End-Stage Liver Disease in HIV Liver Transplantation

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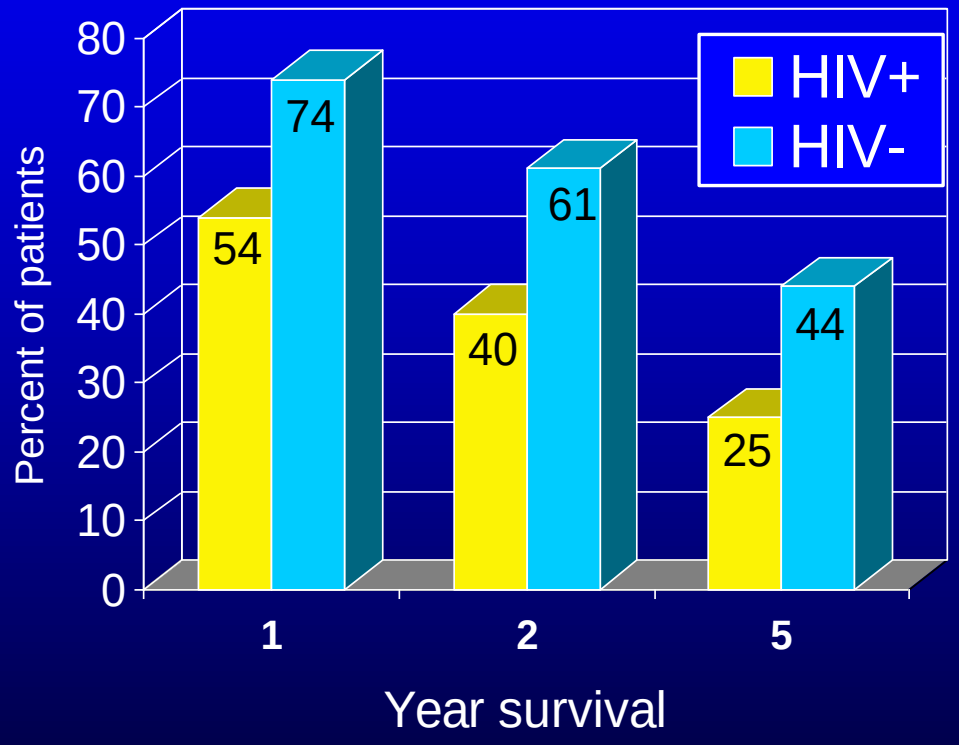
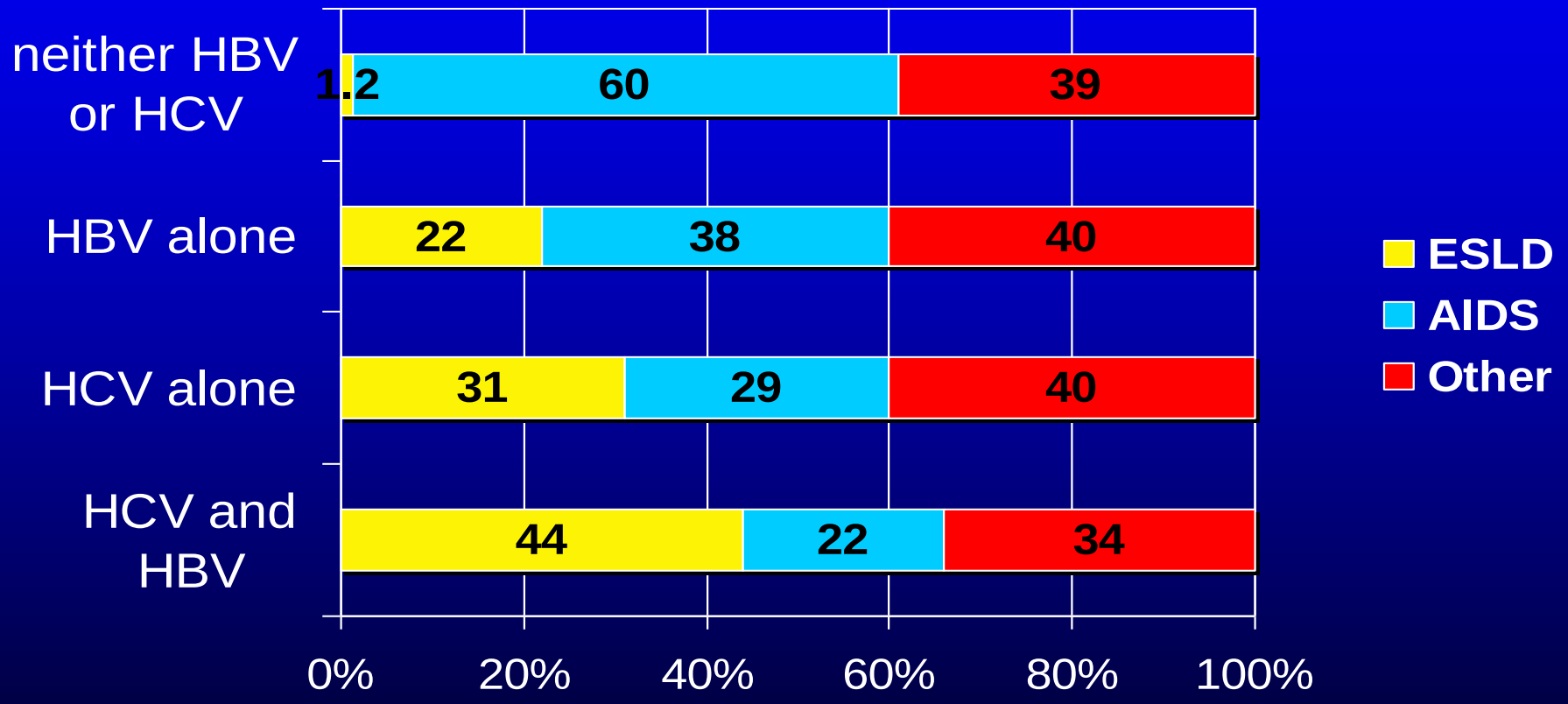
Survival Time from First Liver Decompensation to Death in HCV



