Hepatitis B Pre and Post Liver and Renal Transplant

Fred Poordad, MD
Professor of Medicine
University of Texas Health Science Center
VP, Academic and Clinical Affairs
San Antonio, TX

Disclosures

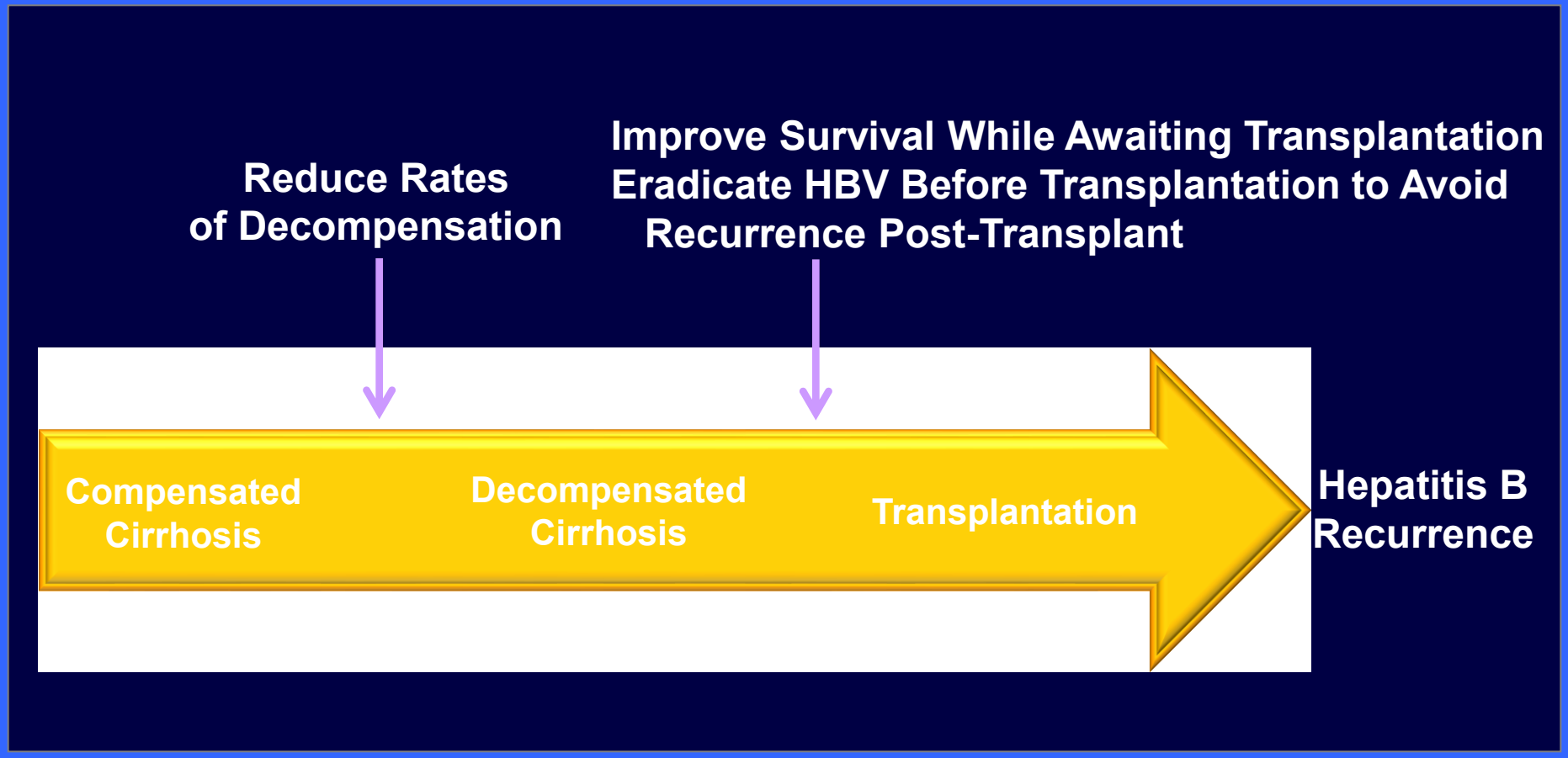
- Dr. Poordad has received grant/research support from AbbVie, Achillion Pharmaceuticals, Anadys Pharmaceuticals, Biolex Therapeutics, Boehringer Ingelheim, Bristol-Myers Squibb, Genentech, Gilead Sciences, GlaxoSmithKline, GlobeImmune, Idenix Pharmaceuticals, Idera Pharmaceuticals, Intercept Pharmaceuticals, Janssen, Medarex, Medtronic, Merck, Novartis, Santaris Pharmaceuticals, Scynexis Pharmaceuticals, Vertex Pharmaceuticals, and ZymoGenetics

Overview of Special HBV Populations

- Decompensated cirrhosis
- Immune suppressed
- Chemotherapy
- Immune tolerant
- Pregnant women
- Liver Transplant
- Renal Transplant

Pre Liver Transplant Population

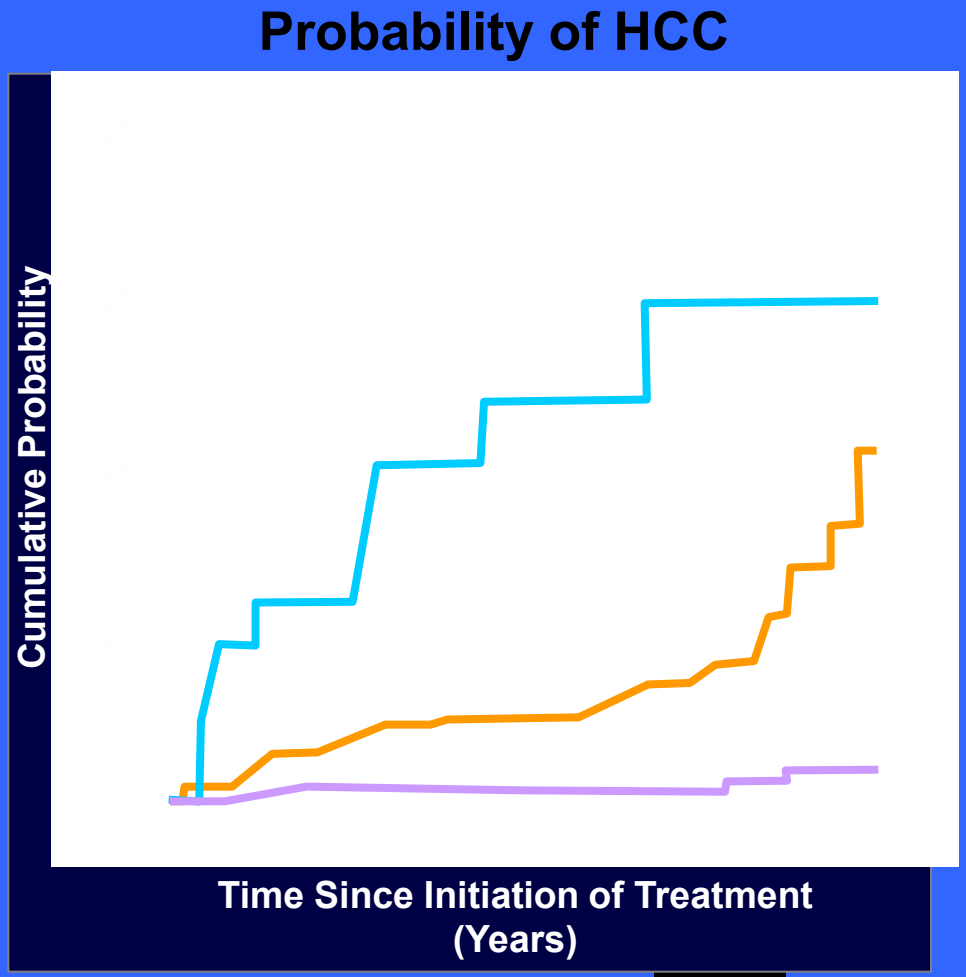
Treatment Goals in HBV-Induced End-Stage Liver Disease



