairman of the BVHG
BHIVA/BVHG Feedback Meeting
May 2017

Hepatology Highlights

Speaker Name	Statement
Ahmed Elsharkawy	Consultancy – Gilead, Chiesi, Abbvie. Speaker fees – Gilead, MSD, Abbvie Research funding – Gilead.
Date	May 2017

Talk Outline

- WHO report and Elimination strategy
- New EASL Clinical Practice Guidelines – significant changes
- Some data on new HBV treatment strategies
- New data on TAF
- Hepatitis delta


it's very COMPETITIVE
it doesn't get easier...
I don't feel "SECURE"
You are never "done"... AMBITION grows as you Progress
SOMETIMES I FEEL LIKE I'M NEARLY THERE... OTHER TIMES I FEEL MILES AWAY FROM MY BIG GOAL
PERHAPS I WILL NEVER BE "DONE" IT SEEMS THERE IS ALWAYS THE NEXT STEP TO TAKE.
#PhD Life
PhD
IT NEVER GETS EASIER BUT YOU DO GET STRONGER
DELAYS in Regulatory approval
Funding
IT'S FRUSTRATING TO KNOW WHAT THE IDEAL THERAPY WOULD LOOK LIKE BUT NOT BEING ABLE TO PROVIDE IT
Number of Clinitians
Competing time demands
THE CLOSER YOU THINK YOU GET TO THE ANSWER THE MORE THERE IS TO ASK...
INFINITY MAZE
I AM NEVER BORED!!! THE VARIETY IS BEAUTIFULLY OVERWHELMING
WHAT UNITES US IN FACING UP TO THE CHALLENGES OF ERADICATION IS MUCH MORE THAN THE PERCEIVED DIFFERENCES IN VARIOUS PARTS OF THE WORLD
AHMED ELSHARKAWY
WHO
AASLD
EASL
APASL
PHARMA
WHA
GOVERNMENTS
BVHG
NGOs
THE GOAL
ELIMINATE HEPATITIS B BY 2030
ORGANISATIONS NEED TO TALK TO EACH OTHER
You Have to look at the BIGGER PICTURE!
John MACRO
CAN YOU BE MORE SPECIFIC?!
Steve MICRO
WE HAVE GREAT NEW DRUGS THAT CURE MORE THAN 95% OF PATIENTS BUT WE DO NOT HAVE A VACCINE TO PREVENT EITHER NEW INFECTIONS OR RE-INFECTIONS IN PEOPLE WHO HAVE HAD THE VIRUS CURED
UNIVERSAL VACCINATION IN ALL COUNTRIES AROUND THE WORLD
EXPAND ACCESS TO TREATMENT
IMPROVE THE PERCENTAGE OF PEOPLE DIAGNOSED WITH HEPATITIS B
REDUCE THE BARRIERS TO ACCESS TO TREATMENT
IF WE TREAT ENOUGH PEOPLE, THE RESERVOIR OF INFECTION WILL FALL AND THE NUMBER OF NEW INFECTIONS WILL FALL
TREATMENT SHOULD BE SIMPLE AND NOT COMPLICATE LIFESTYLE
PIERRE GHOLAM
LET'S GO BACK IN TIME
SOLUTION
PROBLEM
PREVENTATIVE PROGNOSIS
DISEASE IS DIAGNOSED TOO LATE
THERE IS NO MAGIC PILL THAT FITS ALL PATIENTS, SO WE TRY TO FOCUS ON A MORE PATIENT SPECIFIC APPROACH.
PREVENTATIVE METHODOLOGY TO HAVE PROGNOSIS OF A PATIENTS HEALTH.
LIVER CANCER
FATTY LIVER
birth
lifestyle
silent disease
NO PAIN NO SYMPTOMS
Cirrhosis
TOO LATE

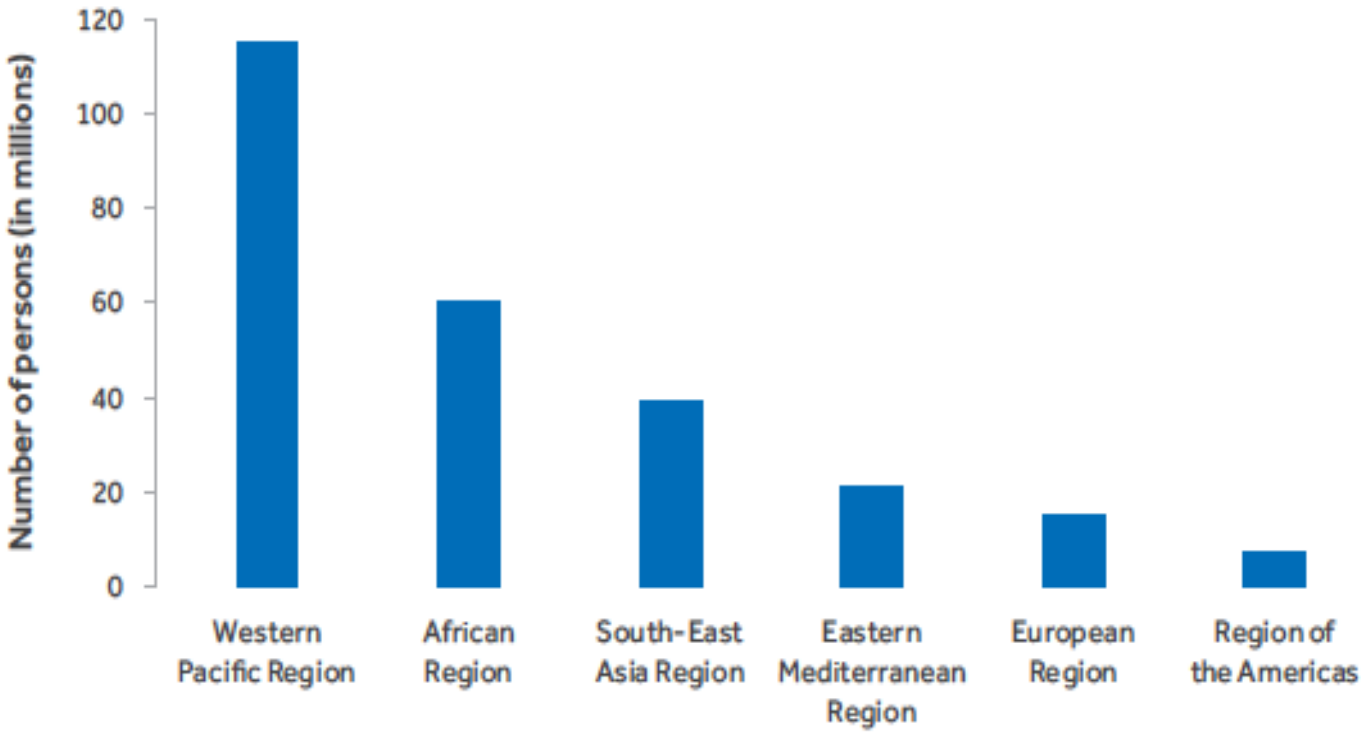
WHO Global Hepatitis Report

World Health Organization

GLOBAL HEPATITIS REPORT, 2017

Number of HBV Infected Individuals Worldwide

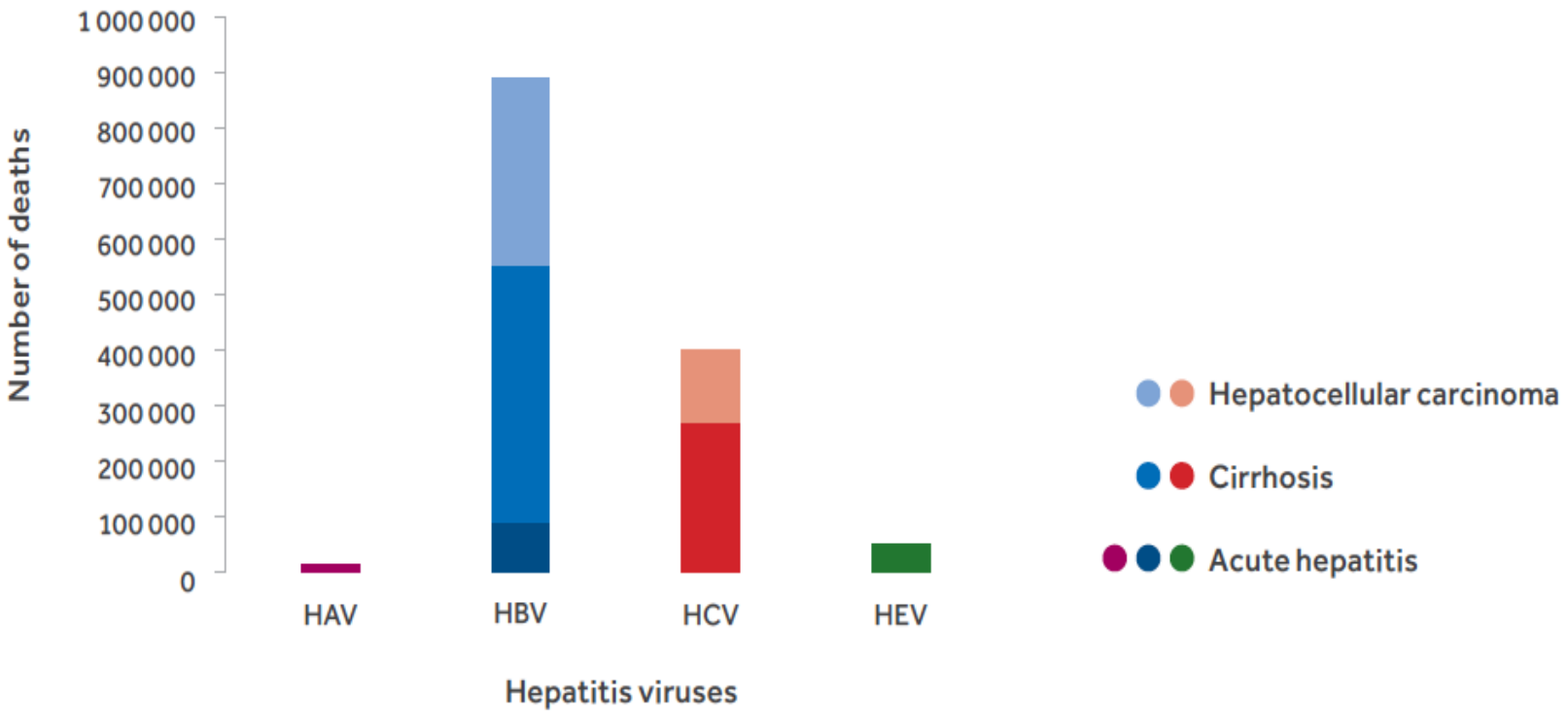
Table 2 (with graph). Prevalence of HBV infection (HBsAg) in the general population by WHO region, 2015: the WHO African and Western Pacific regions have the highest prevalence and the largest number of persons living with HBV



Total Numbers of Individuals Infected Worldwide = 257 million

Deaths from Viral Hepatitis

Fig. 1. Deaths from viral hepatitis, by virus and type of sequelae, 2015:
most viral hepatitis deaths are due to the late complications of HBV and HCV infection



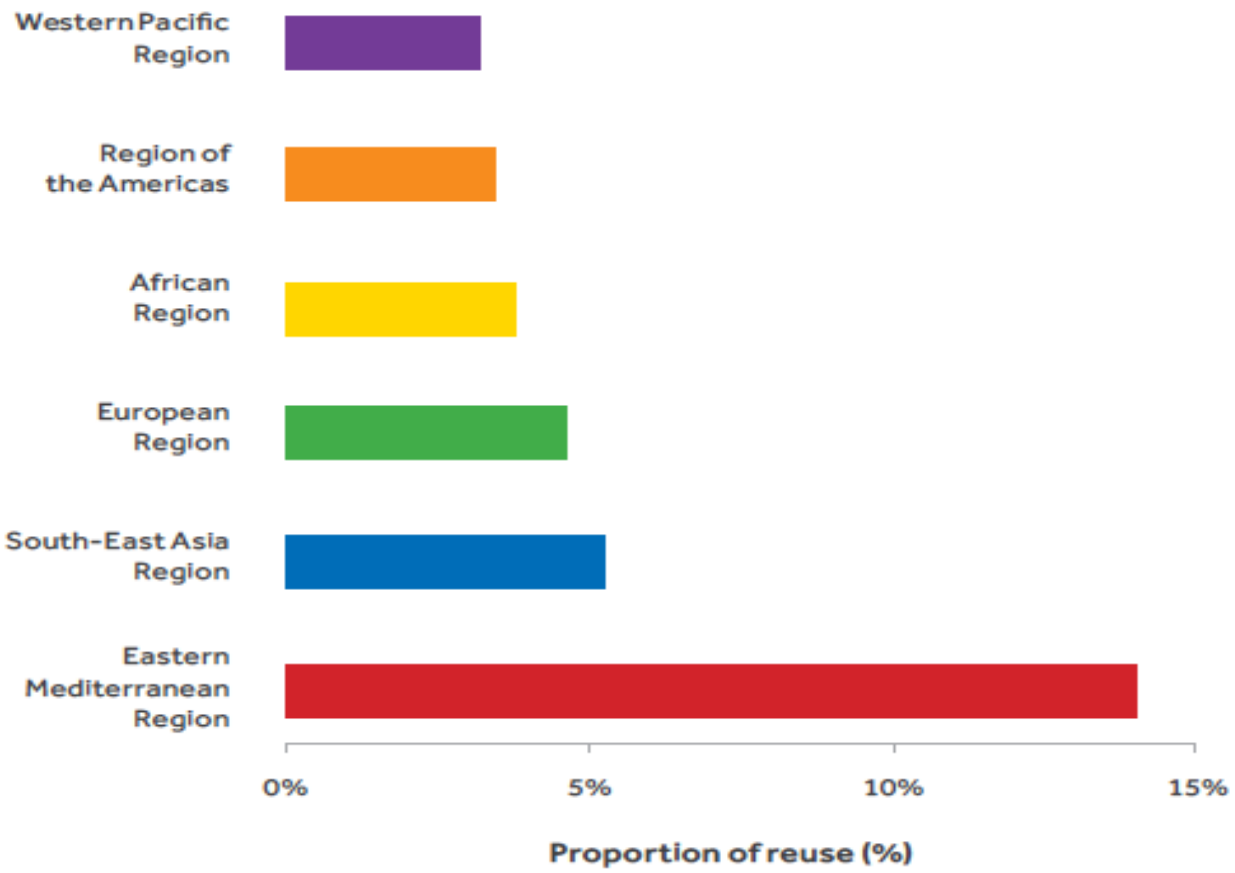
HAV: hepatitis A virus; HBV: hepatitis B virus; HCV: hepatitis C virus; HEV: hepatitis E virus
Source: WHO global health estimates for 2015 published in 2016 (Global Health Estimates 2015: deaths by cause, age, sex, by country and by region, 2000–2015. Geneva: World Health Organization; 2016.)

