Update on Hepatitis B and Hepatitis C

Dr Sulleman Moreea
FRCP(UK) FRCS(Glasg)
Consultant Gastroenterologist
Bradford Hospitals Foundation Trust
Sulleman.moreea@bradfordhospitals.nhs.uk

Introduction

- Set up in Bradford
- Hepatitis B
- Hepatitis C

Introduction

- Set up in Bradford
- Hepatitis B
- Hepatitis C

Bradford Gastroenterology Department

- Catchment area 500 000
- Tertiary referral 1 000 000
- 6 consultants
  - 5 gastroenterologist
  - 1 hepatologist

My Team

- 1 Specialist Registrar
- 1 FY2 – SHO
- 2 FY1's – House Officers
- 2 Viral Hepatitis Nurses
- 1 Alcohol Nurse

My Job

- Acute Medicine
  - Deputy Clinical Director of Acute Medicine
  - 800 in-patients
- Gastroenterology
  - 3 endoscopy lists
    - 580 OGD's,
    - 159 sigmoidoscopies,
    - 215 colonoscopies
- Hepatology
  - 431 new patients, 2000 follow ups (17% DNA's)

- Research
  - On a shoe string!

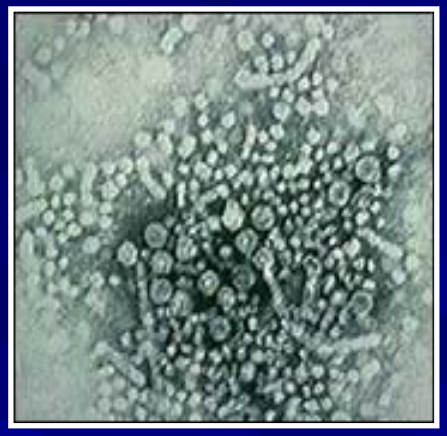
Introduction

- Set up in Bradford
- Hepatitis B
- Hepatitis C

Hepatitis B

- Why is hepatitis B important?
- Recent changes in treatment.
- Hepatitis B in Bradford.

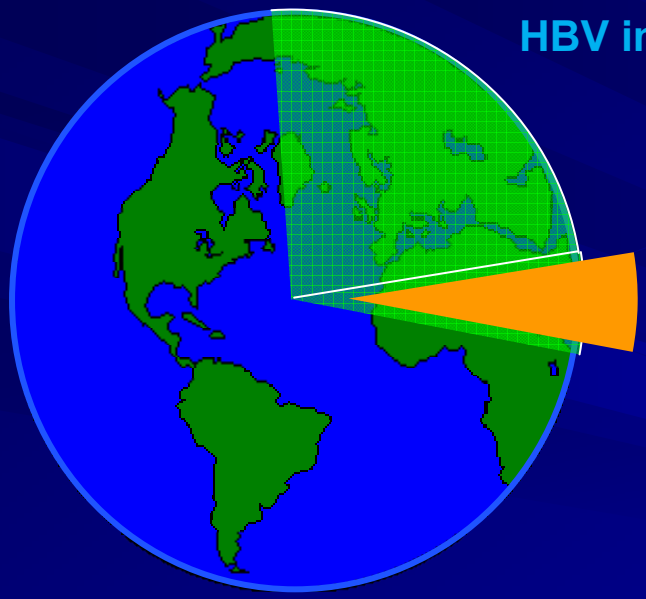
Hepatitis B virus (HBV)



- Member of *Hepadnaviridae* that primarily infects liver cells[1]
- WHO: 'HBV is second only to tobacco as a known human carcinogen'[2]
- 100 times more infectious than HIV[3]
- 10 times more infectious than HCV[3]

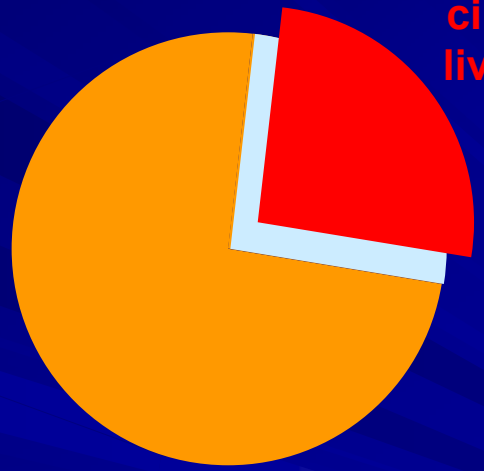
1. NIH 11th Report on Carcinogens, 2004;
2. Department of Communicable Diseases Surveillance and Response; WHO. Hepatitis B. 2002
3. DC. MMWR. 2003;52(RR01):1-33

The global impact of HBV disease



2 billion with evidence of HBV infection[4]

World population ~6 billion

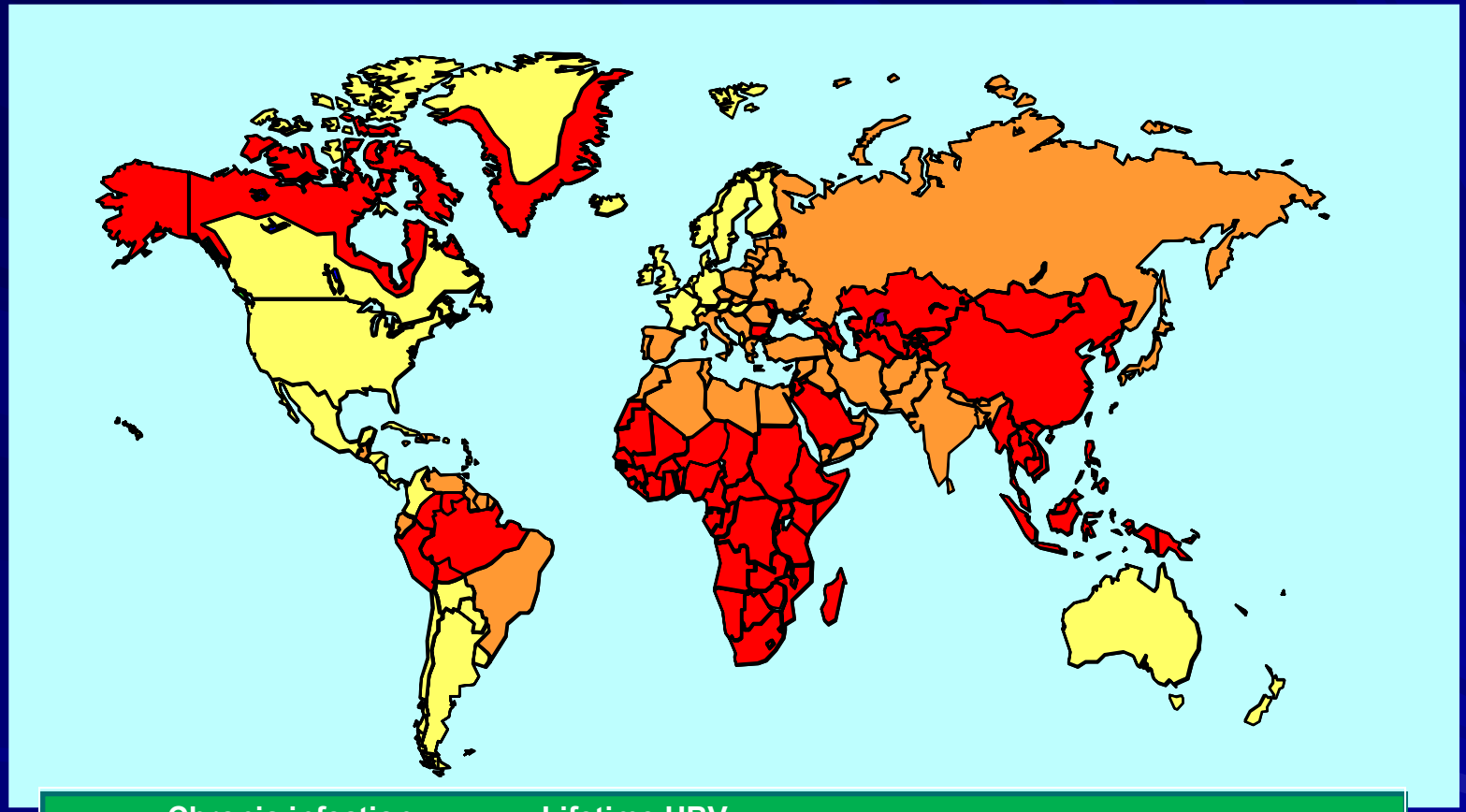


25–40% die of cirrhosis or liver cancer[6]

350–400 million with chronic hepatitis B[4,5]

4. WHO, Fact sheet No. 204;
5.Conjeevaram HS, Lok AS. J Hepatol. 2003;38:S90-103
6. Perrillo, RP et al. Hepatology. 2001;33:424-32

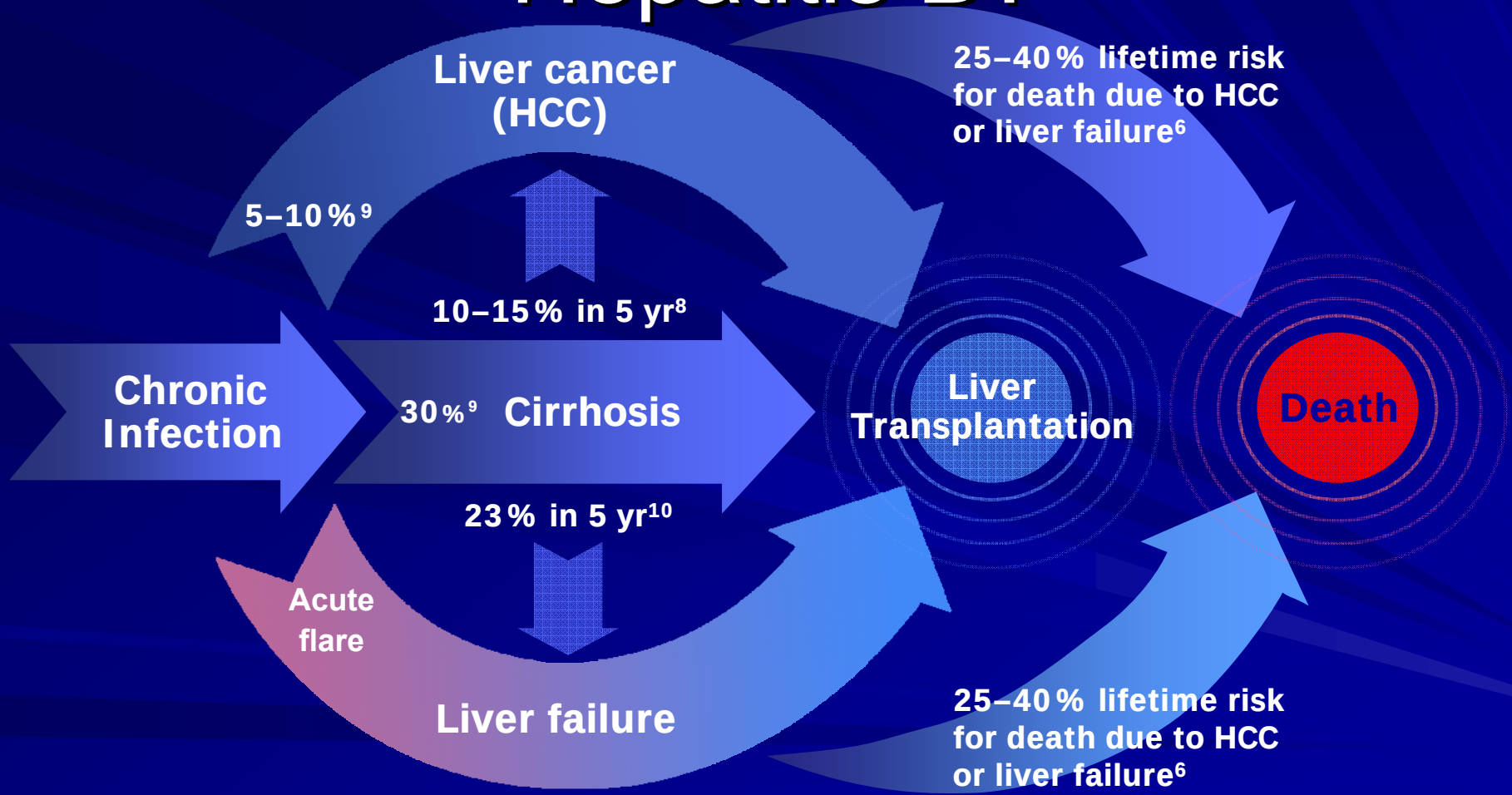
Prevalence of chronic HBV



Chronic infection prevalence	Lifetime HBV infection risk	Predominant age at infection
≥8% – High	>60%	Perinatal and early childhood
2–7% – Intermediate	20–60%	Early childhood
<2% – Low	<15%	Adult

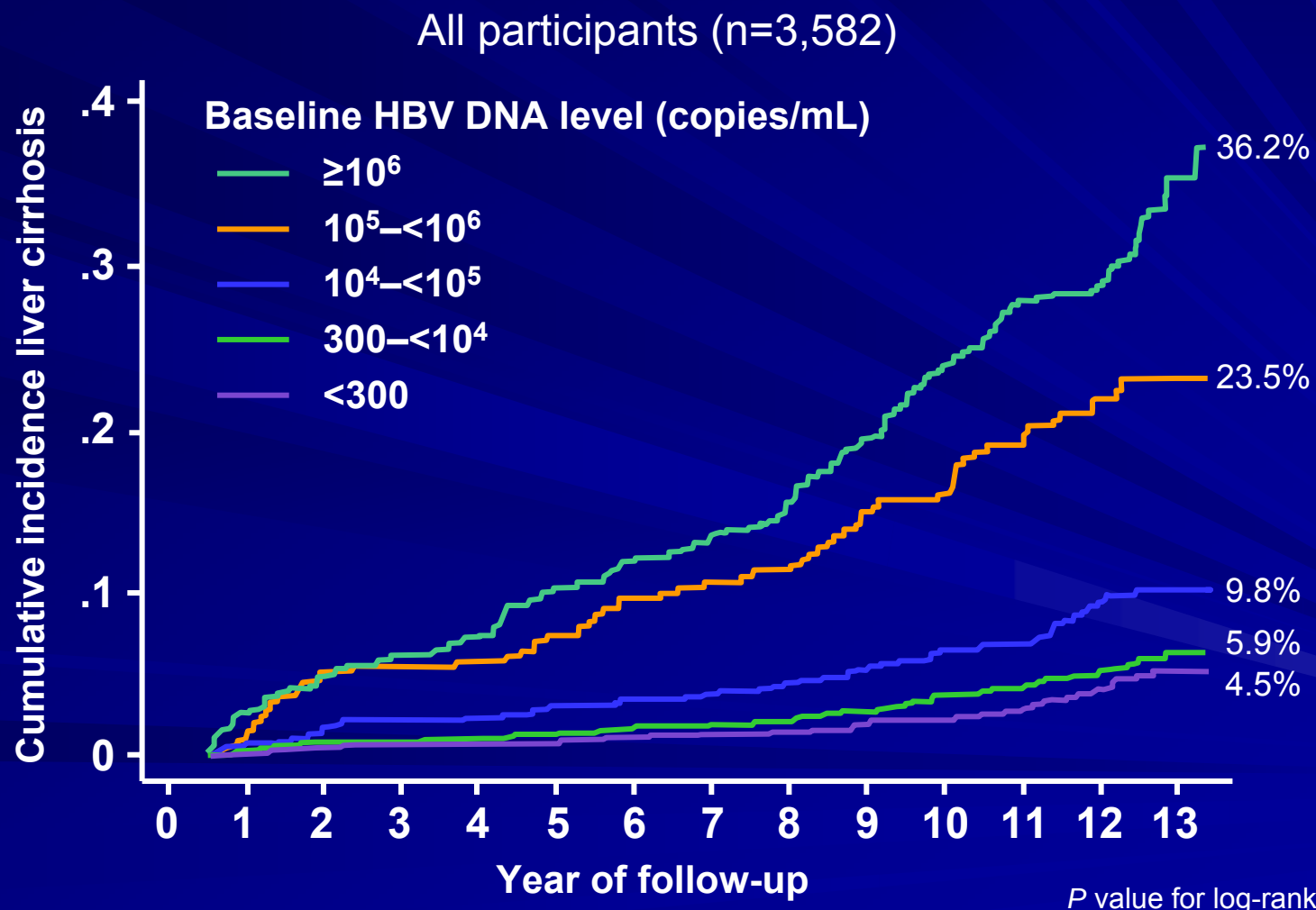
7. Adapted from CDC Hepatitis B slide set

Why do we need to treat Hepatitis B?



