Case presentation

- PN dob 8 Oct 1987; male. Born Burma. Scholar
- **HBeAg positive chronic hepatitis B. Genotype C**
- 2004: ALT 237 U/L, AST 85 U/L,
  - HBeAg positive HBV DNA > 110,000,000 IU/mL
- Liver biopsy 2005:
  - Lobular hepatitis and mild fibrosis on liver biopsy
- Father HBsAg positive. Family history of HCC

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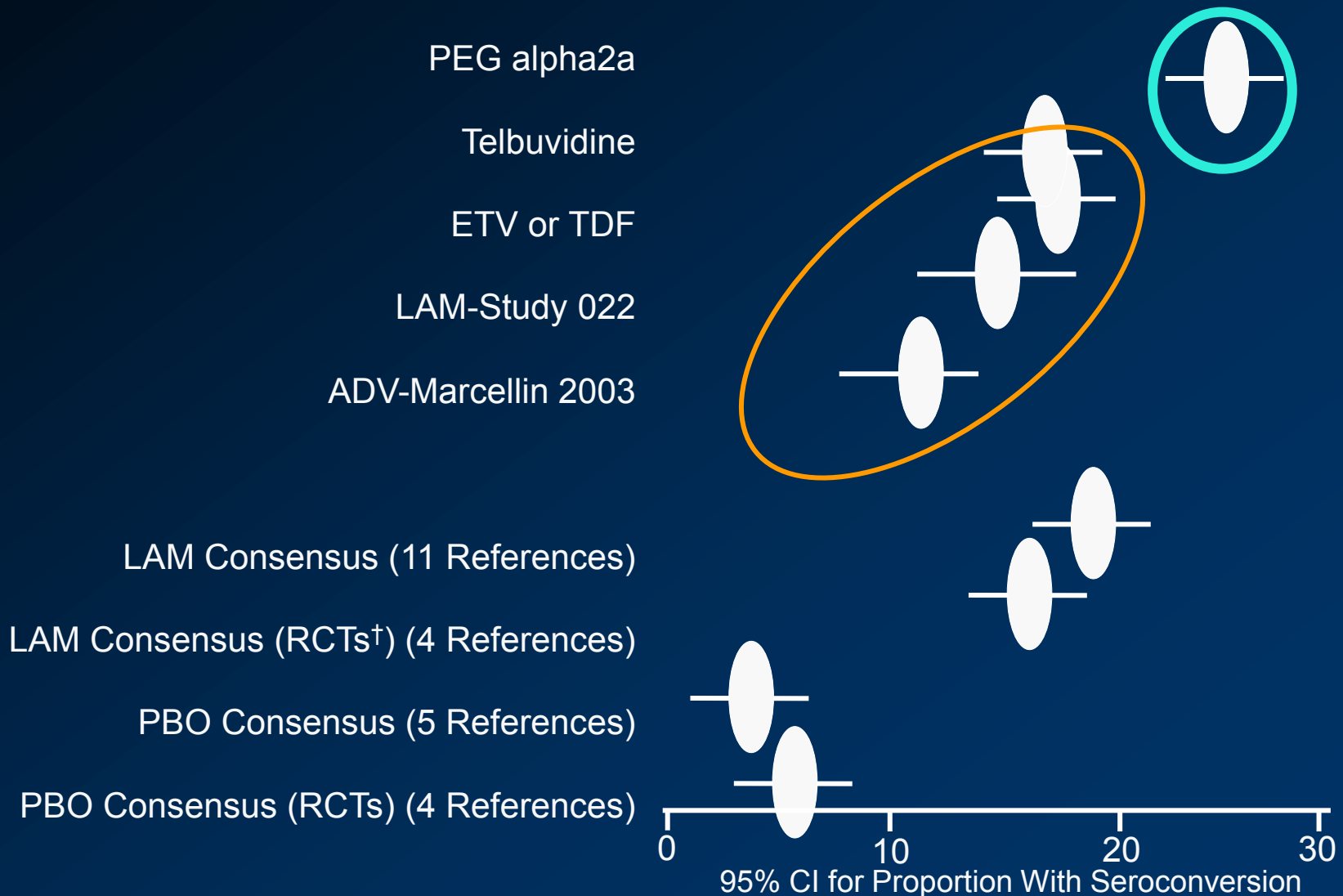
- Started Lamivudine and Adefovir October 2005
- HBV DNA suppression: Normal ALT and AST. HBeAg seroconversion April 2007; stopped April 2008 afterward
- No resistance mutations detected

Date	HBV DNA (IU/mL)	HBeAg	Anti-HBe	ALT (U/L)	AST (U/L)
14 Aug 2008	3.6×10^6	Negative	Positive	225	135
2 Oct 2008	28.3×10^6	Negative	Positive	181	86
Start PEG IFN					
3 Nov 2008	549,656	Negative	Positive	129	62
18 Dec 2008	35,975	Negative	Positive	67	41
16 Mar 2009	11,645	Negative	Positive	90	51
7 May 2009	11,665	Negative	Positive	90	56
13 Aug 2009	35	Negative	Positive	68	42
21 Oct 2009	416	Negative	Positive	54	37
Stop PEG IFN					
26 Nov 2009	5,576	Negative	Positive	33	25
28 Jan 2010	1,509	Negative	Positive	26	23
25 Mar 2010	1,175	Negative	Positive	24	25
8 Jul 2010	5,484	Negative	Positive	27	24
4 Nov 2010	1,615	Negative	Positive	23	22
4 May 2011	270	Negative	Positive	27	23
28 Jul 2011	270	Negative	Positive	22	22

