

# Hepatitis Research Review

Making Education Easy

Issue 5 – 2009

## In this issue:

- *FT-AT for assessing histological changes in HBV infection*
- *IFN- $\alpha$ -related thyroid dysfunction*
- *Risk score for HCC in chronic HBV*
- *HBV relapse after discontinuing successful entecavir*
- *Preventing perinatal HBV transmission with lamivudine*
- *Prolonged peginterferon in advanced chronic HCV*
- *Tenofovir versus adefovir for chronic HBV*
- *Community-based HCV treatment compliance in drug users*
- *Acute HBV vs. acute flare of chronic HBV*
- *Different strategies for occupational HCV exposure*

## Welcome to the latest edition of Hepatitis Research Review.

We have compiled summaries with local commentary on what we think are ten of the most significant recent studies in hepatology. In this month's edition, a model for predicting patients with HBV infection who are at risk of developing hepatocellular carcinoma is presented. We also see that it is necessary to continue antiviral therapy to prevent relapse in patients with HBV infection who have responded to initial antiviral therapy. Finally, the findings of an analysis of strategies for detecting HCV infection following occupational exposure suggest that the use of PCR one month after the potential contamination event is an effective, cost-effective approach that should probably be more extensively utilised.

We hope you enjoy this month's selection, and we welcome your feedback.

Kind regards,

**Associate Professor Ed Gane**

Hepatologist, Auckland DHB

[edgane@researchreview.co.nz](mailto:edgane@researchreview.co.nz)

## Impact of adefovir dipivoxil on liver fibrosis and activity assessed with biochemical markers (FibroTest–ActiTest) in patients infected by hepatitis B virus

**Authors:** Poynard T et al

**Summary:** The utility of FibroTest–ActiTest (FT–AT) for assessing histological changes in chronic hepatitis B was investigated by analysing paired liver biopsies and FT–AT findings from patients with chronic hepatitis B who were randomised to receive adefovir or placebo for 48 weeks. FT–AT area under the receiver operating characteristics curves for diagnoses of bridging fibrosis, cirrhosis and moderate or severe necroinflammatory activity were 0.76, 0.81 and 0.80, respectively. The effects of adefovir on liver fibrosis and activity were similar with both paired biopsy findings (fibrosis stage decreased from 1.6 to 1.4 and activity grade decreased from 2.5 to 1.3) and paired biomarker findings (FT decreased from 0.44 to 0.40 and AT decreased from 0.62 to 0.25).

**Comment:** This is an interesting paper in that it uses a commercial serum marker for fibrosis as a noninvasive means to demonstrate fibrosis regression during long-term adefovir therapy. The FibroTest is excellent for discriminating cirrhosis from no cirrhosis and fibrosis from no fibrosis. It is not particularly accurate however, for distinguishing moderate from mild fibrosis (F2, F3). The new FT–AT has been devised to measure necroinflammation, but this new test has yet to be validated. However, the results from this study are impressive.

One potential advantage of this noninvasive serum marker over Fibroscan™ is that the latter is not accurate in patients with HBV flares (due to interference with direct measurement of liver stiffness because of increased oedema in this condition).

**Reference:** *J Viral Hepat* 2009; 16(3): 203–13

<http://www3.interscience.wiley.com/journal/121477391/abstract>

# COMING SOON to South Africa

## SUBSCRIBE NOW TO RECEIVE YOUR COPY

This publication is a sample copy from New Zealand. The opinions expressed are specific to the New Zealand health environment. South African versions will be available soon.

## Evolution and predictive factors of thyroid disorder due to interferon alpha in the treatment of hepatitis C

**Authors:** Gelu-Simeon M et al

**Summary:** The incidence of thyroid disorders in 301 patients treated with interferon (IFN)- $\alpha$  for chronic hepatitis C infection was 10% in this study (hyperthyroidism 43%, hypothyroidism 37% and biphasic evolution 20%), with a mean delay of 6 months. Thyroid dysfunction occurred more often in women and patients with thyroid peroxidase and thyroglobulin antibodies prior to antiviral therapy. A multivariate analysis revealed that low fibrosis was a significant predictor of thyroid dysfunction.

