HCV: Epidemiology and Screening Recommendations

Stacey Rizza, MD, FIDSA
Associate Professor of Medicine
Chair, Mayo HIV Clinic

Mayo Clinic, Rochester, MN

Division of
INFECTIOUS DISEASES

Mayo Clinic Infectious Diseases Subspecialties Update
May 7-9, 2015

HCV: Epidemiology and Screening Recommendations

Objectives

- **The Virus and Epidemiology**
- **Transmission and Natural History**
- **Diagnosis and Screening**

Hepatitis C
Question 1

Hepatitis C can be transmitted by the following exposures EXCEPT:

A. Intravenous Drug Use
B. Snorting cocaine
C. Sex
D. Childbirth
E. All can result in HCV infection

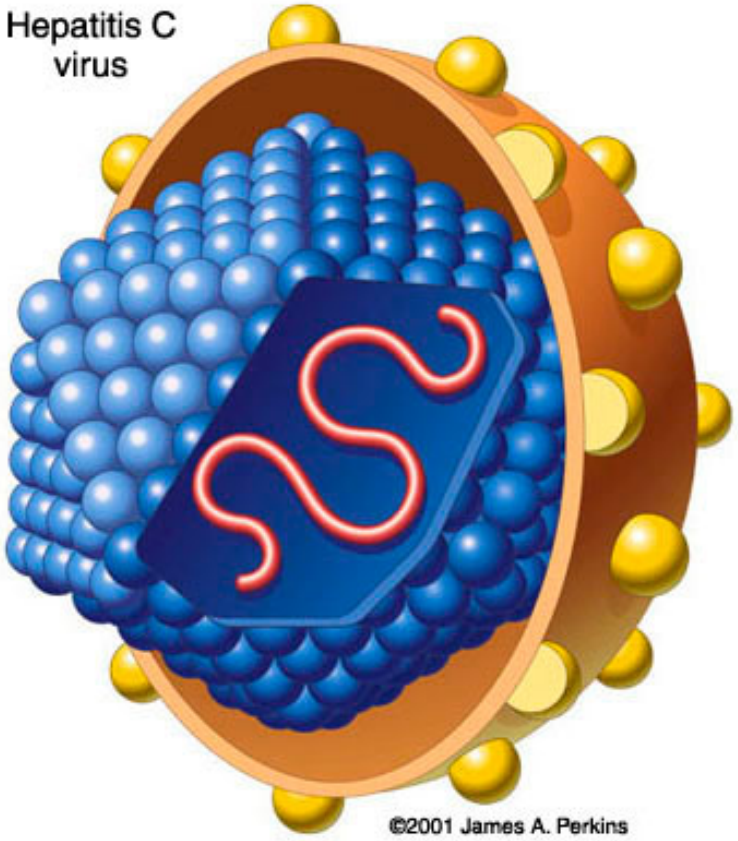
Hepatitis C
Question 2

Who should be screened for Hepatitis C infection?

A. Intravenous Drug Users
B. Anyone born between 1945-1965
C. Men who have sex with Men
D. Anyone with a tattoo
E. All of the above

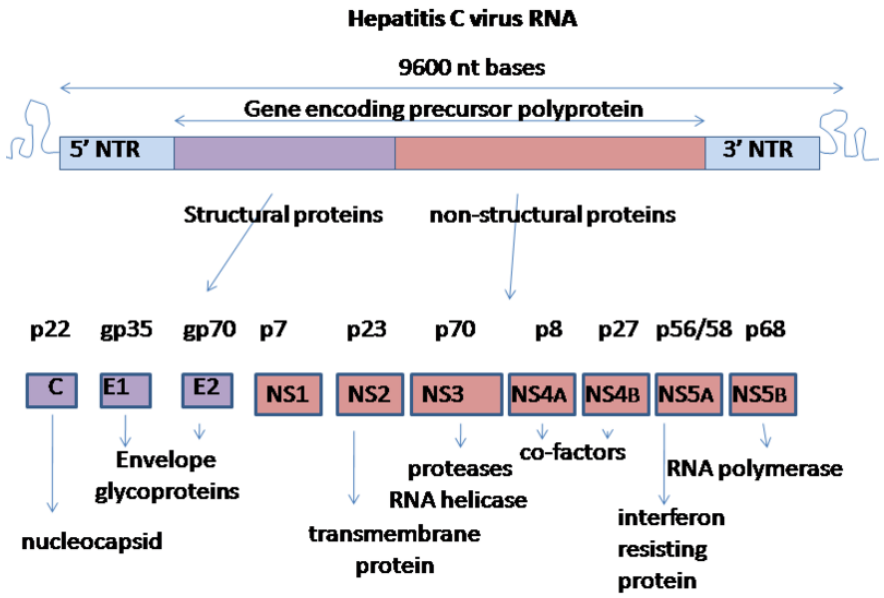
Hepatitis C

- Positive single stranded RNA virus with an open reading frame
- Small, enveloped virus which is a member of the *Flaviviridae* family
- 1989 by Michael Houghton

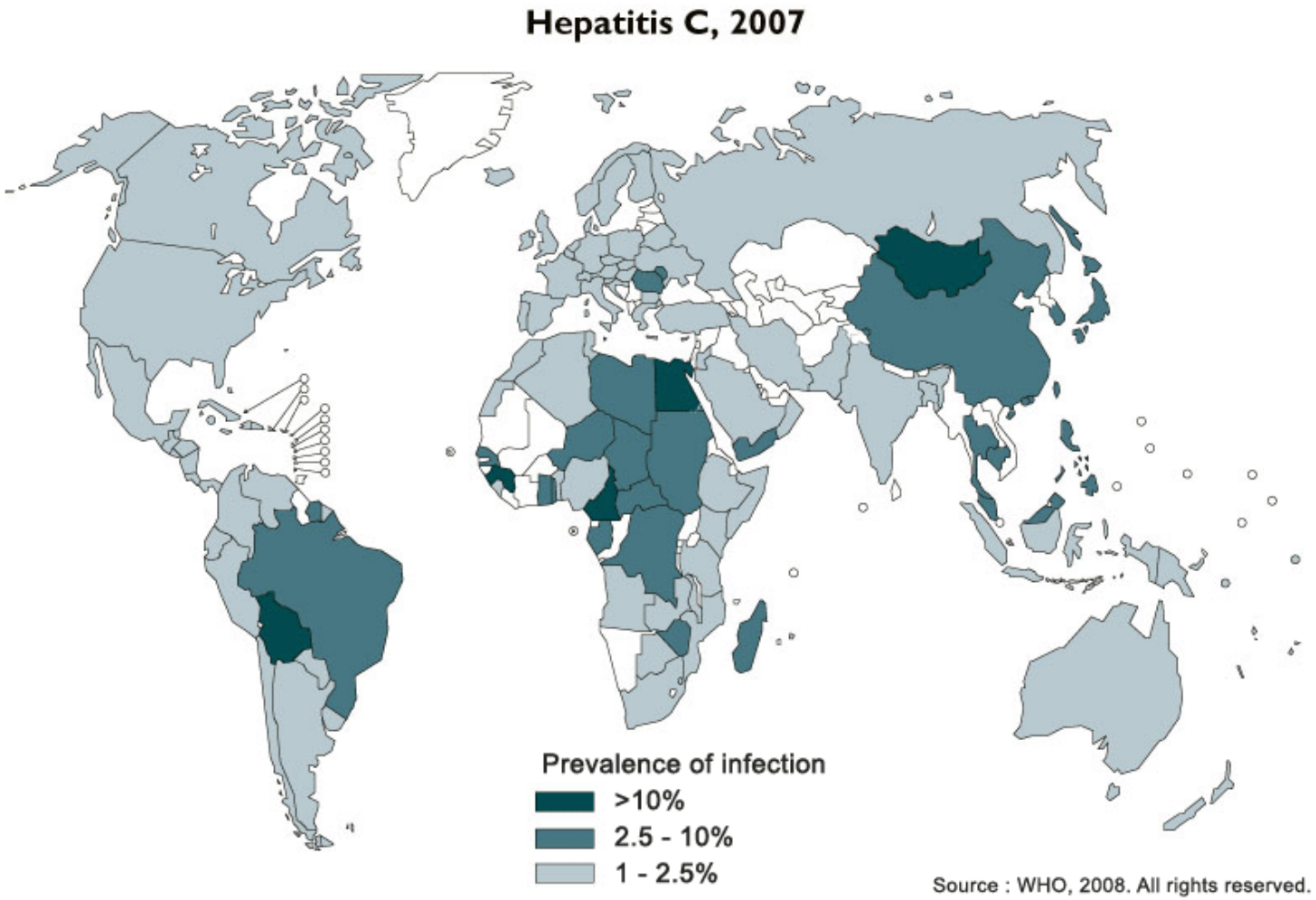


Hepatitis C

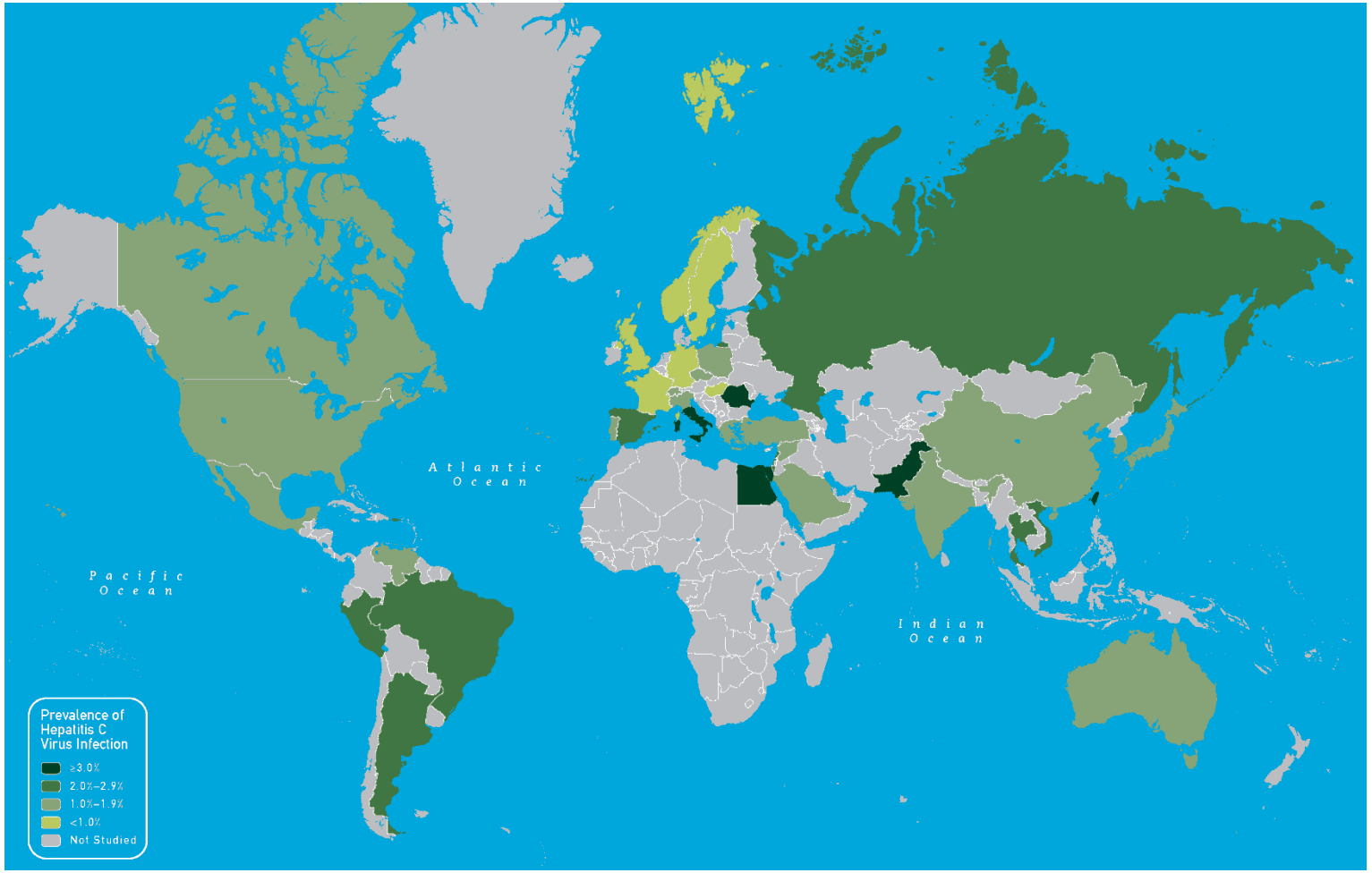
- Open reading frame encodes 10 structural and non-structural proteins
- Infidelity of RNA polymerase leads to many quasispecies
- Highly conserved and highly variable areas
- Only 2 species can be infected with HCV
- No cell culture system



HCV: Epidemiology

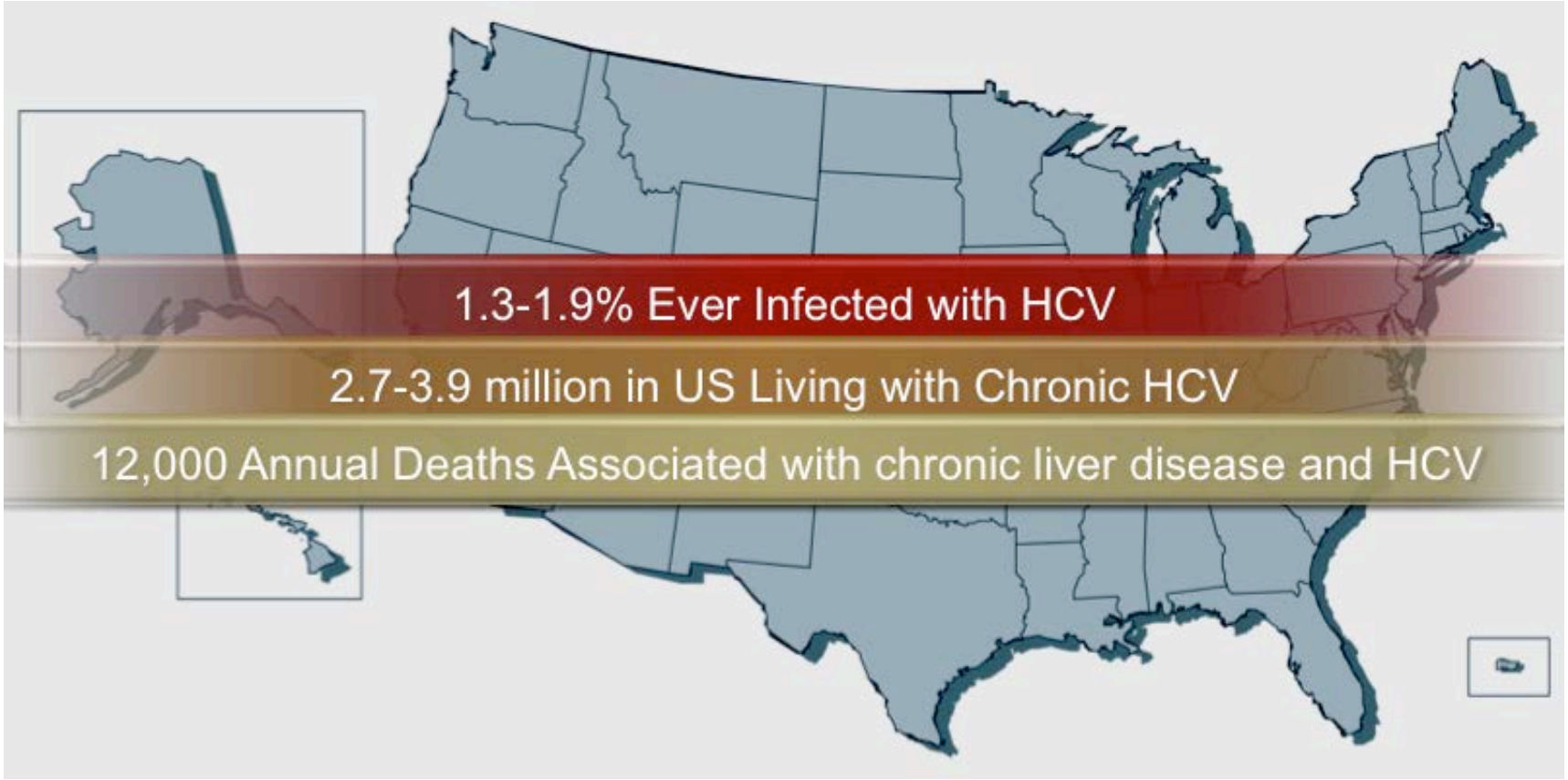


Prevalence of chronic hepatitis C virus infection 2011

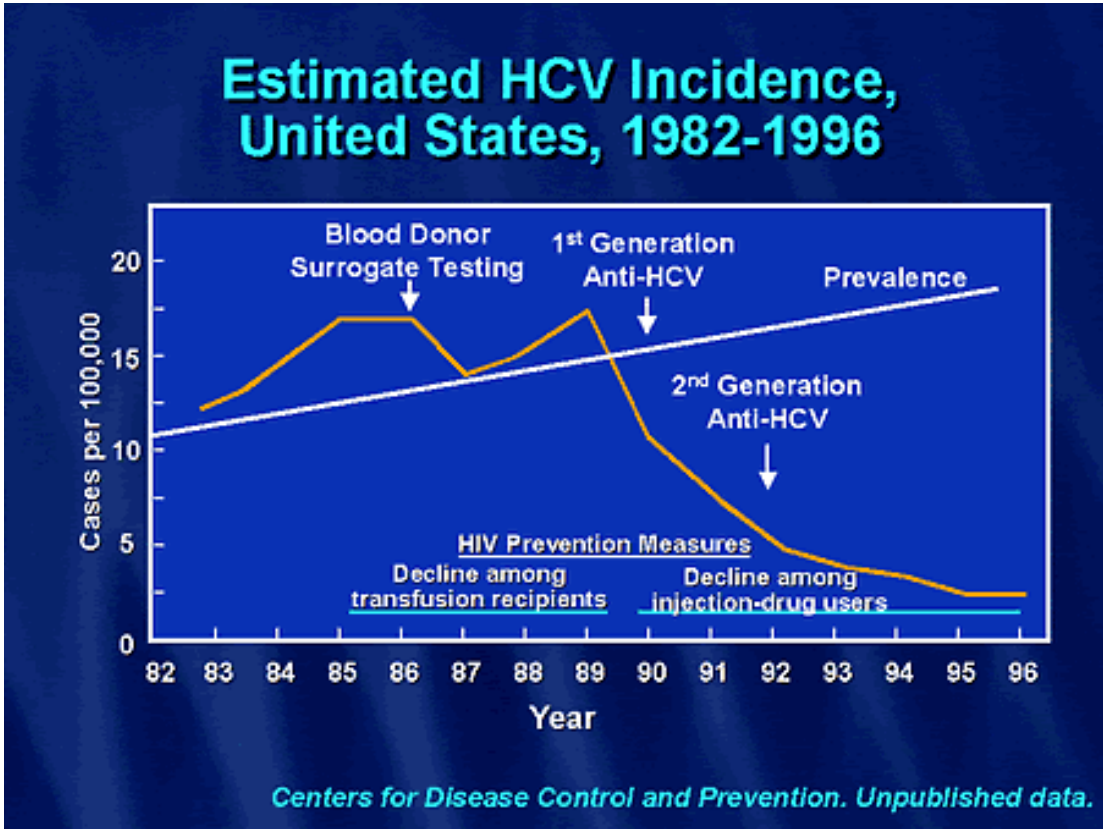


CDC.gov

Hepatitis C in the US



Hepatitis C Incidence in the US



Hepatitis C New Infections in the US

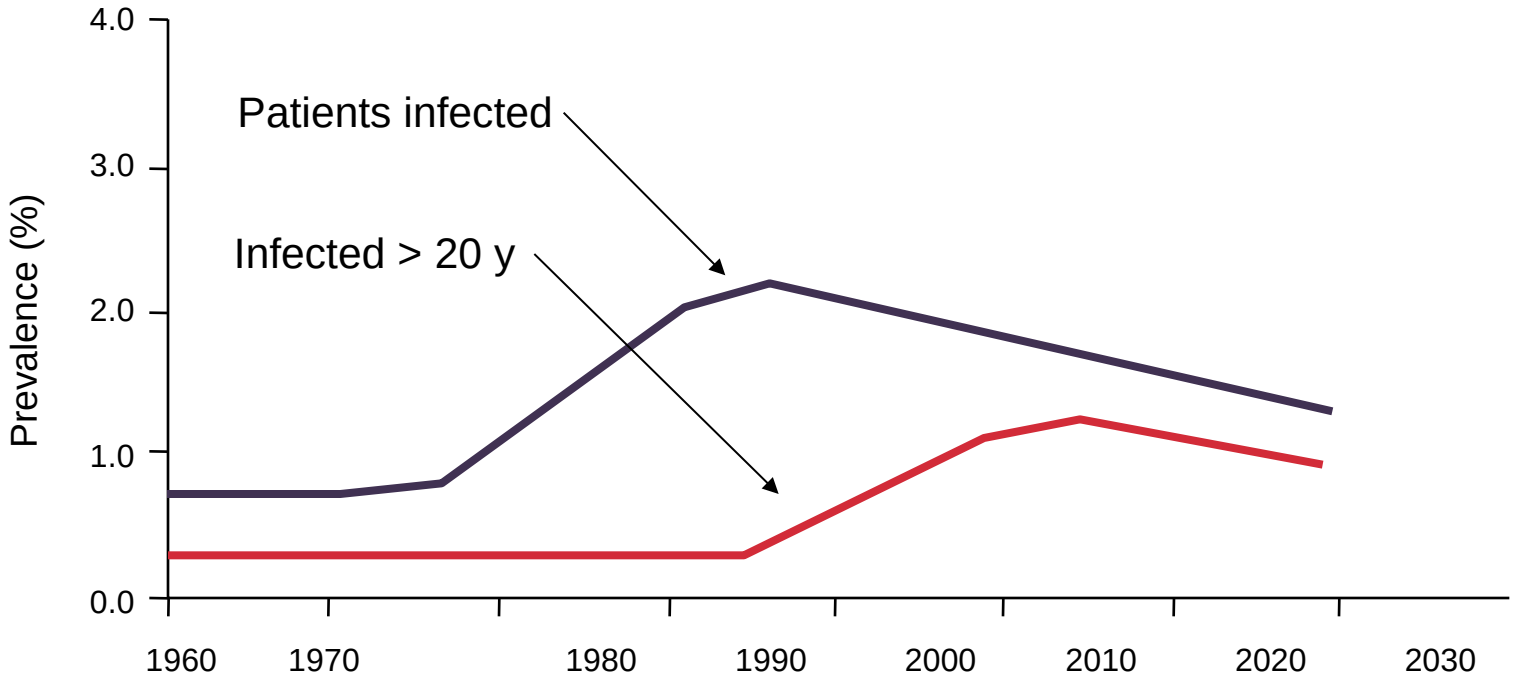
Incidence of New Hepatitis C Infections						
Type of Cases	Year					
	2002	2003	2004	2005	2006	2007
Estimated Number of Acute Clinical Cases*	4,800	4,500	4,200	3,400	3,200	2,800
Estimated Number of New Infections^	29,000	28,000	26,000	21,000	19,000	17,000

*Acute Clinical Cases defined as:(1) acute illness with discrete onset of symptoms (e.g., nausea, anorexia, fever, malaise, or abdominal pain), and (2) jaundice or serum alanine aminotransferase greater than 400 IU/L

^New Infections: includes asymptomatic new diagnosis and takes into account underreporting

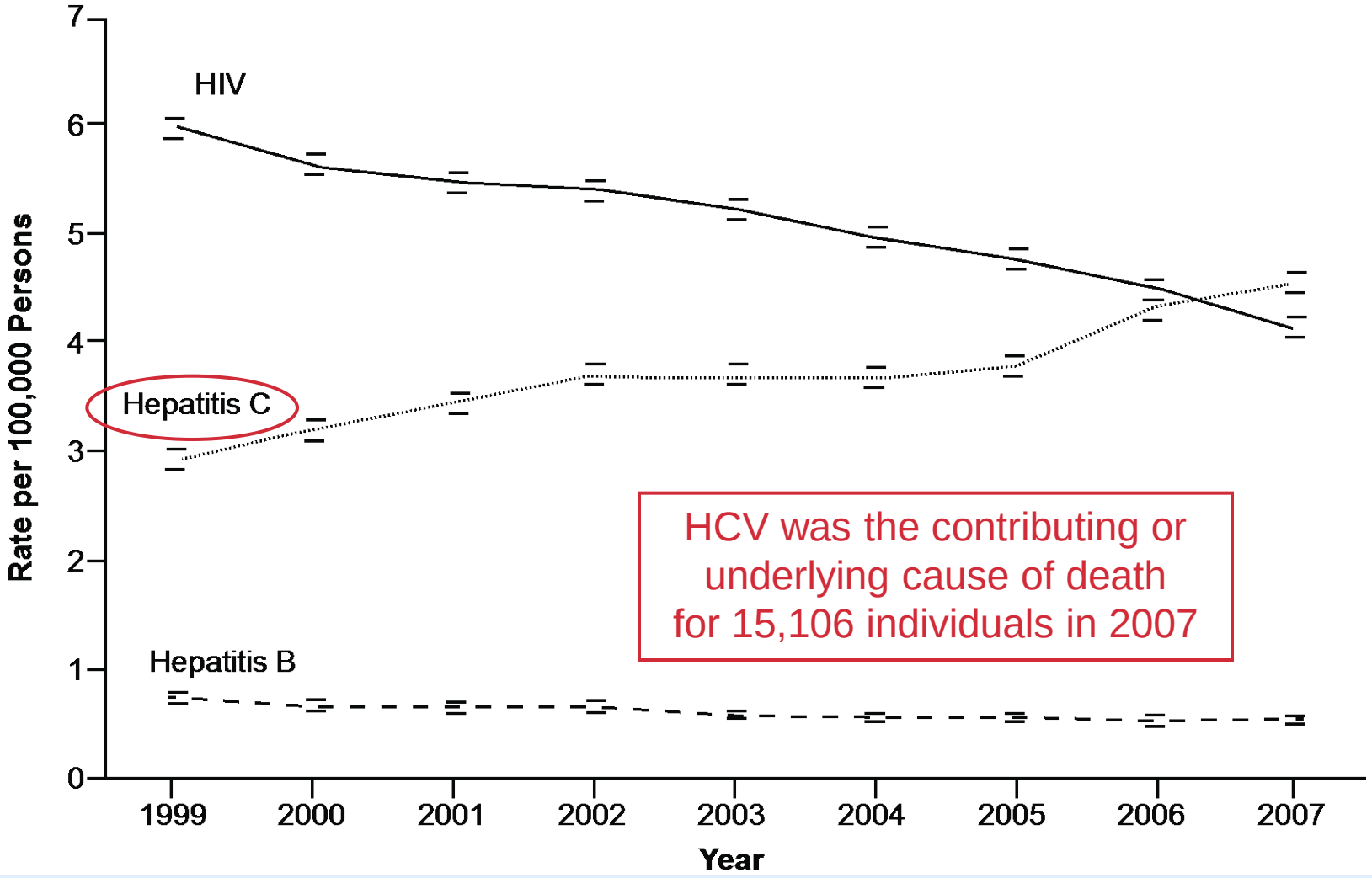
Disease Burden of Patients Infected 20 Years or More is Peaking Now

Complications from chronic hepatitis C develop slowly over a period of 20–30 years



Davis GL. *Rev Gastroenterol Disord* 2004;4:7-17.

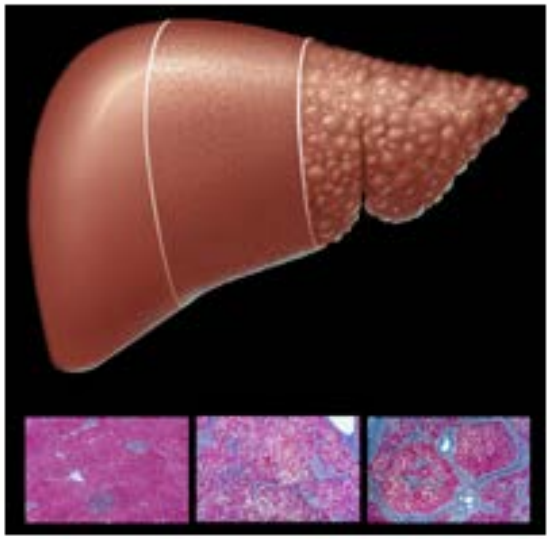
Deaths from HCV in the United States Continue to Rise; Deaths from HBV and HIV are Decreasing



Ly KN et al. *Ann Intern Med* 2012;156:271-278.

HCV Infection

- 4.1 million Americans anti-HCV positive
- 3.2 million Americans infected with HCV
- Over 170 million people world wide are infected with HCV
- Leading cause for Liver transplantation in the US



NIH Consensus Conference 2002

CID 2001;32:492
www.CDC.gov
WHO.int

HCV Infection

- 150, 000 new cases every year in the US
- 3% of the world's population has been infected with HCV
- Annual costs of acute and chronic hepatitis C in the US is over $ 1 billion
- No Vaccine available

hepatitiscnewdrugs.blogspot.com

WHO.int

HCV: Epidemiology and Screening Recommendations

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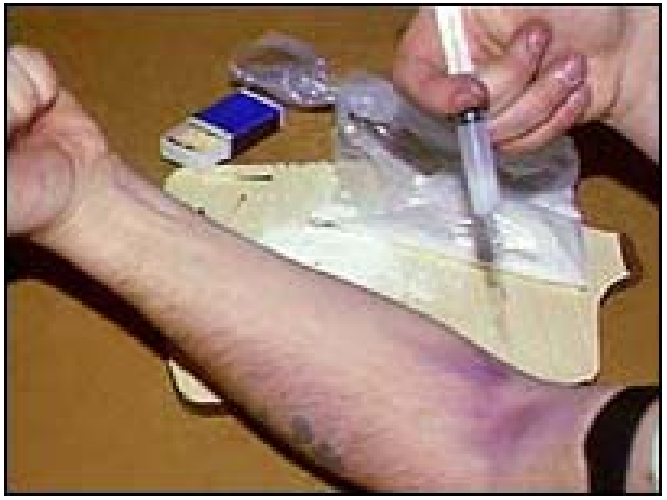
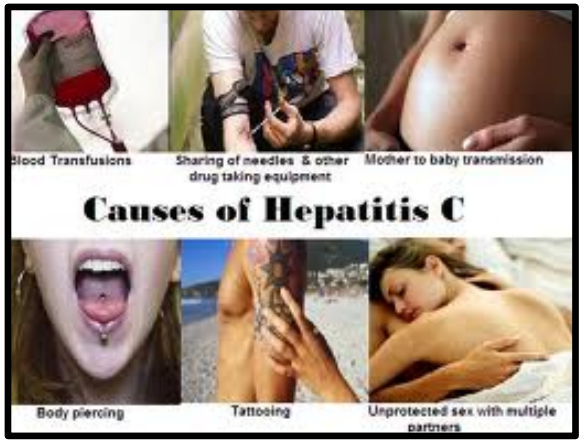
- **The Virus and Epidemiology**
- **Transmission and Natural History**
- **Diagnosis and Screening**

HCV: Transmission

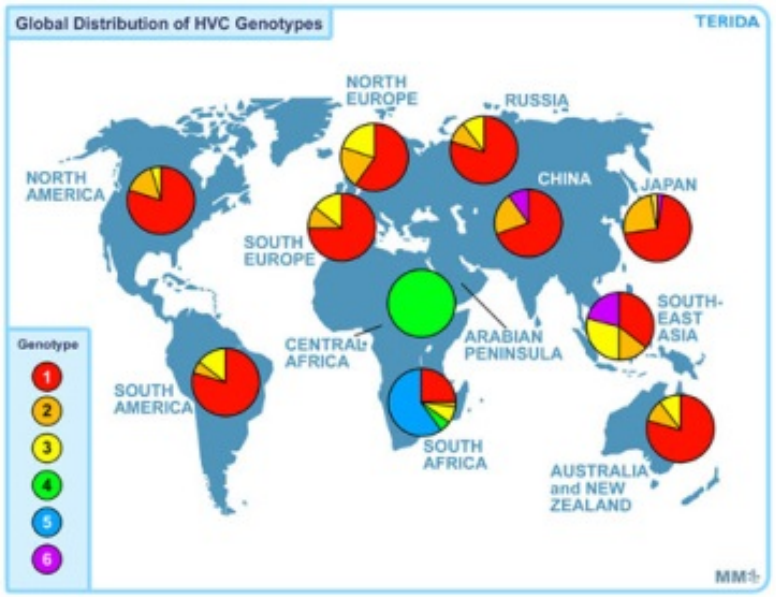




- **60% of HCV in the US is due to IV Drug Abuse**
- IVDU, Tattoos, Snorting cocaine, Sex, Peri-natal, Blood products before 1991
- 45% of persons with HCV infection do not report an exposure

Hepatitis C Virus

- 6 Genotypes:
  - **1a** & **1b** - US and Western Europe (70%)
  - **2 & 3**- Asia / illicit drug users (20;10%)
  - **4**- Africa and Middle East (1%)
  - **5 & 6**- Southeast Asia and South Africa (<1%)



Ann Intern Med 1996;125:634

Hepatitis C Virus
Natural History

40%

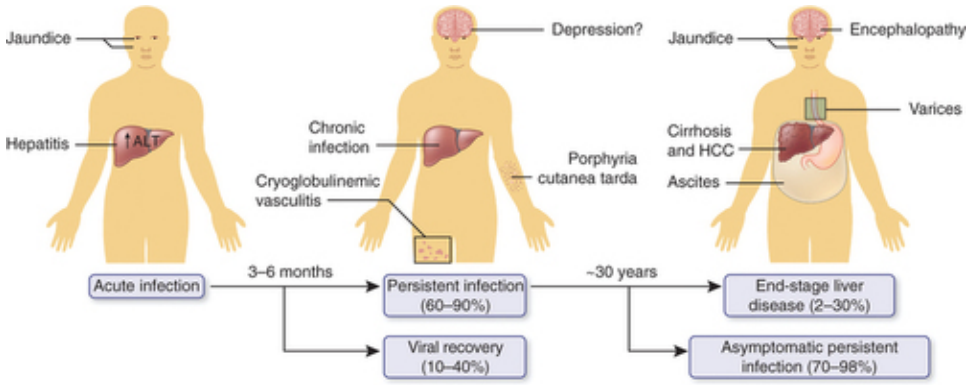
HIV

60%

Stage 1

20%

Male
Smoking
Alcohol
HIV
Obesity



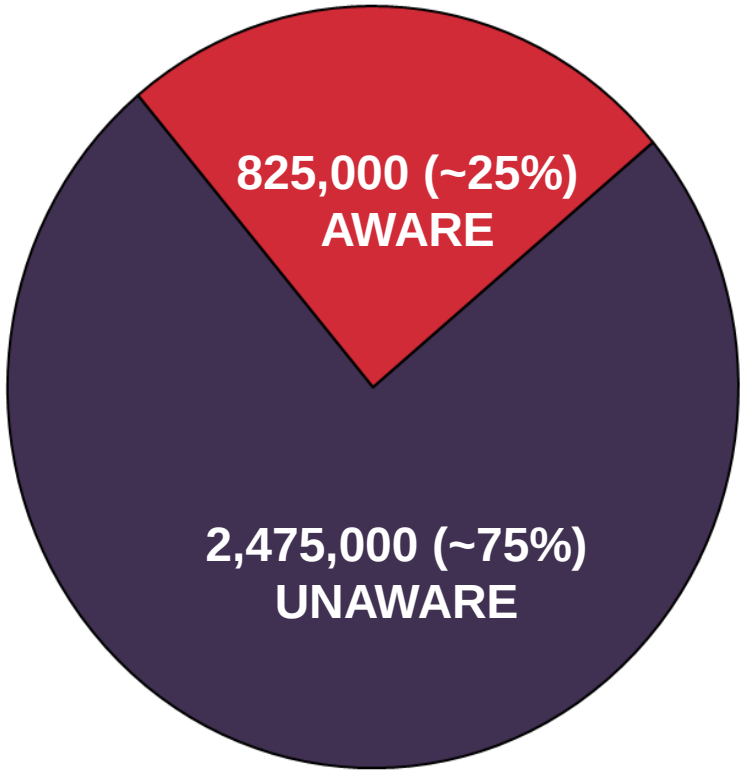
Stage 4

Liver failure
HCC

Nature Medicine; 19:850–858, 2013

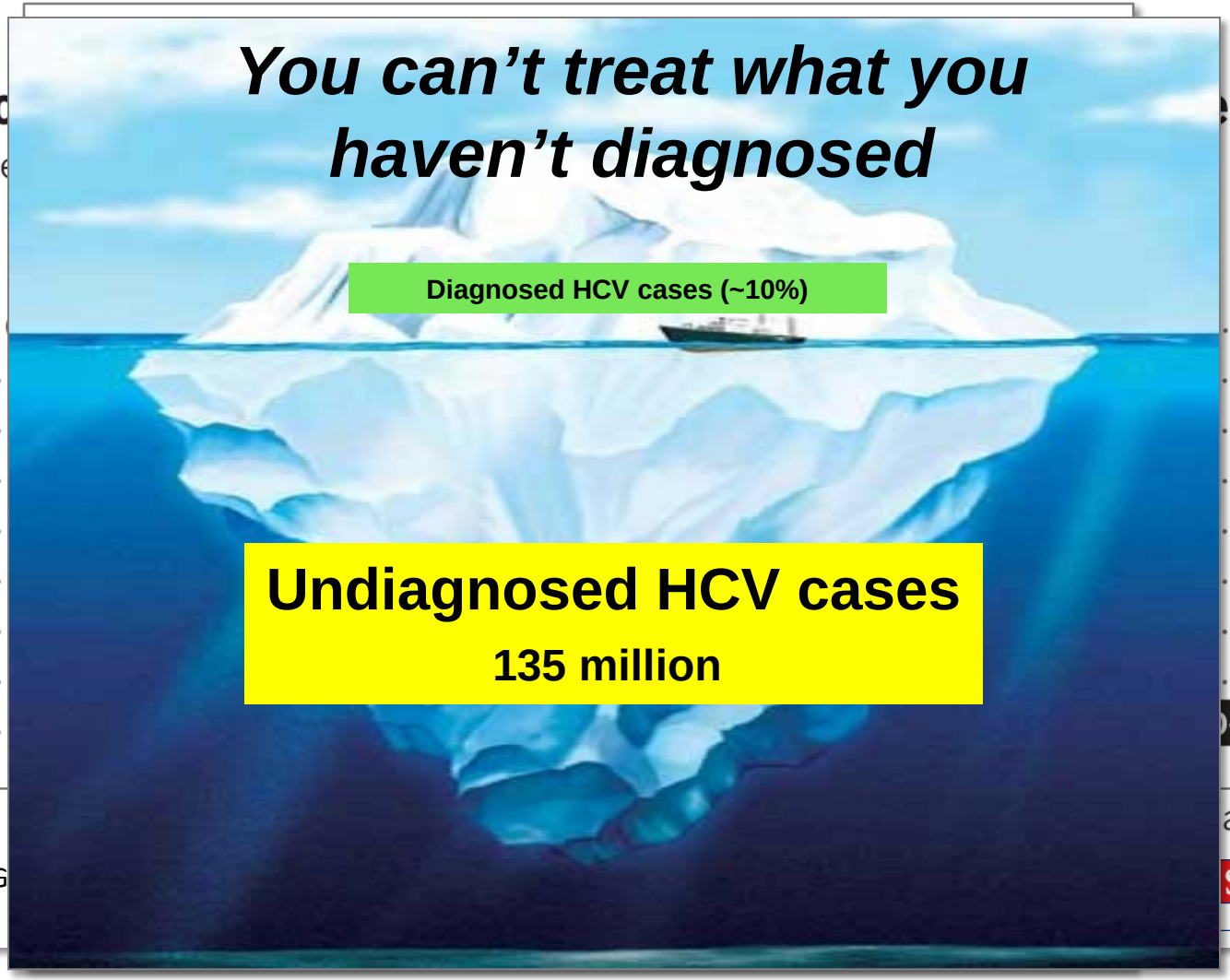
Most Patients with Chronic Hepatitis C in the US Are Not Aware that They Are Infected

- ~3-4 million individuals with HCV in US
- NHANES study (2001 -2008) found that 50.3% of persons infected with HCV were unaware of their status
- 75% of HCV infected Americans were born between 1945-1965

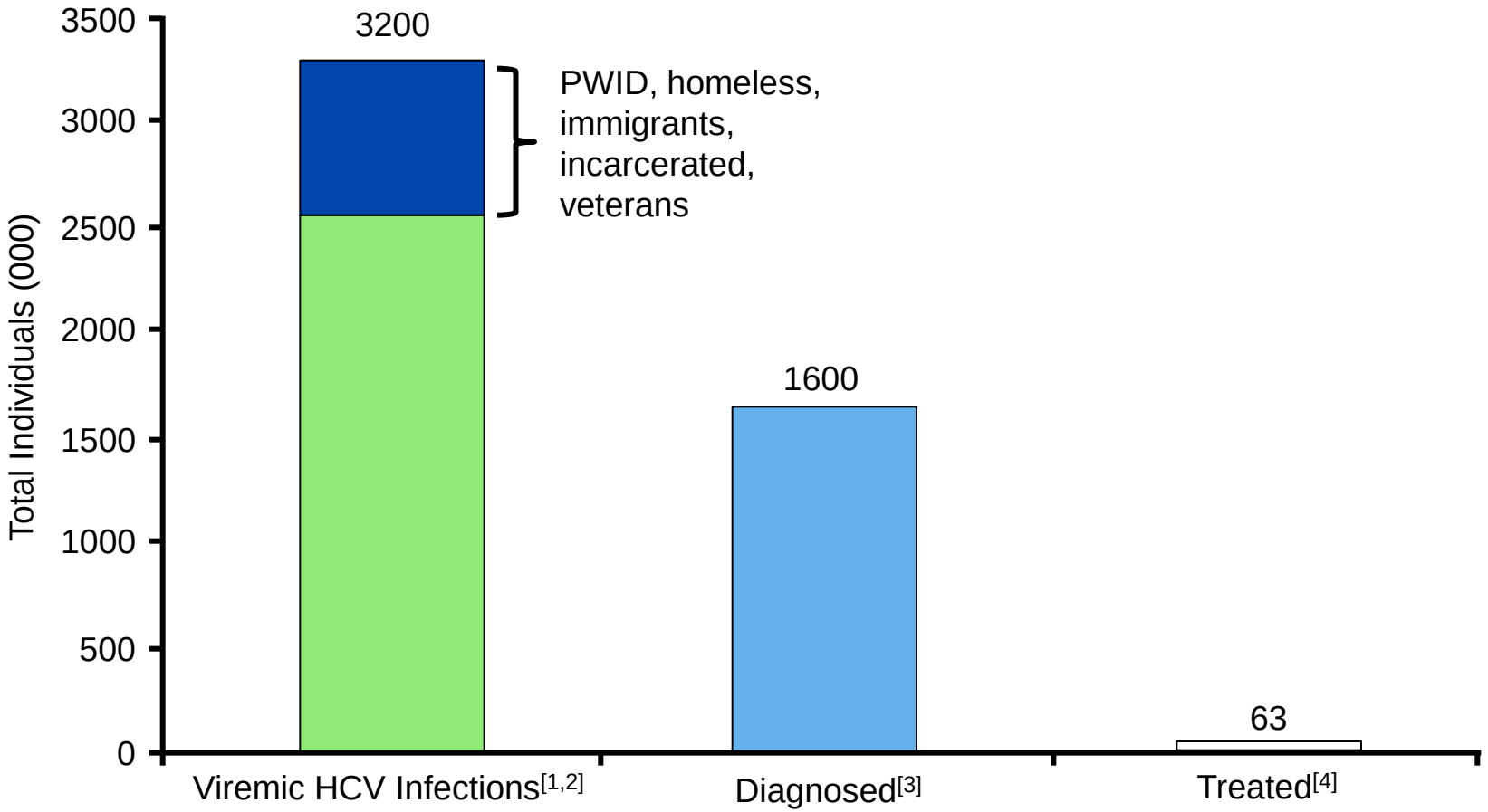


Adapted from Colvin HM, Mitchell AE. Hepatitis and liver cancer: A national strategy for prevention and control of hepatitis B and C. Washington, DC: The National Academies Press; 2010.

But challenges remain…

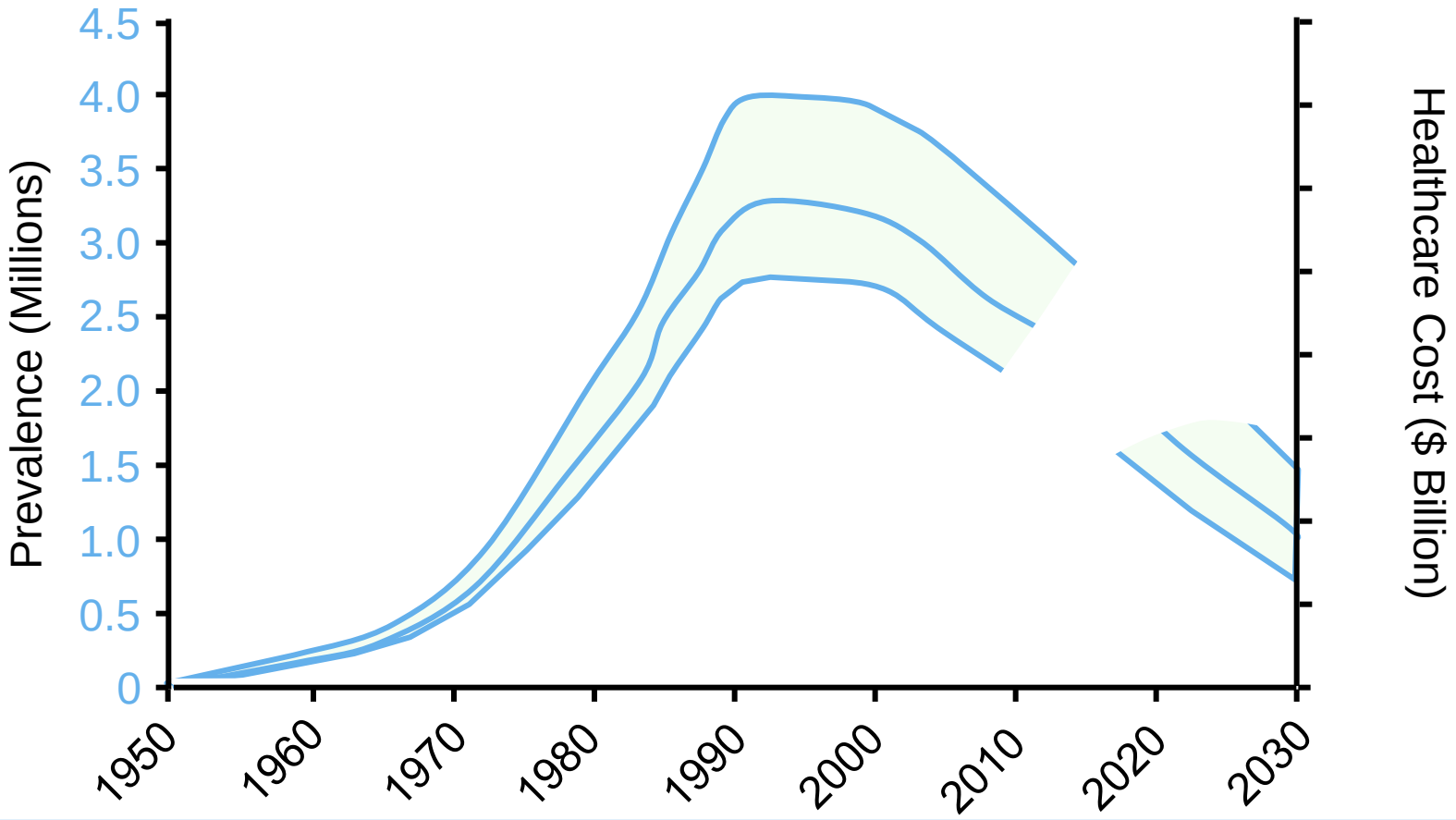


Elimination of HCV in the US: Infected Population, 2013



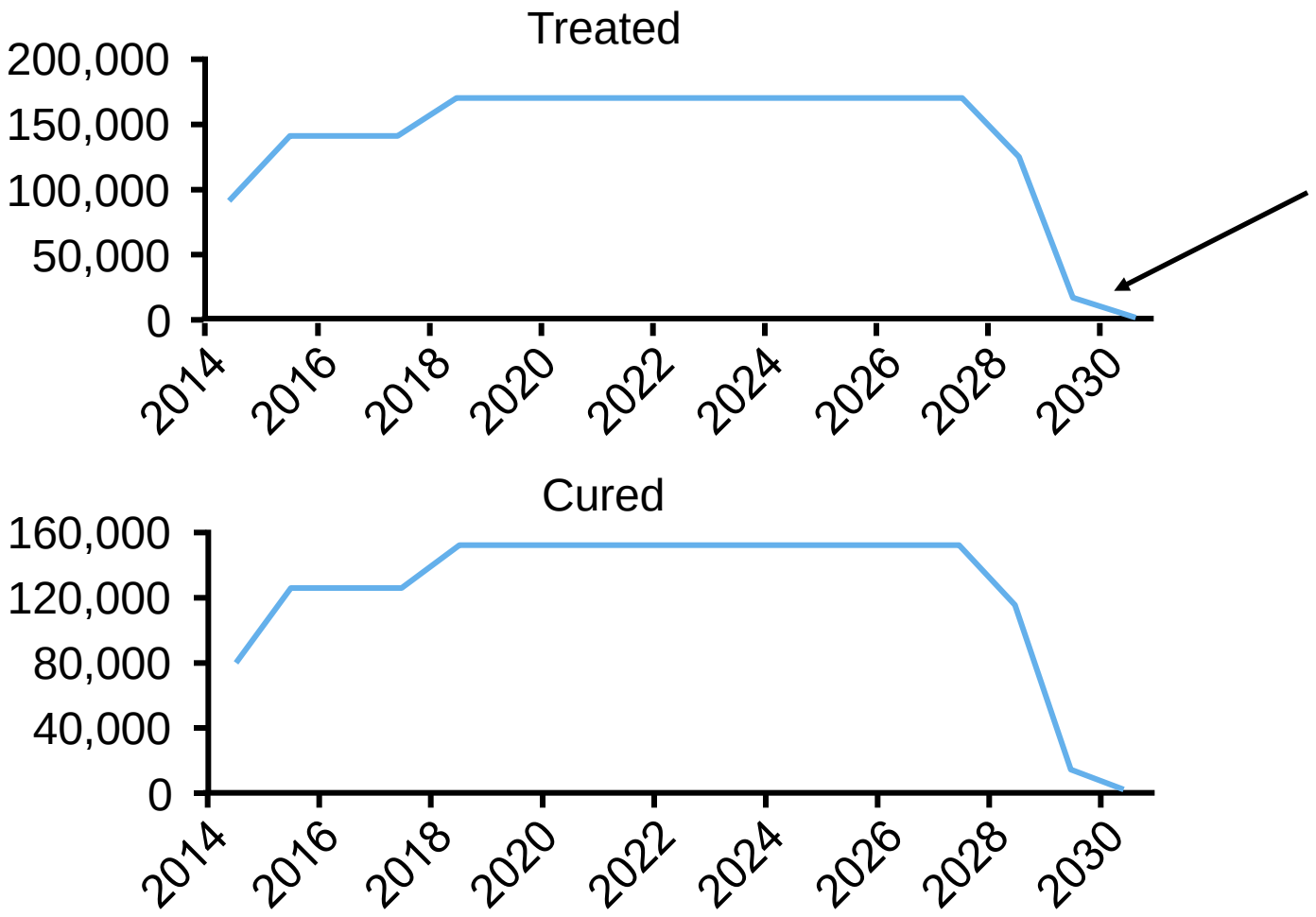
1. Denniston MM, et al. Ann Intern Med. 2014;160:293-300. 2. Chak E, et al. Liver Int. 2011;31:1090-1101.
3. Denniston MM, et al. Hepatology. 2012;55:1652-1661. 4. Razavir H, et al. Hepatology. 2013;57:2164-2170.

Despite Declining HCV Infections, Healthcare Costs Will Increase due to ESLD



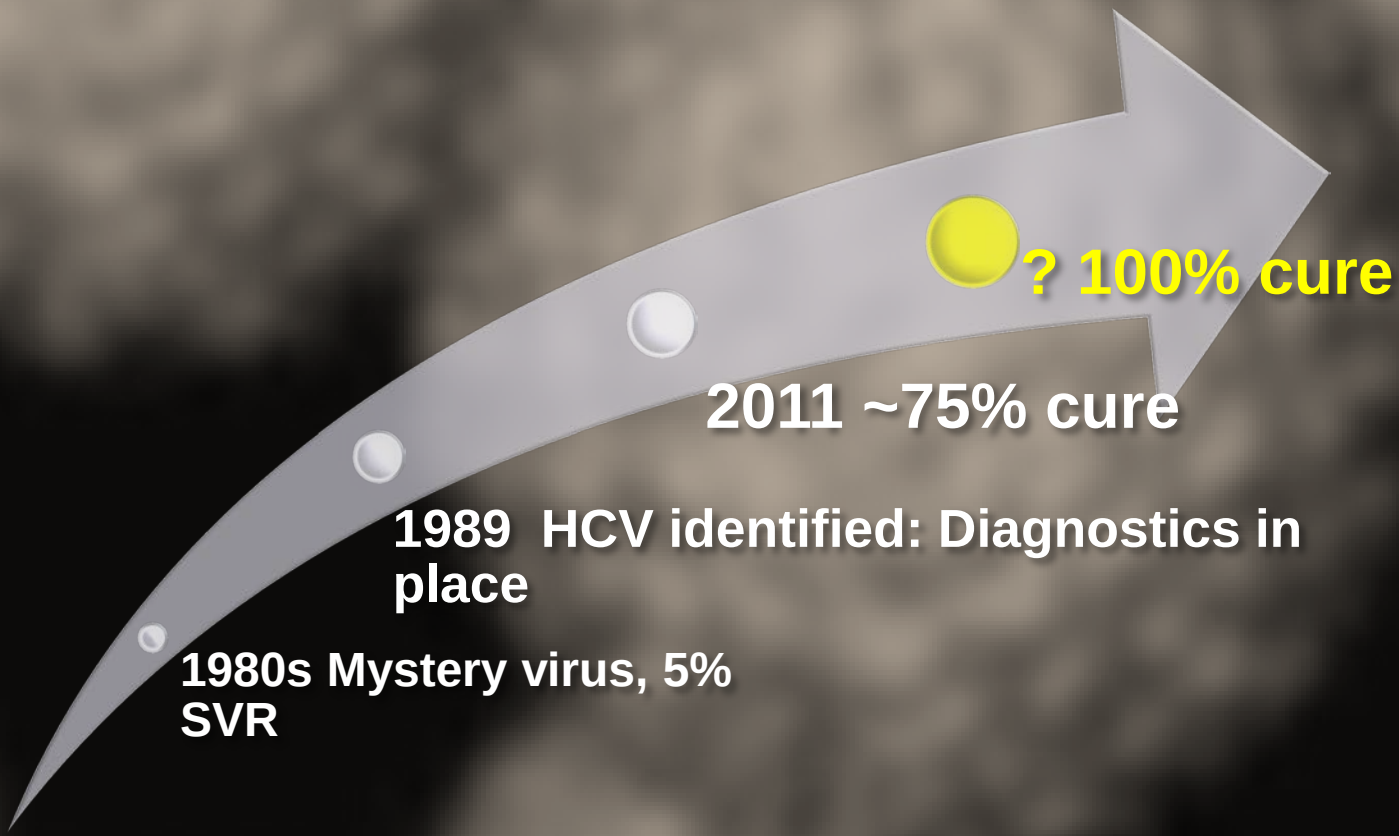
Razavir H, et al. Hepatology. 2013;57:2164-2170.

Increasing Use of High SVR Therapy (~ 90%) Will Eliminate HCV in the US by 2029



Razavir H, et al. Hepatology. 2013;57:2164

Past, present and future



HCV: Epidemiology and Screening Recommendations

Objectives

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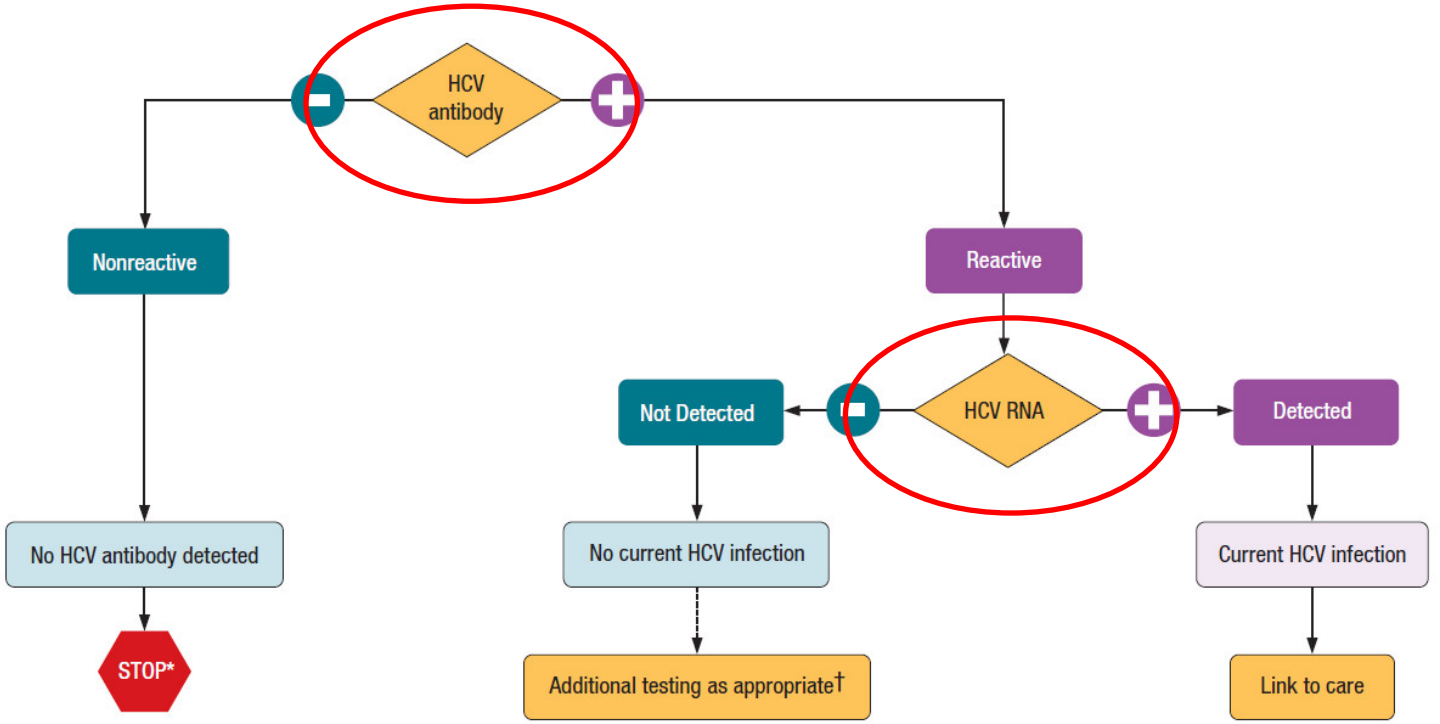
Recommended Testing Sequence for Identifying Current Hepatitis C Virus (HCV) Infection

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention



* For persons who might have been exposed to HCV within the past 6 months, testing for HCV RNA or follow-up testing for HCV antibody is recommended. For persons who are immunocompromised, testing for HCV RNA can be considered.

† To differentiate past, resolved HCV infection from biologic false positivity for HCV antibody, testing with another HCV antibody assay can be considered. Repeat HCV RNA testing if the person tested is suspected to have had HCV exposure within the past 6 months or has clinical evidence of HCV disease, or if there is concern regarding the handling or storage of the test specimen.

Source: CDC. Testing for HCV infection: An update of guidance for clinicians and laboratorians. MMWR 2013;62(18).

Hepatitis C

- Antibody response can take 2 weeks to 9 months
- If anti-HCV antibody is positive and HCV NAT is negative……test again in 6-9 months

Recommendations for the Identification of Chronic Hepatitis C Virus Infection Among Persons Born During 1945–1965

HCV Screening in the United States

- Adults born during **1945–1965** should receive one-time testing for HCV without prior ascertainment of HCV risk.
- People who participate in high risk behavior should be screened for HCV more often
- All persons with HCV infection should receive a brief alcohol screening and intervention as clinically indicated, followed by referral to care for HCV infection.

Diagnosing HCV in the Setting of Immunosuppression

- **HIV/HCV co-infection**
  - Incidence of HCV Ab decreased with decreasing CD4 count (<150 cells/mL)
  - Serological tests underestimated the prevalence of HCV with low CD4 counts

- **Organ Transplant recipients**
  - Often do not seroconvert to the nonstructural proteins
  - Develop antibodies to the envelope glycoproteins and nucleocapsid proteins

CID 1993;17:117
Dig Dis, 2001, 19:333-337

Hepatitis C
Question 1

Hepatitis C can be transmitted by the following exposures EXCEPT:

1. Intravenous Drug Users
2. Snorting cocaine
3. Sex
4. Childbirth
5. All can result in HCV infection

Hepatitis C
Question 2

Who should be screened for Hepatitis C infection?

1. Intravenous Drug Users
2. Anyone born between 1945-1965
3. Men who have sex with Men
4. Anyone with a tattoo
5. All of the above

Hepatitis C Virus:
Who, What and Where

- Hepatitis C is prevalent in the United States and worldwide
- Screen all people born 1945-1965 for HCV
- Order HCV NAT when needed for diagnosis

HCV immunopathogenesis and vaccine prospects

Andrew D Badley MD

Professor of Medicine

Mayo Clinic and Foundation

Division of
INFECTIOUS DISEASES

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May 7-9, 2015

MEDICINE AND MORALS OF ANCIENT ROME ACCORDING TO THE LATIN POETS.

BY DR. EDMOND DUPOUY. 1901

Icterus is the name of a bird that we now call the oriole (the Galbulus of Pliny). This bird had a yellow color, and the ancients thought that when a man attacked by jaundice looked fixedly at the bird for some time, that the bird would die and the man recover his health.

History of hepatitis

New screening approach by Houghton, Choo, and Kuo from virus concentrated from pooled chimp serum (Dan Bradley)

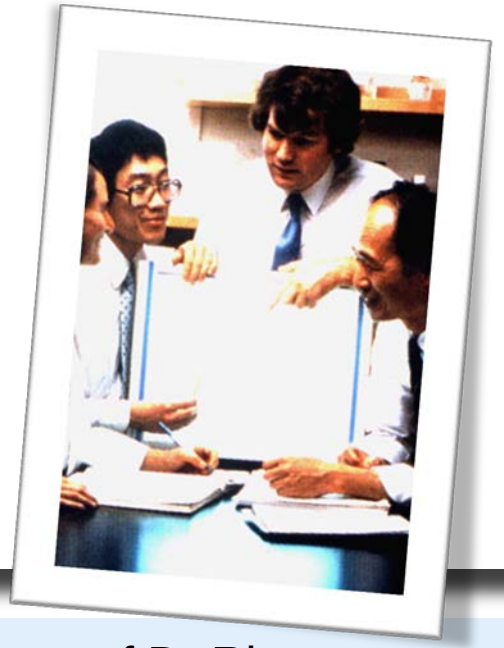
- Bacterial expression of cDNA libraries and screening with convalescent patient serum
- After years of attempts, a *single* clone was finally identified

Isolation of a cDNA Clone Derived from a Blood-Borne Non-A, Non-B Viral Hepatitis Genome

QUI-LIM CHOO, GEORGE KUO, AMY J. WEINER, LACY R. OVERBY, DANIEL W. BRADLEY, MICHAEL HOUGHTON

A random-primed complementary DNA library was constructed from plasma containing the uncharacterized non-A, non-B hepatitis (NANBH) agent and screened with serum from a patient diagnosed with NANBH. A complementary DNA clone was isolated that was shown to encode an antigen associated specifically with NANBH infections. This clone is not derived from host DNA but from an RNA molecule present in NANBH infections that consists of at least 10,000 nucleotides and that is positive-stranded with respect to the encoded NANBH antigen. These data indicate that this clone is derived from the genome of the NANBH agent and are consistent with the agent being similar to the togaviridae or flaviviridae. This molecular approach should be of great value in the isolation and characterization of other unidentified infectious agents.

Science 1989



Courtesy of Dr Rice

17th-19

Outbreaks of jaundice during wars

Timeline of HCV research

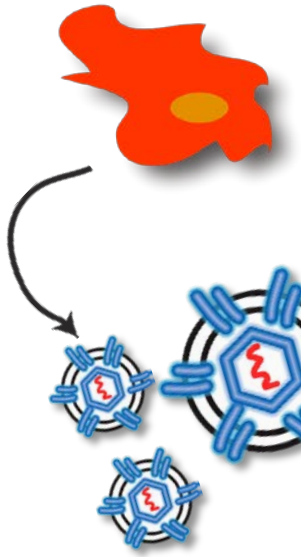
Subgenomic replicon system

2013

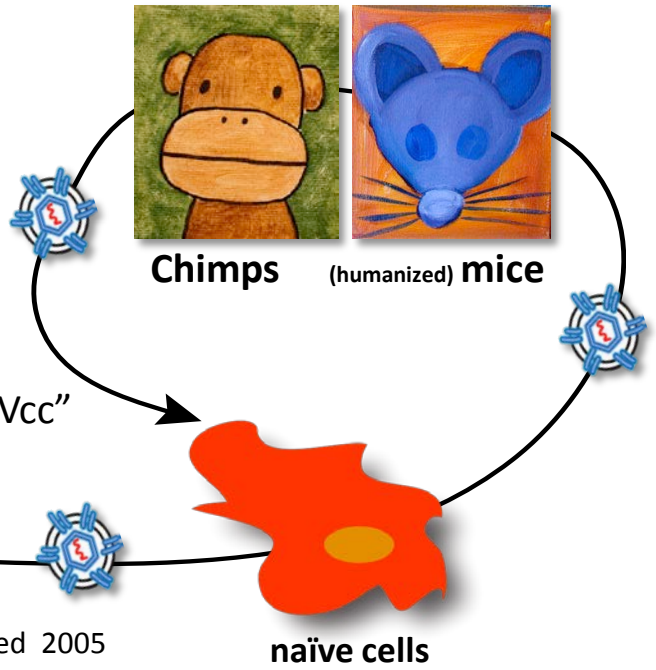
FI-JFH-1 RNA
FI-J6/JFH-1 RNA

Japanese Fulminant Hepatitis isolate

electroporation



HCV virions "HCVcc"



Wakita Nat Med 2005
Lindenbach Science 2005
Lindenbach PNAS 2006
Zhong PNAS 2005

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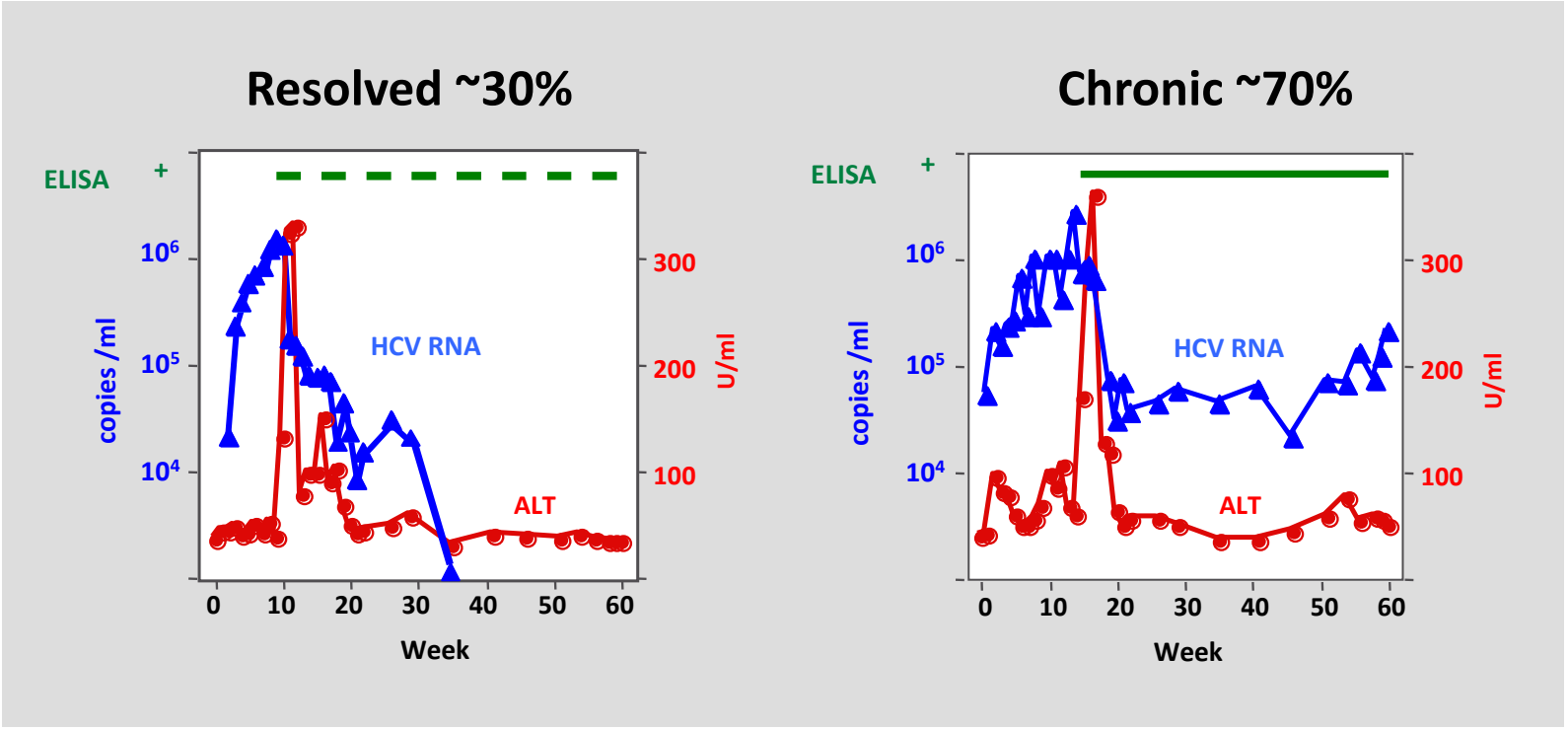
1975

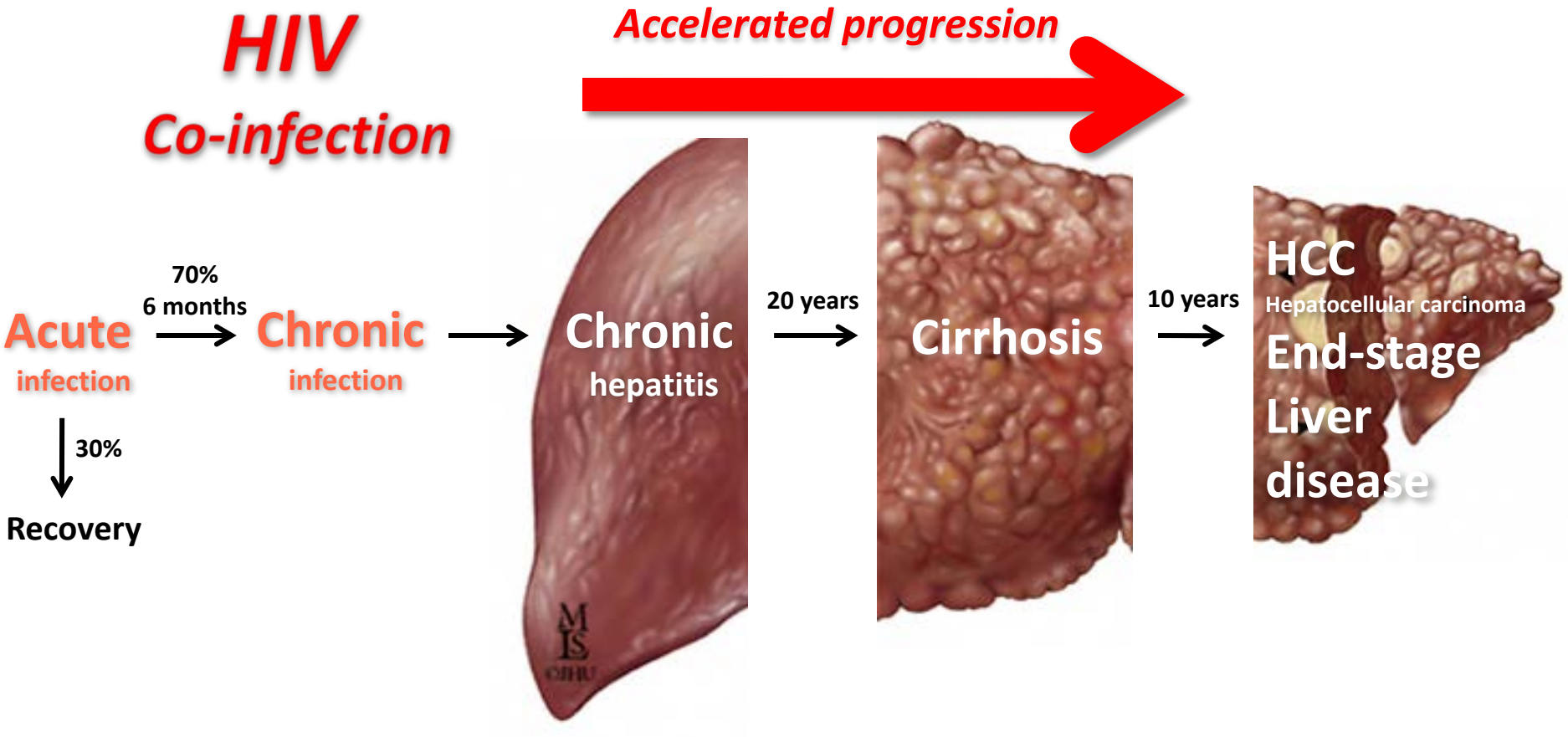
Description of non-A, non-B hepatitis

Courtesy of Dr Rice

Natural history of HCV infection



HCV disease progression

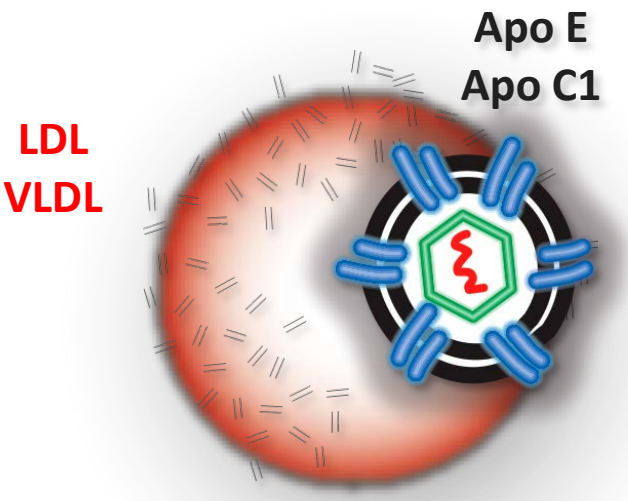


Courtesy of Dr Rice

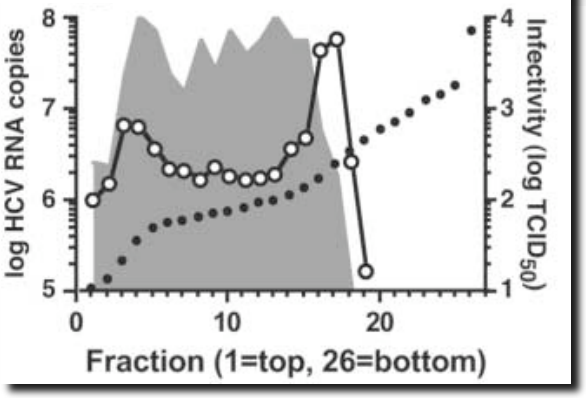
HCV immunopathogenesis

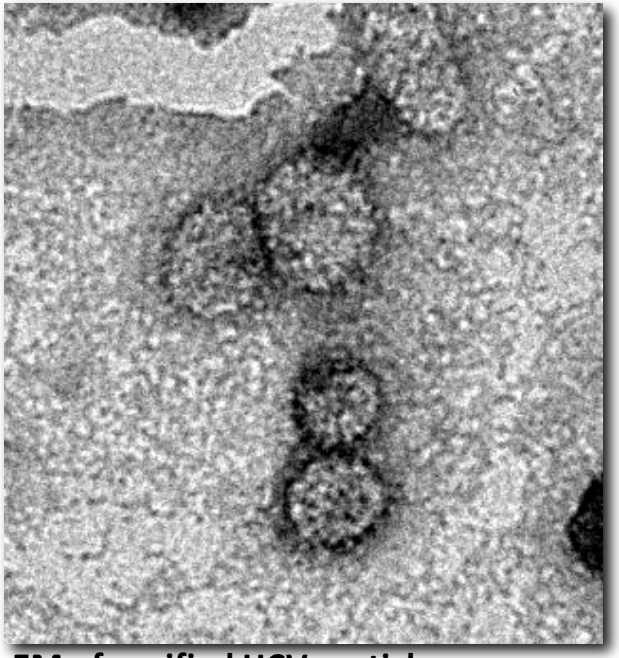
- Lifecycle
- Immune response – Innate
- Immune response – Humoral
- Immune response – T cell
- Correlates of protection
- Prospects for a vaccine

The HCV virion



Heterogeneous density of particles

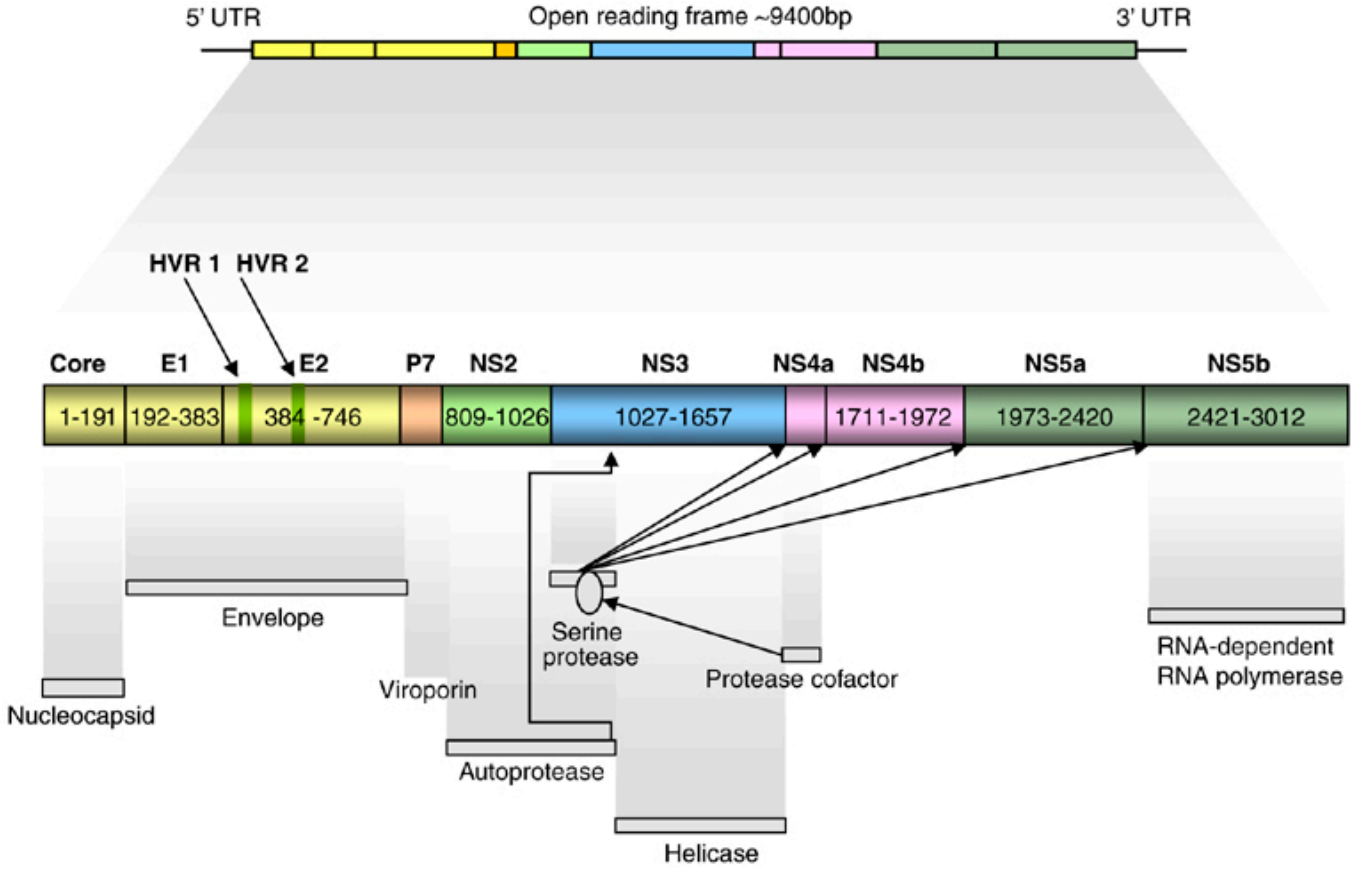




EM of purified HCV particles

Catanese et al. PNAS 2013

HCV Genome



-HCV genome is about 9400 nucleotides long, it is ssRNA and positive sense

-the 10 viral proteins are first made as a large polyprotein

-individual proteins are released from polyprotein by cellular and viral proteases

-core, E1 and E2 are the structural proteins which form the virus particle

-remaining proteins are nonstructural and have roles in viral replication

HCV receptors/entry factors

GAGs

(Barth *et al*., 2003)

Linear polysaccharides on proteins of all human cell surfaces

Provides a way for the virus to stick to cells

CD81

(Pileri *et al*., 1998)

Tetraspanin superfamily member

Expressed in all nucleated cells

Part of B-cell receptor complex

Expression confers susceptibility

SR-BI

(Scarcelli *et al*., 2002)

Scavenger receptor class B member I

HDL receptor (multiple other ligands)

Expressed in hepatocytes, adrenal cortex, gonads (less elsewhere)

Ligands influence infection

Claudin-1

(Evans, von Hahn *et al*., 2007)

Form the backbone of tight junction strands in epithelial tissues

Highest expression in hepatocytes (less elsewhere)

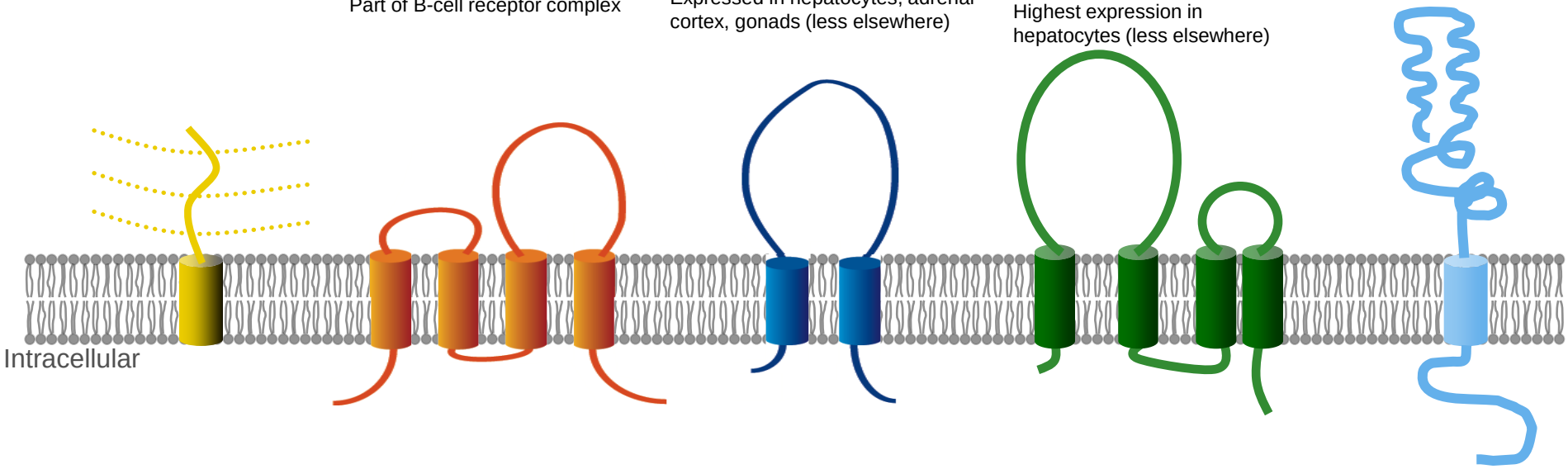
Expression confers susceptibility

LDL-R

(Agnello *et al*., 1999)

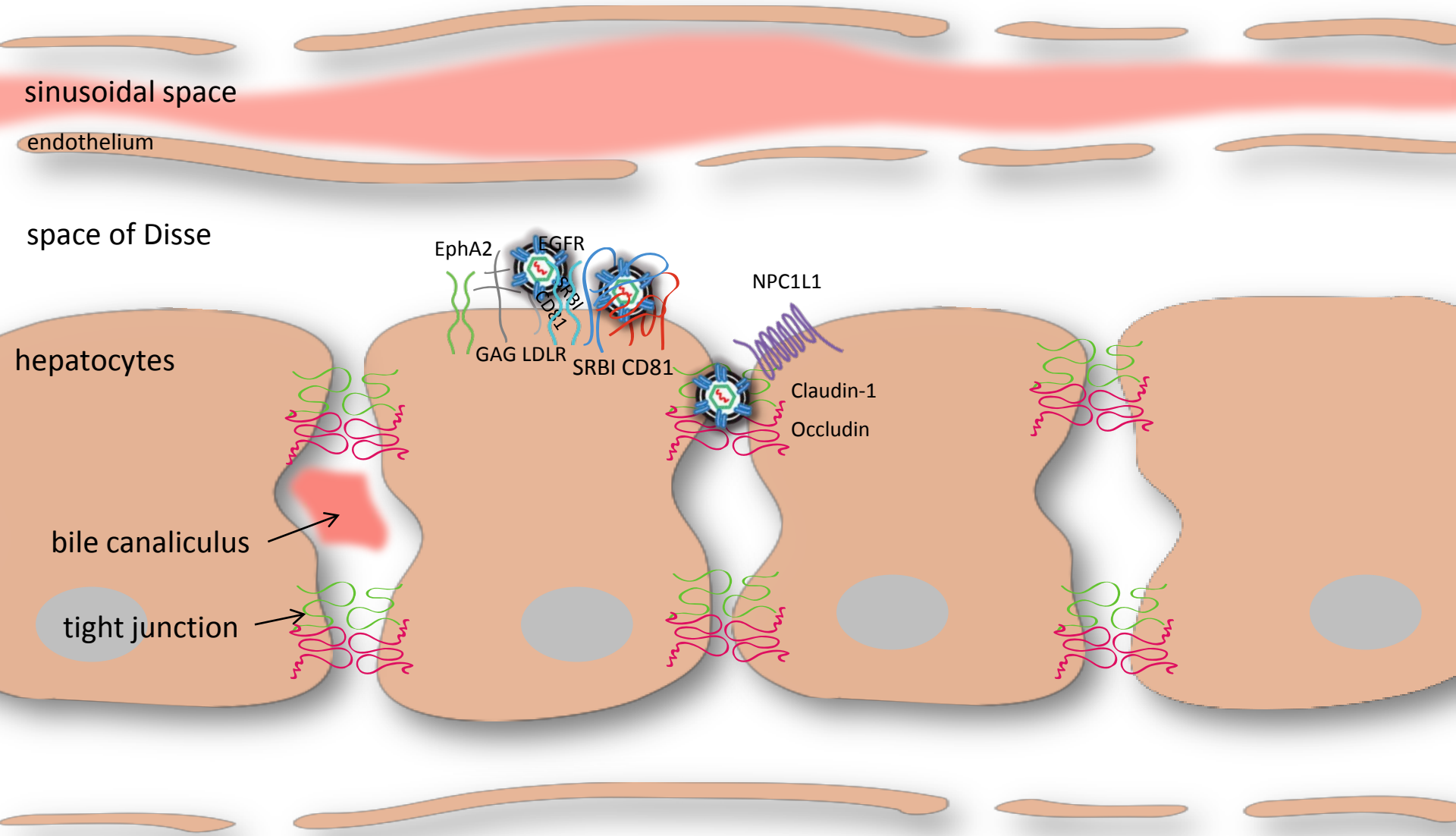
Low density lipoprotein receptor

viral RNA accumulation increased or decreased in parallel with LDLR mRNA expression and LDL entry

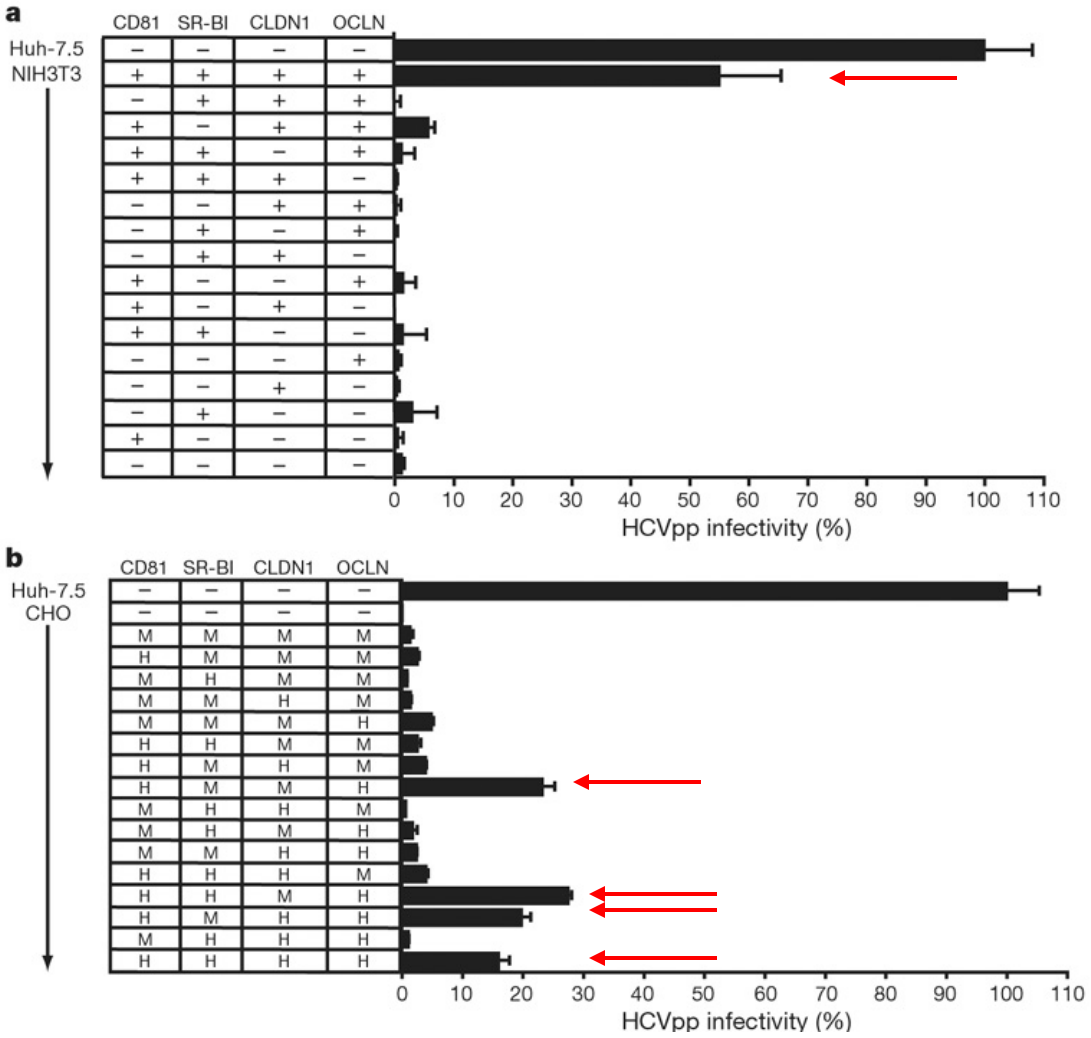


Silencing confers resistance

Current model of HCV entry



Expression of human OCLN and CD81 determines HCV species tropism

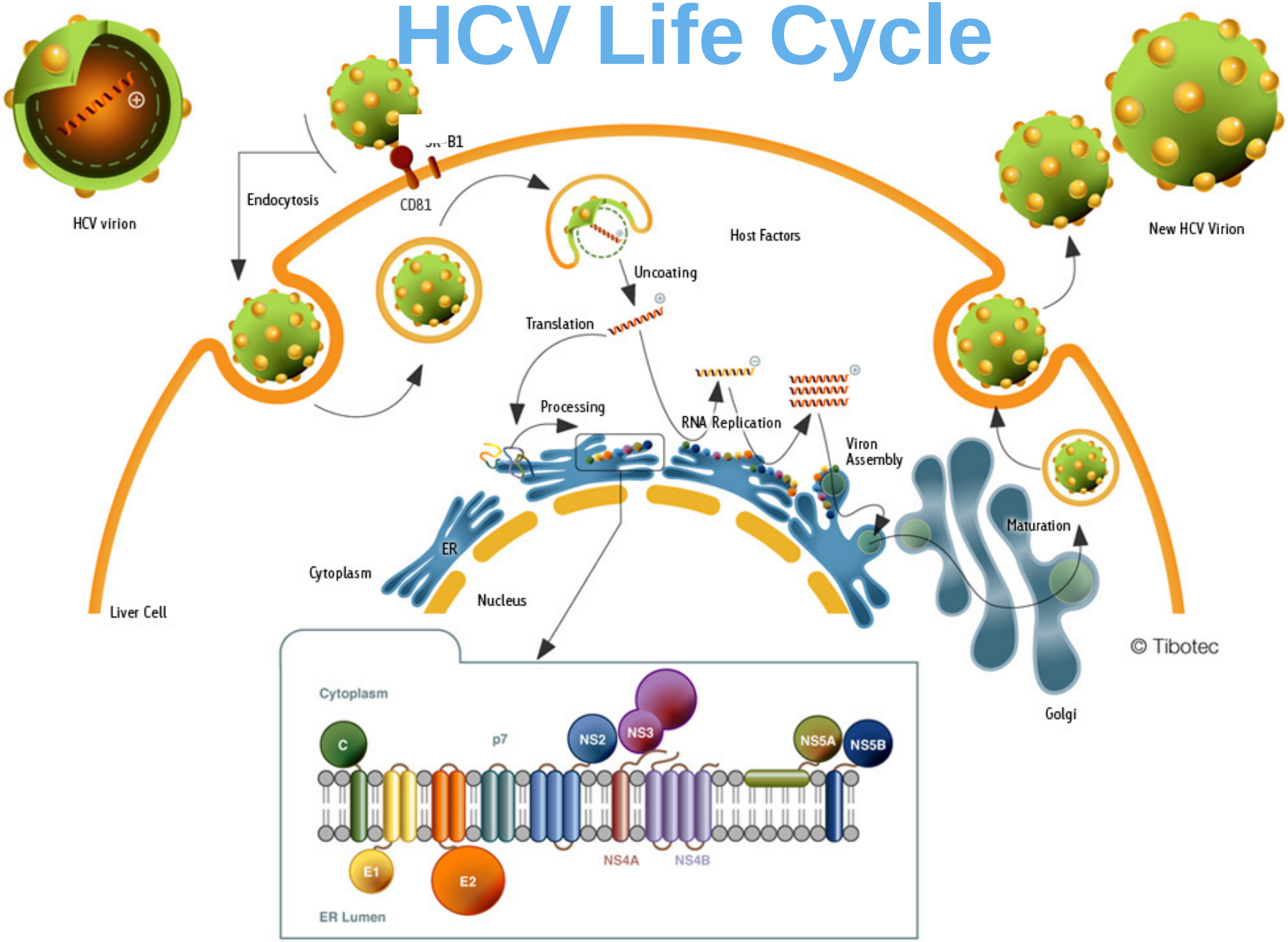


Mouse NIH3T3 cells are only permissive for HCVpp entry when CD81, SR-B1, CLDN1 and OCLN expressed

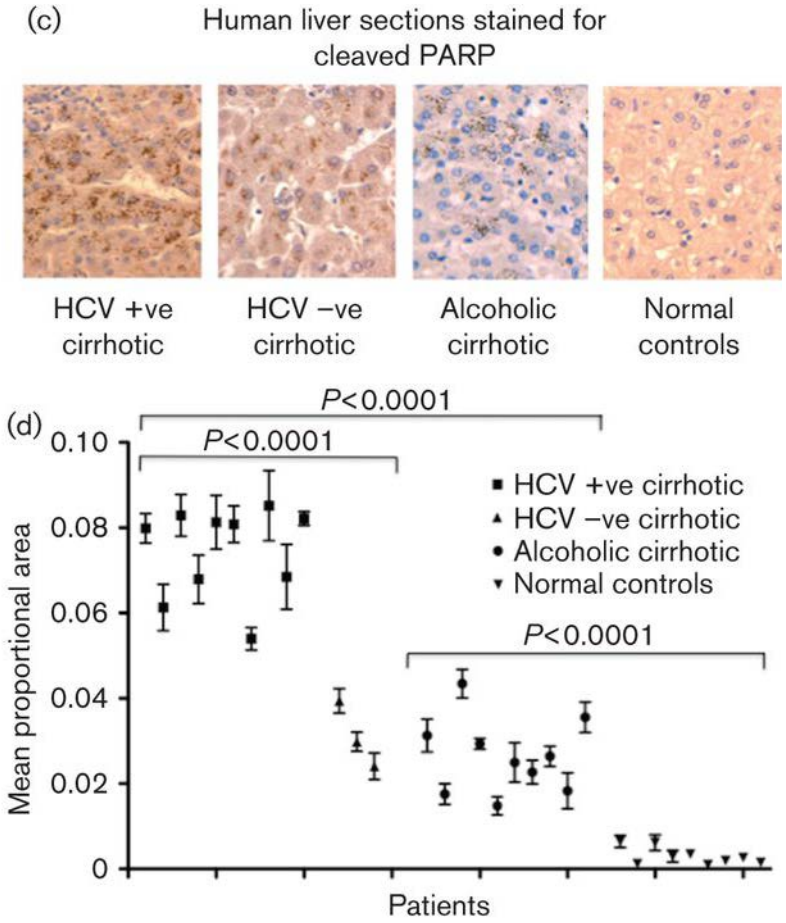
Hamster CHO cells are only permissive for HCVpp entry when human OCLN expressed

A Ploss *et al. Nature* **000**, 1-5 (2009
10.1038/nature07684
nature

HCV Life Cycle



Chronic HCV infection is associated with increased hepatocyte apoptosis



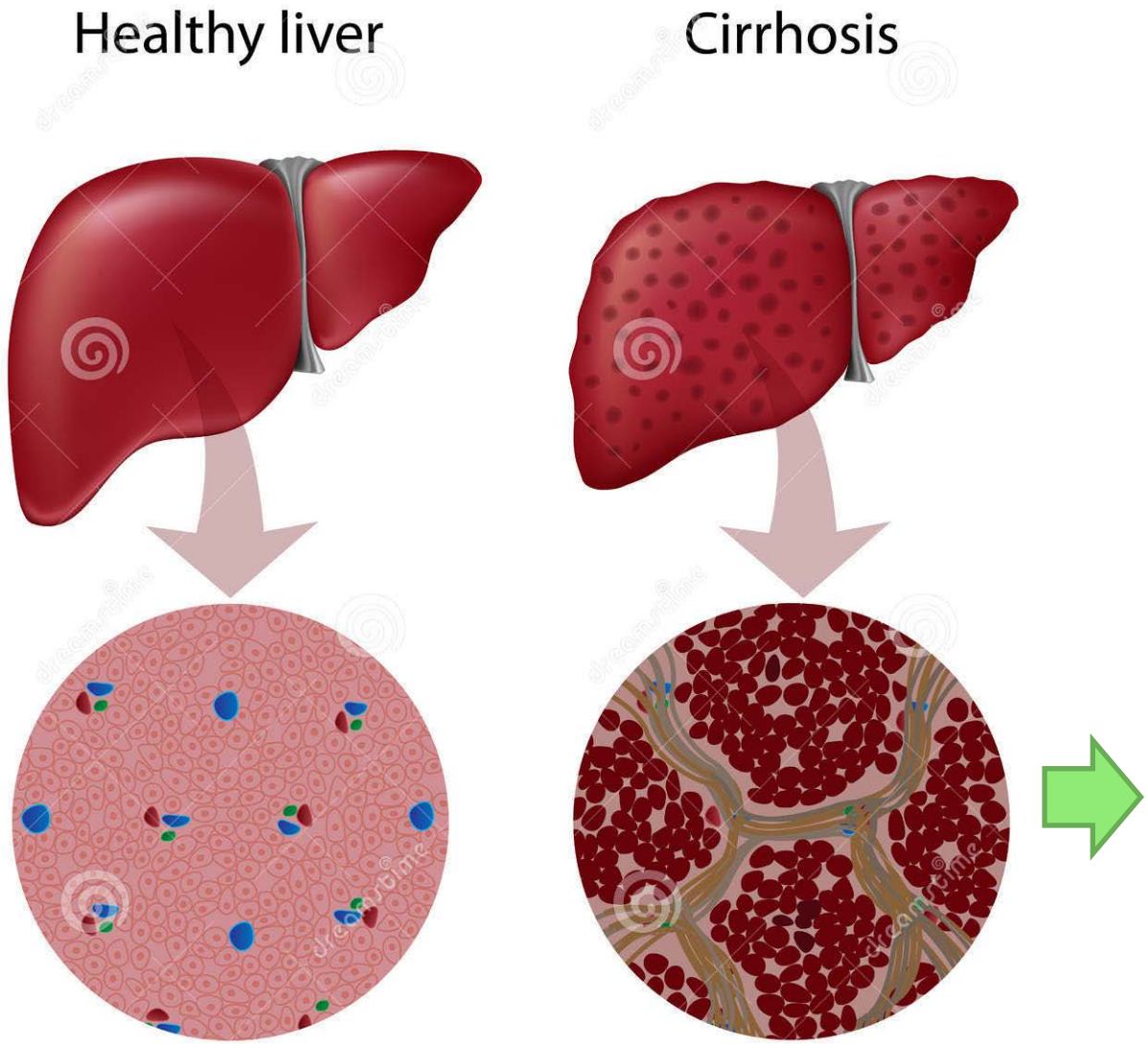
Mechanisms

- Direct viral effect
- CTL
- NK
- Up-regulation of Death Receptors
- Up-regulation of Death ligands

Eu Jin Lim et al. J Gen Virol 2014;95:2204-2215

Immune-mediated liver injury

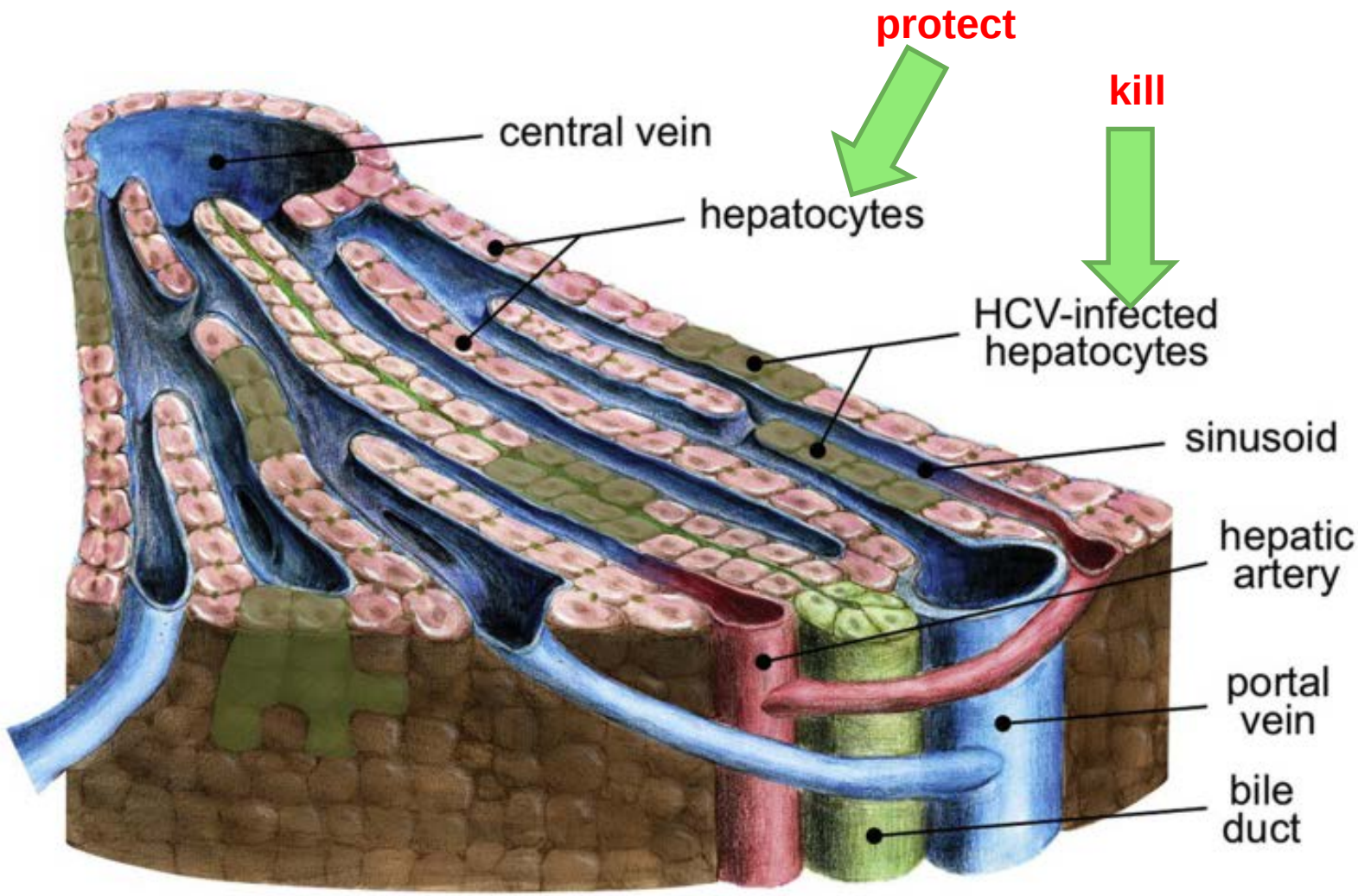
- Mechanisms responsible for liver injury poorly understood
- Host immune response and not viral replication
- High CD8+ in liver → immunopathogenesis and liver injury
- Normal Liver = immuno silent
- HCV liver =
  - Type I IFN production
  - Release of chemokines that promote infiltration of NK cells
  - Induced IFN-γ production in NK cells
  - Expression of chemokines that recruit activated T cells to liver
- Depletion of NK cells before hepatotropic viral infection leads to inhibition of virus-specific T cell response and liver injury


Healthy liver
Cirrhosis
HCC

HCV immunopathogenesis

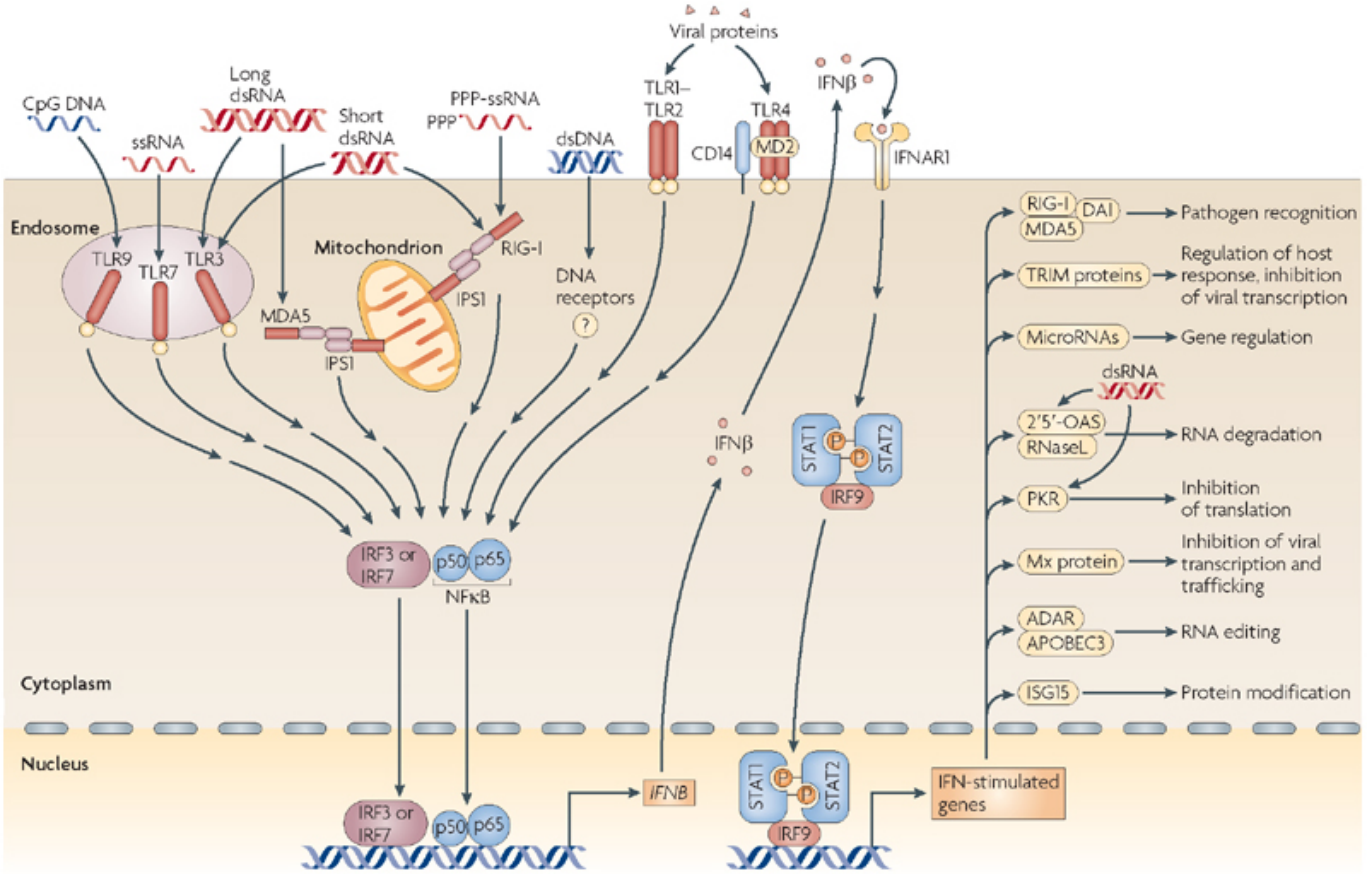
- Lifecycle
- Immune response – Innate
- Immune response – Humoral
- Immune response – T cell
- Correlates of protection
- Prospects for a vaccine

Innate response



Immunity 2014 40, 13-24DOI: (10.1016/j.immuni.2013.12.010)

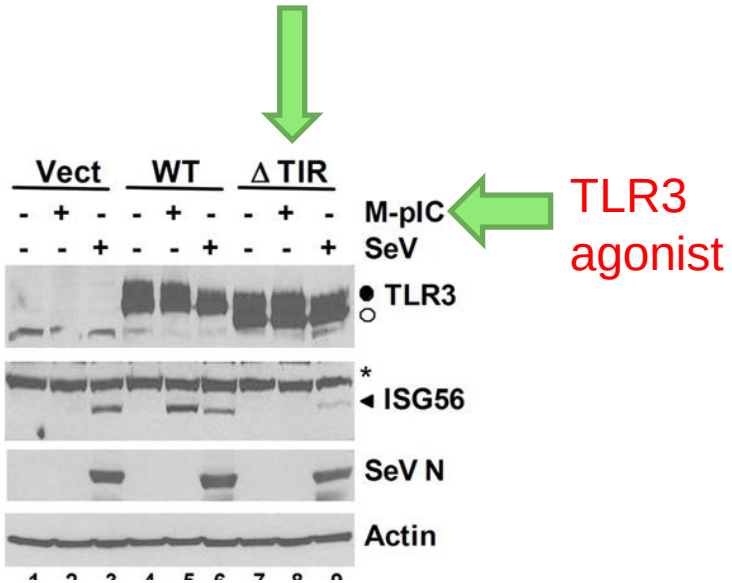
PAMPs and PRR and ISG in viral diseases



Nature Reviews | Immunology

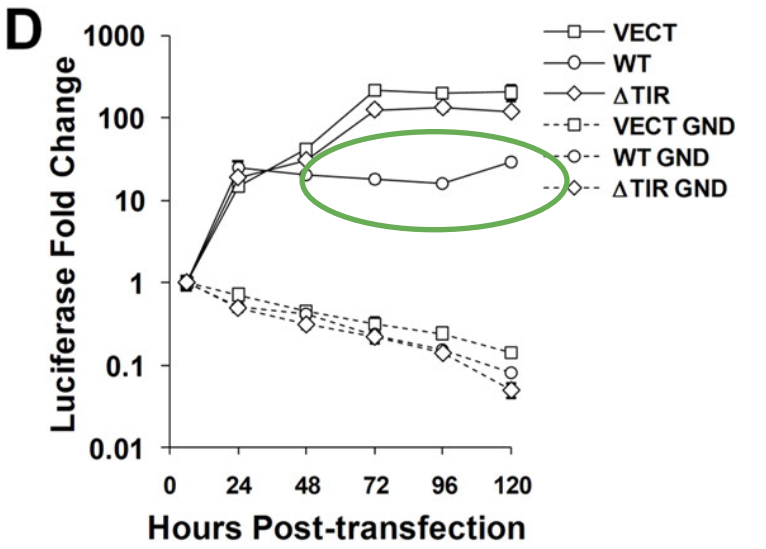
TLR3 recognizes HCV, responds by producing IFNb and inhibits HCV replication

C terminal truncation mutant TLR3



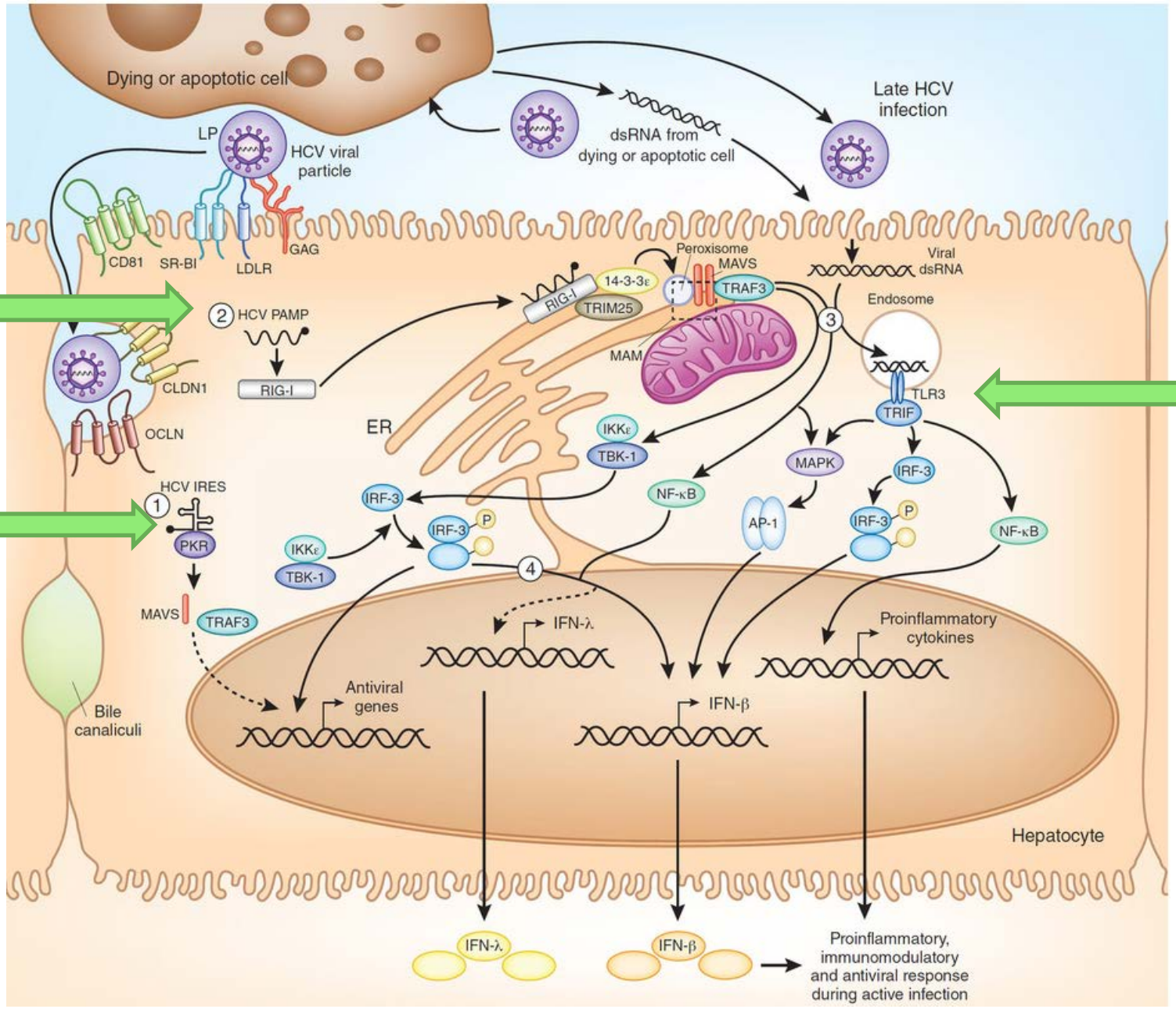
TLR3 agonist

Huh 7 infected with Luc HCV



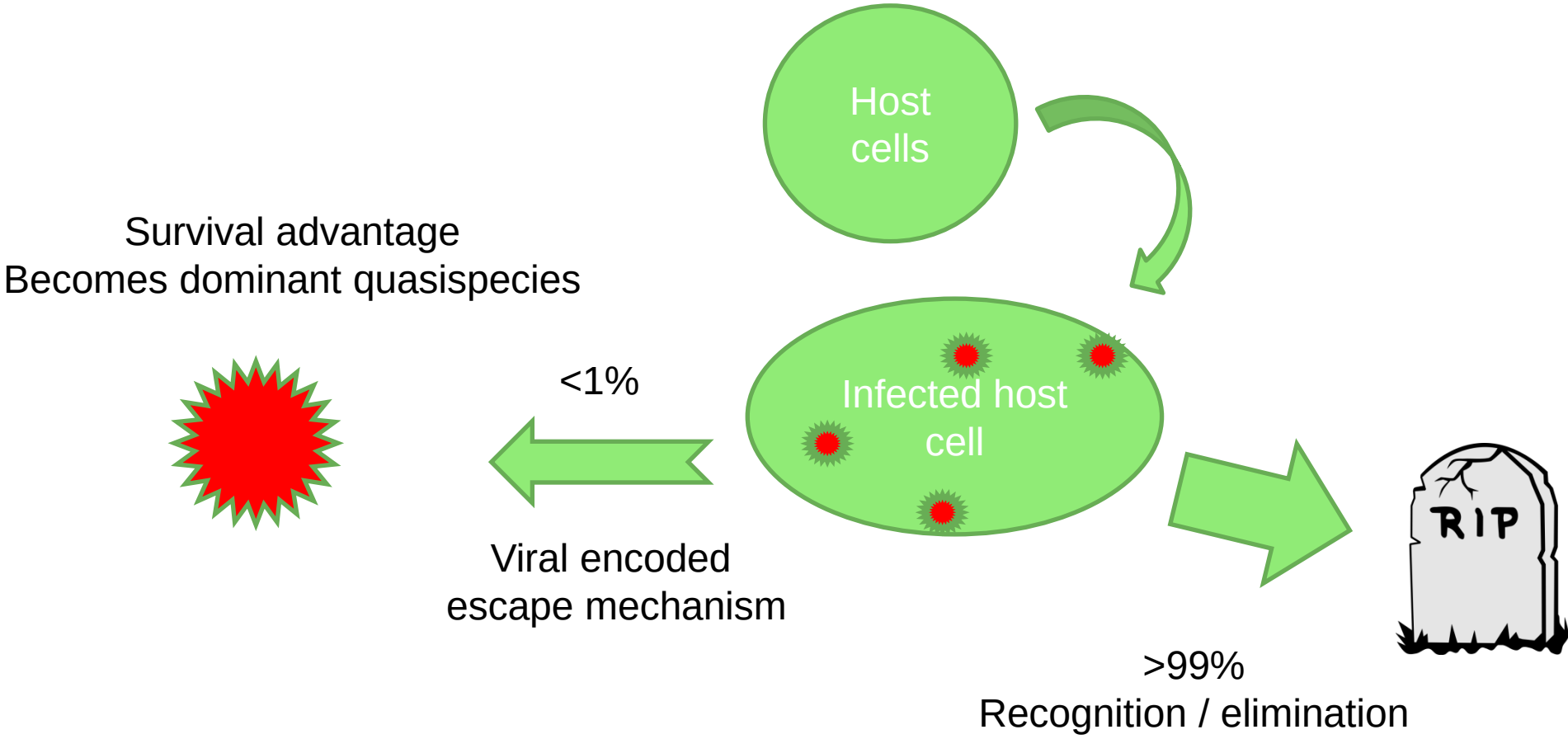
Nan Wang et al. J. Virol. 2009;83:9824-9834

TLR3, RIG-1 and PKR contribute to Innate sensing of HCV

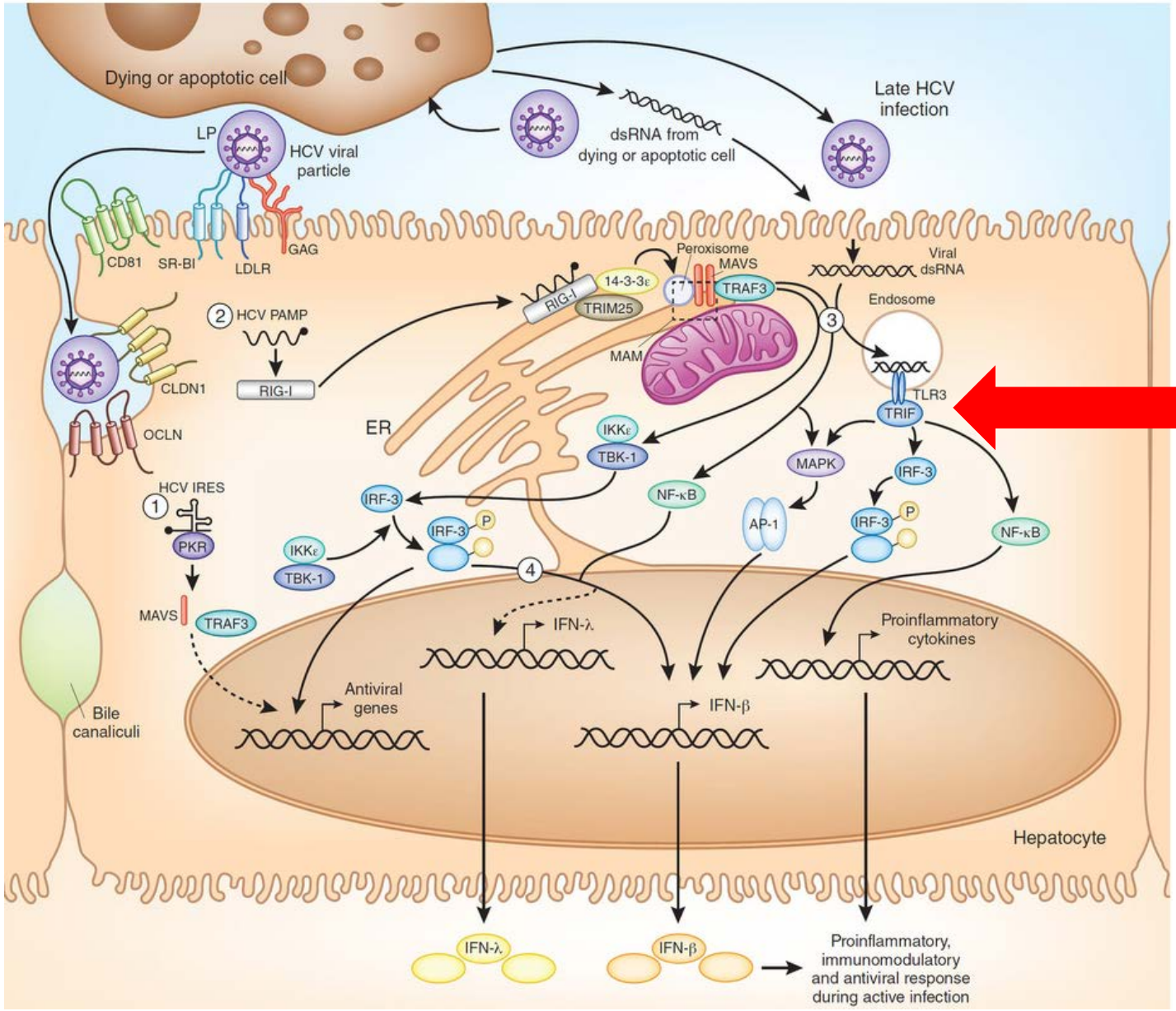


Nature Medicine 19,879-888 (2013)

Host sensing / elimination of infected cells vs Viral evasion of death



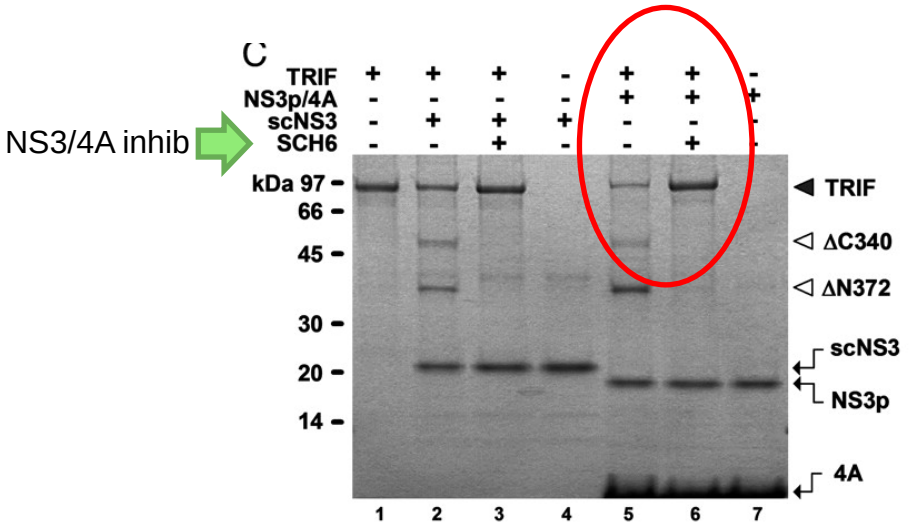
TLR3, RIG-1 and PKR contribute to Innate sensing of HCV

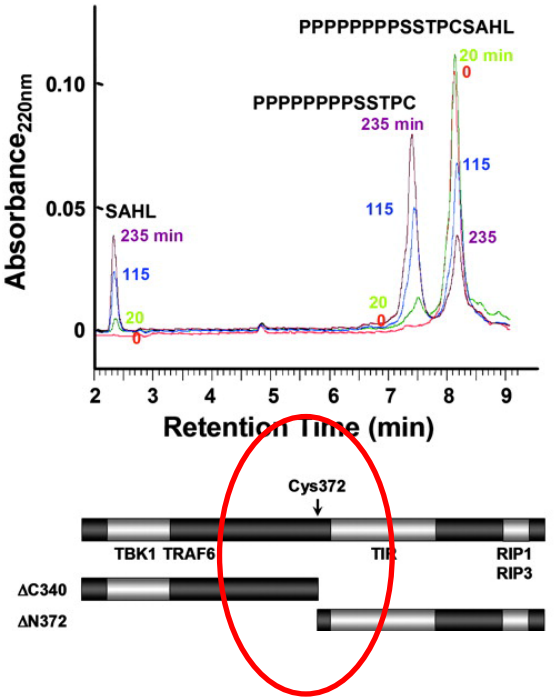


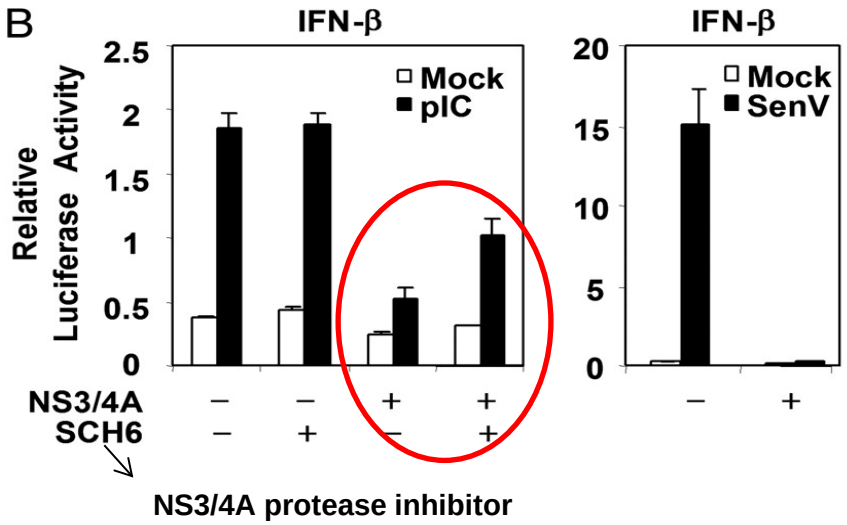
TRIF

Nature Medicine 19,879-888 (2013)

NS3/4A protease Cleaves TRIF and blocks TLR3 induced IFNβ



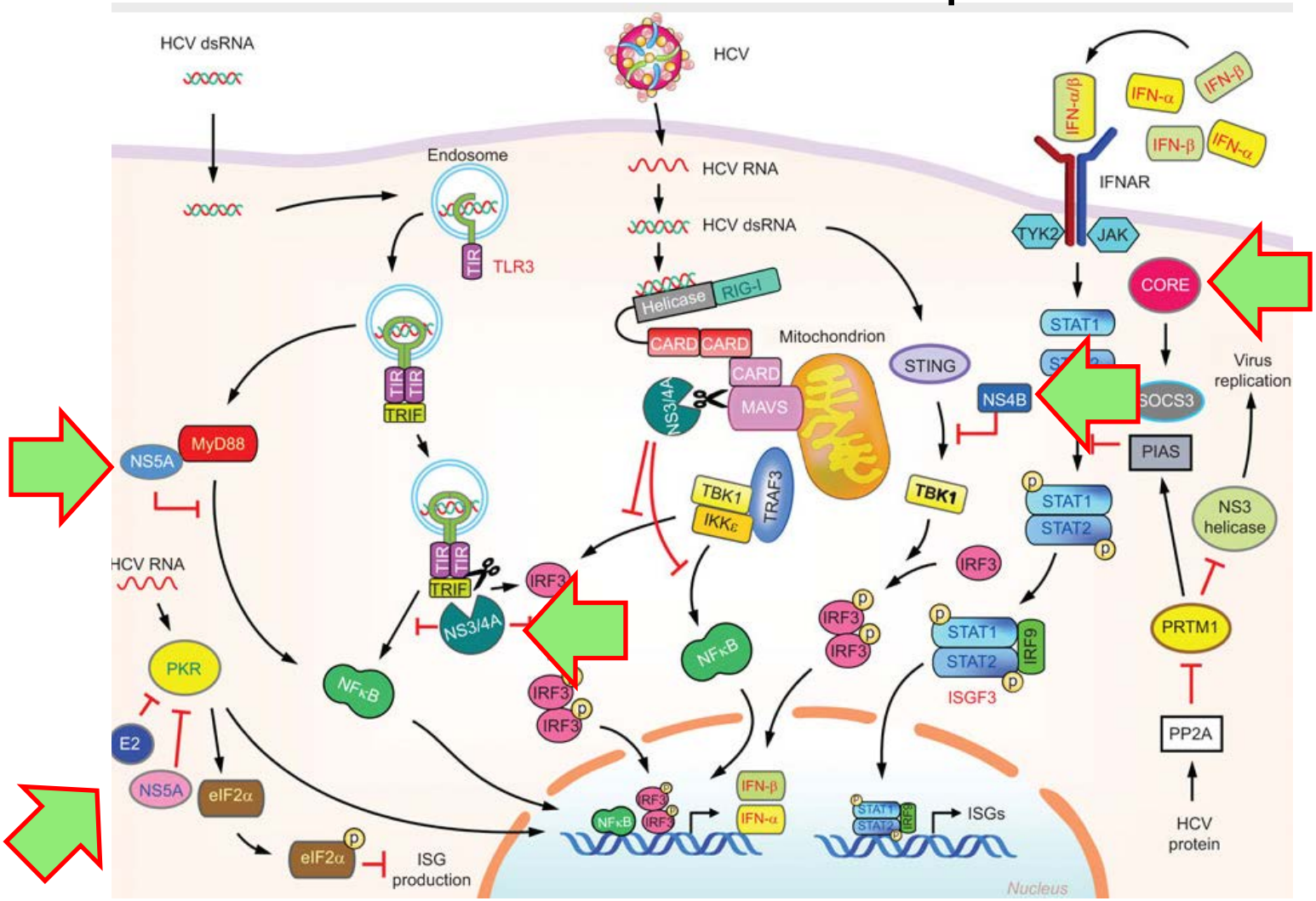




Kui Li et al. PNAS 2005;102:2992-2997

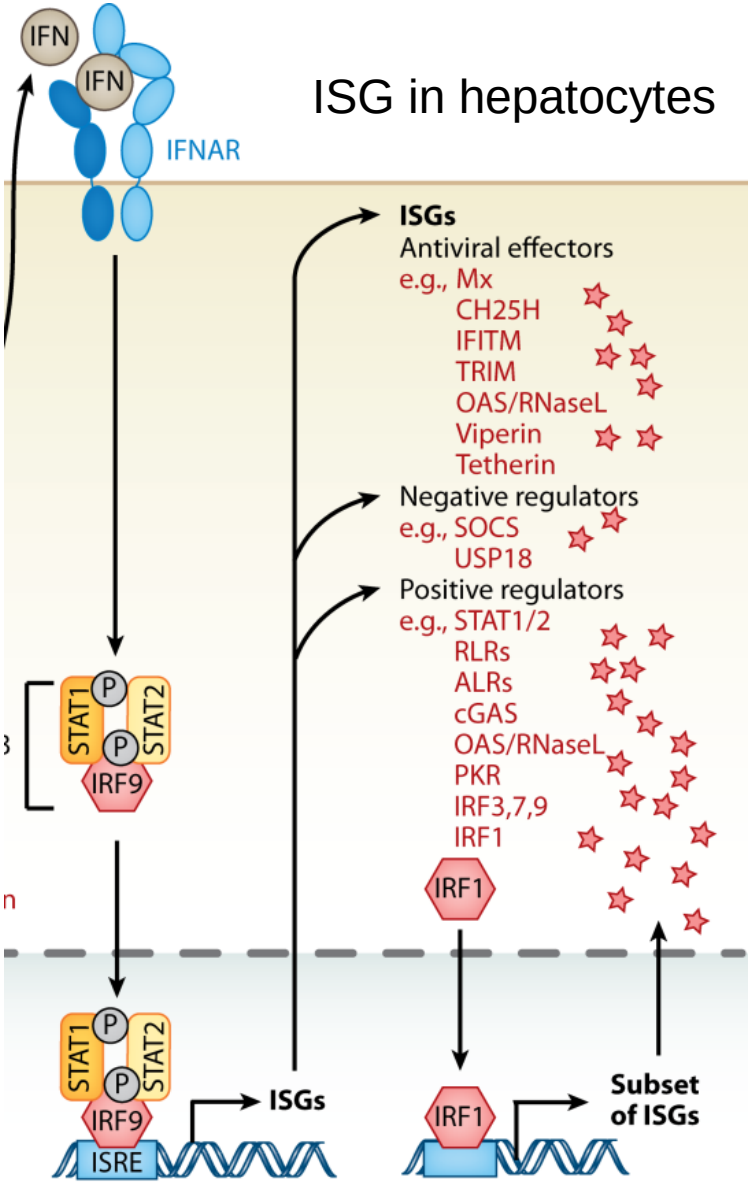
PNAS

HCV employs multiple mechanisms of Innate immune escape



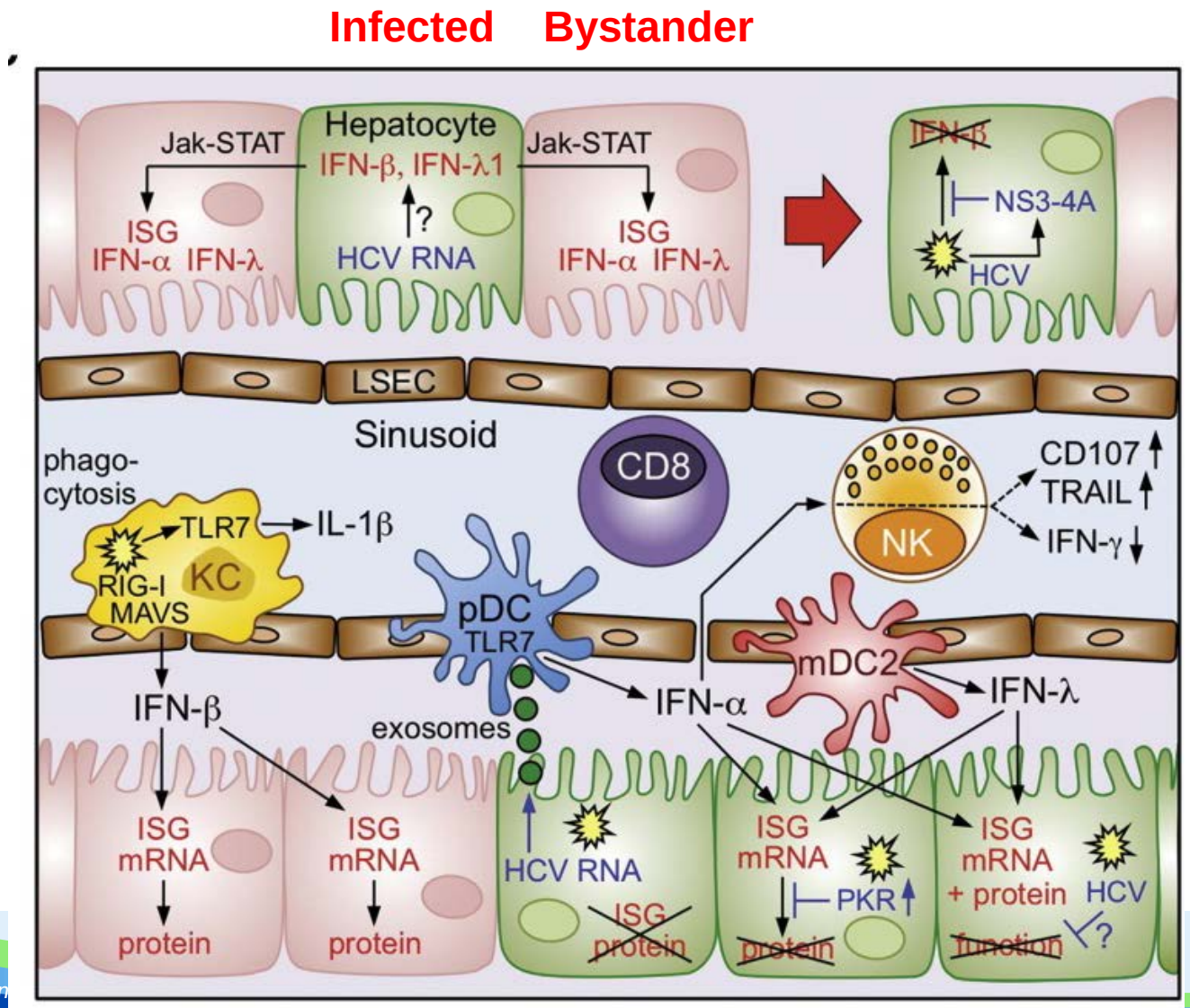
IFNβ from infected cells

- Increase class 1 expression
- Activate NK cells
- Upregulate TRAIL expression by CTL
- Block CD8 apoptosis



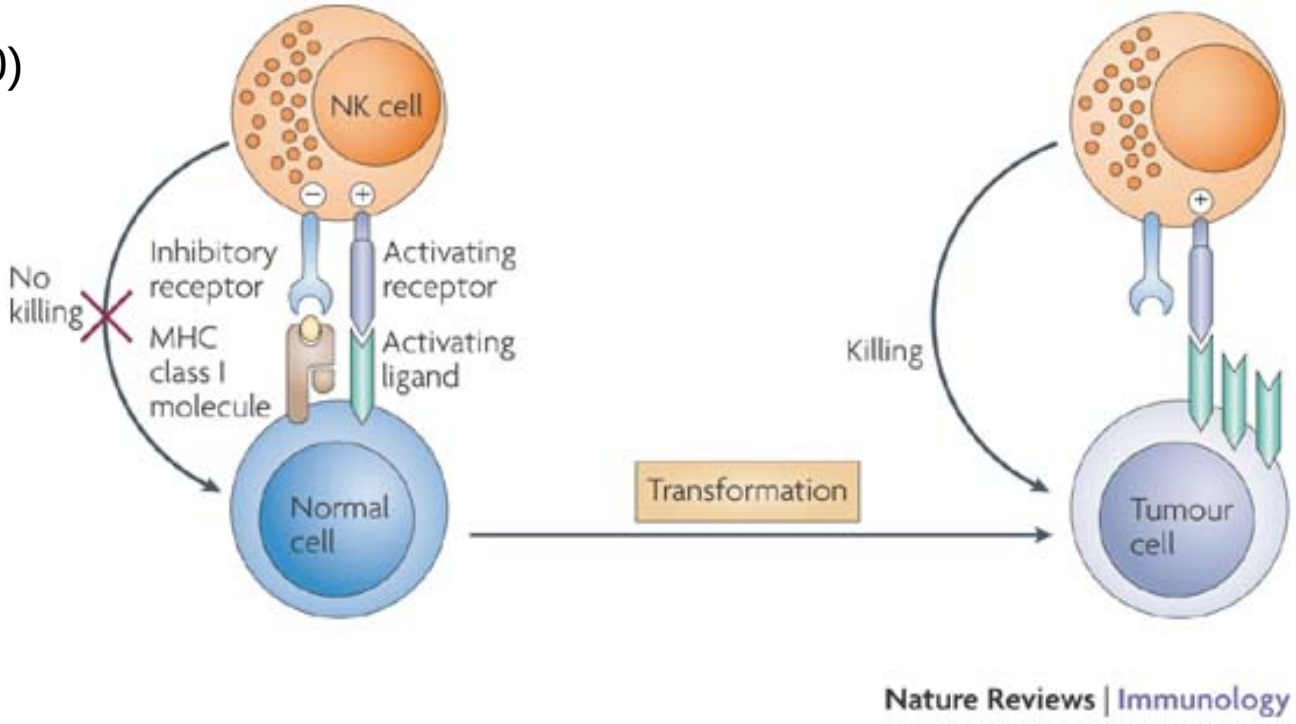
*Differ by cell type & by IFN type.

