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/Consulation:
  - BMS, SciClone, Vertex, Merck, Valeant, Anadys
  - DSMB- Tibotec
  - End Point Adjudication- Pfizer

Learning Objectives

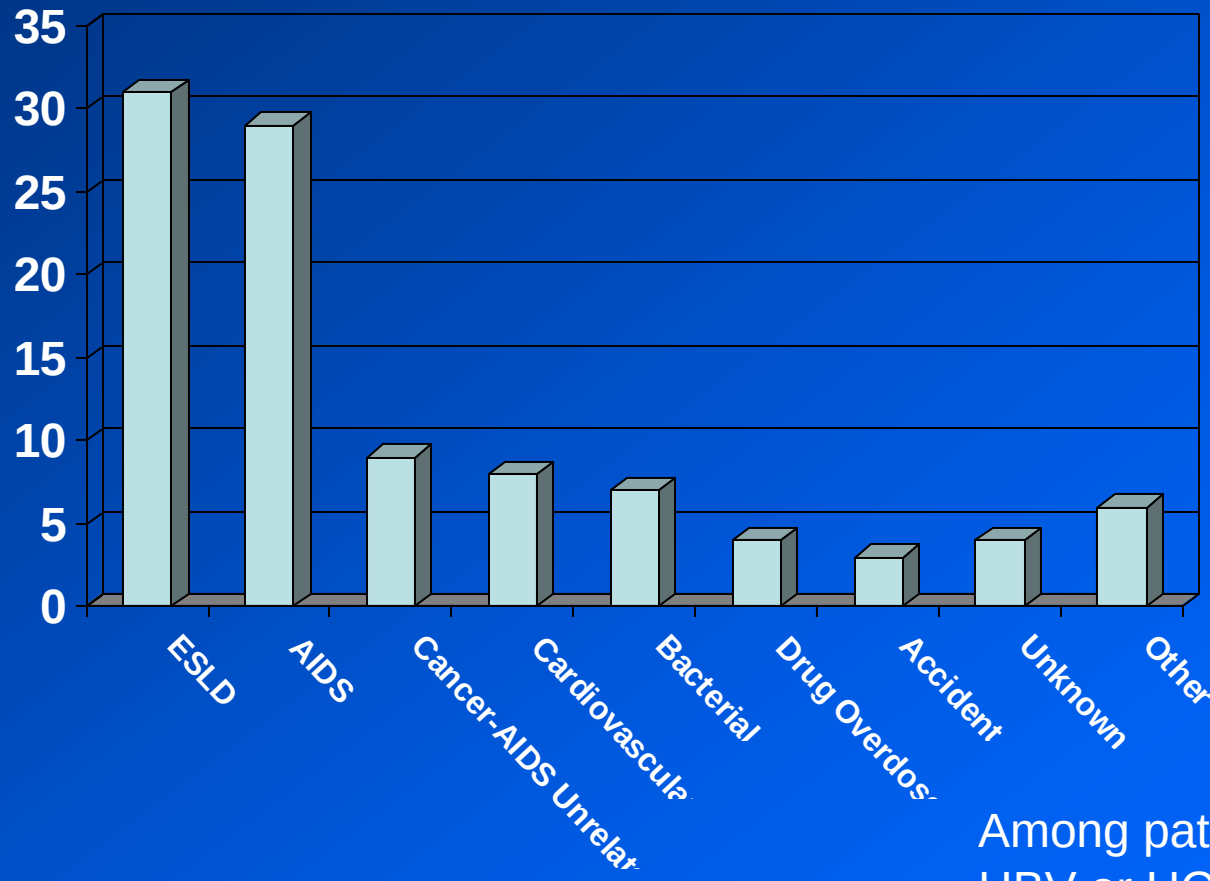
- Upon completion of this activity you will be able to:
  - Recognize the need for screening and managing of viral hepatitis in those with HIV in your practice.
  - Develop a management plan for HBV/HIV coinfection in your practice.
- This presentation will include the discussion of off-label uses.

