2018 11th PARIS HEPATOLOGY CONFERENCE

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New therapeutic strategies in HBV patients

NUCS Discontinuation

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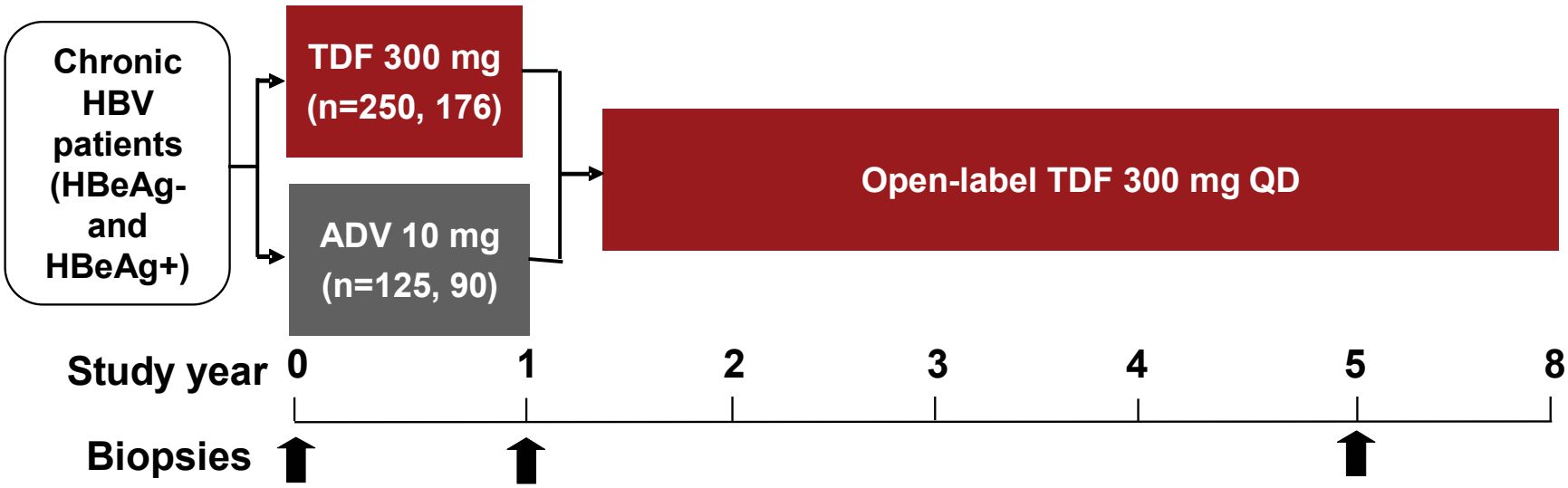
- 63 yrs old man
- Diagnosed with Chronic Hepatitis B in 2004
- HBsAg positive, HBeAg negative, HBV Genotype D
- Anti-HCV, anti-HIV and Anti-HDV negatives
- Previously treated with Lamivudine with VBK
- ALT 62 IU/L ,HBV DNA 41.000IU/ml, normal platelets levels and renal function
- Liver biopsy Knodell 3/3/2 Ishak score 5
- Screening study 102

Study Design 102 (HBeAg-) and 103 (HBeAg+)



Emtricitabin (FTC) could be added if there is confirmed viremia in or after week 72

- Sep 2005, started therapy double blind TDF vs ADV study
- At week 48 ALT 28 HBV DNA 500 IU/ML
- Oct 2016, Liver biopsy Knodell 3/4/3 Ishak 6
- 2006 Open label study with TDF
- Persistently Normal ALT levels, HBV DNA < 169 copies/mL
- At 5 yr of TDF Liver biopsy Knodell 1/1/2 Ishak 3
- Fibroscan 7.8 KPa

- He continuous therapy until March 2013
- Good compliance
- EoT ALT 21 UI/mL, HBV DNA <169, HBsAg 530 IU/mL
- Fibroscan 7,2 Kpa
- He wanted to discontinued therapy

Is he a good candidate for TDF Discontinuation?

- YES
- NO

Is he a good candidate for TDF Discontinuation?

YES

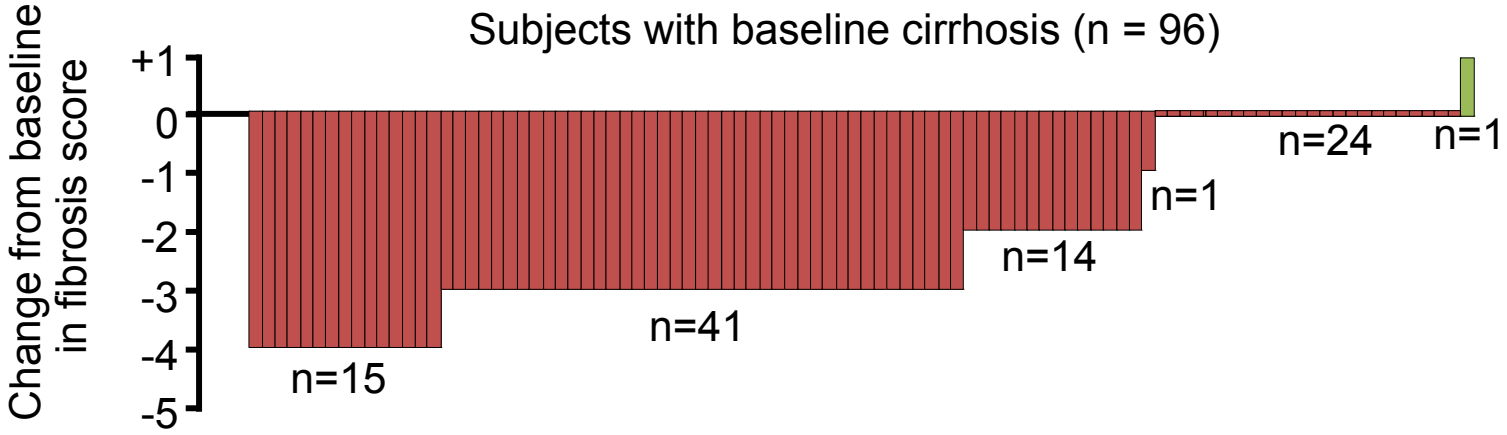
- Complete HBV DNA suppression
- Normal ALT
- Low HBsAg levels
- Good compliance

