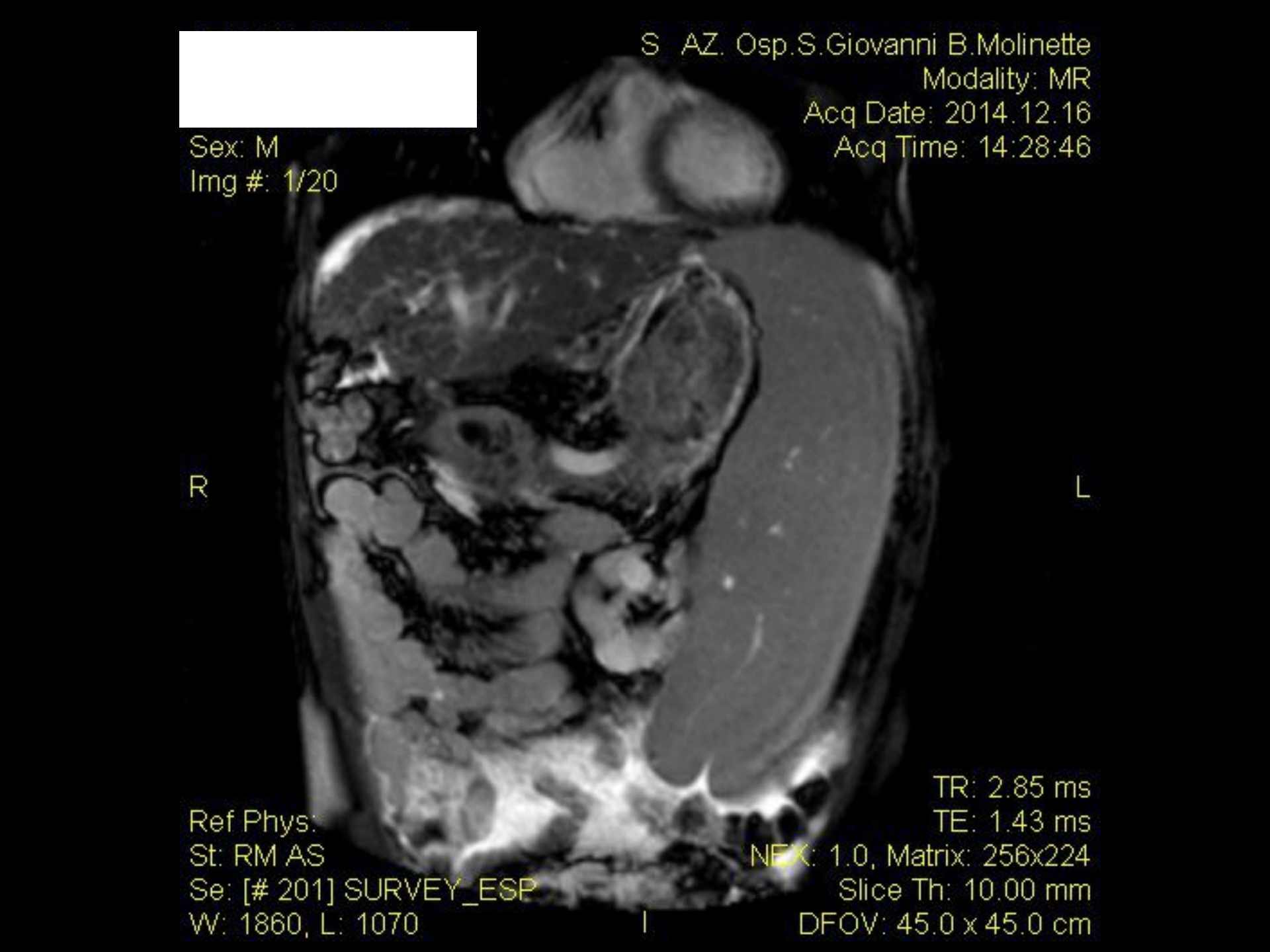
THE LEGACY OF IFN : 6-12 months therapy

IN THE (VERY FEW) PATIENTS WHO CLEAR THE HBsAG:
STOP THERAPY

IN THE HBsAG PATIENTS WHO DO NOT HAVE A HDV- RNA RESPONSE : STOP THERAPY ?

IN PATIENTS WITH A HDV-RNA RESPONSE AND A SIGNIFICANT BUT INCOMPLETE HBsAg RESPONSE:
PROLONG THERAPY ?

IN PATIENTS WITH A HDV- RNA RESPONSE BUT NO HBsAG RESPONSE:
STOP THERAPY ? LONG-TERM FOLLOW UP , FUNCTIONAL CURE ?


S AZ. Osp.S.Giovanni B.Molinette
Modality: MR
Acq Date: 2014.12.16
Acq Time: 14:28:46
Sex: M
Img #: 1/20
R
L
Ref Phys:
St: RM AS
Se: [# 201] SURVEY_ESP
W: 1860, L: 1070
I
TR: 2.85 ms
TE: 1.43 ms
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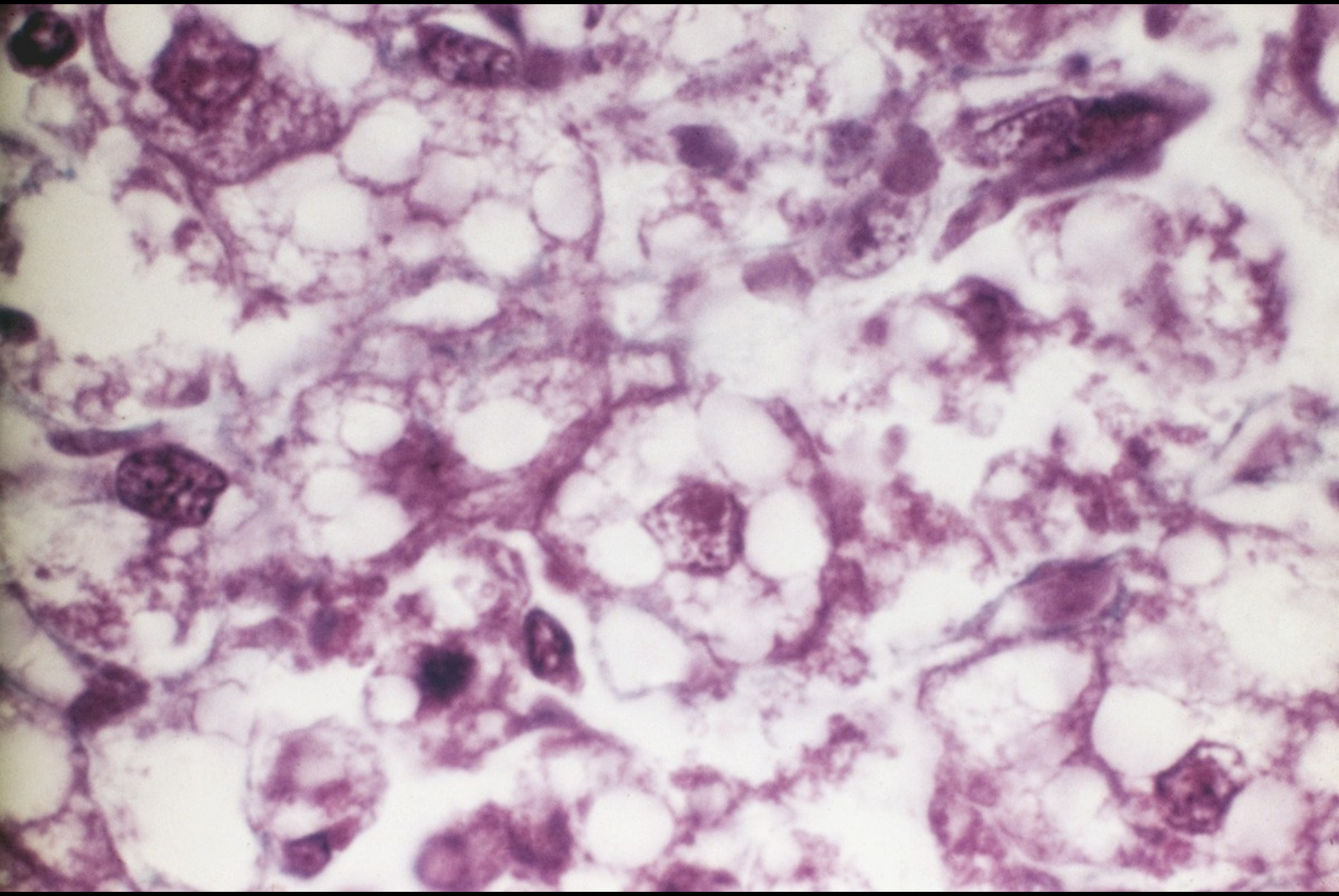
Slice Th: 10.00 mm
DFOV: 45.0 x 45.0 cm



The HDV target : problems

- HBV required only to provide the HBsAg capsid

- replication of HDV indipendent from HBV DNA replication

NO REPLICATIVE FUNCTION OF HDV TO

BE TARGETED BY ANTIVIRALS

The SVR paradigm does not apply to hepatitis D (as long as the HBsAg persists)

HDV transmitted to HBsAg carrier chimpanzees with 1 ml of infectious serum diluted 10-11 (1/100.000.000.000)

A HBsAg background may rescue HDV in amounts far below those detectable by current HDV-RNA assays (10 cp/ml)

HBsAg persisting in the liver can rescue HDV after apparently successful therapy (i.e SVR with clearance of HDV-RNA)

?

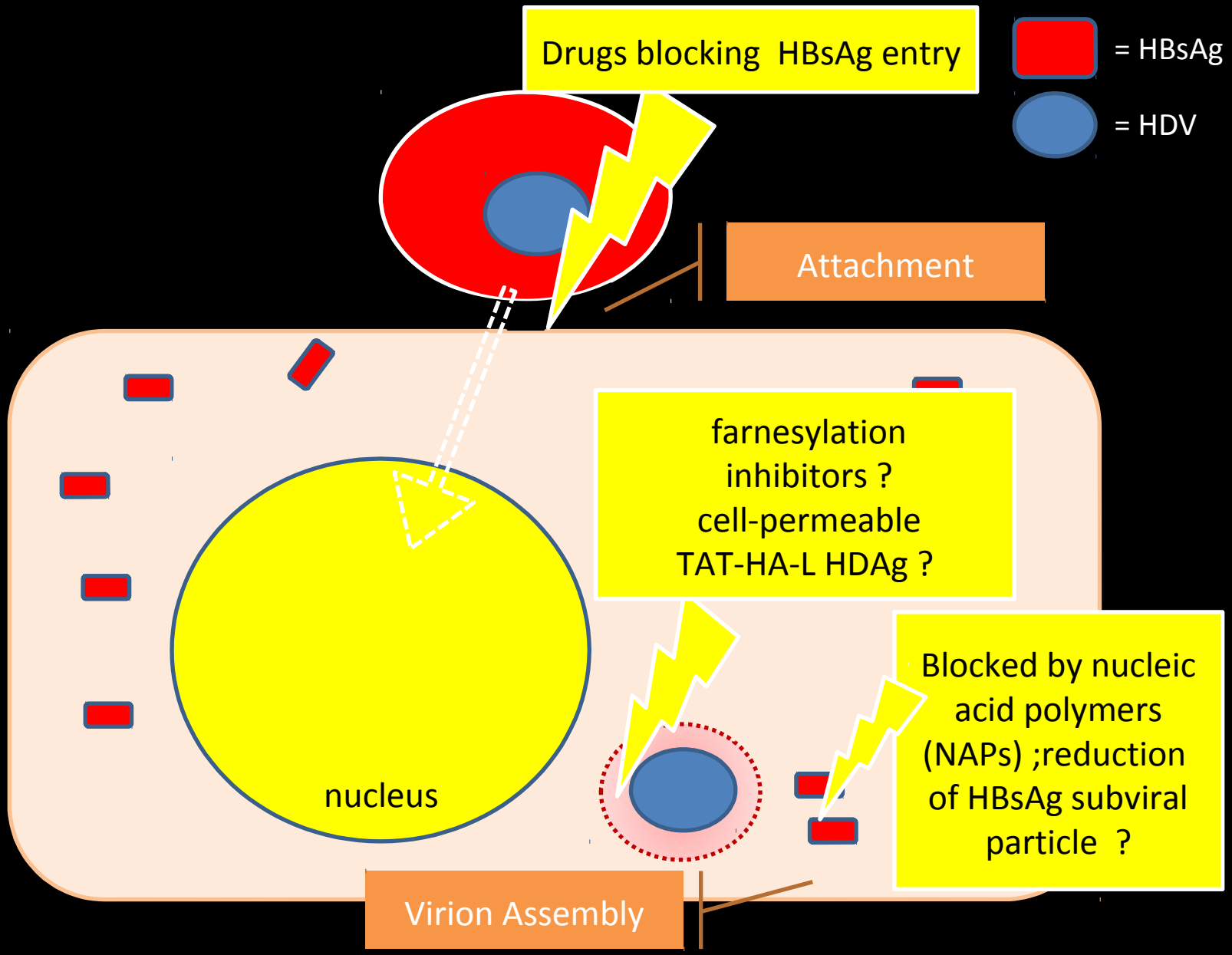
is the clearance of serum HBsAg the only reliable end-point of therapy

