Intesto FR
Centre Fribourgeois de Gastroentérologie
Freiburger Zentrum für Gastroenterologie

Les hépatites virales

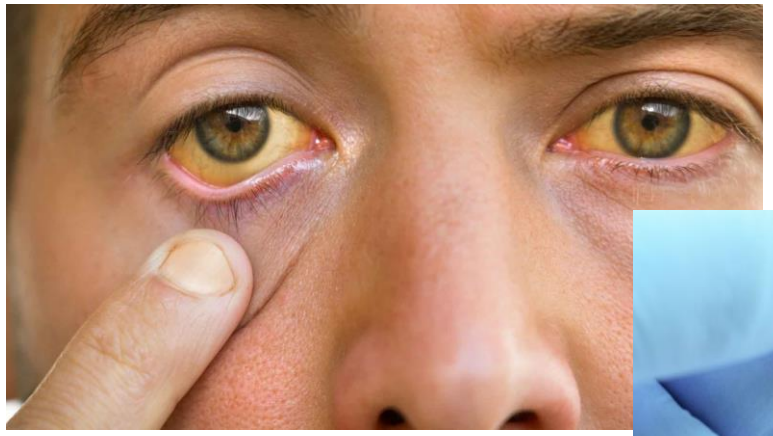
Konstantin Burgmann

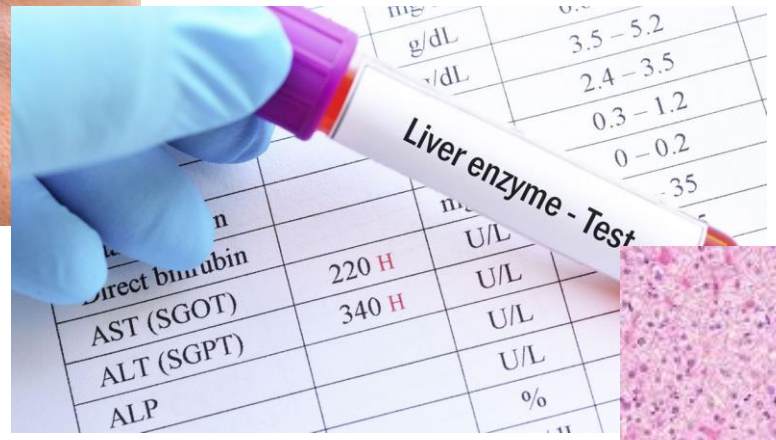
7 mars 2024

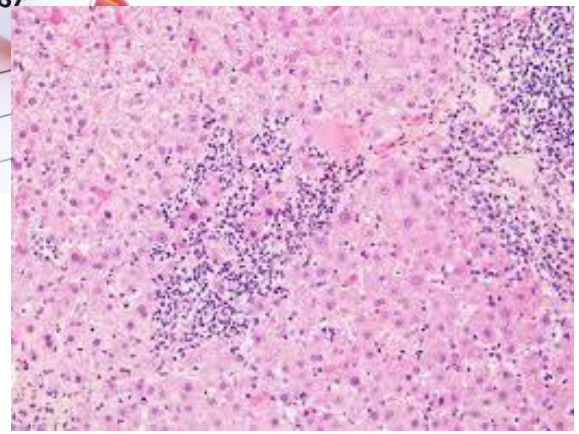
ARL Association des Responsables de Laboratoire de Suisse romande

Introduction

L’hépatite

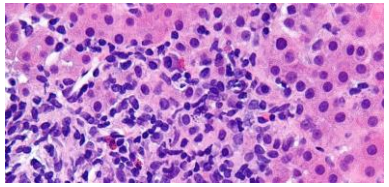


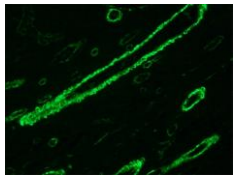

Liver enzyme - Test
AST (SGOT)
ALT (SGPT)
ALP
220 H
340 H
U/L
%
3.5 – 5.2
2.4 – 3.5
0.3 – 1.2
0 – 0.2

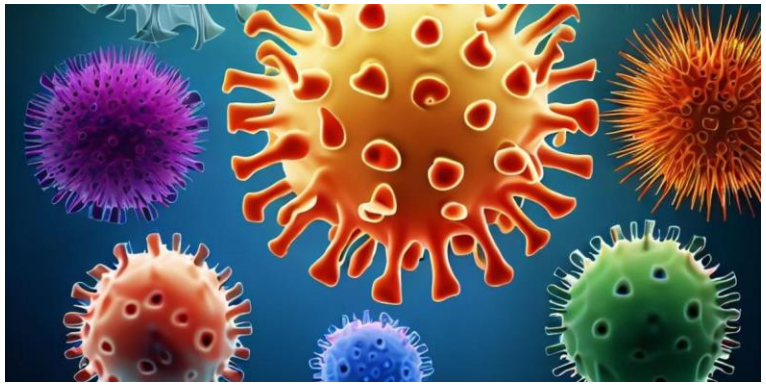


L'hépatite

- Toxique
- Métabolique
- Autoimmune
- Virale
- …







L’hépatite virale

A acute

B boring

C cured

D devil

E emerging

L’hépatite virale

B boring

C cured

E emerging

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L’hépatite B

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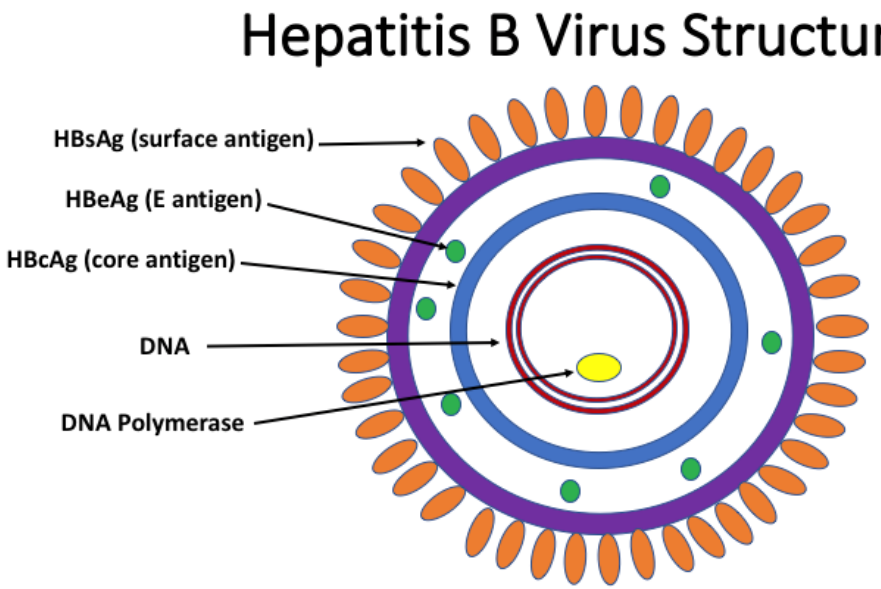
Le virus de l'hépatite B

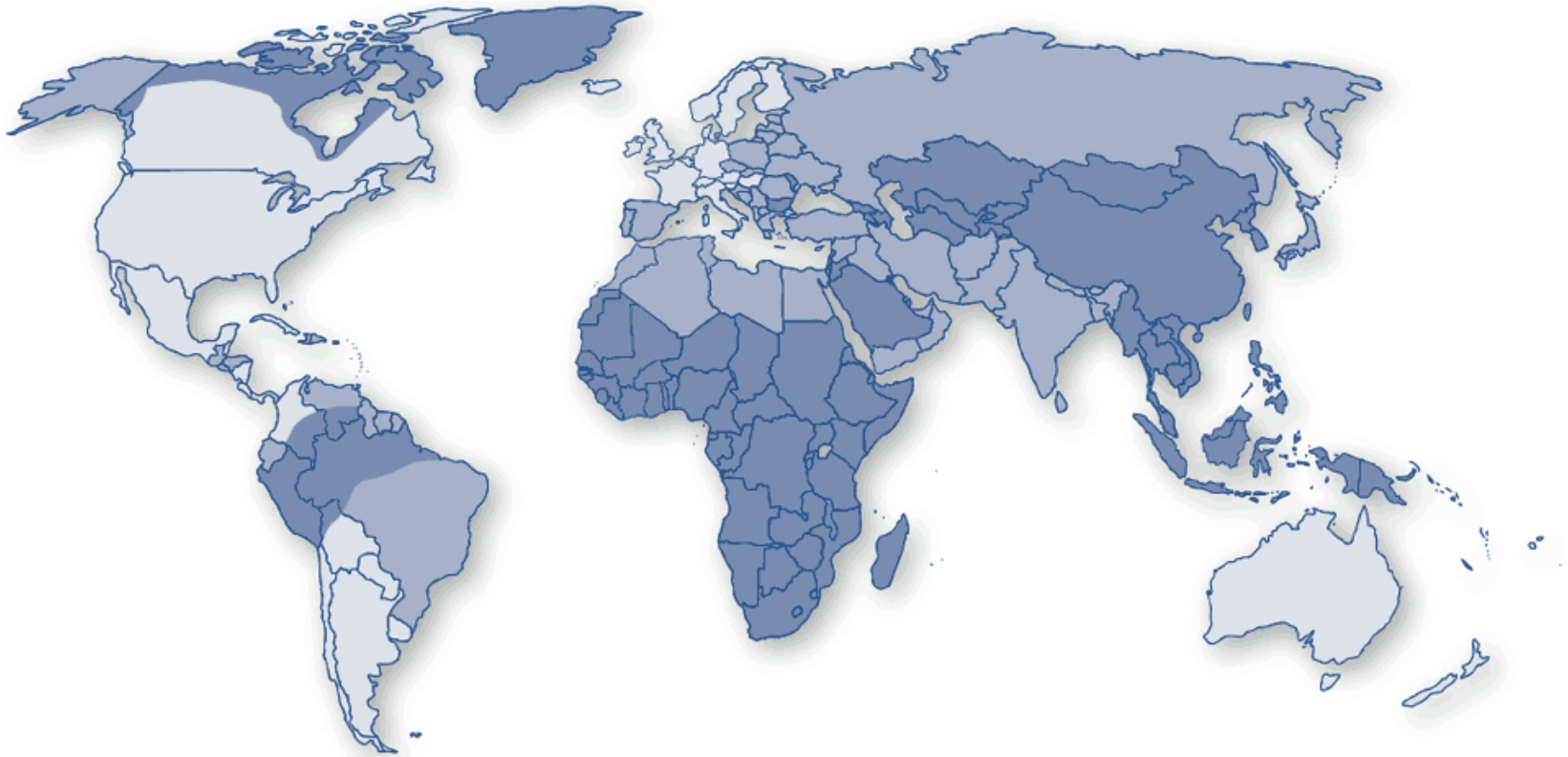


- Famille: Hep**adn**aviridae
- Humain, dans les hépatocytes

- Transmission par sang, salive, sperme/sécrétions vaginales; verticale (mère/enfant)
- Facilement transmissible:

  HBV > HCV > HIV

Prevalence of Hepatitis B Virus Chronic Infection, 2006



Prevalence of hepatitis B surface antigen

- Low <2%
- Intermediate 2% - 7%
- High ≥8%

Acknowledgment: Adapted from Centers for Disease Control and Prevention

HBV Incidence by Year, United States

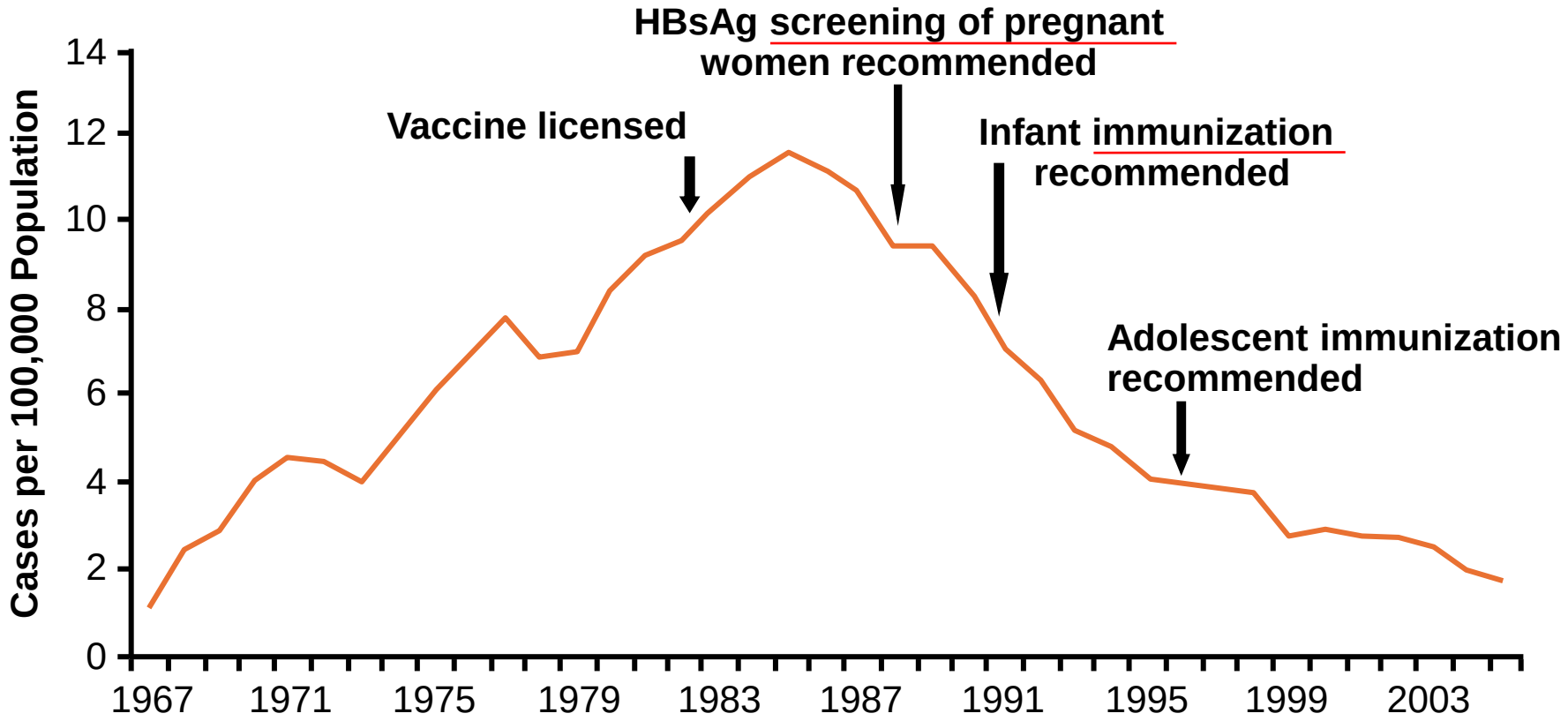


FIGURE 1. Typical serologic course of acute hepatitis B virus infection with recovery

