

# HEPATITIS COINFECTIONS

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# Disclosures

## (Activity w/i 12 months)

- Research Support (to institution):
  - Roche, Schering, SciClone, Vertex, GSK, HGS, Gilead, BMS
- Advisory Board/Consultation:
  - BMS, SciClone, Vertex, Merck, Valeant, Anadys
  - DSMB- Tibotec
  - End Point Adjudication- Pfizer

# Learning Objectives

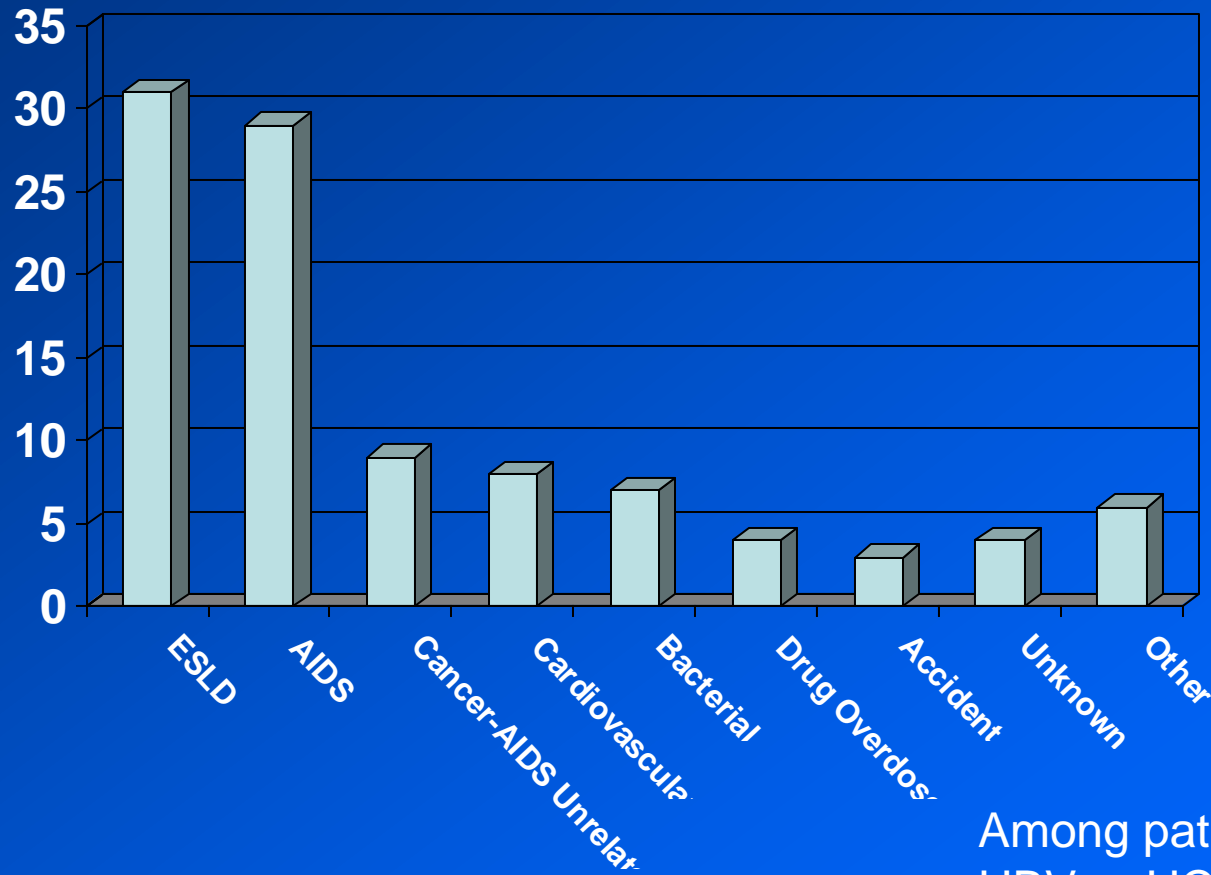
- Upon completion of this activity you will be able to:
  - Recognize the need for screening and managing of viral hepatitis in those with HIV in your practice.
  - Develop a management plan for HBV/HIV coinfection in your practice.
- This presentation will include the discussion of off-label uses.

# WHY DISCUSS HCV/HIV COINFECTION?

- People living with HIV are increasing in number
- Liver disease is an IMPORTANT outcome that ID caregivers are often ill-prepared to evaluate and manage
- Gastroenterologists are frequently uncomfortable with HIV management and with HIV-infected patients

