

Hepatitis B and C Co- Infection

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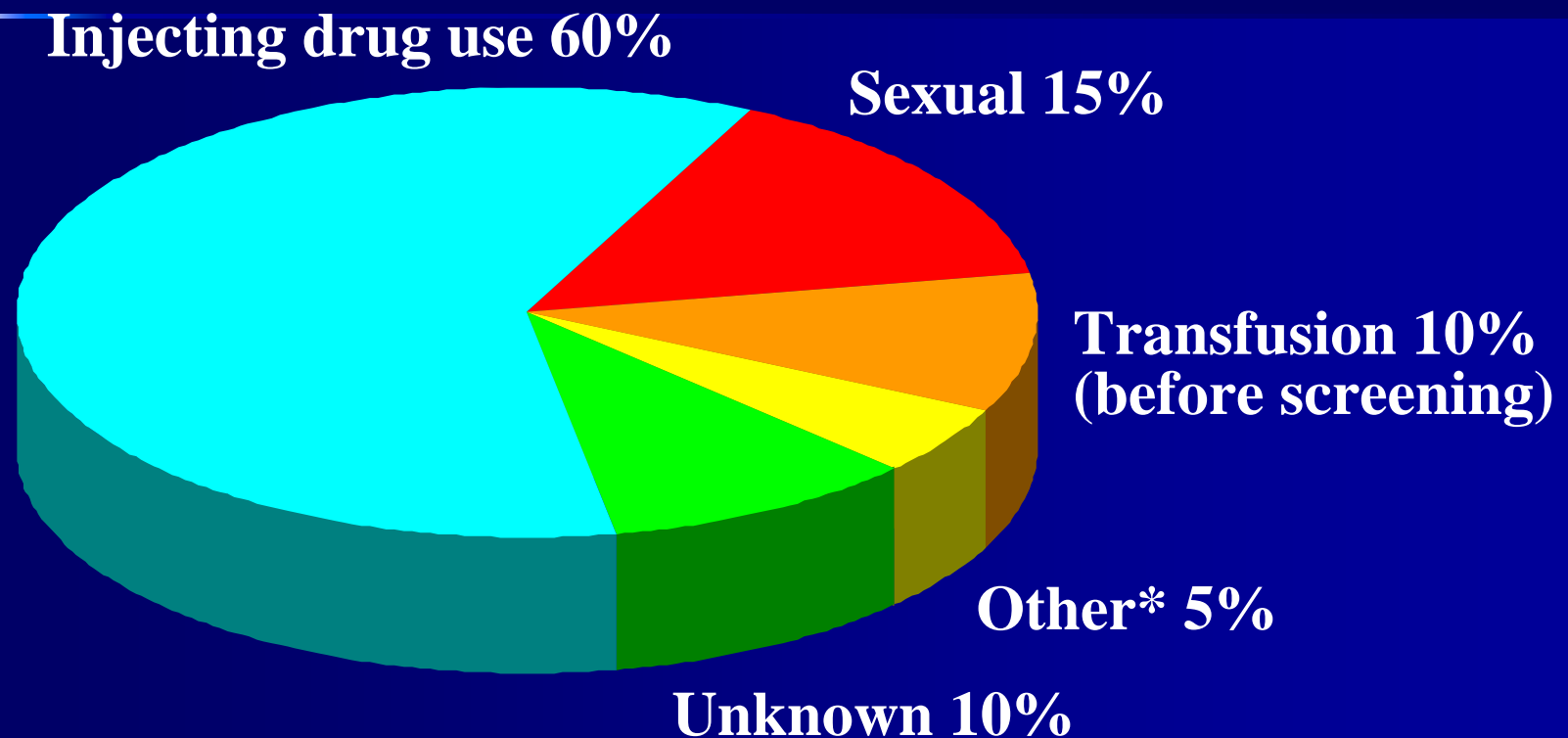
Learning Objectives

- ✓ Identify risk factors for Hepatitis B and C
- ✓ Understand the natural progression of HCV and HBV in HIV patients
- ✓ Understand special issues of HCV in women
- ✓ Know how to initially evaluate and monitor patients with HBV and HCV
- ✓ Know the modalities for treatment available for HBV and HCV in HIV patients

Hepatitis C: Epidemiology

- Worldwide 170 million people infected with Hepatitis C (HCV)
- In the US, 3.9 million people infected with HCV
- Estimated 8,000-10,000 deaths per year
- From 1993 to 1998, rate of HCV-related deaths has increased by 220%
- Leading cause of liver transplantation

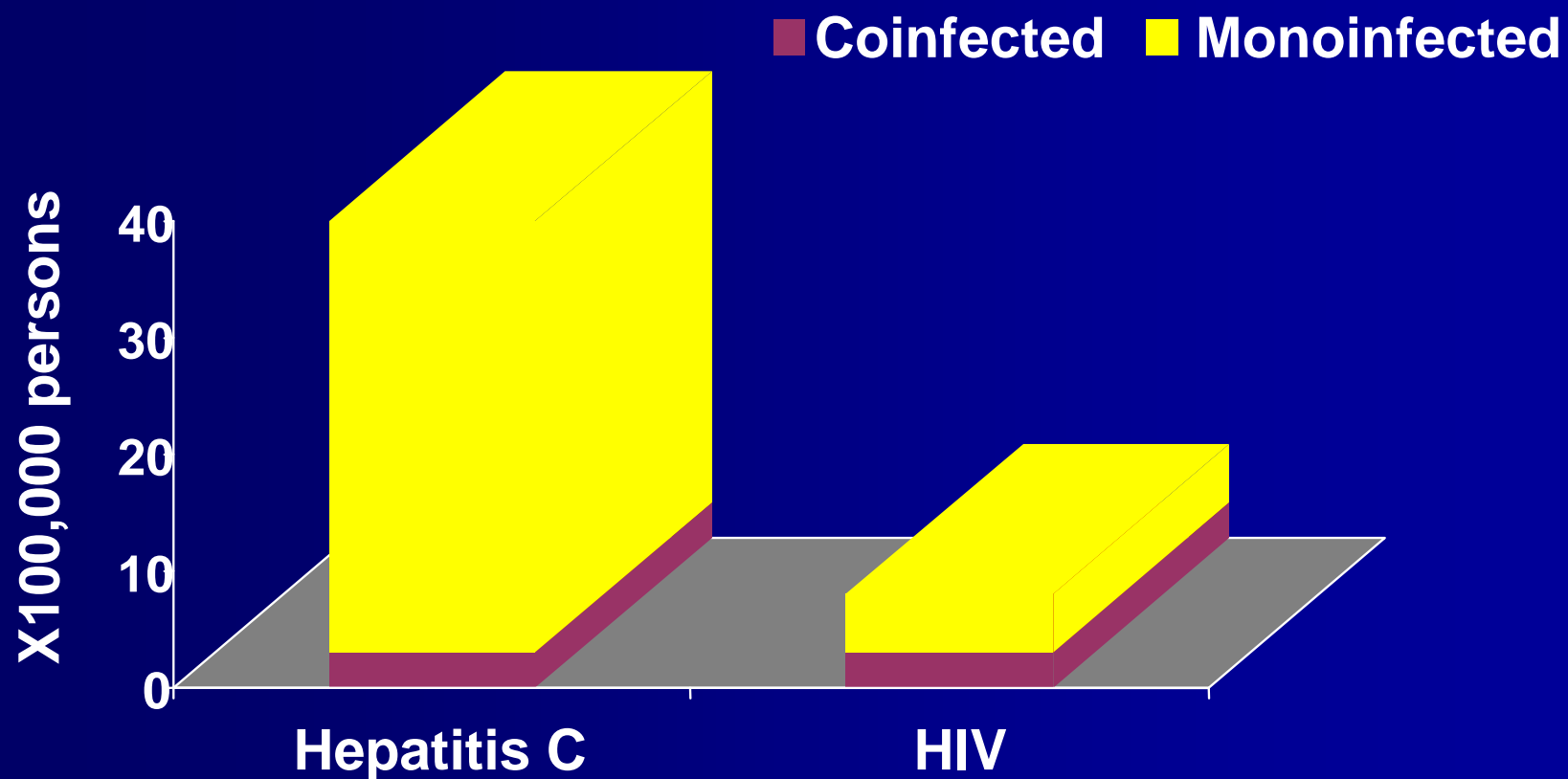
Sources of Infection for Persons with Hepatitis C



*Nosocomial; Health-care work; Perinatal

Source: Sentinel Counties, CDC

HIV/HCV Coinfection in the USA



Courtesy of Dave Thomas, MD
CDC. *MMWR*. 1998; 47(RR-19): 1-39.

