

Blending Clinical Practice and Research
HIV and Hepatitis C in Substance Abuse
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Blending Clinical Practice and Research

- Goals
 - Current Guidelines
 - Linkage of Care
 - Treatment Planning

Case One

- 38 year old man with history of IDU
- Sent by half way house for evaluation
- 2 years ago: CD4 count 80, HVL 52,000
- Never treated in past
- Fever of 101.4 in ER
- Last injection use was 5 weeks ago
- History of + PPD without treatment

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Discussion Points

- CD4 Count
- Viral Load
- ARVT/HAART
- Opportunistic Infections
- + TST (tuberculin skin test) in setting of HIV
- Entry into care

CD4 Count - What is it?

- Measure of the number of T helper cells, a type of white blood cell lymphocyte
- Also known as the T – helper cell
- These cells orchestrate immune response
- Destruction of CD4+ cells is the major cause of immunodeficiency in AIDS

CD4 Count - What does it mean?

- Decreasing CD4 lymphocyte levels appear to be the best predictor of developing opportunistic infections
J Acquir Immune Defic Syndr. 2004 Aug 15;36(5):1028-1033
- Initiating treatment at CD4 counts above 200/microL shows low rates of progression to death and AIDS
JAMA. 2001 Nov 28;286(20):2568-77

CD4 count - Predictors

- <200: Risk of PCP pneumonia
- <100: Risk of toxoplasmosis
- < 50: Risk of *Mycobacterim Avium* complex

Viral Load - What is it?

- A measure of the HIV RNA in the blood
- Expressed as copies per ml of plasma

Viral Load - What does it mean?

- Best predictor of disease progression
- Used to determine response to and when to change therapy

ARVT/HAART - What is it?

- Anti Retro Viral Therapy
- Highly Active Anti-Retroviral Therapy
 - Drug regimen to aggressively suppress viral load and prevent disease progression
 - Usually combines at least three drugs with different mechanisms of action
 - Regimens that can reduce virus in blood to undetectable levels

ARVT/HAART

- NRTIs: Nucleoside Reverse Transcriptase Inhibitors
 - Classic drugs like AZT, 3TC, ddI, d4T, etc.
 - Variety of drug specific reactions such as peripheral neuropathy, hypersensitivity, pancreatitis, gastrointestinal side effects, lipodystrophy

ARVT/HAART

- NNRTIs: Non-Nucleoside Reverse Transcriptase Inhibitors
 - Delavirdine, Efavirenz, Sustiva
 - Rash and increased liver transaminases

ARVT/HAART

- Protease Inhibitors

- Amprenavir, Atazanavir, Indinavir, Ritonavir, Nelfinavir
- Multiple common effects including gastrointestinal symptoms, fat redistribution, liver enzyme elevation, increased blood sugar

Opportunistic Infections

- Illnesses caused by various organisms, some of which usually do not cause disease in persons with normal immune systems.
- Common opportunistic infections include:
 - Pneumocystis carinii pneumonia;
 - Kaposi's Sarcoma;
 - Cryptosporidiosis;
 - Histoplasmosis;
 - Other parasitic, viral, and fungal infections;
 - Some types of cancers

Opportunistic Infections

- Primary prophylaxis
- Secondary prophylaxis
 - Suppressive or chronic maintenance therapy
- Discontinuation of prophylaxis

TB Skin Testing in HIV

- Tuberculin Skin Testing (TST) recommended for all persons when HIV is first diagnosed
- 5 mm or more of induration is considered positive

Entry into care

Medical and Drug Treatment Associated with Less Hospitalization

- Laine C, Hauck WW, Gourevitch MN, Rothman J, Cohen A, Turner BJ. Regular outpatient medical and drug abuse care and subsequent hospitalization of persons who use illicit drugs. *JAMA* 2001;285(18):2355-62.

Regular and Stable Methadone Attendance Was Primary Predictor of HAART Acceptance

- Clarke S, Delamere S, McCullough L, Hopkins S, Bergin C, Mulcahy F. Assessing limiting factors to the acceptance of antiretroviral therapy in a large cohort of injecting drug users. *HIV Med* 2003;4(1):33-7.

Palepu, A., N. J. Horton, et al.
(2004). "Uptake and adherence to
highly active antiretroviral
therapy among HIV-infected
people with alcohol and other
substance use problems: the
impact of substance abuse
treatment." Addiction **99**(3): 361-
8.

Fever in an IDU

Fever in and Injecting Drug User

- Management depends on access to care and continuity of care

Samet, J. H., A. Shevitz, et al.
(1990). "Hospitalization decision
in febrile intravenous drug
users." Am J Med **89**(1): 53-7

Appropriate immunizations

Immunizations in HIV

- May not be effective for CD4 counts less than 200
- Vaccines that contain live component (MMR, Varicella) not given to severely immunocompromised
- Killed or recombinant vaccines generally safe

Immunizations in HIV

<i>Streptococcus pneumoniae</i> ⁵	CD4+ count \geq 200/μL
Hepatitis B virus ^{6,7}	All susceptible (anti-HBc-negative) patients
Influenza virus ^{6,8}	All patients (annually, before influenza season)
Hepatitis A virus ^{6,7}	All susceptible (anti-HAV-negative) patients at increased risk for HAV infection (e.g., illicit drug users, men who have sex with men, hemophiliacs) or with chronic liver disease, including chronic hepatitis B or hepatitis C

Mental health screens – depression, trauma

- PRIME-MD
- Beck Depression Inventory

Case Two

- 24 y/o man presents to a methadone program.
- 5 years prescription drug abuse, a one year history of intermittent injection heroin use
 - Now injecting daily
- Ten year history of increasing alcohol consumption.
 - Now drinking one pint per day

Case Two - Continued.

- Homeless for the last year.
- Recently hospitalized after an episode of jaundice.
 - Paperwork from hospital shows:
 - Hepatitis A Antibody Negative
 - HBsAg - Neg
 - HBCAb Pos; HCV positive.

Discussion Points

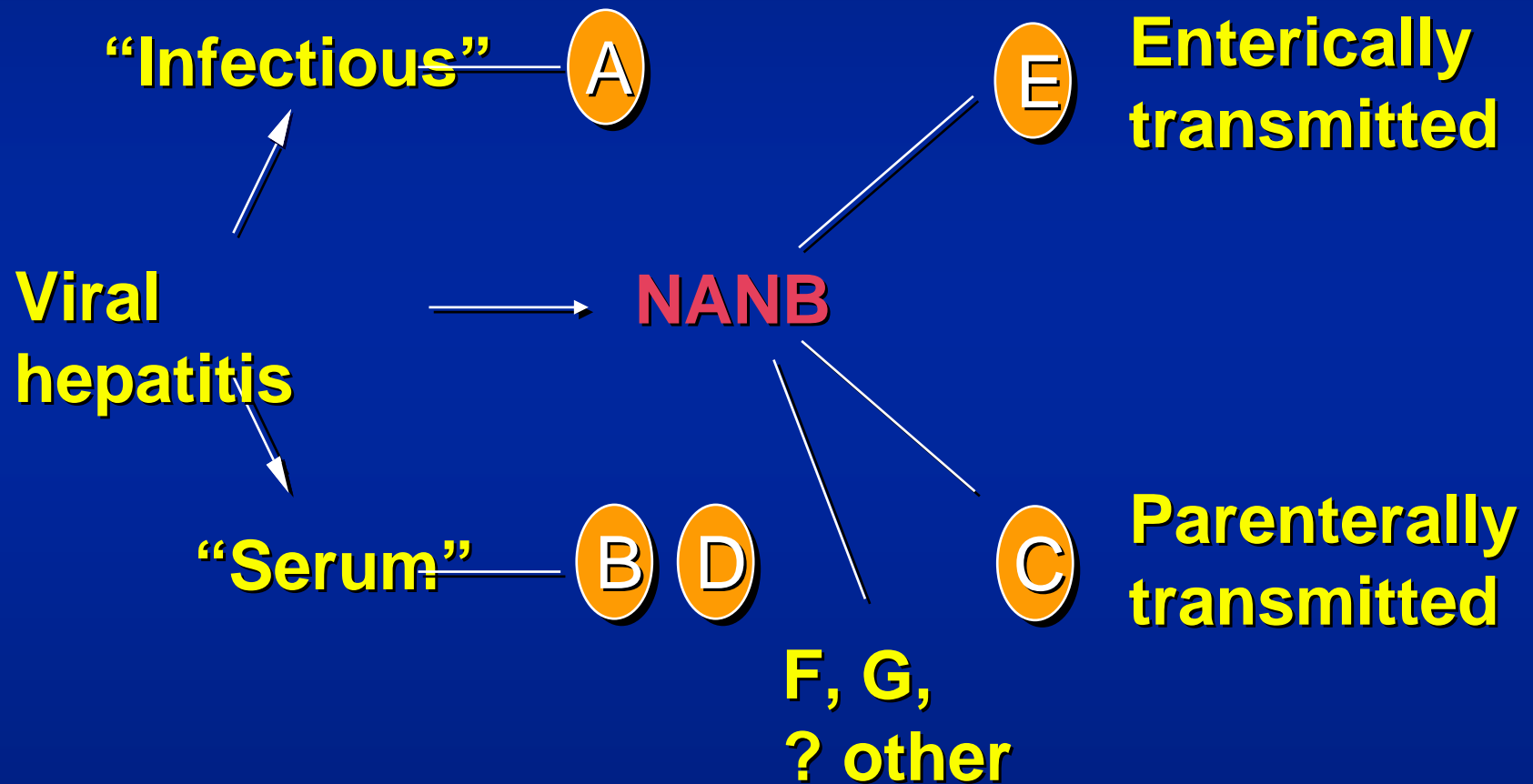
- Hepatitis Serology
- Alcohol use and Hepatitis
- Hepatitis C natural history