NO

- Liver Cirrhosis

Impact of Tenofovir on Liver Fibrosis at Year 5 in Subjects With Cirrhosis at Baseline

- 74% (n = 71) of subjects had Ishak fibrosis score < 5 at Year 5
  - 73% (n = 70) had decreases of ≥ 2 points
  - 25% (n = 24) did not change
  - 1% (n = 1) had 1-point increase in fibrosis score



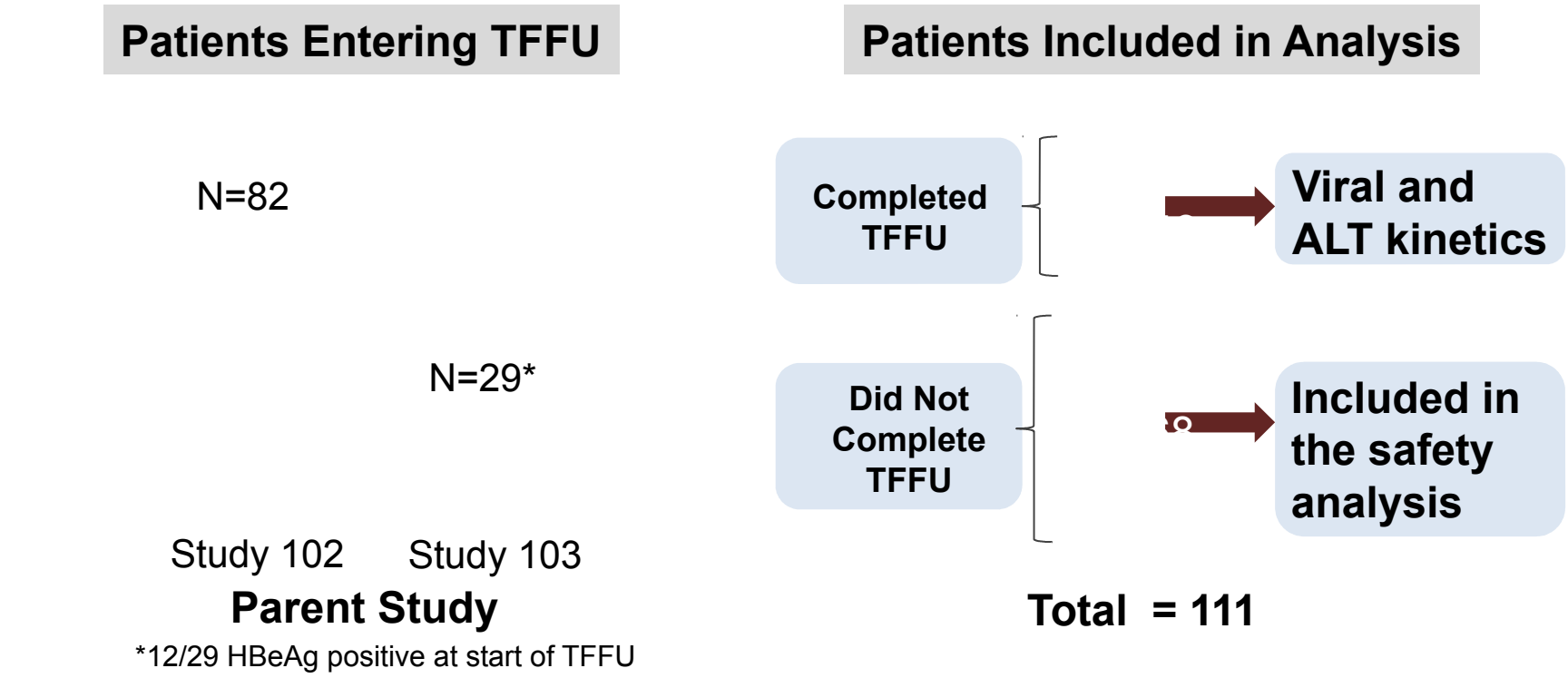
Adapted from Marcellin P, et al. Lancet. 2013;381:468-475.

