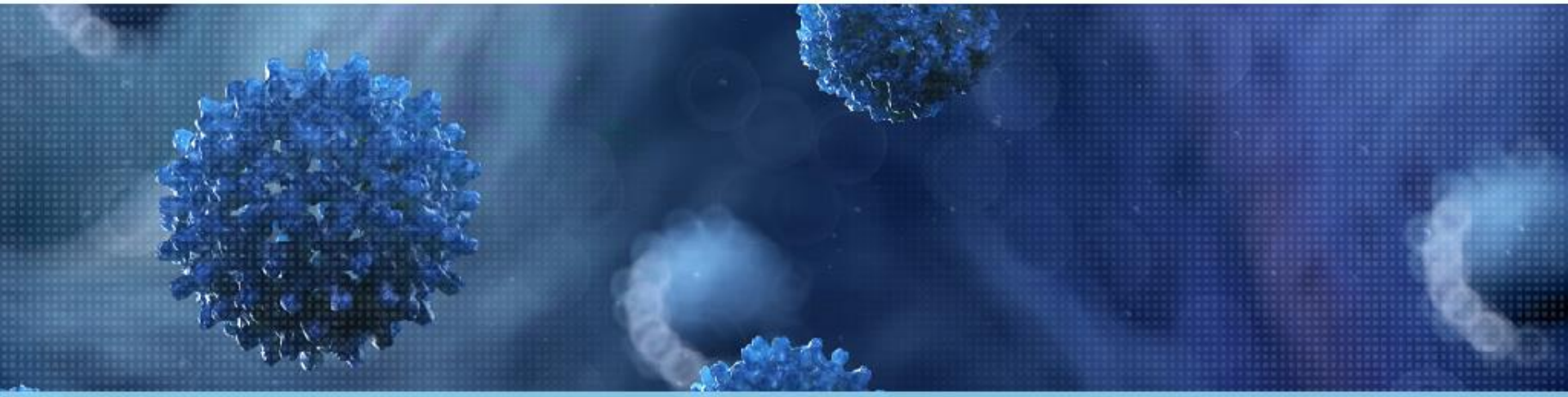
Erasmus MC

Viroscience lab

WHERE SKILLS MEET TO STUDY & PROTECT



Hepatitis E virus infection

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Hepatitis E virus

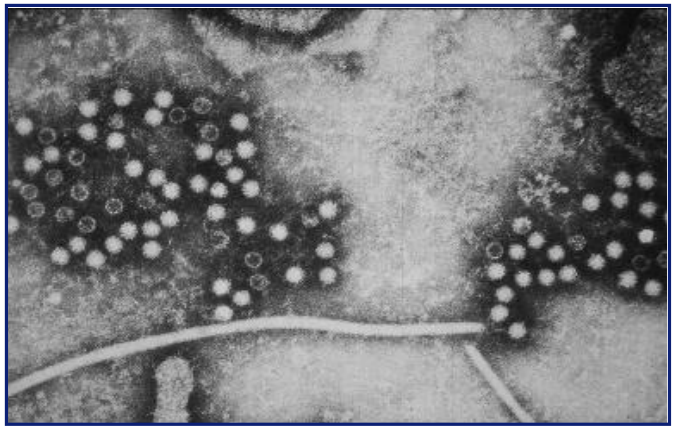
- Wat is hepatitis E?
- Klinische presentatie hepatitis E virus
- Transmissie hepatitis E virus (hoe loop je het op)
- Beloop hepatitis E virus infectie in
  - immuuncompetente patiënten
  - Immuungecompromitteerde patiënten
- Diagnostiek
- Therapie voor hepatitis E virus besmetting
- Extrahepatische manifestaties van infectie met hepatitis E virus

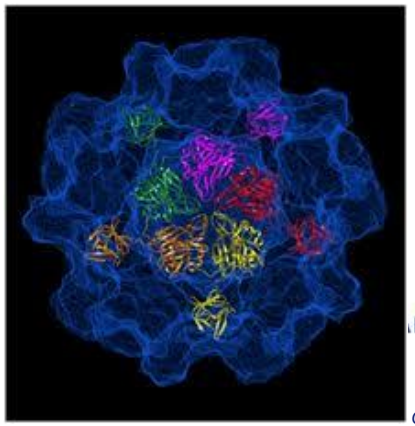
HEV

- Wie heeft wel een een Hepatitis E virus test aangevraagd in zijn/haar patiënt?
- Wie kan op HEV laten testen in zijn eigen ziekenhuis?
- Wie houdt er van droge Franse worstjes?

Hepatitis E Virus

- Non-enveloped RNA virus belonging to Hepeviridae family
- 27-34 nm in diameter, 7.2 kb + sense ssRNA
- Transmission feco-oral, contaminated water/food
- Four genotypes gt 1-2 outbreaks in resource limited countries
  gt 3-4 zoonotic, in humans/pigs/game, in industrialised countries





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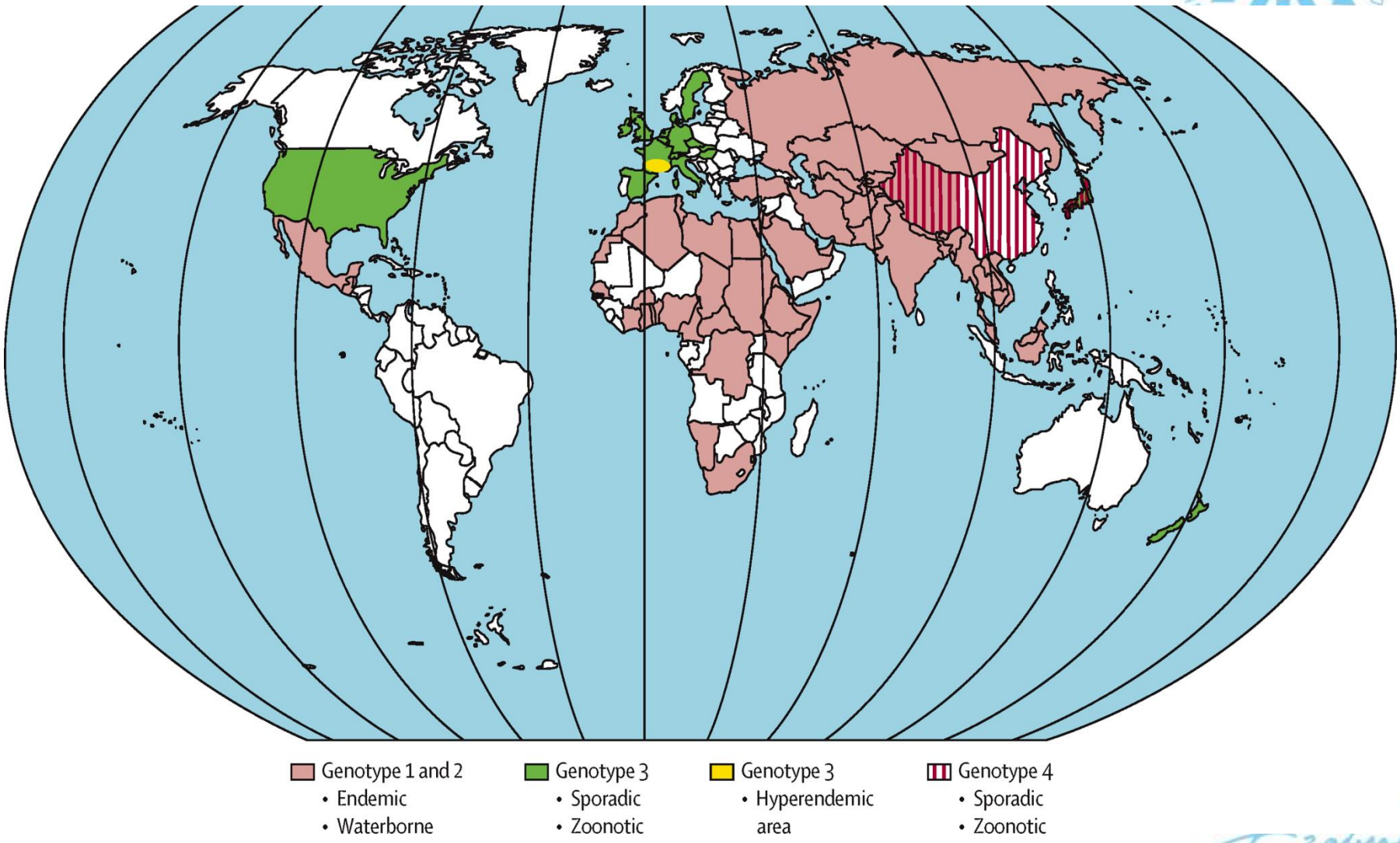
Courtesy: Tao, 2009