**Comment:** Thyroid dysfunction is a relatively common complication of antiviral therapy, reported here in 10% overall and in almost 20% of women. If unrecognised, both hyper- and hypothyroidism may significantly impact quality of life and patient tolerability, and hence adherence to pegylated IFN plus ribavirin. The pathogenesis of this disorder in patients with chronic HCV is not fully understood. Certainly women with pre-existing thyroid antiperoxidase antibodies (TPO) are at very high risk of future thyroiditis and subsequent hypothyroidism. This disorder is usually autoimmune, and therefore the presumption is that IFN expedites the onset rather than is a direct cause of thyroiditis.

The authors emphasise that the onset of thyroid dysfunction should NOT lead to reduction or withdrawal of Peg-IFN or ribavirin but should lead to appropriate treatment of the thyroid dysfunction. The important unresolved issues are (i) when should treatment of hyperthyroidism be considered necessary (as most patients rapidly become hypothyroid) and (ii) when, if ever, can thyroid replacement be withdrawn post-IFN. The data would suggest that patients without autoantibodies were more likely to successfully withdraw from replacement thyroxine.

**Reference:** *World J Gastroenterol* 2009; 15(3): 328-33

<http://www.wjgnet.com/1007-9327/15/328.asp>

## Independent risk factors and predictive score for the development of hepatocellular carcinoma in chronic hepatitis B

**Authors:** Yuen M-F et al

**Summary:** Data from 820 patients with chronic HBV infection followed for a mean of 76.8 months showed 5- and 10-year hepatocellular carcinoma (HCC) occurrence rates of 4.4% and 6.3% respectively. Independent risk factors for the development of HCC included: 1) increasing age (RR 1.07;  $p < 0.001$ ); 2) male gender (2.98;  $p = 0.025$ ); 3) higher HBV DNA levels (1.28;  $p = 0.02$ ); 4) core promoter mutations (3.66;  $p = 0.007$ ); and 5) presence of cirrhosis (7.31;  $p < 0.001$ ). A risk score based on these risk factors was derived with sensitivity and specificity of 84% and 76%, respectively, to assist in identifying patients at high risk of developing HCC.

**Comment:** A prognostic model that uses baseline factors to accurately predict long-term risk for HCC in patients with chronic HBV infection would be extremely useful in determining what level of HCC surveillance is required. This current study is relatively small, and therefore the findings should be interpreted with caution. Much larger studies have shown a clear association between HBV genotype C and risk for developing HCC independent of severity of liver disease (Yang Hl et al. *J Hepatol* 2006; 44 (Suppl 2): S13 (abstract #27); Chan HL et al. *Gut* 2004; 53(10): 1494-8).

It would be interesting to add to this analysis, the impact of a family history of HCC, which reflects the genetic factors involved in hepatocarcinogenesis.

Recent reanalysis of the REVEAL study suggested that the risk of HCC was increased in any HBsAg+ individual with HBV DNA level  $> 3$  logs. It would be interesting to see whether this same observation was found in this study.

**Reference:** *J Hepatol* 2009; 50(1): 80-8

[http://www.jhep-elsevier.com/article/S0168-8278\(08\)00565-5/abstract](http://www.jhep-elsevier.com/article/S0168-8278(08)00565-5/abstract)

## Relapse of hepatitis B in HBeAg-negative chronic hepatitis B patients who discontinued successful entecavir treatment

**Authors:** Shouval D et al

**Summary:** Follow-up (24 weeks) off-treatment durability data, following response to 48 weeks of treatment with entecavir ( $n = 257$ ) or lamivudine (201) in patients with chronic hepatitis B (CHB), showed that HBV-DNA levels were sustained at  $< 300$  copies/mL in 3% and 5% of patients, respectively. In contrast, among those who continued treatment with entecavir ( $n = 26$ ) or lamivudine (28), HBV-DNA levels  $< 300$  copies/mL were maintained in 85% and 57% of patients, respectively.

**Comment:** The 5-year data from the entecavir registration studies are now available. Firstly, they demonstrate excellent maintained viral suppression after 5 years continuous therapy with negligible resistance ( $< 1\%$ ). This current study reports that withdrawal of entecavir in HBeAg-negative CHB is associated with a high virological relapse rate (97%). Hence, the basic principle remains: nucleoside analogue therapy in HBeAg-negative CHB should be considered life-long. Therefore, before any nucleoside analogue therapy is started in HBeAg-negative patients, it is important to determine the need for treatment. Factors to be considered include: severity of fibrosis, history of severe flares and family history of hepatoma.

