HDV therapy—relevant recent findings and suggested endpoints

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Disclosures: Genentech, Merck, Roche, Romark Laboratories,
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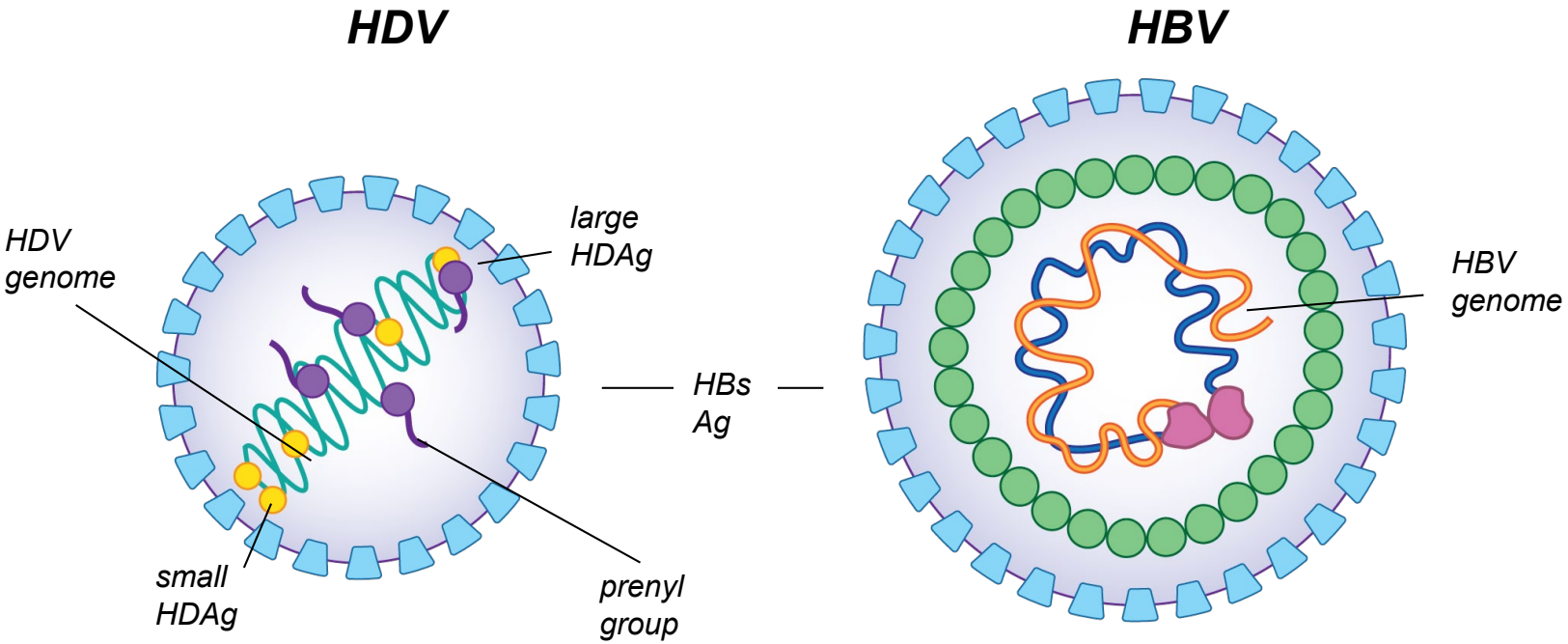
Eiger Group International Inc., Eiger BioPharmaceuticals, Inc.,
Riboscience, LLC, I-Cubed Therapeutics, LLC

Objectives of this session

- Brief overview of HDV life cycle
- Highlighting targets of agents in clinical development
  --Heiner: interferon alpha and NAPs;
  --Stephan: myrcludex-b;
  --Jeffrey: lonafarnib and interferon lambda
- Suggested endpoints for initial approval of new agents
  --perspective of each speaker
- General discussion

