

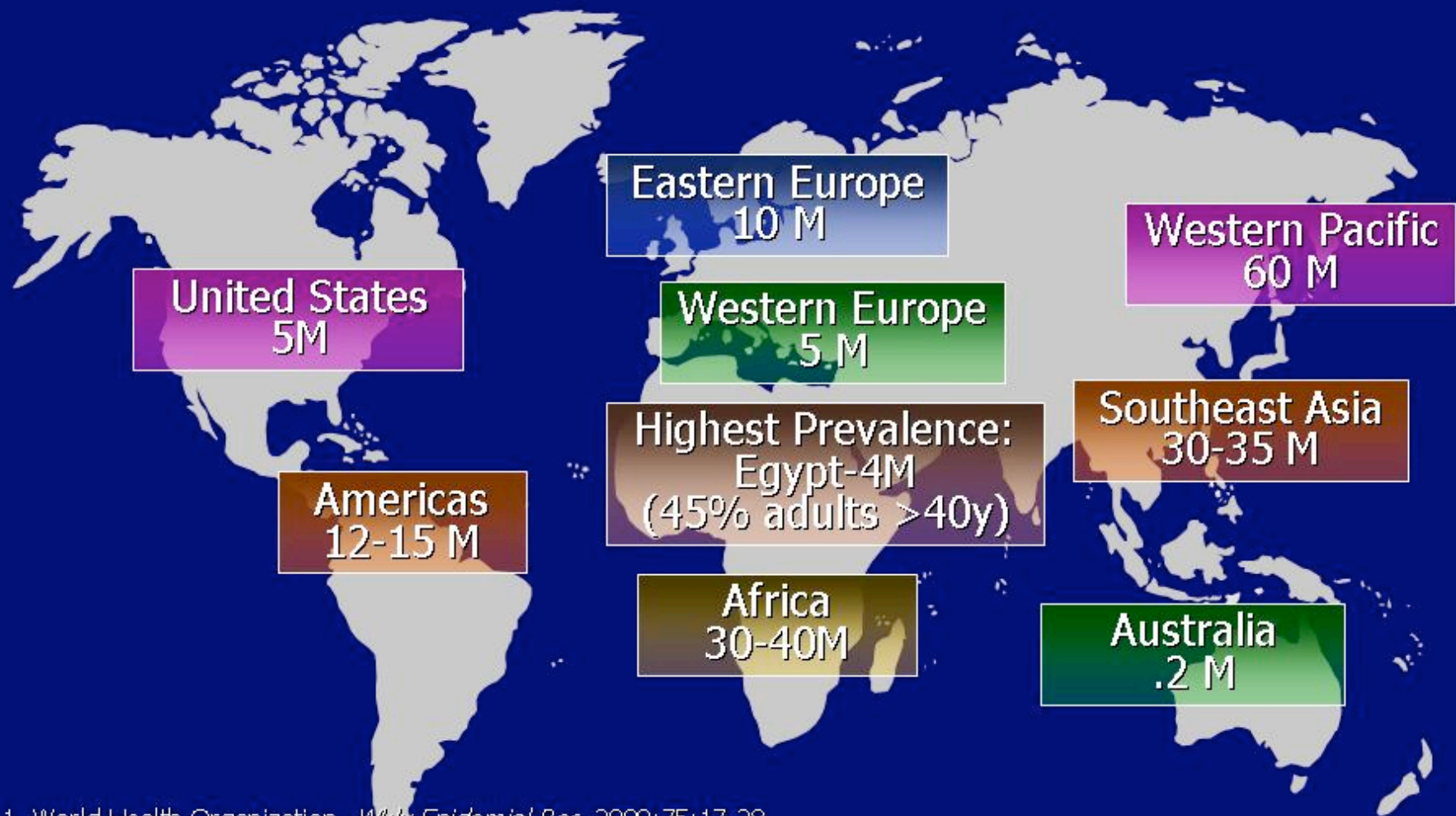


HIV/HCV Coinfection Update 2010

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Seroprevalence of Hepatitis C: 170 to 200 Million Worldwide



1. World Health Organization. *Wkly Epidemiol Rec.* 2000;75:17-28.

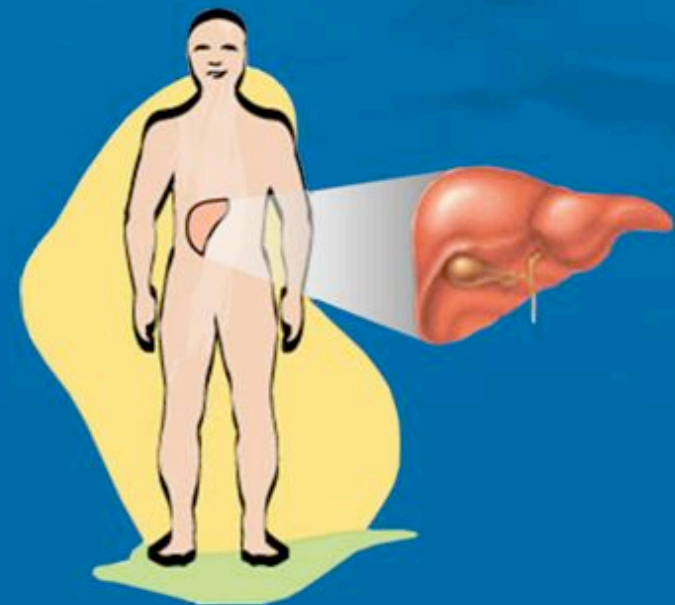
2. Edlin B et al. AASLD; November 11-15; 2005 San Francisco, California. Oral Presentation #44.

3. Fontanet A. Annual Report of Emerging Diseases for Year 2005. Accessed 03/13/06 at

<http://www.pasteur.fr/recherche/RAR/RAR2005/Epimal-en.html>

Why Is Your Liver So Important to Your Health?

- Your liver is one of the largest and most important organs in your body. It is about the size of a football!
- Your liver plays a central role in many vital life processes
- Your liver is an important part of your digestive system
- Your liver helps your body process medicines, including your HIV medicines
- Your liver is responsible for so many things that any damage to it can cause problems in other parts of your body



Your Liver Is Your Body's Factory

- It makes important substances called proteins that assist with many body functions (such as helping with clotting of your blood)
- It plays an important role in blood circulation
- It removes wastes and breaks down harmful substances, such as alcohol
 - **A healthy liver filters about 1.5 quarts of blood per minute... that's 540 gallons a day!!!!**



That Is Why Taking Care of Your Liver Is So Important!

What Is Hepatitis?

- Hepatitis – inflammation (swelling) of the liver
 - **There are over 100 causes of hepatitis and the most common one in the U.S. is alcohol!**
 - Can be caused by medications, alcohol, viruses, genetic diseases or chemicals
- If hepatitis is caused by a VIRUS, it is given a letter like hepatitis A, hepatitis B or **hepatitis C**
- Hepatitis C is also referred to as hep C or HCV (hepatitis C virus)

Hepatitis C Infection

- Most people infected with hepatitis C end up with the chronic (long-term) form of the disease
 - Occurs in 80-85% of infected persons
- In the U.S., it is the most common infection that is spread from blood-to-blood contact
- About 35,000 new cases of hepatitis C are estimated to occur in the U.S. each year
- Untreated hepatitis C can cause many health problems. Since it affects your liver, it can affect your whole body
 - End-stage liver disease is the #1 cause of death among patients with HIV

What Is Fibrosis?

- The beginning of scarring in the liver
- Caused by infection, inflammation (swelling) or injury to liver cells
- Can prevent the liver from working well
 - **Slows down the liver's ability to circulate blood and remove toxins**
- Can lead to severe scarring (cirrhosis)

What Is Cirrhosis?

- Means severe “scarring of the liver”
- Scar tissue has begun to replace normal liver cells. Once the liver has scar tissue, it cannot heal itself completely
- The more scar tissue present, the harder it is for the liver to do its many jobs
- Cirrhosis may put someone at risk for liver failure or liver cancer



What Is Advanced Liver Disease?

- Also called *end-stage liver disease*
 - **The #1 cause of death in patients with HIV who also have hepatitis C**
- Occurs when a lot of severe scarring (cirrhosis) is present in the liver
- Symptoms of this include:
 - **Fatigue (extreme tiredness)**
 - **Difficulty thinking clearly or concentrating**
 - **Yellowing of skin and the white part of the eyes (jaundice)**
 - **Swelling of the lower extremities (ankles and feet)**
 - **Fluid in the abdomen (stomach area)**
 - **Gastrointestinal bleeding (bleeding from stomach or intestines)**
 - **Poor blood clotting**