**Reference:** *J Hepatol* 2009; 50(2): 289-95

[http://www.jhep-elsevier.com/article/S0168-8278\(08\)00715-0/abstract](http://www.jhep-elsevier.com/article/S0168-8278(08)00715-0/abstract)

## Lamivudine in late pregnancy to prevent perinatal transmission of hepatitis B virus infection

**Authors:** Xu W-M et al

**Summary:** This study showed that among 56 infants born to mothers with high hepatitis B viraemia (recruited at 26-30 weeks' gestation and followed until 52 weeks) who had been randomised to receive lamivudine, the incidence of HBsAg seropositivity was 18%, compared with 39% among 59 infants from mothers randomised to receive placebo ( $p = 0.014$ ), and HBV DNA was detectable in 20% and 46% of the infants, respectively ( $p = 0.003$ ); the infants had received immunoprophylaxis at birth with recombinant HBV vaccine and HBIg. Sensitivity analyses accounting for the high dropout rate yielded similar, but statistically nonsignificant, findings. No safety concerns arose in the women who received lamivudine or their infants.

**Comment:** This study addresses the important issue of vertical transmission in mothers with high viraemia ( $> 10^9$  cpm). Despite the administration of accepted 'best practice' prophylaxis with combination neonatal vaccination plus HBIg, almost 40% of infants were infected. Almost certainly, these were in mothers with the highest viral load. Reduction of this viral load prior to delivery should reduce this risk. This of course is the argument for HAART in pregnant mothers with HIV infection. Use during pregnancy appears to be safe from data obtained from thousands of mothers who have received lamivudine for HIV infection - FDA Pregnancy Category B. Despite this, the introduction of new medications during the first trimester is not encouraged. In this study, lamivudine was started in the third trimester, thereby giving 3 months of treatment, which would allow maximal suppression with this drug.

One particular concern was that cessation of lamivudine in the postpartum period would result in severe hepatitis flares secondary to both virological rebound following lamivudine withdrawal and due to immunological reconstitution, which occurs postpartum. However, this was not seen. In many regions of the world where HBV is endemic, HBIg is not available or too expensive. Lamivudine in the third trimester appears to be a safe and effective alternative to preventing vertical transmission of HBV to infants from HBeAg+ mothers.

**Reference:** *J Viral Hepat* 2009; 16(2): 94-103

<http://www3.interscience.wiley.com/journal/121432388/abstract>

**OUT NOW**  
**Travel Medicine**  
**RESEARCH REVIEW**

by Dr Joan Ingram

Go to [www.researchreview.co.za](http://www.researchreview.co.za) to update your subscriptions

*Independent commentary by Associate  
Professor Ed Gane, Hepatologist, NZ Liver  
Transplant Unit, Auckland DHB*

## Prolonged therapy of advanced chronic hepatitis C with low-dose peginterferon

**Authors:** Di Bisceglie AM et al

**Summary:** The effect of long-term antiviral therapy on liver disease progression in patients with chronic HCV infection who had not responded to antiviral therapy was investigated in this study. Participants randomised to receive peginterferon- $\alpha$ -2a 90  $\mu$ g/week for 3.5 years (n=517) had significant decreases in serum HCV RNA levels and histological necroinflammatory markers, but the rate of any primary outcome (death, hepatocellular carcinoma, hepatic decompensation or, for those with baseline bridging fibrosis, increase in Ishak score of  $\geq 2$  points) was not significantly different to that among patients who received no treatment (n=533; 34.1% vs. 33.8%).

**Comment:** In patients with established HBV-cirrhosis, long-term viral suppression with maintenance nucleos(t)ide analogue therapy has been demonstrated to prevent the complications of liver failure and hepatoma. The North American, multicentre, HALT-C study finally addresses the question as to whether these complications are prevented in the analogous situation of HCV-cirrhosis through maintenance pegylated interferon. Surprisingly, none of the recorded complications (hepatoma, variceal haemorrhage, ascites, encephalopathy) were reduced compared to the untreated group and overall survival was the same.

