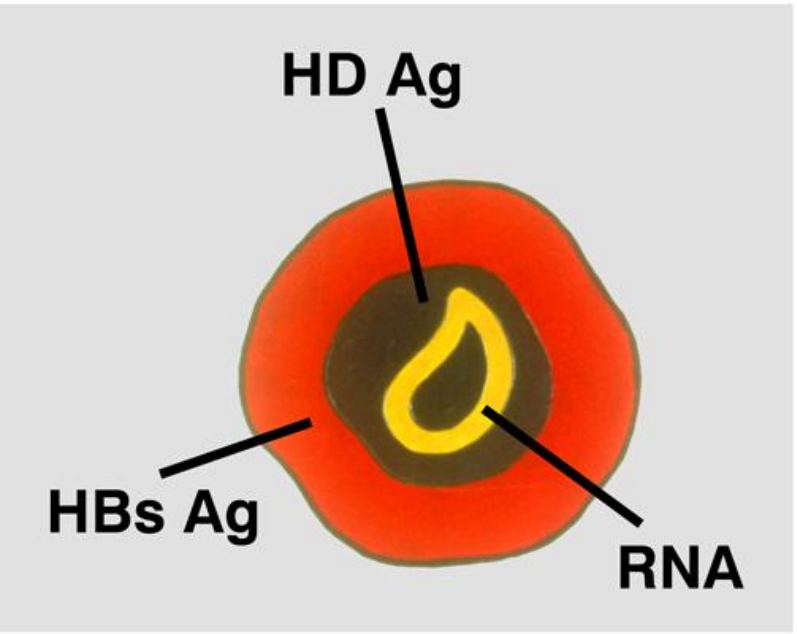
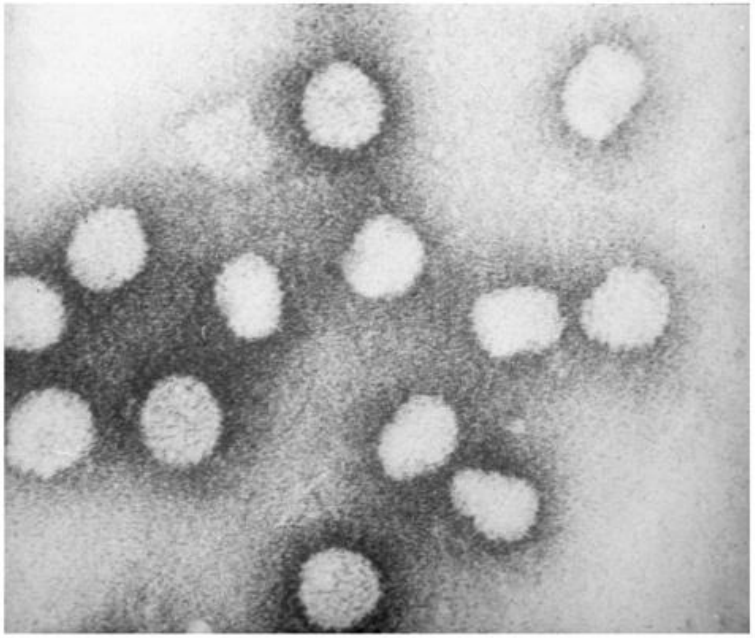
HEPATITIS DELTA VIRUS



