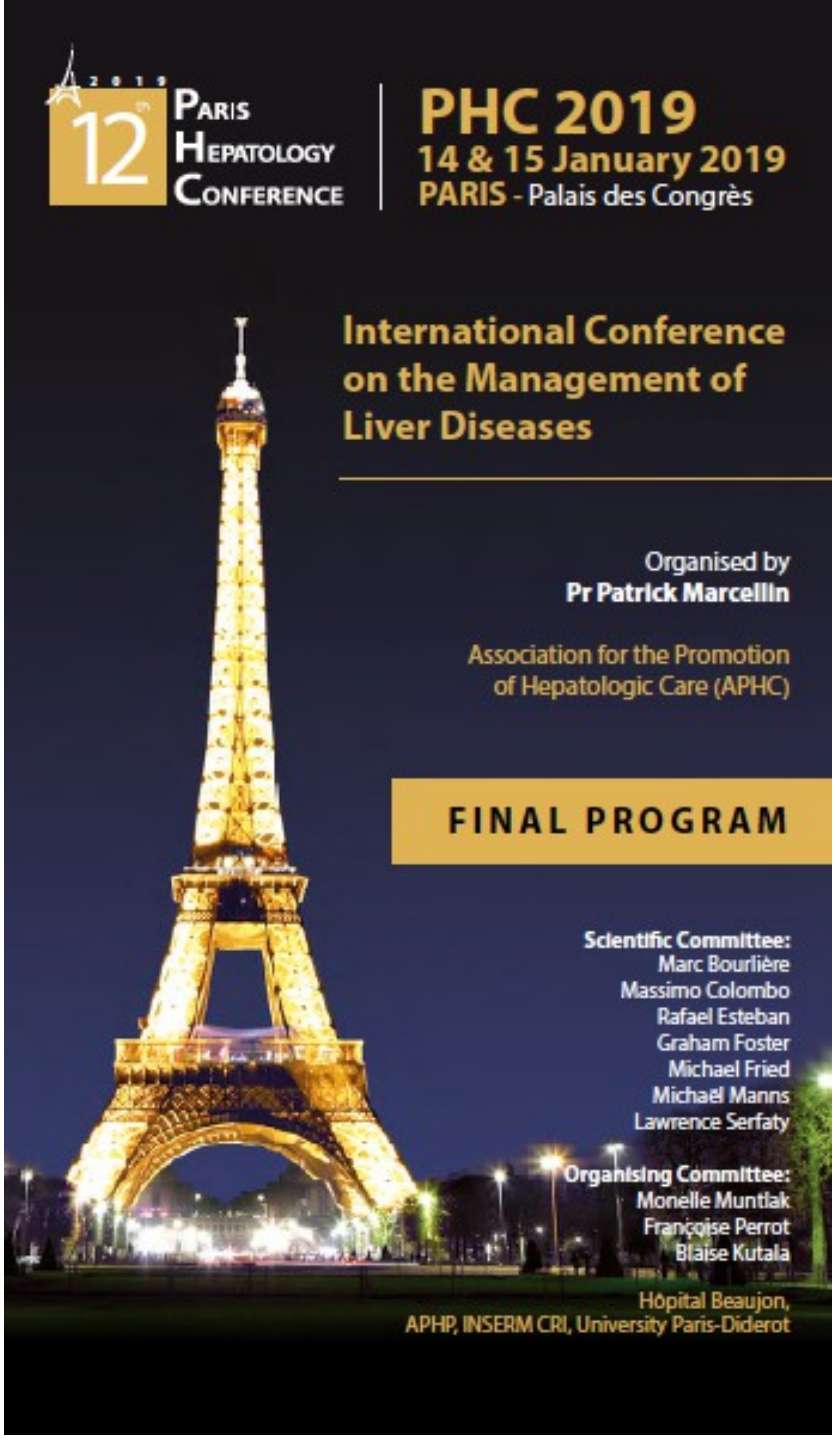

HEV infection in the immunosuppressed patient

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UO Epatologia – Azienda Ospedaliero Universitaria Pisana - Centro Riferimento Regionale *"Diagnosi e trattamento delle epatopatie croniche e del tumore di fegato"*

Disclosures

Advisory board: AbbVie, Gilead, Roche

Speakers' bureau: AbbVie, BMS, Gilead, MSD, Janssen

Research grant: AbbVie, BMS, MSD

First observation: July 2008 because of transaminases elevation

- 37 years old man
- '90 diagnosis of IgA nephropathy → dialysis from '94 –'96 → kidney transplant in 1997
- On treatment with:

  prednisone 5 mg
  mycophenolate mofetil 2 gr/die
  ciclosporin 250 mg/die

Recent history

- March 2008 during a 2 weeks holiday in Peru herpetic conjunctivitis (treated with antivirals) and travelers diarrea (treated with antibiotics)
- June 2008 → periodic blood control: AST 228 U/L, ALT 633 U/L
  asymptomatic (mild asthenia)

Liver disease history

- No history of liver disease, with the exclusion of the evidence in 2001 in 2 separate occasions (June and October) of mild ALT elevation (ALT 80-100 U/L) → spontaneous normalization without any evidence of ALT elevation thereafter
- No major risk factors for liver disease, with exclusion of kidney disease management overtime
- No new drug exposure

