Prevention, diagnosis and treatment of Hepatitis E
Masterclass Infectieziekten 2024

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How to become infected with HEV in Europe

Identification HEV 1983 Balayan

- **Human volunteer exposed to pooled stool extracts of non A-non B hepatitis patients. Intervirology 1983;20(1):23-31**
  - **immune EM faeces identified 27-30nm virus like particles**
- **1990 genome was successfully cloned and sequenced**

Four Genotypes Hepatitis E infect humans with regional restriction

HEV genotype	Geographic distribution
1 (human)	Asia, Africa
2 (human)	Mexico
3 (human & swine)	Europe, United States
4 (human & swine)	China, Taiwan,Japan, (Europe)

Two types of clinical presentation

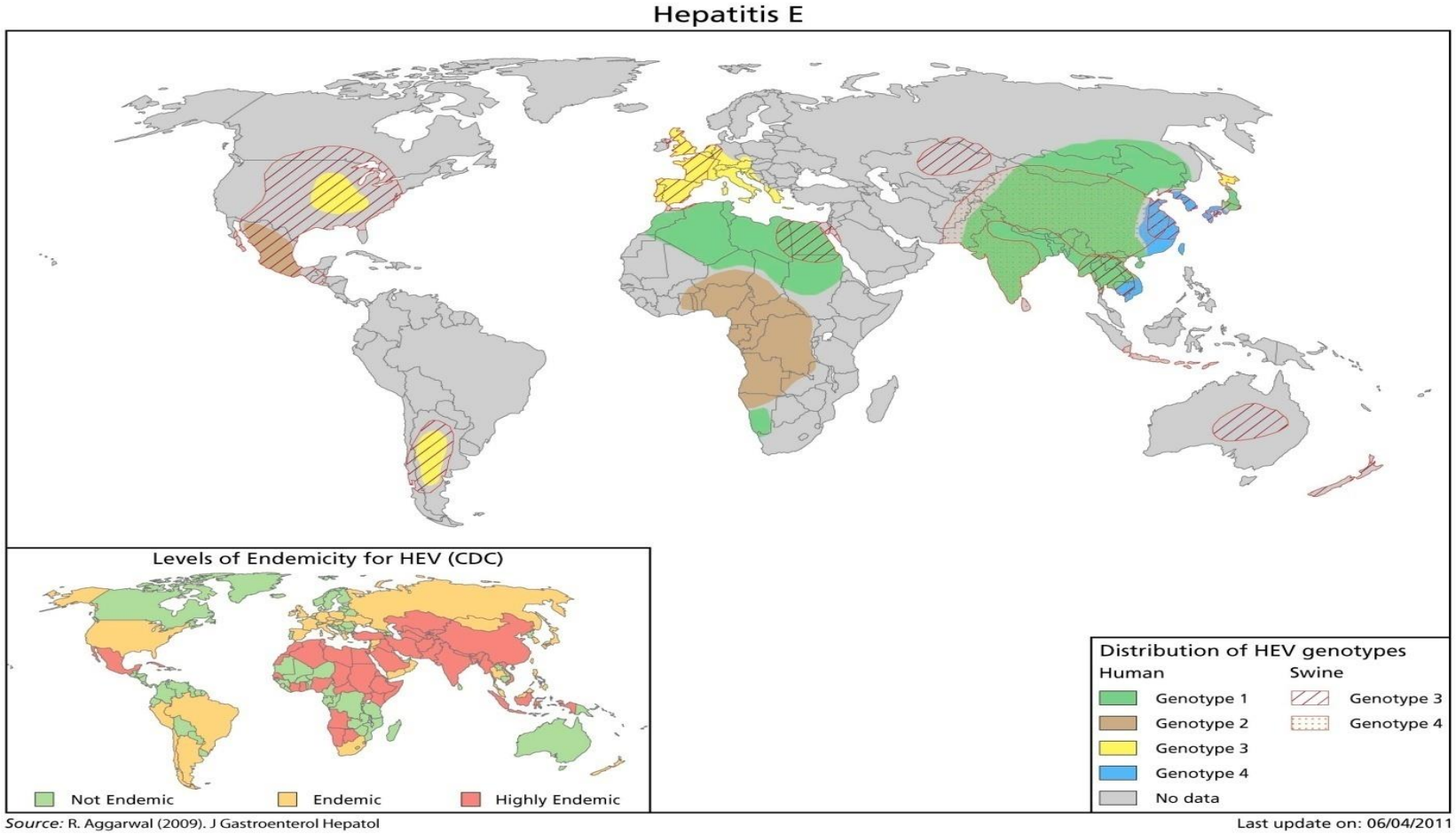
Endemic HEV infection Genotype 1,2

- Outbreaks > 50 people
- Explains 30-70% acute hepatitis in these regions
- Young healthy people
- Severe disease in pregnancy
- Travel related disease in Europe

Sporadic HEV infection Genotype 3, 4

- Sporadic cases
- Older males
- Pre-existing disease
- Relation with (N)ASH
- No severe disease in pregnancy

Sporadic HEV genotype 3 is a zoonose



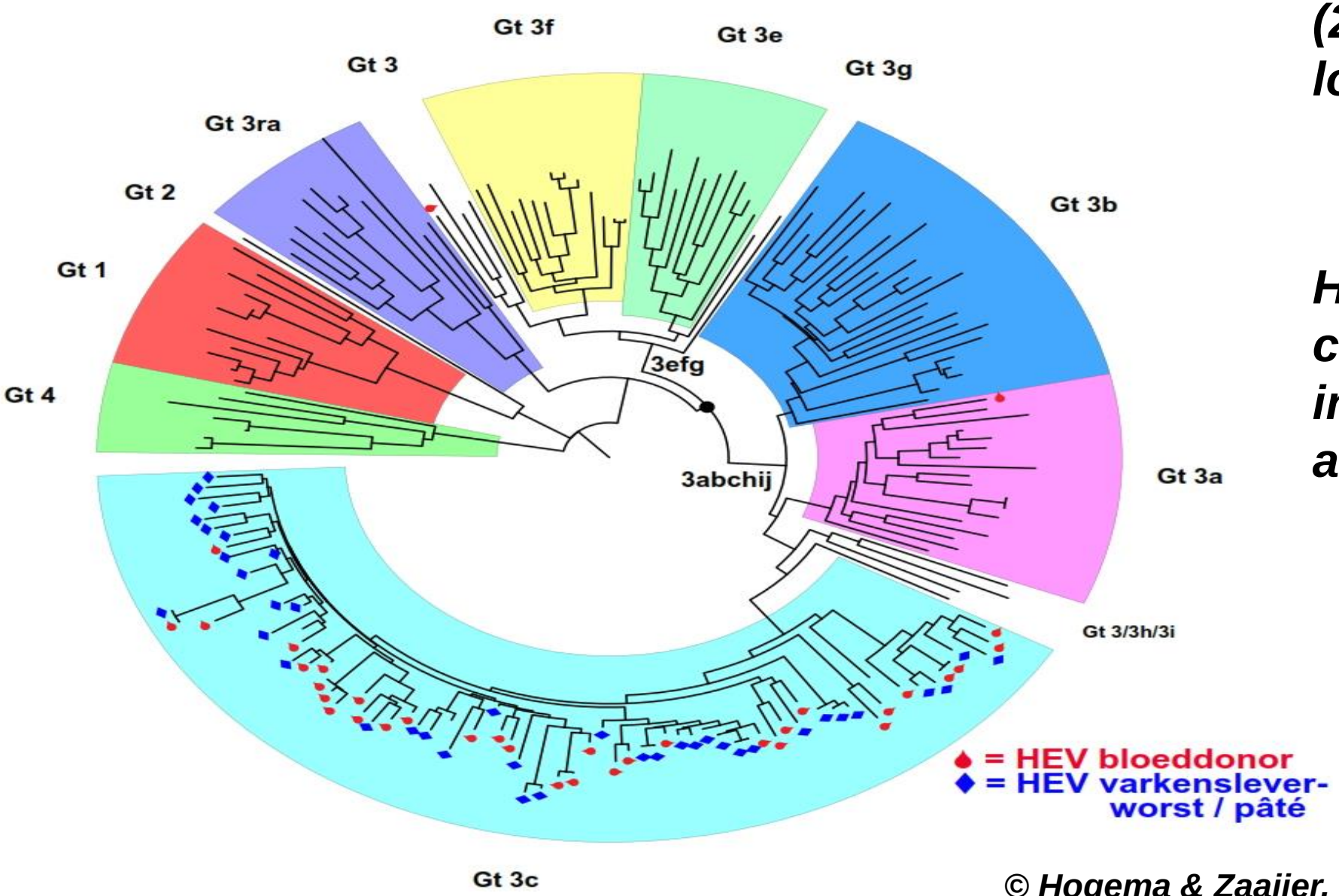
Sporadic HEV genotype 3 is a zoonose

- Zoonotic transmission of hepatitis E virus from deer to human beings. Lancet 2003;362:371-3

- Consumption of wild boar linked to cases of hepatitis E. J Hepatol 2004;40:869-70

- Complete or near-complete nucleotide sequences of hepatitis E virus genome recovered from wild boar, deer and four patients who ate the deer. Virology 2004;330:501-505.

HEV genotyping in the Netherlands

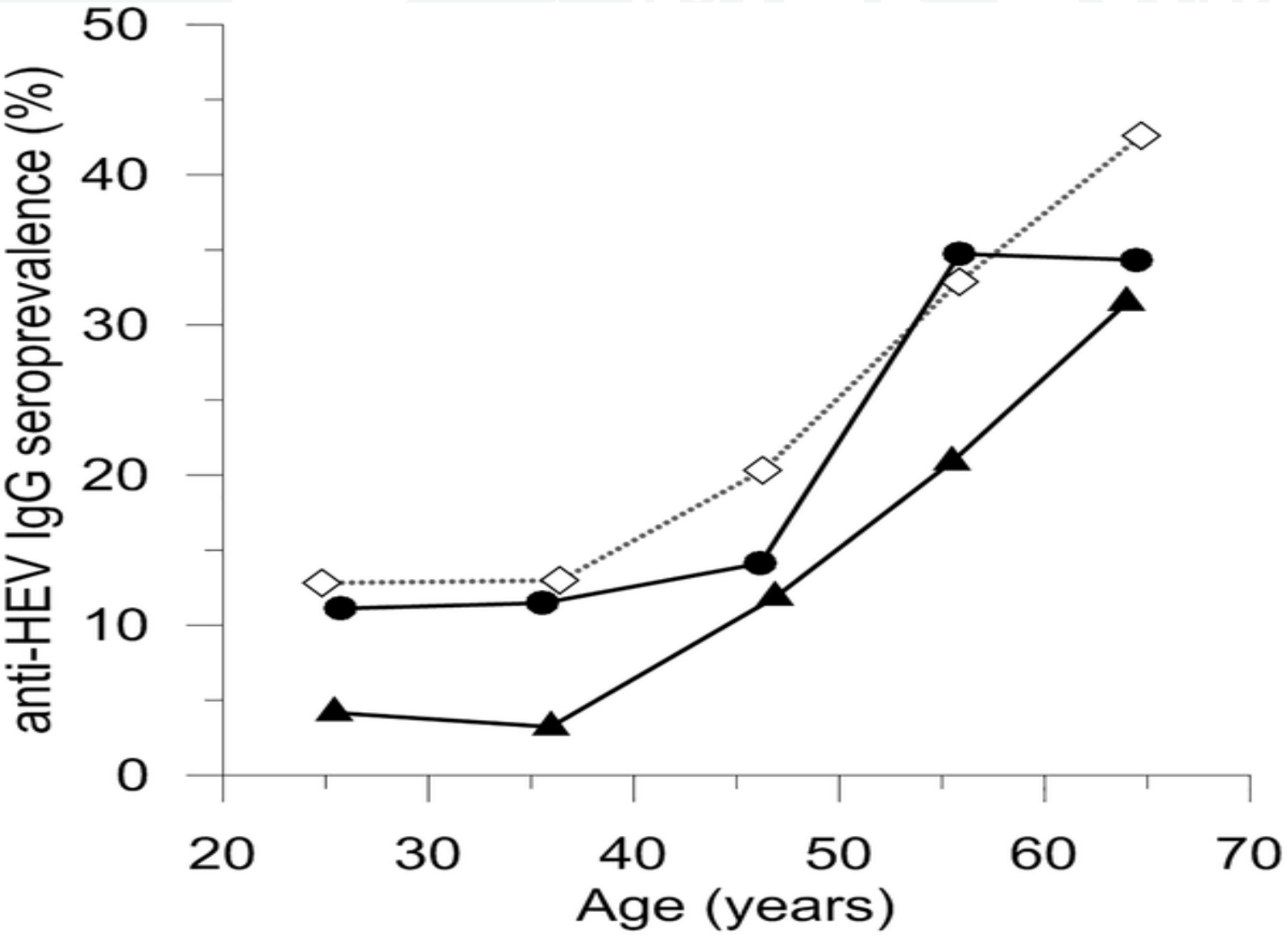


Genotyping performed in 35 blood donors (2016-2017) with higher load:

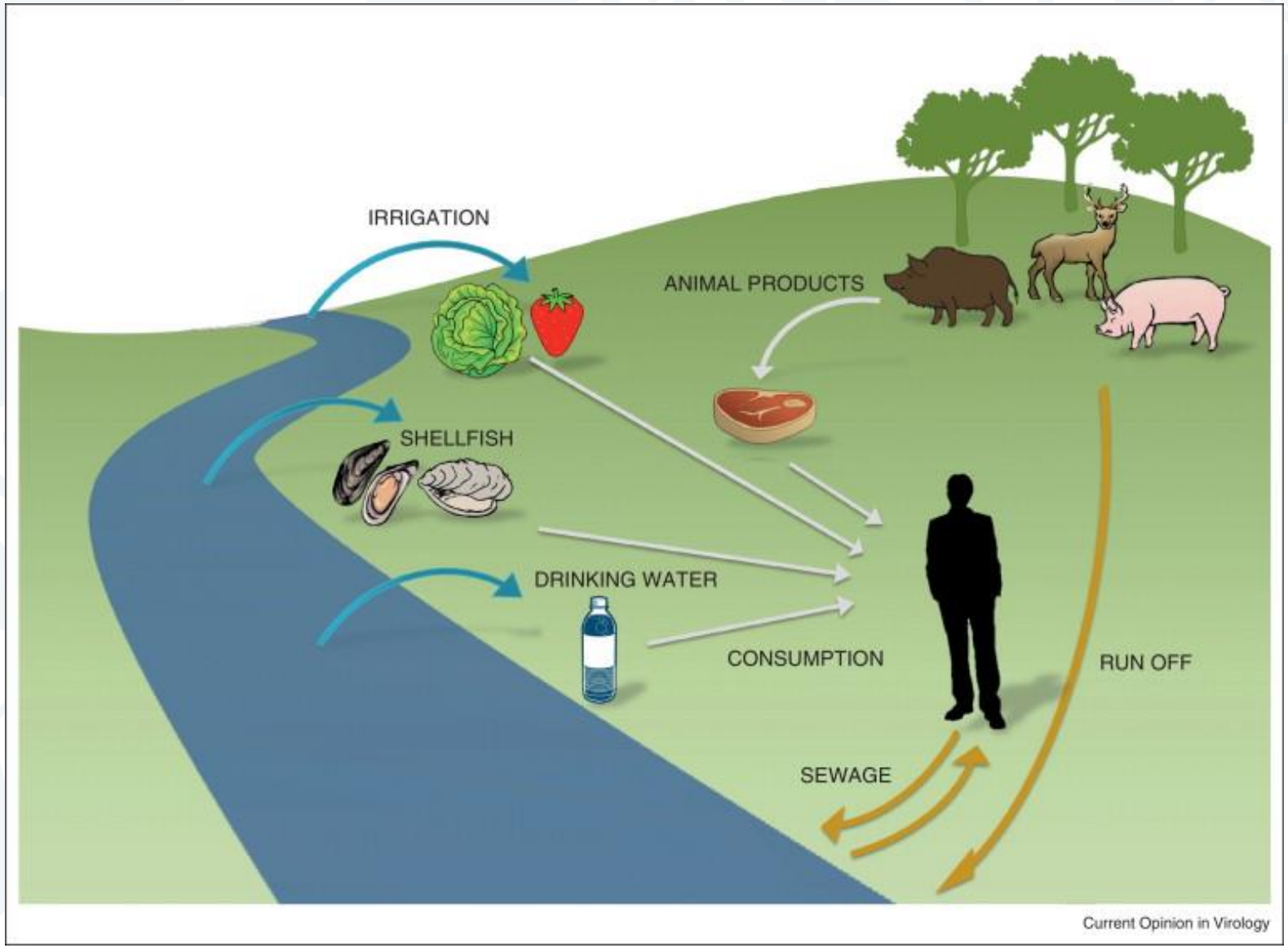
33/35 genotype 3c

HEV sequences did cluster with those found in dutch liver sausages and liver paté

Anti-HEV prevalence in donors with a vegetarian lifestyle (triangles) and donors who consume meat on a daily basis (circles).