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

Salmon-Ceron et al., J HEPATOL 2005

HCV/HIV

Effect on Health Utilization in A5001

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

Linus et. al. CROI 2009 Oral #102

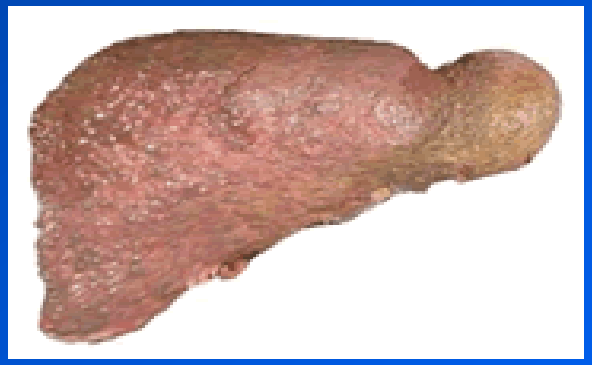
ETIOLOGIES OF LIVER INJURY

HCV or HBV

Steatosis

Mitochondrial Injury

Immune Reactivation



Alcohol
Or other
Drugs

HIV

ART

GUT TRANSLOCATION?

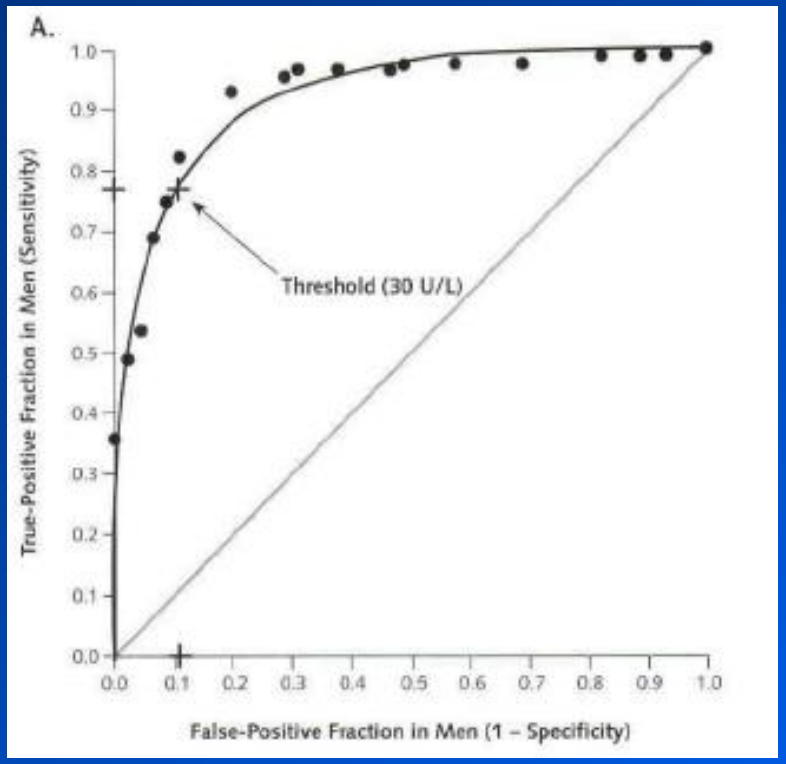
WHO SHOULD BE TESTED?

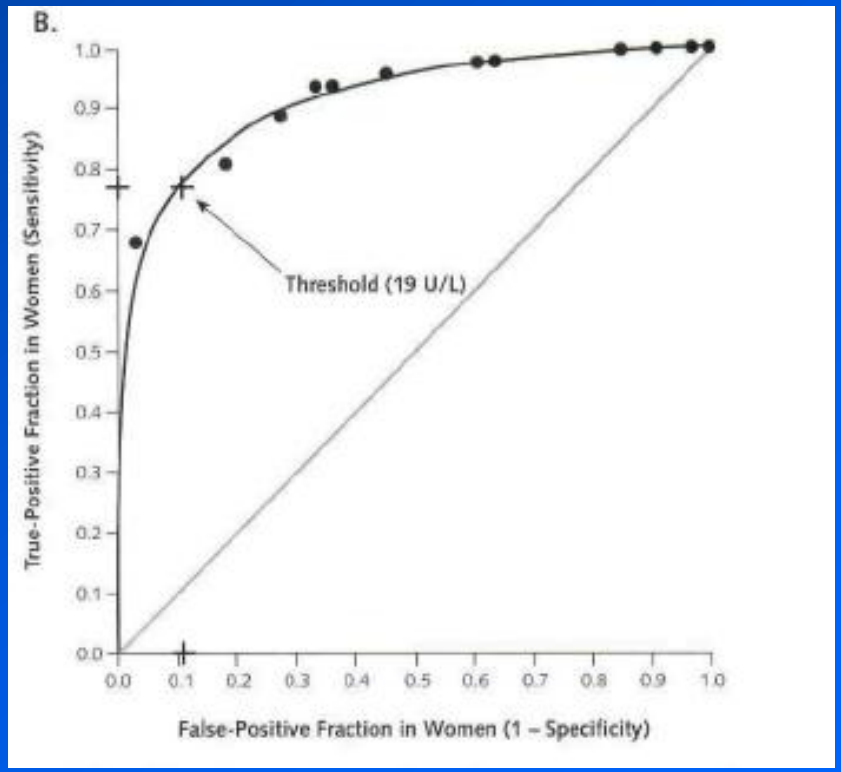
HIV-infected patients should be tested routinely for evidence of chronic HCV infection