Fink SC, et al. *Nat Rev Gastroenterol Hepatol*. 2011;8:285-295.

HCC Risk in Caucasian, Chronic HBV Patients Treated With Entecavir or Tenofovir DF

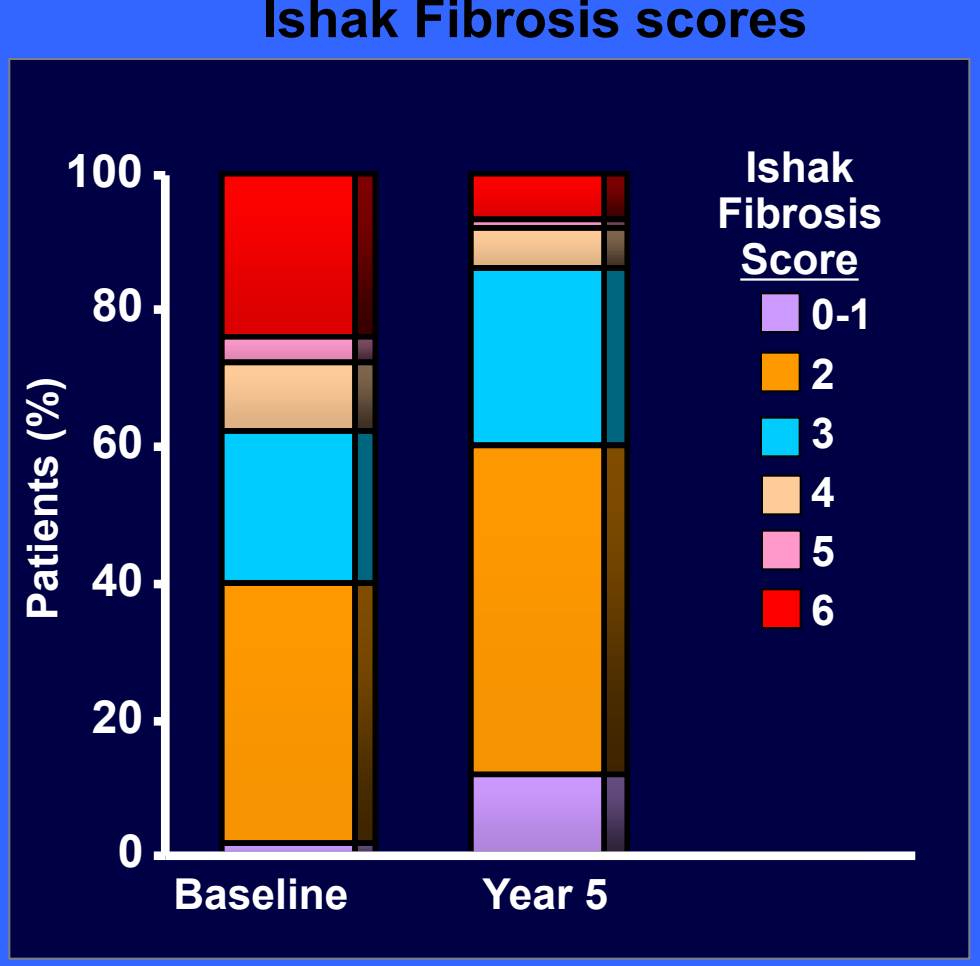
- Multi-country cohort (Greece, Italy, Turkey, Spain, The Netherlands) (n=1231)
  - Chronic HBV with no co-infection, liver transplantation, or HCC
  - Initiated either entecavir (43%) or tenofovir DF (55%)
- HCC 5-year incidence
  - 4.2% at median of 17 months
  - 13.5 new HCC cases/1000 person-years
- Strongest HCC risk factors
  - Decompensated liver disease (HR: 2.78; *P*=0.019), lower platelet count (HR: 0.97; *P*=0.002), older age (HR: 1.05; *P*=0.12)
- Asian-based HCC risk scores may not be applicable to Caucasians with chronic HBV



Papatheodoridis GV, et al. *Hepatology.* 2013;58(suppl 1):302A-303A. Abstract 190.

Study 103 and 102: Tenofovir DF and Regression of Histologic Cirrhosis at Week 240

- **There was a progressive decrease in patients with cirrhosis at baseline to year 5**
- **74% of patients with cirrhosis at baseline treated with tenofovir DF were no longer cirrhotic at year 5**



Paired biopsies at baseline and 240 weeks (n=344).

Marcellin P, et al. *Lancet.* 2013;38:468-475.

Chronic Hepatitis Cohort Study: HBV Therapy and Incidence of HCC

- **Four, large US healthcare systems (n=2671) (1992-2011)**
  - **EHR data: virologic laboratory confirmation and/or ICD9 codes consistent with chronic, and confirmation of chronic HBV with chart abstraction**
- **Antiviral therapy initiated ≥1 year before diagnosis of HCC (n=820)**
- **Time to HCC incidence**
  - **EHR ICD9 codes confirmed via chart review and/or tumor registry report as primary a primary liver tumor**

Baseline Characteristics	Patients (n=2671)
Age (%)	
≤40 years	28
>40 to <50 years	24
50 to <60 years	25
≥60 years	23
Male (%)	56
Asian ethnicity (%)	49
Charlson/Deyo comorbidity index score (%)	
0/1	75/17
2 or 3	9
ALT status (%)	
Abnormal/normal	28/55
Antiviral therapy (%)	
Nucleos(t)ide	85
Interferon	4
Both	10

Gordon SC, et al. *Clin Gastroenterol Hepatol.* 2014.

