Hepatitis D Management Challenges

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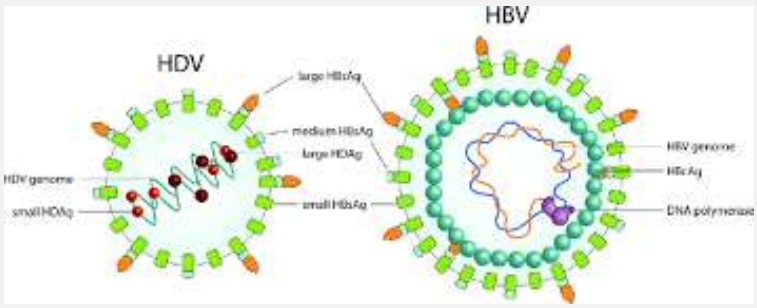
Introduction:

- Ref:
  - Current and Future Management of Chronic Hepatitis D, Patrizia Farci, MD, and Grazia Anna Niro, MDGastroenterology & Hepatology Volume 14, Issue 6 June 2018
  - Up to date
  - Articles as follow

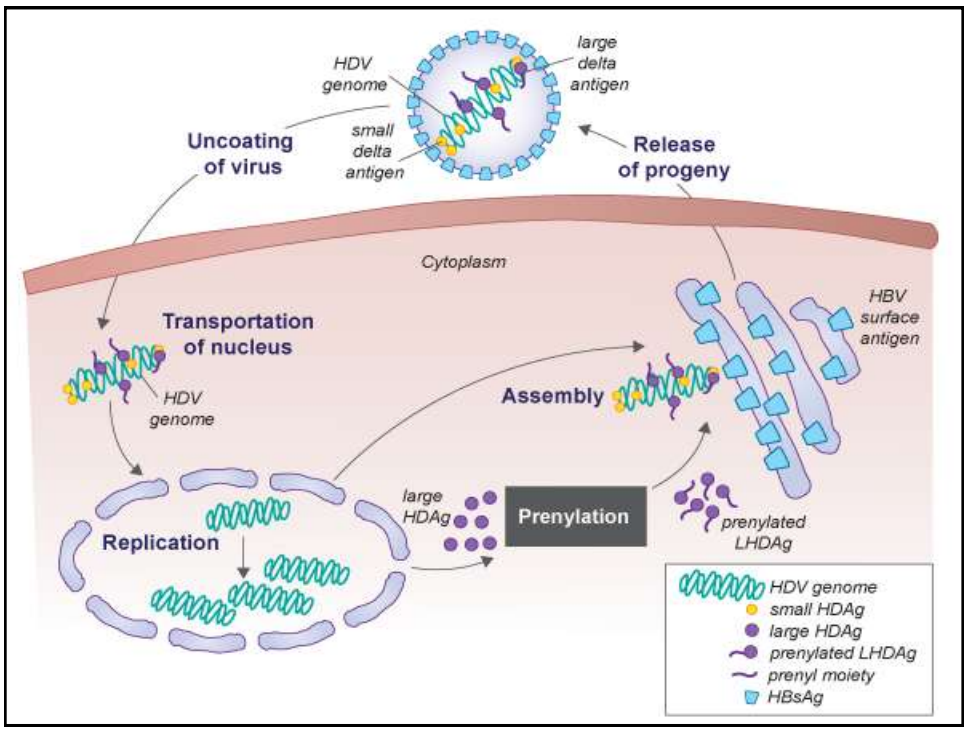
Introduction:

- Hepatitis D virus (HDV) was discovered more than 40 years ago by Rizzetto and colleagues in Italy.
- Initially described as a new antigen-antibody system in chronic hepatitis B carriers, subsequent studies in the early 1980s at the NIH demonstrated that it is a new transmissible virus.



The Virus:

- HDV is a defective RNA virus that requires the HBsAg for virion assembly, release,and transmission.
- It contains in its interior a ribonucleoprotein (RNP) complex, consisting of an RNA genome complexed with a structural protein, HDAg, surrounded by the envelope glycoprotein, HBsAg, which is the only helper function provided by HBV.



The Virus:

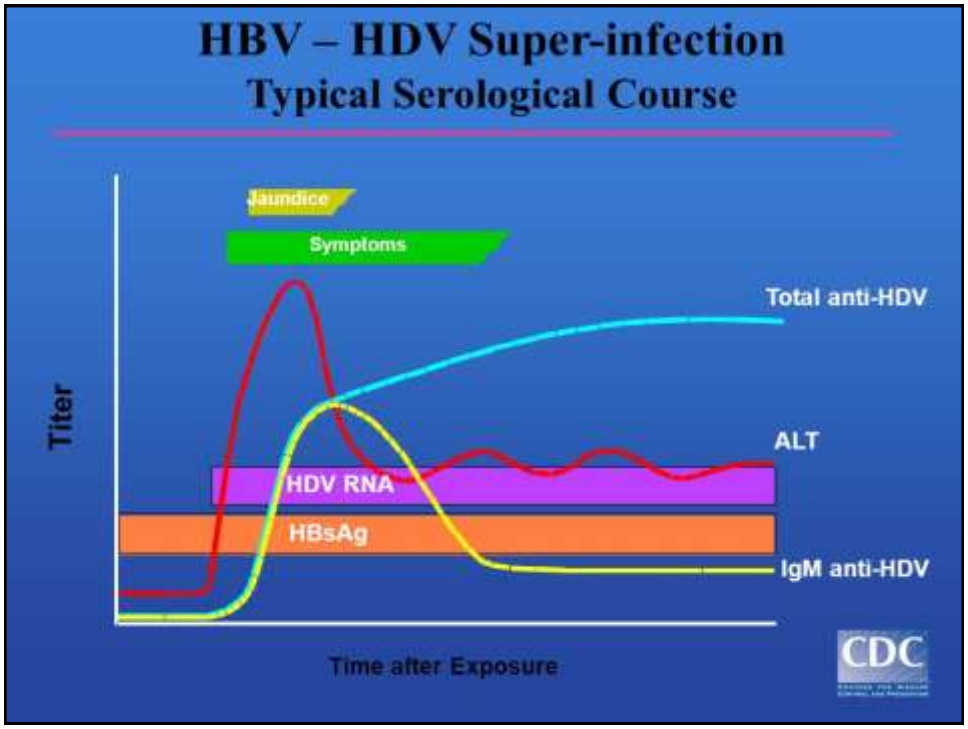
- The RNP without the HBV envelope protein cannot egress the cell and infect other hepatocytes.
- Thus, HDV is a satellite virus of HBV and can only infect individuals who simultaneously acquire HBV (coinfection) or superinfect an HBsAg carrier (superinfection).
- Persons who have antibody to HBsAg, who are immune to HBV infection, are not susceptible to HDV.

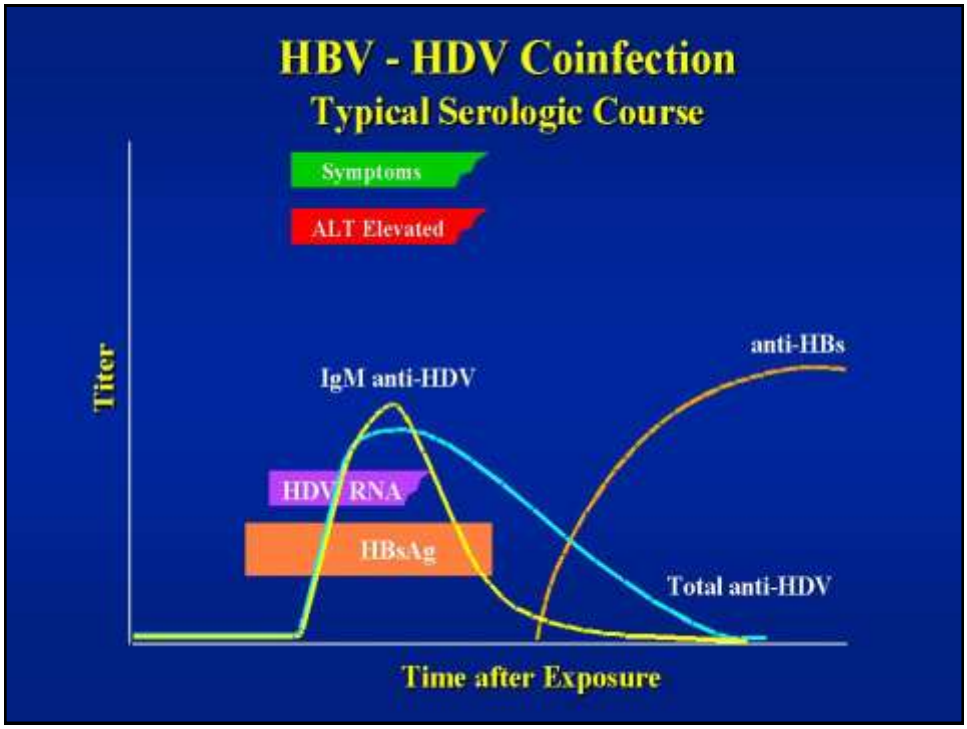
The Virus:

- The replication of HDV occurs in the nucleus of hepatocytes, as the liver is the only organ in which HDV replicates.
- HDV does not encode its own polymerase but exploits the host RNA polymerase II for replication.
- The replication of HDV is completely autonomous from that of HBV, but the assembly, release, and propagation of infectious virions are critically dependent on HBsAg, which encapsidates the HDV RNP.

