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# HBV, HCV / HIV Coinfection

衛生署 疾病管制局  
中區傳染病防治醫療網  
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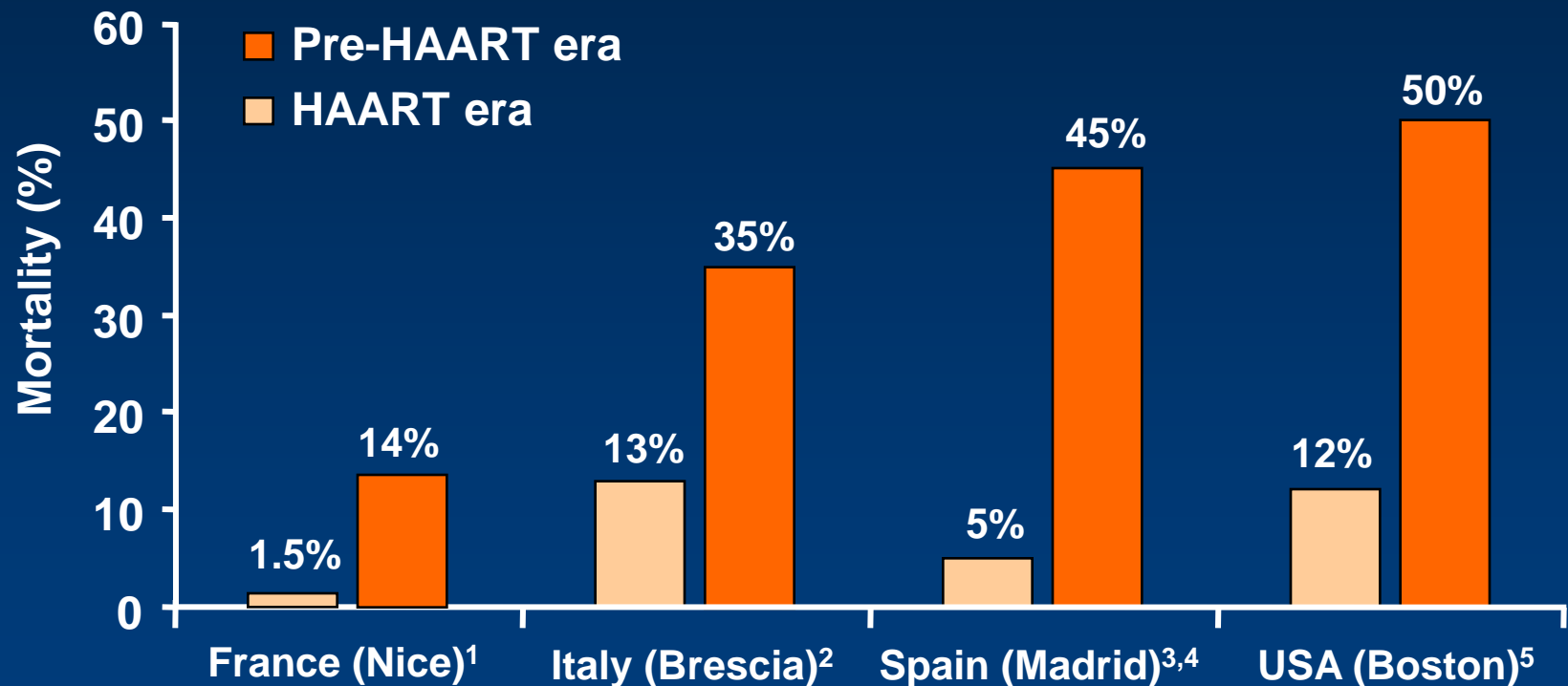
# Epidemiology

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- **HBV** endemic in Africa/Asia/South America
  - low prevalence in the west
- **HCV** high prevalence in Europe/USA/North and South Africa
  - increasing incidence in some regions of sub-Saharan Africa
- **HIV** global epidemic
  - sub Saharan Africa worst hit

# Liver disease: a major cause of death in the HAART era

Mortality from end-stage liver disease as a percentage of all deaths among HIV patients



1. Rosenthal E, et al. AIDS 2003; 17: 1803

2. Puoti M, et al. JAIDS 2000; 24: 211

3. Martín-Carbonero L, et al. AIDS Res Human Retrovirus 2001; 17: 1467

4. Soriano V, et al. Eur J Epidemiol 1999; 15: 1

5. Bica I, et al. Clin Infect Dis 2001; 32: 492

# Routes of Transmission

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	Blood/ Blood products	Mother to child	Sexual
Hep B	+++	++	++
Hep C	+++	+	+
HIV	+++	+++	+++

# Transmissibility through contaminated injections

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- HBV 30%
- HCV 3%
- HIV 0.3%

# Hepatitis B Virus

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- Member of *Hepadnaviridae* that primarily infects liver cells
- Known carcinogen
- 100 times more infectious than HIV
- 10 times more infectious than HCV

Name	Abbreviation	Definition/Comment
Hepatitis B Surface Antigen	HBsAg	Antigen indicating infection
HBV Deoxyribonucleic Acid	HBV DNA	Indicates active viral replication
Alanine Aminotransferase	ALT	An enzyme produced in the liver. Increases in ALT levels are often associated with liver cell inflammation or liver cell injury
Hepatitis B Core Antibody	anti-HBc	Appears at the onset of symptoms in acute hepatitis B and persists for life. The presence of anti-HBc indicates previous or ongoing infection with hepatitis B virus (HBV) in an undefined timeframe.
Hepatitis B Surface Antibody	anti-HBs	Usually indicates immunity
Hepatitis B e Antigen	HBeAg	Antigen correlating with HBV replication and infectivity, but low or undetectable in patients with precore or core mutation

# HBV Disease

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- ACUTE HBV
- CHRONIC HBV (6months)
  - All HBsAg POSITIVE
  - HBeAg positive
  - HBeAg negative