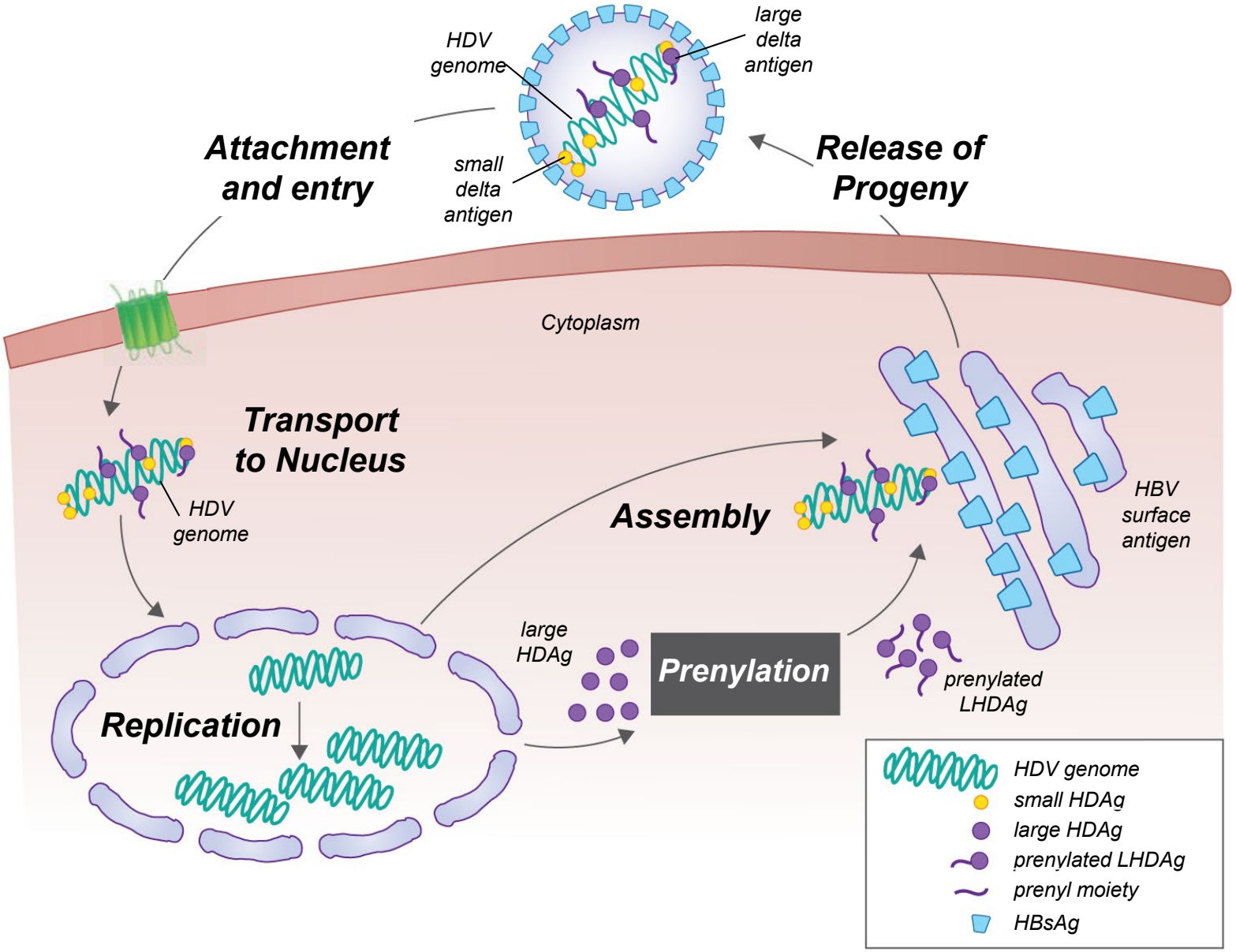
Hepatitis Delta Virus

Requires HBsAg from HBV for Viral Assembly / Packaging

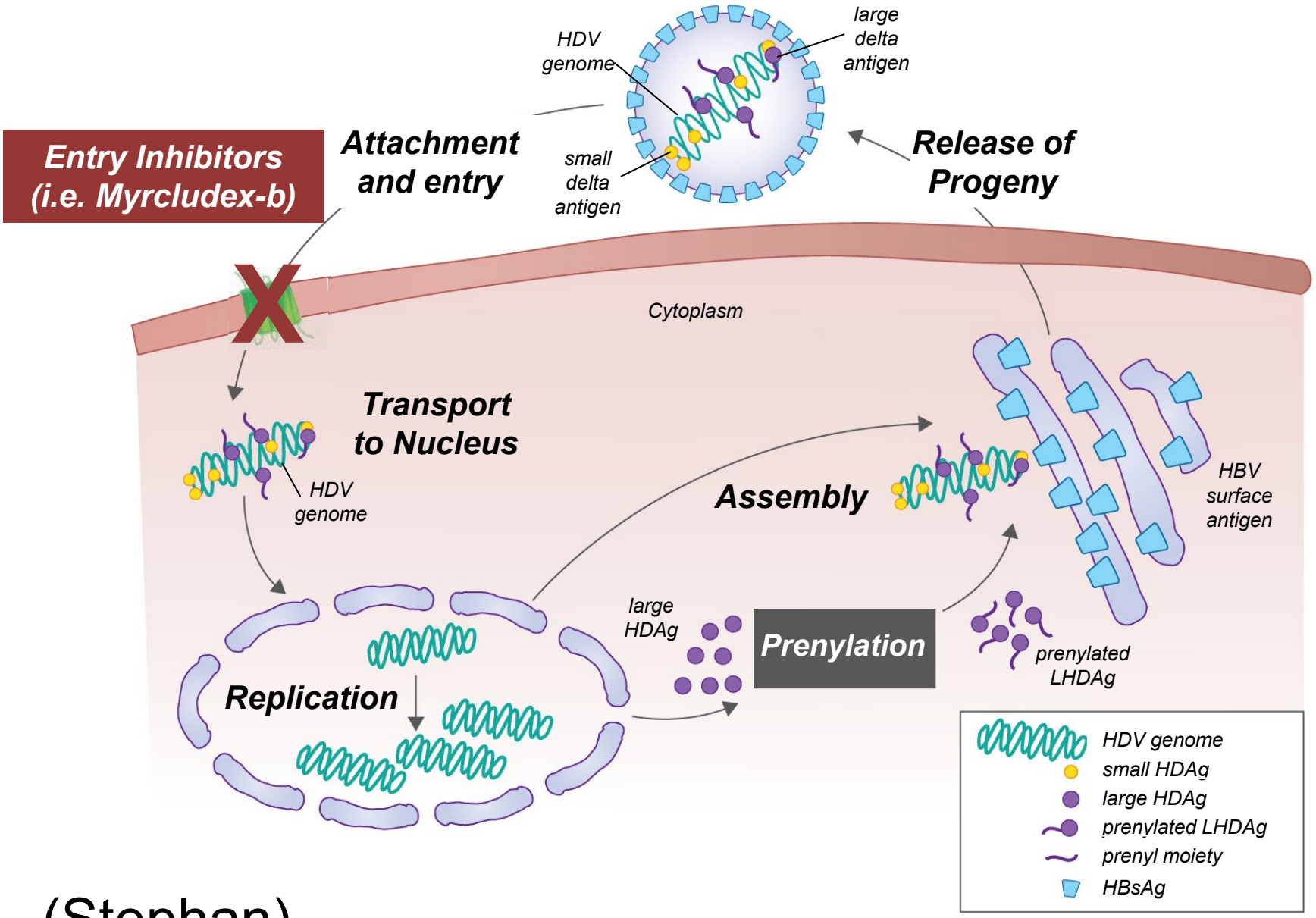


- HDV makes HBV disease worse
- HDV is worst form of human viral hepatitis
- Rapid progression to cirrhosis; HCC; ↓ survival
- ~ 15-20 million world-wide; ~ 100K in U.S.
- No FDA-approved therapy
- IFNalpha suboptimal efficacy (Heiner)

