Acute and chronic viral hepatitis

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Discovery of aetiological agents of VH

- 1965 Hepatitis B surface antigen (HBsAg) isolated (Blumberg)
- 1973 Hepatitis A virus (HAV) identified (Feinstone)
- 1977 Delta agent (HDV) identified
- (Mario Rizzetto)
- 1985 recombinant DNA technology
- 1989 HCV identified (Houghton)
- 1990 HEV identified (Bradley)
- 1995 HGV identified

Etiological agent	HAV enterovirus 72	HBV	HCV
Family	Picornaviridae	Hepadnaviridae	Flaviviridae
Genus	Hepatovirus	Orthohepadnavirus	Hepacivirus
Size	27-28 nm	42 nm	30-60 nm
Genom	RNA	DNA	RNA
Number of genotypes	4 only 1 serotype	8 (A ….H)	> 6 main genotypes > 120 subtypes
Incub. period (days)	15-50	30-180	15-150
Transmission: - fecal-oral	yes	no	no
- parenteral	rarely	yes	yes
- sexual contact	rarely	yes	rarely
- perinatal	yes	yes	rarely
Chronicity	no	newbornes >90%, immunocompetent adults < 5%, imunocompromised adults > 50%	55 - 85%
Diagnostic	anti-HAV IgM	HBsAg, HBeAg and anti-HBc IgM	anti-HCV HCV RNA
Fulminant course	0,1%	0,1 - 1%	extremely rarely
Active and pasive immunization	yes	yes	no

Etiological agent	HDV (delta agent)	HEV (swHEV)	GBV-C (HGV) Non-pathogenic for liver
Family		Hepeviridae	Flaviviridae
Genus	Deltavirus	Hepevirus	
Size	35-37 nm	27-34 nm	
Genom	RNA	RNA	RNA
Number of genotypes	3 (I, II, III)	4	
Incub. period (days)	30-180	15-60	
Transmission: - fecal-oral	no	YES GT 1 and GT 2 contaminated water GT 3 and GT 4 zoonotic transmission (pigs, wild boars, deer)	
- parenteral	yes	rarely	yes
- sexual contact	yes	rarely	
- perinatal	yes	yes	
Chronicity	co-infection < 5% superinfection 80-90%	NO, but exceptions: Pts after organ transplantations, with malignancy, HIV+ pts	Inhibition of HIV replication - progression is slower
Diagnostic	anti-HDV IgM, HBsAg	anti-HEV IgM and/or HEV RNA	anti-HGV, HGV RNA
Fulminant course	co-infection 1% superinfection 5%	1-2%, 3rd trim. grav. 21% (GT 1 and GT 2)	
Active immunization	against HB	recombinant vaccine routine used in China	no

HFV

- In December 1994, researchers published evidence for the transmission of the enteric agent responsible for sporadic non-A, non-E hepatitis to rhesus monkeys
- Virus-like particles (27-37 nm in diameter) were detected in human stool extracts from French patients and in the liver and stool of the inoculated animals
- The authors provisionally named agent hepatitis French (for origin) virus or HFV
- Analysis of the viral genome indicated that it contained double-stranded DNA

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

- We know now, that this discovery was not correct = HFV as well as HF do not exist

HEV resistance on heat I.

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

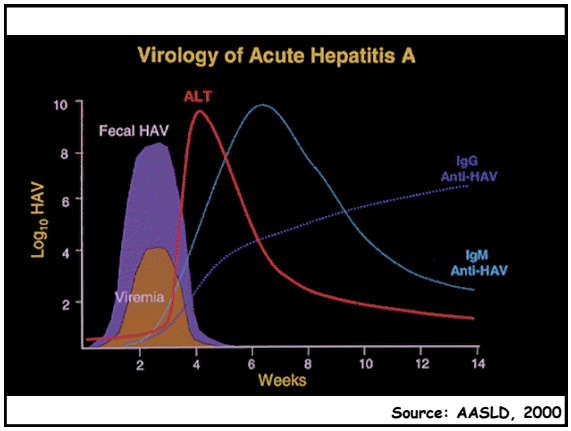
(Barnaud E. et al.: Thermal inactivation of infectious hepatitis E virus in experimentally contaminated food. *Applied and Environmental Microbiology* 2012;78(15):5153-9)

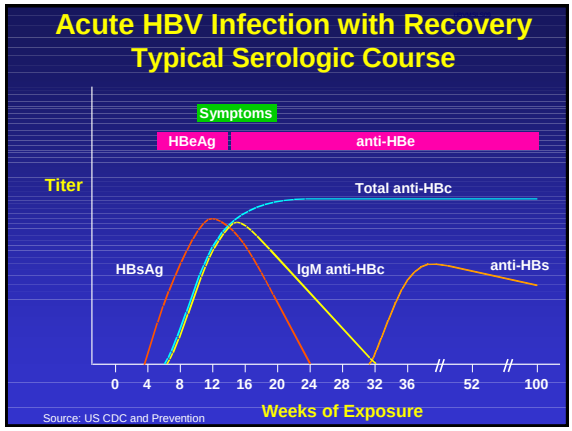
HEV resistance on heat II.