A Shocking Statistic

	Interventions	Indicator	2015 baseline	Targets 2020	Targets 2030
1	Hepatitis B vaccination	HEPB3 coverage	84%	90%	90%
2	HBV PMTCT[a]	HEP vaccine birth dose coverage	39%	50%	90%
3	Blood safety	Donations screened with quality assurance	97%	95%	100%
	Injection safety	Proportion of unsafe injections	5%	0%	0%
4	Harm reduction	Syringes & needles distributed/PWID/year	27	200	300
5	Testing services	% HBV-infected diagnosed	9%	30%	90%
		% HCV-infected diagnosed	20%	30%	90%
	Treatment	% diagnosed with HBV on treatment	8%[b]	–[c]	80%[d]
		% diagnosed with HCV started on treatment	7%[b]	–[c]	80%[d]

And another shocking statistic

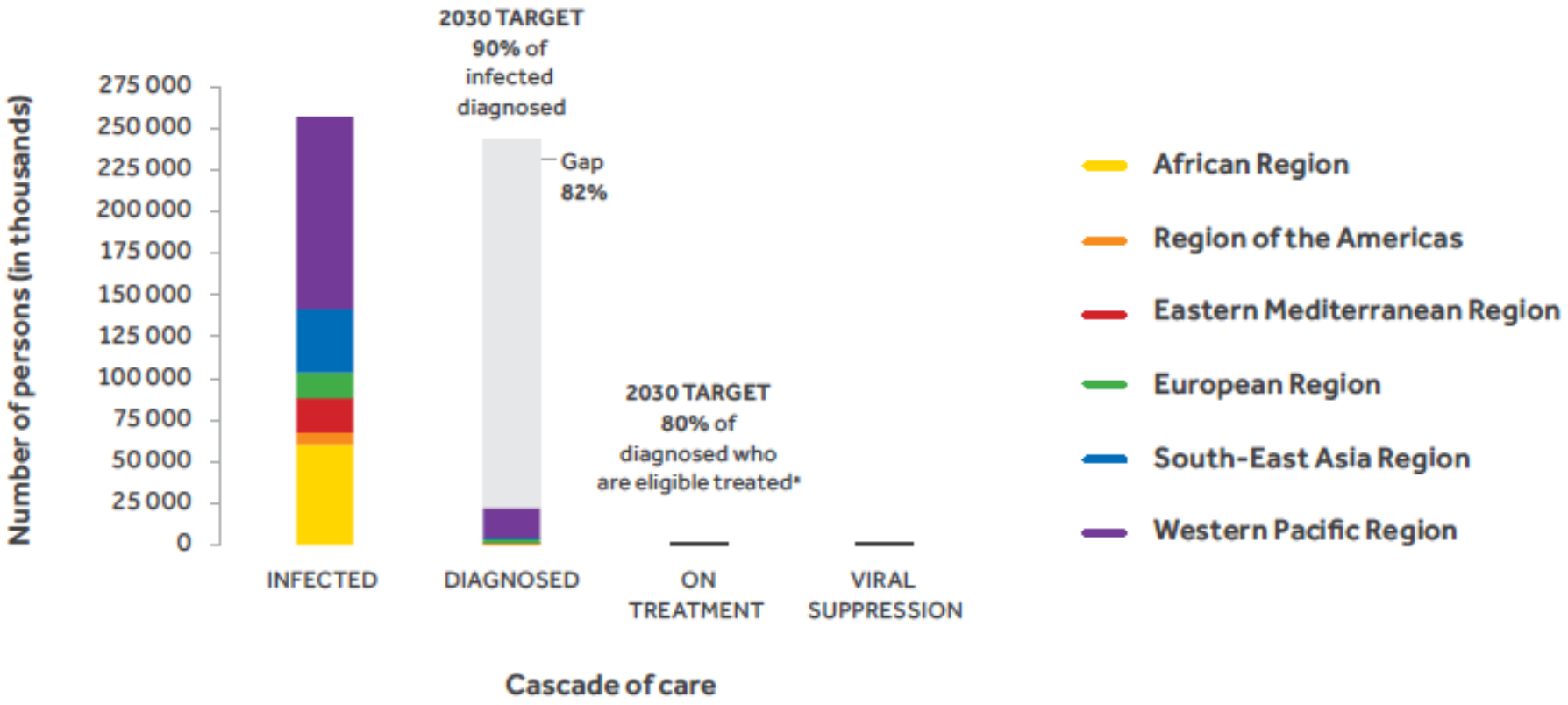
Fig. 6. Proportion of health-care injections given with equipment reused without sterilization, by WHO region, 2010: problems persist specifically in the Eastern Mediterranean and South-East Asia regions



Source: Pepin at al. *(40)*

HBV Cascade of Care

Fig. 7. Cascade of care for HBV infection, by WHO region, 2015: effective treatment is underused in most regions

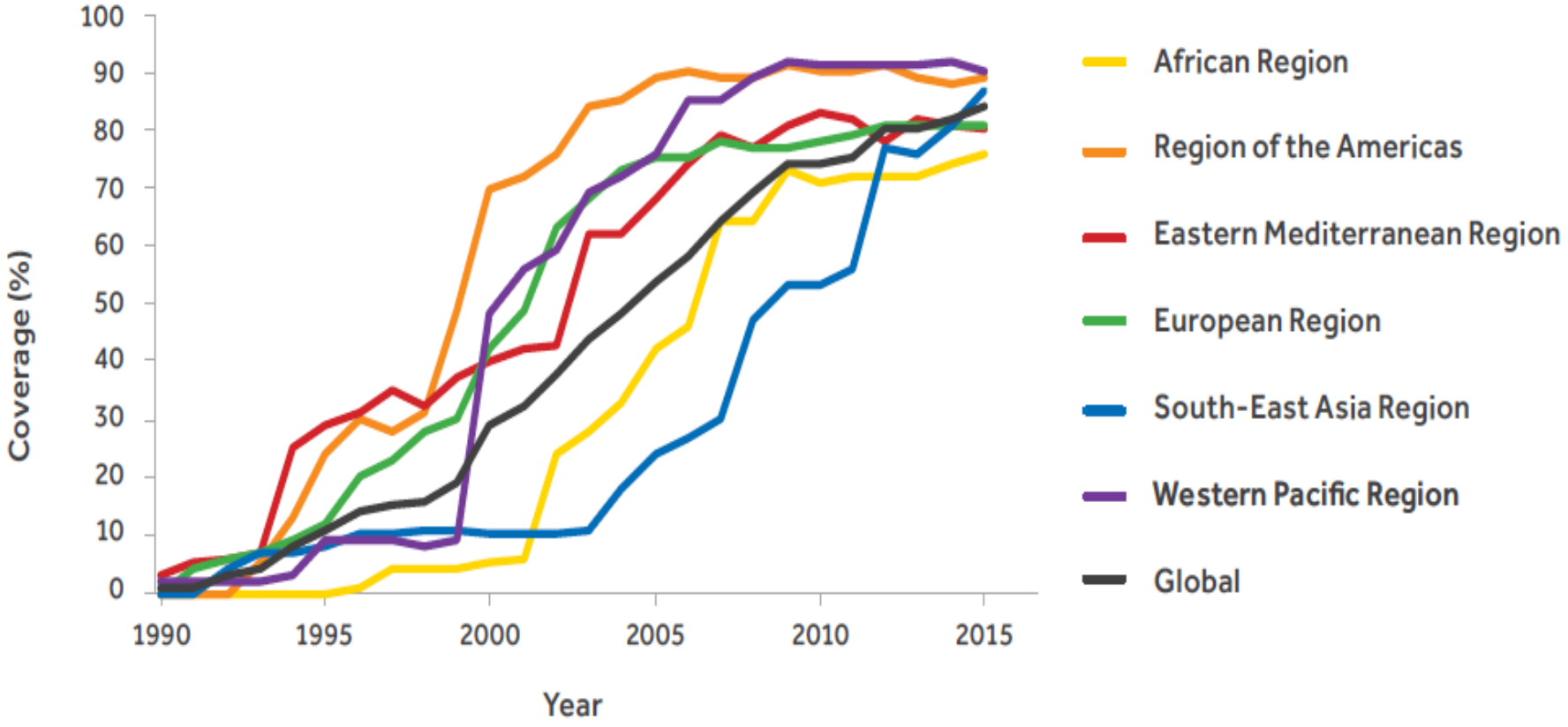


Source: WHO estimates, conducted by the Center for Disease Analysis. *See* Annex 2.

[a] As the proportion of persons eligible for treatment among those diagnosed is unknown, the treatment gap cannot be calculated.

But Some Good News

Fig. 4. Three-dose hepatitis B vaccine coverage, by WHO region, 2000–2015: a major increase in coverage at the beginning of the 21st century



And Finally the UK Has Caught Up

Public Health England

Protecting and improving the nation's health

Issue 261, April 2017

Vaccine update

Important

Change of vaccine for routine primary baby immunisation programme

This is the good news that later this year Infanrix hexa® (DTaP/IPV/Hib/HepB) will replace both Pediacel® and Infanrix-IPV+Hib® (DTaP/IPV+Hib) for primary baby immunisations. This change means that as well as providing protection against diphtheria, tetanus, pertussis, polio and Hib, **babies will also be given protection against hepatitis B virus.**

The planned change only involves the type of vaccine used. There is no change to the immunisation schedule and the current planning assumption is that babies born on or after 1 August will be offered Infanrix hexa® (DTaP/IPV/Hib/HepB) from late September/early October 2017, at the ages of 8, 12 and 16 weeks as part of the routine childhood immunisation schedule.

The exact dates will depend on the remaining availability of pentavalent vaccine.