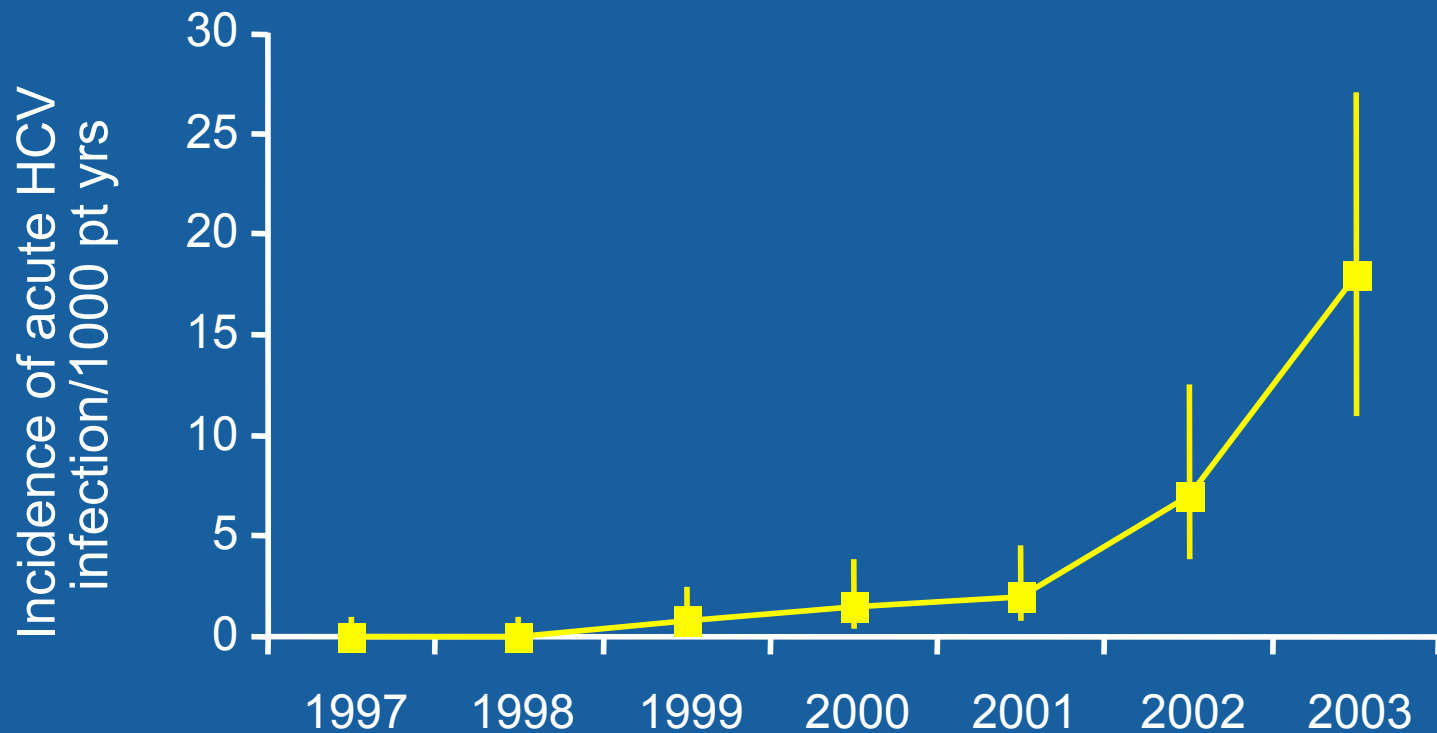
HCV Sexual Transmission

Unlikely in Heterosexual Monogamous Couples

- 895 monogamous heterosexual partners of HCV-infected patients
 - 10-year prospective follow-up study
- 3 HCV infections observed during follow-up (0.37 per 1000 person-years)
 - **None were sexually transmitted from partner**
 - In 1 couple, patient had HCV GT 2a; spouse GT 1b
 - In 2 couples, partners had the same GTs but different strains

Vandelli et al. *Am J Gastroenterol.* 2004;99:855-859.

Significant Increase in New Acute HCV Infections in 2003



- Test for trend p-value using Poisson regression $p < 0.001$
- Error bars = 95% CI

Browne RE, et al. *2nd IAS*. 2003;Abstract 972.

Sexual Transmission of HCV

HCV Monoinfection

- Heterosexual, monogamous couples in Italy¹
 - 3 infections
 - 0.37 per 1000 persons-years
 - Phylogenetic analysis: discordant virus
 - Sexual transmission
 - Extremely low

HIV/HCV Coinfection

- Acute HCV²
 - 44 cases
 - HIV-positive MSM
 - Related to unprotected, receptive anal intercourse
- San Francisco³
 - 10 HCV seropositive cases among 833 MSM

¹Vandelli C, et al. *Am J Gastroenterol*. 2004;99:855-859.

²Nelson M, et al. 9th EAC, 2003. Abstract F12/3.

³Diamond C. *Sex Transm Dis*. 2003;30:425-432.

HCV Sexual Transmission

Increased in HIV-Infected MSM

- HCV(+) semen associated with HCV viremia ($P = .038$)¹
 - HCV(+) semen prevalence rates (%)
 - HCV monoinfection: 18.4%
 - **HIV/HCV coinfection: 37.8% ($P = .033$)**
- Risk factors for HCV transmission in HIV-infected MSM²
 - Unprotected anal intercourse
 - Mucosally traumatic practices: fisting, sex toys
 - Group sex or sex under influence of “club” drugs
 - “Crystal meth”, ketamine, GHB, poppers, LSD, ecstasy

GHB, gamma hydroxybutyrate; MSM, men who have sex with men

Briat et al. *AIDS*. 2005;19:1827-1835.

Danta et al. CROI; February 5-8, 2006; Denver, CO. Abstract 86.

You Can't Get Hepatitis C by:

- Sneezing
- Coughing
- Food or water
- Sharing drinking glasses or eating utensils
- Shaking hands
- Holding hands
- Hugging
- Kissing on the cheek
- Playing with children
- Donating blood

How Do You Know if You Have Hepatitis C?

- Hepatitis C is often known as a “silent” virus. Some people with hepatitis C may not have any symptoms at all!
 - **Some people develop cirrhosis (severe scarring) from hepatitis C before they even have symptoms**
- Symptoms may include:
 - **Feeling like you have the “flu”**
 - **General weakness or feeling tired**
 - **Loss of appetite**
 - **Joint pain**
 - **Problems sleeping**
 - **Mental tiredness**
 - **Poor digestion or diarrhea**
 - **Depression or mood swings**

Extrahepatic Manifestations Associated With HCV

Hematologic

- Mixed cryoglobulinemia¹
- Aplastic anemia²
- Thrombocytopenia²
- Non-Hodgkin's b-cell lymphoma²

Dermatologic

- Porphyria cutanea tarda¹
- Lichen planus²
- Cutaneous necrotizing vasculitis²

Renal

- Glomerulonephritis¹
- Nephrotic syndrome²

Endocrine

- Hypothyroidism²
- Diabetes mellitus²



Ocular

- Corneal ulcer²
- Uveitis²

Vascular

- Necrotizing vasculitis²
- Polyarteritis nodosa²

Neuromuscular²

- Weakness/myalgia
- Peripheral neuropathy
- Arthritis/arthritis

Autoimmune Phenomena²

- CREST syndrome

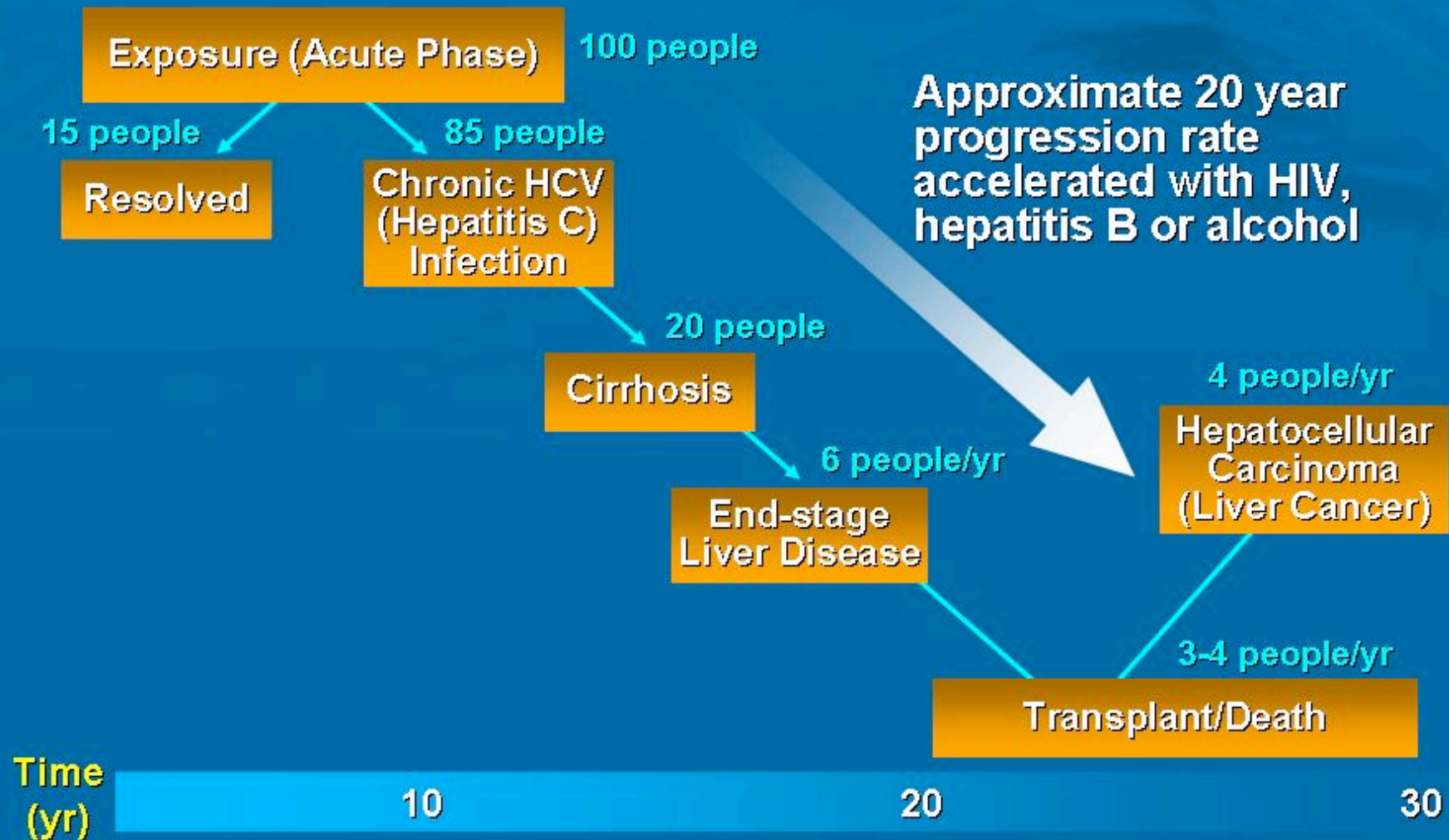
Neuropsychiatric

- Depression¹

¹NIH. *NIH Consensus State Sci Statements*. 2002;19(3):1-46.