- Death during study
  - 366/1037 HCV
  - 100/180 HIV/HCV
- Risk factors for death:
  - HIV
  - Baseline CTP
  - MELD >13
  - Age

Pineda, Hepatology 2005

Proportion of deaths due to ESLD in HIV+



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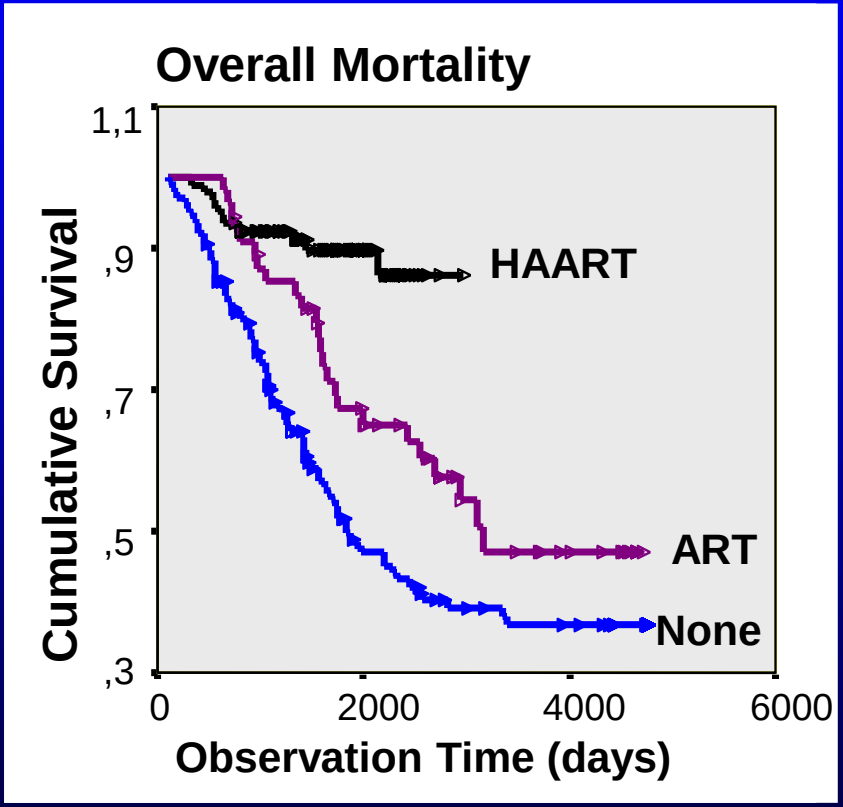
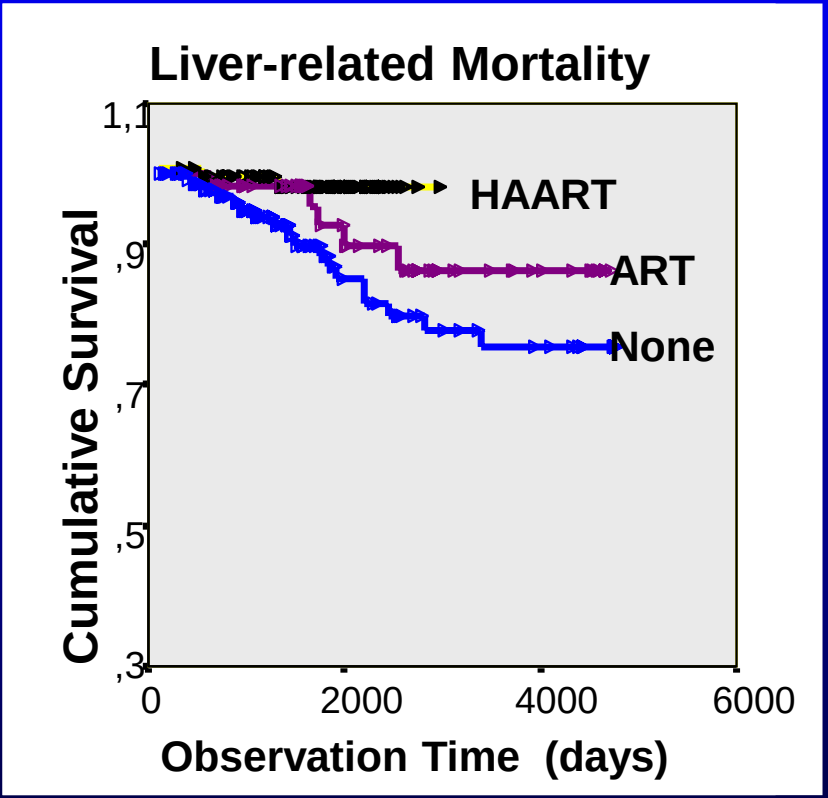
Salmon-Ceron, J Hepatol 2005