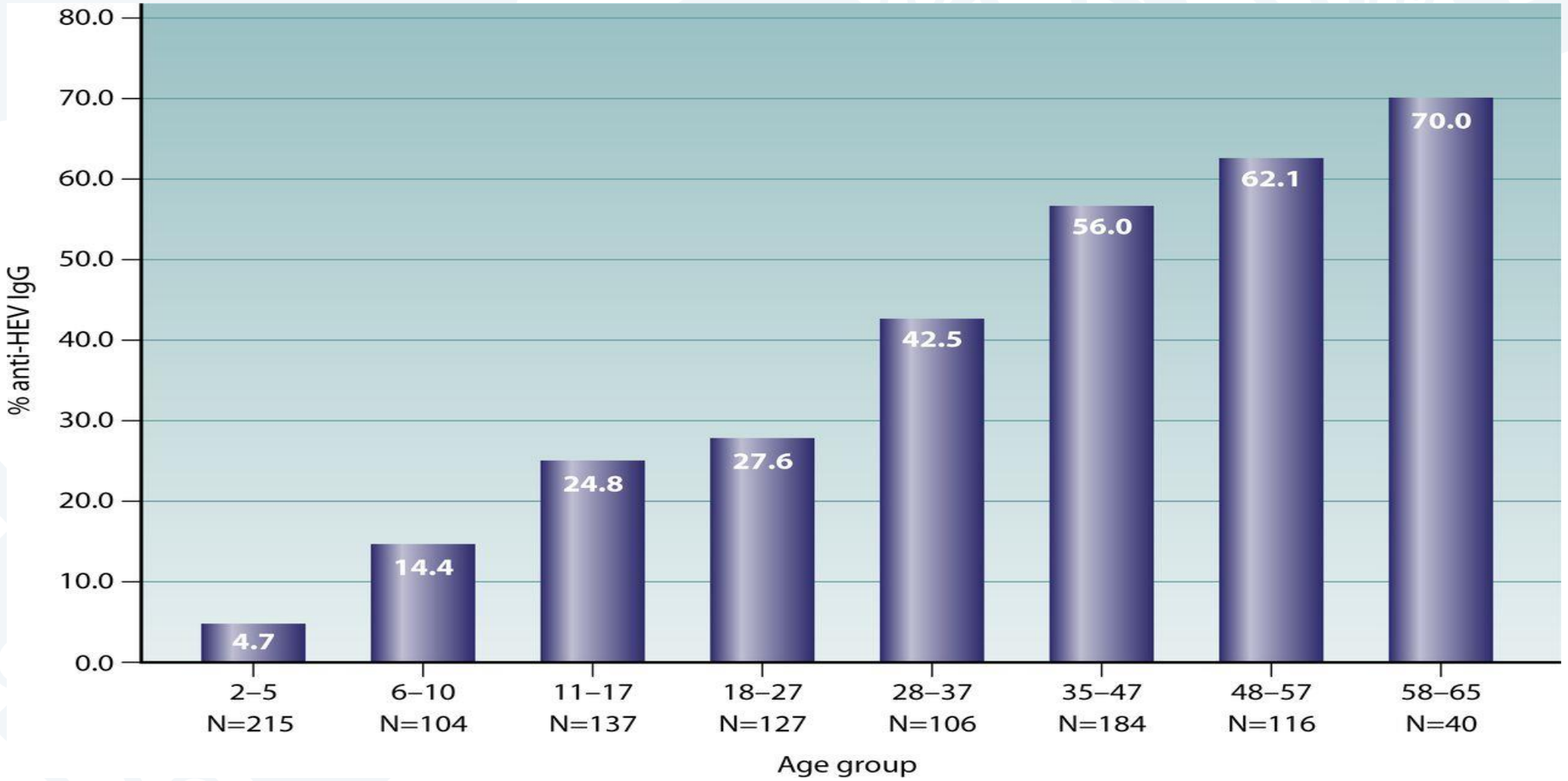


Slot E, et al. PLOS ONE 12(4):2017.



Van de Poel;Curr Opinion Virol 2014

Anti-hepatitis E virus IgG distribution in Midi-Pyrenees area of France, according to age.



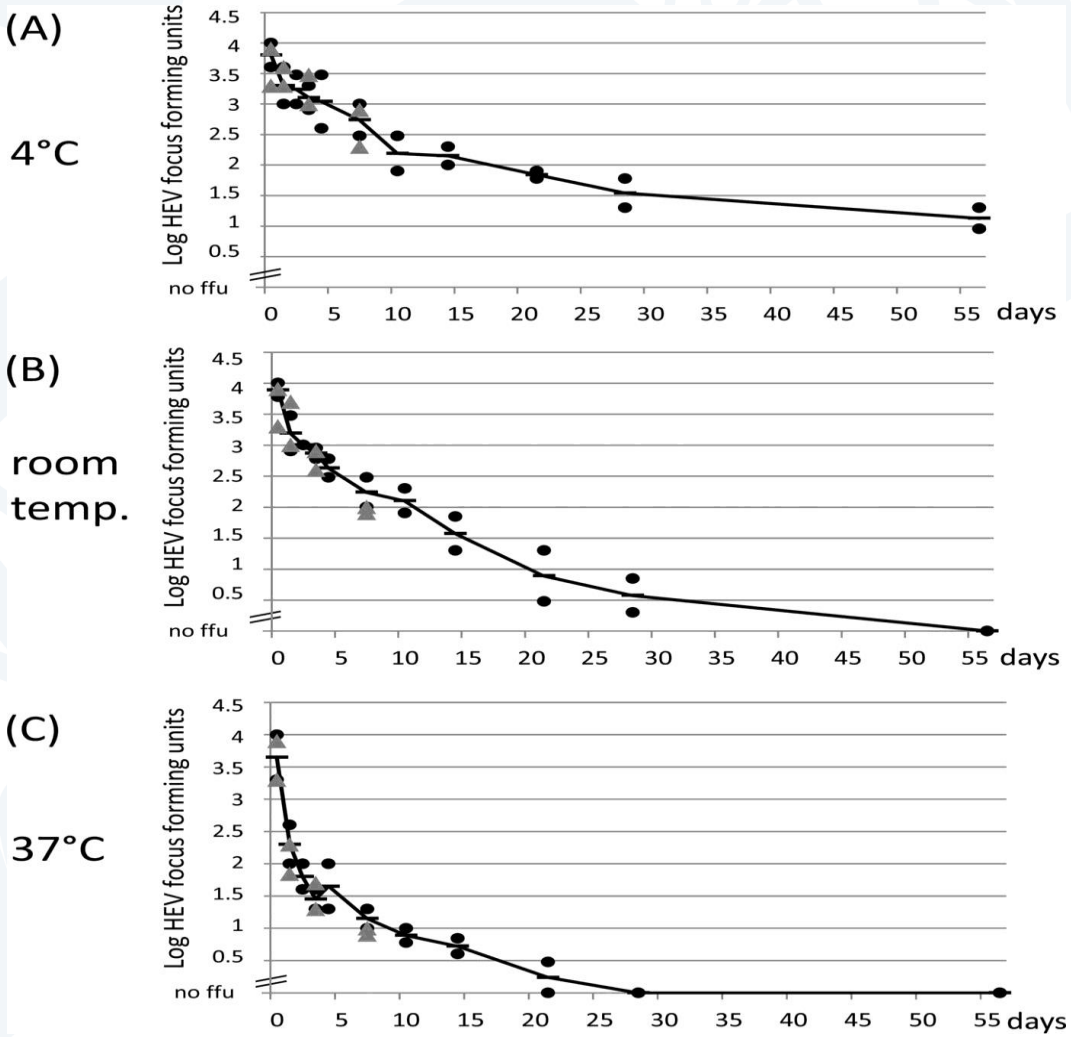
Kamar N et al. Clin. Microbiol. Rev. 2014;27:116-138

How to avoid HEV if a patient is at risk ?

Sorry no dried sausages today !
Written instructions which foods to avoid

Transplantation 2018;102:15-20

Reduction in HEV infectivity by long-term storage at different temperatures.



Reimar Johne et al. Appl. Environ. Microbiol. 2016;82:4225-4231

Thermostability HEV

- Input: faeces or commercialy available raw pork liver

- 56 °C for 30-60 minutes (medium rare)--→alive
- 60 °C 60 minutes (medium rare)----------→ alive

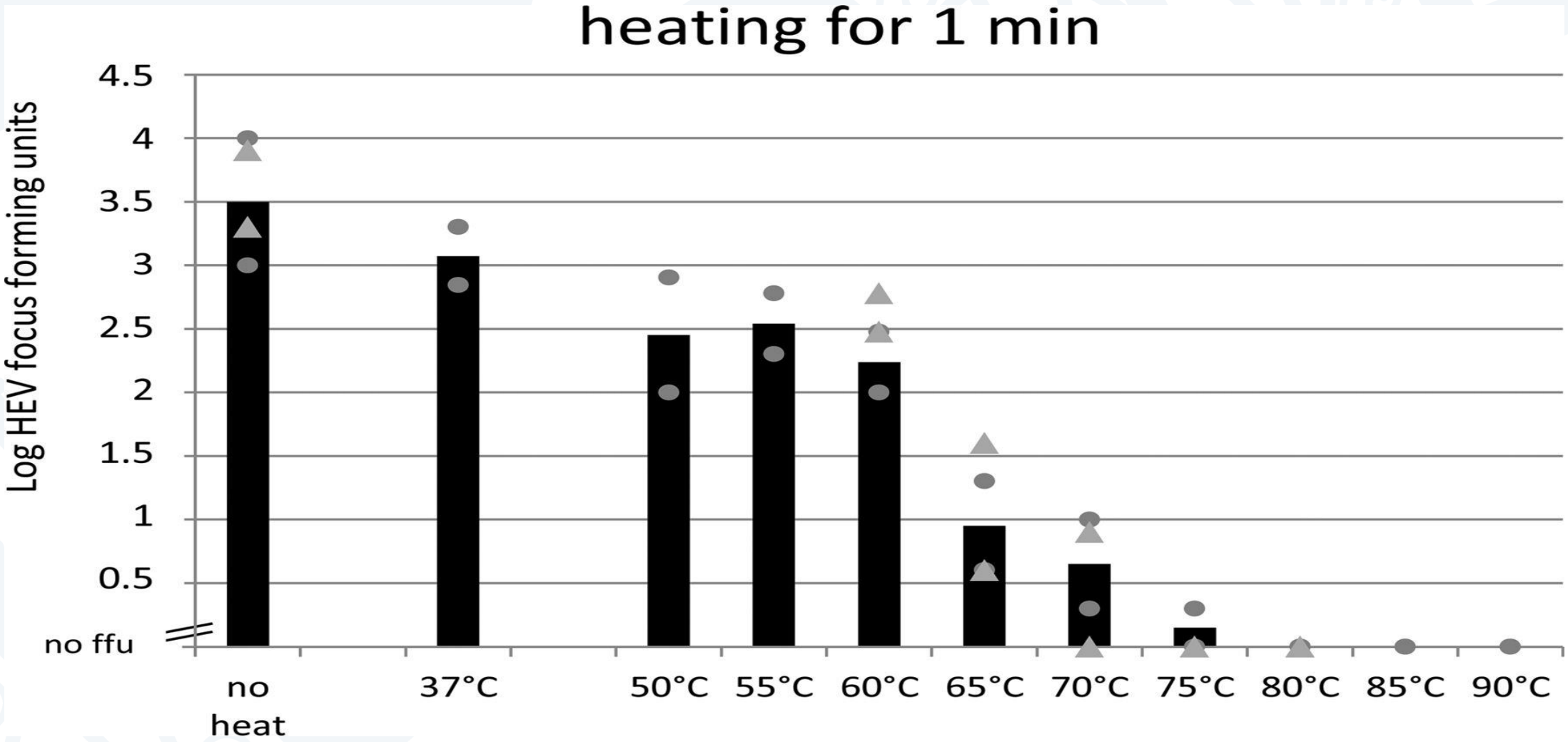
- 70 °C 10 minutes (well done)----------→ no detectable virus

Emerson SU J Infect Dis 2005;192:930-3

Tanakada T J Gen Virol 2007;88:903-11

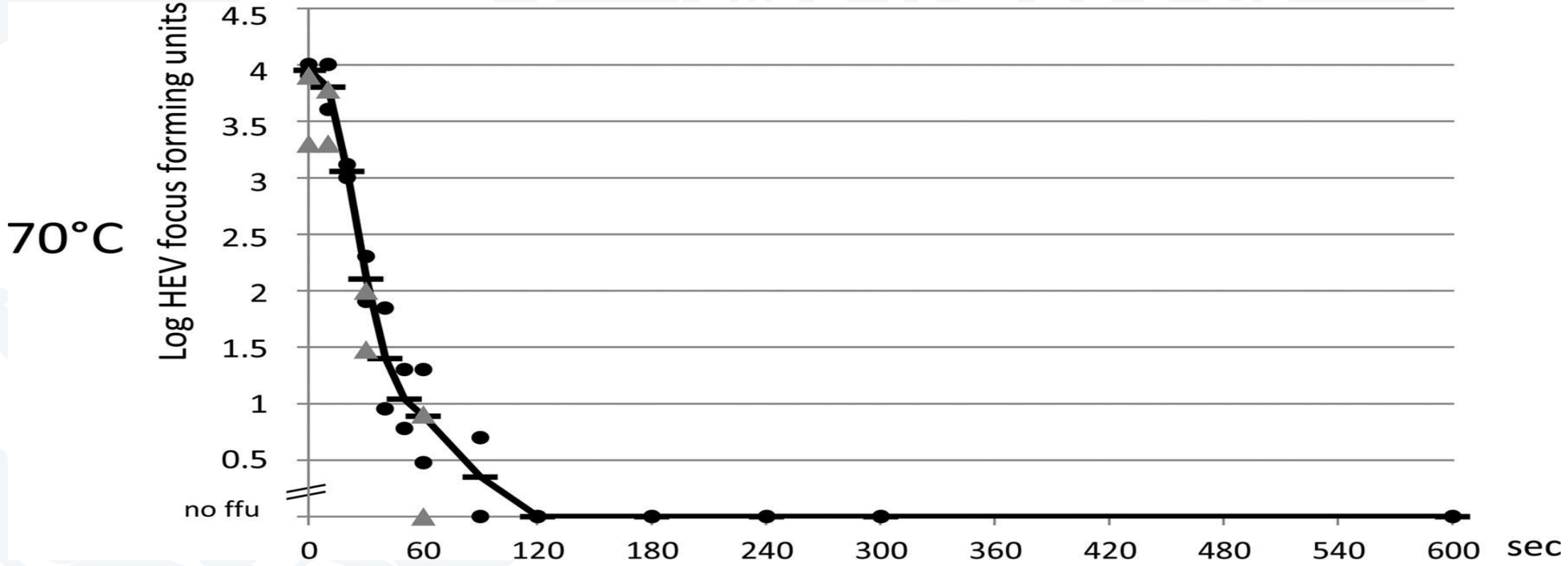
Feagins AR Int J Food Microbiol 2008;123:32-37

Reduction in HEV infectivity by heating at different temperatures for 1 min.



