

When to stop Nas?

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Disclosures

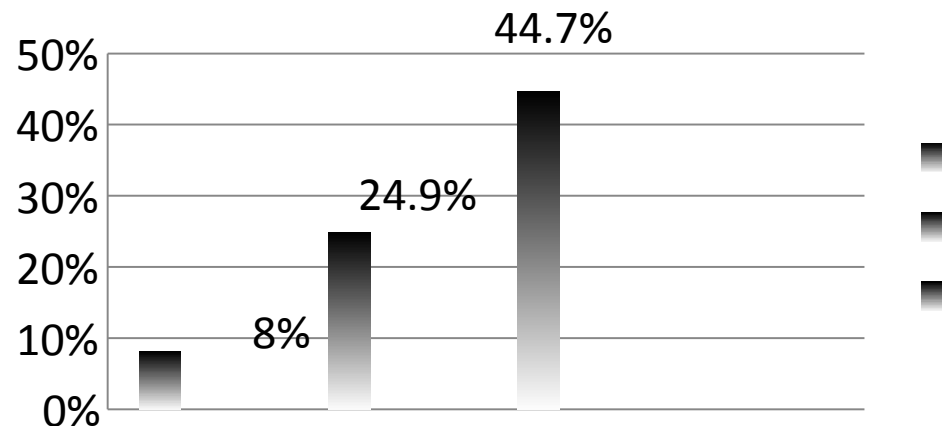
- Advisory board of, and/or, received speaker fee from BMS, Gilead, GSK, MSD, and Novartis

HBsAg clearance is uncommon in the natural history of Chronic Hepatitis B

- Spontaneous HBsAg clearance
 - 0.12-2.38% x year (Asian countries)
 - 0.54-1.98% x year (Western countries)

Chu C-M, et al. Antivir Ther 2010;15: 133–43

- Cumulative HBsAg clearance

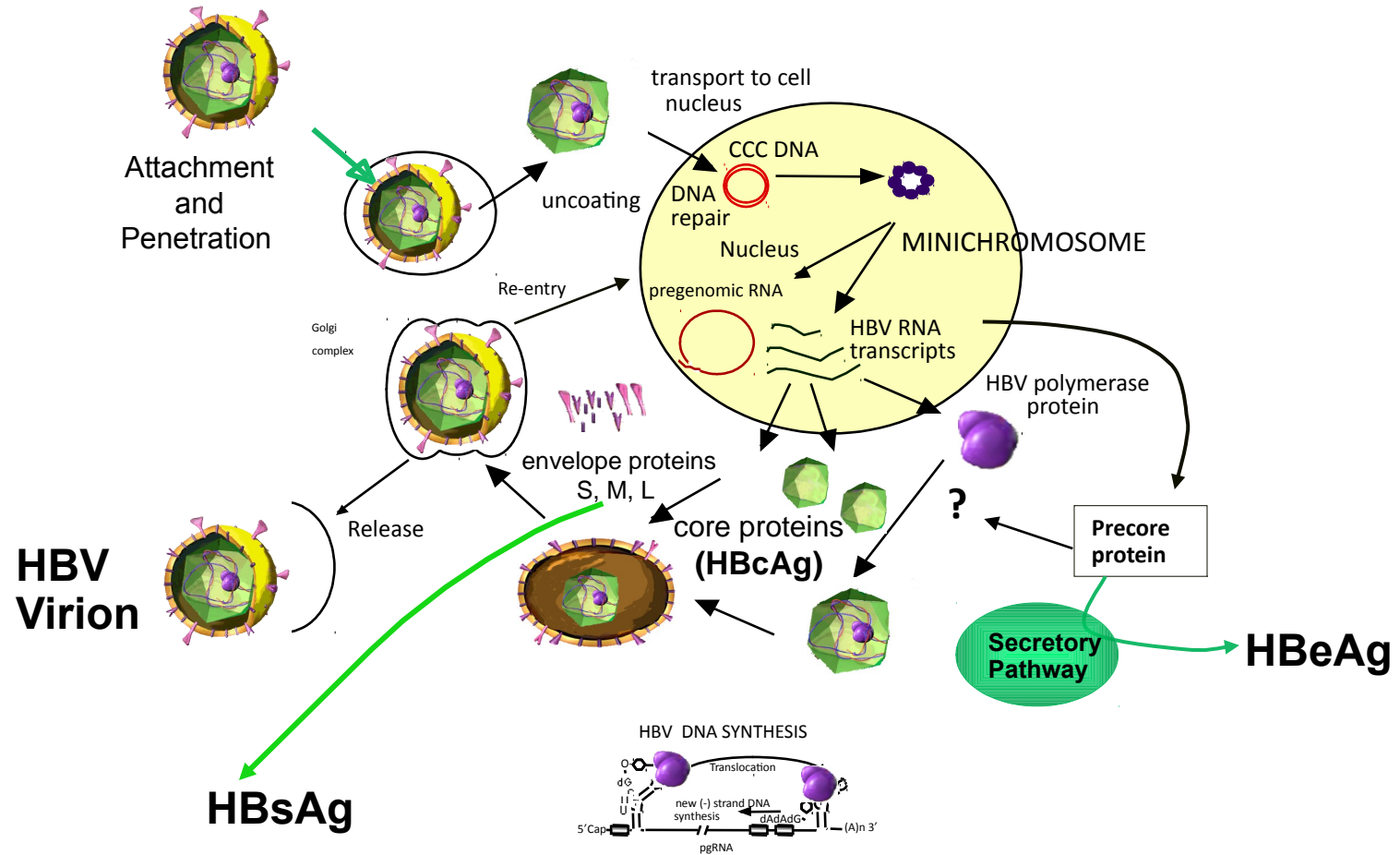


Moucari R, et al. Gastroenterologie Clin Biol 2010; 34(Suppl. 2): S119–25.