Special Issues in Women

Incidence of HCV Infection in Women

- 1517 women followed prospectively
- 1.5% experienced HCV seroconversion
 - HIV (+) 2.7 cases/1000 person-years
 - HIV (-) 3.3 cases/1000 person-years
 - 3 cases/1000 person-years
- New HCV infection
 - associated with drug use
- 5/12 (42%) spontaneously cleared viremia on follow-up
 - 2 with HIV; 3 without HIV

Factors Associated with HCV Viremia

- 1049 HCV Women with HIV+ and HIV-
 - 882 HIV+
- HCV viremic women were:
 - HIV RNA + (>100,000 c/mL)
 - Reported smoking
 - Black
- Reduction of drug and tobacco use may reduce clinical progression, improve treatment response, decrease HCV transmission

Vertical Transmission: HIV & HCV

- 487 HIV+ women followed prospectively
- HIV transmission is higher in mothers who have HCV
 - HIV/HCV infected mothers: 26.1%
 - HIV infected mother: 16.3%

Vertical Transmission: HIV & HCV

■ HIV transmission	21.6%
■ HCV transmission	13.3%
■ HIV/HCV transmission	5.9%

Vertical Transmission: HIV & HCV

- Risk factor for HCV transmission
 - High maternal HCV RNA
 - Female infants 2x more likely to become HCV infected than male infants
- Not associated with transmission
 - Mode of delivery
 - Breast feeding
 - prematurity

Vertical Transmission: HIV & HCV

- Prevention of transmission
 - Cesarean delivery
 - Not recommended in HCV-infected
 - Not clear if transmission may be reduced in HIV/HCV
 - HAART
 - Appears to be protective in preventing mother-to-child transmission of HCV

HCV Treatment & Pregnancy

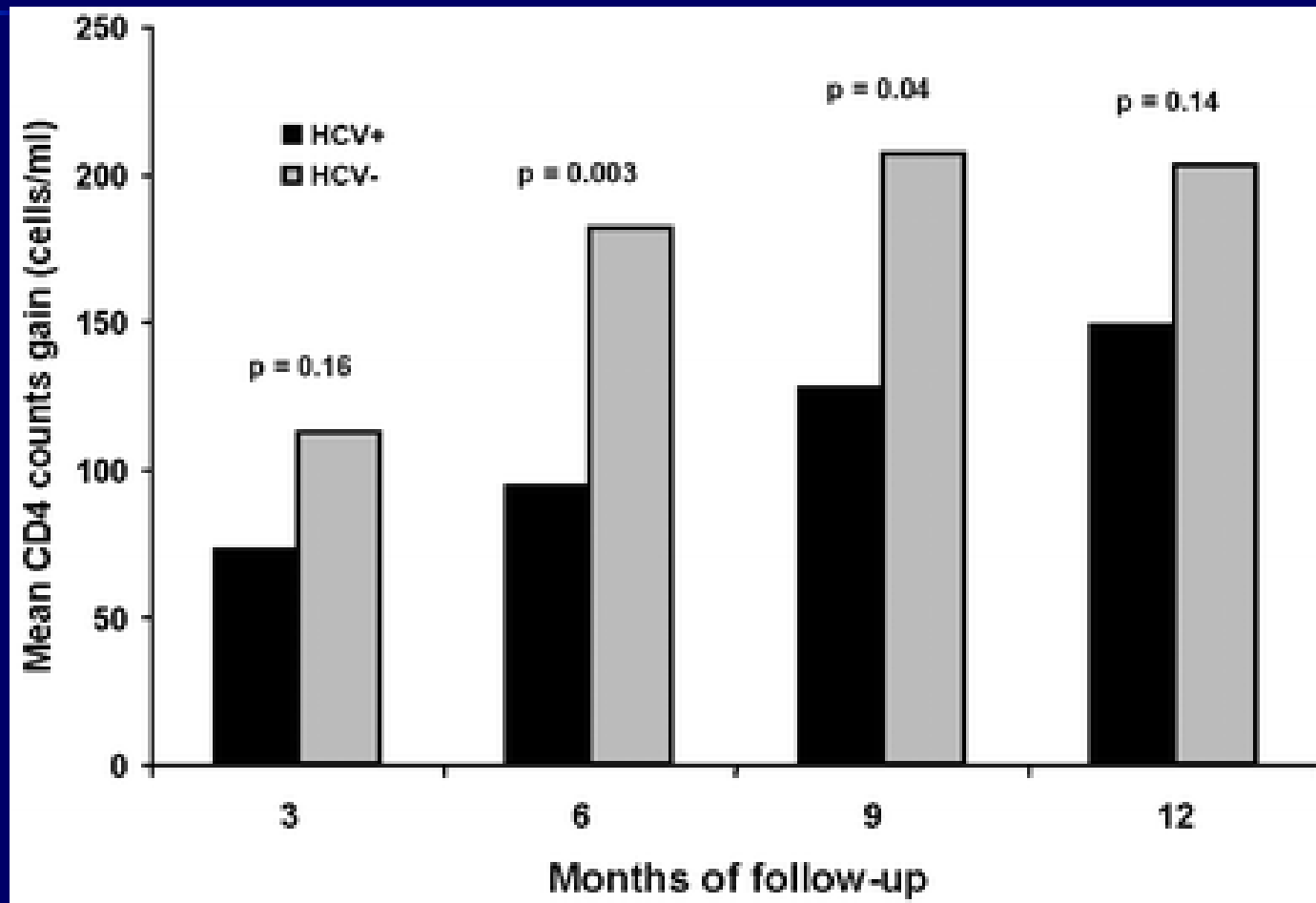
- HCV treatment is not recommended during pregnancy
- Ribavirin is teratogenic in animal models
- Case reports of successful pregnancies
 - mother on interferon (for different indication)
 - father exposed to ribavirin
 - 1 report of mother receiving ribavirin for SARS

