HCV TREATMENT IN PATIENTS WITH INHERITED BLEEDING DISORDERS

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DISCUSSION TOPICS

- HCV TREATMENT TRIALS
  - Current Literature
  - Are HCV responses in Patients with Inherited Bleeding Disorders Different?
- STUDY DESIGN CONSIDERATIONS
- SAFETY ISSUES
  - Liver Biopsy
  - Inhibitors

TREATMENT OF HCV
Patients with Inherited Bleeding Disorders

Author	Reference	N	Treatment	Other	SVR
Zhang	Haemophilia 2010	22 (all HIV+)	PEGIFN		41%
Alavian	Liver International 2010	367 (Naïve/Experienced)	PEGIFN + Riba	29% Non-1,4	61% 43% Among Prior Non-responders
Mancuso	J Thromb Haemost 2009	34 (all HIV+)	PEGIFN + Riba (WB)	63% Non Genotype 1	44%
Denholm	Haemophilia	13 (all HIV +)	PEGIFN + Riba (WB)		8%
Rahmani	Haemophilia 2009	103	IFN + Riba	70% Non Genotype 1	56.3%
Katsarou	Acta Haematol 2008	50	PEGIFN + RIBA		40% 58% HIV- 10.5% HIV+
Maor	Haemophilia 2008	43	PEGIFN or IFN + Riba		46% (PEG group) 37% Geno 1
Mancuso	Haematolog 2006	64 (all HIV neg)	PEGIFN + Riba (WB)	66% Genotype 1	63%
Santagostino	Transfusion, 2004	34	IFN + Riba (WB)		41%
Hanabusa	CID, 2002	30	IFN alfa 2a (9 MU)	56%	40% HIV- 33% HIV+
Fried	Hepatology2002	113	IFN alfa + riba (1000)	32%	29%
Schulman	Haemophilia, 2002	61	IFN alfa 2b + riba		41% 22% geno 1
Burton	Eur J Gastro Hepatol	58	IFN		14%

<800 Patients in Multiple Regimens and with Treatment Naïve/Experienced & HIV

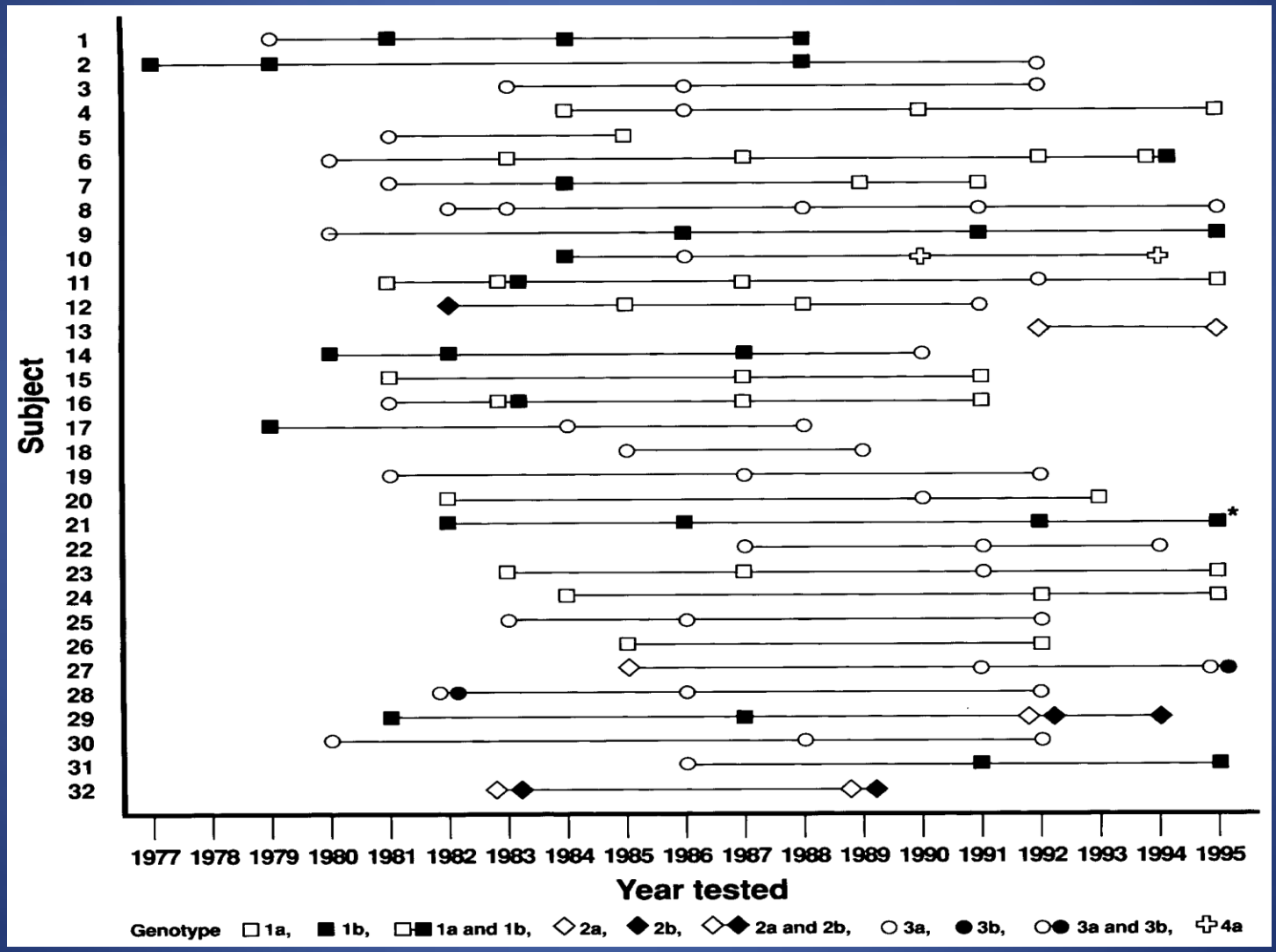
Are Patients with Inherited Bleeding Disorders Different?

