

Liver Disease Management for the HIV Clinician

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Outline

1. Epidemiology of liver disease in HIV
2. Etiology of liver disease in HIV
3. Management
 1. HCV
 2. HBV
 3. Drug
 4. Cirrhosis

HIV Prevalence 2007

Worldwide:

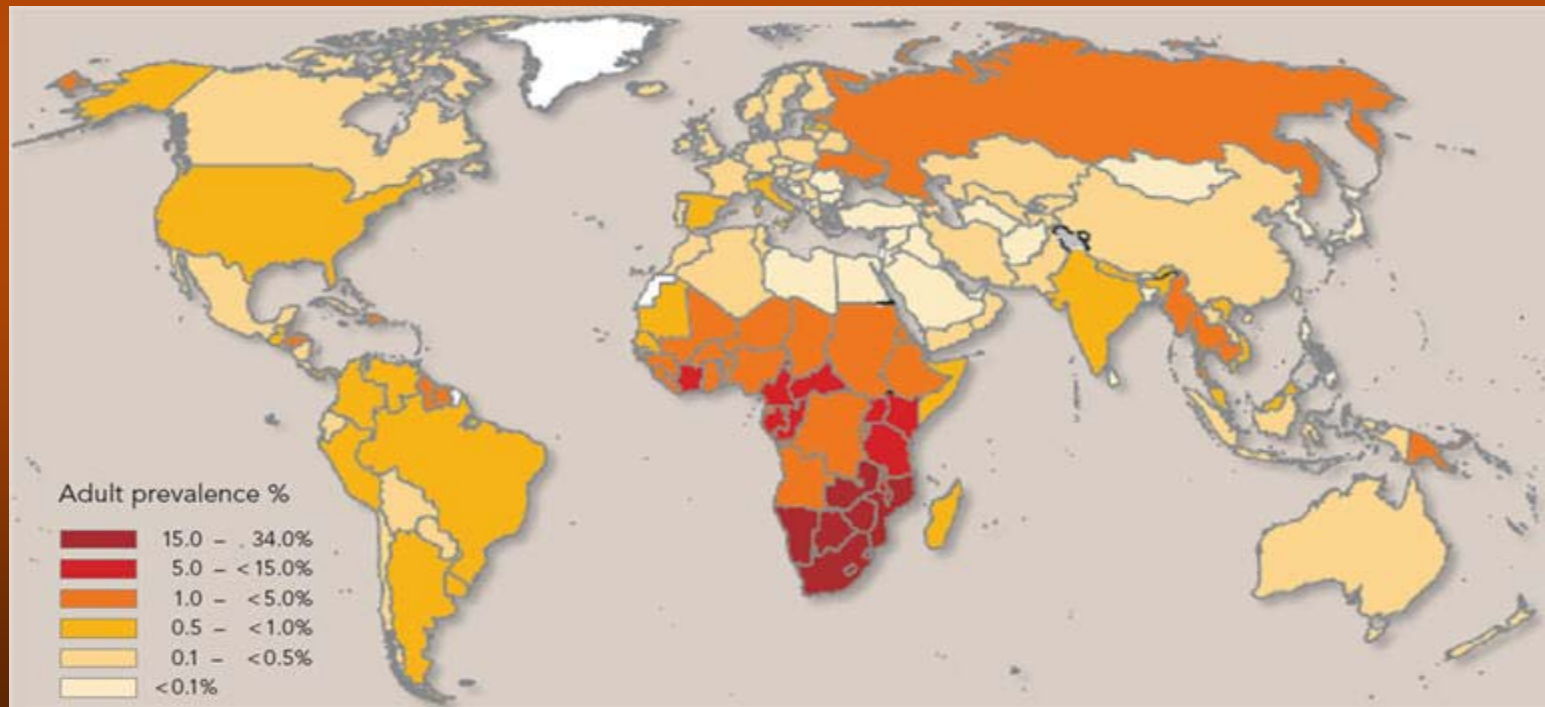
- 33.2 Million affected
 - 15.4 Million women
 - 2.5 Million children

North America

- 1.3 Million

Europe

- 0.76 Million



HAART and Mortality

Highly Active AntiRetroviral Therapy

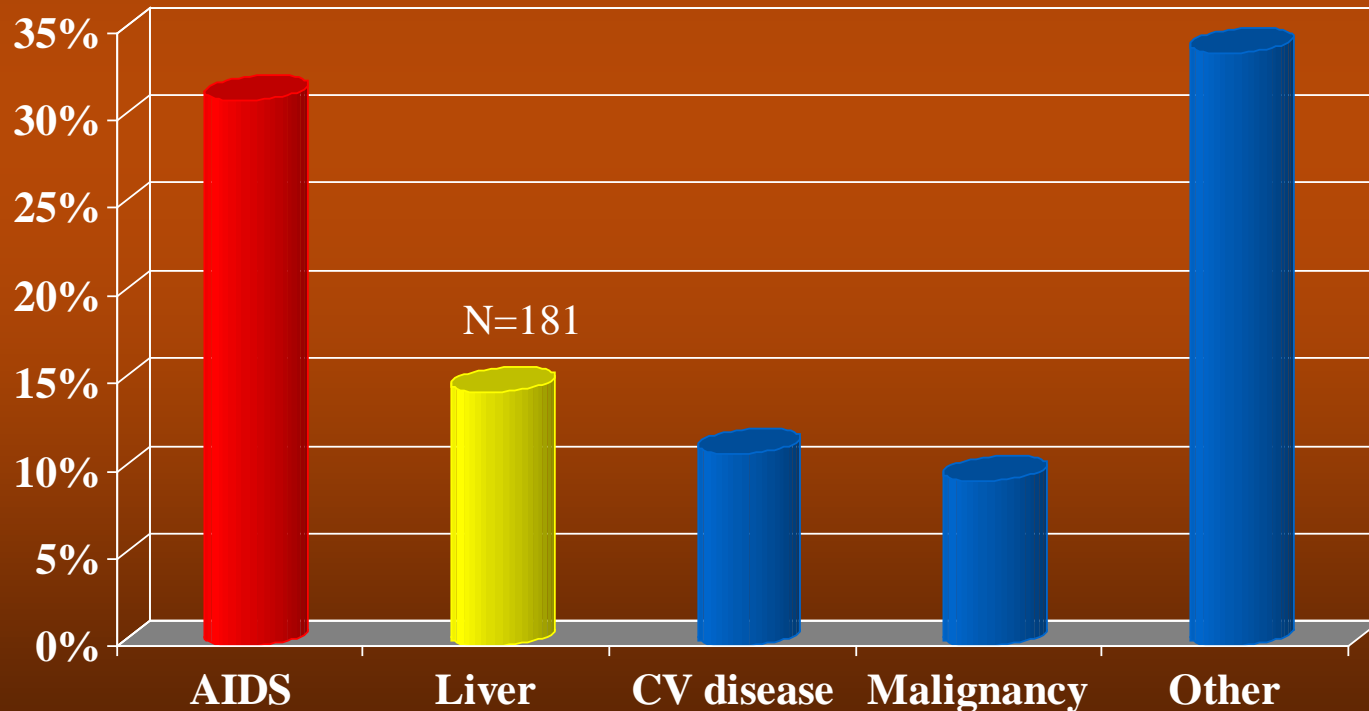
- Introduced in 1995-1996

HIV related mortality in western countries:

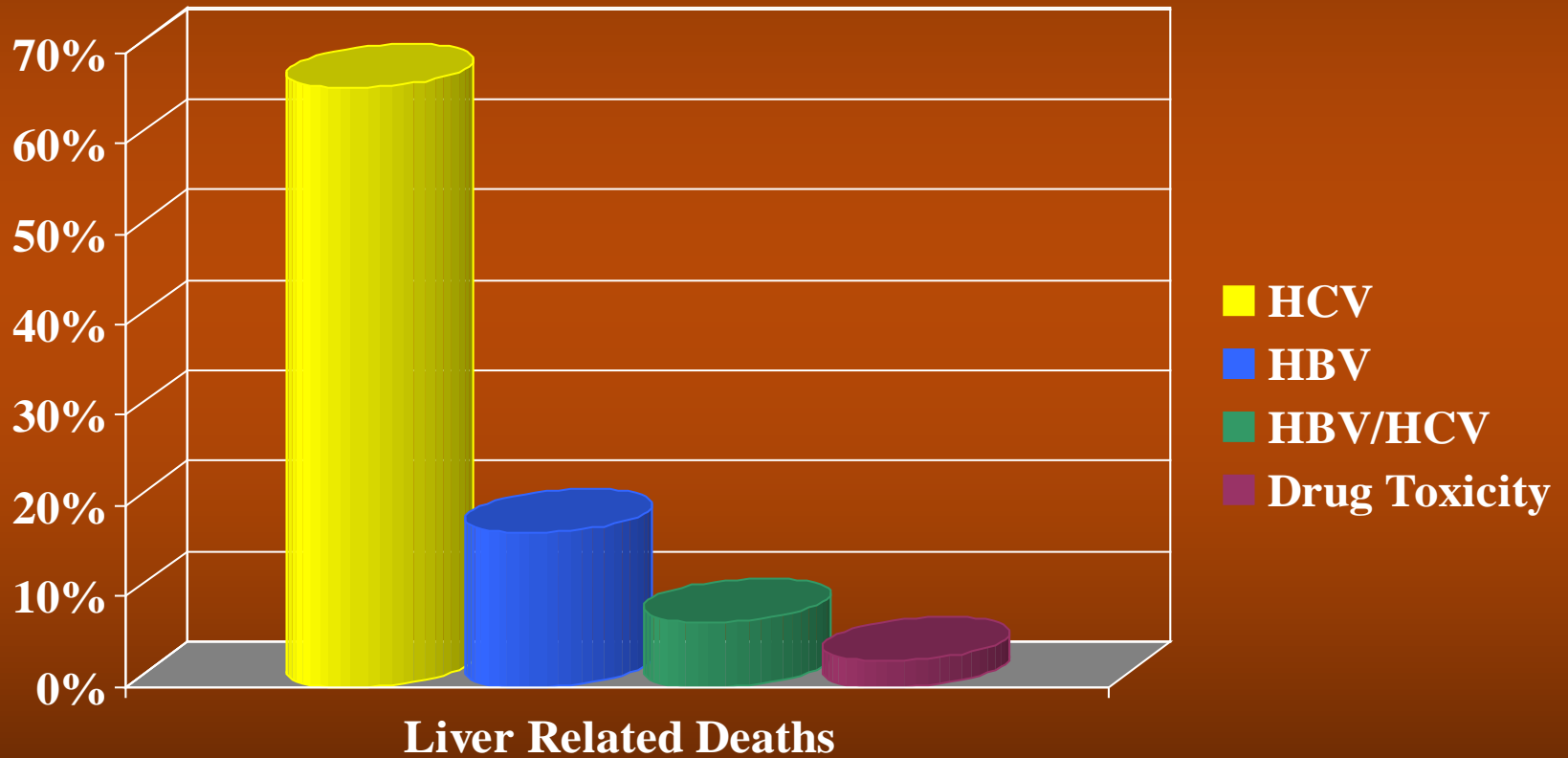
- Prior to 1995
 - 20-30 per 100 person-years
- After 1995
 - 2-5 per 100 person-years

HAART Era Mortality

- International Multicenter Cohort (Europe, US, Aus)
- 23,441 Patients (1999-2004)
- 1246 Deaths



Liver Related Deaths



Causes of Liver Disease in HIV

- Co-infections
- Immune mediated
- Malignancies
- Hepatotoxicity
- Metabolic

Causes of Liver Disease in HIV

Co-Infections:

- HCV – Estimated 4-5 Million (~ 13.5%)
- HBV – Estimated 2-4 Million (~ 9%)
- Opportunistic – CMV, TB + other MB, Bartonella (Peliosis hepatis)
- Tropical infections – Leishmaniasis, Schistosomiasis

Causes of Liver Disease in HIV

Immune mediated

- Immune reconstitution inflammatory syndrome (IRIS) in HBV or HCV coinfection.

Malignancies

- HBV and HCV related – HCC
- HIV related – NHL, Kaposi's
- Metastatic disease

Causes of Liver Disease in HIV

Hepatotoxicity

- Antiretroviral drug-related liver injury (ARLI)
- Non-HIV medication toxicity
- EtOH

Metabolic

- NASH
- Lipodystrophy ?
- Cryptogenic

Drug/Metabolic Liver Injury

ARLI

- Incidence of severe liver toxicity 2-18%
- Cause of liver related death 2.8%
- Occurs within weeks (hypersensitivity) to months
- Moderate or severe – 5 or 10 fold increase in transaminases.
- Predisposing factors: HCV (type 3), HBV, EtOH, Abnormal LFT's prior to starting HAART

Drug/Metabolic Liver Injury

Classes of HIV Drugs:

- Nucleoside Reverse Transcriptase Inhibitors (NRTI)
 - Didanosine (ddI), Stavudine (d4T)
- Non- Nucleoside Reverse Transcriptase Inhibitors (NNRTI)
 - Nevirapine (NVP), Efavirenz (EFV)
- Protease Inhibitors (PI)
 - Ritonavir (RTV), Tipranavir (TPV)

Drug/Metabolic Liver Injury

- Advanced liver disease is rare in the absence of another risk factor.
 - 17 cases of cryptogenic cirrhosis in a cohort of 3200 HIV positive males (0.5%)
 - Eliminated all who had another known cause of liver dz. (Viral hepatitis, EtOH, NASH etc...)
 - Case-control analysis revealed length of Didanosine (ddI) exposure as the only predictor.
 - RR 1.04 (CI, 1.004-1.088; P=0.03)