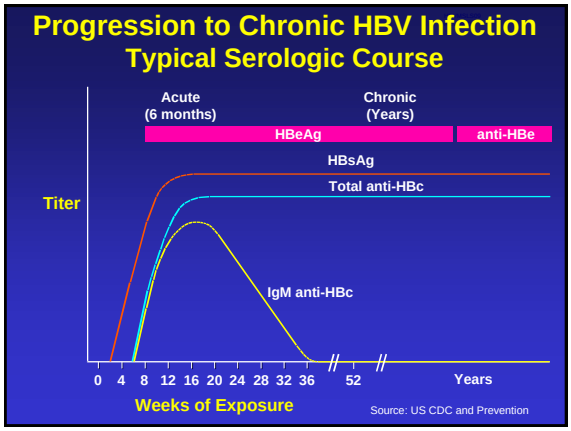
(Feagins AR et al. *Int J Food Microbiol* 2008;123:32-37)

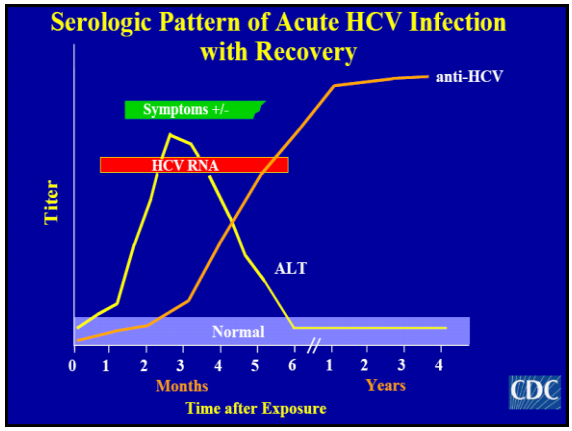
Temp. (ºC)	Time (min)	Cooking methods	Result
56 ºC	30´- 60´	medium rare	HEV is resistant
60 ºC	60´	medium	HEV is residual but alive
66 ºC	10´- 60´	medium well-cooked	HEV inactivation
70-71 ºC	10´- 60´	well done	HEV inactivation

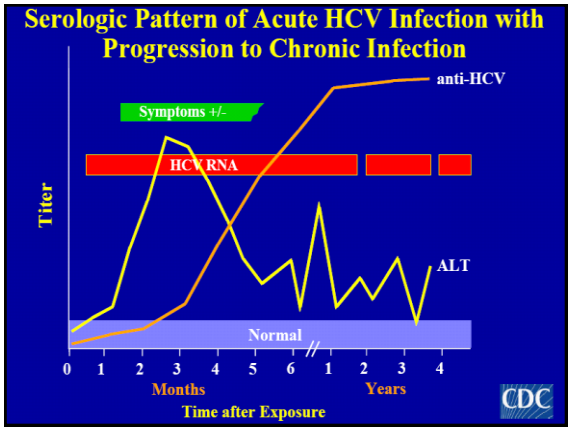
	Anti HAV IgM	HBs Ag	HBe Ag	Anti HBc IgG	Anti HBc IgM	Anti HBs	Anti HCV	Anti HBe	Anti HEV IgM
Acute HA	+	-	-	-	-	-	-	-	-
Acute HB	-	+	+	-	+	-	-	-	-
HBeAg-positive chronic HB	-	+	+	+	-	-	-	-	-
HBeAg-negative chronic HB	-	+	-	+	-	-	-	+	-
Postvaccine immune HBV	-	-	-	-	-	+	-	-	-
Chronic or recent HCV infection	-	-	-	-	-	-	+ and HCV RNA	-	-
Acute HE	-	-	-	-	-	-	-	-	+ and/or HEV RNA

