

Medical Co-Morbidity in Opioid Dependence

**2010 BAT and OBOT
Advances in Indian Health**

Addiction and health behavior

Opioid dependence frequently associated with other medical conditions

Consequences of injection drug use/shared needles

Direct toxic effect of opioids and/or inert substances mixed with heroin

Consequences of risky sexual behavior

Lack of attention to preventive health care

Need to screen for comorbid medical illness and provide treatment or make referral when needed

Outline for This Talk

I. Hepatitis B

II. Hepatitis C

III. HIV/AIDS

IV. Tuberculosis

**V. Preventive health care for opioid
dependent patients**

VI. Summary

Hepatitis B

Epidemiology

Blood borne viral pathogen

Estimated 1.25 million chronically infected in U.S.

Approximately 300,000 new cases per year; 15,000-30,000 chronic infection

Transmission by blood borne (parenteral), sexual, or perinatal routes

Approximately 50% of active injection drug users have serological evidence of prior exposure to HBV

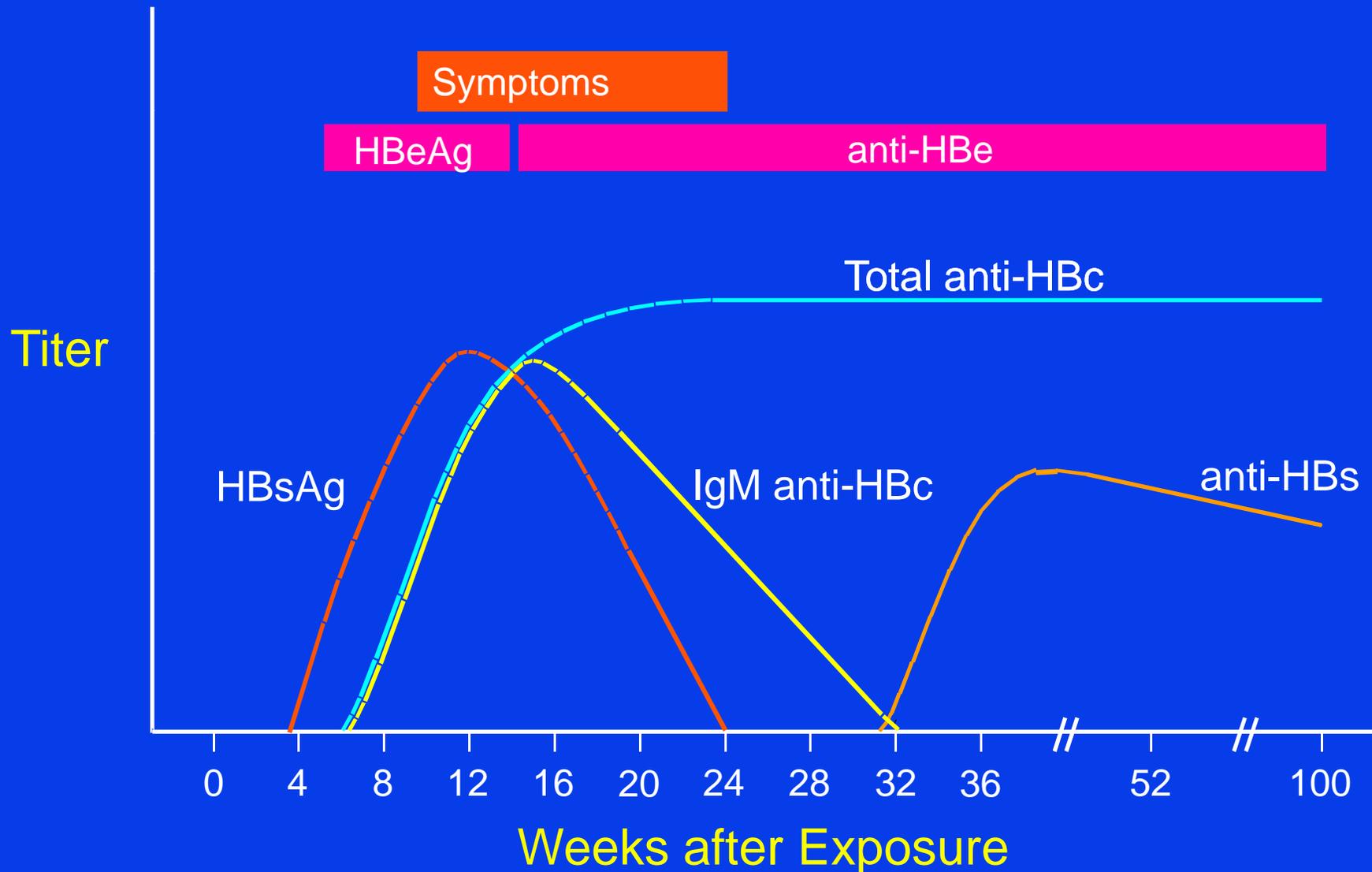
Hepatitis B

Clinical course

Early and mild viral hepatitis manifests with symptoms of hepatic inflammation and damage with elevated serum transaminases (can rise to 10-20x normal)

Chronic viral hepatitis manifests as chronic liver disease with portal hypertension and poor hepatic synthetic function