Treatment of HBeAg positive chronic hepatitis B:
With interferon alpha

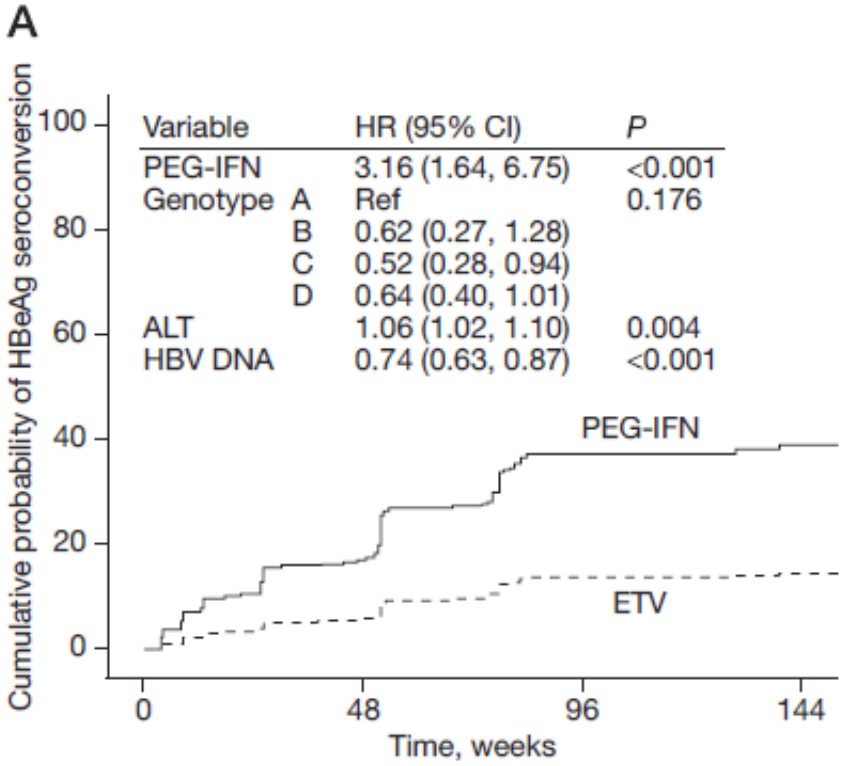
- Goals and endpoints of treatment achieved
  - Suppression of HBV DNA
  - Improve abnormal ALT
  - Improve hepatic histology
  - Slows development of fibrosis
  - Prevents serious disease
  - Accelerates HBeAg seroconversion in some
  - HBeAg loss can lead to HBsAg loss
- Always associated with side effects (injection)
- Host or viral factors leading to response only partially known