Chronic Hepatitis Cohort Study: Predictors of HCC

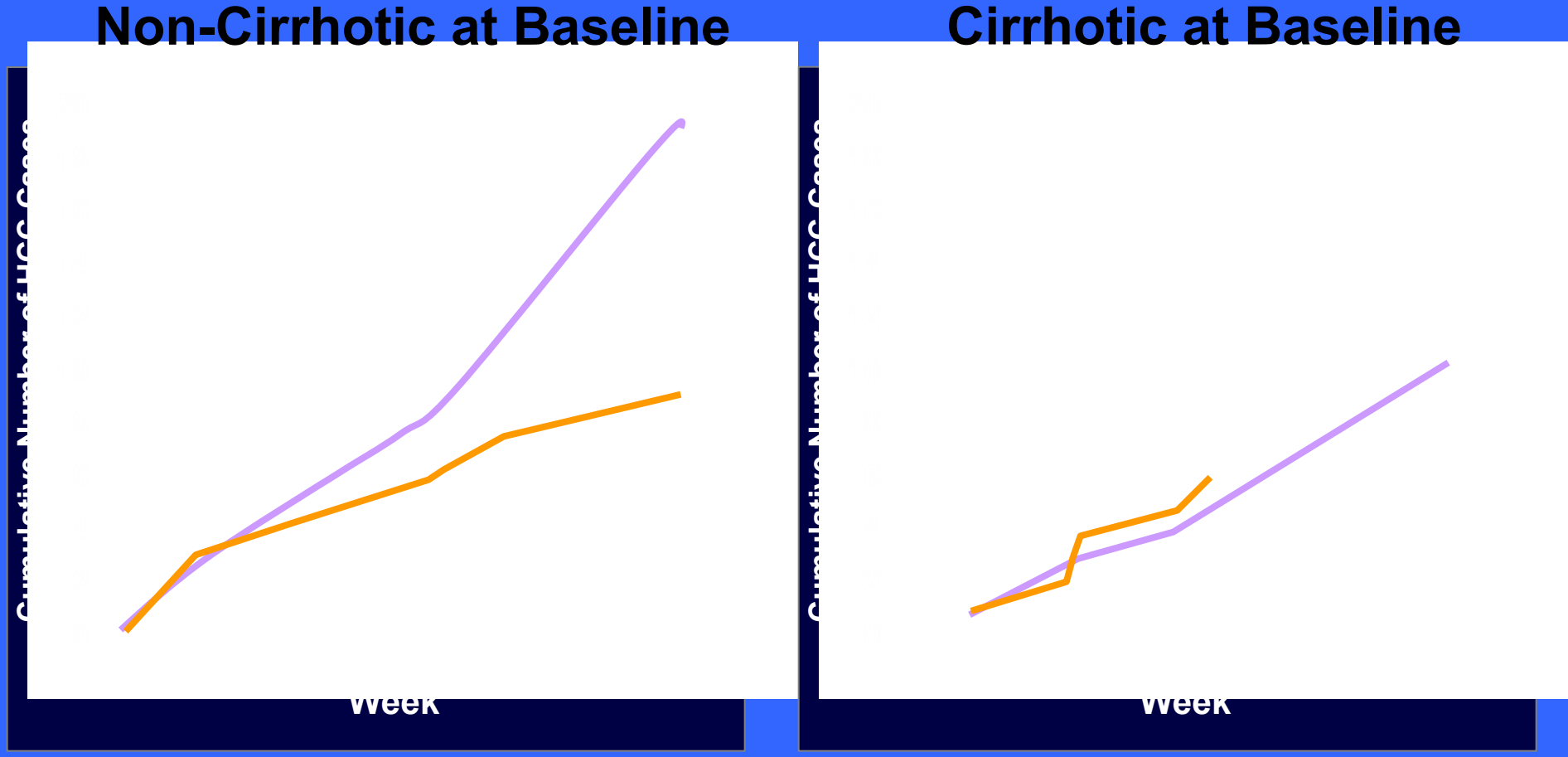
- **HBV antiviral therapy was associated with a 50% decreased risk of developing hepatocellular carcinoma with chronic HBV infection**
  - **Population analyzed consisted of patients across a spectrum of disease severity**
  - **Corroborate evidence from previous studies that suggest a reduced risk of HCC with suppression of HBV DNA replication**
- **Need for prospective studies to substantiate these findings**

	Hazard Ratio for HCC (95% CI)
Antiviral therapy (yes versus no)	0.50* (0.35-0.72)
Age (versus ≤40 years)	
40 to <50 years	5.51† (1.74-17.42)
50 to <60 years	5.55* (1.78-17.28)
≥60 years	13.77* (4.54-41.76)
Charlson/Deyo comorbidity index (versus 0)	
1	1.38 (0.87-2.19)
2 or 3	2.15* (1.46-3.16)
Male (versus female)	1.94* (1.30-2.87)

*P=0.004 and †P<0.001.

Gordon SC, et al. *Clin Gastroenterol Hepatol.* 2014.

Observed Versus Predicted HCC Cases During Long-Term Tenofovir DF Therapy



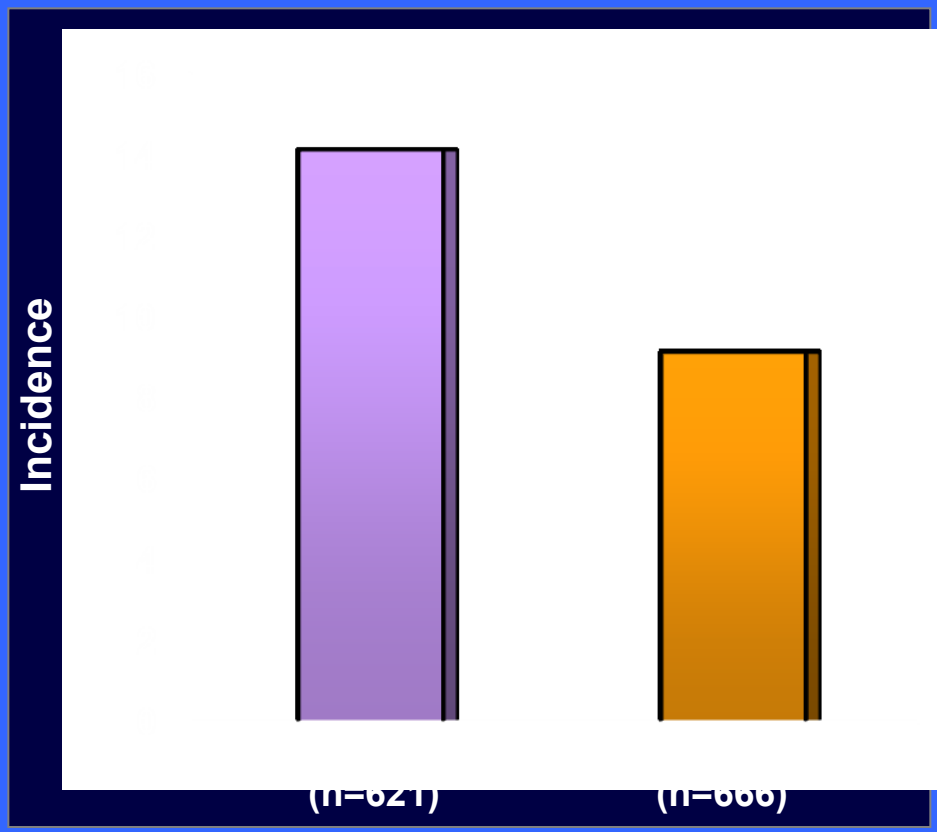
SIR: standard incidence ratios.
***P*<0.05 versus predicted HCC cases.**

Kim WR, et al. *J Hepatol.* 2013;58(suppl 1):S19. Abstract 43.