This large, well-designed study has therefore put to bed, once and for all, the myth that nonresponders to standard-of-care pegylated interferon plus ribavirin should be considered for long-term maintenance interferon therapy.

**Reference:** *N Engl J Med* 2008; 359(23): 2429-41  
<http://tinyurl.com/NEJM-359-2429>

## Tenofovir disoproxil fumarate versus adefovir dipivoxil for chronic hepatitis B

**Authors:** Marcellin P et al

**Summary:** Patients with HBeAg-positive or negative chronic HBV infection randomised to receive tenofovir disoproxil fumarate (oral prodrug of tenofovir) 300 mg/day for 48 weeks were significantly more likely to achieve a plasma HBV DNA level of  $< 400$  copies/mL and histological improvement (primary endpoint) than patients randomised to receive adefovir dipivoxil (oral prodrug of adefovir) 10 mg/day in this study. In addition, participants treated with tenofovir experienced significantly superior findings for viral suppression, ALT level normalisation and hepatitis B surface antigen loss. No HBV DNA polymerase amino acid substitutions associated with resistance to agents used in the treatment of HBV infection, including tenofovir, were identified in any of the patients. Safety profiles associated with the two treatments were similar.

**Comment:** The results from this registration study for tenofovir are long awaited. Data of the safety and efficacy of tenofovir in patients with HBV and HIV co-infection have supported its use in HBV mono-infection for many years.

This study demonstrates that tenofovir is potent ( $> 6$  log reduction in HBV DNA at 48 weeks) and has a very high genetic barrier (no detectable resistance at 48 weeks). Although HBeAg seroconversion rates are not significantly greater than that achieved with other nucleoside analogues, the HBsAg clearance rate is the highest yet reported. The 2-year data (presented last year at AASLD but not yet published) confirm these findings.

Tenofovir has an excellent preclinical safety profile and this agent has been associated with an excellent long-term safety profile in patients with HIV infection. It is the only drug with FDA pregnancy B category and is the ideal choice for patients of child-bearing potential. There is no doubt that tenofovir will be an important addition to the antiviral therapies used in treatment-naïve chronic hepatitis B (CHB). In addition, tenofovir as a nucleotide analogue is very effective against lamivudine-resistant CHB. In New Zealand almost 2000 people are taking lamivudine, and 350 already have established lamivudine resistance. Tenofovir may be the first drug to be used as first-line therapy against both treatment-naïve and lamivudine-resistant CHB.

**Reference:** *N Engl J Med* 2008; 359(23): 2442-55  
<http://content.nejm.org/cgi/content/abstract/359/23/2442>

# COMING SOON to South Africa

## SUBSCRIBE NOW TO RECEIVE YOUR COPY

This publication is a sample copy from New Zealand. The opinions expressed are specific to the New Zealand health environment. South African versions will be available soon.

## Community-based treatment for chronic hepatitis C in drug users: high rates of compliance with therapy despite ongoing drug use

**Authors:** Wilkinson M et al

**Summary:** This paper reported a compliance rate of >80% in 58 drug users with chronic HCV infection who completed an optional community-based treatment programme offering antiviral therapy (60 treatment episodes). Participants who were homeless, were active illicit drug users or had received pretreatment antidepressant therapy were not less likely to comply with treatment. A sustained virological response was seen in 25 of 49 treatment episodes assessed 6 months post-treatment.

**Comment:** The question is: because we can do it, should we?

Although treatment of acute icteric hepatitis C in the active injecting population seems justified because of the very high chance of cure with 3 months interferon monotherapy (the simpler the regimen the more likely an active injector will complete it), the question remains whether treatment of the active injector with established chronic infection is cost-effective and in the best interests of the patient. Interferon is likely to interfere with attempts of rehabilitation in the active injector. Multiple studies have demonstrated that the mortality from continued drug use far exceeds any mortality associated with chronic HCV infection and it would therefore seem logical to direct interventions towards drug rehabilitation, and to defer antiviral therapy until the person's chaotic lifestyle has abated, support is available and chances of adherence to a full 48 weeks of therapy enhanced.

**Reference:** *Aliment Pharmacol Ther* 2009; 29 (1): 29-37

<http://tinyurl.com/APT-29-29>

**Privacy Policy:** Research Review will record your email details on a secure database and will not release it to anyone without your prior approval. Research Review and you have the right to inspect, update or delete your details at any time.