HBeAg Seroconversion after one year treatment

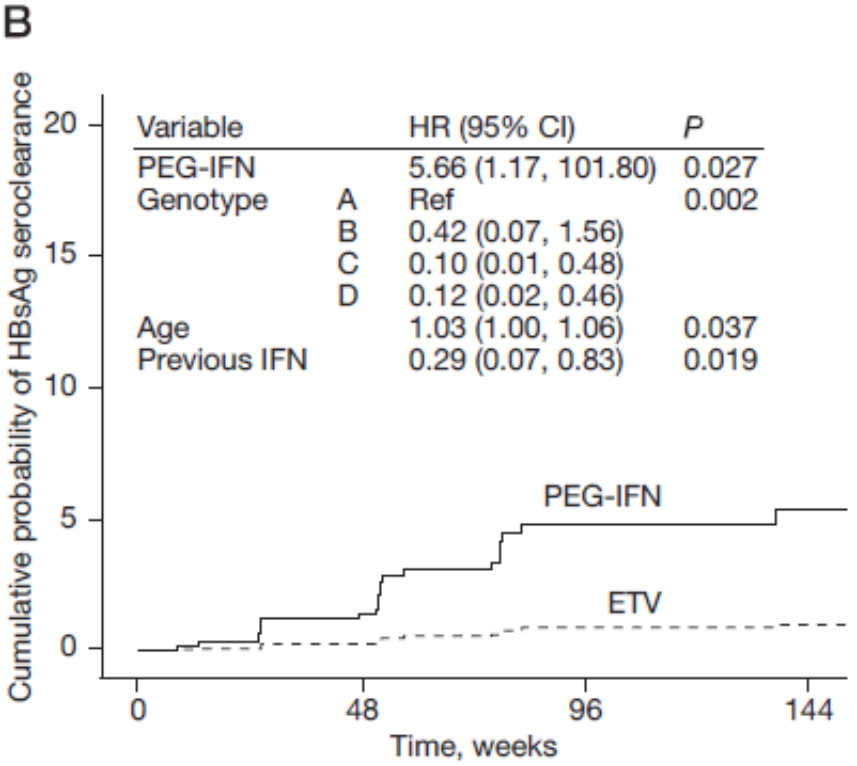


Cumulative probability of response HBeAg positive Interferon or Entecavir

HBeAg clearance



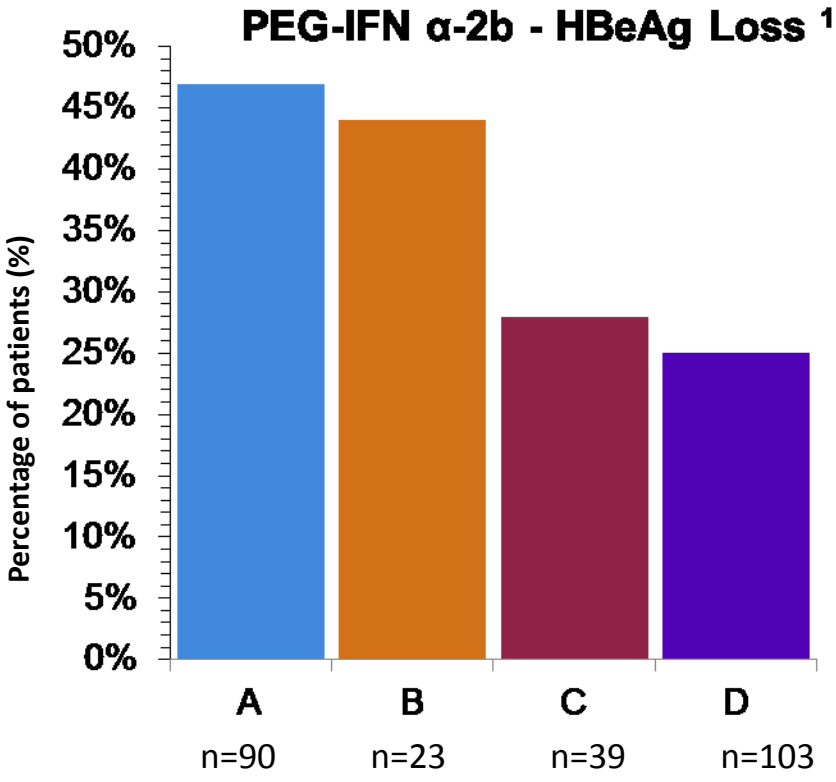
HBsAg clearance

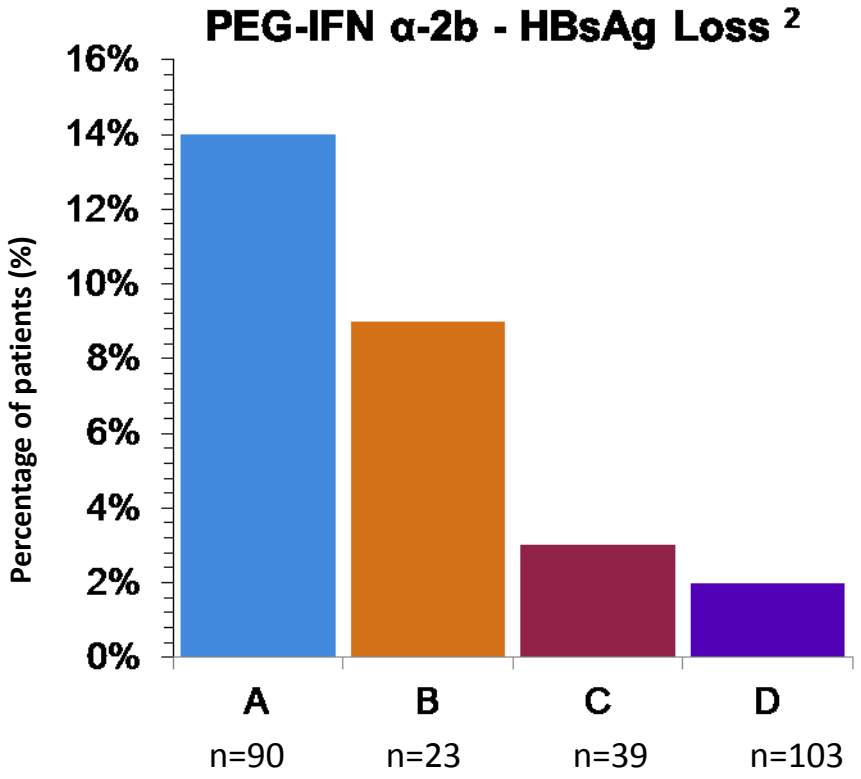


IFN one year; median enteacavir 92 weeks