Follow up after TDF discontinuation

	ALT UI/L	Bilirubin mg/dl	HBV DNA UI/mL	HBsAgIU/mL
EoT	21	0,6	undetectable	530
FU 4 wks	1041	3,5	1,2x105	448
FU 6 wks	1218	5,6	5,5x107	427
FU 12 wks	182	2,6	4,6x105	163
FU 16 wks	128	0,6	7x105	173
FU 24 wks	105	0,5	7,7x105	138

At week 2 of follow up, he started with astenia, coluria and acolia
No other symptoms

Patient Disposition: Completing ≥8 years Therapy

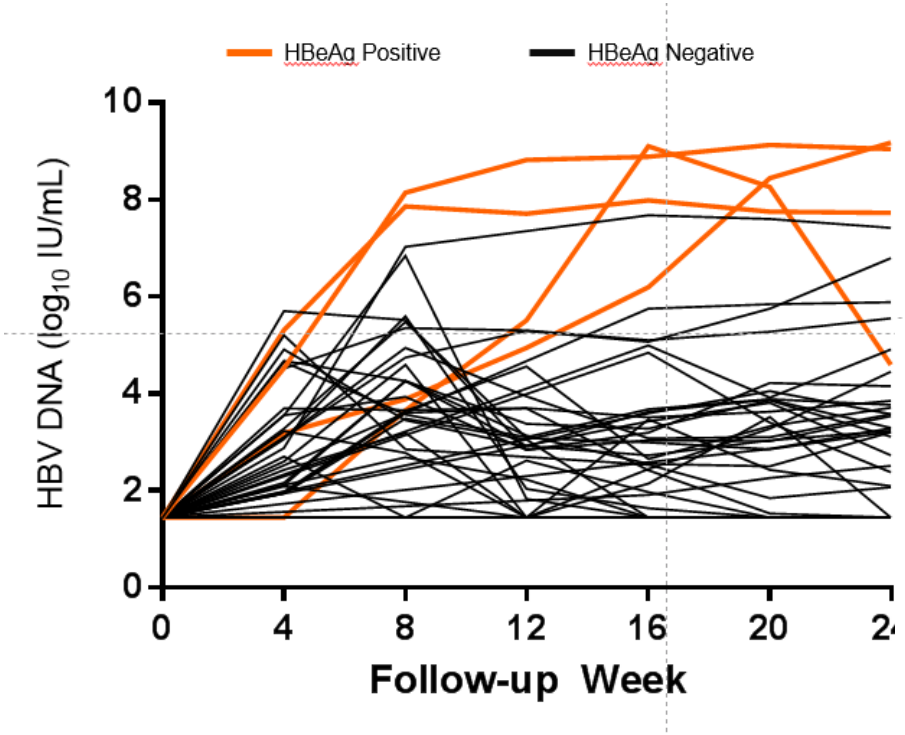


Majority of patients were HBeAg negative at TFFU

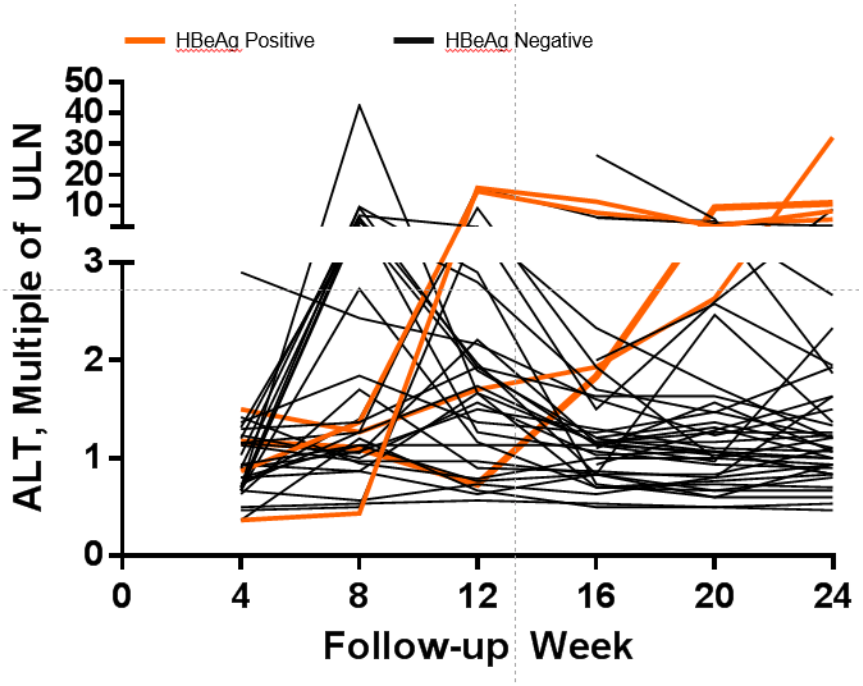
Most patients did not complete 24 weeks of TFFU

