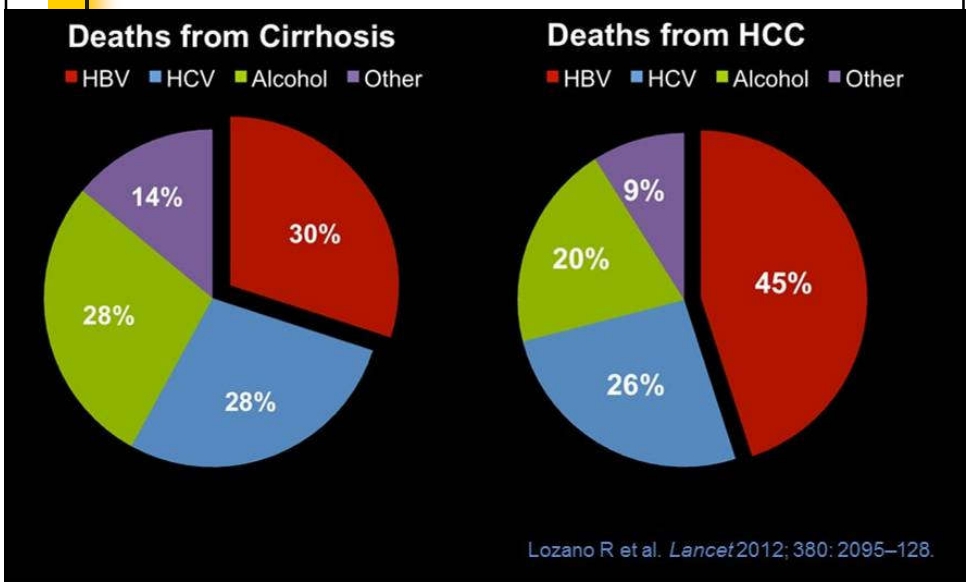
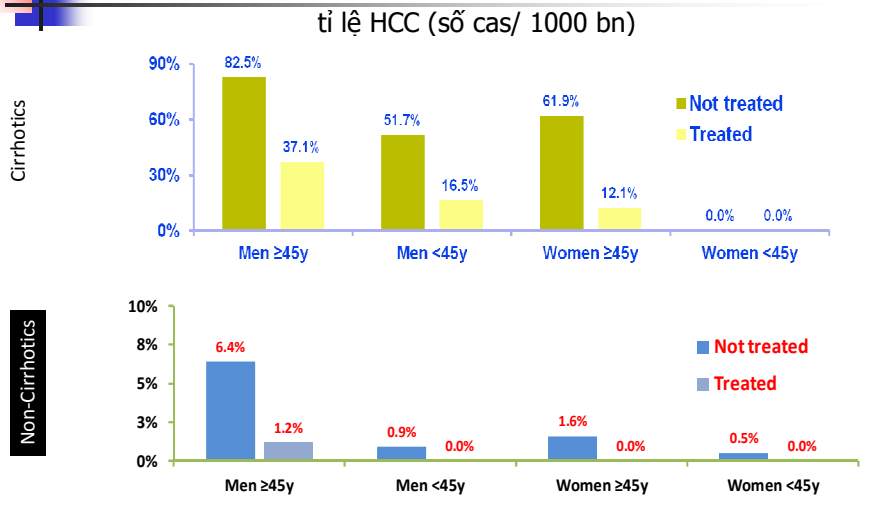
VAI TRÒ ĐỊNH LƯỢNG CÁC KHÁNG NGUYÊN HBV TRONG THỰC HÀNH LÂM SÀNG

TS. BS. Phạm Thị Thu Thủy
Trung tâm Y Khoa MEDIC

Ảnh hưởng HBV đối với xơ gan và ung thư gan

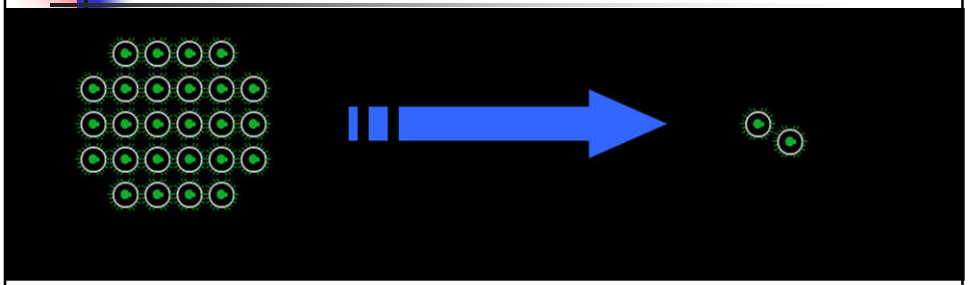


Tỉ lệ HCC trong quần thể bệnh nhân CHB tùy theo tuổi, phái tính, có xơ gan hay không? có điều trị hay không?