C-TEAM Study: Long-Term Entecavir and Incidence of HCC in Chronic HBV Infection

- **Multi-center observational cohort (17 Taiwanese academic centers)**
  - **HBsAg positive, anti-HCV negative**
  - **Treatment-naïve, no HCC development in first year**
  - **HBV DNA ≥2000 IU/mL**
  - **Child A cirrhosis (METAVIR F4 or Ishak ≥5)**
- **Study arms**
  - **Entecavir 0.5 mg (2006-2013; n=666)**
    - **Follow-up: 2.6 years**
    - **HCC cases: 16**
  - **Historical controls (1985-195; n=621)**
    - **Untreated**
    - **Follow-up: 8.5 years**
    - **HCC cases: 141**

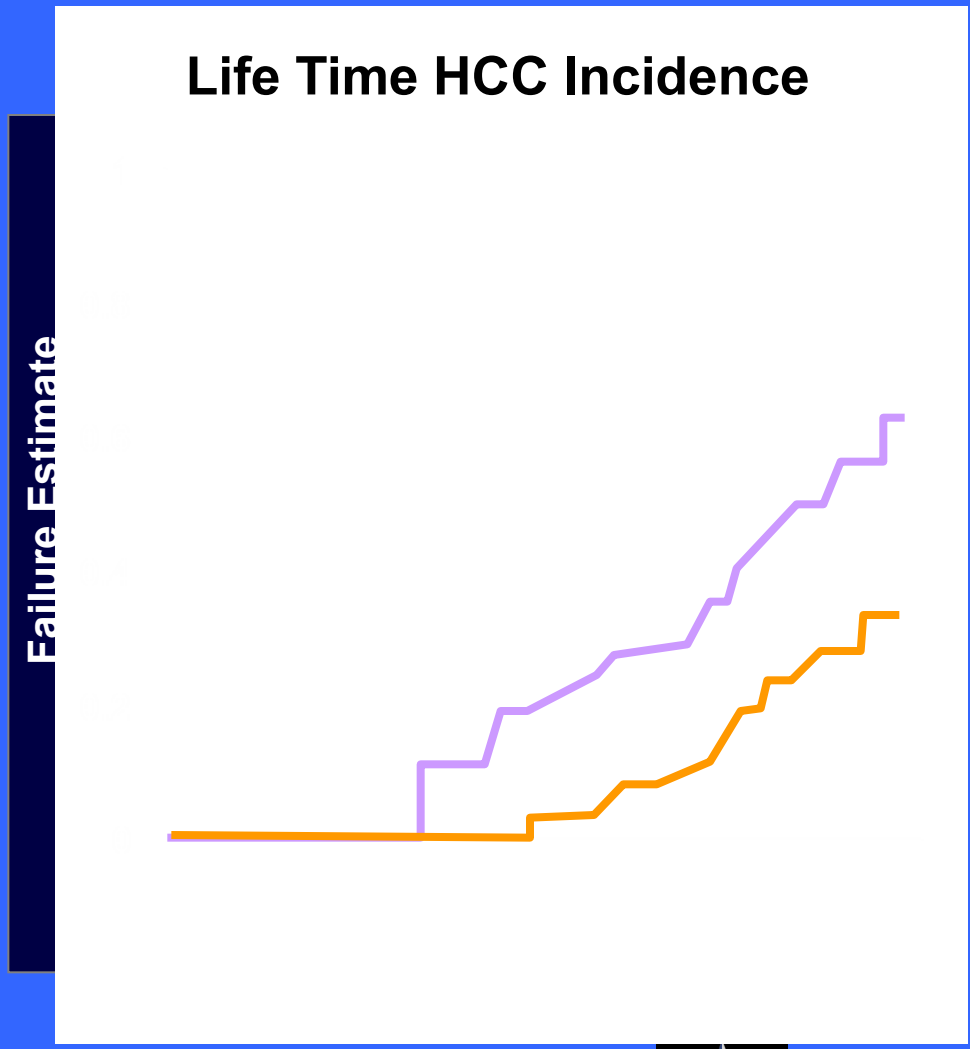
Interim Analysis: HCC Incidence (1st 3 Years)



Su T-H, et al. *Hepatology.* 2013;58(suppl 1):301A-302A. Abstract 189.

C-TEAM Study (Interim Analysis): Impact of Entecavir on HCC and Secondary Outcomes

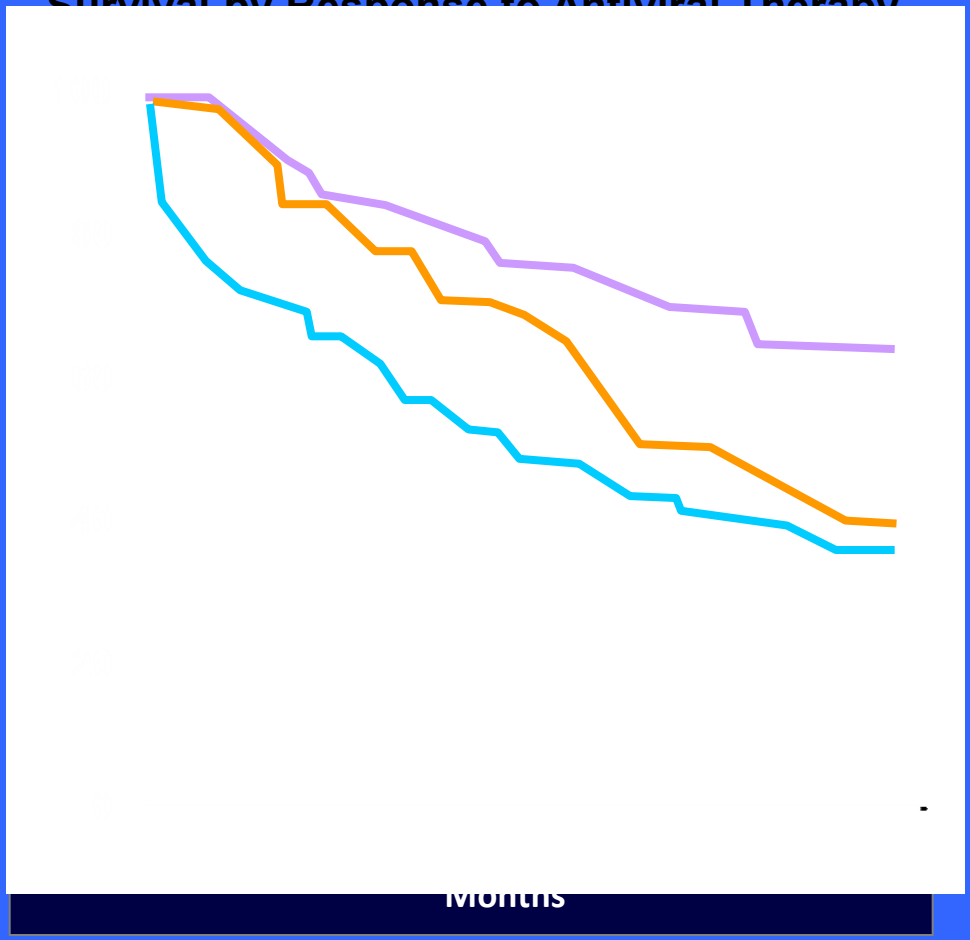
- **Secondary outcomes the 1st 3 years**
  - **No difference between the entecavir and historical control arms**
    - **Esophageal varices/gastric varices, hepatic encephalopathy, spontaneous bacterial peritonitis, liver-related mortality**
- **Limitations of interim analysis**
  - **Follow-up not yet long enough**
  - **Entecavir arm appeared to have less compensated cirrhosis at baseline**
- **Prolonged entecavir therapy possibly reduced HCC development in HBV-related compensated cirrhotic patients**
  - **Longer follow-up is needed to evaluate impact on cirrhotic complications**