Clinical evaluation of July 2008

- The patient is still asymptomatic

Biochemestry

AST/ALT U/L	215/537
GGT/Aph U/L	106/132
Tot Bil/d mg/dl	1.05/0.64
PT	75%
Albumin g/L	4.5

Viral panel

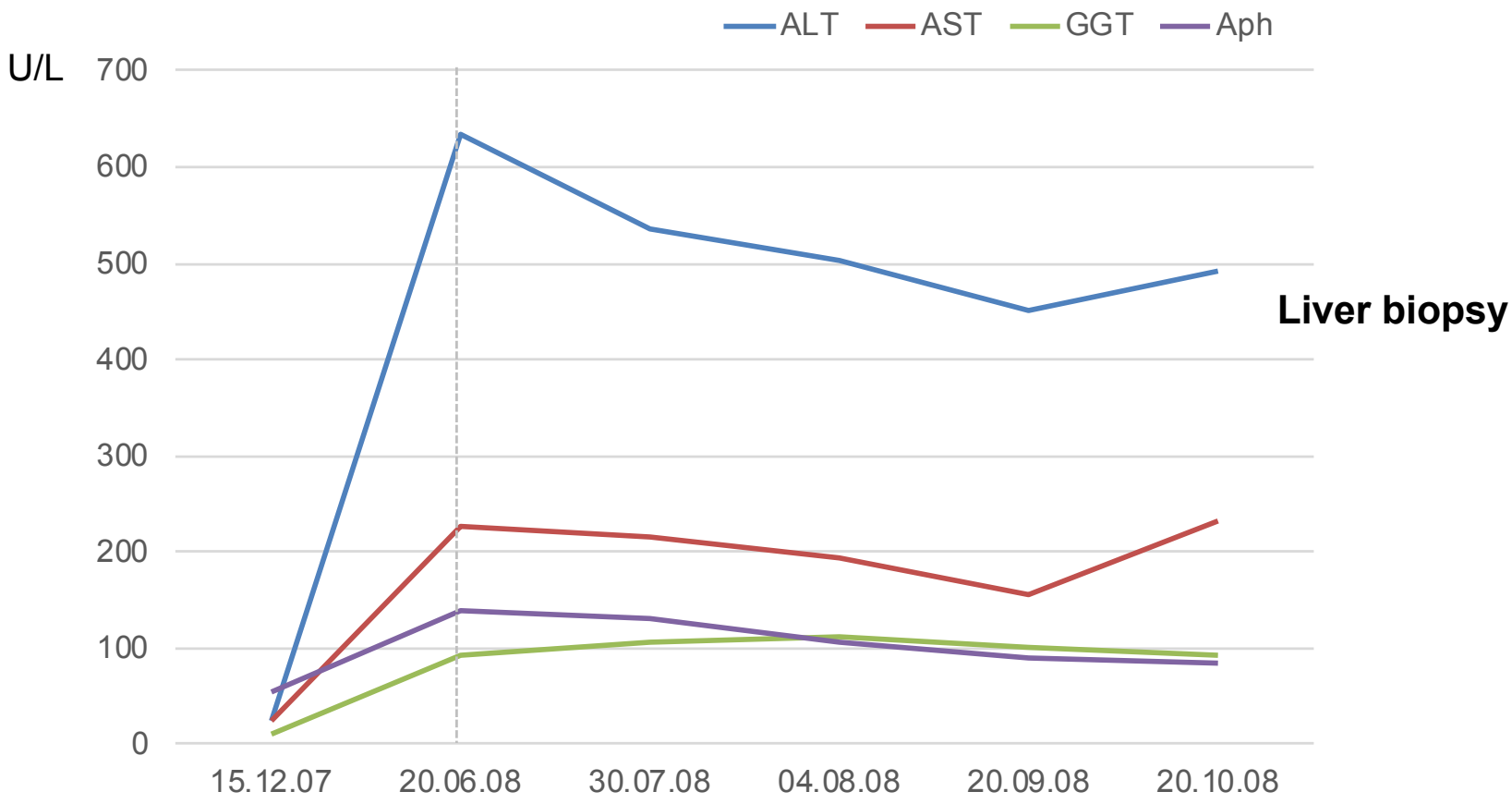
Anti-HBs	positive
Anti-HCV/HCV-RNA	negative
IgM anti-HAV	negative
IgM EBV VCA	negative
IgG EBV VCA	positive
IgG anti-CMV	negative
IgG anti- Herpes I	positive
IgG anti-Herpes II	negative

Clinical evaluation of July 2008

- The patient is still asymptomatic

Fibroscan	**7.8 kPa**
Ultrasound scan	Minimally enlarged liver, with regular profiles. Modest increase of echogenicity. Portal vein patent, of 11 mm Size of spleen within the normal range (12 cm) Known polip of the gallbladder