Drug/Metabolic Liver Injury

Previous study may be an underestimate

- HAART has been associated with hepatic steatosis in the setting of HCV¹
 - 187 patients, 126 with Steatosis
 - Nucleoside analogs – OR 2.14 (P= 0.024)
- Study of 14 consecutive HIV patients with liver biopsies for abnormal LFTs.
 - Steatohepatitis was present in 6 of 9 pts who had insulin resistance and lipodystrophy vs 2/5 without.²

1. McGovern et al. CID 2006; 43:365–72

2. Lemoine et al. AIDS 2006 20:387-395

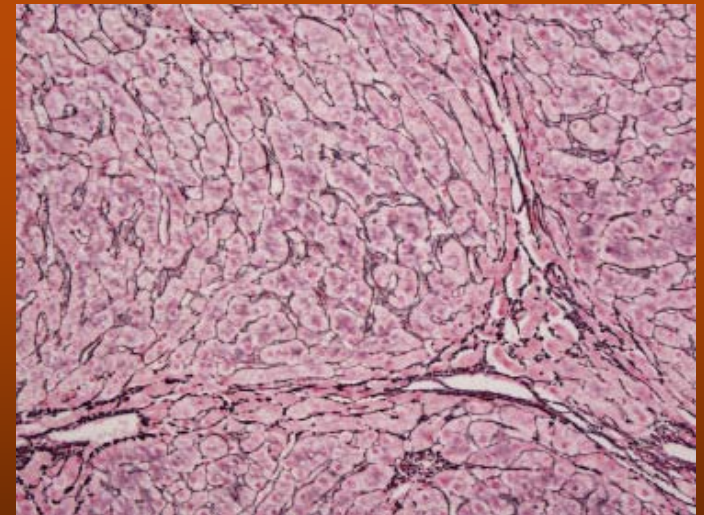
Lipodystrophy

- Side effect of HAART
- Fat redistribution
 - Extremity and head fat wasting
 - Central fat accumulation
- Insulin Resistance
- Hyperlipidemia
- Hepatic Steatosis (microvesicular)
- ? Advanced liver disease

Cirrhosis vs. Nodular Regenerative Hyperplasia

NRH in the setting of HIV ^{1,2}

- Diffuse small regenerative nodules in the absence of significant fibrosis.
- Primary vasculopathy with alterations in blood flow?
- Link to thrombophilic state? ²
- Portal Hypertension
- Near normal INR and bilirubin
- Consider Biopsy and TIPSS



1. Mallet et al. AIDS 2007; 21:187-192
2. Saifee et al. Clin Gastro Hep 2008
3. Dinh et al. HIV Med 2009;10:447-53

Management of ARLI

- HAART related: If >10 fold increase in transaminases or symptomatic, remove the offending agent
 - If TA abnormal prior to HAART, > 5 fold increase
- Mild elevations can frequently improve without removing the drug
- Consider other causes of elevated LFTs

HCV Coinfection

- Acute HCV
 - HIV (-) ~ 52% spontaneous clearance if symptomatic
 - HIV (+) ~8% spontaneous clearance.
 - Peg-IFN and ribavirin x 6 months
- Chronic HCV
 - 6% fail to develop anti HCV
 - Check PCR
 - Consider biopsy

Risk of Progression for HCV/HIV

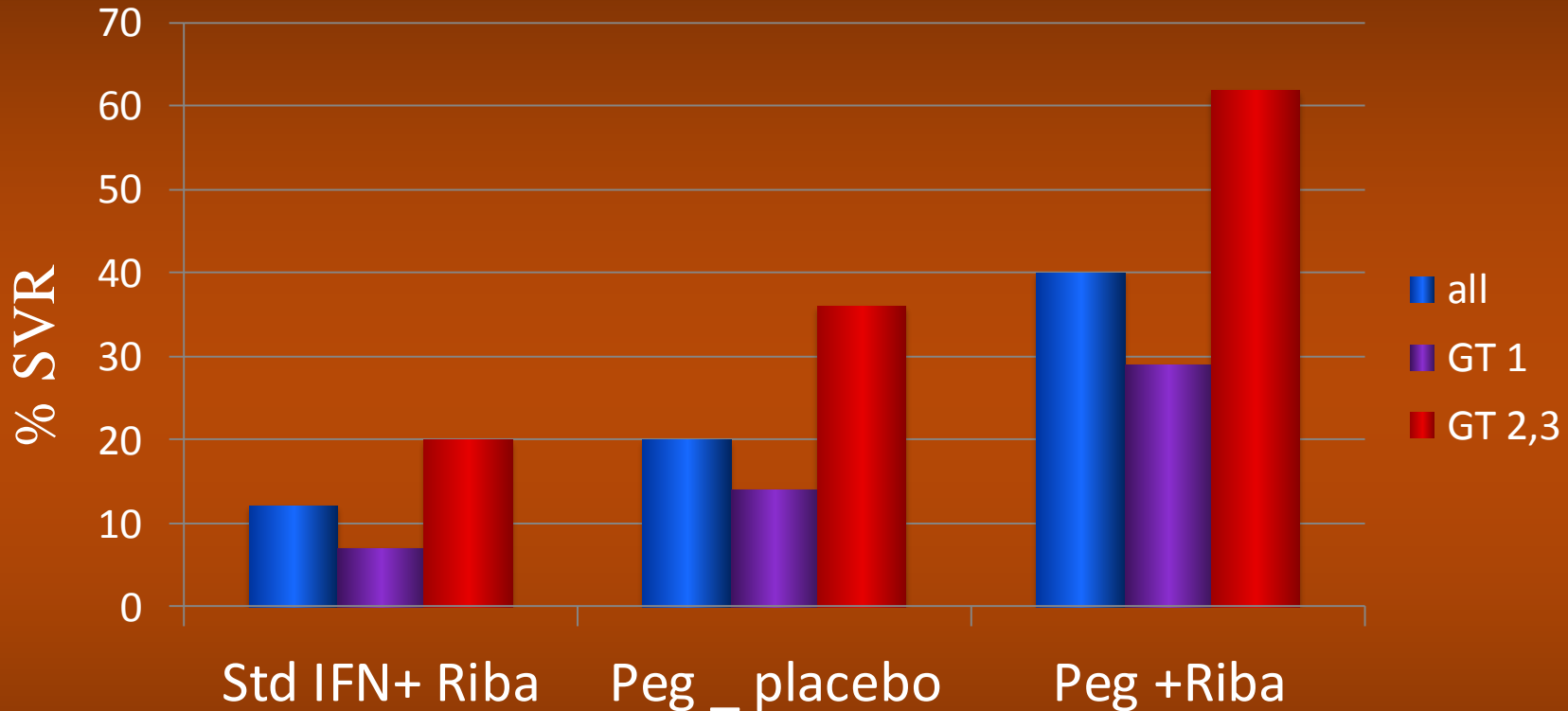
- Hemophilia population with HCV (N= 1816)
 - HCV/HIV 16 year cumulative incidence of ESLD 14% vs 2.6% for HCV alone¹
- Meta-analysis – cirrhosis RR 2.07
 - ESLD RR 6.14²
- HAART era – 1011 patients with HCV/HIV
 - 5% 5 year probability of decompensation³