New therapeutic strategies against the HDV

—

targeted to deprive the HDV of functions critical to its life-cycle , provided by the HBV or by the hepatocyte

HDV: new therapeutic targets



Drugs blocking HBV entry

Irbesartan
Ezetimibe
Ritonavir
Cyclosporin
Cyclosporin derivatives
    SCY 446/SCY 450
Monoclonal Ab 2-H5-A14
MYRCLUDEX B

Drugs impairing HBV/HDV entry through the inhibition of the Sodium Taurochocolate Cotransporter Polypeptide (NTCP)

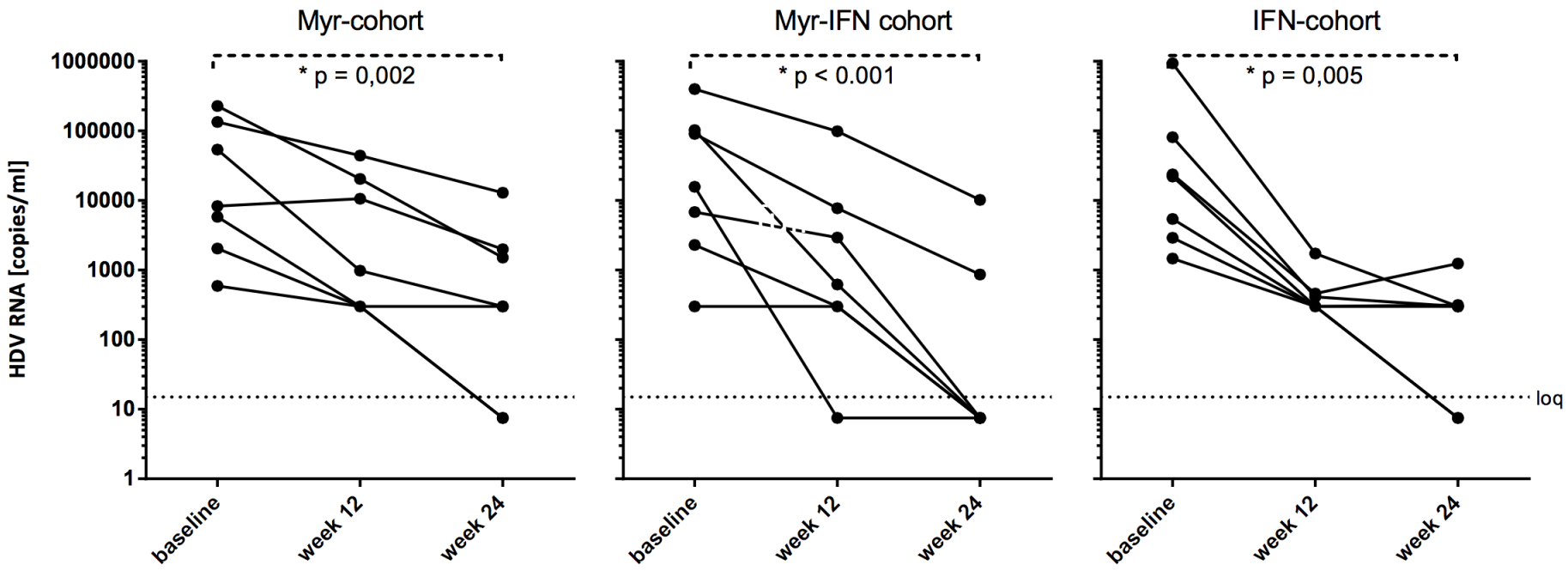
MYRCLUDEX b:

Synthetic N-acylated preS1-derived lipopeptide that inhibits HBV entry in vitro and in vivo with high efficacy

Lemp FA, Urban S, 2014

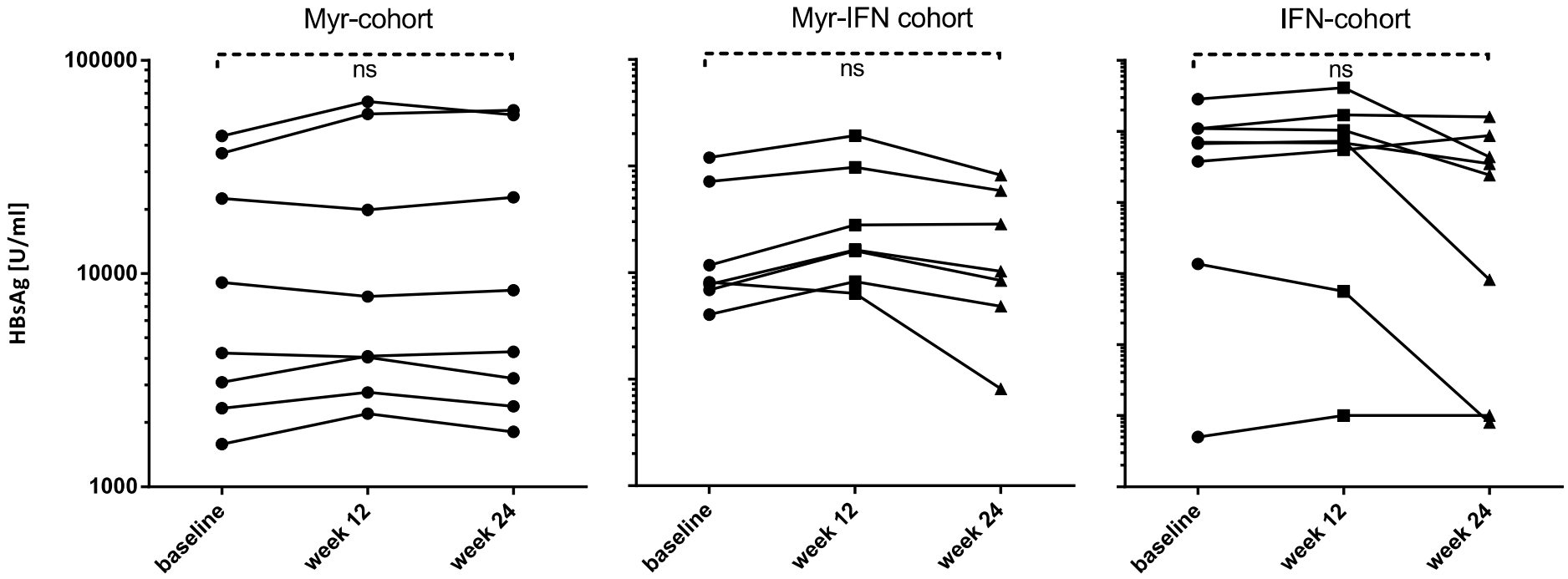
Interim results of a Phase Ib/IIa study of the entry inhibitor myrcludex B in chronic hepatitis infected patients

Figure 3



Interim results of a Phase Ib/IIa study of the entry inhibitor myrcludex B in chronic hepatitis D infected patients

Figure 2



PRENYLATION INHIBITORS

- ✓ prenylation : site- specific lipid modification of proteins
- ✓ widely used among viruses

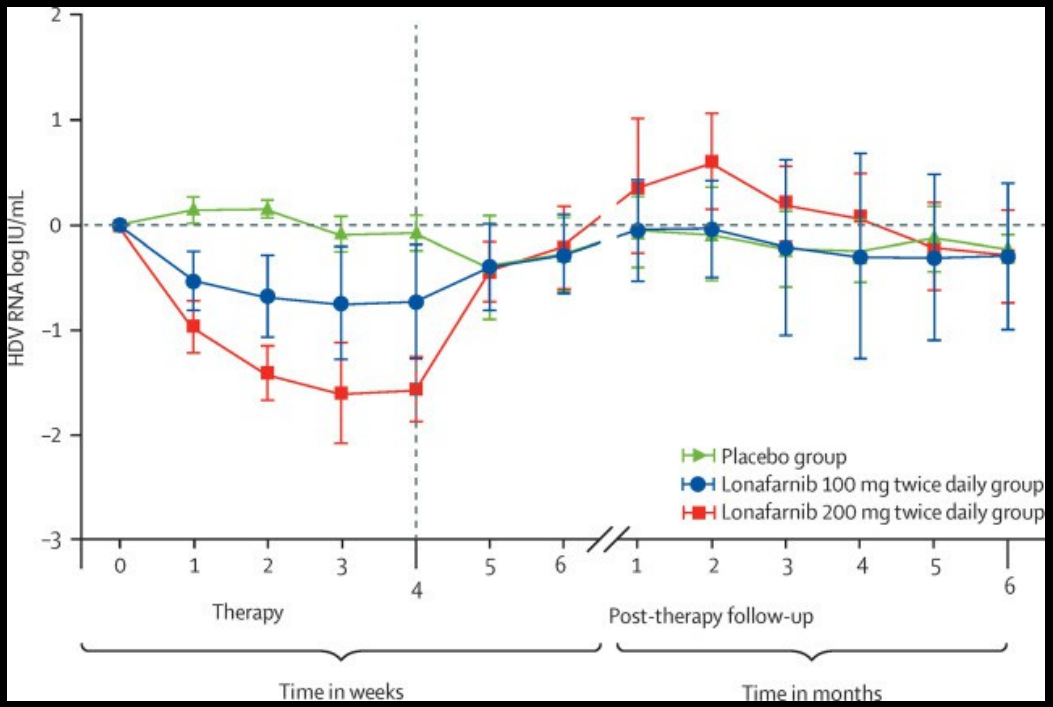
FARNESYLATION OF THE LARGE–HD ANTIGEN BY A HUMAN FARNESYL TRANSFERASE IS NECESSARY TO COMBINE THE HBsAG WITH THE HDV RIBONUCLEOPROTEIN IN ORDER TO ASSEMBLE THE VIRION

HD VIRION ASSEMBLY BLOCKED IN VIVO AND IN VITRO BY FARNESYL-TRANSFERASE INHIBITORS

LONAFARNIB : PROTOTYPE IN HUMAN STUDIES

Glenn JS,,2010

MEAN SERUM HEPATITIS DELTA VIRUS RNA (SD) CHANGE DURING THERAPY WITH LONAFARNIB



Oral prenylation inhibition with lonafarnib in chronic hepatitis D infection: a proof-of-concept randomised, double-blind, placebo-controlled phase 2A trial