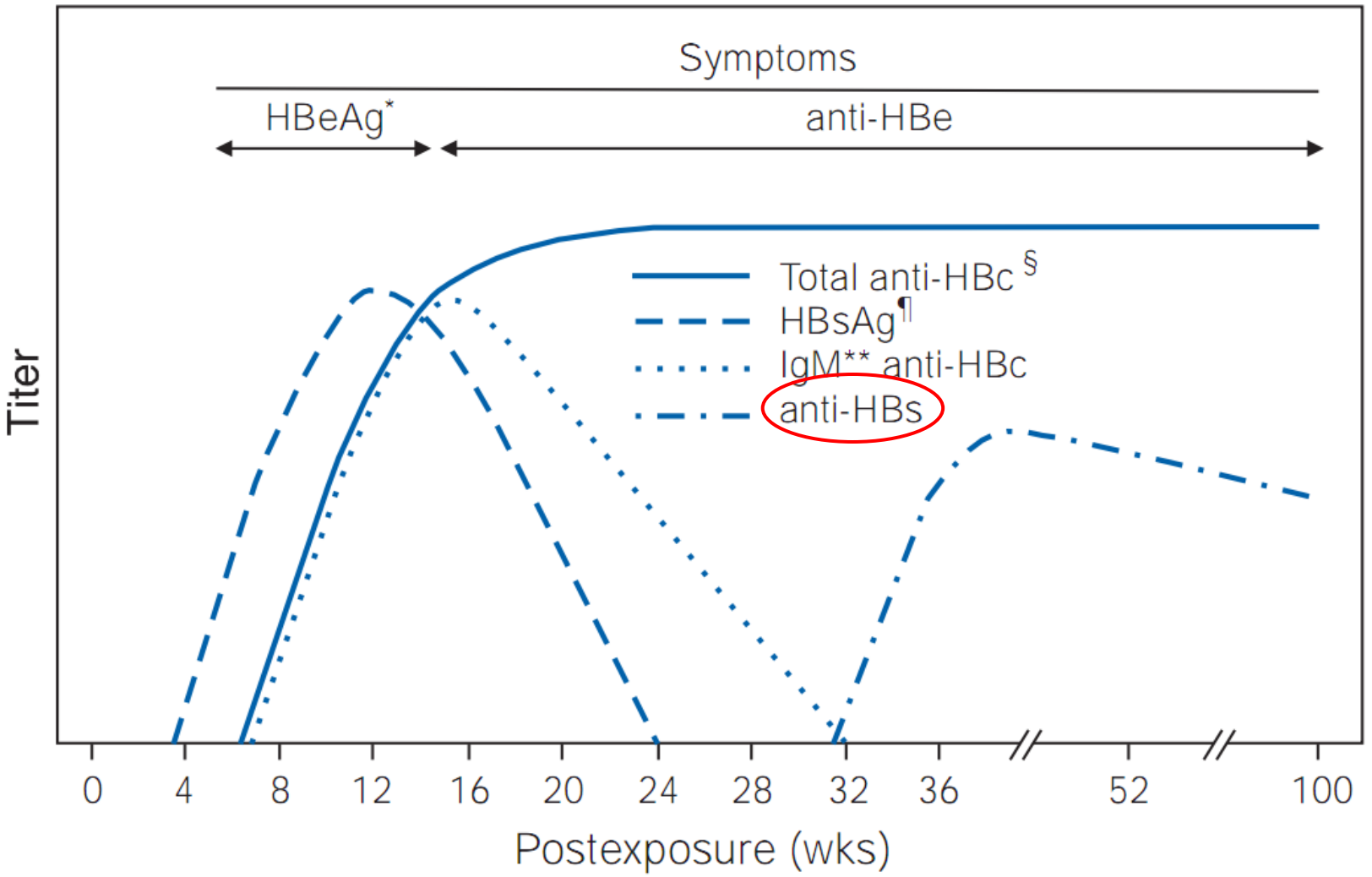
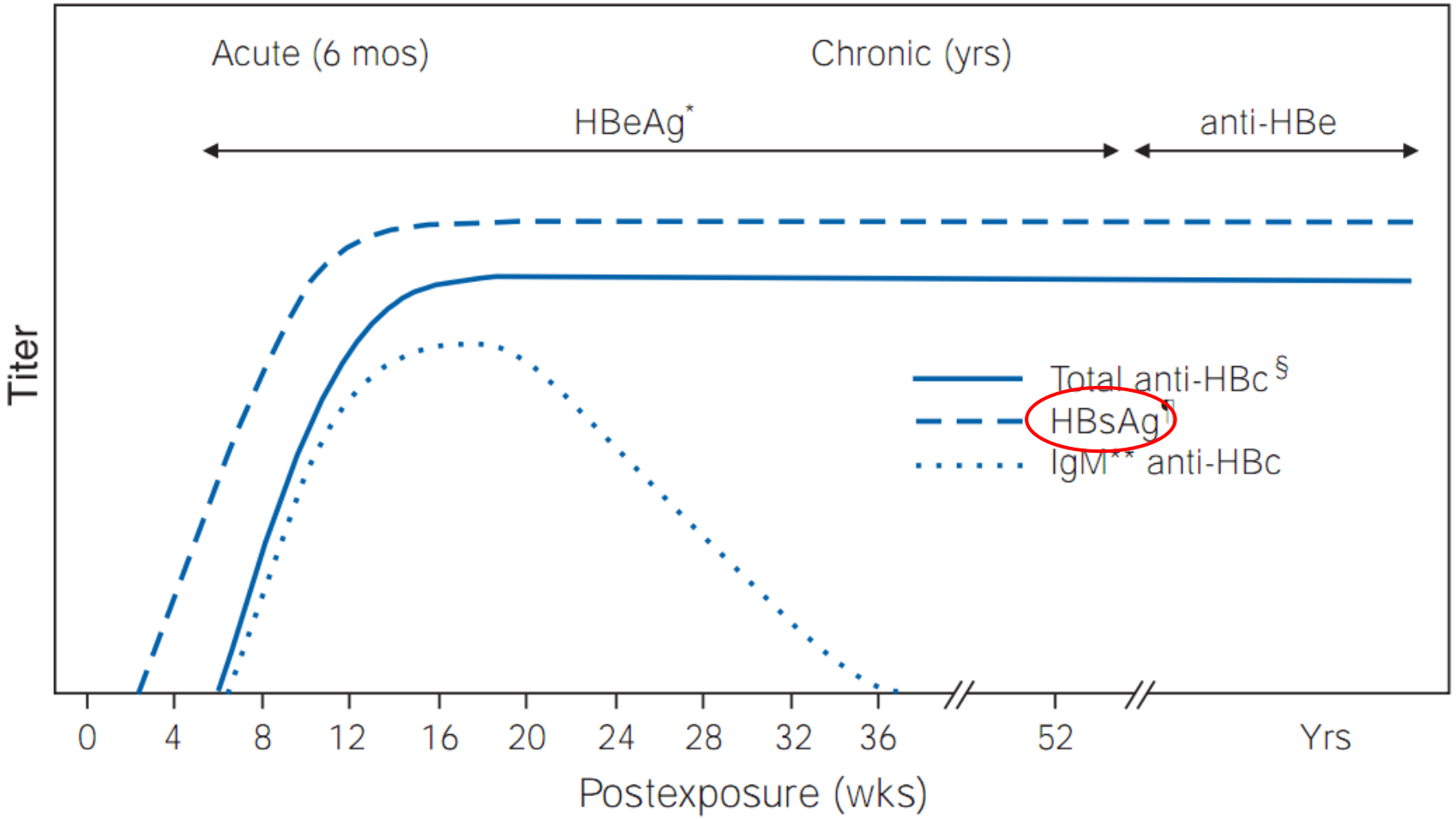
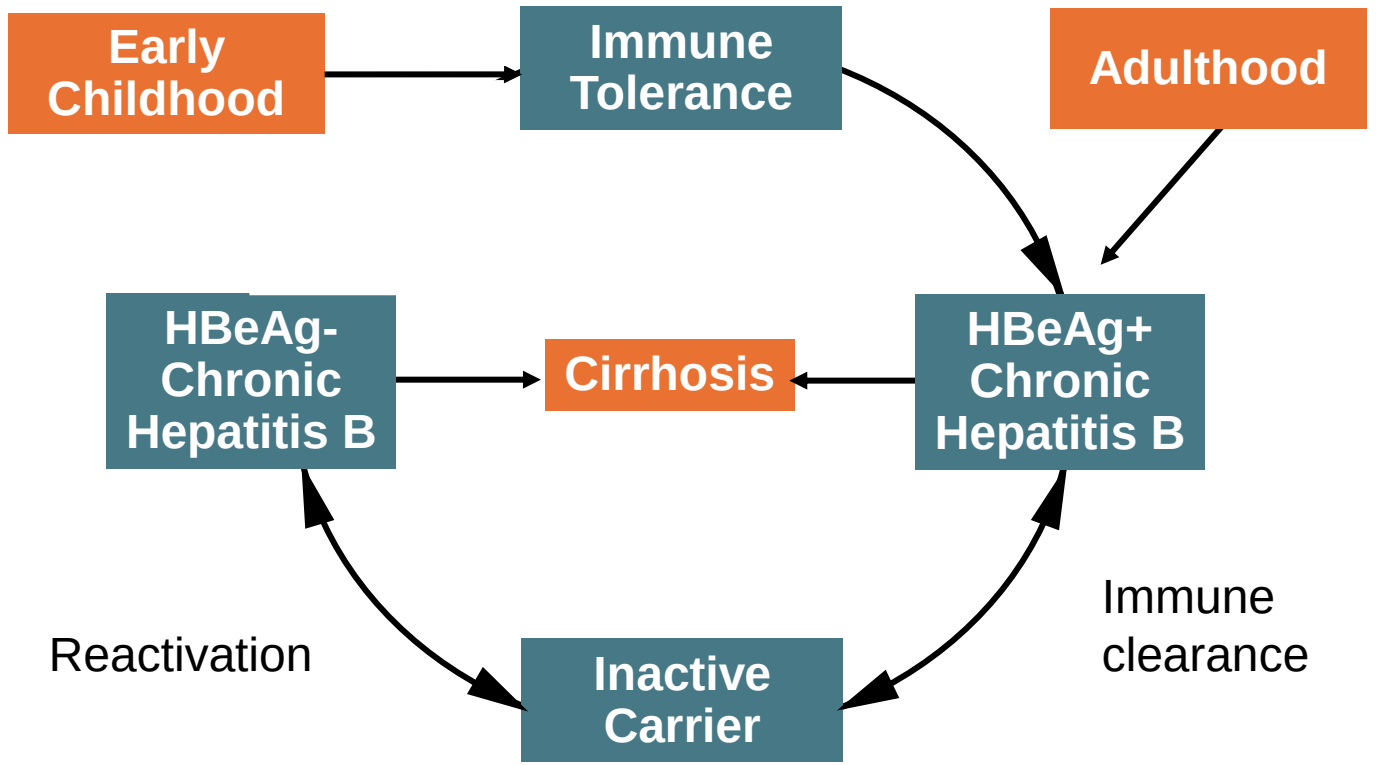


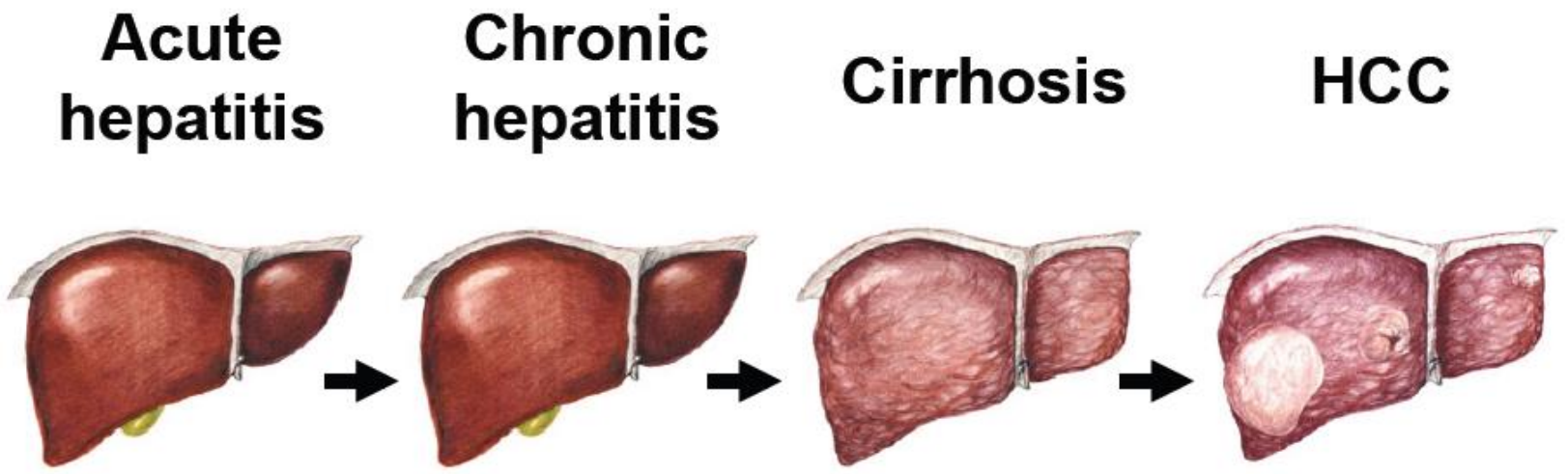
FIGURE 2. Typical serologic course of acute hepatitis B virus (HBV) infection with progression to chronic HBV infection



Histoire naturelle de l'infection chronique HBV



Natural History of Hepatitis B



Dépistage de l'hépatite B

Etape 1

- HBsAg
- anti-HBs
- anti-HBc

Etape 2 (si ABsAg pos)

- HBV-DNA par PCR (virémie)
- HBeAg et anti-HBe
- Dépistage HDV

Classification of HBV Infection

	HBsAg	HBeAg	HBV DNA[1)]	ALT	
HBeAg-pos. CHB	+	+	10^5-10^9	↑	HEPATITE
HBeAg-neg. CHB	+	-	10^3-10^7	↑	
Inactive carrier	+	-	$< 2 \times 10^3$	=	INFECTION
"Immune tolerant"	+	+	10^7-10^{10}	=	
Resolved hepatitis B (anti-HBs)	-	-	-	=	