Course of Hepatitis D

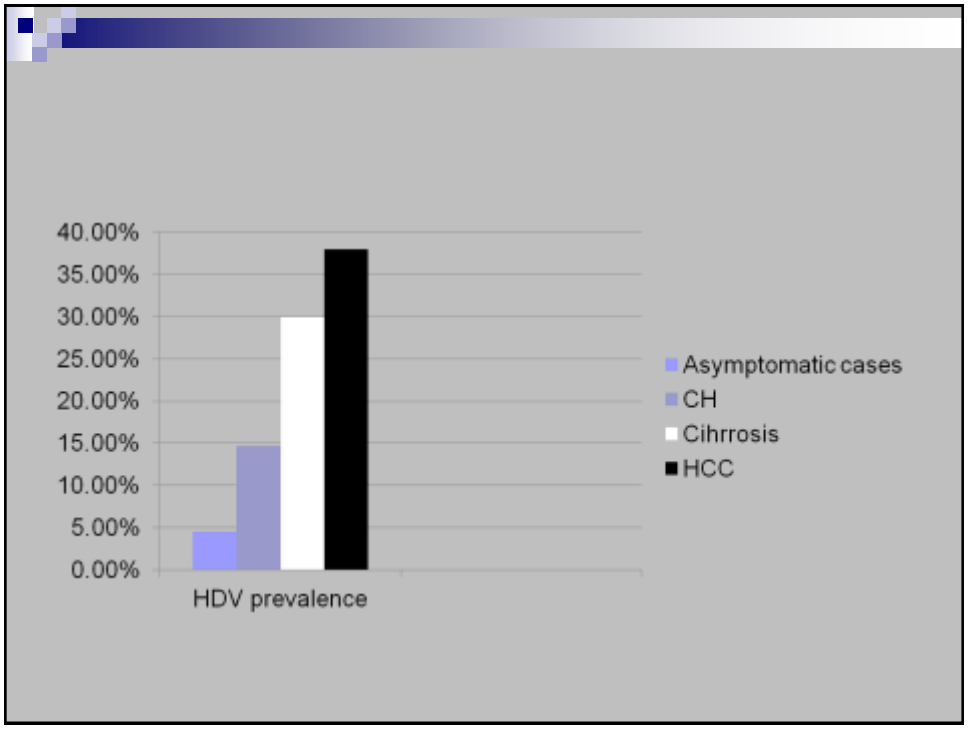
- The clinical outcome of acute hepatitis D differs according to the type of infection.
- Whereas HBV/HDV coinfection evolves to chronicity in only 2% of cases,
- HDV superinfection results in chronic infection in at least 90% of cases.
- HDV causing the least common, but most severe form of chronic viral hepatitis at all ages.
- Cirrhosis develops in approximately 70% to 80% of cases within 10 years from the onset of acute hepatitis.

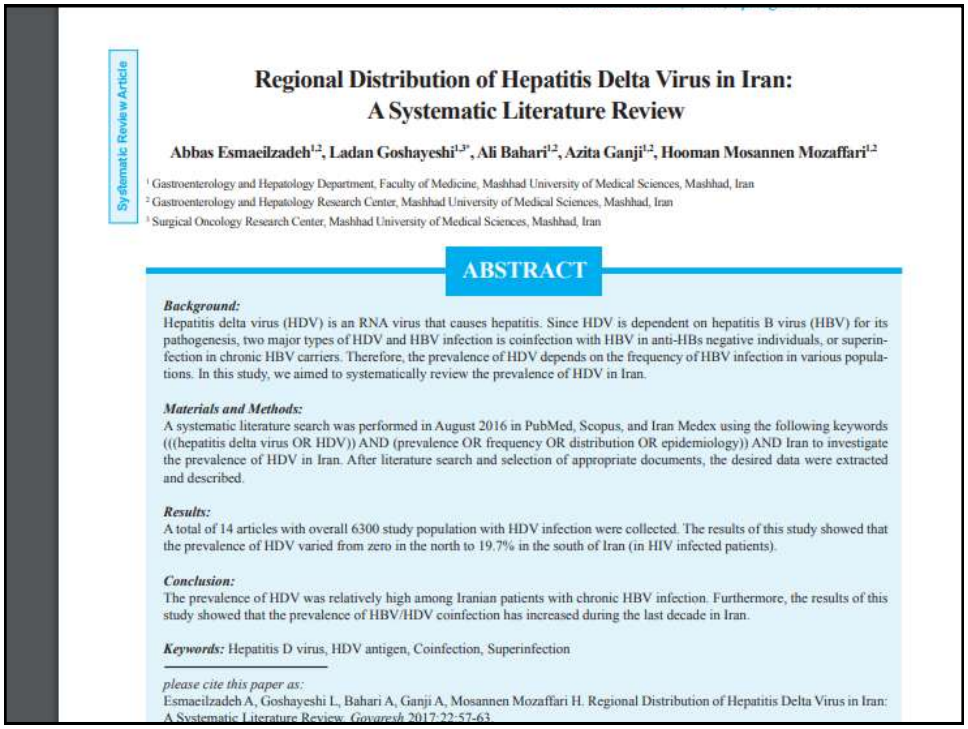




Course of Hepatitis D

- Mashhad study
  - In 350 HBV cases 10% was HDV positive
  - In inactive cases 4.5%
  - In active cases 14.7%
  - In cirrhosis about 30%
  - In HCC about 38%





Systematic Review Article

Regional Distribution of Hepatitis Delta Virus in Iran: A Systematic Literature Review

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ABSTRACT

Background:
Hepatitis delta virus (HDV) is an RNA virus that causes hepatitis. Since HDV is dependent on hepatitis B virus (HBV) for its pathogenesis, two major types of HDV and HBV infection is coinfection with HBV in anti-HBs negative individuals, or superinfection in chronic HBV carriers. Therefore, the prevalence of HDV depends on the frequency of HBV infection in various populations. In this study, we aimed to systematically review the prevalence of HDV in Iran.