Acute Hepatitis B Infection with Recovery



Hepatitis B

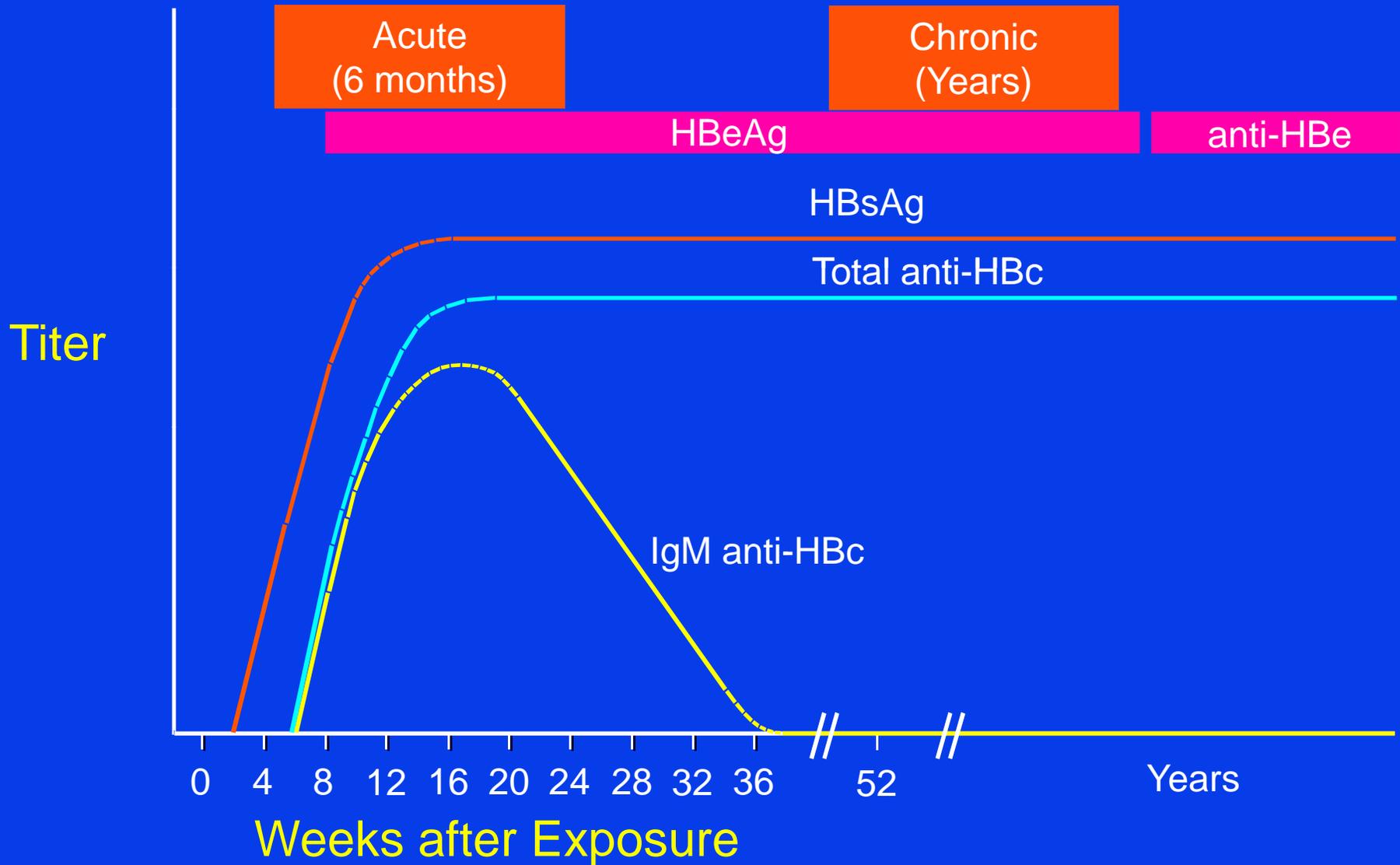
Clinical course (*continued*)

Likelihood of developing chronic infection is related to age:

80 to 90% of infants infected develop chronic disease

only 2 to 10% of infected adults progress to chronic disease

Progression to Chronic Hepatitis B Infection



Hepatitis B

Treatment

Interferon is administered subcutaneously daily three times per week, for 16 weeks

Metaanalysis of 16 randomized controlled trials found loss of HBeAg and HBV DNA in 33 to 37% of interferon treated patients compared with 12 to 17% of controls

Lamivudine: oral, resistance develops, seroconversion response in nearly 33% of patients after one year

Hepatitis B

Treatment (continued)

Famciclovir less effective than lamivudine and is also limited by the development of resistance

Adefovir possesses added benefit of exhibiting no resistant mutations

Vaccination is crucial – a three part series over 6 months

Hepatitis B

Treatment (continued)

Interferon side effects include:

Flu-like symptoms

Fatigue

Headache

Fever

Myalgias

Depression

Hepatitis C

Definition

Hepatitis C (HCV) is the most common bloodborne infection in the U.S.

The viral pathogen established as the major cause of hepatitis previously called nonA, nonB hepatitis

Hepatitis C

Epidemiology: United States

New infections (cases) per year:

1985 to 1989: 242,000 (42,000)

1998: 40,000 (6,500)

Seroprevalence studies reveal that

**approximately 1.8% of the U.S. population are
infected with HCV**

Deaths from acute liver failure are rare

Hepatitis C

Epidemiology: United States (*continued*)

Of the estimated 3.9 million people in the U.S. who are HCV antibody positive, 2.7 million are chronically infected with detectable RNA levels

Chronic liver disease – HCV-related: 40% - 60%

Deaths from HCV chronic disease/year: 8,000-10,000

Most common cause (~40%) of liver transplant in U.S.

Hepatitis C

Epidemiology (continued)

**HCV is more prevalent and more infectious than HIV
with 170 million people infected with HCV worldwide**

**Greater than 90% of injection drug users have
antibodies to HCV**

**In injection drug users, infection results from contact
with contaminated needles, syringes, paraphernalia**

**Blood and blood products are more infectious than
saliva, vaginal secretions, or semen**

Hepatitis C

Epidemiology: Sexual transmission

Efficiency low

Rare, but not absent – estimated 0.03 to 0.6% per year
between long term monogamous discordant partners –
no change in sexual practices recommended