Hepatitis Serology and Nomenclature

Hepatitis Serologies

- Hep A Ab: Hepatitis A antibody
 - IgM - acute antibody
 - IgG - “long term”
- HBsAg: Hepatitis B surface antigen
 - Present after acute infection and chronic disease
- HBsAb: Hepatitis B surface antibody
 - Present after vaccine and in immune patients
- HBcAb: Hepatitis B core antibody
- HCV: Hepatitis C virus

Viral Hepatitis - Historical Perspective

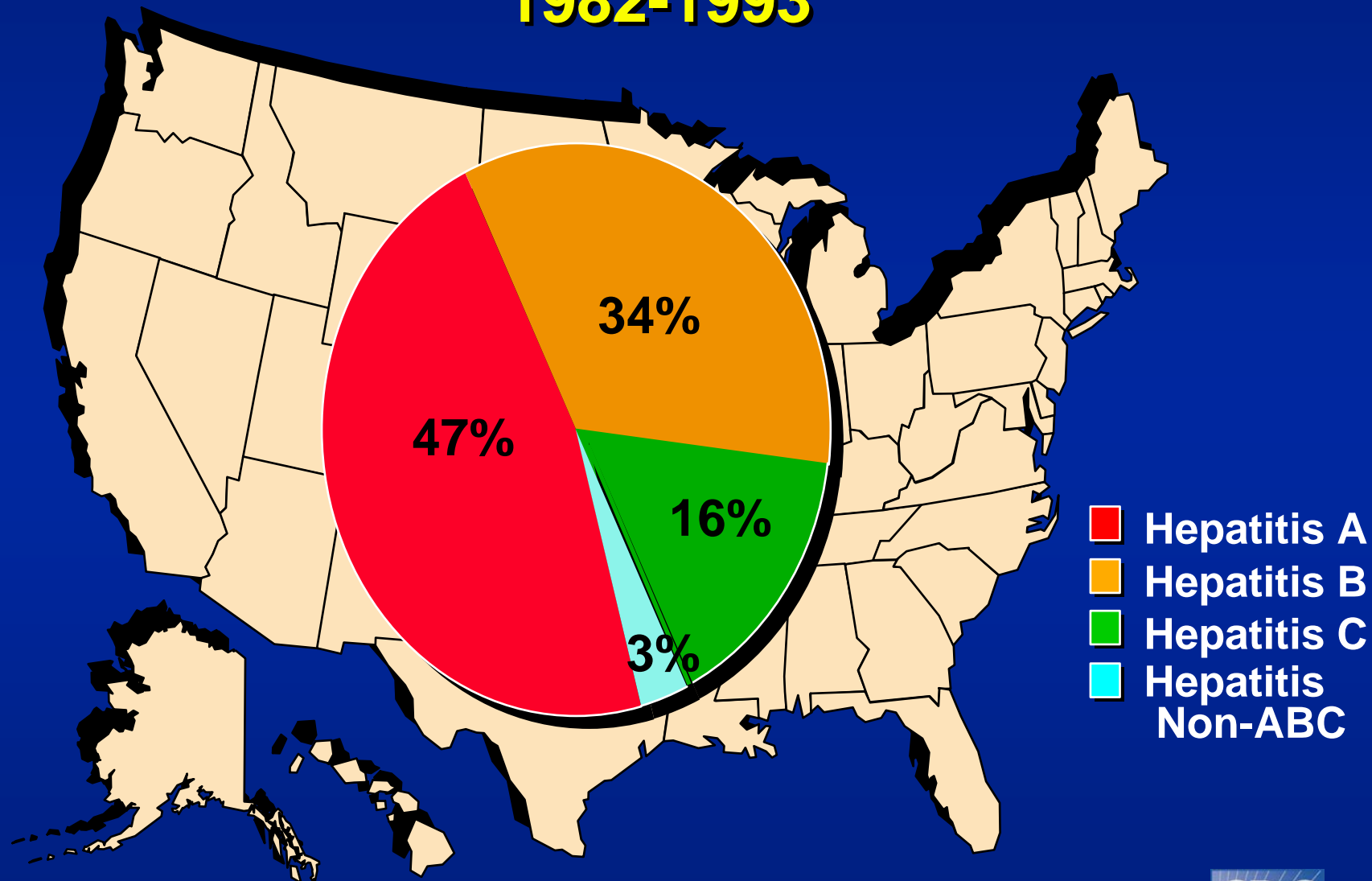


Viral Hepatitis - Overview

Type of Hepatitis

	A	B	C	D	E
Source of virus	feces	blood/ blood-derived body fluids	blood/ blood-derived body fluids	blood/ blood-derived body fluids	feces
Route of transmission	fecal-oral	percutaneous permucosal	percutaneous permucosal	percutaneous permucosal	fecal-oral
Chronic infection	no	yes	yes	yes	no
Prevention	pre/post- exposure immunization	pre/post- exposure immunization	blood donor screening; risk behavior modification	pre/post- exposure immunization; risk behavior modification	ensure safe drinking water

Acute Viral Hepatitis by Type, United States, 1982-1993



Source: CDC Sentinel Counties Study on Viral Hepatitis

Estimates of Acute and Chronic Disease Burden for Viral Hepatitis, United States

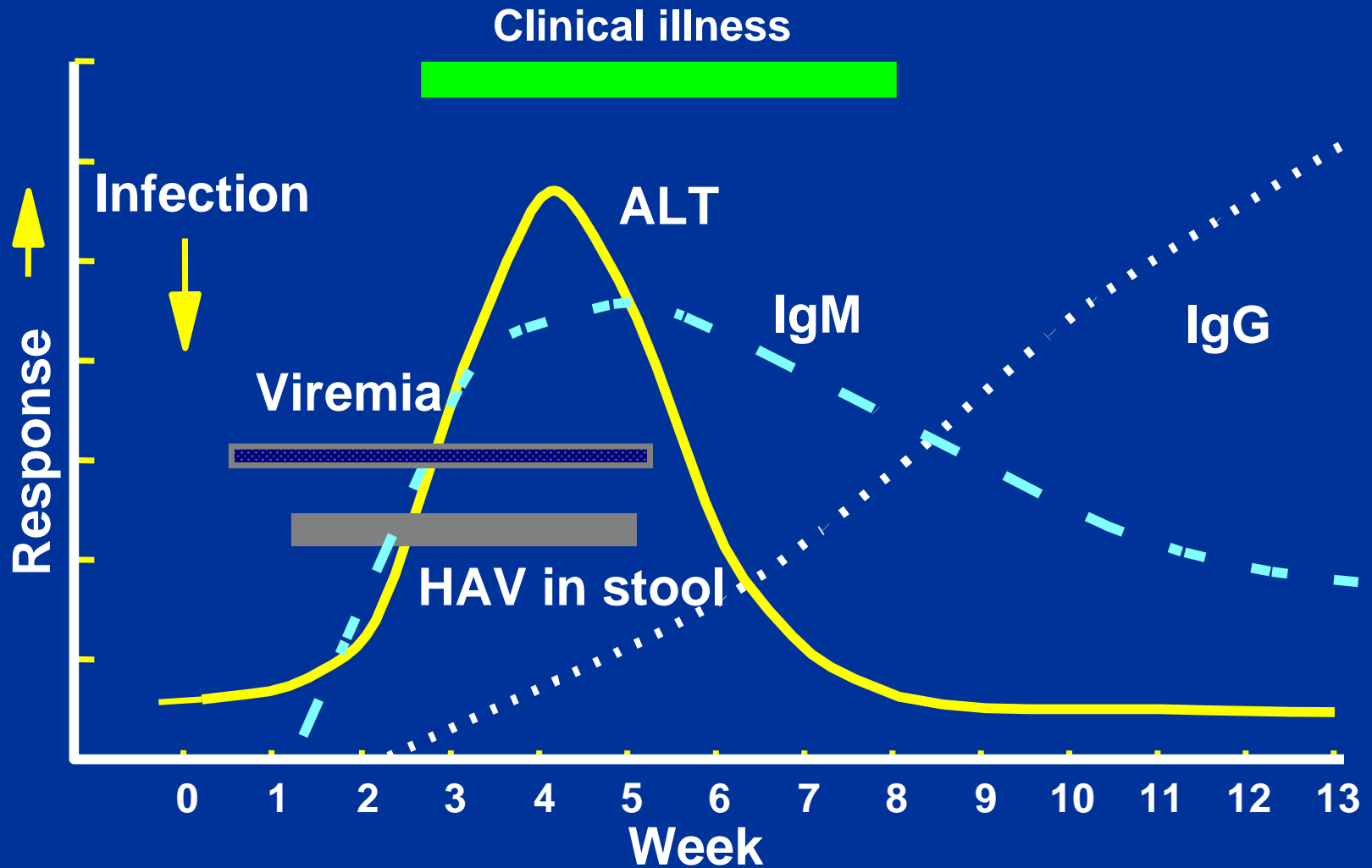
	HAV	HBV	HCV	HDV
Acute infections (x 1000)/year*	125-200	140-320	35-180	6-13
Fulminant deaths/year	100	150	?	35
Chronic infections	0	1-1.25 million	3.5 million	70,000
Chronic liver disease deaths/year	0	5,000	8-10,000	1,000

* Range based on estimated annual incidence, 1984-1994.

