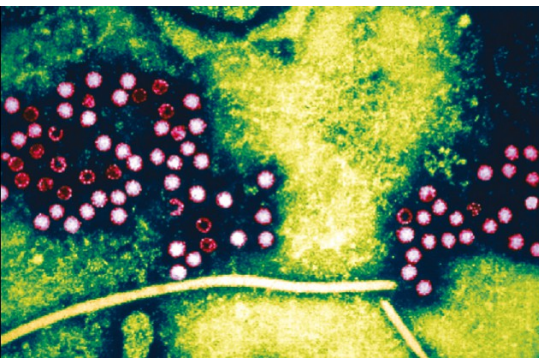


Hepatitis E Virus : the neglected one

Jean-Marie Péron

Service d'Hépatogastro-entérologie
Hôpital Purpan TOULOUSE FRANCE



HEV worldwide

- 1st cause of acute hepatitis
- 20 million infections per year,
 - Over 3 million symptomatic cases,
 - 56 600 hepatitis E related deaths
- New Delhi 1955-56 epidemic : 29 000 symptomatic cases

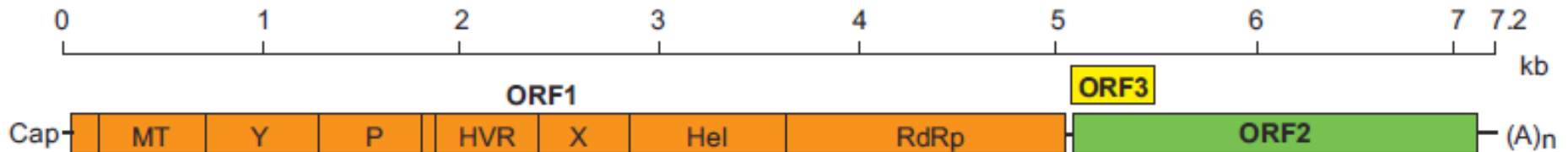
WHO. Viral hepatitis. Jul, 2015
Lozano R Lancet 2012
Indian J Med Res 1957

HEV in Europe

- Isolated cases
- Autochthonous cases (locally acquired)
- Zoonosis
- Neurological symptoms
- Chronic disease in immunosuppressed patients
- Specific treatment

HEV genome

- Genus *Hepevirus* in the *Hepeviridae* family
- Non envelopped virus, icosahedral capsid, size of 30 nm
- Positive-sense single-stranded RNA



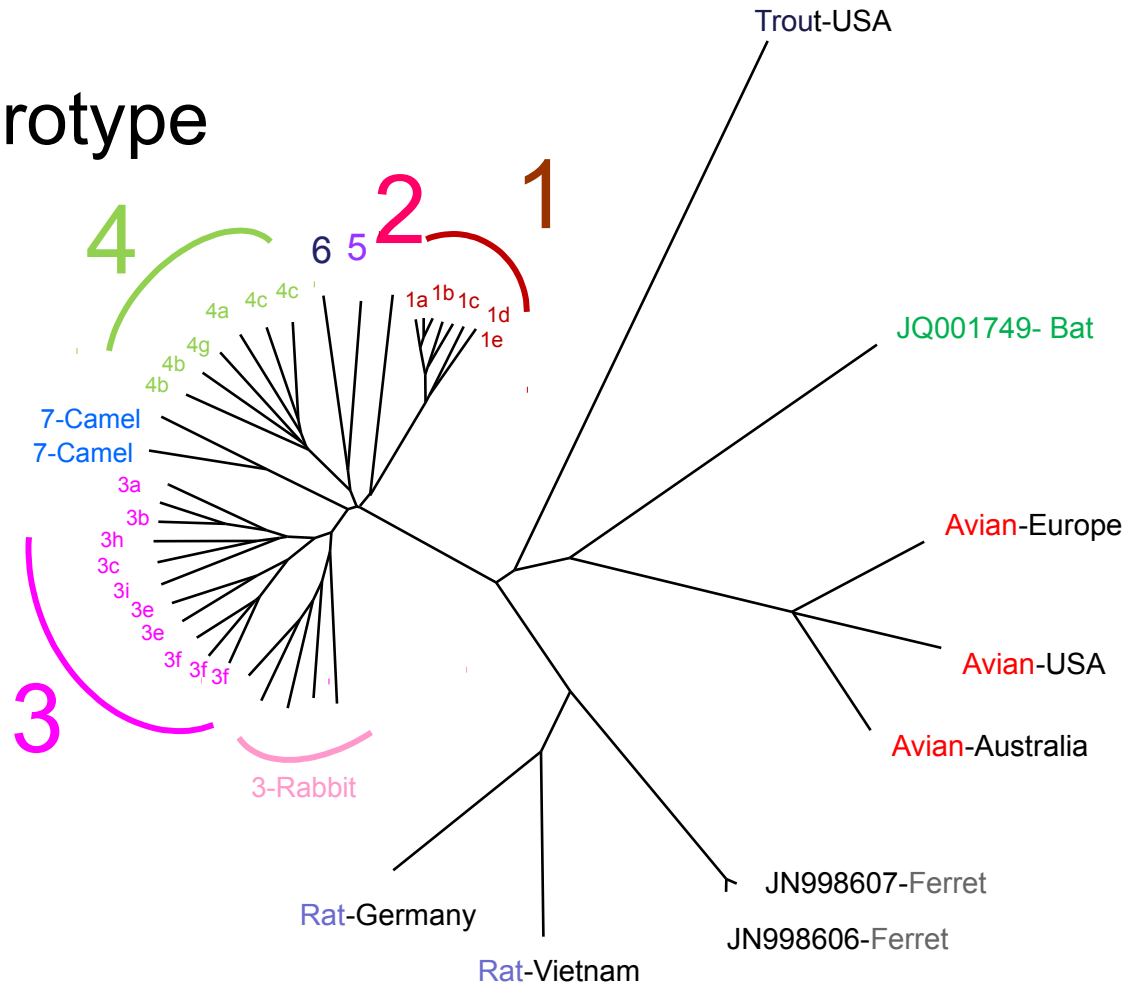
- Quasi species in humans

HEV diversity

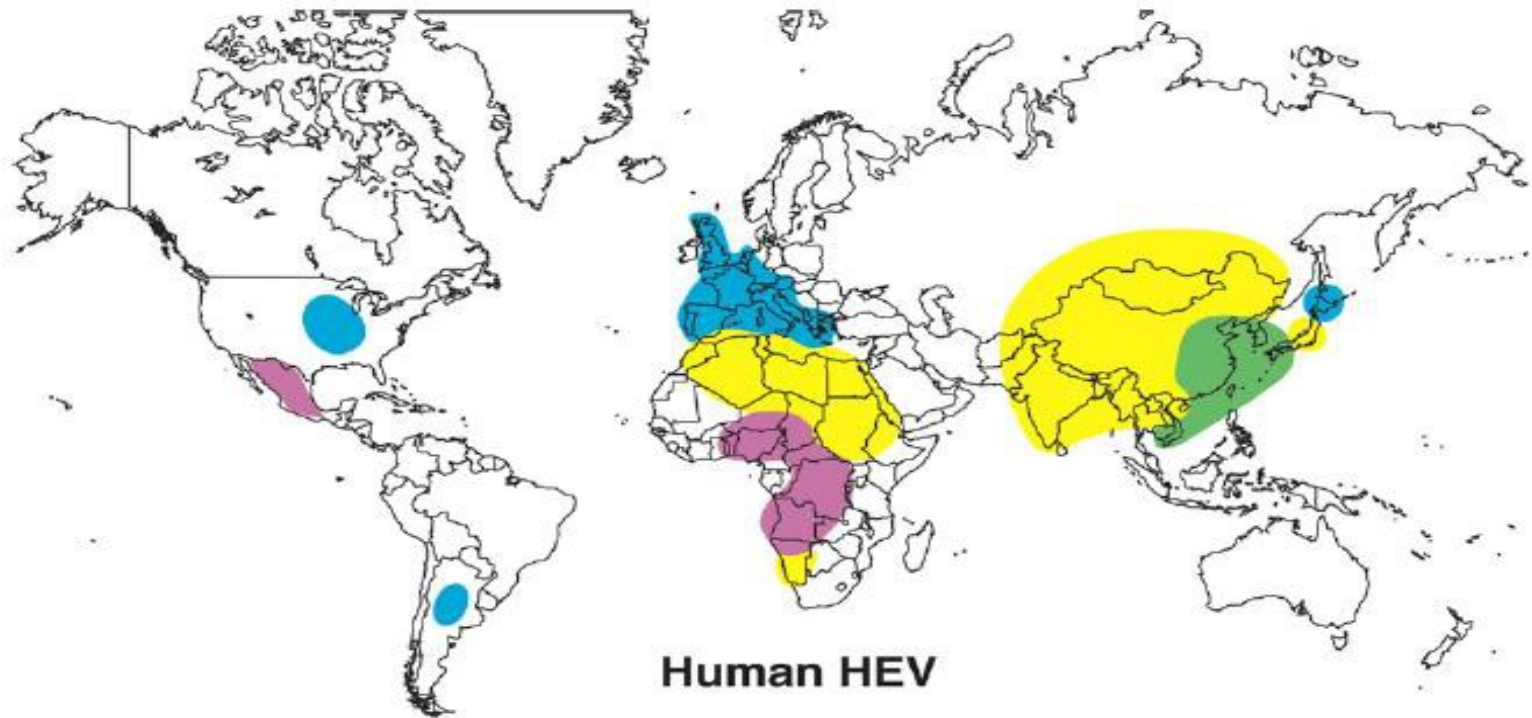
→ 7 genotypes (4 main genotypes)