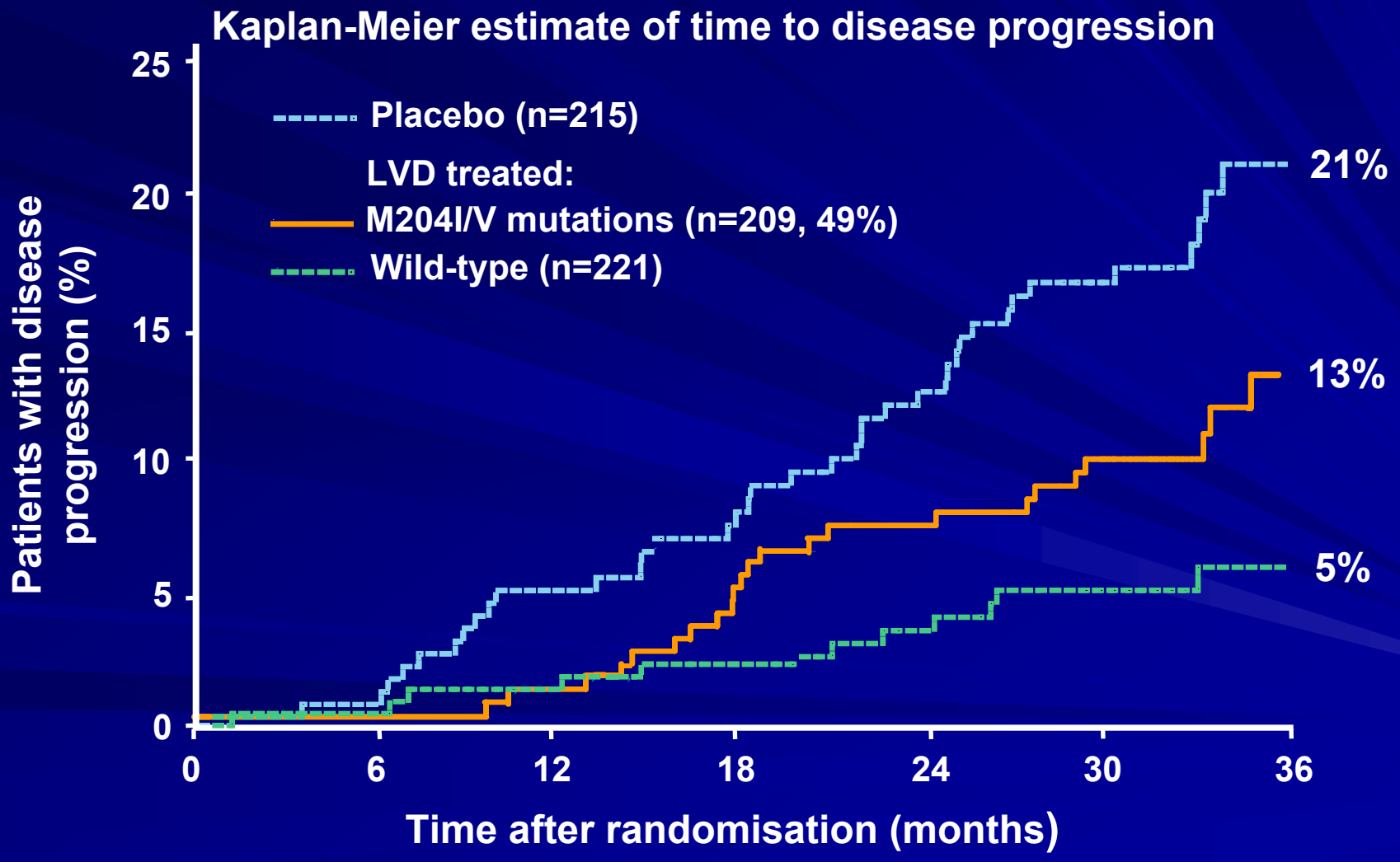
Adapted from: 6.Perrillo RP, et al. Hepatology. 2001;33:424-32
8. Fattovich G, et al. Gastroenterology. 2004;127:S35-50;
9. Torresi J, et al. Gastroenterology. 2000;118:S83-103
10. Fattovich G, et al. Hepatology. 1995;21:77-82.

REVEAL: High HBV viral load associated with increased incidence of cirrhosis



13. Adapted from Iloeje UH, et al. Gastroenterology. 2006;130:678–86

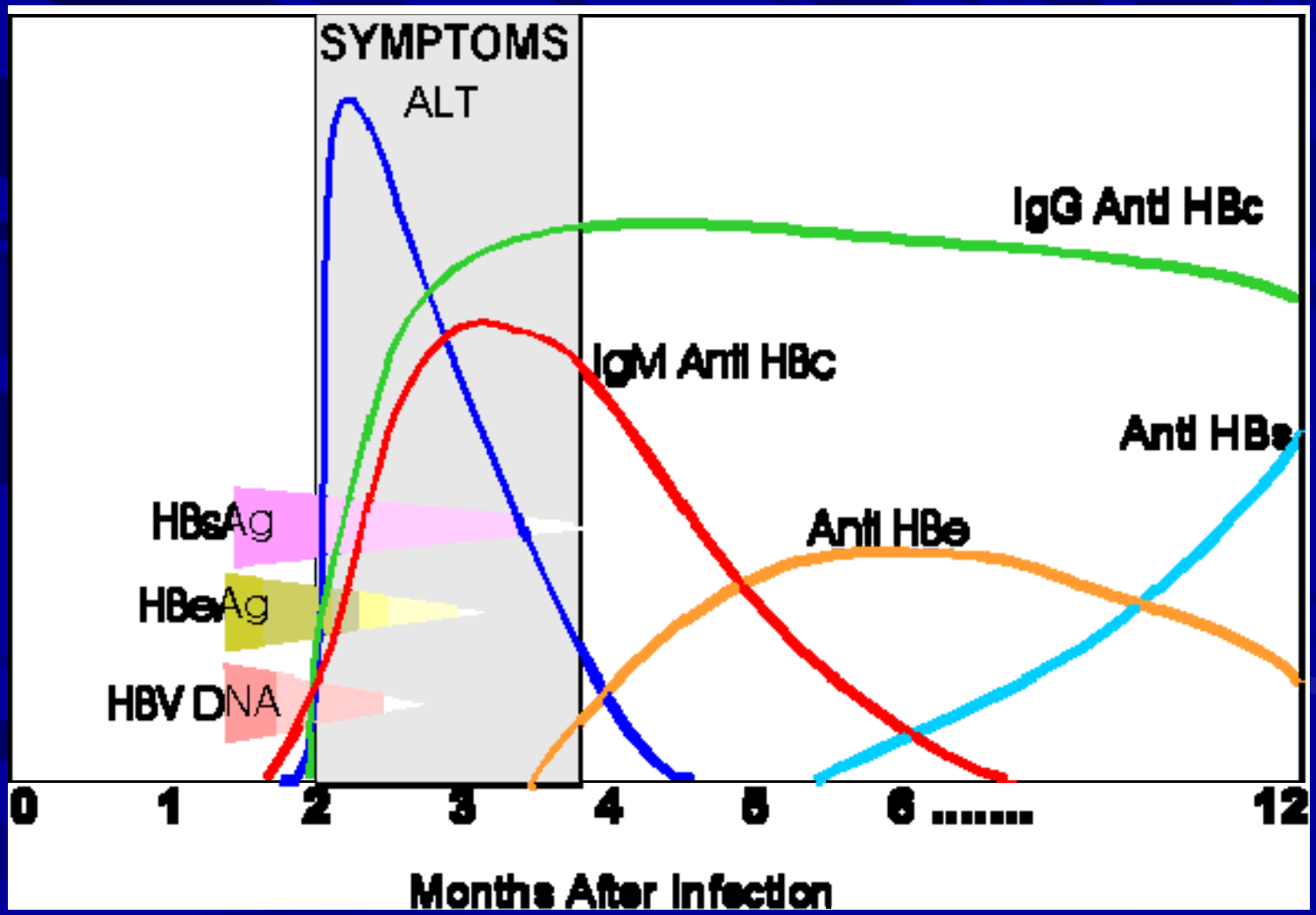
Benefit of treatment in cirrhotic patients with chronic hepatitis B



15. Adapted from: Liaw Y-Fa. Semin Liver Dis. 2005;25:40–7

- What's important in the management of hepatitis B?

Hepatitis B


SYMPTOMS
ALT
IgG Anti HBc
IgM Anti HBc
Anti HBe
Anti HBe
HBsAg
HBeAg
HBV DNA
0
1
2
3
4
5
6 .....
12
Months After Infection

Hepatitis B

- Diagnosis HepBsAg

Hepatitis B

- Diagnosis — HepBsAg
- Markers — eAg positive
  eAg negative

Hepatitis B

- Diagnosis — HepBsAg
- Markers — eAg positive or eAg –ve
- Viral load — Cut off

  eAg +ve>20000 IU/ml

  eAg –ve>2000IU/ml

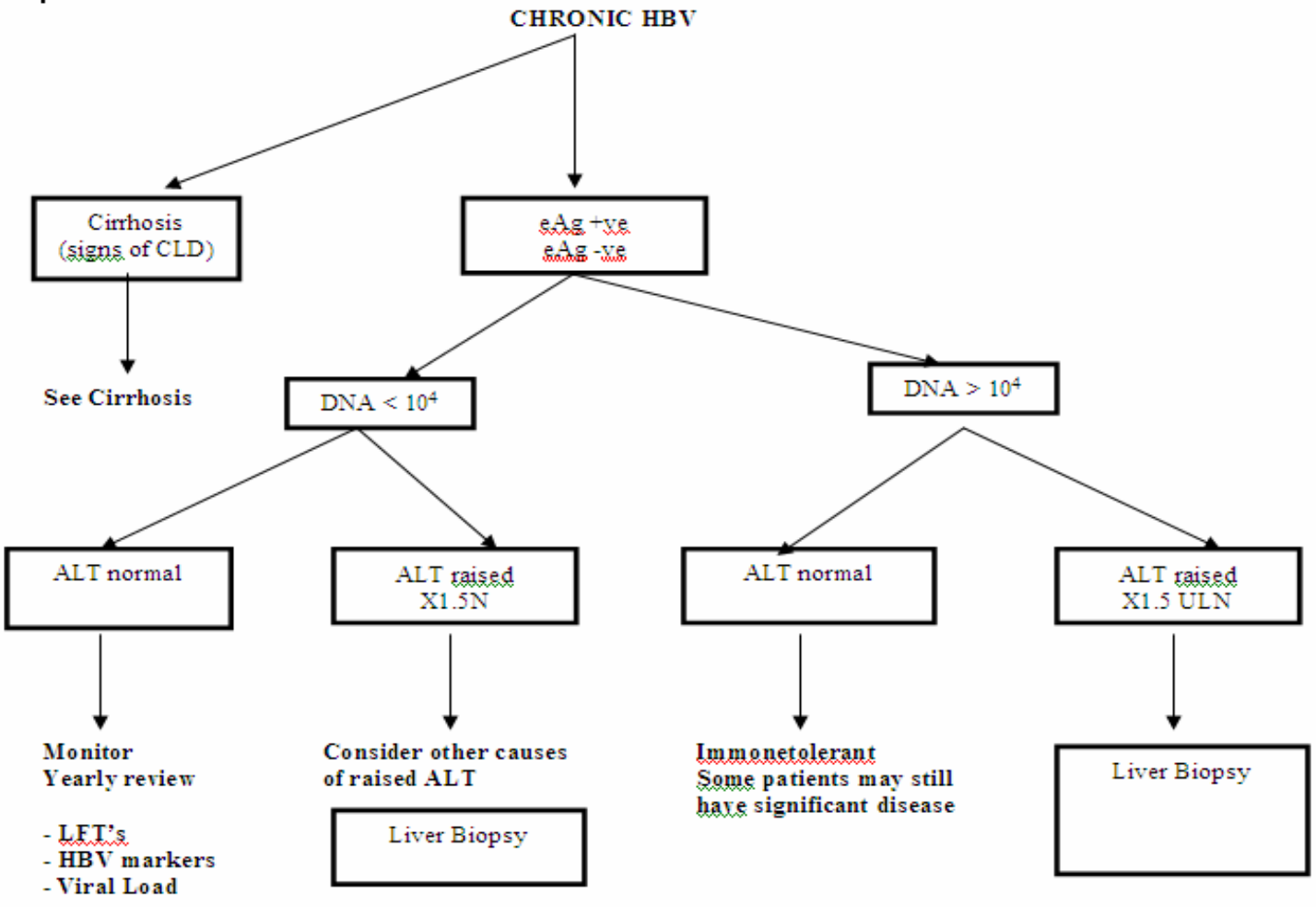
Hepatitis B

- Diagnosis — HepBsAg
- Markers — eAg positive or eAg –ve
- Viral load — Cut off
  eAg +ve>20000 IU/ml
  eAg –ve>2000IU/ml
- ALT — Normal or raised

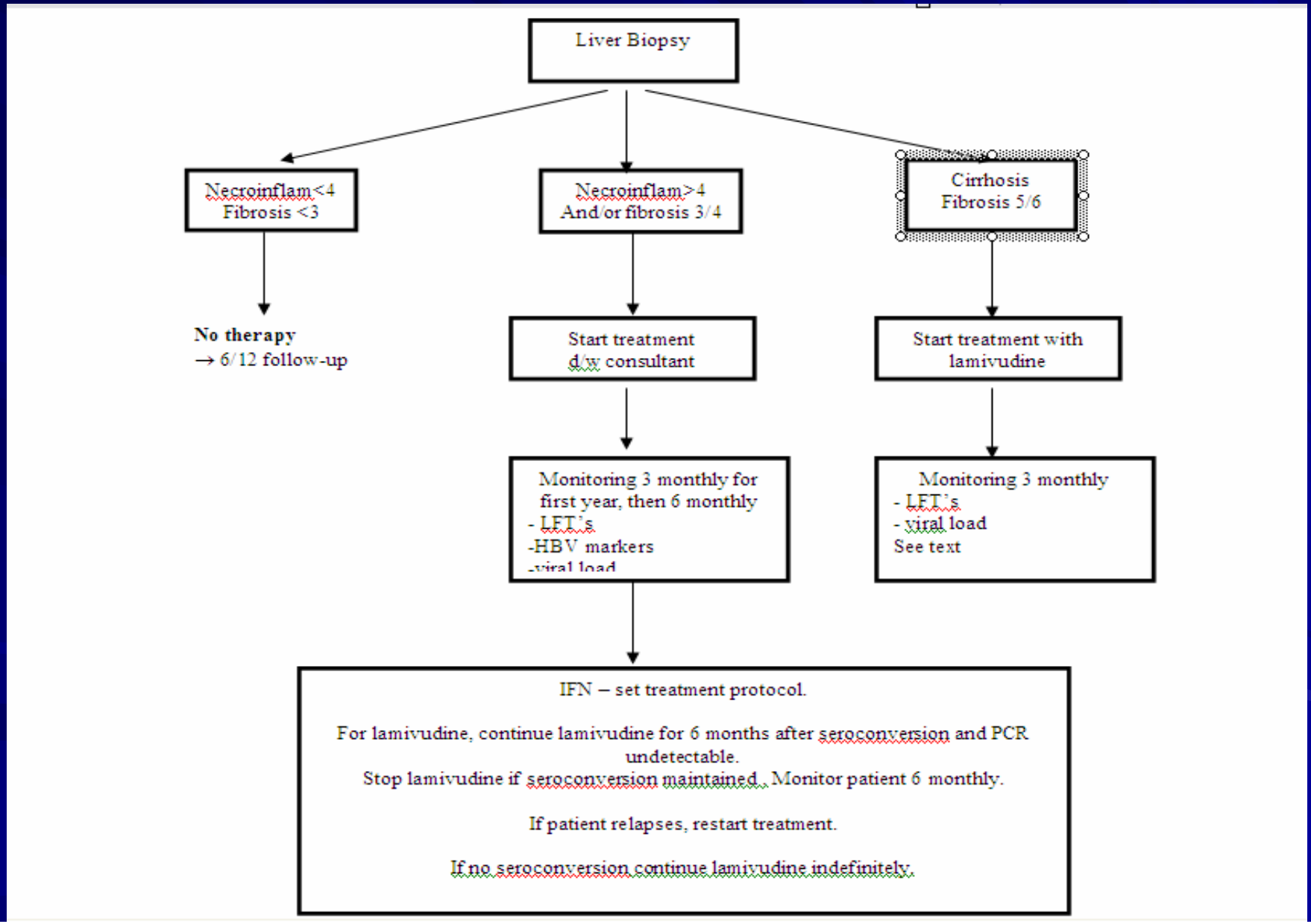
How best to treat chronic HBV? Available guidelines 2004