Su T-H, et al. *Hepatology.* 2013;58(suppl 1):301A-302A. Abstract 189.

Korean Cohort: Antiviral Therapy and Survival in HBV-Related Decompensated Cirrhosis

- Multi-center, prospective cohort (2005-2012)
  - Confirmed onset time and mode of of HBV-related decompensated cirrhosis (n=707)
  - Antiviral therapy (60%)
    - Lamivudine, entecavir, adefovir, clevudine, telbivudine
  - Primary endpoint
    - Survival from 1st decompensation to liver transplantation or death
- Sustained viral remission with antiviral therapy in patients with HBV-related decompensation leads to improved long-term survival



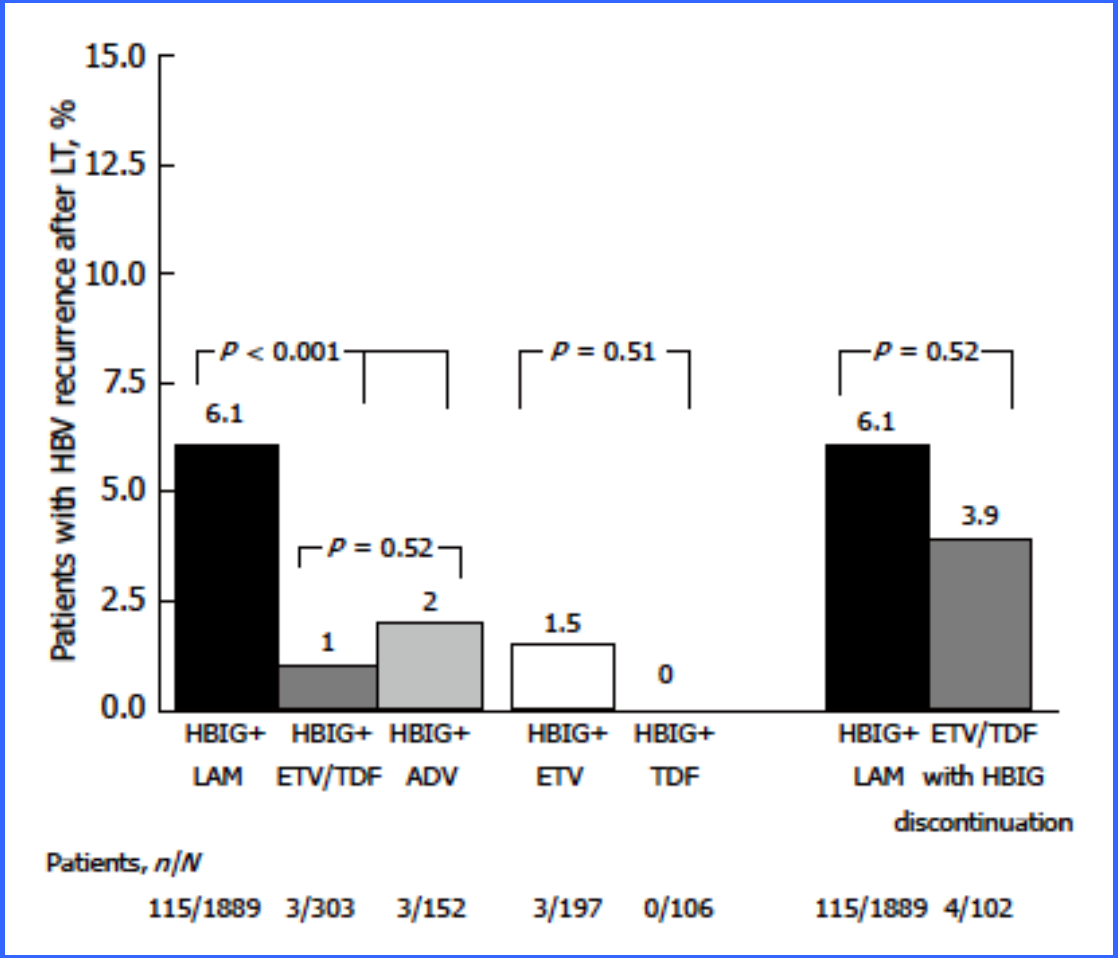
***P*<0.001 versus untreated and *P*=0.01 versus non-sustained suppression.**

Jang JW, et al. *Hepatology.* 2013;58(suppl 1):631A. Abstract 892.