Consider tx Follow (ALT ± AFP/US) Attn IS

[1)] IU/ml

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

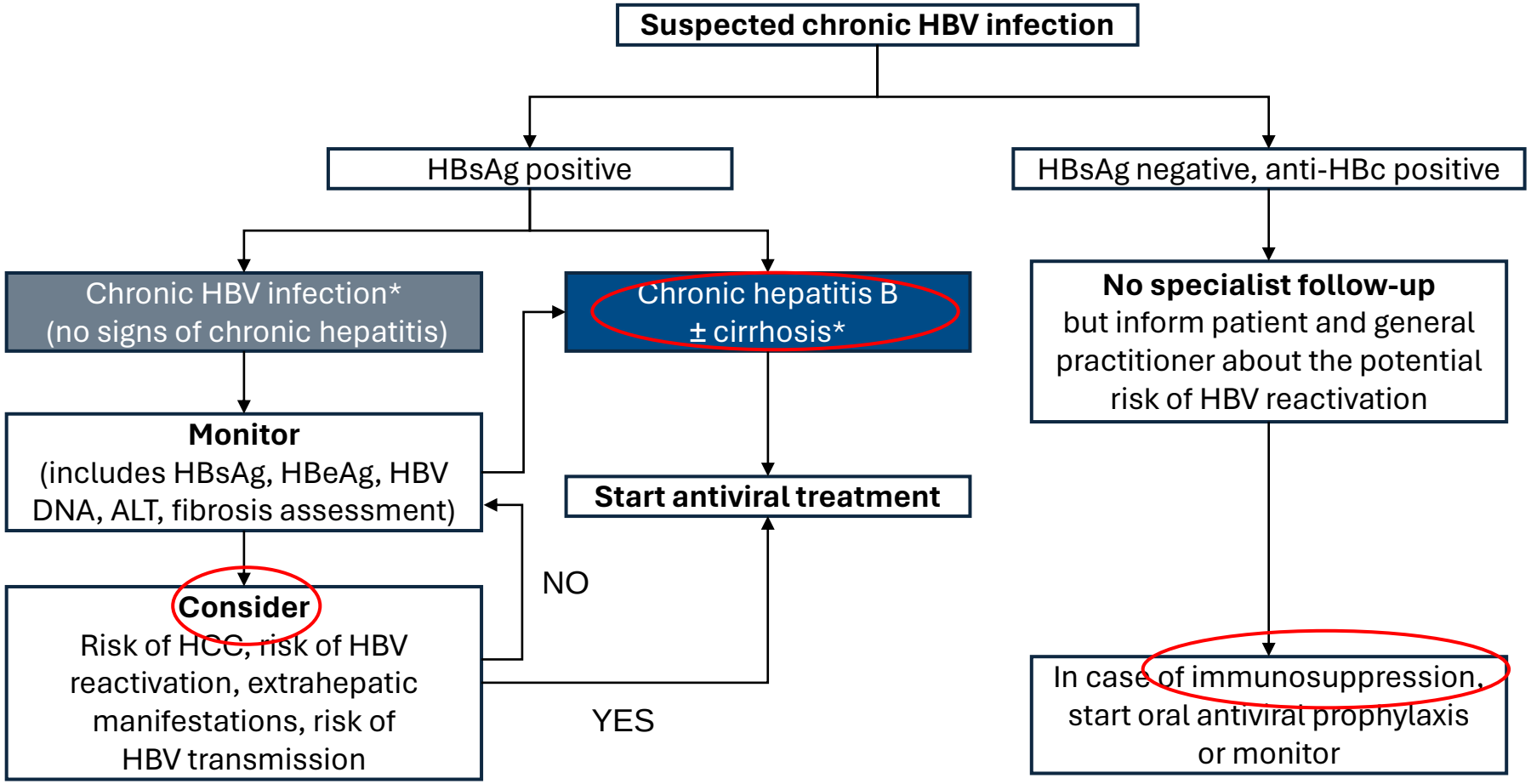
TTT indiqué

(basé sur 3 paramètres: virémie, transaminases, fibrose)

Recommendations	Grade of evidence	Grade of recommendation
Should be treated		
• Patients with HBeAg-positive or -negative chronic hepatitis B*	I	1
• Patients with cirrhosis, any detectable HBV DNA, regardless of ALT level	I	1
• Patients with HBV DNA >20,000 IU/mL and ALT >2x ULN, regardless of severity of histological lesions	II-2	1
May be treated		
• Patients with HBeAg-positive chronic HBV infection† >30 years old, regardless of severity of liver histological lesions	III	2
Can be treated		
• Patients with HBeAg-positive or -negative chronic HBV infection and family history of HCC or cirrhosis and extrahepatic manifestations‡	III	2

*Defined by HBV DNA >2,000 IU/ml, ALT >ULN and/or at least moderate liver necroinflammation (A2) or fibrosis (F2);
†Defined by persistently normal ALT and high HBV DNA levels;
‡Even if typical treatment indications are not fulfilled

Algorithme pour l'infection chronique



EASL CPG HBV. J Hepatol 2017;67:370–98

HBV et immunosuppression

Tableau 1. Risque de poussée du VHB dans un contexte d'immunosuppression
HBsAg: antigène HBs; anti-HBc: anticorps anti-HBc; MTX: méthotrexate; +: positif; -: négatif.

Situations cliniques	HBsAg ou ADN viral +	HBsAg -, anti-HBc +	Anti-HBs+, HBsAg-
		ADN viral -	
	= infection chronique	= presque guéri / faux+	= « guéri »
Immunosuppression à base de rituximab	Risque élevé	Risque modéré	Risque faible
Immunosuppression pour maladies auto-immunes (par exemple: agents biologiques, MTX, azathioprine)	Risque élevé	Risque faible	Risque faible
Traitements de corticoïdes de courte durée (<2 semaines)	Risque faible	Risque faible	Risque faible

Rev Med Suisse 2013; 9: 1566-71

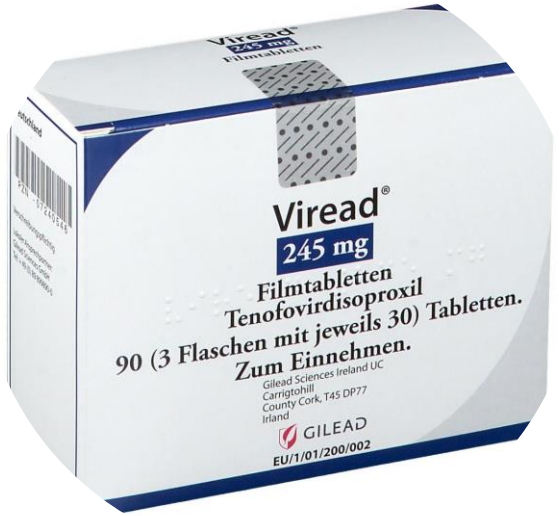
Risque élevé/modéré : traitement prophylactique

Risque faible : surveillance biologique (transaminases, virémie HBV) si traitement >1 mois

Features	PegIFNα	ETV, TDF, TAF
Route of administration	Subcutaneous injections	Oral
Treatment duration	48 weeks	Long-term until HBsAg loss*
Tolerability	Low	High
Long-term safety concerns	Very rarely persistence of on-treatment AEs†	Probably not‡
Contraindications	Many§	None‖
Strategy	Induction of a long-term immune control	Inhibition of viral replication
Level of viral suppression	Moderate	Universally high
Effect on HBeAg loss	Moderate¶	Low in first year, moderate over long term
Effect on HBsAg levels	Variable¶	Low**
Risk of relapse after treatment cessation	Low for those with sustained response 6–12 months after therapy	Moderate if consolidation treatment provided after HBeAg seroconversion. High for HBeAg-negative disease
Early stopping rules	Yes	No
Risk of viral resistance	No	Minimal to none††

*Stopping NAs after some years might be considered in selected cases; †Psychiatric, neurological, endocrinological; ‡Uncertainties regarding kidney function, bone diseases for some NAs; §Decompensated disease, comorbidities etc.; ‖Dose adjustments in patients with eGFR <50 ml/min are required for all NAs except for TAF (no dose recommendation for TAF in patients with CrCl <15 ml/min who are not receiving haemodialysis); ¶Depending on baseline characteristics; **Slowly increases with treatment time in HBeAg-positive patients (a plateau in serological responses has been observed beyond treatment Year 4), usually very low in HBeAg-negative patients; ††So far no TDF or TAF resistance development has been detected

EASL CPG HBV. J Hepatol 2017;67:370–98



env. 500 CHF par mois

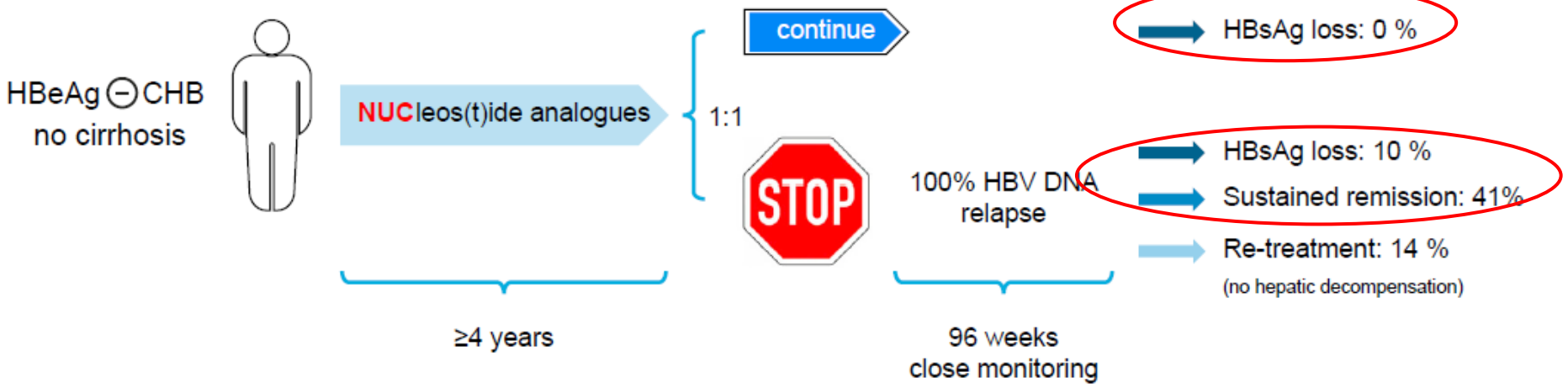
Research Article
Viral Hepatitis

JOURNAL
OF HEPATOLOGY

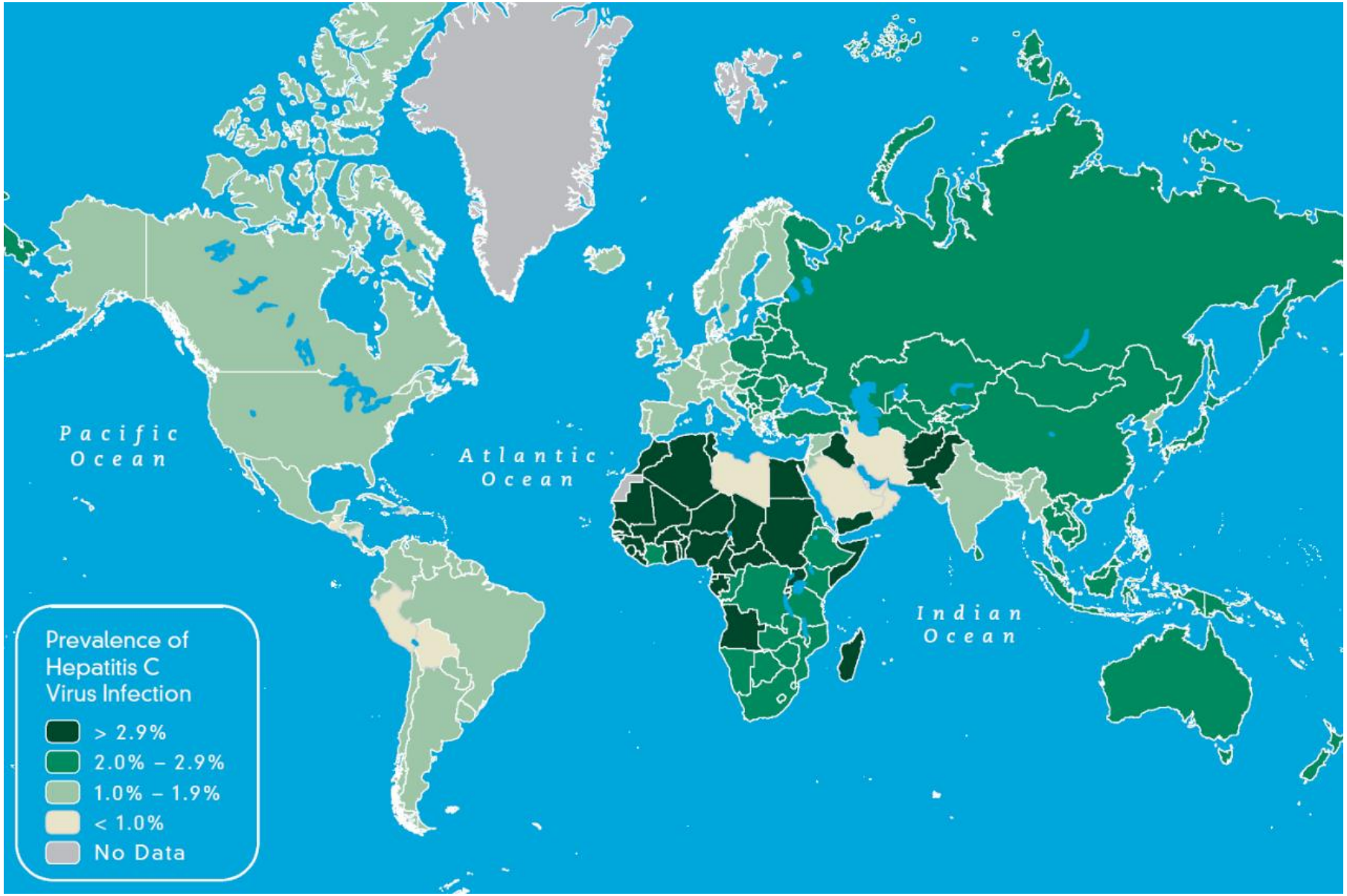
A multicenter randomized-controlled trial of nucleos(t)ide analogue cessation in HBeAg-negative chronic hepatitis B

Florian van Bömmel[1,*], Kerstin Stein[2], Renate Heyne[3], Jörg Petersen[4], Peter Buggisch[4], Christoph Berg[5], Stefan Zeuzem[6], Andreas Stallmach[7], Martin Sprinzl[8], Eckart Schott[9,10], Anita Pathil-Warth[6,11], Ulrike von Arnim[12], Verena Keitel[12,13], Jürgen Lohmeyer[14], Karl-Georg Simon[15], Christian Trautwein[16], Andreas Trein[17], Dietrich Hüppe[18], Markus Cornberg[19,20], Frank Lammert[19,21], Patrick Ingiliz[22,23], Reinhart Zachoval[24], Holger Hinrichsen[25], Alexander Zipprich[7,26], Hartmuth Klinker[27], Julian Schulze zur Wiesch[28], Anett Schmiedeknecht[29], Oana Brosteanu[29,‡], Thomas Berg[1,‡]