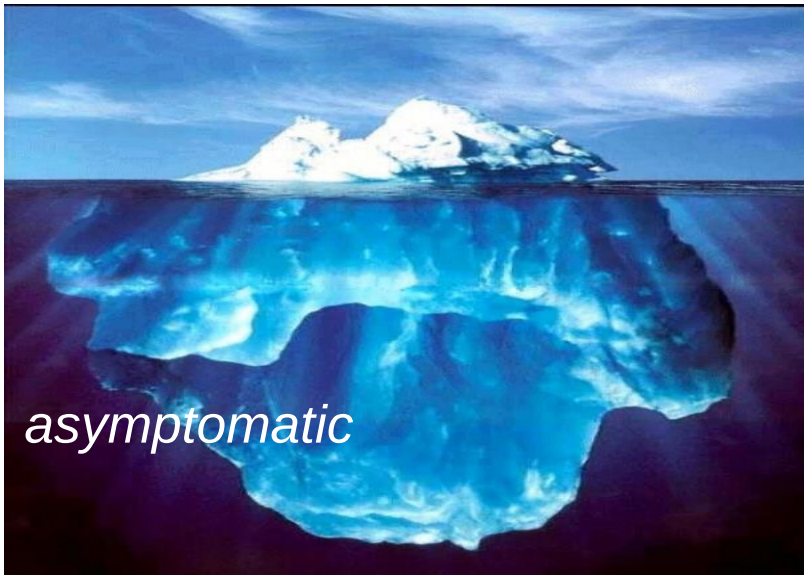
Global distribution of HEV genotypes



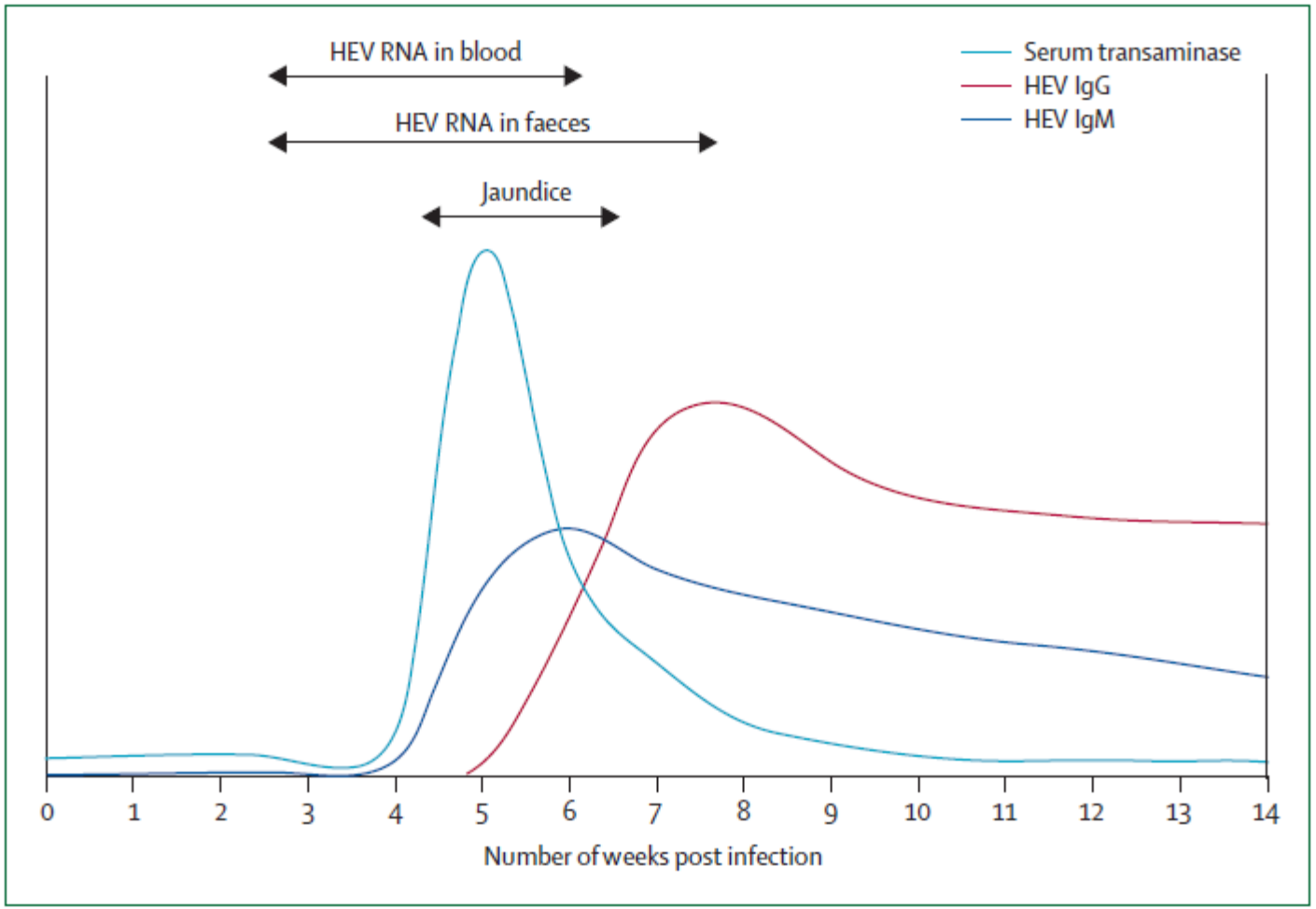
Kamar, Lancet 2012

Clinical presentation of hepatitis E virus

- Fever
- Fatigue
- Loss of appetite
- Nausea
- Vomiting
- Abdominal pain
- Jaundice
- Dark urine
- Clay-colored stool
- Reported range S:AS infection from 1:2 to 1:13.
- Mortality gt1: overall 1-4%, pregnant women 15-25%
- Neurological symptoms



HEV infection in the immunocompetent



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Dalton et al, Lancet 2008

HEV in the news

Wild kan besmet zijn met hepatitis E

Vara vroege vogels

30 november 2010 12:30

Kerstdine

One in ten sausages may carry the hepatitis virus: Cases of rare deadly strain have % in a year

y rare, cases have risen by nearly 40 per cent in a year
ted will die, rising to one in five pregnant women
lerous pork product - they contain liver meat

Daily mail 15-09-13

er 2013 | **UPDATED:** 21:35 GMT, 15 September 2013

17 januari 2014

Artsennet.nl

Hepatitis E kan verlammingen veroorzaken

Het hepatitis E-virus kan niet alleen ernstige leverontsteking veroorzaken, maar ook twee acute zenuwaandoeningen, die gepaard kunnen gaan met verlammingen.

Dit blijkt uit onderzoek van het Erasmus MC gepubliceerd in Neurology. Het gaat om het syndroom van Guillain-Barré en neurologische amyotrofie, ook wel het syndroom van Parsonage -Turner. Beide ziektes kunnen de ledematen ernstig verlammen.

Complicatie

Van beide neurologische aandoeningen was al bekend dat ze konden optreden als ernstige complicatie na een milde infectie. De oorzaak ligt bij een verkeerde reactie van het immuunsysteem op deze infectie, waarbij ook het zenuwweefsel wordt beschadigd.

mensen gevonden, maar waarschijnlijk zijn er veel meer mensen
ken, verloopt net als hepatitis A en geneest na verloop van tijd.

t varkensvirus'

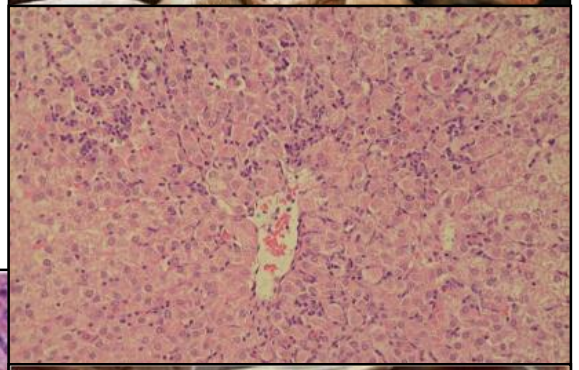
g 28 juni 2011 | 07:52

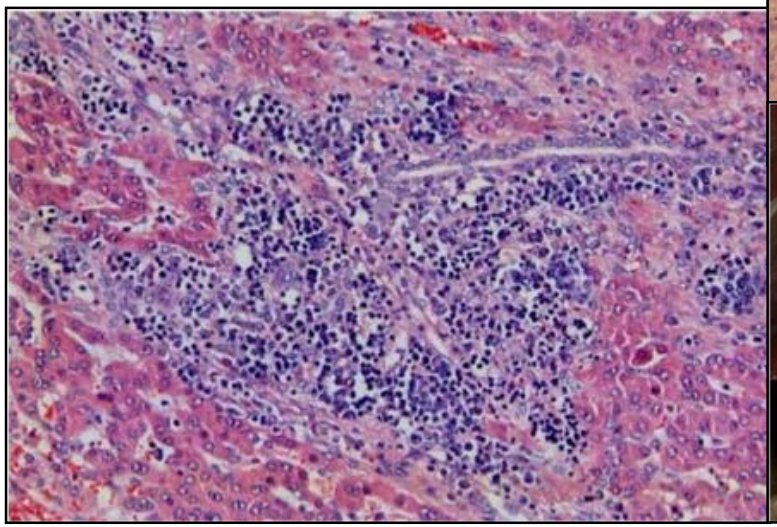
Tekstgrootte

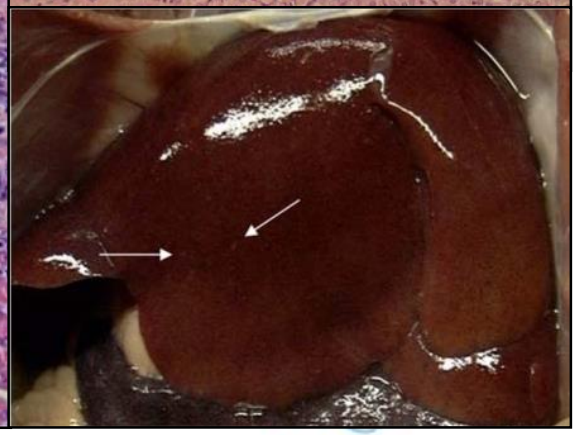
BN-de Stem 28 juni 2011

Association of HEV with pig hepatitis

- HEV antibodies as well as HEV RNA significantly associated with hepatitis in pigs (Martin et al., 2007 (p=0.01 and p=0.03 respectively)
- Hep E virus in Porcine hepatic lesions (Lee et al., 2007)

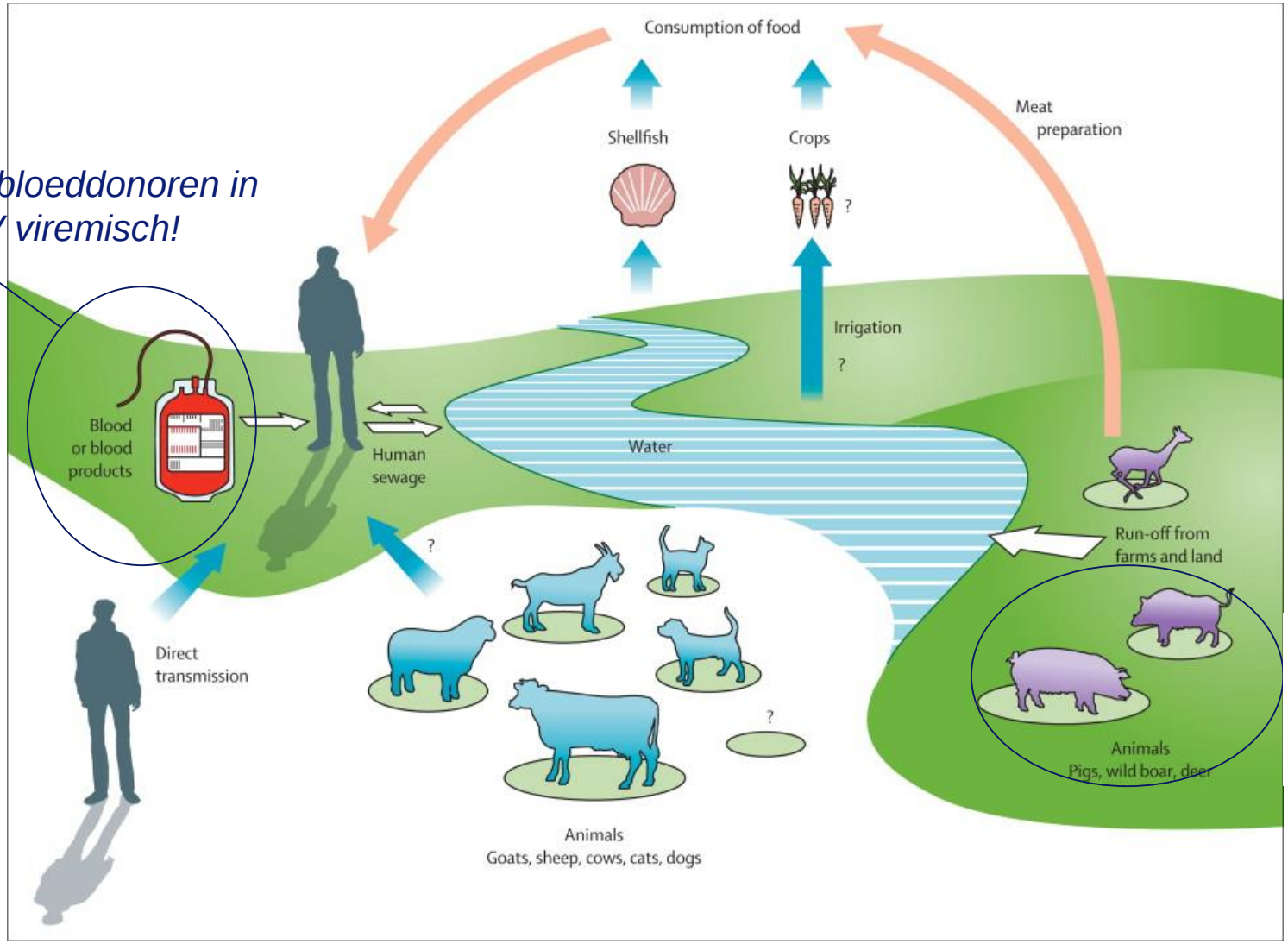






HEV transmission in developed countries - zoonosis

1:1000 bloeddonoren in NL HEV viremisch!



