Hepatit Delta Tedavisinde yeni umutlar var mı?

Dr. Mustafa Kemal ÇELEN

Diyarbakır

Hepatit Delta nedir?

- Bilinen hepatit virüsleri içerisinde prognozu en ağır olanıdır
- Defektif bir virüstür
- Co-infeksiyon veya süperenfeksiyon
- Vakaların %70-90 şiddetli seyretmektedir
- A.B.D.'lerinde en az 125.000 vaka
- Dünya genelinde 12-60 milyon vaka

NVHR
National Viral Hepatitis Roundtable

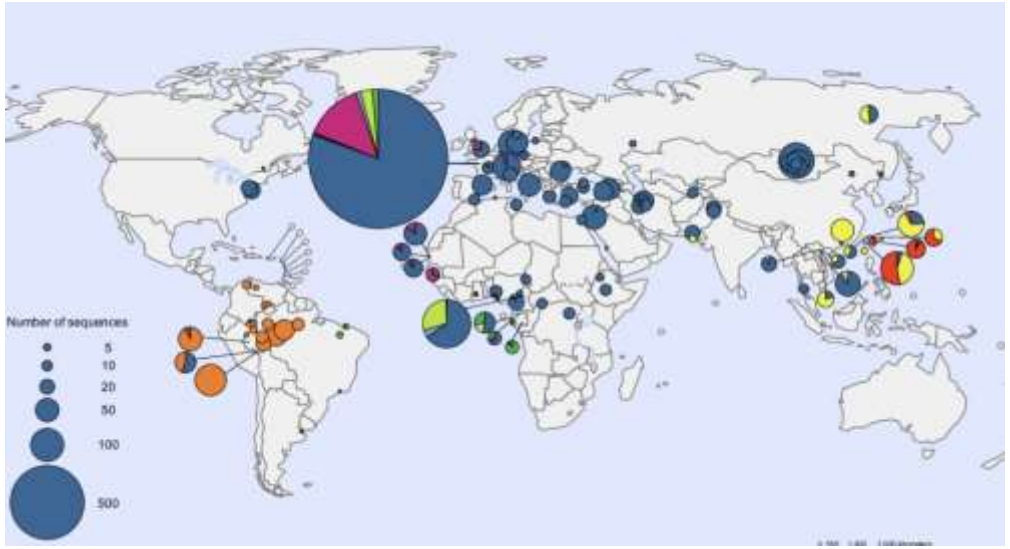
Bulaşma Yolları

- Kan ve diğer vücut sıvılarının teması ile
- Vertikal bulaşı nadir
- HBV ile bulaşı olan herkes risk altındadır
- Uyuşturucu kullananlar, sex işçileri, MSM, HCV ile yaşayanlar ve HIV/HBV'nin yoğun olduğu bölgelerde yaşayanlar risk altındadır

NVHR
National Viral Hepatitis Roundtable

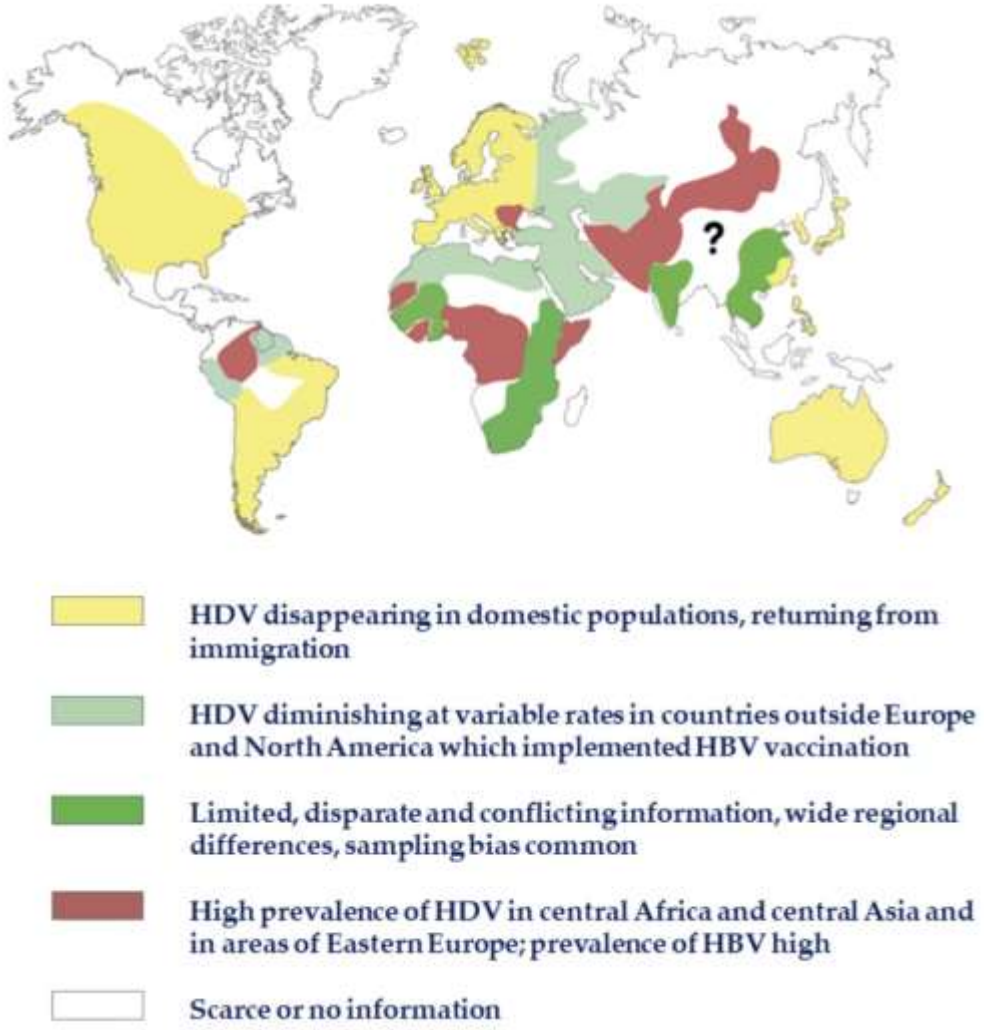
HEPATİT DELTA'DA YENİ GELİŞMELER

- HDV global bir sorundur
- HBV aşısına rağmen 2019 yılında KC-S ve HCC ilişkili 820.000 ölüm
- Gözden kaçan bir hepatit etkeni (CDC)
- Önlenebilir bir hastalıktır



Robinson A. Chronic Hepatitis B Virus and Hepatitis D Virus: New Developments. Clin Liver Dis 2023

HDV Epidemiyolojisi



Kabul edilen epidemiyoloji gerçeği yansıtıyor mu?