# Chronic Hepatitis B: Definition

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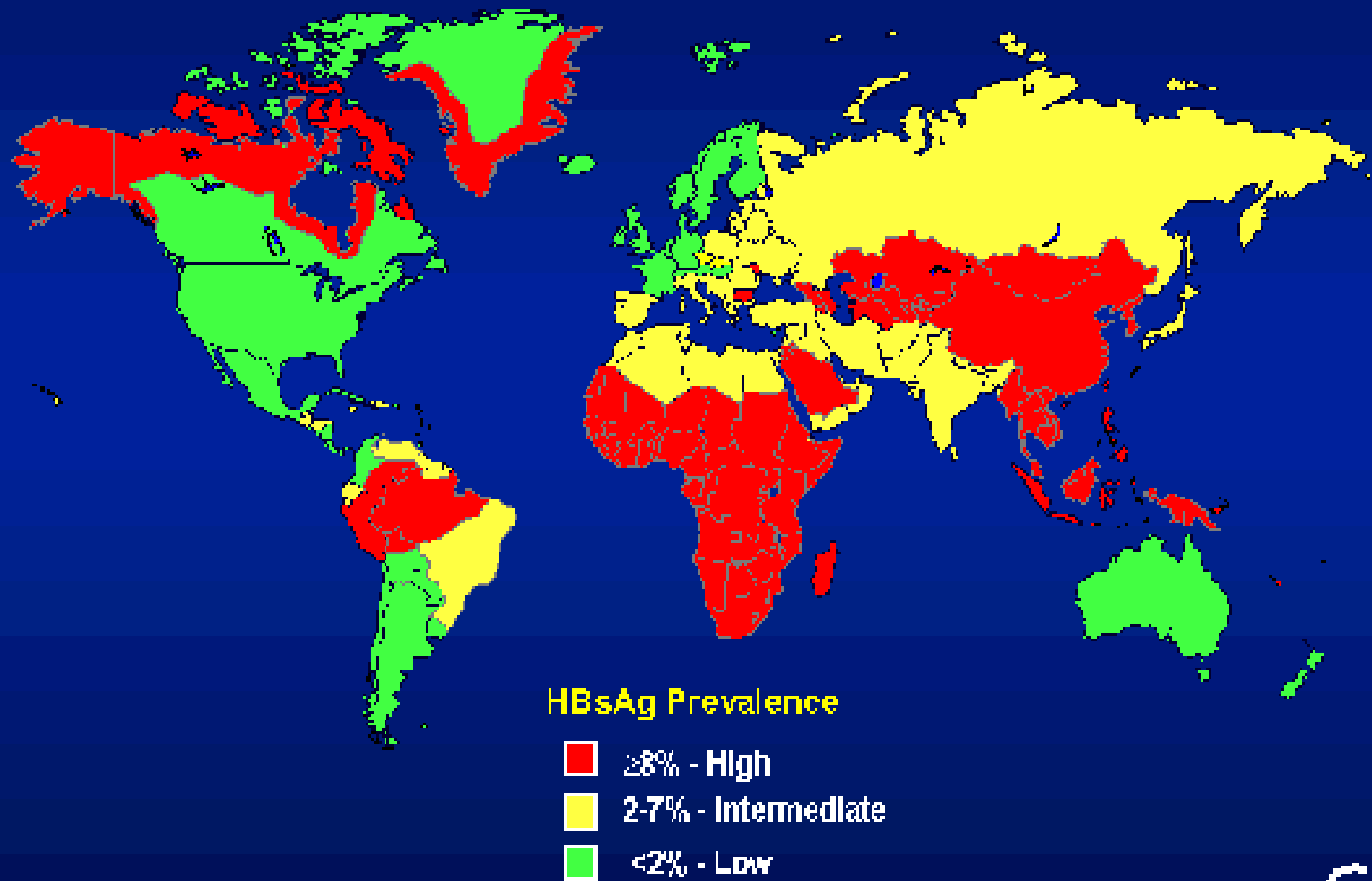
HBsAg-Positive  
≥6 months

Diagnosis made based on supportive clinical and laboratory features.

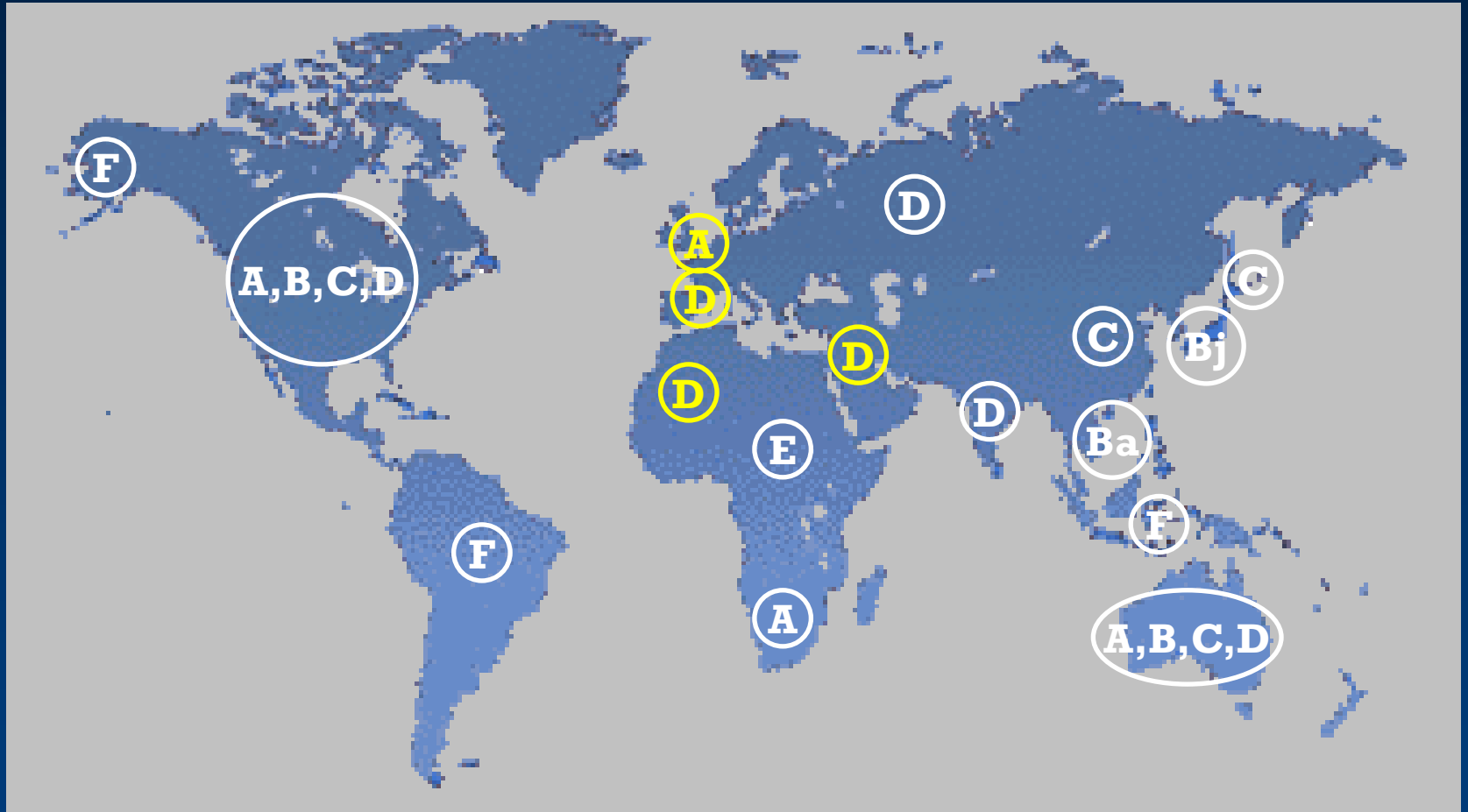
The EASL Jury. *J Hepatol* 2003; 39:S3–S25

Keeffe EB, et al. *Clin Gastroenterol Hepatol* 2006; 4:936–962.

# Geographic Distribution of Chronic HBV Infection



# HBV Genotypes



© This is an oversimplification as populations are not static...

# Chronic HBV: Clinical Features

- Symptoms
  - General: fatigue, anorexia, arthralgia, nausea
  - Advanced: ascites, edema, bleeding GE varices, bruising, enlarged spleen, jaundice, spider nevi, muscle wasting
- Symptoms may not correlate with liver biopsy findings

HBV DNA	HBsAg	HBeAg	ALT (U/L)
+	+	+/-	Normal to ↑

Anti-HBc (IgM) and Anti-HBs will also be negative for patients with chronic hepatitis B.

Dienstag, et al. In: *Harrison's Principles of Internal Medicine*, 15<sup>th</sup> ed. Chap 297.