Impact of HCV on HIV

Impact of HCV on HIV Progression

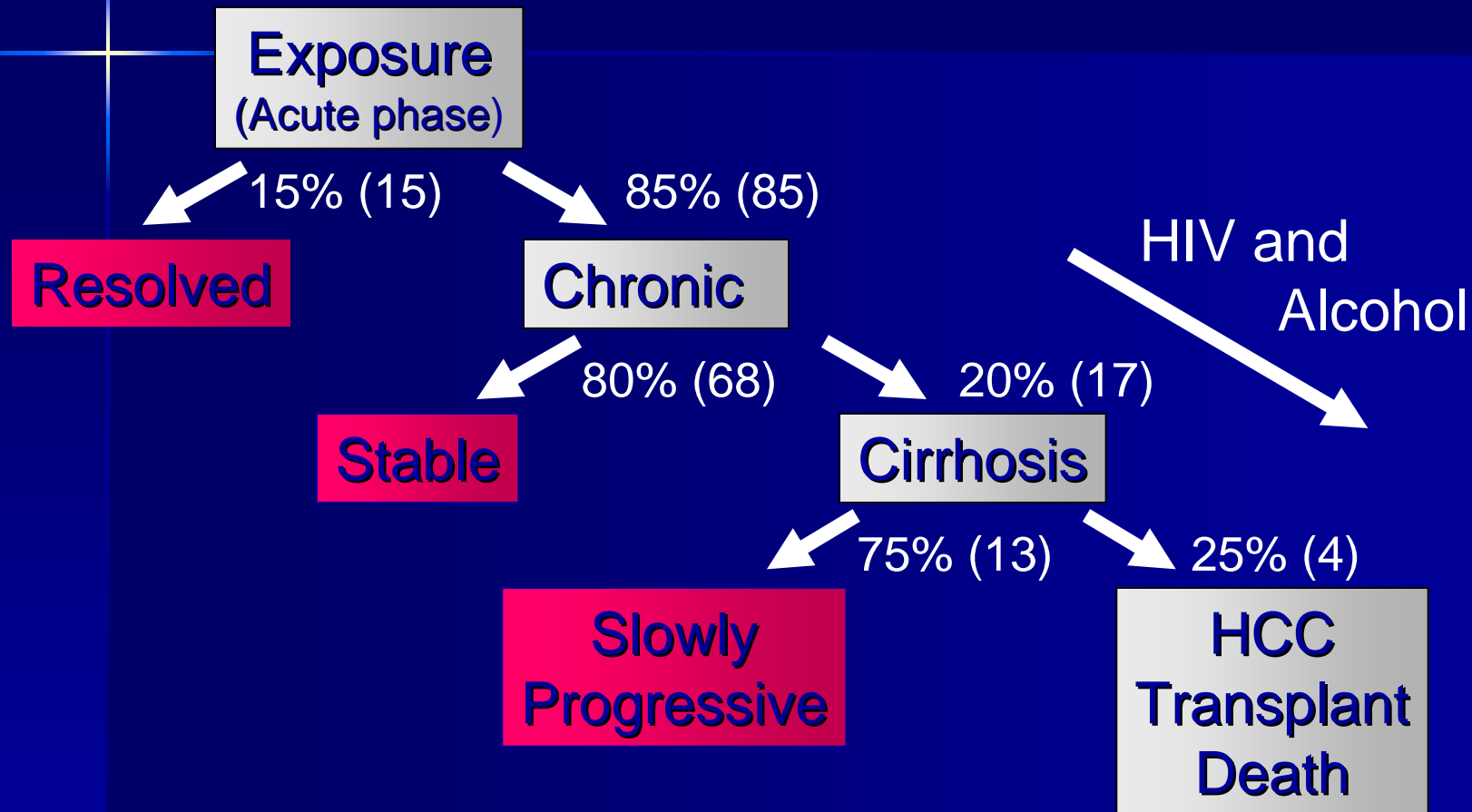
- 1955 persons followed at Hopkins HIV Clinic
 - no difference detected in progression to AIDS/Death
 - adjusted for HAART exposure and HIV suppression
- 3111 persons on HAART- Swiss Cohort
 - modest increased risk for progression to new AIDS-defining event or death
 - smaller increase in CD4 cells in persons with HCV co-infection

Impact of HCV on CD4 Recovery



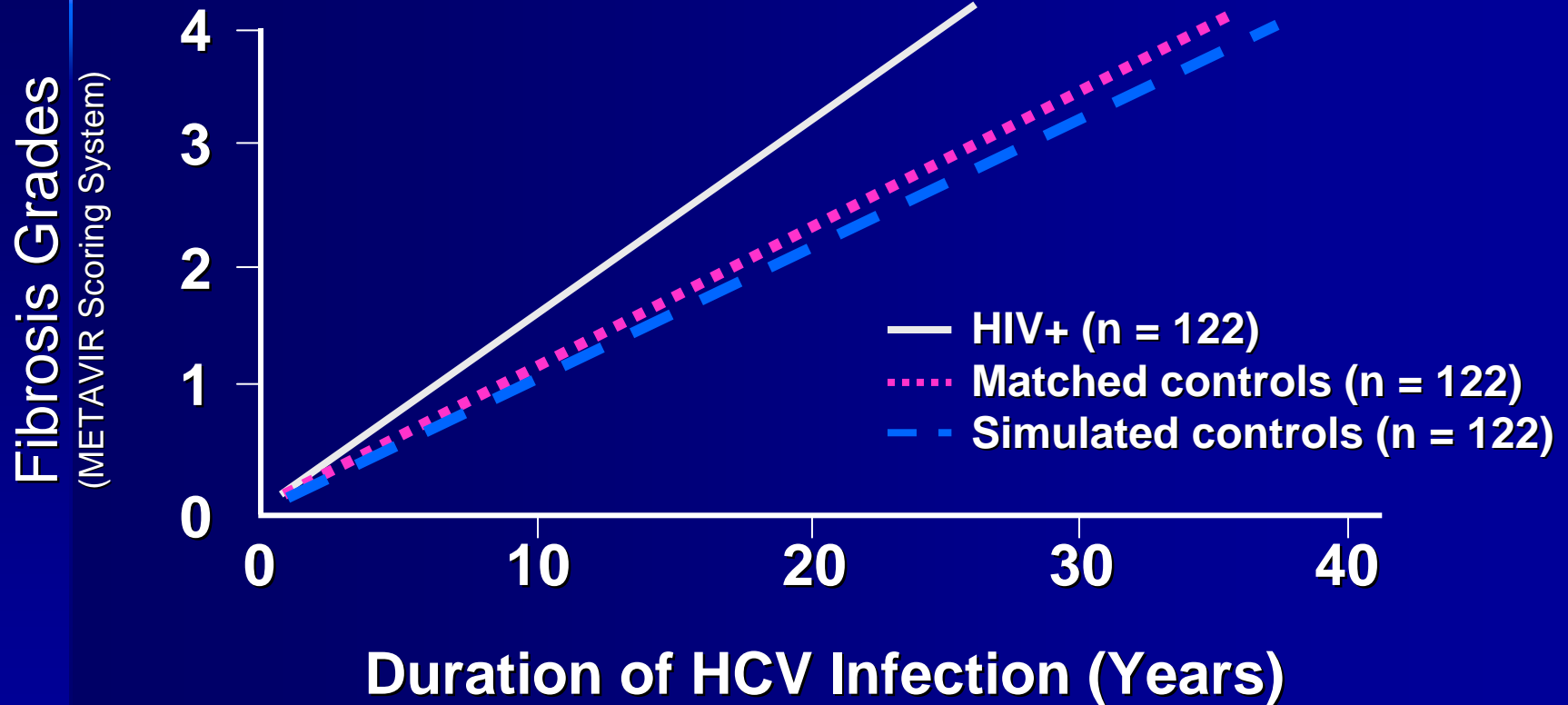
Impact of HIV on HCV Progression

Natural History of HCV Infection



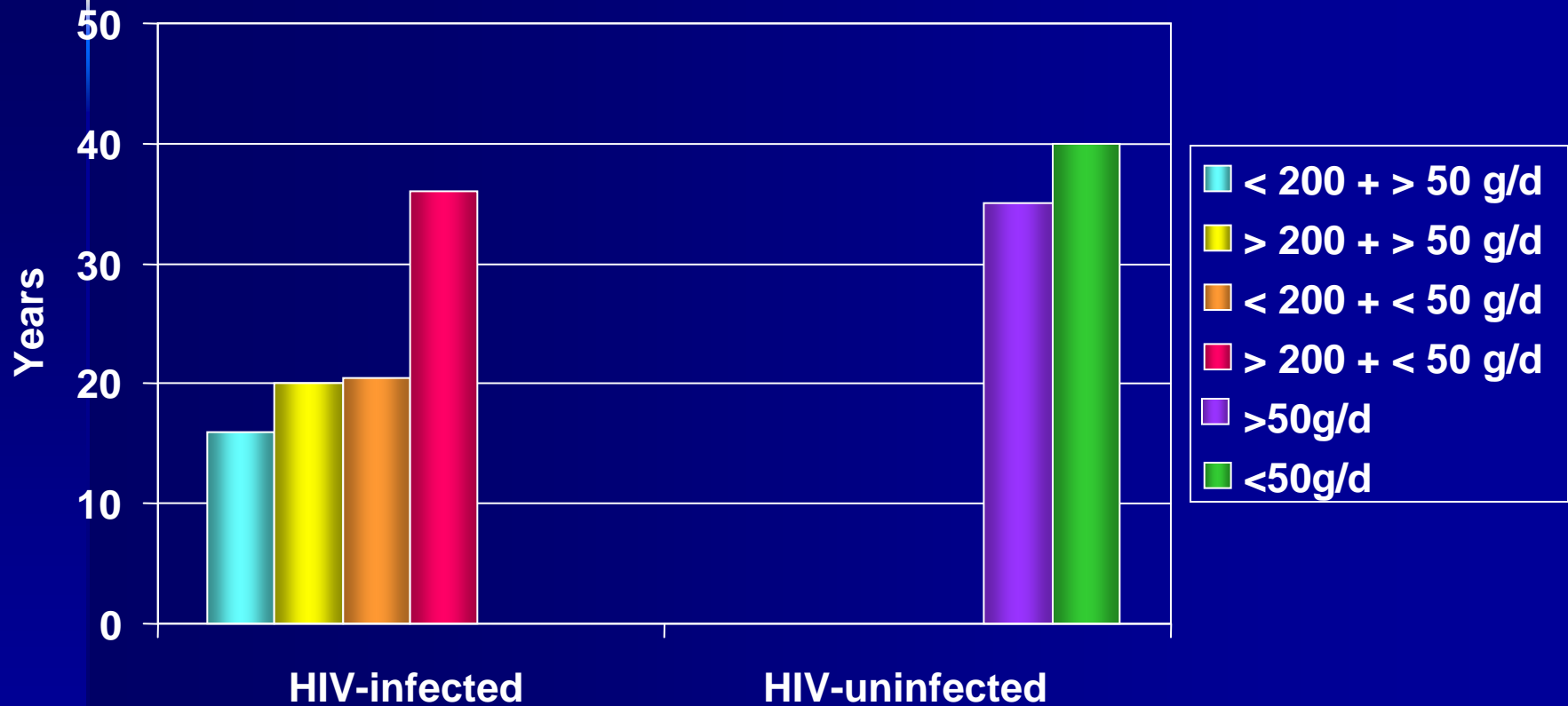
Alter, MJ. Epidemiology of Hepatitis C in the West. *Semin Liver Dis.* 1995; 15: 5-14.
Management of Hepatitis C. *NIH Consensus Statement.* 1997; March 24-26: 15(3).