1. Goedert et al. Blood 2002;100:1584-1589
2. Graham et al. CID 2001;33:562-569
3. Pineda et al. Hepatology 2007;46:622-630

HCV Coinfection

- Treatment considerations
 - Stage of disease- biopsy
 - Genotype
 - Psychiatric comorbidities
 - Active drug use- stop/minimize
 - Treatment for HIV first, if warranted
 - Confusion of side effects
 - Improved response
 - Avoid in decompensated liver disease

HCV Coinfection



- $> 800,000$ IU/mL SVR ~18%

HCV Coinfection

- Factors associated with SVR
 - Genotype 2/3
 - Low HCV viral load
 - High CD4 count \geq 300-500
 - Undetectable HIV RNA
 - Younger age
 - Non-IVDU
 - Weight based Ribavirin

HCV Coinfection

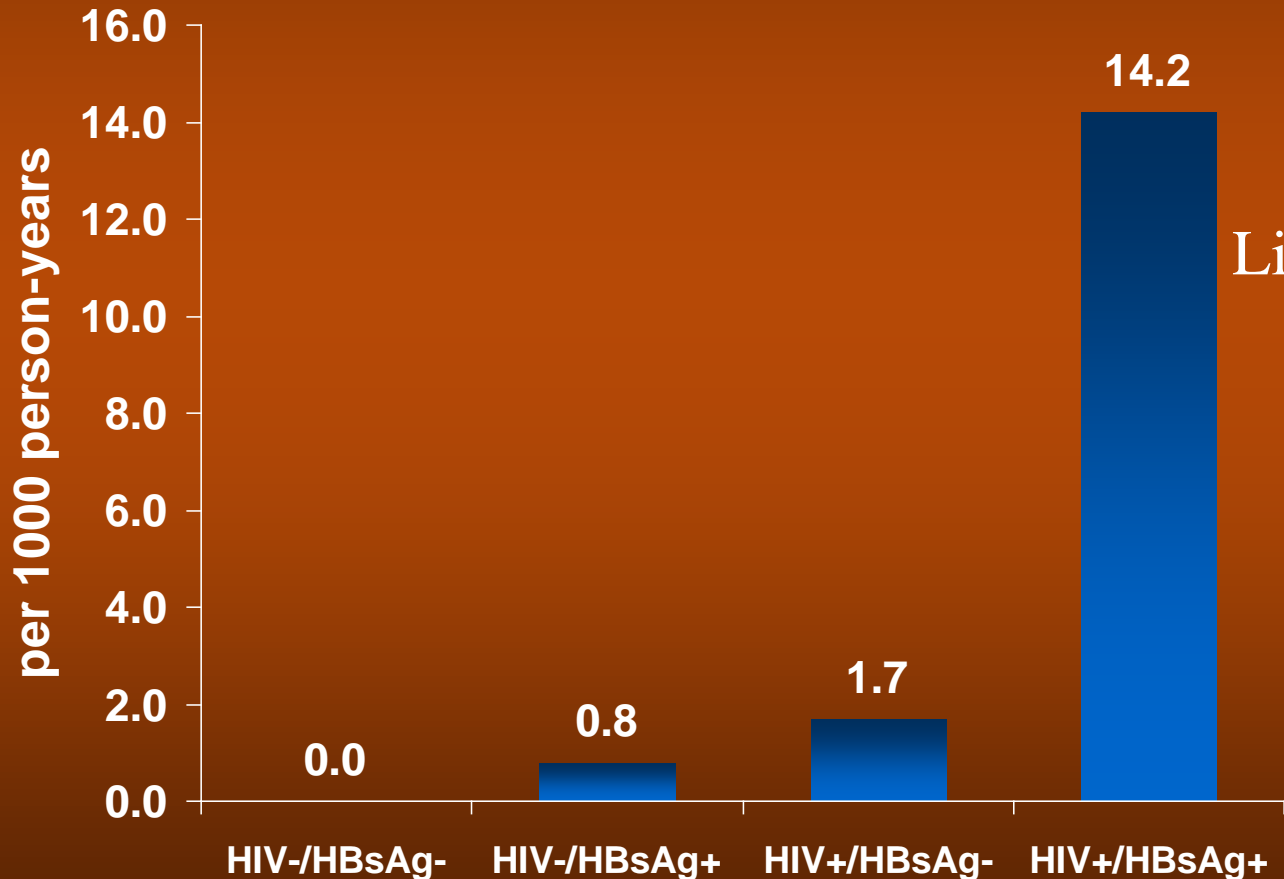
- Safety
 - AZT- Increased hemolysis with AZT
 - ddI- Severe lactic acidosis, pancreatitis
 - Decreased total CD4 but % remains the same.
 - No increase of opportunistic infections
- New agents- data pending
 - Increased risk of resistance (higher HCV viral load and decreased response to IFN)
 - Interference with HAART- CYP450

HBV Coinfection

- Higher levels of HBV DNA
- Lower rates of spontaneous eAg seroconversion
- More severe disease and increased liver related mortality
- Risk of flare with immune reconstitution