Contents

Implications for the neonatal selective immunisation programme for babies at risk of hepatitis B

Vaccine ordering and stock management

Shingles immunisation programme 2017/18

Hepatitis A: preventing infection in men who have sex with men

MMR vaccines

Vaccines for the children's flu programme

Vaccines not procured and supplied centrally

Bank Holiday deliveries

InterVax BCG vaccine and leaflets

Change to Rabipur presentation

EASL CPG on Hepatitis B

ARTICLE IN PRESS

Clinical Practice Guidelines

EASL | JOURNAL OF HEPATOLOGY

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

European Association for the Study of the Liver*

Changes in Terminology

- Immunotolerant e antigen positive hepatitis B now HBeAg positive chronic infection
- Immune reactive e antigen positive hepatitis now HBeAg positive chronic hepatitis
- Inactive e antigen negative hepatitis B now HBeAg negative chronic infection

Changes in first line treatments

- TAF, TDF and ETV as monotherapies are preferred first line treatment
- Patients on TDF at risk of development and/or with underlying renal or bone disease should be considered for a switch to TAF or ETV
- TAF preferred to ETV in patients with previous nucleoside exposure

Indications for selecting TAF or ETV over TDF
Age >60 years
Bone disease • Chronic steroid use or use of other medications that worsen bone density • History of fragility fracture • Osteoporosis
Renal alteration* • eGFR <60 mL/min/1.73 m^2 • Albuminuria >30mg or moderate dipstick proteinuria • Low phosphate (<2.5mg/dL) • Hemodialysis

* ETV dose needs to be adjusted if eGFR <50 mL/min; no dose adjustment of TAF is required in patients with estimated CrCl ≥15 mL/min

EASL Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol 2017; doi: 10.1016/j.jhep.2017.03.021

Indications for treatment

HBeAg Positive or Negative Chronic Hepatitis

All patients with HBeAg-positive or HBeAg-negative CHB, defined by HBV DNA >2000 IU/mL, ALT >ULN and/or at least moderate liver necroinflammation or fibrosis, should be treated (1-I)

Cirrhosis

Patients with compensated or decompensated cirrhosis need treatment, with any detectable HBV DNA level and regardless of ALT levels (1-I)

Obviously active CHB

Patients with HBV DNA >20,000 IU/mL and ALT >2 x ULN should start treatment regardless of the degree of fibrosis (II-2-1)

HBeAg Positive Chronic Infection >30yrs

Patients with HBeAg-positive chronic HBV infection, defined by persistently normal ALT and high HBV DNA levels, may be treated if they are older than 30 years regardless of the severity of liver histological lesions (III-2)

Family History

Patients with HBeAg-positive or HBeAg-negative chronic HBV infection and family history of HCC or cirrhosis and extrahepatic manifestations can be treated even if typical treatment indications are not fulfilled (III-2)

New Stopping Rules for PEG-IFN

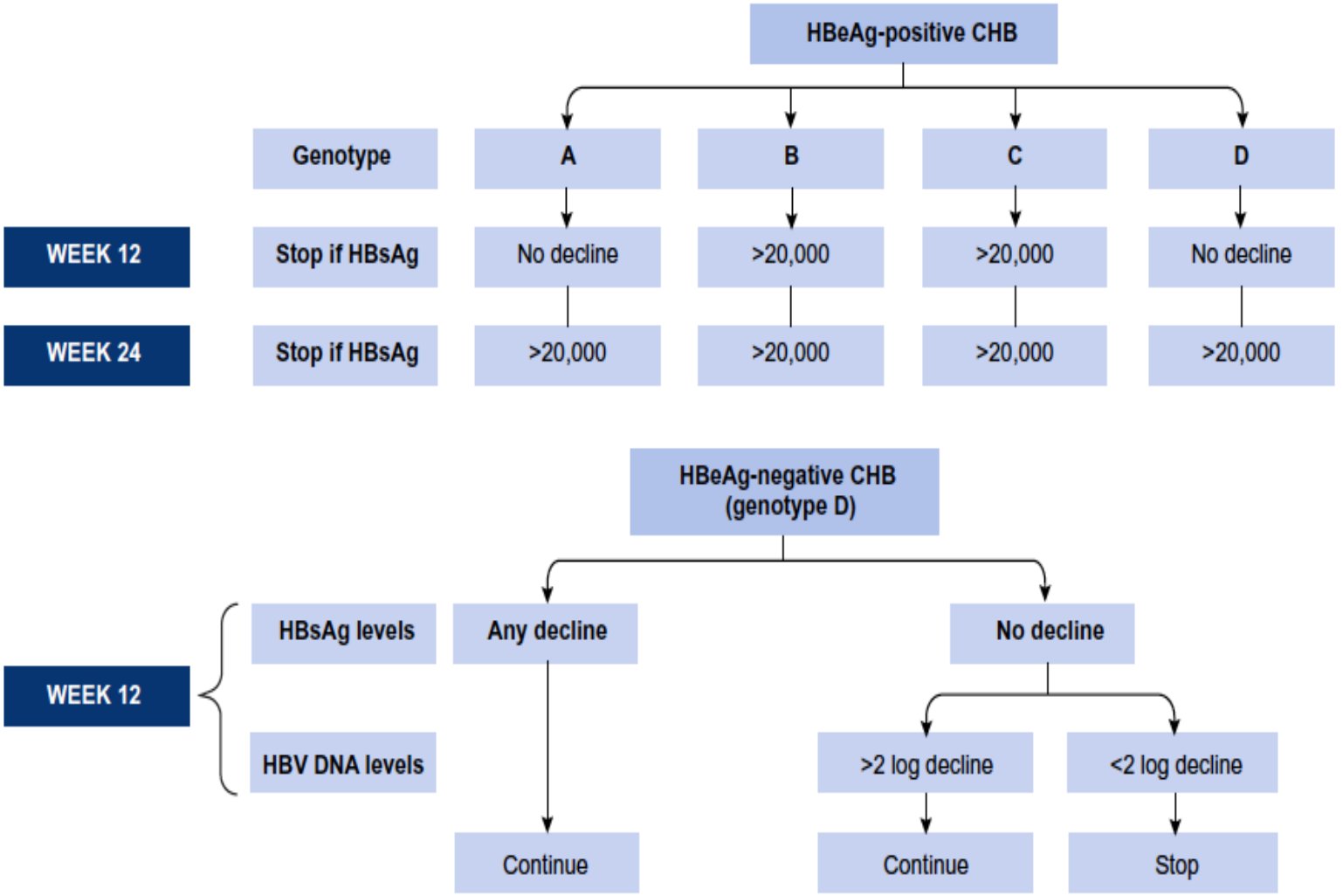
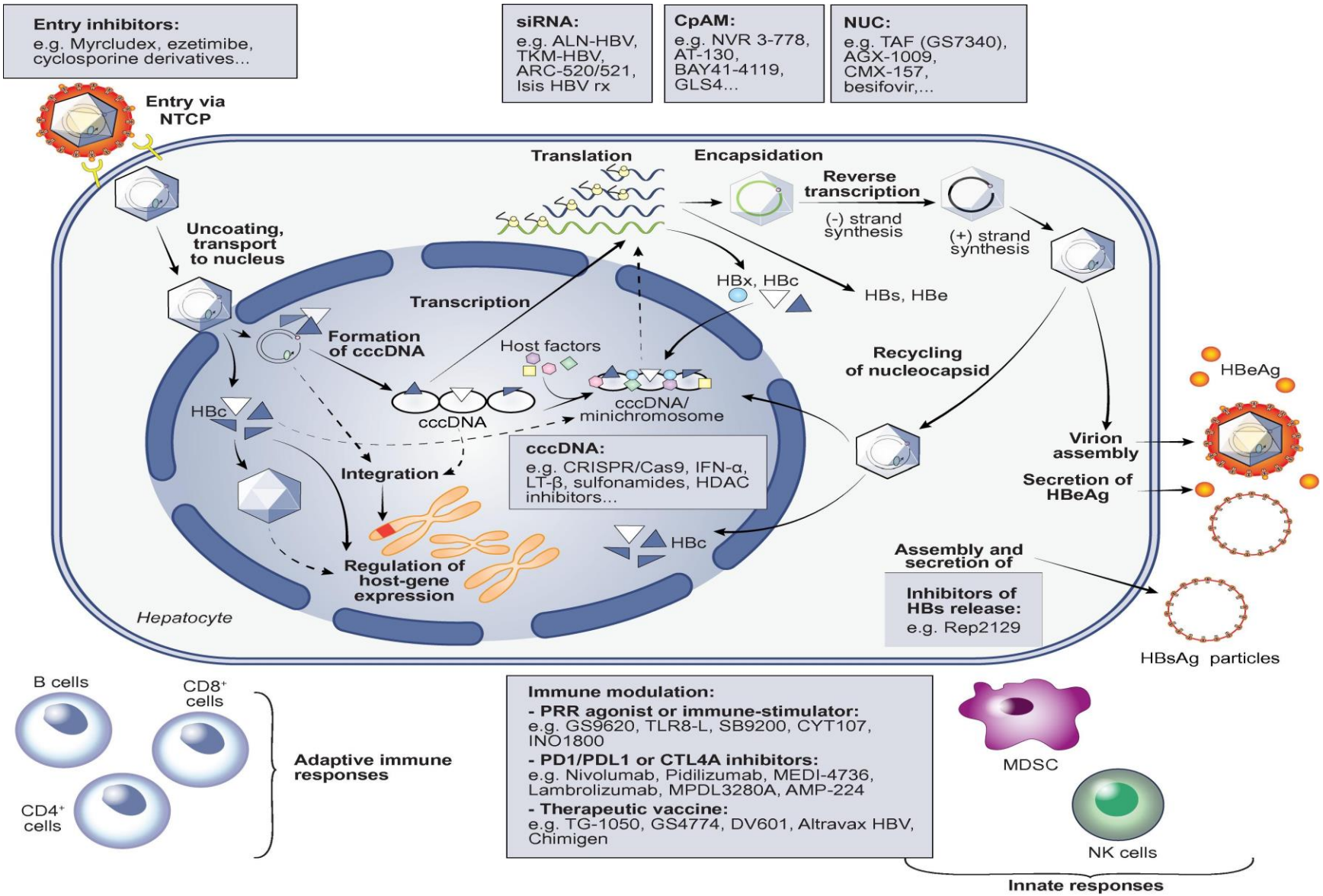


Fig. 4. Week 12 and 24 stopping rules for HBeAg-positive and -negative patients treated with PegIFNα. These rules are based upon viral genotype, HBsAg and HBV levels.

HIV/HBV Co-Infection Recommendations

- All HIV-positive patients with HBV co-infection should start antiretroviral therapy (ART) irrespective of CD4 cell count (Evidence level II-2, grade of recommendation 1).
- HIV-HBV co-infected patients should be treated with a TDF- or TAF-based ART regimen (Evidence level I for TDF, II-1 for TAF, grade of recommendation 1).