Effect of HIV/HCV Coinfection on Fibrosis Progression Rate



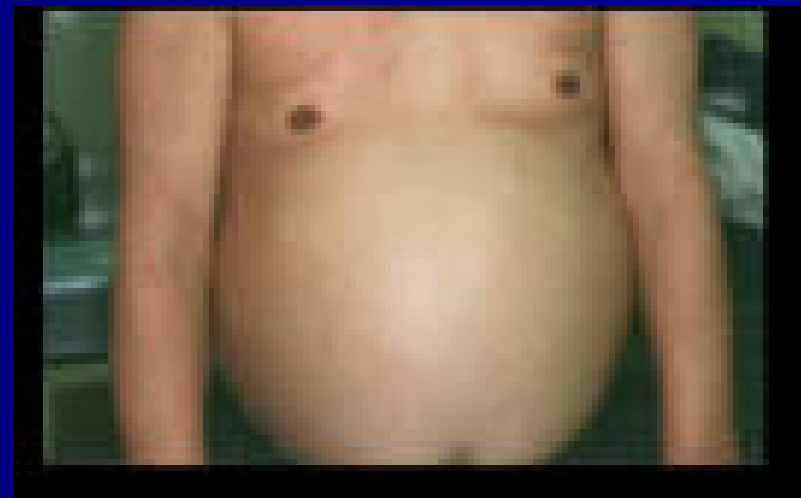
↑ with CD4 < 200/mm³, ETOH, age

Impact of Alcohol Use and CD4 on Progression to Cirrhosis



Progression to ESLD

- Hemophiliacs with HIV/HCV progress faster to ESLD compared to HCV
- Associated with lower CD4 count



Fibrosis Progression: HIV/HCV

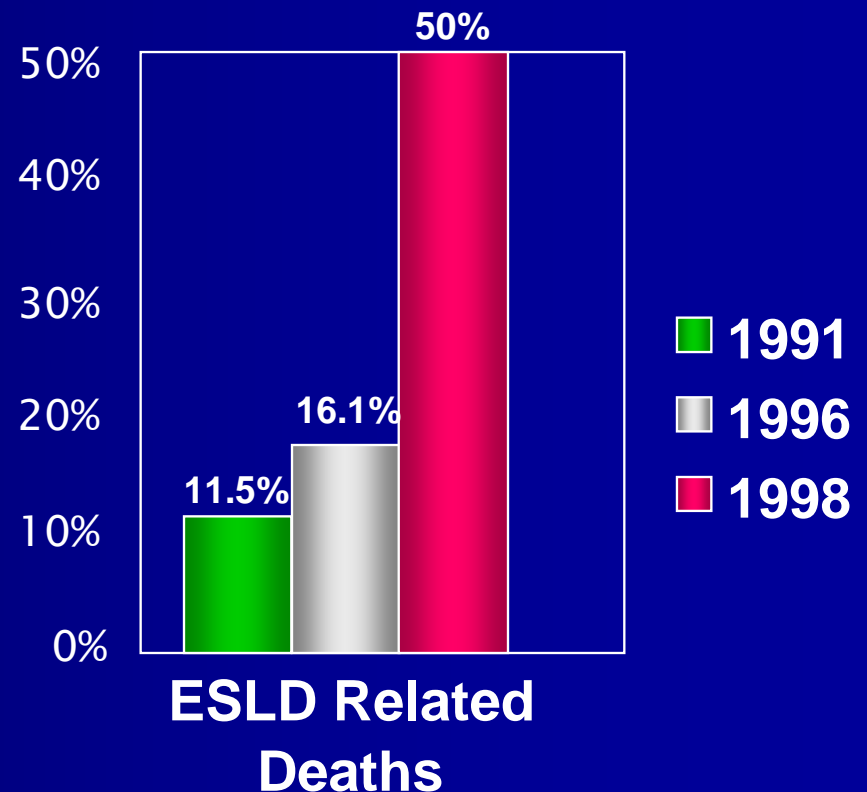
- 383 HIV/HCV who received HCV treatment
- Paired biopsies (n=198)
- 17% worsening fibrosis
- Multivariate analysis: DDI and failure to achieve SVR associated with increased risk of fibrosis
- Conclude mitochondrial toxicity of antiretrovirals may play important role in fibrosis progression

HCC in HIV Pts

Characteristics	Cases	Controls	p Value
Sex, M	7/0	21/10	
Age, yr	42.2 +/- 10.4	68.9 +/- 8.9	<0.001
Alcohol Consumption, >60 g/d (%)	3/7 (42/8%)	11/31 (35/5%)	NS
Duration of HCV Infection, yr	17.8 +/- 2.7	28.1 +/- 10.9	<0.05

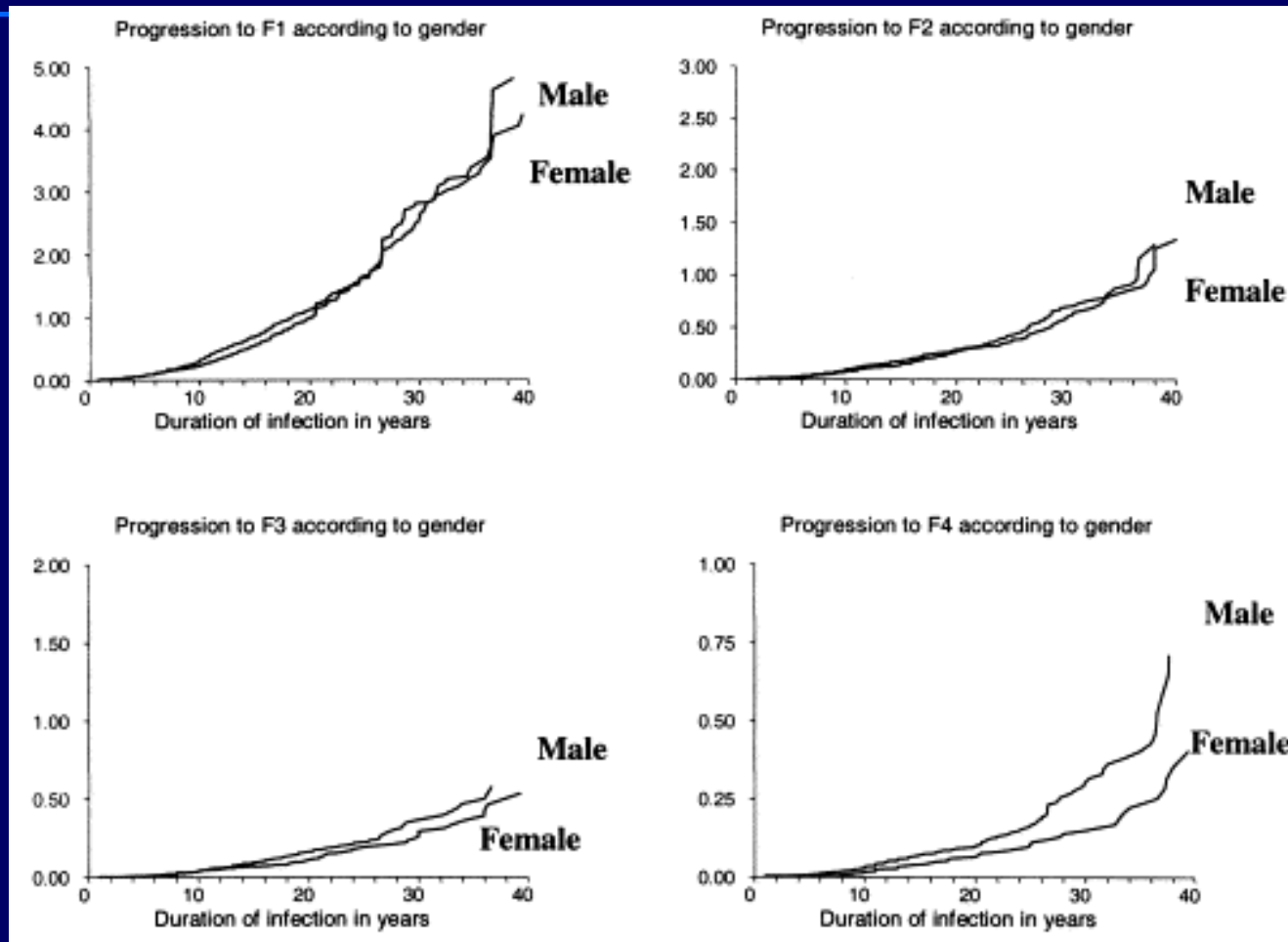
HCV-related Clinical Outcomes: Increased Rate of ESLD