G.I. side effects

No HBsAg effect

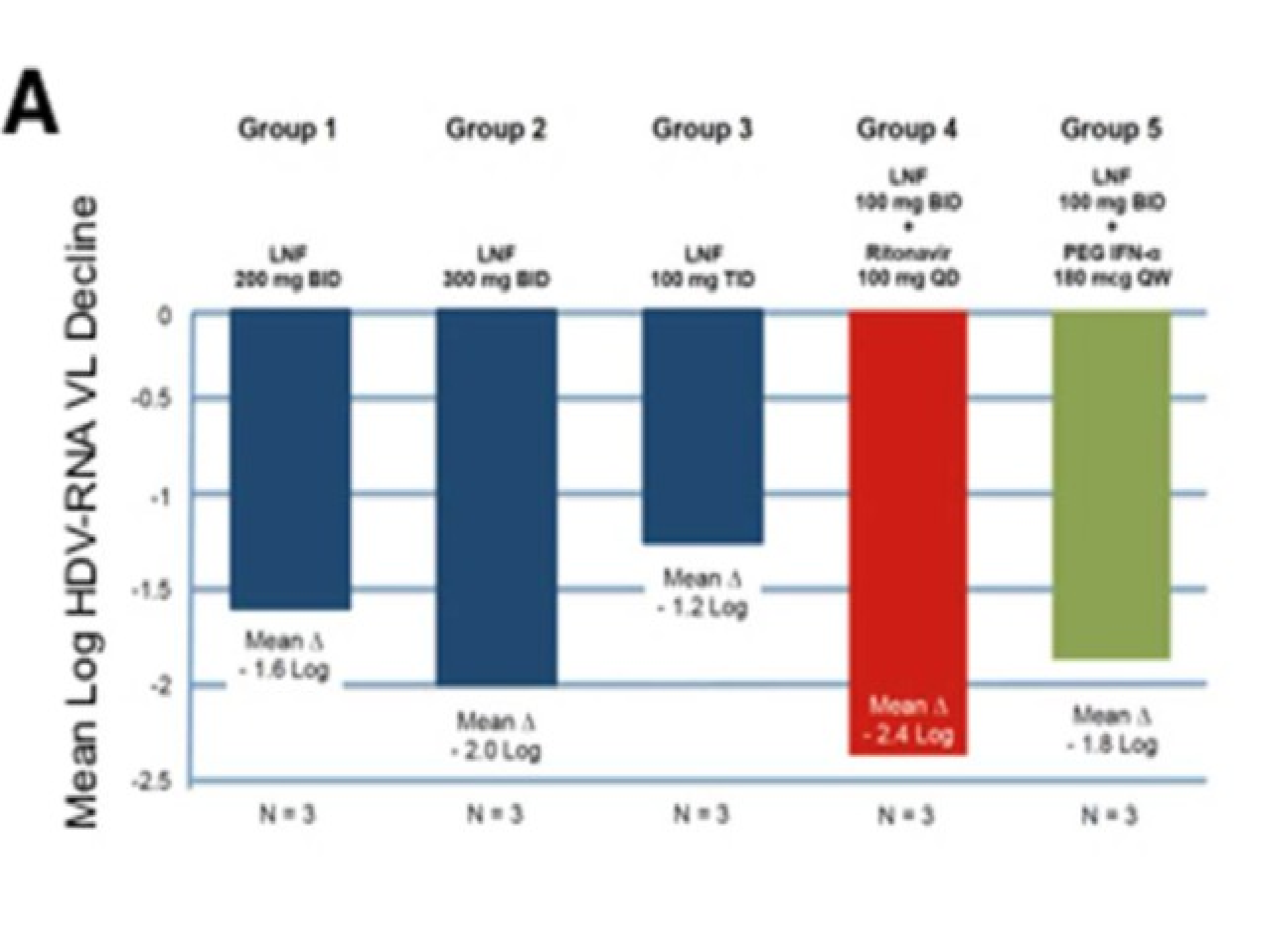
Kol C, et al , Lancet Infect Dis 2015

OPTIMIZING LONAFARNIB TREATMENT FOR THE MANAGEMENT OF CHRONIC DELTA HEPATITIS: THE LOWR HDV – 1 STUDY

-
three patients per group

1) LNF 200 mg BID (12 weeks);
2) LNF 300 mg BID (12 weeks);
3) LNF 100 mg TID (5 weeks);
4) LNF 100 mg BID + ritonavir (RTV) 100 mg QD (8 weeks).
5) LNF 100 mg BID + pegylated interferon alfa (PEG-IFNá) 180 mcg QW (8 weeks);

Yurdaydin C et al 2017

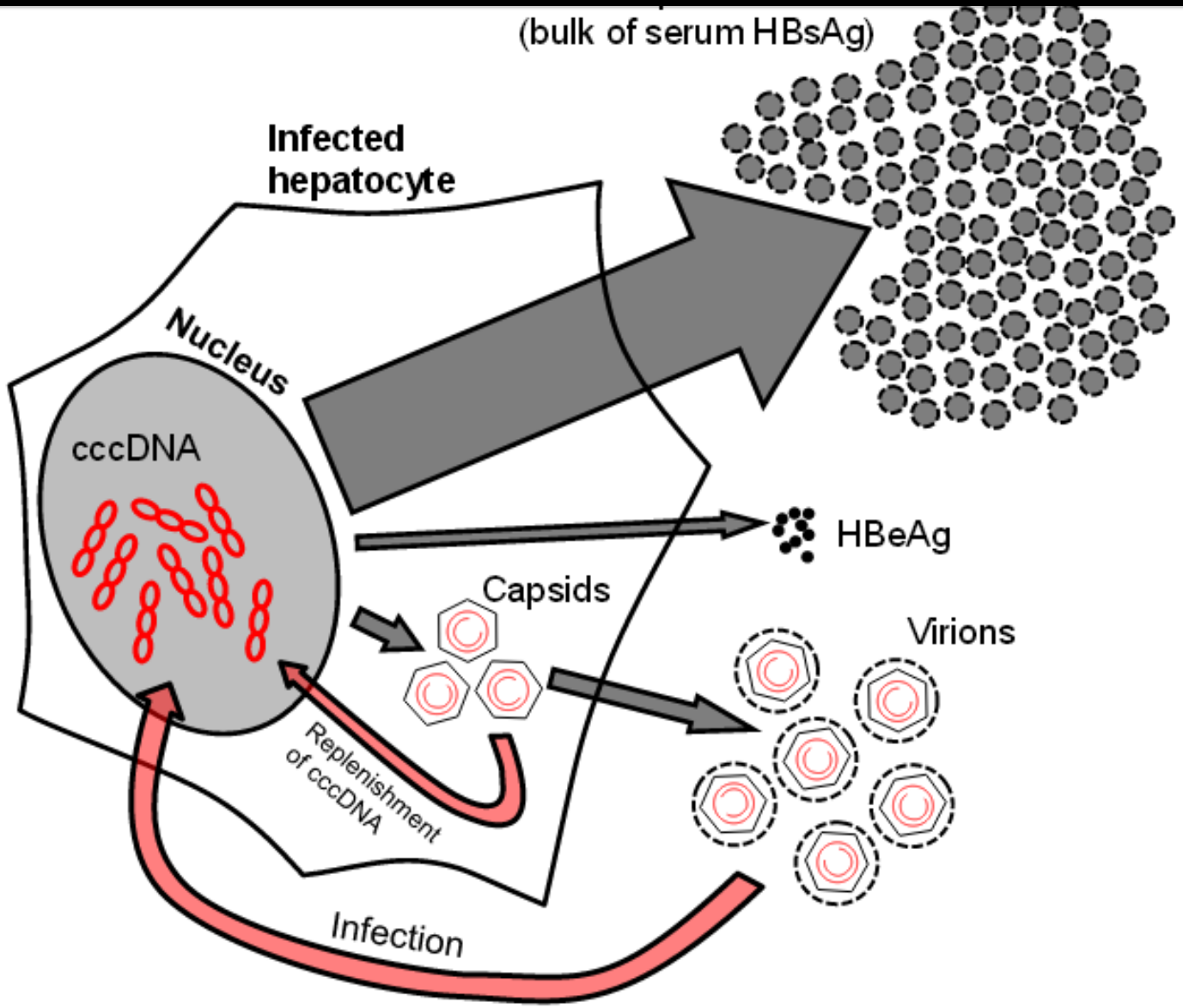

A
Group 1
Group 2
Group 3
Group 4
Group 5
LNF
200 mg BID
LNF
300 mg BID
LNF
100 mg TID
LNF
100 mg BID
+
Ritonavir
100 mg QD
LNF
100 mg BID
+
PEG IFN-α
180 mcg QW
Mean Log HDV-RNA VL Decline
0
-0.5
-1
-1.5
-2
-2.5
Mean Δ
- 1.6 Log
Mean Δ
- 2.0 Log
Mean Δ
- 1.2 Log
Mean Δ
- 2.4 Log
Mean Δ
- 1.8 Log
N = 3
N = 3
N = 3
N = 3
N = 3

NUCLEIC ACID POLYMERS

Nucleic acid polymers (NAPs) are oligonucleotides that bind with high affinity to amphipathic protein structures

Amphipathic targets are required for various stages of viral replication. NAPs effectively block the functions of these proteins, providing a broad-spectrum antiviral activity.

Particle production in HBV infection



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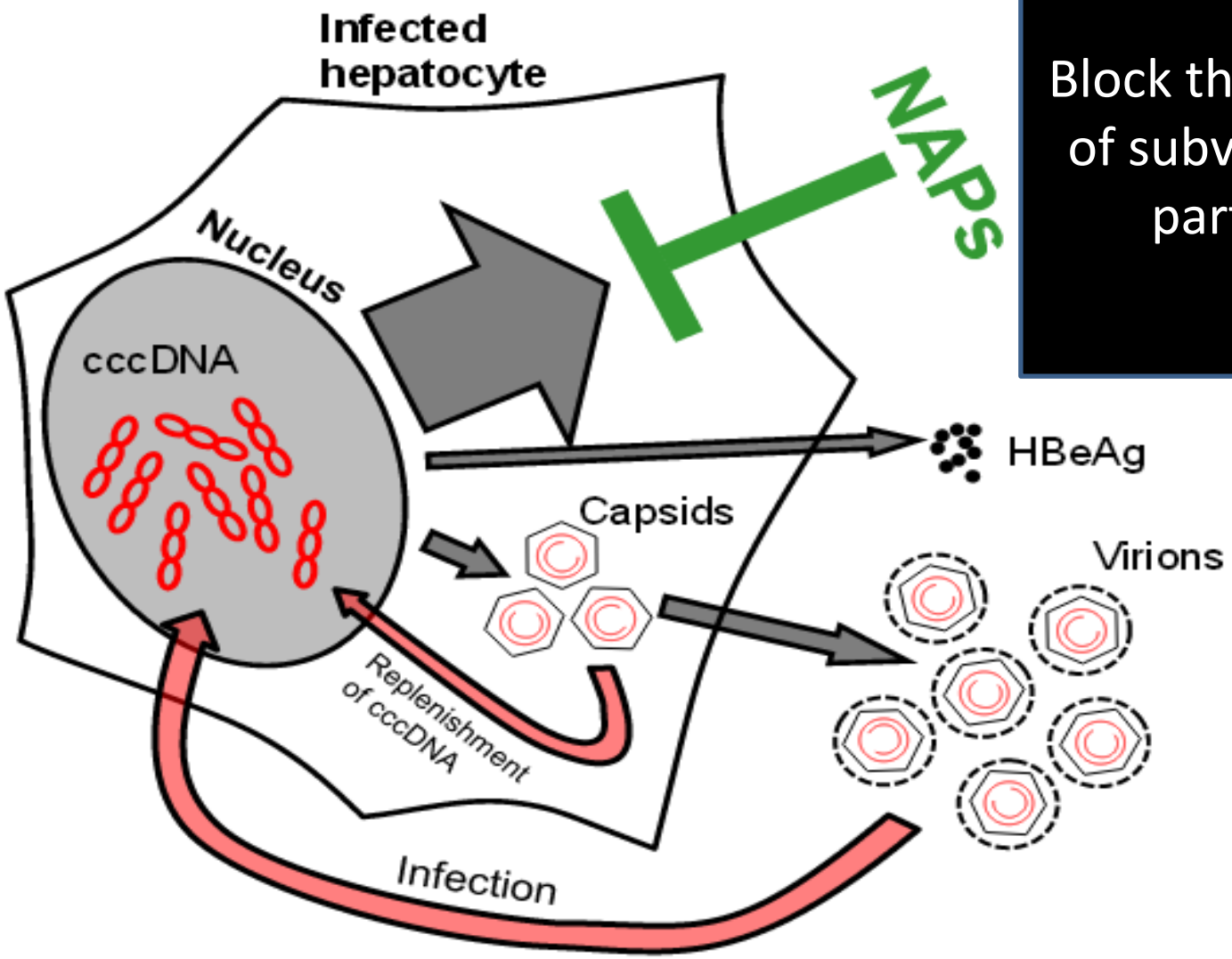


Nuclear Acid Polymers (NAPs)

Block the assembly of subviral HBsAg particles ?