²Sene et al. *Metab Brain Dis*. 2004;19(3-4):357-381.

What Happens to People with Hepatitis C – WITHOUT HIV?



What Speeds the Progression of Hepatitis C?

- Drinking alcohol
- People who got hepatitis C when they were older than 40
- Being male
- Smoking cigarettes
- Hepatitis B infection
- *Having HIV infection*
- Having a weakened immune system



Alcohol content in specific beverages

g/Drink Drinks/50 g



Beer
12 oz at
4%

11

4.5



Wine 5 oz
at 11%

13

3.8



Martini
3 oz at
40%

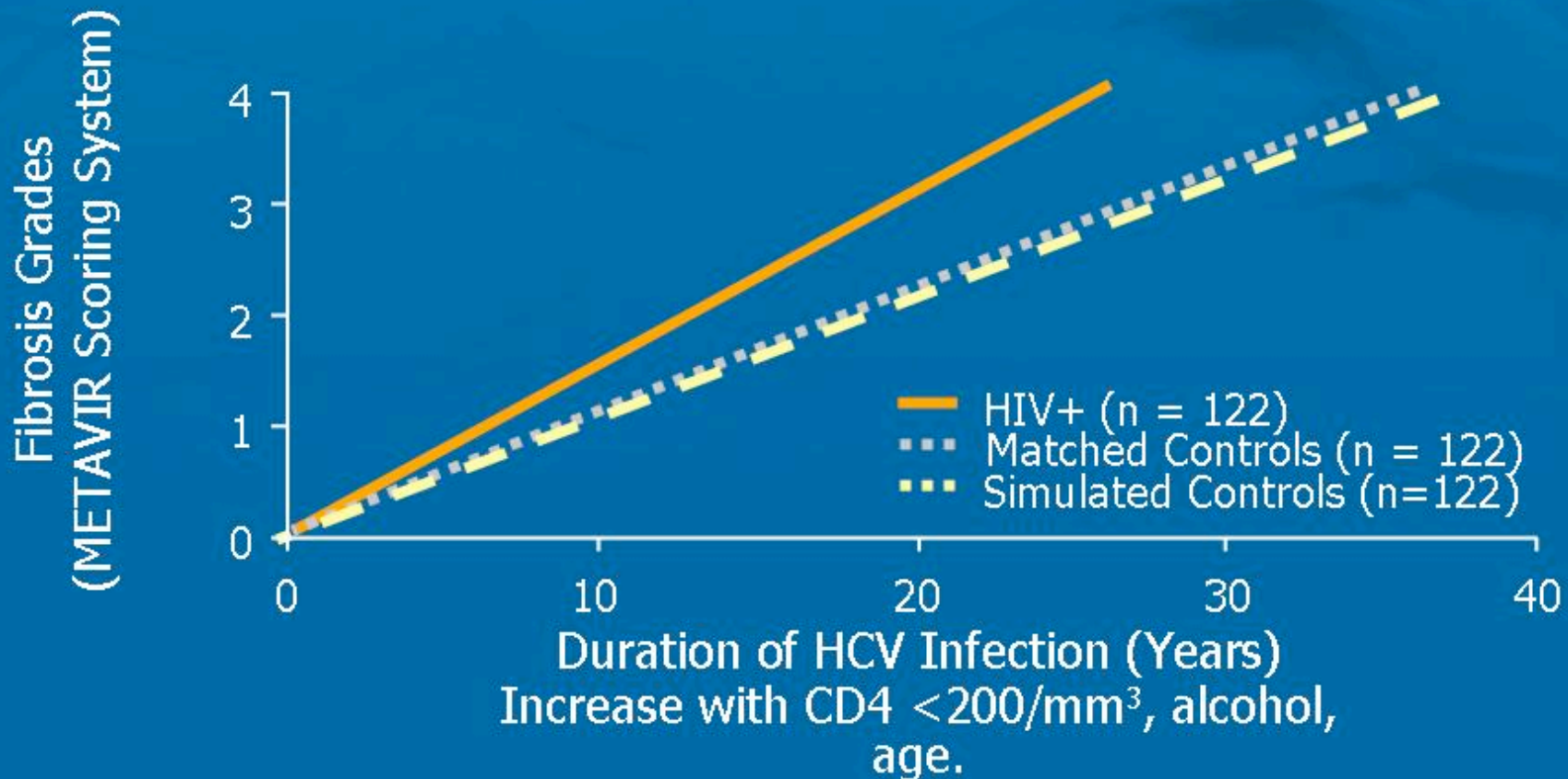
28

1.8

My Doctor said "Only 1 glass of alcohol a day". I can live with that.

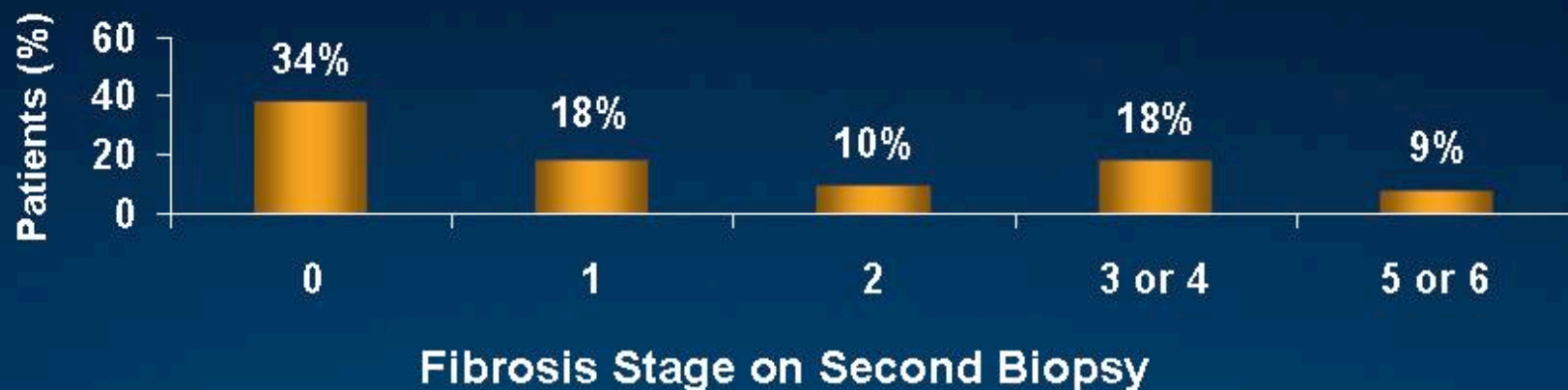


What Happens to People with Hepatitis C and HIV?



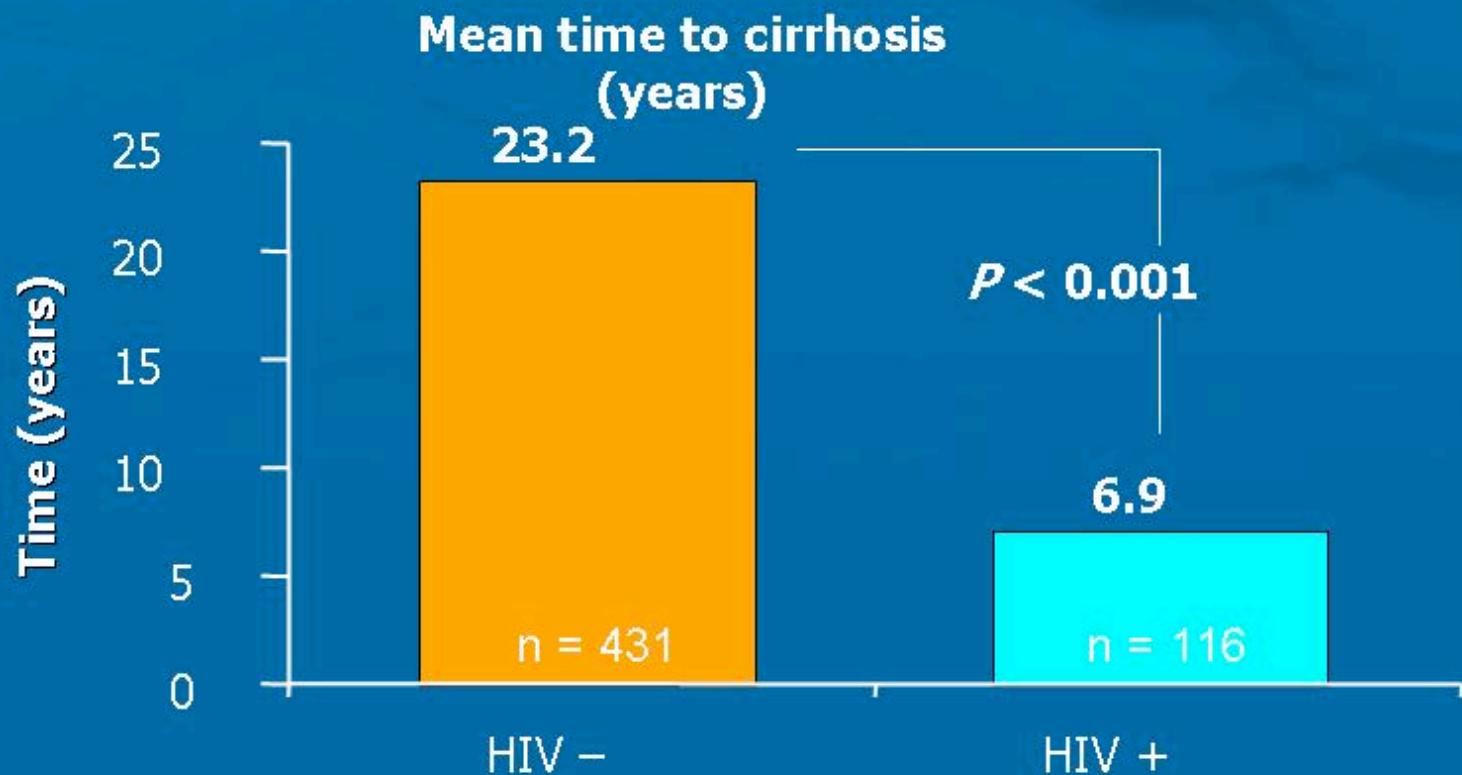
Fibrosis progression is faster and less predictable in patients with HIV

Change in Fibrosis Stage in HCV/HIV Coinfected Patients



- 67 patients with no or minimal fibrosis underwent a second biopsy (Ishak score)
- Median time between biopsies was 2.84 years
- 37% with 2 or more stage progression

What Happens to People with Hepatitis C and HIV?