- Of the patients that died in 1998:
 - 55% had undetectable HIV viral loads or CD4 >200
 - 91% tested for HCV and all were HCV +



Gender Differences with HCV

HCV Progression by Gender



Normal ALT

- Normal ranges set in 1950s
 - Healthy group +/- 2 SD
- Normal range varies by lab
- ALT independently related to:
 - Gender
 - Body mass index (BMI)
 - Abnormal lipid metabolism

Diagnosis and Treatment of HCV in HIV Patients

Evaluation and Treatment

- HCV antibody test
 - May see false negative HCV AB in pts with low CD4 cell count
- HCV RNA
 - quantify HCV viral load and confirm diagnosis
 - Higher viral load lower likelihood of response
- HCV genotype
 - Genotype 1 and 4 less responsive to therapy
 - Genotype 2 and 3 more responsive to therapy
- Ultrasound of liver
 - Evaluate for other causes of abnormal LFTs
 - Screen for HCC
 - Screen for Cirrhosis
 - Evaluate for ascites and portal hypertension
- Liver biopsy
 - Stage liver disease- patients with genotype 1 and mild fibrosis may consider deferring treatment because of poor response

Management of Patient with Cirrhosis

■ Cirrhotic patients

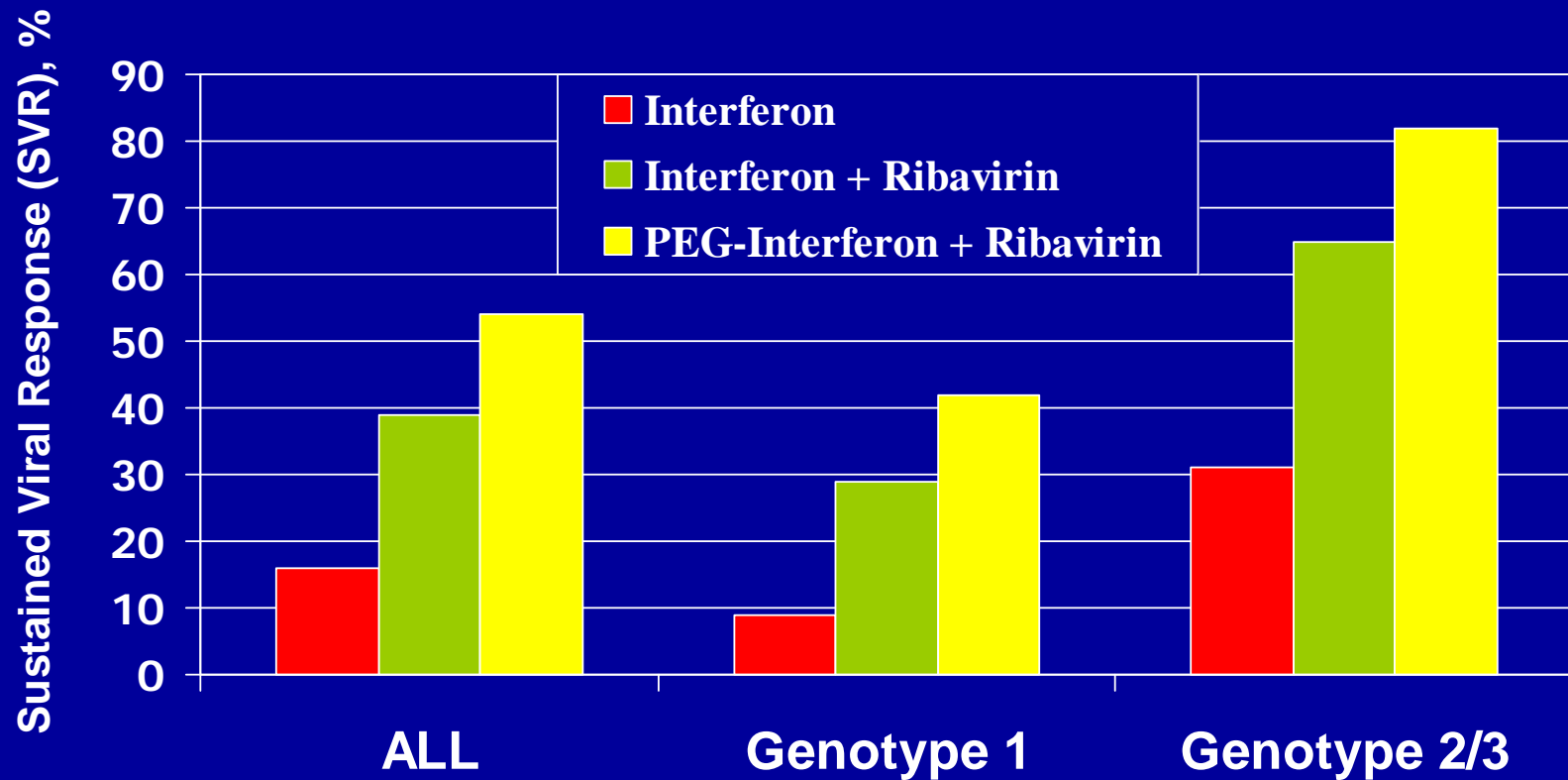
- Vaccinate for Hepatitis A (if HAV negative)
- Vaccinate for Hepatitis B (if HBsAg- and Hbcore Ab -)
- Ultrasound to evaluate for HCC
- Yearly AFP

HCV/HIV Treatment: Who should be considered for treatment?