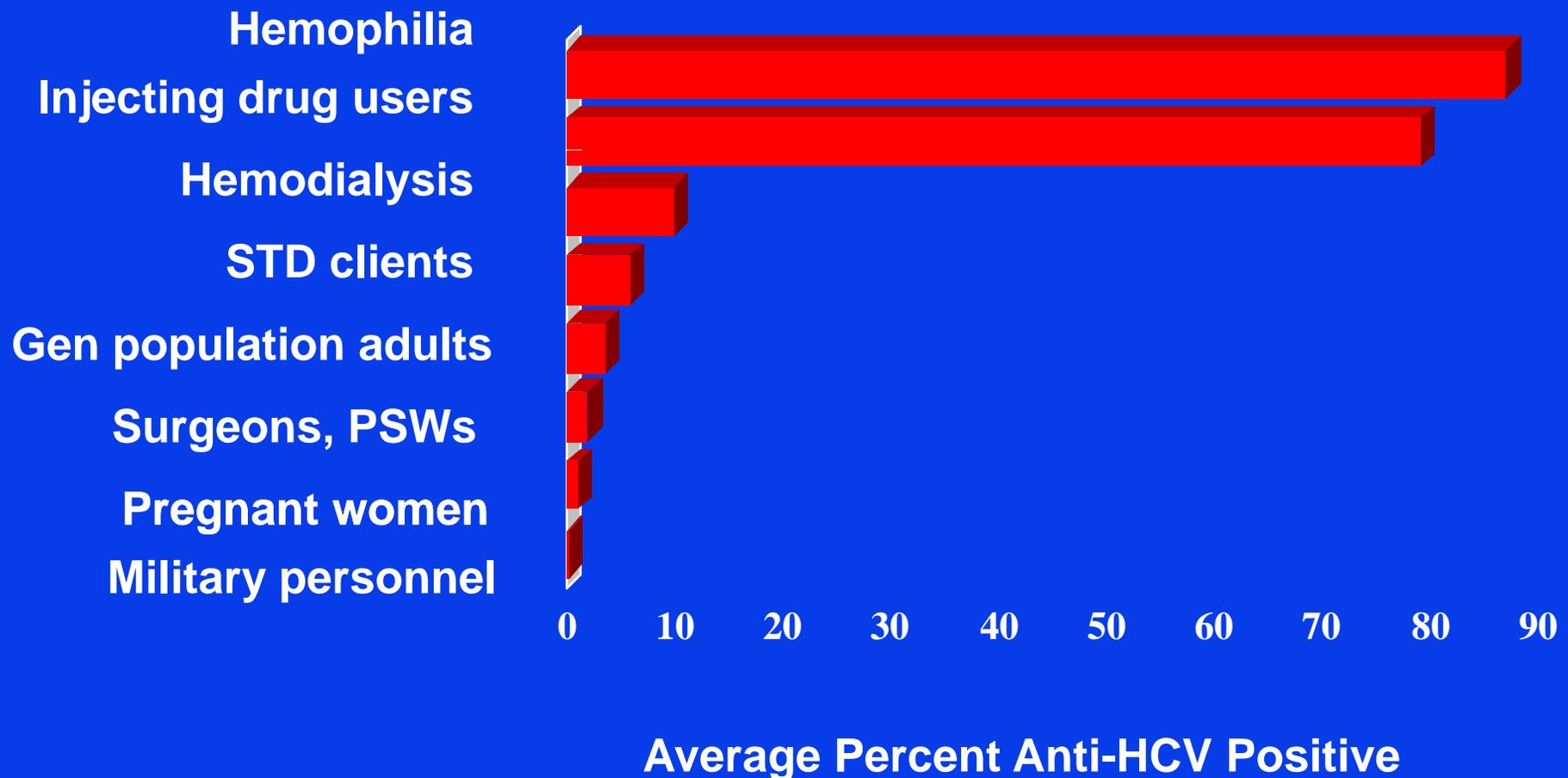
Risk amongst those with multiple sexual partners is 1%
per year – barrier methods or abstinence recommended

Presence of other sexually transmitted diseases increases
risk of transmission

30% of HIV patients coinfecting with HCV

In HIV-infected IDU, rate of coinfection is 50-90%

Hepatitis C: Prevalence by Selected Groups (U.S.)



Hepatitis C

Clinical course: Acute hepatitis C

Incubation period averages 6 to 8 weeks during which time antibodies are undetectable

Symptoms develop in only 25% to 35% patients:

Nonspecific

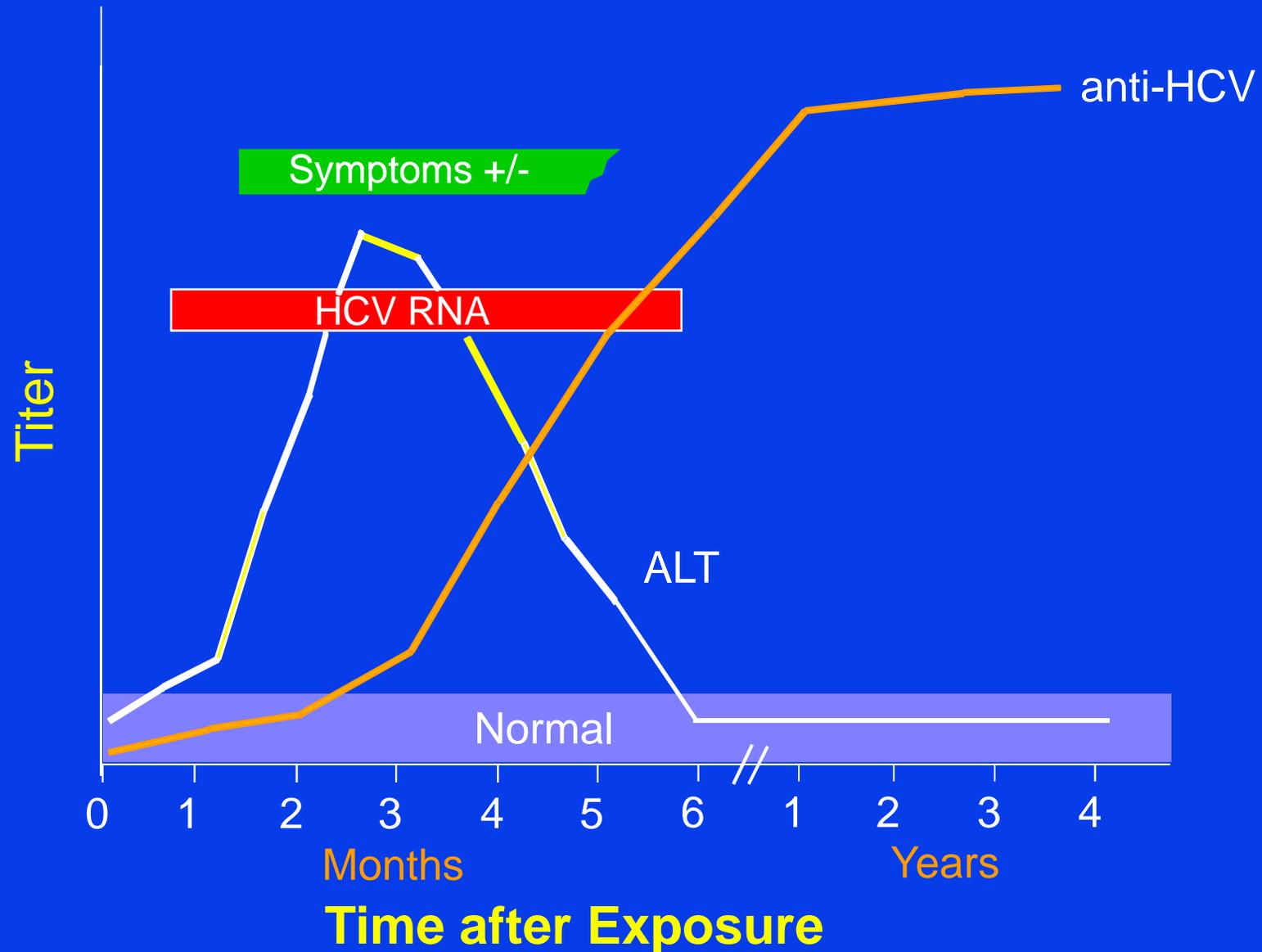
Jaundice in only 20% to 30%

Diagnosis rarely established during acute phase

85% develop persistent infection

Majority develop chronic hepatitis with persistent viremia and intermittently elevated liver function tests

Hepatitis C: Acute Infection with Recovery



Hepatitis C

Clinical course: Chronic hepatitis C

Symptoms: 50% of patients report chronic fatigue and right upper quadrant abdominal discomfort

Serum transaminases: Persistently elevated in 43%, intermittently elevated in 42%, normal in 15%

Risk factors for disease progression include:

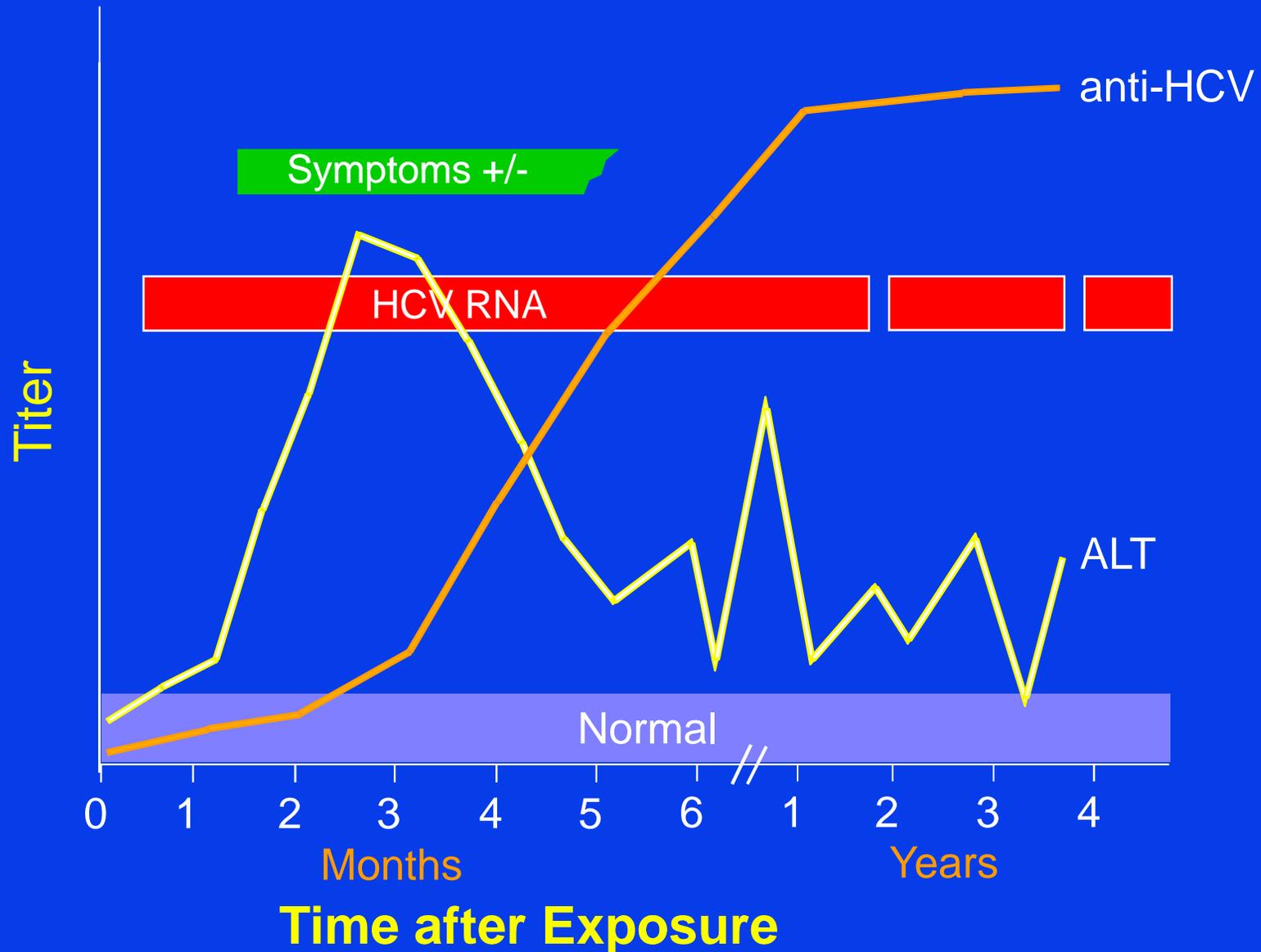
Alcohol use

Co-infection with Hepatitis B virus and/or HIV

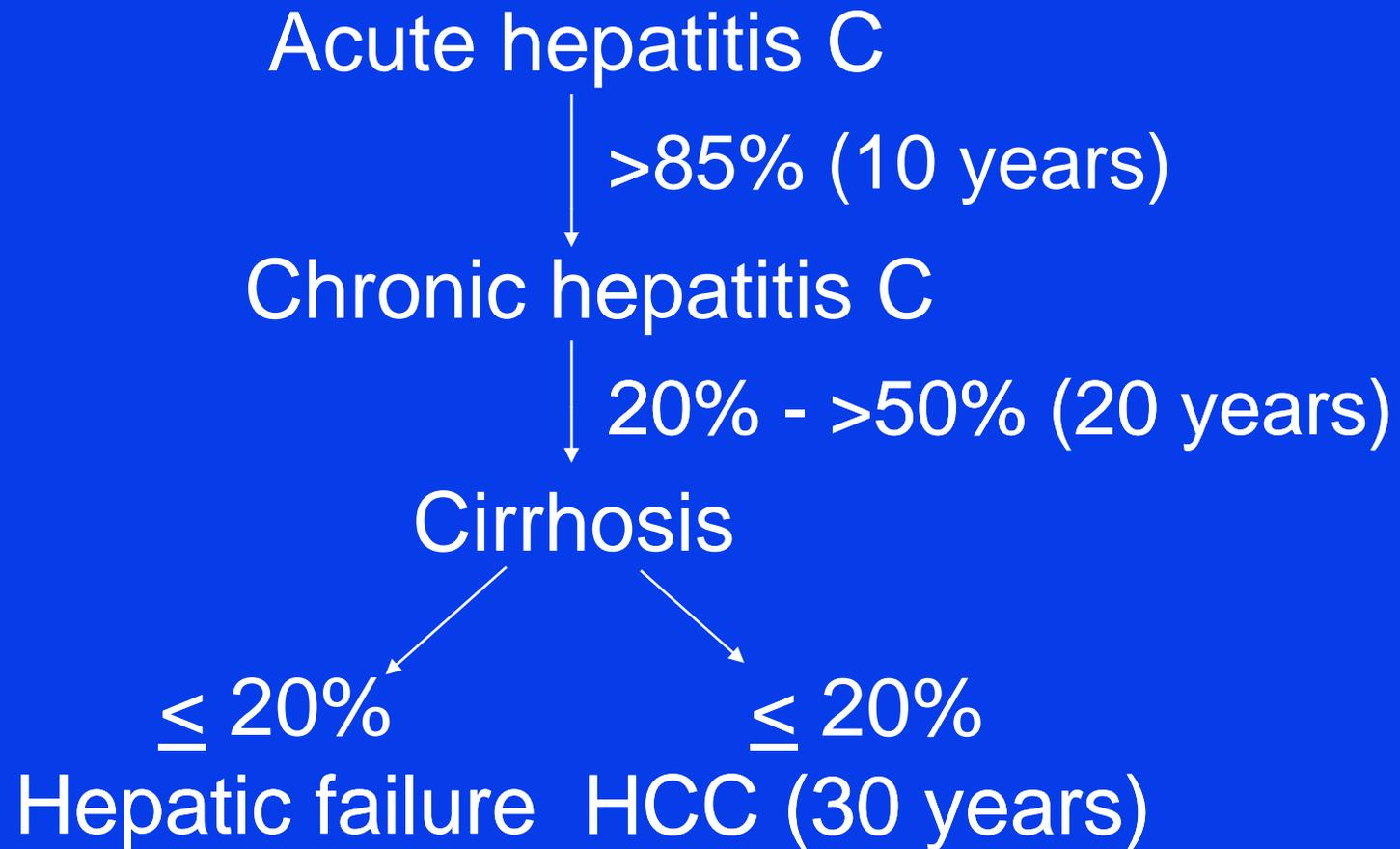
Early onset infection (<40 years old)

Male sex

Hepatitis C: Progression to Chronic Infection



30 Year Progression of Chronic Hepatitis C



Hepatitis C

Clinical course: HCV and HIV co-infection *(continued)*

HIV has a significant effect on progression of liver disease in HCV-infected patients

Must balance hepatotoxicity of HIV therapy with need to treat HIV in HCV-infected patients, while HIV therapy can worsen the symptoms of HCV

Hepatitis C

Treatment: Pretreatment assessment

HCV RNA: Lower viral RNA levels (viral load) appear to predict better treatment response

HCV genotyping:

Has impact on response to treatment

70% of HCV-infected in U.S. have genotype 1, rest are genotypes 2, 3, and 4

Genotype 1 has less favorable prognosis and decreased likelihood for treatment response – requires longer duration of therapy

Hepatitis C

Treatment: Pretreatment assessment (*continued*)

Liver biopsy: Provides information regarding degree of inflammation, fibrosis, or cirrhosis

Rules out other causes of liver disease

Sustained virological response (SVR)=absence of detectable RNA at end of treatment and 24 weeks after end of treatment

Interferon plus ribavirin produced SVR=38 to 43% after 48 weeks of therapy

Pegylated interferon plus ribavirin produced SVR=54-56% after 48 weeks of therapy (82% in genotypes 2 and 3, 42% in genotype 1)

Hepatitis C

Treatment: Side effects

Interferon:

Flu-like syndrome

5%-10% of patients with these side effects
require discontinuation of therapy; 10-40%
require dose reduction

Severe side effects observed <2% of
patients

Ribavirin:

Hemolytic anemia

Hepatitis C

Treatment: Drug users and treatment for HCV

Standard recommendation: ≥ 6 months
“clean”

Arguments for not treating: poor adherence, side effects, re-infection, non-urgent treatment – but data supporting these arguments are lacking, some drug users may do well

Treatment should be based on individual risk-benefit assessments

Hepatitis C

Treatment:

Management of HCV-infected injecting drug users is enhanced by linkage to drug treatment programs

Promotion of collaboration between HCV experts and providers specializing in substance abuse treatment

HCV treatment of active injecting drug users should be considered on a case-by-case basis

Active injecting drug use should not exclude patients from HCV treatment

Prescribing Buprenorphine in Hepatitis

Mechanism of hepatitis associated with buprenorphine:

Buprenorphine inhibits hepatic mitochondrial function at high concentrations

May cause elevation of transaminases

No documented cases of fulminant liver failure due solely to buprenorphine

Studies of Buprenorphine in Hepatitis

120 patients treated with buprenorphine > 40 days:

HCV: ALT and AST increased by 8-9 times upper limit of normal

non-HCV: no change in ALT or AST

Case reports (5):

Transaminase increases, 30-50 times normal, with intravenous buprenorphine in patients infected with Hepatitis C

Prescribing Buprenorphine in Hepatitis

Buprenorphine may elevate transaminases

especially in patients with HCV

especially when administered IV

but less likely when administered sublingually

Monitor liver enzyme levels in patients with hepatitis,

especially those on Buprenorphine/Naloxone

Warn patients not to use Buprenorphine intravenously

HIV/AIDS

Definition

A blood-borne retroviral infection caused by the human immunodeficiency virus (HIV)

AIDS diagnosis made using 1993 CDC classification and case definition system:

CD4 < 200

% CD4 <14%

AIDS defining diagnoses (indicator conditions)

HIV/AIDS

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HIV/AIDS

Epidemiology

Worldwide 58 million people infected with HIV (15,000 new cases/d)

HIV-1 predominates in the U.S.; HIV-2 found in West Africa

1.1 million cases in the US (45,000 new cases per year)

1993-1999 the number of injecting drug users living with AIDS increased from 48,244 to 88,540

15-20% long-term injecting drug users infected

0.7-34% (median 15%) seroprevalence entering substance abuse treatment

43% AIDS in women secondary to injection drug use

HIV/AIDS

Epidemiology (continued)

Injection drug use (IDU) accounts for 43% of AIDS cases in women

25% of the approximately 40,000 new HIV infections per year are through IDU

Transmission is through sexual contact, parenteral exposure, and perinatal or postpartum contact

