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Hépatites chroniques

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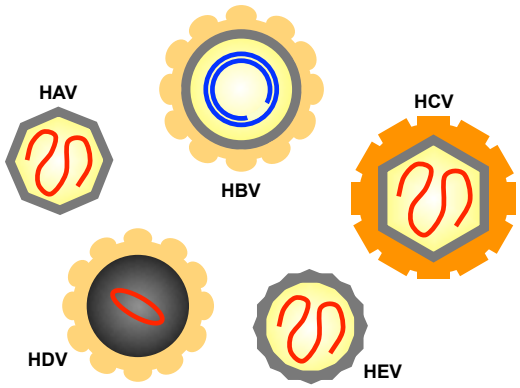
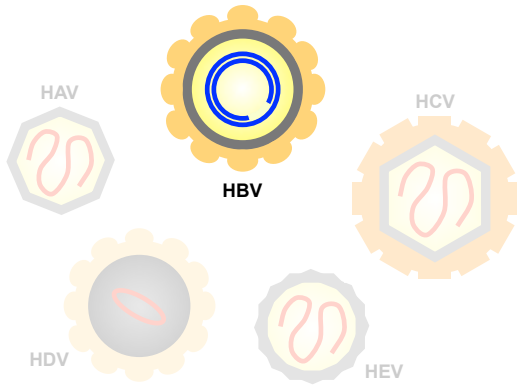
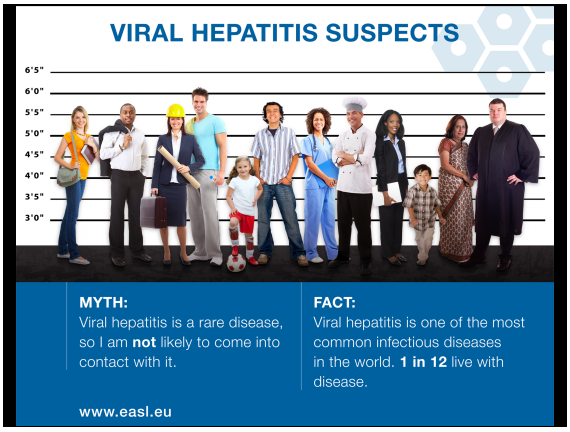
www.gastro-hepato.ch





The Inconvenient Truth about Hepatitis B

- HBV is one of the most common chronic infections worldwide.
- The natural history is very complex.
- Treatment indications and endpoints are evolving.
- HBV is never completely eliminated.
- High replication rate and low fidelity of viral rt as basis for antiviral resistance.
- Pipeline of new drugs very limited.



Health Care Provider-Initiated Testing for Chronic HBV Infection

A. Clinical signs or symptoms of hepatitis

B. Risk factors

- **Medical** (chronic liver disease, hemodialysis, persons with HIV infection or other STD, pts before immunosuppressive therapy, ...)
- **Demographic**
- **Behavioural** (family and household members, sexual partners, MSM, injecting drug use, ...)
- **Occupational**
- **Others** (newborns of HBV-infected mothers, institutionalized persons, imprisonement, ...)

www.sevhep.ch Fretz R *et al.* Swiss Med Wkly 2013;143:w13793.

Hépatite B
Diagnostic

- **Tests sérologiques**
  - **- HBsAg** infection aiguë ou chronique
  - **- anti-HBs** infection résolue / vaccination
  - **- anti-HBc** infection actuelle ou passée
  - **- HBeAg** réplication active
  - **- anti-HBe** infection inactive ou mutant
- **Tests moléculaires**
  - **HBV DNA**
  - **HBV génotypes**
  - **Tests de résistance**

Classification de l'infection HBV

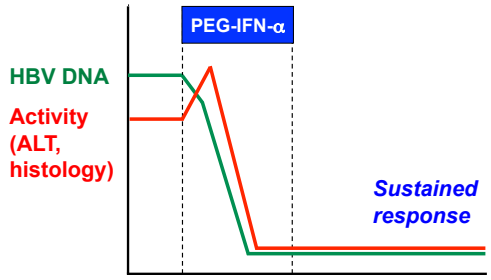
	HBsAg	HBeAg	HBV DNA[1)]	ALAT
Hép. B chron. HBeAg-pos.	+	+	10^5-10^9	↑
Hép. B chron. HBeAg-nég.	+	-	10^3-10^7	↑
Porteur inactif de l'HBsAg	+	-	< 2 x 10^3	=
Immunotolérant	+	+	10^7-10^{10}	=
Hépatite B résolue	- (anti-HBs)	-	-	=

