Hepatitis B: nieuwe ontwikkelingen ivm behandeling

Dutch Liver Week 2018

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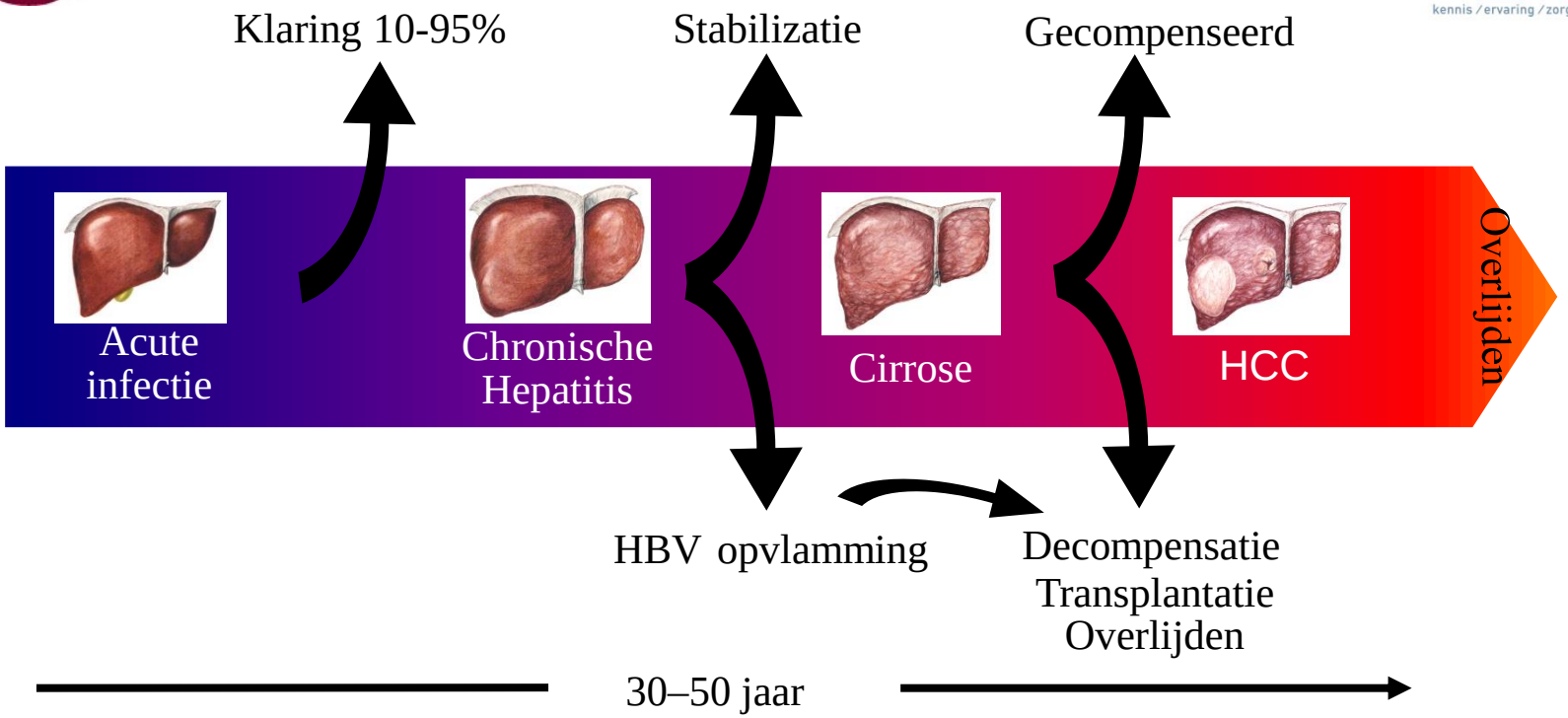
Schema vd presentatie

- Epidemiologie
- Serology
- Natural History: Clinical phases
- Antiviral treatment
- Virological response
  - TAF vs TDF
- Clinical outcome

- Specific patient groups:
  - HBeAg seroconversie stopping rule

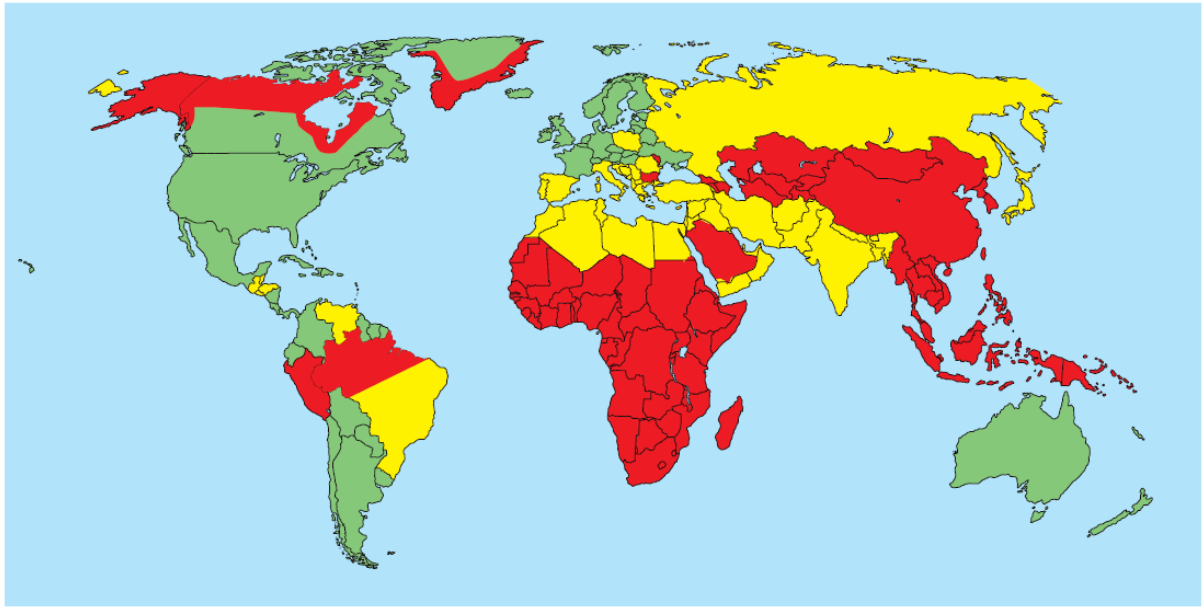
- Near future: Functional cure?

HBV silent killer



HBV: ontdekt in 1970
2 miljard anti-Hbcore +
240-360 miljoen chronisch geïnfecteerd
1 miljoen †/jaar

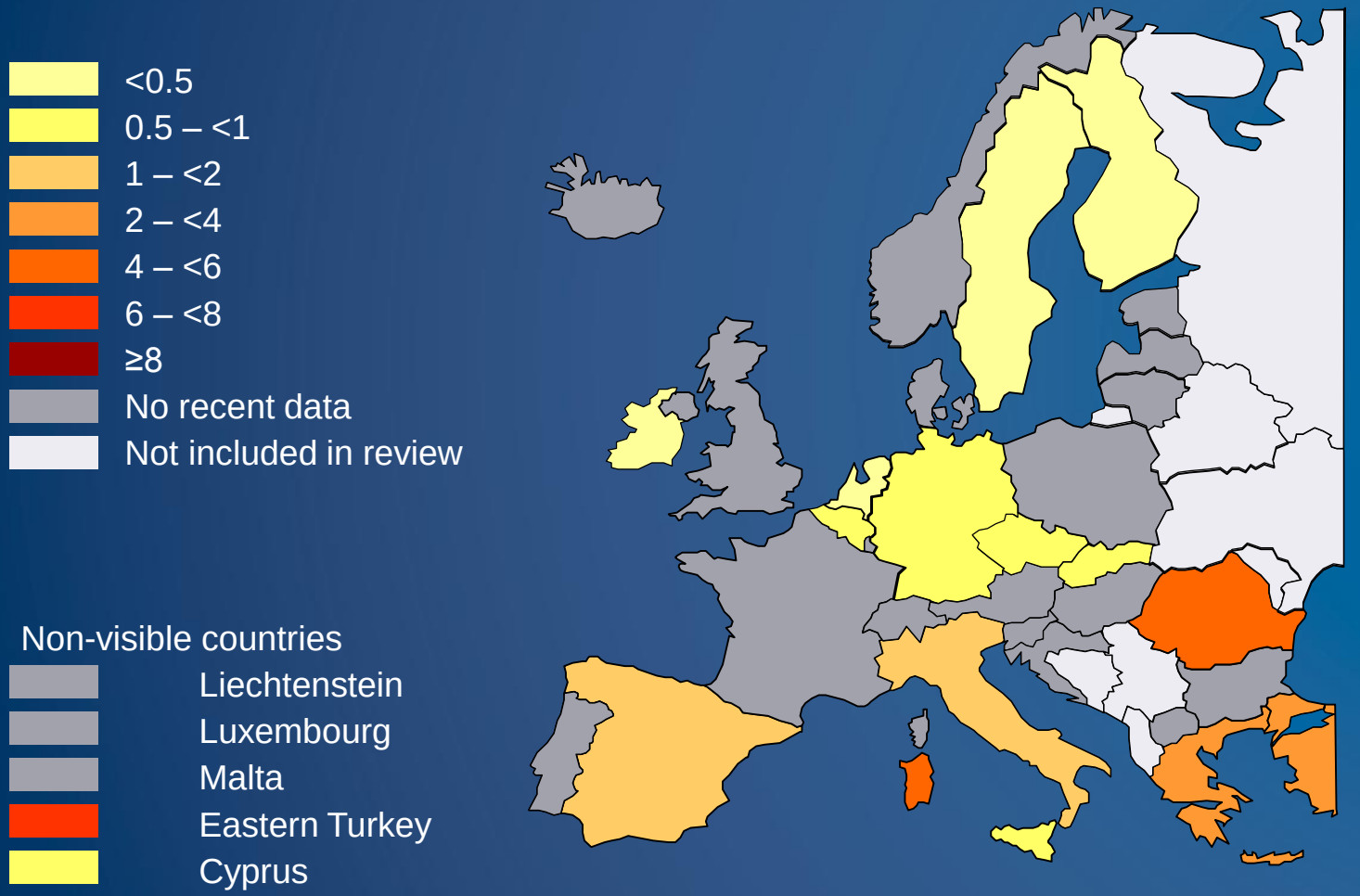
HBsAg Prevalentie



- >8%: Asia, Sub-Saharan Africa, Amazon basin, Pacific Islands
- 2-7%: Mediterranean, Russia, Eastern Europe, South Asia
- <2%: North America, Northwestern Europe, Australia