Lin D. et al, AASLD 2014

Mục tiêu điều trị viêm gan B mạn: Ức chế siêu vi lâu dài



1. Giảm viêm hoại tử, xơ hóa, xơ gan
2. Giảm xơ gan mất bù
3. Giảm tỉ lệ ung thư gan
4. Giảm tử vong

Viêm gan B cũng là bệnh lý được thăm khám phổ biến tại Medic

- Phòng khám gan đạt tỉ lệ bệnh nhân cao nhất trong các phòng khám chuyên khoa tại Medic
  - 12.000 – 13.000 lượt BN khám/chẩn đoán viêm gan/tháng (2015): viêm gan B chiếm 50%, viêm gan C chiếm 30%, bệnh gan khác (20%)
- Số lượng BN viêm gan B mạn hiện đang điều trị tại Medic
  - Chiếm 80% trường hợp nhiễm siêu vi B đến khám tại Medic
  - Tuổi: 20 – 60 tuổi
  - Giới: nam – nữ ngang nhau
  - Vùng địa lý: Đồng Bằng Sông Cửu Long (50%), Tp. HCM (30%), Miền Trung (20%)

Hướng dẫn điều trị theo AASLD 2015

Treatment of Persons With Immune-Active CHB

Recommendations

1A. The AASLD recommends antiviral therapy for adults with immune-active CHB (HBeAg negative or HBeAg positive) to decrease the risk of liver-related complications.

1B. The AASLD recommends Peg-IFN, entecavir, or tenofovir as preferred initial therapy for adults with immune-active CHB.

Technical Remarks

1. *Immune-active CHB is defined by an elevation of ALT >2 ULN or evidence of significant histological disease* plus *elevated HBV DNA above 2,000 IU/mL (HBeAg negative) or above 20,000 IU/mL (HBeAg positive).*
2. *The ULN for ALT in healthy adults is 30 U/L for males and 19 U/L for females.*
3. *There is insufficient evidence for or against use of ALT criterion other than ALT ≥2 ULN. The decision to treat persons with ALT above the ULNs, but <2 ULN, requires consideration of severity of liver disease (defined by biopsy or noninvasive testing). Therapy is recommended for persons with immune-active CHB and cirrhosis if HBV DNA >2,000 IU/mL, regardless of ALT level.*
4. *Additional factors included in the decision to treat persons with immune-active CHB but ALT <2 ULN and HBV DNA below thresholds are:*
   - *Age: Older age (>40 years) is associated with higher likelihood of significant histological disease.*
   - *Family history of HCC*
   - *Previous treatment history:*

Xét nghiệm theo dõi điều trị viêm gan B (Bộ Y Tế 2014)

BỘ Y TẾ

CỘNG HÒA XÃ HỘI CHỦ NGHĨA VIỆT NAM
Độc lập - Tự do - Hạnh phúc

Số: 5448/QĐ-BYT

Hà Nội, ngày 30 tháng 12 năm 2014

QUYẾT ĐỊNH

VỀ VIỆC BAN HÀNH HƯỚNG DẪN CHẨN ĐOÁN, ĐIỀU TRỊ BỆNH VIÊM GAN VI RÚT B

BỘ TRƯỞNG BỘ Y TẾ

3. Theo dõi điều trị:

- Tuân thủ điều trị: cần tư vấn cho bệnh nhân về lợi ích của việc tuân thủ điều trị và các biện pháp hỗ trợ tuân thủ điều trị (phương tiện nhắc uống thuốc).

- Tháng đầu tiên sau khi bắt đầu điều trị: theo dõi AST, ALT, creatinine máu.

- Sau mỗi 3-6 tháng trong quá trình điều trị: theo dõi AST, ALT, creatinine máu, HBeAg, Anti-HBe, HBV-DNA, có thể định lượng HBsAg.

- Nếu điều trị IFN hoặc Peg IFN: theo dõi công thức máu, glucose máu, ure máu, creatinin máu, chức năng tuyến giáp để phát hiện tác dụng không mong muốn của thuốc.

- Sau khi ngưng điều trị:

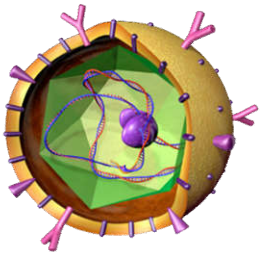
+ Theo dõi các triệu chứng lâm sàng.

+ Xét nghiệm sau mỗi 3 - 6 tháng: AST, ALT, HBsAg, HBeAg, anti-HBe, HBV DNA để đánh giá tái phát.

Xét nghiệm siêu vi B giữ vai trò then chốt trong chẩn đoán, điều trị và tiên lượng bệnh

Định tính

- HBsAg
- HBeAg
- Anti HBe
- Anti HBc total
- HBVDNA
- Genotype
- Đột biến kháng thuốc



