Hepatitis B, C, and Beyond

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HCV/HIV Coinfection

- When?
- With what?
- What next?

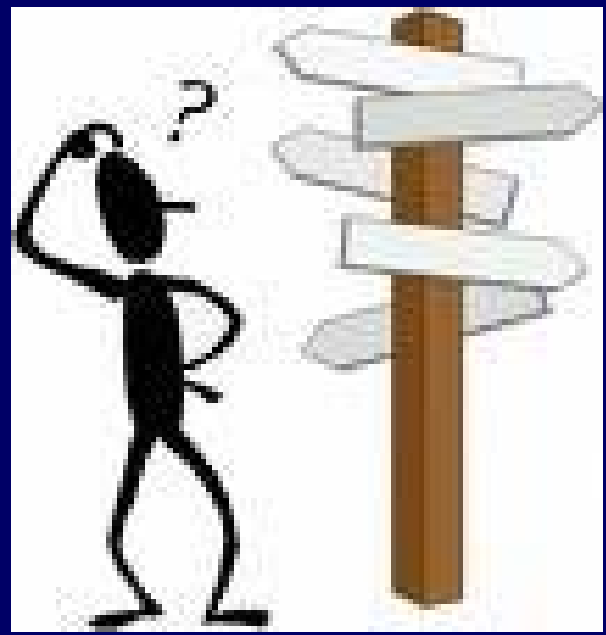
Case #1

- 45 yo W man w/ B2 HIV, CD4 count 390, HIV load 100,000 copies/ml
- HCV+, GT 1a, HCV RNA 3 million IU/ml
- ALT 67 U/L, normal synthetic function
- PTSD, depression, 20 yr h/o IDU, clean for 6 months

What to treat first?

HIV?

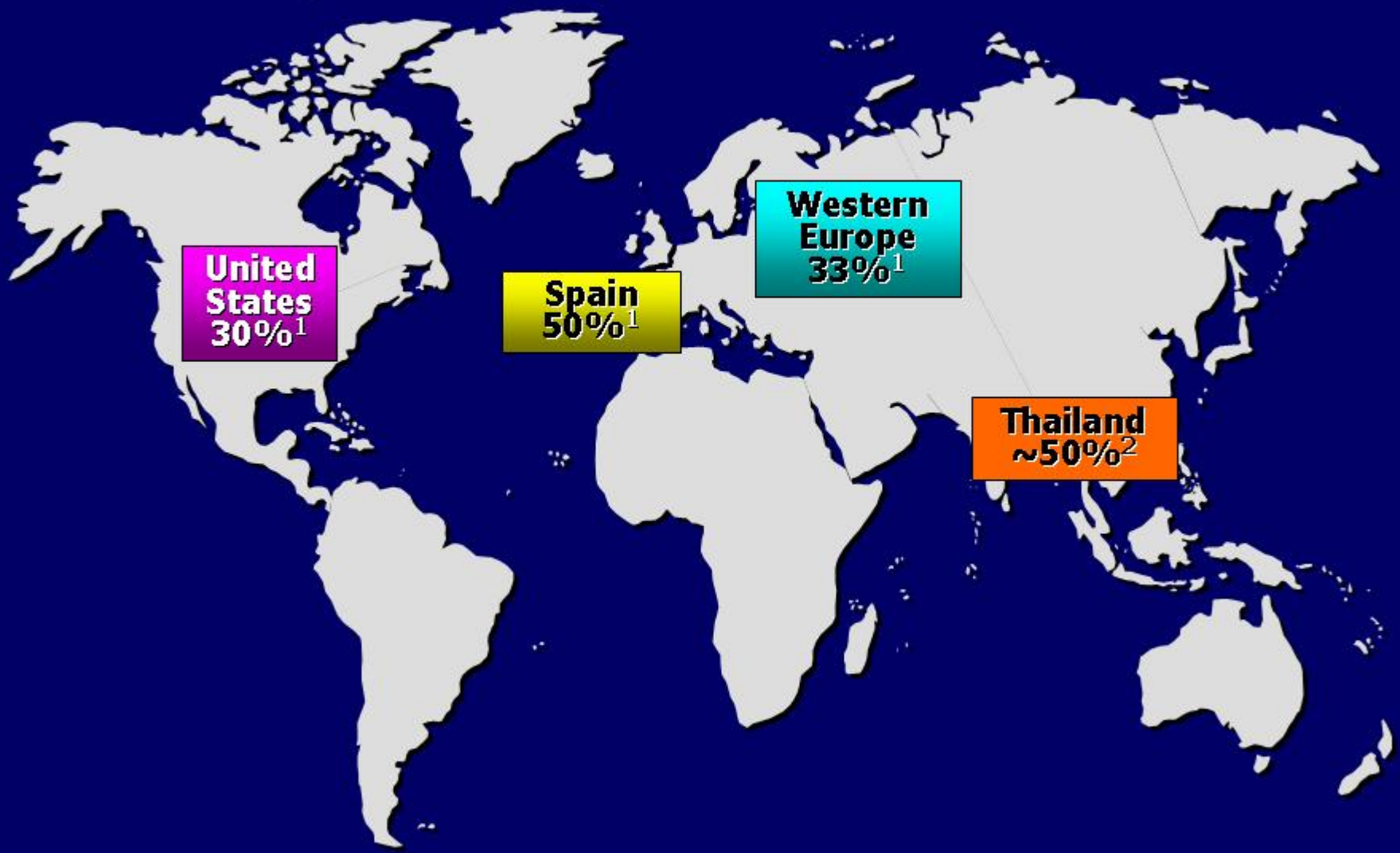
Or HCV?



Why is HCV such a concern in HIV+ patients?

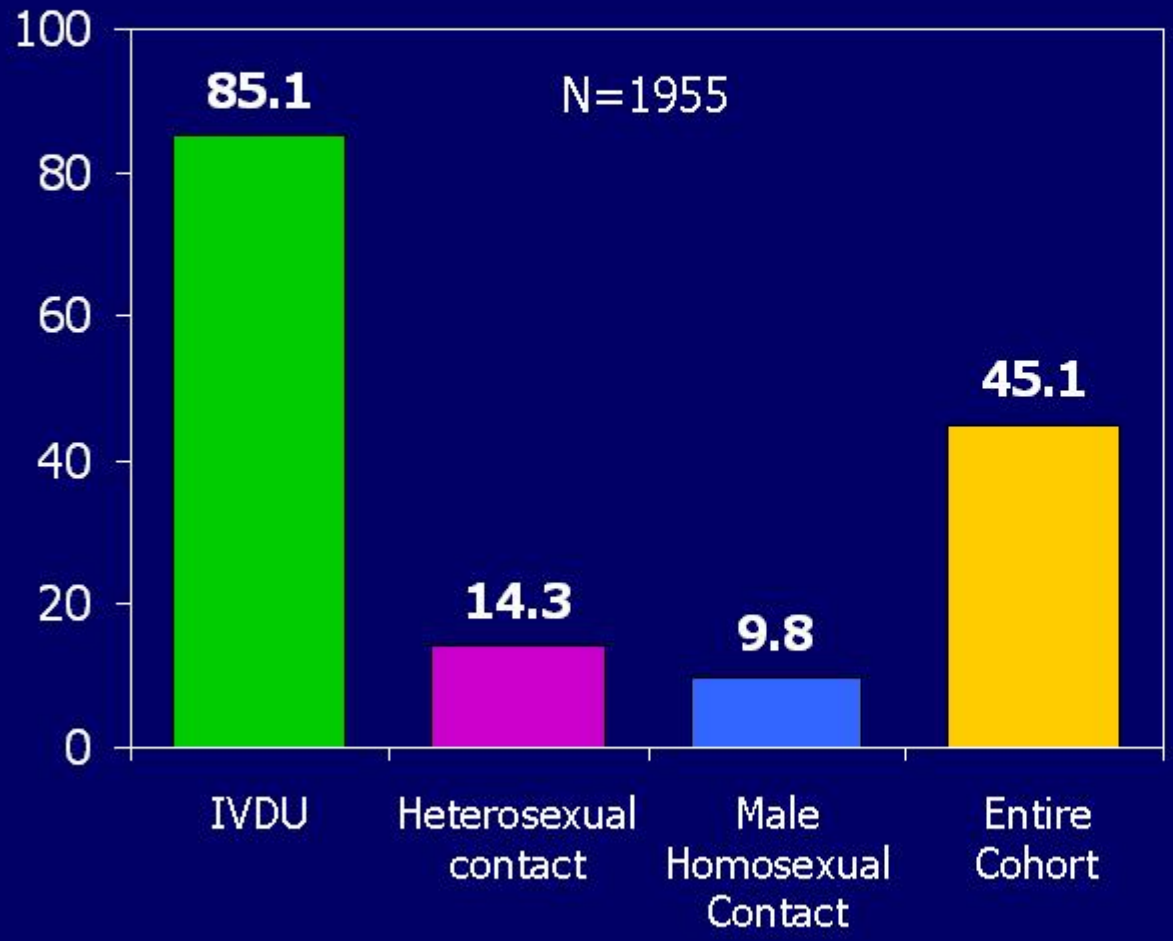
- Common coinfection
- Complicates HAART
- Can lead to rapid progression of liver disease and death