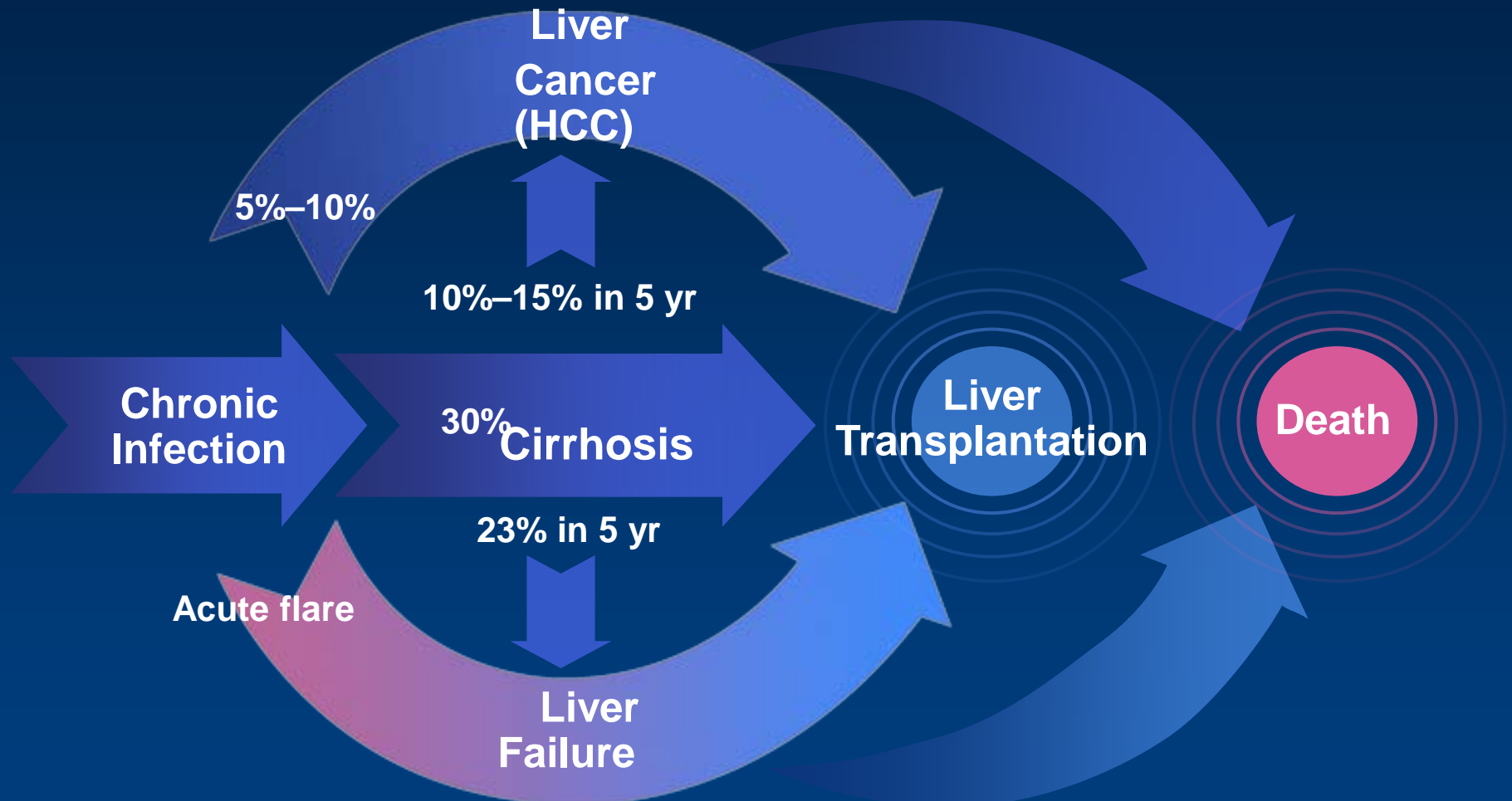
Mahoney. *Clin Microbiol Rev*. 1999;12:351-366.

McMahon. *Semin Liver Dis*. 2004;24:17-21.

CDC. *Epidemiology and Prevention of Vaccine-Preventable Diseases*. Atkinson W, et al, eds. 9<sup>th</sup> ed. 2006.

# Natural Progression of CHB

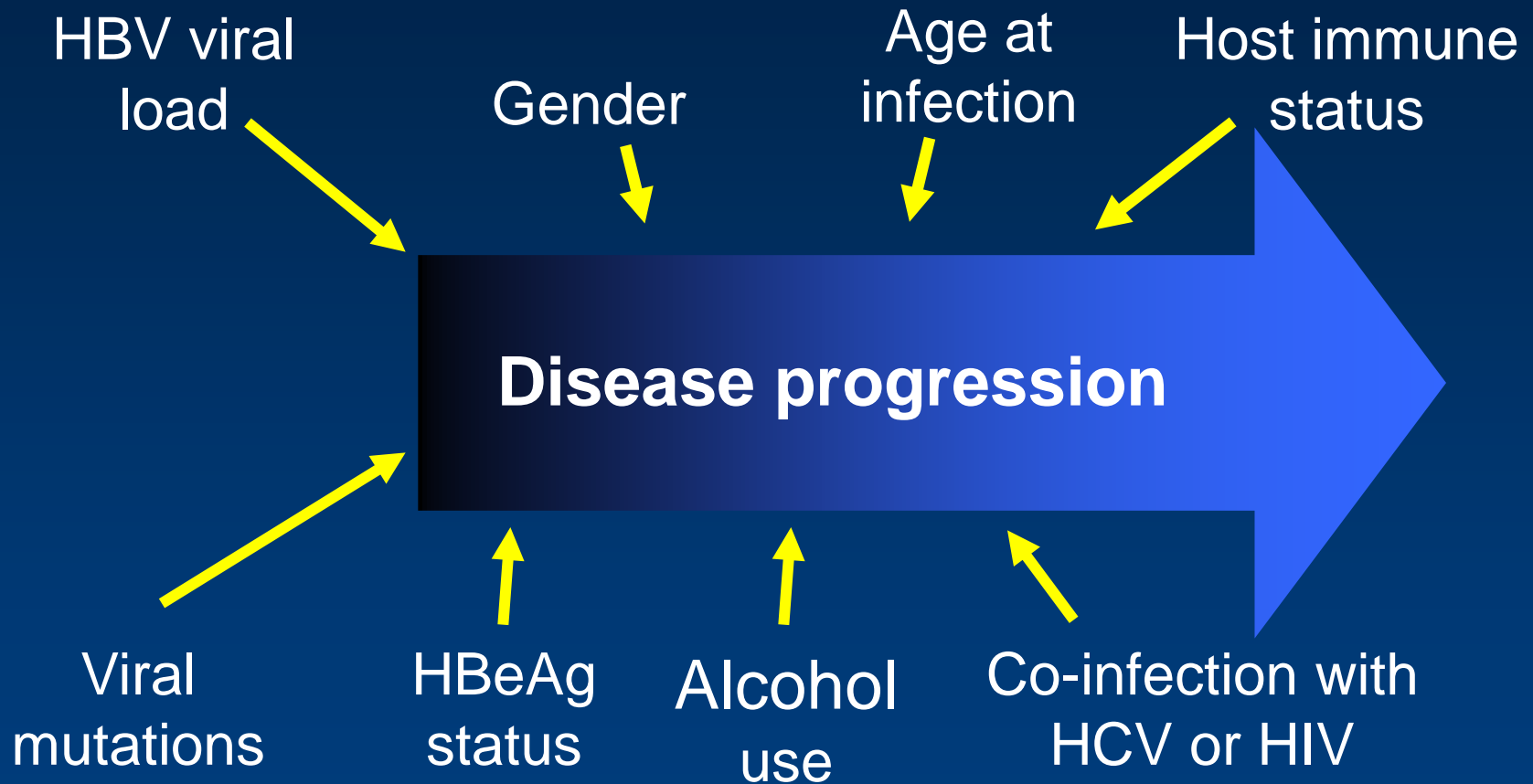
15%–40% of CHB patients may experience disease progression



Adapted from: Fattovich, et al. *Gastroenterology*. 2004;127:S35-S50. Torresi, et al. *Gastroenterology*. 2000;118:S83-S103. Fattovich, et al. *Hepatology*. 1995;21:77-82. Perrillo, et al. *Hepatology*. 2001;33:424-432.