HIV/AIDS

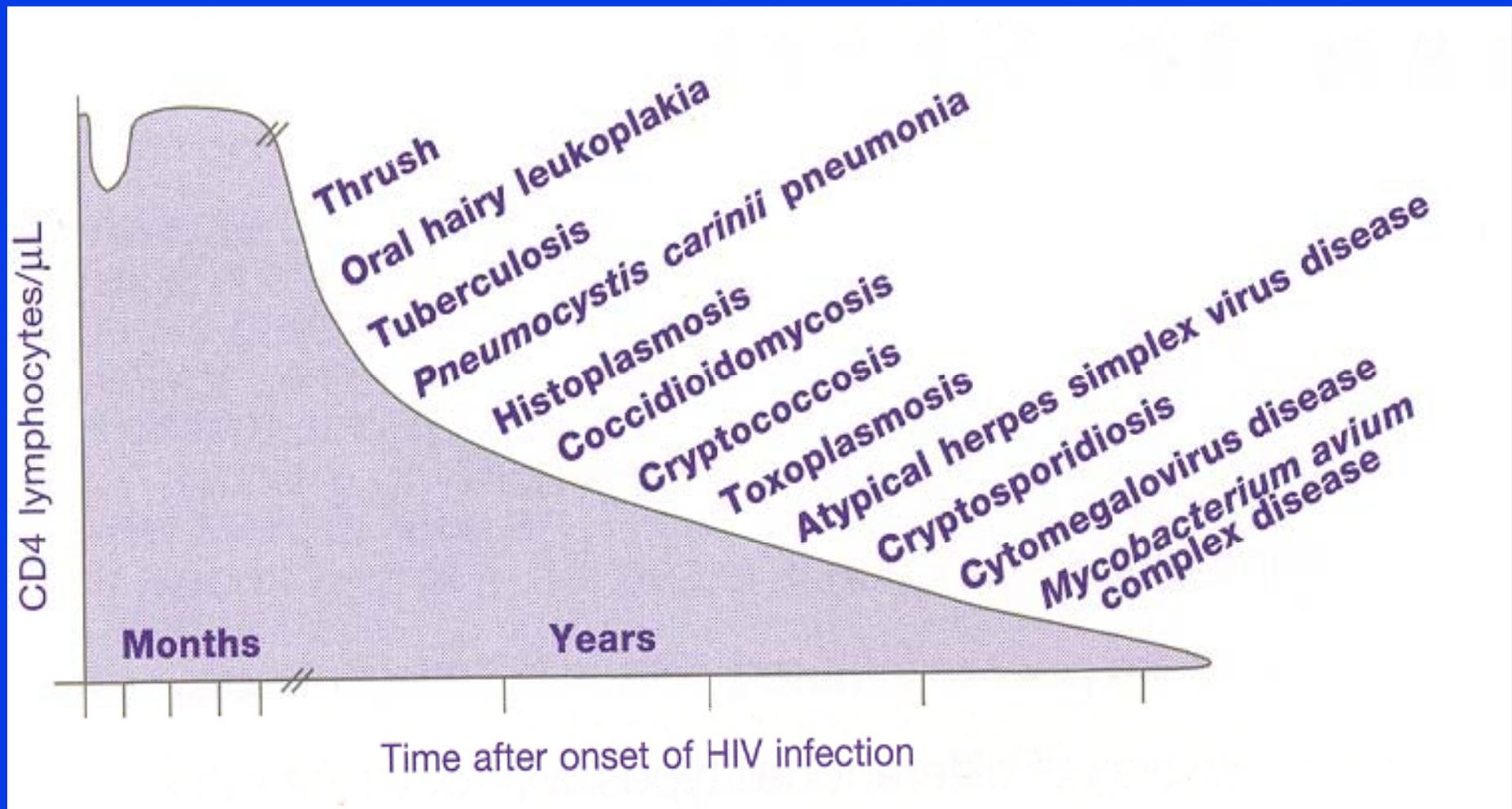
Clinical course

Primary HIV infection can be asymptomatic or result in an acute “viral” syndrome: fever 96%, adenopathy 74%, pharyngitis 70%, rash 70%, myalgia/arthralgia 54%, diarrhea 32%, headache 32%, nausea/vomiting 27%, H/Smegaly 14%, thrush 12%

Initial infection is followed by active viral replication primarily in lymphoid tissue

Course followed clinically with CD4 lymphocyte counts and viral RNA (viral load)

HIV/AIDS: Natural History of HIV-1 Infection



HIV/AIDS

Clinical course: Risk of disease progression

Low CD4 is the strongest predictor of the development of opportunistic infections (OIs)

Most OIs occur at $CD4 < 50$ (at least for patients receiving PCP prophylaxis)

HIV RNA $> 20,000$ confer greater OI risk for any given CD4 count

High HIV RNA is an independent predictor of disease progression

Indications for Treatment (www.hivatis.org)

| Clinical Category | CD4 | HVL | Recommend |
|-------------------|-----------|-----------|---------------------------------|
| Symptomatic AIDS | Any value | Any value | Treat |
| Asymptomatic AIDS | <200 | Any value | Treat |
| Asymptomatic | <350 | Any value | Offer treatment |
| Asymptomatic | >350 | >55,000 | Offer treatment |
| Asymptomatic | >350 | <55,000 | Defer therapy 3 yr risk <15% |

HIV/AIDS

Treatment

Standard is at least a three-drug regimen (called highly active antiretroviral therapy – HAART)

Three classes of medications are effective in helping to decrease retroviral replication:

- a) Nucleoside reverse transcriptase inhibitors (e.g., zidovudine)**
- b) non-nucleoside reverse transcriptase inhibitors (e.g., efavirenz)**
- c) protease inhibitors (e.g., indinavir)**

HIV/AIDS

Treatment (*continued*)

Adherence to HAART can be difficult

Complications of HAART can include nephrolithiasis, anemia, pancreatitis, neuropathy, lipid abnormalities, and fat redistribution

Poor adherence to HAART predicts treatment failure and can lead to development of viral resistance

Clinical trials have demonstrated non-detectable viral loads in 80% of patients receiving HAART

Patients with good adherence to HAART regimens have decreased morbidity, mortality, hospitalization rates, and viral replication

HIV/AIDS

Treatment: HIV and injecting drug users

High risk for non-receipt of antiretrovirals:

2-3 times as likely not to be on antiretroviral treatment if not in SA treatment

High risk for non-adherence:

1998 CDC guidelines recommend delaying HAART until active opioid use has been addressed

However, drug interactions between methadone and antiretrovirals can decrease adherence!

HIV/AIDS

Treatment: HIV and injecting drug users (*continued*)

Methadone has pharmacokinetic/pharmacodynamic interactions with several antiretrovirals, including:

zidovudine

didanosine

stavudine

abacavir

nevirapine

efavirenz

nelfinavir

delavirdine

lopinavir/ritonavir

Extent of buprenorphine interaction with antiretrovirals currently under study in U.S.

HIV/AIDS

Treatment: Buprenorphine in HIV+ injecting drug users;
MANIF 2000 cohort (France):

Risk for HAART non-adherence:

| | Non-adherent | Adherent | OR (adjusted) |
|-----------------------|---------------------|-----------------|-----------------------|
| Buprenorphine | 7 (21%) | 25 (78%) | 1.00 |
| No current IDU | 39 (35%) | 74 (65%) | 2.32 (0.8-6.5) |
| Active IDU | 11 (58%) | 8 (42%) | 5.1 (1.3-20.1) |

HIV/AIDS

Treatment: Buprenorphine in HIV+ injecting drug users; MANIF 2000 cohort (France):

6 month follow-up (median values):

| | Buprenorphine | (n=20) | Ex-IDU(n=83) | P |
|----------------------|---------------|--------|--------------|---|
| Age | 32 | 34 | .04 | |
| CD4 (pre) | 287 | 347 | .16 | |
| CD4 (post) | 344 | 457 | .17 | |
| Viral Load (pre) | 4.8 | 4.4 | .17 | |
| Viral Load (post) | 2.7 | 3.3 | .91 | |
| Months on HAART | 3.7 | 4.0 | .34 | |
| Months Buprenorphine | 10 | NA | NA | |

Tuberculosis

Epidemiology

Worldwide, approximately 2 billion people (1/3 of world population) are infected with *M. tuberculosis*

Since the HIV pandemic began in the U.S. in the mid-1980s, there has been increased concern about TB since it is more common in this population

Tuberculosis is also more common in injection drug users in general and in patients with alcohol use disorders

Tuberculosis

Epidemiology (continued)

Others at high risk for tuberculosis:

Ethnic minorities

Immigrants

Homeless persons

Nursing home residents

Patients with chronic disease or immune dysfunction

Health care personnel (e.g.: physicians, nurses, drug treatment program counselors)

Tuberculosis

Clinical presentation

Tuberculosis infection without disease: PPD+

Tuberculosis infection with disease: most commonly this involves pulmonary infection, although other sites can be involved as well.

