

Epidemiology of HCV and HIV in Patients with Coagulation Disorders

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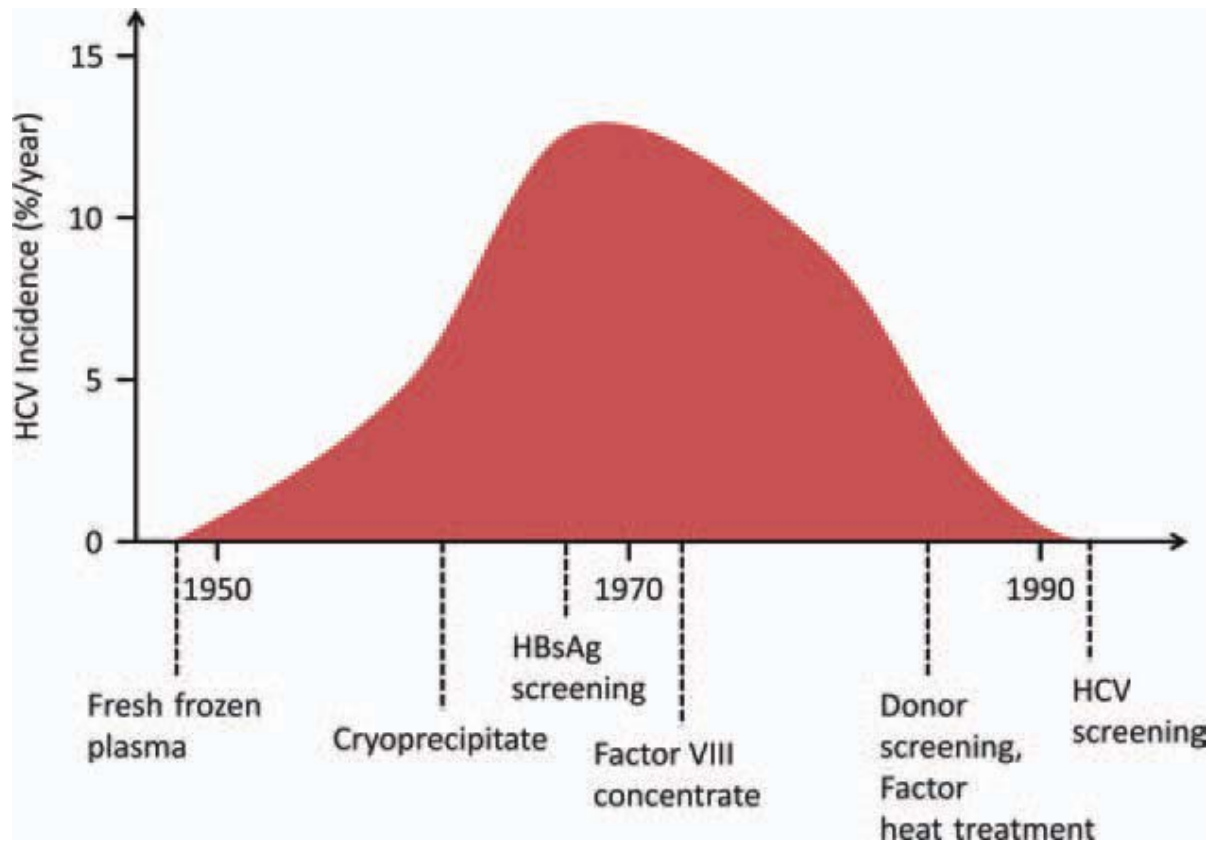
HCV and HIV Infection in Hemophilia

- Since the '70 hemophilia patients were treated with concentrated coagulation factors – Derived from >20,000 donors
- During the '80 most hemophiliacs acquired HCV and many contracted HIV as well
- Many HIV/HCV patients succumbed to AIDS

HCV and HIV Infection in Hemophilia

- Since 1987 all coagulation factor concentrates are undergoing virucidal process
- HAART regimens introduced in the '90 revolutionized the prognosis of HIV infection
- HCV infection has assumed much greater importance among HIV co-infected
- Patients are HCV infected for over 20 years

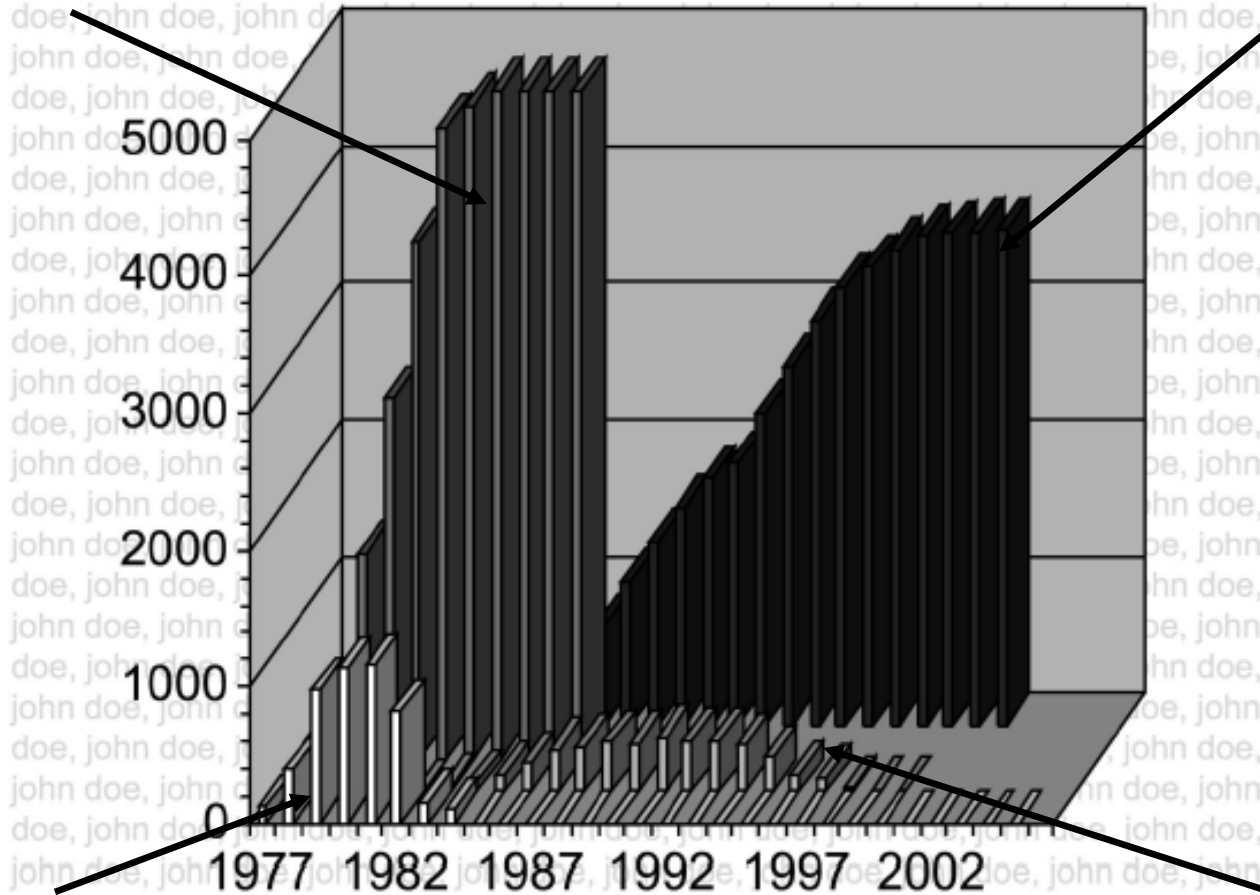
Incidence of HCV Among Hemophilia A Patients in the US*