# Factors Influencing Natural History

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Fattovich. *Semin Liver Dis.* 2003;23:47-58.

Chen, et al. *JAMA.* 2006;295:65-73.

# HBV and HIV Coinfection

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- 70-90% of HIV patients have evidence of past or active HBV infection.
- HBsAg chronic carriage varies with regions but ranges from 1.9% to over 40% <sup>1</sup>
- Lodenyo et al in S.Africa found HBV/HIV coinfection of 41% <sup>2</sup>
- Similar studies from Kenya report equally high figures (Ogutu et al, Lule et al, Okoth et al)

Ref: 1. Sinicco A, et al. Coinfection and superinfection of hepatitis B virus in patients infected with HIV. Scand J Infect Dis 1997; 29:111-5

2. Lodenyo H, et al. Hepatitis B and C virus infections and liver function in AIDS patients at Chris Hani Baragwanath Hospital, Johannesburg. EAMJ Vol 77 No. 1 January 2000, p13

# Influence of HBV on HIV

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## CONFLICTING DATA

- Increased rate of HIV progression to AIDS? <sup>1</sup>
- No change in progression? <sup>2</sup>
- Cohort studies suggest that HBV does not appear to influence the progression of HIV.

Ref : 1.Eskild A, Magnus P, et al. Hepatitis B antibodies in HIV-infected homosexual men are associated with more rapid progression to AIDS. *Aids* 1992;6:571-4

2. Diamondsstone LS, Blakly SA, et al. Prognostic factors for all-cause mortality among hemophiliacs infected with human immunodeficiency virus. *Am J Epidemiol* 1995;142:304-13

# Influence of HIV on HBV

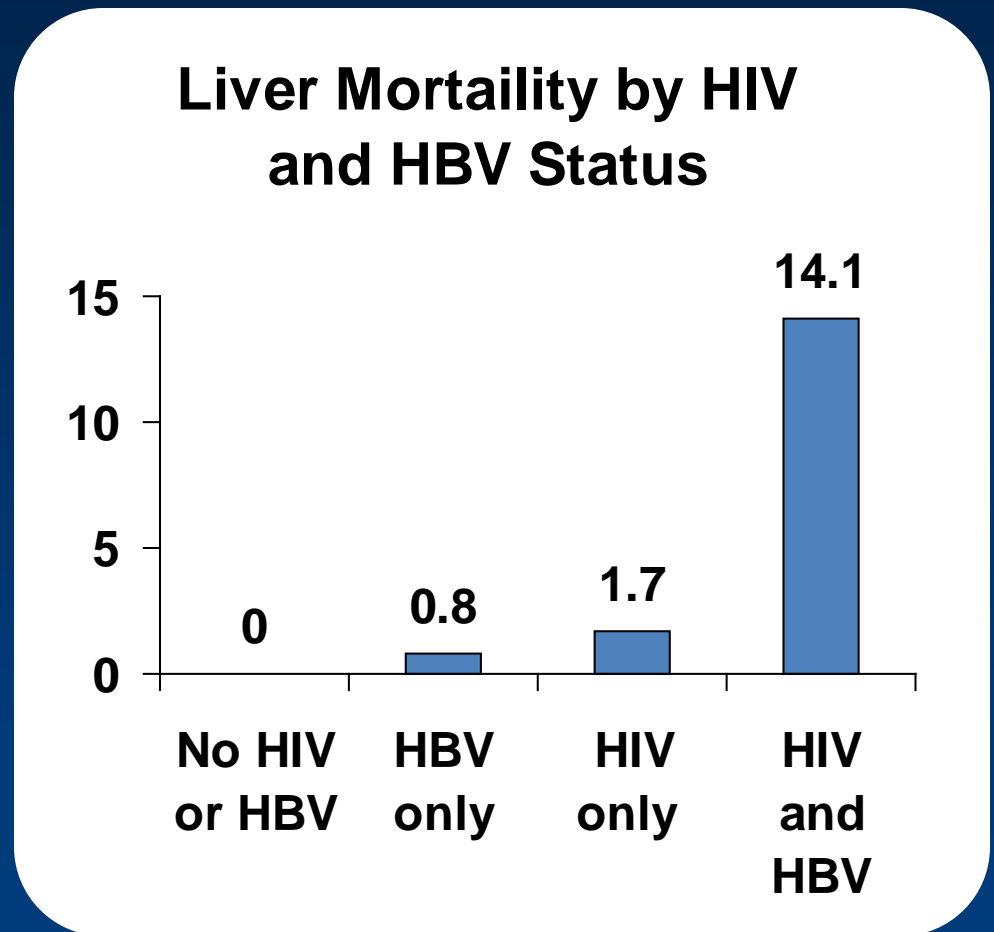
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- Lower rates of clearance of HBeAg
- Increased serum HBV DNA viral load <sup>1</sup>
- Reactivation of hepatitis in asymptomatic carriers
- Increased liver injury
- Faster fibrosis cirrhosis and HCC
- Higher mortality and morbidity

Ref: 1. Perillo RP, Regenstein FG, et al. Chronic hepatitis B in asymptomatic homosexual men with antibody to the human immunodeficiency virus. Ann Intern Med 1986;105:382-3

# HIV Co-infection Increases the Risk of End-Stage-Liver-Disease (ESLD) due to HBV

- MACS, 4,967 men
  - HIV, 47%
  - HBV, 6% (n=326)
  - HIV/HBV, 4.3% (n=213)
- HIV/HBV: **17-fold higher risk of liver death** compared to HBV alone
- Alcohol and low CD4 even increase the risk



# Relevant Investigations

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- When to screen?
- What to screen for?
  - LFTS, HBsAg, HBeAg,
  - HBV-DNA
- On indication
  - Imaging
  - Liver biopsy
  - (Fibroscan)