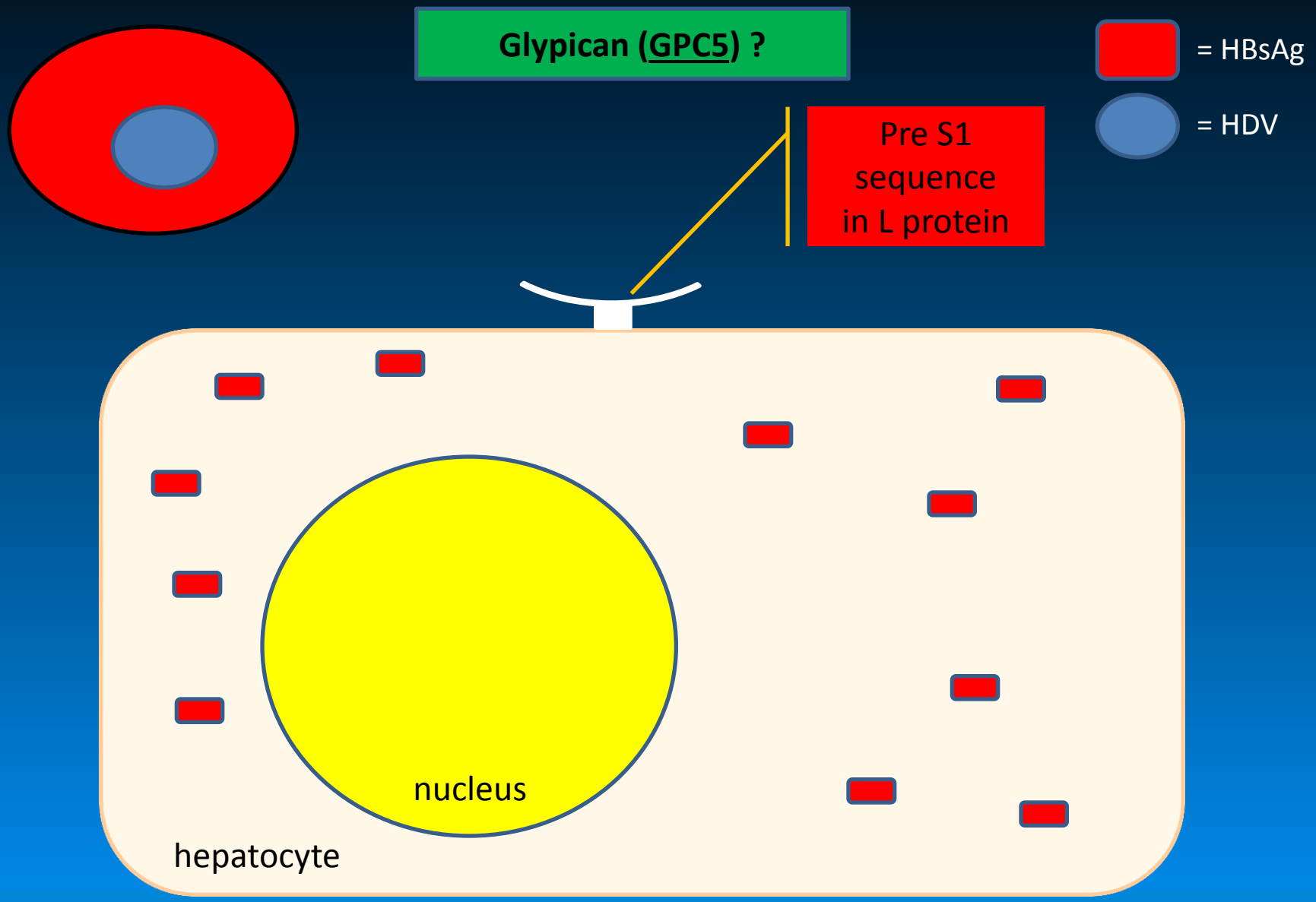


- Dependent for in-vivo infection on helper functions of hepadnaviruses
- Pathogenic
- Related to plant viroids ?

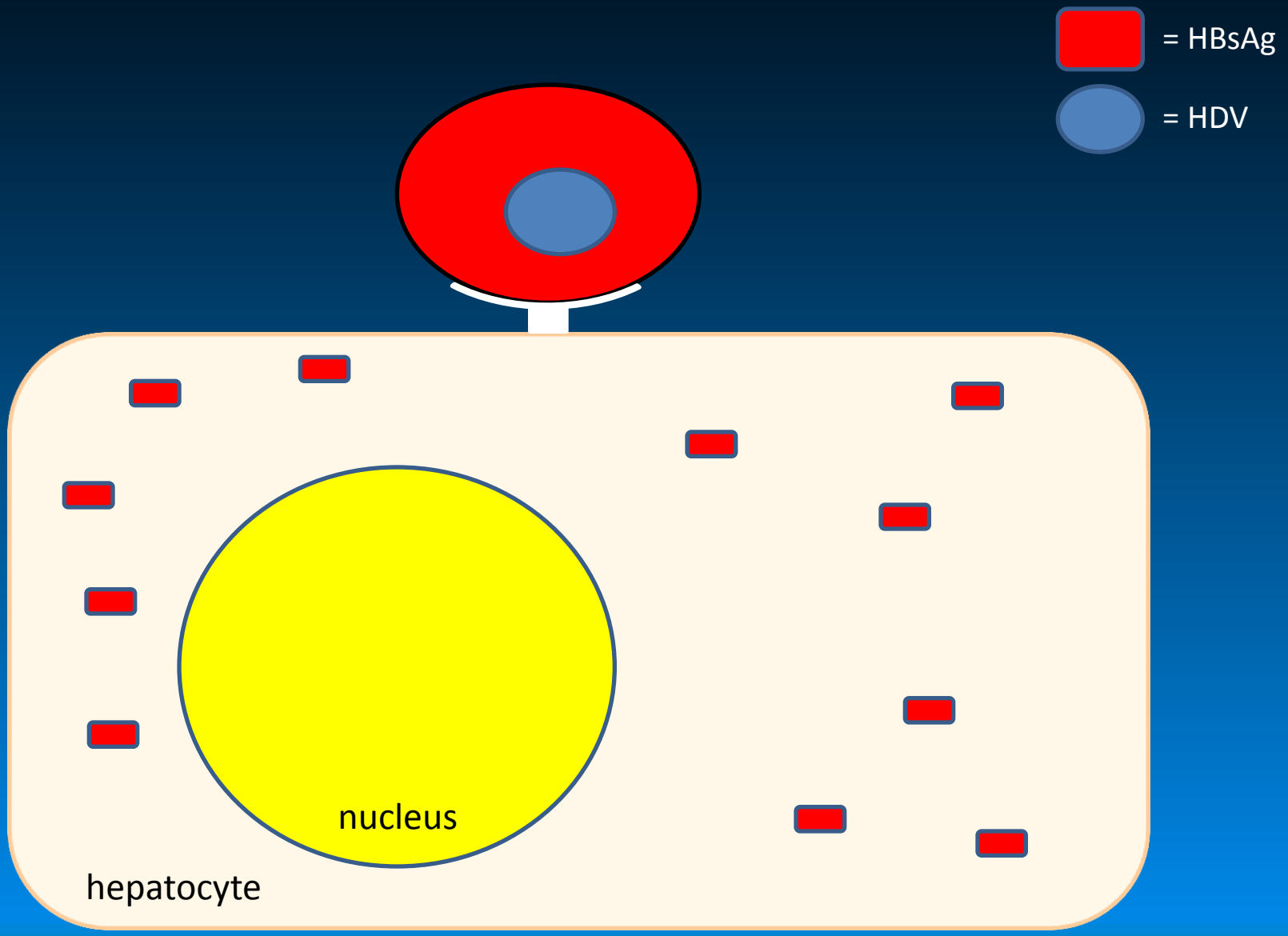
HDV: unique features

- Smallest infectious agent in man: 1700 nt
- Circular, single stranded-negative polarity
- Infectious at 10^{-11} serum dilutions in HBsAg +
- Rolling circle mechanism of replication
- Self-cleaving ribozyme
- Transcription by host-RNA polymerases