- genotypes 3 and 4, 7 : zoonosis

→ 1 serotype



Worldwide distribution

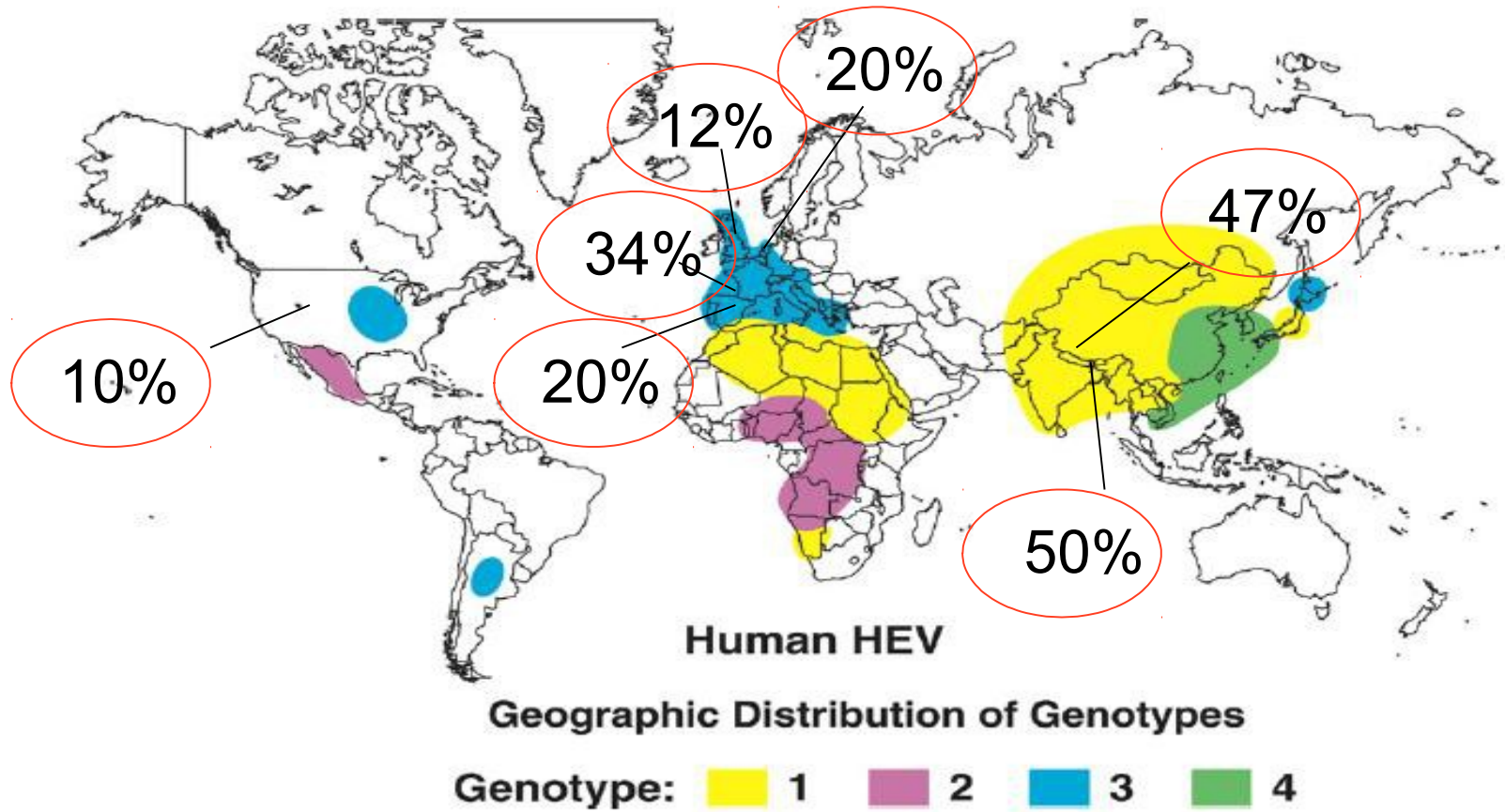


Human HEV

Geographic Distribution of Genotypes

Genotype: 1 2 3 4

Seroprevalence

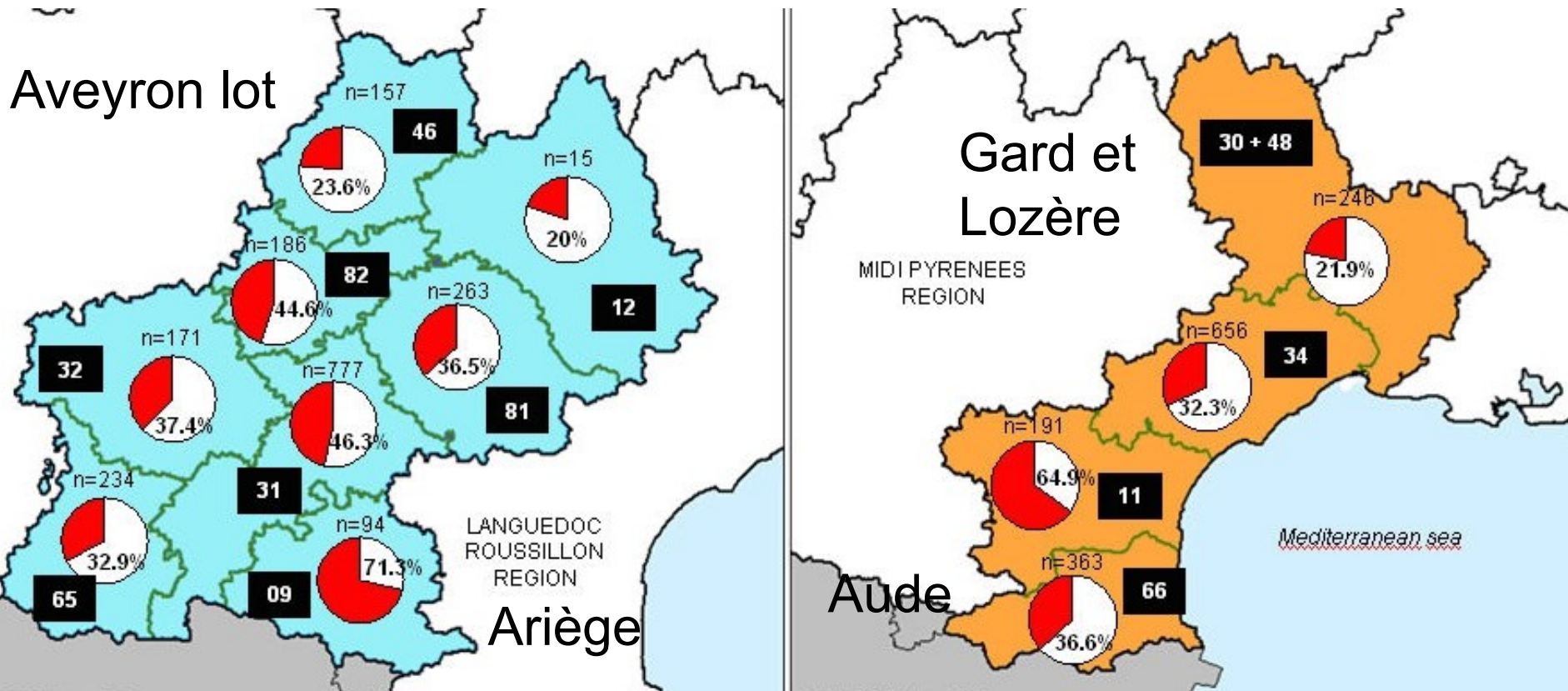


Stramer SL Transfusion 2015

Izopet J Clin Virol 2015

Dalton H Curr Infect Dis Rep 2014

HEV in Southwest France: seroprevalence in blood donors



3353 blood donors : 39,1% (21,9% -71,3%)