HEPATITIS A VIRUS

- RNA Picornavirus
 - Single serotype worldwide
 - Acute disease and asymptomatic infection
- No chronic infection
 - Protective antibodies develop in response to infection - confers lifelong immunity

EVENTS IN HEPATITIS A VIRUS INFECTION



Alcohol use and Hepatitis

- Screening for Alcohol Use
 - CAGE
 - AUDIT
- Alcohol use and progression of liver disease

Hepatitis C natural history



Natural History of Chronic Hepatitis C

Leonard B. Seeff, M.D.

**National Institute of Diabetes and
Digestive and Kidney Diseases**

National Institutes of Health



The Current Status of the Natural History of Hepatitis C

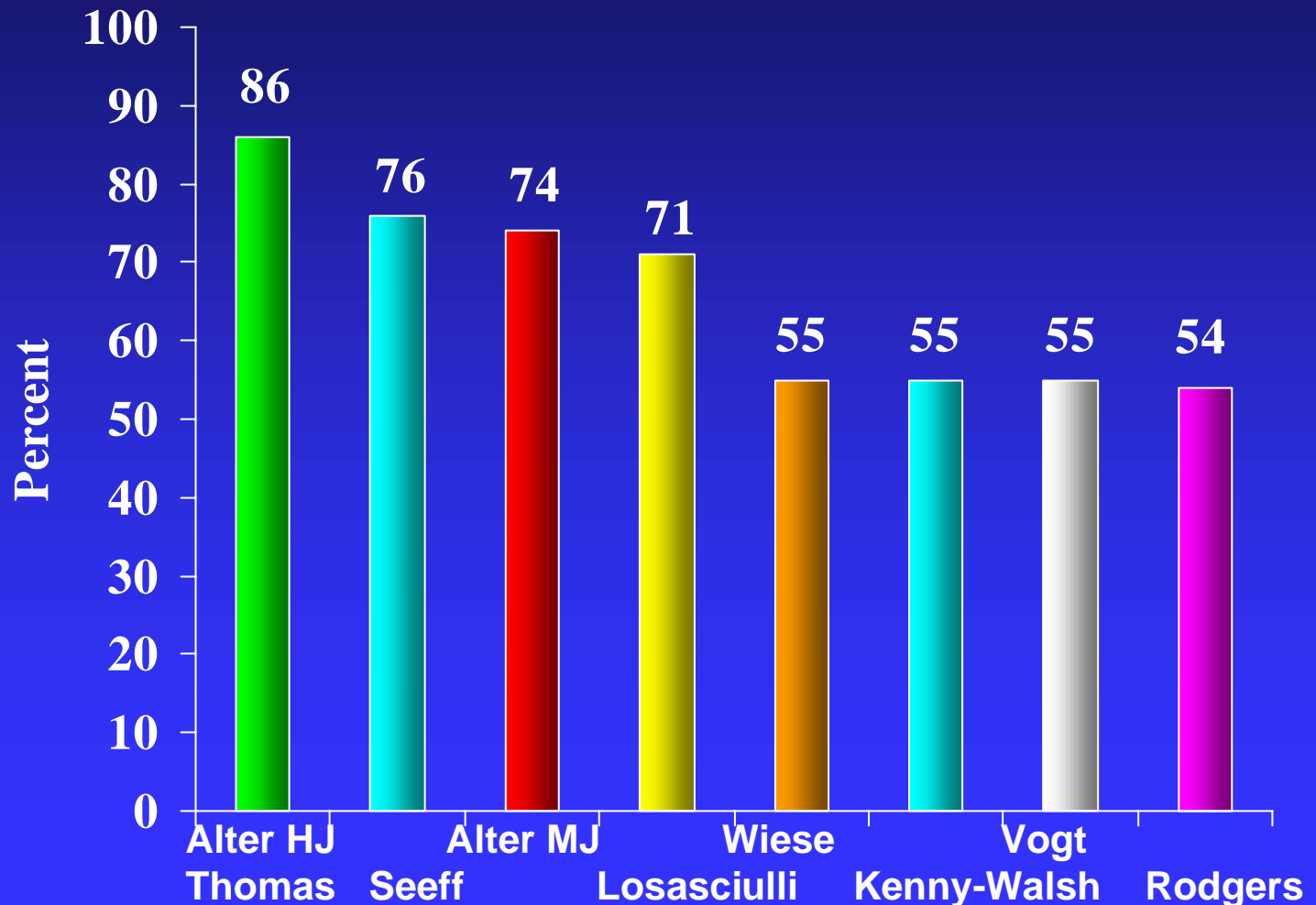
- The natural course of hepatitis C extends over several decades
- The natural history during the first two decades after acute infection is beginning to be established
- The natural history in the period following the first two decade after infection is largely unknown other than through data modeling



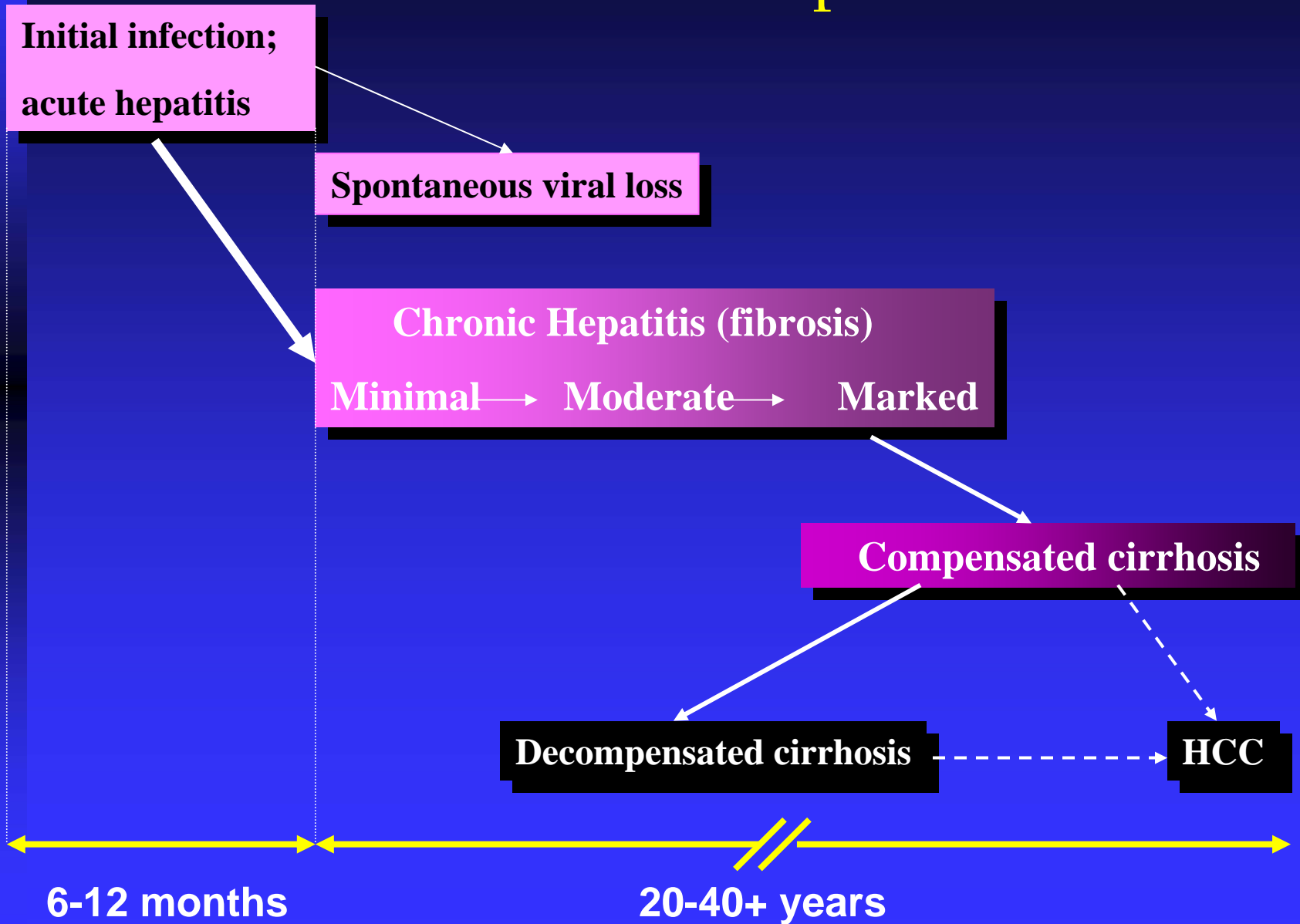
Components that Account for the Natural History of Hepatitis C

The natural history of hepatitis C is a product of the outcome of both *acute hepatitis C* and *chronic hepatitis C*

Rates of Persistence of Hepatitis C Virus Following Acute Infection



Sequence of Events After Acute Infection with the Hepatitis C Virus





Primary Concern in Chronic Hepatitis C

Evolution to increasing degrees of fibrosis!