Reimar Johne et al. Appl. Environ. Microbiol. 2016;82:4225-4231

Reduction in HEV infectivity by short-term heating at 70°C.

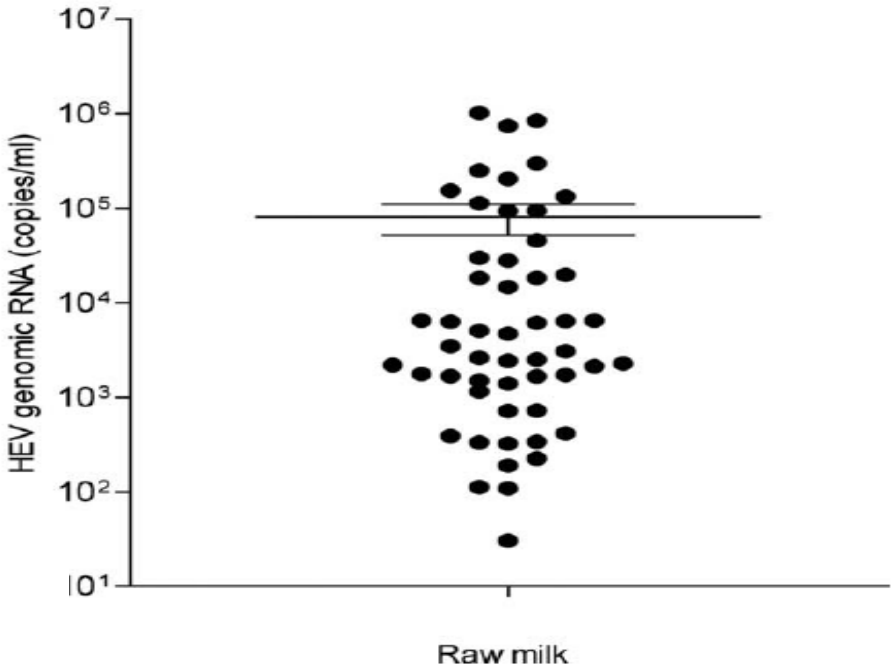


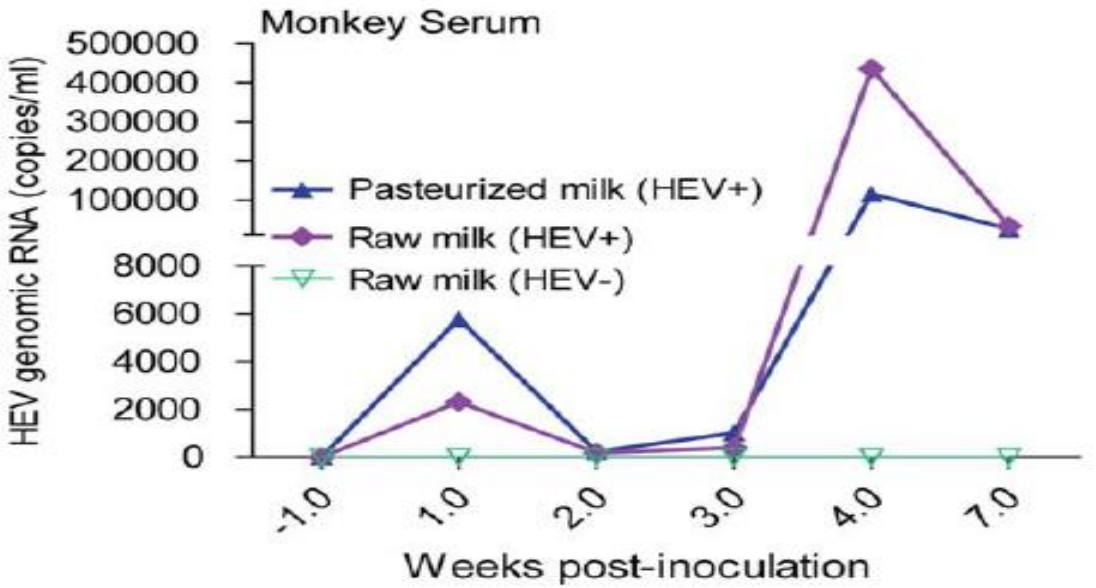
Reimar Johne et al. Appl. Environ. Microbiol. 2016;82:4225-4231

RAPID COMMUNICATION | HEPATOLOGY, VOL. 64, NO. 2, 2016

Excretion of Infectious Hepatitis E Virus Into Milk in Cows Imposes High Risks of Zoonosis

- HEV gt 4 RNA in Cow milk in China
- Transmission in Rhesus monkey (gavage):
- Pasteurisation (30’ 62°C or 72°C): insufficient
- Boiling (3’ 100°C) = sterilisation





Rural China: Mixed Farming

Person to person transmission genotype 3

- In general infectivity is low, very inefficient partner to partner transmission
- Transmission by organ transplantation both solid and BMT is possible
- Outbreaks:
  - cruise ship related to shellfish
  - japanese nursing home related to food

Said B;Emerg Inf Dis 2009;15:1738-44. Ishida S;J Clin Virol 2018;101:23-8.

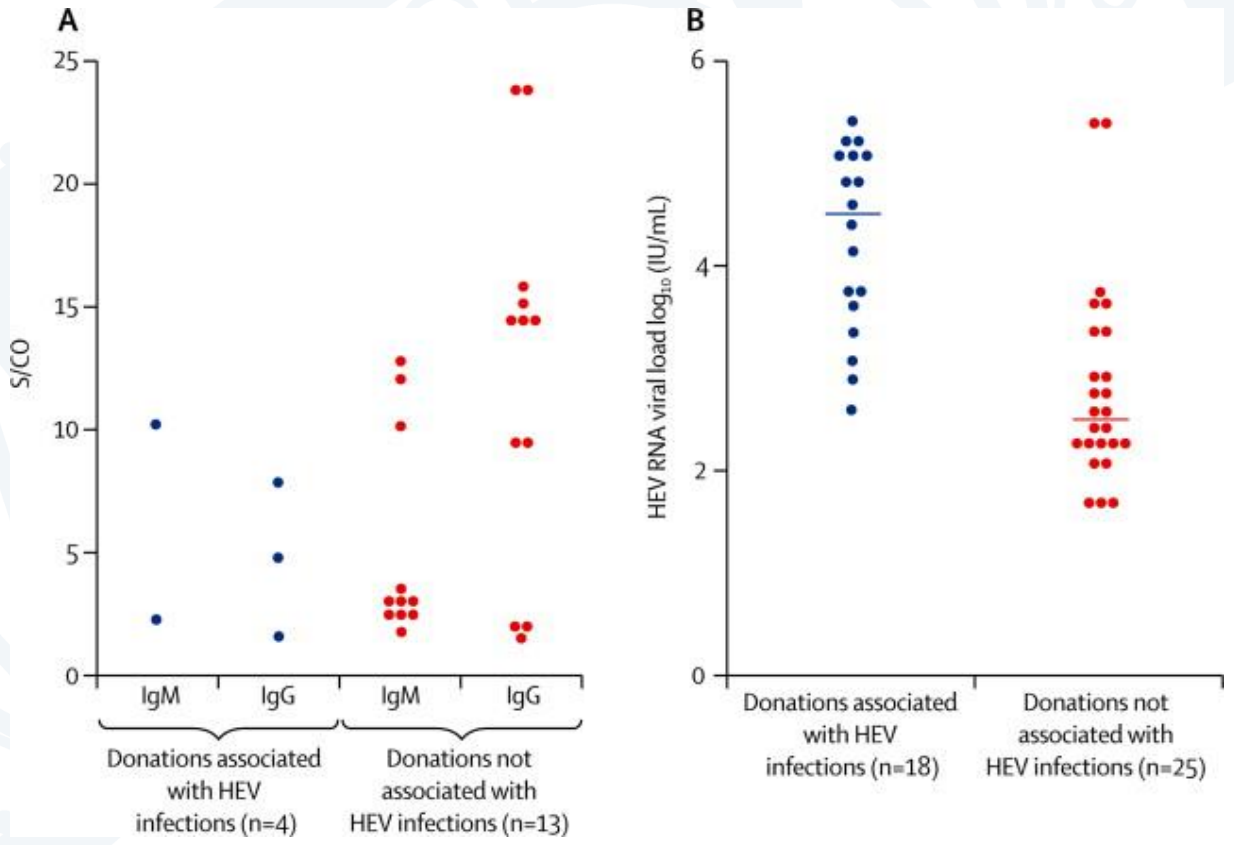
Impact of HEV pcr (+) blood transfusion
South East England Study

- 225.000 blood donations: 79 HEV viraemic (0.035%)
- 129 blood products produced, 43 recipients with follow-up
- Signs of hepatitis in 18 recipients (42%)

- **10/18 patients developed chronic infection**

Hewitt et al, Lancet 2014;384:1766-73

Risk of HEV infection is related to plasma volume transfused and HEV infectious dose



Lowest infectious dose 21.000 IU/ml HEV

Which alternative do you endorse in your practice?

Testing for hepatitis E should be part of a routine work up in patients with acute hepatitis of unknown cause, regardless of travel history.

A) Yes

B) No

Case 1. Acute Hepatitis.

Male, 60 years, overweight BMI 31

Previous history:
Seropositive rheumatoid arthritis in remission
Alcohol exposure: 3 drinks a day

Medication:
Salazopyrine 2 dd 1500 mg, Nivaquine 1 dd 100mg, methotrexate 25 mg / week s.c., adalumimab injections 40 mg/every 14 days.

Referral Hepatology Erasmus MC evaluation disturbed liver biochemistry.

Additional information: Fatigue since 1 week. 4 weeks earlier returned from holidays in Greece. Significant alcohol use in Greece. No other risk behaviour, no other relevant information.

Physical exam: Normal

Lab:

ALT	max 1329	AST max	587
AF	max 332	gGT max	728
CRP	1	Leuco	5
alb	47 g/l	bili	11
PT	10,8 sec	glucose	6,5

Ultrasound: Normal with liver steatosis

Case 1. Acute Hepatitis differential diagnosis.

- Acute viral hepatitis in relation to travel: HAV, HEV
- Drug induced liver injury
- Acute viral hepatitis in relation to drugs used e.g.CMV, EBV, HBV reactivation
- Toxic exogenous hepatitis e.g alcohol induced

Making a diagnosis: which lab test ?

A) None (“typical alcohol hepatitis”)

B) HBsAg, anti HCV, anti HAV.

C) test B + IgG and IgM anti HEV

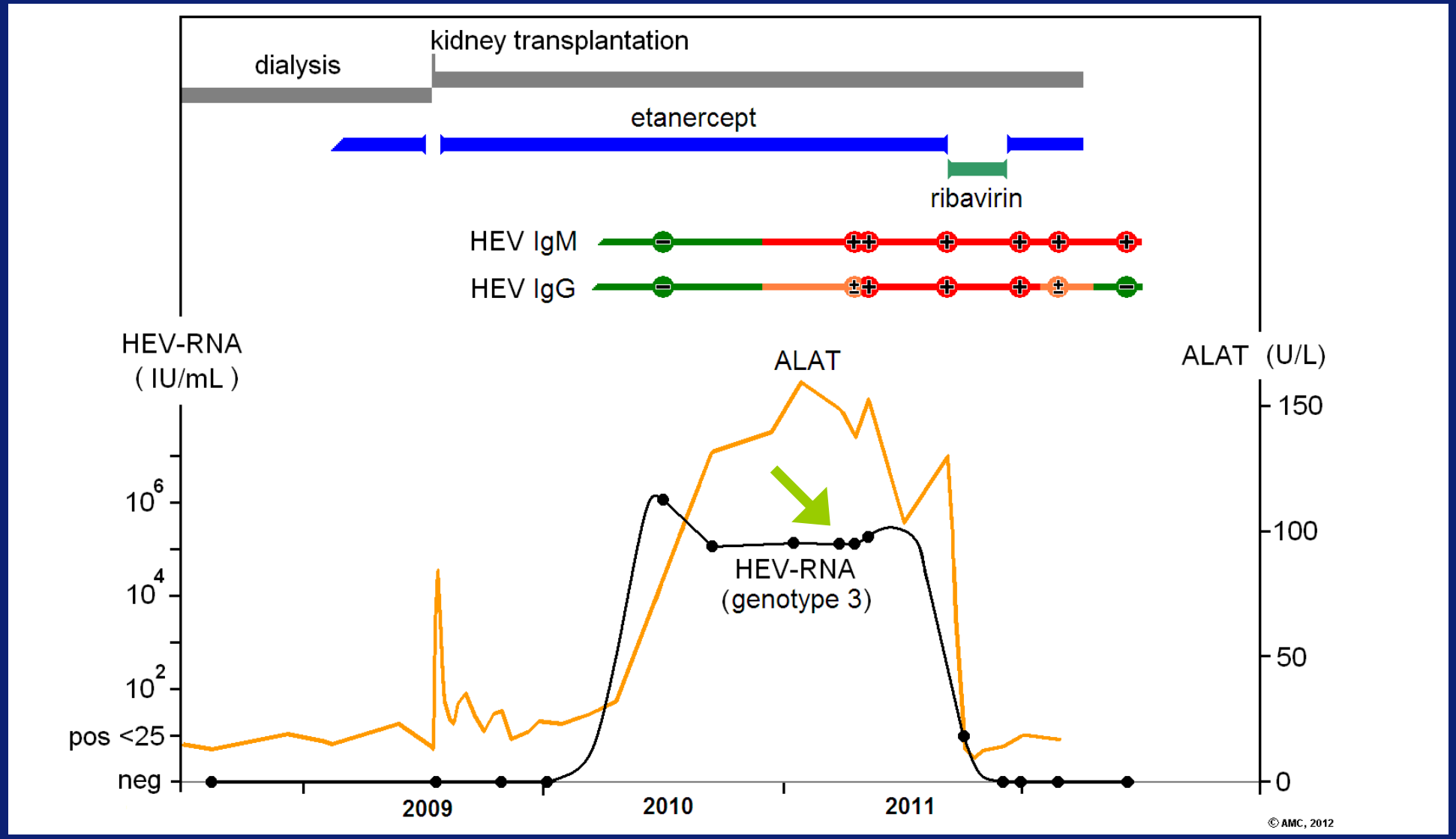
D) Nucleair Acid Testing: EBV pcr, CMV pcr, HEV pcr

Making a Hepatitis E virus diagnosis: which lab test ?

