

Viral hepatitis: Diagnostic conundrums

Valeria Ghisetti

Will Irving

Antenatal screening

- SZ Age 29. 1st pregnancy
 - 13th Oct 2009 Sample sent to Blood Transfusion Service found to be HBsAg +ve, HBeAg +ve
 - Result sent to GP, asking for confirmatory sample to be sent to Nottingham lab
 - 30th Oct GP sample received. HBsAg –ve, HBeAg -ve
 - Any ideas as to what is going on?

- Discussed with BTS - ?wrong results
- Discussed with GP - ?wrong patient
- Rubella sample from 13/10 had been sent to us

13/10/2009

	Nottingham	BTS
• HBsAg	POSITIVE	+ve
• Anti-HBc	Negative	-ve
• Anti-HBc IgM	Negative	-ve
• HBeAg	POSITIVE	+ve
• Anti-HBe	Negative	-ve
• Interpretation?		

- Both BTS and our lab agree sample from 13/10/2009 was HBsAg positive
- Lack of anti-HBc reactivity is unusual
- Sample from GP on 30/10/09 was HBsAg negative in our lab – further testing –
- Anti-HBc POSITIVE
- HBeAg Negative
- Anti-HBe POSITIVE
- i.e. resolved HBV infection
- But HBV DNA 26 IU/ml
- Interpretations?

3rd sample -10/11/2009

- 3rd sample
 - HBsAg Negative
 - Anti-HBc POSITIVE
 - HBeAg Negative
 - Anti-HBe POSITIVE
 - HBV DNA Negative
-
- Same results on 4th sample 11/12/2009

Results Summary

	13/10/09	30/10/09	10/11/09	11/12/09
HBsAg	POS	Neg	Neg	Neg
Anti-HBc (total)	Neg	POS	POS	POS
Anti-HBc IgM	Neg	POS	POS	POS
HBeAg	POS	Neg	Neg	-
Anti-HBe	Neg	POS	POS	-
HBV DNA	High ?vl	26 IU/ml	Neg	Neg
Anti-HBs (miu/ml)	-	0	22	156

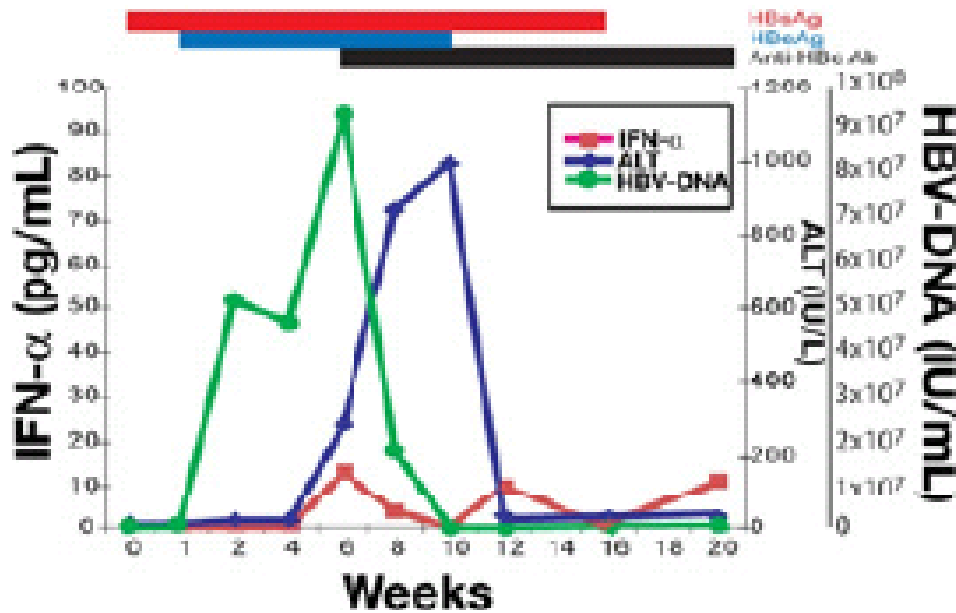
Interpretation

- Hyperacute infection with rapid clearance of viral antigens and appearance of antibodies
- Patient was completely asymptomatic
- Further management?

