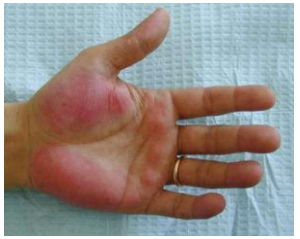
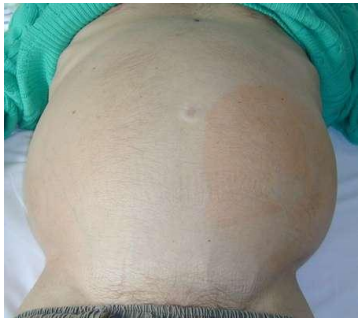
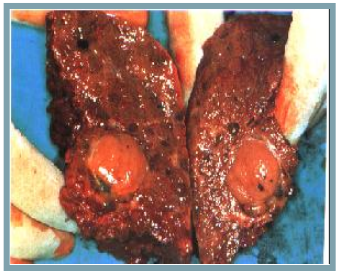
HIV and hepatitis co-infection

Graham Cooke

24th November, 2011

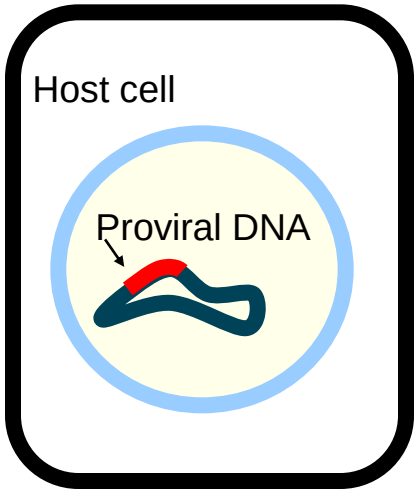






Key differences in the approaches to 3 viruses

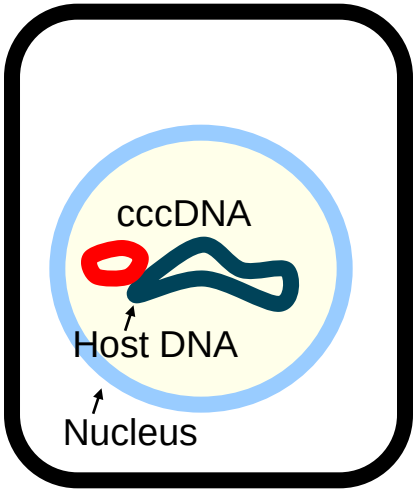
HIV



TREATMENT

Long-term suppression of viral replication[2,3]

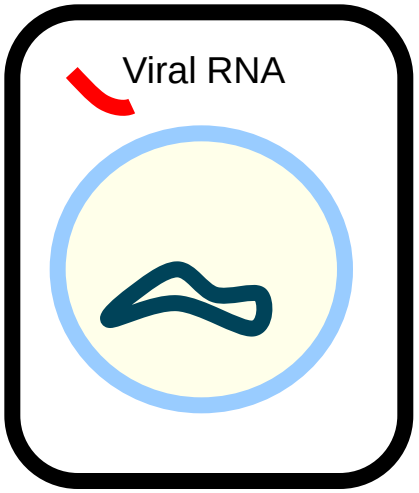
HBV



TREATMENT

Long-term suppression of viral replication

HCV



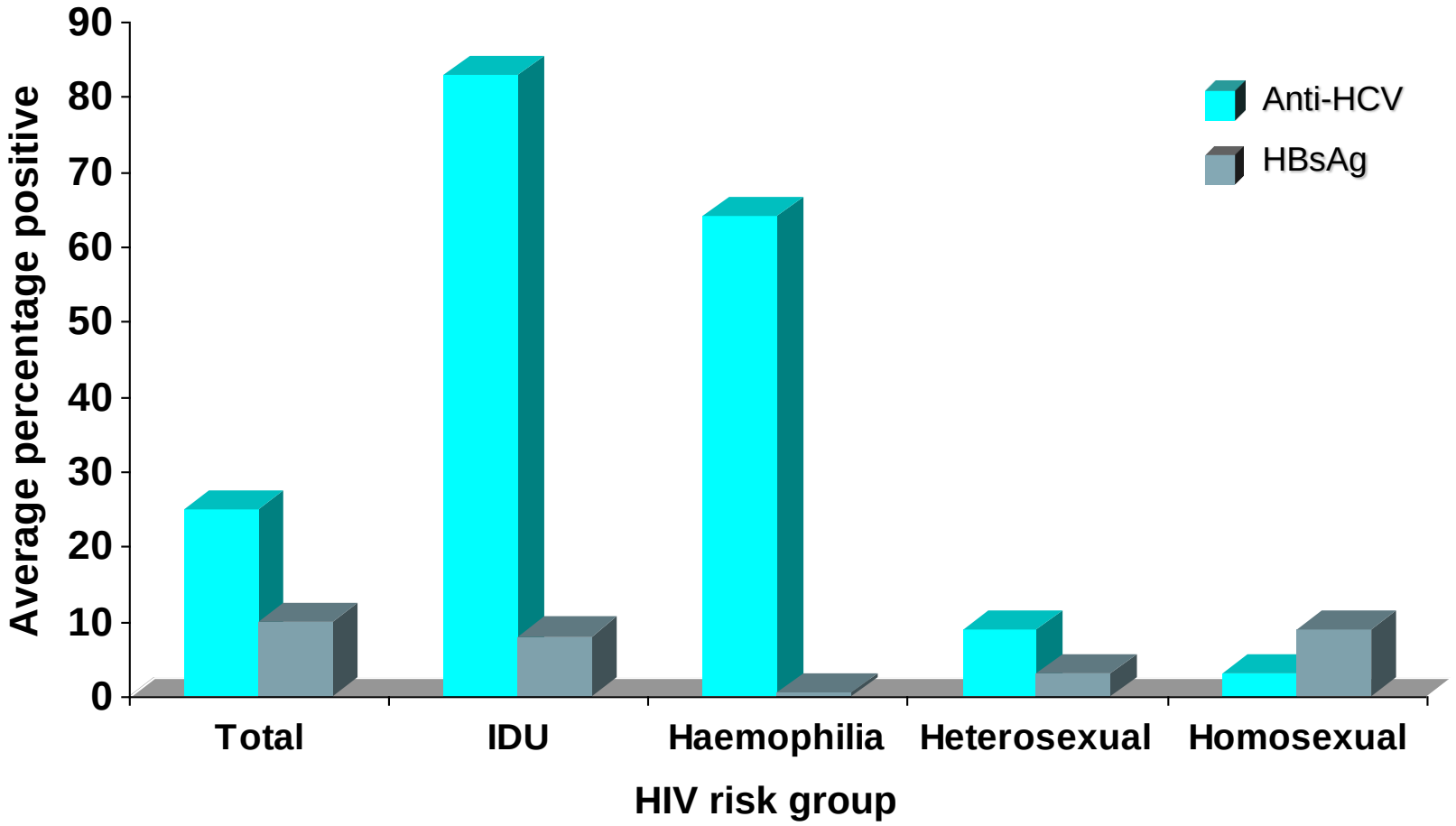
TREATMENT

Viral Eradication = Cure
Genotypes important

cccDNA = covalently closed circular DNA

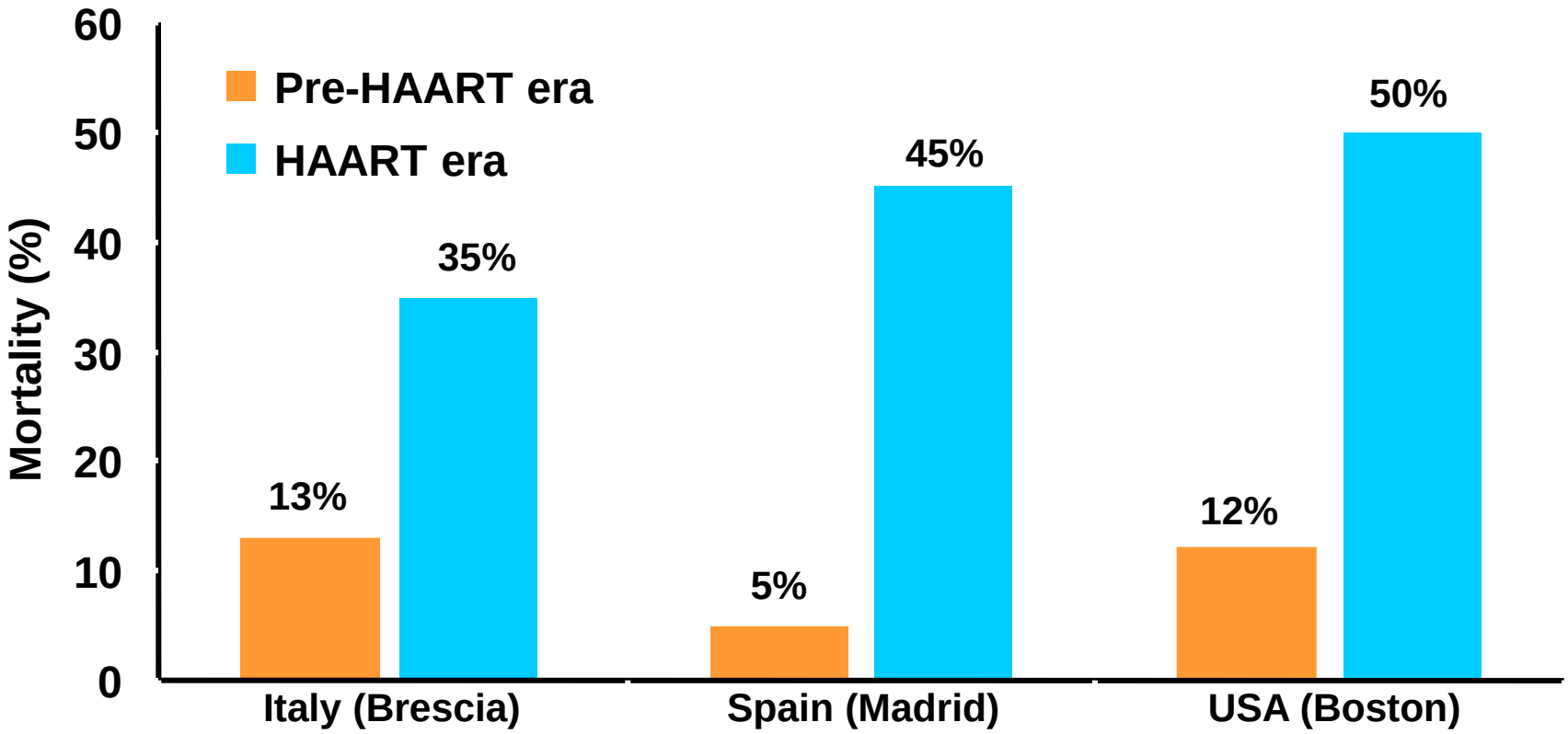
1. Pawlotsky JM. *J Hepatol* 2006;44:S10-S13; 2. Siliciano JD, Siliciano RF. *J Antimicrob Chemother* 2004;54:6-9;
3. Lucas GM. *J Antimicrob Chemother* 2005;55:413-416

Prevalence of Chronic HBV and HCV Infection in HIV Positives by HIV Risk Group



Denis F et al. *Pathol Biol* 1997;45:701–8. Thio CL et al. *Lancet* 2002;360:1921–6. Sherman K et al. *Clin Infect Dis* 2002;35:482–7. Kellerman S et al. *J Infect Dis* 2003;188:571–7. Konopnicki D et al. *AIDS* 2005;19:593–601.

Death from end-stage liver disease (ESLD) as a % of all deaths among HIV patients

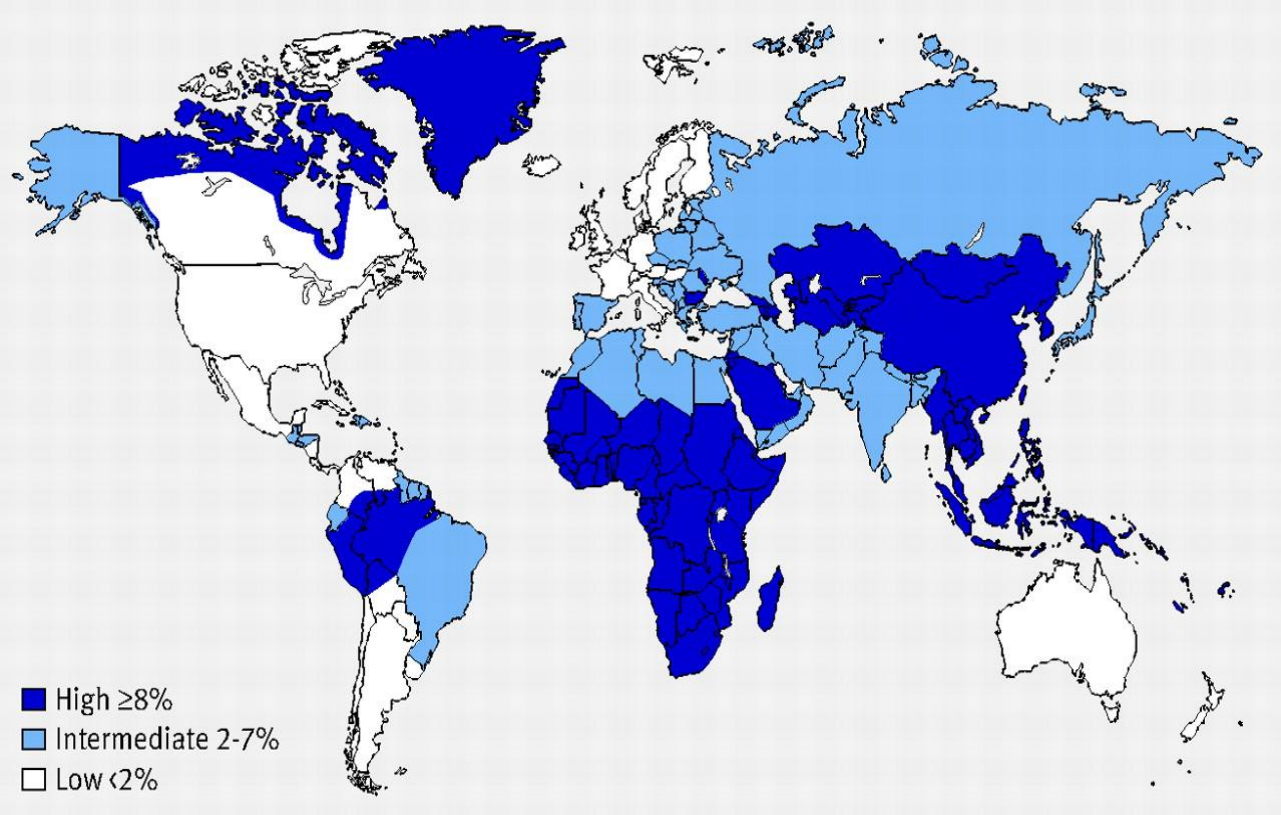


Bica *et al. Clin Infect Dis* 2001; 32:492–497
Puoti *et al. JAIDS* 2000; 24:211–217
Soriano *et al. Eur J Epidemiol* 1999; 15:1–4
Soriano *et al. PRN Notebook* 2002; 7:10–15
Martin-Carbonero *et al. AIDS Res Human Retrovirus* 2001; 17:1467–1471

HBV in co-infected patients

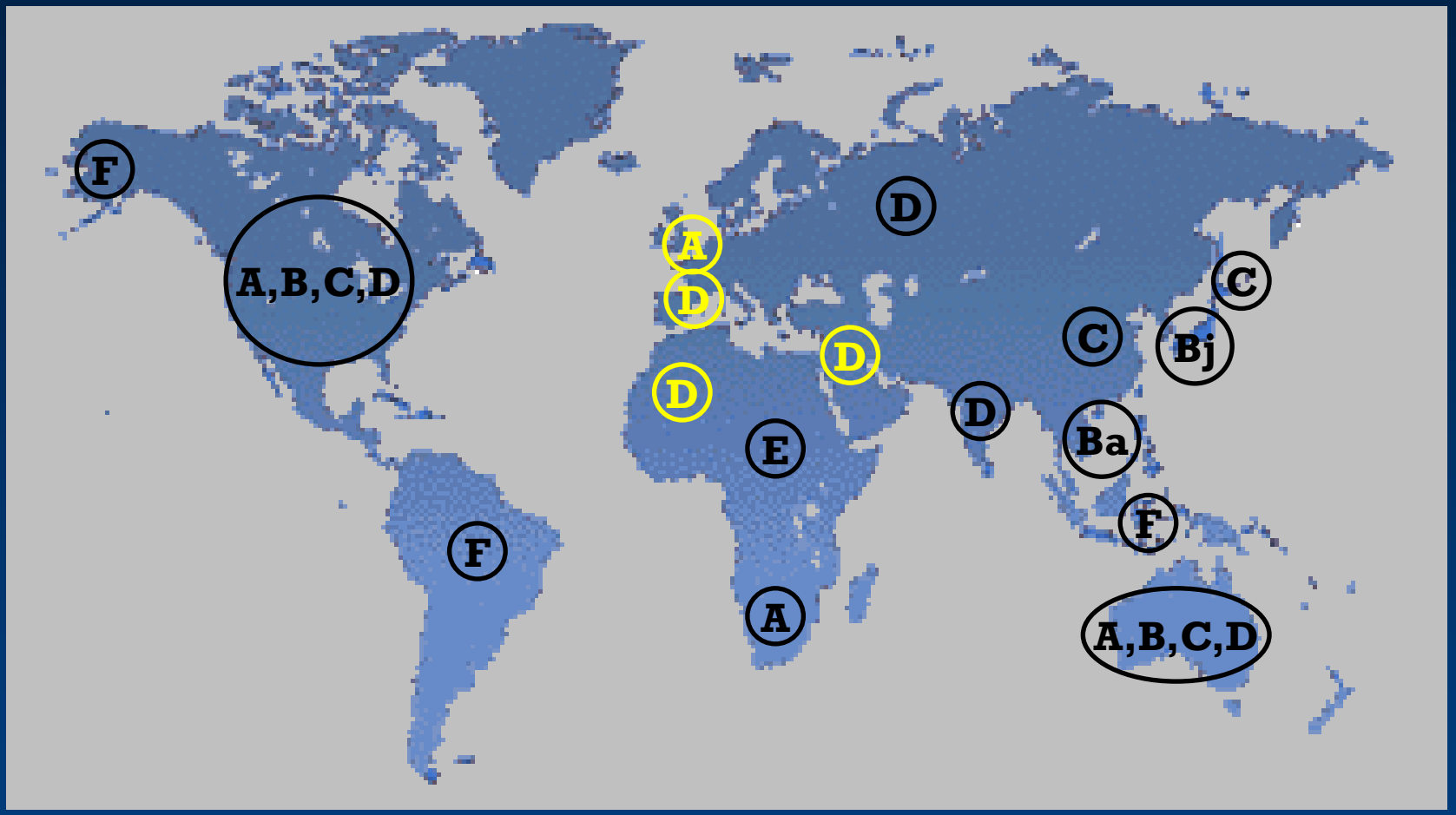
HBV - A Global Health Problem

Country	HBsAg+ (%)
China	5.3–12
South Korea	2.6–5.1
India	2.4–4.7
Taiwan	10–13.8
Viet Nam	5.7–10
Turkey	6.2-8.2
Africa	5–19
Russia	1.4–8
Europe	0.3–12



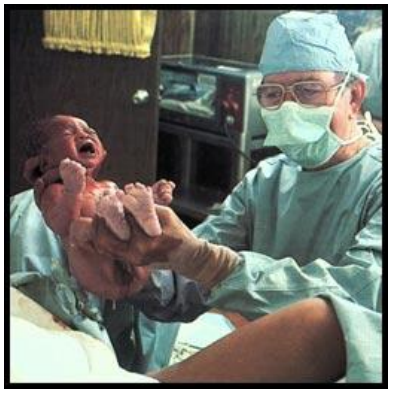
Source: Cooke et al BMJ10

HBV Genotypes



This is an oversimplification as populations are not static…

Transmission of HBV



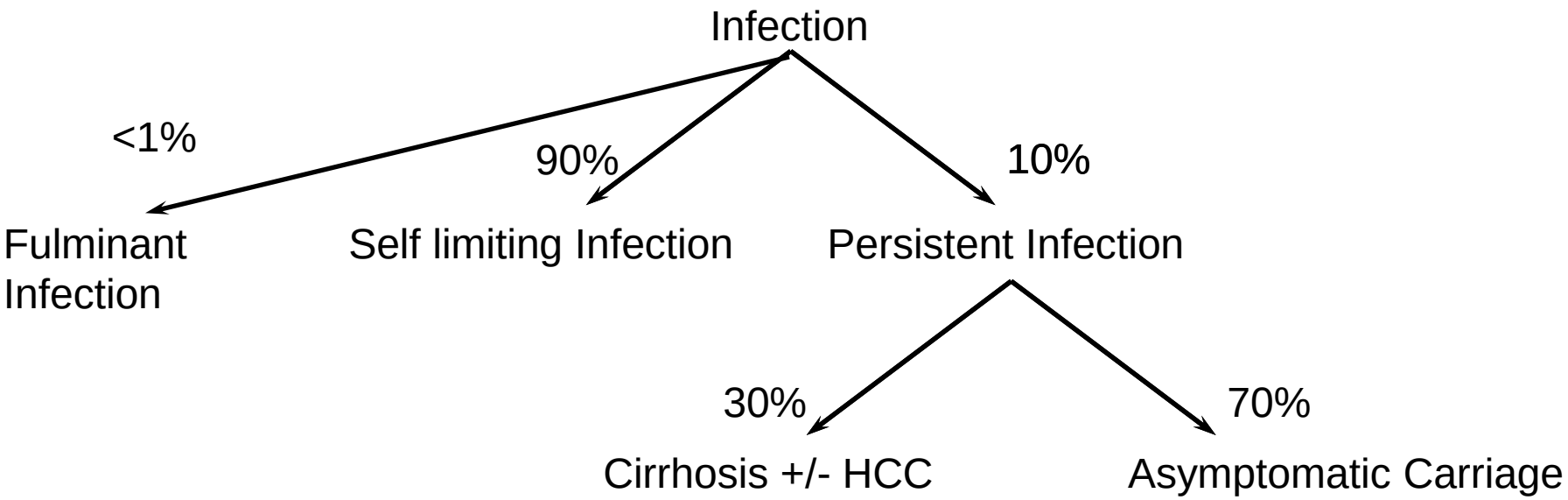
Vertical transmission
(mother to infant)

