Does Curing HCV Lead to HBV Reactivation and Higher Rates of Hepatocellular Carcinoma: Myth or Reality?

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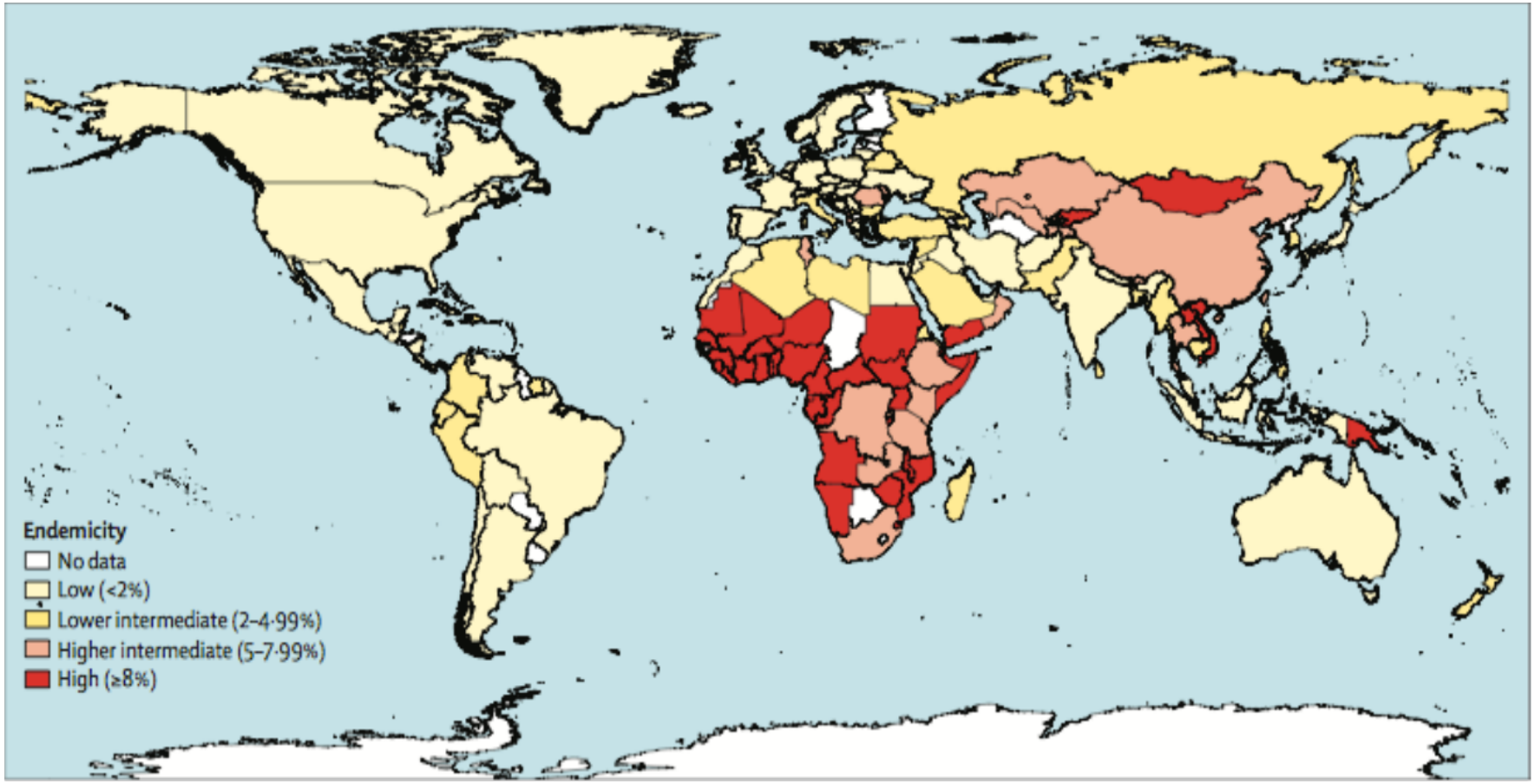
Outline

- Brief overview of the Hepatitis B infection
- HBV reactivation
- Reports of HBV reactivation with new Hep C therapies
- *De novo* HCC in Hep C patients treated with new therapies
- New Hep C therapies in patients with HCC
- Summary

HBV Prevalence

>2 billion people have evidence of HBV infection

>240 million people are chronically infected with HBV worldwide



Ott JJ, Stevens GA, et al.Global epidemiology of hepatitis B virus infection: new estimates of age-specific HBsAg seroprevalence and endemicity. *Vaccine* 2012;30:2212-9.