Transmission (Developing countries genotypes 1 and 2)

- Indirect by ingestion of water contaminated by human feces :
 - 10⁶ to 10⁸ viral particules /g of stools
- Environmental reservoir
- Low person to person transmission : few secondary cases (0,7 to 2% vs 50 to 70% for HAV)
- Washed food, vegetables

Transmission (Developing countries genotypes 1 and 2)

- **Materno-foetal transmission**
 - Foetus contaminated by transplacental during third trimester



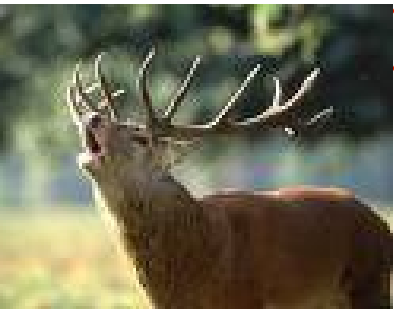
**High morbidity and mortality
For the foetus and the mother**

Transmission

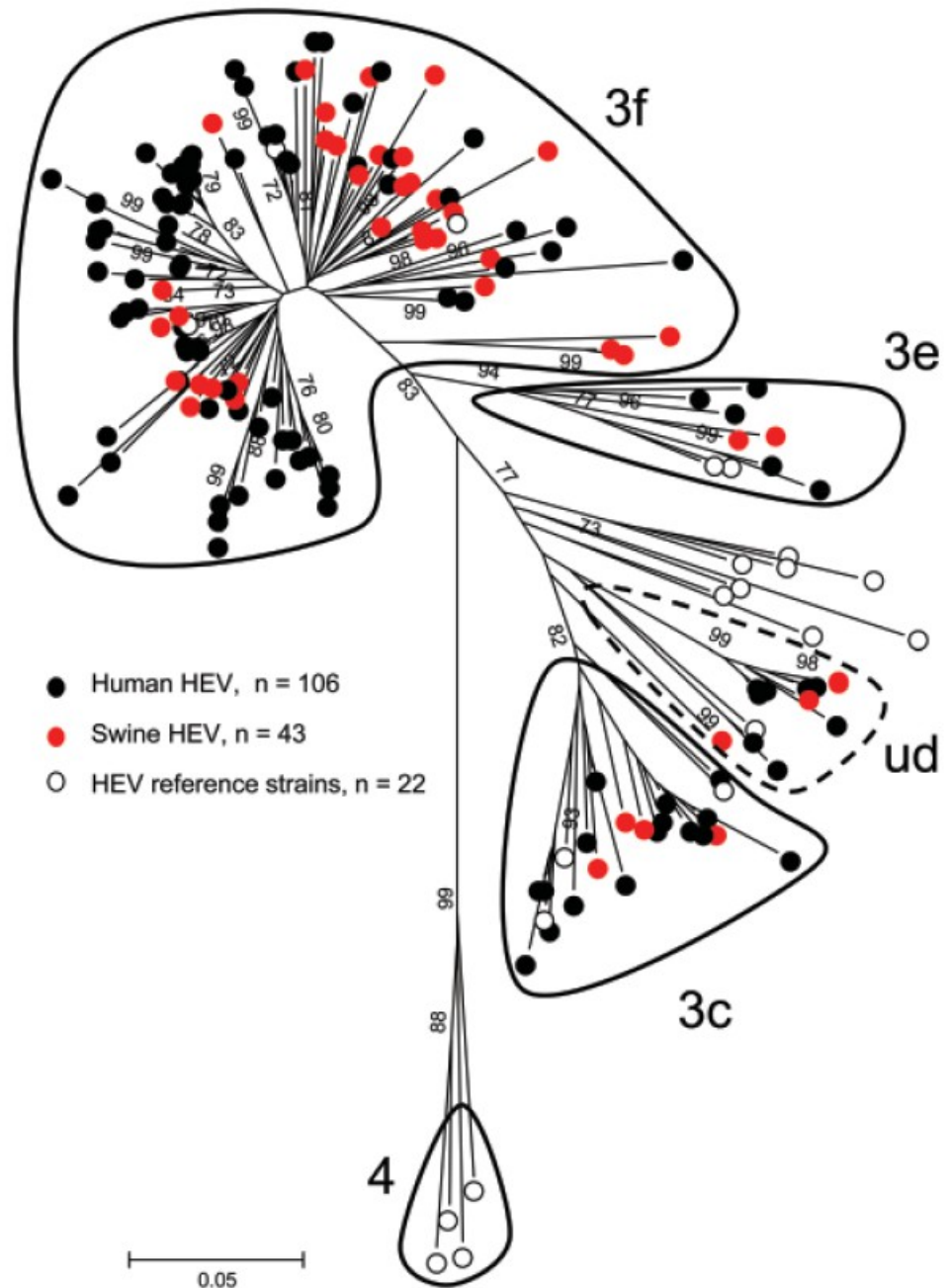
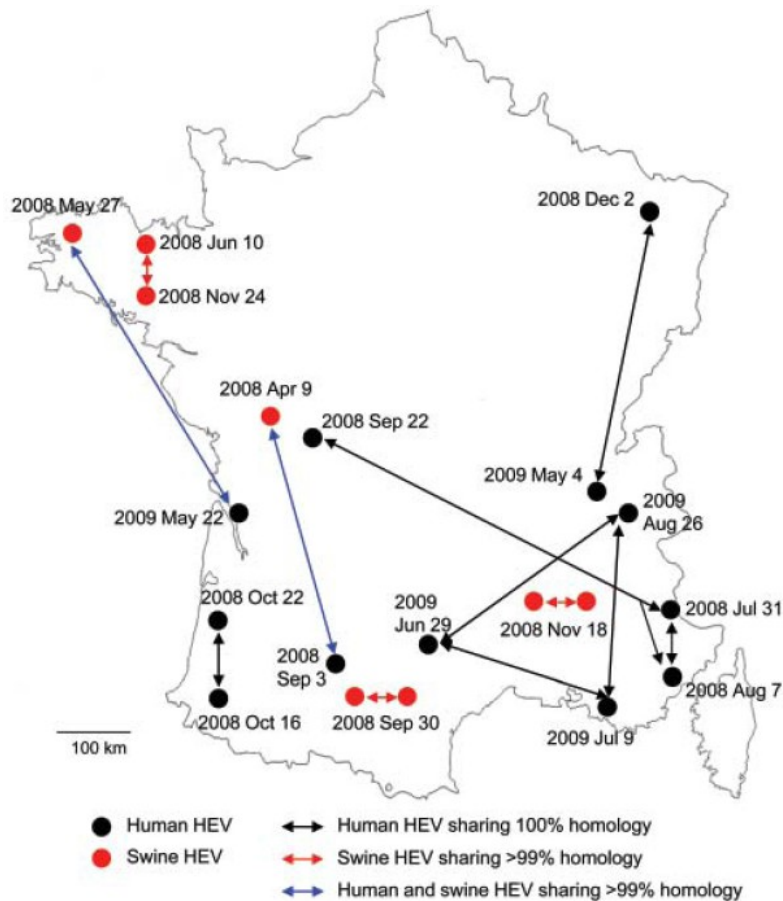
(Developed countries genotypes 3 and 4)

- **Zoonosis** : animal reservoir
 - Domestic pigs, wild boar
 - seroprevalence of 90% in some pig farms,
 - HEV present in 30% of pig farms in France)
 - Cattle, goats, sheep, deer
 - Rabbits

1. No symptoms in the animal host
2. Only **genotypes 3 and 4**



Swine and human strains homology



Transmission

(Developed countries genotypes 3 and 4)



Corsica Figatelli 58%
positive HEV RNA

Colson JID 2010



Liver Sausage in Toulouse
44% positive HEV RNA

Mansuy EID 2011

Transmission (Developed countries genotype 3)

- Transfusion

- England

- Oct 2012 to sept 2013
- 225 000 blood donations , southeast England
- Mini pools of 24 donors
- 1/2848 viremic donors, 71% seronegative
- Transfusion of 62 contaminated blood components
 - 42% HEV infection, 1 apparent clinically mild hepatitis, 10 developed prolonged infection
- Risk factors for HEV transmission:
 - Volume transfused (PFC, platelets)
 - Absence of donor detectable Ab
 - High viral load