Worldwide Prevalence:
% of HIV Patients Who Are Coinfected With HCV



[1]Soriano et al. *AIDS.* 2002;16:813-826
[2]Chanbancherd et al. Southeast Asian J Trop Med Public Health. 2003;Sept;34(3):580-582

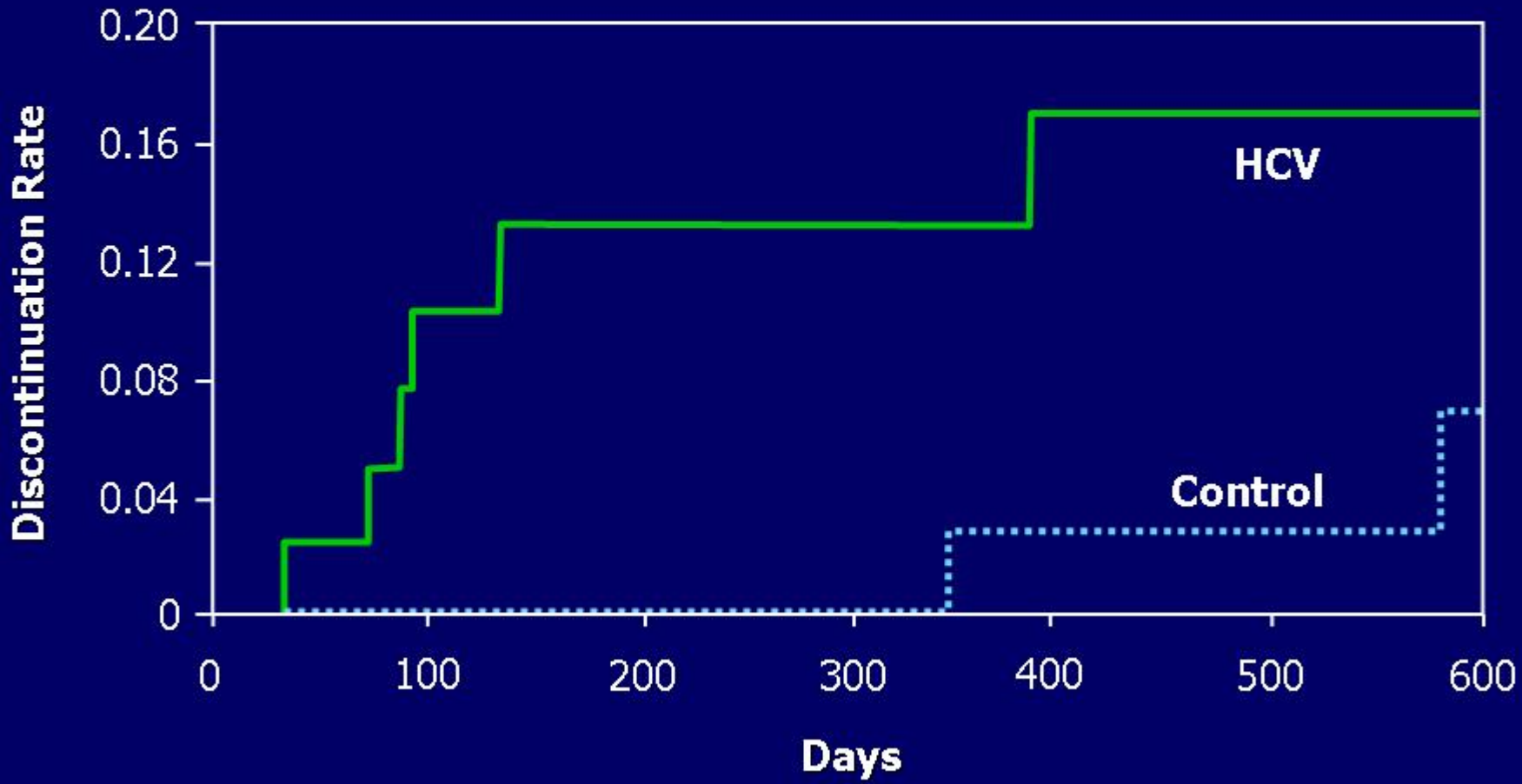
Prevalence of HCV in HIV Infected Persons By Risk Factors



- **In certain subpopulations (IVDU), prevalence may be as high as 90% as is demonstrated in this self-reported survey from Johns Hopkins**

Sulkowski et al. *Ann Intern Med*. 2003;138:197-207.

Hepatotoxicity: HAART Discontinuation Rates in Coinfected Patients



Melvin et al. *AIDS*. 2000;14:463-465.

Mitochondrial Toxicity of ART: Ribavirin and DDI Drug Interaction

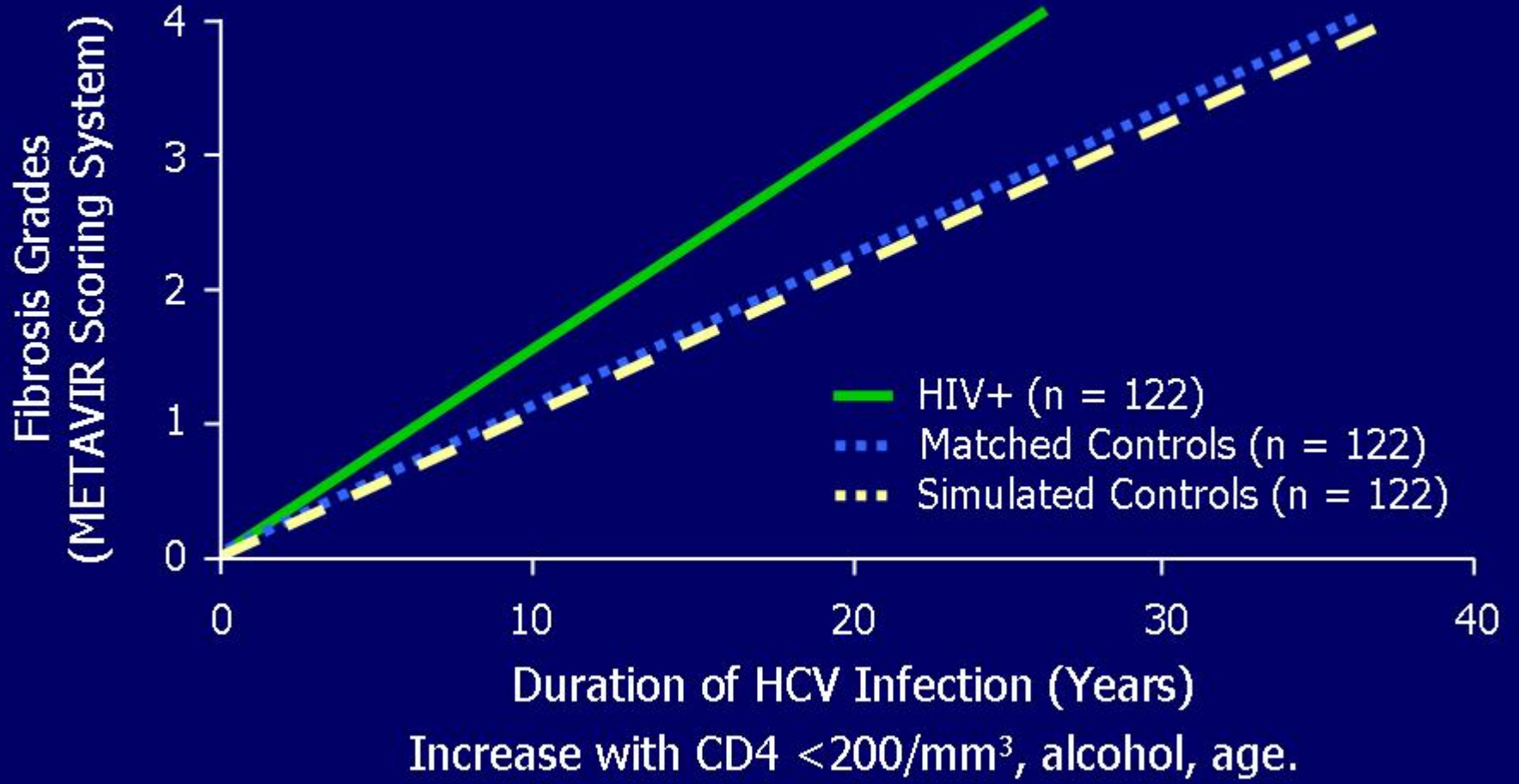
- ddI is contraindicated in cirrhosis and should be avoided in less severe liver disease.
- Ribavirin appears to potentiate ddI mitochondrial toxicity -> increases intracellular accumulation of ddI
- FDA warning (9/27/02) of combination
- Dose dependent?
- DDI and advanced liver disease likely a greater risk than the DDI/RBV drug combination itself