**Disclaimer:** This publication is not intended as a replacement for regular medical education but to assist in the process. The reviews are a summarised interpretation of the published study and reflect the opinion of the writer rather than those of the research group or scientific journal. It is suggested readers review the full trial data before forming a final conclusion on its merits.

## Clinical, biochemical, immunological and virological profiles of, and differential diagnosis between, patients with acute hepatitis B and chronic hepatitis B with acute flare

**Authors:** Han Y et al

**Summary:** This study investigated laboratory differences between patients with acute HBV and those with an acute flare of chronic HBV to provide a means for differentiating between these two distinct patient groups. The main conclusions were: 1) significant differences exist between acute self-limited HBV and acute flares of HBV in clinical biochemical, immunological and virological features; 2) IgM anti-HBc jointing HBV-DNA is the most effective and practicable diagnostic combination for differentiating between the two types of HBV infection; 3) a low HBeAg level is more useful than HBeAg negativity for differentiating between the two types of HBV infection; 4) acute self-limited HBV infection can probably be excluded by a serum alpha-fetoprotein level >10-fold greater than the upper reference limit in patients with a high IgM anti-HBc level.

**Comment:** This study is of relevance to NZ. Almost 2/3 of all cases of acute liver failure referred to NZLTU (total of 10–12 per annum) are HBV related. Approximately half are acute flares in patients with chronic HBV infections (usually Asian, Pacific Islander or Maori) who were infected in early childhood from vertical or early horizontal transmission, whilst the remainder represent true acute infections, usually in Caucasians via sexual transmission from a partner with chronic HBV infection. The clinical presentation is identical with jaundice, coagulopathy, encephalopathy and subsequent renal failure and sepsis. The underlying precipitant in acute-on-chronic HBV is presumed to represent either HBeAg seroconversion or HBeAg-negative flares.

This study has identified a means to distinguish the two causes of acute liver failure from HBV (although in NZ this seems unnecessary as the cause can usually be deduced from ethnicity). Unfortunately, quantitative anti-Hb core is not readily available here in NZ. The question remains whether these two different types of acute liver failure from HBV differ in outcome and in treatment. To date, no study has shown that antiviral therapy will prevent death/transplant in acute liver failure from HBV, whether acute-on-chronic or true acute infection.

**Reference:** *J Gastroenterol Hepatol* 2008; 23(11): 1728-33

<http://www3.interscience.wiley.com/journal/121419713/abstract>

## Costs and cost-effectiveness of different follow-up schedules for detection of occupational hepatitis C virus infection

**Authors:** Deuffic-Burban S et al

**Summary:** Costs and cost-effectiveness for the French, other European and baseline US strategies for healthcare workers following occupational exposure to HCV were compared with an alternate US strategy involving early HCV RNA testing. Costs per person were lowest for the alternate US strategy, which was also found to be 'reasonably' cost effective. The alternate US strategy was also found to shorten the length of the wait before HCV status was known, and was associated with a lower risk of chronic hepatitis C.

**Comment:** This decision-tree analysis compares different strategies for the detection of HCV infection following occupational exposure in healthcare workers. Most current occupational health protocols rely on antibody seroconversion at 6 months. However, recent data support earlier diagnosis in order to facilitate early treatment in those who do not clear HCV spontaneously. This is the rationale behind the proposed American approach – PCR at one month after needle-stick injury. PCR is considerably more costly than antibody testing, but is both more sensitive and more specific for active infection. By providing earlier confirmation, it will increase the chance of early treatment and cure in the 0.5% who develop infection. This analysis shows that this approach is very cost-effective at only €2000 per QALY (European threshold approximately €30,000 per QALY), but more importantly, it will provide reassurance in the 99.5% who do not develop infection. This important fact should be added to the cost-effectiveness argument and should lead to adoption of this more appropriate protocol by occupational health departments in all hospitals.

**Reference:** *Gut* 2009; 58(1): 105-10

<http://gut.bmj.com/cgi/content/full/58/1/105>

# COMING SOON to South Africa

## SUBSCRIBE NOW TO RECEIVE YOUR COPY

This publication is a sample copy from New Zealand. The opinions expressed are specific to the New Zealand health environment. South African versions will be available soon.