Định lượng

- HBsAg
- Anti HBs
- HBeAg
- HBVDNA

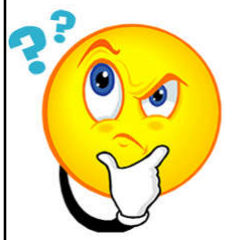
HBsAg

Định tính: Có bệnh hoặc không

Định lượng: Theo dõi điều trị bệnh

Tiên lượng điều trị bệnh

Tiên lượng bệnh



What we currently know about qHBsAg

Steady HBsAg decline /loss is favorable in any kind of treatment

HBsAg levels decline with Peg-IFNα-2a and TBV treatment

qHBsAg has a role in predicting HCC

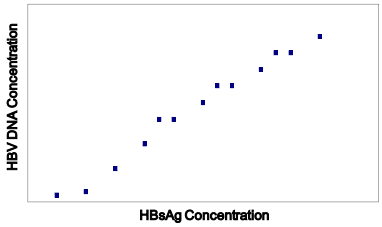
The applications of qHBsAg

- Monitoring monotherapy
- Modifying treatment strategies to improve outcomes
- Peg-IFN and NAs
  - Sequential
  - Adding
  - *De novo* combination
  - Alternating
  - Extending Peg-IFN duration
- NAs
  - Adding or switching when remain stable (step up)
  - Step down
  - Stopping treatment

q = quantified; HBsAg = hepatitis B surface antigen; HCC= hepatocellular carcinoma; Peg-IFN = pegylated interferon; TBV = telbivudine; NAs = nucleos(t)ide analogs.

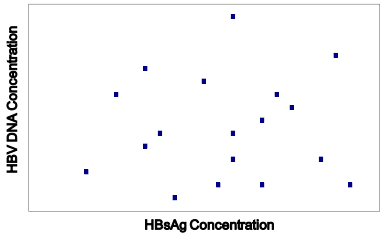
Relationship between HBV DNA and HBsAg concentrations according to Stage of Infection

Early Acute



Good correlation in the rump-up phase

Chronic

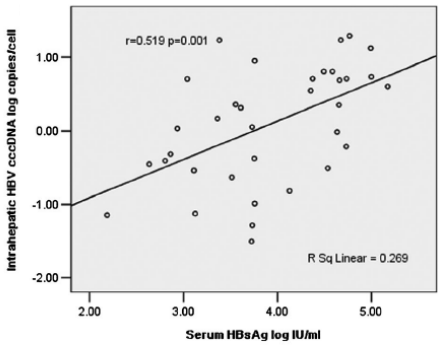


The concentration of serum HBsAg does not correlate with levels of serum HBV-DNA

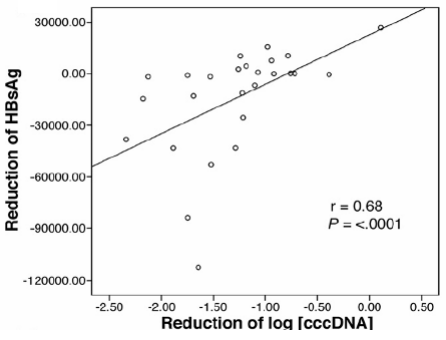
Kuhns and Busch, Mol Diag Ther 2006;10(2):77-91.

qHBsAg is a non-invasive surrogate marker for intrahepatic cccDNA

Significant correlation between HBsAg and cccDNA levels[1]



Significant correlation between reductions of HBsAg and of cccDNA levels[2]



qHBsAg levels provides a non-invasive method of assessing the severity of HBV infection (the number of infected hepatocytes)

cccDNA = covalently closed circular DNA

1. Wang M, *et al. J Med Virol* 2013;8:219-27;
2. Chan HL, *et al. Clin Gastroenterol Hepatol.* 2007;5:1462–8.

Nghiên cứu sử dụng Arc HBsAg định lượng

Author	Year	No. of patients	Treatment	HBeAg	Findings and potential role
Manesis et. Al	2007	63	IFN2b LMV	Neg	HBsAg may predict HBsAg seroconversion. HBsAg decline on-treatment is greater for IFN2b
Chan et al	2007	26	PegIFN 2b + LMV	Pos	HBsAg may predict sustained virologic response.
Takkenberg et al	2008	70	PegIFN 2a +ADV	Both	HBsAg titre predicts HBsAg clearance or seroconversion. HBsAg clearance is higher with combination PegIFN2a+ADV
Lu et al	2008	86	PegIFN 2a +/- LMV	Both	HBsAg is superior to cccDNA, serum HBVDNA in predicting sustained virologic response.
Lau et al	2008	539	PegIFN 2a PegIFN 2a + LMV	Pos	HBsAg decline on-treatment may predict HBeAg seroconversion at 1 year post treatment, as well as a durable off-treatment response.
Marcellin et al	2008	160	PegIFN 2a +/- LMV	Neg	HBsAg level <1500 IU/mL at week 12 is associated with HBsAg clearance at 4 years post treatment (PPV 35%). 97% do not clear HBsAg if HBsAg is >1500 IU/ml at week 12.
Rijckborst et al	2008	133	PegIFN 2a PegIFN 2a+Riba	Neg	HBsAg decline at week 12 may predict sustained virologic response (HBV DNA <10000 c/mL 24 weeks after treatment)
Brunetto et al	2008	80	PegIFN 2a +/- LMV	Neg	Extent of HBsAg decline on-treatment may be genotype dependent.
Moucari	**2009**	**48**	**PegIFN 2a**	**Neg**	**Early serum HBsAg drop is a strong predictor of SVR, better than HBV DNA**