IFNβ recruits, and IFNα activates NK cells



Innate Immunity: NK cells

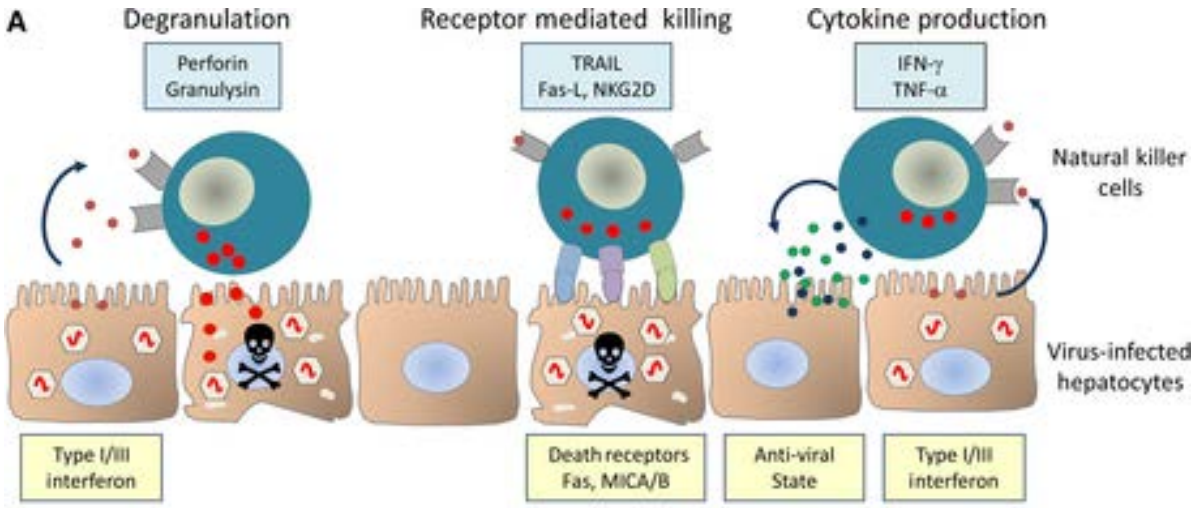
- Inhibitory Receptors
- Activating Receptors
- TIGIT : CD155 (IL-10)
- Secrete:
  - Chemokines
  - IFNγ
  - IL17
  - IL22
- Kill through
  - ADCC
  - Perforin:GrB
  - FasL
  - TRAIL



Multifunctional NK responses (cytotoxicity and IFNγ) are seen in exposed yet uninfected HCW (Hepatology 58: 1621-1631)

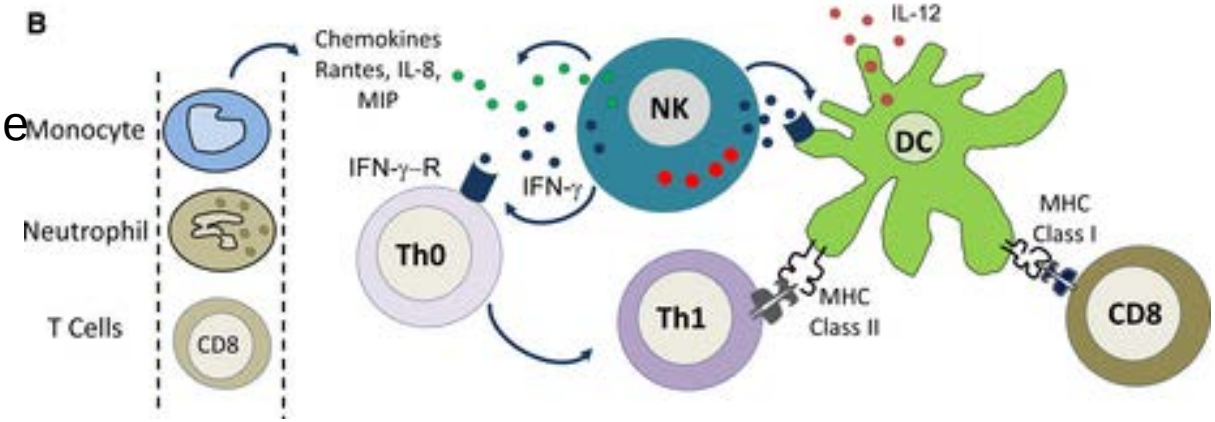
Second line of Defense: NK cells

1
Kill target cells



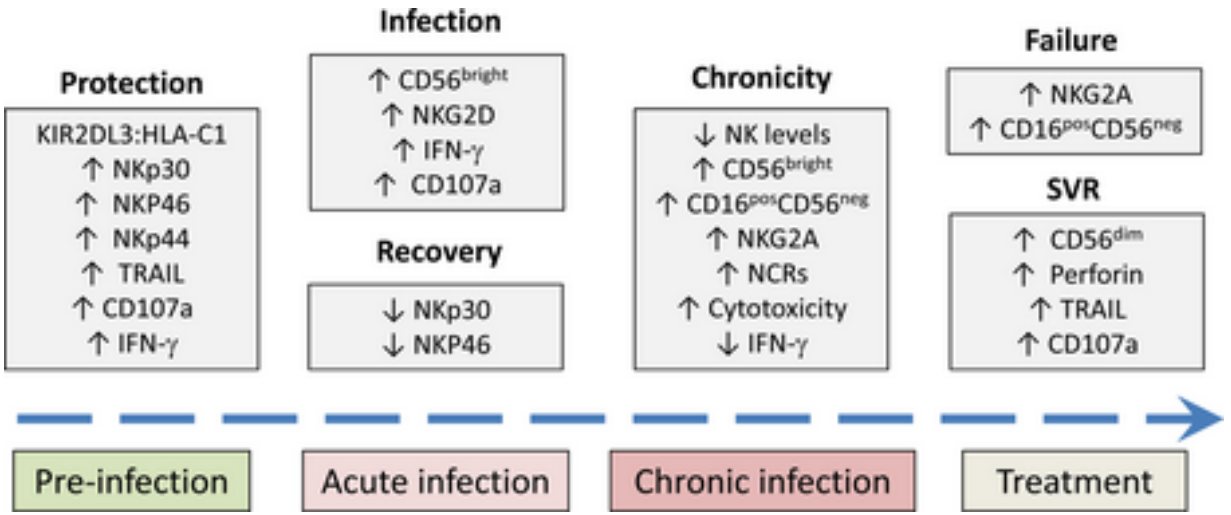
3
IFN protects neighboring cells

2
Recruit Immune subsets



Immunological Reviews
Volume 255, Issue 1, pages 68-81, 15 AUG 2013

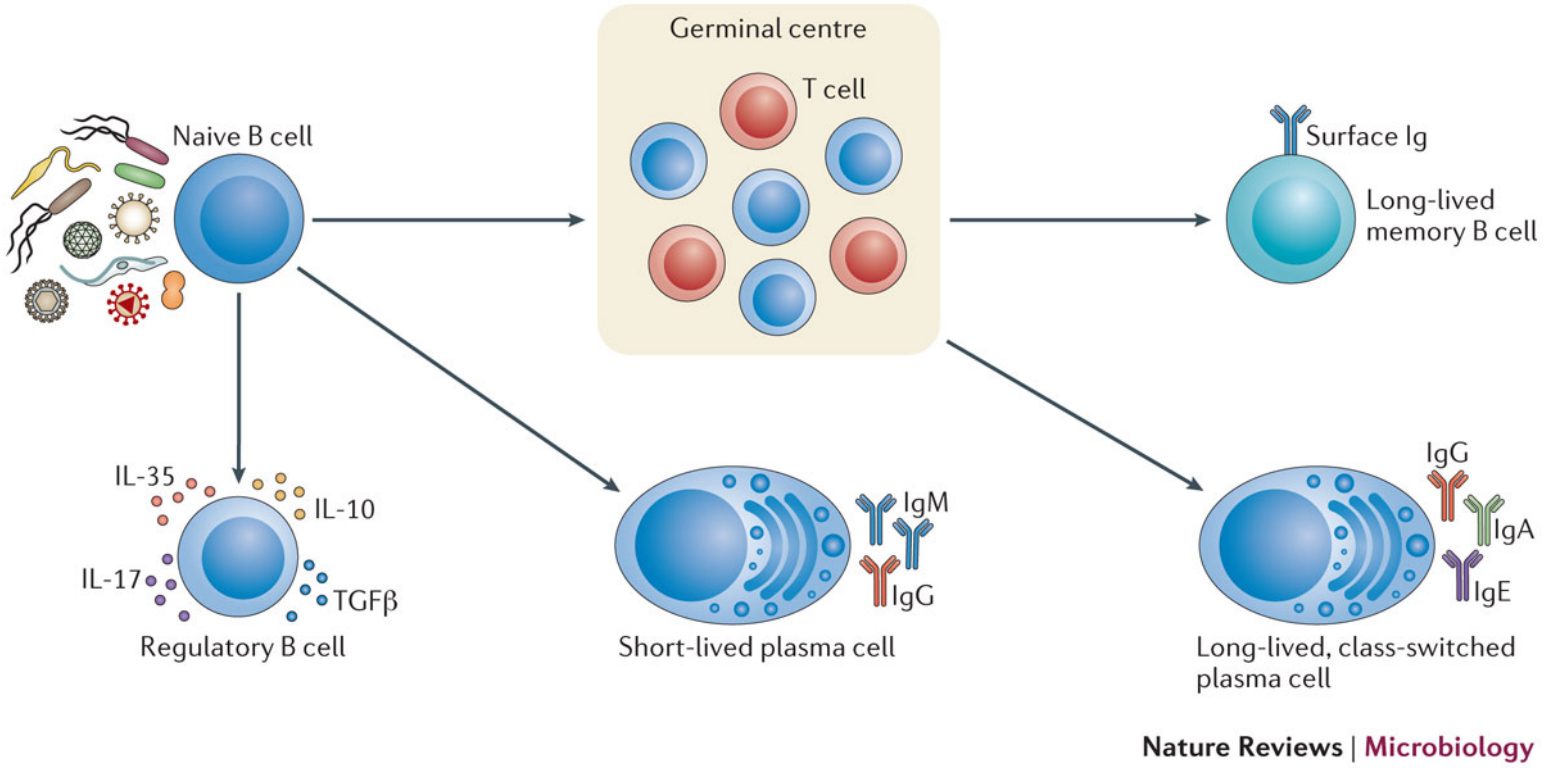
NK cells are the predominant immune cell in the Liver and their activation is associated with HCV outcome



HCW exposed to HCV who clear: Robust multifunctional NK cells

HCV immunopathogenesis

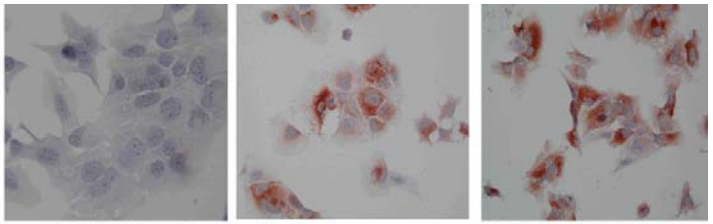
- Lifecycle
- Immune response – Innate
- Immune response – Humoral
- Immune response – T cell
- Correlates of protection
- Prospects for a vaccine

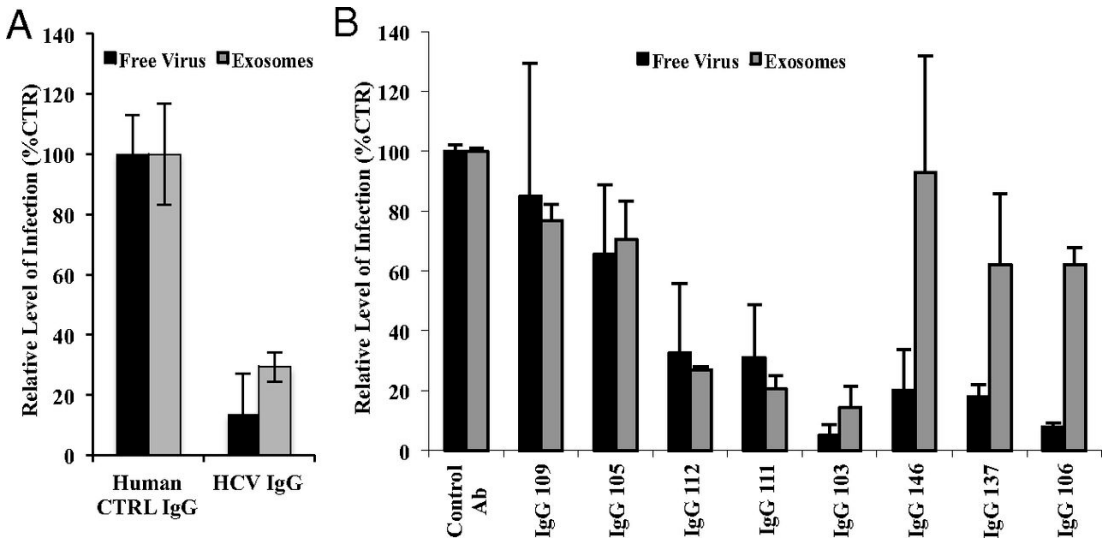

Germinal centre
T cell
Naive B cell
Surface Ig
Long-lived
memory B cell
IL-35
IL-10
IL-17
TGFβ
Regulatory B cell
IgM
IgG
Short-lived plasma cell
IgG
IgA
IgE
Long-lived, class-switched
plasma cell
Nature Reviews | Microbiology

B Cell Response to HCV

- Acute
  - Antibodies generated after 6-8 weeks
- Chronic
  - Antibodies directed against structural & non structural antigens.
- Clearance
  - Has been reported in agammaglobulinemic (Clin Exp Ther 110: 4-8)
  - Broadly neutralizing antibodies appear after months to years of chronic infection (PNAS 101: 10149-10154)
  - E2 envelope is target of BNAb (Science 232: 1090-1094)

Role of membranes on Antibody neutralization





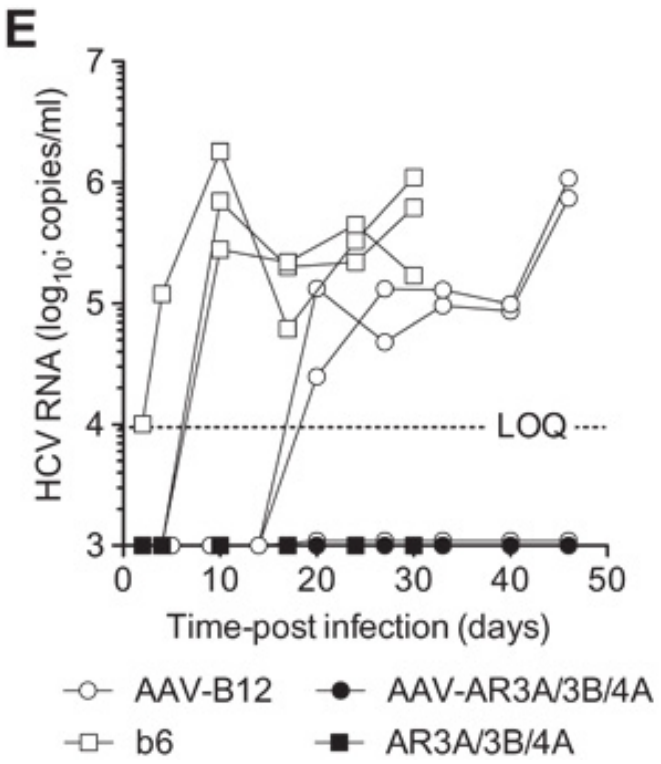
Pt derived serum

Vedashree Ramakrishnaiah et al. PNAS 2013;110:13109-13113

PNAS

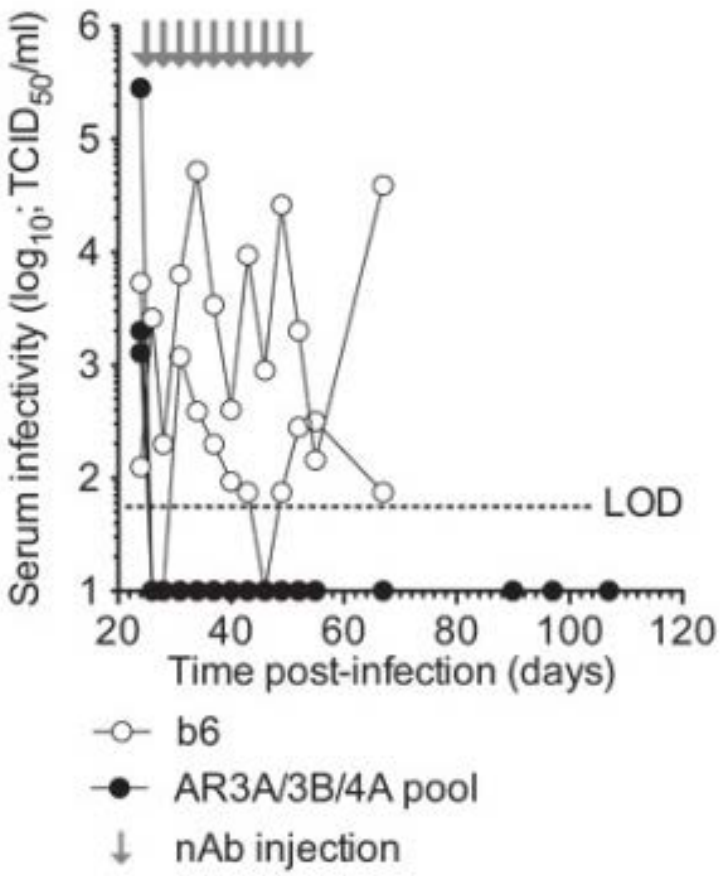
Prophylaxis with broadly neutralizing anti-HCV antibodies (humanized mice).

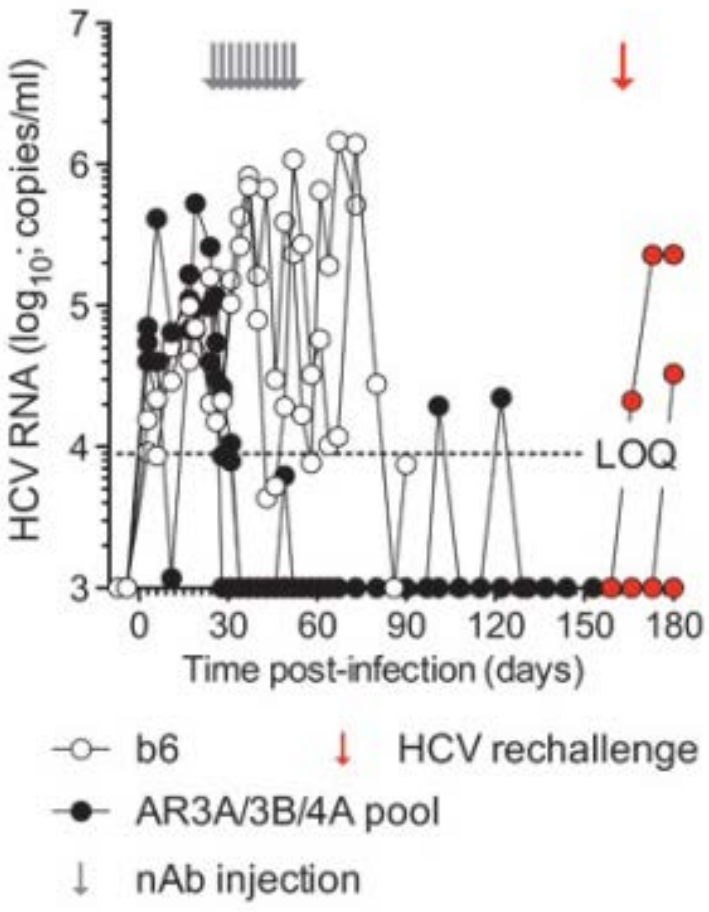
E2 : CD81 interaction
E2 aa 410 – 425
B Sheet conformation
Most neutralizing ab's target



Ype P. de Jong et al., Sci Transl Med 2014;6:254ra129

Treatment of human liver chimeric mice with broadly neutralizing anti-HCV antibodies clears established HCV infection.

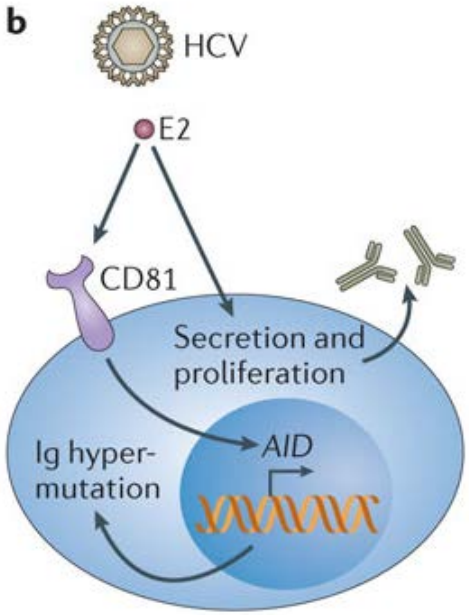




Ype P. de Jong et al., Sci Transl Med 2014;6:254ra129

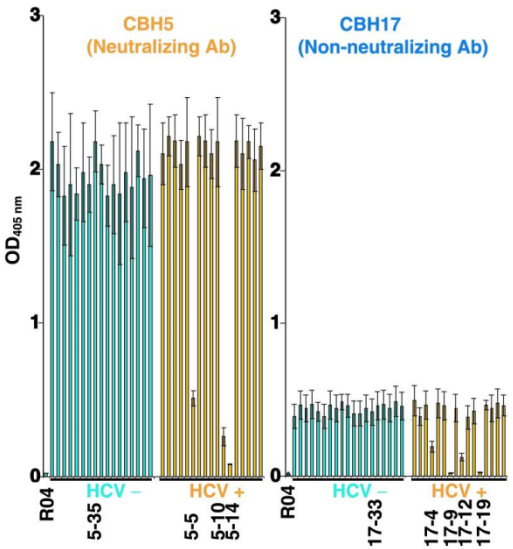
Science Translational Medicine
AAAS

HCV evasion of antibody defense



E2 binding to CD81

- Activation and proliferation
- Enhanced antibody secretion
- Activation of AID
  - Activation Induced Cytosine Deaminase
  - Cytosine➔ Uracil
  - Hypermutation
- Reduces affinity antibodies



Antibodies in HCV

- Role of antibodies controversial
- Virus can be cleared in absence of antibody responses
- Neutralizing antibodies target E2; evidence of prophylactic and therapeutic effect.

HCV immunopathogenesis

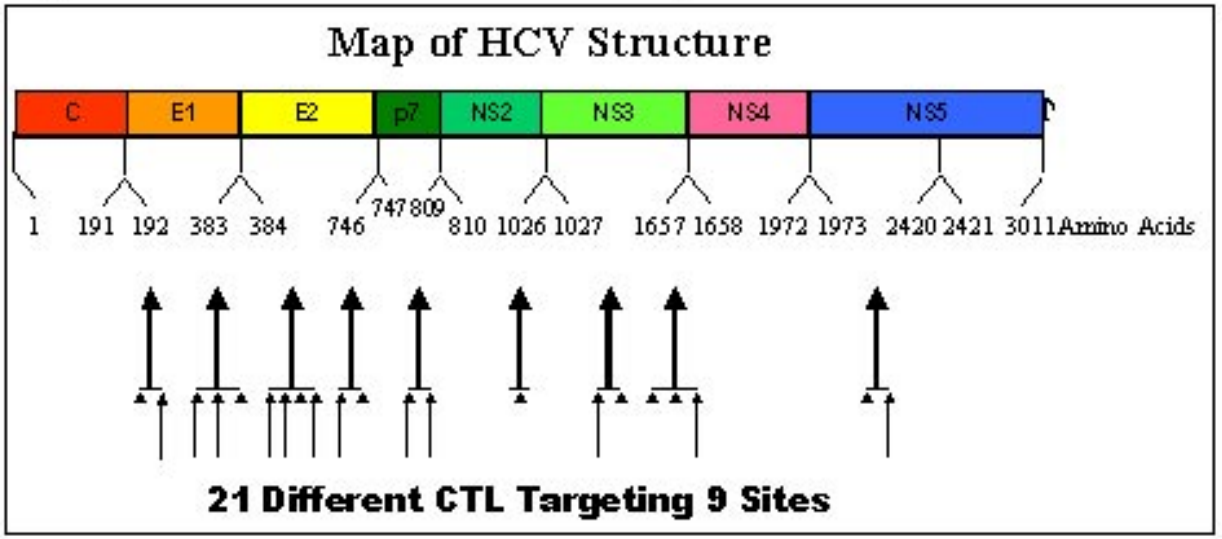
- Lifecycle
- Immune response – Innate
- Immune response – Humoral
- Immune response – T cell
- Correlates of protection
- Prospects for a vaccine

T cell Biology refresher

- CD4 – some cytolytic function, mostly “help” for CD8 cytolytic maturation
- CD8 – mostly cytolytic function, MHCI, CD28. kill through FasL TRAIL TNF perforin Granzyme B
- T reg – suppressive function on CD4 and CD8 T cells TGFβ and IL-10
- Th17 – Subset of CD4 cells, reside at mucosal surfaces, mediate inflammation through IL-17

Robust T cell response to HCV

Figure 2. A Successful Immune Response

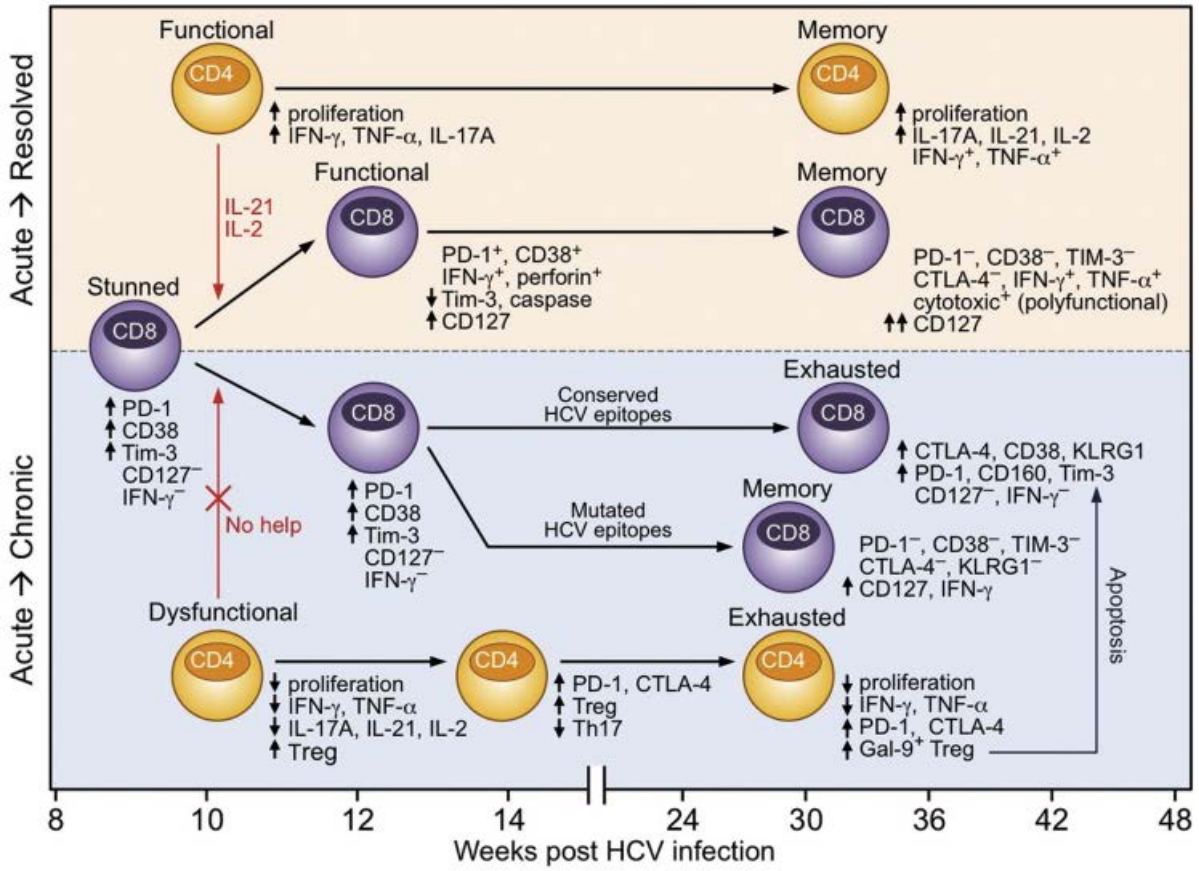


21 CTL clones, depicted by the lowermost thin arrows, target 9 HCV peptide specificities depicted by larger arrows above. Groups of CTL clones target the same peptide epitope presented by a single MHC class I allotype. Some class I molecules present different HCV peptides. Specificity 3 (from left to right) has 4 cognate CTL clones.

T Cell Responses in HCV

- Acute
  - Late appearance of T cell responses (8-12 weeks)
  - T cells have impaired IL2 + IFNγ (Hepatology 41- 1019-28)
  - Express markers of exhaustion: PD-1, Tim-3, CTLA-4 (Gastroenterology 141: 1422-1431)
  - CD8 cells- impaired proliferation, IFNγ, cytotoxicity (J Exp Med 191: 1499-1512)
- Chronic
  - T cell proliferation & production of IFNγ IL2 and TNFα greatest in pts who clear (Lancet 346 1006-7) (JCI 98: 706-14)

- Clearance
  - Associated with rapid expansion of broadly targeted multifunctional.
  - Population of memory T cells persist in chimpanzees who clear HCV, and expand upon re-challenge & subsequent clearance (J Virol 77: 4781-4793)
  - CD8 lose PD-1, upregulate Bcl2 & IL7 receptor (JCI 116 3006-14)
  - Association of HLA B27(Class I) and DRB* 1101 (Class II) alleles and clearance
  - Chimpanzee model of HCV virus clearance abrogated by CD8 depletion (J Exp Med 197: 1645-55)



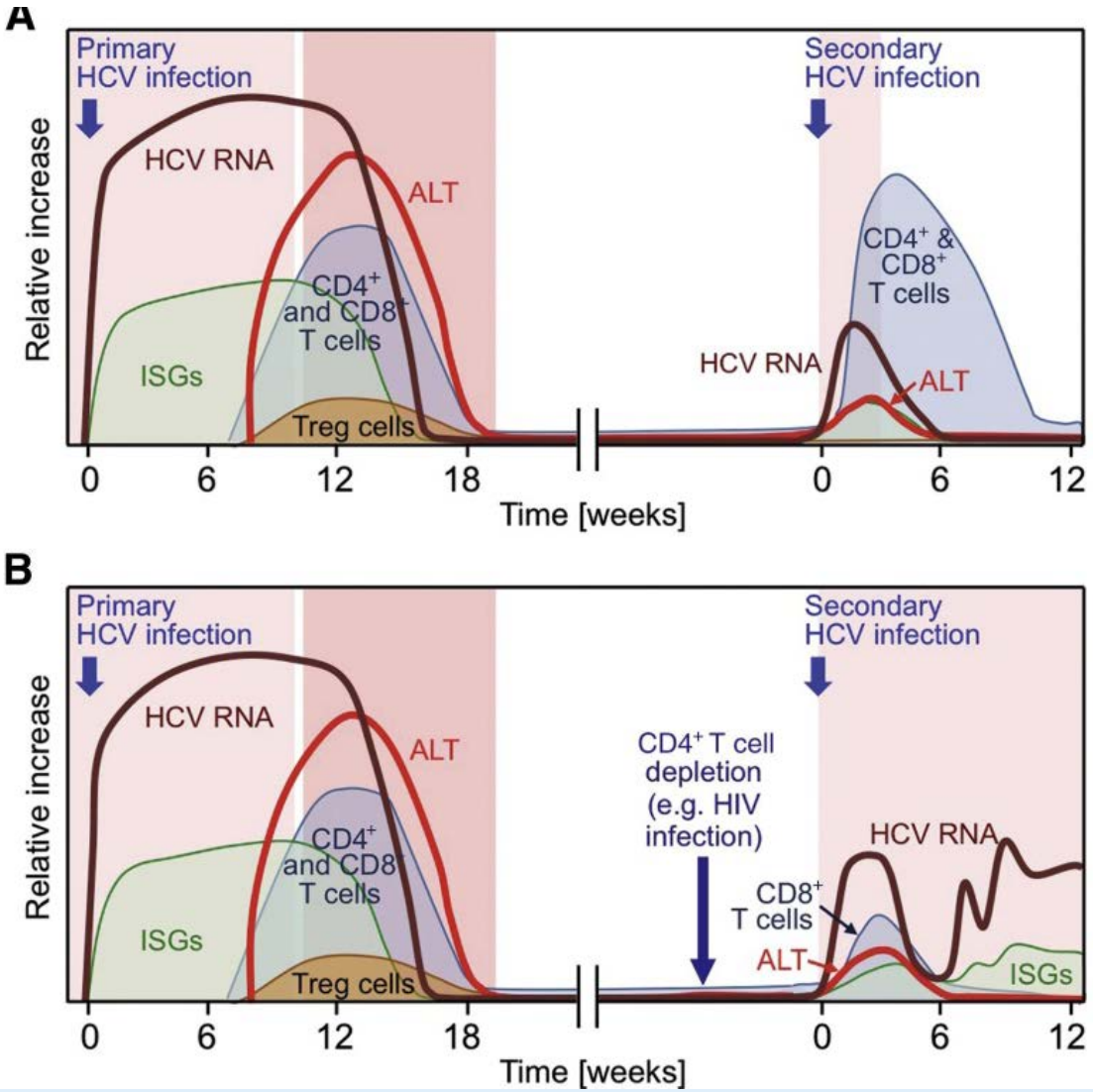
Resolution

- Proliferation
- Polyfunctionality
- PD1-, Tim3 -, CTLA4 –
- IFNγ TNFα

Chronicity

- low Proliferation
- Mono functional
- PD1+, Tim3 +, CTLA4 +
- IFNγ – , TNFα – .

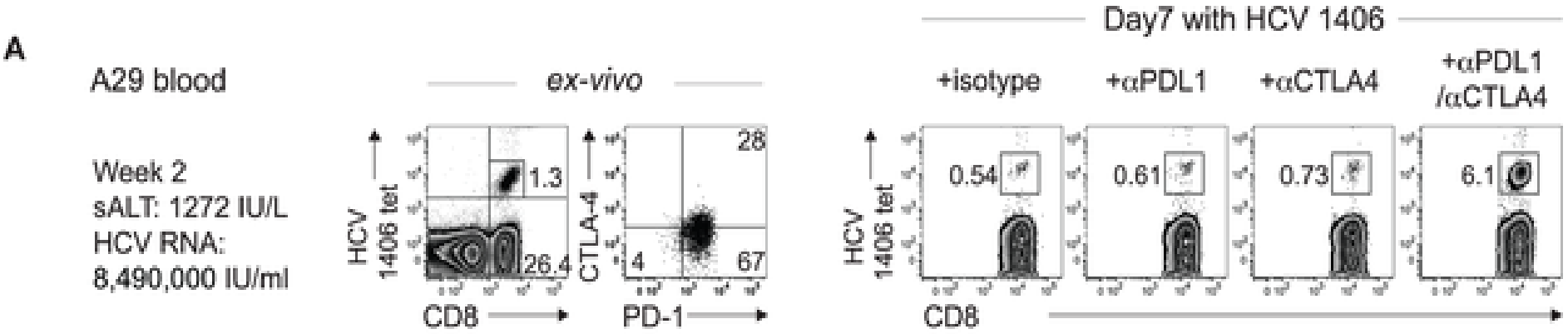
Evidence for Essential role of CD4 in HCV Control



PD-1/CTLA-4 blockade during acute hepatitis C.

PD-1: Programmed cell death protein 1
- Binds PDL-1, PDL-2
- Down regulates T cell activation
- Nivolumab
- Pembrolizumab

CTLA4: CTL associated protein 4
- Binds CD80 or CD86 on APC
- Down regulates T cell activation
- Ipilimumab



PLoS Pathog 5(2): e1000313.

T reg during HCV

- Expanded during acute HCV
- Suppress CTL activity during chronic persistent HCV

Th17 during HCV

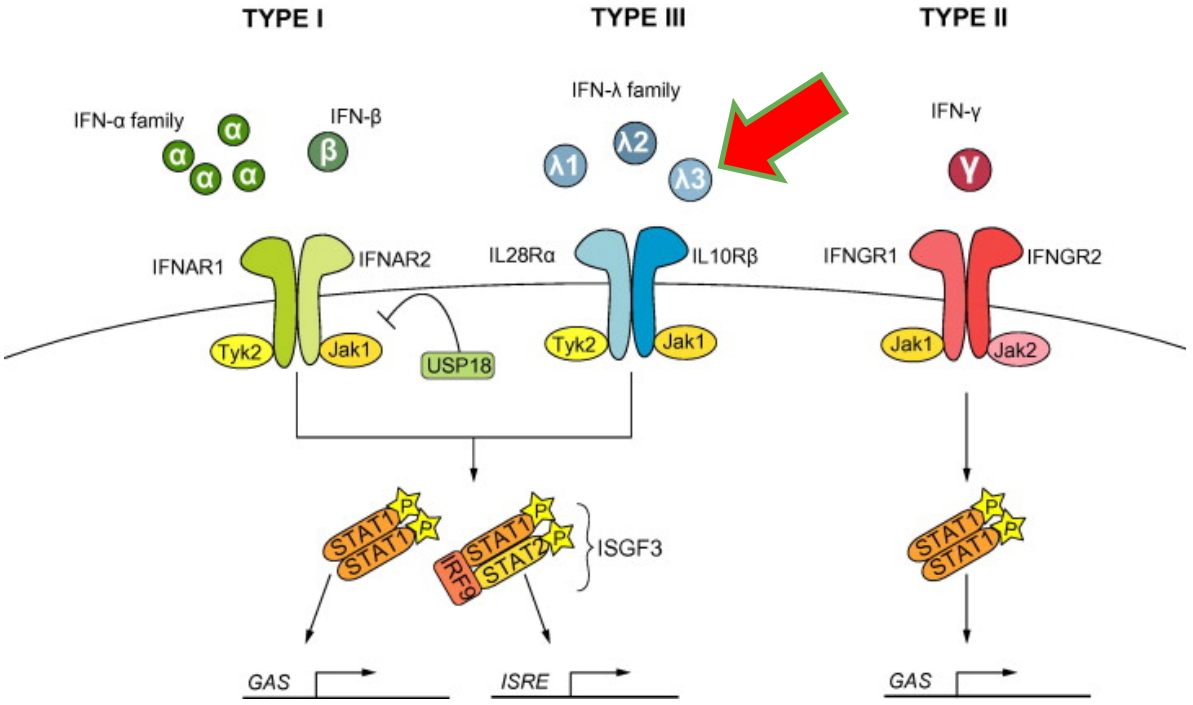
- IL-17 is increased in chronic disease, with severe hepatitis
- Higher levels during acute infection may be associated with clearance.

HCV immunopathogenesis

- Lifecycle
- Immune response – Innate
- Immune response – Humoral
- Immune response – T cell
- Correlates of protection
- Prospects for a vaccine

IL-28B polymorphism and response to HCV

- IL28B = IFN lambda 3, binds to IL28 receptor alpha
- IFNα RBV Rx = SVR 80% in C/C genotype, 40% in C/T genotype, and 35% in T/T patients
- spontaneous clearance 50–60% of C/C, 10–20% in the C/T and T/T group



Journal of Hepatology, Volume 58, Issue 3, 2013, 564 - 574

Genetic associations with HCV control.

Spontaneous clearance

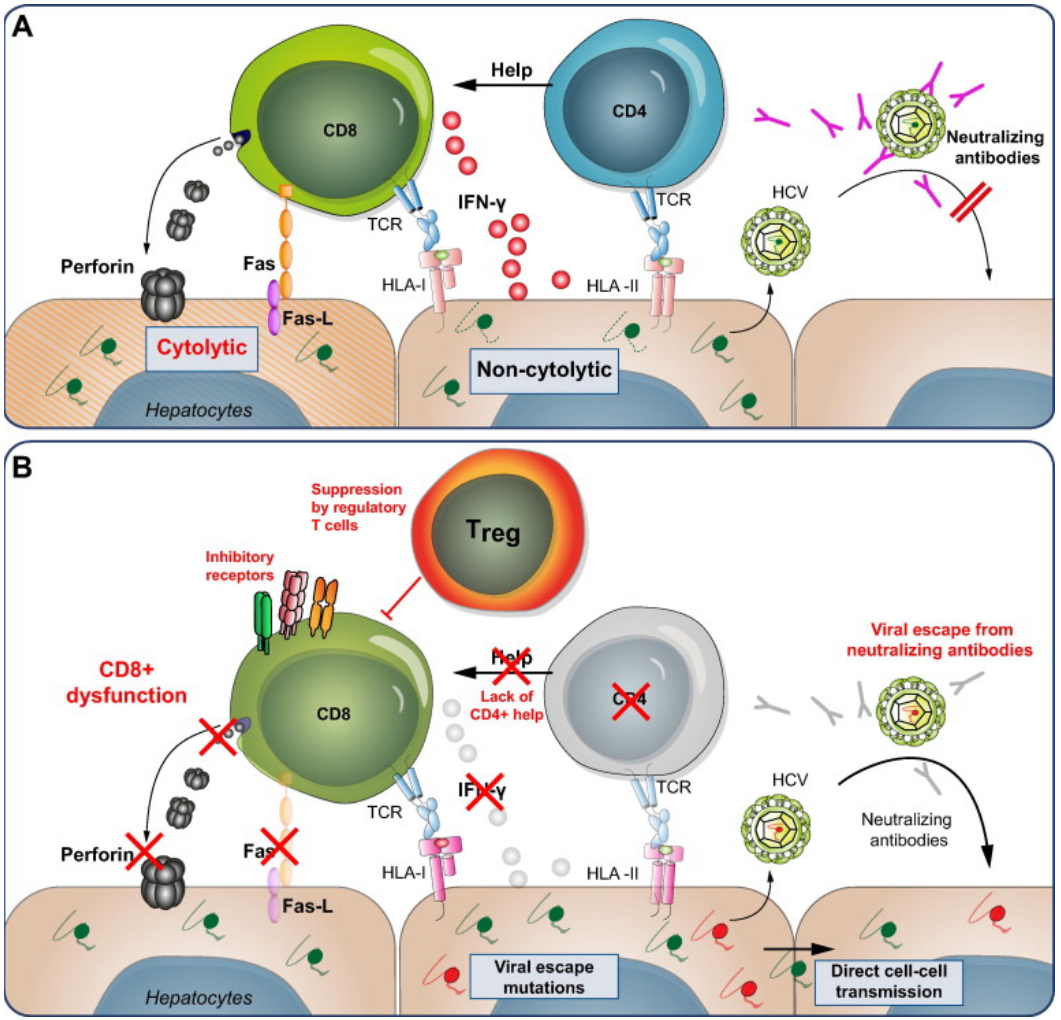
- Clearance of HCV associated with homozygosity of KIR2DL3 (Science 61: 475-81)
- IFNg polymorphism rs2069707
- HLA B57 (Gastroenterology. 2011 Feb;140(2):686-696.e1)
- Class I- HLA B27
- Class II- DRB1* 1101

SVR in response to IFN based therapy

- SVR to IFN based therapy associated with IL28B (CC Genotype)
- Il10R genotype (RR genotype)
- TRAIL-R1 rs4242392

Success

Failure



Journal of Hepatology, Volume 61, Issue 1, Supplement, 2014, S14 - S25

HCV immunopathogenesis

- Lifecycle
- Immune response – Innate
- Immune response – Humoral
- Immune response – T cell
- Correlates of protection
- Prospects for a vaccine

HCV Vaccine 2015

Preventative

- High need
- Challenged by weak animal models
  - (Chimpanzee & Humanized mice)

Therapeutic

- Likely more difficult than prophylactic
  - (Immune escape)
- High need
- Ethical concerns of clinical trial design.
  - Chronic HCV - No Treatment
    - DAA
    - Therapeutic Vaccine

Challenges to an HCV vaccine

- HCV has 7 major genotypes which differs by ~30% sequence diversity
- Within an individual quasispecies differ by ~10% sequence diversity
- HCV polymerase lacks proof reading- high mutation rate (higher than HIV/HBV
- Envelope glycoprotein E2 has hypervariable region- Immunologic pressure results in mutual escape
- Viremia in the presence of neutralizing Ab (Gastroenterology 132:667-678)
- Escape mutations in T cell epitopes also occur(J Exp Med 201 1709-1714)
- Hampered by lack of animal models (Chimp ~ Human)

Approaches to HCV Vaccine

- Genotype specific vaccination
  - (HLA B27 control- conserved immunodominant CD8 epitope)
- Conserved structural intermediates of entry
  - (E.g. VRC01, VRC03)
- VLP
  - (Recapitulate discontinuous epitopes)
- T cell adjuvants
  - (Notably CD4)
- Viral delivery systems
  - (Adeno Vaccinia etc.)

Possible clues for how to design HCV Vaccine

- No single correlate of protective immunity
- Sustained T cell responses with broad repertoire and poly functional (IFNg IL2 TNF-a) (J Clin Invest 119 1745-54)
- T cell responses against NS3 NS5 (J Clin Invest 98: 706-714)
- Envelope glycoproteins weakly immunogenic 2º glycosylation (J Virol 81:8101-8111)
- HCV circulates in host lipoproteins- possible mechanism of Ab escape (J Virol 76:6919-28)

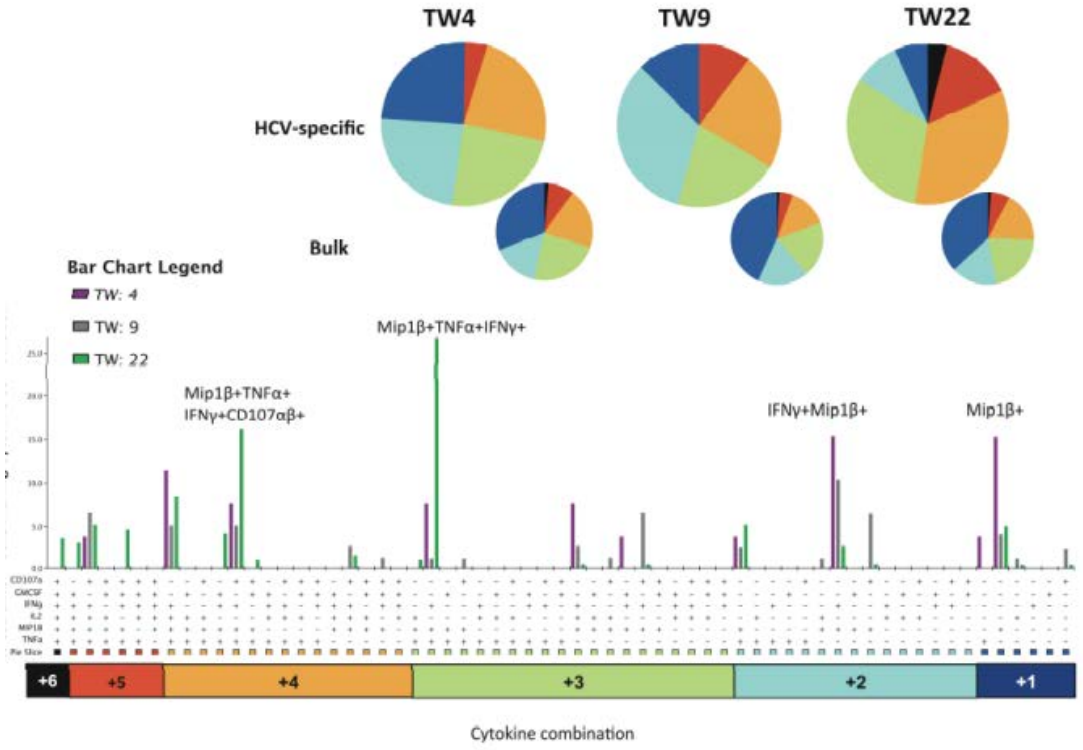
HEPATITIS C VIRUS

A human vaccine strategy based on chimpanzee adenoviral and MVA vectors that primes, boosts, and sustains functional HCV-specific T cell memory

Science Translational Medicine 2014

Prime boost:

- Adeno associated>> Vaccinia
- NS3,HS4,NS5A,NS5B
- Humans
- Polyfunctional responses



Discussion / Questions

HCV Treatment in 2015 and beyond

Hugo E. Vargas, MD

Professor of Medicine

Mayo College of Medicine

Director of Hepatology

Vice Chair, Division of Gastroenterology and Hepatology

May 8 2015

ABIM Disclosure
Hugo E. Vargas, M.D.

- I am a current member of the ABIM Transplant Hepatology Exam Committee.
- To protect the integrity of certification, ABIM enforces strict confidentiality and ownership of exam content.
- As a member of the Board of Directors and of an ABIM exam committee, I have pledged to keep exam information confidential.
- ***No exam questions will be disclosed in my presentation.***

Disclosure:
Sources of Research Support

- **AbbVie**
- **BMS**
- **Eisai**
- **Gilead**
- **Merck**

- **I also belong to the TARGET consortium**

I WILL DISCUSS AGENTS CURRENTLY UNDER INVESTIGATION

MAYO CLINIC

Educational Goals

- Delineate the impact of HCV on the population we serve
- Discuss the new agents introduced in to market and how they have changed the standard of care
- Review the changing treatment strategy in the context of new agents

MAYO CLINIC

Educational Goals

- Caveats:
  - Cannot cover **all** new therapies
  - Recommendations are still germinal,
  - Durability and more applicability data outside clinical trials is beginning to emerge

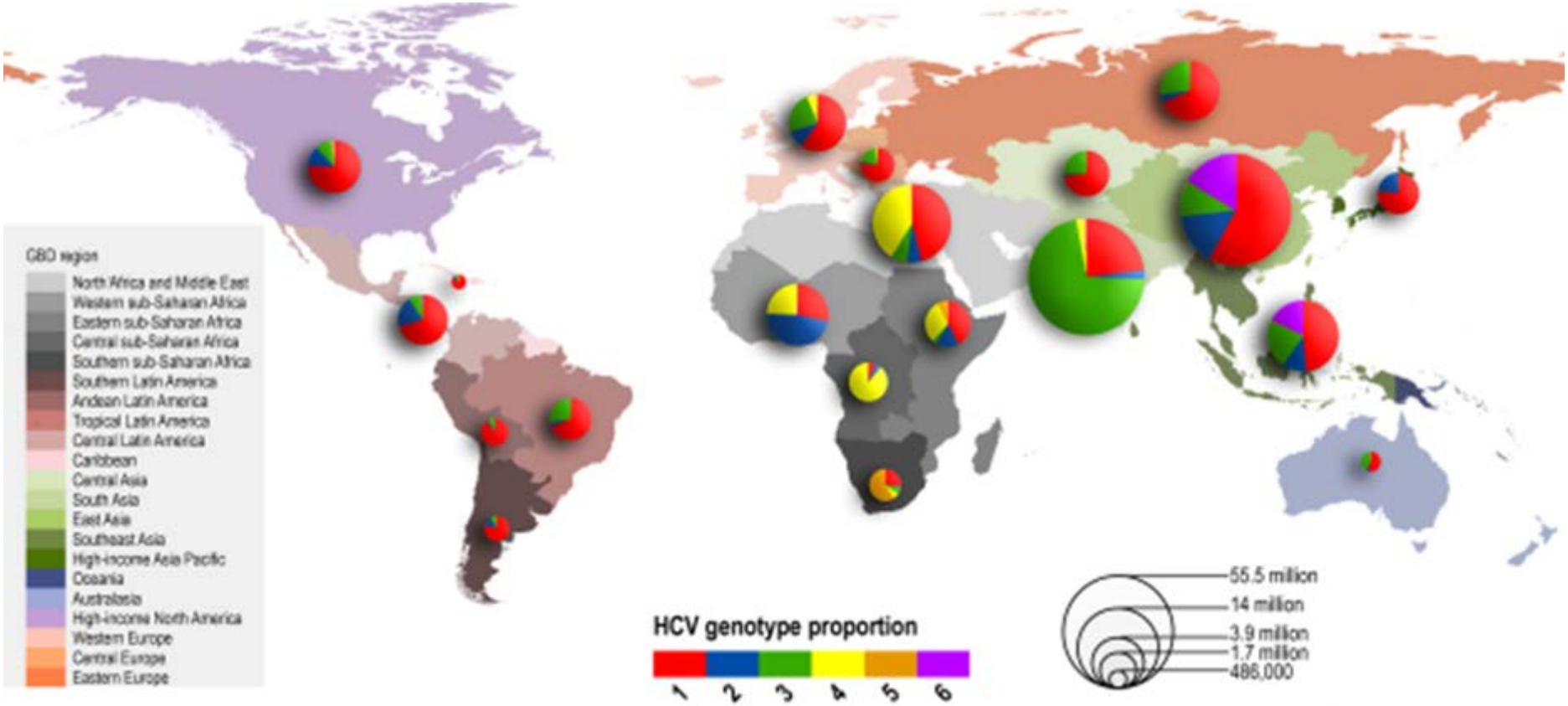
The burden of HCV

MAYO CLINIC

Worldwide Burden of Disease due to HCV is Increasing

- WHO estimates 130-170 million people, (3% of world's population) HCV infected and at risk of cirrhosis/HCC
- There are 3 to 4 million new infections/yr
- HCV is responsible for 50–76% of all HCC and 50-60% of all liver transplants in the developed world
- HCV-associated cirrhosis leads to liver failure and death in about 20%-25% of cirrhotic patients

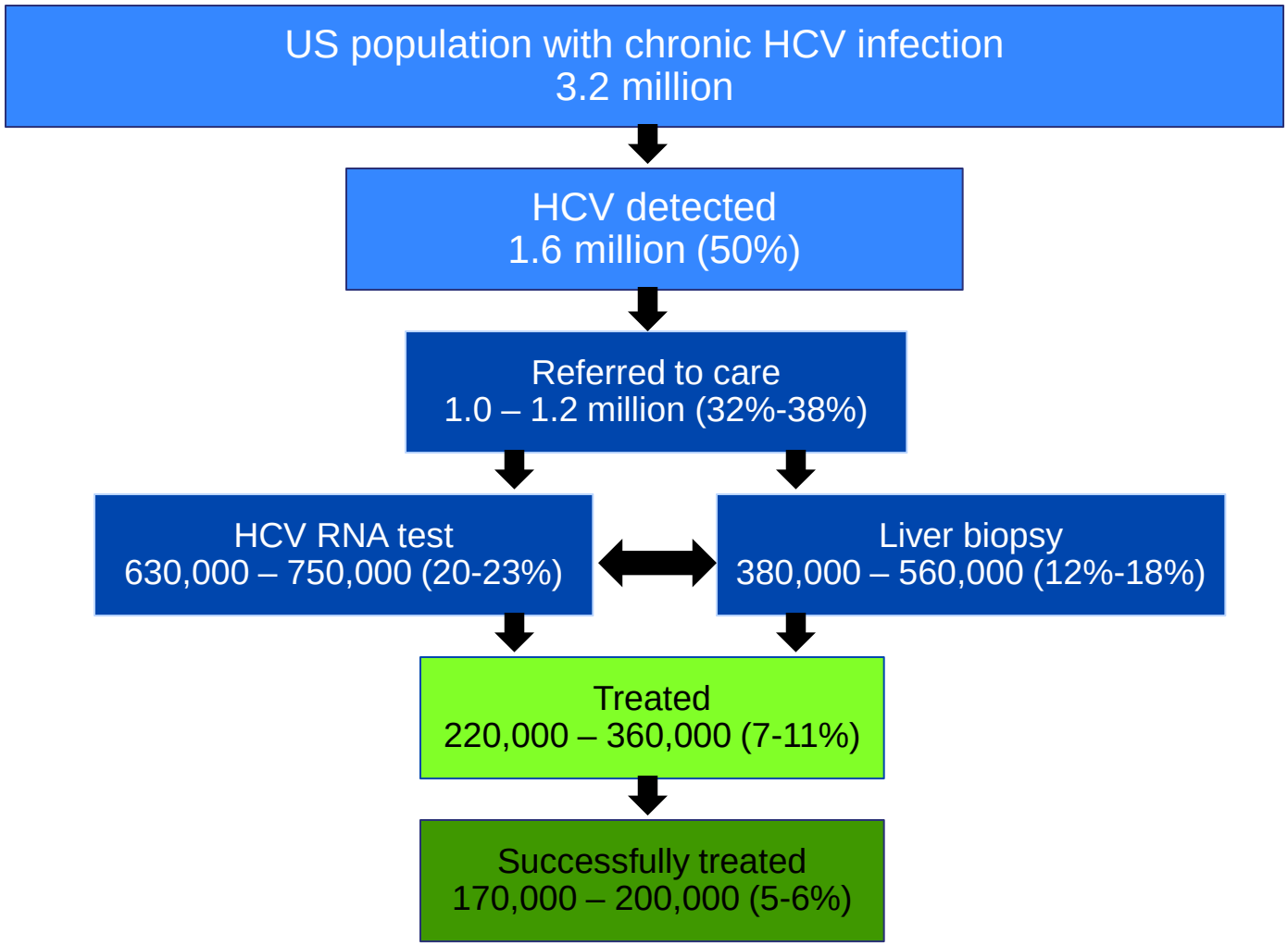
HCV Global Genotype distribution



Messina, Hepatology 2014

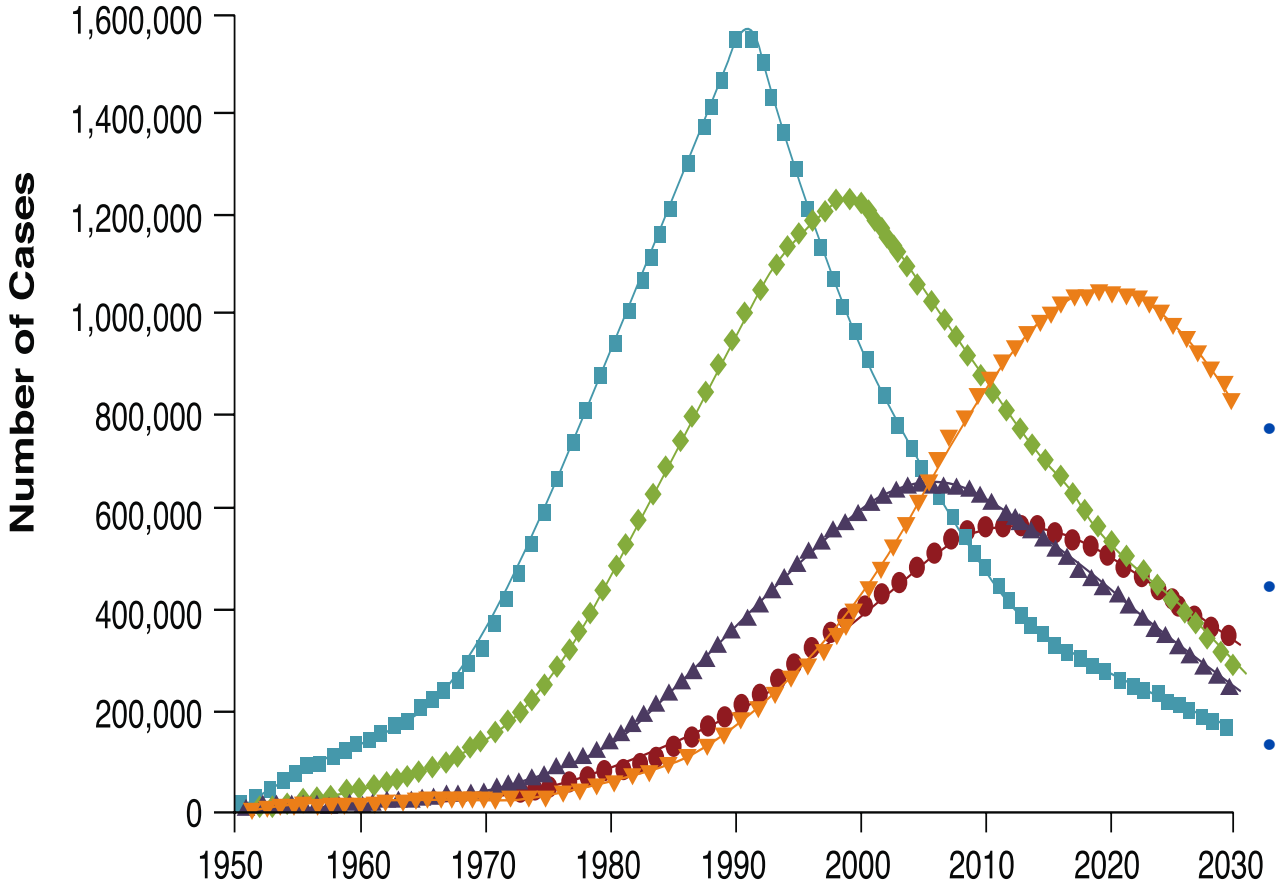
MAYO CLINIC

Current Status of HCV in the US: Screening and Linkage to Care Rates Remain Low



Holmberg, NEJM 2013

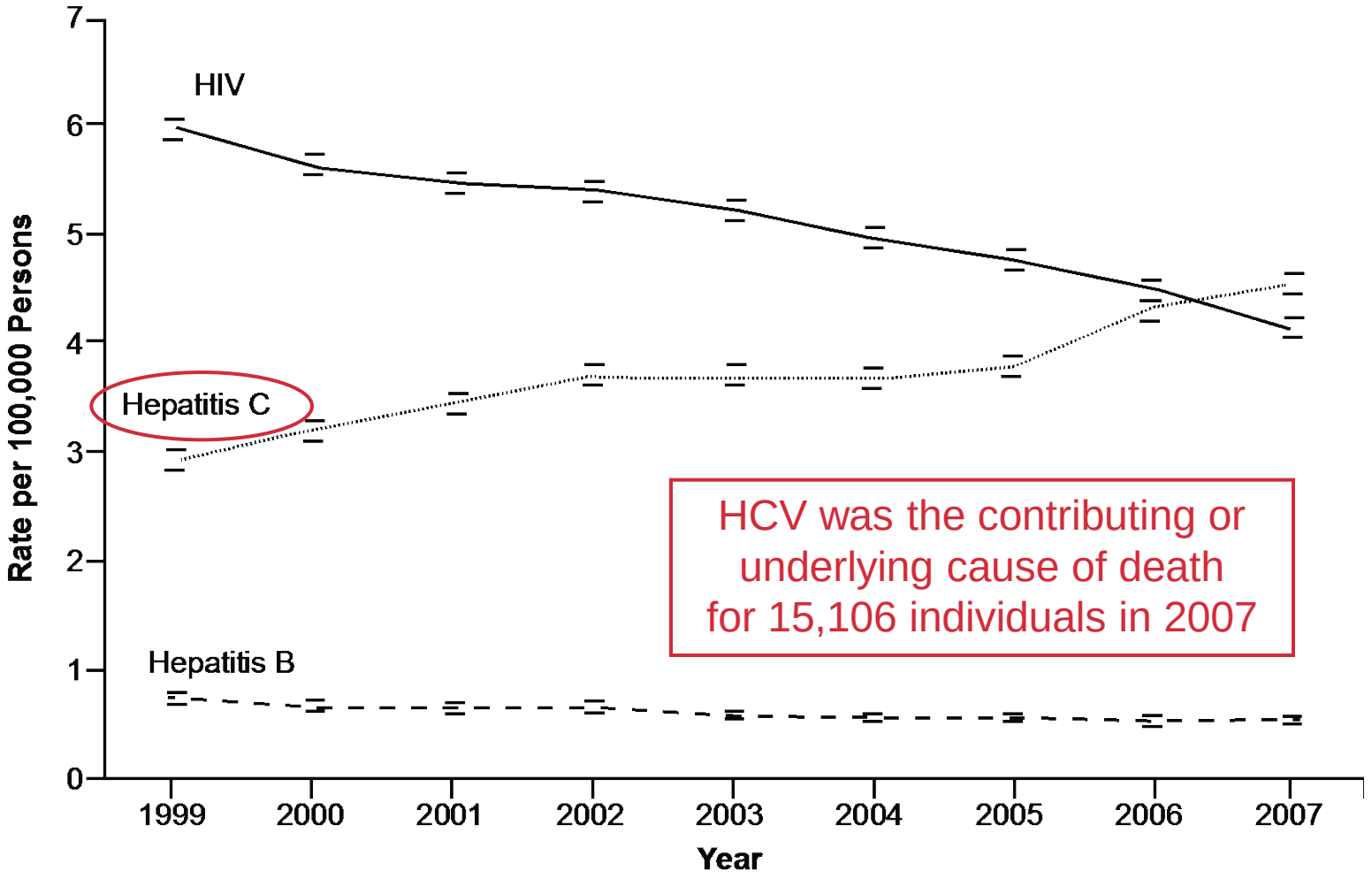
Projected Burden of Advanced Fibrosis Over the Next Decade



- 1990 → 77.6% F0/1; cirrhosis =5%
- 2010 → 41.8% F0/1; cirrhosis =25%
- 2020 → cirrhosis = **37.2%**

Davis, Gastroenterology 2010

Deaths from HCV in the United States Continue to Rise; Deaths from HBV and HIV are Decreasing

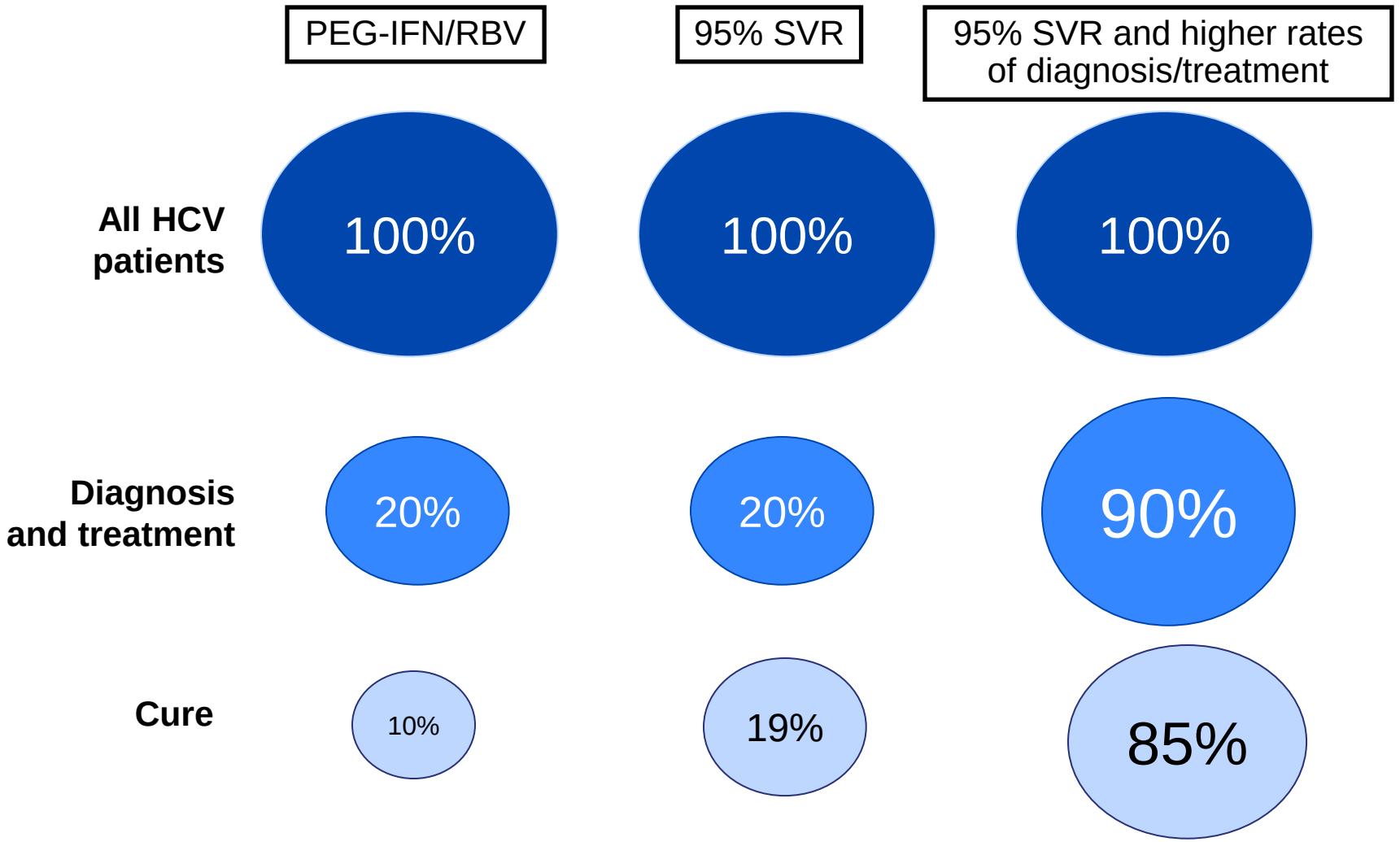


Ly, Ann Intern Med 2012

Persons for whom routine HCV testing is recommended

- Persons who ever injected illegal drugs, including those who injected once or a few times many years ago
- Persons who received a blood transfusion or organ transplant before July 1992
- Persons who received clotting factor concentrates before 1987
- Persons who were ever on long-term dialysis
- Children born to HCV-positive women
- Health care, emergency medical, and public safety workers after needlesticks, sharps, or mucosal exposures to HCV-positive blood
- Persons with evidence of chronic liver disease
- Persons born between 1945-1965

Highly Efficacious Treatments Are Not Enough

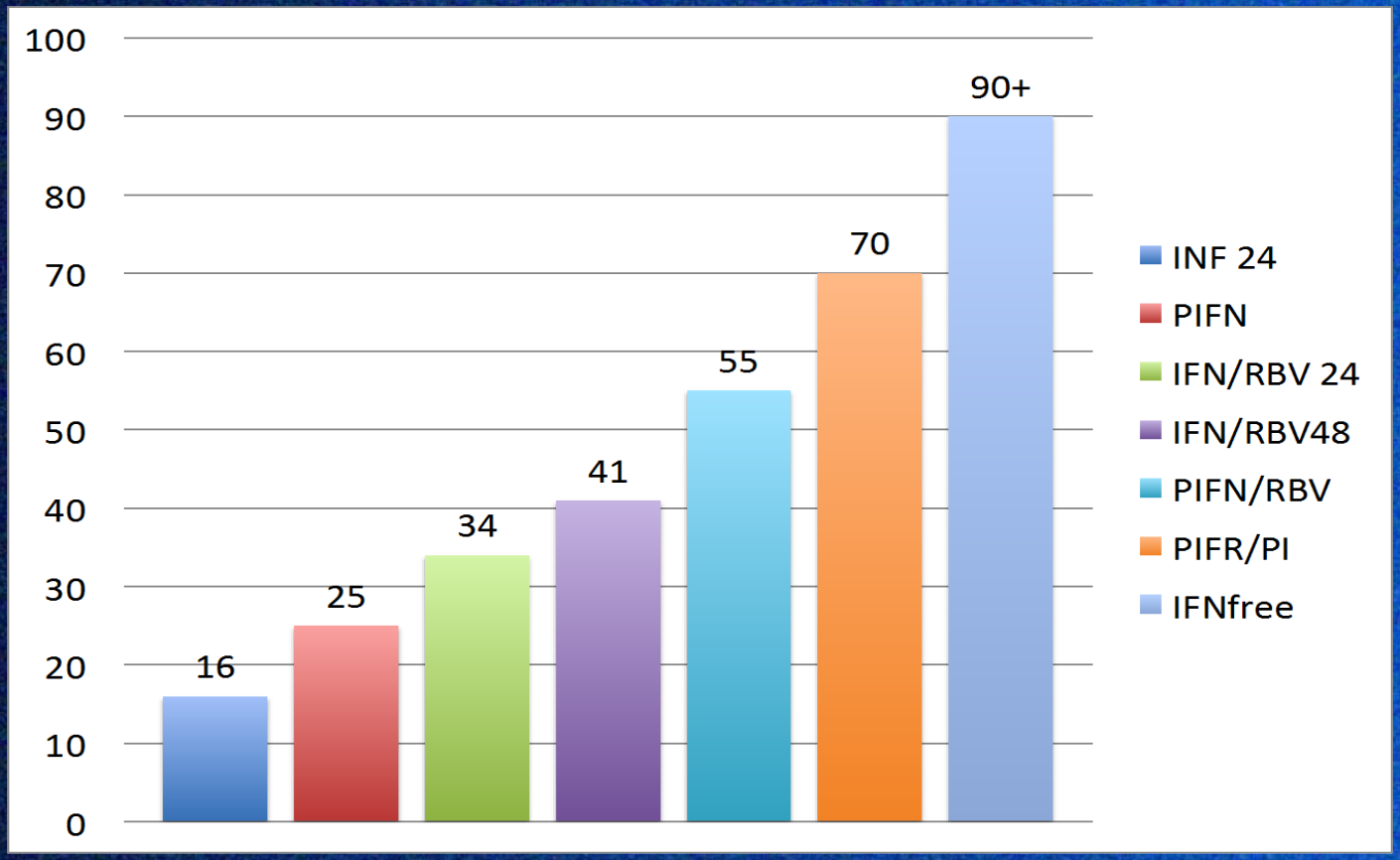


How do we approach treatment?

MAYO CLINIC

The Evolution of HCV treatment

1991 → 2015



PEG-IFN/RBV: Factors Associated with Successful Therapy of HCV

Ancient History

- Genotypes 2 or 3*
- Lower baseline viral levels*
- Less fibrosis on liver biopsy*
- Lower body weight*
- Caucasian race (IL28b polymorphisms)
- Non-insulin resistant

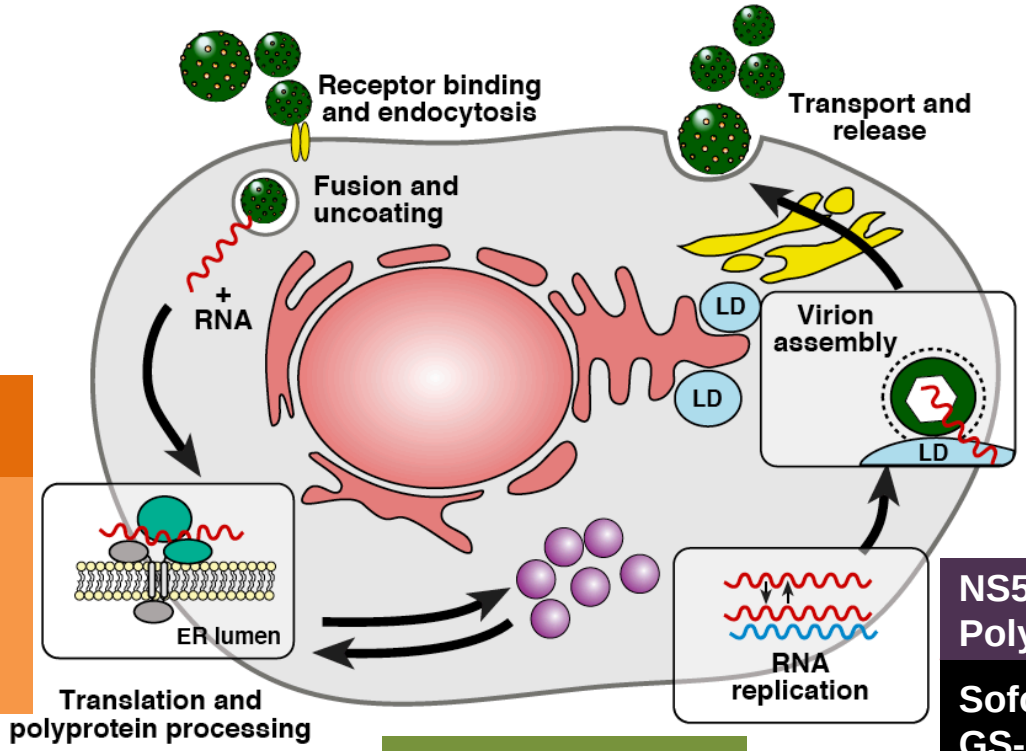
*Adapted from Nation Institutes of Health Consensus Development Conference Statement: Management of Hepatitis C:2002. Hepatology 2002;36:S3-S20.

Direct Antiviral Agents:
The world in 2011

Direct-Acting Antivirals for Hepatitis C

NS3/4 Protease Inhibitors

- Simeprevir
- Asunaprevir
- Paritaprevir/r
- Vedroprevir
- Grazoprevir



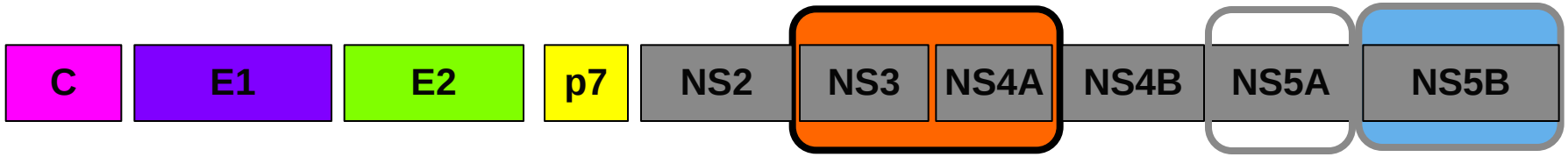
NS5A Inhibitors

- Ledipasvir
- Ombitasvir
- Daclatasvir
- Elbavir

NS5B Polymerase Inhibitors

- Sofosbuvir
- GS-9669
- Beclabuvir
- Dasabuvir

Direct-Acting Antiviral Agents: Key Characteristics



NS3/4A Protease Inhibitors (PI) **-previrs**

High potency

Limited genotypic coverage

Low barrier to resistance

NS5B Nucleos(t)ide Inhibitors (NI) **-buvirs**

Intermediate potency

Pangenotypic coverage

High barrier to resistance

NS5A Inhibitors **-asvirs**

High potency

Multigenotypic coverage

Low barrier to resistance

NS5B Nonnucleoside Inhibitors (NNI)

Intermediate potency

Limited genotypic coverage

Low barrier to resistance

Limitations of the first protease inhibitors

- Telaprevir and boceprevir only approved for Genotype 1
- Interferon backbone required
- Three times per day (TID) dosing for telaprevir/boceprevir
- Response guided therapy (both) and lead-in (boceprevir) complicated
- 24-48 week treatment
- Limited efficacy in difficult to cure patients (e.g., patients with cirrhosis, prior null responders, African-Americans)
- Hematologic (both) and rash/dermatological (telaprevir) adverse events
- Drug-drug interactions

DRUG CLASS SUMMARY
Short Term

Class	Drug
NS3/4A Protease inhibitor	Simeprevir
	Paritaprevir (ABT 450)+RTV
	Asunaprevir (BMS 650032)
	Grazoprevir (MK-5172)
NS5A Inhibitor	Daclatasvir
	Ledipasvir
	Elbasvir (MK-8742)
	Ombitasvir
NS5B non-nucleoside polymerase inhibitor	Dasabuvir
	Beclabuvir (BMS 791325)
NS5B nucleoside polymerase inhibitor	Sofosbuvir

DRUG CLASS SUMMARY
Long Term

Class	Drug
NS3/4A Protease inhibitor	ABT 493
	Vedroprevir (GS-9451)
	GS 9857
NS5A Inhibitor	ABT 530
	GS 5816
	MK 8408
NS5B non-nucleoside polymerase inhibitor	GS-9669
NS5B nucleoside polymerase inhibitor	MK-3682 (formerly IDX21437)

MAYO CLINIC

The new regimens (approved in US since Nov 2013)

Sofosbuvir

FDA approved Dec 6, 2013

Sofosbuvir (GS-7977)

- NS5B nucleoside polymerase inhibitor
- Favorable administration profile
  - Once daily, no food effect
  - No known drug-drug interactions
- FDA approved for G 1,2,3,4 infected pts.
  - G1,4 SOF/P/R 12 weeks
  - G2 SOF/R 12 weeks
  - G3 SOF/R 24 weeks
  - HIV/HCV co-infected (as above for duration, genotype)

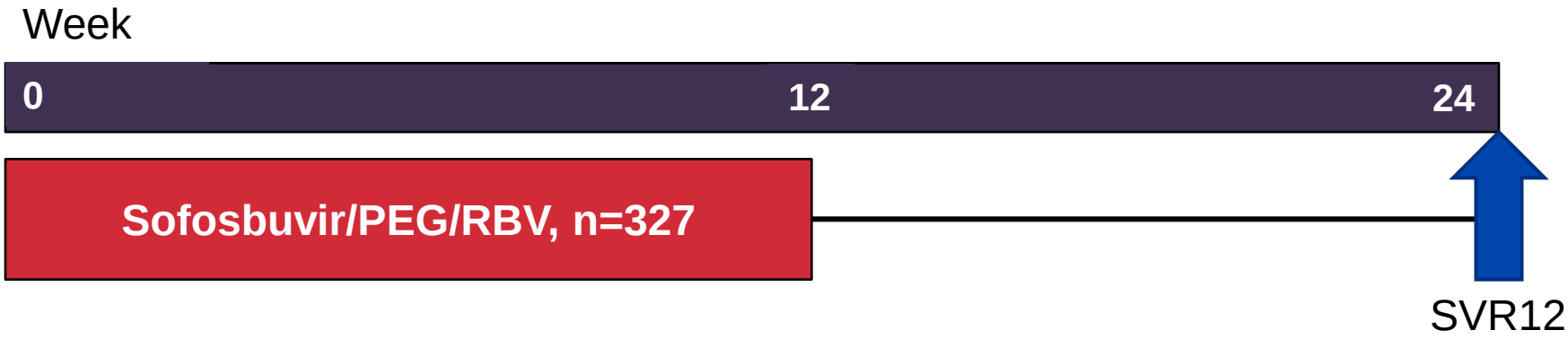
Completed Phase 3 Trials

- NEUTRINO
  - GT* 1, 4, 5, 6; treatment naive
  - No comparator
- FISSION
  - GT 2 and 3; treatment naive
  - Compared to 24 weeks of peginterferon + ribavirin
- POSITRON
  - GT 2 and 3; patients ineligible for or intolerant of interferon therapy
  - Compared to placebo
- FUSION
  - GT 2 and 3; patients unresponsive to prior treatment
  - Compared to 16 weeks of sofosbuvir + ribavirin

NEUTRINO

- Patients
  - GT 1, 4, 5, 6 treatment naive
  - 17% compensated cirrhosis
  - 17% black
  - 29% IL28B genotype CC
- Regimen for all patients
  - Sofosbuvir 400 mg once daily
  - Ribavirin 1000/1200 mg daily in divided doses
  - Peginterferon alfa-2a 180 mcg weekly

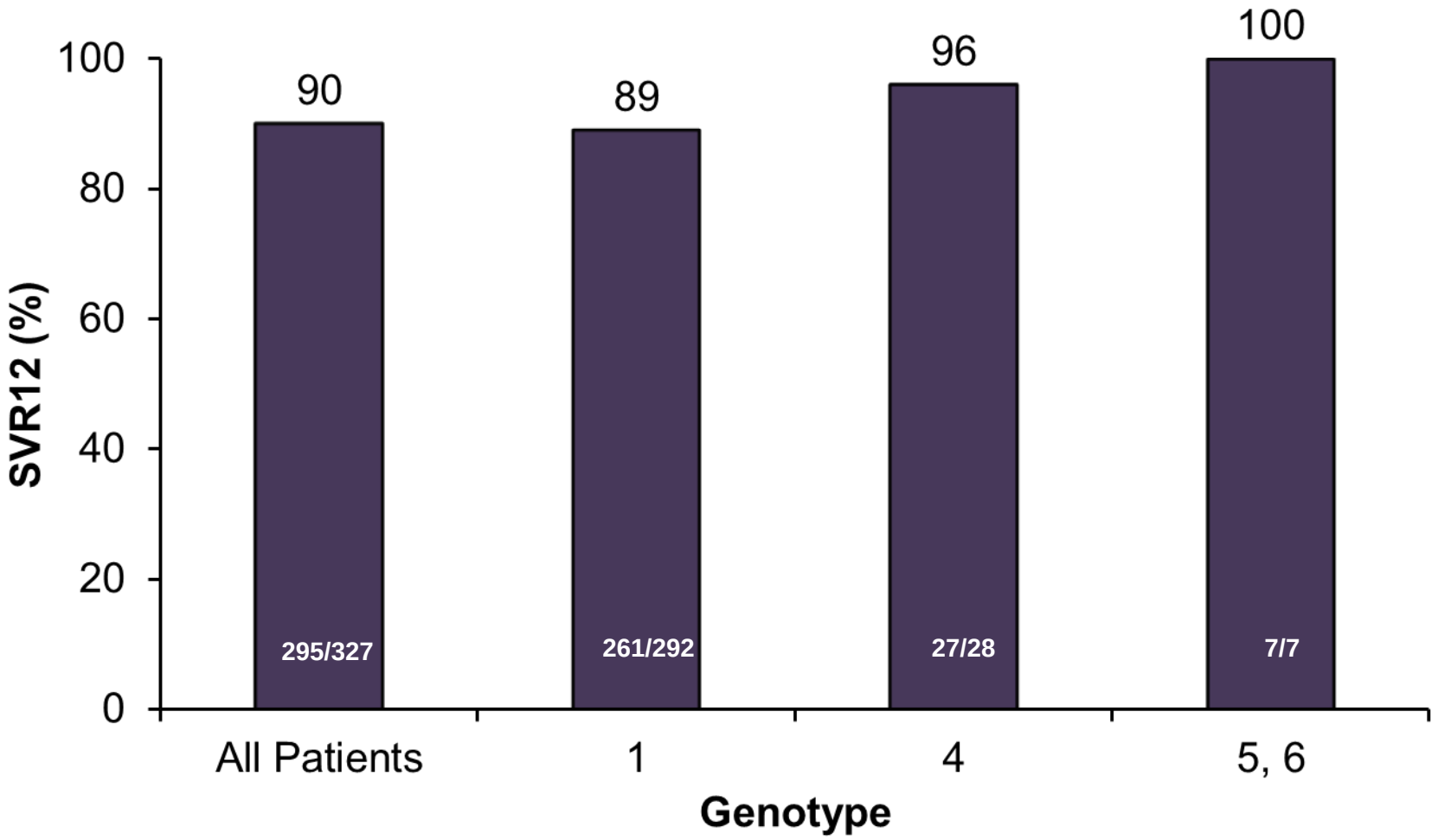
NEUTRINO: Study Design



- Open label
  - SOF+PEG+RBV for 12 weeks (no response-guided therapy)
- Expanded inclusion criteria
  - No upper limit to age or BMI
  - Opiate replacement therapy permitted
  - Platelets ≥90,000/mm^3, neutrophils ≥1,500/mm^3 or 1,000/mm^3 (blacks)

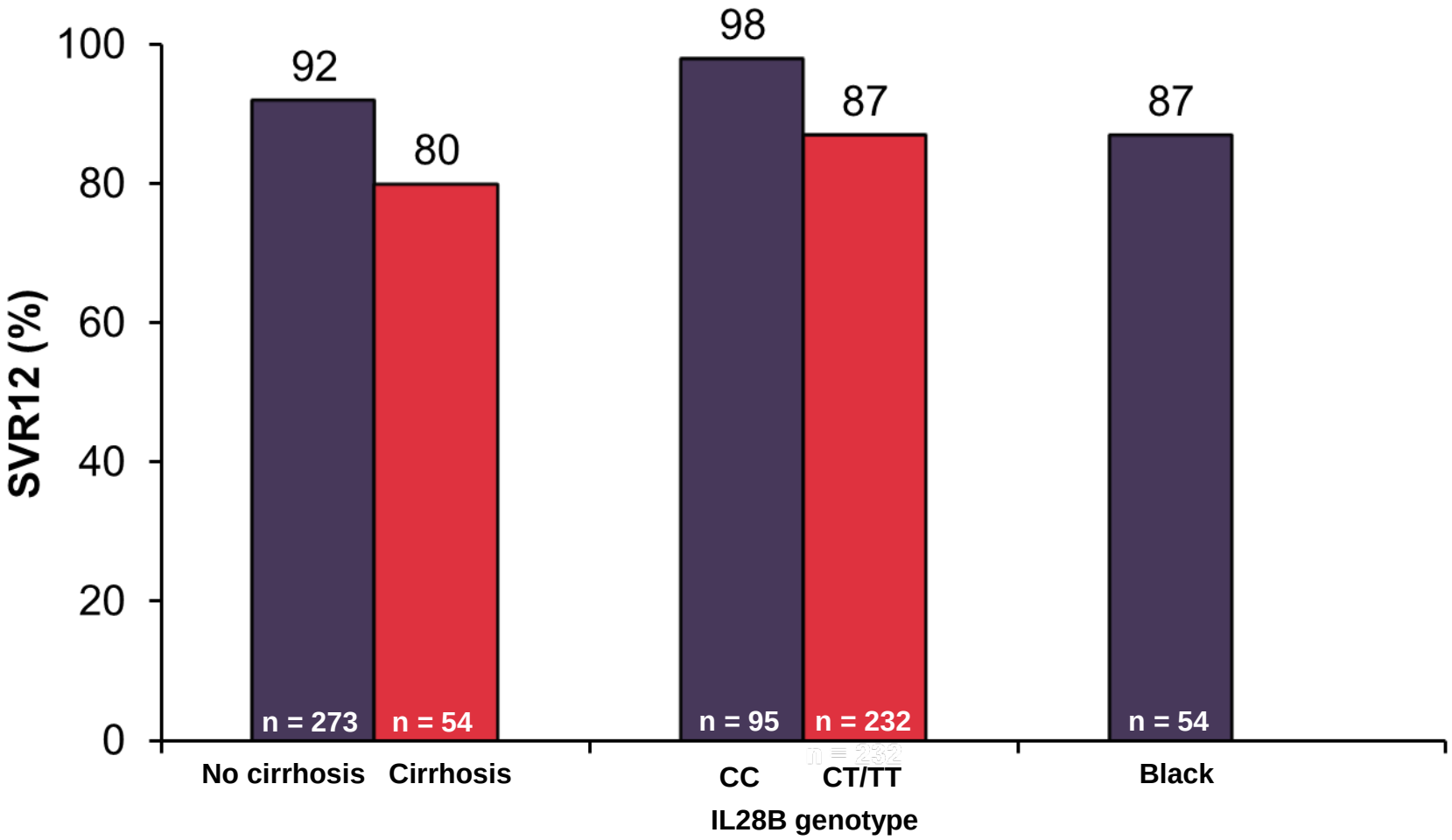
Lawitz, NEJM 2013

NEUTRINO: SVR by Genotype



Lawitz, NEJM 2013

NEUTRINO: SVR by Subgroup



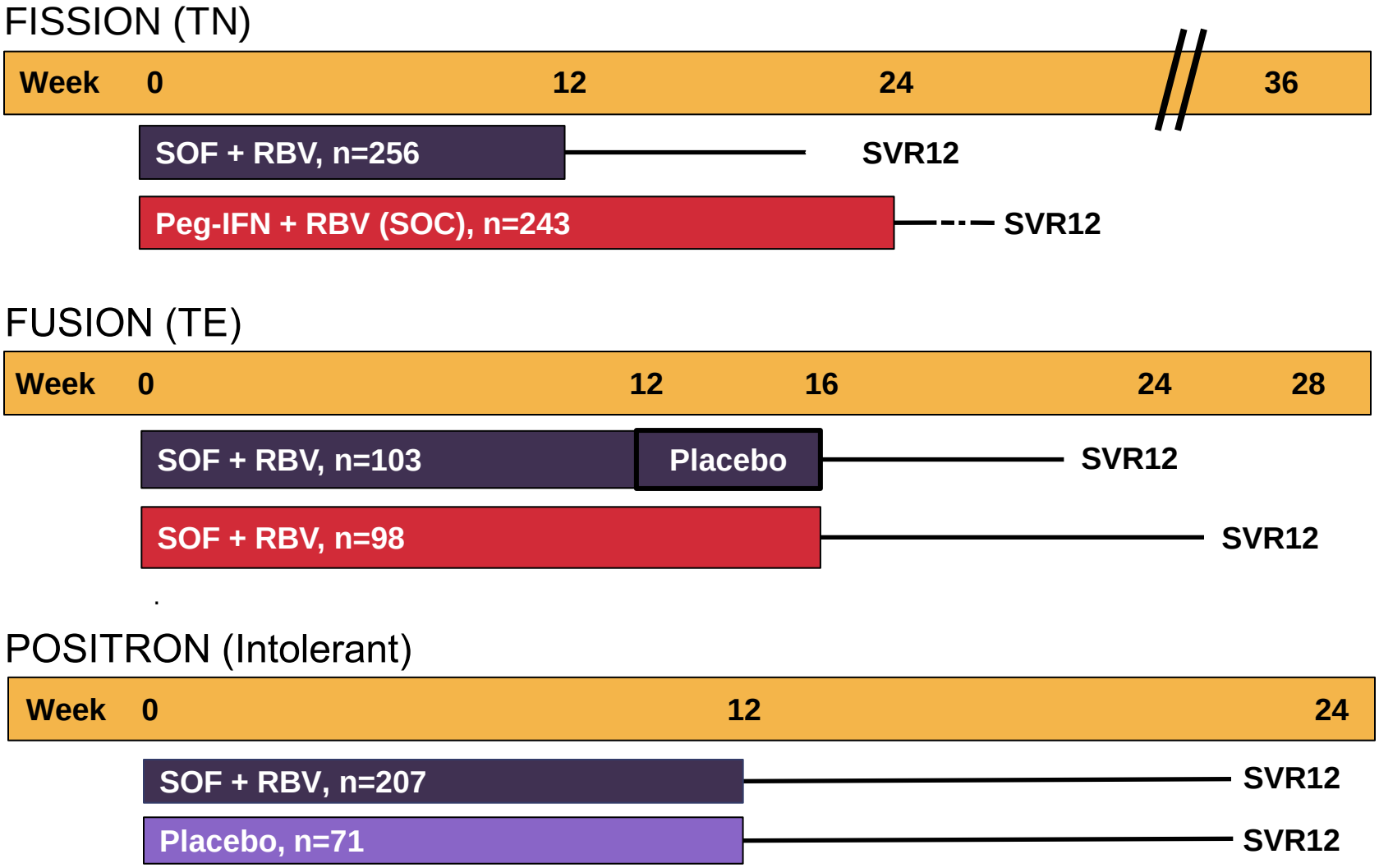
Lawitz, NEJM 2013

Conclusions which led to FDA approval

- 12 weeks of SOF+PEG+RBV achieved 90% SVR in treatment naive patients with GT 1, 4, 5, or 6
- 99% of patients had HCV RNA < LLOQ by treatment week 4 and all virologic failures were due to relapse
- This regimen was well tolerated

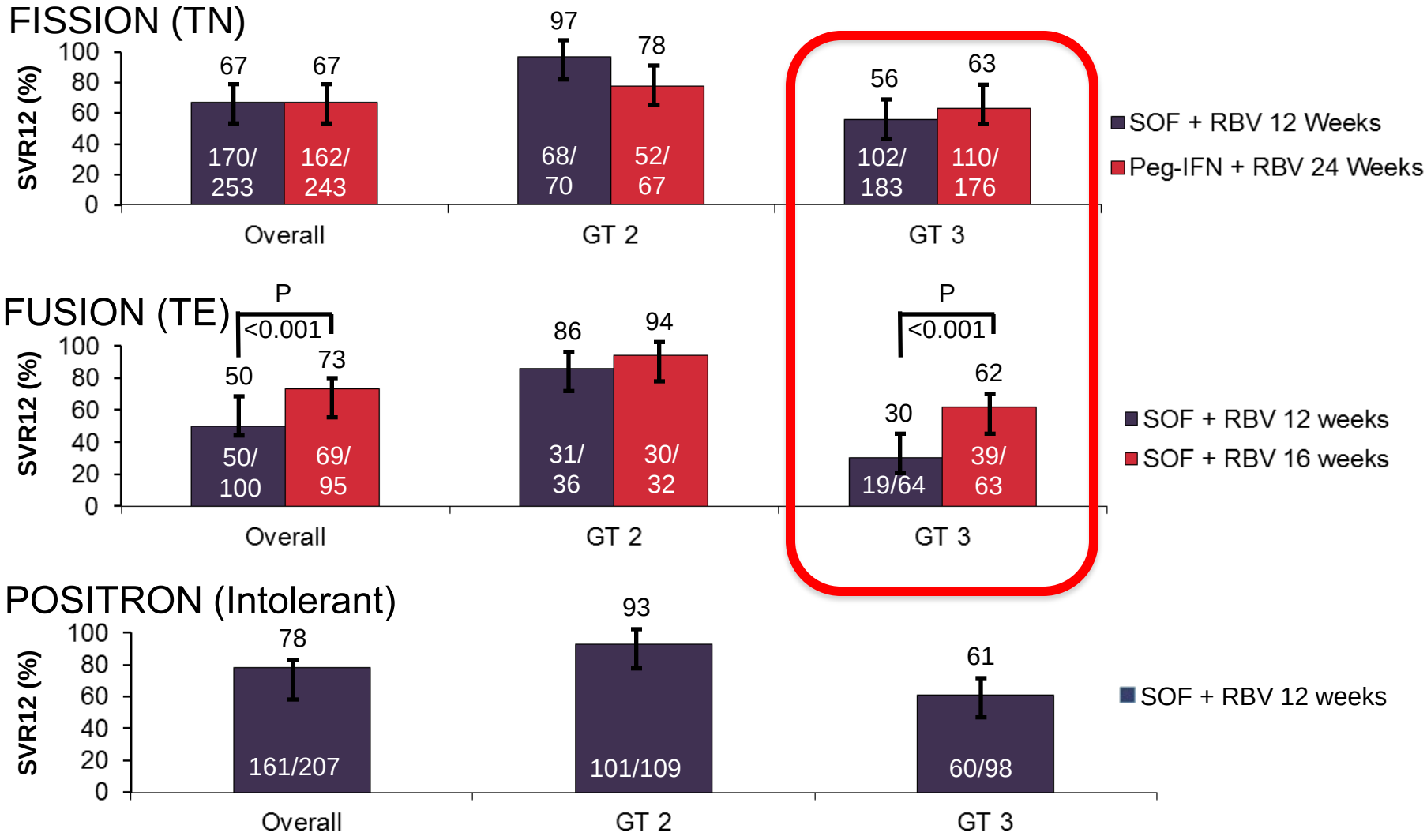
<LLOQ=Below Lower Limit of Quantitation

GT2 and GT 3: Study Designs



Jacobson, NEJM 2013; Lawitz, NEJM 2013

GT2 and GT 3: SVR by Genotype



Jacobson *NEJM* 2013, Lawitz *NEJM* 2013

Genotype 3

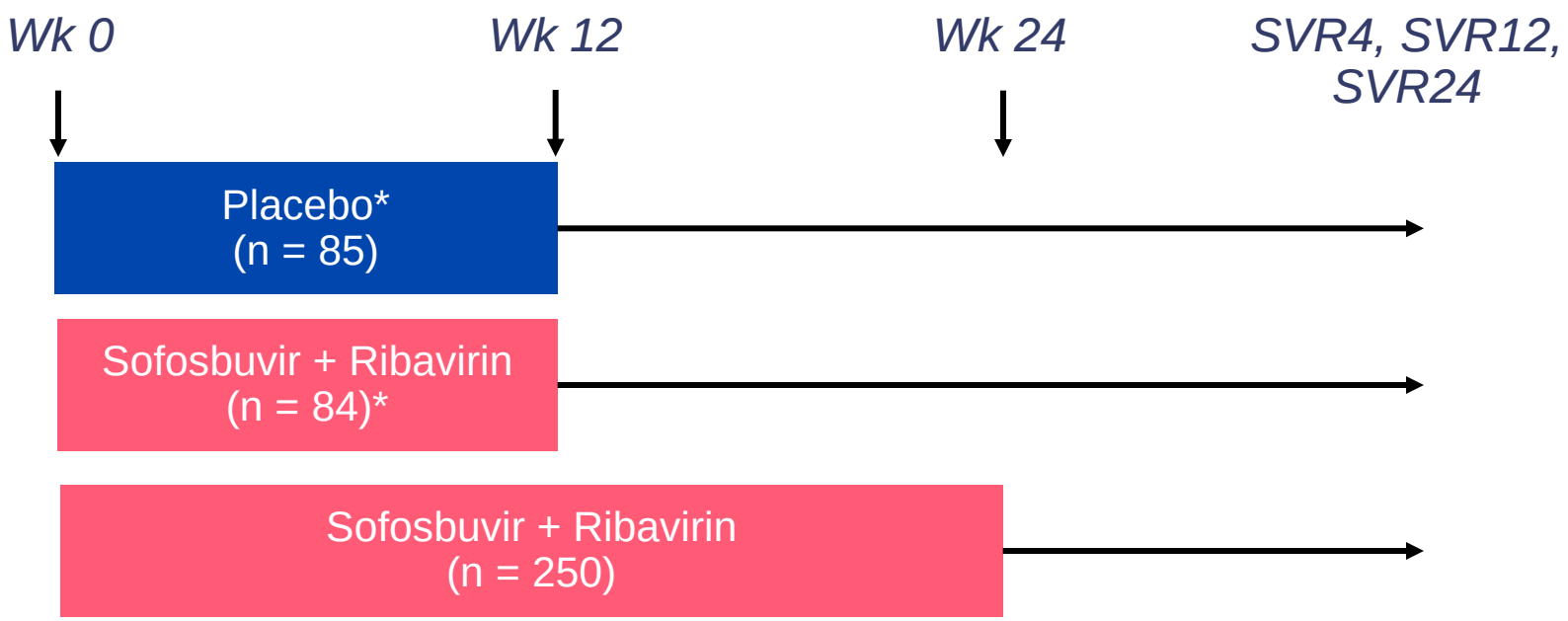
- G2≠G3 with respect to treatment strategy
- G3 may be hardest to treat of all genotypes

MAYO CLINIC

VALENCE

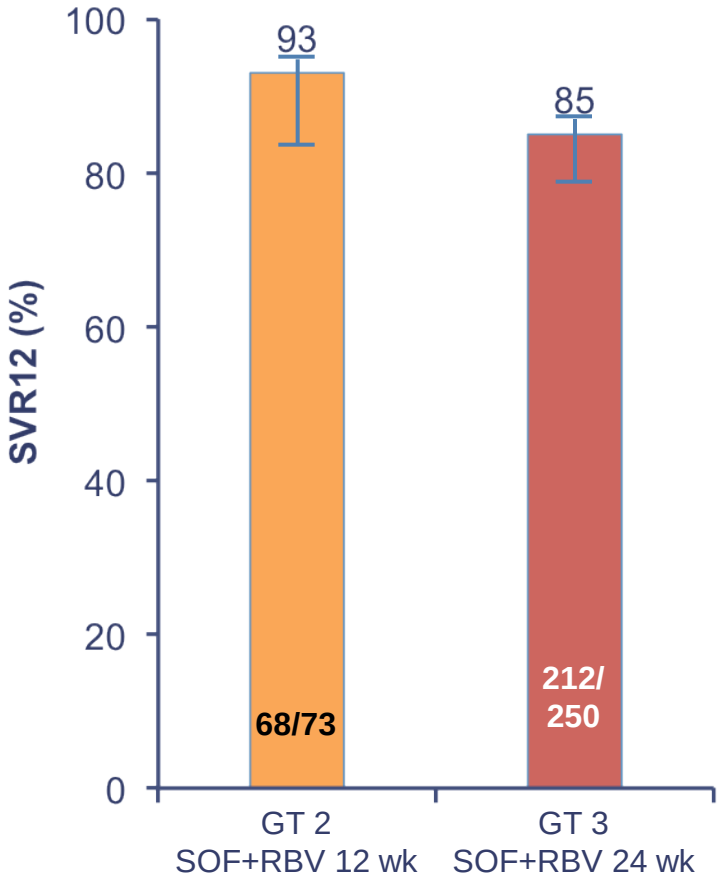
A strategy for G3

VALENCE: Study Design

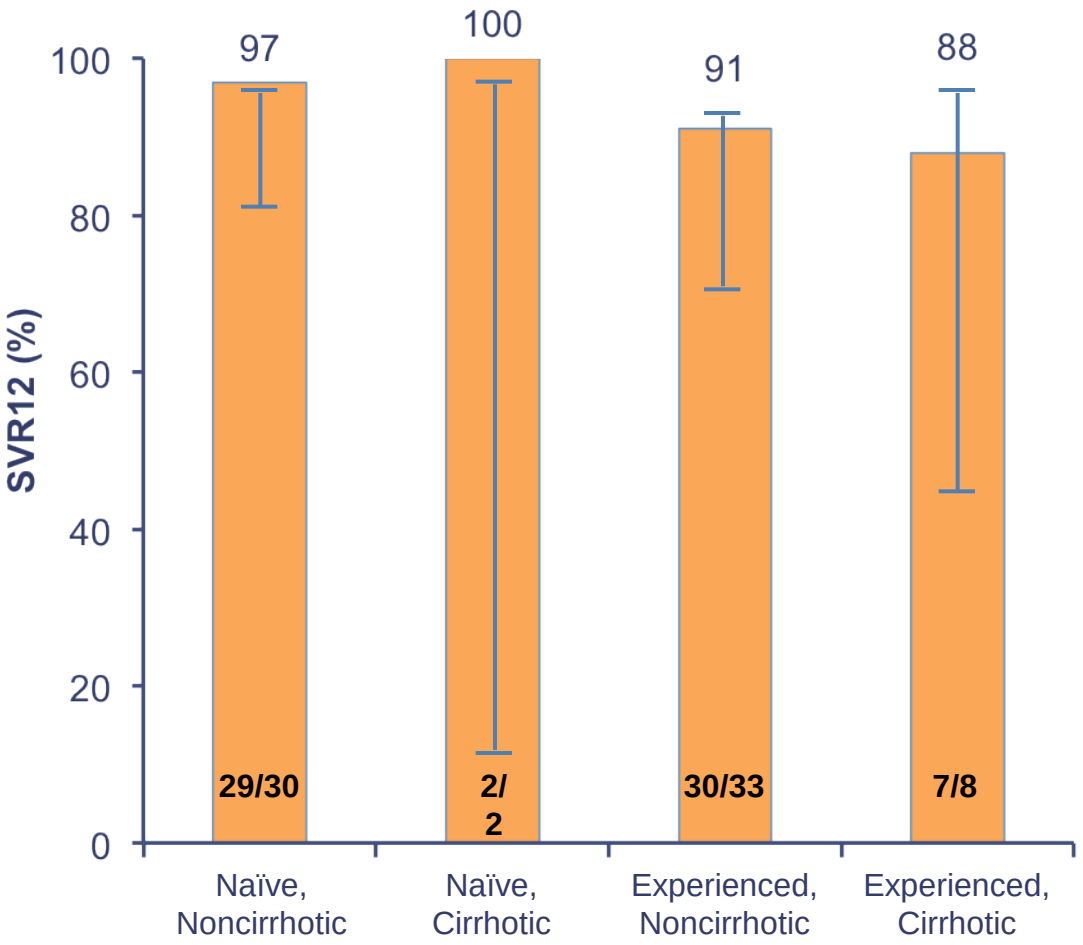


*Protocol amended to eliminate placebo arm and to extend treatment duration to 24 weeks for patients with genotype 3 HCV irrespective of prior treatment history.

SVR12 in GT 2 and 3 Patients*

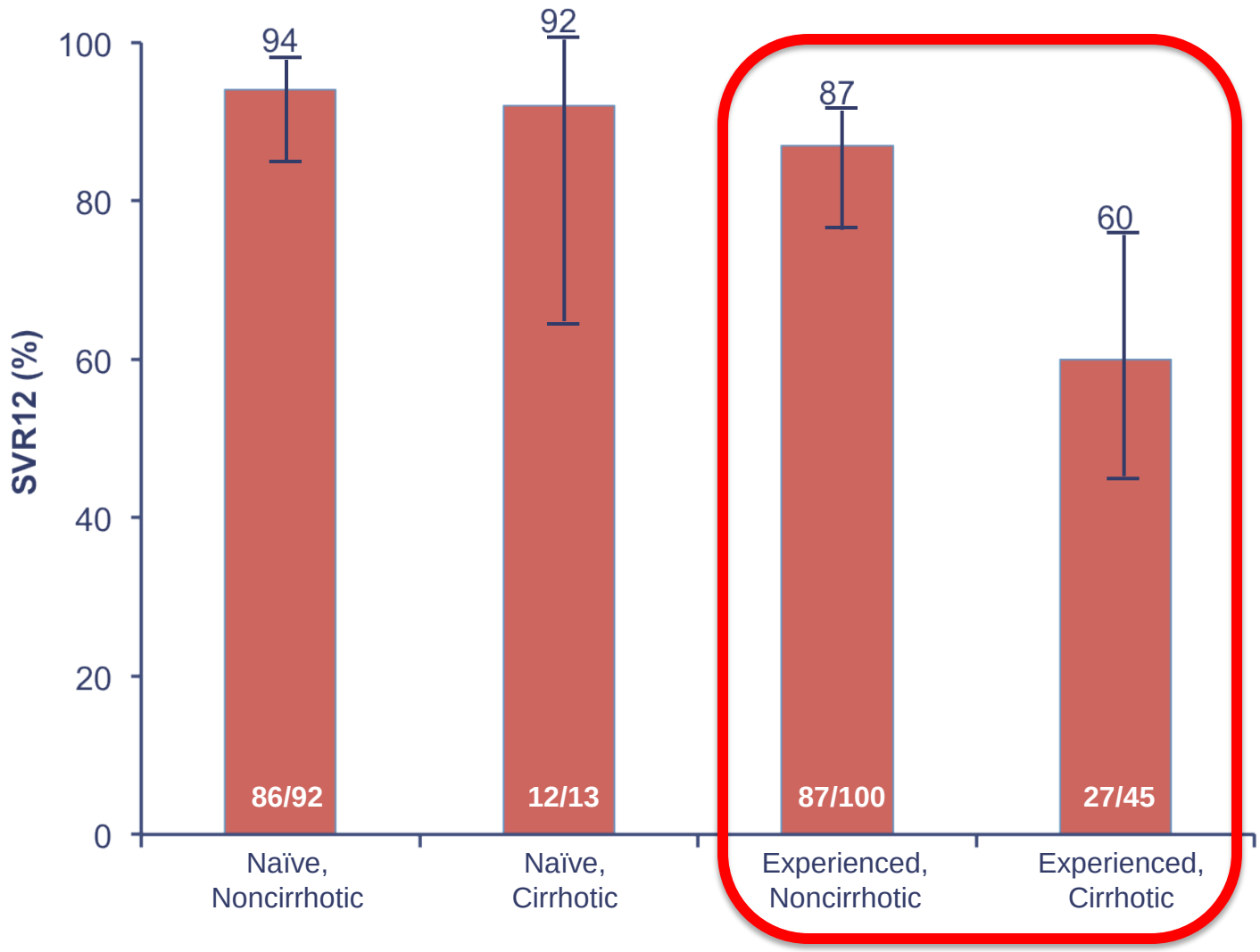


SVR12 in GT 2 Patients Treated for 12 Weeks



*3 of 11 patients (27%) with HCV GT 3 who received 12 weeks of SOF+RBV achieved SVR 12.