- Genotype Change
- Quasispecies Complexity and Polymorphic Expression at Resistance Sites
- Immunologic Responsiveness

GENOTYPE CHANGE

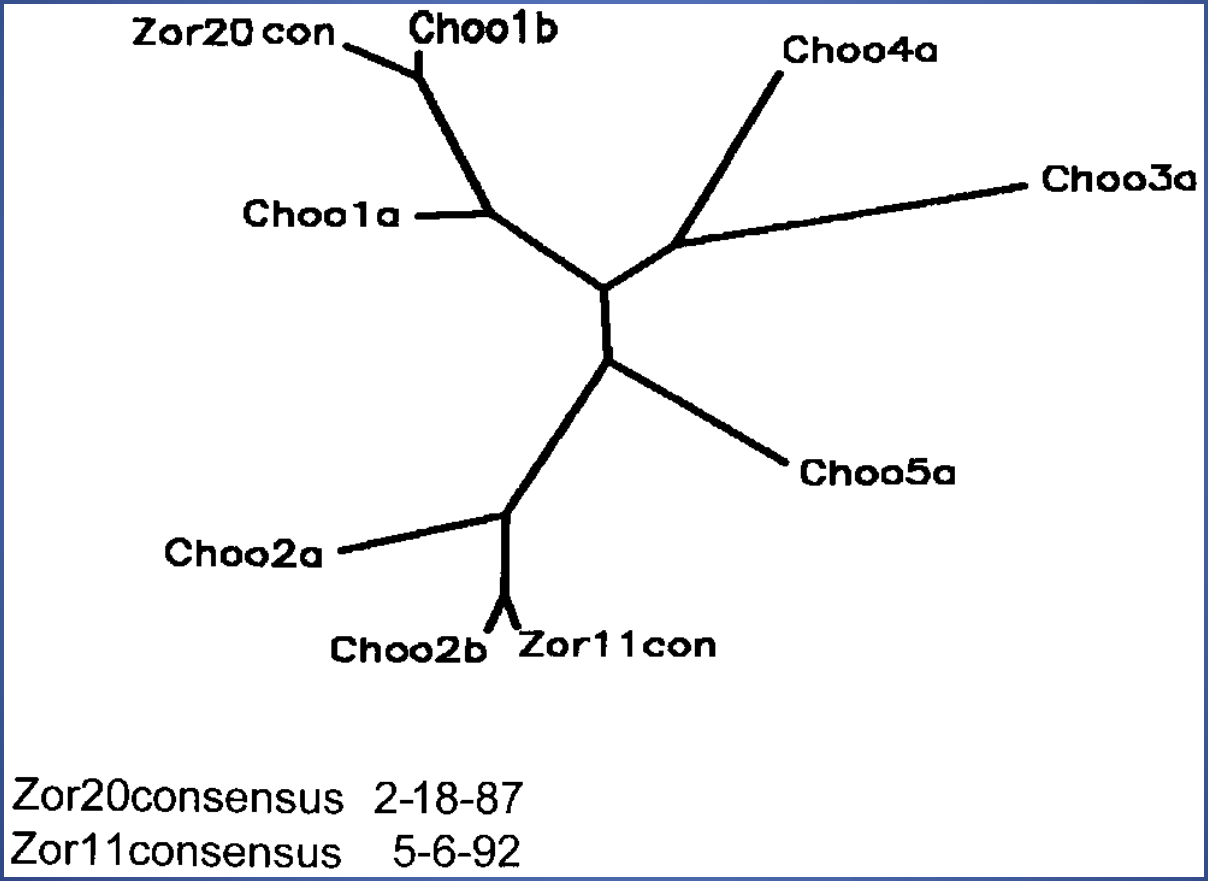
- Mixed Genotypes Rare in HCV
- Mixed Genotype Reported in 1.6-45% of persons with Hemophilia
- Genotype Change Exceedingly Rare Except with Sequential Infections in IDU

GENOTYPE CHANGE



Eyster, Sherman, Goedert, Katsoulidou, Hatzakis for the MHCS, J INF DIS 1999

GENOTYPE CHANGE
Phylogenetic Analysis



Eyster, Sherman, Goedert, Katsoulidou, Hatzakis for the MHCS, J INECT DIS 1999

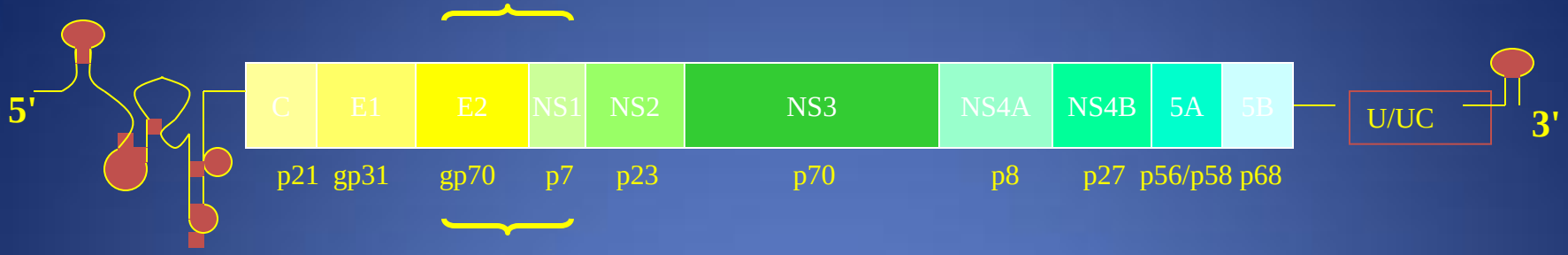
VIRAL HETEROGENEITY

- Genotypes
- Quasispecies
  - Diversity
  - Complexity

Methods: Analyses

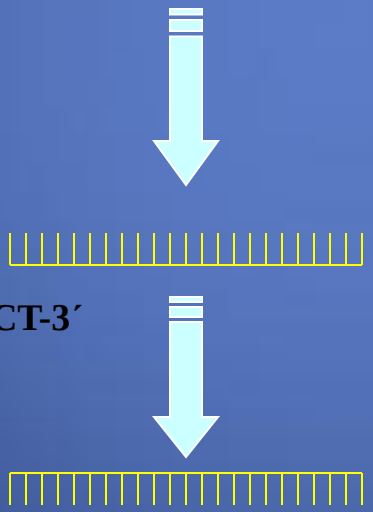
- Quasispecies complexity:
  - Heteroduplex complexity assay (HCA)
  - Cloning and sequence analysis

Amplification of HVR1



136-bp HVR1

Nested PCR



External forward:

5′-GGTGCTCACTGGGGAGTCCT-3′

External reverse:

3′-CATTGCAGTTCAGGGCCGTGCTA-5′

Internal forward:

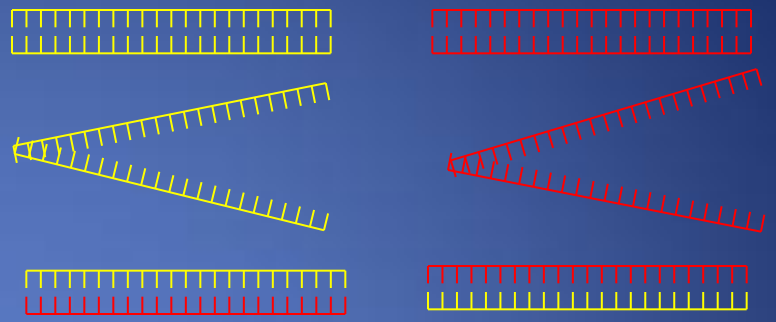
5′-TCCATGGTGGGGAACTGGGC-3′

Internal reverse:

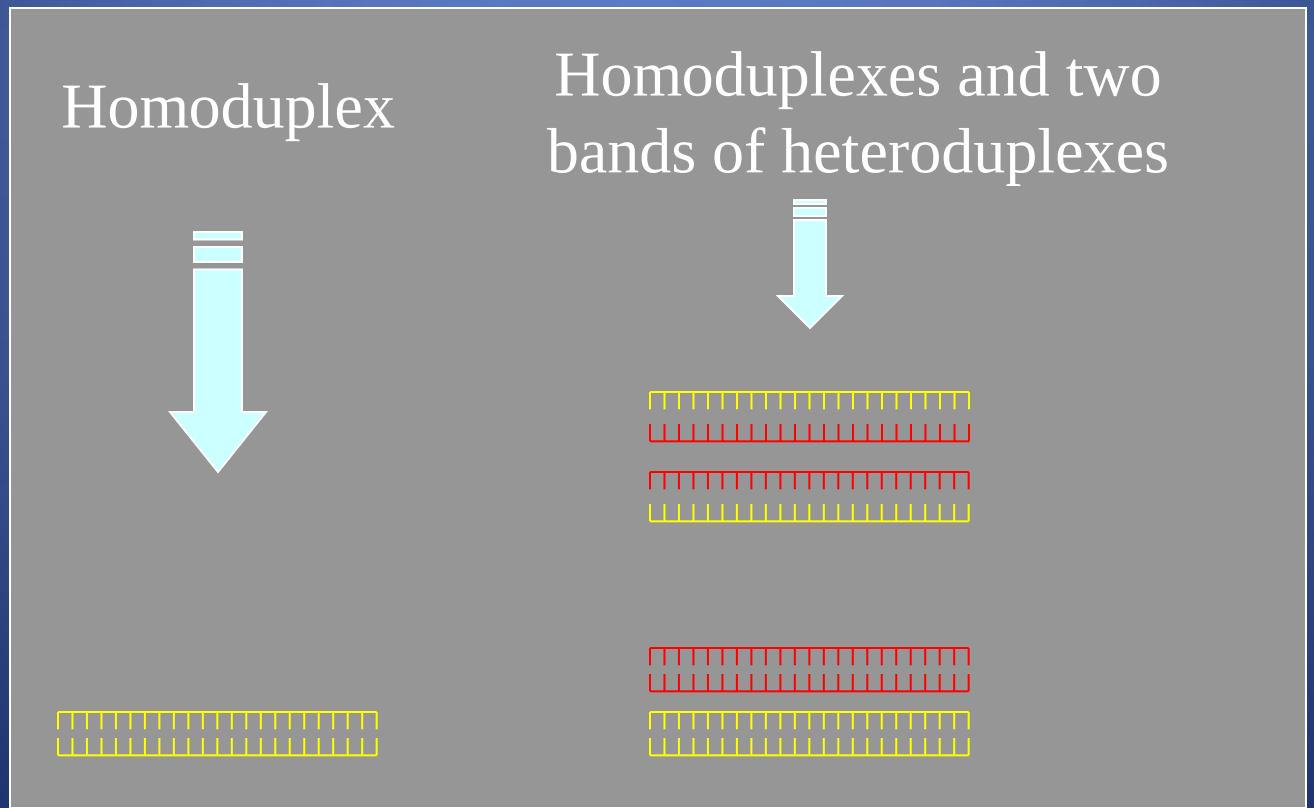
3′-TGCCAACTGCCGTTGGTGTT-5′

Heteroduplex Methodology

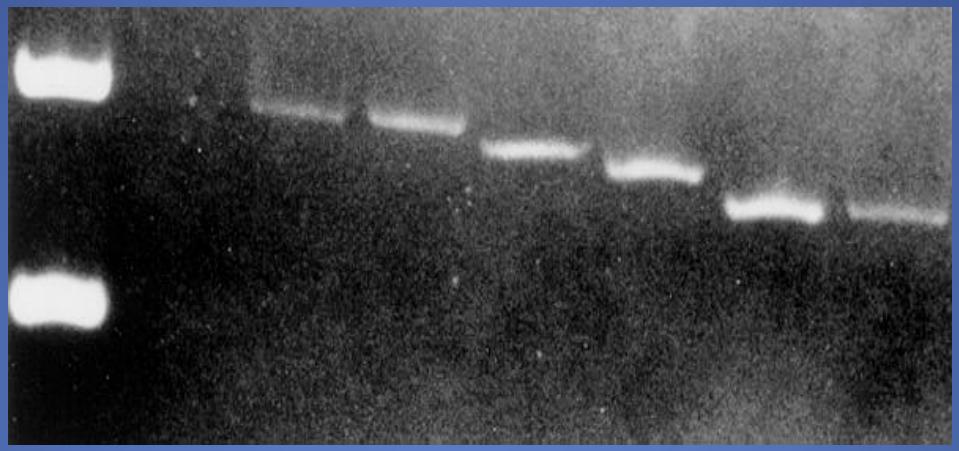
1. Homologous strands are present in the PCR product
2. Denaturation/renaturation
3. Formation of homo and heteroduplexes



Gel Electrophoresis



Clonal Homology and Nucleotide Changes



Rate of migration correlates directly with number of nucleotide substitutions (rho = 0.99, p < 0.005)

