Akutní a chronické virové hepatitidy

Pavel Chalupa

Klinika infekčních a tropických nemocí
1. LF UK a Nemocnice Na Bulovce

2020/2021

Discovery of aetiological agents of VH

- 1965 Hepatitis B surface antigen (HBsAg) was isolated (Blumberg – *1976 The Nobel Prize*)
- 1973 Hepatitis A virus (HAV) was identified (Feinstone)
- 1977 Delta agent (HDV) was identified (Mario Rizzetto)
- 1985 recombinant DNA technology
- 1989 HCV was identified (Alter, Houghton, Rice – *2020 The Nobel Prize*)
- 1990 HEV was identified (Balayan)
- 1994 HFV, but existence of HFV as well as HF was not confirmed later
- 1995 HGV was identified (later renamed on GBV-C)

Původce	HAV = enterovirus 72	HBV	HCV
Čeleď (Family)	Picornaviridae	Hepadnaviridae	Flaviviridae
Rod (Genus)	Hepatovirus	Orthohepadnavirus	Hepacivirus
Velikost	27-28 nm	42 nm	30-60 nm
Genom	RNA	DNA	RNA
Počet genotypů	tři (I, II a III) se subtypy A a B pouze 1 sérotyp	9 (A až I), několik subgenotypů v Evropě nejčastěji A a C v Asii nejčastěji B a C	> 6 genotypů > 120 subtypů
Ink. doba (dny)	15-50	30-180	15-150
Přenos: - enterálně	ano	ne	ne
- krví	vzácně	ano	ano
- sexuálně	vzácně	ano	vzácně
- vertikálně	ne	ano	vzácně
Přechod do chronicity	ne	novor. > 90 %, dětí do 5 let 25-50 %, dospělí: imunokompetentní < 5 %, imunokompromitovaní > 50 %	50 - 90 %
Laboratorní diagnostika akutní infekce	anti-HAV IgM (pozitivita je také po aktivní imunizaci)	HBsAg HBeAg anti-HBc IgM	anti-HCV a HCV RNA
Fulminantní průběh (rozvoj akutního jaterního selhání do 8 týdnů)	0,1 %	0,1 - 1 %	krajně vzácně
Akt. a pas. imunizace	ano	ano	ne

Původce	HDV (delta agens)	HEV swHEV (swine kmeny HEV)	HGV (nyní GBV-C) Nezpůsobuje hepatitidu
Čeleď (Family)		Hepeviridae	Flaviviridae
Rod (Genus)	Deltavirus	Orthohepevirus	
Velikost	35-37 nm	27-34 nm	
Genom	RNA	RNA	RNA
Počet genotypů (GT)	nejméně 8	Osm, ale GT 1, 2, 3 a 4 jsou nejdůležitější	
Ink. doba (dny)	30-180	15-60	
Přenos: - enterálně	ne	ANO u GT 1 a GT 2 kontaminovanou vodou u GT 3 a GT 4 zoonotický přenos (vepři, kanci a jelenovití zvířata)	ne
- krví	ano	vzácně	ano
- sexuálně	ano	vzácně	
- vertikálně	ano	ano	
Přechod do chronicity	koinfekce < 5 % superinfekce 80-90 %	Ve většině případů NE, ale chron. průběh může být u pac. po transplantacích, u maligních, u HIV pozit.	Inhibuje HIV replikaci – tedy zpomaluje progresi HIV infekce
Lab. diagnostika akutní infekce	anti-HDV IgM, HBsAg	anti-HEV IgM a/nebo HEV RNA (ze séra nebo stolice)	anti-HGV a HGV RNA
Fulminantní průběh	u koinfekce 1 % u superinfekce 5 %	1-2 %, 3. trim. grav. kolem 22 % (GT 1 a GT 2)	
Vakcína	proti HB	Rekombinantní; zatím dostupná jen v Číně	ne
Imunoglobulin	proti HB	ne	ne

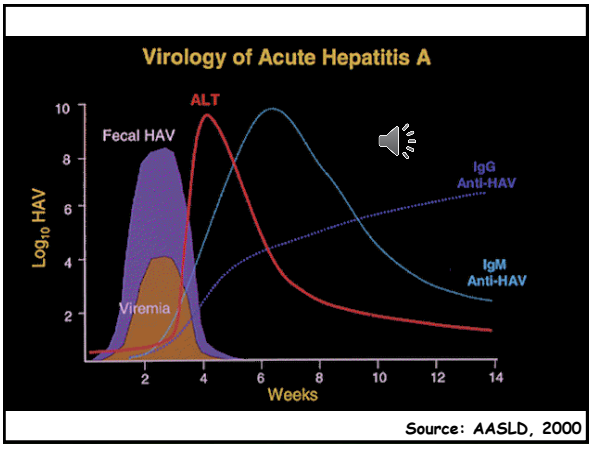
Virus hepatitidy F

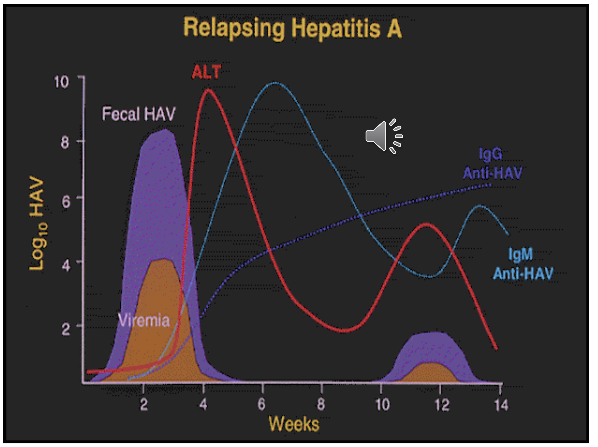
- V prosinci 1994 publikována zpráva o přenosu agens, který způsobuje non-A, non-E hepatitidu u opic
- Virus-like particles o průměru 27-37 nm byly detekovány ve stolici francouzských pacientů a v játrech a stolicích infikovaných zvířat
- Agens bylo označeno jako hepatitis French virus (HFV) a analýzou virového genomu zjištěna dvojvláknitá DNA

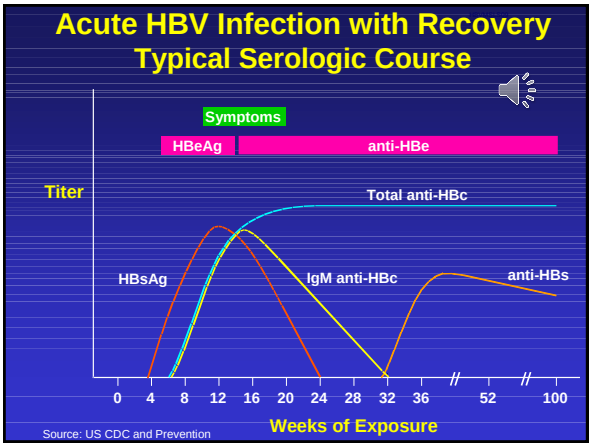
  (*Journal of Gastroenterology and Hepatology 2001;16(2):124-131*)

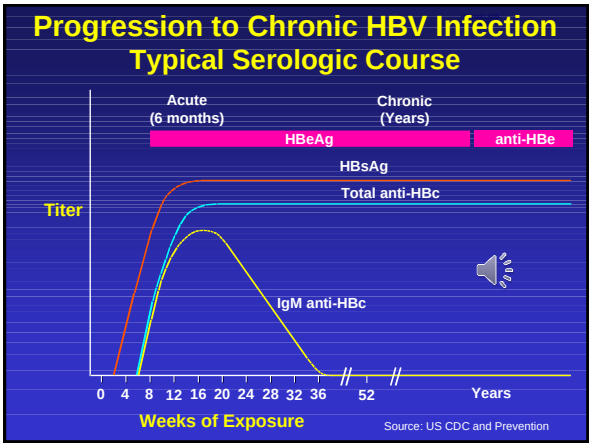
- Existence tohoto viru později potvrzena nebyla!!