# Causes of Death in Coinfection

French Mortality 2000 Cohort



Among patient with markers of  
HBV or HCV infection

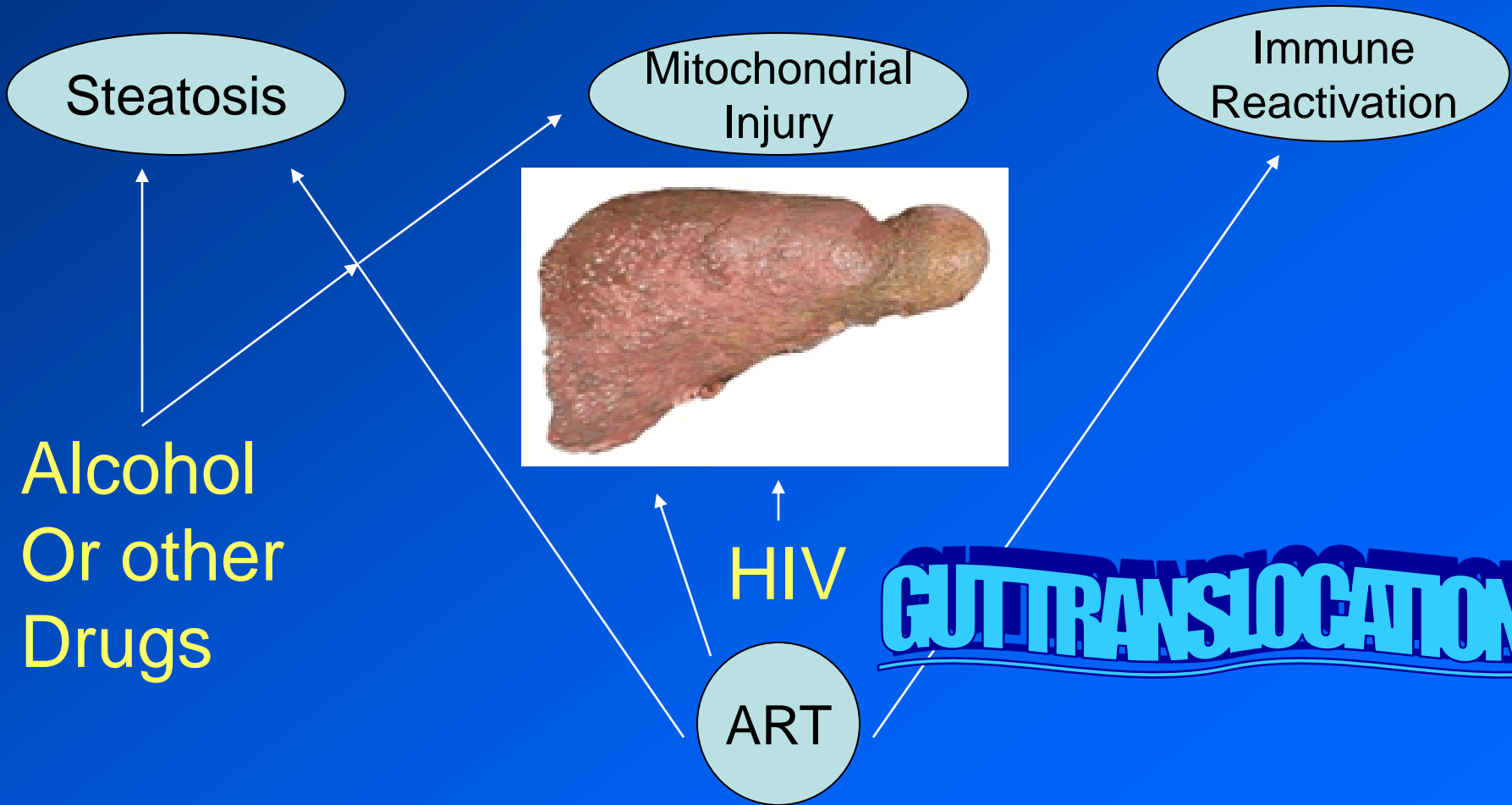
# HCV/HIV

## Effect on Health Utilization in A5001

	<b>HCV/HIV rate* (95%CI)</b>	<b>HIV rate* (95%CI)</b>	<b>Adjusted rate ratio (95%CI)</b>
<b>Nights in hospital</b>	14.2 (13.4– 14.9)	5.8 (5.6– 5.9)	2.5 (1.7–3.6)
<b>Emergency department visits</b>	6.3 (5.8–6.8)	3.4 (3.2– 3.5)	1.5 (1.2–2.0)
<b>Disability days</b>	112.5 (110.3– 114.7)	67.6 (67.0– 68.2)	1.6 (1.2–2.2)