Follow-up


ALT
AST
GGT
Aph
U/L
700
600
500
400
300
200
100
0
15.12.07
20.06.08
30.07.08
04.08.08
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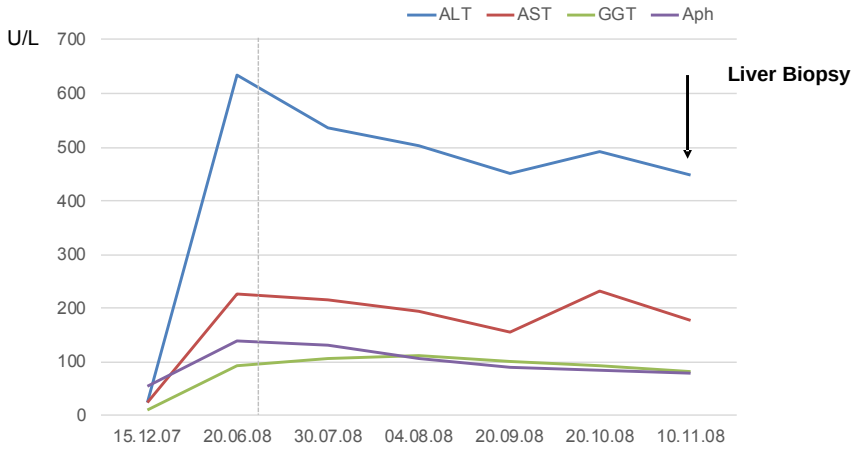
20.10.08
Liver biopsy



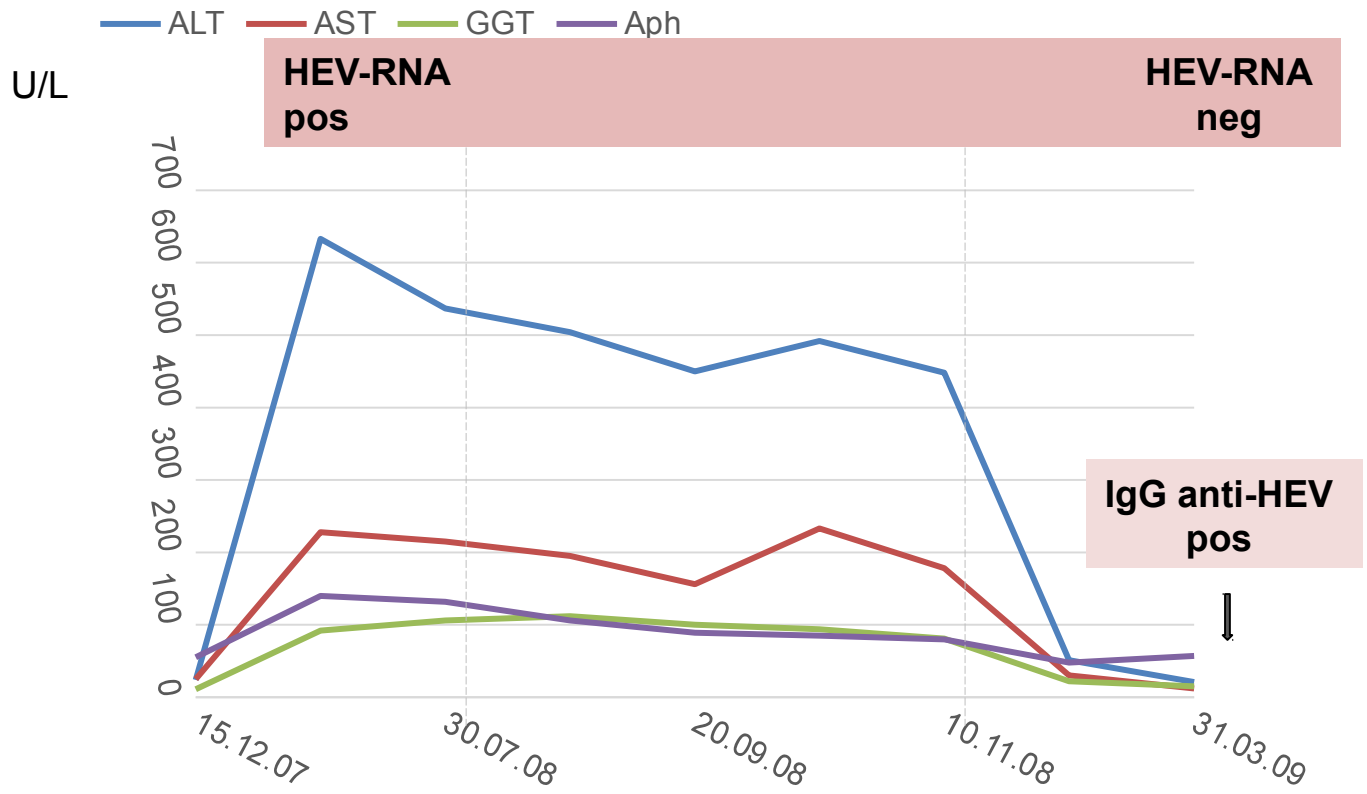
Liver Histology

- Liver architecture is maintained.
- Some portal tracts are significantly enlarged for the presence of small and medium size lymphocytes. Presence of some lymphoid follicols. Both B and T lymphocytes are present.
- The remaining portal tracts show a mild to moderate lymphocitic infiltration with occasional spill over.
- Lobular dissarray and occasional confluent necrosis.
- Bile ducts are surrounded by lymphocytes
- Minimal micro-macro steatosis.
- Immunhistochemestry negative for CMV and EBV