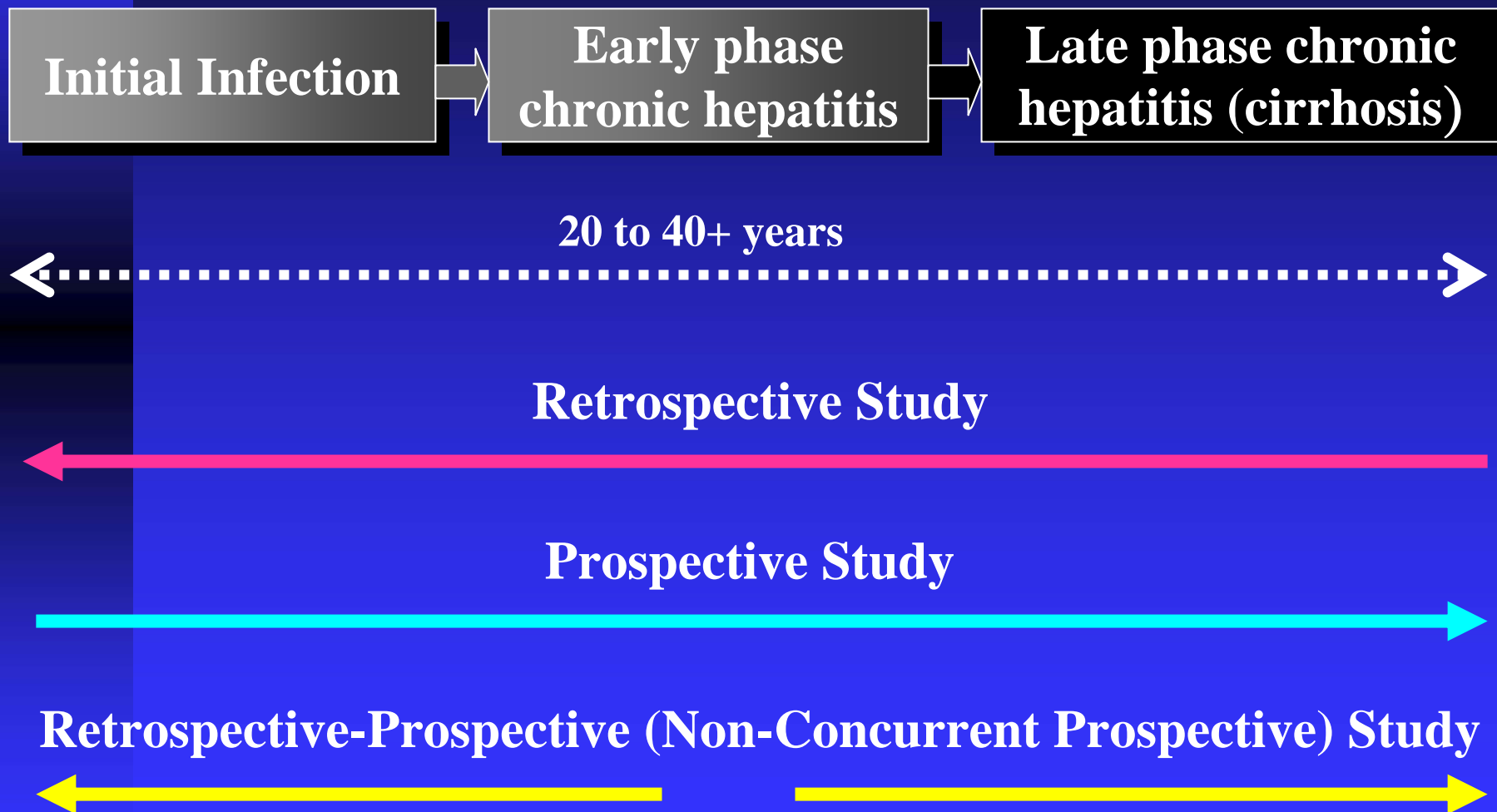
End-stage liver disease and liver cancer rarely develop in the absence of cirrhosis



Factors That Limit the Ability to Define the Natural History of Hepatitis C

- The onset of acute infection is rarely identified
- Evolution from acute to chronic hepatitis occurs in the absence of symptoms
- The course of the chronic phase is also generally devoid of symptoms or is oligosymptomatic
- Duration of chronic phase before reaching overt end-stage liver disease ranges from 20-40+ years
- Associated co-morbid conditions or co-infections have a significant impact on the disease course

Strategies Used to Determine the Natural History of Hepatitis C



Early Retrospective and Prospective Studies of the Natural History of Hepatitis C

➤ Retrospective Studies *

Intervals from exposure	9-29 years
Development of cirrhosis	17-55% (mean, 42%)
Development of HCC	1-23%
Liver-related death	4-15%

*Kiyosawa, Tong, Yano, Niederau, Gordon

➤ Prospective Studies**

Intervals from exposure	8-16 years
Development of cirrhosis	7-16% (mean, 11%)
Development of HCC	0.7-1.3%
Liver-related death	1.3-3.7%

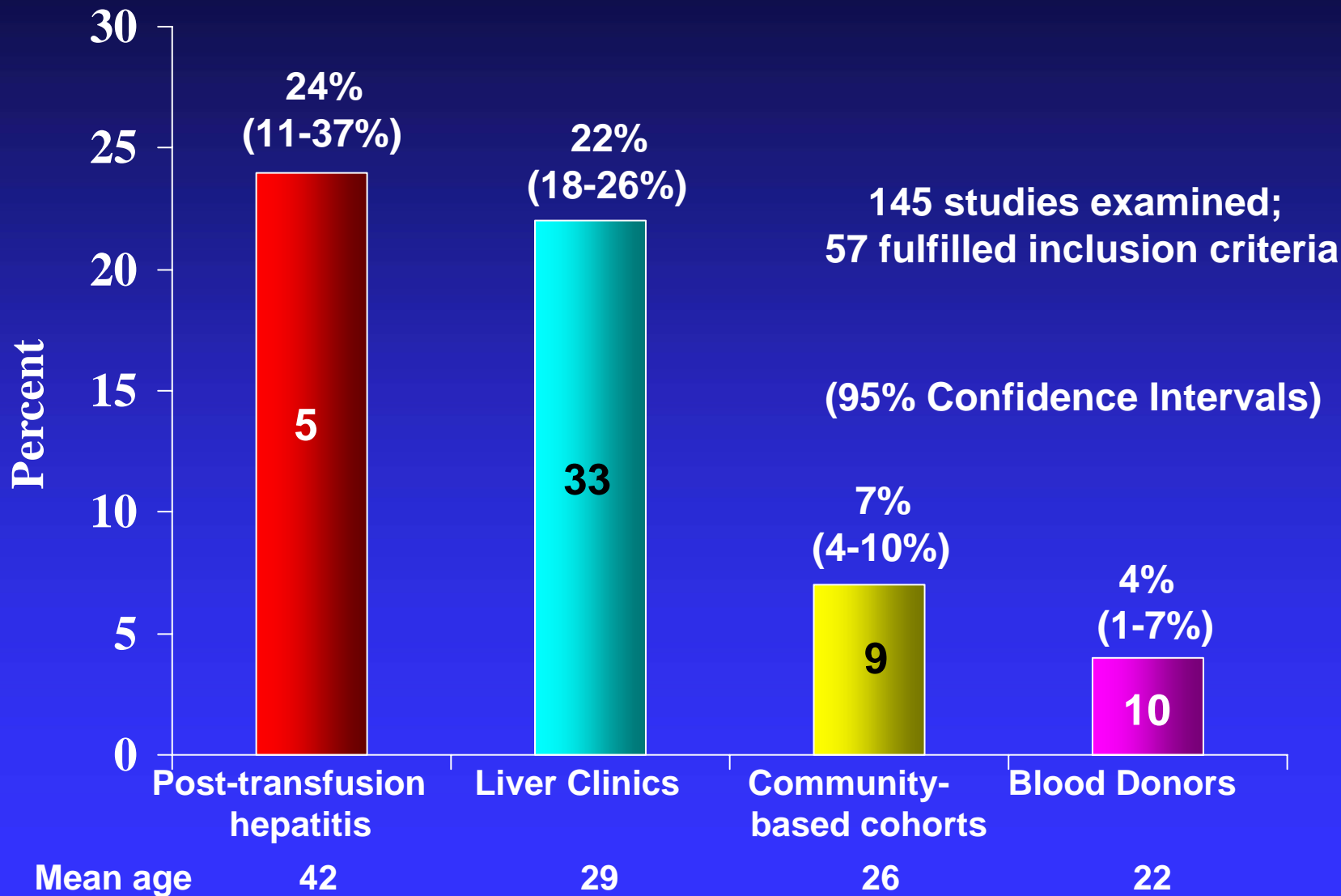
** Di Bisceglie, Koretz, Mattson, Tremolada


