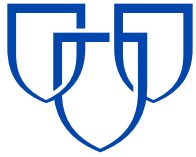


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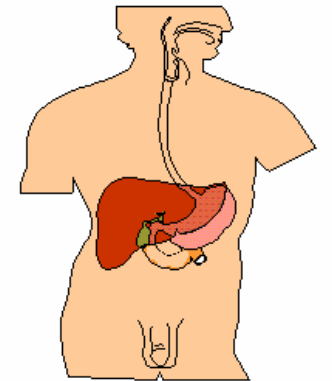
Tuberculosis and Viral Hepatitis



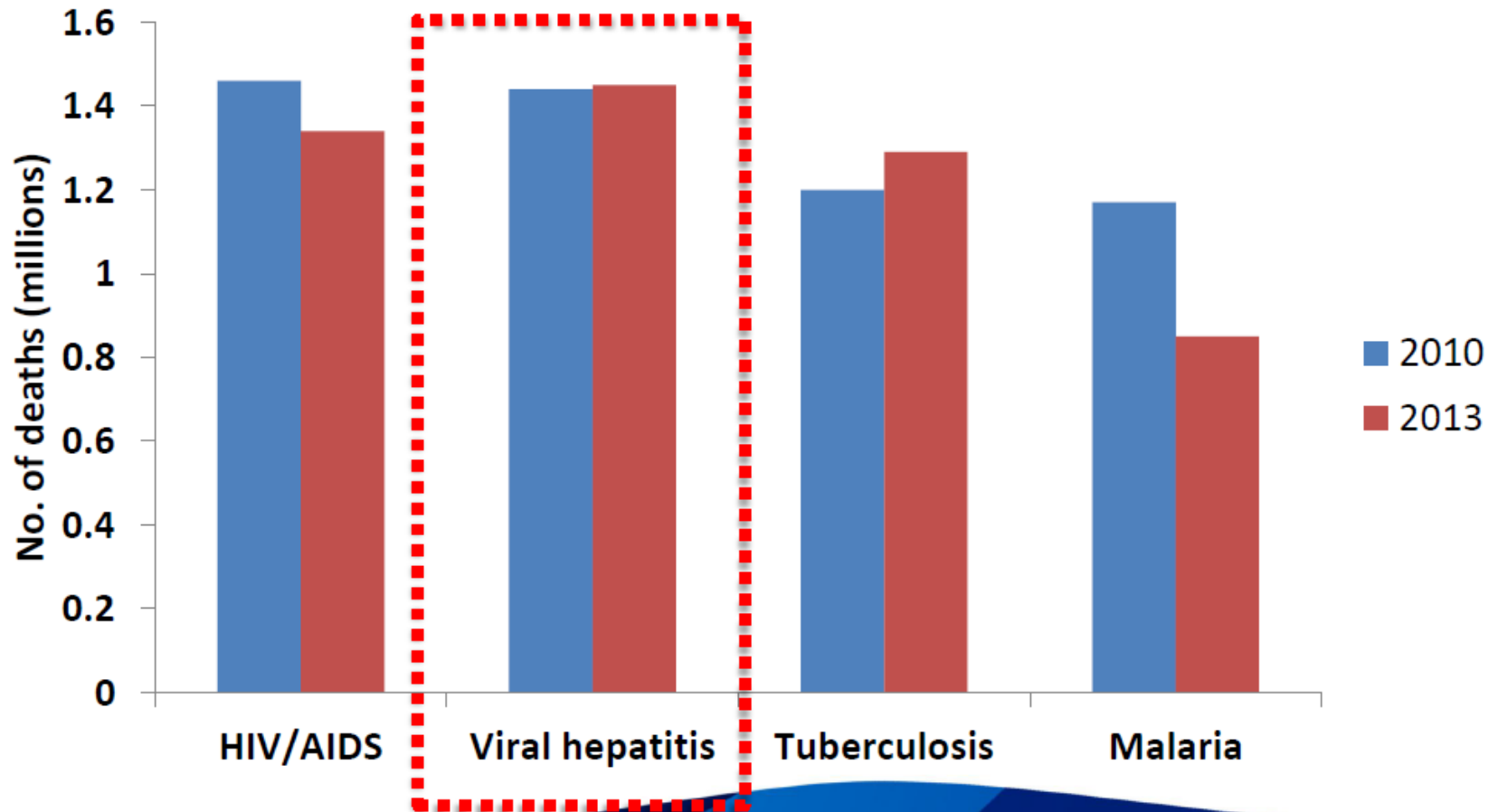
Zelalem Temesgen MD FIDSA AAHIVS
Professor of Medicine
Executive Director, Mayo Clinic Center for Tuberculosis
Director, HIV Program

HEPATITIS VIRUSES

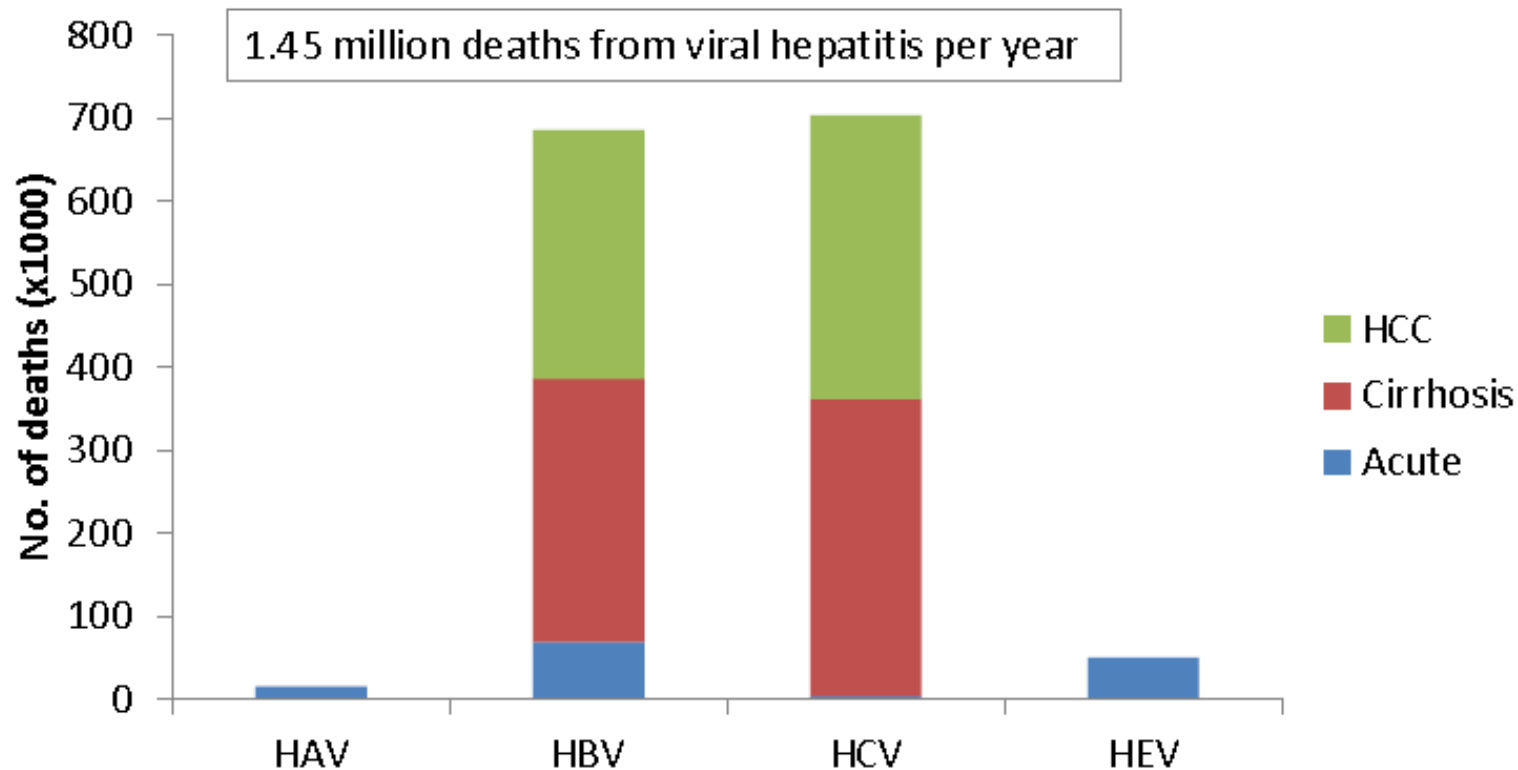
- Hepatitis A (HAV)
- **Hepatitis B (HBV)**
- **Hepatitis C (HCV)**
- Hepatitis D (HDV)
- Hepatitis E (HEV)
- Hepatitis G (HGV)



Number of deaths/year from selected conditions, Global Burden of Disease Study 2010 and 2013



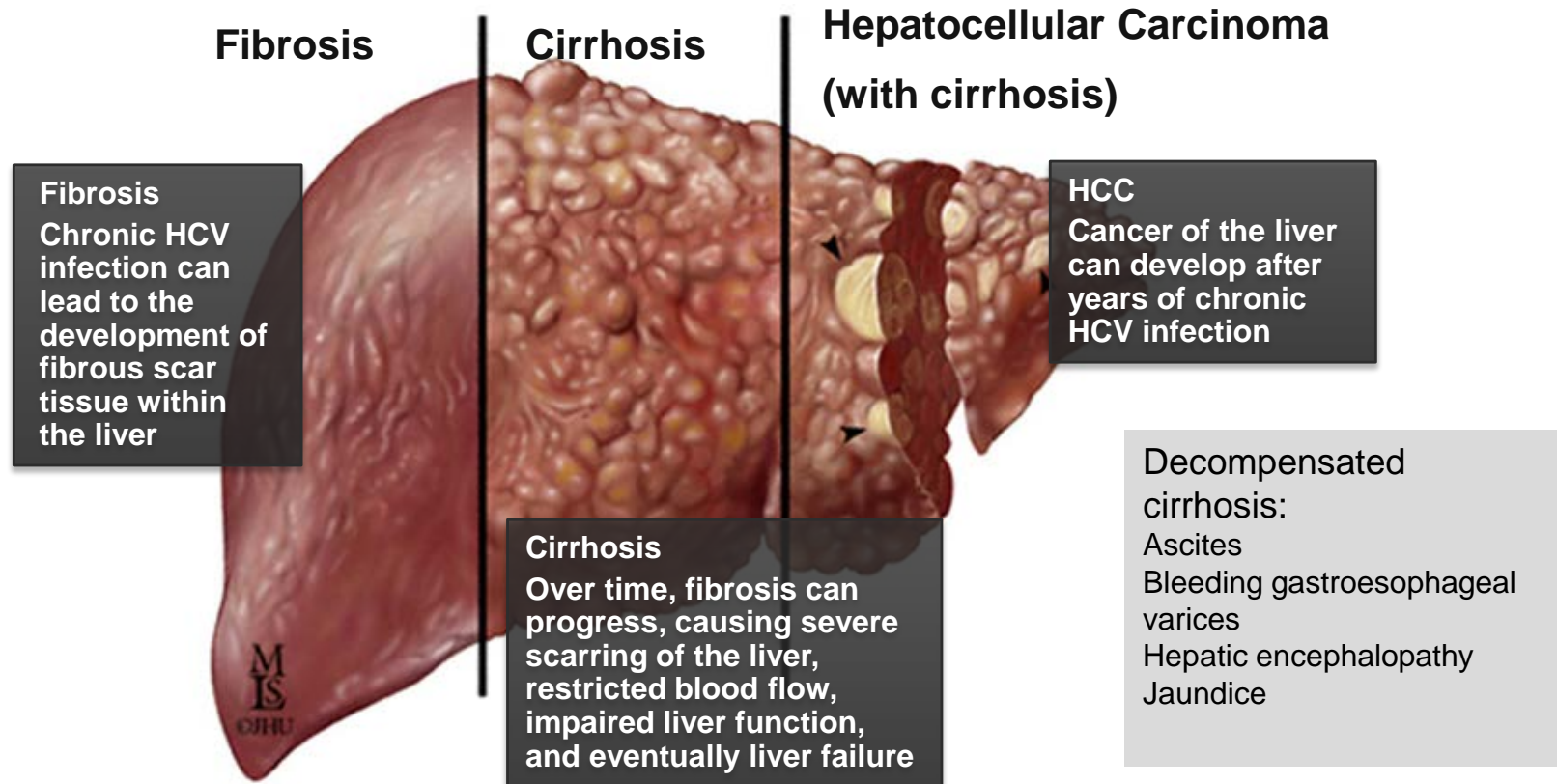
Hepatitis-related mortality, 2013



Global Impact of Viral Hepatitis

- Viral hepatitis accounted for 1.45 million deaths in 2013, a 63% increase compared with the 0.89 million deaths in 1990.
- Increased morbidity - Years lived with disability
 - From 0.65 million to 0.87 million
- Increased morbidity - adjusted life-years
 - From 31.7 million to 42.5 million
- Most of the morbidity and mortality is caused by hepatitis B and C infections