Childhood transmission
?how

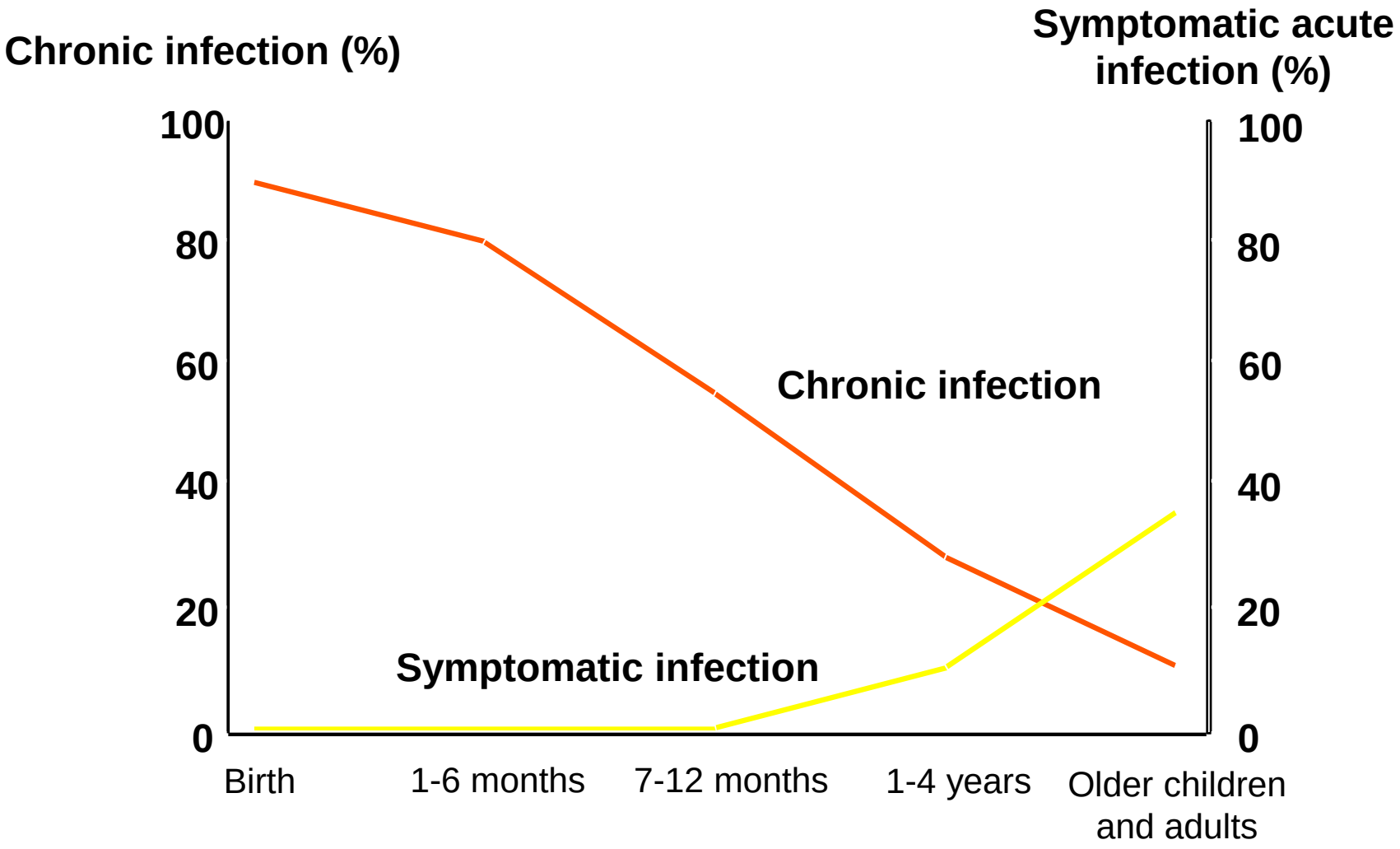
Sexual transmission

Also…
- Injecting drug use
- Blood transfusion/blood products
- Contaminated medical devices/sharps injuries
- Tattooing and body piercing

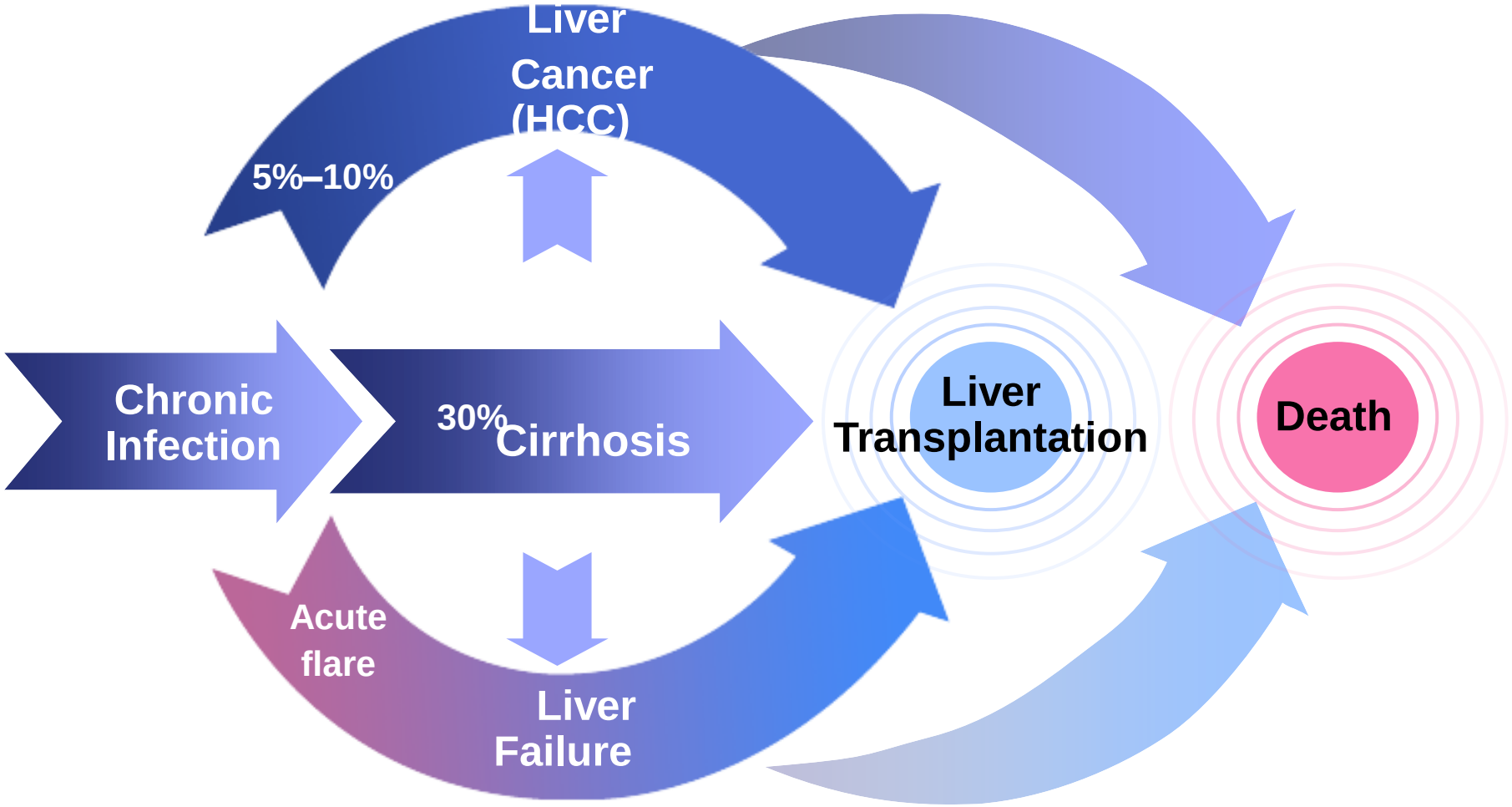
Outcome of HBV Infection



Outcome of HBV infection by age of acquisition

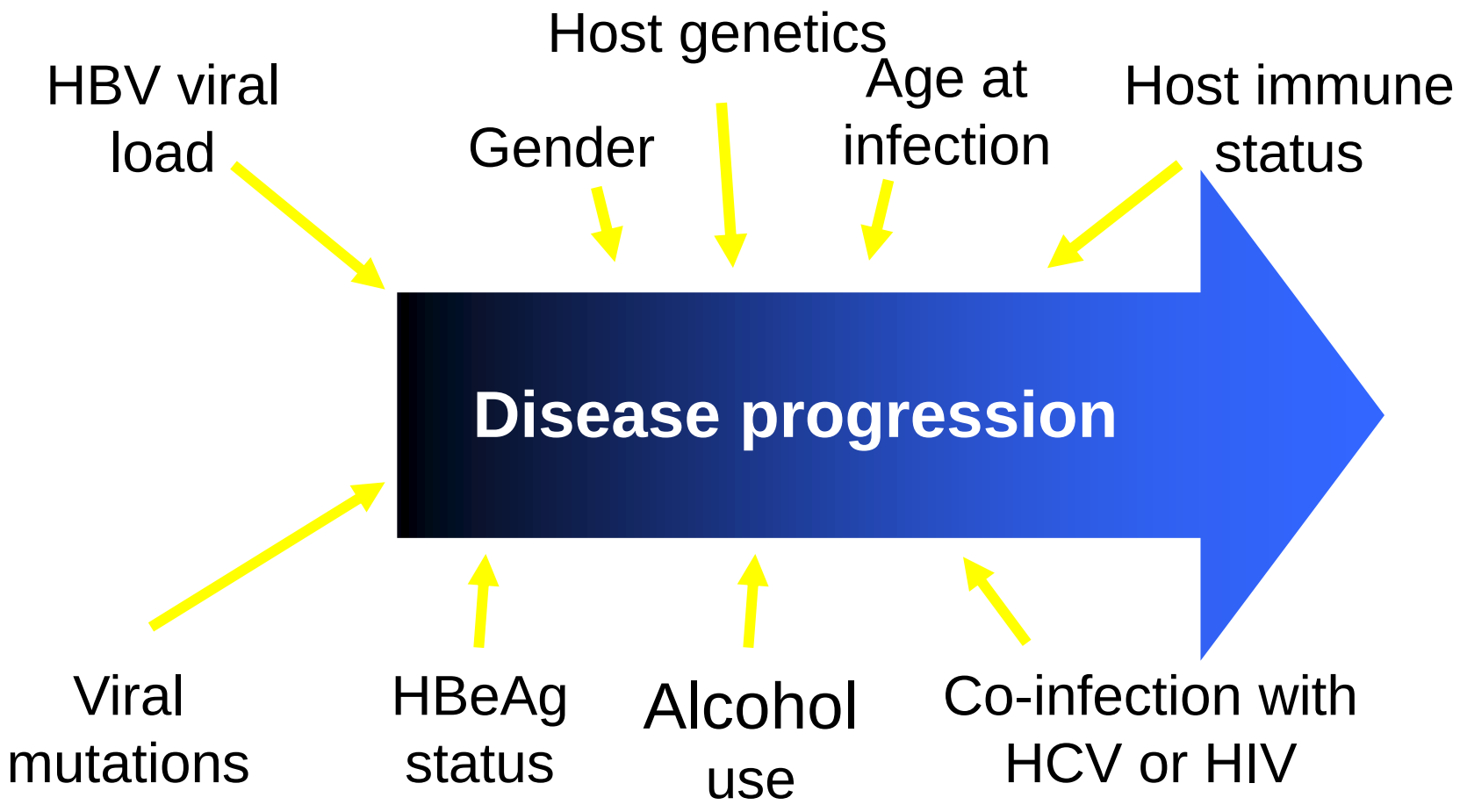


15%–40% of CHB patients may experience disease progression



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.

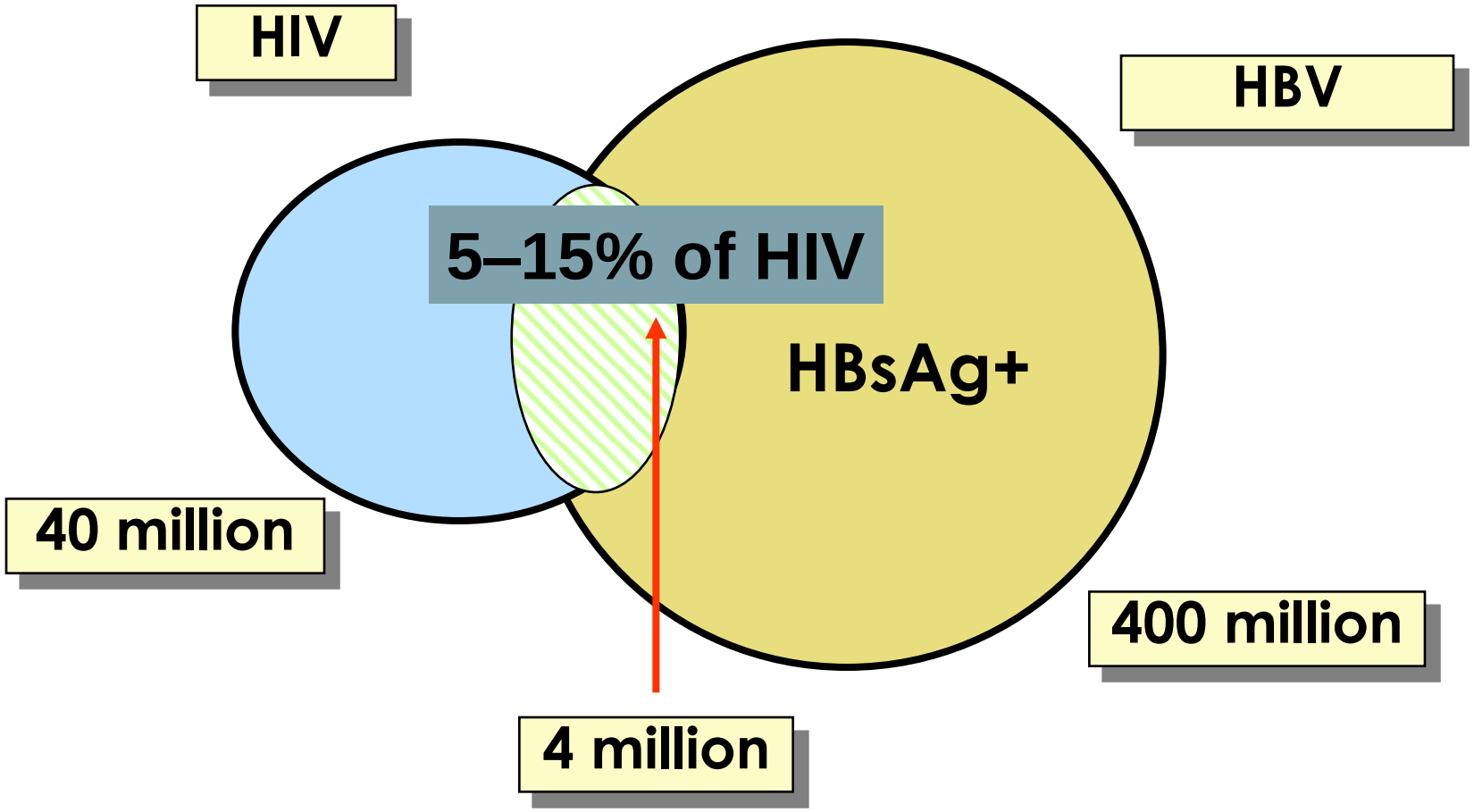
Factors Influencing Natural History



Fattovich. *Semin Liver Dis.* 2003;23:47-58.
Chen, et al. *JAMA.* 2006;295:65-73.

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

Overlapping HBV & HIV Epidemics



Impact of HIV on hepatitis B

- Six times higher risk chronic infection
- Higher eAg positivity and HBV DNA levels
- Higher rate of reactivation
- Lower ALT levels
- More rapid liver disease progression
- Decreases anti-HBe and anti-HBs seroconversion
- Increases hepatic flares
- Decreases efficacy of anti-HBV treatment
  - – decrease response to INF-alpha
  - – increase 3TC resistance mutation

Levy V. CID 2006:43:904-910.

Treatment goals

Inextricably interlinked

Prevent illness and death

by preventing progression of liver disease

by suppression of viral replication

Therapeutic Agents Available for HBV

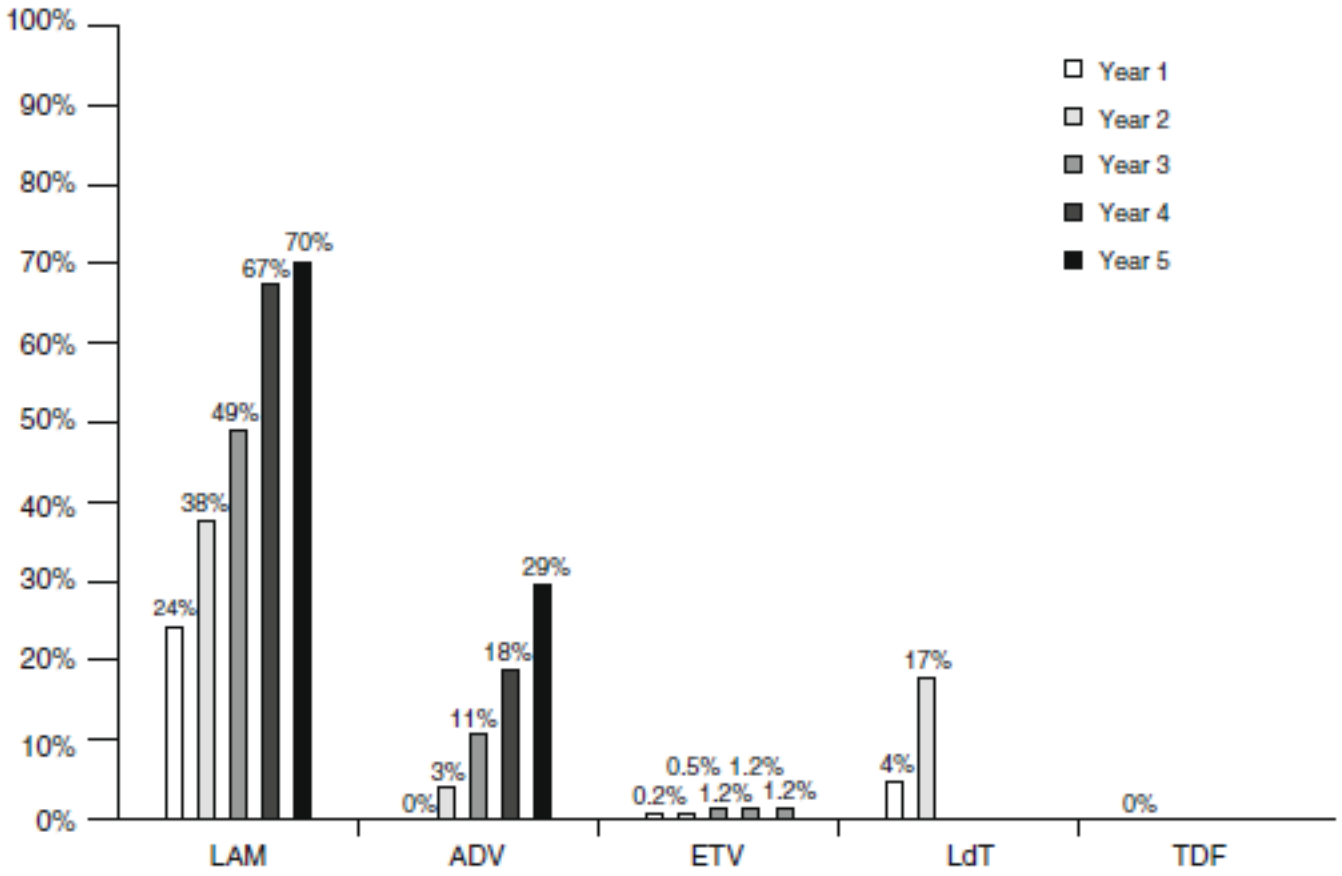
Registered

- Interferon-alpha
- PEG-Interferon
- Lamivudine †
- Adefovir*
- Entecavir
- Telbivudine (L-dT)*??
- Emtricitabine†
- Tenofovir †

† Licensed for the treatment of HIV, but also have anti-HBV activity.