- EASL 2003
  - J Hepatol 2003;39:S3-25
- AASLD 2004
  - Lok and McMahon. Hepatology 2004;39(3):857-61
- US Treatment algorithm 2004
  - Keeffe et al. Clin Gastroenterol Hepatol. 2004;2:87–106

Leeds-Bradford guidelines 2004



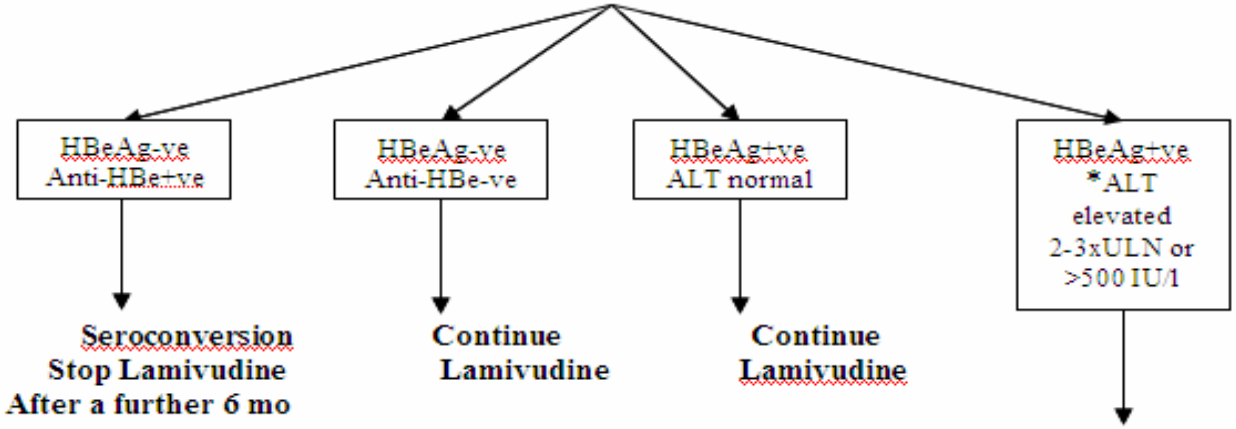
Leeds-Bradford guidelines 2004



Leeds-Bradford guidelines 2004

Clinic follow-up for patients on Lamivudine therapy

ALT monthly for three months, initially and 3-monthly afterwards, then 6 monthly. Test serum HBeAg, anti-HBe, HBV-DNA every 6 months.



***ALT elevation on Lamivudine can be spontaneous fluctuations, seroconversion, emergence of resistant species. If ALT >pre-treatment level consider stopping treatment if < pre-treatment , then continue.**

Clinic follow-up after stopping Lamivudine therapy:

Test serum ALT, HBe and B DNA monthly for 4 months if

- ALT remains normal, HBeAg-ve and anti-HBe+ve then annual follow-up
- ALT elevated, HBeAg+ve or Anti-HBe –ve monitor 3 monthly

NB. Post treatment flares are often asymptomatic, not uncommon (14%) and may have no significance.

Leeds-Bradford guidelines 2004

HBeAg	HBV DNA > 10^5 copies/ml	ALT	Recommendation
+	+	< x1.5	Observe
+	+	>x1.5	Lamivudine min 1 yr Continue 3-6 mo after seroconversion*
-ve	+	>x1.5	Lamivudine until PCR negative*
-ve	-ve	<x1.5	Observe
+/-	+/-	cirrhosis	Comp: Lamivudine Decomp: lamivudine & work-up for OLT

AASLD guidelines (Lok 2004)
The aim of Rx is durable suppression of HBV DNA to the lowest possible level.
The endpoint of Rx is seroconversion from eAg positive to eAb positive
For Lamivudine monitoring see text
* Add Adefovir if resistance develops to lamivudine (DNA rises during treatment) and continue indefinitely. Genetic sequencing may be requested to confirm resistance.

Efficacy of HBV treatment

At 1 year	Lamivudine	IFN alpha 2b
DNA loss	44%	37%
eAg loss	32%	33%
Seroconversion	18%(50% at 5 yr)	18%
Durability of seroconv	77% at 37 mo	90% at 8 yrs
sAg loss	n/a	11%
ALT normalisation	40-70%	23%
Histol improvement	50%	90%
Resistance	14-32% (69% at 5 yr)	Nil

How best to treat chronic HBV? Available guidelines 2007

- EASL 2003
  - J Hepatol 2003;39:S3-25
- AASLD 2004
  - Lok and McMahon. Hepatology 2004;39(3):857-61
- Treatment algorithm 2004
  - Keeffe et al. Clin Gastroenterol Hepatol. 2004;2:87–106
- APASL 2006
  - Liver Int 2006;26:47-58
- US algorithm 2006
  - Keeffe et al. Clin Gastroenterol Hepatol. 2006;4:936-62
- AASLD 2007
  - Lok and Mc Mahon. Hepatology 2007;45:507-39
- NICE 2006

Leeds-Bradford guidelines 2007

Management of chronic HBV

NOTE:

- When considering treatment of HBV the ULN for ALT should be considered to be <19 for women and <30 for men
- HBV DNA results are given in IU/ml, older results and results from other hospitals may be in copies/ml (to convert from copies/ml to IU/ml, divide by 5)
- Note the different cut off in HBV DNA between eAg POS and eAg NEG patients

HBeAg	HBV DNA (IU/ml)	ALT	Action
POS	<20,000	Persistently normal	6 monthly reviews initially, then annual review
POS	>20,000	Persistently normal	Low efficacy with current treatment Repeat LFTs 3 monthly initially and consider biopsy if ALT rises, if family history of HCC or patient age >40
POS	>20,000	1–2x ULN	Consider liver biopsy to determine if ongoing inflammation/fibrosis, otherwise initial 3 monthly LFTs and biopsy if ALT rises to 2x ULN
POS	>20,000	≥2x ULN	Will require treatment but consider biopsy to stage disease
NEG	<2,000	Persistently normal	Observe with repeat LFTs and HBV DNA, biopsy if HBV DNA rise
NEG	<2,000	1–2x ULN	3 monthly LFTs and if ALT rises further for liver biopsy
NEG	<2,000	≥2x ULN	Consider liver biopsy to determine if ongoing inflammation/fibrosis
NEG	2,000–20,000	Persistently normal	3 monthly LFTs and if LFTs become abnormal then liver biopsy
NEG	>20,000	>2x ULN	Will probably require treatment but consider liver biopsy to determine extent of inflammation/fibrosis

Leeds-Bradford 2007 hospital guidelines

Hepatitis B - management

Marker	Viral load IU/ml	ALT	
eAg +ve	<20 000	Normal	

Hepatitis B - management

Marker	Viral load IU/ml	ALT	
eAg +ve	<20000	Normal	
eAg +ve	>20000	Raised	Biopsy and treat

Hepatitis B - management

Marker	Viral load IU/ml	ALT	
eAg +ve	<20000	Normal	
eAg +ve	>20000	Raised	Biopsy and treat
eAg -ve	<2000	Normal	

Hepatitis B - management

Marker	Viral load IU/ml	ALT	
eAg +ve	<20000	Normal	
eAg +ve	>20000	Raised	Biopsy and treat
eAg -ve	<2000	Normal	
eAg -ve	>2000	Raised	Biopsy and treat

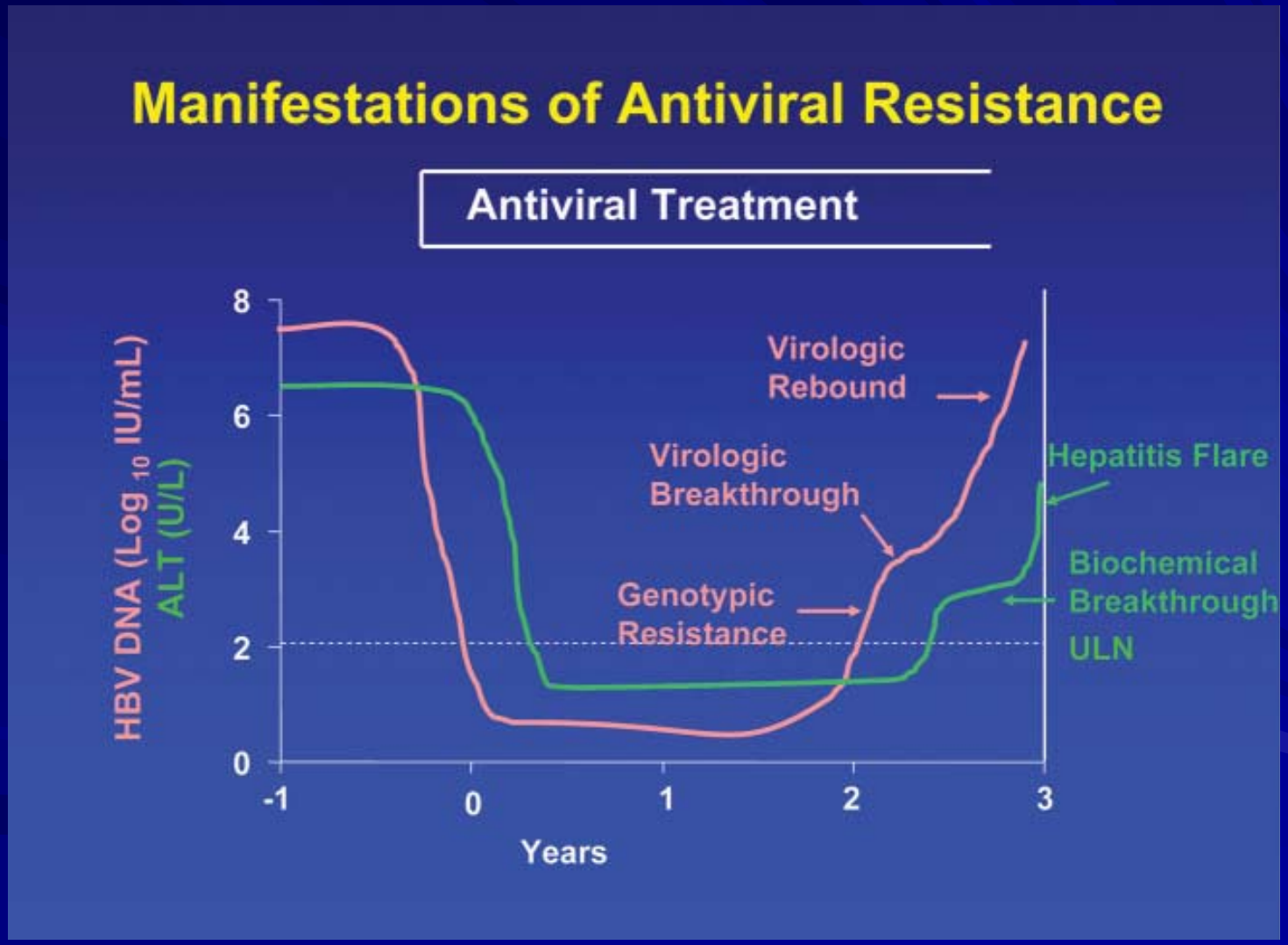
Hepatitis B - Treatment

- No treatment to eradicate hepatitis B
- Treatment aims to keep viral load low
- Current treatment
  - Lamivudine
  - Adefovir
  - Peg Interferon
  - Entecavir
  - Tenofovir

Hepatitis B - Treatment

- Fast acting medication
- Low resistance profile

HBV antiviral resistance



Lok ASF and McMahon BJ. Hepatology 2007;45(2):507-39

Current treatment

- Lamivudine 100mg od + Adefovir 10 mg od
- Pegylated interferon 180 mcg sc weekly – 48 weeks
- Entecavir 0.5mg od
- 3-6 monthly monitoring

Hepatitis B in Bradford

- Extent of the problem to plan services.

Bradford population 2001 census

- Total population[18] 467 665
- Ethnic minority[19] 87 150 (18%)
  - Asian origin 75 050
  - Afro-Caribbean origin 5 950
- Ethnic minority will rise to 26% by 2011[19]

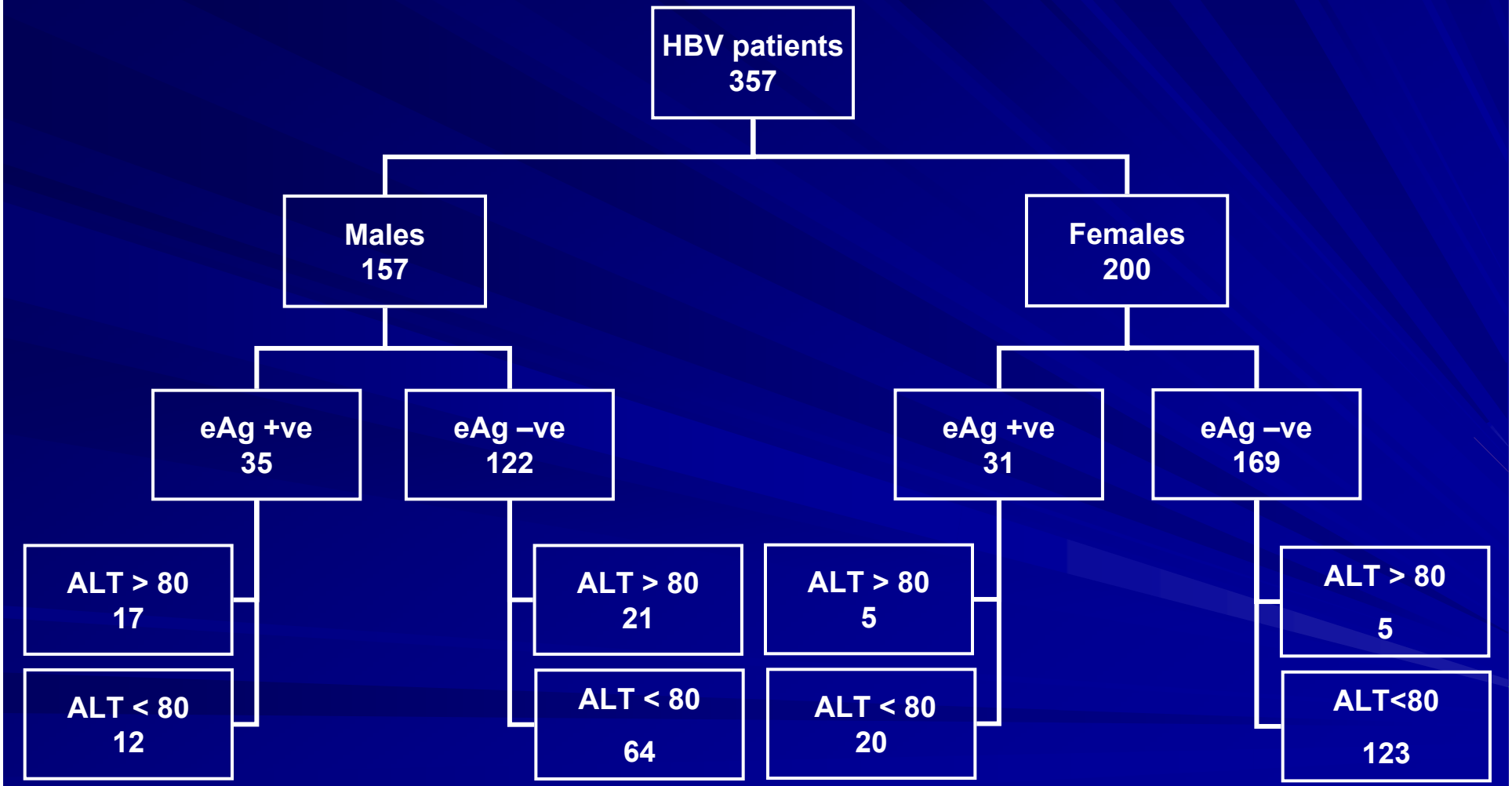
18.National statistics. Available at: http://www.statistics.gov.uk/census2001/profiles/00cx.asp. Last accessed in January 2008.
19. http://www.bradford.gov.uk/life_in_the_community/population_and_migration/people_of_bradford.htm. Last accessed in January 2008.