Transmission (Developed countries genotypes 3)

- Transfusion
 - England

1/2848



80 000 -100 000
HEV infected during the year of the study

Transmission (Developped countries genotypes 3)

- **Transfusion** : viremic donors

- Germany

- 1/1240

Vollmer T J Clin Microbiol 2012

- Netherlands

- 1/762

Hogema BM Transfusion 2015

- France

- 1/ 2200

Gallian EID 2014

- US

- 1/9500

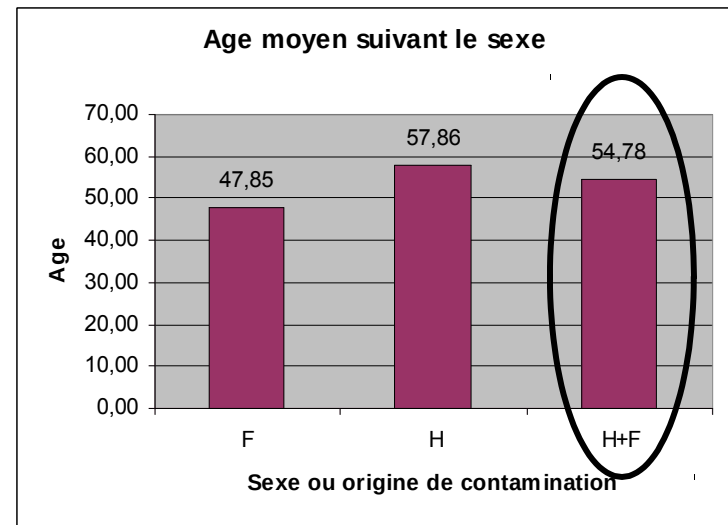
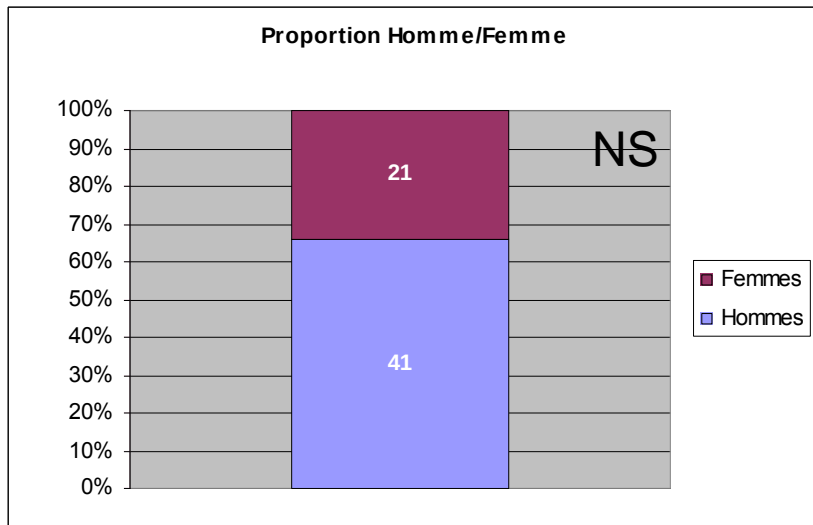
Stramer SL Transfusion 2015

Autochthonous hepatitis E

- Acute hepatitis E, diagnosis
- Severe forms
- Neurological symptoms
- Chronic evolution in immunocompromised patients, treatment

Acute hepatitis : clinical characteristics:

Middle aged/elderly man



62 consecutive patients from 2003 to 2007

HEV infection may be misdiagnosed as a drug-induced liver injury (DILI)

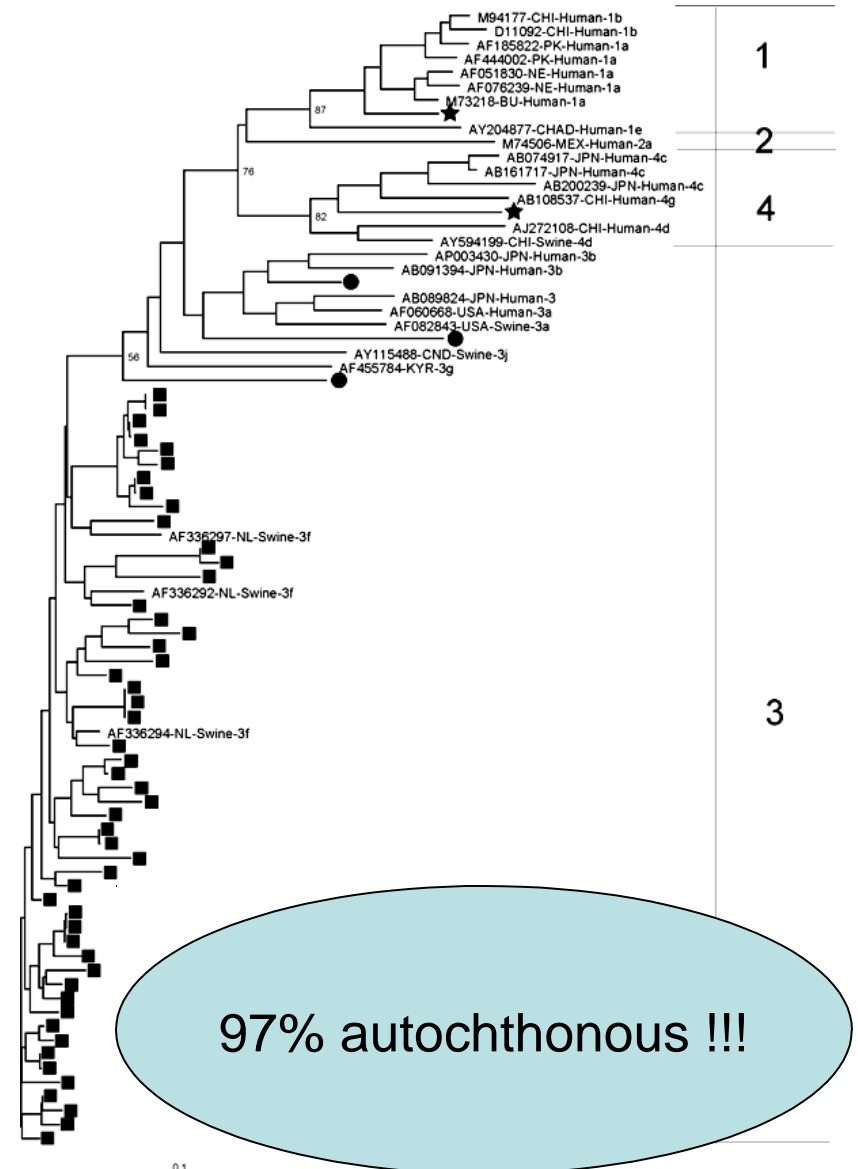
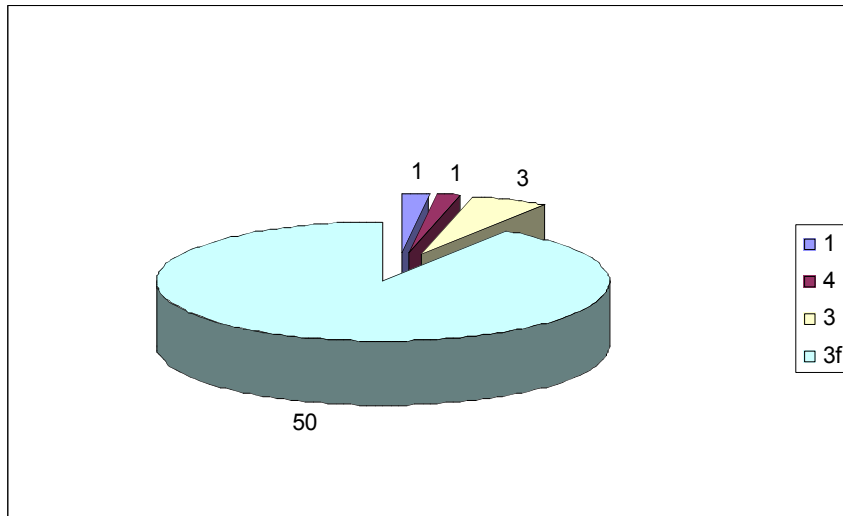
- Occurs more frequently in the elderly in whom polypharmacy is common
- Clinical features may be indistinguishable from DILI