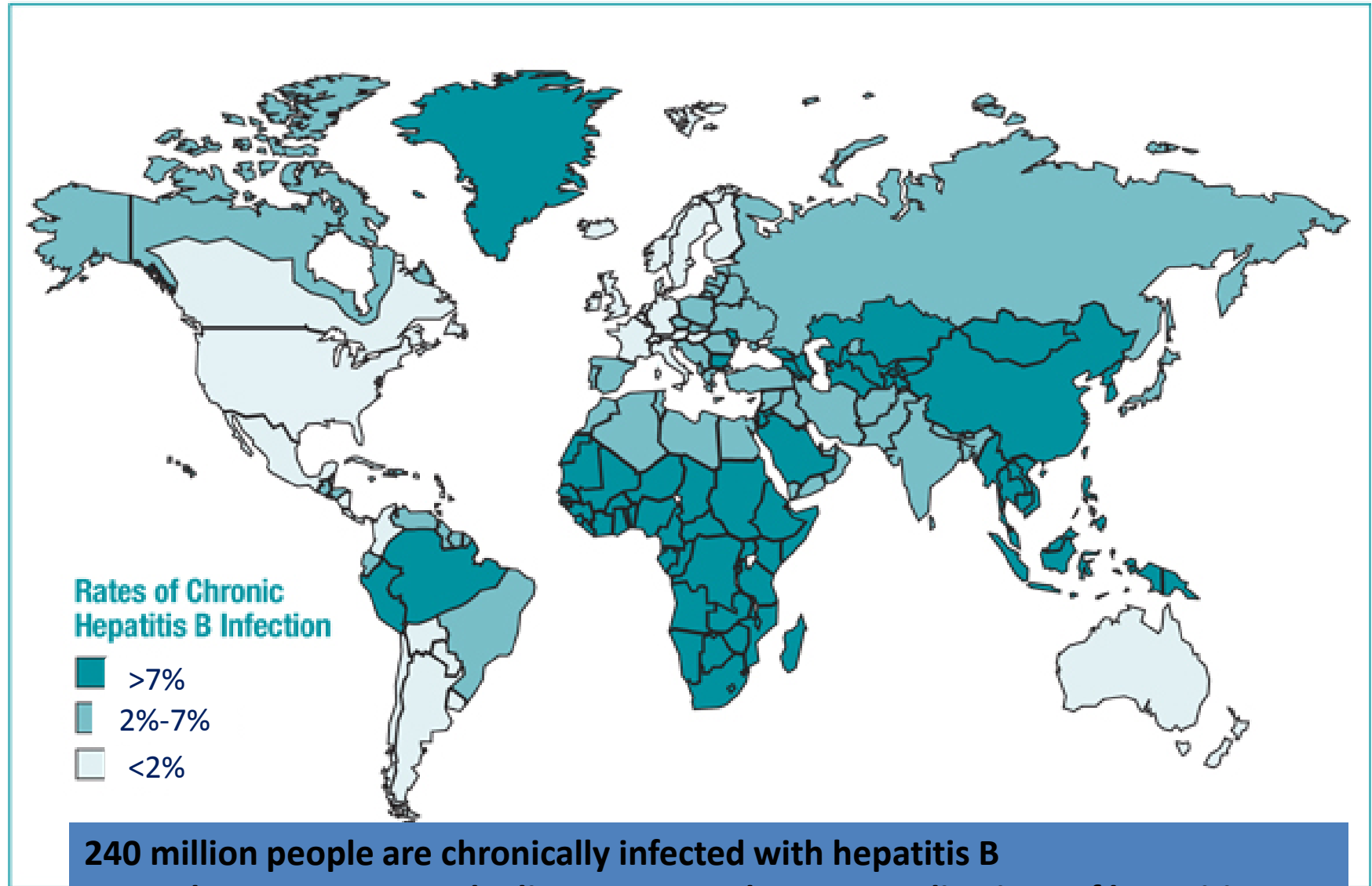
Chronic Hepatitis and its Sequelae



Talk Objectives

- Understand the basic facts about Hepatitis B
- Understand the basic facts about Hepatitis C
- Identify unique features of tuberculosis and viral hepatitis co-infections
- Review the management of tuberculosis and drug-induced hepatitis

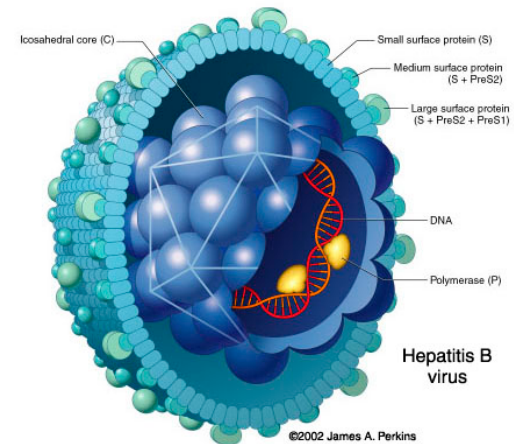
Worldwide Rates of Chronic Hepatitis B



240 million people are chronically infected with hepatitis B
More than 686 000 people die every year due to complications of hepatitis B

Hepatitis B Virus

- Transmission
 - Parental
 - Perinatal
 - Sexual
- Chronic infection develops in
 - 80-90% of those infected as infants
 - 30-50% of children <6 years
 - <10% of those infected as adults
- Chronic infection can lead to chronic liver disease, cirrhosis, liver cancer or liver failure, usually over 20-30+ years



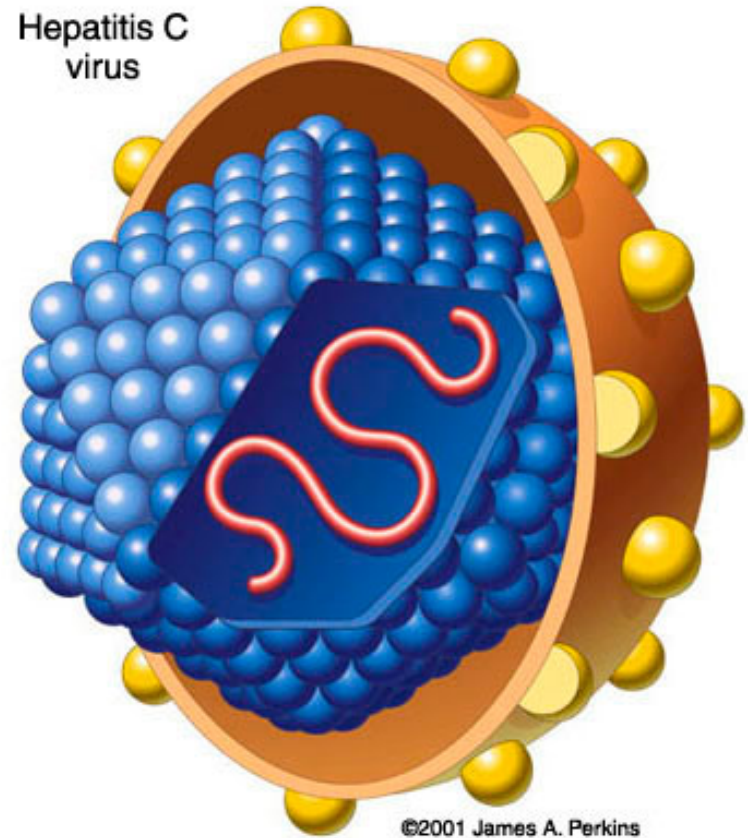
Hepatitis B Treatment

- Goal of treatment = **reduce liver damage, by decreasing viral replication**
- Suppress viral replication as much as possible for as long as possible
- Prevent liver disease and HCC

Hepatology. 2004; 39:857-861

Hepatitis C

- Positive single stranded RNA virus with an open reading frame
- Small, enveloped virus which is a member of the *Flaviviridae* family
- 1989 by Michael Houghton



HCV: Transmission

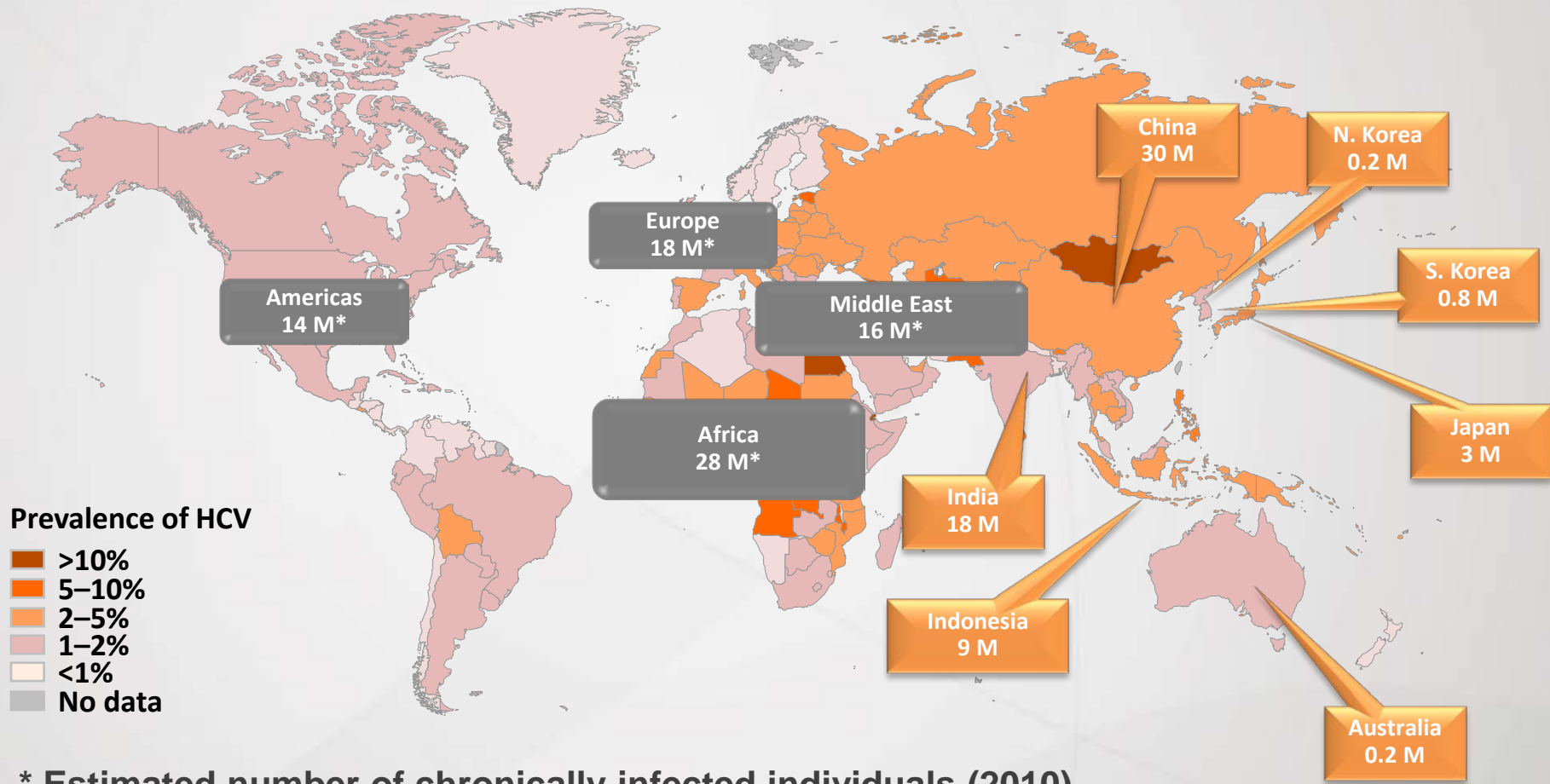


60% of HCV in the US is due to IV Drug Abuse
IVDU, Tattoos, Snorting cocaine, Sex, Peri-natal,
Blood transfusion before 1991