Estimated HBV patients

- Around 3–6% of first generation immigrants
- Assume 30 000
- Therefore, between 900–1800 HBV patients

Personal Communication – Dr Sulleman Moreea

HBV patients in Bradford



No data on 90 patients (25%)

HBV in Bradford

eAg status VL IU/ml	ALT <40	ALT 41 - 80	ALT >80
eAg +ve VL > 20000	11	10	18
eAg +ve VL < 20000	9	2	4
eAg –ve VL > 2000	30	12	15
eAg –ve VL < 2000	121	24	11

HBV in Bradford

eAg status VL IU/ml	ALT <40	ALT 41 - 80	ALT >80
eAg +ve VL > 20000	11	10	18
eAg +ve VL < 20000	9	2	4
eAg –ve VL > 2000	30	12	15
eAg –ve VL < 2000	121	24	11

Patients on Treatment - 2008

Treatment	Males	Females	Total
Lamivudine	16	7	23
LAM + ADV	5	3	8
Pegasys	14	2	16
Entecavir	9	1	10
Total	44	13	57

Increase in work load

Table 1. Possible increase in workload in chronic HBV patients.

	eAg positive n = 25 (11 M, 14 F)		eAg negative n = 122 (44 M, 78 F)	
Viral load	< 20000IU/ml	≥20000 IU/ml	<2000 IU/ml	≥2000IU/ml
ALT >40 IU/ml	1 (0M,1F)	12 (10M,2F)	30 (21M,9F)	17 (10M,7F)
ALT 30-40IU/ml (males) or 19-40IU/ml (females)[a]	4 (0M,4F)	8 (1M,7F)	56 (6M,50F)	14 (5M,9F)
Possible increase in liver biopsy numbers	N/A	67%	N/A	82%
ALT >80 IU/ml	1 (0M,1F)	10 (8M,2F)	13 (10M,3F)	5 (4M,1F)
ALT 60-80IU/ml (males) or 38-80IU/ml (females)[b]	0	2 (0M,2F)	10 (4M,6F)	7 (1M,6F)
Possible increase in treated patients	N/A	20%	N/A	140%

N/A = not applicable

Bholah N, Ford A, Moreea S. British Society Gastroenterology 2007

HBV patients – Ethnicity

	Males	Females	Total
Pakistanis	113	133	246 (70%)
White Caucasians	18	27	45 (13%)
Chinese	11	20	31 (8.6%)
African	11	19	30 (8.4%)

Personal Communication – Dr Sulleman Moreea

Prevalence of HBV in Bradford

- June 05 – Sep 06: 4817 pregnancies
  - 53% Asians
  - 42% Caucasians
  - 3% African
- 99% screened

Mahmood et al. BSG March 2008

Screening in pregnancy

- HBV positive pregnancies 42 (0.88%).
- Asians 29 (69%)
  - 23 of Pakistani origin, of whom
  - 11 born in Pakistan.
- White Caucasian 8 (19%)
- African 5 (12%)

Mahmood et al. BSG March 2008

Screening in pregnancy

- Prevalence of HBV
  - Asian 1.1%
  - White Caucasian 0.4%
  - African 3%

Mahmood et al. BSG March 2008

Screening in pregnancy

- eAg positive 8 (19%)
- eAg negative 34 (81%)

- All of them were referred to the Hepatology clinic – 29/42 (69%) attended.

Mahmood et al. BSG March 2008

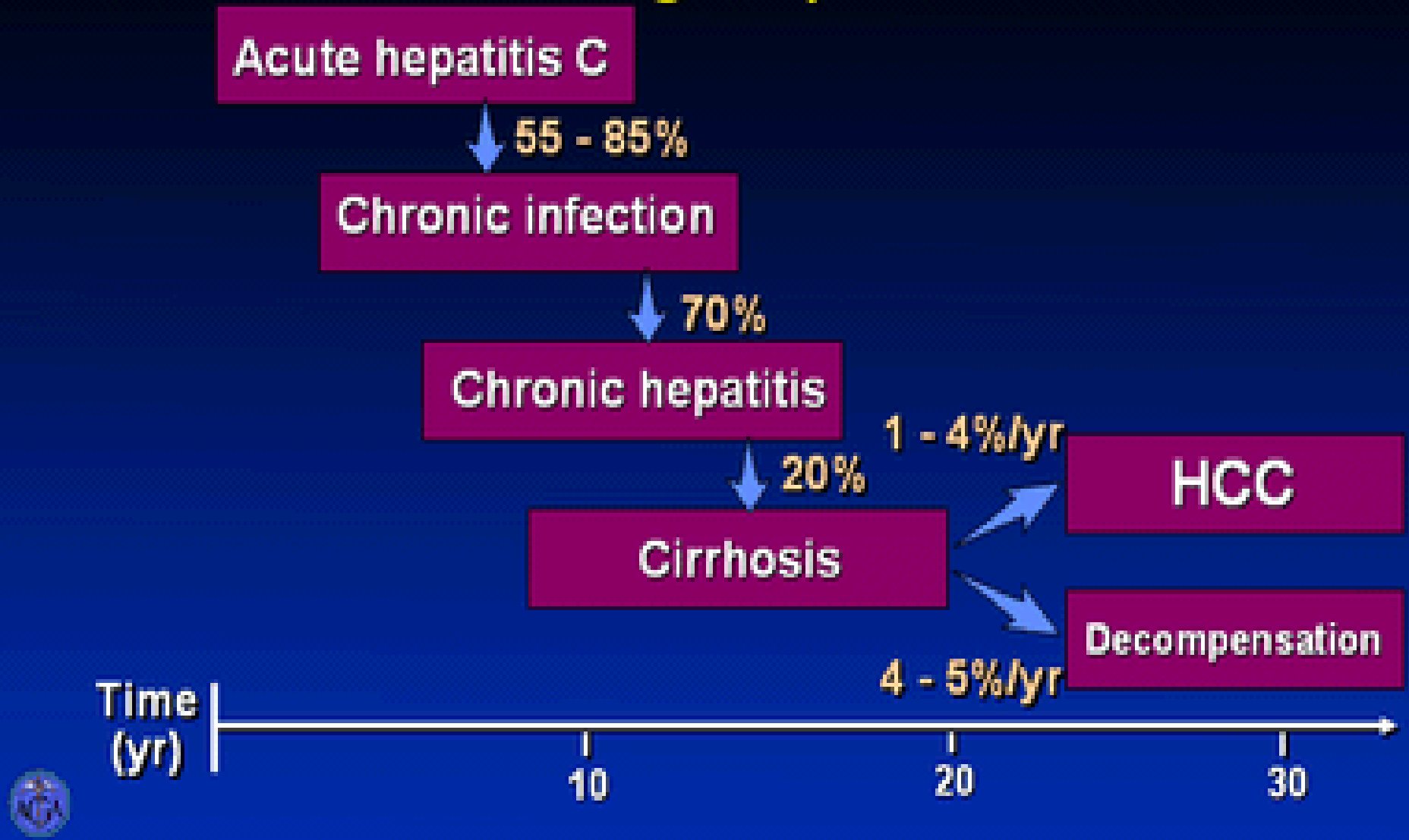
HBV - conclusion

- The large majority of Hepatitis B patients may not know they have the disease
- The morbidity and mortality due to Hepatitis B will be a problem in the future.

- Set up in Bradford
- Hepatitis B
- Hepatitis C
  - What you need to know
  - Bradford experience

HCV - Natural History

Outcome Following Hepatitis C Infection

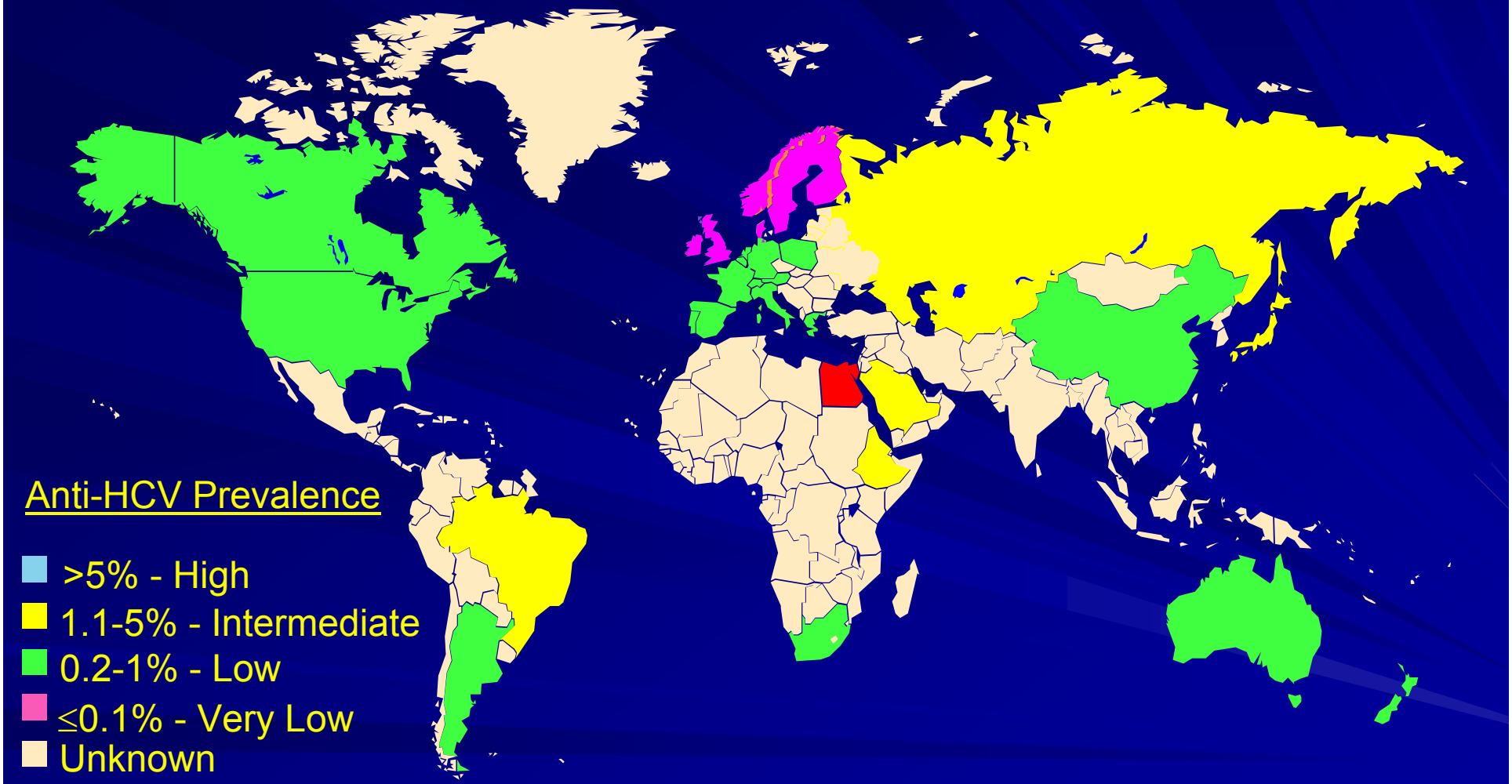


Prevalence In Groups at Risk

Recipients of clotting factors before 1987	75 - 90%
Injection drug users	70 - 85%
Long-term hemodialysis patients	10%
Individuals with ≥ 50 sexual partners	10%
Recipients of blood prior to 1990	5%
Infants born to infected mothers	5%
Long-term sexual partners of HCV positive	1 - 5%
Health workers after random needlesticks	1 - 2%

CDC, MMWR 1998;47(No. RR-19):1

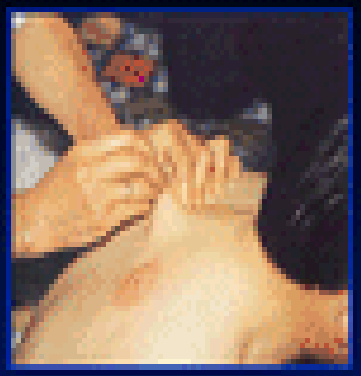
Prevalence of HCV Infection Among Blood Donors*

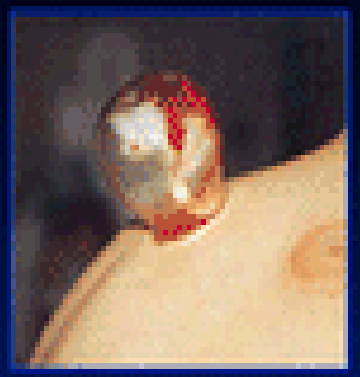


* Anti-HCV prevalence by EIA-1 or EIA-2 with supplemental testing; based on data available in January, 1995

Epidemics From Parenteral Practices

- Japan: cupping





- Egypt: Schistosomiasis treatment
- Italy: home injections

Kiyosawa K et al., Gastroenterology 1994;106:1598
Frank C et al., Lancet 2000;355:877
Chiaramonte M et al., J Hepatol 1996; 24:129

HCV Treatment

Primary objective

- Viral eradication – SVR
- Arrest progression of necrosis/fibrosis

Secondary objective

- Reduce progression of fibrosis/cirrhosis
- Prevent decompensation
- Prevent HCC

SVR = sustained virological response
HCC = hepatocellular carcinoma

Evolution of hepatitis C treatment

Elucidation of HCV genome

Treatment with IFN alfa for 24 or 48 weeks – 3x weekly dosing – Poor outcomes

Addition of RBV to IFN alfa improved outcomes

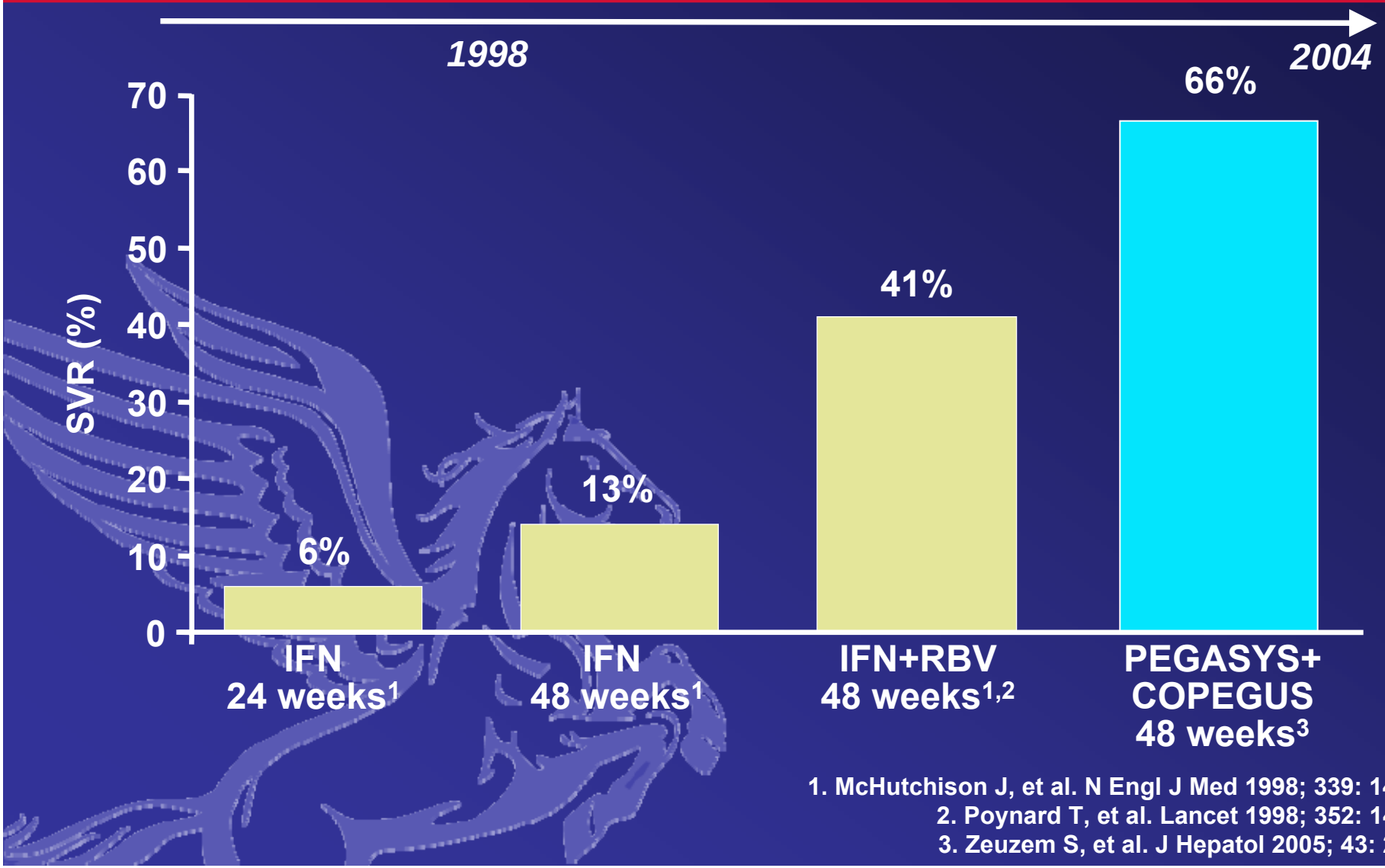
Development of Peg-IFN – once-weekly dosing – Outcomes improved further