Novel HBV Targets

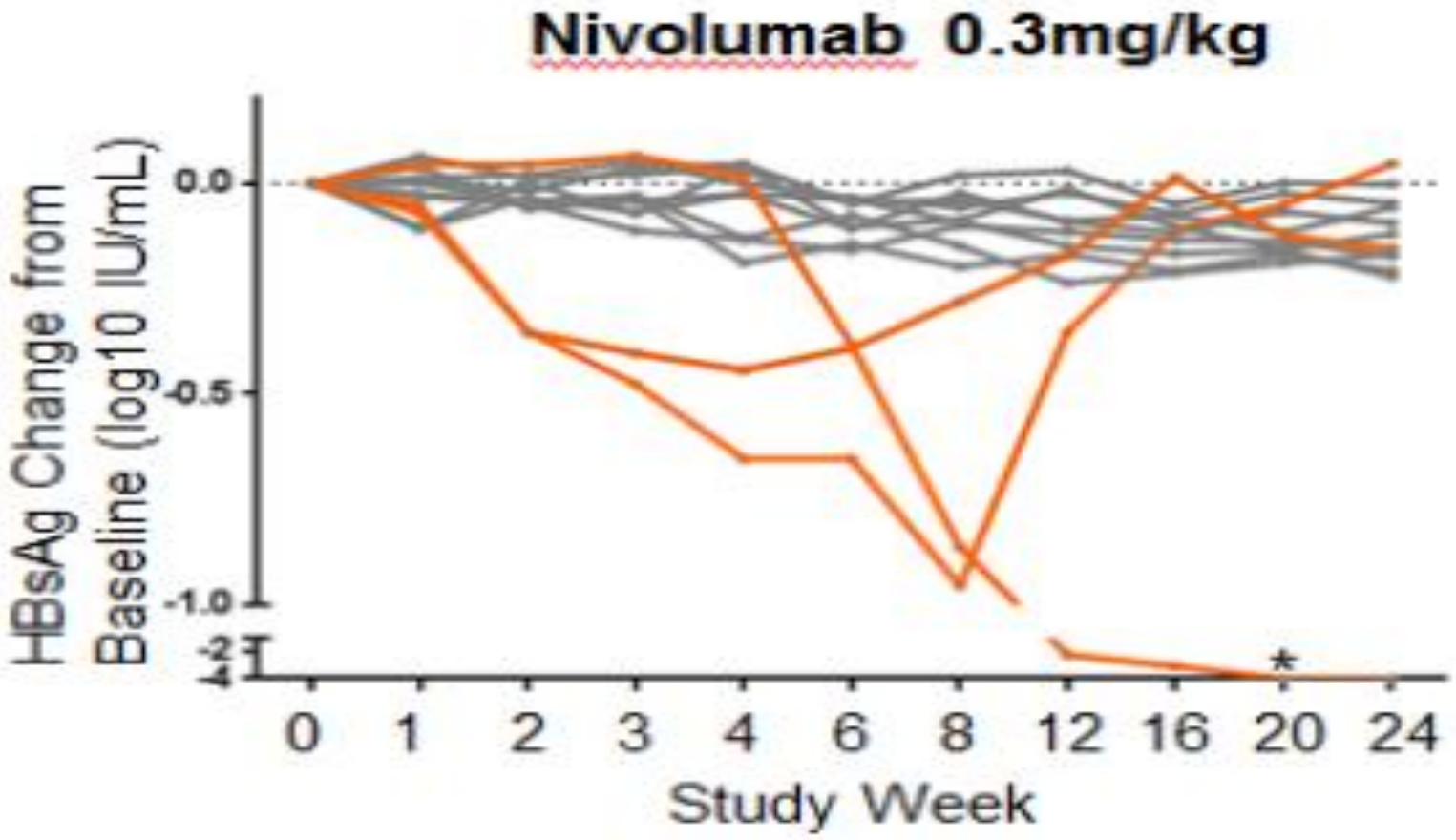


Durantel and Zoulim J Hep 2016

Nivolumab in Chronic HBV

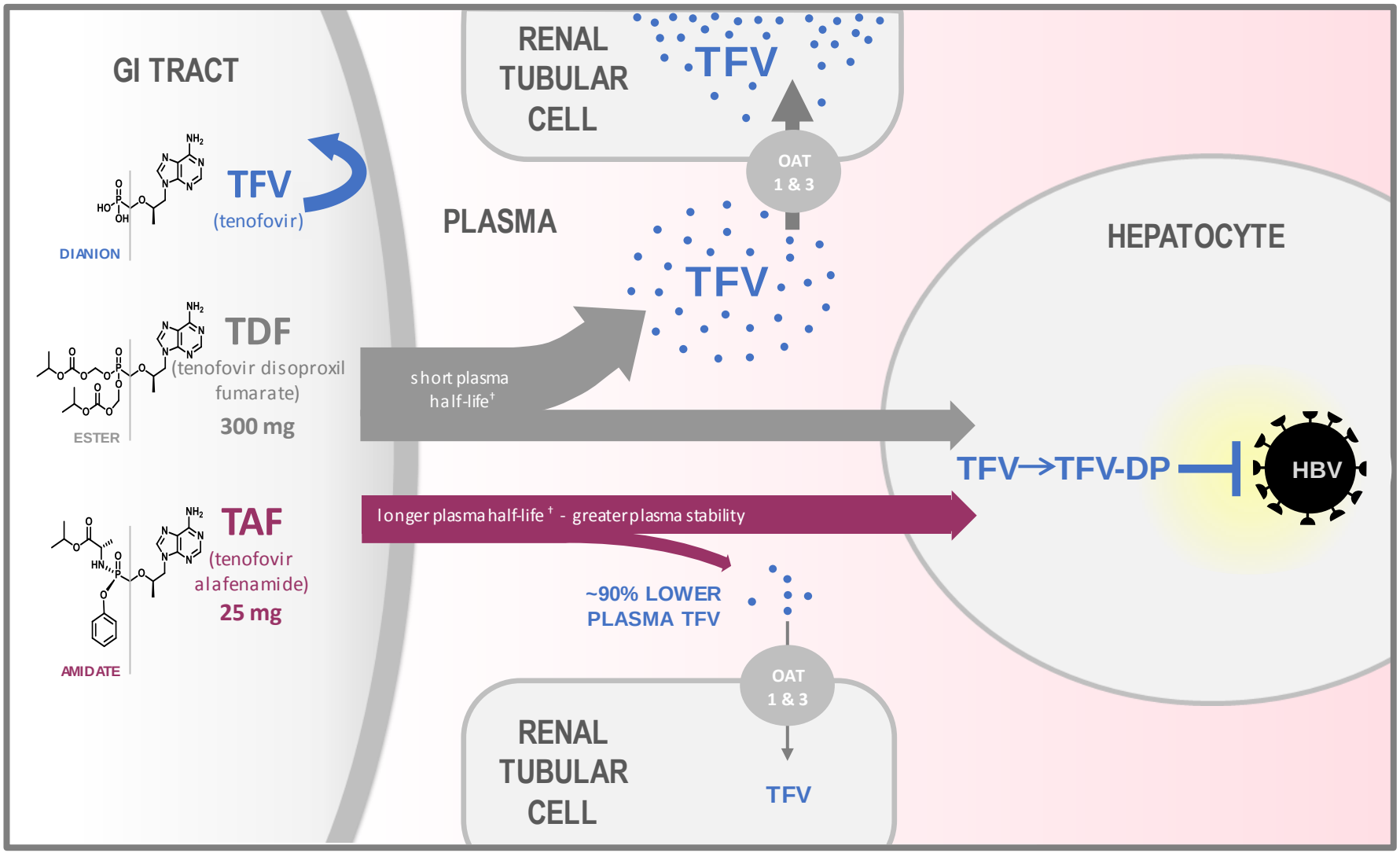
- Checkpoint inhibitor
- Used increasingly in malignant melanoma
- Phase 1 trial – presented by Ed Gane (PS-044)
- E antigen negative patients
- Single injection of 0.3 mg/kg
- Theory is to increase HBV specific T cell activity to encourage viral clearance
- Trial also included an arm with a therapeutic vaccine (this did not add anything)

Results


Nivolumab 0.3mg/kg
HBsAg Change from Baseline (log10 IU/mL)
0.0
-0.5
-1.0
-2
0 1 2 3 4 6 8 12 16 20 24
Study Week
*

TAF in HBV Mono-infection

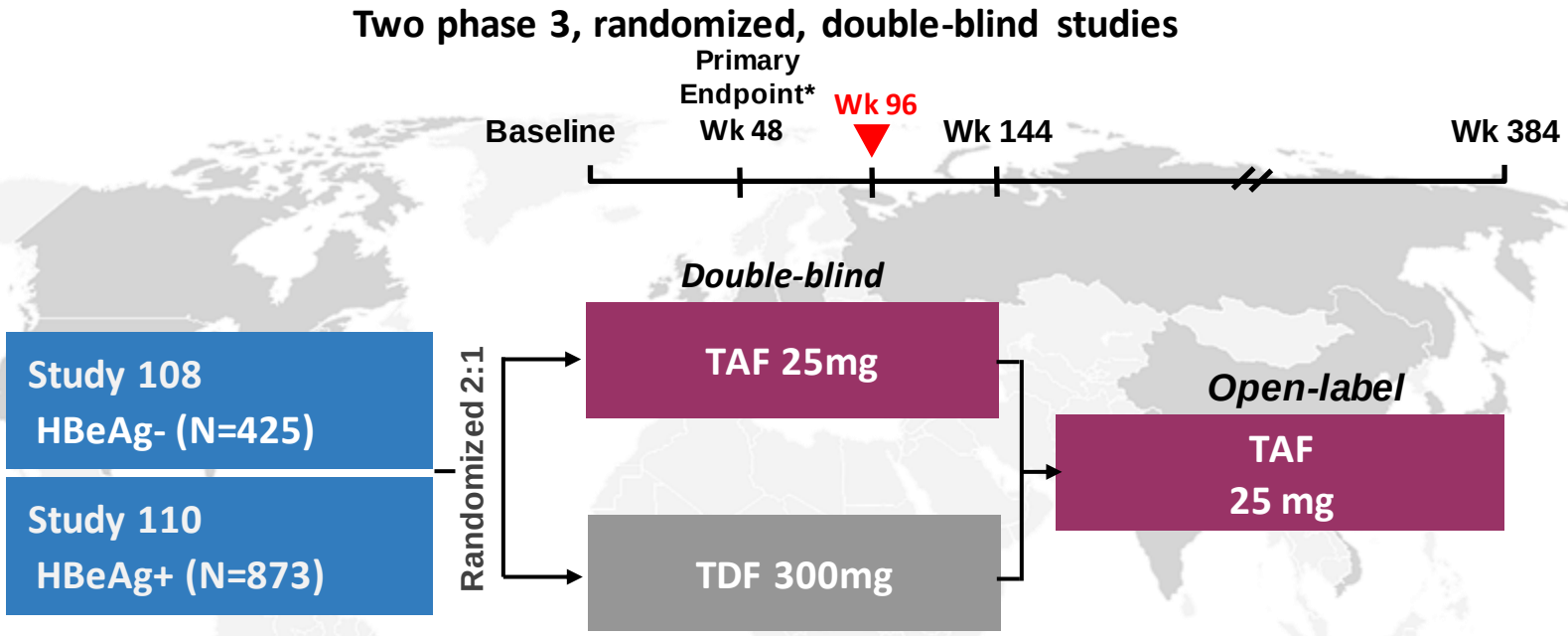
Tenofovir Alafenamide (TAF) – A Novel Prodrug of Tenofovir



† $T_{1/2}$ based on *in vitro* plasma data - TDF = 0.4 minutes, TAF = 30-90 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 M et al. Lancet G&H 2016; doi: 10.1016/S2468-1253(16)30107-8; Chan HLY et al. Lancet G&H 2016; doi: /10.1016/S2468-1253(16)30024-3

TAF HBV Phase 3 Program



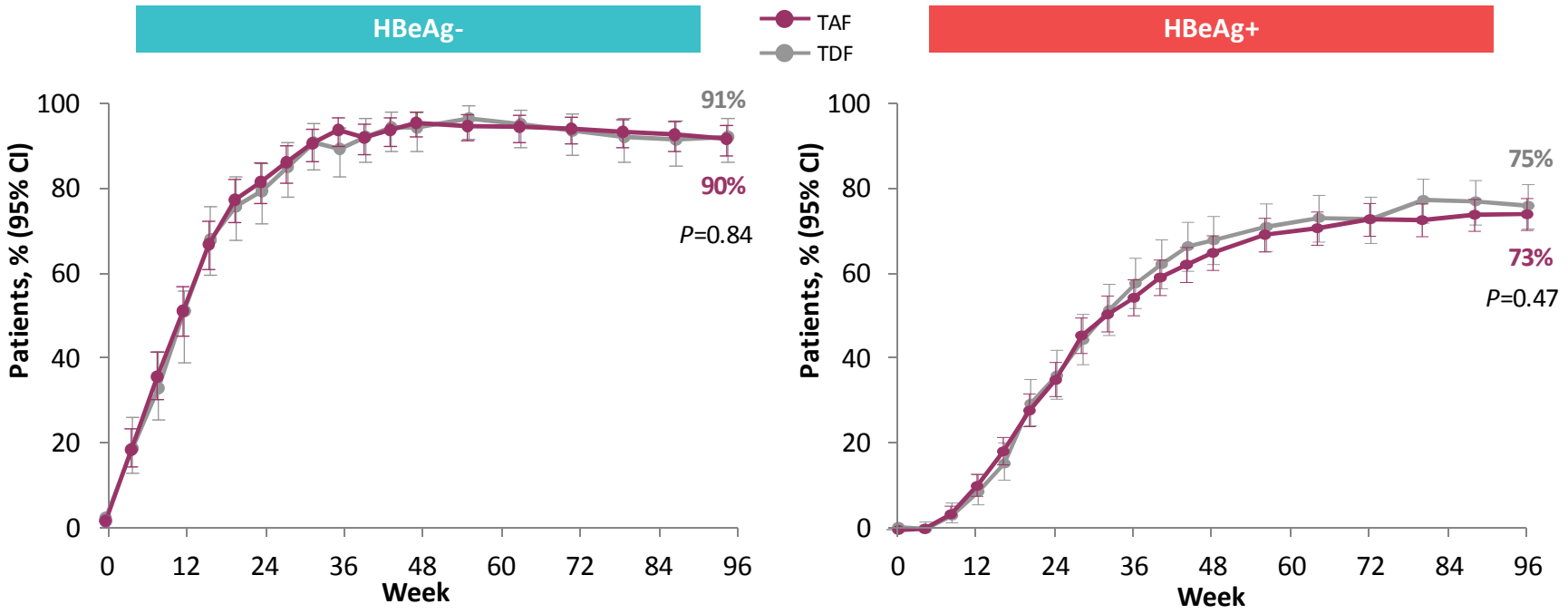
- **Primary endpoint** (non inferiority margin of 10%):
  - HBV DNA <29 IU/mL at Week 48
- **Key secondary endpoints**
  - HBV DNA <29 IU/mL at Week 96
  - ALT normalization (central lab and AASLD criteria)
  - Serology (HBsAg loss/seroconversion)
- 90% retention rate through Week 96
- Inclusion criteria: HBV DNA ≥20,000 IU/mL; ALT >60 U/L (males), >38 U/L (females), $eGFR_{CG}$ >50 mL/min

Buti M et al. Lancet G&H 2016; doi: 10.1016/S2468-1253(16)30107-8;Chan HLY et al. Lancet G&H 2016; doi: /10.1016/S2468-1253(16)30024-3;
Agarwal, EASL 2017, FRI-153; Brunetto, EASL 2017

Antiviral Efficacy of TAF and TDF at Week 96

Rates of Viral Suppression (ITT)