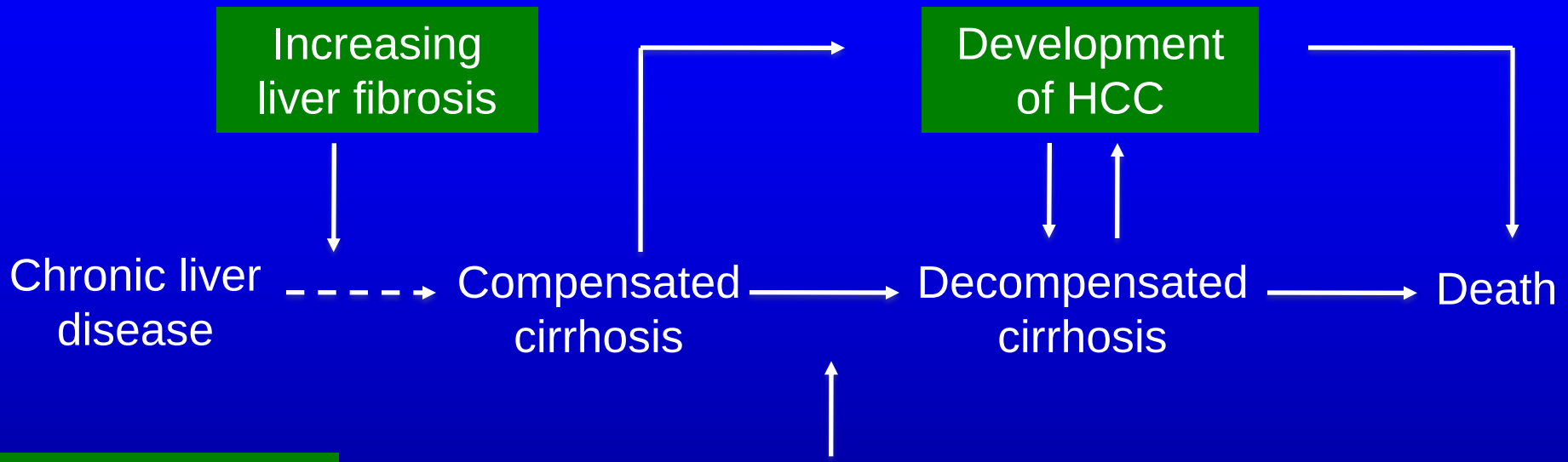
HIV immune reconstitution also improves survival from HCV liver disease





Qurishi, Lancet 2003

Natural History of ESLD



HCC, hepatocellular carcinoma; NASH, nonalcoholic steacohepatitis

Garcia Tsao CCO Hepatitis.com 2008

Natural history of ESLD

- Transition to decompensated cirrhosis: 5% to 7% of patients per year.
- Best predictor of decompensation: hepatic venous pressure gradient (HVPG) > 10 mm Hg
- HCC
  - can trigger decompensation
  - predictor of death in decompensated cirrhosis
- Tools for predicting disease severity and death in decompensated cirrhosis
  - Child-Turcotte-Pugh (CTP) score
  - Model for End-Stage Liver Disease (MELD) score

D'Amico 2006

Child-Pugh-Turcotte Score

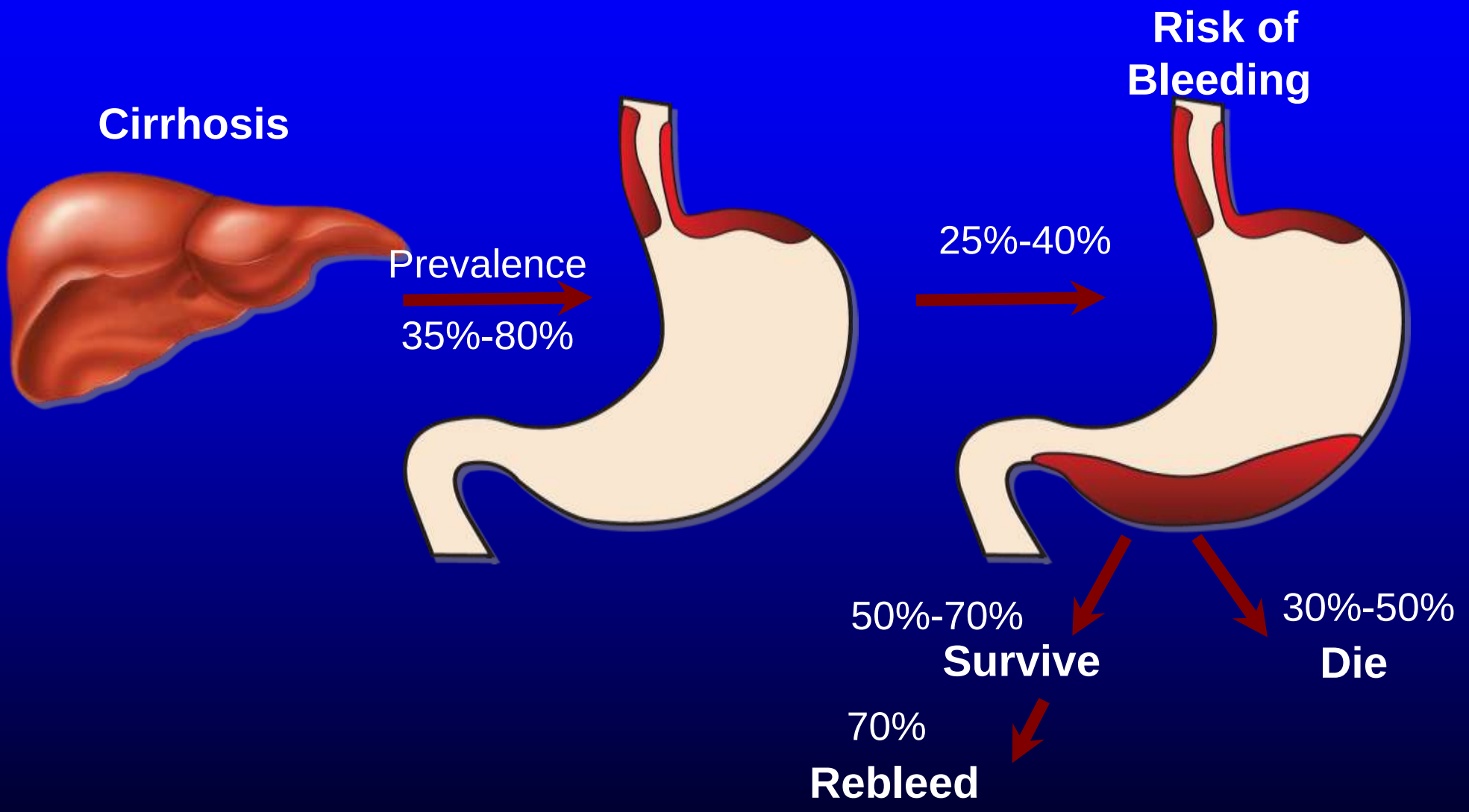
Points	1 (normal)	2	3
Hepatic encephalopathy	None	1-2	3-4
Ascites	None	slight	mod
Bilirubin	<2	2-3	>3
Albumin	>3.5	2.8-3.5	<2.8
PT	<4 secs ↑	4-6 secs	>6 secs
or INR	<1.7	1.7-2.3	>2.3