- In case of an immune compromised host, serology is unreliable always use PCR HEV RNA

- In this case: HEV RNA was positive 100.000 IU/ml

Delayed positive HEV serology



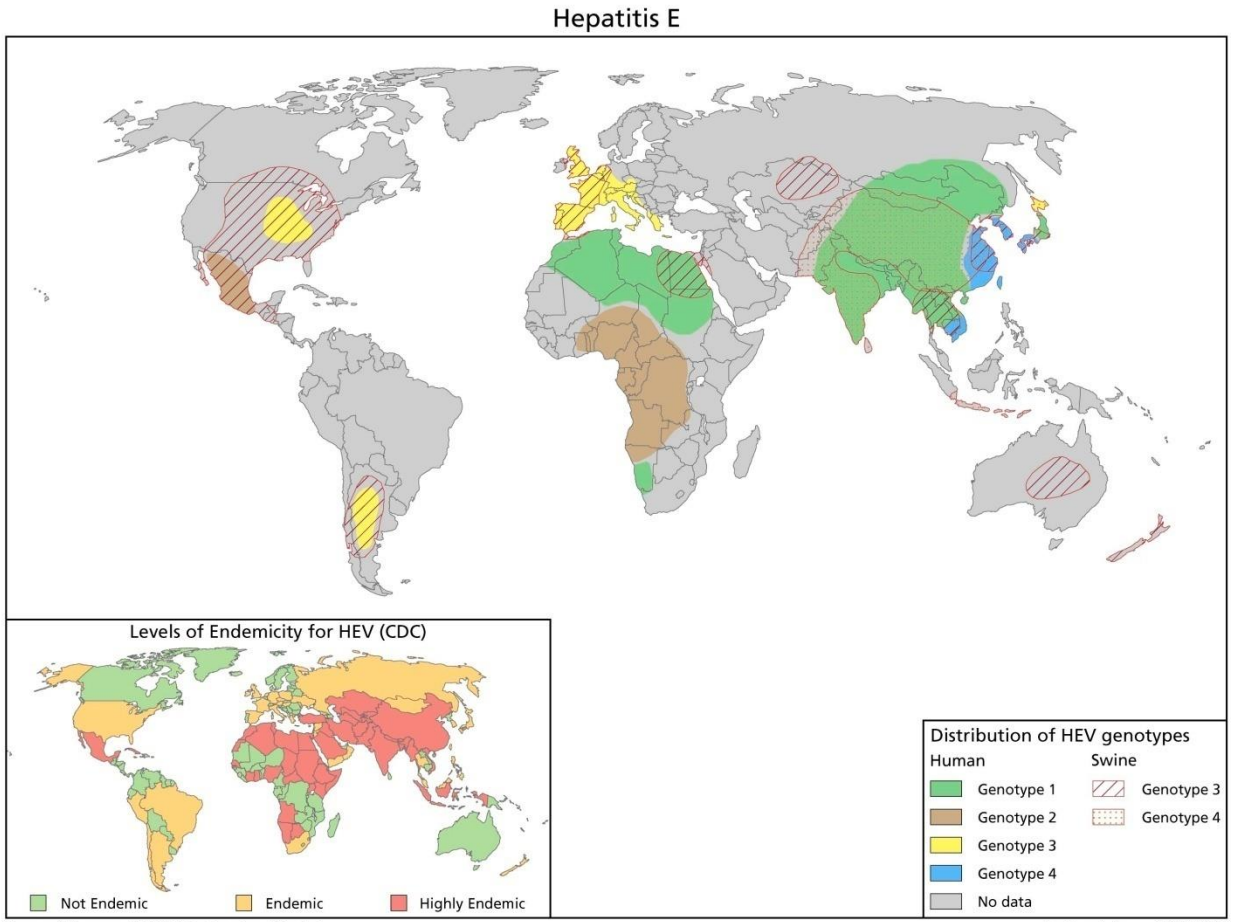
de Niet et al. Neth J Med 2012;70:261-265

Making a Hepatitis E virus diagnosis: which lab test ?

- In case of an immune compromised host, serology is unreliable always use PCR HEV RNA

- Is there a place for genotyping after positive pcr testing ?

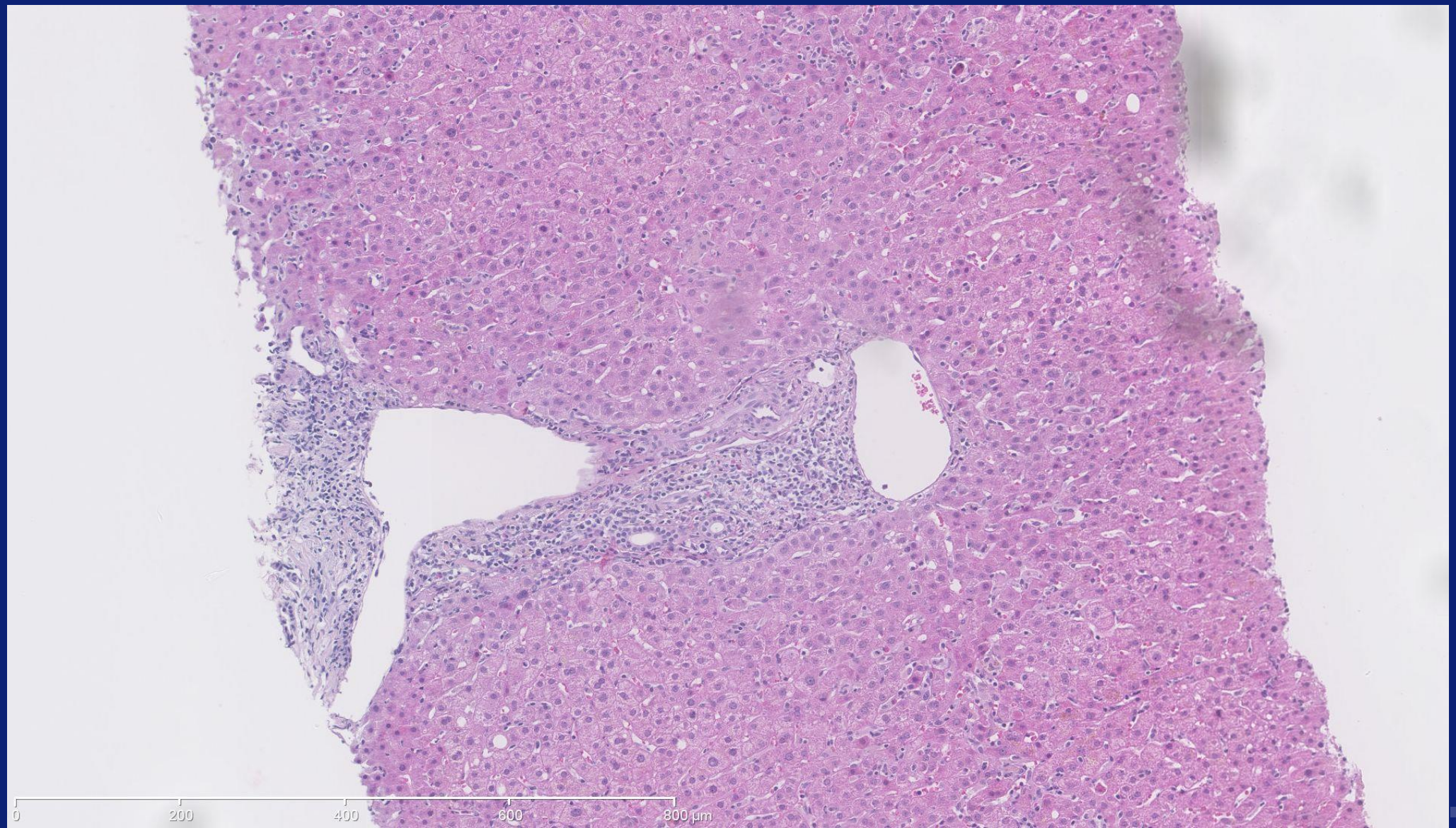
HEV genotype 3 has regional restriction



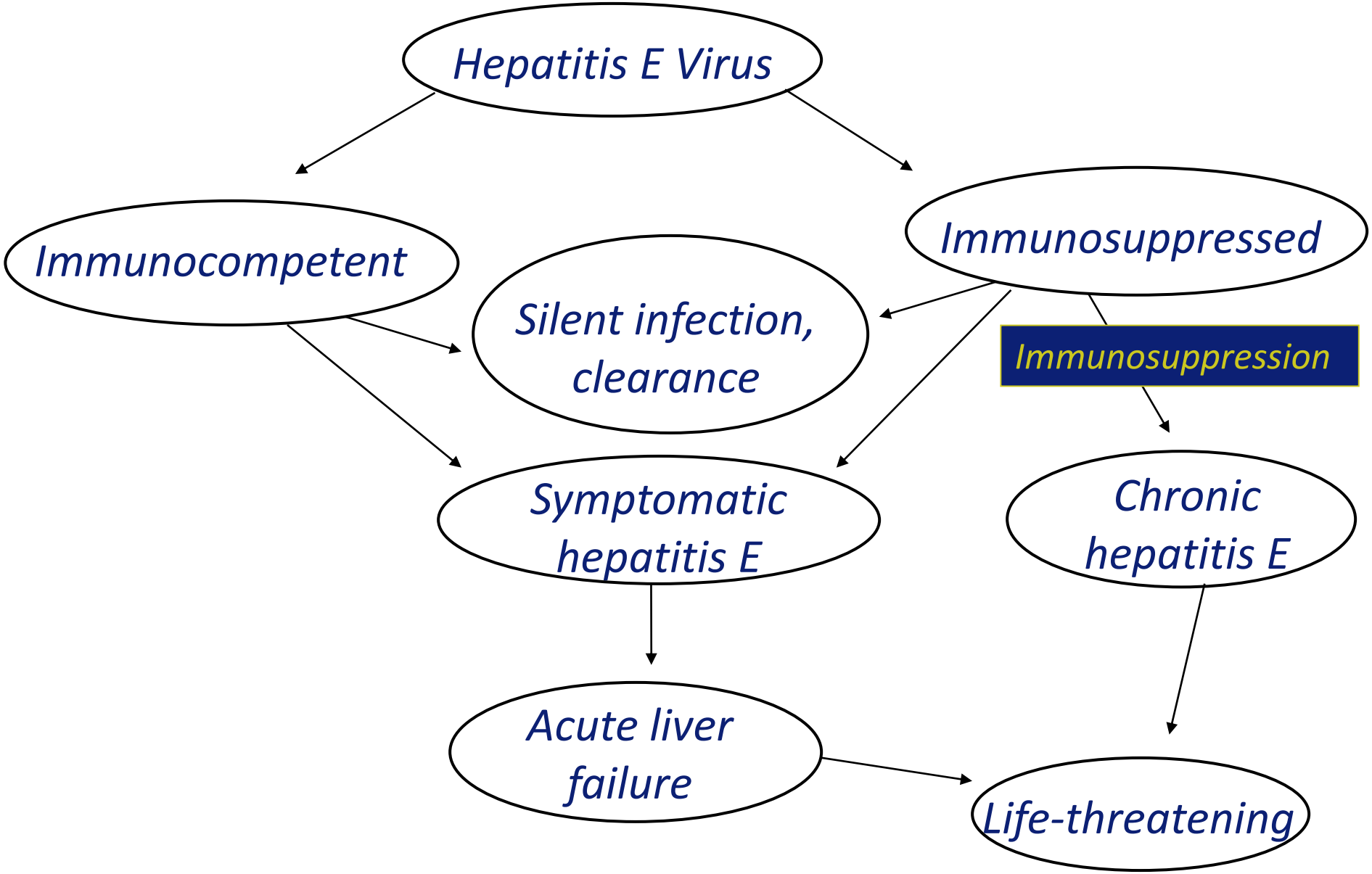
Making a diagnosis: role of HEV genotyping

- Documentation travel hisory will give a clue to genotype
- In case of research into a common source
- As a test with consequences: pregnancy and HEV

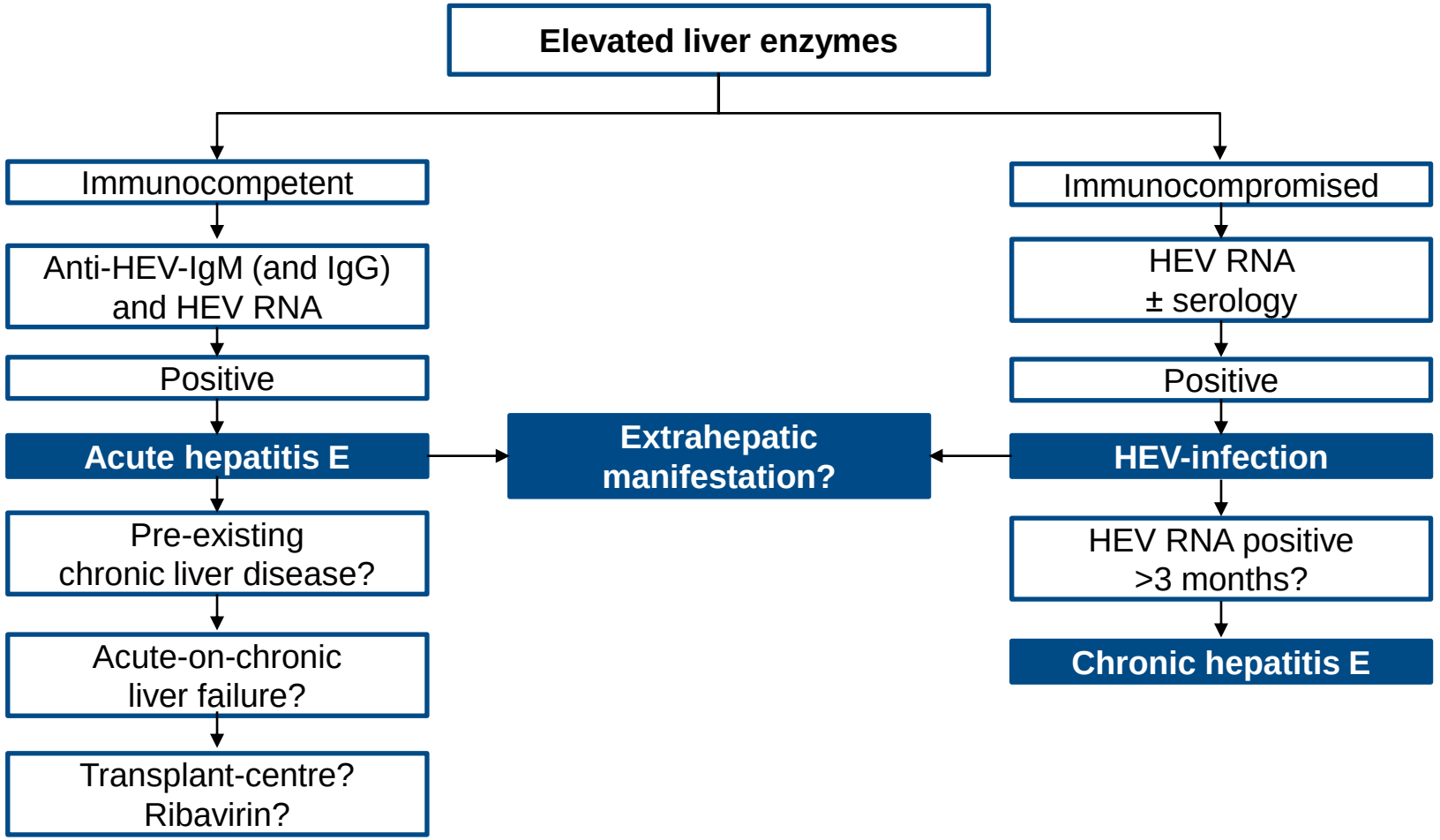
Role of liver biopsy in acute HEV



Courses of hepatitis E



Diagnostic algorithm for HEV infection



Serology and NAT testing are best used in combination, as a negative PCR does not exclude acute infection; serology is sometimes negative in immunosuppressed patients with chronic infection

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

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Treatment of acute HEV infection

- Wait and see policy

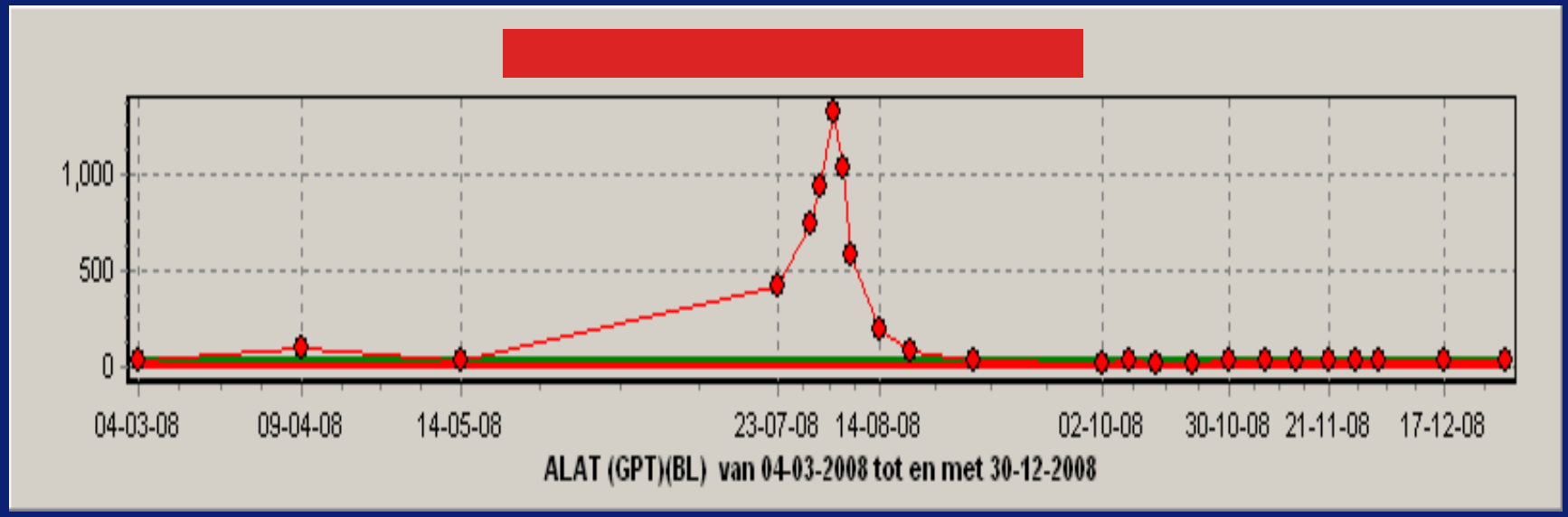
- Reduction of immunosuppression

- Evidence for early Drug treatment ? Unclear (n = 21)
  - Severe disease protrombine time below 50%
  - Age > 70 years
  - Chemotherapy solid cancers

Peron JM, Liver Intern 2016;36:328-33.