HBV DNA <29 IU/mL



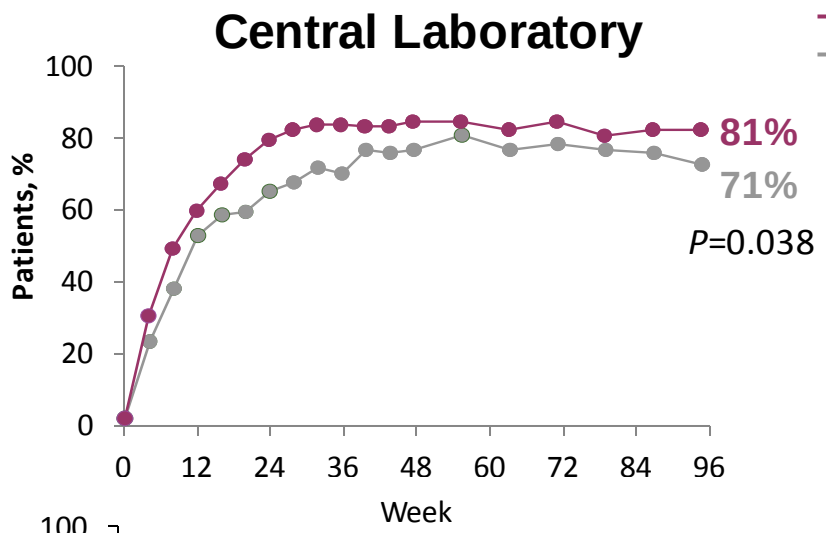
- No resistance was detected through 96 weeks
- No significant difference between TAF and TDF
- 90% retention rate through Week 96
- Similar rates of mean HBV DNA decline (log10 change) at all time points across both studies

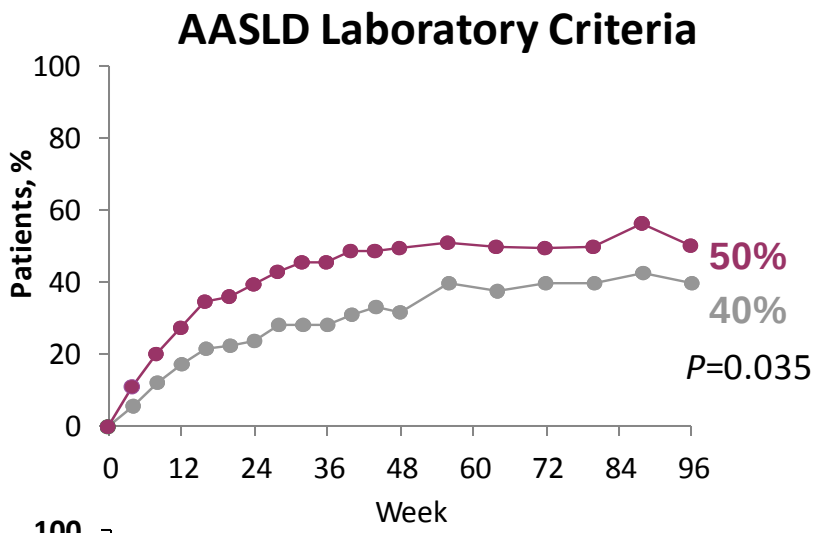
HBV DNA suppression was comparable between TAF and TDF treatment up to Week 96

Agarwal, EASL 2017, FRI-153;
Brunetto, EASL 2017, PS-042; Gilead, Data on File.

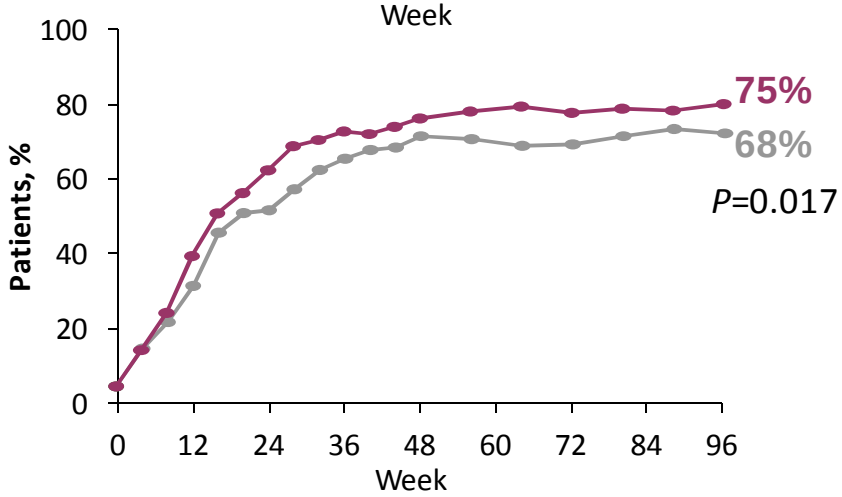
ALT Normalization at Week 96

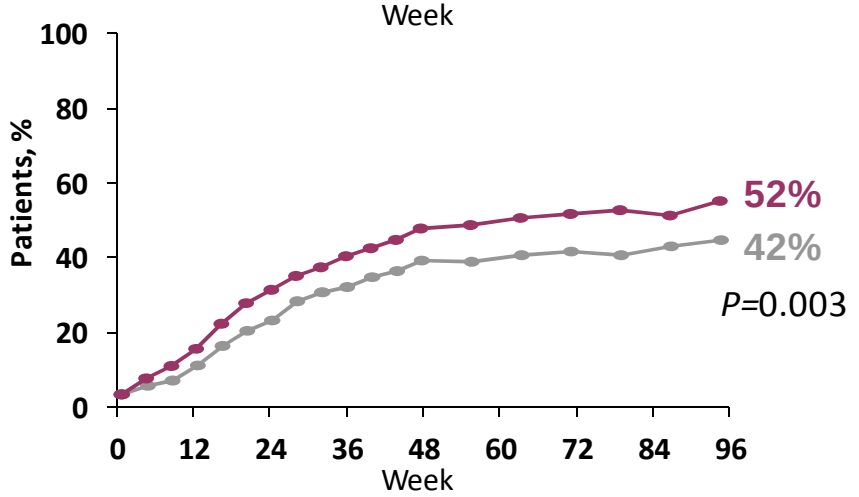
HBeAg-





HBeAg+





Significantly higher ALT normalization rate with TAF vs TDF

Central lab upper limit of normal (ULN): males ≤43 U/L and females ≤34 U/L (≥69 y: males ≤35 U/L and females ≤32 U/L); AASLD criteria ULN: males ≤30 U/L and females ≤19 U/L.

Brunetto, EASL 2017, PS-042; Agarwal, EASL 2017, FRI-153

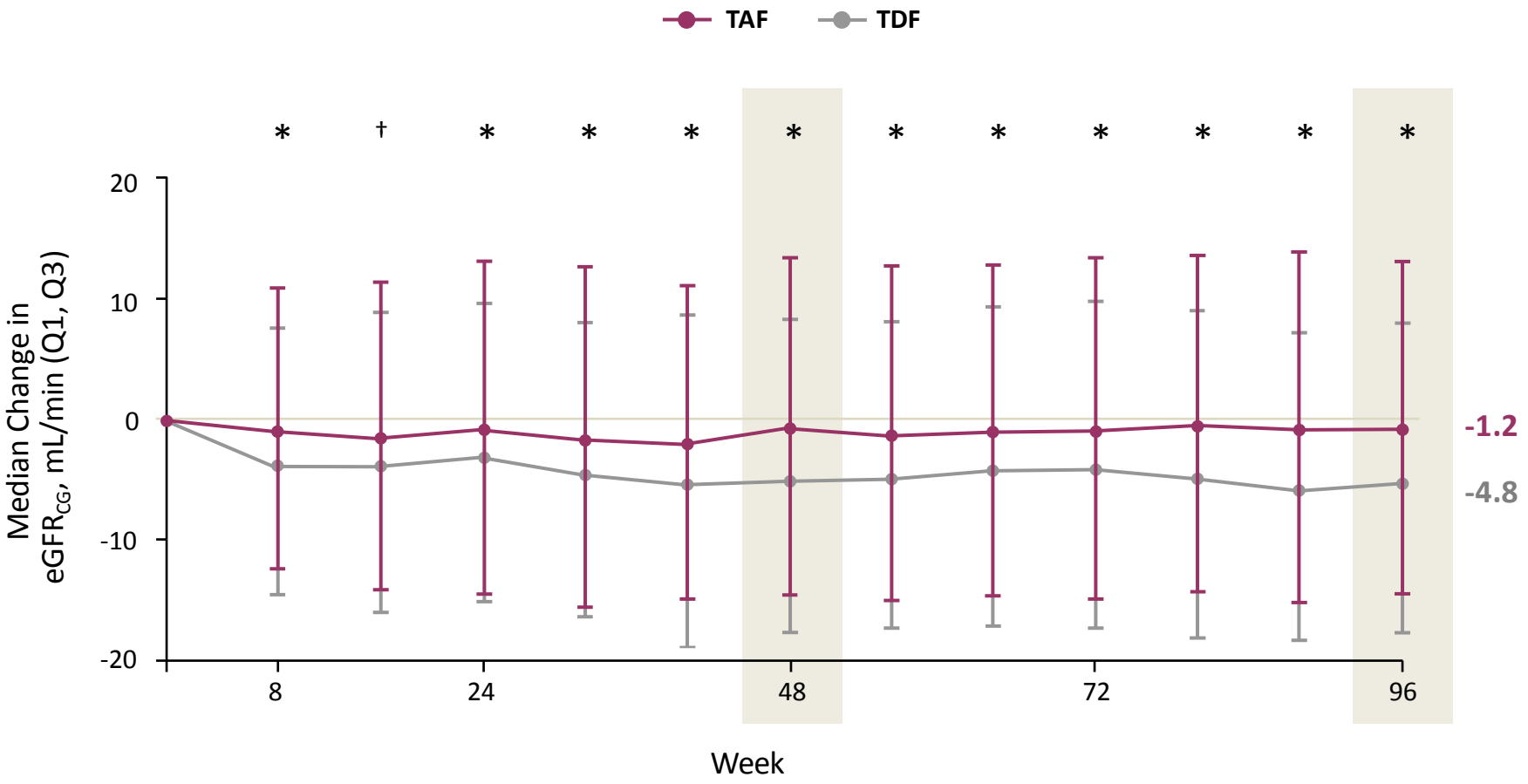
Serologic Response At Week 96

Patients, n/n (%)		Study 108 (HBeAg-) (N=425)			Study 110 (HBeAg+) (N=873)		
		TAF n=285	TDF n=140	*P*-value	TAF n=581	TDF n=292	*P*-value
HBeAg	Loss	-	-		123/565 (22)	51/285 (18)	0.20
	Seroconversion	-	-		99/565 (18)	35/285 (12)	0.05
HBsAg	Loss	1/281 (<1)	0	0.72	7/576 (1)	4/288 (1)	0.88
	Seroconversion	1/281 (<1)	0	0.72	6/576 (1)	0/288 (0)	0.08

Improved serologic responses with higher rates of HBeAg seroconversion with TAF vs TDF – but at limit of statistical significance

Agarwal, EASL 2017, FRI-153; Brunetto, EASL 2017, PS-042, Gilead, Data on File.

Renal Safety Through Week 96

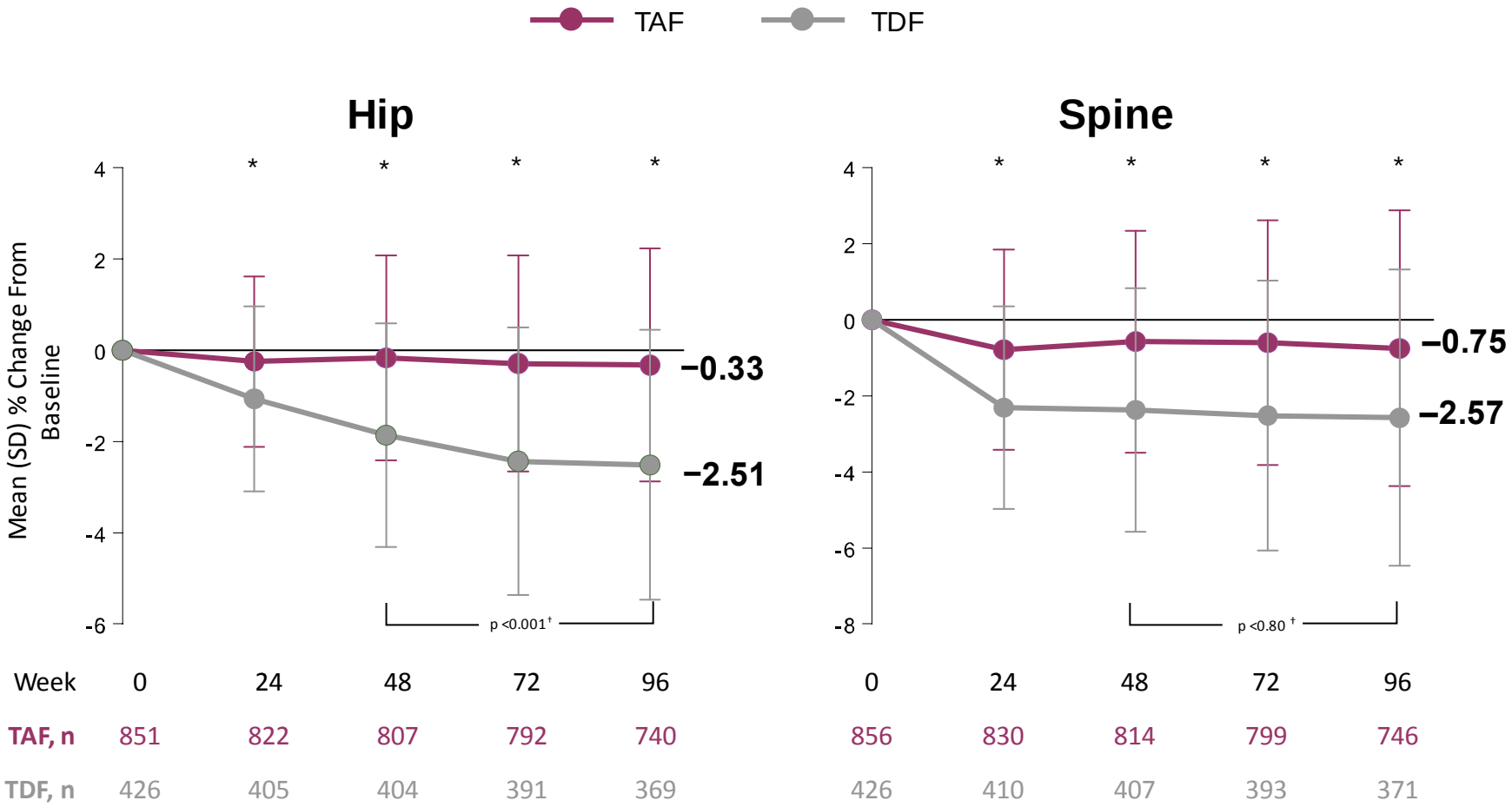


TAF treatment had significantly less impact on eGFR than TDF

*P≤0.001; †P<0.01

Chuang, EASL 2017, SAT-171

Mean Change in BMD Through Wk 96



TAF treatment resulted in smaller declines in hip and spine BMD compared with TDF