A: 5-6; B: 7-9; C: > 9

MELD: Model for End-Stage Liver Disease

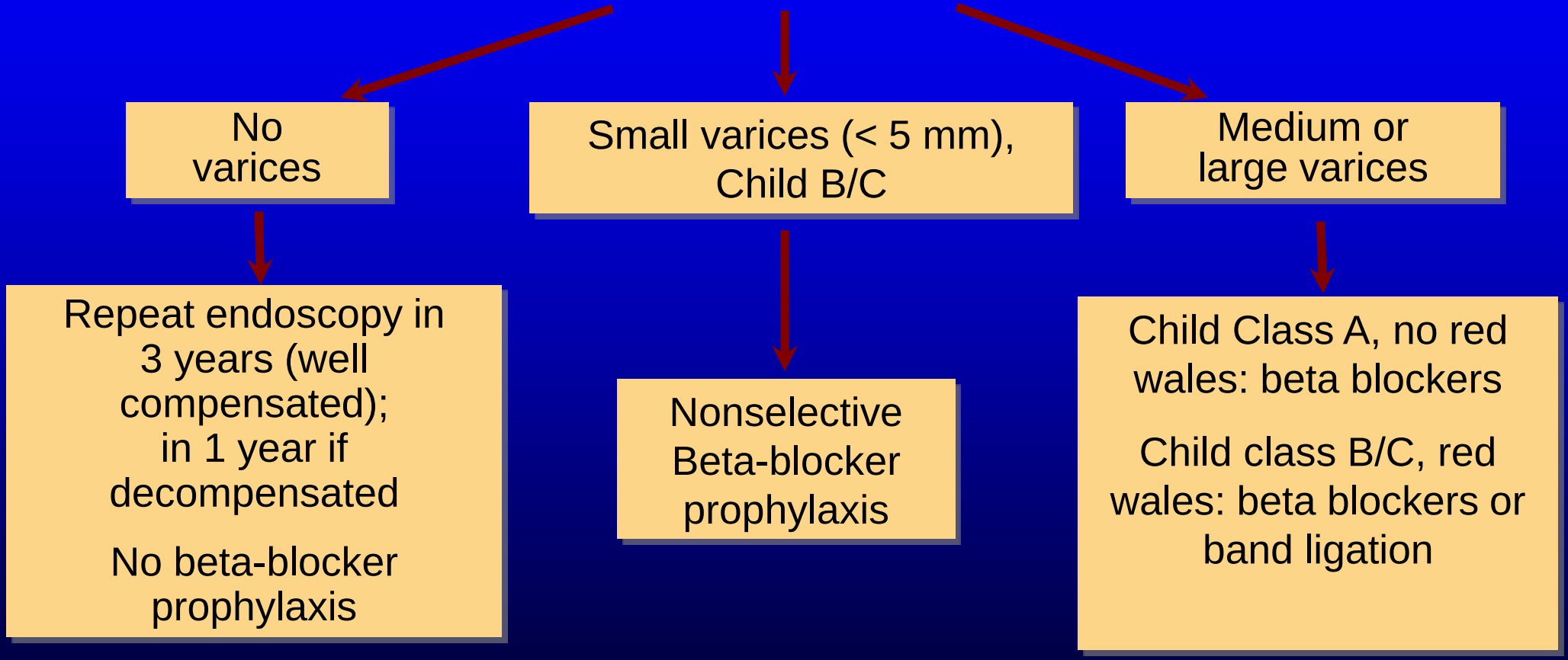
• Bilirubin	2	5	5	5
• INR	1.1	2.0	2.0	3.0
• Creatinine	1.0	1.0	2.0	2.0
• MELD	10	20	27	31