Higher rates of undetectable HBV DNA with entecavir

Sonneveld Antiviral Therapy 17: 8 1605 2012

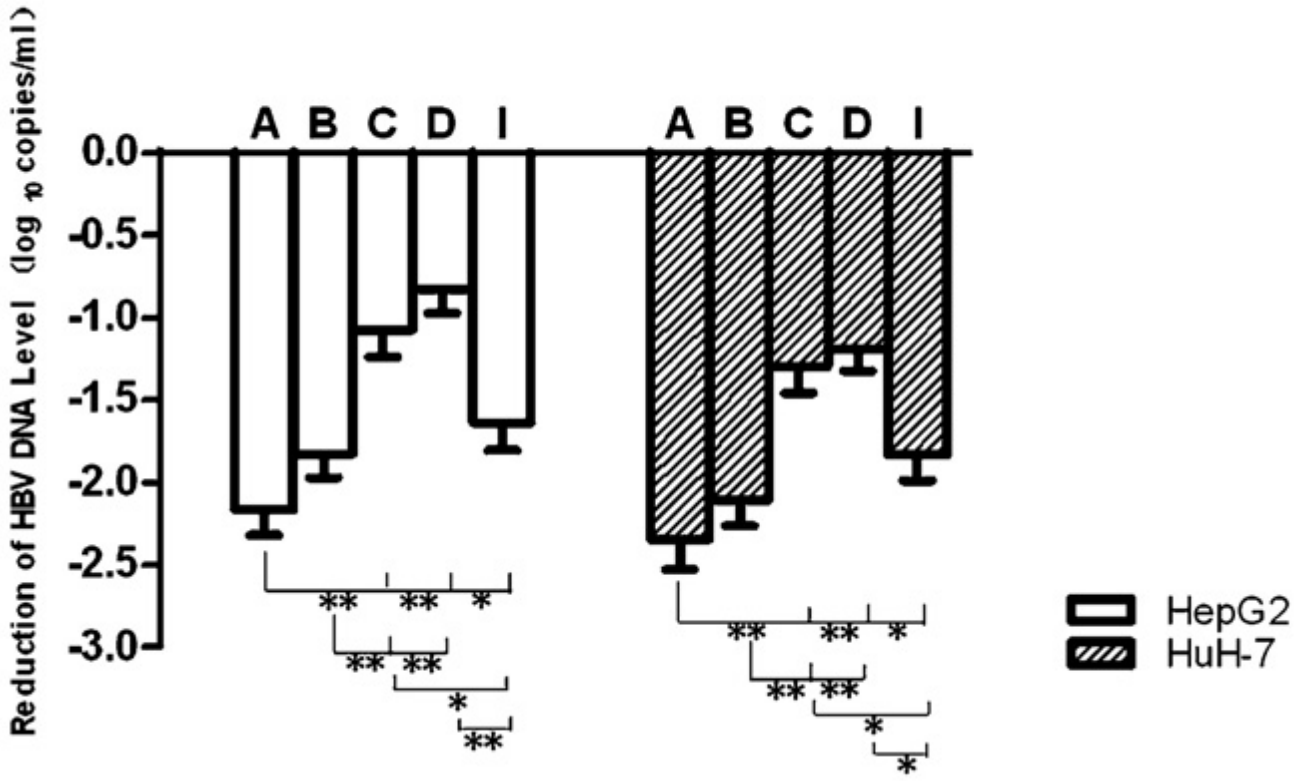
Response to PEG-IFN in HBeAg positive according to HBV genotype





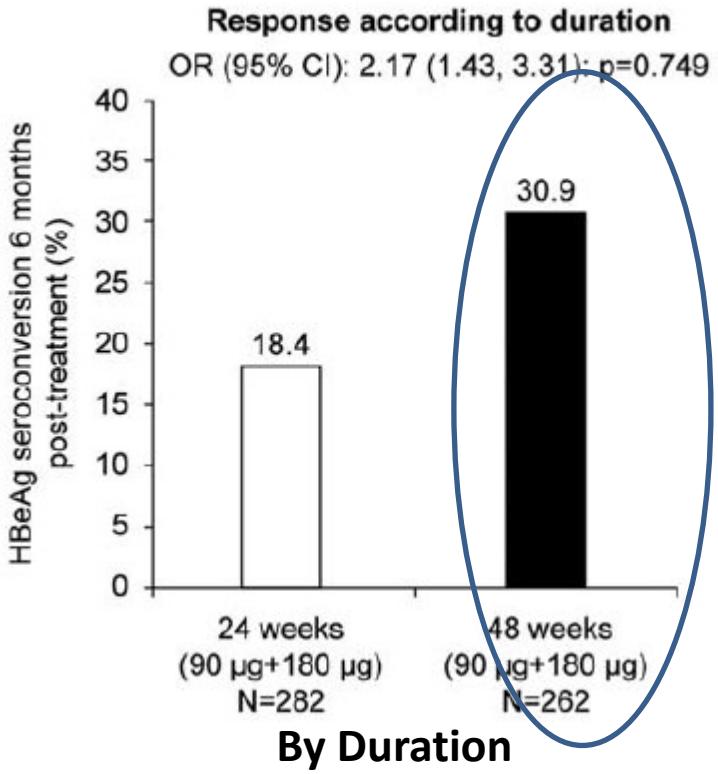
1. Janssen HL, *et al. Lancet* 2005; **363**:123-129. 2. Flink HJ, *et al. Am J Gastroenterol* 2006; **101**:297-303.