Định lượng HBsAg giúp theo dõi & tiên lượng điều trị bệnh

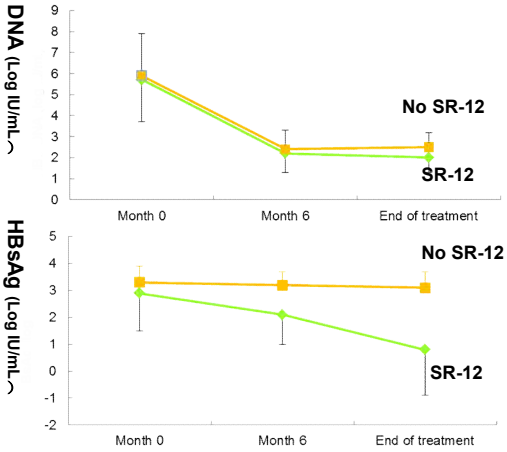
HBsAg (chứ không phải HBV DNA) có thể phân biệt những trường hợp có đáp ứng bền vững hoặc không đáp ứng trên BN dùng lamivudine

53 BN VGB mạn tính, HBeAg(-)

Dùng Lamivudine (LMV) 34±23 (12-76) tháng

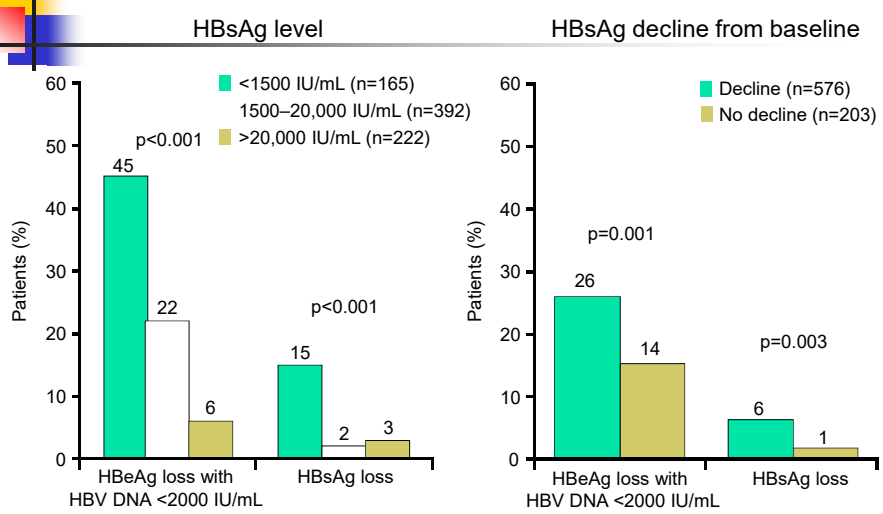
Ngưng LMV for 47±35 (11-116) tháng

Đáp ứng bền vững ở tháng thứ 12 (SR-12) = HBV DNA ≤ 200 IU/ml ở tháng thứ 12 sau khi ngưng LMV



Chan HL, et al. Antivir Ther 2011;16;1249-57

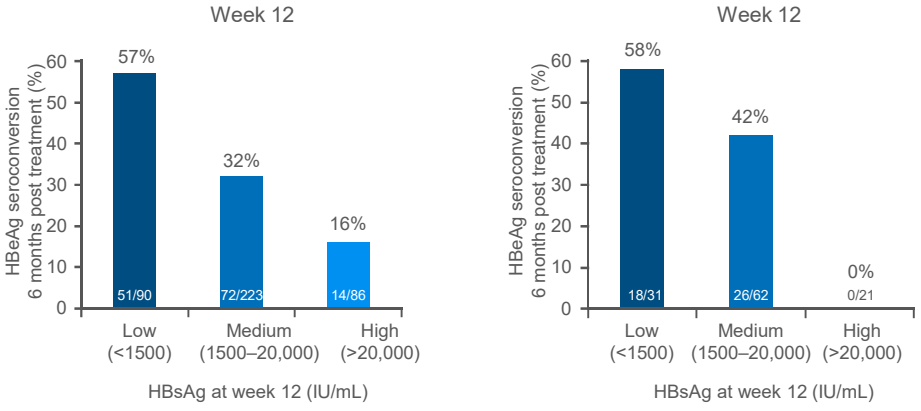
Week 12 HBsAg levels and declines predict response at 6 months post treatment in HBeAg-positive patients



Sonneveld MJ, et al. Hepatology 2013; doi: 10.1002/hep.26436

Low on-treatment HBsAg levels are associated with higher rates of response

HBeAg-positive patients treated with Peg-IFN alfa-2a ± lamivudine for 48 weeks



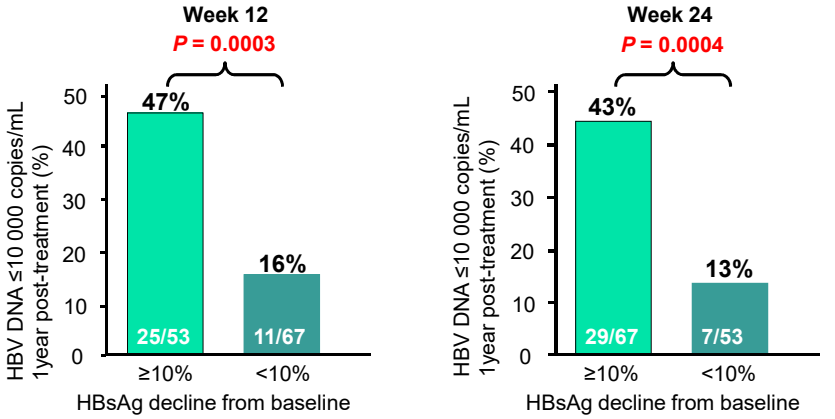
P<0.0001 for <1500 IU/mL vs higher levels