Other issues

- d4T associated w/ acute/chronic steatosis
- Tipranavir can cause hepatotoxicity in 5-20%, dose dependent
- More hepatotoxicity in recently started NVP, high dose ritonavir (>200 mg)
- More frequent anemia in pts on AZT (26% vs. 8%) and neutropenia (52% vs. 31%) for pts receiving IFN + RVN

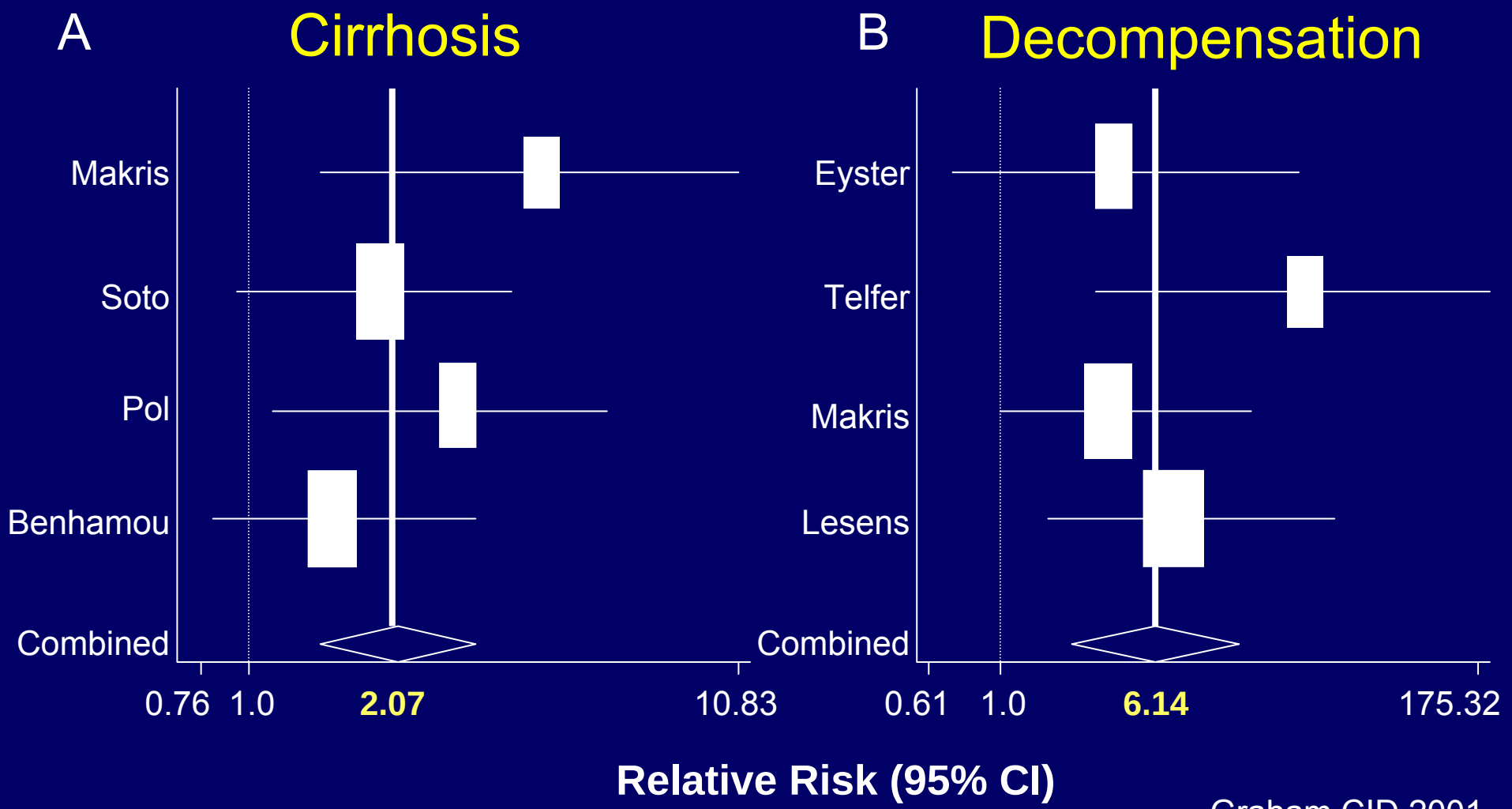
Sulkowski et al. AIDS 2005
Sulkowski M. AASLD 2006