Confidential

HBV DNA Profiles



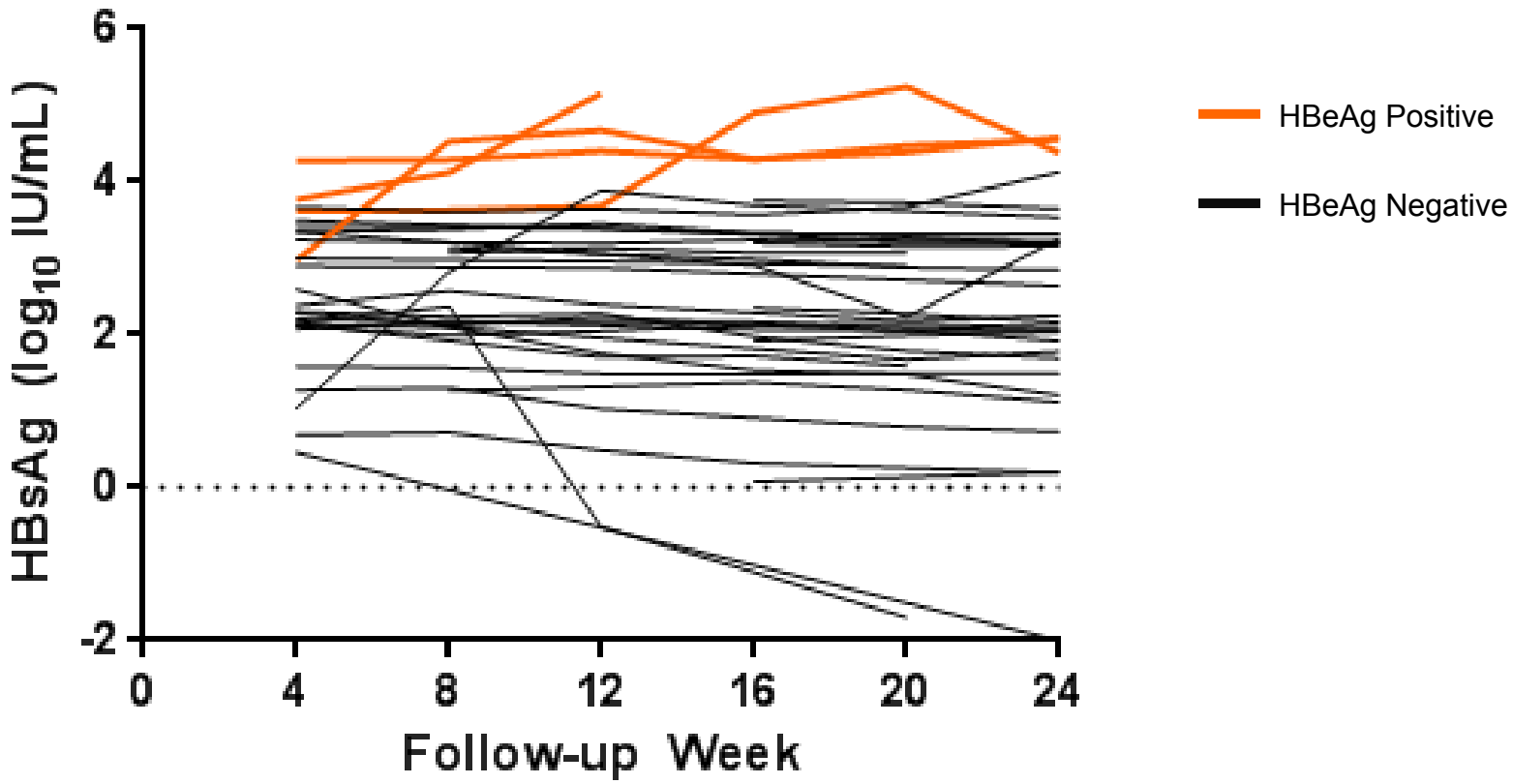
ALT Profiles



Week 24 HBV and DNA: TFFU Completers (N=43)