- CD4 > 500: treat
 - goal: SVR
- CD4 200-500: consider treatment
 - goal: SVR or to:
 - reduce risk of HAART related hepatotoxicity
 - reduce risk of progression to ESLD
 - may benefit from therapy if plasma HIV RNA < 5000 copies/ml
- CD4 < 100: do not treat
 - therapy should not be initiated in any person with an active opportunistic infection

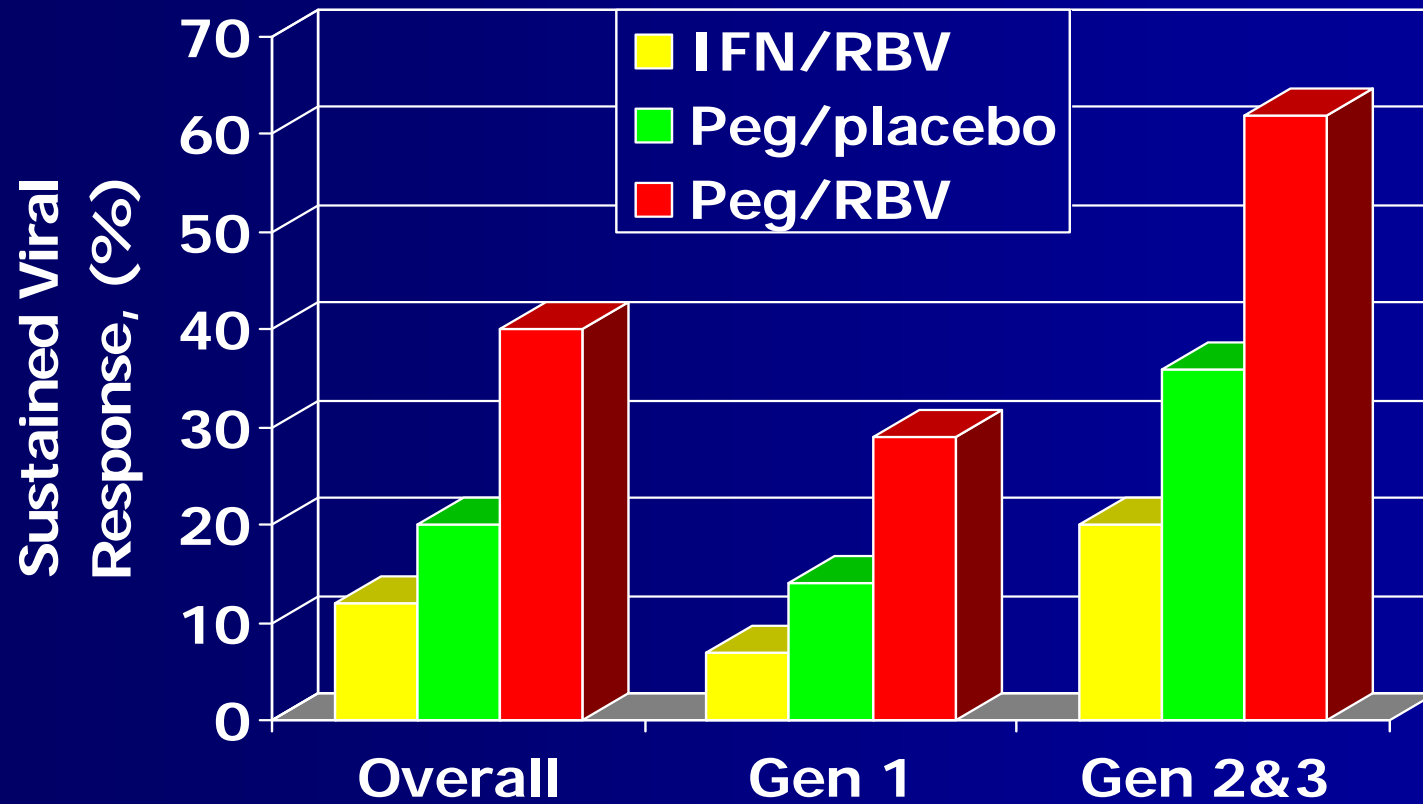
HCV Treatment

Therapy can eradicate disease



APRICOT:

AIDS Pegasys Ribavirin International Co-Infection Trial



Ribavirin Interaction with Other HIV Medications

- In vitro data shows that ribavirin antagonizes the anti-HIV activity of other NRTIs through inhibition of intracellular phosphorylation
 - Zidovudine (AZT)
 - Zalcitabine (DDC)
 - Stavudine (D4T)

Ribavirin Interaction with Other HIV Medications

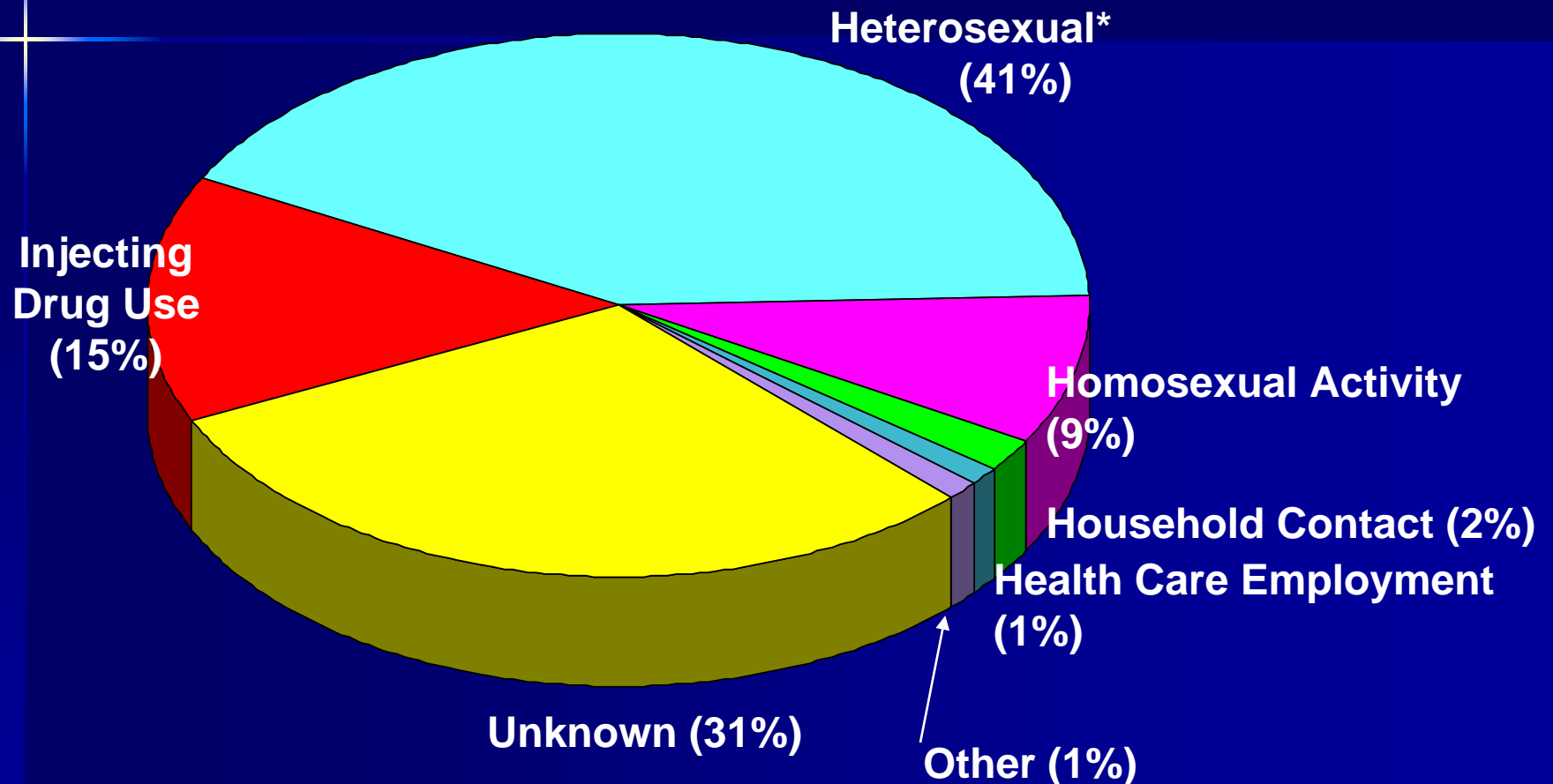
- Ribavirin inhibits inosine-5'-monophosphate dehydrogenase-which facilitates conversion of didanosine to its active metabolite
 - May lead to increase in vivo mitochondrial toxicity
 - symptomatic and fatal hyperlactatemia reported
 - Ribavirin **SHOULD NOT** be administered to persons receiving **DIDANOSINE (DDI)**