The pathologist hypothesized the presence of a lymphoproliferative disorder

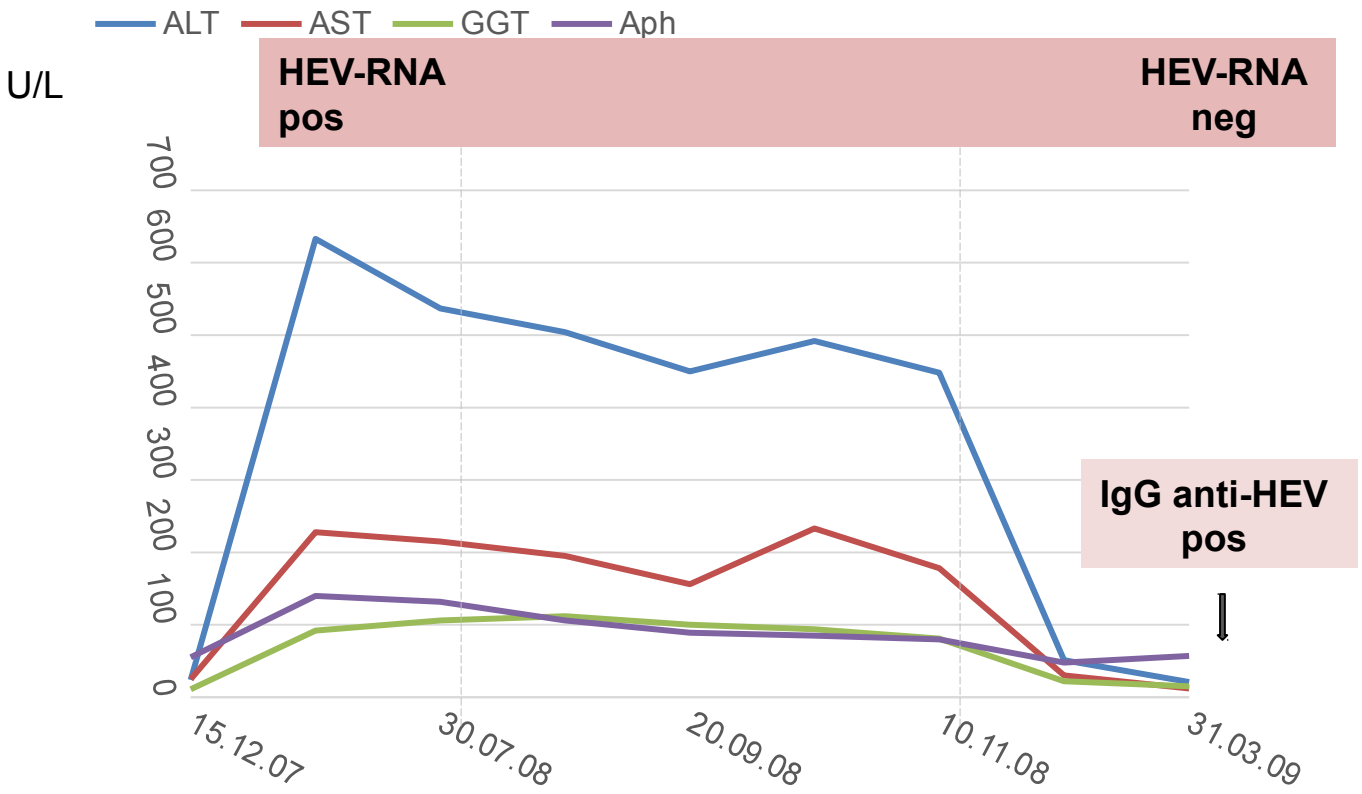
Haematological evaluation was negative

Follow-up of the patient



The patient normalized ALT within 6 months and had evidence of HEV-RNA clearance 10 months after the first evidence of infection

Follow-up of the patient



Primary HEV infection with a late viral clearance in a kidney transplanted patient

Can HEV infection become chronic ?

- Yes, about 60% of immunosuppressed patients fail to clear HEV infection
- They may develop chronic hepatitis, but at present this has been seen only in GT3 and 4 infected individuals

Which is the definition of chronic HEV infection?

- Persistence of HEV replication for 6 months
- However in an observational study in solid organ transplant recipients, it was observed that no spontaneous HEV clearance occurred between 3 to 6 months after infection → spontaneous clearance was observed only during the first 3 months after infection

Who are the patients at risk?

- Organ transplant recipients
- Patients with haematological disorders
- HIV infected subjects
- Patients with rheumatic didorders receiveing heavy immunosuppression

EASL CPG HEV infection, 2018; Kamar et al Am. J Transplant 2013;Meisner D et al Am. J Transplant 2015