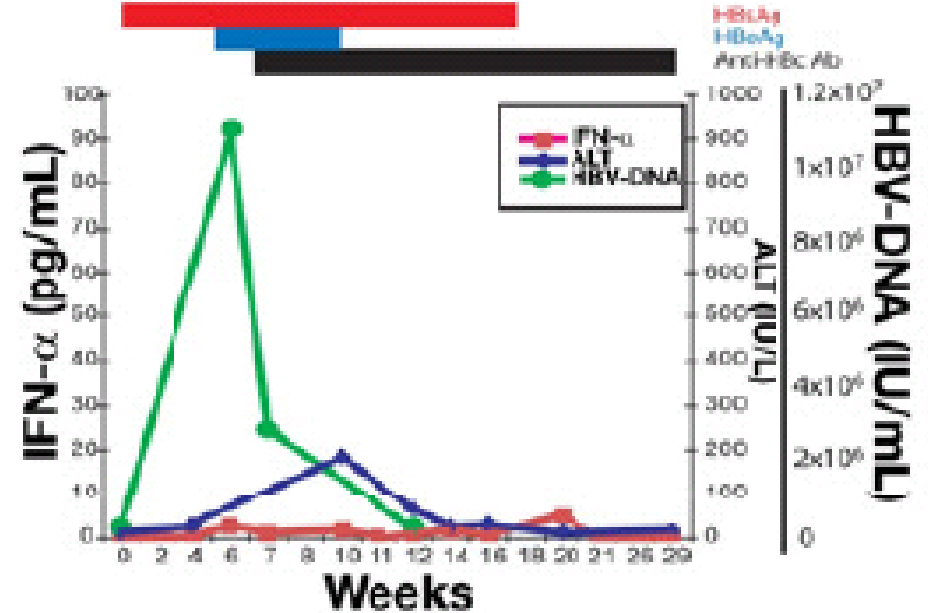
Further management

- Husband found to be HBsAg positive
- Baby offered vaccination at birth, 1, 2, and 12 months