Retrospective-Pro prospective Cohort Studies of the Natural History of Chronic Hepatitis C

Author	Group	Exposure Interval (yrs)	Cirrhosis %	HCC %	Liver Death (%)
Vogt	Children	17	0.3	0	0
Kenny-Walsh	Women (yng)	17	2.0	0	0
Wiese	Women(yng)	20	0.4	0	0
Seeff	Men (yng)	45-50	5.9	0	0
Thomas	IDU	9	1.0	0	2.1
Rodgers	Com. Acq	25	4.0	0	1.0
Seeff	PTH	23	15.0	1.9	2.8

Mean, 2.1%

Rate of Progression to Cirrhosis by 20 Years Based on the Mode of Study Recruitment





Factors That Could Have An Impact on Progression of Chronic Hepatitis C

- **Viral-related**
- **Host-related**
- **External factors**



Viral-Related Factors

- **Viral concentration (load)** **No effect**
- **Viral genotype** **Probably no effect**
- **Viral quasispecies** **May effect evolution from acute to chronic viremia but not actual progression of chronic hepatitis**



Host-Related Factors

- **Age at the time of infection, or aging**
- **Gender**
- **Race**
- **Co-infection - HIV, HBV**
- **Co-morbid conditions - hemochromatosis**
 - NASH, obesity
 - schistosomiasis
- **Genetic - HLA class II antigens**
- **Disease expression – normal aminotransferases**



External Factors That Could Promote Progression of Chronic Hepatitis C

- **Alcohol**
- **? Smoking**
- **? Environmental contaminants or toxins**



Factors Associated with Liver Fibrosis Progression In Patients with Chronic Hepatitis C

- **Cross sectional liver biopsy study**
- **Rate of fibrosis progression 0.133 fibrosis units/year**
- **Independent risk factors:**
 - Age at infection >40 years**
 - Daily alcohol intake of 50g or more**
 - Male sex**
- **Median duration to development of cirrhosis, 30 years**
 - Men who drink, infected older than 40, 13 years**
 - Women who don't drink infected under 40, 42 years**



Natural History of Hepatitis C

Summary - 1

- **Once established, chronic HCV infection almost always persists for life**
- **The essential component of progression is increasing degrees of fibrosis.**
- **In general, liver disease progression occurs at a slow pace over decades**
- **Manifest liver disease is uncommon during the first two decades of established chronic liver disease**



Natural History of Hepatitis C

Summary - 2

- The rate of liver disease progression is highly variable, affected by host characteristics (age, gender, race, genetic influences) and by external or environmental influences (alcohol, possibly smoking or other toxins)
- Important modifying influences are co-infection with other viruses (HIV, HBV), parasitic agents (schistosomiasis), or other co-existing conditions (NASH, hemochromatosis)
- Current data *suggest* that absent modifying factors, 50-70% of persons with chronic hepatitis C are unlikely to suffer from or die of liver disease, even without treatment

Case Two - continued

- 2 months after intake:
 - Six weeks ago he was tested with a rapid HIV oral test, which was negative
 - Hepatitis serologies reviewed:
 - Has done well methadone program
 - Attending 12 Step meetings three times a week
 - Wants to consider Hepatitis C treatment

Discussion Points

- Hepatitis C general information
- Hepatitis C evaluation
- Hepatitis C treatment

Hepatitis C

Prepared by
Division of Viral Hepatitis
Centers for Disease Control and
Prevention

1/17/03



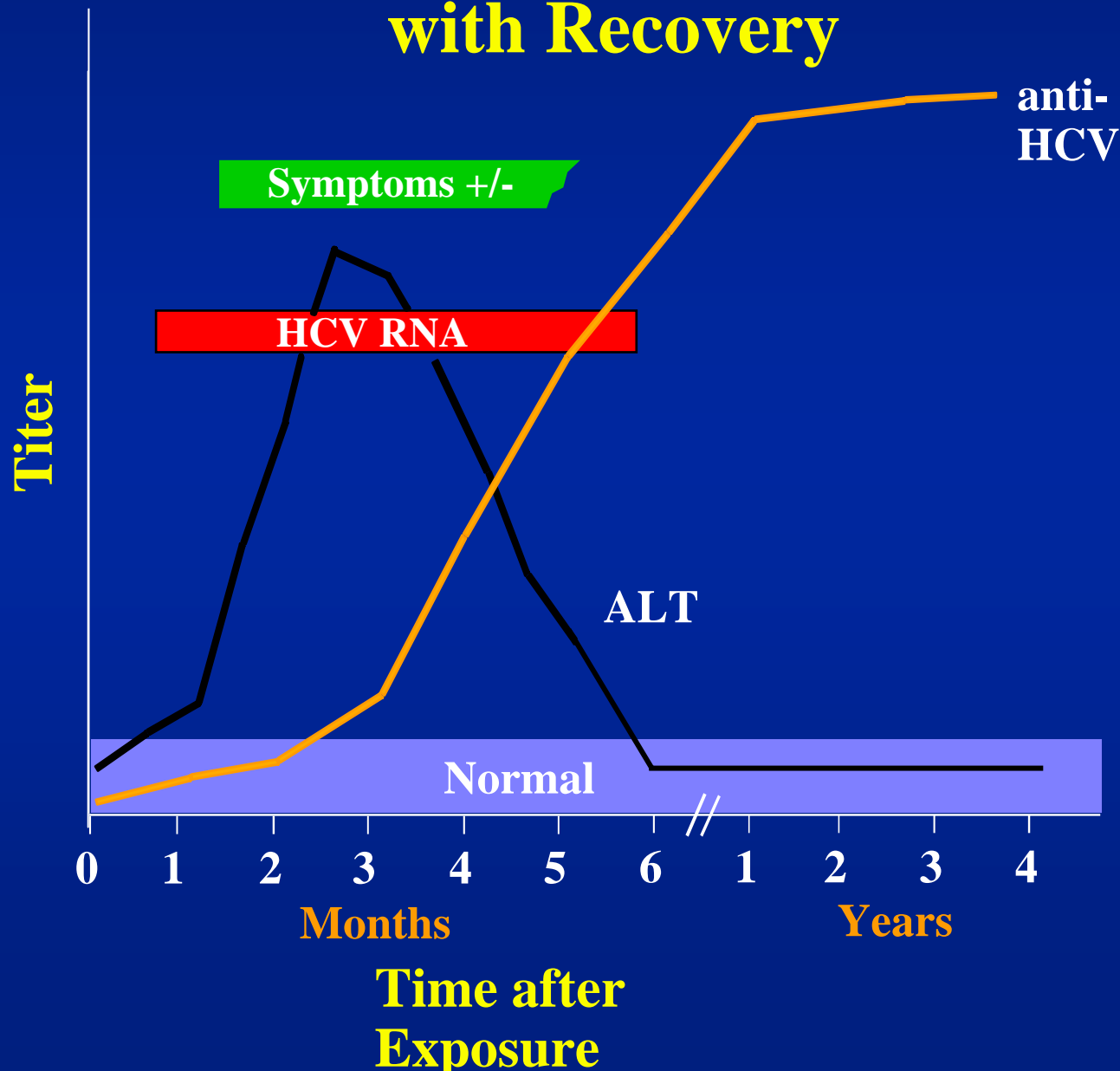
Features of Hepatitis C Virus Infection

Incubation period	Average 6-7 weeks Range 2-26 weeks
Acute illness (jaundice)	Mild ($\leq 20\%$)
Case fatality rate	Low
Chronic infection	60%-85%
Chronic hepatitis	10%-70% (most asx)
Cirrhosis	<5%-20%
Mortality from CLD	1%-5%