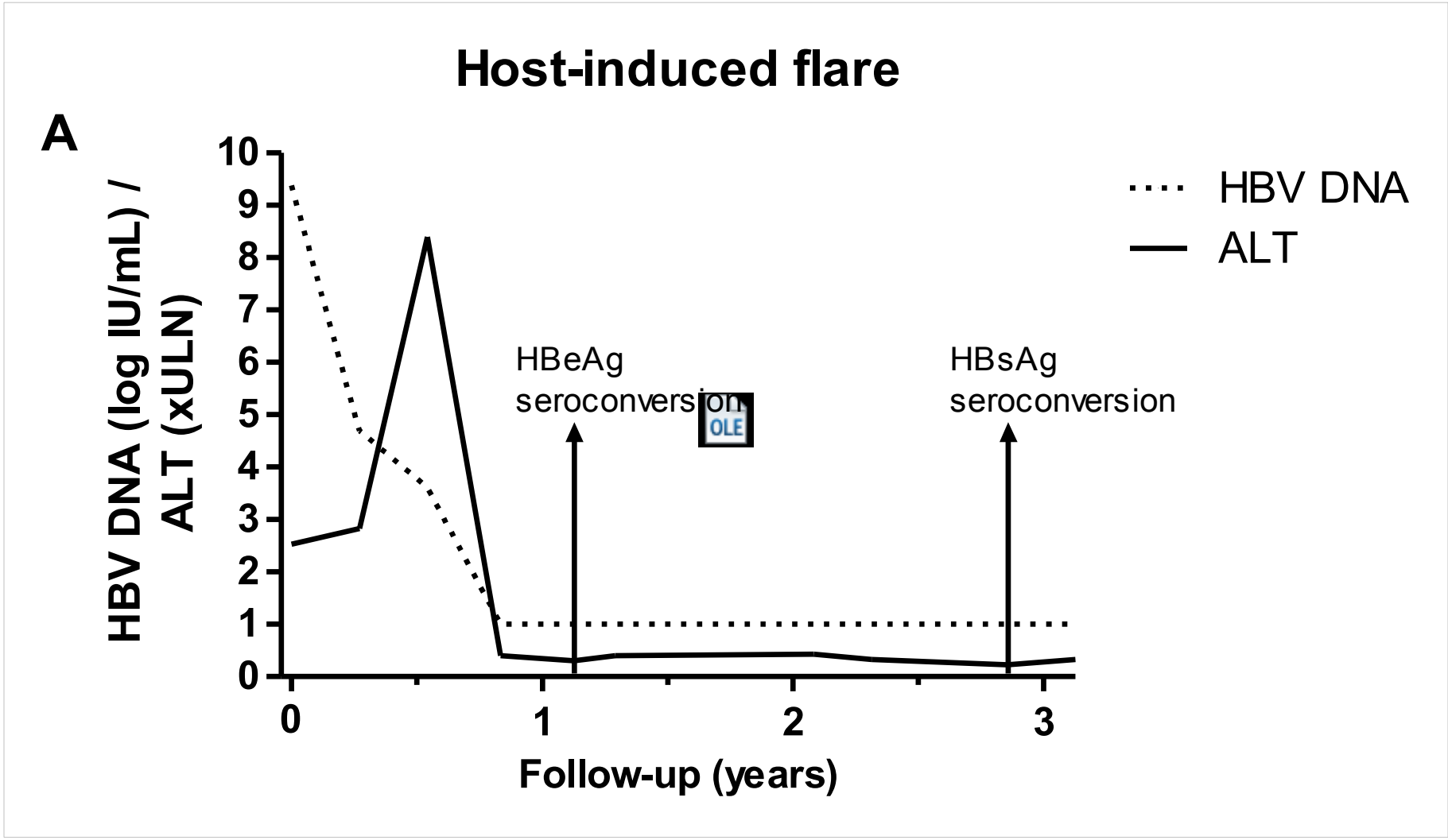
N (%)	
11 (26)	HBV DNA <2000 IU/mL ALT <ULN
14 (33)	HBV DNA <2000 IU/mL ALT >ULN
5 (12)	HBV DNA >2000 IU/mL ALT <ULN
13 (30)	HBV DNA >2000 IU/mL ALT >ULN

Quantitative HBsAg during TFFU: TFFU Completers (N=31)