HBV Genotype and response
Reduction of HBV DNA levels from baseline in HepG2 and HuH7 cells.
Genotypes A, B, C, D and I

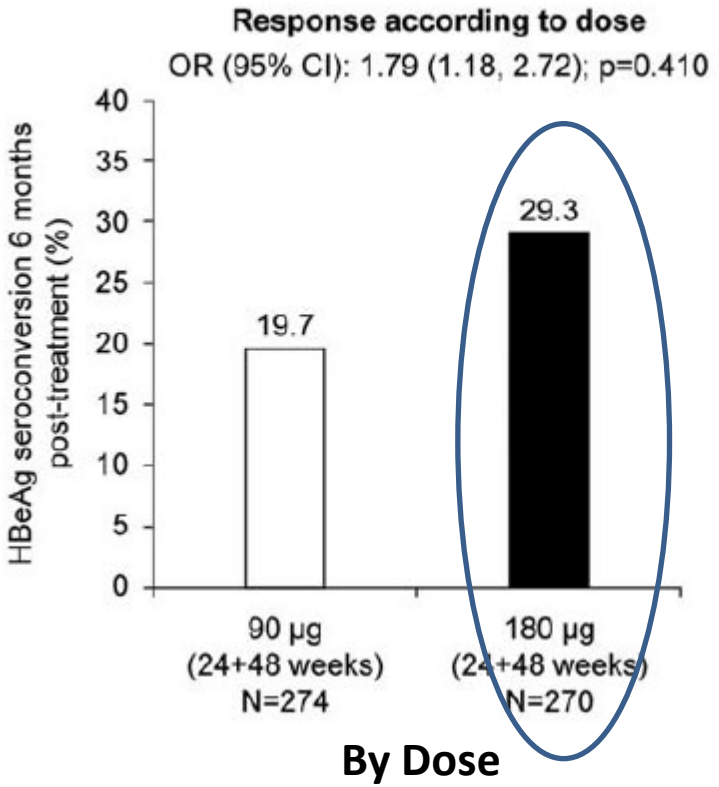


Zhang Y Vir Res 2012

Optimising use: HBeAg seroconversion
180ug 48 weeks optimal
Neptune study



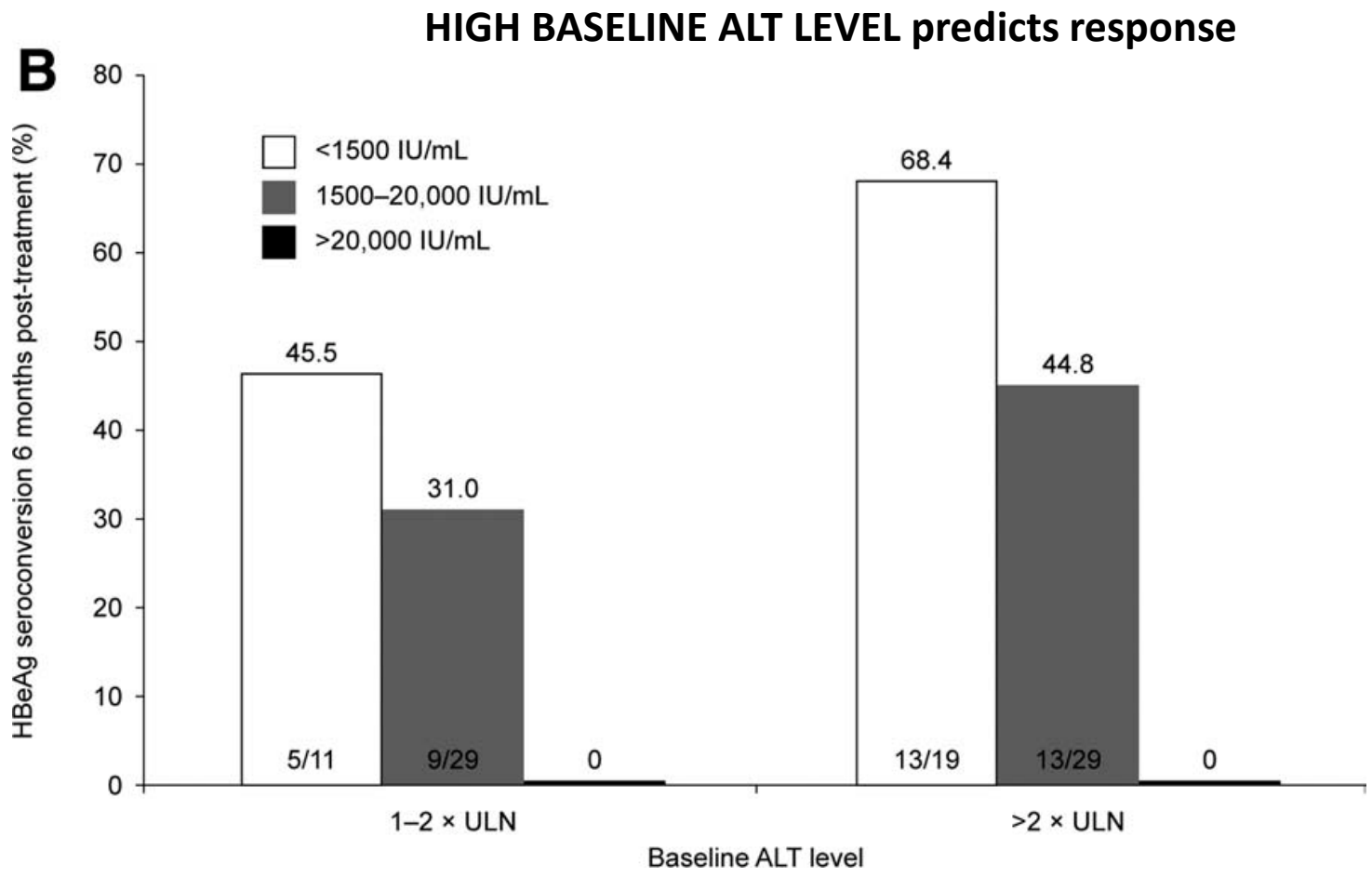
By Duration



By Dose

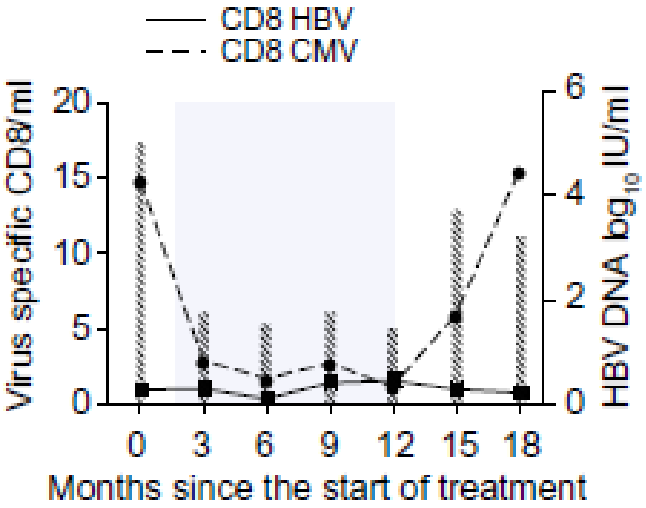
Liaw et al 54: 1591, 2011

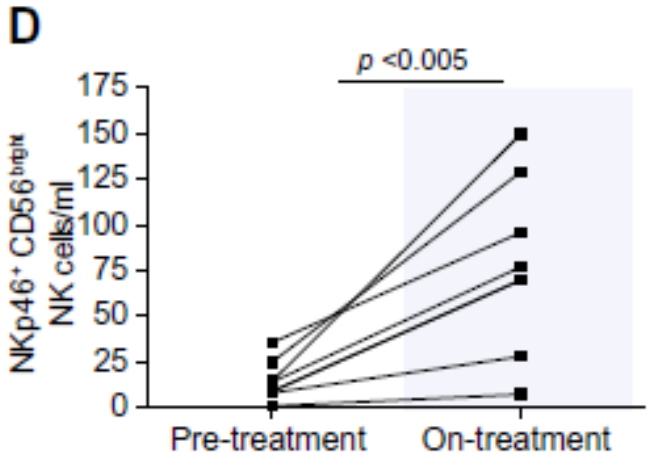
Predicting response: Neptune study: Factors associated with response