Phase III study
Piratvisuth et al. Hepatol Int. 2011: DOI 10.1007/s12072-011-9280-0

NEPTUNE
Liaw YF, et al. Hepatology 2011;54:1591–9

HBsAg decline is significantly associated with sustained immune control

230 patients with HBeAg–ve CHB treated with Peg-IFNα-2a (40 KD)± LAM*
No HBsAg decline is associated with a low chance of response

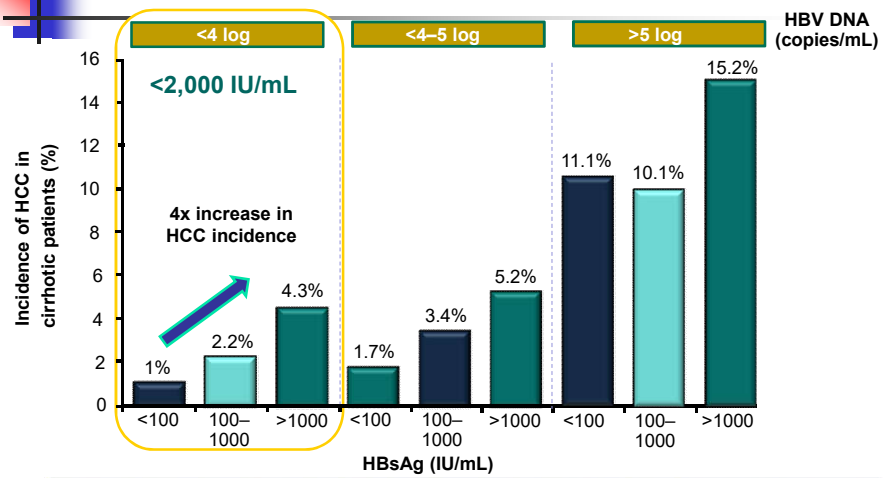


* Based on 120 patients with available HBsAg data at all time points

Marcellin P *et al, Hepatol Int* 2012

Định lượng HBsAg tiên lượng diễn tiến bệnh

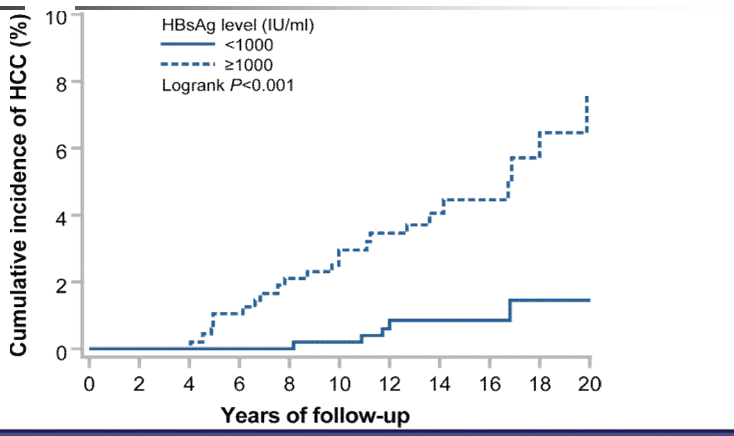
REVEAL-HBV: HBsAg independently predicts HCC risk when HBV DNA < 2,000 IU/mL



HBsAg is a recognized independent predictor of HCC in low viral loads

Chen CJ, *et al.* AASLD 2011 abstract 1095 (poster).

ERADICATE-B: HBsAg >1,000 IU/mL predicts HCC risk in HBeAg-ve CHB with HBV DNA < 2,000 IU/mL

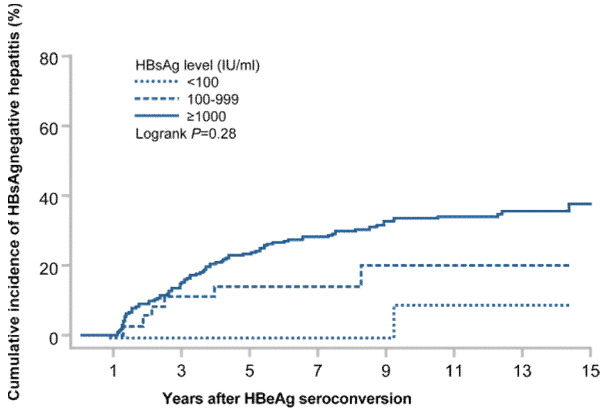


In patients with HBV DNA levels < 2,000 IU/mL, **HBsAg level > 1,000 IU/mL** was identified as an independent risk factor for development of HCC

Figure adapted from Tseng TC, *et al.*

Tseng TC, *et al. Gastroenterology* 2012;142:1140–9.
Lin CL, Kao JH. *J Gastroenterol Hepatol*. 2013;28:10–7.

