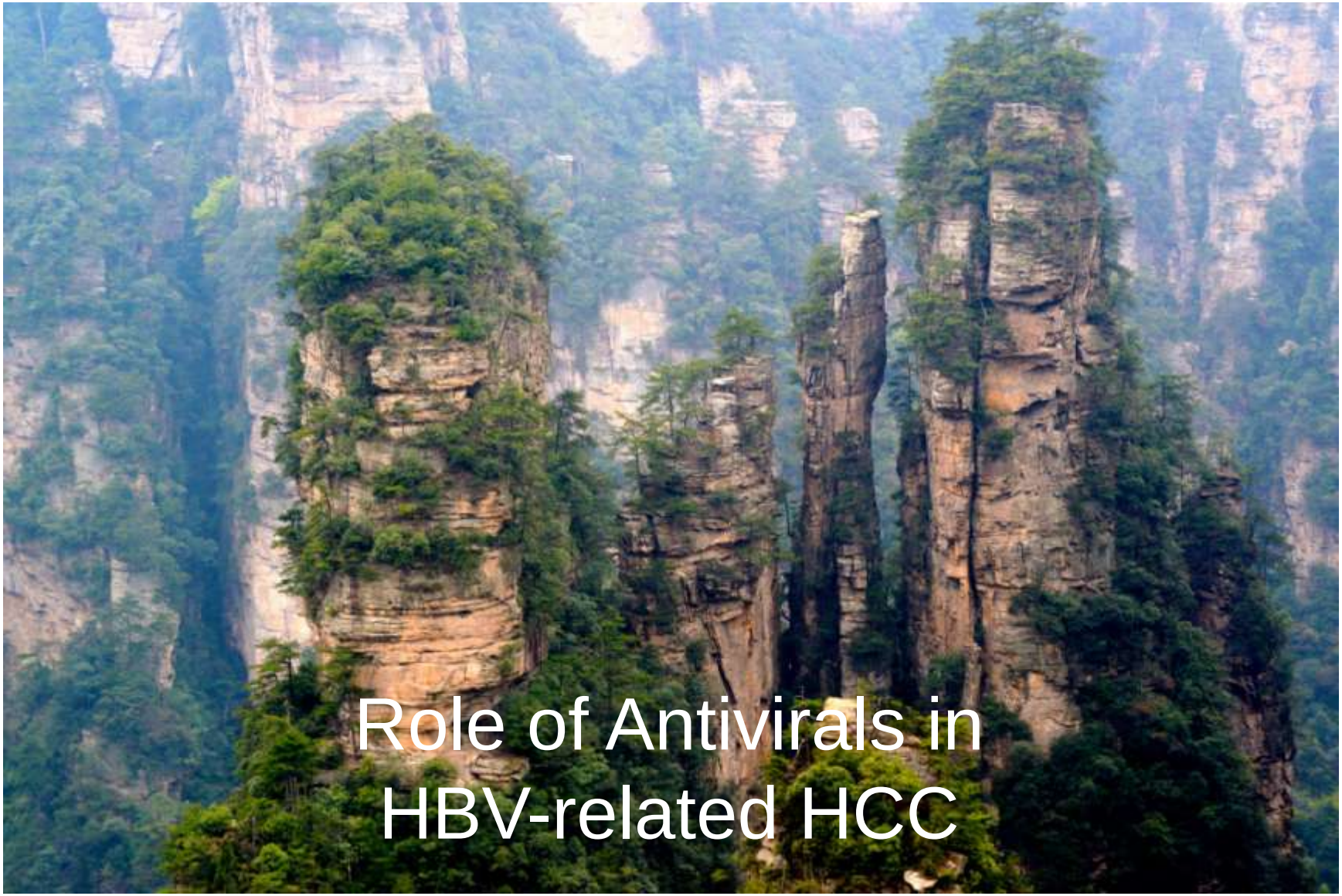
Professor CL Lai
University of Hong Kong


Role of Antivirals in
HBV-related HCC

Prevention of HBV- related HCC

- Interferon treatment
- Nucleos/tide analogue treatment


Interferon Treatment

Interferon Treatment

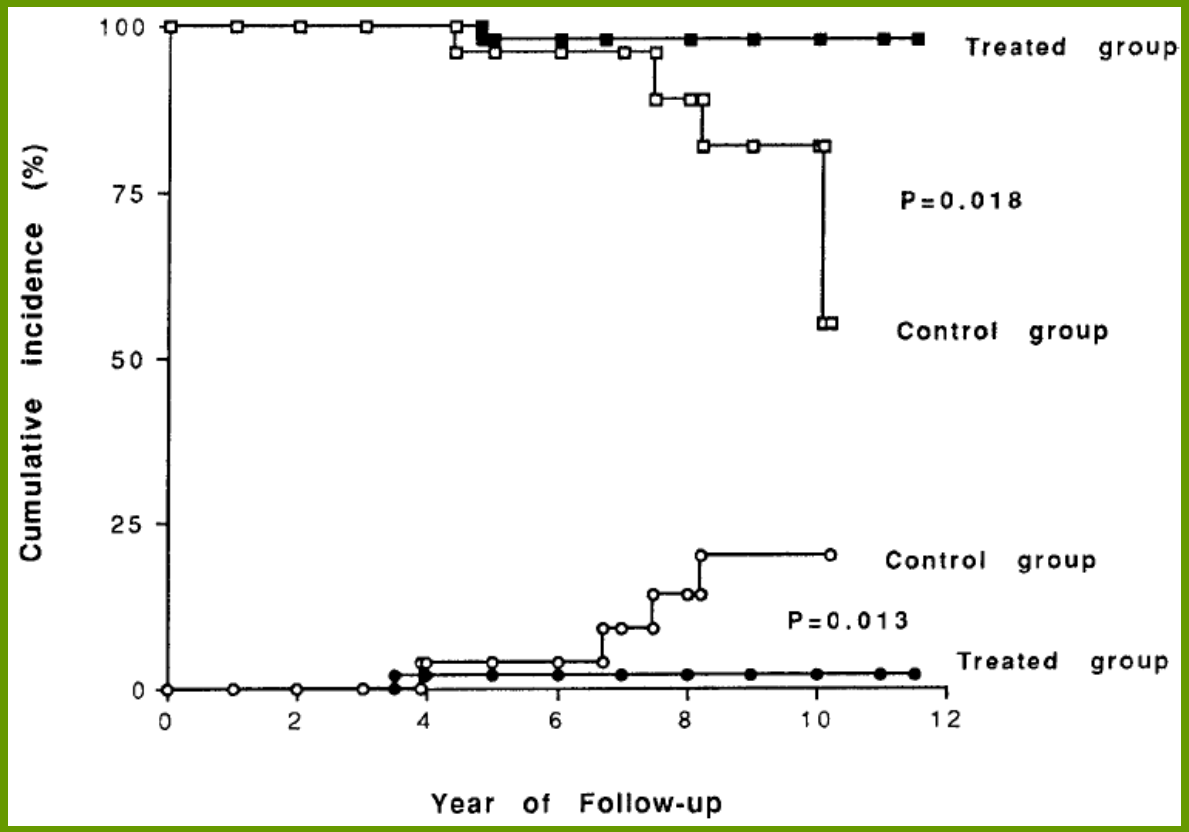
- 10 trials with long-term FU on HCC development
- 6 meta-analyses