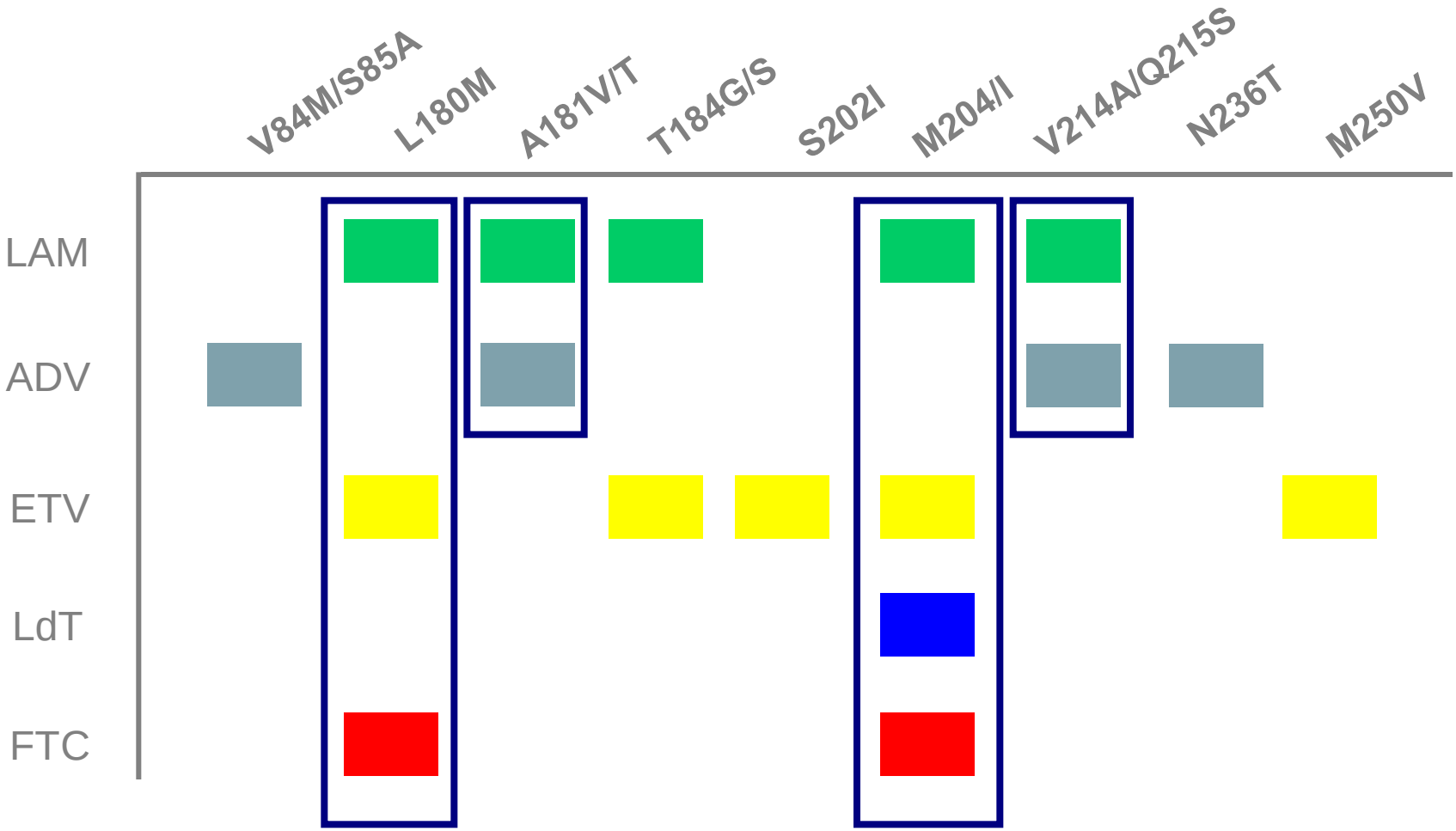
***No HIV activity in doses used for HBV treatment**

Resistance to newer antivirals



Sources: EASL 09, Pawlotsky 08

Resistance Mutations Associated with Viral Breakthrough in Patients on Treatment



Selection of LAM-Resistant Mutants Affects Future Treatment Options

Locarnini S et al. Antivir Ther 2004;9:679–93.

BHIVA Guidelines for the management of HIV-1 co-infection with chronic hepatitis B or C. 2010

- ALT elevation is less sensitive in co-infection
- HBV-DNA is essential - decisions to treat and monitor
- Assessment for liver fibrosis should be performed on all patients to define Rx strategy
- All patients with ALT above ULN not fulfilling other criteria for treatment and with no other obvious cause should have a liver biopsy
- CD4 count of >500 cells/ mm3, HBV treatment should be commenced using the same criteria (HBeAg, HBV-DNA, fibrosis assessment, and ALT) as in HIV-negative

British HIV Association
BHIVA

BHIVA Guidelines for the management of HIV-1 co-infection with chronic hepatitis B or C. 2010

- All with significant fibrosis (Metavir ≥F3 or Ishak ≥S3 or FibroScan ≥9kPa) should be treated if HBV DNA detectable, at any level. Cut-offs for Fibroscan are not as clearly defined for HBV as they are for HCV co-infection.

- All patients with an HBV-DNA >2000 IU/ml should be considered for treatment.

- The only exception may be < 20 years old with CD4 count >500 cells/ml, persistently normal LFTs, and no fibrosis – ? immune-tolerant, HBV careful monitoring may be an alternative.

- The presence of significant liver damage, but a low or undetectable viral load for HBV should prompt exclusion of hepatitis delta.

BHIVA Guidelines for the management of HIV-1 co-infection with chronic hepatitis B or C. 2010

Recommendations for patients with a CD4 ≥500 cells/mm3

- No HBV therapy is recommended if HBsAg and HBV-DNA negative, but HBcAb positive

- HBsAg +ve, HBV-DNA <2000 IU/L and no significant fibrosis (Metavir ≤F1 or Ishak ≤S1 or FS ≤8kPa) should not be treated → 3-6/12 monitoring with HBV-DNA and ALT

- 12 months pIFN is an option in HBeAg positive, raised ALT, low HBV-DNA, minimal fibrosis and (if tested) genotype A. Lack of HBV-DNA response (<1 Log10 reduction at 12 weeks and >2000 IU/L at 24 weeks) → discontinuation.

BHIVA Guidelines for the management of HIV-1 co-infection with chronic hepatitis B or C. 2010

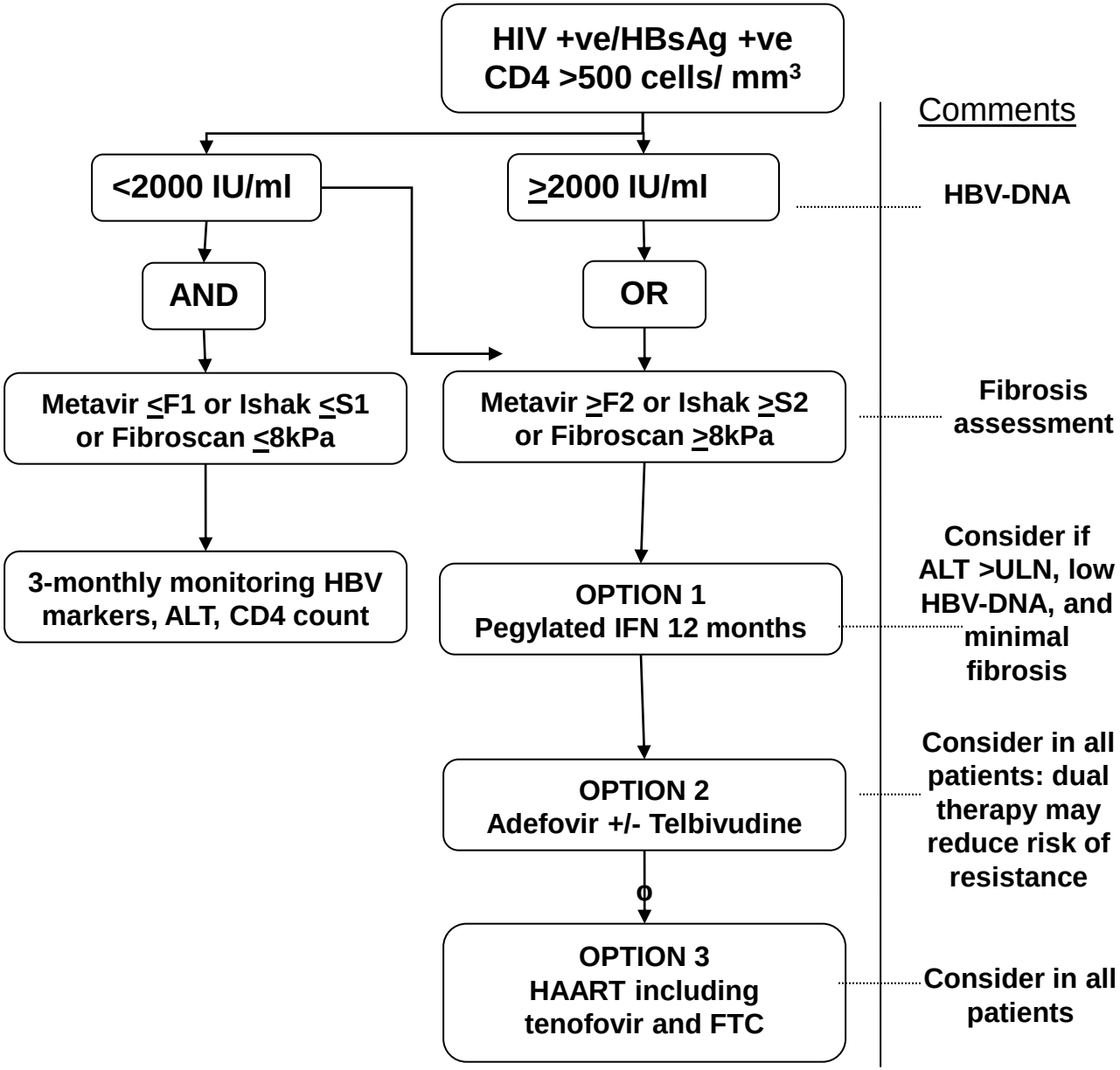
Recommendations for patients with a CD4 ≥500 cells/ mm3 (cont)

- Telbivudine should not be used alone because of the high rate of HBV resistance AND the potential for anti-HIV activity in telbivudine is currently unknown.

- Adefovir and telbivudine given together is an option and is likely to reduce risk of resistance to telbivudine.

- Patients started on adefovir with or without telbivudine who have suppressed HBV-DNA should remain on these drugs until HAART is started

- Early introduction of ARVs inclusive of tenofovir and FTC should be considered as an option for naïve patients


HIV +ve/HBsAg +ve
CD4 >500 cells/ mm3
<2000 IU/ml
≥2000 IU/ml
AND
OR
Metavir ≤F1 or Ishak ≤S1
or Fibroscan ≤8kPa
Metavir ≥F2 or Ishak ≥S2
or Fibroscan ≥8kPa
3-monthly monitoring HBV
markers, ALT, CD4 count
OPTION 1
Pegylated IFN 12 months
OPTION 2
Adefovir +/- Telbivudine
or
OPTION 3
HAART including
tenofovir and FTC
Comments
HBV-DNA
Fibrosis
assessment
Consider if
ALT >ULN, low
HBV-DNA, and
minimal
fibrosis
Consider in all
patients: dual
therapy may
reduce risk of
resistance
Consider in all
patients

How to monitor for hepatocellular carcinoma (HCC)

The following patient groups are at high risk for developing HCC and should be entered into monitoring / surveillance programmes

At-risk groups

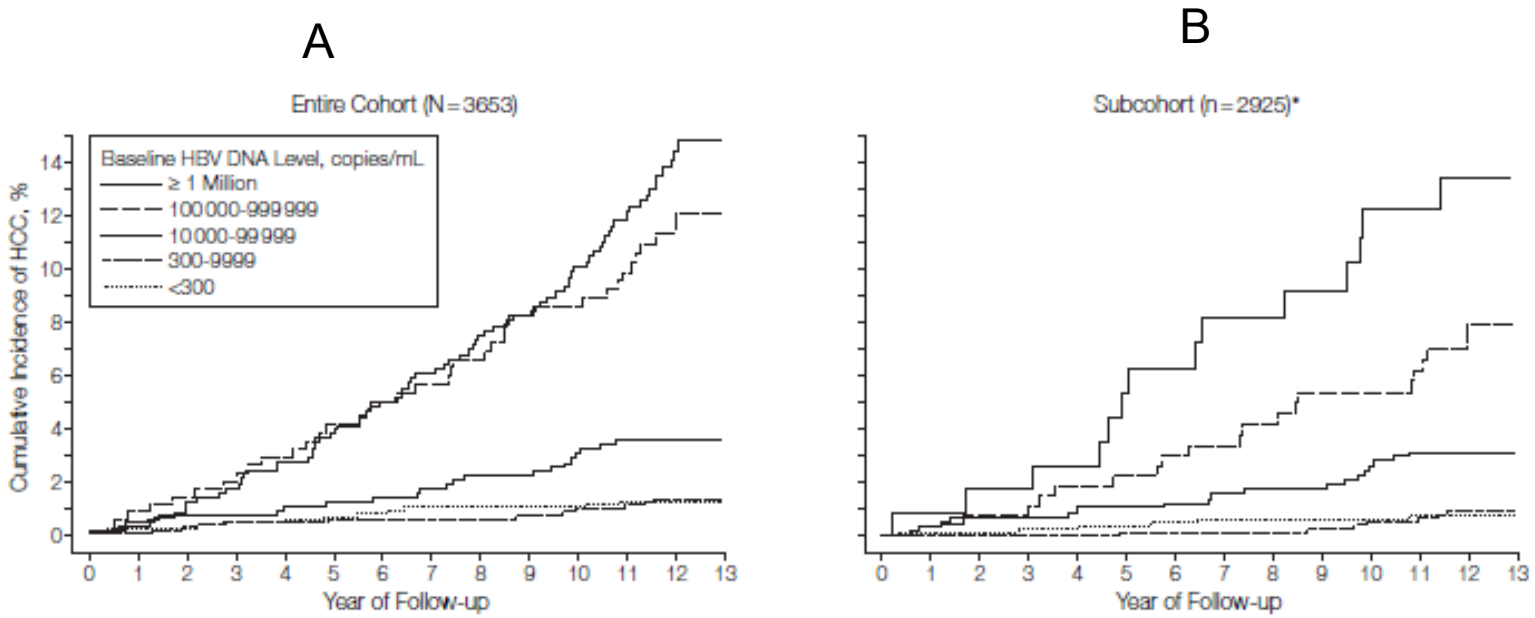
- **Hepatitis B carriers**
  - Asian males ≥ 40 years
  - Asian females ≥ 50 years
  - All active hepatitis B carriers
  - Family history of HCC
  - Africans over age 20
- Non-hepatitis B **cirrhosis**
  - Hepatitis C
  - Alcoholic cirrhosis
  - Genetic hemochromatosis
  - Primary biliary cirrhosis
- Other groups at risk (monitoring benefit unknown)
  - Alpha1-antitrypsin deficiency
  - Non-alcoholic steatohepatitis
  - Autoimmune hepatitis

How to monitor

- Monitoring for HCC should be performed using ultrasonography
- AFP alone should not be used for sceening unless ultrasound is not available
- Patients should be screened at 6 month intervals
- The screening interval does not need to be shortened for patients at higher risk of HCC

Bruix, J. & Sherman, M., (2005) Management of hepatocellular carcinoma. *Hepatology* 42(5):1209-1236

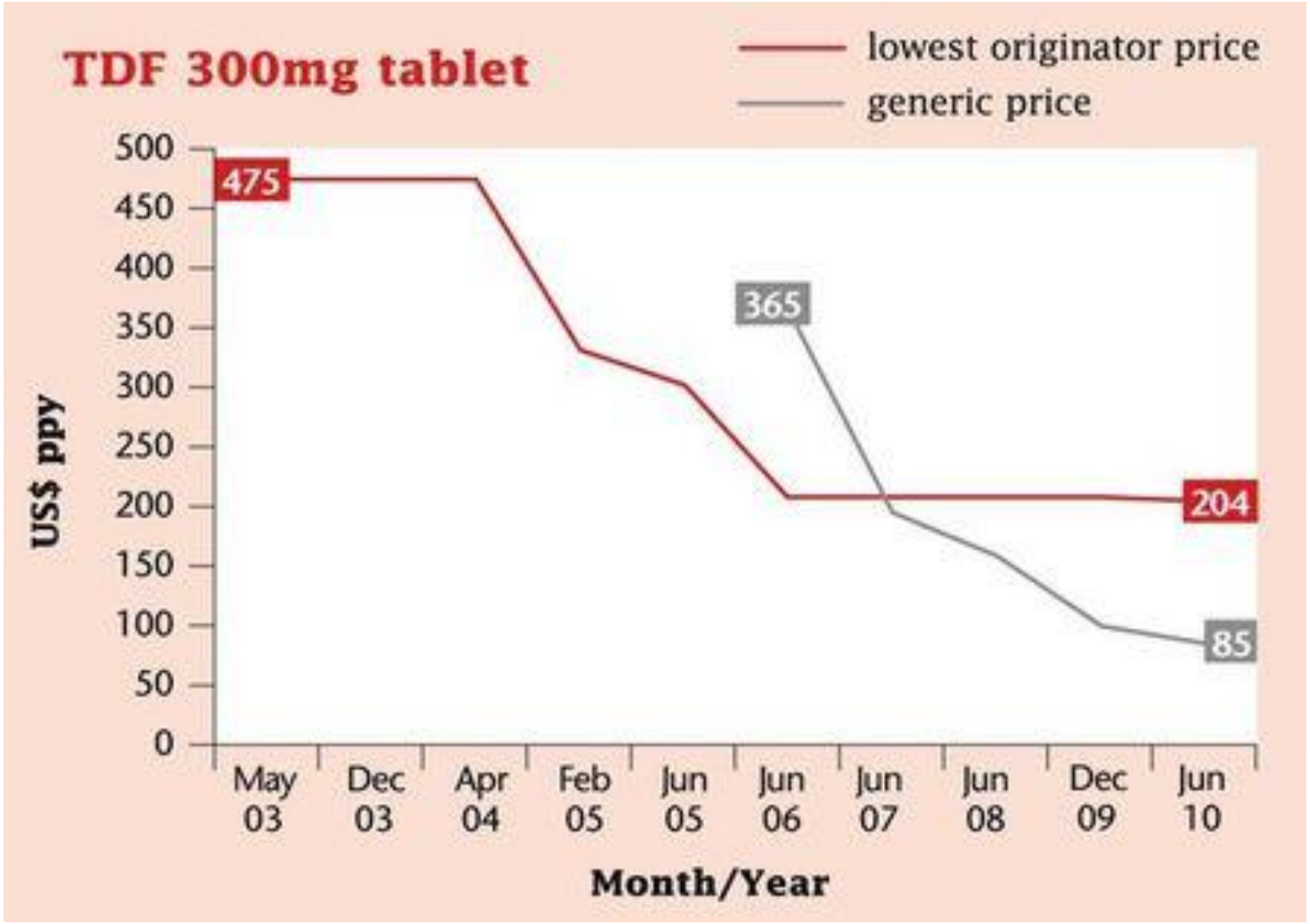
HBV viral load predicts risk of HCC independently of cirrhosis



eAg –ve, ALT normal, no cirrhosis

REVEAL-HBV Chen et al JAMA 2006

Tenofovir Cost Improvement



Source: MSF Campaign for Access

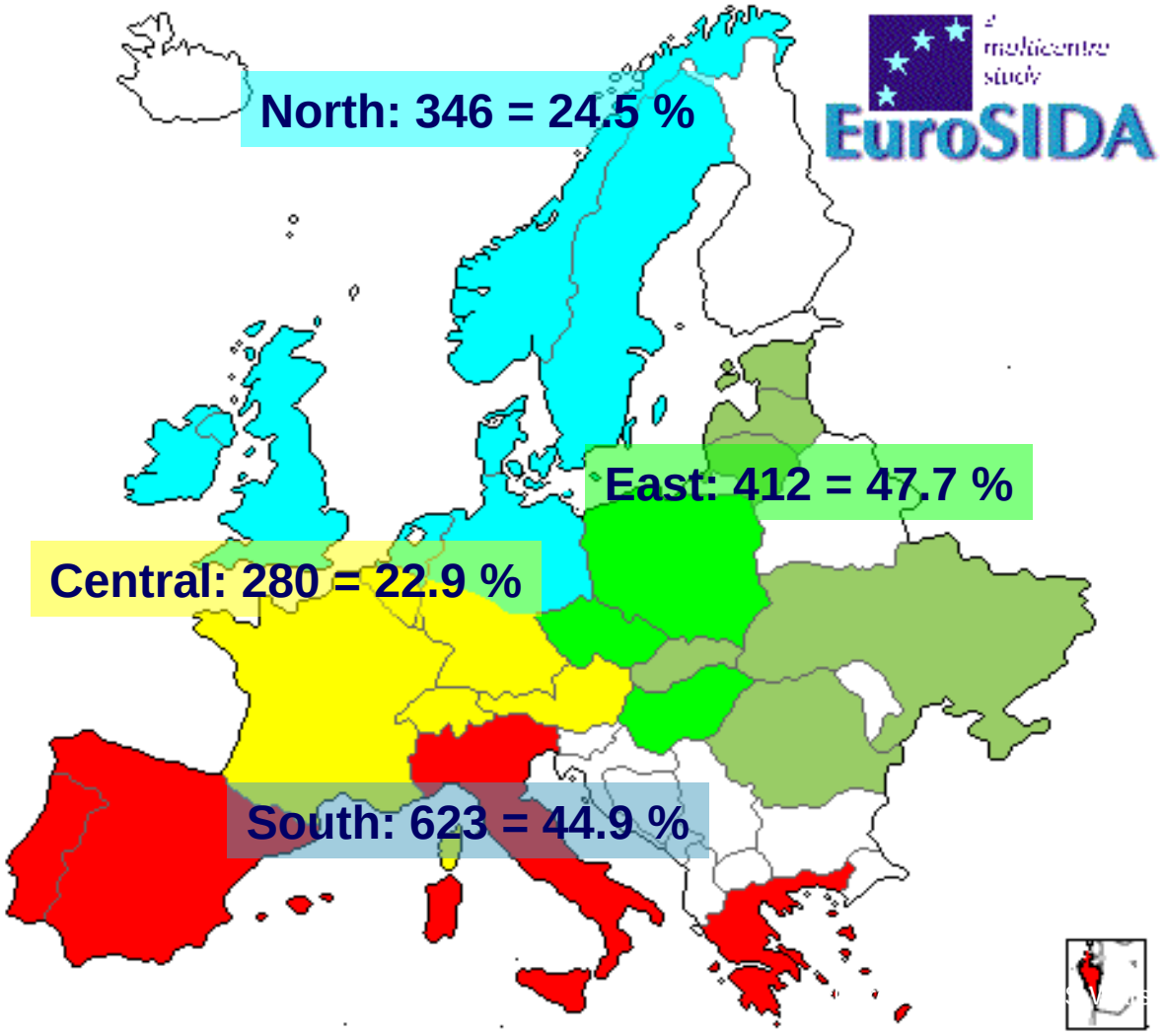
HCC in HIV+ patients

- Younger than HIV- patients (52 vs. 64yrs)
- More often with HCV and HBV (97% vs. 73%, $p<0.001$),
- HCC developed faster in HCV/HIV cf. HCV (26 vs. 34 yrs)
- Higher median AFPs
- Similar median survivals