Rate of Fibrosis Progression Is Increased Amongst HCV/HIV Coinfected Patients



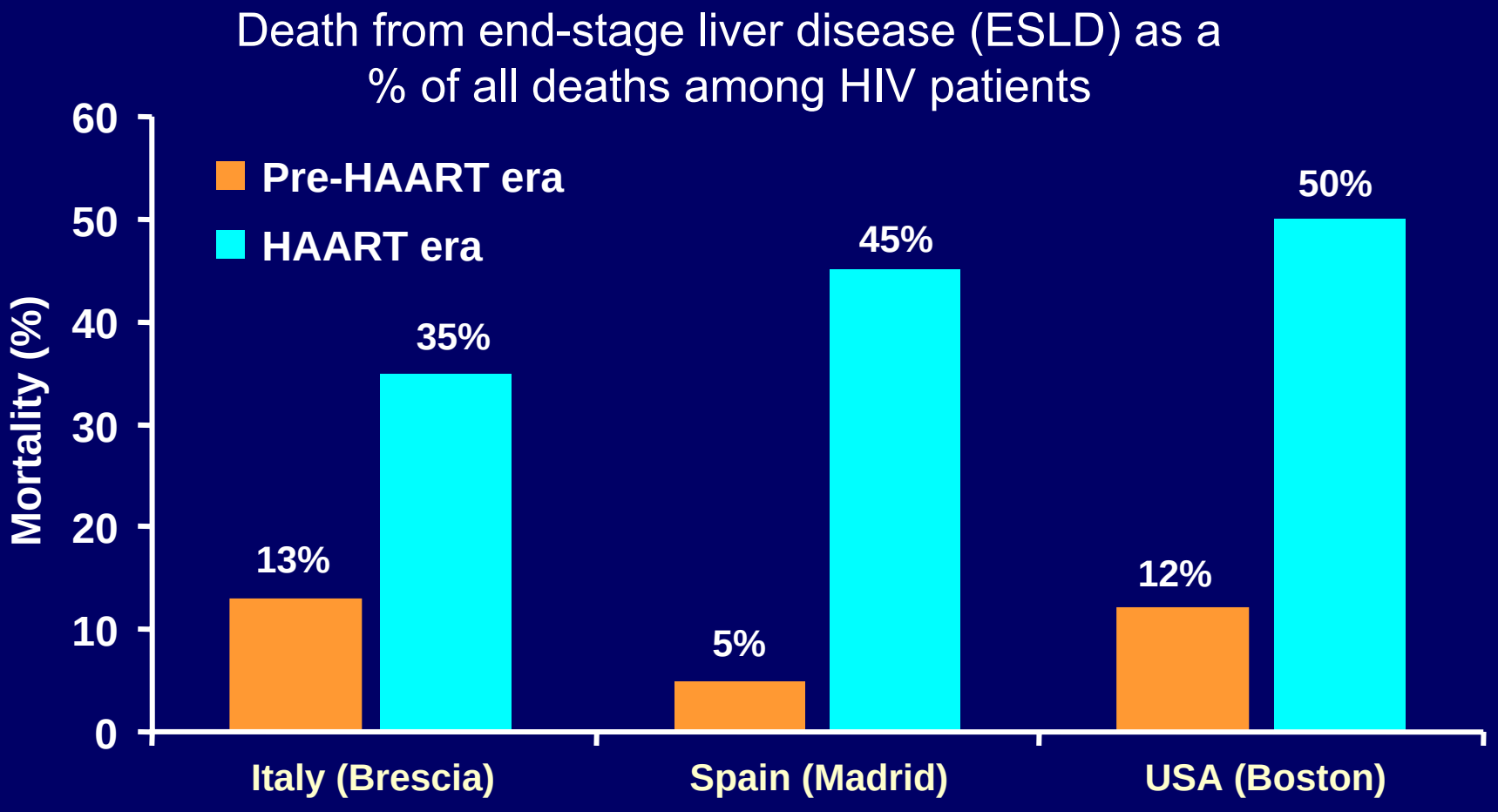
Benhamou et al. *Hepatology*. 1999;30:1054-1058.

Impact of HIV on HCV



Graham CID 2001

Liver Disease has Emerged as a Major Cause of Death in the HAART Era



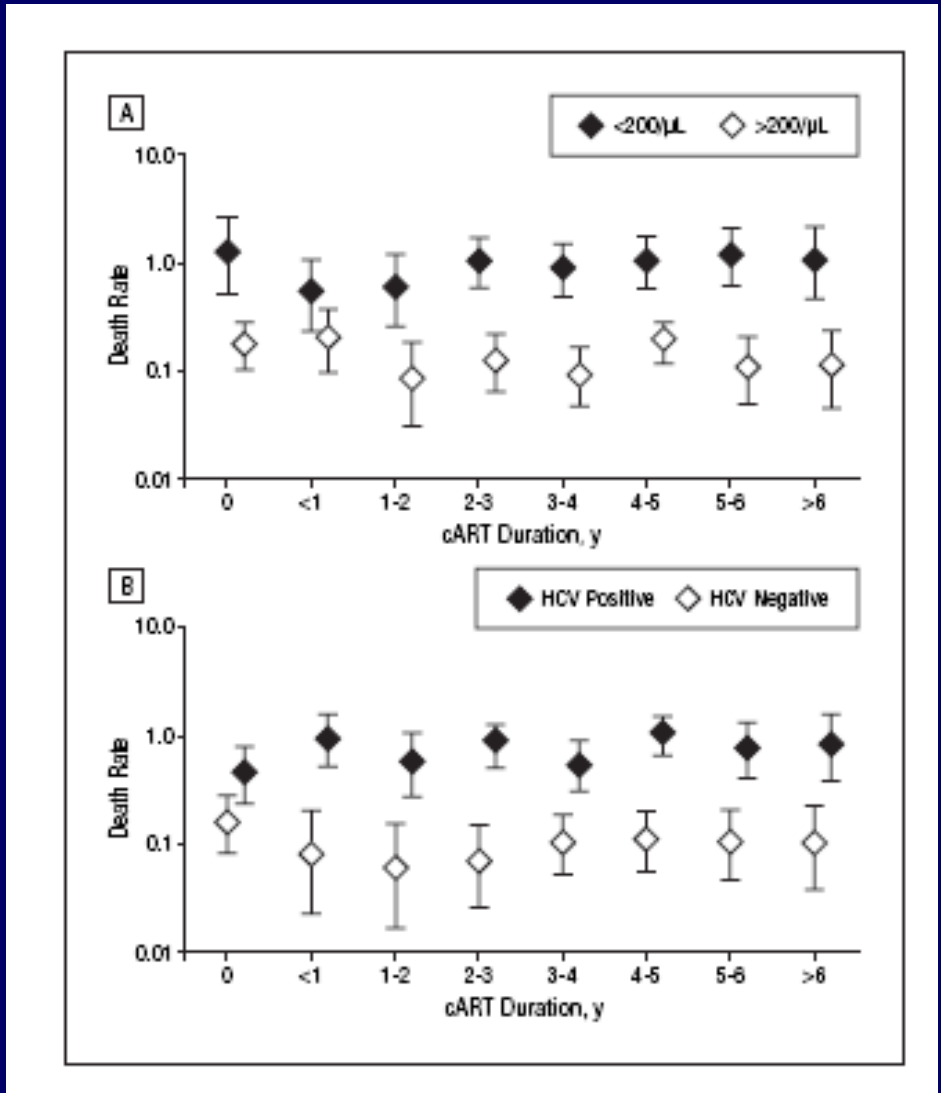
Bica *Clin Infect Dis* 2001; Puoti *JAIDS* 2000; Soriano *Eur J Epidemiol* 1999; Soriano *PRN Notebook* 2002; Martin-Carbonero *AIDS Res Human Retrovirus* 2001

Liver-related mortality:

#1 cause of non-AIDS deaths

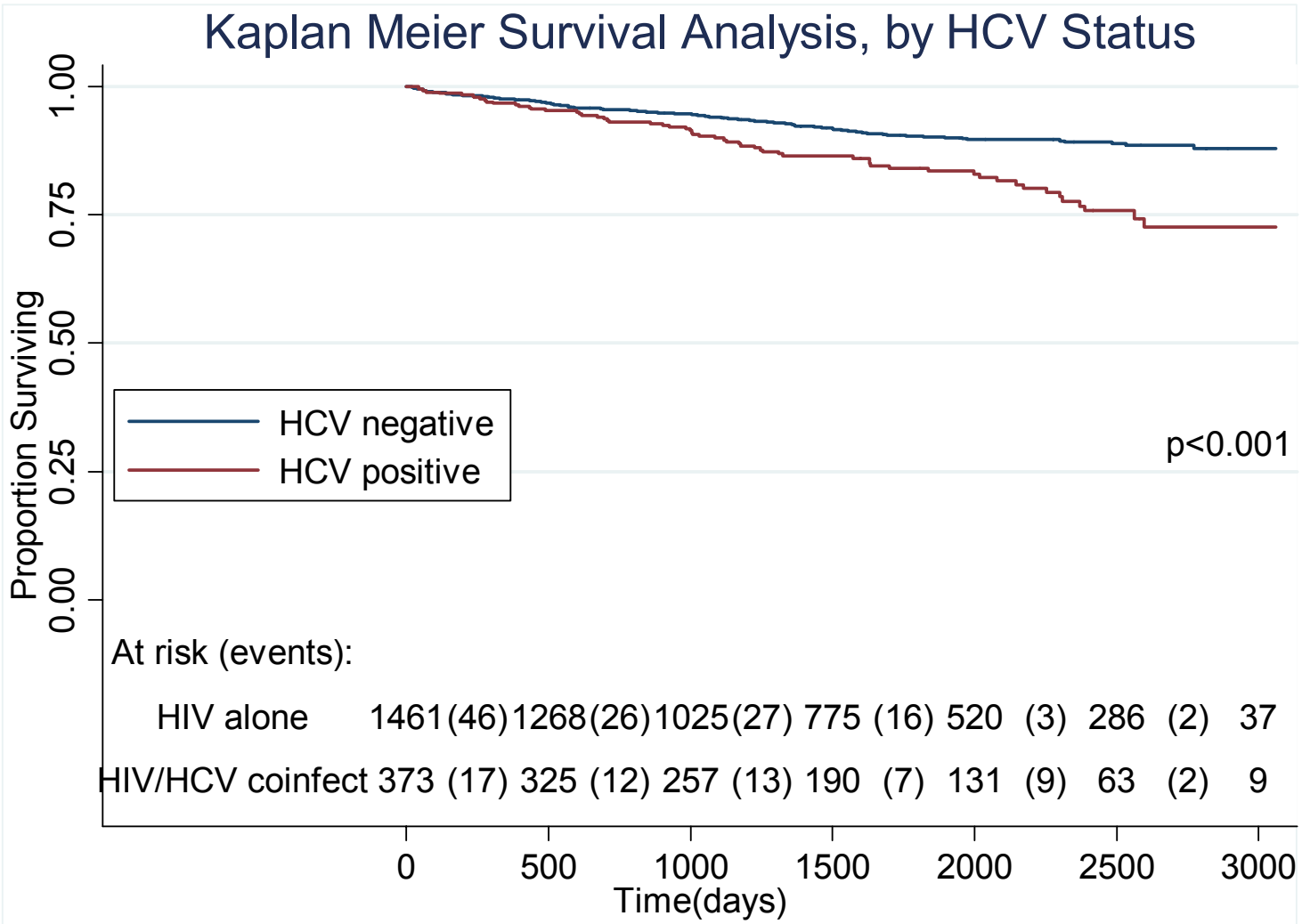
14.5% deaths

2/3 Hep C

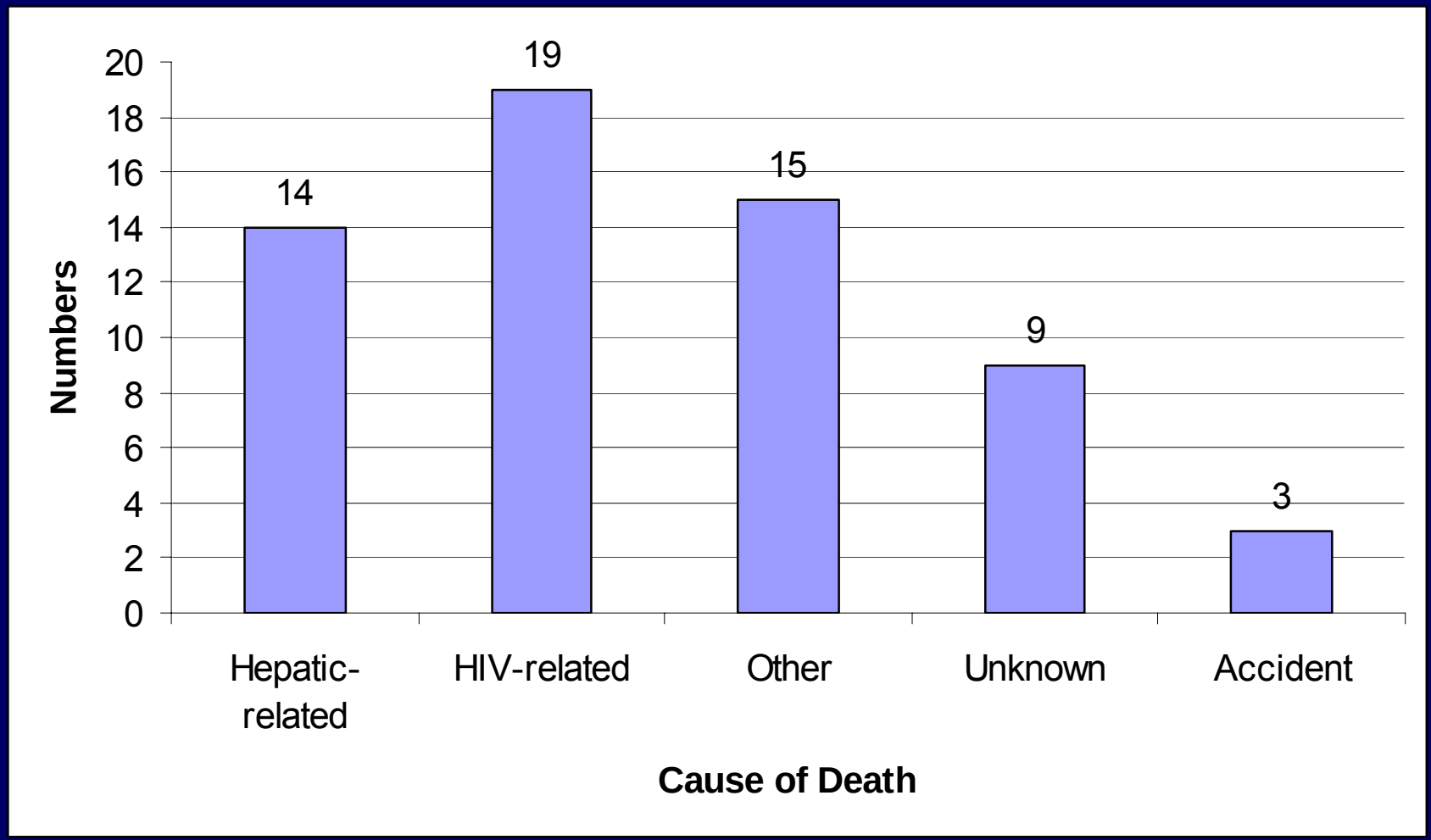


D:A:D Study. Arch Intern Med 2006; 166:1632-41

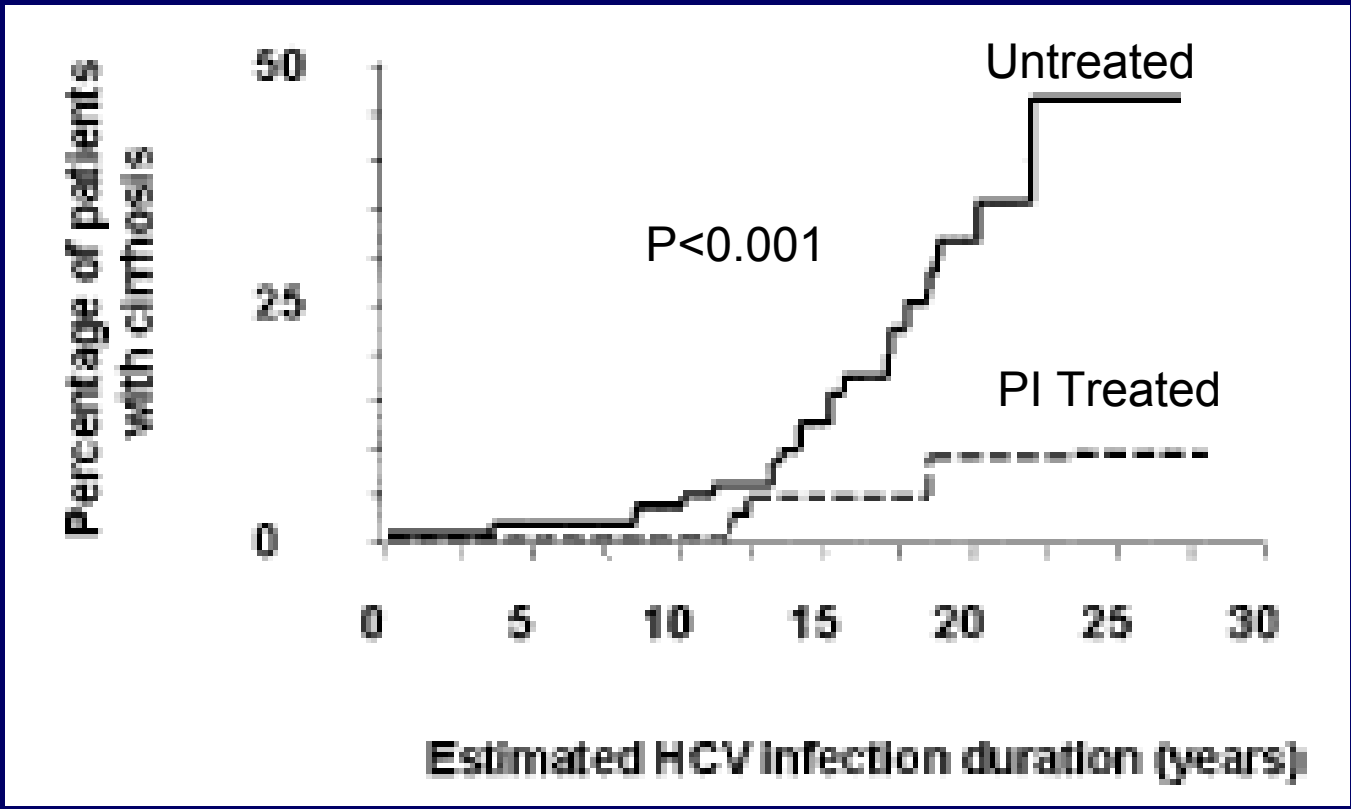
Effect of HCV on Mortality in HIV Patients: Harborview HIV Clinic, 1997-2005