Regimens Post Liver Transplant

- HBIg
- NA
- Combination
- Accelerated Double Dose Vaccination

Recurrence Rates Vary by Regimen

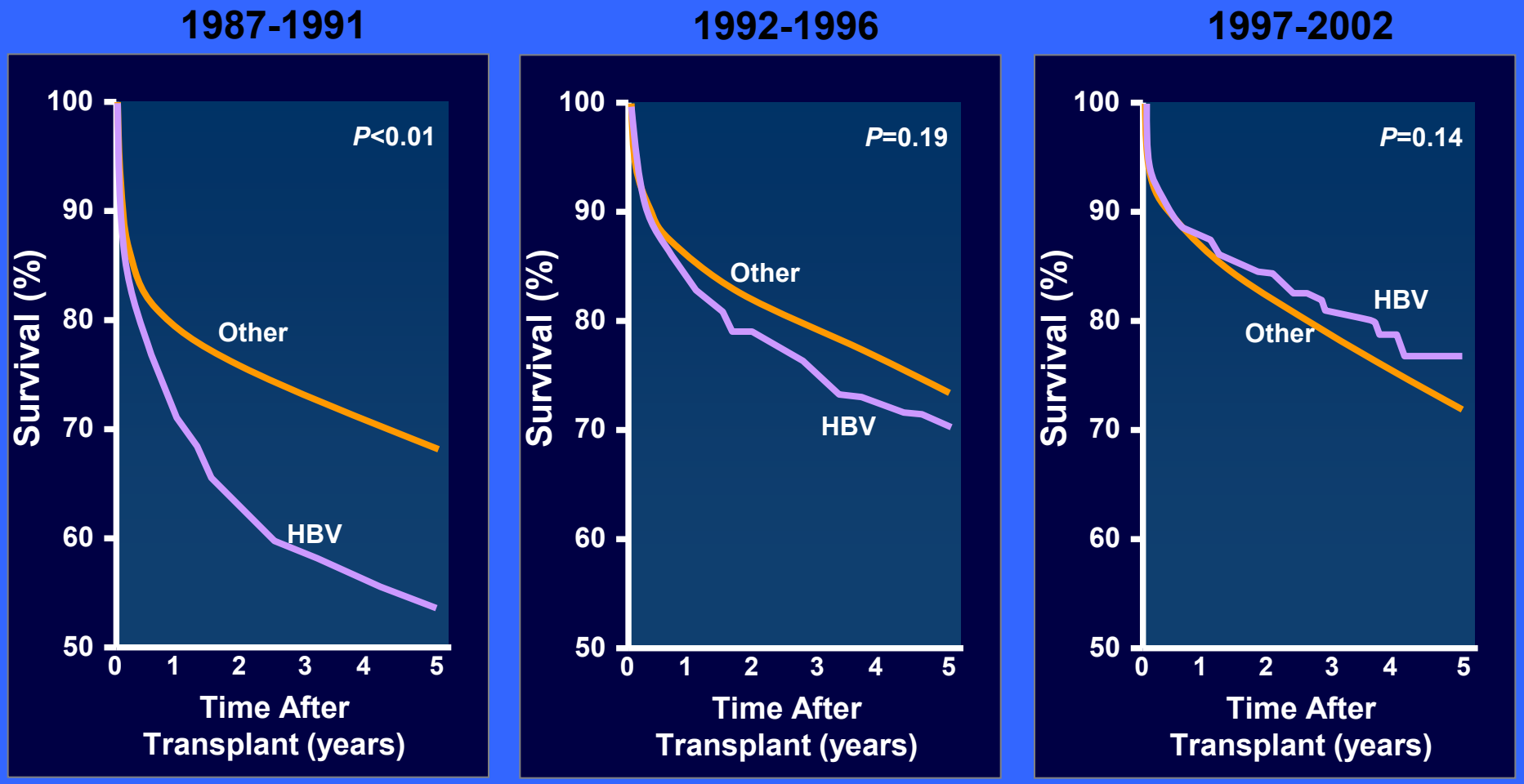


HBV Reinfection After Liver Transplantation

- HBV reinfection after liver transplantation
  - Patients at high-risk for reinfection
    - Cirrhosis (HBeAg positive or negative) plus high HBV DNA levels
    - Antiviral resistance prior to transplantation
  - Patients at low-risk for reinfection
    - Fulminant HBV or co-infection with HDV
    - Cirrhotic, HBeAg negative with low serum HBV DNA levels
  - What is the cut-off for high versus low HBV DNA level?
    - >5 or >3 to 4 $\log_{10}$ copies/mL
- De novo HBV infection/reactivation following liver transplantation
  - Up to 10% in HBsAg-negative liver recipients
  - Risk higher when donors are HBsAg negative but anti-HBc positive

Lok AS. 2011UpToDate®.
Vargas HE, et al. *Liver Transpl.* 2002;8:2-9.
Omata M. *Hepatology.* 1990;12:364-366.
Marzano A, et al. *Liver Transpl.* 2005;11:402-409.

Survival After Liver Transplantation in Recipients With HBV and Other Diagnoses



Kim WR, et al. *Liver Transpl.* 2004;10:968-974.

HBV Prophylaxis for Recipients of Hepatitis B Core Antibody-Positive Liver Grafts

- **Immunoprophylaxis regimens after liver transplantation**
  - **Lamivudine with no HBIG (n=6 studies)**
  - **Lamivudine + HBIG (n=7 studies)**
- **Prevention of de novo flares in core positive livers**
- **Adjunct HBIG and lamivudine alone demonstrated similar efficacy**

		Number of Patients	
HBsAg	Anti-HBc	Lamivudine Alone	Lamivudine + HBIG
+	+	0/13	0/7
+	–	0/25	1/7
–	+	1/17	3/20
–	–	1/18	0/76
	Total	2.3%	3.6%

Saab S, et al. *Liver Transpl.* 2010;16:300-307.

Hong Kong Cohort: Oral Nucleosides Without HBIG After Liver Transplantation

- **Single-center cohort study (2003-2011)**
  - Chronic HBV patients undergoing liver transplantation (n=362)
  - HBeAg-positive ≥6 months at time of liver transplantation
- **Antiviral prophylaxis**
  - 2003-2007: lamivudine 100 mg/day
  - 2007-2011: entecavir 0.5 mg/day
  - Patients with rt204 mutation: combination therapy*
  - All patients: HBIG not used before, during, or after transplantation
- **Patients followed-up at 3 month intervals (or shorter)**
  - Virologic rebound (HBV DNA ≥1 $\log_{10}$ IU/mL)

Baseline Characteristics

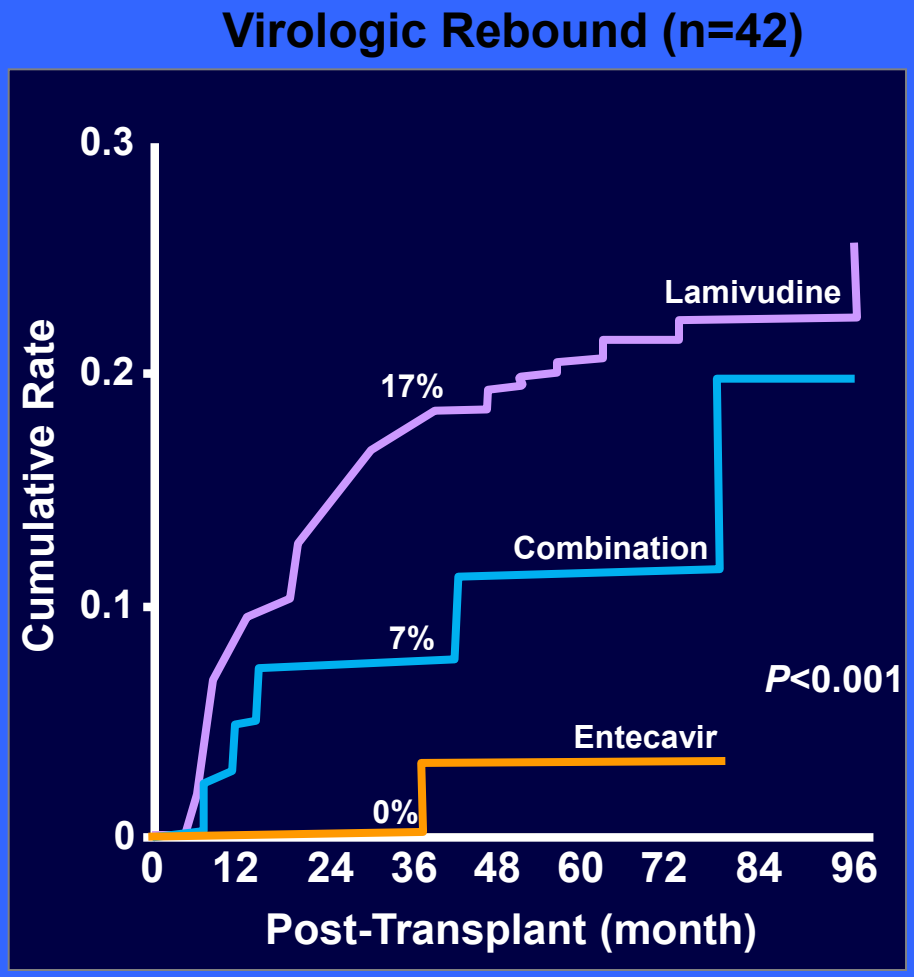
	LVD (n=176)	ETV (n=142)	Combination (n=44)
Age (years)	51	52	55
Male (%)	84	85	84
MELD score	26	28	17 (*P*=0.002)
Transplant type (%)			
Deceased donor	34	44	45
Living donor	66	56	55
Pre-transplant			
Nucleosides (%)	30	58	98 (*P*<0.001)
HBeAg positive (%)	29	25	57 (*P*<0.001)
HBV DNA ($\log_{10}$ IU/mL)	3.6	2.7	3.0 (*P*=0.011)
Donor anti-HBs positive (%)	63	67	74