# ETIOLOGIES OF LIVER INJURY

## HCV or HBV



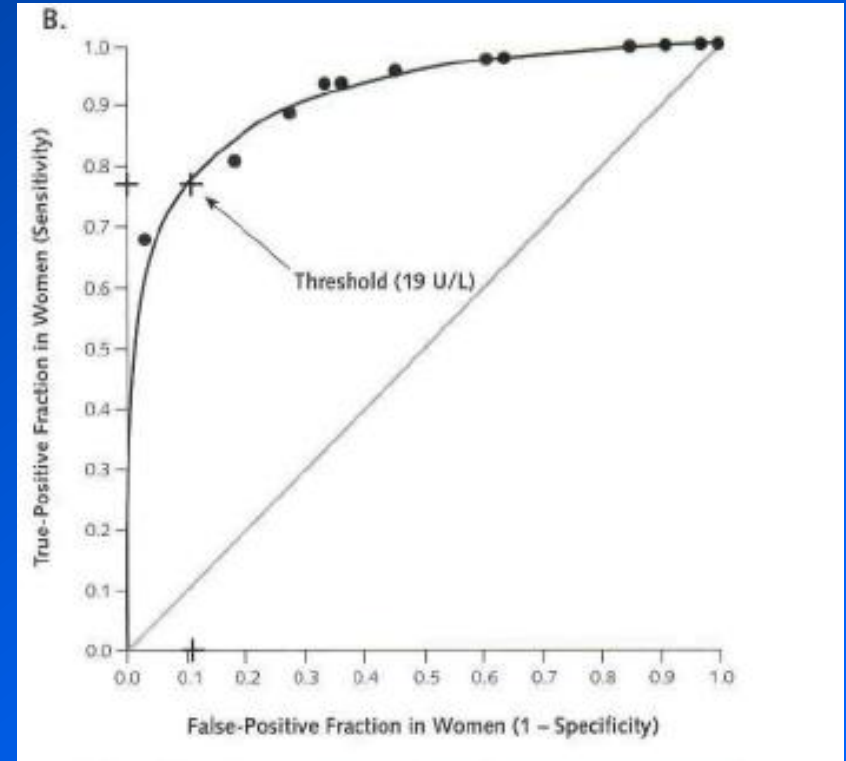
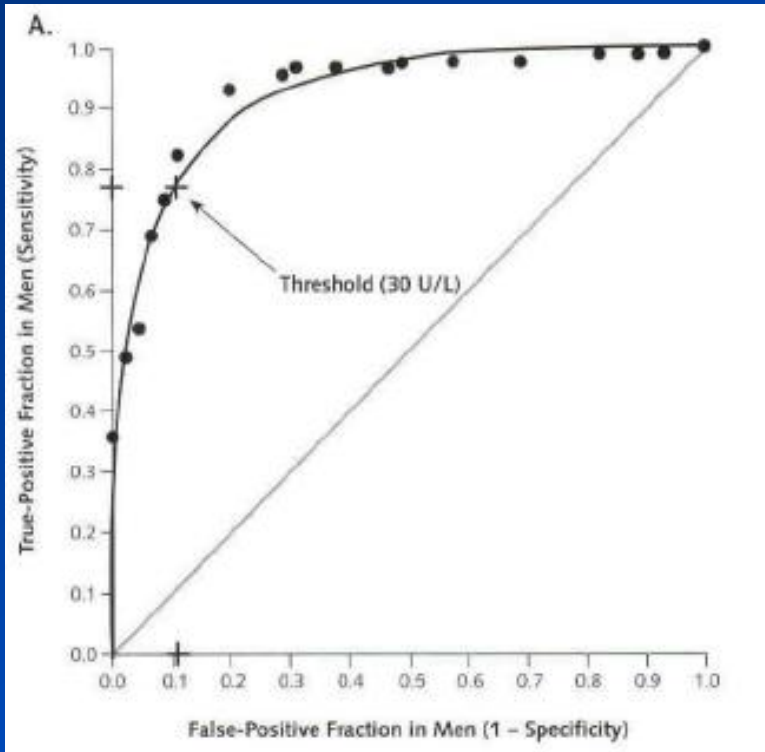
# WHO SHOULD BE TESTED?

HIV-infected patients should be tested routinely for evidence of chronic HCV infection

Initial testing for HCV should be performed using the most sensitive immunoassays licensed for detection of antibody to HCV (anti-HCV)

USPHS GUIDELINES, MMWR, 2009

# Updated ALT Ranges

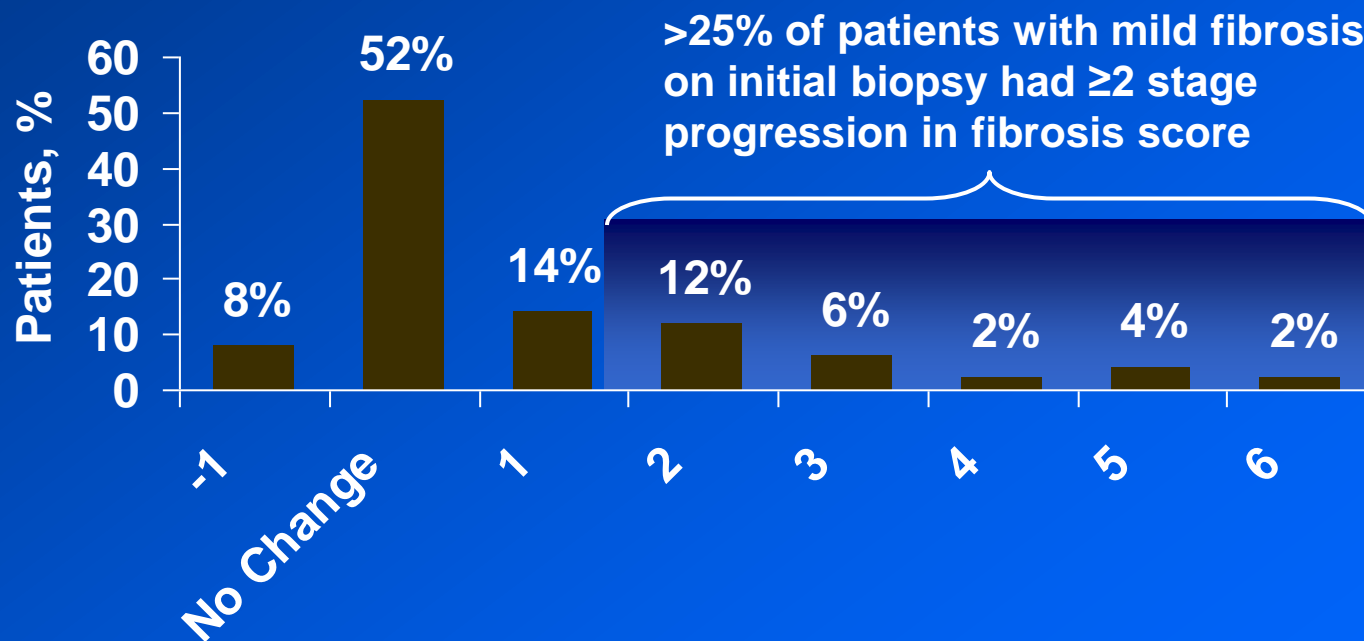


Newly calculated healthy limits are indicated in each panel. A) Male participants. B) Female participants. To convert the alanine aminotransferase thresholds to nkat/L, multiply by 16,667.