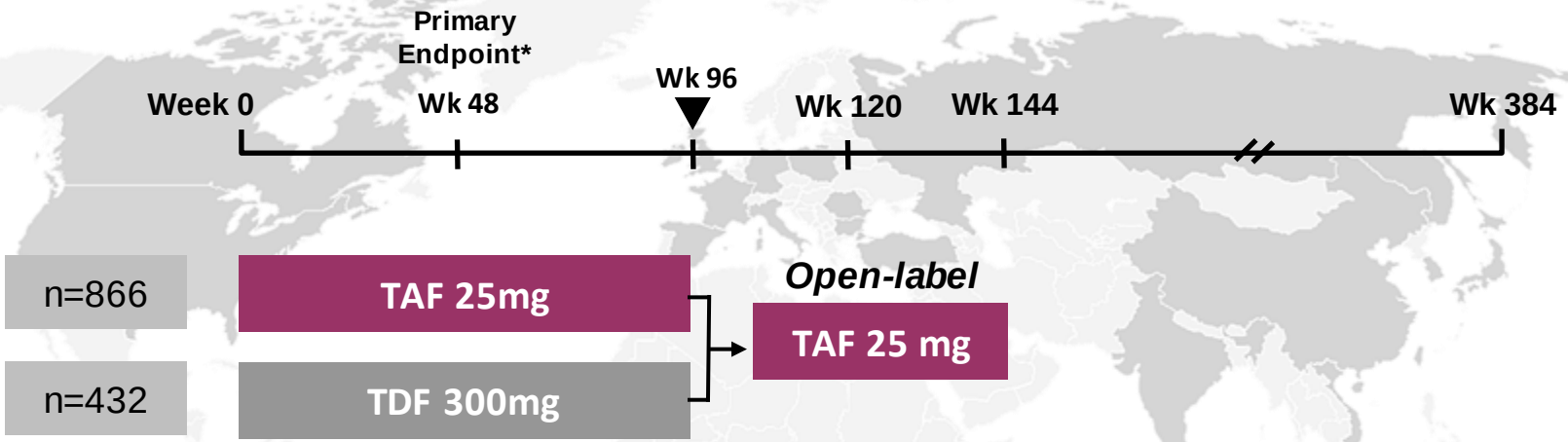
* *P*<0.001, p-values from analysis of variance model including treatment as a fixed effect; † p-values from mixed model repeated measures

Fung, EASL 2017, SAT-162

Big Proviso

No clinically meaningful outcomes have been presented

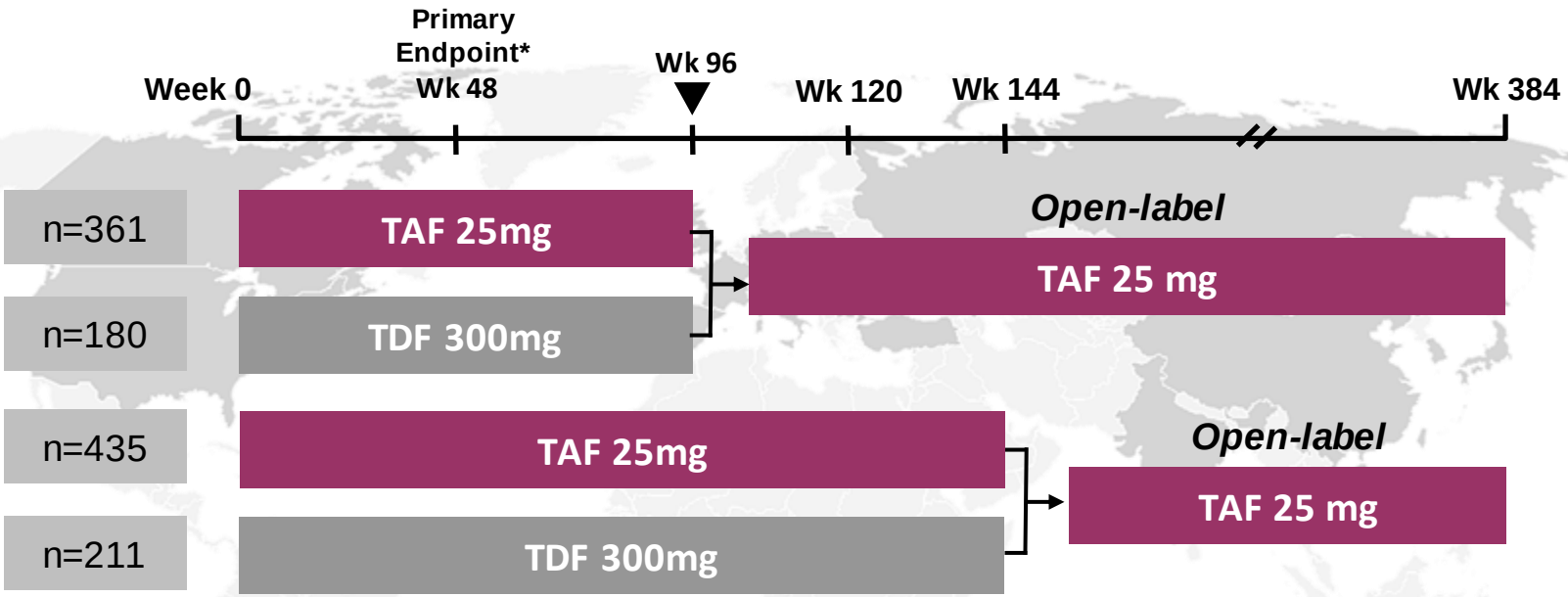
Study Design



- Two Phase 3, randomized, double-blind, active-controlled trials
  - Study 108 (N=425): HBeAg-negative patients
  - Study 110 (N=873): HBeAg-positive patients
- Key inclusion criteria (both studies)
  - HBV DNA ≥20,000 IU/mL; ALT >60 U/L (males) >38 U/L (females); eGFR ≥50 mL/min
- 2:1 randomization
  - Stratified by HBV DNA level and treatment status (naïve/experienced)

Chan, EASL 2017, PS-041

Study Design



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Chan, EASL 2017, PS-041

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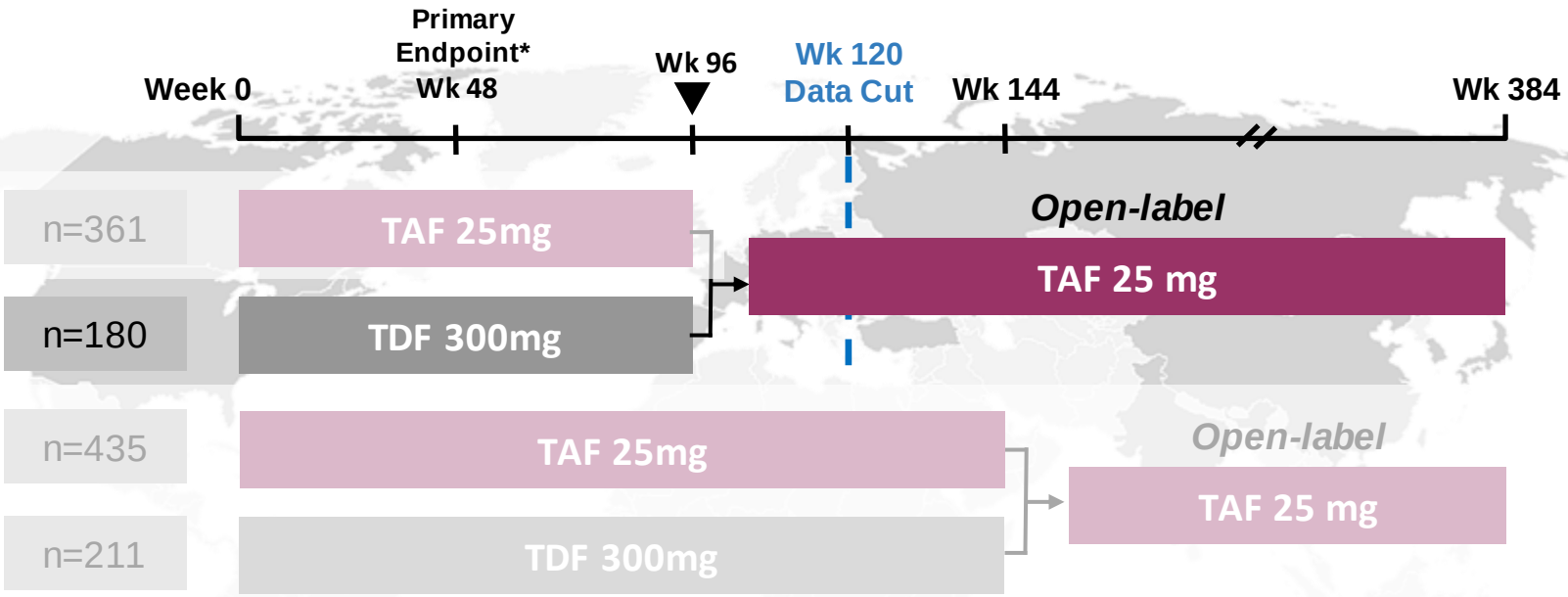

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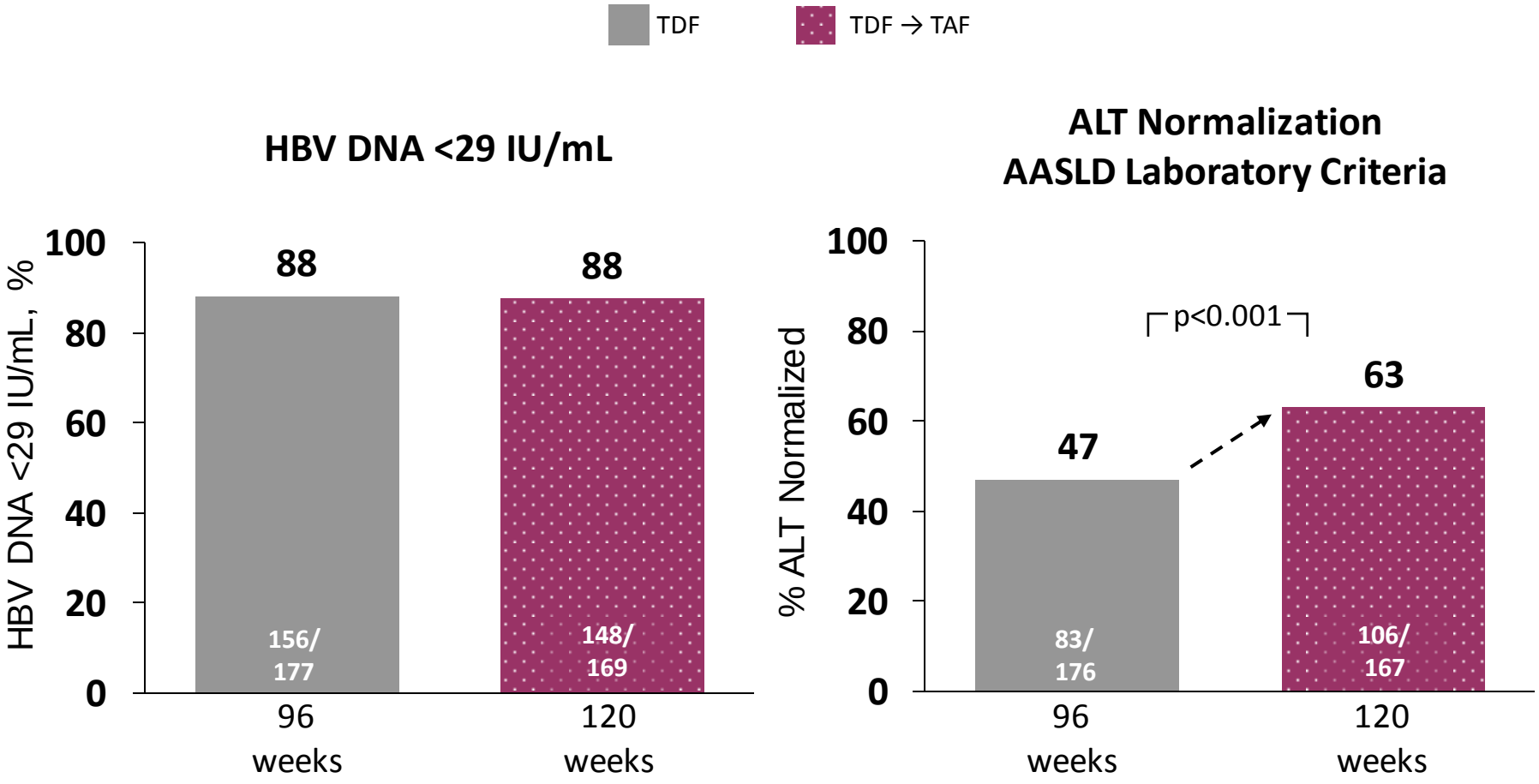
Chan, EASL 2017, PS-041