This is referred to as extra-pulmonary tuberculosis (and can involve sites such as bone, lymph node, kidneys, and other intra-abdominal organs)

Tuberculosis

Screening for tuberculosis infection

Should be performed annually on all patients with a history of a substance use disorder who have previously been PPD negative and have no prior history of tuberculosis

Patients who have had a previously positive PPD should not receive repeat PPD testing, but should be followed with annual chest x-rays

Tuberculosis

Interpretation of PPD results

PPD read as positive if:

5 mm of induration: Patients with HIV infection, those with close contact to documented cases, and those who have chest x-rays suggestive of tuberculosis

10 mm of induration: Individuals from population groups with a high prevalence of tuberculosis infection including immigrants, injection drug users, homeless persons, immigrants from endemic areas

15 mm of induration: Individuals with no known risk factors for tuberculosis

Tuberculosis

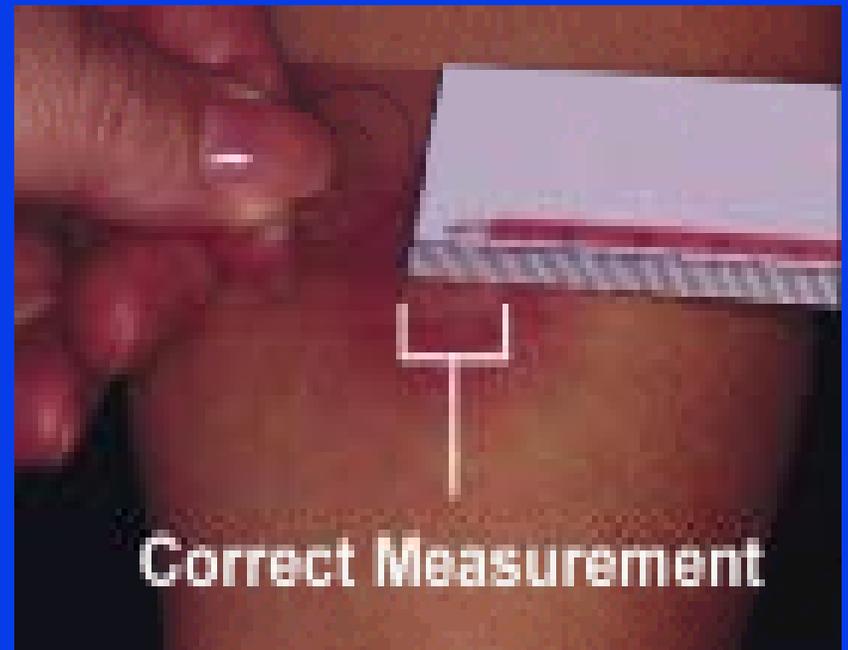
Reading the Tuberculin Skin

Test:

Read reaction 48-72 hrs after
injection

Measure only induration

Record reaction in mm



Tuberculosis

Assessment of patients with a positive PPD

History and physical exam focusing on risk factors for tuberculosis

Chest x-ray

Sputum studies (AFB smear and culture in individuals with chest x-ray evidence of possible tuberculosis)

Tuberculosis

Treatment: If no evidence of active disease

Criteria for which PPD+ patients should receive chemoprophylaxis have been developed by the CDC and other groups. Generally, patients under 35 years of age with a recent PPD conversion should be considered for INH chemoprophylaxis. However, all individuals who are HIV+, regardless of age, should be considered.

Tuberculosis

Treatment: No evidence of active disease (*continued*)

Isoniazid (INH) 300 mg po qd (plus daily vitamin B6) for six months is the standard therapy in immunocompetent patients

Isoniazid (INH) 300 mg po qd (plus daily vitamin B6) for one year is the standard therapy for HIV+ patients

INH hepatotoxicity is a concern, especially in patients with other reasons to have liver disease.

Regular monitoring of liver enzymes (e.g., monthly) is important, especially in drug users

Tuberculosis

Treatment: Evidence of active disease

Most common presentation is pulmonary tuberculosis

Multidrug regimens utilized: may include isoniazid (INH), rifampin, pyrazinamide, ethambutol, and other agents

Directly observed therapy may be particularly important when treating substance users who have active tuberculosis and has been shown to be efficacious (e.g. INH mixed with methadone)

Physicians need to be aware of the potential for drug resistant strains of *M. tuberculosis* in their patients and provide additional treatment as appropriate

Preventive Health Care

Infectious diseases commonly seen in opioid dependent patients

Viral (Hepatitis A, B, C; HIV)

Tuberculosis (pulmonary, extrapulmonary)

Bacterial infections (soft tissue infections, pneumonia, endovascular infections (endocarditis))

Sexually transmitted diseases (e.g., syphilis, human papillomavirus)

Preventive Health Care

Other medical conditions commonly seen in patients with opioid dependence

Alcoholic hepatitis

Cervical cancer

**Respiratory tract cancers including lung,
oropharynx, and larynx**

Preventive Health Care

Routine screening activities for patients with opioid dependence

Viral: Hepatitis B, C: Screening antibody tests and liver enzymes

Tuberculosis: Annual screening with PPD and/or chest x-ray

Syphilis: Annual VDRL or RPR (and FTA if indicated)

HIV infection: HIV antibody testing to be offered initially and repeatedly as indicated

HIV+: typically followed with CD4 cell counts and viral load studies

Cervical cancer: Yearly screening, more frequent (q6month) in those with prior abnormalities or very high risk

Preventive Health Care

Routine vaccinations to be considered in patients with opioid dependence

Pneumococcal vaccine

Influenza vaccine

Haemophilus influenza vaccine

Hepatitis A

Hepatitis B

Tetanus, Tdap

HPV

Summary

Patients with opioid dependence frequently have comorbid medical conditions, especially infectious diseases

Important to screen for these disorders, and to provide treatment and prevention, or to be aware of and familiar with screening, treatment, and prevention services if they are done elsewhere

Linkage of substance abuse treatment with medical treatments and prevention for comorbid disorders can enhance medical treatment outcomes