# Rapid Progression of Liver Disease in HIV/HCV-Coinfected Patients

- Prospective study of fibrosis progression in 67 coinfecting patients
- 2 biopsies; median time between biopsies was 2.84 years

## Patients With Mild Fibrosis ( $\leq F1$ ) on First Biopsy



## Change in Ishak Score From First to Second Biopsy

# TREATMENT & MANAGEMENT PRINCIPLES

# HCV TREATMENT

## Standard of Care 2010

Confirm HCV Present  
Determine VL and Genotype  
Evaluate Histology  
Evaluate Contraindications to Rx

### Genotype 1 or 4

Peg IFN alfa 2a or 2b +  
Ribavirin for 48 wks



EVR Evaluation → Early d/c



SVR  
40-45%



### Genotype 2 or 3

Peg IFN alfa 2a or 2b + ribavirin  
800 mg/qd for 24 wks

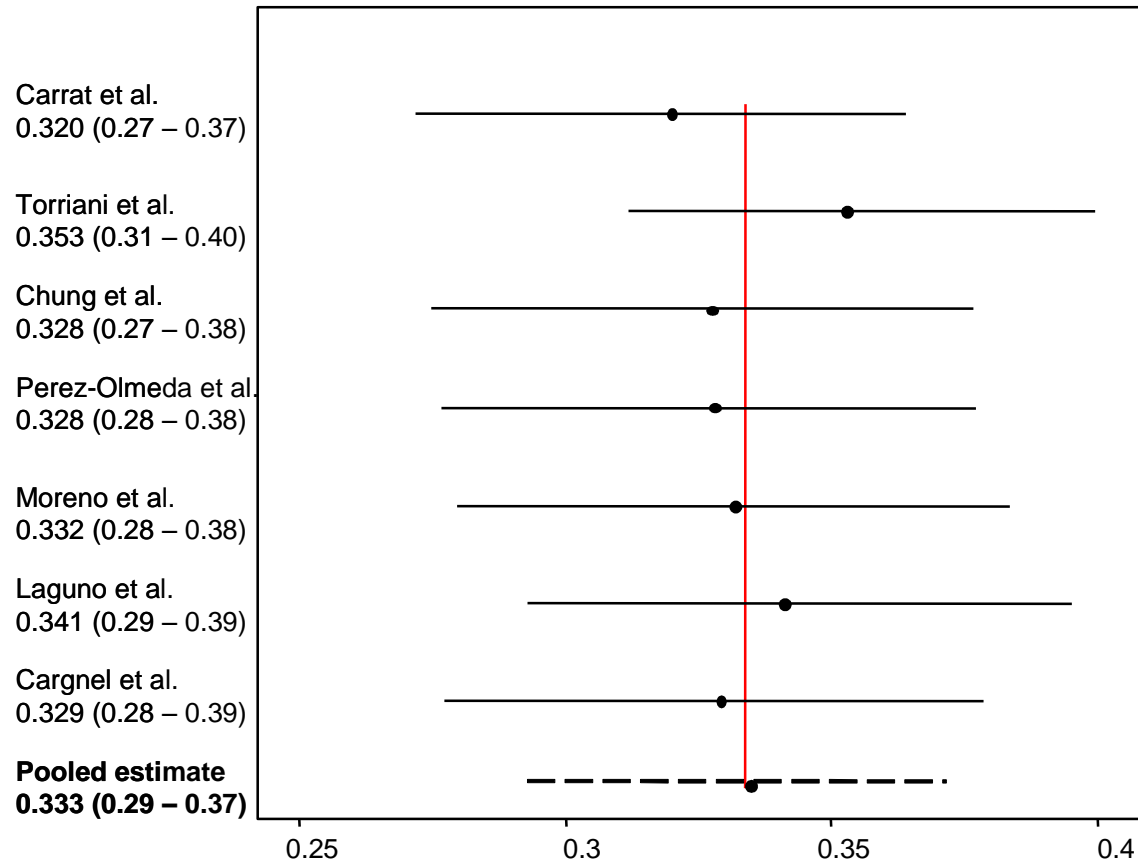


SVR  
70-85%%



Pooled SVR  
50-55%

# PEG-IFN + RIBAVIRIN Metanalysis for SVR



# TREATMENT RECOMMENDATIONS in HIV

- PegIFN + Ribavirin is the recommended treatment (A1)
  - Genotype 1 SVR 14-29%
  - Genotype 2, 3 SVR 43-73%
- Many experts recommend weight-based ribavirin (A2) despite PARADIGM trial
- 48 Weeks of Therapy in All Patients (A1)
- Acute HCV should be treated with same regimen for >24 weeks (B3)