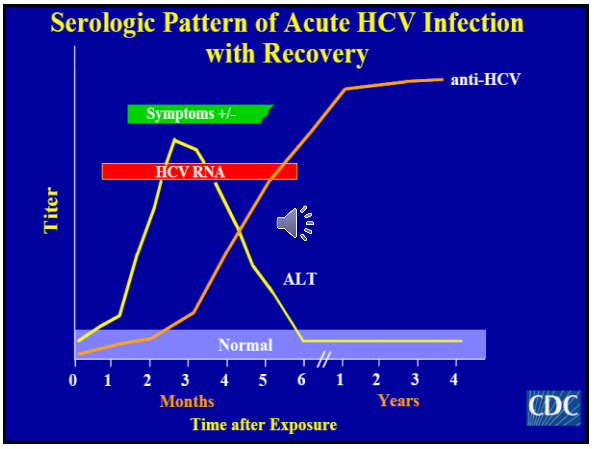
	Anti HAV IgM	HBs Ag	HBe Ag	Anti HBc IgG	Anti HBc IgM	Anti HBs	Anti HCV	Anti HBe	Anti HEV IgM
HA akutní	+	-	-	-	-	-	-	-	-
HB akutní	-	+	+	-	+	-	-	-	-
HB chronická HBeAg pozitivní (dříve označována jako infekce divokým typem viru HB)	-	+	+	+	-	-	-	-	-
HB chronická HBeAg negativní (dříve nazývána infekce e-minus mutantou)	-	+	-	+	-	-	-	+	-
St. po vakcinaci proti HB	-	-	-	-	-	+	-	-	-
HC akutní nebo chronická	-	-	-	-	-	-	+ a HCV RNA	-	-
HE akutní	-	-	-	-	-	-	-	-	+ a/nebo HEV RNA

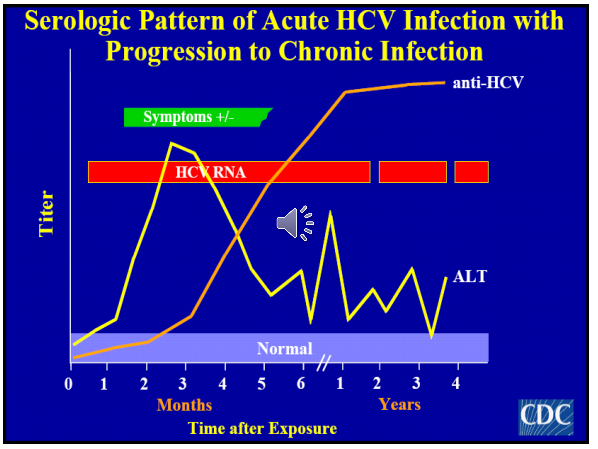

Virology of Acute Hepatitis A
ALT
Fecal HAV
IgG
Anti-HAV
IgM
Anti-HAV
Viremia
Log10 HAV
Weeks
Source: AASLD, 2000

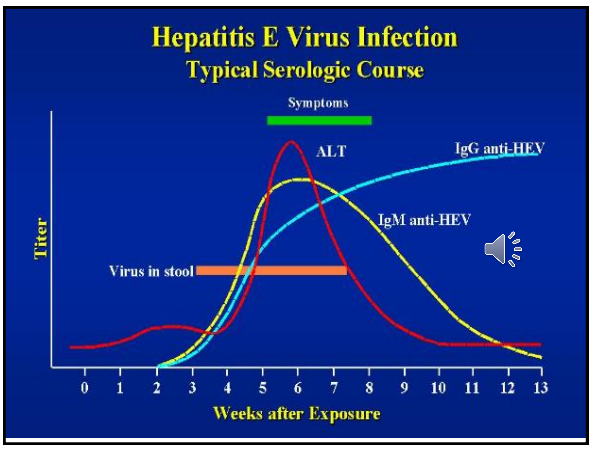

Relapsing Hepatitis A
ALT
Fecal HAV
IgG
Anti-HAV
IgM
Anti-HAV
Viremia
Log10 HAV
Weeks

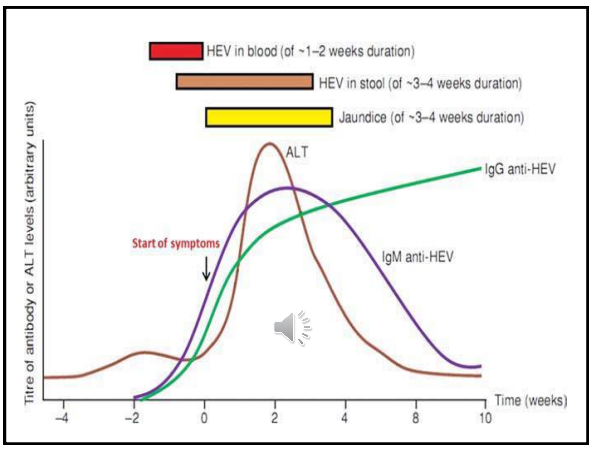

Acute HBV Infection with Recovery
Typical Serologic Course
Symptoms
HBeAg
anti-HBe
Titer
Total anti-HBc
HBsAg
IgM anti-HBc
anti-HBs
Weeks of Exposure
Source: US CDC and Prevention


Progression to Chronic HBV Infection
Typical Serologic Course
Acute
(6 months)
Chronic
(Years)
HBeAg
anti-HBe
HBsAg
Total anti-HBc
Titer
IgM anti-HBc
Years
Weeks of Exposure
Source: US CDC and Prevention


Serologic Pattern of Acute HCV Infection
with Recovery
anti-HCV
Symptoms +/-
HCV RNA
Titer
ALT
Normal
Months
Years
Time after Exposure
CDC

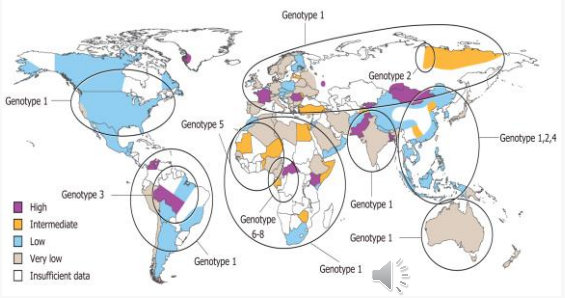

Serologic Pattern of Acute HCV Infection with
Progression to Chronic Infection
anti-HCV
Symptoms +/-
HCV RNA
Titer
ALT
Normal
Months
Years
Time after Exposure
CDC





Odhadovaná prevalence HDV infekce

(World Journal of Gastroenterology 2019;25(32):4580-4597)