Journal of Hepatology **2023**. vol. 78



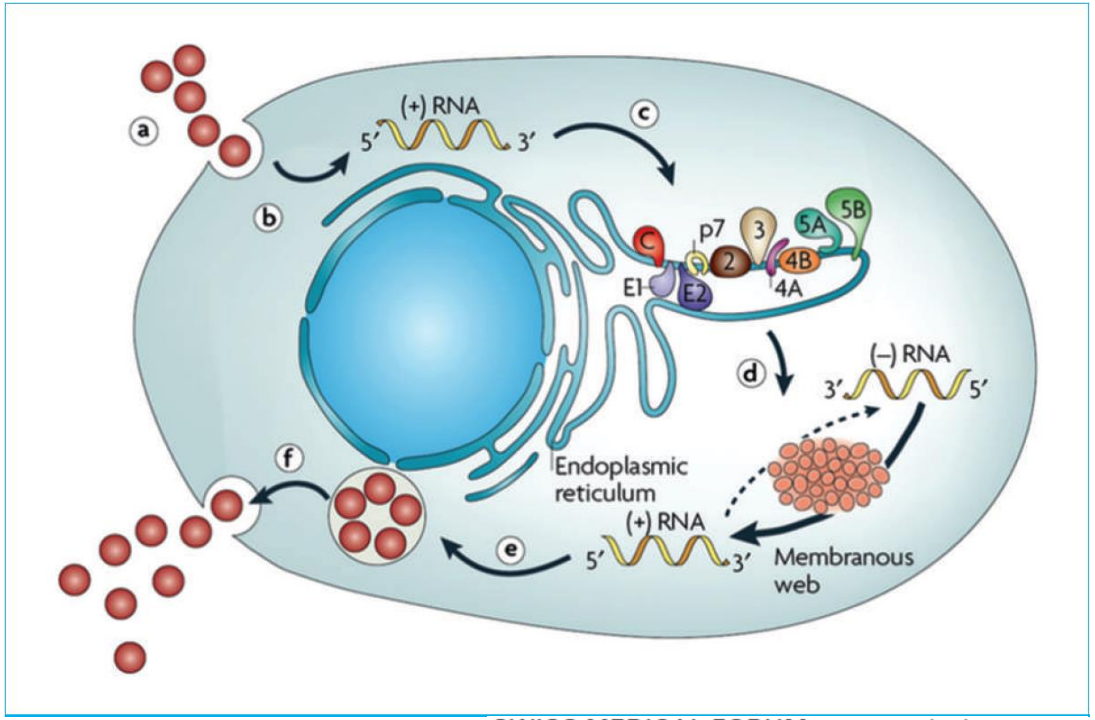
L’hépatite C


Pacific Ocean
Atlantic Ocean
Indian Ocean
Prevalence of Hepatitis C Virus Infection
> 2.9%
2.0% – 2.9%
1.0% – 1.9%
< 1.0%
No Data

Le virus de l'hépatite C (HCV)

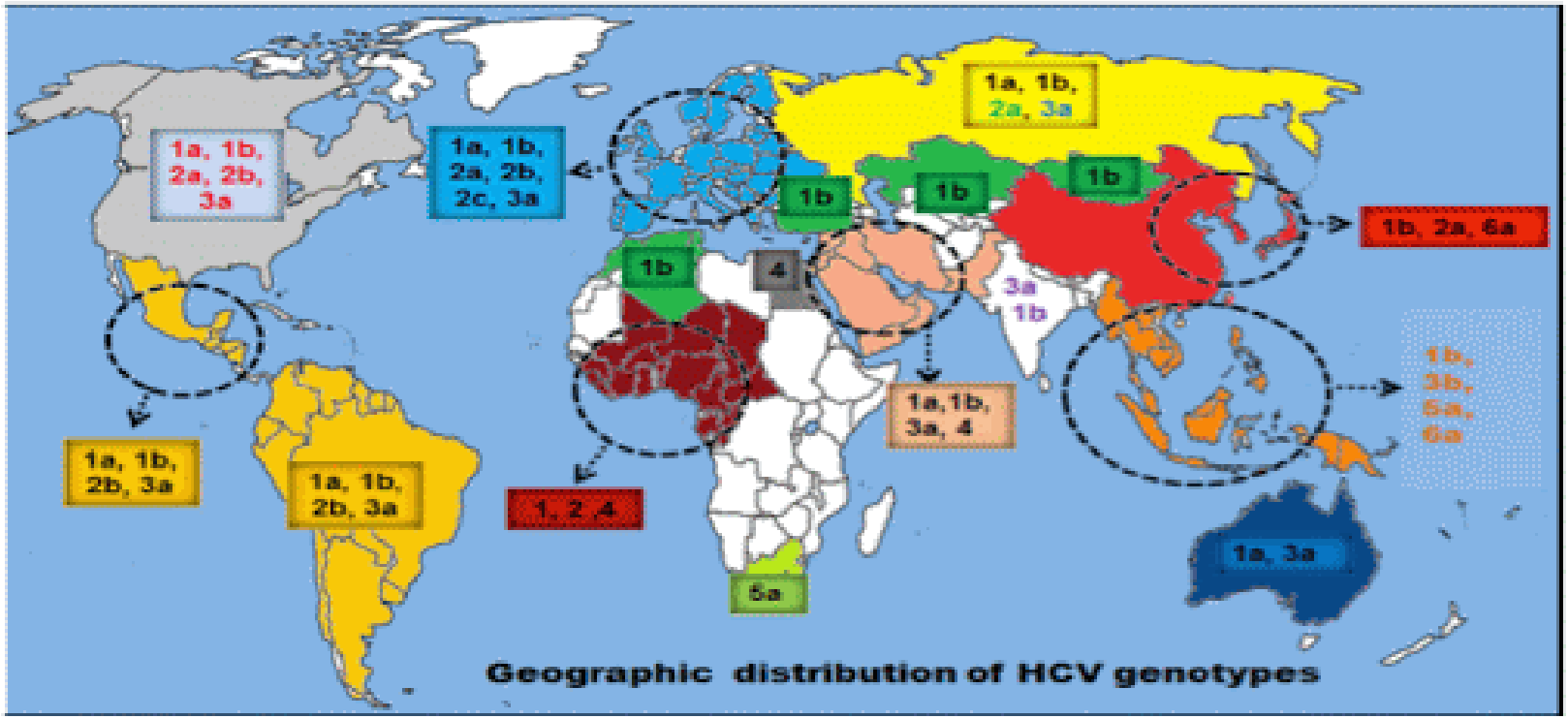
- Flaviviridae, génotype 1-7
- Petit virus à ARN
- Identifié 1989 (avant: non-A/B)

- Transmission principalement par le sang (IVDA, transfusions)



SWISS MEDICAL FORUM 2015;15(17):360–365

L'hépatite C

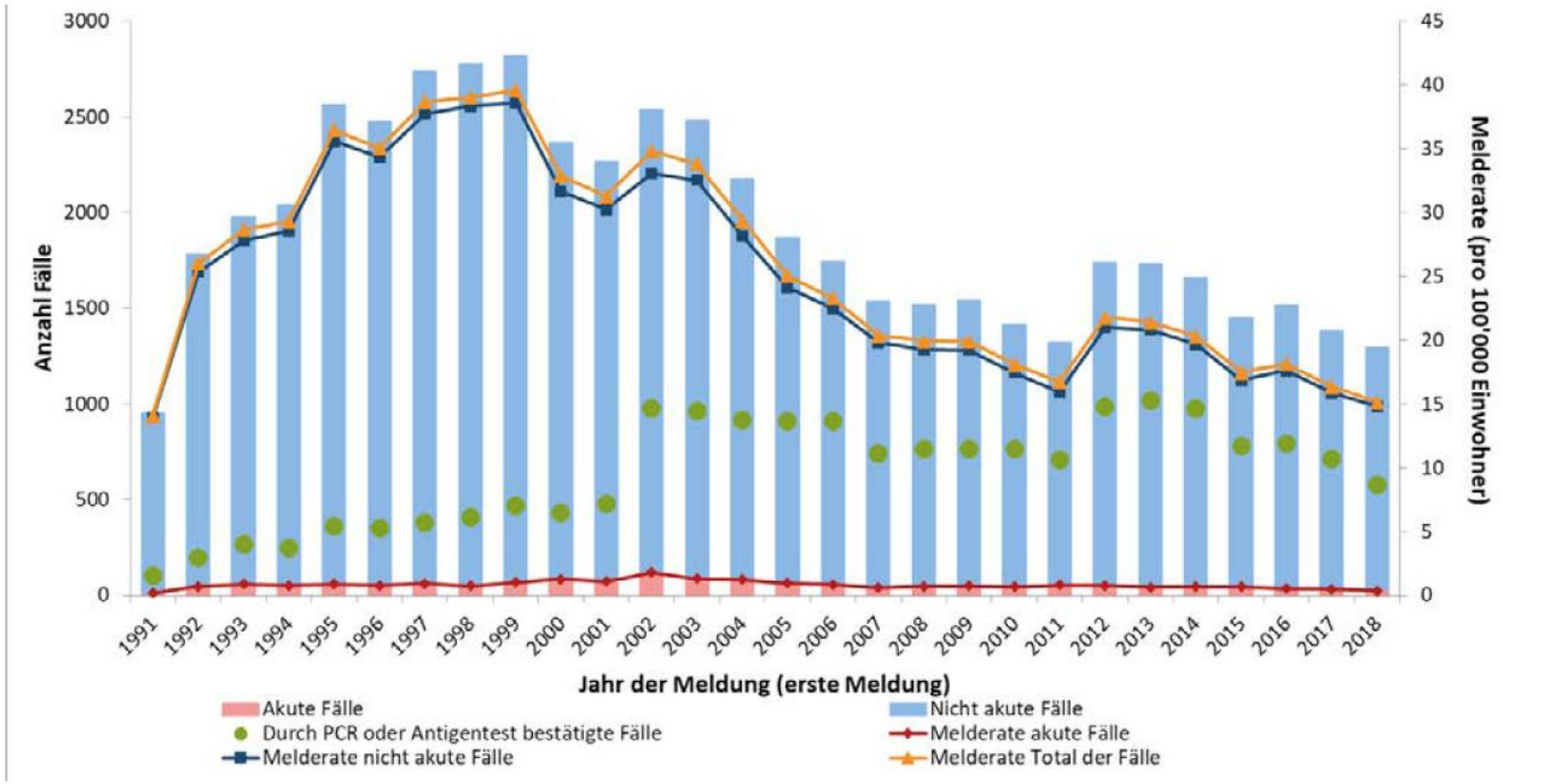


- > 70'000'000 infectés
- 400'000 morts par année (cirrhose, CHC)

- GT1 et GT3 >50%
- GT4 en Egypte

L'hépatite C en Suisse

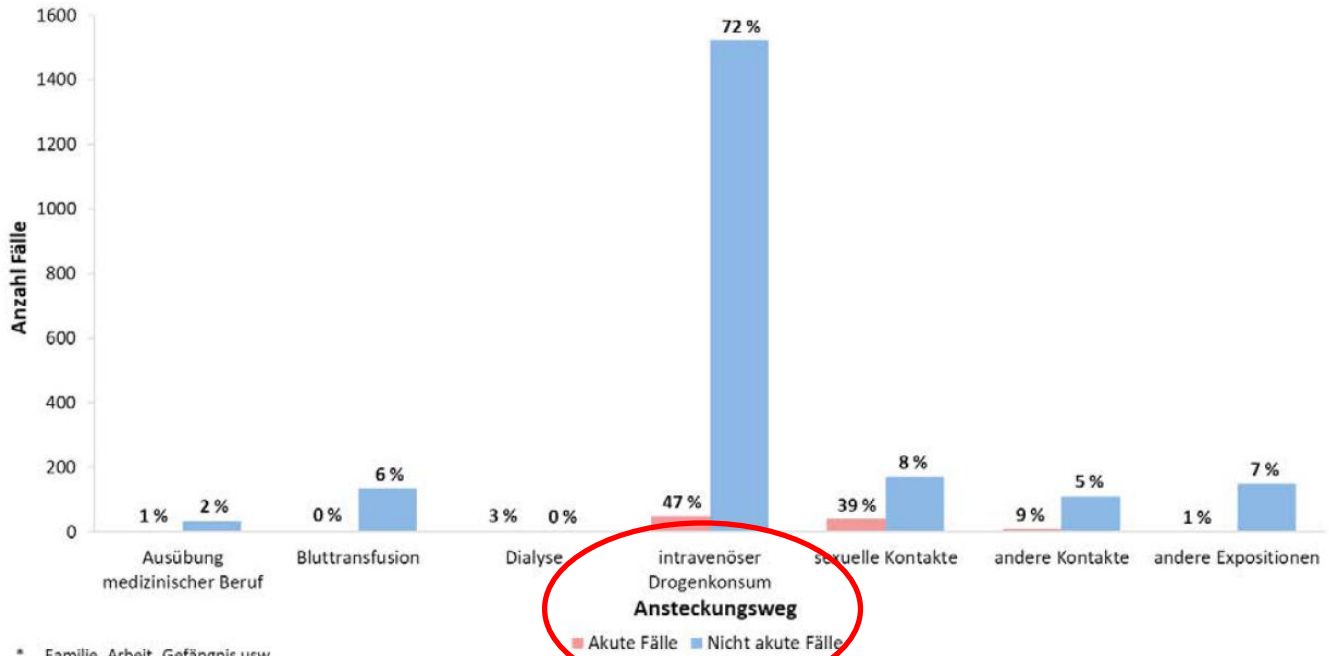
Gemeldete Fälle akuter und nicht akuter Hepatitis C mit entsprechenden Melderaten, pro Jahr, Schweiz, 1991–2018



La transmission de l'HCV en Suisse

Akute und nicht akute Fälle von Hepatitis C, nach vermutetem Ansteckungsweg, Schweiz, 2015–2018

Anzahl Fälle, gewichtet nach der Anzahl erwähnter Ansteckungswege pro Fall (eine Angabe insgesamt pro Fall), und prozentualer Anteil am Total der Fälle mit mindestens einem aufgeführten Ansteckungsweg. Der Ansteckungsweg war unbekannt oder wurde nicht aufgeführt in 38 % der akuten und in 61 % der nicht akuten Fälle.



* Familie, Arbeit, Gefängnis usw.
** perinatale Übertragung und Übertragung auf Kleinkind, iatrogene Ansteckung, chirurgischer Eingriff, zahnärztliche Behandlung, Tätowierung, Piercing, nicht-medizinischer Beruf usw.