*Mostly lamivudine + adefovir.

Fung J, et al. *Am J Gastroenterol.* 2013;108:942-948.

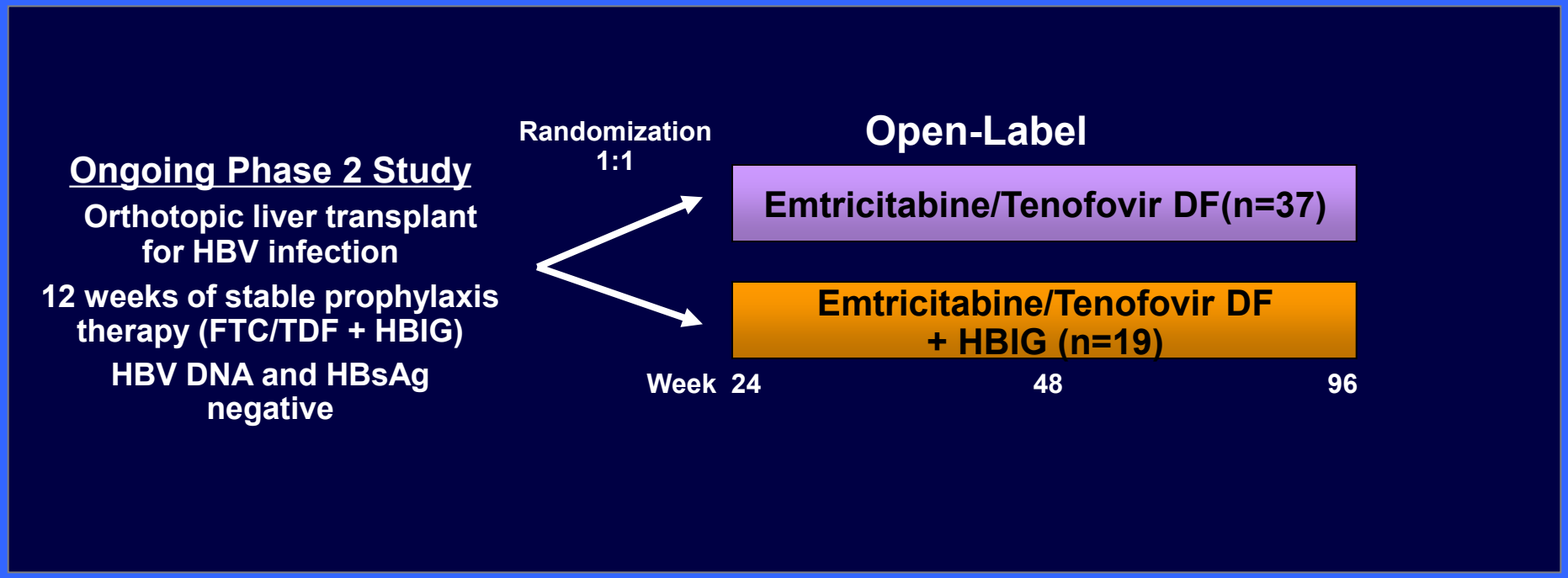
Hong Kong Cohort: Long-Term Survival and Virologic Rebound

- Long-term survival: 83% at 8 years
- Relative risk of virologic rebound after liver transplantation
  - Lamivudine: 15.21 (2.04-113.29)
  - HCC: 7.48 (1.84-30.37)
  - HBV DNA $\geq$3 $\log_{10}$ IU/mL: 4.17 (1.81-9.62)
- Use of antiviral with high barrier to resistance is recommended
- Significance of HBsAg status post-liver transplantation remains to be determined



Fung J, et al. *Am J Gastroenterol.* 2013;108:942-948.

Study 107: Emtricitabine/Tenofovir DF and HBIG Withdrawal in Post-Orthotopic Liver Transplantation



Other eligibility criteria: age 18-75 years; no chronic HBV recurrence after transplant; creatinine clearance ≥40 mL/min; no prior tenofovir or emtricitabine/tenofovir treatment after treatment; HCV, HIV, and HDV sero-negative

Teperman L, et al. *Liver Transplant.* 2011;17(suppl S1):S94. Abstract O-50.

Study 107: Emtricitabine/Tenofovir DF and HBIG Withdrawal in Post-Orthotopic Liver Transplantation: Week 96 Results

	Emtricitabine/ Tenofovir DF (n=18)	Emtricitabine/ Tenofovir DF + HBIG (n=19)
HBV DNA negative (%)	100	100
Remained HBsAg negative (%)	100	100
Evidence of HBV recurrence (%)	0	0
Re-initiation of HBIG (%)	0	--
Resistance to emtricitabine/tenofovir DF (%)	0	0
Serous adverse events (%)	17	32
Grade 3/4 laboratory abnormalities (%)		
Hyperglycemia	0	0
Hypernatremia	8	5
Glucosuria	0	5
Prothrombin time	0	11
Transaminitis	0	11
Creatine kinase	0	5
Hyperbilirubinemia	0	5

Teperman L, et al. *Liver Transplant.* 2011;17(suppl S1):S94. Abstract O-50.

HBV Prophylaxis: Liver Transplantation

- Availability of HBIG and antiviral therapy
  - Outcomes of liver transplantation for end-stage HBV disease are now similar to or better than that for other indications
- Treatment goals
  - Reverse cirrhosis complications and need for transplant (ideal)
  - Suppress HBV DNA to the lowest possible level before transplantation

Lok AS, et al. *Hepatology*. 2009;50:661-662. Available at: http://www.aasld.org.
Keeffe EB, et al. *Clin Gastroenterol Hepatol.* 2008;6:1315-1341.