HIV Infection in Hemophilia Patients

Cumulative infections by year

Cumulative deaths by year



Individuals infected by year

Deaths due to AIDS by year

Characteristics of HIV/HCV Co-Infected Hemophilic Patients

- A higher rate of progression to cirrhosis
- Accelerated progression to liver failure
- 21-fold more likely to develop hepatic decompensation after a median of 15 years
- Sevenfold increased liver-related death
- Hepatocellular carcinoma appears to develop after a shorter duration of infection

The Israeli National Hemophilia Center INHC

- Hemophilia patients in Israel were treated at one center from the beginning of the '70
- The INHC was officially founded in 1987

The Israeli National Hemophilia Center - INHC

- Multidisciplinary management of patients with bleeding disorders under one roof including:
 - Hematology - Coagulation experts
 - Nurses
 - Orthopedic surgeons
 - Physical therapists
 - Social worker
 - Psychologist
 - HIV and Hepatology experts

Specialized in coagulation disorders

HCV and HIV/HCV at the INHC

- Since 2000 regular hepatology consultation was established
- All patients with hemophilia and other coagulation disorders were screened for HCV and HIV – Targeting mainly those born <1986
- Patients were evaluated for the characteristics of their viral infection and severity of liver disease

HCV and HIV/HCV at the INHC

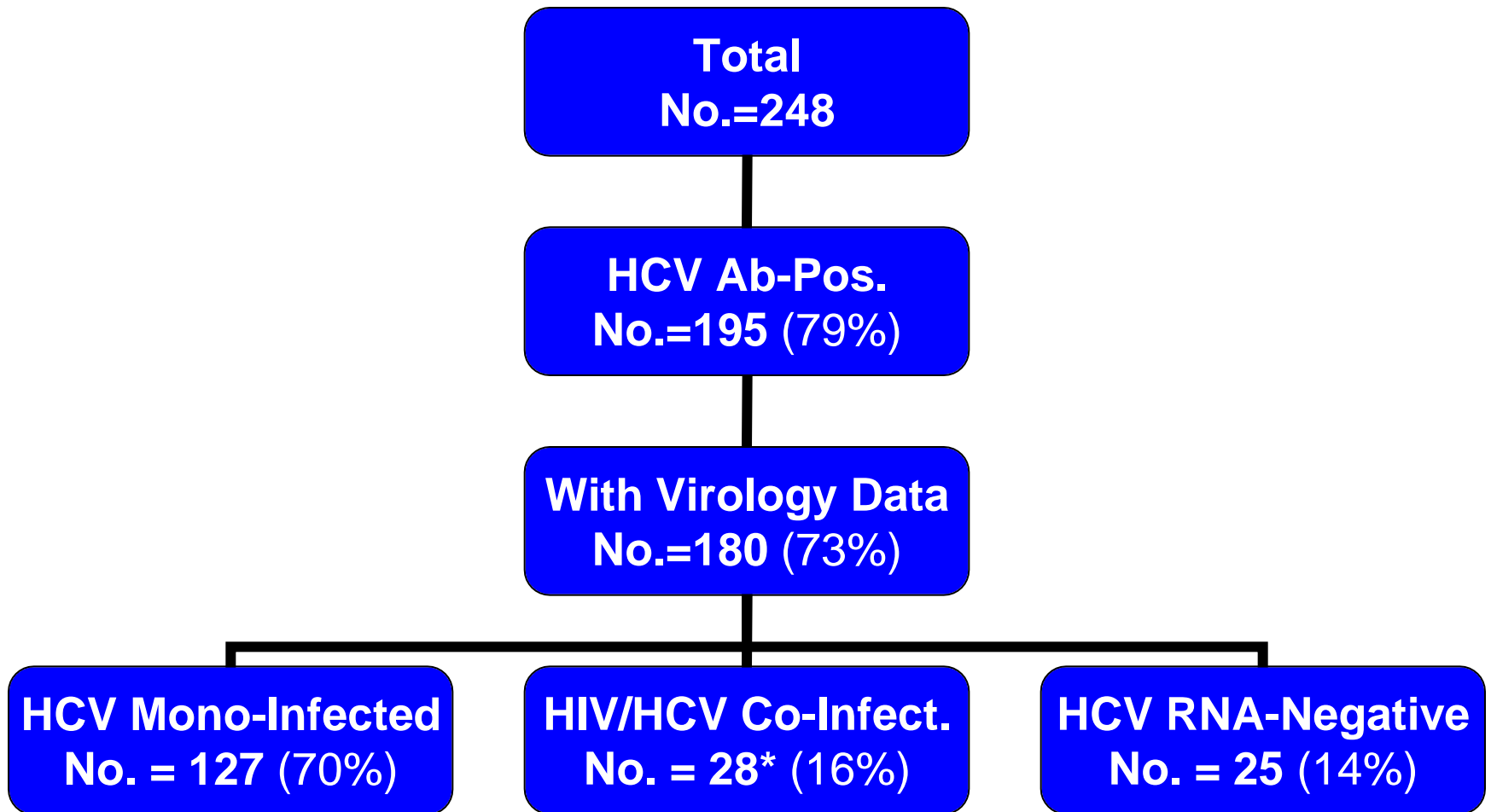
- Patients were consulted, and closely followed throughout their anti-HCV treatment
- Treatment was coordinated with both:
Hemophilia Nurse and **HIV specialist**