Cause of Death in Harborview HIV Clinic Patients with HCV

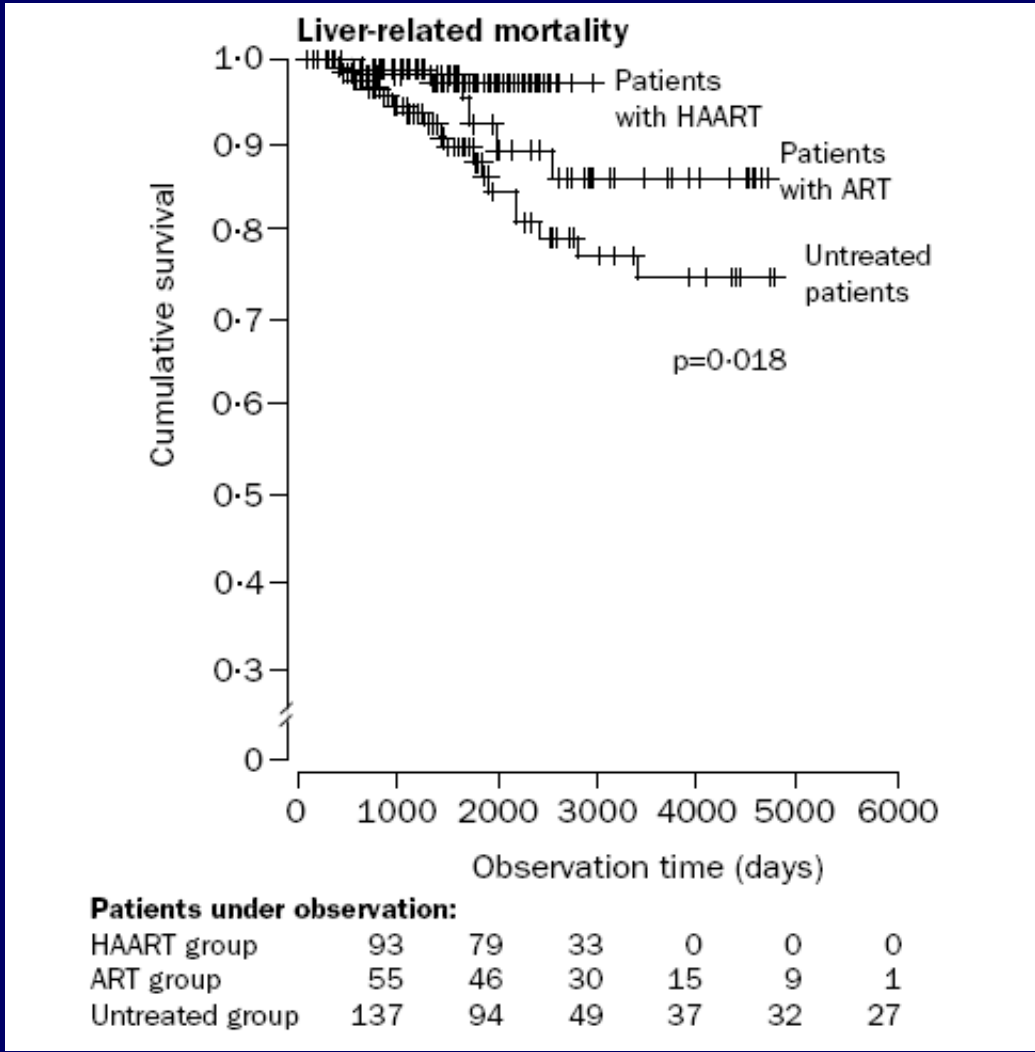


Decreased cirrhosis with HAART



Benhamou et al. *Hepatology* 2001; 34:283-7

Decreased liver-related mortality with HAART



Qurishi et al. Lancet 2003; 362:1708-13

Back to Case #1

- 45 yo W man w/ B2 HIV, CD4 count 390, HIV load 100,000 copies/ml
- HCV+, GT 1a, HCV RNA 3 million IU/ml
- ALT 67 U/L, normal synthetic function
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Considerations and Recommendations

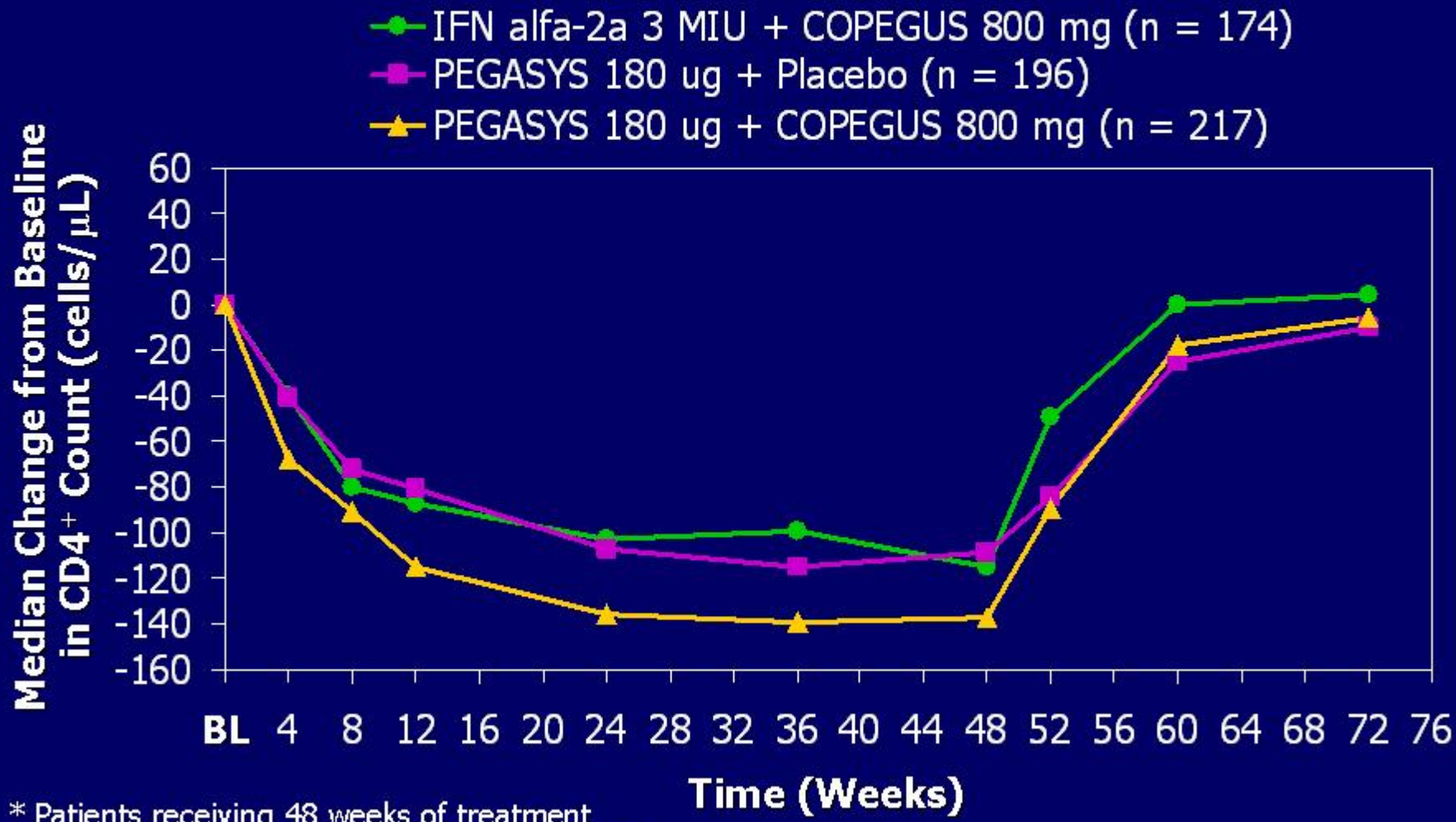
- Efficacy of HCV tx not affected by CD4 count
- IFN causes mean CD4 decline of 140 cells/ml
- Immune reconstitution syndrome?
- ACTG study ongoing
- CD4<200, treat HIV
- CD4>350 and low HIVL, ideal candidate for HCV tx
- CD4 200-350, tx HIV first or HCV cautiously