Gian PC. A Review of HDV Infection. Viruses 2022.

TEDAVİ...

Published in final edited form as:
Gastroenterology. 2019 January ; 156(2): 461–476.e1. doi:10.1053/j.gastro.2018.09.058.

Pathogenesis of and New Therapies for Hepatitis D

Christopher Koh[1], **Theo Heller**[1], and **Jeffrey S. Glenn, MD**[2]

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[2]Division of Gastroenterology and Hepatology, Stanford University School of Medicine, Stanford, California, USA

Abstract

Hepatitis delta virus (HDV) infection of humans was first reported in 1977, and now it is now estimated that 15–20 million people are infected worldwide. Infection with HDV can be an acute or chronic process that occurs only in patients with an HBV infection. Chronic HDV infection commonly results in the most rapidly progressive form of viral hepatitis; it is the chronic viral infection that is most likely to lead to cirrhosis, and it is associated with an increased risk of hepatocellular carcinoma. HDV infection is the only chronic human hepatitis virus infection without a therapy approved by the Food and Drug Administration. Peginterferon alpha is the only recommended therapy, but it produces unsatisfactory results. We review therapeutic agents in development, designed to disrupt the HDV life cycle, that might benefit patients with this devastating disease.

Received: 18 January 2021 | First decision: 27 February 2021 | Accepted: 30 April 2021

DOI: 10.1111/apt.16408

APT Alimentary Pharmacology & Therapeutics WILEY

Uzun süreli PEG-INF ????

Durable virological response and functional cure of chronic hepatitis D after long-term peginterferon therapy

Julian Hercun[1] | Grace E. Kim[1] | Ben L. Da[1] | Yaron Rotman[1] | David E. Kleiner[2] | Richard Chang[3] | Jeffrey S. Glenn[4] | Jay H. Hoofnagle[5] | Christopher Koh[1] | Theo Heller[1]

- Toplamda 12 vaka
- %83 beyaz ırk
- %92'si erkek
- Tedavi: 74 ay Peg-INF
- Takip süresi 104 ay
- SVR oranı %58
- HBsAg kaybı %33

Summary

Background: Hepatitis delta virus (HDV) infection is the most aggressive form of chronic viral hepatitis. Response rates to therapy with 1- to 2-year courses of pegylated interferon alpha (peginterferon) treatment are suboptimal.

Aims: To evaluate the long-term outcomes of patients with chronic hepatitis D after an extended course of peginterferon.

Methods: Patients were followed after completion of trial NCT00023322 and classified based on virological response defined as loss of detectable serum HDV RNA at last follow-up. During extended follow-up, survival and liver-related events were recorded.

Results: All 12 patients who received more than 6 months of peginterferon in the original study were included in this analysis. The cohort was mostly white (83%) and male (92%) and ranged in age from 18 to 58 years (mean = 42.6). Most patients had advanced but compensated liver disease at baseline, a median HBV DNA level of 536 IU per mL and median HDV RNA level of 6.86 $\log_{10}$ genome equivalents per mL. The treatment duration averaged 6.1 years (range 0.8-14.3) with a total follow-up of 8.8 years (range 1.7-17.6). At last follow-up, seven (58%) patients had durable undetectable HDV RNA in serum, and four (33%) cleared HBsAg. Overall, one of seven (14%) responders died or had a liver-related event vs four of five (80%) non-responders.

Conclusions: With further follow-up, an extended course of peginterferon therapy was found to result in sustained clearance of HDV RNA and favourable clinical outcomes in more than half of patients and loss of HBsAg in a third.

Clinical Trial > Lancet Infect Dis. 2019 Mar;19(3):275-286. doi: 10.1016/S1473-3099(18)30663-7.

Peginterferon alfa-2a plus tenofovir disoproxil fumarate for hepatitis D (HIDIT-II): a randomised, placebo controlled, phase 2 trial

Heiner Wedemeyer [1], Cihan Yurdaydin [2], Svenja Hardtke [3], Florin Alexandru Caruntu [4], Manuela G Curescu [5], Kendal Yalcin [6], Ulus S Akarca [7], Selim Gürel [8], Stefan Zeuzem [9], Andreas Erhardt [10], Stefan Lüth [11], George V Papatheodoridis [12], Onur Keskin [13], Kerstin Port [14], Monica Radu [4], Mustafa K Celen [6], Ramazan Idilman [13], Kristina Weber [15], Judith Stift [16], Ulrike Wittkop [17], Benjamin Heidrich [3], Ingmar Mederacke [14], Heiko von der Leyen [18], Hans Peter Dienes [16], Markus Cornberg [14], Armin Koch [15], Michael P Manns [19], HIDIT-II study team

Affiliations + expand

PMID: 30833068 DOI: 10.1016/S1473-3099(18)30663-7

14 merkezli bir çalışma
Randomize plasebo kontrollü
59 hastaya PEG-INF+TDF
61 hastaya PEG-INF+plasebo

944 AO izlendi
SVR açısından fark yok ☹

Kombinasyon tedavileri...???

HDV ve KÜR !?!?

- Hepatit D, karaciğer ilişkili mortalitesi en yüksek olan viral hepatit tipidir.

Prenylation inhibitörleri

Giriş yolu inhibitörleri

Nükleik asid polimeraz blokerleri

- Ciddi yan etkiler ve uzun dönem takiplerde relaps oranı yüksektir
- Acil olarak yeni tedavi seçeneklerine ihtiyaç var.

Wranke A, Wedemeyer H. Antiviral therapy of hepatitis delta virus infection - progress and challenges towards cure. Curr Opin Virol. **2016 Oct 25;20:112-118**.

Pegylated Interferon Lamda (NCT05070364)

- Tıp III interferon reseptör agonisti
- Hepatosite virüslerin girişini bloke etmektedir
- Yan etkileri daha düşük
- Etkinliği daha yüksek
- Faz-2 LIMIT 002 çalışmasında TS sonu viral yanıt %36, SVR ise %19 gibi düşük bir oranda bulundu
- Faz-3 çalışması devam etmektedir

Pegylated Interferon Lamda (NCT05070364)

DEAR INVESTIGATORS!