Risk of Bleeding from Esophageal Varices



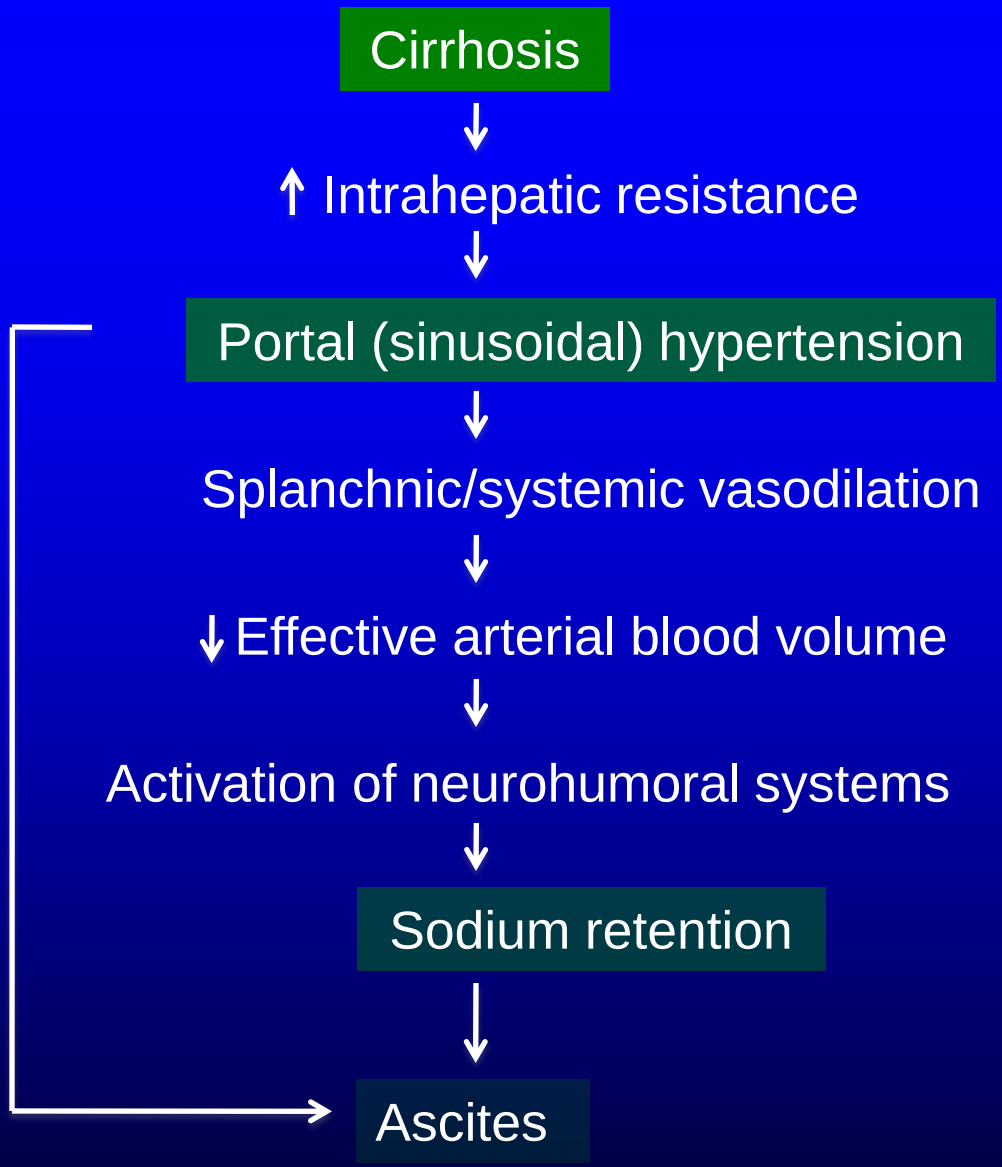
Variceal Surveillance

All cirrhotics require Esophagogastroduodenoscopy



Garcia-Tsao G, et al. Hepatology. 2007;46:932-938.

Ascites: Pathogenesis and Mechanism of Action of Different Therapies



Liver transplantation

TIPS

Albumin

PVS

Spironolactone ± Furosemide*

Paracentesis (LVP)

PVS

LVP, large-volume paracentesis; PVS, peritoneovenous shunt.

*Furosemide should only be used in conjunction with spironolactone.