HBV

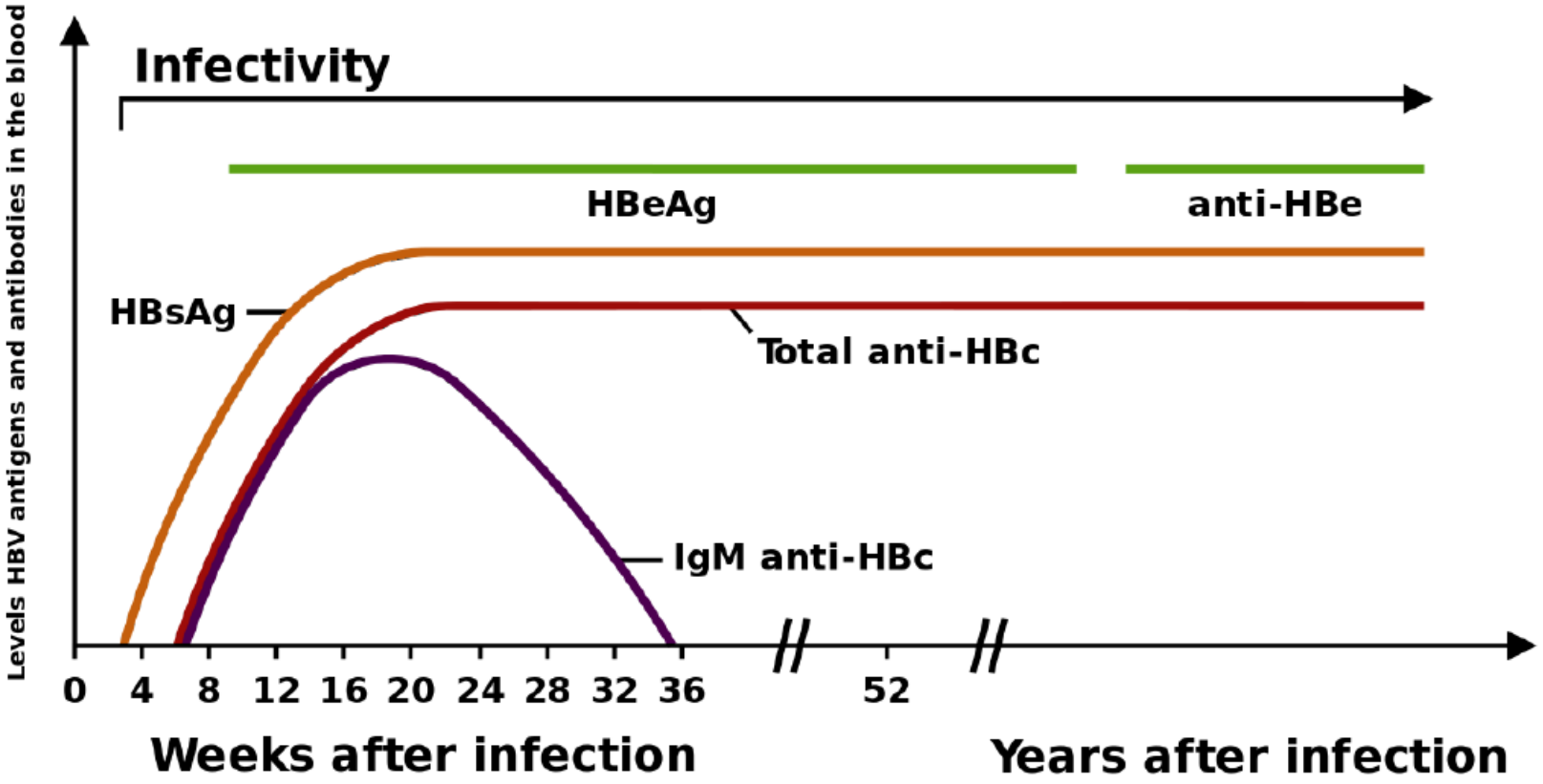
HBsAg prevalentie in Europa

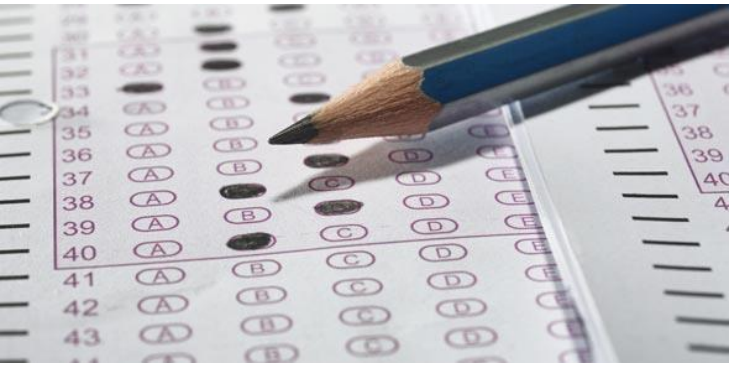


Adapted from ECDC Technical Report: Hepatitis B and C in the EU neighbourhood: prevalence, burden of disease and screening policies. September 2010. Available at http://ecdc.europa.eu/en/publications/Publications/TER_100914_Hep_B_C%20_EU_neighbourhood.pdf.

HBV Serologie

HBV DNA





Man, 51 jaar

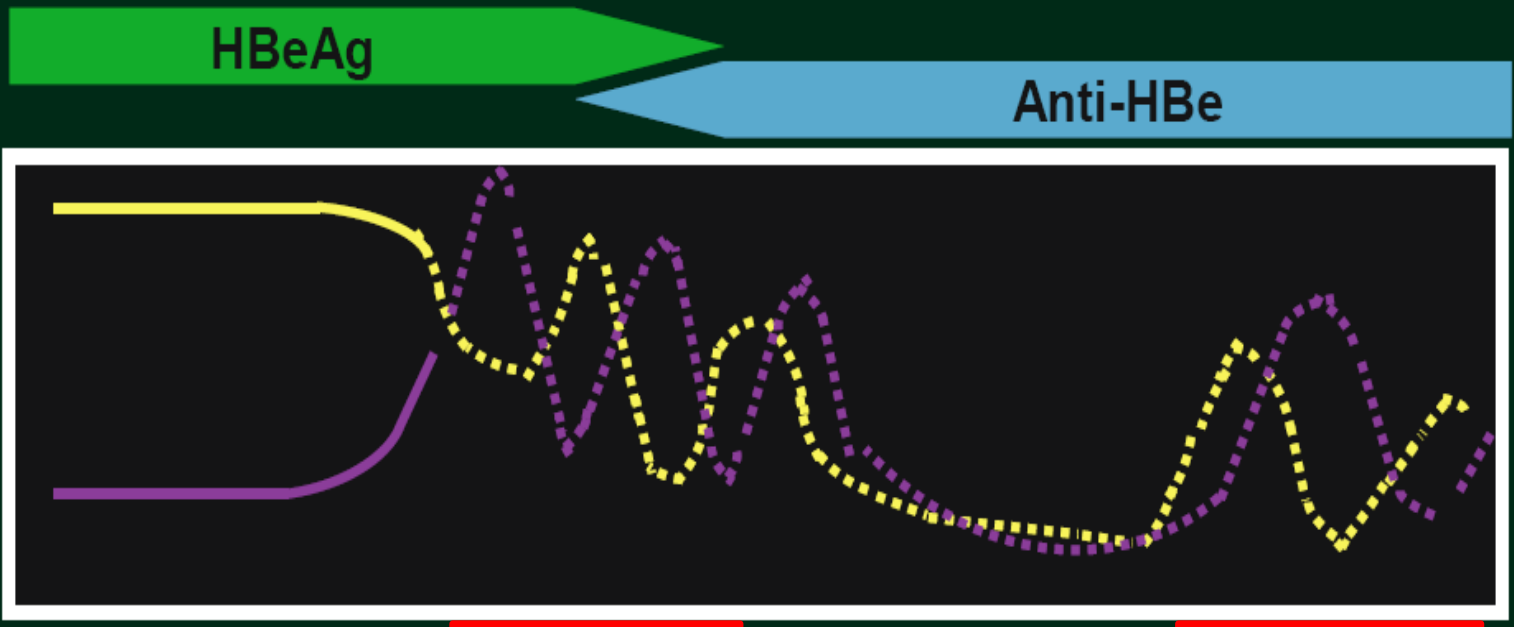
- Congolese origine
- Chronische HBV
- 2009: gedilateerde post-alcoholische cardiomyopathie, EF 15%.
  - Volledige alcoholstop
- 2011:
  - ALT 10
  - HBeAg-, anti-Hbe antilichamen+
  - HBV-DNA 2.7 log IU/ml
  - Echo: normaal
  - LBx A0, F2, geen steatose, HBsAg+ minimaal

Behandelen?

1. Neen
2. Ja

4 Phases of Chronic HBV Infection

Current Understanding of HBV Infection



Phase	Immune Tolerant	Immune Clearance	Inactive Carrier State	Reactivation
Liver	Minimal inflammation and fibrosis	Chronic active inflammation	Mild hepatitis and minimal fibrosis	Active inflammation

Optimal treatment times

Yim HJ, et al. Hepatology. 2006;43:S173-S181.

Behandelindicaties

- HBsAg > 6 maand
- ALT > ULN, 2x (minstens 1 mnd interval)
  - Niet bij cirrose (EASL, NVMDL, HBV richtsnoer)
- HBV DNA >2000 IU/ml
  - Niet bij cirrose (EASL, NVMDL, RIZIV)
- Leverbiopt toont AxF0/A0Fx (RIZIV), of Elastometrie Fx (EASL, NVMDL)

<u>Praktisch.</u>

- Evaluatie ernst leverziekte (INR, alb, bili, echo, elastometrie +/- LBx)
- Partner(s), eerste graad familieleden/huisgenoten evalueren
- Sluit andere oorzaken leverziekte uit:
  - HAV/HCV/HIV/HDV (vaccineer tegen HAV)
  - metabool, auto-immuun
  - NAFLD, alcohol

EASL CPG 2017, www.HBVrichtsnoer.nl

Man, HBeAg-, nl ALT, F2, Behandelen?

1. Neen
2. Ja

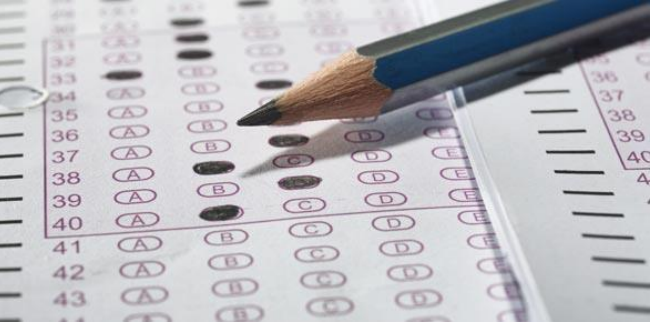
Doel van behandeling?

HBV DNA ~ HCC en fibrose /cirrose progressie

- Virologische suppressie
  - HBV DNA ondetecteerbaar
  - HBeAg seroconversie → STOP behandeling?
  - HBsAg klaring/seroconversie= “klaring” → STOP

- Lange termijn klinische doelstellingen:
  - Voorkomen van leverdecompensatie
  - Voorkomen van progressie naar cirrose en HCC
  - Overleving verlengen

Fung S, Lok ASF. Clinical Gastroenterol Hepatol. 2004;2(10):839–848



Man, 52 jaar

- 2012: uitwerking voor harttransplantatie
  - ALT 15
  - Creatinine 1,27 mg/dL, eGFR 59 ml/min
  - HBeAg-, anti-HBe antilichamen+
  - HBV DNA 2,1 log IU/mL
  - Echo abdomen: normaal

- Groen licht van cardiologen en chirurgen

Behandelen?

1. Neen
2. Ja met pegIFN
3. Ja met Nucleo(s)tide Analogen

Extra Behandelindicaties (EASL, HBV richtsnoer)

- >F2 and HBV DNA >2000 IU/mL (even if ALT nl)
- Family history of HCC or cirrhosis
- Extrahepatic manifestations (vasculitis, purpura, GN, cryoglobulinemia)
- HBeAg+ HBV > 30 yrs, with persistent nALT

- Pregnancy: HBV DNA>200,000 IU/mL (qHBsAg>4log IU/mL)
  - TDF from 3e trim – 12 wks postpartum

- Immuunsuppressie:
  - HBsAg+: NA to prevent flare ( :LMV in SOTx/BMTx)
  - HBsAg-, anti-HBcAb+: NA if B cell depletion or BMTx

SOT and HBsAg+

untreated HBsAg+ HTx recipients (n=345)

† liver failure 27%

F3-F4 in 53%

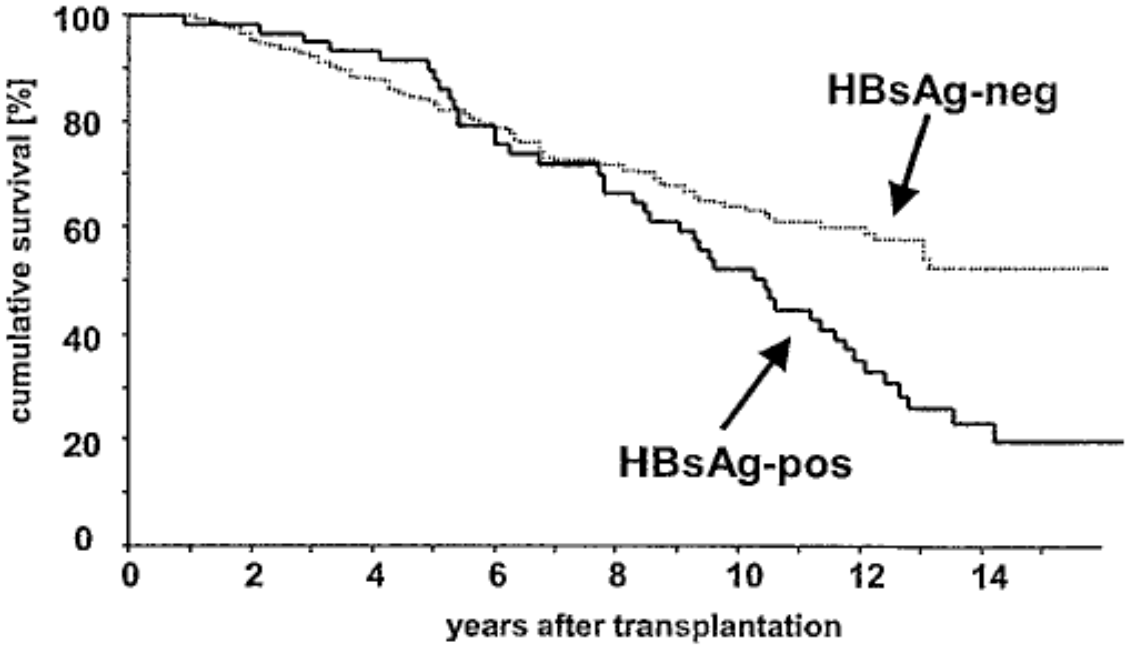


Figure 1. Survival curves of untreated HBsAg-positive (n = 58) and HBsAg-negative (n = 271) heart transplant recipients.

GASTROENTEROLOGY Vol. 120, No. 5

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UZA

kennis / ervaring / zorg

Behandelen?