55% fecal tanks HEV RNA Pos

Kamar et al, Lancet 2012

Foodborne HEV infection

- HEV infection wild boar meat barbecue (Japan 2003)
- HEV infection from deer meat (Tei et al., 2003)
- HEV detected in oysters (Koizumi et al., 2004)
- HEV (RNA) detected in swine livers at retail (Bouwknegt et al., 2007; Savic et al., 2010)
- HEV infection from pig liver sausage (Figatelli) (Colson et al., 2010)

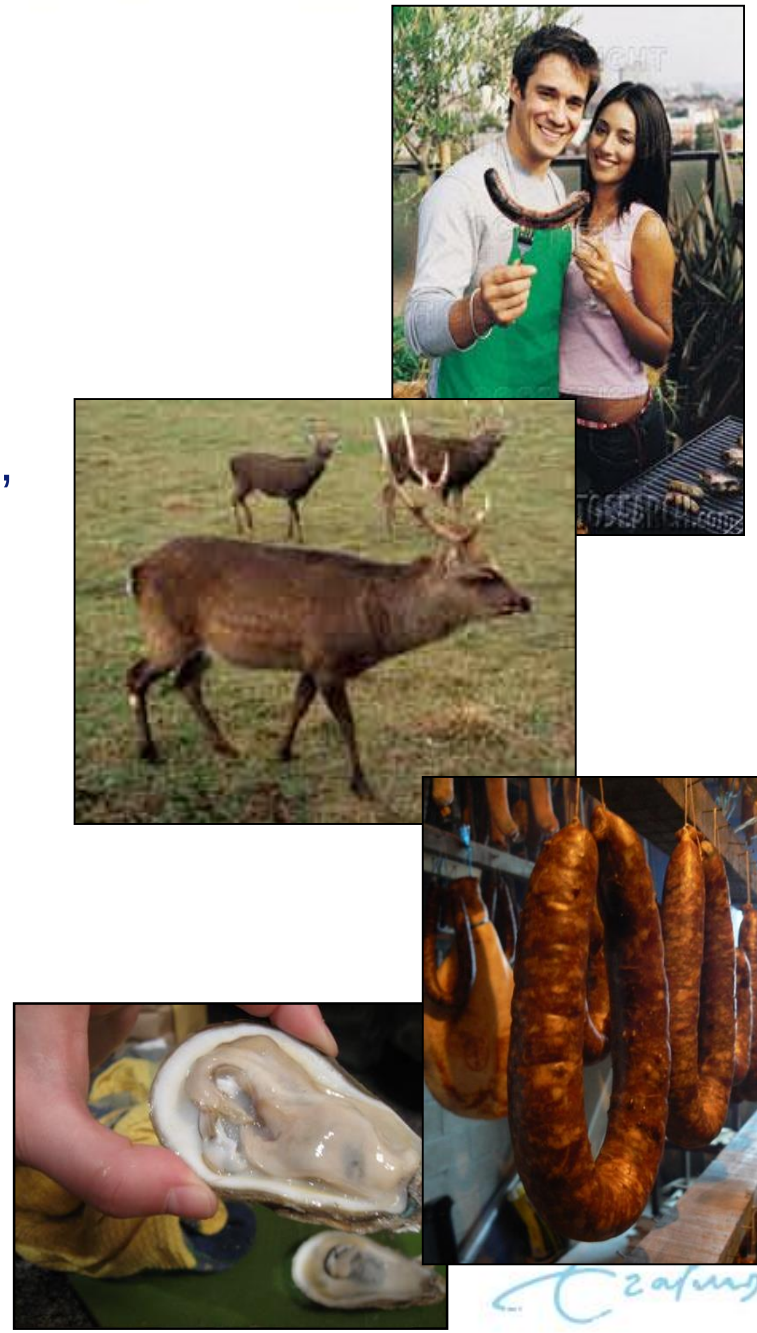
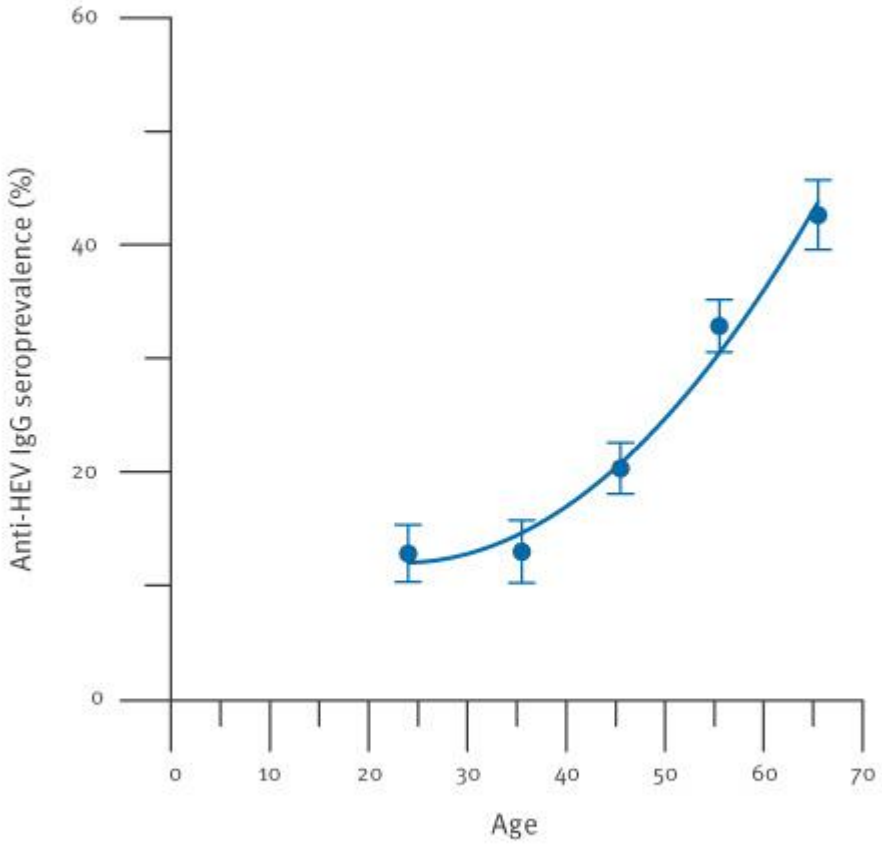


FIGURE 2

Anti-hepatitis E virus IgG seroprevalence in 10-year age groups of blood donors, the Netherlands, 2011–2012 (n=5,239)



The first group represents donors between 18 and 29 years rather than a 10-year group. Error bars indicate the 95% confidence interval for each age group.

HEV IgG seroprevalence ranged from 13% among donors younger than 30 years to 43% in donors older than 60 years

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HEV infection

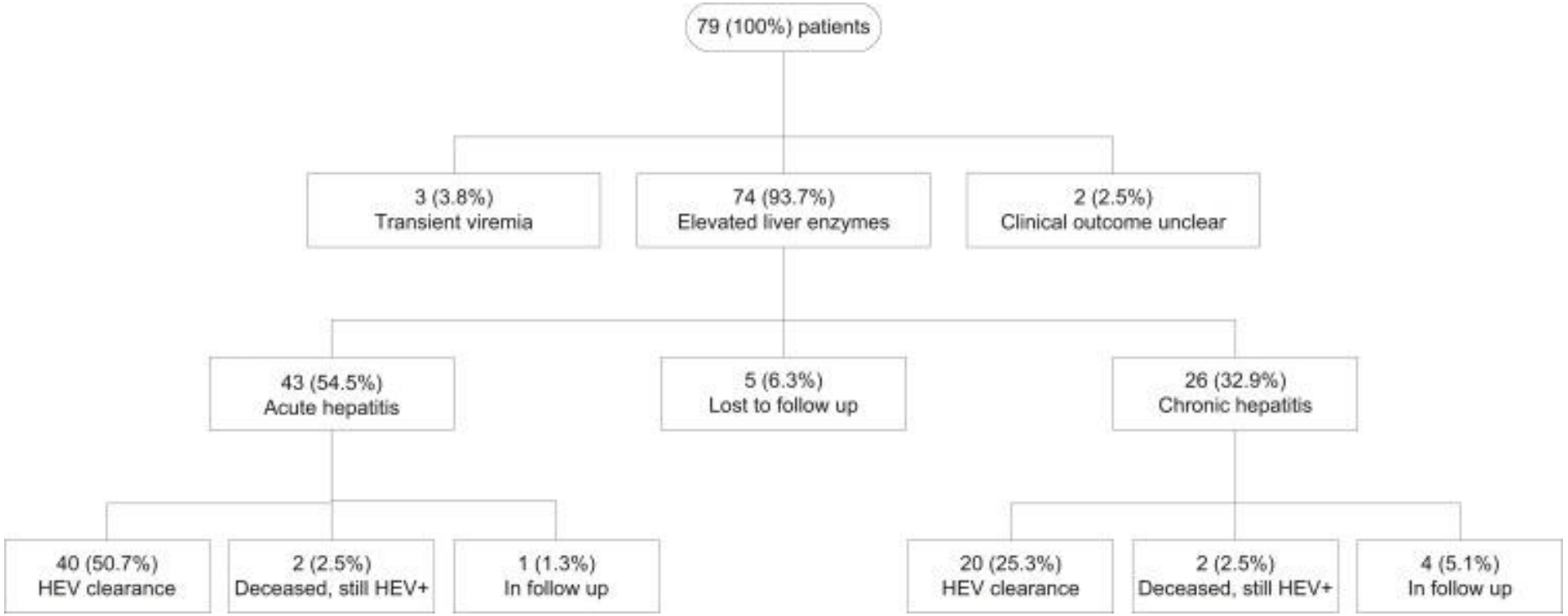
- Chronic HEV infection is reported in the transplant setting (both SOT and hematological patients)
  - Persistent viraemia
  - Persistently raised transaminase activity
  - Histological features associated with chronic hepatitis
  - Evidence of rapid development of cirrhosis

- PCR is superior to serology to detect infection in immunocompromised patients

HEV in the Erasmus MC

- 79 patients
  - 61 immunocompromised
    - 35 solid organ recipients
    - 18 hematological patients
    - 2 both SOT/haematological malignancy
    - 6 other
  - 18 “immune competent”
    - 15 patients received no immunesuppressants
    - 2 patients received prednisolone and 1 patient received methotrexate

Flowchart of the clinical course in HEV-infected patients of the cohort



Pas SD et al. EID 2012, Versluis J and Pas SD et al, Blood 2013
CM Nijskens, SD Pas et al, J Clin Virol 2016 Jan; 74 (82-7)

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Parameters of HEV confirmed cases of SOT and AlloHSCT group

	SOT - recipients Median (range)	Allo-HSCT recipients Median (range)	ULN (F/M)
Peak ALAT (U/L)	329 (70-909)	430 (213 – 1507)	33/44
Peak HEV RNA (log IU/ml)	7.21 (6.15 – 8.30)	7.26 (5.34-8.49)	NA
period of HEV RNA positivity (mos)	10.8 (6.3 -55.1)	6.4 (1.6 – 42.4)	NA
time between the Tx and first HEV-RNA positive (mos)	23.9 (-3.6 – 240)	4.6 (-2.1 – 18.3)	NA
Lag time PCR pos prior to HEV IgM (days)	64 (-35 – 842)	65 (0 -245)	NA
Lag time PCR pos prior to HEV IgG (days)	129 (0- 842)	126 (-594 – 351)	NA