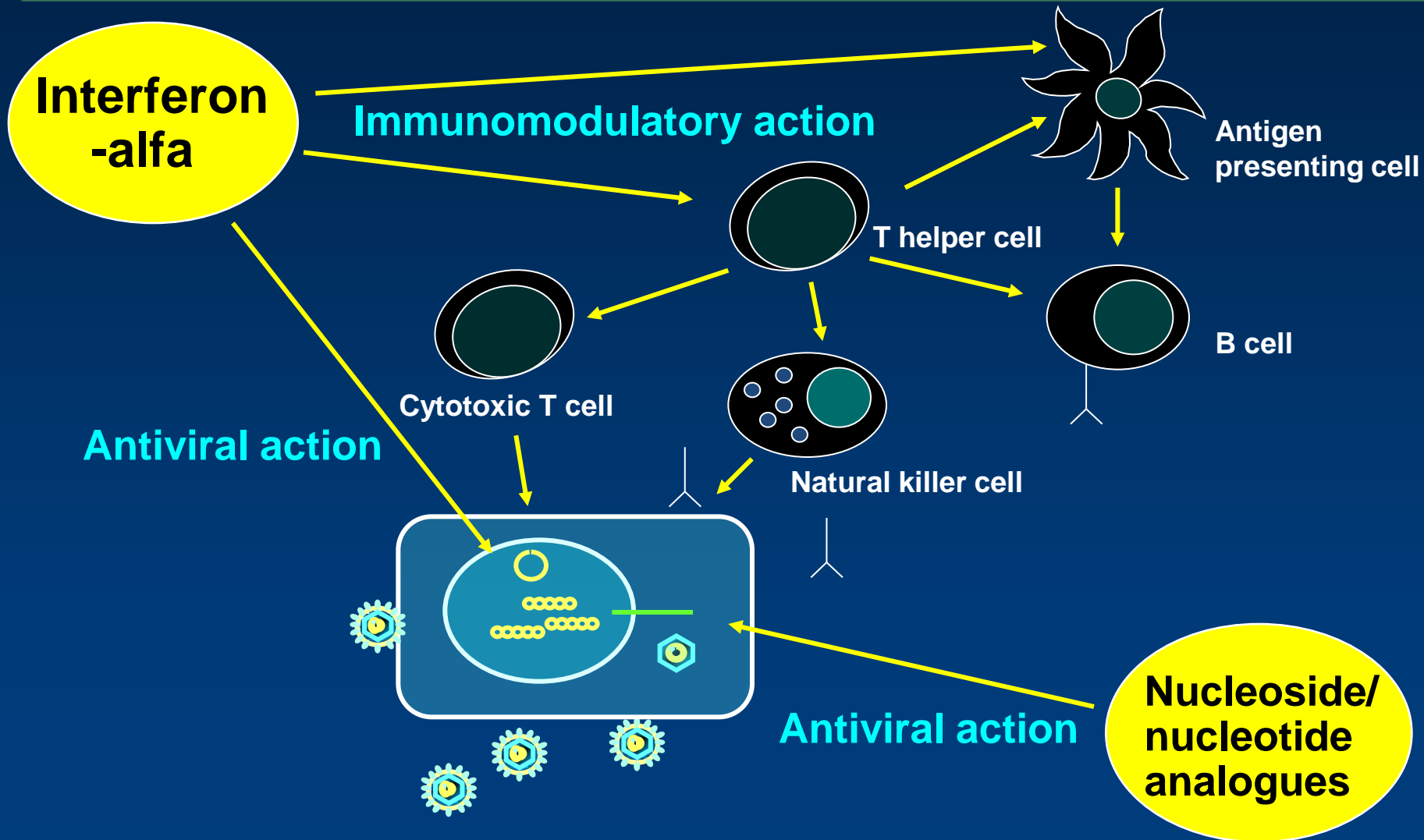
# When to Treat

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	HBV DNA (IU/mL)
• HBeAg +	20,000
• HBeAg –	2,000

1 IU/mL = 5 to 6 copies/mL

# Treatment Options for CHB



# Treatment Options

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## AVAILABLE DRUGS

- Nucleoside/ nucleotide analogues
  - LAM(3TC), ADV, ETV, FTC, TDF
- Newer agents
  - TELBUVIDINE (LdT), CLEVUDINE, PREDOFOVIR
- Interferons
  - conventional
  - pegylated

# Aims of Therapy for HBeAg-positive CHB

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- Short-term measurable 'surrogate' markers of treatment efficacy
  - recommended endpoint: HBeAg seroconversion<sup>1</sup>
  - other endpoints: HBV DNA suppression, ALT normalisation
- Long-term goals
  - prevent/stop/reduce
    - liver necrosis
    - progression to cirrhosis, decompensated cirrhosis or HCC
- Ultimate goal
  - HBsAg seroconversion
  - prolong 'event-free' survival

# Treatment of HBeAg-Negative Chronic Hepatitis B

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- With nucleotide/nucleoside analogs
- With interferons (conventional/pegylated)

# Challenges Of Therapy

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- Rational drug use
  - Both require treatment
  - Treat HBV alone or treat HIV alone
- Screening?
- Liver biopsy?
- Treatment complications and their management
- Viral resistance

# Lamivudine (LAM,3TC)

## Monotherapy for HBV

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- Resistance rates (HBV)

1 <sup>st</sup> year	-	15 – 32%
2 <sup>nd</sup> year	-	38%
3 <sup>rd</sup> year	-	56%
4 <sup>th</sup> year	-	67%

Emergence of mutants associated with phenotypic resistance, viral breakthrough, with frequent hepatic failure.

# Adefovir (ADV)

## Monotherapy for HBV

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- Resistance rates (HBV)
- 70 HBeAg negative patients 5 years of therapy with ADV
  - 1 year - 0%
  - 2 years - 3%
  - 3 years - 11%
  - 4 years - 18%
  - 5 years - 29%

*Hadziyannis et al Hepatology 2005; 42:754*

# Combination Therapy

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- NUCLEOS(T)IDES?
  - TRUVADA
- NUCLEOS(T)IDE + PEGYLATED INF
  - PEGaLAM STUDY

# Treatment Goals in CHB: Remission

## Differences between the two strategies

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**Maintained Remission**

=

Reduction in viraemia

ALT normalisation

Continued need for  
antiviral drugs

**VIRAL CONTROL  
ONLY**

**Sustained Remission**

=

Reduction in viraemia

ALT normalisation

No need for  
antiviral drugs

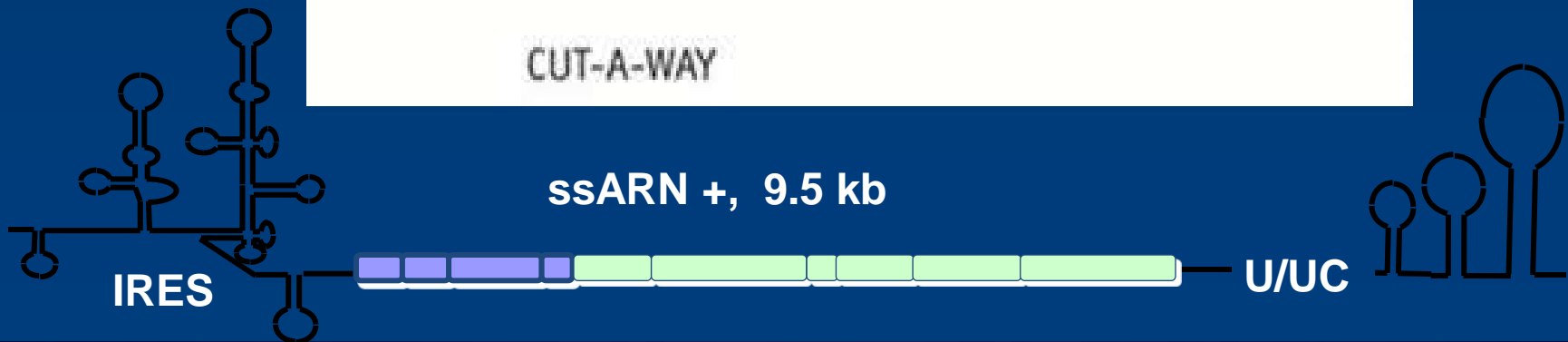
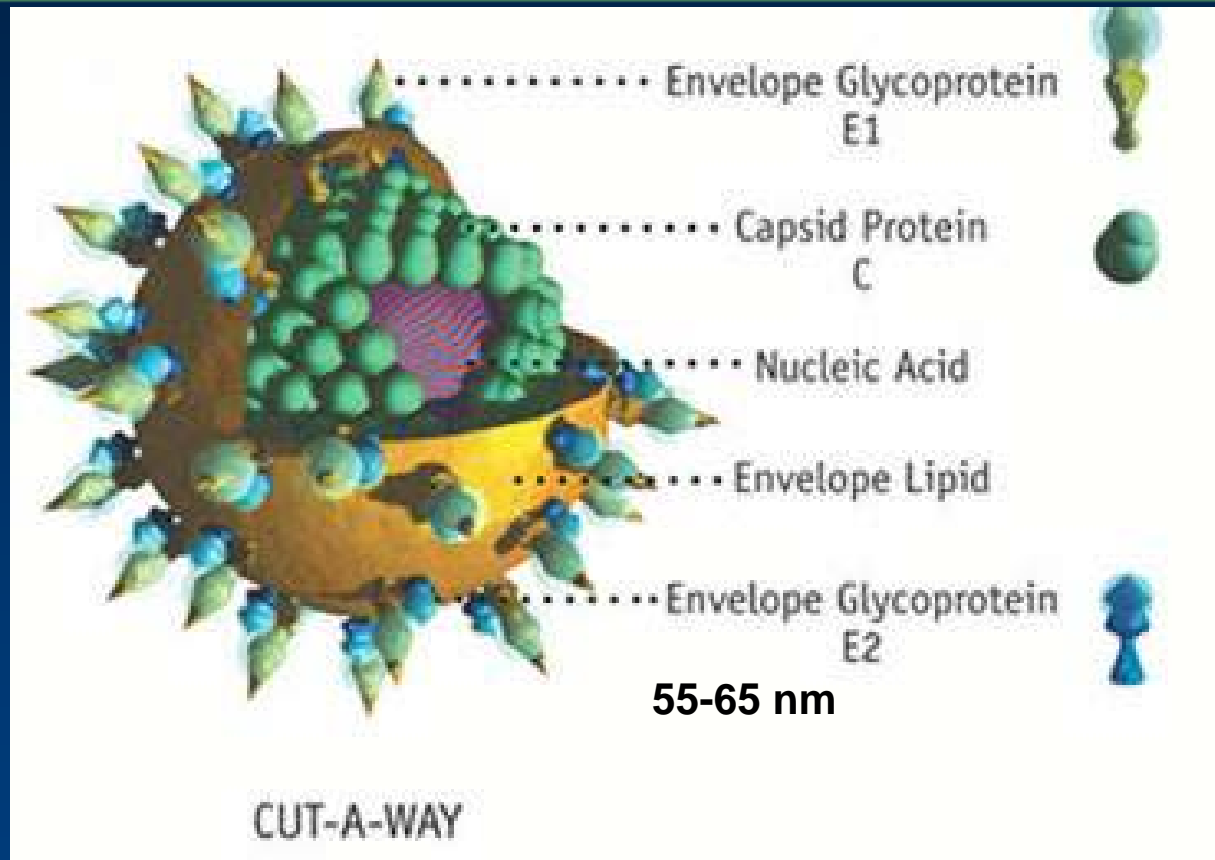
**IMMUNE  
CONTROL**