The HDV Life Cycle

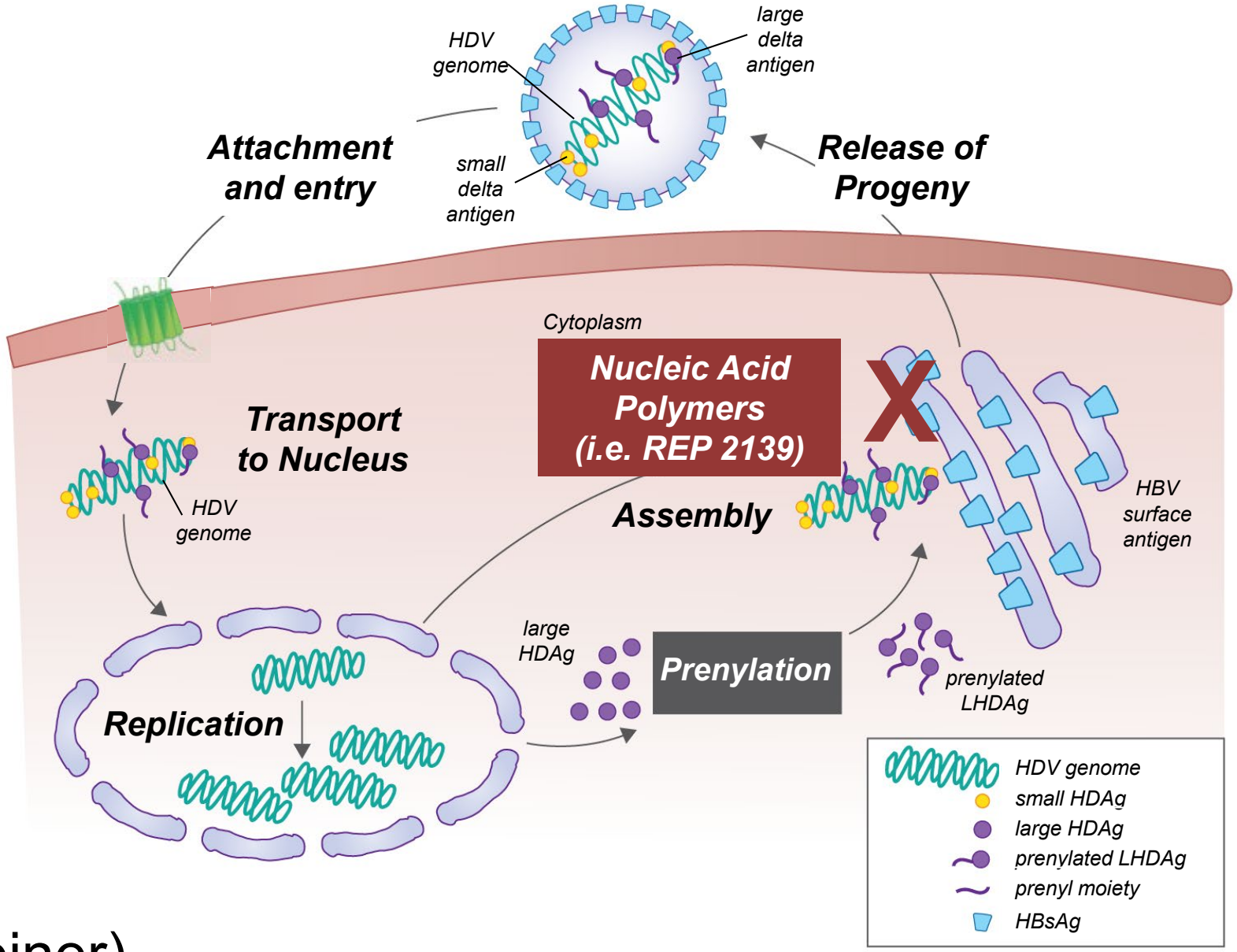


The HDV Life Cycle



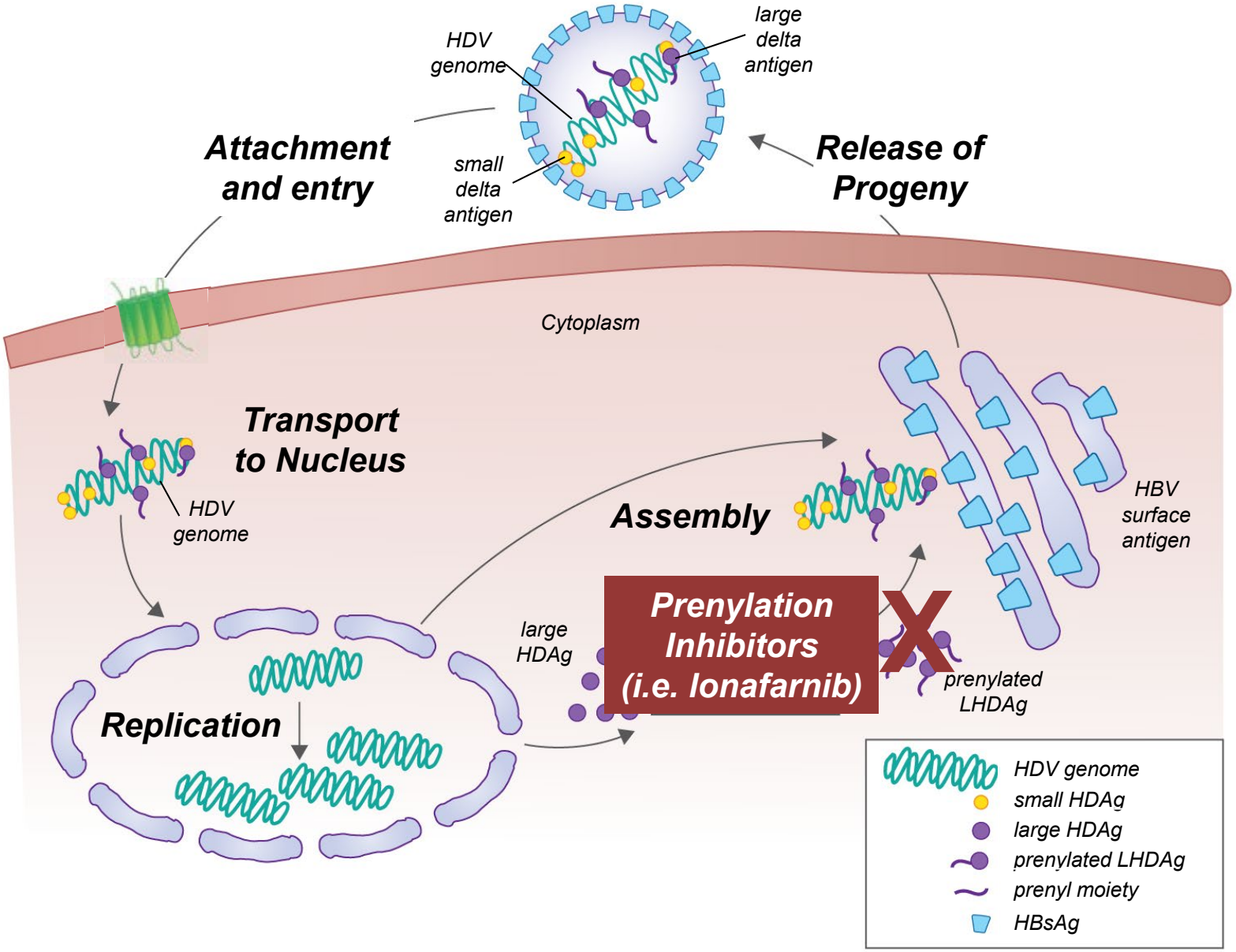
(Stephan)

The HDV Life Cycle



(Heiner)