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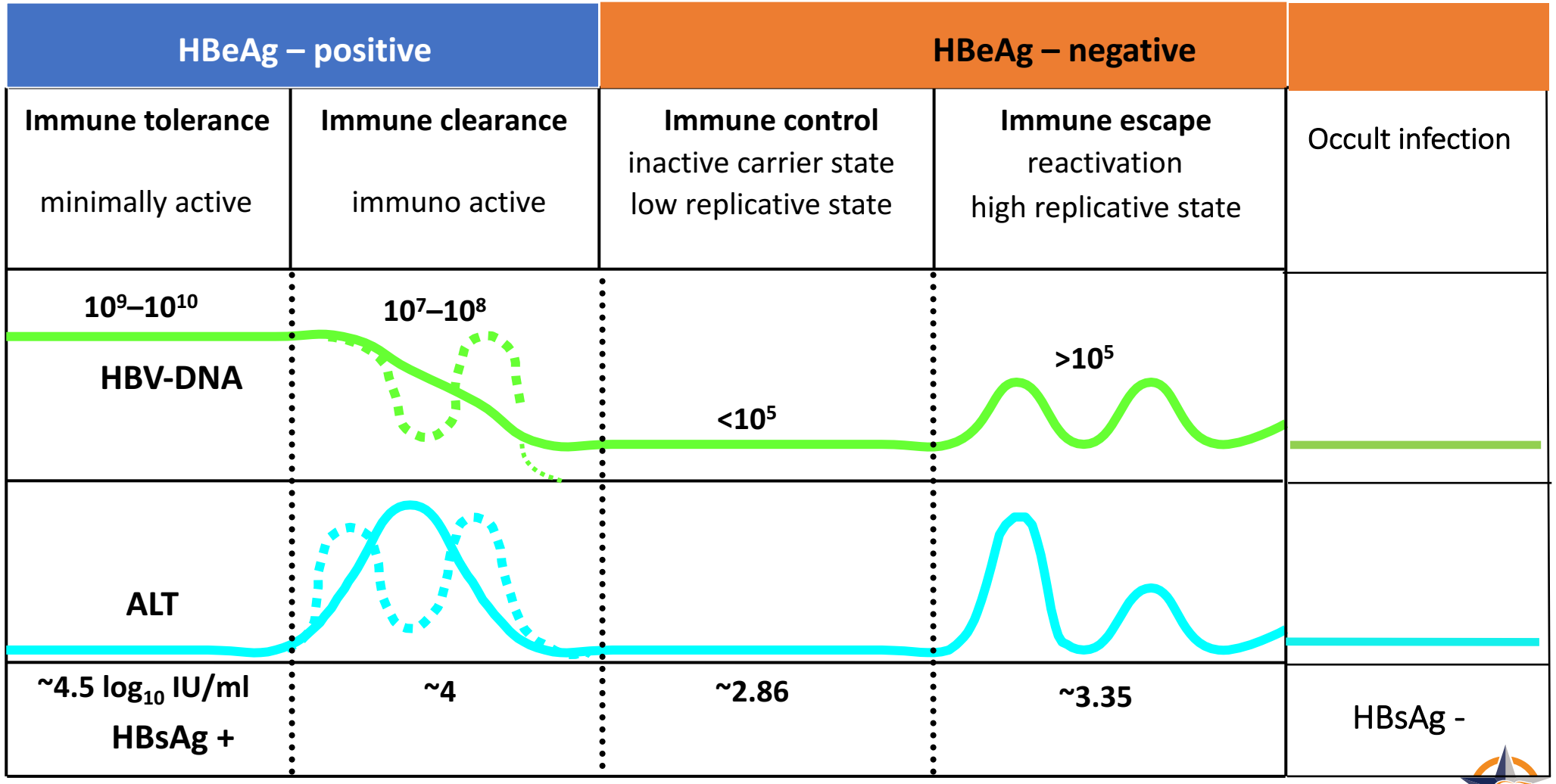
Phases of Chronic Hepatitis B