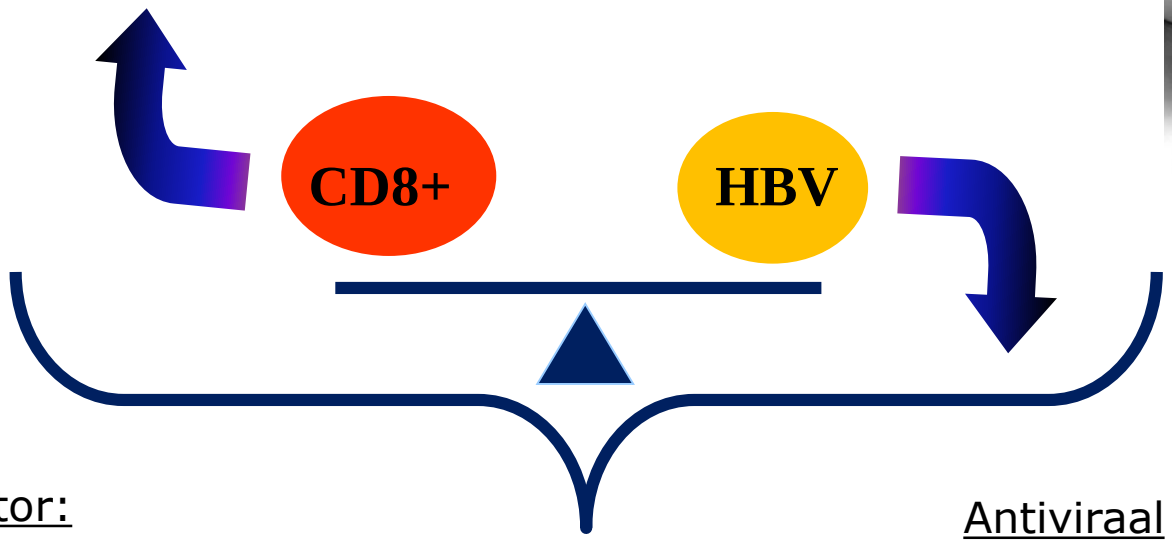
1. Neen
2. Ja met pegIFN
3. Ja met Nucleo(s)tide Analogen → Lamivudine

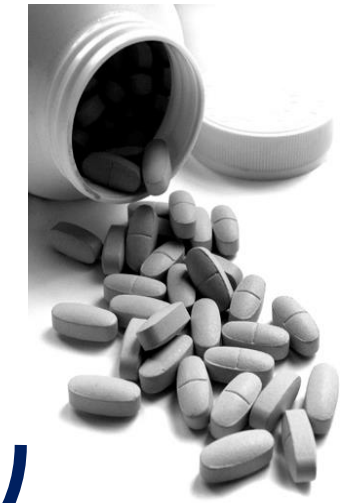
HBV Antivirale middelen

(Peg)interferon

Nucleos(t)ide analogen

Behandelopties





Immuno-modulator:
IFNα
Peg IFN 180 ug/wk SC
48 weken

combinaties?

Antiviraal
Lamivudine
Adefovir
Entecavir 0,5 – 1 mg dd
Emtricitabine
Telbivudine
TAF ↔ **Tenofovir 245 mg dd**

LTFU post pegIFN

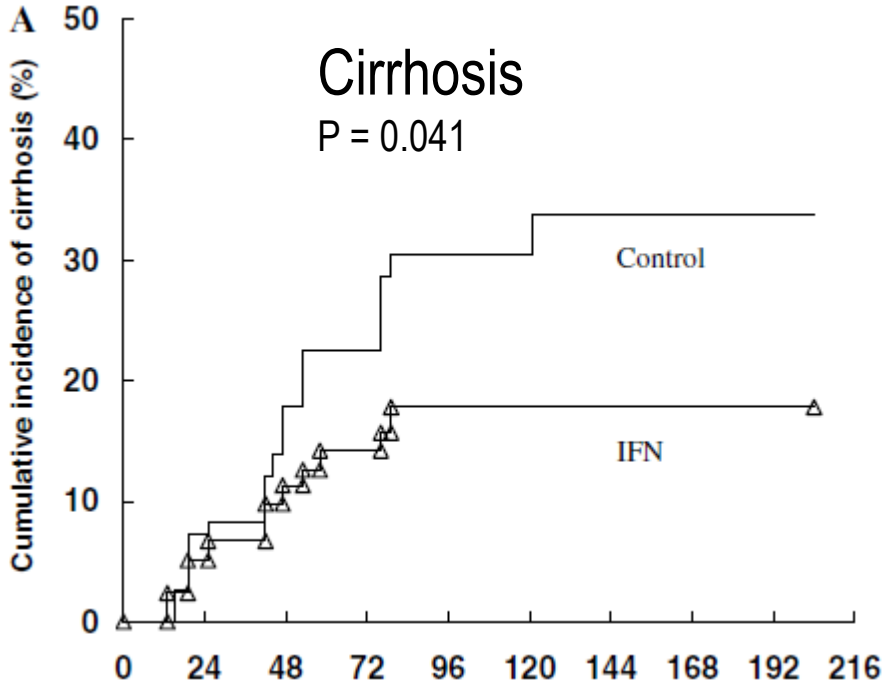
- Global prospective pegIFN study
- N=1200 (HBeAg+ and HBeAg-)
- Combined reponse:
  - HBV DNA < 2000 IU/ml + ALT nl
  - @ year 3: 15-20%

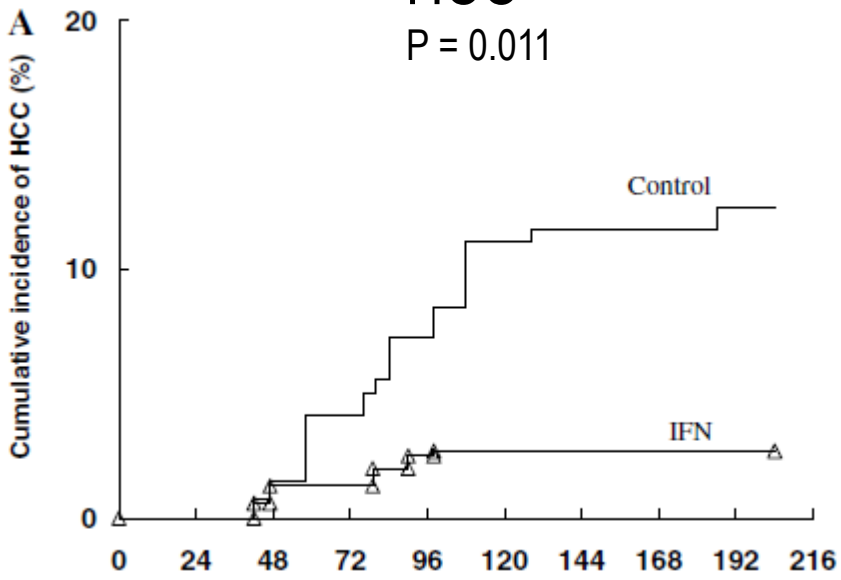
- HBsAg loss: low
  - 2% (HBeAg+)
  - 5% (HBeAg-)

Marcellin et al. EASL 2016 #137

LTFU na pegIFN: Klinisch

Cirrose ↓ na IFN (na 5 jaar)
HCC ↓ na IFN (na 5 jaar)
PS: effect vnl in HBeAg- (ook bij spontane HBeAg-)





N Engl J Med 1996;334:1422-7.; J Hepatol 2007; 46: 45–52; Am J Gastroenterol 1998;93:896-900

Peginterferon bijwerkingen

Dose reduction	n (%)	Early discontinuation	n (%)
Neutropenia	36 (52)	Psychiatric	10 (36)
Thrombocytopenia	7 (10)	Flu like syndrome	3 (11)
Leucopenia	2 (3)	Patient lost to follow-up	4 (14)
Combined hematological	6 (8)	Anemia	1 (4)
Flu like syndrome	7 (10)	Neutropenia	1 (4)
Psychiatric	4 (6)	Thrombocytopenia	1 (4)
Fatigue	2 (3)	Flare	1 (4)
Local reaction	1 (1)	Seizures	1 (4)
Anorexia	1 (1)	Acute pancreatitis	1 (4)
Myalgia	1 (1)	Decompensated liver disease	1 (4)
Other	2 (3)	Pneumonia	1 (4)
		Other	3 (11)

van Zonneveld, AP&T 2005

Peginterferon

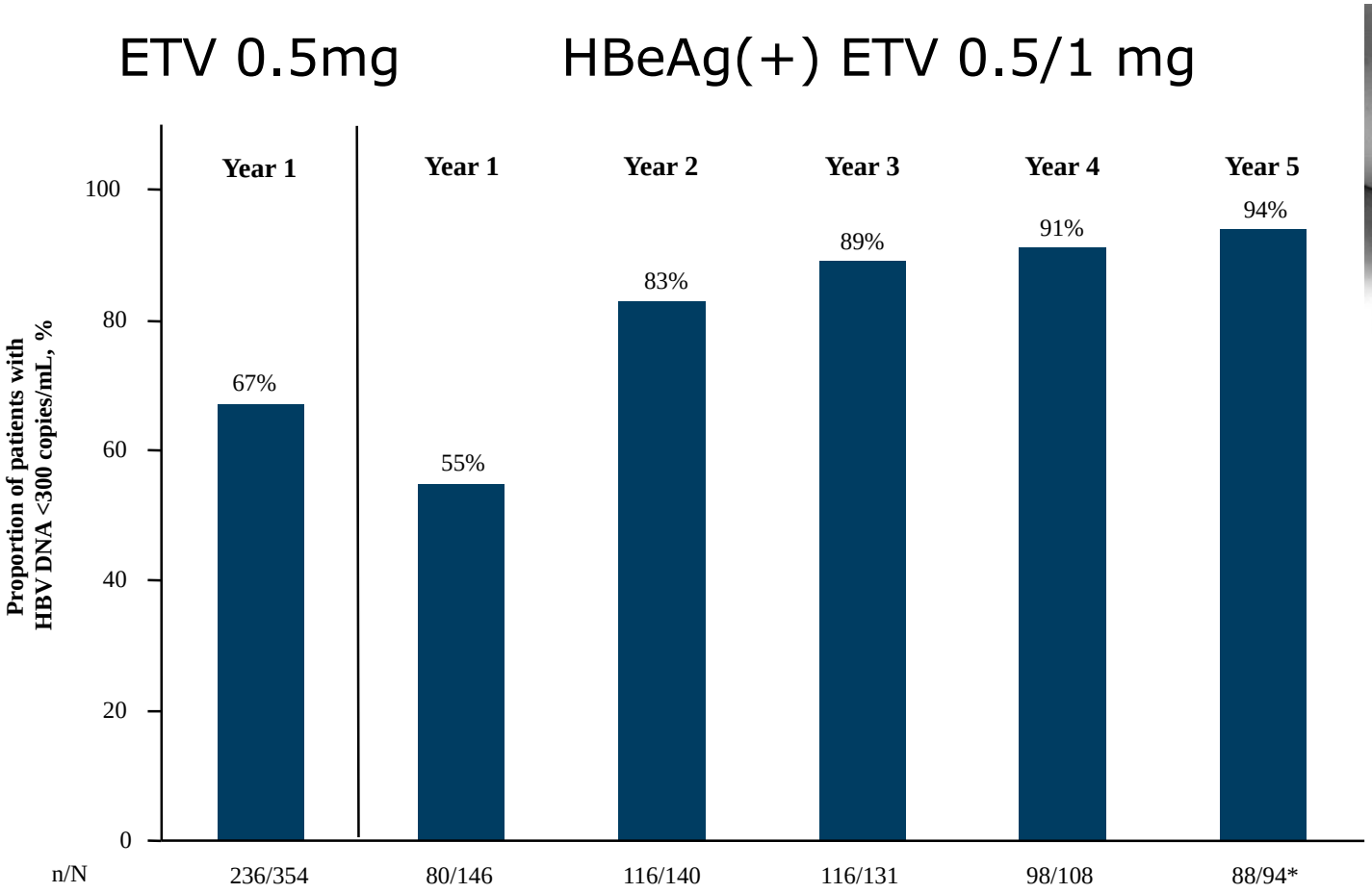
Voordelen:

- Tijdelijk (1 jr)
- HBeAg seroconversie
- HBsAg seroconversion
- Geen antivirale resistentie

Nadelen:

- Injecties
- Bijwerkingen
- Contra-indicatie:
  - LTX
  - Gedecompenseerde cirrose

Entecavir Respons: Virologie



Chang TT, et al. Hepatology 2010; 51:422-430. 2. Tenney DJ, et al. Hepatology 2009; 49:1503-1514.

Tenofovir Respons: Virologie

HBeAg loss/seroconversion: 55% /40% (na 7 jr)

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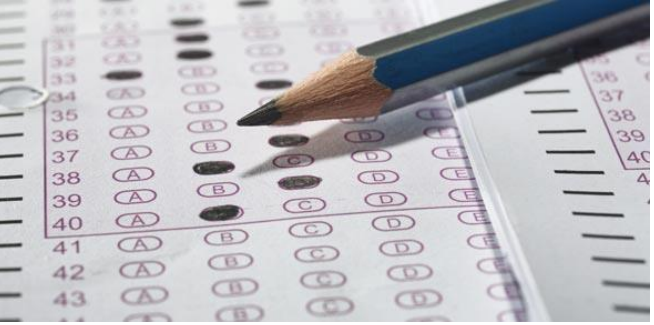
Marcellin et al. AASLD 2013, Washington, DC. Poster #926
Data on file.

[1] By Kaplan-Meier analysis.