Hepatitis B Co-infection

Chronic HBV Epidemiology

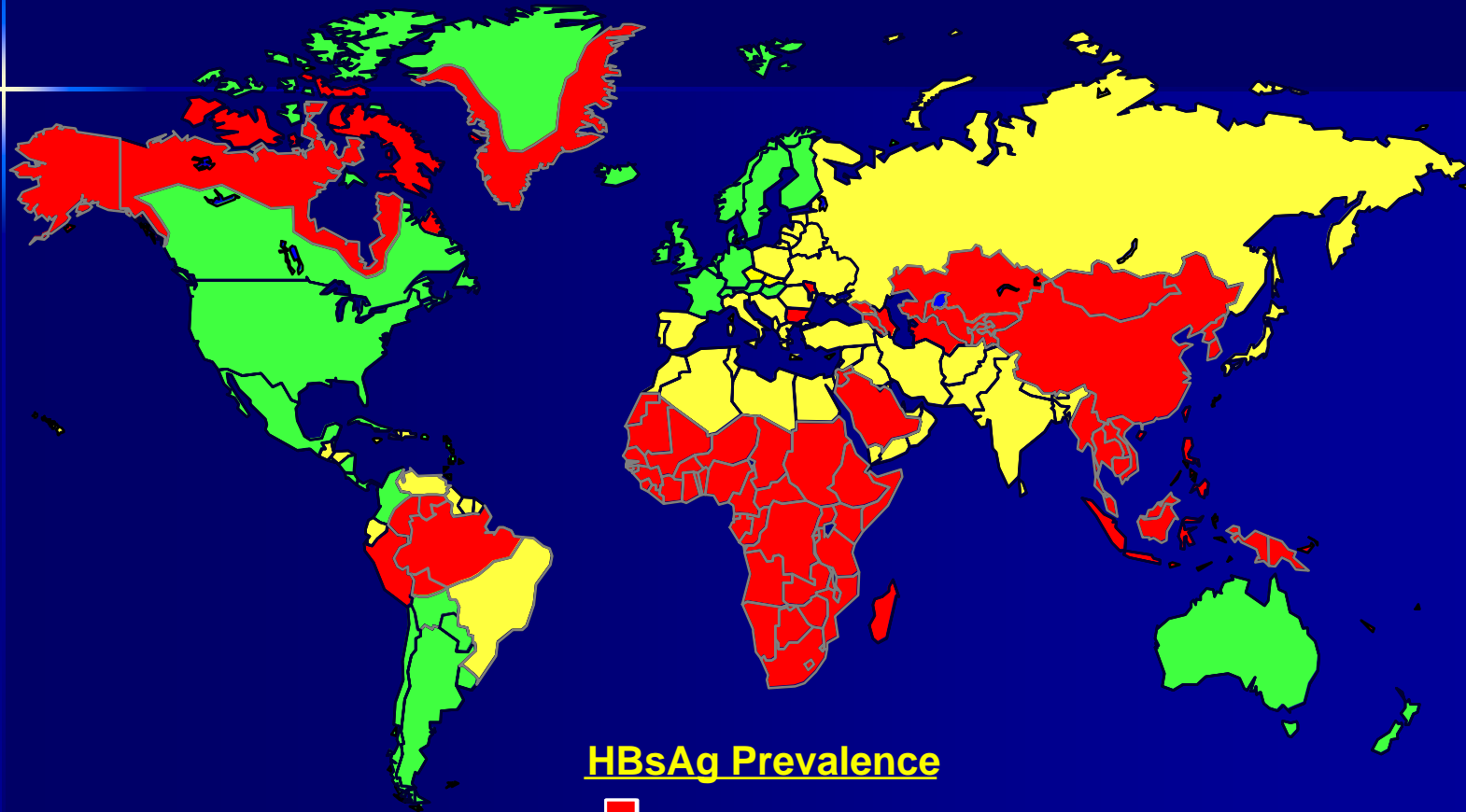
- Worldwide
 - 350 million persons chronically infected
 - 9th leading cause of death
- United States
 - 1.2 million chronic HBV carriers
 - ~30% acquired perinatally or during early childhood
 - 11,000 - 17,000 hospitalizations/yr
 - 4,000 - 5,500 deaths/year

Risk Factors for Acute Hepatitis B United States, 1992-1993



* Includes sexual contact with acute cases, carriers, and multiple partners.
Source: CDC Sentinel Counties Study of Viral Hepatitis

Geographic Distribution of Chronic HBV Infection



HBsAg Prevalence

- $\geq 8\%$ - High
- 2-7% - Intermediate
- $< 2\%$ - Low

HBV

Diagnostic Criteria

Chronic Hepatitis B

- HBsAg+ > 6 months
- Serum HBV DNA >10⁵ copies/mL
- Persistent or intermittent elevation of ALT/AST
- Liver biopsy showing chronic hepatitis

Resolved Hepatitis B

- Previous known history of acute or chronic hepatitis B or the presence of anti HBc ± anti-HBs
- HBsAg –
- Undetectable serum HBV DNA
- Normal ALT levels

MACS Cohort: HBV Mortality

- 5293 MSM
- 326 (6%) HBsAg+
 - 213 (65%)- HIV+
- 4967 HBsAg-
 - 2346 (47%)- HIV+

MACS Cohort: HBV Mortality

- Liver Related Mortality 1.1/1000 person years
 - HIV/HBsAg+: 14.2/1000 person years
 - HIV+: 1.7/1000 person years (p<0.01)
 - HBsAg+: 0.8/1000 person years (p<0.001)
- Highest risk of liver-related mortality

CD4 nadir	Relative risk (95%CI)
>250	6.8 (2.0-20.6)
101-250	8.8 (3.3-22.8)
<100	11.6 (4.6-28.7)
Study Period	
Before 1996	7.6 (4.0-14.1)
1996-2000	11.4 (3.4-38.0)

Treatment and Management of HBV

Treatment of HBV in HIV-Infected

Treatment	Log Reduction	HBeAg Seronversion	Resistance (YMDD)
Lamivudine	2.7 log	22-29%	14-38% at 1 yr 50% at 2 yr
Tenofovir	3-5 log	25%	Active against YMDD; 1 reported case
Emtricitabine	2.92 log*	33%*	9% at 48 weeks* 18% at 96 weeks*

Combination pills: Combivir (**lamivudine** and zidovudine) * Data not available in HIV/HBV
 Trizivir (**lamivudine**, abacavir, and zidovudine)
 Truvada (**tenofovir** and **emtricitabine**)
 Atripla (efavirenz, **tenofovir**, and **emtricitabine**)

Dore. *J Infect Dis* 1999; 180:607-13
 Hoff. *Clin Infect Dis* 2001; 32:963-9
 Pillay. *AIDS* 2000;14:1111-6

Benhamou. *N Engl J Med* 2003;348:177-8
 Sheldon. *Antivir Ther* 2005;10:727-34
 Gish. *Arch Int Med* 2006;166:49-56

Evaluation of HBV

- We asked how well do HIV providers evaluate and monitor HBV in HIV/HBV patients?
- To evaluate response to HBV therapy, measurement of HBV DNA is need at baseline and then during therapy.

HIV/HBV Patients Initiating HAART 1999-2003

Baseline Characteristics (n=155)	N (%)
CD4 (cells/ μ L), median [range]	137 [1-1089]
CD4 < 200 cells/ μ L	90 (58)
Log HIV viral load (copies/mL), median [range]	4.81 [1.69-6.11]
ALT (IU/L) , median [range]	34 [6-481]
AST (IU/L), median [range]	37 [13-389]

Active HBV Therapy

Any active HBV therapy	142 (92)
Lamivudine	137 (88)
Tenofovir	18 (12)
Emtricitabine	2 (1)
Adefovir	1 (<1)