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Stages of ascites

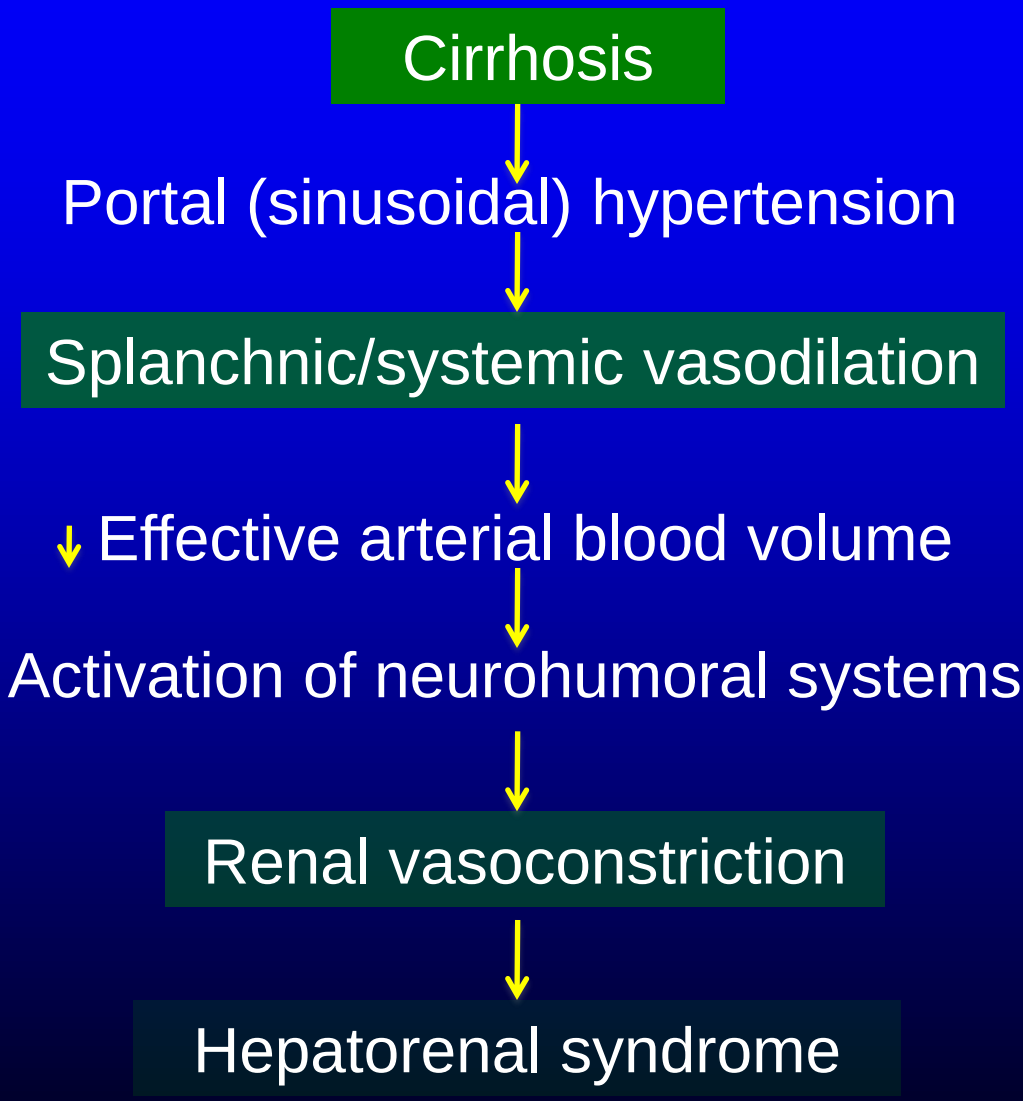
- Diuretic-responsive ascites
- Refractory ascites
- Hyponatremia
- Hepatorenal syndrome (HRS)

Each stage reflects a more deranged circulatory state.

Treatment of ascites

- Diuretic-responsive ascites
  - Sodium restriction
  - Spironolactone (75-100 mg) and furosemide (20-40 mg)
- Refractory ascites
  - Large volume paracentesis with 25% albumin (50 cc/L)
  - TIPS- higher OLT free survival, higher PSE
  - TIPS HVP <12 mm Hg
  - Albumin, midodrine and octreotide- vasoconstriction
  - Experimental: clonidine, vasopression 2 R antagonists
- Hyponatremia
  - Fluid restriction, vasopression 2R antagonists, midodrine

Pathogenesis Hepatorenal syndrome: HRS



Hepatorenal syndrome (HRS)

- Acute renal failure occurs in 14% to 25% of hospitalized patients with cirrhosis
- Most commonly prerenal failure (accounting for 60% to 80% of the cases)
  - HRS is a form of prerenal failure
- Then acute tubular necrosis (20% to 40%)

Hepatorenal syndrome

- results from vasodilatation and marked reduction in effective arterial blood volume leading to renal vasoconstriction
- occurs in patients with refractory ascites and/or hyponatremia.
- Type 1 HRS: rapidly progressive renal failure in 2 weeks
  - with a doubling of serum creatinine to a level > 2.5 mg/dL
  - or halving creatinine clearance to < 20 mL/min
  - Prognosis: < 50% survival at 1 month

HRS-contd

- Type 2 HRS: slowly progressive
  - increase in serum creatinine level to > 1.5 mg/dL
  - a creatinine clearance of < 40 mL/mi
  - or a urine sodium < 10 mEq/d
  - associated with ascites that is unresponsive to diuretic medications
  - median survival: ~ 6 months

HRS treatment

- OLT
- Midodrine and octreotide
  - HRS due to extreme splanchnic and systemic vasodilatation
  - Drugs → vasoconstriction
- Albumin to increase intravascular volume

Spontaneous bacterial peritonitis (SBP)

- Most common type of bacterial infection in hospitalized cirrhotic patients
- Clinical suspicion:
  - <50%: fever, abdominal pain or tenderness, and leukocytosis
  - unexplained encephalopathy, jaundice
  - worsening renal failure
- Diagnose: tap ascites: WCC>500, PMN > 250 cells/mm^3
  - Place ascites in blood culture bottles
- Start treatment immediately before culture results

SBP treatment

- Cephalosporins
- Renal dysfunction is main cause of death
  - prevented by the use of intravenous albumin if
  - serum bilirubin > 4 mg/dL
  - serum creatinine > 1 g/dL
  - or blood urea nitrogen level > 30 mg/dL
- Prevent recurrence: ciprofloxacin, TMP/SMX, norfloxacin
- Primary prophylaxis: ciprofloxacin weekly if MELD >9