This month we celebrate another remarkable success of the **EIG-LMD-002 study** with a total of **147** subjects randomized to date. We are rapidly approaching our randomization goal andthis achievement would not have been possible without your diligence and strong determination. Thank you to all for your unwavering support! Please continue with your outstanding work as we strive to reach more study milestones.
Please contact your CRA for any questions about the study.

ENROLLMENT UPDATES

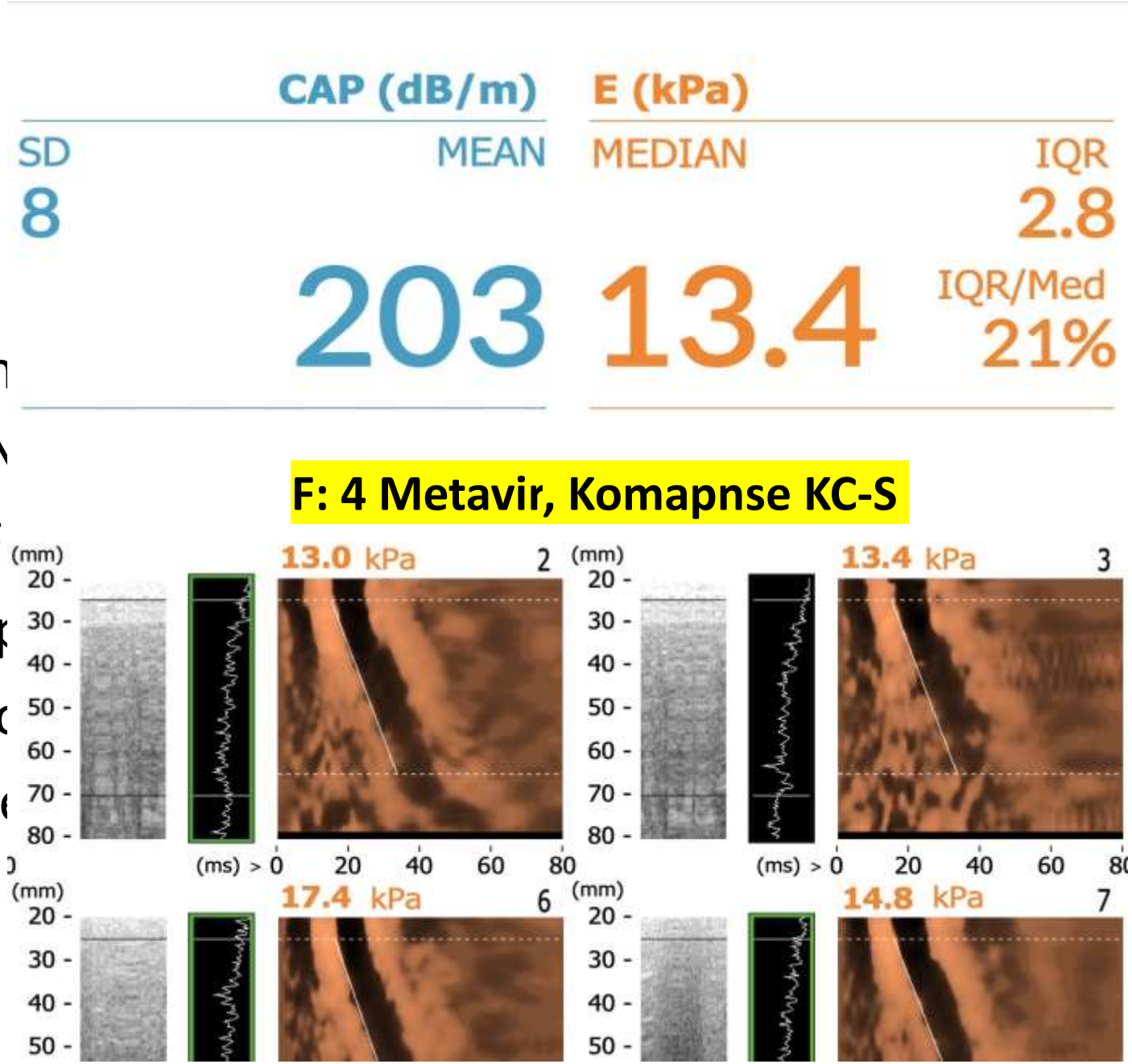
The total number of active sites is **44**. Out of the **273** screened subjects, **147** have been randomized. The top **6** sites with randomized subjects are presented in the table below.

PI	Country	No. of Randomized Subjects
Dr. Elena Laura Iliescu	Romania	25
Dr. Adela Turcanu	Moldova	18
Dr. Mustafa Kemal Celen	Turkey	16
Dr. George Sebastian Gherlan	Romania	14
Dr. Alexandru Florin Caruntu	Romania	13
Dr. Cihan Yurdaydin	Turkey	11

OLGU

- 53 yaş, kadın
- 2011 yılında tan
- ALT 118, HDVRN
- T.Bil normal, AF
- USG; karaciğer p
- Dalak normal bo
- 2014 ve 2017 d

OAV başlandı…



PEG-INF LAMDA 180 mcg/hafta

- Tedavinin 8.haftasında ALT 390, T.Bil 5.1, INR normal
- İdrar rengi koyu, kaşıntı mevcut, iştahsızlık ve kilo kaybı var
- Ne olmuş olabilir? Ne yapmak gerekir?

□ □

SİROTİK HASTAYA PEG-INF LAMDA

Tedavisine ara verildi ve izlendi

- 2 hafta sonra ALT 150, T.Bil 1.1
- Hastaya tedavisi 120 mcg/hafta olarak yeniden başlandı
- TX 16. haftasında HDVRNA 3.400, ALT 91
- TX 48. haftasında HDVRNA negatif ve ALT 32

SVR gelişti... ☺

Bulevirtide (Formerly Myrcludex B)

- HBV zarf proteinin Pre-S1 alanından üretilen ve deri altına enjekte edilen sentetik lipopeptittir
- NTCP reseptörüne bağlanarak HBV'nin girişini engeller
- Faz çalışmalarında ALT normalizasyonu
- HDV-RNA kaybı (2 log düşüş)
- Ancak SVR oranı düşük, daha uzun süreli tedavi???
- Bir hastada HBsAg kaybı gelişmiş (PEG-INF+BLV)
- Düşük advers olay

Editorial

EASL JOURNAL OF HEPATOLOGY

Journal of Hepatology **2016** vol. 65 | 465–466

Myrcludex B, a novel therapy for chronic hepatitis D?