Acute VH in CR reported to Epidat and to ISIN

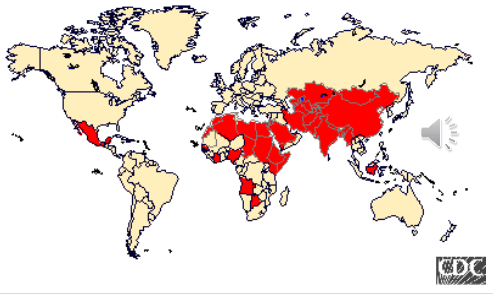
(HC = *acute HC + chronic HC firstly diagnosed* together)

	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
HA	1195	904	933	614	325	127	114	70	322	132	128	1648	1104	862	264	284	348	673	724	930	772	211	240
HB	564	575	636	604	457	413	370	392	361	307	307	306	247	244	192	154	133	105	89	73	85	54	41
HC	273	448	634	637	798	858	846	868	844	1022	980	974	836	709	812	794	873	867	956	1104	992	1050	1138
HE	5	17	5	12	13	12	21	36	37	35	43	65	99	72	163	258	218	289	412	339	344	272	268

Previous theory about HE prevalance

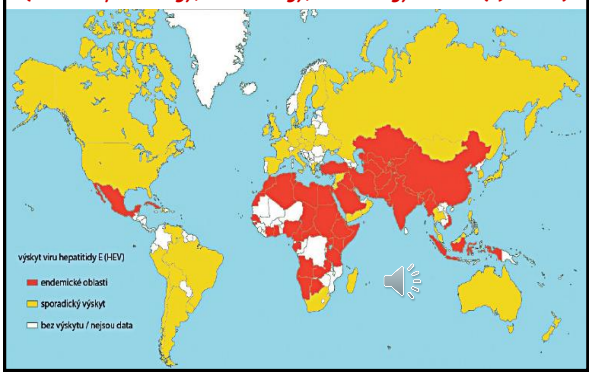
Geographic Distribution of Hepatitis E

Outbreaks or Confirmed Infection in > 25% of Sporadic Non-ABC Hepatitis



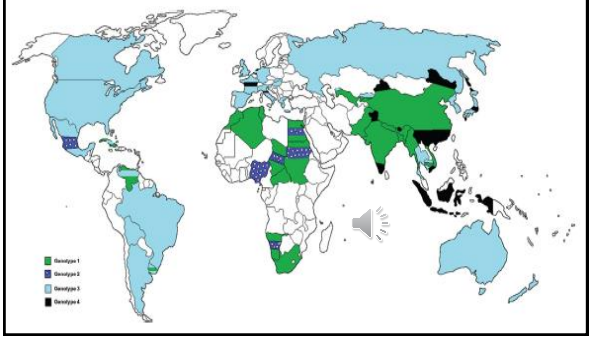
Výskyt HE ve světě

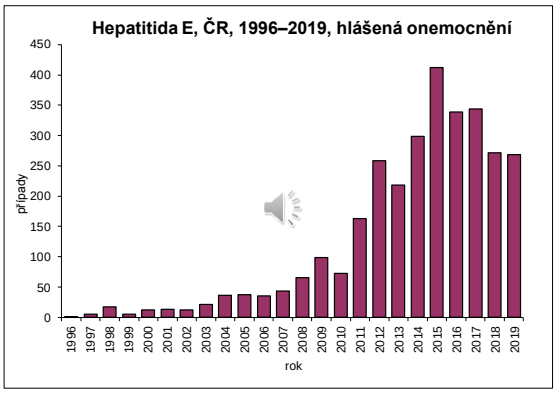
(Journal Epidemiology, Microbiology, Immunology 2015;64(2):72-78)

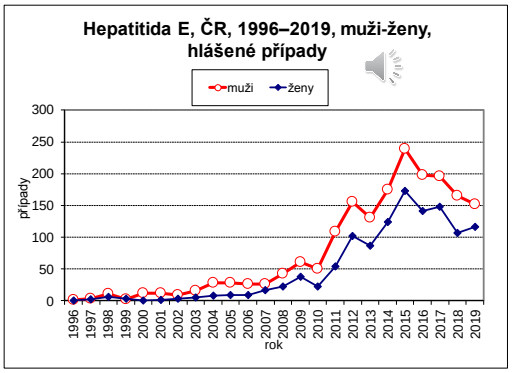


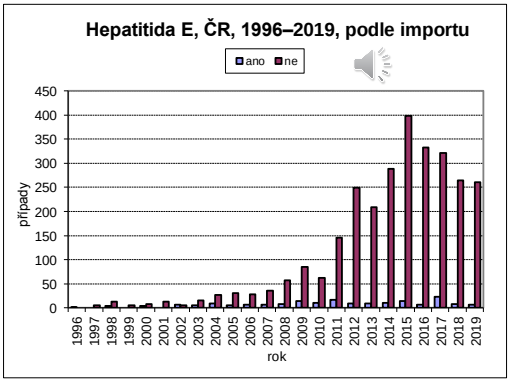
Výskyt genotypů HEV ve světě

(*Hepatic Medicine:Evidence and Research 2014;6:45-59*)









Virology of HEV

***Hepeviridae* viruses infect mammals, birds and fish**

Strains infecting humans belong to the *Orthohepevirus* genus, species A

Species A comprises **8 genotypes**

Virus family: ***Hepeviridae***

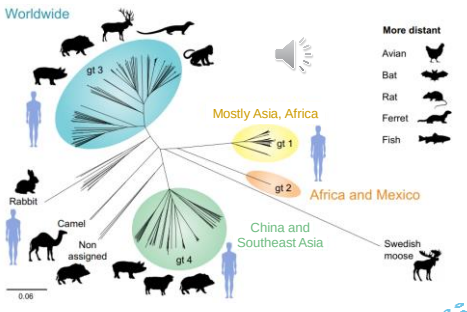
Genus: ***Orthohepevirus***

Species: **A** | B | C | D

GT 1	GT 2	GT 3	GT 4	GT 5	GT 6	GT 7	GT 8
• **Only infect humans** • **Faecal–oral spread via contaminated water** • **Large outbreaks** • Brief, **self-limiting** • **Never chronic** • **High mortality in pregnancy (25%)**		• **Endemic** in animal species; eg, pigs and wild boar • **Zoonotic infections in humans** • High-income countries • **China: GT 4 most common** • S. America: GT 3 only		• **Have only been reported in wild boar**		• **GT 7 identified in patient regularly consuming camel meat and milk** • Have since been identified in camels	

EASL CPG HEV. J Hepatol 2018;doi: 10.1016/j.jhep.2018.03.005 [Epub ahead of print]

Phylogenetic relationship of hepeviruses identified in various hosts



Debing Y, et al. J Hepatol 2016;65:200–12

Promyka mungo či promyka indická

Promyka mungo (*Herpestes edwardsii*, angl. mongoose) je promykovitá šelma a vyskytuje se na jihu Asie. Loví i velké a prudce jedovaté hady. Indové ji s oblibou dávají dětem a nechávají ji přespávat v dětských pokojích (jako domácího mazlíčka, ale i jako ochranu před hady).