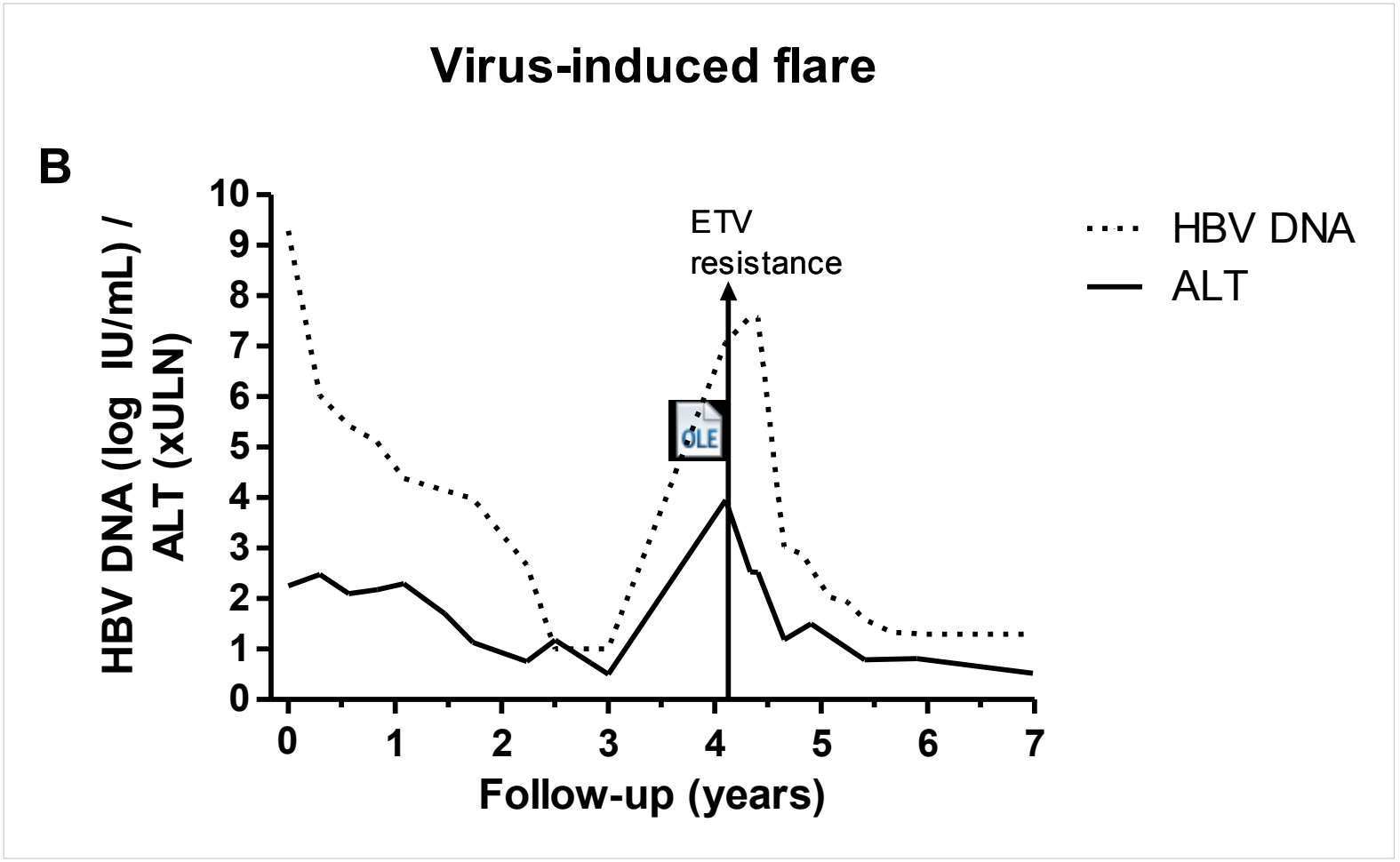


Which type of ALT flare has the patients?

- Virus induced flare
- Host Induced flare

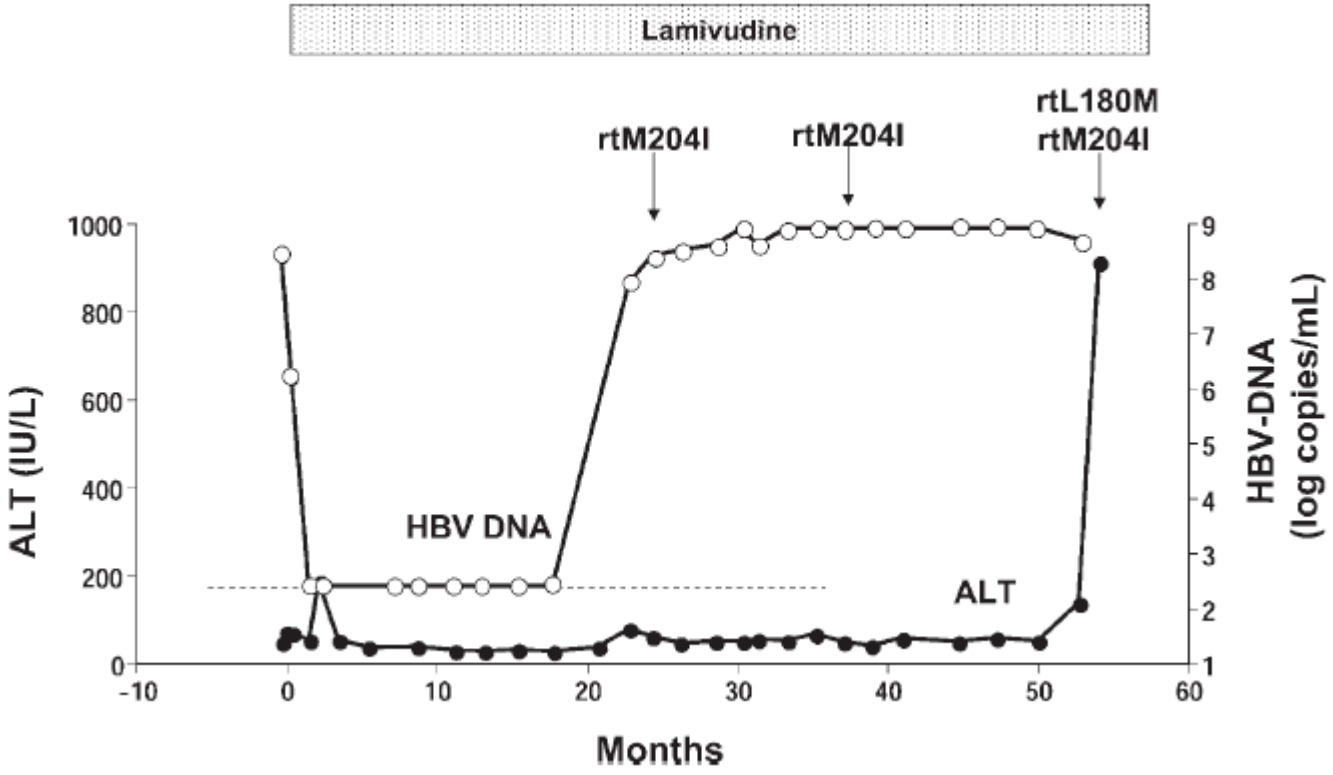


Chi H, et al. J Gastroenterol Hepatol 2016



Chi H, et al. J Gastroenterol Hepatol 2016

Viral resistance induced flares



Enomoto, J Med Virol 2007

Management of HBV Flares

- Initiate anti-viral therapy before HBV flare, when HBV DNA is rising
- After stopping anti-viral therapy, viral resistance, post partum
- **Treatment of flares**
- - Initiate anti-viral therapy as soon as possible
- – Monitor for improvement in ALT, Bil and INR

Chang M, Liaw YF. J Hepatol 2014

Outcome

Re-start TDF

	ALT UI/mL	HBV DNA	HBsAg
Baseline	121	8,5x105	125
3 months	56	1,2x103	123
6 months	19	Undetectable	100
12 months	23	Undetectable	92
2 yrs	22	Undetectable	87
3 yrs	15	Undetectable	46