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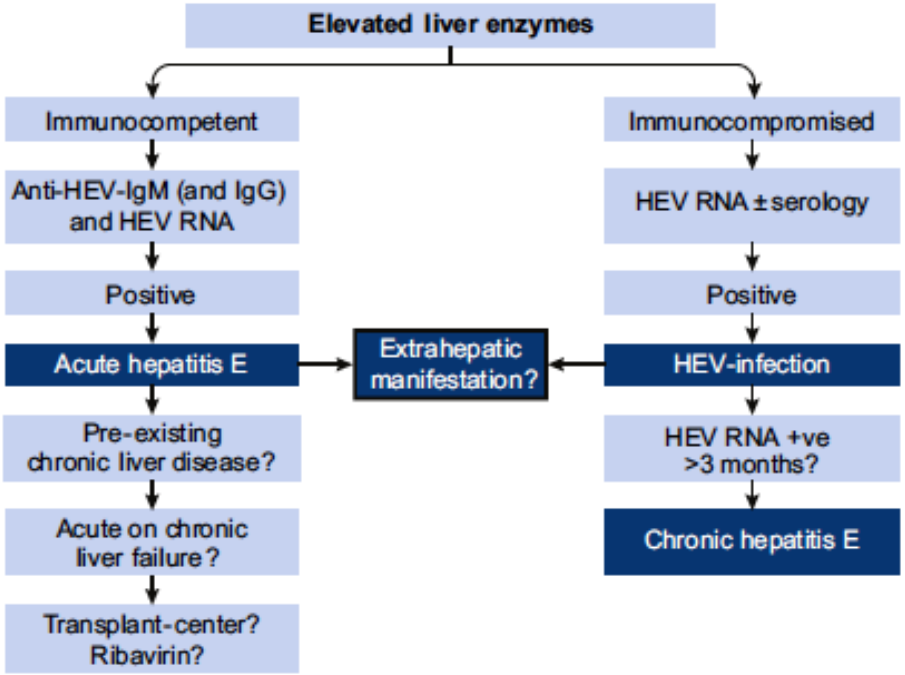
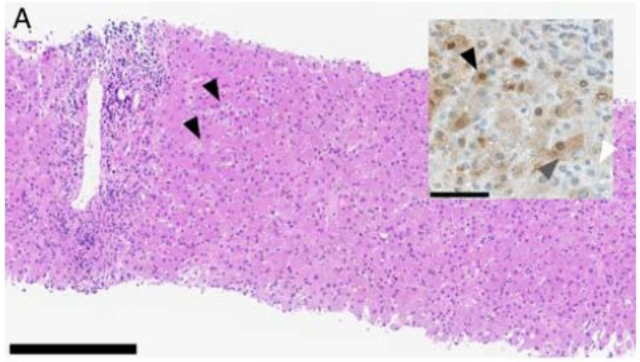


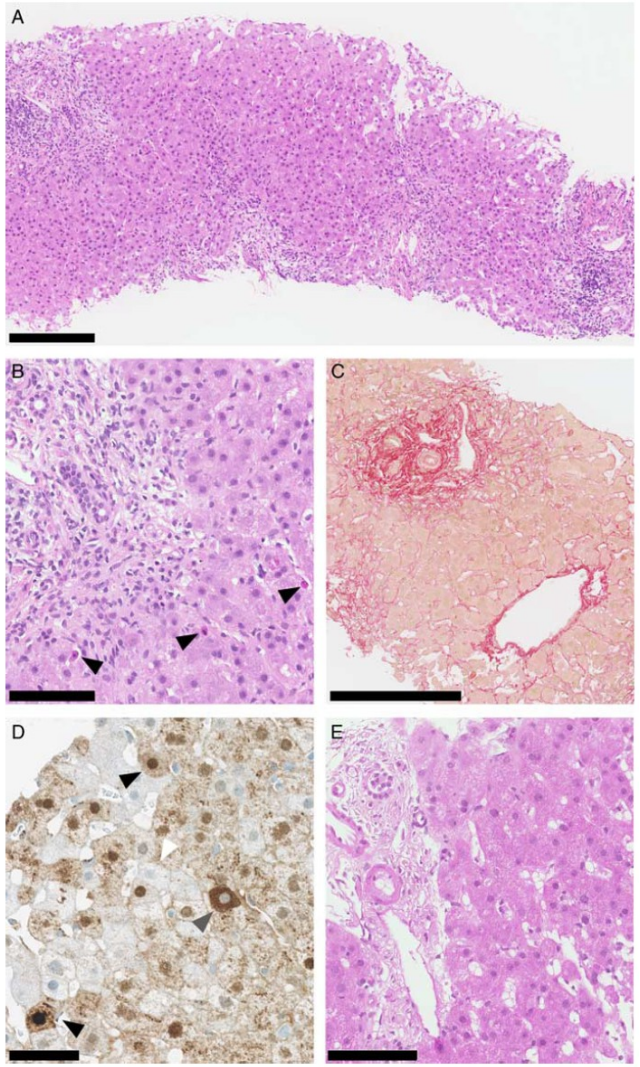
Anti-HEV IgG and IgM may be undetectable in immunocompromised patients

EASL recommends HEV testing in all immunosuppressed patients with unexplained abnormal LFTs (**A1**)



Acute self-limiting hepatitis E, occuring following a trip to India.

- Lobur disarray, portal and lobular inflammation and Kuppfer cell hyperplasia
- Immunohistochemestry for HEV ORF2 protein with both nuclear and cytoplasmic reactivity



Autochthonous hepatitis E (Gt 3) in patient with liver tranplant.