# Issues Limiting Treatment of HCV

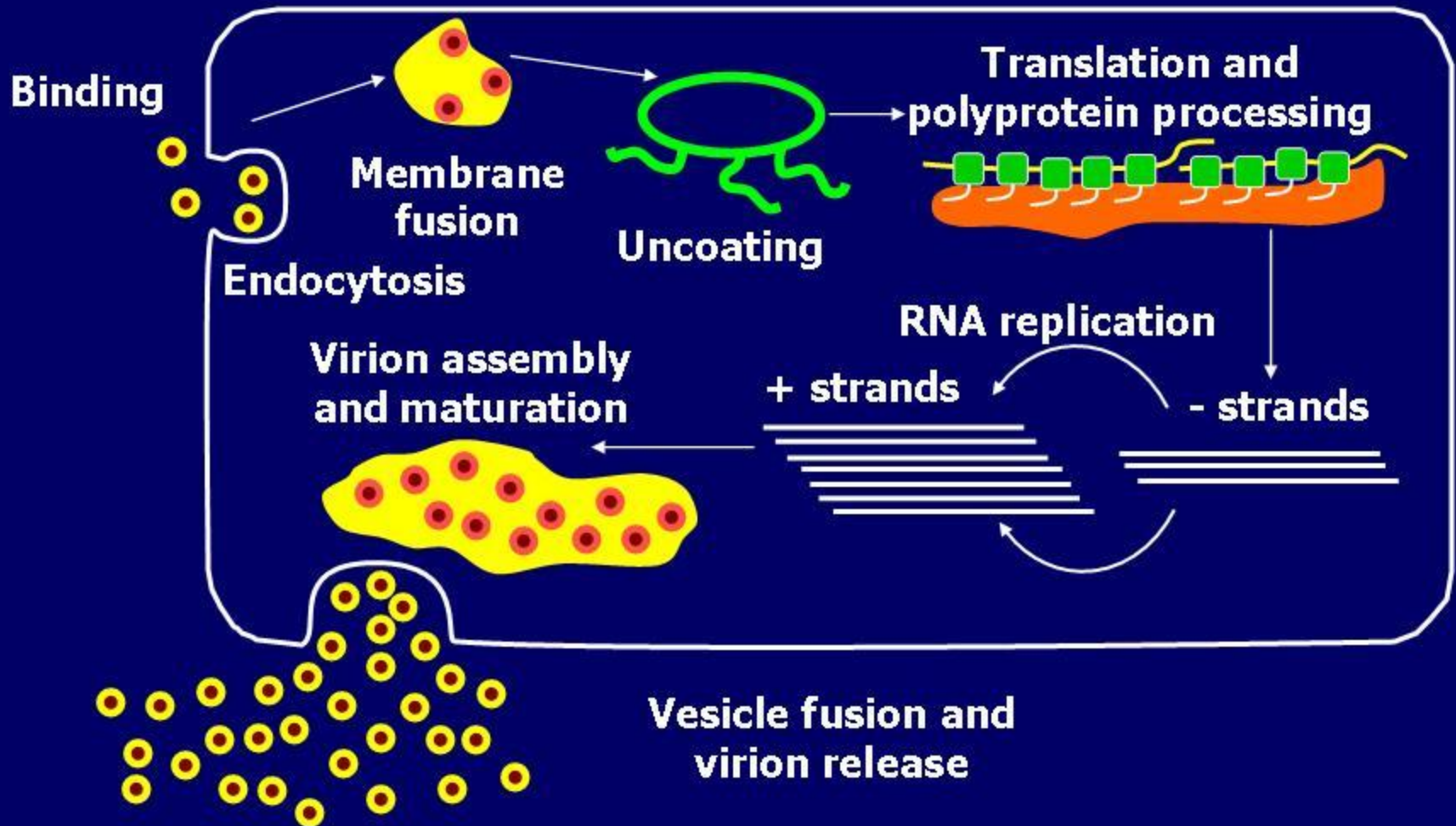
- Inexperience using agents
- Liver Disease too Advanced
- Psychiatric complications
- Anemia
- Neutropenia
- Weight loss
- Drug Interactions

# NEW TREATMENTS FOR HCV

# FDA ANTIVIRAL ADVISORY COMMITTEE OCTOBER 2006

- Superiority should be required for first approval of small molecules
- Combination small molecule trials may be appropriate after Phase 2b evaluation of individual agents
- Prior to NDA studies must be initiated in special populations
  - HCV/HIV coinfection
  - Decompensated Liver Disease
  - Pediatric populations
- Appropriate representation of high prevalence minority groups is essential