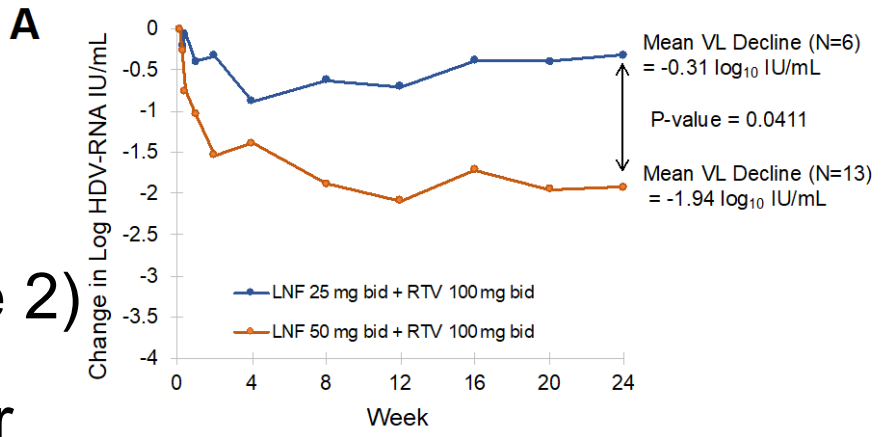
The HDV Life Cycle



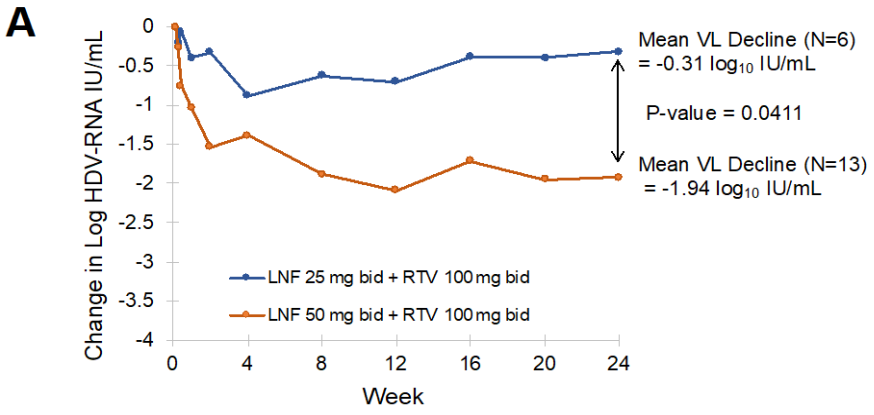
Lonafarnib for HDV

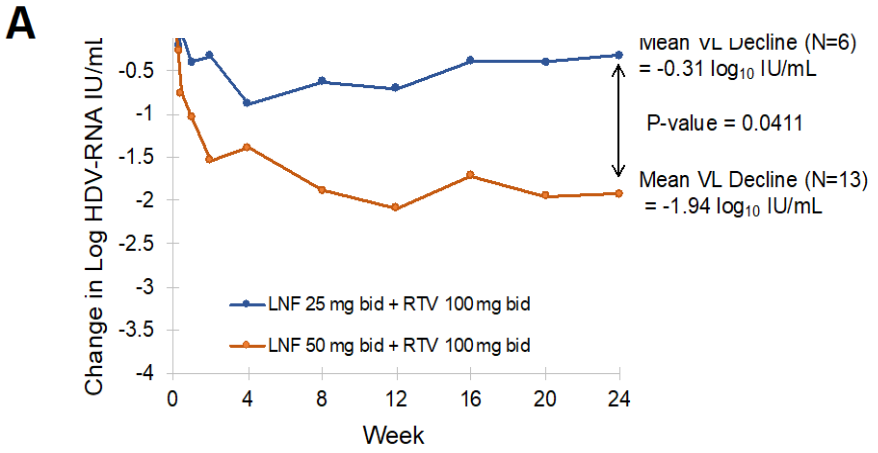
Well-Characterized Clinical Stage Lead Compound

- Lonafarnib (LNF) small molecule, oral, prenylation inhibitor
- Over 120 HDV patients dosed across international sites (phase 2)
- Well-tolerated doses identified for phase 3