Immunization

- International guidelines recommend universal HAV and HBV immunization for patients with inherited coagulation disorders
- Both HCV infected and non-infected hemophilia patients were screened for HAV and HBV and immunized
- An annual follow-up of antibodies is conducted

HCV and HIV at the Israeli National Hemophilia Center - INHC

HCV Infection in Hemophilia Patients Born Before 1986



*3 patients were HCV RNA-negative

Demographics

	HCV (No.=127)	HCV/HIV (No.=28)	RNA-Neg (No.=25)
Age	36 ± 14 (16 – 71)	37 ± 10 (26 – 64)	35 ± 15 (16 – 58)
Female (%)	6 (5)	1 (4)	1 (4)
Israeli (%)			
Jews	53 (45)	20 (83)	9 (39)
Arabs	12 (10)	3 (13)	3 (13)
Immigrants (%)			
Former USSR	39 (33)	0*	10 (44)
Arab Countr.	9 (7)	1 (4)	1 (4)
Other	6 (5)		

* $p < 0.001$ for HIV/HCV vs. HCV and vs. RNA-Neg.

Coagulation Disorder

	HCV (No.=127)	HCV/HIV (No.=28)	RNA-Neg (No.=25)
Hemophilia (%)			
Hemophilia A			
Severe	93 (74)	25 (93)*	16 (64)
Mild/Moderate	11/1 (9/0.8)	0/2 (0/7)	5/1 (20/4)
Hemophilia B			
Severe	5 (4)		
Mild/Moderate	1/2 (0.8/2)		
Other (%)			
vWD	6 (5)		1 (4)
Glanzmann	3 (2)		1 (4)
Other	4 (3)		1 (4)

* $p=0.01$ for HIV/HCV vs. RNA-Neg.; $p=0.03$ for HIV/HCV vs. HCV

Coagulation and Blood Products

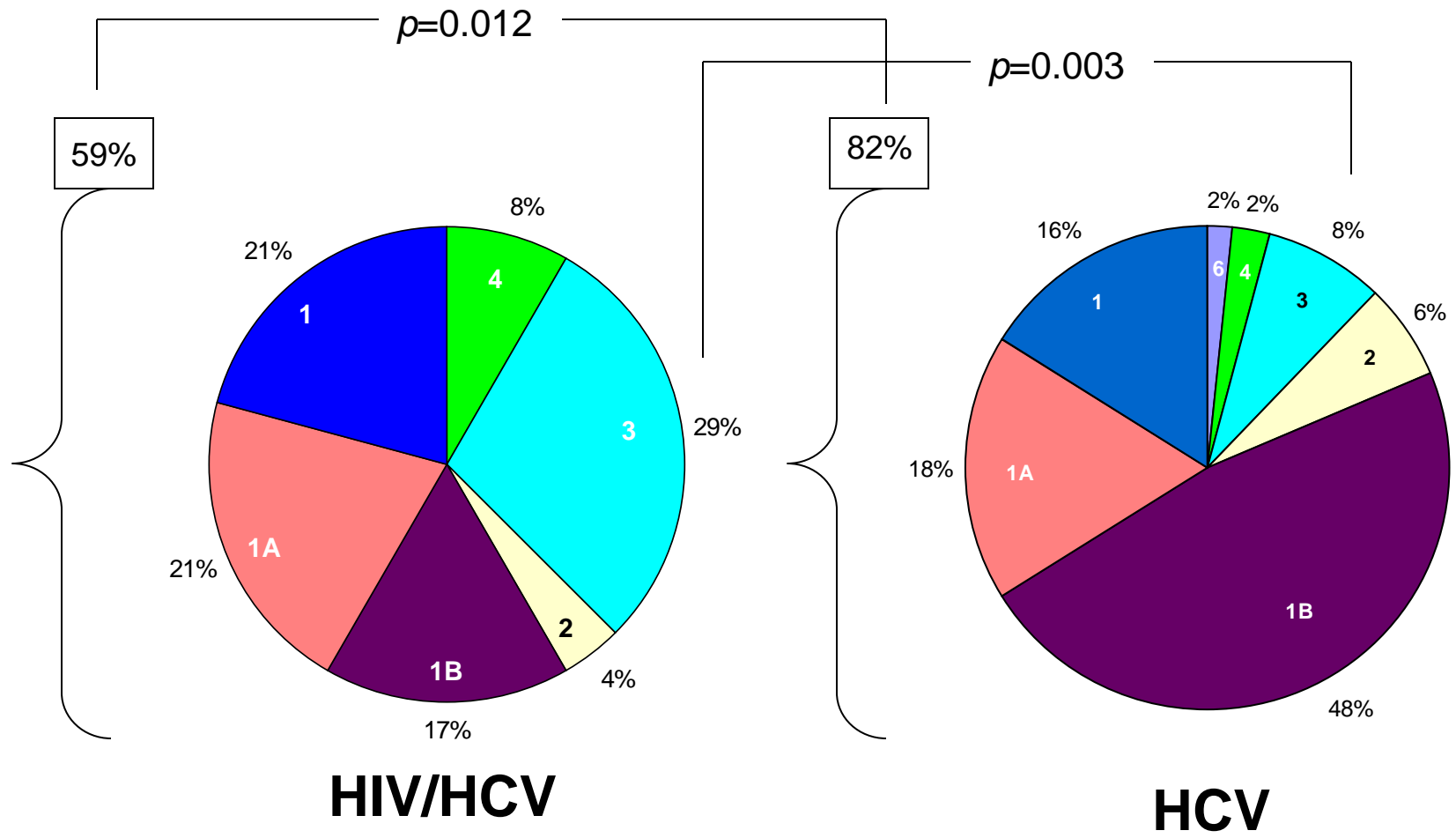
	HCV (No.=127)	HCV/HIV (No.=28)	RNA-Neg (No.=25)
Coagulation Factors (%)			
< 1987	51 (48)	23 (96)*	6 (35)
> 1987	55 (52)	1 (4)	11 (65)
Frequency (%)			
High (>/1 mo.)	63 (58)	13 (54)	8 (50)
Medium (</1 mo.)	14 (13)	5 (21)	
Low (</3 mo.)	31 (29)	6 (25)	8 (50)
Blood Trans. (%)	73 (70)	12 (52)	13 (72)

* $p < 0.001$ for HIV/HCV vs. HCV and vs. RNA-Neg.