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





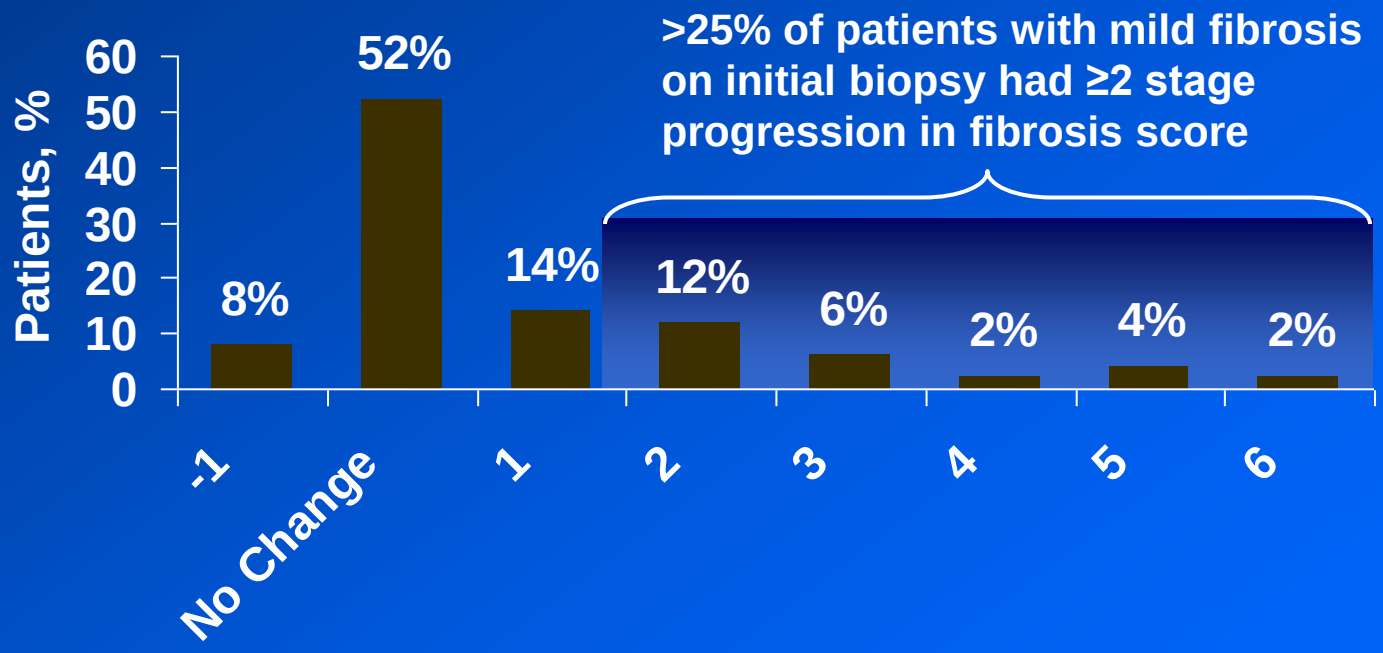
Newly calculated healthy limits are indicated in each panel. A) Male participants. B) Female participants. To convert the alanine aminotransferase thresholds to nkat/L, multiply by 16,667.