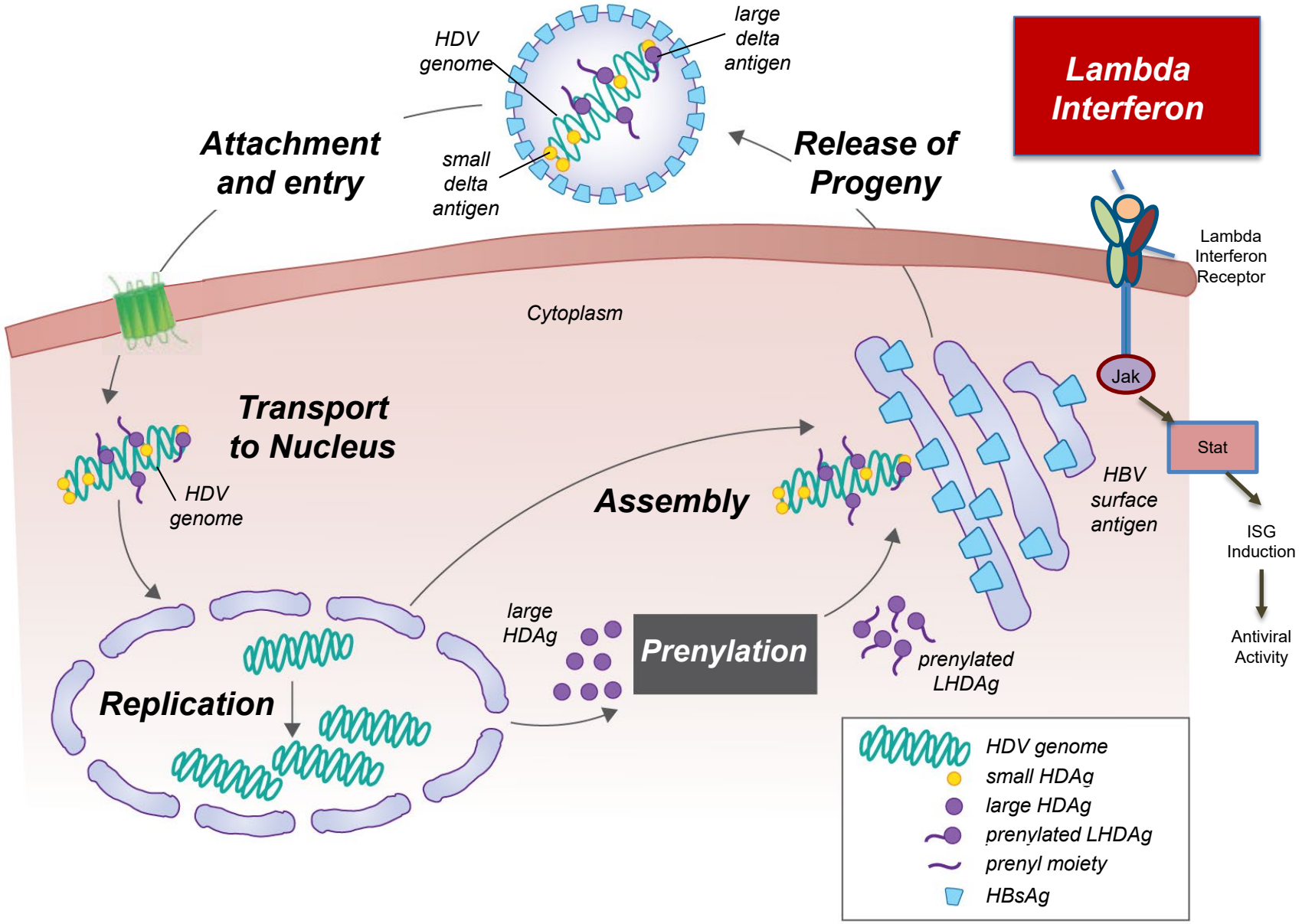
Dose-dependent efficacy





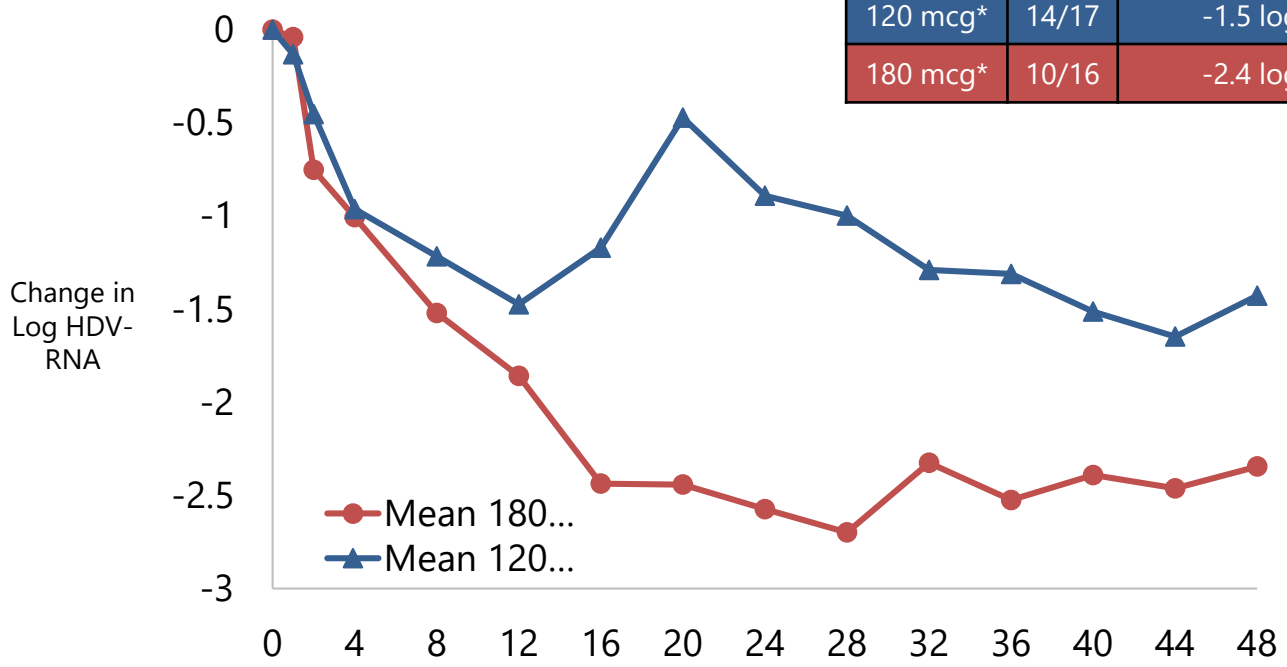
Synergy with interferon alpha

The HDV Life Cycle



Pegylated interferon lambda for HDV

Week 48	N	Mean VL Decline	≥ 2 Log Decline
120 mcg*	14/17	-1.5 log	6 of 14 (42.9%)