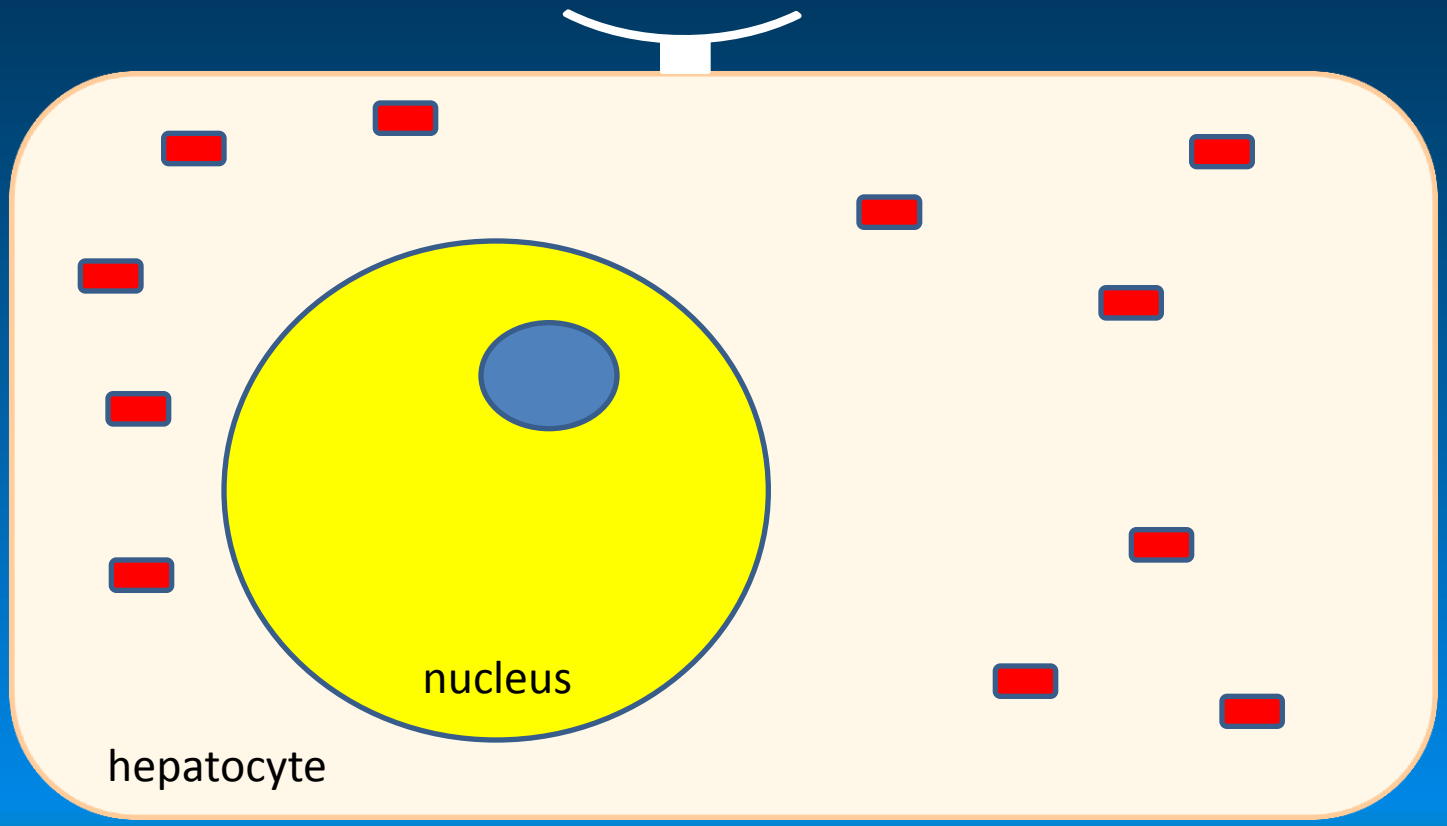
Attachment of HDV



HDV transferred to nucleus



HDV transferred to nucleus



Replication of HDV-RNA

Cell Ligase
HDV Ribozyme?