SVR12 in GT 3 Patients Treated for 24 Weeks

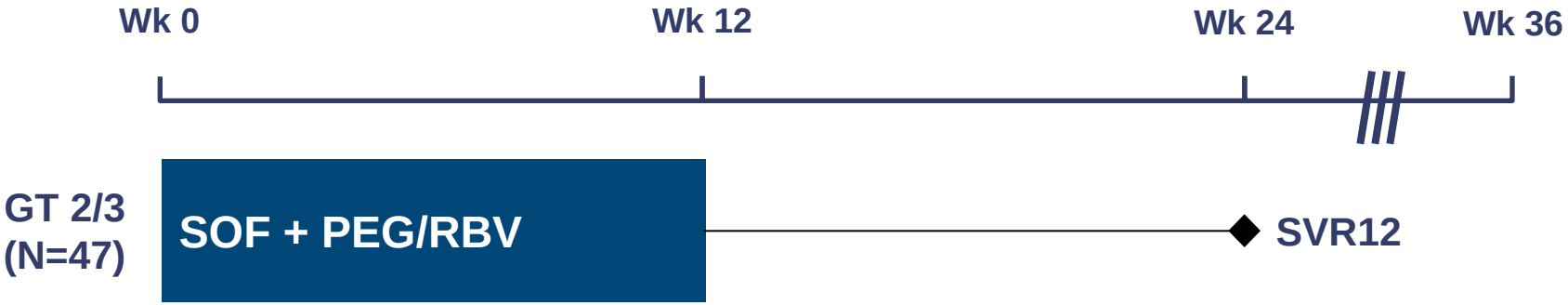


Zeuzem NEJM 2014

LONESTAR-2

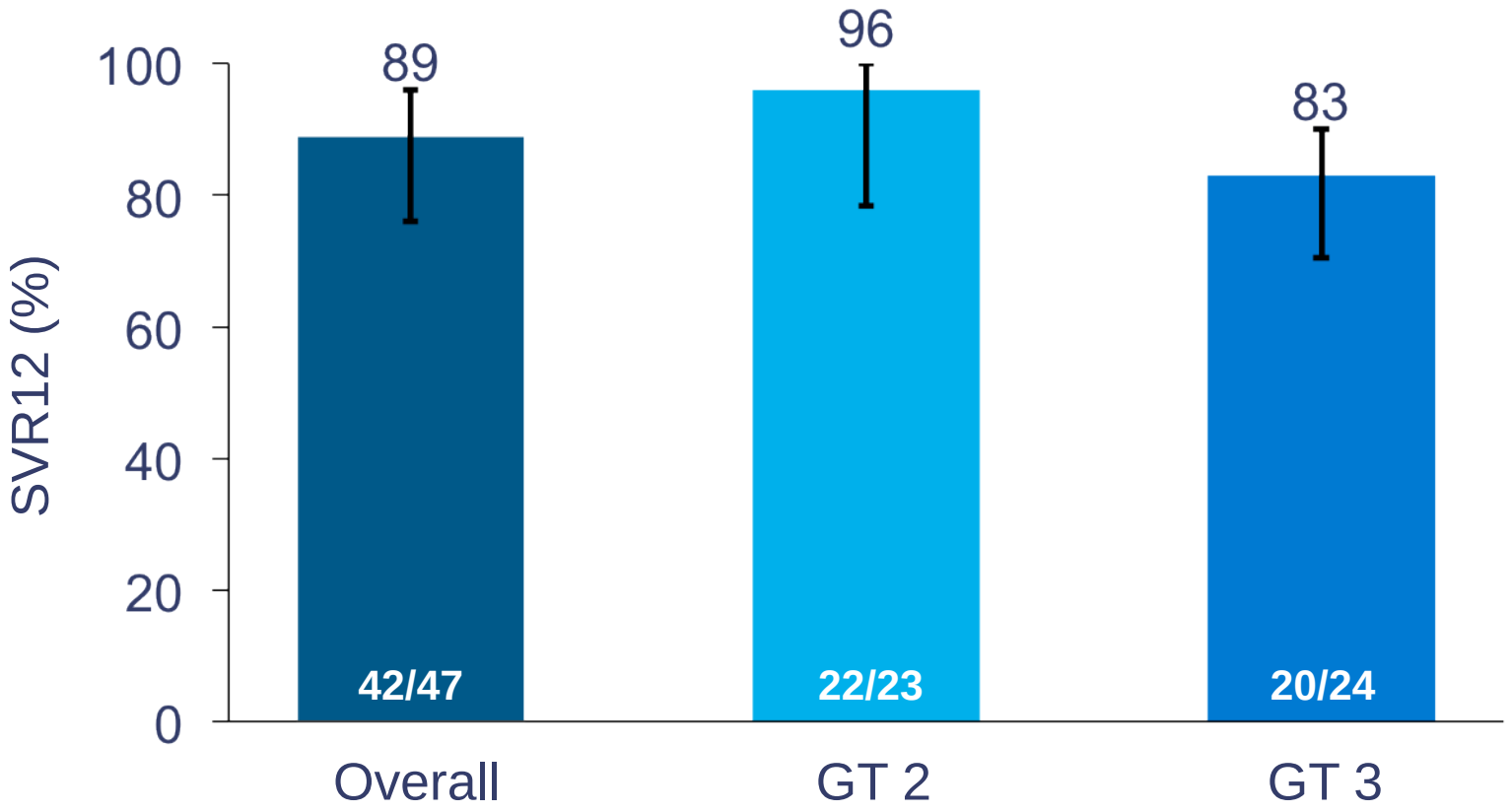
A second strategy for G3

Study Design

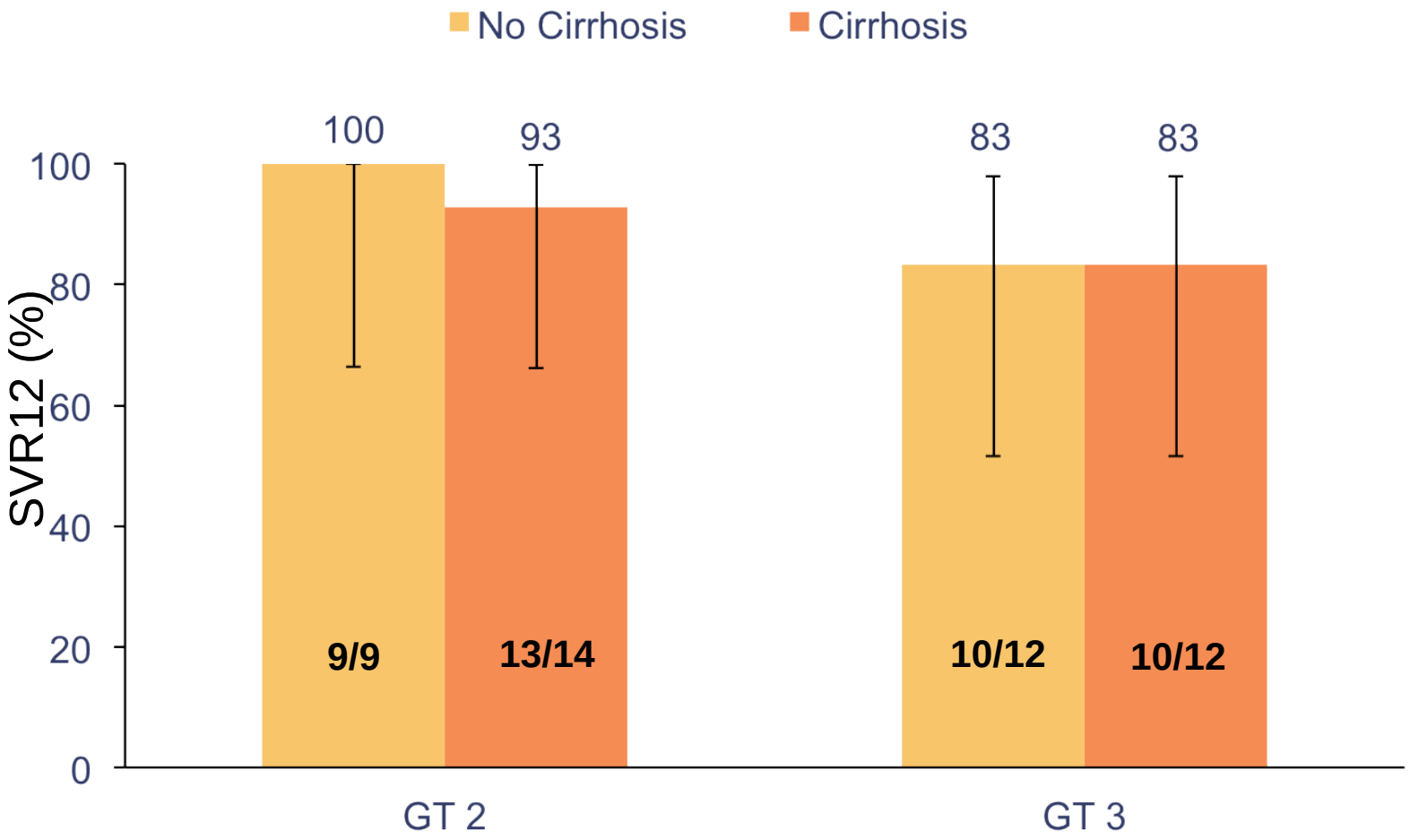


- Study population
  - HCV GT 2 or 3
  - Failed treatment with pegylated interferon and ribavirin
  - Approximately 50% with compensated cirrhosis
  - HIV and HBV coinfected patients excluded

Results: SVR12 by HCV Genotype

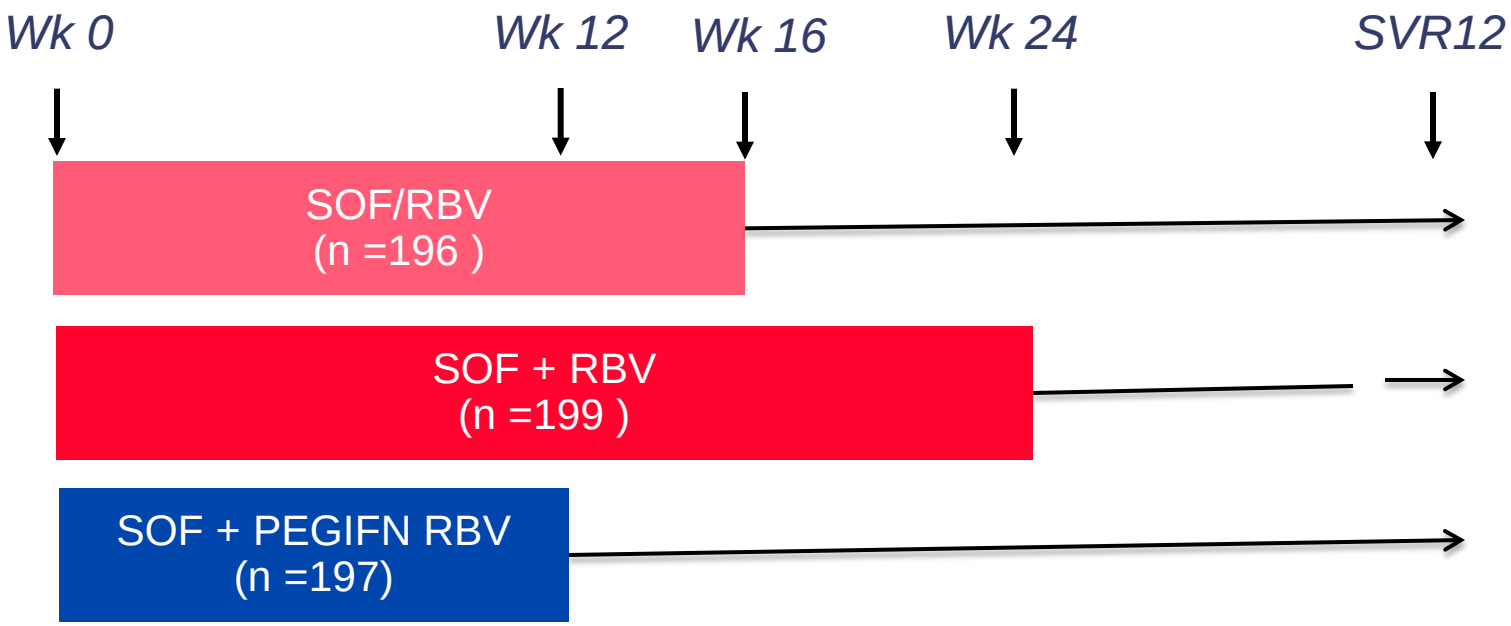


Results: SVR12 by Cirrhosis Status



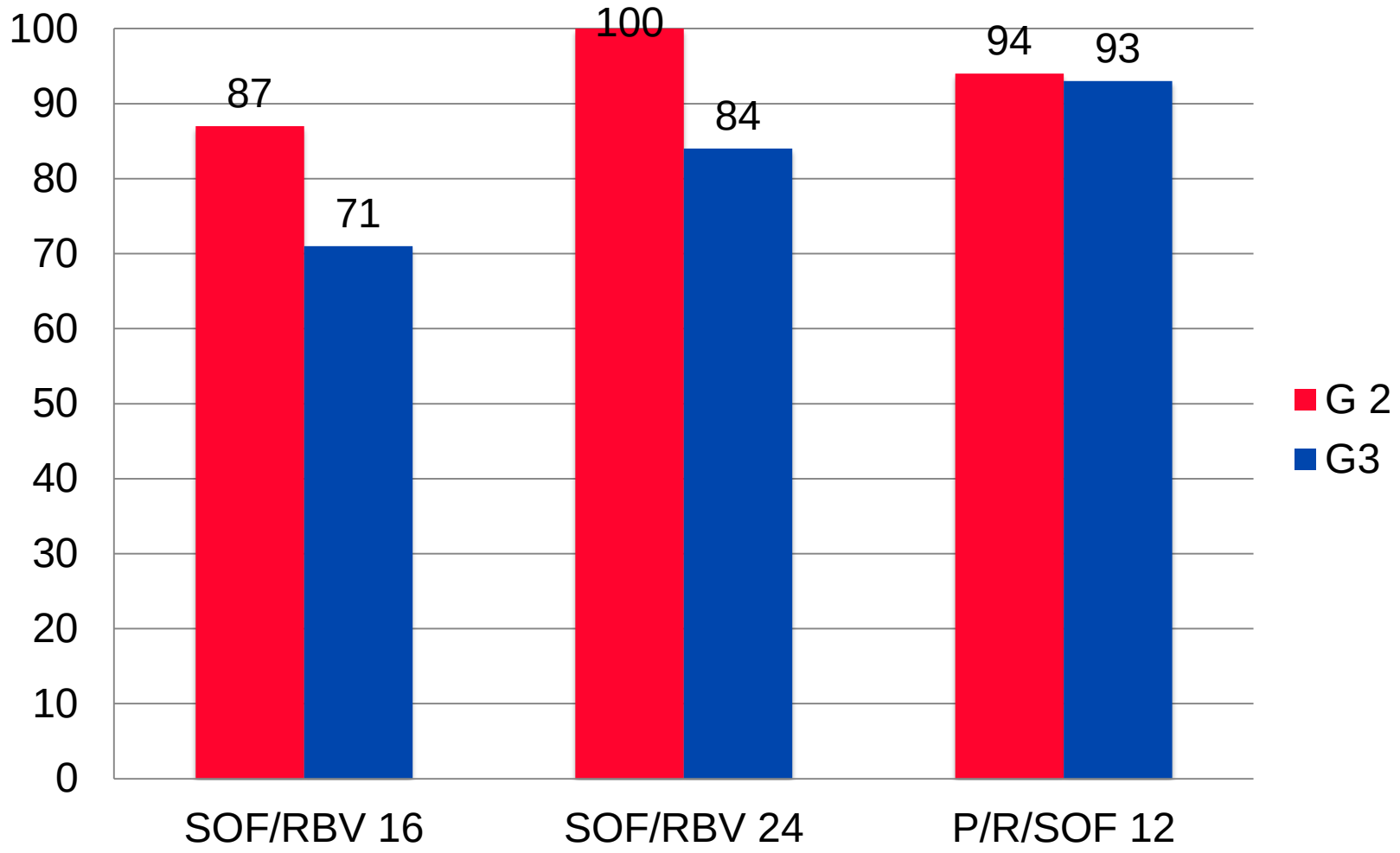
Error bars represent 95% confidence intervals.

BOSON: Study Design

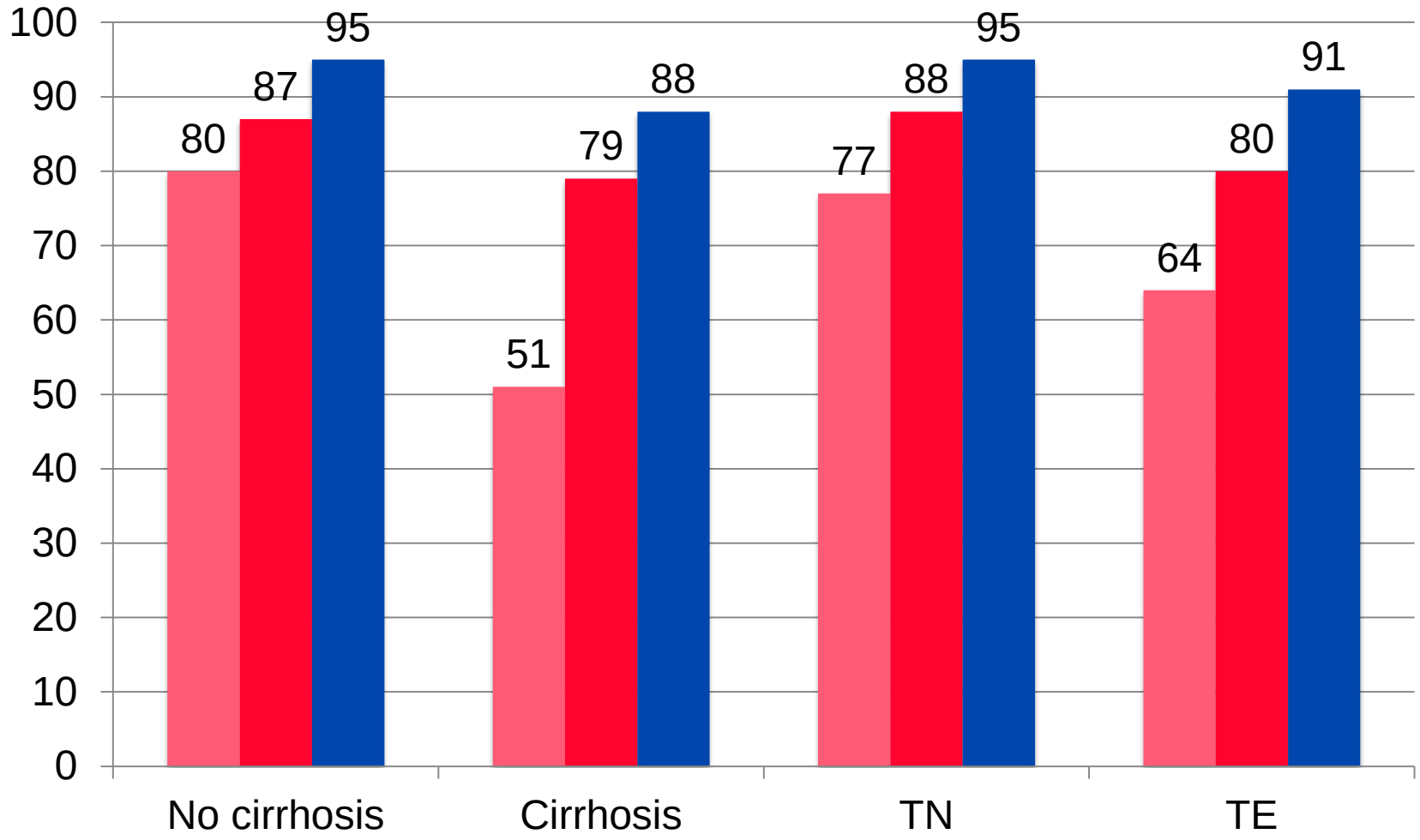


G3 Naïve and NR, cirrhotics allowed
G2 Cirrhotic non-responders

BOSON:
Results by Genotype



BOSON: Genotype 3



Foster EASL 2015

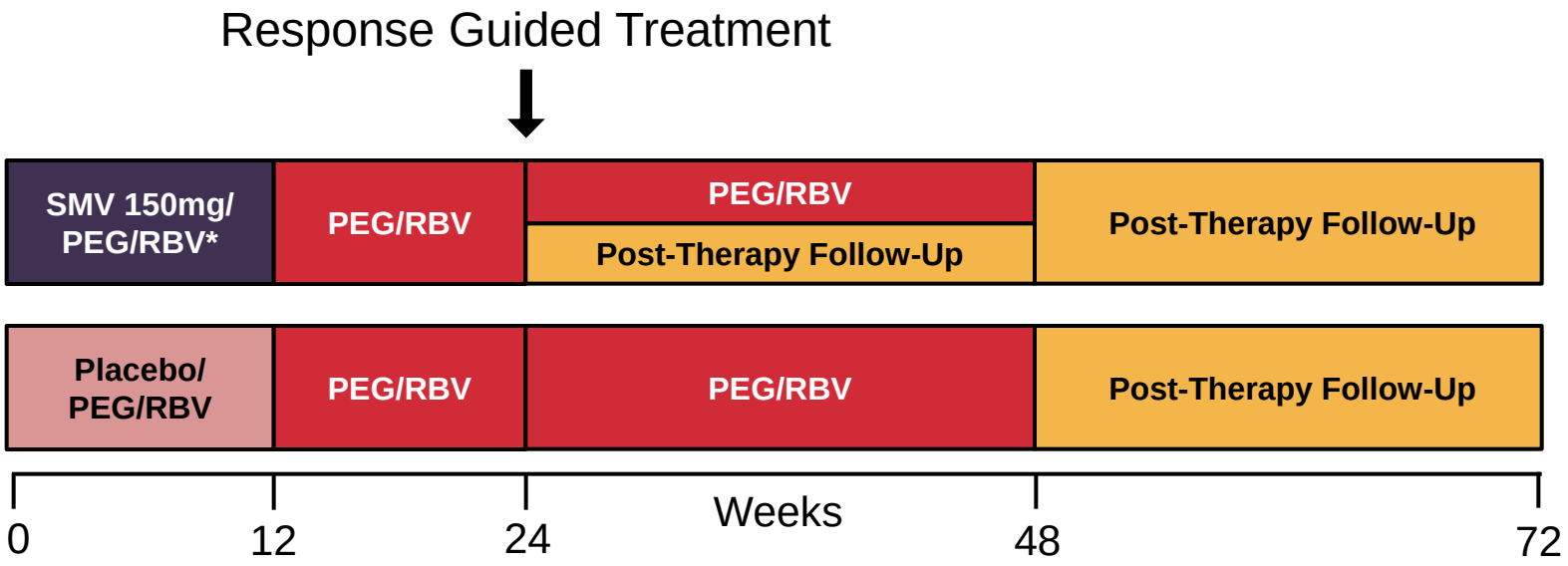
Simeprevir

FDA approved Nov 24, 2013

Simeprevir (TMC 435)

- NS3/4A protease inhibitor
- Antiviral activity against GT 1, 2, 4, 5 and 6
- One capsule, once per day
- FDA approved for G1 infected pts, in combination with P/R, for 24 weeks (RGT)
  - Not to be used by itself!

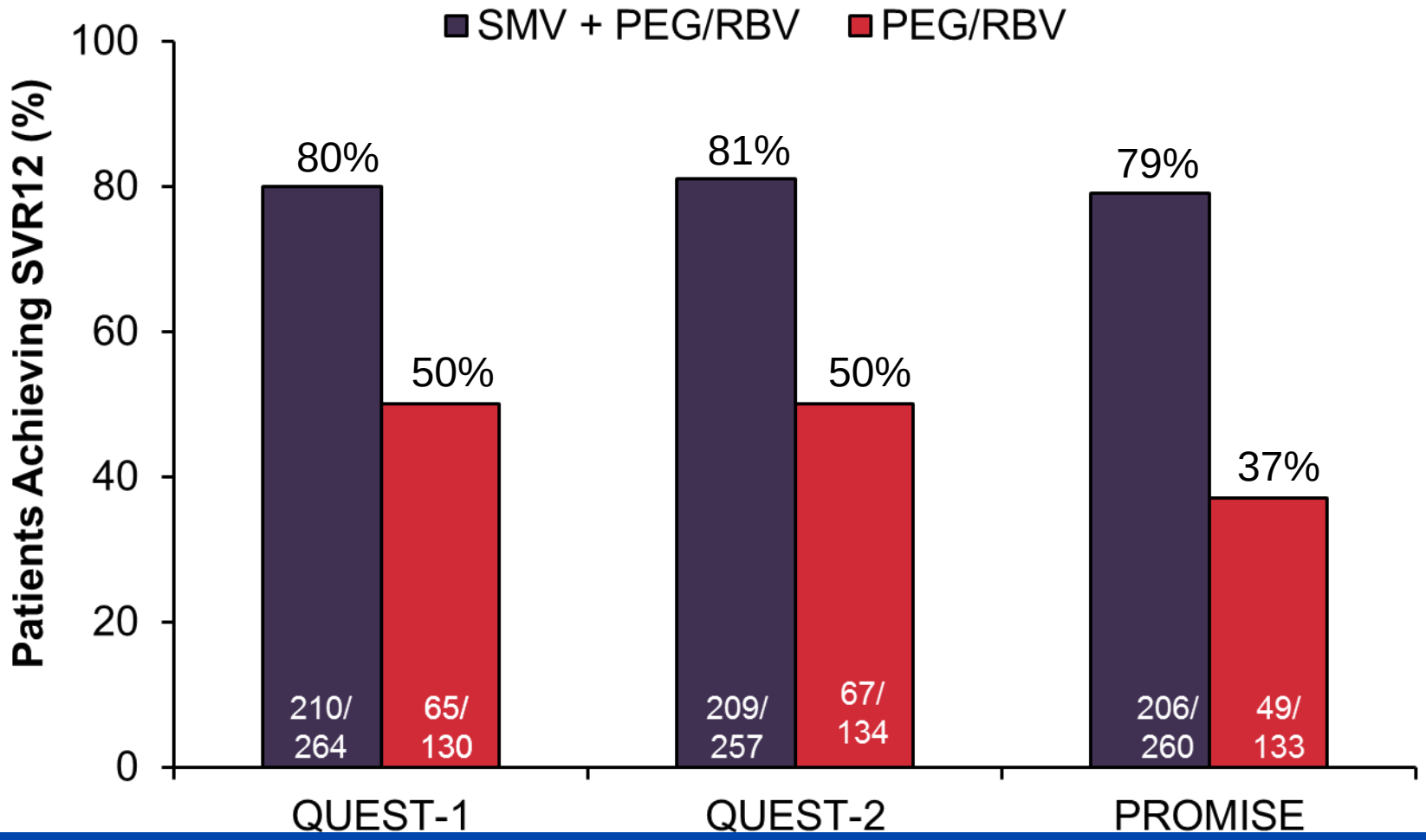
QUEST-1, QUEST-2 and PROMISE Study Designs



- Response Guided Therapy: if HCV RNA <25 International Units/mL at Week 4 and undetectable at Week 12, complete treatment at Week 24
  - 85-93% of patients met the criteria and qualified for total treatment duration of 24 weeks.

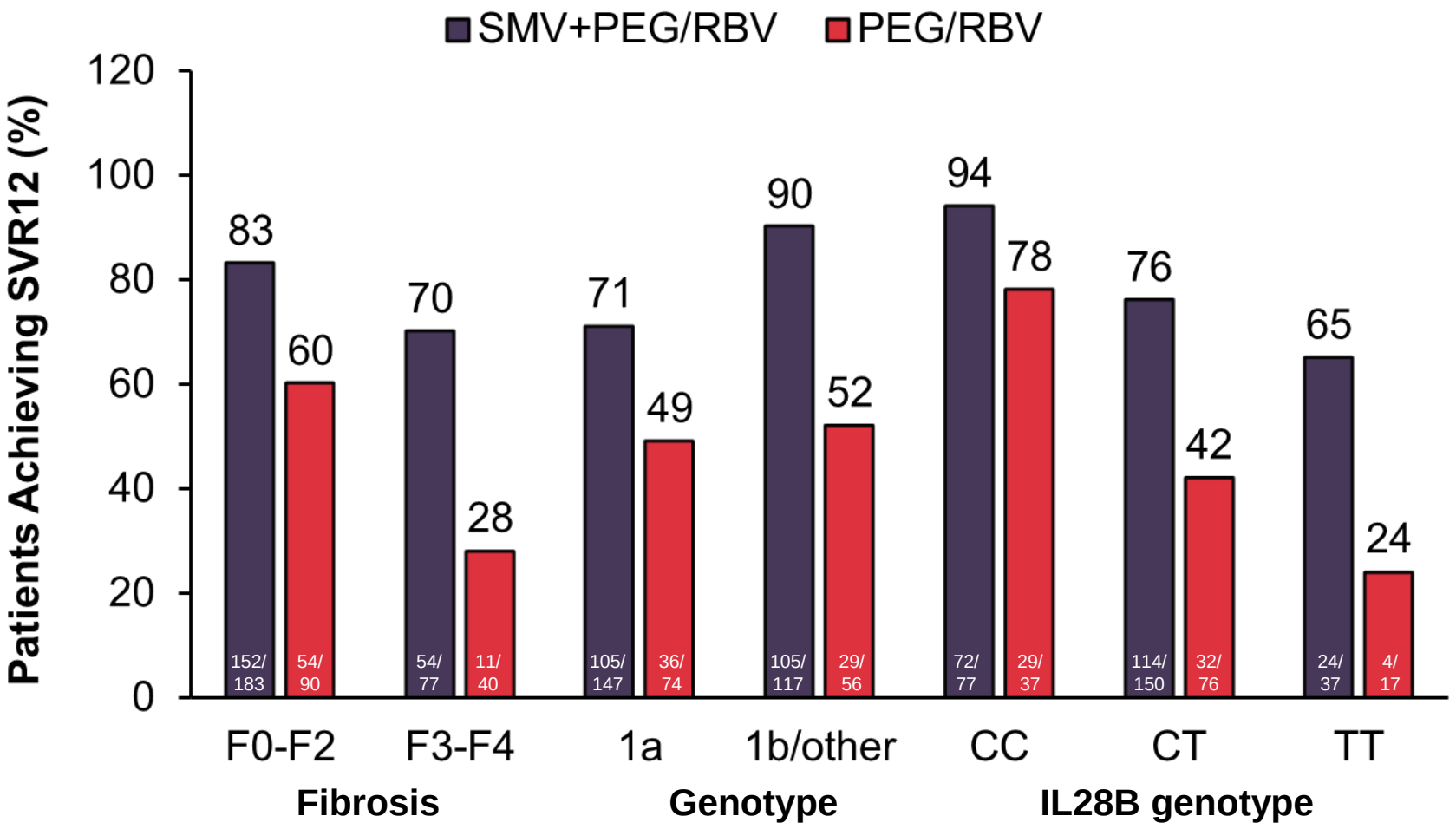
Forns, Gastro 2014; Manns, Lancet 2014; Jacobson, Lancet 2014

Simeprevir + PEG/RBV Achieved SVR in ~80% of Treatment Naive and Prior Relapsers



Forns, Gastro 2014; Manns, Lancet 2014; Jacobson, Lancet 2014

QUEST-1: SVR by Subgroup



Jacobson Lancet 2014

Conclusions which led to FDA approval

- Simeprevir 150 mg + PEG/RBV was highly effective against GT 1 treatment naive patients with SVR (80%)
- Most patients (85%) receiving simeprevir were able to shorten therapy to 24 weeks
- Simeprevir 150 mg + PEG/RBV was generally well tolerated
  - Rates of anemia and rash were similar in the simeprevir and placebo groups

Forns, Gastro 2014; Manns, Lancet 2014, Jacobson, Lancet 2014

New era: WONDERFUL!

But what was missing?: FREEDOM from IFN

Simeprevir + Sofosbuvir

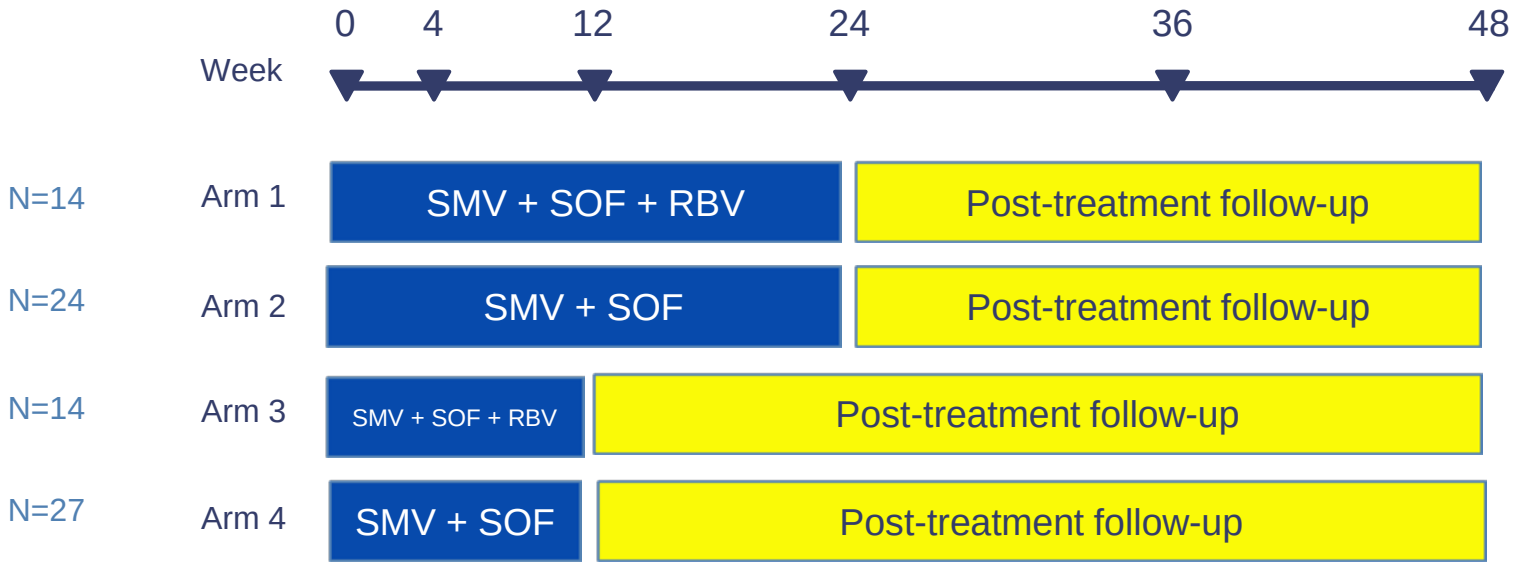
FDA approved Nov 5, 2014

Background

- COSMOS is a Phase IIa, randomized, open-label study investigating simeprevir + sofosbuvir +/- ribavirin
- Both compounds were FDA approved, **but not initially** for this combination

Lawitz, Lancet 2014

COSMOS: Study design

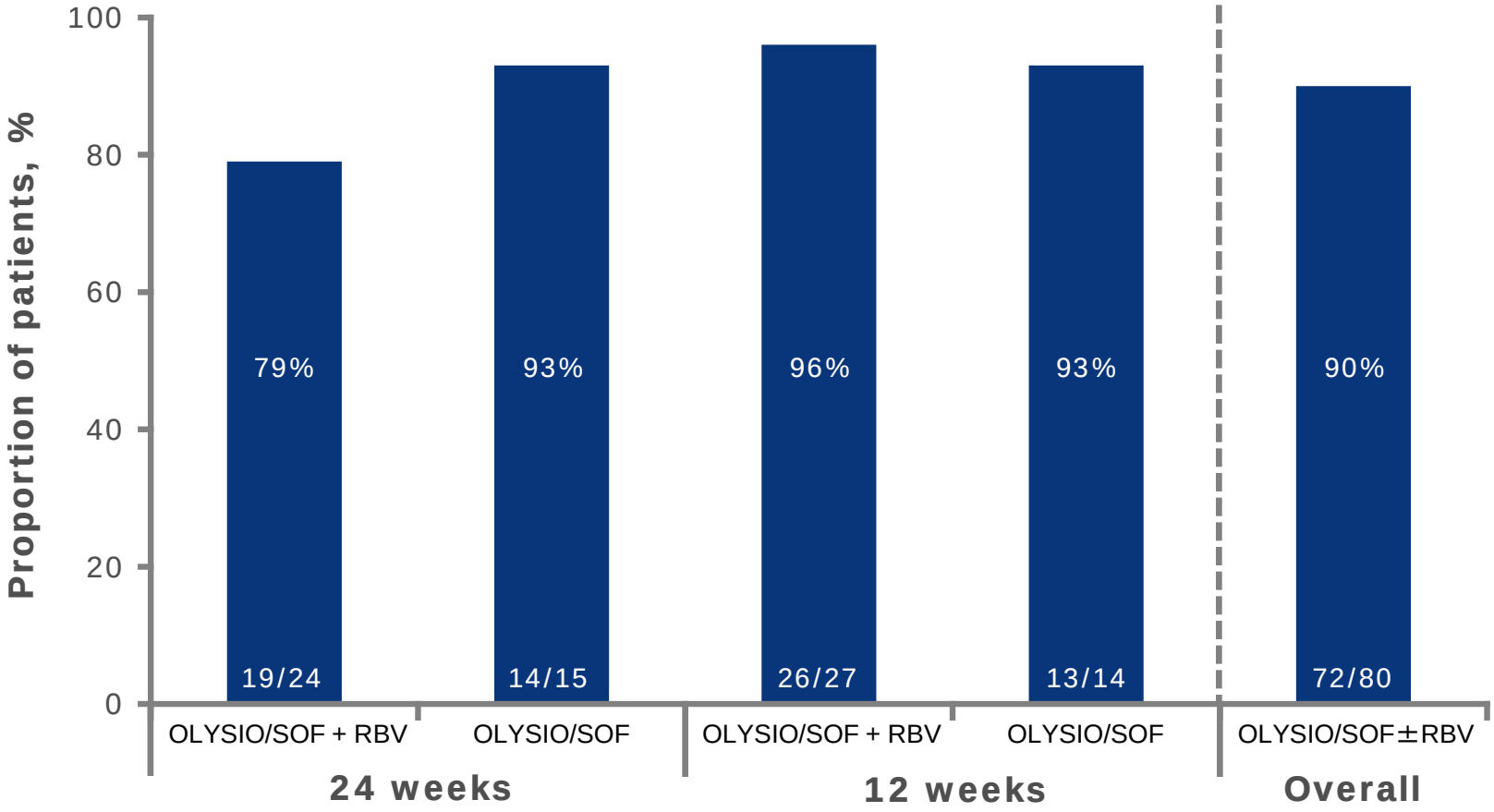


Enrollment ratio 2:1:2:1

- Cohort 1: Prior null responders (METAVIR F0-F2)
  - Final SVR12 for all arms
- Cohort 2: Treatment-naïve and prior null responders (METAVIR F3-F4)
  - Interim SVR4 for Arms 3 and 4

Lawitz, Lancet 2014

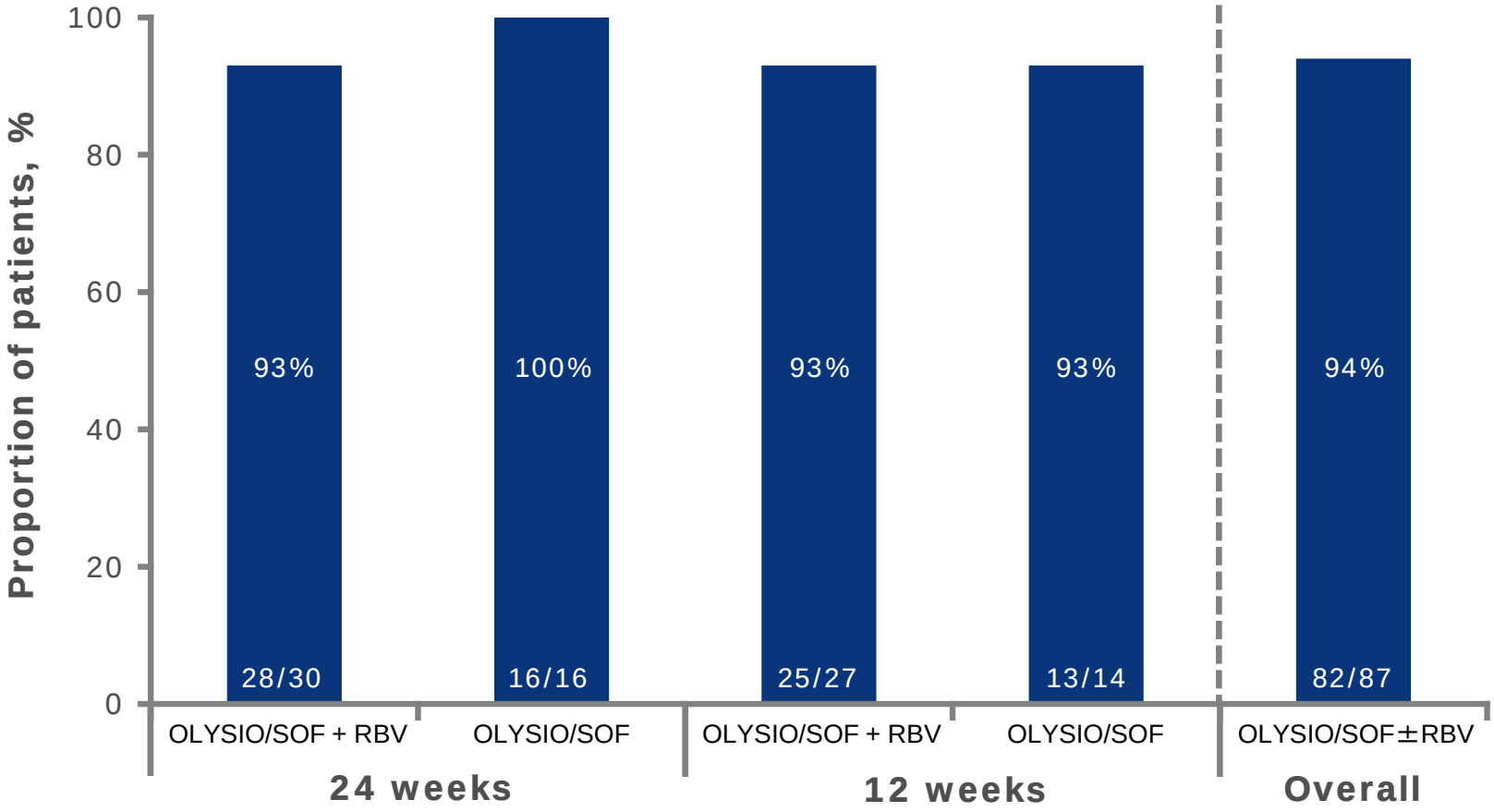
COSMOS: SVR12 – Primary Endpoint (ITT Population – Cohort 1)



SVR12, sustained virologic response 12 weeks after planned treatment end;
ITT, intent-to-treat; SOF, sofosbuvir; RBV, ribavirin

Lawitz, Lancet 2014

COSMOS: SVR12 – Primary Endpoint (ITT Population – Cohort 2)



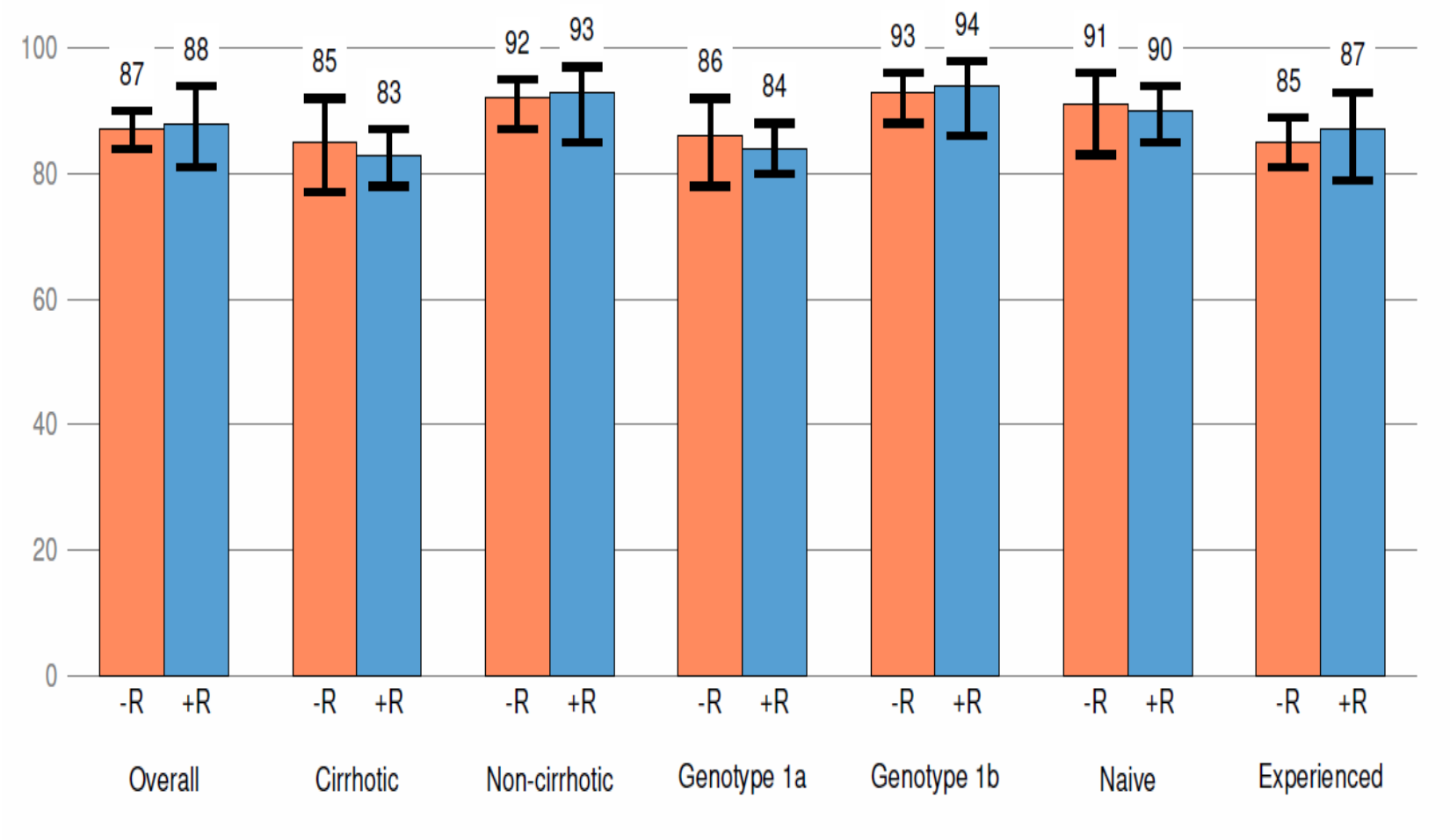
SVR12, sustained virologic response 12 weeks after planned treatment end;
ITT, intent-to-treat; SOF, sofosbuvir; RBV, ribavirin

Conclusion

- Treatment with SMV + SOF ± RBV results in:
  - High SVR12 rates in HCV GT 1 null responder patients
  - High SVR4 rates in naïve and null-responder patients with METAVIR F3-F4
- Addition of RBV to SMV + SOF may not be needed to achieve high rates of SVR in this patient population
- 12 weeks of treatment may confer similar SVR rates compared with 24 weeks of treatment
- SMV + SOF ± RBV was generally well tolerated
- FDA approved regimen for 12 weeks for non-cirrhotics, 24 weeks for cirrhotics (RBV recommened)

Lawitz, Lancet 2014

Crude SVR 12 for SOF/SMV±RBV (HCV TARGET)



SOF, Ledipasvir (LDV, NS5A inhibitor) +/- RBV

FDA Approved in Oct 10, 2014

ION Studies: Pivotal SOF/LDV studies

- ION-1: FDC for 12 or 24 weeks ± RBV in treatment naïve patients Afdhal, NEJM 2014
- ION-3 FDC for 8 weeks± RBV vs 12 weeks in treatment naïve patients Afdhal, NEJM 2014
- ION-2 FDC for 12 or 24 weeks ± RBV in treatment experienced patients (cirrhotics included) Kowdley, NEJM 2014

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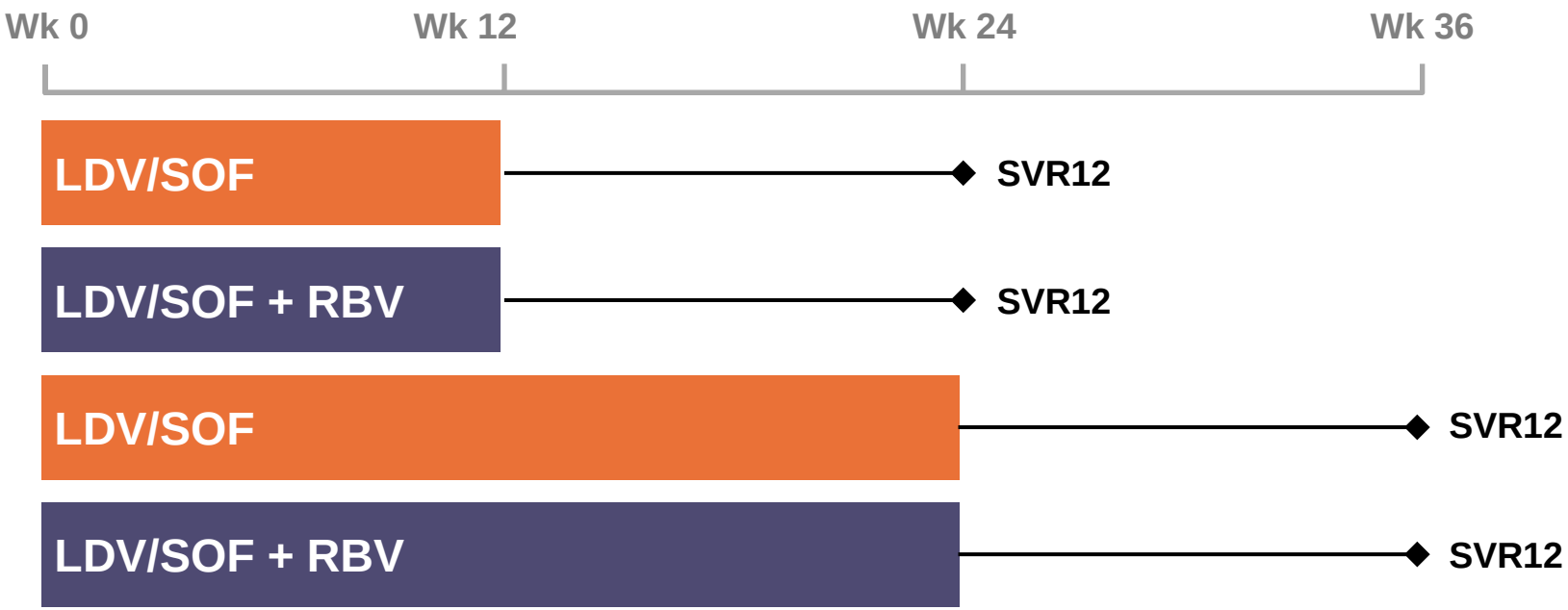
Study Design

GT 1 Treatment-Naïve (ION-1)

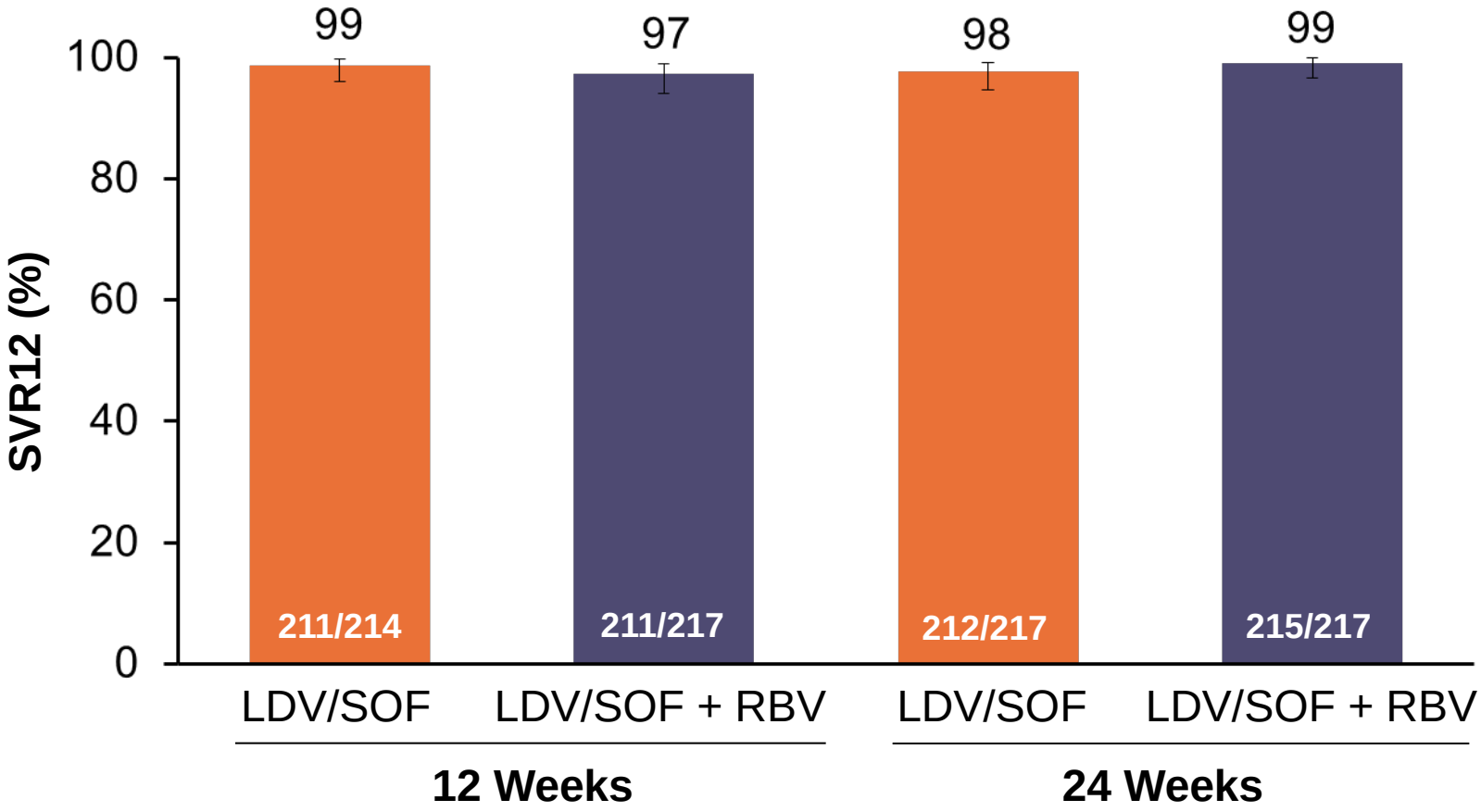


- GT 1 HCV treatment-naïve patients in Europe and USA
- 865 patients randomized 1:1:1:1 across four arms
- Stratified by HCV subtype (1a or 1b) and cirrhosis

Afdhal, NEJM 2014

Results: SVR12

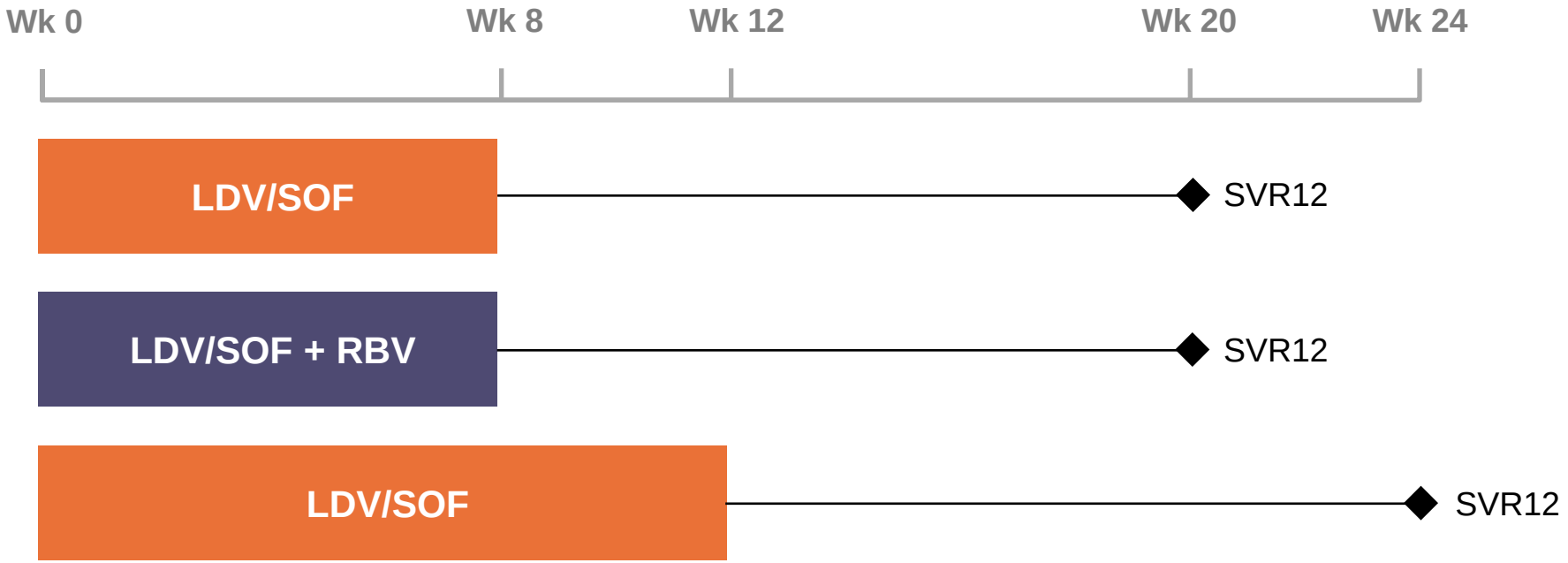
GT 1 Treatment-Naïve (ION-1)



Error bars represent 95% confidence intervals.

Study Design

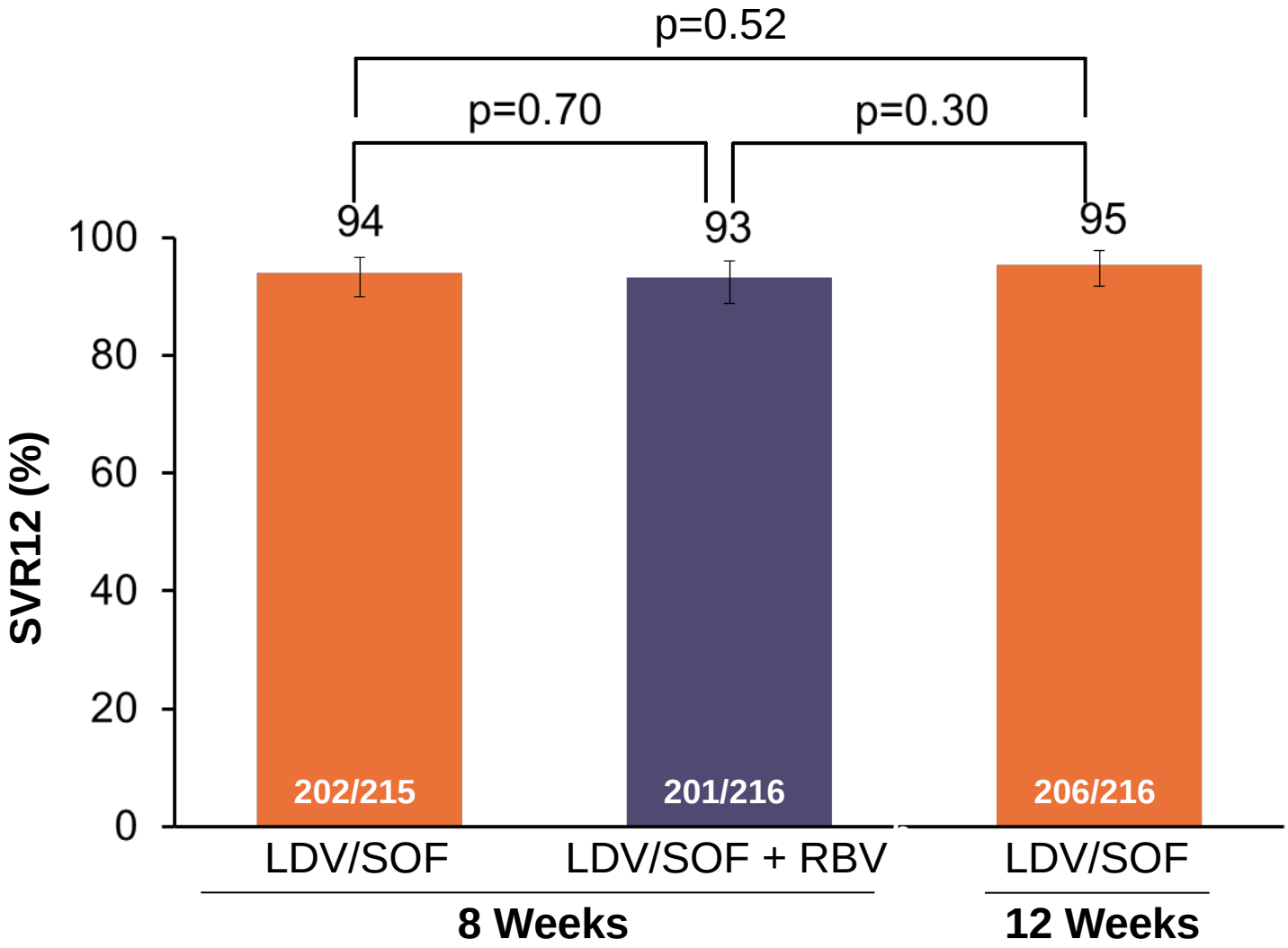
GT 1 Treatment-Naïve (ION-3)



- GT 1 treatment-naïve patients **without** cirrhosis
- 647 patients randomized 1:1:1 across three arms
- Stratified by HCV subtype (1a or 1b)

Results: Non-Inferiority Comparison

GT 1 Treatment-Naïve (ION-3)

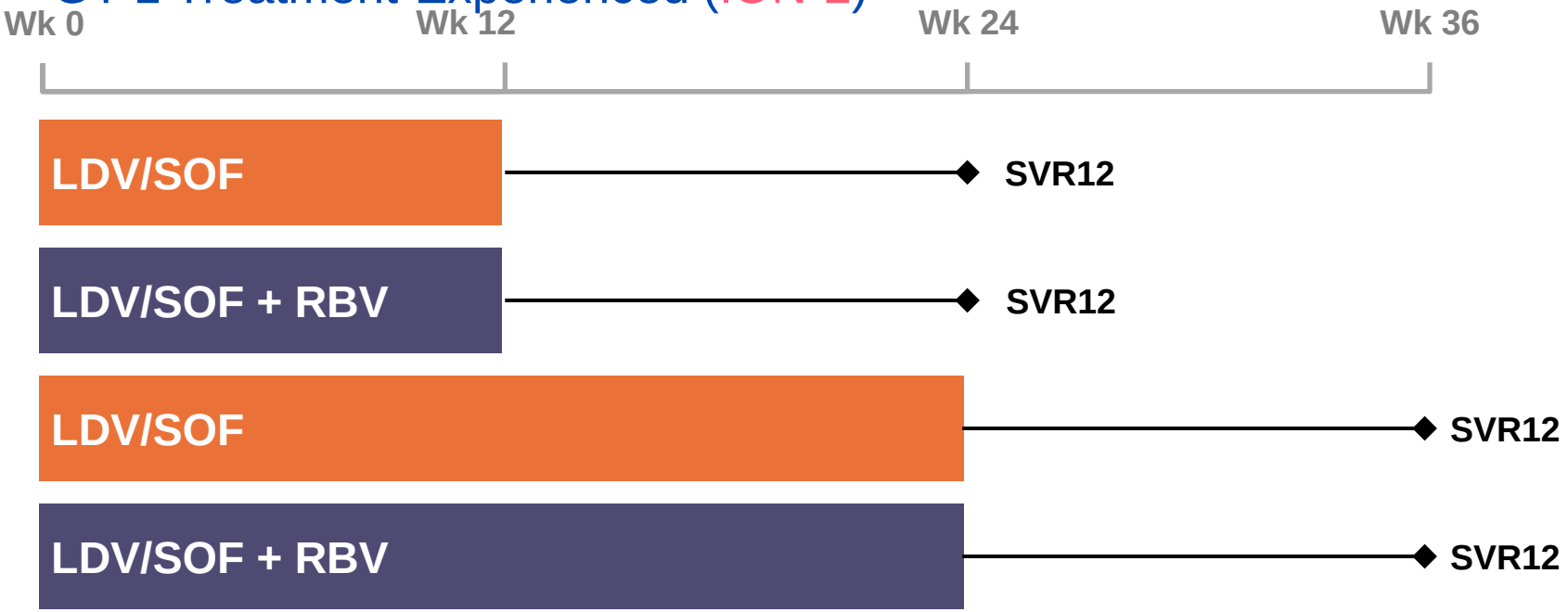


Error bars represent 95% confidence intervals.

Kowdley, NEJM 2014

Study Design

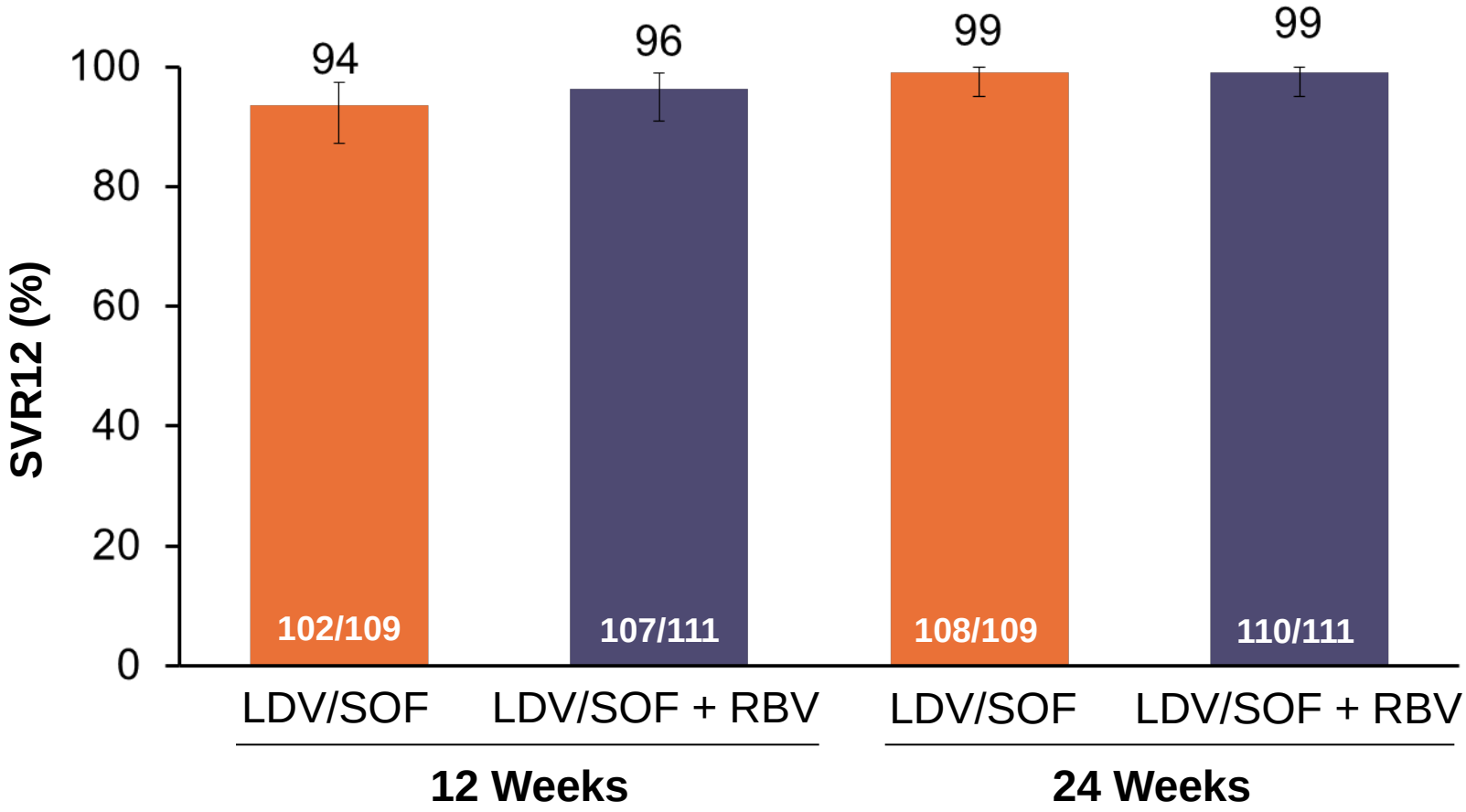
GT 1 Treatment-Experienced (ION-2)



- GT 1 HCV patients who had failed prior IFN-based therapy, including regimens containing a NS3/4A protease inhibitor
- Broad inclusion criteria
- 440 patients randomized 1:1:1:1 across four arms
- Stratified by HCV subtype (1a or 1b), cirrhosis, prior treatment response

Results: SVR12

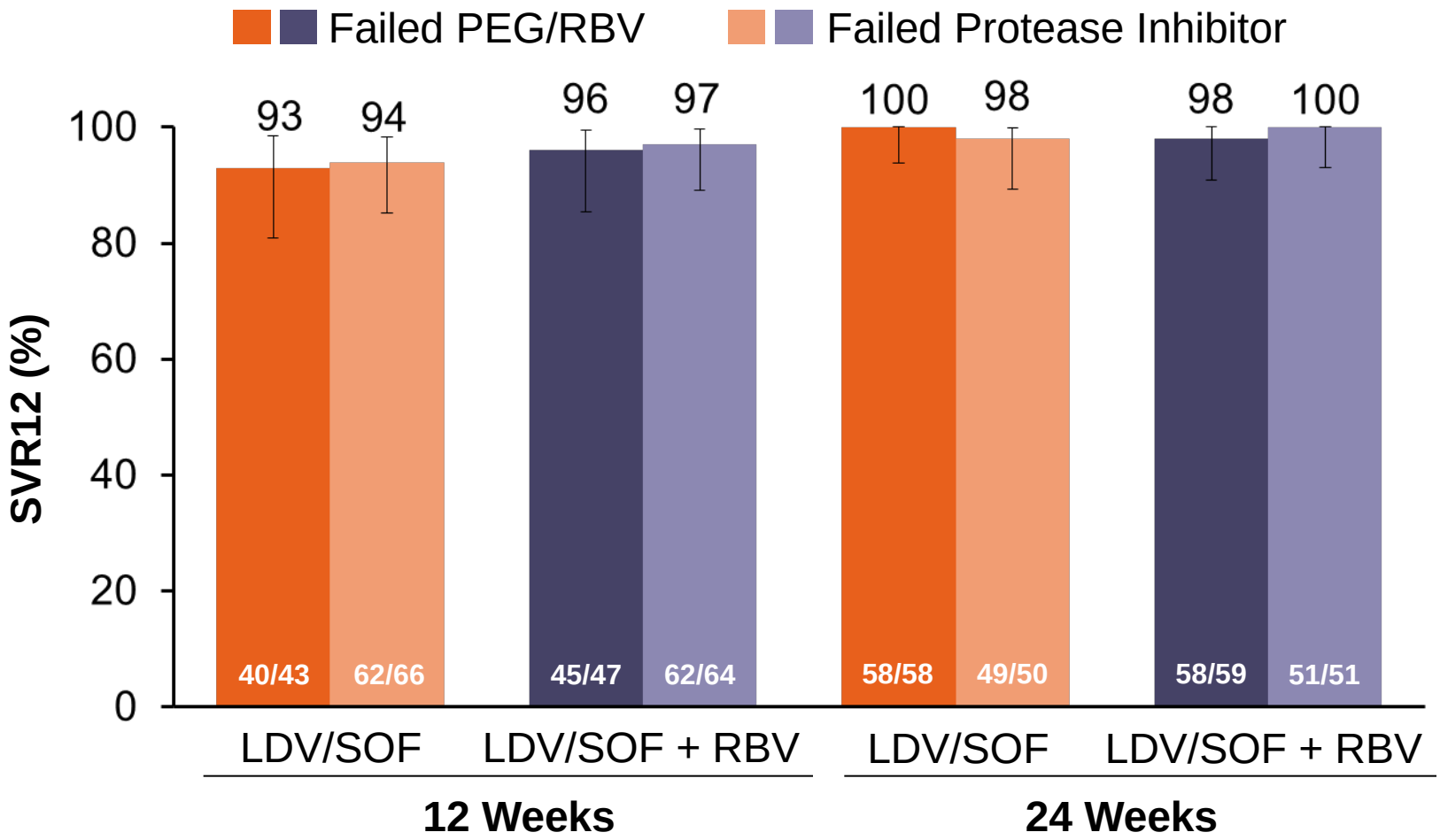
GT 1 Treatment-Experienced (ION-2)



Error bars represent 95% confidence intervals.

SVR12: PEG/RBV vs PI + PEG/RBV Failures

GT 1 Treatment-Experienced (ION-2)

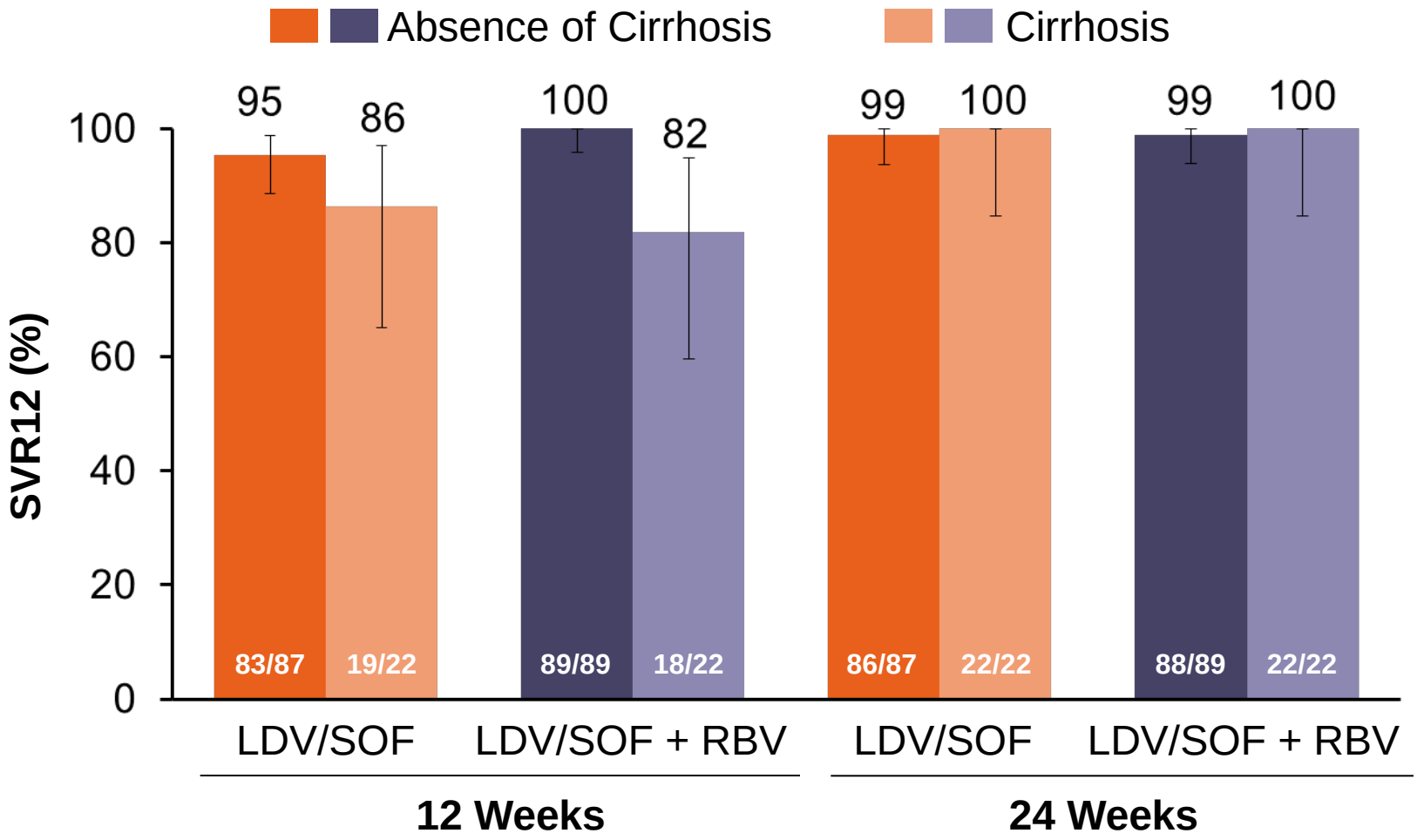


Error bars represent 95% confidence intervals.

Afdhal, NEJM 2014

SVR12: Absence of Cirrhosis vs Cirrhosis

GT 1 Treatment-Experienced (ION-2)



Error bars represent 95% confidence intervals.

Conclusions Across Phase 3 SOF/LDV Studies

- SOF/LDV effective across G1 patients
  - Treatment naive
    - No additional benefit to 24 weeks – 12 weeks adequate
    - 8 weeks adequate for non-cirrhotic patients
    - RBV of no benefit
    - No breakthrough and relapse rare
  - Treatment experienced
    - Very effective
    - 12 weeks adequate for non-cirrhotic
    - 24 weeks preferable for cirrhotic
    - RBV of no benefit

Afdhal, NEJM 2014

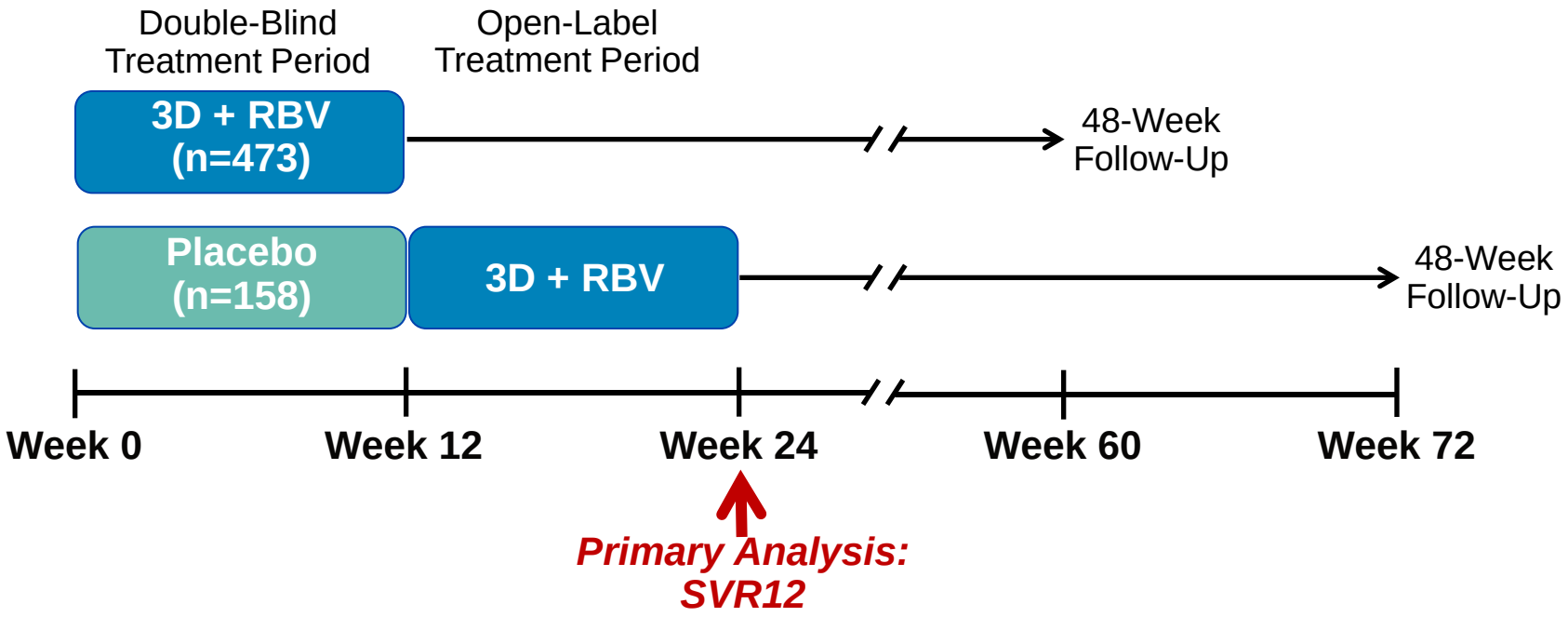
Paritaprevir/r (PI with ritonavir), ombitasvir (NS5A inhibitor) and dasabuvir (non nuc)

The so called 3D regimen FDA approved 12/19/2014

Pivotal 3D regimen studies

- SAPPHIRE I: Placebo-Controlled, 12-Week Regimen Of Paritaprevir/r/Ombitasvir, Dasabuvir, and Ribavirin in **Treatment-Naïve** Adults With HCV Genotype 1 Feld, NEJM 2014
- SAPPHIRE II: Placebo-Controlled, 12-Week Regimen Of Paritaprevir/r/Ombitasvir, Dasabuvir, and Ribavirin in **Treatment-Experienced** Adults With HCV Genotype 1 Zeuzem, NEJM 2014
- TURQUOISE-II: Open label, 12 vs 24-week Regimen Of Paritaprevir/r/Ombitasvir, Dasabuvir, and Ribavirin in HCV G1-infected patients with **Compensated Cirrhosis** Poordad, NEJM 2014

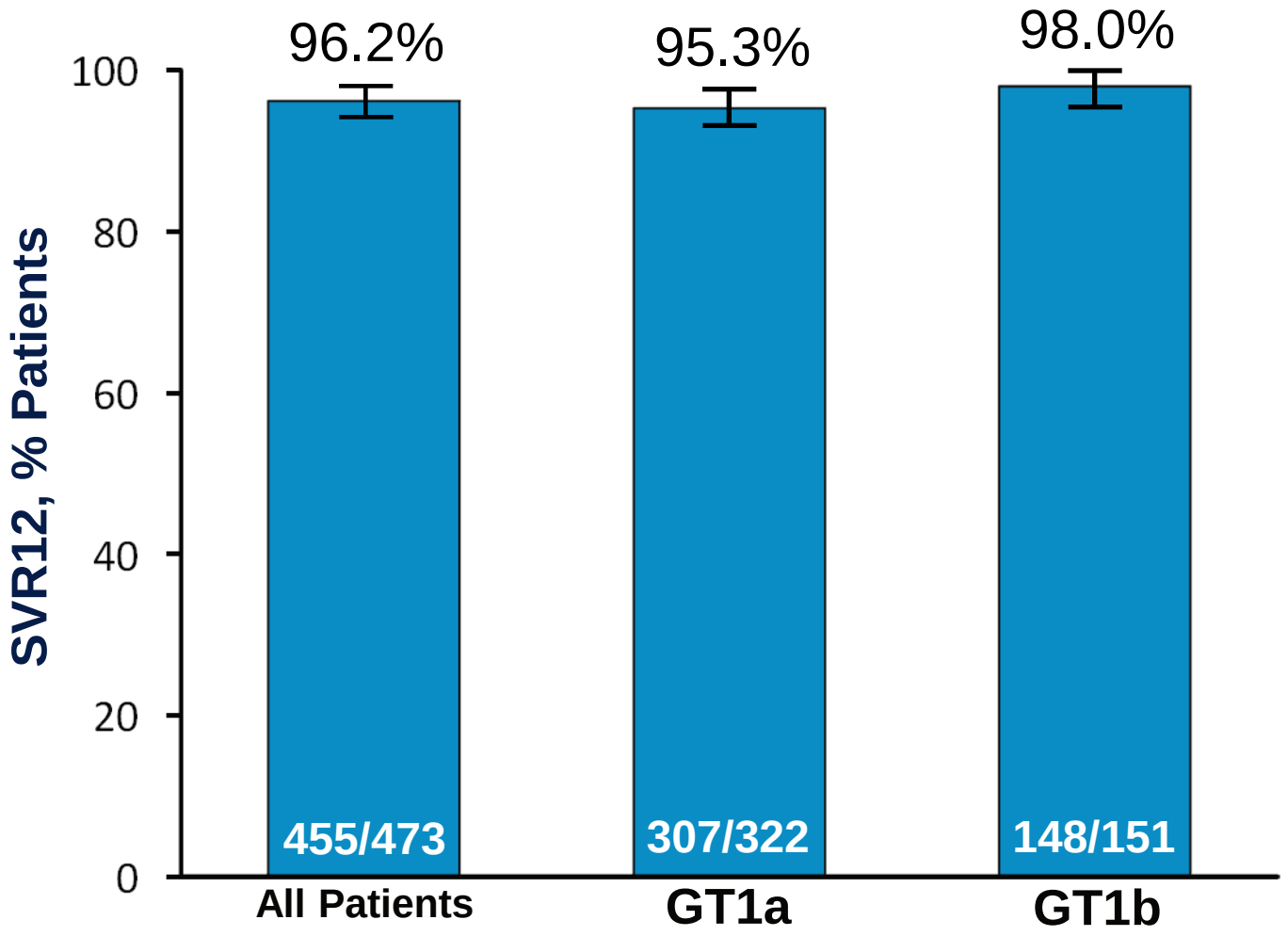
SAPPHIRE-I: Placebo-Controlled Design (N=631)



- 3D: co-formulated ABT-450/r/ombitasvir, 150 mg/100 mg/25 mg QD; dasabuvir, 250 mg BID
- RBV: 1000-1200 mg daily according to body weight (<75 kg and >75kg, respectively)

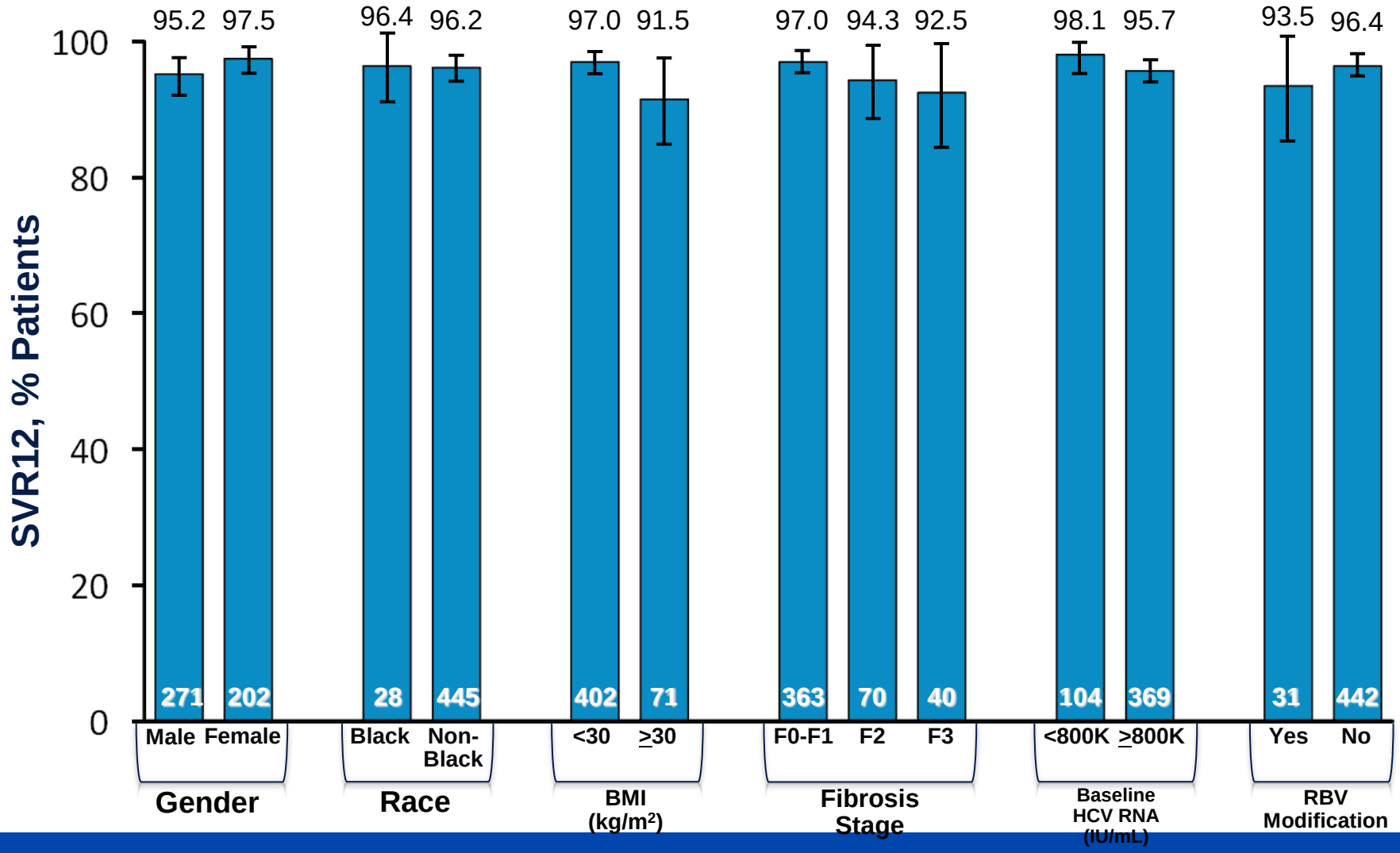
Feld, NEJM 2014

SAPPHIRE-I Results: ITT SVR12 Rates (Superiority to Historical Rate)



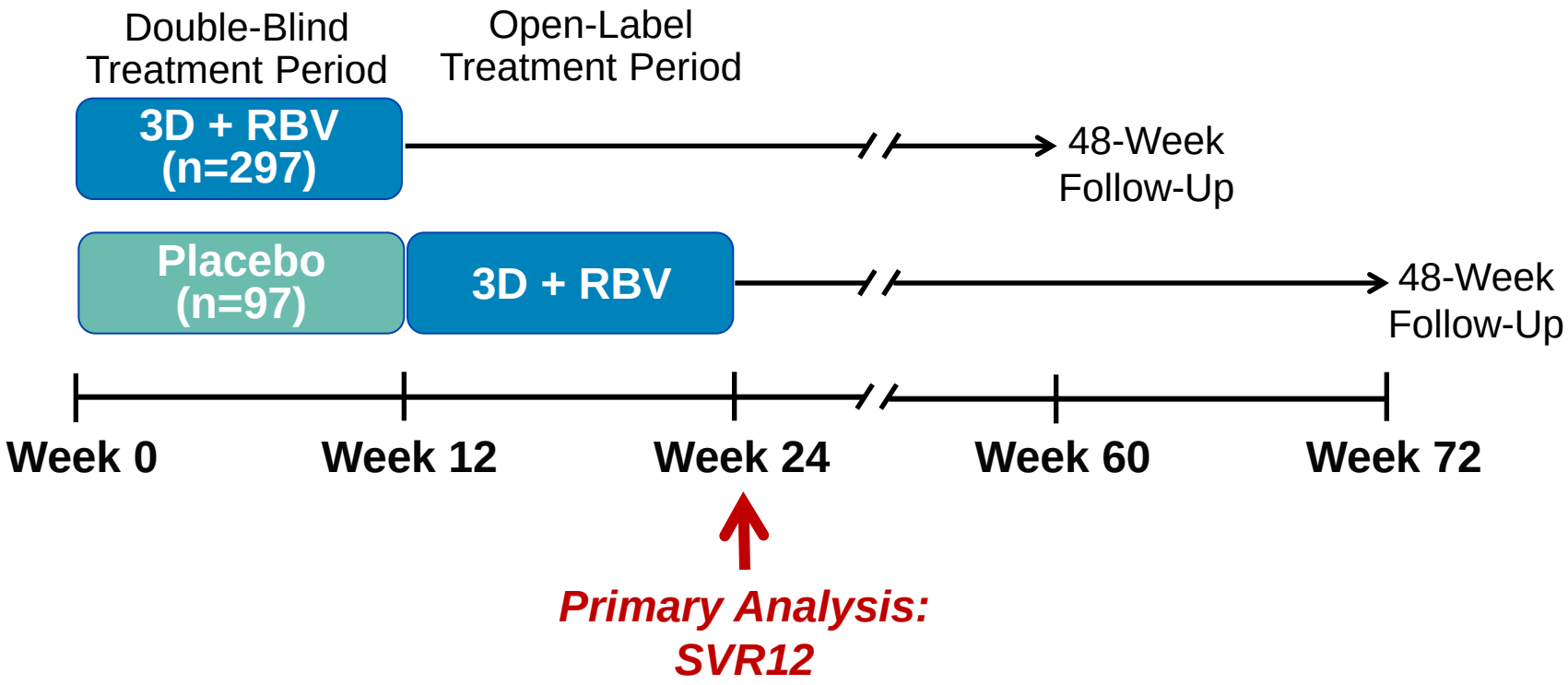
Feld, NEJM 2014

SAPPHIRE-I: ITT SVR12 Rates in Subpopulations



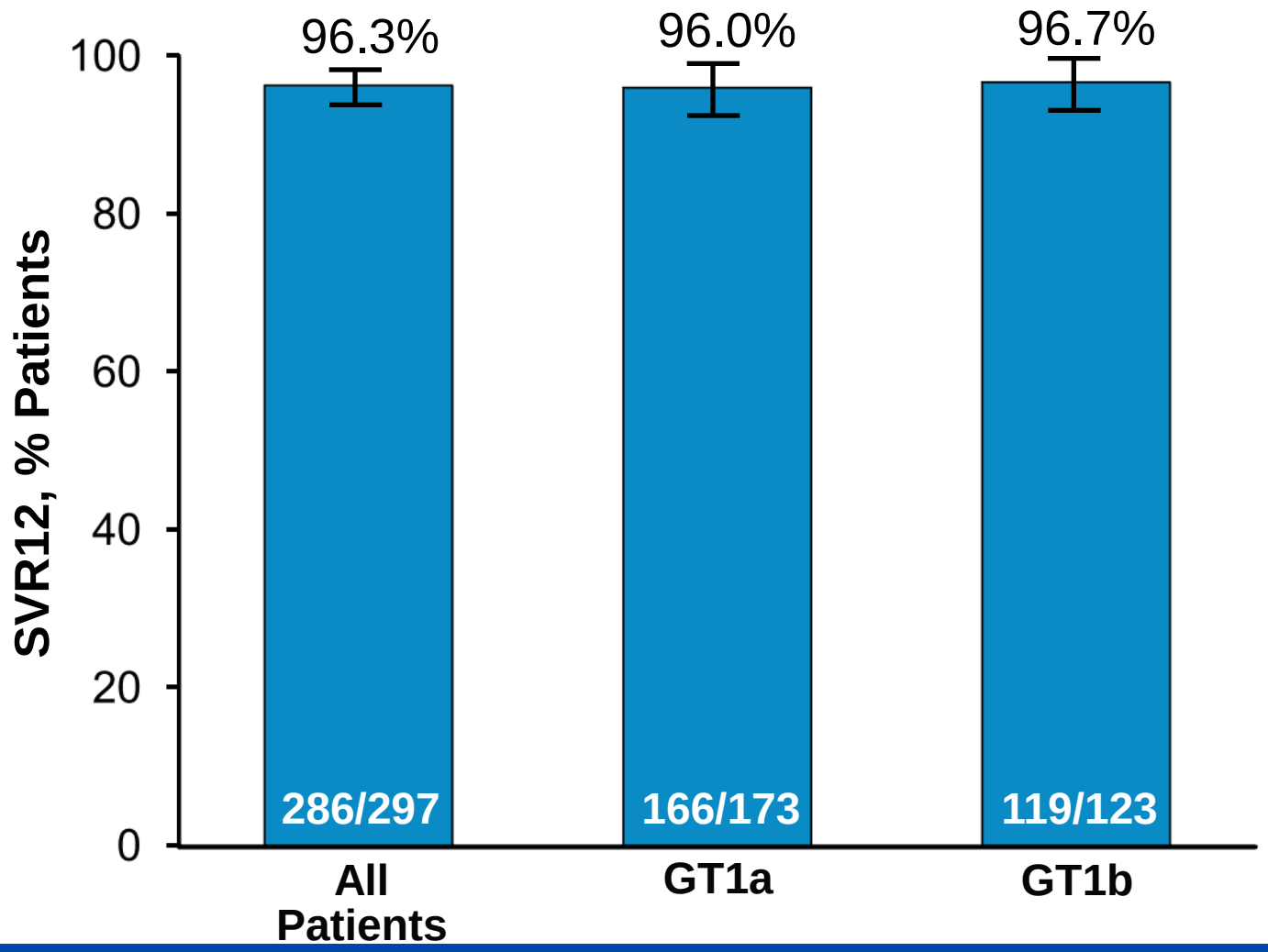
Feld, NEJM 2014

SAPPHIRE-II: Placebo-Controlled Design (N=394)



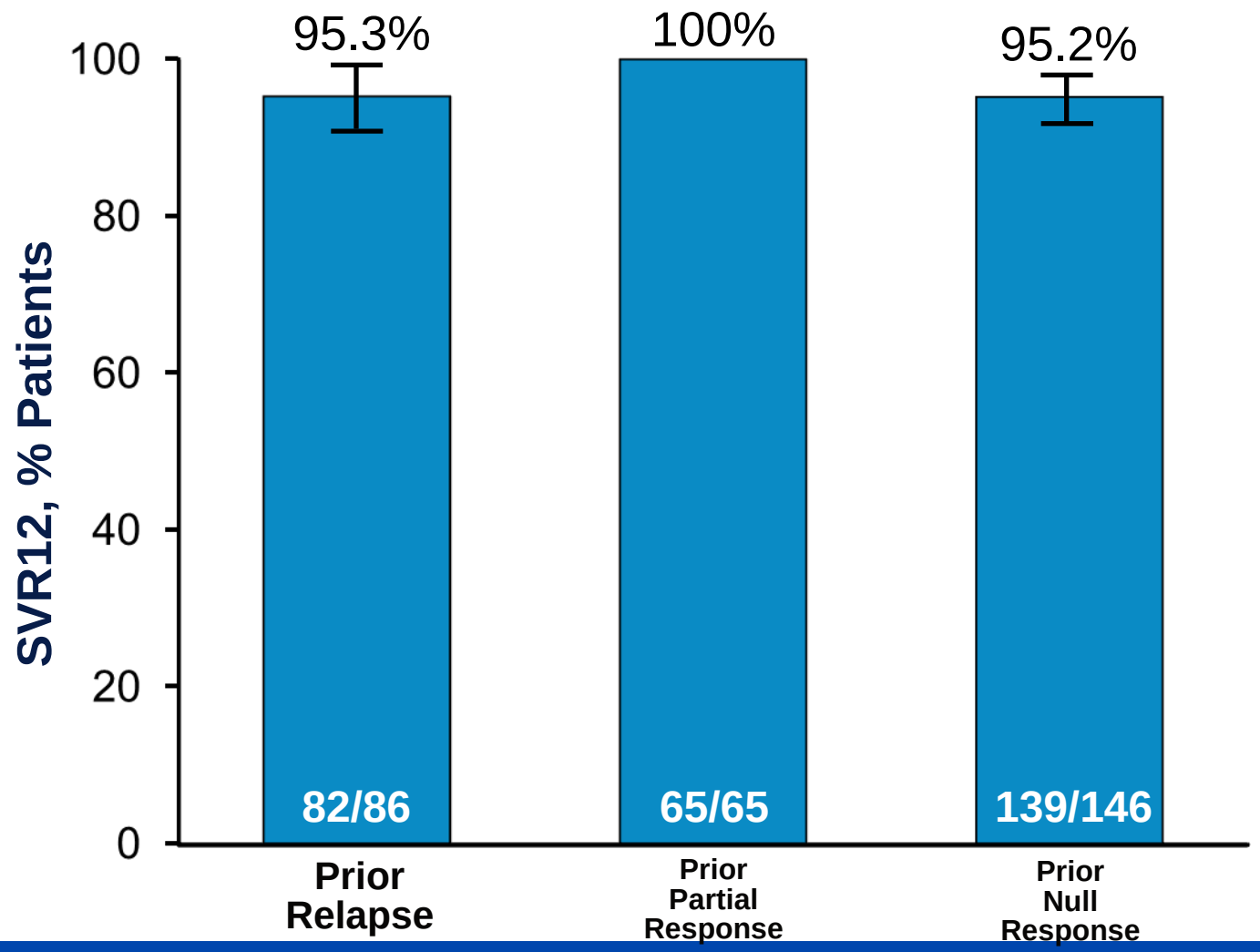
- 3D: co-formulated ABT-450/r/ombitasvir, 150 mg/100 mg/25 mg QD; dasabuvir, 250 mg BID
- RBV: 1000-1200 mg daily according to body weight (<75 kg and >75kg, respectively)

SAPPHIRE-II Results: ITT SVR12 Rates (Superior to SOC)



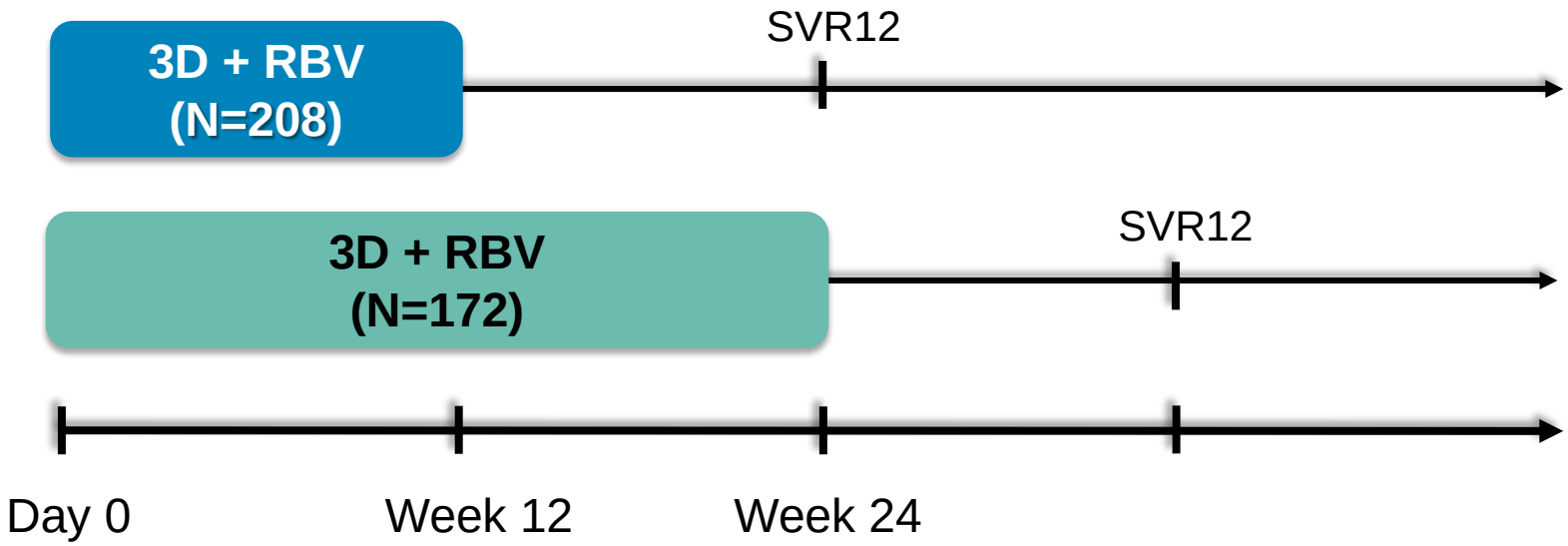
Zeuzem, NEJM 2014

SAPPHIRE-II Results: ITT SVR12 Rates >95% in All Prior PEG/RBV Non Response Groups



Zeuzem, NEJM 2014

TURQUOISE-II Study Design: Phase 3 Trial Conducted Exclusively in GT1-Infected Cirrhotic Patients (N=380)



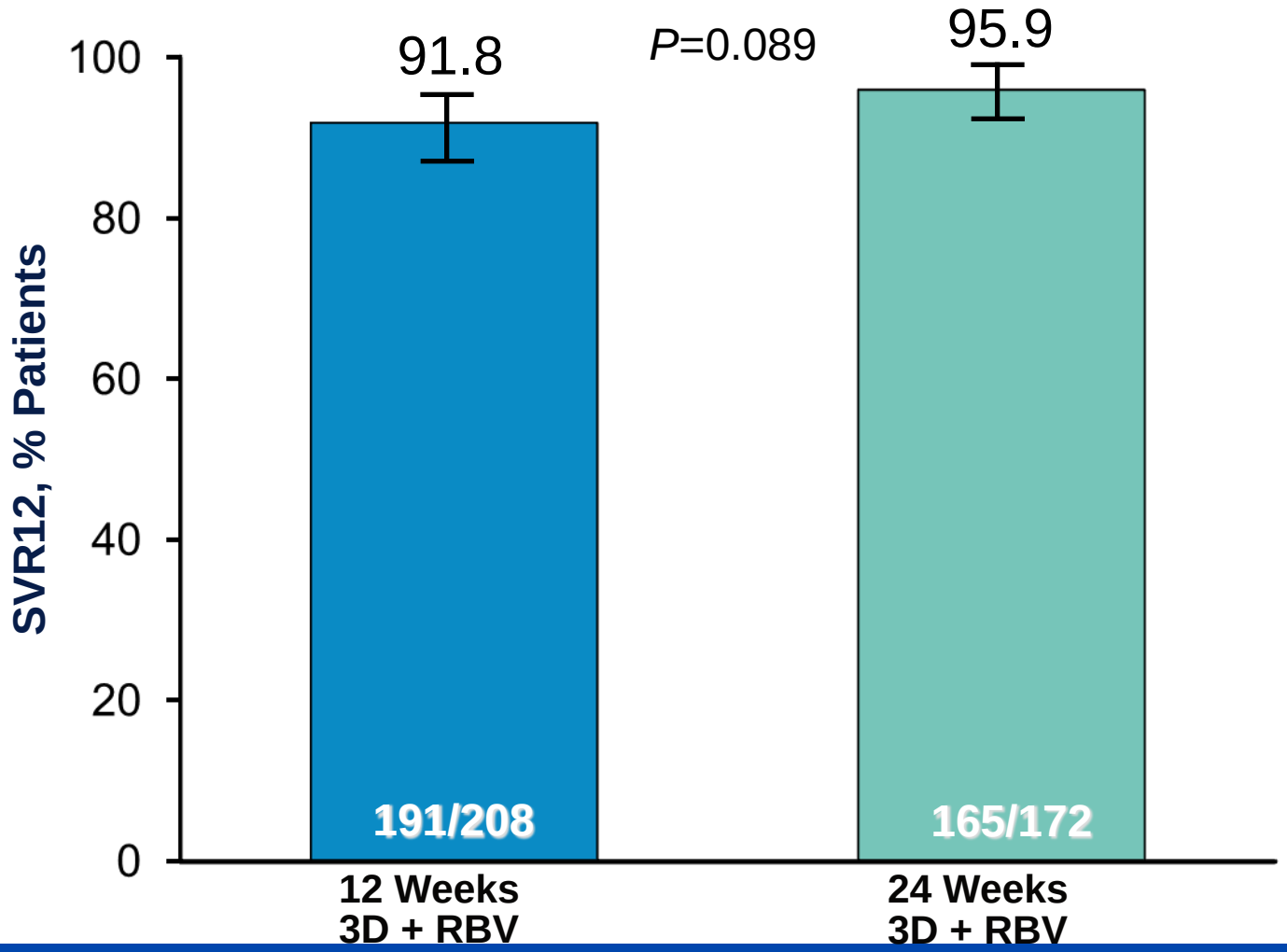
- 3D: co-formulated ABT-450/r/ombitasvir, 150 mg/100 mg/25 mg QD; dasabuvir, 250 mg BID
- RBV: 1000-1200 mg daily according to body weight (<75 kg and ≥75kg, respectively)

TURQUOISE-II: Eligibility Criteria

- Treatment-naïve and pegIFN/RBV-experienced genotype 1 HCV infected patients, with no prior therapy with direct acting antiviral agents
- Compensated (Child-Pugh A) cirrhosis at screening
- Cirrhosis documented using liver biopsy, or FibroScan (≥14.6 kPa) within 6 months of or during screening
- Platelet count ≥60,000 cells/mL
- Serum albumin ≥2.8 g/dL
- Total bilirubin <3 mg/dL
- INR ≤2.3
- AFP ≤100 ng/mL
- Patients with radiographic ascites and patients with varices were allowed

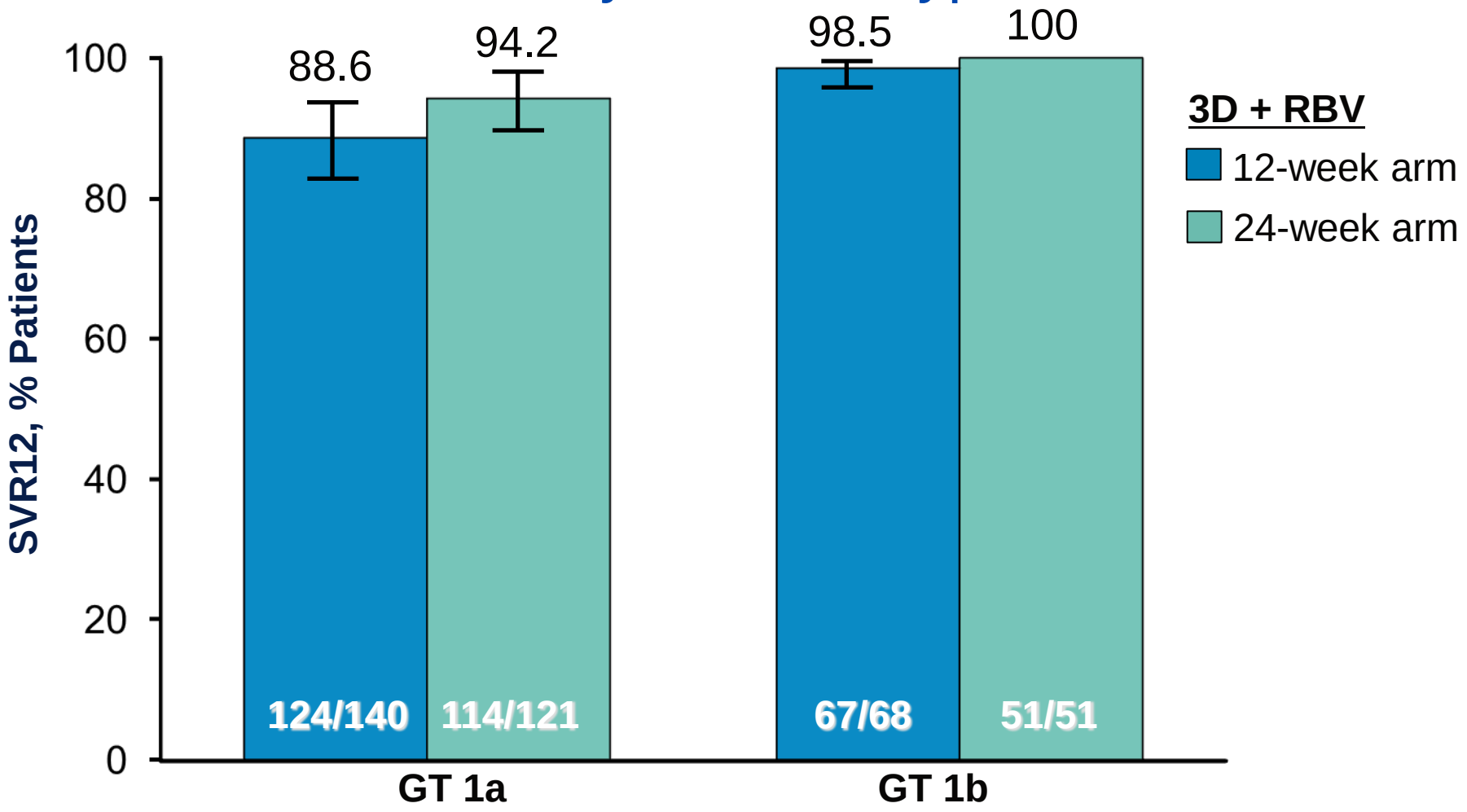
Poordad, NEJM 2014

TURQUOISE-II Results: ITT SVR12 Rates of 92% to 96%



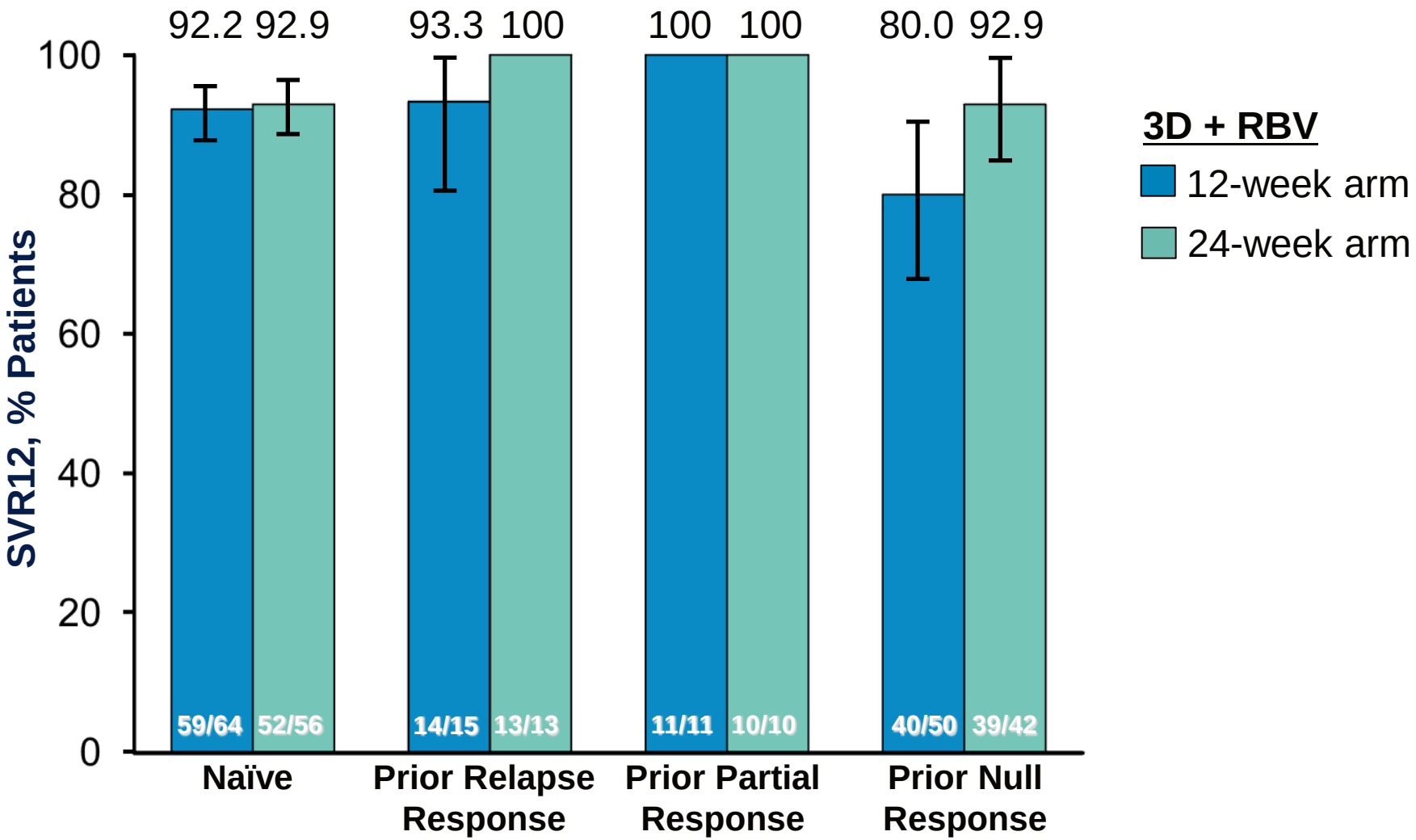
Poordad, NEJM 2014

TURQUOISE-II Results: ITT SVR12 Rates by HCV Subtype



Poordad, NEJM 2014

TURQUOISE-II Results: ITT SVR12 Rates by Prior Treatment Response in HCV **Subtype 1a**



Poordad, NEJM 2014

Conclusions G1 Phase 3 Program 3D regimen

- Treatment with PI + NS5A + NNI + RBV
- Treatment-naïve & Treatment experienced non-cirrhotic
  - Very effective 12 week regimen – 96% SVR
  - Very well tolerated – compared to placebo
  - Similar G1a and G1b
  - 1 breakthrough, infrequent relapse
  - Cirrhosis
  - Largest cirrhotic trial
  - Highly effective
  - 24 weeks necessary for G1a null responders, 12 adequate for everyone else
  - Safe in cirrhosis

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Treatment Recommendations

Genotype 1 (and 4/5/6) Interferon free

- SOF/LDV for12 weeks (8 for naïve with <6M IU)
- Paritaprevir/r/Ombitasvir, Dasabuvir, and Ribavirin for 12 weeks
  - RBV not needed for 1b (except in cirrhosis)
  - Treatment for 24 weeks in cirrhosis
- SOF/SMV for 12 weeks (24 for cirrhotics/NR)
  - Based on COSMOS data, confirmed by recent TARGET observational data
  - SVR 85-90%

Genotype 2

- SOF/RBV for 12 weeks
  - Expect SVR 90%+
  - May get lower rate in cirrhotics
  - Extend to 16 weeks if slow on treatment response

Genotype 3

- SOF/RBV for 24 weeks
  - Expect SVR 90%+
  - May get lower rate in cirrhotics
- SOF/PEG/RBV for 12 weeks may be optimal until we have new agents, particularly in cirrhosis

Take Home points

- Screen pts born between 1945-65 (without cause) HIV positive patients respond very well
- Refer those positive for treatment: IFN is dead!
- Our regimens are DDA, all oral, well tolerated
- HCV infection is treatable and curable in most patients

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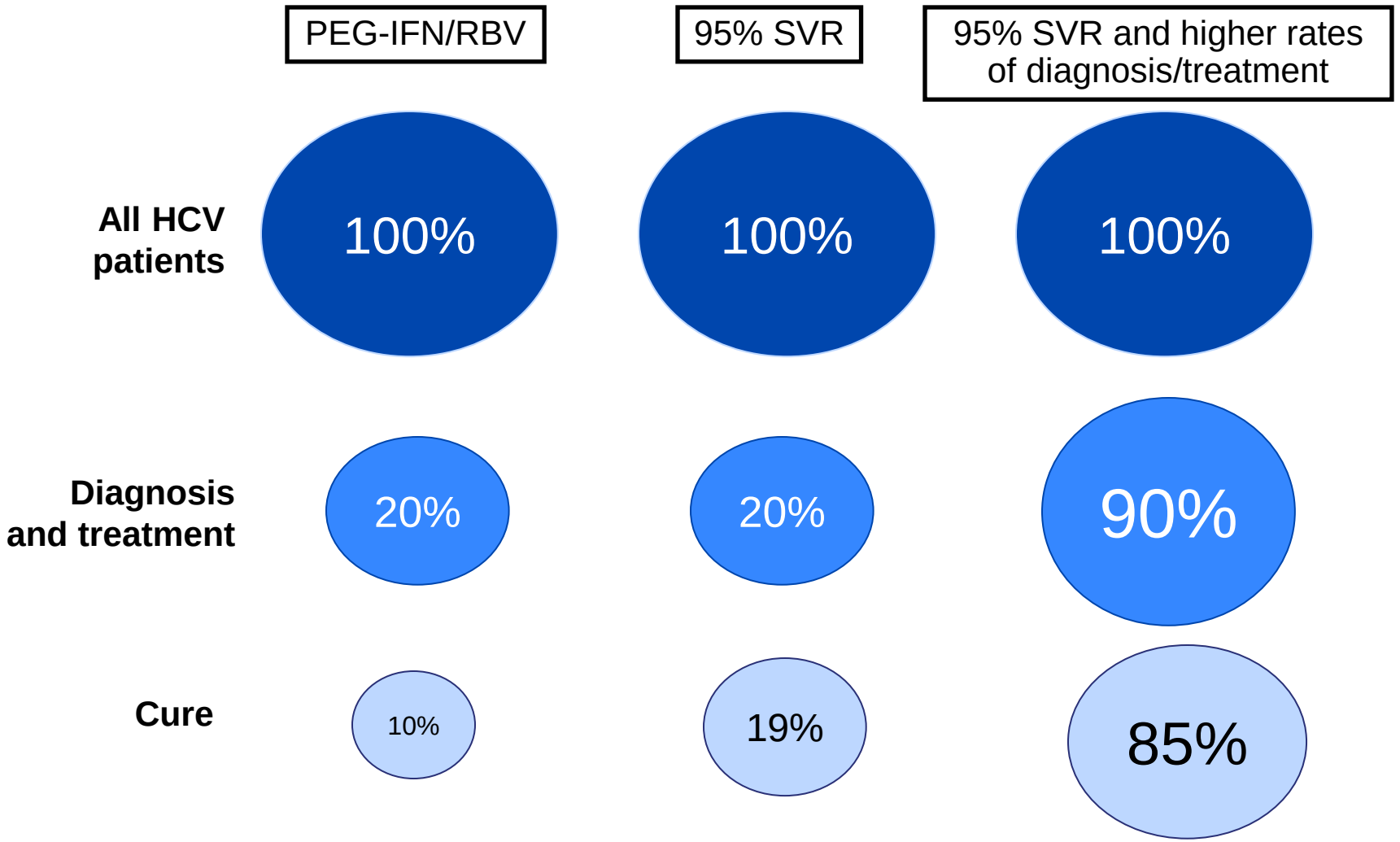
Highly Efficacious Treatments Are Not Enough

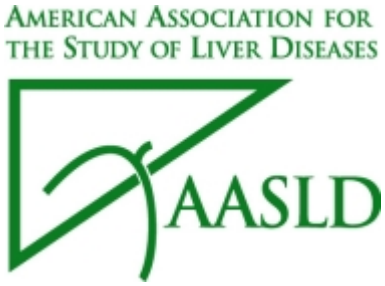


What the future will look like

- Treatment will be shorter
- Possibility for PCP's to get engaged
- One approach for all genotypes may be a reality
- Not many "special" populations
  - Transplant
  - HIV
  - Renal disease
  - Children

http://www.hcvguidelines.org/

Recommendations for Testing, Managing, and Treating Hepatitis C



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Where do we go from here?

- We now have well tolerated, all oral treatment for all genotypes
  - Data is not very complete for G4,5,6
  - Genotype 3 data is very disappointing
  - New agents with broad genotypic range are coming
- Duration of care can still be improved
  - Shorter duration without relapse penalty
- Special need groups still need better definition:
  - Decompensated cirrhotics
  - Post-LT
  - Renal failure and kidney Tx
  - Prior DAA failures

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Genotype 3

Genotype 3

- Has proven difficult to treat
  - Challenge is greatest with high fibrosis
  - Present regimens are adequate with treatment naïve, low fibrosis TE patients
- The options for cirrhotic patients and non-responders hinge on two fronts:
  - GS 5816 + SOF +/- RBV (some data available)
  - ABT 493 + ABT 530
  - GRZ+EBV+SOF
- Protease inhibitors so far do not seem to help (ie SMV not helpful!)