Materials and Methods:
A systematic literature search was performed in August 2016 in PubMed, Scopus, and Iran Medex using the following keywords (((hepatitis delta virus OR HDV)) AND (prevalence OR frequency OR distribution OR epidemiology)) AND Iran to investigate the prevalence of HDV in Iran. After literature search and selection of appropriate documents, the desired data were extracted and described.

Results:
A total of 14 articles with overall 6300 study population with HDV infection were collected. The results of this study showed that the prevalence of HDV varied from zero in the north to 19.7% in the south of Iran (in HIV infected patients).

Conclusion:
The prevalence of HDV was relatively high among Iranian patients with chronic HBV infection. Furthermore, the results of this study showed that the prevalence of HBV/HDV coinfection has increased during the last decade in Iran.

Keywords: Hepatitis D virus, HDV antigen, Coinfection, Superinfection

please cite this paper as:
Esmaeilzadeh A, Goshayeshi L, Bahari A, Ganji A, Mosannen Mozaffari H. Regional Distribution of Hepatitis Delta Virus in Iran: A Systematic Literature Review. *Govaresh* 2017;22:57-63.

Course of Hepatitis D

- Once established, cirrhosis may be a stable disease for another decade, although later in the course of disease, a high proportion of patients die of liver decompensation or HCC unless they undergo liver transplantation.
- The estimated annual incidence of liver decompensation in HDV cirrhosis ranges from 2.6% to 3.6% and from 2.6% to 2.8% for HCC.
- Over the past 2 decades, there has been a significant decline in the incidence of HDV infection in developed countries, especially in Southern Europe, because of universal HBV vaccination and improved socioeconomic conditions.

Treatment of Chronic Hepatitis D

- **Challenges:**
- **Although significant advances have been made in the treatment of chronic viral hepatitis over the past decade but targeting HDV remains a major challenge because of**
  - **The unconventional nature of this virus**
  - **Severity of its disease**
  - **Lack of a virus-specific polymerase**
  - **Vital link of HDV with HBV but completely autonomous replication**

Treatment of Chronic Hepatitis D

- Goals
  - To eradicate HDV and HBV
  - To prevent the long-term sequelae of chronic hepatitis D—cirrhosis, liver decompensation, and HCC

Treatment of Chronic Hepatitis D

- Goals
  - To eradicate HDV and HBV
  - To prevent the long-term sequelae of chronic hepatitis D—cirrhosis, liver decompensation, and HCC

- However, these goals are not commonly achieved, and treatment of chronic hepatitis D remains unsatisfactory.

Treatment of Chronic Hepatitis D

- Current management
  - Interferon-α
  - PEG Interferon

Treatment of Chronic Hepatitis D

- Current management
  - Interferon-α
    - Thirty years use
    - One year course of highdose standard IFN-α induced only a 10% to 20% rate of sustained HDV clearance and a 10% rate of HBsAg clearance
    - Higher doses and longer durations?

Treatment of Chronic Hepatitis D

- Current management
  - Interferon-α
    - Thirty years use
    - One year course of highdose standard IFN-α induced only a 10% to 20% rate of sustained HDV clearance and a 10% rate of HBsAg clearance
    - Higher doses and longer durations?
  - PEG Interferon
    - Better efficacy (about 25%)
    - PEG INF response is same in CH and ALD

Treatment of Chronic Hepatitis D

- Current management
  - INF and PEG INF
    - Long term results

- A prospective study of 36 patients followed for up to 20 years after 1 year of treatment showed a significant improvement in the long-term clinical outcome and survival of patients who received high doses of standard IFN-α. Reversion of advanced hepatic fibrosis occurred in some patients with an initial diagnosis of active cirrhosis.
- HIDIT trial using pegylated IFN-α,in which 75% of the patients were prospectively followed over a median period of 4.5 years after completion of therapy.This long-term study documented a late relapse in HDV RNA in more than half of the patients (58%) who were negative for HDV RNA 6 months after therapy