\+

\+

\- = genomic HDV-RNA

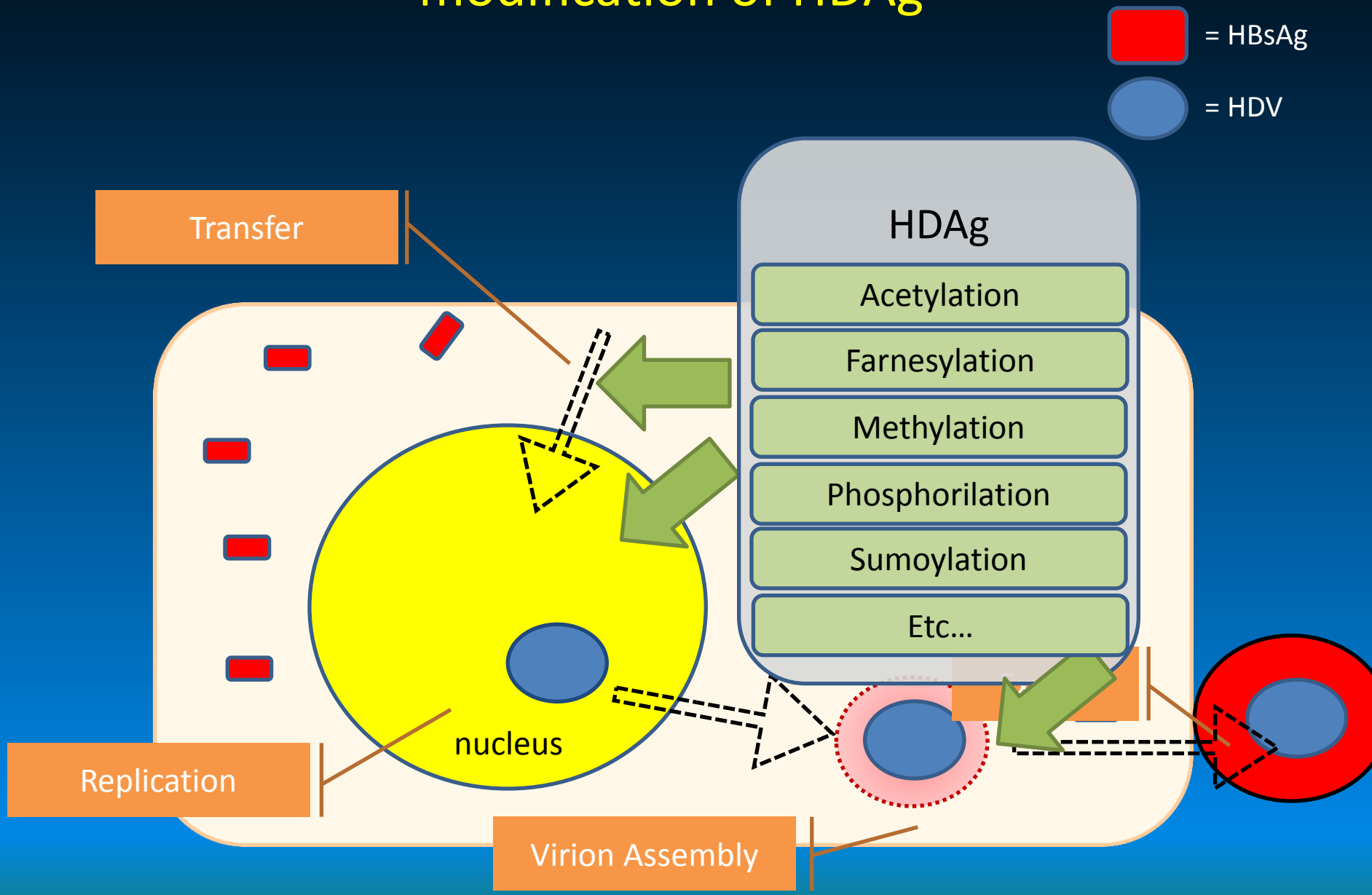
\+ = antigenomic HDV-RNA

HOST
RNA polymerase II, I, III

HDV Ribozyme

\-

Life cycle of HDV directed by post-translational modification of HDAg



Corollaries

HDV latency,

theoretically HDV may survive in the absence of HBV as helper virus

Hepatitis D therapy,

no replicative target for antivirals

Latency of HDV

in HBsAg-negative transplanted livers

• **Torino**: subclinical HDV-RNA blips over 34 months of follow-up in 5% of 117 pts

Rizzetto M, 2006

• **Paris**: among 76 pts, HD-Ag in liver or HDV-RNA in serum in:

- 88% during the first year post-transplant
- 5% after the second year post-transplant

Samuel D, 2006

• **Hannover**: HD-Ag stainable in liver grafts of 6 pts up to 19 months post-transplant (in the absence of liver HBV-DNA and of serum HDV-RNA)

Mederacke I, 2006

Latency of HDV

in the experimental model

- survival of HDV monoinfection for up to 38 days in woodchucks

Netter HJ, 1994

- HDV monoinfection persisting in mice for at least 6 weeks before conversion to HBV/HDV infection by HBV rescue

Giersch K, 2014

- in vitro and in vivo HDV survives liver regeneration, propagates and amplifies among cells, despite absence of HBV

Giersch K, 2015

Hammerhead and HDV-like self-cleaving ribozymes ubiquitous, expressed along the tree of life (worms, mosquitos, see urchins, plants…)

Scale of genomic sizes, in DNA base pairs. Phage MS2, HDV, viroids in RNA bases

Flores R et al, Seminars in liver Disease, 2012

Properties of HDV and of viroids/satellite RNAs of plants

	HDV	Viroids	Satellite RNAs
Size (nucleobases)	1700	246-267	194-1500
Helper dependent	+	–	+
Encapsidate in helper virus cost	+	–	+
Translation of RNA	+	–	±
Ribozyme	+	+	±
Rolling circle replication	+	+	+

HDV origin

HDV evolved from a viroid-like RNA that captured the m-RNA encoding the HD-Ag protein

Taylor, 2010

HDV origin:

From HBV?

- Transcription of many viral sequences during HBV replication, some of which undergo splicing with the potential to form a stable RNA circle

- A rare RNA circle selected for the capacity to undergo RNA-directed replication using host-polymerases, and to express a short protein intrinsically disordered (favoring multimerization) and positively charged (favouring RNA binding)

- Many nucleotide changes in the replicating RNA sequence; ultimately it is unrecognizable relative to HBV sequences, and becomes the HDV-RNA

Taylor J, 2014

HDV therapy

HDV therapy problems

Hepatitis D results from a double viral infection. The evaluation of therapeutic goals requires consideration and targeting of two viral infections, adding complexity to the management of the HDV patient

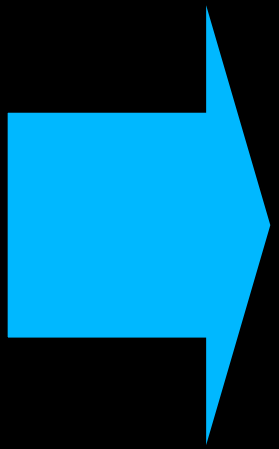
HDV therapy

problems

- HBV required only to provide the HBsAg capsid
- replication of HDV indipendent from HBV replication (i.e. from HBV-DNA levels)
- NO OWN REPLICATION FUNCTION OF HDV to be targeted by antivirals

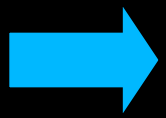
Drugs Evaluated for the Treatment of Chronic Hepatitis D