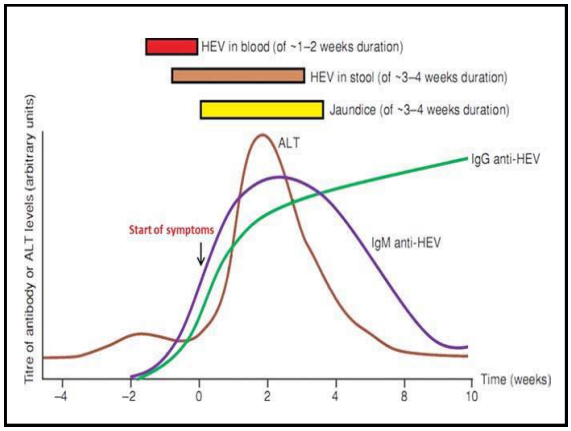


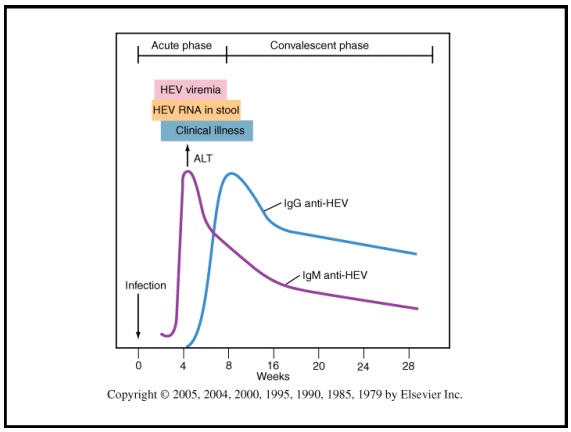












Acute VH in CR (Epidat)

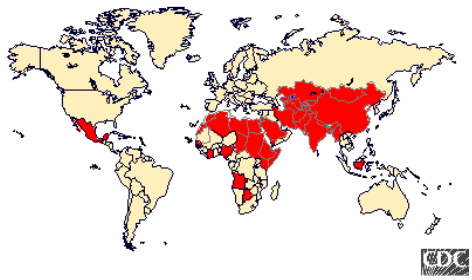
(HC = acute HC + chronic HC firstly diagnosed)

	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
HA	1195	904	933	614	325	127	114	70	322	132	128	1648	1104	862	264	284	348	673	724	930	772
HB	564	575	636	604	457	413	370	392	361	307	307	306	247	244	192	154	133	105	89	73	85
HC	273	448	634	637	798	858	846	868	844	1022	980	974	836	709	812	794	873	867	956	1104	992
HE	5	17	5	12	13	12	21	36	37	35	43	65	99	72	163	258	218	299	412	339	344

Previous theory about HE prevalance

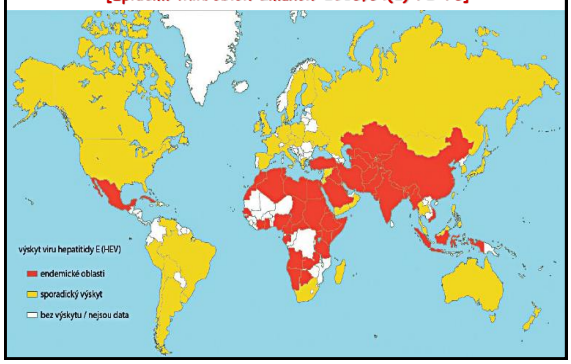
Geographic Distribution of Hepatitis E

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



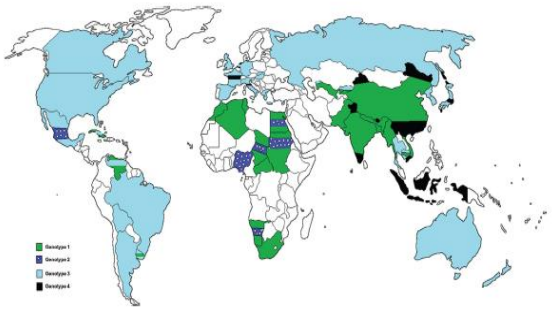
HE prevalence in the world

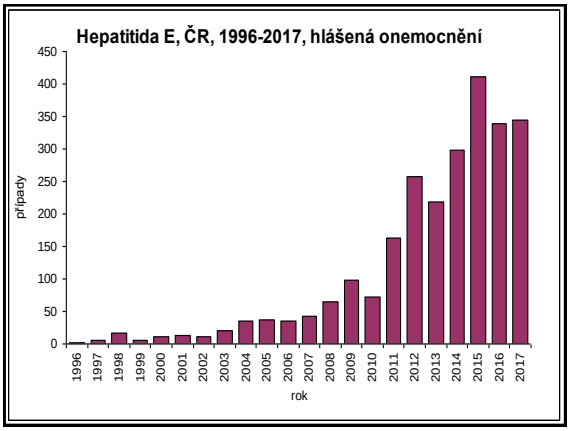
[Epidem. Mikrobiol. Imunol. 2015;64(2):72-78]