180 mcg*	10/16	-2.4 log	6 of 10 (60.0%)

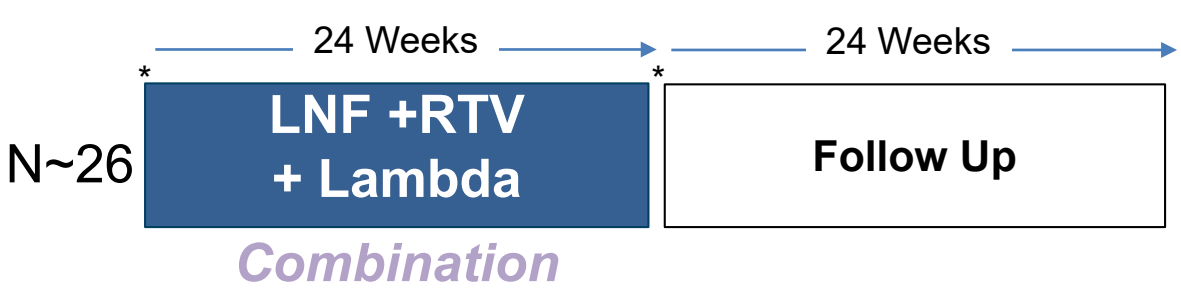


- Comparable activity to historical PEG IFN-alfa-2a
- Significantly better tolerated than PEG IFN-alfa-2a
- Durable response data at oral late-breaker (Etzion et al).