Mario Rizzetto[1,*], Grazia Anna Niro[2]

[1]*Department of Internal Medicine – Gastroenterology, University of Torino, Italy;* [2]*IRCCS "Casa Sollievo Sofferenza" Hospital, Gastroenterology Unit, San Giovanni Rotondo (FG), Italy*

See Articles, pages 483–489 and pages 490–498

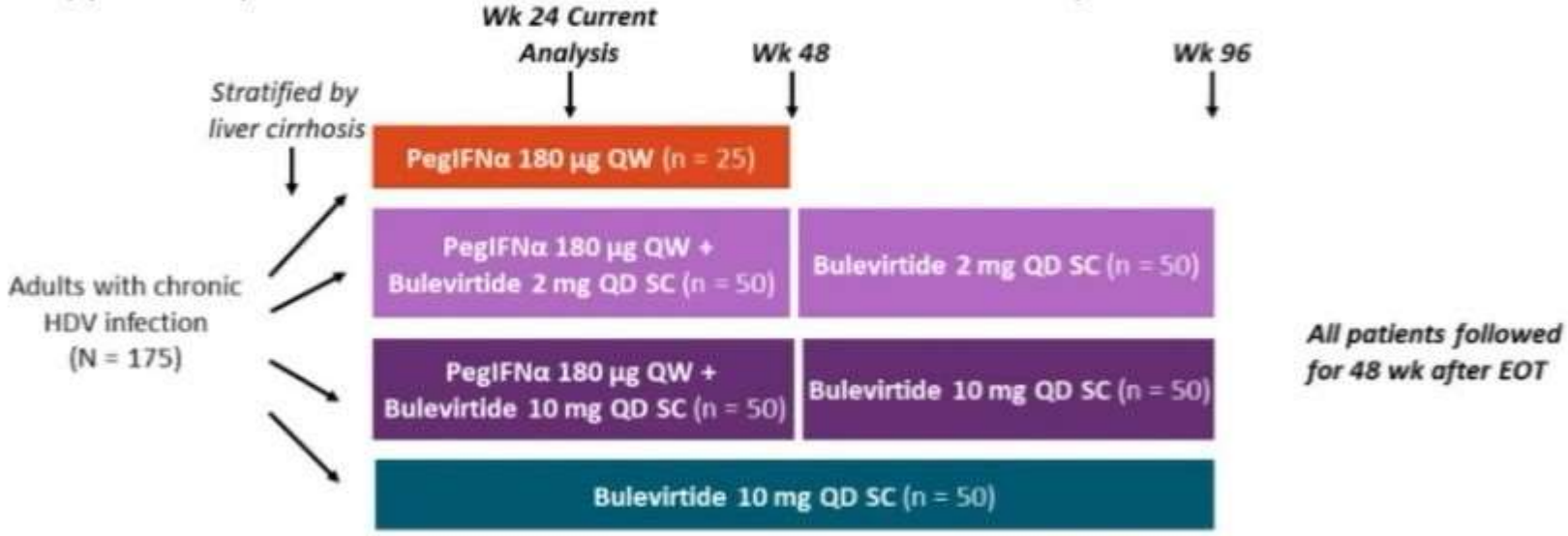
The second paper (Treatment of chronic hepatitis D with the entry inhibitor myrcludex B – first results of a Phase Ib/IIa study; Pavel Bogomolov *et al.*) reported the interim results of the use of Myrc in CHD, and aimed to provide a proof of concept of the blocking strategy. The rationale was that the prolonged inhibition of the HDV entry by the HBsAg block should protect uninfected hepatocytes from new HDV infection, ultimately leading to the eradication of the virus.

Myrcludex B 2 mg/gün s.c. 24 hafta

MYR204: FAZ IIB

MYR204: Bulevirtide Alone and Combined With PegIFNα-2a for Chronic HDV Infection: Wk 24 Analysis

- Multicenter, international, open-label, randomized phase IIB trial of bulevirtide, entry inhibitor approved by EMA for use in adults with chronic HDV and compensated cirrhosis

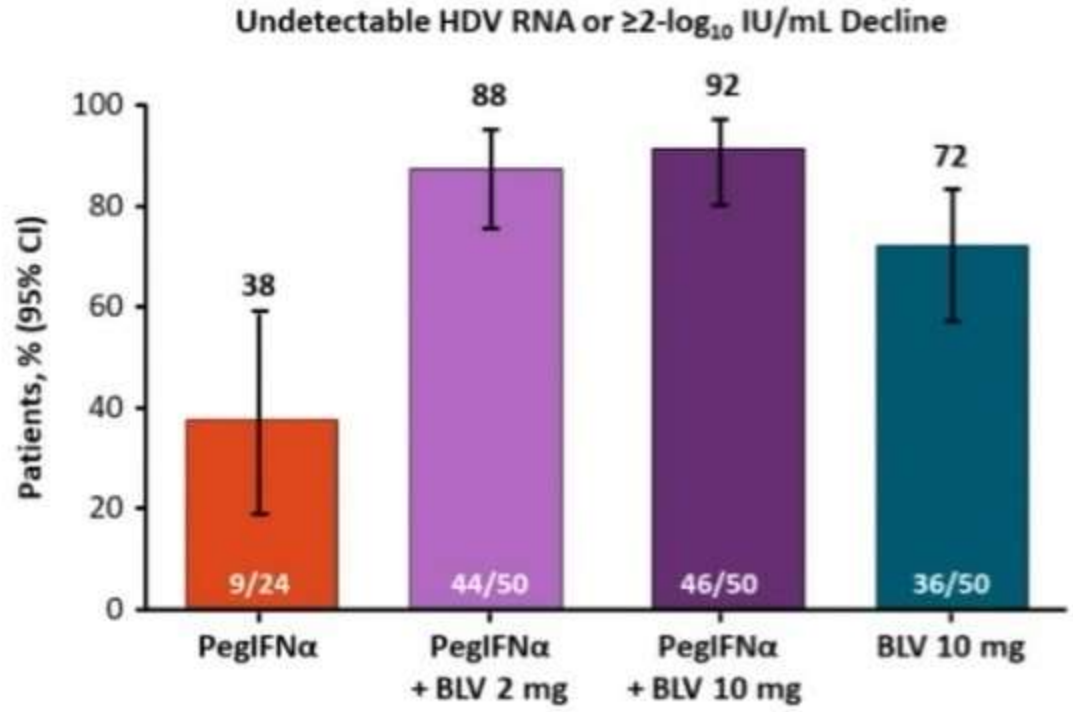


- Primary endpoint: Undetectable HDV RNA (LLD: 6 IU/mL) at Wk 24 after EOT

Asselah. EASL 2020. Abstr 2717.