HBV Prophylaxis in Liver Transplantation: Prevention of HBV Reinfection

- No consensus on the most appropriate initial antiviral therapy in this setting
- High-risk patients
  - Nucleoside-naïve patients: entecavir or tenofovir DF
  - Lamivudine-resistant: adefovir or tenofovir DF + lamivudine
  - Monitor regularly, initiate HBIG at the time of transplant and continue antiviral therapy
- Low-risk patients
  - Pre-transplant: benefit of antiviral therapy not established
  - Post-transplant: continue or initiate antiviral therapy
  - HBIG: role is unclear

Lok AS. 2011UpToDate®.
Saab S, et al. *Liver Transpl.* 2010;16:300-307.

HBV Prophylaxis in Liver Transplantation: Treatment of HBV Recurrence

- No consensus on the most appropriate initial antiviral therapy in this setting
- Treatment depends on prior prophylactic therapy and presence of drug-resistant mutations
  - No prophylaxis or HBIG
    - Tenofovir DF or entecavir
  - Prior lamivudine (most likely lamivudine resistant)
    - Combination therapy with tenofovir DF

Lok AS. 2011UpToDate®.
Saab S, et al. *Liver Transpl.* 2010;16:300-307.

Renal Disease and HBV

- Nephropathies
  - MGN
  - MPGN
  - IgA glomerulopathy
  - Polyarteritis nodosa
- Dialysis
- Renal transplant recipients

Renal Dose Adjustment for NAs

CrCl (mL/min)	Lamivudine	Telbivudine	Adefovir	Entecavir[1]	Tenofovir
⩾ 50	100 mg/d	600 mg/d	10 mg/d	0.5 mg/d	245 mg/d
30-49	50 mg/d	600 mg/2nd day	10 mg/2nd day	0.25 mg/d	245 mg/2nd day
10-29	25 mg/d	600 mg/3rd day	10 mg/3rd day	0.15 mg/d	245 mg/3rd-4th day
< 5-10 or HD[2]	10 mg/d	600 mg/3rd-4th day	10 mg/wk	0.5 mg/wk	245 mg/wk[3]

Pre Renal Transplant Evaluation

- 0-20% prevalence of HBV in HD populations
- HBV DNA
- eAg status
- HDV assessment
- Fibrosis staging
  - Biopsy still the gold standard
  - Elastography and non invasive serum markers with normal imaging and biochemical panels

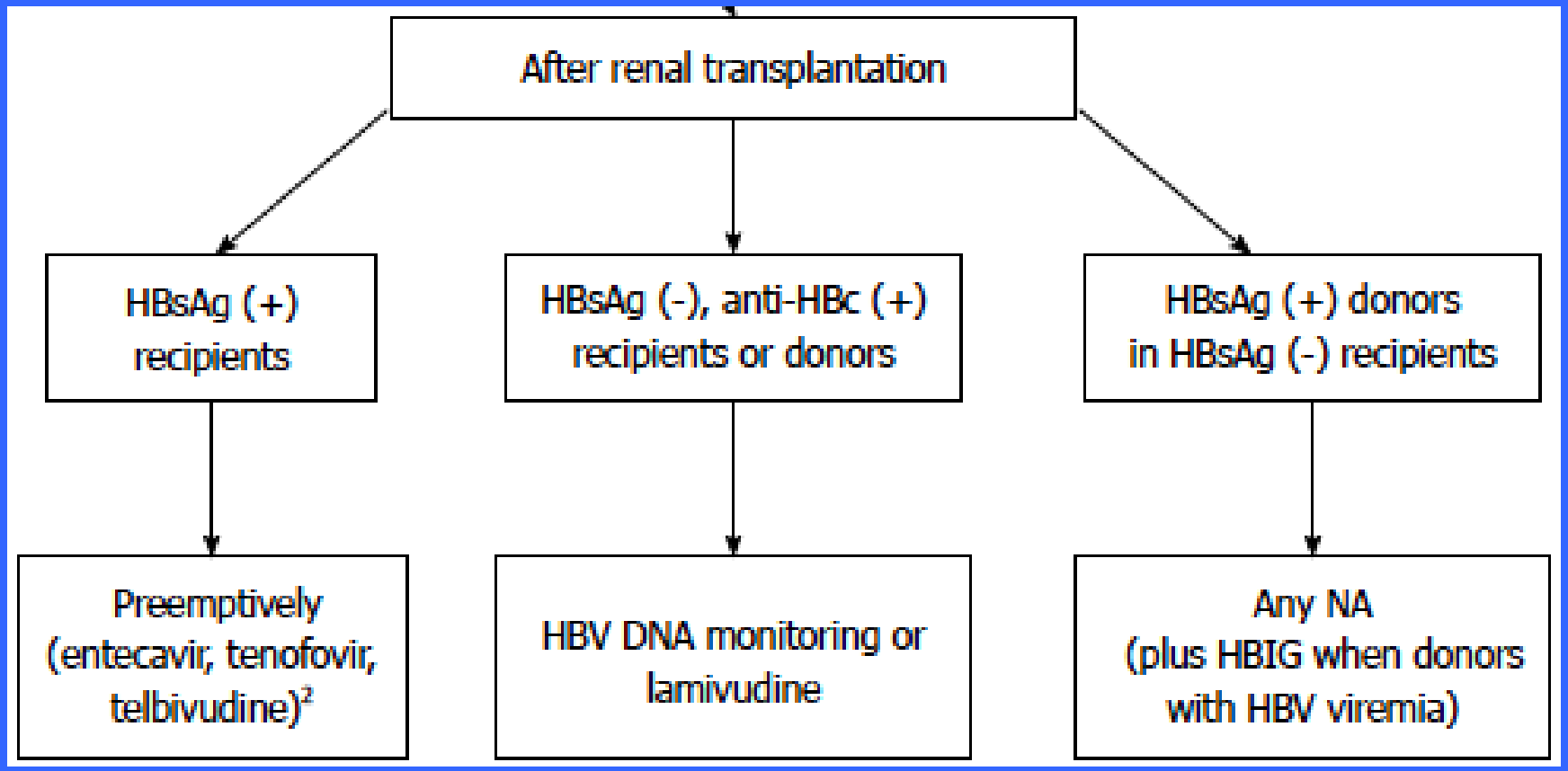
Urbanek, Kidney Blood Press Res 2012;35:454-467

Prophylaxis Post Transplant

- sAg positive
  - Long term therapy recommended

- cAb positive recipient with or without sAb titers
  - No clear data on risk of reactivation
  - Prophylaxis not routinely given, but can be considered
- cAb positive donor
  - Can monitor or give NA prophylaxis

Post Renal Transplant HBV Therapy



Cholangitas, E, et al. World J Gastroenterol 2015

Summary

- Hepatitis B in renal and liver transplant population can be safely and effectively managed
- Renal function should be monitored, esp with nucleotide analogs
- Long term monitoring of HBV DNA and liver chemistries suggested

Conclusion

- HBV in the pre transplant setting must be treated to full suppression if possible
- Recurrence in active infection post transplant can be achieved with NA alone, but perhaps short course HBIG in high risk patients
- Donor positive organs into negative recipients should generally be prophylaxed if close monitoring not feasible