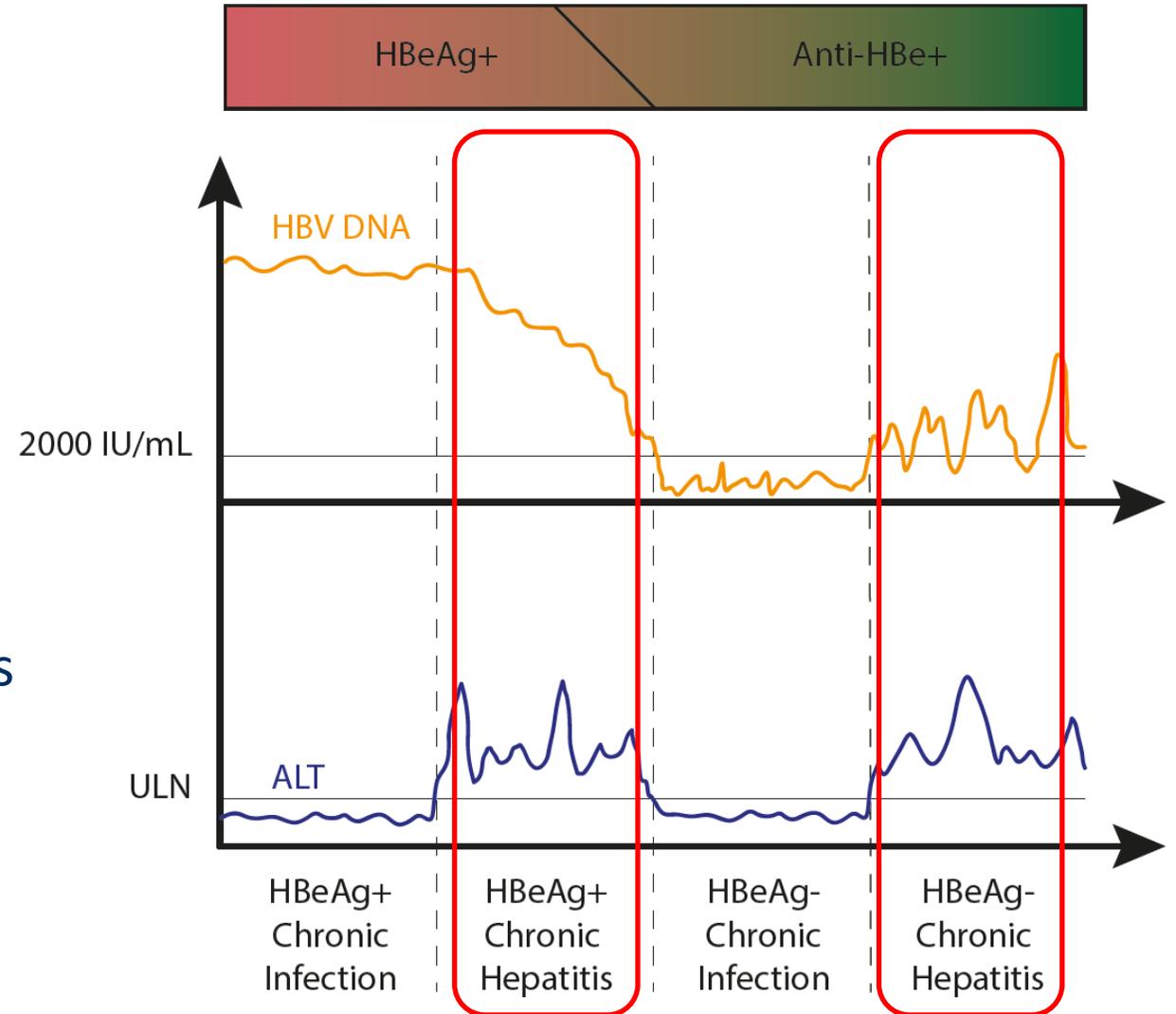


Clinical management and long-term treatment outcomes of hepatitis B

Thomas Vanwolleghem
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University of Antwerp

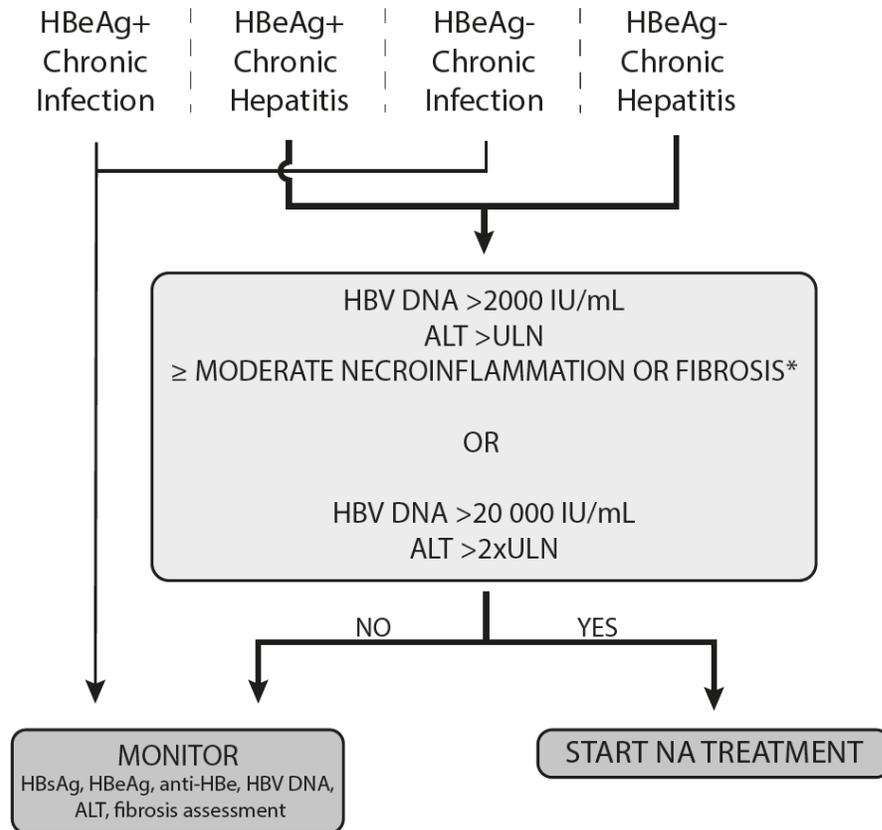
CHB NATURAL HISTORY

- **4 distinct phases based on:**
 - HBeAg status
 - HBV DNA level
 - ALT
- **‘New’ EASL terminology**
 - Chronic infection vs chronic hepatitis
- **Hepatitis phases: persistent ALT↑**
→ Treatment indication



TO TREAT OR NOT TO TREAT?