Consid. ttt Suivi (ALAT ± AFP/US) Attn IS

[1)]IU/ml

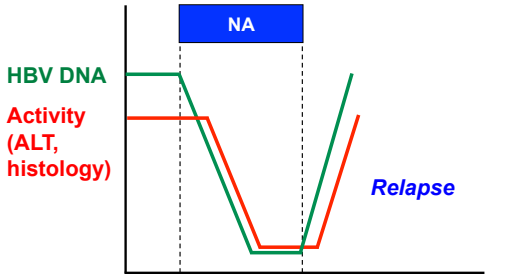
Adapté de Hoofnagle JH *et al.* Hepatology 2007;45:1056-1075, Lok ASF and McMahon BJ. Hepatology 2009;50:1-36 et EASL Clinical Practice Guideline. J Hepatol 2012;57:167-185.

Therapy of Chronic Hepatitis B
PEG-IFN-α



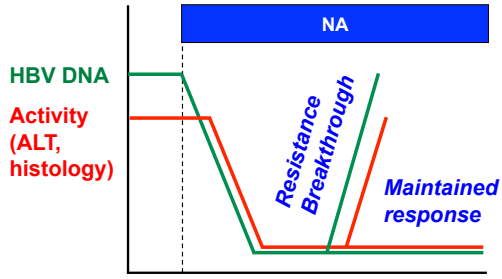
Adapted from Marcellin P *et al.* J Viral Hepat 2005;12:333-345.

Therapy of Chronic Hepatitis B
Nucleos(t)ide Analogs



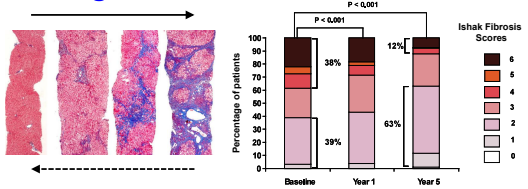
Adapted from Marcellin P *et al.* J Viral Hepat 2005;12:333-345.

Therapy of Chronic Hepatitis B
Nucleos(t)ide Analogs



Adapted from Marcellin P *et al.* J Viral Hepat 2005;12:333-345.

Regression of Cirrhosis in CHB



- n = 348 pts with CHB treated for ≥ 5 yrs with TDF, with baseline and 5-yr follow-up liver biopsy
- Decrease in fibrosis stage in 51%; 71 of the 96 cirrhotic pts (74%) no langer had cirrhosis
- High BMI associated with lack of cirrhosis regression

Marcellin P *et al.* Lancet 2013;381:468-475.
See also D'Ambrosio R *et al.* Hepatology 2012;56:532-543.
Liver biopsy images courtesy of Pierre Bedossa

Chronic Hepatitis B
Therapy 2013

PEG-IFN-α

Pro:
- Finite duration
- Durable response
- No resistance

Con:
- Moderate antiviral
- Adverse effects
- Contraindications

Nucleos(t)ide analogs

Pro:
- Potent antiviral
- Tolerability
- Expanded use

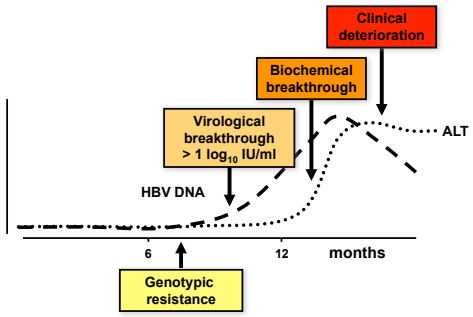
Con:
- Indefinite duration
- Resistance
- Long-term safety?

Doerig C *et al.* Rev Med Suisse 2010;6:168-173.
EASL Clinical Practice Guideline. J Hepatol 2012;57:167-185.