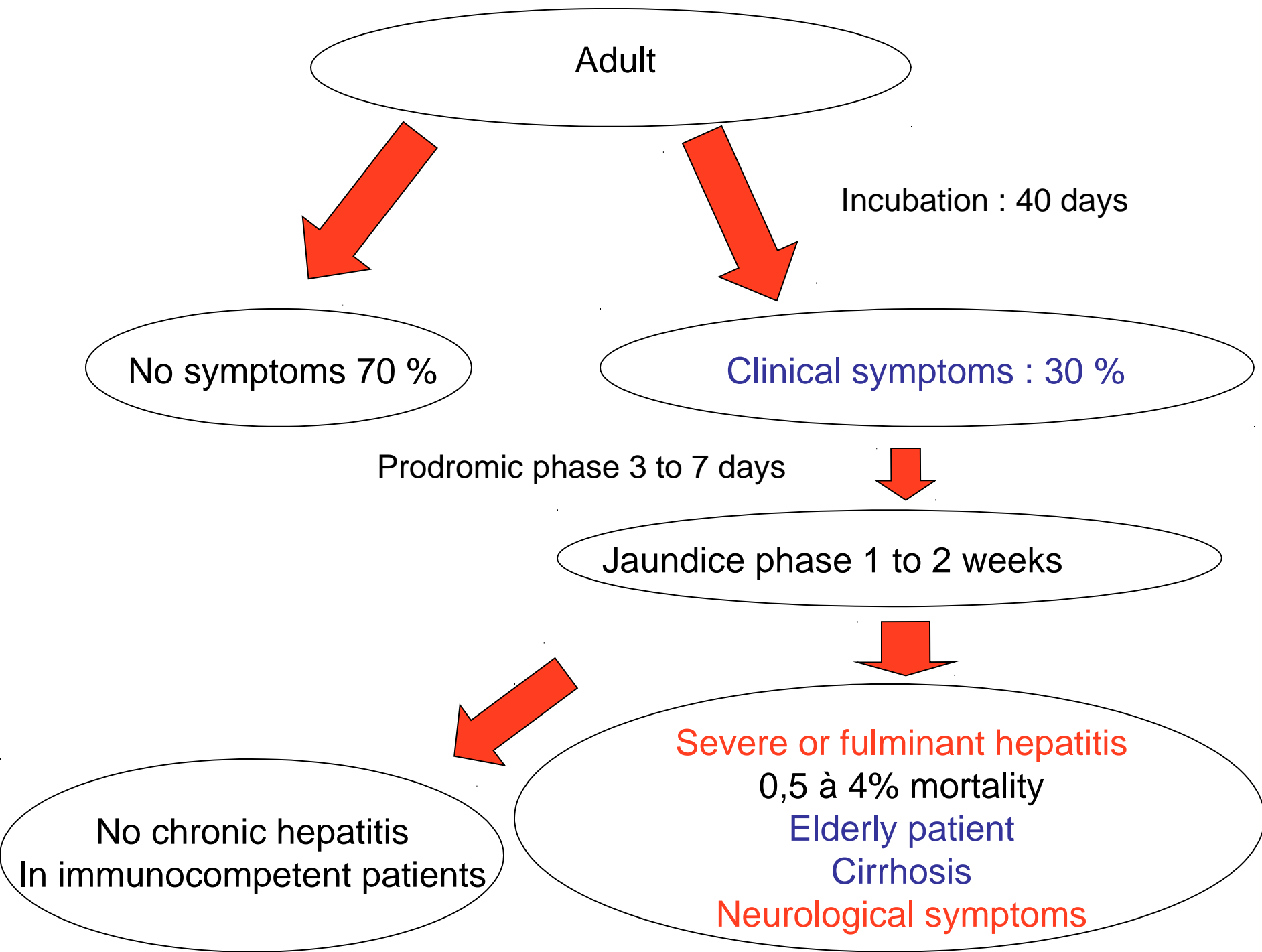
❑ **Study from England in 2007** : 12% of patients with criterion-referenced DILI from Southwest England retrospectively tested had HEV infection

❑ **Study from the US in 2011** : 3% of patients with criterion-referenced DILI from the USA had HEV infection

Hepatitis E southwest France

- Genotypes
 - 55 patients
 - Genotype 3
 - sub-type 3f +++





Diagnosis

- Indirect diagnosis : serum anti-HEV antibodies
 - No genotype specific serologic testing
 - No cross reactivity of HEV antigen with another pathogen
 - Presence of IgM :
 - Marker of acute infection
 - Sensitivity : 80 à 90%
 - Specificity : > 99.5%

Legrand-Abravanel Clin Vaccine Immunol 2009

- Presence of IgG :
 - Marker of past infection
 - Available assays vary considerably in their performance
 - Variable sensitivity, newer more sensitive assays i.e. Wantai test

Diagnosis

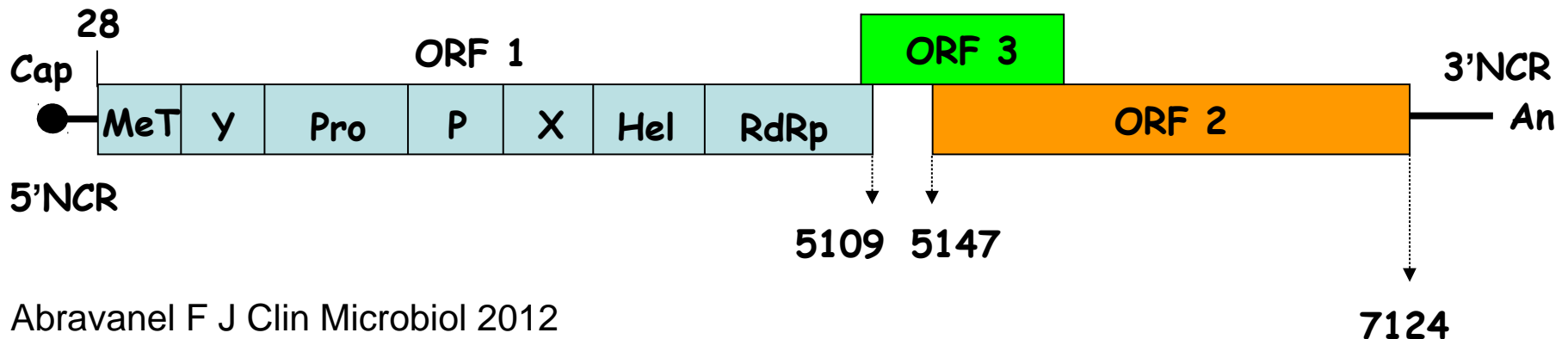
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 - Sensibilité variable, newer more sensitive assays i.e. Wantai test

Legrand-Abravanel

Highly accurate in immunocompetent patients

Diagnosis

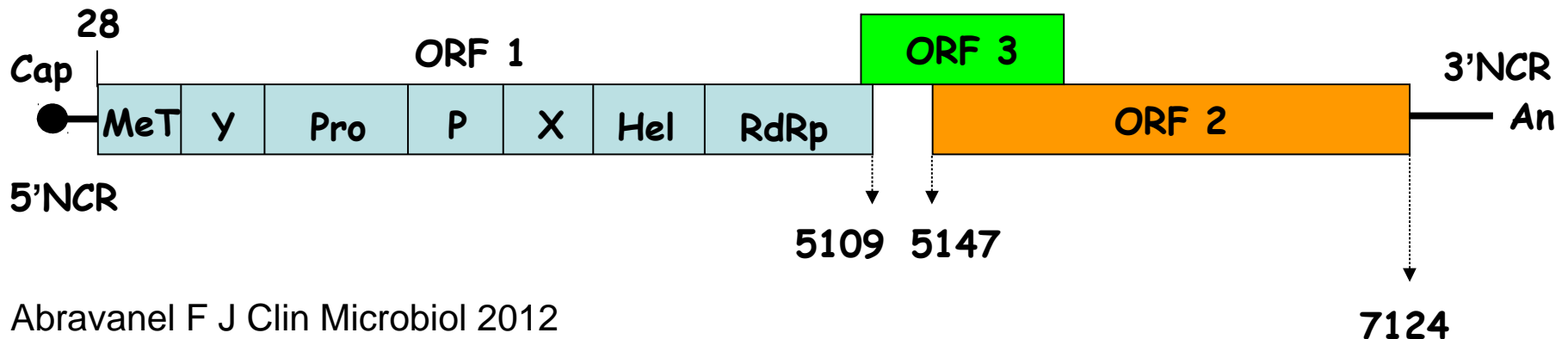
- **Direct diagnosis : gold standard**
 - Detection of viral genome by » polymerase chain reaction »
 - Optimal performance for assays based on primers targeting the **ORF3 region**
 - In stools or serum (or cerebrospinal fluid, urine)
 - Viral load
 - Commercial HEV RNA assays now available