Progression to cirrhosis can occur in as little as 7 years in patients with HIV

Increased Risk of Cirrhosis and ESLD in HCV/HIV Coinfected Patients

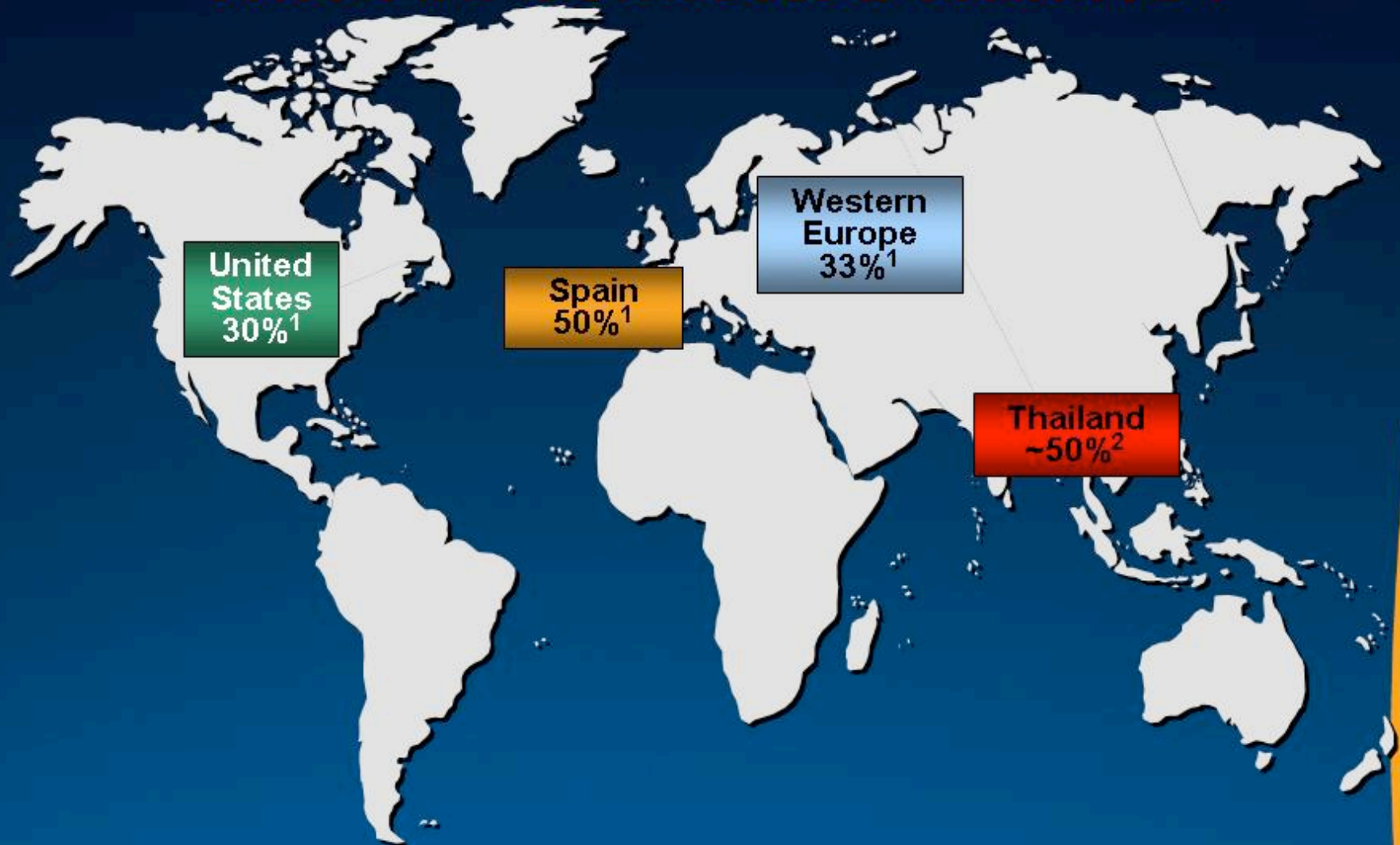


CI = Confidence interval
ESLD = End stage liver disease
HCV = Hepatitis C virus
HIV = Human immunodeficiency virus

HCV and HIV Coinfection

- **Coinfection** – a medical term meaning that there are two or more infections in your body at the same time
- HIV and HCV are very different, so it is important that you learn about both of them
- About 1 million Americans have HIV – 1 out of 3 also has hepatitis C
 - **It has been estimated that about 90% of HIV-infected intravenous drug users (IVDU) are coinfecting with HCV**

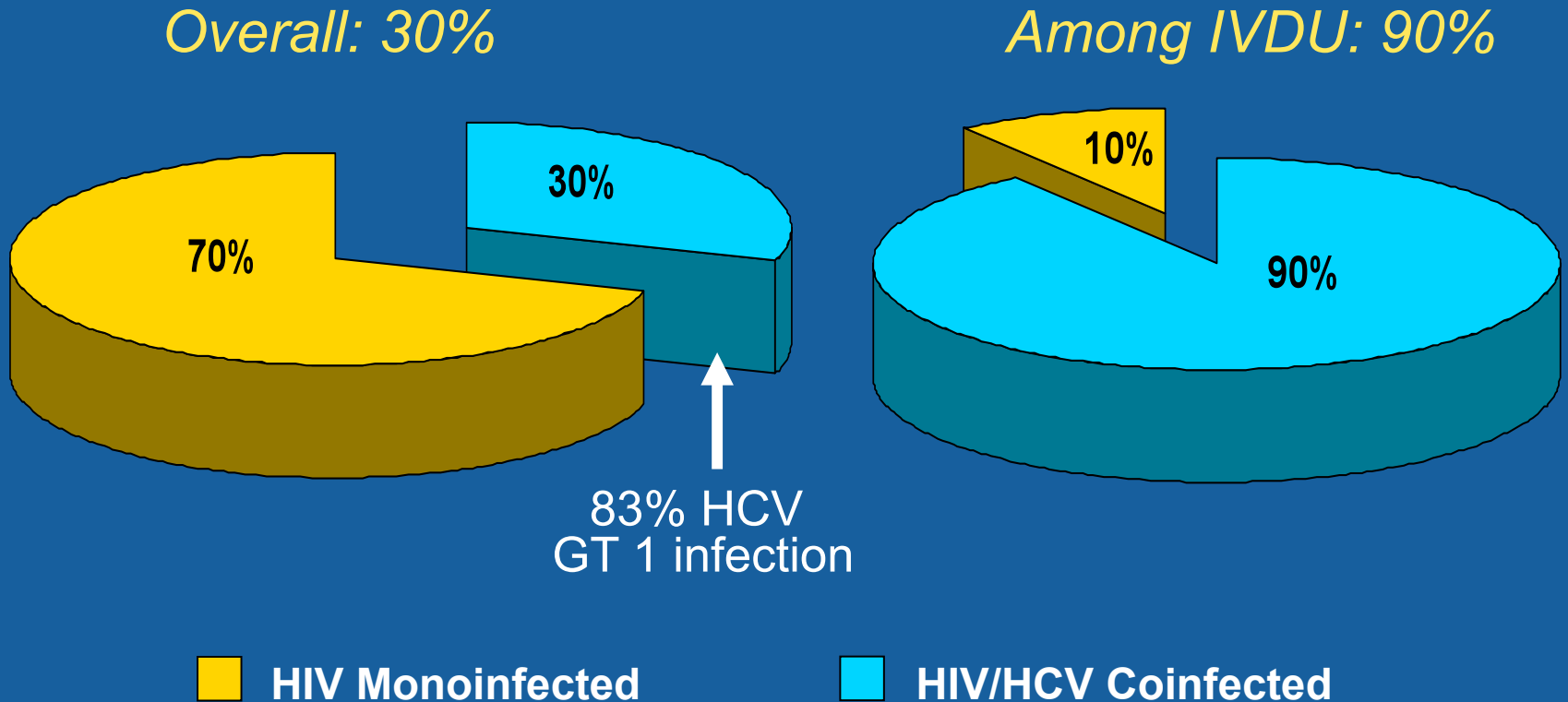
Worldwide Prevalence: % of HIV Patients Who Are Coinfected With HCV



¹Soriano V, et al. *AIDS*. 2002;16:813-826.

²Charbancherd P, et al. *Southeast Asian J Trop Med Public Health*. 2003;Sept;34:580-582.

US Prevalence of Comorbid HCV Infection in HIV-Infected Patients



IVDU, intravenous drug users

Thomas. *Hepatology*. 2002;36:S201-S209.

Sherman et al. *Clin Infect Dis*. 2002;34:831-837.

Sulkowski, Thomas. *Ann Intern Med*. 2003;138:197-207.