Lai CL & Yuen MF. Hepatology 2013; 57:399.

Interferon Treatment

- Prospective randomized study:

  67 IFN ± prednisolone (10.3% with cirrhosis) vs
  34 controls (14.7% with cirrhosis) (mean FU 7.4 / 6.5 years)



Lin et al., Hepatology 1999;29:971-5

Interferon Treatment

- Prospective randomized trial IFN treated vs controls

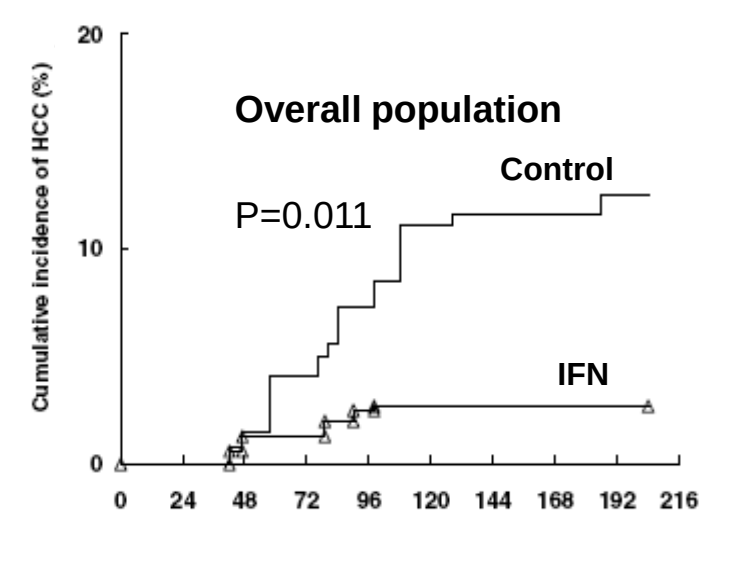
  - HCC in only 1 of the 67 (1.5%) treated patients vs 4 of the 34 controls (12%) (p=0.043).

  - no differences in the development of new cirrhosis and cirrhosis complications

Lin et al., Hepatology 1999;29:971-5

Interferon Treatment

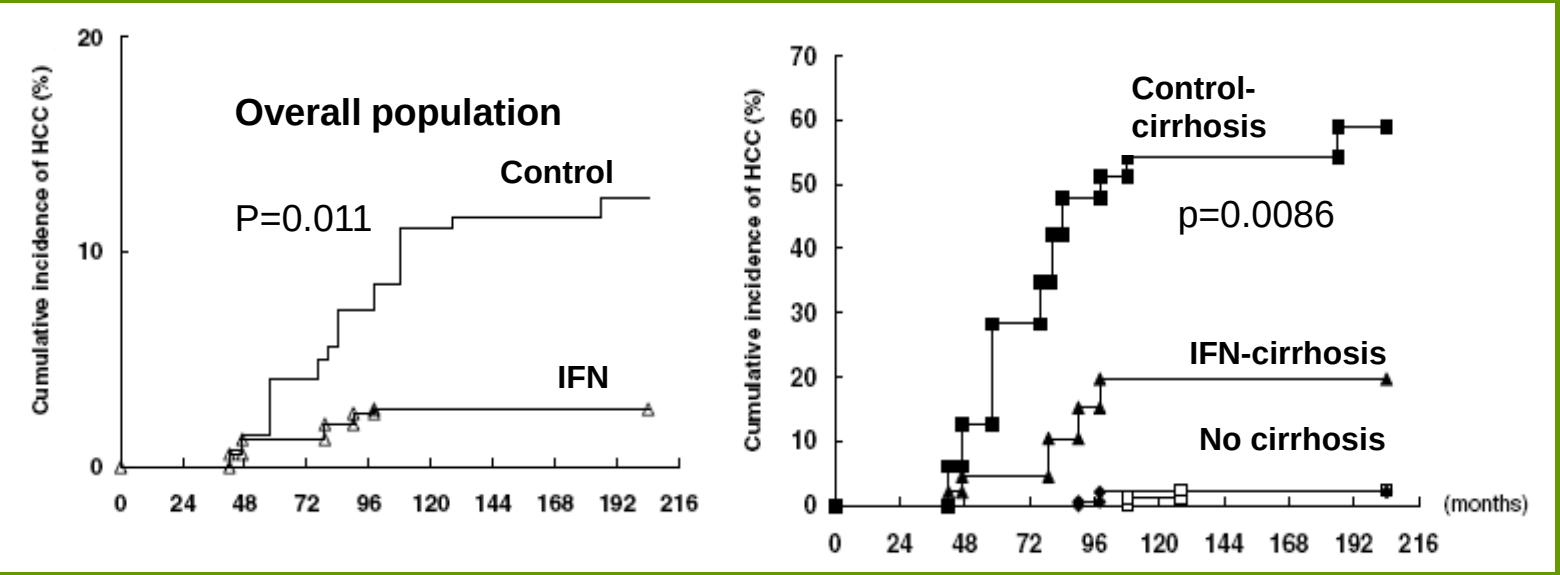
- 233 IFN-treated vs. 233 matched controls



Lin et al., J Hepatol 2007;40:45-52

Interferon Treatment

- 233 IFN-treated vs. 233 matched controls



NB: HCC was reduced significantly *only* in patients with pre-existing cirrhosis (3/19 IFN vs 14/24 controls; p<0.01)

Lin et al., J Hepatol 2007;40:45-52

Interferon Treatment

- Conflicting results in the 2 studies from the same center!
  - Did the reduction in HCC development of their previous study also apply only to the 10-15% of patients with preexisting cirrhosis?
  - The earlier study showed that IFNα treatment had no effect on the development of new cirrhosis and cirrhosis complications.