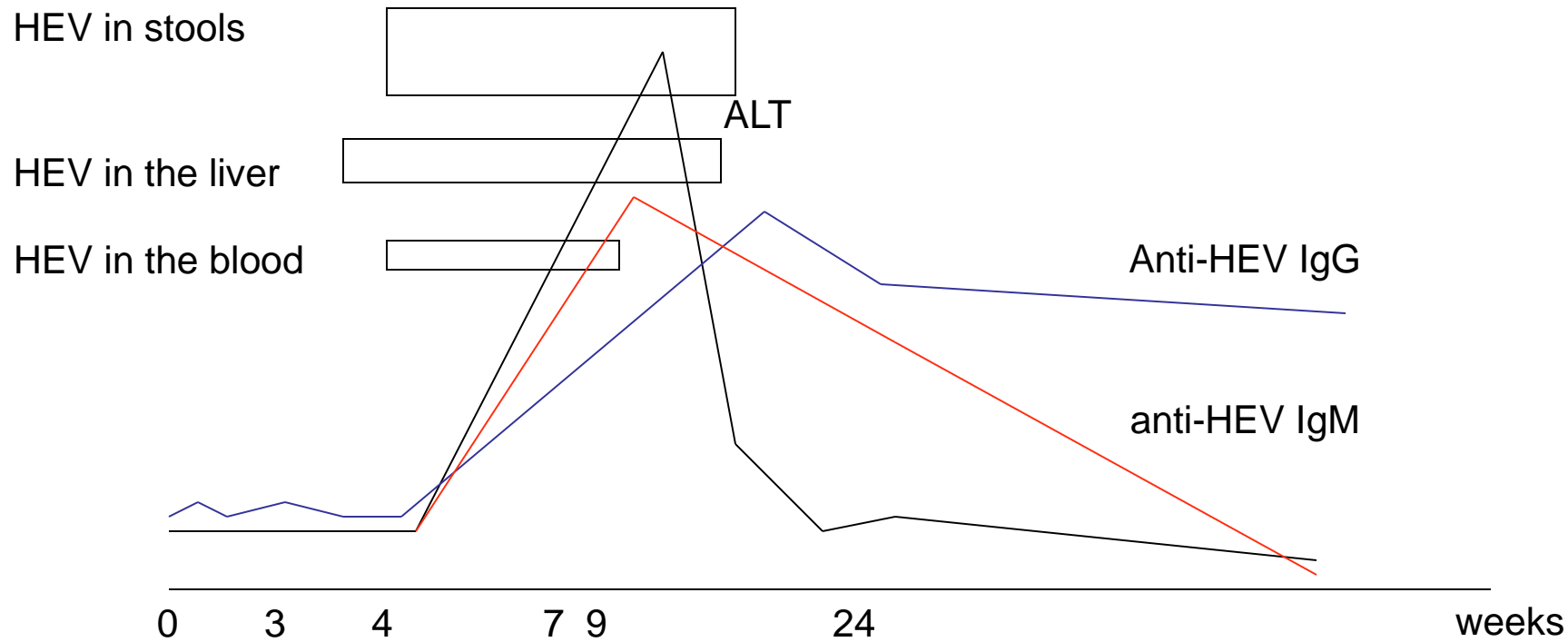


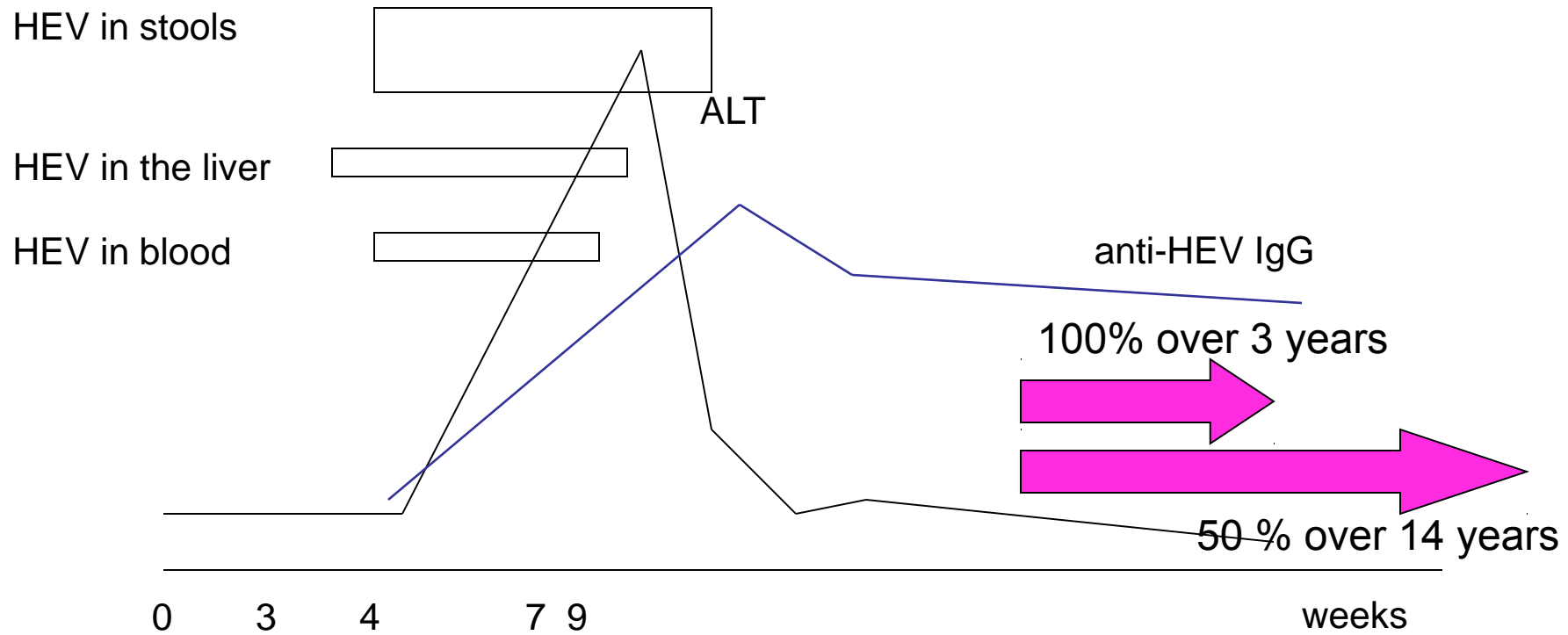
Diagnosis

- **Direct diagnosis : gold standard**
 - Detection of viral genome by » polymerase chain reaction »
 - In stools or blood (or ~~serum~~ ~~urine~~)
 - Serum HEV RNA copies/ml in
 - Optimal performance in immunocompromised patients
 - Primers targeting the **ORF3 region**
 - Commercial HEV RNA assays now available

Mandatory for immunocompromised patients







contamination

Chadha MS J Viral Hepat 1999
 Khuroo MS Hepatol Intern 2010

Autochthonous hepatitis E

- Acute hepatitis E, diagnosis
- **Severe forms**
- Neurological symptoms
- Chronic evolution in immunocompromised patients, treatment

Toulouse experience : fulminant liver failure

Variables	Severe form (encephalopathy) (n = 7)	Mild form (no encephalopathy) (n = 33)	Univariate analysis
Age (Year)	65 ± 11	56 ± 18	NS
Sex (M/F)	5/2	25/8	NS
Active alcohol abuse > 40g/day (Yes/no)	5/2	6/27	p = 0.04
Chronic liver disease (Yes/no)	6/1	4/29	p < 0.0005
Length of hospitalisation (Days)	21 ± 18	6 ± 6	p < 0.0005
Death (Yes/no)	5/2	0/33	p < 0.0005
Aspartate transaminase AST* (< 35 IU/L)	3181 ± 1512	1833 ± 1498	p = 0.037
Alanine transaminase ALT* (< 45 IU/L)	3239 ± 2003	2498 ± 1855	NS
Alkaline phosphatase (100-280 IU/L)	430 ± 217	650 ± 410	NS
γGT (11-60 IU/L)	207 ± 118	408 ± 258	p = 0.053
Bilirubin(μmol/L)	350 ± 218	134 ± 107	p < 0.0005
Prothrombin index (%) ^Φ	37 ± 16	78 ± 24	p < 0.0005
Accelerin (%) ^Φ	56 ± 24	112 ± 41	p = 0.002

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Mortality in the presence of encephalopathy : 71%

Autochthonous hepatitis E

- Acute hepatitis E, diagnosis
- Severe forms
- **Neurological symptoms**
- Chronic evolution in immunocompromised patients, treatment