Factors associated with HBsAg clearance

- Older age
- Normal ALT
- Cirrhosis
- HBeAg negative
- Undetectable HBV-DNA
- Genotypes A and B

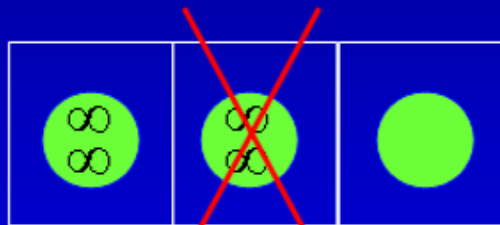
HBV Replication: Recycling or Release



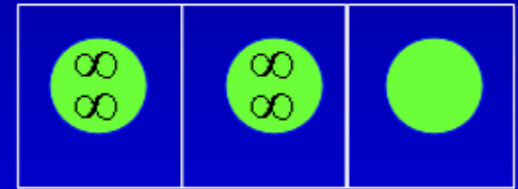
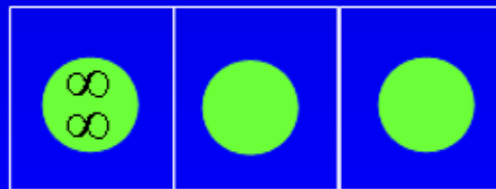
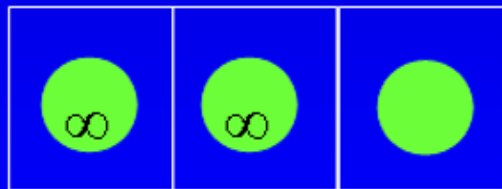
How is ccc DNA cleared?

Cytolytic mechanism

Noncytolytic mechanism



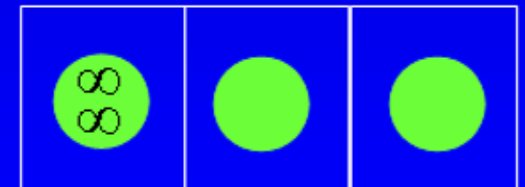
Cell death



IFN- γ

TNF- α

Cell 'cure'



- Replacement by infected hepatocyte
- Dilution of ccc DNA content

- Replacement by uninfected hepatocyte

International Guidelines

Indications for stopping NA

	EASL1	APASL2	AASLD3
HBeAg positive	Anti-HBe positive and undetectable DNA for 12 months	Anti-HBe positive and undetectable DNA for 12 months	Anti-HBe positive and undetectable DNA for 6 months

1. EASL clinical practice guidelines. *J Hepatol*. 2012 Jul;57(1):167-85; 2. Liaw Y-F, et al. *Hepatol Int* 2012; 6: 531–61; 3. Lok ASF, et al. *Hepatology* 2009; 50: 661–2.

Serological and virological efficacy of NA therapy.
 Results for HBeAg positive patients at 12 months of therapy

	LAM	ADV	LdT	TDV	ETV
AntiHBe seroconversion	16-18%	12-18%	22%	21%	21%
DNA <60 IU/mL	36-44%	13-21%	60%	76%	67%
HBsAg loss	0-1%	0%	0.5%	3.2%	2%

HBsAg loss with NAs at 1, 2 and 5 years of treatment in HBeAg positive patients in the registration studies

Antiviral treatment	1 year	2 years	5 years
Lamivudine	0-1%	--	--
Adefovir	0%	--	--
Telbivudine	0.5%	--	--
Tenofovir	3%	8%	10%
Entecavir	2%	5%	--

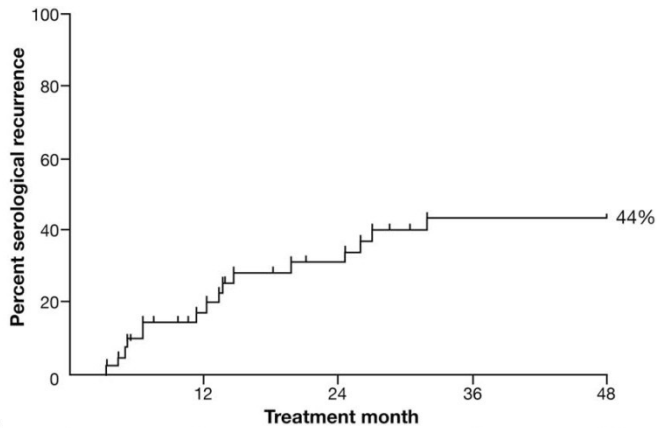
Virological Relapse and HBeAg reversion after HBeAg seroconversion in HbeAg +ve patients treated with NA

Study	Drug	N	Virological relapse	HBeAg reversion	ALT flares
Song 2000	LMV	98	49% in 2 years	13%	15%
Chien 2003	LMV	82	48% in 1 year	28%	43%
Dienstag 2003	LMV	39	28% in 3 years	28%	37%
Ryu 2003	LMV	85	31% in 2 years	13%	94% of those with relapse
Fung 2009	LMV	22	100% in 5 years	9%	44%
Lee 2010	LMV	178	30% in 5 years	17%	-
Wu 2008	ADV	45	45% in 3 years	9%	-

Song et al. Hepatology 2000, Chien et al. Hepatology 2003, Dienstag et al. Hepatology 2003, Ryu et al. J Hepatol 2003, Fung et al. Am J Gastroenterol 2009, Lee et al. Hepatology 2010, Wu et al. Clin Infect Dis 2008

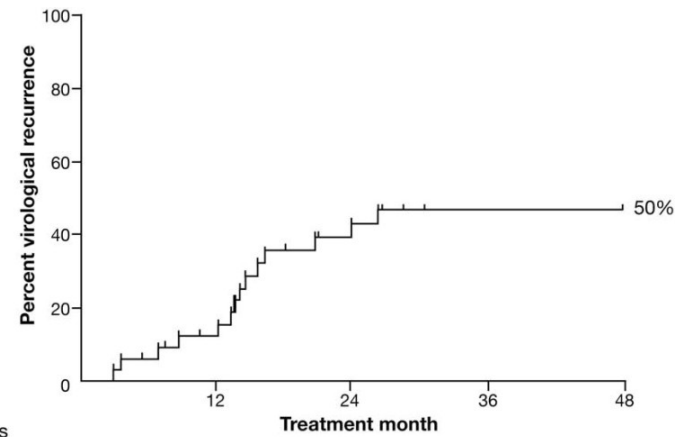
NA Only Induce Temporary HBeAg Seroconversion in Most Patients With Chronic Hepatitis B