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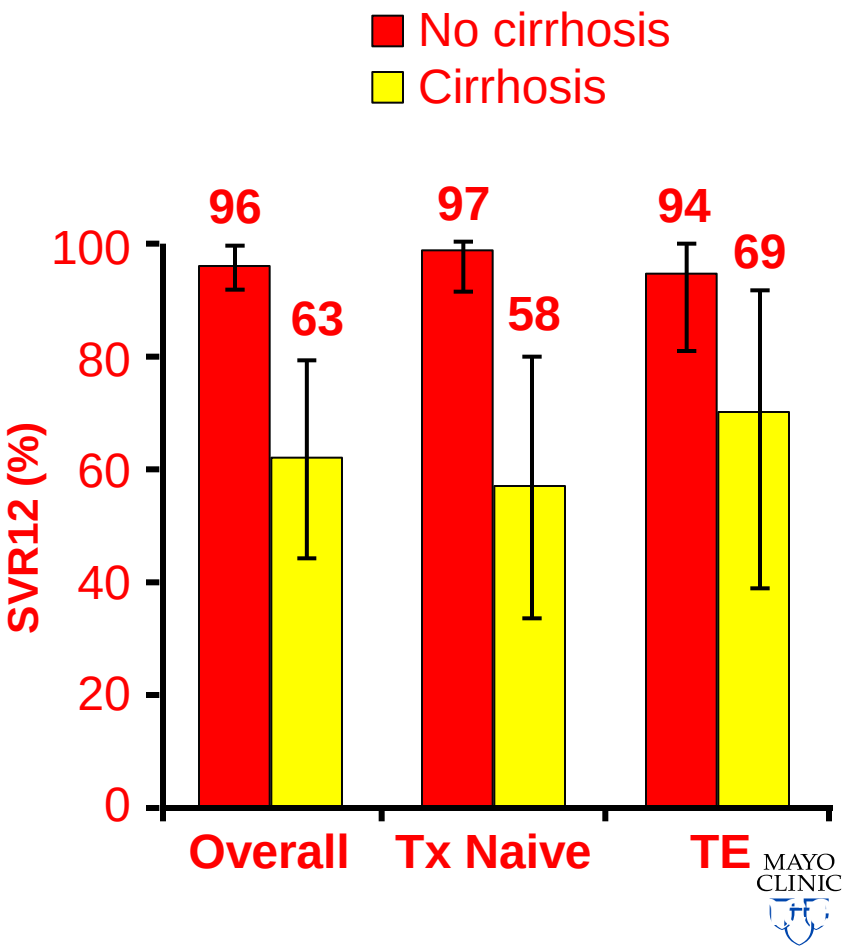
Treatment Options for GT3 HCV

Regimen	Duration	n (GT3)	Previous Treatment	Cirrhosis	SVR12, %
PegIFN/RBV + SOF[1]	12 wks	10	No	Yes	83
SOF/LDV + RBV[2]	12 wks	28	Yes	No	89
SOF/LDV + RBV[2]	12 wks	22	Yes	Yes	73
SOF/DCV ± RBV[3]	24 wks	18	No	No	89
GZR+EBR+SOF[4]	12wks	41	Yes	Yes	95

1. Lawitz E, et al. AASLD 2013. Abstract LB-4.
2. Gane EJ, et al. AASLD 2014. Abstract LB-11.
3. Sulkowski MS, et al. N Engl J Med. 2014;370:211-221.
4. Poordad et al EASL 2015

ALLY-3:
SOF + DCV x 12wk, Naive and TE GT3

- N = 152 pts with GT3 HCV
  - 66% tx naive, 34% TE
  - 19% of tx-naïve, 25% TE had cirrhosis
  - 61% of TE relapsed
  - 14% had NR
- 1 SAE, grade 3/4 lab abnormalities in 2% of pts



Nelson DR, et al. Hepatology 2015 (online first pub)

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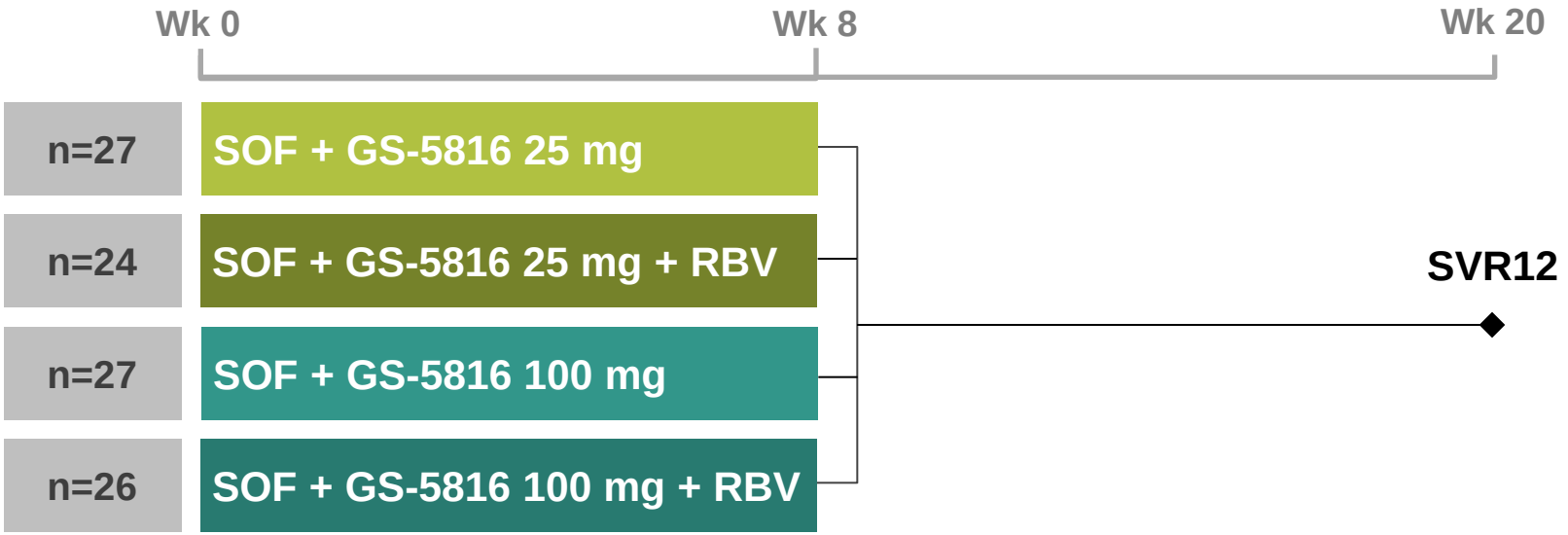
ELECTRON 2:
SOF With GS-5816 for 8 wks +/- RBV in HCV Genotype 3 Without Cirrhosis



- Open label
- Treatment-naïve patients with HCV GT 3 without cirrhosis
- GS-5816 is a pan-genotypic NS5A complex inhibitor

Gane, AASLD 2014 Parallel 12

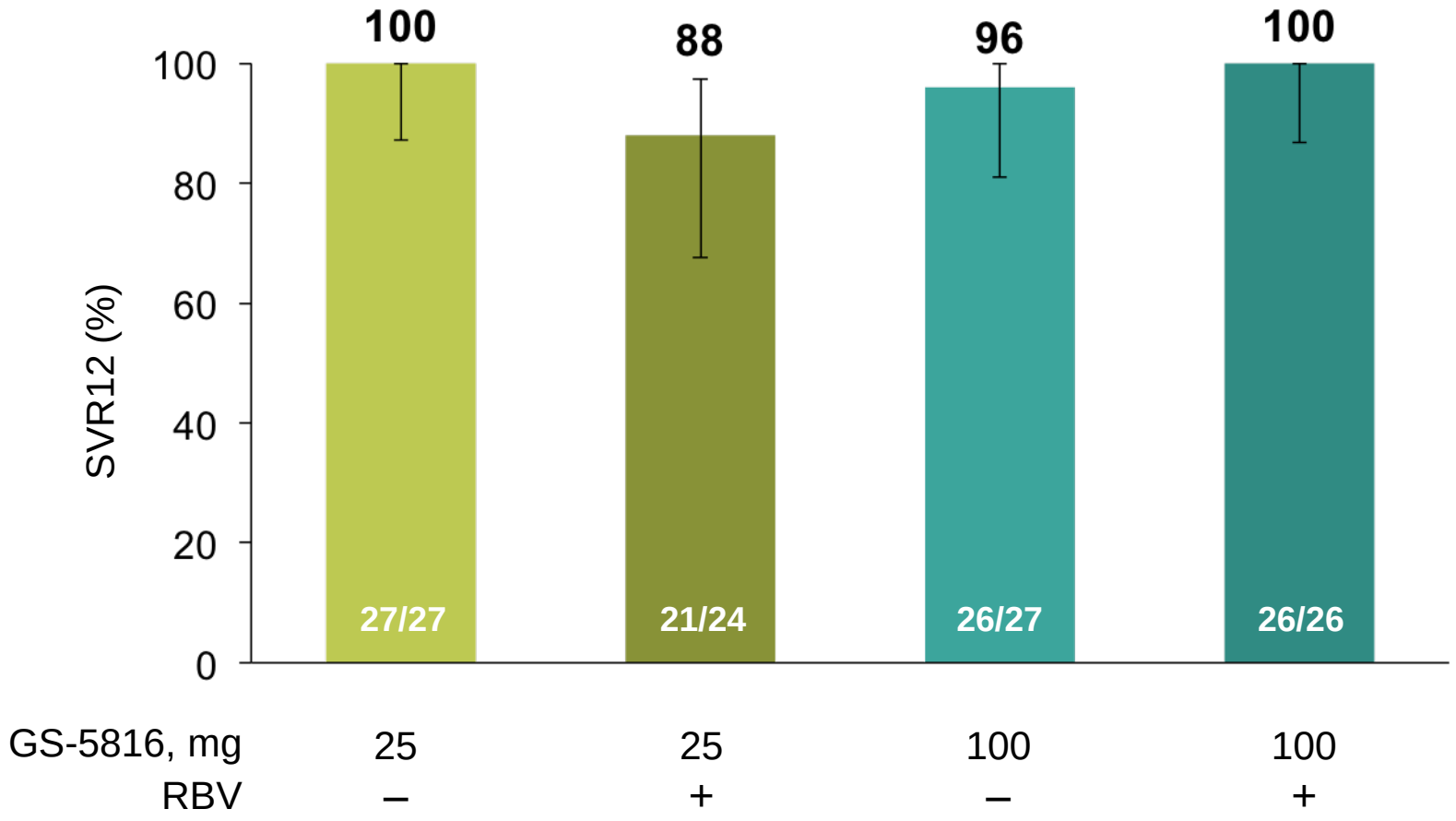
Results: Demographics

	SOF + GS-5816 25 mg n=27	SOF + GS-5816 25 mg + RBV n=24	SOF + GS-5816 100 mg n=27	SOF + GS-5816 100 mg + RBV n=26
Mean age, y (range)	48 (29−59)	47 (35−61)	50 (20−63)	47 (29−64)
Men, n (%)	17 (63)	18 (75)	17 (63)	11 (42)
White, n (%)	20 (74)	20 (83)	20 (74)	19 (73)
Mean BMI, kg/m^2 (range)	25.1 (19.5−31.4)	25.5 (18.2−37.9)	26.4 (19.3−31.1)	26.4 (18.4−36.2)
IL28B CC, n (%)	10 (37)	6 (25)	15 (56)	14 (54)
GT, n (%)				
3	2 (7)	1 (4)	0	0
3a	25 (93)	22 (92)	27 (100)	26 (100)
3k	0	1 (4)	0	0
Mean HCV RNA, $\log_{10}$ IU/mL (range)	5.9 (4.2−7.5)	6.3 (5.3−7.3)	6.0 (4.8−7.1)	6.2 (4.0−7.4)

Gane, AASLD 2014 Parallel 12

MAYO CLINIC

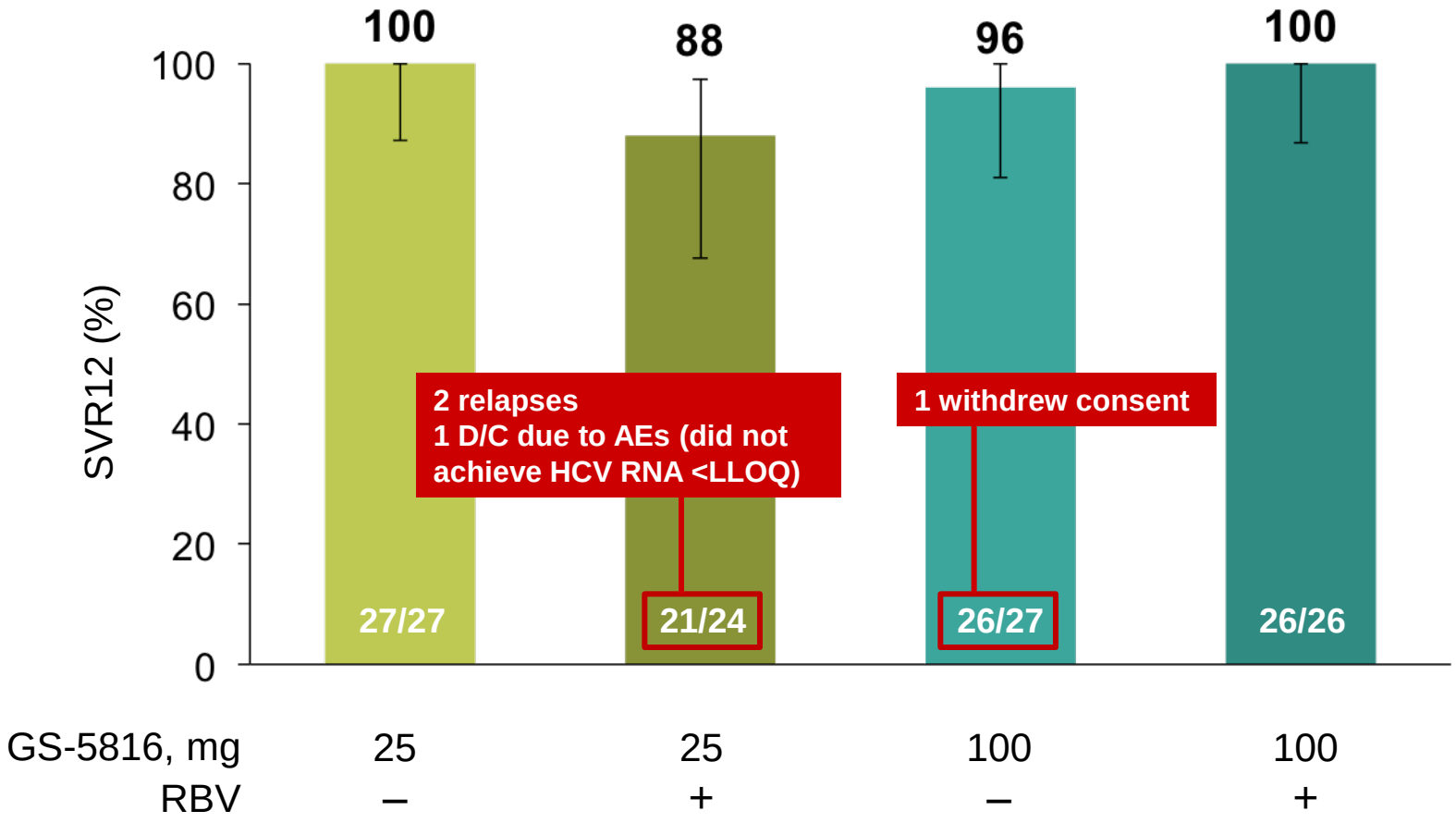
Results: SVR12



Gane, AASLD 2014 Parallel 12

MAYO CLINIC

Results: SVR12



Gane, AASLD 2014 Parallel 12

Gap #1

- We need stronger agents for most difficult to treat patients
- There remains a strong pipeline in all DAA families
- We need to overcome potential resistance associated variants (RAV) which will hamper results
  - NS5A resistance may be biggest challenge
  - Several papers coming highlight persistence of RAV

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- Is treatment for 12-24 wks truly necessary?

Treatment Duration

- With unprecedented cost, reduction of treatment duration may be a means to reduce expense
- Many regimens have been proposed at less than 12 week duration but relapses increase as duration decreases
- The introduction of more potent agents may bring the day of <6 weeks duration of Tx
  - Synergy trial
  - FOURward Study

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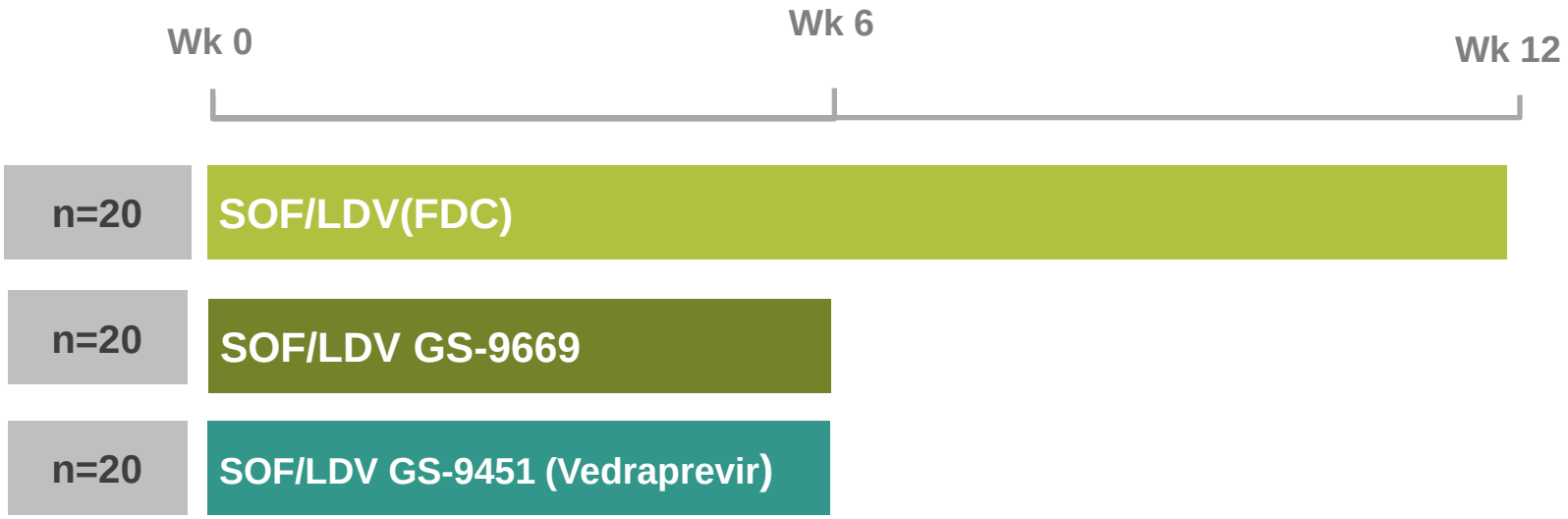
Synergy:
SOF/LDV+RBV for 12wks vs. SOF/LDV + GS9669 or GS 9451RBV in HCV Genotype 1 patients

- Open label
- Treatment-naïve patients with HCV GT 1a/1b without cirrhosis (except SOF/LDV for 12 w, where cirrhosis was allowed)
- Frequent kinetic studies were conducted

Kohli, *et al.* Lancet 2015 (online pub)

MAYO CLINIC

Synergy:
SOF/LDV+RBV for 12wks vs. SOF/LDV + GS9669 or GS 9451RBV in HCV Genotype 1 patients



Kohli, *et al.* Lancet 2015 (online pub)

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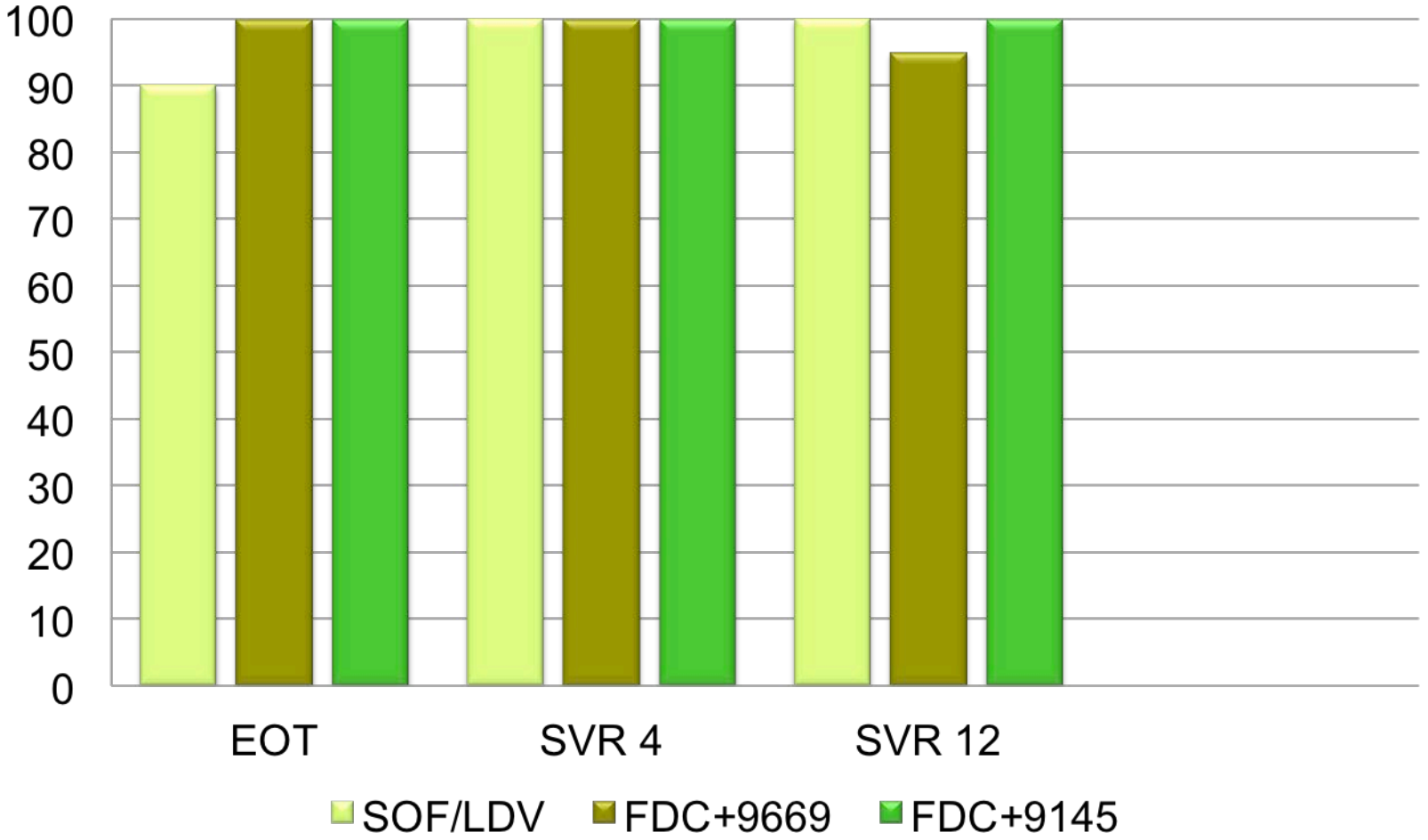
Synergy: Viral response



Kohli, *et al.* Lancet 2015 (online pub)

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FOURward Study NCT02175966

- This clinical trial will aim to enroll patients into 2 arms:
  - Sofosbuvir, daclatasvir, asunaprevir and beclabuvir for 4 weeks vs 6 weeks
  - There will be 2 rescue arms chosen by investigators containing PEG-IFN/RBV and SOF
- Primary efficacy will be proportion of patients who achieve SVR, attention to be paid to relapsers and factors for relapse

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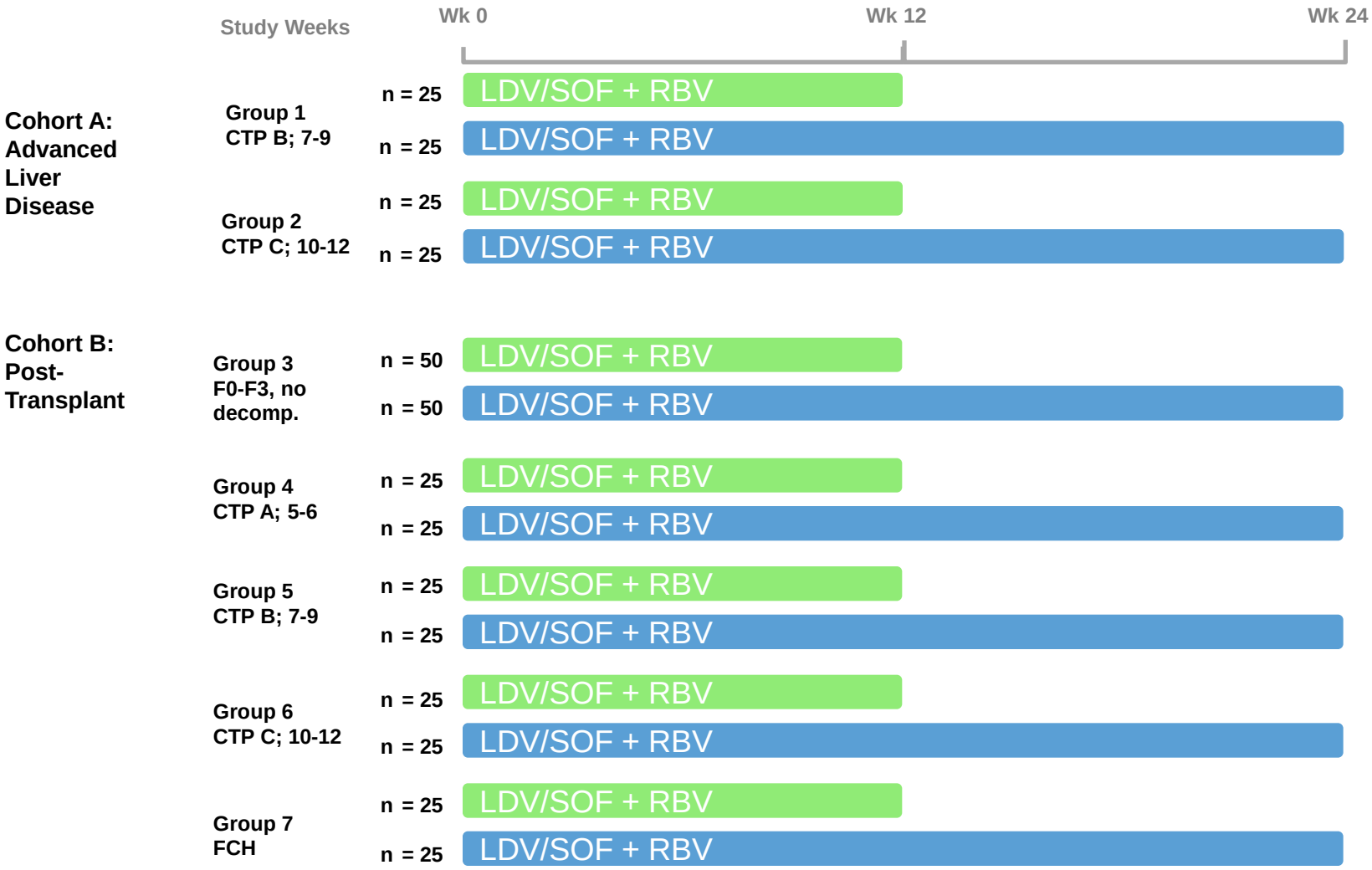
Gap #2

- We need shorter duration regimens that can be simple to administer and will reach larger segments of the population
- Additionally greater numbers of treaters can be involved who could in turn reach segments of the population which may be a high societal risk: incarcerated, IVDA

- What about special populations?
  - HIV?
  - African American?
  - Compensated cirrhosis?
- Who do we have to consider?
  - Decompensated Liver disease
  - Post-LT patients
  - ESRD/Kidney transplatation

LDV/SOF + RBV for Treatment of HCV in Patients with Decompensated Cirrhosis or Post-Transplant Recurrence

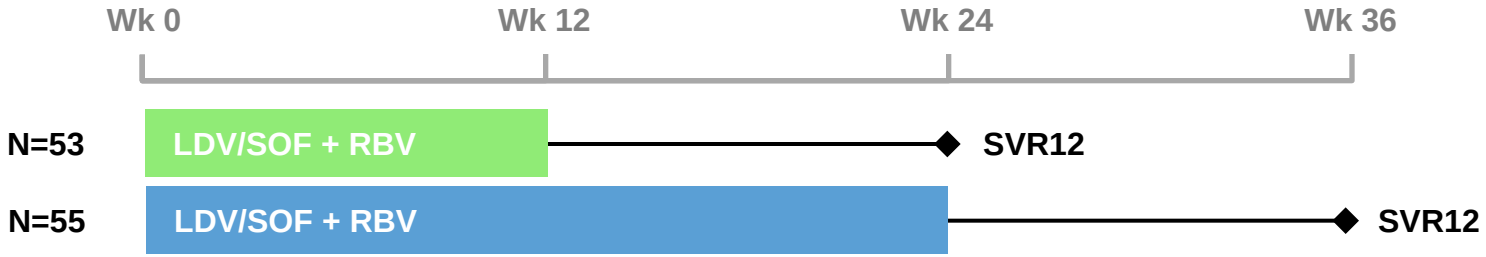


All arms continue with 5 years of long-term follow-up for clinical outcomes

Clinicaltrials.gov NCT01938430

LDV/SOF + RBV for HCV Patients with Decompensated Cirrhosis

Prospective, multicenter study of 12 or 24 weeks of LDV/SOF + RBV in TN and TE HCV GT 1 and 4 patients with CTP B (N=59) or CTP C (N=49) clinically decompensated cirrhosis

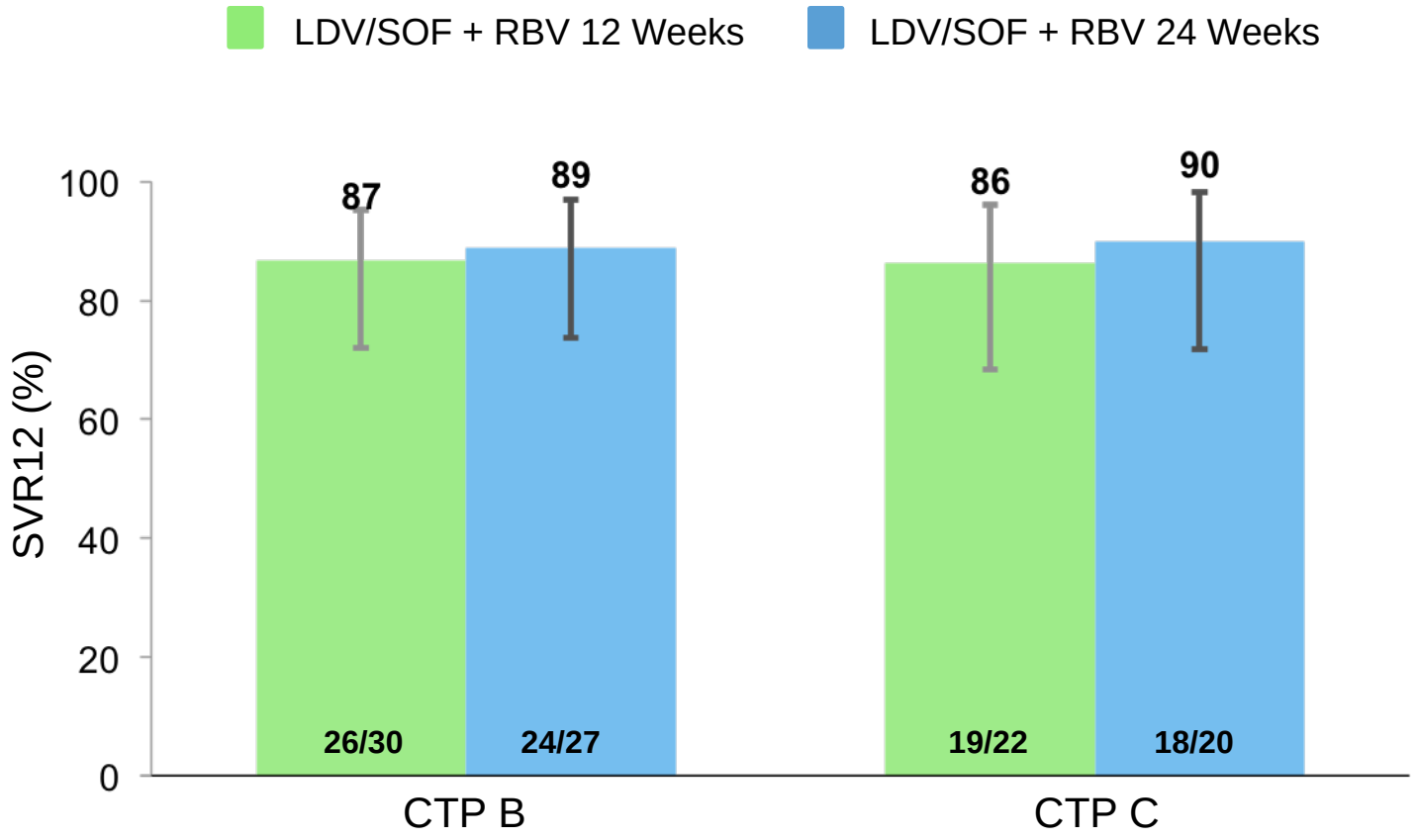


- 108 patients randomized 1:1 to 12 or 24 weeks of treatment
- Stratified by CTP class B [7-9] or C [score 10–12]*
- Broad inclusion criteria:
  - No history of major organ transplant, including liver
  - No hepatocellular carcinoma (HCC)
  - Total bilirubin ≤10 mg/dL, Hemoglobin ≥ 10 g/dL
  - CrCl≥ 40 mL/min, Platelets > 30,000
- RBV dosing: dose escalation, 600–1200 mg/d

Flamm, AASLD, 2014, Oral #239

*Patients with CTP scores 13-15 were excluded

Results: SVR12

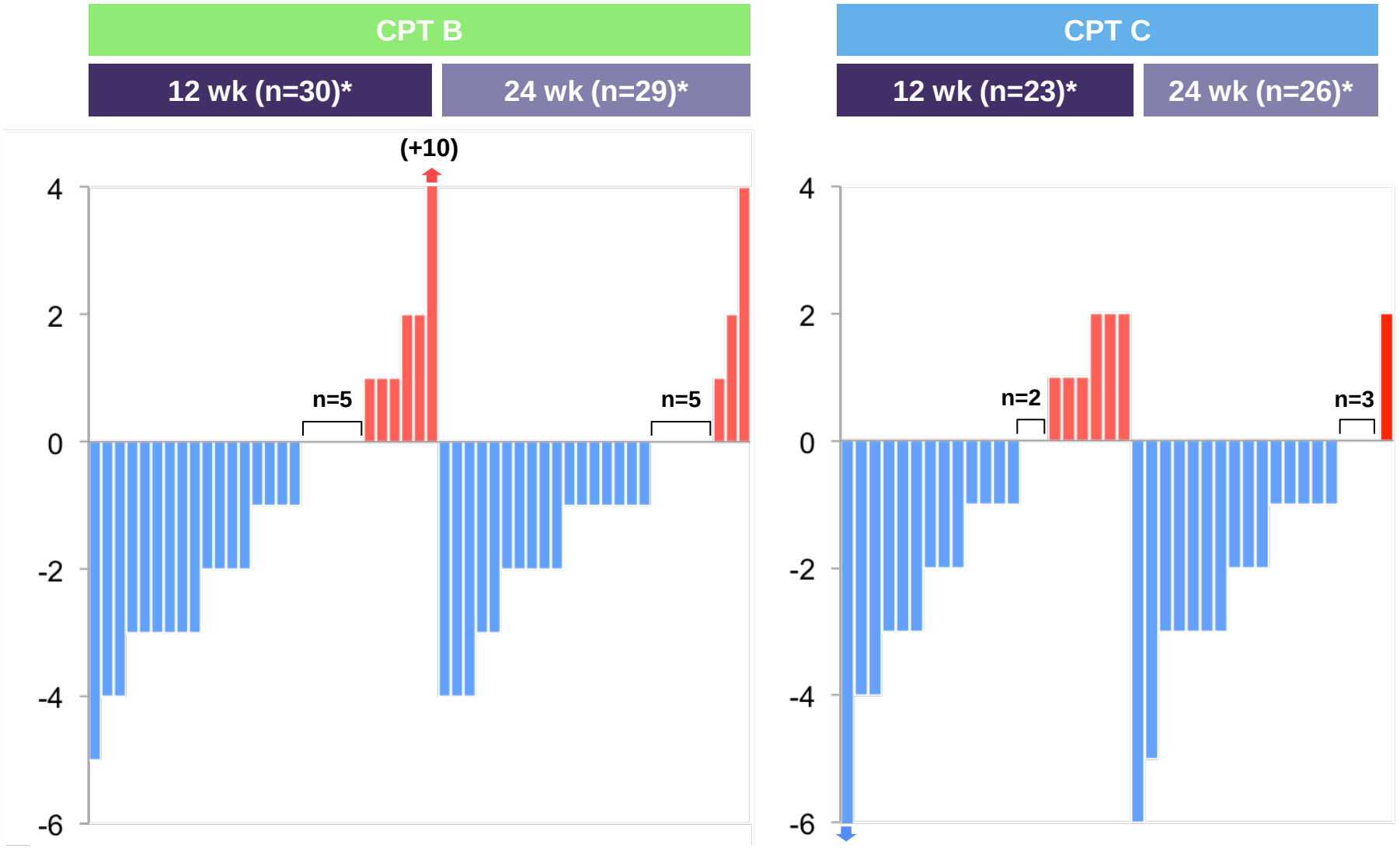


SVR rates were similar with 12 or 24 weeks of LDV/SOF + RBV

Error bars represent 90% confidence intervals.

Flamm, AASLD, 2014, Oral #239

Change From Baseline to Follow-Up Week 4



*Missing FU-4: n=2 CPT B 12 wk; n=4 CPT B 24 wk; n=2 CPT C 12 wk; n=7 CPT C 24 wk.

Flamm, AASLD, 2014, Oral #239

Results: Overall Safety Summary

Patients, n (%)	CTP B		CTP C	
	12 Weeks n=30	24 Weeks n=29	12 Weeks n=23	24 Weeks n=26
Any AE	29 (97)	27 (93)	23 (100)	26 (100)
Grade 3/4 AE	2 (7)	8 (28)	6 (26)	11 (42)
SAEs	3 (10)	10 (34)	6 (26)	11 (42)
Tx Related SAEs	2 (7)	0	0	2 (8)
D/C due to AE	0	1 (3)	0	2 (8)
Death	1 (3)	2 (7)	2 (9)	1 (4)

- Related SAEs: Anemia (2), hepatic encephalopathy, peritoneal hemorrhage
- Early discontinuations: Sepsis, hepatic encephalopathy, peritoneal hemorrhage
- Deaths: septic shock (2), multi-organ failure and septic shock (2), oliguric renal failure, cardiac arrest
- Patients continue to be followed for 5 years for long-term outcomes

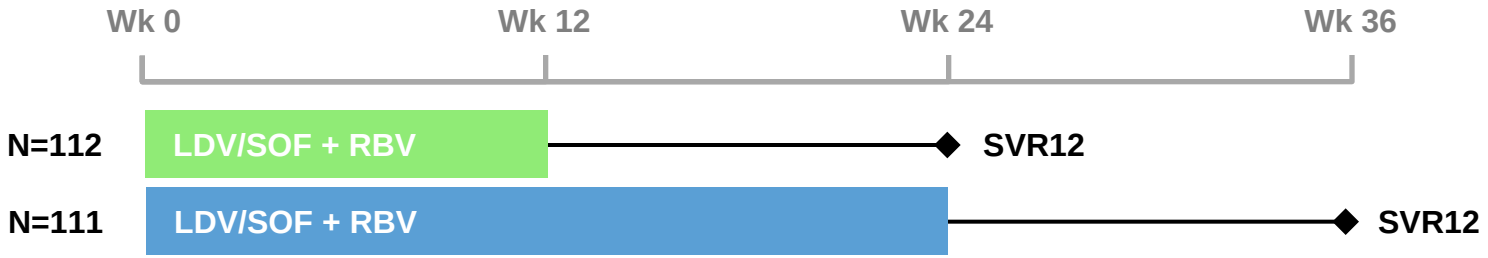
LDV/SOF + RBV for Treatment of HCV in Patients with **Decompensated Cirrhosis**

- LDV/SOF + RBV for 12 weeks resulted in a high SVR12 rate in HCV patients with GT 1 and 4 and advanced liver disease
  - Relapse rates were similar to relapse rates in patients with compensated cirrhosis
  - Extending treatment duration to 24 weeks did not increase the response rate
- Virologic response was associated with improvements in bilirubin, albumin, MELD and CPT scores in both CPT class B and C patients

Flamm, AASLD, 2014, Oral #239

LDV/SOF + RBV for Treatment of HCV in Patients with **Post-Transplant Recurrence**

Prospective, multicenter study in TN and TE HCV GT 1 and 4 patients, who were post-liver transplantation received 12 or 24 weeks of LDV/SOF + RBV



- 223 patients randomized 1:1 to 12 or 24 weeks of treatment
- ≥3 months from liver transplant
- No hepatocellular carcinoma
- Stratified at screening: F0–F3, CTP A, B, C
- Broad inclusion criteria:
  - Total bilirubin ≤10 mg/dL, Hemoglobin ≥ 10 g/dL
  - CrCl≥ 40 mL/min, Platelets > 30,000
- RBV dosing
  - F0–F3 and CTP A cirrhosis: weight-based (<75 kg = 1000 mg; ≥75 kg = 1200 mg)
  - CTP B and C cirrhosis: dose escalation, 600–1200 mg/d

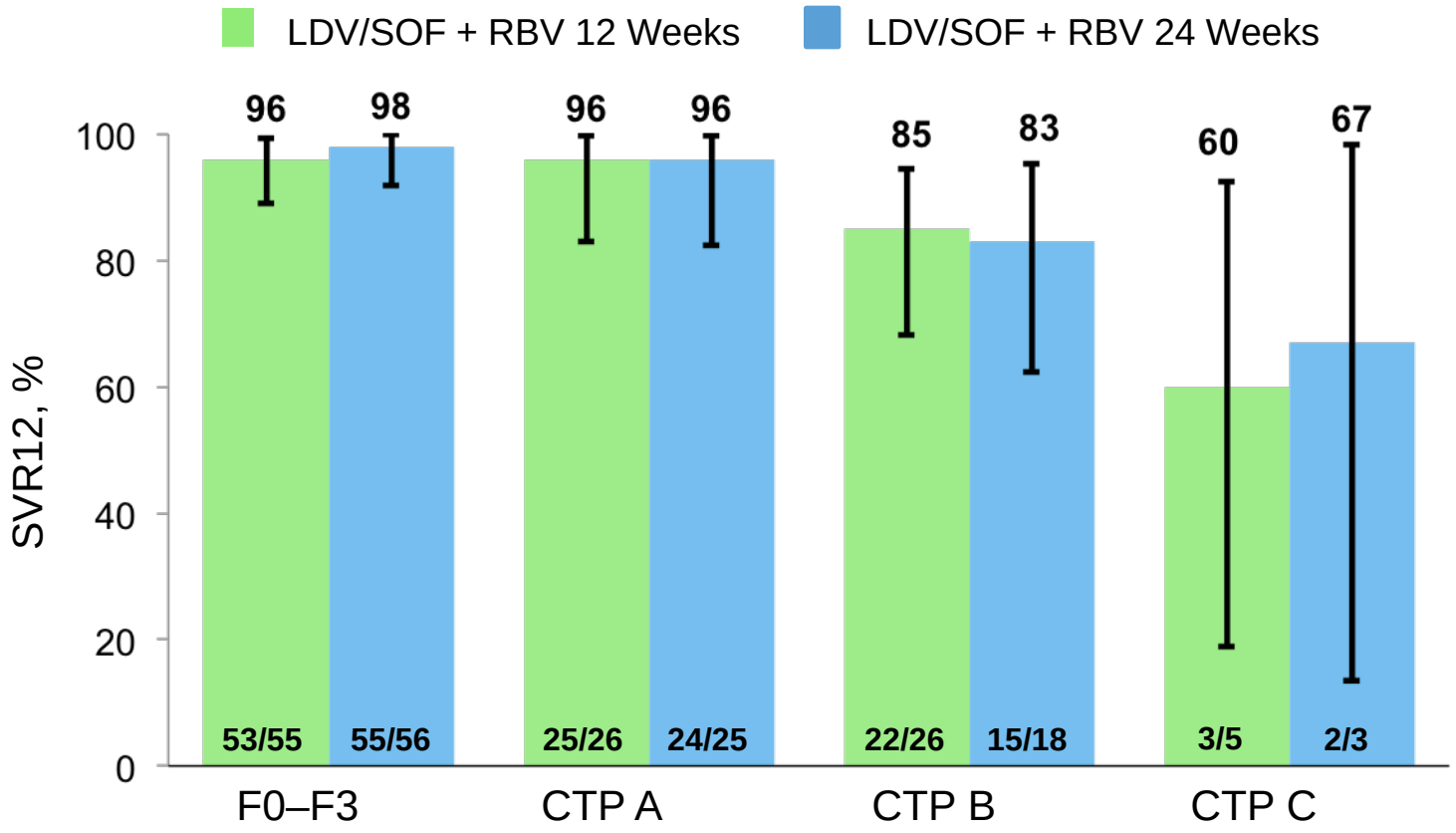
Reddy, AASLD, 2014, Oral #8

Demographics

	F0-F3 n=111	CTP A n=51	CTP B n=52	CTP C n=9
Median age, y (range)	59 (26-72)	60 (21-81)	61 (37-72)	60 (57-66)
Male, n (%)	91 (82)	41 (80)	45 (87)	9 (100)
White, n (%)	99 (89)	41 (80)	45 (87)	8 (89)
Median HCV RNA, $\log_{10}$ IU/mL (range)	6.6 (2.4-7.8)	6.6 (4.6-7.6)	6.4 (4.4-7.2)	6.3 (5.8-6.8)
GT 1a, n (%)	80 (72)	34 (67)	38 (73)	7 (78)
IL28B non-CC, n (%)	90 (81)	43 (84)	44 (85)	6 (67)
Median years from OLTx (range)	2.9 (0.4-18.2)	8.1 (0.8-23.3)	5.6 (0.9-22.5)	5.2 (1.2-15.5)
Prior HCV treatment, n (%)	87 (78)	46 (90)	44 (85)	8 (89)
MELD (n, %)				
<10	N/A	28 (55)	13 (25)	1 (11)
10-15	N/A	20 (39)	33 (63)	5 (56)
16-20	N/A	3 (6)	4 (8)	2 (22)
21-25	N/A	0	2 (4)	1 (11)
Ascites, n (%)	2 (2)	2 (4)	40 (77)	9 (100)
Encephalopathy, n (%)	1 (1)	3 (6)	23 (44)	7 (78)

Reddy, AASLD, 2014, Oral #8

Results: SVR12



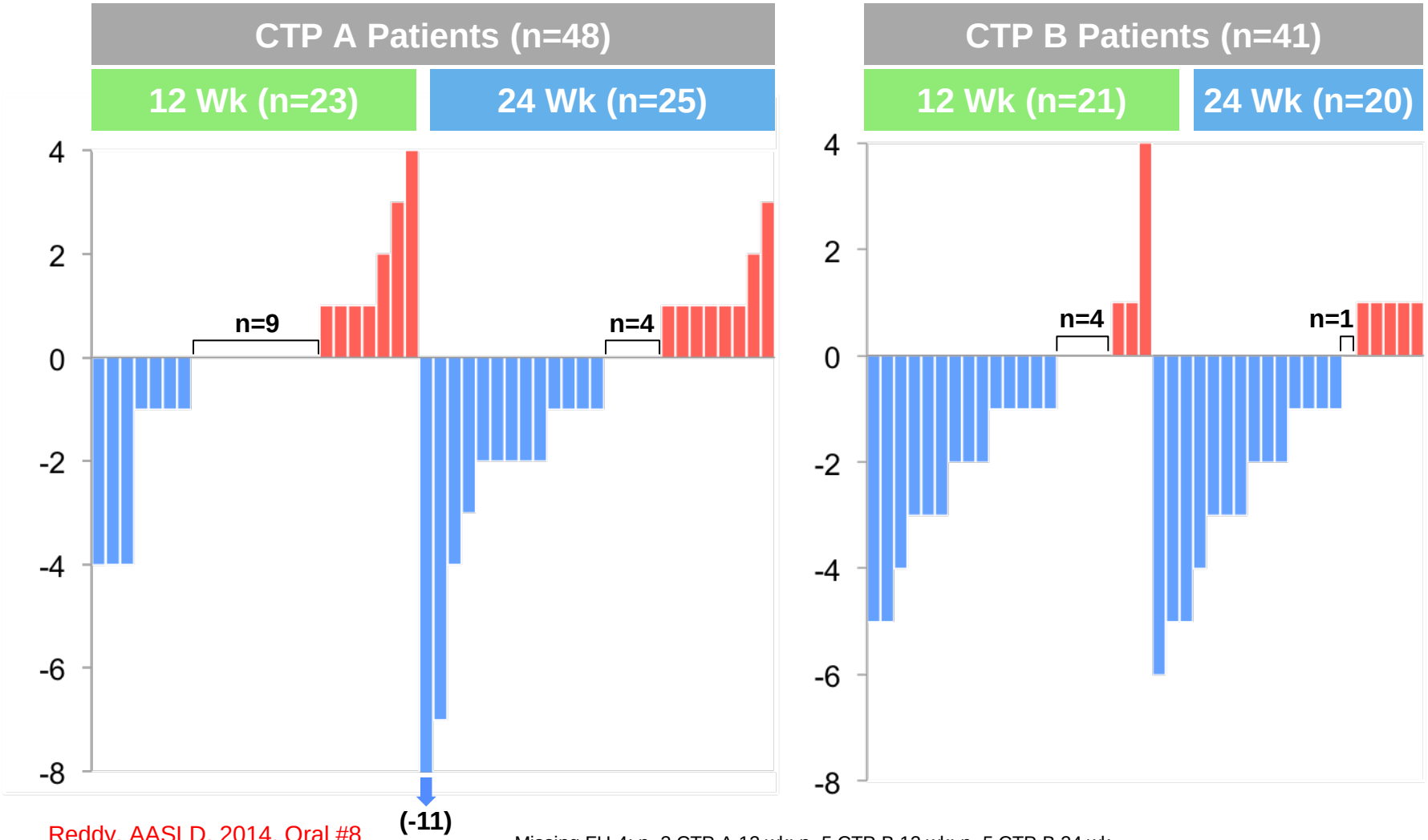
SVR rates were similar with 12 or 24 weeks of LDV/SOF + RBV

Error bars represent 2-sided 90% exact confidence intervals.

Reddy, AASLD, 2014, Oral #8

Change in MELD Score

Change from Baseline to Follow-Up Week 4



Reddy, AASLD, 2014, Oral #8

Missing FU-4: n=3 CTP A 12 wk; n=5 CTP B 12 wk; n=5 CTP B 24 wk

Results: Overall Safety Summary

Patients, n (%)	F0-F3		CTP A		CTP B		CTP C	
	12 Wk n=55	24 Wk n=56	12 Wk n=26	24 Wk n=25	12 Wk n=26	24 Wk n=26	12 Wk n=5	24 Wk n=4
AEs	55 (100)	55 (98)	25 (96)	24 (96)	25 (96)	26 (100)	5 (100)	4 (100)
Grade 3–4 AEs	15 (27)	14 (25)	4 (15)	7 (28)	6 (23)	9 (35)	1 (20)	1 (25)
Serious AEs	6 (11)	12 (21)	3 (12)	4 (16)	5 (19)	11 (42)	1 (20)	4 (100)
Serious and related AEs	2 (4)	1 (2)	2 (8)	2 (8)	0	1 (4)	0	0
Treatment DC due to AE	0	2 (4)	1 (4)	0	0	3 (12)	0	0
Treatment emergent death	0	0	1 (4)	0	1 (4)	2 (8)	0	0

- AEs leading to DC: shortness of breath, hemoperitoneum, thoracic aorta aneurysm dissection, seizure, elevated ALT/AST, dyspnea
- Treatment-emergent death: progressive multifocal leukoencephalitis, thoracic aorta aneurysm dissection, internal bleeding, complications of cirrhosis

Reddy, AASLD, 2014, Oral #8

LDV/SOF + RBV for Treatment of HCV in Patients with Post-Transplant Recurrence

- In HCV post LT, treatment with LDV/SOF+RBV for 12 or 24 weeks resulted in:
  - High rates of SVR12, irrespective of disease severity or duration of therapy (ie, 12 = 24 weeks)
  - Early post-treatment improvements in bilirubin and albumin
  - Decreases in MELD scores
- No on-treatment virologic failure
- LDV/SOF+RBV for 12 or 24 weeks in post LT pts was safe and well tolerated with low rates of treatment discontinuation due to AEs

Reddy, AASLD, 2014, Oral #8

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CORAL-I

Phase 2 study CORAL-I examined the safety and efficacy of open-label ABT-450/r/ombitasvir, dasabuvir, and RBV (3D + RBV) in adult liver transplant recipients with recurrent HCV GT1 infection and **mild to moderate** liver fibrosis

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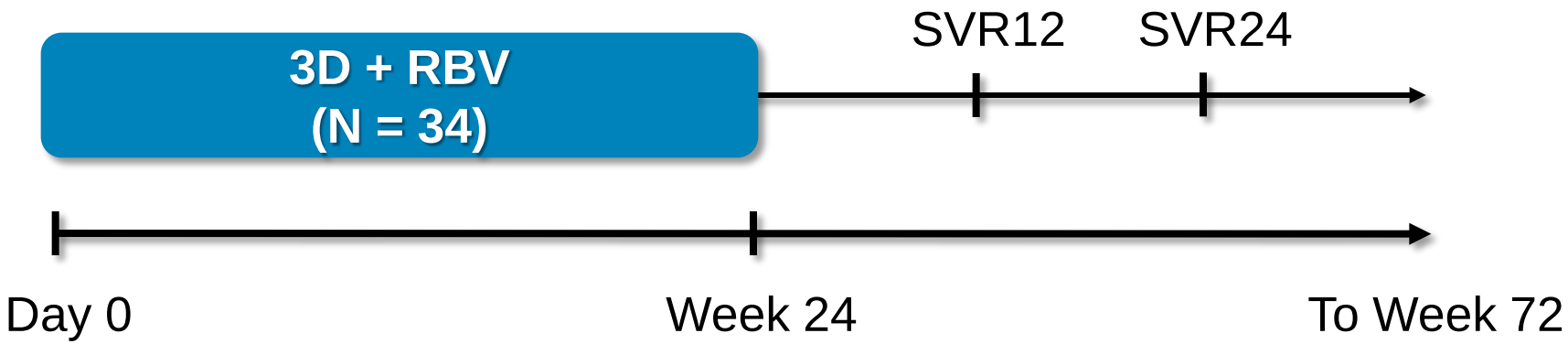
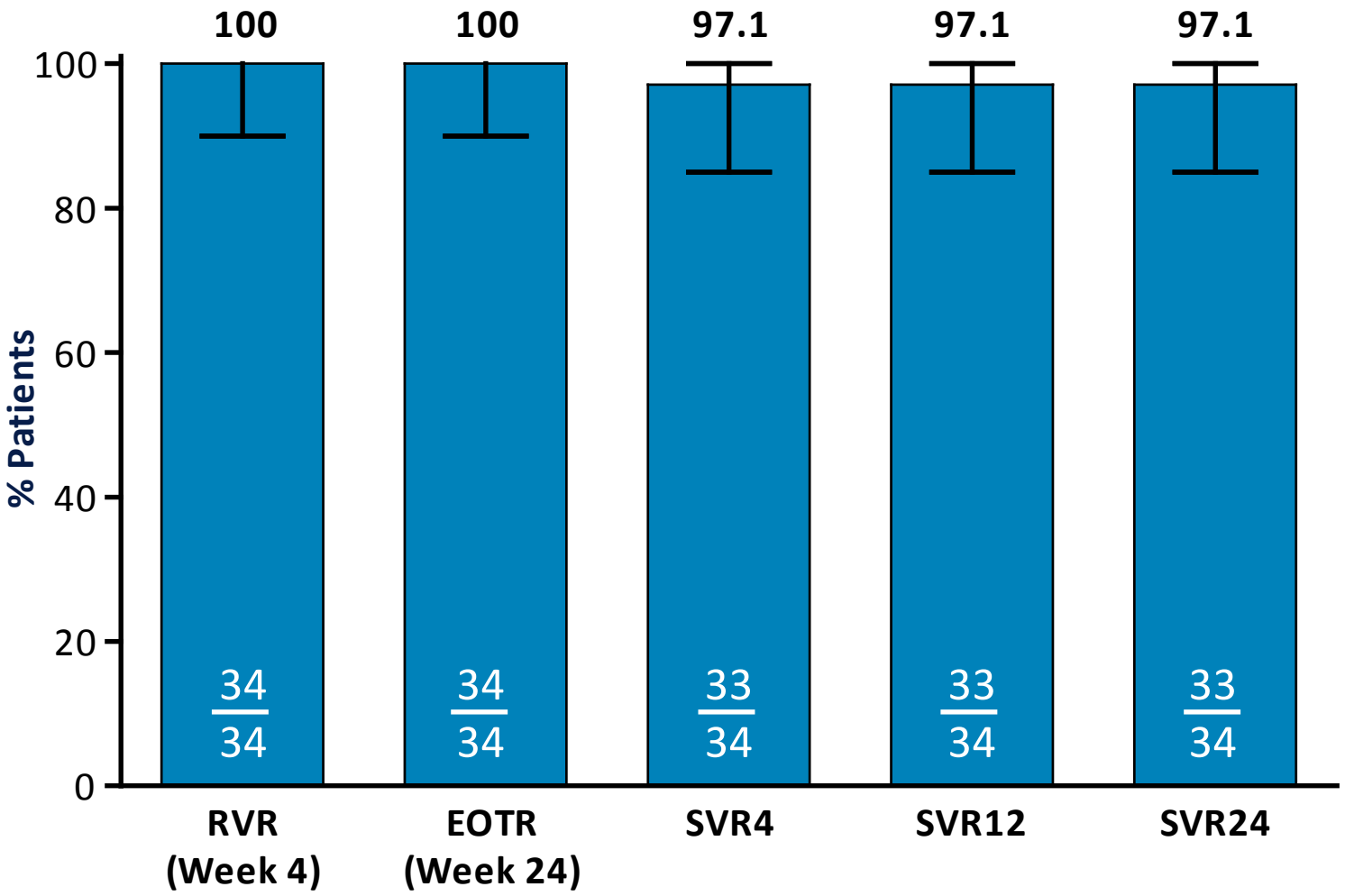
CORAL-I: Study Design



3D: ABT-450/r/ombitasvir, 150 mg/100 mg/25 mg QD; dasabuvir 250 mg BID

RBV dosing was managed at the discretion of the investigator and closely monitored per protocol

CORAL-I: Efficacy Results



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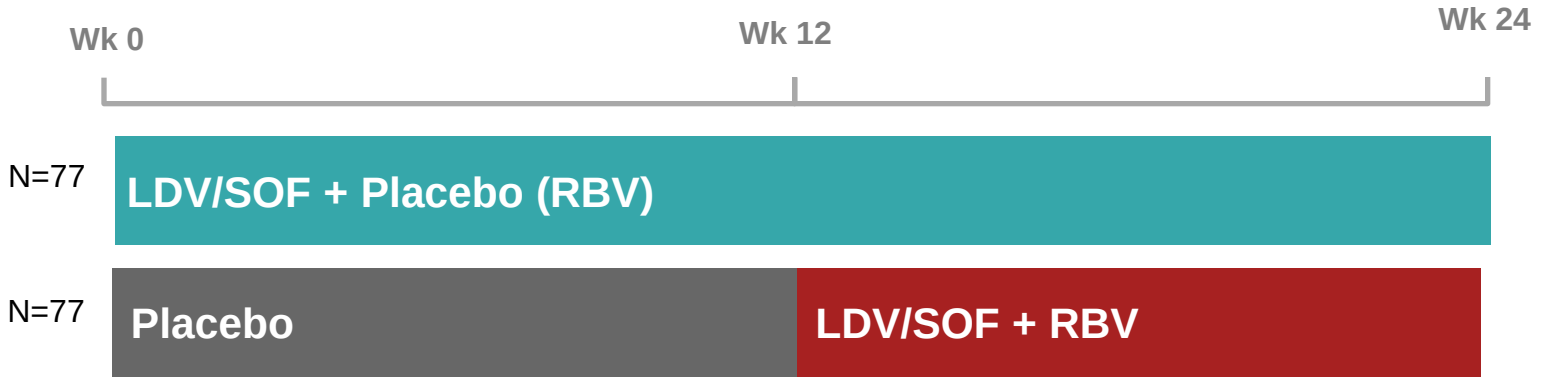
Prior Treatment Failures

LDV/SOF in Cirrhotic PI-Based Triple Therapy Failures



30% of patients were previously enrolled in the **CUPIC** cirrhotic study

- RBV dosing was weight-based

Randomization was stratified by:

HCV genotype

1a vs. 1b

Prior HCV therapy treatment response

Never achieved HCV RNA <LLOQ vs. Achieved HCV RNA <LLOQ

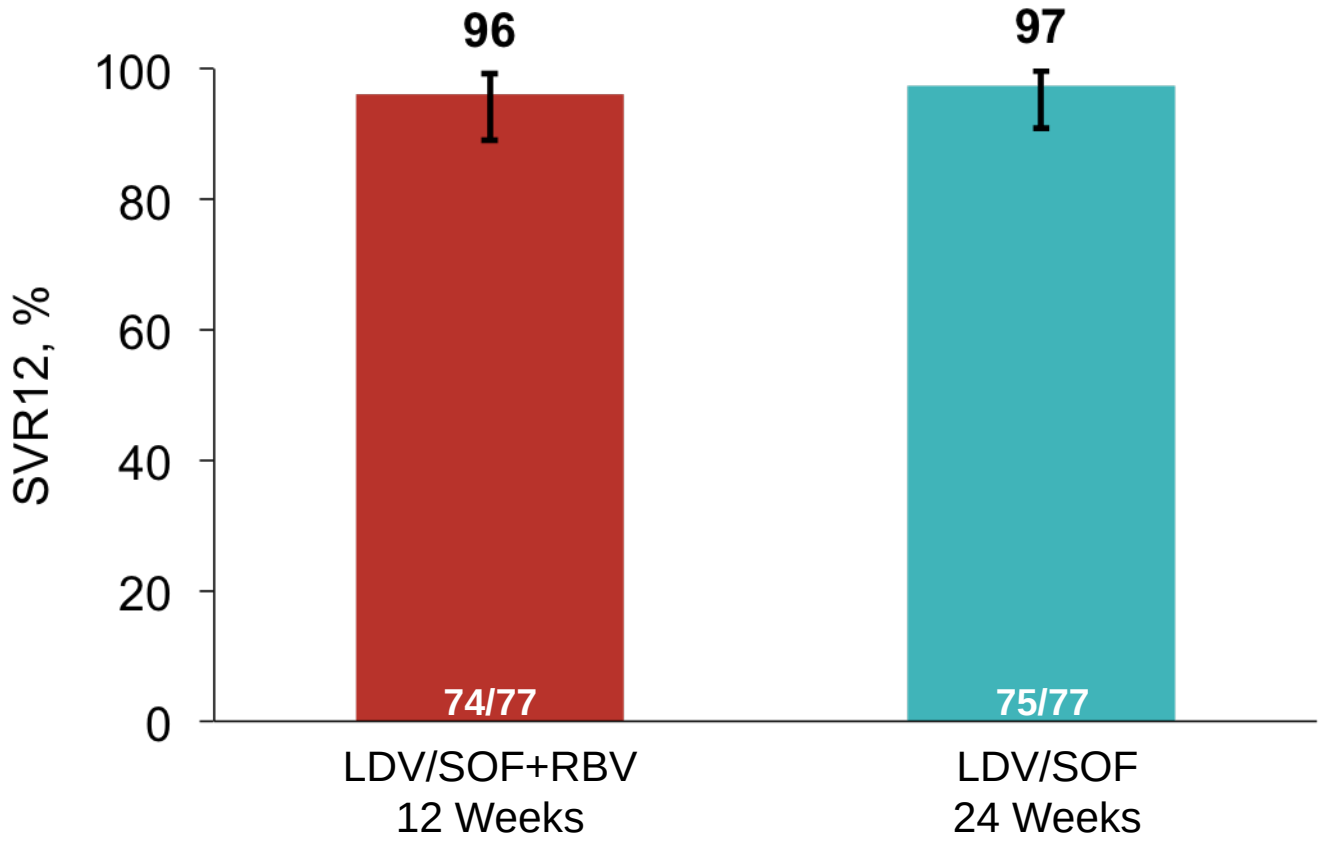
Cirrhosis was determined by:

Biopsy, Fibroscan >12.5 kPa, or FibroTest® score of >0.75 **AND**

APRI of >2

Bourliere, AASLD, 2014, Oral #LB-6

Siruius:
LDV/SOF in Treatment Experienced Cirrhotic Patients: SVR12

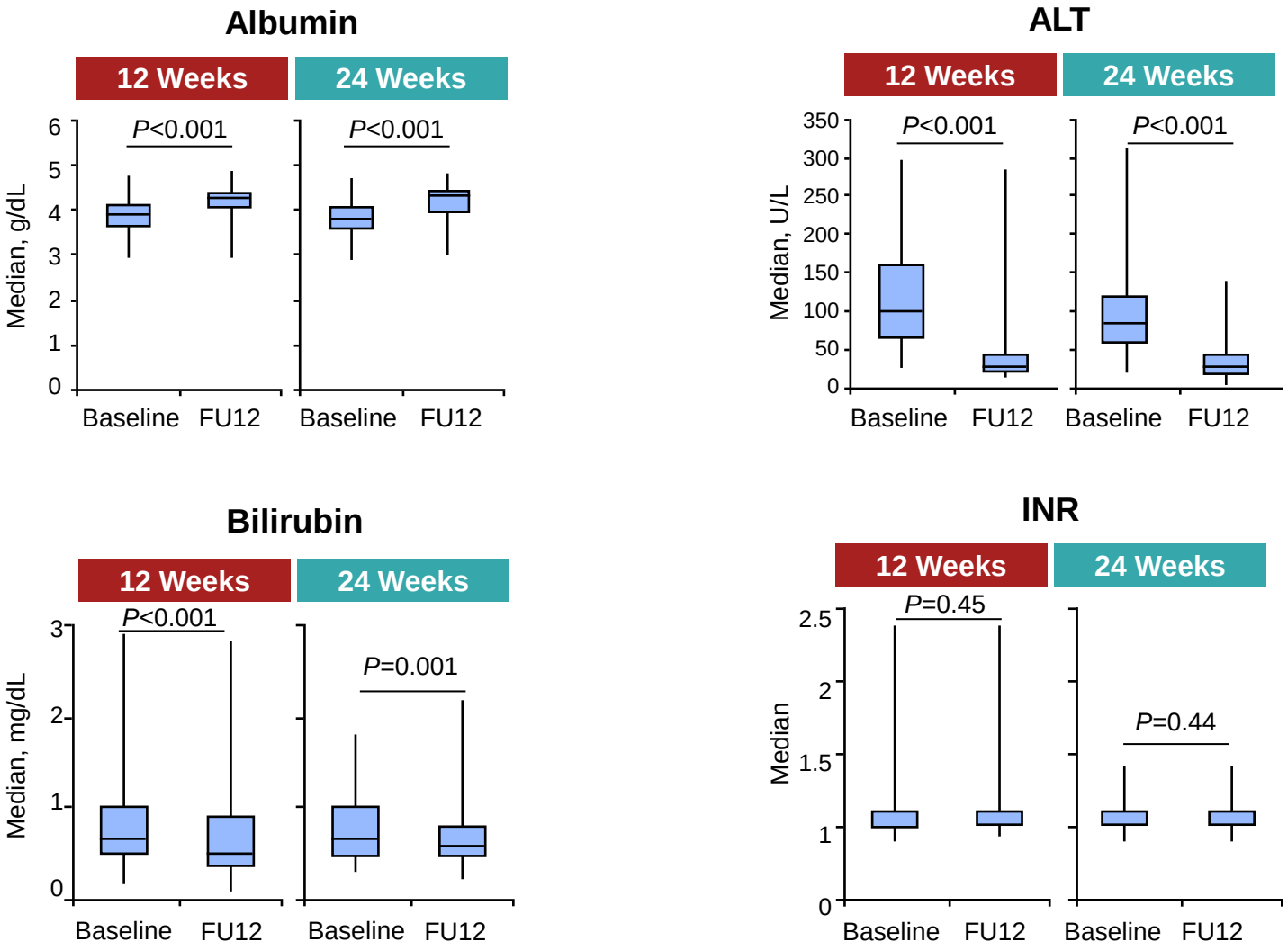


TE cirrhotics had a similar response to LDV/SOF+RBV for 12 weeks and LDV/SOF for 24 weeks

Error bars represent 95% confidence intervals.

Bourliere, AASLD, 2014, Oral #LB-6

Results: Change in Laboratory Parameters



Bourliere, AASLD, 2014, Oral #LB-6

Sirius: Conclusions

- 97% of prior PI-failure patients with cirrhosis achieved SVR12
  - Similar SVR12 rates after 12 weeks of LDV/SOF with RBV compared with 24 weeks of LDV/SOF
- LDV/SOF with and without RBV was safe and well tolerated
  - Only two AEs (headache and fatigue) occurred at a higher frequency with LDV/SOF compared with placebo
  - The majority of these AEs were mild to moderate in severity
- 12 weeks of LDV/SOF with RBV results in high SVR rates among treatment-experienced patients with cirrhosis who have failed a prior PI-based regimen

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Synergy Retreatment in SOF failure

- 14/17 SOF/RBV failures from NIH based study were treated with SOF/LDV (no RBV) for 12 wks
- Large proportion of advanced fibrosis, AA, CT and TT IL28B genotype were included
- SVR 12 was 100%
  - Despite low numbers, proof of concept for SOF in retreatment is valid
  - Concerns exist about re-treating SOF/SMV without RBV, thus conservative recommendations by AASLD/IDSA for SOF/LDV/RBV for 24 weeks

Osinusi *Ann Intern Med.* 2014

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Gap # 3

- Many populations, by virtue of the characteristics seen need to be treated with specific objectives in mind
  - Avoid decompensation
  - Monitor IS
  - Avoid toxicity due to renal disease

Questions & Discussion

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HCV/HIV Co-infection

Zelalem Temesgen MD FIDSA AAHIVS

Division of
INFECTIOUS DISEASES

Mayo Clinic Infectious Diseases Subspecialties Update
May 7-9, 2015

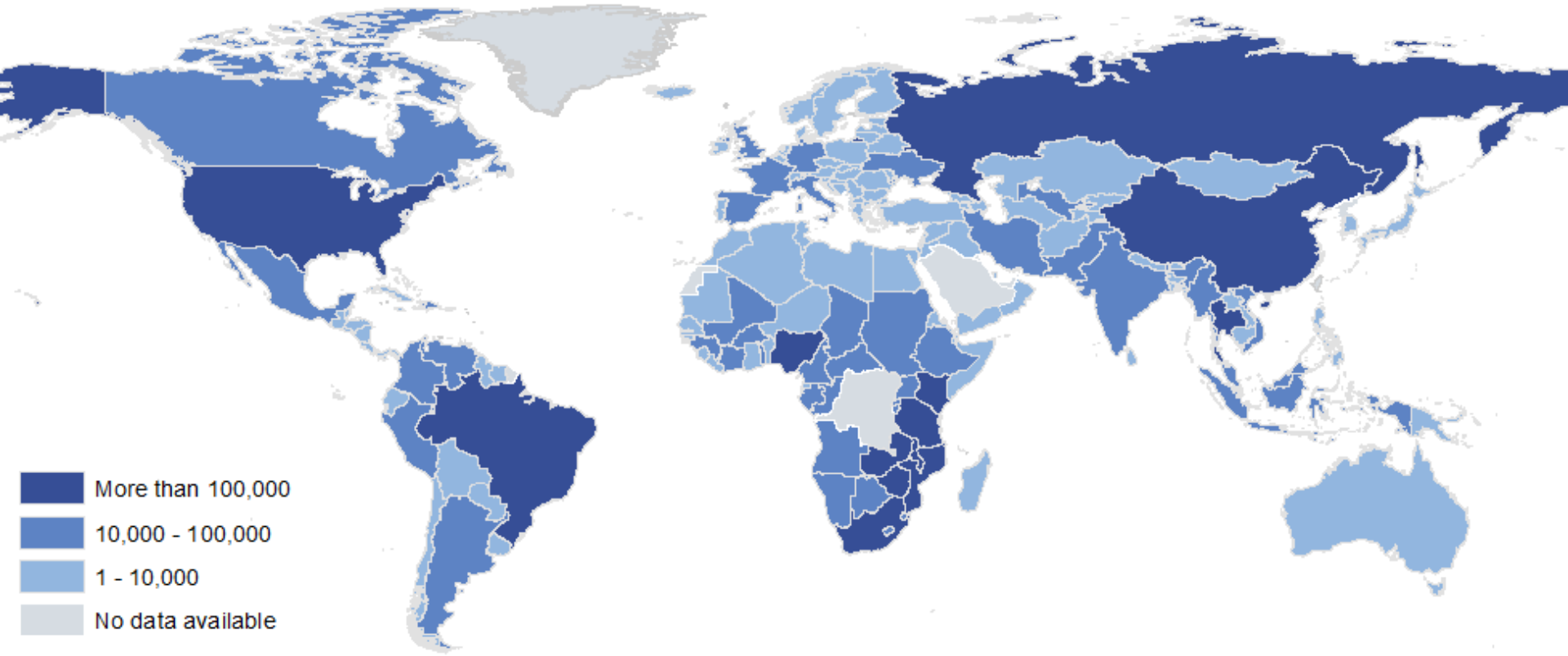
Outline

- Epidemiology
- Biology
- Natural history
- Diagnosis
- Treatment

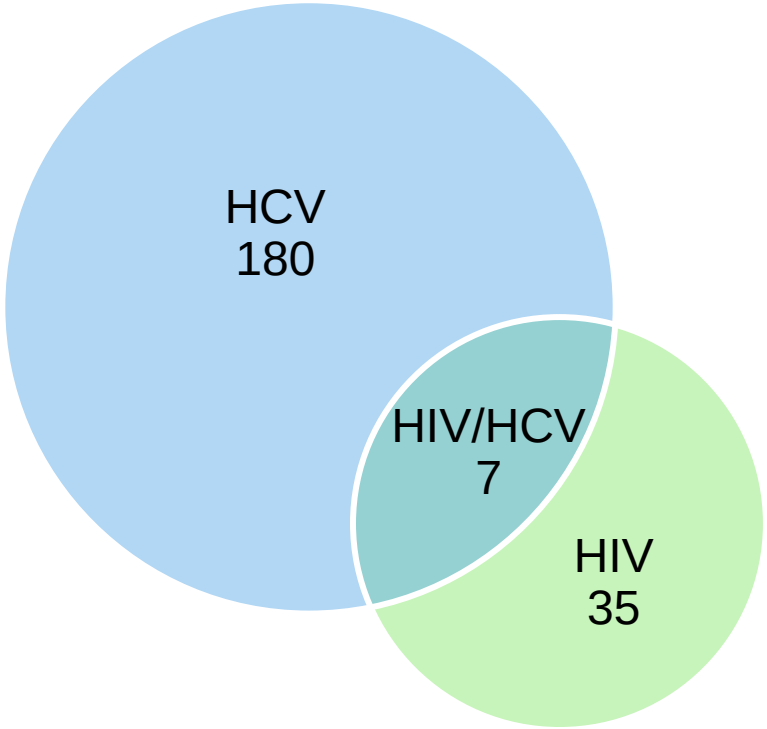
Epidemiology

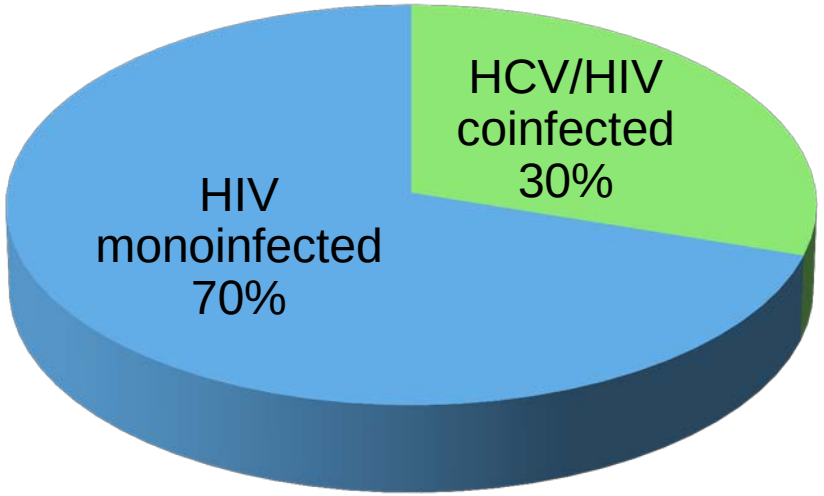
HIV and Hepatitis C:

Number of HIV+ Individuals With HCV Co-infection, by Country



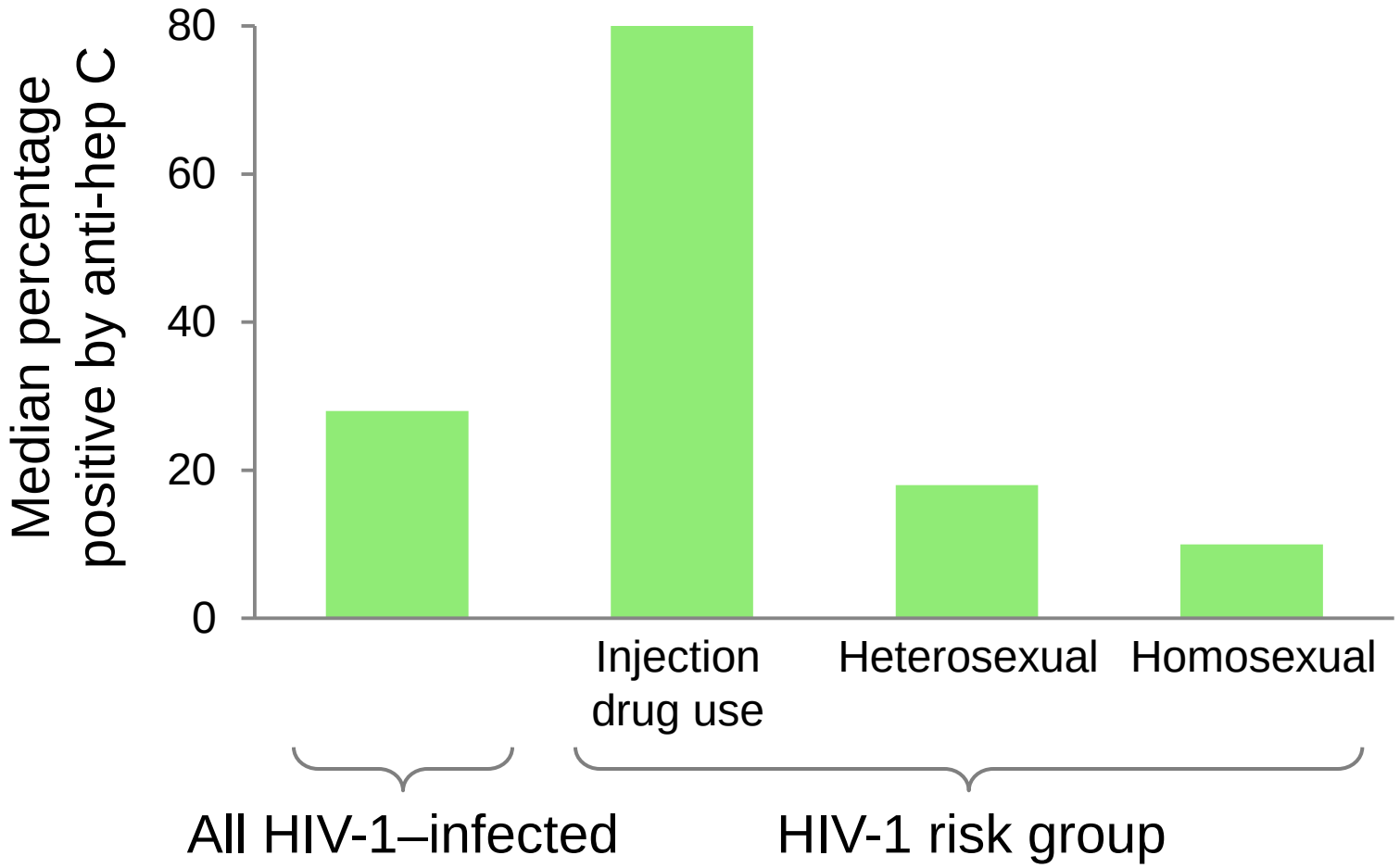
Prevalence of HIV/HCV Coinfection





[1] Fernandez-Montero JV, et al. *Best Pract Res Clin Gastroenterol.* 2012;26:517-530
[2] Armstrong GL, et al. *Ann Intern Med*. 2006;144:705-714
[3] Adapted from CDC. *MMWR*. 2011;60:1616-1623
[4] CDC Fact Sheet. HIV and Viral Hepatitis. Last modified: May 17, 2013 http://www.cdc.gov/hiv/pdf/library_factsheets_HIV_and_viral_Hepatitis.pdf. Accessed May 20, 2013
[5]Sulkowski M, et al. *Ann Intern Med.* 2003;138:197-207
[6]Thomas D. *Hepatology.* 2002;36:S201-S209

Estimated Prevalence of Hep C Coinfection in HIV-1–Infected Patients by HIV-1 Risk Group



Alter MJ: J Hepatol 44:S6, 2006

HCV Transmission: Serodiscordant Heterosexual Couples

		No.	Incidence (per year)
Piazza	Italy (1997)	499	1%
Kao	Taiwan (2000)	112	0.23%
Vandelli	Italy (2004)	776	0%
Tahan	Turkey (2005)	216	0%
Terrault	Unites States (2013)	500	0.07%

Piazza et al: Arch Intern Med 157:1537, 1997; Kao et al: J Gastroenterol Hepatol 15:391, 2000; Vandelli et al: Am J Gastroenterol 99:855, 2004; Tahan et al: Am J Gastroenterol 100:821, 2005; Terrault et al: Hepatology 57:881, 2013

Geographical Distribution of Acute HCV in HIV-positive MSM in Europe and the USA

A map of Northern Europe and USA showing cities where acute HCV cohorts have been reported

Emma C. Thomson et al: J Gen Virol 92:2227, 2011

HCV Transmission: HIV+ MSM

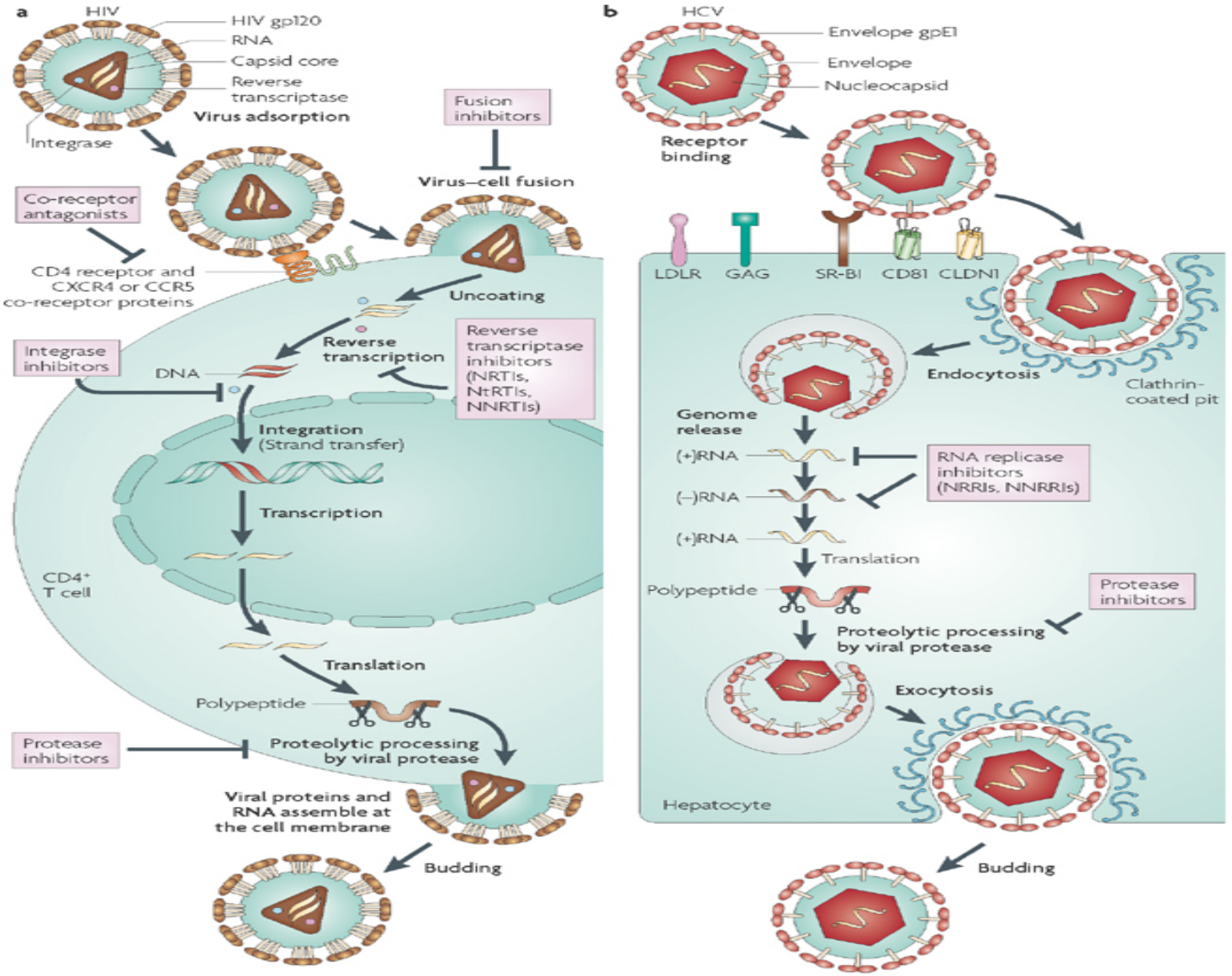
- 2004/2005: Clusters of acute HCV in HIV+ MSM reported in US, Europe, Australia
  - Ulcerative STI's more common in HCV incident cases
  - Molecular genetics more similar to each other than in IDU-associated HCV isolates
- Linkages made to
  - High-risk sexual behavior (fisting, group sex, traumatic and receptive intercourse)
  - Recreational (not-injected) drugs

Browne et al: Sex Transm Infect 80:326, 2004; Gilleece et al: J Acquir Immune Defic Syndr 40:41, 2005; Gambotti, et al: Euro Surveill 10:115, 2005; Ghosn, et al: HIV Med 5:303, 2004; Gotz et al: AIDS 19:969, 2005; Luetkemeyer et al: J Acquir Immune Defic Syndr 41:31, 2006; Fierer, et al: J Infect Dis 198:683, 2008

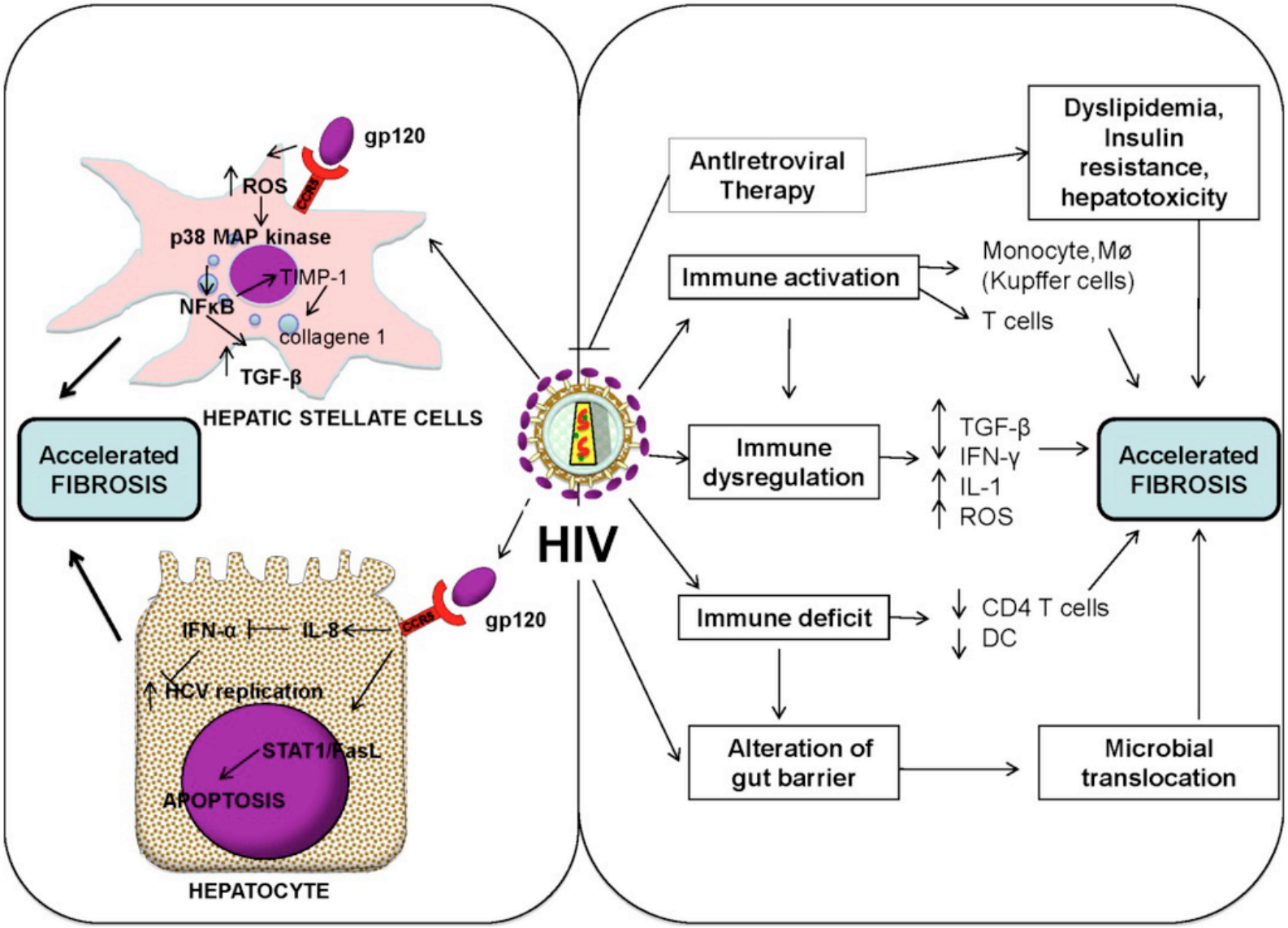
Biology

HIV vs. HCV

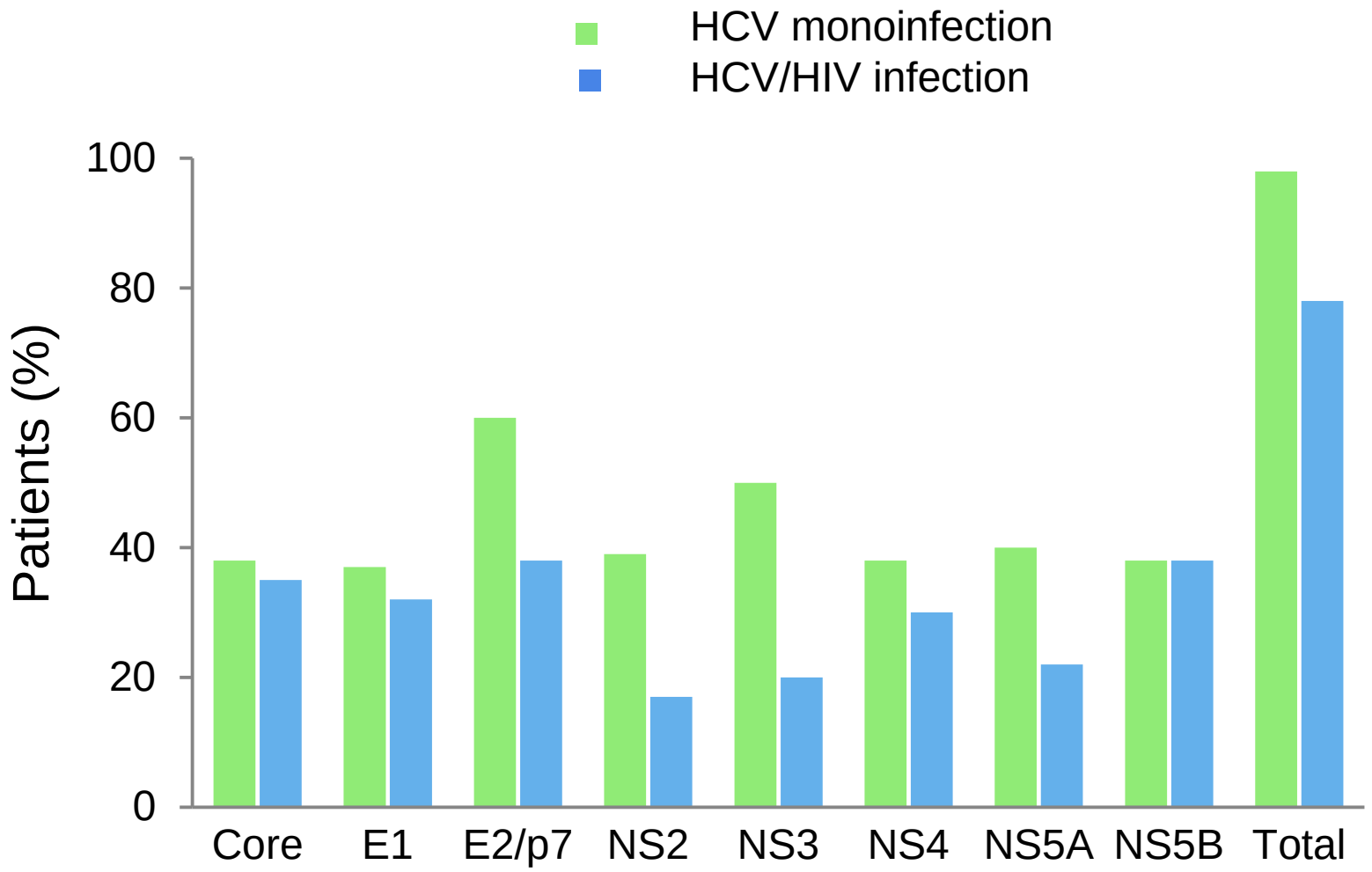
Virus	HIV	HCV
Genome	RNA	RNA
Mutation rates	Very high	Very high
Virions produced daily	10^{10}	10^{12}
Long-lived viral reservoir	Yes	No
Viral targets of therapy	Multiple	Multiple
Cure with current therapy?	No (integrated viral DNA)	Yes
Current therapeutic goal	Lifelong suppression	**Cure** or eradication of HCV infection



Nature Reviews | Drug Discovery

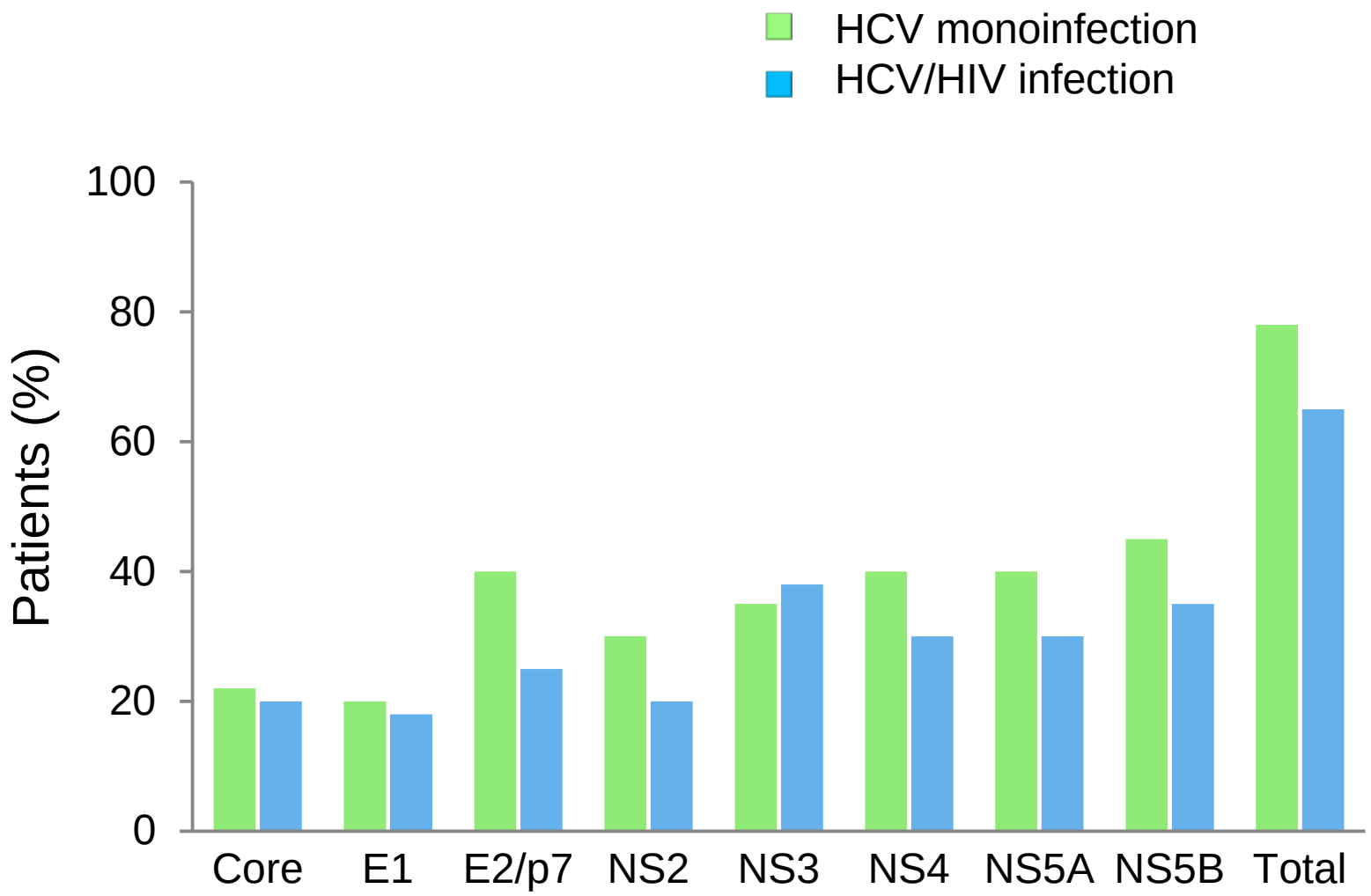


CD4 Response Against Different HCV Proteins



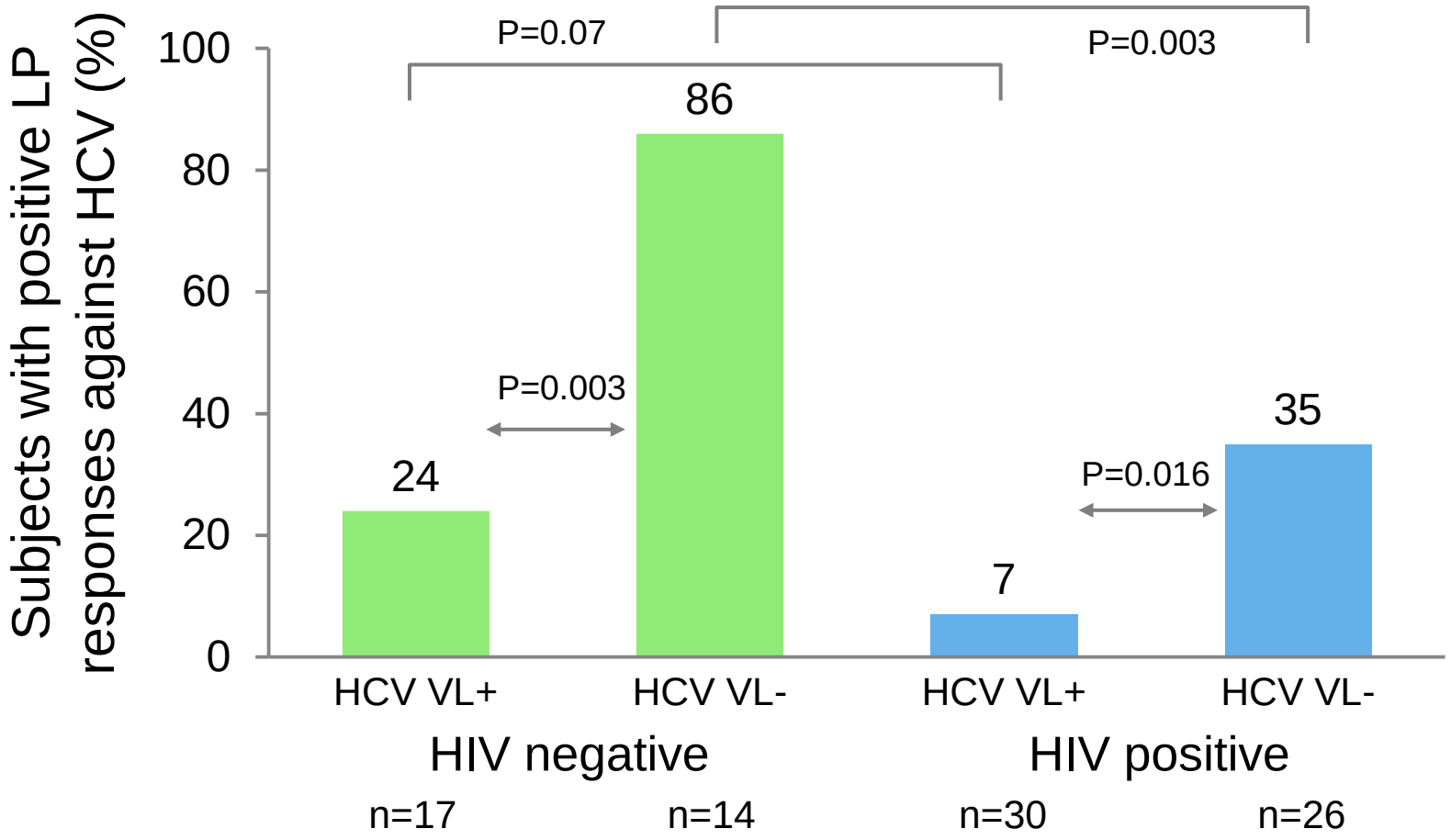
Capa L et al: J Med Virol 79:503, 2007

CD8 Response Against Different HCV Proteins



Capa L et al: J Med Virol 79:503, 2007

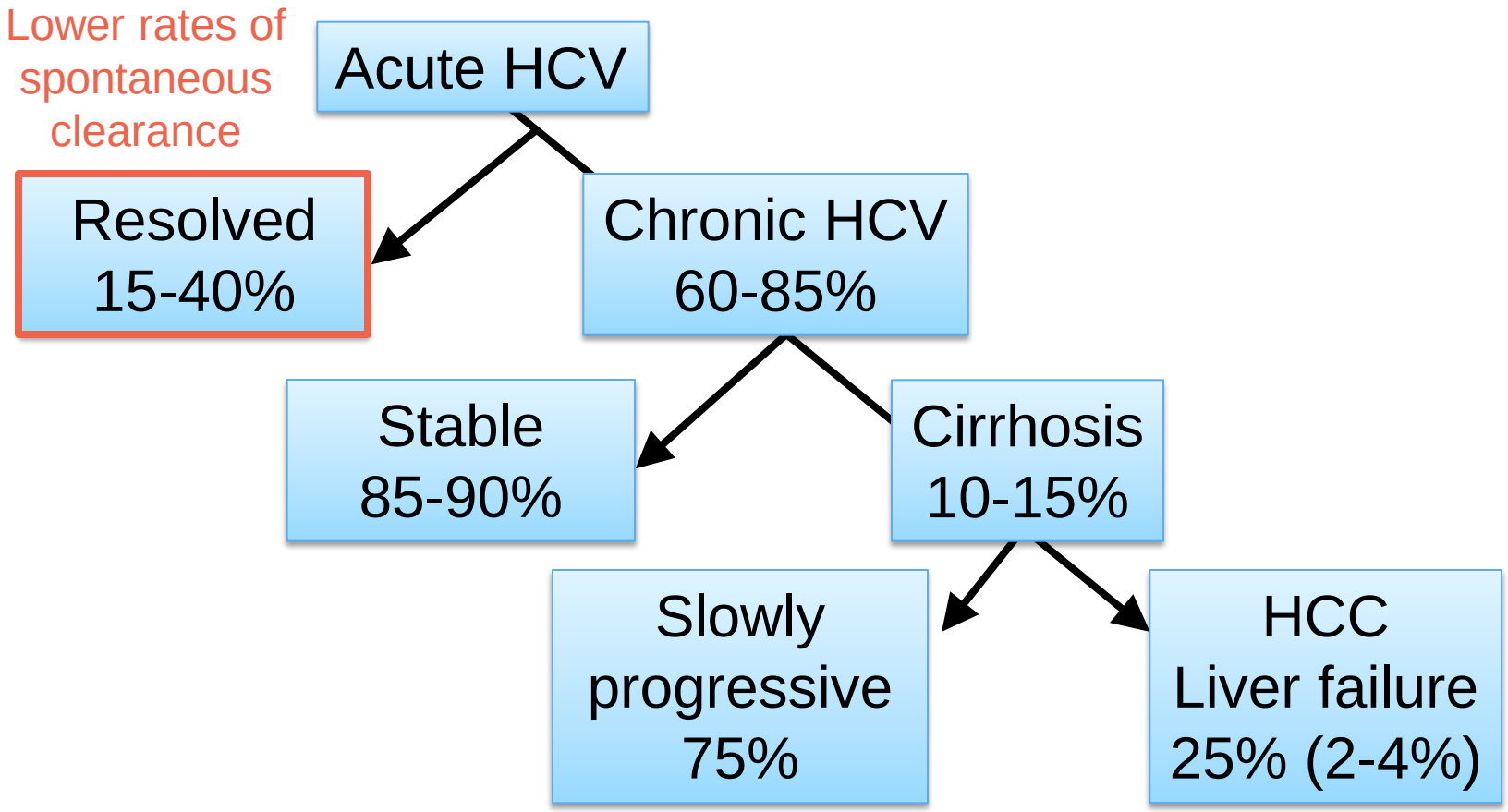
Lymphoproliferative (LP) Responses Against HCV Antigens by HIV Status and HCV Viremia



Kim AY et al: PLoS Med 3(12):e492, 2006

Natural History

Natural History of HCV



NIH Management of Hepatitis C Consensus Conference Statement. June 10-12, 2002.

Characteristics of Coinfected and Monoinfected Individuals in Immunological and Virological Studies

Patient (age in yr, sex)	Symptomatic (icteric)	HCV genotype	HCV load (log IU/mL)	Peak ALT level (IU/mL)	CD4 cell count (cells/μL)	Receivin HAART at diagnosis	Outcome (clear)	Estimated duration of infection (wk)
Coninfected								
1 (42, M)	No	1	6.1	235	362	Yes	No	26
2 (34, M)	Yes	1	6.9	1504	821	Yes	No	6
3 (32, M)	No	1	4.6	2428	712	No	No	256
4 (35, M)	Yes	3a	6.4	5104	847	Yes	Yes	6
5 (30, M)	No	1	6.4	74	544	No	No	26
6 (31, M)	Yes	1	6.9	2258	1283	Yes	Yes	6
7 (31, M)	No	3a	6.3	389	437	Yes	No	26
8 (37, M)	No	1	6.0	349	530	Yes	No	16
9 (37, M)	No	1	5.2	498	266	Yes	No	6
10 (29, M)	No	1	6.3	272	844	No	No	6
11 (42, M)	No	3a	6.7	465	862	Yes	No	20
12 (24, M)	No	1	6.3	384	427	No	No	8
13 (39, M)	Yes	1	6.9	1415	337	Yes	No	6
14 (35, M)	No	1	5.8	89	966	Yes	No	12
15 (32, M)	No	1	6.0	412	740	No	No	6
16 (34, M)	No	1	6.9	2282	1008	Yes	No	6
Monoinfected								
1 (42, M)	Yes	1a	5.1	1139			Yes	6
2 (24, M)	Yes	1b	5.0	1290			Yes	6
3 (32, M)	Yes	3a	6.6	1985			No	14
4 (26, F)	No	1a	5.5	354			No	9
5 (62, M)	Yes	2	4.3	1725			Yes	8
6 (76, F)	No	1b	6.7	695			No	6
7 (33, M)	No	1b	Not known	1453			No	6
8 (25, F)	No	1a	Not known	1285			No	6

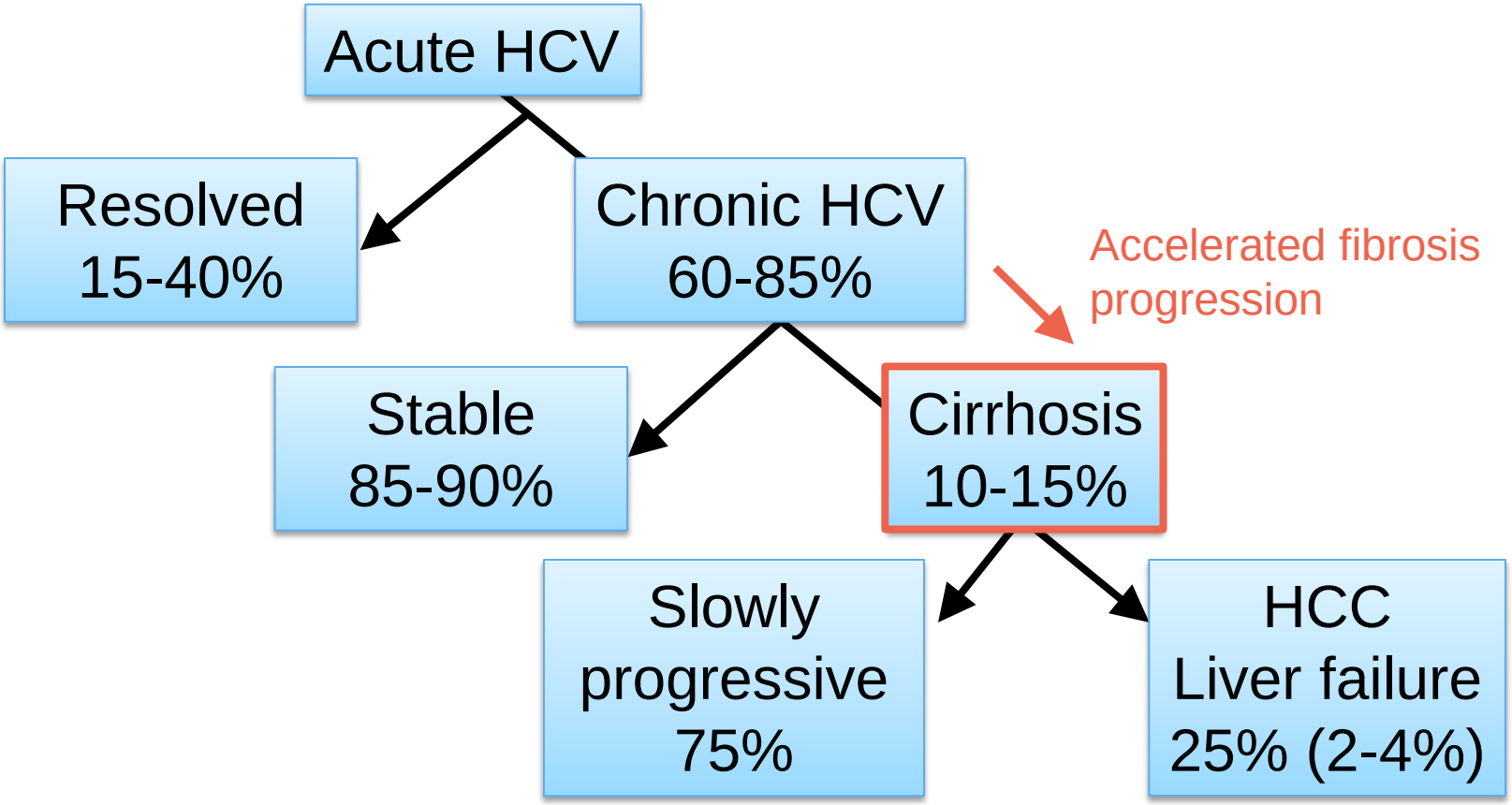
M Danta et al: J Infect Dis 197:1558, 2008

Spontaneous Clearance of Acute HCV in HIV-1-infected Men

Clinical measure (units, normal range)	Spontaneous clearance (median, 95% CI)	Progression		Range	HR (95% CI)	P
		Plateau viraemia (median, 95% CI)	Fluctuating viraemia (median, 95% CI)			
Number	17 (15%)	53 (47.5%)	42 (37.5%)	–	–	–
Age (years)	37 (32 to 44)	39 (37 to 42)	39 (37 to 40)	HR represents change in hazard per year of age	1.00 (0.94 to 1.06)	1.00
Baseline HCV VL log_{10} (IU/ml)	6.11 (1.79 to 7.35)	6.25 (5.71 to 6.44)	5.89 (5.06 to 6.13)	HR represents change in hazard per log10 change in VL	0.75 (0.55 to 1.01)	0.06
Peak HCV VL log_{10}(IU/ml)	6.11 (1.79 to 7.35)	6.52 (6.36 to 6.88)	6.21 (5.87 to 6.72)		0.61 (0.46 to 0.80)	<0.0001**
HIV VL (copies/ml)	<50 (<50 to 7044)	<50 (<50 to 1185)	87 (<50 to 6847)		1.00 (1.00 to 1.00)	0.40
CD4 count (300–1400 $\times 10^6$/l)	650 (490 to 829)	510 (439 to 640)	520 (453 to 619)	<650 ≥650	2.66 (1.02 to 6.91) 1	0.045*
Nadir CD4 (300–1400 $\times 10^6$/l)	340 (200 to 519)	310 (280 to 350)	315 (270 to 367)	≥200 <200	1 1.51 (0.52 to 4.35)	 0.45
HAART	11/Gut. 2011 Jun; 60(6): 837–845.15 (73%)	31/53 (58%)	23/42 (55%)	All patients were MSM and had had recent unprotected sex	1.63 (0.57 to 4.70)	0.36

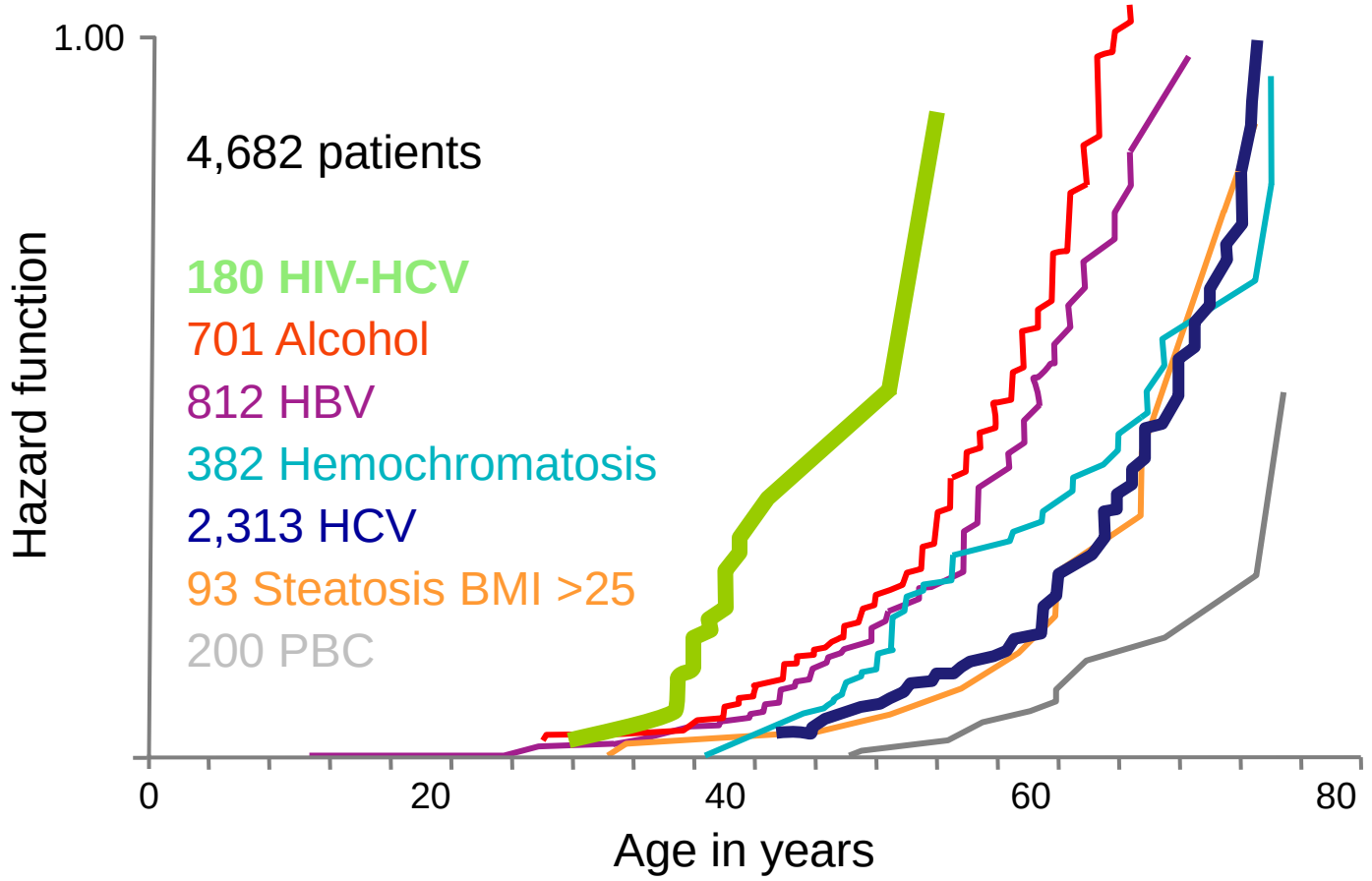
Thomson EC et al: Gut 60(6): 837, 2011

Natural History of HCV



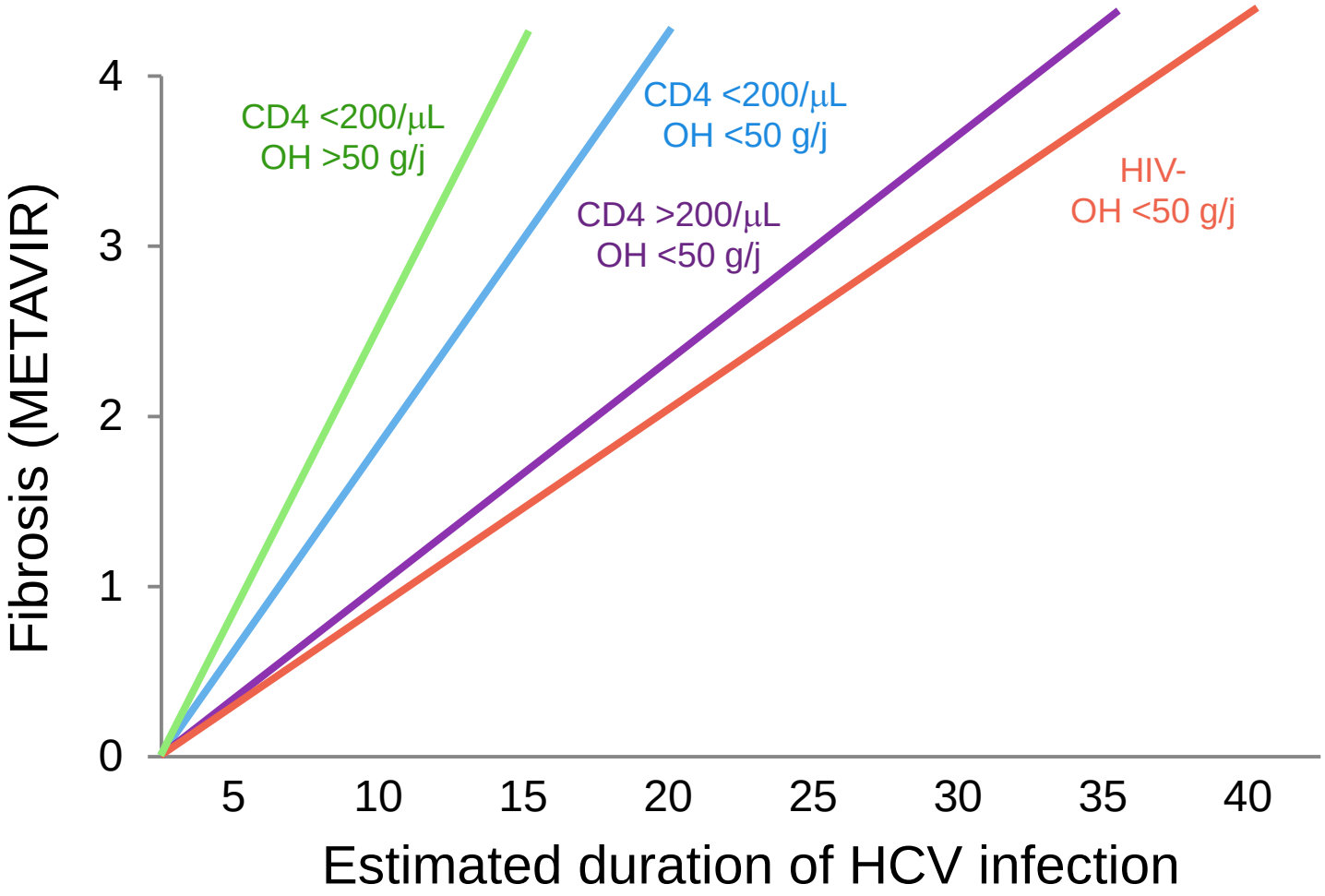
NIH Management of Hepatitis C Consensus Conference Statement. June 10-12, 2002.

Progression to Cirrhosis



Poynard T et al: J Hepatol 38:257, 2003

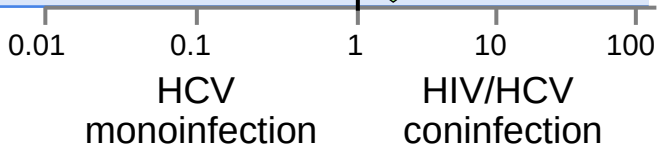
Progression to Cirrhosis Influence of Alcohol and Immune Status



Benhamou et al: Hepatology 30:1054, 1999

HAART Era: Cirrhosis Risk

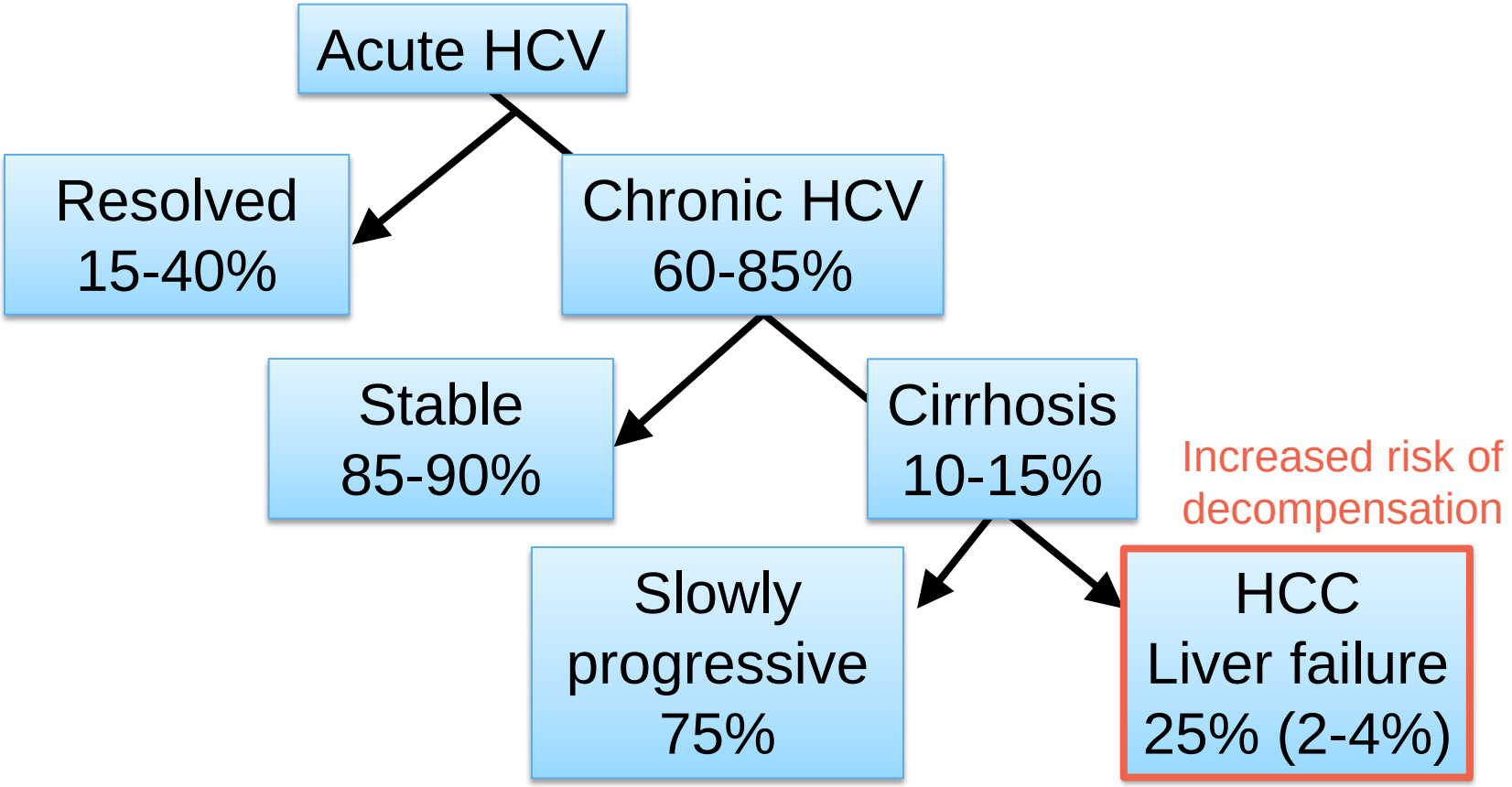
Benhamou, 1999	1.484	0.733	3.004	1.096	0.273
Brau, 2006	1.404	1.010	1.951	2.019	0.044
Gaslightwala & Bini, 2006	7.289	4.938	10.760	9.998	0.000
Gonzalez, 2006	2.037	0.789	5.254	1.471	0.141
Macias, 2005	1.698	0.911	3.165	1.666	0.096
Marine'-Barjoan, 2004	5.000	1.940	12.887	3.332	0.001
Martinez-Sierra, 2003	4.195	1.665	10.567	3.042	0.002
Mohsen, 2003	1.814	0.958	3.434	1.830	0.067
Monto, 2005	0.778	0.327	1.854	-0.566	0.572
Rodriques-Torres, 2006	0.384	0.225	0.656	-3.501	0.000
Sarmento-Castro, 2007	1.595	0.322	7.904	0.572	0.567
Valle Tovo, 2007	0.727	0.457	1.156	-1.346	0.178
Verma, 2006	2.015	1.421	2.858	3.928	0.000
Fixed effects	1.754	1.509	2.038	7.329	0.000
Random effects	1.723	1.059	2.804	2.191	0.028



3567 individuals coinfected with HIV/HCV
(n = 17 studies)

Thein et al: AIDS 22:1979, 2008

Natural History of HCV



NIH Management of Hepatitis C Consensus Conference Statement. June 10-12, 2002.

The Spectrum of Liver Disease Among HIV-Positive Patients Has Shifted in the ART Era

Most Common Causes of Liver Dysfunction in the Pre-ART Era

- Opportunistic infections
  - Cytomegalovirus
  - Mycobacterium
- AIDS-related neoplasms
  - Lymphoma
  - Kaposi sarcoma

Most Common Causes of Liver Dysfunction in the ART Era

- *Chronic HCV infection*
- *Chronic HBV infection*
- Medication-related hepatotoxicity
- Alcohol abuse
- Nonalcoholic fatty liver disease

Price JC et al: Clin Gastroenterol Hepatol 8:1002, 2010

The Effect of HIV Infection, Immunodeficiency, and Antiretroviral Therapy on the Risk of Hepatic Dysfunction.