SEARCH-B: qHBsAg predicts long-term risk of HBV reactivation in HBeAg seroconverters



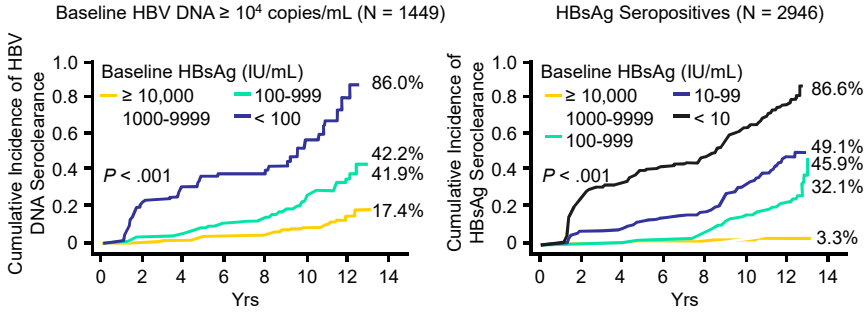
HBsAg level ≥ 1,000 IU/mL predicts a higher probability of developing HBeAg-ve CHB over time

SEARCH-B = Study of E Antigen seRoClearance of Hepatitis B

Tseng TC, *et al, Gastroenterology* 2011;141:517–25.

Quantitative HBsAg as Predictor of Outcomes in Chronic Hepatitis B

- Patients with chronic hepatitis B enrolled 1991-1992 (N = 4155) and followed until 2004
  - Natural history study of previously untreated patients
- In multivariate analysis, baseline HBsAg level independently predicted spontaneous HBV DNA and HBsAg clearance



Liu J, et al. AASLD 2011. Abstract 239.

qHBsAg can predict spontaneous HBsAg loss in HBV carriers

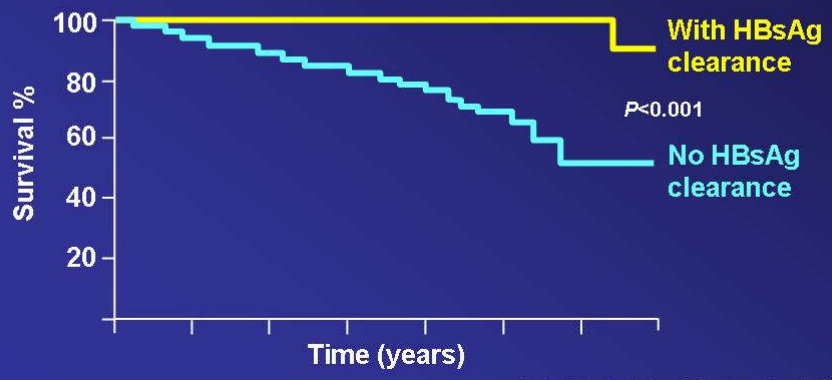
- **Serum HBsAg level <100 IU/ml at 1 year post-HBeAg seroconversion can predict HBsAg loss within 6 years**[1]
- **HBsAg <10 IU/ml is the strongest predictor of HBsAg loss in HBeAg-negative patients who have HBV DNA <2000 IU/ml**[2]
- **Decreasing HBsAg level (<200 IU/ml or a decrease of ≥1 log 10 IU/ml) can predict HBsAg seroclearance in inactive CHB patients**[3]

1. Tseng, Kao et al. Gastroenterology 2011
2. Tseng, Kao et al. Hepatology 2012
3. Chen YC, et al. Clin Gastroenterol Hepatol 2011

HBsAg clearance – Improves survival

Survival in patients with and without HBsAg seroconversion

Retrospective study of 309 patients over mean follow-up of 5.7 years



Fattovich et al. Am J Gastroenterol 1998

HBeAg

Định tính: Tình trạng nhân đôi của siêu vi B

Định lượng: Theo dõi và tiên lượng điều trị bệnh

Định lượng HBeAg trong theo dõi điều trị viêm gan B bằng Entecavir giúp tiên lượng chuyển đổi huyết thanh HBeAg

Journal of Viral Hepatitis, 2012, 19, 724–731 doi:10.1111/j.1365-2893.2012.01599.x

Prediction of response to entecavir therapy in patients with HBeAg-positive chronic hepatitis B based on on-treatment HBsAg, HBeAg and HBV DNA levels

J. W. Shin,[1] S. W. Jung,[1] B. R. Park,[2] C. J. Kim,[2] J. B. Eum,[1] B. G. Kim,[1] I. D. Jeong,[1] S.-J. Bang,[1] S.-H. Lee,[3] S. R. Kim[3] and N. H. Park[1,2] [1]Department of Internal Medicine, University of Ulsan College of Medicine, Ulsan University Hospital, Ulsan, Korea; [2]Biomedical Research Center, University of Ulsan College of Medicine, Ulsan University Hospital, Ulsan, Korea; and [3]Department of Laboratory Medicine, University of Ulsan College of Medicine, Ulsan University Hospital, Ulsan, Korea