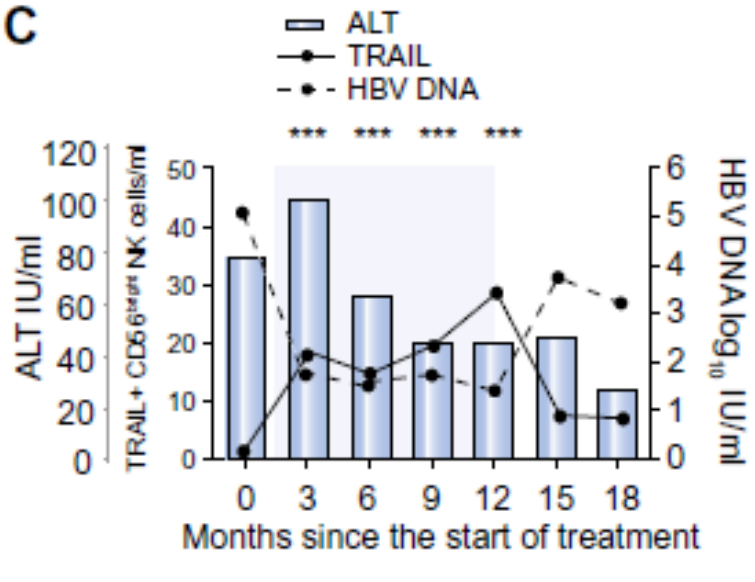


Liaw et al 54: 1591, 2011

Differential boosting of innate and adaptive responses IFN therapy HBV

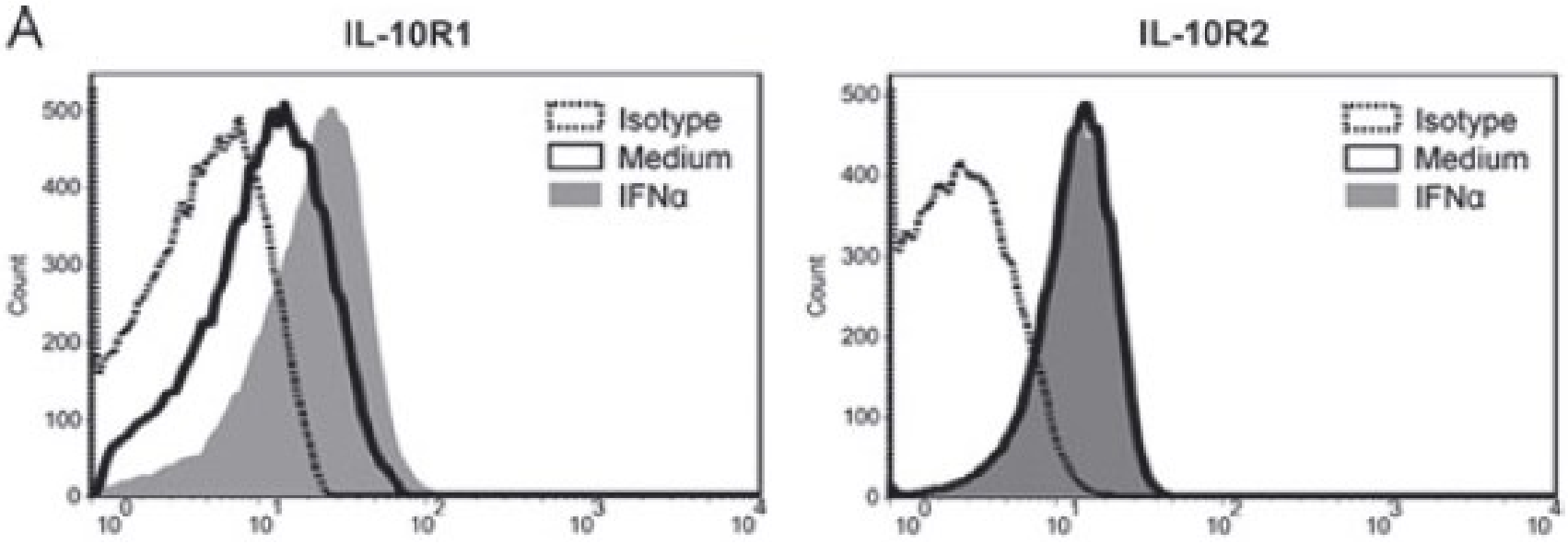






Micco et al J Hepatology 2012 epub

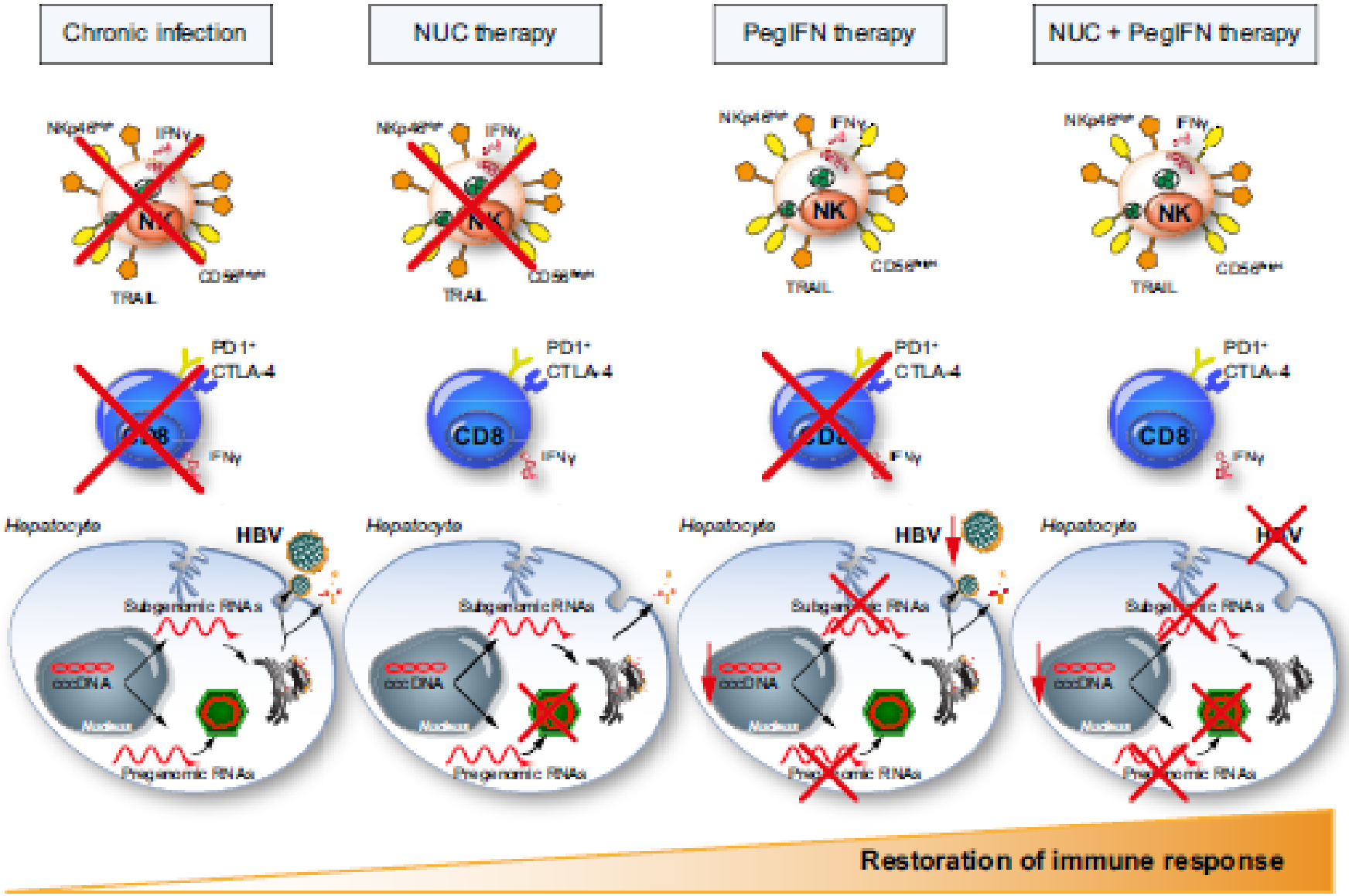
IFN-α upregulates IL-10R1 expression on the surface of monocytes:



IFN-α induces suboptimal activation of monocytes.