Sherman et.al. HEPATOLOGY, 1999

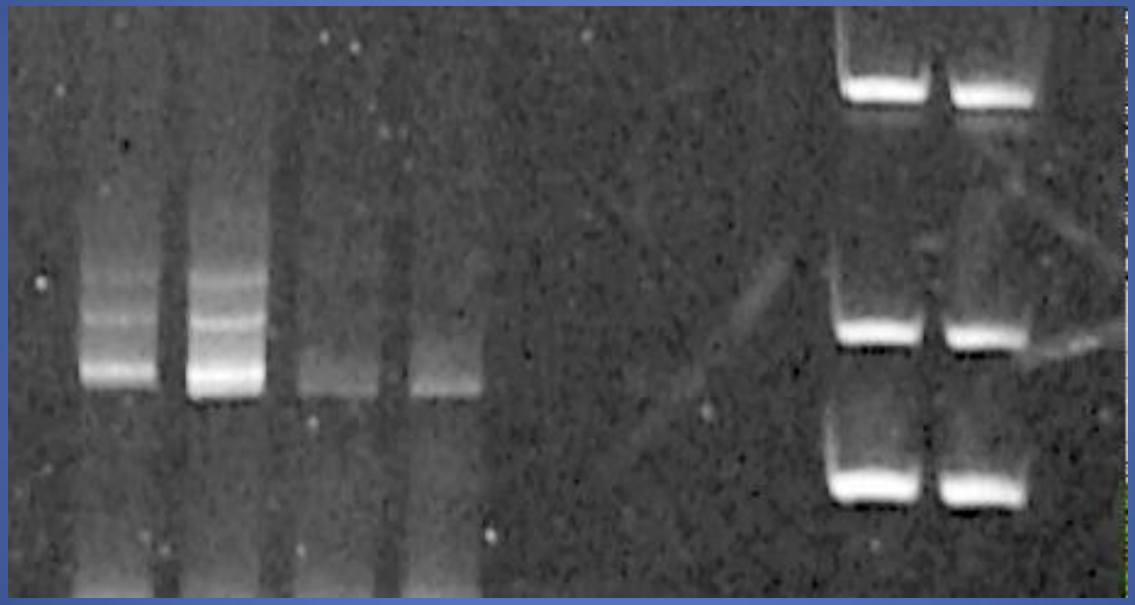
Results: Study Population (1)

- 19 patients
  - Male = 17
  - Hemophilia = 17
  - Von Willebrand's = 1
  - Factor VII deficiency = 1
- 18 samples were able to be amplified

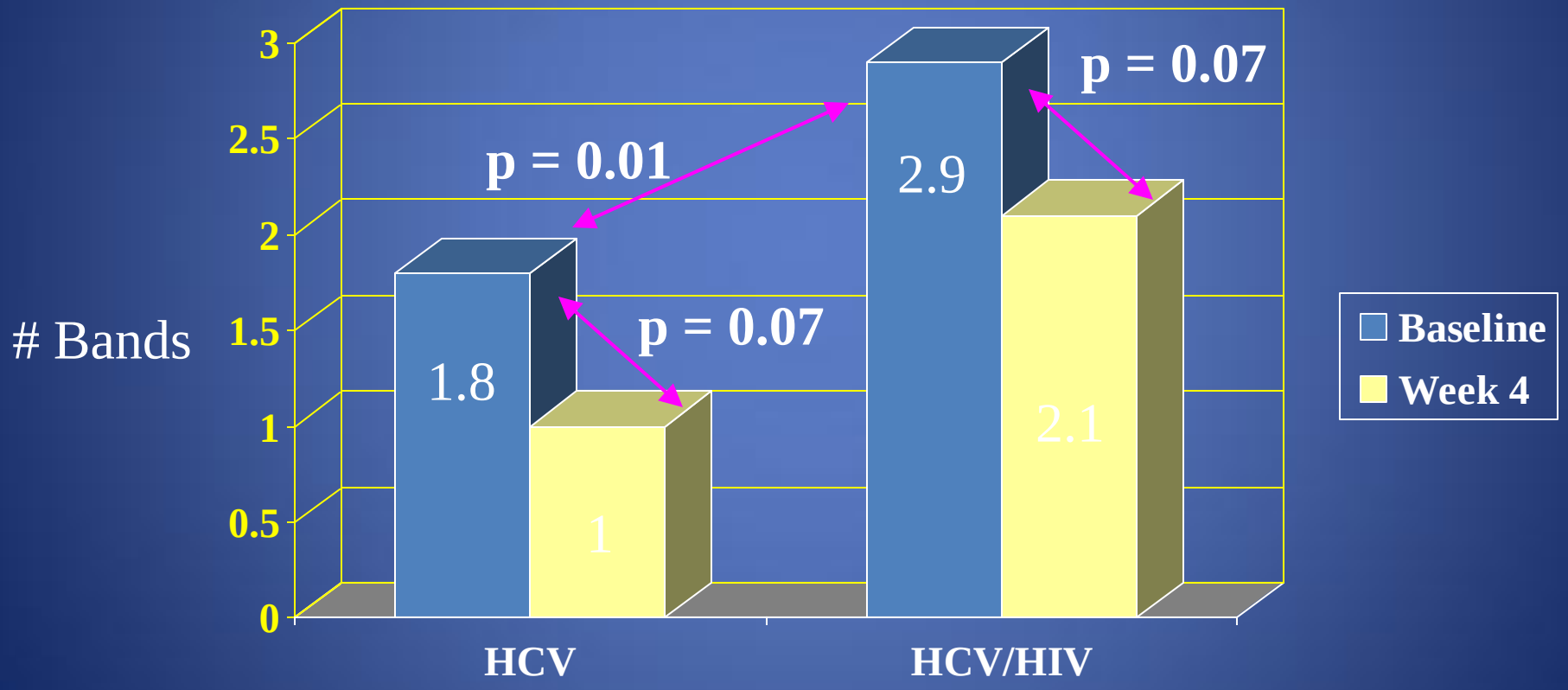
Results: Study Population (2)

	Age (mean)	Genotype	Baseline HCV viral load (mean IU/mL)	Baseline CD4+ (mean cells/mL)
HCV Monoinfected (n = 10)	38.7	1 = 6 2 = 2 3 = 2	6.73 (SE 0.19)	765 (SE 114) Range 249 - 1217
HCV/HIV Coinfected (n = 8)	36.1	1 = 6 4 = 2	6.57 (SE 0.10)	737 (SE 116) Range 328 – 1214