Peg-IFN alfa plus RBV becomes gold standard

1989

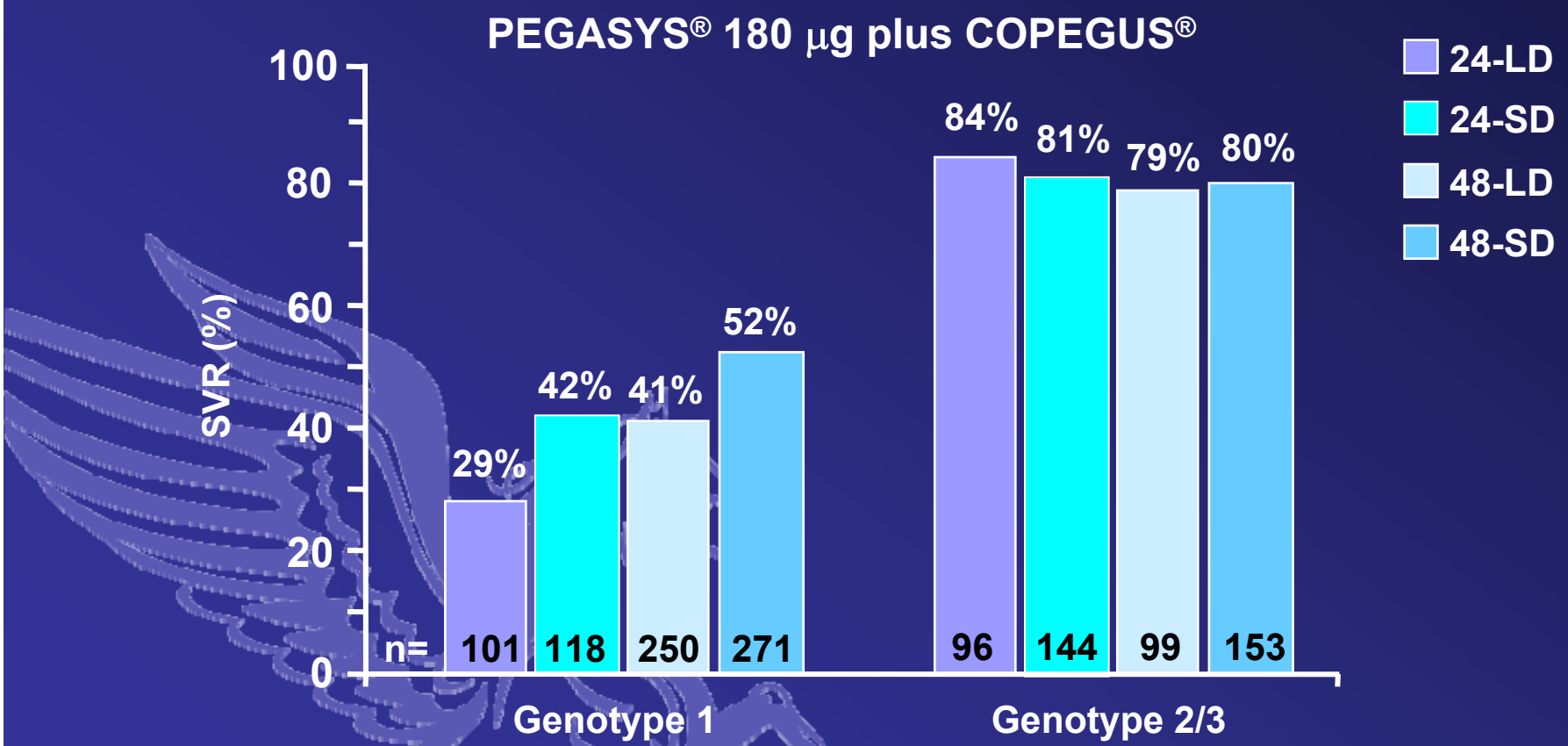
2006

Pegylated interferons lead to a significantly better treatment outcome



1. McHutchison J, et al. N Engl J Med 1998; 339: 1485
2. Poynard T, et al. Lancet 1998; 352: 1426
3. Zeuzem S, et al. J Hepatol 2005; 43: 250

Approved treatment duration is 48 weeks for genotype 1 and 24 weeks for genotype 2/3



LD = RBV 800 mg/day
SD = RBV 1000–1200 mg/day

Hadziyannis S, et al. Ann Intern Med 2004; 140: 346

Prognosis and response to IFN-based treatment vary with baseline factors

- Viral factors
  - Genotype (1 and 4 versus 2 and 3)
  - Viral load (high versus low viral load)
- Patient-specific factors
  - Age
  - Liver histology (cirrhosis versus no cirrhosis)
  - Race
  - Body weight
  - Alcohol/drug use
  - Gender

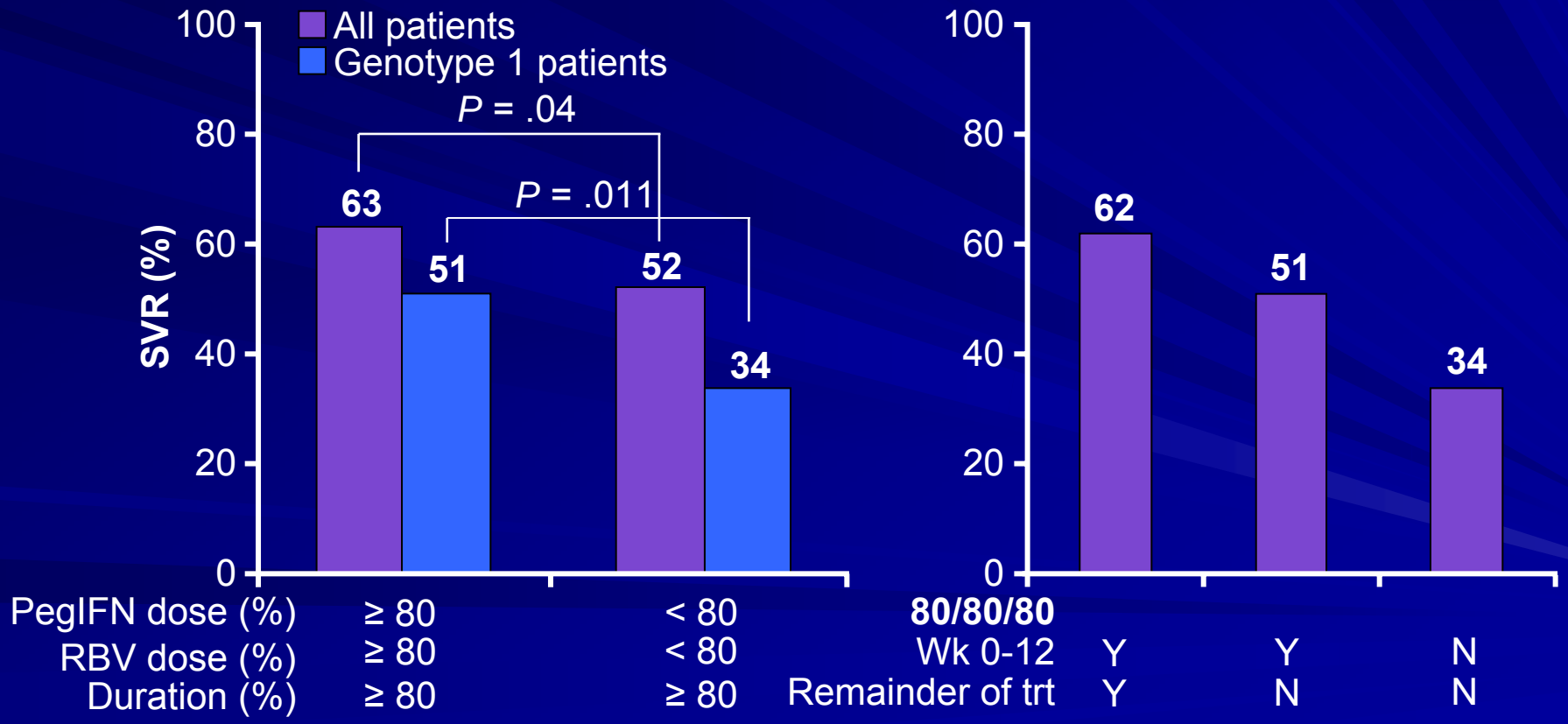
1. Trepo C. J Viral Hepat 2000; 7: 250
2. Davis G & Lau G. Hepatology 1997; 26: 122S
3. Lee S, et al. Hepatology 2000; 32(4, pt 2): 370A
4. Poynard T, et al. Lancet 1998; 352: 1426
5. Schalm S, et al. Hepatology 1997; 26: 128S

Which Pegylated Interferon?

- Roche – Pegasys
  - Fixed dose
- Schering-Plough – Viraferon Peg
  - Weight-based

SVR: the 80% rule

- Retrospective analysis of pegIFN alfa-2b/RBV phase trials



McHutchison JG, et al. Gastroenterology. 2002;123:1061-1069.

Definitions of Response

Rapid virological response (RVR)

- Undetectable HCV RNA levels at week 4

Early virological response (EVR)

- ≥ 2 $\log_{10}$ drop in HCV RNA at week 12

Slow virological response

- HCV RNA positive at weeks 4 and 12, negative at week 24

End-of-treatment response (EOT)

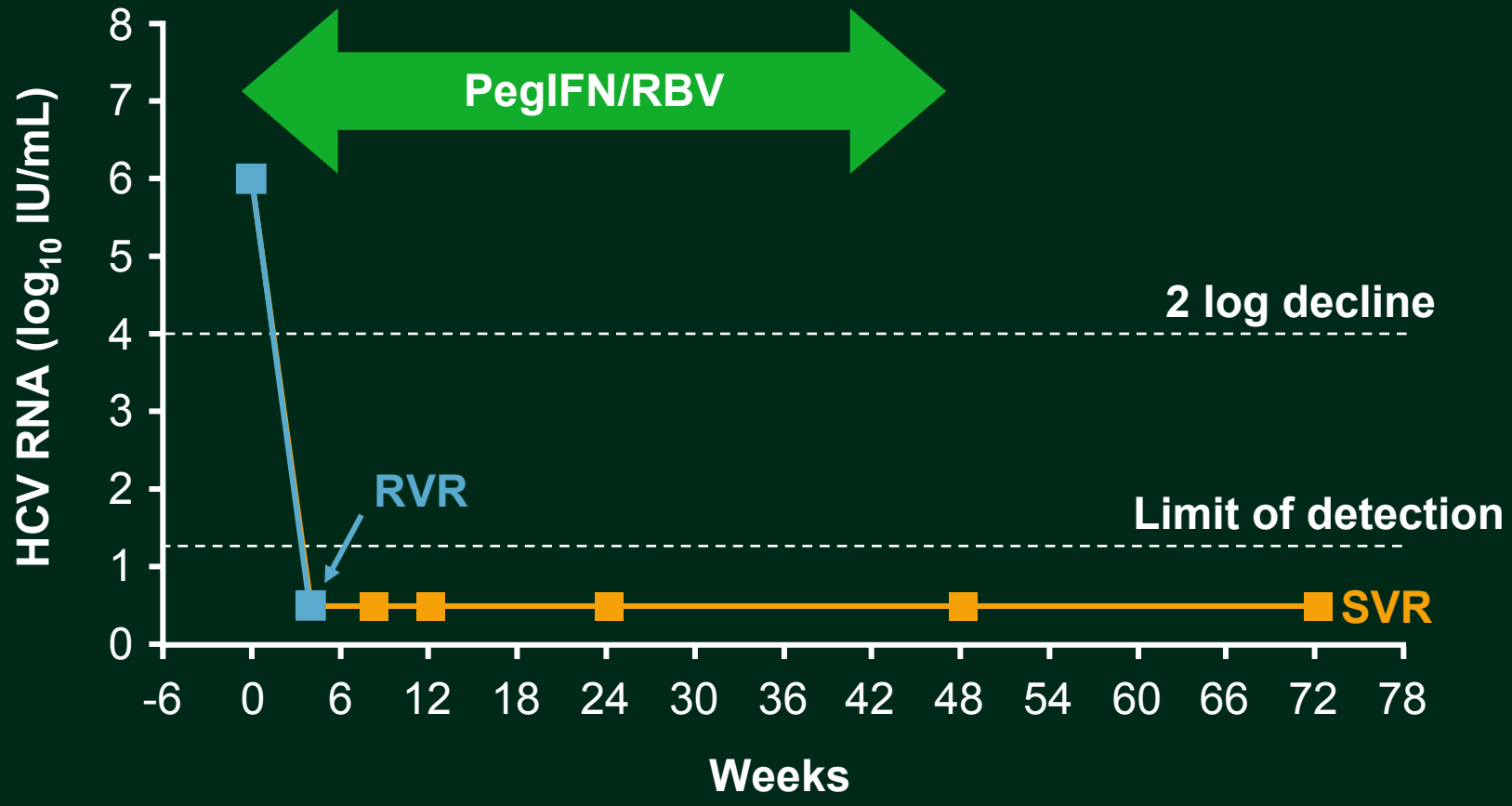
- Undetectable HCV RNA levels at end of treatment (24 weeks for HCV genotype 2/3, 48 weeks for HCV genotype 1)

Sustained virological response (SVR)

- Undetectable HCV RNA levels at end of treatment and follow-up (24 weeks post-treatment)