Neurological disorders during HEV infection

- 126 patients with locally acquired acute or chronic hepatitis HEV3 infection
- 2 hospitals (Toulouse, Truro UK), 2004-2009
- **Neurological symptoms : 5,5%**
 - Inflammatory polyradiculopathy (n=3)
 - Guillain Barre syndrome (n=1)
 - Encephalitis (n=1)
 - Ataxia/proximal myopathy (n=1)

Neurological disorders during HEV infection

- French retrospective study,
- Immunocompetent patients, 2006-2013
- Wide range of neurological disorders
- 14 patients
- 4 main entities
 - Mononeuritis multiplex (n= 6)
 - Neuralgic amyotrophy (Parsonage Turner syndrome) (n=3)
 - Meningoradiculatis (n=3)
 - Acute demyelinating neuropathy (GBS) (n=2)

Hépatite E et formes neurologiques

- **Neuralgic amyotrophy (Parsonage Turner syndrome)**
 - Royal Cornwall hospital UK, Radboud University Nijmegen MC, Netherlands
 - **10 %** : 5/47 patients
- **Guillain Barré syndrome**
 - Royal Cornwall hospital UK, Radboud University Nijmegen MC, Netherlands
 - **5%** : 10/201 patients



Neurological disorders during HEV infection

- **Immunomediated mechanism :**
 - Neuralgic amyotrophy (PTS)
 - Guillain Barré
 - Persisting symptoms, sequelae+++
- **Direct mechanism**
 - Mononeuritis multiplex
 - Meningitis
 - No sequelae

Autochthonous hepatitis E

- Acute hepatitis E, diagnosis
- Severe forms
- Neurological symptoms
- Chronic evolution in immunocompromised patients, treatment

HEV infection in the transplant patient

- Few symptoms
 - No symptoms in 63 % of cases
- Moderate transaminase elevation (2xN)
- PCR need for diagnosis, low sensitivity for serology
- Chronic evolution in 60 % of cases

Kamar NEJM 2008
Gérolami NEJM 2008

- Transfusion transmission of HEV ?
 - 5 cases in 367 transplant patients (Paul Brousse, Créteil)

Féray C Lancet 2014

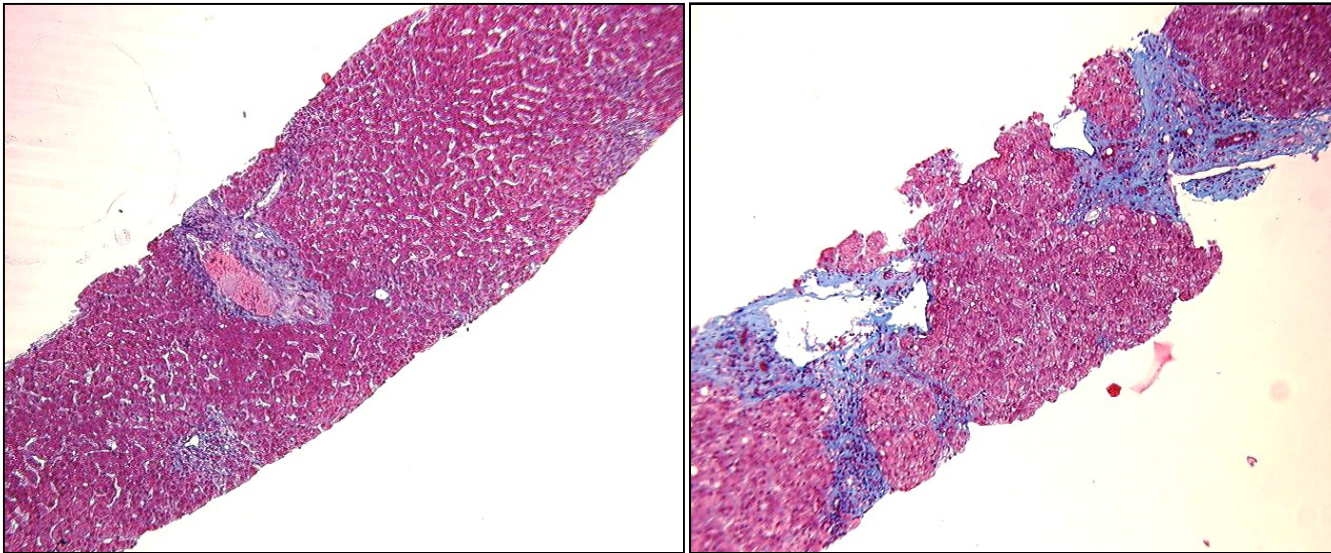
The evolution of chronic hepatitis E is cirrhosis

Gérolami NEJM 2008

Haagsma Liver Transplant 2008

Haagsma Liver Transplant 2009

Pischke Liver Transplantation 2009



Original Article

Ribavirin for Chronic Hepatitis E Virus Infection in Transplant Recipients

Nassim Kamar, M.D., Ph.D., Jacques Izopet, Pharm.D., Ph.D., Simona Tripon, M.D., Michael Bismuth, M.D., Sophie Hillaire, M.D., Jérôme Dumortier, M.D., Ph.D., Sylvie Radenne, M.D., Audrey Coilly, M.D., Valérie Garrigue, M.D., Louis D'Alteroche, M.D., Matthias Buchler, M.D., Ph.D., Lionel Couzi, M.D., Ph.D., Pascal Lebray, M.D., Sebastien Dharancy, M.D., Ph.D., Anne Minello, M.D., Maryvonne Hourmant, M.D., Ph.D., Anne-Marie Roque-Afonso, M.D., Ph.D., Florence Abravanel, Pharm.D., Ph.D., Stanislas Pol, M.D., Ph.D., Lionel Rostaing, M.D., Ph.D., and Vincent Mallet, M.D., Ph.D.

N Engl J Med
Volume 370(12):1111-1120
March 20, 2014



The NEW ENGLAND
JOURNAL of MEDICINE

Original Article

Ribavirin for Chronic Hepatitis E Virus Infection in Transplant Recipients

- 59 patients
 - 37 renal transplants
 - 10 liver transplants
 - 5 heart transplants, 5 pancreas, 2 lung transplants
- Ribavirin started 9 months (1-82) after HEV infection diagnosis
- Median dosage 600 mg/day (29-1200)
- Median duration 3 months (1-18)