Acute HEV: withdraw immunosuppression if possible

Wait and see policy: HEV clearance



Risk profile clinical presentation in acute HEV gt-3

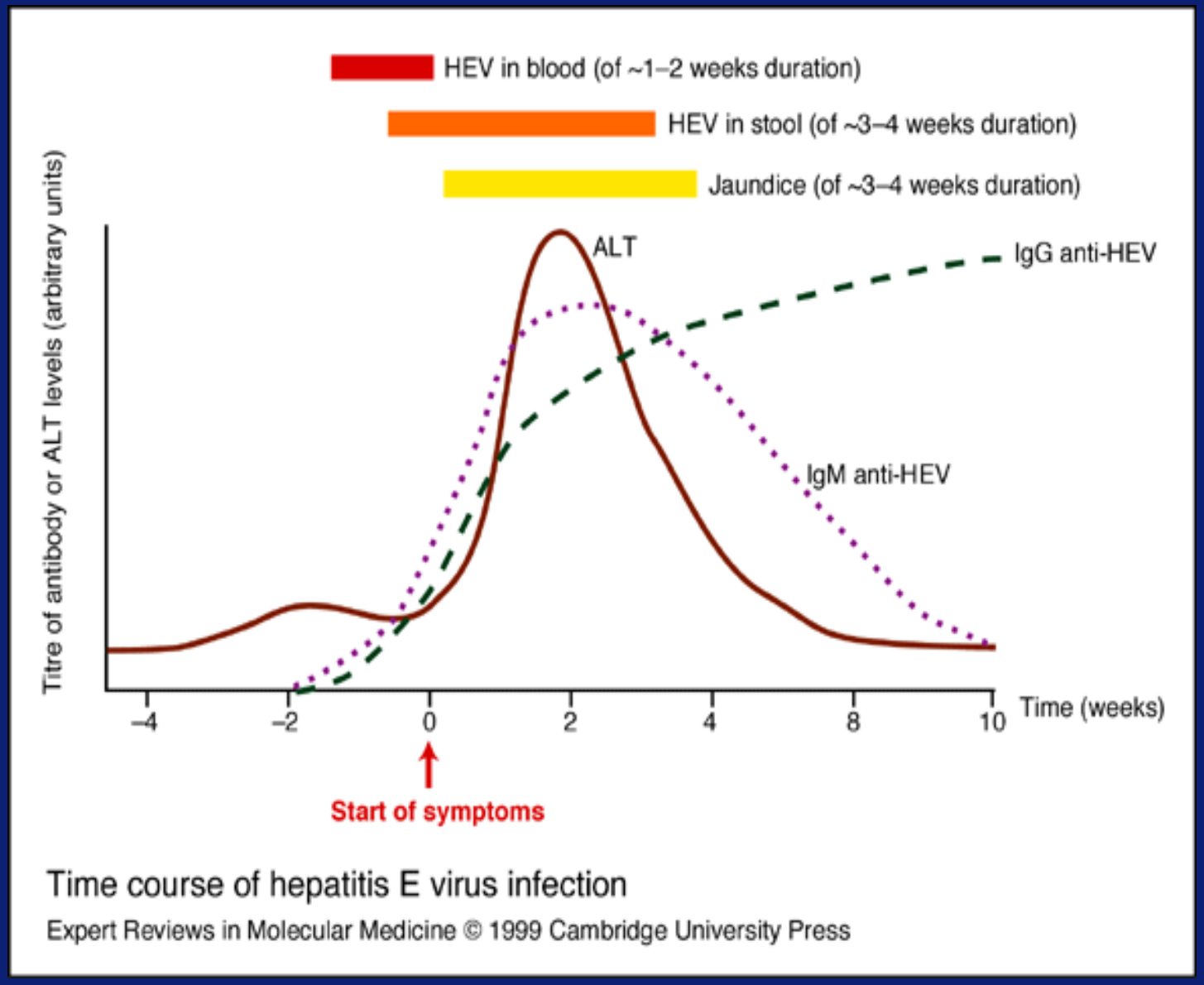
- Sporadic cases in older males

- Pre-existing disease
- Alcohol consumption

  (>22 drinks/week)

- Probably no severe disease in pregnancy

Acute HEV in the immunocompetent host: serology and liver inflammation



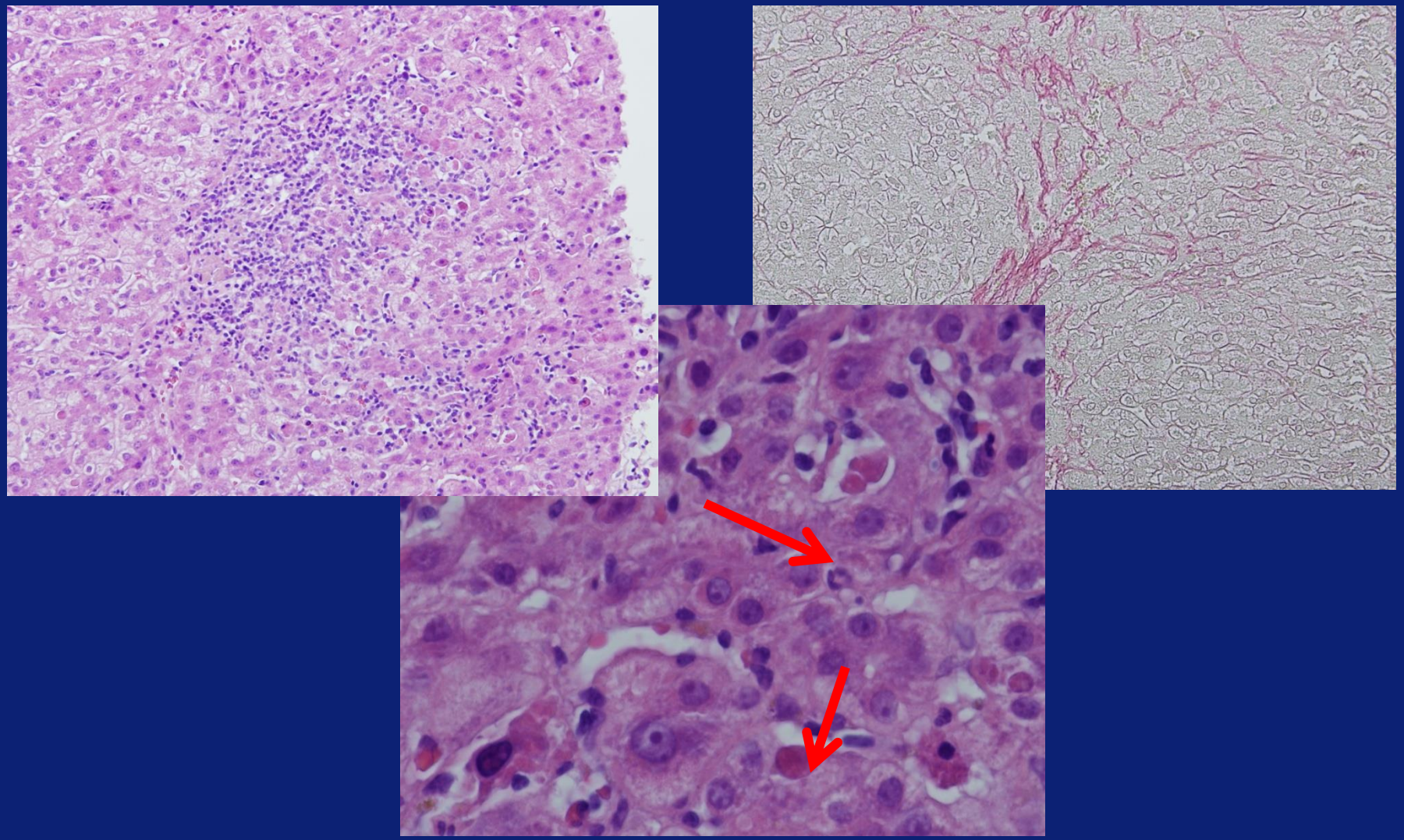
Time course of hepatitis E virus infection

Risk groups chronic HEV infection

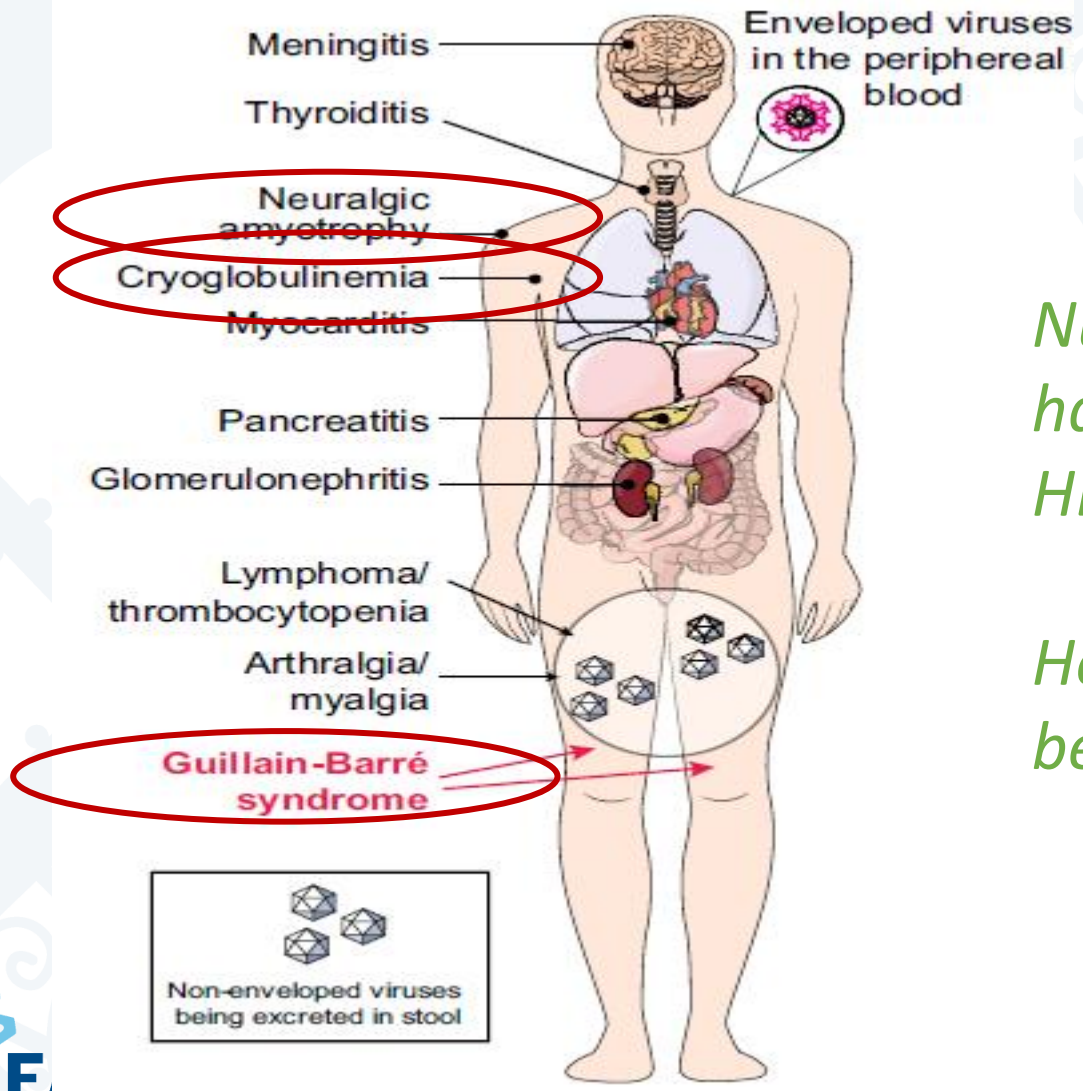
- Solid organ transplantation (SOT)
- Bone Marrow transplantation

- Disease modifying therapy e.g. in rheumatoid arthritis
- Specific anti T-cell therapy
- Cancer Chemotherapy
- (HIV infection)

HEV infection innocent bystander or agressive liver disease ?



Extrahepatic manifestations?

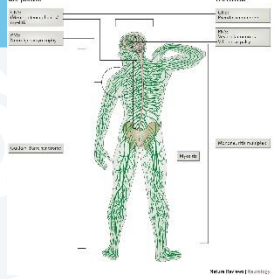


Numerous extrahepatic manifestations have been observed in the context of HEV infections.

However, the causal link has still not been determined.

Pischke et al. Journal of Hepatology 2016

HEV and neurological injury



>150 cases, worldwide

Guillain−Barré syndrome, neuralagic amyotrophy

Encephalitis, VII & VIII nerve palsy, myosotis, mononeuritis multiplex

Incidence:

5.5% - 7.5%

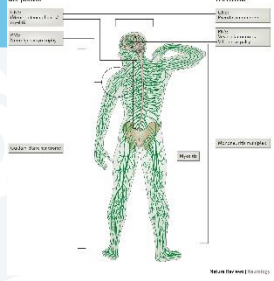
Occurs in:

Acute and chronic HEV

Developed and developing countries

Neurological symptoms and signs dominate clinical picture

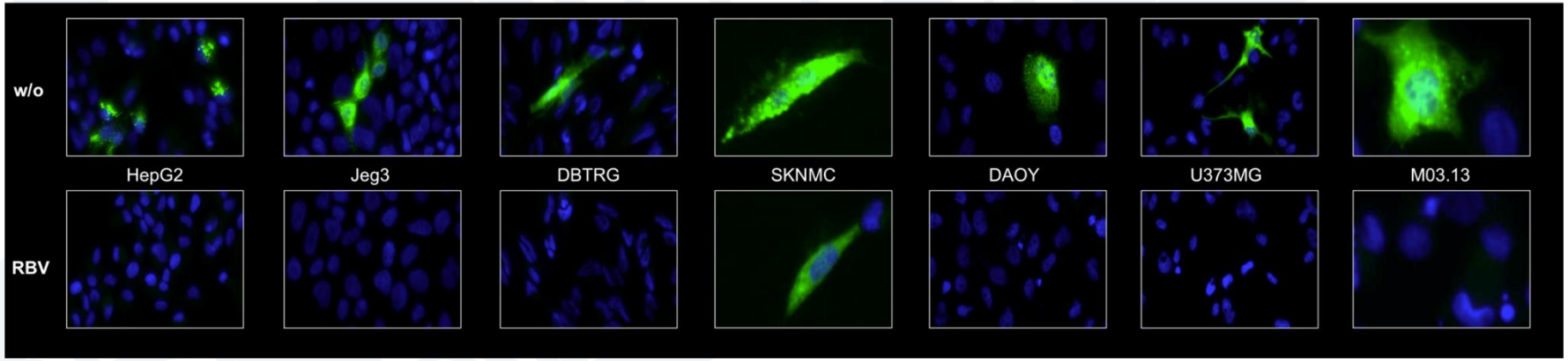
Kamar et al Emerg Inf Dis 2011, Woolson et al APT 2014, Dalton et al Nature Neurol Rev 2016



HEV & neurological syndromes:
evidence for causality

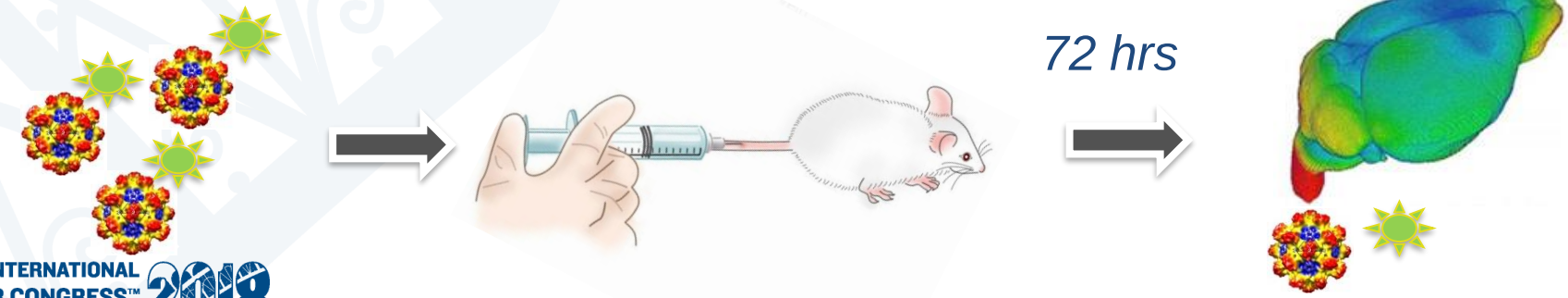
HEV infects neurological cell lines:

Replication of full length HEV genotype 3 Kernow-C1 p6 strain in different neuronal and placental cell lines



Drave et al J Viral Hep 2016

HEV crosses blood brain barrier in mice



Xhou et al J Inf Dis 2017

Extrahepatic manifestations
HEV can enter and replicate in neural tissue.