Man, HTx, 56 jaar

- 2013-2015: HBV DNA <det limit

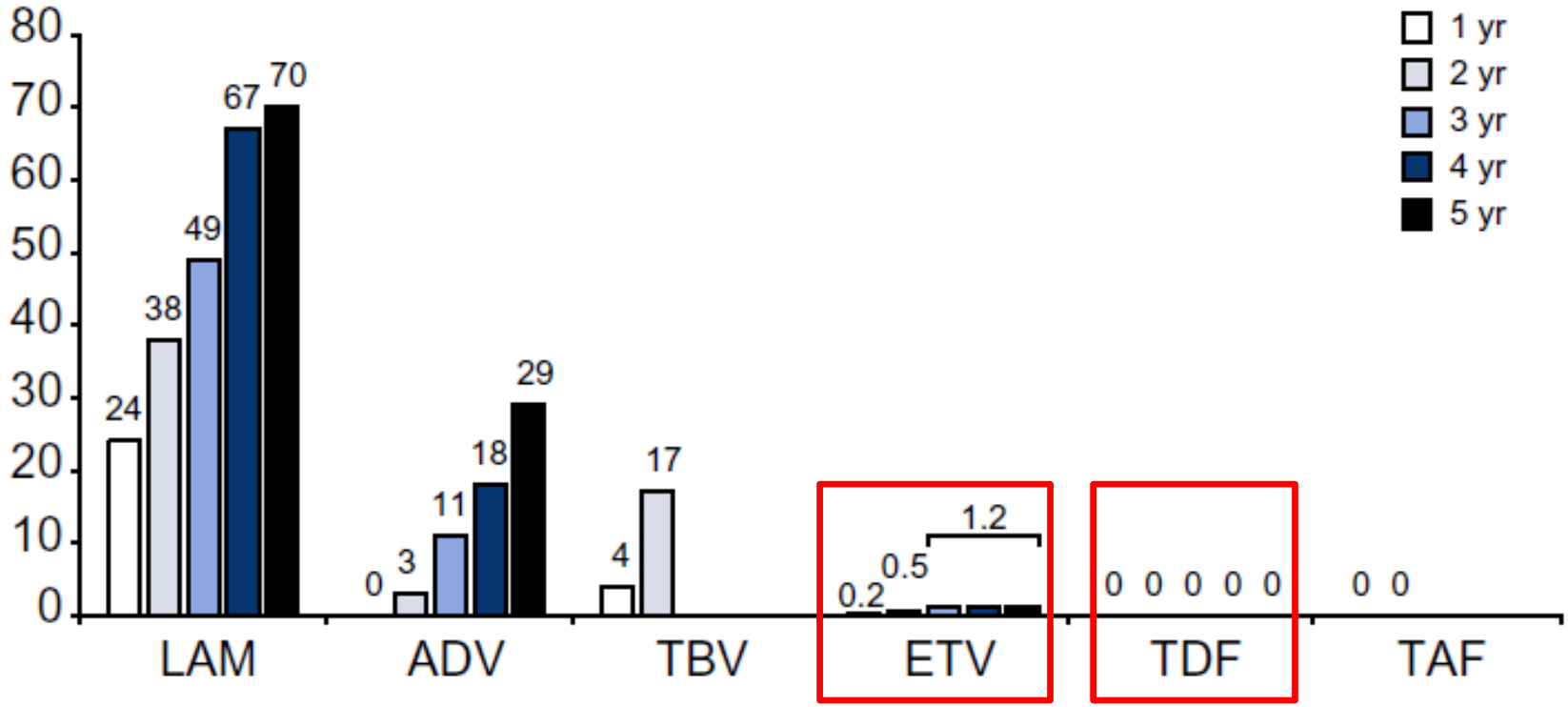
- 9/2016:
  - ALT 20, HBeAg-
  - HBV DNA 3.10 log IU/mL; 1244.5 IU/mL
  - Creatinine 1,55 mg/dL; eGFR 49 mL/min

- 12/2016:
  - ALT 19, HBeAg-
  - HBV DNA 4.19 log IU/mL; 15 310.9 IU/ml
  - Creatinine 1,58mg/dL; eGFR 48 mL/min
  - aFP 4,3
  - Echo abdomen: normaal

Beleid?

1. Aanpassen dosis lamivudine
2. Resistentie analyse en wacht
3. Resistentie analyse en switch naar entecavir
4. Resistentie analyse en switch naar tenofovir (TDF of TAF)

Cumulatieve resistentie Nucleos(t)ide Analogen (NA)



EASL Guidelines HBV, 2017

NA resistance, FU case

- TAF 1 dd opgestart

- HBV genotype E
- HBV polymerase: L180M, M204V

→ Resistent aan LAM en ETV

Table 6. Cross-resistance data for the most frequent resistant HBV variants.

HBV variant	LAM	LDT	ETV	ADV	TDF/TAF*
Wild-type	S	S	S	S	S
M204V	R	S	I	I	S
M204I	R	R	I	I	S
L180M + M204V	R	R	I	I	S
A181T/V	I	I	S	R	I
N236T	S	S	S	R	I
L180M + M204V/I ± I169T ± V173L ± M250V	R	R	R	S	S
L180M + M204V/I ± T184G ± S202I/G	R	R	R	S	S

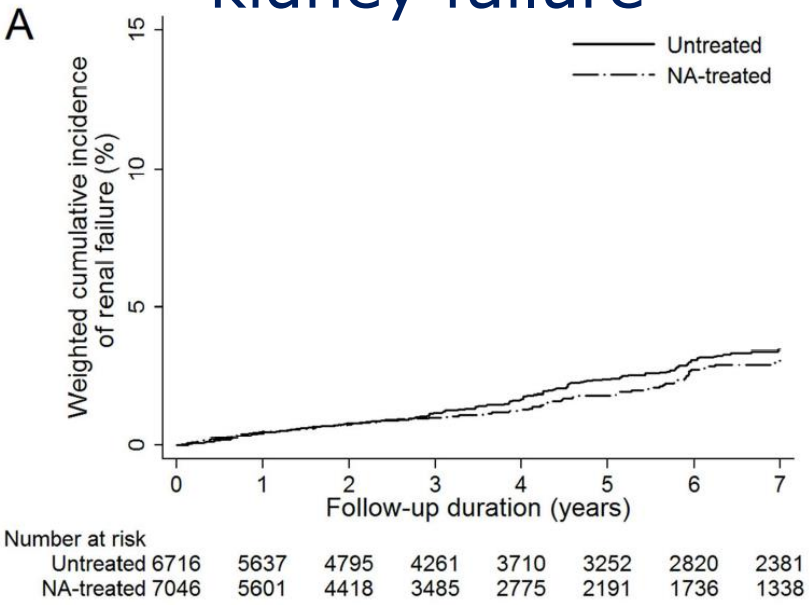
The amino acid substitution profiles are shown in the left column and the level of susceptibility is given for each drug: S (sensitive), I (intermediate/reduced susceptibility), R (resistant).
ETV, entecavir; TDF, tenofovir disoproxil fumarate; TAF, tenofovir alafenamide; LAM, lamivudine; ADV, adefovir.
* *In vitro* data for tenofovir, *in vivo* data for TDF, no clinical data for TAF.

Bijwerkingen Nucs Analogues

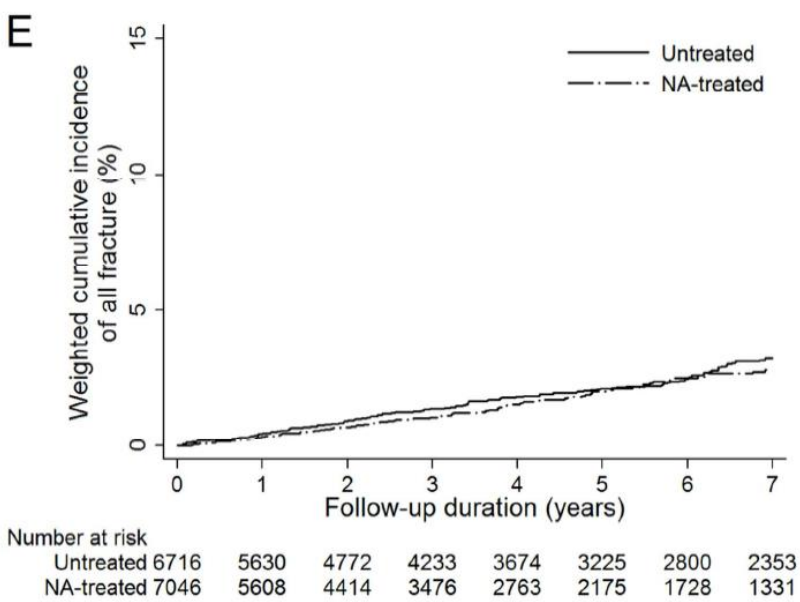
- In principe geen
- TDF:
  - Hypofosfatemie
  - Renale tubulopathie? In HIV (HAART-PI boosted)
  - Osteomalacie?
- ETV
  - Lactaat acidose? Bij gedecompenseerde cirrose

Nucs: Kidney and Bone ?

kidney failure



total fractures



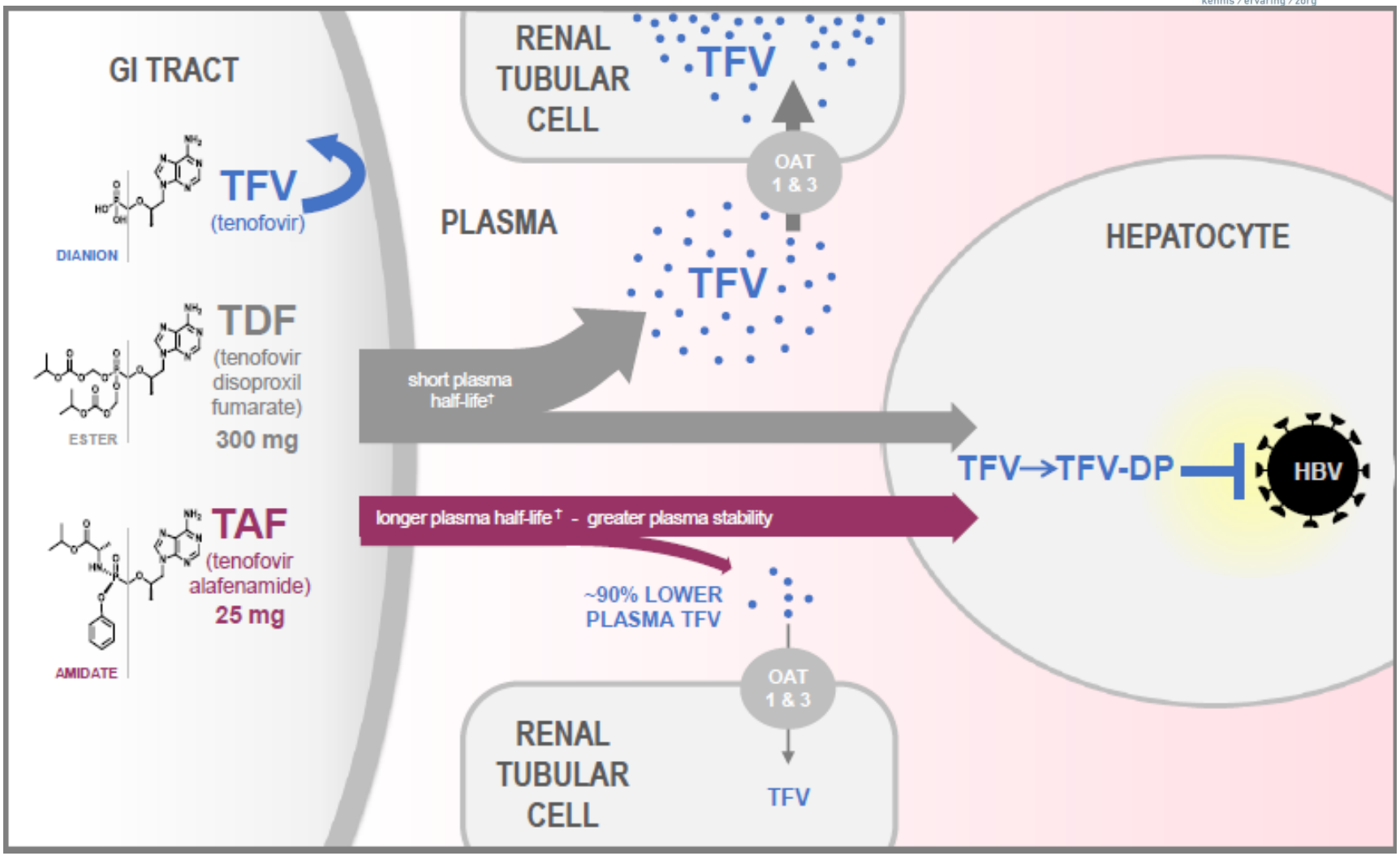
Nucleotide vs Nucleoside analogues:

Higher risk of hip fracture (HR 5.69, P=0.001)