Torriani et al. NEJM 2004; 351:438-50
Sulkowski MS. J Hepatol 2006; 44: S49-55
VA Guidelines. Am J Gastroenterol 2005; 100:2338-54
Rockstroh and Spengler. Lancet Inf Dis 2004; 437-44

HIV/HCV Coinfection Trials

	ACTG	RIBAVIC	APRICOT	Laguno
# pts	134	412	860	95
% genotype 1	78%	66%	61%	49%
fibrosis score	2.5	2.3	16% cirrhotic	30% st 3 or 4
Mean CD4	475	515	530	560
Overall SVR	27%	26%	40%	44%
SVR GT 1	5%	15%	29%	38%
SVR non-1	30%	43%	62%	53%
d/c rate (ea arm)	12%	42%	30-40%	17%

Median Change from Baseline in CD4+ Counts*



* Patients receiving 48 weeks of treatment

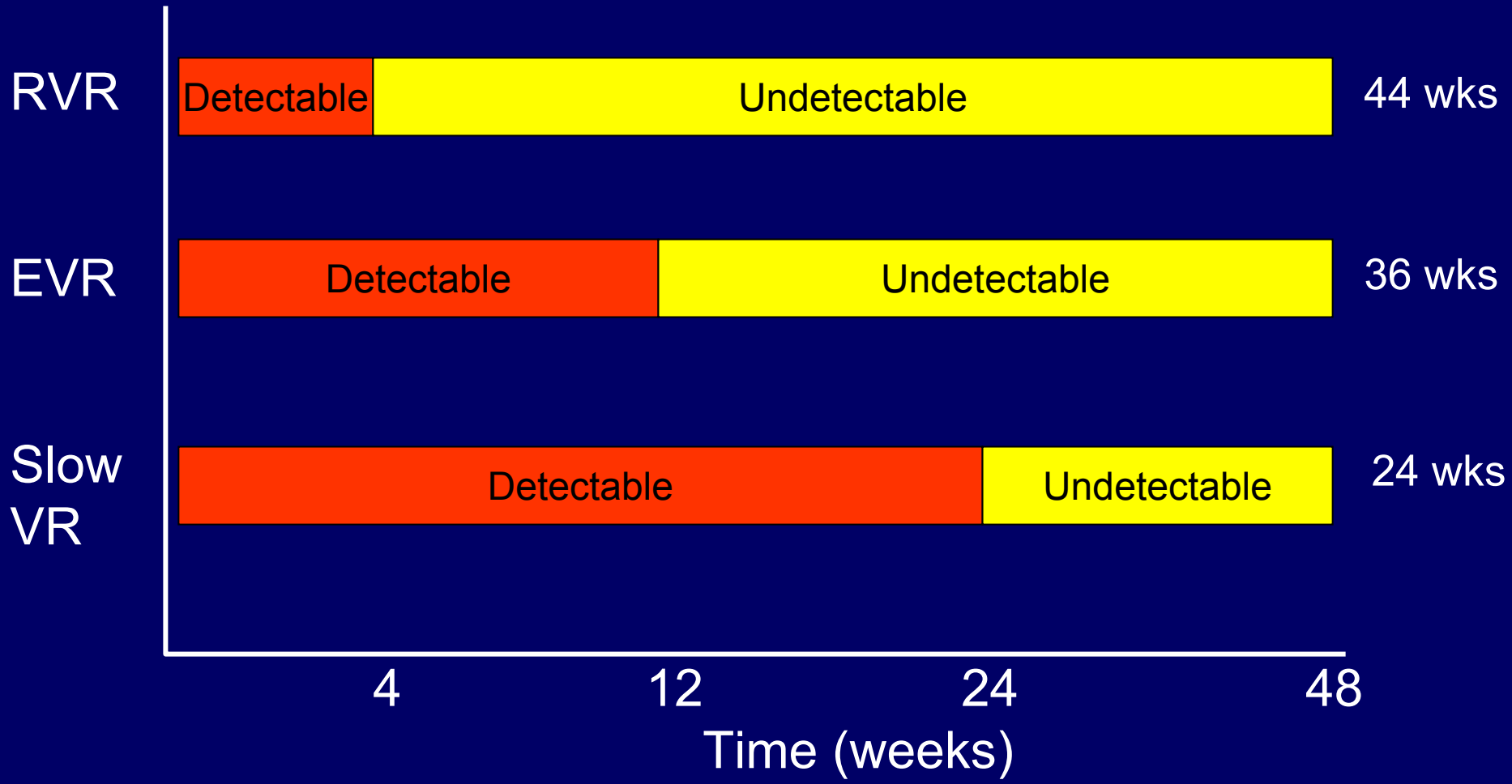
Torriani et al. *N Engl J Med.* 2004;351:438-450.

Extended treatment for HCV

- Mathematical models show that viral suppression necessary for at least 36 weeks
- HCV monoinfected trial showed that if HCV RNA + at wk 12 but – at wk 24, SVR increased from 17% to 29% with add'l 24 weeks of therapy
- Goal: reduce relapse rate

Drusano GL. 2004 J Infect Dis 189:964-70
Berg T. 2006 Gastro 130:1086-97.

Duration of Detectability (DUD)