# HCV Life Cycle

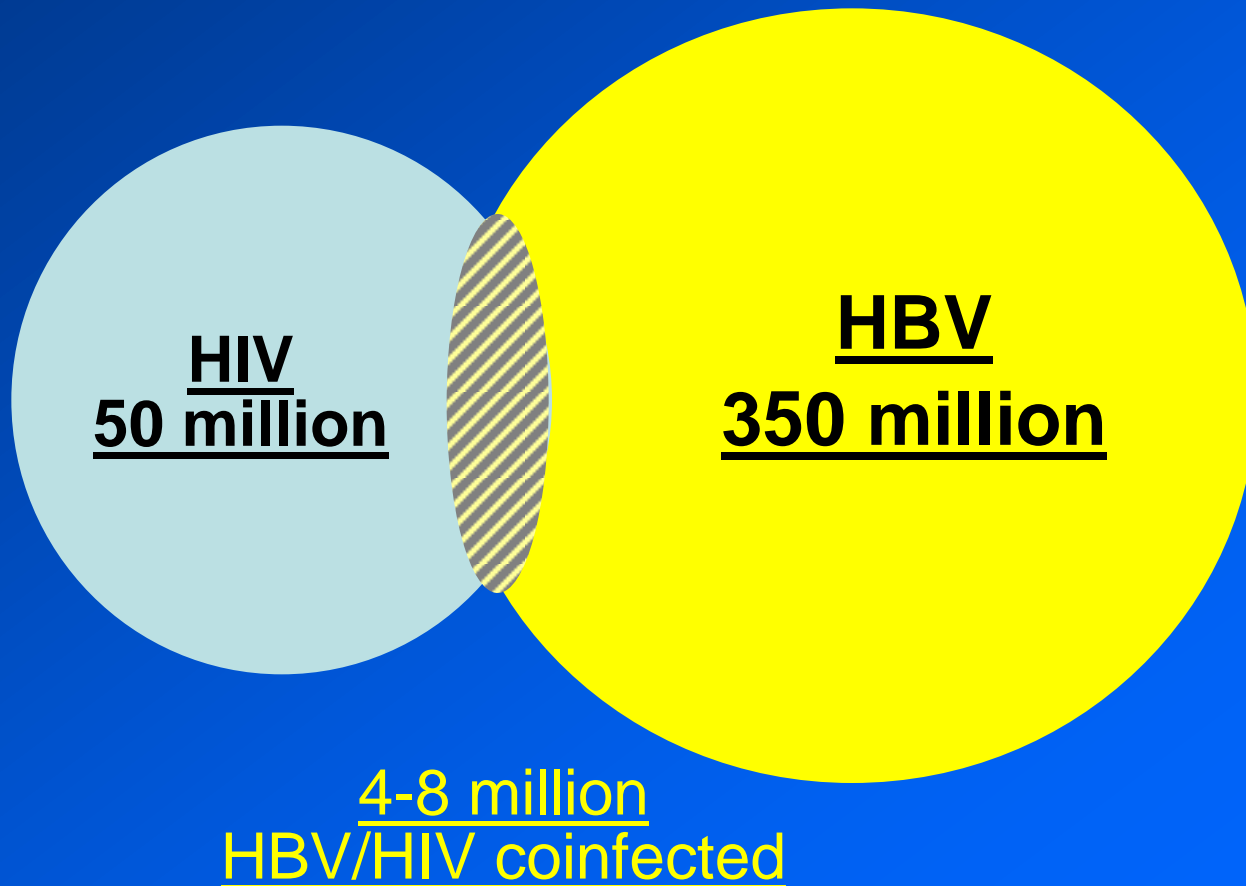


# SUMMARY OF NEW TREATMENTS

- Many targets for directed HCV therapy are available
- Some agents show promise, but development is slow and should not delay treatment in individual patients now
  - New Agent Approval- ?2011
- Expect need for Pegylated Interferon and ribavirin for the foreseeable future