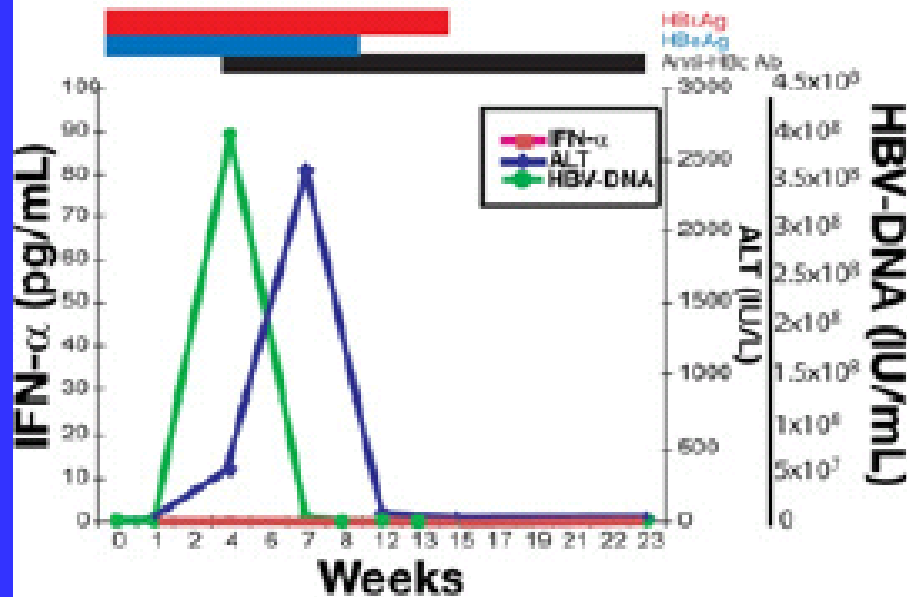
Patient 1



Patient 2



Patient 3



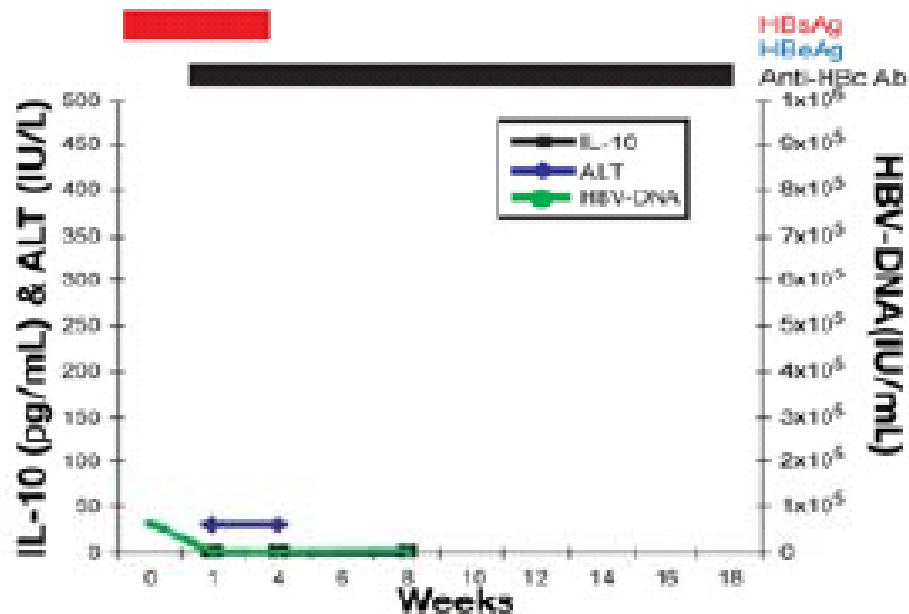
Dunn C et al

Temporal analysis of early immune responses in patients with acute hepatitis B virus infection