# Local Experience

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- LAM MONOTHERAPY
- OTHER NUCLEOTIDE ANALOGUES
- PEGYLATED INTERFERONS

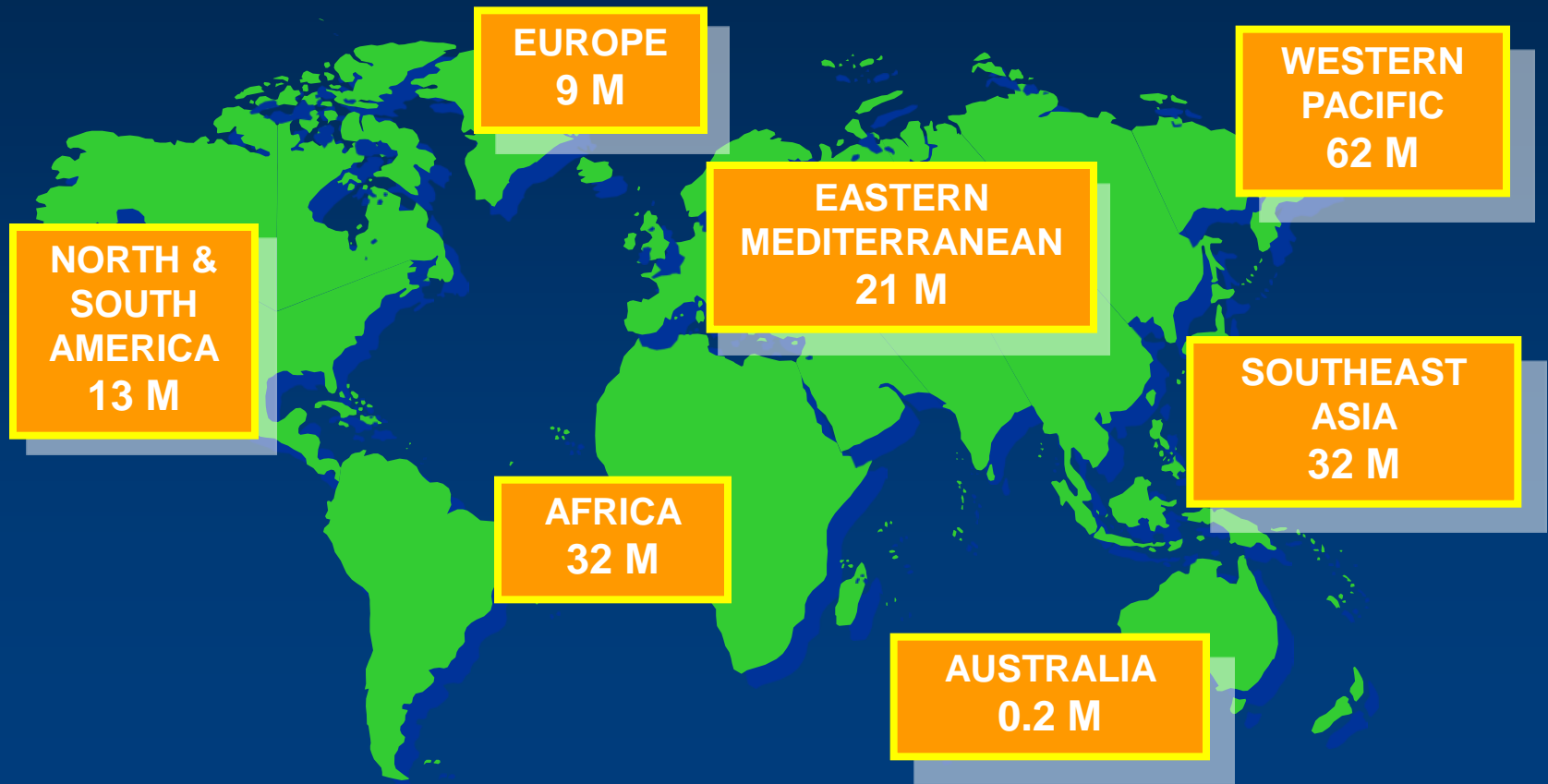
# Hepatitis C Virus



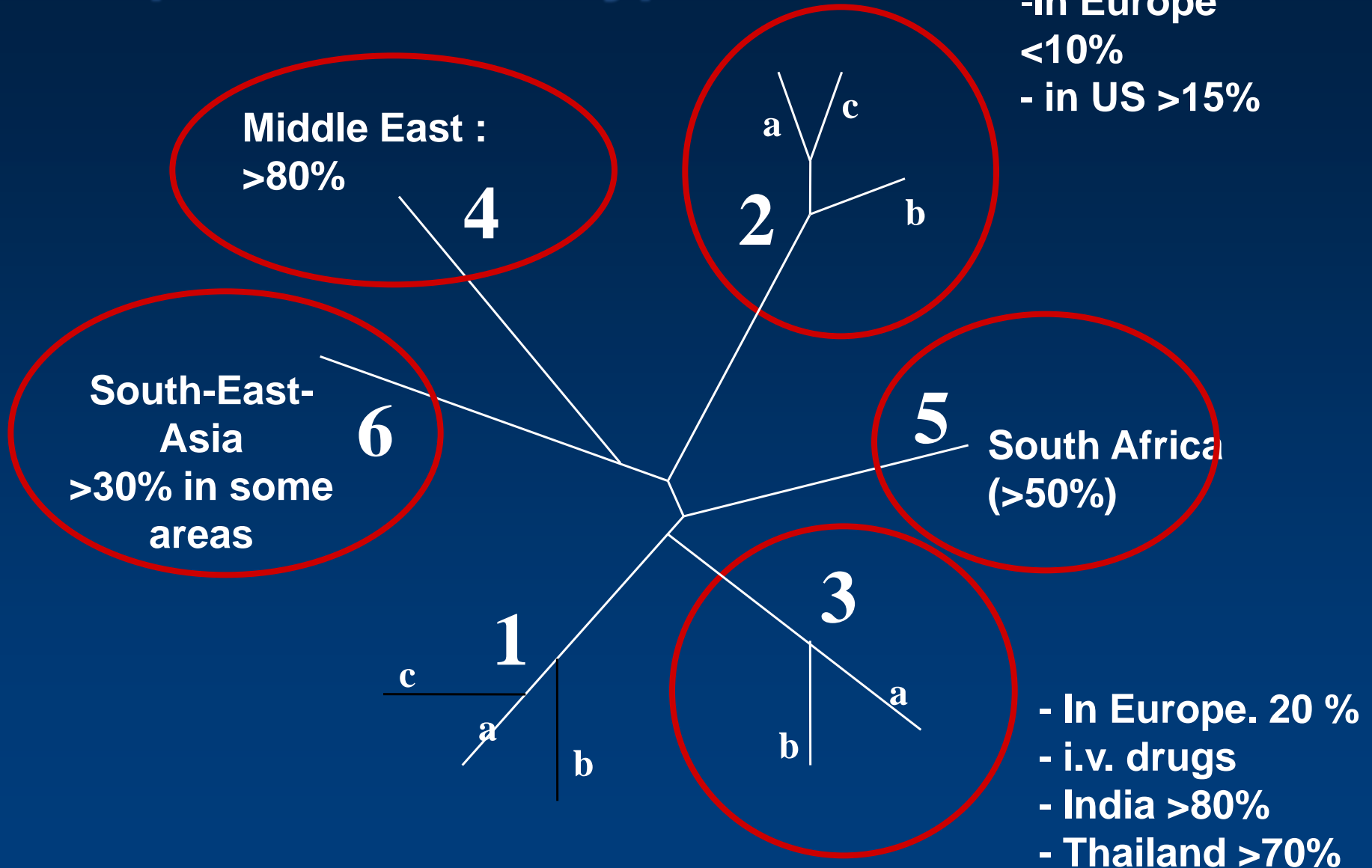
# Hepatitis C: A Global Health Problem

>170 Million Infected Worldwide

3-4 Million New Cases/Year



# Hepatitis C Genotypes



# HCV

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- Lule et al in 1995 found the prevalence rate of HCV to be 2.8% among patients with chronic liver disease in Kenyatta National Hospital.
- Mwangi (1998), found a prevalence rate of 1.8% in blood donors.

# Natural History of Hepatitis C

*Most patients with chronic HCV infection are asymptomatic*

10-20 years



**Acute Hepatitis C**



**Chronic Hepatitis**  
**75%-85 %**



**Cirrhosis 20 %**

# HCV HIV Co-infection

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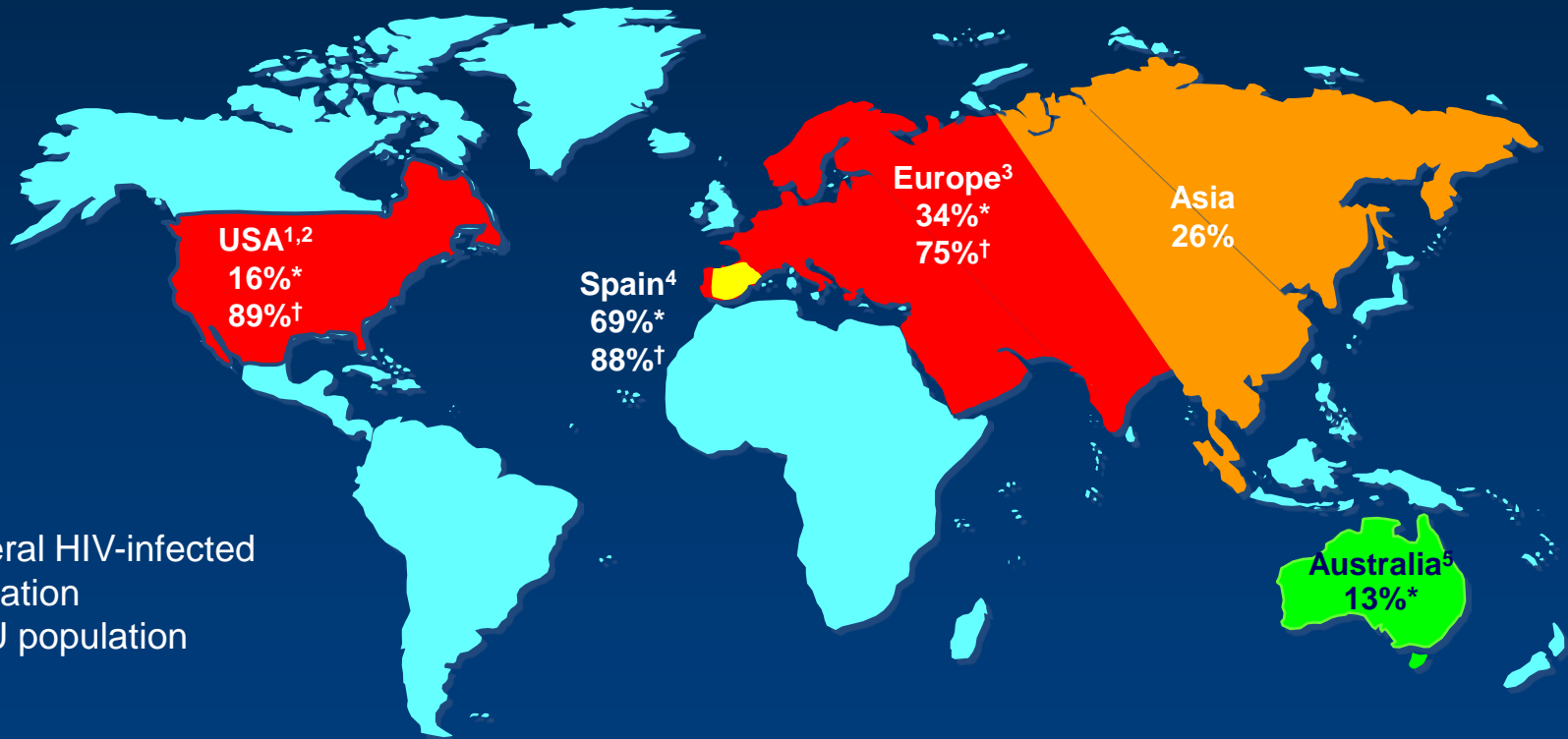
- Worldwide 170 Million Chronic HCV Carriers
- Estimated global prevalence 3% with regional differences up to 40%
- In specific populations
  - IDUS coinfectd 50-90% <sup>2</sup>
  - Hemophiliacs coinfectd 85% <sup>1</sup>

Ref: 1. Dietch DT, et al. Activity of combination therapy with interferon alfa-2b plus ribavirin in chronic hepatitis c patients co-infected with HIV. Semin Liver Dis 1999;19. Suppl 1:87-94

2. Huemer HP, et al. Correlation of hepatitis c virus antibodies with HIV-1 seropositivity in intravenous drug addicts. Infection 1990;18:122-3

# Worldwide prevalence of HCV in patients with HIV infection

30% of patients with HIV infection are co-infected with HCV; among HIV-infected intravenous drug users (IVDUs), this figure rises to 75–90%