Lin et al., Hepatology 1999;29:971-5
Lin et al., J Hepatol 2007;40:45-52

Interferon Treatment

Prospective, non-randomized study of HBeAg-negative CHB patients in Greece

- 209 interferon treated vs 195 untreated patients
- Mean follow-up 6 years (1 – 13.5 yrs)
- HCC development:
  - IFN-treated 8.1% (n=17; 1 in sustained responders; 16 in non-responders)
  - untreated 7.7%

Paptheodoridis et al., J Hepatol 2001; 34: 306

Interferon Treatment

637 patients from 21 centers in Italy and Argentina in a retrospective cohort study

- HCV patients who developed HCC
  - 9.1% IFN-treated vs. 18.5% untreated (RR 31.4, 95% CI 1.46 – 6.8)
- HBV patients who developed HCC
  - 16% IFN-treated vs. 10% untreated (RR 0.98, 95% CI 0.33 – 2.92)

Conclusion: IFN does not change risk of HCC in HBV patients

International Interferon-α Hepatocellular Carcinoma Study Group
The Lancet 1998;23:1535-9

Interferon Treatment

- 208 HBeAg-positive IFN-treated (27 with cirrhosis) vs 203 matched controls in Hong Kong
- Median follow up 107 vs. 108 months
  - cirrhotic complications: 9 IFN vs 2 controls (p= 0.062)
  - HCC: 5 IFN vs 0 controls

Yuen et al., Hepatology 2001;34:139-45

Meta-analysis of IFN Treatment & HCC

6 Meta-analysis of IFN Treatment & HCC

Authors	No of pts treated vs controls	Relative risk (95% CI)	P value	Comments
Camma et al 2001[17]	853 vs 652 (all cirrhotic patients)	4.8%* (0.11 – 0.015)	NS	Significant inconsistency in Oriental studies. European studies no preventive effect
Miyake et al 2009[18]	553 vs 750	5.0%* (9.4 – 0.5)	0.028	Effect not shown in European studies.
Sung et al 2008[19]	1,292 vs 1,458	0.66 (0.48 – 0.89)	0.006	No effect in non-cirrhotic patients.
Yang et al 2009[20]	1,006 vs 1,076	0.59 (0.43 – 0.81)	0.001	Patients with normal ALT excluded.
Zhang et al 2011[21]	176 vs 171	0.23 (0.05 – 1.04)	NS (0.056)	Only included 2 randomized control trials
Jin et al 2011[22]	1,291 vs 1,048	0.274 0.059 – 1.031	NS	

NS = not significant

Lai CL & Yuen MF. Hepatology 2013; 57: 399.

Prevention of HCC by IFN in CHB

- Meta-analysis: 10 studies (n=2742)
  - IFN-treated vs controls:

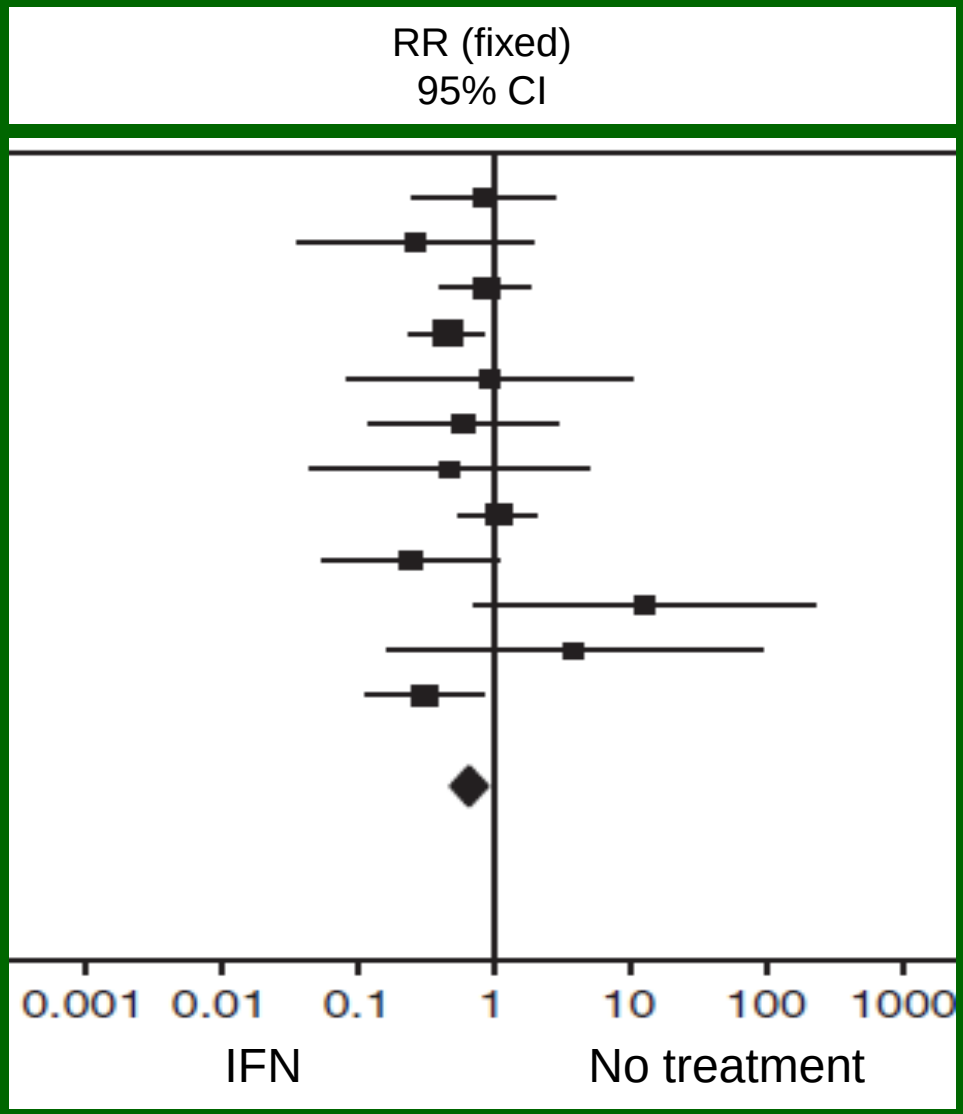
    whole group: 4.6% vs. 9% (RR 0.66) p = 0.006