Adapted from Ghany MG; 2010 Annual Liver Meeting Postgraduate Course

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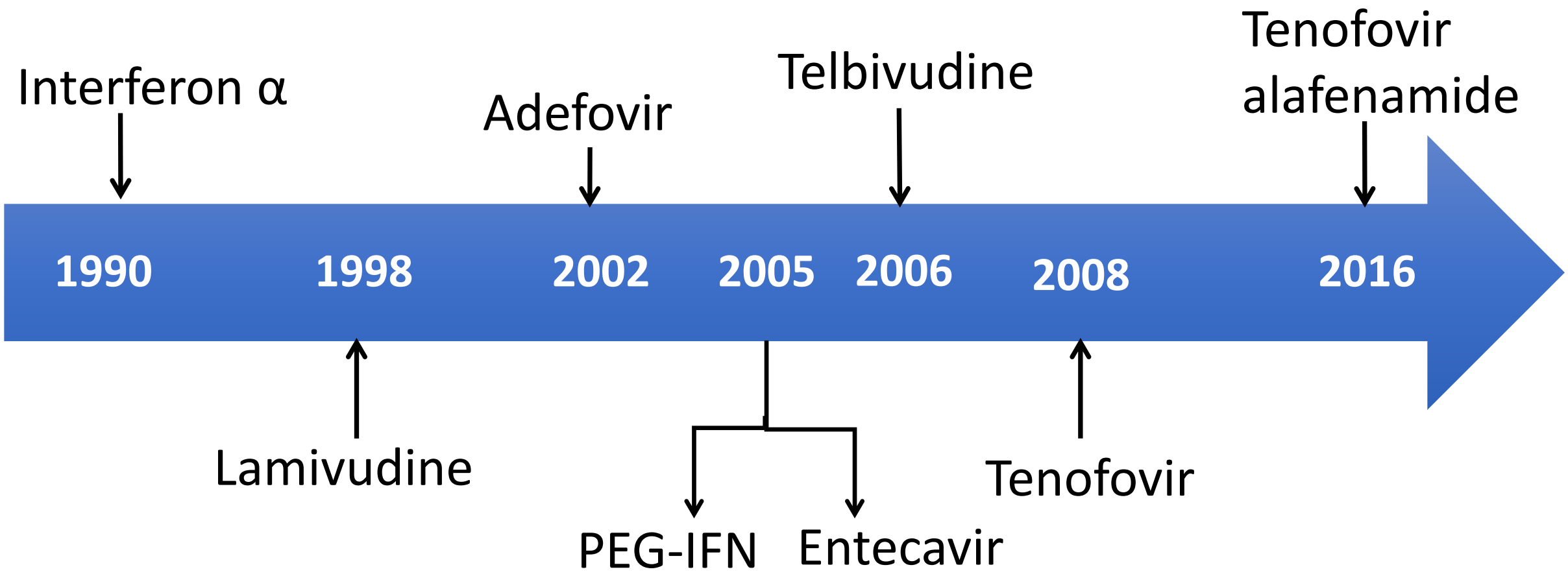
Evolution of HBV Therapies



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Unique Features of HBV

- Ability to persist in hepatocytes because of ccc-DNA
- Oral therapy is often indefinite
- No cure with current therapies
- Highly replicative virus when active
- Notorious for reactivation from a dormant state in immunosuppressed patients
- Common clinical scenarios where HBV reactivation is encountered
  - Cancer chemotherapy, particularly B-cell depleting agents
  - Biologic agent therapy

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Risk of HBV Reactivation

- Based on a systematic review* of HBsAg positive pts receiving chemotherapy, incidence of:
  - HBV reactivation: 37% (24%-88%)
  - HBV-related hepatitis: 33% (24%-88%)
  - HBV-related liver failure: 13% (5%-33%)
  - HBV-related death: 7% (0%-63%)

*Loomba R, Rowley A, et al. Systematic review: The effect of Lamivudine on HBV reactivation; *Ann Int Med*; 2008; Apr 1.148 (7);519-28

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HBV/HCV Coinfection

- Shared risk factors
- Prevalence rates of coinfection vary (6-30%)* among Chronic Hep C pts
- Up to 60% of Chronic Hep C pts can have evidence of prior HBV (isolated Hepatitis B core antibody)*
- Typically one virus remains suppressed while the other is active – exact mechanism unknown
- Rare cases of HBV reactivation during IFN therapy of Hep C were reported

*Bini EJ, Perumalswami PV. HBV infection among American pts with CHC…; *Hepatology*; 2010; Mar.51(3);759-66

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Does HCV DAA Therapy Lead to Reactivation of HBV in HCV/HBV Co-infected Individuals?