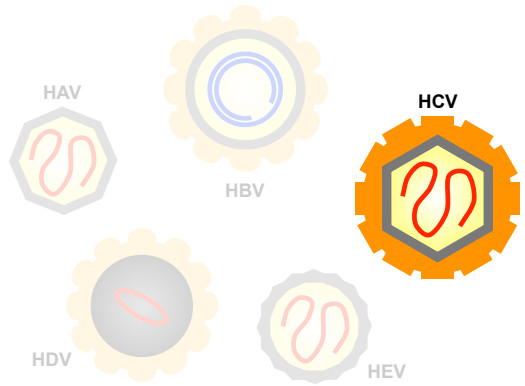
Chronic Hepatitis B
Therapy 2013

			Status CH 2013
PEG-IFN-α2a		Pegasys®	licensed 1st line
Lamivudine	LAM	Zeffix®	licensed 1st line
Adefovir	ADV	Hepsera®	licensed 2nd line
Telbivudine	LdT	Sebivo®	licensed 1st line
Entecavir	ETV	Baraclude®	licensed 1st line
Tenofovir	TDF	Viread®	licensed 1st line
Emtricitabine	FTC	+ TDF = Truvada®	licensed for HIV

Emergence of Antiviral Resistance



Doerig C *et al.* Rev Med Suisse 2009;5:203-208.



Significance of Hepatitis C

- 120-200 million chronically infected individuals worldwide
- 1% of the population in Switzerland
- > 50% are unaware of their infection
- Most common cause of chronic hepatitis, liver cirrhosis and HCC in the West
- Most common indication to liver transplantation
- Peak of disease burden expected ~2025

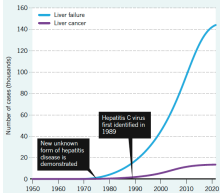
INTRODUCTION

A smouldering public-health crisis

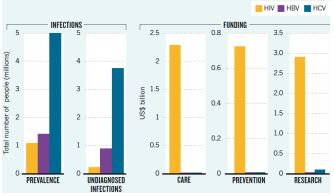
HEPATITIS C OUTLOOK

Long overshadowed by HIV, the hepatitis C virus is starting to take its toll. And the heat is on to find and treat those affected.

The coming problem



US response to HIV and viral hepatitis epidemics



Gravitz L. Nature 2011;474:S2-S4.
Edlin BR. Nature 2011;474:S18-S19.
www.nature.com/nature/outlook/hepatitis-c

Health Care Provider-Initiated Testing for Chronic HCV Infection

A. Clinical signs or symptoms of hepatitis

B. Risk factors

- **Medical** (recipients of blood products or solid organs before 1992, hemodialysis, persons with HBV or HIV infection, ...)
- **Demographic**
- **Behavioural** (injecting or intranasal drug use, MSM, sexual partners)
- **Occupational**
- **Others** (imprisonement, piercing or tattoos, children of HCV-infected mothers, ...)

www.sevhep.ch Fretz R *et al.* Swiss Med Wkly 2013;143:w13793.

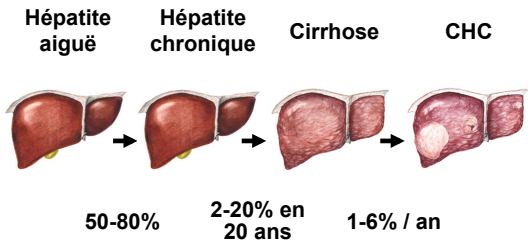
Centers for Disease Control and Prevention
MMWR Morbidity and Mortality Weekly Report
Recommendations and Reports / Vol. 61 / No. 4 August 17, 2012

Recommendations for the Identification of Chronic Hepatitis C Virus Infection Among Persons Born During 1945–1965

- Persons born between 1945 and 1965 account for ¾ of all HCV infections in the US
- Additional target population for HCV screening

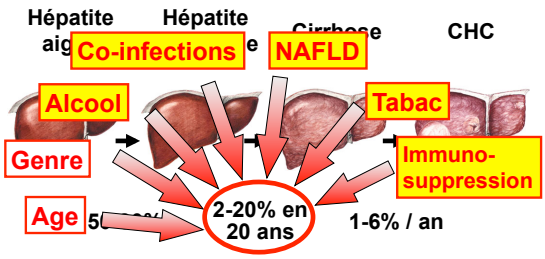
Smith BD *et al.* MMWR Recomm Rep 2012;61(RR-4):1-32.

Evolution de l'hépatite C



Basé sur EASL Clinical Practice Guideline. J Hepatol 2011;55:245-264, AASLD Practice Guideline. Ghany M *et al.* Hepatology 2011;54:1527-1537, SASL Expert Opinion Statement. Swiss Med Wkly 2012;142:w13516.

Cofacteurs de progression



Missiha SB *et al.* Gastroenterology 2008;134:1699-1714. Bihl F *et al.* Rev Med Suisse 2010;6:174-179.