→ Absolute risk still very low, 0.7% in 3 years vs 0.2% in untreated

Wong G-L et al. Hepatology 2015. **N=53500 HBV** 3-year cumulative risk analysis

TAF vs TDF



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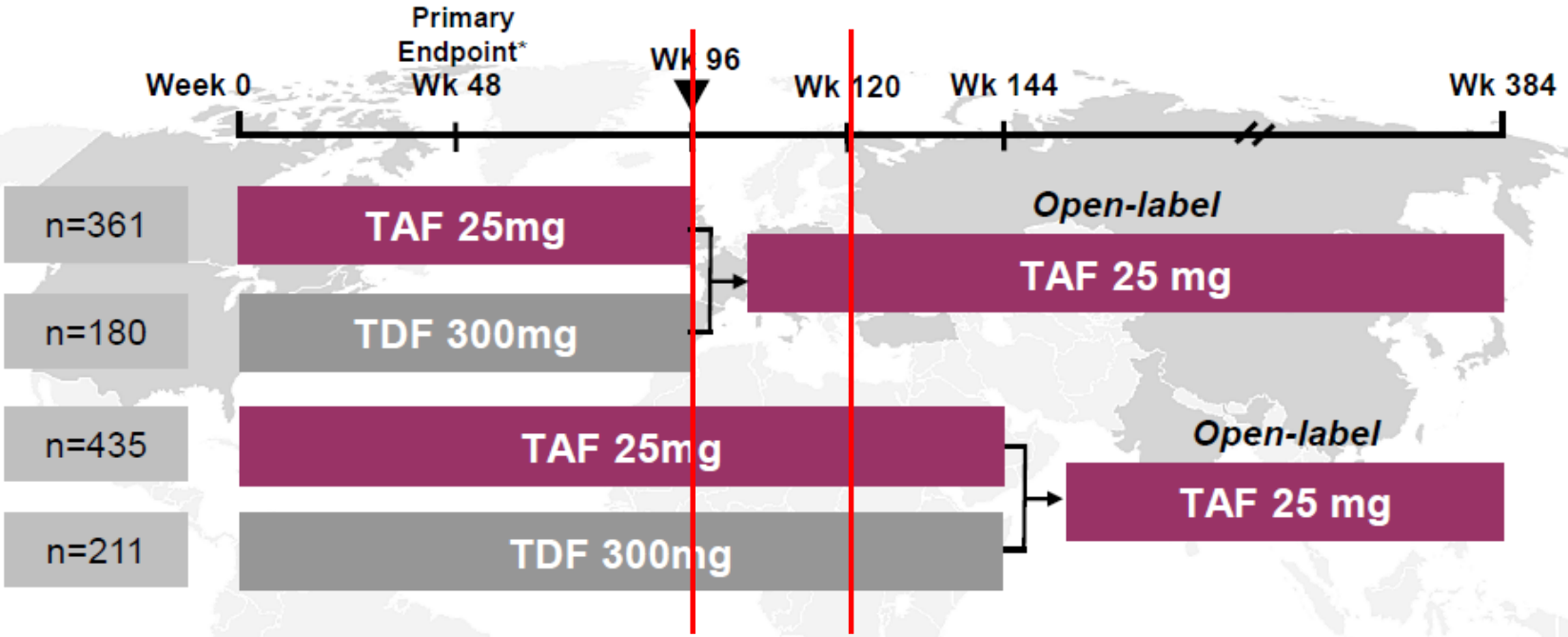
Buti et al. Chan et al Lancet Gastro&Hep 2016

TAF registration trials



Two Phase 3, randomised, double-blind, active-controlled trials

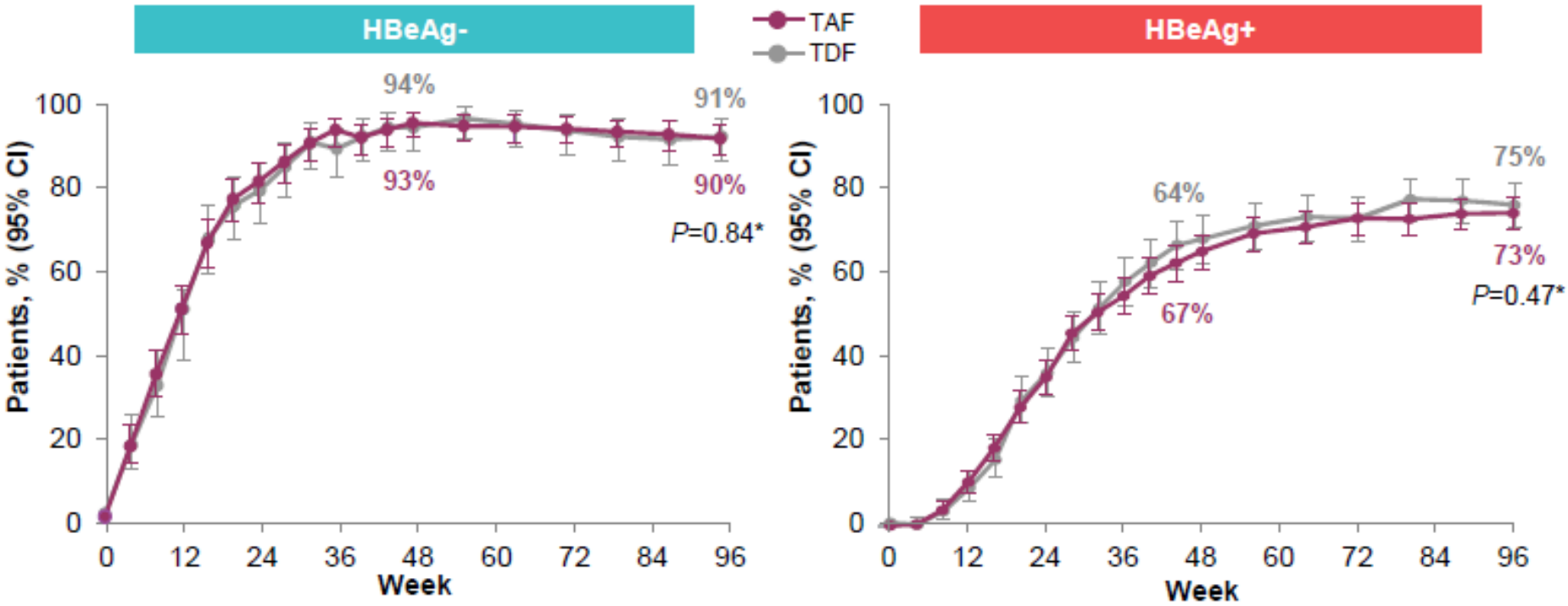
- Study 108 (N=425): HBeAg-negative patients
- Study 110 (N=873): HBeAg-positive patients

eGFR > 50ml/min

- virology
- renal and bone safety

Buti et al. Chan et al Lancet Gastro&Hep 2016

TAF vs TDF: Virology

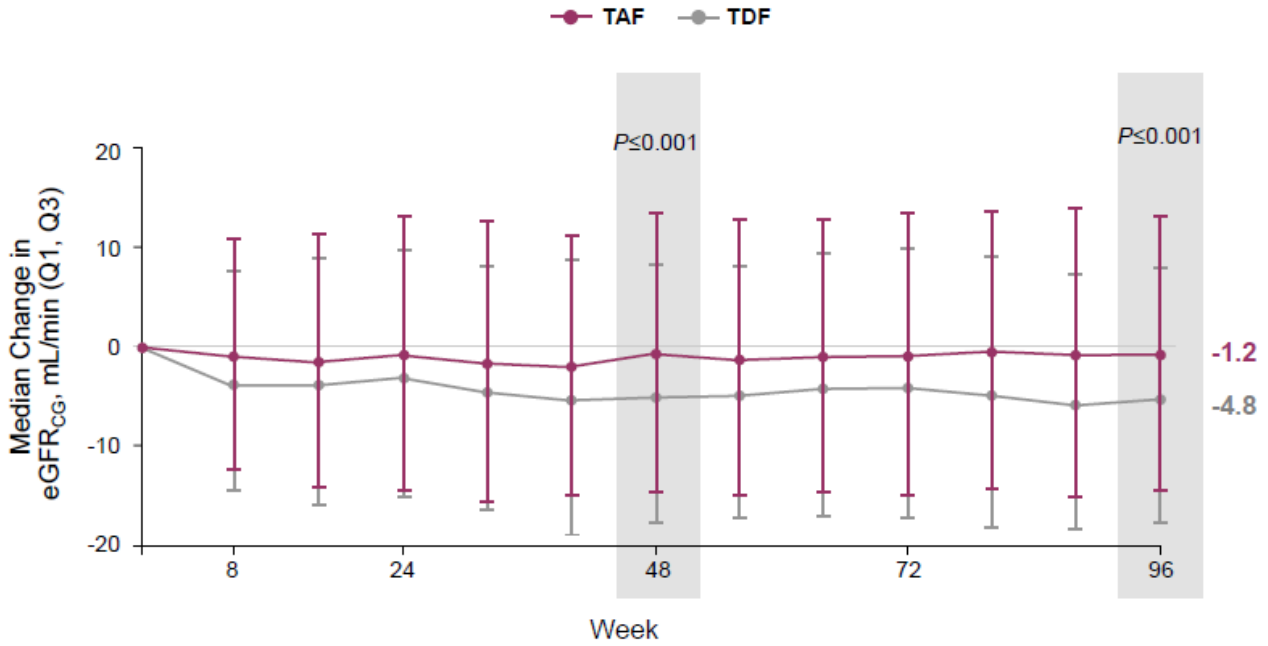


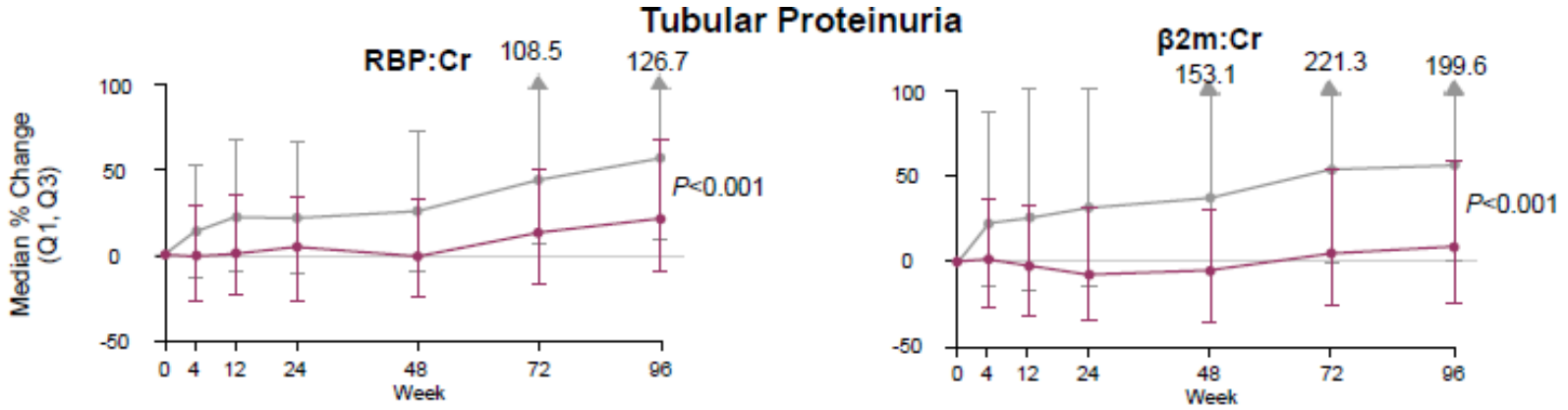
HBeAg seroconversion: 8 vs 10%

HBsAg loss: <1% vs <1%

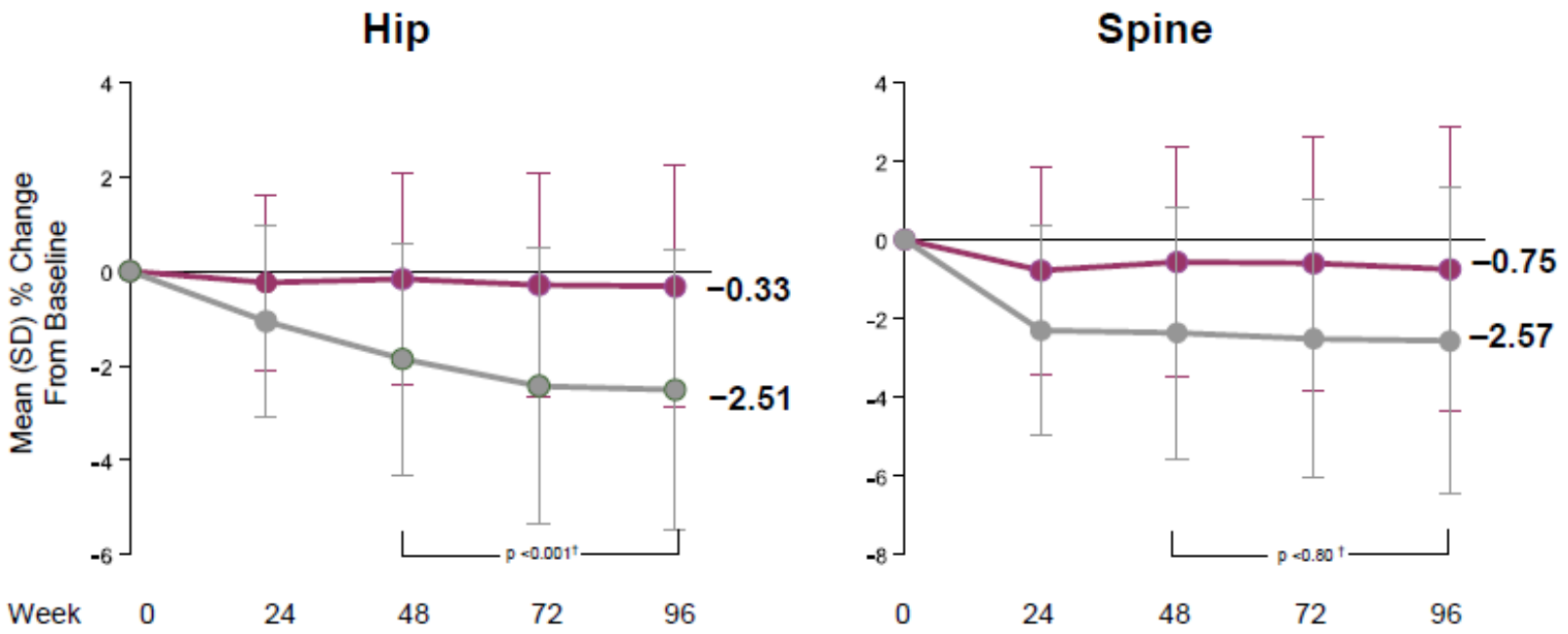
Buti et al. Chan et al Lancet Gastro&Hep 2016