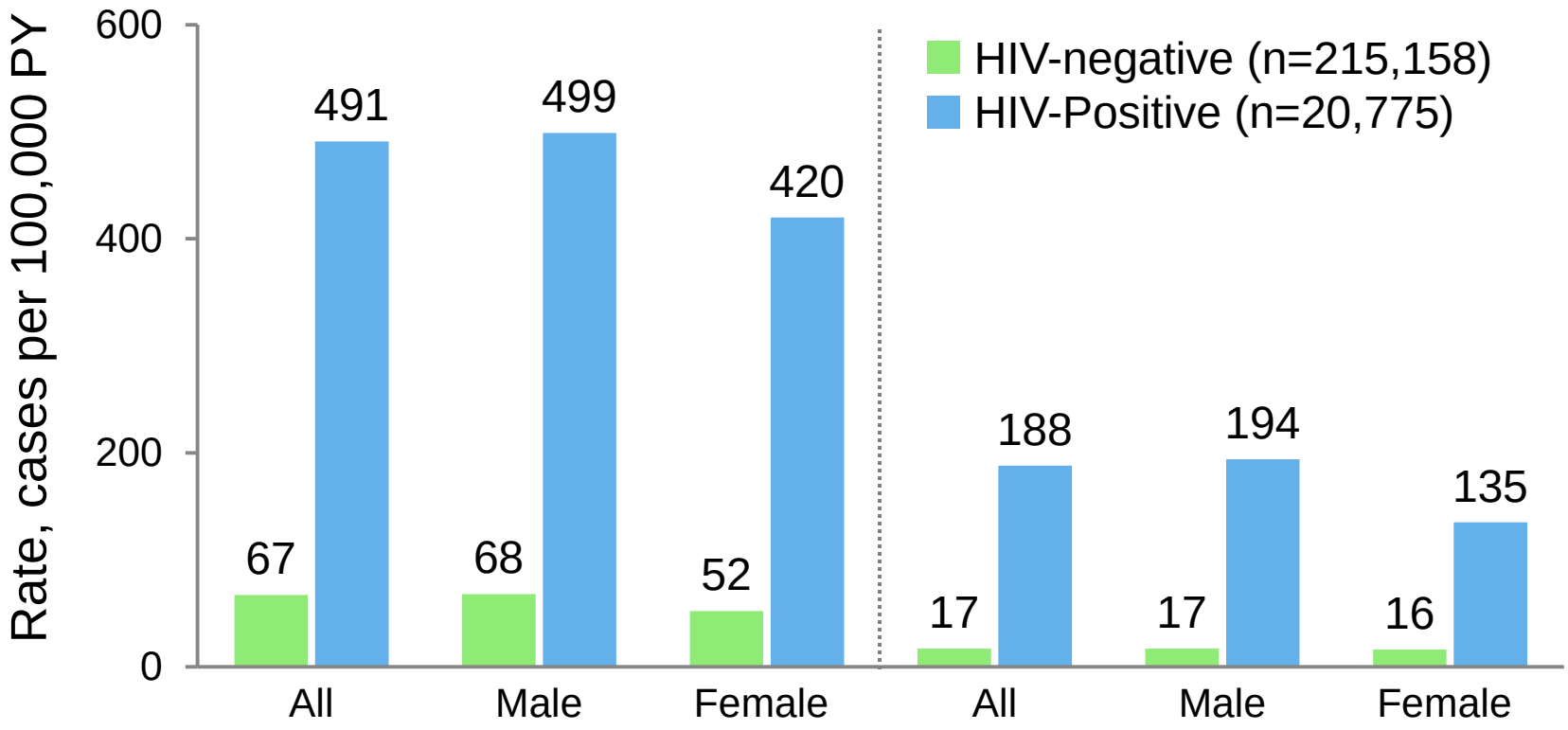
Towner, William; Xu, Lanfang; Leyden, Wendy; Horberg, Michael; Chao, Chun; Tang, Beth; Klein, Daniel; Hurley, Leo; Quesenberry, Charles; Silverberg, Michael; PhD, MPH

JAIDS Journal of Acquired Immune Deficiency Syndromes. 60(3):321-327, July 1, 2012.
DOI: 10.1097/QAI.0b013e31824e9ef2

A cohort study from Kaiser Permanente
1996 to 2008
20,775 HIV-infected and 215,158 HIV-uninfected individuals
10:1 age-matched and sex-matched

Higher Rate of HD and HDRD in Patients With HIV

HD and HDRD in a Cohort of Patients Within the Kaiser Permanente Health Care System, 1996-2008



Towner WJ et al: J Acquir Immune Defic Syndr 60:321, 2012

Hepatic Dysfunction and Hepatic Dysfunction-Related Death: Incidence Rates and RRs by HIV Infection Status

	HIV+			HIV-			Adjusted RR*	
	No.	Rate†	95% CI	No.	Rate†	95% CI	RR	95% CI
HD								
All pt	437	491	445.3-537.5	755	67	62.1-71.6	3.5	3.0-4.0‡
Men	400	499	450.3-548.1	697	68	63.4-73.5	3.5	3.0-4.0‡
Women	37	420	284.9-555.9	58	52	37.8-65.6	3.3	2.0-5.5‡
Yr 1996-200	143	679	567.4-789.9	158	57	48.4-66.3	5.4	4.2-7.0‡
Yr 2001-2008	294	433	383.7-482.8	597	70	64.3-75.5	4.1	3.4-5.0‡
KPNC	252	482	422.4-541.4	422	61	55.3-67.0	3.7	3.1-4.4‡
KPSC	185	505	432.2-577.8	333	76	67.7-83.9	3.2	2.6-3.9‡
Pt index yr ≥2000	240	463	404.8-522.0	432	68	61.9-74.8	3.1	2.6-3.7‡
Pt with HCV/HBV	213	1828	1,582.5-2,073.4	203	816	703.6-928.0	2.3	1.9-2.8‡
Pt without HCV/HBV	224	290	251.9-327.8	552	50	45.8-54.1	4.4	3.8-5.2‡
HDRD								
All pt	170	188	159.9-216.5	192	17	14.6-19.4	5.9	4.7-7.4‡
Men	158	194	163.7-224.2	174	17	14.5-19.6	6.0	4.7-7.6‡
Women	12	135	58.7-211.6	18	16	8.7-23.6	5.6	2.4-12.6‡
Yr 1996-2000	65	305	230.5-378.6	37	13	9.1-17.7	12.7	8.1-19.8‡
Yr 2001-2008	105	152	123.1-181.3	155	18	15.2-20.9	8.1	5.8-11.4
KPNC	84	158	124.2-191.7	87	13	9.9-15.2	7.1	5.1-9.8‡
KPSC	86	232	182.6-280.4	105	24	19.3-28.4	4.7	3.4-6.5‡
Pt index yr ≥2000	106	202	163.6-240.5	126	20	16.4-23.4	5.1	3.8-6.8‡
Pt with HCV/HBV	87	708	559.3-856.9	45	174	123.2-225.0	4.5	3.1-6.5‡
Pt without HCV/HBV	83	106	83.5-129.2	147	13	11.1-15.4	6.5	4.9-8.6‡

20,775 HIV-infected and 215,158 HIV-uninfected individuals.

Towner WJ et al: JAIDS Journal of Acquired Immune Deficiency Syndromes 60(3):321, 2012

Adjusted RR for Hepatic Dysfunction for Selected Risk Factors in HIV-Infected Patients

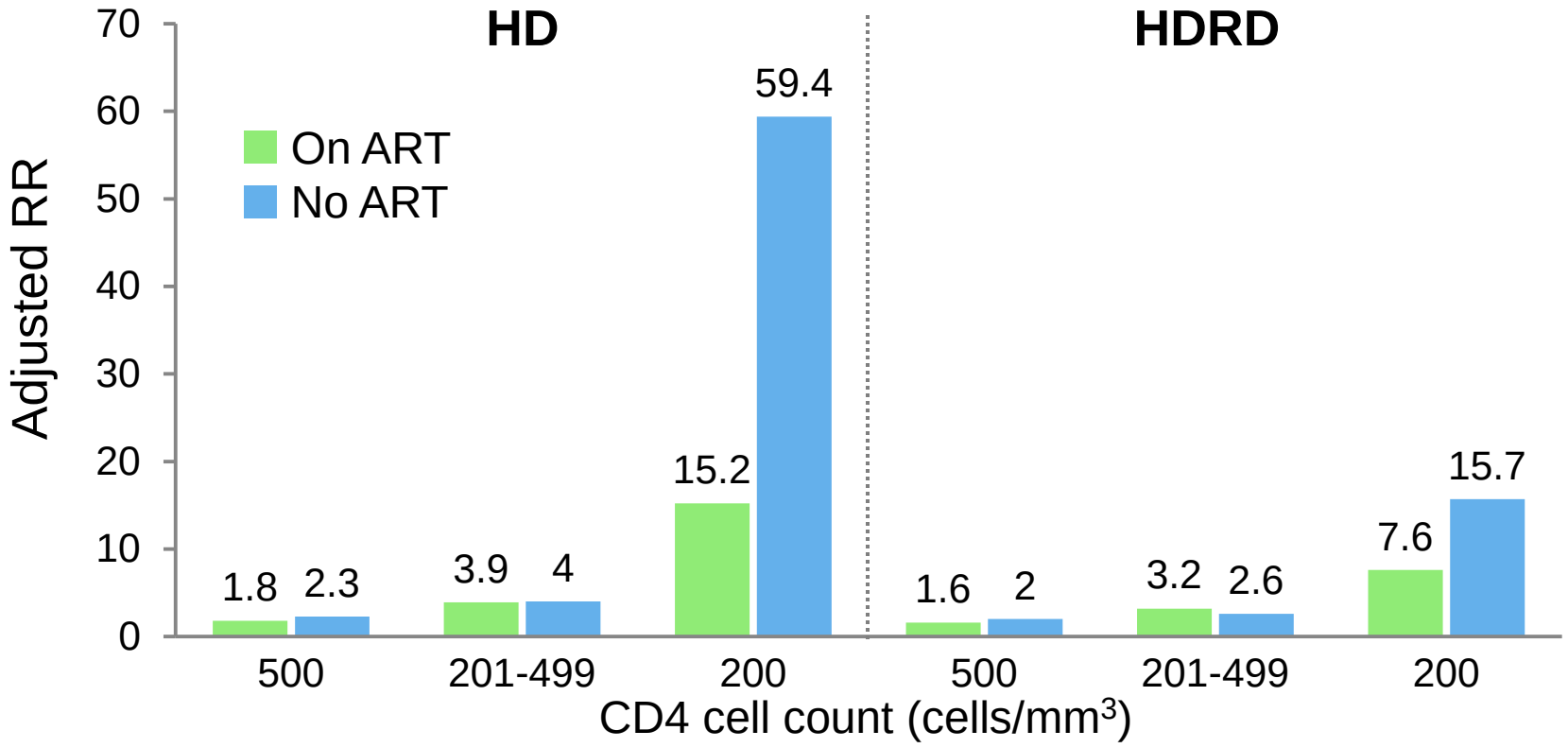
	Adjusted RR*	95% CI	P
ART use	0.9	0.7-1.2	0.52
Recent CD4 ≤200 vs >200	2.5	2.0-2.3	<0.001
Lowest KP CD4 ≤200 vs >200	1.5	1.2-2.0	0.003
HIV RNA ≥500 vs <500	1.7	1.4-2.1	<0.001
Ever alcohol or drug abuse	1.6	1.3-2.0	<0.001
Hepatitis B or C	5.3	4.3-6.4	<0.001
Diabetes	1.9	1.4-2.5	<0.001
Female sex	0.9	0.6-1.3	0.46
Black vs White	1.1	0.9-1.4	0.35
Hispanic vs White	1.6	0.8-1.4	0.50
Hypertension	1.1	0.9-1.4	0.37
Lipid-lowering drug use	1.2	0.9-1.5	0.24

*RRs adjusted for all other variables presented

Towner WJ et al: JAIDS Journal of Acquired Immune Deficiency Syndromes 60(3):321, 2012

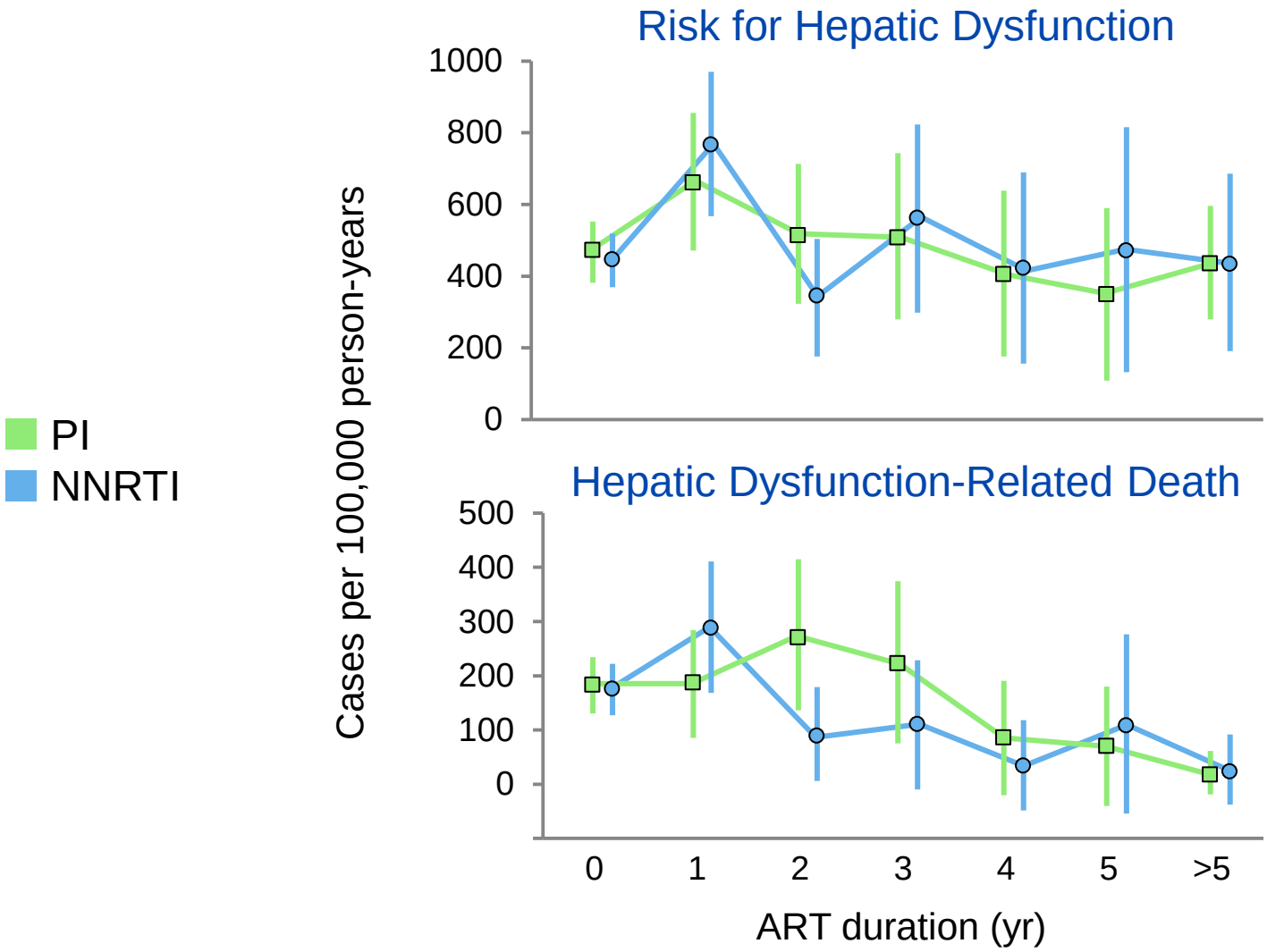
ART Reduces the Risk of HD and HDRD in HIV-Positive Adults With CD4 Cell Counts ≤200

Adjusted RRsa of HD and HDRD Among 20,775 HIV-Positive Patients Within the Kaiser Permanente Health Care System, 1996-2008



Towner WJ et al: J Acquir Immune Defic Syndr 60:321, 2012

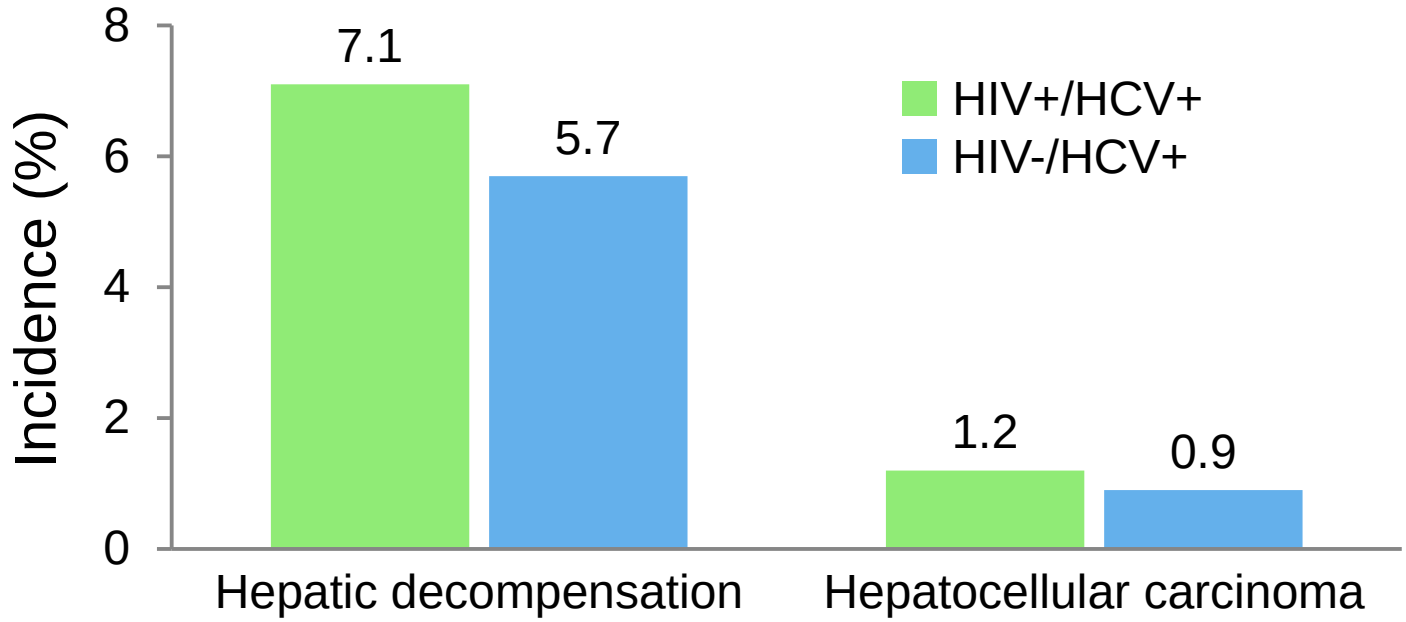
Effect of Cumulative use of PI or NNRTI Therapy



Towner WJ et al: JAIDS Journal of Acquired Immune Deficiency Syndromes 60(3):321, 2012

ART-Treated HIV/HCV-Coinfected Patients Have a Higher Risk of Decompensation and HCC

Incidence of Hepatic Decompensation and HCC in 4286 ART-Treated HIV/HCV-Coinfected and 6639 HCV-Monoinfected Veterans in Care (Veterans Aging Cohort Study, 1997-2010)

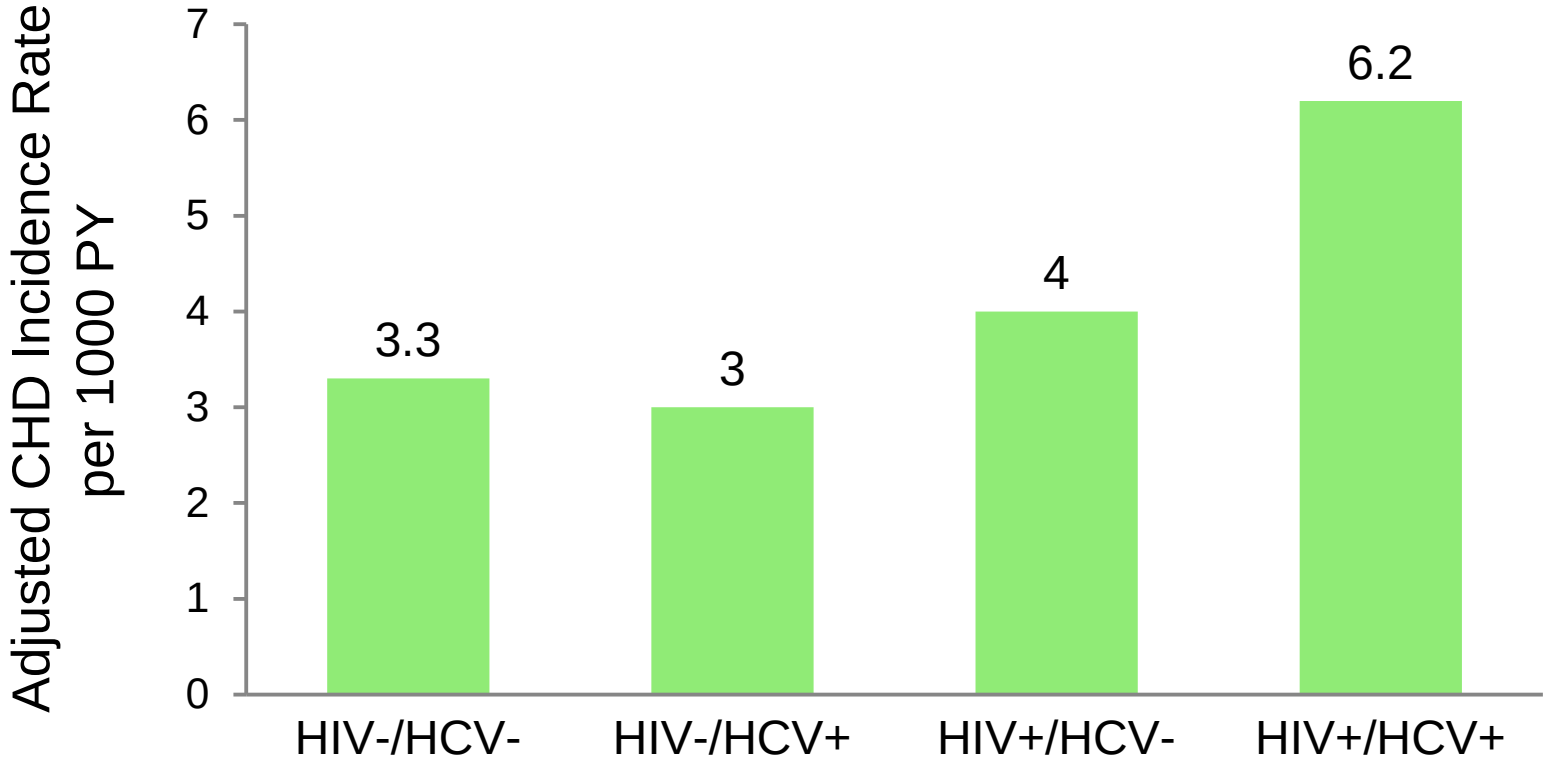


After decompensation, mortality was higher in coinfected patients (75.2%) vs HCV-monoinfected patients (56.8%); P <0.001

Lo Re V et al: IAC 2012. Washington, DC. WEAB0102

HIV/HCV-Coinfected Patients Are at Increased Risk for CHD

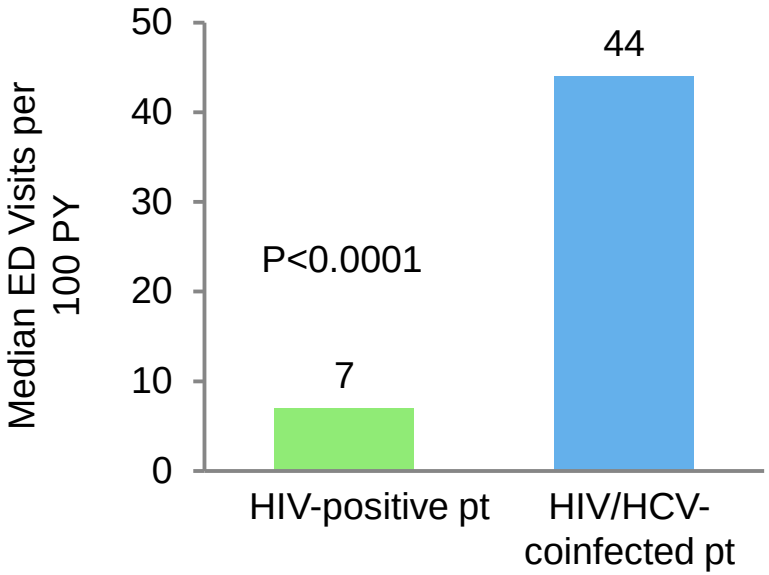
Rate of CHD Among Participants of the Veterans Aging Cohort Study Who Are Infected or Not Infected With HIV and/or HCV, 2000-2007 (n=8579)



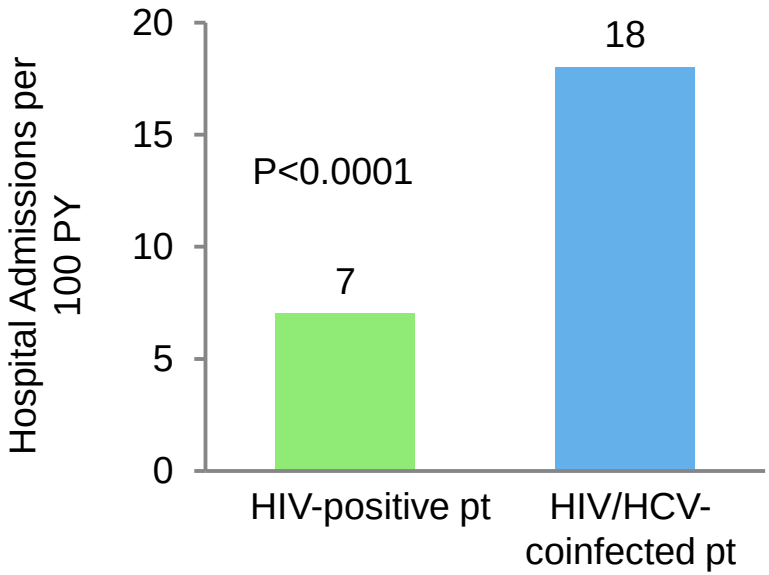
Freiberg MS et al: Circ Cardiovasc Qual Outcomes 4:425, 2011

HIV/HCV Coinfection Leads to Higher Utilization of Health Care Resources

ED Visits Among 165 HIV-Positive Patients and 96 HIV/HCV-Coinfected Patients



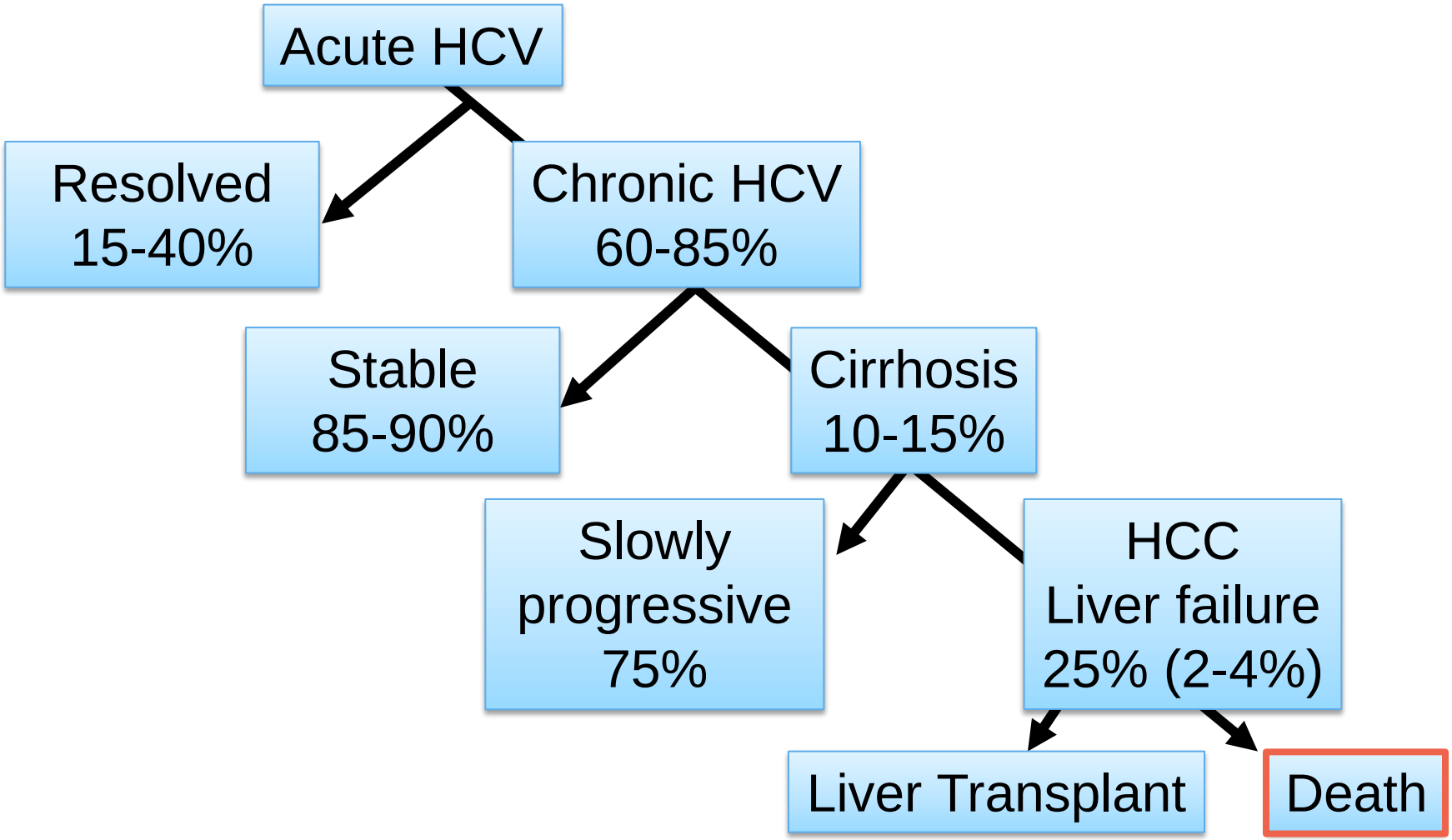
Hospital Admissions Among 165 HIV-Positive Patients and 96 HIV/HCV-Coinfected Patients



- Renal disease, diabetes, psychiatric/substance abuse, and liver-related hospitalizations and ED visits were more common among the HIV/HCV-coinfected group
- The HIV monoinfected cohort had a longer duration of HIV infection compared with the coinfected cohort, with medians of 14 and 12 years, respectively (P=0.03)
- Median CD4 cell count was slightly higher among the HIV/HCV coinfected (486 vs 389; P=0.04)

Norton B et al: AIDS Patient Care STDs 26:541, 2012

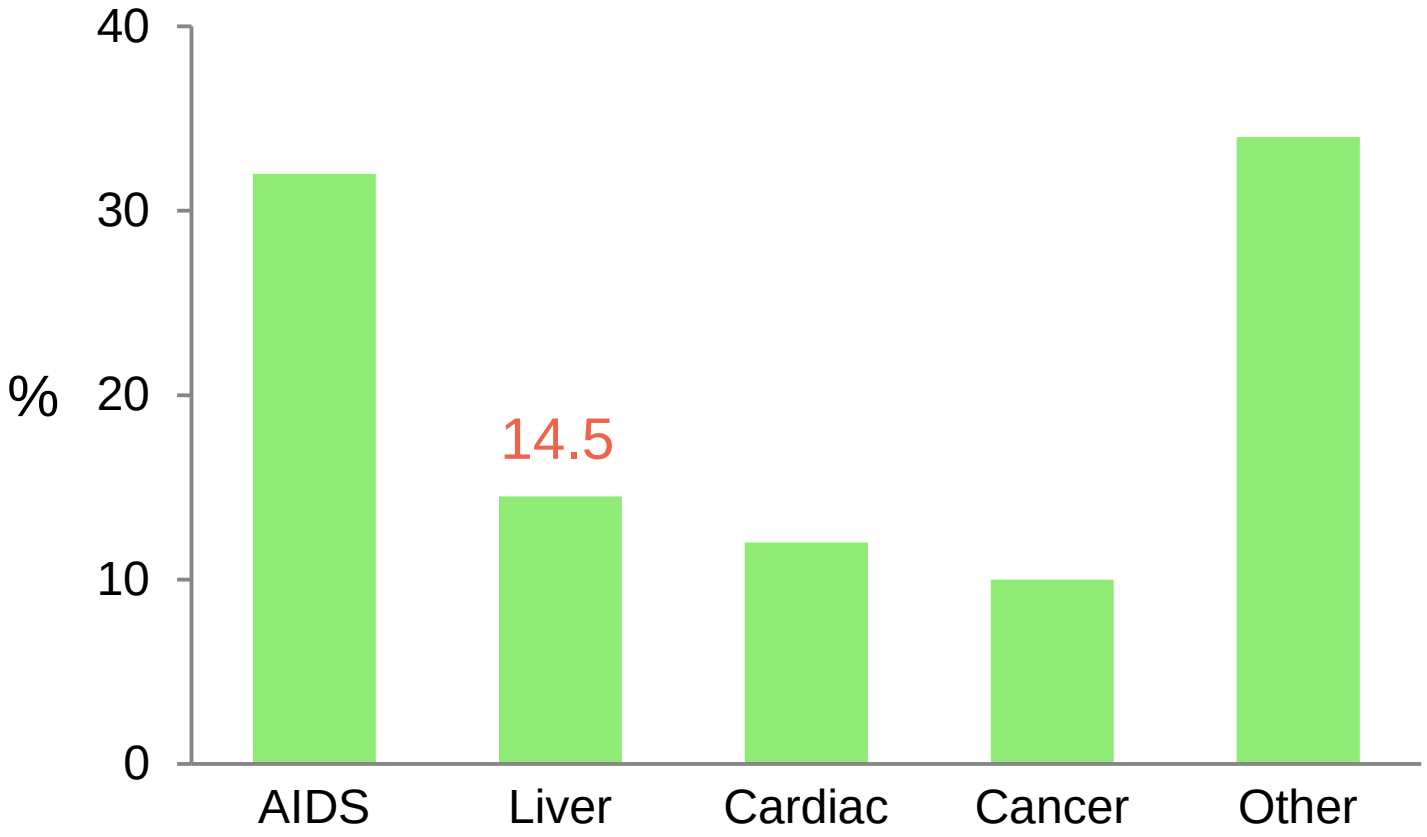
Natural History of HCV



Shorter survival after decompensation

NIH Management of Hepatitis C Consensus Conference Statement. June 10-12, 2002.

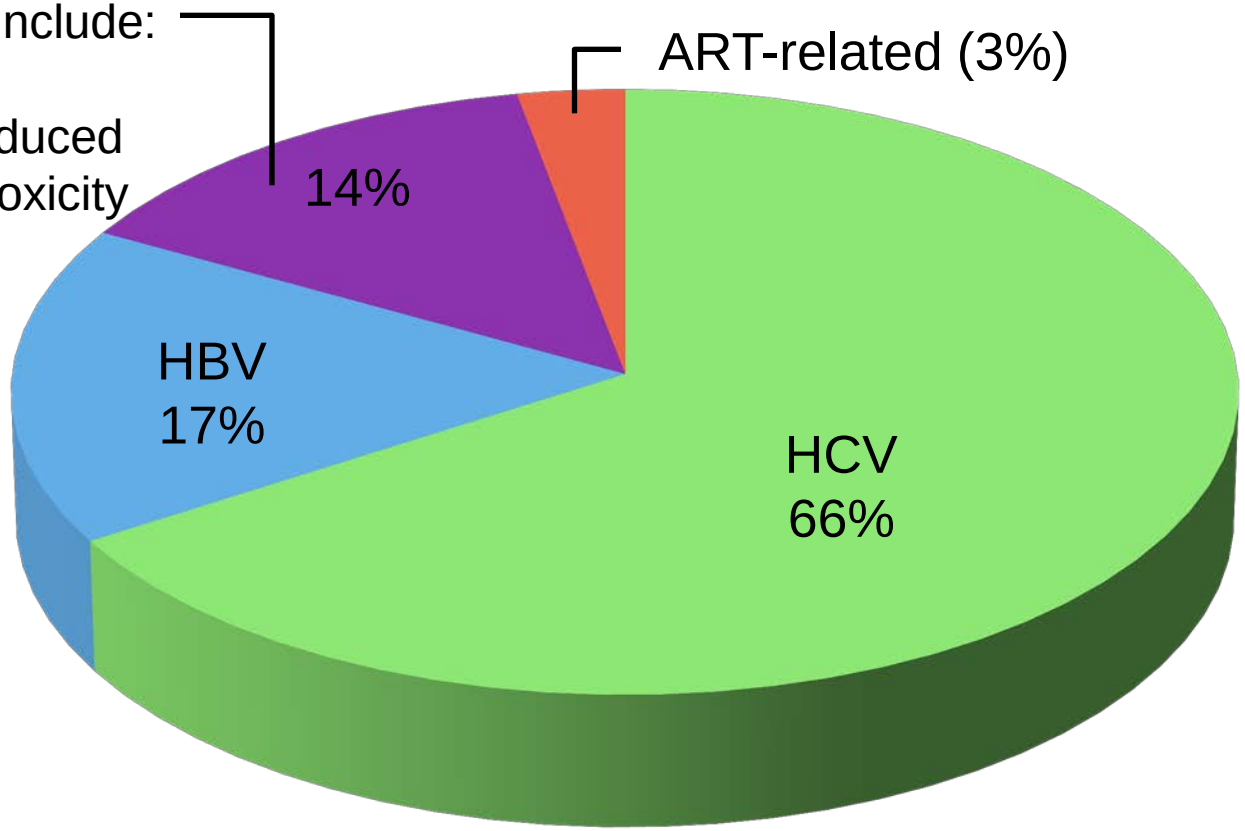
D:A:D Study: Liver-Related Deaths in Persons with HIV



DAD Study Group, Arch Intern Med 2006

Coinfection With HBV or HCV Is a Common Cause of Liver Disease-Related Death in Patients With HIV

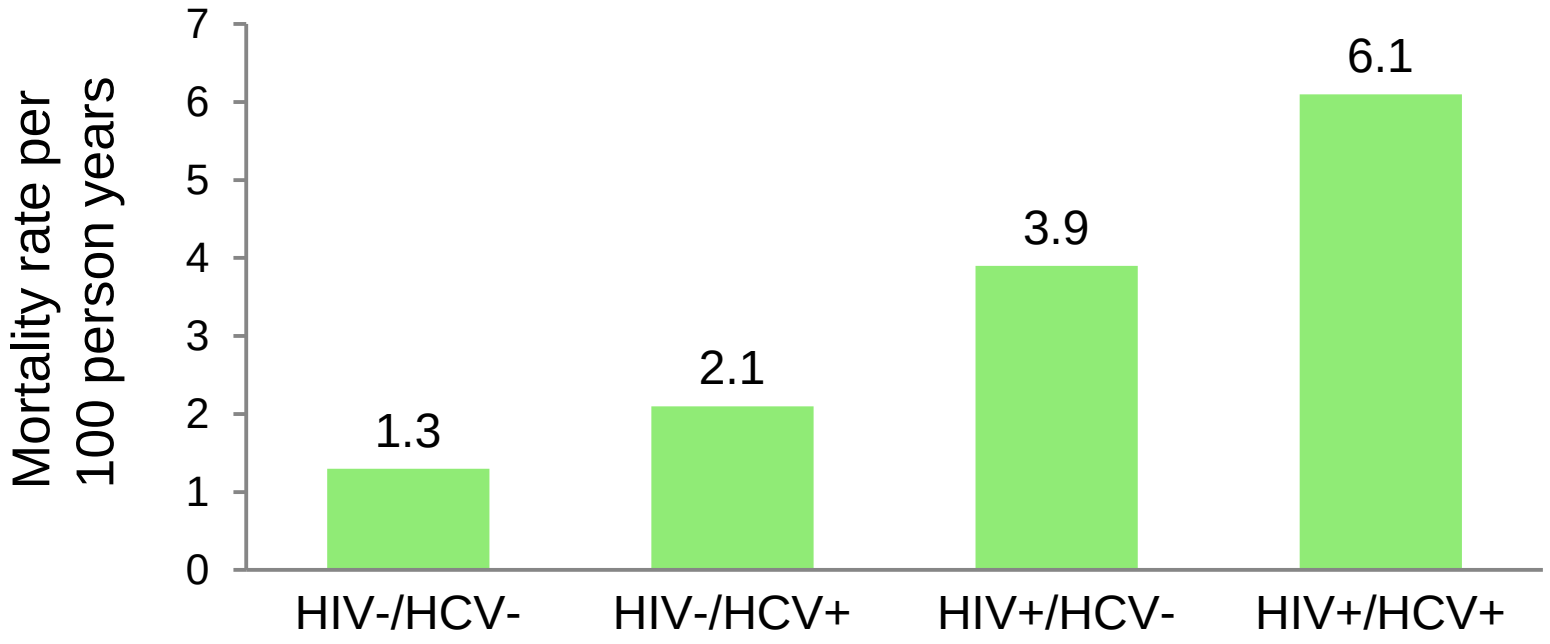
Other causes include:
- Alcohol
- Drug-induced hepatotoxicity
- NAFLD



Joshi D et al: Lancet 377:1198, 2011

HIV/HCV-Coinfected Patients Have a Higher All-Cause Mortality Rate

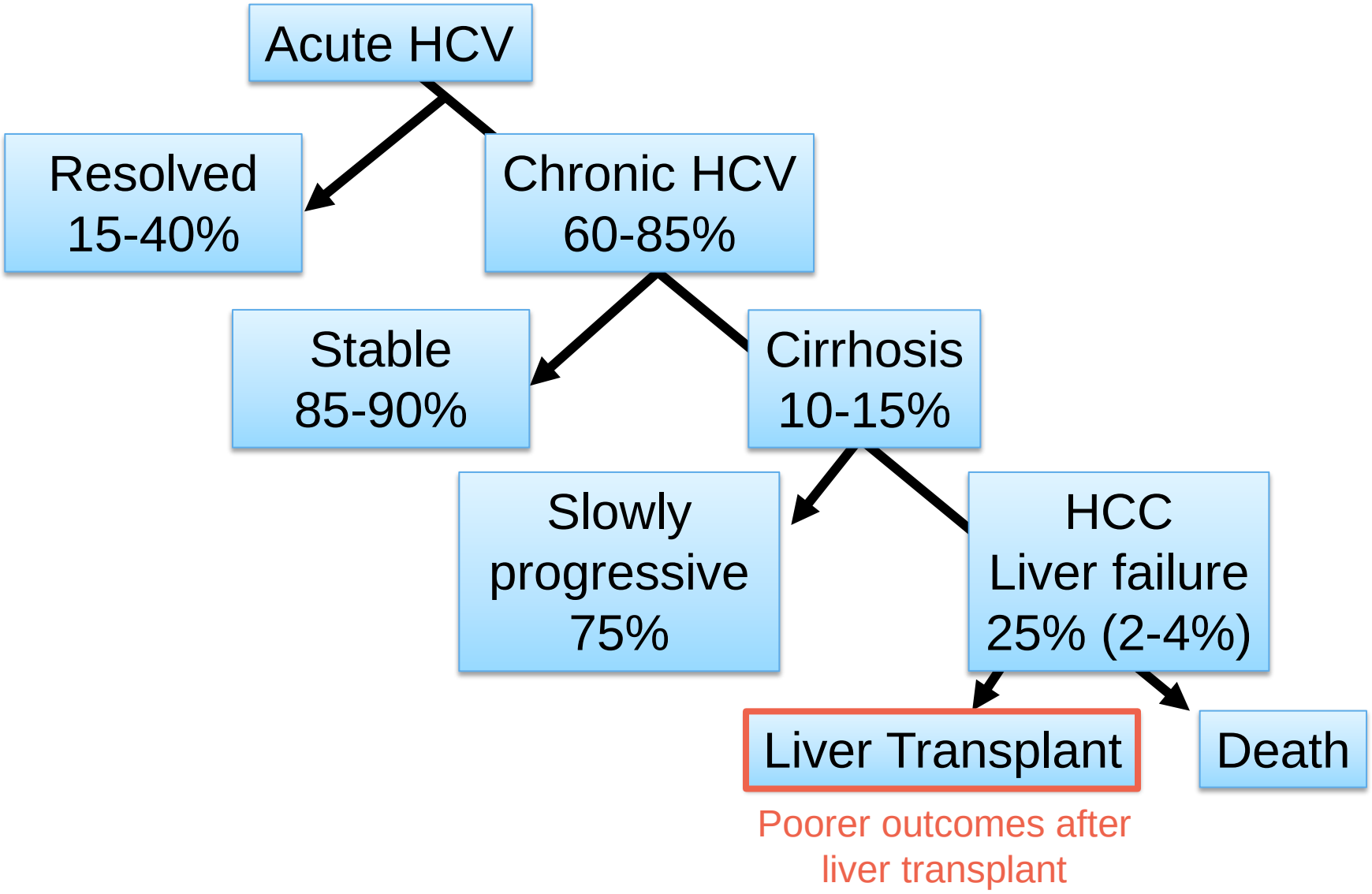
All-Cause Mortality Rate Among 8579 Patients Infected or Not Infected With HIV and/or HCV (Veterans Aging Cohort Study, 2000-2007)[1]



Similar results were reported by a recent study of 8214 HIV-positive subjects conducted in Spain (AIDS Research Network, 1997-2010)[2]

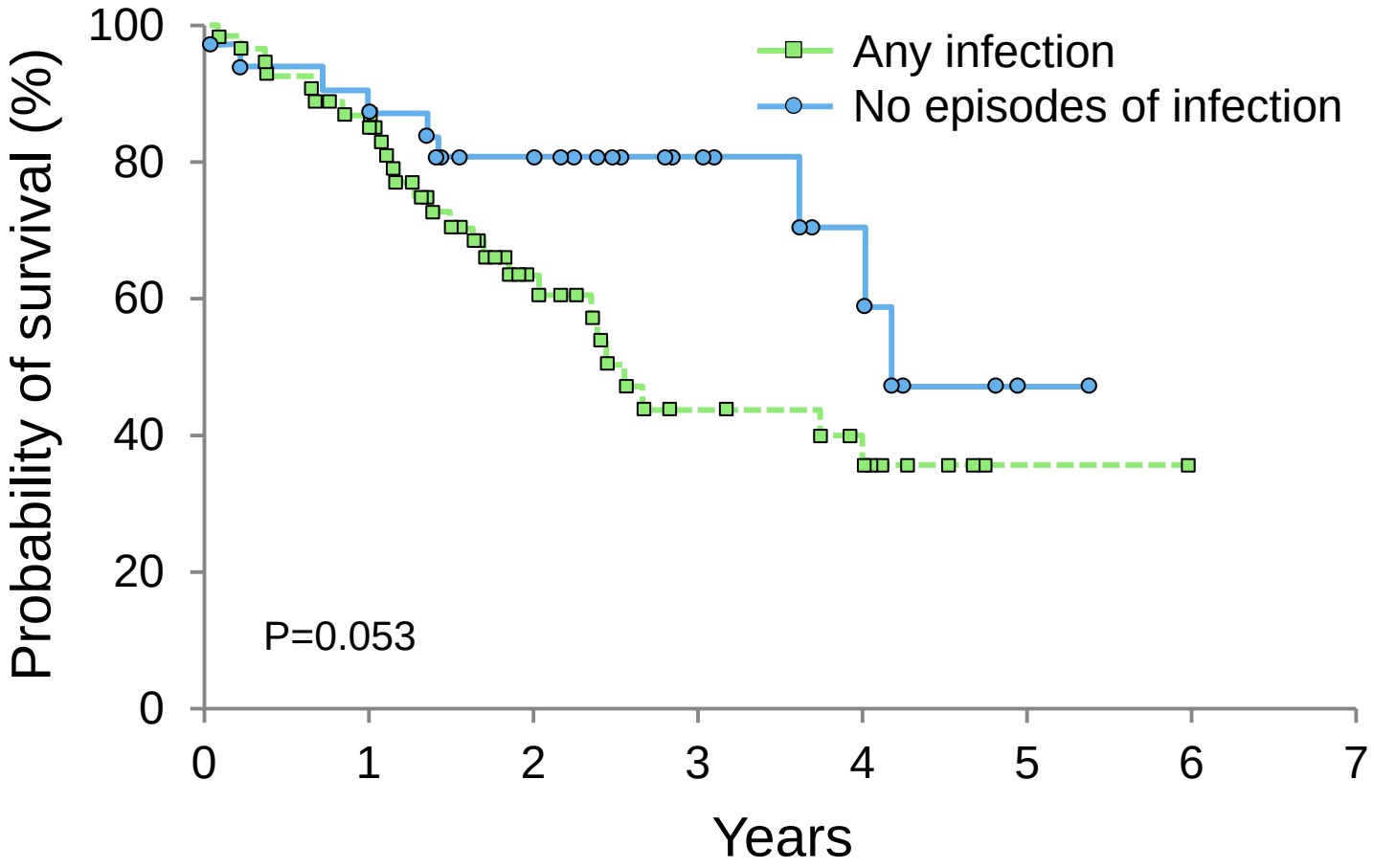
[1] Freiberg MS et al: Circ Cardiovasc Qual Outcomes 4:425, 2011
[2] Hernando V et al: BMC Infect Dis 13:382, 2013

Natural History of HCV

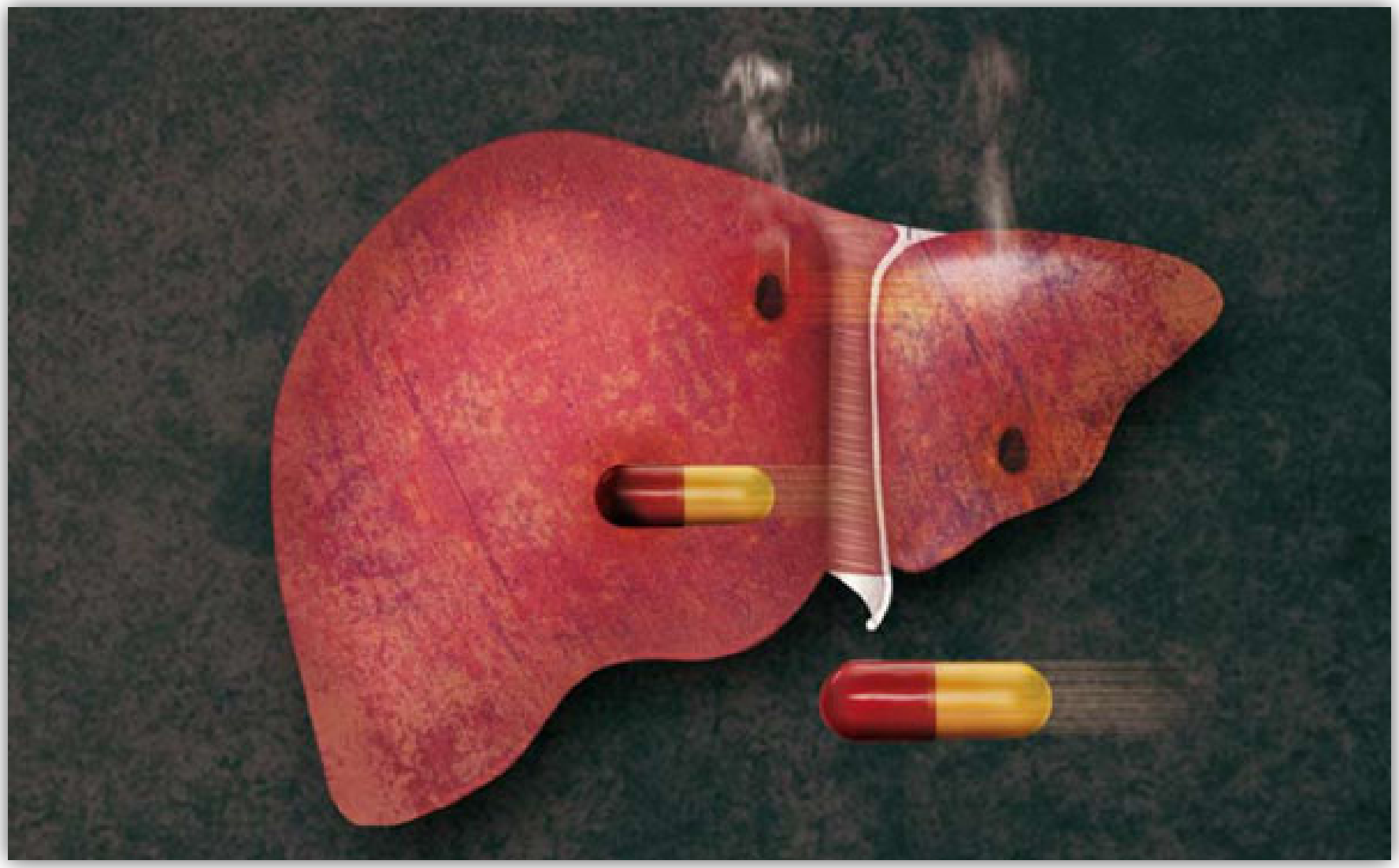


NIH Management of Hepatitis C Consensus Conference Statement. June 10-12, 2002.

Liver-Transplant Recipients Coinfected with HIV and HCV Who Experience a Post-Surgical Infection Have Reduced Survival



Moreno A et al: Liver Transplantation 18:70, 2012



Mark S: Sulkowski Clin Infect Dis 38:S90, 2004

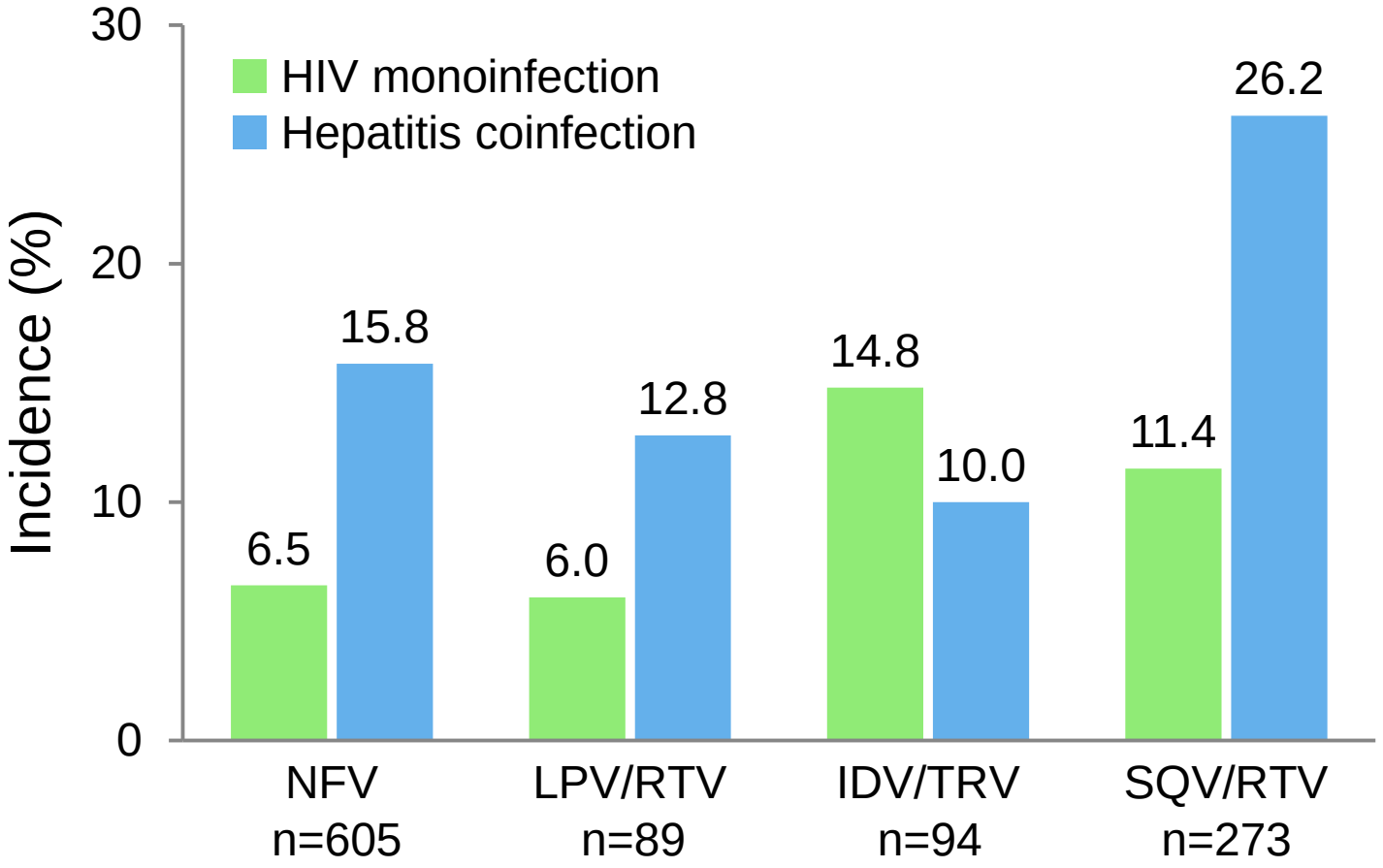
Incidence of Hepatotoxicity in Registration Trials for Selected HIV-1 Protease Inhibitors

Drug	Definition of liver injury	No. of pt studied	Incidence (cases/100 pt exposed)
Saquinavir [10]	ALT or AST >5x ULN	442	5.7
Indivavir [5]	ALT or AST >5x ULN	1220	2.6-4.9
	Total bilirubin, 2.5x ULN		6.1-11.9
Ritonavir [9]	ALT >215 IU/L, AST >180 IU/L	1270	5.3-9.5
Lopinavir/ritonavir [11]	ALT >215 IU/L,AST >180 IU/L	612	2.2-9.5
Nelfinavir [7]	ALT or AST >5x ULN	>297	1-2
Atazanavir [6]	ALT or AST >5x ULN	1056	2-7
	Total bilirubin >2.5x ULN		22-47

NOTE: Data are abstracted from the US Food and Drug Administration-approved prescribing information for each drug

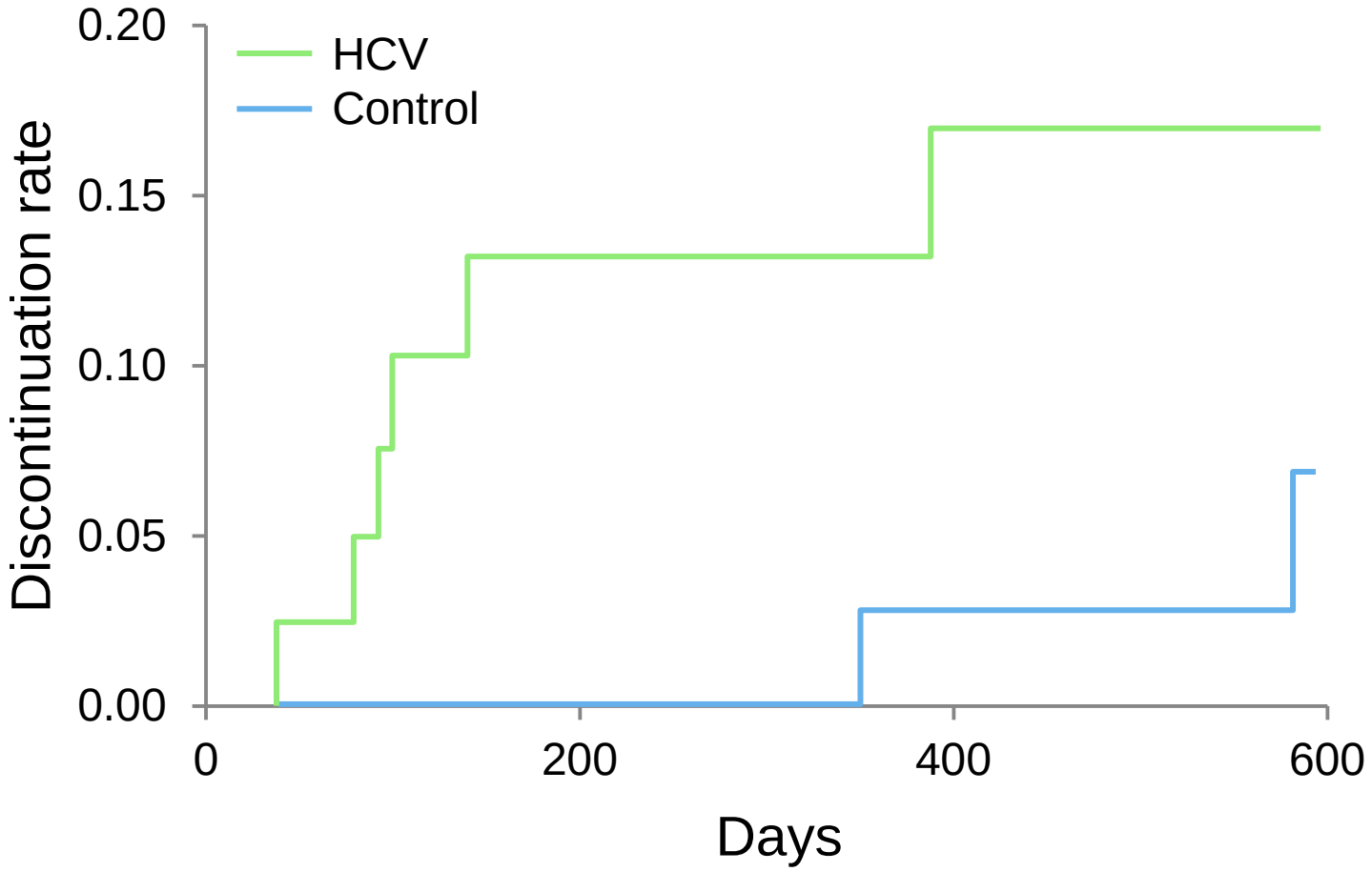
Mark S: Sulkowski Clin Infect Dis 38:S90, 2004

Incidence of Severe Hepatotoxicity With Different Protease Inhibitors



Mark S: Sulkowski Clin Infect Dis 38:S90, 2004

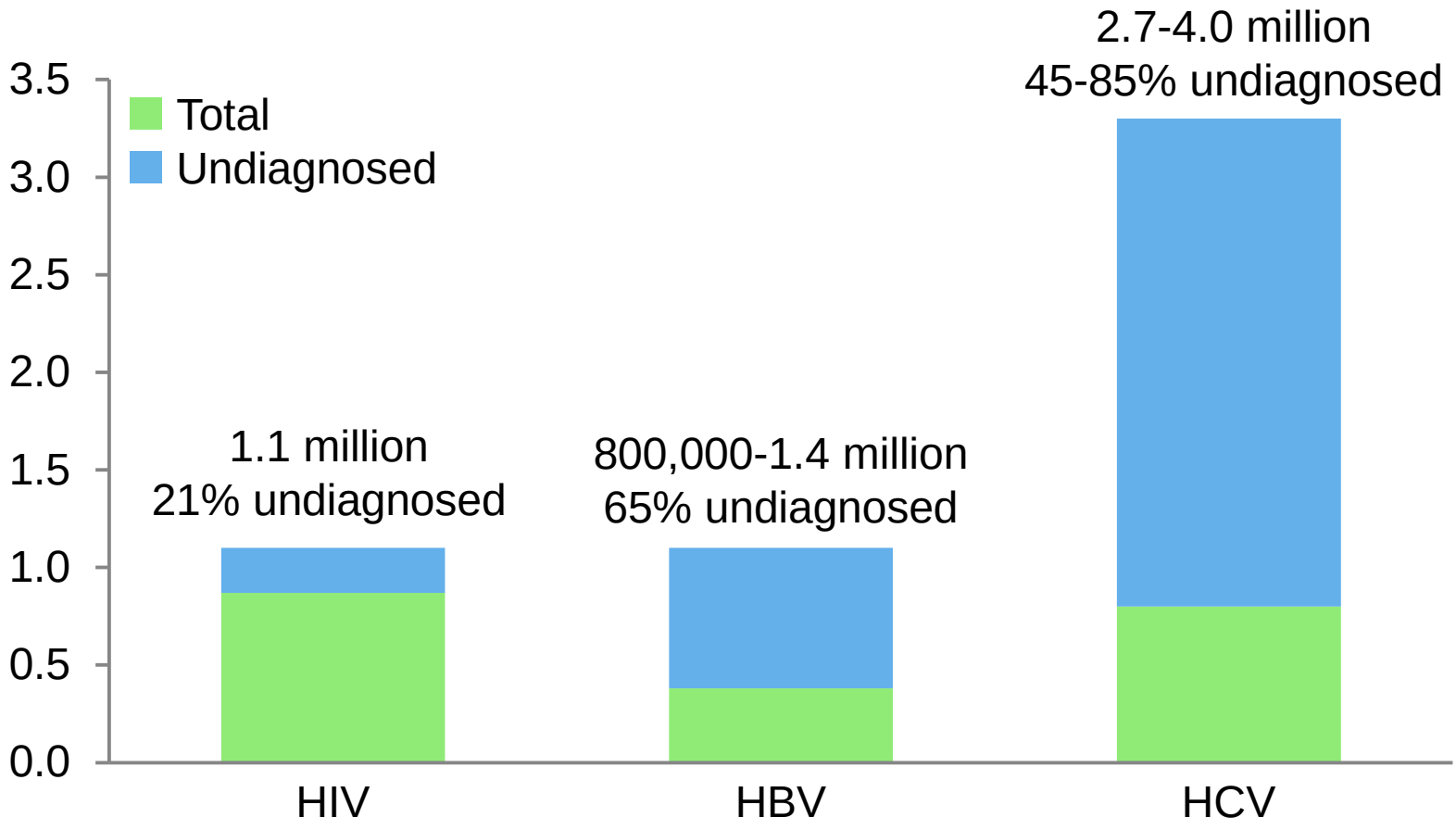
HAART Discontinuation Rates Due to Hepatic Toxicity in HIV/HCV Coinfected Patients



Melvin DC: et al AIDS 14:463, 2000

Diagnosis

The Problem of Undiagnosed Infection



Institute of Medicine. Hepatitis and Liver Cancer: A National Strategy for Prevention and Control of Hepatitis B and C. Washington, DC: The National Academies Press; 2010

HCV Screening Guidelines

Anyone born between 1945 and 1965

- HIV-infected
- History of illicit injection drug use or intranasal cocaine use, even if only used once
- Received clotting factors made before 1987
- Ever on chronic hemodialysis
- Persistently elevated ALT level
- Informed that they received blood from a donor who later tested positive for HCV
- Received blood/organs before July 1992
- Children born to HCV-infected mothers.
- Needle stick injury or mucosal exposure to HCV+ blood

Smith, et al: MMWR Recomm Rep 61:1, 2012

HCV Screening Among HIV+

- All patients should be screened for **HCV at least once**
- Annual HCV testing recommended for*
  - Injection drug users
  - HIV+ men who have unprotected sex

*European AIDS Clinical Society recommends annual HCV screening in all HIV+ persons

IDSA Primary Care Guidelines for Management of Persons Infected with HIV: 2013 Update

AASLD/IDSA Recommendations for Testing, Managing, and Treating Hepatitis C: 2014

HCV Screening

Anti-HCV antibody

- If positive → HCV RNA confirmatory testing

HCV RNA testing

- Anti-HCV positive
- Anti-HCV negative but suspect acute HCV
- Anti-HCV negative but severely immunocompromised

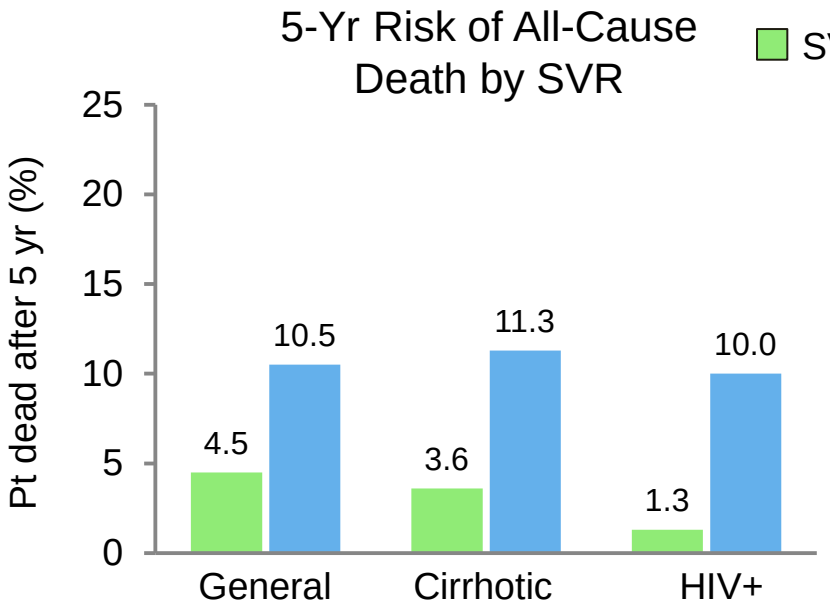
Treatment

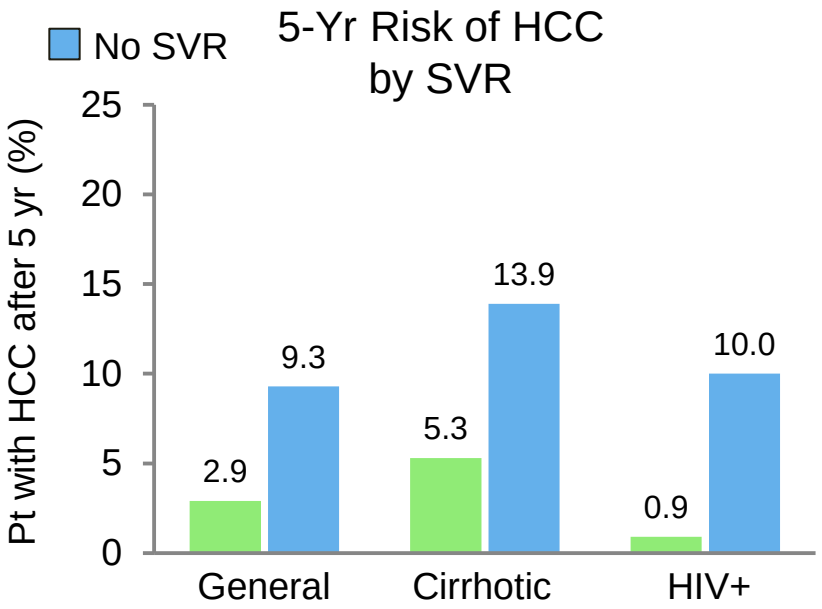
Does SVR Confer Benefit to HIV coinfected patients too?

SVR Associated With Reduced 5-Yr Risk of Death and HCC in All Populations

SVR on IFN-based therapy was associated with substantial benefit vs no SVR

- 62% to 84% reduction in all-cause mortality, 90% reduction in liver transplantation, 68% to 79% reduction in HCC

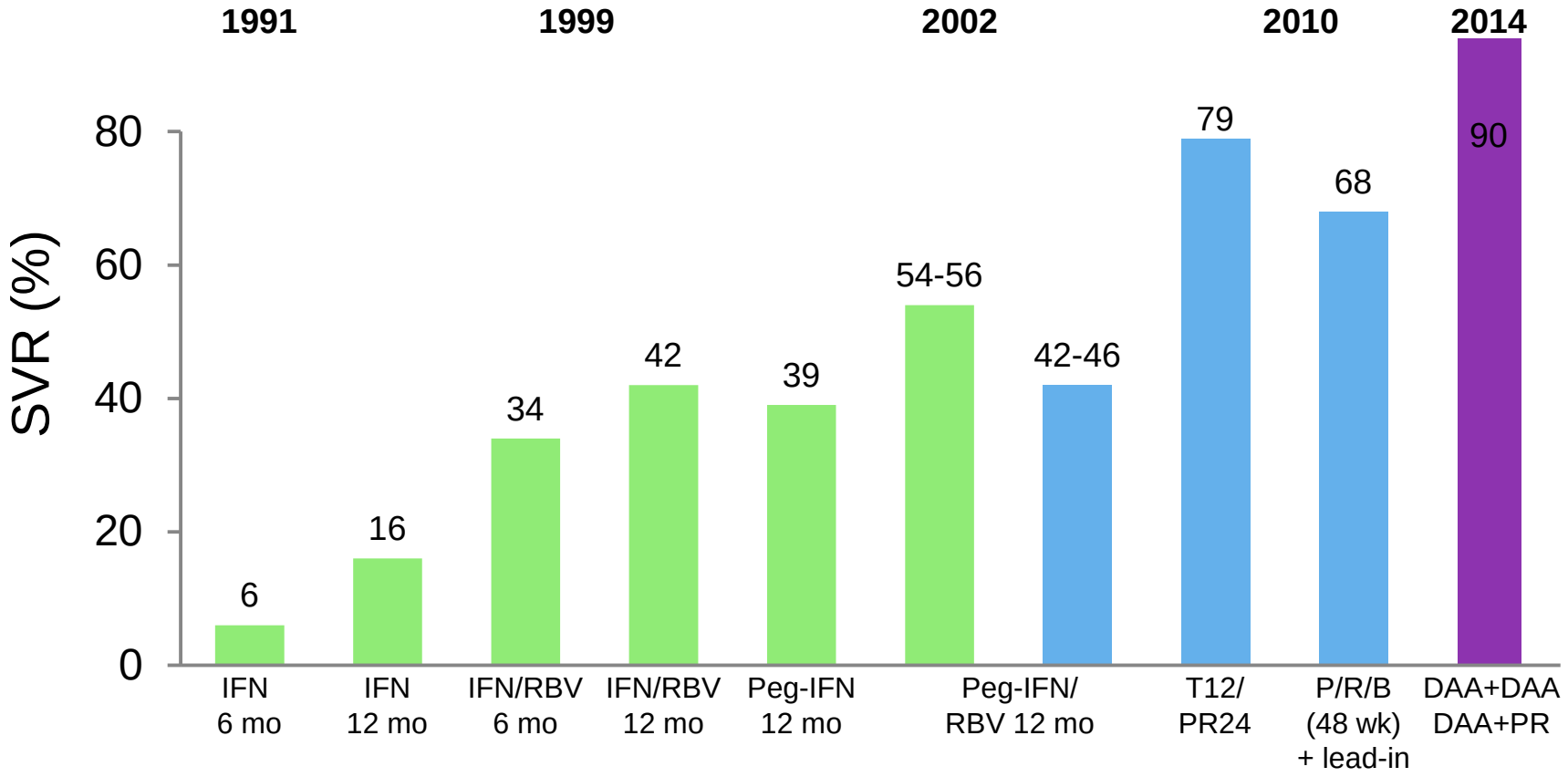




Hill AM et al: AASLD, 2014. Abstract 44

How Good are HCV Treatment Responses in HIV Coinfected Patients

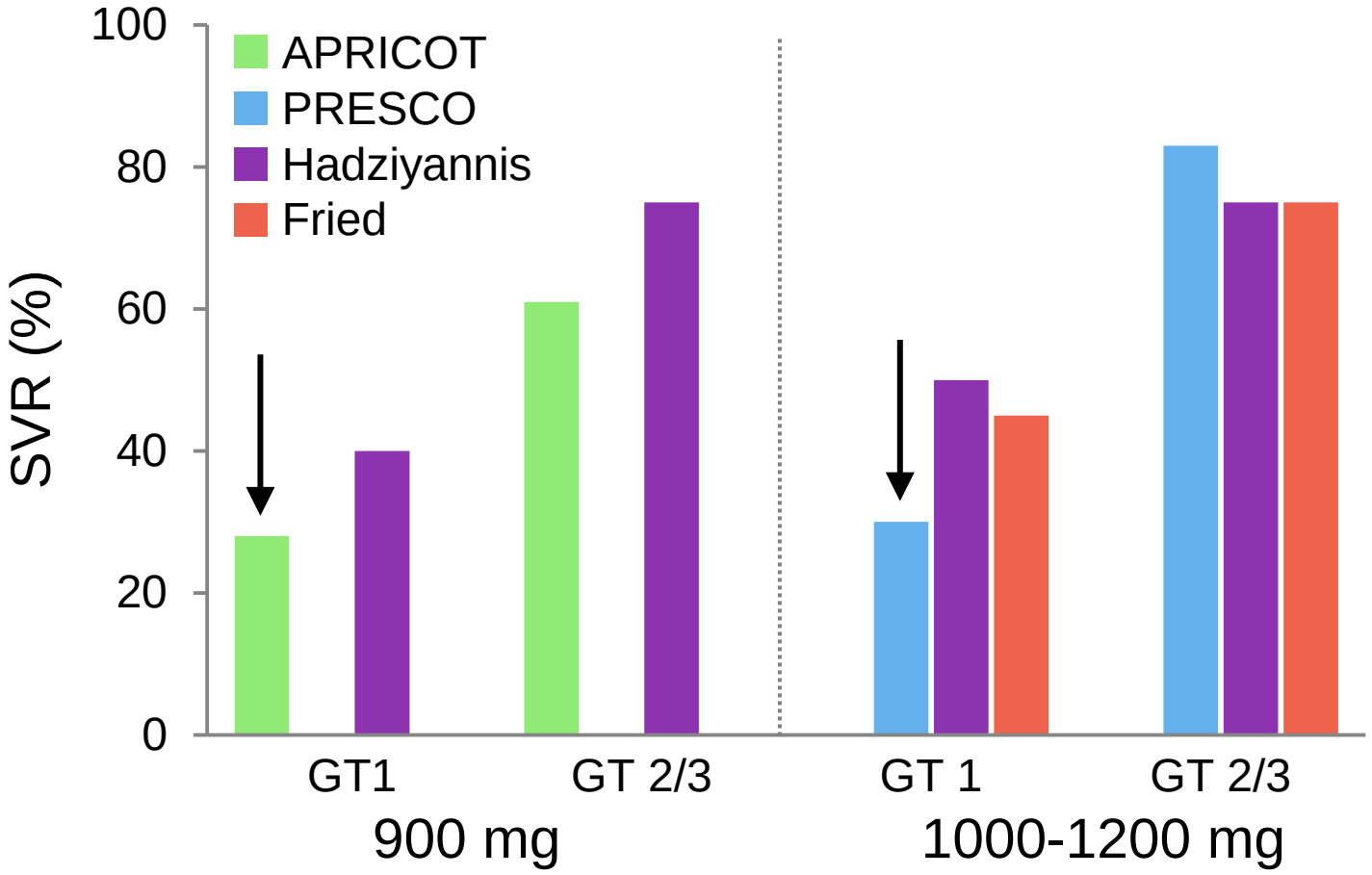
Milestones in Therapy of HCV: Overall SVR Rates (Mono-infection)



Adapted from Strader DB, et al. Hepatology. 2004;39(4):1147-1171. Hezode C, et al. N Engl J Med. 2009; 360(18):1839-1850. Kwo P, et al. Presented at: EASL; April 23, 2009; Copenhagen, Denmark. Abstract 4. Kwo PY, et al. Lancet. 2010;376(9742):705-716. Jacobson IM, et al. N Engl J Med. 2011;364:2405-2416; Poordad F, et al. N Engl J Med. 2011;364(13):1195-1206. Telaprevir prescribing information at http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/201917lbl.pdf. Accessed September 12, 2012.

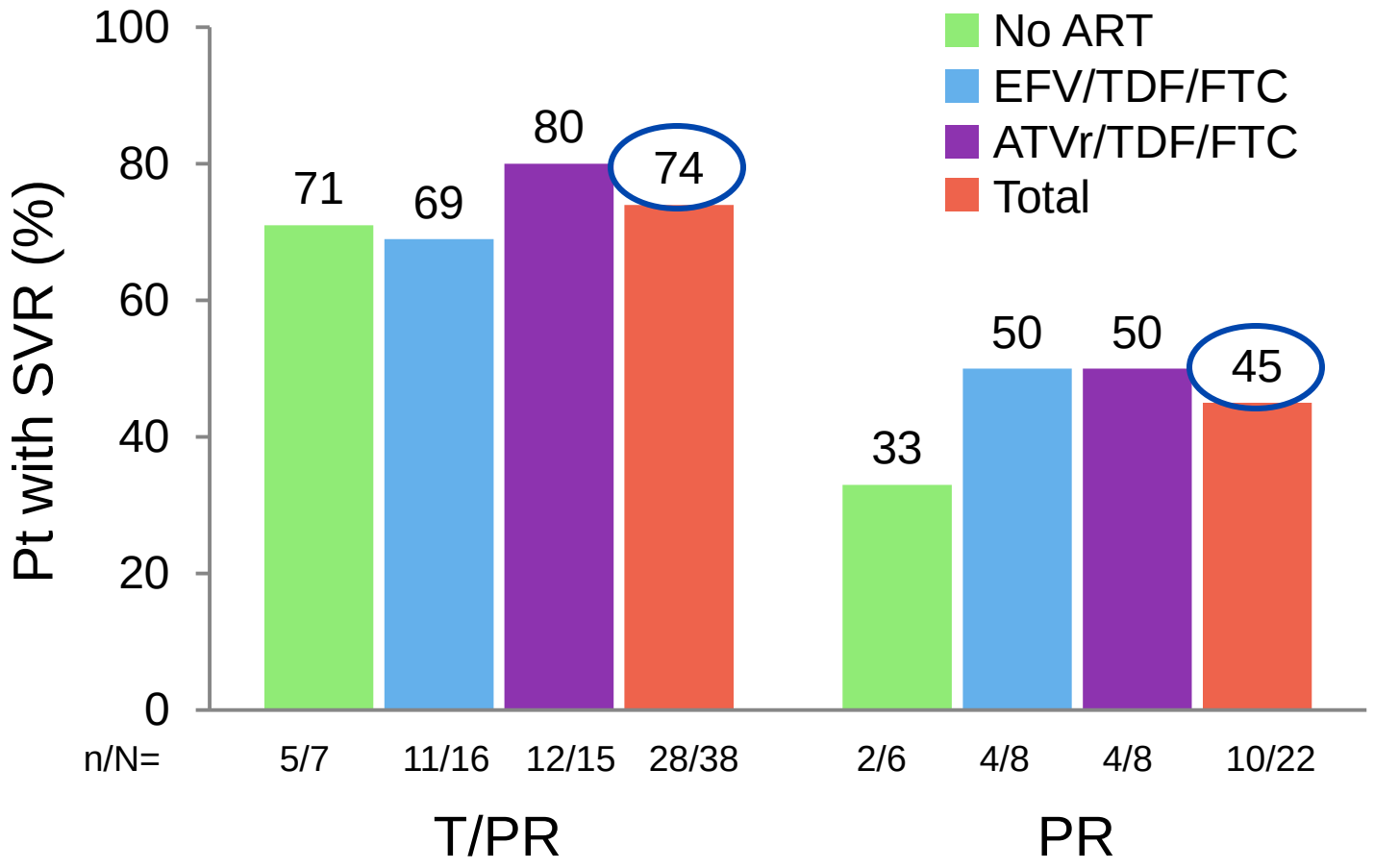
The historical Perspective

Treatment of Coinfection vs Monoinfection
48 weeks PEG+RBV



Hadziyannis et al. Ann Int Med 2004; Fried et al. NEJM 2002; Torriani et al NEJM 2004; Nunez et al (PRESCO) AIDS Res Human Retro 2007

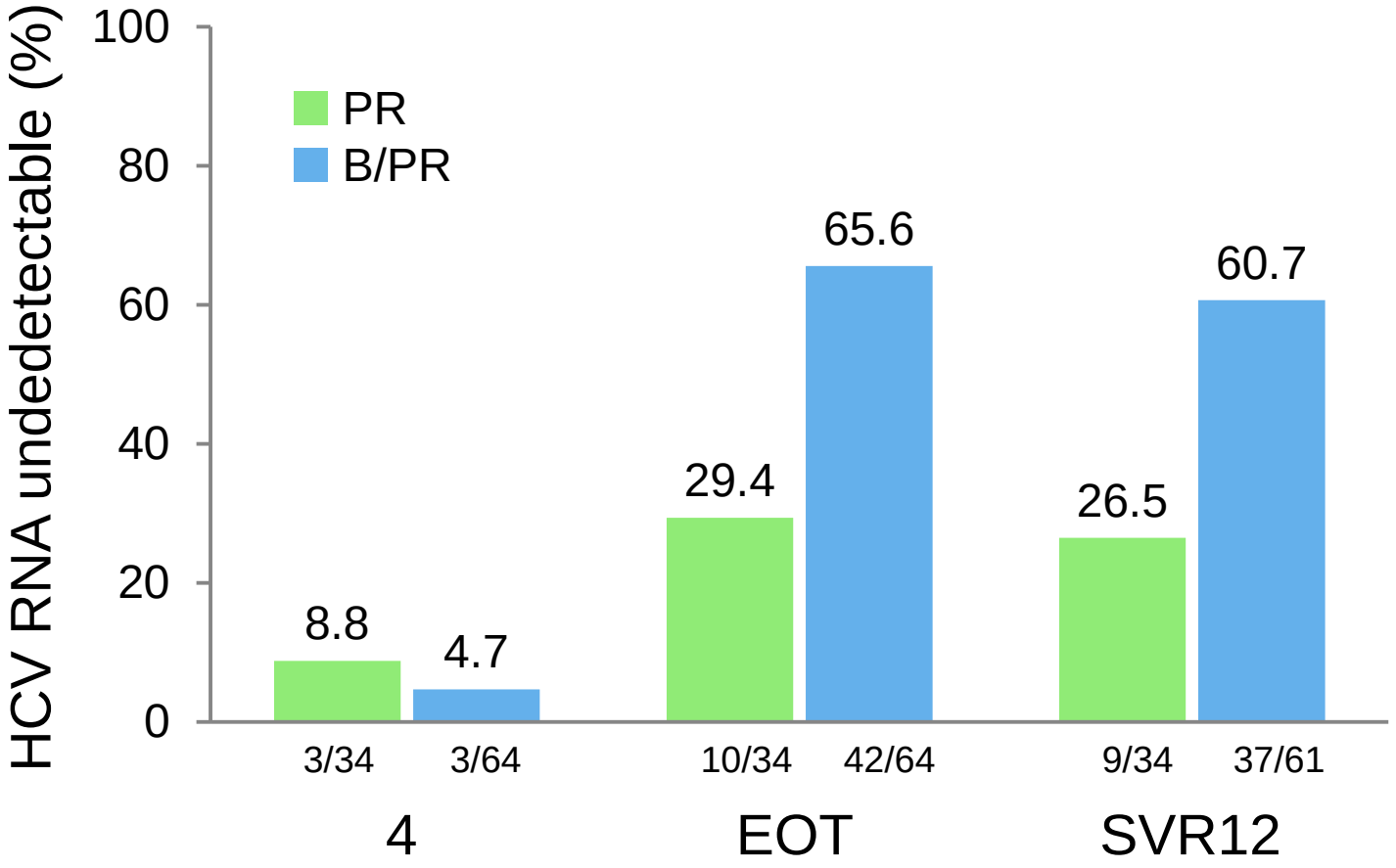
TVR+PEG+RBV
SVR 12



*Patient was defined as SVR12 if HCV RNA was <LLOQ in the visit window

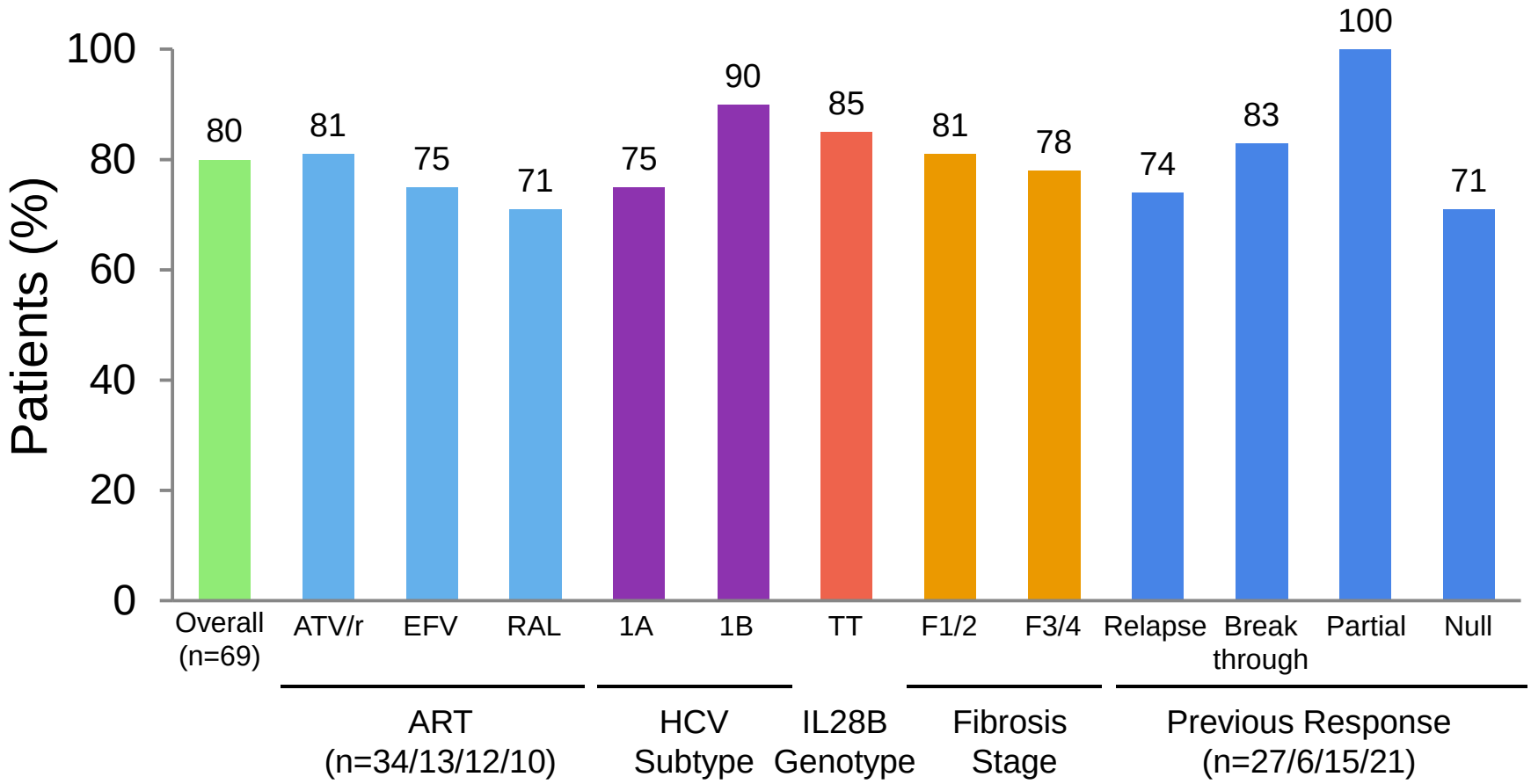
Dieterich D et al: 19th CROI; Seattle, WA; March 5-8, 2012; Abst 46

BOC+PEG+RBV Naïve G1 with HIV Virologic Response Over Time



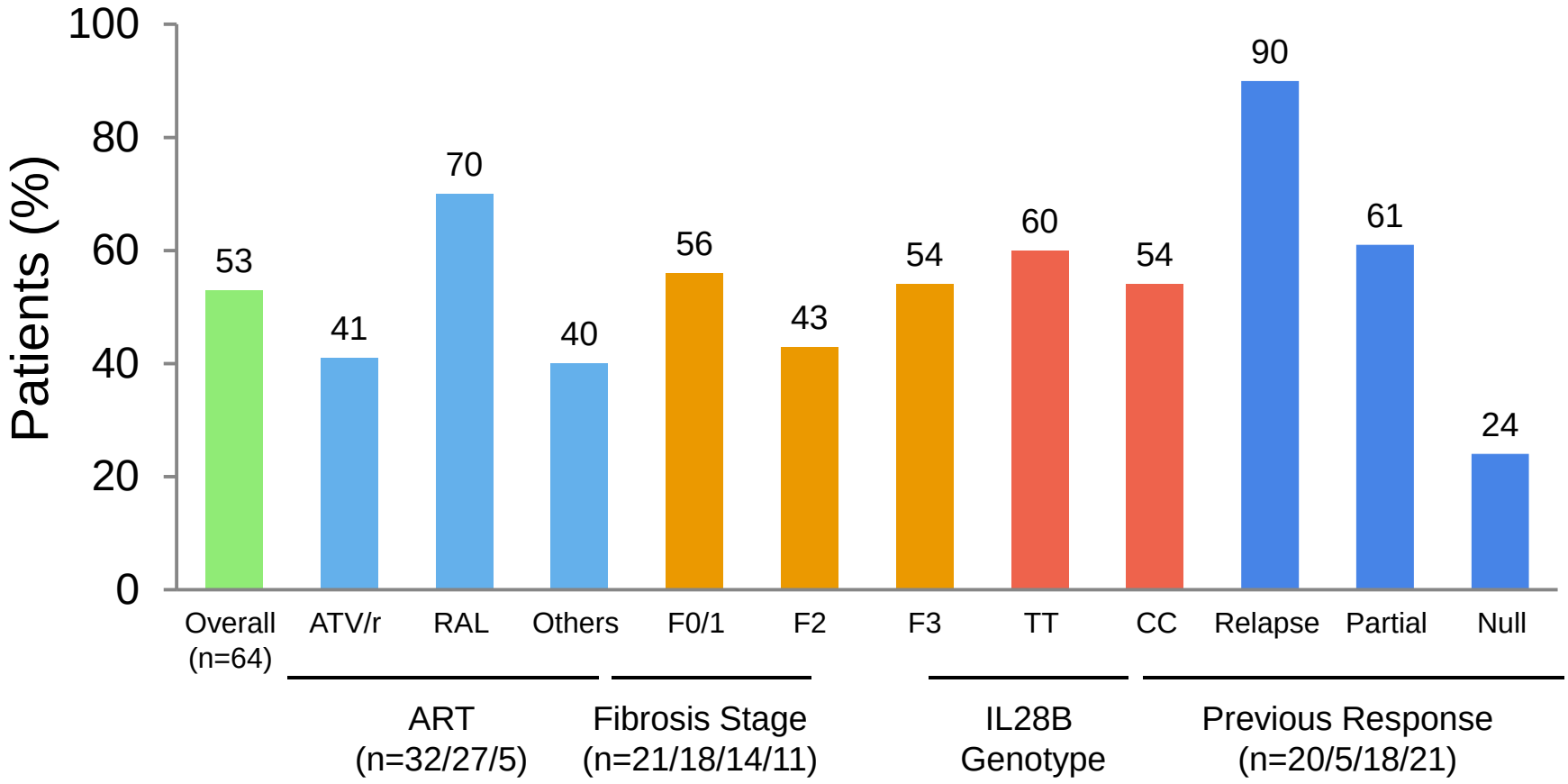
Sulkowski M et al: Abstract #47 CROI 2012

ANRS HC26 TelapreVIH Study
SVR24 by Baseline Characteristics



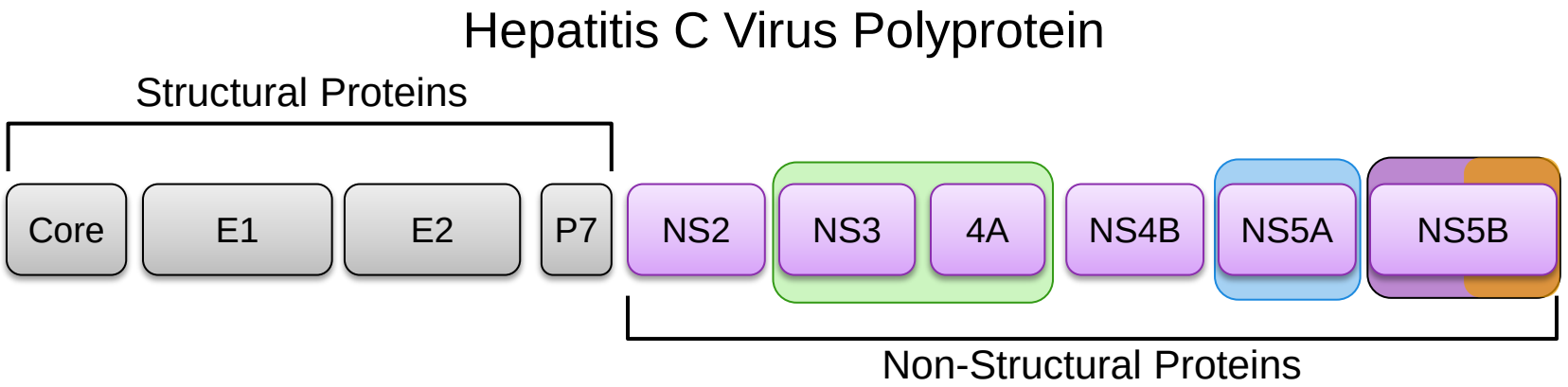
Cotte L et al: 21th CROI, 2014. Abstract 668

ANRS HC27 BocepreVIH Study: SVR_{12} Results



Cotte L et al: 21th CROI, 2014. Abstract 668

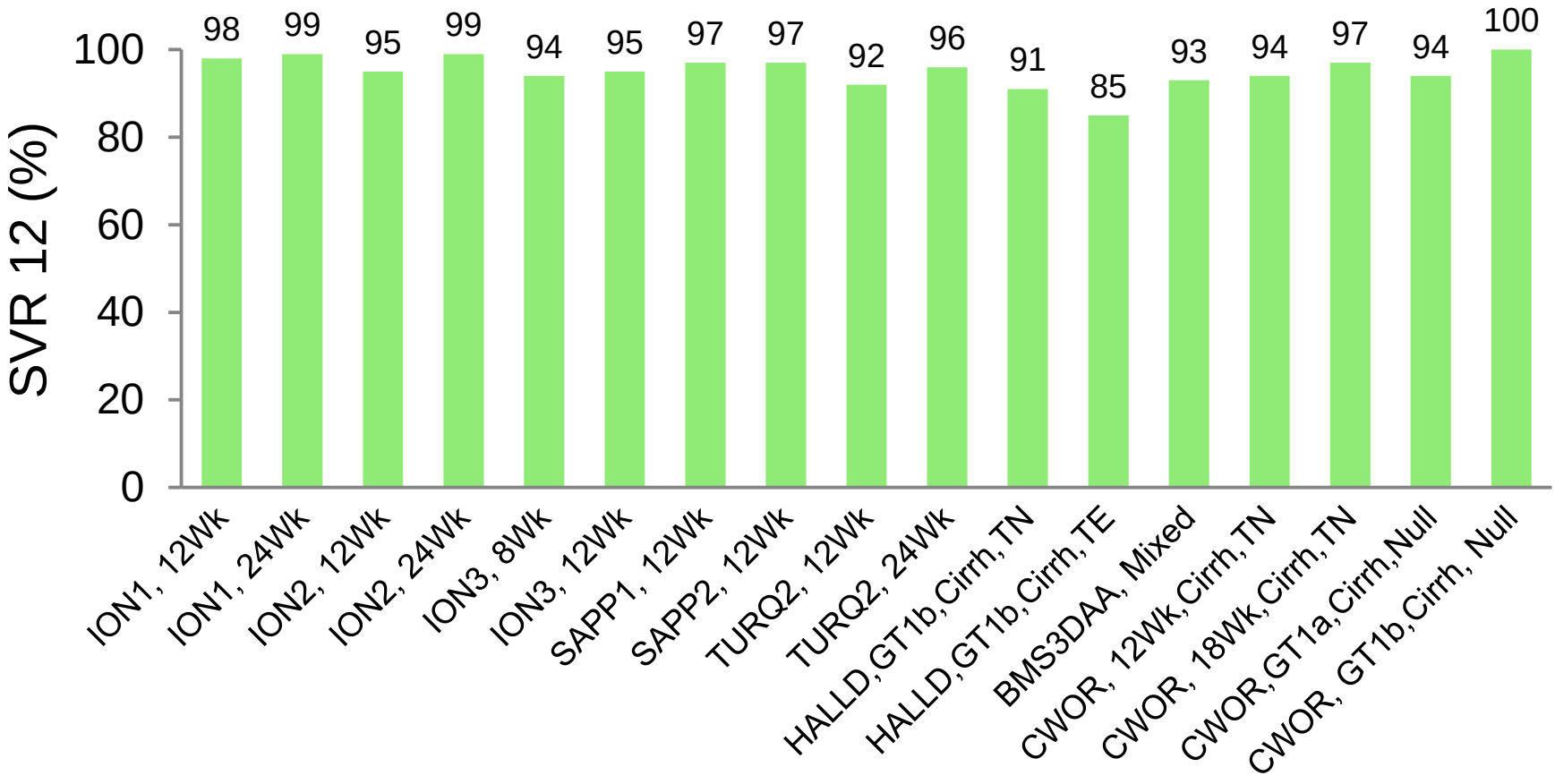
Therapeutic Targets for Direct Acting Antiviral Drug Development



Protease inhibitors	NS5A Inhibitors	NS5B Nucleoside Inhibitors	NS5B Non-Nucleoside Inhibitors
• High Potency • Multi-genotypic coverage • Intermediate to high barrier to resistance	• High Potency • Multi-genotypic coverage • Low to intermediate barrier to resistance	• Intermediate Potency • Pan-genotypic coverage • High barrier to resistance	• Intermediate Potency • Limited genotypic coverage • Low barrier to resistance

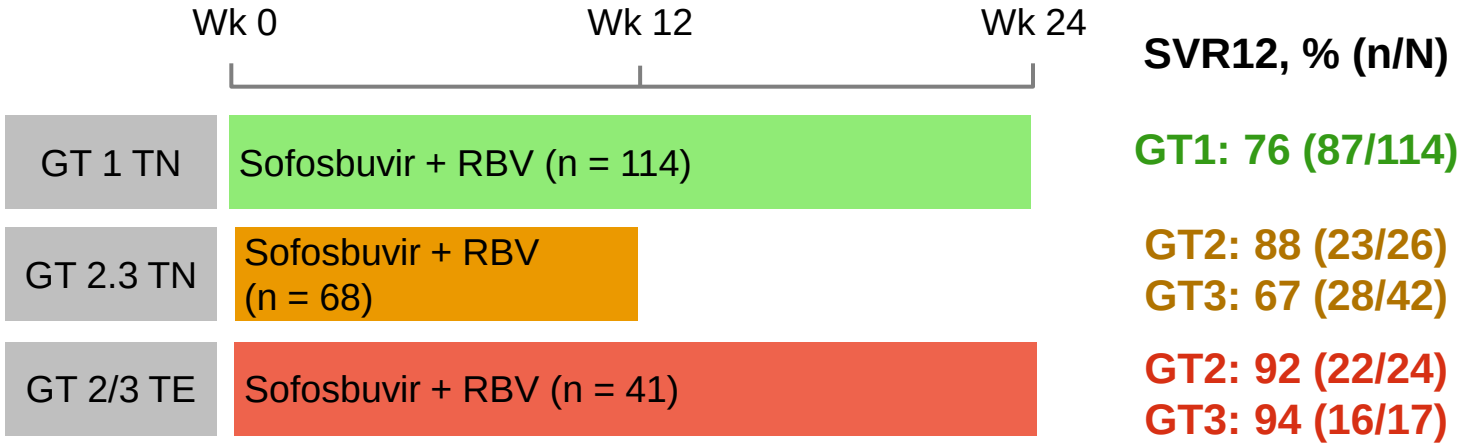
Poordad: J Viral Hep 19:449, 2012

Reported SVR12 of IFN-free, Multi-DAA Rx



PHOTON-1: Sofosbuvir + RBV in GT1-3 HIV/HCV-coinfected

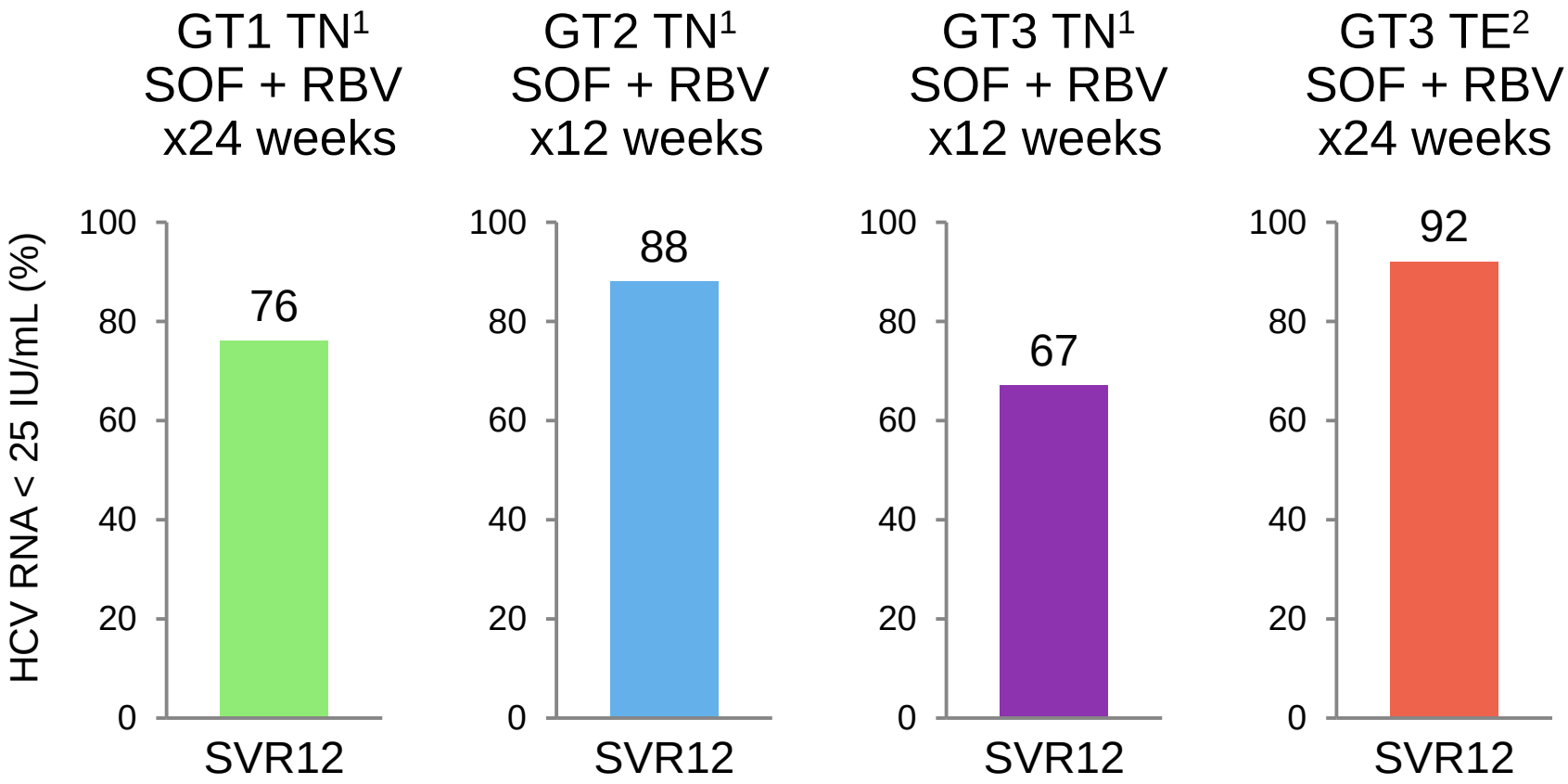
- Nonrandomized, open-label phase III study; primary endpoint: SVR12
- Stable ART (HIV-1 RNA < 50 copies/mL for > 8 wks before enrollment)
  - 95% on ART: TDF/FTC, 100%; EFV, 35%; ATV/RTV, 17%; DRV/RTV, 15%; RAL, 16%; RPV, 6%
- Cirrhosis at baseline: GT1, 4%; GT2/3 tx naive, 10%; GT2/3 tx-exp'd: 24%



Sofosbuvir 400 mg QD; weight-based RBV 1000 or 1200 mg/day

Sulkowski MS et al: JAMA 312:353, 2014

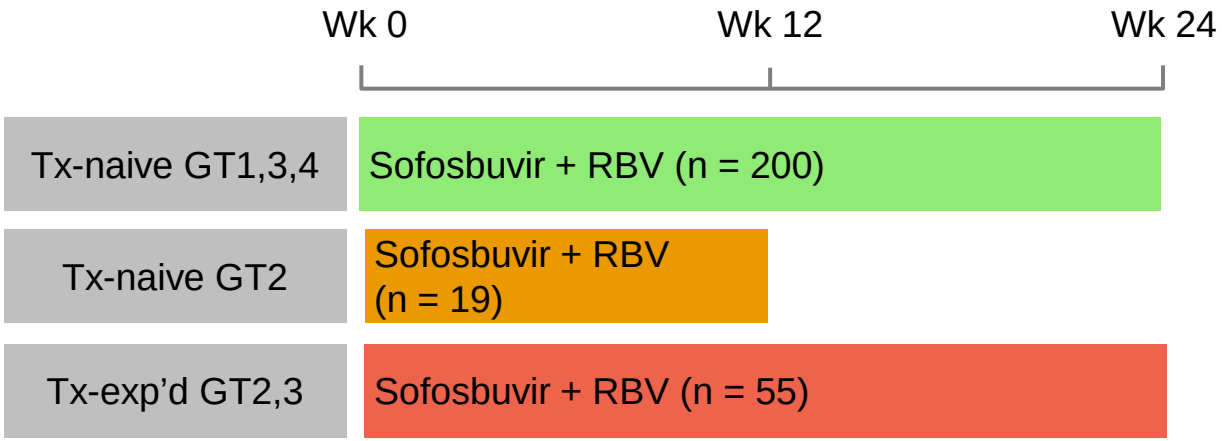
PHOTON-1 SVR12: SOF + RBV in GT1, 2, 3 HCV Treatment-Naive and GT 3 Treatment-Experienced/HIV Co-infection



1. Sulkowski MS, et al. AASLD 2013. Washington, DC. Oral #212;
2. SOVALDI™ [PI]. Gilead Sciences, Inc. Foster City, CA December 2013

PHOTON-2: Sofosbuvir + RBV in GT1-4 HIV/HCV-coinfected

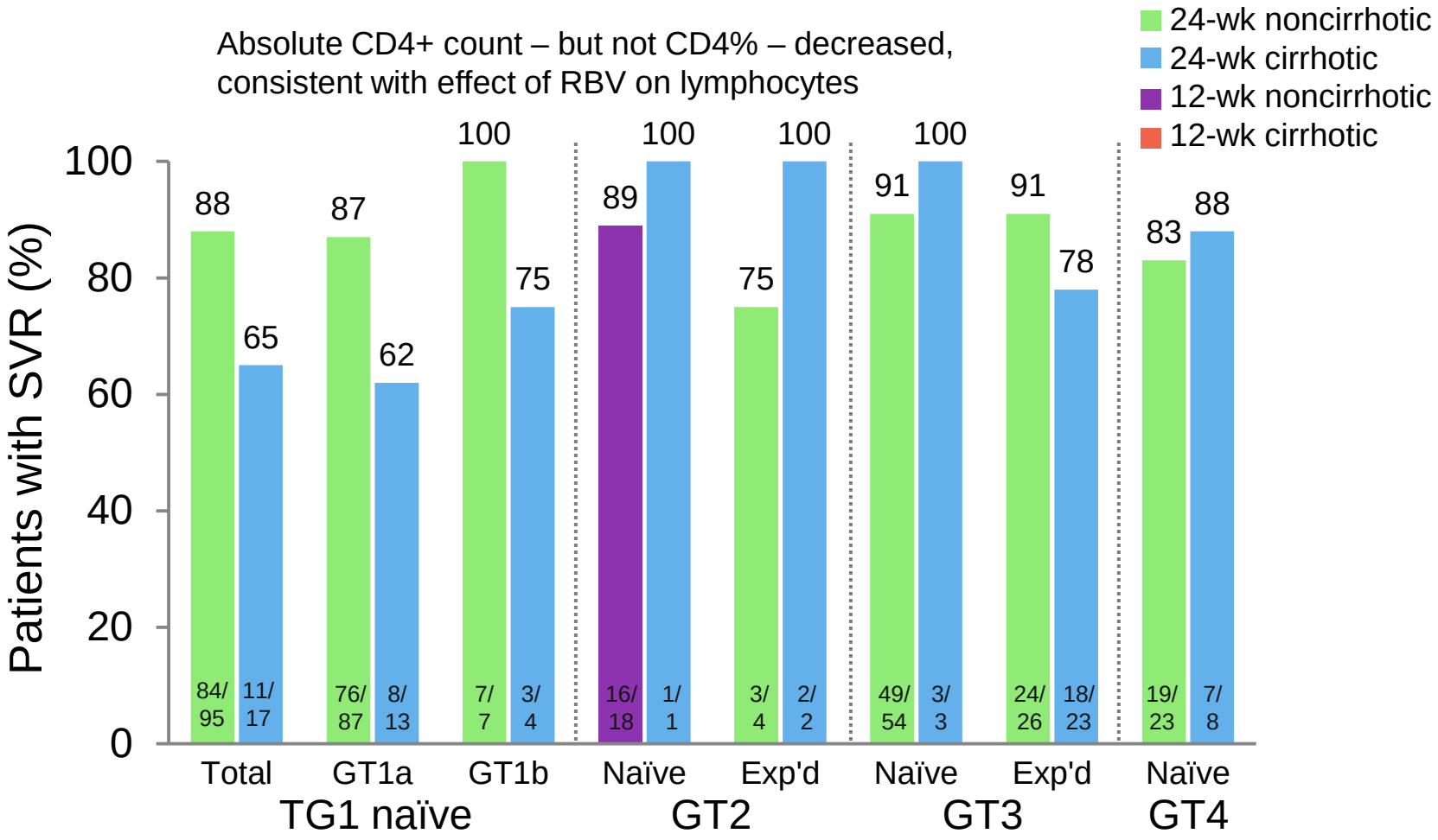
- Nonrandomized, open-label phase III study; primary endpoint: SVR12
- Stable ART (HIV-1 RNA < 50 copies/mL for ≥ 8 wks before enrollment)
  - 97% on ART: TDF/FTC, 100%; EFV, 25%; ATV/RTV, 17%; DRV/RTV, 21%; RAL; 23%; RPV, 5%
- Cirrhosis at baseline: All pts, 20%; tx-naive patients, 13%; tx-exp'd patients, 45%



Sofosbuvir 400 mg QD; weight-based RBV 1000 or 1200 mg/day

Molina JM et al: AIDS, 2014. Abstract MOAB0105LB.

PHOTON-2: SVR12 by Genotype and Cirrhosis



Molina JM et al: AIDS, 2014. Abstract MOAB0105LB.

Ledipasvir-Sofosbuvir in GT1 with HIV Coinfection

NIAID ERADICATE Trial: Features

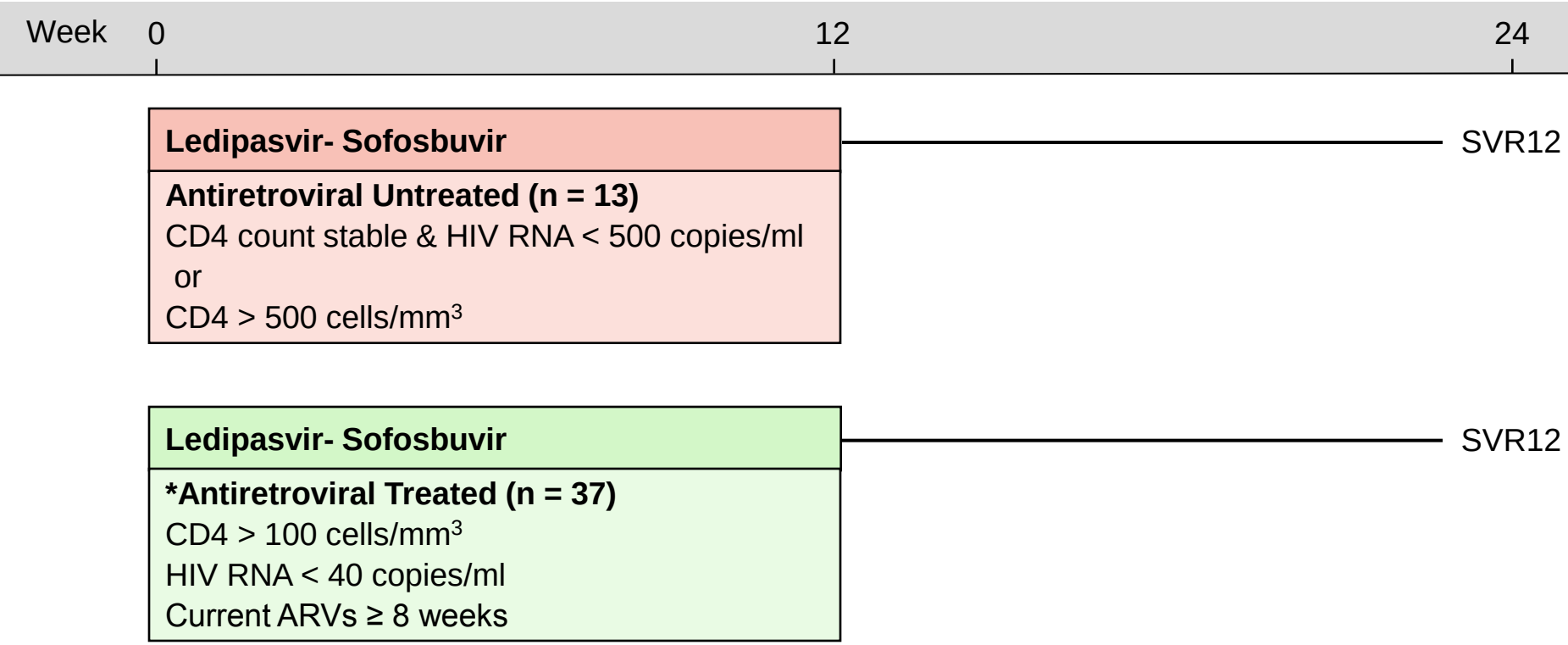
NIAID ERADICATE Trial

- Design: Open-label, phase 2, using fixed dose combination of ledipasvir-sofosbuvir for 12 or weeks in treatment-naïve GT 1 and HIV coinfection
- Setting: one center in United States
- Entry Criteria
  - Chronic HCV Genotype 1
  - HCV Treatment Naïve
- Patient Characteristics (range in different treatment arms)
  - n=50 adult patients
  - Cohort A: Antiretroviral Untreated
  - Cohort B: Antiretroviral Treated
  - Fibrosis stage 0-3 (patients with cirrhosis excluded)
- End-Points: Primary = SVR12; safety and tolerability

Osinusi A et al: 65th AASLD, 2014: Abstract 84.

Ledipasvir-Sofosbuvir in GT1 with HIV Coinfection

NIAID ERADICATE Trial: Study Design



Drug Dosing: Ledipasvir-sofosbuvir (90/400 mg): fixed dose combination; one pill once daily

***Antiretrovirals allowed**: tenofovir-emtricitabine, efavirenz, rilpivirine, and raltegravir

Osinusi A et al: 65th AASLD, 2014: Abstract 84.

Ledipasvir-Sofosbuvir in GT1 with HIV Coinfection

NIAID ERADICATE Trial: Antiretroviral Regimens

Antiretroviral agent	Antiretroviral received (n = 37)
Tenofovir-emtricitabine	37 (100)
Efavirenz	15 (41)
Raltegravir	10 (27)
Rilpivirine	8 (21)
Rilpivirine + Raltegravir	3 (8)
Efavirenz + Raltegravir	1 (3)

Osinusi A et al: 65th AASLD, 2014: Abstract 84.

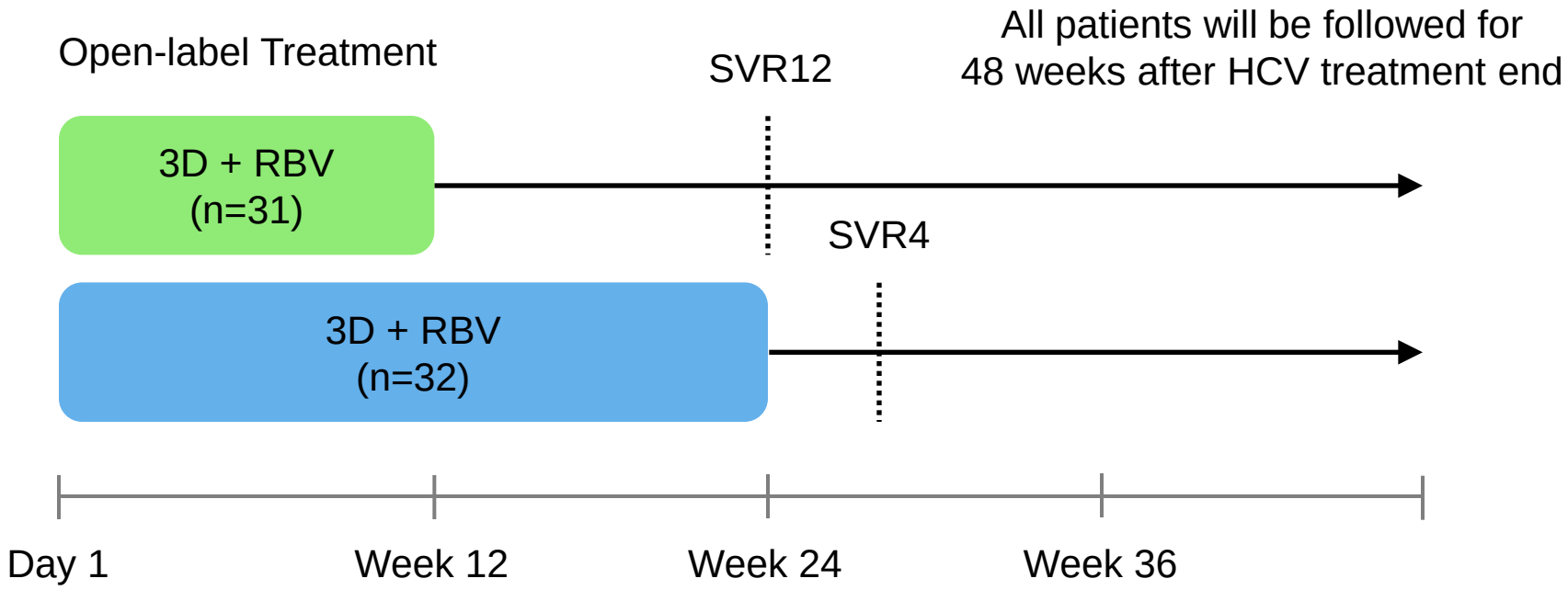
Ledipasvir-Sofosbuvir in GT1 with HIV Coinfection

NIAID ERADICATE Trial: Antiretroviral Regimens

HCV RNA < LLOQ, %	**ARV Untreated** (n=13)	**ARV Treated** (n=37)
Week 4	100 (n=13)	100 (n=37)
Week 8	100 (n=13)	100 (n=37))
Week 12 (EOT)	100 (n=13)	100 (n=37)
SVR 4	100 (n=13)	97 (n=36)
SVR 8	100 (n=13)	97 (n=36)
SVR 12	100 (n=13)	97 (n=36)

Osinusi A et al: 65th AASLD, 2014: Abstract 84.

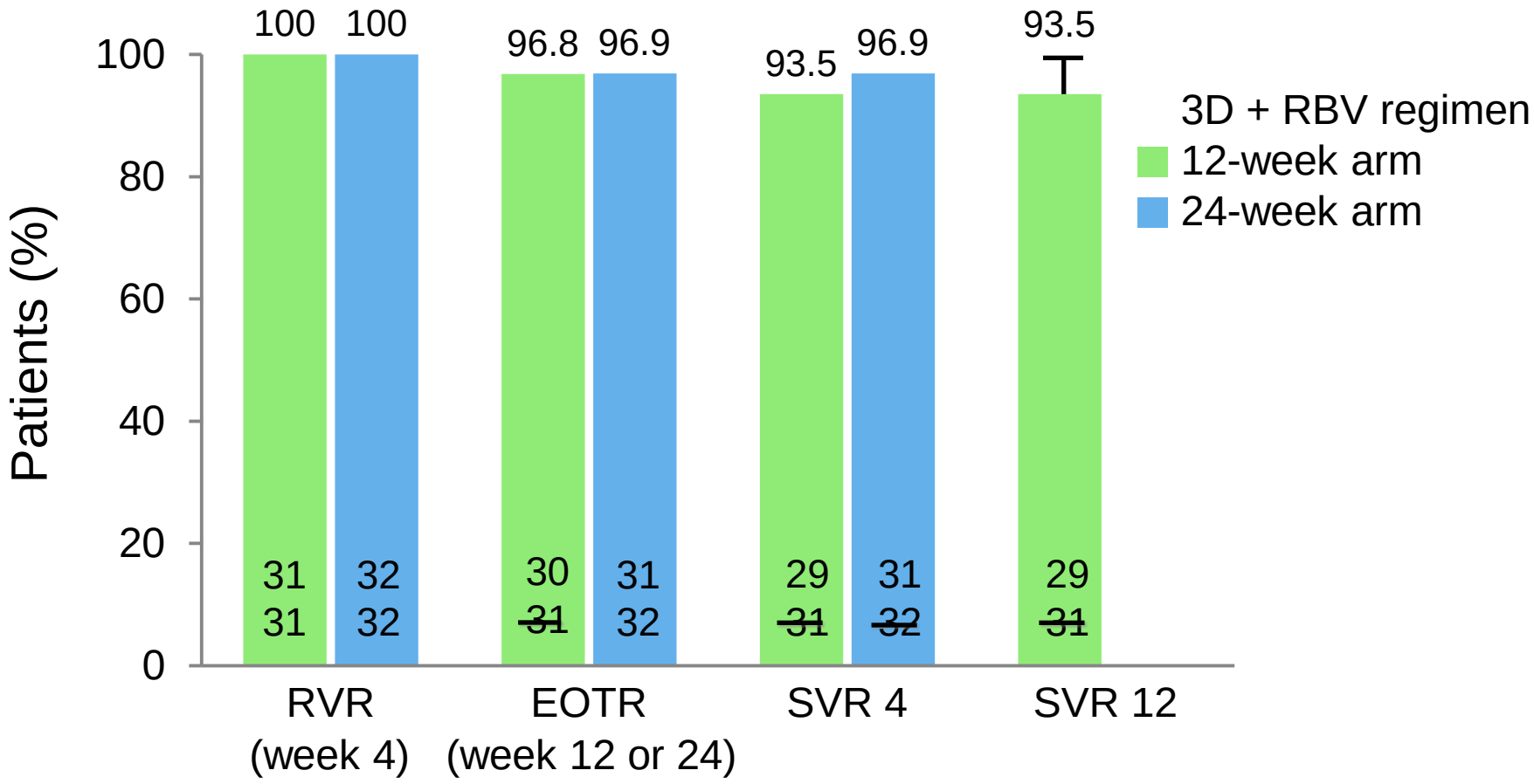
TURQUOISE-I: SAFETY AND EFFICACY OF ABT-450/R/OMBITASVIR, DASABUVIR, AND RIBAVIRIN IN PATIENTS CO-INFECTED WITH HEPATITIS C AND HIV-1, Part 1 Study Design



- **Key Eligibility Criteria:** HCV GT1 infection, HCV treatment-naïve or pegIFN/RBV-experienced, Child-Pugh A Cirrhosis allowed, Stable HIV-1 infection on ATV or RAL-inclusive ART regimen

Sulkowski et al: IAS 2014, Melbourne, Australia

TURQUOISE-I Results: Virologic Response Rates



Sulkowski et al: IAS 2014, Melbourne, Australia

AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES
AASLD

IDSA
Infectious Diseases Society of America

Collaborating Partner
IAS–USA
International Antiviral Society–USA

Printable version of the Full Report

Full Report Menu

When and in Whom to Initiate HCV Therapy Table 1. Settings of Liver-Related Complications and Extrahepatic Disease in Which HCV Treatment is Most Likely to Provide the Most Immediate and Impactful Benefits

Highest Priority for Treatment Owing to Highest Risk for Severe Complications

Advanced fibrosis (Metavir F3) or compensated cirrhosis (Metavir F4)
Rating: Class I, Level A

Organ transplant
Rating: Class I, Level B

Type 2 or 3 essential mixed cryoglobulinemia with end-organ manifestations (eg, vasculitis)
Rating: Class I, Level B

Proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis
Rating: Class IIa, Level B

High Priority for Treatment Owing to High Risk for Complications

Fibrosis (Metavir F2)
Rating: Class I, level B

HIV-1 coinfection
Rating: Class I, Level B

Hepatitis B virus (HBV) coinfection
Rating: Class IIa, Level C

Other coexistent liver disease (eg, [NASH])
Rating: Class IIa, Level C

Debilitating fatigue
Rating: Class IIa, Level B

Type 2 Diabetes mellitus (insulin resistant)
Rating: Class IIa, Level B

Porphyria cutanea tarda
Rating: Class IIb, Level C

Ratings refer to the strength and level of evidence with regard to benefits of treatment in these settings.

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HIV/HCV-coinfected persons should be treated and retreated the same as persons without HIV infection

Recommended Regimens for HCV/HIV-Coinfected Patients

Genotype	Recommended Regimens
Genotype 1	
HCV treatment-naïve, no cirrhosis	Ledipasvir- Sofosbuvir for 12 wks Ombitasvir-paritaprevir-ritonavir and dasabuvir for 12 wks (+ RBV for genotype 1a) Sofosbuvir + simeprevir ± RBV for 12 wks
HCV treatment-naïve, cirrhosis	Ledipasvir- Sofosbuvir for 12 wks Ombitasvir-paritaprevir-ritonavir and dasabuvir + RBV (24 weeks for genotype 1a) Sofosbuvir + simeprevir ± RBV for 24 wks
Genotype 2	
	Sofosbuvir + RBV for 12 wks (16 weeks if cirrhosis)
Genotype 3	
	Sofosbuvir + RBV for 24 wks
Genotype 4	
	Ledipasvir- Sofosbuvir for 12 wks Ombitasvir-paritaprevir-ritonavir and dasabuvir + RBV for 12 weeks Sofosbuvir + RBV for 24 wks
Genotype 5	Sofosbuvir + pegIFN/RBV for 12 wks
Genotype 6	Ledipasvir- Sofosbuvir for 12 wks

AASLD/IDSA/IAS–USA. Recommendations for testing, managing, and treating hepatitis C. http://www.hcvguidelines.org

Any Special Precautions when Treating HCV-HIV Coinfected Patients?