Prati, et al. 2002, Ann of Int Med

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

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

Patients With Mild Fibrosis (≤F1) on First Biopsy



Change in Ishak Score From First to Second Biopsy

Sulkowski M et al. AIDS, 2007

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%

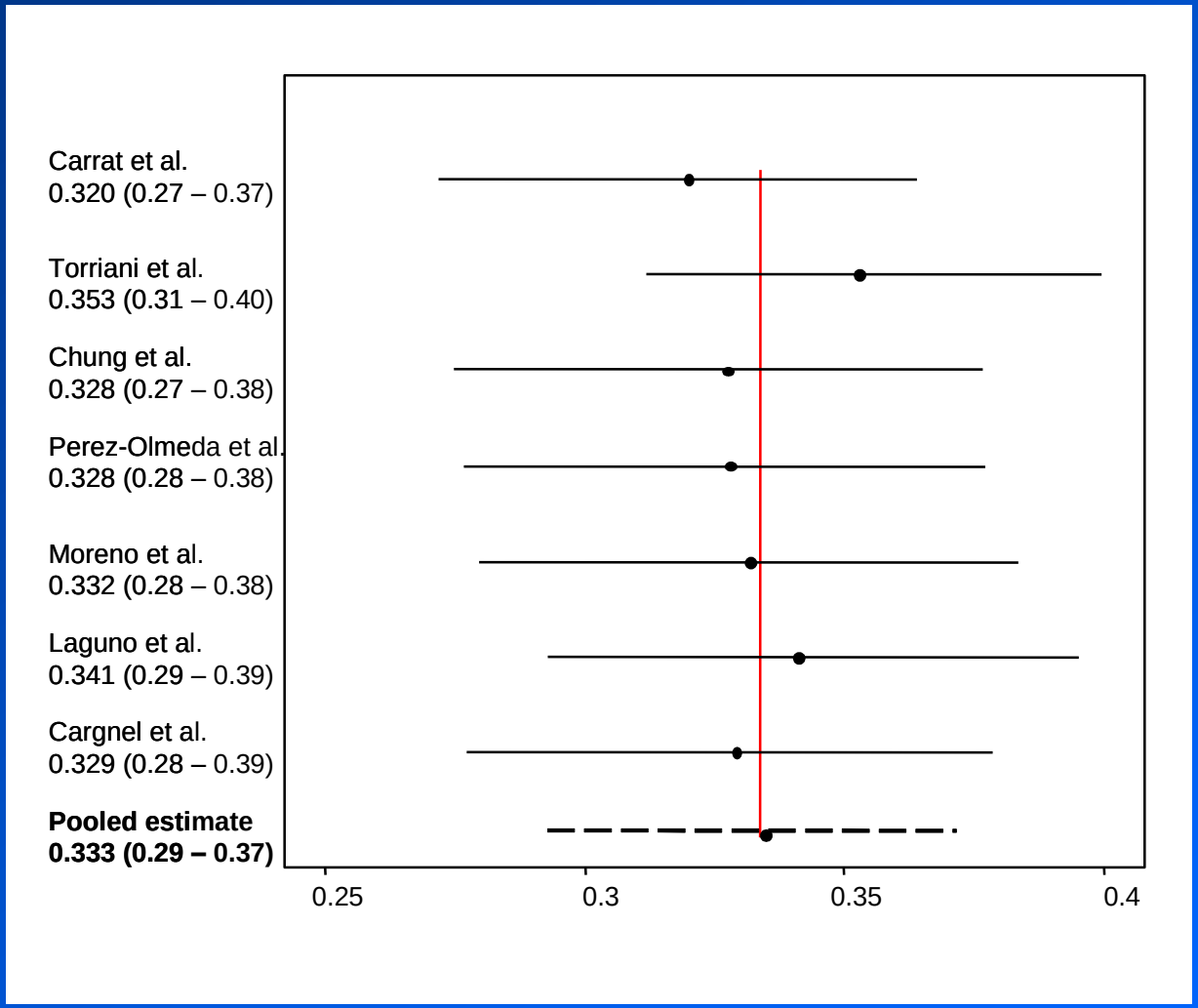
Genotype 2 or 3

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



Shire et. al., J VIRAL HEP, 2007

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)