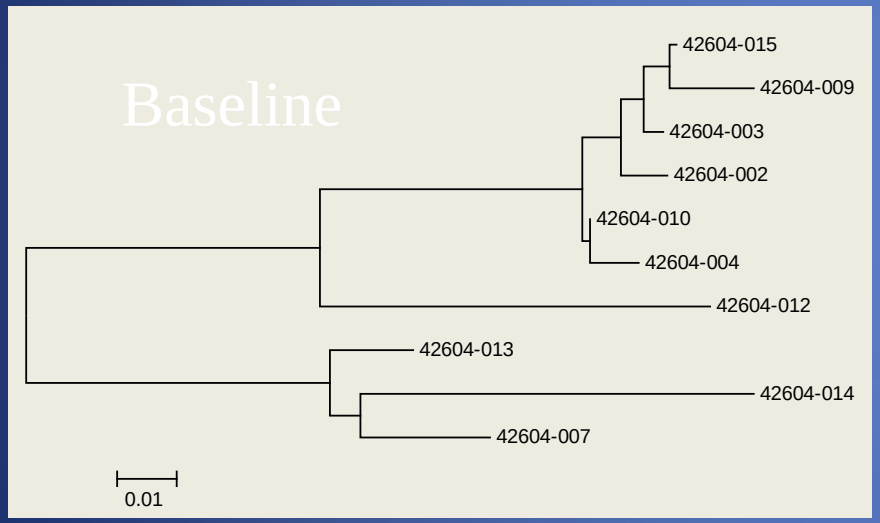
Quasispecies Change Over Time

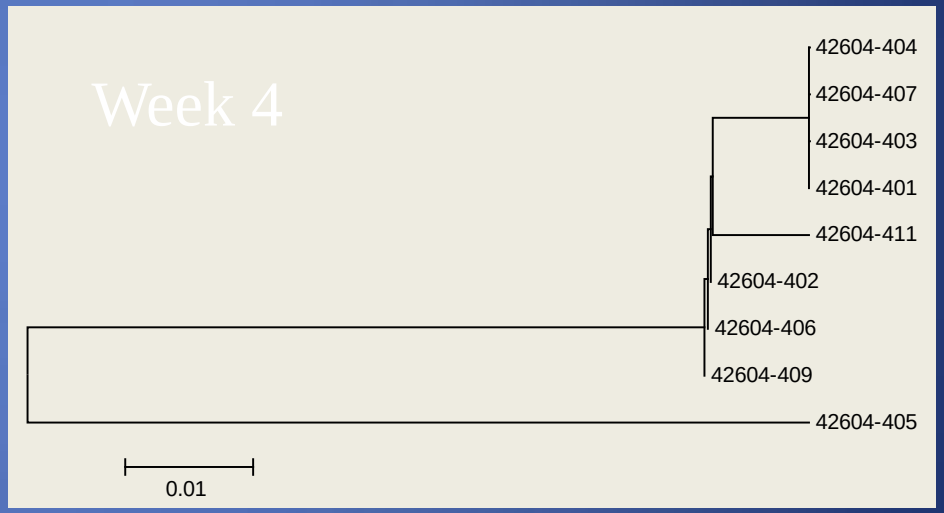


Complexity


Bands
3
2.5
2
1.5
1
0.5
0
p = 0.01
p = 0.07
p = 0.07
1.8
1
2.9
2.1
HCV
HCV/HIV
Baseline
Week 4