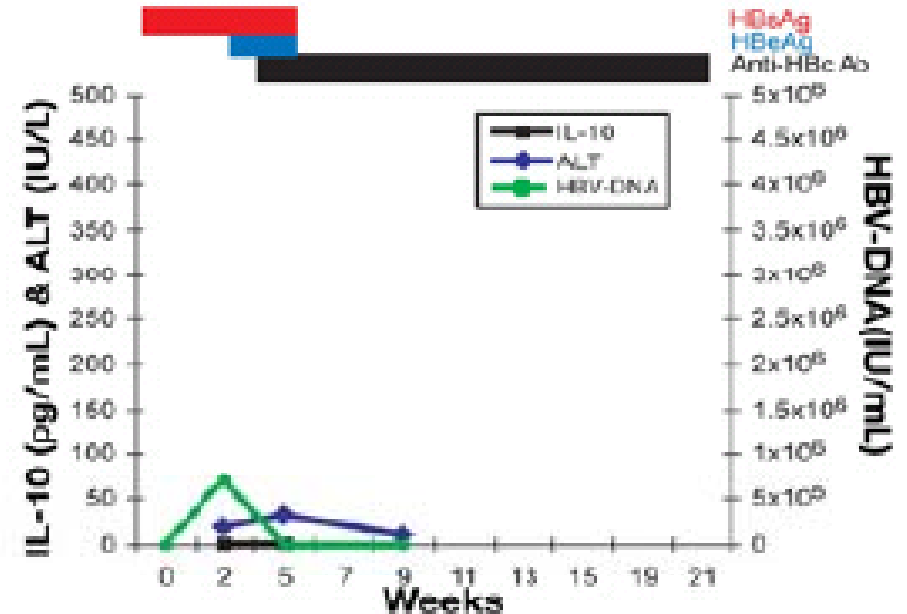
Gastroenterology 2009; 137: 1289

2 asymptomatic patients

Patient 20

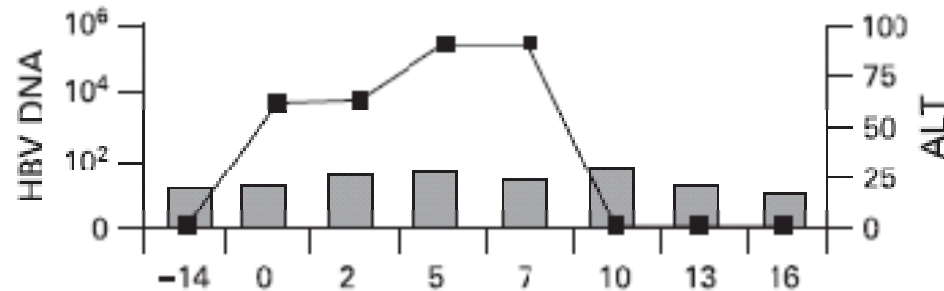


Patient 21

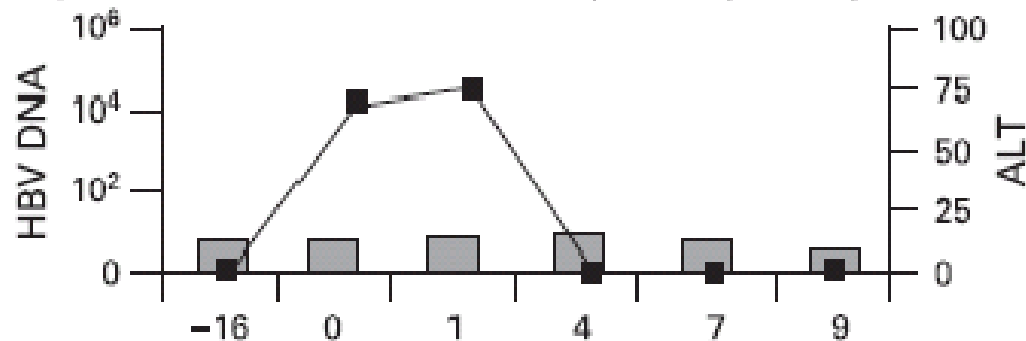


Dunn et al. Gastroenterology 2009

HBsAg	-	+	+	+	+	+	-	-
Anti-HBs U/I	-	-	-	0.1	0.1	0.4	10.6	25.3
Anti-HBc IgM	-	-	-	-	-	+	+	+
HBeAg	-	-	-	+	+	-	-	-
Anti-HBe	-	-	-	-	-	+	+	+



HBsAg	-	+	+	-	-	-
Anti-HBs U/I	-	-	1.3	5.5	181	405.4
Anti-HBc IgM	-	-	-	+	+	+
HBeAg	-	+	+	-	-	-
Anti-HBe	-	-	-	+	+	+



Fisicaro et al.

Early kinetics of innate and adaptive immune responses during hepatitis B virus infection.

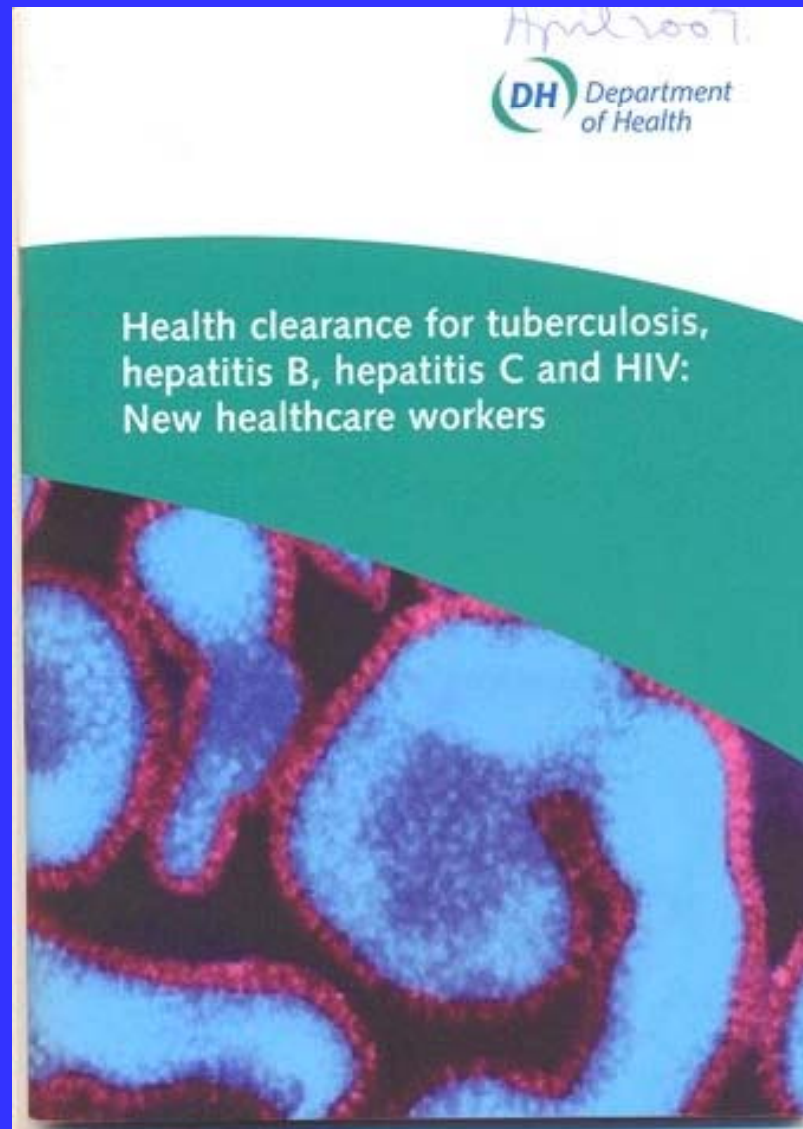
Gut 2009; 58: 974-982

2 asymptomatic blood donors found to seroconvert for HBsAg during 3 monthly routine screening