59 Transplant recipients with HEV viremia

59 Received ribavirin therapy

56 Had a response

2 Had an unknown response status

1 Had a partial response

78%

46 Had a sustained virologic response

10 Had a recurrence of HEV replication

2 Died
2 Did not undergo re-treatment

6 Underwent re-treatment

1 Underwent re-treatment

90%

4 Had a sustained virologic response

1 Had HEV clearance and was still receiving therapy

1 Had HEV clearance by 3 mo after the end of therapy

1 Had HEV clearance and was still receiving therapy

Risk factors for viral relapse

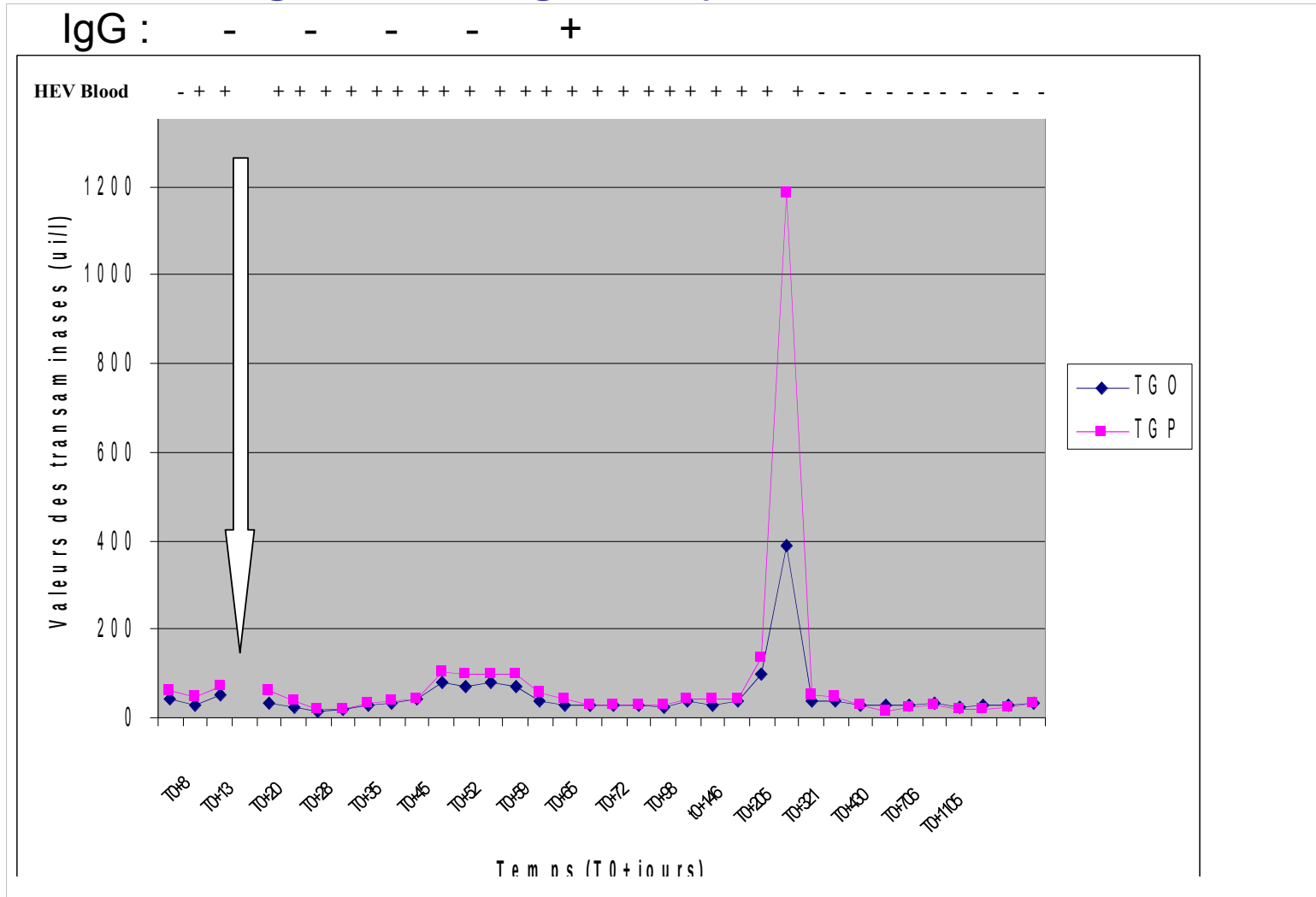
- Lymphocyte count at the start of ribavirin
- Serum HEV RNA detectable at 1 month
- Stool HEV RNA at the end of treatment+++

Kamar N NEJM 2014
Abravanel CID 2014

- Mutation of G1634R viral polymerase : enhances replication

Debing Y Gastroenterology 2014

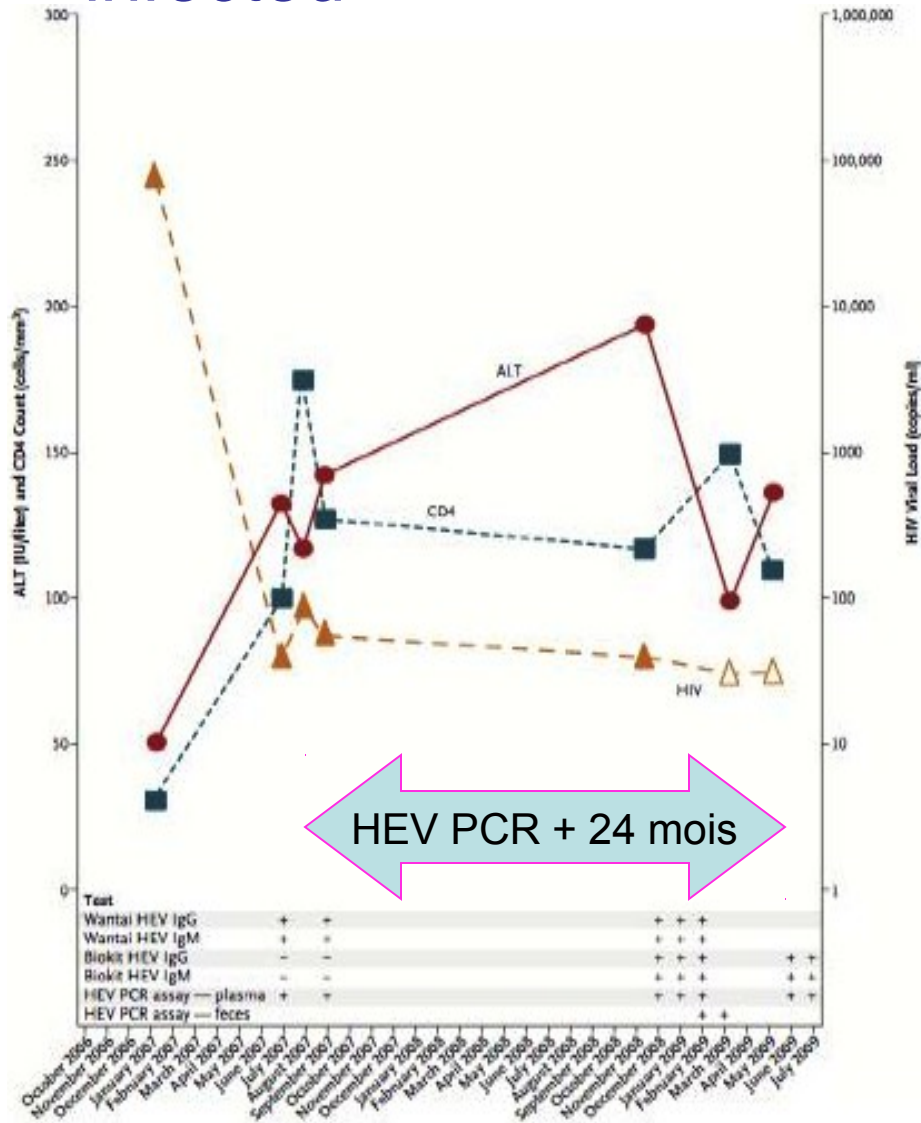
HEV infection in patients treated for a hematological malignancy



Ms D 40 years
Acute myeloblastic leukemia

Tavitian J Clin Virol 2010
Tavitian EID 2015

Chronic HEV infection in patients HIV infected



- CD4 count < 200
- PCR mandatory
- Risk of cirrhosis

Should we treat acute HEV infection ?

- Multicentric french study
- 21 patients treated with ribavirin during an acute infection
 - 9 patients for a severe hepatitis (PT < 50%)
 - 6 patients > 70 years
 - 4 patients treated with immunosuppressive drugs for auto-immune disease
 - 2 patients undergoing chemotherapy for solid tumor cancer
- « A la carte treatment » : ribavirin for the duration of viremia, stopped when HEV became undetectable in the serum (median 26 days)
- Good tolerance
- HEV undetectable in a median 29 days

Should we treat acute HEV infection ?

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- « A la carte treatment » : ribavirin for the duration of viremia, stopped when HEV became undetectable in the serum (median 26 days)
- Good tolerance
- HEV undetectable in a median 29 jours

Conclusion

When should you test for HEV infection ?

1. First line for an acute hepatitis
2. Especially for a middle aged/elderly man
3. If you're thinking about a Drug Induced Liver Injury
4. Patient with elevated transaminases and neurological symptoms
5. Elevated enzymes (even moderate +++) in an immunocompromised patient

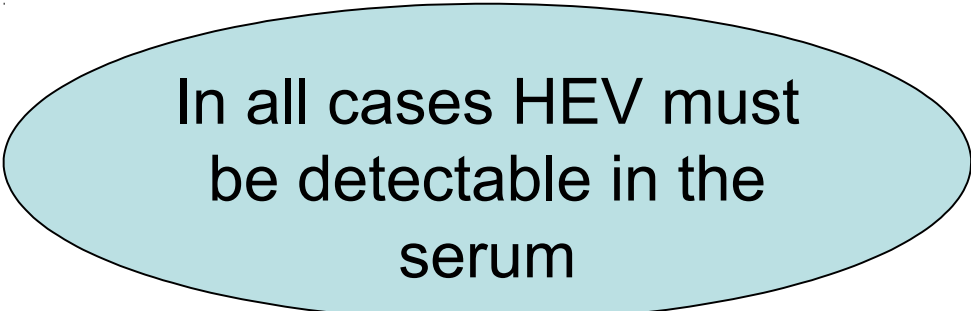
Conclusion

Who should be treated?

1. Chronic hepatitis in a transplant patient, or patient with a hematological malignancy

(author's personal opinion)

2. Acute hepatitis in a patient treated with chemotherapy
3. If the patient presents neurological symptoms
4. Patient > 70 years
5. Patient with cirrhosis ?



In all cases HEV must be detectable in the serum

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