Monitoring of HBV in HIV/HBV Patients

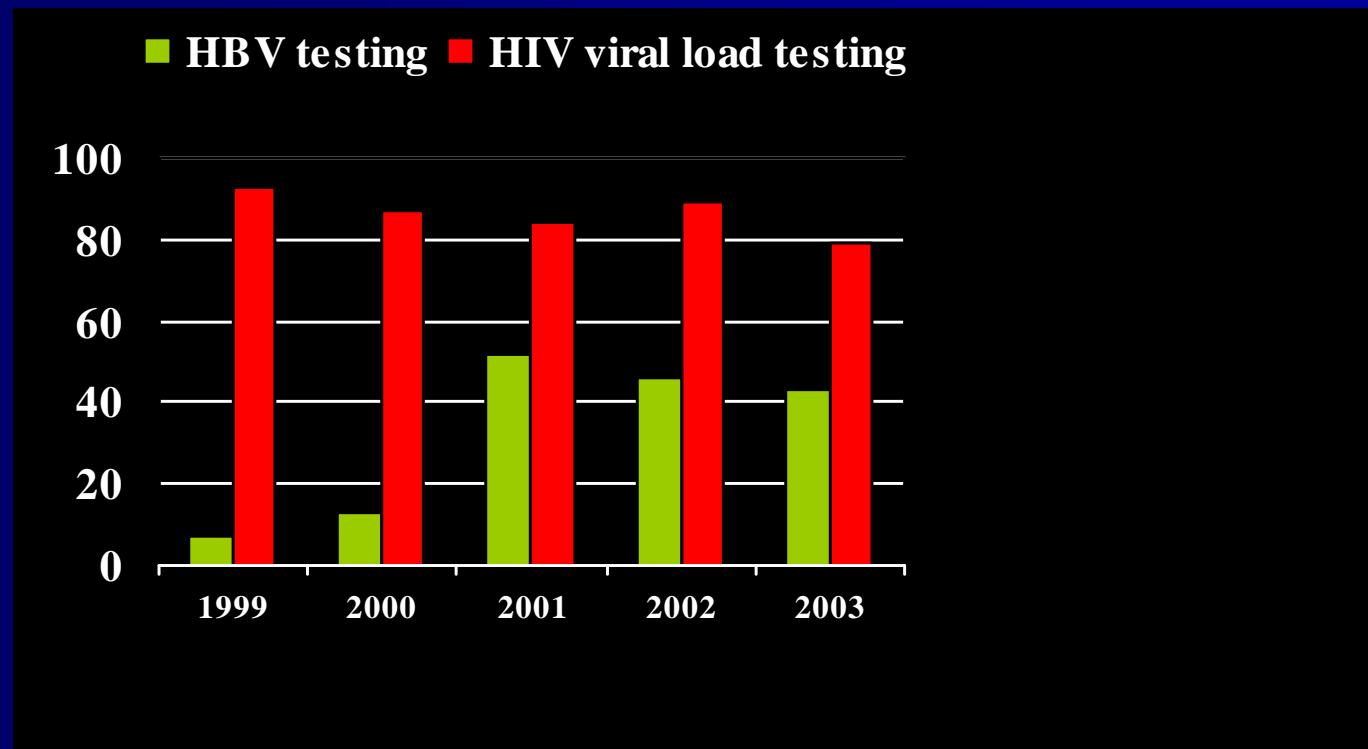
■ Testing for HBV or HIV prior to starting HAART

- HIV RNA prior to HAART 99%
- HBV DNA prior to HAART 16%

■ Monitoring of HIV and HBV during the first year of HAART

- HIV RNA 1st year of Rx 497 (median 3/pt)
- HBV DNA 1st year of Rx 85 (median <1/pt)

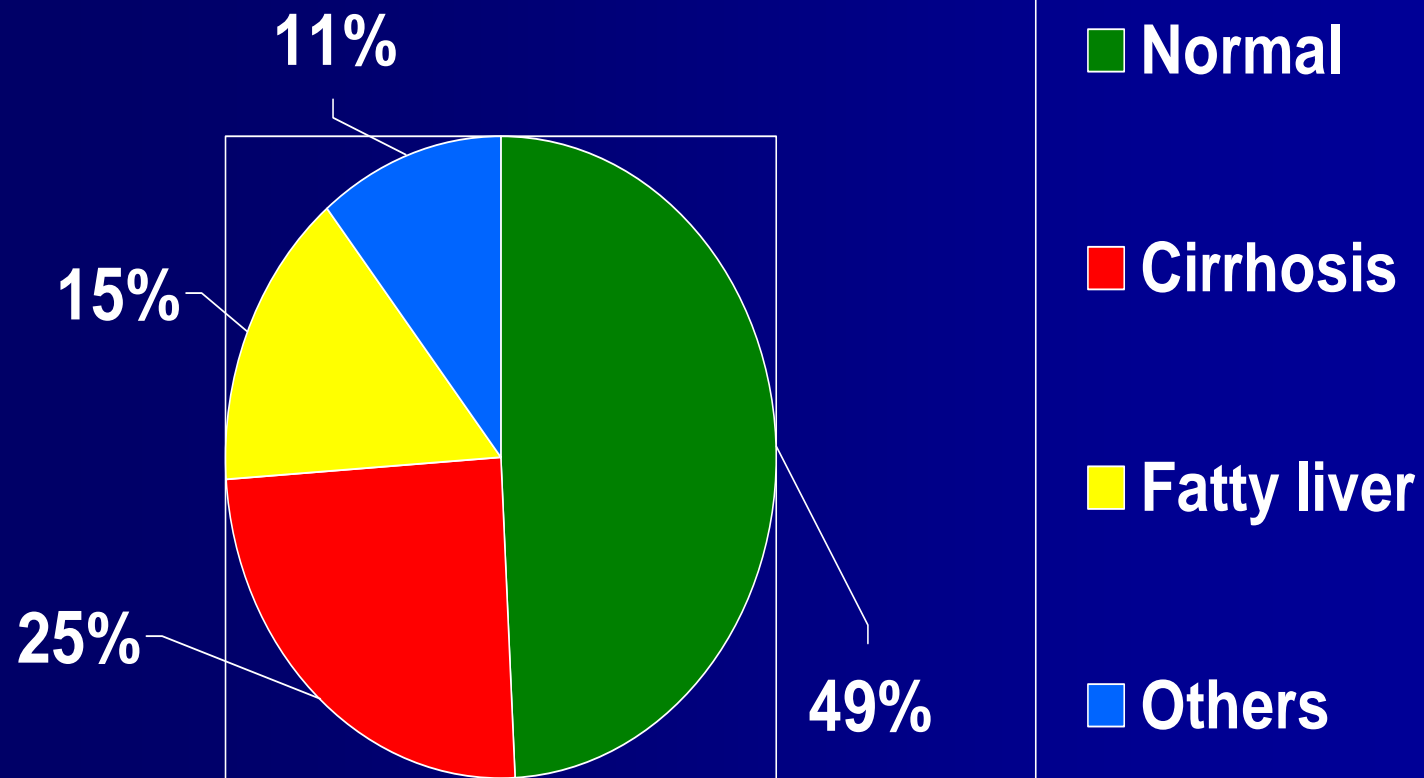
HBV Tests vs. HIV Tests



HBV Tests: HBV DNA or HBeAg/anti-HBe
HIV Tests: HIV RNA

Results

Liver sonograms



Vertical Transmission HIV/HBV

- Vertical transmission of HBV is a common route of HBV transmission in Asia
- US women are screened for HBV
- Prevention
 - Infants born to HBsAg+ women given HBIG
 - Maternal treatment of HBV may reduce HBV load and decrease transmission
- No data available in HIV/HBV

Management of Hepatitis B

- HIV/HBSAg+ to begin ART:
 - ✓ Hepatitis B DNA
 - quantify HBV viral load prior to initiation of ART
 - ✓ Hepatitis B e Antigen
 - indicates ongoing viral replication and can be used as a marker of active disease
 - ✓ Hepatitis B e Antibody
 - will become positive when patient has seroconverted
 - ✓ Ultrasound of liver
 - Cirrhosis and HCC
 - ✓ Consider Liver biopsy to stage disease

Management of HBV

- Confirm HBV viremia
- Start HAART (if indicated) which includes one or two agents active for HBV
- If HAART not indicated but patient with HBV viremia
 - Consider treatment with Adefovir, Interferon, or newer agents with no activity for HIV
- Monitor HBV DNA
 - Every 3-4 months
 - Once HBV DNA suppressed
 - Check HBeAg to determine if seroconversion has occurred
- Monitor for HCC
 - Ultrasound every year
 - Yearly AFP

Conclusions

- IDU is the main risk factor for HCV in women
- HIV/HCV women at increased risk for HIV and HCV transmission to neonate
- HCV may impair response to HAART
- HIV accelerates HCV progression
- Women may not progress as fast men
- Women may have lower normal ALT
- Treatment for HCV is effective in HIV/HCV
- Hepatitis B is a sexually transmitted disease

Conclusions

- HIV/HBV co-infection may lead to increased liver-related mortality
- HBV increased risk for HCC and requires monitoring
- Treatment of HBV utilizes some of the same nucleosides used to treat HIV
 - Lamivudine, emtricitabine, tenofovir
- Monitoring of HBV treatment and complications is needed