    early cirrhosis: 11.6% vs. 21.5% (RR 0.53) p = 0.001

    no cirrhosis: 0.9% vs. 1.1% (RR 0.72) p = 0.66

Sung et al., Aliment Pharmacol Ther 2008;28:1067-77

Prevention of HCC by IFN in CHB



Sung et al., Aliment Pharmacol Ther 2008;28:1067-77

Conclusions for IFN and HCC Prevention

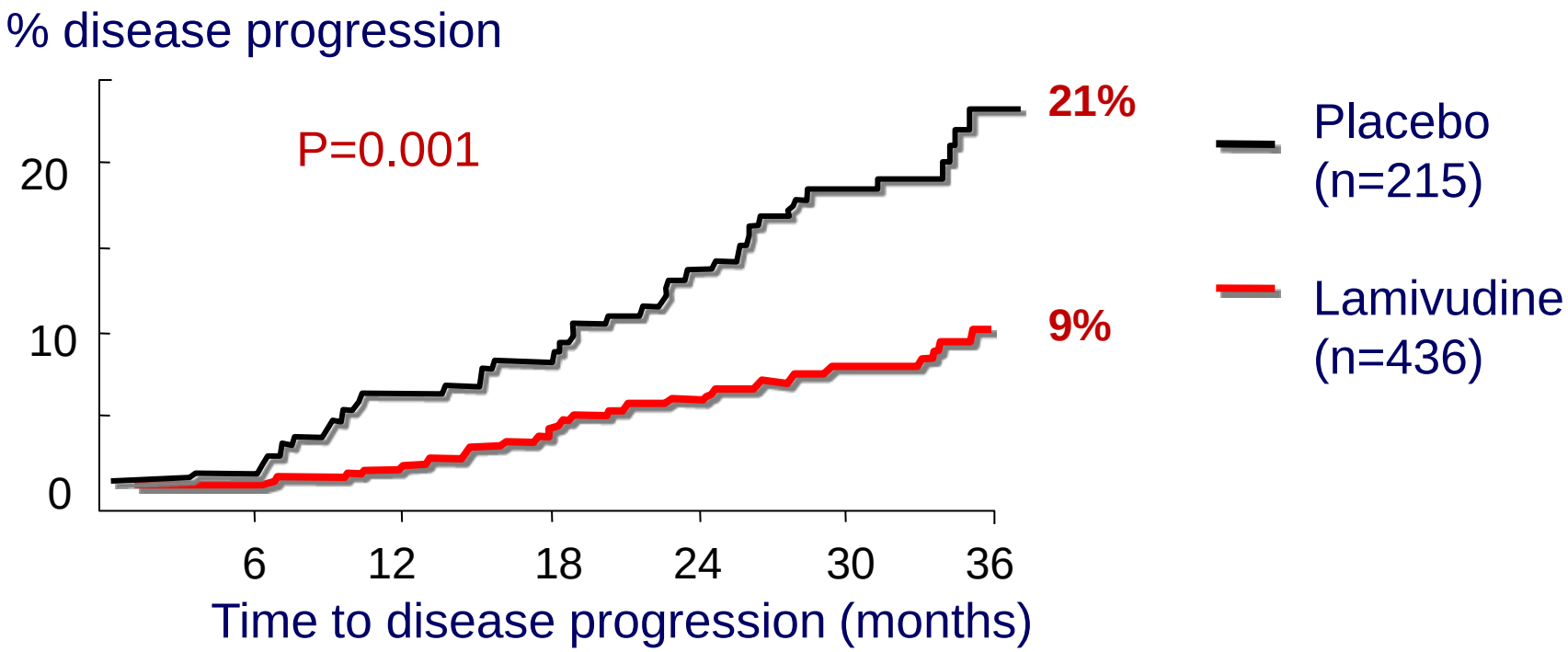
- Data not unidirectional for IFN on HCC
- Only 3 out of 10 studies showed benefit
- ? Decrease the risk of HCC in selected group of patients
    - responders to IFN
    - patients with cirrhosis

Lai CL & Yuen MF. Hepatology 2013; 57:399.

Prevention of HBV-related HCC with Nucleos/tide Analogues

Lamivudine treatment in Cirrhotic Patients

- 651 cirrhosis patients with evidence of viral replication



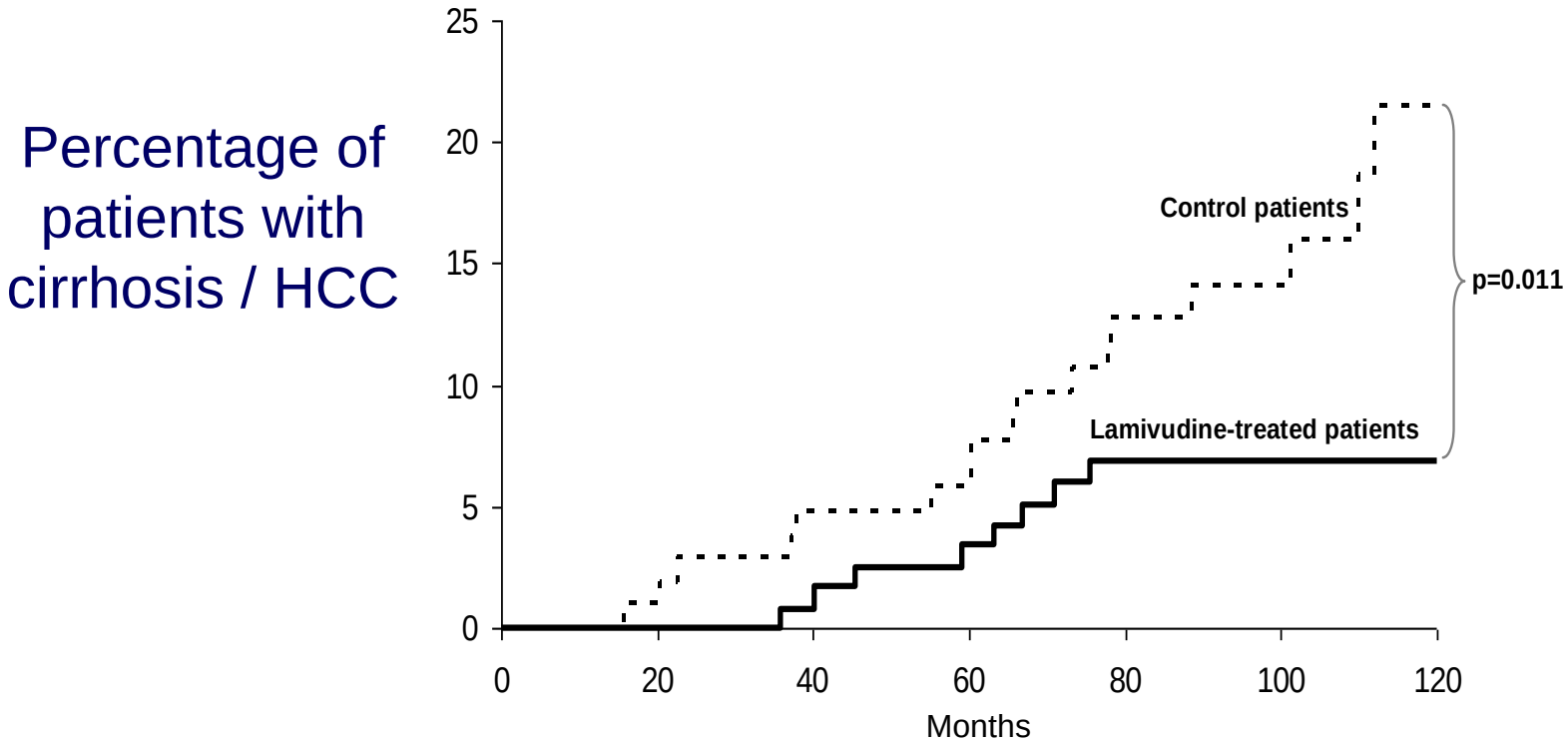
- Child-Pugh score p=0.02; HCC p=0.047*
- Benefit reduced with YMDD emergence