Liu et al Eur J Immunol 42(9) 2431 2012

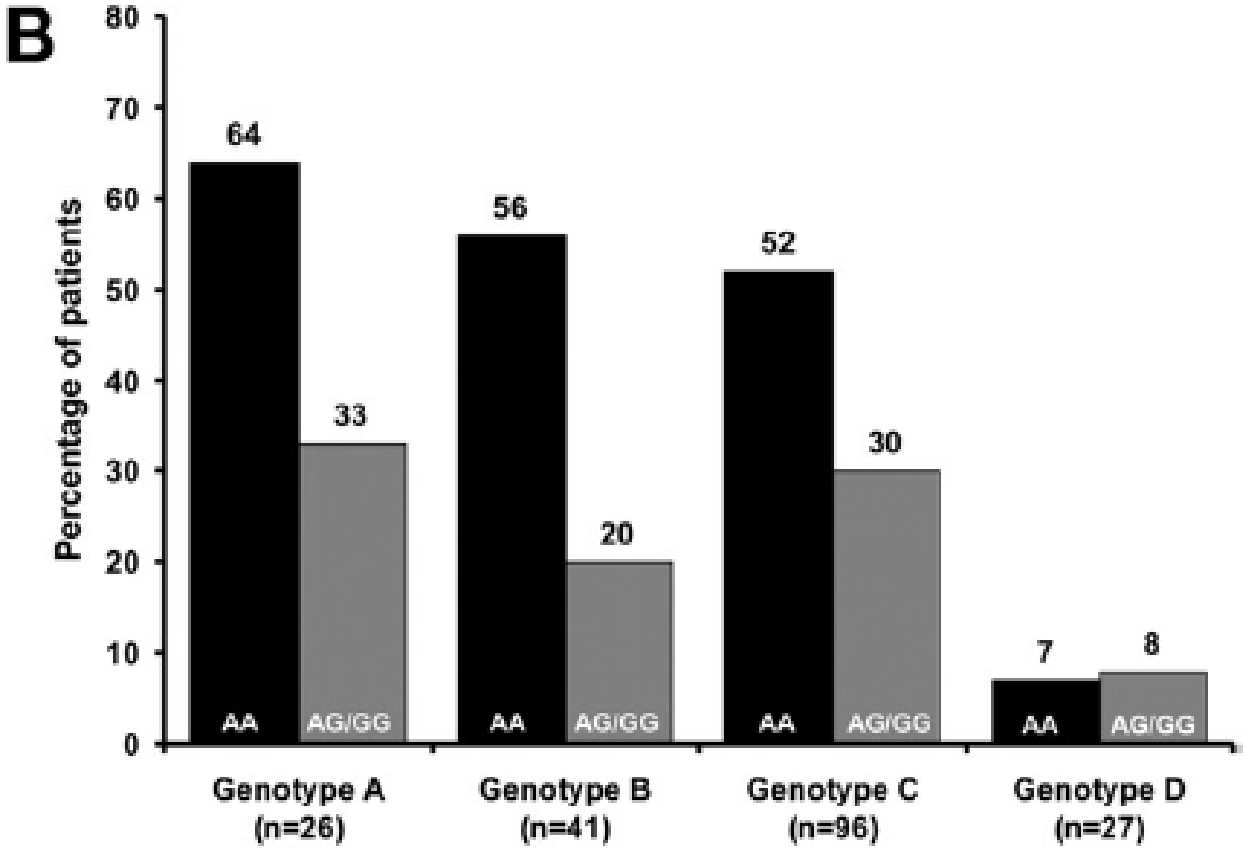
Restoration of the arms of the immune system that are dysfunctional during hepatitis B
PegIFNa and NUCs have differential effects on the innate and adaptive immune responses



Thimme R J Hepatology 2012 epub

Response by IL28b genotype

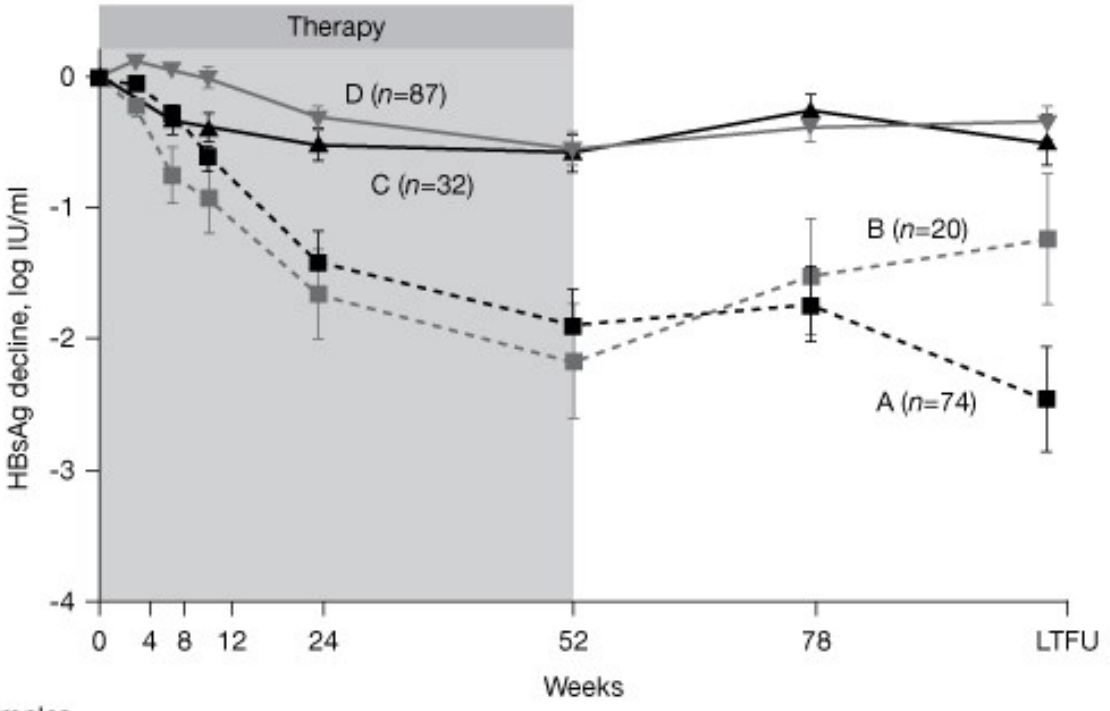
By HBV genotype



205 HBeAg positive treated IFN: HBeAg seroconversion

Sonneveld Gastro 142: 3 212

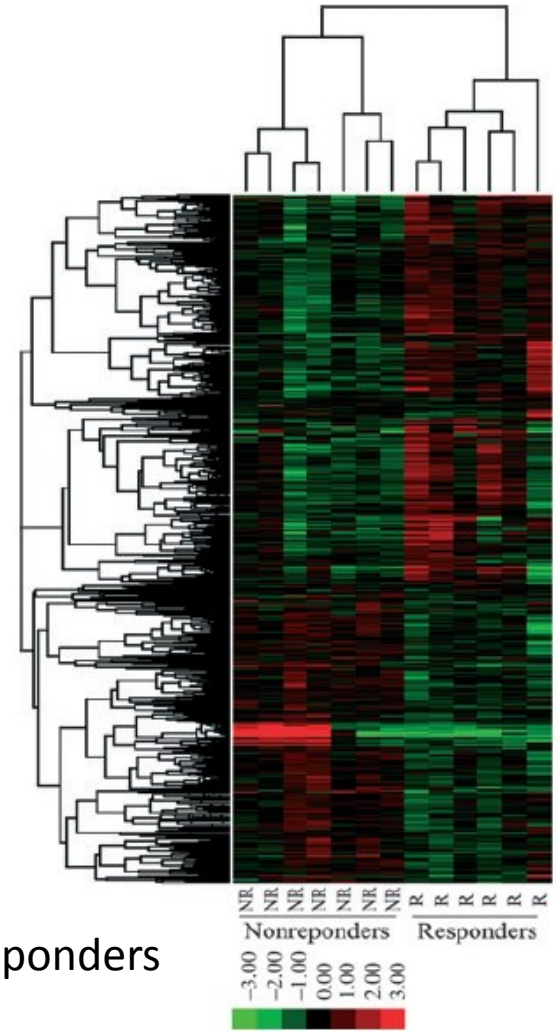
HBsAg decline according to HBV genotype IFN treatment. HBeAg positive