- Portal and lobular inflammation and some loular disarray
- predominantly portal inflammation and piecemeal necrosis with apoptotic hepatocytes
- Immunohistochemestry for HEV ORF2 protein with both nuclear and cytoplasmic reactivity

Hepatitis E histopathologic patterns significantly overlaps with that of hepatitis of other etiology (viral, autoimmune and drug induced): the histopathologic diagnosis being therefore challenging. IHC for ORF can be an useful additional tool

Lenggenhager D et al, Adv Ant Pathol 2018

Outcome of chronic hepatitis E infection

- Chronic HEV infection is usually asymptomatic and associated with mild to moderate elevation of transaminases (AST/ALT median value 155±25 U/L, 260±38 U/L) and GGT (308 ± 56 U/L). Neverthelss some patients may have normal or very slightly elevated transaminases.
- Progression of chronic hepatitis to cirrhosis had been reported in solid organ transplant recipients, even in short time frames (1-2 years).
- Available data did not show a correlation between HEV-RNA levels and progression of liver disease
- Tacrolimus treatment seems to be associated with a higher risk of chronicity after primary HEV infection
- Like in acute infection, extrahepatic manifestations (neurological and kidney injury, cryoglobulinemia, haematological disorders) can occur in chronically infected patients

EASL CPG HEV infection, 2018; Kamar et al Gastroenterology 2011; Gerolami R at al NEJM 2008

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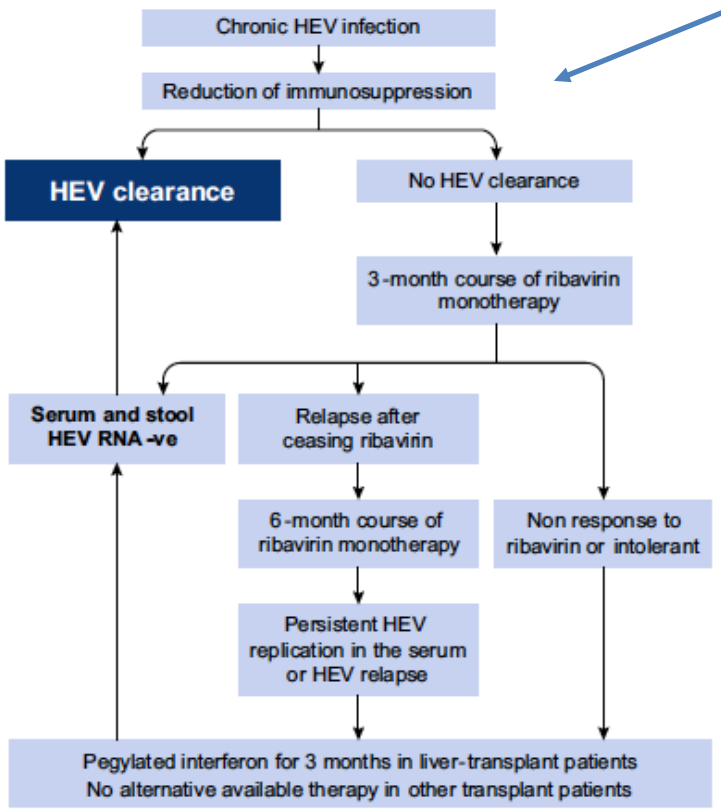
Management of chronic HEV infection



- The evidence that patients who spontaneously clear HEV have lower tacrolimus levels and lower steroids daily dose compared to those without clearance brought to the indication, as initial therapeutic option, to reduce immunosuppression, especially drugs targeting T-cells

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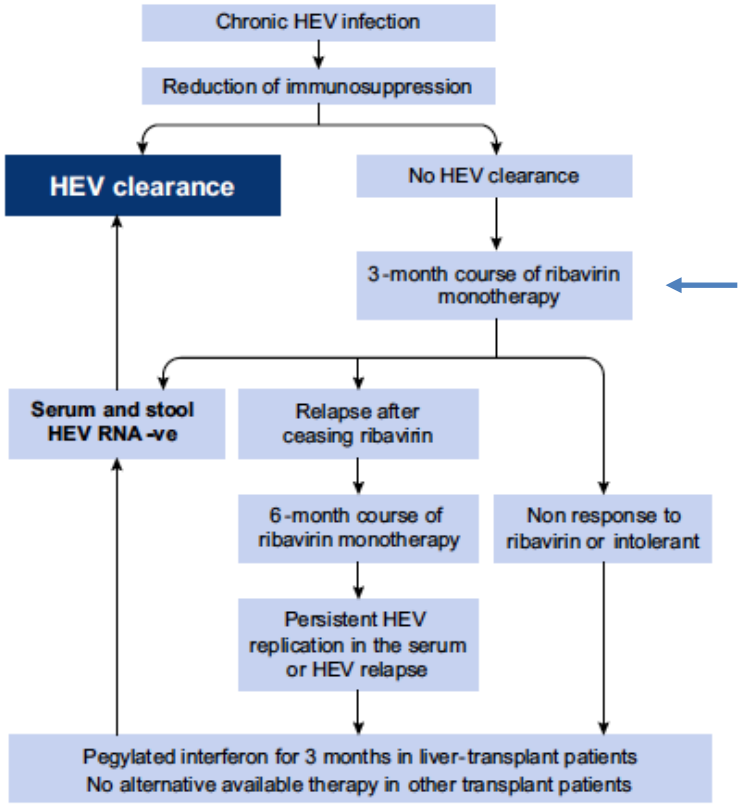
Management of chronic HEV infection



- No placebo controlled trials using RBV are available
- The recommendation to RBV use results from reports of many small series where high SVR (78%) were achieved with 3 month courses
- 0.5 log10 IU/ml HEV-RNA decline at day 7 could be a predictor of response
- At the end of treatment HEV-RNA pos. in the stools, even when HEV-RNA is undetectable in the serum could be associated with the risk of viremia relapse