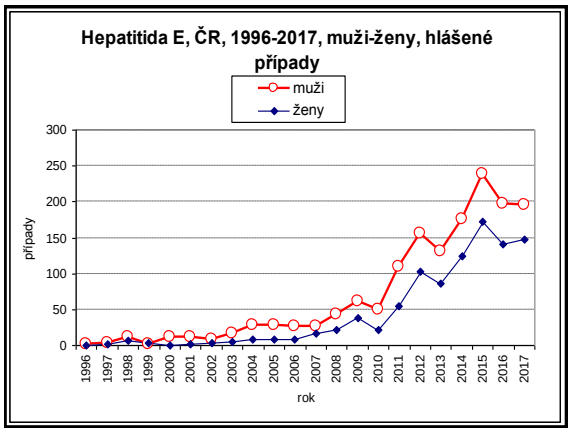


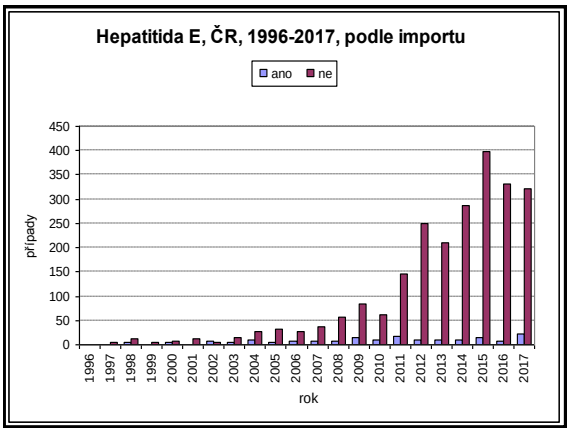
Genotypes of HE in the world

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









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. I Přehled vakcín proti VHA a VHB registrovaných v ČR

Hepatitis B: Some Sobering Facts

- 350 million people chronically infected
- 2 billion with evidence of past or present infection
- Country of origin is THE major risk factor

World Health Organization. Hepatitis B Fact Sheet. Centers for Disease Control and Prevention. CDC Health Information for International Travel 2012. New York: Oxford University Press; 2012.

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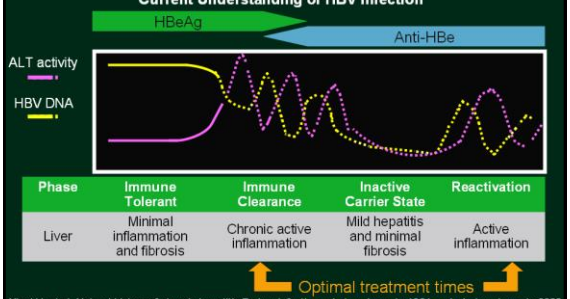
4 Phases of Chronic HBV Infection

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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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.

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Treatment of HCV with direct-acting antivirals (DAAs) may cause reactivation of HBV (*Clinical Practice Guidelines, EASL 2017*)

Patients fulfilling the standard criteria for HBV treatment should receive nucleos(t)ide analogue (NA) treatment

HBsAg-positive patients undergoing DAA therapy should be considered for concomitant NA prophylaxis until week 12 post DAA, and monitored closely

HBsAg-negative, anti-HBc positive patients undergoing DAA should be monitored and tested for HBV reactivation

J Hepatol 2017;67:370-98

HBV Reactivation (HBVr) Risk Based on Serologic Status and Immunosuppressive Potency

Risk Level (anticipated incidence of HBVr)	Serological Risk Status	Immunosuppressive Agent Risk Status
High (>10% of cases)	HBsAg+, high HBV DNA, or HBeAg+	▪ B-cell–depleting agents (are used in pts with leukemias, non-Hodgkin lymphoma, cryoglobulinemia, rheumatoid arthritis, idiopathic thrombocytopenic purpura) – rituximab (anti-CD20), ofatumumab ▪ Systemic chemotherapy ▪ Moderate/high-dose corticosteroids
Intermediate (1% to 10% of cases)	HBsAg-, anti-HBc+, anti-HBs-	▪ TNF inhibitors – etanercept, adalimumab, certolizumab, infliximab ▪ Tyrosine kinase inhibitors – imatinib, nilotinib ▪ Other cytokine and integrin inhibitors – abatacept,ustekinumab,natalizumab,vedolizumab ▪ Transarterial chemoembolization ▪ Low/moderate/high-dose corticosteroids
Low (<1% of cases)	HBsAg-, anti-HBc+, anti-HBs+ (anti-HBs positivity may provide additional protection against HBVr)	▪ Methotrexate ▪ Azathioprine ▪ 6-mercaptopurine ▪ Low-dose corticosteroids

high-dose corticosteroids (> 20 mg prednisone daily or equivalent) for ≥ 4 weeks or moderate-dose corticosteroids (10-20 mg prednisone daily or equivalent) for ≥ 4 weeks or low-dose corticosteroids (< 10 mg prednisone daily or equivalent) for ≥ 4 weeks.