Quantitative HBeAg Level at month 12 during Entecavir treatment to predict HBeAg seroconversion at year 3 of treatment

in 26 (31.7%) patients. On-treatment HBeAg levels performed better with respect to the prediction of seroconversion than HBsAg and HBV DNA levels. The best cut-off value for the HBeAg level at month 12 for the prediction of seroconversion was 0.62 $\log_{10}$ PEIU/mL. Although the HBsAg

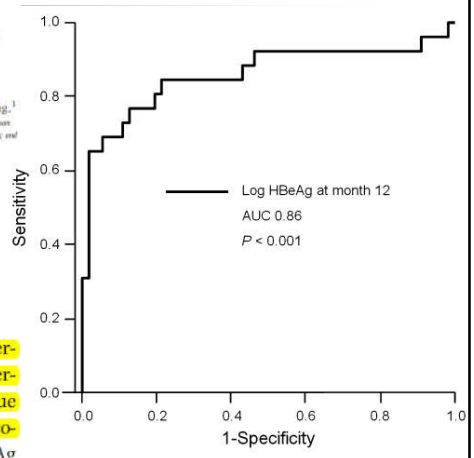


Fig. 3 Areas under the curve (AUROC) curve of quantitative HBeAg Level at month 12 during entecavir treatment to predict HBeAg seroconversion at year 3 of treatment.

J. W. Shin et al., Predictors of response to entecavir therapy, Journal of Viral Hepatitis, 2012, 19, 724–731

HBeAg and Hepatitis B Virus DNA as Outcome Predictors During Therapy with Peginterferon Alfa-2a for HBeAg-Positive Chronic Hepatitis B

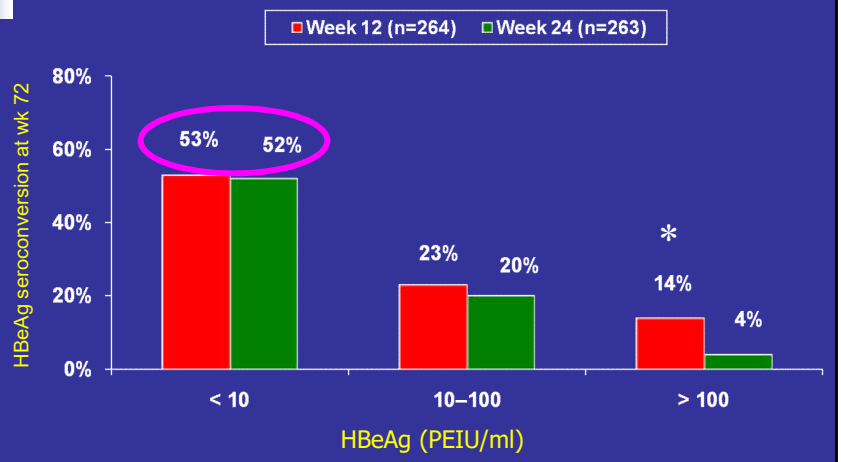
Michael W. Fried,[1] Teerha Piratvisuth,[2] George K. K. Lau,[3] Patrick Marcellin,[4] Wan-Cheng Chow,[5] Graham Cooksley,[6] Kang-Xian Luo,[7] Seung Woon Paik,[8] Yun-Fan Liaw,[9] Peter Button,[10] and Matei Popescu[11]

in-house reference standards obtained from the Paul Ehrlich Institute (PEIU/mL). In patients who achieved HBeAg seroconversion, levels of HBeAg consistently decreased during treatment and remained at their lowest level during the 24 weeks of posttreatment follow-up. After 24 weeks of treatment, 4% of patients with the highest levels of HBeAg (≥100 PEIU/mL) achieved HBeAg seroconversion, yielding a negative predictive value of 96%, which was greater than that obtained for levels of HBV DNA (86%). Late responders to peginterferon alfa-2a could also be differentiated from nonresponders by continued decrease in HBeAg values, which were not evident by changes in HBV DNA. *Conclusion:* These analyses suggest quantitative HBeAg is a useful adjunctive measurement for predicting HBeAg seroconversion in patients treated with peginterferon when considering both sensitivity and specificity compared with serum HBV DNA. (HEPATOLOGY 2008;47:428-434.)

Định lượng HBeAg trong theo dõi điều trị viêm gan B bằng Peg_INF giúp tiên lượng chuyển đổi huyết thanh HBeAg

View issue TOC
Volume 47, Issue 2
February 2008
Pages 428–434

Quantitative HBeAg at weeks 12 and 24 relationship to HBeAg seroconversion

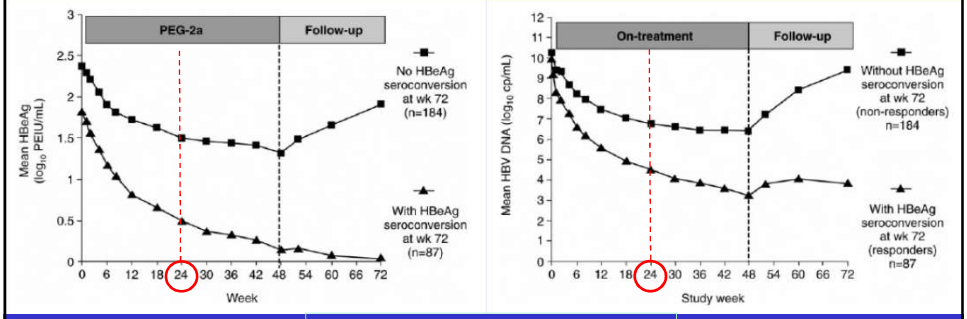


*P=0.059

Fried, et al. Hepatology. 2008;47:428-434.