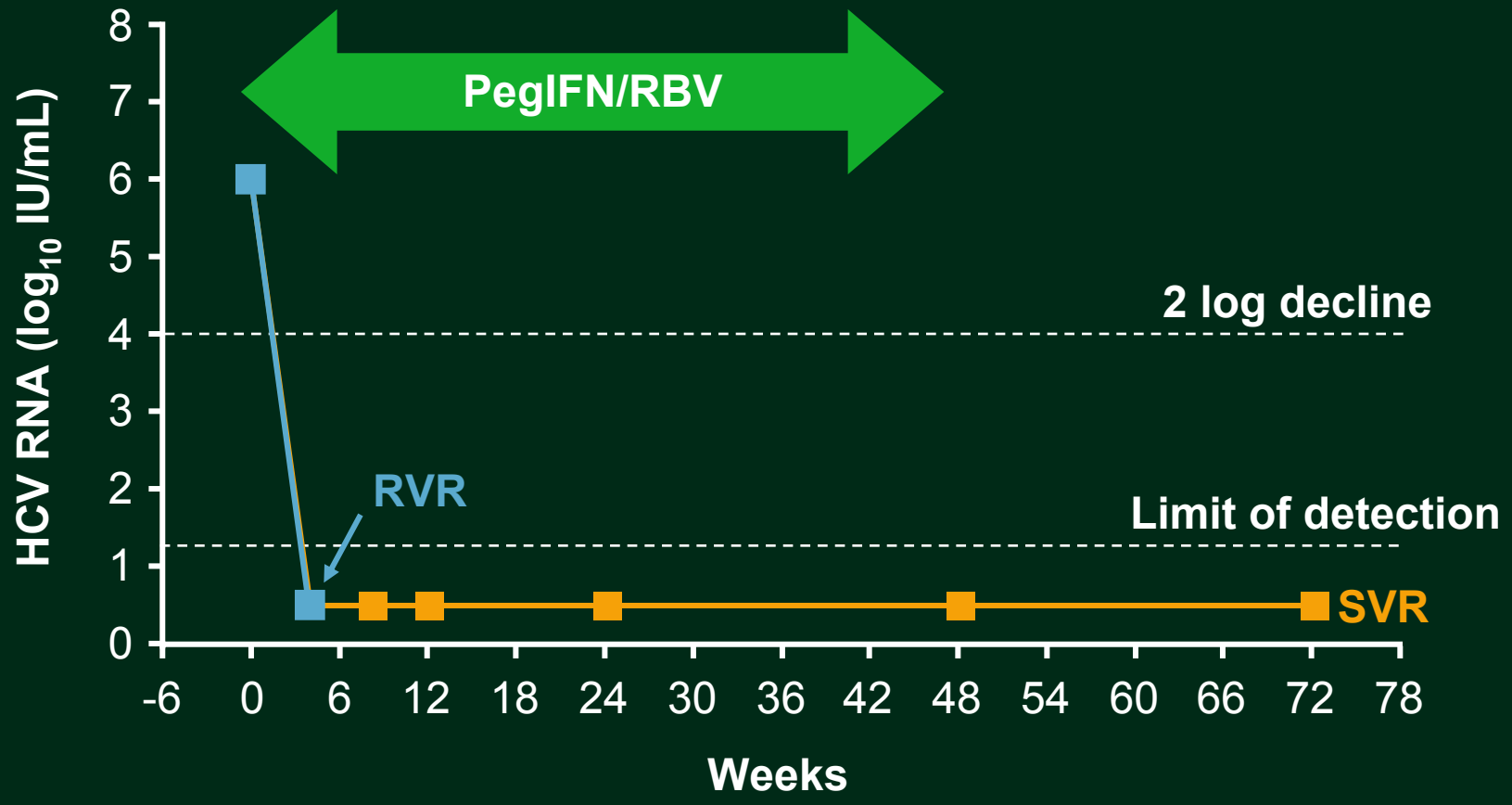
1. Jensen D, et al. Hepatology 2006; 43: 954
2. Strader D, et al. Hepatology 2004; 39: 1147

Rapid Virologic Response (RVR):
HCV RNA Undetectable at Week 4



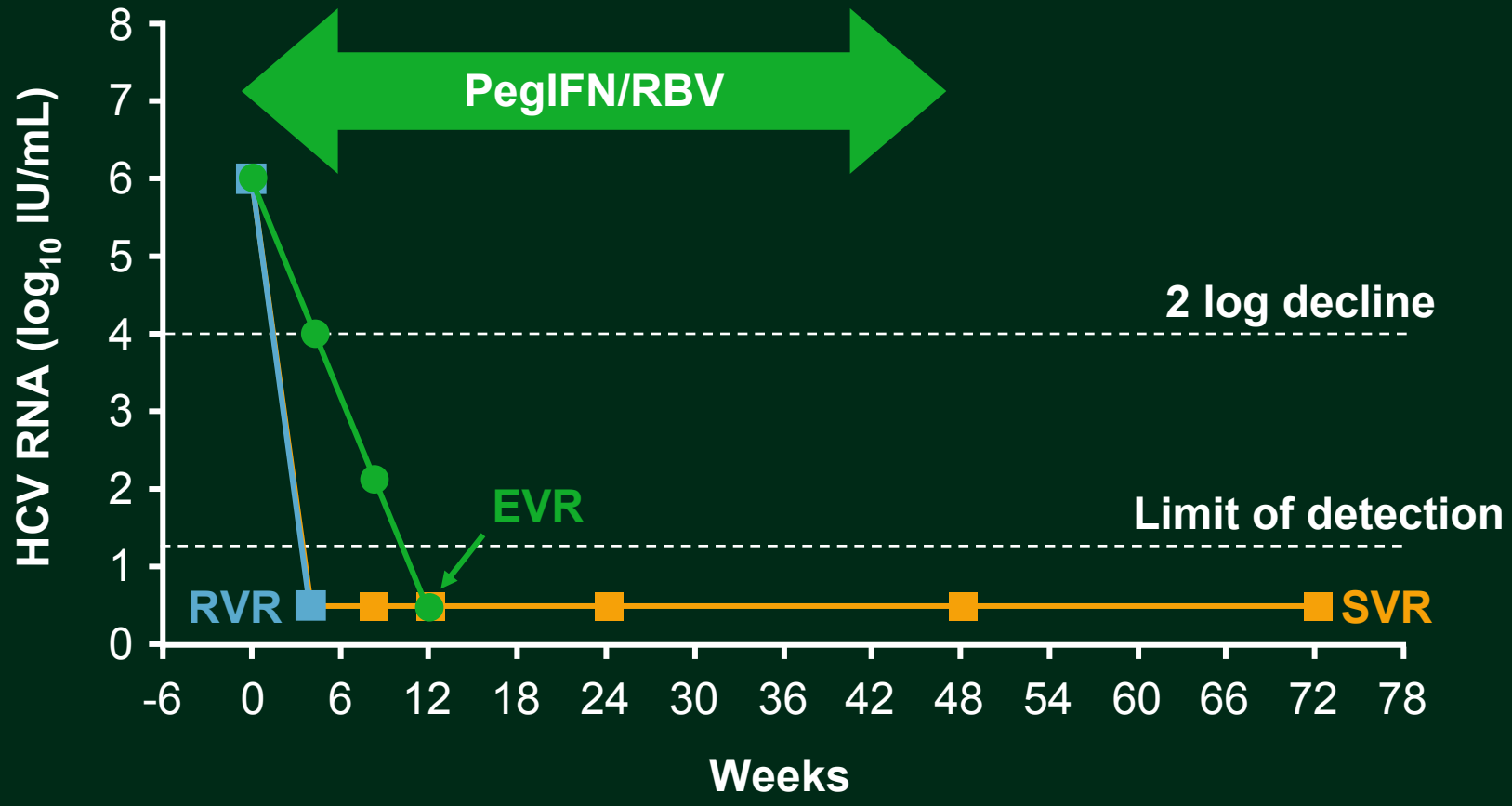
Rapid Virologic Response (RVR):

Super Responders



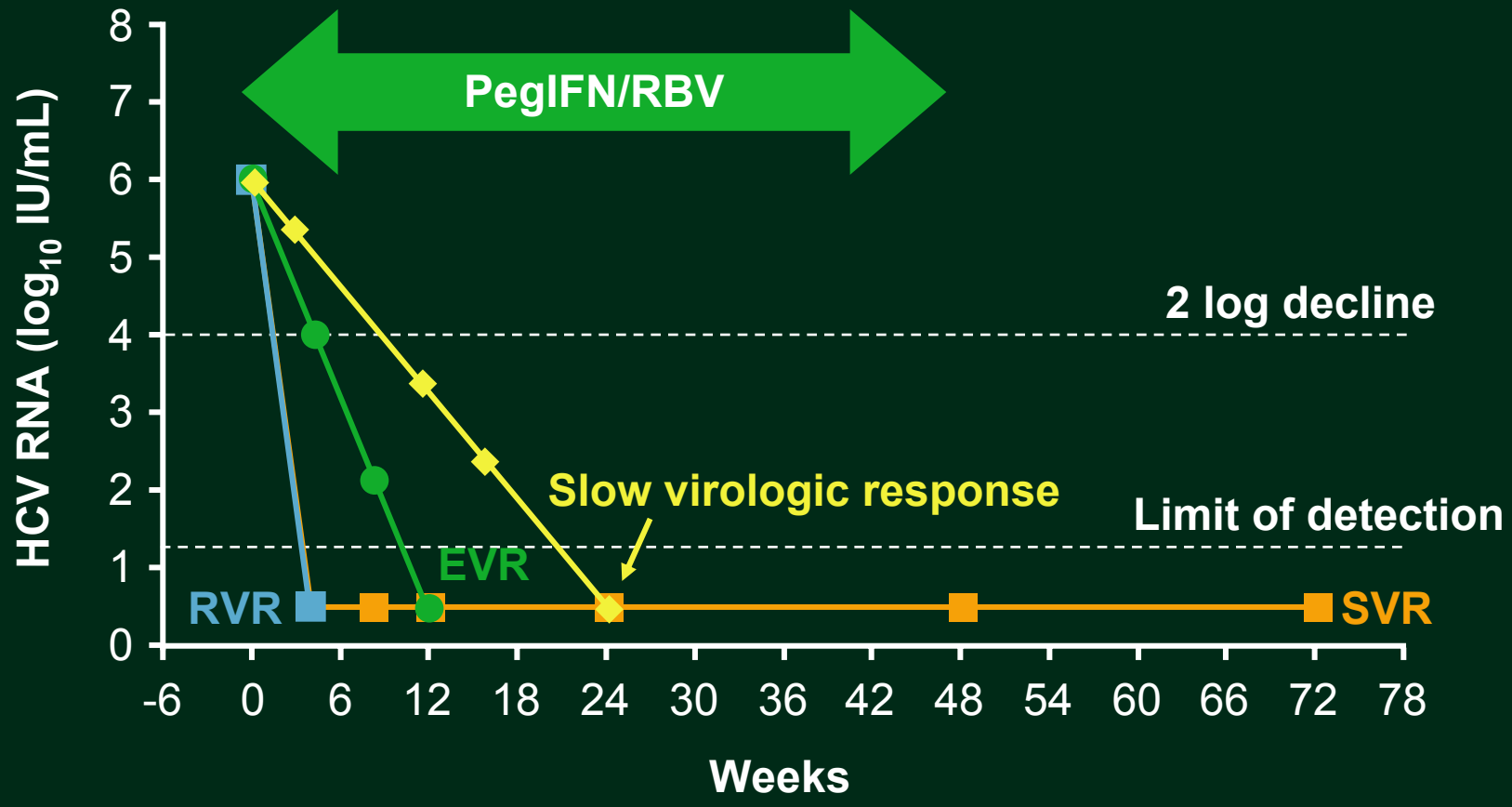
Early Virologic Response (EVR):

HCV RNA ↓ ≥ 2 logs or Undetectable at Week 12



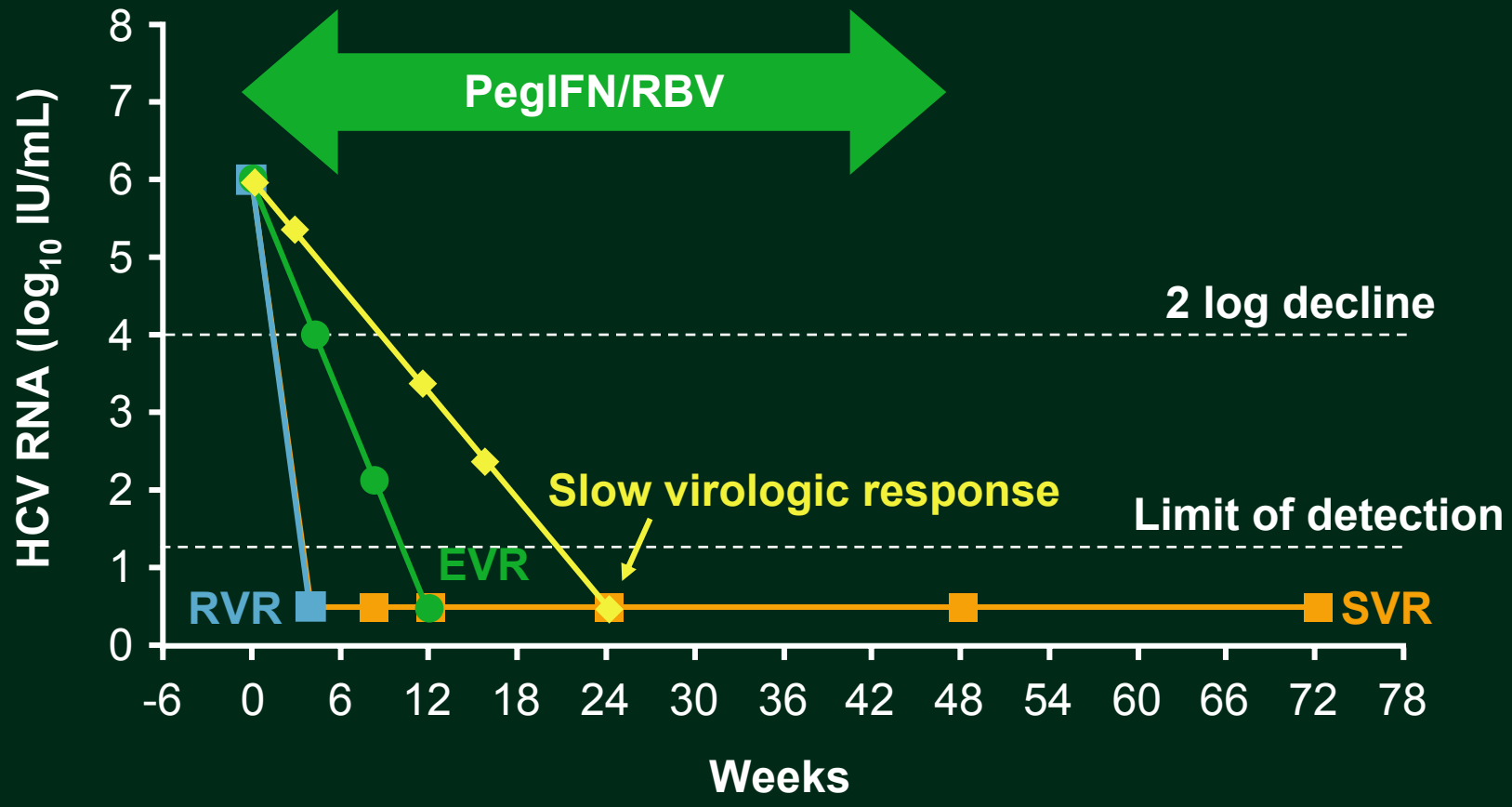
Slow Virologic Response:

HCV RNA Undetectable at Week 24

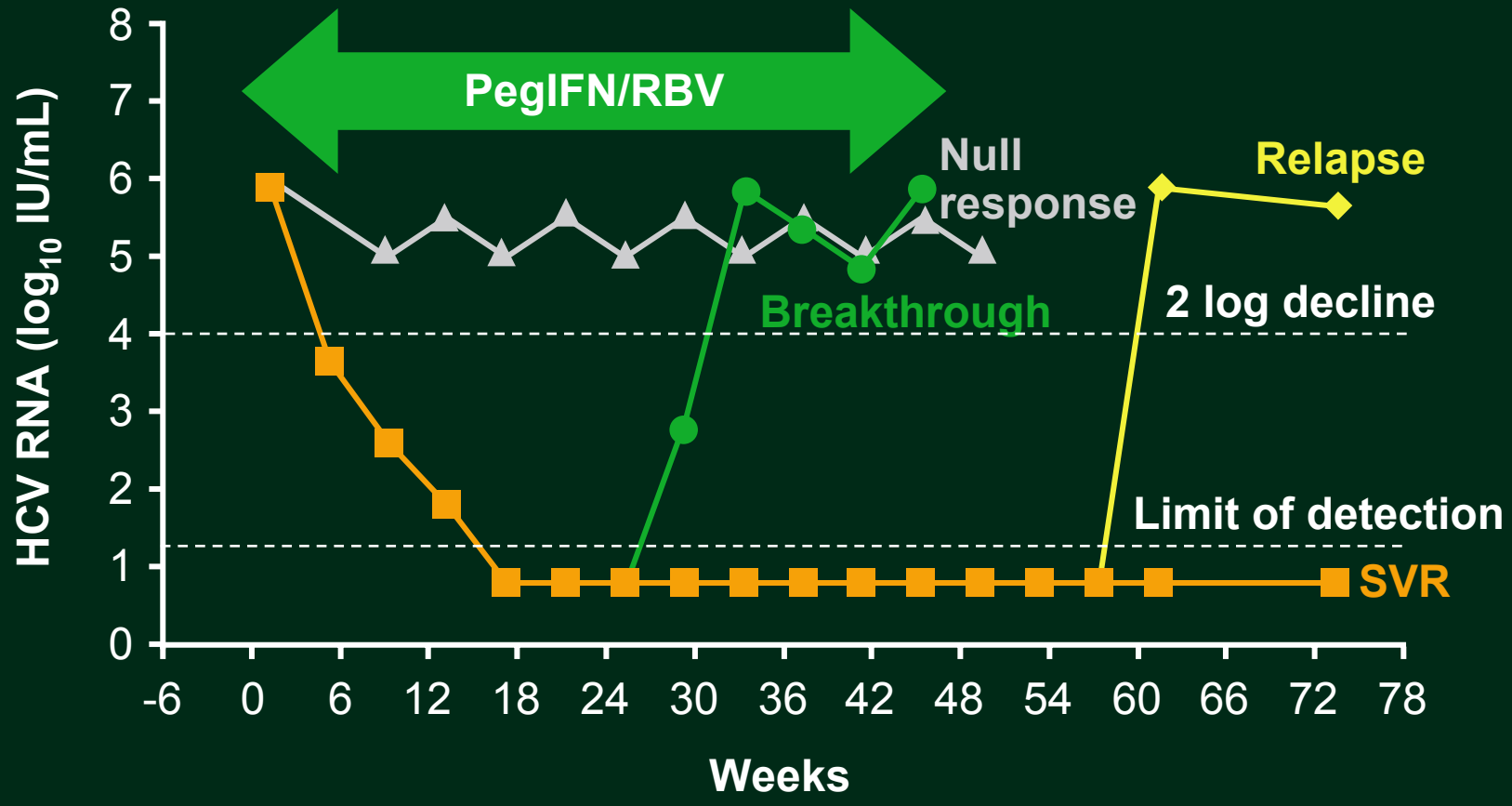


Slow Virologic Response:

Slow Responders



Null Response, Breakthrough and Relapse



Treatment failure: definitions

Non-response

- Detectable HCV RNA levels at the end of treatment or end of follow-up

Breakthrough

- HCV RNA levels become undetectable during treatment, but virus reappears while still on treatment

Relapse

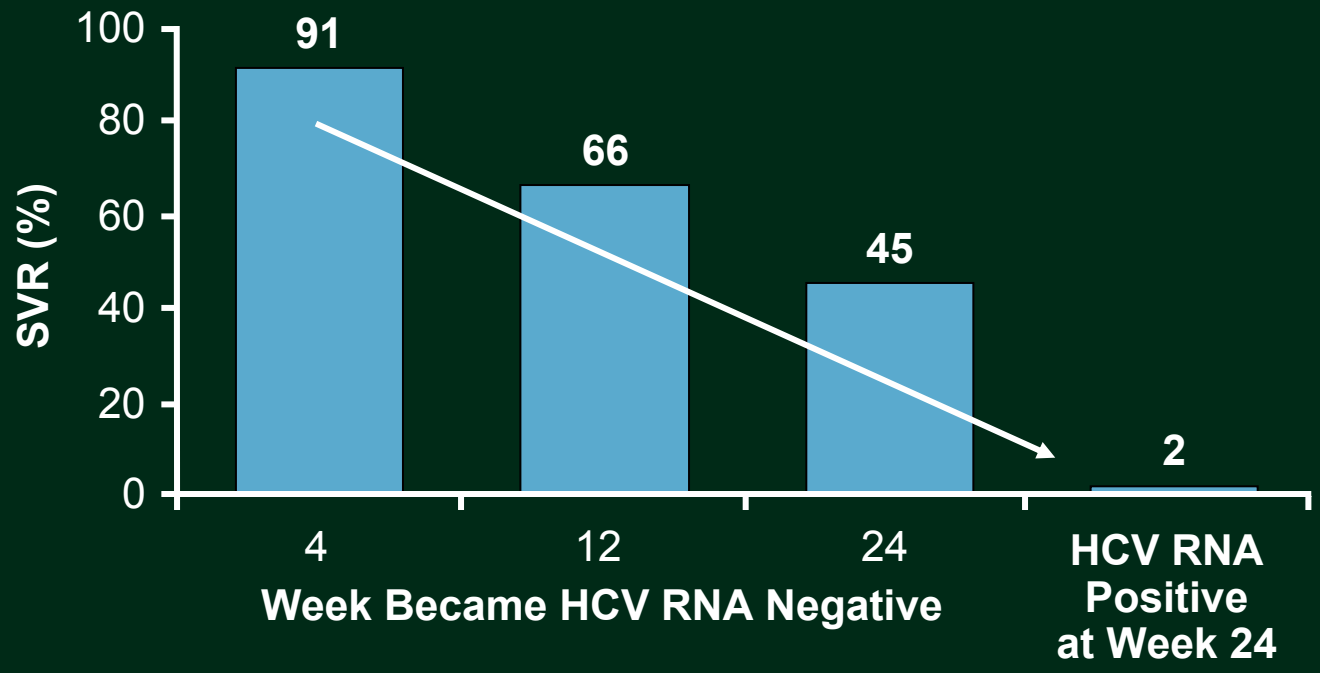
- HCV RNA negative at the end of treatment but subsequently positive during the follow-up period

1. Strader D, et al. Hepatology 2004; 39: 1147
2. Farci P, et al. PNAS 2002; 99: 3081

Importance of EVR on SVR

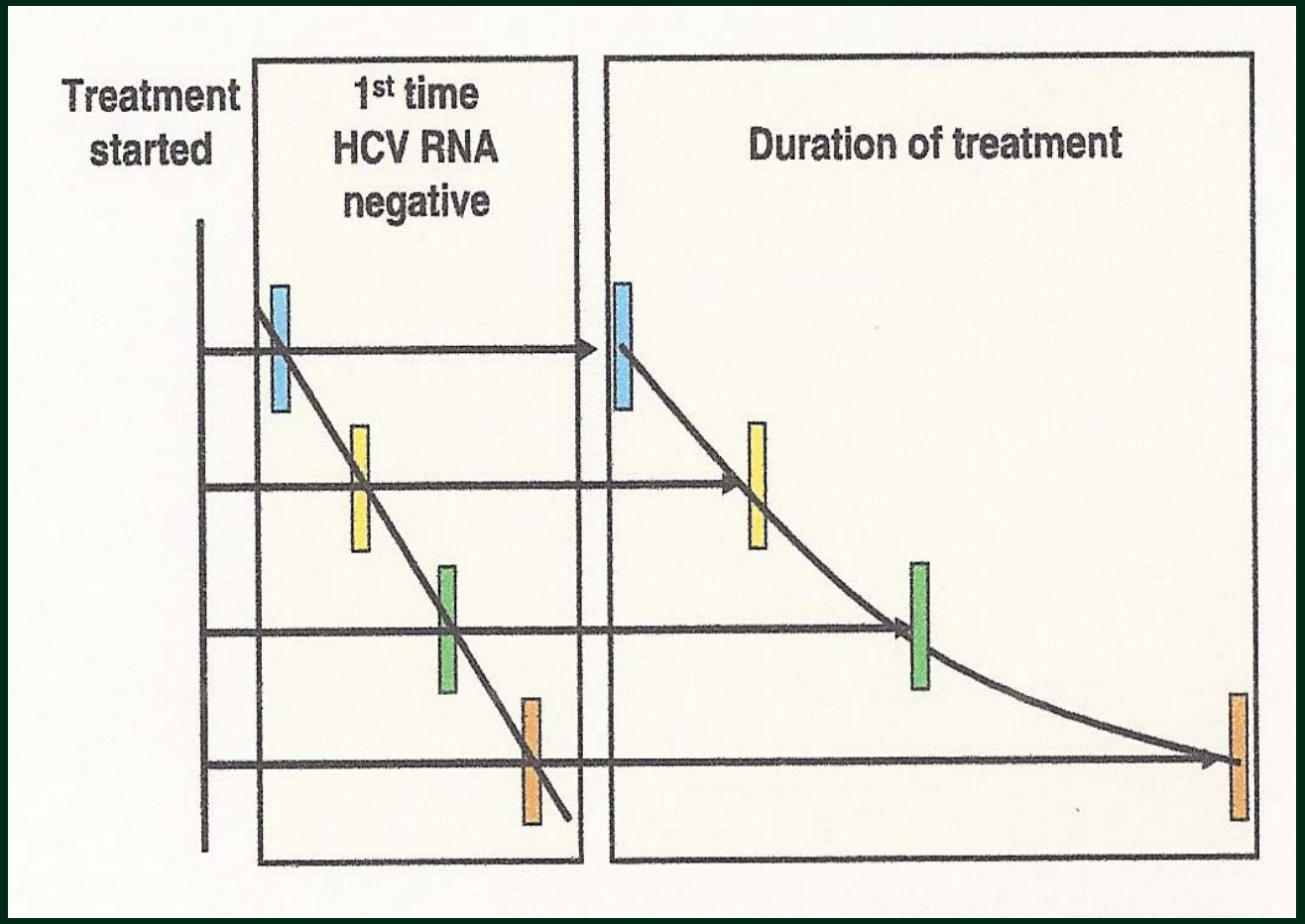
Predictive value of RVR/EVR on SVR

- Retrospective analysis of genotype 1 patients receiving 48 weeks of pegIFN alfa-2a + RBV (N = 453)



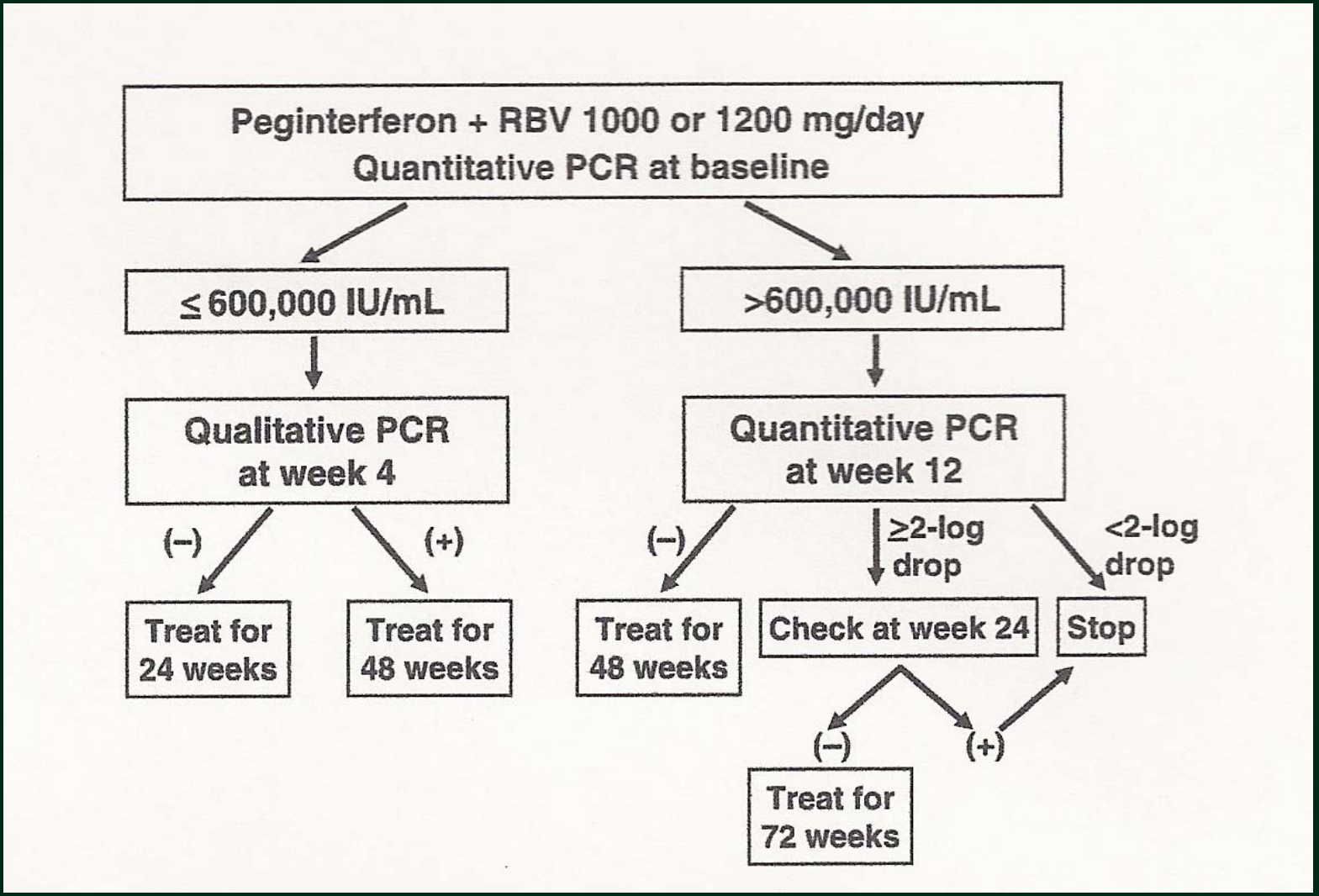
Ferenci P, et al. J Hepatol. 2005;43:425-433.

Mathematical model – the Accordion Principle



Marcellin et al Journal of Hepatology 47 (2007) 580–587

G1 algorithm



Who has Hepatitis C in the UK

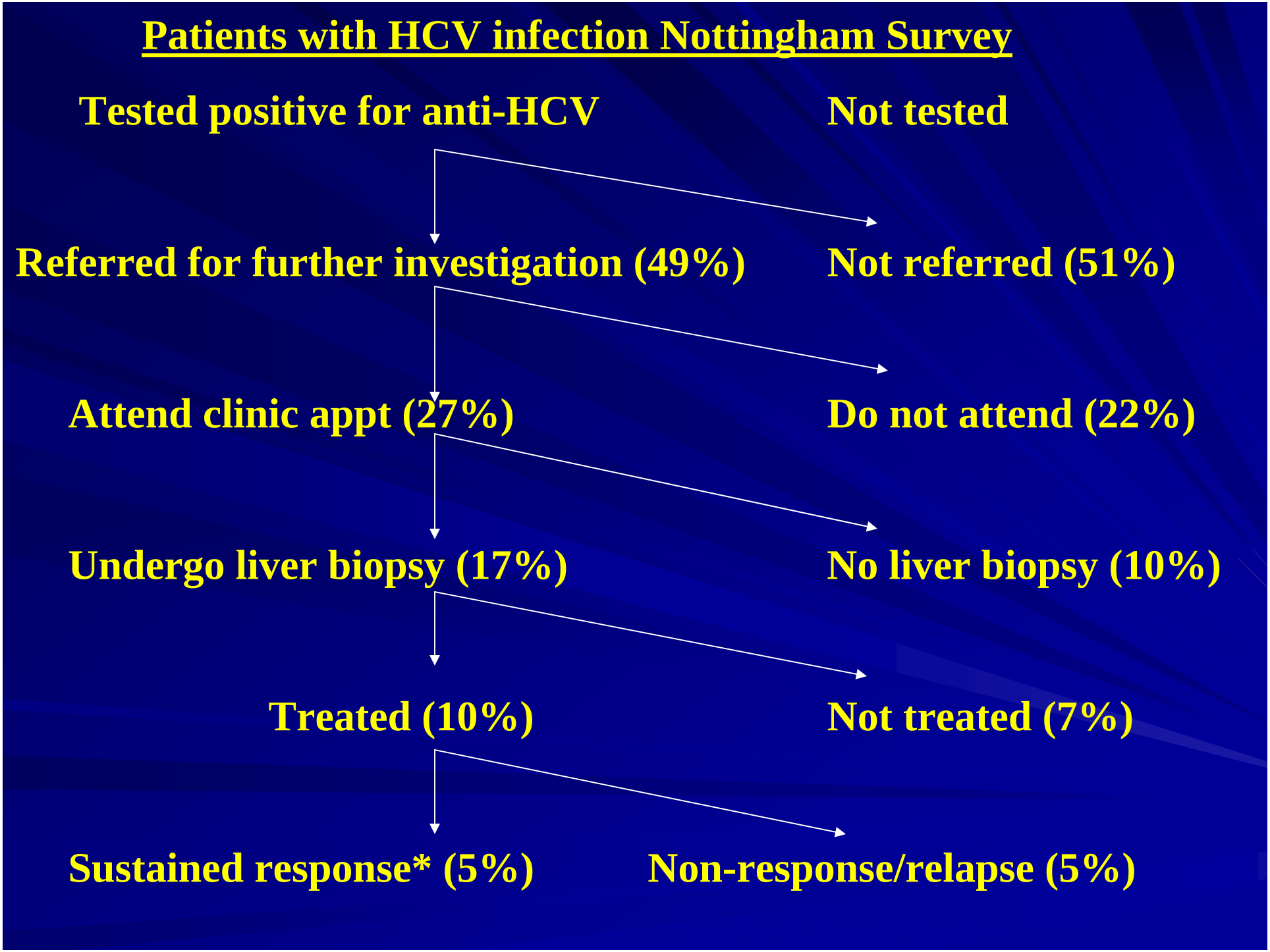
- IV drug users ? Prevalence
- People from high endemic areas