General

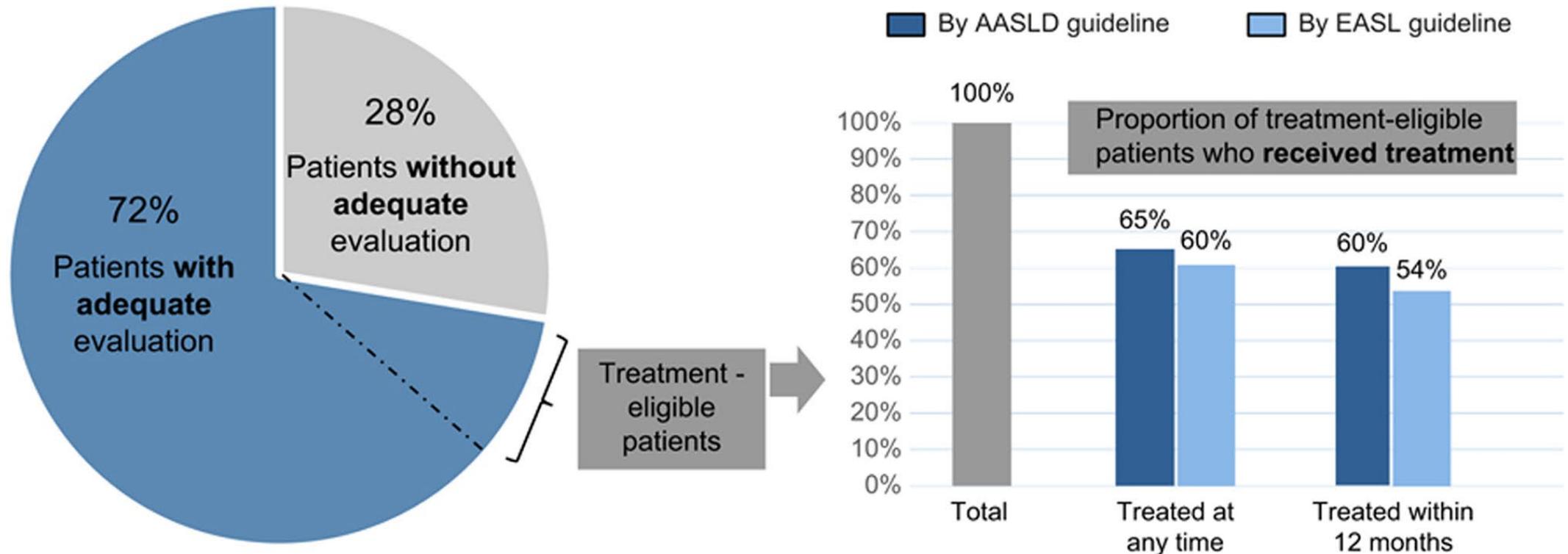


Exceptions

- Family history of HCC or cirrhosis
- Risk for transmission
- Previous treatment history
- Extrahepatic manifestations
- Compensated or decompensated cirrhosis
- Co-infected patients
- Pregnancy
- Patients undergoing immunosuppressive therapy or chemotherapy

Real world practice: Gaps in evaluation and treatment

Chronic HBV infection in the United States
2003-2019, N = 12,608



GOALS OF CHB TREATMENT

- **Improve clinical outcomes:**
 - Prolong survival
 - Prevent liver decompensation
 - Prevent progression towards cirrhosis/HCC
- **HBV DNA ~ HCC and cirrhosis progression (REVEAL-HBV cohort)**
- **Virological endpoints (=surrogate):**
 - HBV DNA < det limit
 - HBeAg seroconversion
 - HBsAg clearance/seroconversion = “functional cure” → NUC STOP

SHORT TERM VIROLOGICAL OUTCOMES

Virological outcomes of the registrational trials after 48 weeks of treatment

	PegIFN-α2a		ETV		TDF		TAF	
	HBeAg+	HBeAg-	HBeAg+	HBeAg-	HBeAg+	HBeAg-	HBeAg+	HBeAg-
Number of patients (n=)	271	177	354	325	176	250	581	285
Virologic response*	25	63	67	90	76	93	64	94
ALT <ULN (%)	39	38	68	78	68	76	72	83
HBsAg loss (%)	+/- 3°	+/- 4°	2	0	3.2	0	1	0
HBeAg seroconversion (%)	27	/	21	/	21	/	10	/

*HBV DNA<400 copies/mL(PegIFN-α2a), <300 copies/mL (ETV), <69 IU/mL (=400 copies/mL) (TDF); <29 IU/mL(TAF)

° at 6 months after 48 weeks of therapy

LONG TERM VIROLOGICAL OUTCOMES

HBeAg Positive	Peg-IFN*	Entecavir [†]	Tenofovir Disoproxil Fumarate [†]	Tenofovir Alafenamide [‡]
% HBV-DNA suppression (cutoff to define HBV-DNA suppression) [§]	30-42 (<2,000-40,000 IU/mL) 8-14 (<80 IU/mL)	61 (<50-60 IU/mL)	76 (<60 IU/mL)	73 (<29 IU/mL)
% HBeAg loss	32-36	22-25	—	22
% HBeAg seroconversion	29-36	21-22	21	18
% Normalization ALT	34-52	68-81	68	—
% HBsAg loss	2-7 11 (at 3 years posttreatment)	4-5	8	1
HBeAg Negative	Peg-IFN	Entecavir	Tenofovir Disoproxil Fumarate [†]	Tenofovir Alafenamide [‡]
% HBV-DNA suppression (cutoff to define HBV-DNA suppression)	43 (<4,000 IU/mL) 19 (<80 IU/mL)	90-91 (<50-60 IU/mL)	93 (<60 U/mL)	90 (<29 IU/mL)
% Normalization ALT [¶]	59	78-88	76	81
% HBsAg loss	4 6 (at 3 years posttreatment)	0-1	0	<1

HBV DNA suppression:

↑ NUC treatment vs low after pegIFN

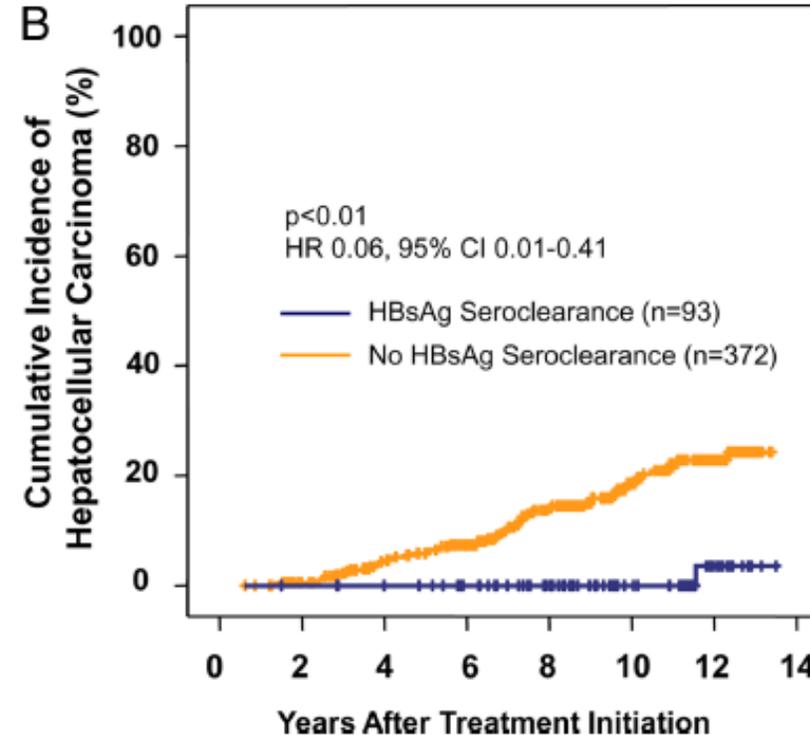
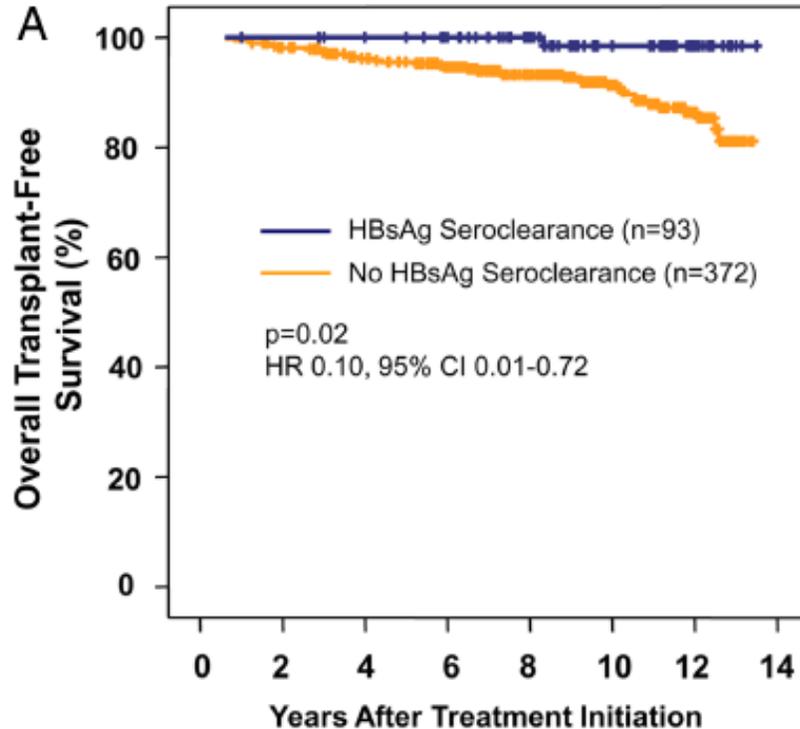
HBsAg loss:

↑ after pegIFN with longer FU duration, but low in NUC-treated HBeAg- CHB

NUC induced HBsAg loss: Clinical outcomes

Korea 1999-2011. n= 5409 R/LAM or ETV, median FU 6 yrs
HBsAg loss; n=110 → HBsAg loss: 0,33%/year

n=1, cirrhosis



n=1, cirrhosis

Excellent outcomes after HBsAg seroclearance

Only baseline cirrhosis associated with residual risk for adverse outcomes

NUC Treatment outcome: Survival

- Europe. n=1951 R/ TDF or ETV since 2012
- Excellent survival rates
 - 94% after 8 years of NUCs = general population
- Cirrhosis: ↑ overall and liver-related death
- HCC: ↑ transplantation and liver-related mortality
 - HR 169.80; P <0.001

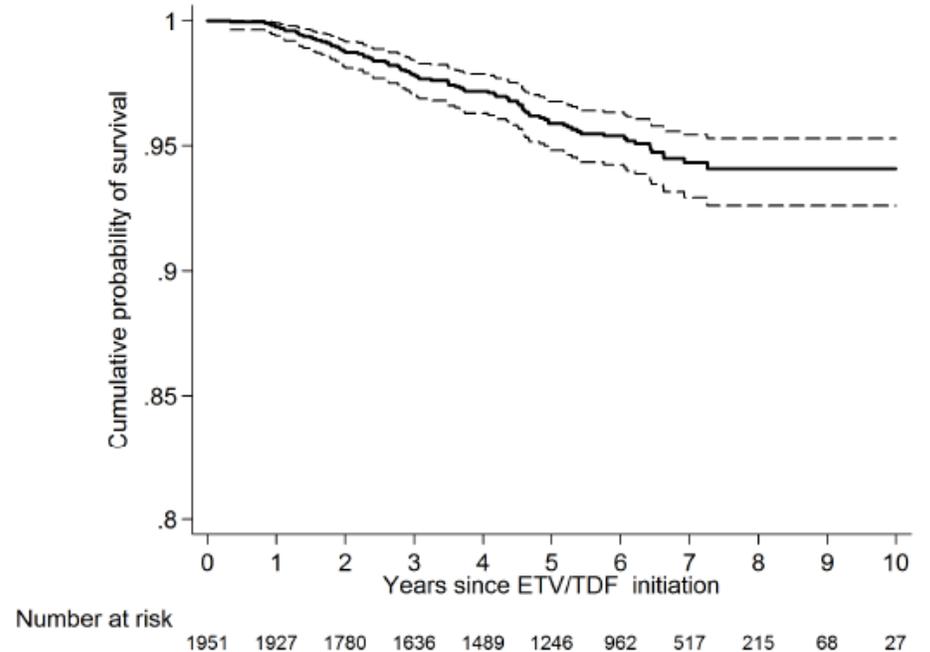


Table 2. Deaths or liver transplantation in 1,951 Caucasian patients with CHB who received long-term entecavir or TDF therapy.

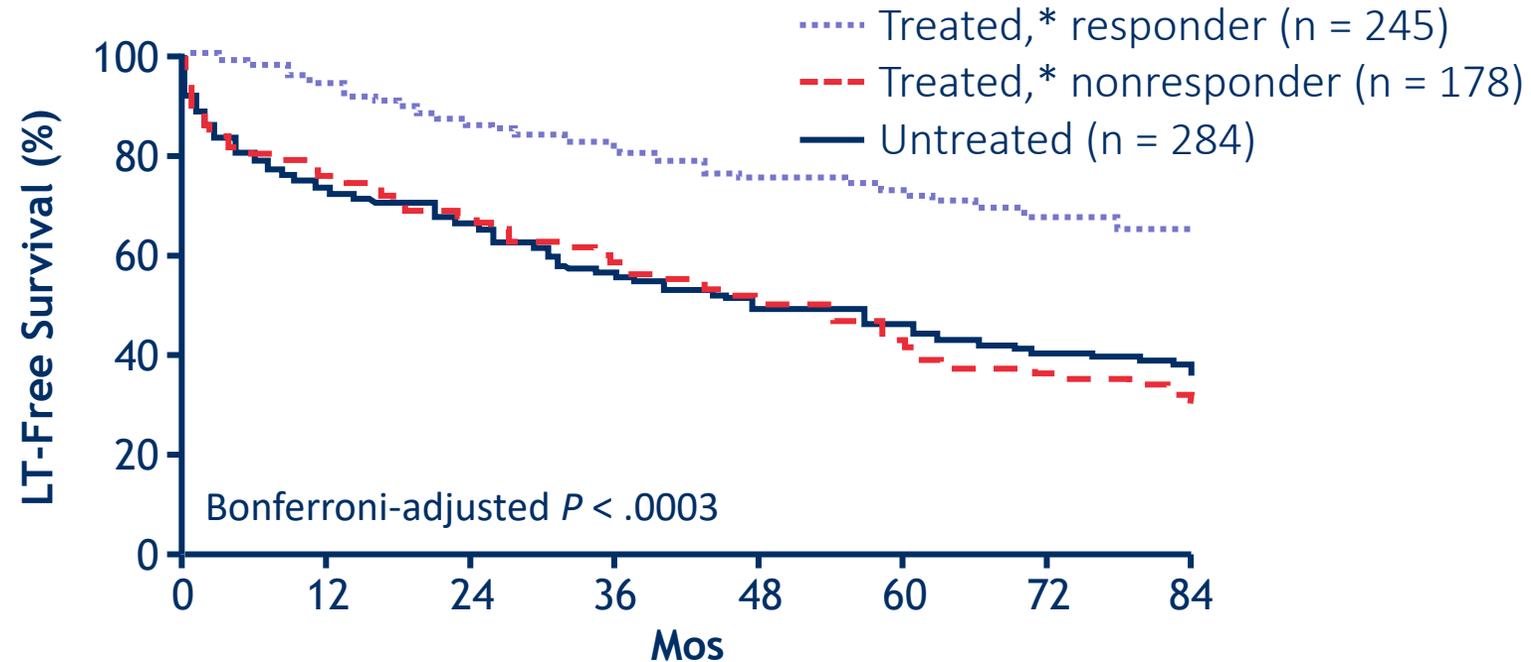
	Total (N = 1,951)	No cirrhosis (n = 1,379)	Cirrhosis (n = 526)	p value [†]
Death from any cause	84 (4.3%)	37 (2.7%)	44 (8.4%)	<0.001
Liver-unrelated death	50 (2.6%)	27 (2.0%)	21 (4.0%)	0.018
Liver-related death	34 (1.7%)	10 (0.7%)	23 (4.4%)	<0.001
Liver transplantation	17 (0.9%)	8 (0.6%)	9 (1.7%)	0.027
Liver-related death/liver transplantation				
In patients with HCC	44/118 (37.3%)	17/37 (45.9%)	26/80 (32.5%)	0.231
In patients without HCC	7/1,833 (0.4%)	1/1,342 (0.01%)	6/446 (1.3%)	0.001