Serological Recurrence



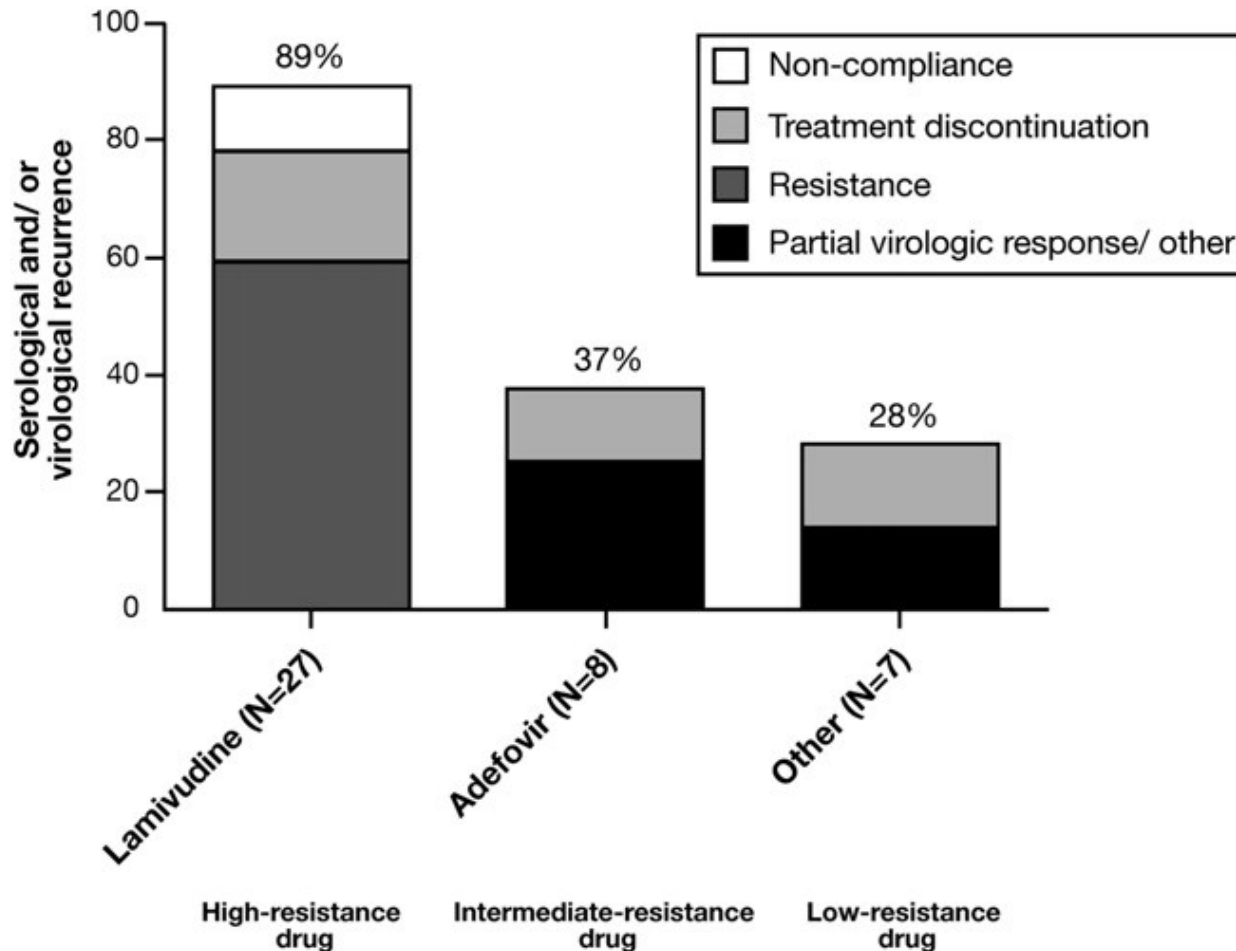
		12	24	36	48
Number of patients without serological recurrence ^a	42	31	24	17	17
Total number of patients ^b in follow-up	42	38	34	30	28

Virological Recurrence



		12	24	36	48
Number of patients without virologic recurrence ^a	34	27	16	11	11
Total number of patients ^b in follow-up	34	31	28	24	24

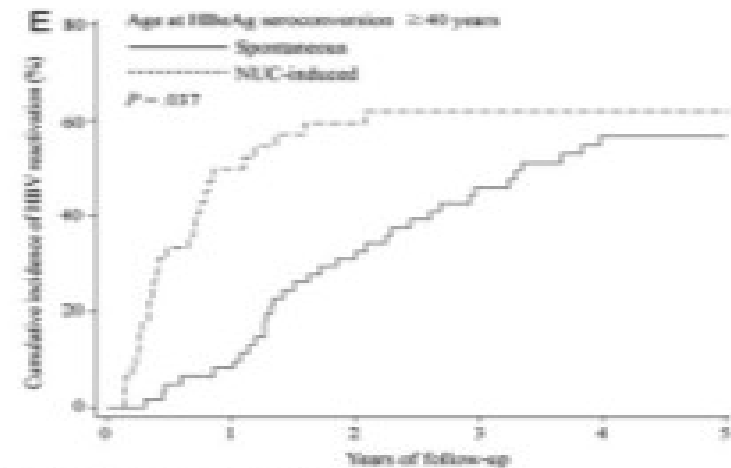
Serologic and/or virologic recurrence after NA-induced HBeAg seroconversion and their causes