Slide credit: clinicaloptions.com

MYR204 Interim Wk 24 Analysis: Virologic Response



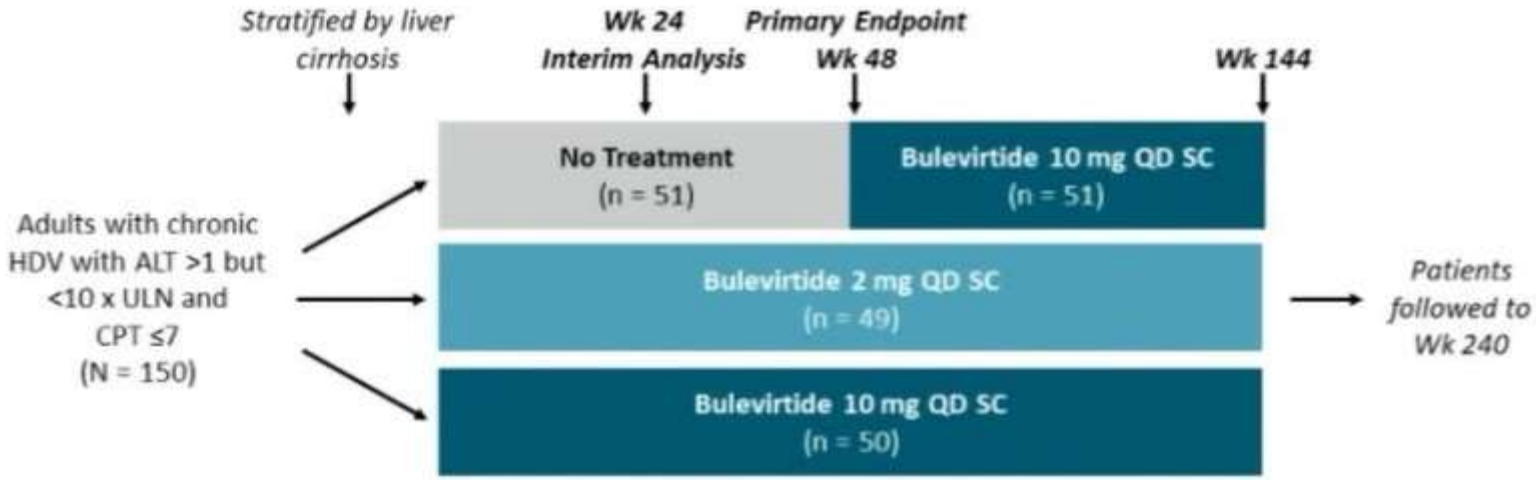
Asselah. EASL 2020. Abstr 2717.

Slide credit: clinicaloptions.com

MYR301: FAZ III

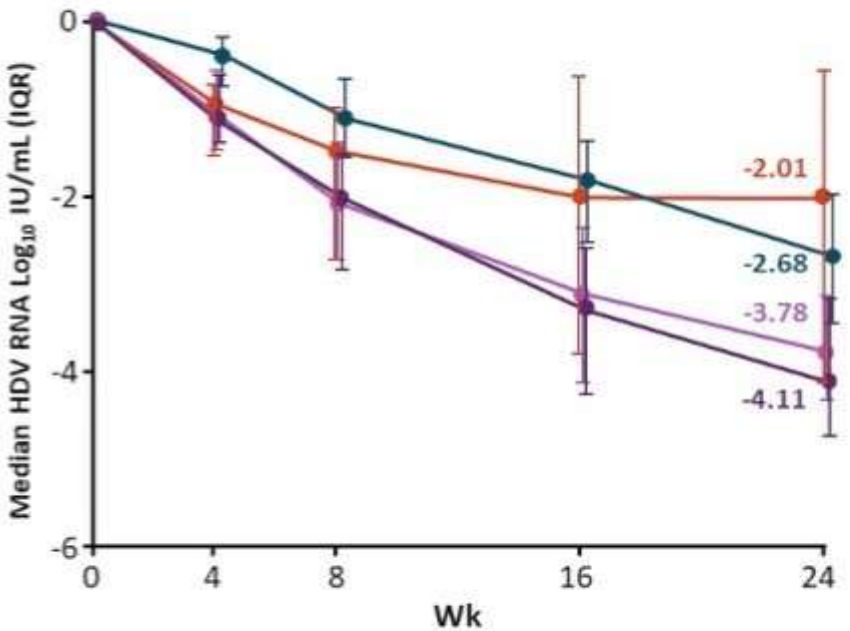
MYR301: High- vs Low-Dose Bulevirtide Monotherapy in Patients With Chronic HDV Infection

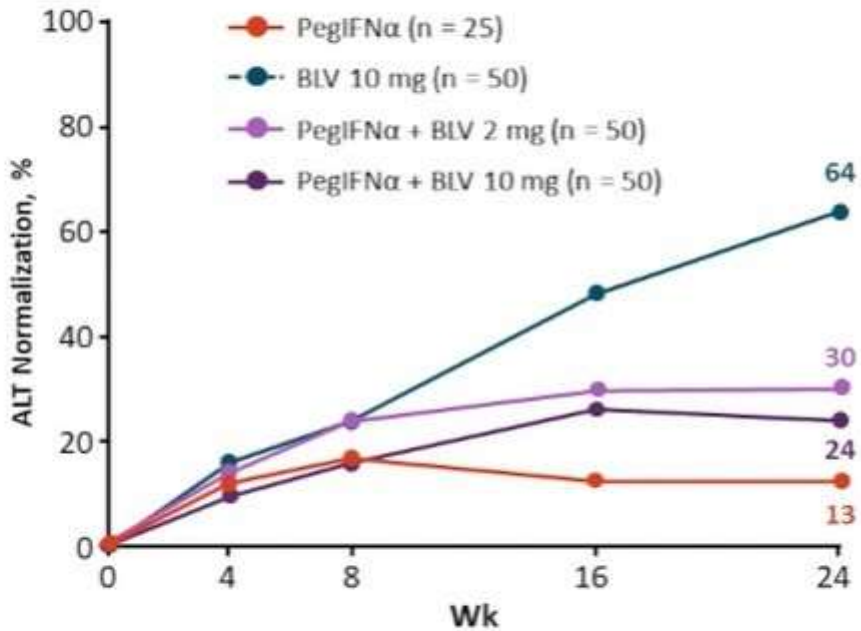
- Multicenter, open-label, randomized, phase III trial