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FDA Blackbox Warning

"FDA is requiring a Boxed Warning (Black Box), our most prominent warning, about the risk of HBV reactivation to be added to the drug labels of DAAs directing health care professionals to screen and monitor for HBV in all patients receiving DAA treatment."

October 16, 2016

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Basis for FDA Warning

- FDA Post-marketing surveillance
- Recommendations based on 24 cases of HBV reactivation including 2 deaths and 1 transplant
- Average duration of DAA therapy before HBV reactivation: 4-8 weeks
- In 8 cases – DAAs stopped due to suspected liver toxicity
- 3 out of 24 were isolated anti-HBc +ve at baseline and 10 had unclear serology – course not described

Estimates of Incidence

-Prospective study from Hong Kong

-327 consecutive CHC pts treated with DAAs

-3/10 HBsAg+ pts relapsed

-None of the occult HBV pts relapsed

		HBsAg negative		
	HBsAg positive N = 10	OBI positive N = 124	OBI negative N = 193	*P* value[a]
Hepatitis				.003
No	7 (70.0)	121 (97.6)	189 (97.9)	
Yes	3 (30.0)	3 (2.4)	4 (2.1)	
	n = 3	n = 3	n = 4	
Median time to onset of hepatitis, *wk* (range)[b]	8 (4–10)	8 (2–12)	4 (4–12)	.90
Severity of hepatitis				.60
Anicteric	1 (33.3)	3 (100)	4 (100)	
Icteric	1 (33.3)	0 (0.0)	0 (0.0)	
Hepatic failure	1 (33.3)	0 (0.0)	0 (0.0)	
Cause of hepatitis				.01
HBV reactivation	3 (100.0)	0 (0.0)	0 (0.0)	
TCM/other medications	0 (0.0)	1 (33.3)	3 (75.0)	
Alcohol	0 (0.0)	2 (66.7)	0 (0.0)	
Others or unknown	0 (0.0)	0 (0.0)	1 (25.0)	

Wang C, Ji D, et al. Hepatitis due to HBV reactivation in DAA treated CHC; *CGH*; 12/2016; 15; 132-6

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Estimates of Incidence

- In a VA analysis of 62,920 pts completing HCV DAA therapy:
  - 85.5% were tested for HBsAg prior to HCV therapy
  - Of those, 0.70% (377/53,784) were HBsAg+
- Only 9 of 62,290 treated pts **(0.0001%)** had HBV reactivation:
  - 8 of 9 in HBsAg+ patients
  - 1 of 9 in patient with isolated anti-HBc+
  - Only 3 of the 9 had peak ALT elevations >2 ULN
  - 17 other patients <3 log increases in HBV DNA that did not qualify as reactivation
- HBV reactivation not affected by HCV genotype, DAA regimen, cirrhosis
- HBV reactivation had no effect on chance of Hep C SVR

Belperio P, Shahoumian A, et al. Evaluation of HBv reactivation among 62,920 veterans. *Hepatology*; 2017; Feb.

Prevention of HBV Reactivation During DAA Therapy

- Test HBsAg, anti-HBs and anti-HBc in all pts being considered for DAA therapy for Hep C
- If HBsAg+ & not on HBV suppressive therapy:

  - Monitor HBV DNA during & after DAA therapy
    - Start HBV antiviral treatment if treatment criteria are met
- If HBsAg- with isolated HBcAb+
  - Monitor ALT during DAA therapy
  - Test for HBV DNA if ALT rises or fails to normalize
  - Start HBV antiviral treatment if treatment criteria are met

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Does HCV DAA Therapy Lead to higher rates of Hepatocellular Carcinoma (HCC)?