Dépistage de l'hépatite C

Etape 1

- anti-HCV

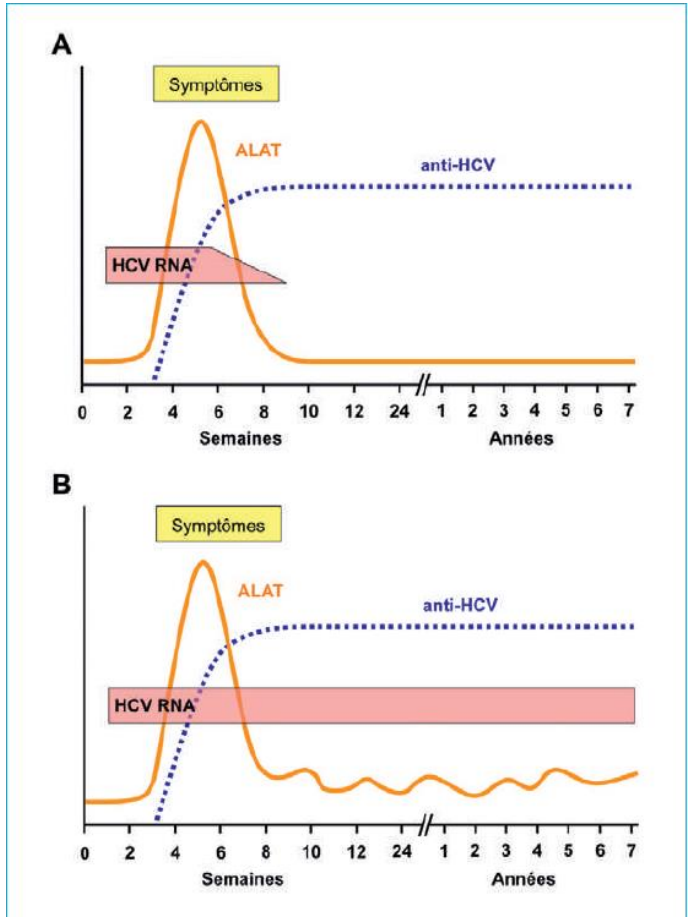
Etape 2 (si anti-HCV pos)

- HCV-RNA par PCR (virémie)
- Dépistage HBV
- Dépistage HIV

L'hépatite C aiguë et chronique

Infection HCV avec résolution spontanée

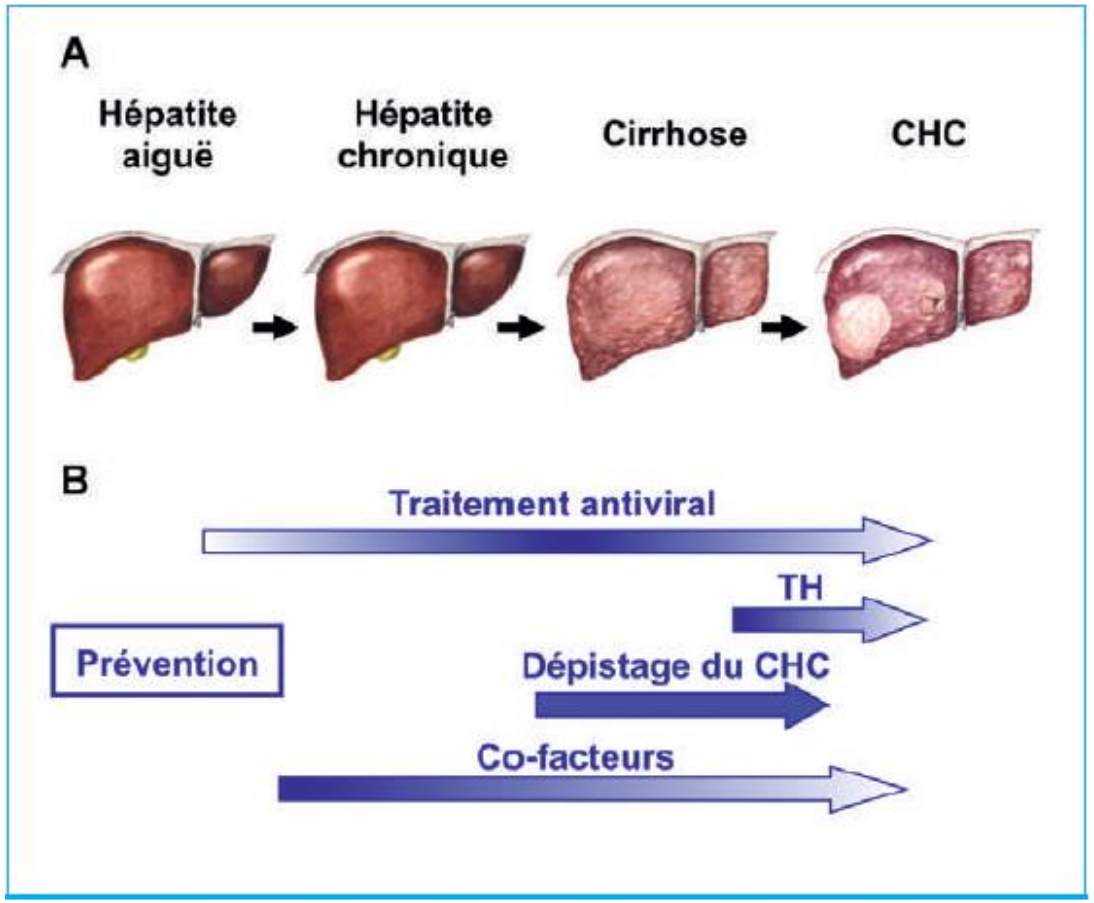
Infection HCV avec persistance chronique



REVUE MÉDICALE SUISSE 2015;11(471):896–901

- L'infection passe souvent inaperçu (hépatite aiguë sous-clinique)
- Evolution en infection chronique dans 50-80% des cas
- Symptômes non-spécifiques: fatigue, perte pondérale, nausée
- Manifestations extra-hépatiques: vasculitides, cryoglobulinémie, glomérulonephrite, lymphomes, …

Histoire naturelle et prise en charge



REVUE MÉDICALE SUISSE 2015;11(471):896–901

- Évolution très variable
- FR pour cirrhose: OH, tabac, co-infection HBV/HIV, NASH, GT3, immunosuppression, …
- Risque de cirrhose 20% sur 20 ans et 30% sur 30 ans
- Risque de CHC 5% par année en cas de cirrhose
- **Indication pour ttt anti-viral: TOUT sujet infecté** (+/- cirrhose)

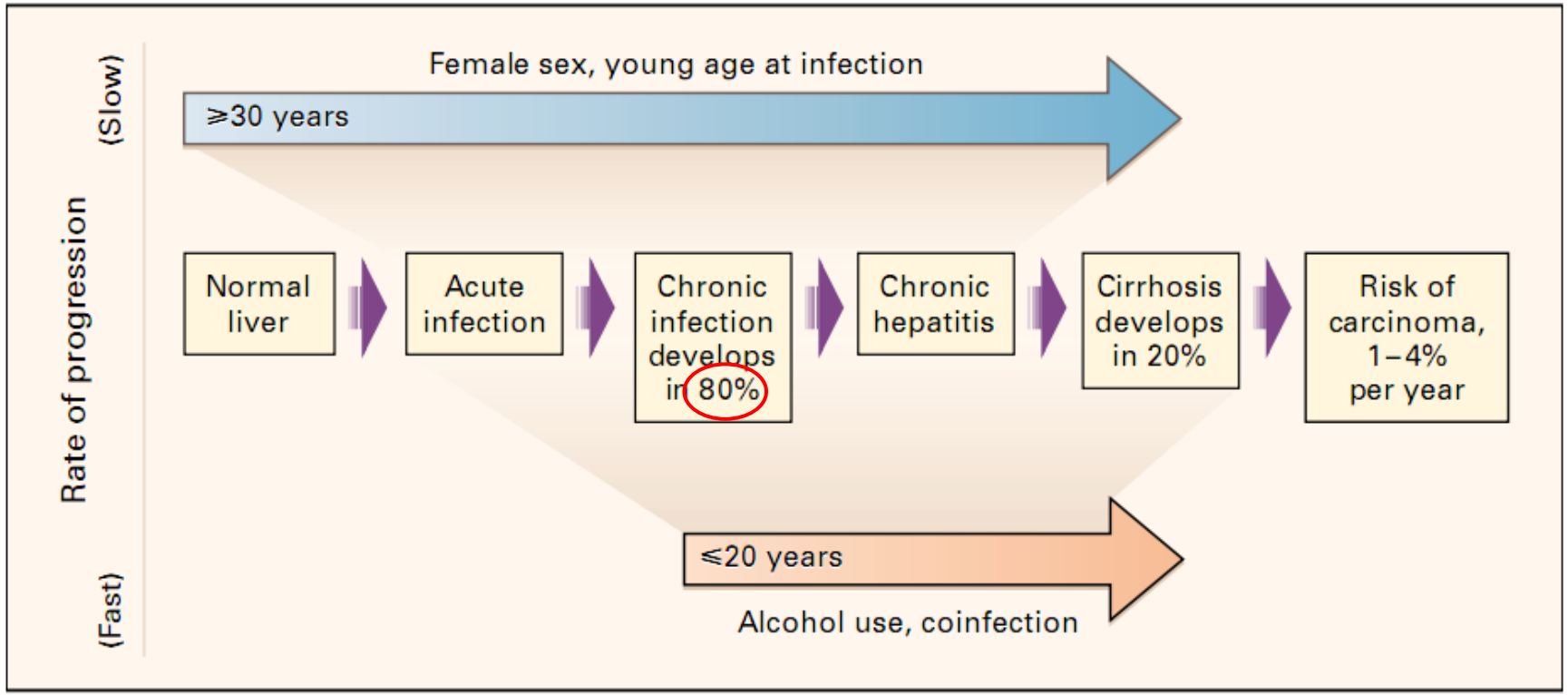
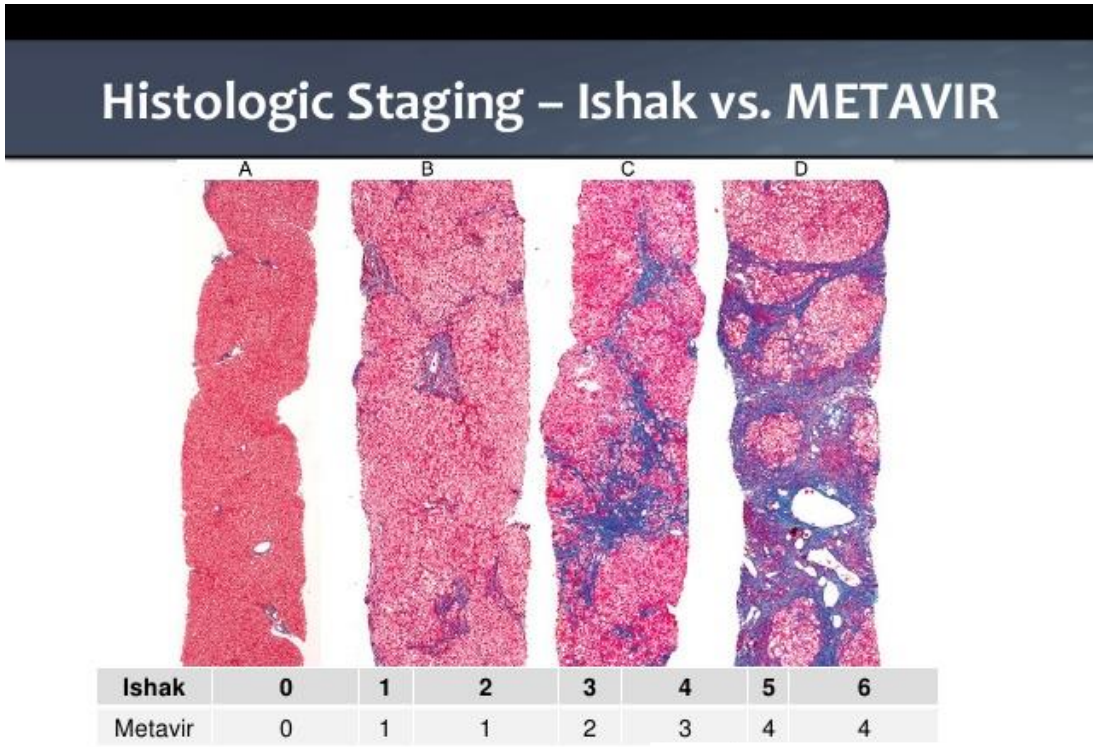


Figure 2. The Natural History of HCV Infection and Its Variability from Person to Person.

Le score métavir (PBF)



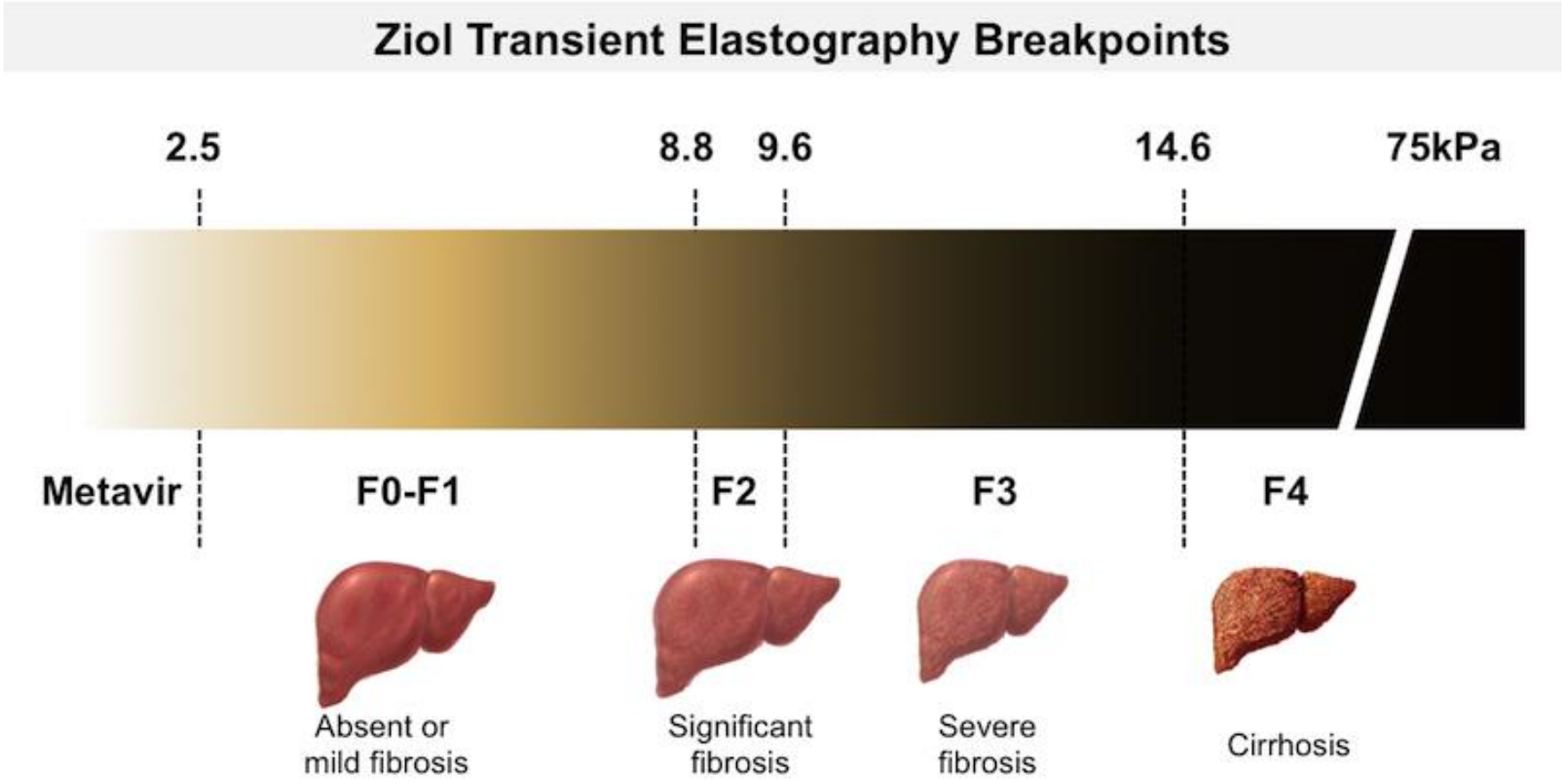
Ishak	0	1	2	3	4	5	6
Metavir	0	1	1	2	3	4	4