CHB, chronic hepatitis B; HCC, hepatocellular carcinoma; TDF, tenofovir disoproxil fumarate.

[†] For cirrhosis vs. no cirrhosis by chi-square test.

NUC Treatment outcome: Prevent Transplantation

- Korea 2005-2012. Prospective cohort study ; R/ LAM/ETV
- CHB (n=707) with first-onset complications of decompensated cirrhosis

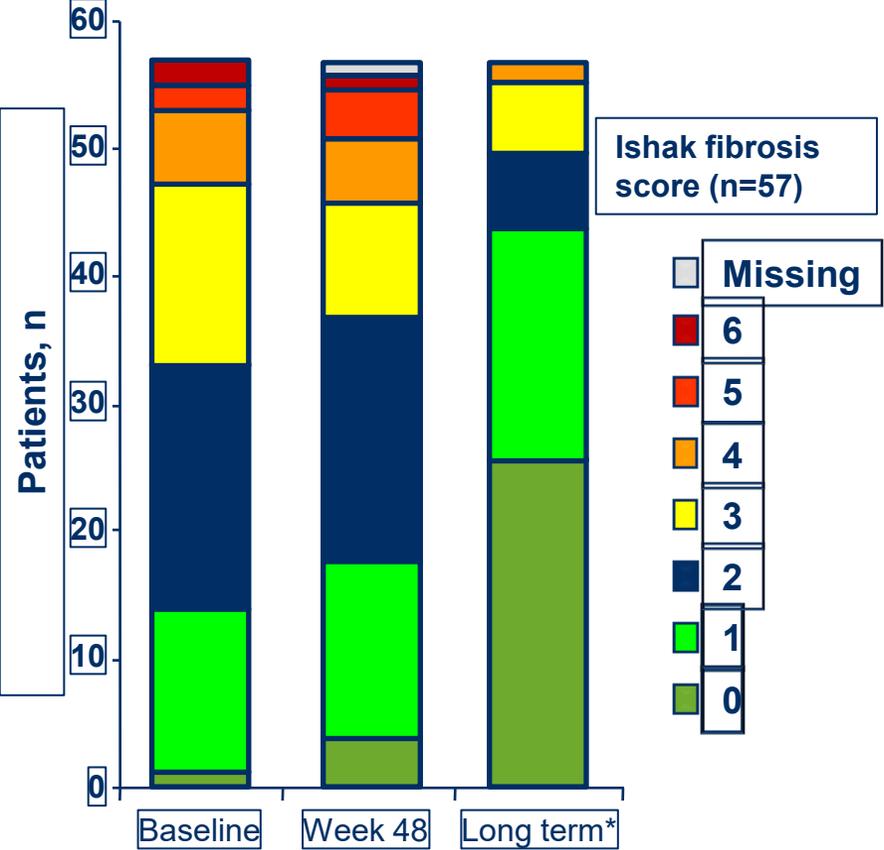


*Treated predominantly with lamivudine (n = 203) or entecavir (n = 198).

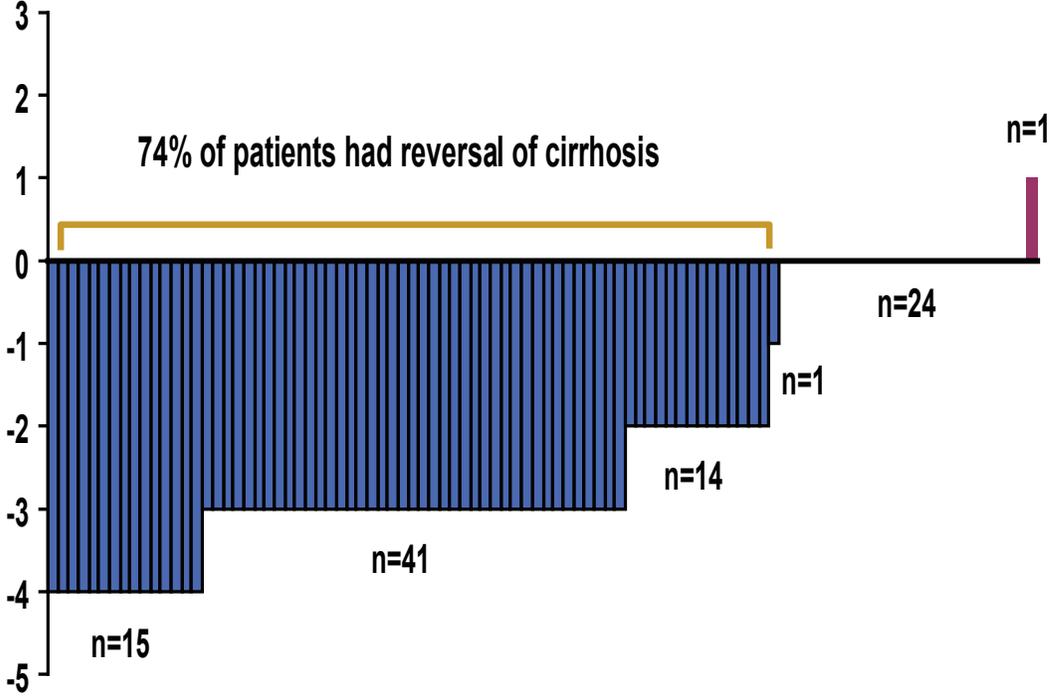
- NUC treatment with viral suppression improved transplant-free survival over 5 yrs ($P = .0098$ vs untreated)