How Does HIV Affect Hepatitis C?

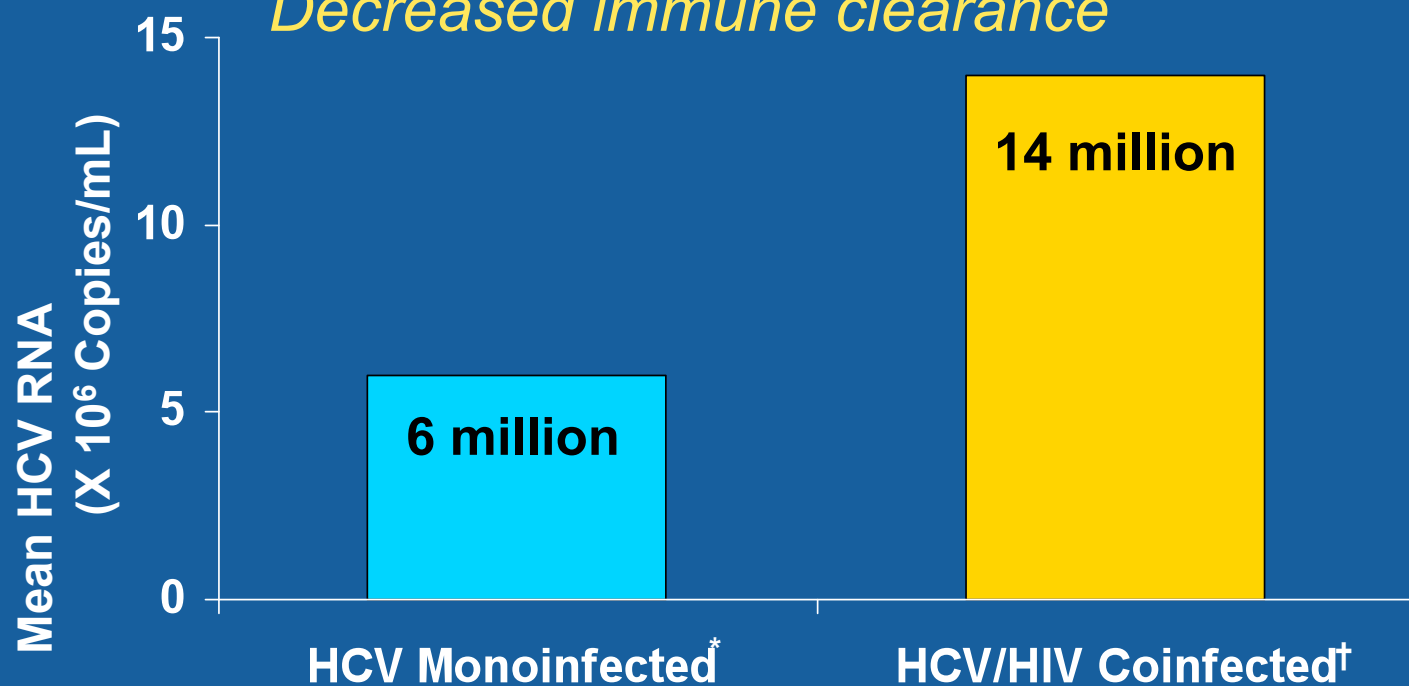
- HIV can make hepatitis C worse. People with HIV tend to have hepatitis C that *gets worse, faster*.
- Some medicines that are used to treat HIV may cause damage to your liver.
- HIV affects your entire immune system, including your body's ability to fight off hepatitis C.

How Does HIV Affect Hepatitis C?

- When you have HIV, it is harder for your body to fight the hepatitis C virus. That is why people with HIV tend to have hepatitis C that gets worse faster.
- Without treatment, people may progress to fibrosis (scarring), cirrhosis (severe scarring) or end-stage liver disease. They may also die from untreated hepatitis C and its complications.

HIV Infection Is Associated With Increased HCV RNA Concentrations

*Increased HCV viral production
Decreased immune clearance*



†Torriani et al. *N Engl J Med.* 2004;351:438-450.

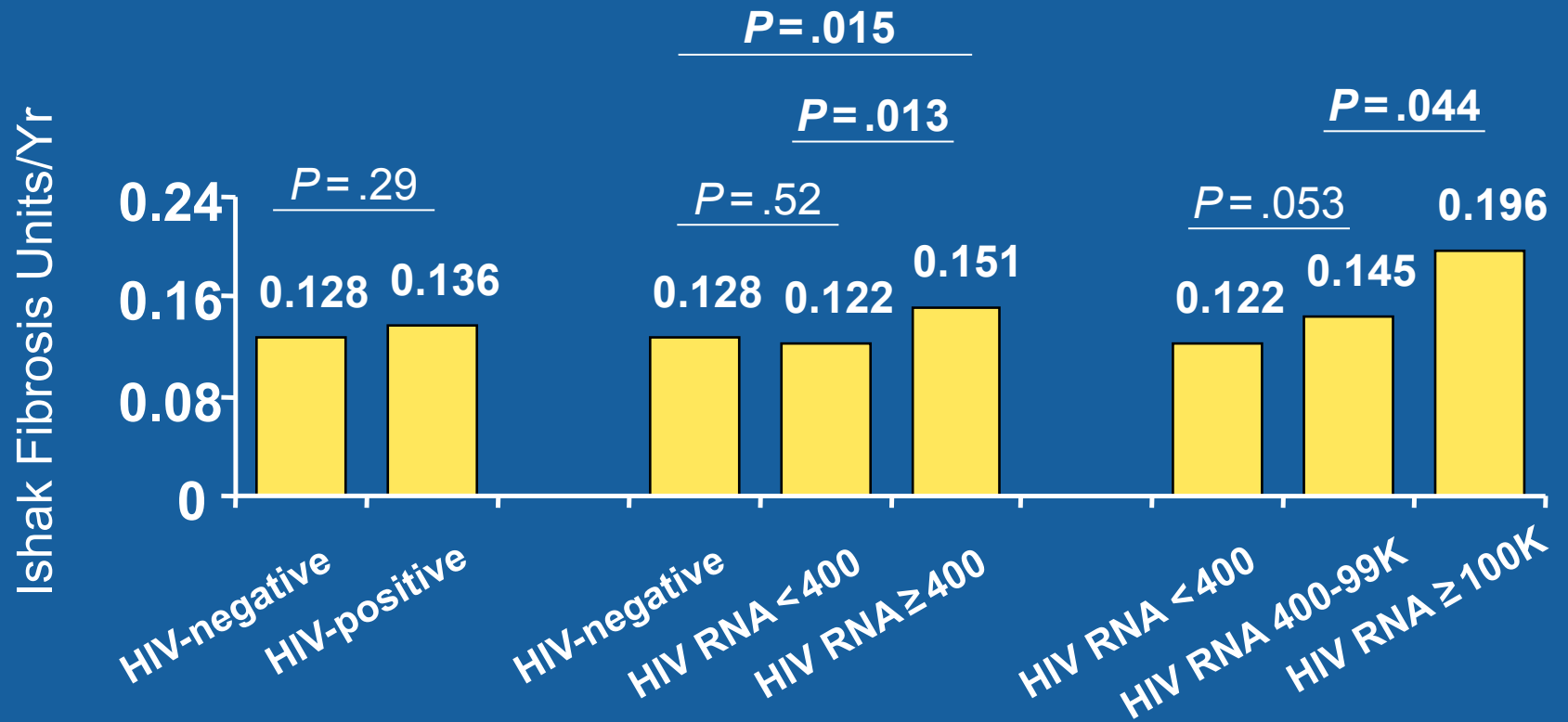
*Fried et al. *N Engl J Med.* 2002;347(13):975-982.

Eyster et al. *Ann Intern Med.* 1991;115:764-768.

Eyster et al. *Blood.* 1994;84:1020-1023.

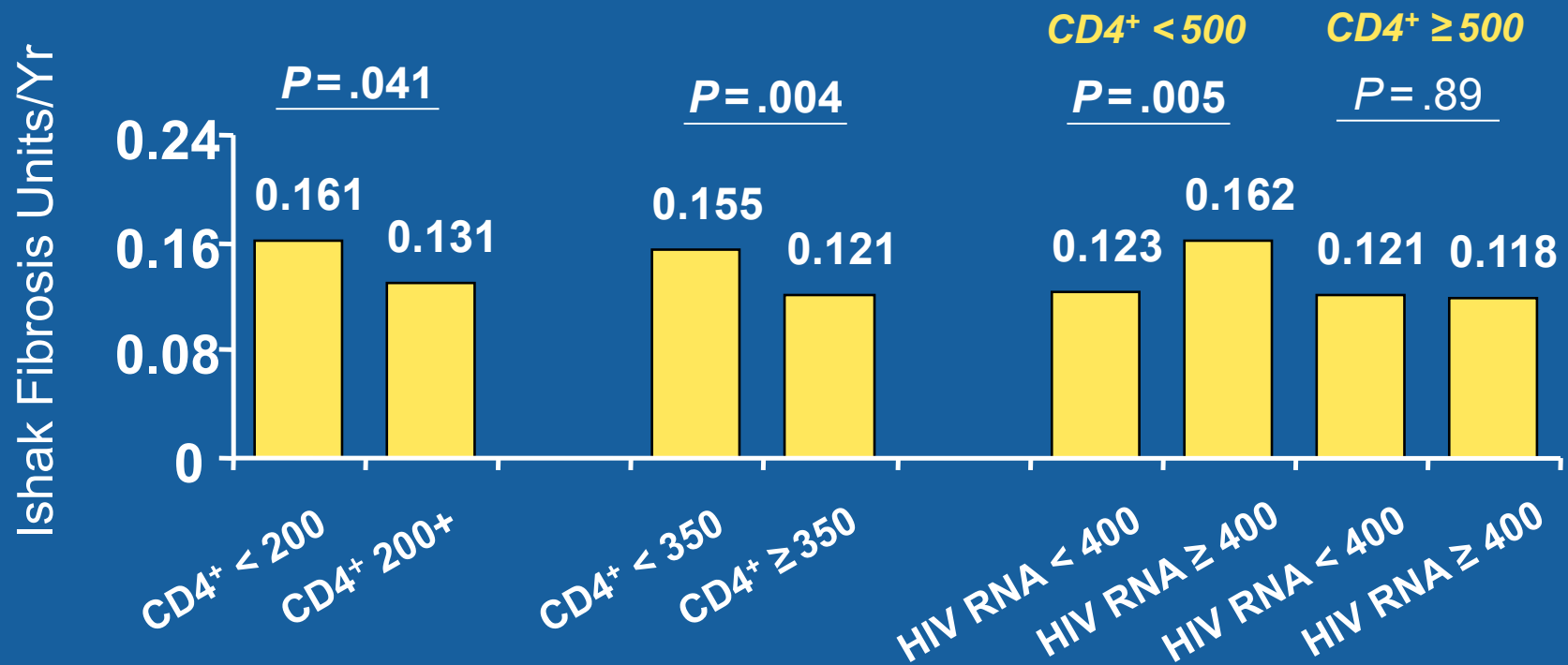
Zanetti et al. *Lancet.* 1995;345:289-291.