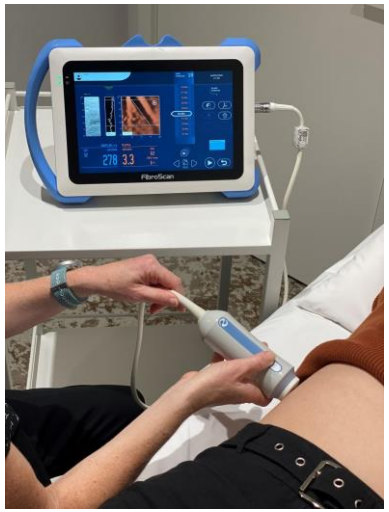
Brau N, Clin Infect Dis 2013; 56(6): 853-60

- **Activity grade**
- **A0**: no activity
- **A1**: mild activity
- **A2**: moderate activity
- **A3**: severe activity

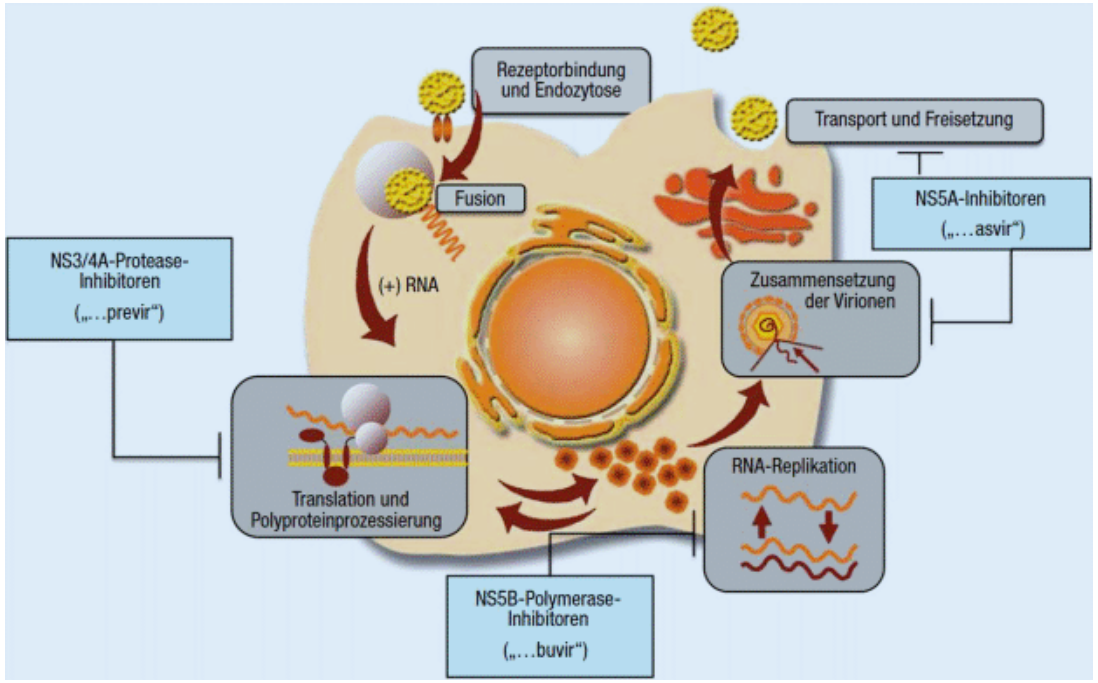
- **Fibrosis stage**
- **F0**: no fibrosis
- **F1**: portal fibrosis without septa
- **F2**: portal fibrosis with few septa
- **F3**: numerous septa without cirrhosis
- **F4**: cirrhosis

Elastographie (ARFI, FIB)





TTT anti-HCV



- Inhibiteur de la **polymérase NS5B**: sofosbuvir (SOF)
- Inhibiteur de la **protéase NS3-A4**: glécaprévir (GLE)
- Inhibiteurs de la **protéine NS5A**: pibrentasvir (PIB), velpatasvir (VEL)

TTT anti-HCV

VEL/SOF (Epclusa®)

- *velpatasvir* 100mg (NS5A)
  + *sofosbuvir* 400mg (NS5B)
- POS: 1x1 cps, avec/sans repas
- EID: céphalées, fatigue, nausée
- CI: insuffisance rénale (GFR <30ml/min), amiodarone!

GLE/PIB (Maviret®)

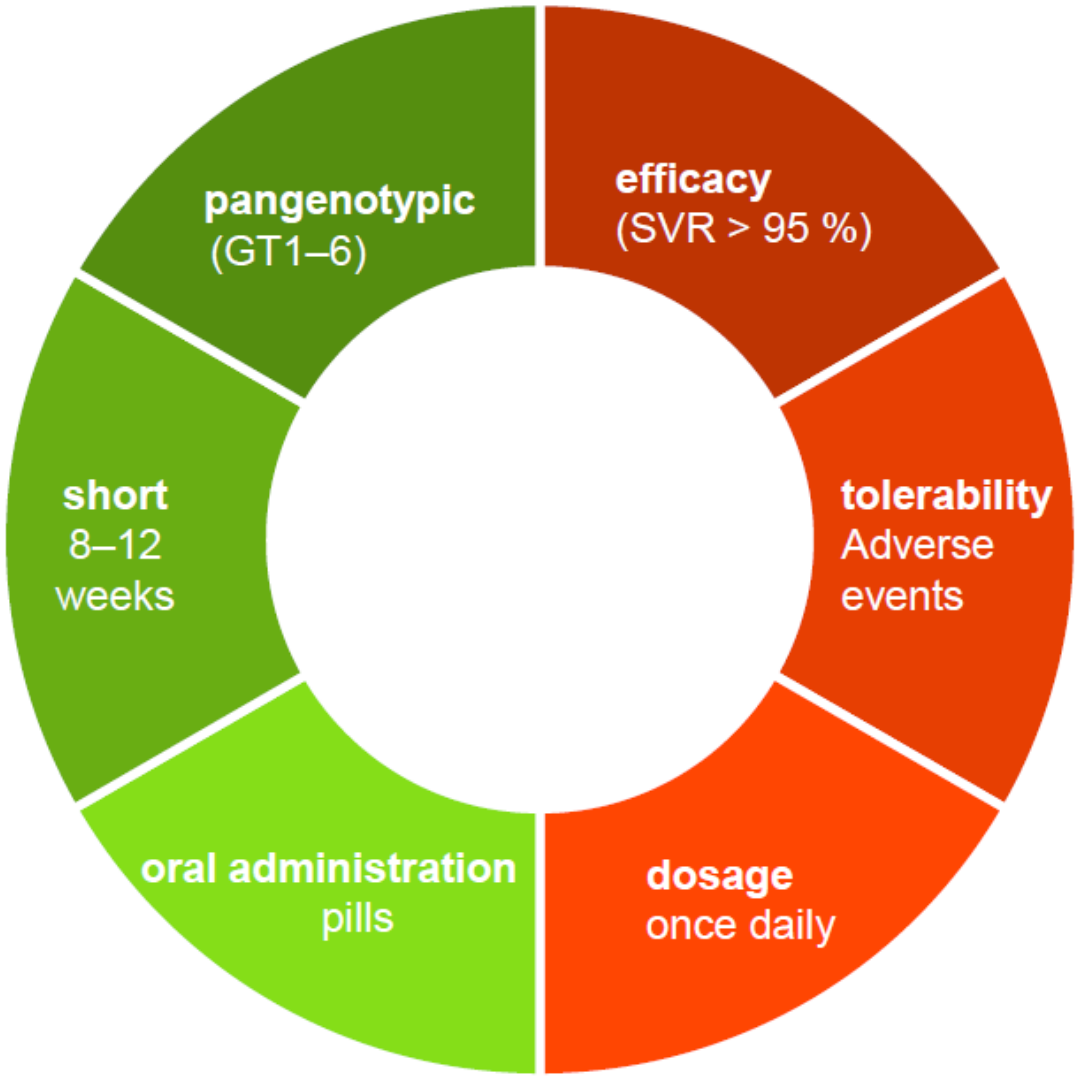
- glécapévir 100mg (NS3-A4)
  + *pibrentasvir (NS5A)*
- POS: 1x3 cps, avec un repas
- EID: céphalée, fatigue
- CI: insuffisance hépatique, s.p. décompensation

TTT anti-HCV

	GT	Ohne Zirrhose		Zirrhose (CTP A)	
Therapie-naiv	1	VEL/SOF GLE/PIB	12 Wo 8 Wo	VEL/SOF GLE/PIB	12 Wo 8 Wo
	2	VEL/SOF GLE/PIB	12 Wo[1] 8 Wo	VEL/SOF GLE/PIB	12 Wo 8 Wo
	3	VEL/SOF GLE/PIB	12 Wo 8 Wo	VEL/SOF/RBV GLE/PIB	12 Wo[2] 12 Wo
	4	VEL/SOF GLE/PIB	12 Wo 8 Wo	VEL/SOF GLE/PIB	12 Wo 8 Wo
	5	VEL/SOF GLE/PIB	12 Wo 8 Wo	VEL/SOF GLE/PIB	12 Wo 8 Wo
	6	VEL/SOF GLE/PIB	12 Wo 8 Wo	VEL/SOF GLE/PIB	12 Wo 8 Wo

	GT	Ohne Zirrhose		Zirrhose (CTP A)	
Nach Therapie°	1	VEL/SOF GLE/PIB	12 Wo 8 Wo	VEL/SOF GLE/PIB	12 Wo 12 Wo
	2	VEL/SOF GLE/PIB	12 Wo 8 Wo	VEL/SOF GLE/PIB	12 Wo 12 Wo
	3	VEL/SOF +/- RBV GLE/PIB	12 Wo[3] 16 Wo	VEL/SOF/RBV GLE/PIB	12 Wo[4] 16 Wo
	4	VEL/SOF GLE/PIB	12 Wo 8 Wo	VEL/SOF GLE/PIB	12 Wo 12 Wo
	5	VEL/SOF GLE/PIB	12 Wo 8 Wo	VEL/SOF GLE/PIB	12 Wo 12 Wo
	6	VEL/SOF GLE/PIB	12 Wo 8 Wo	VEL/SOF GLE/PIB	12 Wo 12 Wo

«C is cured»


pangenotypic
(GT1–6)
efficacy
(SVR > 95 %)
short
8–12
weeks
tolerability
Adverse
events
oral administration
pills
dosage
once daily

Hépatite E

ÜBERSICHTSARBEIT

Hepatitis E in Deutschland – eine unterschätzte Infektionskrankheit

Sven Pischke, Patrick Behrendt, Claus-Thomas Bock, Wolfgang Jilg, Michael P. Manns, Heiner Wedemeyer

ZUSAMMENFASSUNG

Hintergrund: Mindestens 17 % der in Deutschland lebenden Bevölkerung haben eine Infektion mit dem Hepatitis-E-Virus (HEV) durchgemacht. Somit ist diese Infektion in Deutschland häufiger als bislang angenommen. Demgegenüber wurden an das Robert Koch-Institut 2013 weniger als 500 HEV-Infektionen gemeldet.

Methode: Selektive Literaturrecherche in PubMed

Ergebnisse: Die Hepatitis E wird in Deutschland zumeist autochthon durch unzureichend gegartes, infiziertes Schweinefleisch übertragen und nur in Einzelfällen als Tropenkrankheit importiert. HEV kann durch Blutprodukte und Bluttransfusionen sowie Organspenden übertragen werden. Eine HEV-Infektion verläuft in über 99 % der Fälle asymptomatisch und ist selbstlimitierend. Es gibt jedoch auch schwerwiegende Verläufe mit akutem Leberversagen. Bei immunsupprimierten Patienten sind chronische Verläufe möglich, die innerhalb weniger Jahre zu Leberzirrhosen mit lebensgefährlichen Komplikationen führen können. HEV-Infektionen sind mit extrahepatischen Manifestationen wie zum Beispiel dem Guillain-Barré-Syndrom assoziiert worden. In zwei retrospektiv ausgewerteten Failserien zeigte Ribavirin eine antivirale Wirkung gegen HEV und kann deshalb bei akuten oder chronischen HEV-Infektionen eingesetzt werden.

Schlussfolgerungen: Die Hepatitis-E-Infektion sollte in der Differenzialdiagnose erhöhter Leberwerte, aber auch bei unklaren System- und neurologischen Erkrankungen berücksichtigt werden. Die Infektion ist in der Regel selbstlimitierend, bei immunsupprimierten können jedoch schwerwiegende Verläufe auftreten. Bei schwer verlaufenden Infektionen steht mit Ribavirin eine antivirale Therapie zur Verfügung.

► **Zitierweise**
Pischke S, Behrendt P, Bock CT, Jilg W, Manns MP, Wedemeyer H: Hepatitis E in Germany—an underreported infectious disease. Dtsch Arztebl Int 2014; 111: 577–83. DOI: 10.3238/arztebl.2014.0577

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Seit den 1970er-Jahren war bekannt, dass in den Tropen neben dem Hepatitis-A-Virus noch ein weiteres fäkal-oral übertragbares Hepatitis Virus existieren muss (1). Es gelang dem russischen Wissenschaftler M.S. Balayan sich selbst mit diesem Virus zu infizieren, indem er gepoolte Extrakte von Stuhlproben eines Patienten mit akuter Non-A-Non-B-Hepatitis oral zu sich nahm. Daraufhin erkrankte er an einer Hepatitis und das Hepatitis-E-Virus (HEV) wurde elektronenmikroskopisch in seinem Stuhl nachgewiesen (1).