Additional Risk Factors

	HCV (No.=127)	HCV/HIV (No.=28)	RNA-Neg (No.=25)
Risk Factors (%)			
Tattoo	1 (1)	2 (8)	
Alcohol	15 (14)	4 (17)	3 (15)
Tattoo+Alcohol	2 (2)		2 (10)
IVDA			1 (5)
HBV Serology		HBsAg-Pos. DNA-Neg.-1	HBsAg-Pos. DNA-Neg.-1
		HBcAb-1	

Distribution of HCV Genotypes



HCV - Viral Load

Viral Load	HCV (No.=122)	HIV/HCV (No.=24)*
< 800,000 IU/mL (%)	66 (54)	10 (42)
≥ 800,000 IU/mL (%)	56 (46)	14 (58)

*Not including 3 patients with persistent HCV RNA-negative

Characteristics of HIV Patients (No.=28)

HRT Treatment (%)	27
CD₄⁺ (Cells/mm³)	382 ± 207 (139 – 1,117)
Viral Load	
<LDL (%)	16 (62)
Detectable HIV RNA (%)	10 (38)
Median (Range) (Copies/mL)	2,350 (95 – 920,000)

Evaluation of Fibrosis in HCV and HIV/HCV Infected Hemophilia Patients

Non-Invasive Methods

Liver Biopsy in Hemophilia Patients

- Can safely be performed with no reported major complications
- Coagulation factor administration to achieve 100% replacement is costly
- Is met with reluctance from patients and care providers alike
- ❖ Therefore – Hemophilia patients are the most appropriate target for implementation of non-invasive methods