- Guillain Barré syndrome
- Neuralgic Amyotrophy

- Encephalitis/ myelitis

Nat Reviews Neurol 2016;12:77-85; J Vir Hepatis 2016;23:512-521

Extrahepatic manifestations

- Extrahepatic manifestations of HEV are increasingly recognized

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

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

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Extrahepatic manifestations

- Existence of extrahepatic manifestations of HEV means that testing is warranted in a number of patient populations

Recommendations	Grade of evidence	Grade of recommendation
Testing for HEV recommended in:*		
• Patients with neuralgic amyotrophy	B	1
• Patients with Guillain–Barré syndrome	B	1
Testing for HEV suggested in:		
• Patients with encephalitis/myelitis	C	2
Testing for proteinuria suggested in:		
• HEV-infected patients	C	2
• Patients with acute or chronic HEV infection who develop new-onset proteinuria may be considered for a renal biopsy	C	2
Treatment		
• Antiviral treatment suggested for patients with chronic HEV infection and associated glomerular disease	C	2

*Irrespective of LFT results

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

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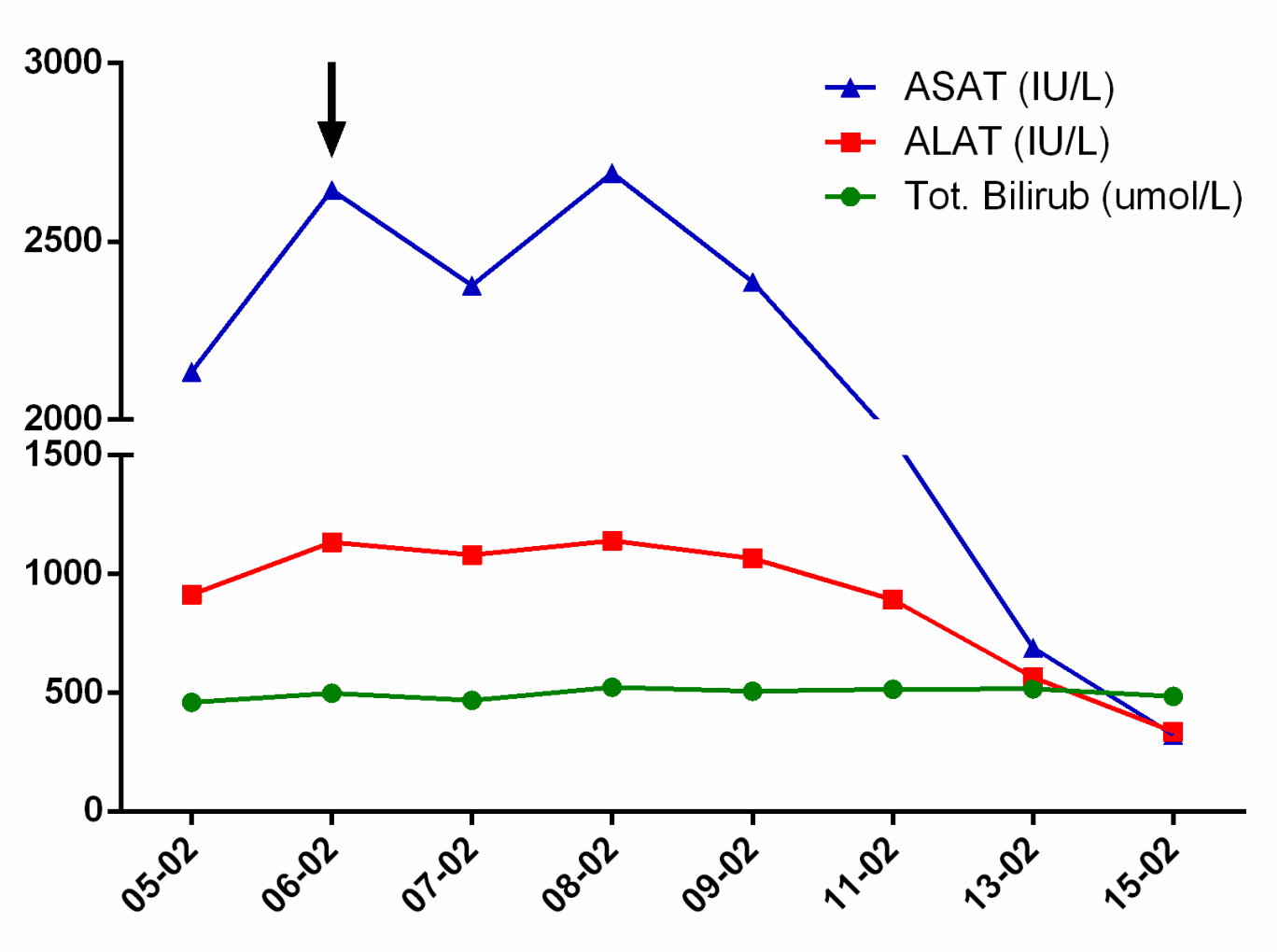
Cryoglobilinaemia in HEV infection

Extrahepatic manifestations
HEV RNA is detected in kidney and urine

- Cryoglobulinaemia
- Membranoproliferative and membranous glomerulonephritis
- Acute Tubular Necrosis

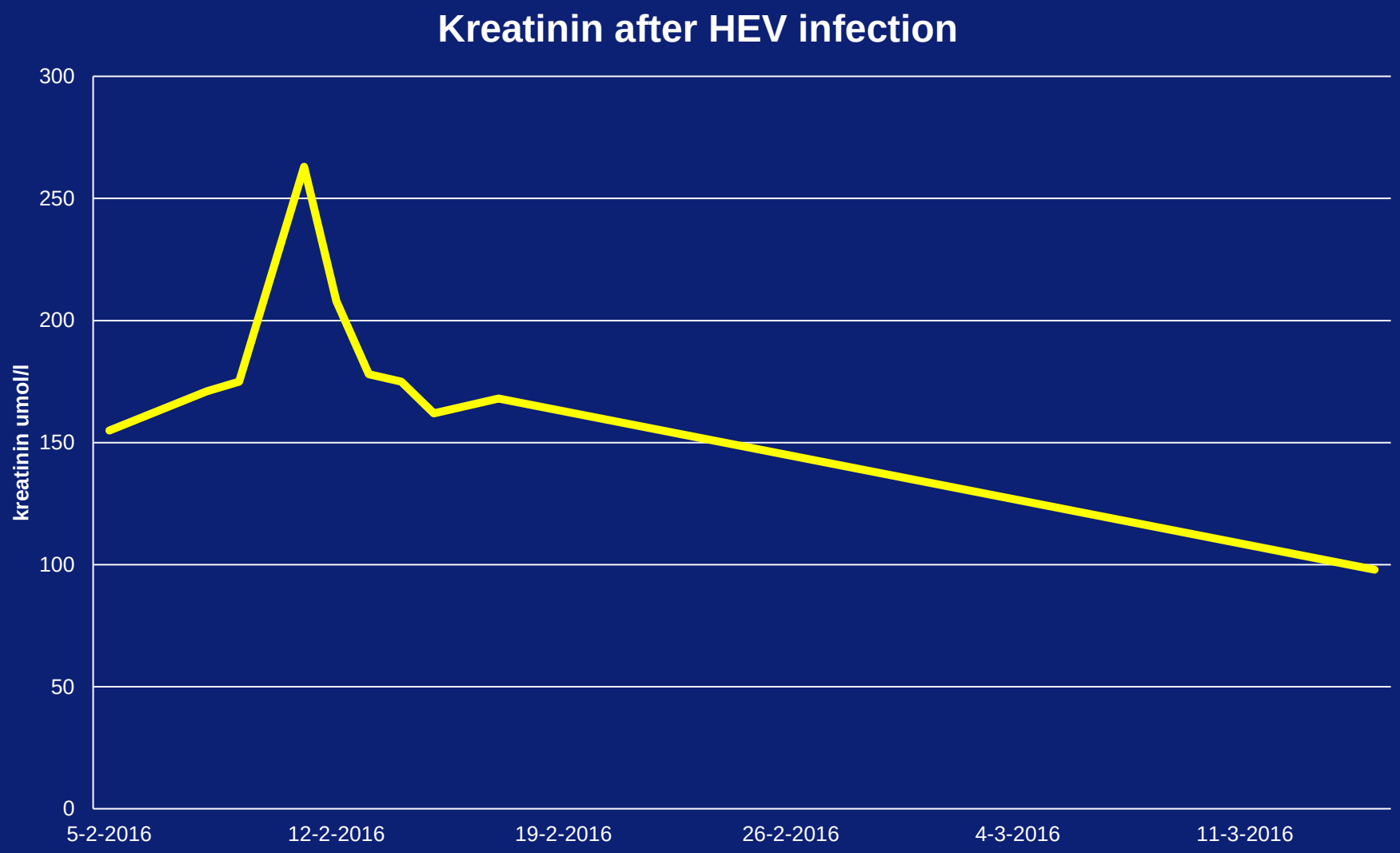
J Hepatol 2016 ;65:200. Liv Int April 2016. Lancet Infect Dis

Acute HEV in elderly male using Methotrexate



Erasmus MC

Acute renal dysfunction after HEV infection



Drug Treatment for chronic HEV

Table 1. Overview of approved drugs affecting hepatitis E virus (HEV) replication.

Drug	*In vitro* effect	*In vivo* effect	Mechanism of action
Ribavirin	Inhibition of HEV replication	HEV clearance in chronic hepatitis E; occasional cases of treatment failure	Intracellular GTP depletion through inosine 5'-monophosphate dehydrogenase inhibition
PegIFNα	Inhibition of HEV replication	HEV clearance in chronic hepatitis E	Immune activation
Sofosbuvir	Inhibition of HEV replication	Unknown	Nucleotide analog; inhibition of the viral RNA-dependent RNA polymerase
Mycophenolic acid (including prodrug mycophenolate mofetil)	Inhibition of HEV replication	Unclear, possibly associated with HEV clearance in chronic hepatitis E	Intracellular GTP depletion through inosine 5'-monophosphate dehydrogenase inhibition; immune suppression
mTOR inhibitors (rapamycin, everolimus)	Stimulation of HEV replication	Higher HEV RNA levels in patients with chronic hepatitis E on mTOR inhibitors	Inhibition of an eIF4E binding protein 1-dependent antiviral signaling pathway downstream of mTOR
Calcineurin inhibitors (cyclosporin A, tacrolimus)	Stimulation of HEV replication	Unknown; tacrolimus use associated with increased risk of viral persistence	Inhibition of cyclophilin A and B

Gastro 2011;140:1481 . J Hepatol 2016 ;65:200–12

Case 2. Chronic HEV in a heart transplant recipient.

- There is no approved therapy for chronic HEV infection
- Therapy is on a compassionate use basis only
- Explicit informed consent is needed
- Reimbursement may be a problem

Ribavarin treatment

- Case definition of chronicity: 3 months HEV RNA positive
- Dose of ribavarine from 200 mg to 1200 mg daily dose has been used
- Role of Therapeutic Drug Monitoring (TDM)
- Duration of treatment 3 months but SVR endpoint is negative HEV RNA in stool
- Resistance ?

Case 2. Ribavarin management

- There is no formal dose finding study in HEV treatment
- Plasma steady state takes up to 6-weeks exposure

- Dose adjustment to renal function

- Therapeutic drug monitoring week 2, 4 and 8

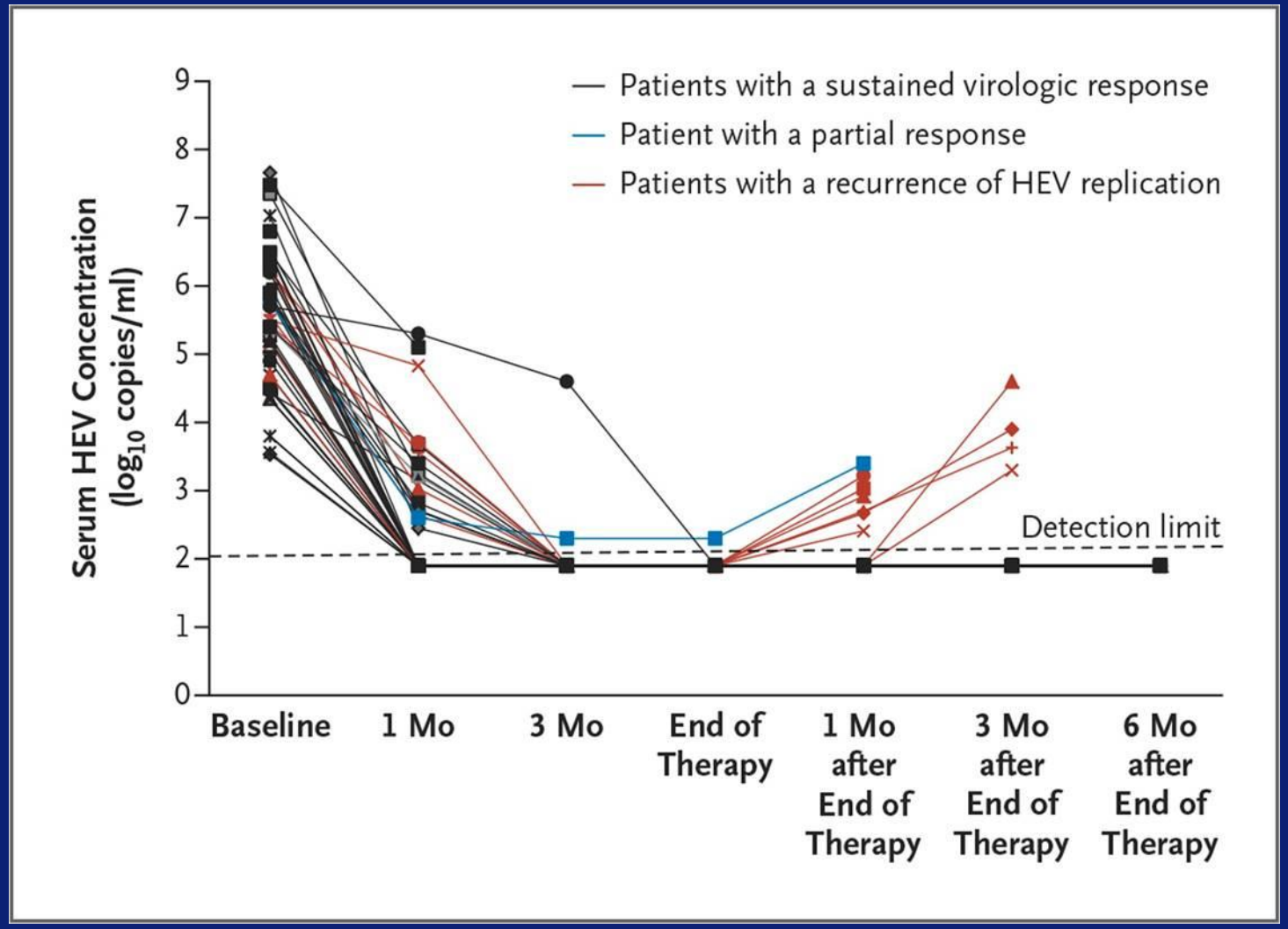
- Potential role for algorithm UMCU:
  - - [RBV]ss = 1,164 + 0,755 x [RBV]wk2 (mg/L)
  - - [RBV]ss = 0,734 + 0,804 x [RBV]wk4 (mg/L).