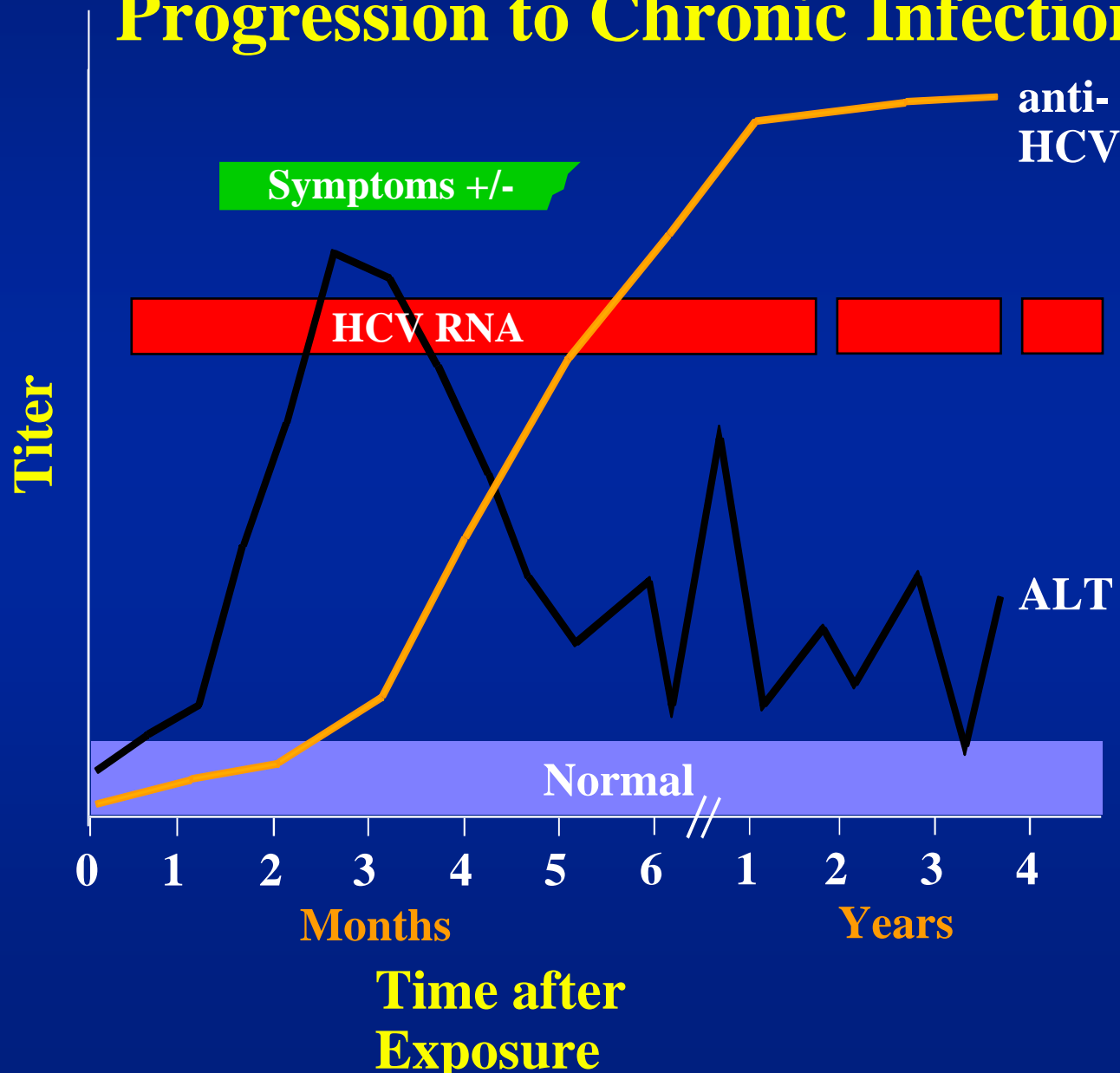
Chronic Hepatitis C Factors Promoting Progression or Severity

- Increased alcohol intake
- Age > 40 years at time of infection
- HIV co-infection
- Other
 - Male gender
 - Chronic HBV co-infection

Serologic Pattern of Acute HCV Infection with Recovery



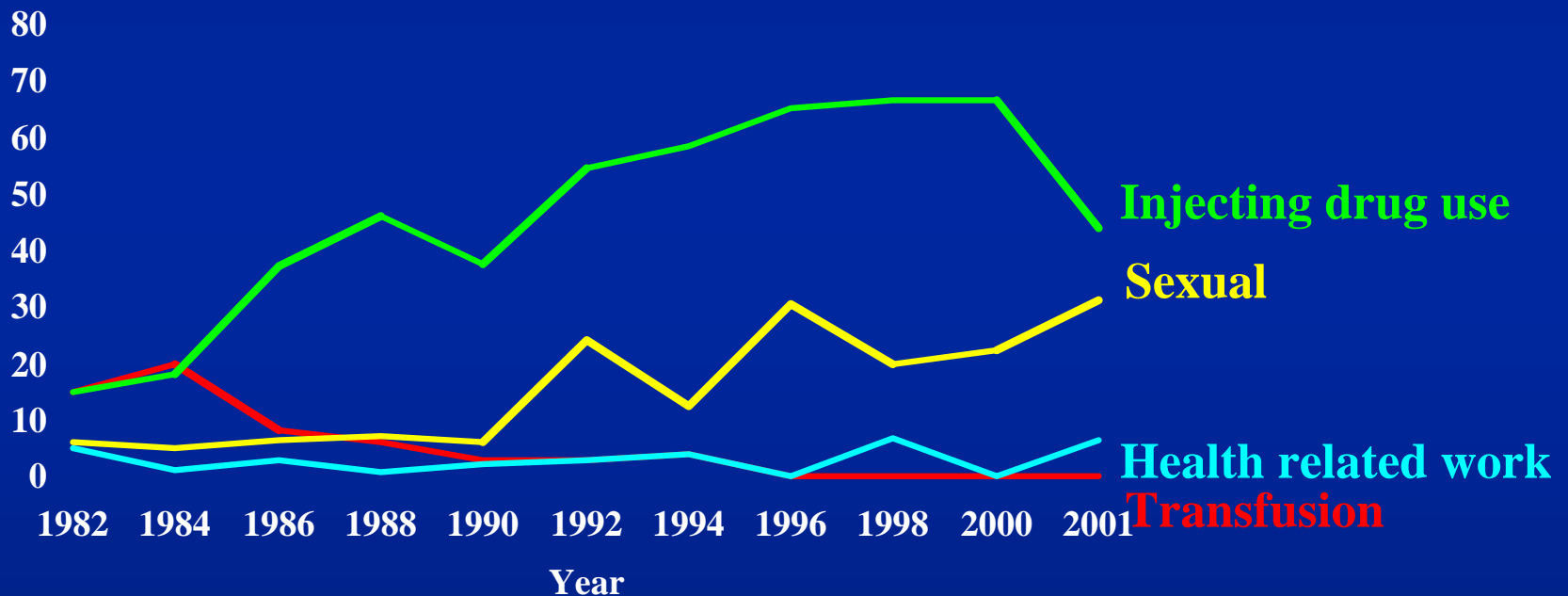
Serologic Pattern of Acute HCV Infection with Progression to Chronic Infection



Exposures Known to Be Associated With HCV Infection in the United States

- Injecting drug use
- Transfusion, transplant from infected donor
- Occupational exposure to blood
 - Mostly needle sticks
- Iatrogenic (unsafe injections)
- Birth to HCV-infected mother
- Sex with infected partner
 - Multiple sex partners

Reported Cases of Acute Hepatitis C by Selected Risk Factors, United States, 1982-2001*



* 1982-1990 based on non-A, non-B hepatitis



Hepatitis C evaluation

Hepatitis C

Clinical Evaluation

- Asymptomatic Patient (majority of cases)
 - HCV RNA by PCR
 - Tested, but level does not correlate with disease
 - Genotype
 - Predicts response to treatment
 - Other hepatitis serologies (A and B)
 - Vaccinate if indicated
 - Liver enzymes (AST, ALT) and function (albumin, prothrombin time)
 - Consider ultrasound

Medical Evaluation and Management for Chronic HCV Infection

- Assess for biochemical evidence of CLD
- Assess for severity of disease and possible treatment, according to current practice guidelines
 - 40-50% sustained response to antiviral combination therapy (peg interferon, ribavirin)
 - Vaccinate against hepatitis A
- Counsel to reduce further harm to liver
 - Limit or abstain from alcohol

Hepatitis C treatment

Hepatitis C Treatment

- Who to treat
- Medications for Treatment
- Treatment Results

Who to Treat

- Degree of fibrosis and inflammation on liver biopsy primarily directs therapy
- Can patients on methadone be treated?
 - Mauss S, Berger F, Goelz J, Jacob B, Schmutz G. A prospective controlled study of interferon-based therapy of chronic hepatitis C in patients on methadone maintenance. *Hepatology*. 2004 Jul;40(1):120-4.

Medications for Treatment

- Interferon alpha
- Pegylated interferon
 - Myalgia, fever, nausea, irritability, depression
- Ribavirin
 - Hemolytic anemia
- Drop out rates of at least 10%

Treatment Results

- Depends on Genotype
 - Type 1 most difficult to treat
- Peg interferon plus ribavirin shows best response
 - Sustained virologic response >50%
 - Response in genotype 1 less (40%?)

Case 3

- MN is a 32-year-old woman with a history of crack cocaine use
- Presents for a primary care appointment after referral from a detoxification unit
- Chief complaint: vaginal discharge
- Just started a six-week intensive outpatient treatment program.

Case 3 - continued

- Admits to alcohol use three to four times a week, typically six beers each occasion
- Never used injection drugs
- Denies previous HIV testing
- Depressed, without current suicidal ideation.
 - History of a suicide attempt after being beaten by a known male assailant two years previously.
- Two sexual partners
 - Uses condoms but not regularly
- Told in the past that she had hepatitis but was uncertain of what type it was.

Elements for Discussion

- Testing for HIV and Hepatitis
- Transmission of hepatitis
- Victimization
- Depression
- Vaginitis; Gyn care
- Alcohol use and hepatitis (again, if needed)
- Coinfection with HIV/HCV
- Coordination of care
- HIPAA and Confidentiality Issues

Testing for HIV and Hepatitis

Samet, J. H., K. P. Mulvey, et al.
(1999). "HIV testing in substance
abusers." Am J Drug Alcohol
Abuse **25**(2): 269-80.