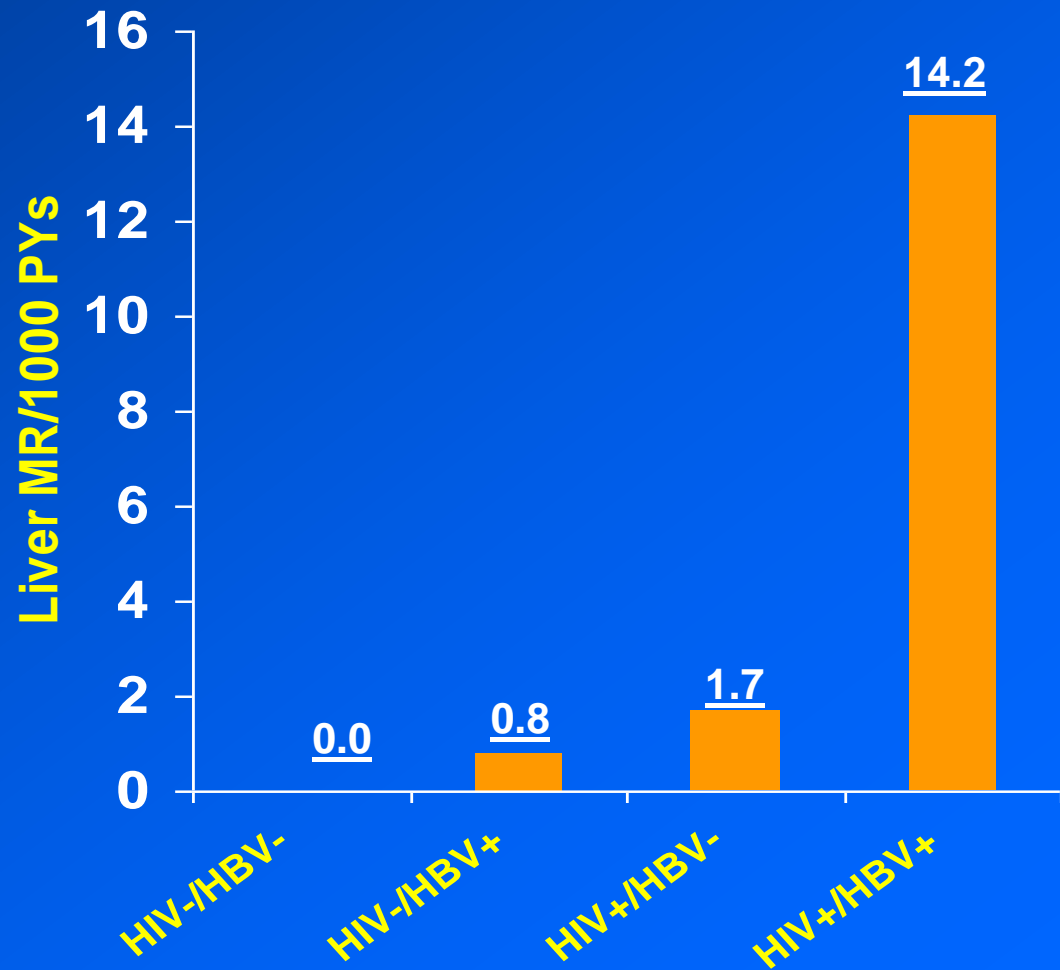
# HBV/HIV Disease Burden

## Worldwide Prevalence of Chronic Hepatitis B and HIV



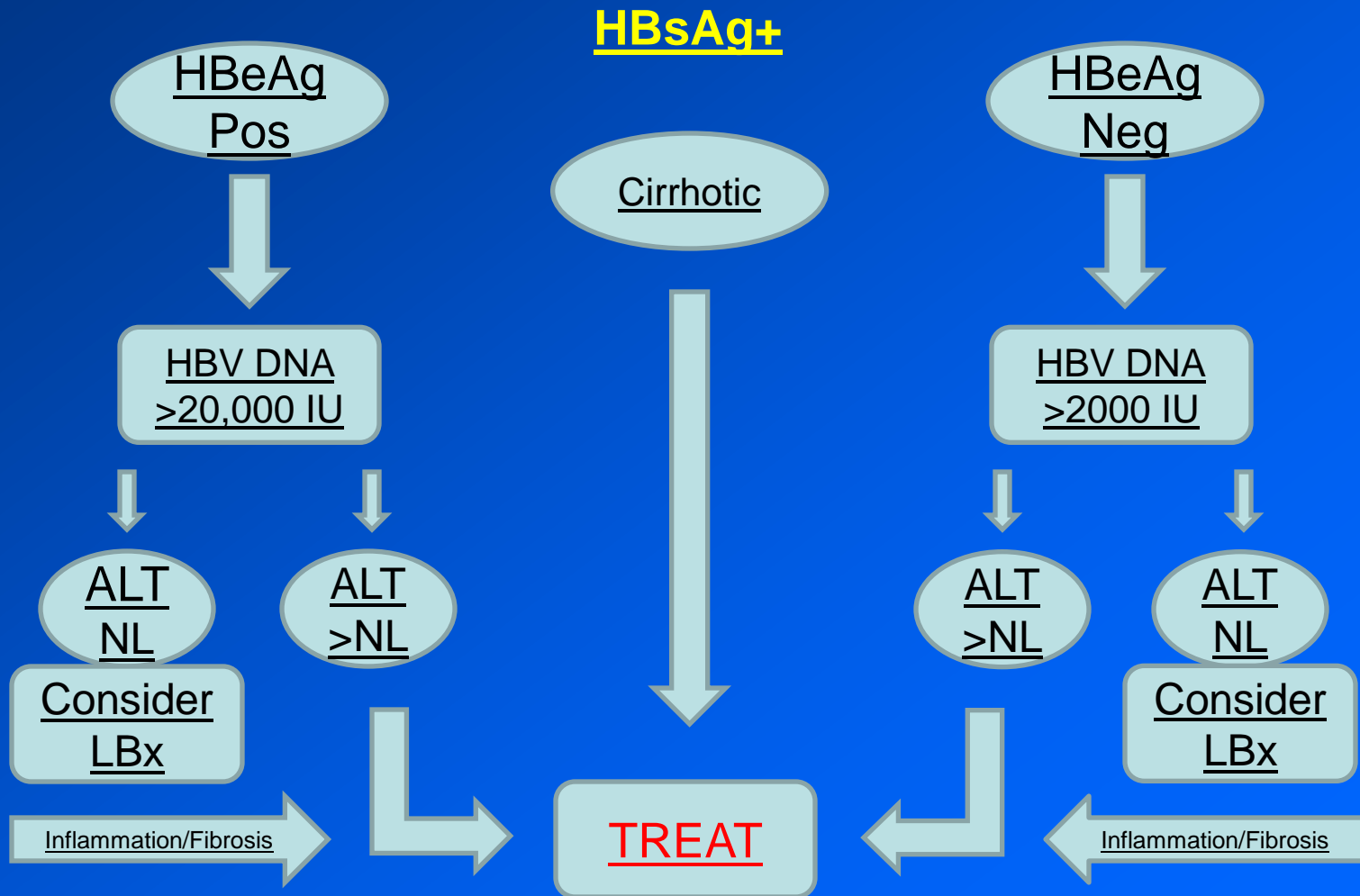
# Increased Liver Mortality in HIV/HBV Coinfected Men: MACS

- 5293 men (326 HBsAg+ baseline)  
followed 10.5  
years



# HBV/HIV: Deciding Who to Treat

Guidelines for Prevention and Treatment of Opportunistic Infections  
in HIV-Infected Adults and Adolescents; MMWR 2009