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New nomenclature for the chronic states of HBV infection

- ***Phase 1:*** **HBeAg-positive chronic HBV infection previously *„immune tolerant" phase***
- ***Phase 2:*** **HBeAg-positive chronic hepatitis B**
- ***Phase 3:*** **HBeAg-negative chronic HBV infection previously termed *„inactive carrier" phase***
- ***Phase 4:*** **HBeAg-negative chronic hepatitis B**
- ***Phase 5:*** **HBsAg-negative phase also known as *„occult HBV infection"***

(J Hepatol 2017;67:370-98)

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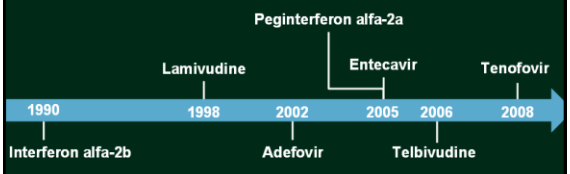
Evolution of Chronic HBV Therapy Over Time



Effects of interferon alfa

- IFN alfa inhibits the synthesis of viral nucleid acids and structural and nonstructural viral proteins
- Immunomodulatory effect:
  IFN alfa increases the activity of cytotoxic T lymphocytes (CTLs) and NK cells,
  stimulates T lymphocytes and macrophages to the production and secretion of next cytokines
- IFN alfa increases the expression of HLA antigens of the 1st class on the health and viral inficated cells and therefore inficated hepatocytes are then more sensitive to CTLs

Nucleos(t)ide analogues

*famciklovir – *analogue of deoxygunosin*
*lamivudine (3TC, LAM) – *analogue of deoxycytidin*
*adefovir dipivoxil (ADV) – *analogue of dAMP*
*tenofovir – *similar as ADV*
TDF = tenofovir disoproxil fumarate
TAF = tenofovir alafenamide
*entecavir (ETC) –*analogue of deoxyguanin*
*emtricitabine (FTC) – *analogue of cytosinu*
*clevudine (LFMAU) –*analogue of pyrimidin*
*telbivudine (LdT) – *analogue of L-deoxythymidin*

Indication for the treatment of HBV infection

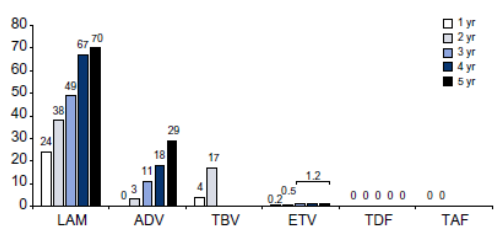
(EASL 2017 Clinical Practice Guidelines)

- HBV DNA >2,000 IU/ml
- Elevated ALT and/or at least moderate histological lesions (i.e. HBeAg-positive or HBeA-negative chronic HB)
- All cirrhotic patients with detectable HBV DNA
- The prevention of mother to child transmission in pregnant women with high viremia (i.e. > 200 000 IU/ml) *– Czech recommendation (from SEP 2017) is to use tenofovir (TDF) from 24th to 28th week of gravidity and stop this prophylaxis during the next 12 weeks after the birth*
- Prevention of HBV reactivation in patients requiring immunosuppression or chemotherapy
- Patients with HBeAg-positive chronic HBV infection with normal ALT and high HBV DNA (i.e. previously termed „immune tolerant" phase) if they are older than 30 years
- Patients with severe acute HB, characterised by coagulopathy or protracted course, should be treated with nucleos(t)ide analogue (NA) therapy and considered for liver transplantation
- Tenofovir (TDF) is recommended for pregnant women with CHB and advanced fibrosis or cirrhosis

Duration of the therapy of chronic HB

	HBeAg pos.	HBeAg neg.
PEG-IFN alfa	48 wks	48 wks
Nucleos(t)ide analogues (LAM,ADV,TDF,ETC)	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	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*)



Long-term Oral HBV Therapy is Highly Effective

- Suppresses HBV DNA[1,2]
- Normalizes ALT[2,3]
- Prevents fibrosis progression[3,4]
- Promotes fibrosis regression, even in cirrhosis[4]
- Prevents and even reverses hepatic decompensation[1]
- ***Reduces, but does not eliminate, the risk of HCC[1,5]***
- ***Long-term therapy is effective . . . but low rates of HBsAg loss[6]***

1. Lim YS, et al. Gastroenterology. 2014;147:152-161.2. Chang TT, et al. Hepatology. 2010;51:422-430. 3. Zoutendijk R, et al. Gut. 2013;62:760-765. 4. Marcellin P, et al. Lancet. 2013;381:468-475. 5. Papatheodoridis GV, et al. J Hepatol. 2015;62:363-370. 6. Papatheodoridis GV, et al. Hepatol. 2016;63:1481-1492.