HIV Viremia Is Associated With Increased Fibrosis Progression Rates in Coinfection



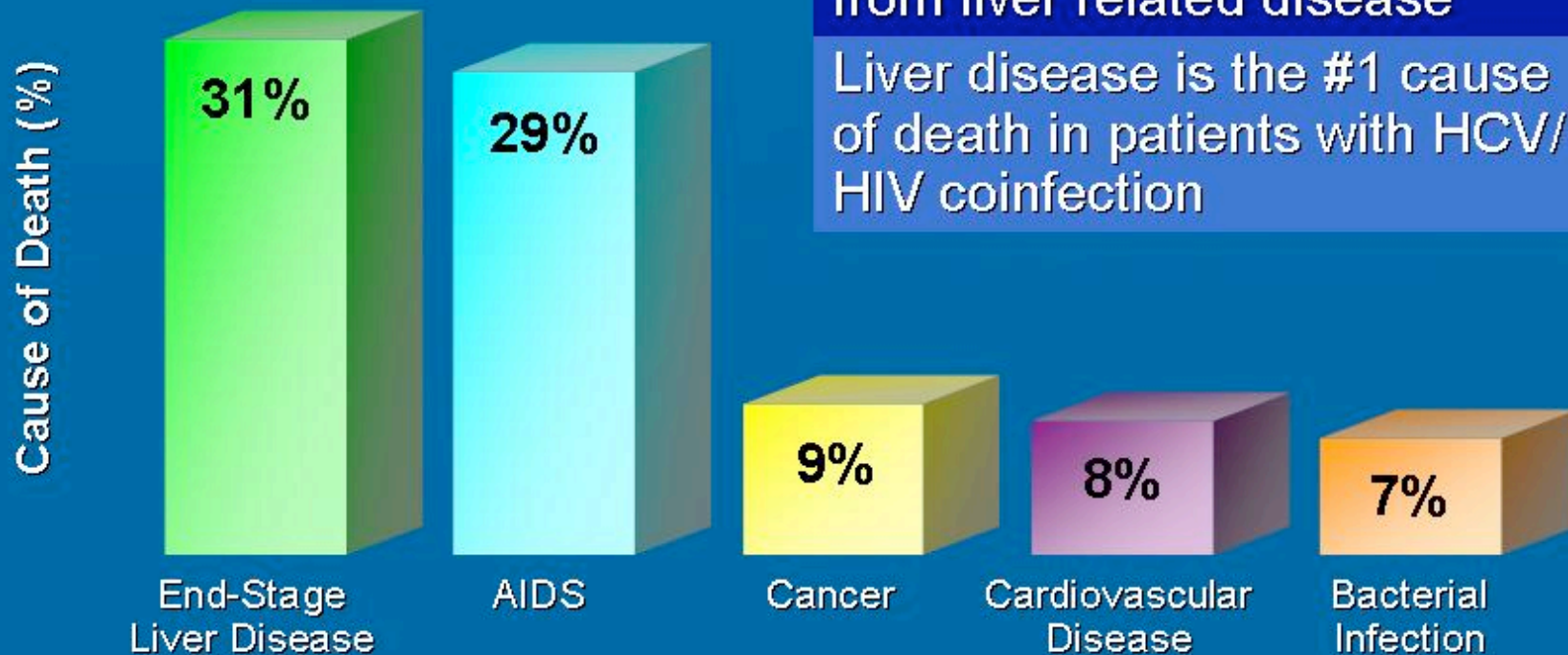
Bräu et al. *J Hepatol.* 2006;44:47-55.

Low CD4⁺ Cell Count Is Associated With Increased Fibrosis Progression Rates in Coinfection



Bräu et al. *J Hepatol.* 2006;44:47-55.

Most Common Causes of Death in HCV/HIV Coinfected Patients



Now that HIV medications work so well, more patients are dying from liver related disease

Liver disease is the #1 cause of death in patients with HCV/HIV coinfection

Current Treatment Options

**The Centers for Disease Control (CDC)
Recommends that Antiviral Treatment
Be Considered for All HIV Patients
Coinfected with Chronic Hepatitis C Infection**

Why Is It Important That You Talk to Your Healthcare Provider about Hepatitis C Treatment?

- **The longer hepatitis C goes untreated, the greater the risk for further liver damage**
- **Starting therapy earlier, rather than later, may help your liver by stopping the virus from causing more damage**
- **Hepatitis C medication may work better if used before there is serious liver damage**
- **If you have hepatitis C and HIV coinfection, ask your healthcare provider if treatment is right for you**

What Are the Treatment Goals of Hepatitis C Medication?

- The most important goal is to achieve a sustained virologic response (SVR)
 - This means that the medication was successful because the virus cannot be measured in your blood 6 months after you finish treatment
- Another possible goal of treatment is:
 - To stop more liver damage from occurring

Current Treatment for HCV Infection

- Peginterferon Alpha 2 a/b once a week with Ribavirin .
- In genotype 2 treat for 24 to 48 weeks
- In genotype 1-4 treat for 48 weeks or longer if needed.
- Ribavirin dose will be 400mg in AM and 600mg in PM if the weight is <75 KG and if the patient is >75 KG , the dose would be 600mg twice a day.