Select ARV Drugs by Drug Class	HCV Drugs						
	HCV Direct-Acting Antiviral Agents					HCV Non-Direct-Acting Antiviral Agents	
	NS5B Inhibitor	Co-Formulated NS5A/NS5B Inhibitor	HCV Protease Inhibitors				
				No Longer Recommended by HCV Guidelines			
	Sofosbuvir	Ledipasvir/ Sofosbuvir	Simeprevir	Boceprevir	Telaprevir (Discontinued from U.S. market in October 2014)	Ribavirin	Pegylated interferon alpha
Nucleoside Reverse Transcriptase Inhibitors							
FTC	✓	✓	✓	✓	✓	✓	✓
3TC	✓	✓	✓	✓	✓	✓	✓
ABC	✓	✓	✓	✓	✓	✓	✓
TDF	✓	✓[b]	✓	✓	✓ Monitor for TDF toxicity due to ↑TDF level.	✓	✓
ZDV	✓	✓	✓	✘[a]	✘[a]	✘[a]	✘[a]
HIV Protease Inhibitors							
ATV, ATV/r, or ATV/cobi	✓	✓[b]	✘	✘	✓	✓	✓
DRV/r or DRV/cobi	✓	✓[b]	✘	✘	✘	✓	✓
FPV or FPV/r	✓	✓[b]	✘	✘	✘	✓	✓
LPV/r	✓	✓[b]	✘	✘	✘	✓	✓
SQV/r	✓	✓[b]	✘	✘	✘	✓	✓
TPV/r	✘	✘	✘	✘	✘	✓	✓

Select ARV Drugs by Drug Class	HCV Drugs						
	HCV Direct-Acting Antiviral Agents					HCV Non-Direct-Acting Antiviral Agents	
	NS5B Inhibitor	Co-Formulated NS5A/NS5B Inhibitor	HCV Protease Inhibitors				
				No Longer Recommended by HCV Guidelines			
	Sofosbuvir	Ledipasvir/ Sofosbuvir	Simeprevir	Boceprevir	Telaprevir (Discontinued from U.S. market in October 2014)	Ribavirin	Pegylated interferon alpha
Non-Nucleoside Reverse Transcriptase Inhibitors							
EFV	✓	✓ If EFV used with TDF/FTC, monitor for TDF toxicity due to ↑ TDF level.	✘	✘	✓ ↑ telaprevir dose to 1125 mg q8h	✓	✓
ETR	✓	✓	✘	✓ ***EXCEPTION*** ETR + boceprevir **is not recommended** when coadministered with drugs that may further decrease ETR (e.g., TDF, DRV/r, LPV/r, SQV/r).	✓	✓	✓
NVP	✓	✓	✘	?	?	✓	✓
RPV	✓	✓	✓	✓	✓	✓	✓
Integrase Strand Transfer Inhibitors							
DTG	✓	✓	✓	✓	✓	✓	✓
EVG/cobi/ TDF/FTC	✓	✘	✘	✘	✓	✓	✓
EVG + (PI/r without cobi)	Refer to recommendations for specific ritonavir-boosted PI						
RAL	✓	✓	✓	✓	✓	✓	✓

Select ARV Drugs by Drug Class	HCV Drugs						
	HCV Direct-Acting Antiviral Agents					HCV Non-Direct-Acting Antiviral Agents	
	NS5B Inhibitor	Co-Formulated NS5A/NS5B Inhibitor	HCV Protease Inhibitors				
				No Longer Recommended by HCV Guidelines			
	Sofosbuvir	Ledipasvir/ Sofosbuvir	Simeprevir	Boceprevir	Telaprevir (Discontinued from U.S. market in October 2014)	Ribavirin	Pegylated interferon alpha
CCR5 Antagonist							
MVC	✓	✓	✓	✓ ↓MVC dose to 150 mg BID	✓ ↓MVC dose to 150 mg BID	✓	✓

[b] Concomitant use of ledipasvir/sofosbuvir with TDF and an HIV PI/r (or ATV/cobi or DRV/cobi) may lead to increased TDF exposure; consider alternative HCV or ARV therapy, especially in patients at risk of renal injury. If co-administration is necessary, monitor for TDF-associated adverse reactions.

Summary

- HCV and HIV – Substantial Global Burden
- HIV negatively affects the natural history of HCV at multiple points
- All HCV-infected patients should be screened for HIV and vice versa
- All HCV/HIV coinfected patients should be considered for treatment of HCV
- HCV/HIV coinfected patients should be treated similar to HCV monoinfected patients
- Pay attention to potential for drug interactions

Thank you to:

- Phyllis Tien
- Rohit Talwani
- Maggie Hoffman-Terry

MAYO CLINIC

Transplant Infectious Diseases

Raymund R. Razonable, MD
Stacey V. Rizza, MD
Randall C Walker, MD

Division of
INFECTIOUS DISEASES

Mayo Clinic Infectious Diseases Subspecialties Update
May 7-9, 2015

Disclosures

Grant support: Roche, Genentech, Qiagen (all funds given to the institution)

DSMB and Adjudication Committee: Astellas, Chimerix

Off-label Use: YES, commonly! (I will indicate so)

AST Infectious Diseases Guidelines. *American Journal of Transplantation*. March 2013 supplement. Blumberg, Danzinger, Kumar, Michaels and Razonable (eds).

In your line of work, you see transplant recipients:

A. Regularly
B. Occasionally
C. Rarely
D. Never

Basic Principles in Transplant ID

- Risk of infection: two major factors
  - Exposures of donor and recipient
  - Net state of immunosuppression
- High degree of clinical suspicion → early diagnosis
  - Attenuated clinical presentation
- Prevention and Treatment
  - Safe living practices, vaccines, prophylaxis, surveillance
  - Early antimicrobial treatment – preemptive or targeted
  - Reduce immunosuppression (caution: risk of rejection)
  - Source control (e.g., surgery)
  - Multi-disciplinary approach: ID/IPAC, surgeon, medicine, pharmacy, social work, nursing, environmental personnel, others

Infections after Solid Organ Transplantation

First month	Months 2-6	Beyond 6 months
Hospital acquired; surgical issues; donor-derived; active infections at tx	Opportunistic infections; impaired T cell function	Min immunosuppression; minority with augmented immunosuppression
Bacteremia (line-related) Fungemia (at risk) UTI (catheter-related) VAP SSI *C difficile* Herpes simplex Donor-derived infections*	CMV, HHV-6, Parvovirus B19 *M tuberculosis* *Nocardia* sp. *Pneumocystis jiroveci* Aspergillosis Zygomycosis Endemic mycoses Toxoplasmosis *Strongyloides* *T cruzi*	Community infections Zoster EBV PTLD, HCV, HBV Atypical fungi (alternaria) Augmented IS (same as months 2-6)

Infections after Allogeneic HSC Transplantation

Day 0-30	Day 31-100	Beyond day 100
Pre-engraftment neutropenia; disruption of mucocutaneous barriers	**Early post-engraftment** impaired cellular and humoral immunity; restricted T cell repertoire	**Late post-engraftment** impaired cellular and humoral immunity
Fever and shock (neutropenic fever, bacteremia, candidemia, viridans group streptococci) **Vascular catheter-related infections** (bacteria, fungi) **Diarrhea** (neutropenic colitis, *C. difficile*, enteroviruses) **Mucositis** (*Candida*, HSV) **Pneumonia** (bacteria, fungi, viral, rare parasites) **Hepatitis (**HSV, adenovirus, *Candida* sp., HHV-6) **Hemorrhagic cystitis** (adenovirus, BKV)	**Pneumonia** (*P. jiroveci*, *Aspergillus* sp., other moulds, influenza and other respiratory viruses, CMV, *S. stercoralis*, bacterial pathogens) **Diarrhea** (CMV, adenovirus, *C. difficile*, enteric pathogens) **Hepatitis** (CMV, HHV-6, adenovirus, HBV) **Hemorrhagic cystitis** (BKV, adenovirus, CMV) **Encephalitis** (HHV-6, HSV, CMV, JC virus, adenovirus, WNV, toxoplasmosis)	Infections due to **encapsulated** bacteria (e.g., *S. pneumoniae*): sinopulmonary infections, bacteremia **VZV** Infections among **high-risk** patients (GVHD, CMV D-/R+, myeloablative and radiation-based conditioning regimens): similar to early post-engraftment period

MAYO CLINIC

ABCs of Viral Infections in Transplantation

Raymund R. Razonable, MD, FIDSA, FAST

Professor of Medicine
Chair, Transplant Infectious Diseases
Mayo Clinic, Rochester, Minnesota

Division of
INFECTIOUS DISEASES

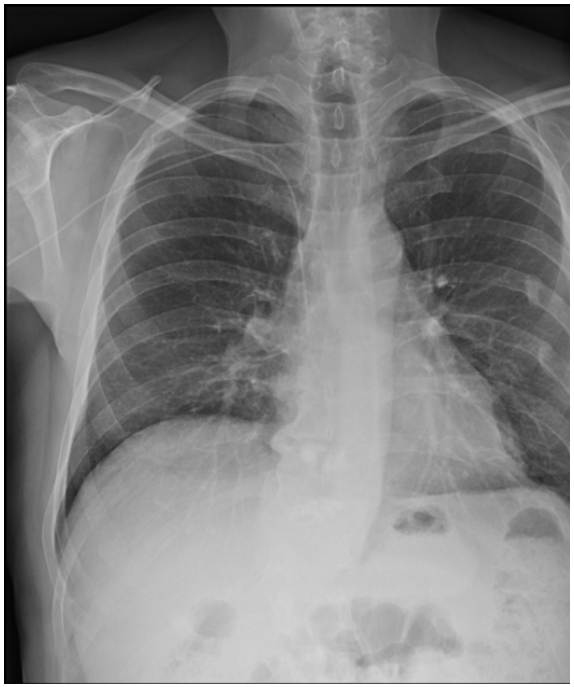
Mayo Clinic Infectious Diseases Subspecialties Update
May 7-9, 2015

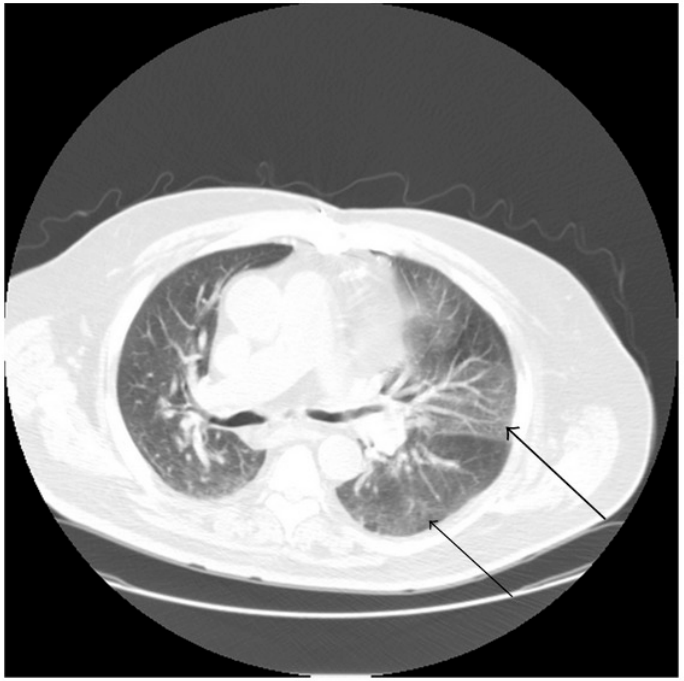
Objectives

- To appreciate the epidemiology and manifestations of selected viruses affecting transplant recipients.
- To identify methods for diagnosis of selected viruses after transplantation.
- To understand the guidelines for the prevention and treatment of selected viruses in transplant recipients.

Cough in a Transplant Recipient

A 70-year-old allogeneic BMT recipient presented with 5-day history of rhinorrhea, myalgias and subjective low-grade fevers. A day prior, he started to develop dyspnea and cough productive of whitish sputum.





Which of the following is the likely diagnosis?

A. Influenza
B. Respiratory syncytial virus
C. Metapneumovirus
D. Coronavirus
E. Parainfluenza virus
F. Adenovirus

Respiratory Virus Infections in Transplantation

Virus	Precautions	Prevention	Treatment
Influenza	Contact, droplet	Vaccination Antivirals (select)	Antivirals (neuraminidase inhibitors oseltamivir, zanamivir)
RSV	Contact	Palivizumab	Ribavirin, IG (IVIg, RSV-Ig, palivizumab), steroids (off label)
Parainfluenza	Contact	None	Ribavirin, IVIg (off label)
Metapneumovirus	Contact	None	None
Rhinovirus	Contact, droplet	None	None
Coronavirus	Variable	None	None

Seasonal viral infections
Clinical **manifestations**: rhinorrhea, tracheobronchitis, bronchiolitis, pneumonia
Viral **shedding** is prolonged (drug resistance and nosocomial spread)
Secondary **complications**: bacterial and fungal pneumonia
Risks for LRTI: intense immunosuppression, low T cell counts, GVHD, low Ig levels, lung transplant, allogeneic HSCT recipients
Indirect effects: acute and chronic rejection (especially lung transplants - BOS)

Manuel O et al. *American Journal of Transplantation* 2013;13:212
Kim et al. *J Infect Dis* 2014; 209:1195; Renaud C. et al. *Biol Bone Marrow Transplant* 2013;19:1220

American Transplant Congress 2015 Updates

- Outbreak of pandemic influenza virus infection in a kidney transplant unit (Helanter et al C84)
  - 23 patients developed influenza during the early period after transplantation (200 transplants/year)
  - Illness was more common in unvaccinated patients and associated with high morbidity
  - Preventable mortality (60% in unvaccinated cohort)
  - Outcome was better in patients who received vaccine
  - **Importance of seasonal influenza vaccination** - some have refrained use due to the potential risk of rejection (this has not been confirmed)
  - (NOTE: **do not use any live vaccines post-transplant**)

Adenovirus Infections

- Non-enveloped, ds-DNA viruses
  - Endemic in children and those living in closed quarters
- Seven subgroups (A-G); **52 distinct serotypes**
- Clinical manifestations: **variable**
  - Asymptomatic infection
  - Clinical disease: respiratory, gastrointestinal (including hepatitis), conjunctival, urinary tract disease
    - Localized or disseminated
    - Allograft involvement (direct and indirect effects)
- Incidence: variable
  - More common in **children** than adults (19% increase risk per year decrease in age)

Florescu and Hoffman. *American Journal of Transplantation* 2013;13:206

Adenovirus Serotypes and Associated Diseases

Subgroup	Serotypes	Common Clinical Presentations
A	12, 18, 31	Disseminated disease
B1	3, 7, 16, 21, 50	Respiratory tract disease, hepatitis, myocarditis, hemorrhagic cystitis, conjunctivitis, meningitis and encephalitis
B2	11, 14, 35, 35	Respiratory tract disease, hemorrhagic cystitis, disseminated disease
C	1, 2, 5, 6	Respiratory tract disease, conjunctivitis, hepatitis, meningoencephalitis, disseminated disease
D	8-10, 13, 15, 17, 19, 20, 22-30, 32, 33, 36-39, 42-49, 51	Keratoconjunctivitis
E	4	Respiratory tract disease, conjunctivitis
F	40, 41	Gastroenteritis, disseminated disease
G	52	Gastroenteritis

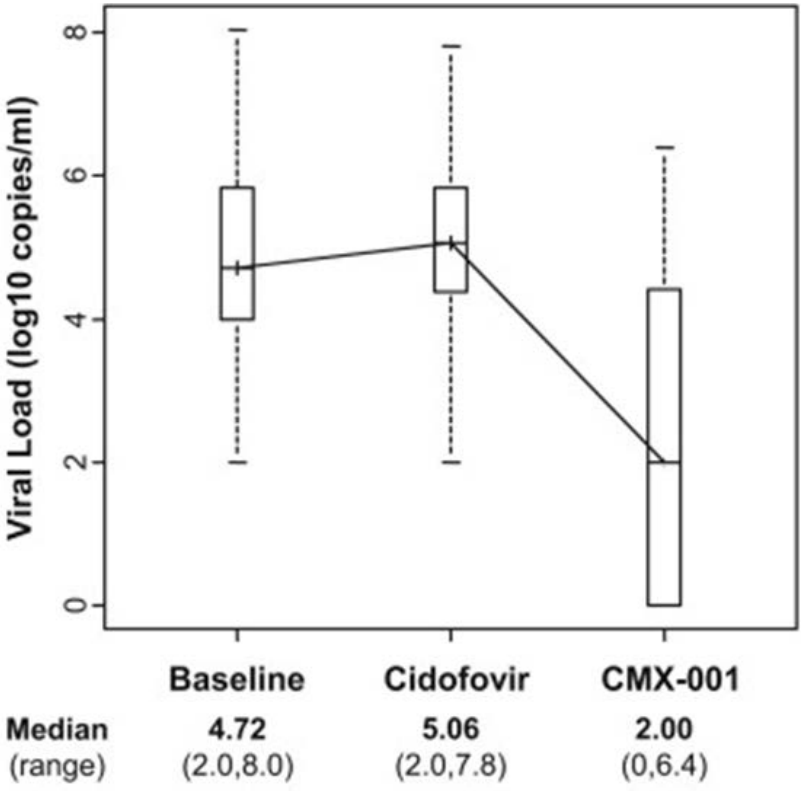
Florescu and Hoffman. *American Journal of Transplantation* 2013;13:206

Adenovirus Infections: Management

- **Diagnosis:**
  - Culture, molecular test (PCR), and histology (gold standard for invasive disease)
    - Caution: prolonged asymptomatic shedding in respiratory, urine and stool samples – correlation with clinical symptoms
    - Detection in two or more sites: consider invasive disease!
    - Molecular methods: quantitation guides management
- **Treatment:**
  - Supportive care. Reduction in immunosuppression!
    - Contact and droplet precautions (note: prolonged shedding)
  - No FDA-approved antiviral drugs (all off-label)
    - Cidofovir – severe, progressive, disseminated disease
      - 1-mg/kg 3x/week or 5-mg/kg every 2 weeks
    - Others (questionable): Ribavirin (subtype C) and Ganciclovir

Florescu et al. *American Journal of Transplantation* 2013;13:206
Matthes-Martin S et al. *Expert Rev Anti Infect Ther*. 2013 Oct;11(10):1017-28

Investigational Brincidofovir for Adenovirus Infections



13 patients (1 SCID, 1 small bowel transplant recipient, 11 allogeneic SCT recipients)

Median 75 days after transplantation

All received cidofovir for median of 21 days (5-90) before CMX001 therapy.

Eight (61.5%) had a ≥1 log10 drop in viral load after one week. By week 8, nine (69.2%) had satisfactory virologic response (median time 7 days)

Randomized clinical trials needed/ongoing!

Florescu et al. Safety and Efficacy of CMX001 as Salvage Therapy for Severe Adenovirus Infections in Immunocompromised Patients. Biology of Blood and Marrow Transplantation, Volume 18, Issue 5, 2012, 731 - 738

Renal Dysfunction in a Kidney Recipient

- 45-year-old diabetic man received a deceased donor kidney transplant
- Thymoglobulin induction
- Maintenance with MMF, tacrolimus, and prednisone
- CMV D+/R-, valganciclovir for 6 months
- TMP-SMX prophylaxis for *Pneumocystis jiroveci*
- UTI due to *Escherichia coli* at 1 month (Bactrim R)

- Serum creatinine at 8 months: doubled to 2.6

What is the most likely diagnosis?

A. Acute allograft rejection

B. Polyomavirus associated nephropathy

C. CMV nephritis

D. Recurrent bacterial pyelonephritis

E. Drug toxicity

BK Virus Infections

- Widespread infection in humans
  - >90% seroprevalence
    - Latency in GU tract: asymptomatic urinary shedding
- Major polyomavirus infection in transplant recipients
  - **Two major clinical syndromes**:
    - Polyomavirus-associated nephropathy
      - 1-10% of kidney transplant recipients
      - Gradual rise in serum creatinine
    - Hemorrhagic cystitis
      - 5-15% of allogeneic BMT recipients
- Rarely affects non-kidney solid transplant recipients

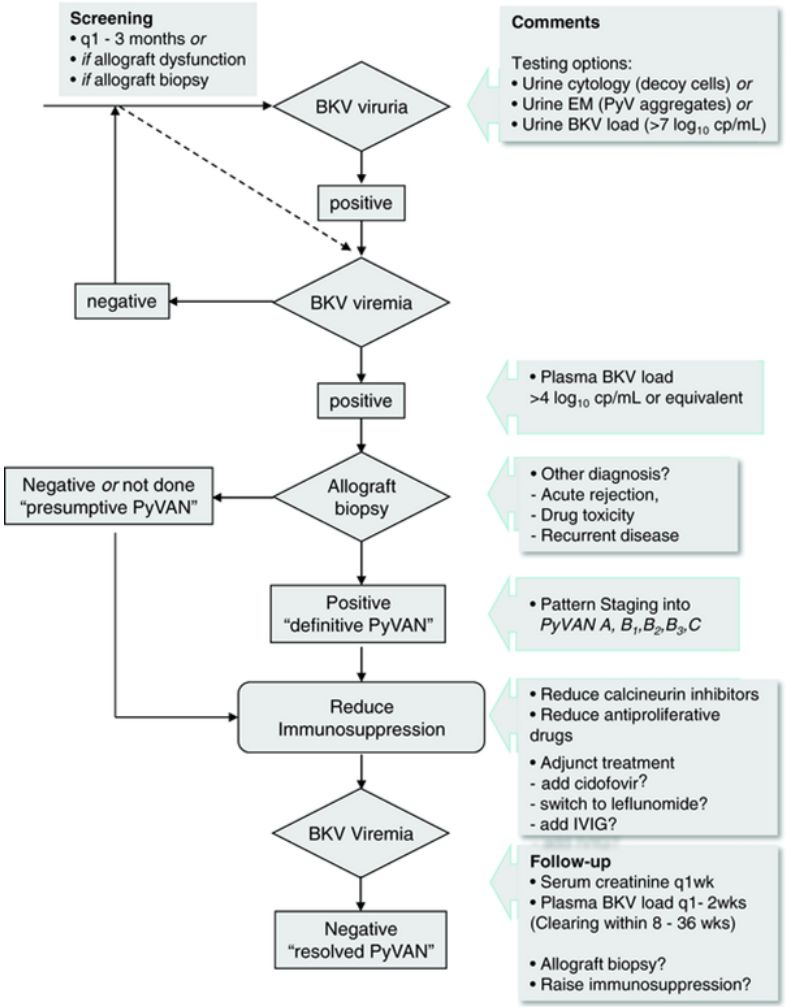
Hirsch et al. *American Journal of Transplantation* 2013; 13 (S4): pages 179-188

AST Guidelines for Screening, Classification, and Intervention of BKV Replication and Nephropathy

Testing	Findings	Possible	Probable	Proven
Urine	High level viruria: Decoy cells >7log$_{10}$ BKV DNA copies/mL	+	+	+
Plasma	>4log$_{10}$ BKV DNA copies/mL	-	+	+
Biopsy	Cytopathic changes (A) Tubulitis/inflammation (B) Fibrosis and atrophy (C)	-	-	+
Therapy		No	Yes	Yes

Hirsch et al. *American Journal of Transplantation* 2013; 13 (S4): pages 179-188

Screening and Treatment of Polyomavirus Nephropathy



Hirsch et al. *American Journal of Transplantation* 2013; 13 (S4): pages 179-188

BK Virus Infections: Treatment

- **Reduction in immunosuppression** – first line and mainstay
  - Tacrolimus trough <6 ng/ml
  - Cyclosporine trough <150 ng/mL
  - Sirolimus trough <6 ng/mL
  - Mycophenolate mofetil dose <1 gram/day
- **Immunosuppression switch**
  - Tacrolimus to low-dose cyclosporine
  - CNI to sirolimus
- **Antiviral agents** (all off label)
  - Cidofovir (investigational brincidofovir under study)
  - Leflunomide
  - IVIG
  - Fluoroquinolones

Hirsch et al. *American Journal of Transplantation* 2013; 13 (S4): pages 179-188

ATC 2015 BK Virus Updates

- **Incidence**:
  - BKV infection 8% in 4.5 years, with 4% developing definite PVAN (Favi et al A24)
- **Treatment strategies**:
  - Switching from tacrolimus to low-dose cyclosporine is associated with preserved allograft function in cases of presumptive and definitive PVAN (Huang et al A32)
  - Leflunomide use at higher doses (60 mg per day) is better than 40-mg daily in patients with PVAN (Nesselhauf et al A31)
  - Leflunomide use was not effective (Jonchie et al A30)
  - Adoptive immunotherapy (transfer of BKV-specific T cells) remains experimental.

You have a kidney transplant patient who lost his kidney allograft due to BK virus nephropathy. He is very interested, and is asking you if he can get a second kidney transplantation.

What would you advise him?

A. **Yes**, if there is a suitable kidney donor and he can be monitored routinely for BK virus infection

B. **No**, PVAN is a contraindication to another kidney transplantation

C. **I do not know** but let me ask the Transplant ID specialist.

Retransplantation after BKV Nephropathy

- OPTN Database Review (up to 2009):
  - 823 graft losses due to or partly due to BK virus
    - 126 have received repeat kidney re-transplant at a median of 314 days after graft failure
  - Outcomes of re-transplantation:
    - 118 (94%) functioning grafts at last follow-up
    - Failures (n=8):
      - Three failure (BKV, acute rejection, chronic rejection)
      - Five grafts: status unknown
        - Two patients died from intraabdominal infection and cerebrovascular hemorrhage
    - Treatment for BKV in 17.5% of re-transplants
    - One-year survival K-M rate: 98.5% (92.8–100.0%)

Dharnidharka et al. *American Journal of Transplantation* 2010;10:1312
Hirsch et al. *American Journal of Transplantation* 2013;13 (S4):179-188

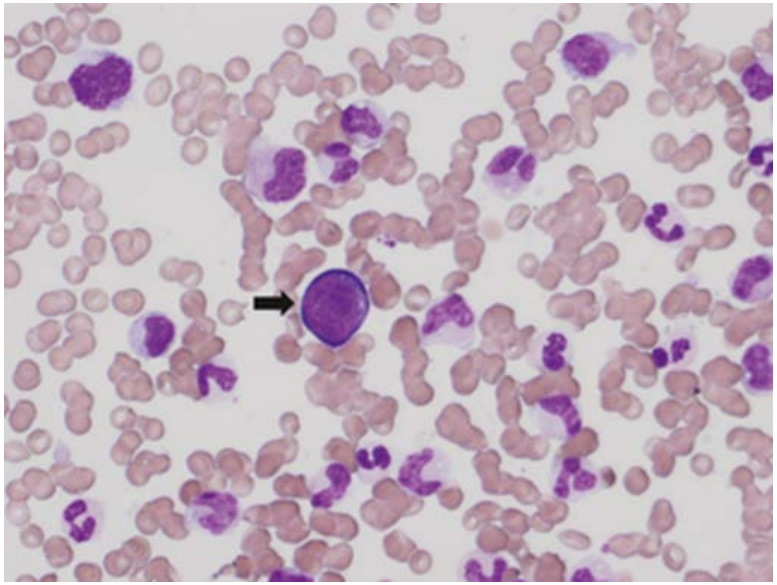
JC Virus

- Rare infection after transplantation
  - Progressive multifocal leukoencephalopathy (PML)
  - Few cases of PVAN
- Review of SOT recipients with PML
  - **Clinical presentation**: median 37 months (5-120)
    - Motor weakness (42%), speech abnormalities (40%), cognitive abnormalities (36%), headache (32%), visual defects (32%), ataxia (21%), aphasia (17%), cranial nerve deficits (13%), sensory deficits (9%), seizure (4%)
  - **Diagnosis:** JC in CSF; characteristic brain MRI changes
  - **Outcome**: poor prognosis; mortality in 9/13 kidney recipients
  - **Treatment**:
    - Reduction/discontinuation of immunosuppression
    - No proven role for antivirals (cidofovir)

Crowder CD et al. *Am J Transplant* 2005;5:1151-8

A 44-year-old Man with Refractory Anemia

- He received autologous PBSCT. Because of poor response, he underwent allogeneic BMT from ABO-matched, HLA-mismatched unrelated donor.
- Preparative regimen consisted of fludarabine, melphalan, and ATG. Tacrolimus and methotrexate as GVHD prophylaxis.
- Neutrophil and platelet engraftments on days 14 and 16, respectively. Anemic and reticulocytopenic. Red blood cell transfusion-dependent.
- Bone marrow examination:



Koda et al. *Transplant Infectious Disease*. 2013 15 (6): E239-E242

How do you manage this case?

A. Systemic ribavirin
B. Intravenous ganciclovir
C. Intravenous foscarnet
D. Intravenous immunoglobulin
E. Repeat stem cell infusion

Parvovirus B19

- Clinical manifestations:
  - **Anemia** (99%): severe, erythropoietin-resistant +/- pancytopenia
  - Fever (25%), arthralgia (7%), lacy rash (6%)
  - Organ-invasive disease (probable)
- Diagnosis:
  - Serology (**delay** in IgM seroconversion)
  - Nucleic acid testing – **prolonged** detection after acute infection
  - **Bone marrow**: giant pronormoblasts and red cell aplasia
- Treatment:
  - IVIG: dose and duration variable (off label)
  - Reduction in immunosuppression
  - Standard and droplet precautions (to prevent nosocomial spread – note ***prolonged shedding*** *may typically occur*)

Eid A et al. *American Journal of Transplantation*. 2013 13:201

A 37-year-old Lung Transplant Recipient with Fever

- Single lung transplant in for lymphangioleiomyomatosis.
- CMV D+/R- mismatch; antiviral prophylaxis for 5 years
- No cellular or antibody-mediated rejection.
- Mycophenolate mofetil, tacrolimus and prednisone
- Six weeks after stopping ganciclovir prophylaxis:
  - Fever and constitutional symptoms.
  - No diarrhea.
  - No cough or dyspnea.
  - No visual symptoms.

Kijpittayarit et al. *Transplantation* 2006; 81(1):137-138

Which of the following statements is TRUE?

A. pp65 antigenemia is the most sensitive method for diagnosis of this infection.

B. Intravenous foscarnet is first line treatment of patients who received prolonged oral ganciclovir prophylaxis.

C. UL97 mutation confers resistance only to ganciclovir.

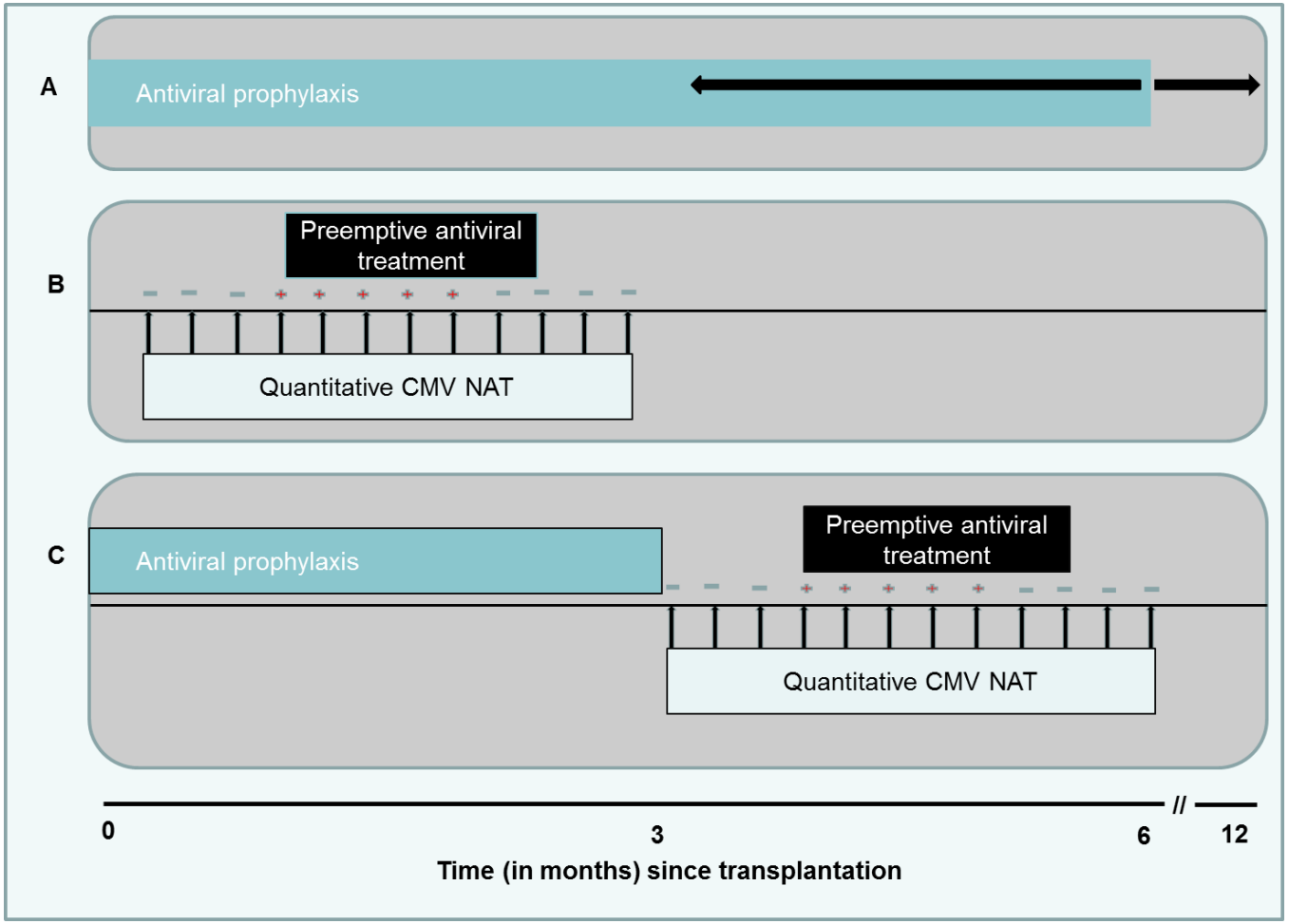
D. Treatment duration with antiviral drug is 2 weeks only.

Cytomegalovirus

- Major risk factor is immune deficiency
  - CMV D+/R- SOT and CMV R+ (D-) HSCT
  - T cell deficiency (global and CMV-specific): number and function
  - Allograft rejection and GVHD
- Clinical manifestations
  - CMV syndrome: fever and bone marrow suppression
  - Tissue-invasive disease: GI is most common; pneumonia could be fatal especially in lung and HSCT; retinitis is rare
- Diagnosis
  - Nucleic acid testing (NAT, PCR): quantitation and standardization
  - pp65 antigen testing
  - Histology: limited by invasive nature
  - Serology (limited to pre-transplant screening)
  - Viral culture: poor sensitivity

Razonable and Humar. *American Journal of Transplantation*. 2013 13:93-106

Cytomegalovirus: Prevention Strategies



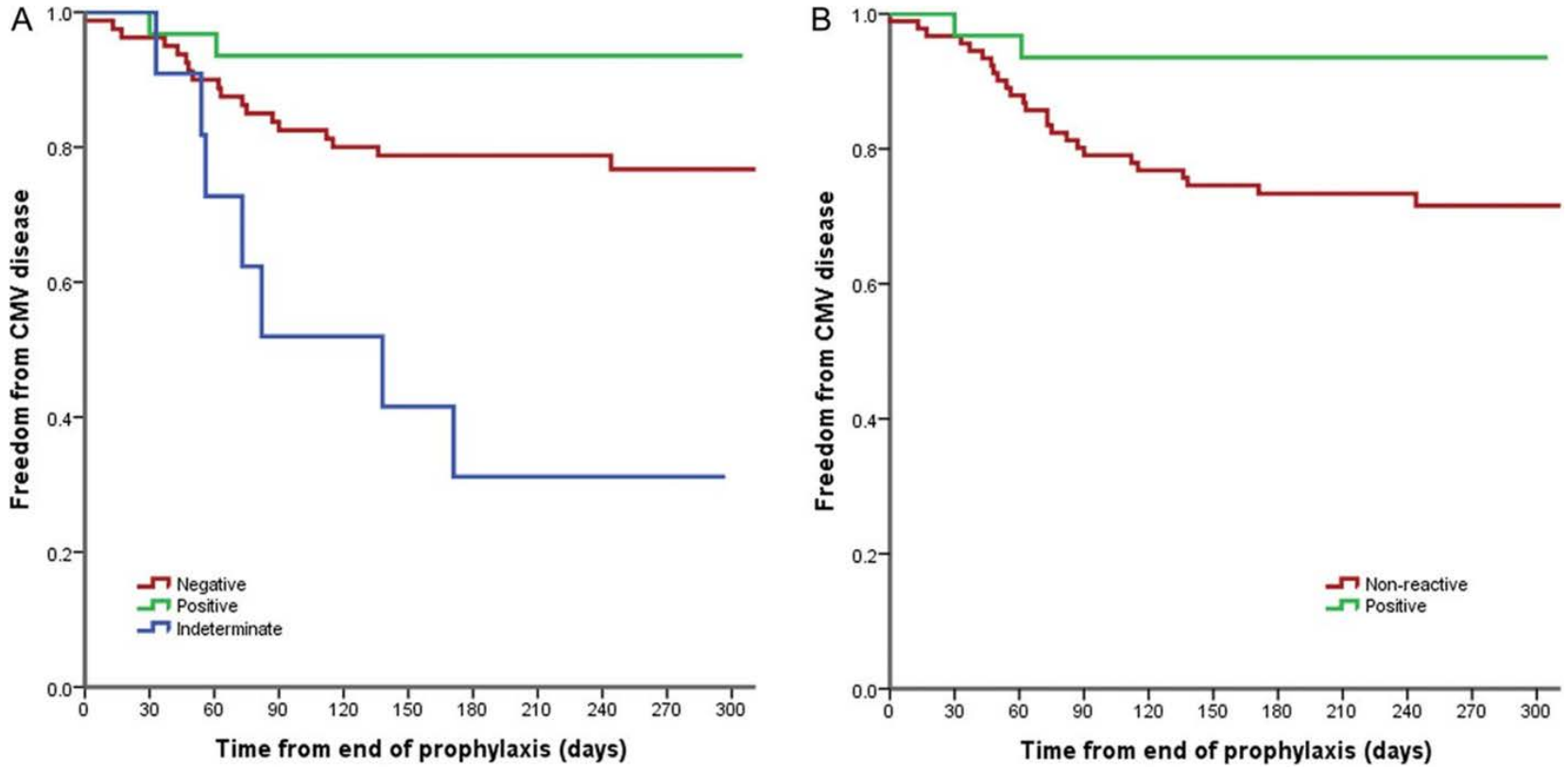
Razonable and Hayden. *Clinical Microbiology Reviews*. 2013

AST Guideline for Prevention of CMV Disease in SOT

Transplant	Category	Recommendations
Kidney, Pancreas, Liver, Heart	CMV D+/R-	Antiviral prophylaxis is preferred Drugs: valganciclovir, oral or IV ganciclovir (valacyclovir for kidneys only) Duration: 3-6 months Preemptive therapy is an option Weekly CMV NAT or pp65 for 12 weeks If above threshold: Valganciclovir or IV ganciclovir (treatment dose)
	CMV R+	Antiviral prophylaxis Drugs: valganciclovir, oral or IV ganciclovir (valacyclovir for kidneys only) Duration: 3 months Preemptive therapy Weekly CMV NAT or pp65 for 12 weeks If above threshold: Valganciclovir or IV ganciclovir (treatment dose)
Lungs Heart-lungs	CMV D+/R- and all R+	Antiviral prophylaxis (preemptive therapy not recommended) Drugs: valganciclovir or IV ganciclovir Duration: 6-12 months (R+); at least 12 months (CMV D+/R-)
Small bowel, CTA	CMV D+/R- and all R+	Antiviral prophylaxis (preemptive therapy not recommended) Drugs: valganciclovir or IV ganciclovir Duration: 3-6 months

Razonable and Humar. *American Journal of Transplantation*. 2013 13:93-106

Role of Immune Monitoring:
Interferon-gamma Release Assay (Quantiferon-CMV)



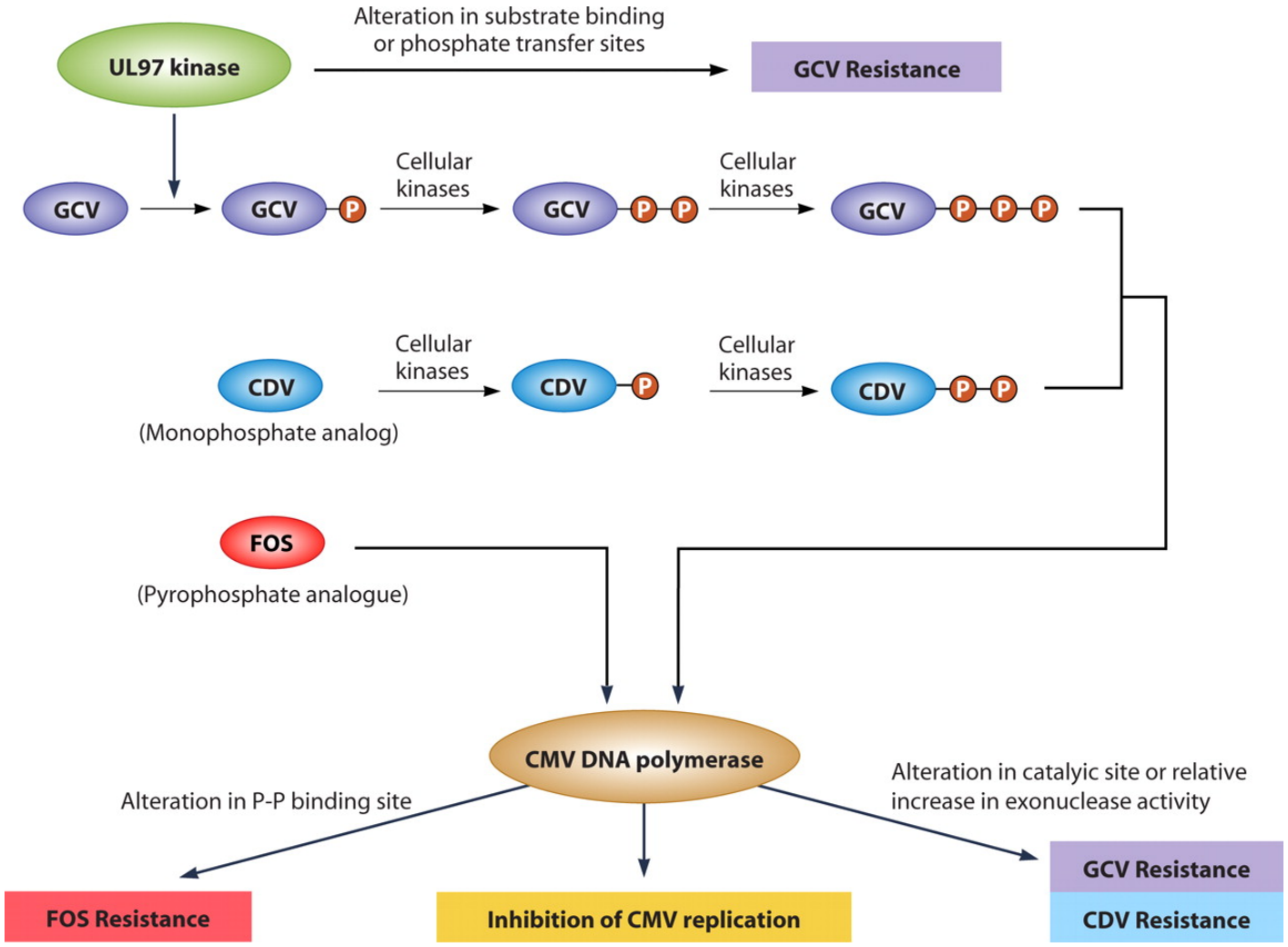
Oriol Manuel et al. *Clin Infect Dis*. 2013;56:817-824

Cytomegalovirus: Treatment

- IV Ganciclovir and oral Valganciclovir: first line drugs
  - Similar efficacy for mild to moderate cases
  - **IV ganciclovir is first line for**
    - Severe case, poor GI absorption, high viral load (20,000 IU/ml)
  - Oral ganciclovir is not well absorbed (**do not use**!!!)
  - Duration of treatment: clinical resolution and virologic clearance
- Alternatives: reserved for ganciclovir-resistant cases and those unable to tolerate ganciclovir
  - Foscarnet – renal and electrolyte disturbance
  - Cidofovir – renal and ocular toxicity
- Adjunctive immunoglobulin (IVIG, CMV-Ig)
- Investigational and off-label drugs: maribavir, letermovir, brincidofovir, artesunate, leflunomide

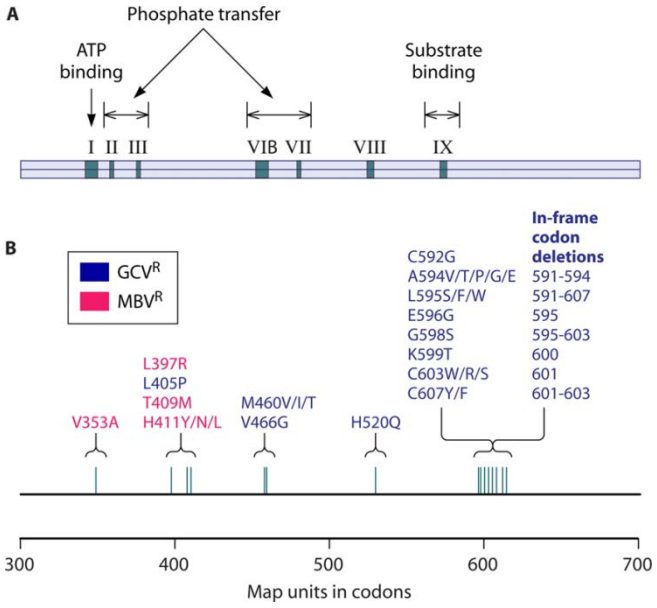
Razonable and Humar. *American Journal of Transplantation*. 2013 13:93-106

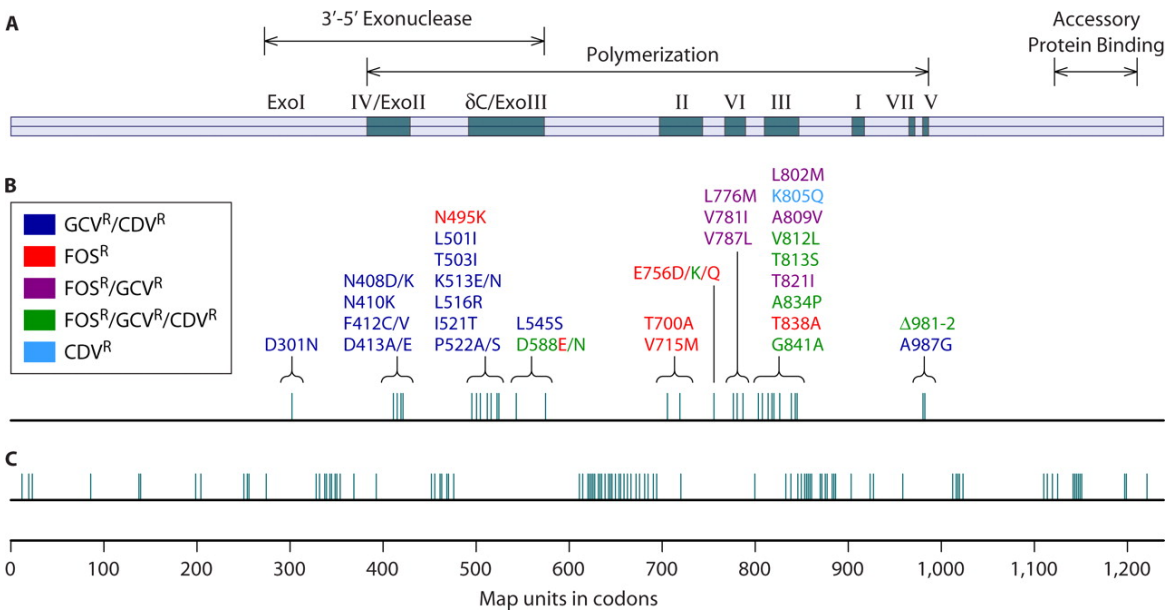
Anabolism of approved CMV antiviral drugs



Lurain N S , and Chou S *Clin. Microbiol. Rev.* 2010;23:689-712

UL97 and UL54 Mutations Conferring Drug Resistance





Lurain N S , and Chou S *Clin. Microbiol. Rev.* 2010;23:689-712

Other Herpes Virus Infections in Transplantation

Virus	Major Disease	Prevention	First-line Treatment
HSV1, HSV2	Mucocutaneous disease; may disseminate (fulminant hepatitis)	Acyclovir PO for >4 weeks (or valganciclovir for CMV)	Acyclovir PO/IV Valacyclovir
VZV	Varicella, zoster	Pre-transplant vaccine (if susceptible)	IV acyclovir Valacyclovir
EBV	PTLD	Screening for high-risk (EBV D+/R-); preemptively lower degree of immunosuppression	Reduce immunosuppression Rituximab; chemotherapy No role for antivirals
HHV6	Fever, encephalitis	Not defined	Ganciclovir, foscarnet, cidofovir
HHV7	?	Not defined	Foscarnet, cidofovir
HHV8	KS, Castleman's disease, primary effusion lymphoma	Not defined (some use valganciclovir in endemic regions)	Reduce immunosuppression Chemotherapy

Wilck and Zuckermann. *Am J Transplant* 2013;13:121; Pergam and Limaye. *Am J Transplant* 201; 13:138; Allen and Preiksaitis. *Am J Transplant* 2013;13:107; Razonable. *Am J Transplant* 2013 13:67-77

Hepatitis E Virus

- Transmission: fecal-oral route; ingestion of infected animal meat
- Genotype: 1 and 2 (humans only); 3 and 4 (other mammals)
- Clinical presentation
  - **Acute** hepatitis (high mortality in pregnant, elderly and chronic liver disease)
  - **Chronic** hepatitis in transplant recipients (60%)
    - Over half of infected transplant recipients develop chronic infection and 30% will have cirrhosis
- Diagnosis: serology and HEV RNA testing
- Treatment: reduce immunosuppression; pegylated interferon (risk of rejection); ribavirin (off label)
  - Prevention is key: avoid consumption of uncooked meat and contaminated water

Conclusions

- Reviewed the epidemiology and manifestations of selected viruses affecting transplant recipients.
- Reviewed methods for diagnosis of selected viruses after transplantation.
- Reviewed guidelines for the prevention and treatment of selected viruses in transplant recipients.

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Send CV and letter of interest to:
Raymund R. Razonable, M.D., FIDSA, FAST, Program Director (razonable.raymund@mayo.edu)
Cindy Domonoske, Education Program Coordinator (domonoske.cynthia@mayo.edu)

Invasive Fungal Infections in Solid Organ Transplantation

Randall Walker MD

Mayo Clinic Rochester Minnesota

Division of
INFECTIOUS DISEASES

Mayo Clinic Infectious Diseases Subspecialties Update
May 7-9, 2015

Disclosures: None

What is your practice?

A. Occasional Kidney Transplant patients
B. Regularly see Abd Tx patients, Kidney and/or Liver
C. Regularly see Abdominal and Thoracic Tx pts.
D. See both SOT and Stem Cell Tx patients.
E. See SCTx pts, but not SOT
F. Heme-Onc patients only, but no Tx patients.

Main Points Today

- Late IFIs in SOT will become part of every ID practice
- Rapid Diagnosis includes testing and communication.
- Guidelines require clinical interpretation
- Have the Transplant service manage immunosuppresson. Stopping CNIs in IFI can cause organ rejection without improving Infection outcomes.
- Engage the surgeons early; CNS IA is not as bleak as it used to be.
- Starting Rx for Mucor <1 wk from onset improves survival.
- Background of prior antifungal use. Specific Dx with Culture and Susceptibility now more important

Invasive Fungal Infections: Leading Cause of Infection Related mortality in SOT patients.

"Because of improvement in
diagnosis and treatment of other infections,
such as Cytomegalovirus infections,
invasive fungal infections (IFIs)
have now become
the leading cause of
infection-related mortality
following transplantation."

Yoann Crabol and Olivier Lortholary , Paris

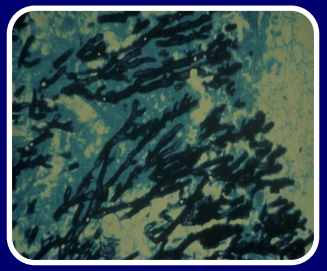
Invasive Mold Infections in Solid Organ Transplant Recipients

Scientifica

Volume 2014 (2014), Article ID 821969,

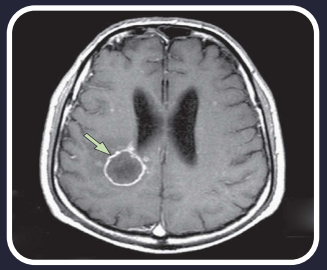
http://dx.doi.org/10.1155/2014/821969

Topics to Cover



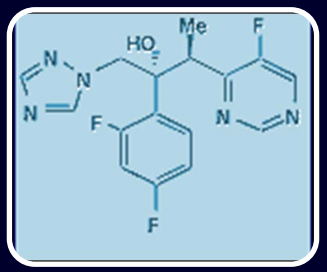
Principles of Fungal Infection in Transplantation

- Epidemiology
- Mycology
- Pathogenesis



Major Fungal Infections in SOTx

- Cryptococcus
- Aspergillus
- Zygomycosis
- Other



Management of Fungal Infections in SOTx

- Diagnostics
- Antifungal Agents: Prophylaxis and Treatment
- Surgical Intervention for Diagnosis and Treatment

Pathogens and Transmission -- an Impression

- Viruses – from other people
- Bacteria – from the hospital
- Fungi – from the outside world

(with exceptions that prove the rule in each case).

So, as we transplant more people, and succeed in getting them back out into the outside world, there will be more cases of fungal infection in transplantation.

First Human to Jump to the Earth from Outer Space (120,000 feet)

"Trust me, when you stand up there on top of the world, you become so humble.

It's not about breaking records anymore.

It's not about getting scientific data.

It's all about coming home," Mr. Baumgarter said after returning by helicopter to mission control in Roswell.

"It was harder than I expected," he said.

Epidemiology … in humans

National Science Foundation: Press Release

Climate Change Drives Widespread Amphibian Extinctions

Warmer temperatures enhance growth conditions of fatal fungus

Epidemiology … in humans

White Nose Fungus in North America Bats

First Documented in NY in 2006.

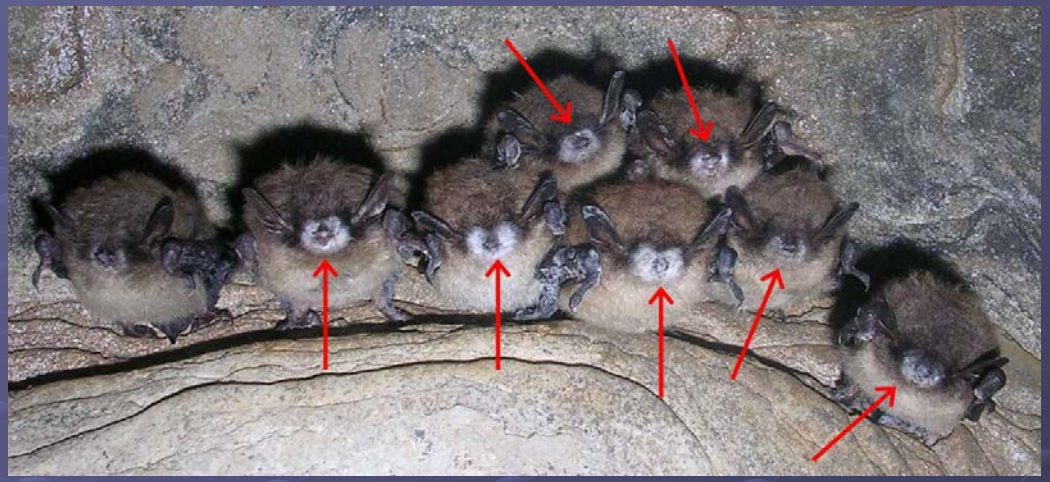
Bats displaced from usual caves by urban sprawl

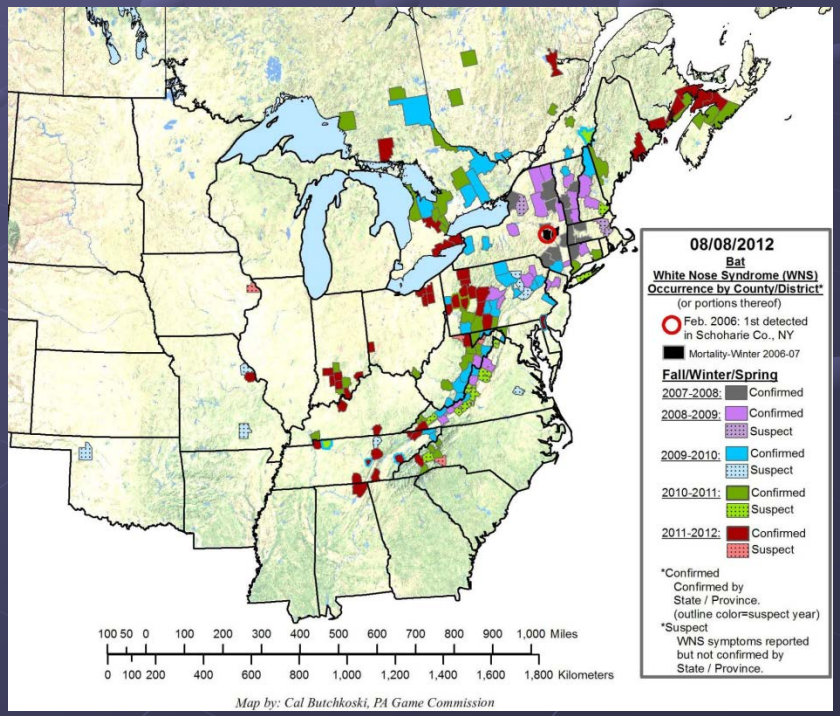
Hibernating bats huddle together in new caves, but noses stay cold

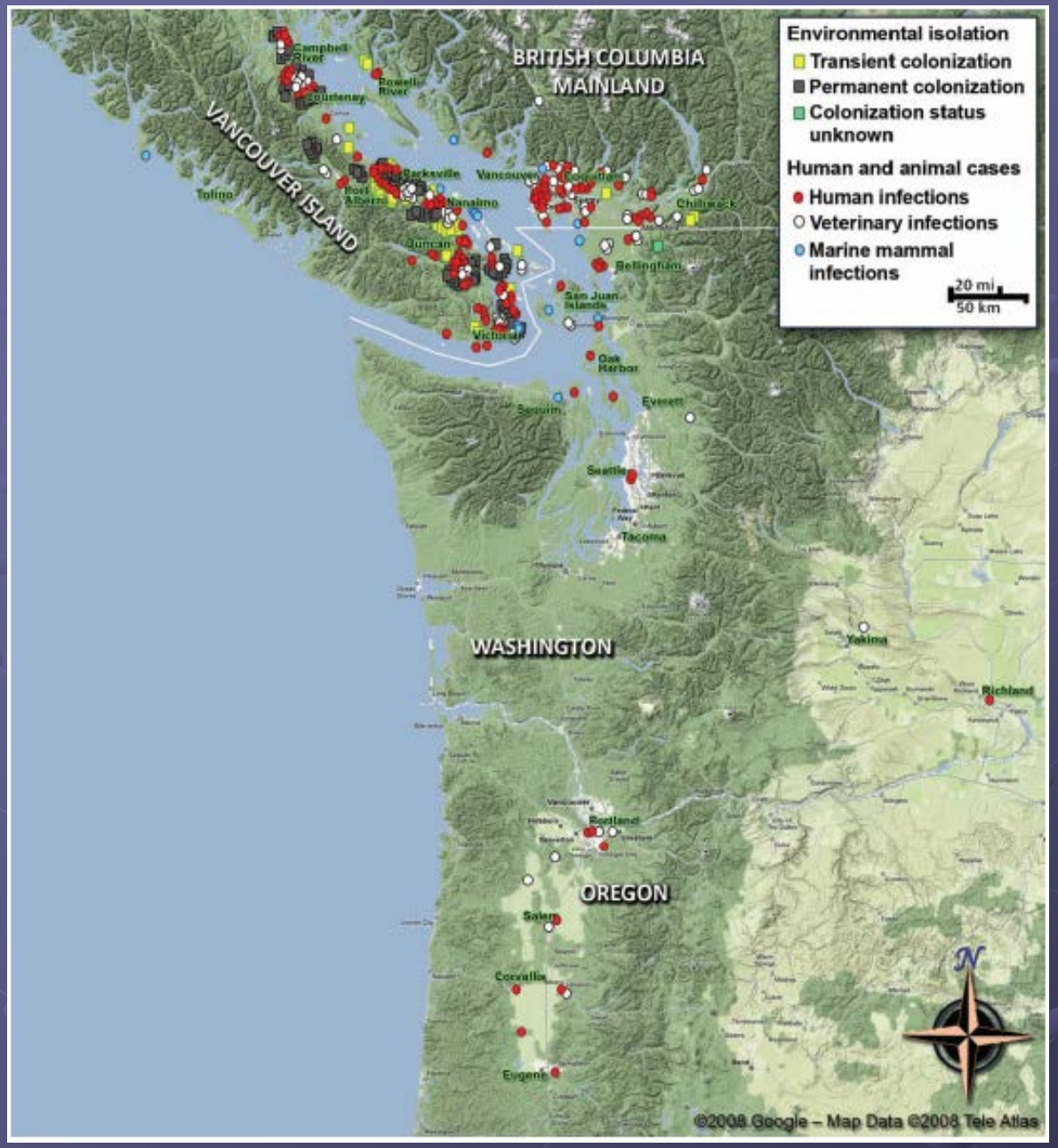
A newly discovered fungus, *Geomyces destructans*, brought over from Europe by spelunkers (no disease in European bats).

Fungus spreads while bats hibernate, infects cold noses

5 million US bats killed so far; ate insects that cost $5 billion in insecticides ($1000/bat/year).







Spread of *Cryptococcus gattii into Pacific Northwest Region of the United States*

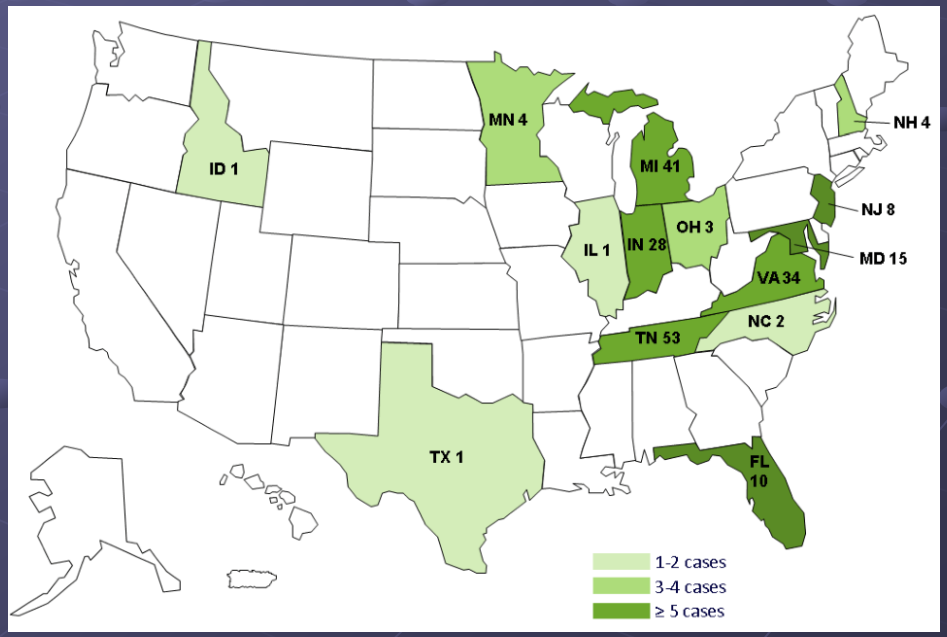
Prior to 1999, only found in tropical and subtropical regions

Pathogenic in humans, including ICH and normal hosts

Fungal Meningitis

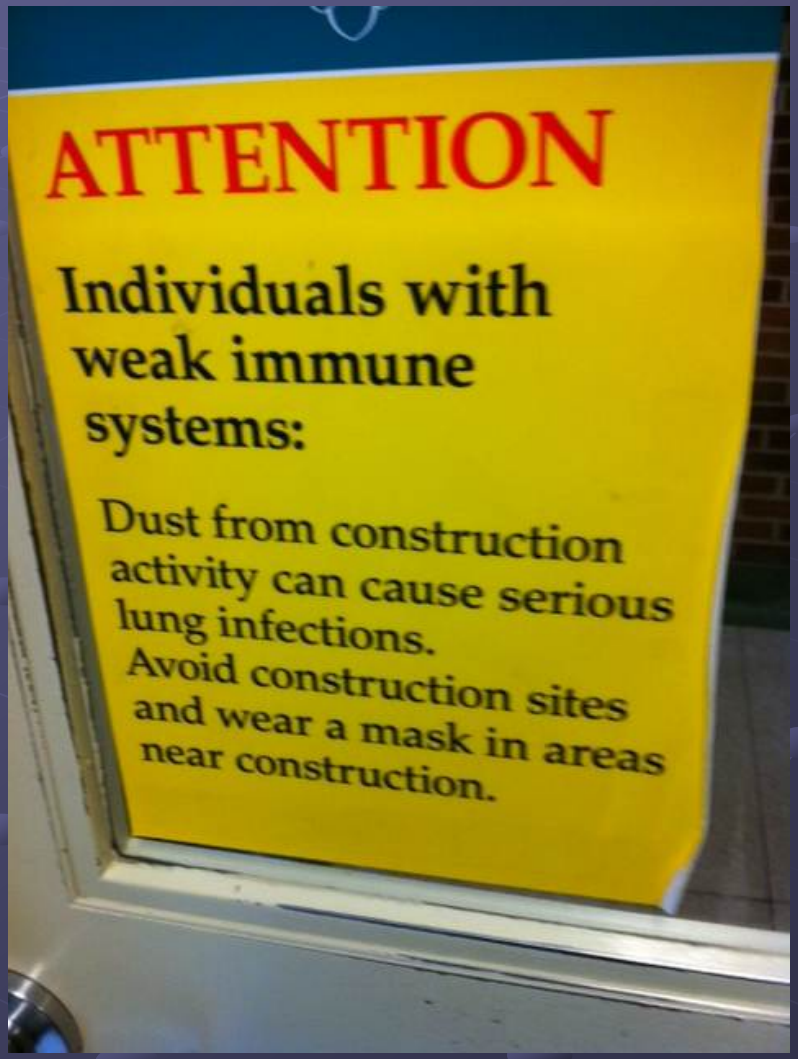
"More than 200 diagnosed in fungal meningitis outbreak"

Aspergillus fumigatus
and
Exserohilum rostratum



Distribution of cases.
205 total, 15 fatal

Local Environments



Local Environments

Invasive filamentous fungal infections associated with renal transplant tourism

- 19 cases of invasive fungal infections post commercial kidney transplant
  - *Aspergillus* species (12/19; 63%),
  - *Zygomycetes* (5/19; 26%),
  - and other fungi (2/19; 5%).

In transplanted graft in 6/17 patients (35%)

Graft loss or death in 13/17 (76%)

Overall mortality (10/17) 59%.

S. Shoham, Washington DC

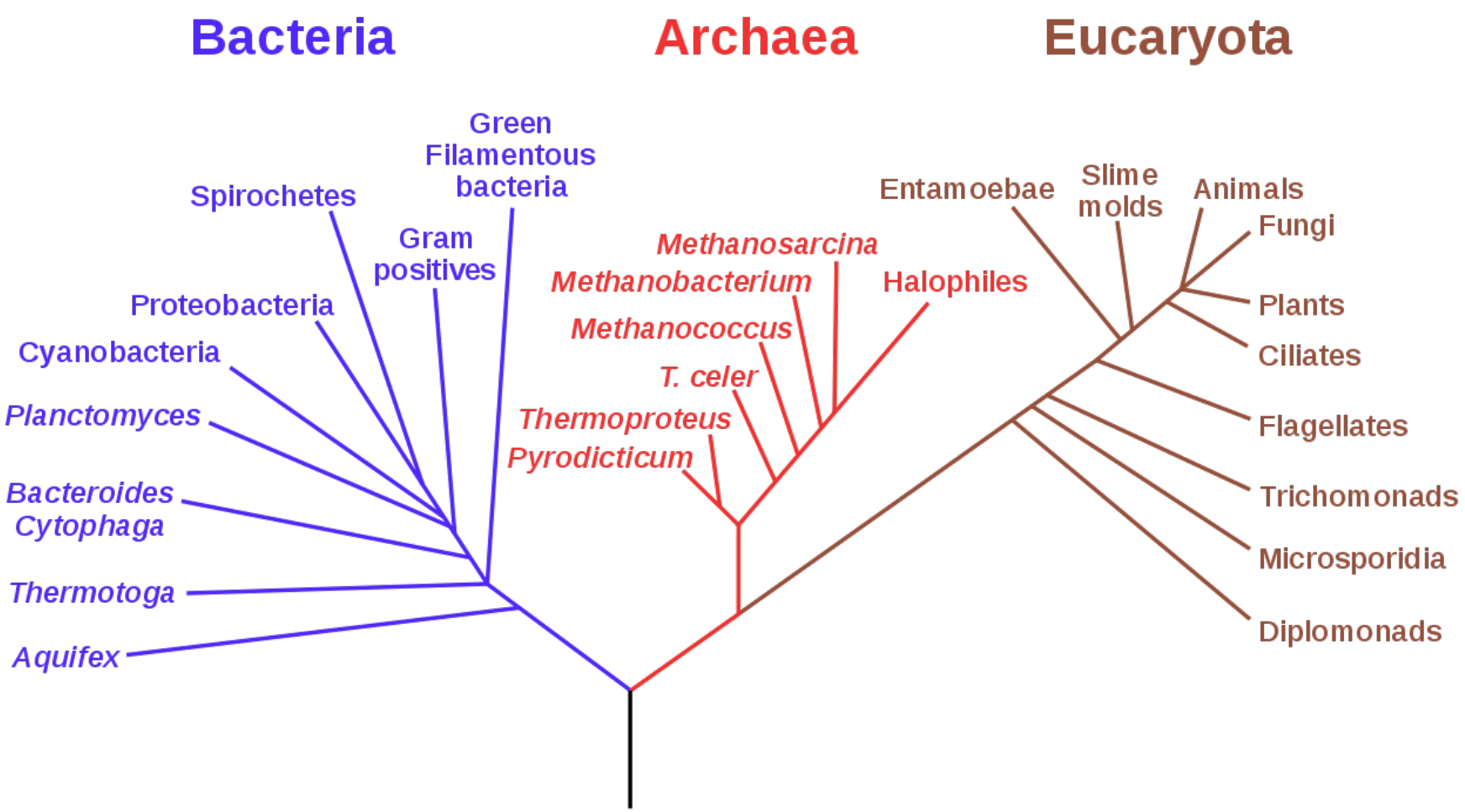
Transplant Infectious Disease

Volume 12, Issue 4, pages 371–374, August 2010

Common Pathogenic Fungi

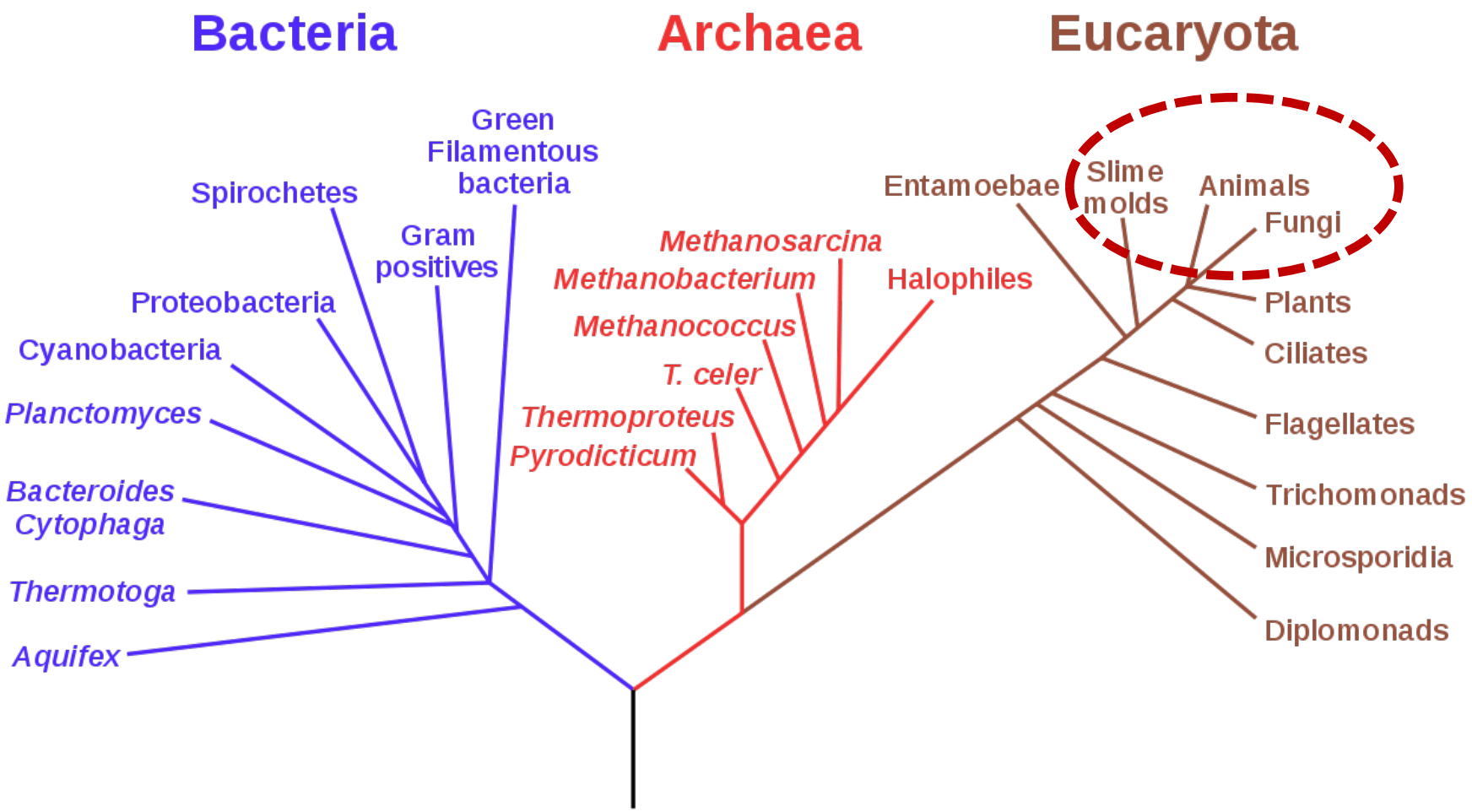
Yeasts		**Molds**	
Endogenous	***Exogenous***	***Dimorphic & Geographic***	***Filamentous & Ubiquitous***
Candida	Cryptococcus	Histoplasmosis	Aspergillus
		Blastomycosis	Mucor
		Coccidiodes	Fusarium

Phylogenetic Tree of Life

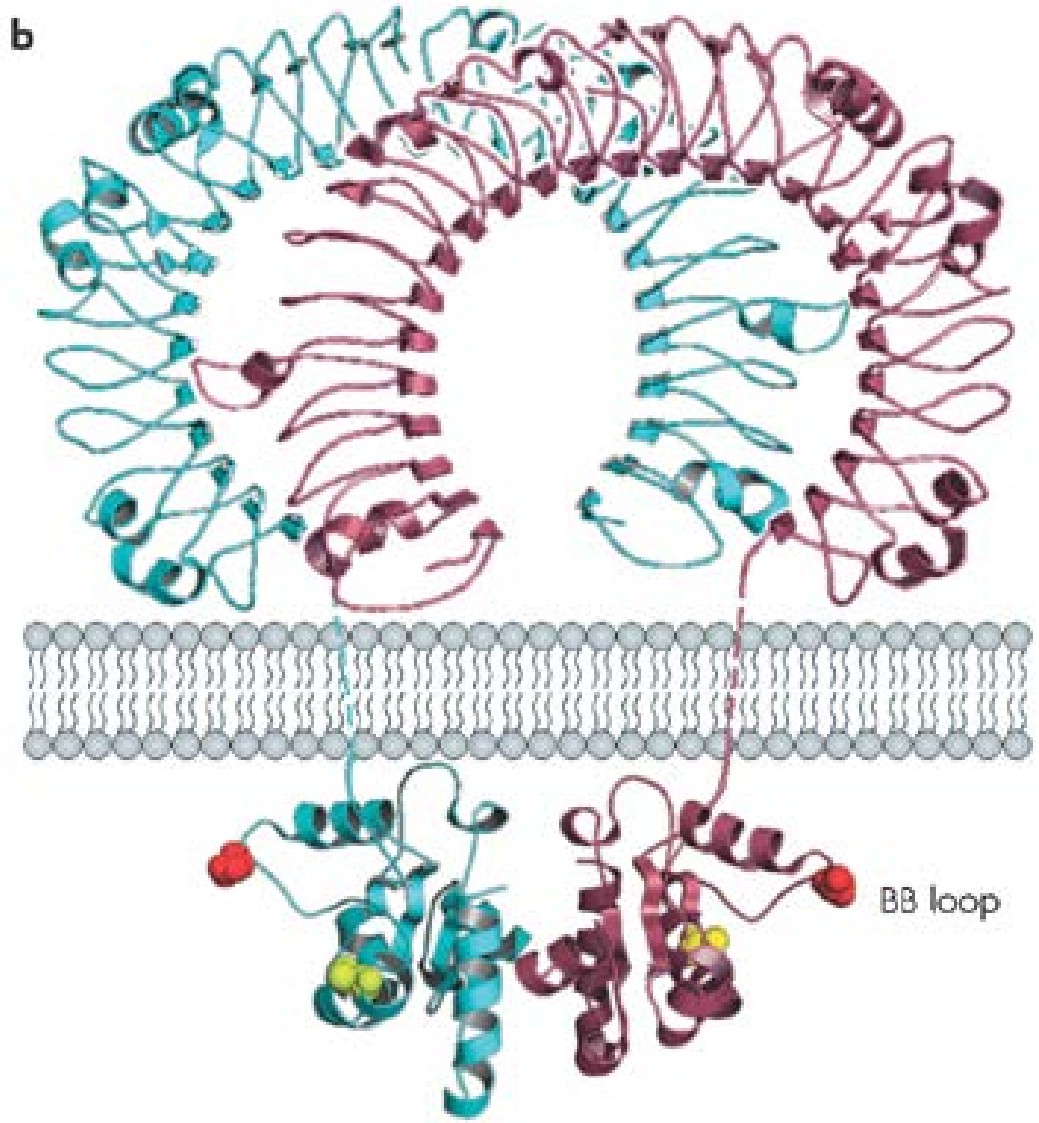


based on rRNA data

Phylogenetic Tree of Life



based on rRNA data



Toll-Like Receptors:

Ten TLRs containing polymorphisms associated with several infectious or inflammatory diseases have been identified in humans.

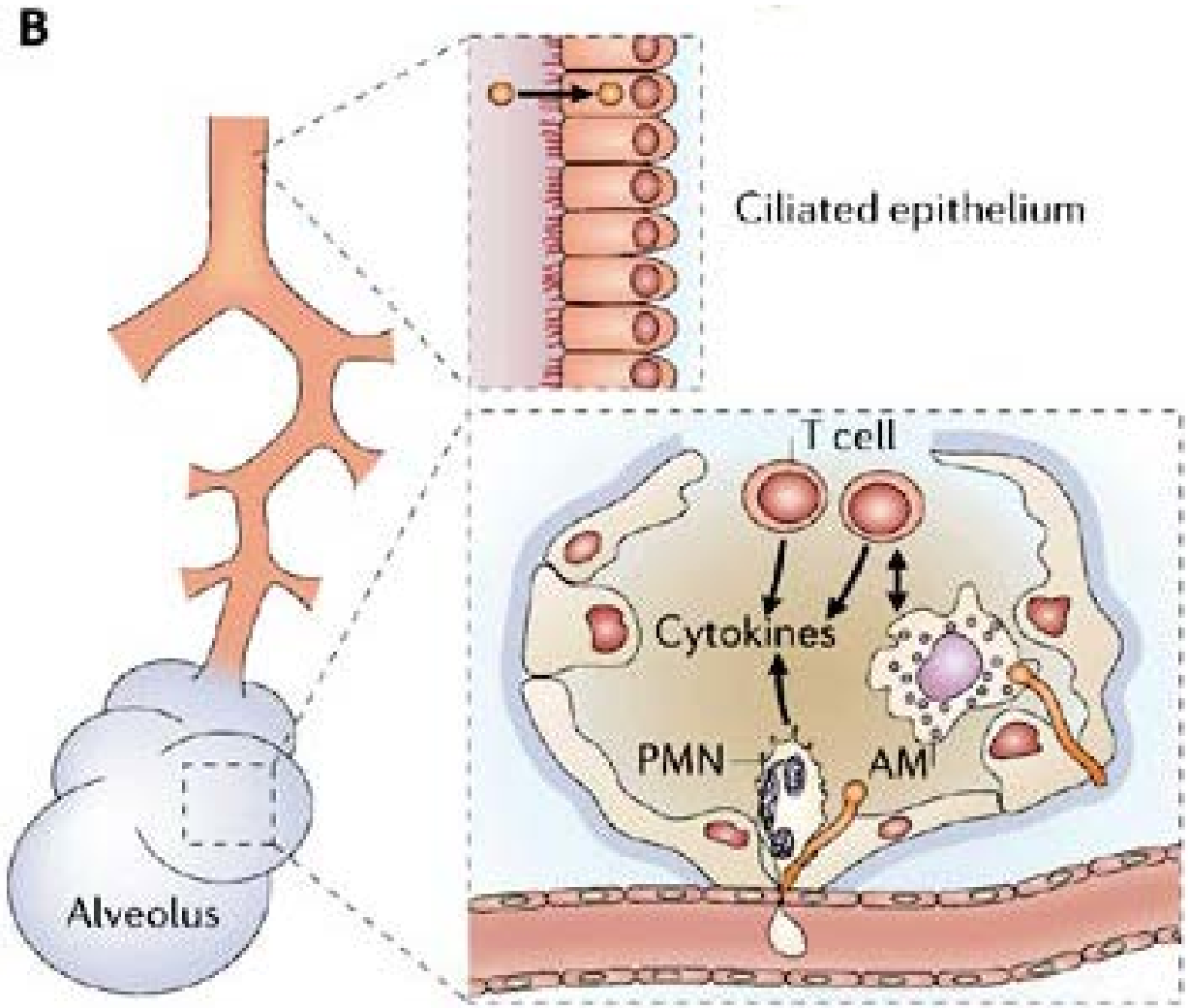
Although there is probably redundancy between human TLRs for protective immunity to most microorganisms, they seem to be non-redundant for protective immunity to particular infections.

The ectodomain forms a horseshoe-shaped solenoid and the intracellular domain is compact and globular.

The BB loop site is essential for interactions between TLRs and most intracellular signalling adaptors.

François Leulier & Bruno Lemaitre. **Toll-like receptors — taking an evolutionary approach.**

Nature Reviews Genetics 9, 165-178 (March 2008) doi:10.1038/nrg2303



Chauhan *et al. Nature Reviews Microbiology* **4**, 435–444 (June 2006) | doi:10.1038/nrmicro1426

Aerosols of Aspergillus fumigatus conidia are inhaled and travel to the alveoli.

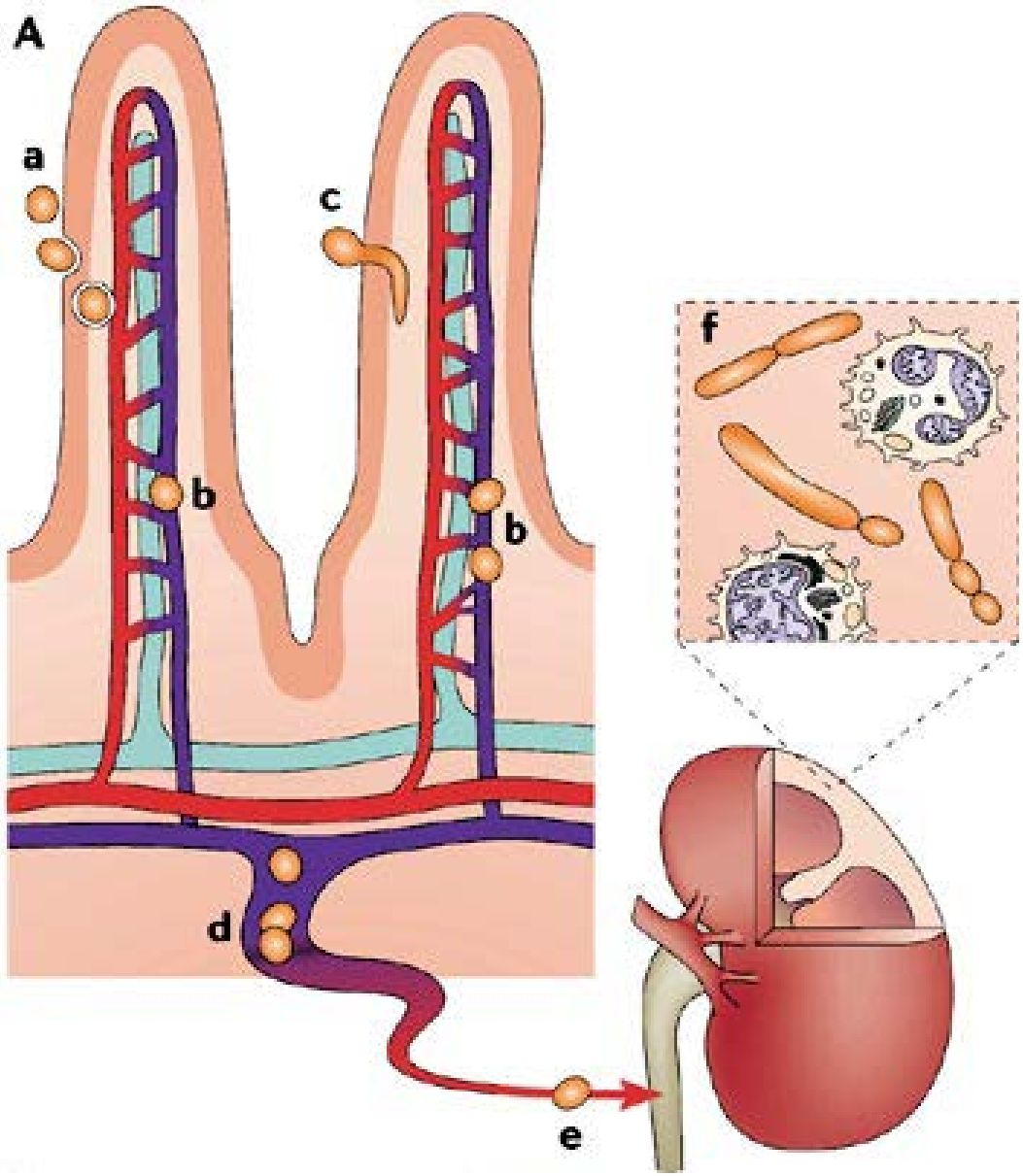
In the healthy host**, alveolar macrophages (AM) phagocytose and kill the organism after swelling of the conidium, an essential pre-germination stage**.

Production of reactive oxygen intermediates by AM is required to eliminate the organism, but PMNs also contribute.

In ICH, reduced numbers of PMNs and inefficient AM allow growth of the fungus.

Consequently, the conidia germinate and escape from the AM.

Direct invasion of the ciliated epithelium has also been reported (upper panel).



Disseminated candidiasis can originate at a gastrointestinal site.

Candida albicans enters epithelial microvilli through persorption of yeast cells or by germination (a,c).

In both cases, organisms enter the vasculature (b,d) for dissemination into tissues such as the kidney (e).

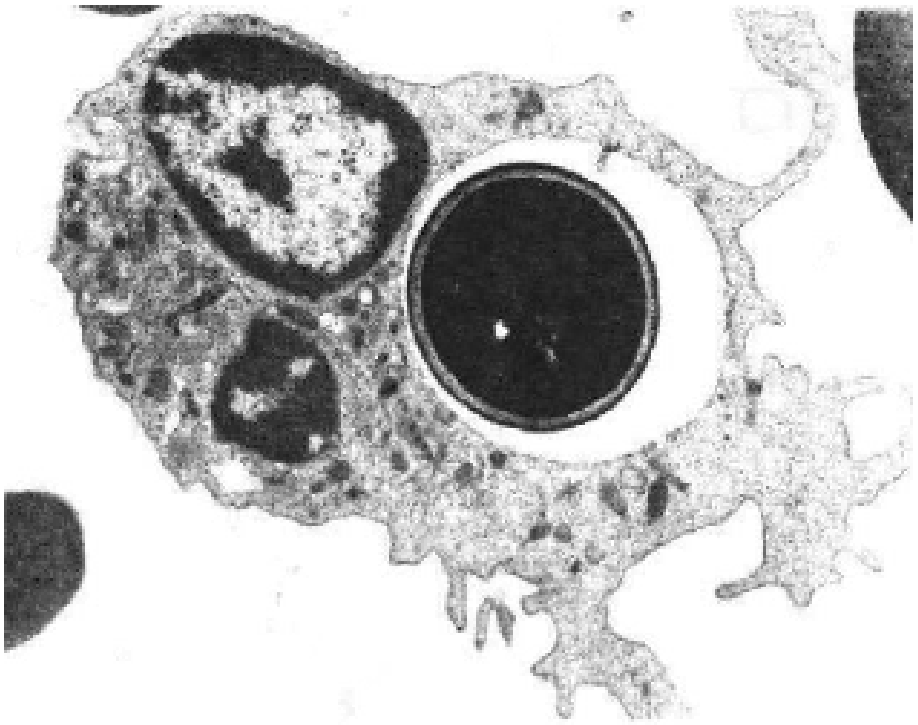
Typically, it localizes in the cortex (f) where it grows as pseudohyphae.

A vigorous host response occurs at this site consisting of both mononuclear and polymorphonuclear leukocytes.

Virulence factors (adhesins, morphogenesis, switch phenotypes, antioxidant proteins and invasive enzymes) promote the invasion of the organism.

Chauhan *et al. Nature Reviews Microbiology* **4**, 435–444 (June 2006) | doi:10.1038/nrmicro1426

Neutrophil Phagocytosis of Yeast

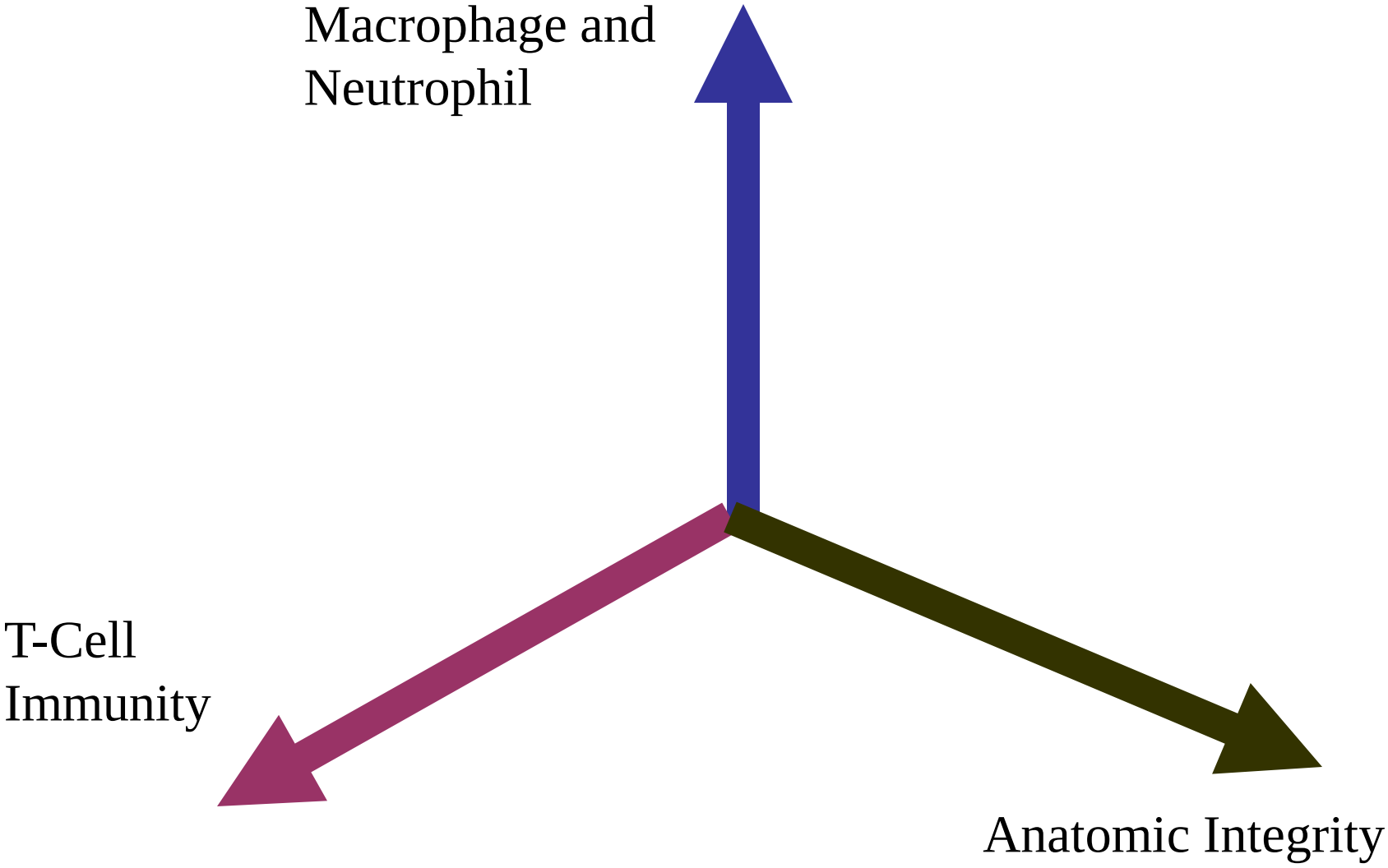


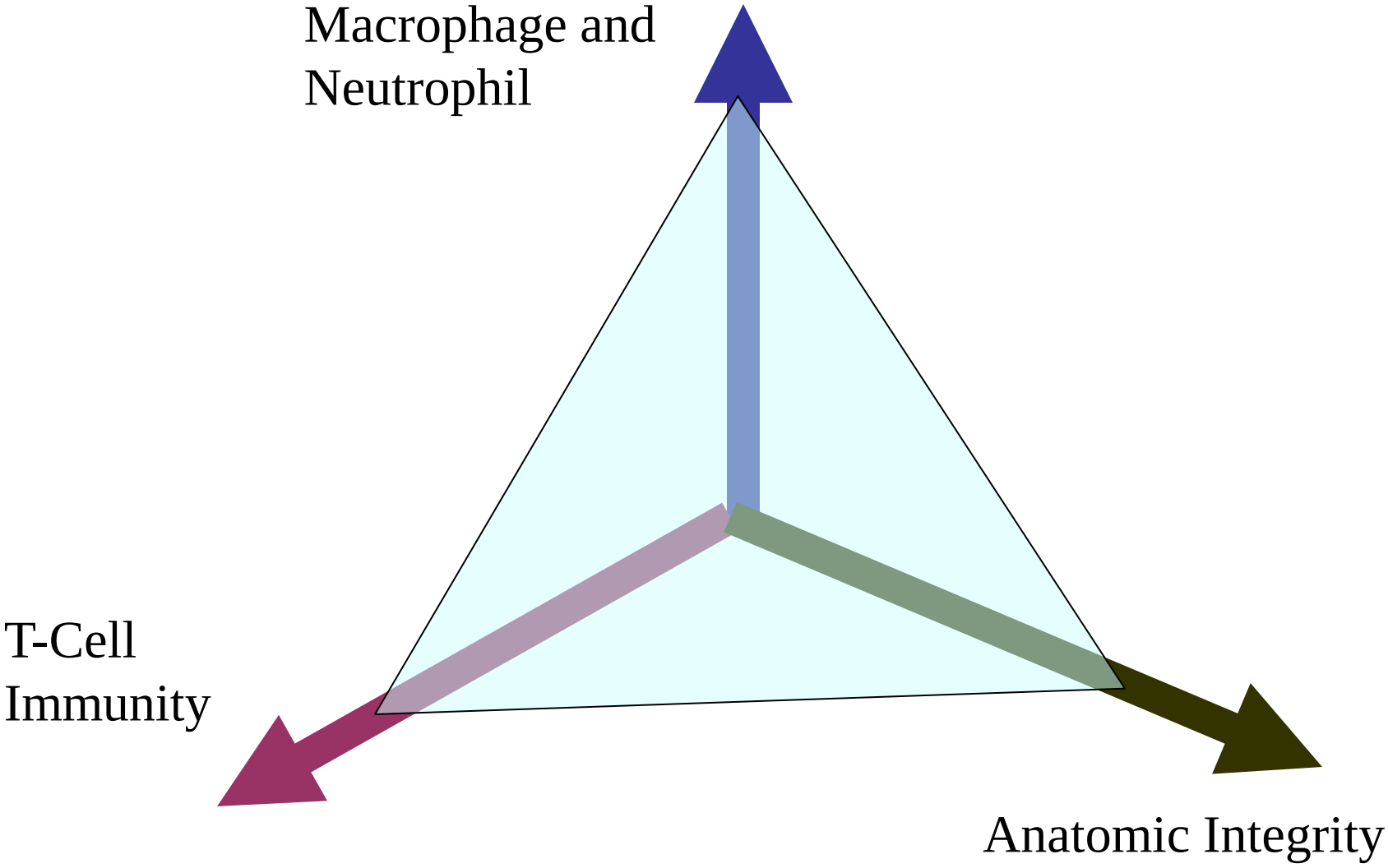
Neutrophil engulfing a single cell of Candida albicans

Note how the Candida cell is completely enclosed within a large vacuole inside the neutrophil.

Lysosomes are about to discharge their contents into the vacuole in order to destroy the fungal cell.

After this process is complete the neutrophil itself will also die.


Macrophage and
Neutrophil
T-Cell
Immunity
Anatomic Integrity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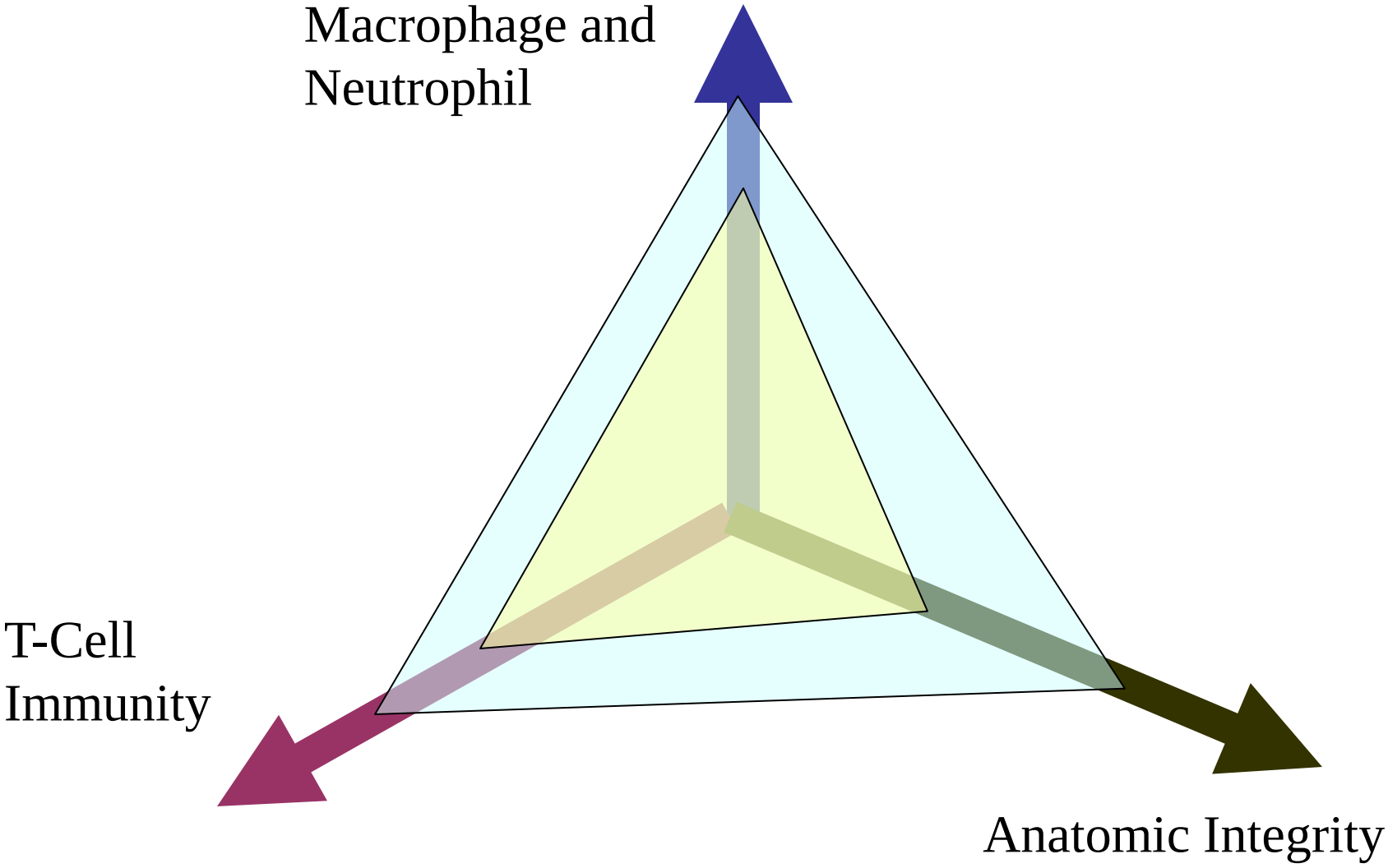
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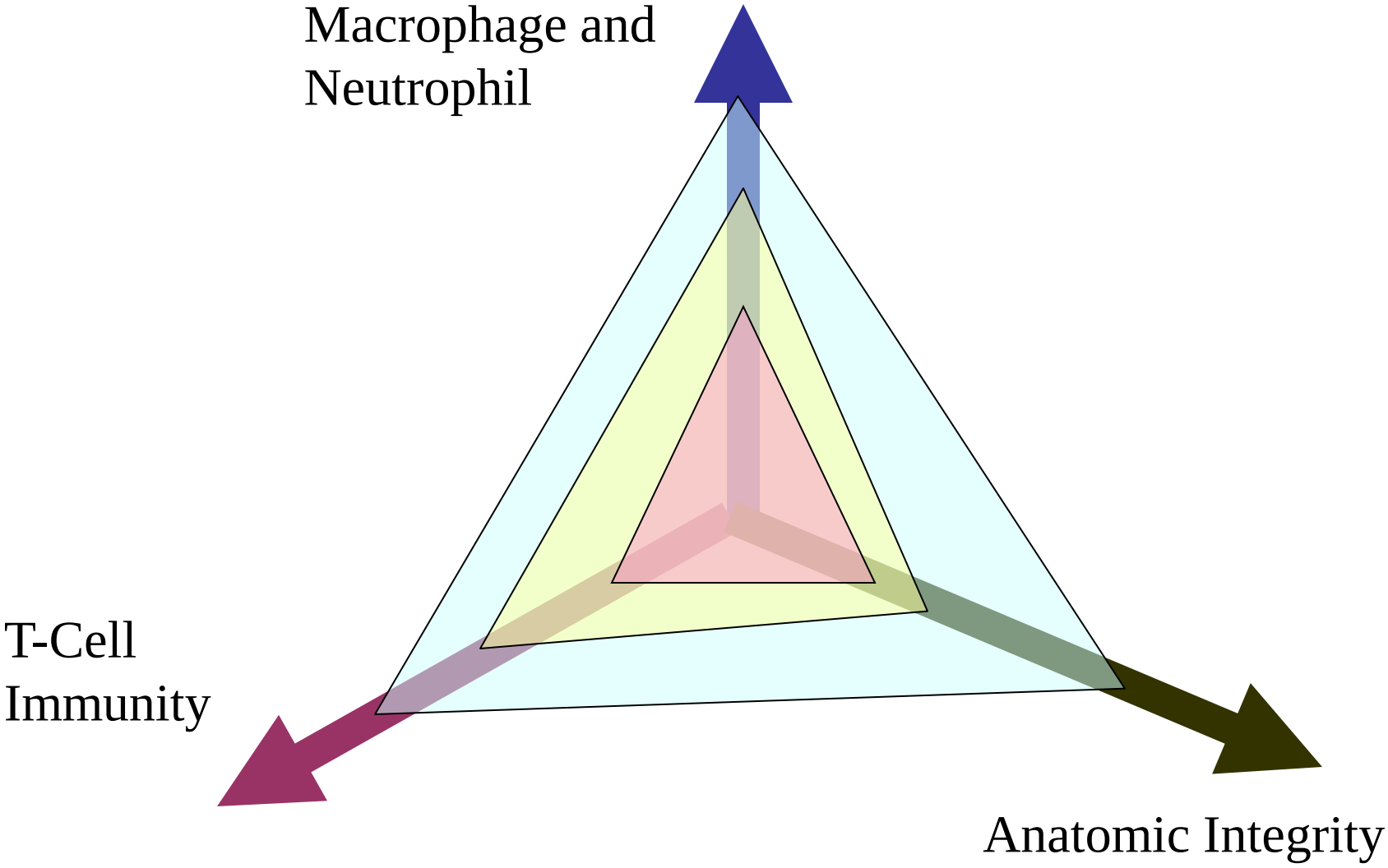

Macrophage and
Neutrophil
T-Cell
Immunity
Anatomic Integrity

A Recent Case

HPI

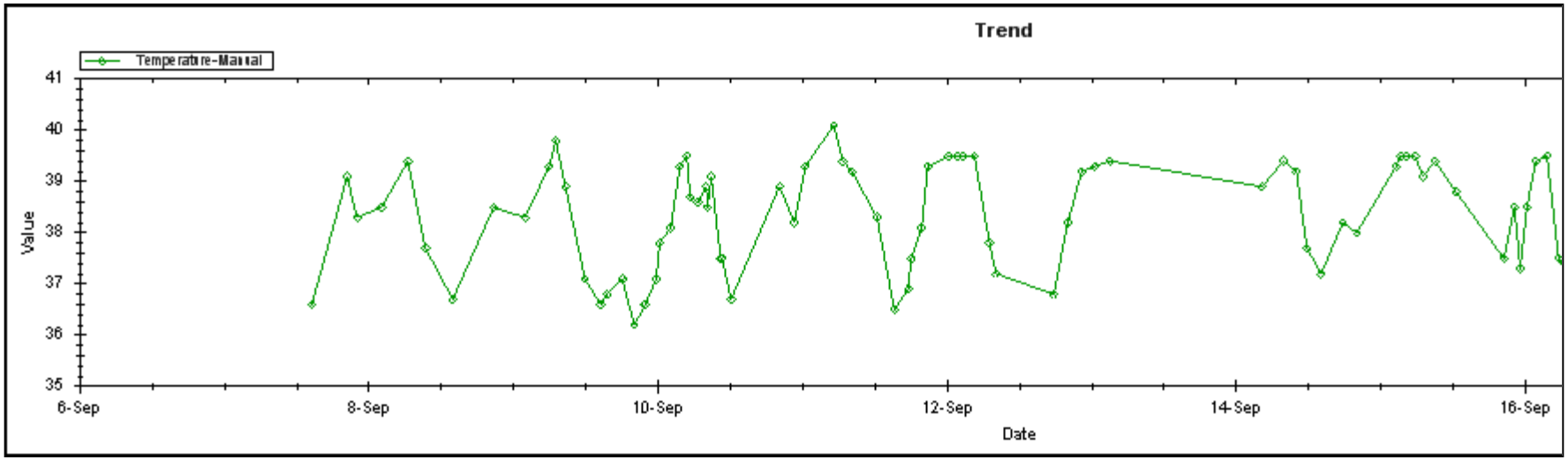
- 43yo F with DM I s/p pancreas only transplant 1999, subsequent Prograft nephrotoxicity
- 0 mismatch sibling kidney transplant May 2001
- Now has interstitial fibrosis and tubular atrophy of renal allograft, with a Creatinine of 3.
- Admitted for evaluation of fever for 1 week duration
- Immunosuppression: Cellcept, Prograf, Prednisone
- No antimicrobial prophylaxis
- CMV and EBV positive prior to transplant

HPI

- Presented to local urgent care for **2 day history of worsening nausea, vomiting, 1 episode of diarrhea, malaise, headache, and fever 101 F**
  - UA: 3-5 wbc, 6-10 rbc, (+) leukocyte esterase, 3-5 squams
  - Given 1 dose of levofloxacin for presumed UTI
- Returned to ED the next day, for **persistent nausea, vomiting,** admitted to local hospital for dehydration
  - Continued levofloxacin for presumed UTI/pyelonephritis
  - Spiking high grade fevers up to 40C nightly with sweats from 7-8pm till 7-8am despite levofloxacin
  - Blood and urine cultures remained negative
  - Levofloxacin stopped after 7 d, because no effect on fever

HPI

- After multiple investigations and no known source and persistent fever, patient **was transferred to Mayo Clinic after 10 days at local hospital.**
- Fever curve during week of work-up at Mayo Clinic, while on broad-spectrum antibiotics for possible UTI:



Social / Exposure History

- Lives in Western Wisconsin with fiance
- Nonsmoker, no alcohol use, no illicit drug use
- Likes to garden and walk her new 8 month puppy, noted lots of ticks in June on her puppy, healthy/received all shots
- Camping at Rock Fest this summer, stayed in air-conditioned camper. Was in Florida 5 years ago
- They recently bought a foreclosed house and did some renovation during the winter, in a wooded area
- Cares for 4 yo nephew who recently started daycare
- No Sick Contacts

Physical Exam – essentially unremarkable

- Wgt 53kg, BP 96/47, P 87, 95% RA, RR 16
- GEN: White female, non-toxic appearing, awake
- HEENT: tiny lower lip ulcer
- LYMPH: none
- CV: RRR, 2/6 early-mid systolic murmur, old
- PULM: Clear to ausculation
- ABD: S/NT/ND, NABS, no hepatosplenomegaly, transplant surgery scars.
- EXT: no edema
- MSK: L posterior superior iliac crest point tenderness, no joint inflammation
- SKIN: no rash

Labs

12 **Cr 2.9 (baseline 2)**

3.6 >----------< 93

37.5

AlkP 84, AST 23, ALT 19, Tbili 0.2

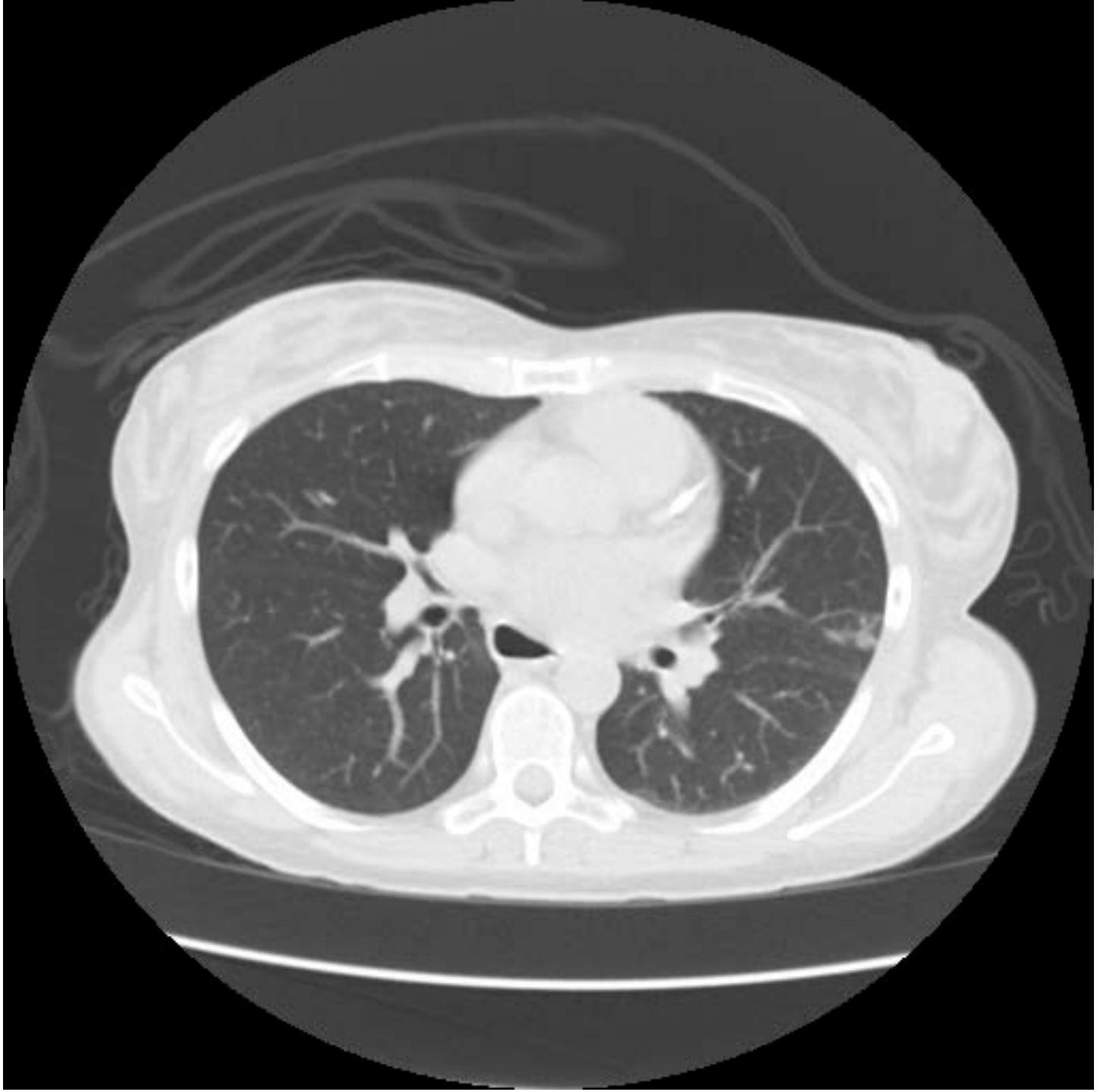
UA: 3-5 wbc, 6-10 rbc, (+) leukocyte esterase, 3-5 squams

Multiple Blood Cultures are negative

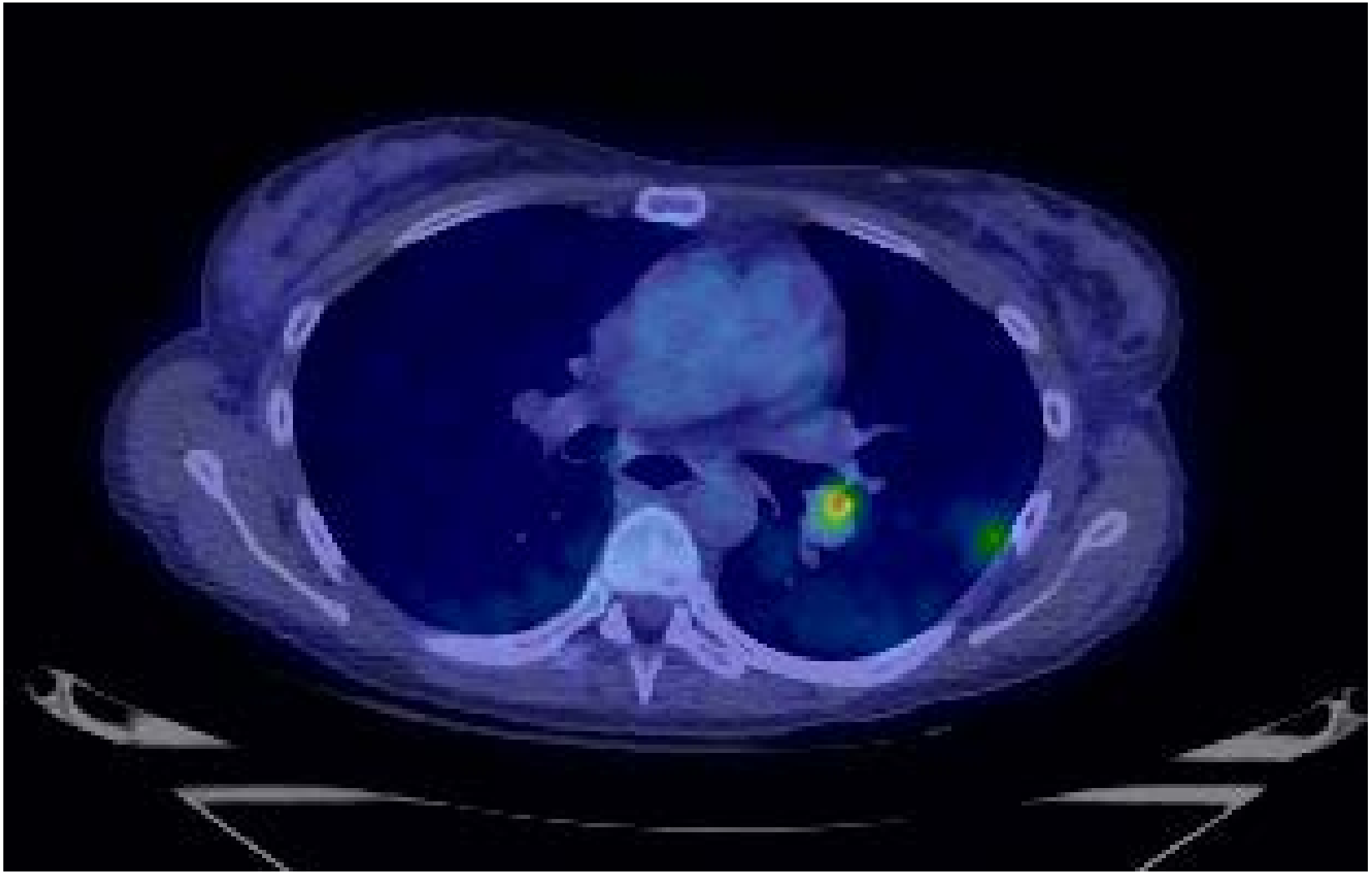
CXR is negative

ID Workup: Negative Tests (many)

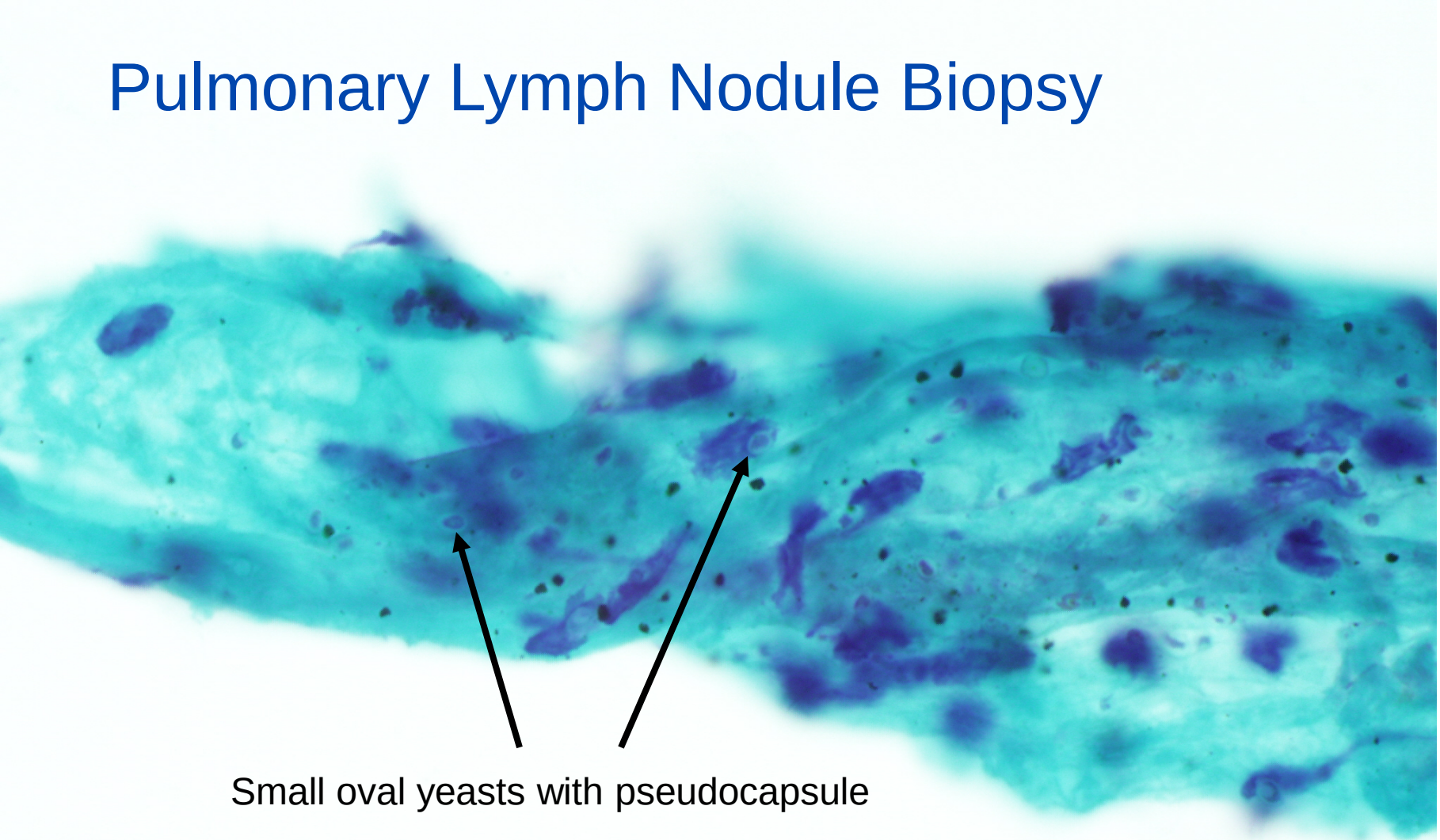
- Bartonella PCR neg
- Lyme disease serology neg
- Brucella IgG/IgM neg
- Legionella Urine Ag neg
- MTB Quantiferon
- Q Fever all neg
- Blastomyces Immunodiffusion
- Cocci Ab/Immunodiffusion
- Crypto Ag screen, Crypto Urinary Ag
- Histoplasma Ab Screen
- Babesia microti PCR
- HIV serology
- BK virus PCR, urine
- CMV DNA QN, PCR
- CMV PCR Quant
- EBV PCR
- HHV6 PCR
- Parvovirus B19 PCR
- WNV Ab IgG (+), IGM (-)
- Erlichia/Anaplasma DNA PCR



PET Scan

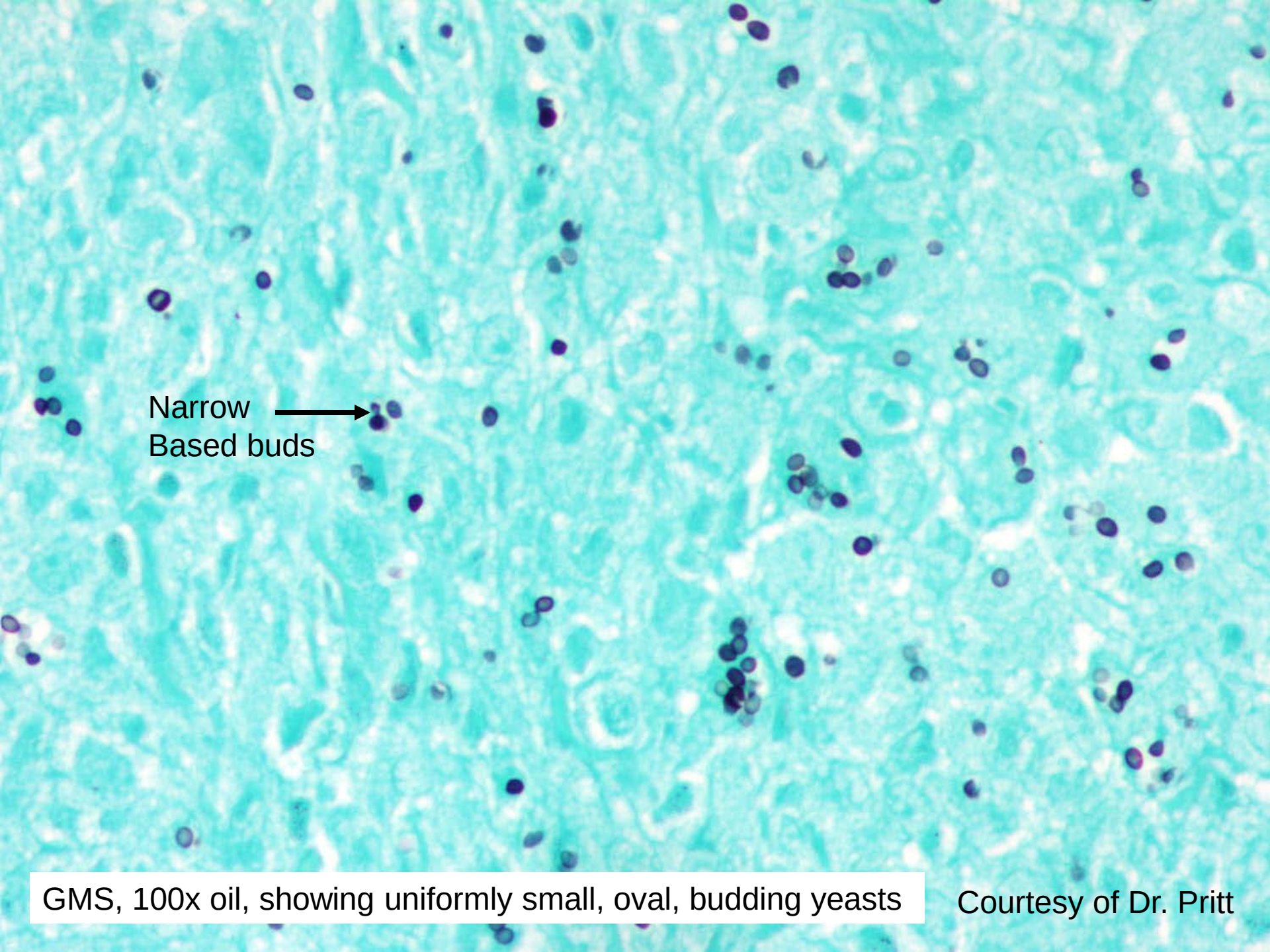


Pulmonary Lymph Nodule Biopsy



Courtesy of Dr. Pritt

Pap stain, 100x oil, showing pseudocapsule (poorly staining cell wall)



GMS, 100x oil, showing uniformly small, oval, budding yeasts

Courtesy of Dr. Pritt

Diagnosis

- ICH protocol BAL: Histoplasmosis Culture with PCR (+)
  - BAL: cloudy, TNC 9, 93 Alveolar Macrophage, 6 L, 1N
  - Fungal stain: Yeast (Culture also grew Candida)
  - Aspergillus Ag BAL < 0.5 (can be false + in Histoplasmsosis)
  - All other ICH tests were negative.
  - (had had a negative BAL at the OSH prior to transfer)
- Transbronch Bx of Lymph node: + pathology for fungus; tissue culture (+) and tissue direct PCR + for Histosplasmosis
- Urine Histoplasmosis Antigen positive at 6.7 ng/mL (+ >0.50), ***results had been faxed to outside hospital.***
- Fungal/TB Blood culture – Histoplasma capsulatum grew in 7 days– 3 separate days

Pathology

- Lymph Node: necrotizing granulomatous inflammation containing histoplasma capsulatum on GMS stain, AFB neg

Special Microbiology PCR Studies

LYMPH NODE, TISSUE

FUNGAL CULTURE, ROUTINE

- HISTOPLASMA CAPSULATUM Identified by Rapid PCR.