REP 2139 for chronic hepatitis D

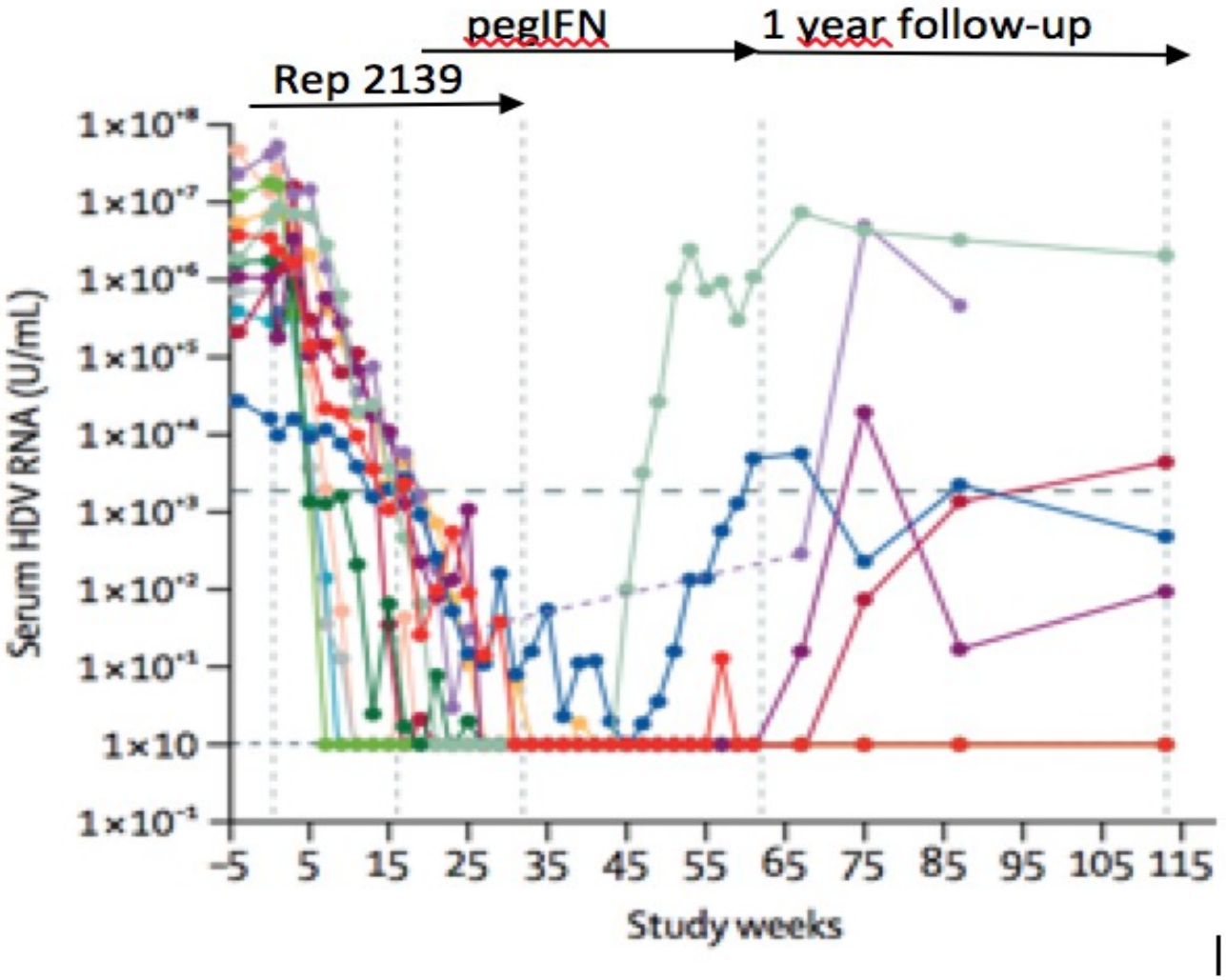
15 weeks	15 weeks	33 weeks	24 weeks
500 mg, qw, 2h inf.	250 mg, qw, 1h inf. + Peg-IFN, 180 ug, qw	Peg-IFN, 180 ug, qw	Tx-free Follow-up

12 HDV–RNA positive patients without cirrhosis

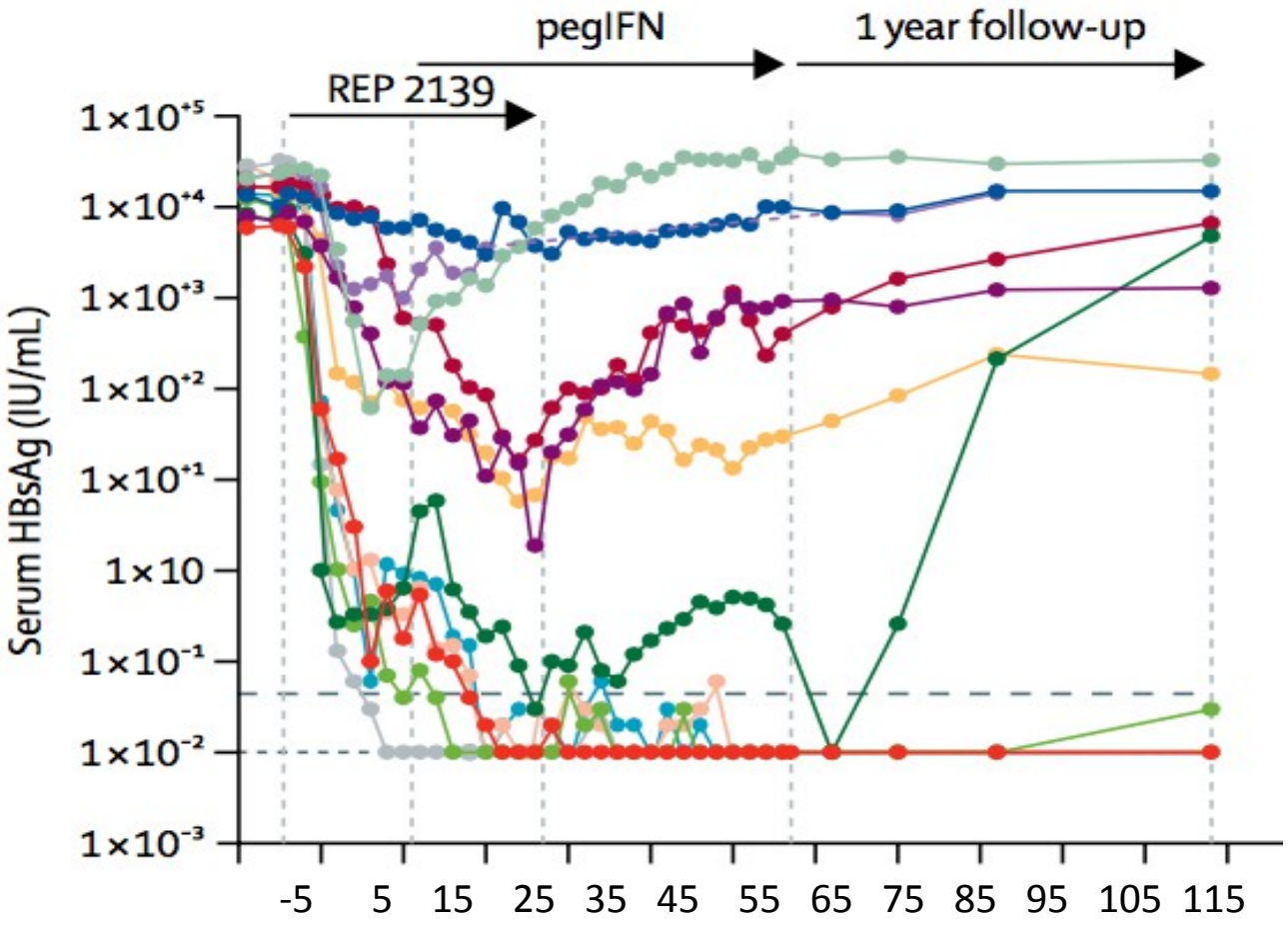
Primary end point: Safety

Secondary end point: Antiviral efficacy

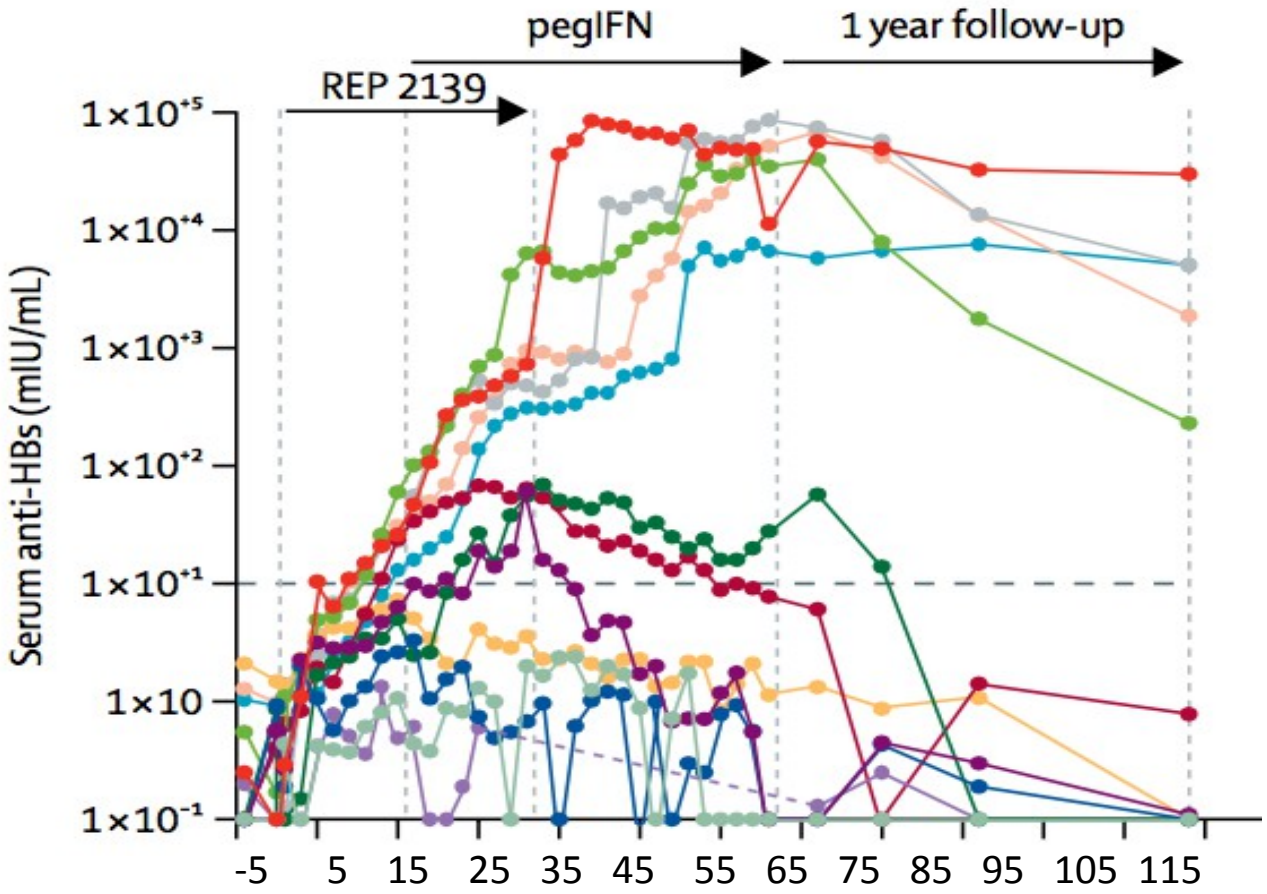
Bazinet M et al, Lancet Gastroenterol Hepatol



Bazinet M :Lancet Gastroenterol Hepatol. 2017 Sep 27. pii: S2468-1253(17)30288-1. doi: 10.1016/S2468-1253(17)30288-1. [Epub ahead of print] PMID: 28964701



Bazinet M :Lancet Gastroenterol Hepatol. 2017 Sep 27. pii: S2468-1253(17)30288-1. doi: 10.1016/S2468-1253(17)30288-1. [Epub ahead of print] PMID: 28964701



Reference: Bazinet M :Lancet Gastroenterol Hepatol. 2017 Sep 27. pii: S2468-1253(17)30288-1. doi: 10.1016/S2468-1253(17)30288-1. [Epub ahead of print] PMID: 28964701

Summary

Single center study in Moldovia

1 year post-treatment

- HDV RNA negative in 7/12 (58%)
- HBsAg negative in 5/12 (42%)
- Anti- HBs positive at high titers in 5/12 (42%)

best results reported so far in the therapy of chronic hepatitis D

REP 2139 : confirmations

Randomized controlled trial, patients stratified according to cirrhosis – or +

Safety in cirrhotics (consistent ALT flares during therapy !)