Treatment of Chronic Hepatitis D

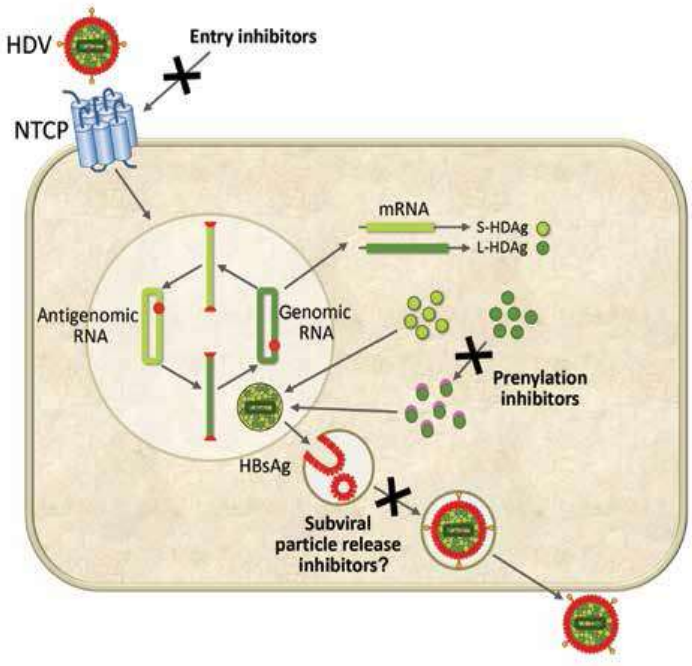
- Current management
  - INF and PEG INF
  - Long term results
- A prospective study of 36 patients followed for up to 20 years after 1 year of treatment showed a significant improvement in the long-term clinical outcome and survival of patients who received high doses of standard IFN-α. Reversion of advanced hepatic fibrosis occurred in some patients with an initial diagnosis of active cirrhosis.
- HIDIT trial:
- The loss of HDV RNA at the end of therapy as well as during follow-up has been associated with a favorable outcome and fewer liver-related complications.

Treatment of Chronic Hepatitis D

- Current management
  - Combination of INF / PEG INF with:
    - Ribavirin
    - Lamivudine
    - Adefovir

Treatment of Chronic Hepatitis D

- Future management
  - New therapies are needed because of:
    - Low response rate
    - High relapse rate
    - High adverse effects

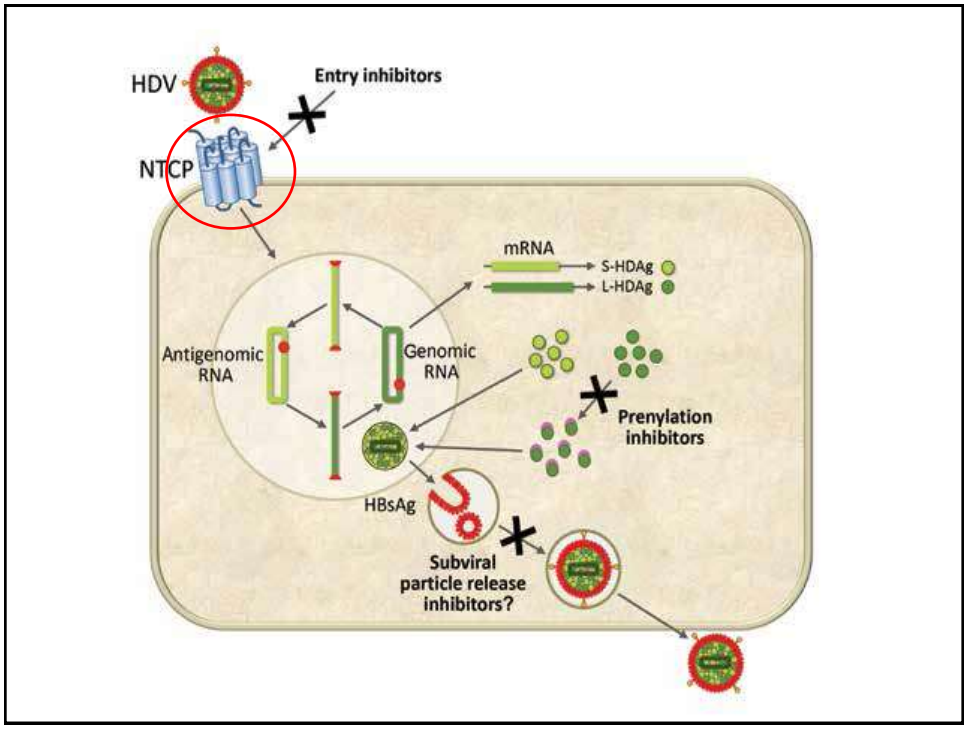


Treatment of Chronic Hepatitis D

- Future management
  - New therapies are needed
    - Low response rate
    - High relapse rate
    - High adverse effects
  - New therapies according to HDV life cycle
    - Inhibitors of the NTCP receptor
    - Farnesyltransferase inhibitors (FTIs)
    - Nucleic acid polymers (NAPs)

Treatment of Chronic Hepatitis D

- Future management
  - New therapies are needed
    - Low response rate
    - High relapse rate
    - High adverse effects
  - New therapies according to HDV life cycle
    - Inhibitors of the NTCP receptor *Myrcludex B*
    - Farnesyltransferase inhibitors (FTIs) *Lonafarnib*
    - Nucleic acid polymers (NAPs) *REP2031*



Research Article

Myr cohort

Screening	Myrcludex B 2 mg/day	PegINFα-2a 180 µg/week	Follow-up

Myr-IFN cohort

Screening	Myrcludex B 2 mg/day PegINFα-2a 180 µg/week	PegINFα-2a 180 µg/week	Follow-up

IFN cohort

Screening	PegINFα-2a 180 µg/week	Follow-up

Baseline | Week 12 | Week 24 | Week 36 | Week 48 | Week 60 | Week 72

Treatment of Chronic Hepatitis D

- Future management
  - New therapies according to HDV life cycle
    - Inhibitors of the NTCP receptor *Myrcludex B*
      - In patients treated with Myrcludex B plus pegylated IFN-α 2a, HDV RNA became negative in 5 patients, and HBV DNA decreased significantly only in this group.