Pas SD et al. EID 2012, Versluis J and Pas SD et al, Blood 2013

Patient characteristics of the Allo-HSCT cohort (n=328)

Median age of transplantation (years)		50.4 (17-66)	
Sexe (number, %)	Male	178	54%
	Female	150	46%
Type of alloHSCT	UCB	48	15%
	MUD	141	43%
	SIB	149	45%
Liver GVHD (number, %)	Acute grade I	42	13%
	Acute grade II-IV	130	40%
	Chronic limited	32	10%
	Chronic extensive	122	37%
Number of Patients alive at EOF(n, %)		180	55%
Median Time to follow-up (range, months)		40.9 (10-77)	

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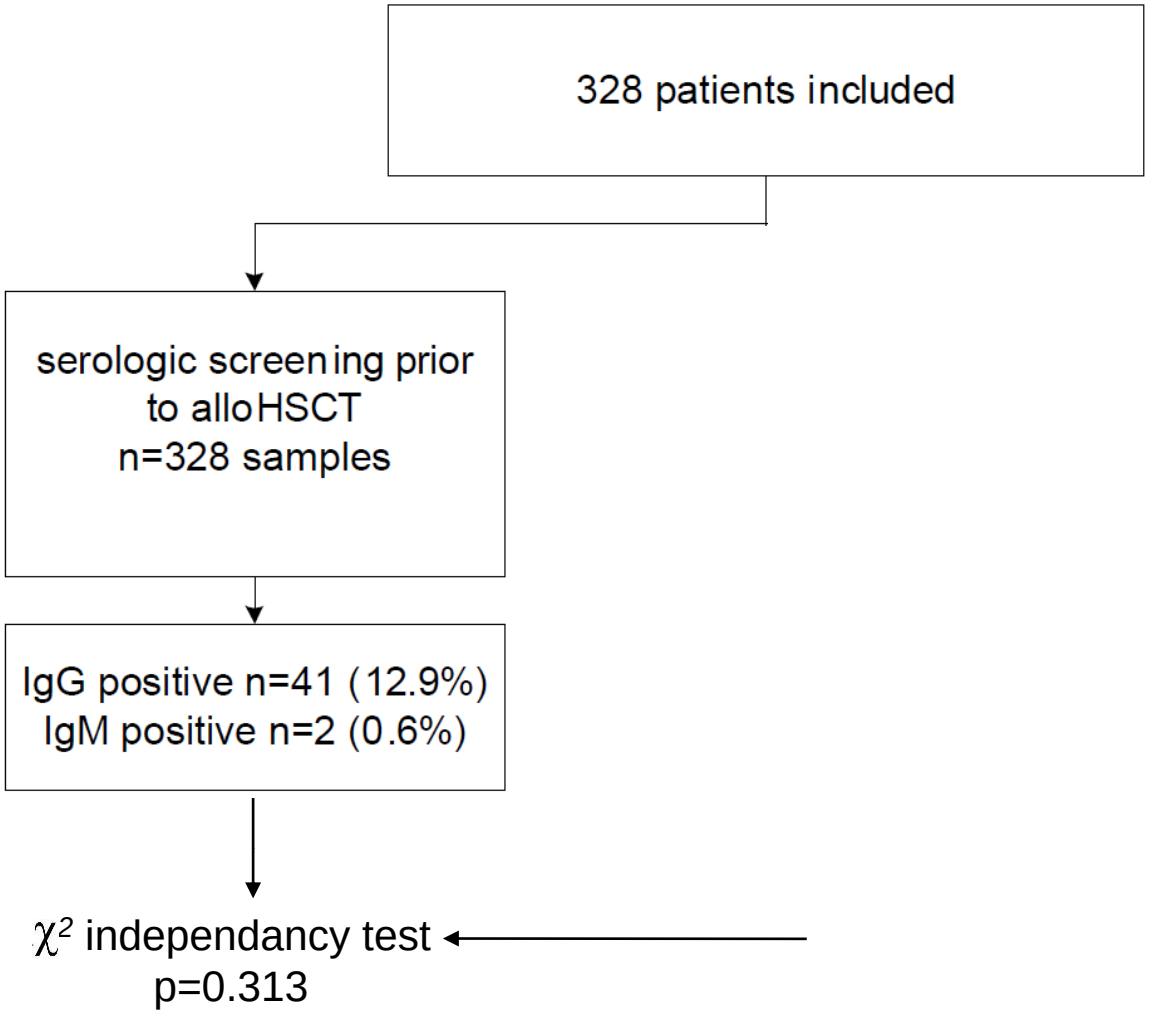
GVHD, graft versus host disease; UCB, umbillical cord-blood; MUD, matched- unrelated donor; SIB, sibling; EOF end of follow up

Study results

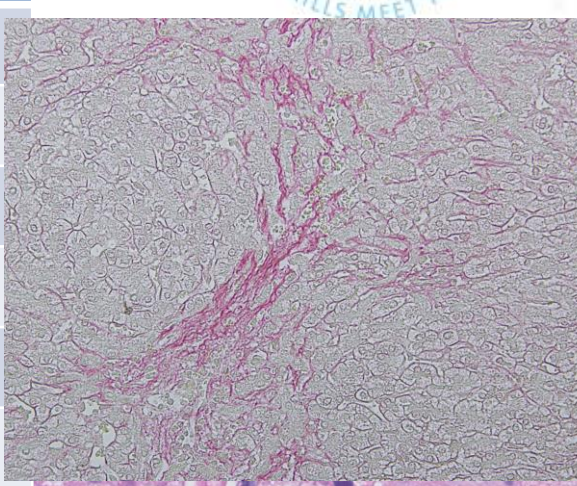


Characteristics of HEV confirmed patients (n=8)

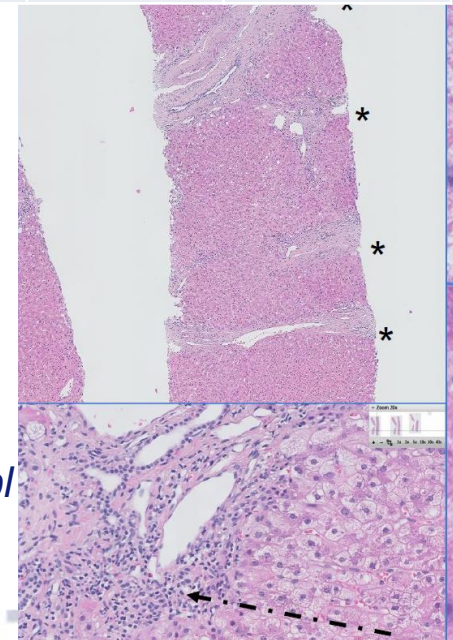
Patient	Sexe	Heam. disorder	Stem cell source
1	M	AML	UCB
2	F	NHL	MUD
3	F	MDS	MUD
4	M	CLL	MUD
5	M	AML	MUD
6	M	NHL	MUD
7	F	SAA	UCB
8	M	AML	UCB

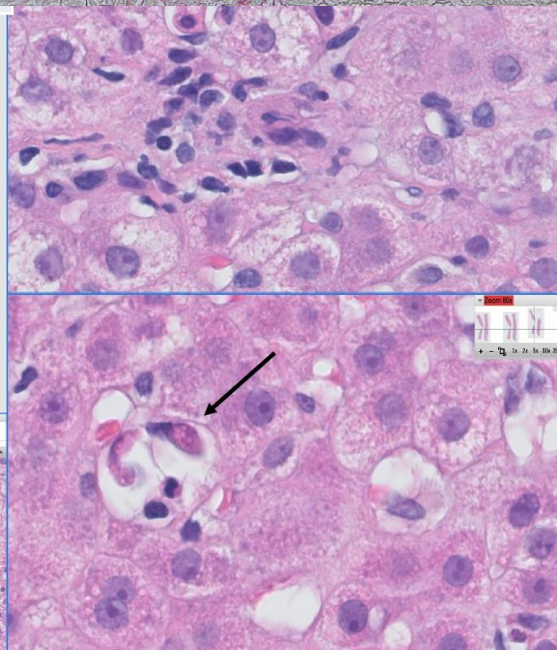
AML, acute myeloid leukemia;CLL, chronic lymphoid leukemia;MDS, myelodysplastic syndrome; NHL, non-Hodgkin lymphoma; SAA, severe aplastic anemia;
* Patient died having a HEV viremia

Infection time (months)	Periportal necrosis	Intralobular Inflamma-tion	Portal inflamma-tion	Fibrosis	Total HAI score
9	1	3	2	3	9
5	1	2	1	3	7
7	3	3	3	3	12
5	0	1	0	0	1
22	3	3	3	3	12
8	1	1	1	1	4



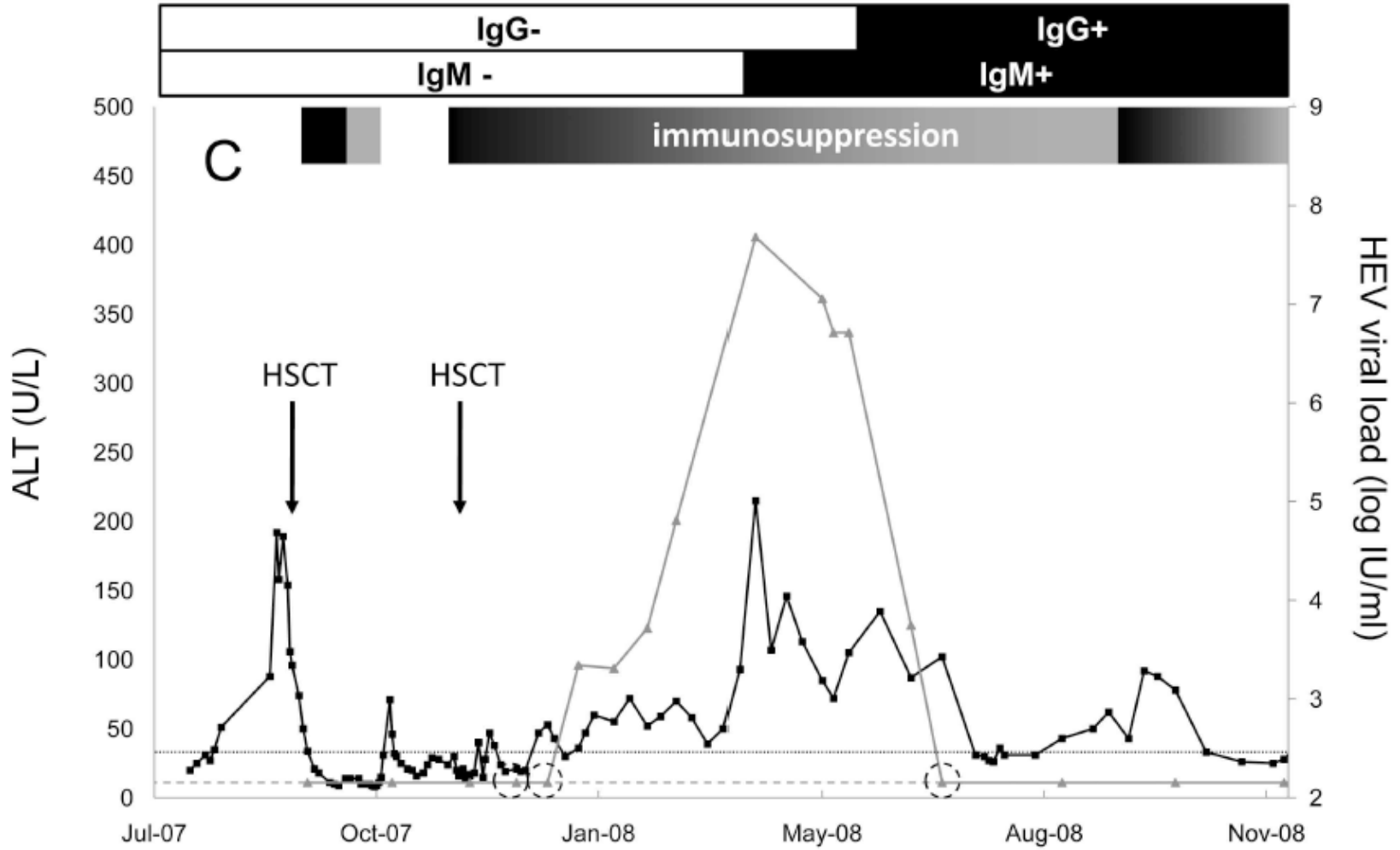
Individual Knodell score (HAI) of liver biopsy specimens heart transplant recipients