Available samples					
A	74	65	68	73	41
B	20	19	20	20	12
C	32	32	32	32	27
D	87	86	81	87	56

Sonneveld M et J Virol 17 (1) 9-17 2012; Buster CJ, *et al. Gastroenterology* 2008;**135** 459–67 2. Marcellin P, et al. *Gastroenterology* 2009;**136**:2169–2179; 3. Flink HJ et al. *Am J Gastroenterol* 2006;**101**:297–303.;Sonneveld M et al Antiviral Therapy 17: 9-17 2012

Expression profiling responders non responders non responders hepatitis B



Responders

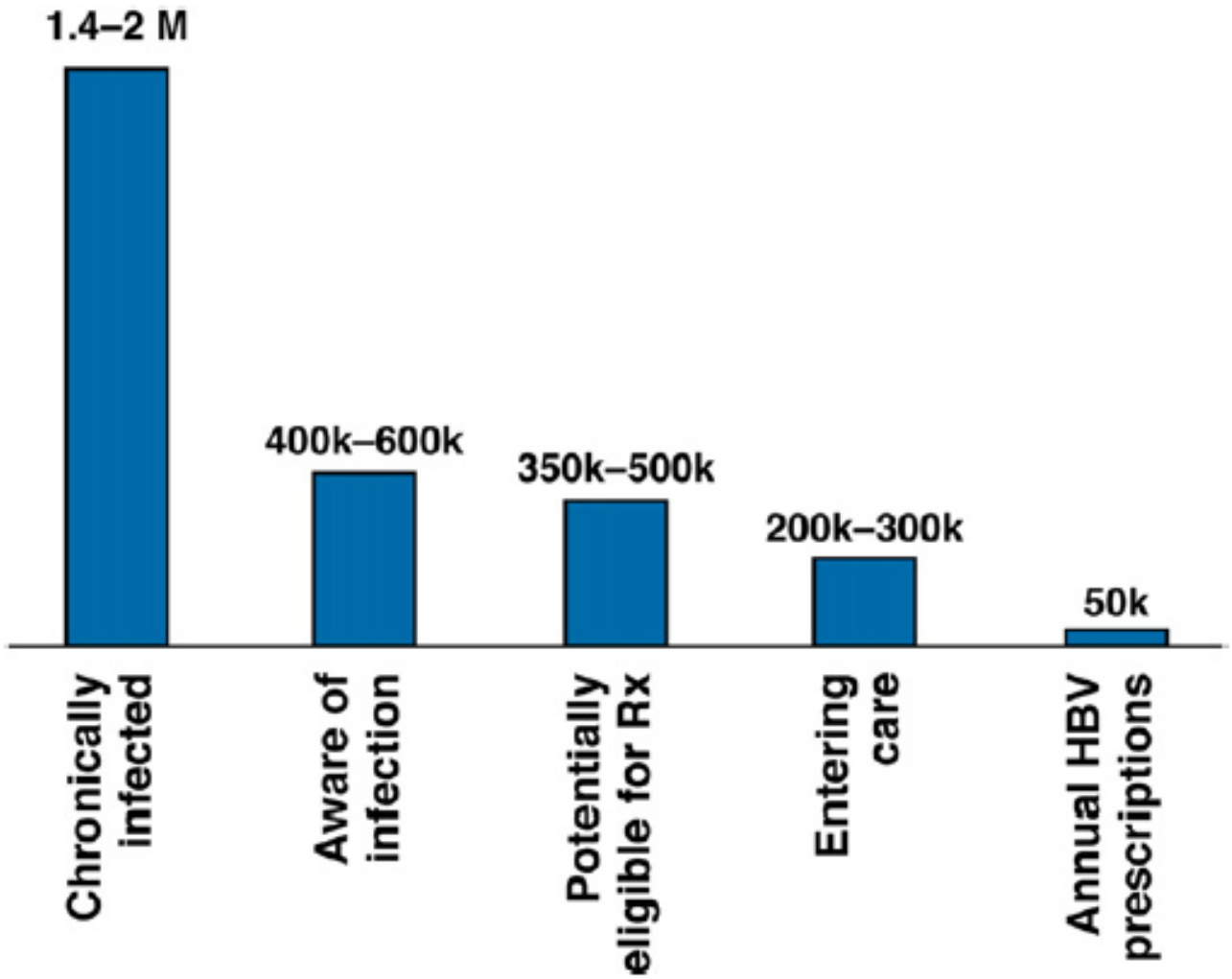
Non responders

Xiao J Viral Hep 19(2) 2012

Utility of nucleosides vs interferon

- **Nucleoside use preferred in**
  - **Decompensated cirrhosis**
  - **Fulminant hepatitis**
  - **Prophylactic use with chemotherapy**
  - **Use in immunosuppressed patients**
  - **Use in HIV co-infected patients?**
  - **Use in pregnancy**
  - **Combination therapy:**
  - **Restoration both arms of the immune system?**

From efficacy to effectiveness of treatment of hepatitis B effectiveness of current treatments in reducing burden HBV



Scaglione S Gastroenterology 142: 1360 2012

Optimal use Interferon

- IFN versus nucleos(t)ides
- Different modes of action
  - Need to be able to better select patients for therapy
    - High chance of response with IFN (side effects)
    - Pre-treatment factors
    - On treatment response factors
  - Stopping /futility rules: stop unnecessary treatment
  - Cost effective use developing countries
  - Lambda interferon?
  - Improve therapeutic outcomes in most cost effective manner

Why I prefer pegylated interferon therapy HBeAg positive chronic hepatitis B

- INF not yet exited the stage
- Weak immunomodulatory effect; not well understood
- Higher serological responses?
- Permits first use in HBeAg positive: young
- Need early prediction of failed treatment
- Prolonged use difficult
- Pre-treatment predictive factors?
- ALT, DNA genotype, age IL28b
- Only a minority respond

- No role in fulminant hepatitis, cautious use in cirrhosis, problematic in decompensated cirrhosis
- Frequent side effects and need for close monitoring
- Patient choices?
- Additive use with nucleosides not fully explored.