Multiple Anti-HCV Drugs Are In Development

Linear class

Telaprevir
Boceprevir
Narlaprevir

**NS3
Protease**

Macrocyclic class

RG7227/ITMN-191
TMC 435350
MK 7009
BI 201335
BMS-650032

NS5A

BMS-790052

Cyclophilin

Debio 025
NIM 811

Active site

RG7128
IDX184
PSI-7977

**NS5B
Polymerase**

Palm

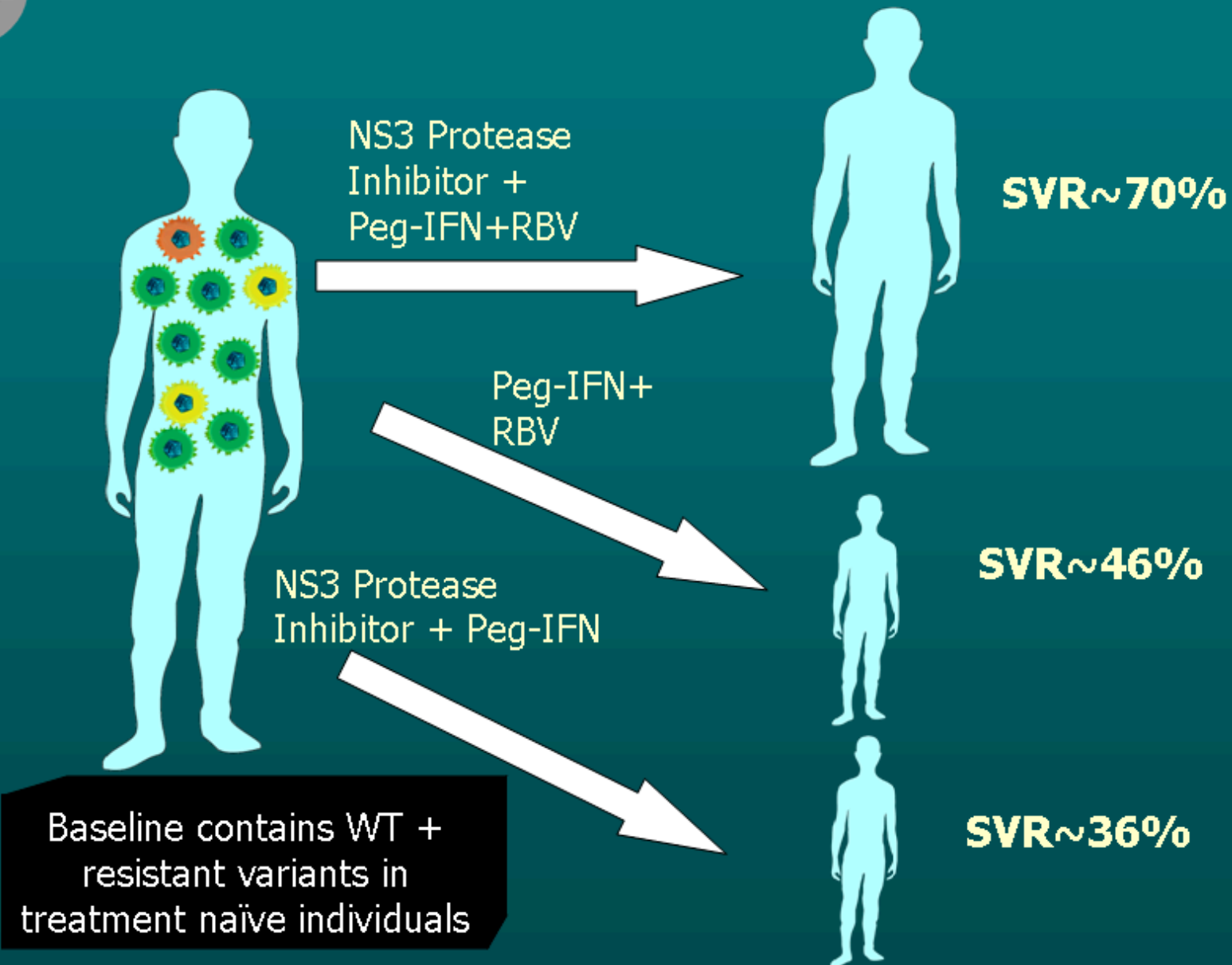
ABT-333
ABT-072
GS 9190
ANA598

Thumb

VCH-759
VCH-916
VX-222
BI 207127
Filibuvir

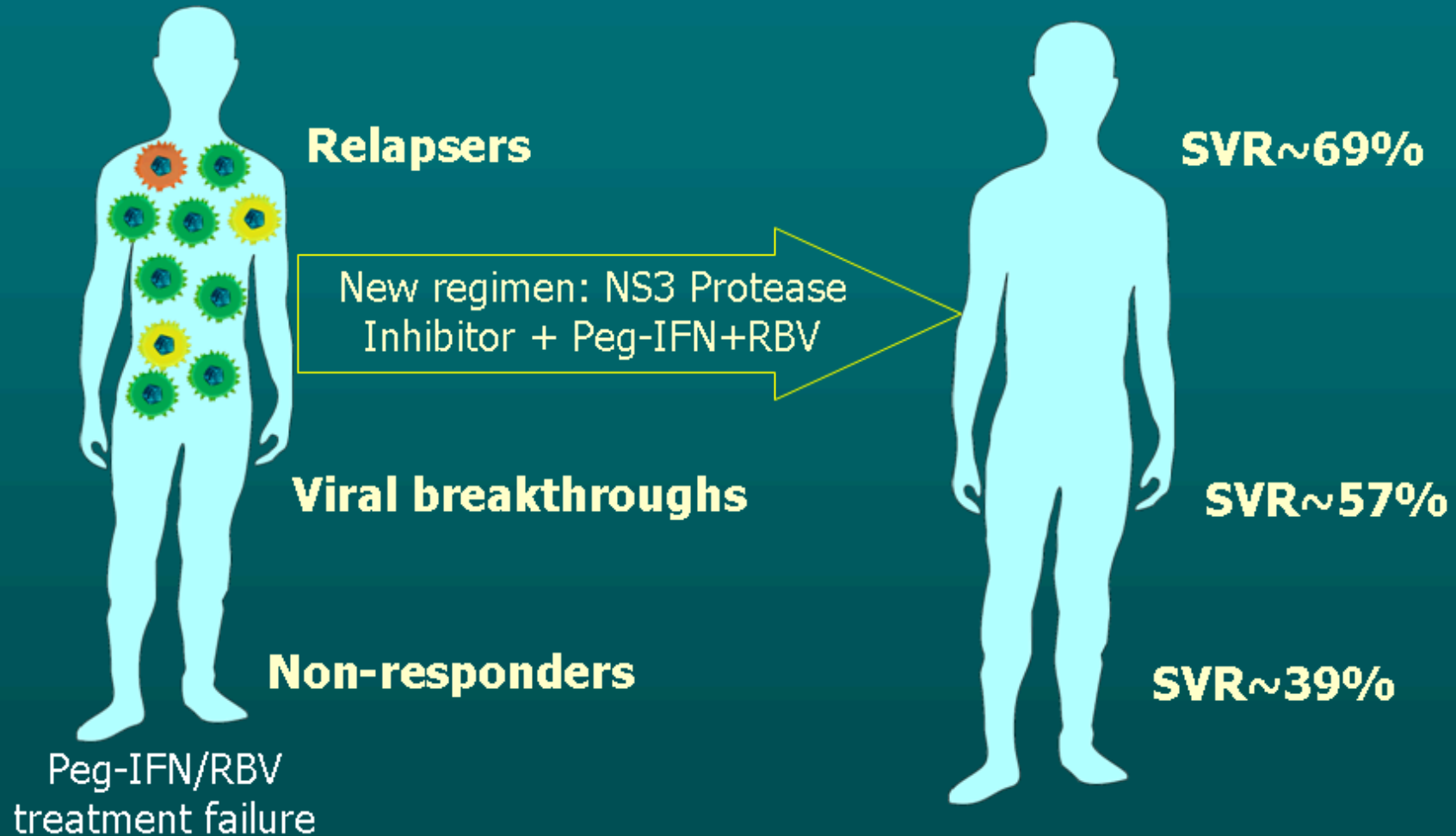


Contribution Of Peg-IFN/RBV To SVR





Peg-IFN/RBV Treatment Experienced Patients Can Be Re-treated

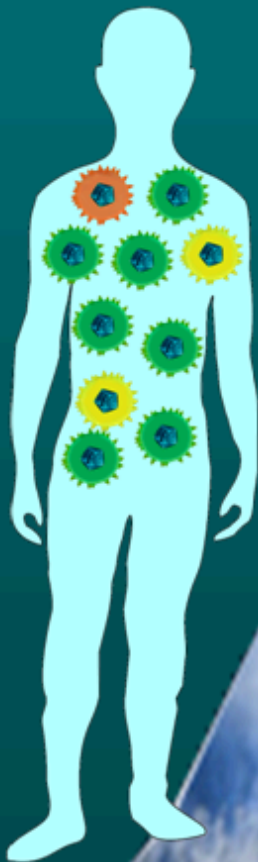




Patient Factors Can Affect Ability To Respond To Therapy



SVR



**Age
>50yrs**

Unmanaged Depression

Non-adherence

Male

**Insulin
resistance**

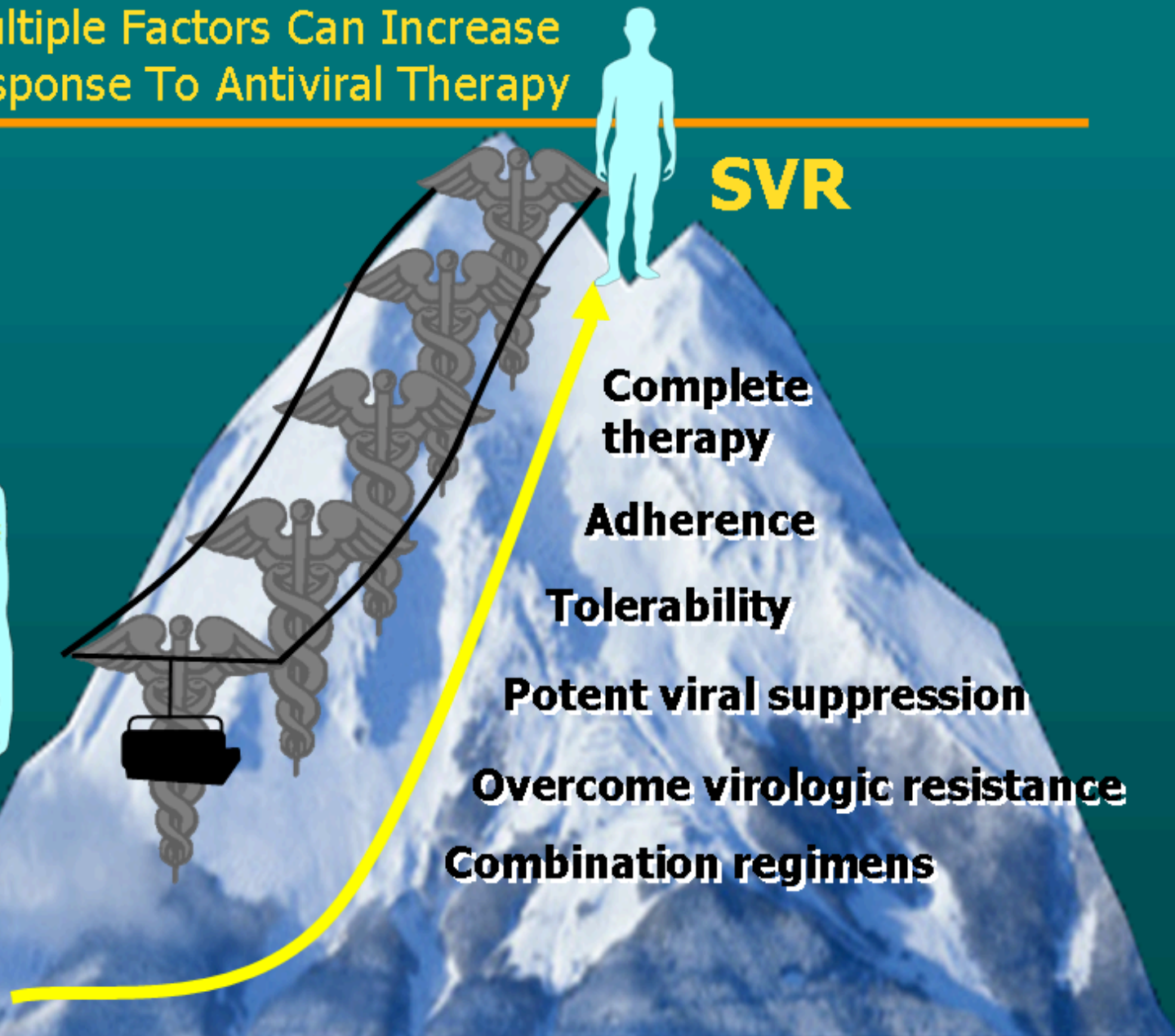
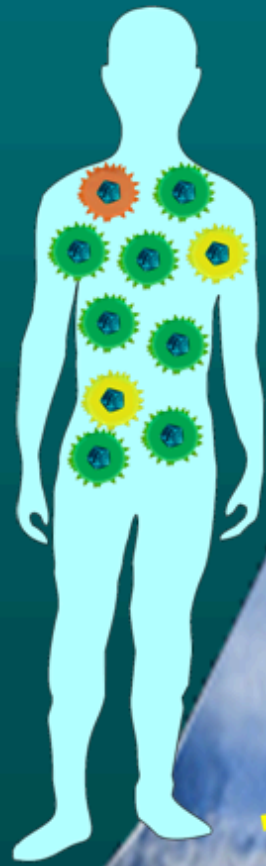
**African
American**