NUC Treatment outcome: Fibrosis Regression

ETV: LBx 3 to 7 yrs after start

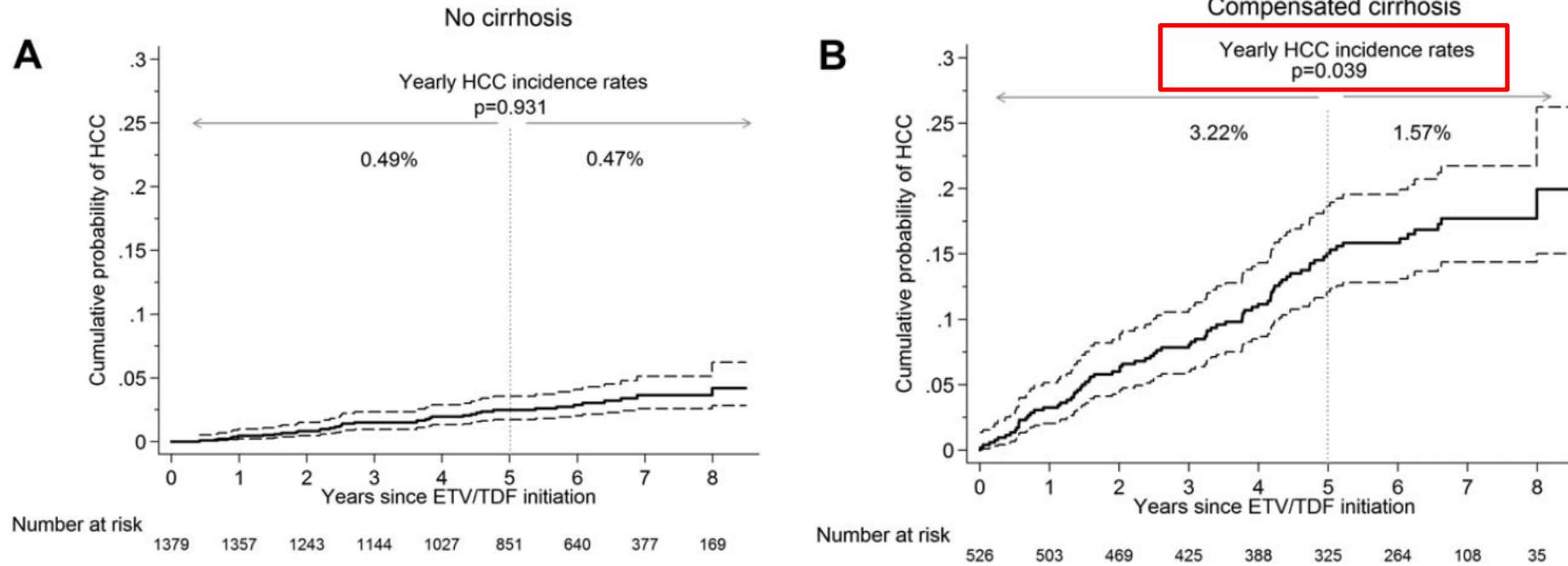


TDF: Lbx 5 yrs after start (cirrhotic patients)



NUC Treatment outcome: HCC Prevention

Europe. n=1951 R/ TDF or ETV since 2012

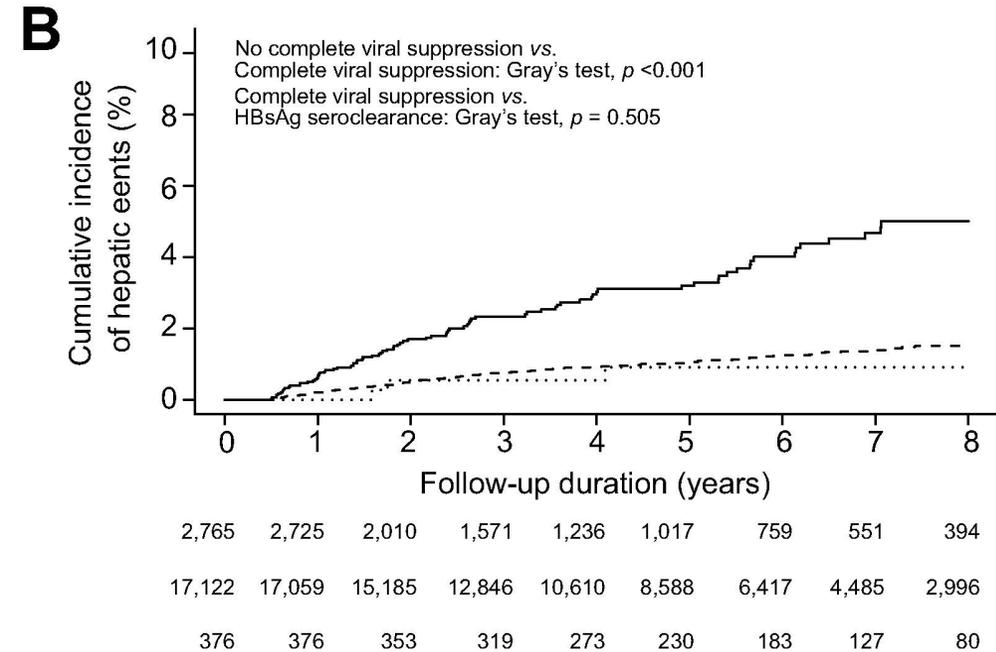
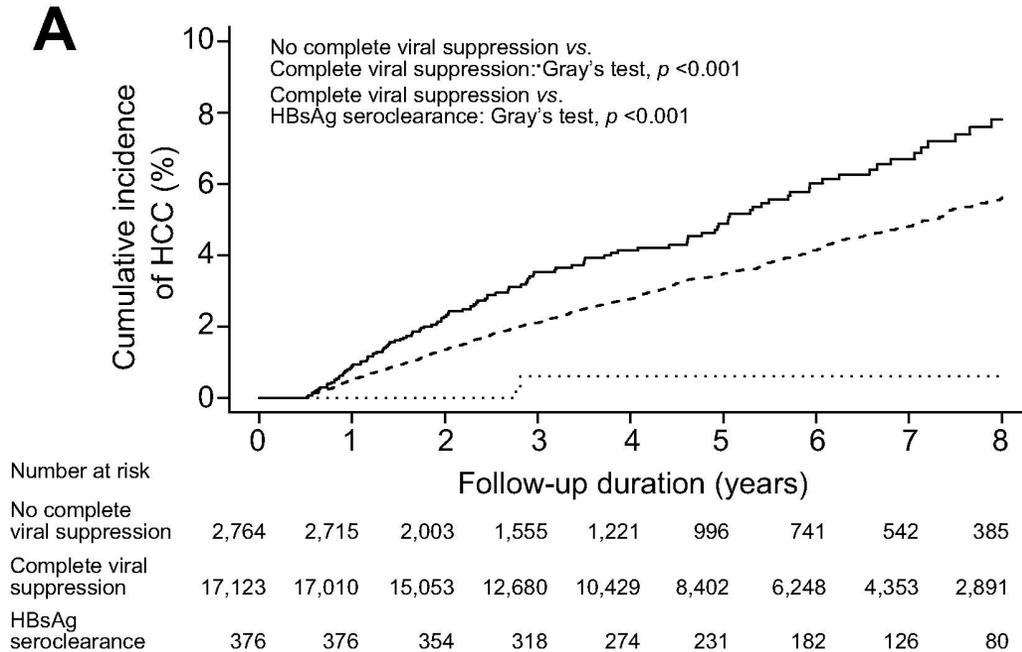


Non-cirrhotic CHB: Persistent low risk of HCC

Cirrhotic CHB: Drop in HCC risk treated for 5 years
→ But > 1,5%: Continuous HCC surveillance