Ribavarin treatment: outcome

- N= 59 cases Solid Organ Transplantation
- Ribavarin 600 mg/day (29-1200 mg/day)
- 66% 3-months or less treated
- SVR 6 months post-treatment 46/59 (78%)
- Relapse n=10; re-treatment: SVR in 4/6
- Side effect: anemia

Kamar N; N Engl J Med 2014;370:111-20

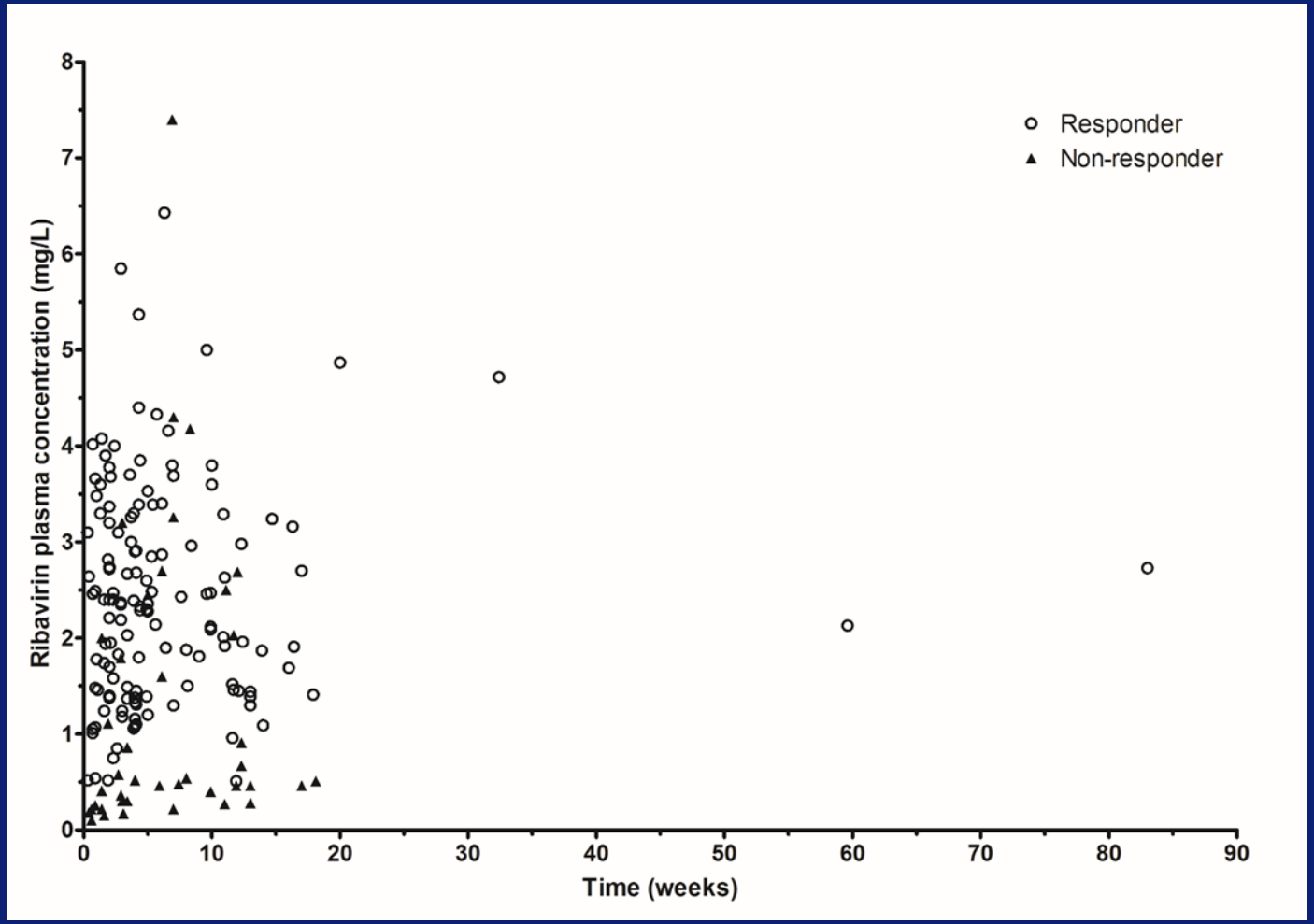
Ribavarin in chronic HEV infection



Kamar N; N Engl J Med 2014;370:111-20

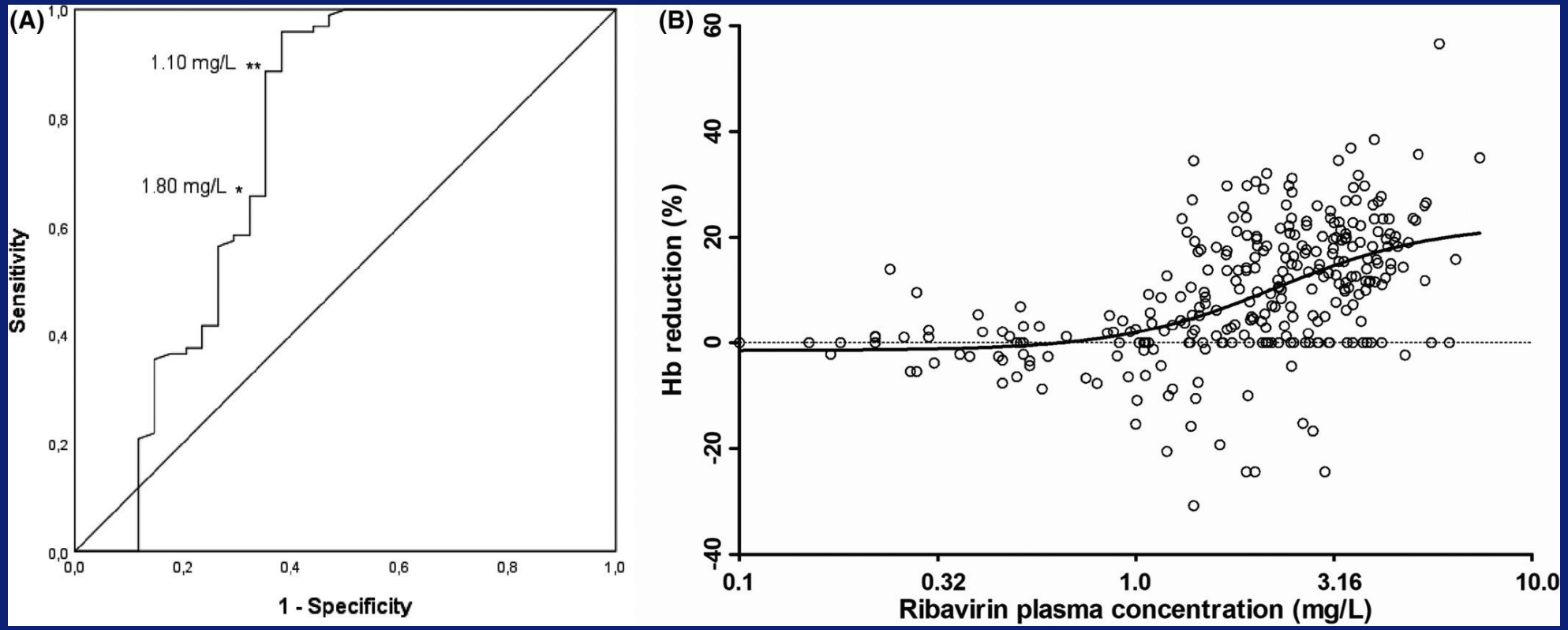
Ribavarin TDM in relation to therapy response

Mulder et al; J Vir hepatitis 2020



Ribavarin TDM in relation to therapy response

Mulder et al; J Vir hepatitis 2020



Changes in virus host interaction

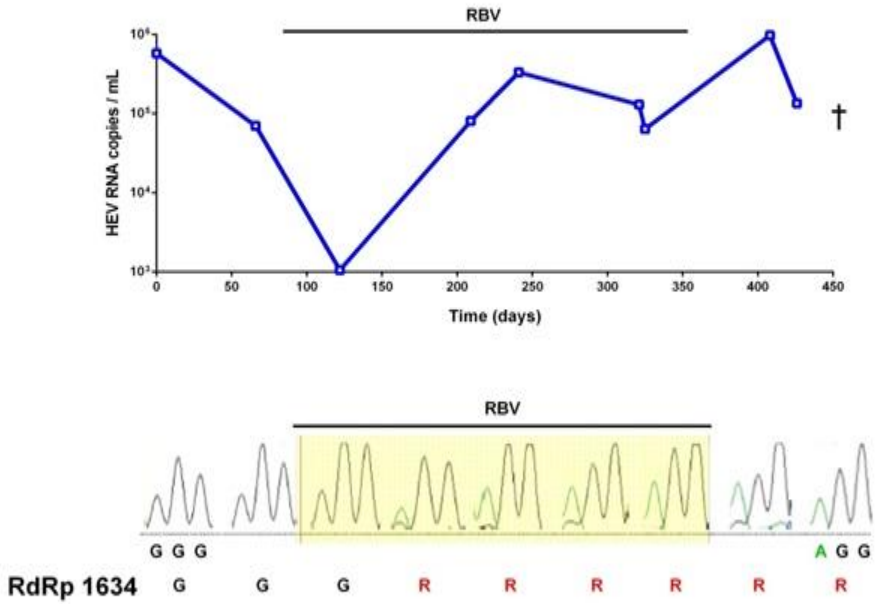
- Acute Liver failure needing transplantation is related to certain viral mutations

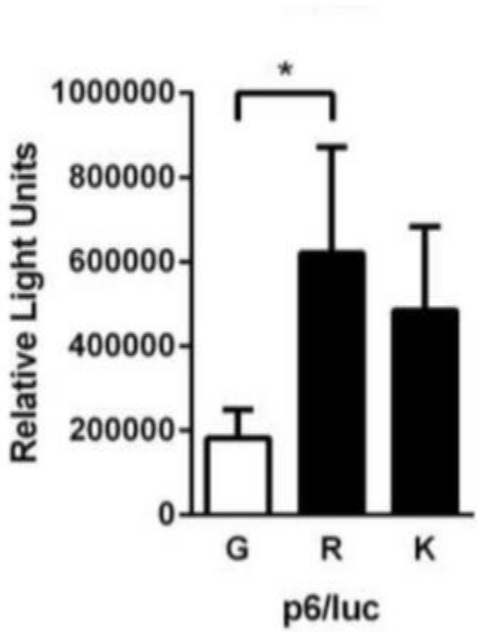
- During ribavirin treatment evolution of HEV quasispecies; G1634R mutation

- Selection of drug resistant mutants has been documented in non-responders to ribavirin

Todt D,Gut 2016;65:1734-44 Debbing ,J Hepatol 2016;65:499-508

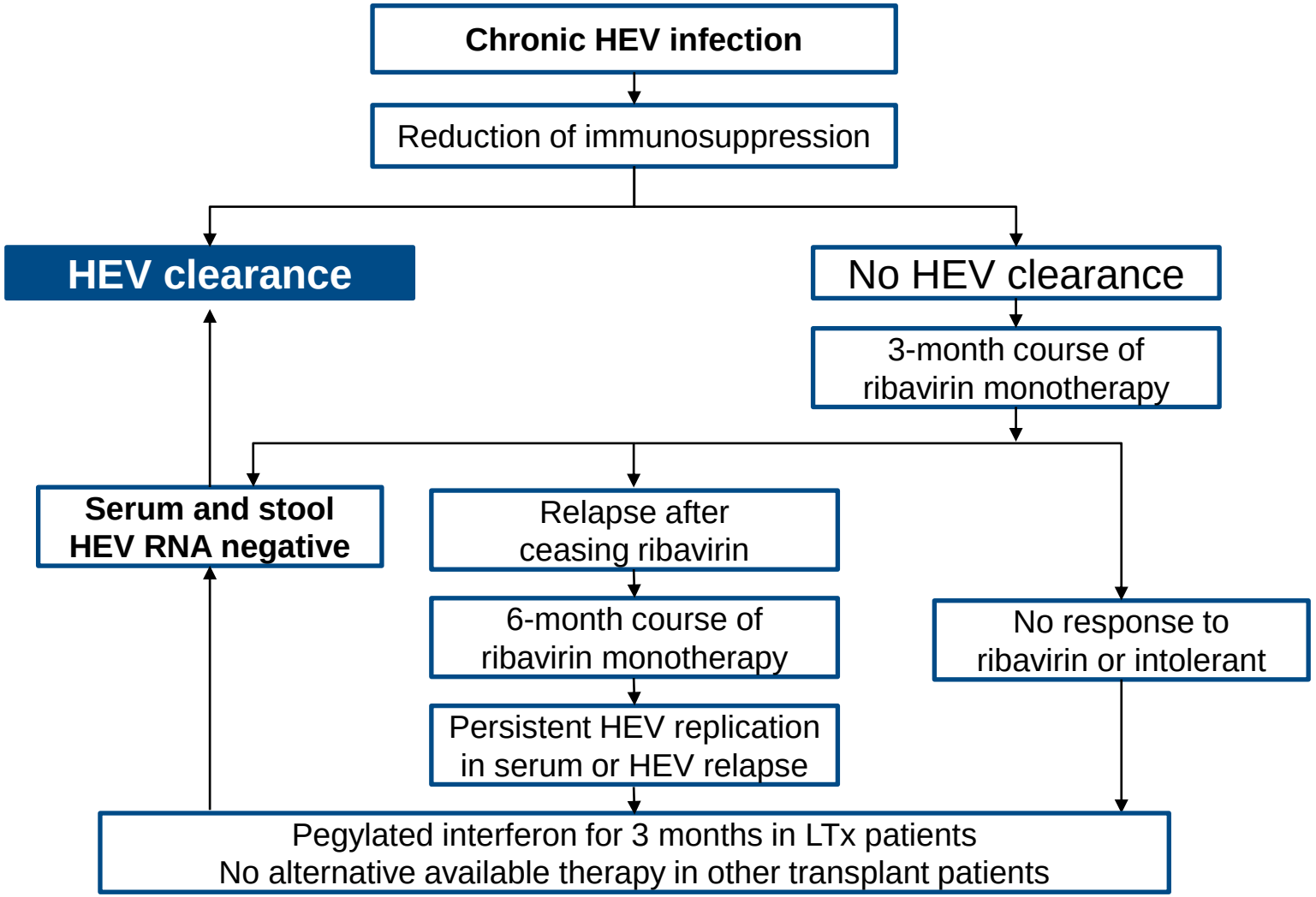
Selection of an HEV-variant with increased replication fitness during treatment with ribavirin (G1634R)