- Thymosin
- Ribavirin
- Lamivudine
- Famciclovir
- Adefovir
- Entecavir



- No Efficacy

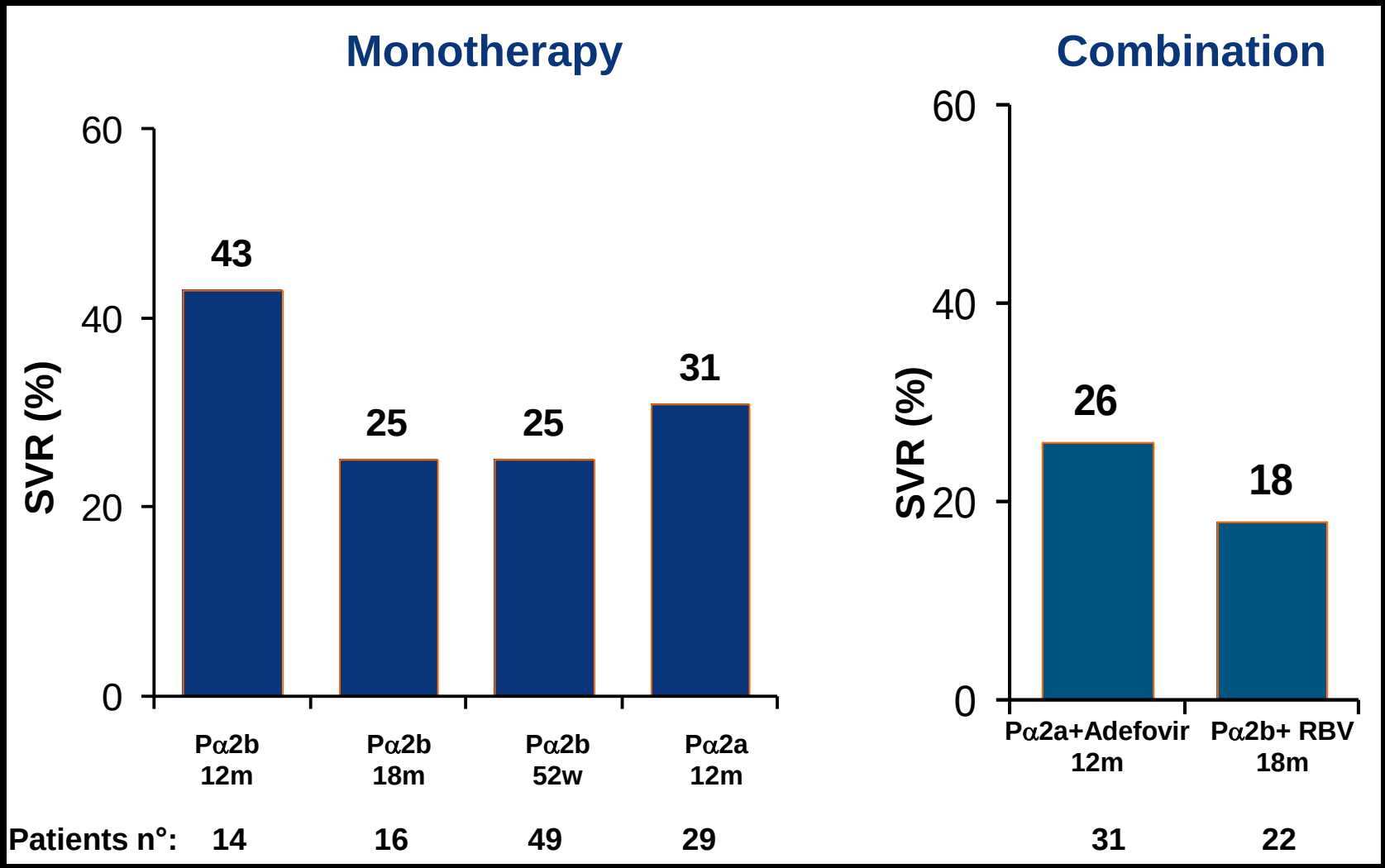
- IFN/Peg IFN



Limited Efficacy

Therapy of chronic hepatitis D with Peg-IFN

Sustained virologic response (SVR)



m = months w = weeks P = Peg-IFN RBV = ribavirin

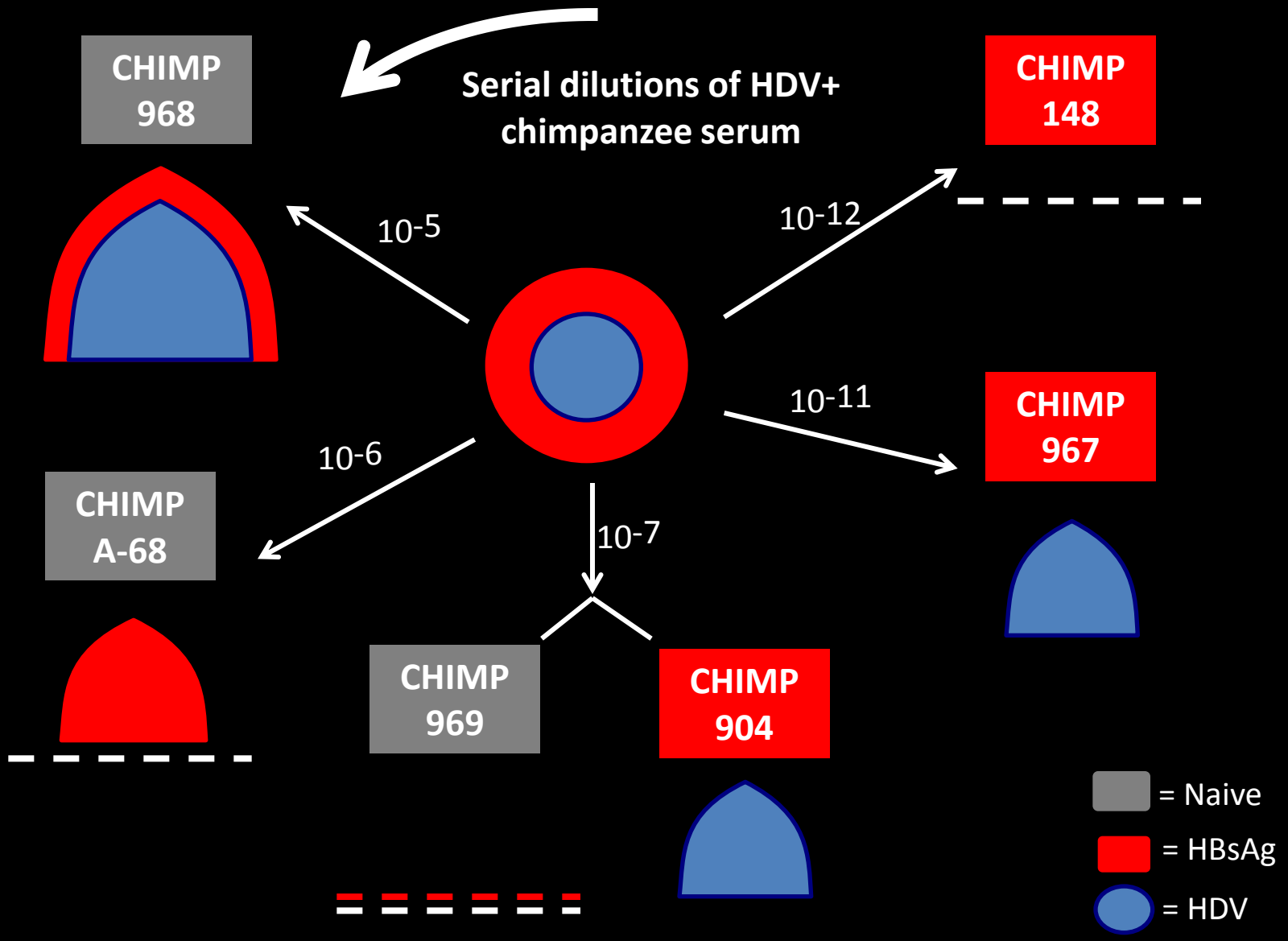
Peg-IFN therapy: caveats

- small series of patients
- different designs and protocols
- ↓ ALT vs clearance HDV-RNA not consistent
- on treatment kinetics of HDV-RNA not predictive of response
- clearance of HDV-RNA vs histology not consistent
- no advantage to treat up to 24 vs 12 months in controlled series