FibroTest

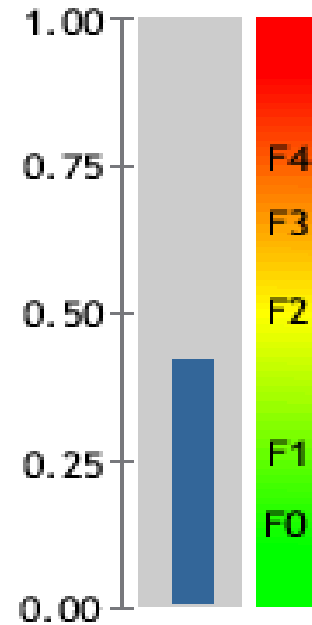


Bilirubin
 α_2 Macroglobulin
GGT



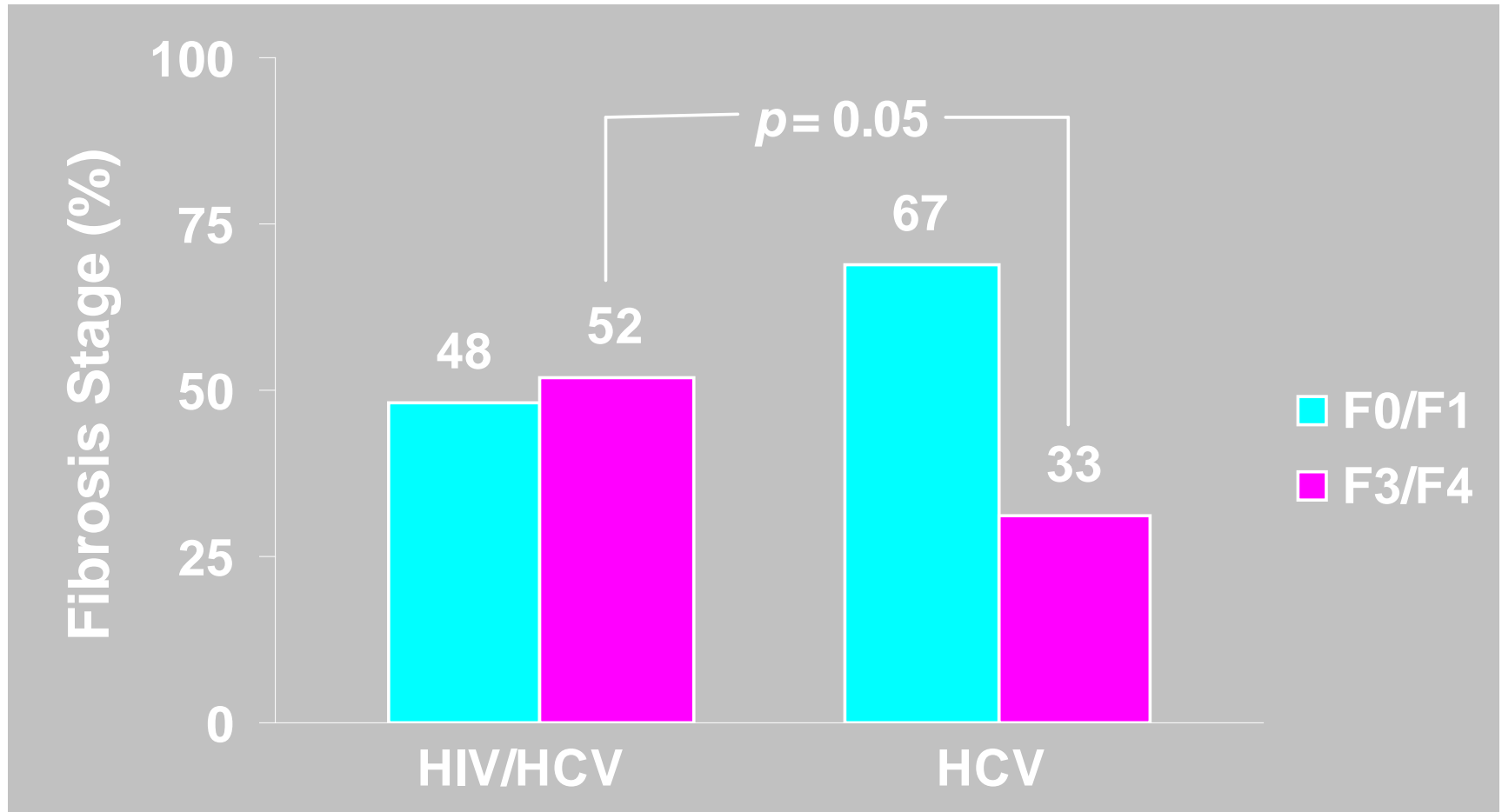
Haptoglobin
Apolipoprotein A1

FibroTest



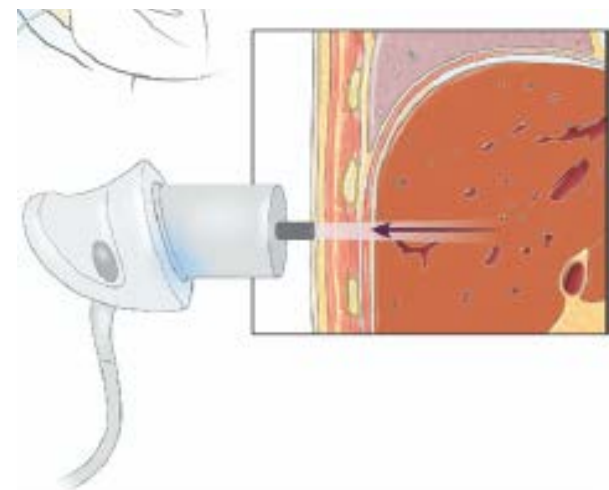
Score : 0.42
(F1-F2)

Fibrosis Stage by FibroTest

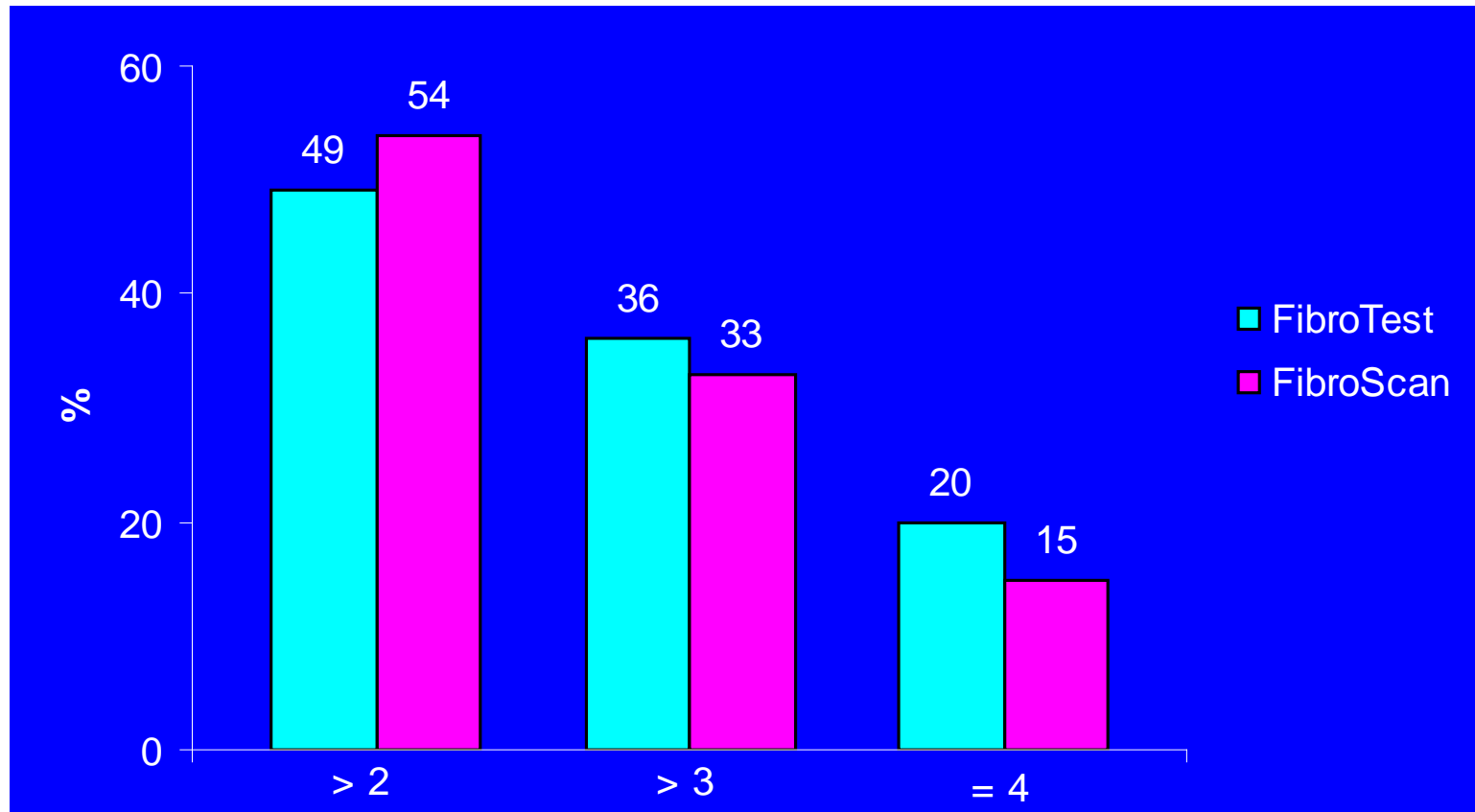


FibroScan

- Echo-wave velocity measurement provides a measure of liver stiffness (kilopascals-kPa)
- Liver stiffness correlates with stage of fibrosis