- Primary endpoint: Combined response defined by undetectable HDV RNA or decrease by ≥2 $\log_{10}$ IU/mL from baseline + normalized ALT at Wk 48

MYR204 Interim 24-Wk Analysis: HDV RNA



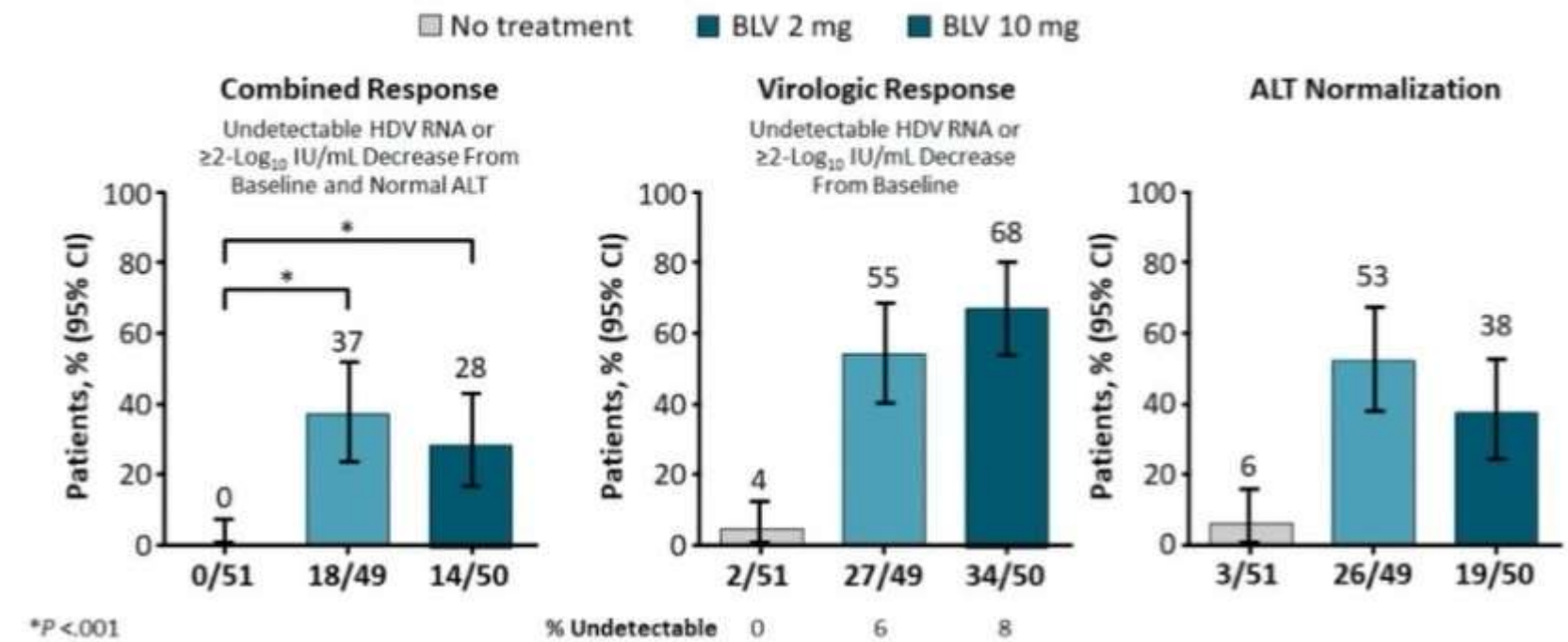


- No serious AEs related to bulevirtide use or AEs leading to d/c in bulevirtide-treated patients
- ISRs observed in patients receiving bulevirtide mostly mild; frequency 8% to 16% across arms

Asselah. EASL 2020. Abstr 2717.

Slide credit: clinicaloptions.com

MYR301 Interim Analysis: Virologic Efficacy at Wk 24



Key Questions on Emerging Treatments for Hepatitis Delta

Heiner Wedemeyer, MD

Professor and Chairman
Department of
Gastroenterology, Hepatology
and Endocrinology
Hannover Medical School
Hannover, Germany

?

Bulevirtid kullanımını optimize etmek için cevaplanması gereken sorular var

Kombinasyon tedavisi ve tedavi süresi?

- İnterferon ile kombinasyon tedavisi bir seçenek midir?
- Kombinasyon tedavisinde sinerjik etkiler görüldü, veriler henüz yetersiz
- Hastalarda her iki ilacı da bıraktığında ne olduğunu henüz biliminmemekte
- Devam eden MYR204 çalışma sonuçları beklenmektedir

Yanıtsız hastalar !!!

- Bulevirtid tedavisine yanıt vermeyebilecek hastalar var mı?
- Hangi faktörler tedavi yanıtını etkiler?
- Tedaviyi bıraktıktan sonra nüks?
- Bu vakalardan herhangi biri doğruysa, bulevirtide ek alternatif tedavilere ihtiyacımız olabilir mi?

Lonafarnib

- Farnesil transferaz inhibitörüdür
- Prenilasyonu engelleyerek HDV virion oluşumunu engeller
- Lonafarnib 100 mg ve 200 mg günde iki kez ve 28 gün alındı ve 6 ay takip edildi (faz II)
- Ritonavirli ve ritonavirsiz gruplarda HDV RNA düşüşü görüldü
- PEG-INF ile kombine edildi
- GIS yan etkileri yüksek
- ALT normalizasyonu %52

- Lonafarnib + PEG-INF
- PEG-INF
- Lonafarnib
- 18 hasta dahil edildi
- SVR %30
- AE çok fazla

LMT-2 NEWSLETTER

EIGER BIOPHARMACEUTICALS

biorasi Faster Trials

EIG-LMD-002 | July 2022 | ISSUE #1

SCREENING & ENROLLMENT UPDATES

There are **109 patients screened** in the study and **18 sites activated** in Romania, Moldova, Turkey, Spain, USA, Israel and Germany.