Role of Age at seroconversion and the risk of HBV reactivation

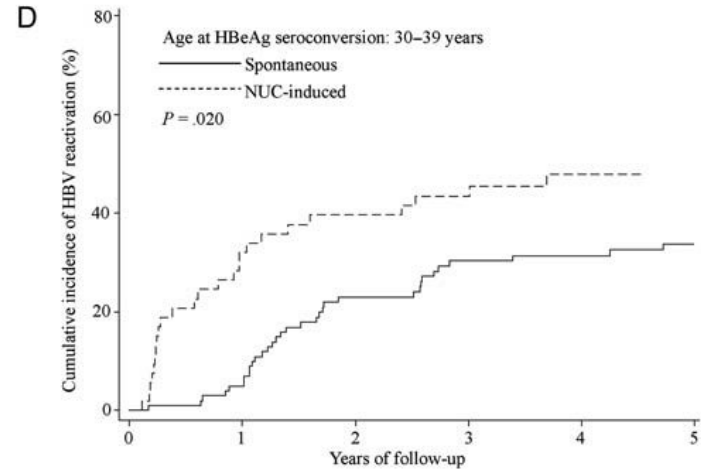
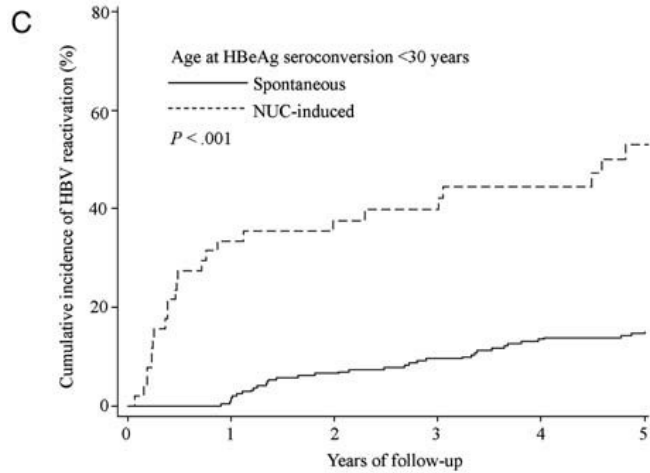


Number of HBeAg seroconverters at risk						
Spontaneous	244	240	225	211	196	184
NUC-induced	50	32	28	25	19	15



Number of HBeAg seroconverters at risk						
Spontaneous	62	56	41	32	25	19
NUC-induced	42	23	17	15	13	11

Spontaneous and NA-induced HBeAg seroconversion by cumulative incidence of HBV reactivation categorized by different ages at HBeAg seroconversion

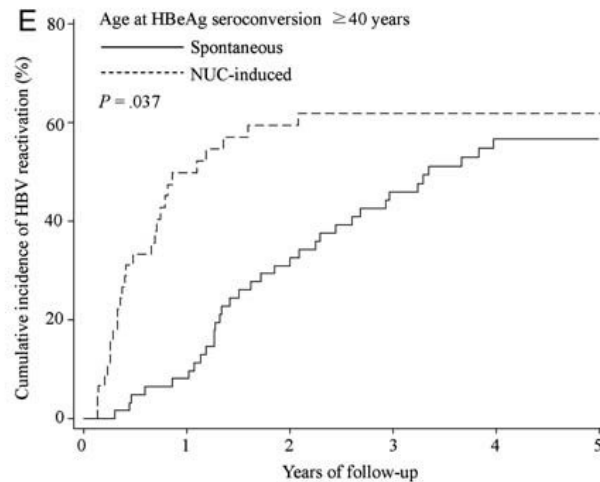


Number of HBeAg seroconverters at risk

Spontaneous	244	240	225	211	196	184
NUC-induced	50	32	28	25	19	15

Number of HBeAg seroconverters at risk

Spontaneous	101	96	75	66	60	53
NUC-induced	53	36	28	26	21	19



Number of HBeAg seroconverters at risk

Spontaneous	62	56	41	32	23	19
NUC-induced	45	21	17	15	13	11

International Guidelines

Indications for stopping NA

	EASL1	APASL2	AASLD3
HBeAg-negative	Not recommended until HBsAg loss	Minimum 2 years with undetectable DNA in 3 occasions, 6 months apart	Not recommended until HBsAg loss

1. EASL clinical practice guidelines. *J Hepatol.* 2012 Jul;57(1):167-85; 2. Liaw Y-F, et al. *Hepatol Int* 2012; 6: 531–61; 3. Lok ASF, et al. *Hepatology* 2009; 50: 661–2.

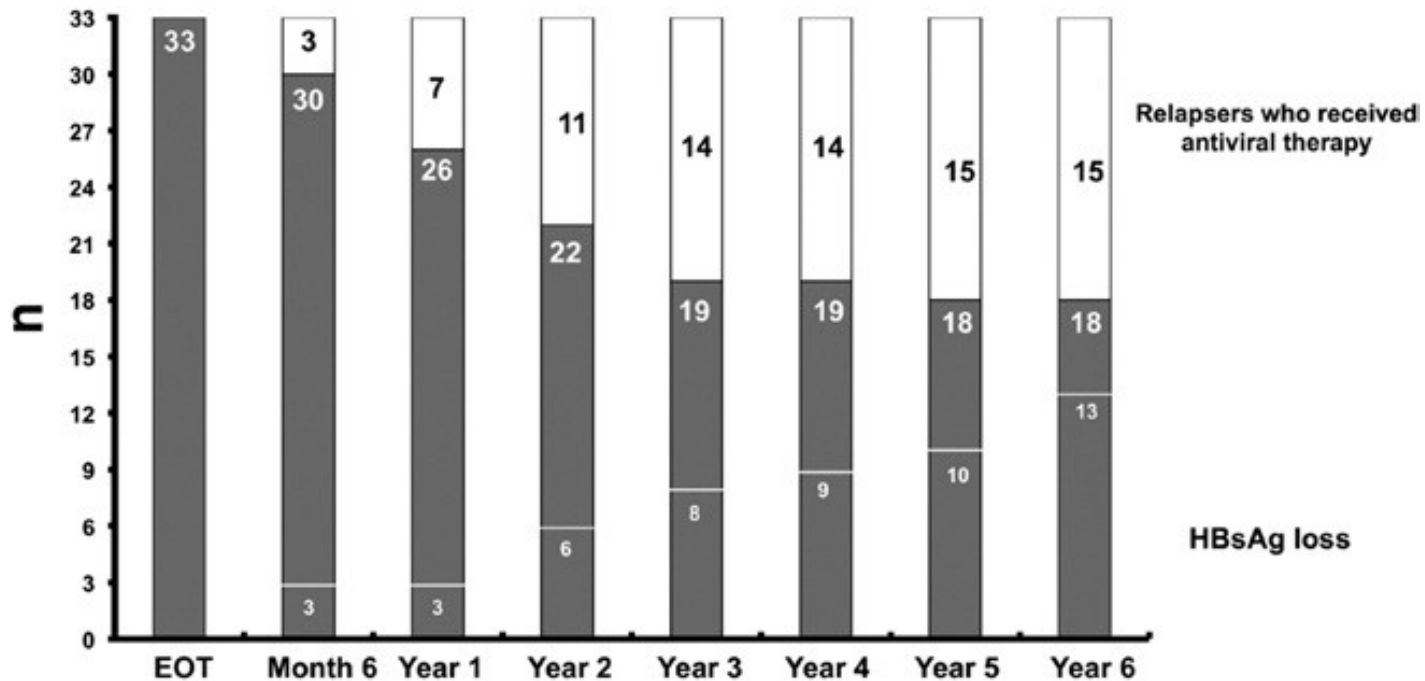
Serological and virological efficacy of NA therapy.
Results for HBeAg negative at 12 months of therapy