USPHS GUIDELINES, MMWR, 2009

Issues Limiting Treatment of HCV

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

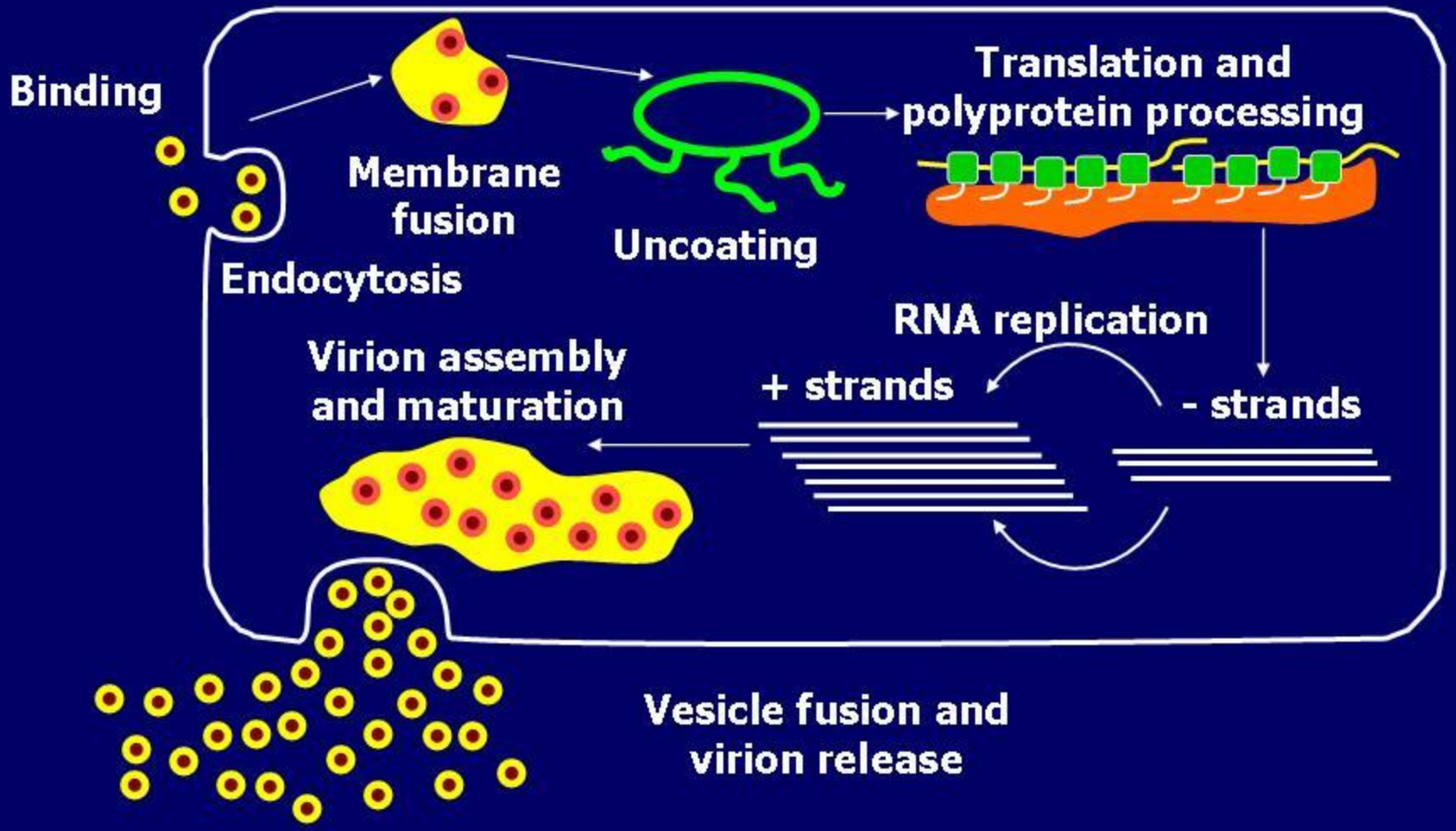
NEW TREATMENTS FOR HCV

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

Sherman et. al, HEPATOLOGY, 2007

HCV Life Cycle



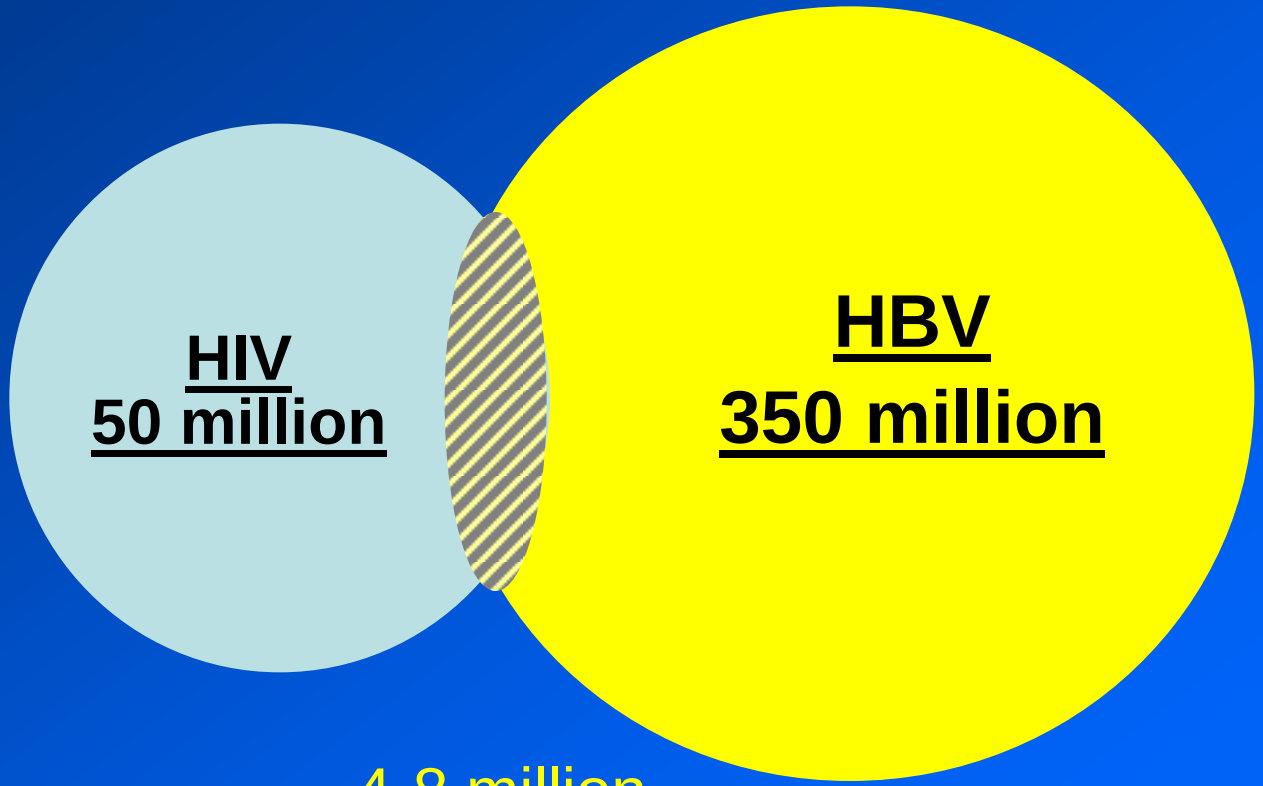
Davis G et al. *Semin Liver Dis.* 1999(suppl 1):103-112.