RBV daily dose: 600-1000 mg

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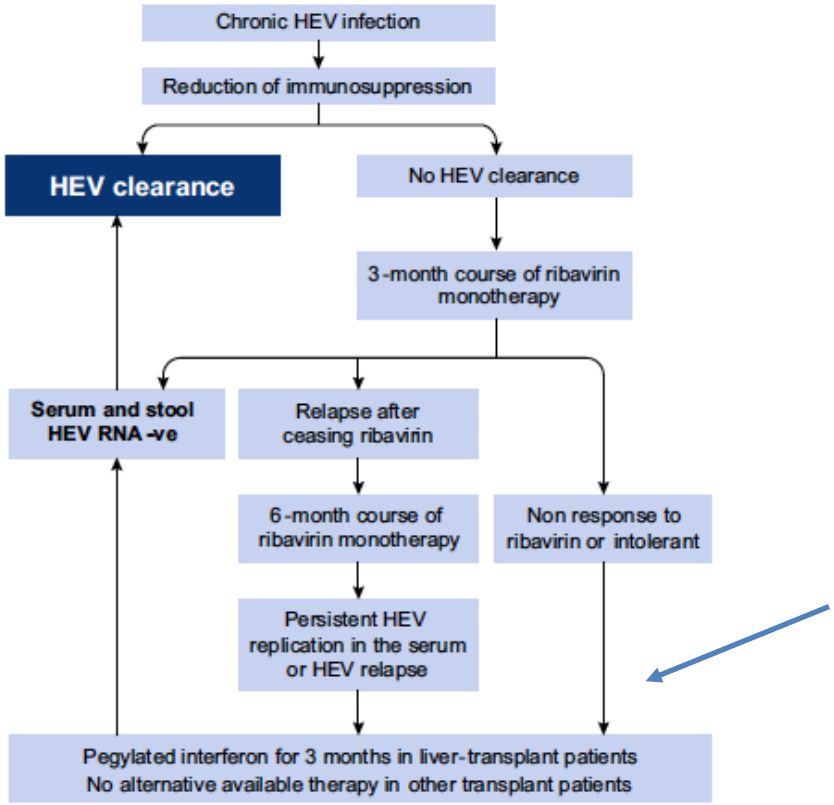
Management of chronic HEV infection

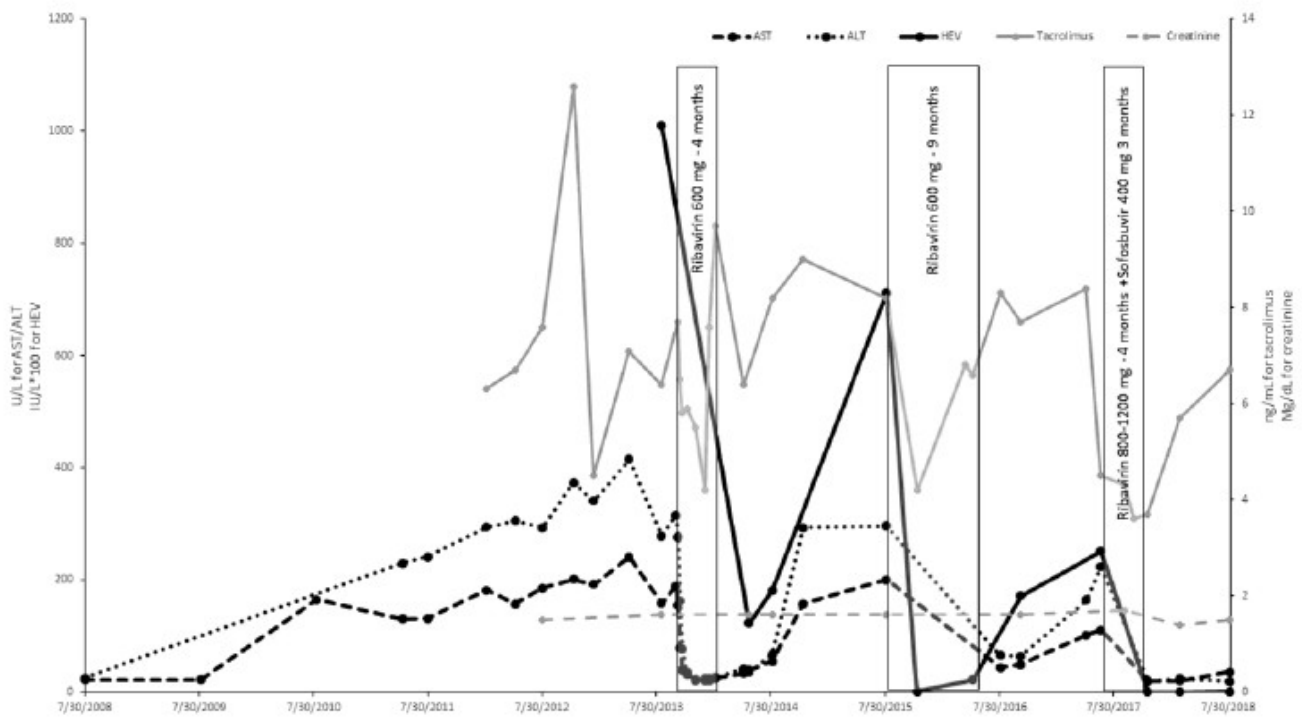


- Peg-IFN ± RBV has been used occasionally in patients with haematological disorders or HIV infected
- However Peg-IFN cannot be used in many immunosuppressed patients