J Hepatol. 2016;65(3):490-498.

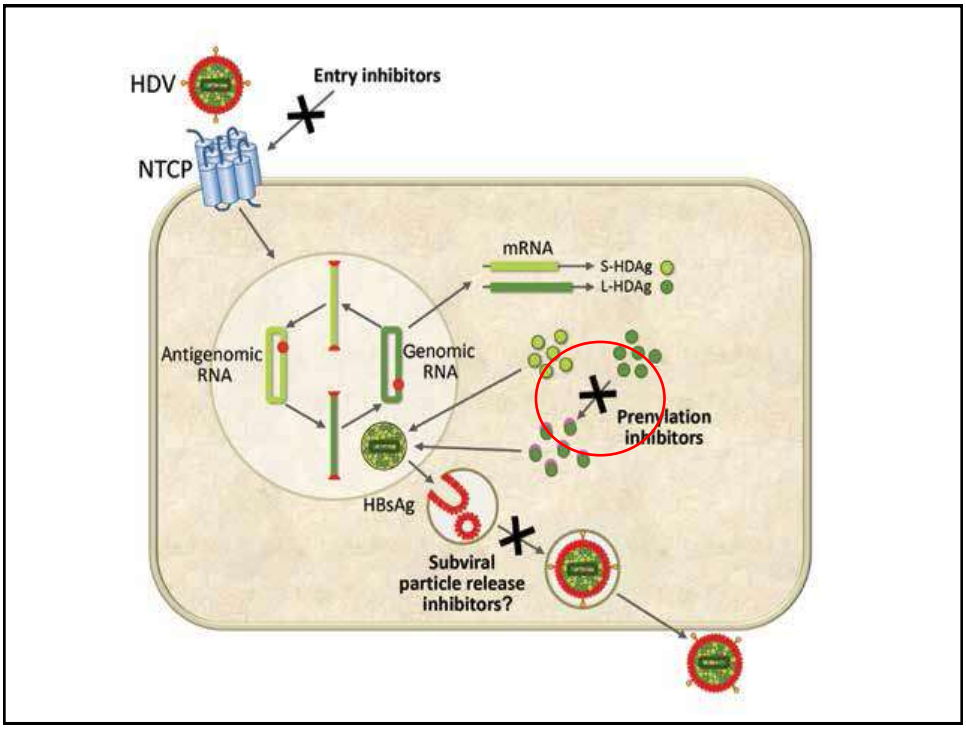
Treatment of Chronic Hepatitis D

- Future management
  - New therapies according to HDV life cycle
    - Inhibitors of the NTCP receptor *Myrcludex B*
      - In patients treated with Myrcludex B plus pegylated IFN-α 2a, HDV RNA became negative in 5 patients, and HBV DNA decreased significantly only in this group.

      - But the effects are transient

Treatment of Chronic Hepatitis D

- **Future management**
  - **New therapies according to HDV life cycle**
    - **Inhibitors of the NTCP receptor**
    - **Farnesyltransferase inhibitors (FTIs)** ***Virus Assembly Inhibitor Lonafarnib***
    - **Nucleic acid polymers (NAPs)**



Treatment of Chronic Hepatitis D

- **Future management**
  - **New therapies according to HDV life cycle**
    - **Farnesyltransferase inhibitors (FTIs)** ***Lonafarnib***
      - **The antigenomic HDV RNA strand encoding theS-HDAg is edited by a cellular enzyme**
      - **This posttranscriptional RNA editing results in the production of the L-HDAg, which undergoes farnesylation, an essential modification to anchor the HDV RNP to the HBsAg during the assembly of HDV infectious particles**

Published in final edited form as:
Lancet Infect Dis. 2015 October ; 15(10): 1167–1174. doi:10.1016/S1473-3099(15)00074-2.