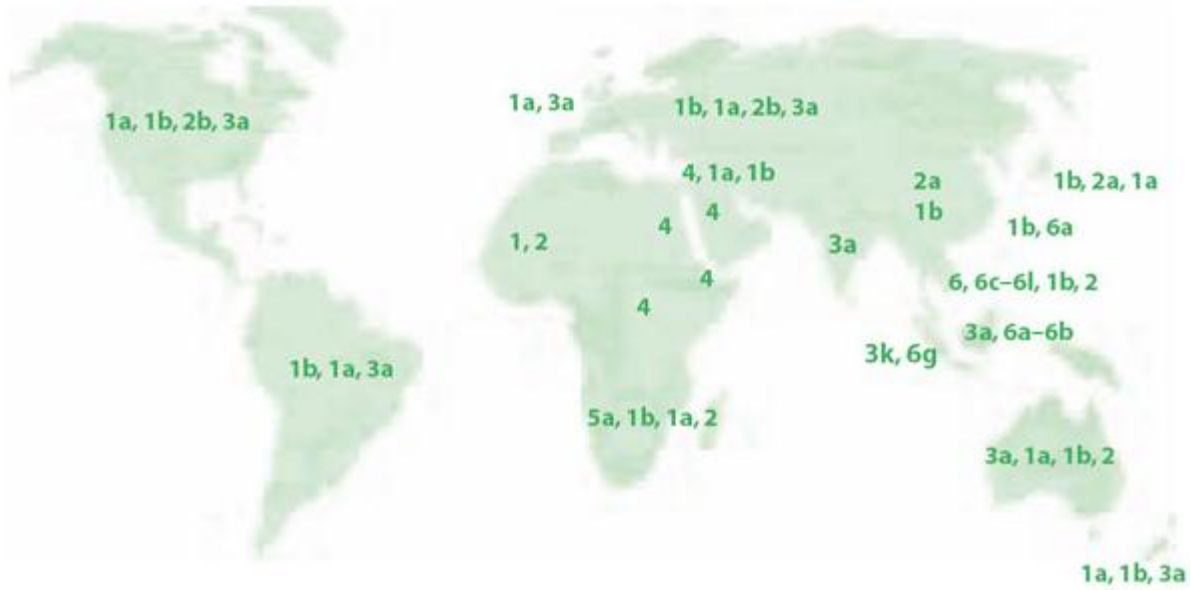
Brau et al. J Hepatology 2007

HCV in co-infected patients

Prevalence of Hepatitis C/HIV Co-infection in Europe (1685/4957 patients = 33.9%)



HCV Genotypes



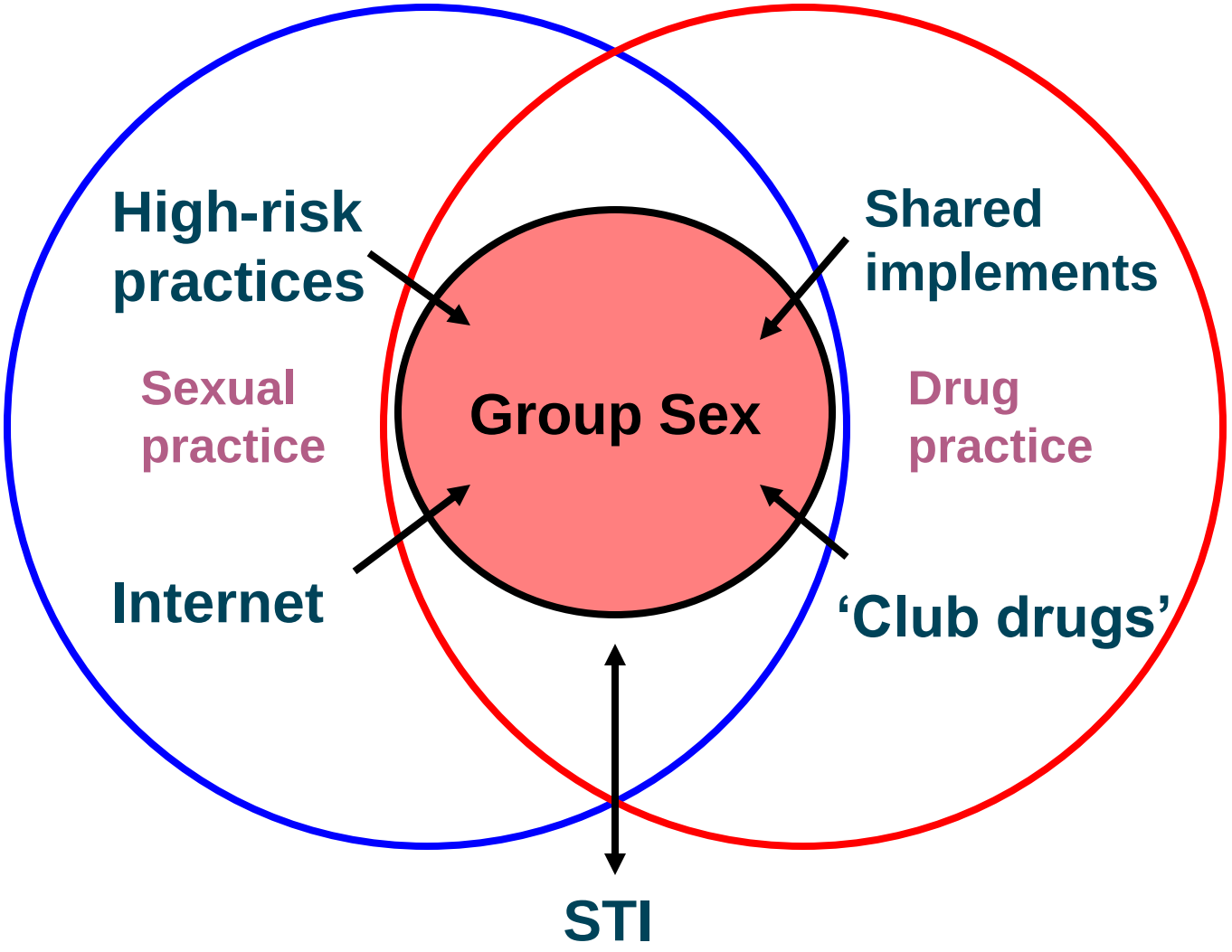
- At least 6 distinct HCV genotypes identified
- It is possible to be infected with 2 genotypes, but rare.
- Genotypes 2 & 3 are almost three times more likely than genotype 1 to respond to combination therapy
- Genotypes 2 and 3 may only require 24-week course of combination treatment, whereas for patients with genotype 1, a 48-week course is recommended.

Acute HCV in MSM

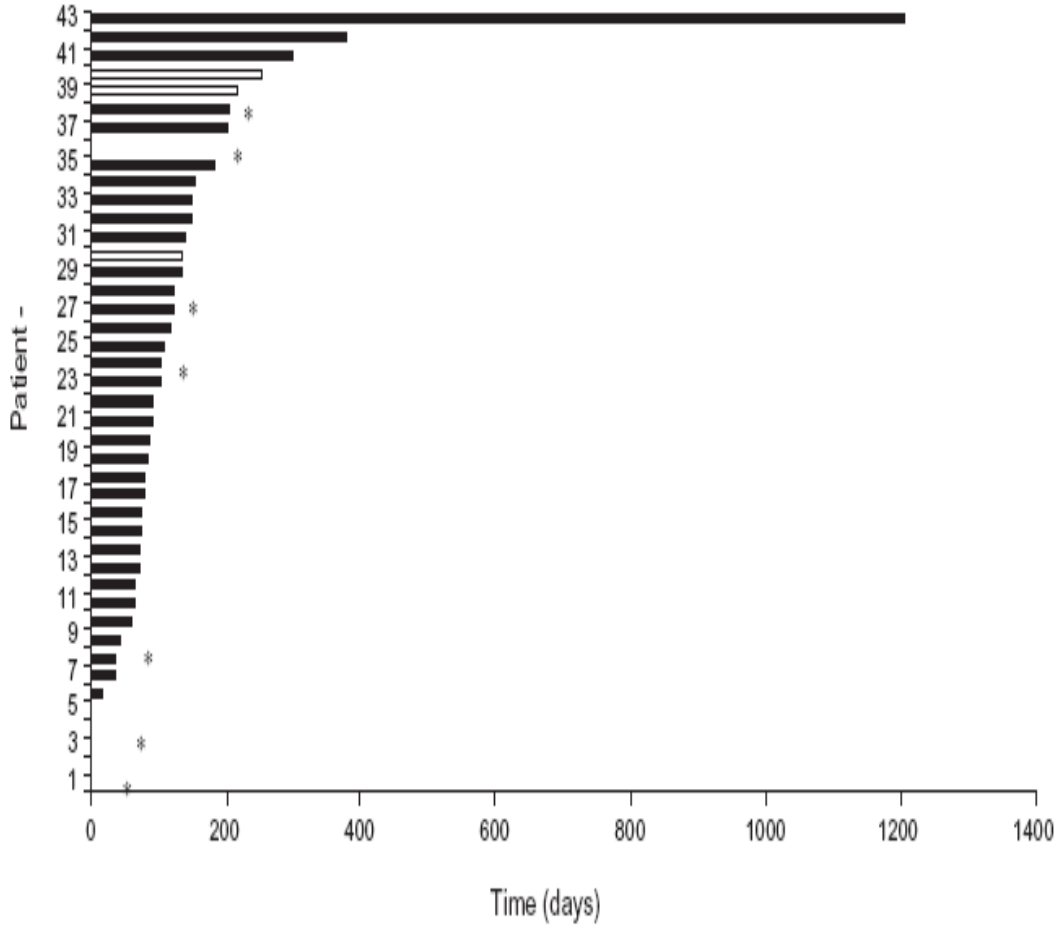
- Rise in acute HCV in HIV positive MSM has been reported in Western European countries, North America and Australia
- European network identified
- Higher-risk behaviour, concurrent sexually transmitted infections, drug use
- Good responses to treatment with pegylated interferon/ ribavirin in the acute phase

Gambotti L et al. *Euro Surveill* 2005;10:969–74.

Risk Factors for Acute HCV in MSM



HCV-seroconversion delayed

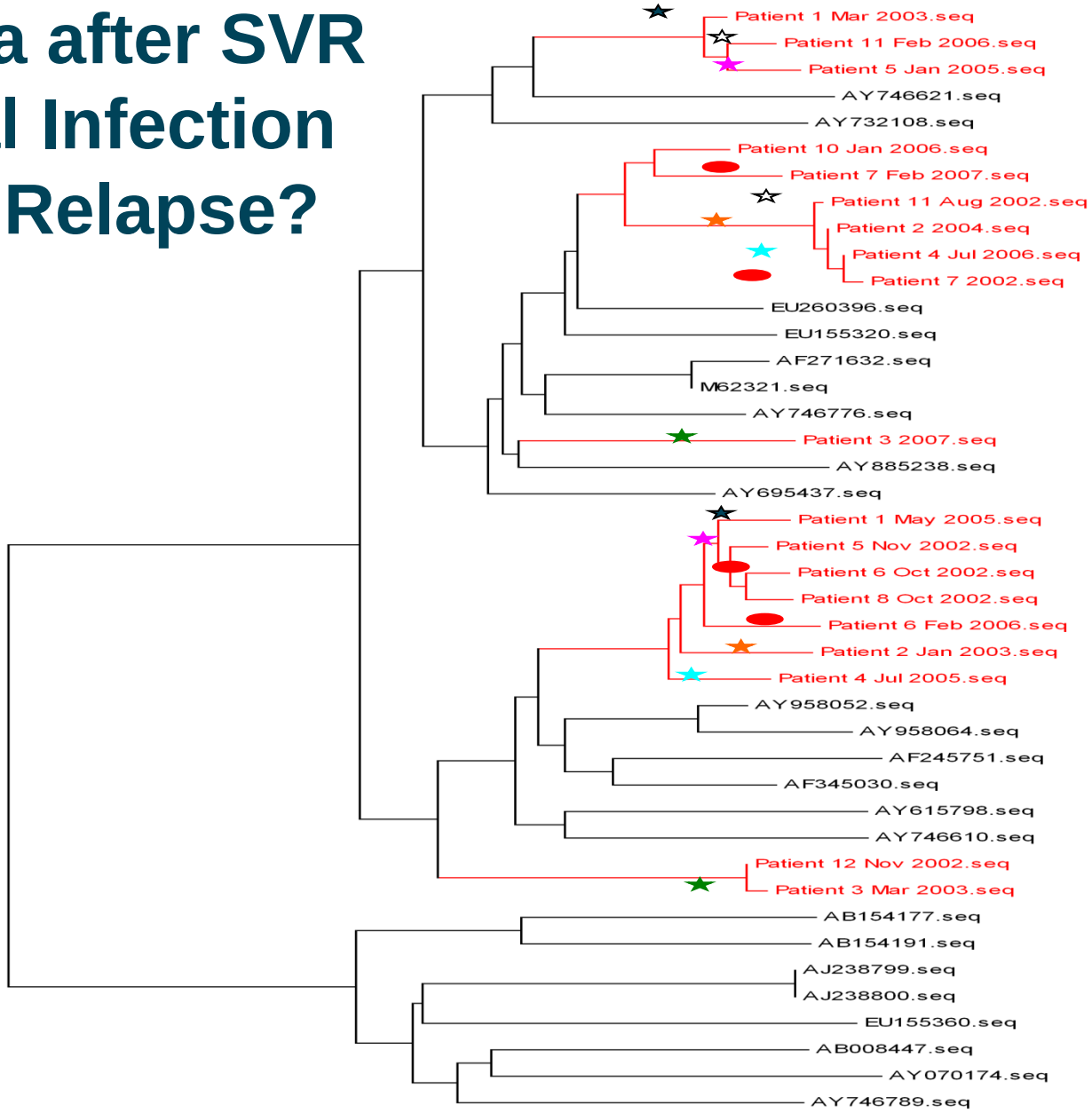


- Median time from HCV RNA to Ab(+) = 91 days (0-1206)
- 10% Ab(-) after 9 months
- 5% Ab(-) after 12 months
- Low ALT/low nadir CD4 associated with delayed/null AB response

Thomson E, et al. AIDS 2009; 23: 89-93

Is HCV Viraemia after SVR Following Initial Infection Re-infection or Relapse?

Phylogenetic Tree Constructed from Analysis of Paired Samples (red) Compared with Genebank Samples (black)



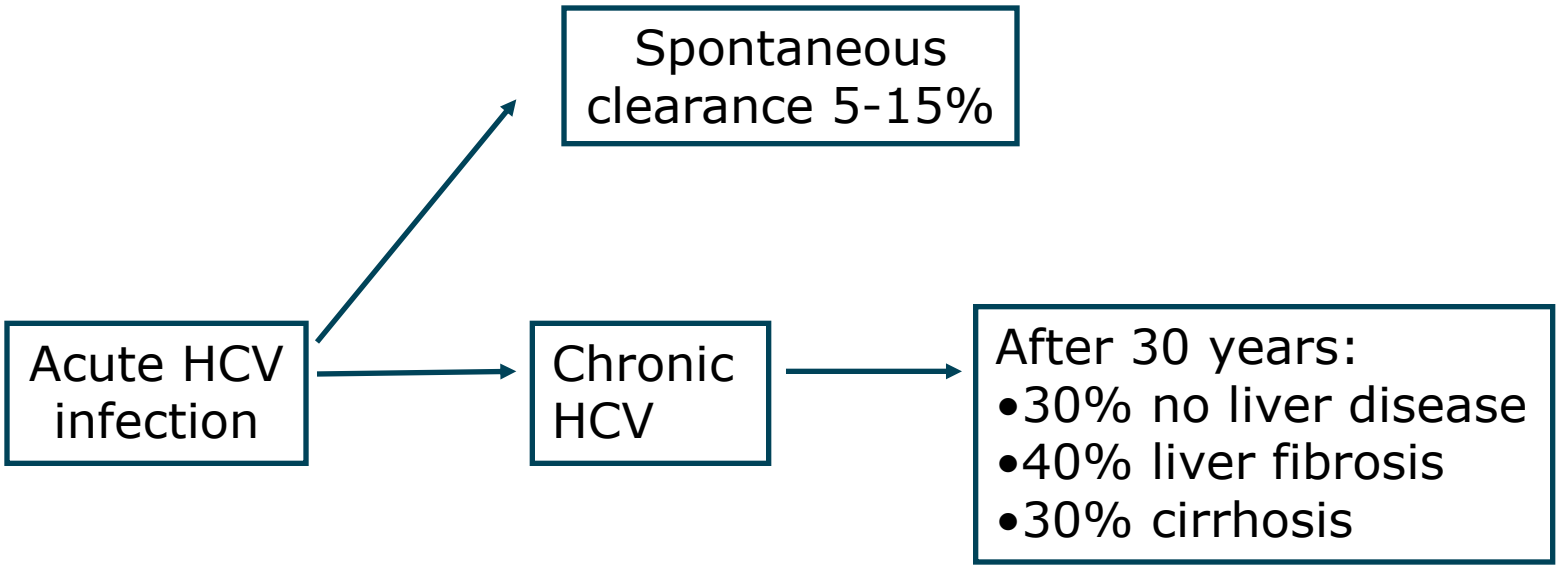
Jones et al. CROI 2008;Oral Abstract 64LB.

Spontaneous clearance of HCV in HIV-infected MSM – European Collaborative study

- 150 patients with acute HCV (median CD4 550)
- 23 (15%) HCV RNA negative by week 12
  - Associated with absolute CD4 count, baseline HCV RNA and peak ALT
- However…
  - 18 reverted back to HCV RNA+ after week 12
  - ONLY 5 (3%) remained HCV RNA neg after 48 weeks

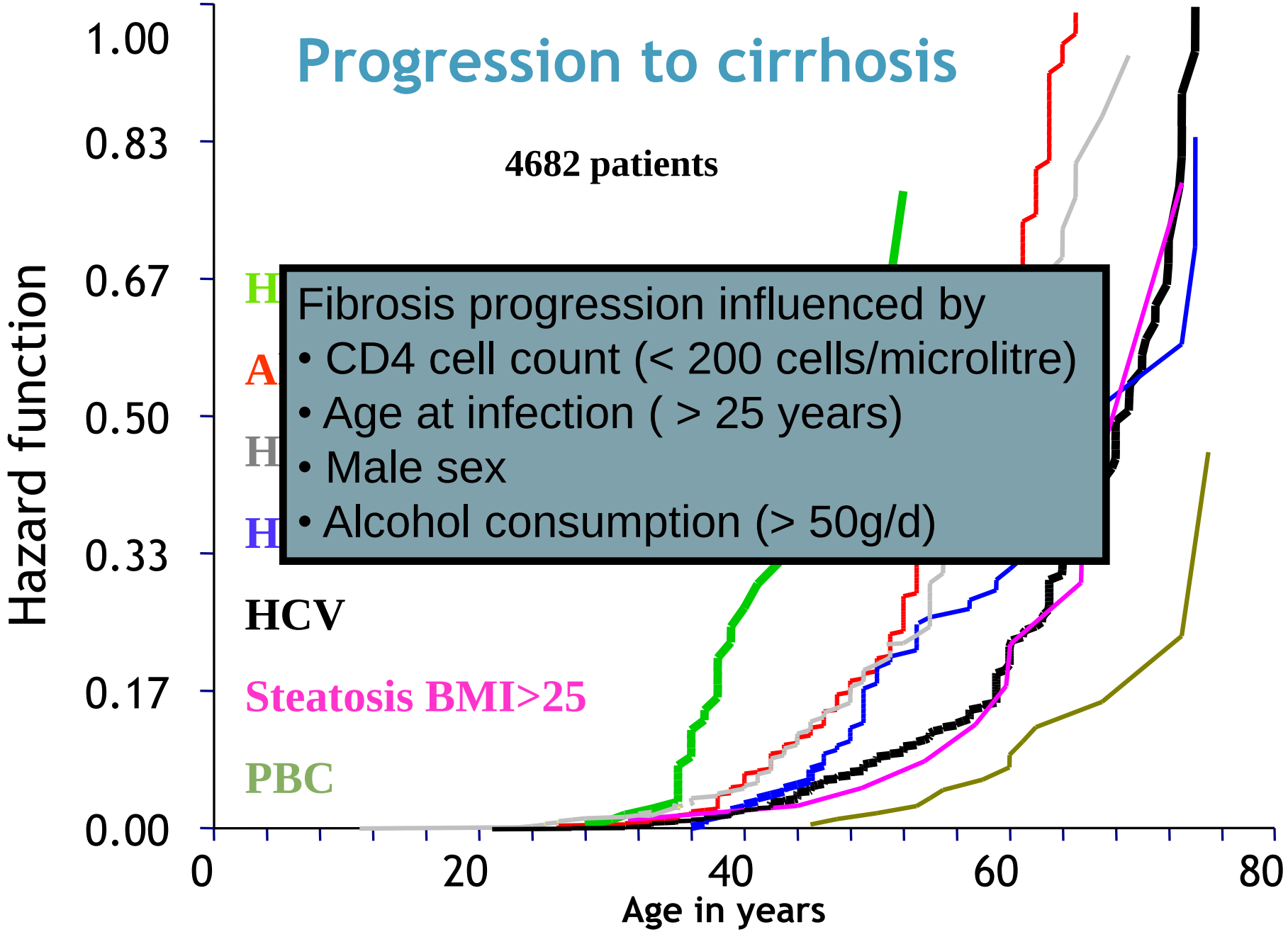
Aswad A, et al. EACS Conference 2007.