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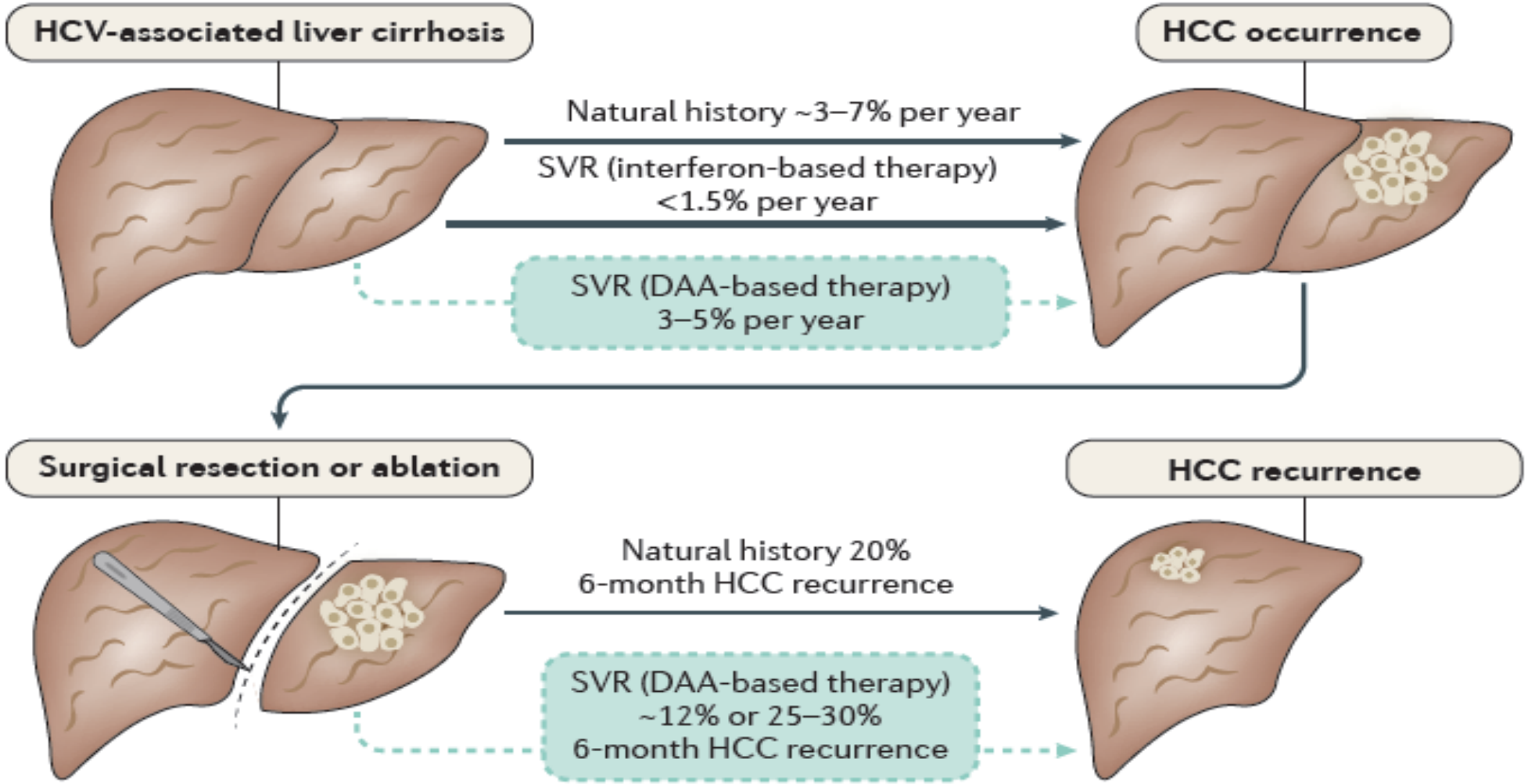
De novo HCC & HCC recurrence after DAA therapy



Llovet & Villanueva *Nat Rev Gastro Hep* 2016

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De Novo HCC After DAA Therapy

- Italian study of 285 cirrhosis pts without prior HCC followed for 24 weeks after DAA therapy*:
  - 9/285 (3%) developed *de novo* HCC

- UK study of 315 cirrhosis pts who achieved SVR24 after 12 weeks of DAA therapy**:
  - 15/315 (4.7%) developed De novo HCC
  - *De novo* HCC rate ~11% in non-SVR pts; 4.2% in a comparative untreated cohort