NUC Treatment outcome: HCC Prevention

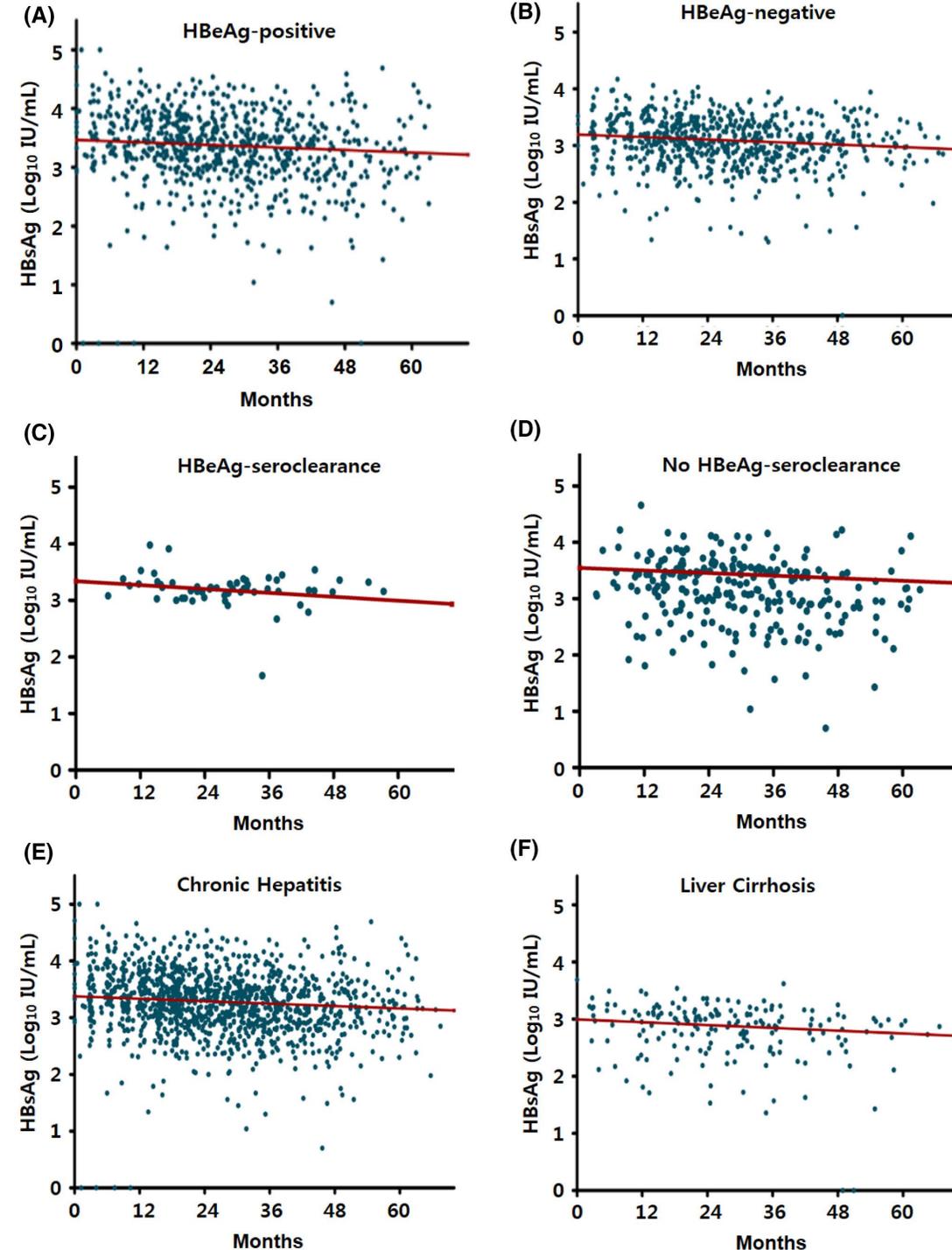
Hong Kong 2005-2016. n= 20,263 ETV/TDF. HBsAg loss: n= 376 (2.1%)



- **Additional benefit of HBsAg loss over HBV DNA suppression**
- **HCC incidence:**
 - N= 603 (3.5%) with viral suppression
 - N= 121 (4.4%) without complete viral suppression ($P < 0.001$)
 - N= 2 (0.5%) with HBsAg seroclearance ($P < 0.001$)
- **Hepatic events:** viral suppression \sim HBsAg loss ($P = 0.505$)

Duration of NUC Treatment

- **Very slow HBsAg decline on NUC treatment:**
 - Caucasians 0.084 Log₁₀ IU/ml/yr
 - Asians 0.043 - 0.044 log₁₀ IU/mL/yr
- **Estimated duration of NUC treatment :**
 - Caucasians: 52.2 years (IQR 30.8–142.7 yrs)
 - Asians: 73.5-74.1 years
 - “Lifelong”



Conclusion: Long term benefit of NUC treatment

- **Virological:**

- HBV DNA suppression almost universal with 2nd generation NUCs
- HBsAg loss very rare : 0.33%/year
- Lifelong NUC treatment anticipated

- **Excellent long-term clinical outcomes:**

- Survival similar to general population, only cirrhosis/HCC impacting survival
- Prevention of Liver Transplantation/Recompensation
- Regression of liver fibrosis
- Additional benefit of HBsAg loss

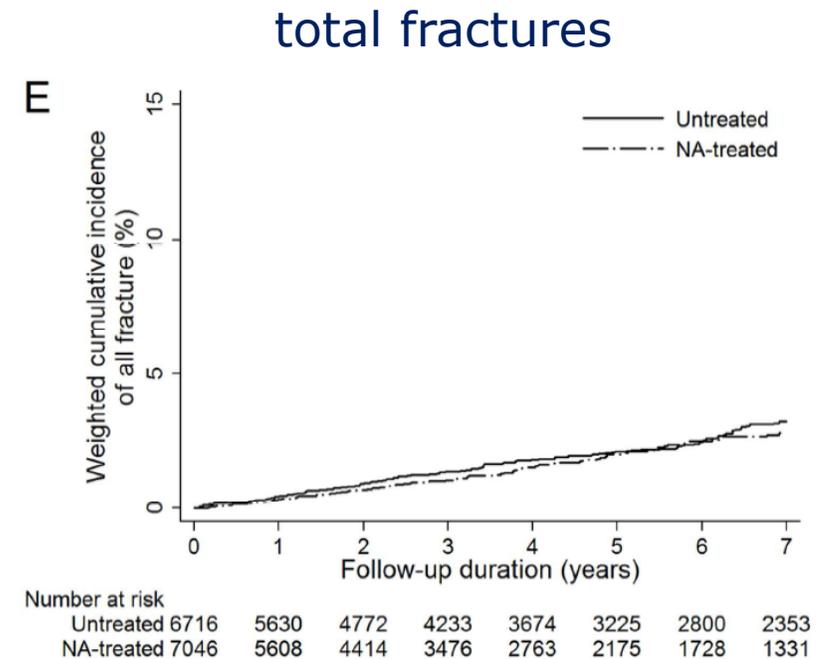
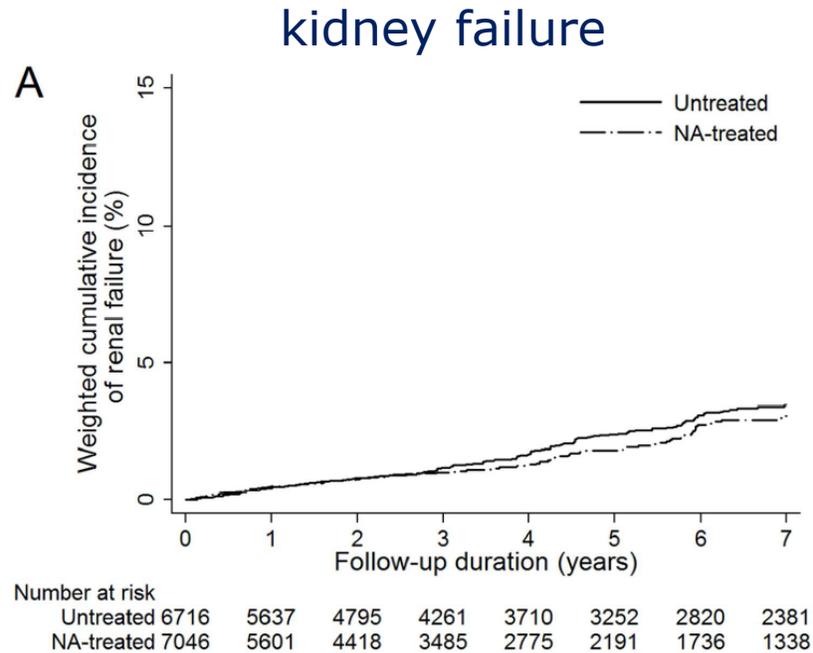
SAFETY OF CHB TREATMENT