Natural history



Major risk factors for disease progression

- Male
- Older age at acquisition
- Alcohol



Poynard, T. et al., (2003) A comparison of fibrosis progression in chronic liver disease. *Journal of Hepatology* 38:257-265

Key components of Chronic HCV management

A Attention to alcohol intake

B Screening for previous/chronic hepatitis B and previous hepatitis A
➡ immunization in non-immunes

C Aim to clear HCV in order to improve quality of life and reduce risk of cirrhosis and HCC
➡ consider combination antiviral treatment with pegylated interferon + ribavirin

D Drug use – not a contraindication to treatment but need specialist service involvement

Main reasons to treat chronic HCV in HIV-infected patients

- Faster progression to liver cirrhosis
- Increased mortality due to end stage liver disease
- Higher risk of hepatotoxicity following treatment with ART drugs

Patient Evaluation

Does the patient need treatment now?

Is the patient ready for treatment?

Is it safe to treat this person?

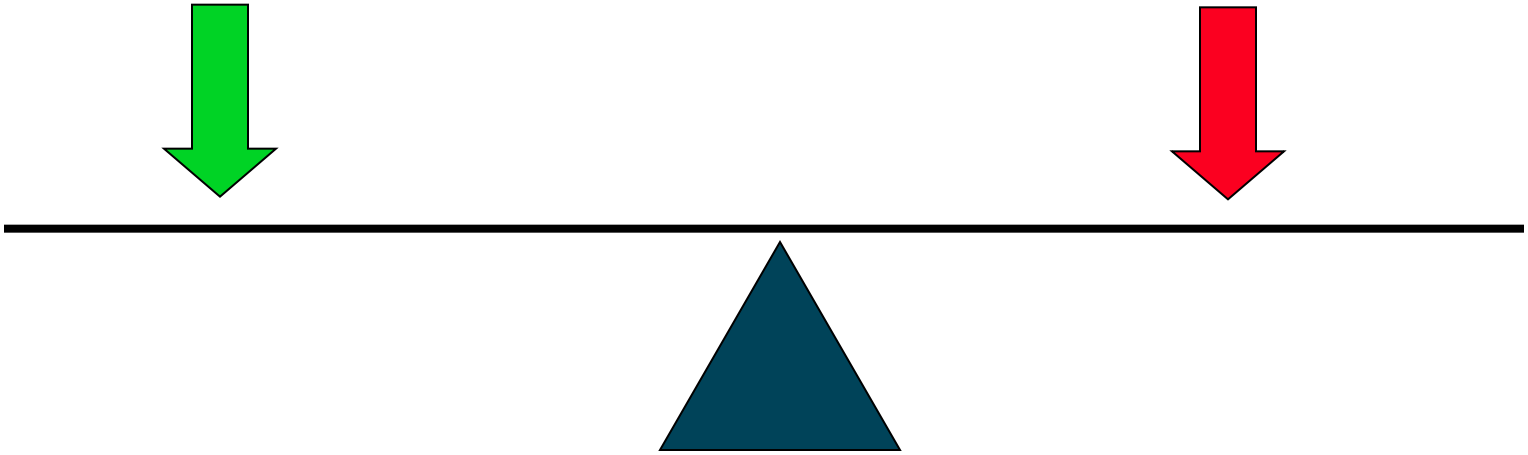
Will the benefits outweigh the risks?

Do we have time to wait for access to better drugs?

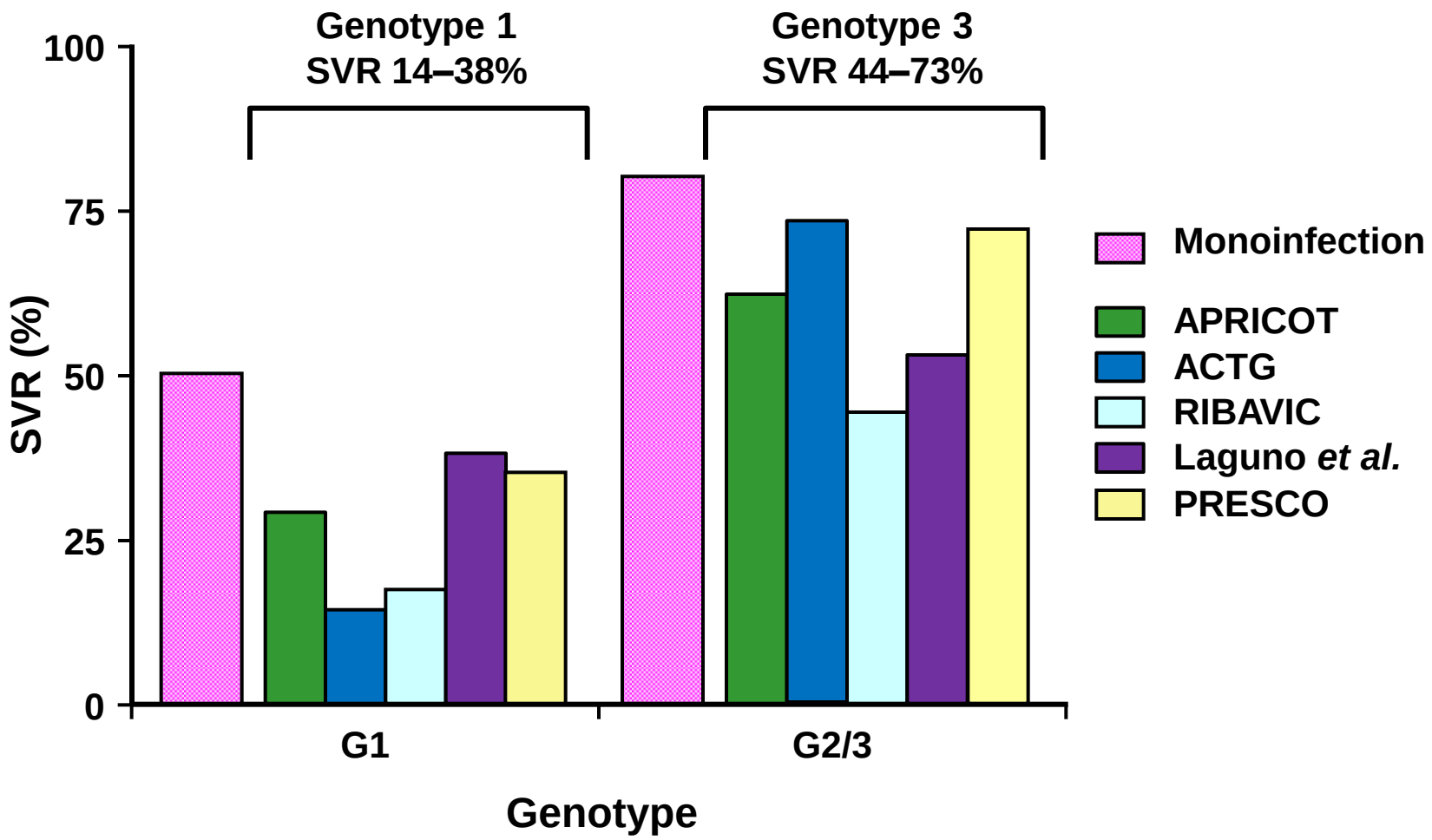
Patients not populations

Chance of cure (SVR)
Improve quality of life
Prevent cirrhosis/HCC
Prevent transmission

Chance of failure (no SVR)
Serious adverse effects of Rx
Quality of life during Rx
May have low risk of disease complications
New treatments - sometime…



HCV/HIV treatment outcomes with pegIFN and Ribavirin



Fried et al, NEJM 2002, 347: 975-982, Torriani et al, NEJM 2004; 351: 438-50, Chung R, et al, NEJM 2004: 351; 451-9, Carrat F, et al, JAMA 2004: 292: 2839-42, Laguno et al, AIDS 2004; 18: F27-F36, Nunez et al, JAIDS 2007: 45: 439-44

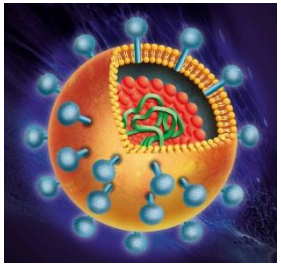
Baseline factors negatively associated with SVR

HCV virus

- Genotypes 1 & 4 (vs. 2 & 3)
- High HCV viral load (>400,000 IU/ml)

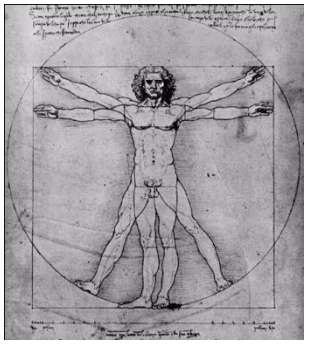
HIV

Low CD4 %

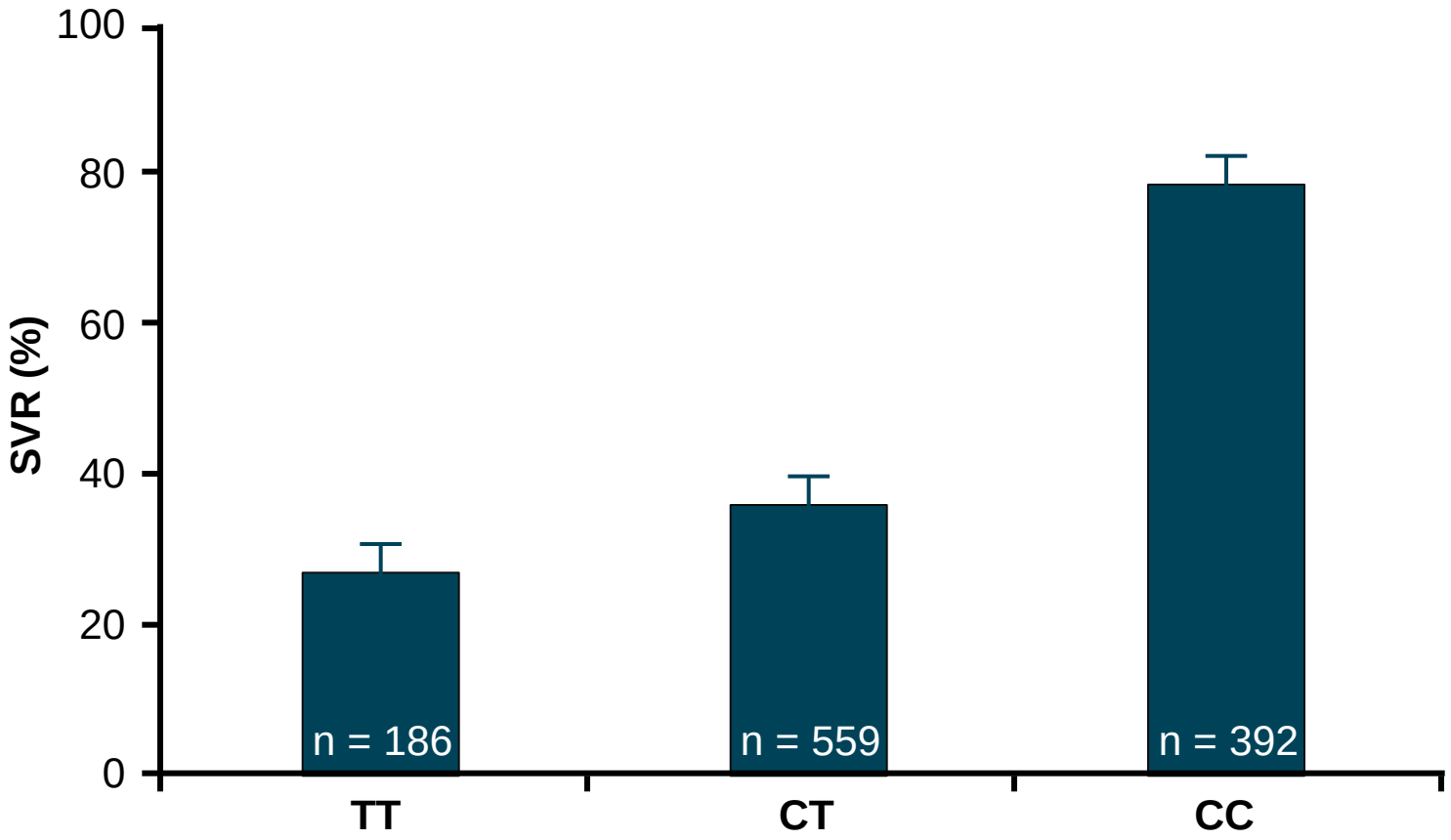


Patient

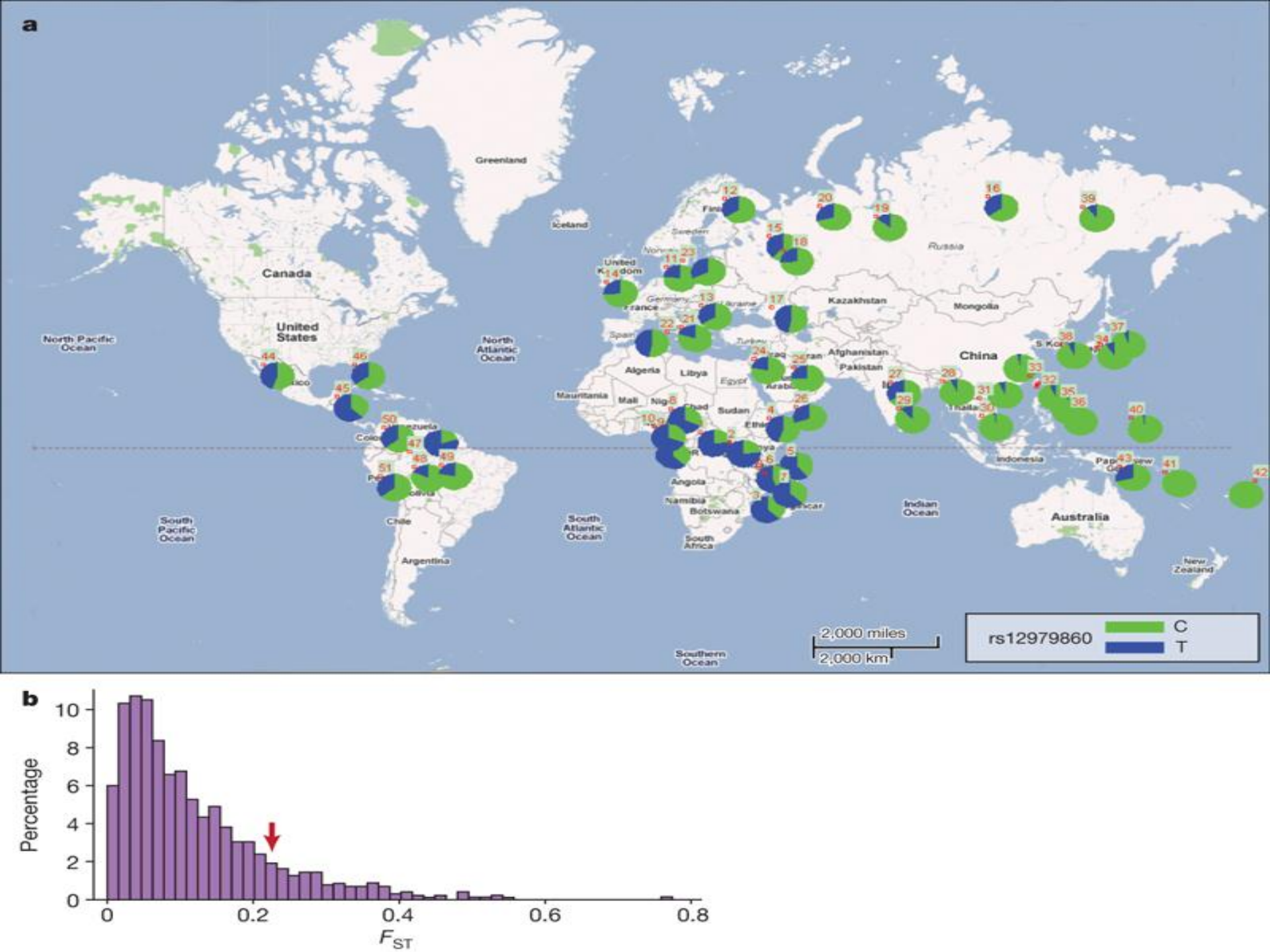
- Older age
- More advanced liver fibrosis (cirrhosis)
- Male sex
- High BMI/Insulin resistance
- Hepatic steatosis
- Alcohol
- IL-28B status



IDEAL Trial: SVR Rates According to IL28B SNP rs12979860 (chromosome 19)



Ge D, et al. Nature. 2009;461:399-401.


a
Greenland
Iceland
Canada
United States
North Pacific Ocean
North Atlantic Ocean
South Pacific Ocean
South Atlantic Ocean
Indian Ocean
Southern Ocean
Russia
Kazakhstan
Mongolia
China
Afghanistan
Pakistan
Algeria
Libya
Egypt
Mauritania
Mali
Chad
Sudan
Angola
Namibia
Botswana
South Africa
Australia
Indonesia
New Zealand
Chile
Argentina
2,000 miles
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rs12979860
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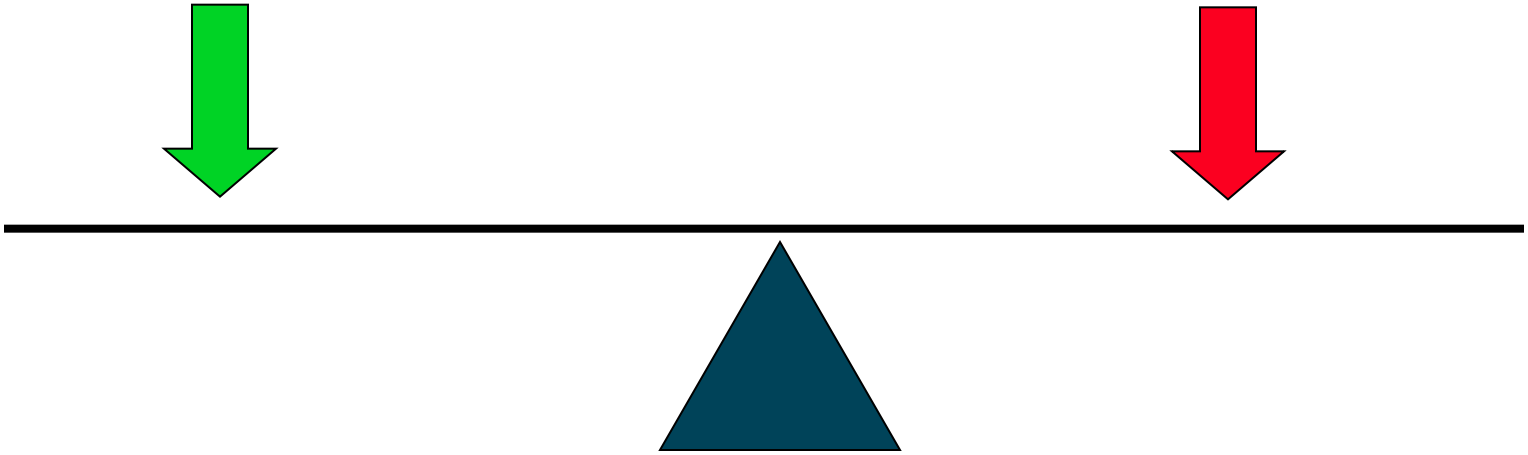
Percentage
0
2
4
6
8
10
0
0.2
0.4
0.6
0.8
F_{ST}

Patients not populations

Chance of cure (SVR)
Improve quality of life
Prevent cirrhosis/HCC
Prevent transmission

Chance of failure (no SVR)
Serious adverse effects of Rx
Quality of life during Rx
May have low risk of disease complications
New treatments - sometime…



Pegylated interferon	Ribavirin
Once weekly subcutaneous	Oral
Immune activation	Antiviral

Major adverse effects of antiviral therapy

Pegylated interferon

- neutropaenia
- thrombocytopaenia
- ‘flu-like symptoms
- depression, suicidal ideation
- irritability
- insomnia
- anorexia
- myocardial dysfunction
- hair loss
- skin rashes
- thyroid dysfunction