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

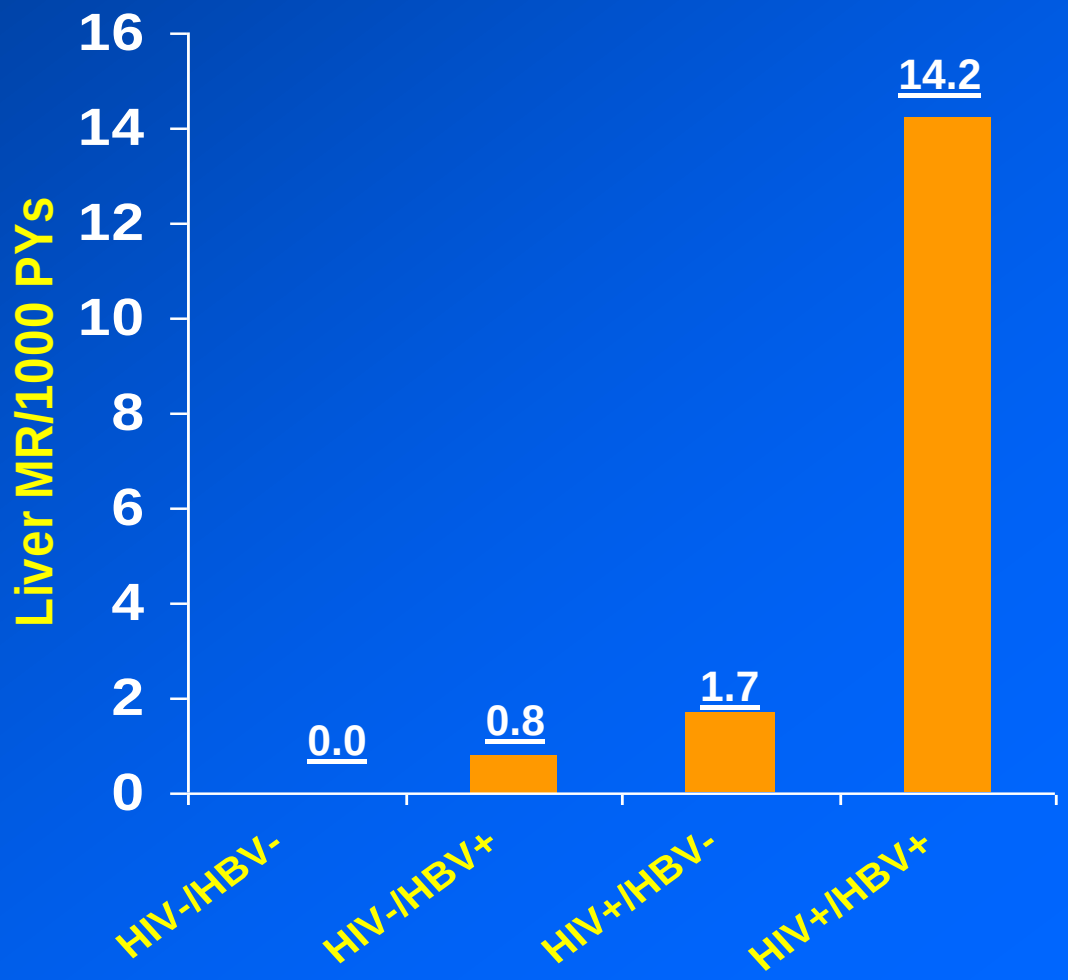
Worldwide Prevalence of Chronic Hepatitis B and HIV



4-8 million