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

In the HBsAg setting, HDV may remain infectious at 10^{-11} serum dilutions, i.e. at titers far below the sensitivity threshold of current HDV-RNA assays (10 cp/ml)

HDV titration studies



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

Current therapy conclusions

The current recommendation is pegylated

Interferon-alfa weekly for 12 to 18 months

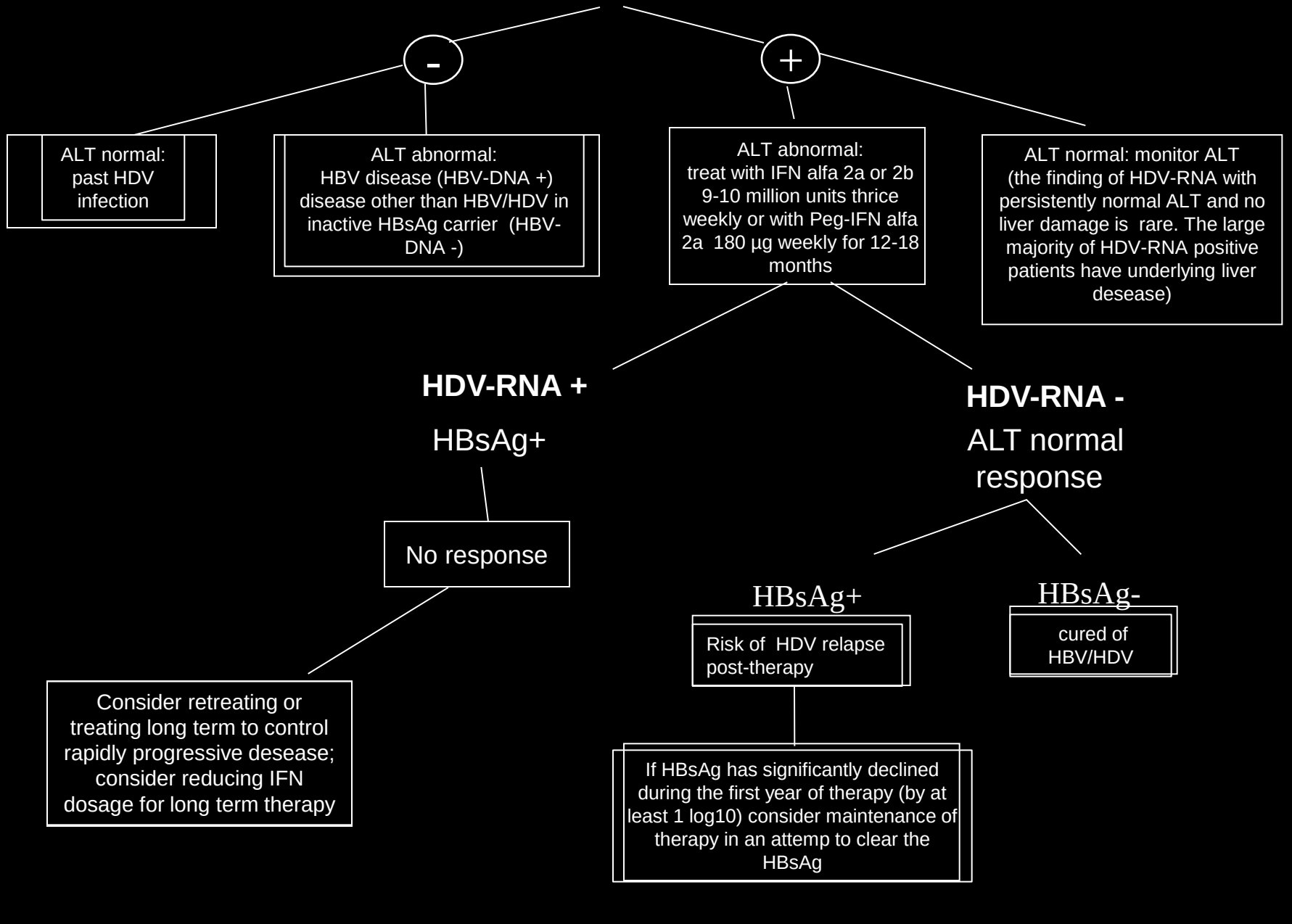
20%-25% of the patients respond; HDV may relapse as long as HBsAg is around

Only reliable end-point of therapy is the clearance of the HBsAg

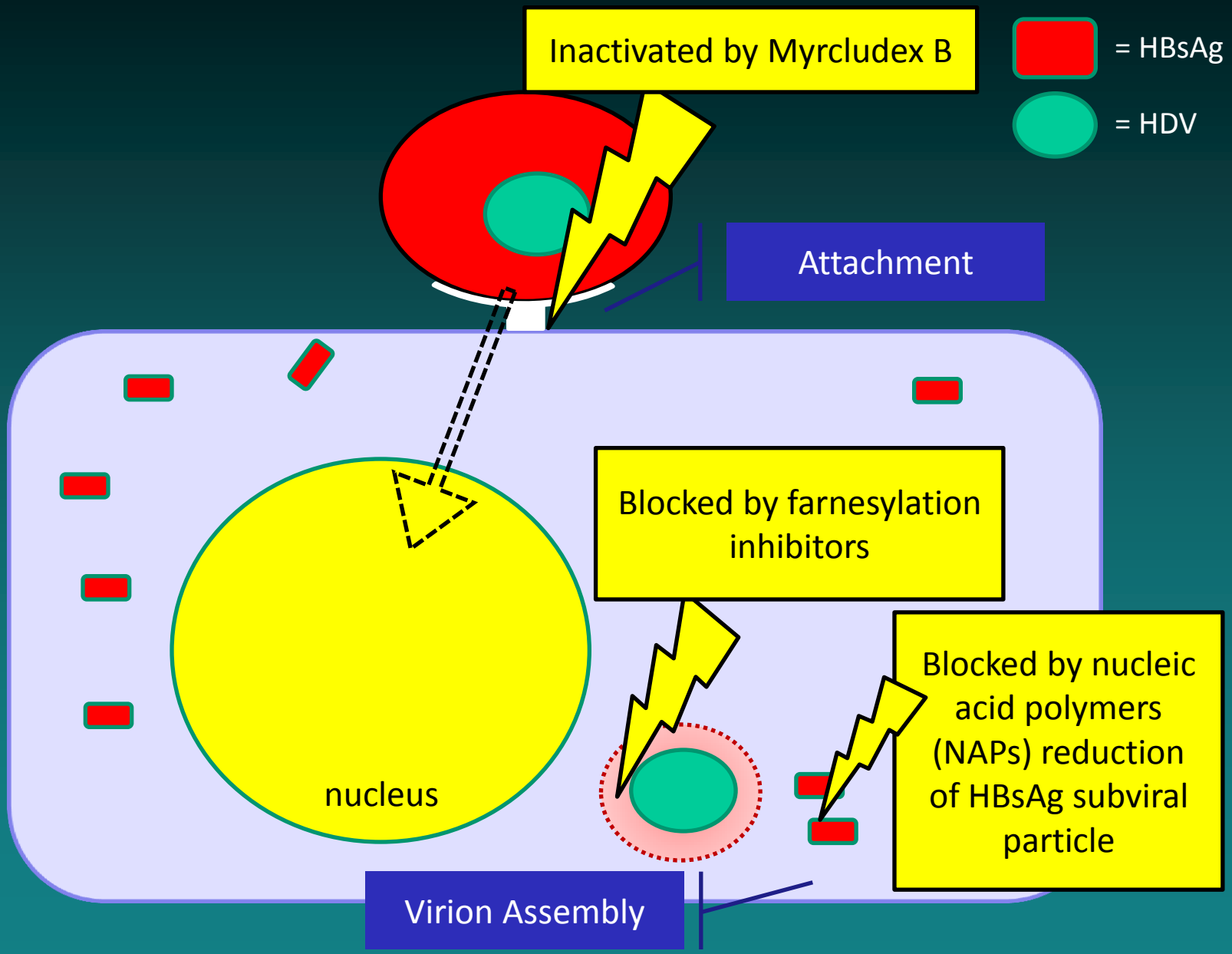
HDV: Loss of HBsAg with IFN/Peg-IFN therapy