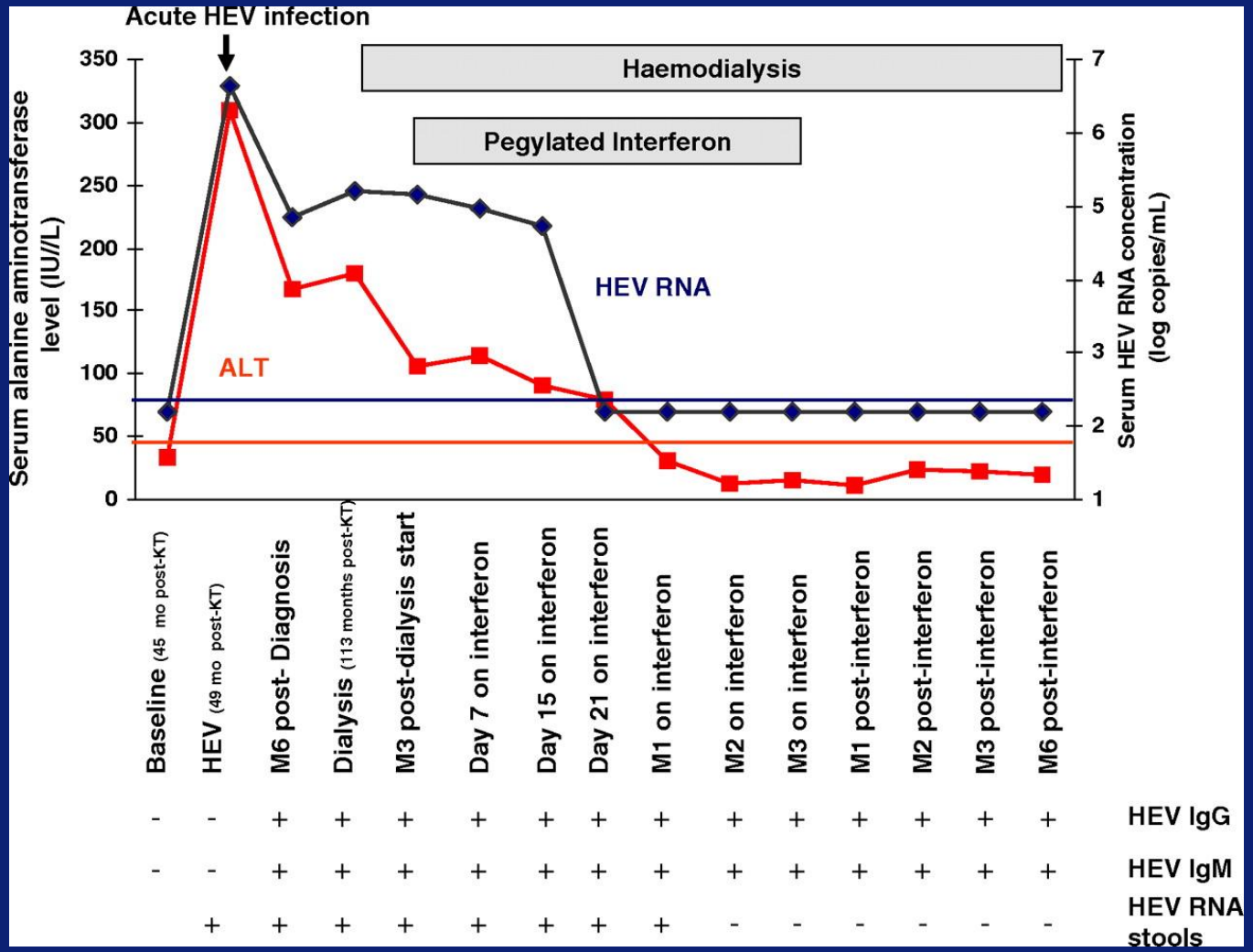
Debing, Gisa, ... Wedemeyer, Suneetha, Neyts, Gastroenterology 2014

Management of patients not clearing HEV infection



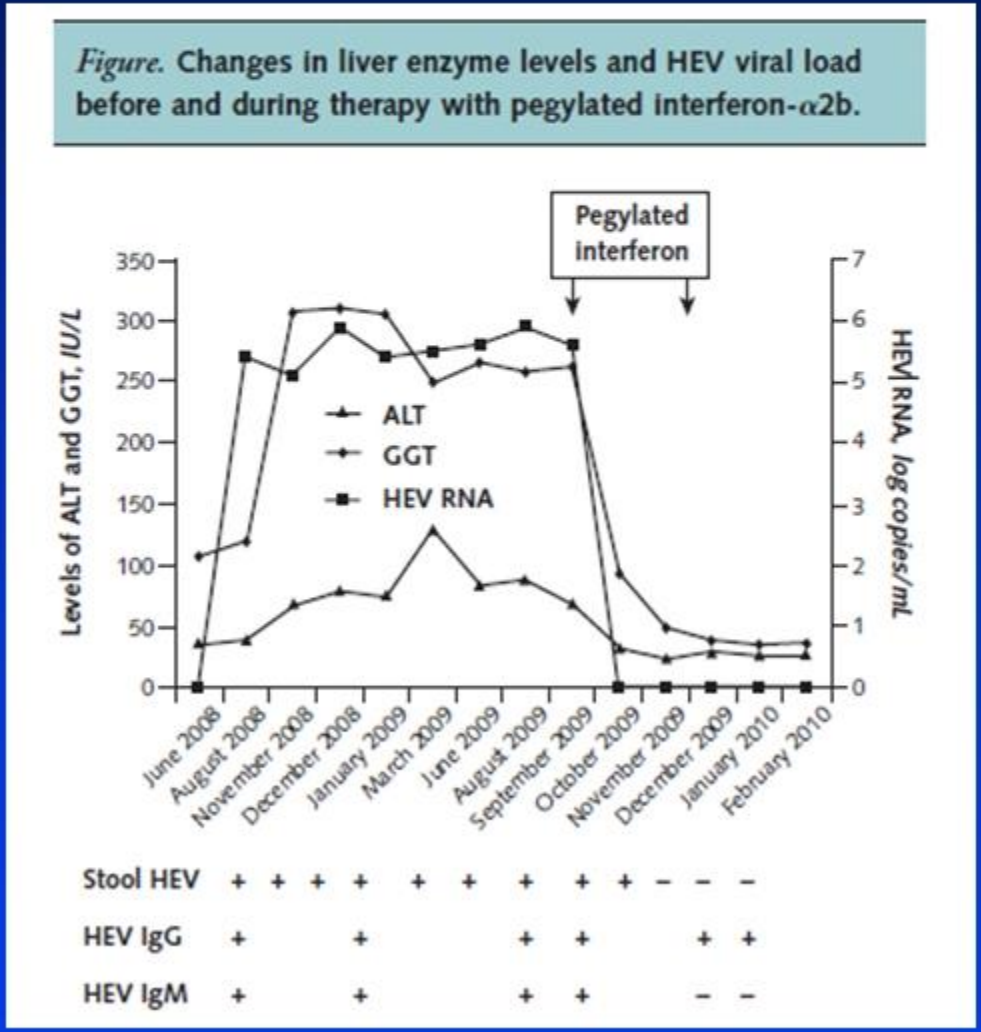
EASL CPG HEV. J Hepatol 2018;doi: 10.1016/j.jhep.2018.03.005 [Epub ahead of print]

Peg-interferon in a hemodialysis patient



Kamar N et al. Nephrol. Dial. Transplant. 2010;25:2792-2795

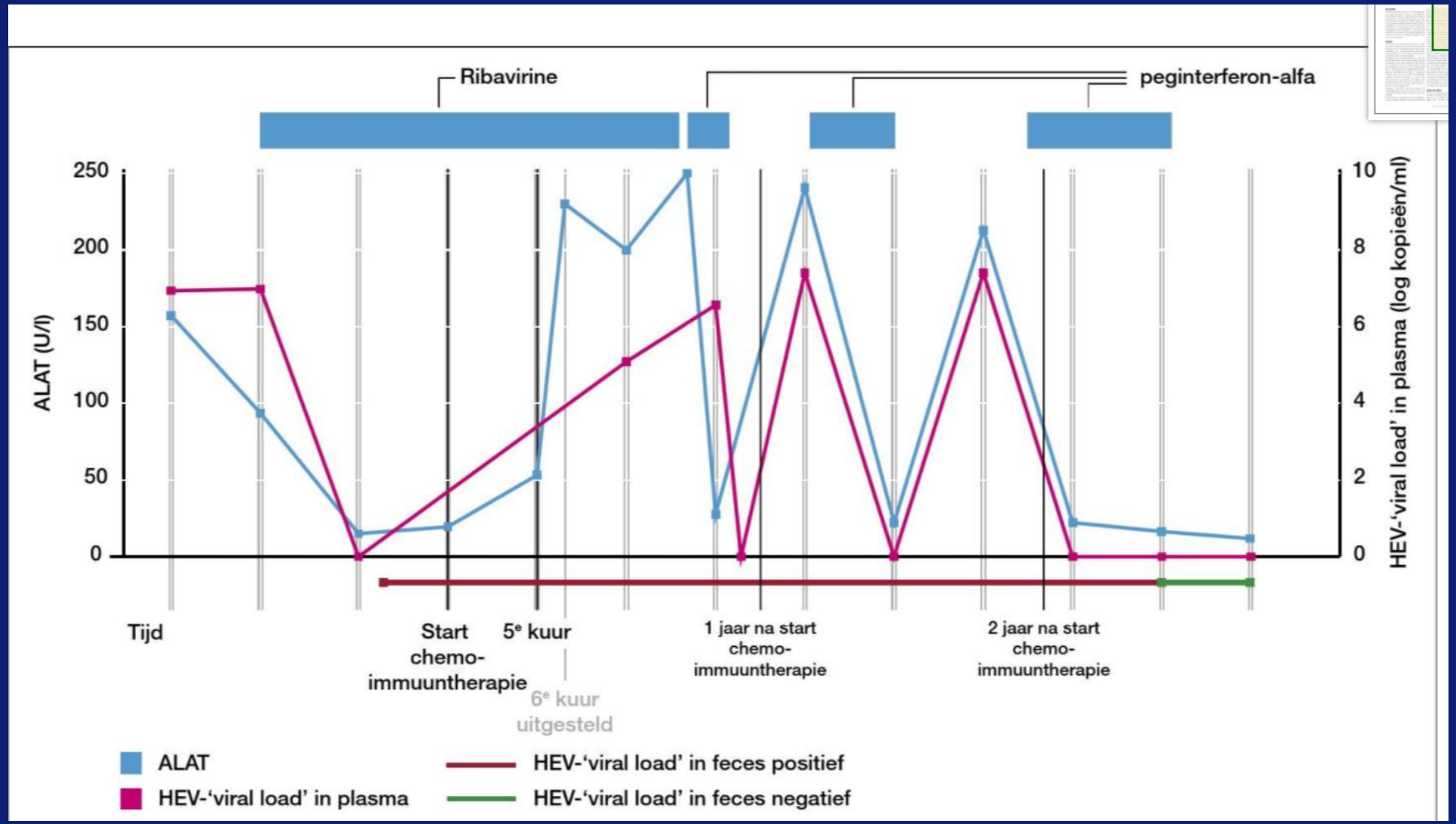
Chronic Hepatitis E: Therapy



- 57 year old with hairy cell leukemia and chronic hepatitis E
- Treated with peginterferon α2b [1 µg/kg] weekly for 3 months

Alric et al. Ann Intern Med 2010

Peg-interferon in CLL with Ribavarin resistance



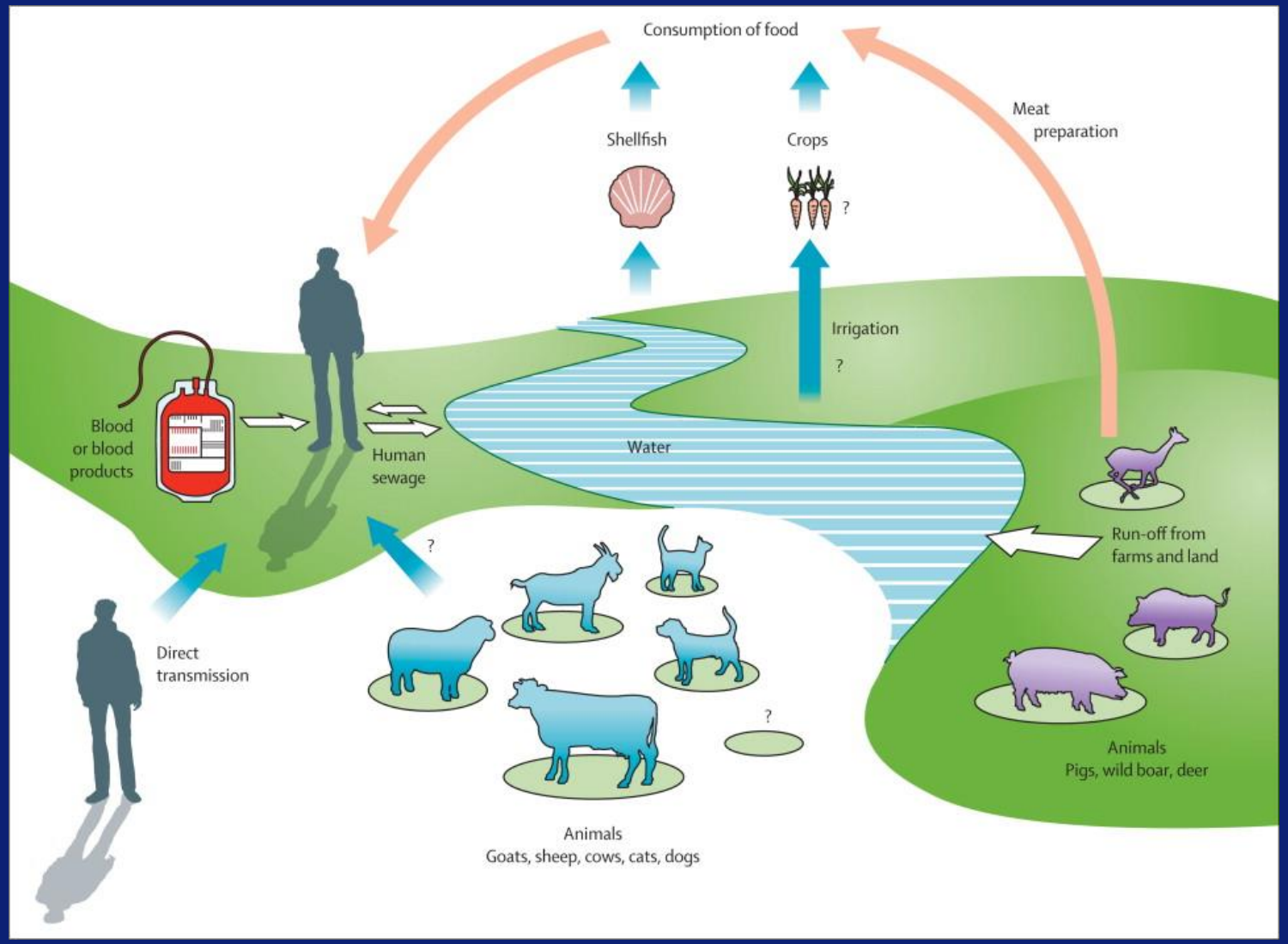
No protective immunity after SVR

Life style changes needed

- “Voor transplantatiepatiënten kan hepatitis E wel schadelijk zijn. Daarom adviseert het RIVM mensen die een transplantatie hebben ondergaan geen producten te eten waar varkenslever in zit die niet goed is door gegaard. Het gaat om leverworst en paté. De reden is dat hierdoor mogelijk een besmetting met het hepatitis E-virus kan worden overgedragen. Bij mensen die afweeronderdrukkende medicijnen slikken is er een grote kans dat zo'n besmetting chronisch wordt en leidt tot leverproblemen.”

http://www.rivm.nl/Onderwerpen/H/Hepatitis_E

HEV transmission in developed countries



Kamar et al, Lancet 2012;379:2477-88

Take home message: treatment chronic HEV

- Reduce or stop immunosuppressive drugs
- 3-months Ribavarin estimated SVR 78%
- SVR is based on HEV RNA in stool

- Use of TDM to optimize treatment and limit side effects

- In carefully selected cases do not forget peg-interferon alpha

- Counsel the patient on the modes of transmission

Prevention, diagnosis and treatment of Hepatitis E
Masterclass Infectieziekten 2024

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