Reduce or Eliminate Risks for Acquiring HCV Infection

- Screen and test donors
- Virus inactivation of plasma-derived products
- Risk-reduction counseling and services
 - Obtain history of high-risk drug and sex behaviors
 - Provide information on minimizing risky behavior, including referral to other services
 - Vaccinate against hepatitis A and/or hepatitis B
- Safe injection and infection control practices

MMWR 1998;47 (No. RR-19)

Reduce Risks for Disease Progression and Further Transmission

- Identify persons at risk for HCV and test to determine infection status
 - Routinely identify at risk persons through history, record review
- Provide HCV-positive persons
 - Medical evaluation and management
 - Counseling
 - Prevent further liver damage
 - Prevent transmission to others

MMWR 1998;47 (No. RR-19)

HCV Testing Routinely Recommended

Based on increased risk for infection

- Ever injected illegal drugs
- Received clotting factors made before 1987
- Received blood/organs before July 1992
- Ever on chronic hemodialysis
- Evidence of liver disease

Based on need for exposure management

- Healthcare, emergency, public safety workers after needle stick/mucosal exposures to HCV-positive blood
- Children born to HCV-positive women

Routine HCV Testing Not Recommended (Unless Risk Factor Identified)

- Health-care, emergency medical, and public safety workers
- Pregnant women
- Household (non-sexual) contacts of HCV-positive persons
- General population

Routine HCV Testing of Uncertain Need

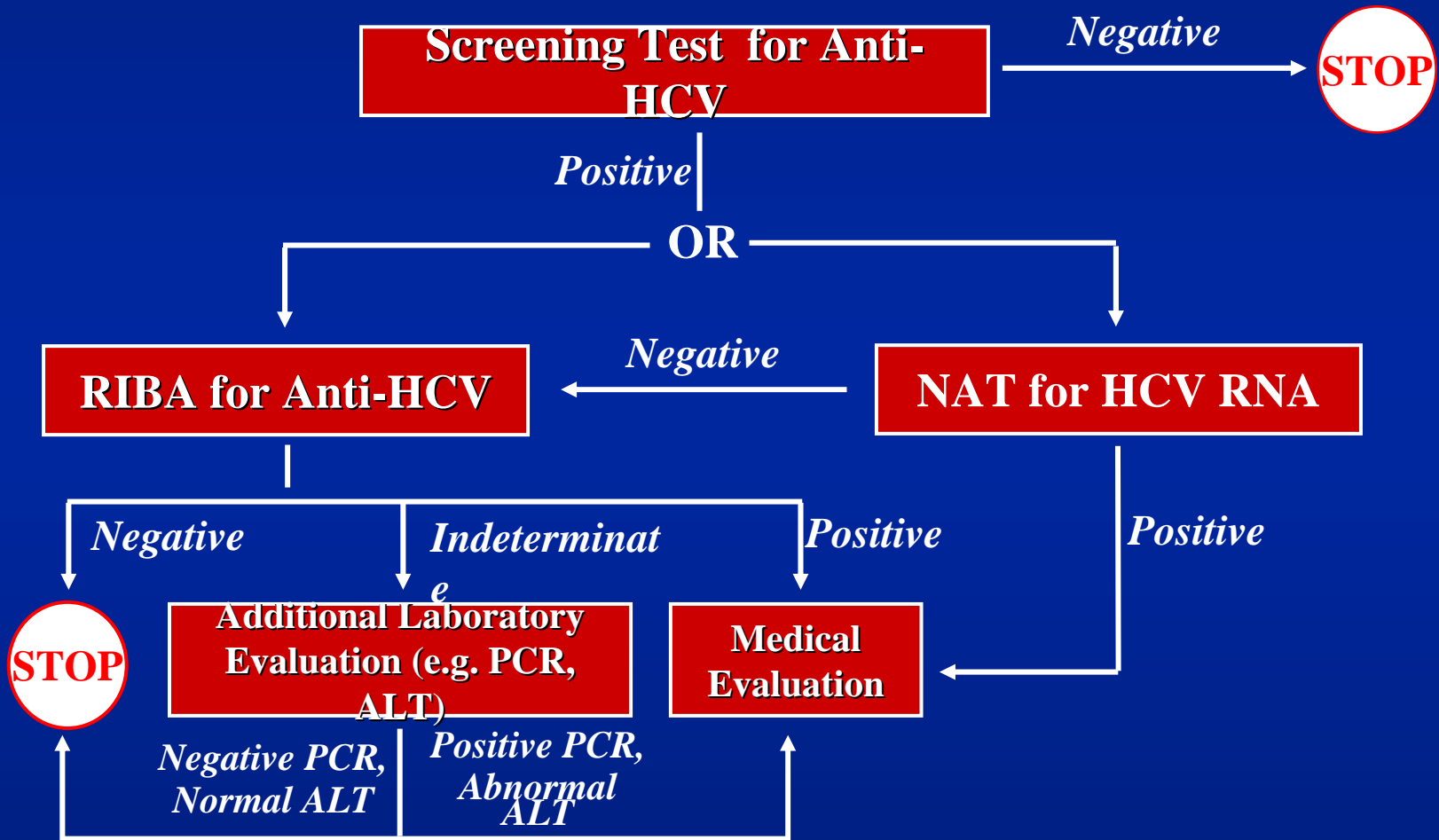
Not confirmed as risk factor/prevalence low or unknown

- Recipients of transplanted tissue
- Intranasal cocaine or other non-injecting illegal drug users
- History of tattooing, body piercing

Confirmed risk factor but prevalence of infection low

- History of STDs or multiple sex partners
- Long-term steady sex partners of HCV-positive persons

HCV Infection Testing Algorithm for Diagnosis of Asymptomatic Persons

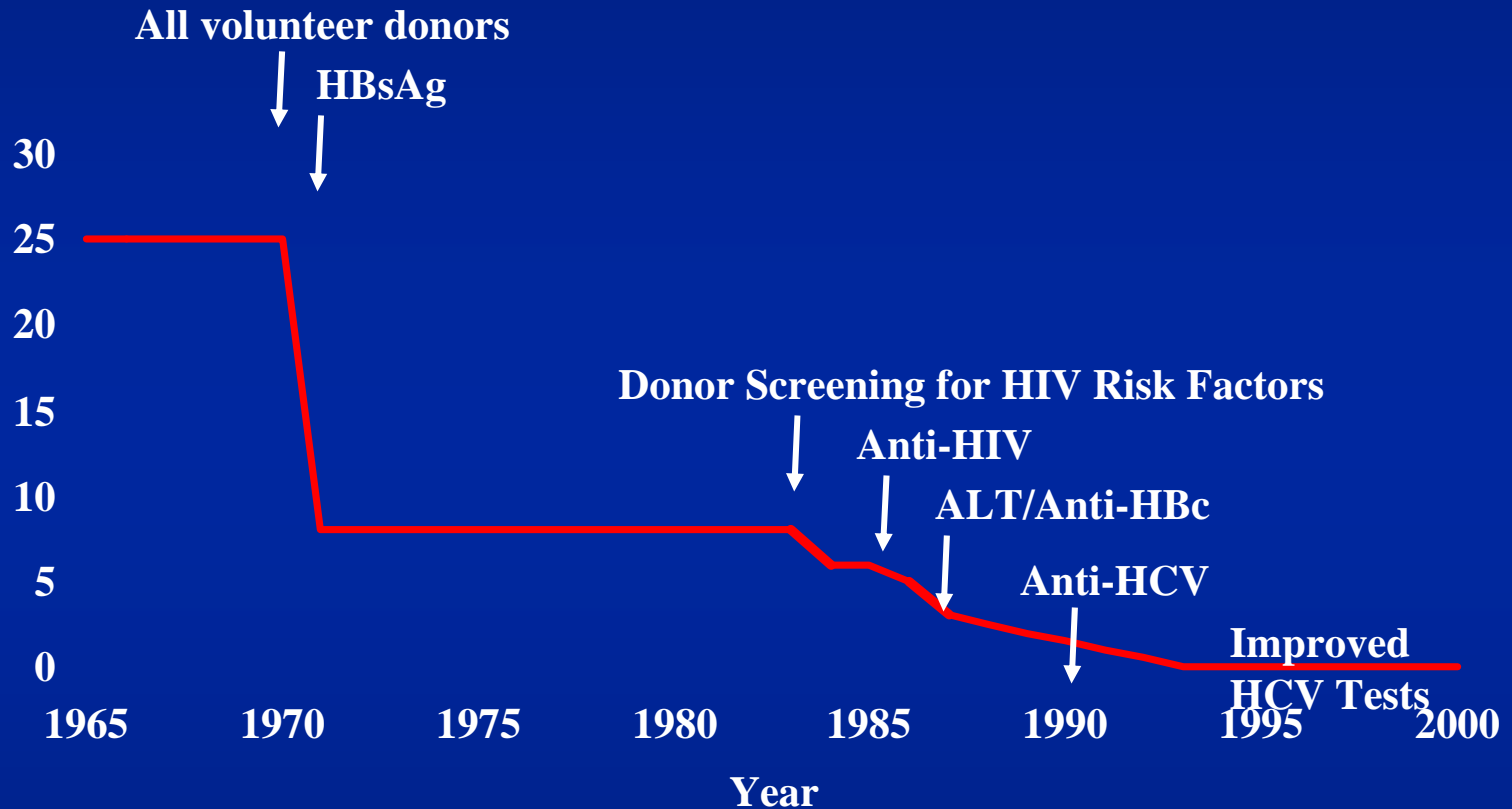


Transmission of Hepatitis and Sources of Infection

Injecting Drug Use and HCV Transmission

- Highly efficient
 - Contamination of drug paraphernalia, not just needles and syringes
- Rapidly acquired after initiation
 - 30% prevalence after 3 years
 - >50% after 5 years
- Four times more common than HIV