Problems in the UK

- Finding the patients
- Treatment
  - Cost
  - Side effects

Hepatitis C in the UK

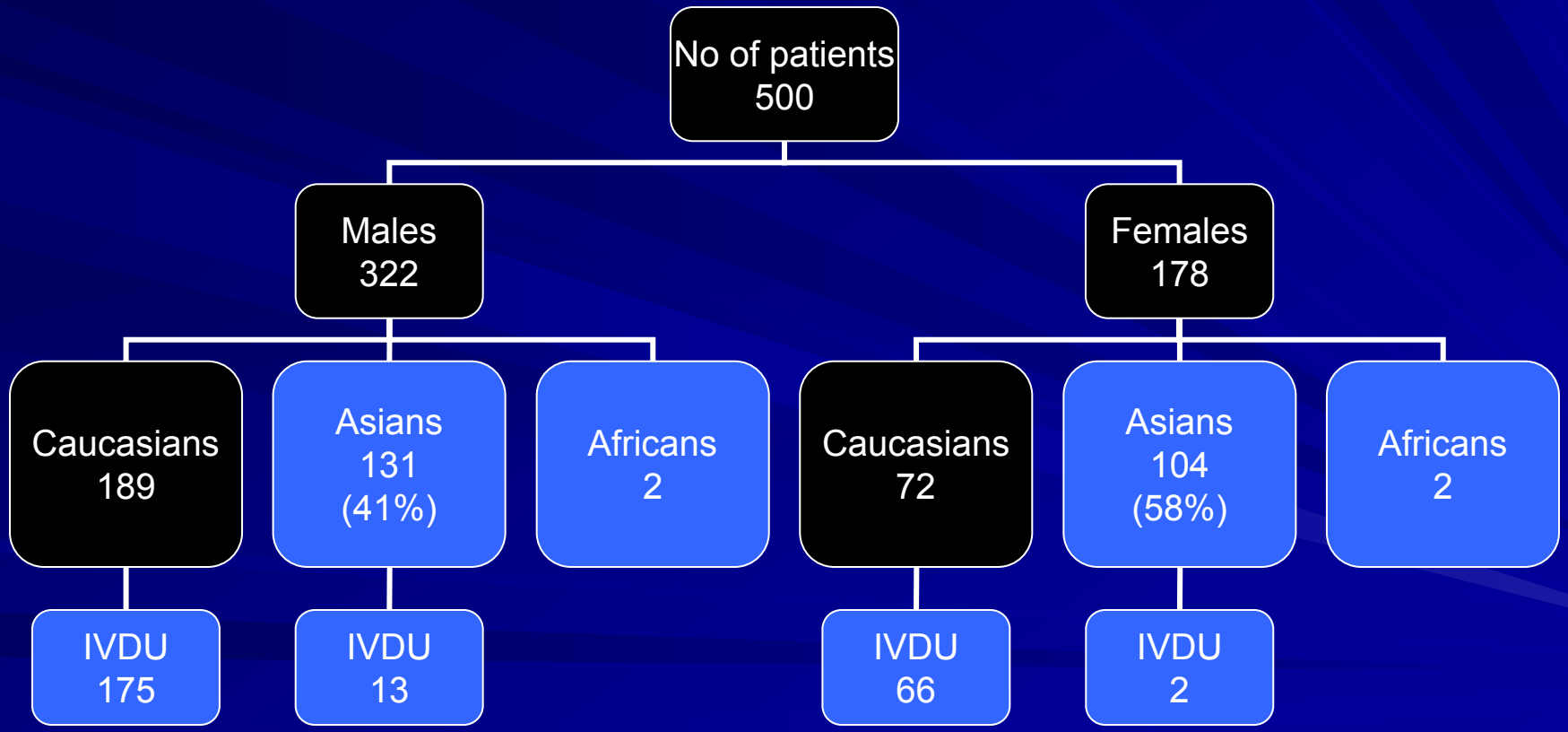
- 466,000 people in the UK are infected with hepatitis C
- 86% of people infected are unaware of their status, putting others at risk
- Only 1 in 7 of those infected have been diagnosed
- 1-2% of people with hepatitis C are treated with NICE approved therapies
- Unless urgent action is taken, 116,000 people will develop liver cirrhosis


Patients with HCV infection Nottingham Survey
Tested positive for anti-HCV
Not tested
Referred for further investigation (49%)
Not referred (51%)
Attend clinic appt (27%)
Do not attend (22%)
Undergo liver biopsy (17%)
No liver biopsy (10%)
Treated (10%)
Not treated (7%)
Sustained response* (5%)
Non-response/relapse (5%)

HCV burden in Bradford

- Based on the national figures – at least 1750 cases in Bradford

HCV seen in the BRI - 2008



Genotypes

Genotype	Males	Females	Total
1a	47	17	64
1b	26	11	37
2	10	6	16
3a	120	82	202
3b	1	1	2
4	8	2	10
N/A	110	59	169

Genotypes

Genotype	Males	Females	Total
1a	47	17	64
1b	26	11	37
2	10	6	16
3a	120	82	202
3b	1	1	2
4	8	2	10
N/A	110	59	169

Patients treated in Bradford

- 180 patients treated so far since 2005

Bradford – the community study

- DoH funded study in conjunction with London
- Mouth swabs from Asians in the community – mosques and community centres.

Bradford – the community study

- 1457 people from Oct 07 – Aug 08
  - Aged 16 and over
- Data from 1413 analysed

Results

Total	1413
males	1100
females	313

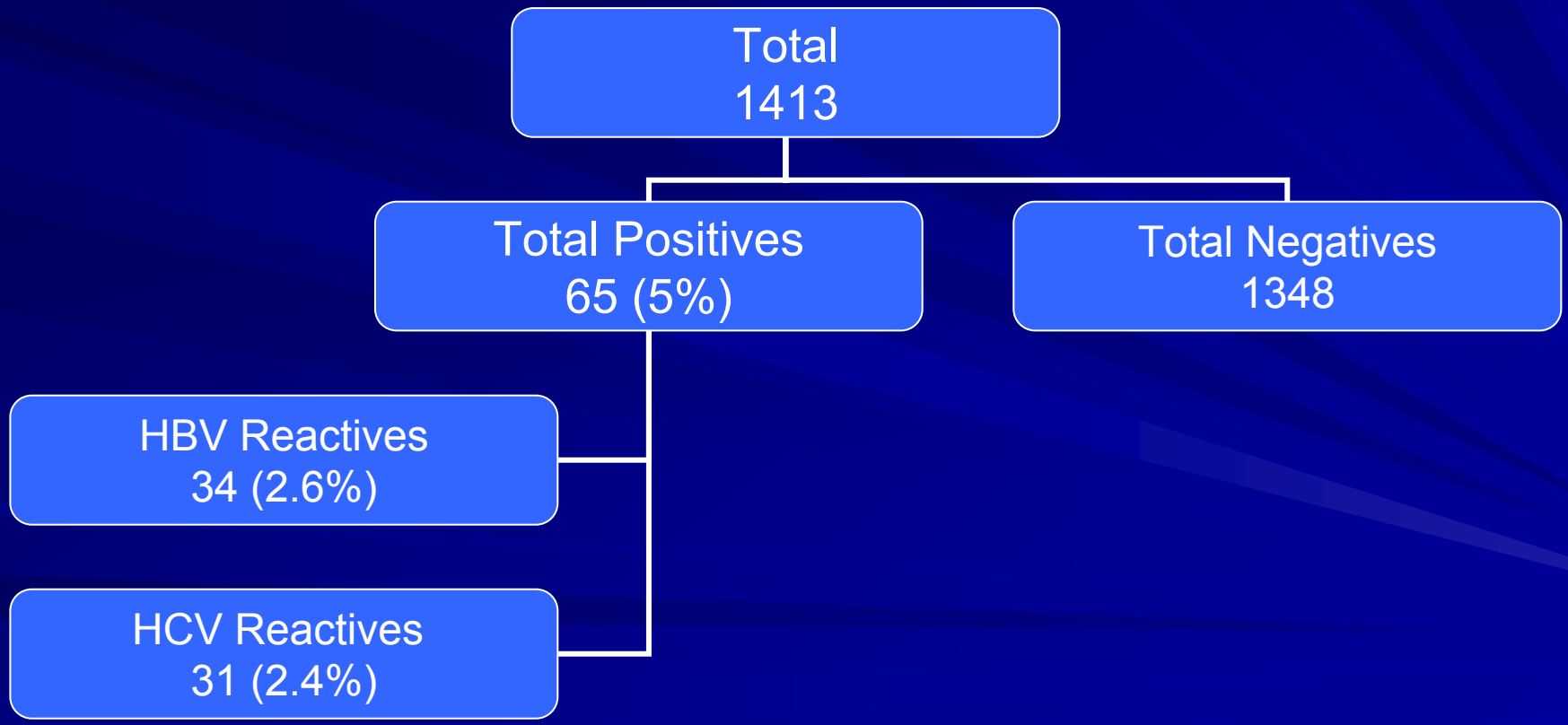
Alam S - Personal communication

Results

Breakdown of different population groups

Country/Ethnic group	Total	%	Males	Females
Pakistan	962	68%	769	193
Bangladesh	112	8%	107	5
India	57	4%	51	6
Afghanistan	15	1%	11	4
Burma	1	0.07%	1	
UK (UK born asians)	266	19%	161	105

Results



Alam S - Personal communication

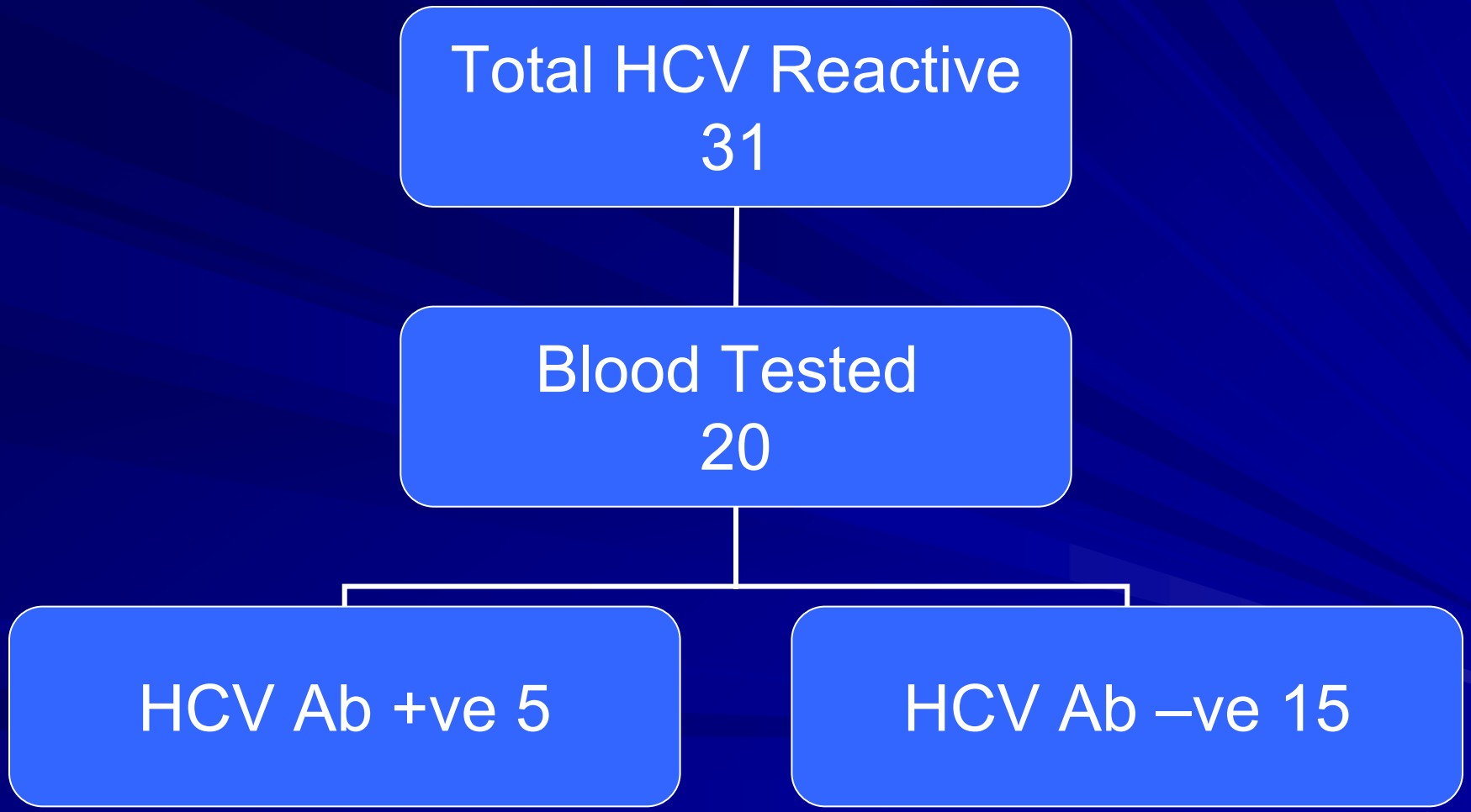
Results

Results of Mouth Swabs

HBV REACTIVE			HCV REACTIVE		
Total	Males	Females	Total	Males	Females
34	23	11	31	19	12
2.6%	2.1%	3.5%	2.2%	1.7%	3.8%

Alam S - Personal communication

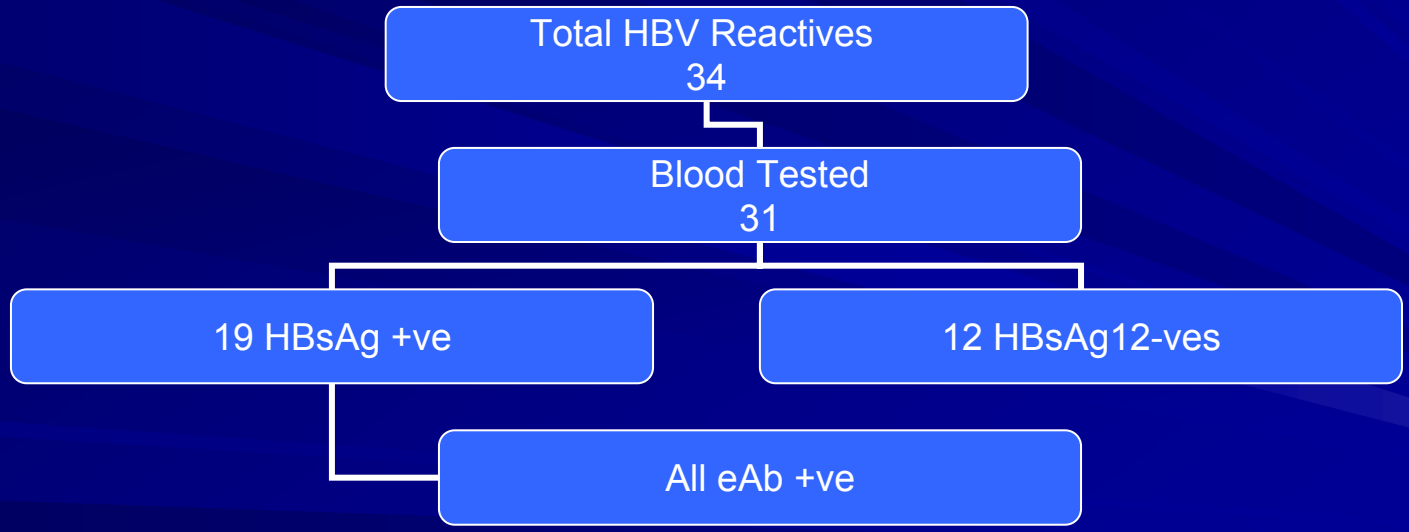
Results



Alam S - Personal communication

Results

Blood Test Results of subjects tested positive with mouth swab



Alam S - Personal communication

To conclude

- There are a lot of similarities between Bradford and Mauritius.
- The management of viral hepatitis is changing all the time – need for regular updates.