cdc.gov

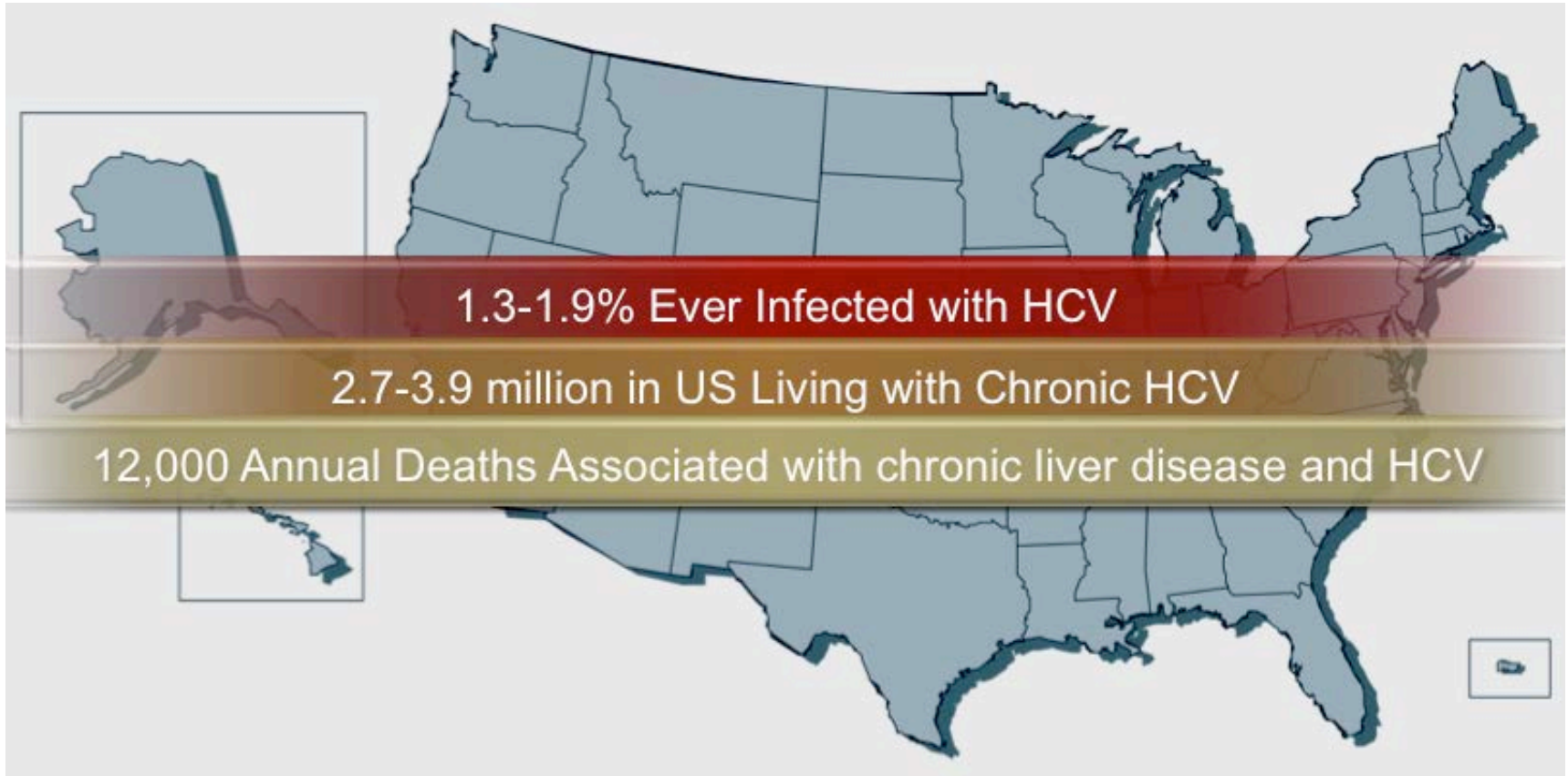
HCV distribution across the world

130–170 million people world wide are infected with HCV



* Estimated number of chronically infected individuals (2010)

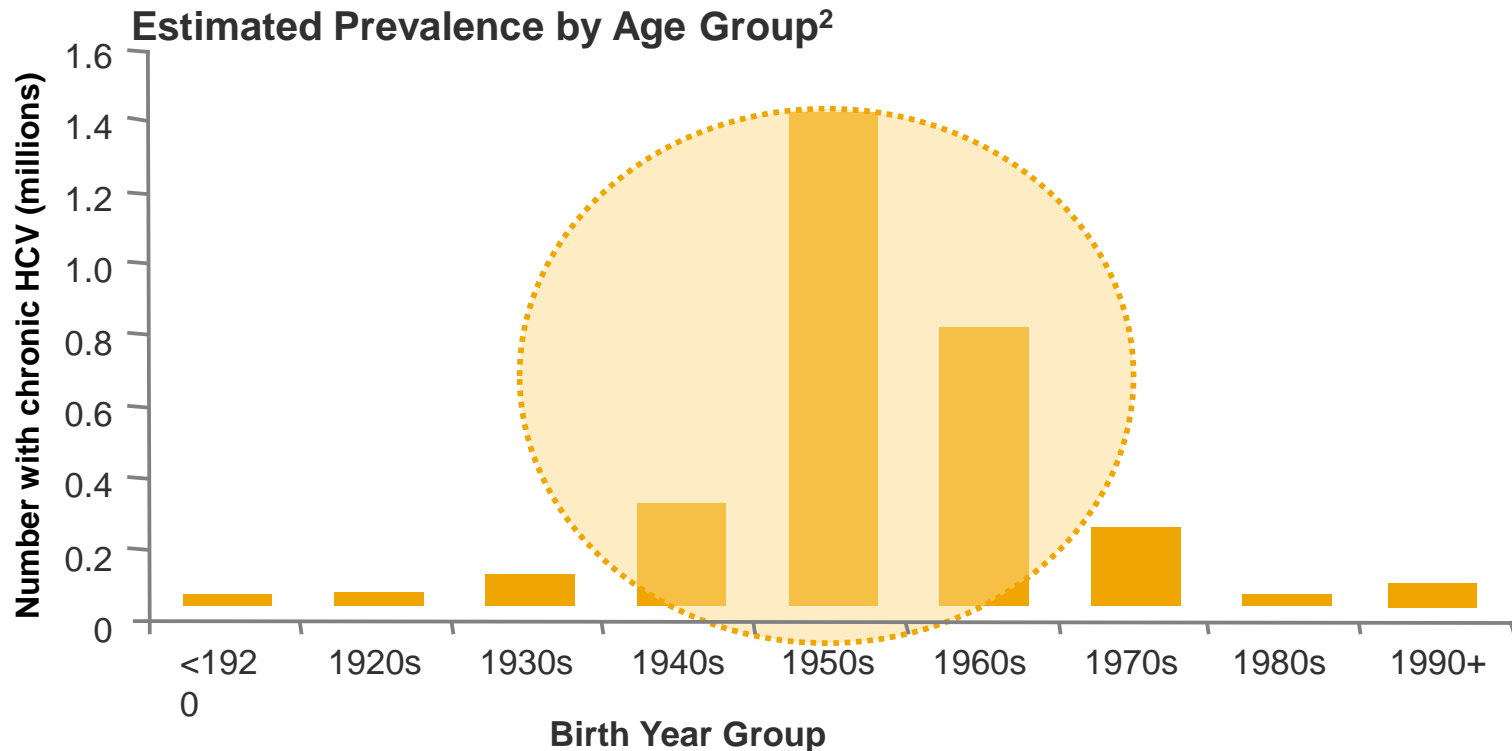
Hepatitis C in the US



150, 000 new cases every year in the US

Annual costs of acute and chronic hepatitis C in the US is over \$ 1 billion

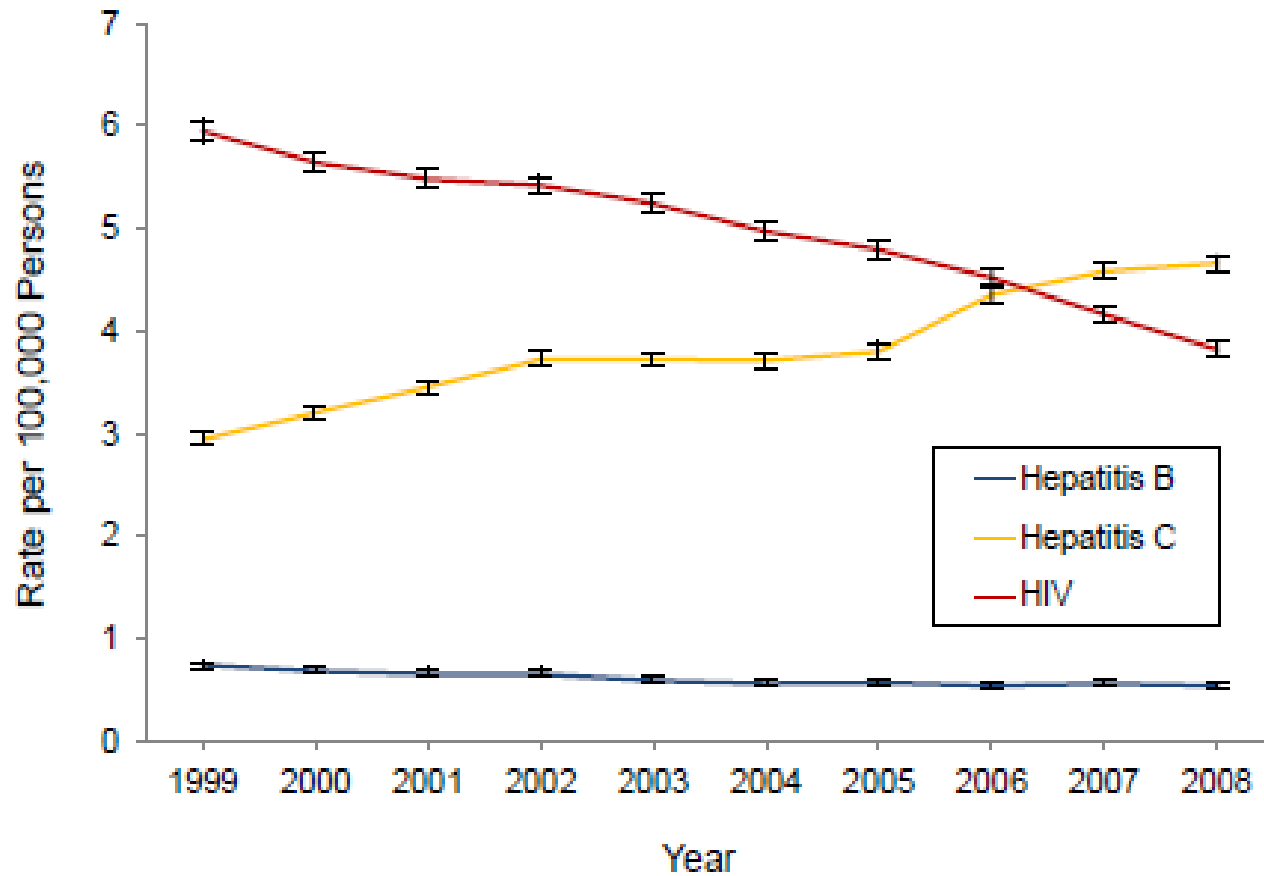
Baby Boomers (Born in 1945–1965) Account for 76.5% of HCV in the US¹



An estimated 35% of undiagnosed baby boomers with HCV currently have advanced fibrosis (F3-F4; bridging fibrosis to cirrhosis)³

1. Centers for Disease Control and Prevention. *MMWR*. 2012;61:1-32; Adapted from Pyenson B, et al. *Consequences of Hepatitis C Virus (HCV): Costs of a baby boomer Epidemic of Liver Disease*. New York, NY: Milliman, Inc; May 18, 2009. <http://www.milliman.com/expertise/healthcare/publications/rr/consequences-hepatitis-c-virus-RR05-15-09.php> Milliman report was commissioned by Vertex Pharmaceuticals; 3. McGarry LJ et al. *Hepatology*. 2012;55(5):1344-1355.