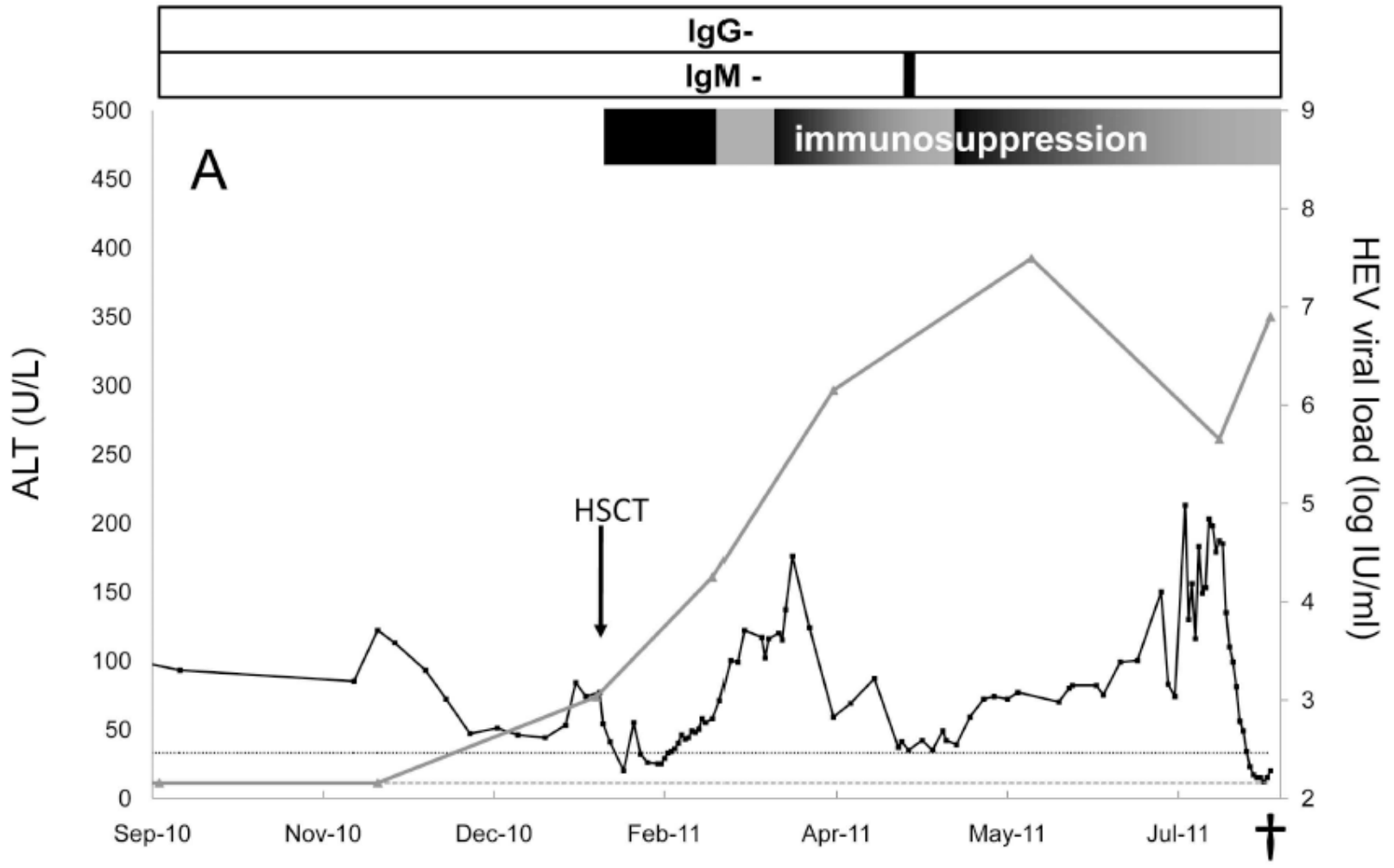


Versluis J and Pas SD et al, Blood 2013
Koning L, Pas SD et al J Heart and Lung Transpl

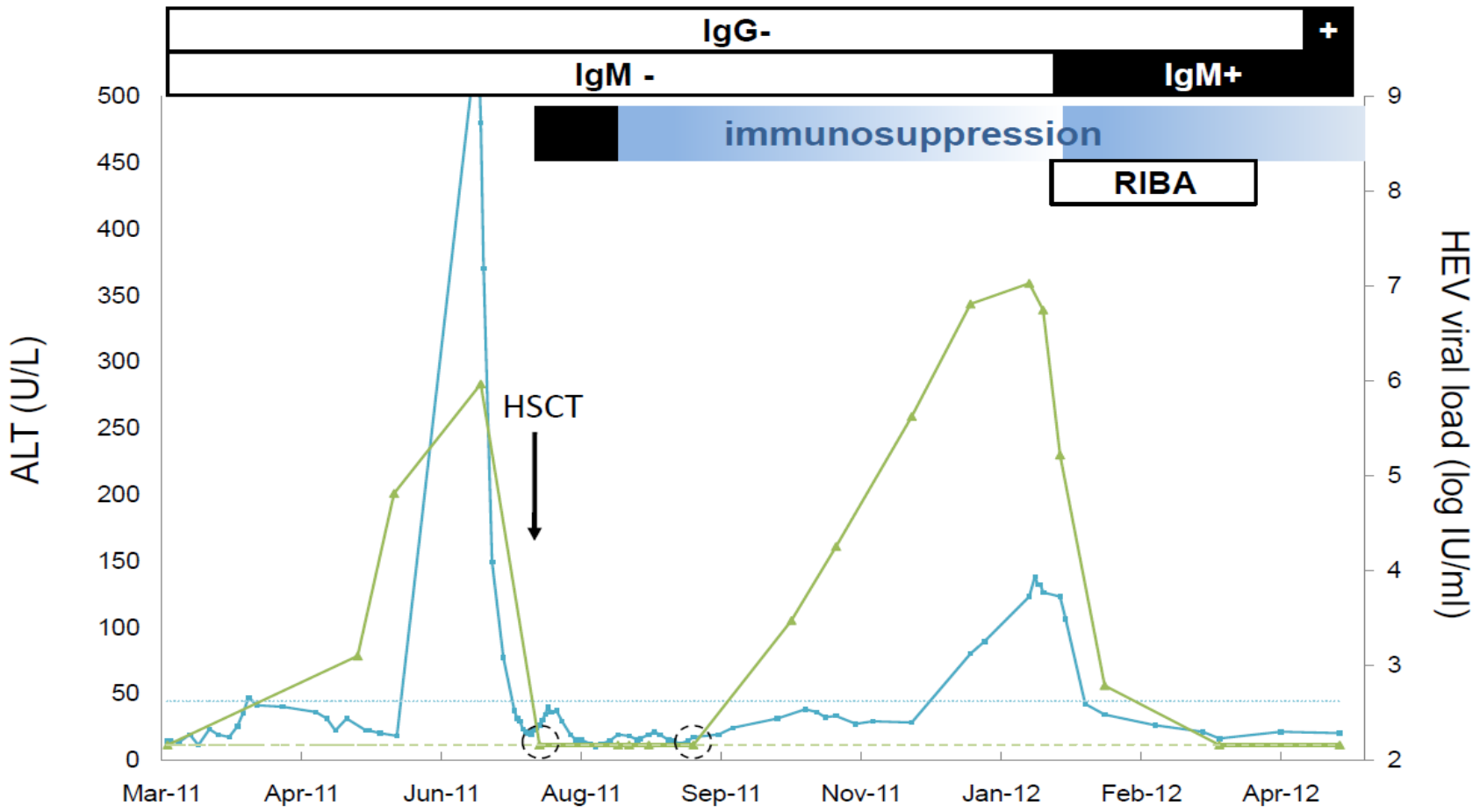
Course of infection in AlloHSCT recipient



Course of infection in an alloHSCT recipient



Reactivation in an alloHSCT recipient



ALT (U/L)

upper normal limit ALT (U/L)

HEV viral load (log IU/ml)

HEV LOD (2.16log IU/ml)

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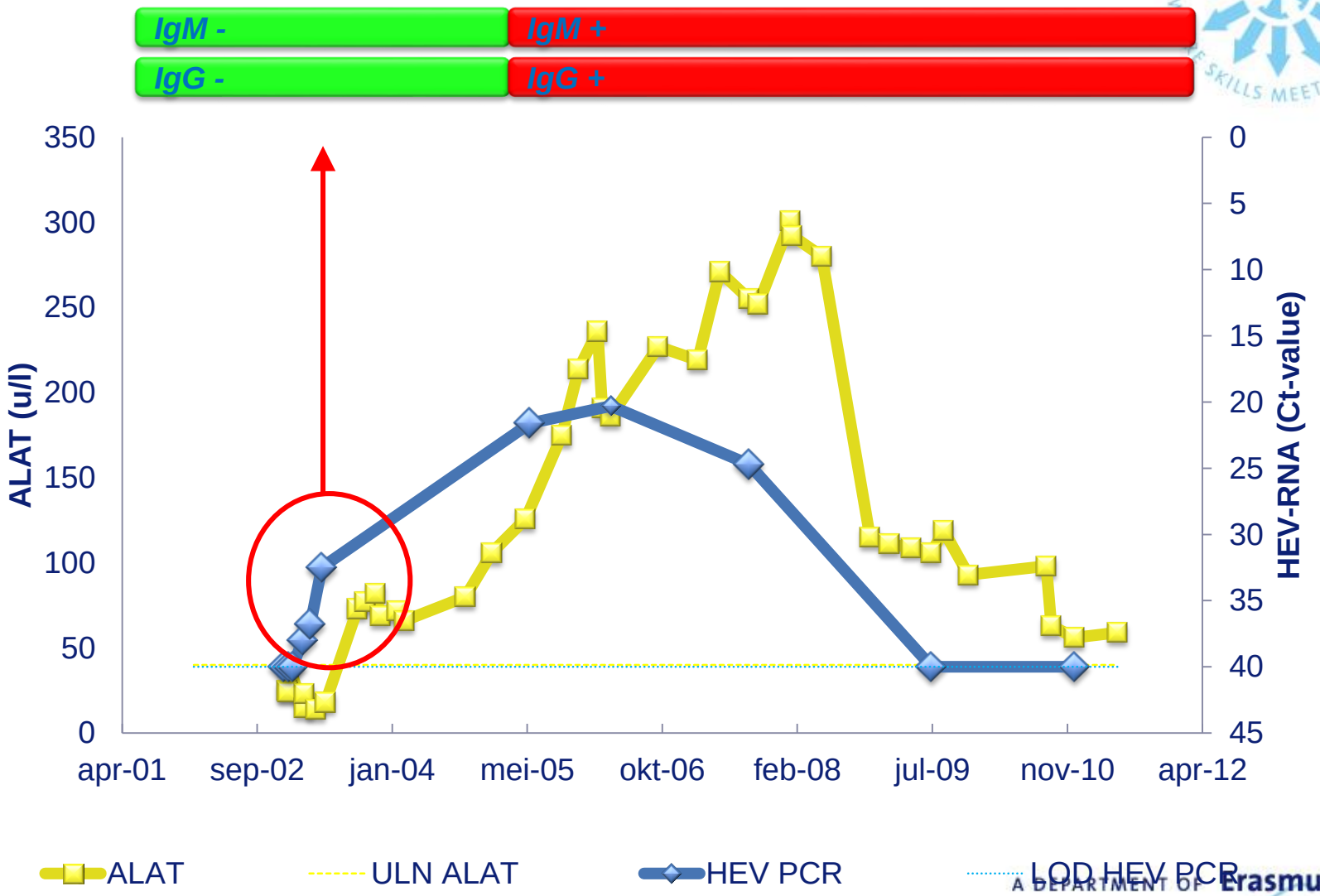
Therapeutic options for chronic HEV