Risk of Progression for HBV/HIV

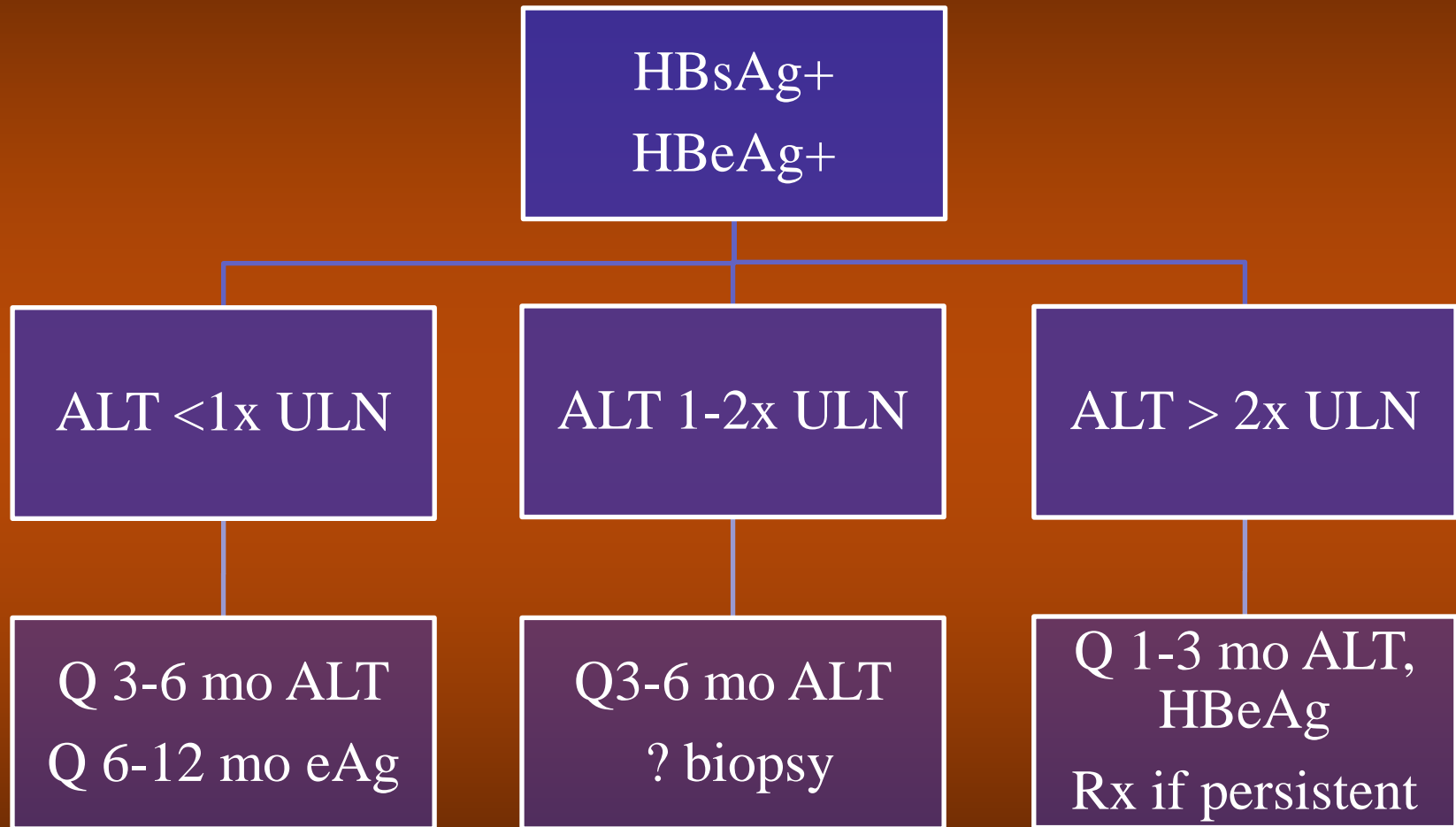
- Prospective Cohort 5622 men- Liver related mortality



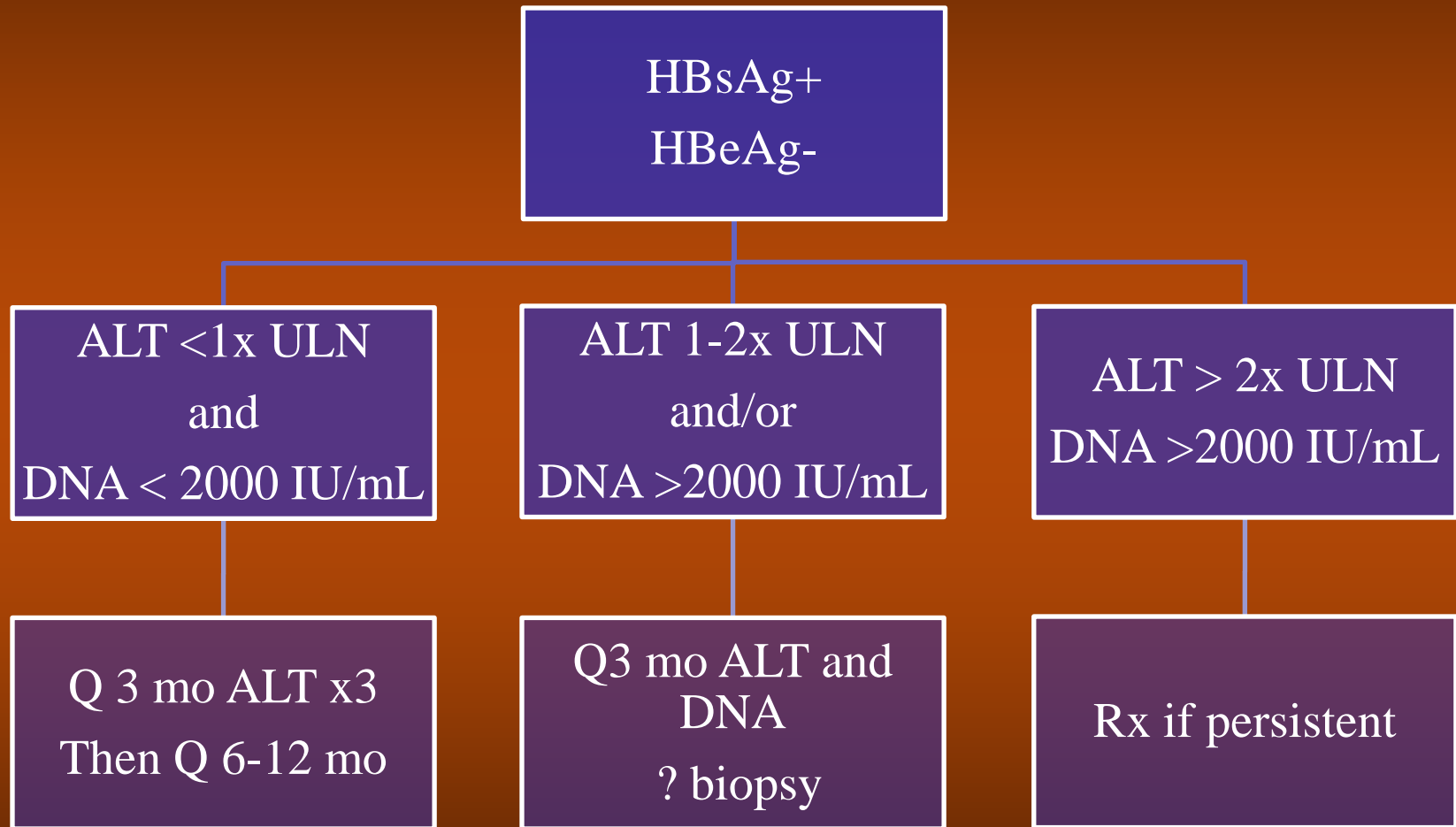
Liver related deaths post HAART rose from 2.5/1000 PY to 4.0/1000 PY

– Confounder of time.

HBV Coinfection Management



HBV Coinfection Management



HBV Coinfection Management

- Resistance
 - Lamivudine- cross resistance to entecavir- use TDF
- Those who require Rx for HIV
 - Dual therapy: Tenofovir + emtricitabine, Lamivudine or entecavir
 - Avoid stopping Rx for HBV- risk of flare
 - Consider adefovir if no HAART
 - Add entecavir if ongoing HAART

HBV Coinfection Management

- Those who do not require Rx for HIV
 - Consider treating for both anyway.
 - CD4 \leq 500 – advanced liver disease
 - HIV Resistance: tenofovir, emtricitabine, lamivudine, entecavir.
 - Peg-IFN if eAg +, genotype A, CD4 > 350 and $\uparrow\uparrow$ ALT
 - Telbivudine + low dose adefovir?