  * 5 cases of HCC in year 1 excluded, p=0.052

Liaw et al. NEJM 2004; 351:1521

Lamivudine Treatment in *Non*-Cirrhotic Patients

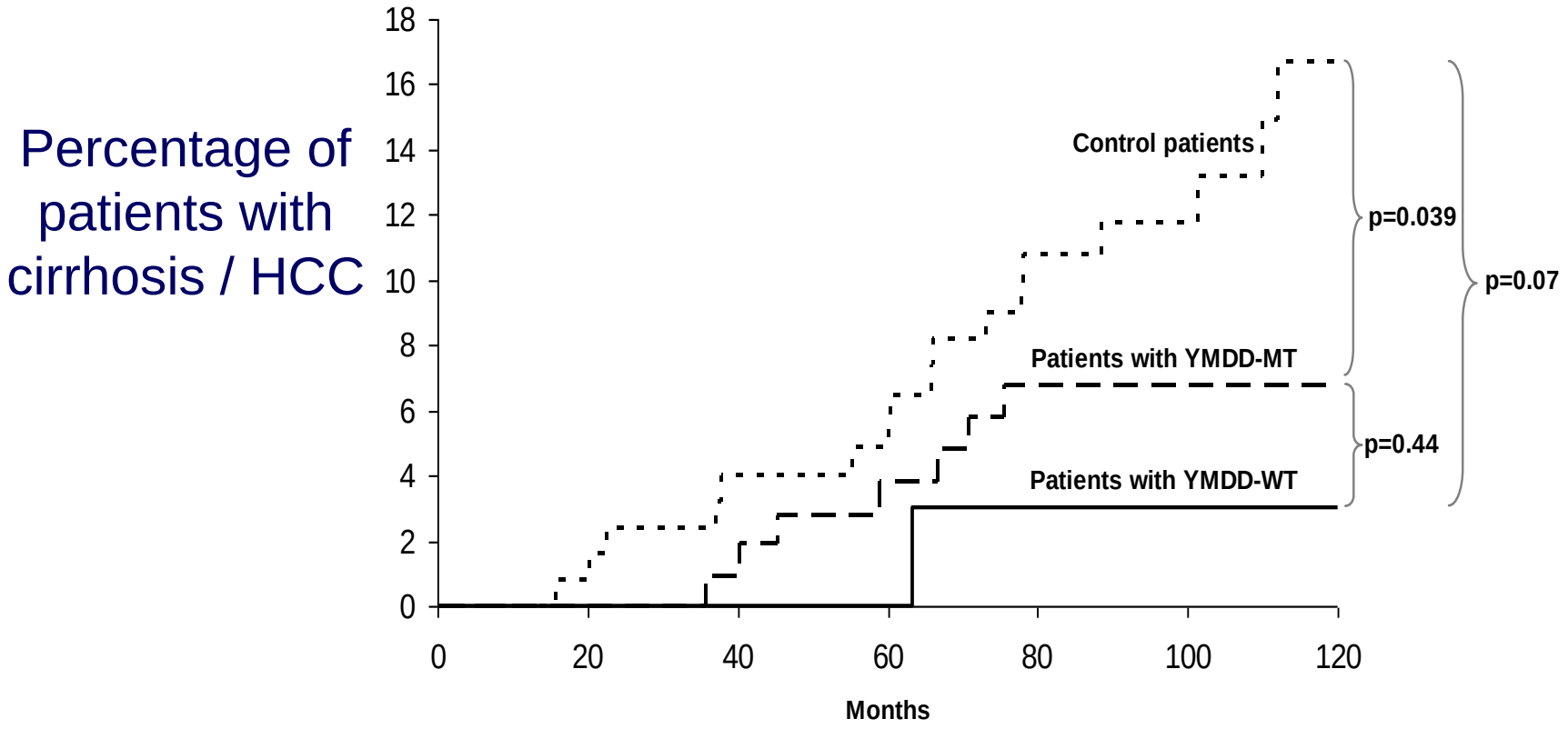
142 *non*-cirrhotic patients on continuous lamivudine for a median of 89.9 months (vs 124 untreated controls)