- tapering immunosuppression

  a reduction in immunosuppressive therapy, mainly immunosuppressants that target T cells, results in HEV clearance in nearly 30% of solid-organ transplant recipients with chronic hepatitis

Course of chronic HEV infection in LuTX patient



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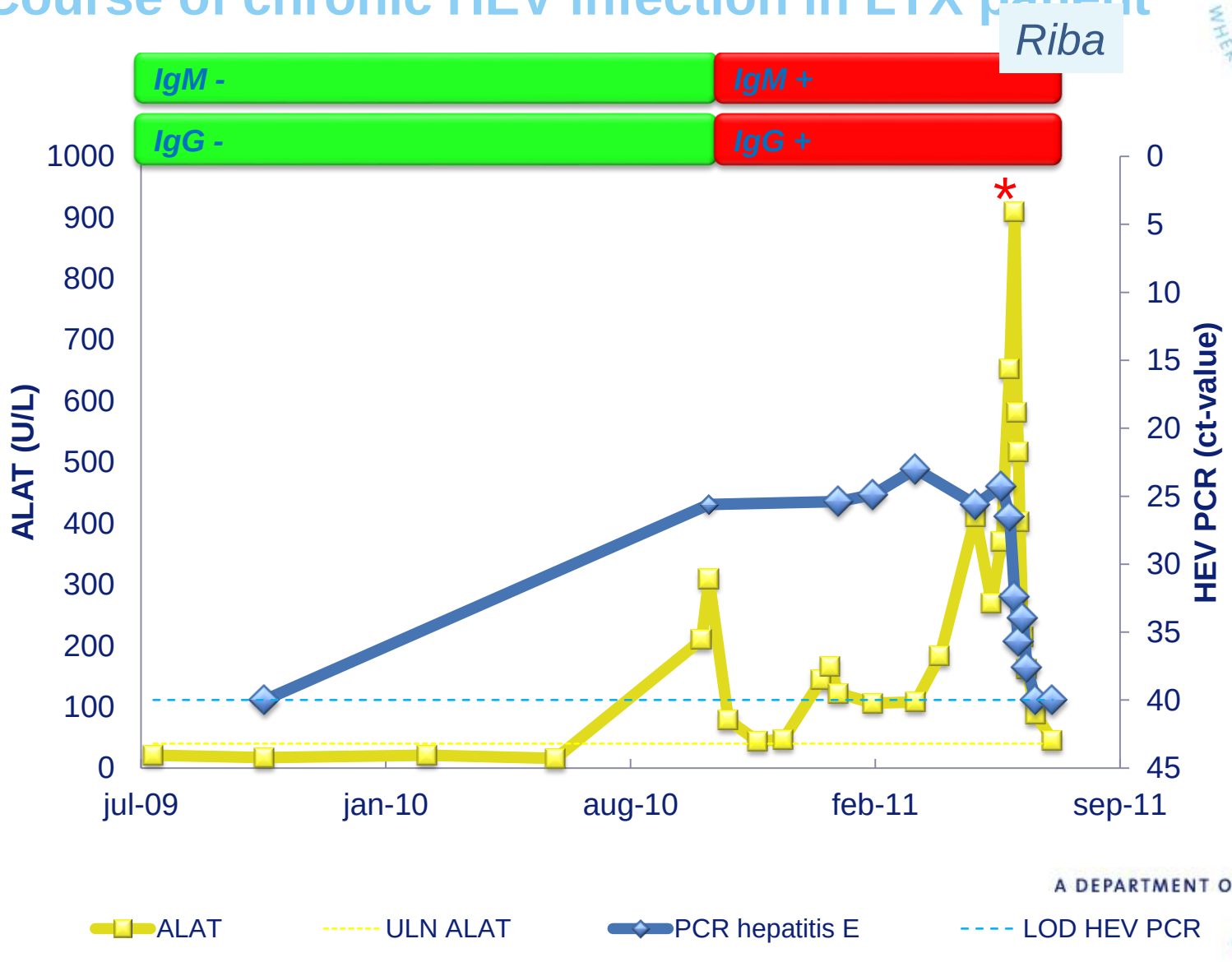
Therapeutic options for chronic HEV

- Tapering immunosuppression
- Peg-interferon
- Ribavirine

Course of chronic HEV infection in LTX patient



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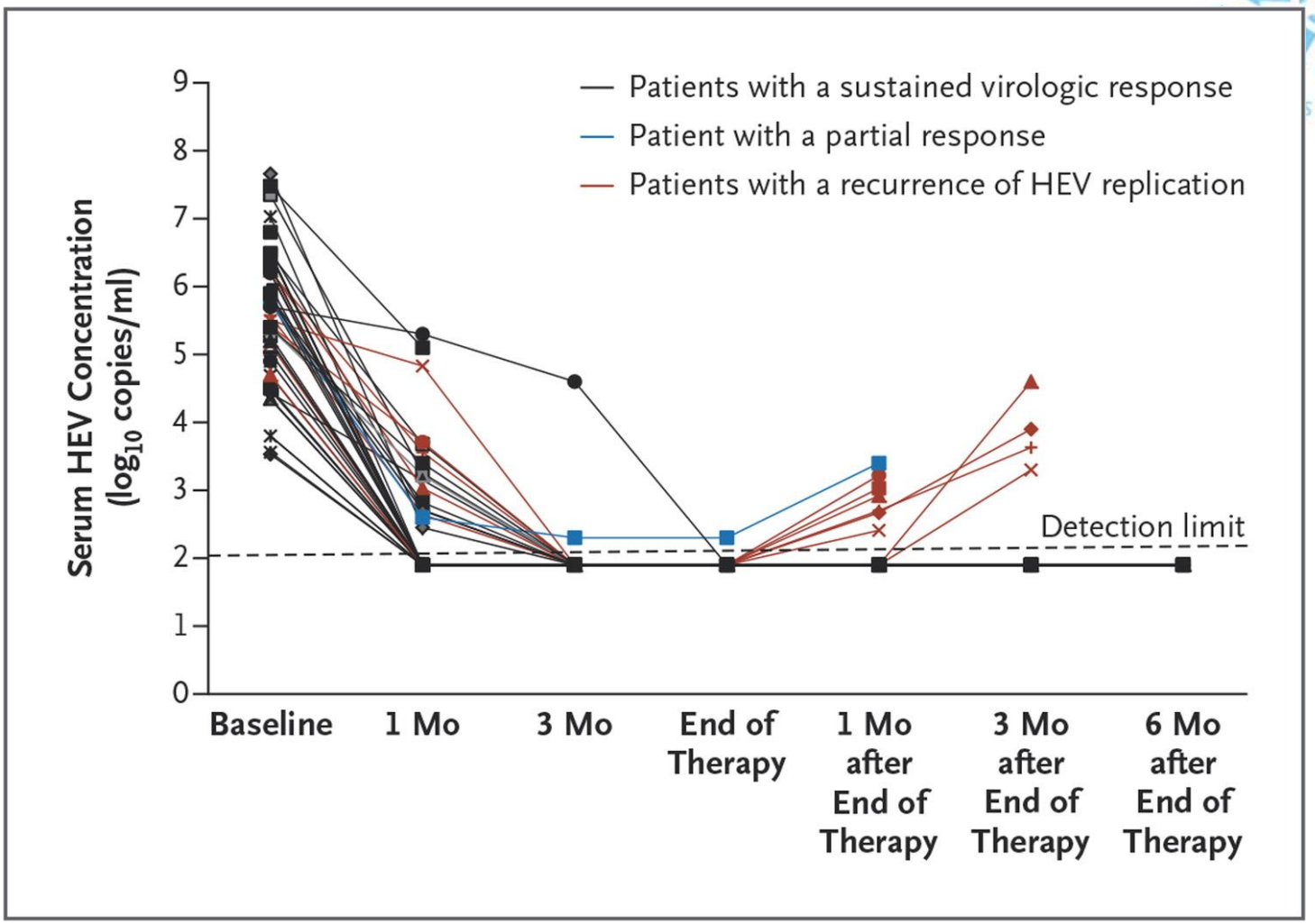
HEV concentration during ribavirin therapy