- **NUCs generally well tolerated**
 - ETV: Lactic acidosis in decompensated cirrhosis
 - TDF:
 - Hypophosphatemia
 - Renal tubulopathy?
 - Osteomalacia?

- **IFN: specific side effects**

Safety NUCS: Kidney and Bone ?

Hong Kong 2000-2012: n=53,500 chronic HBV, n=7,046 NUC-treated
3-year cumulative risk analysis



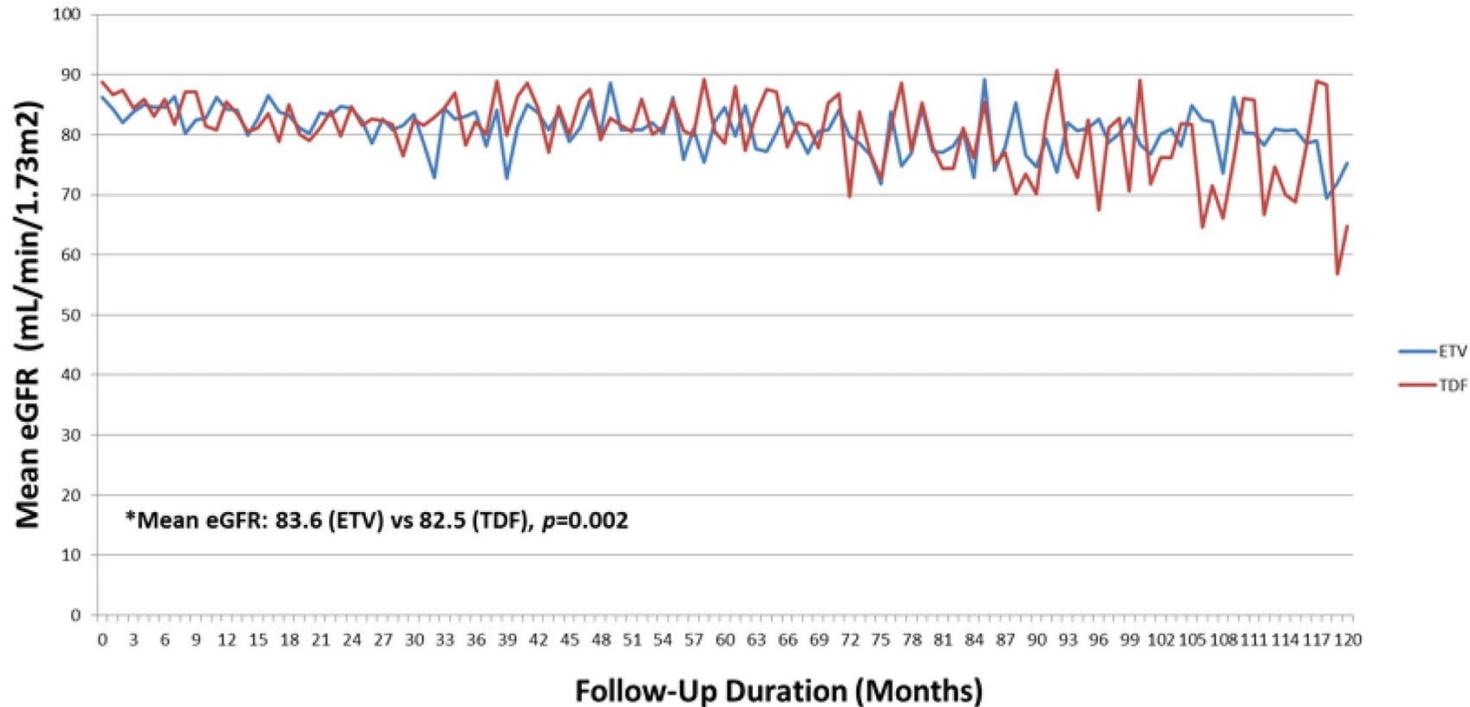
Nucleotide vs Nucleoside analogues:

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

Renal Safety of NUCS: Real World ETV vs TDF

- Retrospective analysis; 25 centers, USA, Hong Kong, Korea, Taiwan, Japan, Singapore, Mainland China
- TDF (n= 2482) vs ETV (n=3707)
- Adjusted mean eGFRs lower in TDF vs. ETV during 10 years of follow-up (all $p < 0.01$)

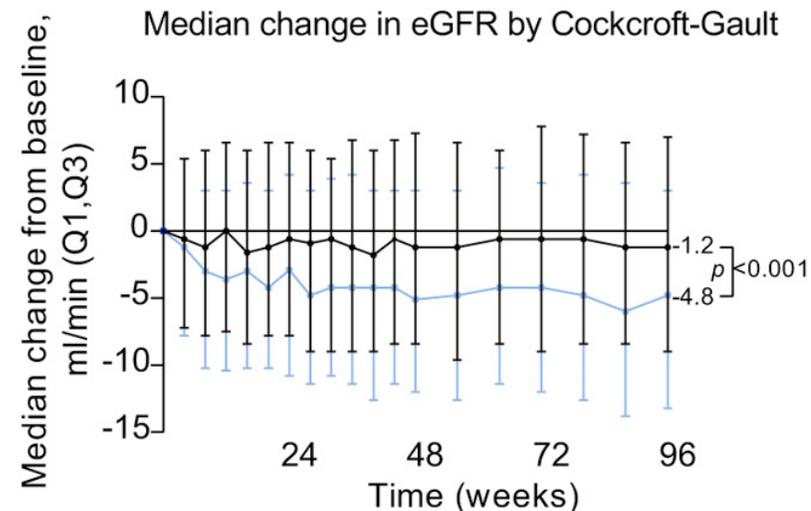
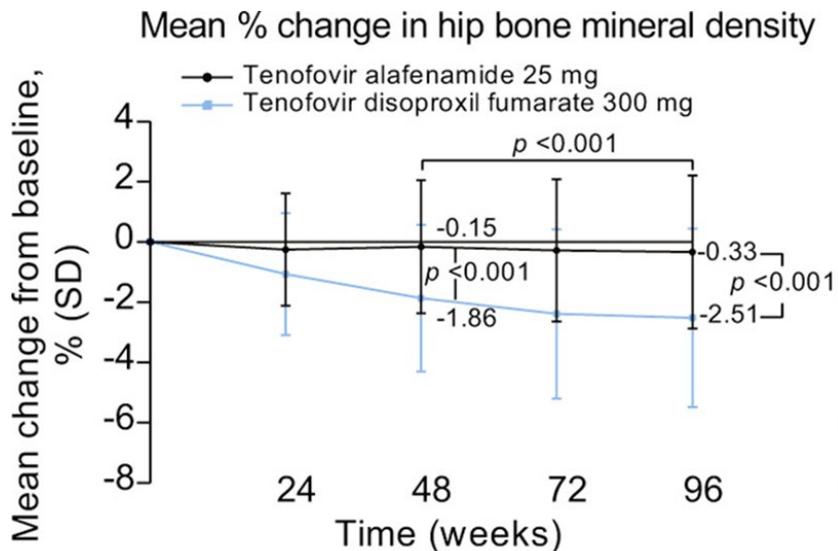