Ribavirin

- haemolytic anaemia
- rash
- birth defects

Probable contraindications to pIFN/Rib treatment

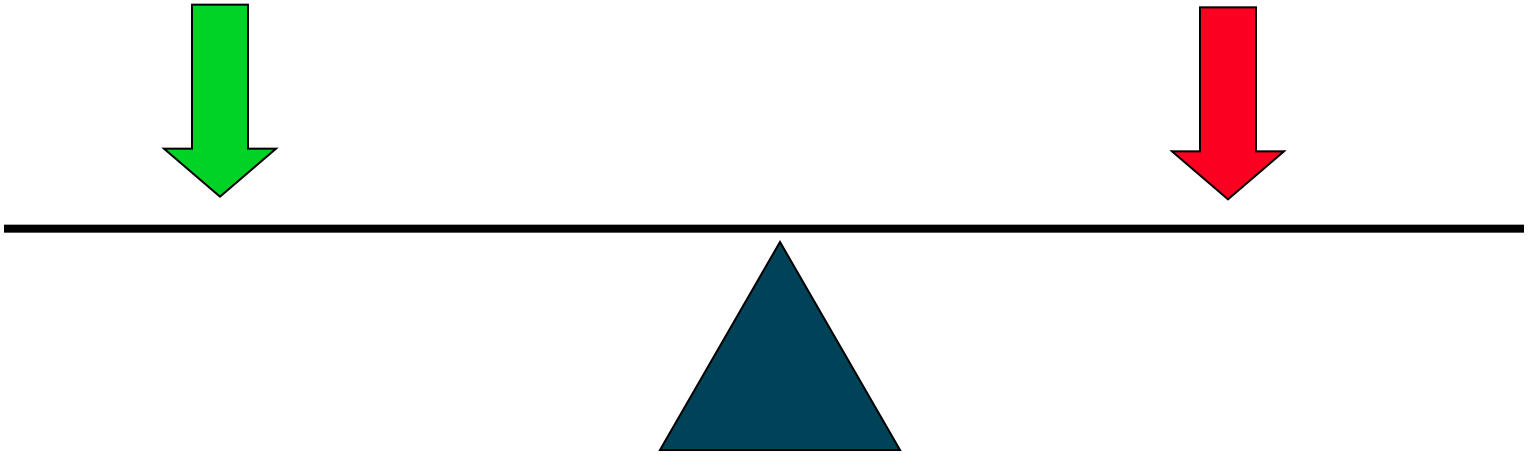
- Advanced cirrhosis
- Severe depression/psychiatric disorder
- Thyroid disease, untreated
- Severe autoimmune diseases
- Unstable alcohol/drug dependency

- Pregnancy

Patients not populations

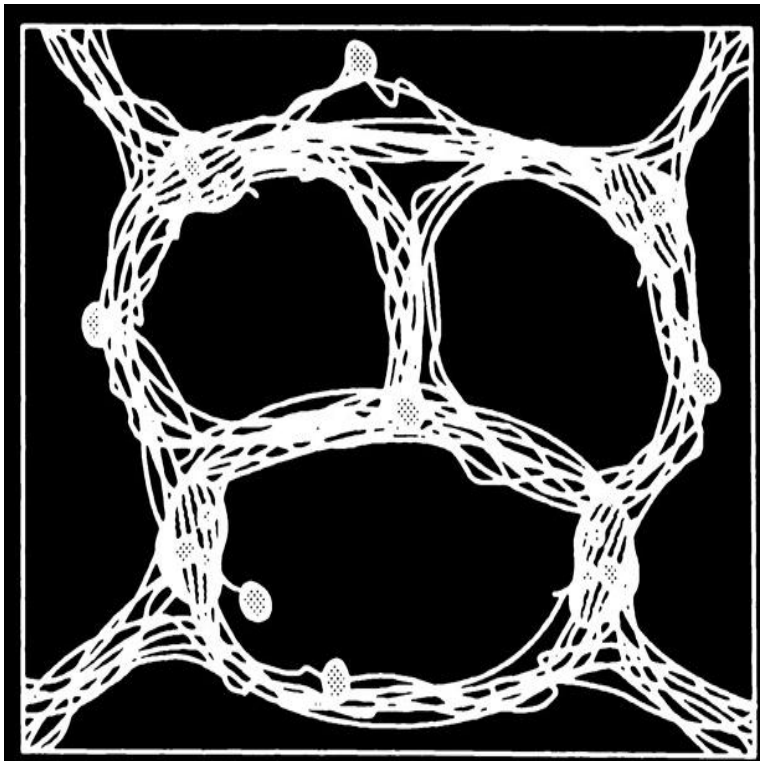
Chance of cure (SVR)
Improve quality of life
Prevent cirrhosis/HCC
Prevent transmission

Chance of failure (no SVR)
Serious adverse effects of Rx
Quality of life during Rx
May have low risk of disease complications
New treatments - sometime…



Progression of fibrosis in chronic viral hepatitis

Chronic liver injury → Necroinflammatory changes with progressive fibrosis → Cirrhosis



CIRRHOSIS

Fibrosis Stage

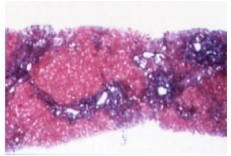
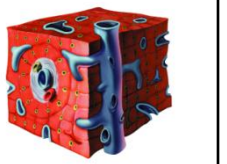
Symptoms

Staging of fibrosis in chronic viral hepatitis

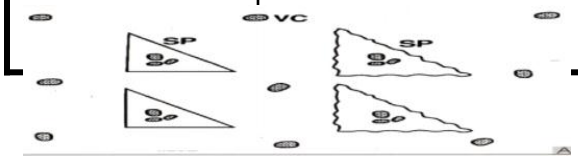
Definition	No Fibrosis	Fibrous Portal Expansion	Few Bridges or Septa	Numerous Bridges or Septa	Cirrhosis
IASL	No Fibrosis	Mild Fibrosis	Moderate Fibrosis	Severe Fibrosis	Cirrhosis
Metavir	F0	F1	F2	F3	F4

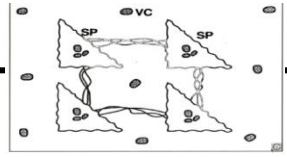


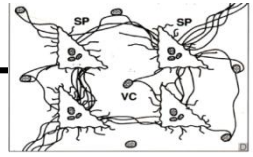


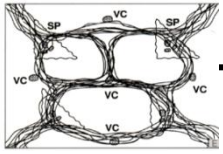







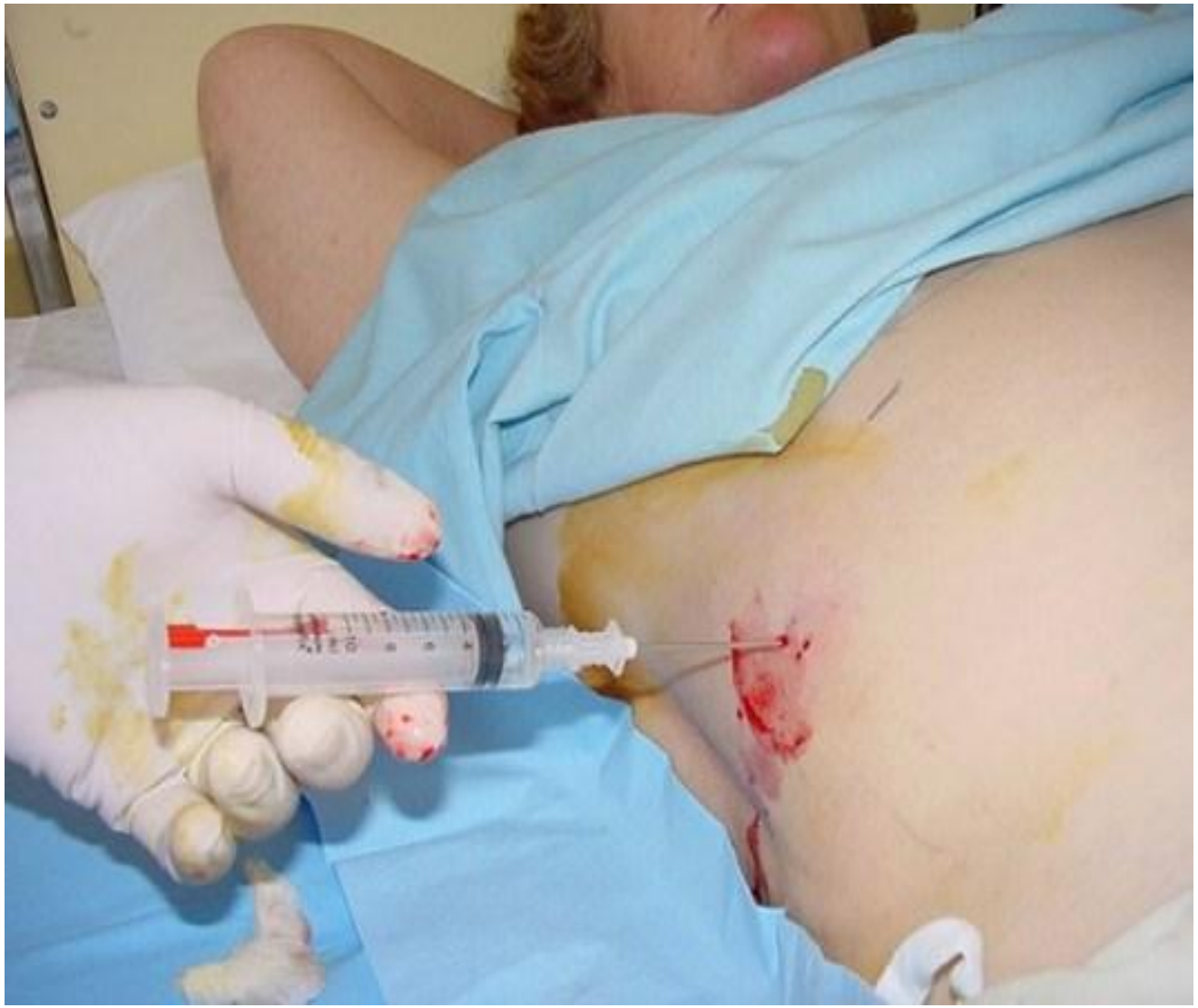






Goodman Z et al. J Hepatol 2007;47:598-607

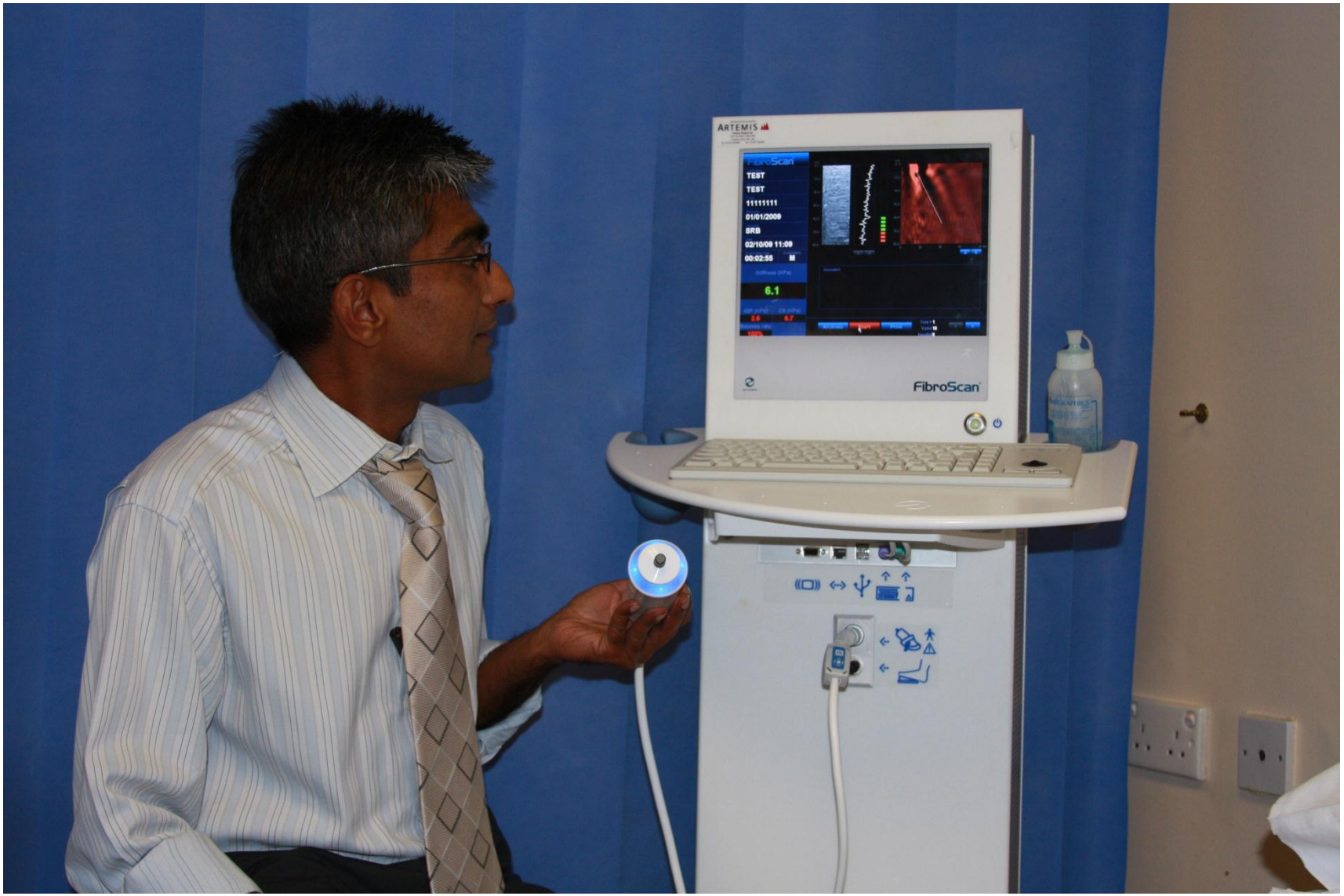
Liver biopsy

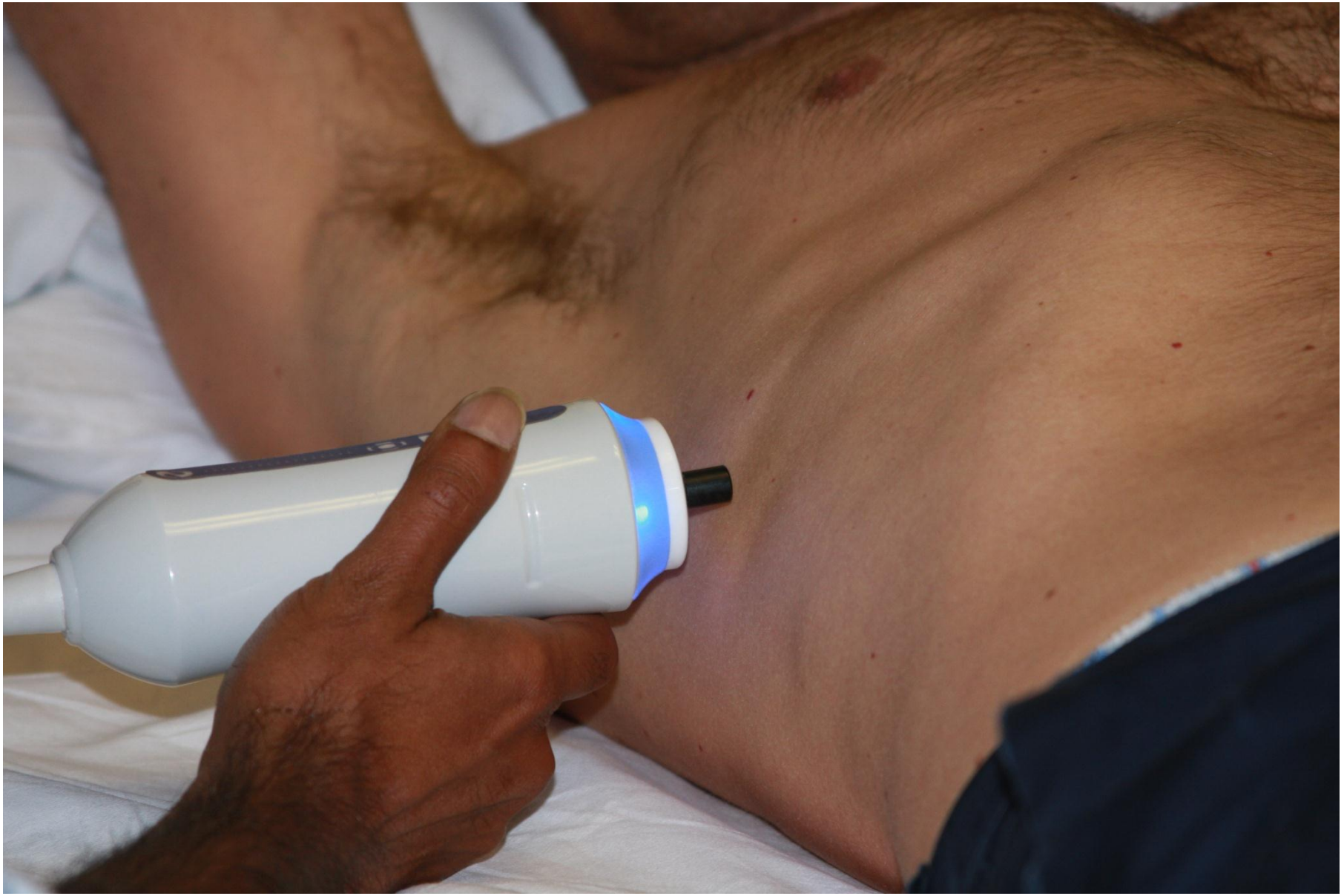


Currently available blood test panels

- Fibrotest
- Fibrospect II
- SHASTA index
- Forns
- APRI
- European Liver Fibrosis (ELF) Score
- PGA index
- Hepascore
- FPI (incorporates insulin resistance)
- FIB-4 (APRICOT)

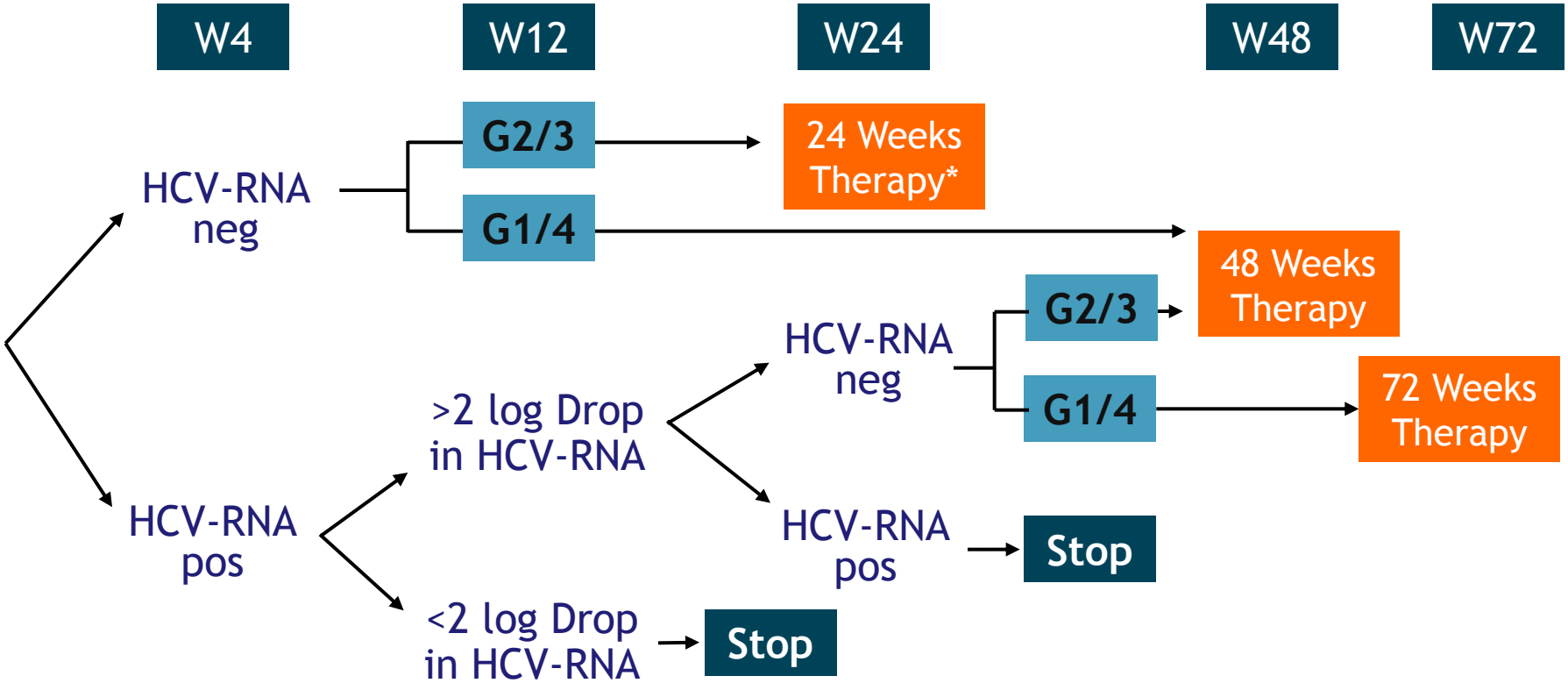
Transient elastography (Fibroscan®, Echosens, Paris)