More prolonged follow-up (late relapses possible in HDV)

Therapeutic mechanisms largely unknown (putative blocking of the secretion of subviral HBsAg particles….?)

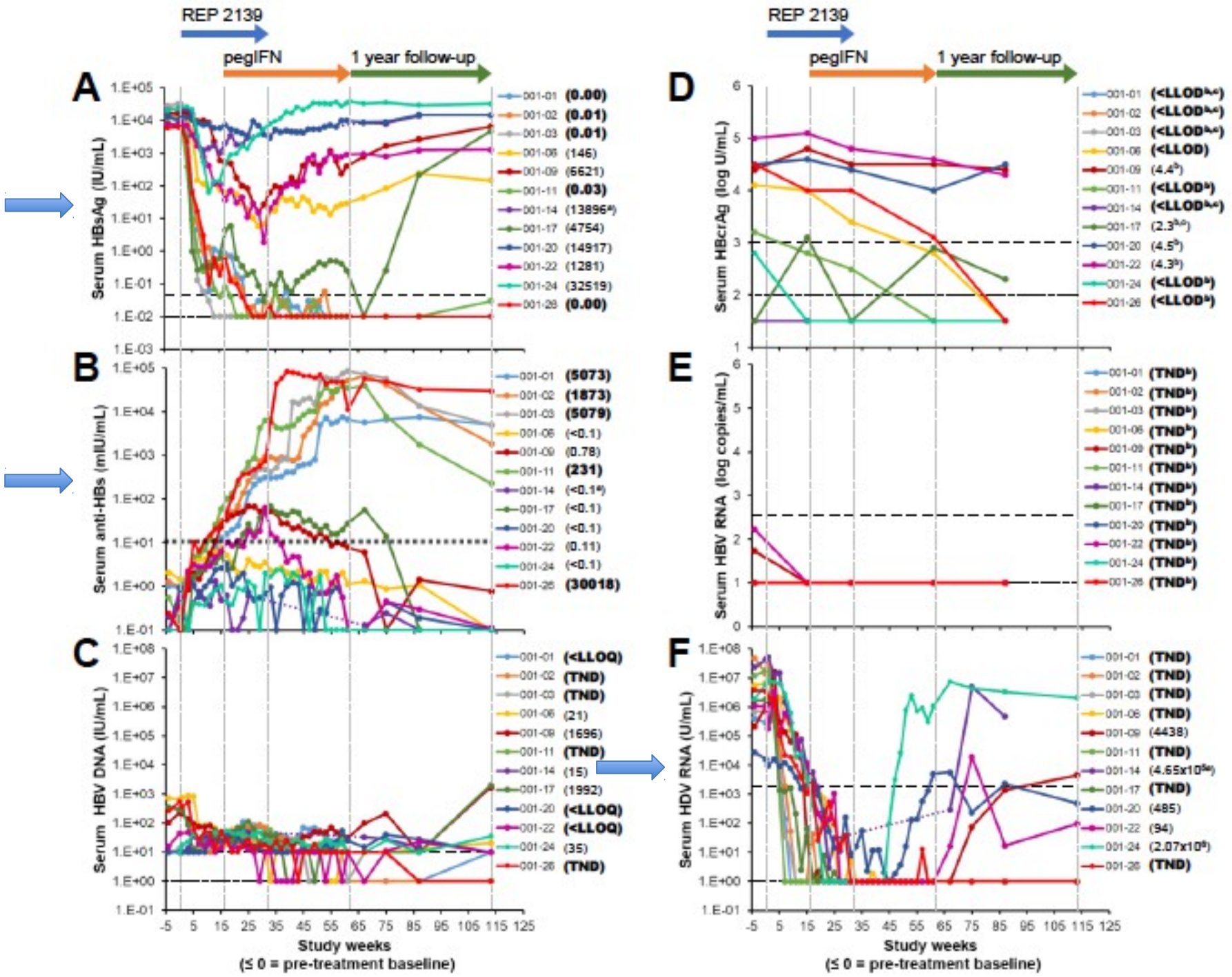
PROBLEMS IN THE THERAPY OF HDV

The HDV needs from the HBV only the HBAg coat for the morphogenesis of its virion .

THE LIFE-CYCLE OF THE HDV IS INDEPENDENT FROM HBV REPLICATION (FROM HBV-DNA…)

The HDV-RNA is replicated by RNA-polymerases of the cell , deceived to copy the viral genome as if it were a cellular DNA.

THE HDV IS NOT VULNERABLE BY CONVENTIONAL ANTIVIRALS TARGETED TO SPECIFIC ENZYMATIC FUNCTIONS OF VIRUSES (POLYMERASES ,PROTEASES)


REP 2139
pegIFN
1 year follow-up
A
Serum HBsAg (IU/mL)
001-01 (0.00)
001-02 (0.01)
001-03 (0.01)
001-06 (146)
001-09 (5621)
001-11 (0.03)
001-14 (13896[4])
001-17 (4754)
001-20 (14917)
001-22 (1281)
001-24 (32519)
001-26 (0.00)
B
Serum anti-HBs (mIU/mL)
001-01 (5073)
001-02 (1873)
001-03 (5079)
001-06 (<0.1)
001-09 (0.78)
001-11 (231)
001-14 (<0.1[4])
001-17 (<0.1)
001-20 (<0.1)
001-22 (0.11)
001-24 (<0.1)
001-26 (30018)
C
Serum HBV DNA (IU/mL)
001-01 (<LLOQ)
001-02 (TND)
001-03 (TND)
001-06 (21)
001-09 (1696)
001-11 (TND)
001-14 (15)
001-17 (1992)
001-20 (<LLOQ)
001-22 (<LLOQ)
001-24 (35)
001-26 (TND)
-5 5 15 25 35 45 55 65 75 85 95 105 115 125
Study weeks
(≤ 0 = pre-treatment baseline)
REP 2139
pegIFN
1 year follow-up
D
Serum HBcrAg (log U/mL)
001-01 (<LLOD[3,4])
001-02 (<LLOD[3,4])
001-03 (<LLOD[3,4])
001-06 (<LLOD)
001-09 (4.4[3])
001-11 (<LLOD[3])
001-14 (<LLOD[3,4])
001-17 (2.3[3,4])
001-20 (4.5[3])
001-22 (4.3[3])
001-24 (<LLOD[3])
001-26 (<LLOD[3])
E
Serum HBV RNA (log copies/mL)
001-01 (TND[3])
001-02 (TND[3])
001-03 (TND[3])
001-06 (TND[3])
001-09 (TND[3])
001-11 (TND[3])
001-14 (TND[3])
001-17 (TND[3])
001-20 (TND[3])
001-22 (TND[3])
001-24 (TND[3])
001-26 (TND[3])
F
Serum HDV RNA (U/mL)
001-01 (TND)
001-02 (TND)
001-03 (TND)
001-06 (TND)
001-09 (4438)
001-11 (TND)
001-14 (4.65x10[5a])
001-17 (TND)
001-20 (485)
001-22 (94)
001-24 (2.07x10[5])
001-26 (TND)
-5 5 15 25 35 45 55 65 75 85 95 105 115 125
Study weeks
(≤ 0 = pre-treatment baseline)

Nucleic acid polymers (NAPs) are oligonucleotides whose biochemical function is strictly dependent on the polymer chemistry of oligonucleotides.

They bind with high affinity to amphipathic protein structures

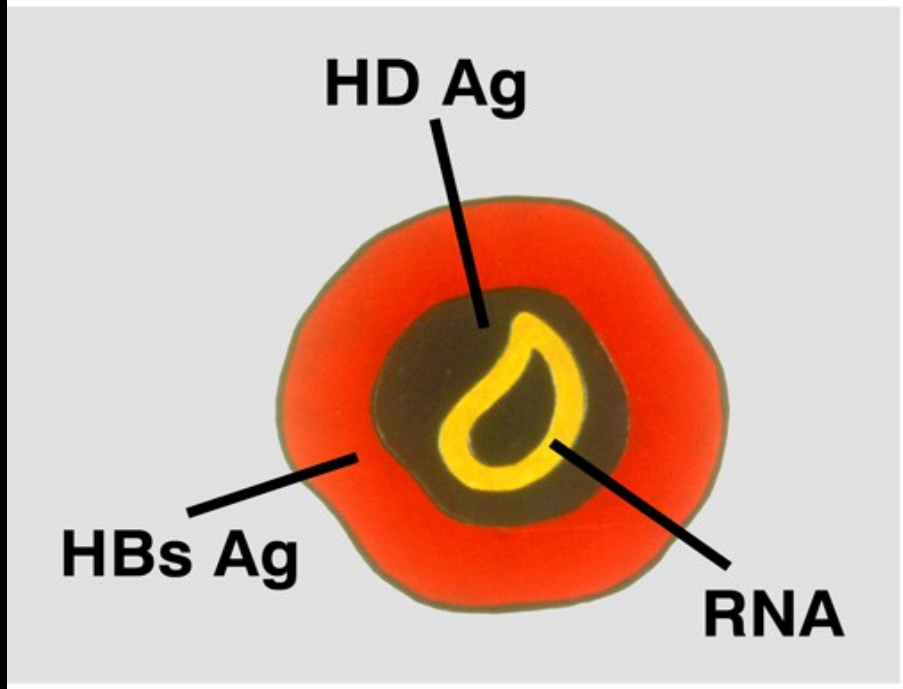
These amphipathic protein structures are very rare in normal human biology (with each other inside proteins where they help stabilize the protein structure).

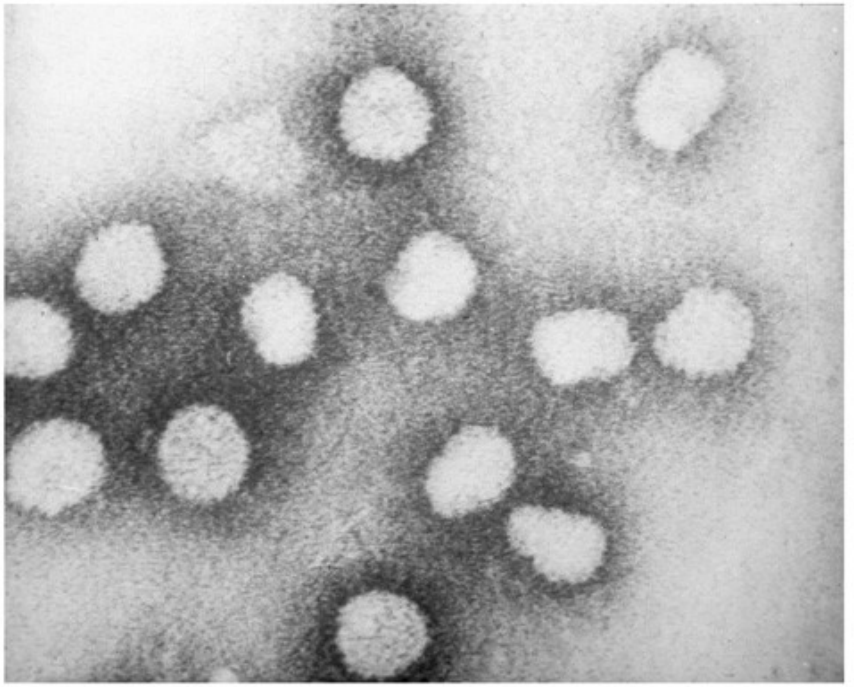
However amphipathic targets are required for various stages of viral replication. NAPs effectively block the functions of these proteins, providing an effective, broad-spectrum antiviral activity.