Number of patients observed by months

Months	0	12	24	36	48	60	72	84	96	108	120
ETV	3707	3701	3227	2532	1529	1145	890	739	525	335	33
TDF	2482	2460	2089	1605	691	500	368	261	133	81	10

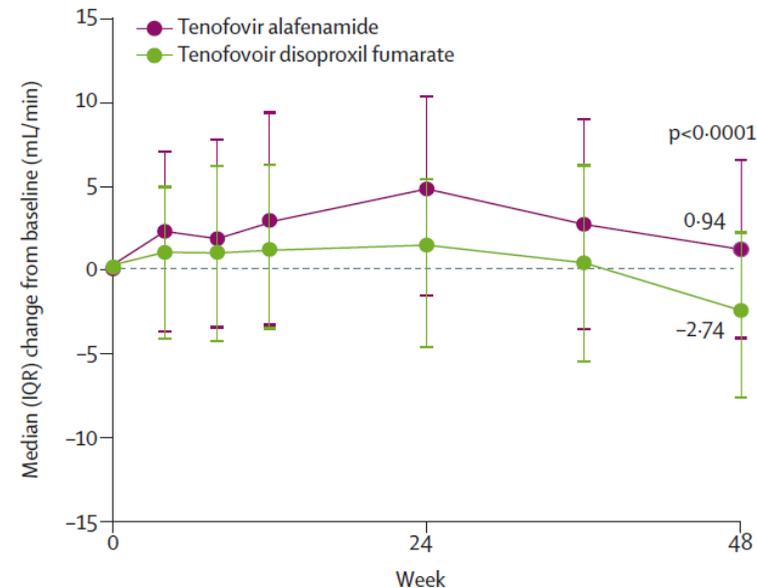
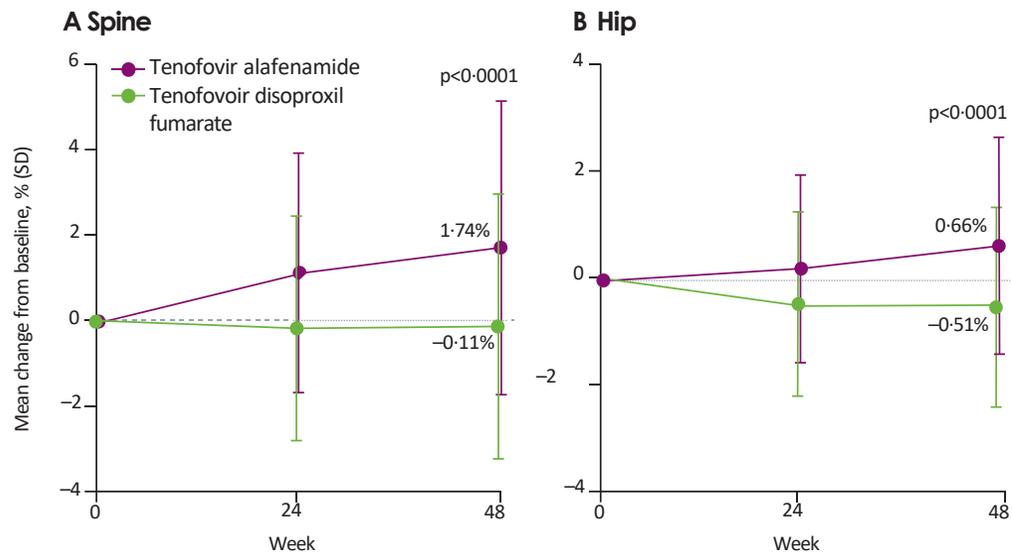
Safety of NUCS: 96 weeks of TDF vs TAF non-inferiority RCT

- Viral endpoints:
 - HBV DNA < 29 IU/mL:
 - **HBeAg+**: 73% (423/581) (TAF) vs 75% (218/292) (TDF); P=0.47
 - **HBeAg-**: 90% (257/285) (TAF) vs 91% (127/140) (TDF); P= 0.84
 - HBsAg loss:
 - **HBeAg+**: 7/576 (1%) (TAF) vs 4/288 (1%) (TDF); P=0.88
- Biochemical changes:
 - grade 3 fasting LDL levels: 6% TAF vs TDF 1% (“lipid lowering effect of TDF”)
- Bone Mineral Density and Creatinin Clearance



Safety NUCS: Switch TDF to TAF, non-inferiority RCT

- Long term TDF treatment, per protocol switch to TAF or continue TDF
- Viral endpoints:
 - HBV DNA > 20 IU/mL: 1 (<1%) (TAF) vs 1 (<1%) (TDF); P=0.95
 - HBsAg loss: 0/243 (TAF) vs 5/245 (2%) (TDF); P=0.028
- Biochemical changes:
 - Median fasting lipid parameters ↑ after TAF switch
- Bone Mineral Density and Creatinin Clearance



Choice of 2nd generation NUCS?

TAF vs TDF: Non-inferiority \neq Superiority

- Viral endpoints similar
- HBsAg loss significantly higher on continuous TDF vs switch to TAF
- Lipids higher on TAF vs TDF
- Bone and Kidney parameters significantly better on TAF vs TDF
- Long-term results?

EASL CPG:

- ETV \sim TAF \sim TDF
- Chronic kidney or bone disease: ETV \sim TAF $>$ TDF

Overall long-term outcome of NUC treatment

- **Excellent clinical outcomes**
- **Residual HCC risk in baseline cirrhosis**
- **Additional benefit after HBsAg loss**
- **Lifelong NUC treatment anticipated**
- **Kidney and bone safety good compared to untreated CHB patients**
- **Long-term side effect profile of different 2nd generation NUCs requires further study**

Acknowledgements

- **Viral Hepatitis Prevention Board**



Viral Hepatitis Prevention Board

- **Stichting tegen Kanker**



Stichting
tegen Kanker

- **FOD Volksgezondheid, Veiligheid van de Voedselketen en Leefmilieu**



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