Yuen et al. Antivir Ther 2007; 12: 1295

Lamivudine Treatment in *Non*-Cirrhotic Patients

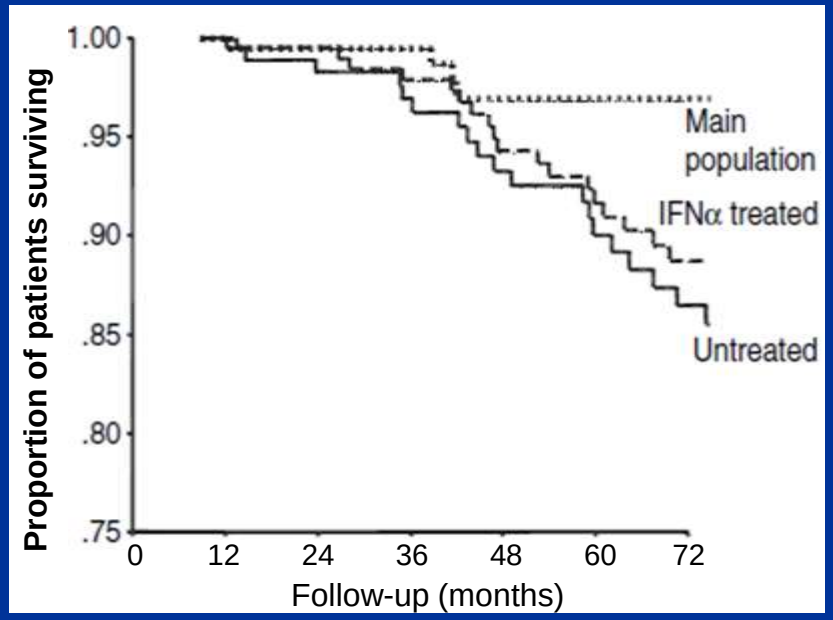
- 76.3% YMDD mutations at yr 6, with no new mutations thereafter

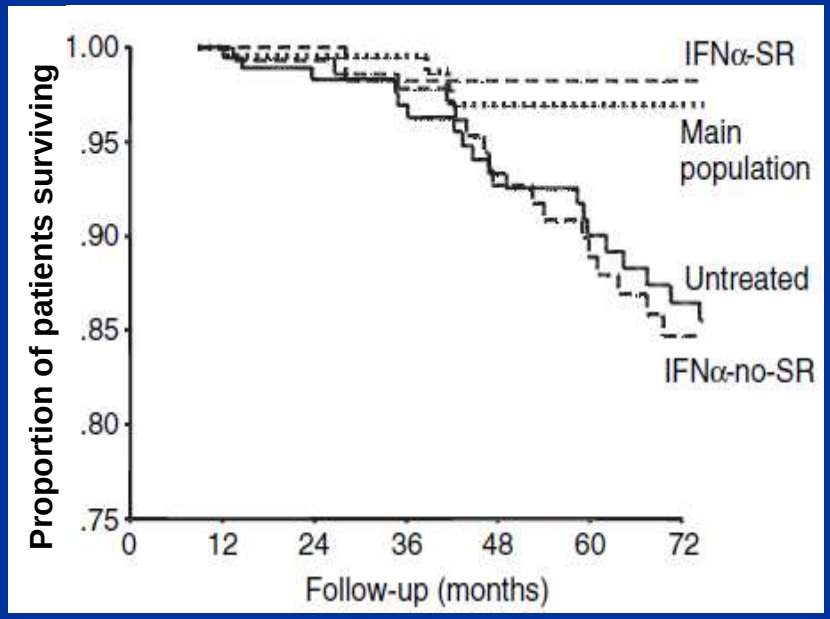


Yuen et al. Antivir Ther 2007; 12: 1295

Lamivudine Treatment in HBeAg-negative CHB

201 lam-treated vs 209 IFN-treated vs 195 untreated pts





Conclusions: Long-term nucleos/tide, starting with lamivudine, improves survival and reduces risk of complications

Paptheodoridis et al., Hepatology2005; 42: 121

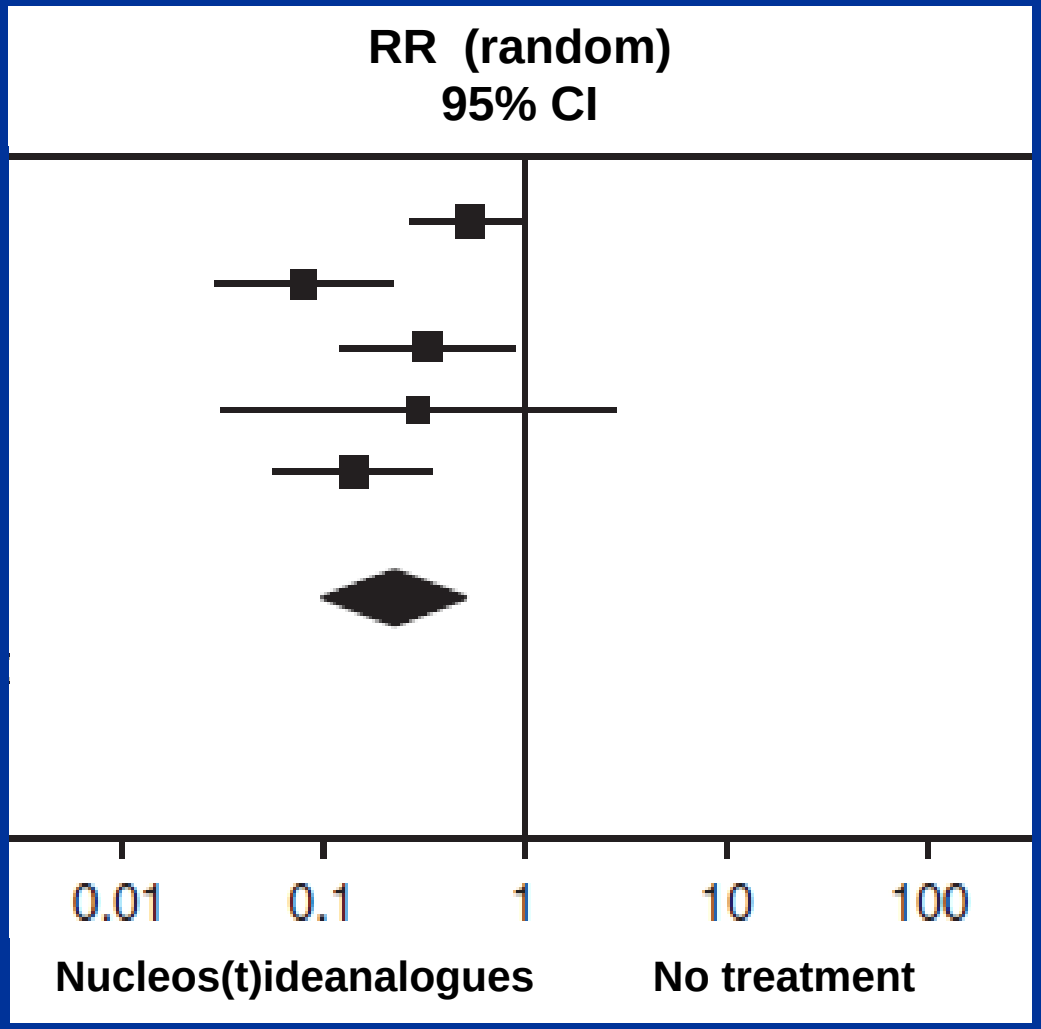
Prevention of HCC by Lamivudine/ Adefovir