\* General HIV-infected population

† IVDU population

1. Sherman K, et al. Clin Infect Dis 2002; 34: 831
2. Strasfeld L, et al. J Acquir Immune Defic Syndr 2003; 33: 356
3. Rockstroh J, et al. 9th European AIDS Conference 2003; Abstract F12/4
4. Roca B, et al. J Infect 2003; 47: 117
5. Dore G and Sasadeusz J, ed. Australasian Society for HIV Medicine 2003

# HCV/HIV in Kenya

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## POPULATION STUDIED      COINFECTION RATE

- 6184 blood donors      0.02%
- 353 VCT attendants      0
- 458 medical inpatients      3.7%

# Impact of Co-infection

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- HIV accelerates the clinical course of HCV-related liver disease:
  - Faster time to cirrhosis<sup>1-2</sup>
  - Faster time to HCC<sup>3</sup>
  - More patients develop cirrhosis within a given time frame
  - Alcohol has an additional aggravating effect
- HCV co-infection:
  - Increases the risk of antiretroviral drug-associated hepatotoxicity
  - Dampens the CD4 response to antiretroviral therapy during treatment<sup>4</sup>

1. Soto B, et al. J Hepatol 1997; 26: 1

2. Mohsen A. Gut 2003; 52: 1035

3. Giordano T, et al. 2nd IAS Conference on HIV Pathogenesis and Treatment 2003; Abstract 213

4. Braitstein P, et al. 2nd IAS Conference on HIV Pathogenesis and Treatment 2003; Abstract 214

# Investigations

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- Liver function tests
- Screening test for HCV antibody
- HCV viral load
- HCV genotype
- ?liver biopsy/fibroscan/imaging

# Indications for HCV Treatment

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- Well-controlled HIV (ART or CD4  $>350$  cells/mm<sup>3</sup>)
- Histological evidence of advanced Hepatitis C-related liver disease (fibrosis or cirrhosis)
- HIV therapy interrupted by recurrent ART-induced hepatotoxicity

# Available Treatment

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Combination therapy:

- Interferons (pegylated)
- Ribavirin

# Predictors of Success of Treatment

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- Rapid virological response (RVR)  
(4 weeks)
- Early virological response (EVR)  
(12 to 16 weeks)
- Sustained virological response (SVR)  
(6 months after stopping treatment)

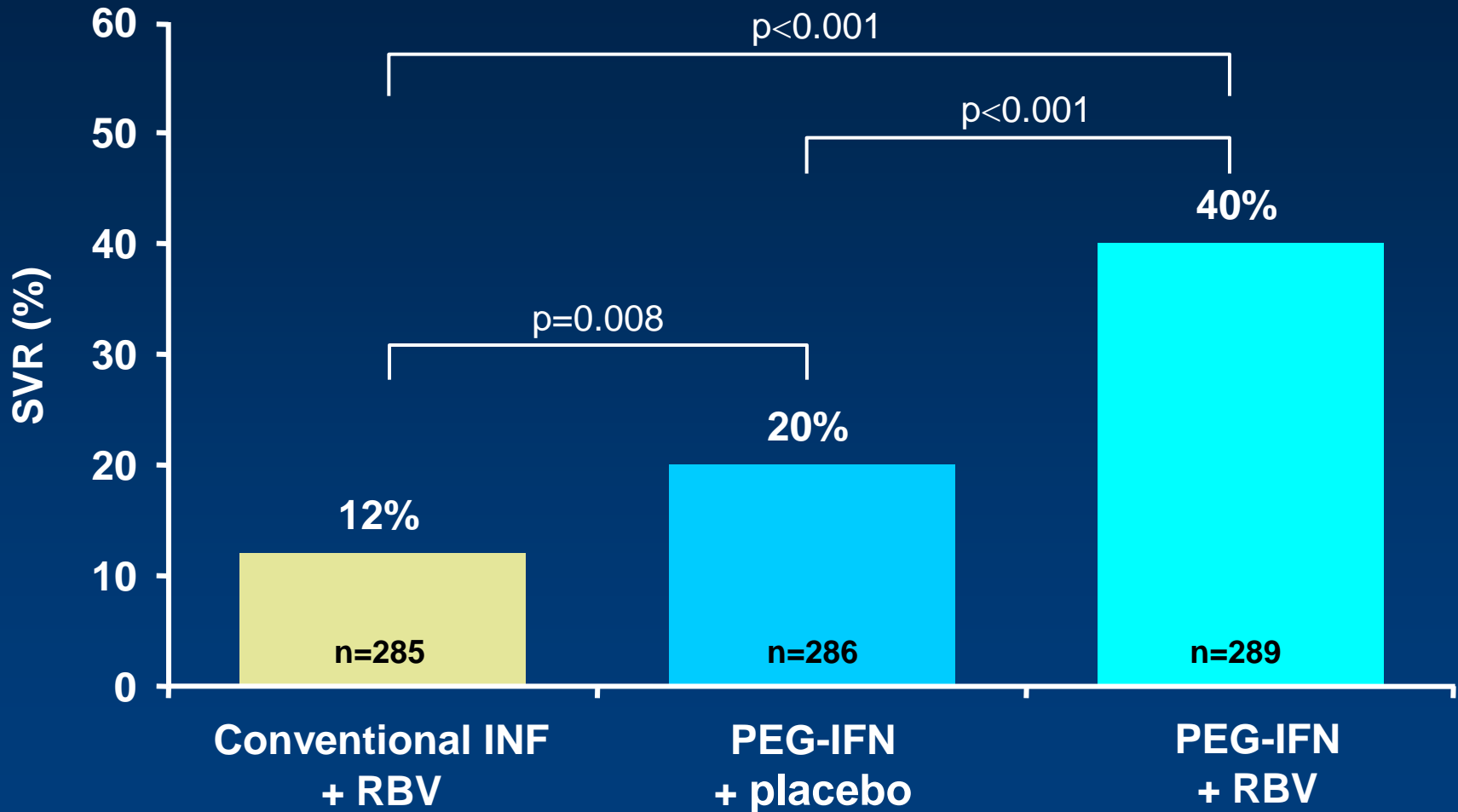
# Genotype and Response to Therapy in HCV (PegIFN + RBV)

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GENOTYPE	DURATION OF TREATMENT	SUSTAINED VIRAL RESPONSE (SVR)
2 and 3	SHORT	(78-81%)
4,5,6	LONG	ONGOING TRIALS
1	LONG	70%

- IN ALL GROUPS RVR HAVE HIGHER SVR RATES
- THE LOWER THE HCV RNA, THE HIGHER THE SVR

# Combination Therapy Superior



SVR defined as <50 IU/mL HCV RNA at week 72; ITT

Torriani F, et al. N Engl J Med 2004; 351: 438

# Future Treatments

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- Enzyme Inhibitors
  - HCV-RNA polymerase inhibitor
  - HCV-Protease Inhibitor
- Combinations With Each Other and/or PEG-INF + RBV

# Challenges

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- Screening issues
- Complications and management

# Drug interactions in Co-infection

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- DDI and D4T plus interferon/ribavirin cause mitochondrial toxicity  
(Avoid in HCV/HIV)
- ZIDOVUDINE with ribavirin associated with higher anemia rates.
- SOME NRTIs, all NNRTIS and PIs are hepatotoxic requiring frequent LFTs.

# Take Home

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- HBV/HCV + HIV is common
- Screen For HBV in HIV infection
- HBV vaccination for all HIV+ patients who are HBsAg-
- Treat HBV where indicated and carefully select your nucleotides

Screen for HCV in selected patients locally

- Treat HCV where indicated/possible
- Beware of hepatotoxicity and dangerous combinations

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***THANK YOU!***