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

Christopher Koh*, **Laetitia Canini**, **Harel Dahari**, **Xiongce Zhao**, **Susan L Uprichard**, **Vanessa Haynes-Williams**, **Mark A Winters**, **Gitanjali Subramanya**, **Stewart L Cooper**, **Peter Pinto**, **Erin F Wolff**, **Rachel Bishop**, **Ma Ai Thanda Han**, **Scott J Cotler**, **David E Kleiner**, **Onur Keskin**, **Ramazan Idilman**, **Cihan Yurdaydin**, **Jeffrey S Glenn***, and **Theo Heller***
Translational Hepatology Unit, Liver Diseases Branch (C Koh MD, V Haynes-Williams BSN, M Ai Thanda Han MD, T Heller MBBch) and Office of the Director (X Zhao PhD), National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD, USA; The Program for Experimental & Theoretical Modeling, Division of Hepatology, Loyola University Medical Center, Maywood, IL, USA (L Canini PhD, H Dahari PhD, S L Uprichard PhD, G Subramanya MS, Prof S J Cotler MD); Centre for Immunity, Infection and Evolution, University of Edinburgh, Edinburgh, UK (L Canini); Theoretical Biology & Biophysics Group, Los Alamos National Laboratory, Los Alamos, NM, USA (H Dahari); Departments of Medicine (Division of Gastroenterology and Hepatology) and Microbiology & Immunology, Stanford School of Medicine, Stanford, CA, USA (M A Winters MS, J S Glenn MD); Division of Hepatology, California Pacific Medical Center, San Francisco, CA, USA (S L Cooper MD); Urologic Oncology Branch (P Pinto

Treatment of Chronic Hepatitis D

- Future management
  - New therapies according to HDV life cycle
    - Farnesyltransferase inhibitors (FTIs) *Lonafarnib*
      - Interpretation—Treatment of chronic HDV with lonafarnib significantly reduces virus levels. The decline in virus levels significantly correlated with serum drug levels, providing further evidence for the efficacy of prenylation inhibition in chronic HDV

Lancet Infect Dis. Author manuscript; available in PMC 2016 October 01.