Prediction of response to PEGASYS: HBeAg vs. HBV DNA

Mean HBeAg (PEIU/mL) | Mean HBV DNA (log cp/mL)



Week 24:
HBeAg >100 U/mL: NPV 96%
HBV DNA > 9 log: NPV 86%

HBeAg is a better negative predictor of response than HBV DNA

Fried et al. Hepatology 2008.

J Gastroenterol Hepatol. 2010 Sep;25(9):1498-506. doi: 10.1111/j.1440-1746.2010.06282.x.

Quantitative serum HBsAg and HBeAg are strong predictors of sustained HBeAg seroconversion to pegylated interferon alfa-2b in HBeAg-positive patients.

Ma H[1], Yang RF, Wei L.

⊕ Author information

Abstract

BACKGROUND AND AIM: To evaluate the usefulness of quantitative hepatitis B surface antigen (HBsAg) and hepatitis B e antigen (HBeAg) for predicting HBeAg seroconversion in chronic hepatitis B patients treated with conventional interferon (IFN) alfa-2b or PegIFN alfa-2b.

METHODS: Fifty-eight patients were enrolled; 29 for the training group and 29 for the validating group. Quantification of HBsAg and HBeAg was carried out at baseline, week 12, week 24, and then again at 12 and 24 weeks follow up, respectively, for two groups. Sixteen patients in the training group were followed up for 5 years.

RESULTS: The cutoff of 1500 IU/mL in serum HBsAg at week 12 had a positive predictive value (PPV) of 33% and a negative predictive value (NPV) of 91%, and 2890 IU/mL at week 24 had a PPV of 43% and an NPV of 95% for HBeAg seroconversion at week 48. The cutoff of 17.55 Paul Ehrlich Institute units/mL (PEI-U/mL) in serum HBeAg at week 12 had a PPV of 38% and an NPV of 95%, and 8.52 PEI-U/mL at week 24 had a PPV of 44% and a NPV of 100% for HBeAg seroconversion at week 48. Moreover the HBsAg and HBeAg levels of PegIFN alfa-2b group were lower than those of the conventional IFN alfa-2b group. During follow up, patients with HBeAg seroconversion remained HBeAg negative and none of them progressed to cirrhosis, but among the patients with non-HBeAg seroconversion, two progressed to cirrhosis. Two additional patients with negative HBeAg were observed.

CONCLUSIONS: On-treatment serum HBsAg and HBeAg had high predictive values to predict sustained HBeAg seroconversion by PegIFN alfa-2b. Patients who cleared HBeAg had better survival free of hepatic complications during long-term follow-up study.

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The importance of the serum quantitative levels of hepatitis B surface antigen and hepatitis B e antigen in children with chronic hepatitis B

LIVER

Kaan Demirören, Halil Kocamaz, Yaşar Doğan
Department of Pediatric Gastroenterology, Fırat University Faculty of Medicine, Elazığ, Turkey

Results: Significant differences were found between groups of pre- and post treatment quantitative levels of HBsAg, HBeAg, HBV DNA, and ALT. Comparison of HBsAg, HBeAg, HBV DNA, and ALT levels before the treatment and decrease ratios of these levels after treatment according to HAI and fibrosis scores did not show any statistically significant differences. There was a positive correlation between pretreatment HBV DNA load and HBeAg levels, and a negative correlation between pretreatment HBV DNA and ALT levels. There was a negative correlation between decrease ratios of HBsAg and ALT levels after treatment. Patients with post treatment HBeAg seroconversion had a lower post treatment HBV DNA load and a higher decrease ratio of HBsAg than patients who did not have HBeAg seroconversion.

Conclusion: The present study indicated that HBsAg and HBeAg levels significantly decreased during treatment and that HBeAg correlated with HBV DNA load. Quantitative HBeAg and HBsAg assays could therefore have an important role in treatment of CHB.

Kết luận

- Viêm gan siêu vi B vẫn còn là 1 thách thức cho thầy thuốc
- Vai trò chìa khóa của xét nghiệm trong bệnh viêm gan siêu vi B: Từ chẩn đoán, điều trị, tiên lượng bệnh đến phòng ngừa
- Nhiều tiến bộ của xét nghiệm đã góp phần trong cuộc chiến chống lại HBV

  Các xét nghiệm định lượng kháng nguyên HBV là công cụ mới giúp ích nhiều trong việc điều trị HBV còn nhiều khó khăn và đầy thử thách
- Phòng ngừa vẫn giữ 1 vị trí cực kỳ quan trọng

CÁM ƠN QUÝ VỊ ĐÃ CHÚ Ý THEO DÕI