Case 2

- Mr CM, age 35.
- Egyptian
- Obstetrician, trained in Egypt
- Applied to hospital in UK for consultant post – was offered the post, subject to occupational health clearance
- Qu – what tests will OH wish to perform on this individual?

New entrants to the NHS: OH clearance



HEPATITIS SURGEON INFECTS PATIENTS

by JO REYLL
Health Correspondent

A SURGEON who contracted the hepatitis C virus while operating on a patient has infected two others.

Today, urgent checks are being made on nearly 2,000 other patients he has operated on in the past six years.

The doctor, who has not been identified, first only discovered he had the virus after two of his patients became infected. He may have been working for up to six years at three London hos-

Rush to find and check 2,000 he operated on

pitals with the virus, which causes inflammation of the liver.

In most cases, the infection is symptomless but in a third of patients it causes sickness and jaundice and can lead to chronic liver disease and, in rare cases, liver cancer.

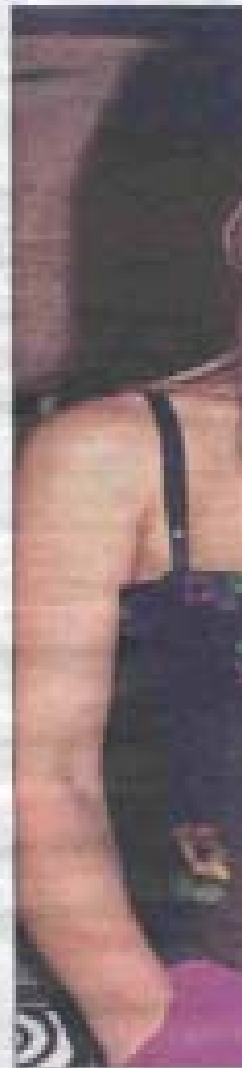
Patients who were operated on by the surgeon, between early 1994 and the

end of 1999 may have been exposed to the infection at the operating theatre, if the surgeon unwittingly nicked himself with a sharp instrument and his blood came into contact with theirs.

The chances of this happening are rare but today 1,800 patients are being contacted by health officials through their GPs and asked if they will have a blood test to see if they are carrying the virus.

From 1994 to 1999, the surgeon worked at the Central Middlesex Hospital in Park Royal and two private hospitals, the Clementine Churchill in Harrow and the Pyramus Clinic in

Continued on Page 2 Col 6



New cast as Julie

SHE PLAYED a final film for the advertising firm last night. She even performed in a song. It was a sophisticated night at West End. The star the third.

New entrants to the NHS: OH clearance

- “New” HCW coming to NHS who will perform Exposure Prone Procedures (EPPs) must be screened for evidence of HBV, HCV and HIV infection
- Therefore test for
 - anti-HIV
 - HBsAg
 - Anti-HCV

Exposure prone procedures

.... are those where there is a risk that injury to the worker may result in the exposure of the patient's open tissues to the blood of the worker”

These include procedures where “...the worker's gloved hands may be in contact with sharp instruments/tissues ...inside a patient's open body cavity, wound or confined anatomical space where the fingertips may not be visible.”

Case 2 – results for Mr CM

- Anti-HIV negative
- HBsAg negative
- Anti-HBs > 100 iu/l
- Anti-HCV positive

- What now?

Further results

- HCV RNA 1.4×10^4 iu/ml
 - Genotype 1
 - ALT in normal range on 3 occasions
-
- Would you let him operate?
 - Would you perform a liver biopsy?
 - Would you offer him treatment?

Answers

- Would you let him operate – NO
 - Viral loads associated with HCW-to-patient are not known
 - Therefore UK guidance – known HCV RNA positive HCWs are NOT allowed to perform EPPs irrespective of viral load
 - US proposal – only restrict if $>10^4$ GE/ml

Answers

- Would you perform a liver biopsy?
- Yes? Why?
- No? Why not?