Abdominal US every 6 months: Normal

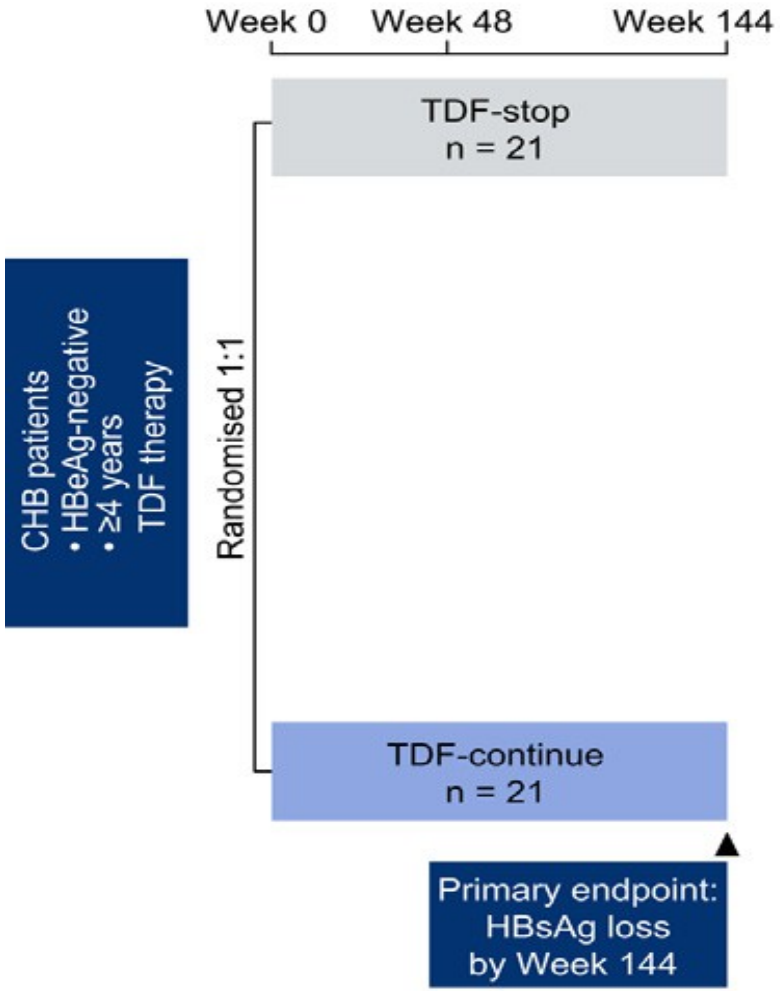
Stopping rules with NUCs for HBV therapy?

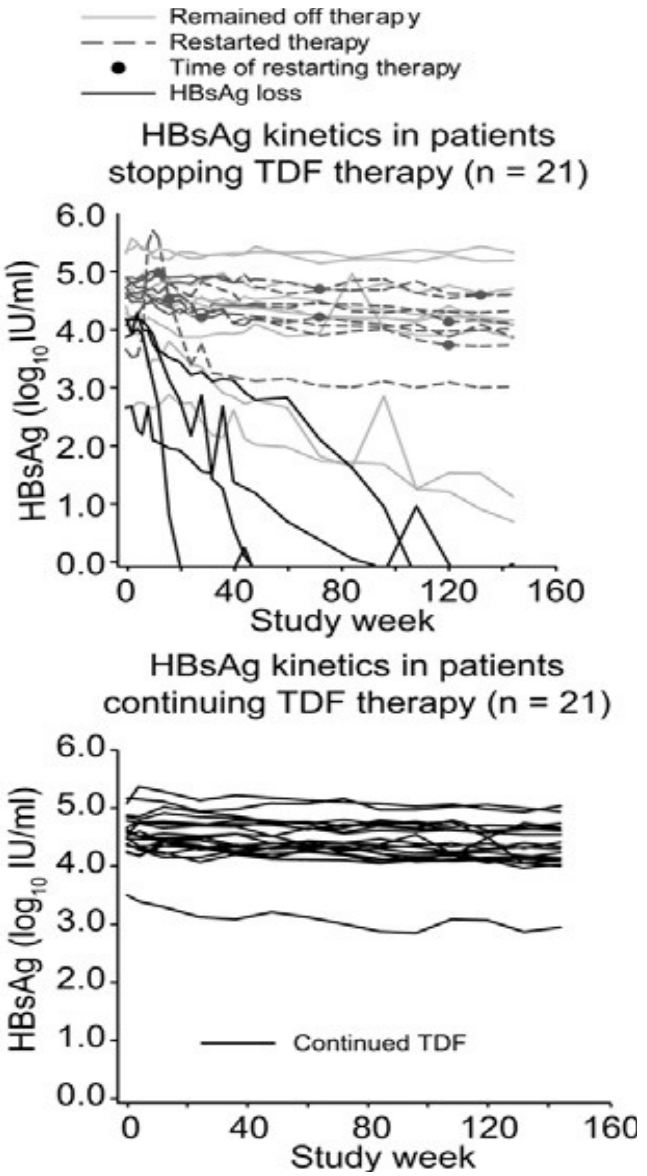
CHB treatment guidelines	EASL (2017)	AASLD (2015)	APASL (2016)
HBeAg-ve	Discontinuation of NAs in selected non-cirrhotic HBeAg-negative patients who have achieved long-term (P3 years) virological suppression under NA may be considered if close post-NA monitoring can be guaranteed	**Continue until HBsAg clearance**	**Continue until HBsAg clearance**