Potential for combination Rx

LIFT study

Lambda InterFeron combination Therapy



Primary Endpoint:

- ≥ 2 Log HDV RNA reduction at EOT

Secondary Endpoint:

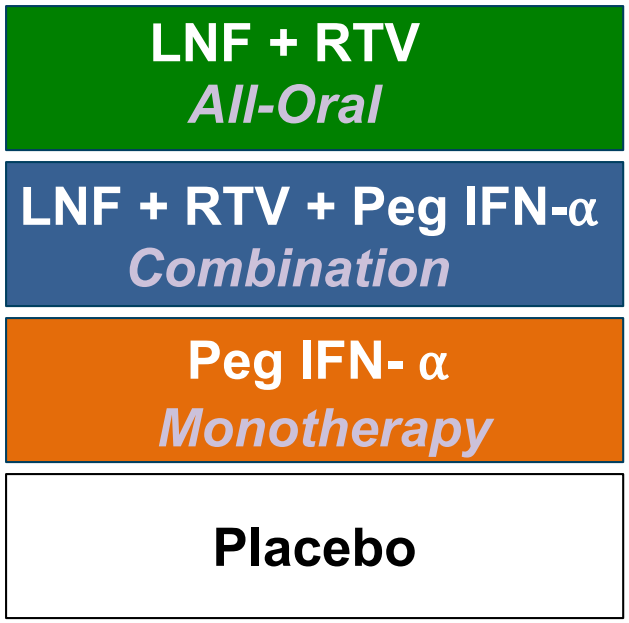
- Histological Improvement

- Open-label, Phase 2 study evaluating Lambda + LNF + RTV

EIGER BIOPHARMACEUTICALS

D-LIVR : FIRST-EVER REGISTRATION STUDY IN HDV

Delta Liver Improvement and Virologic Response in HDV



N ~ 400

- LNF arms compared to Placebo
- Superiority over PEG IFN-α not required
- PEG IFN-α arm to assess contribution only

All patients will be on background HBV nuc therapy

Primary Endpoint at Week 48

- ≥ 2 log decline in HDV RNA

+

- Normalization of ALT

Stay tuned!

Suggested endpoints for trials of novel agents

Key considerations:

- Relatively small numbers of HDV patients available for clinical trials
- Lack of a “magic bullet” for HDV
  (>25 years to get sofosbuvir for HCV)
- All drugs have side effects
- The most effective anti-HDV regimen is likely to involve a cocktail of agents

HDV meets criteria for Accelerated Approval

- Drugs for serious conditions
- Fill an unmet medical need
- Can be approved based on a surrogate endpoint
- Definitive clinical benefit to be proven in post-approval Phase 4 studies

Primary endpoint for Accelerated Approval:

- EOT ≧ 2 log drop in HDV RNA (+/- ALT normalization)
- Data showing significant long-term clinical benefit

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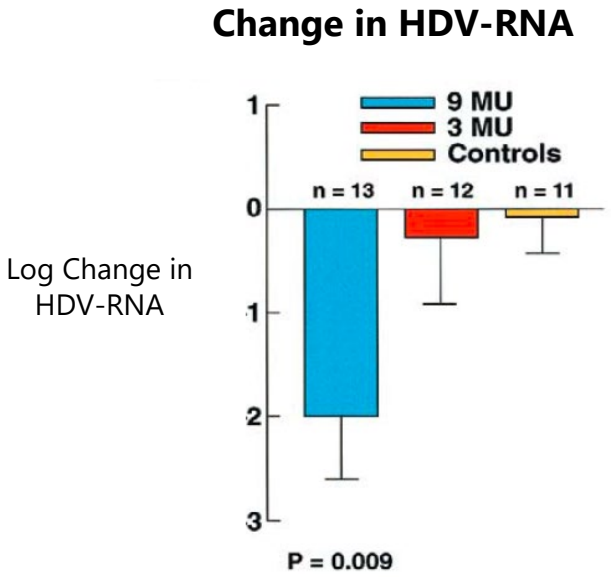
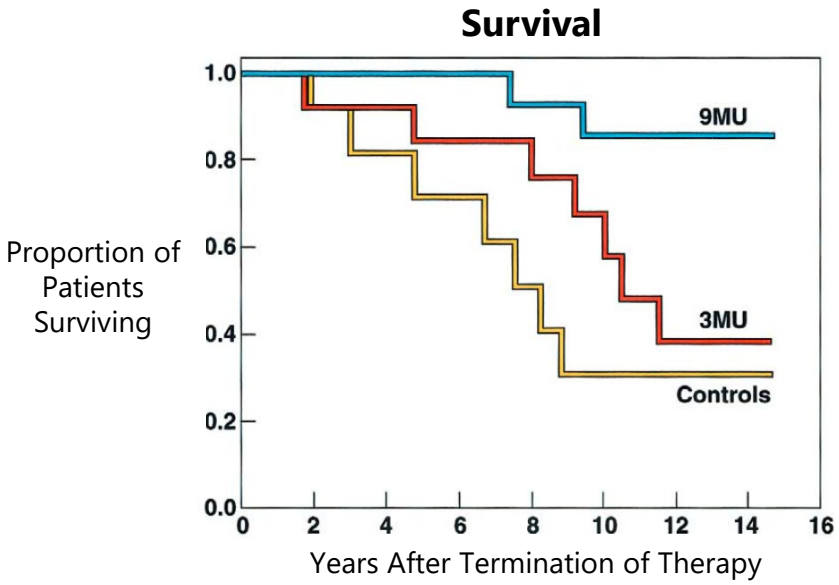