Complications of Cirrhosis

- Varices
- Encephalopathy
- Fluid overload
- Hepatocellular cancer

Diagnosis

- Symptoms elicited are often nonspecific
 - Weakness
 - Fatigue
 - Anorexia
 - Weight loss
 - Poor memory/sleep disturbances

Diagnosis

Clinical manifestations

- Physical exam findings

- Jaundice

- Spider angiomas

- Palmar erythema

- gynecomastia

- organomegaly

- ascites

- History obtained

- h/o hepatitis

- Alcohol consumption

- Metabolic syndrome

- Drug use

- f/h of liver disease

- h/o autoimmune dz

Diagnosis

- Specificity of abdominal imaging is high, although sensitivity is low.
- Coarsened echotexture on US
- Lobular liver contour, shrunken liver, collateral veins, splenomegaly
- Consistent laboratory data





Studies

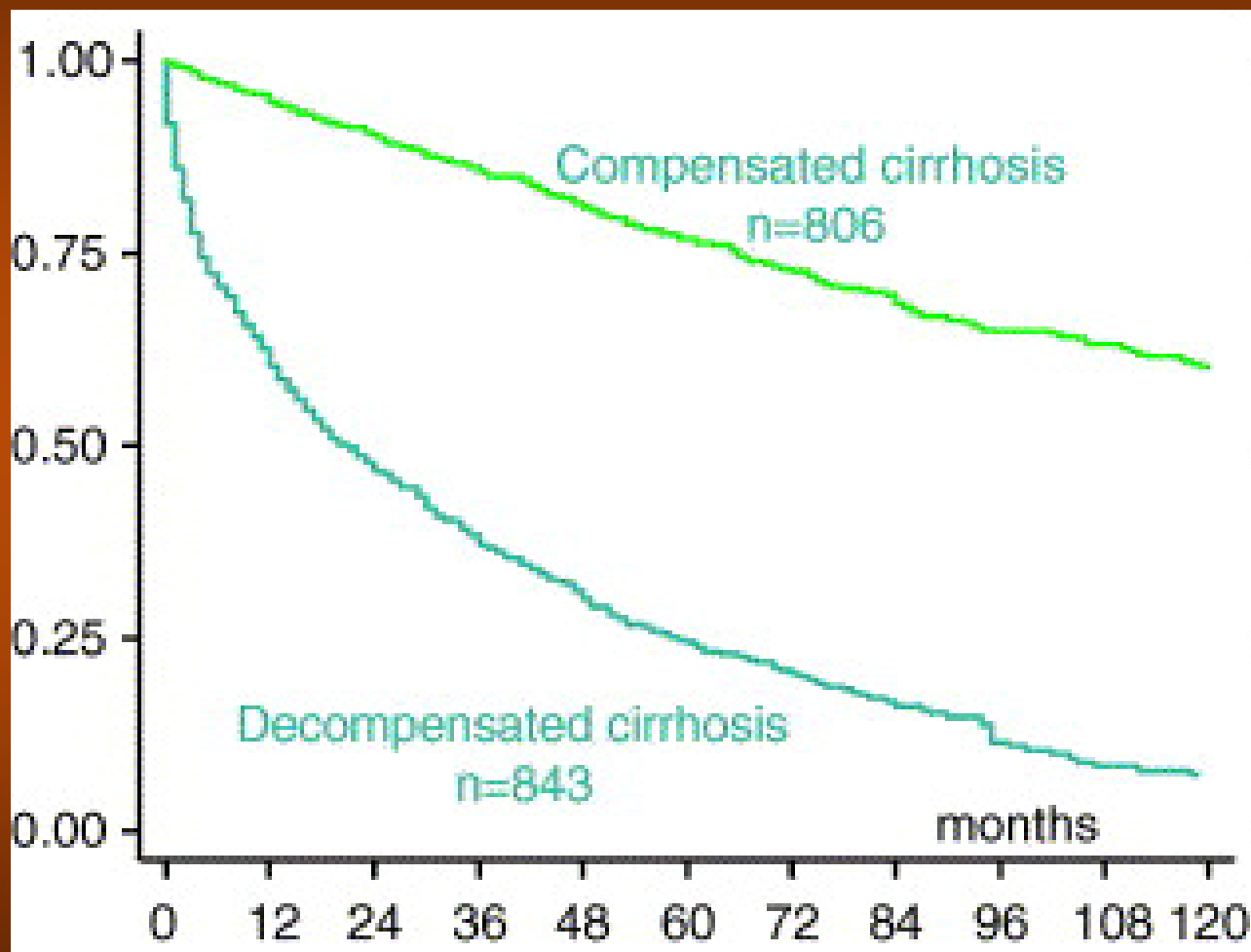
- AST/ALT ratio
- Bilirubin
- Albumin
- Prothrombin time/INR
- Serum sodium
- Thrombocytopenia
- Leukopenia
- Biopsy “gold standard”



Management of Cirrhosis

- Supportive care
 - Treat underlying condition
- Nutrition
- Vaccination: HAV, HBV
- Close monitoring for complications
 - Monitor symptoms
 - Monitor for evidence of decline of liver function
 - Surveillance for varices/hepatocellular cancer

Survival with Cirrhosis



Ascites

- The most common complication of cirrhosis
- 85% of cases of ascites are due to cirrhosis
- Formation of ascites is governed by vascular permeability, oncotic, and hydrostatic forces.
- Arterial splanchnic vasodilatation is central to the development of ascites
- Vasodilation is mediated by NO, glucagon, prostaglandins
- Activation of RAAS, ADH, and sympathetic nervous system.

Management of Ascites

- Goal is to obtain a net negative sodium balance
- Dietary sodium restriction (2000 mg/day or less) is first step
- Initiation of diuretics (spironolactone +/- furosemide) increases urinary sodium excretion.
 - Spironolactone:furosemide- 100:40

Spontaneous Bacterial Peritonitis

- An infection of pre-existing ascitic fluid without secondary source
- Diagnosed by elevated neutrophil count in ascites (≥ 250 cells/mm³)
- Mortality is high so prevention and early treatment are crucial.
- Prophylaxis- prior episodes, ascitic TP <1
 - Daily quinolone
- Treatment- 3rd gen Cephalosporin,
Albumin- 1.5 gm/kg day 1, 1gm/kg day 3