HEV tritt in vielen tropischen Ländern endemisch auf und ist dort für zahlreiche Ausbrüche von Hepatitiden verantwortlich, insbesondere in Zusammenhang mit Flutkatastrophen oder in Flüchtlingslagern (1, 2). Schätzungen zufolge kommt es in den Tropen jedes Jahr bedingt durch HEV zu mehr als drei Millionen symptomatischen HEV-Infektionen und circa 70 000 Todesfällen (3). Insbesondere bei Schwangeren und bei Patienten mit chronischen Lebererkrankungen treten fulminante Verläufe gehäuft auf (1). Eine HEV-Infektion kann Symptome einer Lebenentzündung verursachen wie Ikterus, Pruritus und Oberbauchschmerzen. Darüber hinaus wurden unspezifische und extrahepatische Manifestationen wie Arthralgien oder das Guillain-Barré-Syndrom im Verlauf einer HEV-Infektion beschrieben (4, 5).

Wahrnehmung und Einschätzung der Hepatitis E haben sich in den letzten Jahren gewandelt: Eine zunehmende Anzahl an HEV-Infektionen, die in Europa erworben wurden, sowie die Entdeckung der chronischen Hepatitis E bei Immunsupprimierten, gaben dieser Infektionskrankheit in Industrienationen eine neue Bedeutung jenseits der bisherigen Annahme einer nur akut verlaufenden Tropenkrankheit (1). In Deutschland stieg die Zahl der dem Robert-Koch-Institut gemeldeten Hepatitis-E-Fälle in den letzten Jahren deutlich; ebenso die Anzahl der in PubMed gelisteten Publikationen über HEV *(Grafik 1)*, während die anti-HEV-Seroprävalenz seit 1993 konstant blieb (6). Diese Beobachtungen legen nahe, dass der Anstieg der an das Robert Koch-Institut gemeldeten Hepatitis-E-Fälle am ehesten in einer gesteigerten Aufmerksamkeit der Ärzteschaft für diese Erkrankung begründet ist (6).

Epidemiologie und Übertragungswege des Hepatitis-E-Virus

Es gibt 5 HEV-Genotypen. Die Genotypen 1–4 sind humanpathogen, während Genotyp 5 nur in Vögeln vorkommt. Die weltweite Verbreitung der Genotypen

Dt. Ärzteblatt 2014

Medical education reform in China

On July 11, the State Council of China introduced bold plans to revolutionise medical education, effective immediately. Gone will be Soviet-era training in which doctors spent their career in one hospital, and overcrowded outpatient clinics that too often underutilised the expertise of staff and underserved the needs of patients. Instead, medical schools are asked to admit more, higher calibre students, and provide better quality teaching that is accredited by the Chinese Medical Doctor Association. After 5 years of medical school, graduates will enter a 3-year standardised residency programme at the start of specialisation. New 5+3 doctors must demonstrate adequate competencies, confirmed by examination, before a nationally recognised certificate is issued. Once in practice, distance-learning will support lifelong professional development. This is arguably the most important directive since medical reform was accelerated in 2009, and will reshape the delivery of care in China.

The patient-centred approach intends to provide access to doctors with the right skills and attitudes to achieve the Healthy China 2030 targets. This plan requires more general practitioners, paediatricians, psychiatrists, and geriatricians, among others, and inducements to ensure good-quality care in rural areas. A radical overhaul in medical education and workforce planning is needed to meet that goal, as described by Jiming Zhu and colleagues in *The Lancet* last year. But with more than 3 million doctors in China, half of whom do not have bachelor degree-level education, there is much to do before health equity is assured and less formal training programmes disappear. Some might question the feasibility of such large changes, so quickly, and the adequacy of funding.

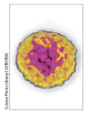
Professional attitudes need to be caught as well as taught: communication, compassion, empathy, respect, and ethics must become as recognisable a mark of doctors in China as a stethoscope. If done well, the reforms will benefit patients, doctors, and hospitals. For doctors in China, the reforms herald a rising professional status and opportunity for greater leadership, with commensurate mobility, salary, and responsibilities. ■ *The Lancet*

For **Statement on the reform and development of medical education** see http://www.gov.cn/zhengce/content/2012-12/12/content_5209661.htm

For **Healthy China 2030** see http://en.nhfpc.gov.cn/2016-11/07/c_79516.htm

See Review *Lancet* 2016; **388**: 1922–29

Growing concerns of hepatitis E in Europe



Hepatitis E virus (HEV) infection is an important cause of acute viral hepatitis worldwide, with an increasing incidence in Europe since 2010. Although it is difficult to know the real incidence because most HEV infections are asymptomatic or self-limiting, in some people—such as immunosuppressed individuals or those with pre-existing liver disease—HEV infection can progress to chronic disease.

Ahead of World Hepatitis Day on July 28, a surveillance report on the incidence of HEV infection in Europe, published by the European Centre for Disease Prevention and Control (ECDC) on July 11, shows cause for concern. The reported incidence in Europe over 10 years has grown by ten times: from 514 cases in 2005, to 5617 cases in 2015. Another cause for concern is that testing, case definitions, diagnosis, and surveillance for HEV infection vary extensively across Europe, with only 20 member states actively monitoring HEV infection. Most reported cases were in men older than 50 years, caused by genotype 3, and reported in the UK, France, and Germany, where surveillance is in place. Incidence also increased in countries without a surveillance system, indicating that reporting of the incidence might not be the only reason for the surge in infections.

Has there been a genuine rise in the number of new cases throughout Europe, or are we seeing the benefits of greater awareness of HEV infection or better diagnostic techniques? In the context of increasing incidence, a greater understanding of risk factors and effective prevention methods is key. A report from the European Food Safety Authority provides further evidence that most HEV infections in Europe are due to the consumption of undercooked or raw pork meat and liver, highlighting the need for clearer guidance on the appropriate preparation of these foods to suppress the rise in cases.

Following on from this report, the ECDC will now undertake a wider investigation. Consistent methods must be adopted throughout Europe to provide a better understanding of the burden of this emerging, under-recognised pathogen, and of modifiable risk factors that can be targeted to prevent further infections ■ *The Lancet*

For the **ECDC report** see https://ecdc.europa.eu/en/publications-data/hepatitis-e-cases-2005-2015

For the **European Food Safety Authority report** see http://www.efsa.europa.eu/en/efsajournal/pub/4886

Lancet 2017

EASL Clinical Practice Guidelines on hepatitis E virus infection☆

European Association for the Study of the Liver*

Summary: Infection with hepatitis E virus (HEV) is a significant cause of morbidity and mortality, representing an important global health problem. Our understanding of HEV has changed completely over the past decade. Previously, HEV was thought to be limited to certain developing countries. We now know that HEV is endemic in most high-income countries and is largely a zoonotic infection. Given the paradigm shift in our understanding of zoonotic HEV and that locally acquired HEV is now the commonest cause of acute viral hepatitis in many European countries, the focus of these Clinical Practice Guidelines will be on HEV genotype 3 (and 4).

Introduction

As a cause of significant morbidity and mortality, infection with hepatitis E virus (HEV) represents an important global public health problem. The European Association for the Study of Liver (EASL) invited a panel of experts in the field to develop Clinical Practice Guidelines (CPGs) with a particular focus on HEV genotype (gt) 3. The objective of these CPGs was not to draft a review article on hepatitis E but rather to define specific suggestions for the management of distinct features of HEV infection, even though the supporting evidence may be weak in many cases. In order to keep the manuscript and the reference list to a reasonable length, these CPGs frequently refer to previous review articles which summarise the evidence on distinct topics in more detail. In addition, despite the increasing knowledge, areas of uncertainty exist and unanswered questions should be defined. Therefore, clinicians, patients and public health authorities must continue to make choices on the basis of the evolving evidence.

Methodology

These EASL CPGs have been prepared by a panel of experts invited by the EASL Governing Board. The recommendations were approved by the EASL Governing Board. They are based as far as possible on evidence from existing publications and presentations at international meetings as well as, if evidence was unavailable, the experts' personal experiences and opinions. Wherever possible, the level of evidence and recommendation are cited. The evidence and recommendations have been graded according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.[1] Thus, the strength of recommendations reflects the quality of underlying evidence. The quality of the evidence in the recommendations has been classified into one of three levels: high (A), moderate (B) or low (C). The GRADE system offers two grades of recommendation: strong (1) or weak (2). Thus, the recommendations consider the quality of evidence; the higher the quality of evidence, the more likely a strong recommendation is warranted; the greater the variability in values and preferences, or the greater the uncertainty, the more likely a weaker recommendation is warranted. It must be noted that only the review of literature was used to inform recommendations. Other criteria or support of recommendations such as cost, feasibility, acceptability, or cost-effectiveness were not considered (Table 1).

Background

HEV was discovered in the early 1980s. At that time, Soviet troops in Afghanistan were affected by large outbreaks of unexplained hepatitis (testing negative for hepatitis A virus [HAV] and hepatitis B virus [HBV]). A pooled sample of affected soldiers' stool was ingested by a Russian scientist. He developed a brisk hepatitis, and a new virus was found in his stool by electron microscopy.[2] Subsequently the viral genome was cloned and named HEV.[3]

Term	Definition
HEV	Hepatitis E virus
HEV infection	Infection caused by HEV which is either symptomatic or asymptomatic, including extrahepatic manifestations (e.g. neurological)
Hepatitis E	Clinical or biochemical evidence of hepatitis caused by HEV
Extrahepatic	Damage to tissues/organs outside the liver associated with/caused by HEV (see Table 2)
SVR	Sustained virologic response
R_0	**The basic reproductive rate** This term equates to the number of individuals infected by an index case with an infectious disease. If R_0 is >1 then the infection will spread through a naïve population. The R_0 of HEV in the pig population is up to 8. This means that HEV is highly infectious in the pig population, to a similar extent to measles in a measles naïve human population