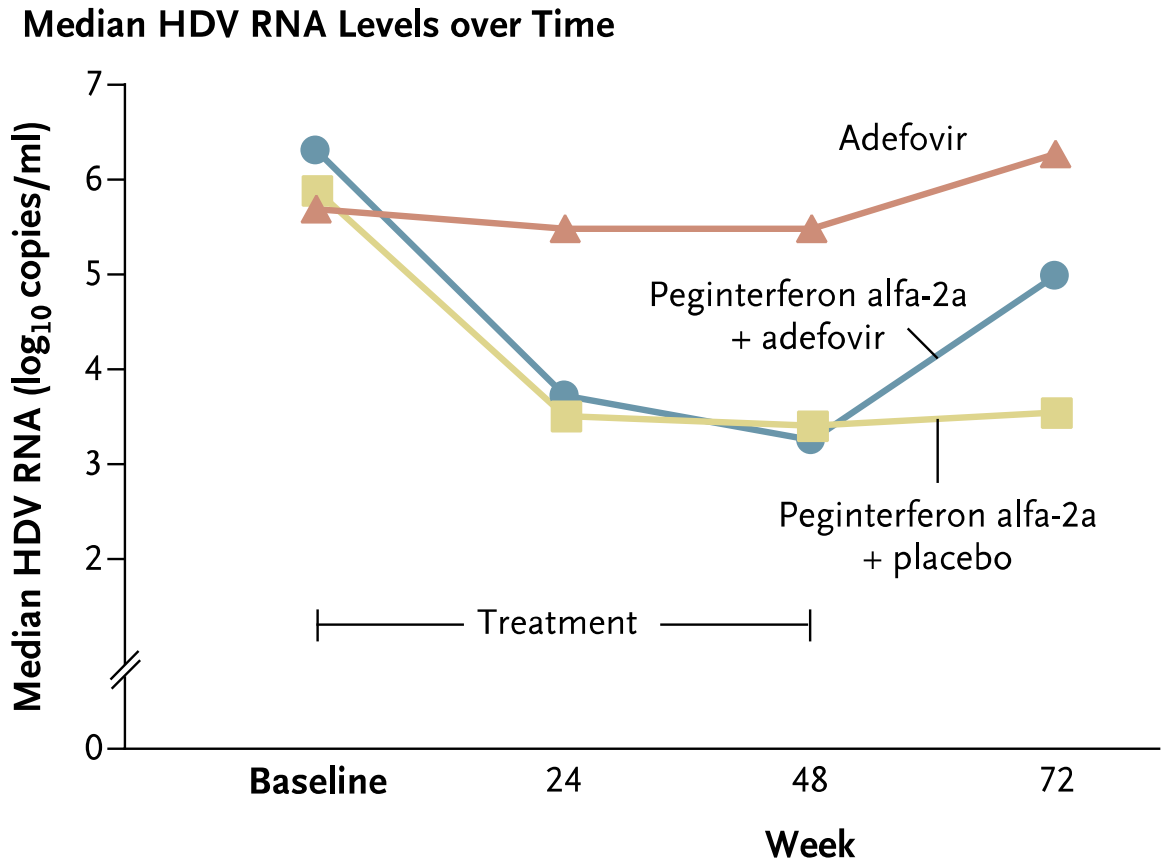


- Endorsed in recent White Paper (HDV KOLs)

Farci et al, Gastroenterology **2004**: Long-Term Benefit of Interferon-α Therapy of Chronic HDV: Regression of Advanced Hepatic Fibrosis

Endpoint assessment: 24 weeks

- Captures the time interval during which the greatest rates of HDV RNA declines are observed (including for interferon alpha);



(Wedemeyer et al. NEJM 2011):

Endpoint assessment: 24 weeks

- Captures the time interval during which the greatest rates of HDV RNA declines are observed (including for interferon alpha);
- Minimizes excess exposure to drug beyond period of maximum efficacy;
- Allows for a common endpoint against which all therapies can be benchmarked;
- Shortens the duration of clinical trials, accelerating the ability to iterate protocols using combinations of agents;

→ maximally enable arriving at the optimal cocktail in the shortest time frame

Conclusions

- HDV--fascinating collection of biology and important cause of human viral hepatitis; most severe form

- Study of HDV life cycle has identified several targets for antiviral intervention (entry, prenylation, HBsAg secretion, IFN lambda signaling)

- HDV screening of HBV pts. important (use best tests!)

- Several drugs have demonstrated clinical efficacy

- Potential for combination therapy with drugs each:
  -- determined to be safe
  -- demonstrated to have significant anti-HDV activity

Conclusions

- Opportunity to bring a significant clinical benefit to patients with most severe form of human viral hepatitis

- Beginning of new era; much to be done