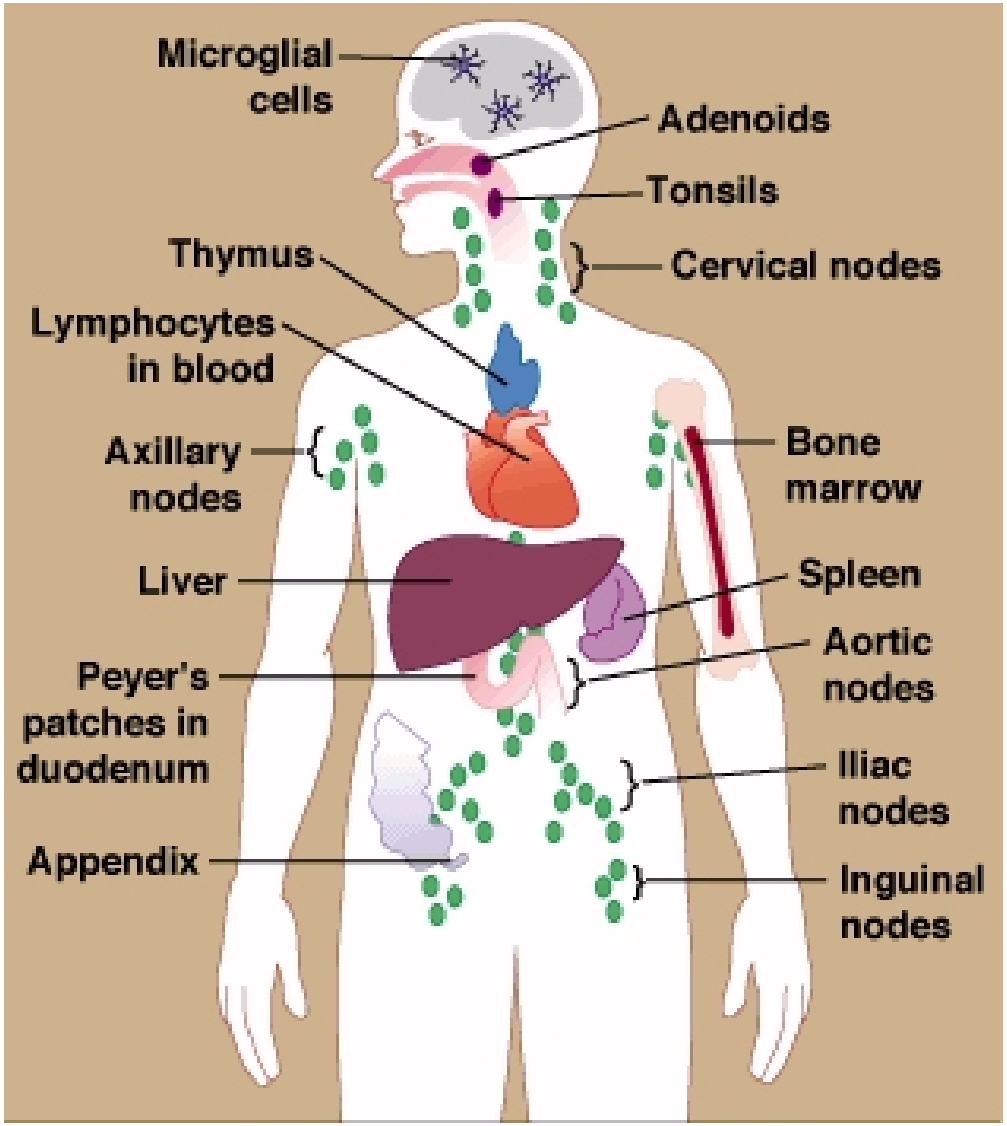
Histoplasma/Blastomyces -- Direct PCR.

- Positive for Histoplasma capsulatum
- Specimen Source (Histo/Blasto PCR) LYMPH NODE

BRONCHOALVEOLAR LAVAGE, ICH LINGULA FUNGAL CULTURE,

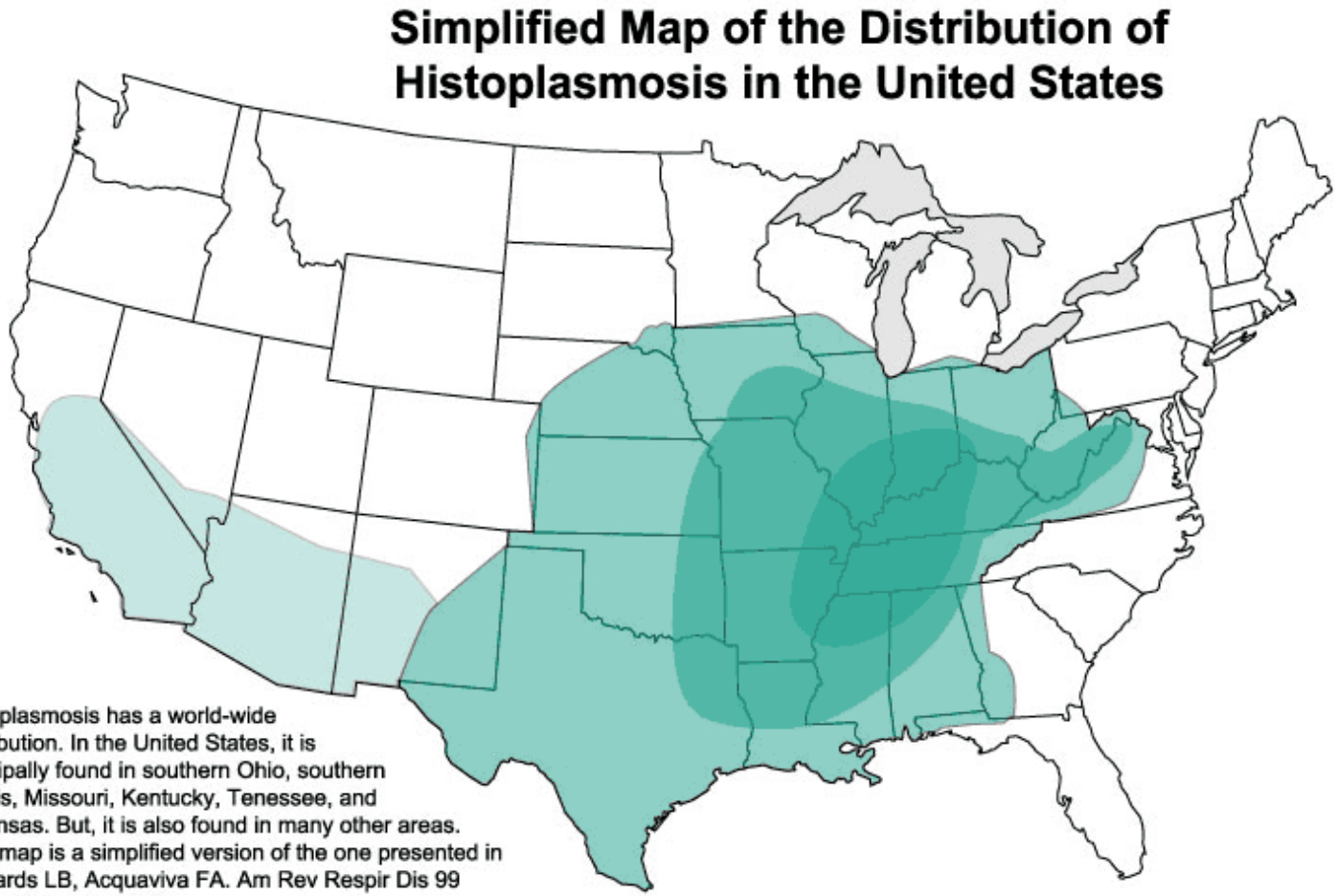
- HISTOPLASMA CAPSULATUM
- Reportable Disease. Identified by Rapid PCR.

Histoplasmosis and the RES



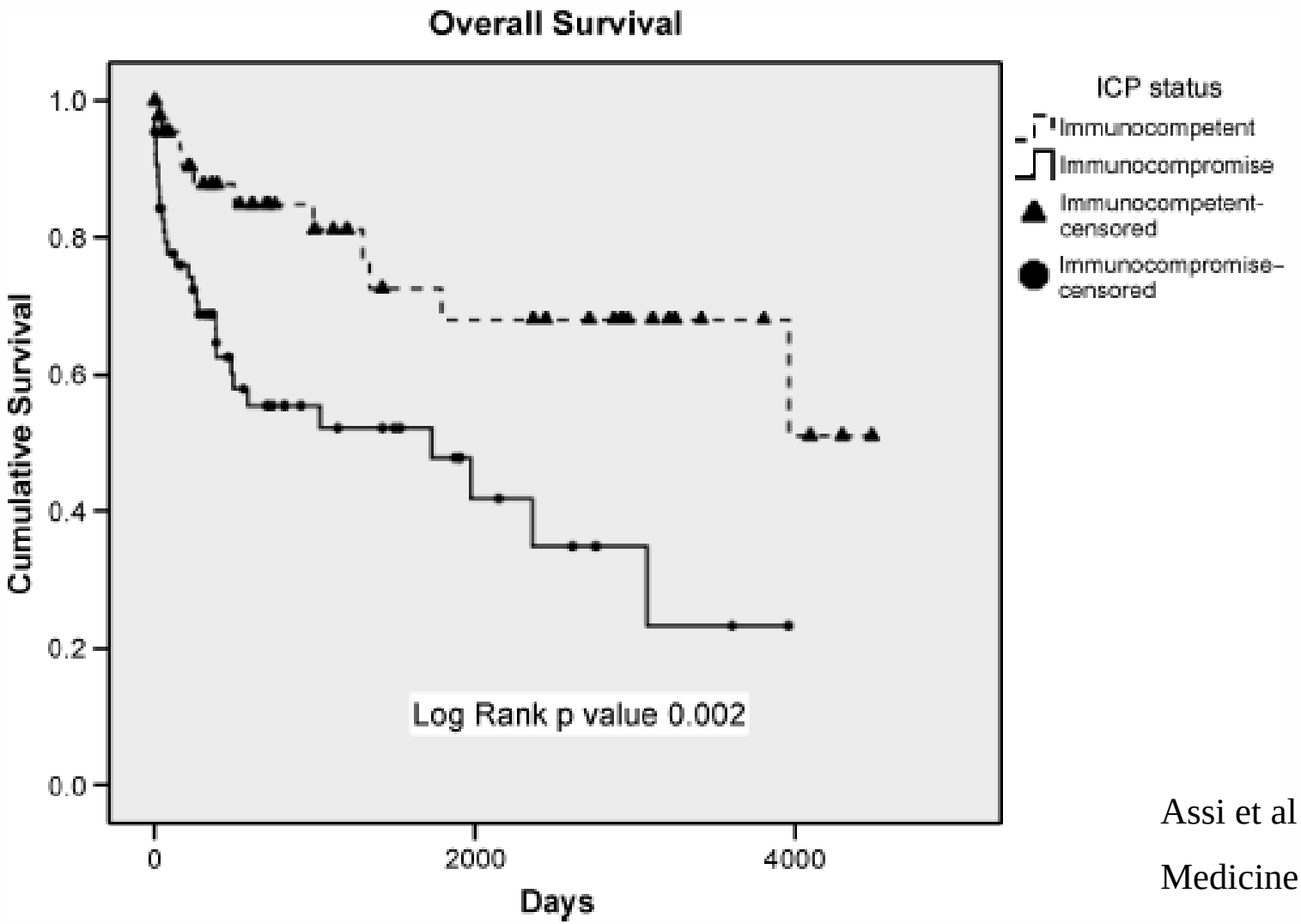
Source: Medical College of Georgia

Histoplasmosis in US



Histoplasmosis has a world-wide distribution. In the United States, it is principally found in southern Ohio, southern Illinois, Missouri, Kentucky, Tenessee, and Arkansas. But, it is also found in many other areas. This map is a simplified version of the one presented in Edwards LB, Acquaviva FA. Am Rev Respir Dis 99 (Suppl.): 1-132, 1969

Survival in Systemic Histoplasmosis – ICH vs Normal Host



Assi et al

Medicine

May 2007

How would you treat this patient?

A. Induction with Ambisome 3mg/kg, until controlled, then step down to itraconazole, for at least one year

B. Initial treatment with Itraconazole, continue for at least one year.

C. Initial treatment with high dose Fluconazole, 800 mg/day (w Renal Function adjustment), continue for at least one year.

D. Initial treatment with Posaconazole, indefinitely, higher dose until controlled, then lower dose life-long.

E. Initial treatment with Voriconazole, indefinitely, higher dose until controlled, then lower dose life-long

AST Guidelines for Histoplasmosis in SOT– Singh et al – AJT Sept 2012

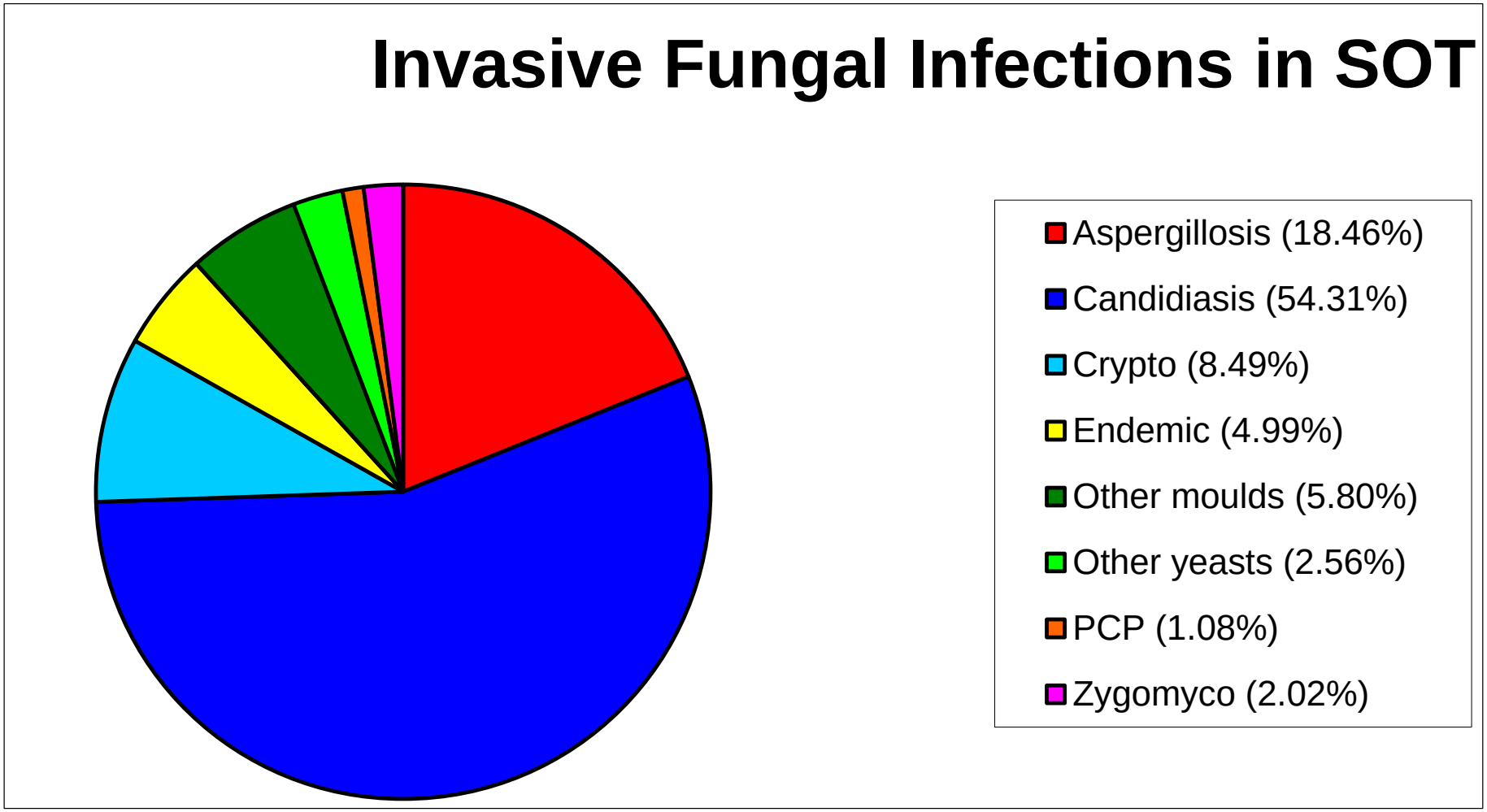
Table 4: Treatment of histoplasmosis in organ transplant recipients

Medication	Indication	Dose	Duration
First line treatments			
Liposomal amphotericin B[1]	Moderately-severe or severe infection	3 mg/kg/day	Until the infection is controlled, then transition to an azole alone
Itraconazole[2]	Mild infection and stepdown after response to liposomal amphotericin B	200 mg BID	At least one year. Longer duration may be required if immunosuppression cannot be reduced, or if relapse occurs after treatment is stopped

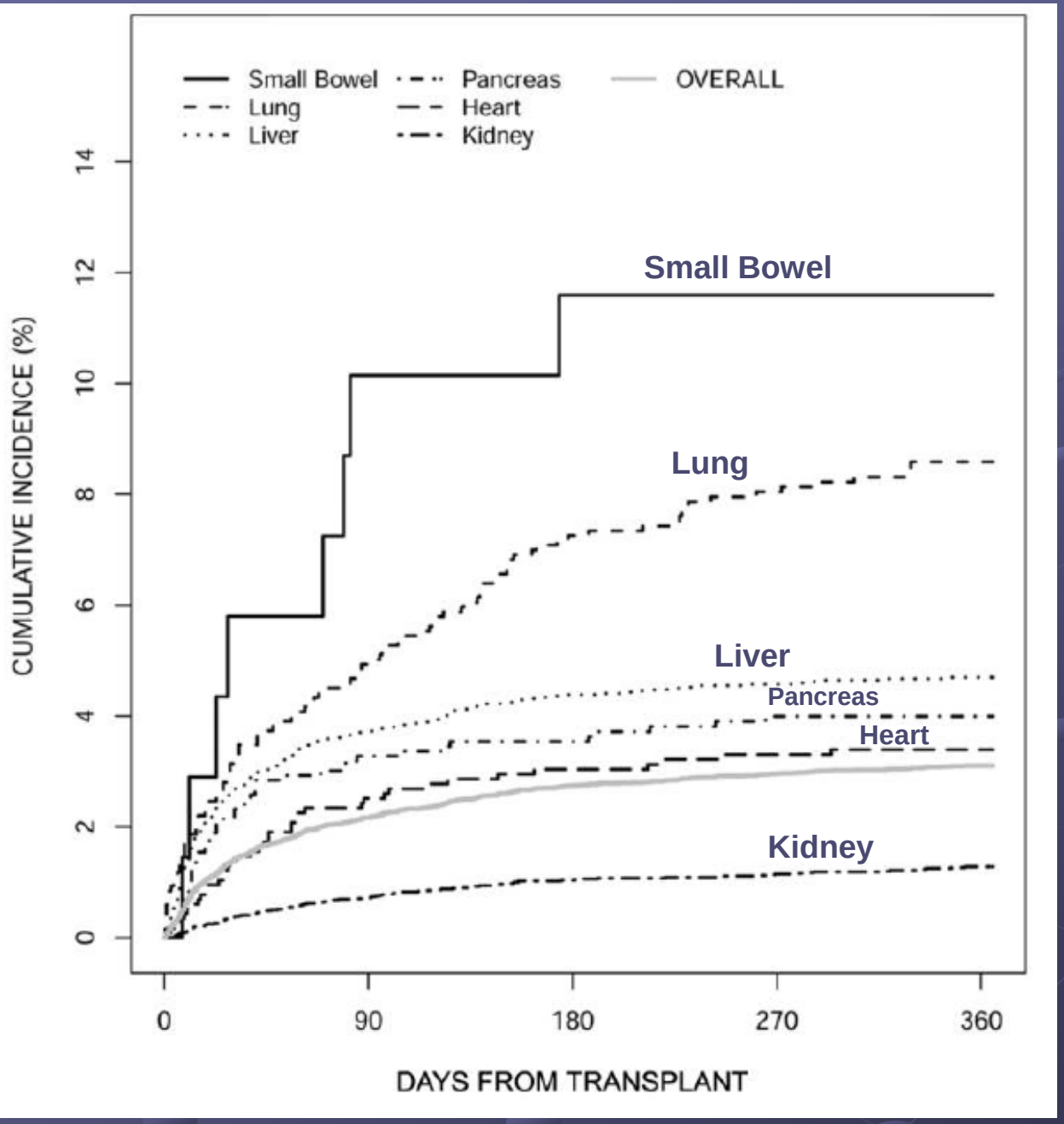
AST Guidelines for Histoplasmosis in SOT– Singh et al – AJT Sept 2012

Second line treatments			
Fluconazole	Mild infection and stepdown after response to liposomal amphotericin B	800 mg daily[3]	At least one year. Longer duration may be required if immunosuppression cannot be reduced, or if relapse occurs after treatment is stopped
Posaconazole[2]	Mild infection and stepdown after response to liposomal amphotericin B	400 mg BID orally	Indefinite duration; full treatment dose until completely resolved, then consider a lower dose as secondary lifelong prophylaxis.
Voriconazole[2]	Mild infection and stepdown after response to liposomal amphotericin B	6 mg/kg BID × 2 doses, then 4 mg/kg BID, or 200–300 mg BID	Indefinite duration, full treatment dose until completely resolved, then consider the lower dose as secondary lifelong prophylaxis.

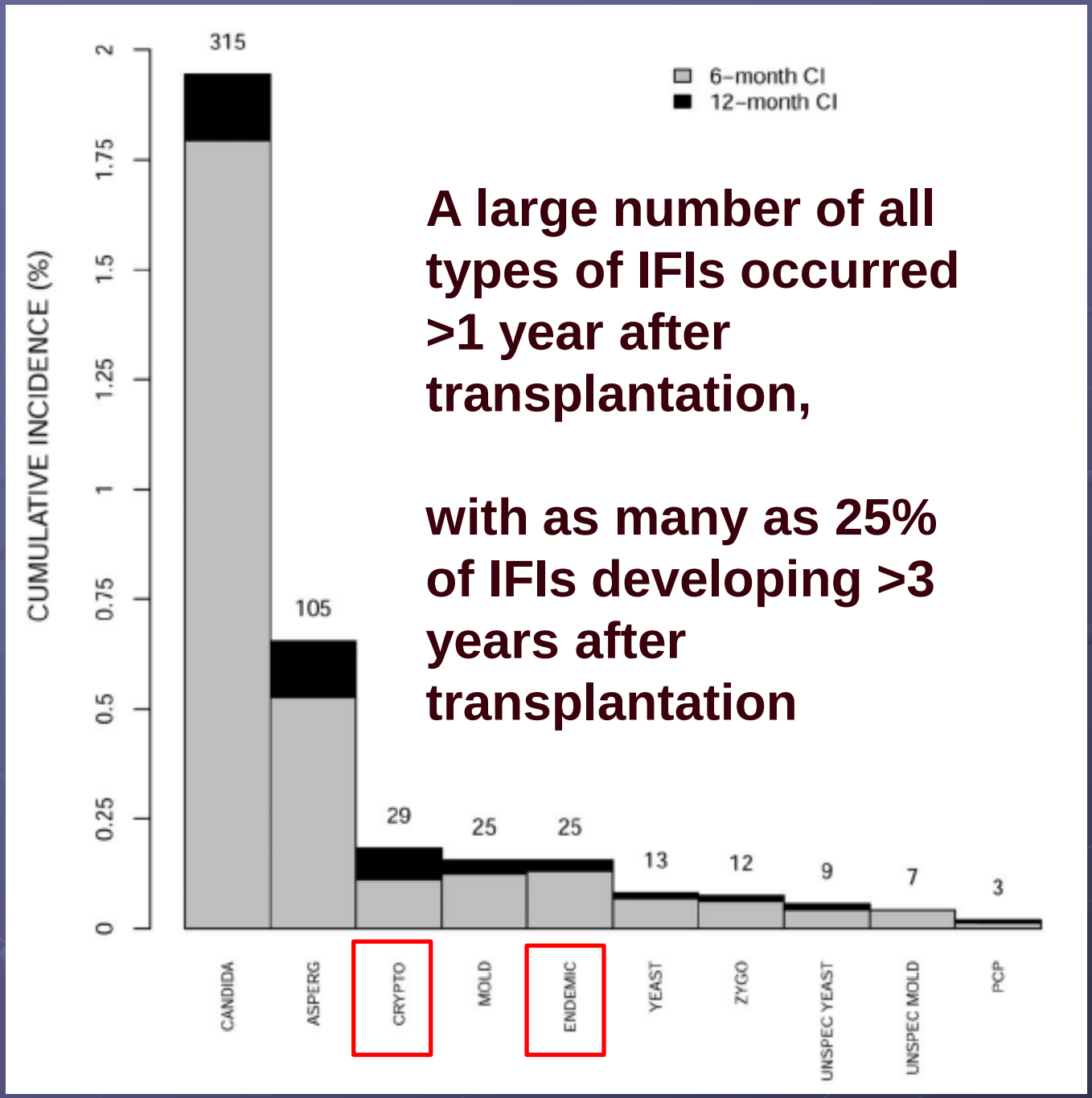
TRANSNET: Organisms



Cumulative Incidence of IFI in SOT, by Organ Transplant Type



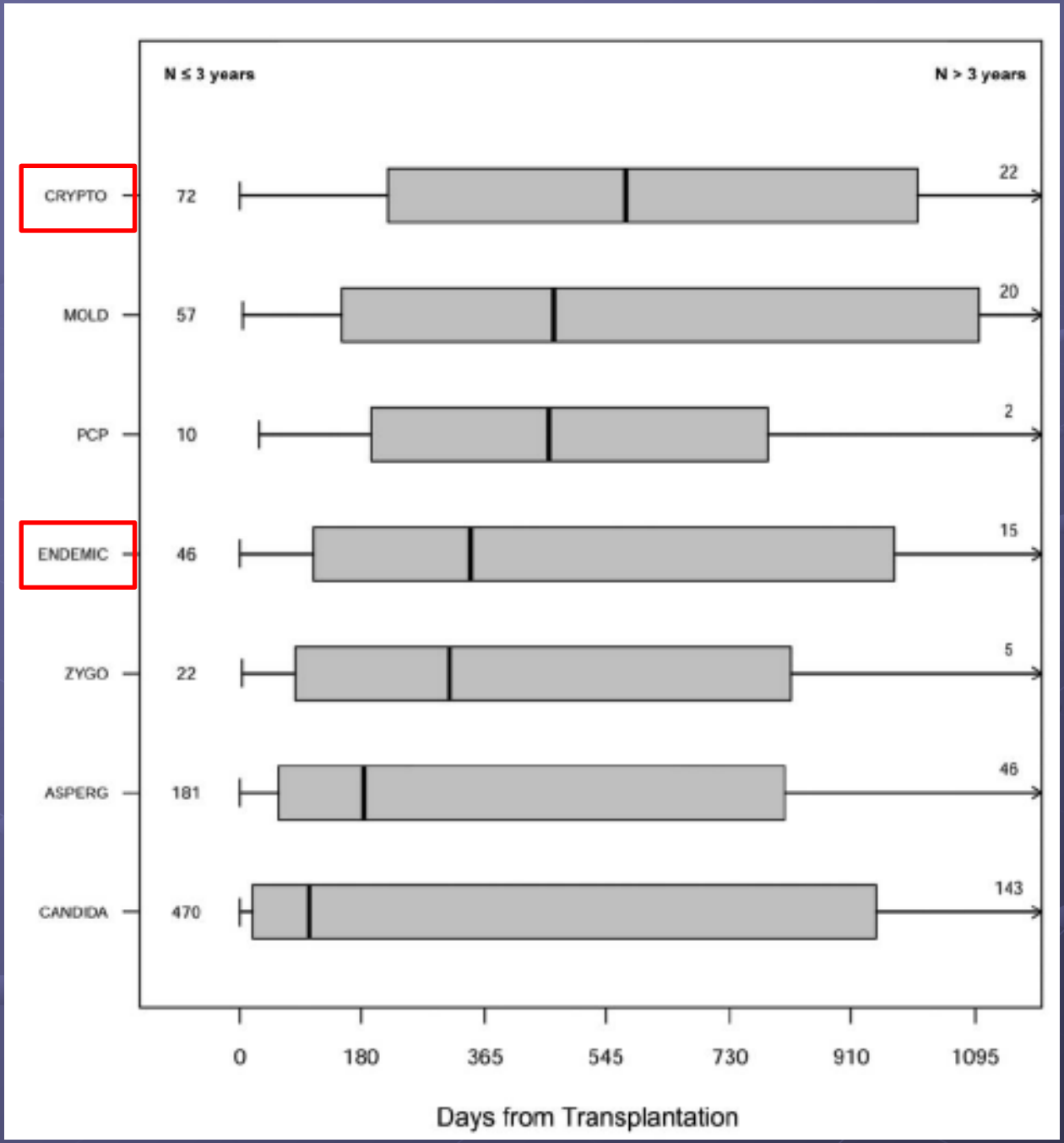
Pappas et al, CID 2010; 50:1101–1111
DOI: 10.1086/651262



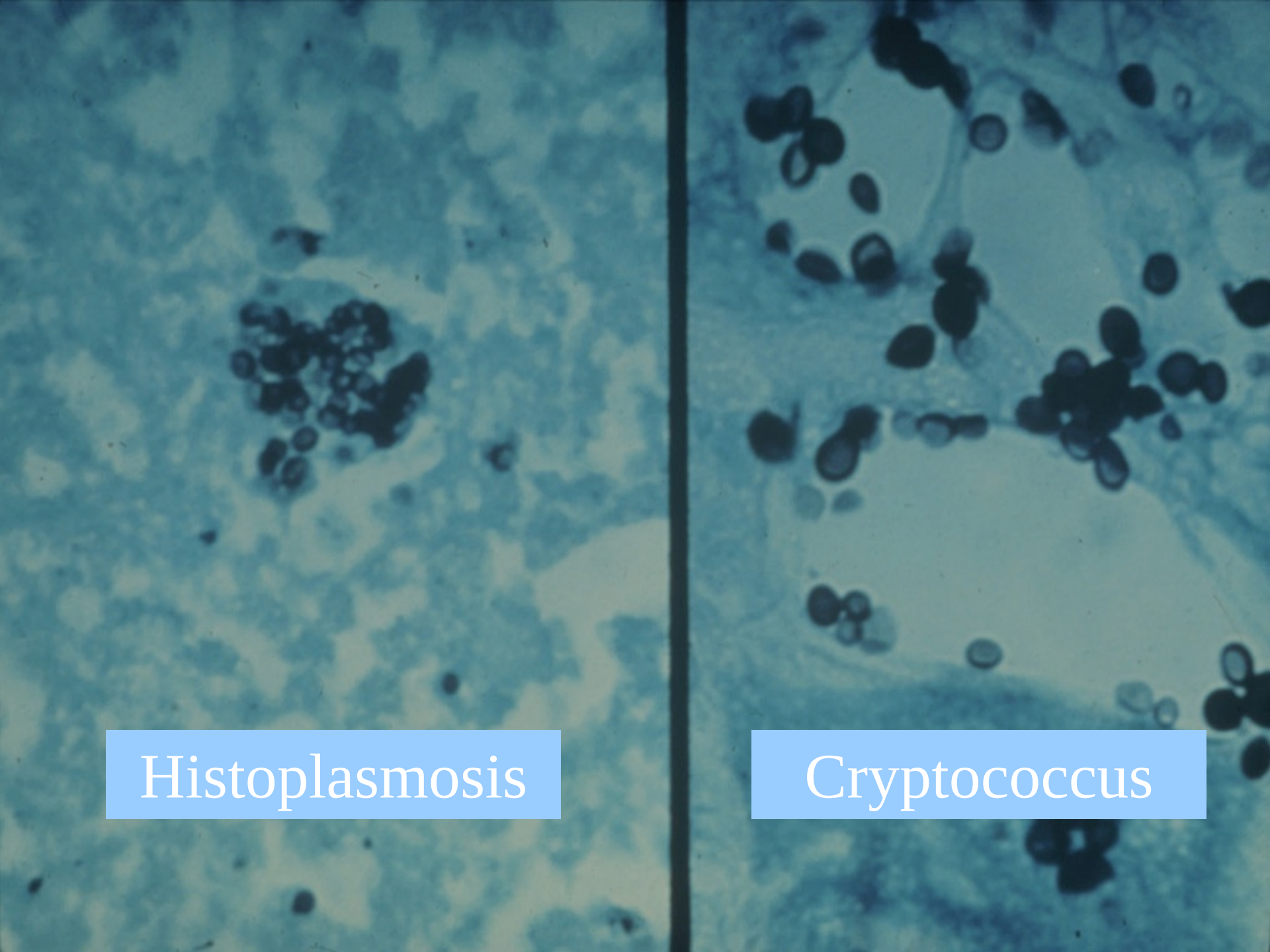
A large number of all types of IFIs occurred >1 year after transplantation,

with as many as 25% of IFIs developing >3 years after transplantation

Pappas et al, CID 2010; 50:1101–1111
DOI: 10.1086/651262



Pappas et al, CID 2010; 50:1101–1111
DOI: 10.1086/651262


Histoplasmosis
Cryptococcus

Identifying Predictors of Central Nervous System Disease in Solid Organ Transplant Recipients With Cryptococcosis

Factor	OR (95% CI)	*P*
Late-onset disease (onset >24 mo)	5.0 (1.5–17)	0.009
Abnormal mental status	7.1 (1.2–43)	0.033
Serum cryptococcal antigen titer >1:64	8.7 (2.5–30)	0.001
Fungemia	7.2 (1.3–40)	0.024

Osawa et al, Transplantation 2010;89: 69–74

Central Nervous System Cryptococcosis in SOTx: Clinical Relevance of Abnormal Neuroimaging Findings

- Central nervous system (CNS) involvement has been documented in 25% to 72% of organ transplant recipients with cryptococcal disease.
- Mortality in patients with cryptococcosis ranges from 10% to 25%, and approaches 40% in those with CNS disease
- Mortality rate was 50% (3/6) in patients with parenchymal, 12.5% (1/8) in leptomeningeal, and 0/2 in hydrocephalus.
- 19% of the CNS lesions developed after initiation of antifungal therapy with Immune Reconstitution Syndrome, with no mortality

Singh et al, *Transplantation 2008;86: 647–651)*

Treatment of CNS Cryptococcus in SOTx

Singh et al. *American Journal of Transplantation* 2012; 12: 2414–2428. September 2012

Induction	Duration
Preferred therapy	
Liposomal amphotericin B 3–4 mg/kg/day or amphotericin B lipid complex 5 mg/kg/day plus 5 flucytosine 100 mg/kg/day[1]	2 weeks
Alternative therapy liposomal amphotericin B 3–4 mg/kg/day or amphotericin B lipid complex 5 mg/kg/day	4 weeks
Consolidation	
Fluconazole 400–800 mg/day[1]	8 weeks
Maintenance	
Fluconazole 200 mg/day	6–12 months[2]
Isolated pulmonary cryptococcosis[3]	
Fluconazole 400 mg/day[4]	6–12 months

Immune Reconstitution Syndrome (IRS) in Solid Organ Transplant (SOT) Recipients with Invasive Cryptococcal Infection (ICI)

- From 12 Transplant Centers, International
- 89 SOT patients with ICI, with 1 year of follow-up.
- Kidney 39%, liver27%, heart 9%, lung 8% , pancreas 2 %
- Median time to onset of ICI: 17 months post Tx (range 6.5 to 45 months); 41% within first year post Tx.
- Pulmonary: 65%; limited to lungs, 39%
- CNS: 46%
- Disseminated 57%
- Positive Blood Cx, 37%
- Serum Crypto Ag + in 82%; titers >/=1:64 in 62%

Clin Inf Dis. 2015: 60 1 Jan, Sun et al.

Immune Reconstitution Syndrome (IRS) in Solid Organ Transplant (SOT) Recipients with Invasive Cryptococcal Infection (ICI)

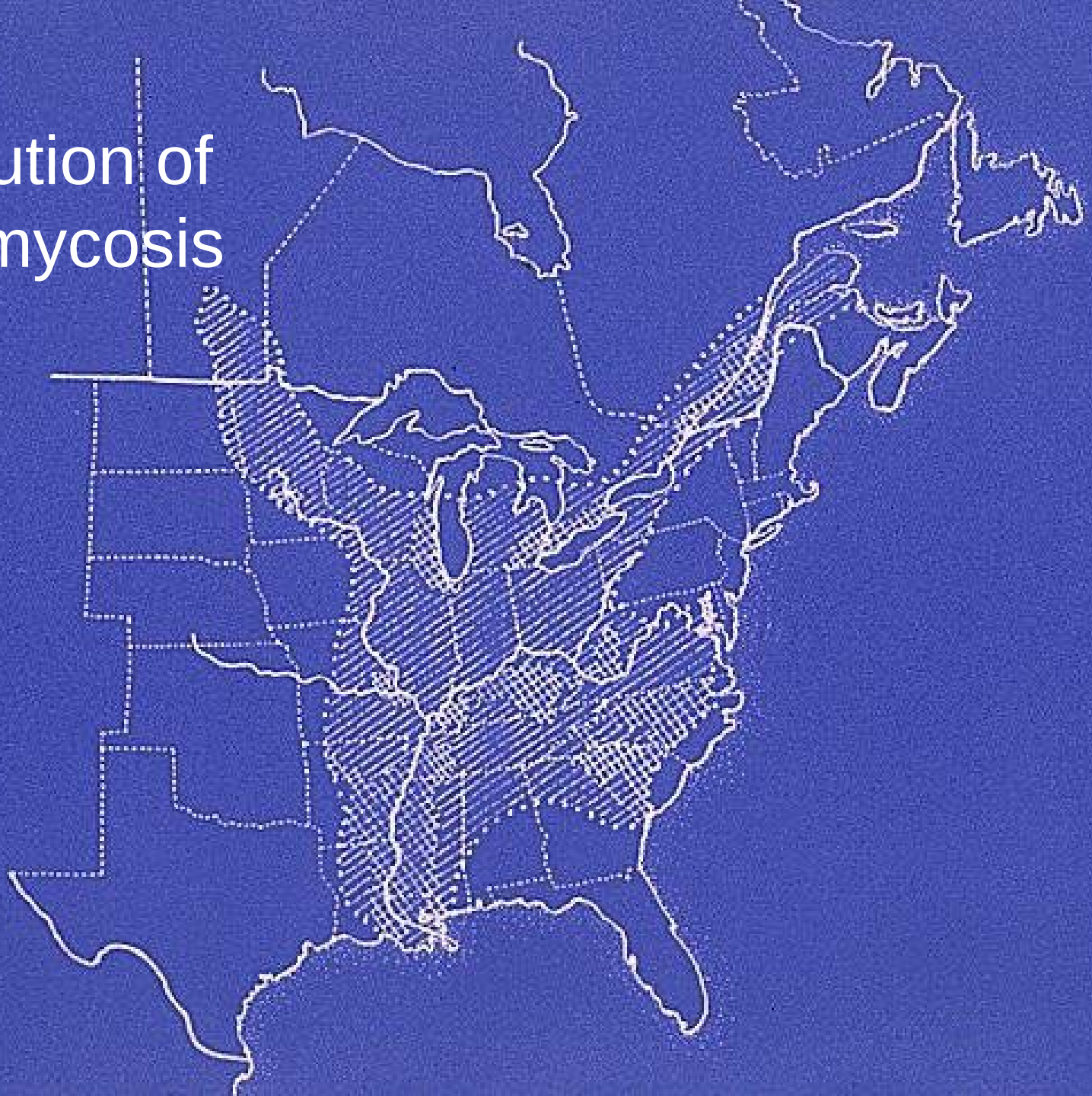
- Of 89 SOT patients with Crypto Infx, 13 (14%) developed IRS.
- Onset of IRS: median 45 days (IQR 15-76), after start of antifungal therapy.
- Risk factors for IRS included:
  - CNS infection , Adj. OR: 6.23, (p=.03)
  - Discontinuation of Calcineurin Inhibitor, AOR: 5.11, ((p=/02)
  - Combination of these risk factors was syngergistic:
    - Neither 2.6%, one (19%), both 50% (p=.0001).
- Crypto CNS infection with neuroimaging abnormalities more predictive or IRS than Crypto Ag titers.
- No difference in mortality with or without IRS (~14%)
- ***Organ rejection 7-fold higher in IRS group (assoc with stopping CNI).***
- ***In SOT patients with Cryptococcal infection, lower immunosuppression (~50%), but do not stop Calcineurin Inhibitors***

Clin Inf Dis. 2015: 60 1 Jan, Sun et al.

Size and CNS Pathogenesis

- **Yeast Forms** (up to 20 micrometer in diameter) -- Candida, Cryptococcus, Histoplasma, Coccidioides, Blastomyces, Sporotrichum.
  - Have access to the microcirculation. Seed the Subarachnoid space. Reach small arterioles and capillaries producing leptomeningitis and subpial ischemic lesions.
- **Intermediate sizes** pseudohyphae such as Candida species:
  - Occlude small vessels, produce local tissue necrosis that transforms into abscesses.
- **Large Hyphal forms** of variable size (septate Aspergillus, non-septate Zygomyces, Cladosporium) :
  - Obstruct large and intermediate size arteries and occasionally veins, giving rise to large infarcts.

Distribution of blastomycosis in US



CNS Blastomycosis RX

- Surgery recommended for DX of CNS blastomycosis as well as for management of osteomyelitis and for mass lesions
- if blastomycosis is diagnosed at a non-CNS site, it is reasonable to treat empirically for CNS blastomycosis in patients with abnormal CNS imaging or CSF results

22 cases of CNS Blastomycosis CT/MRI

Right frontal lobe mass	Bilateral cerebellar masses; obstructive hydrocephalus; tonsillar herniation	Posterior fossa leptomeningeal enhancement	Left temporoparietal abscess
Multiple cerebellar lesions	Basilar meningeal enhancement	Dilated ventricles	Ventricular dilation
Lesions in right and left cerebellum	Cerebellar mass lesion	Cerebellar mass	Suprasellar mass
Diffuse leptomeningeal enhancement; ventricular dilation; infarct along superior cerebellum	Left temporal lobe mass	Left cerebellar lesion	Left occipital lobe mass
Mass in right retina	Ventricular enlargement	Right basal ganglia lesion; diffuse meningeal enhancement	Right frontal lobe mass; diffuse leptomeningeal enhancement
		Thoracic epidural abscess	Infarcts in brainstem and basal ganglia and cerebellum

Barriola, et al. CID 2010; 50:797–804 DOI: 10.1086/650579

22 cases of CNS Blastomycosis CT/MRI

Right frontal lobe mass	Bilateral cerebellar masses; obstructive hydrocephalus; tonsillar herniation ★	Posterior fossa leptomeningeal enhancement	Left temporoparietal abscess
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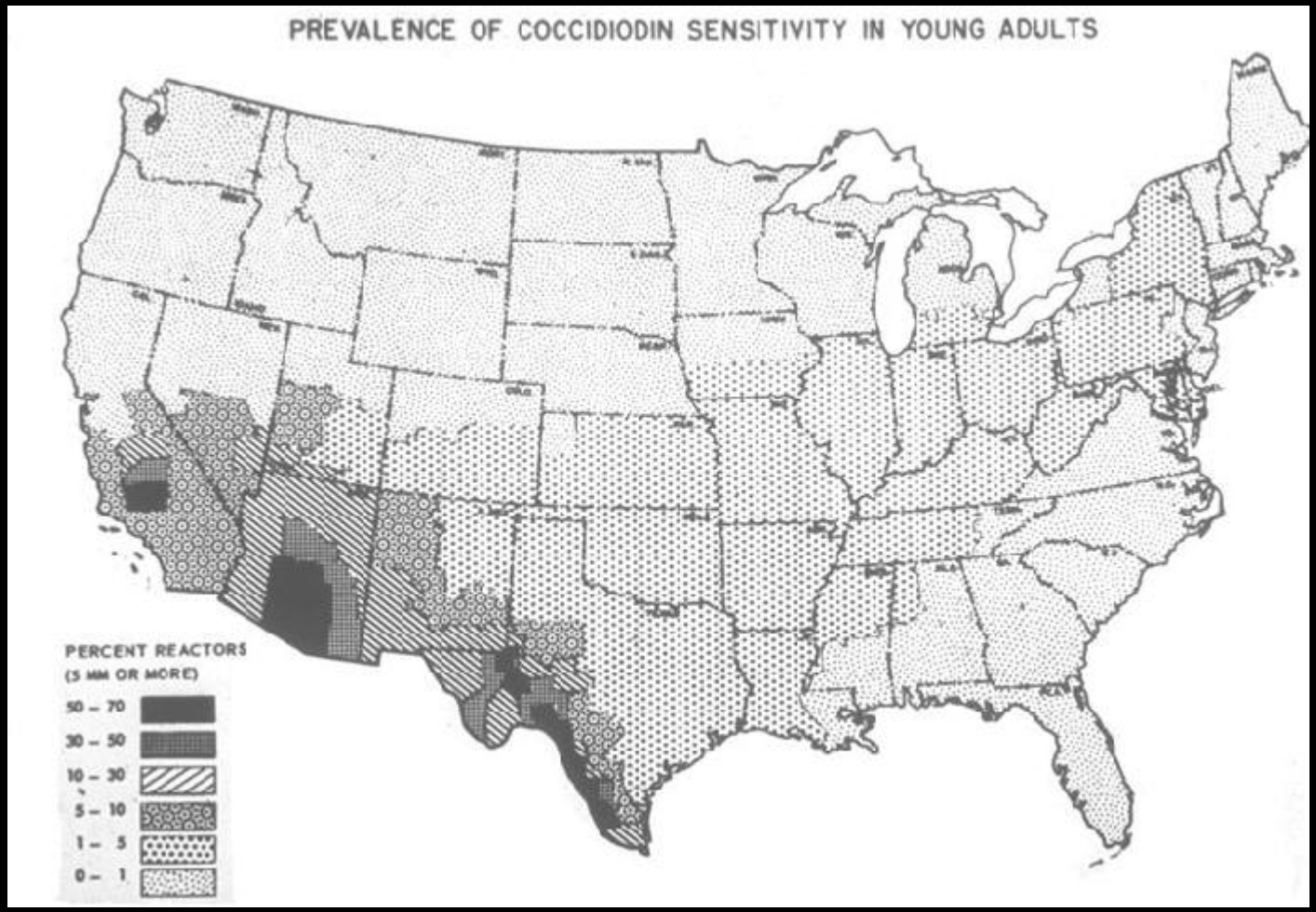
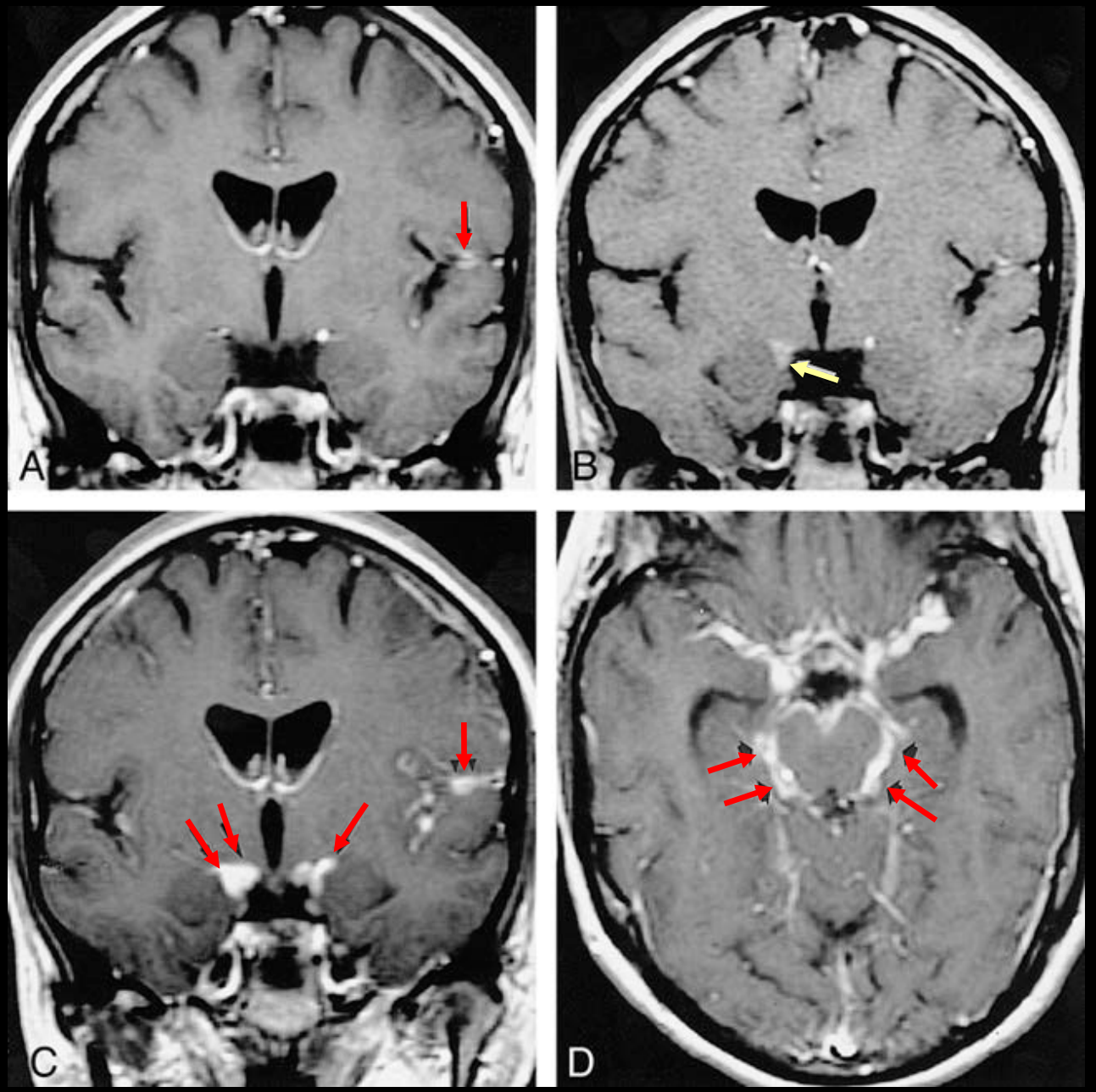
Lesions in right and left cerebellum ★	Cerebellar mass lesion ★	Cerebellar mass ★	Suprasellar mass
Diffuse leptomeningeal enhancement; ventricular dilation; infarct along superior cerebellum ★	Left temporal lobe mass	Left cerebellar lesion ★	Left occipital lobe mass
Mass in right retina	Ventricular enlargement	Right basal ganglia lesion; diffuse meningeal enhancement	Right frontal lobe mass; diffuse leptomeningeal enhancement
		Thoracic epidural abscess	Infarcts in brainstem and basal ganglia and cerebellum ★

Barriola, et al. CID 2010; 50:797–804 DOI: 10.1086/650579

Distribution of Coccidioidomycosis in US





Coccidioidomycosis Meninginitis

AJNeuroRad 1999

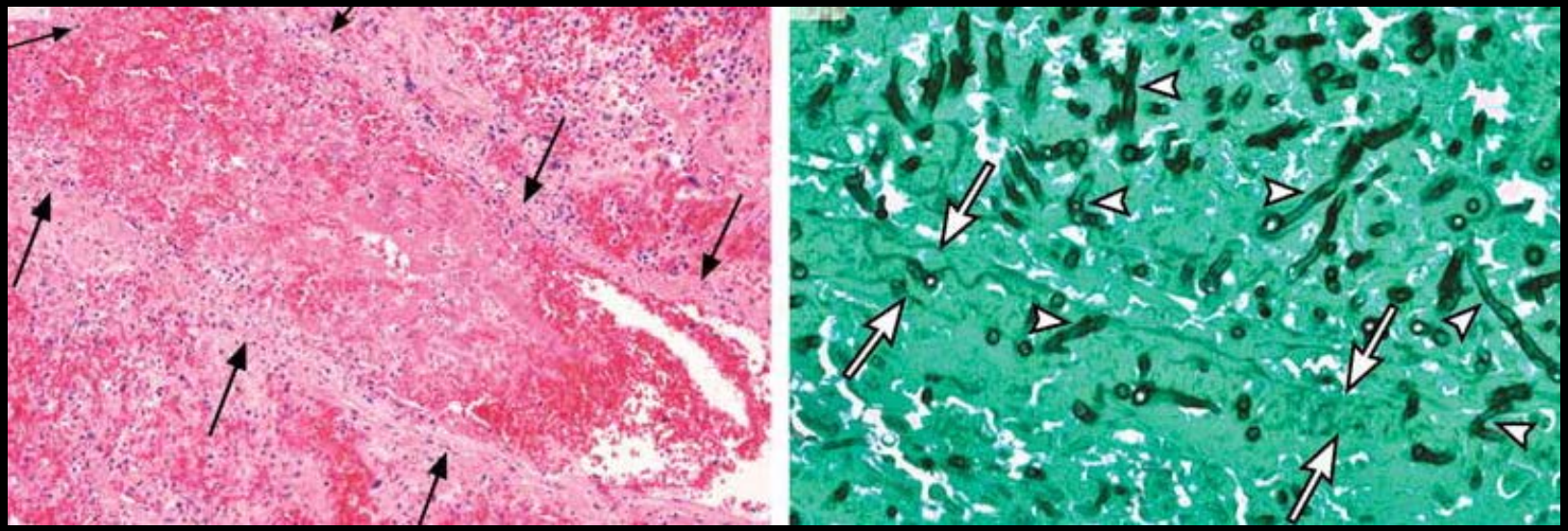
Aspergillus

Host Factors in Radiologic and Pathologic Features of Invasive Aspergillosis

vascular invasive aspergillosis

Low-Power: vascular thrombosis, surrounded by coagulative necrosis and hemorrhage (H&E stain)

High-Power: hyphae transversing the blood vessel wall and intravascular invasion (siver stain, with hyphal walls staining dark).

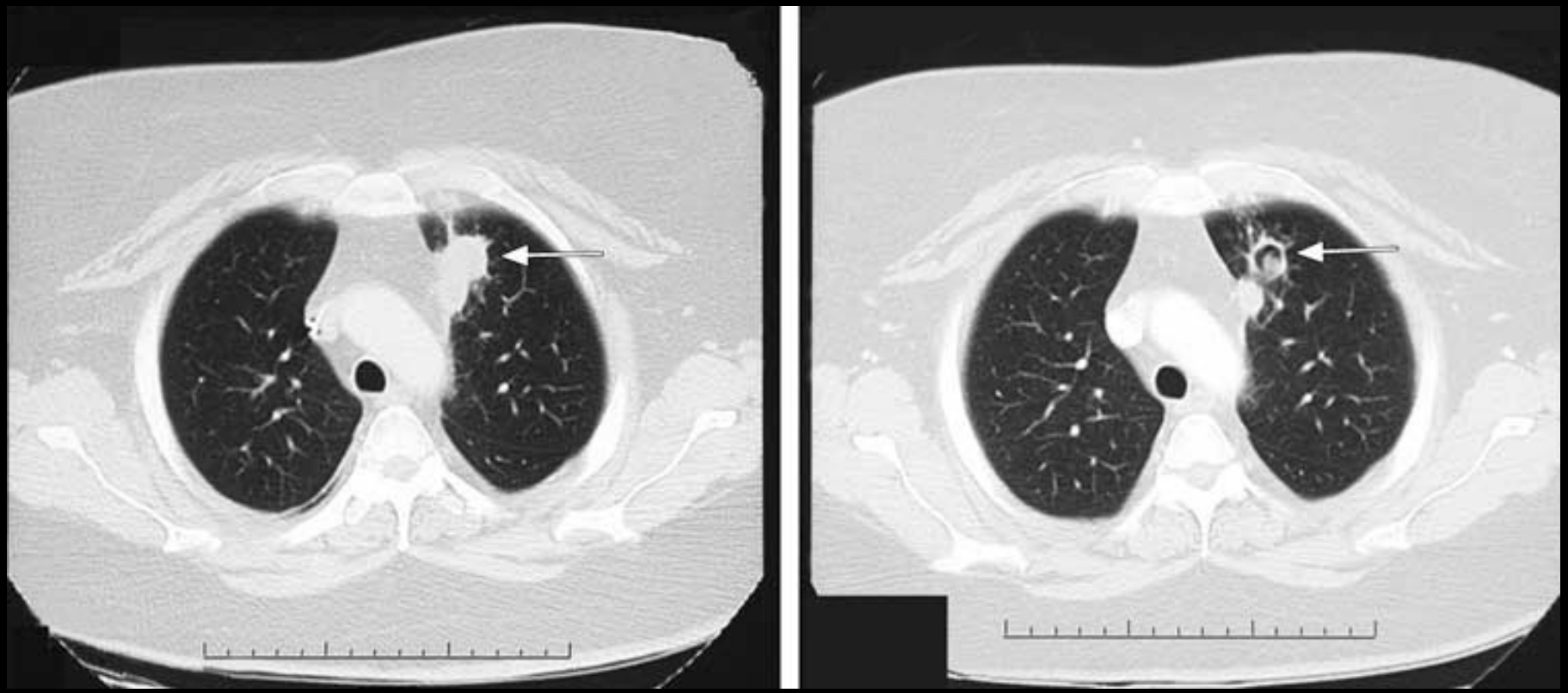


Segal B. N Engl J Med 2009;360:1870-1884

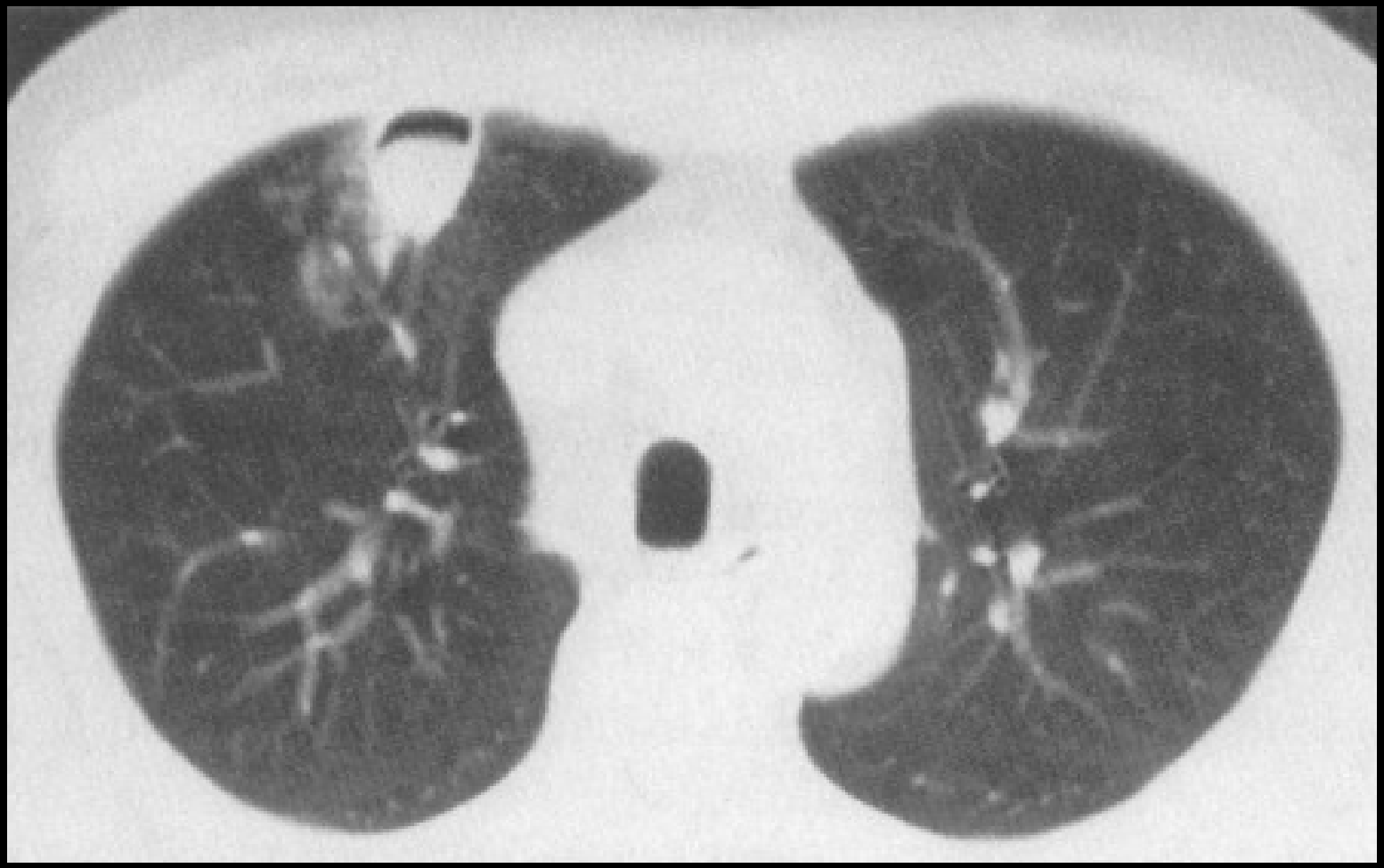
Host Factors in Radiologic and Pathologic Features of Invasive Aspergillosis

While Neutropenic

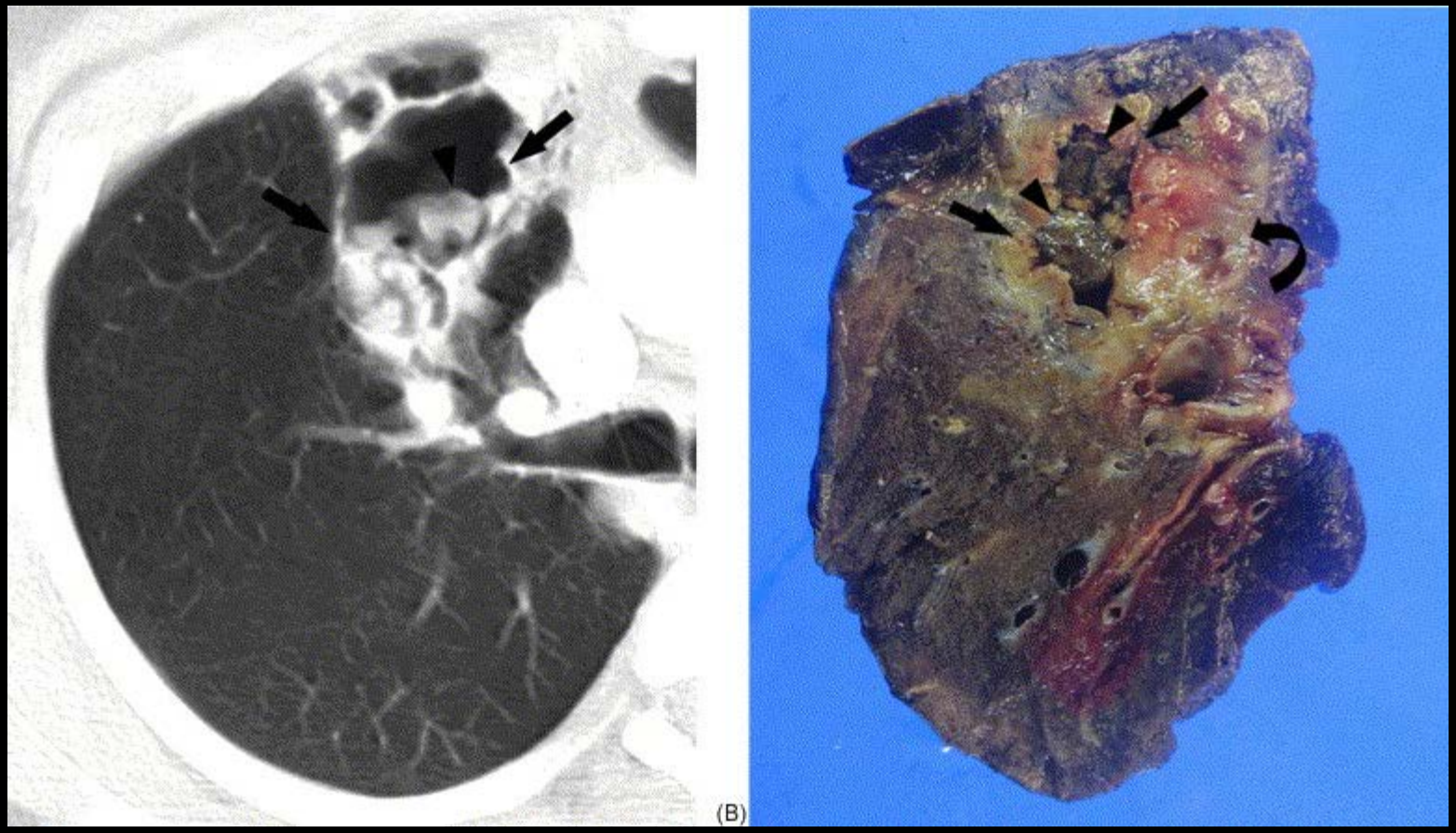
Neutropenia Resolved



Segal B. N Engl J Med 2009;360:1870-1884

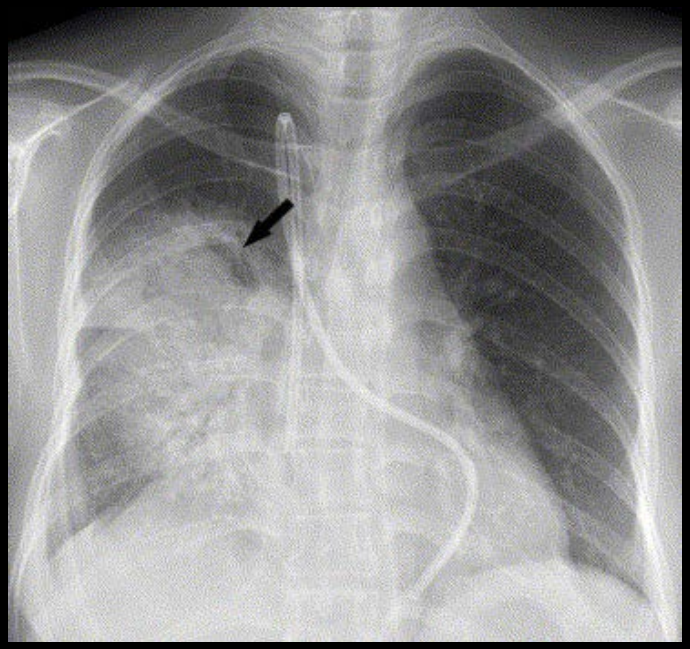


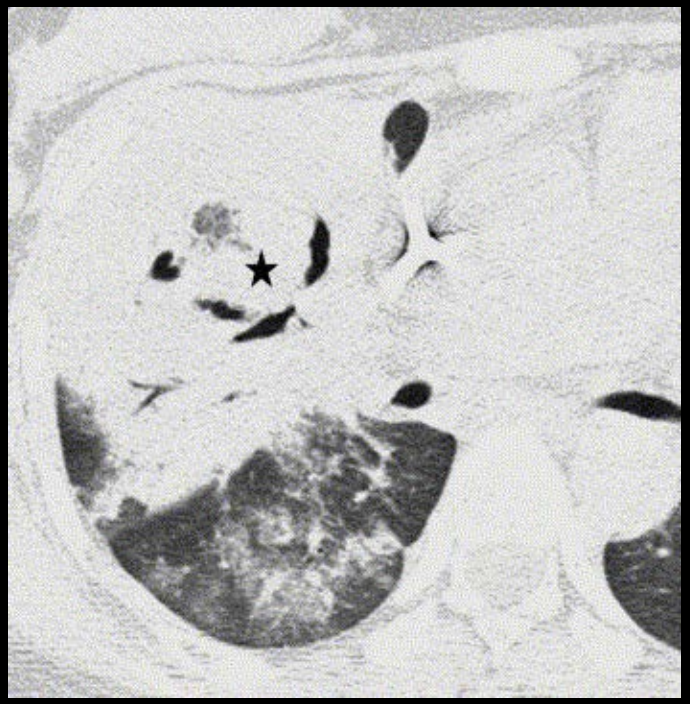
IA crescent sign

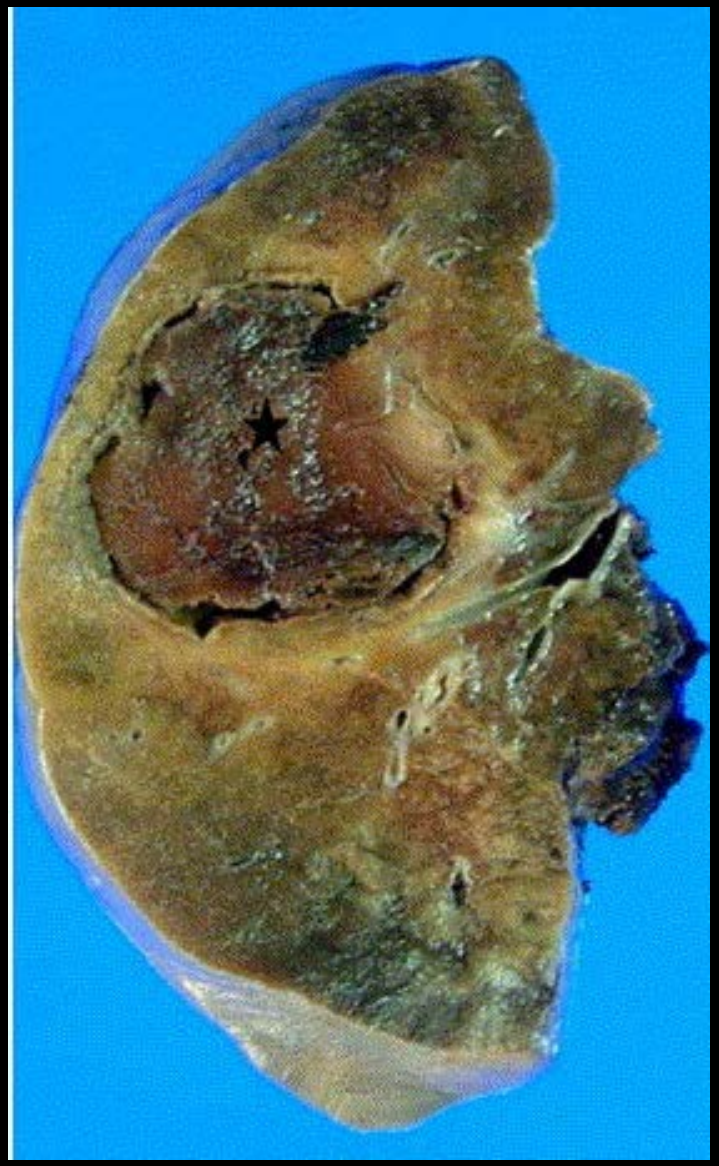


Invasive Aspergillosis Eur. J. Rad. 2006

Invasive Aspergillosis

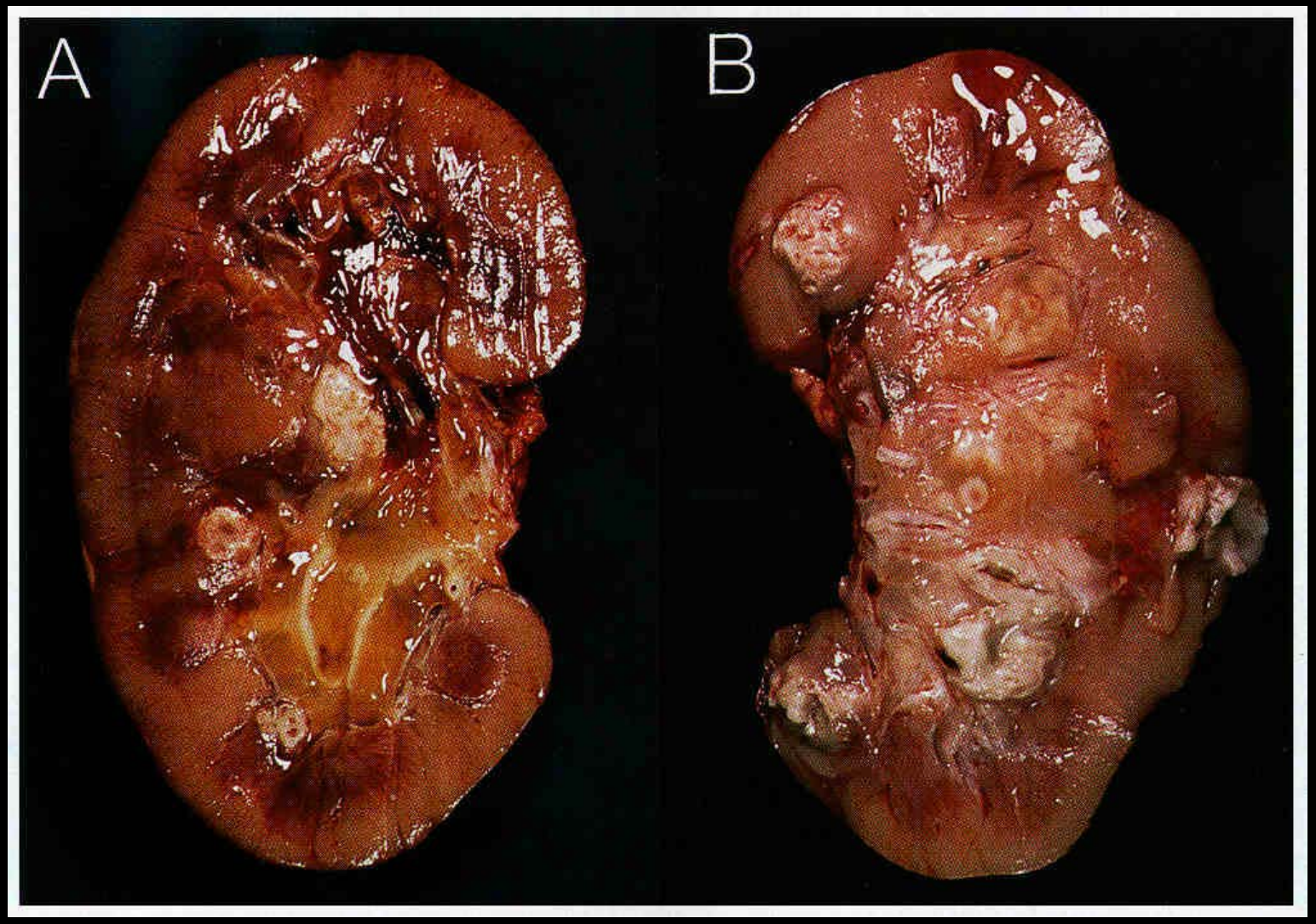




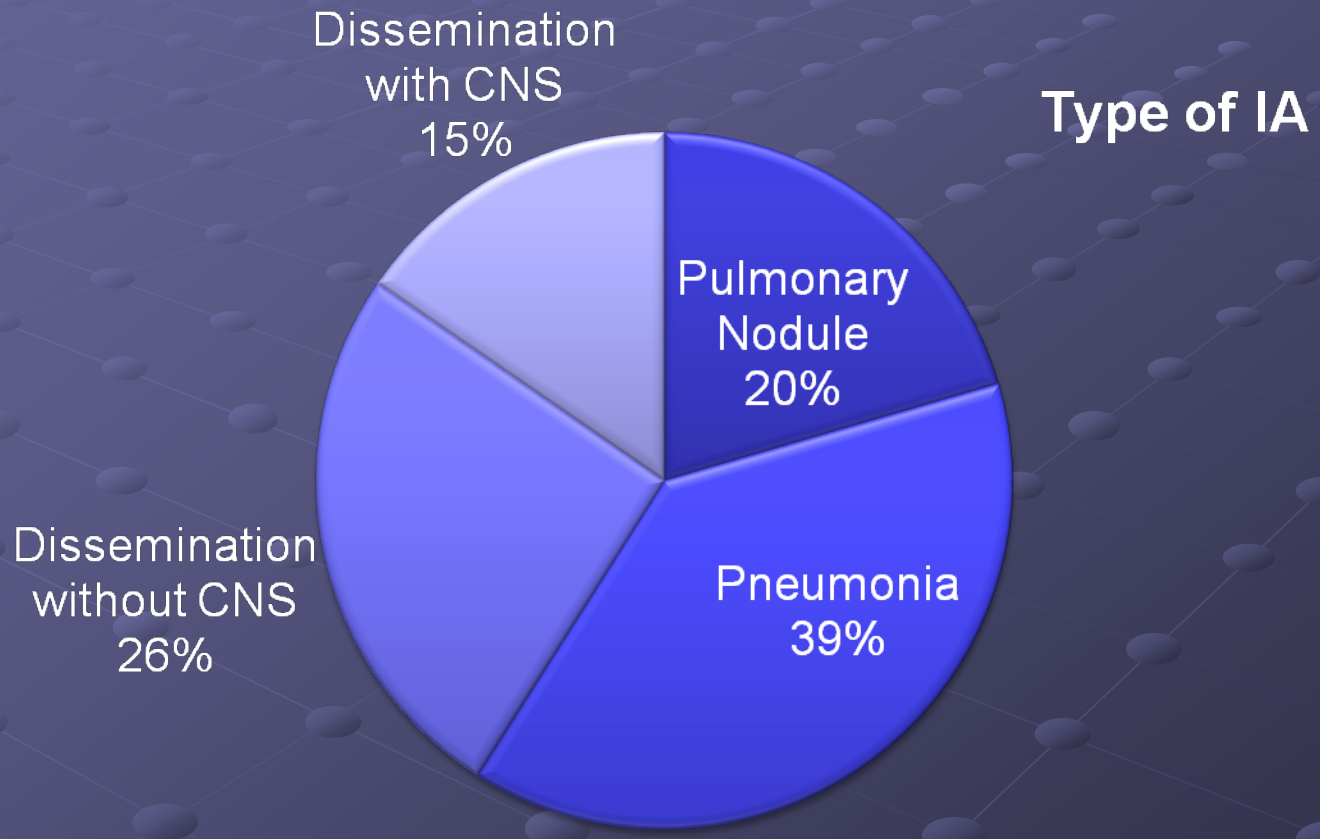


Eur J Rad. 2006

Renal Aspergillosis



Invasive Aspergillosis after Solid Organ Transplantation



Galvada et al, **Clinical Infectious Diseases 2005; 41:52–9**

Risk Factors for *Early* Invasive Aspergillosis after (< 3 mo) Solid Organ Transplantation

Variable	Multivariate analysis	
	OR (95% CI)	*P*
Additional ICU stay	2.9 (1.2–7)	.021
Posttransplantation renal failure	4.9 (2.4–9.8)	<.0001
Posttransplantation hemodialysis	3.2 (1.3–8.1)	.014
>1 Episode of bacterial infection	3.2 (1.4–7.4)	.006
OKT3 use	1.7 (0.9–3.2)	.071
CMV disease	2.3 (1.1–4.9)	.029

Galvada et al, **Clinical Infectious Diseases 2005; 41:52–9**

Risk Factors for *Late* Invasive Aspergillosis after (>3 mo) SOT

Variables	Multivariate analysis	
	OR (95% CI)	*P*
SOT at age >50 years	2.5 (1.3–5.1)	.009
Additional intervention	…	…
Additional ICU stay	…	…
Renal failure after SOT	3.9 (1.9–7.8)	<.0001
Hemodialysis after SOT	…	…
>6 g Cumulative dose of steroids at month 3	…	…
>2 Boluses of steroids	…	…
Blood levels of Tac >15 ng/mL or CyA >500 ng/mL at month 3	2.5 (1.2–5)	.011
Use of Tac and CyA for the same patient	3.2 (1.1–9.4)	.032
>1 Episode of bacterial infection	7.5 (3.2–17.4)	<.0001
>1 Episode of CMV disease	…	…
Significant leukopenia (<3000 leukocytes/mm^3)	1.9 (0.9–3.7)	.056
Immunosuppression-related neoplasm	69.3 (6.4–753)	<.0001
Chronic graft rejection	5 (1.9–13)	.001

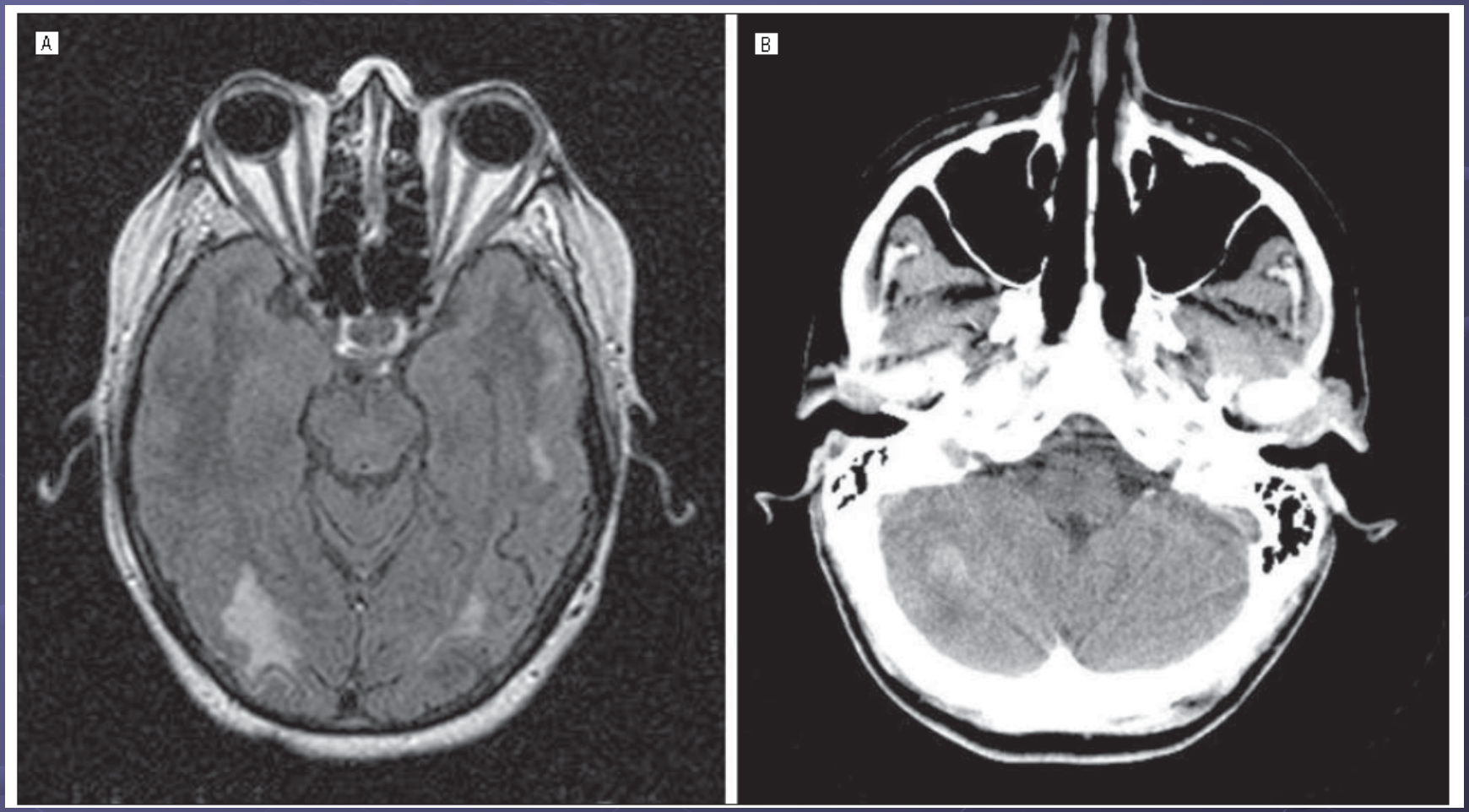
Risk Factors for Invasive Aspergillosis after SOT
Distribution of Cases

Type of transplant	No. of patients	No. (%) of patients with IA episode, by clinical form of IA			
		Pulmonary nodular	Pulmonary pneumonia	Disseminated with no CNS involvement	Disseminated with CNS involvement
Liver	80	8 (10)	31 (38.7)	28 (35)	13 (16.2)
Heart	47	16 (34)	14 (29.7)	9 (19.1)	8 (17)
Lung	17	5 (29.4)	7 (41.1)	3 (17.6)	2 (11.7)
Kidney	10	3 (30)	6 (60)	0	1 (10)
Pancreas-kidney	2	0	2 (100)	0	0
Total	156	32 (20.5)	60 (38.5)	40 (25.6)	24 (15.4)

Galvada et al, **Clinical Infectious Diseases 2005; 41:52–9**

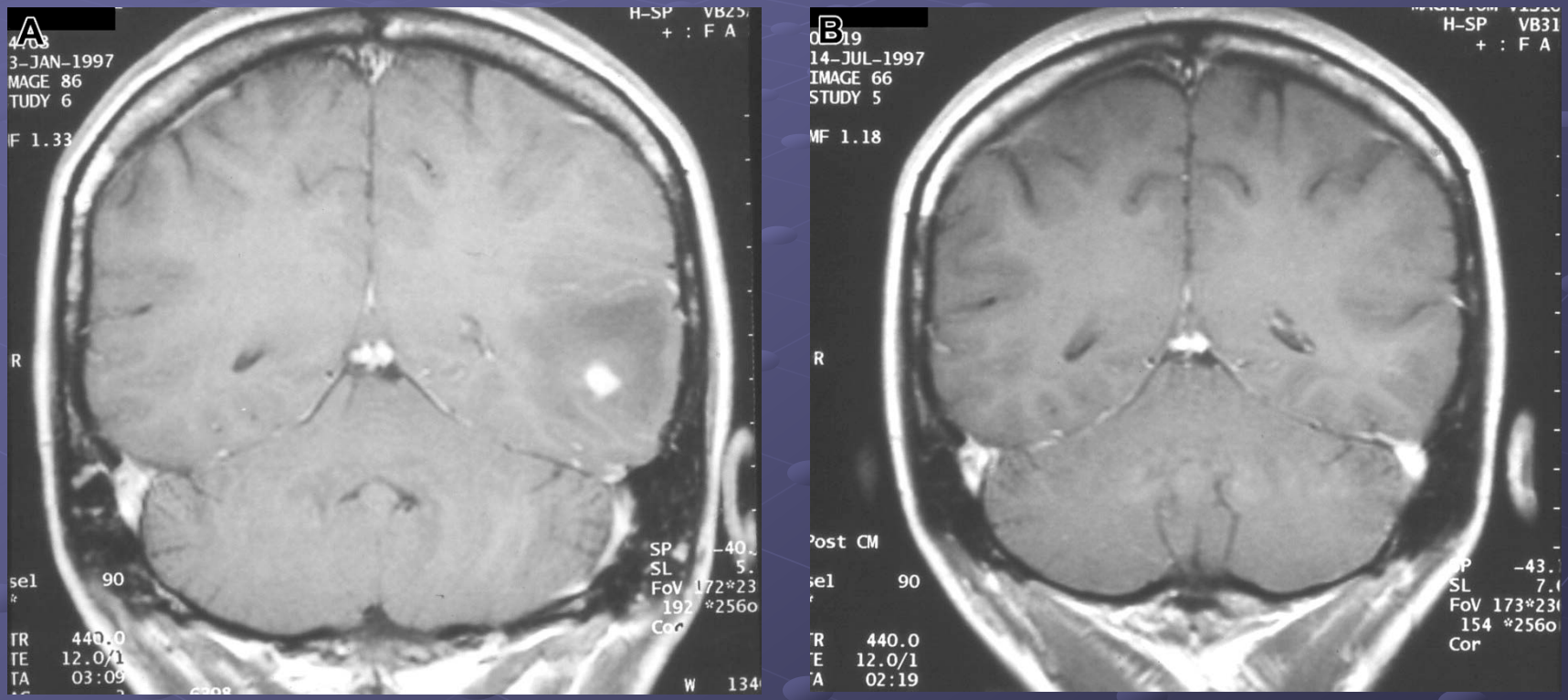
CNS Aspergillosis in Heart Tx Patient

(Diagnosis made at autopsy)



van de Beek et al, ARCH NEUROL/VOL 64 (NO. 12), DEC 2007

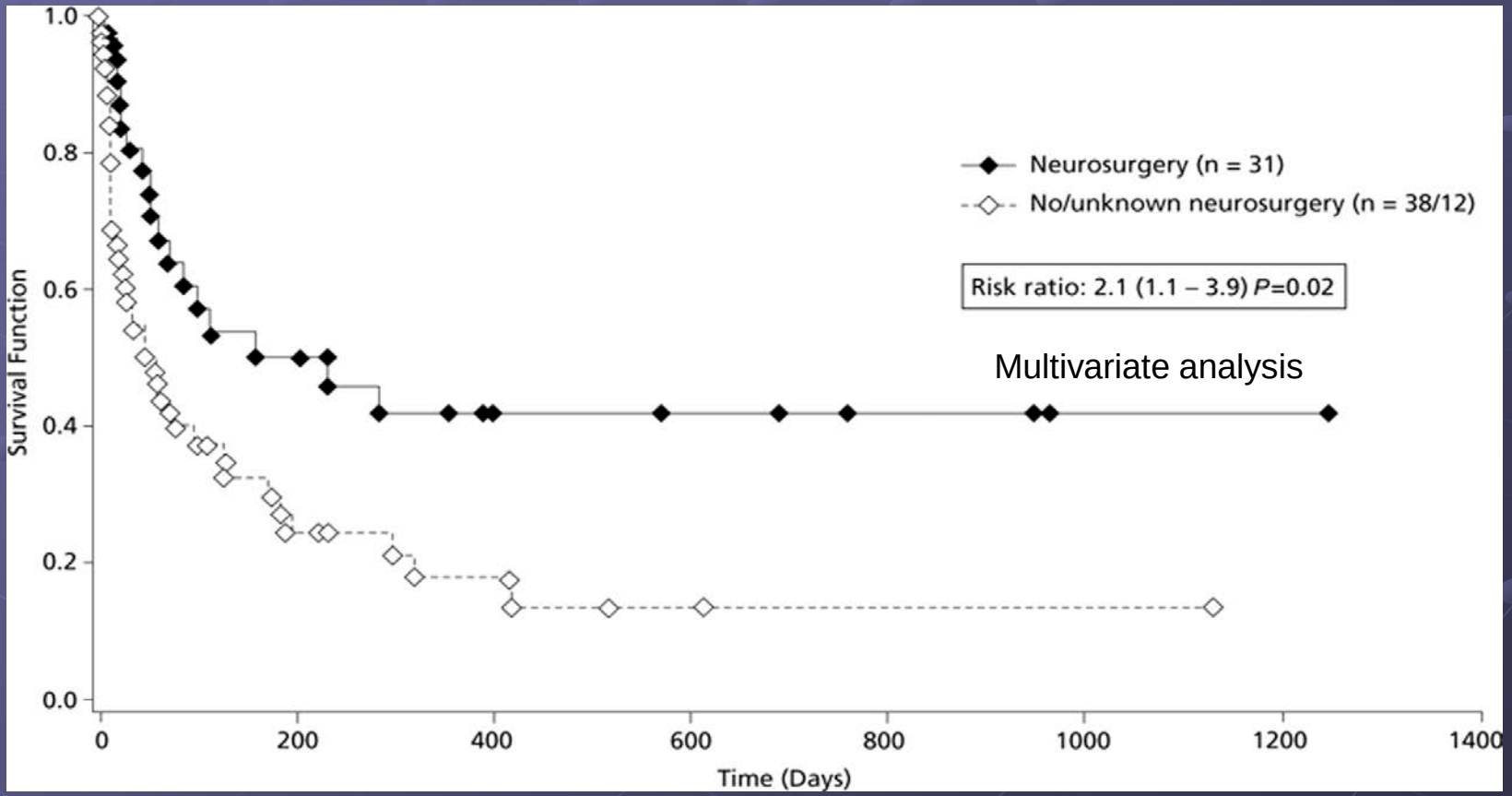
CNS Aspergillosis: Response to Voriconazole



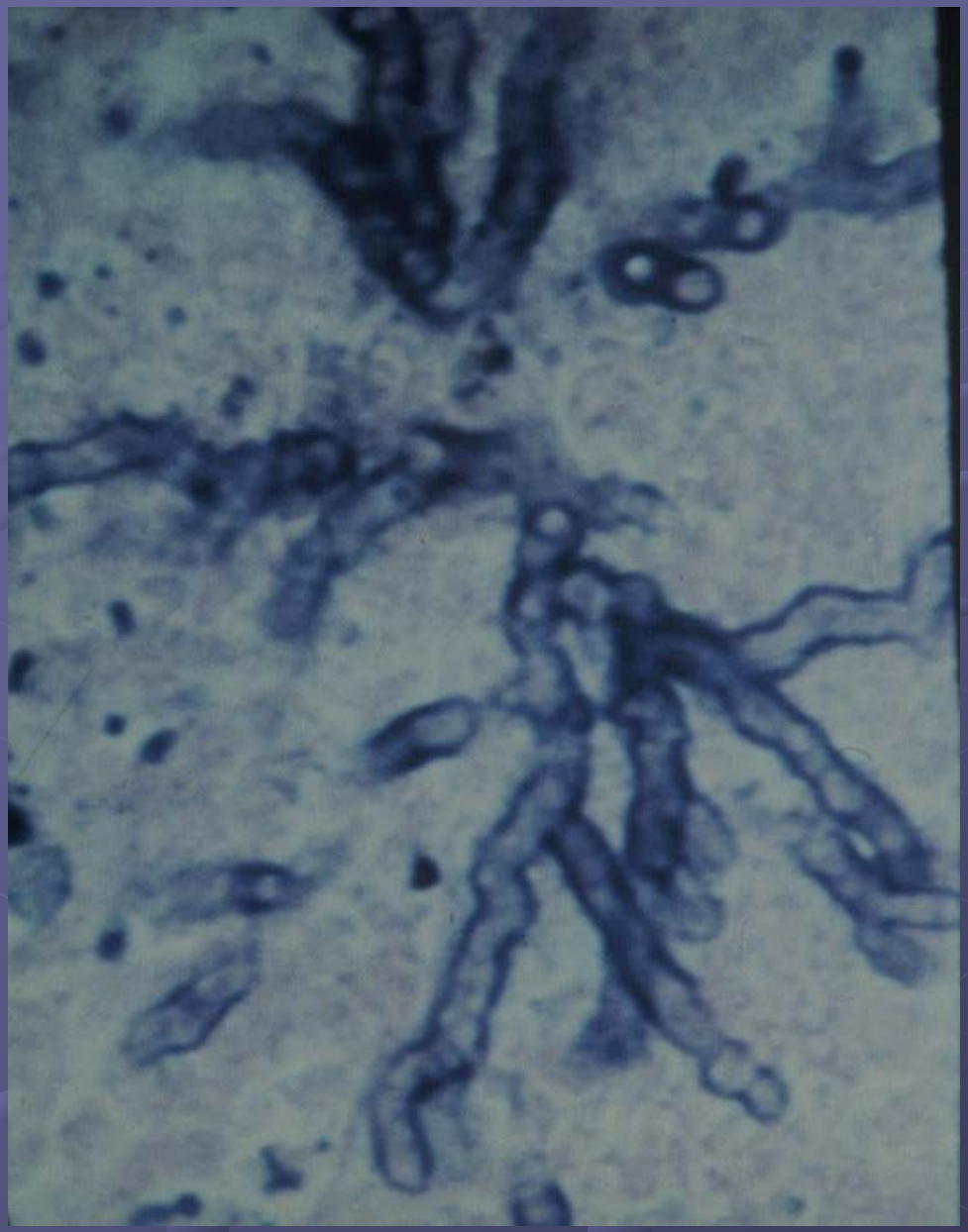
Schwartz et al, Blood, 15 October 2005, Vol. 106, No. 8, pp. 2641-2645.
DOI 10.1182/blood-2005-02-0733

CNS Aspergillosis – Survival with NS and w/o NS

at any time after initial diagnosis of CNS IA

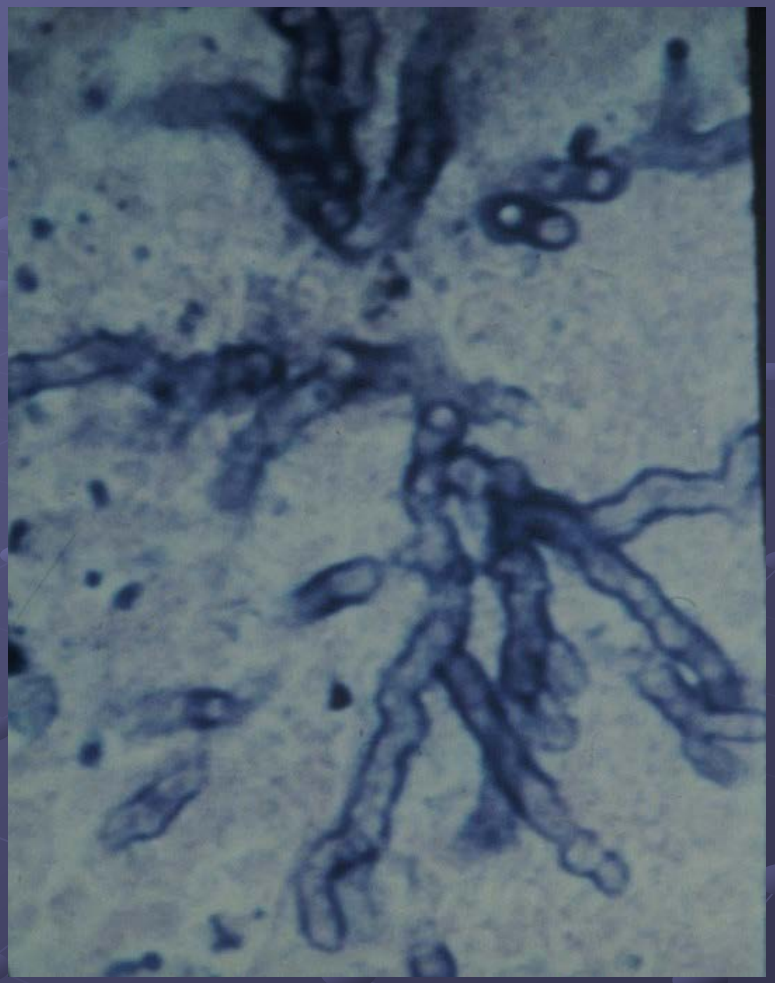


Schwartz S et al, Bood 2005; 106:2641-5



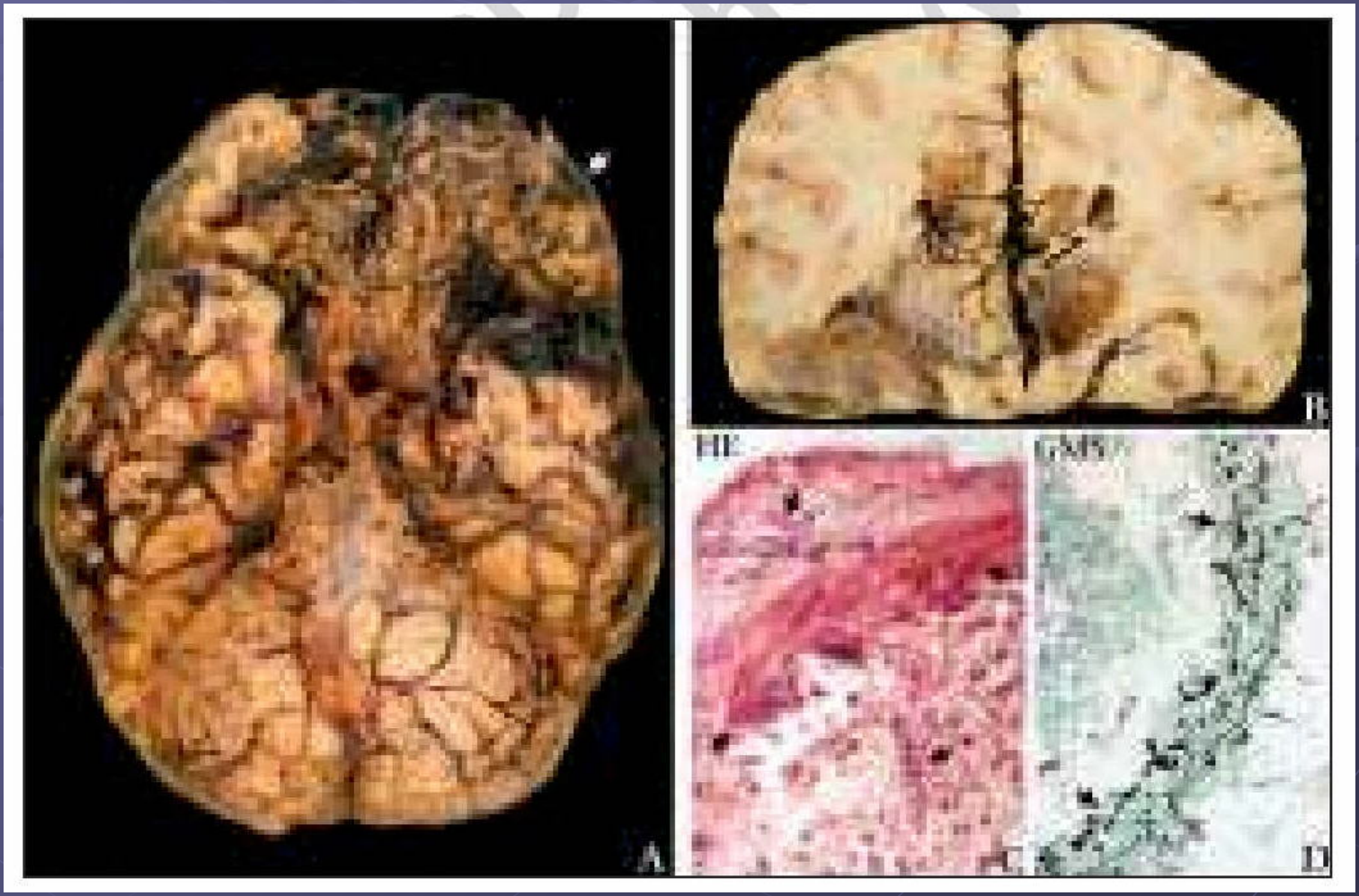
Zygomycosis

Aspergillus



Mucor

Zygomycosis



Shankar et al, Neurology India . July-September 2007 | Vol 55 | Issue 3

Emerging therapeutic options in fulminant invasive rhinocerebral mucormycosis

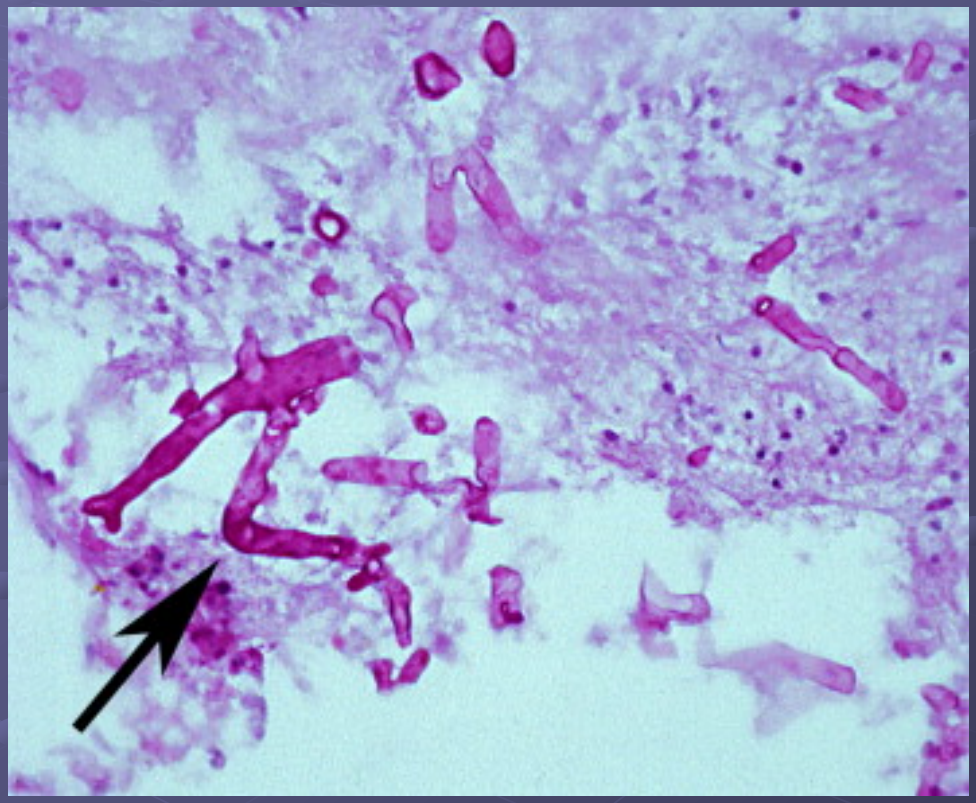
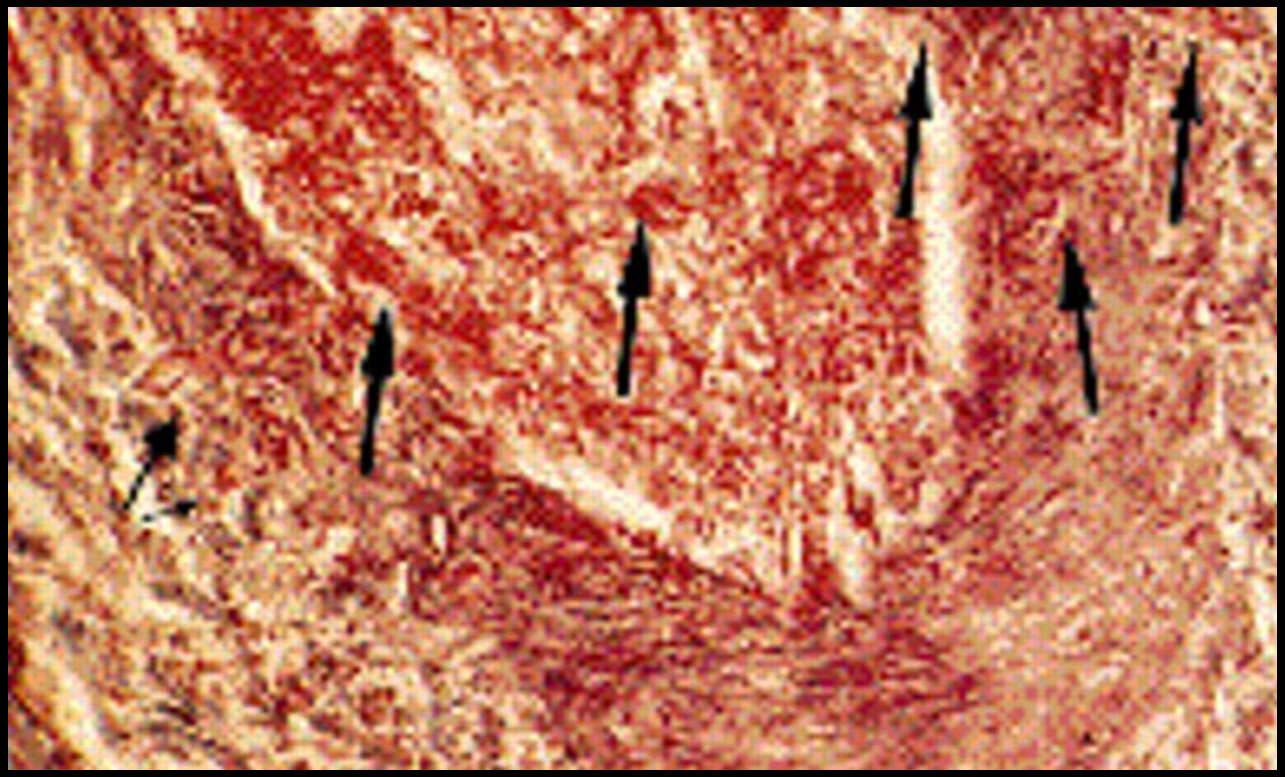


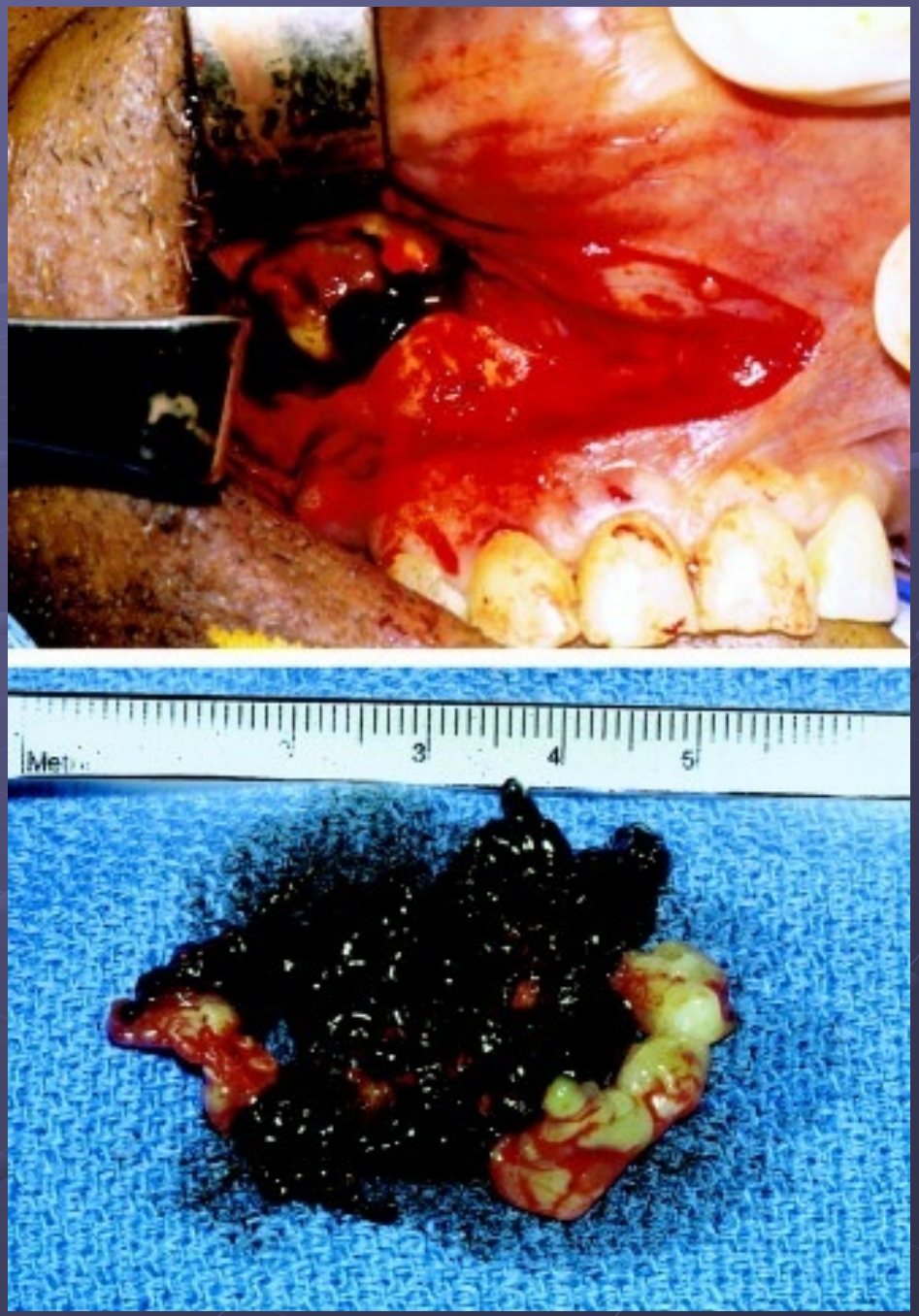
Fig. 4. Histological characteristics of mucormycosis as shown in biopsy specimen of case 1. Hyphae are broad, often distorted and frequently appear twisted. Branching is right-angled (arrow) and septae are absent (PAS stain).

Auris Nasus Larynx Volume 37, Issue 3, June 2010, Pages 322-328

Angioinvasion by Mucor

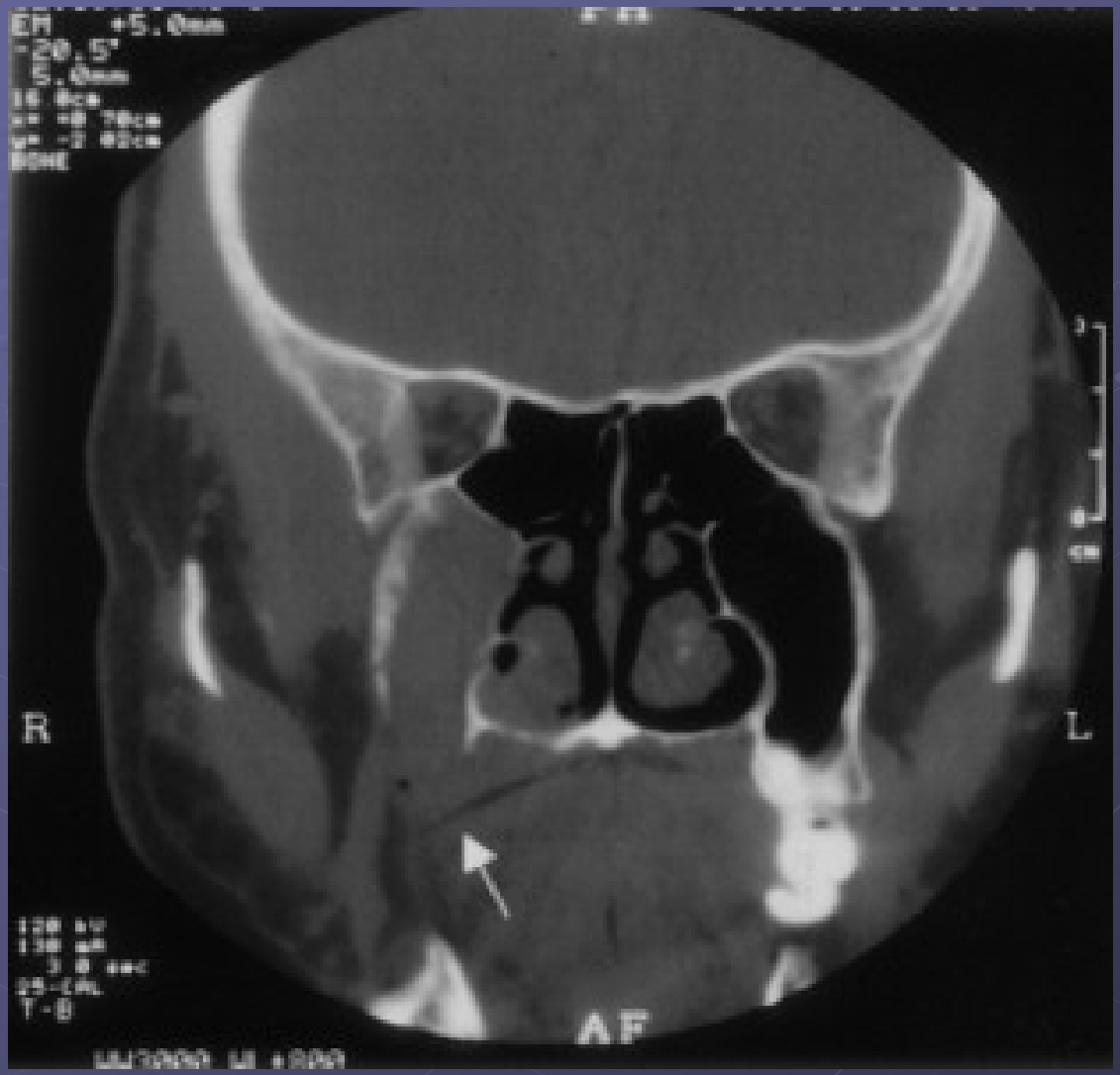


Black Necrotic Infiltrating Lesion, and Resection



Garcia-Diaz JB. CID; 2001;32:e166-e170

CT: Erosion of Floor of Maxillary Sinus



Garcia-Diaz JB. Clinical Infectious Diseases 2001;32:e166-e170

Emerging therapeutic options in fulminant invasive rhinocerebral mucormycosis

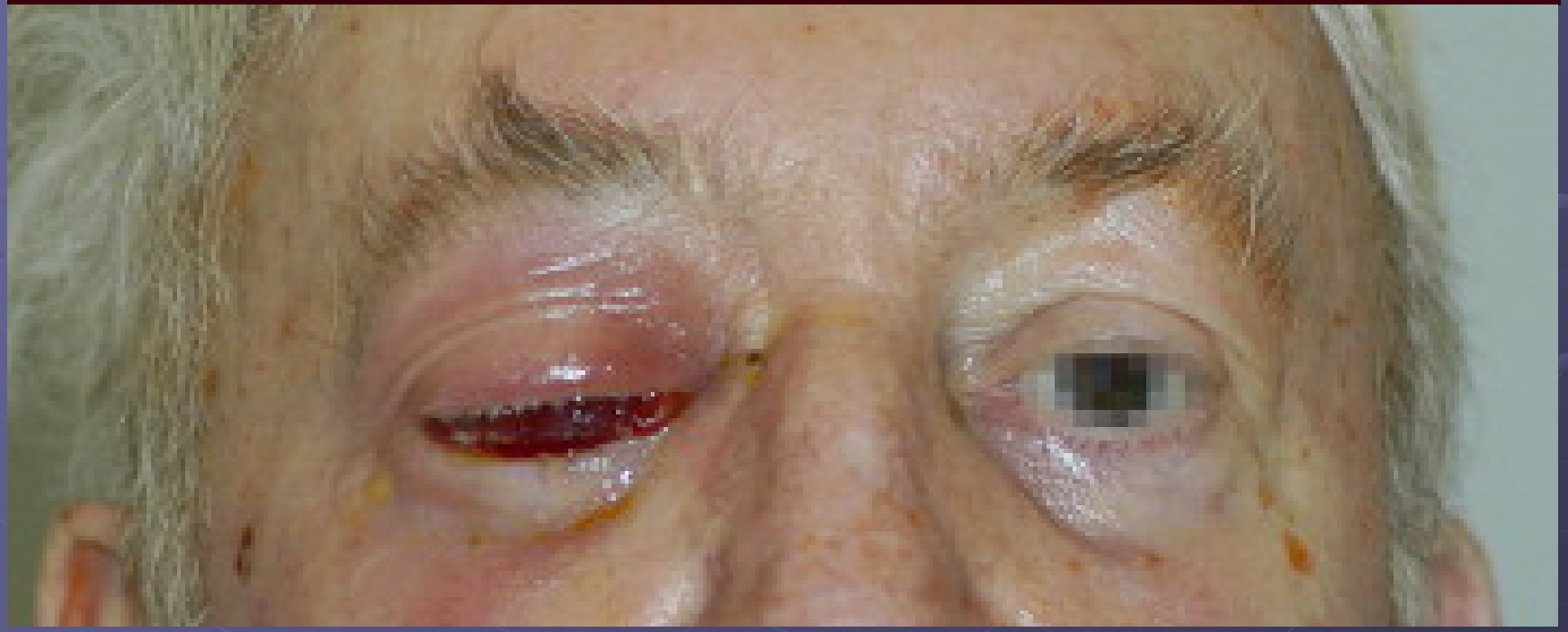
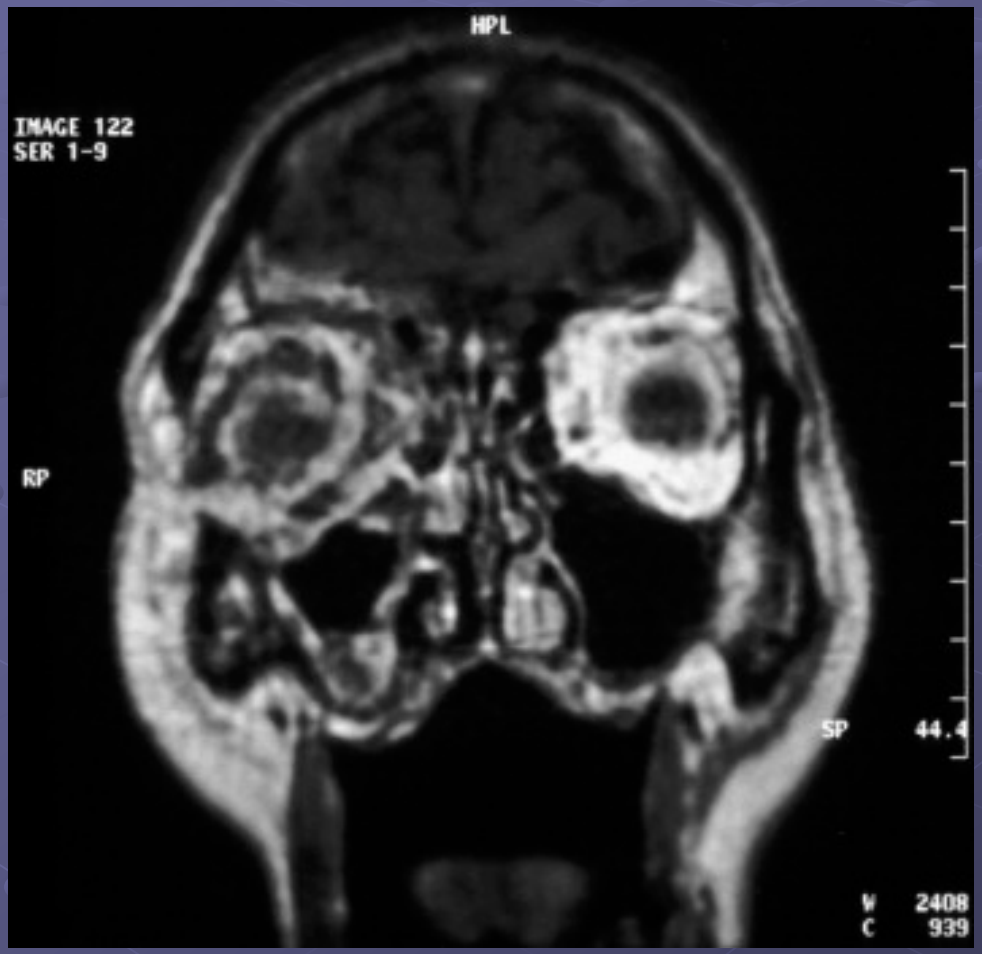


Fig. 3. Clinical picture of case 2 as an example for orbital involvement. Swelling and inflammation of the right eye-lid and conjunctiva.

In the 5 cases reported in this series, posaconazole appears to be a more effective alternative to amphotericin

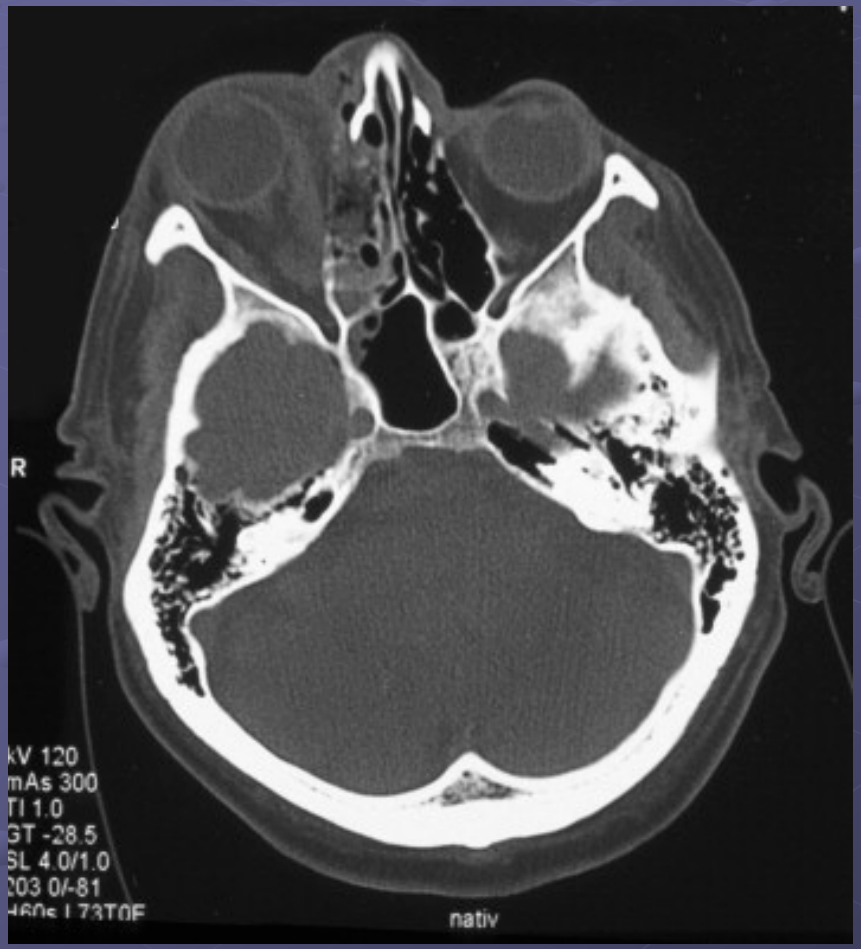
Emerging therapeutic options in fulminant invasive rhinocerebral mucormycosis



Coronal MRI-scan (T2) of after one week as an example for meningeal involvement in developing disease.

Enhancement of the meninges on the right side as a sign of intracerebral invasion of the fungal infection. and decalcification of the lamina orbitalis on the right side.

Emerging therapeutic options in fulminant invasive rhinocerebral mucormycosis



Axial CT scan at onset of the disease as a typical CT finding of this stage of the disease.

Opacification of the ethmoid sinus, thickening of the orbital muscles, and decalcification of the lamina orbitalis on the right side.