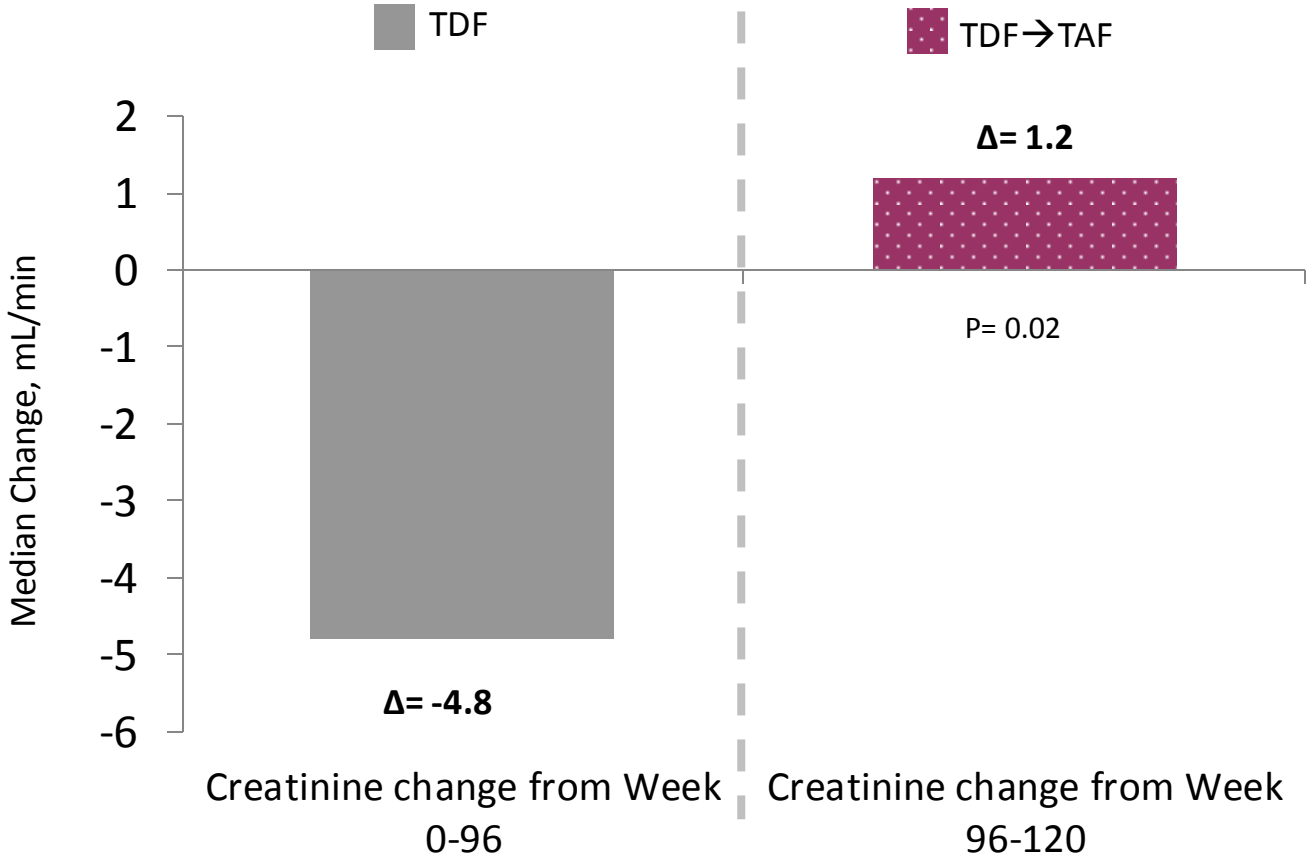
Switch from TDF to TAF: Efficacy analysis



Viral suppression was maintained and ALT normalization rate increased upon switch from TDF to TAF

Chan, EASL 2017, PS-041

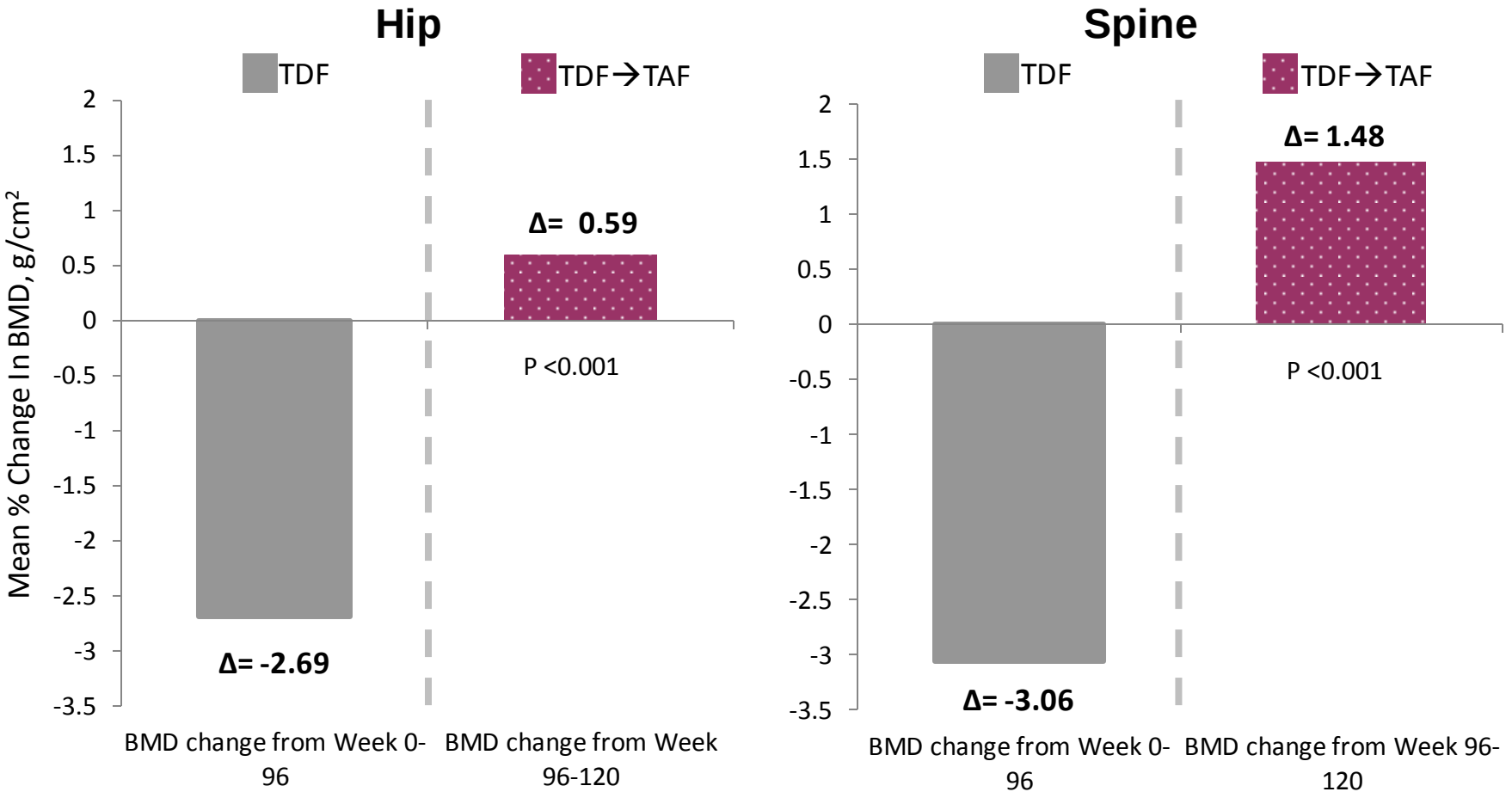
Creatinine Levels in CHB Patients Treated with TDF Switched to TAF



Significant improvement in CrCl was observed at 24 Weeks after switching from TDF to TAF

CrCl, creatinine clearance.
Chan, EASL 2017, PS-041

Changes in BMD in CHB Patients Treated with TDF Switched to TAF



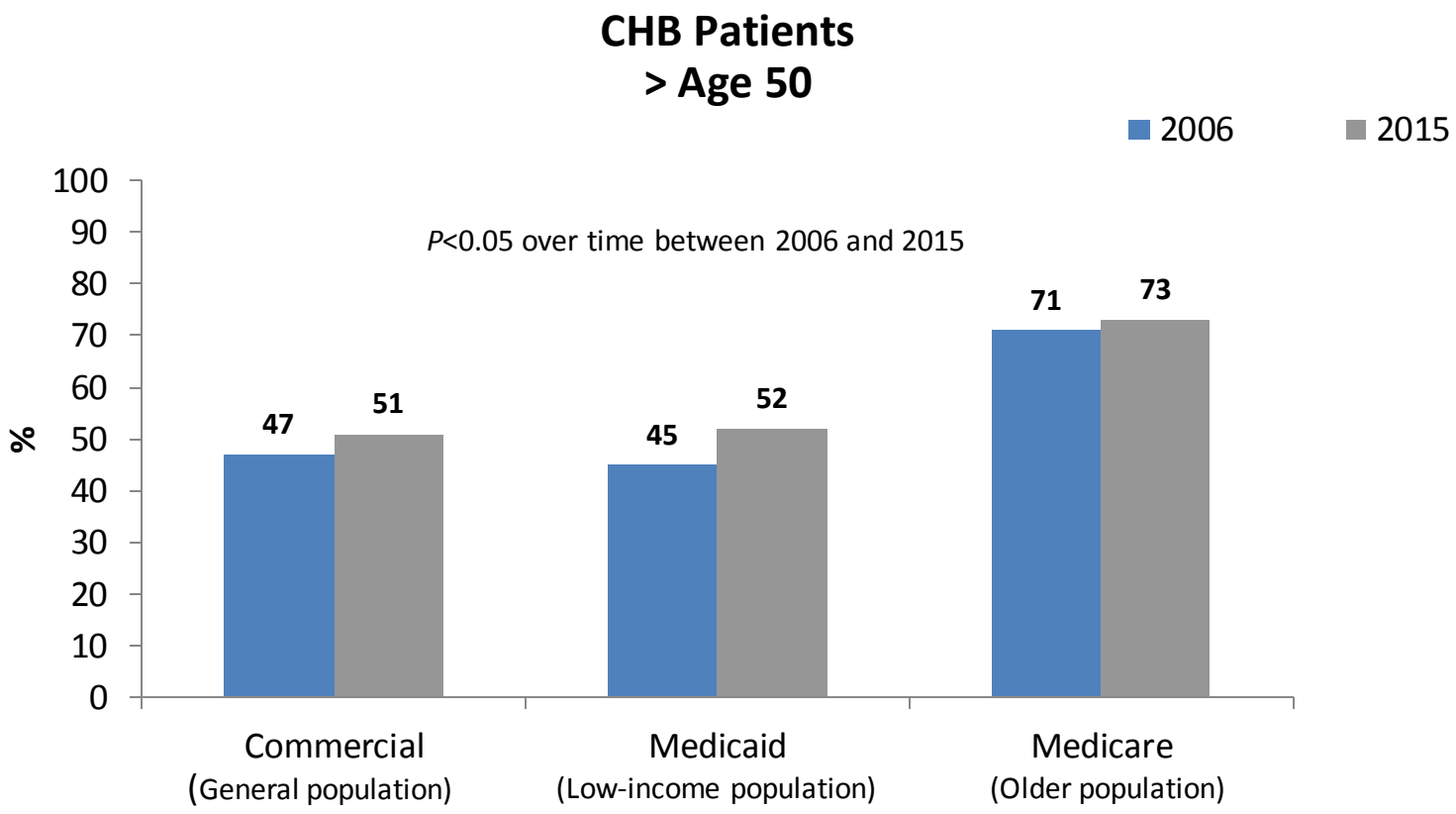
Significant improvements in hip and spine BMD were observed at Week 120 in patients who switched from TDF to TAF at 96 Weeks