	LAM	ADV	LdT	TDV	ETV
DNA <60 IU/mL	72-73%	51-63%	88%	93%	90%
HBsAg loss	0%	0%	0%	0%	0%

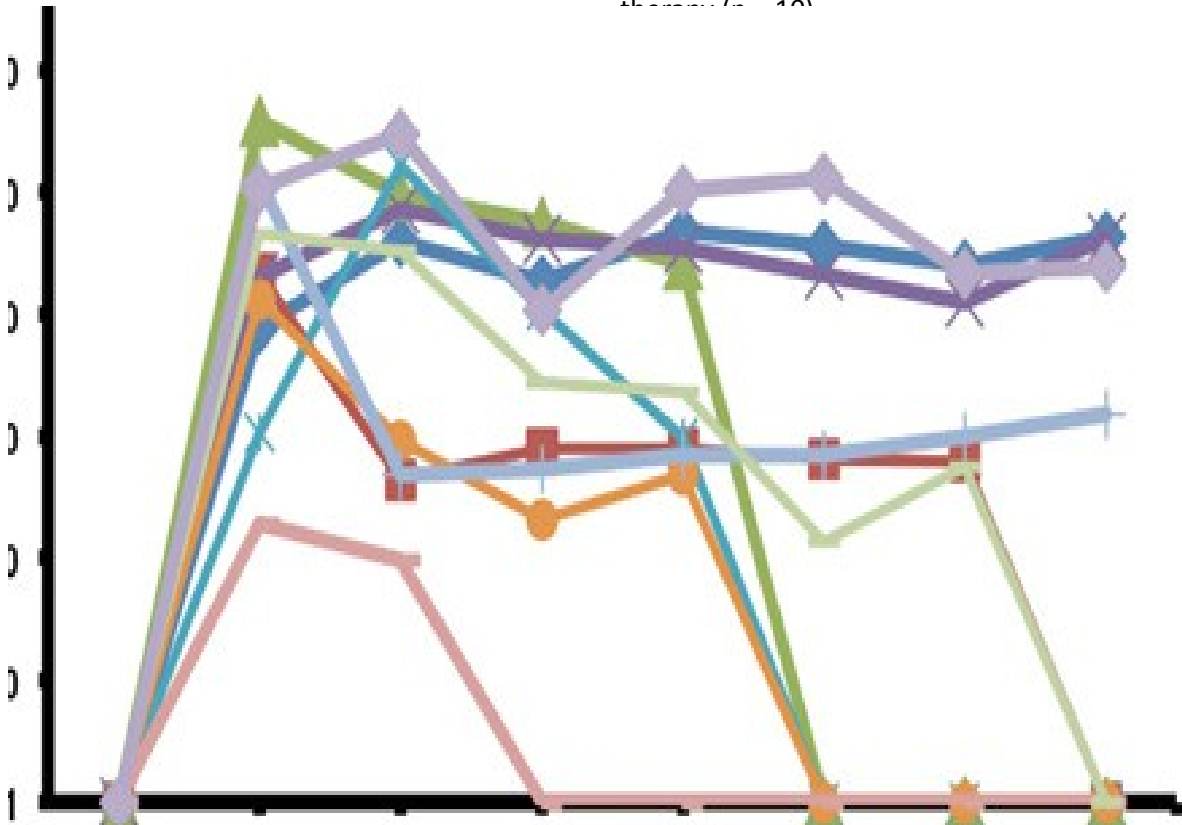
HBsAg loss with NAs at 1, 2 and 5 years of treatment in HBeAg negative patients.

Antiviral treatment	1 year	2 years	5 years
Lamivudine	0%	--	--
Adefovir	0%	--	--
Telbivudine	0%	--	--
Tenofovir	0%	0%	0%
Entecavir	0%	0%	--