Chronic Hepatitis C Role of Liver Biopsy

- Grading
- Staging → *treatment indication*
- Recognition of cofactors
- *Prediction of treatment outcome*

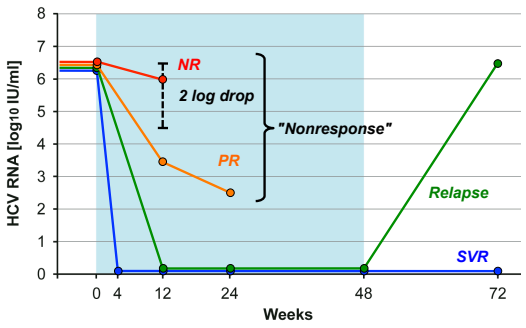
Staging of Chronic Hepatitis C

Fibrosis	Ishak	METAVIR
None	0	0
Portal fibrosis (some)	1	1
Portal fibrosis (most)	2	
Bridging fibrosis (few)	3	2
Bridging fibrosis (many)	4	3
Incomplete cirrhosis	5	4
Cirrhosis	6	

Ishak K *et al.* J Hepatol 1995;22:696; Bedossa P *et al.* Hepatology 1996;24:289.

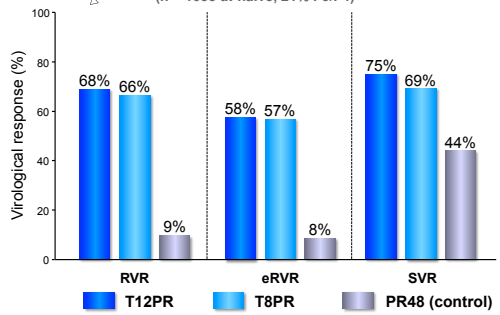
HCV ≠ HBV or HIV

Definition of Virological Response Patterns



ADVANCE

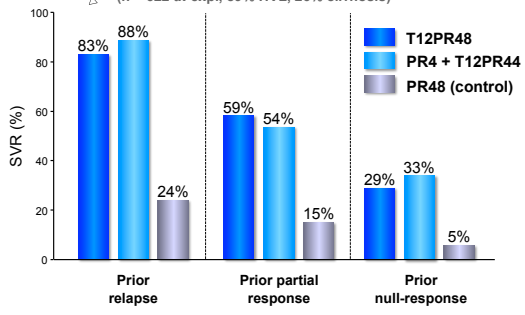
Telaprevir-based triple therapy
(n = 1088 tx-naïve, 21% F3/F4)



Jacobson IM *et al.* N Engl J Med 2011;364:2405-2416.

REALIZE

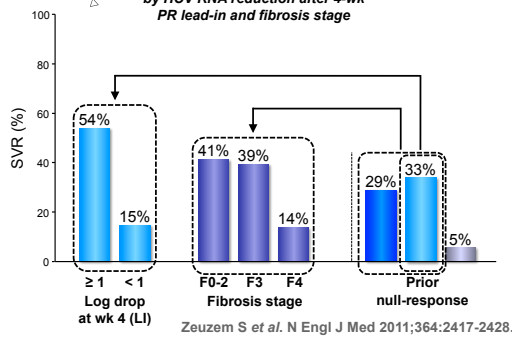
PEG-IFN-α2a + RBV ± TPV 750 mg q 8 h
(n = 622 tx-exp., 89% HVL, 26% cirrhosis)



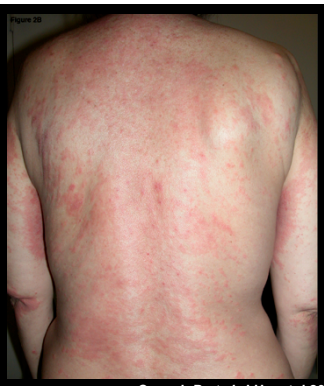
Zeuzem S *et al.* N Engl J Med 2011;364:2417-2428.

REALIZE

SVR in prior null-responders by HCV RNA reduction after 4-wk PR lead-in and fibrosis stage



Zeuzem S *et al.* N Engl J Med 2011;364:2417-2428.



Cacoub P *et al.* J Hepatol 2012;56:455-463.
Roujeau JC *et al.* JAMA Dermatol 2013;149:152-158.