HEV GT 1 and 2 in brief

- ~20 million infections worldwide
  - 3 million symptomatic cases and 70,000 deaths/year*
  - WHO guidelines should be consulted for management of outbreaks of acute HEV in resource-limited settings
- Brief, self-limiting, usually in young adults
- **Never chronic**
  - Acute-on-chronic liver failure possible
- **High mortality in pregnancy (25%)**

Recommendations		
• **Travellers with hepatitis returning from areas endemic for HEV GT 1 or 2 should be tested for HEV**		
• **Pregnant women with HEV GT 1 or 2 should be transferred to a liver transplant unit if liver failure occurs**		

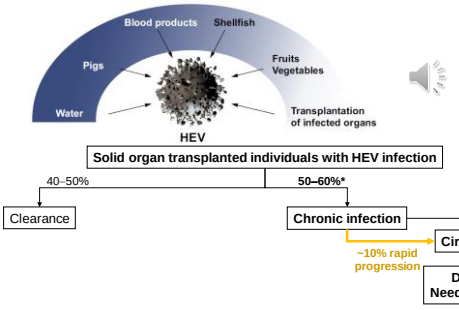
*Data from 2005
EASL CPG HEV. J Hepatol 2018;doi: 10.1016/j.jhep.2018.03.005 [Epub ahead of print]

HEV GT 3 and 4: epidemiology

- Endemic in some developing countries, as well as most high-income countries
- **HEV GT 3 are the most common cause of acute viral hepatitis in many European countries**
- Estimated that ≥2 million locally acquired HEV infections/year
  - Most as a result of zoonotic infection
    - Primary hosts are pigs
- **HEV GT 3 and 4 tend to affect older males**
  - In an English study, male:female ratio was 3:1; median age, 63 years[1]
- Incidence varies between and within countries, and over time
  - Multiple 'hotspots' of HEV infection in Europe

1. Dalton HR, et al. Eur J Gastroenterol Hepatol 2008;20:784–90;
EASL CPG HEV. J Hepatol 2018;doi: 10.1016/j.jhep.2018.03.005 [Epub ahead of print]

Transmission and disease progression in transplanted individuals



*Possible increased likelihood for LTx recipients, only GT 3
Behrendt P, et al. J Hepatol 2014;61:1418–29

Treatment of acute HEV infection

- **Acute HEV infection does not usually require antiviral therapy***
- **Most cases of HEV infection are spontaneously cleared**
  - **Some patients may progress to liver failure**
  - Ribavirin
    - Early therapy of acute HEV may shorten course of disease and reduce overall morbidity

Recommendation	Grade of evidence	Grade of recommendation
• **Ribavirin treatment may be considered in cases of severe acute hepatitis or acute-on-chronic liver failure**	C	2

*Grade of evidence A
EASL CPG HEV. J Hepatol 2018;doi: 10.1016/j.jhep.2018.03.005 [Epub ahead of print]

Management of chronic HEV infection I.

Recommendations	Grade of evidence	Grade of recommendation
• **Decrease immunosuppression at diagnosis of chronic HEV infection in solid organ transplant recipients, if possible**	B	1
• **Give ribavirin for 12 weeks in patients with persisting HEV replication 3 months after detection of HEV RNA**	B	1
Monitoring of HEV RNA •Assess in serum and stool at the end of scheduled period of ribavirin therapy	B	1
•Stop ribavirin if undetectable in both serum and stool	C	2

EASL CPG HEV. J Hepatol 2018;doi: 10.1016/j.jhep.2018.03.005 [Epub ahead of print]

Management of chronic HEV infection II.

- Optimal treatment duration in patients who test HEV RNA positive after 4 or 8 weeks of therapy and who are HEV RNA negative after 12 weeks of therapy is unknown*
- Optimal therapeutic approach unknown in patients who show no response to ribavirin and/or who relapse after retreatment*

Recommendations	Grade of evidence	Grade of recommendation
• **If HEV RNA is still detectable in serum and/or stool after 12 weeks, ribavirin monotherapy may be continued for an additional 3 months (6 months therapy overall)**	C	2
• **Liver transplant recipients who show no response to ribavirin can be considered for treatment with pegylated interferon-α**	C	2

*Grade of evidence C
EASL CPG HEV. J Hepatol 2018;doi: 10.1016/j.jhep.2018.03.005 [Epub ahead of print]

Extrahepatic manifestations of HEV are increasingly recognized

Organ system	Clinical syndrome	Notes
Neurological	• **Neuralgic amyotrophy*** = brachial plexus involvement Parsonage-Turner syndrome (usually bilateral and asymmetric) • **Guillain–Barré syndrome*** • **Meningoencephalitis*** • Mononeuritis multiplex • Myositis • Bell's palsy, vestibular neuritis and peripheral neuropathy	• ~150 cases of neurological injury (in HEV GT 3); mainly Europe • Most (>90%) cases in the immunocompetent
Renal*	• **Membranoproliferative and membranous glomerulonephritis** • **IgA nephropathy**	• Mainly immunosuppressed GT 3-infected patients • Renal function improves and proteinuria levels decrease following HEV clearance
Haematological	• Thrombocytopenia • Monoclonal immunoglobulin • Cryoglobulinaemia • Aplastic anaemia† • Haemolytic anaemia†	• Mild thrombocytopenia is common; occasionally severe • Reported in 25% of cases of acute HEV in UK study • Occurs mainly in association with renal disease
Other	• Acute pancreatitis • Arthritis† • Myocarditis† • Autoimmune thyroiditis†	• 55 cases worldwide. HEV GT 1 only; usually mild

***There is good evidence to support a causal role for HEV and these associated conditions. For the other extrahepatic manifestations, causality remains to be established; †Case reports only**
EASL CPG HEV. J Hepatol 2018;doi: 10.1016/j.jhep.2018.03.005 [Epub ahead of print]

HEV resistance on heat

Heating the food to an internal temperature of 71 °C for 20 min is necessary to completely inactivate HEV

(Barnaud E. et al.: Thermal inactivation of infectious hepatitis E virus in experimentally contaminated food. *Applied and Environmental Microbiology* 2012;78(15):5153-9)

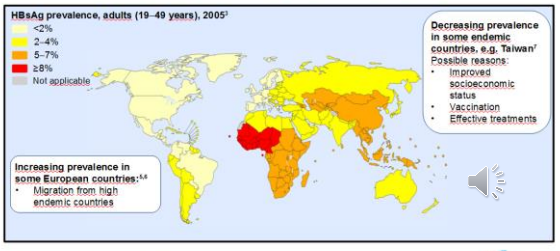
Onemocnění	Název vakcíny	Počet dávek	Množství antigenu	Schéma	Indikace	Objem
VHA	HAVRIX	2	A: 720 EU A:1440 EU	M 0–(6–12)	1– 5 let ≥ 16 let	0,5 ml 1,0 ml
	AVAXIM	2	A: 160 AU	M 0–(6–18)	≥ 2 let	0,5 ml
	VAQTA	2	A: 25 IU A: 50 IU	M 0–(6–18)	2–17 let ≥ 18 let	0,5 ml 1,0 ml
VHB	ENGERIX –B	3	B: 10 µg B: 20 µg	M 0–1–6 (M 0–1–2–12)	0–15 let ≥ 16 let	0,5 ml 1,0 ml
	HB VAX PRO	3	B: 5 µg B: 10 µg	M 0–1–6 (M 0–1–2–12)	0–15 let ≥ 16 let	0,5 ml 1,0 ml
	FENDRIX	4	B: 20 µg	M 0–1–2–6	≥ 15 let	0,5 ml
VHA+VHB	TWINRIX	3	A/B:360 EU/10 µg A/B:720 EU/20 µg	M 0–1–6 (D 0–7–21 + M 12)	1–15 let ≥ 16 let	0,5 ml 1,0 ml