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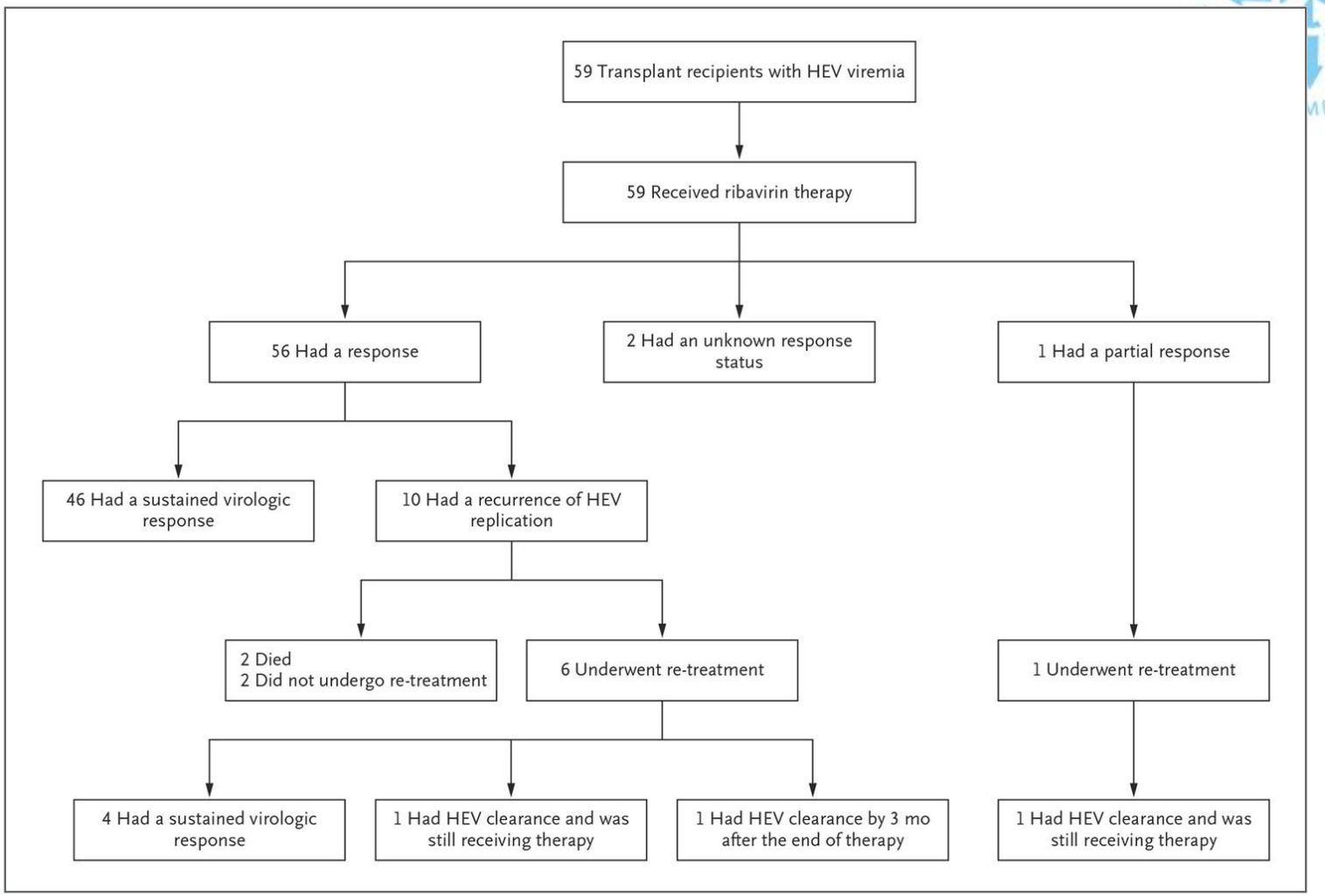
Kamar N et al. N Engl J Med 2014;370:1111-1120.

Outcomes of ribavirin therapy in SOT with HEV



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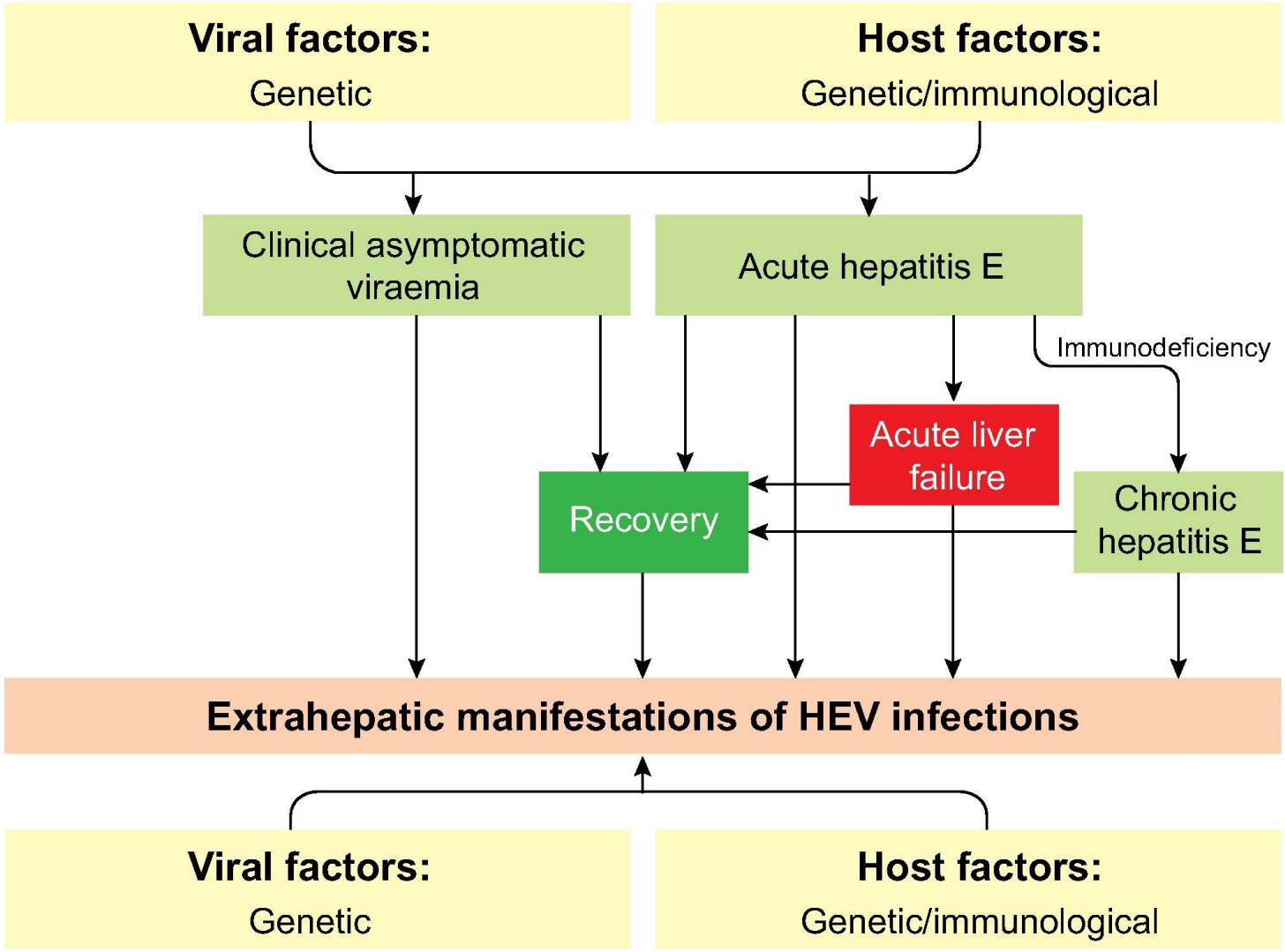
Kamar N et al. N Engl J Med 2014;370:1111-1120.

Non-response treatment with ribavirin

- No resistance; ribavirin has no known direct effect on a specific viral target
- Recurrence of HEV replication after cessation of ribavirin tx: although lack of detection of HEV in the serum, HEV replication may persist at other sites such as the gut
- G1634R mutation: virulence mutation; increased replication capacity
- Side effects ribavirin:
  - Reduction ribavirin dose (29%)
  - Use of erythropoietin (54%)
  - Blood transfusion (12%)

Conclusion:

- Ribavirin as monotherapy may be effective in treating chronic HEV infection.
- A 3-month course seems to be an appropriate duration for this therapy, though a longer therapy can be given to
  - heavily immunosuppressed patients
  - patients who still have viremia 1 month after the initiation of therapy.
  - patients with shedding of HEV in faeces, while serum is negative
- Prospective studies are required to determine the most beneficial dose and duration of ribavirin therapy.



Extrahepatic manifestations of HEV infection

Neurological

- Guillan Barre Syndrome
- Neuralgic amyotrophy
- Encephalitis/myelitis

Nephrological

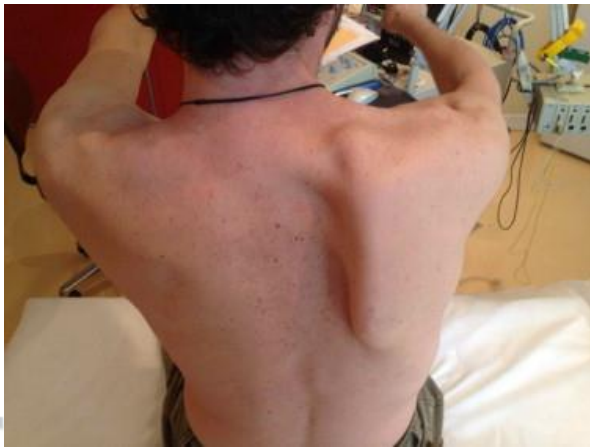
- Glomerulonephritis

Hematological

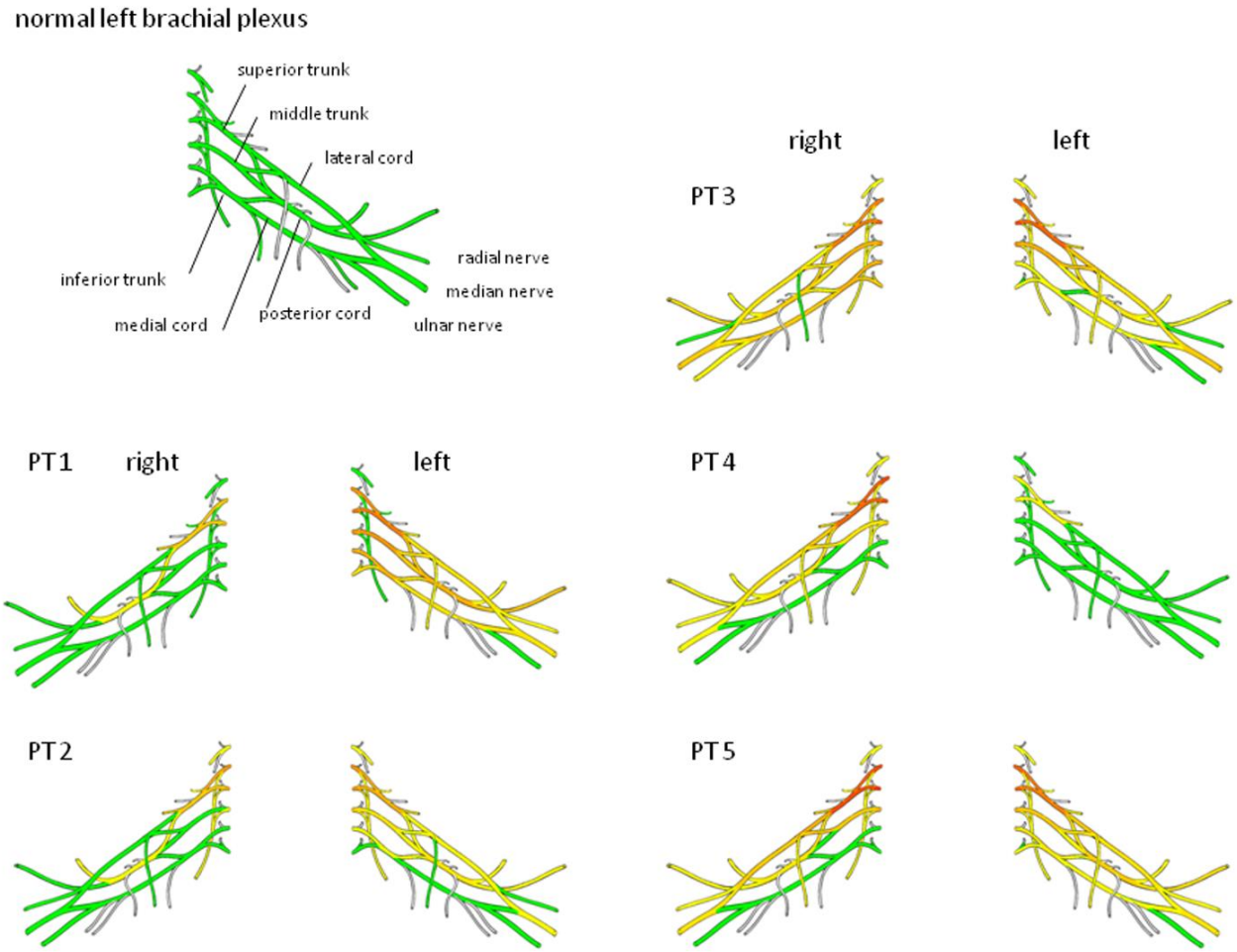
- Thrombocytopenia
- Cryoglobulinemia
- MGUS