Encephalopathy

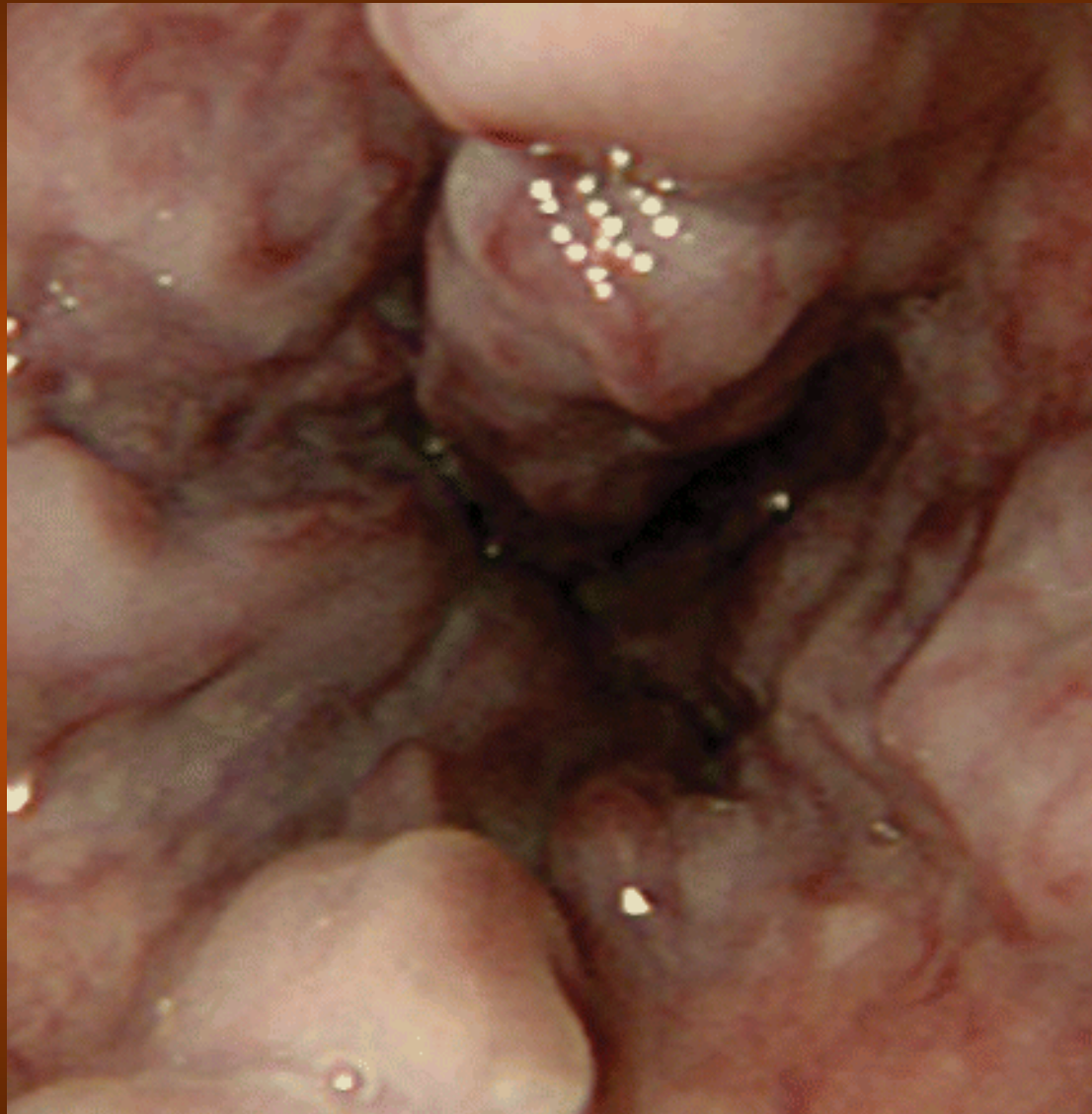
- Spectrum can be from disturbance in sleep, to confusion, to overt coma. Presence of asterixis noted
- Diagnosis is made clinically and with the exclusion of other causes
- Elevated ammonia not required to make the diagnosis and an elevated ammonia level is nonspecific (i.e. Not Useful)

Treatment of Encephalopathy

- Identification of a precipitating cause and therapy directed at this is of central importance
- Non-absorbed disaccharides has been the mainstay of therapy (lactulose)
- Nonabsorbed antibiotics are also useful, usually as adjunctive therapy (neomycin 1000 mg bid, rifaximin 550-600 mg bid).

Treatment of Encephalopathy

- Additional agents may be of some use:
 - Lactulose or cathartic enemas
 - Probiotics
 - Sodium benzoate
- The use of benzodiazepines or narcotics in the combative encephalopathic patient should be strictly avoided



Variceal Hemorrhage

- Assessment of Risk
 - All patients with cirrhosis should be screened for the presence of varices
 - ~ 50% have varices (85% of Child C)
 - 1/3 of patients with varices will bleed
 - 60-70% mortality in 2 years after variceal hemorrhage
 - EGD remains standard screening test

Variceal Hemorrhage

- If no varices seen
 - Repeat EGD in 2-3 years
- If small varices seen (<5 mm)
 - Repeat EGD in 1-2 years
- If large varices seen (≥ 5 mm), or small varices with red marks +/- CTP B/C
 - Prophylactic therapy should be offered

Prophylaxis Against Bleeding

- Beta-blockers
 - Reduce risk of first variceal bleeding by up to 50%.
 - Prophylaxis of patients without varices does not prevent the development of varices
 - Have a lot of side effects and may not be well tolerated
 - Dose at night
- Band Ligation
 - Greater benefit in prevention of first variceal bleed, but overall mortality similar
 - Generally reserved beta-blockers intolerance
 - Performed every few weeks eradication is obtained
- Combination therapy not indicated

Hepatocellular Cancer

- Develops at a rate of 2-5% per year
- 25% of liver deaths post HAART
- Also can be seen in chronic HBV without cirrhosis
- Screening recommendations are:
 - Cirrhosis due to viral liver disease, EtOH, metabolic liver disease
 - Chronic HBV
 - Asian males >40, Asian females >50
 - African people >20
 - Family history of HCC

HCC Screening Modalities

- Abdominal imaging
 - Ultrasound every 6-12 months
 - CT? MRI?
- Alpha-fetoprotein
 - Improves sensitivity, but decreases specificity, increases cost (\$2000 vs \$3000/per tumor found)
 - Should not be used alone unless imaging not available

When to refer?