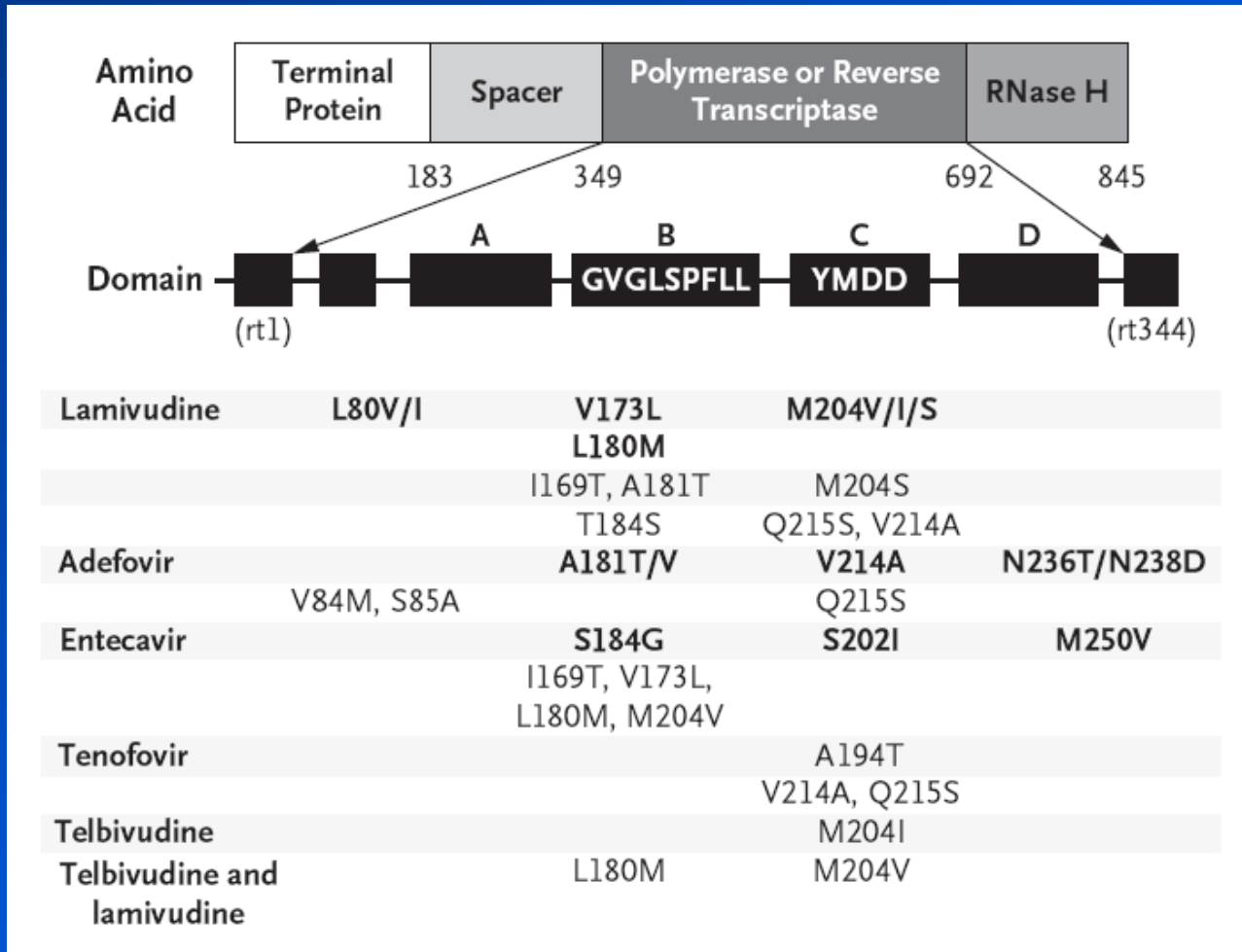
# Agent Comparison

AGENT	EFFICACY	RESISTANCE	COST
Lamivudine	+++	+++++	+
Adefovir	++	++	+++
Entecavir	+++++	++	+++
Telbivudine	+++++	++	+++
Tenofovir	+++++	+	+++
PegIFN	+++++	+	++

# HBV Mutation

- Arises due to the relatively low fidelity of the HBV polymerase
- Mutation rate of approximately  $3 \times 10^{-4}$   
(Park et al., *Eur J Biochem*, 2004)
- 10-fold higher than most DNA viruses

# HBV Polymerase Key Mutations



# Consequences of Sequential MonoTherapy

- Flares in Infected Individuals
- Development of Multidrug Resistant HBV
- Transmission of Resistant Virus
- Development of Compensatory Mutations Affecting Vaccine and Adaptive Immunity

# Co-Inhibition of HIV

AGENT	STRONG	WEAK
Lamivudine	X	
Tenofovir	X	
Tenofovir/ Emtricitibine	X	
Emtricitibine	X	
Adefovir		X
Entecavir		X
Telbivudine		?
PegIFN		X

# Conserved Pol Domains HIV and HBV



# PUBLIC HEALTH CONCERNS

- Sequential therapy for HBV has the potential to lead to widespread multidrug resistance with clinical and public health consequences
- Under certain conditions, all NA HBV agents MAY inhibit HIV replication and permit selection of HIV drug resistant populations

# HBV/HIV Conclusions

- All patients with HIV should be screened for HBV and evaluated for treatment candidacy
- Treatment goal is complete suppression of HBV viral replication
- To prevent development widespread multidrug resistance, two agents with non-overlapping HBV resistance profiles should be considered whenever possible
- In patients with existing drug resistance, addition of a new agent with a different resistance profile rather than sequential therapy is preferred
- Careful evaluation of ART in the setting of HBV is indicated in both initial and subsequent patient encounters
- In most circumstances, the decision to treat HBV should be linked with the decision to treat HIV

...and miles to go before we sleep.

paraphrased from Robert Frost- 1923