PEG-Interferon in chronic hepatitis D

- ✓ SVR (clearance of serum HDV-RNA) 6 months post-therapy in less than 30 %
- ✓ no advantage with the combination of HBV antivirals
- ✓ persistence of serum HBsAg in most patients
- ✓ high rate of relapses

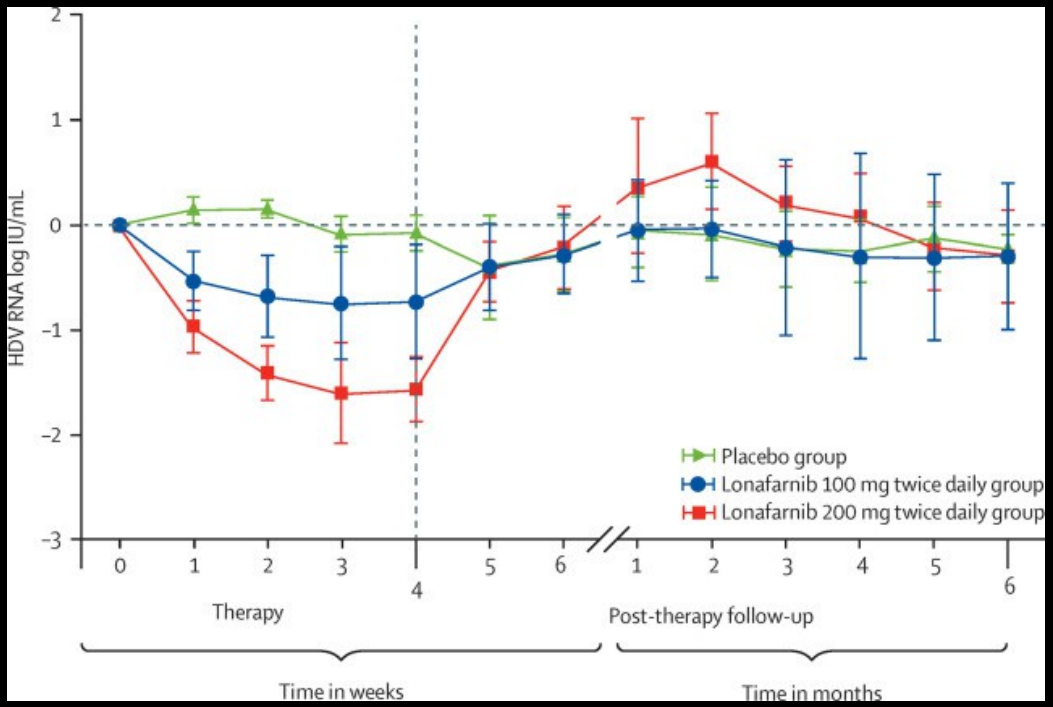
HEPATITIS DELTA VIRUS





- **Dependent for in-vivo infection on helper functions of hepadnaviruses**
- **Pathogenic**

MEAN SERUM HEPATITIS DELTA VIRUS RNA (SD) CHANGE DURING THERAPY WITH LONAFARNIB



Oral prenylation inhibition with lonafarnib in chronic hepatitis D infection: a proof-of-concept randomised, double-blind, placebo-controlled phase 2A trial

Warning:

GI side effects

No HBsAg effect

Kol C, et al , Lancet Infect Dis 2015

Hep-Net International Delta Hepatitis Intervention trials (HIDIT-1 and HIDIT-2)

HDV RELAPSES

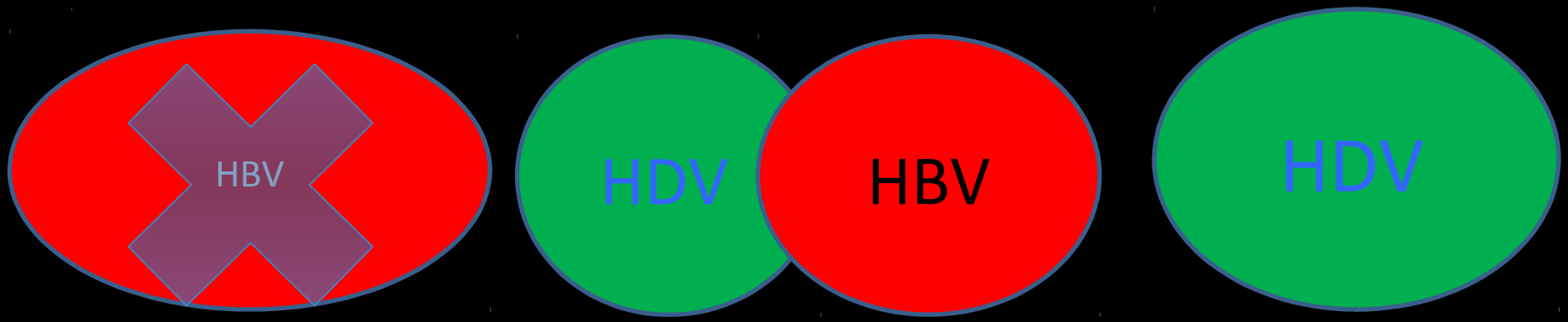
HIDIT-1 Pegasys 180 for 48 weeks : in 9/16 (56%) of HDV-SVR followed for a median of 4.5 years post-therapy

Heidrich B, 2014

HIDIT-2 Pegasys 180 for 96 weeks : in 38% patients negative for HDV-RNA at end of treatment

Wedemeyer H, 2014

HDV and HBV therapeutic targets



Antivirals against HBV

- Peg-IFN
- **MircludexB Peg IFN-**
- REP 2139 (NAPs) Peg IFN

- **Lonafarnib** Peg-IFN

Current Therapy

-- EMPIRICAL , BASED ON IFN/PEG IFN , INTRODUCED IN THE 1980S ON THE WAKE OF ITS EFFICACY IN HBV DISEASE .ANTIVIRAL ACTIVITY ?, IMMUNOMODULATION ?

The current recommendation is pegylated IFN-alfa weekly for 12 to 18 months

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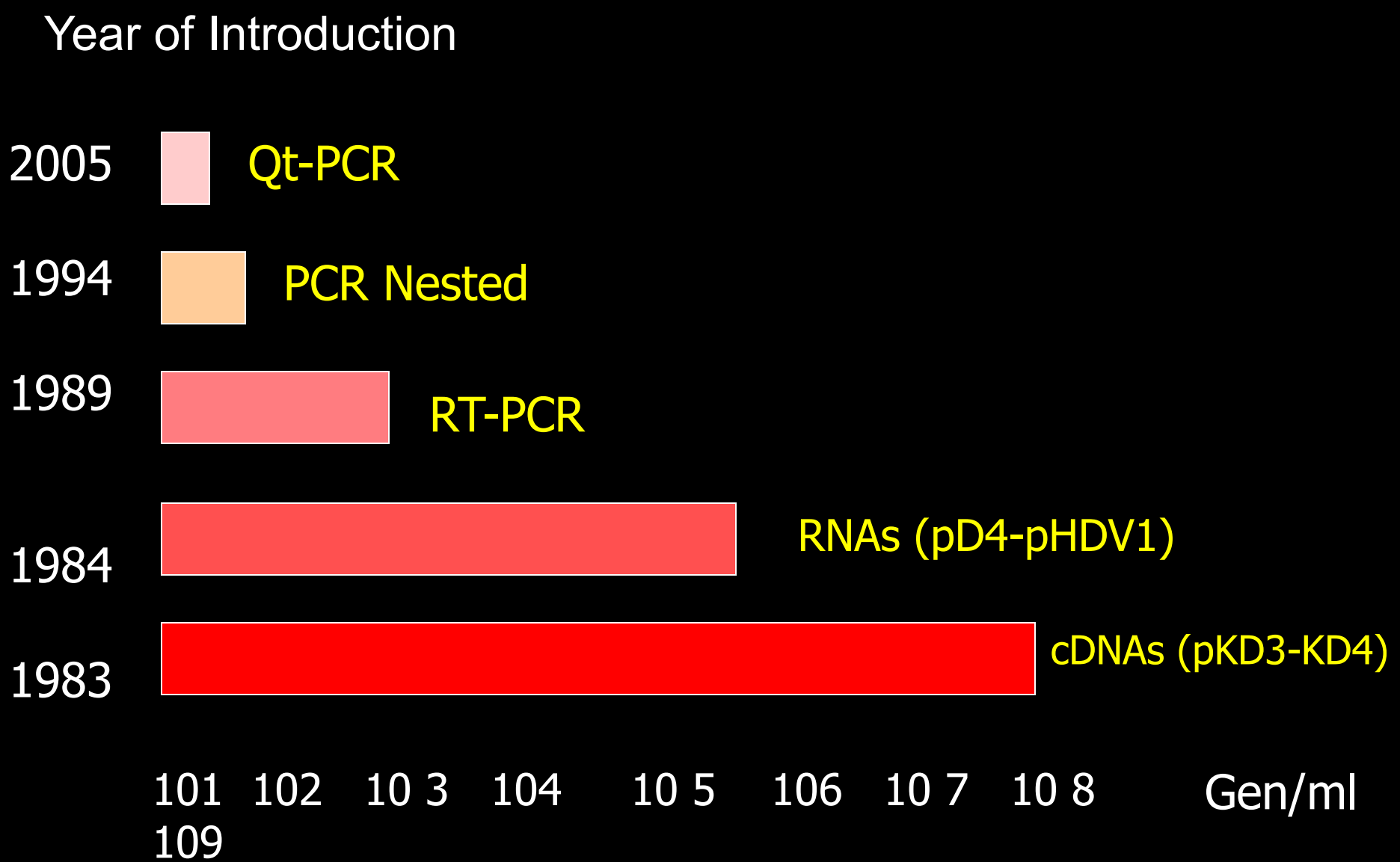
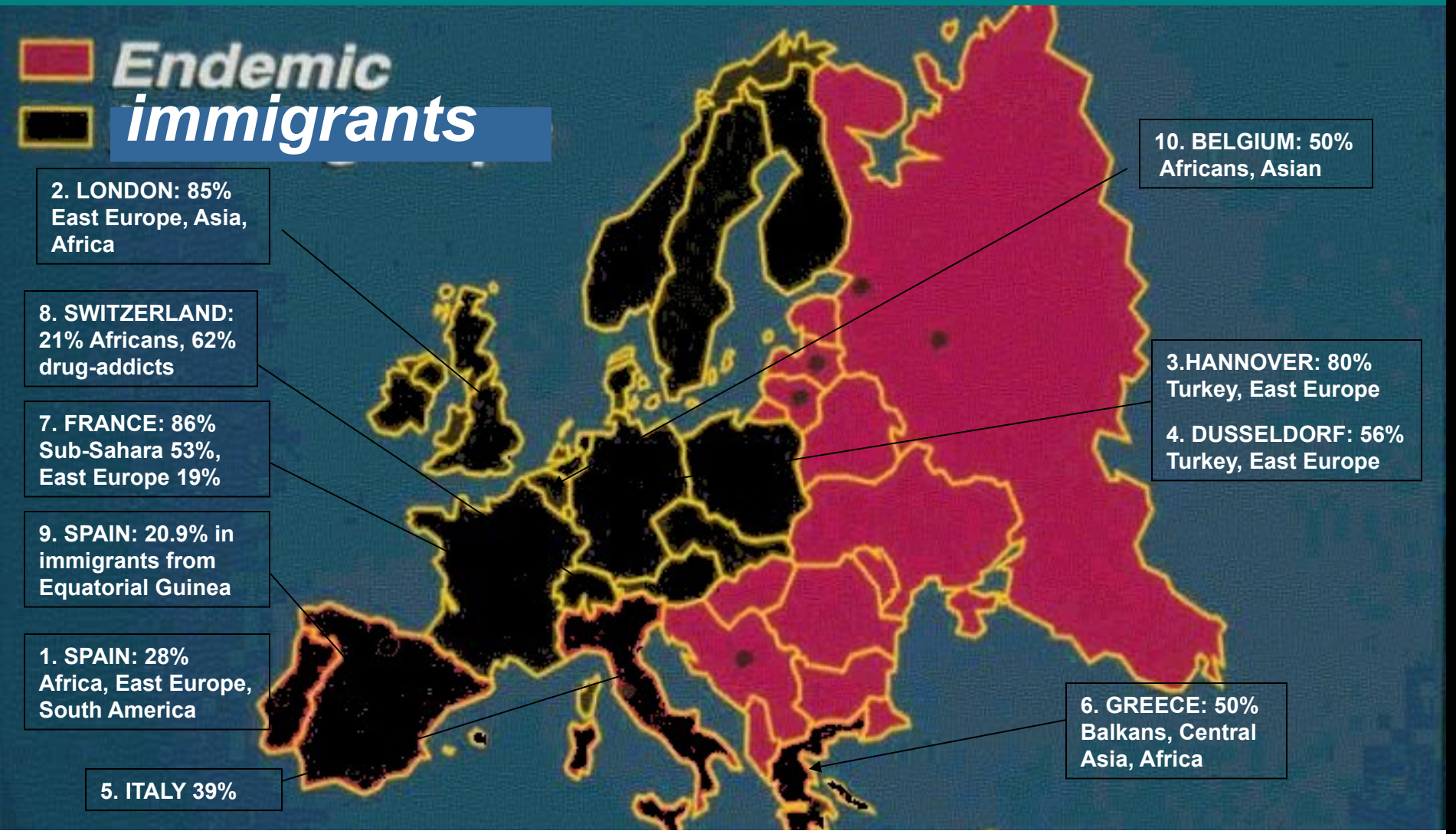
HDV-RNA Assays