D – den, M – měsíc

Tab. 1 Přehled vakcín proti VHA a VHB registrovaných v ČR

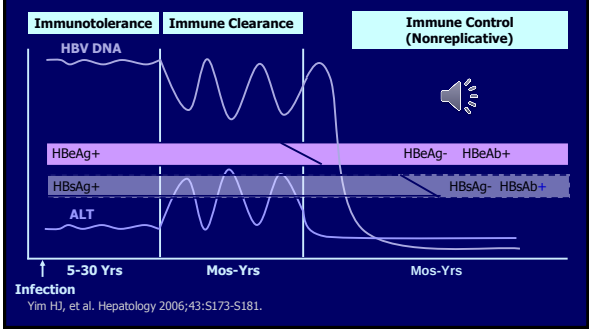
Epidemiology and public health burden[1]

- Worldwide ≈250 million chronic HBsAg carriers[2,3]
- 686,000 deaths from HBV-related liver disease and HCC in 2013[4]



1. EASL CPG HBV. J Hepatol 2017;67:370–98. 2. Schweitzer A, et al. Lancet 2015;386:1546–55. 3. Ott JJ, et al. Vaccine 2012;30:2212–9. 4. GBD 2013 Mortality and Causes of Death Collaborators. Lancet 2015;385:117–71. 5. Coppola N, et al. Euro Surveill 2015;20:30009. 6. Hampel A, et al. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 2016;59:578–83. 7. Chen C-L, et al. J Hepatol 2015;63:354–63.

Natural History of Chronic HBV Infection



Yim HJ, et al. Hepatology 2006;43:S173-S181.

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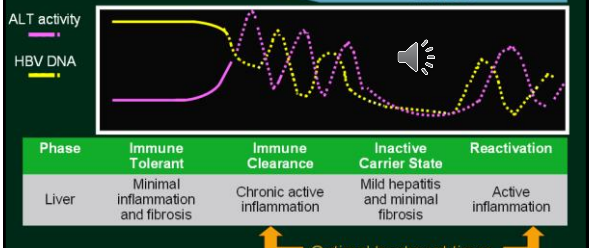
CLINICAL CARE OPTIONS HEPATITIS

4 Phases of Chronic HBV Infection

Current Understanding of HBV Infection



Phase	Immune Tolerant	Immune Clearance	Inactive Carrier State	Reactivation
Liver	Minimal inflammation and fibrosis	Chronic active inflammation	Mild hepatitis and minimal fibrosis	Active inflammation

Optimal treatment times

Yim HJ, et al. Natural history of chronic hepatitis B virus infection: what we knew in 1981 and what we know in 2005. Hepatology. 2006;43:S173-S181. Copyright © 1999–2012 John Wiley & Sons, Inc. All Rights Reserved.

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CLINICAL CARE OPTIONS HEPATITIS

Subset of Agents Reported to Cause HBV Reactivation

Class	Agents
Corticosteroids	Dexamethasone, methylprednisolone, prednisolone
Antitumor antibiotics	Actinomycin D, bleomycin, daunorubicin, doxorubicin, epirubicin, mitomycin-C
Plant alkaloids	Vinblastine, vincristine
Alkylating agents	Carboplatin, chlorambucil, cisplatin, cyclophosphamide, ifosfamide
Antimetabolites	Azauridine, cytarabine, fluouracil, gemcitabine, mercaptopurine, methotrexate, thioguanine
Monoclonal antibodies	Alemtuzumab, rituximab
Others	Colaspase, docetaxel, etoposide, fludarabine, folinic acid, interferon, procarbazine

Yeo W, et al. Hepatology. 2006;43:209-220.

HBV Reactivation: Overview

- Clinical syndrome characterized by an increase in HBV DNA and ALT/AST with or without symptoms or jaundice
- Occurs in pts with active (HBsAg+) and resolved (HBsAg-, anti-HBc+) HBV infection
- Wide clinical spectrum

  Ranges from silent to acute liver failure (fibrosing cholestatic hepatitis)
- Can occur during treatment with many immunosuppressive agents

  May also occur up to 12 mos after treatment
- Preventable by antiviral prophylaxis

Di Bisceglie AM, et al. Hepatology. 2015;61:703-711.
Perrillo RP, et al. Gastroenterology. 2015;148:221-244.

Slide credit: clinicaloptions.com

Nová nomenklatura chronické HBV infekce

- **Chronická HBV infekce = dynamický proces odrážející interakce mezi replikací HBV a imunitním systémem**
- **Ne všichni pacienti s chronickou HBV infekcí mají chronickou hepatitidu B**

1. **HBeAg pozitivní chronická HBV infekce (dříve „imunotolerantní fáze“)**
2. **HBeAg pozitivní chronická hepatitida B**
3. **HBeAg negativní chronická HBV infekce (dříve „inaktivní nosičství“)**
4. **HBeAg negativní chronická hepatitida B**
5. **HBsAg negativní fáze (také „okultní HBV infekce“)**

Natural History of HBV: New Nomenclature From EASL

Parameter	HBeAg Positive		HBeAg Negative		Resolved HBV Infection
	Chronic *Infection*	Chronic *Hepatitis*	Chronic *Infection*	Chronic *Hepatitis*	
HBsAg	High	High/ intermediate	Low	Intermediate	Negative
HBeAg	Positive	Positive	Negative	Negative	Negative
HBV DNA	> 10^7 IU/mL	10^4 to 10^7 IU/mL	< 2000 IU/mL*	> 2000 IU/mL	Undetectable‡
ALT	Normal	Elevated	Normal	Elevated†	Normal
Liver disease	None/minimal	Moderate/severe	None	Moderate/severe	None§
Older term	*Immune tolerant*	*Immune reactive HBeAg positive*	*Inactive carrier*	*HBeAg negative chronic hepatitis*	*HBsAg negative, anti-HBc positive*

*HBV DNA levels up to 20,000 IU/mL can occur without signs of chronic hepatitis. †Persistently or intermittently.
‡cccDNA frequently detected in the liver. §Residual HCC risk only if cirrhosis developed before HBsAg loss.

EASL. J Hepatol. 2017;67:370.