Anti-HIV agent	Anti-HCV agent	Reason for concern	Recommendation
Abacavir	Ribavirin	Reduced intracellular ribavirin levels ? leading to impaired anti-HCV therapy	Possibly avoid concomitant use
Atazanavir	Interferon/ribavirin	Increased hyperbilirubinaemia	Observe
Didanosine	Ribavirin	Significant toxicity; fatal lactic acidosis	**Absolute contraindication**
Efavirenz	Interferon	Increased CNS disturbance	Close observation and individualised case management
Stavudine	Ribavarin	Significant mitochondrial toxicity	Avoid if possible
Zidovudine	Interferon/ribavirin	Increased myleosuppression	Avoid if possible

Proposed optimal duration of HCV therapy in HCV/HIV-coinfected patients

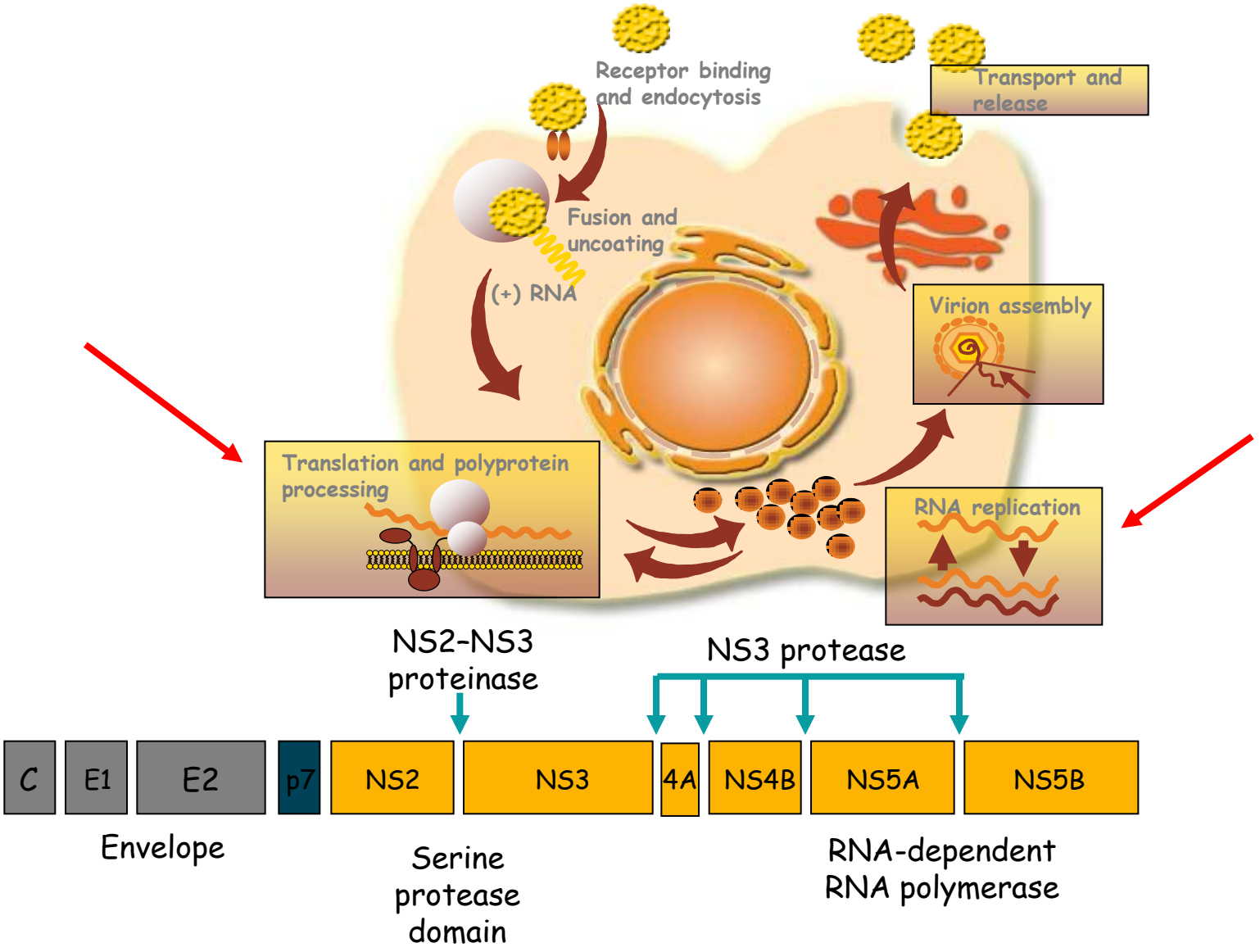


***In patients with baseline low viral load and minimal liver fibrosis.**

1. *J Rockstroh et al. European Aids Clinical Society (EACS) Guidelines for The Clinical Management and Treatment of Chronic Hepatitis B And C Coinfection In Hiv-infected Adults. Hiv Med. 2008;9:82-8.*

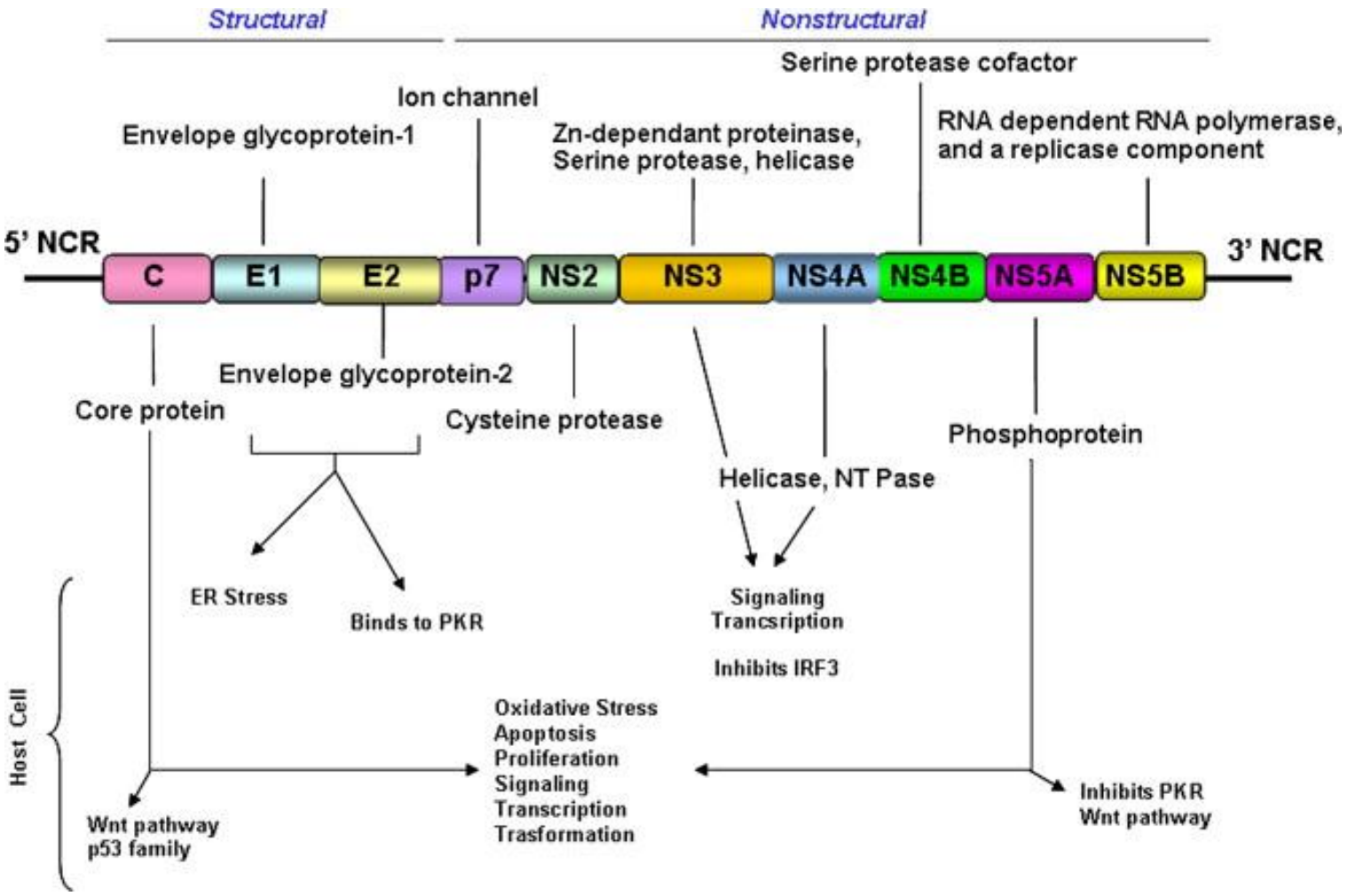
New drugs for HCV

HCV lifecycle provides multiple targets for new drugs



1. Lindenbach BD & Rice CM. Unravelling hepatitis C virus replication from genome to function. *Nature* 2005;436:933-938

HCV virus


Structural
Nonstructural
Serine protease cofactor
Ion channel
Envelope glycoprotein-1
Zn-dependant proteinase, Serine protease, helicase
RNA dependent RNA polymerase, and a replicase component
5' NCR
C
E1
E2
p7
NS2
NS3
NS4A
NS4B
NS5A
NS5B
3' NCR
Envelope glycoprotein-2
Core protein
Cysteine protease
Phosphoprotein
Helicase, NT Pase
ER Stress
Binds to PKR
Signaling Trancsription
Inhibits IRF3
Host Cell
Oxidative Stress
Apoptosis
Proliferation
Signaling
Transcription
Trasformation
Wnt pathway
p53 family
Inhibits PKR
Wnt pathway

Drugs in development

Drug	Mechanism	Company	GT	R&D	Phase 1	Phase 2	Phase 3	NDA	Co-infection
Telaprevir	NS3/4a ProtI	J&J/Tibotec	1				ADVANCE ILLUMINATE		Starting
Boceprevir	NS3/4a ProtI	Merck	1				SPRINT-2 RESPOND-2		Underway
BI 201335	NS3/4a ProtI	J&J/Tibotec				SILEN-C1/2/3			Starting
TMC435	NS3/4a ProtI	Medivir/J&J	1			PILLAR ASPIRE DRAGON	QUEST1/2 PROMISE		
INX-189	NS5B	Inhibitex							
Alispore	Cyclophilin	Novartis							
PSI-7977	Polymerase	Pharmasset/Gilead	1-4			ELECTRON ATOMIC PROTON	FISSION NEUTRINO POSITRON		

Issues in HCV drug development

- Toxicity
- Resistance

Toxicity

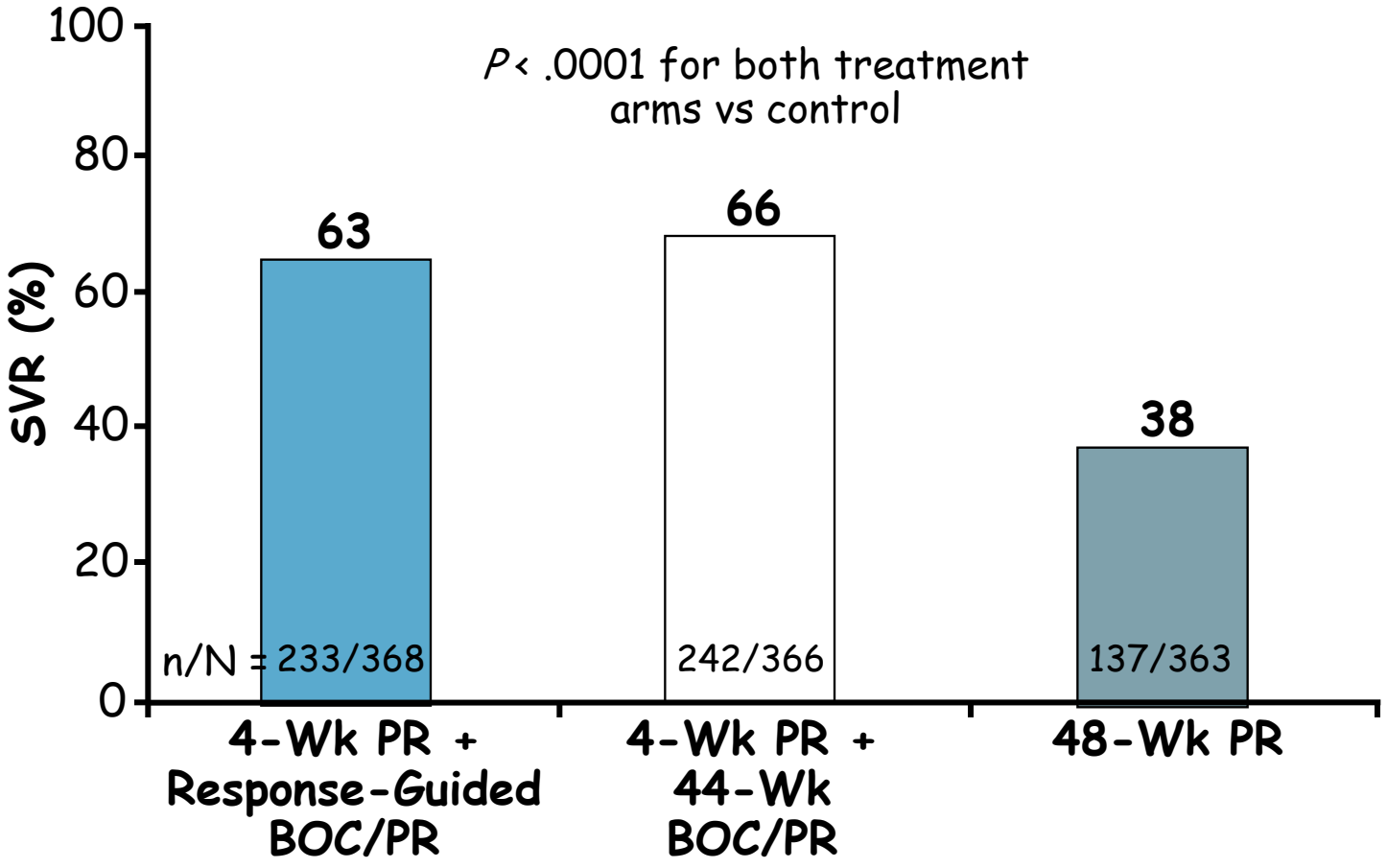
- *Myocardial Toxicity*
- *Gut Toxicity*
- *Nephrotoxic*
- *Hepatotoxic*
- *Severe lymphopenia*

- PI resistance is selected, not generated
- Resistance is cross class
- Questions:
  - How quickly does resistance arise?
  - Is there a sub-type difference?
  - How often and at what level do they pre-exist?
  - How quickly, if ever, do they “disappear” off therapy?

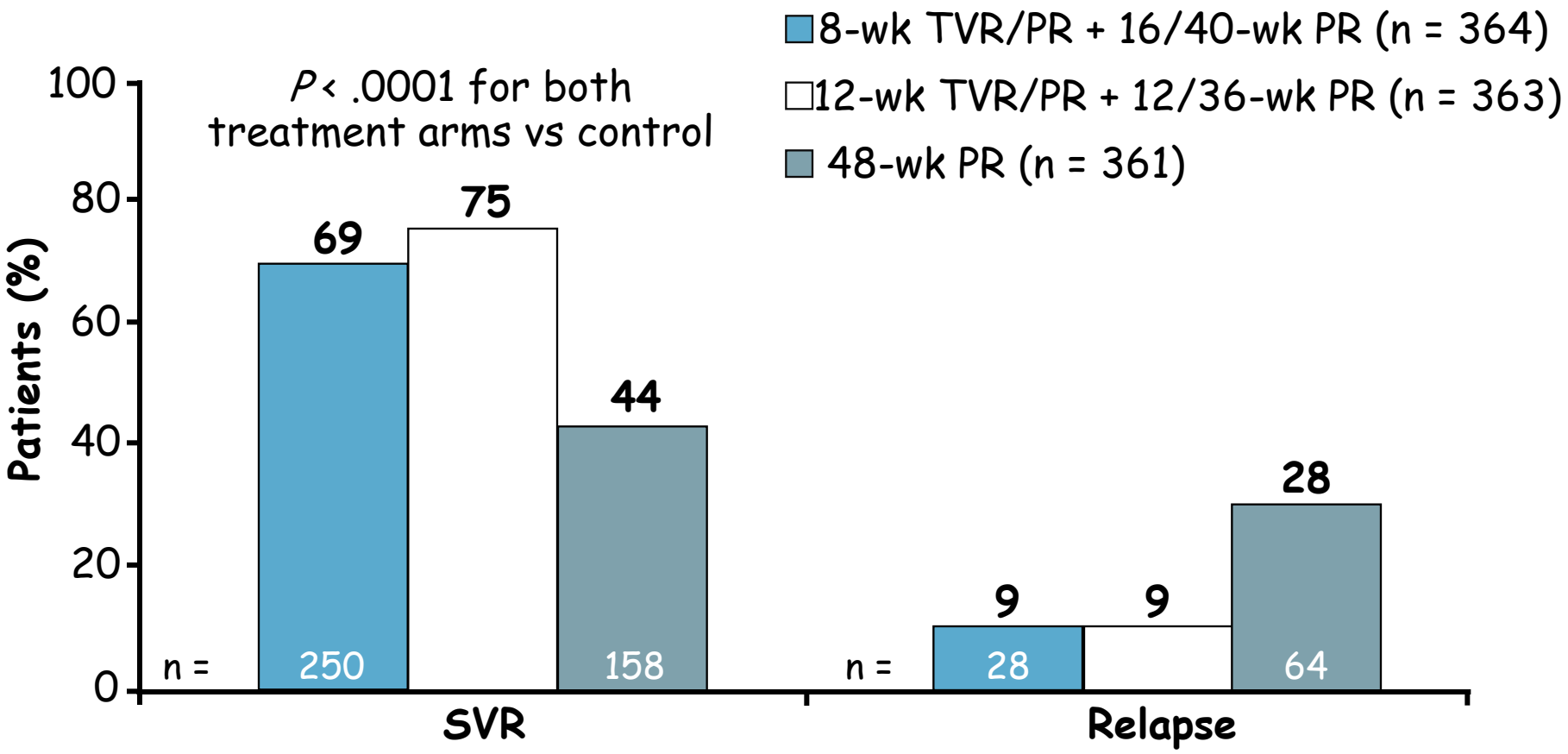
Recently licensed

- Telepravir
- Bocepravir
- Common issues for ALL first generation PIs
  - Activity targeted at Genotype 1 NS3/4
  - Some activity against Genotype 2/4
  - Very little activity against Genotype 3

SPRINT-2: Overall SVR Rates (BOC in Tx Naïve)



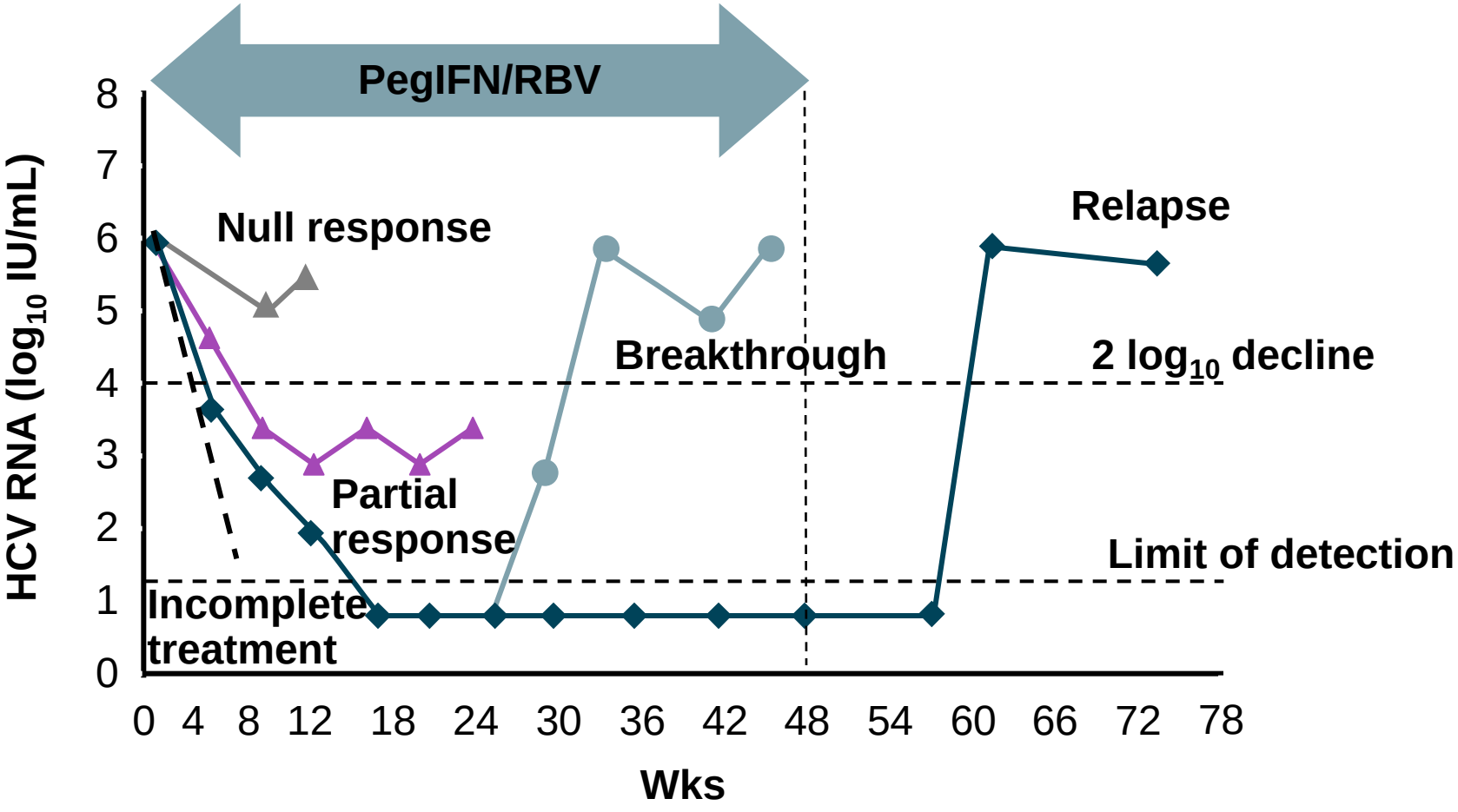
ADVANCE (TVR): Overall SVR and Relapse Rates



Jacobson IM, et al. AASLD 2010. Abstract 211.