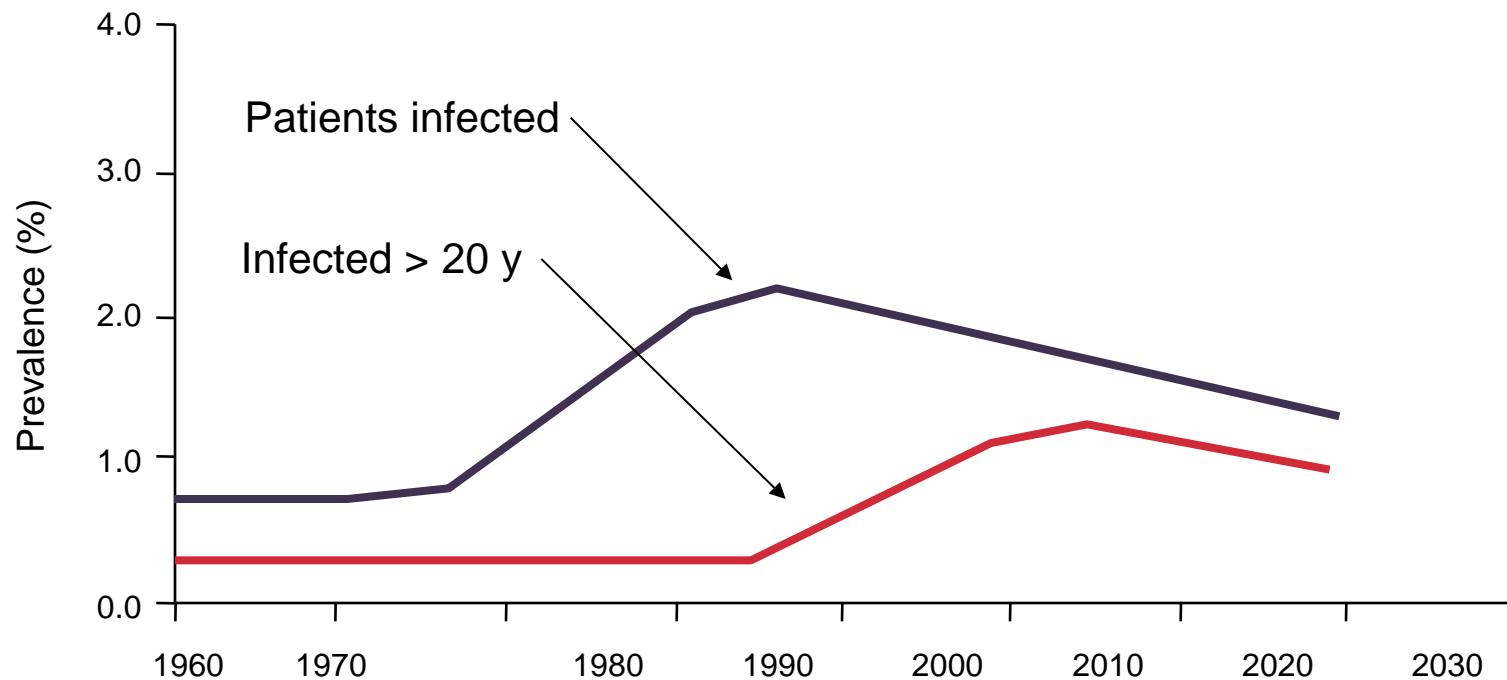
Mortality associated with Hepatitis B, Hepatitis C, and HIV United States, 1999 – 2008



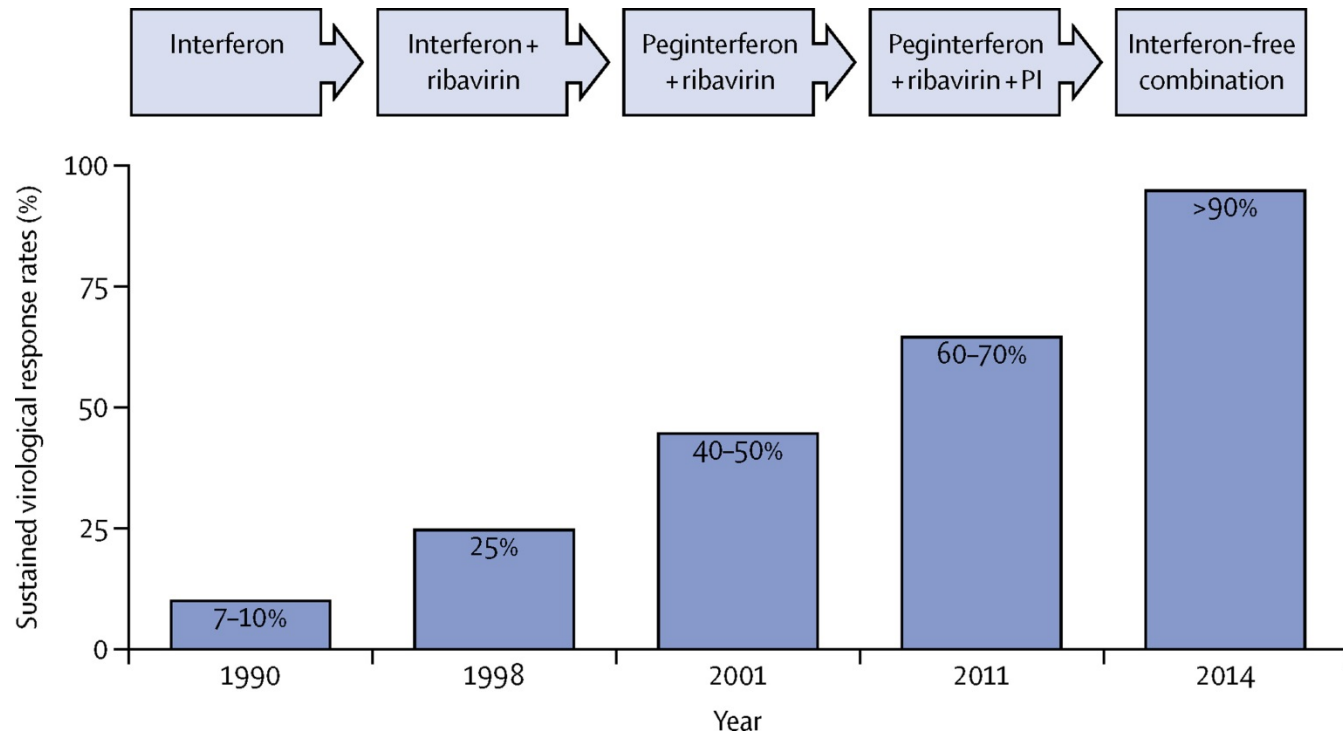
K Ly et al, *Ann Intern Med* 2012

Disease Burden of Patients Infected 20 Years or More is Peaking Now

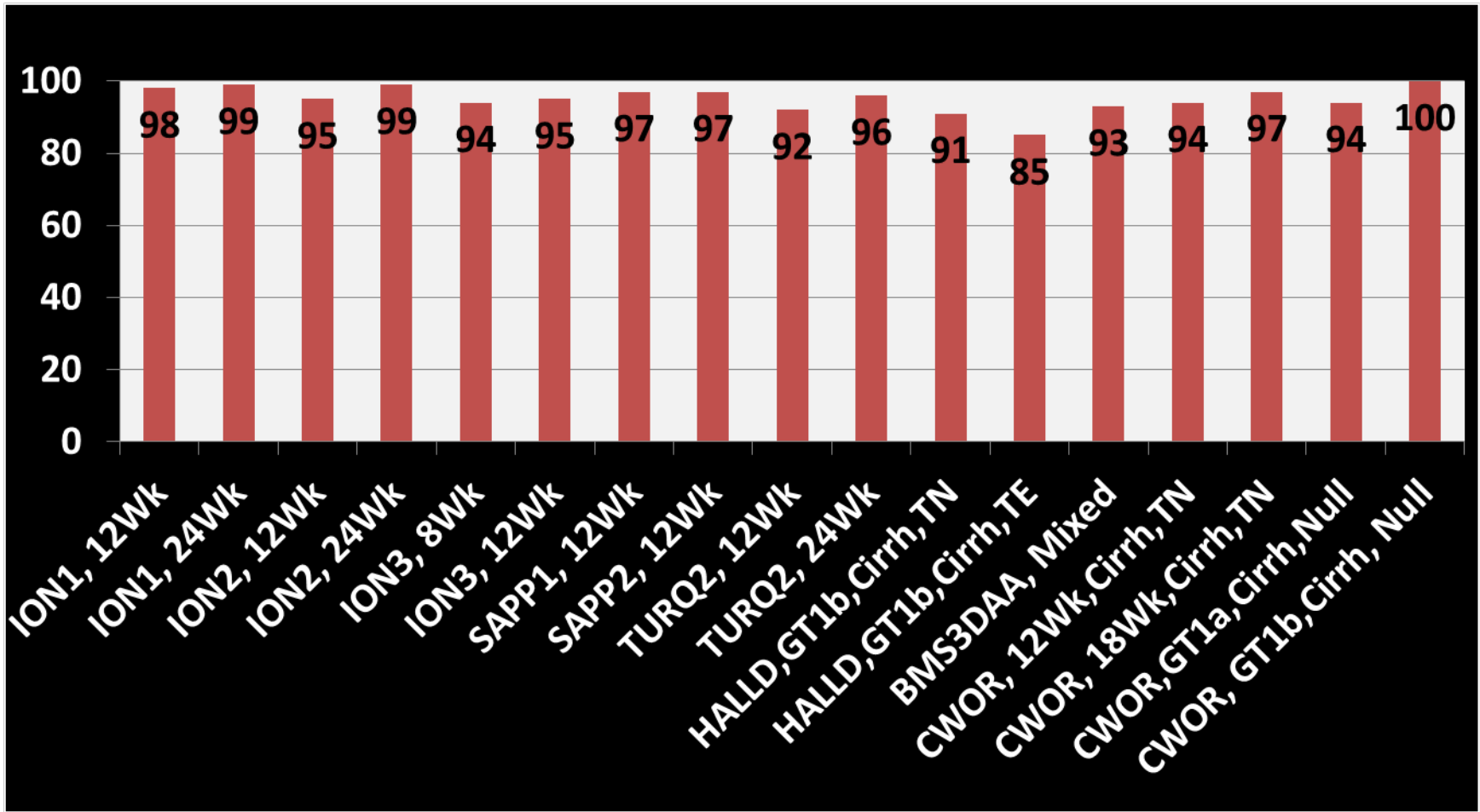
Complications from chronic hepatitis C develop slowly over a period of 20–30 years