Treatment of CHC Genotype 1 With Triple Therapy Comprising TPV or BOC

- SVR rates increased to ~70%, with shortened treatment duration in ~½
- Advances come at the expense of new adverse effects and increased cost
- Antiviral therapy has become much more complex (patient education, adherence, treatment milestones, AE management, DDIs, laboratory turnaround time, resistance)
- Resources are stretched

Swiss Association for the Study of the Liver. SMW 2012;142:w13516.
Hézode C *et al.* J Hepatol 2013;59:434-441.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Outcomes of Treatment for Hepatitis C Virus Infection by Primary Care Providers

- ECHO model to improve access to care for under-served populations with complex health problems
- Training of primary care providers by videoconferences
- UNM HCV Clinic (n = 146) *vs.* 21 ECHO sites (n = 261) in rural areas and prisons in New Mexico
- SVR 58% *vs.* 58% (genotype 1 46% *vs.* 50%)
- Rate of SAEs 14% *vs.* 7%

Arora S *et al.* N Engl J Med 2011;364:2199-2207.

What is the Goal?

- Interferon-free combination therapy
- High barrier to antiviral resistance
- Once daily oral therapy
- Pan-genotypic antiviral activity
- Reasonable safety and minimal drug-drug interactions
- Short duration (12 weeks)
- SVR rates > 90%

Inspired by Jordan Feld and Donald Jensen

HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases
EDITORIALS

Informed Deferral: A Moral Requirement for Entry Into the Hepatitis C Virus Treatment Warehouse

Defer treatment
- Early fibrosis stages (slow progression)
- Toxicity of triple therapy
- Promising more potent DAAs

« Treat now »
- Inability to accurately predict fibrosis progression
- Availability (when?) of new DAAs?
- Adverse effects of new DAAs?
- Efficacy in cirrhotics and previous NR?

Aronsohn A and Jensen D. Hepatology 2012;56:1591-1592.
Moradpour D and Frossard J-L. Rev Med Suisse 2013, in press.

Key Points

- Screen persons at risk (HBsAg, anti-HCV)
- Liaise with expert → collaboration
- Deliberate treatment indication crucial (Treat the disease, not the infection!)
- Duration of current treatment for CHB is often indefinite (monitoring, adherence)
- Current triple therapy of CHC gt 1 increases SVR rates to ~70%, with shortened treatment duration in ~½

Key Points

- Advances come at the expense of new adverse effects and involve challenging treatment regimens
- Transition period → informed deferral
- The future is around the corner and looks bright!
- Collaboration between primary care physicians and specialists is more important than ever

Diagnostic différentiel et investigation d'une perturbation chronique des tests hépatiques

Cause	Diagnostic primaire	Diagnostic complémentaire
Hépatite alcoolique	Anamnèse	PBF
Hépatite médicamenteuse	Anamnèse	PBF
Hépatite virale	HBsAg; anti-HCV	HBeAg/anti-HBe, HBV-DNA; anti-HDV, HDV-RNA; HCV-RNA, génotype HCV; PBF
Stéatohepatite non-alcoolique (NASH)	Syndrome métabolique, exclusion d'autres causes	PBF
Hépatite auto-immune	Auto-anticorps anti-nucléaires et anti-muscle lisse, électrophorèse	Exclusion d'autres causes, IgG, anti-LKM1, anti-SLA, PBF
Cirrhose biliaire primitive (CBP) et cholangite primaire sclérosante (CPS)	Auto-anticorps anti-mitochondries (CBP); cholangio-IRM (CPS)	anti-M2, IgM (CBP); coloscopie, év. ERCP (CPS)
Hémochromatose héréditaire	Ferritine, CST	Test génétique (gène *HFE*), év. PBF
Maladie de Wilson	Céruloplasmine	Cuprurie de 24 h, examen ophthalmologique (anneau de Kayser-Fleischer), PBF avec dosage du cuivre, test génétique
Déficit en α1-antitrypsine	Electrophorèse, α1-antitrypsine	Focalisation iso-électrique, test génétique
Hépatopathie vasculaire	Examen clinique (congestion cardiaque D), US-Doppler (syndrome de Budd-Chiari)	Examen cardiologique, examen d'hémostase
Maladie coeliaque	anti-tTG	Biopsie duodénale
Dysfonction thyroïdienne	TSH	Examen endocrinologique

Anti-LKM1, auto-anticorps contre les *liver kidney microsomes*; anti-SLA, auto-anticorps contre le *soluble liver antigen*; anti-tTG, auto-anticorps contre la *tissue transglutaminase*; PBF, ponction biopsie du foie.