Hepatic Encephalopathy

- Classified as
  - episodic (previously acute)
  - persistent (previously chronic)
  - or minimal (previously subclinical)
- Results from a combination of
  - Portosystemic shunting and
  - failure to metabolize neurotoxic substances
  - Ammonia remains the most important neurotoxic substance but poorly correlates with stage

Hepatic Encephalopathy

- Precipitants
  - Infection- especially SBP or UTI
  - Bleeding
  - Electrolyte imbalance
  - Portal vein thrombosis
  - Worsening liver disease

Hepatic Encephalopathy

- Treatment aims to reduce production of ammonia from the colon through
  - nonabsorbable disaccharides
    - lactulose, lactitol, and lactose
  - nonabsorbable antibiotics
    - neomycin, rifaximin
  - Protein restriction promotes protein degradation and, if maintained for long periods, worsens nutritional status and decreases muscle mass
    - No longer recommended

HCC Monitoring Guidelines for HIV Cirrhotic Patients

- All patients with cirrhosis
- Patients with HBV (>40y) and family history
- Screening strategy
  - serum alpha-fetoprotein (AFP) testing
  - ultrasonography at intervals of 6 or 12 months
- Based on
  - low incidence of HCC in those at risk: 1-4% /y
  - slow growth of these tumors, mean estimated doubling time of 136 days

Indications for Liver Transplantation

- Development of decompensation (ascites, variceal hemorrhage, HE) in patients with cirrhosis is associated with a median survival of only 1.5 years

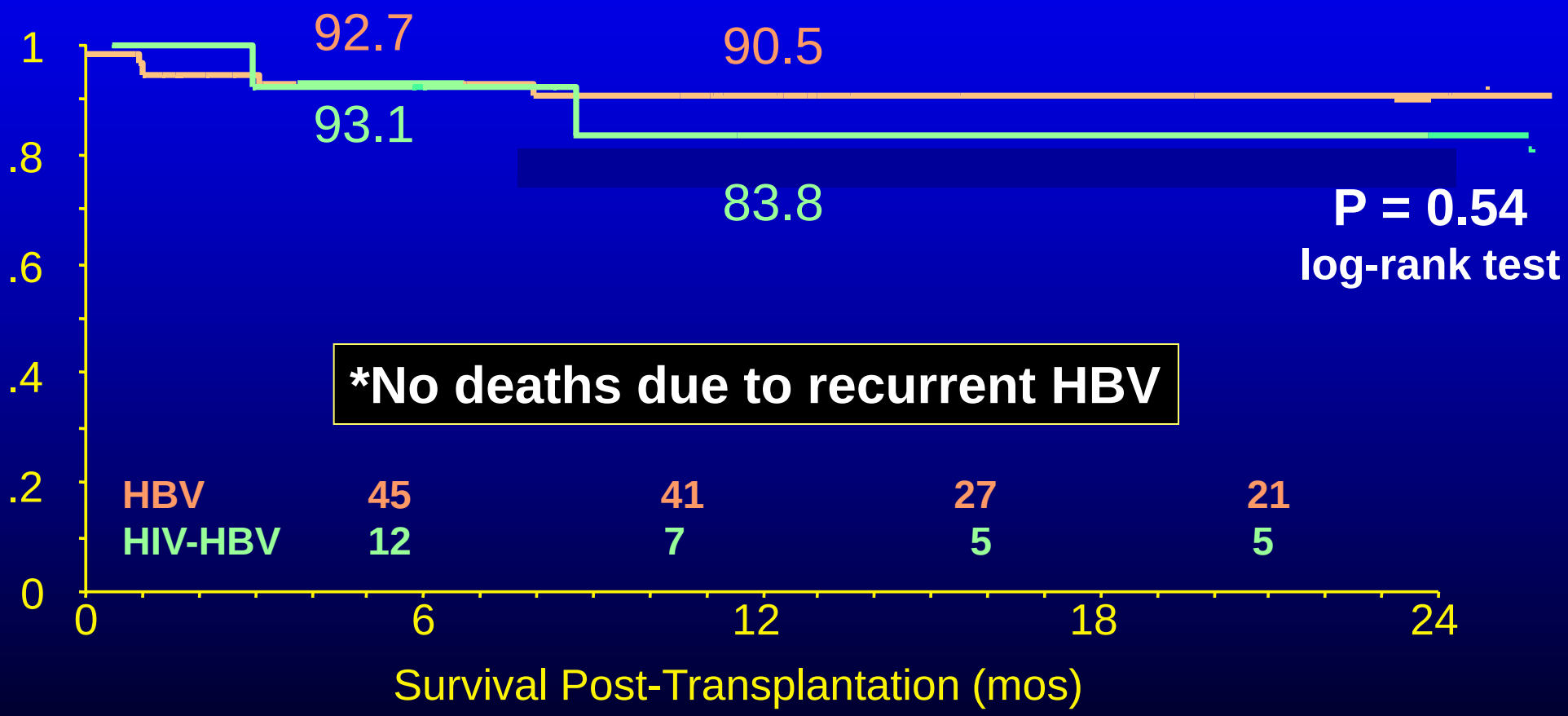
Liver Transplantation

- MELD
- Serum sodium
- Underestimated
  - chronic encephalopathy
  - hepatic hydrothorax
  - hepatopulmonary syndrome
  - portopulmonary hypertension

OLT in HIV: Why Now?