- Meta-analysis: 5 studies (n=2289)
  - Lamivudine/adefovir vs controls:

whole group: 2.5% vs. 11.7%	(RR 0.22) p = 0.01
early cirrhosis: 3.9% vs. 22.4%	(RR 0.17) p = 0.02
no cirrhosis: 1.8% vs. 8.0%	(RR 0.21) p = 0. 0001
with drug resistance: 3.3% vs. 6.4	(RR 0.52) p = 0.04

Sung et al., Aliment Pharmacol Ther 2008;28:1067-77

Prevention of HCC by Lamivudine/ Adefovir



Sung et al., Aliment Pharmacol Ther 2008;28:1067-77

Prevention of HCC by Entecavir

Prevention of HCC by Entecavir

- Entecavir vs historical controls

  - Japan:

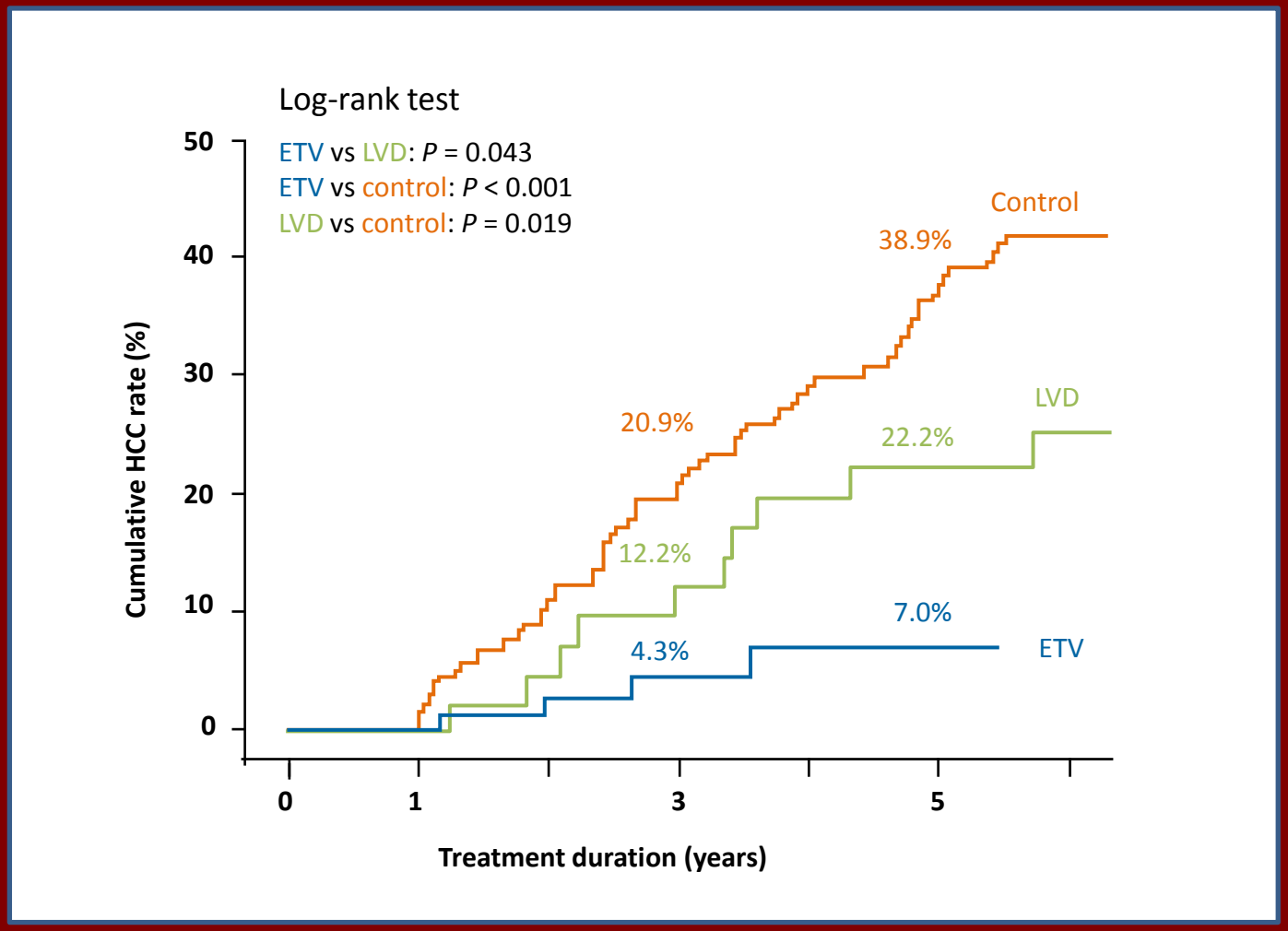
    HCC incidence 76/10,000 pt-yrs for entecavir vs 116/10,000 pt-yrs in controls matched by propensity score ($p < 0.001$) ($n = 316$ vs 316)

    Hosaka T et al. Hepatology 2013; 58: 98.

  - Hong Kong:

    Reduction in hepatic events (HCC, $p=0.049$, as well as mortality, $p<0.001$) in cirrhotic patients with maintained viral suppression ($n = 482$ vs 69)

    Wong GLH et al. Hepatology 2013; 58: 1537.