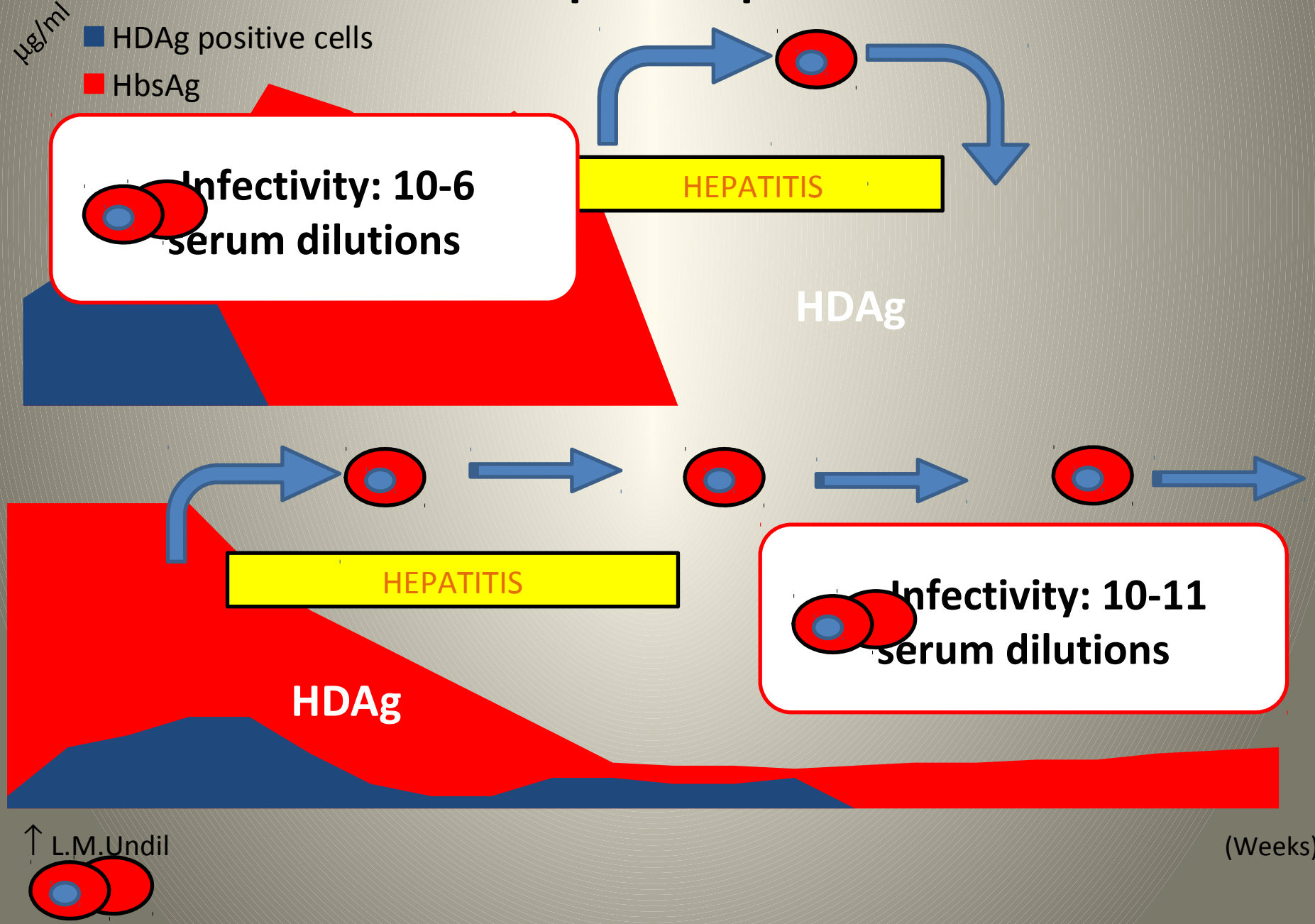


Epidemiology of HDV in Europe: 2015 Prevalence of immigrants among HDV +



1. Buti M, 2011; 2.Cross JT, 2008; 3. Heidrich B, 2009; 4. Erhardt A, 2003; 5. Brancaccio G, 2014; 6. Manesis EK, 2013; 7. Brichler S, 2015; 8. Gennè D, 2011; 9. Rivas P, 2013; 10. Ho E, 2013.

HDV Chimps Experiments



% anti-HD in chronic HBsAg hepatitis in Western Europe in the last decade

2% to 9%

Hannover, 2009	9%	(252/2363)	Heidrich B
Italy, 2014	8.4%	87/1011)	Brancaccio G
London, 2008	8.5%	(82/962)	Cross TJS
London, 2013	2.1%	(22/1048)	William Tong CY
London, 2015: Clinic led testing Reflex testing	 6% 4.5%	 (4/67) (158/3543)	El Bouzidi K
Belgium registry, 2013	5.5%	(44/800)	Ho E
Athens, 2013	4.7%	(101/2137)	Manesis EK
France National Reference Center Database, 2015		1112 Cases collected	Brichler

REP 2139 for chronic hepatitis D

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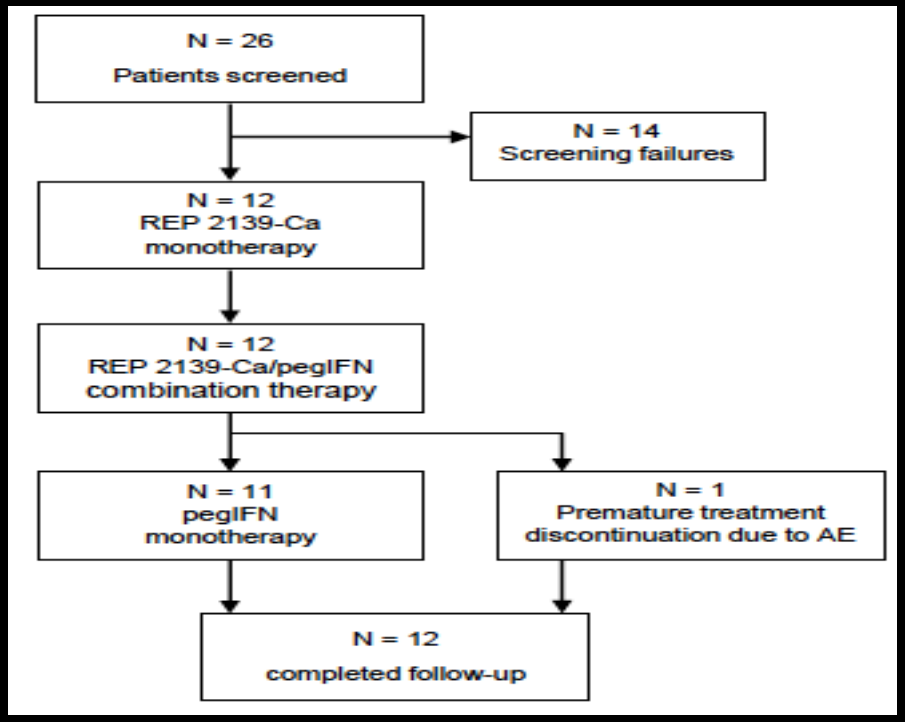
500 mg, qw, 2h inf.	250 mg, qw, 1h inf. + Peg-IFN, 180 ug, qw	Peg-IFN, 180 ug, qw	Tx-free Follow-up