**Genetics
IL28B**

Fatty Liver



Multiple Factors Can Increase Response To Antiviral Therapy





Resistant Variants Occur Naturally



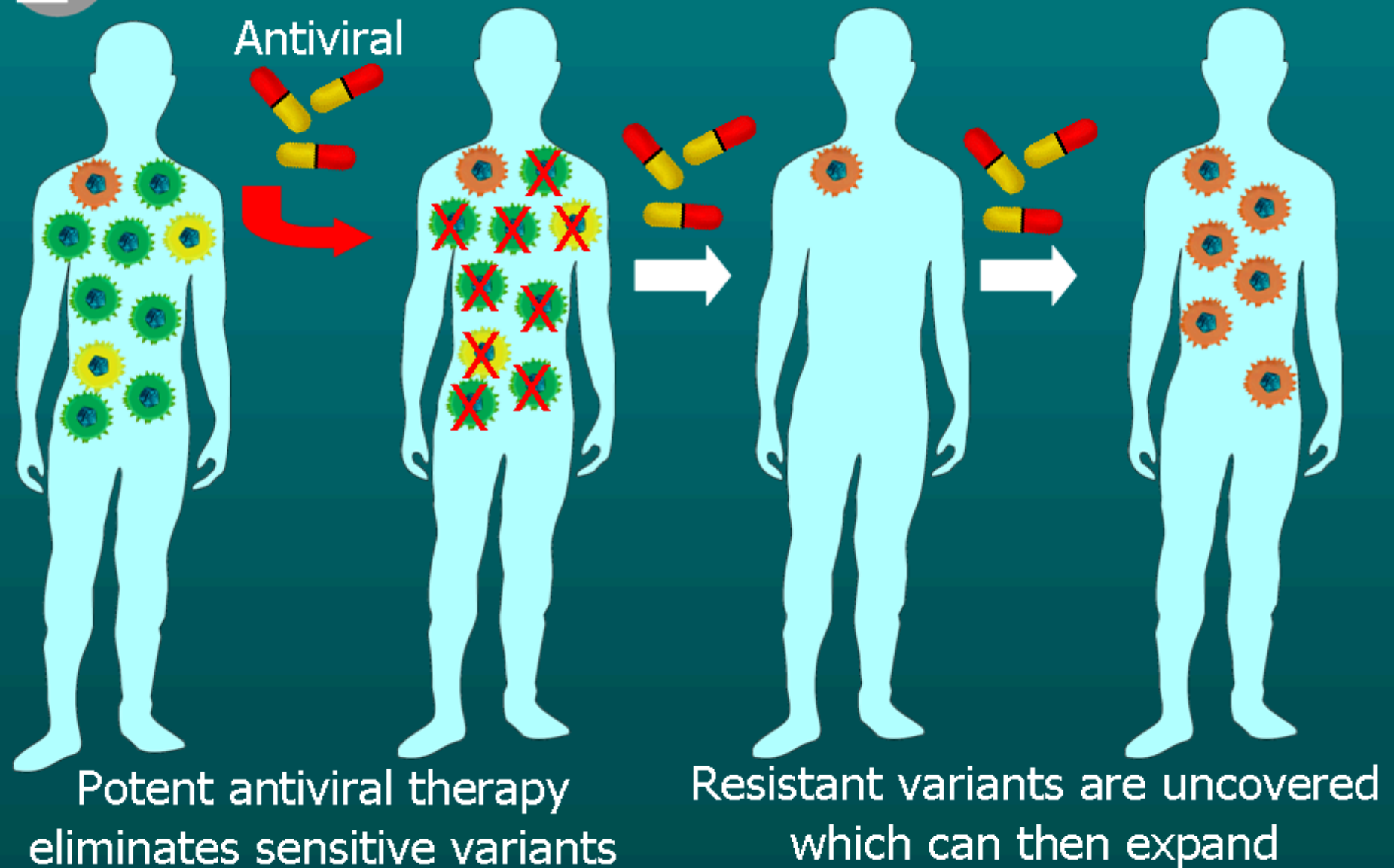
Resistant Variants Are Present Before Treatment



- HCV exists as a mixture of populations of genetically distinct, but closely related, virions in every patient¹
 - $\sim 10^{12}$ viruses produced per day
 - ~ 1 mutation per virus produced
- Most resistant variants are relatively unfit and are undetectable prior to therapy with current technology^{2,3}

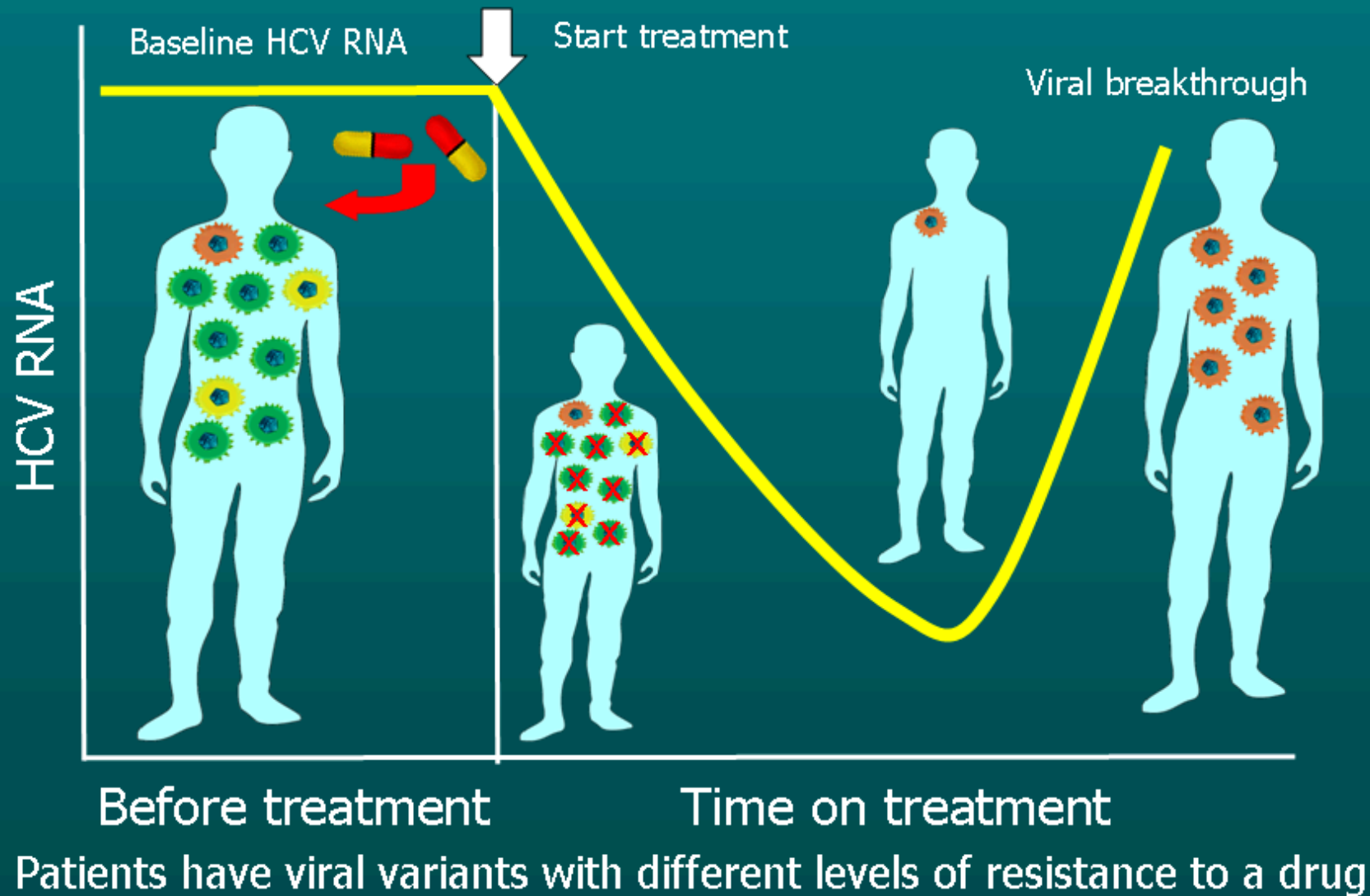


Resistant Variants Can Be Selected During Treatment





Frequent Monitoring Of HCV RNA Levels Can Detect Treatment Failure And Resistance



Summary

- HCV makes HIV worse and HIV makes HCV liver damage worse
- HCV is a multisystem disease
- Liver biopsy helps in deciding if you need HCV treatment or not
- HCV is treated with Peginterferon and Ribavirin at present time but many drugs in development
- Future treatment may be less toxic and shorted duration with better success rates!!!
- HIV CAN BE CURED!!!



*TO TREAT NOW OR
TREAT LATER ?*

*THAT IS THE
QUESTION !*

Thank you

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