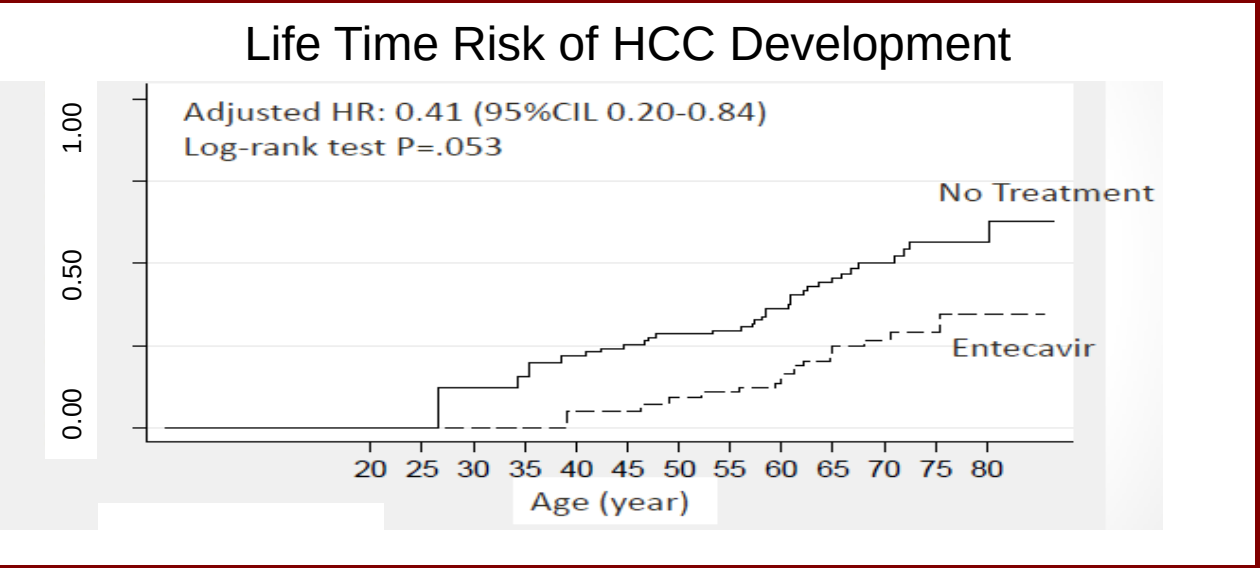
The fact that entecavir has greater effect than lamivudine implies that the effect is due to viral suppression.

Hosaka T et al. Hepatology 2013; 58: 98.

Prevention of HCC by Entecavir

- Entecavir vs historical controls
  - Taiwan:

    HCC incidence reduced to 9.19 per 1,000 person-year from 14.19 per 1,000 person-year in historic controls, p = 0.08 (n = 6666 vs 621) (HR 0.41)

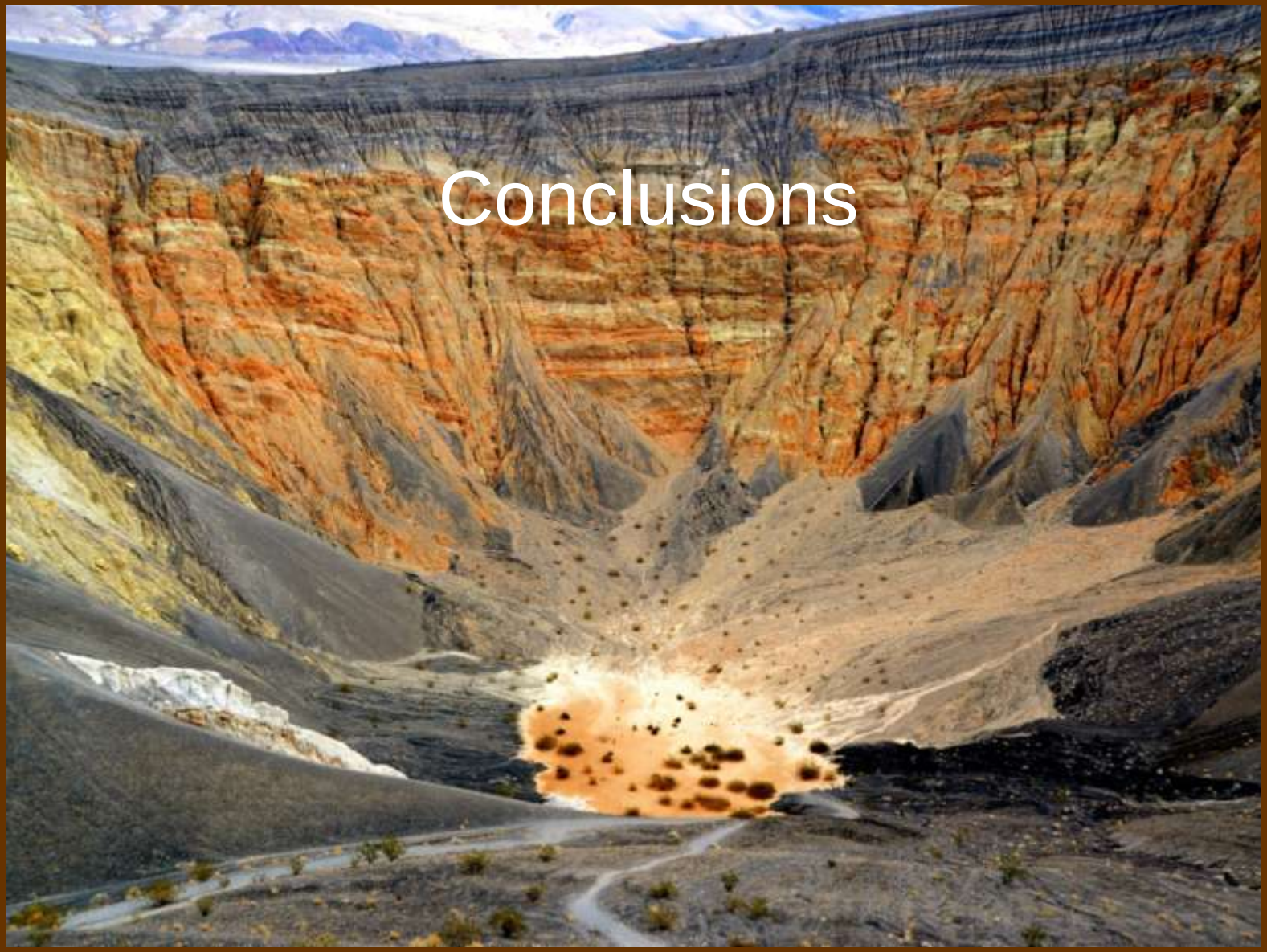


Su TH et al. AASLD 2013.

- Prevention of HBV-related HCC

  - effect of tenofovir not yet known
  - theoretically better than lamivudine/adefovir and same as entecavir

Lai CL. Yuen MF. Hepatology 2013; 57: 399


Conclusions

Conclusions

- The protective effect of IFNα is likely to be limited to cirrhotic patients with sustained response, a relatively small proportion of patients.
- Nucleoside analogues are more effective, probably through more potent and persistent suppression of viral replication, though the effect may be blunted with the occurrence of resistance.

Lai CL & Yuen MF. Hepatology 2013; 57:399.

Thank you!

Manila Bay