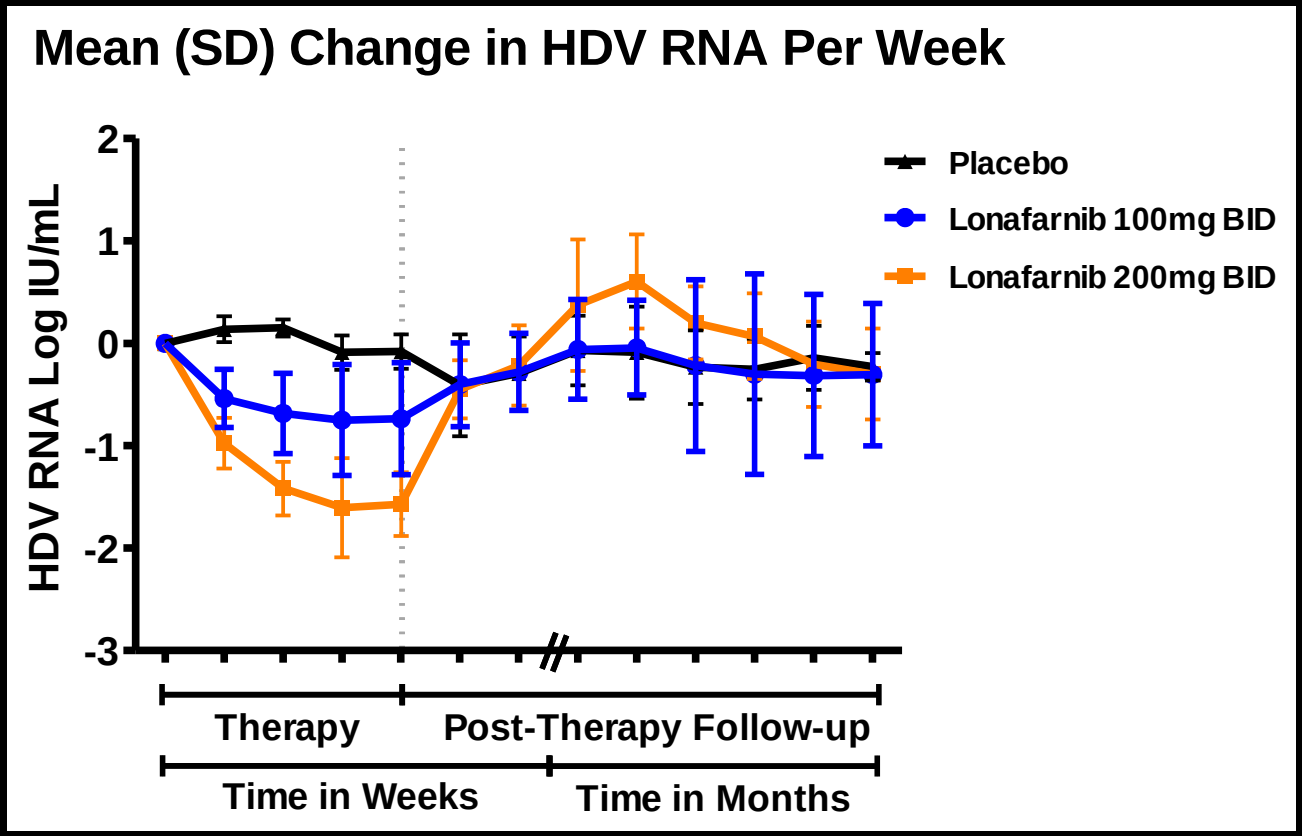


Primary end point: Safety

Secondary end point: Antiviral efficacy

Bazinet M et al, Lancet Gastroenterol Hepatol 2017

Treatment of CDH with Lonafarnib



Koh C et al, Lancet Infect Dis 2015

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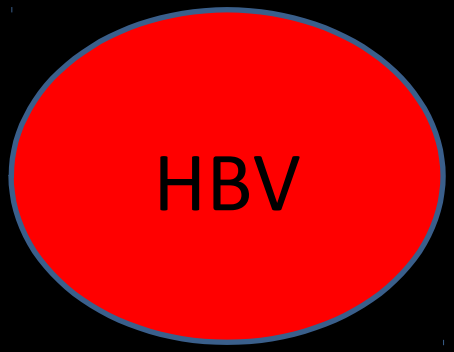
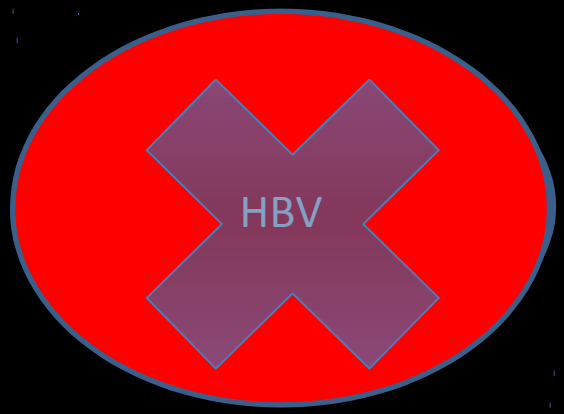
HDV and HBV therapeutic targets



Antivirals against the HBV

HDV and HBV therapeutic targets



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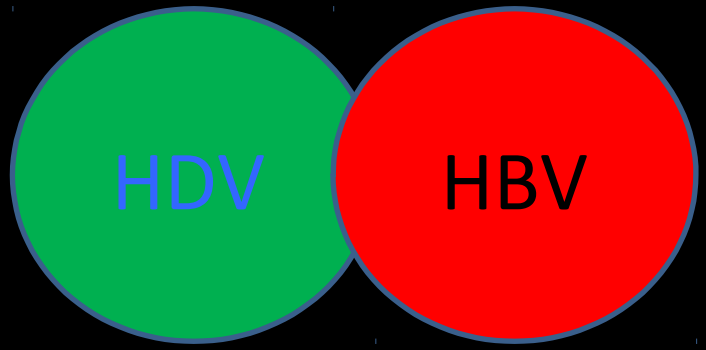
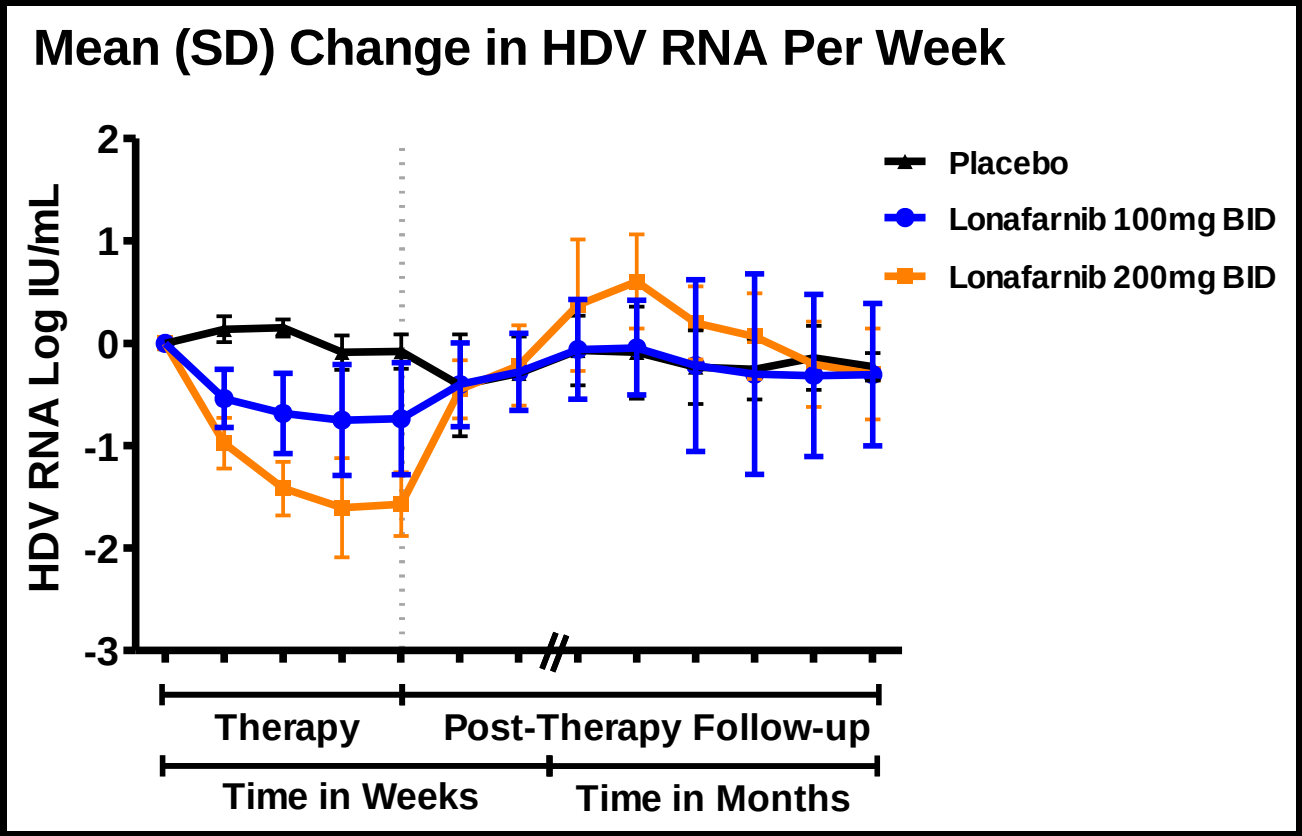


- **Peg-IFN**

Treatment of CDH with Lonafarnib



Koh C et al, Lancet Infect Dis 2015

Drugs Evaluated for the Treatment of Chronic Hepatitis D

- Thymosin
- Rib
- Lam
- Fam
- Ade
- Ent

No role for antivirals that inhibit HBV-DNA but leave the HBsAg unaffected

acy

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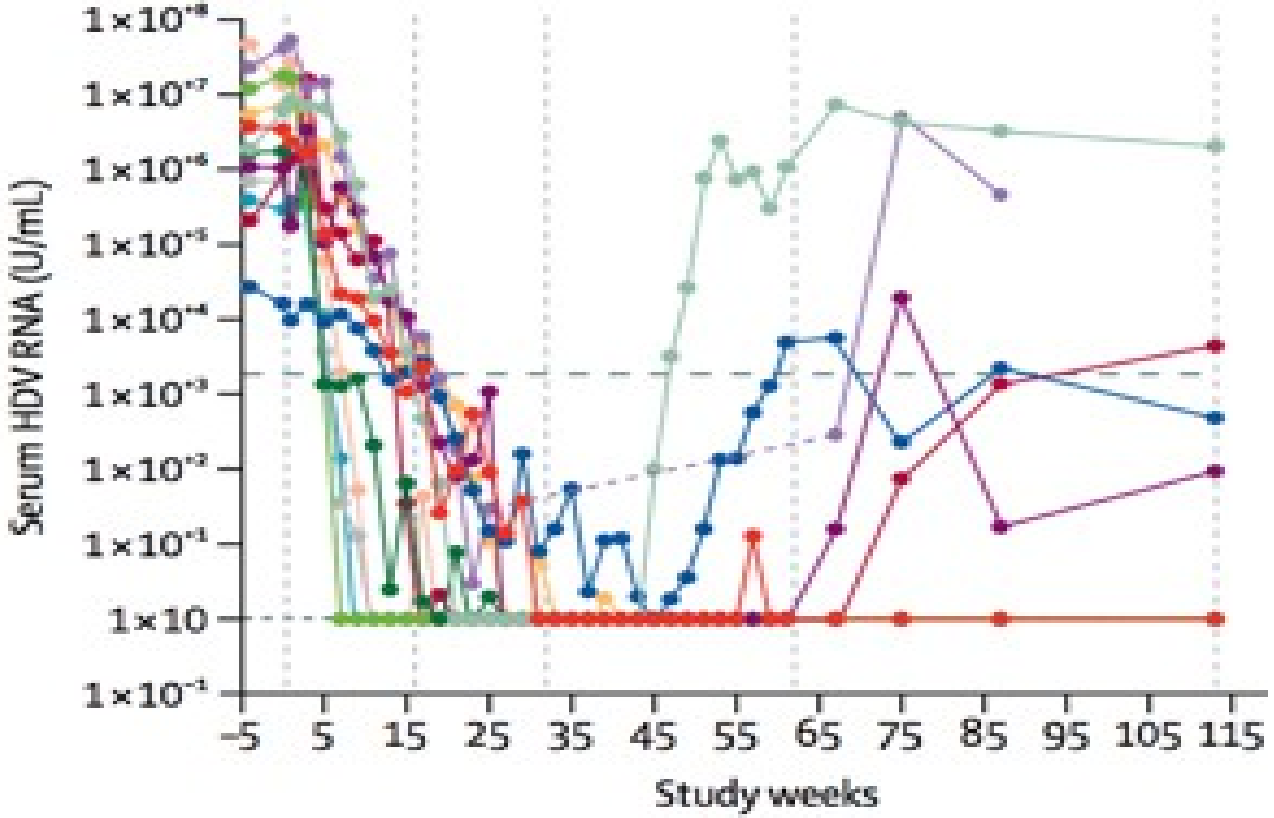

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- ✓ SVR (clearance of serum HDV-RNA) 6 months post-therapy in less than 30 %
- ✓ no advantage with the combination of HBV antivirals
- ✓ results worse in cirrhotics
- ✓ persistence of serum HBsAg in most patients
- ✓ high rate of relapses

PROBLEMS IN THE THERAPY OF HDV

The HDV needs from the HBV only the HBAg coat for the morphogenesis of its virion .

THE LIFE-CYCLE OF THE HDV IS INDEPENDENT FROM HBV REPLICATION (FROM HBV-DNA…)

The HDV-RNA is replicated by RNA-polymerases of the cell , deceived to copy the viral genome as if it were a cellular DNA.

THE HDV IS NOT VULNERABLE BY CONVENTIONAL ANTIVIRALS TARGETED TO SPECIFIC ENZYMATIC FUNCTIONS OF VIRUSES (POLYMERASES ,PROTEASES)

DIAGNOSTIC SERUM MARKERS SPECIFIC TO THE HDV ARE :

the IgG (total Ig) antibody to the HDAg (measured by radio or enzyme immuneassays) = anti-HD

anti-HD is a general marker of exposure; it provides the initial screening test and a marker of infection/disease

the IGM antibody to the HDAg, (measured by radio immuneassays) =IgM anti-HD

IgM anti-HD is a marker of HDV-related liver disease

HDV-RNA , measured by ……..

HDV-RNA is a marker of HDV replication and active infection

HDV replication and active infection can be also diagnosed in immunohistochemistry by the finding of the HDAg in liver biopsies using peroxidase - or fluorochrome- conjugated antisera to the HDAg

Chronic hepatitis D: features

- rapid progression to cirrhosis
- anti-HBe+; IgM anti-HBc –
- HBV-DNA low or absent
- no specific clinical/histologic features
- occasionally splenomegaly +++

Chronic hepatitis D: features

- markers of HDV infection
- HBV-DNA low or absent
- no specific clinical/histologic features
- rapid progression to cirrhosis

Markers of HDV infection

- IgG (total) anti-HD = exposure , infection
- IgM anti-HD =HDV-related liver disease
- HDV-RNA = active infection, viral replication