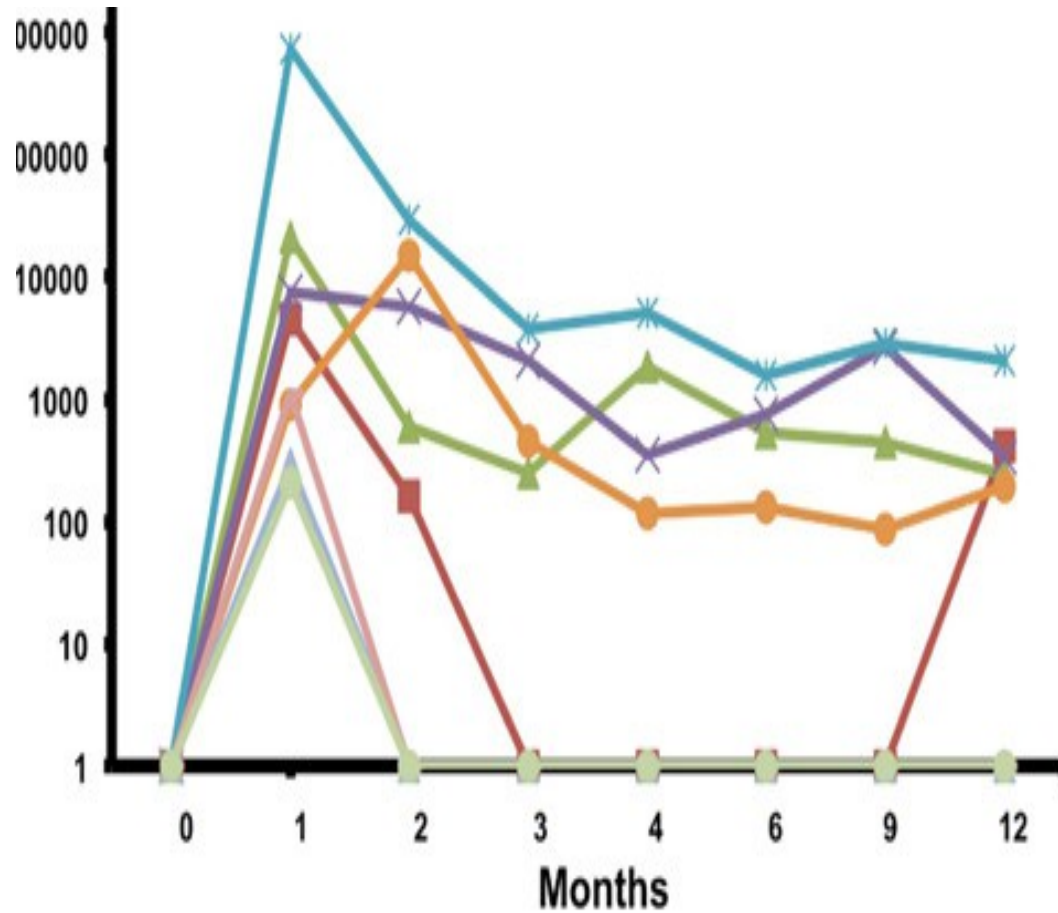
The number of relapsers or lost HBsAg among patients who discontinued NA. Athens Experience



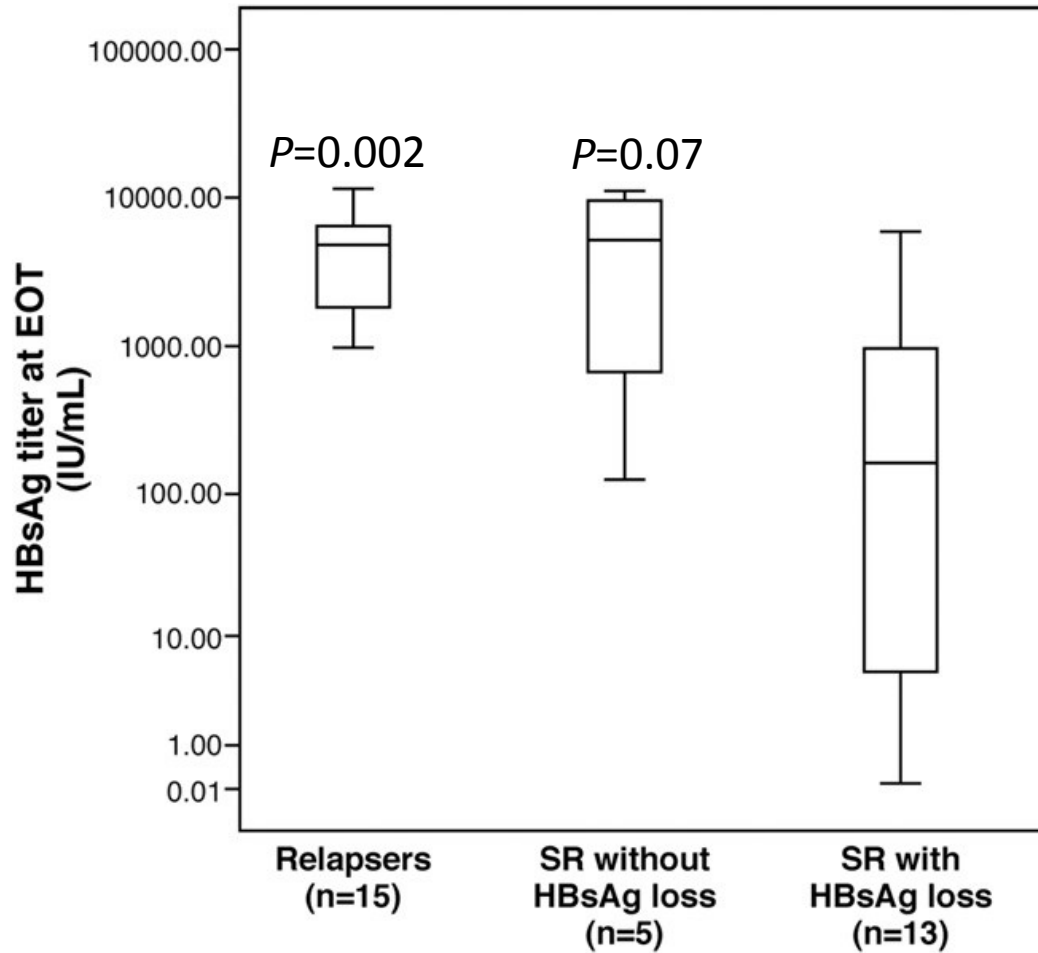
The course of HBV DNA during the first 12 months off treatment in patients with biochemical relapse who remained without antiviral



The course of HBV DNA during the first 12 months off treatment in the 8 patients who did not receive antiviral therapy and did not show biochemical relapse