FibroTest vs. FibroScan in HCV and HIV/HCV Infected Hemophilia Patients



Concordance: 62%

69%

85%

Kappa Score: 0.24

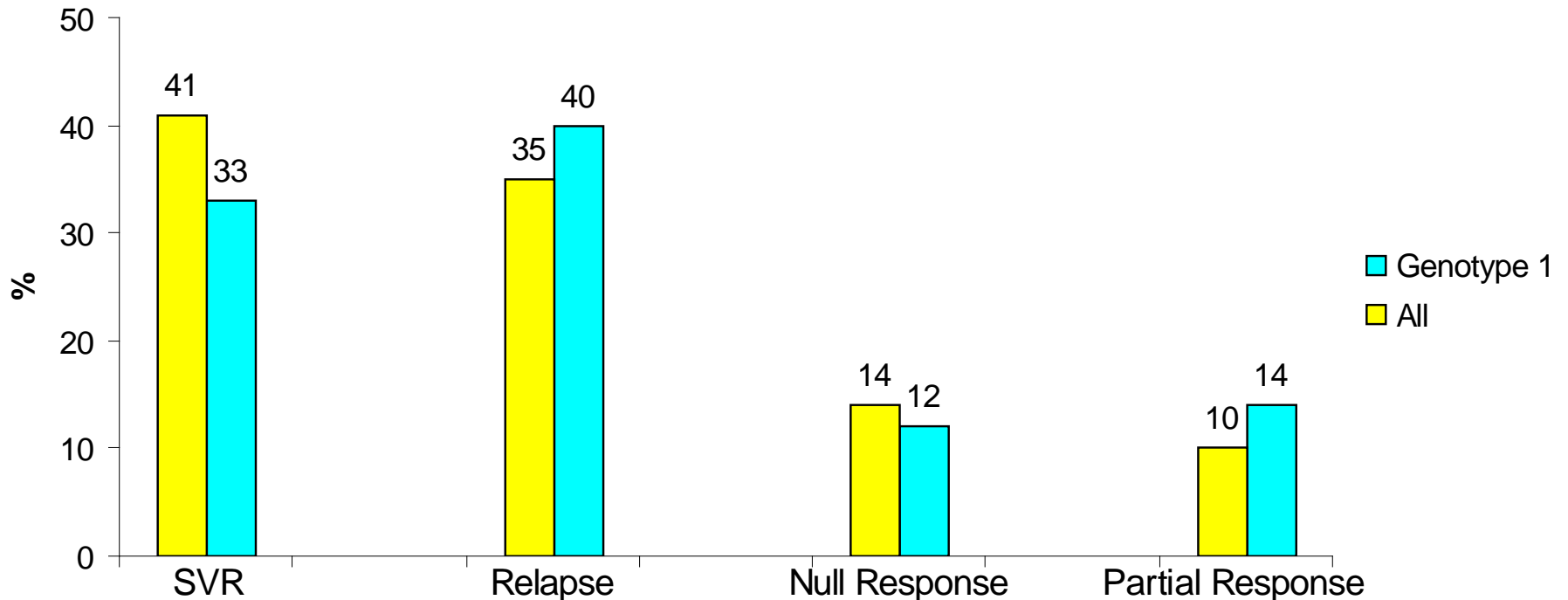
0.32

0.44

Treatment of HCV and HIV/HCV Hemophilia Patients

- 62 hemophilia patients were treated:
HCV - 51; HIV/HCV - 11
- 58 patients received Peg-IFN + ribavirin
- 4 patients received standard interferon + ribavirin
- Duration of treatment :
 - Genotype 1: - 12 months
 - Genotypes 2/3:
 - HCV - 6 months
 - HIV/HCV - 12 months

Virological Response – HCV Mono-Infection (No.= 51)



Virological Response – HIV/HCV Co-Infection (No. = 11)

- **Sustained Viral Response** - **3 (27%)**
- Relapse - 1
- Non-Response
 - Null Response - 2
 - Partial Response - 2
 - Suppression treatment with cont.
Standard Daily IFN + Ribavirin - 1

Adverse Effects - Anemia

- Significant anemia (Hb <10 mg/dL) occurred in:
 - HCV mono-infection - 12 (24%)
 - HIV/HCV co-infection - 2 (18%)
- Patients did not report:
 - Increase in bleeding episodes
 - More frequent use of coagulation factors

Treatment Discontinuation

- HCV mono-infection - 10 (20%)
- HIV/HCV co-infection - 2 (18%)
- Major reasons for treatment D/C:
 - Anemia (Including aplastic anemia)
 - Rash
 - Sepsis
 - Depression
 - Hepatic encephalopathy

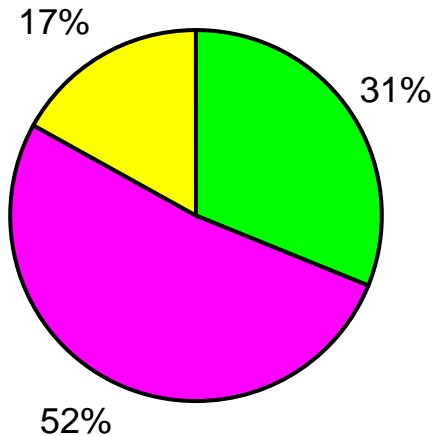
IL28B Haplotypes and HCV

- Single-nucleotide polymorphism (SNP) in the region of the *IL28B* gene is:
 - A key predictor of viral response to treatment
 - Important for spontaneous clearance of HCV