Slide credit: clinicaloptions.com

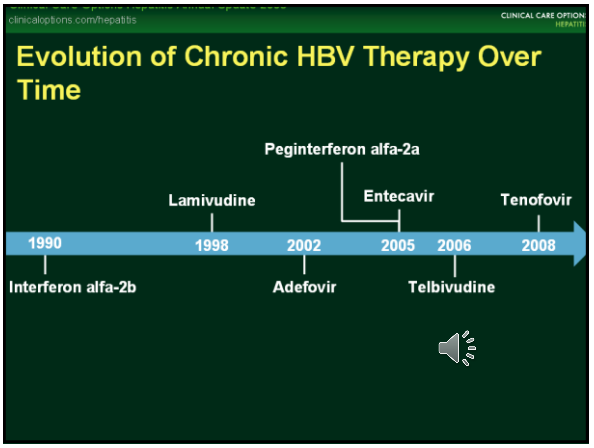
Natural History of HBV and Treatment Indications

Parameter	HBeAg Positive		HBeAg Negative		Resolved HBV Infection
	Chronic *Infection*	Chronic *Hepatitis*	Chronic *Infection*	Chronic *Hepatitis*	
Old terminology	Immune tolerant	Immune reactive HBeAg positive	Inactive carrier	HBeAg negative chronic hepatitis	HBsAg negative, anti-HBc positive
HBsAg	High	High/intermediate	Low	Intermediate	Negative
HBeAg	Positive	Positive	Negative	Negative	Negative
HBV DNA	> 10^7 IU/mL	10^4 to 10^7 IU/mL	< 2000 IU/mL*	> 2000 IU/mL	Undetectable
ALT	Normal	Elevated	Normal	Elevated†	Normal
Liver disease	None/minimal	Moderate/severe	None	Moderate/severe	None
Disease progression	Low	**Moderate to high**	Low	**Moderate to high**	None (HCC)
Treatment	Not indicated‡	**Indicated**	Not indicated	**Indicated**	Not indicated§

*HBV DNA levels up to 20,000 IU/mL can occur without signs of chronic hepatitis. †Persistently or intermittently. ‡Treatment is indicated in some patients. §Prophylaxis for select cases.

EASL. J Hepatol. 2017;67:370.

Slide credit: clinicaloptions.com



Nucleos(t)ide analogues (NA)

*famciklovir – *analogue of deoxygunosin (Famvir™)*

*lamivudine (3TC, LAM) – *analogue of deoxycytidin (Zeffix™)*

*adefovir dipivoxil (ADV) – *analogue of dAMP (Hepsera™)*

*tenofovir – *similar as ADV*
TDF = *tenofovir disoproxil fumarate (Viread™)*
TAF = *tenofovir alafenamide (Vemlidy™)*

*entecavir (ETC) –*analogue of deoxyguanin (Baraclude™)*

*emtricitabine (FTC) – *analogue of cytosinu (Emtriva™)*

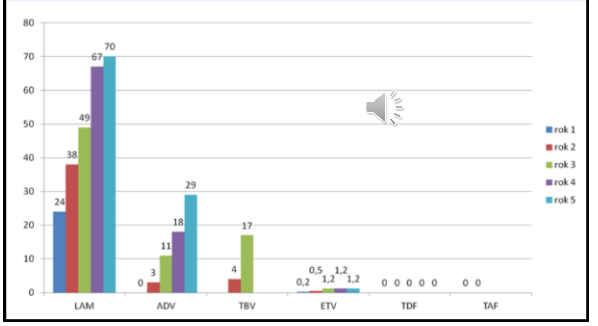
*clevudine (LFMAU) –*analogue of pyrimidin (Levoril™, Revovir™)*

*telbivudine (LdT) – *analogue of L-deoxythymidin (Sebivo™)*

Duration of the therapy of chronic HB

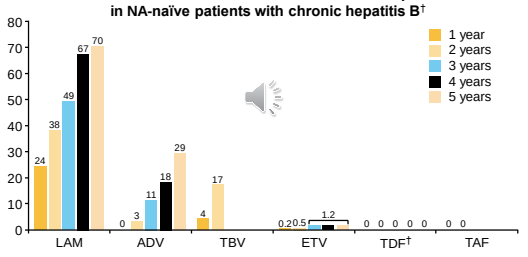
Therapeutic approach	HBeAg pos.	HBeAg neg.
PEG-IFN alfa	48 wks	48 wks
Nucleos(t)ide analogues (TDF, ETC, TAF)	*Pts without CIH:* To HBeAg disappearance and next 12 months	To HBsAg disappearance X HBsAg persistency very often to the end of the life
Initiation of antiviral therapy depends of viremia	HBV DNA >2 000 IU/mL (>10^4 copies/mL)	HBV DNA >2 000 IU/mL (>10^4 copies/mL)

Cumulative incidence of HBV resistance for lamivudine (LAM), adefovir (ADV), telbivudine (TBV), entecavir (ETV), tenofovir (TDF) and tenofovir alafenamide (TAF) in pivotal trials in nucleos(t)ide-naïve patients with chronic HB (*Hepatology 2014;60:313A-317A*)



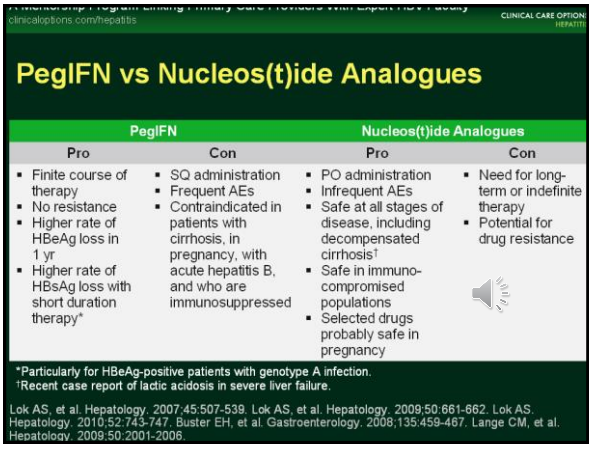
Prevention of resistance should rely on the use of first-line NAs with a high barrier to resistance*

Cumulative incidence of HBV resistance to NAs in pivotal trials in NA-naïve patients with chronic hepatitis B†



*Evidence level I, grade of recommendation 1; †Collation of currently available data – not from head-to-head studies; ‡No evidence of resistance has been shown after 8 years of TDF treatment
EASL CPG HBV. J Hepatol 2017;67:370–98

EASL



Indikace k použití antivirotik u pacientů s HBV infekcí

(*EASL 2017 Clinical Practice Guidelines*)

- HBeAg-pozitivní nebo HBeA-negativní chronická HB (jsou zvýšené hodnoty ALT a je alespoň minimální histologické postižení jater a HBV DNA > 2 000 IU/ml)
- Všichni pacienti s cirhózou a detekovatelnou HBV DNA
- V prevenci přenosu infekce z matky na dítě u těhotných s vysokou virémií (HBV DNA > 200 000 IU/ml)
- V prevenci HBV reaktivace u pacientů vyžadujících imunosupresi nebo chemoterapii
- U pacientů s HBeAg-pozitivní chronickou HBV infekcí s normální biochemickou aktivitou, ale s vysokou HBV DNA (dle dřívějšího označení „imunotolerantní fáze"), pokud jsou starší 30 let, nebo pokud je v rodině HCC nebo cirhóza
- U pacientů se závažně probíhající akutní HB – tj. s koagulopatií nebo s protrahovaným průběhem, by měli být léčeni nukleos(t)idovými analogy, případně je třeba u nich uvažovat o transplantaci jater
- Tenofovir (TDF) se doporučuje v těhotenství u pac. s chronickou HB a pokročilou fibrózou nebo cirhózou, ale nepodává se během kojení

Těžký průběh akutní HB

Charakteristickým rysem těžkého průběhu akutní HB je zejména koagulopatie (INR >1,5)

Protrahovaný průběh akutní HB je většinou definován perzistencí symptomů nebo zřetelného ikteru > 4 týdny

Byl prokázán příznivý vliv časně zahájené terapie NA na snížení rizika vzniku akutního jat. selhání, potřeby TJ a na snížení mortality