Slide credit: clinicaloptions.com

Long-term Oral HBV Therapy: Downsides

- Toxicity
  - Potential for renal, bone complications with TDF
- Resistance
  - High with lamivudine (not preferred by guidelines)[1]
  - Very low with entecavir—unless already LAM resistant[2]
  - None with TDF in clinical trials (similar expected with TAF)[3]
- Cost
- Adherence

1. Hadziyannis SJ, et al. Hepatology. 2000 ;32:847-51.
2. 2. Gish SR, et al. Gastroenterology. 2007;133:1437-44. 3. Buti M, et al. Dig Dis Sci. 2015;60:1457-1464.

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PegIFN vs Nucleos(t)ide Analogues

PegIFN		Nucleos(t)ide Analogues	
Pro	Con	Pro	Con
▪ Finite course of therapy ▪ No resistance ▪ Higher rate of HBeAg loss in 1 yr ▪ Higher rate of HBsAg loss with short duration therapy*	▪ SQ administration ▪ Frequent AEs ▪ Contraindicated in patients with cirrhosis, in pregnancy, with acute hepatitis B, and who are immunosuppressed	▪ PO administration ▪ Infrequent AEs ▪ Safe at all stages of disease, including decompensated cirrhosis† ▪ Safe in immuno-compromised populations ▪ Selected drugs probably safe in pregnancy	▪ Need for long-term or indefinite therapy ▪ Potential for drug resistance

*Particularly for HBeAg-positive patients with genotype A infection.
†Recent case report of lactic acidosis in severe liver failure.

Lok AS, et al. Hepatology. 2007;45:507-539. Lok AS, et al. Hepatology. 2009;50:661-662. Lok AS. Hepatology. 2010;52:743-747. Buster EH, et al. Gastroenterology. 2008;135:459-467. Lange CM, et al. Hepatology. 2009;50:2001-2006.

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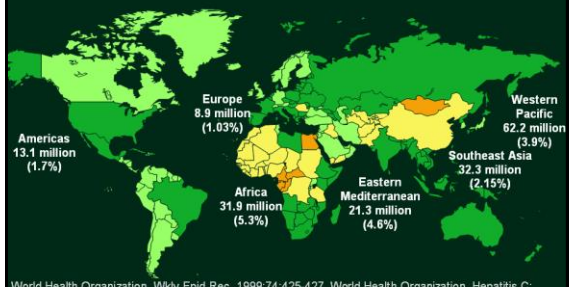
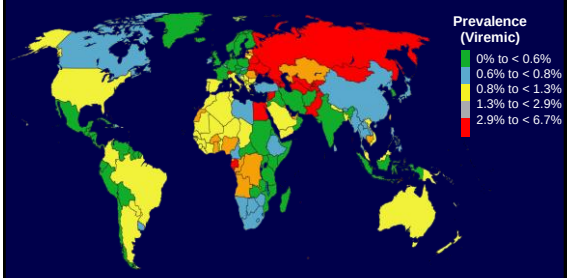
Screening: Identifying Estimated 170 Million Persons With HCV Infection Worldwide



World Health Organization. Wkly Epid Rec .1999;74:425-427. World Health Organization. Hepatitis C: Global Prevalence: Update. 2003. Farci P, et al. Semin Liver Dis. 2000;20:103-128. Wasley A, et al. Semin Liver Dis. 2000;20:1-16.

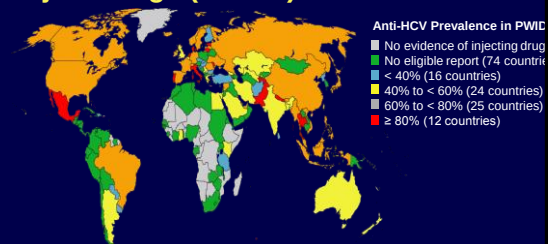
Estimated 70 Million Persons Living With HCV



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

Nelson P, et al. Lancet. 2011;378:571-583.