IL28B Haplotypes in HIV/HCV Co-Infected Hemophilia Patients

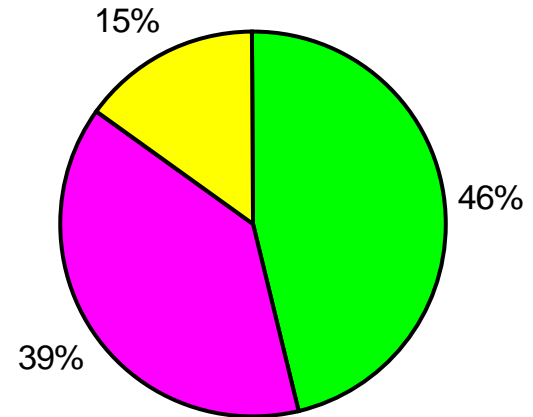
rs12979860

■ CC ■ CT ■ TT



HCV

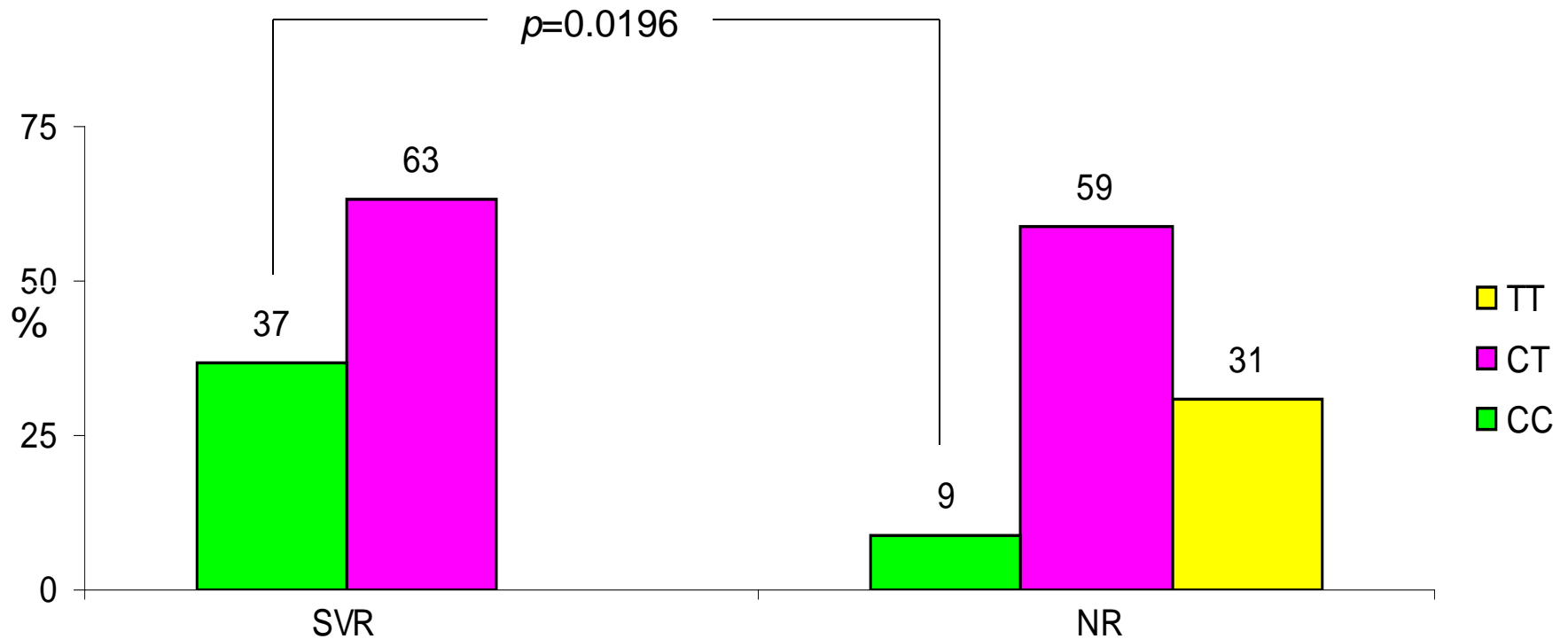
NS



HIV/HCV

CC = Favorable haplotype

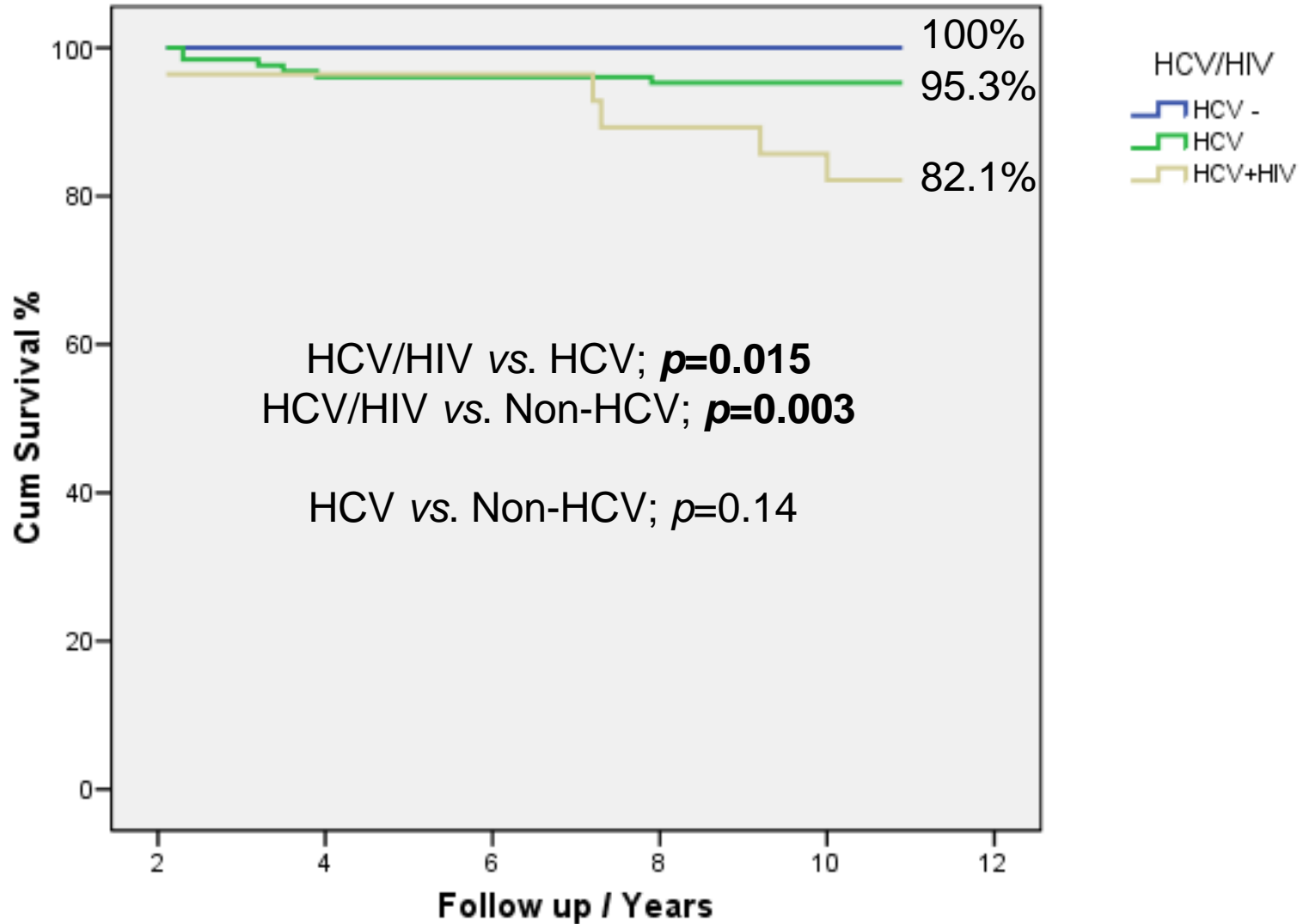
CC Haplotype of rs12979860 and Virological Response