Jsou příznivá data o léčbě TDF, ETV i LAM, ale vhodnější jsou NA s vyšší genetickou bariérou k rezistenci (tj. TDF nebo ETV). Léčba LAM pouze pokud není možné podávat ETV nebo TDF

Délka léčby:
- nejméně ještě 3 měsíce po sérokonverzi HBsAg/anti-HBs nebo
- 12 měsíců po sérokonverzi HBeAg/anti-HBe

(DP diagnostiky a léčby HBV infekce ČHS a ČIS ČLS JEP ze září 2017)

Prevence perinatálního přenosu HBV u hyperviremických matek v ČR

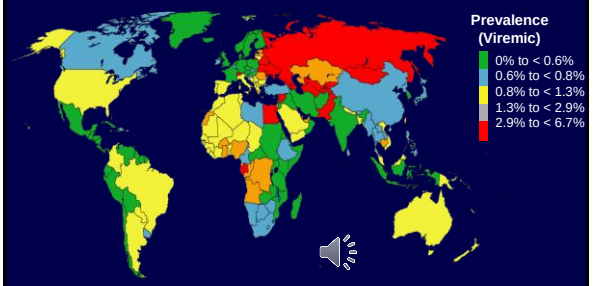
- Profylaktické podávání LAM, TBV nebo TDF v posledním trimestru u pacientek s vysokou HBV DNA v séru (> 200 000 IU/ml) zvyšuje u novorozence účinnost pasivní a aktivní imunizace proti HB
- Přednost má TDF – tento je indikován u gravidních žen s hodnotami HBV DNA v séru > 200 000 IU/ml od 24. – 28. týdne gravidity

Tedy:

- U všech těhotných žen s vysokou sérovou HBV DNA (> 200 000 IU/ml) by měla dle doporučeného postupu probíhat profylaxe TDF, která začíná ve 24. – 28. gestačním týdnu a měla by pokračovat ještě 12 týdnů po porodu

(DP diagnostiky a léčby HBV infekce ČHS a ČIS ČLS JEP ze září 2017)

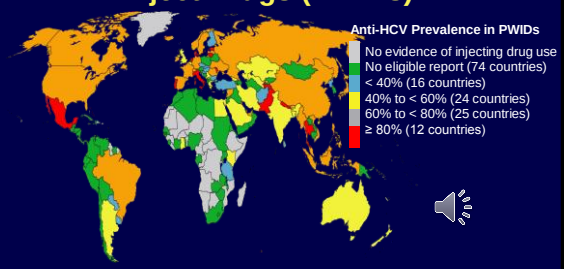
Estimated 70 Million Persons Living With HCV



Polaris Observatory HCV Collaborators. Lancet Gastroenterol Hepatol. 2017;2:161-176.

Slide credit: clinicaloptions.com

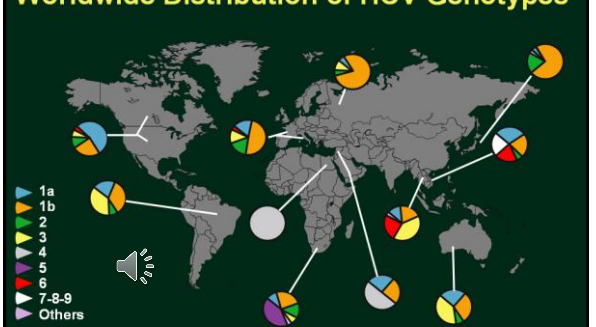
HCV Infection Among Persons Who Inject Drugs (PWIDs)



- In most developing countries, injection drug use is primary source of new infections
- HCV treatment must be coupled with harm reduction measures to reduce total infections

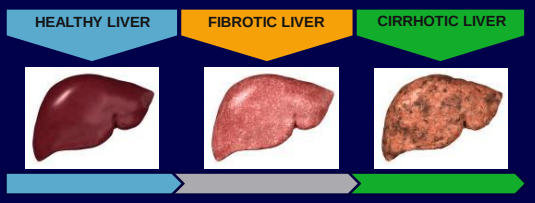
Slide credit: clinicaloptions.com

Worldwide Distribution of HCV Genotypes



Zein N. Clin Microbiol Rev. 2000;13:223-235. Reproduced with permission. http://cmr.asm.org/cgi/content/full/13/2/223?view=long&pmid=10755999.

Chronic Hepatitis C Is a Progressive Disease



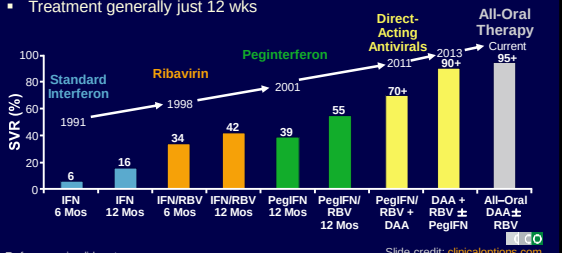
- Few or no symptoms; can progress without signs for decades[1]
- Most pts asymptomatic until serious liver complications arise[2]

1. CDC. MMWR Morb Mortal Wkly Rep. 1998;47(RR-19):1-39.
2. Heidelbaugh JJ, et al. Am Fam Physician. 2006;74:756-762.

Slide credit: clinicaloptions.com

Nearly Everyone With HCV Can Now Be Treated Successfully

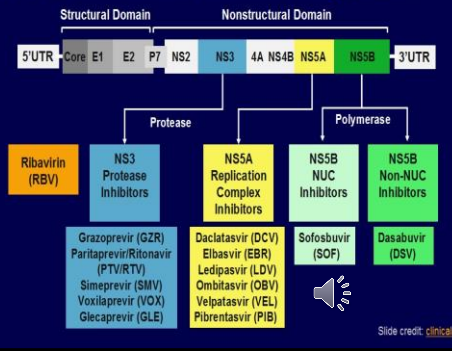
- Very high SVR rates; therapies highly tolerable
- All-oral therapy for almost every pt
- Treatment generally just 12 wks



References in slidenotes.

Slide credit: clinicaloptions.com

Approved DAAs From Multiple Classes: Basis of 2018 Combination HCV Regimens



Slide credit: clinicaloptions.com

Dostupné varianty IFN-free režimů pro jednotlivé genotypy HCV
(Doporučený postup ČHS ČLS JEP z r. 2017)

kombinace	genotypy HCV				
	GT 1	GT 2	GT 3	GT 4	GT 5 a 6
sofosbuvir/ledipasivir ± ribavirin	ano	ne	ne	ano	ano
sofosbuvir/velpatasvir ± ribavirin	ano	ano	ano	ano	ano
ombitasvir/paritaprevir/(r) + dasabuvir ± ribavirin *	ano	ne	ne	ne	ne
ombitasvir/paritaprevir/(r) ± ribavirin *	ne	ne	ne	ano	ne
grazoprevir/elbasvir ± ribavirin	ano	ne	ne	ano	ne
sofosbuvir + daclatasvir ± ribavirin	ano	ano	ano	ano	
sofosbuvir + simeprevir ± ribavirin	suboptimální	ne	ne	ano	ne

sofosbuvir+ledipasvir = HARVONI™ (Gilead)
sofosbuvir+velpatasvir = EPCLUSA™ (Gilead)
ombitasvir+paritaprevir = VIEKIRAX™ (AbbVie)
dasabuvir = EXVIERA™ (AbbVie)
(r) = ritonavir
grazoprevir+elbasvir = ZEPATIER™ (MSD)
asunaprevir = SUNVEPRA™ (BMS)
sofosbuvir = SOVALDI™ (Gilead)
daclatasvir = DAKLINZA™ (BMS)
simeprevir = OLYSIO™ (Janssen)
sofosbuvir+velpatasvir+voxilaprevir = VOSEVI™ (Gilead)
glecaprevir+pibrentasvir = MAVYRET™ (AbbVie) - US
glecaprevir+pibrentasvir = MAVIRET™ (AbbVie)-EU, Japan