HBV/HIV coinfected

Increased Liver Mortality in HIV/HBV Coinfected Men: MACS

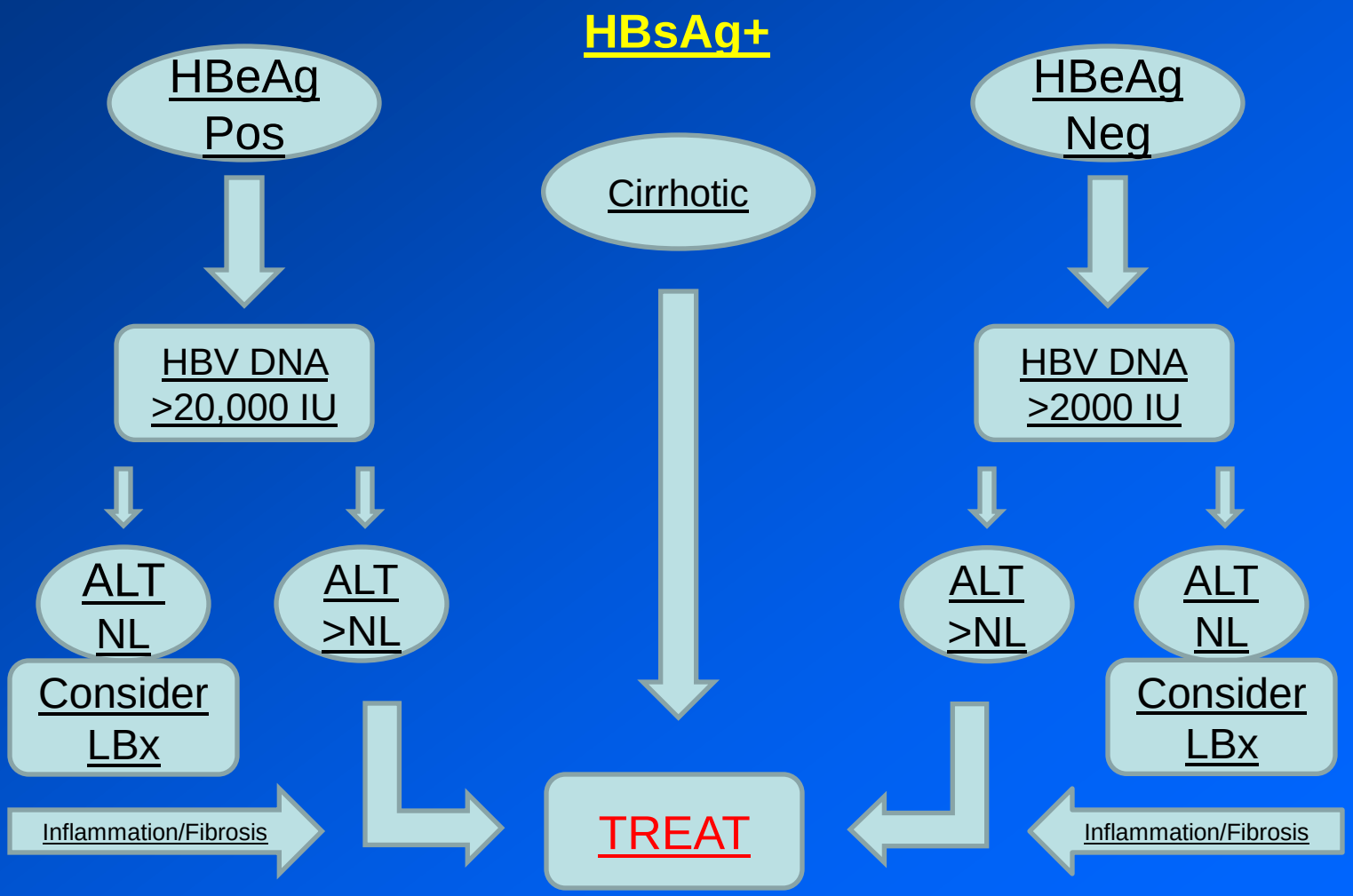
- 5293 men (326 HBsAg+ baseline) followed 10.5 years