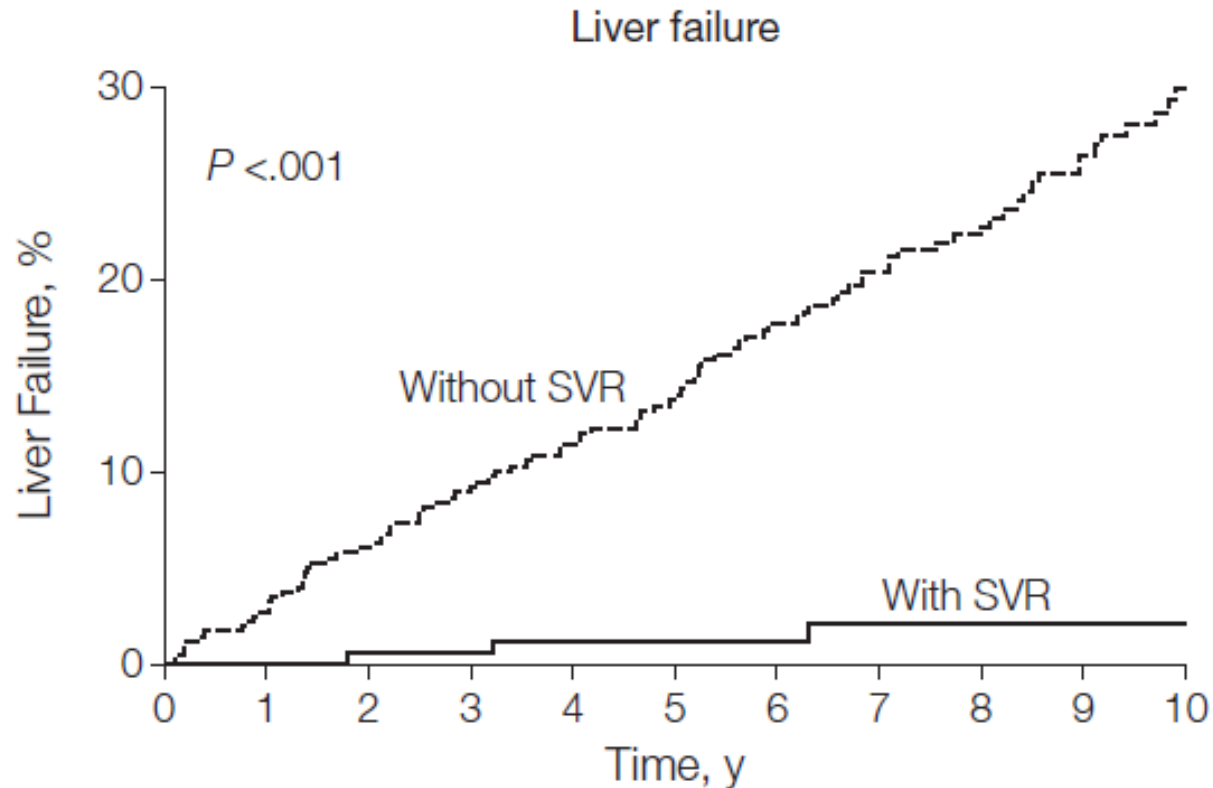
Evolution of Standard of Care in HCV Therapeutics



Reported SVRs of IFN-free, Multi-DAA Rx



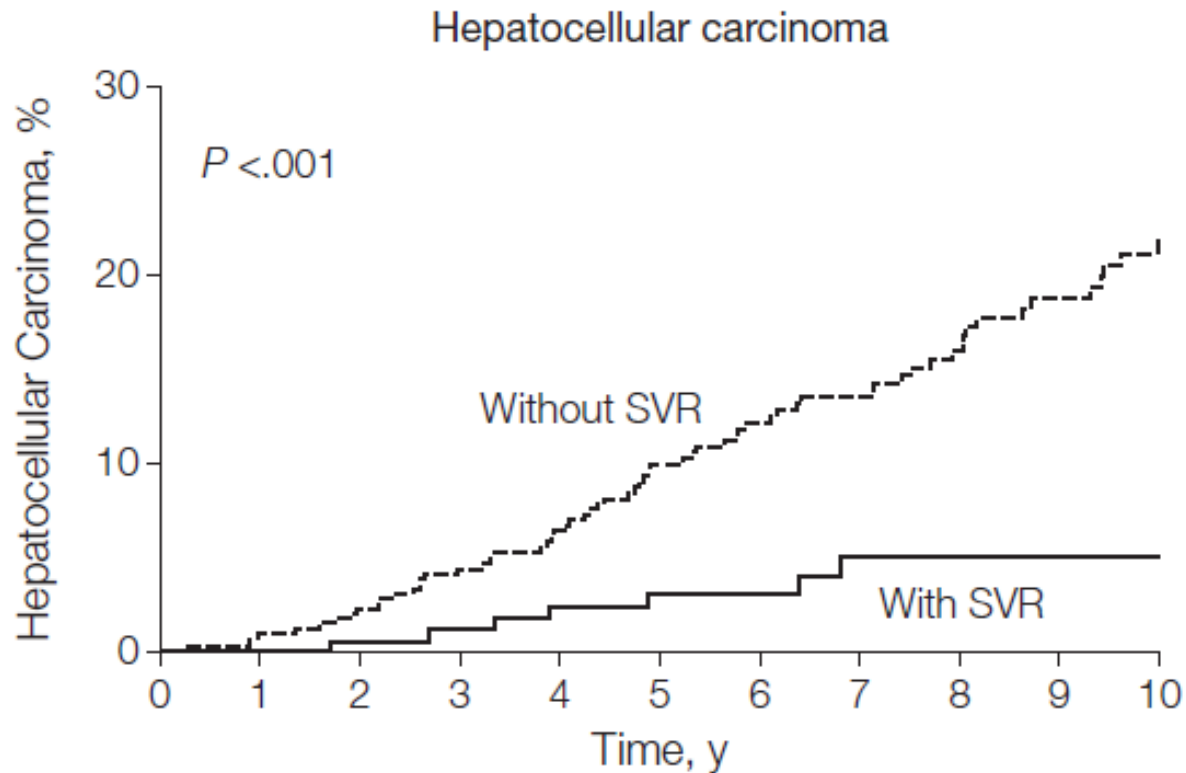
Impact of Treatment on Liver Failure



No. at risk

Without SVR	405	384	361	337	314	288	259	216	184	143	113
With SVR	192	180	166	160	152	141	123	88	56	40	28

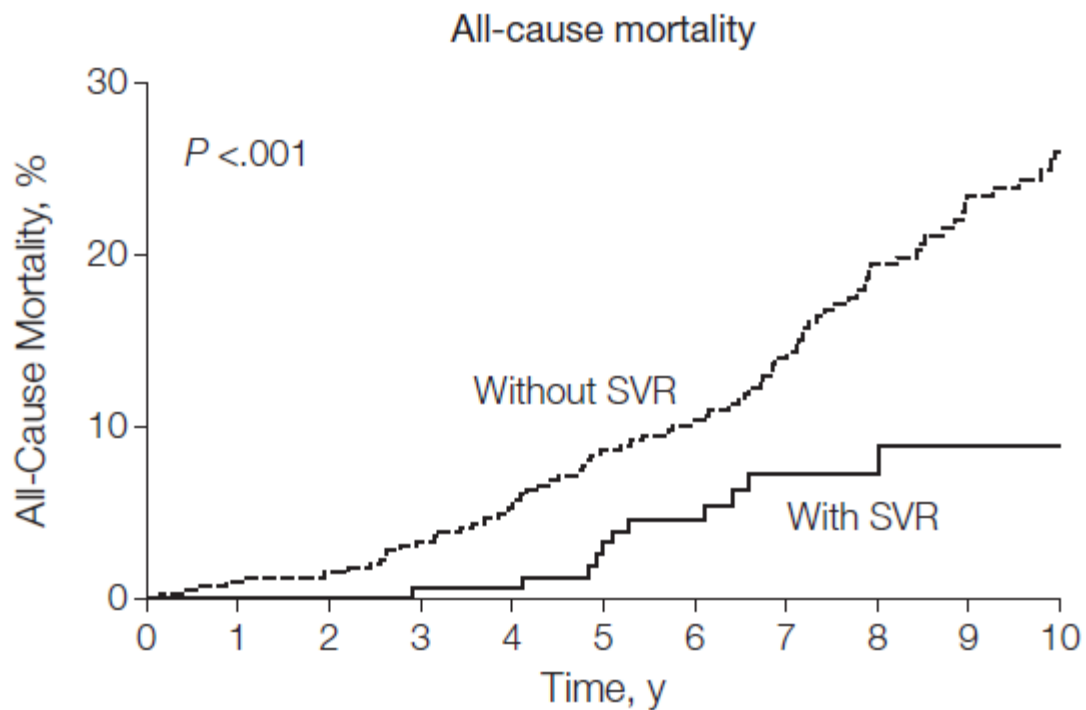
Impact of Treatment on HCC



No. at risk

Without SVR	405	390	375	349	326	294	269	229	191	151	122
With SVR	192	181	167	161	152	142	124	86	54	39	27

Treatment Reduces All-Cause Mortality in Patients With Advanced Fibrosis



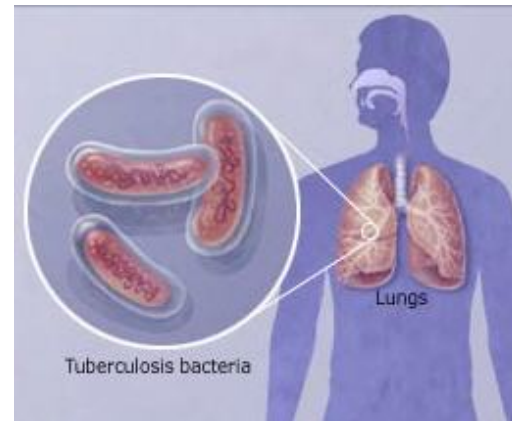
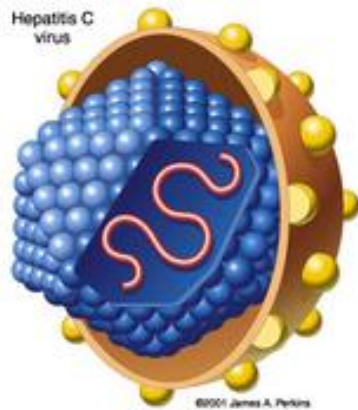
No. at risk

Without SVR	405	393	382	363	344	317	295	250	207	164	135
With SVR	192	181	168	162	155	144	125	88	56	40	28

HCV Screening Guidelines

- Anyone born between 1945 and 1965
- HIV-infected
- History of illicit injection drug use or intranasal cocaine use, even if only used once
- Received clotting factors made before 1987
- Ever on chronic hemodialysis
- Persistently elevated ALT level
- Informed that they received blood from a donor who later tested positive for HCV
- Received blood/organs before July 1992
- Children born to HCV-infected mothers.
- Needle stick injury or mucosal exposure to HCV+ blood