Posttransfusion Hepatitis C



Adapted from HJ Alter and Tobler and Busch, Clin Chem 1997



Occupational Transmission of HCV

- Inefficient by occupational exposures
- Average incidence 1.8% following needle stick from HCV-positive source
 - Associated with hollow-bore needles
- Case reports of transmission from blood splash to eye; one from exposure to non-intact skin
- Prevalence 1-2% among health care workers
 - Lower than adults in the general population
 - 10 times lower than for HBV infection

Perinatal Transmission of HCV

- Transmission only from women HCV-RNA positive at delivery
 - Average rate of infection 6%
 - Higher (17%) if woman co-infected with HIV
 - Role of viral titer unclear
- No association with
 - Delivery method
 - Breastfeeding
- Infected infants do well
 - Severe hepatitis is rare

Sexual Transmission of HCV

- Case-control, cross sectional studies
 - Infected partner, multiple partners, early sex, non-use of condoms, other STDs, sex with trauma, BUT
 - MSM no higher risk than heterosexuals
- Partner studies
 - Low prevalence (1.5%) among long-term partners
 - infections might be due to common percutaneous exposures (e.g., drug use), BUT
 - Male to female transmission more efficient
 - more indicative of sexual transmission

Sexual Transmission of HCV

- Occurs, but efficiency is low
 - Rare between long-term steady partners
 - Factors that facilitate transmission between partners unknown (e.g., viral titer)
- Accounts for 15-20% of acute and chronic infections in the United States
 - Sex is a common behavior
 - Large chronic reservoir provides multiple opportunities for exposure to potentially infectious partners

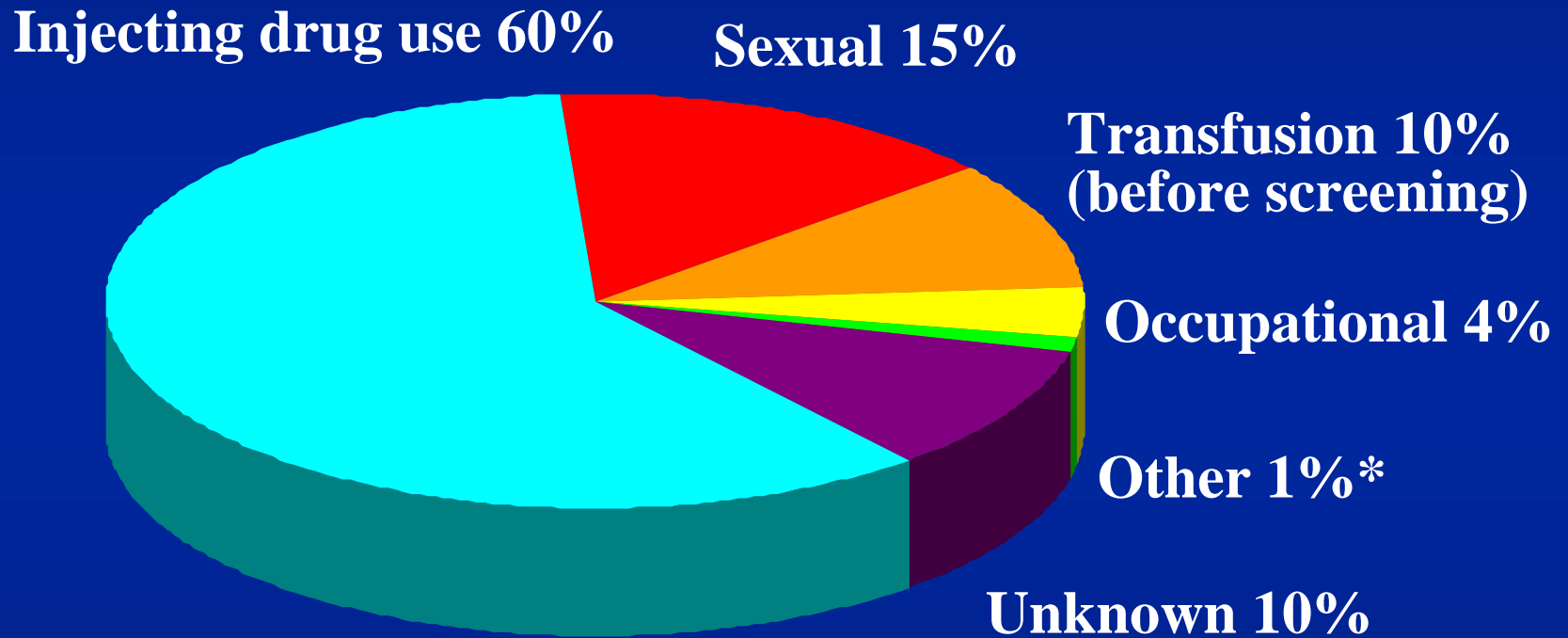
Household Transmission of HCV

- Rare but not absent
- Could occur through percutaneous/mucosal exposures to blood
 - Contaminated equipment used for home therapies
 - IV therapy, injections
 - Theoretically through sharing of contaminated personal articles (razors, toothbrushes)

Other Potential Exposures to Blood

- No or insufficient data showing increased risk
 - intranasal cocaine use, tattooing, body piercing, acupuncture, military service
- No associations in acute case-control or population-based studies
- Cross-sectional studies in highly selected groups with inconsistent results
 - Temporal relationship between exposure and infection usually unknown
 - Biologically plausible, but association or causal relationship not established

Sources of Infection for Persons With Hepatitis C



* Nosocomial; iatrogenic; perinatal

Source: Centers for Disease Control and Prevention



Hepatitis C Counseling Issues

HCV Counseling

- Prevent transmission to others
 - Direct exposure to blood
 - Perinatal exposure
 - Sexual exposure
- Refer to support group

Preventing HCV Transmission to Others

Avoid Direct Exposure to Blood

- Do not donate blood, body organs, other tissue or semen
- Do not share items that might have blood on them
 - personal care (e.g., razor, toothbrush)
 - home therapy (e.g., needles)
- Cover cuts and sores on the skin

Persons Using Illegal Drugs

- Provide risk reduction counseling, education
 - Stop using and injecting
 - Refer to substance abuse treatment program
 - If continuing to inject
 - Never reuse or share syringes, needles, or drug preparation equipment
 - Vaccinate against hepatitis B and hepatitis A
 - Refer to community-based risk reduction programs

Mother-to-Infant Transmission of HCV

- Postexposure prophylaxis not available
- No need to avoid pregnancy or breastfeeding
 - Consider bottle feeding if nipples cracked/bleeding
- No need to determine mode of delivery based on HCV infection status
- Test infants born to HCV-positive women
 - >15-18 months old
 - Consider testing any children born since woman became infected
 - Evaluate infected children for CLD

Sexual Transmission of HCV

Persons with One Long-Term Steady Sex Partner

- Do not need to change their sexual practices
- Should discuss with their partner
 - Risk (low but not absent) of sexual transmission
 - Counseling and testing of partner should be individualized
 - May provide couple with reassurance
 - Some couples might decide to use barrier precautions to lower limited risk further

Sexual Transmission of HCV

Persons with High-Risk Sexual Behaviors

- At risk for sexually transmitted diseases, e.g., HIV, HBV, gonorrhea, chlamydia, etc.
- Reduce risk
 - Limit number of partners
 - Use latex condoms
 - Get vaccinated against hepatitis B
 - MSMs also get vaccinated against hepatitis A

Other Transmission Issues

- HCV not spread by kissing, hugging, sneezing, coughing, food or water, sharing eating utensils or drinking glasses, or casual contact
- Do not exclude from work, school, play, child-care or other settings based on HCV infection status

Victimization

Depression

Vaginitis; Gyn care

- Gynecologic care
 - Vaginitis
- Sexually transmitted infections

Liebschutz, J.M, E.P. Finley, et al. (2003). “Screening for sexually transmitted infections in substance abuse treatment programs.” *Drug and Alcohol Depend* 70(1):93-9.

Alcohol use and hepatitis

Coinfection with HIV/HCV

- More rapid progression to HCV liver disease
- http://www.cdc.gov/hiv/pubs/facts/HIV-HCV_Coinfection.htm

Coordination of care

- HIPAA and Confidentiality Issues