Sofosbuvir and Ribavirin eradication of refractory hepatitis E in an immunosuppressed kidney transplant recipient

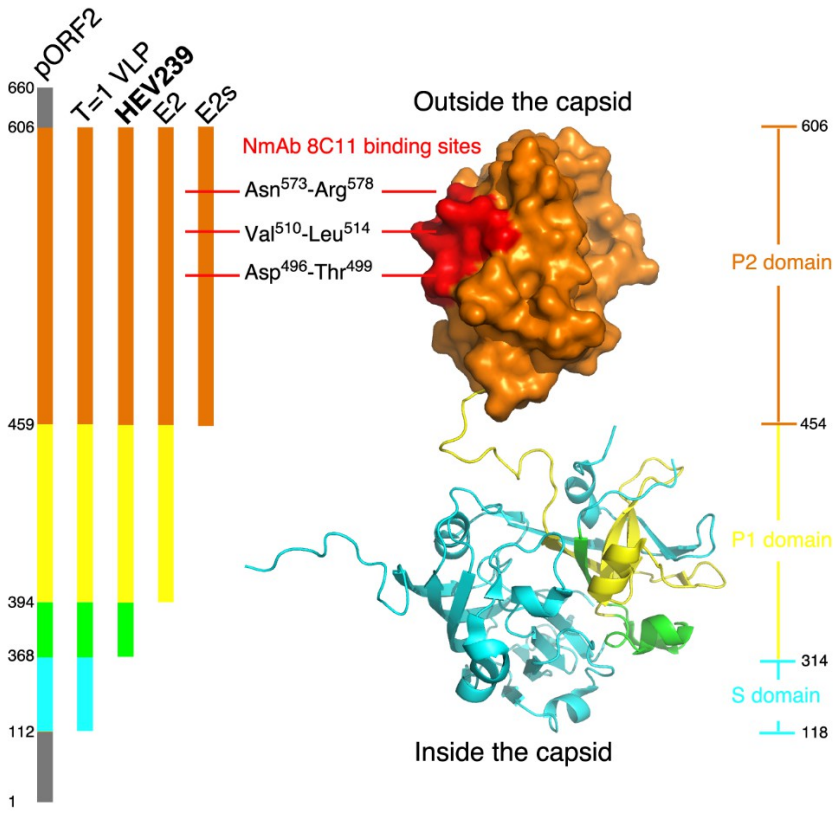
- Sofosbuvir (NS5B RNA-dependent RNA polymerase inhibitor) shows activity againsti GT 3 HEV in replicon and cell culture model, with an additive effect of RBV
- Sofosbuvir IC50 for HEV was 10 fold higher than for HCV

- SOF +RBV treatment was attempted in a 57 year old man with kidney/pancreas transplant, who failed 2 RBV courses



Drinane M et al, Hepatology 2018

Two recombinant vaccines, based on p56kDa (T=1 VLP) or HEV 239, had been tested in human trials.



The structure of p56kDa and HEV 239 are rendering in surface mode (P2 domain) and cartoon mode (P1 and S domain).

- Both vaccine antigens are Highly immunogenic VLPs
- After 14-years' development, HEV 239 is the only licensed HEV vaccine（China, 2012）

- One vaccine seems sufficient, because all 4 genotypes appear to represent a single serotype and have analogous overall structural features of the outer protrusions on the virion surface, and similar cross-neutralization epitope have been identified among them

Li et al., Human Vac 2015

Efficacy of p239 vaccine: A randomized controlled double-blinded clinical trial in China

Vaccine: Hecolin® (p239), 30 μg/dose

Control: HepB vaccine, 5 μg/dose

Schedule: 0m, 1m, 6m

Participants: 112,604 healthy adults, with a mean age of 44.1±11.4 years (range, 16 to 65), were enrolled. Of them, 47% have detectable preexisting anti-HEV.

- The vaccine efficacy against clinical HE was 100.0%(72.1-100.0) and 95.5% (66.3-99.4) in per-protocol and intention-to-treat analysis, respectively.
- Two doses vaccination is protective for at least 5 months, with the efficacy of 100.0%(9.1-100.0).
- Up to 4.5 years, the long-term efficacy against clinical HE was 93.3% (78.6-97.9) and 86.8% (71.0-94.0) in per-protocol and intention-to-treat analysis, respectively.
- the efficacy of the HEV vaccine against Gt 3 remains to be determined
- Vaccine efficacy did not appear to decrease over time.

Zhu et al., Lancet 2010; Zhang et al. N Engl J Med 2015

Target populations

- Hyper Endemic area (> 40% antibody positivity) to reduce disease burden in:
  - General population, childhood, pregnant women and elderlies
- Endemic area (with 30-40% antibody positivity) to lower risk of infection in:
  - Child bearing woman; pregnant woman, young children and elderly
- Low endemic area, (with 20% positive blood donor) to avoid complications in
  - High risk CLD population, transplant recipients, immune compromised patients, blood donors
- Special populations
  - food handlers, military and peace keepers, travelers, hunters,

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Current prevention of HEV infection

Immunocompromised individuals and those with Chronic Liver Disease should avoind consumption of undercooked meat (pork, wild boar and venison) and shellfish

EASL suggests that immunocompromised patients consume meat only if has been cooked to temperatures of at least 70 °C