Tuberculosis and Viral Hepatitis



When the Lung needs the Liver

Treating Tuberculosis

Common Side-effects of TB drugs

Side Effect	Drug
GI side effects	<ul style="list-style-type: none"> ■ Ethionamide ■ Fluoroquinolones ■ Para-aminosalicylate (PAS) ■ Clofazimine ■ Rifabutin ■ Aminoglycosides
Headache	<ul style="list-style-type: none"> ■ Fluoroquinolones ■ INH ■ Cycloserine ■ Ethambutol (EMB) ■ Ethionamide
Skin problems	<ul style="list-style-type: none"> ■ Clofazimine ■ Cycloserine ■ INH ■ Rifabutin ■ PAS ■ Ethionamide ■ EMB
Photosensitivity	<ul style="list-style-type: none"> ■ Clofazimine ■ Fluoroquinolones
Hepatotoxicity (early symptoms are anorexia and malaise, then abdominal pain, vomiting, jaundice)	<ul style="list-style-type: none"> ■ INH ■ Rifabutin ■ Ethionamide ■ PZA ■ PAS ■ Fluoroquinolones ■ Rifampin (RIF)
Behavioral changes	<ul style="list-style-type: none"> ■ INH ■ Cycloserine ■ Ethionamide ■ Fluoroquinolones
Musculoskeletal / joint / tendons	<ul style="list-style-type: none"> ■ Fluoroquinolones ■ PZA ■ Rifabutin ■ RIF ■ INH (positive antinuclear antibody [ANA])
Visual changes, eye pain, change in color vision	<ul style="list-style-type: none"> ■ EMB ■ Rifabutin ■ Clofazimine ■ high-dose INH ■ Linezolid
Hearing loss, ringing in the ears, vestibular toxicity	<ul style="list-style-type: none"> ■ Aminoglycosides ■ Capreomycin
Dizziness	<ul style="list-style-type: none"> ■ Cycloserine ■ Fluoroquinolones ■ Aminoglycosides / capreomycin (as manifestation of vestibular toxicity)
Peripheral neuropathy	<ul style="list-style-type: none"> ■ INH ■ Ethionamide ■ Cycloserine ■ Linezolid
Hypothyroidism	<ul style="list-style-type: none"> ■ Ethionamide ■ PAS
Hypokalemia / hypomagnesemia	<ul style="list-style-type: none"> ■ Aminoglycosides ■ Capreomycin

Tuberculosis and Hepatitis



- Reported incidence of hepatitis with first line anti-TB medications (INH, Rif, PZA) varies widely: **2.5-35%**
- The mechanism of drug induced hepatotoxicity is not fully understood
- Can be symptomatic or asymptomatic

Int J Tuberc Lung Dis 2004;8:1499
Am J Ther 2010 Jan-Feb;17(1):17
Liverfoundation.org

Tuberculosis and Hepatitis

- Causes symptoms
- Risks treatment interruption
 - Loss to follow up
 - Inducing drug resistance
 - Continued infectivity
- Death (3% vs. 13%)



Betterhealth.com

Am J Ther 2010 (1):17

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Tuberculosis and Hepatitis

- **Factors that exacerbate hepatitis during treatment:**
 - Advanced age
 - Female sex
 - Alcohol use
 - Malnutrition
 - HIV co-infection
 - Underlying Liver disease
 - **HBV co-infection**
 - **HCV co-infection**

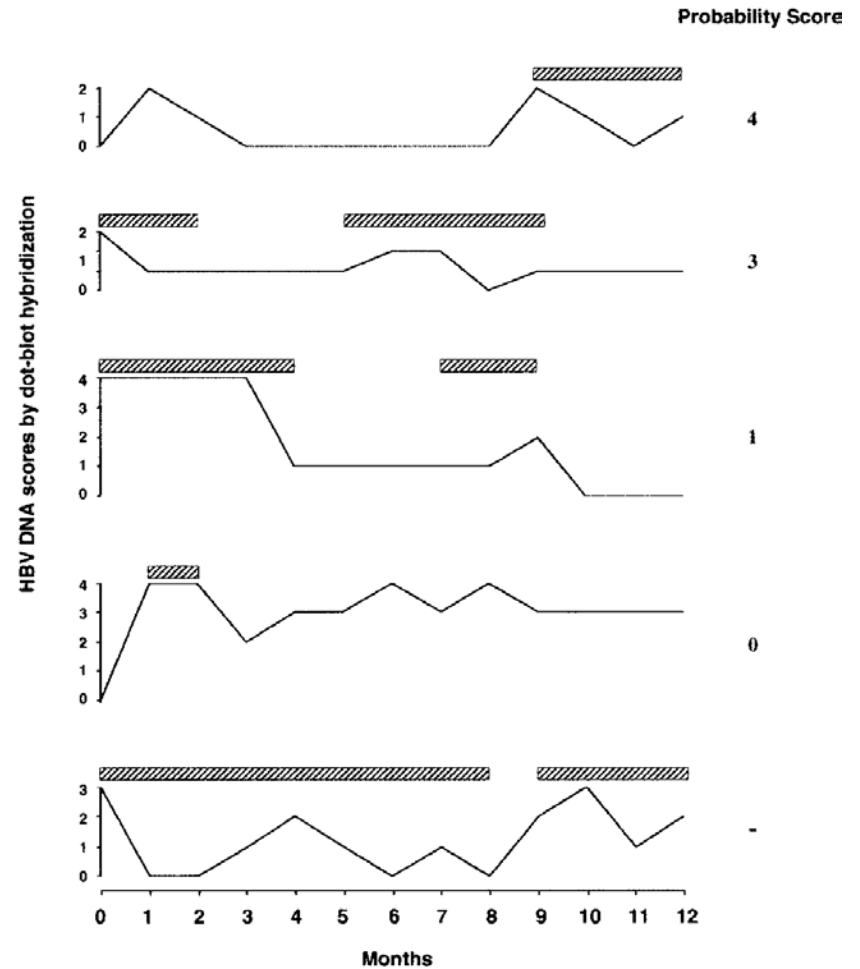
Int J Tuberc Lung Dis 2004;8:1499

Tuberculosis and HBV

- Many high incidence TB countries are also high incidence for HBV
 - Asia- 10% of population are HBV infected
- Active, replicating HBV can predict hepatotoxicity, but with low precision
 - Int J Tuberc Lung Dis 2010;14:332
- HBV infection resulted in a higher proportion of people developing drug-induced hepatotoxicity (34% vs 9%)
 - Hepatology 2003;31:200

Tuberculosis and HBV

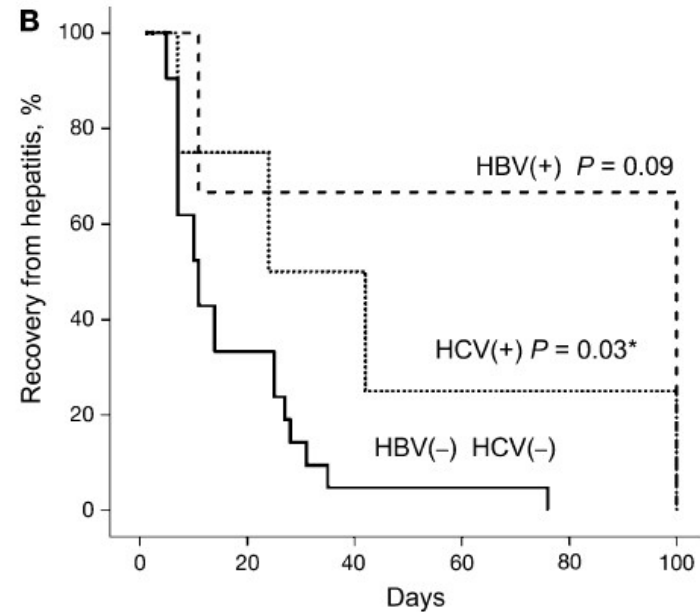
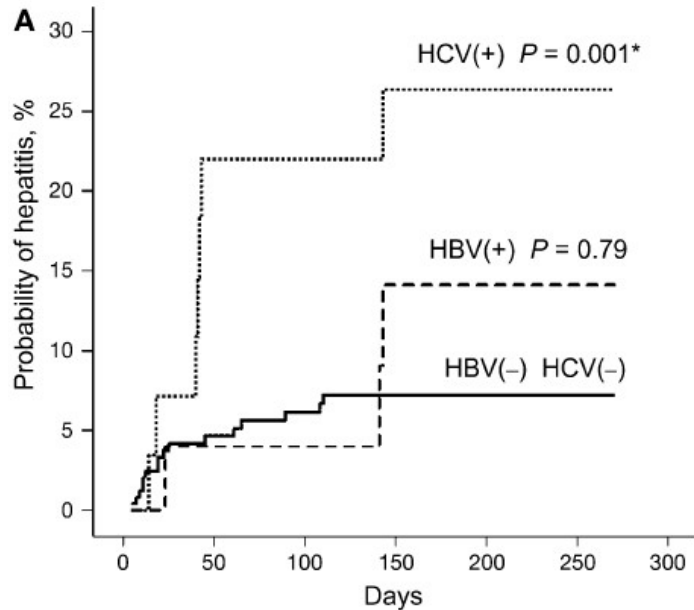
- HBV infected individuals had more drug-induced hepatotoxicity than non-infected individuals
- Hepatotoxicity correlated with HBV DNA levels



Hepatology 2003;31:200

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HBV and Tuberculosis



- 8% were HBV co-infected
- HBV + had a similar rate of hepatitis than HBV-
- Of those who developed hepatitis with HBV
 - Higher peak ALT
 - Occurred later in the course

Int J Tuberc Lung Dis 2010;14:616

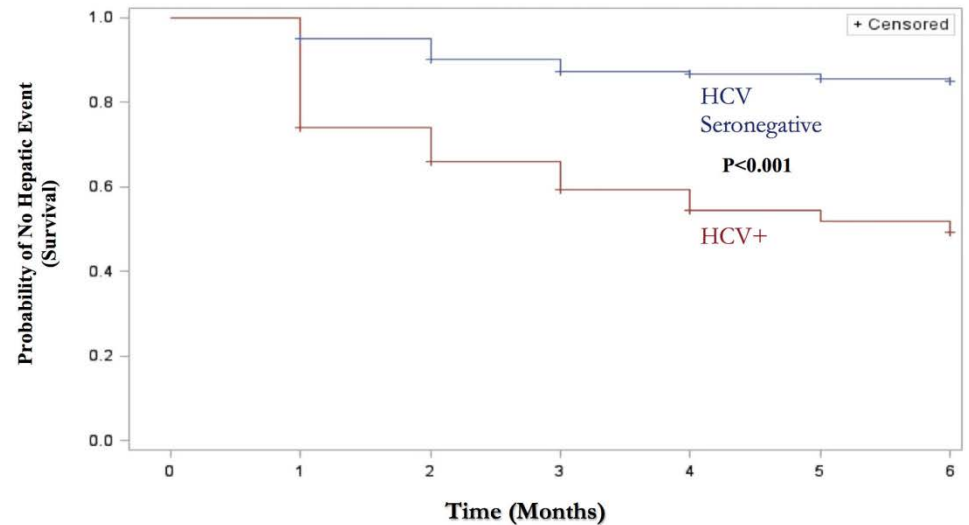
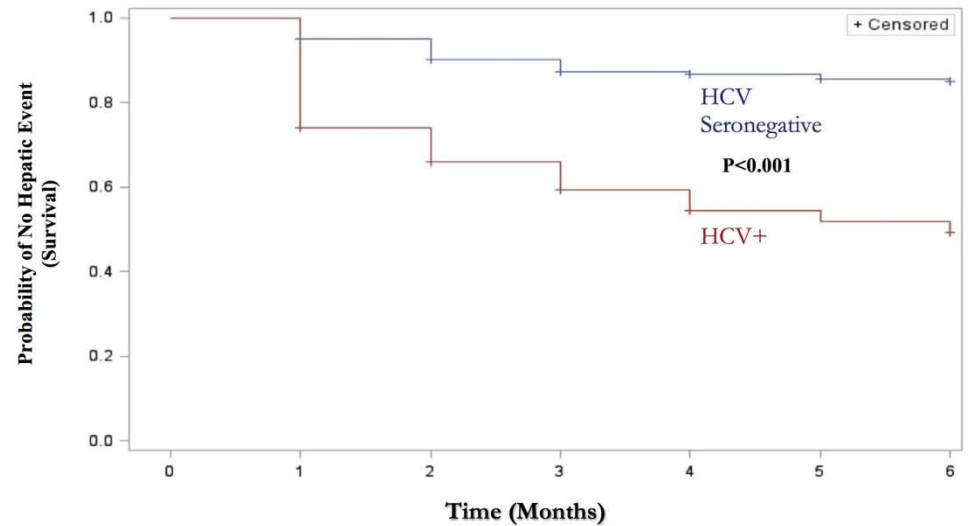
Tuberculosis and HCV