Monoinfected Patient: Phylogenetic Analysis of Clones

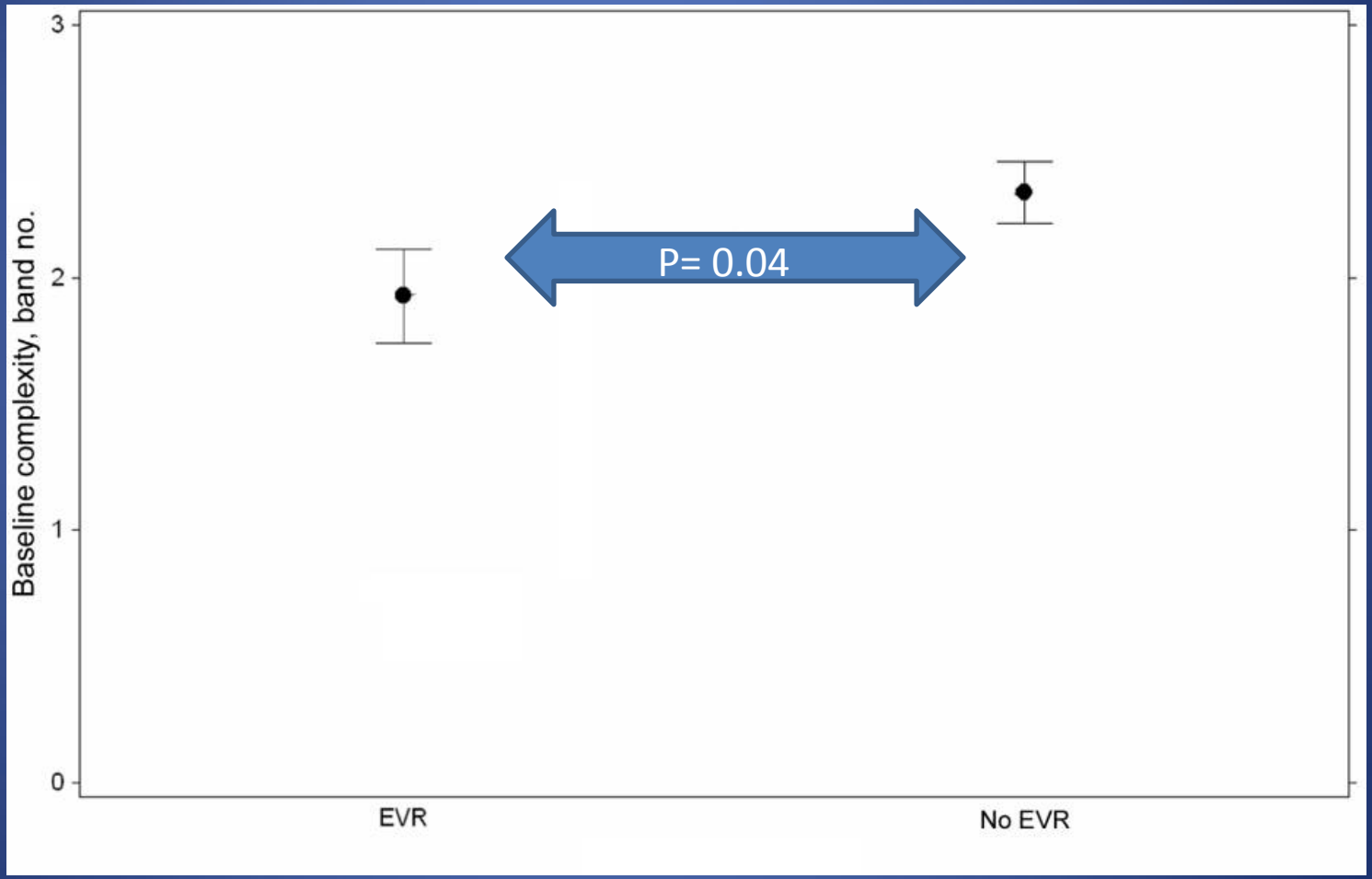




Mean genetic distance: 0.13

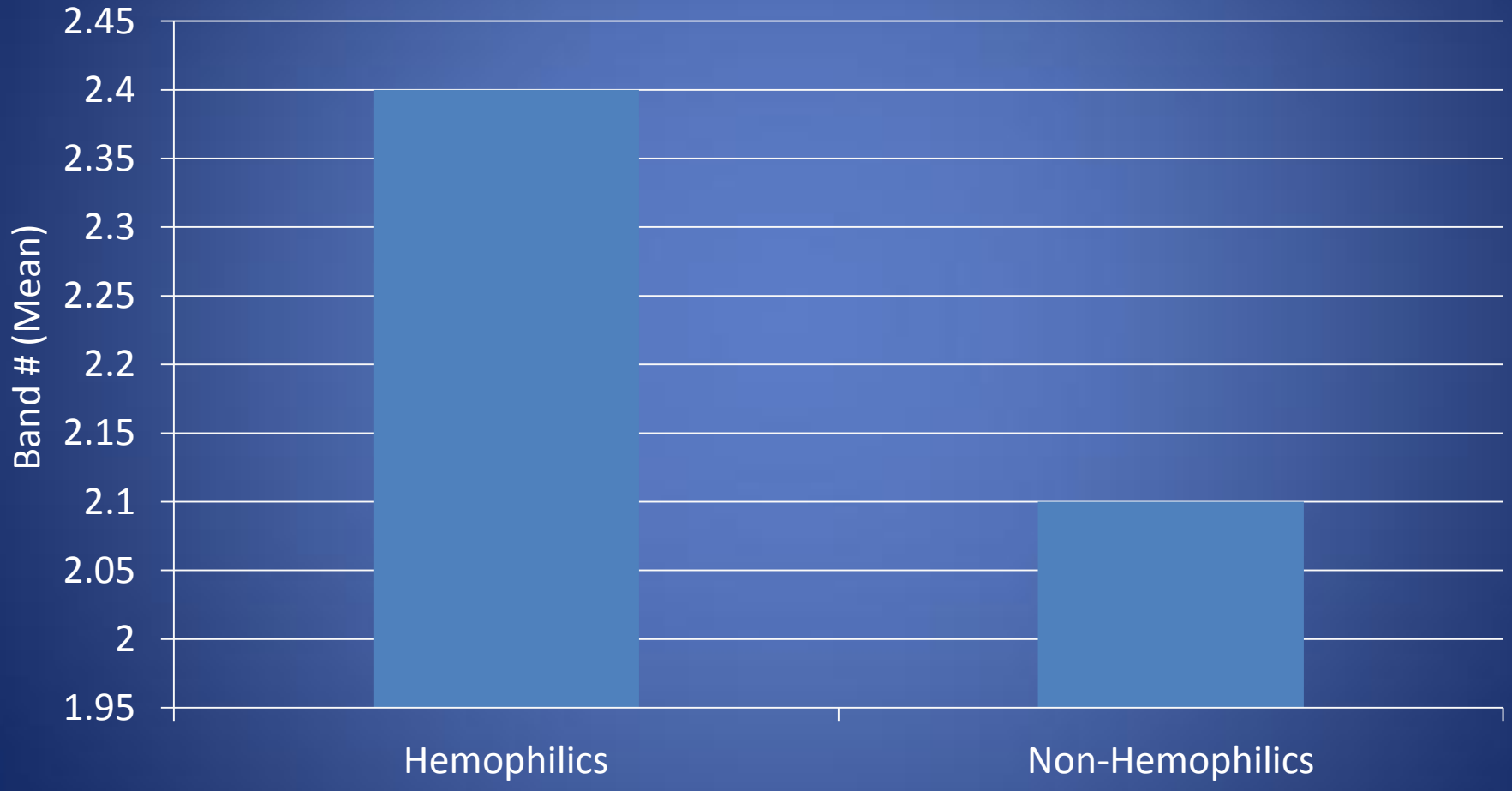
Mean genetic distance: 0.02

QUASISPECIES EFFECT ON HCV CLEARANCE IN HCV/HIV INFECTED PATIENTS



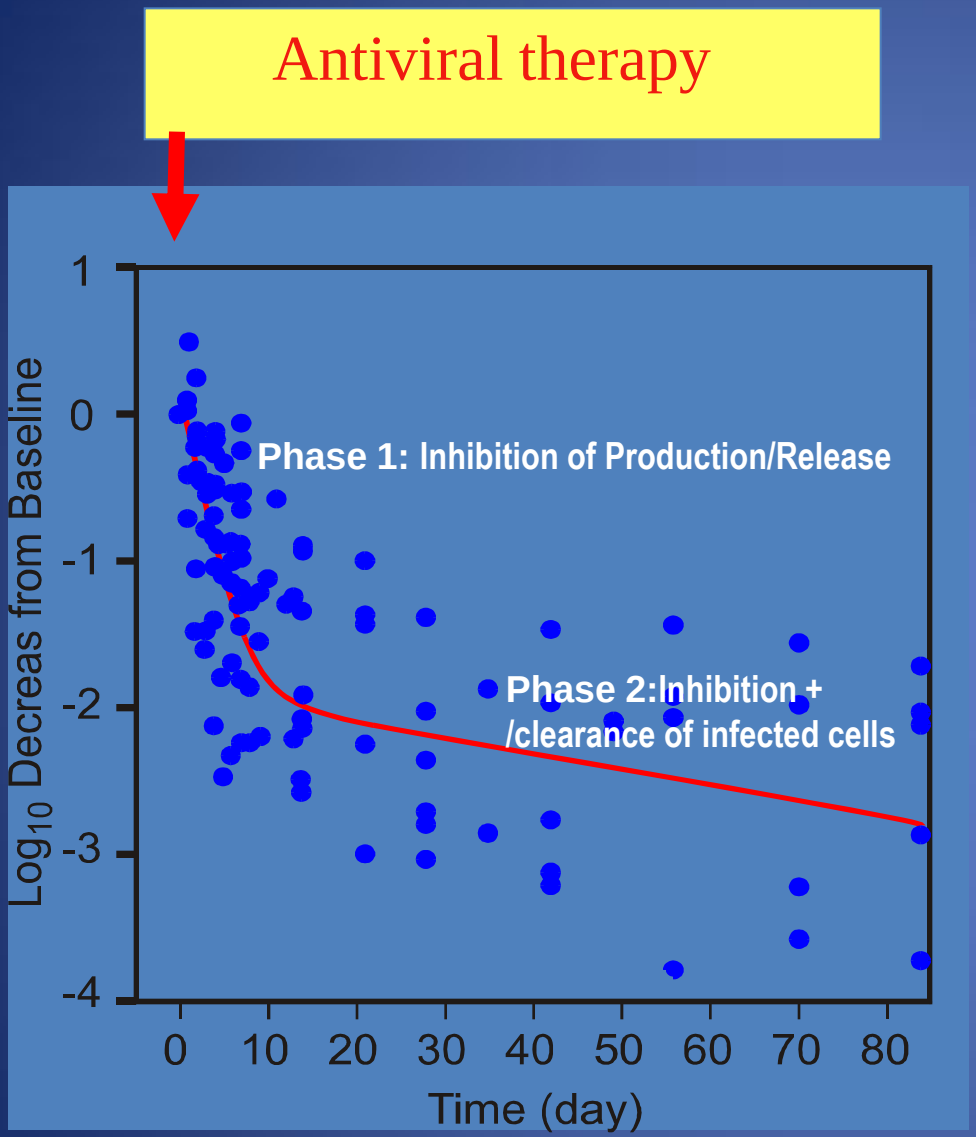
Sherman et. al, J INFECT DIS, 2010

QUASISPECIES COMPLEXITY HCV/HIV HEMOPHILICS VS NON



Shire et. al., HEPATOLOGY, 2005
Sherman et. al., J INFECT DIS 2010