- Diagnostic dilemma- considering biopsy
- Considering treatment for HCV in setting of compensated cirrhosis
- Decompensated disease
- HCC

Liver Transplantation in HIV

- Prior to the HAART era, HIV was an absolute contraindication for liver transplant
- Reports 1987-1993

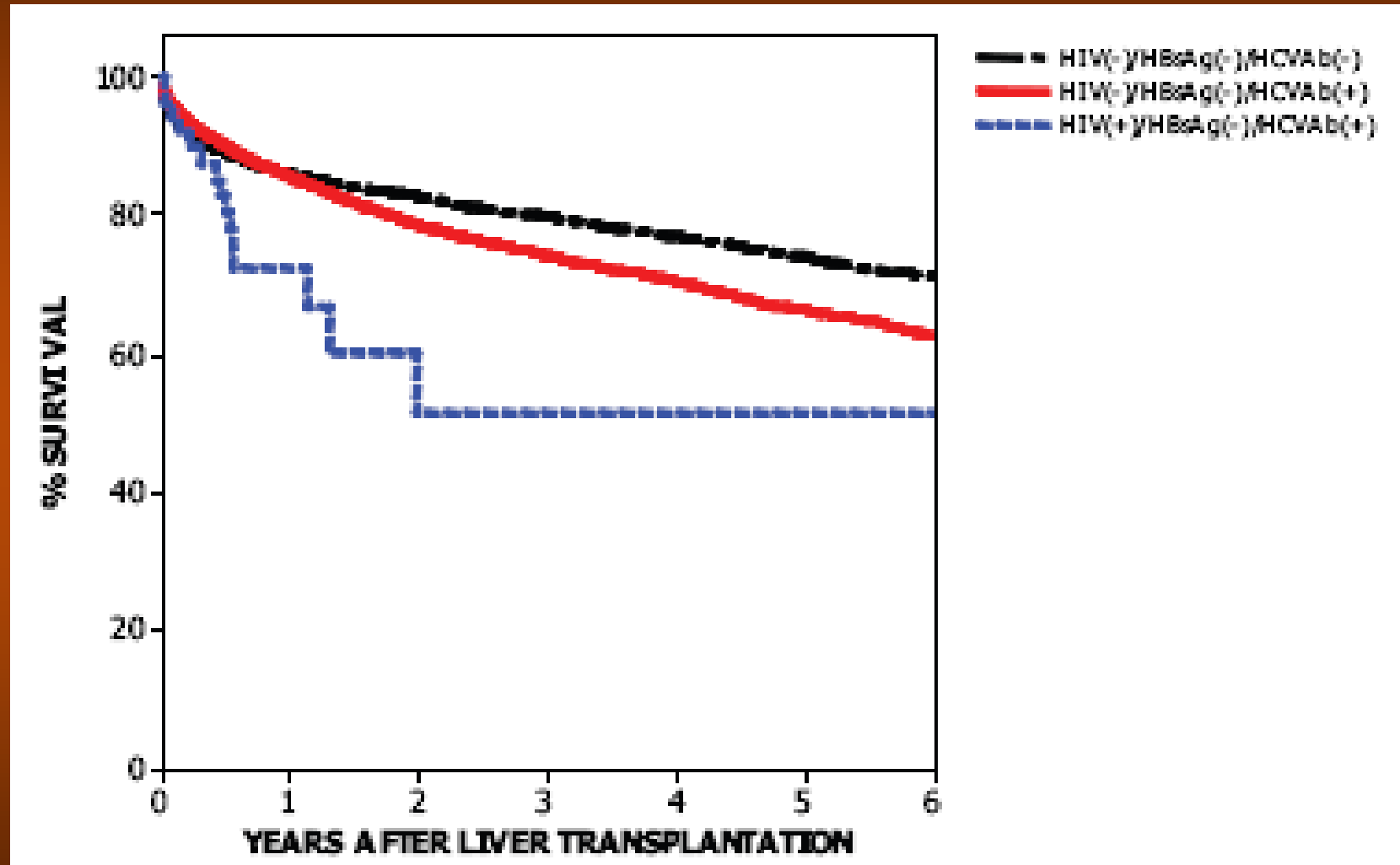
TABLE 1. HIV-positive patients at the time of transplantation, previously reported

No	Age	Center	Diagnosis	Immunosuppression	Rejection/Treatment	AIDS-Defining Illness	Outcome
1	48	Pittsburgh	N/A	C+P+OKT3	No	No	A:8m
2	15	Pittsburgh	HBV/HDV/NANB/H-A	C+P+OKT3	No	Yes: To (41 m); CMV (44 m)	D:44m
3	48	Pittsburgh	HBV/ALD/H-A	C+P	Yes:1 (OKT3+MoAb)	Yes: PCP (3 m)	D:4m
4	0.5	Pittsburgh	N/A	C+P+OKT3	No	No	D:9m
5	32	Pittsburgh	N/A	C+P+OKT3	No	Yes: immunoblastic sarcoma	D:8m
6	42	Pittsburgh	N/A	C+P	No	No	D:6m
7	3	Pittsburgh	N/A	C+P	No	No	A:68m
8	21	Pittsburgh	HBV/H-A	Not applicable	Not applicable	Not applicable	IOD
9	35	Mass. General	NANB/H-A	C+P+Az	Yes: 3 (steroids)	Yes: Cr (14 m); PCP (21 m)	D:27m
10	N/A	Deaconess	N/A	C+P	Yes: 3 (steroids+OKT3)	Yes: HSV, CMV	D:11m
11	N/A	Cambridge	ALD	C	Yes: 1 (steroids)	No	A:100m
12	35	Pittsburgh	HBV	T+C+P+PGE ¹ /PGE ²	Yes: 3 (steroids)	Yes: CMV	D:70d
13	N/A	Omaha	N/A	N/A	N/A	N/A	D:2m
14	N/A	Omaha	N/A	N/A	Yes	Yes: herpes zoster	A:9m

Liver Transplant post HAART

	Patients	Deaths	2 Year Survival	3 Year Survival	P-value
All HIV (+)	138	27	70%	66%	0.047
All HIV (-)	30,520	7,242	81%	77%	
HIV/HCV Ab (+/+)	58	15	52%	NR	0.006
HIV/HCV Ab (-/+)	11,637	3,027	79%	NR	
HIV/HCV Ab (+/-)	24	0	n/a	n/a	

HCV vs. HIV/HCV



Selection Criterion for HIV

Tenth Forum on Liver Transplantation

- Evolving
- CD4 > 100 cells/ml
 - Formerly >200 cells/ml (criteria for other organs)
 - Splenic sequestration
 - Further decrease with decompensation
 - Decrease with Interferon
- Undetectable viral load not necessary if patients have to come off of HAART

Selection Criterion for HIV

Exclusion:

- Multidrug resistant HIV
- Formerly, a history of opportunistic infection
 - Now, PML, Chronic Crypto, Multi drug resistant fungi.
- AIDS associated lymphoma
- Active Kaposi's sarcoma

$MELD = 3.78[\text{Ln Tbil (mg/dL)}] + 11.2[\text{Ln INR}] + 9.57[\text{Ln sCr(mg/dL)}] + 6.43$

- accurately predicts mortality.

Samuel D et al. J Hepatology 2008; 48:697-707

Subramanian et al. Gastroenterology 2010;138:159-164

Conclusions

- Liver disease is a significant cause of morbidity and mortality in the HIV population.
- Though the vast majority of liver disease is related to co-infection, HAART and metabolic derangements may be a primary or contributing factor to liver disease.
- Management of HCV/HBV is effected by HIV status
- Management of cirrhosis should involve primary providers
- Liver transplant is an option with similar mortality to non-HIV infected individuals.
 - HCV coinfection has poorer outcomes.