Chan, EASL 2017, PS-041

Population Based Study of HBV Co-Morbidities

Age and Comorbidities in CHB Patients

Retrospective, observational study to determine prevalence of comorbidities in 44,026 CHB patients from Commercial, Medicare, and Medicaid databases from 2004–2015



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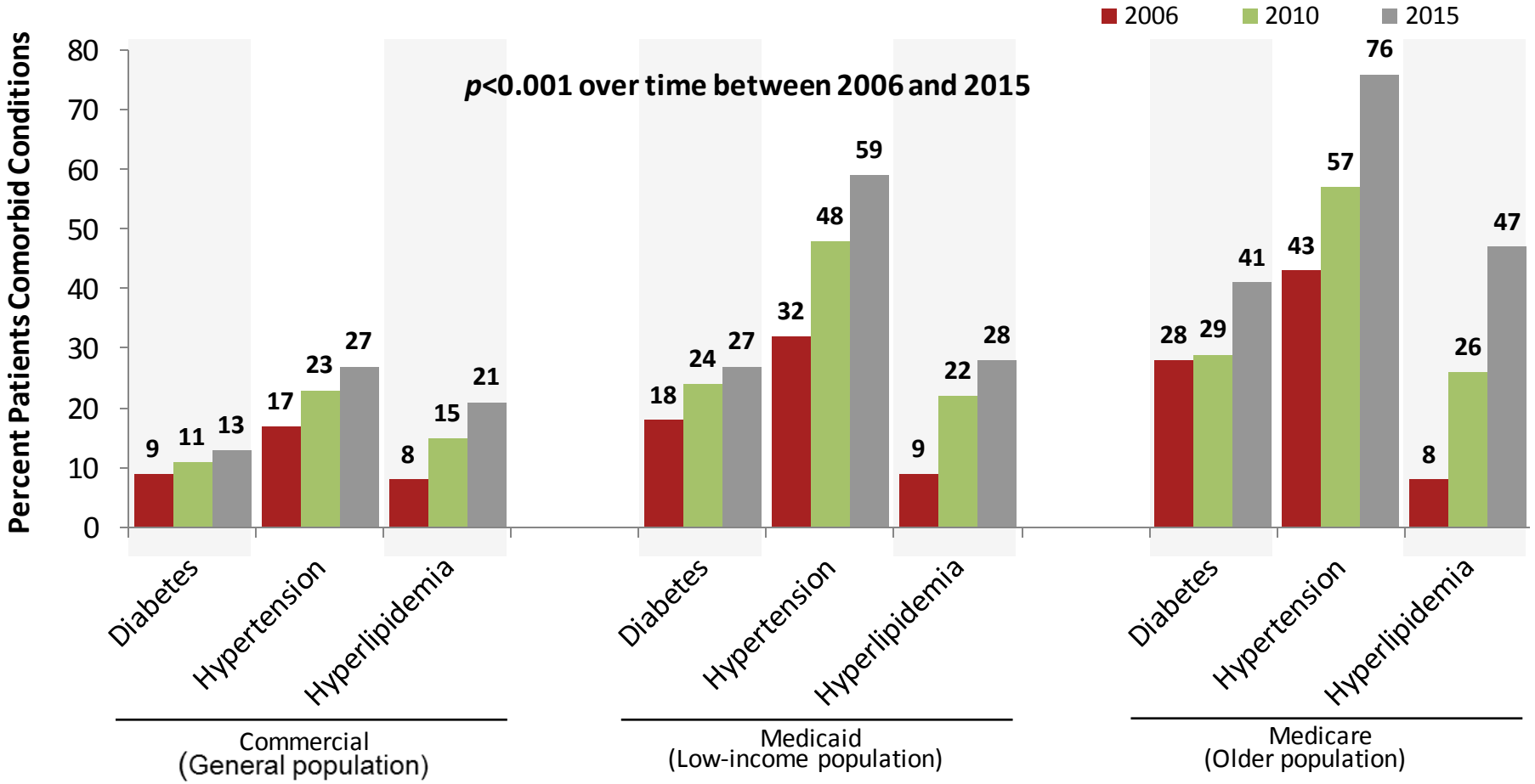
Nguyen, EASL 2017, PS-107

The proportion of CHB patients with metabolic comorbidities

Retrospective, observational study to determine prevalence of comorbidities in 44,026 CHB patients from Commercial, Medicare, and Medicaid databases from 2004–2015

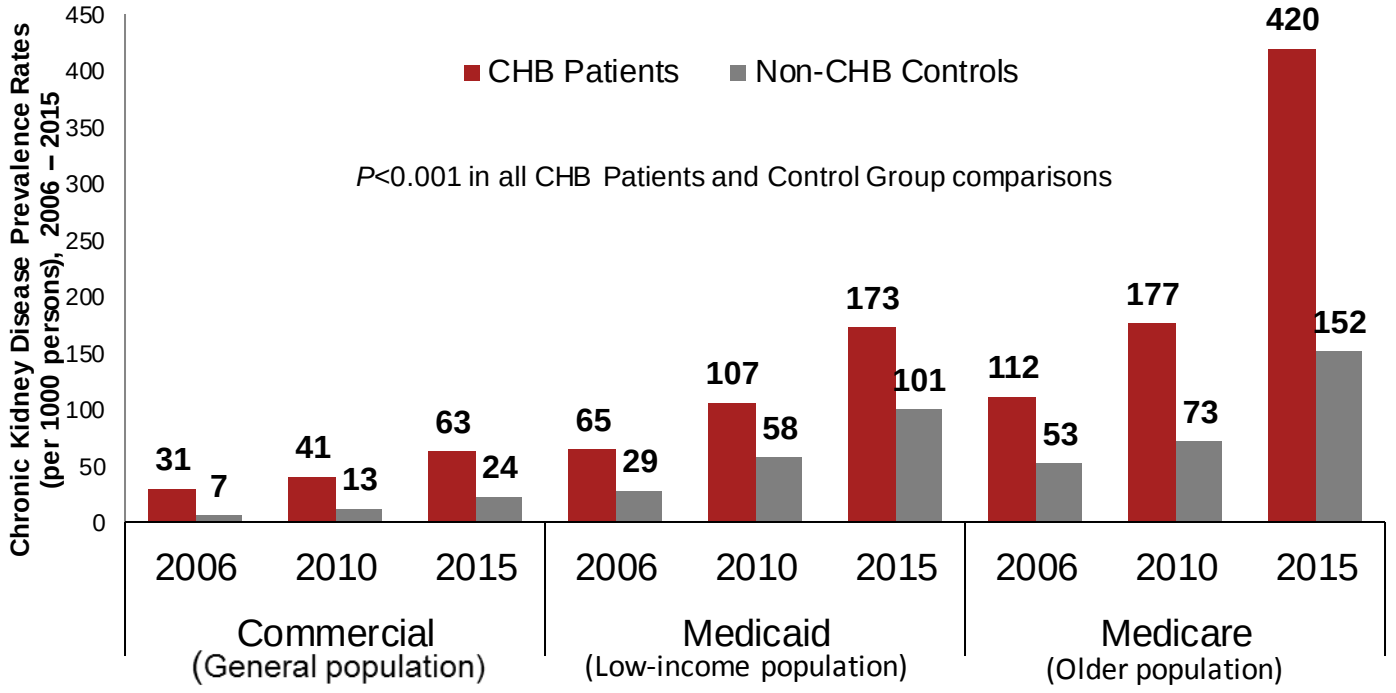


The proportion of CHB patients with metabolic comorbidities significantly increased between 2006 and 2015

Nguyen, EASL 2017, PS-107

Renal Impairment and CKD in CHB Patients

Case-control study of prevalence and incidence of CKD among 44,026 CHB patients and 121,568 non-CHB controls from Commercial, Medicare, and Medicaid databases from 2004–2015



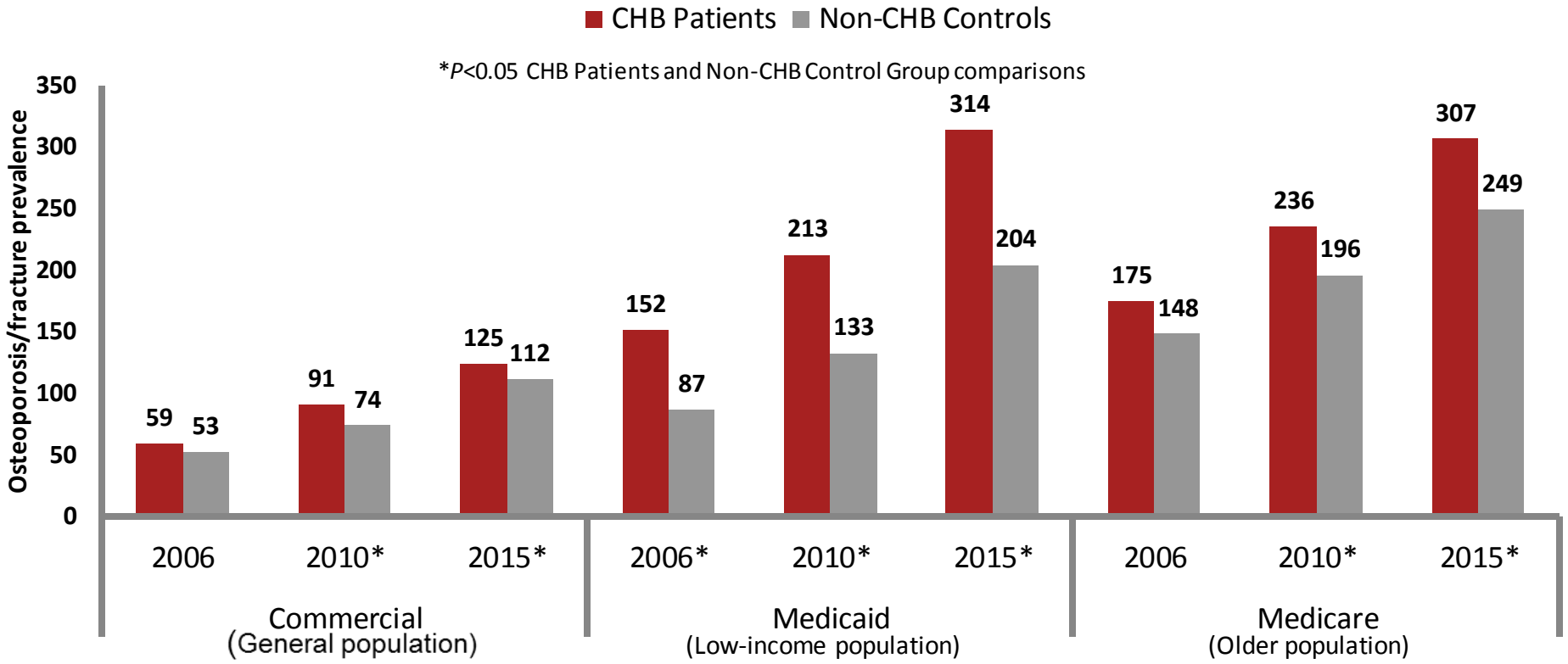
Prevalence of CKD in CHB patients has increased by 2- to 4-fold from 2006 to 2015, and the prevalence of CKD was significantly higher for CHB patients than matched non-CHB controls (*P*<0.05)

CKD was defined as chronic kidney disease stages I-IV, unspecified chronic kidney disease, end stage renal disease, hypertensive chronic kidney disease stages I-IV, hypertensive heart and chronic kidney disease stages I-IV, or dialysis

Nguyen, EASL 2017, SAT-132

Osteoporosis and Bone Fracture in CHB Patients

Case-control study of prevalence and incidence of osteoporosis and fracture among 44,026 CHB patients and 121,568 non-CHB controls from Commercial, Medicare, and Medicaid databases from 2004–2015



Prevalence of bone fracture and osteoporosis increased consistently over the past decade. In addition, the prevalence of bone fracture and osteoporosis was significantly higher for CHB patients than matched non-CHB controls for most payers and years (P<0.05).

Gordon, EASL 2017, PS-109

Hepatitis Delta

- The final frontier in viral hepatitis
- PEG-IFN therapy sub-optimal in many
- Increasing interest in this
- Prenylation inhibitor Lorafarnib featured strongly at EASL
- 2 oral presentations and one poster
- All phase 2 studies
- Seems to be promising

Limitations

- Triple therapy still requires PEG-IFN
- Need to see significantly bigger number of patients treated
- Delta relapse often occurs late and so need to see 48-96 week post treatment follow up

Summary

- Huge burden of undiagnosed HBV worldwide
- New infections should reduce with better vaccination but prevalent population will continue to die
- EASL CPG has defined new terminology and made some interesting treatment recommendations
- New agents for HBV that are modulatory of the immune system are showing early promise – but you need to pick your target cleverly
- Hepatitis delta remains a problem but there is increasing focus on this

Acknowledgements

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