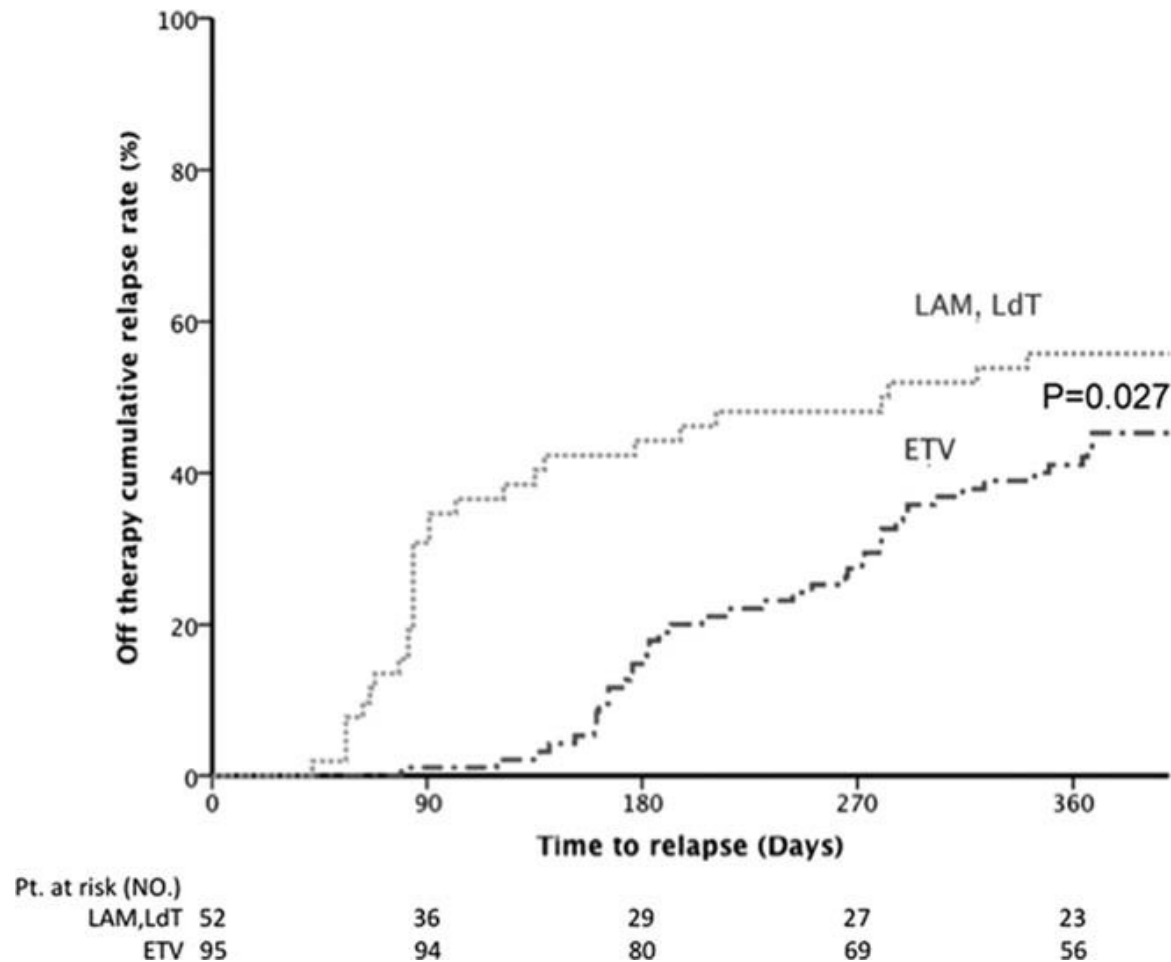
End Of Treatment HBsAg levels in patients with SR and HBsAg loss vs patients with virological and biochemical relapse or patients with SR without HBsAg loss.



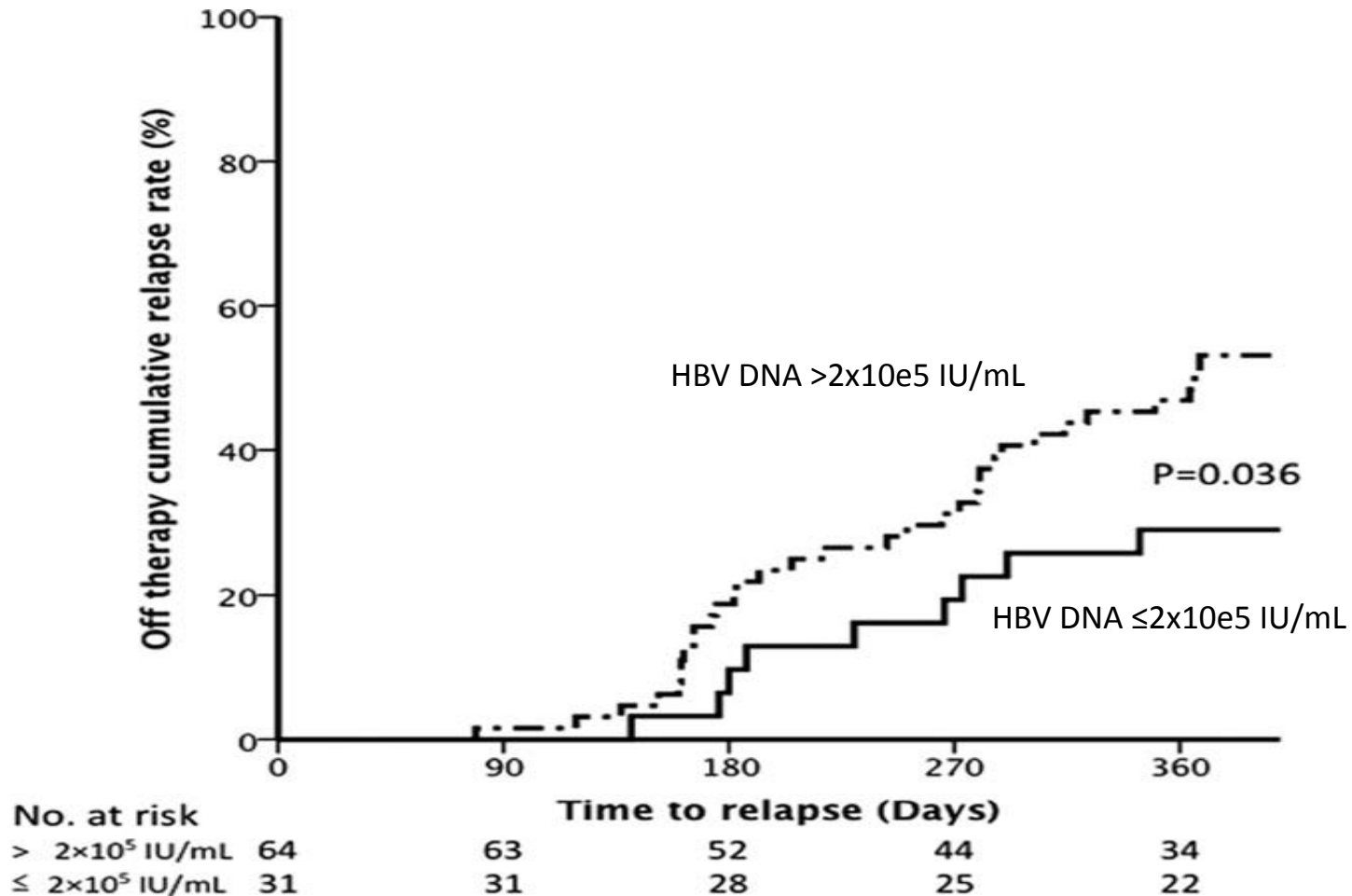
Stopping long-term NA therapy before HBsAg loss in HBeAg negative CHB patients: follow-up of long term responders