S.Y. Lau, 1999	4/6 (66%)	Standard IFN for at least 11 m.
M.G. Niro, 2014	9/43 (21%)	5.3 ± 2.8 years from end of therapy (15 months ± 4.8)
T.H. Heller, 2014	3/14 (21%)	In therapy for up to 5 years
H. Wedemeyer, 2014	7/130 (5.3%)	96 weeks of therapy

Treatment algorithm and follow-up in the HBsAg- positive subjects with anti-HD



HDV: therapeutic targets



Block of HDV entry via the Sodium Taurochocolate Cotrasporting Polypeptide (NTCP)

- irbesartan
- ezetimibe
- ritonavir

in Huh 7 cells

- primary biliary acids (in human hepatoma cells)
- Myrcludex-B (in HBV-mice)
- Cyclosporin (in hepa-cell lines)

Myrcludex-B

Long-term treatment needed to disease HDV-viremia

Volz T, 2015

LONAFARNIB 28 DAYS

14 HDV patients; 71% males, median age 38 y, Asian 50%, Caucasian 43%.

	Group 1	Group 2
Lonafarnib	6 pts 100 mg t.d.	6 pts 200 mg t.d.
Placebo	2 pts	2 pts
Median baseline features	- Ishak: S3 - HBV-DNA: < 21 IU ml - HDV-RNA: 106 IU ml	

Koh C, 2014

LONAFARNIB AFTER 28 DAYS OF THERAPY

	GROUP 1	GROUP 2	PLACEBO
HDV-RNA, mean log change (IU/ml) from baseline	- 0.74	- 1.68	- 0.13

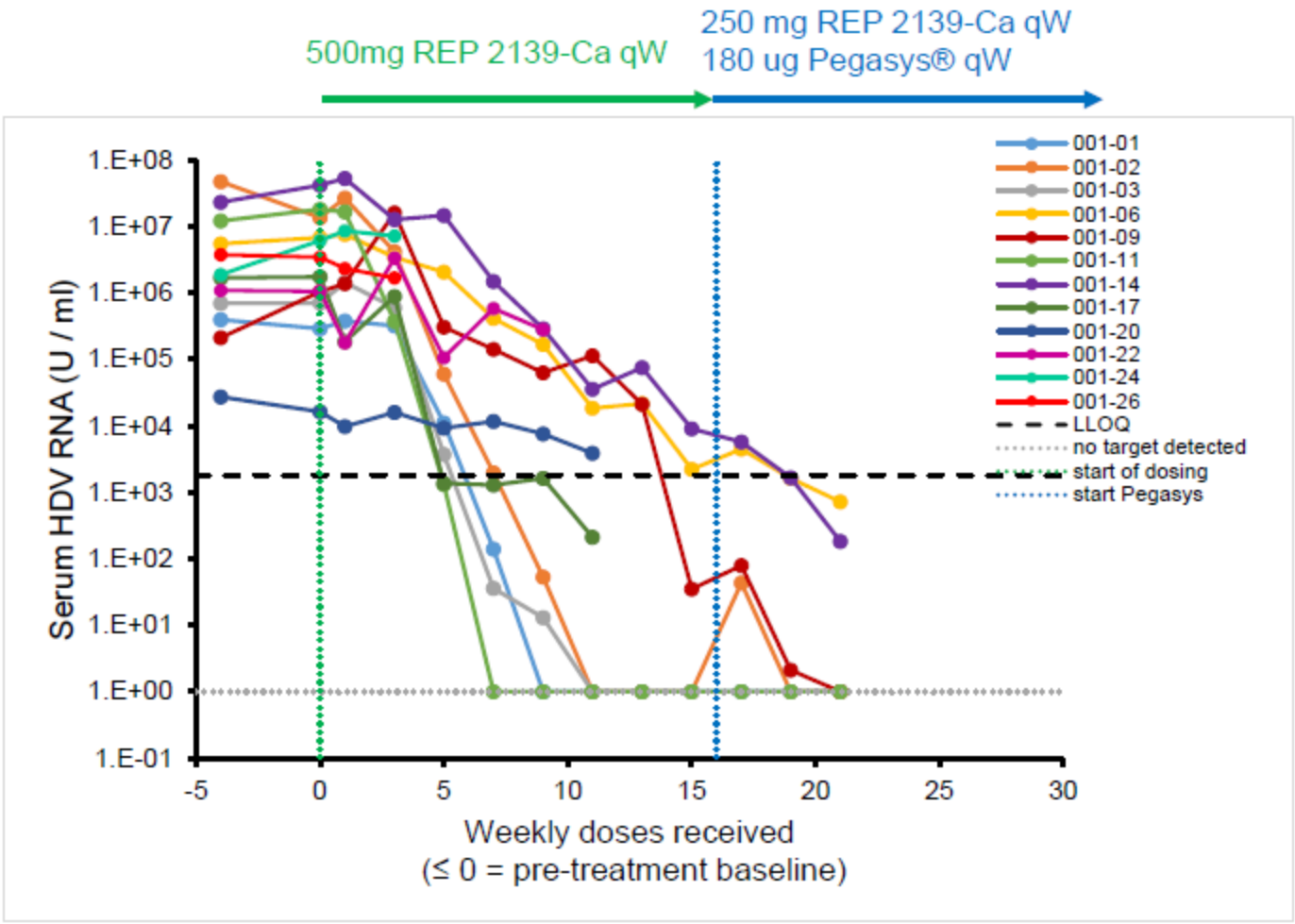
Frequent mild to moderate adverse events: nausea, vomiting, dyspepsia, anorexia, diarrhea, weight loss