1. EASL Clinical Practice Guidelines. J Hepatol 2017
2.Terrault N , et al. Hepatology 201
3. Sarin SK , et al. Hepatol Int 2016

APASL: Asian Pacific Association for the Study of the Liver
HBeAg: hepatitis B e antigen; HBsAg: hepatitis B surface antigen;
HBV: hepatitis B virus

FINITE Study



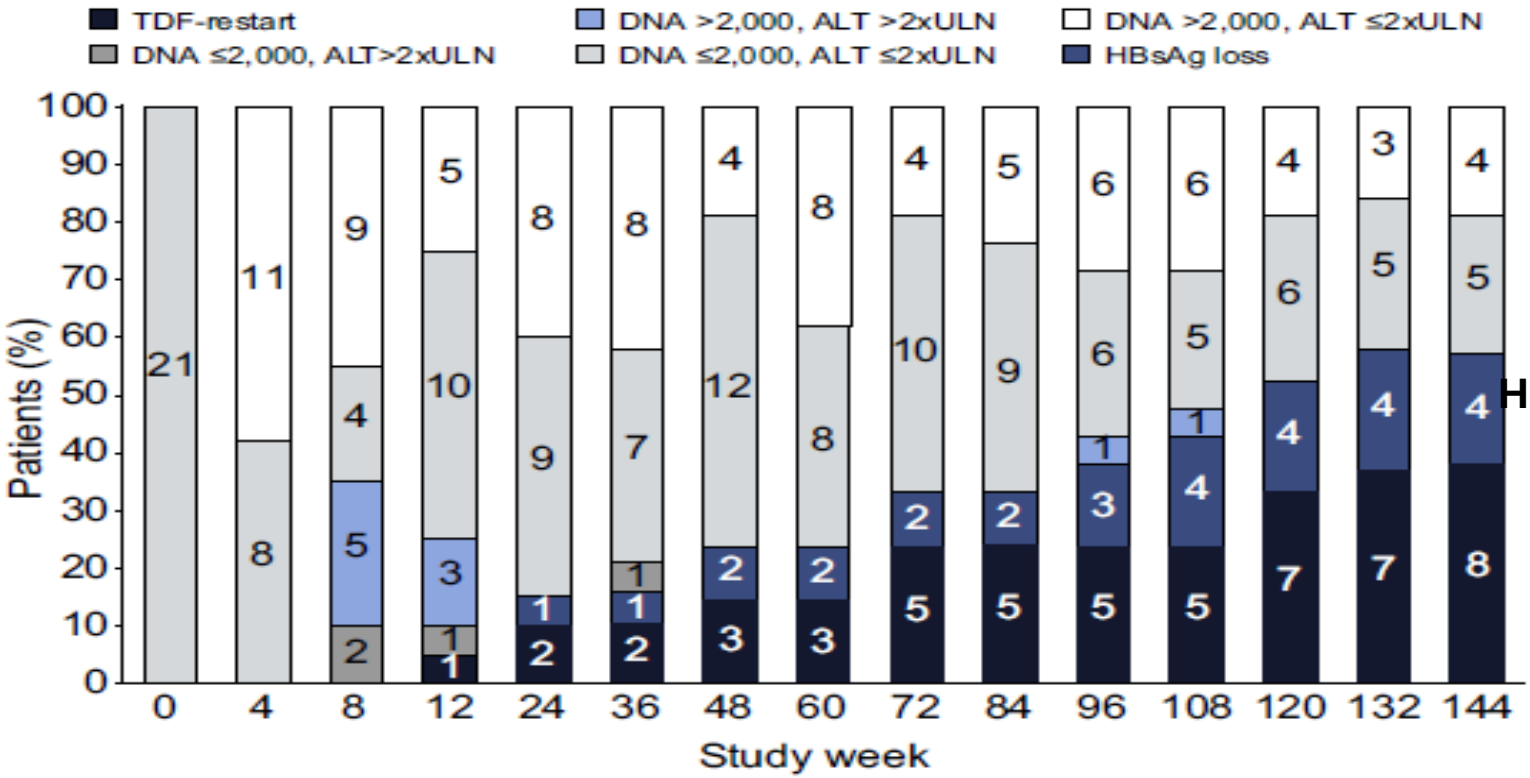


No cirrhosis (Fibroscan ≤10 kPa), normal ALT, HBeAg-, antiHBe +

antiHBe +

Berg T et al J Hepatol 2017

Serological, Virologic and Biochemical outcome after stopping TDF (n=21)



Berg T et al. *J Hepatol 2017*

Summary

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Discontinuing NUCs therapy in patients with cirrhosis can led to severe ALT flares and hepatic decompensation

NUCS discontinuation is not indicated in patients with cirrhosis, even after years of persistent viral suppression

The outcome of discontinuation NUCs in patients with cirrhosis regression is unclear