- Limited data on the impact of viral hepatitis during TB treatment
- High incidence Country (Georgia)
 - 326 pt pulmonary pan-sensitive TB
 - Treated with INH, Rif, Ethambutol, PZA
 - 21% HCV co-infected



PLoS One 2013;8:12

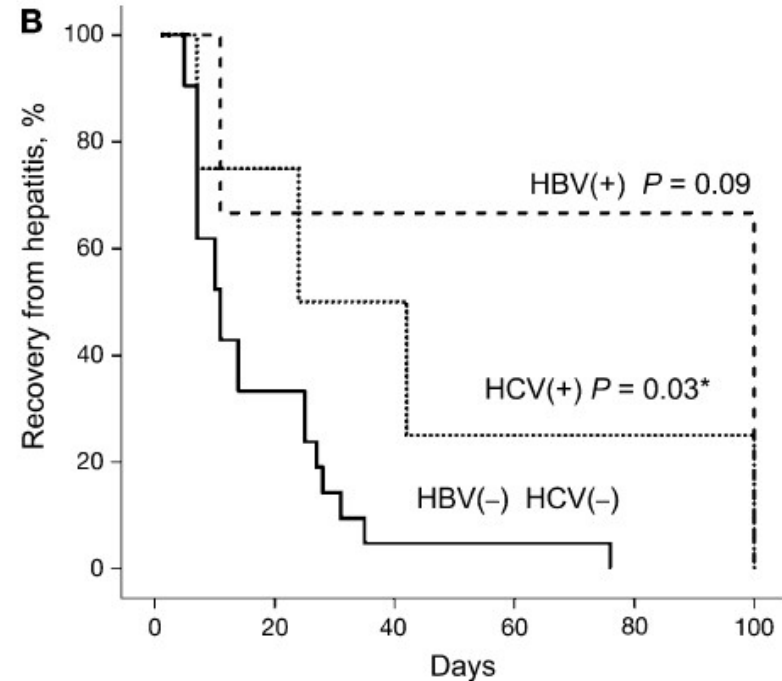
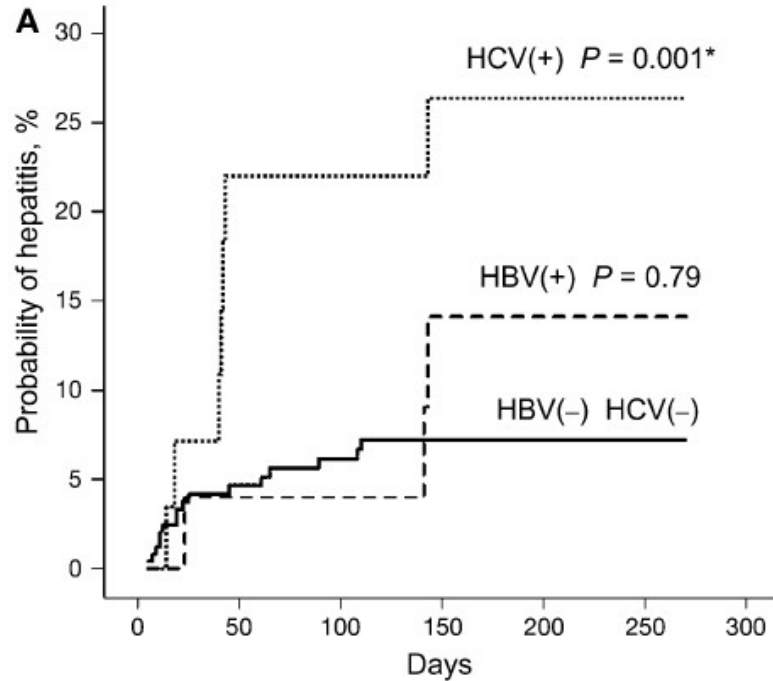
- HCV co-infection was an independent risk factor for anti-TB drug hepatotoxicity
- 43% HCV+ vs. 18% HCV-
- HCV + developed toxicity faster than HCV -
- No medication discontinuation was required



Tuberculosis and HCV

- What about people with normal liver tests?
- 295 patients with pulmonary TB, normal liver tests at baseline (Hong Kong)
- 10% HCV positive
- On first line anti-TB therapy

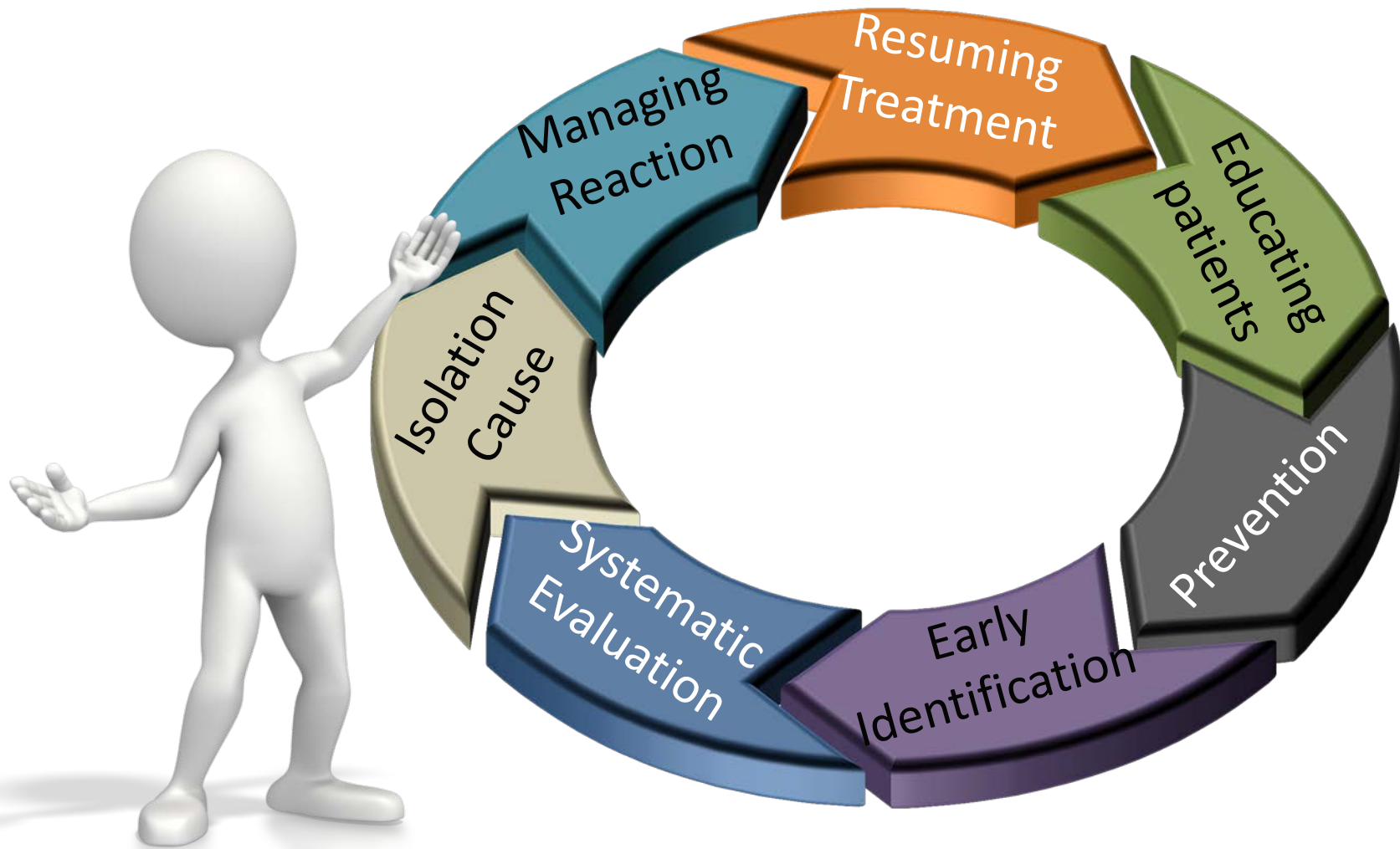
Int J Tuberc Lung Dis 2010;14:616

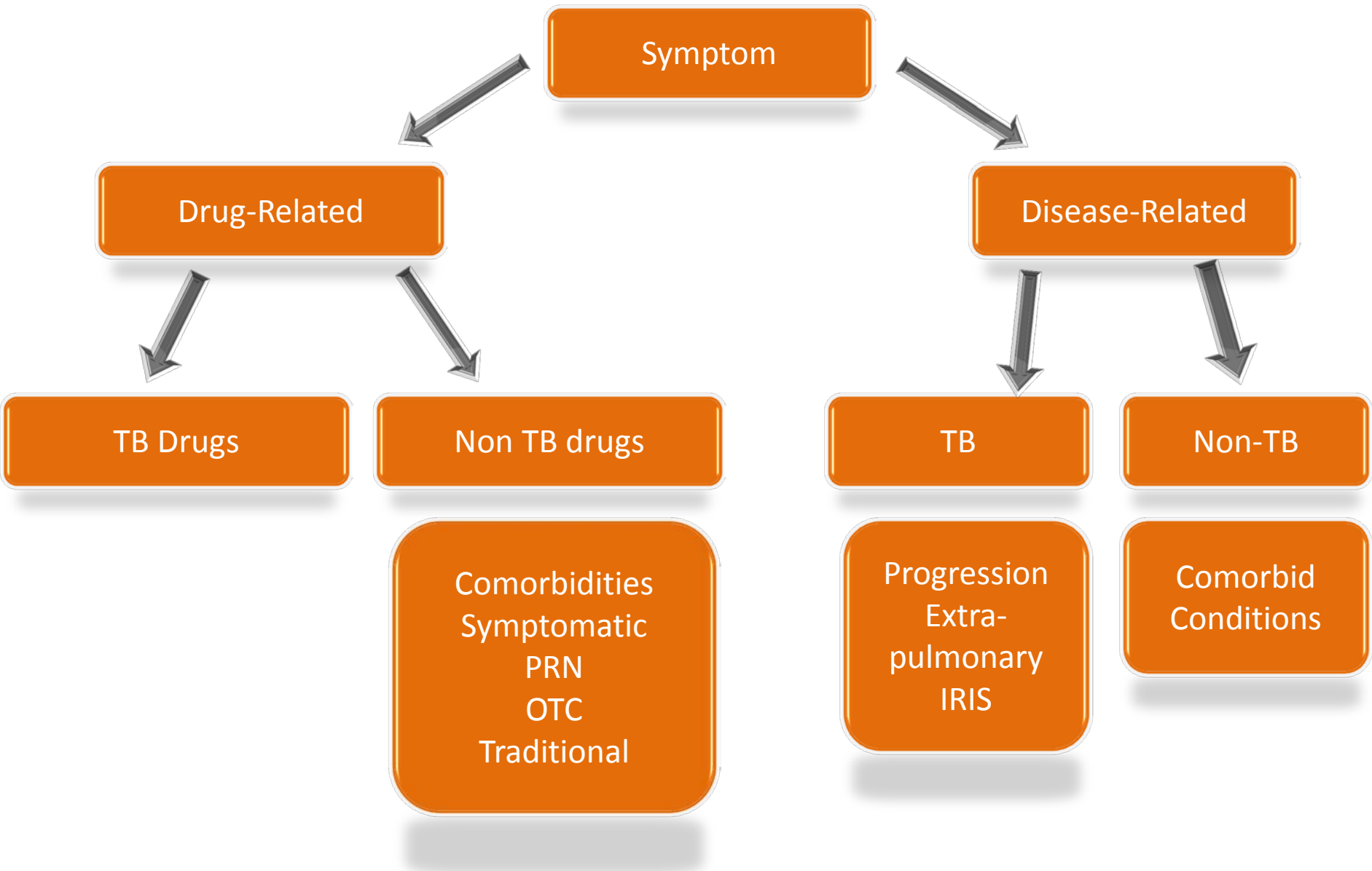


- HCV was a significant risk factor for drug induced hepatotoxicity
- Onset of HCV hepatotoxicity was early
- Hepatotoxicity was more prolonged
- Hepatitis had an increased mortality, but not associated with viral hepatitis co-infection