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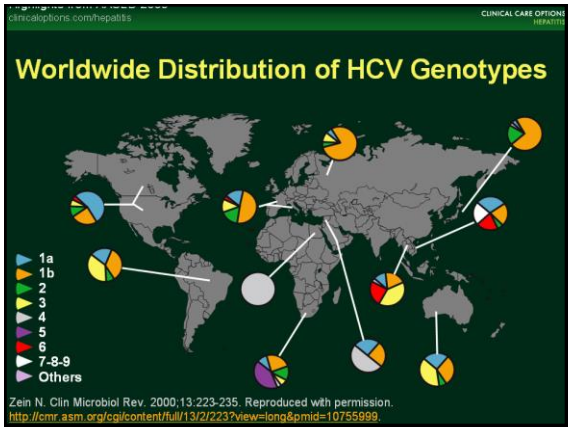
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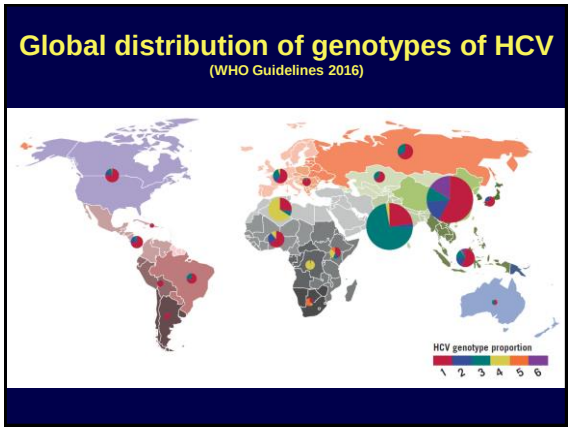
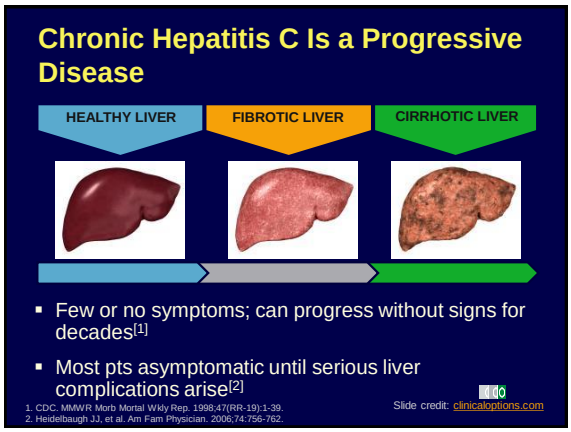
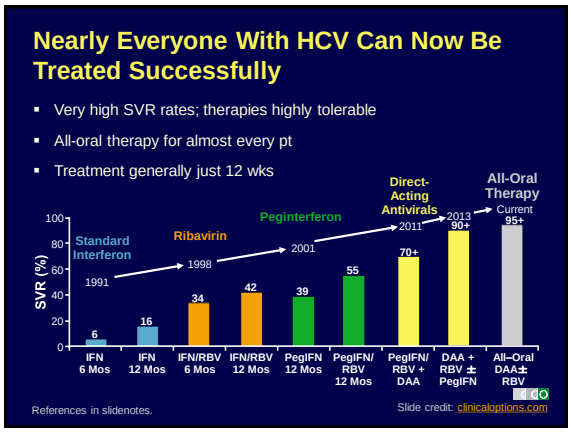
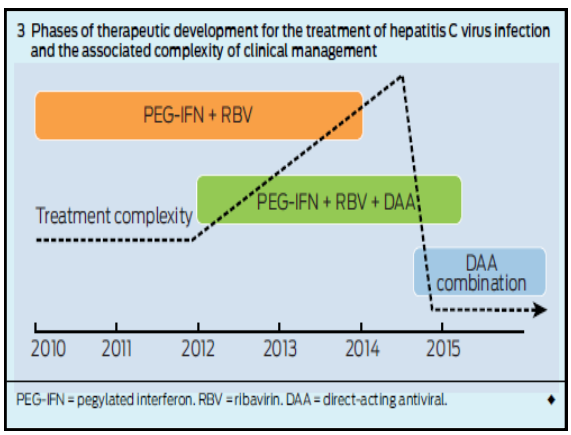
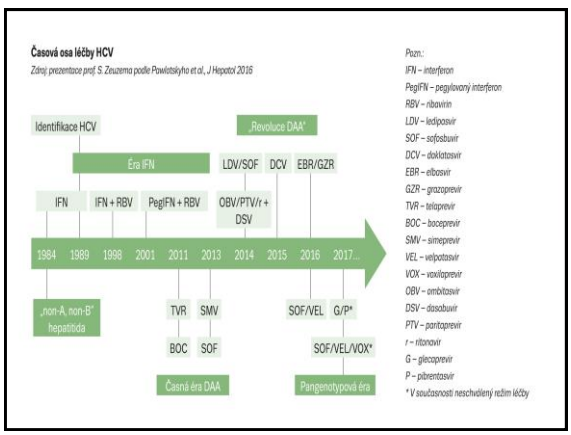
HEPATITIS
Worldwide Distribution of HCV Genotypes
1a
1b
2
3
4
5
6
7-8-9
Others
Zein N. Clin Microbiol Rev. 2000;13:223-235. Reproduced with permission.
http://cmr.asm.org/cgi/content/full/13/2/223?view=long&pmid=10755999.