TAF vs TDF: Renal safety

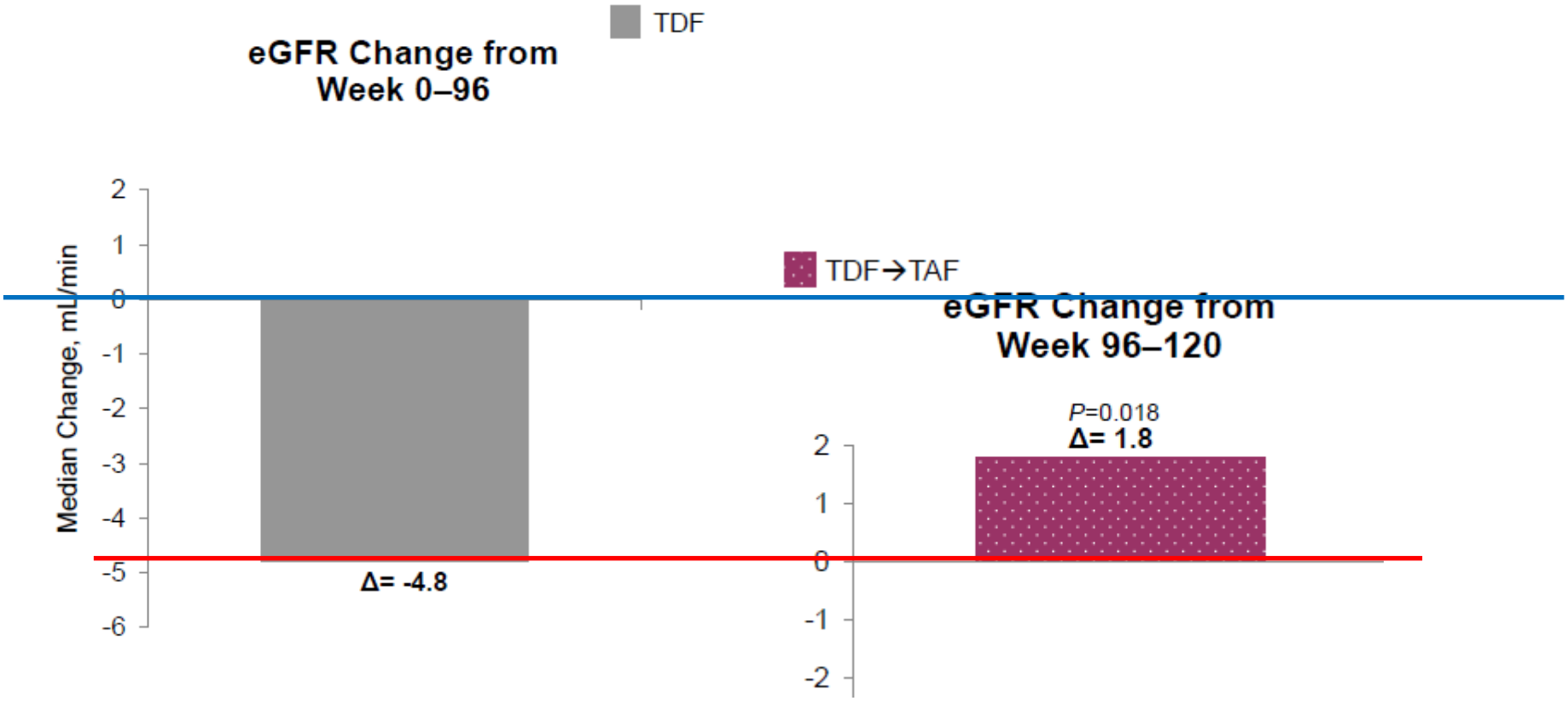




TAF vs TDF: Bone safety

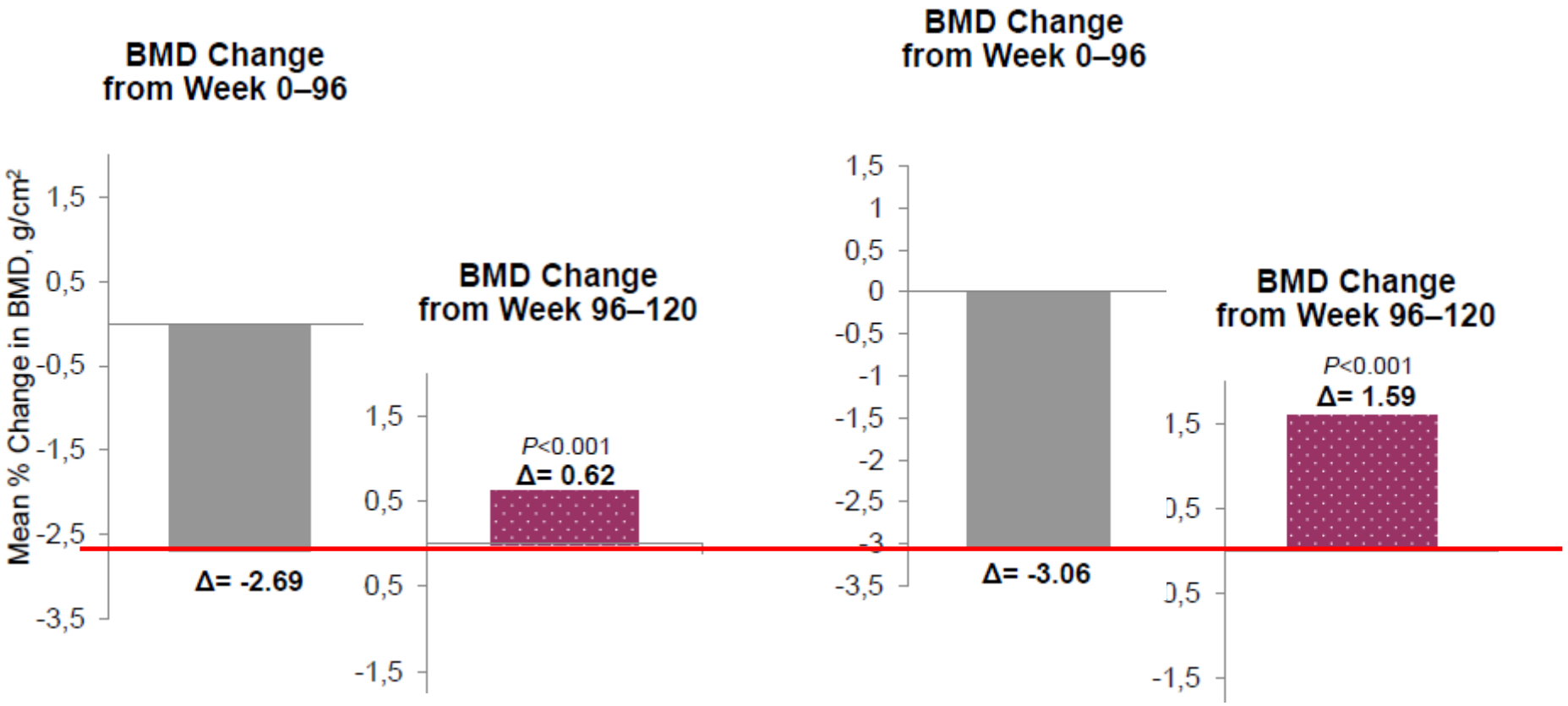


TDF-TAF switch 24wks



TDF-TAF switch 24wks

HIP **SPINE**

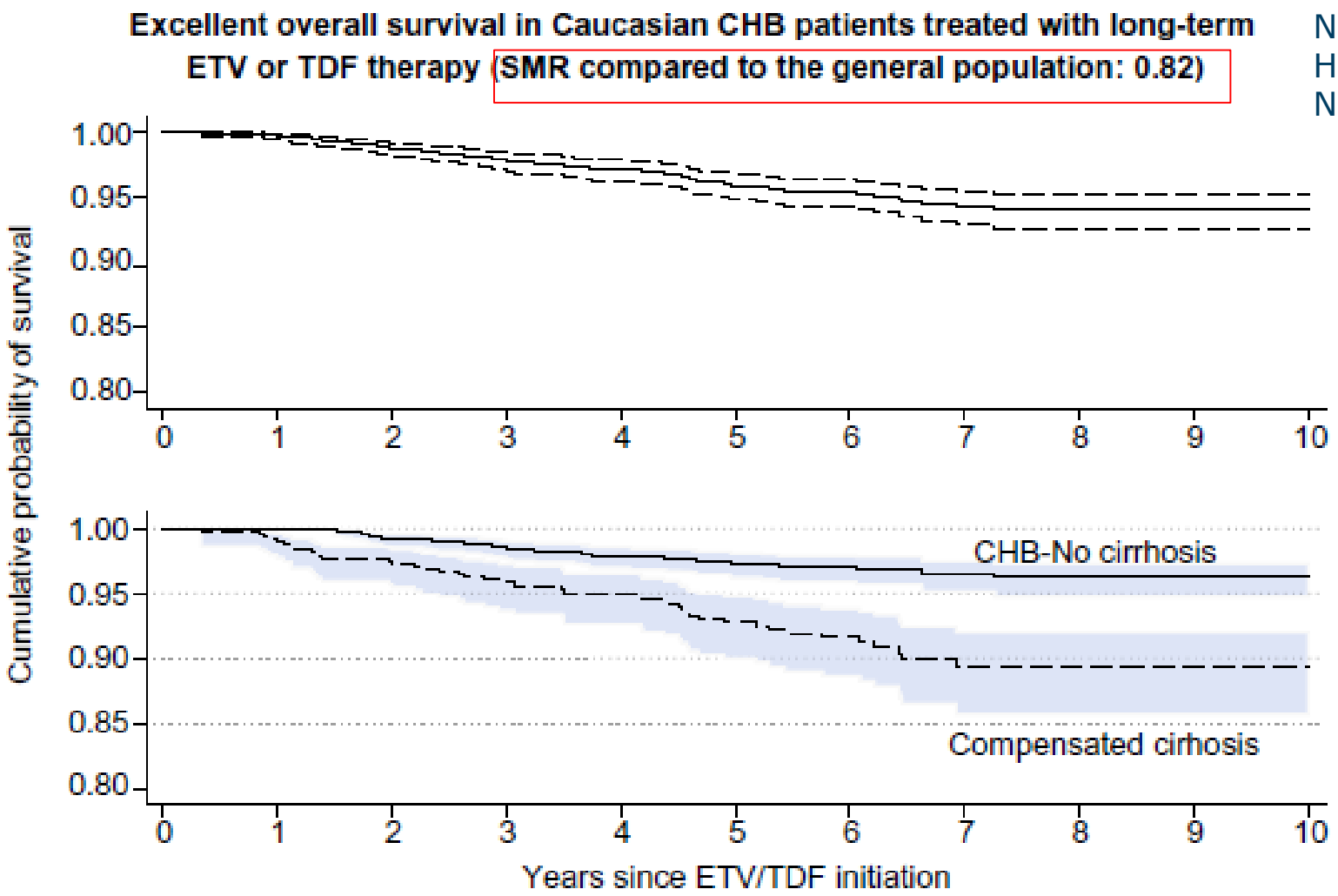


TAF vs TDF: conclusion

- Antiviral activity:
  - similar
- Creatinin clearance:
  - TDF: Early, maintained < 3ml/min
- Renal tubulopathy of TDF:
  - Objective
  - Subclinical/minimal
- BMD:
  - TDF: Early, maintained < 2%

HBV behandeling met NA: harde eindpunten

-
-
-
-

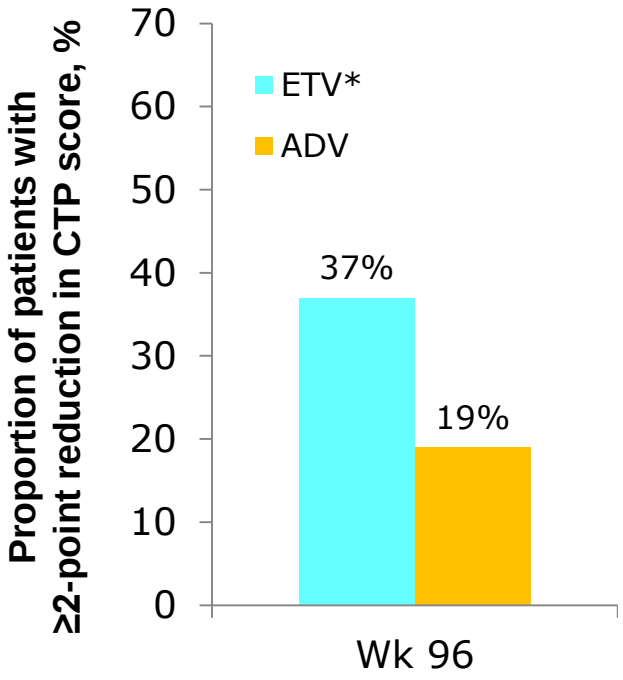


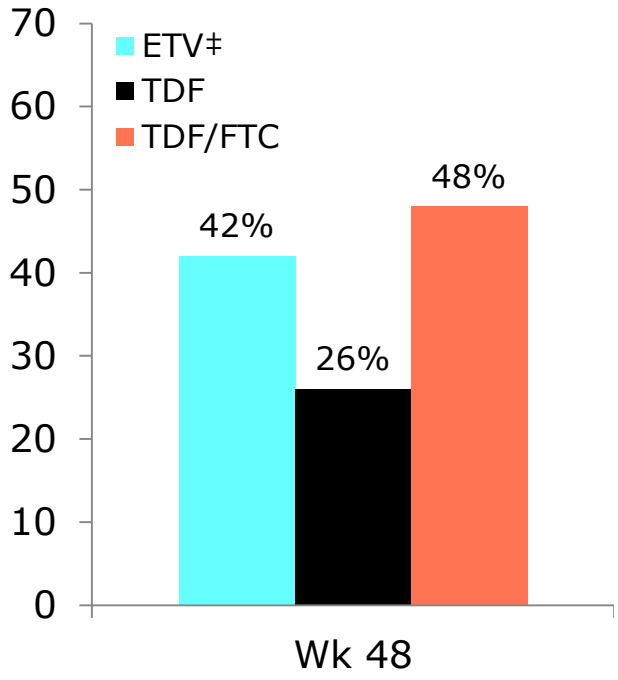
N=1951
HCC
N=118

Journal of Hepatology **2018** vol. 68 | 1129–1136

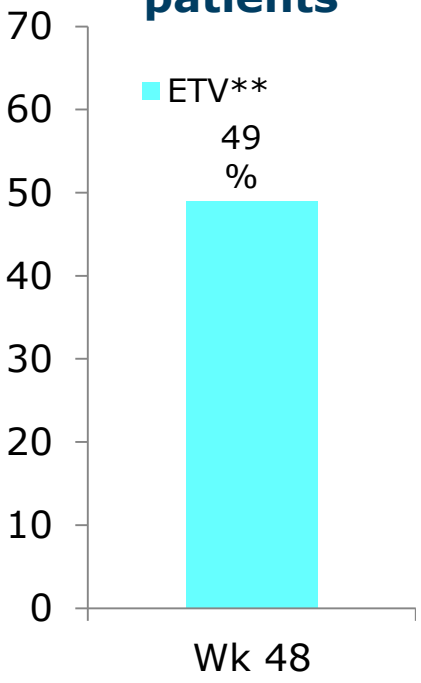
ETV vs TDF: Gedecompenseerde cirrose

RCTs in NUC-naïve or -experienced patients





Single centre cohort in NUC-naïve patients[3‡]