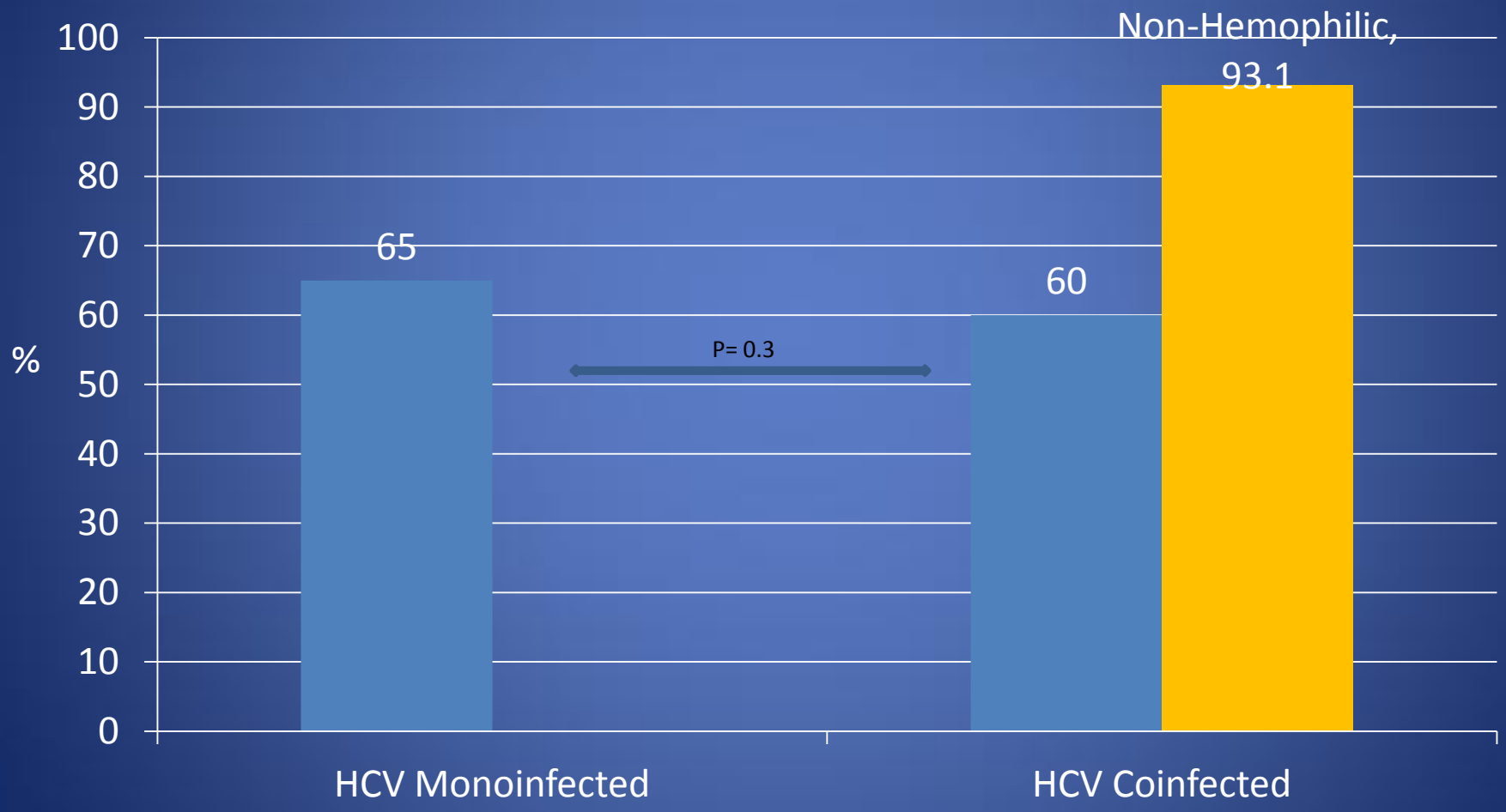
Biphasic viral dynamic model



Therapeutic Implications

- When E < 1, biphasic: at the same e, therapeutic outcome relies on the 2nd decline phase (i.e., Infected cell death rate by individual's immune activity).
- Drug or dosing efficacy is a key parameter in the initial viral decline phase.
- Estimated Time to Clearance is based upon the combination of E and the 2nd Phase Decline slope

Efficiency of Phase 1 Decline In Hemophiliacs vs. Non-Hemophiliacs (ε)