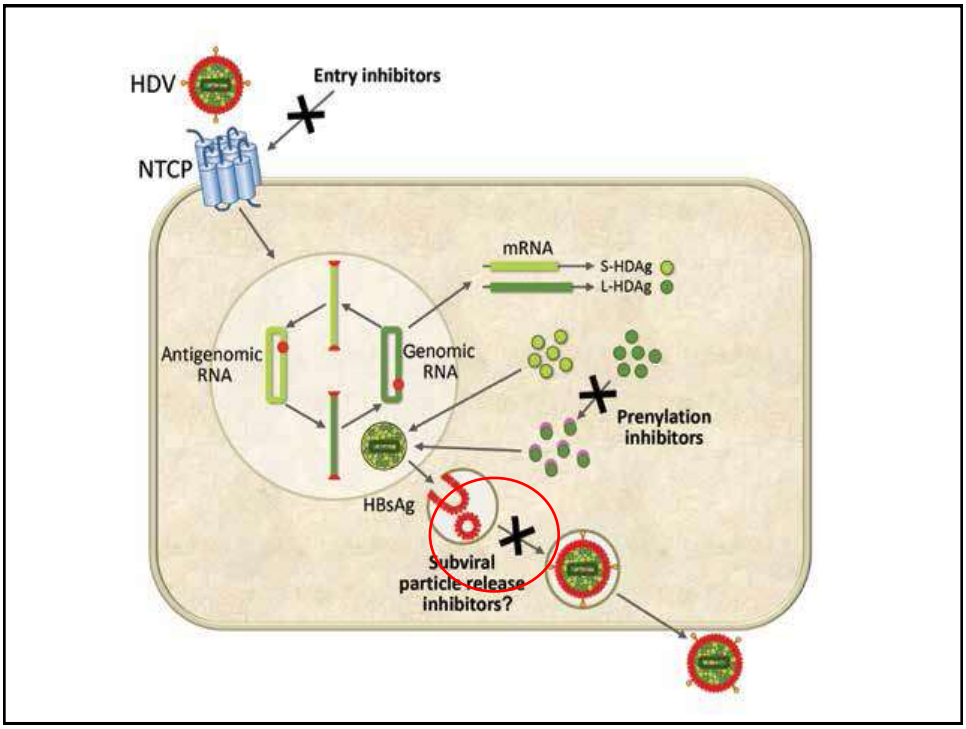
Treatment of Chronic Hepatitis D

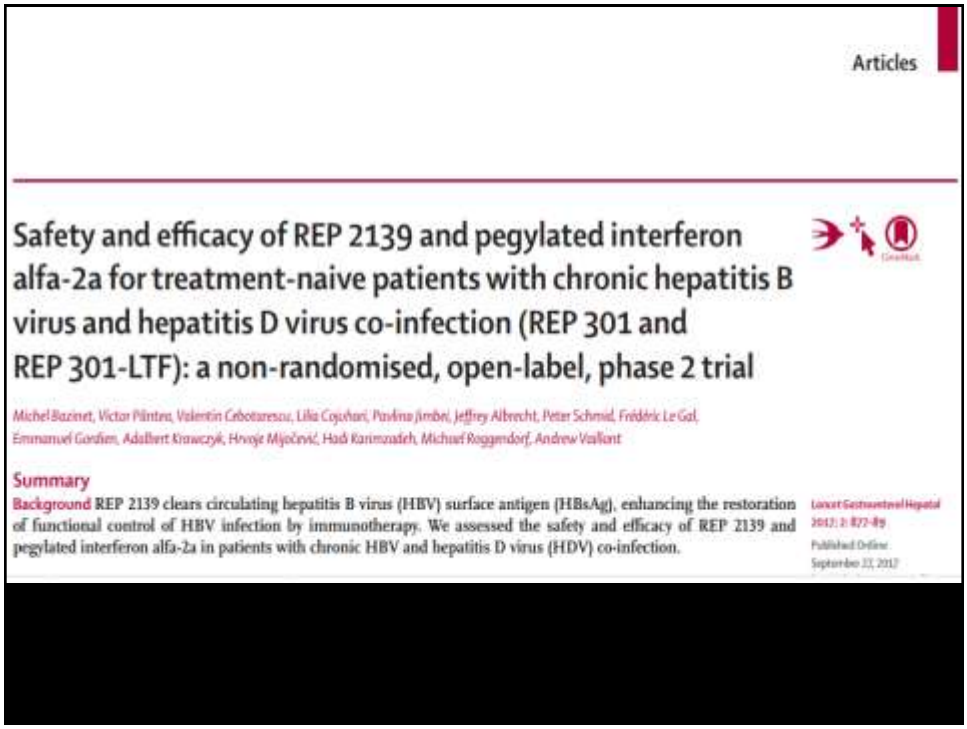
- Future management
  - New therapies according to HDV life cycle
    - Farnesyltransferase inhibitors (FTIs) *Lonafarnib*

- The effects of intracellular accumulation of RNP particles are not fully understand.
- Moreover, farnesyltransferase is an important cellular enzyme; therefore, it will be essential to fully elucidate the effects of its blockade on various intracellular pathways.

Treatment of Chronic Hepatitis D

- **Future management**
  - **New therapies according to HDV life cycle**
    - **Inhibitors of the NTCP receptor**
    - **Farnesyltransferase inhibitors (FTIs)**
    - **Nucleic acid polymers (NAPs)** ***REP 2139***





Articles

Safety and efficacy of REP 2139 and pegylated interferon alfa-2a for treatment-naive patients with chronic hepatitis B virus and hepatitis D virus co-infection (REP 301 and REP 301-LTF): a non-randomised, open-label, phase 2 trial

Michel Bazinet, Victor Pântea, Valentin Cebotarescu, Lilia Cojuhari, Pavlina Jimbei, Jeffrey Albrecht, Peter Schmid, Frédéric Le Gal, Emmanuel Gordien, Adalbert Krawczyk, Hrvoje Mijočević, Hadi Karimzadeh, Michael Roggendorf, Andrew Vaillant

Summary

Background REP 2139 clears circulating hepatitis B virus (HBV) surface antigen (HBsAg), enhancing the restoration of functional control of HBV infection by immunotherapy. We assessed the safety and efficacy of REP 2139 and pegylated interferon alfa-2a in patients with chronic HBV and hepatitis D virus (HDV) co-infection.

Lancet Gastroenterol Hepatol 2017; 2: 877-89
Published Online September 22, 2017

Treatment of Chronic Hepatitis D

- **Future management**
  - **RESULTS :**
    - **In 12 pts enrolled 6 cases had HBS Ag level > 50Iu,**
    - **6 had HBSAb positive**

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Treatment of Chronic Hepatitis D

- **Future management**
  - **PRETATION :**
    - **Combined REP 2139 and pegylated interferon alfa-2a therapy is safe, well tolerated, and establishes functional control of HBV and HDV co-infection and normalisation of serum aminotransferases in a high proportion of patients 1 year after therapy.**
    - **This combination therapy approach might provide a new treatment option for patients with HBV and HDV co-infection**

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Treatment of Chronic Hepatitis D

- **Future management**
  - **New therapies according to HDV life cycle**
  - **Nucleic acid polymers (NAPs)** ***REP 2139***
  - **CHALLENGES:**
    - **All non cirrhotic patients**
    - **Nature and function of early and high titers of anti-HBs**
    - **The molecular mechanisms underlying the inhibition of the release of HBsAg subviral particles are still unknown.**
    - **As a consequence, it is unclear if and how HBsAg is revented from accumulating inside hepatocytes, which may result in liver damage and increased risk of HCC**

Hepatitis Delta Drug Watch

DRUG	MECHANISM	COMPANY	STATUS
Lambda (Pegylated Interferon)	Immune Response Stimulator	Eiger BioPharma, USA	*FDA Orphan Drug Designation* Phase III (Projected 2018)
Myrcludex B	Entry Inhibitor	MYR-GmbH, Germany	*EMA PRIME Eligibility* Phase II
Lonafarnib	Prenylation Inhibitor	Eiger BioPharma, USA	*FDA Fast Track Designation* Phase II
Ezetimibe	NTCP Inhibitor	Ziauddin University Hospital, Pakistan	Phase II
REP 2139 REP 2165	HBsAg Inhibitor	Replicor, Canada	Phase II
GI-18000	Immune Response Stimulator	GlobeImmune, USA	Pre-clinical
ALN-HDV	RNAi Gene Silencer	Alnylam, USA	Pre-clinical