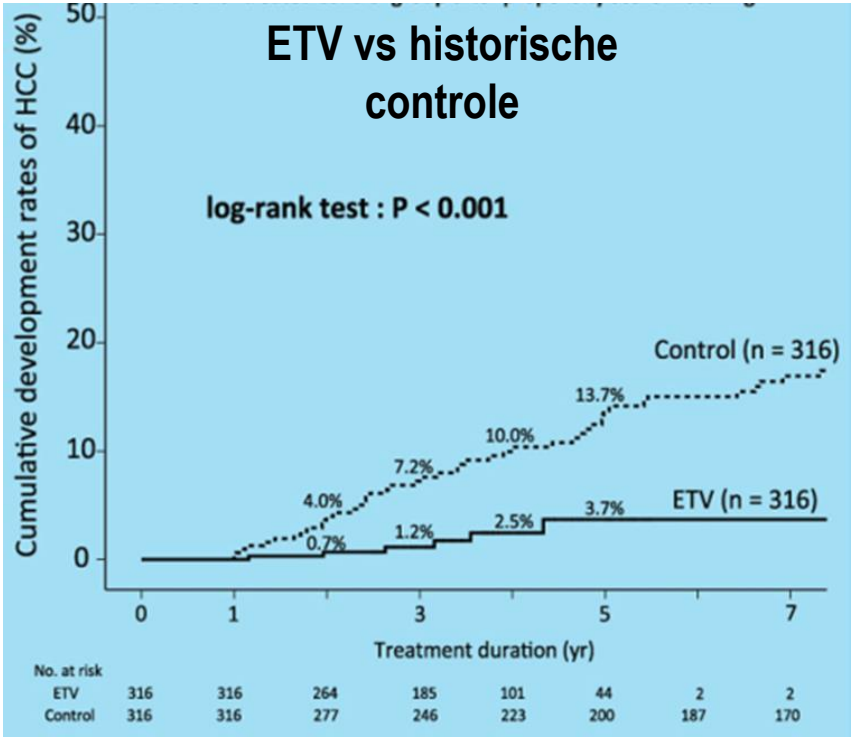


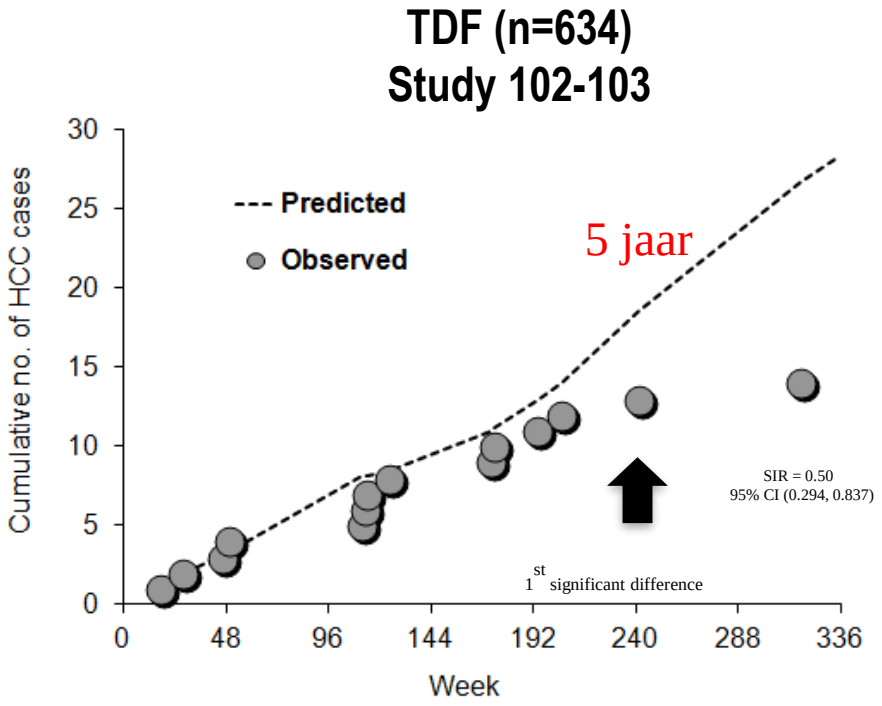
CTP, Child–Turcotte–Pugh.

1. Cheinquer H, et al. Hepatology International 2011;5:272, abstract PP13-104.
2. Liaw YF, et al. Hepatology 2011;53:62-72. 3. Shim JH, et al. J Hepatol 2010;52:176-187.

[1] By Kaplan-Meier analysis.

ETV vs TDF:HCC

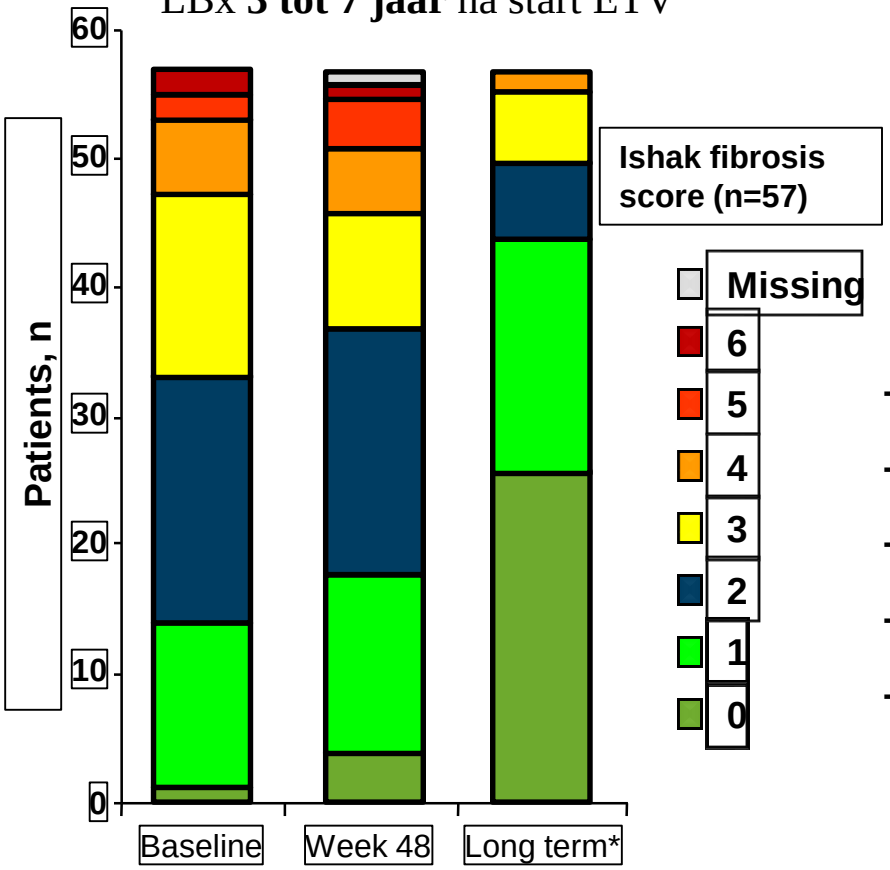




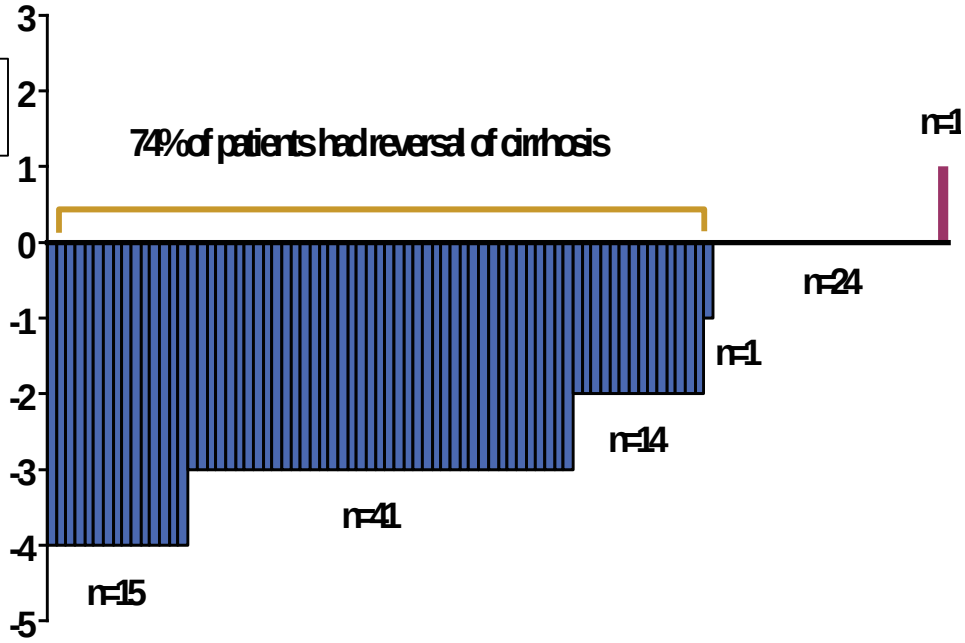
Hosaka T, et al. AASLD 2012, Boston, MA. Poster 357.
Kim WR, et al. J Hepatol 2013 Supp 1;58(43):S19 – AASLD 2013, Oral#43

ETV vs TDF: fibrose regressie

LBx **3 tot 7 jaar** na start ETV



Fibrose regressie bij cirrotici na TDF **(5 jr)**



Chang TT, et al. Hepatology 2010;52:886-893. 2. Schiff ER, et al. Clin Gastroenterol Hepatol. 2011; 9:274-276. Marcellin P, et al. The Lancet 2013; 381(9865): 468-475.

Wanneer Welke Therapie?

PegInterferon	Nucleos(t)ide analogues
Baseline HBV DNA $\leq 10^9$ copies/ml	Baseline HBV DNA $>10^9$ copies/ml
HBeAg+	
Baseline ALT >2 x ULN	Baseline ALT minimally elevated or very high
Genotype A or B	Genotype C or D
Compensated liver disease	Compensated or decompensated liver cirrhosis
Young age	
Toekomstige zwangerschapswens	

Keuze 1ste lijns NA

HBV richtsnoer: 1ste keus ETV of TDF

/EASL CPG: TAF ~ TDF ~ETV, no RIZIV criteria

Tabel: Patiëntengroepen waarbij ETV of TAF de voorkeur hebben boven TDF.