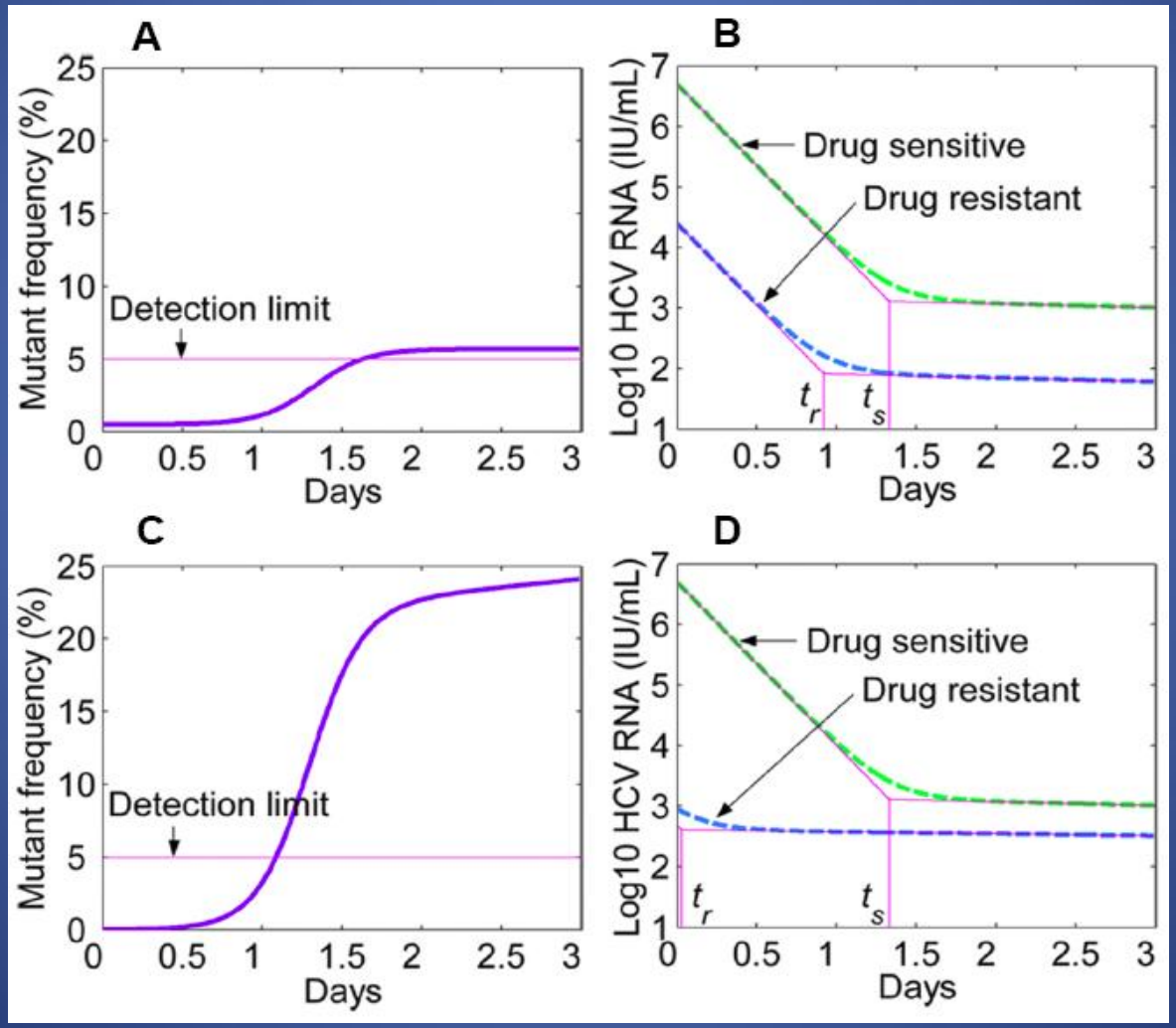


Shire et. al., HEPATOLOGY, 2005
Sherman et. al., GASTROENTEROLOGY 2005

BASELINE DAA MUTATIONS

- Frequency unknown in Multi-transfused Population
- Significance
  - Baseline signature mutations did not appear to affect SVR rates in pivotal boceprevir and telaprevir trials

LEAD-IN STRATEGY



Rong et al, Sci Transl Med. 2010 May 5; 2(30):

FACTORS AFFECTING VALUE OF LEAD-IN

- Baseline Viral Load
- Proportion of Drug Resistant Mutants in Population
- Efficacy of Drug (Phase 1 Decline)
- Relative Response to Covering Agent
  - Interferon
  - Other Class

LIVER BIOPSY
Consensus Statement

"Although the data are limited, the procedure does not appear to pose excessive risk to the patient with inherited disorders of coagulation, provided that adequate haemostasis can be achieved prior to the liver biopsy and the procedure is performed by an experienced individual."

"Indications for liver biopsy should be the same in patients with haemophilia as in other populations."

Theodore et al., HAEMOPHILIA, 2004

ISSUES IN BIOPSY

- Cost
  - Factor replacement
  - Hospital Observation
    - May not be required (Saab et al., HAEMOPHILIA, 2004)
  - Increased Use of Transjugular Approach

ALTERNATIVES TO LBX

- Biochemical Non-Invasive Markers
- Transient Elastography

SUMMARY OF NON-INVASIVE METHODS

- Limited Direct Comparison Data
  - Posthouwer et al, HAEMOPHILIA, 2008
    - 63 Patients with LBx underwent transient elastography
    - 81% Positive Predictive Value of Moderate Fibrosis
- Numerous Papers Telling Results of Non-invasive Marker Tests without Validation

INHIBITORS AND HCV TREATMENT

- 4 cases of development of Factor VII inhibitor in HCV infected hemophiliacs treated with interferon-based therapy described in literature
  - 3 HCV
  - 1 HCV/HIV
- Other cases described where interferon used for treatment of malignancy

CLINICAL TRIALS
Design Options for Consideration

- TREATMENT TRIALS- HOW
  - Permit patients to enter planned trials
    - Pros
      - Special trials not needed
    - Cons
      - High cost of entry biopsy or ability to use poorly validated non-invasive markers
      - Unclear whether differences in population affect outcome
      - Limited ability to gather safety data due to low enrollment in any one trial
  - Inherited Bleeding Disorder Only Large Multicenter Trials (300-500 patients)
    - Pros
      - Opportunity to focus on special population
      - Comparison with non-hemophilic arm would definitively address questions of comparability
    - Cons
      - Limited qualified sites
      - Costly for relatively small and heterogenous population
        - » Treatment naïve vs. Experienced; HIV+ vs HIV-
  - Targeted Small Trials (1-3 center/20-50 patients)
    - Pros
      - Safety
      - Intense sampling, dynamic modeling

CONCLUSION

- Treatment of HCV in patients with inherited bleeding disorders has not been adequately studied
- Limited evidence raises the possibility that unique biological factors could influence outcomes
- Liver biopsy is safe and well tolerated, and non-invasive markers are poorly validated in this population
- Study designs should attempt to answer key questions in the most efficient manner
  - A mix of small and large studies might permit evaluation of key issues