- 32 HBeAg negative patients who stopped NA treatment. Follow-up 24 months.
- 9 patients without relapse:
 - EOT qHBsAg <1000 IU/ml: 100%
 - 6 patients lose HBsAg (3 antiHBs seroconversion)
 - Progressive reduction qHBsAg during follow up.
- qHBsAg <1000 IU/ml could be used as a stopping rule in HBeAg negative CHB patients with no advanced fibrosis who remains with undetectable DNA.

One-year cumulative relapse rate after cessation of ETV therapy was lower and relapses occurred later than those after cessation of LAM or LdT

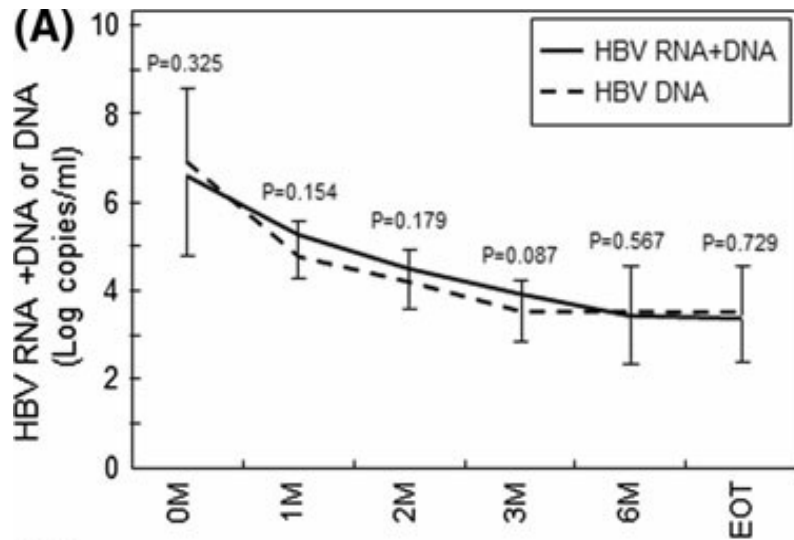


The cumulative relapse rate in patients with a baseline serum HBV DNA $\leq 2 \times 10^5$ IU/mL was significantly lower than those with a level $> 2 \times 10^5$ IU/mL

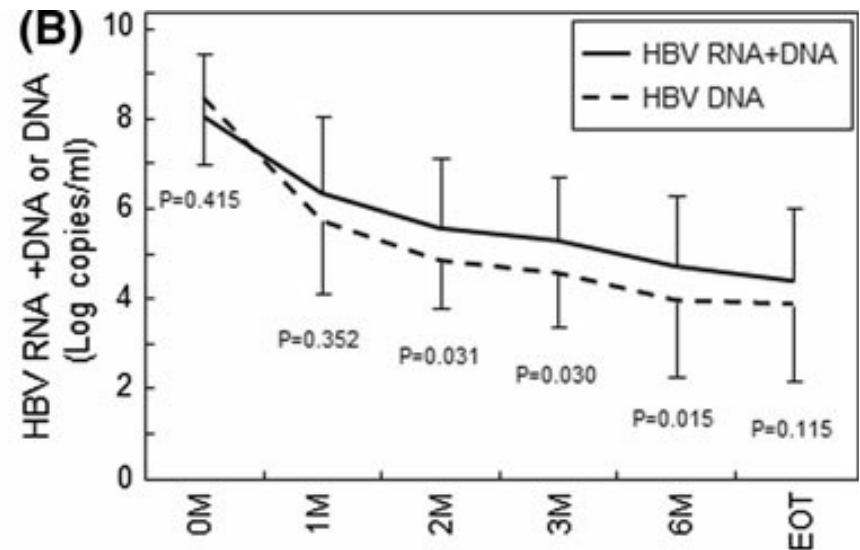


Changes in HBV DNA and HBV DNA + RNA titers during NA therapy

Non-relapsers



Relapsers



Summary

Recommended	All patients: HBsAg loss HBeAg positive patients: HBeAg seroconversion and undetectable HBV DNA after 9-12 months of consolidation therapy
Controversial	HBeAg negative patients: Undetectable HBV DNA and very low titers of HBsAg after at least 2 years?????
Not recommended	All other patients