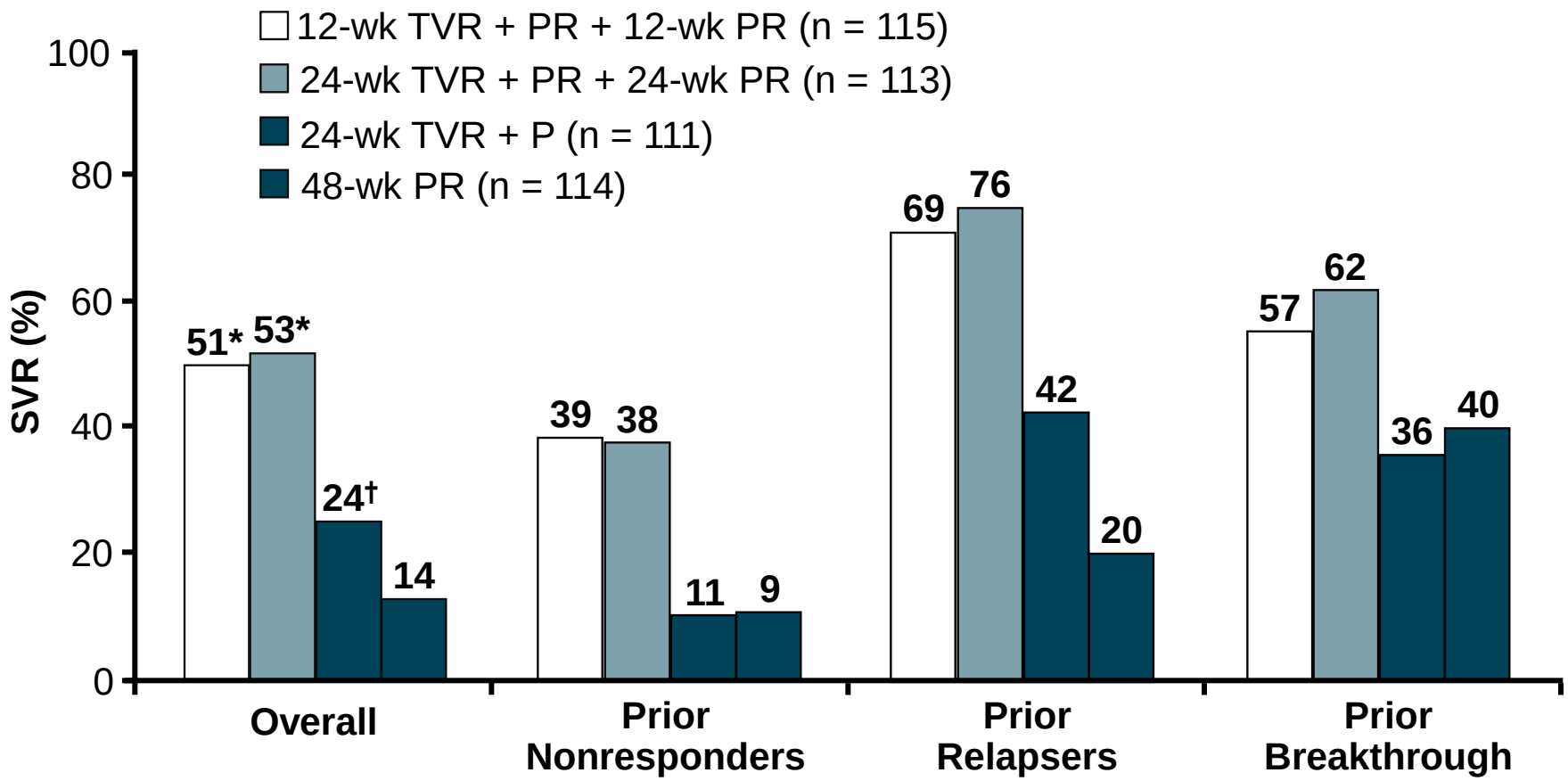
What about PI therapy in patients that have failed prior therapy with PegIFN + Ribavirin

Suboptimal Virologic Responses



McHutchison JG, et al. N Engl J Med. 2009;361:580-593.

PROVE 3 (TVR): SVR Rates According to Prior Response



*P < .001 vs control. †P = .02 vs control.

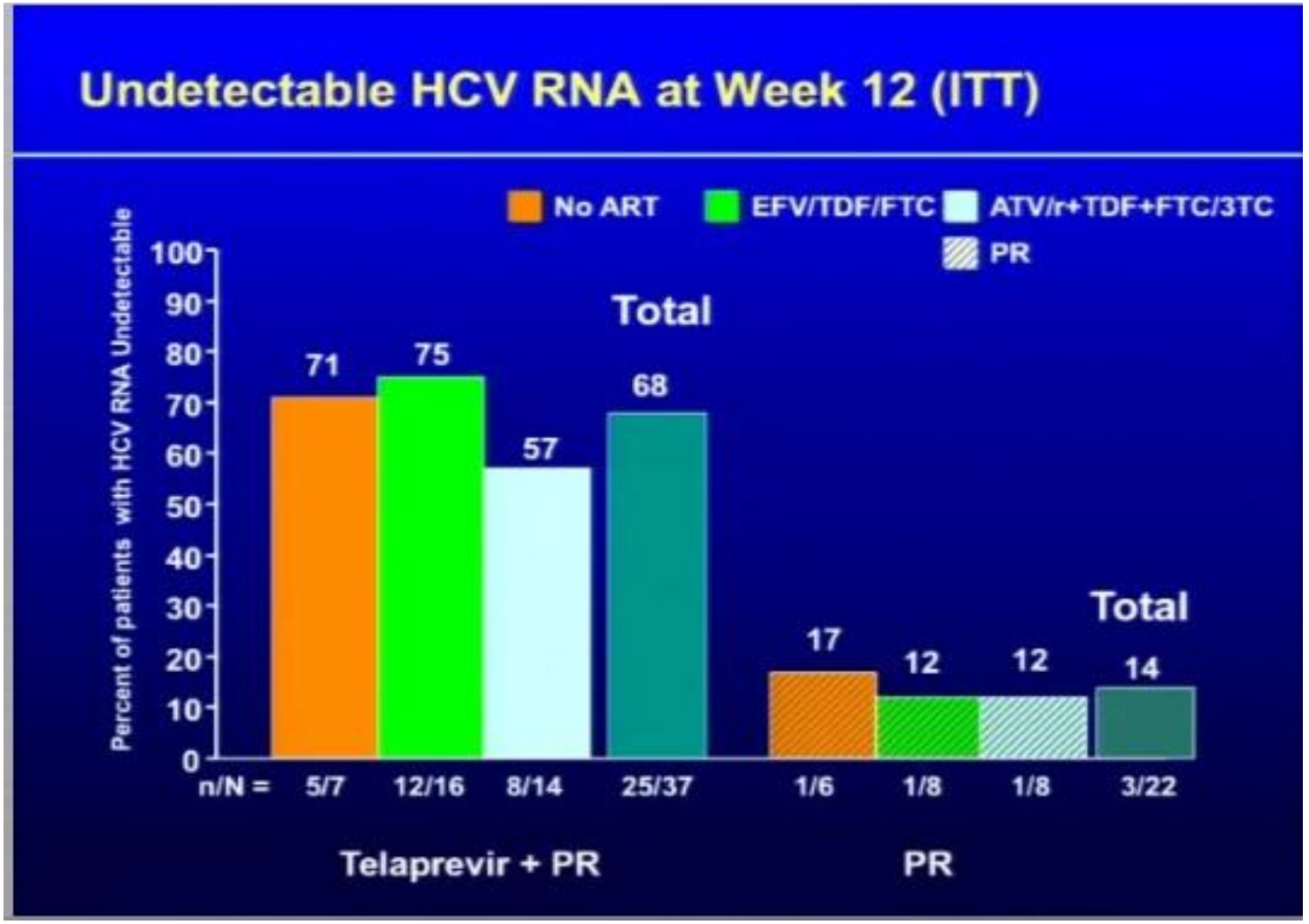
McHutchison JG, et al. N Engl J Med. 2010;362:1292-1303.

Even those still in development have toxicity problems

- Telaprevir – pruritis, nausea, anaemia, skin rash
- Bocepravir - anaemia, dygeusia

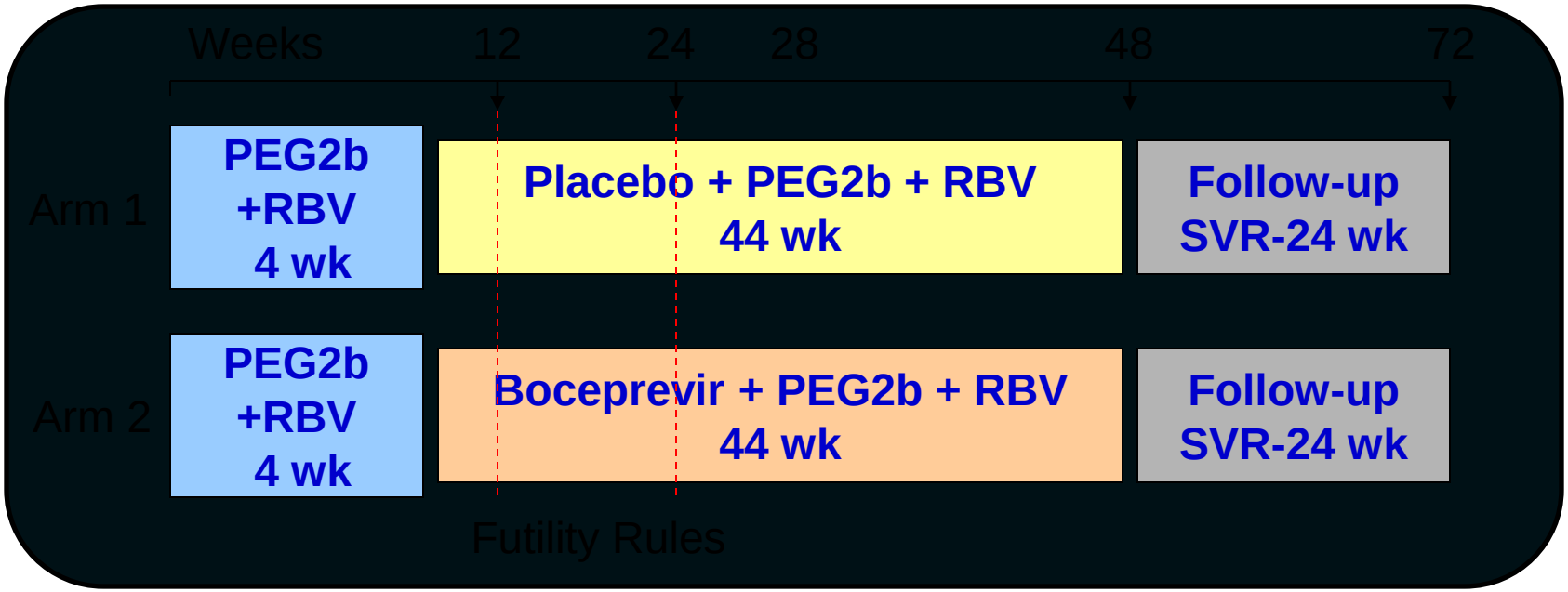
Telaprevir and Boceprevir – next steps

- Little data in patients with highest need
  - HIV/HCV co-infection
  - ESRD
  - Pre/post transplant
- Drug-drug interactions (some data at CROI 2011)
- Predictive value of IL28B
- Risk of mutations
- Long term persistence of resistance variants
- Price
- Access in developing countries



Interim Analysis of a Phase 2a Double-blind Study of TVR in Combination with pegIFNα-2a and RBV in HIV/HCV Co-infected Patients. CROI 2011

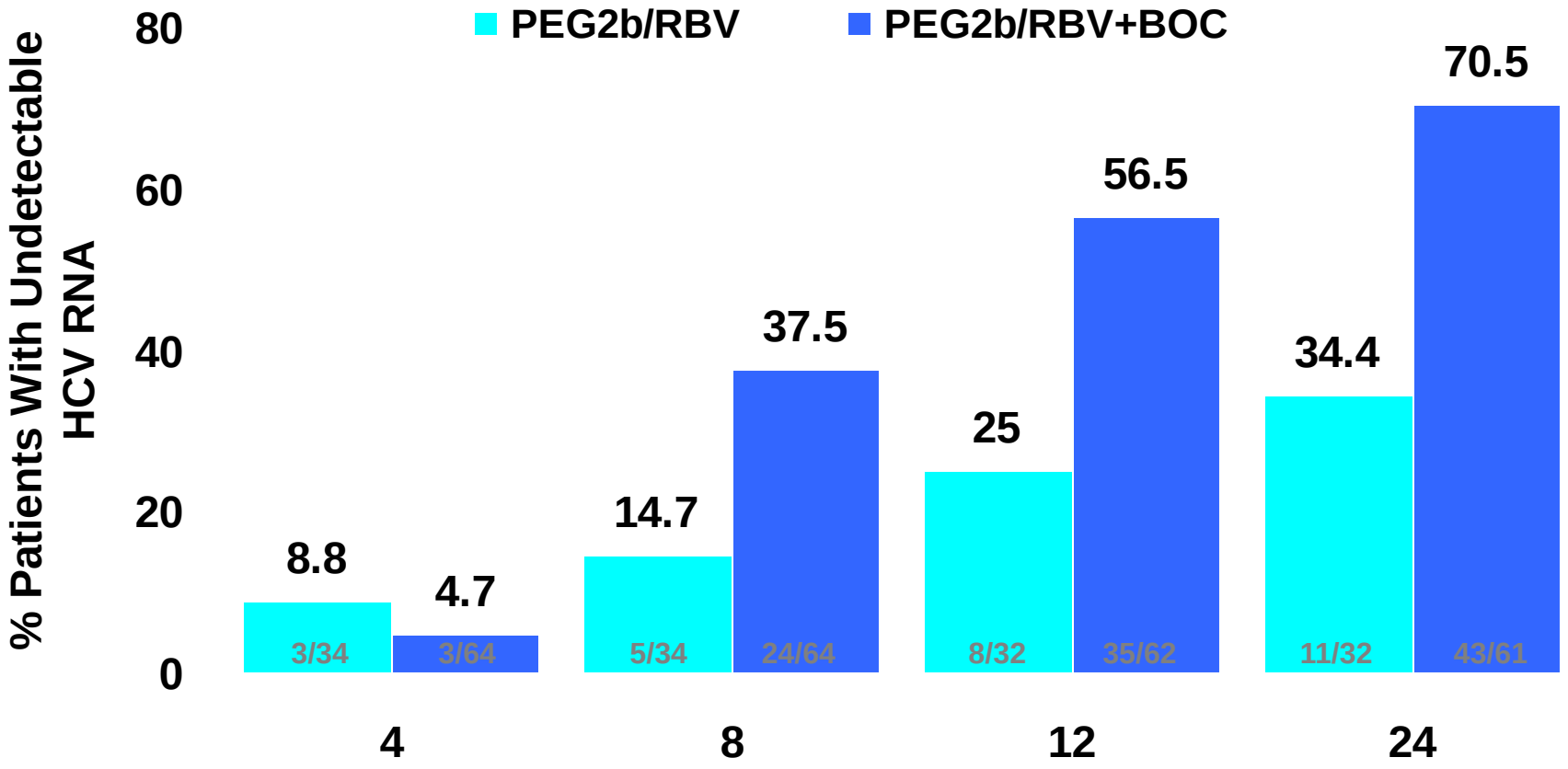
Boceprevir Plus Peginterferon/Ribavirin for the Treatment of HCV/HIV Co-Infected Patients



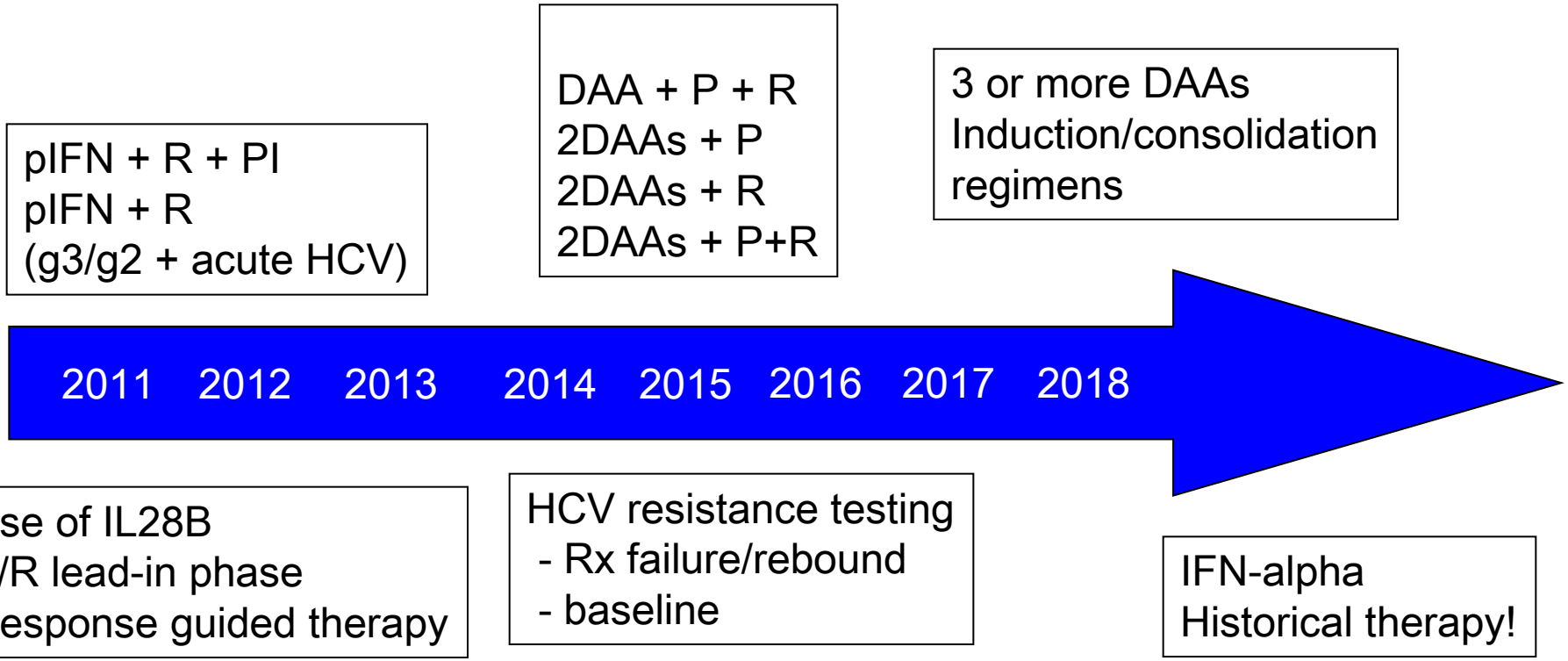
- Two-arm study, double-blinded for BOC, open-label for PEG2b/RBV
  - 2:1 randomization (experimental: control)
  - Boceprevir dose 800 mg, TID
- 4-week lead-in with PEG2b/RBV for all patients
  - PEG-2b 1.5 µg/kg QW; RBV 600-1400 mg/day divided BID
- Control arm subjects with HCV-RNA ≥ LLQ at TW 24 were offered open-label PEG2b/RBV+BOC via a cross-over arm

Late Breaker Oral Abstract LB-37 Infectious Diseases Society of America (IDSA) 49th Annual Meeting
Boston MAOctober 22nd, 2011

Virologic Response Over Time (% HCV RNA Undetectable)



HCV Rx landscape – the future?



Drug Combinations - Specifically Targeted Antiviral Therapy For HCV (STAT-C)
8 Projects

COMPANY	DRUG	Research	Preclin	Phase 1	Phase 2	Phase 3	NDA
Vertex	Telaprevir (VX-950) PI + (VX-222 Non-nucleoside) PI w&wo RBV/PIFN						
Bristol-Myers Squibb	BMS-790052 NS5A Inhibitor + BMS-650032 Protease Inhibitor w&wo RBV/PIFN						
Gilead	GS 9190 NN Polymerase Inhibitor + GS 9256 PI w&wo RBV/PIFN						
Bristol-Myers Squibb / Pharmasset	BMS-790052 NS5A inhibitor + PSI-7792 Nucleotide Polymerase inhib. w&wo RBV						
Boehringer Ingelheim trial status	BI 201335 Protease Inhibitor plus BI 207127 Polymerase inhib. w&wo Ribavirin						
Idenix trial status	IDX184 Nucleoside Polymerase Inhibitor plus IDX320 Protease Inhibitor						
Hoffmann-La Roche trial status	R7128 (RO5024048) Nucleoside Polymerase Inhibitor + ITMN-191 R7227 PI						
Pharmasset	PSI-7977 a pyrimidine and PSI-938 a purine nucleotide analog polymerase inhibitors						