*Conti F, et al. *J Hepatol.* 2016; **Cheung MCM, et al. *J Hepatol.* 2016

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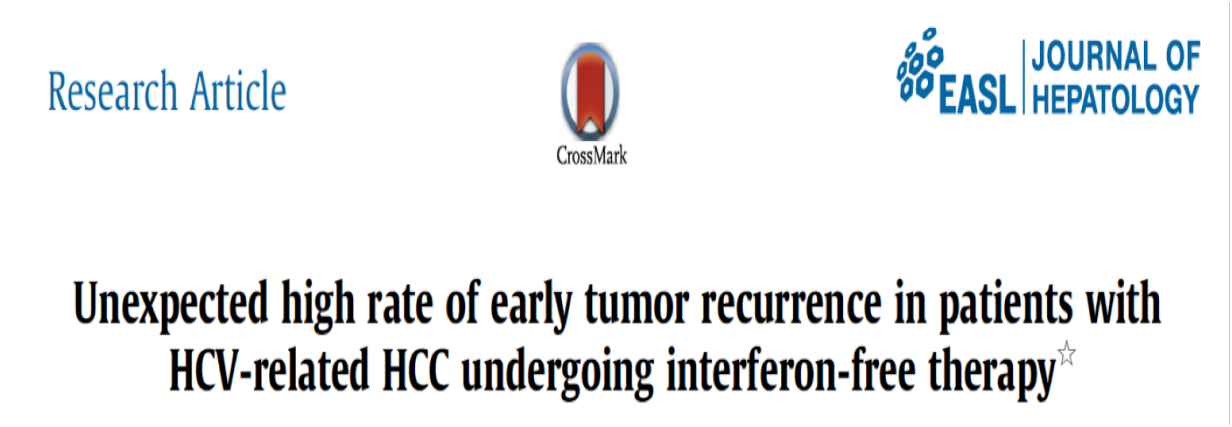
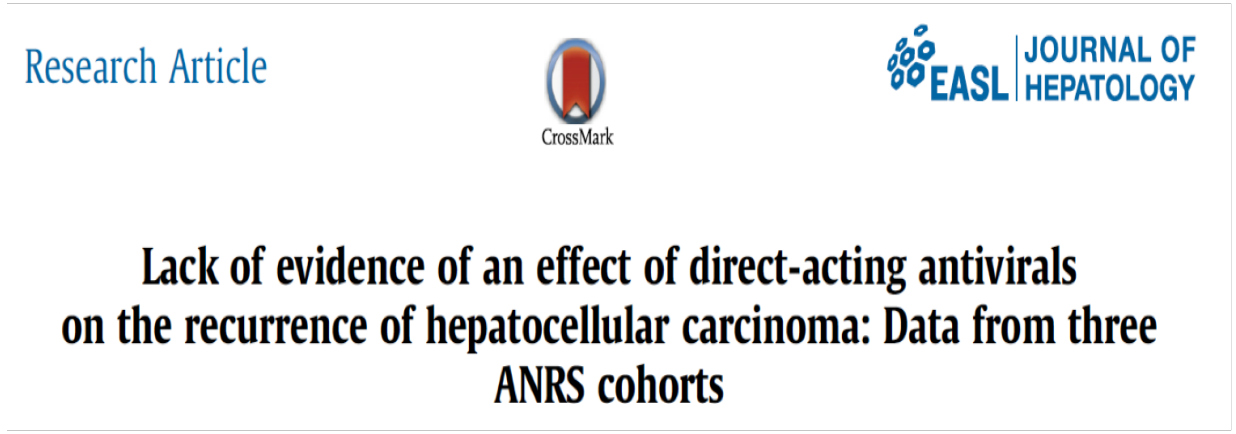
HCC Recurrence After DAA Therapy



- Spanish DAA study of 58 pts with prior HCC
- Treated & responded (resection, TACE)
- 16/58 (27.6%) recurrent HCC
- Median time to recurrence: 3.5 months after DAA start



- French DAA study of 660 pts with prior HCC in 3 cohorts
- I. 267 pts - Recurrent HCC: 0.73 vs 0.66/100 pers.-mos. in DAA vs no-Rx
- II. 79 pts – 7.7% vs 47% HCC recurrence in DAA vs no-Rx group
- III. 314 LT pts got DAA: Recurrent HCC rate 2.2%

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HCC After DAA Therapy

- Is there a causative relation?
  - Do DAAs abrogate immune cancer surveillance?
  - Do DAAs favor rapid expansion of neoplastic cells?
- Is it an illusion?
  - DAAs being used to treat sicker pts that were never treated during the IFN era
  - HCC caused by prior damage not by DAAs
  - Risk shown only in small, uncontrolled studies

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Summary

- HBV reactivation with DAA therapy
  - Risk depends on population being treated
  - Screen for HBsAg in all → consider treatment if +ve
  - Screen for anti-HBc → if +ve, monitor closely
- *De novo* HCC after DAA therapy
  - Not caused by DAAs but likely to see more as sicker pts get treated
  - Continued post-SVR surveillance critical for cirrhotic patients
- HCC recurrence with DAA therapy
  - Conflicting results

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Roundtable/Q&A

Drs. Hubbard, Poordad and Gara

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15 Minute Break

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