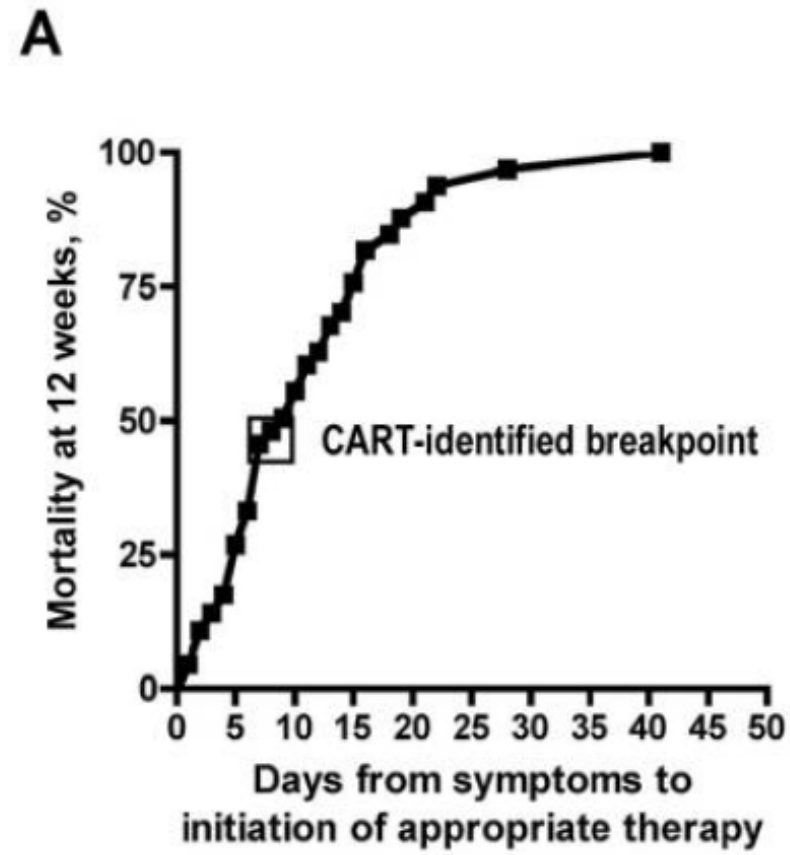
Sheckenback et al, Auris Nasus Larynx 37 (2010) 322–328

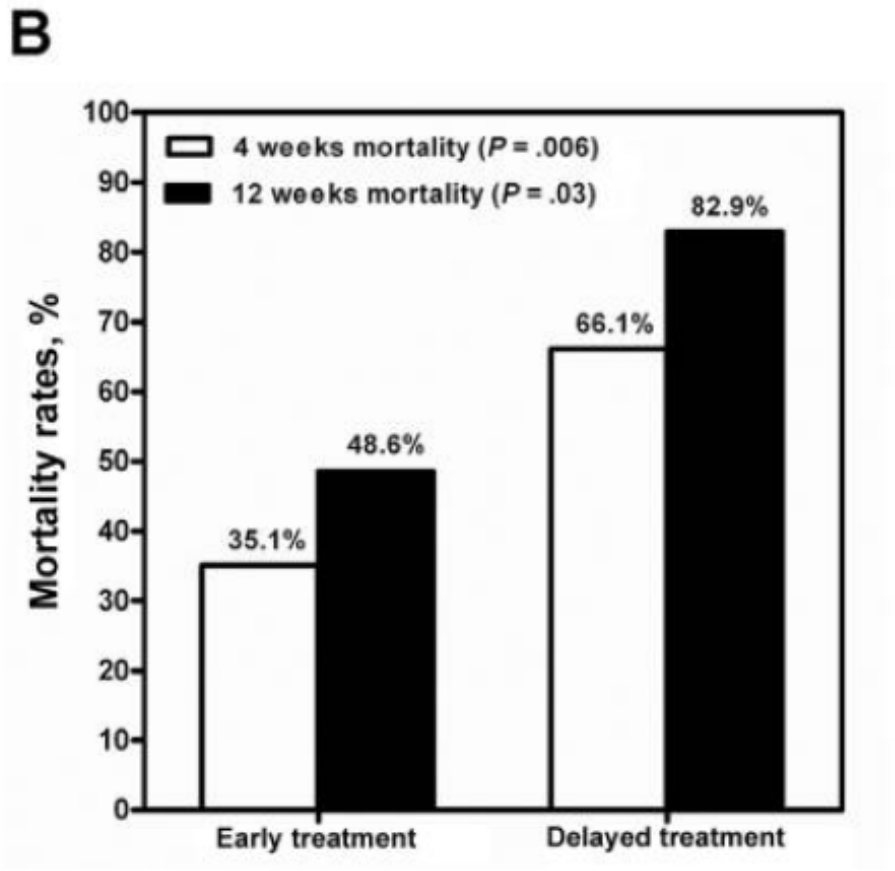
Zygomycosis in SOTx: 50 cases

Treatment	Surgical resection	Success rate
AmB deoxycholate (n = 5)	2/5 (40)	3/5 (60)
AmB lipid complex (n = 8)	4/8 (50)	5/8 (63)
Liposomal AmB (n = 17)	12/17 (71)	16/17 (94)
Posaconazole (n = 5)	2/5 (40)	3/5 (60)
Combination therapy[a] (n = 6)	4/6 (67)	3/6 (50)

Singh, et al. JID 2009; 200:1002–11 DOI: 10.1086/605445

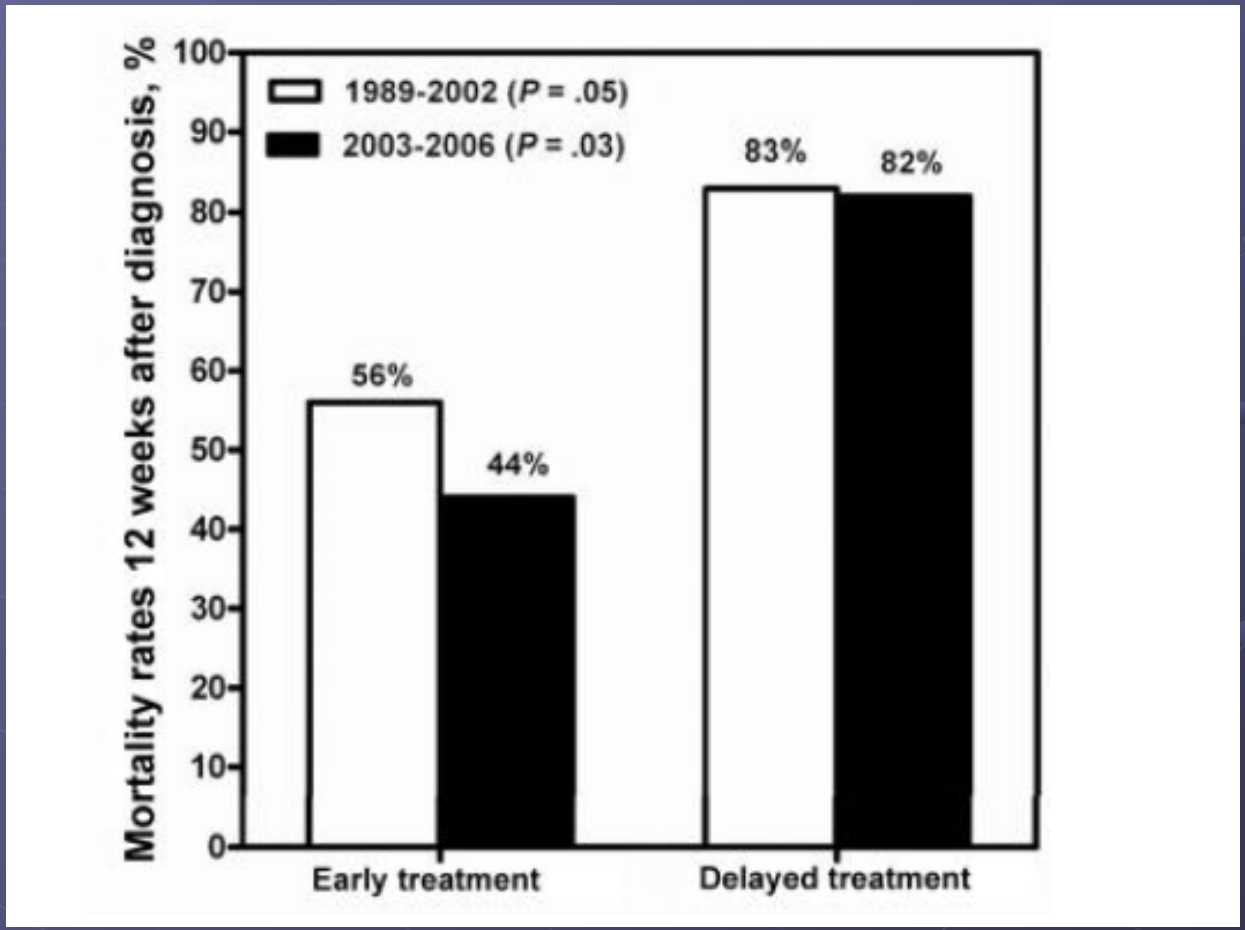
Delay of AmphoB (>1 week from onset of symptoms): Impact on Mortality of Zygomycosis in Heme-Onc





CID 2008:47 (15 August) • Chamilos et al.

Delay of AmphoB (>1 week from onset of symptoms): Impact on Mortality of Zygomycosis in Heme-Onc



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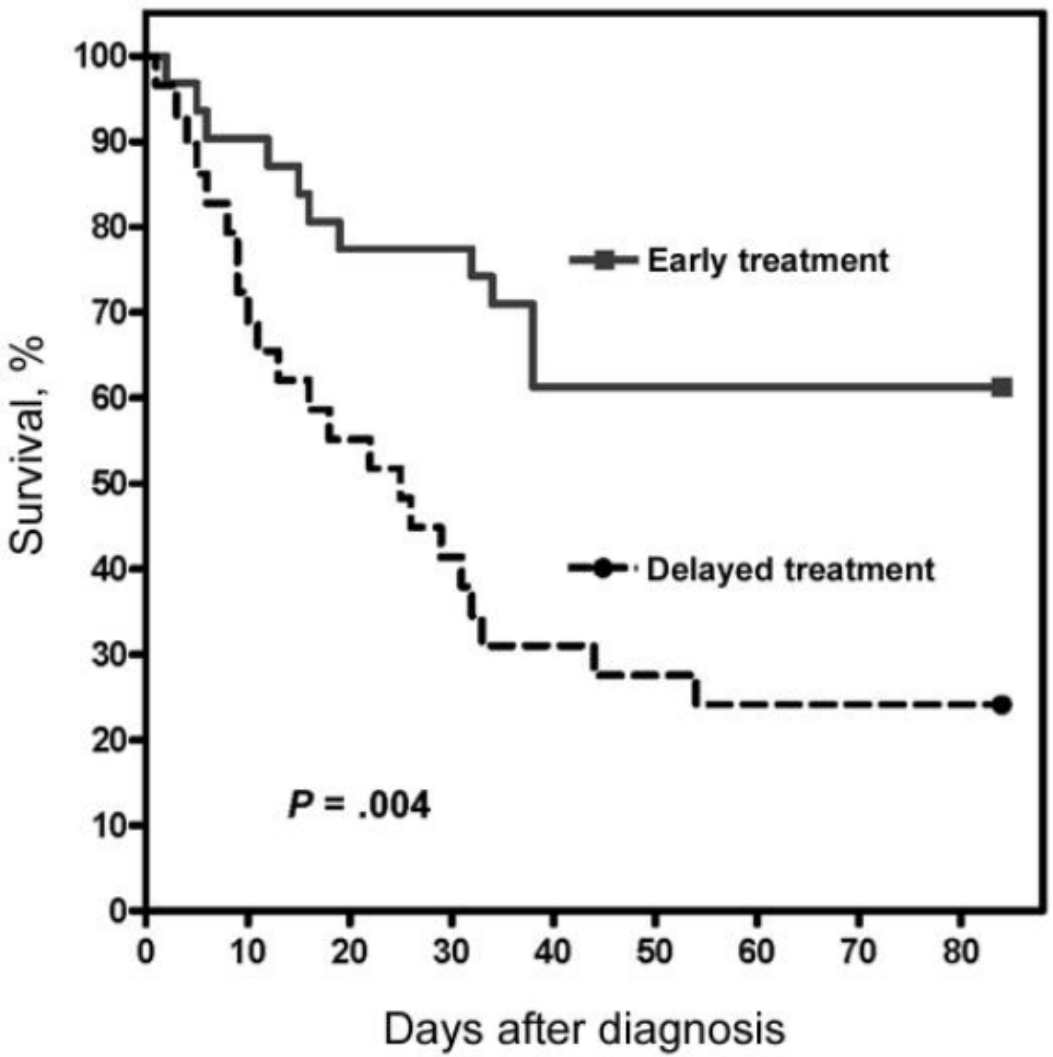


CID 2008:47 (15 August) • Chamilos et al.

Risk factors for Zygomycosis in SOTx: 50 cases (%)

Site of involvement[a]	
Pulmonary	
Any	24 (48)
Only	18 (39)
Rhino-orbital-cerebral	
Any	13 (26)
Rhino-orbital	11
Rhino-orbital-cerebral	2
Cutaneous-soft tissue	
Any	11 (22)
Surgical wound site	4
Ulcerative/necrotic lesions	4
Vascular catheter site	2
Necrotizing fascitis	1
Gastrointestinal (any)	6 (12)
Disseminated disease[b]	13 (26)

Singh, et al. JID 2009; 200:1002–11 DOI: 10.1086/605445

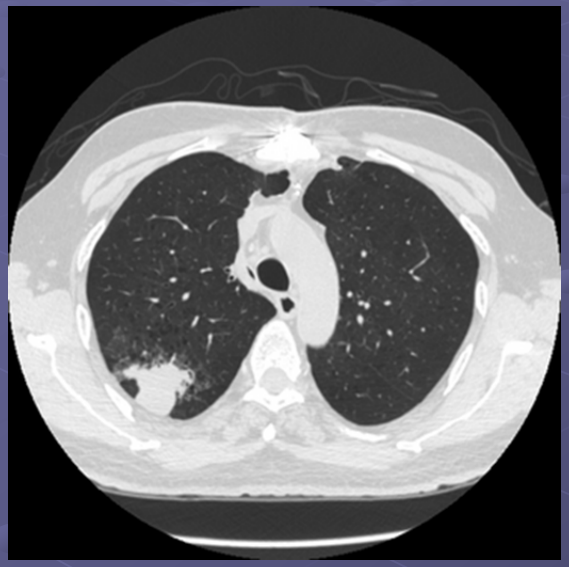
Risk factors for Zygomycosis in SOTx

Variable	Multivariate analysis	
	OR (95% CI)	*P*
Age	…	
Retransplant	5.67 (0.86–37.5)	.072
Diabetes mellitus	8.11 (2.70–24.4)	<.001
Prior rejection	2.62 (0.79–8.71)	.115
Renal failure at baseline	3.17 (1.31–7.65)	.010
Dialysis at baseline	…	
Cytomegalovirus infection	…	
Prior voriconazole or caspofungin use	4.41 (1.12–17.3)	.033
Immunosuppression		
Tacrolimus	0.23 (0.09–0.57)[a]	.002

Singh, et al. JID 2009; 200:1002–11 DOI: 10.1086/605445

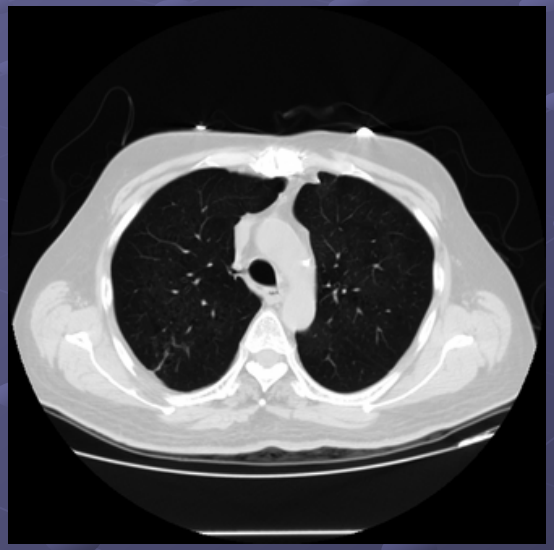
Zygomycosis over-infection during voriconazole therapy for aspergillosis in a heart transplant patient, successfully treated with liposomal amphotericin and posaconazole

3 weeks post HTx w early rejection, steroid Rx.



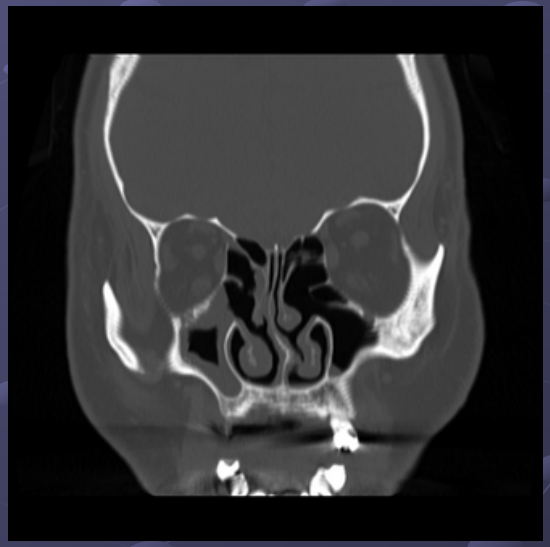
Plasma and BAL galactomannan antigen + for Aspergillus
Culture + Aspergillus fumigatus

After 3 wks Asper. Rx



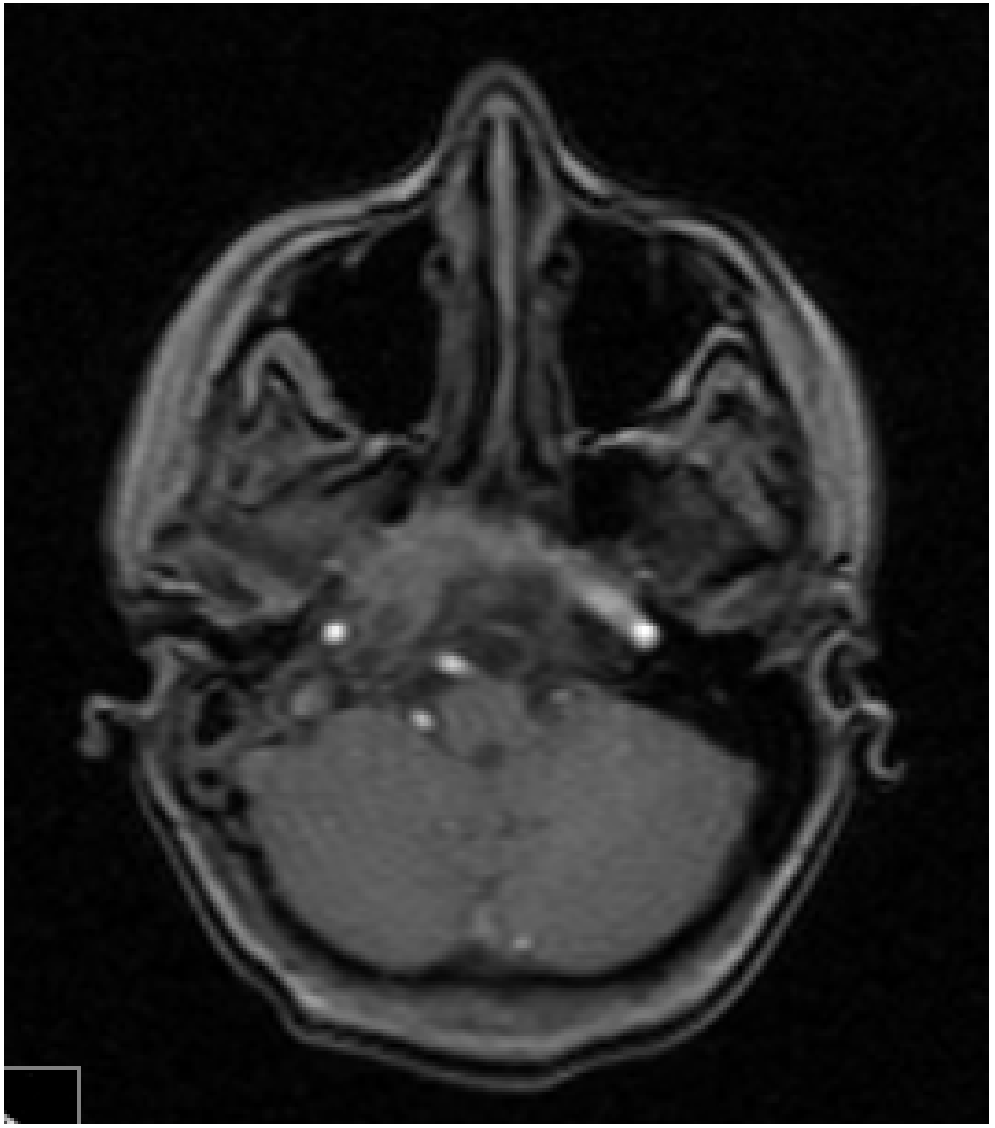
Vori + Caspo x 2w
Vori alone x 1 w

New HA
2 wks later, on Vori



No response to AmBisome 5mg/kg x 2wk + Surg x 2: Response to Ambisome 7.5mg/kg, but RF; then posa x 80d

Bourke et al. Transplant Infectious Disease 2012: 14: E56–E59



MRI of the head, suprahyoid neck, and central skull base without and with intravenous contrast and head MRA without contrast

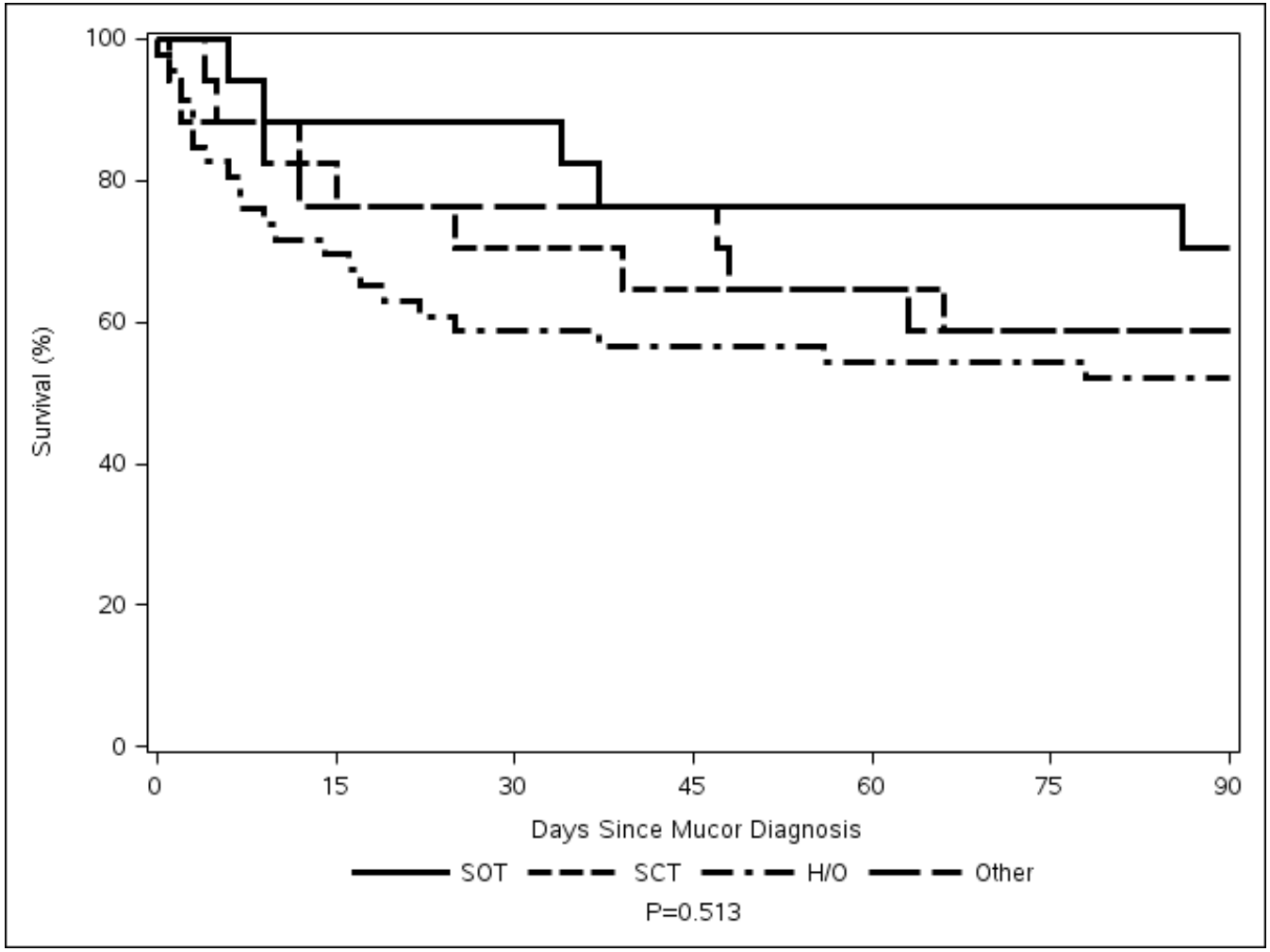
shows continued resolution of central skull base osteomyelitis with interval decrease in the inflammatory changes within the right prevertebral and nasopharyngeal region when compared to the last two examinations 8-17-xx and 7-25-xx.

Persistent mild narrowing of the petrous right ICA is unchanged when compared to the last exam.

Persistent obstructive changes within right mastoid air cells, unchanged. Intracranially, the study is normal. No new abnormalities are detected today.

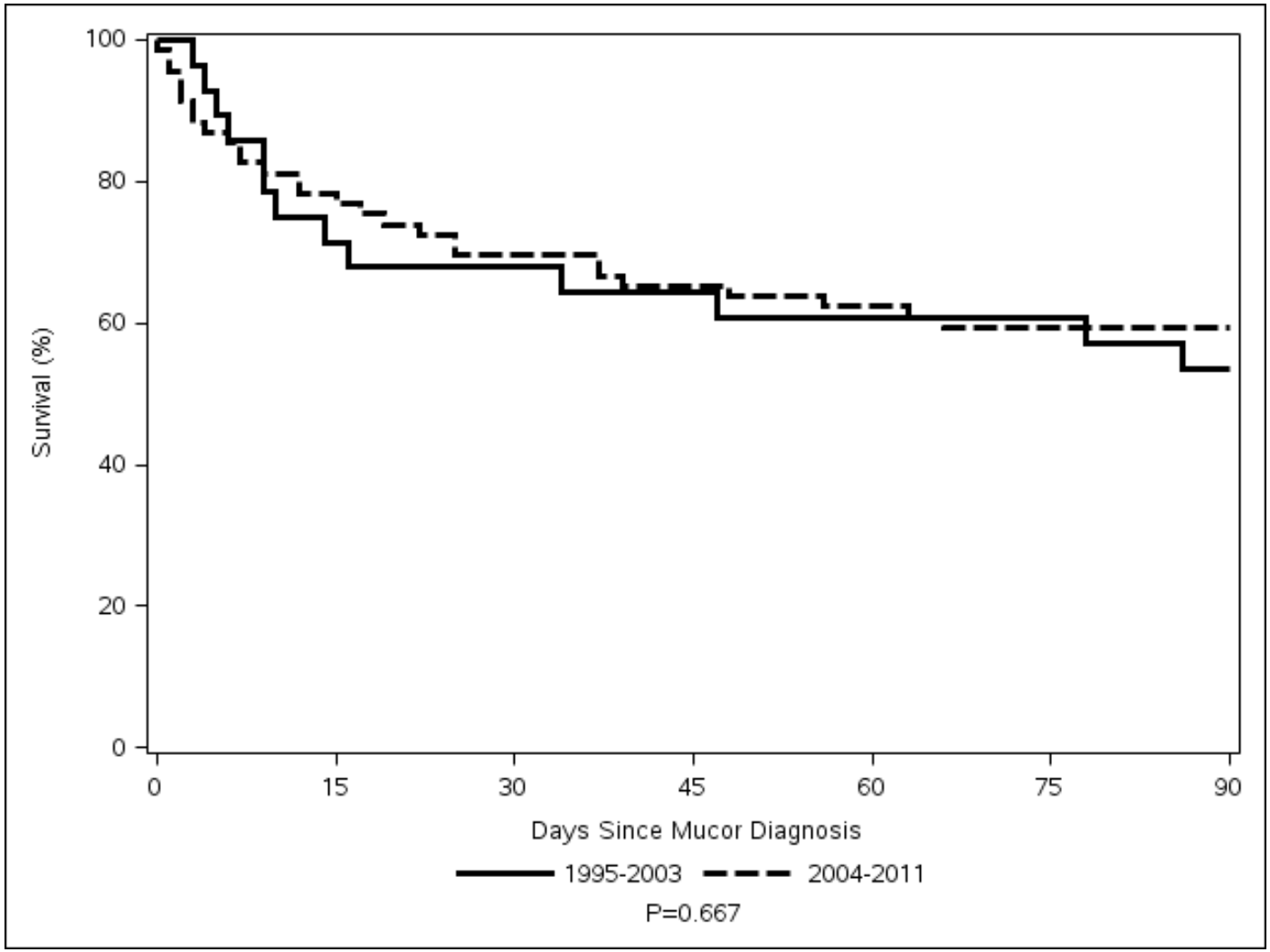
Mixed Aspergillus and Mucor (Blakeslea trispora) Sinus and Skull Base Infection in KPTx – response to posaconazole

Survival after Invasive Mucormycosis across Risk Groups

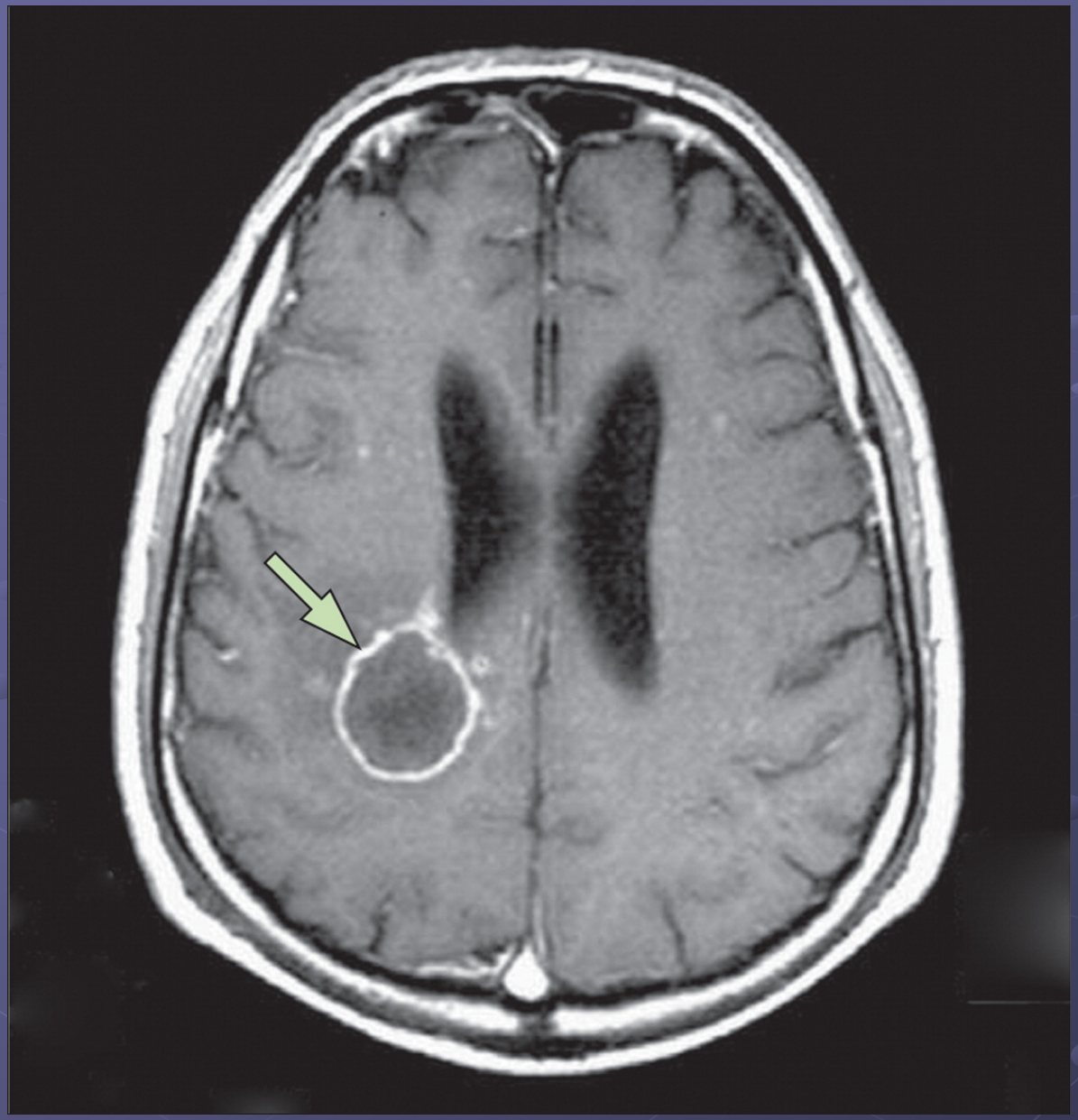


M. Abidi: Mycoses. Nov. 2014.

Invasive Mucormycosis: no improvement in survival in “combination era”



M. Abidi: Mycoses. Nov. 2014.



Black mold abscess

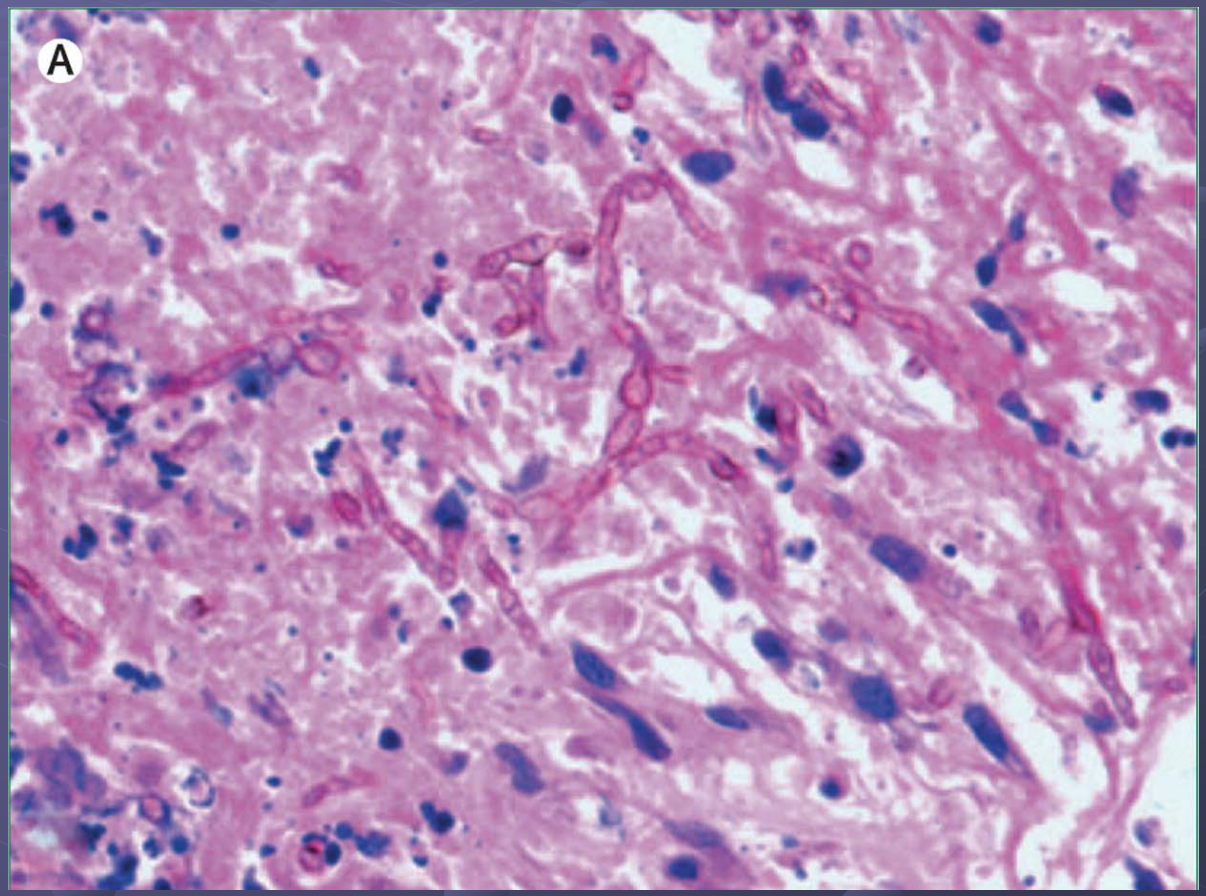
Cerebral phaeohyphomycosis

Lancet ID. Volume 9, Issue 6, June 2009, Pages 376-383

doi:10.1016/S1473-3099(09)70131-8 |

Black mold abscess

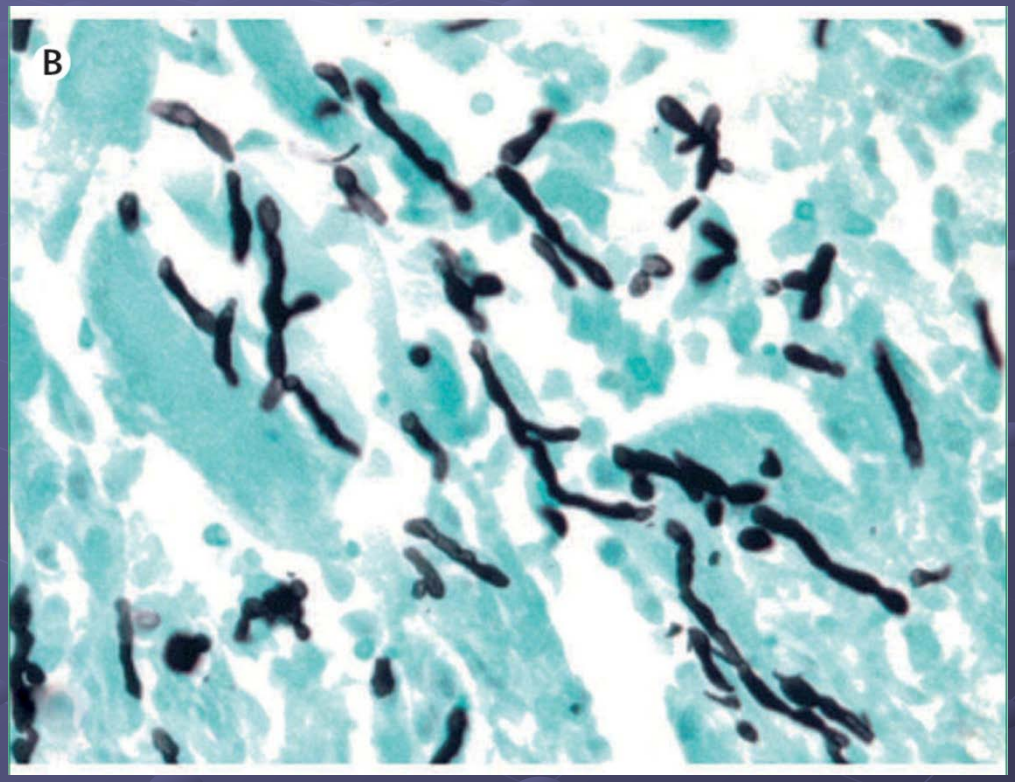
Cerebral phaeohyphomycosis



Pigmented fungal hyphae (A), elongated, and septate with unicellular lemon-shaped conidia (haematoxylin and eosin stain).

Black mold abscess

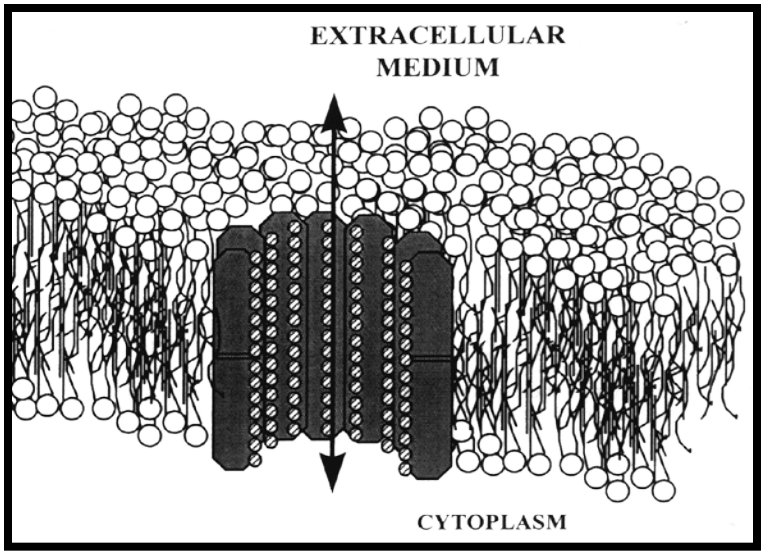
Cerebral phaeohyphomycosis



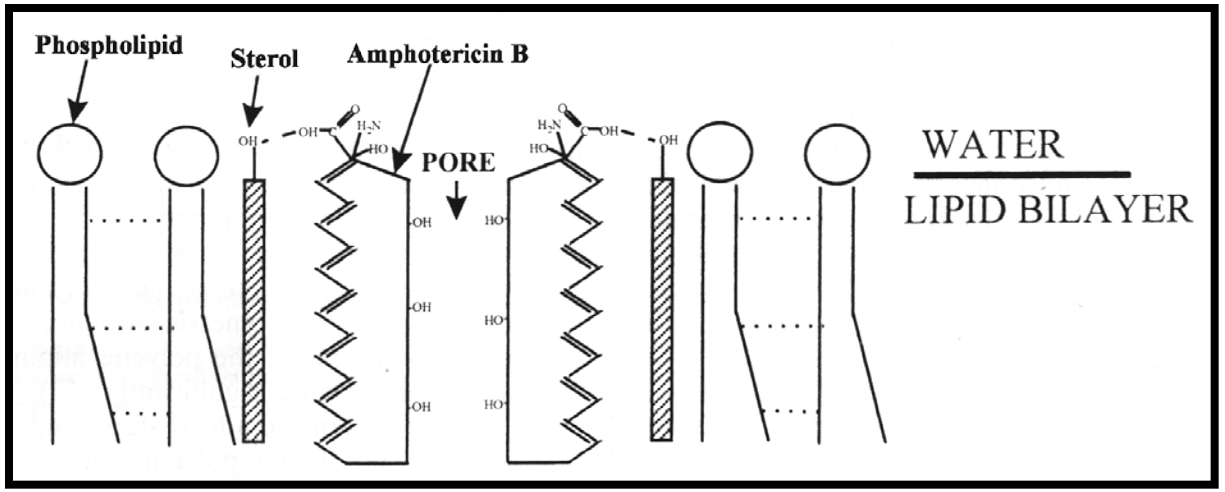
The fungal elements (B) are intensely positive with Grocott's methenamine silver.

Most melanized fungi appear to be resistant to echinocandins, probably due to the reduced presence of beta-glucan in the cell walls.

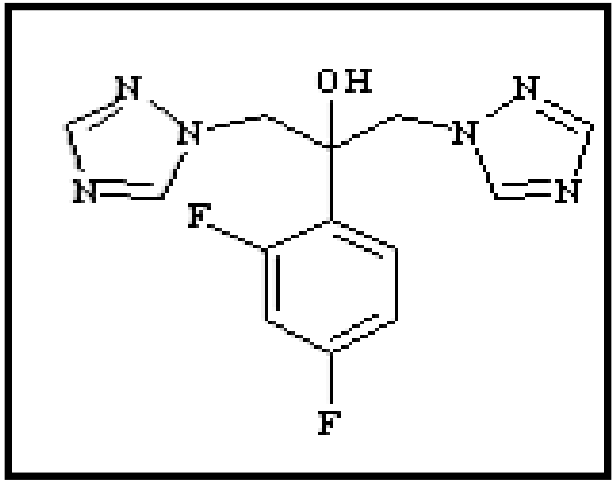
Amphotericin B binds to ergosterol and generates pores



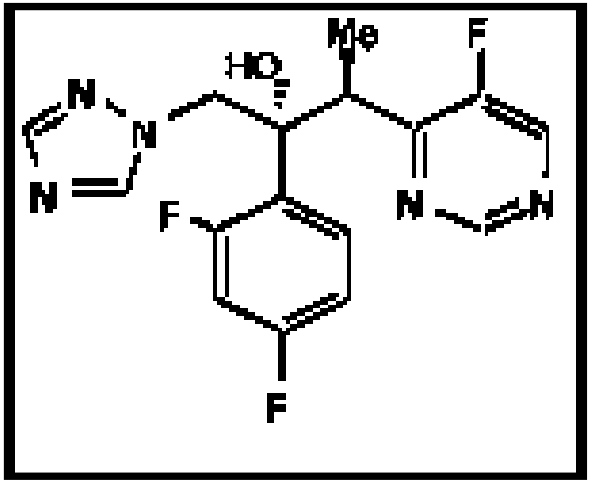
Clin Microbiol Rev
1999; 12: 501

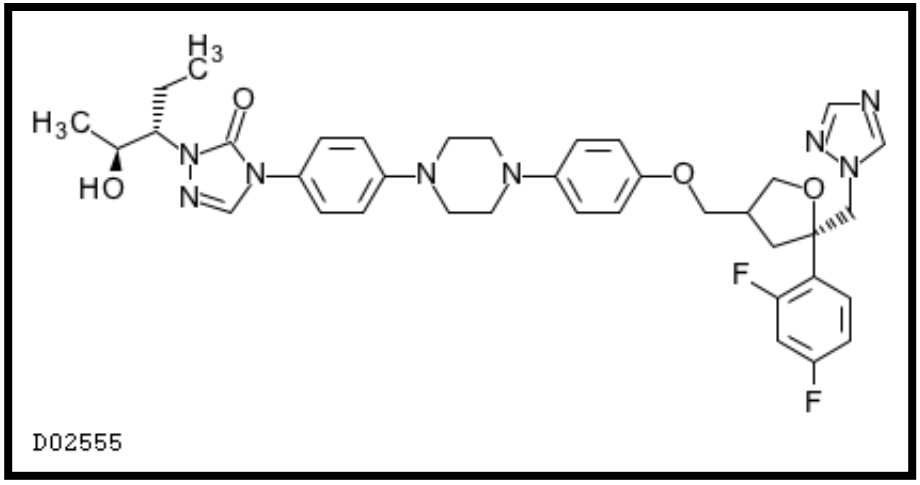


fluconazole

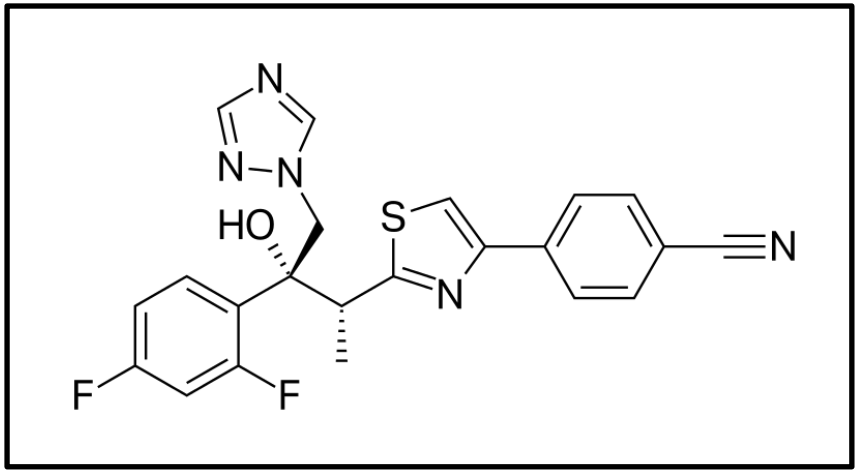


voriconazole





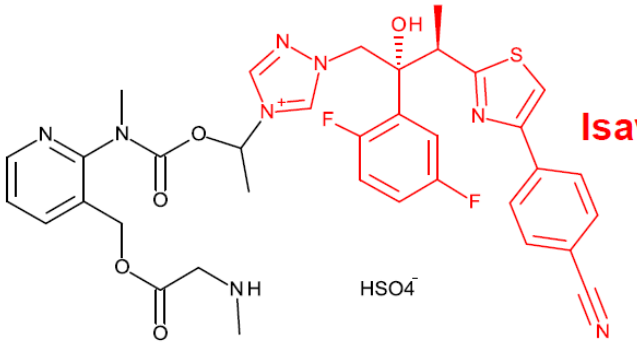
posaconazole



isavuconazole

Isavuconazonium: Novel Prodrug

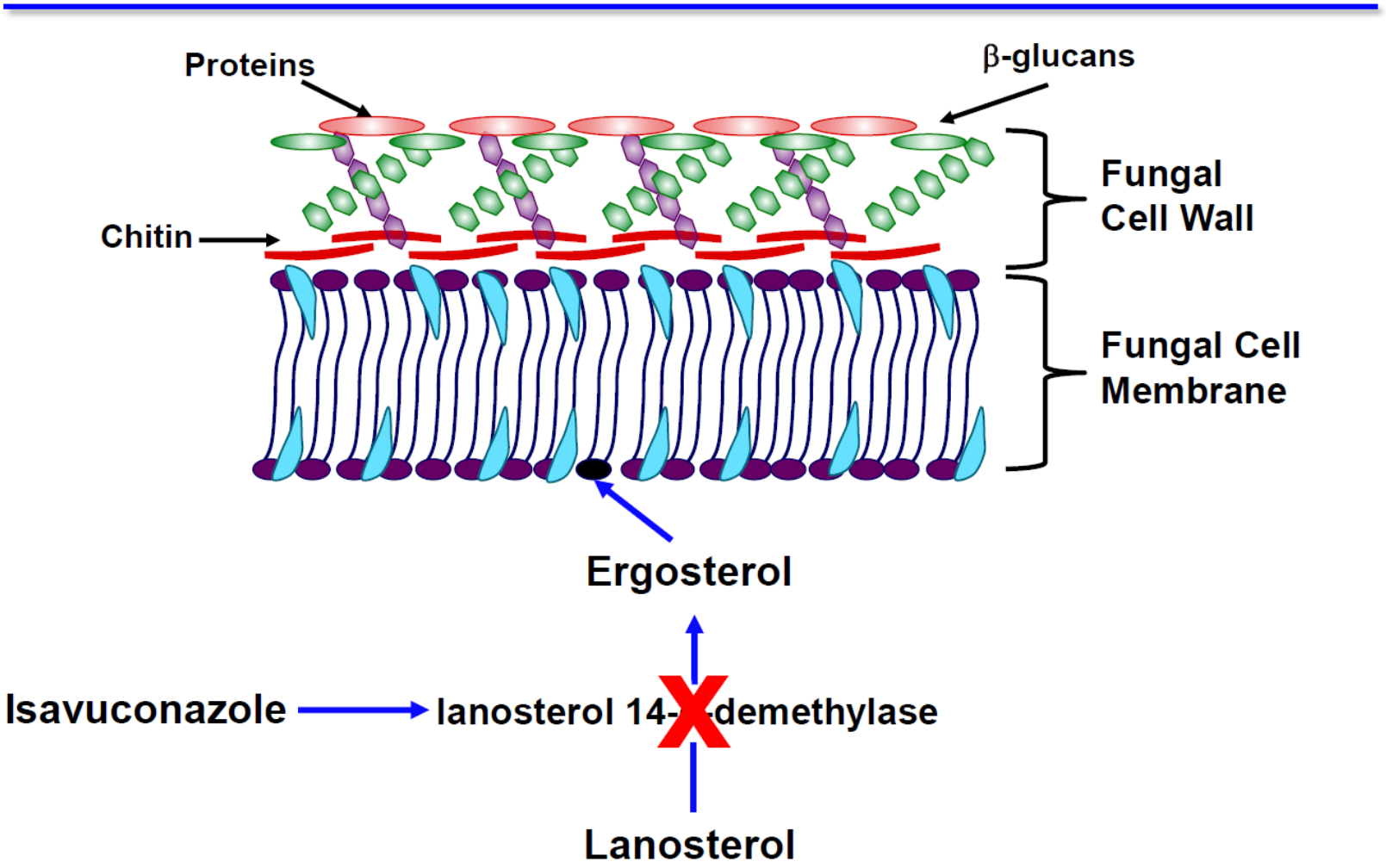
Cleavage Product



Isavuconazole (ISA)

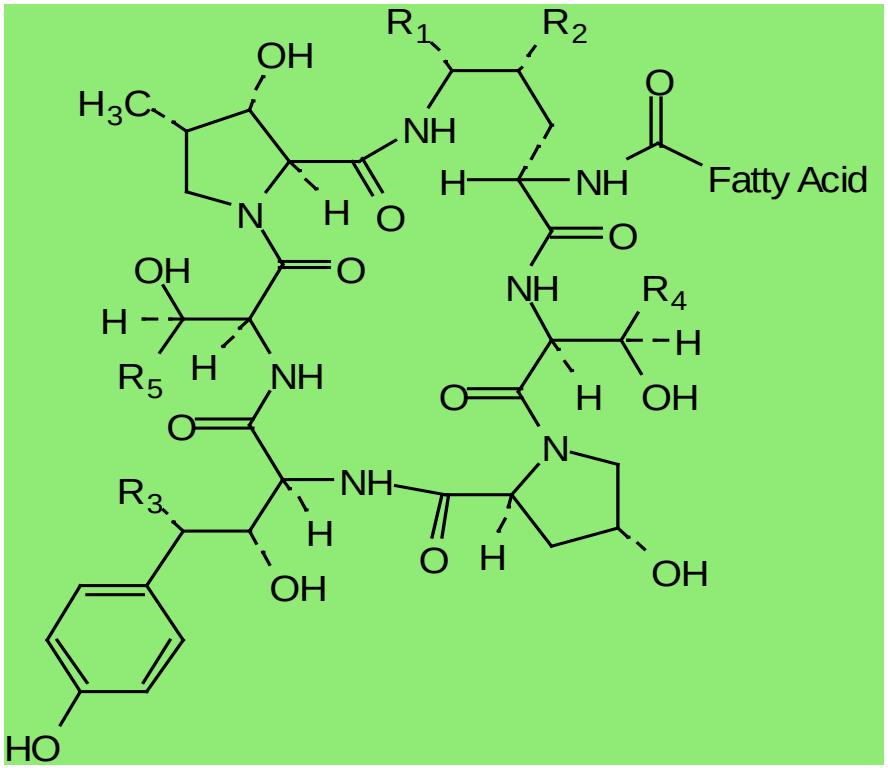
- IV and oral formulations
- Rapidly hydrolyzed by esterases
- Active moiety isavuconazole
- Highly water soluble prodrug
  - IV formulation: no cyclodextrin

From Astellas Presentation to FDA



From Astellas Presentation to FDA

Echinocandins: Glucan Synthesis Inhibitors



Cyclic hexapeptide; N-linked lipid side-chain

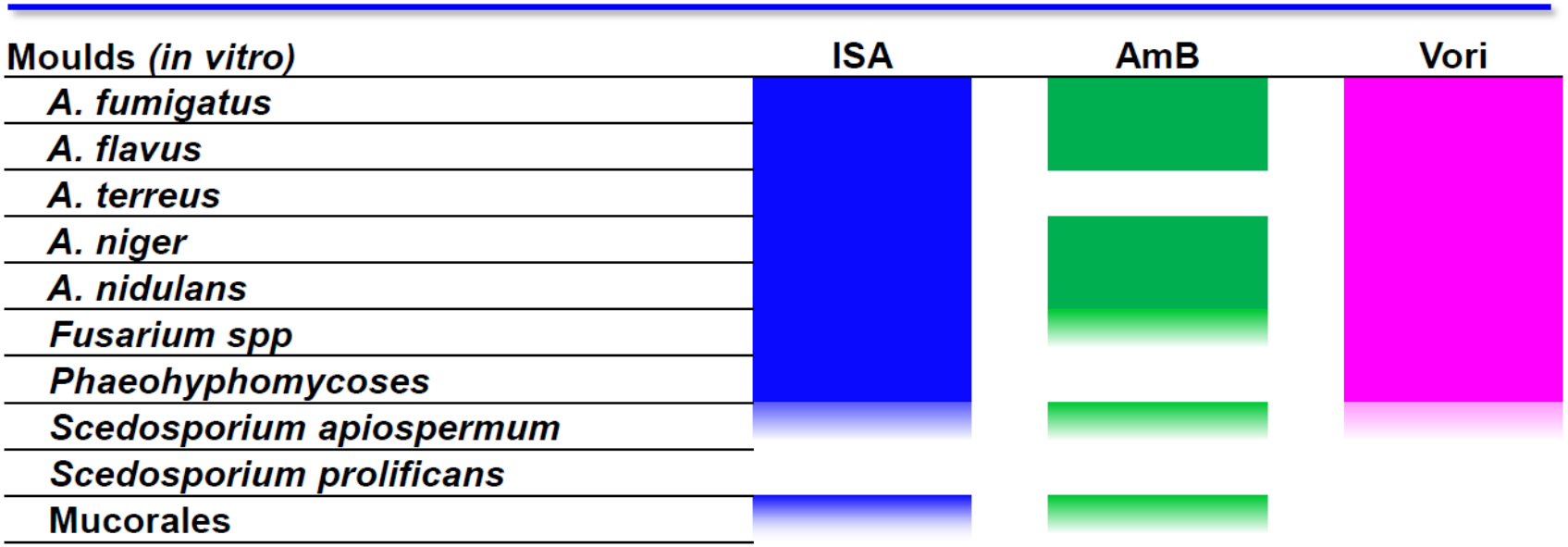
Others compound classes are active: Onishi et al, AAC 44:368, 2000

Comparative Spectra

	FLUCO	*VORI*	*POSA*	*ISAVU*	*Echino-candin*	*AMB*
C. ALBICANS	+	+	+	+	+	+
C. GLABRATA	N	+	+	+	+^	+
CRYPTO NEO	$+_m$	+	+	+	N	$+_i$
ASPERGILLUS	N	+	+	+	+	+
MUCOR	N	N	+	+	N	+*
FUSARIUM	N	+	+	+	N	N

m= maintenance; i= induction w 5FC
*high dose, ^emerging resistance

Comparative Spectra



From Astellas Presentation to FDA

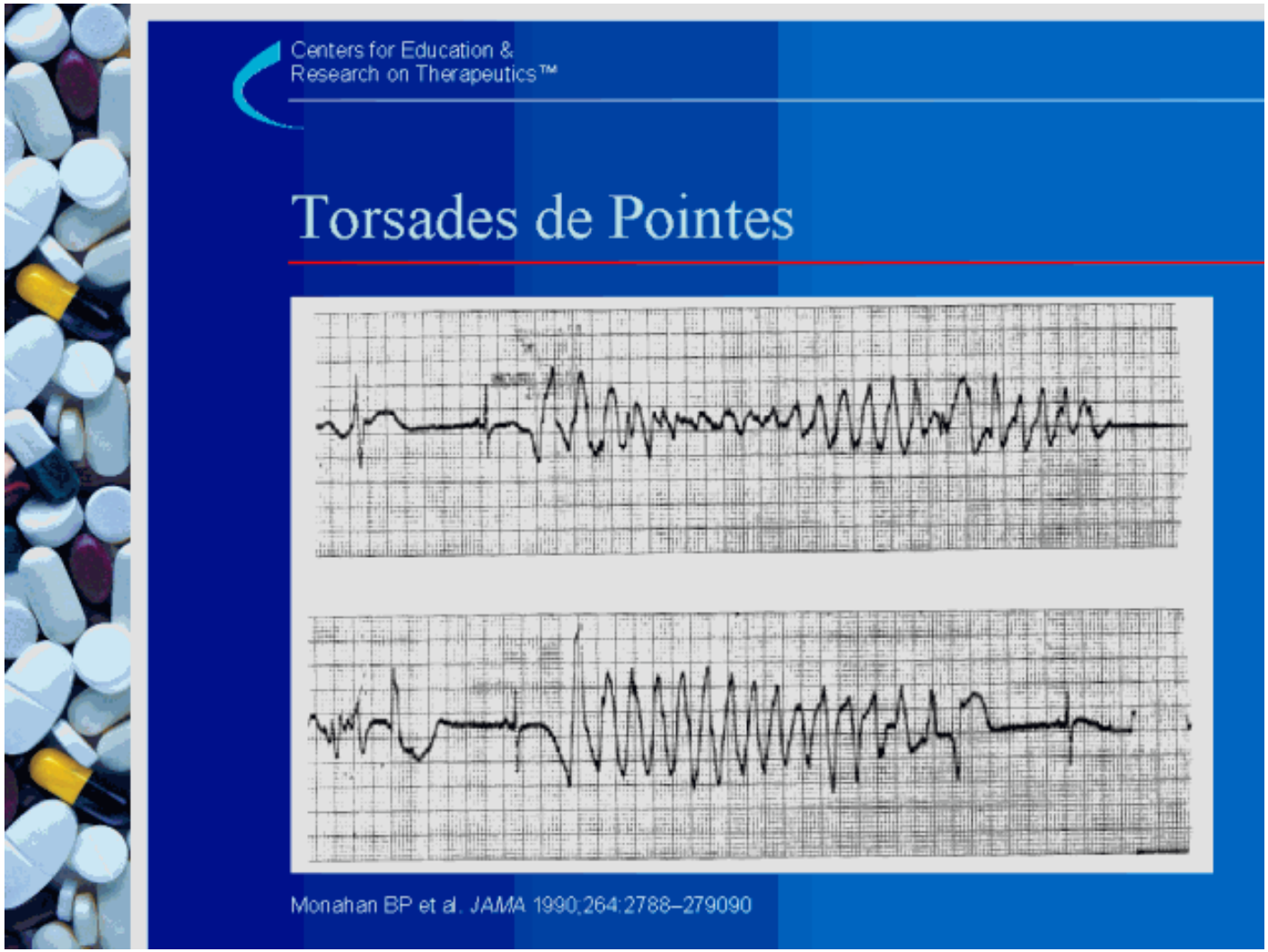
Comparative Spectra vs. “Emerging Fungi”

	FLUCO	*VORI*	*POSA/ ISAVU*	*Echino-candin*	*AMB*
Mucormycosis	**N**	**N**	**+**	**N**	**+**
FUSARIUM	**N**	**+**	**+**	**N**	**N**
Trichosporon	**+**	**+**	**+**	**N**	**N**
ASPERGILLUS TERREUS	**N**	**+**	**+**	**N**	**N**
Phaeohypho-mycoses	**N**	**+**	**+**	**N**	**N**
Scadesporium prolificans	**N**	**N**	**N**	**N**	**N**

Indications/Uses & Shortcomings of Major Anti-Fungals

	FLUCO	*VORI*	*POSA^ ISAVU**	*Echino-candin*	*AMB*
Indications	**Rx most Candida; Proph in K, P & LiTx**	**1st line in Aspergillus**	**Prophylaxis in Neutropenia^**	**Candida (C. Glabrata)**	**1st line in Crypto (with 5-FC)**
	2º proph. In Crypto. Meng.	**Febrile Neutropenia**	**Proph. in AlloSCT^**	**Febrile Neutropenia: Salvage Rx in Aspergillus**	**1st line in severe Zygomycete**
	Coccidiod. (high dose if CNS)	**Polyene Resistant Fungi**	**Zygomycete* & Polyene Resist. IFI**	**Combination for Possible Synergy**	**1st line in severe Histo, other**
Shortcomings	**C. Glabrata Resistant**	**Visual Hallucination**	**PO only ^**	**C parapsa. R; low CNS penetration**	**Renal Toxicity**
	Some Drug-Drug Interactions	**Drug-Drug Interactions**	**Drug-Drug Interactions^**	**IV only**	**IV, monitoring**

From FDA Website



Thank you

- Late IFIs in SOT will become part of every ID practice
- Rapid Diagnosis includes testing and communication.
- Guidelines require clinical interpretation
- Have the Transplant service manage immunosuppresson. Stopping CNIs in IFI can cause organ rejection without improving Infection outcomes.
- Engage the surgeons early; CNS IA is not as bleak as it used to be.
- Start Rx for Mucor in <1 wk from onset improves survival.
- Background of prior antifungal use. Specific Dx with Culture and Susceptibility now more important

MAYO CLINIC

Donor Derived Infections:

What you need to know and when to suspect it

Raymund R. Razonable, M.D., FIDSA, FAST

Professor of Medicine

Mayo Clinic College of Medicine

Chair, Transplant Infectious Diseases

Division of
INFECTIOUS DISEASES

Mayo Clinic Infectious Diseases Subspecialties Update
May 7-9, 2015

Disclosures

Grant support: Roche, Genentech, Qiagen (all funds given to the institution)

DSMB and Adjudication Committee: Astellas, Chimerix

Off-label Use: YES, commonly! (I will indicate so)

AST Infectious Diseases Guidelines. *American Journal of Transplantation*. March 2013 supplement. Blumberg, Danzinger, Kumar, Michaels and Razonable (eds).

Objectives

- To discuss donor-transmission infection events in organ transplantation
- To identify donors considered at increased risk of infectious disease transmission
- To appreciate the benefits and limitations of donor screening
- To understand the recommendations for reporting of suspected donor-transmitted infection

Clinical Case

- A 58-year-old man with HCV-cirrhosis received liver transplant from a deceased donor
- Uneventful immediate postoperative course; hospital discharge on post-op day 10
- 18 days after liver transplantation
  - Headache, neck stiffness, fever, ataxia, altered mentation
  - CT head: multiple brain infarcts and moderate edema
  - CSF: TCC 975 cells/µL (63% PMN, 20% macrophages, 16% lymphocytes); protein 221 mg/dL; glucose normal
  - Negative blood, CSF and urine cultures
  - Rapid neurologic and clinical decline → withdrawal of care

Gupte et al. *Am J Transplant* 2014;14(6):1417-1424

What is the likely diagnosis?

A. Lymphocytic choriomeningitis virus

B. Rabies virus

C. *Balamuthia mandrillaris*

D. West Nile virus

Critical Questions

- What is the **diagnosis** of the clinical illness?
  - Is this donor-derived infection?
    - If suspected, what is your responsibility?
- Who is the organ **donor**?
  - What is the cause of donor's death?
  - Is the donor at increased risk?
- What is the **status** of the other organ recipients?
  - Why is it important to know their condition?
  - How do you know who the other recipients are?

CNN.com Rabies-infected organs kill 3 patients

Thursday, July 1, 2004 Posted: 7:49 PM EDT (2349 GMT)

ATLANTA, Georgia (CNN) -- Rabies spread by organs taken from an infected donor has killed three transplant recipients, the Centers for Disease Control and Prevention said Thursday.

"This has never happened before," said Dr. Mitch Cohen, an infectious disease expert at the CDC, in a conference call with reporters.

A fourth recipient died during the actual transplant operation, before there was time to develop the disease, officials said.

Rabies was also determined to be responsible for the death of the organ donor.

The unprecedented case began nearly two months ago, shortly after an Arkansas man suffered a brain hemorrhage and died at Christus Saint Michael Healthcare Center in Texarkana, Texas.

CDC Lymphocytic Choriomeningitis Virus Infection in Organ Transplant Recipients --- Massachusetts, Rhode Island, 2005

On May 3, 2005, CDC received a report of severe illness in four patients who had received solid organ transplants from a common donor. All four organ recipients were found to have evidence of infection with lymphocytic choriomeningitis virus (LCMV), a rodent-borne Old World arenavirus. Preliminary findings indicate the source of infection likely was an infected hamster in the donor's home.

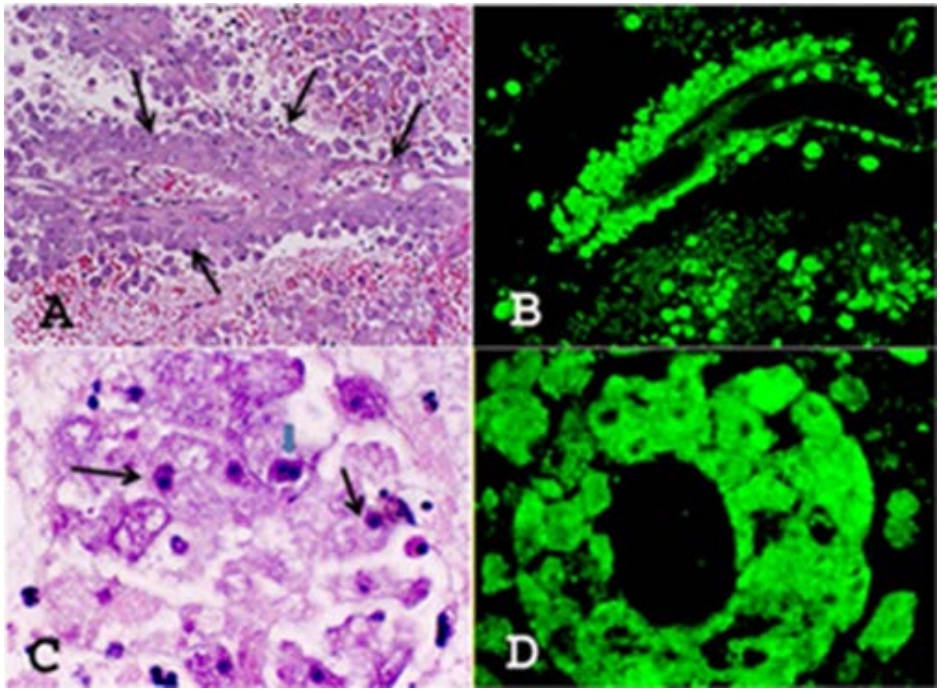
In early April, in Rhode Island, a woman with a medical history remarkable only for hypertension and 1 week of headache had sudden onset of hemiplegia caused by a stroke, followed by brainstem herniation and brain death within 3 days. Family members consented to donation; organs were recovered, including the liver, the lungs, both kidneys, both corneas, and skin.

Within 3 weeks after transplantation, the four persons who received the liver, lungs, and two kidneys had abnormalities of liver function and coagulation, and dysfunction of the transplanted organ. Signs, symptoms, and clinical laboratory test results varied in these patients and included fever, localized rash, diarrhea, hyponatremia, thrombocytopenia, hypoxia, and kidney failure.

Three of the four organ recipients died, 23--27 days after transplantation. The fourth patient, a kidney recipient, survived.

Clinical Case (continued)

- Autopsy was requested and consent obtained
- Brain had structures consistent with ameba on histopathology. Positive for *Balamuthia* by immunohistochemistry and PCR.



Gupte et al. *Am J Transplant* 2014;14(6):1417-1424

The Organ Donor

- 39-year-old man with head trauma secondary to an assault during an altercation. Seizure event.
- Evaluation at hospital: Lethargic and confused. Contusion in his posterior scalp.
- PMH: Seizure disorder (Rx: carbamazapine), substance abuse
- Social History: Previously homeless; history of incarceration 3 years ago
- Laboratory examinations: WBC 18 600 cells/μL; positive screen for cocaine. Head CT showed frontal, parietal and temporal contusions.
- Cause of death: blunt trauma to the head

Gupte et al. *Am J Transplant* 2014;14(6):1417-1424

Organ Donor Testing

- Immunohistochemistry was negative for *Balamuthia* and other free-living amebae on donor brain, lung and kidney tissue.
- PCR for *Balamuthia* and other free-living amebae was negative on formalin-fixed brain and lung tissue.
- Archived donor serum and plasma were positive for anti-*Balamuthia* antibodies with titers of 1:64 by IFA.

Responsibilities

OPTN (Organ Procurement and Transplantation Network, HRSA, DHHS) Policy 4.5

- Organ procurement organizations and transplant centers should report any "**unexpected"** potential donor-derived infection in a recipient to the OPTN **within 24 hours** of initial suspicion.

- Reporting may be triggered by "**new**" **donor information** relevant to acute patient care learned after recovery and/or transplant of donor organs (autopsy report or final culture results).

Other Organ Recipients

	Heart	R Kidney	L Kidney	Iliac Vessel
Age (years)	62	60	69	61
Disease	Ischemic heart disease	HTN, DM	HTN, DM	Alcohol
Clinical course	Leukocytosis	Asymptomatic	Asymptomatic	Asymptomatic
CSF PCR	Negative	Negative	Negative	Negative
MRI brain	Negative	Negative	Negative	Negative
Serology	1:512	1:256	1:128	1:128
Treatment	Azithromycin, albendazole, fluconazole, sulfadiazine, pentamidine, miltefosine	Azithromycin, albendazole, fluconazole, sulfadiazine, pentamidine, miltefosine	Clarithromycin, fluconazole, albendazole, miltefosine, azithromycin	Azithromycin, albendazole, fluconazole, pentamidine, miltefosine
Outcome	Survived	Survived	Survived	Survived

Gupte et al. *Am J Transplant* 2014;14(6):1417-1424

Donor-Derived Infections

- Common and predictable (expected; screened)
  - Cytomegalovirus, Epstein-Barr virus
  - Some bacterial infections (5% of donors have bacteremia)
- Less common but predicted
  - *Trypanosoma cruzi*, *Toxoplasma gondii*, *Strongyloides stercoralis*, *Coccidioides immitis*
  - HIV, HCV, HBV (if donor infection is known or suspected)
  - Some bacterial infections (drug-resistant)
- Rare and unpredicted (lack or failed screening)
  - Lymphocytic choriomeningitis virus, Rabies virus, *Balamuthia mandrillaris*, *Mycobacterium tuberculosis*
  - HIV, HCV, West Nile virus

Notable Transplant-Transmitted Infections Investigated by Public Health Authorities, USA

HIV (1985)

HCV (2000), Chagas disease (2001), WNV (2002), LCMV (2003), Rabies (2004), LCMV (2005)

Chagas (2006), HIV/HCV (2007), MTb (2007), LCMV (2008), Babesiosis (2008), WNV (2008) Zygomycosis, Coccidiodes, M tuberculosis (2009)

Balamuthia (2010), HIV in a living donor (2010), WNV (2011), HCV (2011), Microsporidium (2012), Rabies (2013), LCMV (2013), Microsporidium (2014)

1% of transplants result in suspected unexpected disease transmission: 0.2% are confirmed

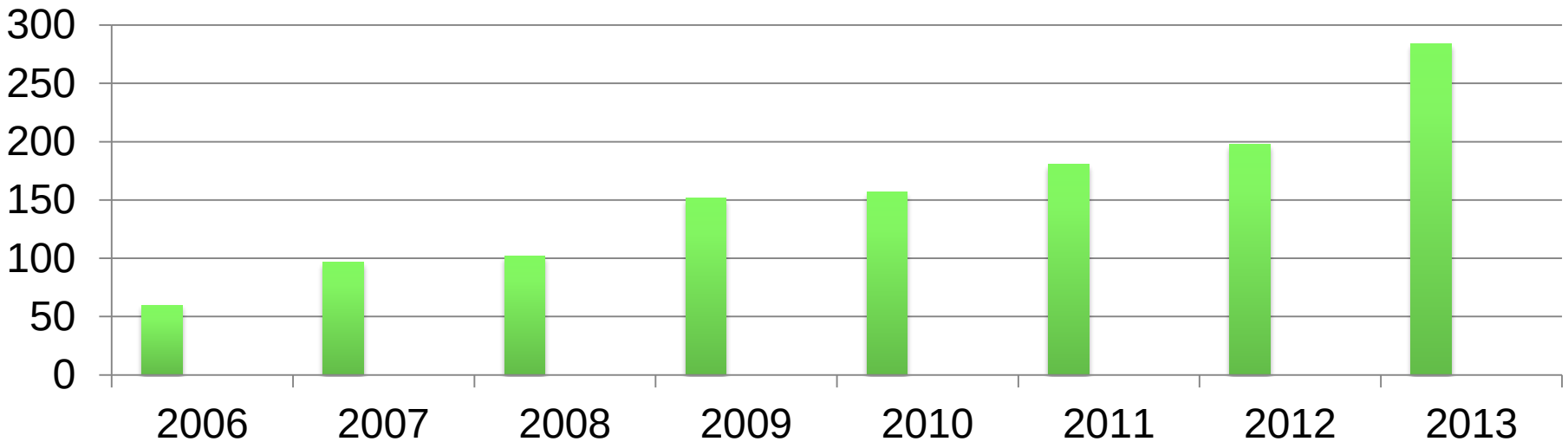
CDC. *American Transplant Congress* Philadelphia May 2015

Common Themes in Unusual Donor-Derived Infection Clusters

- Donor infection is unrecognized
  - Disease is rare and infrequently encountered
  - Donors without evidence of infectious cause of death
- Risk factors for the disease are not known
- Donor screening test is not available
- Donor risks and exposures are not clearly identified
  - Next of kin who completes donor history questionnaire is unaware of exposures and certain behaviours
- Lack of active surveillance
- Gaps in communication

Potential Donor-Derived Transmission Events

Report from DTAC (Disease Transmission Advisory Committee) American Transplant Congress, May 2015



Kaull. *Am Transplant Congress 2015* Philadelphia, May 2015

Summary of Potential Donor-Derived Infectious Disease Transmissions in US (OPTN), 2005-2011

Infection type	Number of donor reports	Number of recipients with confirmed transmission	Number of DDI-attributable recipient deaths
Viruses	166	48	16
Bacteria	118	34	9
Fungi	75	31	10
Mycobacteria	53	10	3
Parasites	35	22	7

Viruses: adenovirus, HBV, HCV, HEV, HIV, HTLV, HSV, LCMV, PIV, PVB19, rabies, WNV
Bacteria: *Acinetobacter*, *Brucella*, enterococcus, *Erlichia* spp., *E coli*, *Borrelia burgdorferi*, *Nocardia*, *Pseudomonas*, RMSF, *Serratia*, *S. aureus*, *Streptococcus* spp., *T pallidum*
Fungi: *Aspergillus* spp., *Candida* spp., *Coccidiodes immitis*, *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Scopulariopsis*, zygomyces
Mycobacteria: tuberculosis, non-tuberculous mycobacteria
Parasites: *Babesia*, *Balamuthia mandrillaris*, *Trypanosoma cruzi*, *Naegleria fowleri*, Schistosomiasis, *Strongyloides stercoralis*

Ison and Grossi. *Am J Transplant* 2013;13:22

Onset of Donor Derived Infections

Infection	0-30 days	31-90 days	91-180 days	>180 days
Virus	LCMV, WNV, RSV	CMV, WNV, PVB19	HCV	HBV
Bacteria	Most bacteria			
Fungi	*Candida, Coddidiodes, Aspergillus, Cryptococcus*, Zygomycete	*Aspergillus, Coccidiodes, Histoplasma*		
Mycobacteria	*M tuberculosis*	*M tuberculosis*	*M tuberculosis*	
Parasites	*Toxoplasma, Balamuthia*	*Strongyloides, Toxoplasma, Ecephalitozoon*	*Toxoplasma Strongyloides, Encephalitozoon, Balamuthia*	

Kaull. *Am Transplant Congress 2015* Philadelphia, May 2015

Donor Derived Bacterial Infections

- Drug-S and -R bacteria (pan or multi)
  - High attack rates: 65% (13/19 exposed to GNB)
- "***ESKAPE***" pathogens – unlikely to be covered by standard peri-operative antibiotics (e.g., cefazolin)
  - Gram-positive cocci
    - **E**nterococci, including VRE
    - ***S****taphylococcus aureus* (MRSA) and MRSCN
  - Gram-negative bacilli – ESBL, CRE, AmpC, others
    - ***K****lebsiella pneumoniae*
    - ***A****cinetobacter baumanni*
    - ***P****seudomonas aeruginosa*
    - ***E****nterobacter* sp. and other Enterobacteriaceae

Impact of Donor Derived Bacterial Infections

- Overall mortality
  - CR-KP vs. CS-KP in liver: 86% vs. 29% 1-year mortality
  - CR-KP vs. CS-KP in kidney: 46% vs. 0% 200-d mortality
  - CR-AB in SOT: 60-70% “in-house” mortality
- Higher rejection and impaired allograft survival
  - 69% graft loss or death in patients with MDR GNB DDI
  - Potential reasons
    - Antigen cross-presentation
    - Immune dysregulation due to sepsis
    - Lowered immunosuppression
- Beyond the patient
  - Introduction of “MDR” to the environment and risk of horizontal transmission to transplant unit and hospital

Kaull. *Am Transplant Congress 2015* Philadelphia, May 2015

OPTN Policy to Mitigate Risk of Donor Transmission

- OPO should determine conditions that influence donor acceptance (lab test, physical exam, medical/behavioral history, review of donor's medical records) by transplant centers
  - **Restricted timeline** – incomplete data (deceased donors)
  - Donor history **incomplete** – medical history (infections, others)
    - Social history is often a **second-hand story**
  - Serology-based screening: **window period** – lag time between primary infection and antibody detection
  - Limited and variable NAT capacity among organ procurement organizations

Ison & Nalesnik. *Am J Transplant*. 2011; 11: 1123–1130

Sentinel Events Call for Optimized Screening

The New York Times

Four Transplant Recipients Contract H.I.V.

Published: November 13, 2007

Four transplant recipients in Chicago have contracted H.I.V. from an organ donor, the first known cases in more than a decade of the virus being spread by organ transplants.

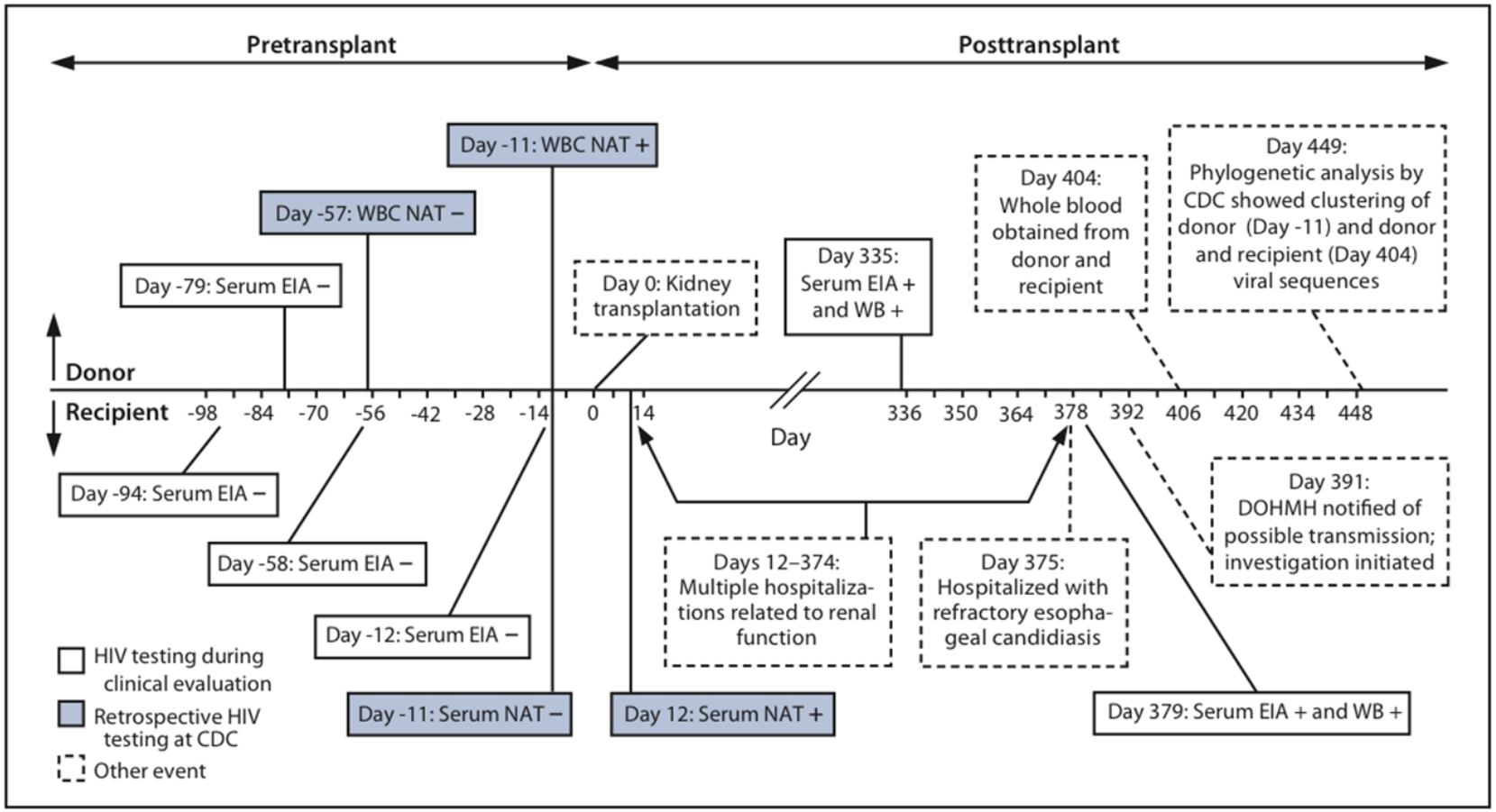
The organs also gave all four patients hepatitis C, in what health officials said was the first reported instance of the two viruses being spread simultaneously by a transplant.

Though exceedingly rare, this type of transmission highlights a known weakness in the system for checking organ donors for infection: the most commonly used tests can fail to detect viral diseases if they are performed too early in the course of the infection.

Officials say the events in Chicago may lead to widespread changes in testing methods.

HIV Transmission from Living Donor

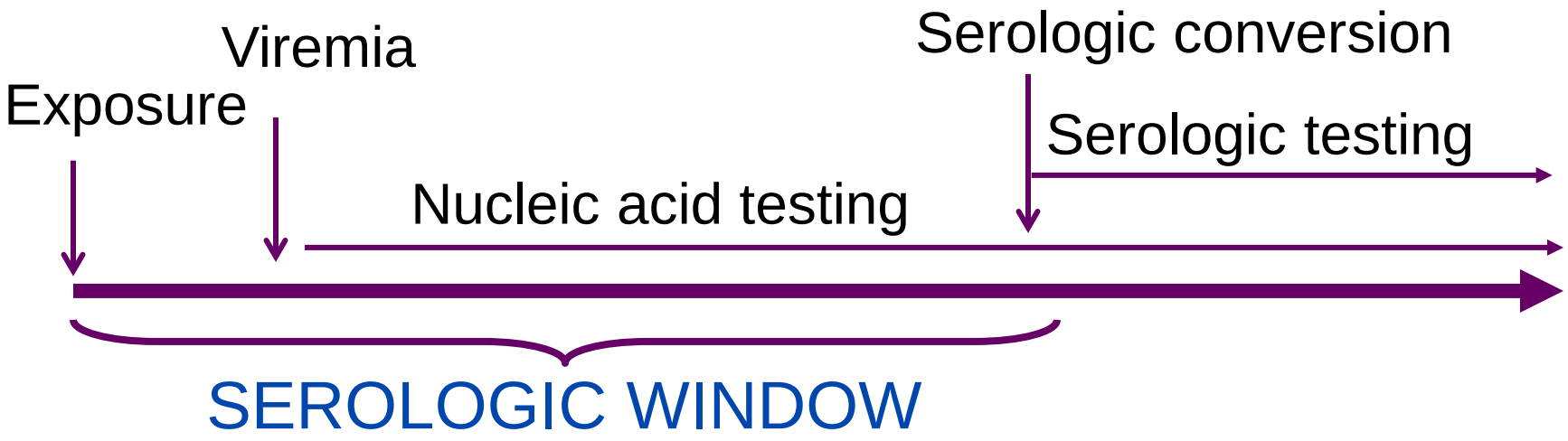
FIGURE. Timeline of events involving HIV transmission from a living organ donor — New York City, 2009



Abbreviations: HIV = human immunodeficiency virus; EIA = HIV enzyme immunoassay; HIV = human immunodeficiency virus; NAT = nucleic acid test; WB = HIV Western blot; WBC = white blood cell; DOHMH = New York City Department of Health and Mental Hygiene.

MMWR. 2011; 60: 297-301.

Serology versus NAT for HIV, HBV and HCV



Virus	Serology	NAT
HIV	22 days	9 days
HBV	44 days	22 days
HCV	66 days	7 days

AST IDCOP Guidelines. *Am J Transplant*. 2010; Suppl 4: 8-21; Kucirka L *et al*. *Am J Transplant* 2011;11(6):1188-200; Kucirka L *et al*. *Am J Transplant* 2011;11(6):1176-87.

Who among these potential donors is NOT considered at "an increased risk" based on the current PHS guidelines?

A. A 24-year-old homeless man who had last injection drug use 9 months ago

B. A 30-year-old woman who last had sex in exchange for drugs 3 years ago

C. A 40-year-old woman who had sex with a man who have active sexual relations with another man

D. A 19-year-old man who sustained massive blood loss from car accident and received >50 units of blood products

E. A 16-year-old adolescent incarcerated in a juvenile correction facility for 4 days 6 months ago

PHS Guidelines for Increased Risk Donor

People who have had sex with a person known or suspected to have HIV, HBV or HCV infections in the preceding 12 months
Men who have sex with men (MSM) in the preceding 12 months
Women who have had sex with a man with a history of MSM behavior in the preceding 12 months
People who have had sex in exchange for money or drugs in the preceding 12 months
People who have had sex with a person who had sex in exchange for money or drugs in the preceding 12 months
People who have had sex with a person who had injected drugs by IV, IM or SQ route for nonmedical reasons in the preceding 12 months
People who have injected drugs by IV, IM or SQ route for nonmedical reasons in the preceding 12 months
People who have been in lockup, jail, prison, or juvenile correction facility for >72 hours in the preceding 12 months
People who have been newly diagnosed with or have been treated for syphilis, gonorrhea, chlamydia, or genital ulcers in the preceding 12 months
People who have been on hemodialysis in the preceding 12 months (HCV only)
Children <18 months of age and born to mothers infected with or at risk for HIV, HBV or HCV Child who is breastfed within 12 months and mother is infected with or at risk for HIV, HBV or HCV

Informed Consent of Transmissible Disease Risk

- Transplant programs must obtain specific informed consent before transplant of any organ when ***any*** of the following occurs:
  - The donor has a known medical condition that may, in the transplant hospital's judgment, be transmissible to the recipient.
  - The donor meets any of the criteria for increased risk of transmitting HIV, hepatitis B, and hepatitis C.
  - When a hemodiluted specimen is used for donor HIV, hepatitis B, or hepatitis C screening.

http://optn.transplant.hrsa.gov/ContentDocuments/OPTN_Policies.pdf.

Who among these potential donors is likely to be rejected for organ donation?

A. A 35-year-old previously healthy woman who died of encephalitis of unknown cause

B. A 20-year old previously healthy woman with meningococcal meningitis

C. A 35-year-old man with bacteremic pneumonia due to *Streptococcus pneumoniae*

D. A 40-year-old man with bacteremia due to MRSA

Unusual Transplant-Transmitted Infectious Encephalitis Clusters, 2002-2014, USA

Infectious Agent	Total donors and clusters	Total recipients	Total deaths
West Nile virus	6	16	4
LCMV	4	13	10
Rabies	2	8	5
Balamuthia	2	7	3
Microsporidia	1	3	1
Total	15	47	23

CDC. *American Transplant Congress* Philadelphia May 2015

Donors with Infectious Encephalitis

- **Avoid** donors with encephalitis of unknown cause
  - Risk of transmission of rabies, WNV, LCM, parasitic infections (and malignancies)
- Donors with bacterial meningitis **may donate**
  - Treat donors for at least 24-48 hours before donation (ideally with clinical response – negative cultures)
  - Treat organ recipients for 7-14 day course of effective antibiotic regimen
- Donors with *Naegleria fowlerii* meningoencephalitis
  - Limited to the CNS; low risk of transmission
- Meningitis due to highly virulent (intracellular) organisms such as *Listeria monocytogenes* = relative contraindication

Ison and Grossi. *Am J Transplant* 2013;13:22

Donors with Bacteremia

- Estimated 5% of donors have bacteremia at the time of organ procurement
- Risk of transmission is high and outcome is poor
  - Gram-negative bacilli > Gram-positive cocci
  - Adjust perioperative prophylaxis, as guided by culture data
- Treat potential donors for at least 24-48 hours before procurement (ideally with clinical response – negative cultures)
- Treat recipients for 7-14 days of effective antibiotics
  - Antimicrobial susceptibility: caution MDR organisms

Ison and Grossi. *Am J Transplant* 2013;13:22

Communication is Essential

- A study of donor-derived infection transmission events reported to OPTN DTAC - **delays and errors in communication are frequent and occur at multiple levels**.
  - Web-based reporting mechanism: **OPTN Patient Safety Portal**
  - Complex networks among geographically diverse laboratories, organ procurement organizations, and recipient transplant centers
- Communication *gaps* contributed to adverse outcomes among transplant recipients, in some cases even leading to potentially preventable recipient deaths.
- *Effective* communication resulted in minimized or averted infection in transplant recipients through implementation of preventive or preemptive treatment strategies.

Miller R et al. *American Journal of Transplantation* 2015, 15:1: 259–264

Patient Safety Contact

- Required of each OPO and transplant program
- Responsibilities:
- 1. Be available 24 hours a day.
- 2. Receive notifications of potential disease transmission.
- 3. Receive medical information that may affect recipient care.
- 4. Communicate information regarding potential disease transmissions to the medical staff within 24 hours.
- 5. Facilitate communication about the clinical status of any recipient.

http://optn.transplant.hrsa.gov/ContentDocuments/OPTN_Policies.pdf.

Reporting of Potential and Proven Disease Transmissions in Recipients

- When a recipient is suspected to have, confirmed positive for, or has died from a potential transmissible disease, and there is substantial concern that it could be from the donor, the transplant program must do *both* of the following:
- 1. Notify the institution that recovered the organ (OPO or living donor recovery hospital), without waiting for all medical documentation, by phone and provide documentation as soon as possible but no later than 24 hours.
- 2. Report through the OPTN Improving Patient Safety Portal.

http://optn.transplant.hrsa.gov/ContentDocuments/OPTN_Policies.pdf.

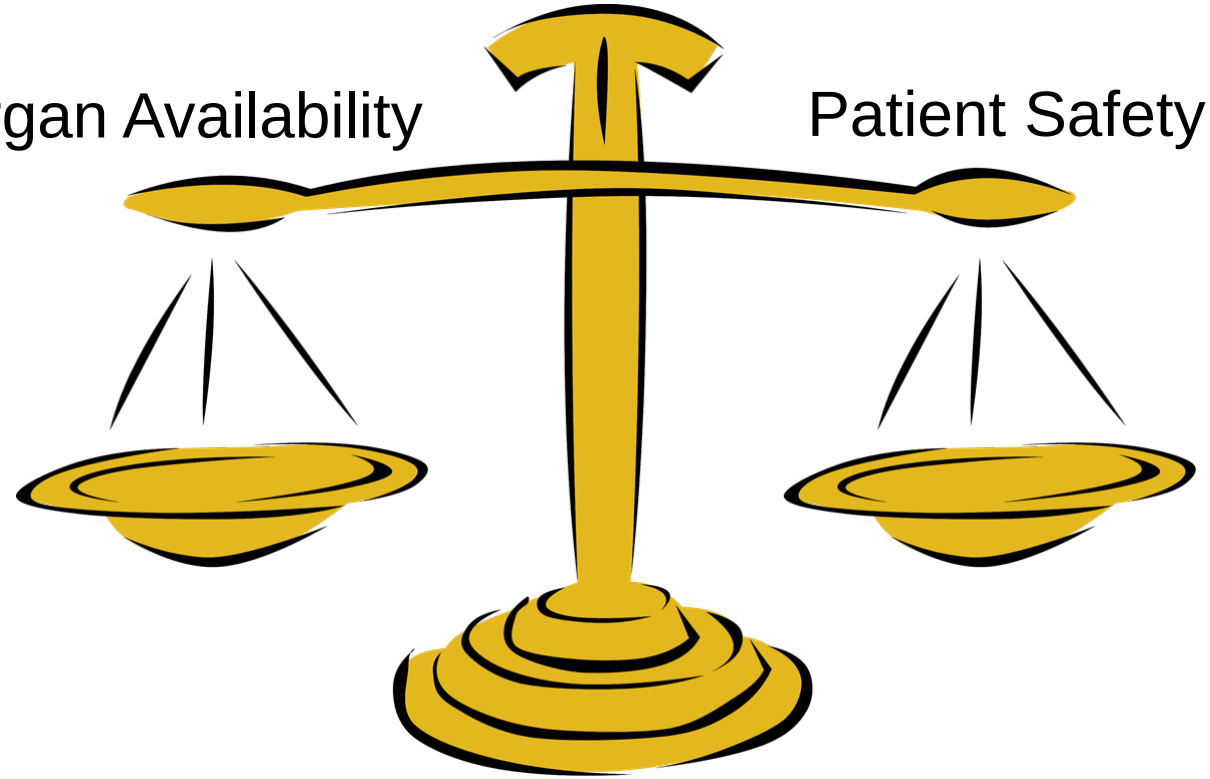
Requirements for Post-Transplant Discovery of Donor Disease

- If new, clinically relevant findings about a deceased or living donor are discovered after transplant, the transplant program must complete *all* of the following;
- 1. Notify the recipient of the risk of transmissible disease that was not previously identified
- 2. Document new information about the donor and potential risk for disease in the recipient's medical record.
- 3. Clinical follow up of the a recipient for the development of the disease after transplant.
- 4. Offer testing, monitoring, and treatment as appropriate, in addition to routine follow up care.

http://optn.transplant.hrsa.gov/ContentDocuments/OPTN_Policies.pdf.

A Balancing Act

As of 4:55 am today: 123,442 people need SOT (79,097 active)



Conclusions

- Discussed donor-transmission infection events in organ transplantation
- Reviewed criteria for donors at increased risk of disease transmission
- Enumerated the benefits and limitations of donor screening
- Outlined the recommendations for the reporting of suspected and confirmed donor-transmitted infection

MAYO CLINIC
TRANSPLANT INFECTIOUS DISEASES FELLOWSHIP

Training Tomorrow's Infectious Diseases Physician Leaders with Expertise in Transplant Infections

Transplant ID Fellowship Provides Exposure to:

- Pre-transplant assessment of candidates and potential donors
- Prevention and management of infections in the early and late period after transplantation
- State-of-the-art diagnostic modalities
- Multidisciplinary team-based approach to patient care
- Highly dedicated and experienced mentors and faculty with primary focus in Transplant ID

Fellowship Rotation Schedule includes:

- Six months of clinical rotation in solid organ and hematopoietic stem cell transplantation
- Five months of basic, translational, or clinical research
- One month of clinical or research elective, with Clinical Microbiology rotation as an option

MAYO CLINIC

MAYO CLINIC

Solid Organ Transplantation in HIV Infected Patients

Stacey Rizza, MD, FIDSA
Associate Professor of Medicine
Chair, Mayo HIV Clinic

Division of
INFECTIOUS DISEASES

Mayo Clinic Infectious Diseases Subspecialties Update
May 7-9, 2015

Solid Organ Transplantation in HIV Infected Patients

Objectives

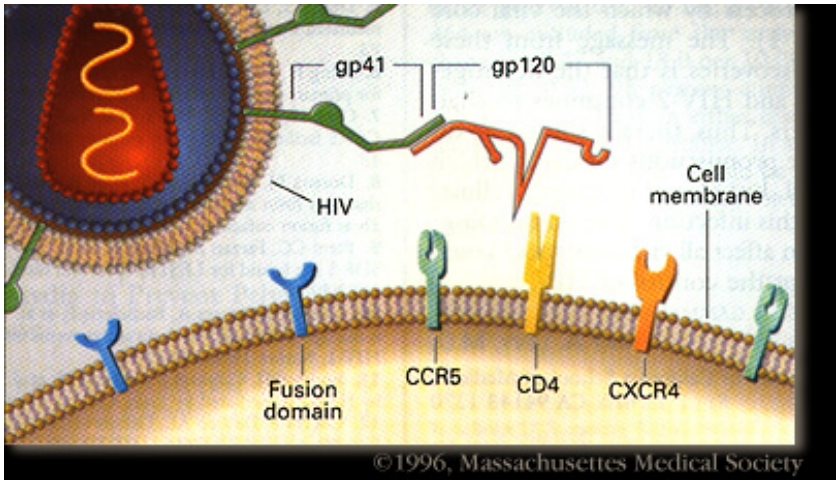
- HIV and End Organ Disease
- HIV and Kidney Transplant
- HIV and Live Transplant
- HIV and Other Organ Transplants
- Drug Issues
- Future of HIV and Organ Transplantation

HIV

- HIV infects over 40 million people world wide
- 1.2 million Americans are estimated to be HIV infected
- Infection rates continue to increase in young adults, women, minorities
- Universal screening will lead to more diagnosis

Direct Effects of HIV

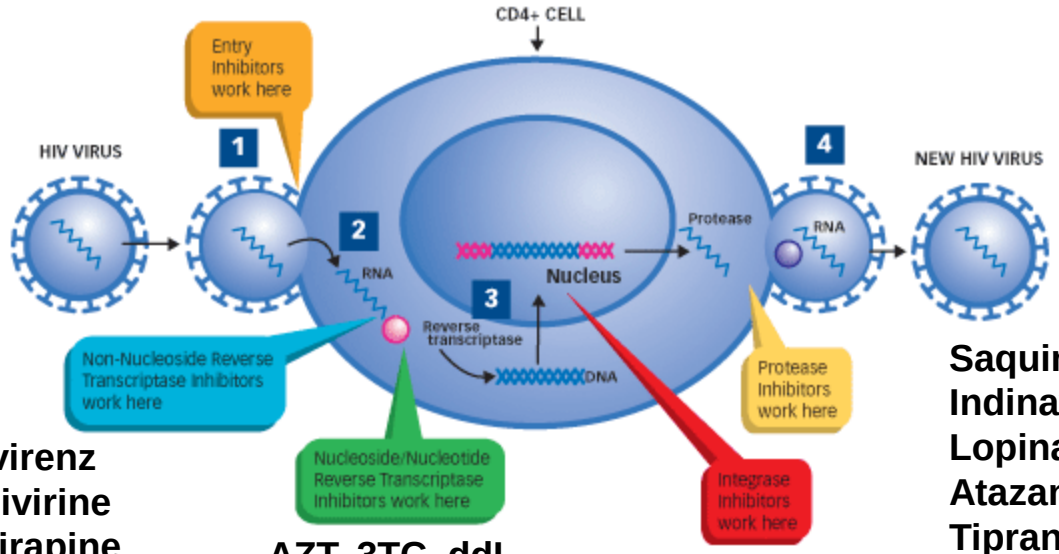
- HIV Associated Nephropathy
- HIV dementia
- Osteoporosis
- Cardiovascular disease
- Liver disease



In the cART era, the direct effects of HIV are leading to **End Stage Organ Disease**

Anti-Retroviral Therapy

T20
Maraviroc



Efavirenz
Rilpivirine
Nevirapine
Delavirdine

AZT, 3TC, ddI, d4T,Abcavir, Tenofovir, FTC

Raltegravir
Elvitegravir

Saquinavir, Ritonavir, Indinavir, Nelfinavir, Lopinavir, Fosamprenavir, Atazanivir, Darunavir, Tipranavir

3 active drugs from at least two different classes

In some cases this can be done with one pill a day

cART

- HIV viral load decreases within days and (hopefully) becomes undetectable
- CD4 T cell count increases
- Fewer Opportunistic Infections/cancers
- Mortality decreased
- **End organ damage slows**

Paul

- 52 year old man from Iowa. Diagnosed with HIV in 1989 contracted through unprotected heterosexual sex. Diagnosed during insurance screen.
- CD4 count was 450 cells/mcL at diagnosis and he reports no opportunistic infections or cancers in the past.
- His first ART program was AZT, 3TC, Indinavir. The patient developed a renal stone which he passed. Serum creatinine was 1.6 mg/dL.
- ART is now Atripla (Tenofovir, FTC, Efavirenz)

Paul

- Current CD4 T cell count is 891 cells/mcL and HIV vl is undetectable.
- He has a history of hypertension and cardiovascular disease requiring coronary stent placement 4 years ago
- Over the past several years patient has complained of worsening shortness of breath, leg swelling and fatigue.
- Renal ultrasound showed mild cortical thickening, with normal sized kidneys.
- Patient had nephrotic range proteinuria.
- Renal biopsy showed Focal Segmental Glomerulosclerosis

Paul

- Patient was diagnosed with HIV Associated Nephropathy and advised to start Hemodialysis.
- Patient works as a software engineer. Married for 16 years. His wife remains HIV neg.

- **Patient asks if he can receive a kidney transplant rather than a lifetime of dialysis?**

HIV and Transplant

- Immunosuppression on top of an immunocompromised state
- Limited life expectancy
- Drug/Drug interactions
- Already limited organ pool

HIV and Transplant

- With cART, HIV replication can be suppressed
- Better screening and prophylaxis for opportunistic infections and cancers
- Drugs used to suppress the immune system may actually have anti-viral/anti-HIV benefits

Cyclosporin

- Blocks IL2 dependent T cell proliferation
  - Suppress HIV replication
- Binds cyclophilin A
  - Prevents HIV gag/pol/cyclophilin complex and nuclear import
- Studies suggest that adding cyclosporine to HAART improves CD4 T cell counts

Transplantation 1993;55:95
Virology 1998; 245:197
JCI 2002;109:681

Mycophenolate mofetil

- Inhibits inosine monophosphate dehydrogenase and decreases the pool of intracellular nucleotides

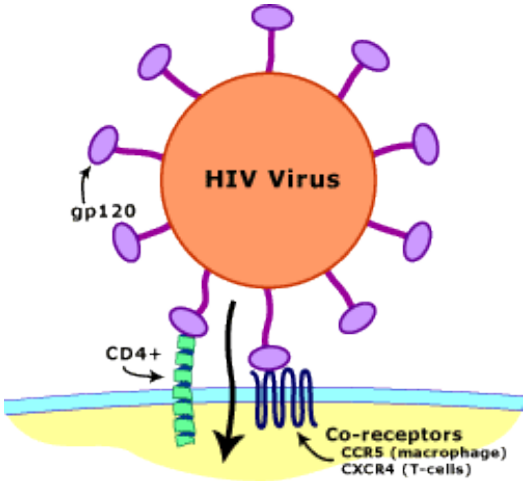
- Can act synergistically with Nucleoside analogs, particularly Abacavir.

- Theoretical concern (with some *in vitro* data) that MMF may be competitive and antagonistic with other NRTI.

J Acquir Immune Defic Syndr 1999;22:406
J Acquir Immune Defic Syndr 1999;21:362

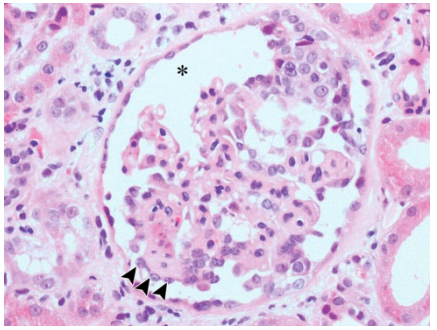
Sirolimus

- Down regulates the CCR5 chemokine co-receptor on CD4 T cells
- Blocks immune activation through blunted IL2 effects
- Fewer activated T cells means fewer new cells to be infected and replicate



PNAS 2003;100:10411

HIV and Kidney Transplant



Radiographics.com

- In the Western world 1% of people with ESRD are also living with HIV
- 30% of people living with HIV have kidney disease
- HIV Associate Nephropathy is the third most common cause of kidney disease amongst African Americans in the US
- HIV patients also have kidney disease from HCV/HBV co-infections, IgA nephropathy, HIV medications

HIV and Kidney Transplant

- Multicenter nonrandomized trial – 150 HIV+ kidney transplant recipients followed for 3 years
- CD4 T cell count >200 cells/cmL
- Undetectable HIV viral load
- Stable HAART for 16 weeks prior to transplant

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Outcomes of Kidney Transplantation in HIV-Infected Recipients

Peter G. Stock, M.D., Ph.D., Burc Barin, M.S., Barbara Murphy, M.D., Douglas Hanto, M.D., Ph.D., Jorge M. Diego, M.D., Jimmy Light, M.D., Charles Davis, M.D., Emily Blumberg, M.D., David Simon, M.D., Ph.D., Aruna Subramanian, M.D., J. Michael Millis, M.D., G. Marshall Lyon, M.D., Kenneth Brayman, M.D., Doug Slakey, M.D., Ron Shapiro, M.D., Joseph Melancon, M.D., Jeffrey M. Jacobson, M.D., Valentina Stosor, M.D., Jean L. Olson, M.D., Donald M. Stablein, Ph.D., and Michelle E. Roland, M.D. for the HIV-TR Investigators

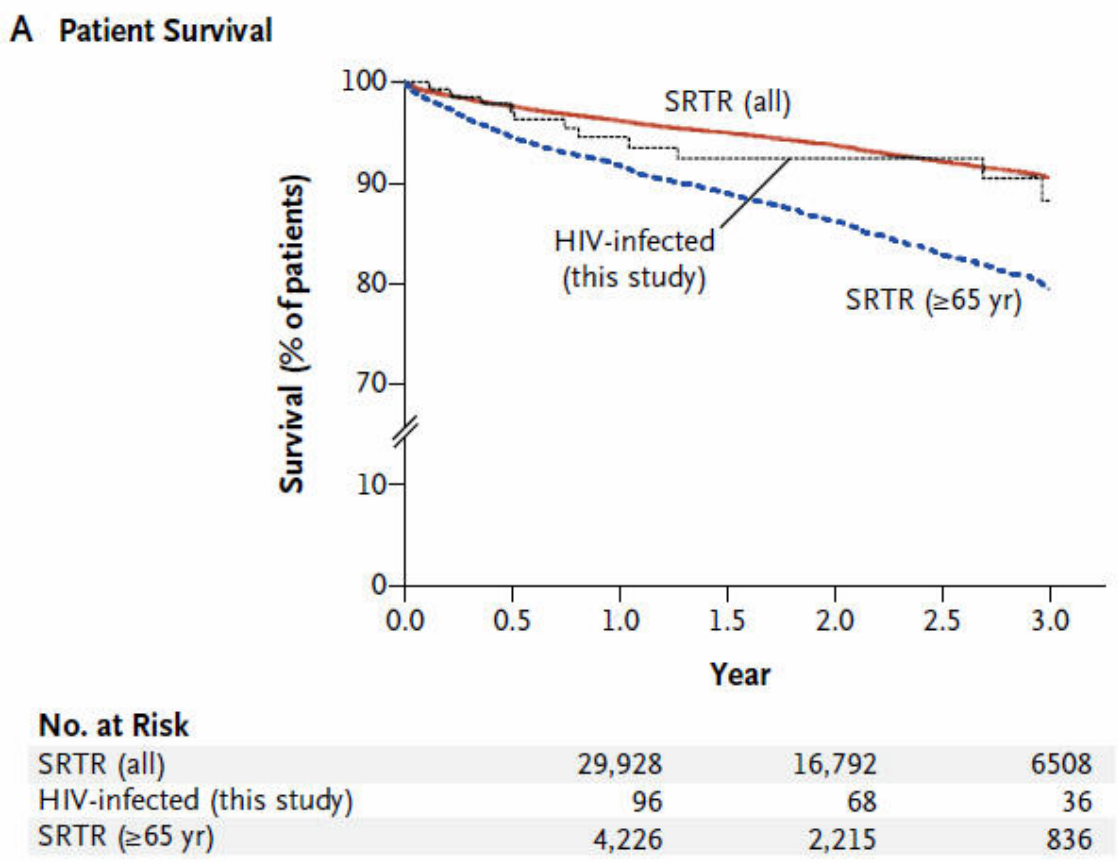
NEJM 2010;363:21

HIV and Kidney Transplant

- Living and deceased donor kidneys
- Glucocorticoids, cyclosporine or tacrolimus, MMF and Sirolimus were used
- IL2 blockers, antithymocyte globulins were used at the discretion of the center
- No cART restrictions

NEJM 2010;363:21

HIV and Kidney Transplant

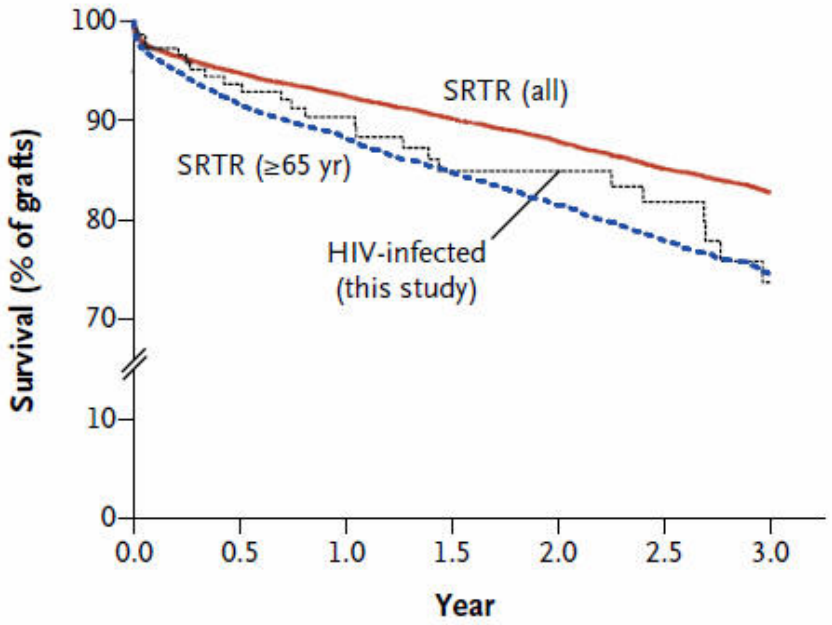


Scientific Registry of Transplant Recipients

NEJM 2010;363:21

HIV and Kidney Transplant

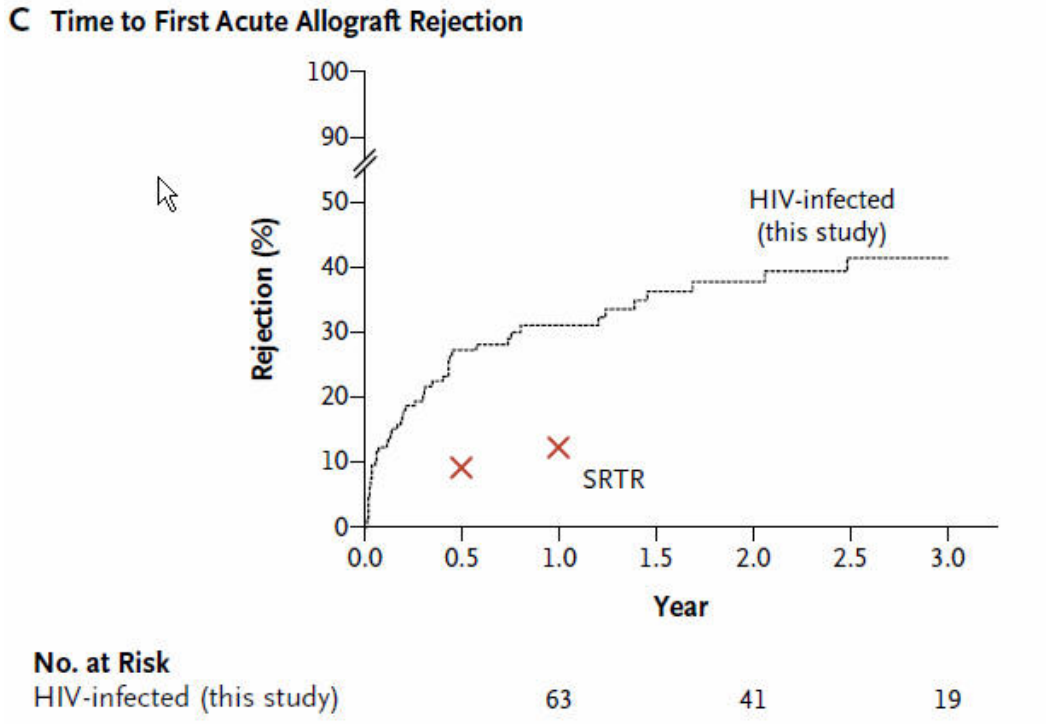
B Graft Survival



No. at Risk			
SRTR (all)	29,064	16,114	6215
HIV-infected (this study)	93	64	31
SRTR (≥65 yr)	4,103	2,133	807

NEJM 2010;363:21

HIV and Kidney Transplant- Rejection!!



33 Kidney transplant recipients had **67 episodes of acute rejection**

42- Acute cellular rejection
4- Acute vascular rejection
7- Acute cellular and vascular rejections

NEJM 2010;363:21

Acute Rejection

- 34% Cyclosporine
- 57% Tacrolimus
- 48% responded to Glucocorticoid therapy
- Multivariate proportional-hazards model increased risk of rejection from:
  - Deceased donor graft
  - Cyclosporine use
  - Higher post-transplant CD4 T cell was slightly protective

NEJM 2010;363:21

HIV Disease After Kidney Transplant

- 2 cases of KS, 1 case of thrush, 1 case of PJP
- 2 patients had newly diagnosed HIVAN
  - 1 patient had worsening kidney function
- CD4 T cell count change post-transplant
  - No induction therapy -135 cells/mcL
  - Induction therapy -238 cells/mcL
- HIV vl post-transplant
  - 48 patients (32%) had detectable vl at some point at year 1
  - Only 1 patient had detectable HIV at year 4

NEJM 2010;363:21

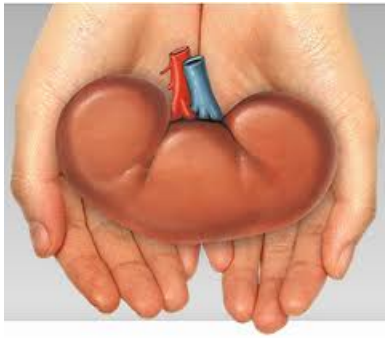
Infections in HIV patients

After kidney transplant

- 38% of recipients had 140 infections that needed hospitalization
  - 69% bacterial
  - 9% fungal
  - 6% viral
  - 1% protozoal
- Genitourinary tract 26%
- Respiratory 20%
- Blood in 19%
- Most infections occurred the first 6 months after transplant

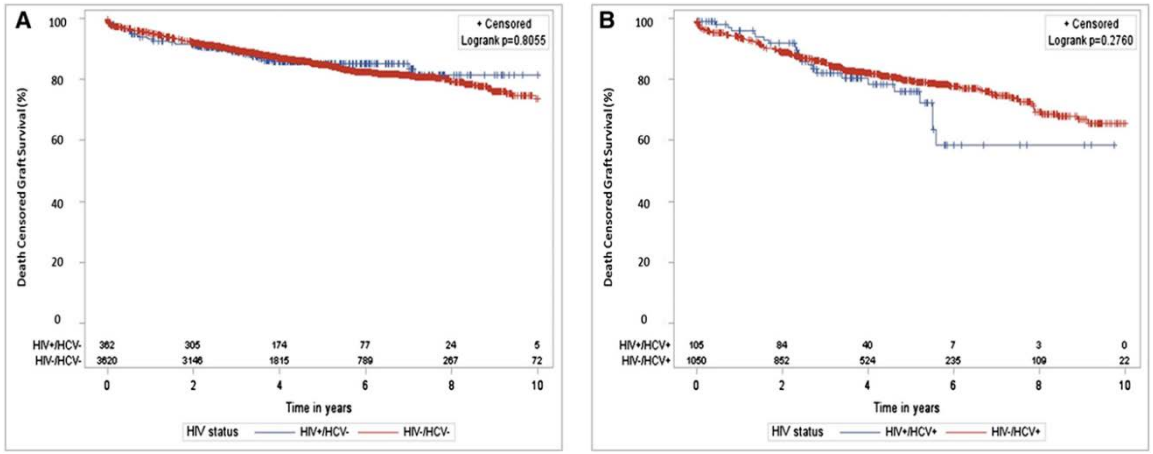
NEJM 2010;363:21

HIV and Kidney Transplant
Conclusions



- Feasible
- Patient and graft survival match those of HIV – transplant recipients
- Results may be influenced by selection biased
  - Very compliant patients
  - Otherwise fairly healthy
- No evidence of acceleration of HIV disease
- **Higher rejection rates** in HIV infected recipients
- Tacrolimus seems preferable to Cyclosporine (less rejection)
- Antithymocyte globulin induction therapy being used more frequently, safely and may reduce HIV burden

HIV and Kidney Transplant
The real world



- HIV mono-infection 5 and 10 year graft survival and patient survival equals or exceeds national registry

J Am Soc Nephrol 26:2015

Why is there a higher rate of rejection with HIV?

- HIV can capture HLA molecules from the host
- The T cell expansion during HIV infection is predominately a Memory T cell phenotype. Which is associated with greater alloimmunity.
- Prior infections may have lead to alloreactive memory T cells.
- Fewer Tregs?
- Drug interactions

NEJM 2010;363:21

HIV and Liver Transplant

- 90% of patients with HIV from parental sources are co-infected with HCV or HBV
- HIV accelerates liver disease with HCV/HBV or no co-infection
- ESLD is #2-3 cause of death in HIV infected people in the US
- ART related liver toxicity

HIV and Liver Transplant

- Historically, 1 year survival rates ranged from 60-100%
- Poorer survival results were associated with:
  - HCV co-infection
  - Intolerance of HIV meds post-transplantation
  - Post-transplant CD4 T cell counts <200 cells/dL
- HCV mono-infected survival rates were similar to HIV/HCV co-infected survival rates.

JID 2003;188:1412

HIV and Liver Transplant
Newer Trials

- Liver transplant outcomes in HIV patients depended upon the underlying liver disease.
- No progression of HIV disease post-transplant
- HCV recurrence post-transplant occurred at equal rates in HIV+ or HIV – recipients, but outcomes worse in HIV/HCV co-infection

Table 3. Patient survival after transplantation in HCV/HIV-coinfected and HCV-monoinfected liver recipients in France [8], Spain [9], and the USA [10].

Country	1 year	2 years	3 years	4 years	5 years	*p* value
France						
HCV/HIV coinfection (N = 44)	-	73%	-	-	51%	0.004
HCV monoinfection (N = 35)	-	91%	-	-	81%	
Spain						
HCV/HIV coinfection (N = 84)	88%	71%	62%	60%	54%	0.008
HCV monoinfection (N = 252)	90%	81%	76%	73%	71%	
United States						
HCV/HIV coinfection (N = 89)	76%	-	60%	-	-	<0.001
HCV monoinfection (N = 235)	92%	-	79%	-	-	

Transplantation 2007;84:563
Journal of Hepatology 2015; 62: 701

HIV/HCV co-infection and Liver Transplant

- Histologic severity of HCV recurrence was similar between HCV and HIV/HCV
- US recommendations in order to avoid increased mortality in HIV/HCV co-infected liver transplant recipients:

Table 4. Predictive factors of mortality in HCV/HIV-coinfected liver recipients in the French, Spanish, and US cohorts [8–10].

	HCV/HIV and HCV liver recipients	Including only the HCV/HIV cohort
French cohort		n.p.
HIV-1 infection	1.91 (0.7-5.18)*	
MELD score (1-unit increase)	1.08 (1.01-1.15)	
Donor age	1.04 (1.00-1.07)	
Spanish cohort		
HIV-1 infection	2.20 (1.42-3.41)	n.a.
HCV genotype 1	2.14 (1.24-3.41)	2.98 (1.32-6.76)
Donor risk index	3.03 (1.57-5.83)	9.48 (2.75-32.73)
Negative plasma HCV RNA viral load**	0.23 (0.10-0.49)	0.14 (0.03-0.62)
US cohort		
HIV-1 infection	2.3 (1.3-3.8)	n.a.
BMI at listing <21		3.2 (1.3-7.7)
Combined kidney-liver transplant		3.8 (1.6-9.1)
Anti-HCV positive donor		2.5 (1.1-5.6)
Donor age (by decade)		1.3 (1.0-1.6)

n.p., analysis not performed; n.a., not applicable; BMI, body mass index.
*Hazard ratio (95% confidence interval).
**RNA HCV clearance with/out anti-HCV therapy before or after liver transplantation.

Transpl Proc 2011;43:1119
Journal of Hepatology 2015; 62: 701

HIV/HCV Liver Transplant

- Life beyond Hepatitis C!:
  - Sofosbuvir/Ledipasvir
  - Viekira Pak- Ombitasvir, Paritaprevir, Ritonavir; Dasabuvir

HIV/HBV co-infection and Liver Transplant

- Preliminary studies show very good outcome in HIV/HBV co-infection and liver transplant
- Excellent, well tolerated oral anti-HBV drugs many of which are treating the HIV as well
- Good results controlling HBV replication post-transplantation

HIV/HBV co-infection and Liver Transplant

Virologic and Clinical Outcomes of Hepatitis B Virus Infection in HIV-HBV Coinfected Transplant Recipients

C. S. Coffin[a,†], P. G. Stock[b], L. M. Dove[c], C. L. Berg[d], N. N. Nissen[e], M. P. Curry[f], M. Ragni[g], F. G. Regenstein[h], K. E. Sherman[i], M. E. Roland[a] and N. A. Terrault[a,b,*]

- 22 HBV/HIV patients 20 HBV patients 3.5 years
- 1 and 3 year graft survival rates were similar
- No patients had had recurrence of HBV

Am J of Transpl 2010;10:1268

HIV/HBV co-infection and Liver Transplant Rejection

Table 4: Acute rejection episodes in HBV-HIV coinfected patients

ID	Time to acute rejection (mos)	IMS at time of acute rejection	Drug level at time of acute rejection	CD4 T-cell count prior to AR (cells/mm^{3})	Treatment given	Outcome
1	1.5	Cyclosporine Mycophenolate mofetil	244 ug/L	86	Pulse steroids (failed), OKT3	Resolved
2	4	Cyclosporine Prednisone	196 ug/L	149	Steroid bolus Increased CSA	Resolved
3	6	Sirolimus Prednisone	4.3 ng/mL	55	Pulse steroids	Resolved
4	18	Cyclosporine Mycophenolate mofetil	200 ug/L	216	Oral steroid taper	Resolved
5	18	Tacrolimus Mycophenolate mofetil	4.8 ng/dL	134	Increased tacrolimus dose (HCV coinfected)	Resolved

- Acute rejection in 5 HIV/HBV patients
- Acute rejection in 1 HBV patient

Am J of Transpl 2010;10:1268

HIV and the Other Organs

- Heart:
  - 1984 -Transplant in Germany Diagnosed with HIV 2.5 years after transplant. No AIDS after 6 years.
  - 1985, 1987 –transplants in Italy and developed HIV during surgery from blood. Both developed AIDS and died by 1 year.

  - Post- HAART- over 30 patients transplanted in the US:
    - Undetectable HIV vl
    - CD4 T cell >200 cells/dL
    - Outcomes comparable to HIV- Heart transplant recipients- **higher levels of rejection**.

J Heart and Lung Transplant 2011;epub

J Heart Lung Transplant 2009;28: 667–669

HIV and the Other Organs

- HIV and Lung transplant –
  - 2 patients with Cystic Fibrosis- doing well 4 and 5 years out
  - 1 patient with HIV-associated pulmonary arterial hypertension- recalcitrant acute rejection requiring a lymphocyte-depleting agent with subsequent rapid development of bronchiolitis obliterans syndrome.
  - 2 patients with idiopathic pulmonary fibrosis- mild acute rejection but remain free from chronic rejection at 4 and 2 years after transplant

- HIV and kidney/Pancrease transplants

Am J Transplant 2009; 9:2190–2196
Ann Am Thorac Soc 2014;11(6):882-9

Challenges: Drug-Drug Interactions

Keep in mind:

- HIV Protease Inhibitors- slower metabolism of calcineurin inhibitors and Sirolimus
- Efavirenz- accelerates the metabolism of calcineurin inhibitors
- Drug levels must be monitored closely

Don’ts:

- AZT- Anemia
- Atazanavir- diminished absorption with gastric acid suppression. Causes hyperbilirubinemia
- ddI-pancreatitis “don’t do it”

HIV Positive Donors

- National Organ Transplant Act was amended in 1988 to exclude HIV + organs
- Over 100 HIV+ patients are now on the waiting list for organ transplantation. Could these organs be used in the post-cART era?
- HIV superinfections??
- December 2013 **HIV Organ Policy Equity (HOPE) Act** was signed by President Obama to allow research into organ donation from deceased donors with HIV to recipients with HIV.