Let us continue working together as we are looking to screen up to 200 more patients.

Congratulations to **Dr. Grambihler** on your site's recent activation! We wish you and your study participants the best of luck!

Site	Country	No. of Patients
Dr. Elena Laura Iliescu	Romania	23
Dr. George Sebastian Gherlan	Romania	20
Dr. Adela Turcanu	Moldova	16
Dr. Mustafa Kemal Celen	Turkey	16
Dr. Alexandru Florin Caruntu	Romania	13
Dr. Liliana Baroiu	Romania	7
Dr. Maria Buti	Spain	7
Dr. Ho Bae	United States	4
Dr. Yana Davidov	Israel	2
Dr. Dieterich	United States	1

Olgu-I

- 40 yaş, erkek, (2019)
- Bursa
- 10 yıl önce tanı almış
- HBV+HDV
- HBVDNA 167 IU/ml
- HDVRNA 40.000
- ALT 89
- İki kez PEG-INF almış

- Non sirotik
- USG de dalak normal
- Anti-HCV negatif
- Steatoz yok
- AST 40
- Trombosit 239.000
- Tedavi almaya istekli

D-LIVER ÇALIŞMASINA DAHİL OLDU…

- Pegasys 180 mcg/haftalık + Lonafarnip
- Tx 10. haftası ALT 399, Trombositler 115.000
- Ne yapmalı??? Ve ne olmuş olabilir??

Tedaviye devam edildi...

- 12. haftada HDV-RNA 2.300 IU/ML
- 16. haftada ALT 33
- 24. haftada HDV-RNA negatif
- 48. haftada HDV-RNA negatif

Advers Olaylar

- Hasta toplamda 9 kg verdi
- 7. ayda antidepresan başlandı
- PEG-INF uyumu %98
- Bulantı, kusma, halsizlik, kas ağrısı, baş ağrısı
- Uykusuzluk

Tedavi Sonu Takipleri

- 6. ay HDVRNA negatif, ALT N
- 12.ay HDVRNA negatif, ALT N
- 24.ay HDVRNA negatif, ALT N

Olgu II

- 41 yaşında erkek hasta
- 15 yıldır HDV+HBV
- 2010 ve 2015 da iki kez Peg INF tedavisi almış
- Nüks
- Non sirotik hasta
- HBV DNA negatif
- HDV RNA 109.000 kp/ml, ALT 71

Faz III çalışamasına dahil oldu

- Lonafarnib+PEG
- Tedavinin 12 haftasında kilo kaybı %4
- Bulantı, kusma ve İshal mevcut
- HDV RNA 1.240 kopya/ml

- Tedavinin 48 haftasında HDV RNA negatif
- ALT normal

Zor bir tedavi, çok sayıda AO mevcut

TS 6. ay hasta iyi ve HDV RNA negatif ☺

Nucleic Acid Polymers (NCT02233075, NCT02876419)

- Fosforotiat nükleik asit polimerlerinin (NAP'ler) etki mekanizması henüz açıklığa kavuşturulmamıştır
- Kanıtlar bunların subviral HBsAg partiküllerinin hücresel salınımına müdahale ettiğini göstermektedir
- REP 2055 ve REP 2139 HBeAg pozitif HBV hastalarında HBsAg ve HBVDNA düzeyini azalttığı görüldü. SVR %70 olarak saptandı
- Hastalar tarafından IV uygulanan REP 2139'un tolere edilebildiği görüldü, ancak çalışmada %33 oranında SAE saptandı
- Hastalar 15 hafta boyunca haftada 500 mg REP 2139 IV olarak aldı

2021 Aralık ☺

Received: 22 December 2021 | Accepted: 3 January 2022

DOI: 10.1111/jvh.13651

INVITED REVIEW

Chronic hepatitis D—What is changing?

David Yardeni | Theo Heller | Christopher Koh

Liver Diseases Branch, National Institute of Diabetes & Digestive & Kidney Diseases, National Institutes of Health, Bethesda, Maryland, USA

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Email: christopher.koh@nih.gov

Abstract

Hepatitis D virus (HDV) infection is a chronic viral disease of the liver that is still largely considered to be incurable due to lack of effective treatment options. Without treatment, the risk for the development of advanced liver disease, cirrhosis and hepatocellular carcinoma is significantly high. Currently, new therapeutic options are emerging out of ongoing phase 3 clinical trials, promising a new hope of cure for this devastating liver infection. Recently, bulevirtide, a first in its class HDV entry inhibitor, has received conditional authorization of use from the European Medicines Agency (EMA) and was also submitted for approval in the United States. Other novel therapeutic options in clincal trials include interferon lambda, the prenylation inhibitor lonafarnib and nucleic acidic polymers (NAPs). This review describes all recent advances and ongoing changes to the field of HDV therpaeutics.

KEYWORDS
chronic liver disease, hepatitis D, treatment

Kombinasyon Tedavileri

- PEG-INF LAMDA
- BLUVERTIDE
- LONAFARNIP
- NAP

Digestive Diseases and Sciences
https://doi.org/10.1007/s10620-023-07960-y

REVIEW

Check for updates

Diagnosis and Management of Hepatitis Delta Virus Infection

Calvin Pan[1,2] · Robert Gish[3,4] · Ira M. Jacobson[5] · Ke-Qin Hu[6] · Heiner Wedemeyer[7] · Paul Martin[8]

Received: 8 July 2022 / Accepted: 24 April 2023

Received: 30 October 2022 | Accepted: 25 November 2022
DOI: 10.1111/jvh.13797

INVITED REVIEW

Delta hepatitis epidemiology and t

Tatyana Kushner

Division of Liver Diseases, Icahn School of Medicine at Mount Sinai, New York, New York, USA