Other

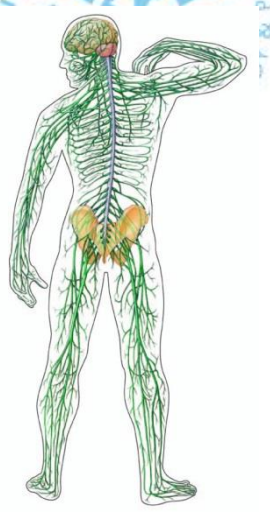
- Acute pancreatitis



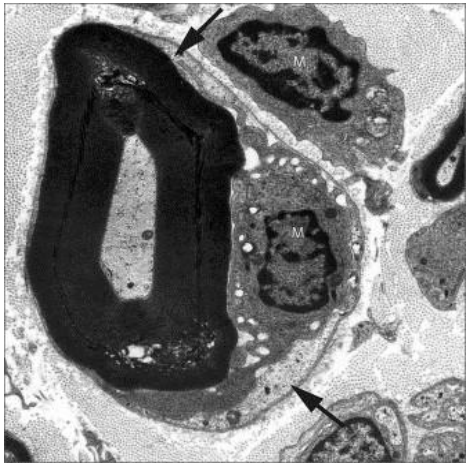
Brachial plexograms of anti-HEV IgM associated NA patients



Guillain-Barré syndrome (GBS)



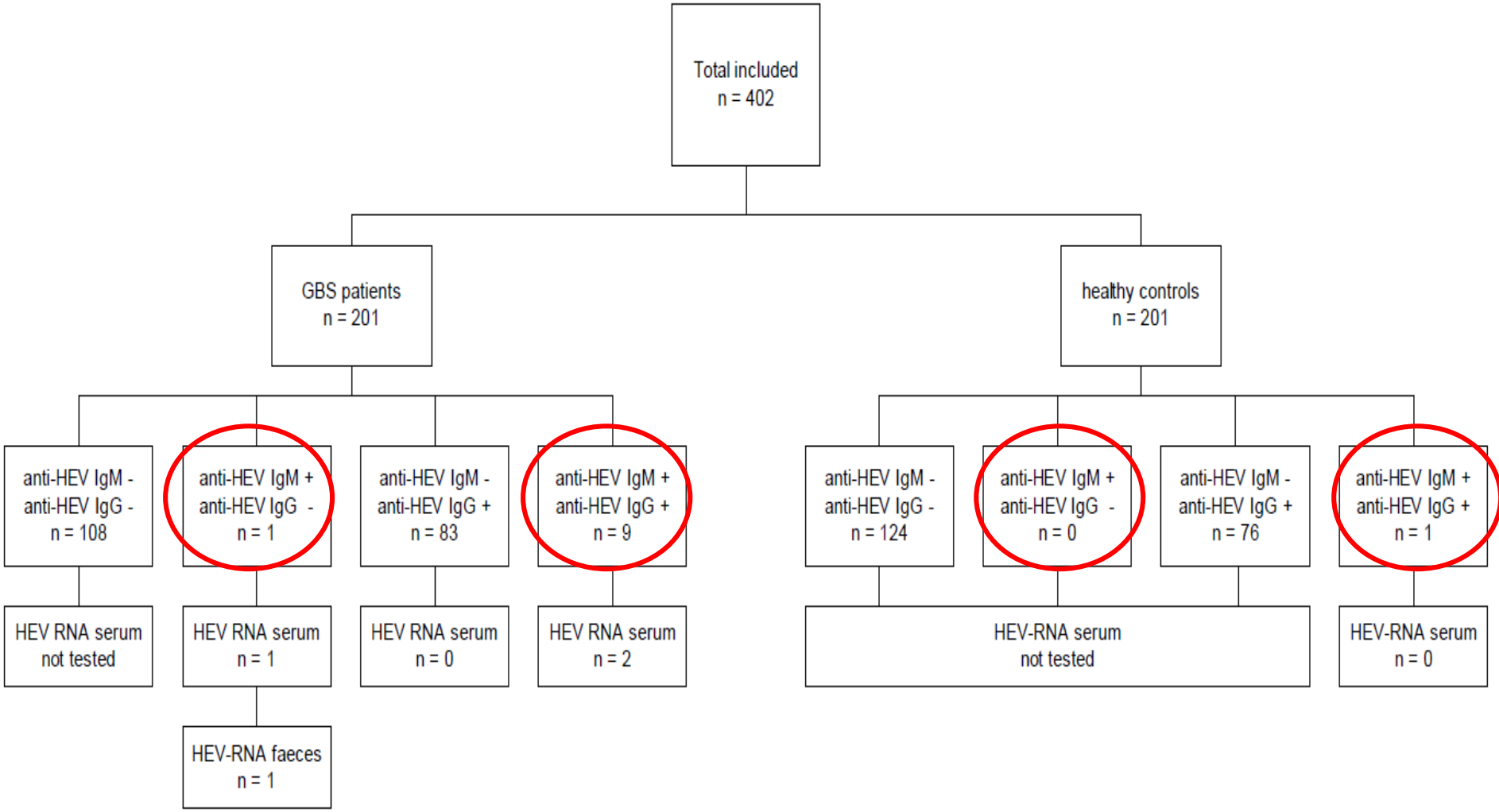
- Post-infectious immune-mediated polyradiculoneuropathy
- Incidence 1-2/100.000/year (life-time risk of 1:1000)
- Clinical features:
  - rapidly progressive weakness in legs and arms
  - proportion with involvement cranial and/or sensory nerves
  - respiratory failure requiring ventilation at ICU (25%)



- Pathology:
  - Demyelination and macrophage infiltration:
  - (axonal degeneration)

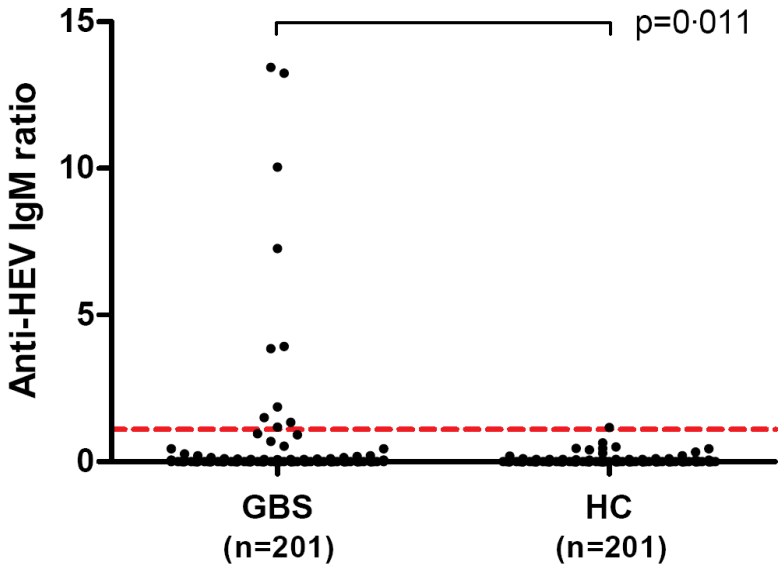
- Clinical course:
  - acute onset and monophasic
  - frequent residual disability (15% wheelchair bound)

Results: Flowchart of included patients and HC

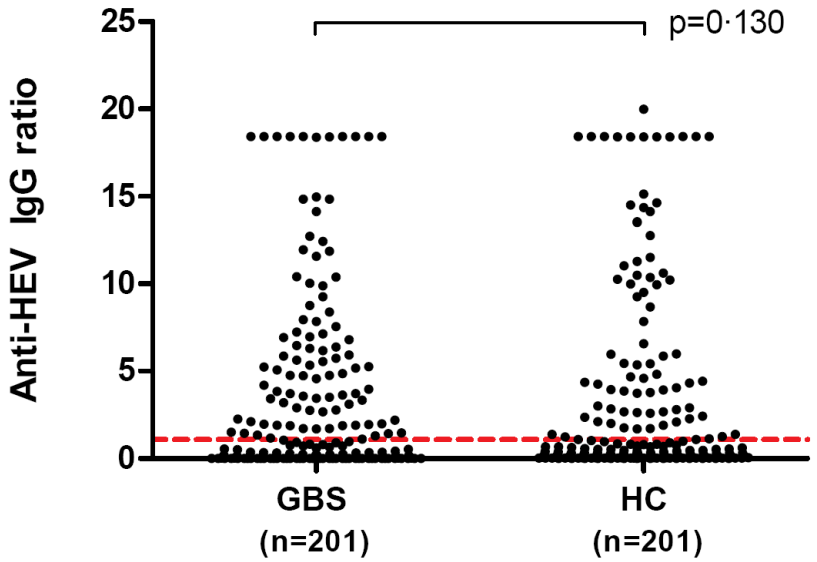


Anti-HEV antibodies in GBS patients vs healty controls

Serum anti-HEV IgM



Serum anti-HEV IgG



Sero-prevalence	**5.0%**	0.5%	45.8%	38.3%

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GBS patients versus healthy controls

HEV serology	Odds ratio (CI)	p-value	Adjusted Odds ratio (CI)	Adjusted p-value
Anti-HEV IgM positive	**10.5 (1.3-82.6)**	**0.011**	**9.7 (1.2-77.0)**	**0.032**
Anti-HEV IgG positive	1.4 (0.9-2.0)	0.130	1.4 (0.9-2.1)	0.149

Clinical features of HEV associated GBS cases (n=10)

- 70% had elevated ALT levels (median 70 IU/L, range 26-921)

- No antibodies against gangliosides.

- The majority of HEV-associated cases of GBS had a sensory-motor and demyelinating form of GBS, the predominant subtype of GBS in The Netherlands

- The presence of anti-HEV IgM in GBS patients was *not* related
  - age
  - gender
  - disease progression
  - disease severity
  - cranial nerve deficits
  - sensory deficits
  - treatment
  - electrophysiological subtype
  - clinical outcome after six months

HEV

- Wie denkt dat hij/zij in de toekomst een Hepatitis E virus test gaat aanvragen in zijn/haar patiënt?
- Wie houdt nog steeds van droge Franse worstjes?

Conclusions

- Chronic HEV infection is reported in the transplant setting (both SOT and hematological patients)
  - Persistent viraemia
  - Persistently raised transaminase activity
  - Histological features associated with chronic hepatitis
  - Evidence of rapid development of cirrhosis
- PCR is superior to serology to detect infection in immunocompromised patients
- Therapeutic options for chronic HEV includes tapering immunosuppressiva and secondly ribavirine, (PEG-IFN)
- Extrahepatic manifestations have been associated with HEV

Acknowledgements

- Department of Cardiology
- Dr. A.H.M.M. Balk, Dr K. Caliskan

- Department of Respiratory Medicine
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- Dr . D.A. Hesselink

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- J. Versluis
- Prof. Dr. J.J. Cornelissen

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