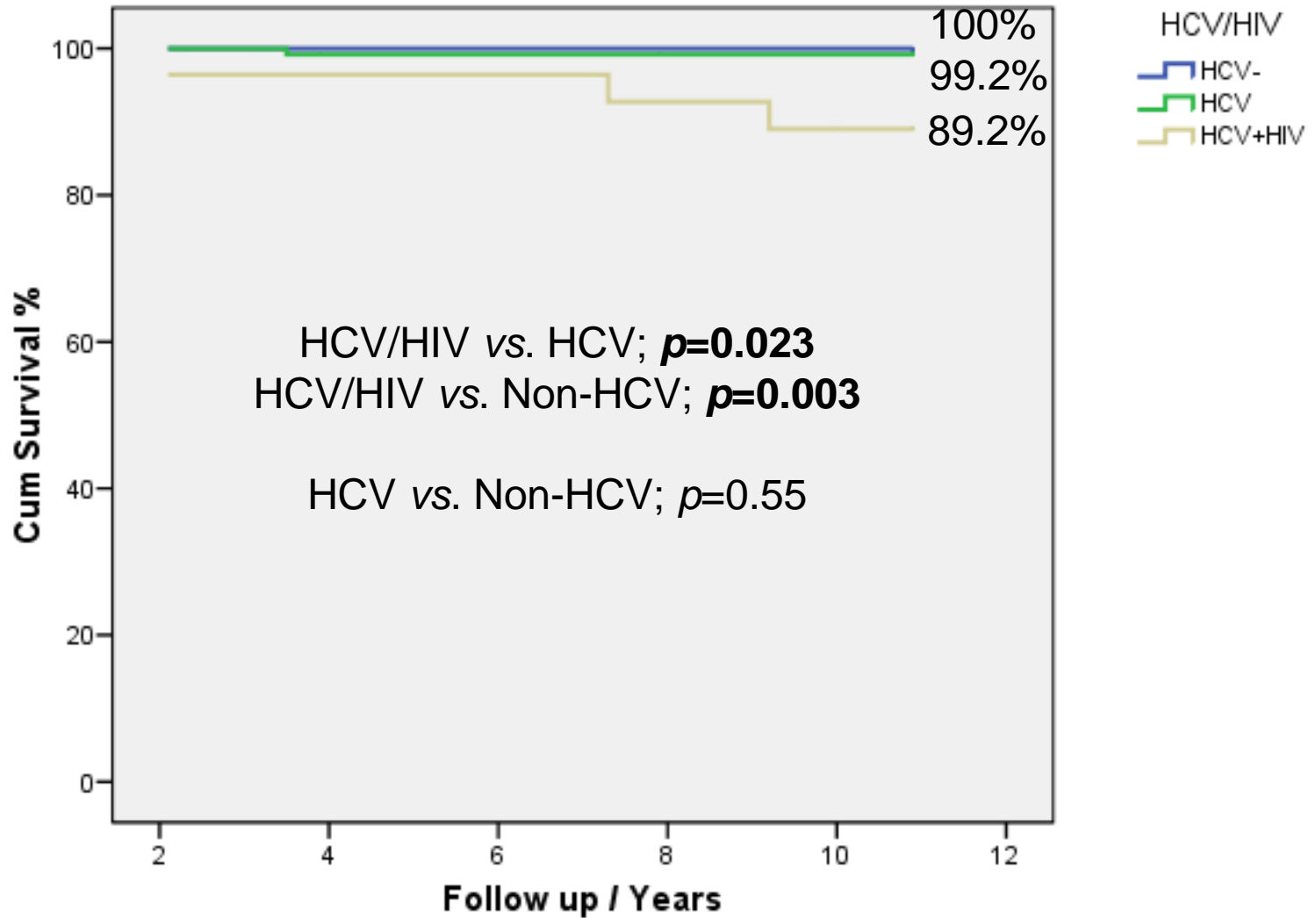
Natural History of HCV and HIV/HCV Infected Hemophilia Patients

Impact of Anti-HCV Treatment

Survival Functions



Survival Functions / Hepatic Mortality



Causes of Death

	HCV	HIV/HCV
End-Stage Liver Disease	1	3
Liver Transplantation	1	1
Septic Arthritis	2*	
Major Bleeding	2	
Suicide	1	
HIV		1
Dementia		1

*1 with clinical cirrhosis

Variables	Survived	Dead	RR	95% CI	p-value
No.	189	11			
<u>Age (years)</u>	33.1 ± 13.4	45.5 ± 12.8			0.006
HCV (%)	76.2	100.0			0.066
<u>HIV (%)</u>	12.2	45.5	5.120	1.674 - 15.651	0.002
Severe Hemophilia (%)	75.1	100.0			0.59
<u>Clinical Cirrhosis (%)</u>	2.1	45.5	17.685	6.633 - 47.150	<0.000
High Viral Load* (%)	53.3	50.0	0.859	0.260 - 2.840	0.803
F3-F4 (by FT**) (%)	35.4	75.0	5.957	0.575 - 49.892	0.097
Treated (%)	41.0	27.3	0.563	0.155 - 2.038	0.371
SVR (%)	40.7	33.3	0.740	0.071 - 7.730	0.8
<u>Genotype 1 (%)</u>	81.3	50.0	0.263	0.081 - 0.851	0.019

*≥800,000 IU/mL; FT-FibroTest

HCV and HIV/HCV in Hemophilia - Summary

- The majority of hemophilia patients born <1986 are infected with HCV
- ~15% are HIV/HCV co-infected
- All hemophilia patients with HIV were exposed to HCV
 - Suggesting that hemophilia patients contracted HCV first
- The majority HIV/HCV co-infected have severe hemophilia and received coagulation factors before 1987

HCV and HIV/HCV in Hemophilia - Summary

- Non-invasive monitoring of liver disease is feasible and a desirable method to prioritize treatment and assess disease progression
- The success rate anti-HCV treatment was inferior compared with other reports
- The prognosis of HIV/HCV co-infected is worse than of HCV mono-infected hemophilia patients
 - Mainly due to liver related mortality

- Israeli National Hemophilia Center -

- INHC

- Dalia Bashari – Head Nurse
 - Jonathan Schapiro – HIV Specialist
 - Uri Martinowitz – Head of INHC

For their devoted care of hemophiliacs!

- Special Thanks

- Philippe Halfon – Laboratoire Alphabio France

For making everything possible!