Thio C et al. *Lancet.* 2002;360:1921-26.

HBV/HIV: Deciding Who to Treat

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



Agent Comparison

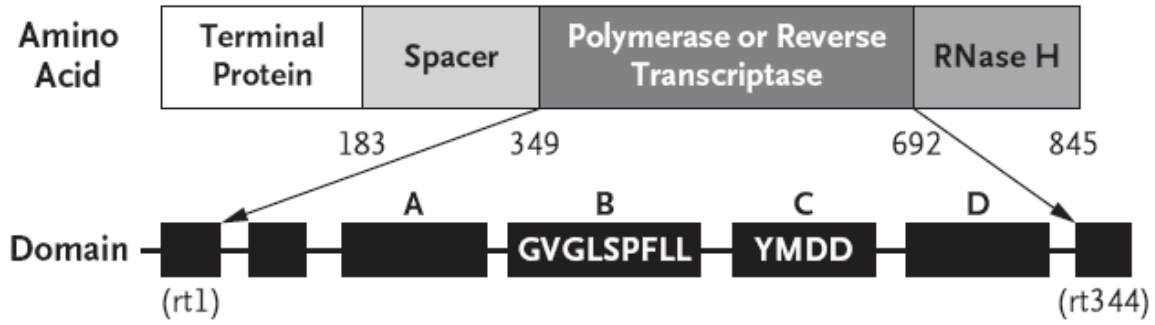
AGENT	EFFICACY	RESISTANCE	COST
Lamivudine	+++	++++	+
Adefovir	++	++	+++
Entecavir	++++	++	+++
Telbivudine	++++	++	+++
Tenofovir	++++	+	+++
PegIFN	++++	+	++

Level A/B

HBV Mutation

- Arises due to the relatively low fidelity of the HBV polymerase
- Mutation rate of approximately $3x10^{-4}$
  (Park et al., *Eur J Biochem*, 2004)
- 10-fold higher than most DNA viruses

HBV Polymerase Key Mutations



Lamivudine	**L80V/I**	**V173L**	**M204V/I/S**	
		L180M		
		I169T, A181T	M204S	
		T184S	Q215S, V214A	
Adefovir		**A181T/V**	**V214A**	**N236T/N238D**
	V84M, S85A		Q215S	
Entecavir		**S184G**	**S202I**	**M250V**
		I169T, V173L, L180M, M204V		
Tenofovir			A194T	
			V214A, Q215S	
Telbivudine			M204I	
Telbivudine and lamivudine		L180M	M204V	

Koziel and Peters, *NEJM*, 2007

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

Level A/B

Conserved Pol Domains HIV and HBV

Bartholomeusz et al., *Antiviral Therapy*, 2004

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