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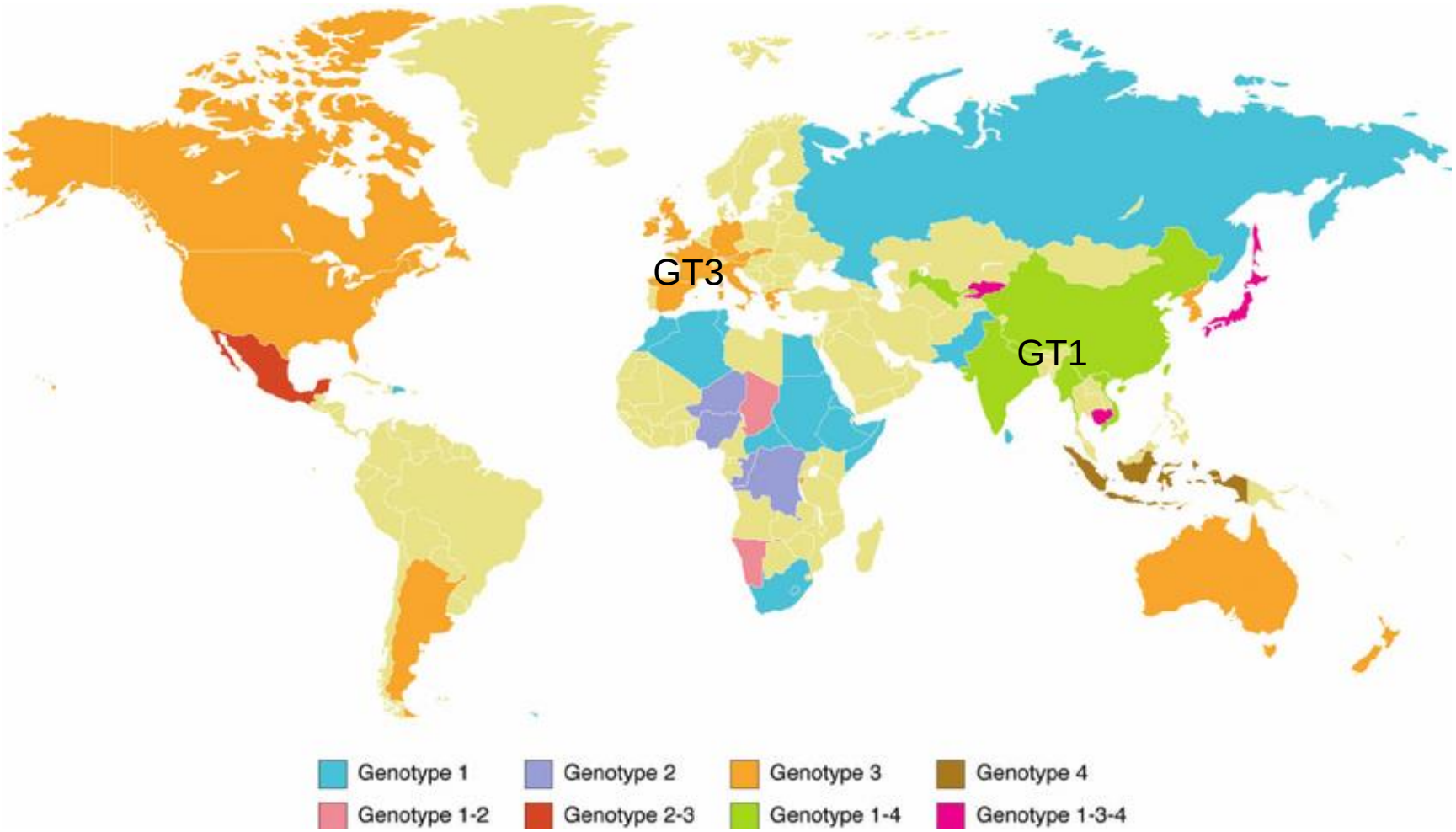
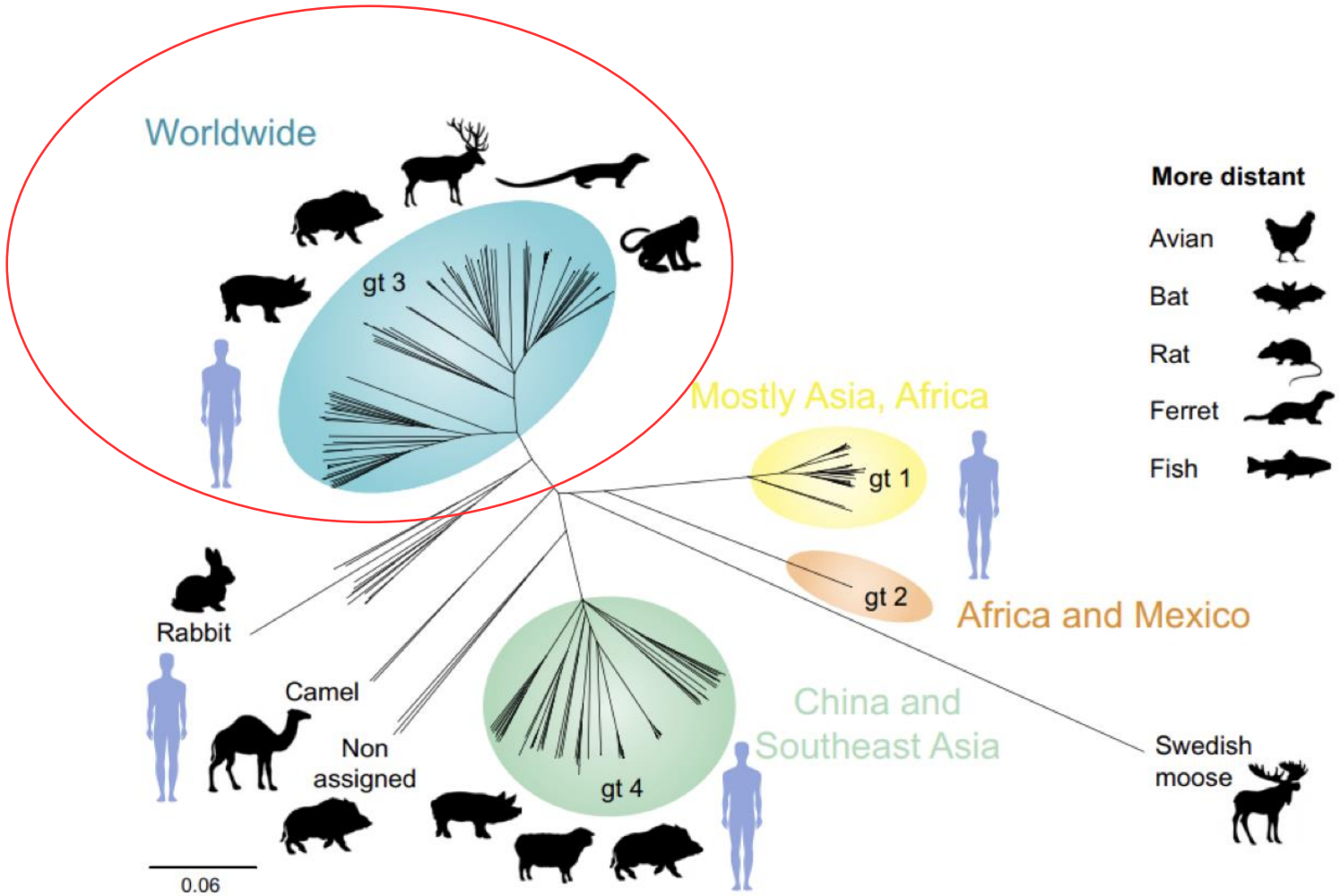
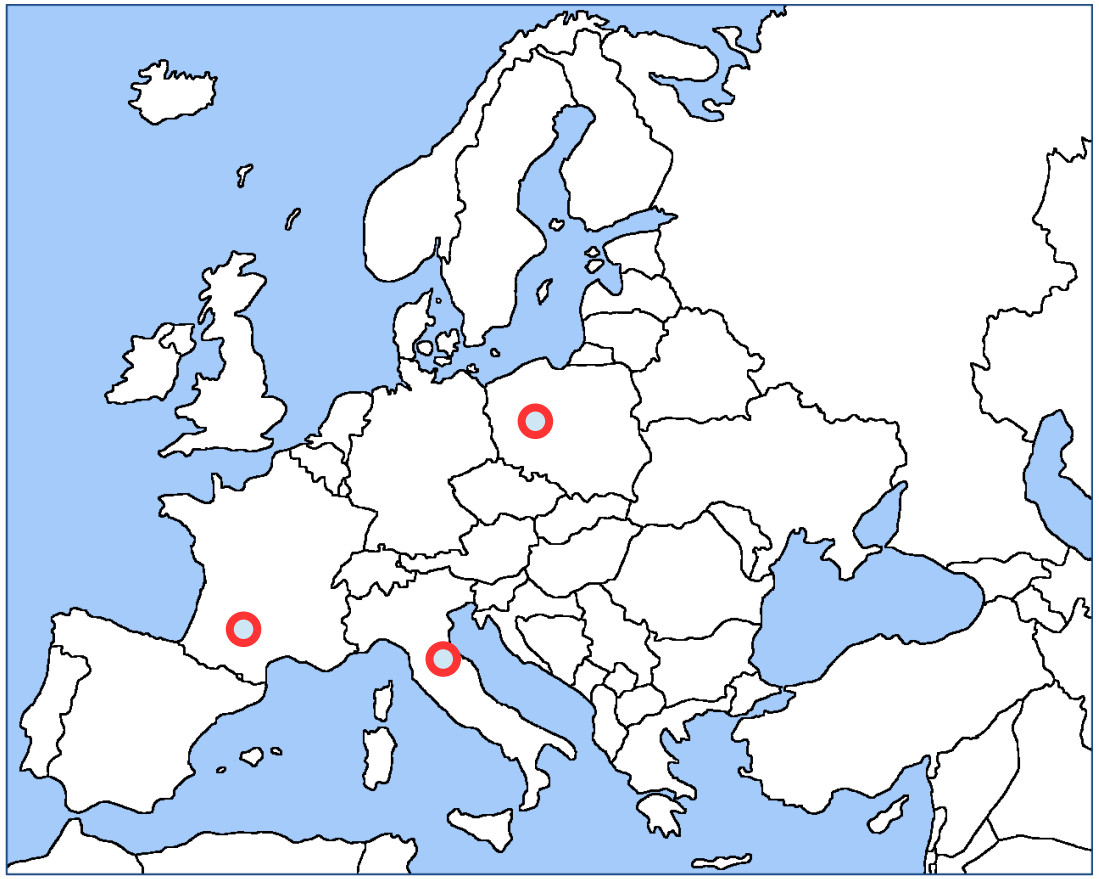
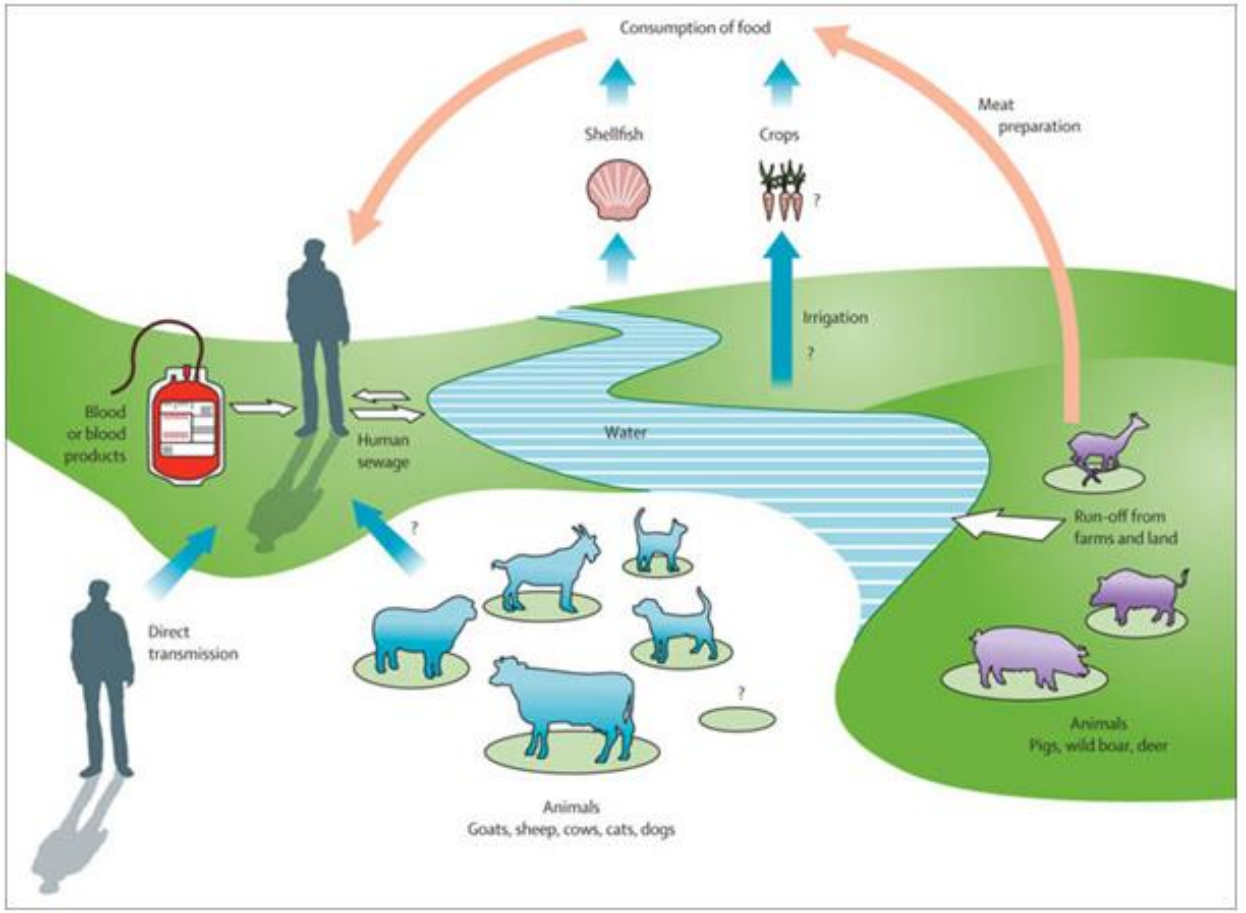

GT3
GT1
Genotype 1
Genotype 2
Genotype 3
Genotype 4
Genotype 1-2
Genotype 2-3
Genotype 1-4
Genotype 1-3-4


Worldwide
gt 3
Mostly Asia, Africa
gt 1
gt 2
Africa and Mexico
China and
Southeast Asia
gt 4
Rabbit
Camel
Non
assigned
Swedish
moose
0.06
More distant
Avian
Bat
Rat
Ferret
Fish

Hotspots



Scotland, 2016: 1:2,481 donors viraemic[1]
SW France, 2016: incidence 3–4%[2]
The Netherlands, 2014: 1:600 donors viraemic[3]
Western Germany, 2015: 1:616 donors viraemic[4]
Czech Republic, 2015: 400 lab-confirmed cases[5]
Abruzzo, Italy, 2016: seroprevalence 49%[6]
Western/Central Poland, 2017: seroprevalence 50%[7]


Consumption of food
Shellfish
Crops
?
Meat
preparation
Irrigation
?
Blood
or blood
products
Human
sewage
Water
Run-off from
farms and land
?
Direct
transmission
?
Animals
Pigs, wild boar, deer
Animals
Goats, sheep, cows, cats, dogs

L'hépatite E – génotypes

Génotype 1

- Strictement humain
- Transmission par l'eau contaminée
- Surtout jeunes adultes
- Aiguë, spontanément résolutif (jamais chronique)
- Haute mortalité en cas de grossesse (25%)

Génotype 3

- Zoonose (porc, chasse)
- Viande contaminée, transfusions
- Endémique, No 1 en UE, variante spécifique CH
- hommes âgés?
- >95% asymptomatiques
- Rarement chronique (immunosuppression)

L'hépatite E - labo

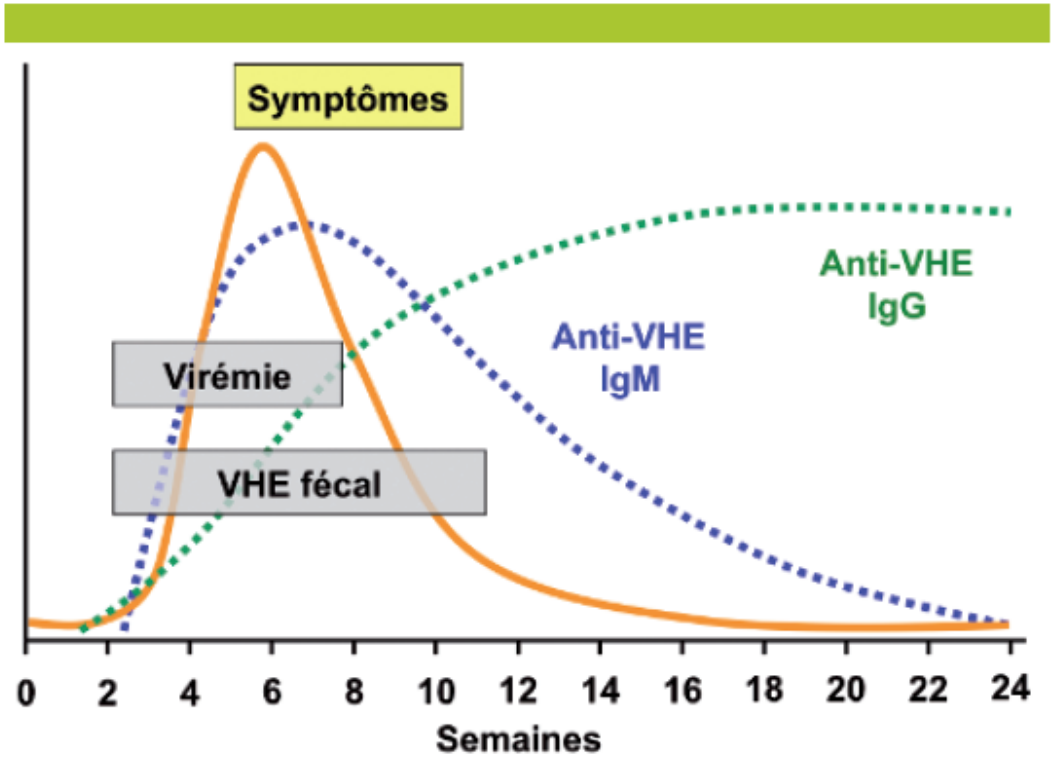


Figure 2. Représentation schématique d'une infection aiguë par le virus de l'hépatite E (VHE)

- Temps d'incubation: 15-60j
- ARN dans sang/selles (semaines)
- Toujours sérologie **+ PCR**

L’hépatite E - clinique

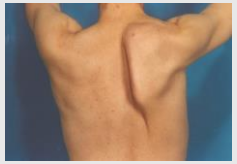
Aiguë

- Probablement No1 en Europe
- DD: DILI, HAV, AIH
- <5% symptômes d’hépatite, rarement neuro/nephro
- Spontanément résolutive

Chronique

- Uniquement si immunosuppression (Tx: élimination 50%)
- Souvent asymptomatique
- Progression rapide en cirrhose

Symptomes extra-hépatiques

Organ system	Clinical syndrome	Notes
Neurological	• Neuralgic amyotrophy* • 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

L’hépatite E - traitement

Aiguë

- Symptomatique
- Hygiène/isolement
- RBV si insuffisance hépatique

Chronique

- Réduction de l’immunosuppression
- RBV, LTx

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ATTENTION SELON SWISSMEDIC (EDITION DE JANVIER 2022), CE MEDICAMENT EST OU SERA HORS COMMERCE EN SUISSE DEPUIS LE 06.06.2022

L'hépatite virale

B ~~boring~~

C cured ✓

E No 1 (+ chronique)

Merci!