Int J Tuberc Lung Dis 2010;14:616

Managing Hepatitis During TB Treatment





Symptom

Drug-Related

Disease-Related

TB Drugs

Non TB drugs

TB

Non-TB

Comorbidities
Symptomatic
PRN
OTC
Traditional

Progression
Extra-pulmonary
IRIS

Comorbid
Conditions

Managing Hepatitis During TB Treatment

General Principles

- Not unusual for patients just starting combination TB therapy to experience upset stomach
 - Pts need counseling that this is **NOT uncommon**
 - INH, Rifampin, PZA all can produce gastritis
 - Symptoms can be similar to hepatitis, but LFTs remain normal
- Patients who develop anorexia, nausea, vomiting, abdominal pain, jaundice – more concerning
 - Stop all medications promptly, examine patient and check LFTs



Managing Hepatitis During TB Treatment

General Principles

- ALT is more specific for hepatocellular injury
 - AST can also be produced from muscle, heart, etc.
- If $AST > ALT$, assess for excessive alcohol intake
- 10-20% of patients on **INH** will have asymptomatic rise in transaminases
 - Tends to occur during 1st few months on INH
 - Not a toxicity and does not require cessation of therapy
 - Improves with continuation of therapy

Managing Hepatitis During TB Treatment

Follow Up Assessments



- Stop meds with any abnormal LFTs and the presence of adverse symptoms
 - Some guidelines state adverse symptoms and transaminases ≥ 3 x upper limits of normal range
- If LFTs abnormal (AST or ALT > 5 x upper limit of normal) or if bilirubin is elevated, with or without symptoms, all TB drugs should be promptly stopped
- Patient should have LFTs checked 1x – 2x weekly
 - If symptoms persist > 2 weeks off TB medications or if LFTs continue to worsen, then should suspect progressive hepatitis or an unrelated cause of hepatitis – may need hospitalization
 - E.g. HCV, HBV, HAV, other medications (non-TB); alcoholism, etc
- As soon as hepatitis is identified, viral hepatitis should be ruled out

Managing Hepatitis During TB Treatment

Important Notes

- If the patient has extensive pulmonary, meningeal or disseminated TB – then may not be able to temporarily observe off therapy:
 - Start a new combination drug regimen that is non-liver metabolized (i.e. EMB, FQ, AMK), while awaiting LFTs to improve:
 - Minimizing risk of further hepatotoxicity
 - May be started even before LFTs return to normal.
- Pattern of LFT abnormalities – clues to offending agent
 - Rifampin- **cholestatic pattern** (bilirubin & Alk phos. out of proportions to AST/ALT)
 - INH, RFP, PZA - **hepatocellular pattern** (AST/ALT elevated out of proportion to bilirubin or Alk phos)

Managing Hepatitis During TB Treatment

Restarting Drugs after LT improve

- **Hepatocellular pattern:**

- Start with Ethambutol and Rifampin x 1 week
 - Recheck LFTs – if stable/improved:
- Add INH or PZA (*either – which drug to add is debated*)
 - Recheck LFTs – if they remain stable:
 - Continue with EMB / Rifampin / INH or EMB / Rifampin / PZA for the duration of therapy
 - At least monthly LFTs (more frequently early on)



- Notes:

- INH and PZA are most commonly associated with hepatotoxicity
 - Some reports implicate PZA more frequently
 - Combination using PZA may be more problematic
 - PZA less important in combination TB drug regimen

AJRCCM 2003 167:1472-77

Managing Hepatitis During TB Treatment

Restarting Drugs after LT improve

- **Cholestatic pattern:**

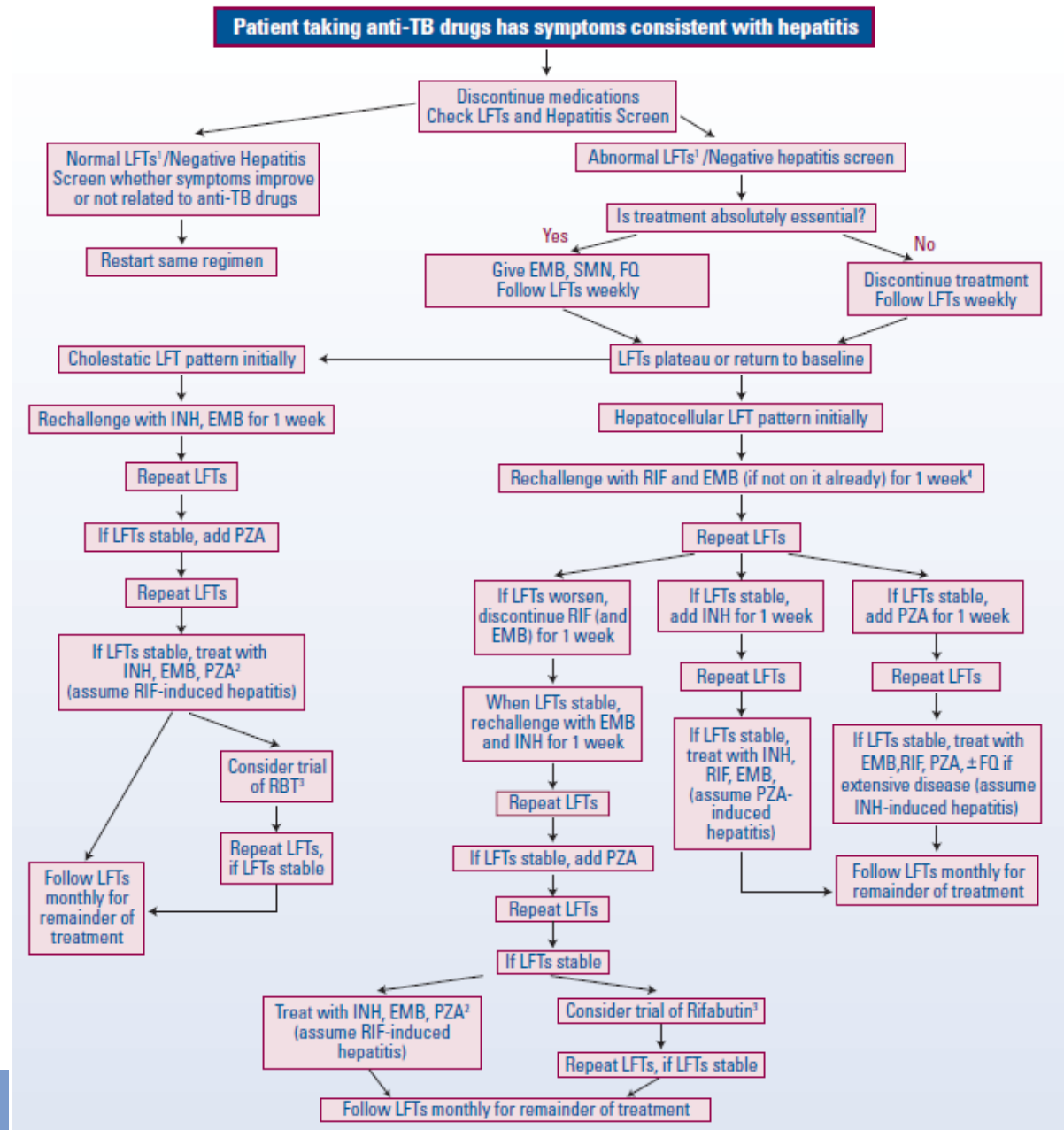
- Start with INH and ethambutol x 1 week
 - Recheck LFTs – if stable/improved:
- Add PZA
 - Recheck LFTs – if they remain stable:
 - Continue with INH/EMB/PZA – consider adding FQ
 - At least monthly LFTs (more frequently early on)

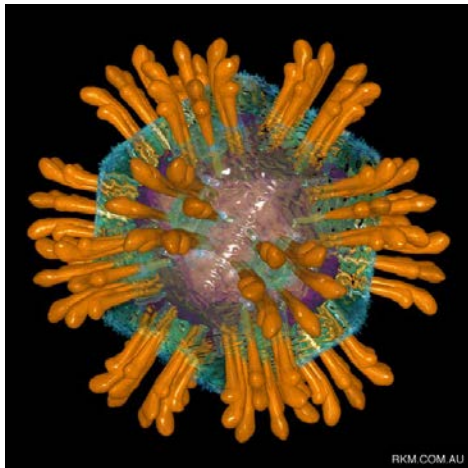
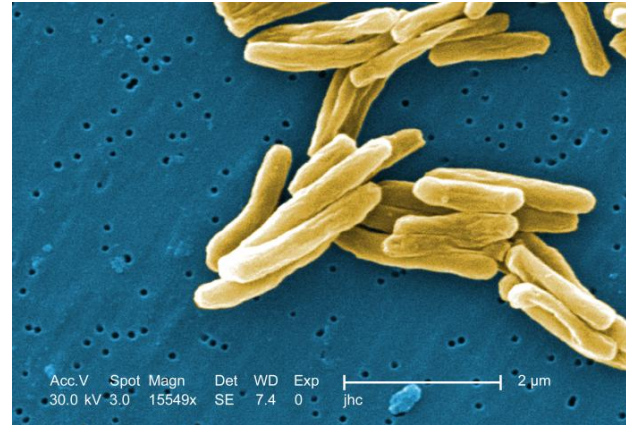
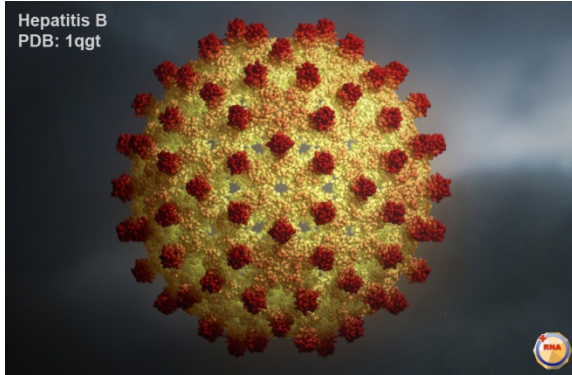


- If symptoms are not related to TB drugs, then restart entire drug regimen promptly and observe

Restarting Anti-TB Medications in Patients with Drug-Induced Hepatitis

Clinical Policies and Protocols
 Bureau of Tuberculosis Control
 New York City Department of
 Health and Mental Hygiene
 4th ed. 2008





TB Eradication needs treatment
Treatment needs medications
Medications need the liver

Look for HBV and HCV co-infection!



Questions & Discussion