EASL 2018 HCV Treatment Guidelines

- Recommendations for treatment-naive patients and patients previously treated with pegIFN/RBV ± SOF or SOF + RBV, with or without compensated cirrhosis

HCV Genotype	SOF/VEL (Epclusa™)	GLE/PIB (Maviret™)	SOF/VEL/VOX (Vosevi™)	LDV/SOF (Harvoni™)	EBR/GZR (Zepatier™)	OBV/PTV/RTV + DSV (Viekirax™ + Exviera™)
1a	Yes	Yes	No*	Yes†	Yes‡	No
1b	Yes	Yes	No*	Yes	Yes	Yes
2	Yes	Yes	No*	No	No	No
3	Yes‖	Yes	Yes§	No	No	No
4	Yes	Yes	No*	Yes†	Yes#	No
5 or 6	Yes	Yes	No*	Yes†	No	No

*Triple combination effective but not needed because double combinations comparably effective. †Tx naive ± compensated cirrhosis. ‡Tx naive or tx experienced without cirrhosis or with compensated cirrhosis and HCV RNA ≤ 800,000 IU/mL. §Tx naive or tx experienced without cirrhosis. ‖Tx naive or tx experienced with compensated cirrhosis. #Treatment naive without cirrhosis or with compensated cirrhosis and HCV RNA ≤ 800,000 IU/mL.

EASL HCV Guidelines. 2018. In press.

Slide credit: clinicaloptions.com

Dostupné varianty IFN-free režimů pro jednotlivé genotypy HCV
(Doporučený postup ČHS ČLS JEP z ledna 2019)

HCV GT	Pangenotypové režimy			Genotypově-specifické režimy		
	SOF/VEL Epclusa™	GLE/PIB Maviret™	SOF/VEL/VOX Vosevi™	SOF/LDV Harvoni™	GZR/EBR Zepatier™	OBV/PTV/r Viekirax™ + DSV Exviera™
1a	Ano	Ano	Ne[a]	Ano[a]	Ano[b]	Ne
1b	Ano	Ano	Ne[a]	Ano	Ano	Ano
2	Ano	Ano	Ne[a]	Ne	Ne	Ne
3	Ano[c]	Ano	Ano[d]	Ne	Ne	Ne
4	Ano	Ano	Ne[a]	Ano[a]	Ano[e]	Ne
5	Ano	Ano	Ne[a]	Ano[a]	Ne	Ne
6	Ano	Ano	Ne[a]	Ano[a]	Ne	Ne

[a] V této indikaci je kombinace SOF/VEL/VOX účinná, nicméně upřednostněno podání dvojkombinačních režimů
[b] Dosud neléčení bez CIH nebo s kompenzovanou CIH
[b] Dosud neléčení i v minulosti léčení bez CIH nebo s komp. CIH a HCV RNA ≤ 800 000 IU/ml
[c] Dosud neléčení i v minulosti léčení bez CIH
[d] Dosud neléčení nebo v minulosti léčení s kompenzovanou CIH
[e] Dosud neléčení bez CIH nebo s komp. CIH a HCV RNA ≤ 800 000 IU/ml

sofosbuvir+velpatasvir = EPCLUSA™
glecaprevir+pibrentasvir = MAVIRET™
sofosbuvir+velpatasvir+voxilaprevir = VOSEVI™
sofosbuvir+ledipasvir = HARVONI™
grazoprevir+elbasvir = ZEPATIER™
ombitasvir+paritaprevir = VIEKIRAX™
r = ritonavir (k potencování účinku)
dasabuvir = EXVIERA™

SVR12 a SVR24

Cílem antivirové léčby je vyléčení HCV infekce, tj. dosažení trvalé eliminace viru. Eliminace viru brání rozvoji jaterních i mimojaterních komplikací HCV infekce, včetně pokročilé jaterní fibrózy, CIH, dekompenzované CIH a vzniku HCC.

Eliminací infekce je myšleno dosažení setrvalé virologické odpovědi (SVR, sustained viral response) = dosažení negativity HCV RNA v séru ve 12. nebo 24. týdnu po ukončení protivirové léčby (ve zkratce SVR12 a SVR24). SVR12 a SVR24 spolu korelují v 99 % případů.

Dle dlouhodobých studií znamená dosažení SVR v 99 % případů trvalé vyléčení HCV infekce, tedy u osob, které dosáhly SVR, nedochází k pozdním relapsům a je dosaženo zastavení další progrese onemocnění.

Pangenotypální režimy

Epclusa™ (Gilead)

= sofosbuvir + velpatasvir

Vosevi™ (Gilead) – vhodný pro případy, kdyby po IFN-free léčbě nedošlo k SVR

= sofosbuvir + velpatasvir + voxilaprevir

Maviret™ (AbbVie) – EU, Japan

Mavyret™ (AbbVie) - US

= glecaprevir + pibrentasvir

Management of Pts With HCV Who Achieved SVR

- SVR associated with myriad clinical benefits
- Mandatory to continue HCC surveillance post SVR in pts with F3/F4 fibrosis; ultrasound every 6 mos
  - Consider assessing AFP levels as well for these pts
  - Less evidence to support continued screening of F0-F2 but remains a theoretical concern
- Indefinite screening for varices not warranted if varices absent at baseline: 1 more exam after SVR?
  - Surveillance of small varices if no other liver disease present requires further study but advisable
  - Large varices require ongoing management and surveillance
- Routine monitoring for fibrosis regression not the standard of care; further studies may change this
- For pts with ongoing risk for HCV infection after SVR, counsel and test HCV RNA annually

Slide credit: clinicaloptions.com

Main extrahepatic manifestations in pts with HCV infection

(*Therapeutic Advances in Infectious Dissease 2016;3(1):3-14*)

Immune-related extrahepatic manifestations

- **Mixed cryoglobulinemia**
- **Cryoglobulinemic vasculitis**
- **B-cell non-Hodgkin's lymphoma**
- Sicca syndrome (Sjögren´s syndrome)
- Arthralgia/myalgia
- Autoantibody production (i.e. cryoglobulins, rheumatoid factor, and antinuclear, anticardiolipin, antithyroid and anti-smooth muscle antibodies)
- Polyarteritis nodosa
- Monoclonal gammopathies
- Immune thrombocytopenia

Inflammatory-related extrahepatic manifestations

- **Type 2 diabetes mellitus type 2**
- Insulin resistance
- **Glomerulonephritis (membranoproliferative)**
- **Renal insufficiency**
- Fatigue
- Cognitive impairment
- Depression
- Impaired quality of life
- Polyarthritis/fibromyalgia
- **Cardiovascular disorders (i.e. stroke, ischemic heart disease)**

Děkuji Vám za pozornost

pavel.chalupa@bulovka.cz