- HAART-associated improvements:
  - decreased mortality
  - decreased incidence of opportunistic infections
  - decreased hospitalization rates
- Immunosuppressives may have anti-HIV effects
  - cyclosporine, MMF, rapamycin
- Better prophylaxis for opportunistic infections

Patient and Graft Survival
HBV vs HBV-HIV*



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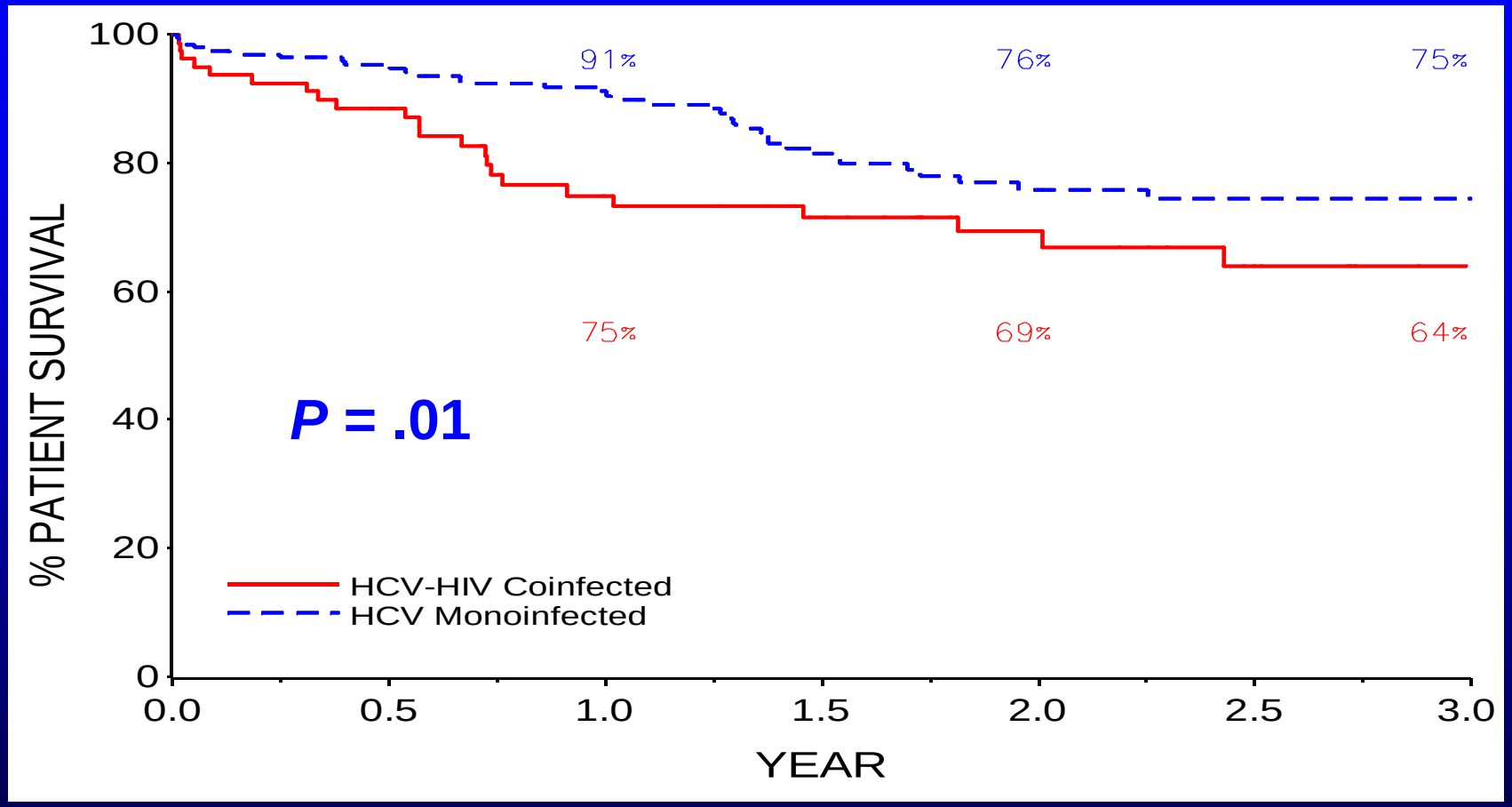
Terrault 2007

Patient Survival: HCV



HCV mono-infected	n=135	n=67	n=22
HCV-HIV co-infected	n=46	n=28	n=14

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Terrault N, et al. AASLD 2009. Abstract 195.

Potential factors contributing to poor outcomes in HCV+ liver recipients

- Donor HCV+ (p=.02)
- MELD (p=.01)
- BMI <21 at enrollment (p=.0001)
- Dual organ (p=.01)
- Detectable HIV RNA at enrollment (p=.005)
- Initial IS of tacrolimus vs CsA: p=.04
- Donor age? No difference seen between age groups >40 vs ≤40 (p=.75)

NIH HIV study data

HIV OLT SUMMARY

- Recurrent hepatitis B controlled with combination therapy and monthly HBIg
- Recurrent HCV may be a significant problem, with an increased risk of morbidity and mortality
- HPV – anal CA; HHV8 – KS - problematic
- HAART regimens including PI require major adjustments in Calcineurin inhibitor dosing

ESLD and HIV

- Liver disease has become a major cause of death in people infected with HIV
- Prevalence of HCV coinfection is high (30%)
- Prevalence of HBV coinfection ~ 10%
- Progression to cirrhosis is rapid in coinfected pt
- ESLD common
- Monitor ascites and infection (SBP prophylaxis)
- EGD for varices, imaging for HCC
- Consider OLT early