Global distribution of genotypes of HCV
(WHO Guidelines 2016)
HCV genotype proportion
1 2 3 A 5 6

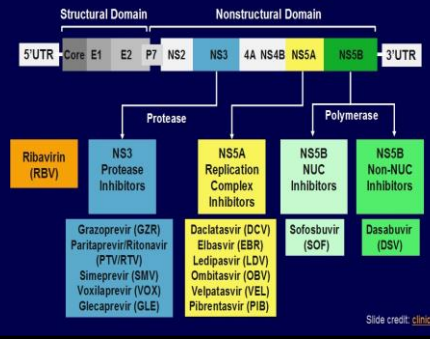

Chronic Hepatitis C Is a Progressive Disease
HEALTHY LIVER
FIBROTIC LIVER
CIRRHOTIC LIVER
Few or no symptoms; can progress without signs for decades[1]
Most pts asymptomatic until serious liver complications arise[2]
1. CDC. MMWR Morb Mortal Wkly Rep. 1998;47(RR-19):1-39.
2. Heidelbaugh JJ, et al. Am 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
SVR (%)
Standard Interferon
Ribavirin
Peginterferon
Direct-Acting Antivirals
All-Oral Therapy
1991
1998
2001
2011
2013
Current
6
16
34
42
39
55
70+
90+
95+
IFN 6 Mos
IFN 12 Mos
IFN/RBV 6 Mos
IFN/RBV 12 Mos
PegIFN 12 Mos
PegIFN/ RBV 12 Mos
PegIFN/ RBV + DAA
DAA + RBV ± PegIFN
All–Oral DAA± RBV
References in slidenotes.
Slide credit: clinicaloptions.com


3 Phases of therapeutic development for the treatment of hepatitis C virus infection and the associated complexity of clinical management
PEG-IFN + RBV
Treatment complexity
PEG-IFN + RBV + DAA
DAA combination
2010
2011
2012
2013
2014
2015
PEG-IFN = pegylated interferon. RBV = ribavirin. DAA = direct-acting antiviral.


Časová osa léčby HCV
Zdroj prezentace prof. S. Zeuzema podle Pawlotskyho et al., J Hepatol 2016
Identifikace HCV
„Revoluce DAA"
Éra IFN
LDV/SOF
DCV
EBR/GZR
IFN
IFN + RBV
PegIFN + RBV
OBV/PTV/r + DSV
1984
1989
1998
2001
2011
2013
2014
2015
2016
2017...
„non-A, non-B" hepatitida
TVR
SMV
BOC
SOF
SOF/VEL
G/P*
SOF/VEL/VOX*
Časná éra DAA
Pangenotypová éra
Pozn.:
IFN – interferon
PegIFN – pegylovaný interferon
RBV – ribavirin
LDV – ledipasvir
SOF – sofosbuvir
DCV – daklatasvir
EBR – elbasvir
GZR – grazoprevir
TVR – telaprevir
BOC – boceprevir
SMV – simeprevir
VEL – velpatasvir
VOX – voxilaprevir
OBV – ombitasvir
DSV – dasabuvir
PTV – paritaprevir
r – ritonavir
G – glecaprevir
P – pibrentasvir
* V současnosti neschválený režim léčby

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



Slide credit: clinicaloptions.com

EASL 2018 HCV Treatment Guidelines

- Recommendations for treatment-naive patients and patients previously treated with pegIFN/RBV ± SOF or SOF + RBV, ± 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

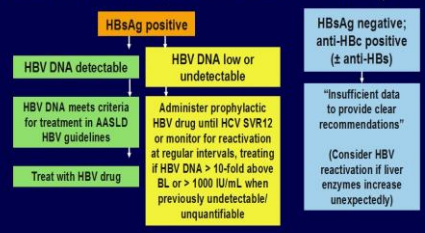
Dostupné varianty IFN-free režimů pro jednotlivé genotypy HCV (*DP ČHS ČLS JEP 2017*)

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)
grazoprevir+elbasvir = ZEPATIER™ (MSD)
sofosbuvir = SOVALDI™ (Gilead)
daclatasvir = DAKLINZA™ (BMS)
simeprevir = OLYSIO™ (Janssen)
(r) = ritonavir
sofosbuvir+velpatasvir+voxilaprevir = VOSEVI™ (Gilead)

HBV Testing/Monitoring During HCV DAA Therapy

- Test all pts initiating HCV therapy for HBsAg, anti-HBc, and anti-HBs
  - Vaccinate if no HBV markers; follow flow chart below if HBV markers present



AASLD/IDSA. HCV guidance. September 2017.

Slide credit: clinicaloptions.com

University of Liverpool hepatitis drug interactions website (*HEP Drug Interaction Checker*)

http://www.hep-druginteractions.org/

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
(Ther Adv Infect Dis 2016;3(1):3-14)

Immune-related extrahepatic manifestations
- Mixed cryoglobulinemia
- Cryoglobulinemic vasculitis
- B-cell NHL (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)