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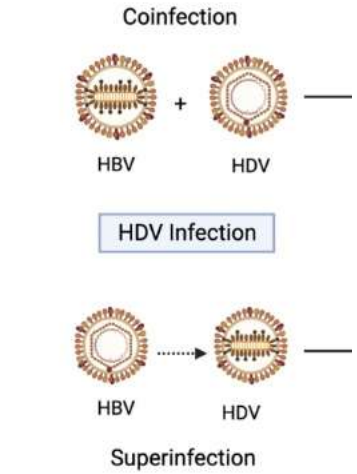
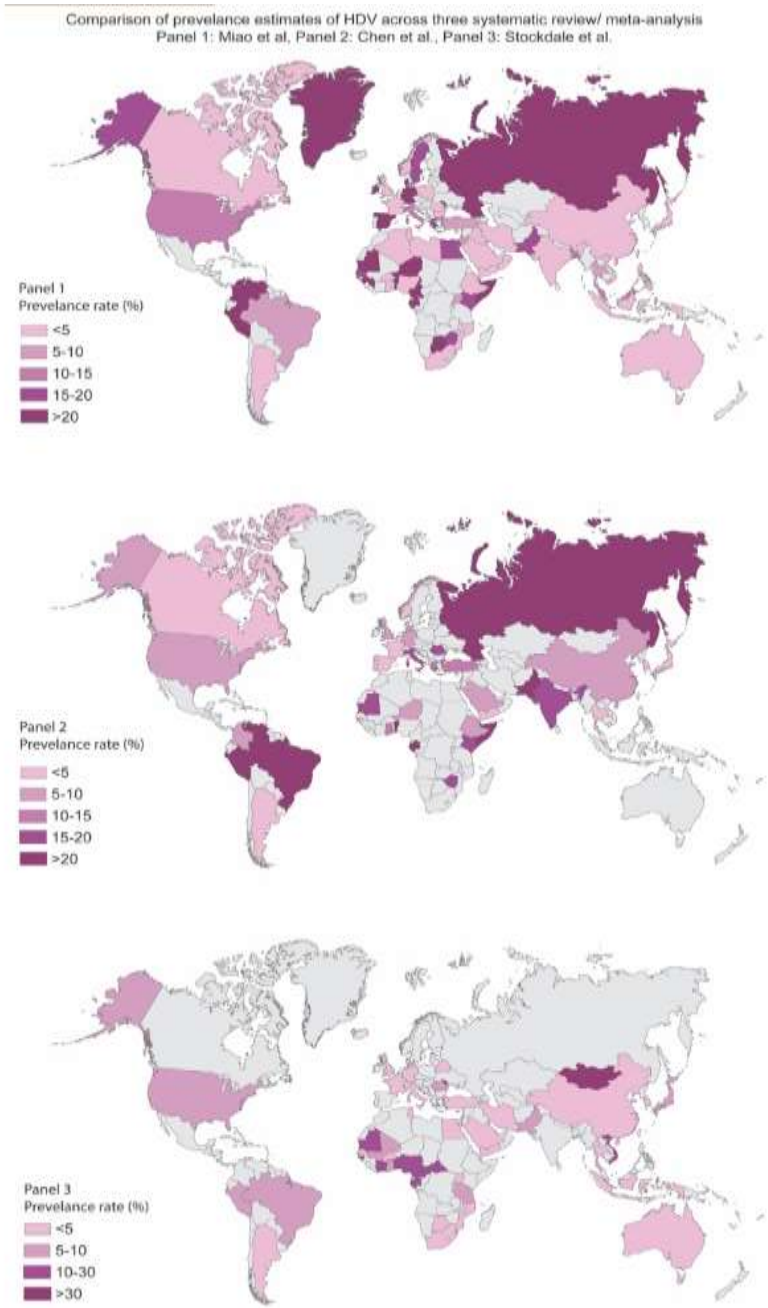
Email: tatyana.kushner@mssm.edu

Abstract





sk factors associated with delta hepatitis.

countries	Low-income countries
g use	HIV infection
rom endemic regions	Sexual transmission
nission	Intrahousehold transmission
	Iatrogenic
	Cultural practices

Journal of Hepatology, **August 2023**. vol. 79 | 433–460

Clini Digestive Dis
https://doi.o

REVIEW

Received: 25 January 2022 | Revised: 27 May 2022 | Accepted: 8 June 2022

DOI: 10.1111/liv.15338

MINI REVIEW

Liver INTERNATIONAL WILEY

OLOGY

IS☆

Euro

Diagnc

Hepatitis delta virus infection prevalence, diagnosis and treatment in the Middle East: A scoping review

Calvin Par

Jeffrey V. Lazarus[1,2] | Ahmad Al-Rifai[3] | Faisal M. Sanai[4] | Abdullah Saeed Alghamdi[5] | Ala I. Sharara[6] | Motaz Fathy Saad[7] | Lena van Selm[1] | Saleh A. Alqahtani[8,9]

Summary

Hepatitis D virus damage in humans. HDV is responsible for rare acute and chronic liver diseases and is considered the most aggressive hepatitis virus. Acute infection can cause acute liver failure, while persistent infection typically causes a severe form of chronic hepatitis which is associated with rapid and frequent progression to cirrhosis and its end-stage complications, hepatic decompensation and hepatocellular carcinoma. Major diagnostic and therapeutic innovations prompted the EASL Governing Board to commission specific Clinical Practice Guidelines on the identification, virologic and clinical characterisation, prognostic assessment, and appropriate clinical and therapeutic management of HDV-infected individuals.

GAEP

"Alfa Çalışma Grubu"

SITU(HD)V'ATION TURKEY

FIND HDV AND DETERMINE ITS STATUS IN TURKEY

Sonuç Olarak…

Review

HBV/HDV Co-Infection: Epidemiological and Clinical Changes, Recent Knowledge and Future Challenges

Caterina Sagnelli, Evangelista Sagnelli *, Antonio Russo, Mariantonietta Pisaturo, Laura Occhiello and Nicola Coppola

En habis hepatotrop virüs olduğu kesin

Dekompanse Siroz artışı HBV'ye göre 7 kat fazla

HCC gelişimi HBV'ye göre 3 kat fazla

Orta Afrika'dan, Avrupa'ya Genotip 5-8 olan HDV enfeksiyonlarında artış

Pegile-İnterferon da SVR (%20-30)

HBV'de kullanılan OAV tedaviler HDV'de etkin değil

Lonafarnib, Bulevirtide ve Nucleic Acid Polymers daha etkin ancak AO az değil

Kombinasyon Tedavileri