Koh C, 2014

Nucleic Acid Polymers (NAPs) in HBV therapy

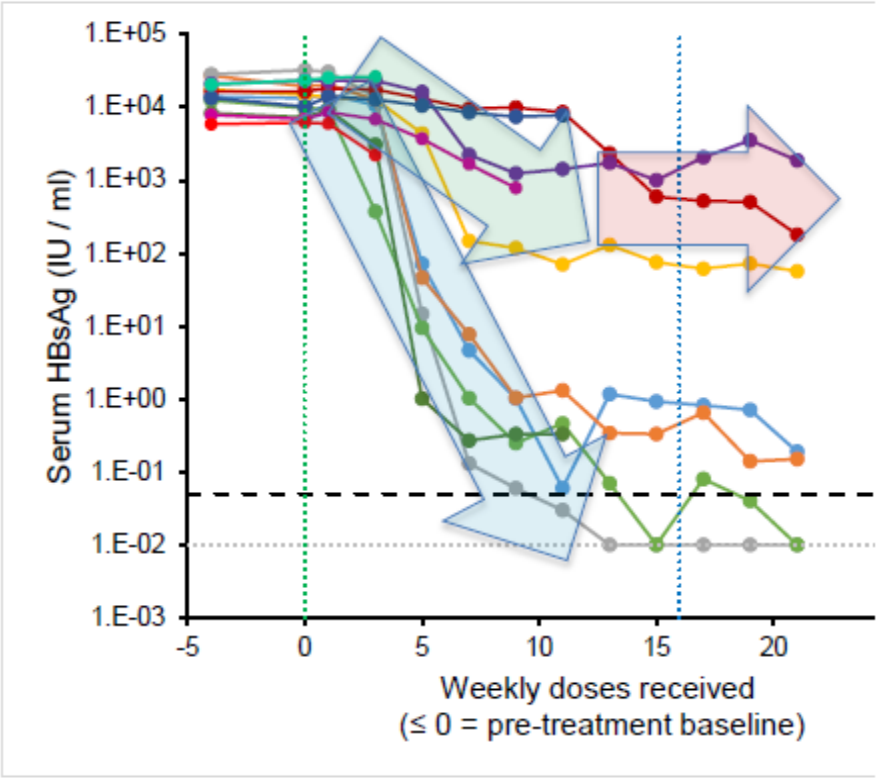
- Two antiviral mechanisms HBV infection:
  - block HBV entry
  - post entry activity: blocks subviral particle (SVP) formation
    - leads to clearance of serum HBsAg in patients
  - **production of virions is not targeted by NAPs**

Interim REP 301 Efficacy Data (serum HDV RNA)

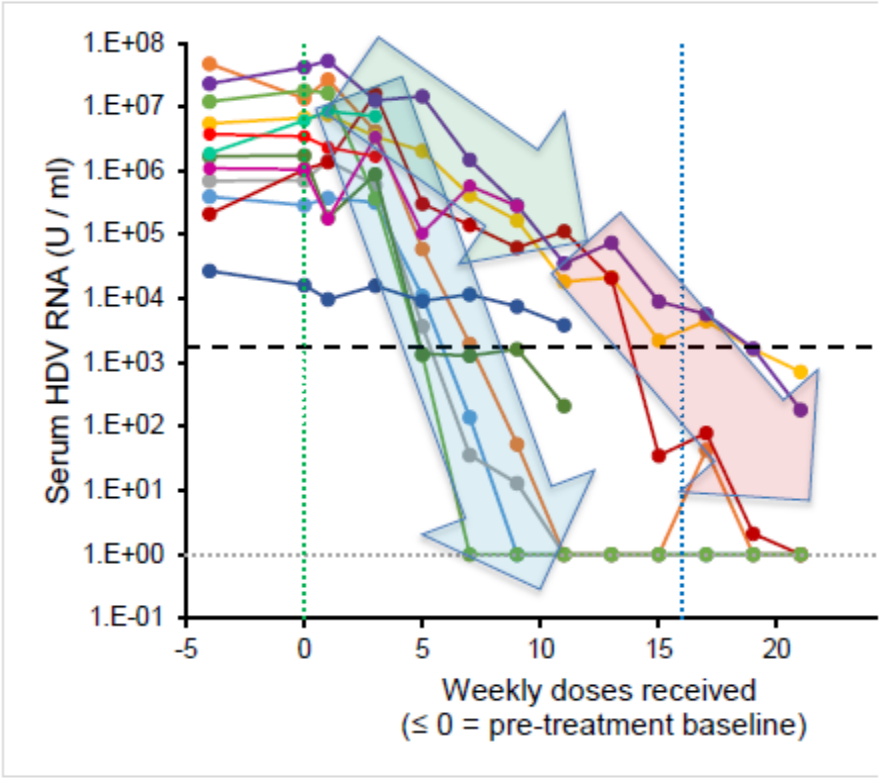


HBsAg versus HDV RNA response

HBsAg



HDV RNA



Multiple antiviral effects may be present

Entry inhibitors in combination with antivirals could block reinfection and shield naive hepatocytes that emerge from natural liver turnover