Answers

- Would you offer him treatment? – YES

Technology Appraisal Guidance - No.14



*National Institute for
Clinical Excellence*

*Guidance on
the use of
Ribavirin and
Interferon Alpha
for Hepatitis C*

October 2000

Answers

- Would you offer him treatment? – YES
- He is started on PEG-IFN and RV
- When would you next test him for HCV RNA?

Mr CM - Progress

- At 4 weeks of therapy
 - HCV RNA negative by Roche Amplicor assay (lower limit of detection 50 iu/ml)
- Interpretation?
- Retest in QPCR assay
 - 40 iu/ml
- Interpretation?
- Next step?

Monitoring of therapy

- Rapid virological response (RVR) assessed at 4 weeks.
- Definition not clear, as different reports used different cut-offs.

What is an RVR?

- Mangia et al Hepatology 2008; 47: 43-50
 - Roche amplicor 50 iu/ml
- Liu et al Clin Inf Dis 2008; 47: 1260-9
 - Roche Taqman 25 iu/ml
- Yu et al Hepatology 2008; 47: 1884-93
 - Method not stated!
- Yu et al Gut 2007; 56: 553-9
 - Roche Amplicor 50 iu/ml
- von Wagner et al Gastroenterology 2005; 129: 522
 - Roche Monitor 600 iu/ml
- Berg et al Hepatology 2009; 50: 369-77
 - bDNA 615 iu/ml

RVR

- If RVR is achieved, on which patients does this allow shortening of therapy?
- Genotype 1 patients with low viral load (defined how?) – shorten from 12 to 6 months
- Genotype 2/3 patients with low viral load – (defined how?) shorten from 24 to 16 (or ?12) weeks

What is a low viral load?

- For PEG-2a = 800,000 iu/ml

Roche UK. Summary of Product Characteristics - Peginterferon alfa-2a (Pegasys).
Electronic Medicines Compendium 2009.

<http://emc.medicines.org.uk/medicine/10081/SPC/Pegasys+135mcg+and+180mcg+solution+for+injection+in+Pre-filled+Syringes/> (accessed 18 May 2009)

- For PEG-2b = 600,000 iu/ml

Schering-Plough. Summary of Product Characteristics - Peginterferon alfa-2b
(ViraferonPeg). Electronic Medicines Compendium 2009.

<http://emc.medicines.org.uk/medicine/10321/SPC/ViraferonPeg+Pen+50%2c+80%2c+100%2c+120+or+150+micrograms++powder+and+solvent+for+solution+for+injection+in+pre-filled+pen/> (accessed 18 May 2009)

Example of RVR guidelines

- Italian – AISF/SIMIT/SIMAST
- Digestive and Liver Diseases 2010;42:81
- Shorten therapy IF:
 - G-1 (to 24 weeks) or G-3 (to 12-16 weeks)
 - Baseline HCV RNA <600,000 iu/ml
 - RVR (not defined) after 4 weeks of Rx
 - Absence of severe liver disease
 - G-2 (to 12-16 weeks)
 - As above, but no viral load stipulation

Mr CM

- Pre-treatment G-1, viral load 1.4×10^4 iu/ml
- 4 weeks Rx – 45 iu/ml
- Should he have had a pretreatment liver biopsy?
- When would you next check his viral load?

- 12 weeks – HCV RNA negative (lower limit detection 30 iu/ml)
- By definition, has achieved an Early Virological Response (EVR)

EVR

- At 12 weeks, viral load is either
 - Not detectable = complete EVR
 - 2 log drop = partial EVR
- If EVR is NOT achieved – very little chance of SVR
 - i.e. EVR defines a STOPPING RULE
- If partial EVR, then re-test at 24 weeks, and stop Rx if HCV RNA is still detectable

EoT, SVR

- G-1 test at 48 weeks = End of treatment response - ?usefulness
- Outcome of therapy assessed at 6 months post Rx
- Sustained Virological Response = HCV RNA undetectable

Can SVR be assessed at 12 weeks post therapy?

- Martinot-Peignoux et al, Hepatology 2010; 51: 1122-1126
- 573 pts, all with EoT response
- 408 had SVR at 24 weeks post Rx
- At week 12 post Rx 409 were RNA negative, 408 went on to achieve SVR
- PPV at week 12 99.7%