	1e keuze	2e keuze
Nierziekten		
eGFR 50 – 60 ml/min	ETV[1]	TAF[1]
eGFR < 50 ml/min of hemodialyse	TAF[2]	ETV[2]
albuminurie >30mg/dag en/of hypofosfatemie (< 0.81 mmol/L)	ETV[1]	TAF[1]
(verhoogd risico op) botziekten		
Chronisch gebruik medicatie die botdichtheid beïnvloedt	ETV[1]	TAF[1]
Osteoporose of osteoporotische botfractuur in voorgeschiedenis	ETV[1]	TAF[1]

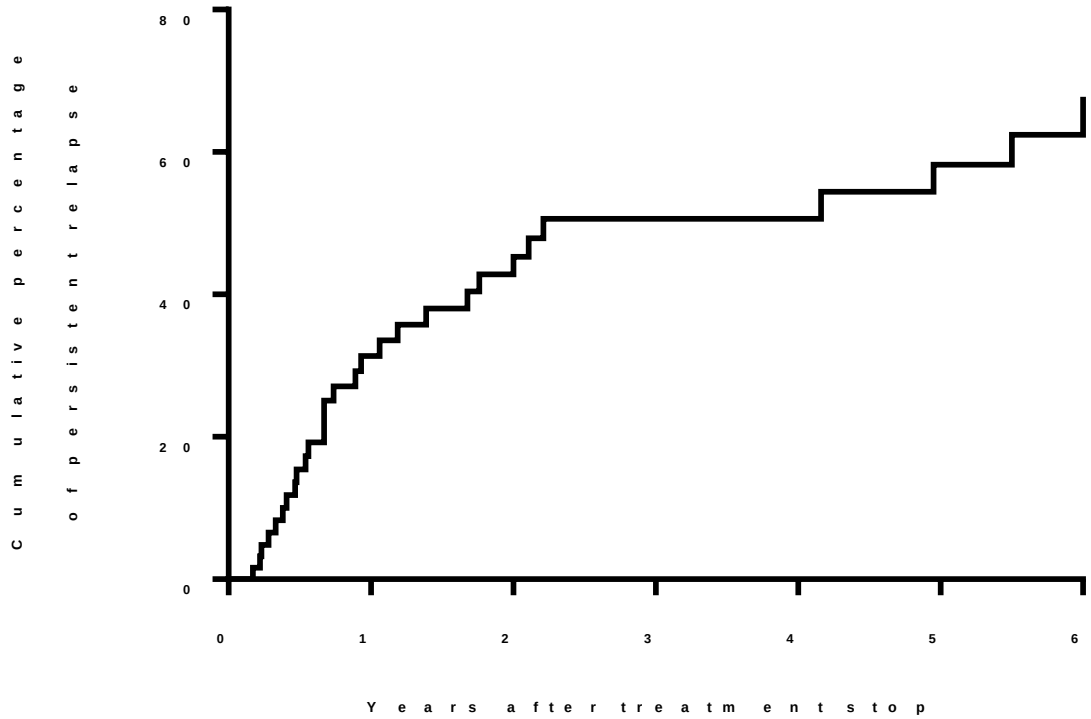
HBeAg+: finite NA treatment?

- HBeAg seroconversie → consolidatie behandeling:
  - 12 mnd (EASL CPG 2017; HBV richtsnoer) “mogelijk”
  - 6 mnd (BASL guidelines, RIZIV-terugbetaling)

- HBeAg seroconversie → continueren tot HBsAg loss:
  - Alle cirrose patiënten, EASL CPG 2017; HBVrichtsnoer
  - ( : LMV in cirrose met onderdrukt HBV DNA)

Colle et al Acta Gastroenterol Belg 2007; NVMDL richtlijn 2012

Relapse after stopping NA



2 fatale relapses! N=356 → n=70 Nuc stop

→ Volg patiënt van nabij op (België): zeker 3 maandelijks
→ Alternatief: niet stoppen

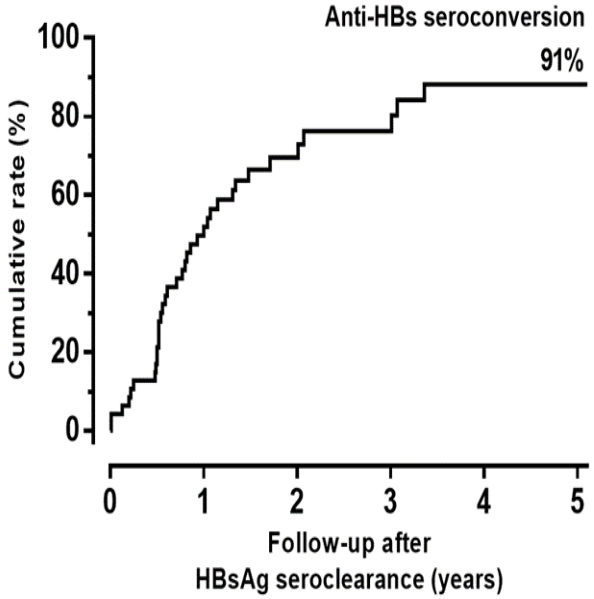
HBV Functional Cure

Nucs levenslang?

Tot HBsAg loss?

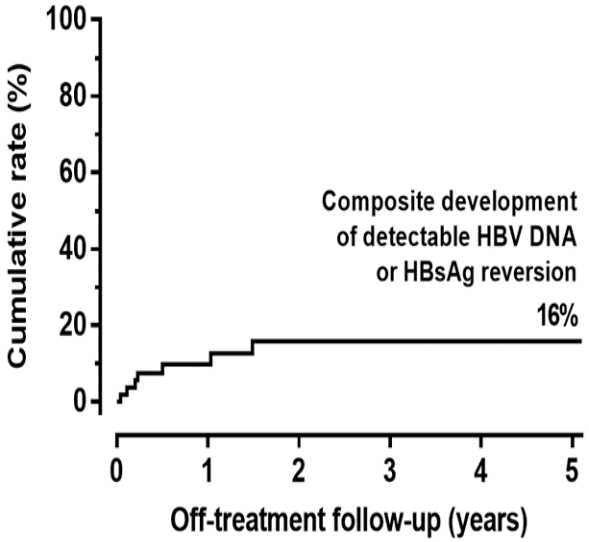
… en de verdere toekomst?

HBsAg loss: safe NUC stop



N= 5872 CHB R/Nuc

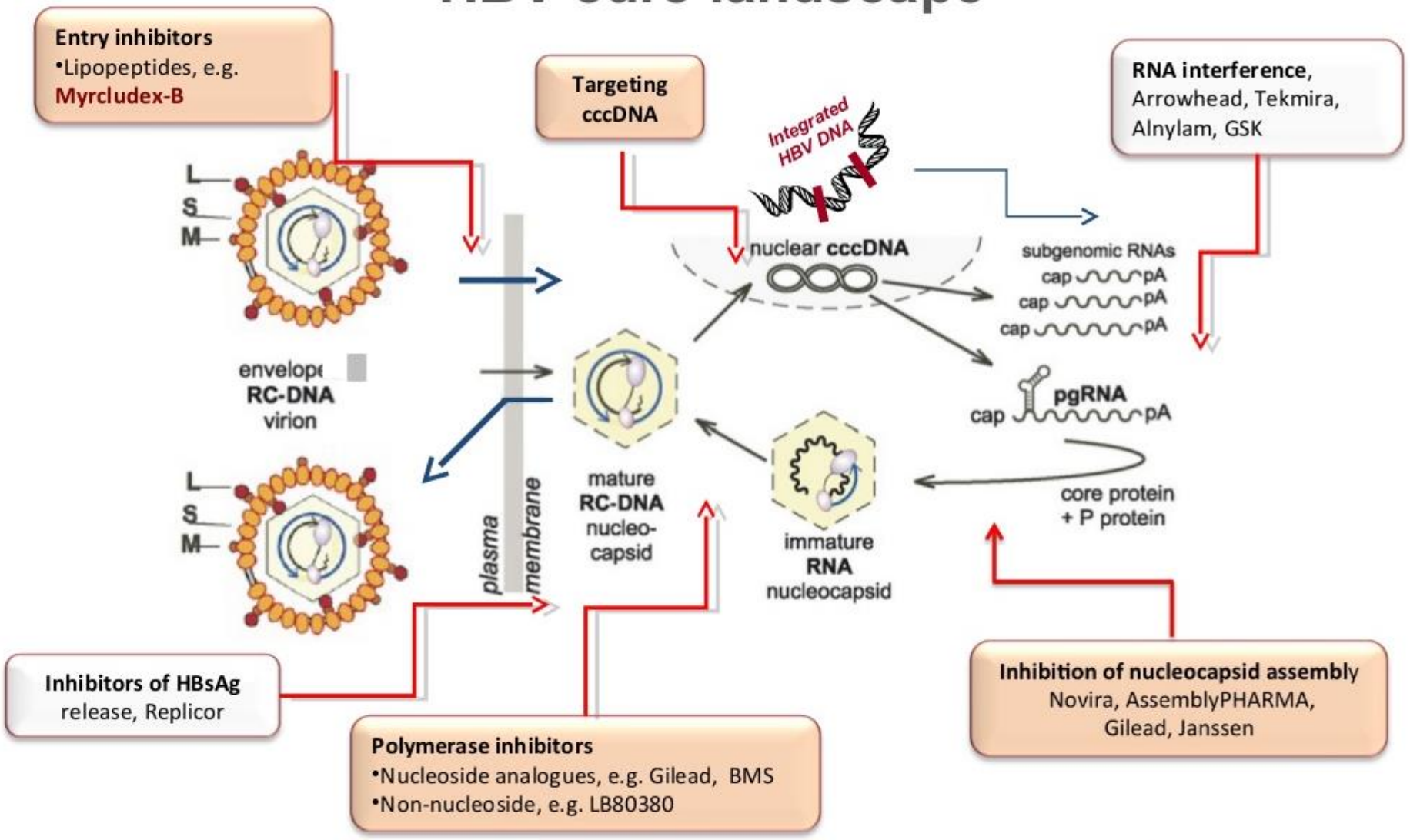
→ n=70 HBsAg loss



N= 54 Nuc stop after HBsAg loss

→ n=5 HBV DNA+ (1-3 log) wo HBsAg
→ n=2 HBsAg reversion wo HBV DNA
→ No ALT > 2ULN, low HBV DNA
→ No clinical events

HBV cure landscape

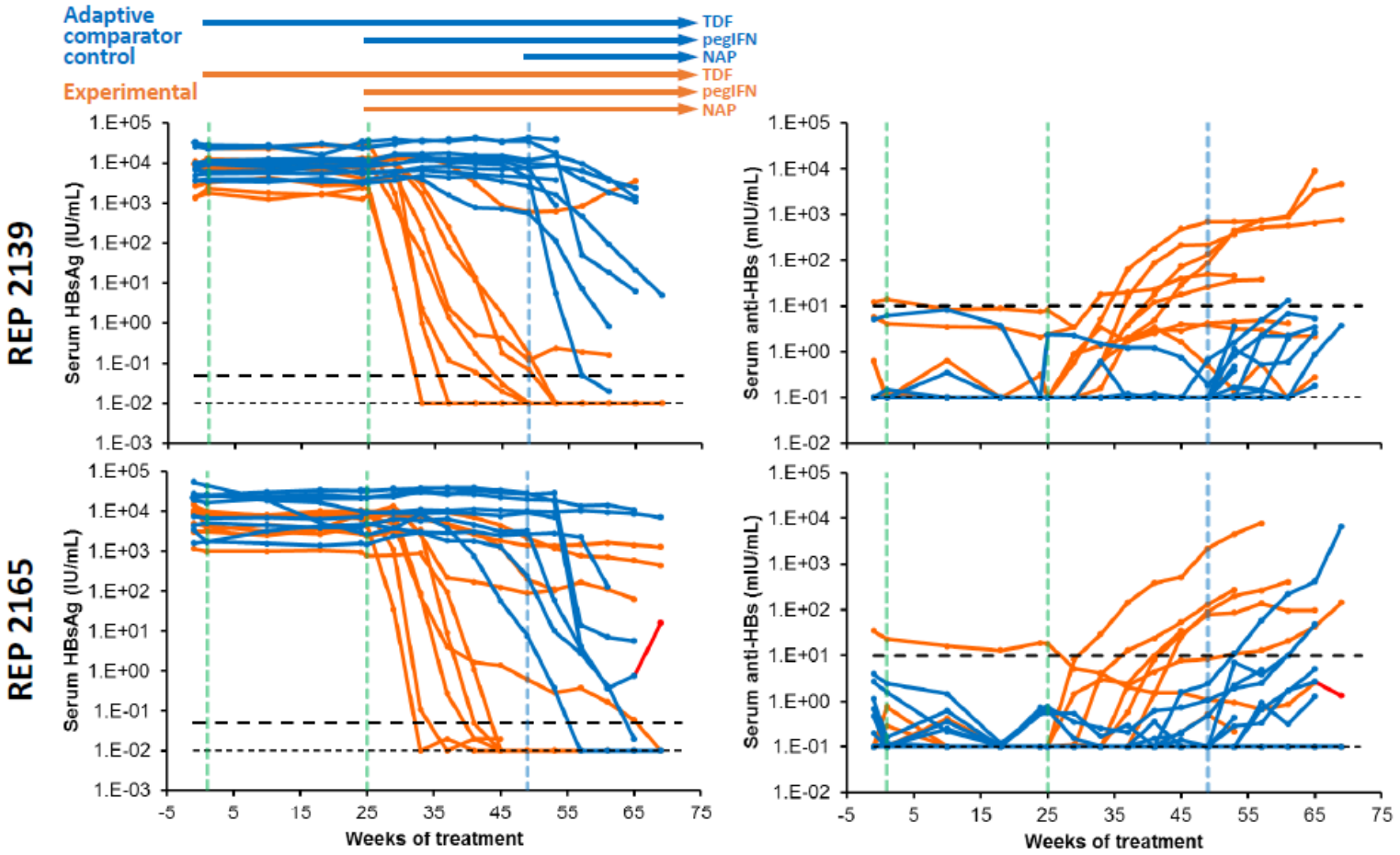


Immune modulation

- ***Toll-like receptors agonists***, Gilead, Roche
- ***Anti-PD-1 mAb***, BMS, Merck
- ***Vaccine therapy***: Transgene, Gilead, Roche Innovio, Medimmune, ITS

Nucleic acid polymers (NAPs)

HBeAg – hepatitis, n= 30 → early HBsAg loss



Further Reading

EASL HBV CPG 2017 (www.easl.eu)

HBV richtsnoer(www.hbvrichtsnoer.nl)

BASL richtlijn 2007 (Acta Gastroenterol Belg 2007)