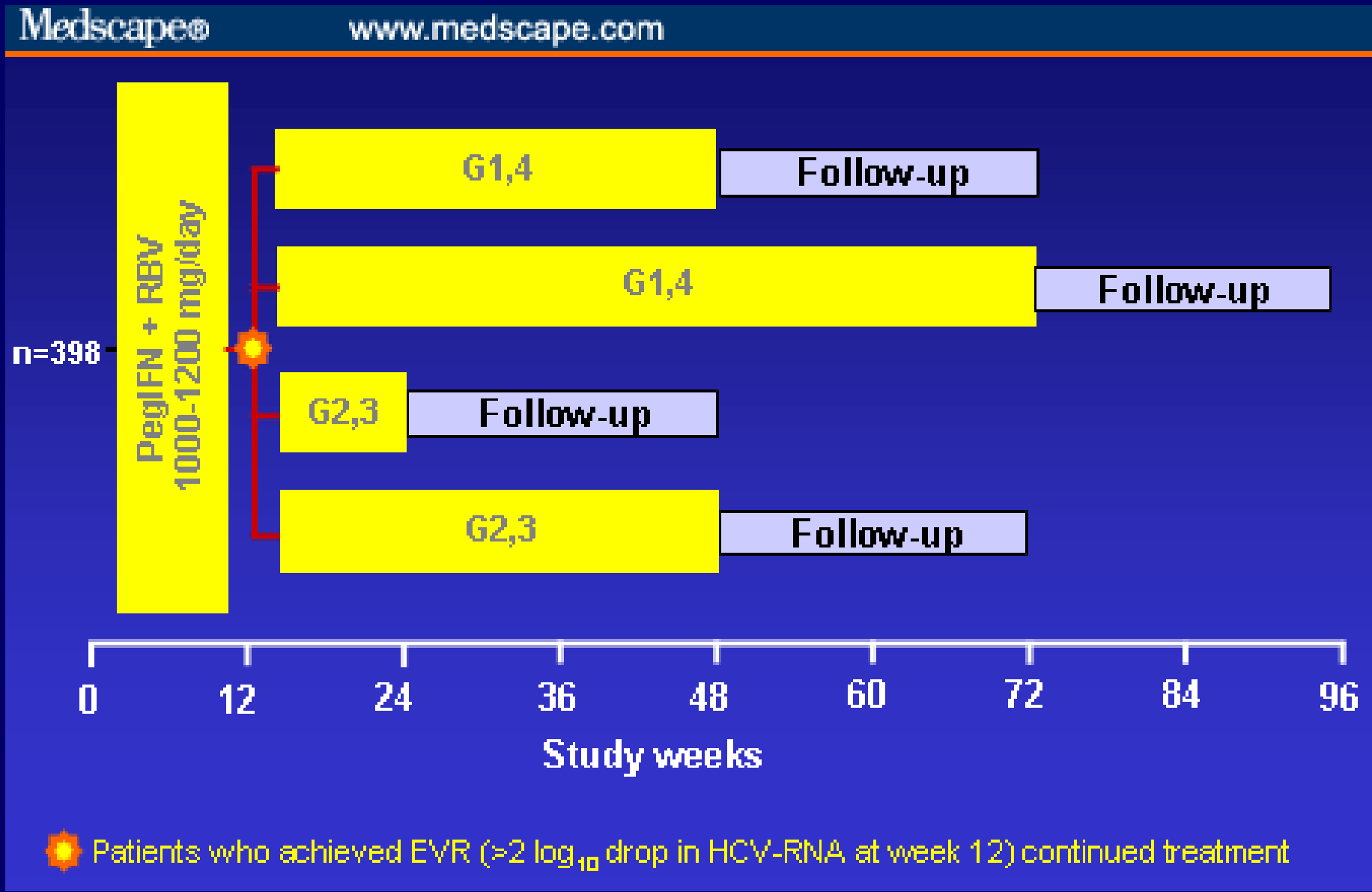


Ferenci 2005, Fried 2006

PRESCO

- Ongoing Spanish study of 398 stable coinfected pts (mean CD4 562 cells/mm^3)
- All are receiving 180 mcg PegIFNα2a (Pegasys) and wt-based RBV (1000 or 1200 mg/d)
- Comparing extended tx w/ std tx:
  - 48 weeks for GT non-1
  - 72 weeks for GT 1

Soriano, et al. AASLD Meeting 2006; Abstract #365


n=398
PegIFN + RBV
1000-1200 mg/day
G1,4
Follow-up
G1,4
Follow-up
G2,3
Follow-up
G2,3
Follow-up
0
12
24
36
48
60
72
84
96
Study weeks
Patients who achieved EVR (>2 log10 drop in HCV-RNA at week 12) continued treatment

PRESCO Results

- ITT analysis: overall SVR 49% (71% GT 2,3 and 35% GT 1)
- No significant differences in relapse rates by duration of therapy (26% vs 17%)
- Ribavirin dosage more important than duration of therapy

Soriano, et al. AASLD Meeting 2006; Abstract #365

Novel Therapies

- Serine protease inhibitors
- Polymerase inhibitors
- Helicase inhibitors
- Antisense therapy
- siRNA
- Toll-like receptor agonists
- Cyclosporine analog
- Improved Ribavirin and Interferon
- Therapeutic vaccination

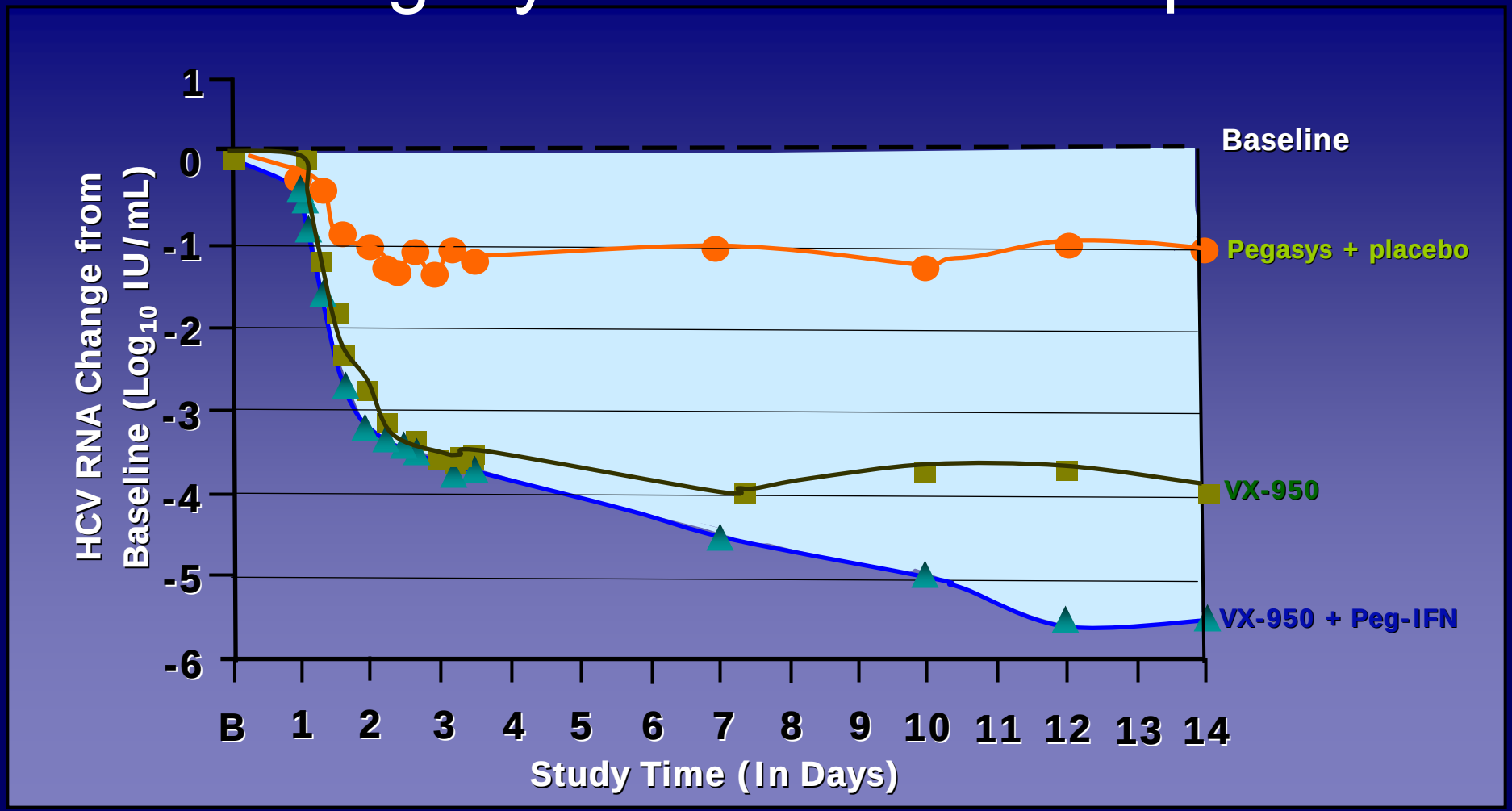
→ Specifically Targeted Antiviral Therapy (STAT)

Review: McHutchison JG. 2006 J Hepatol 44:411-21

STAT-C

- Very potent!
- Three potential problems:
  - Rapid development of resistance
  - Importance of precise dosing and adherence
  - Possibility of synergistic side effects

VX-950 Alone or in Combination with Pegasys: Mean Viral Response



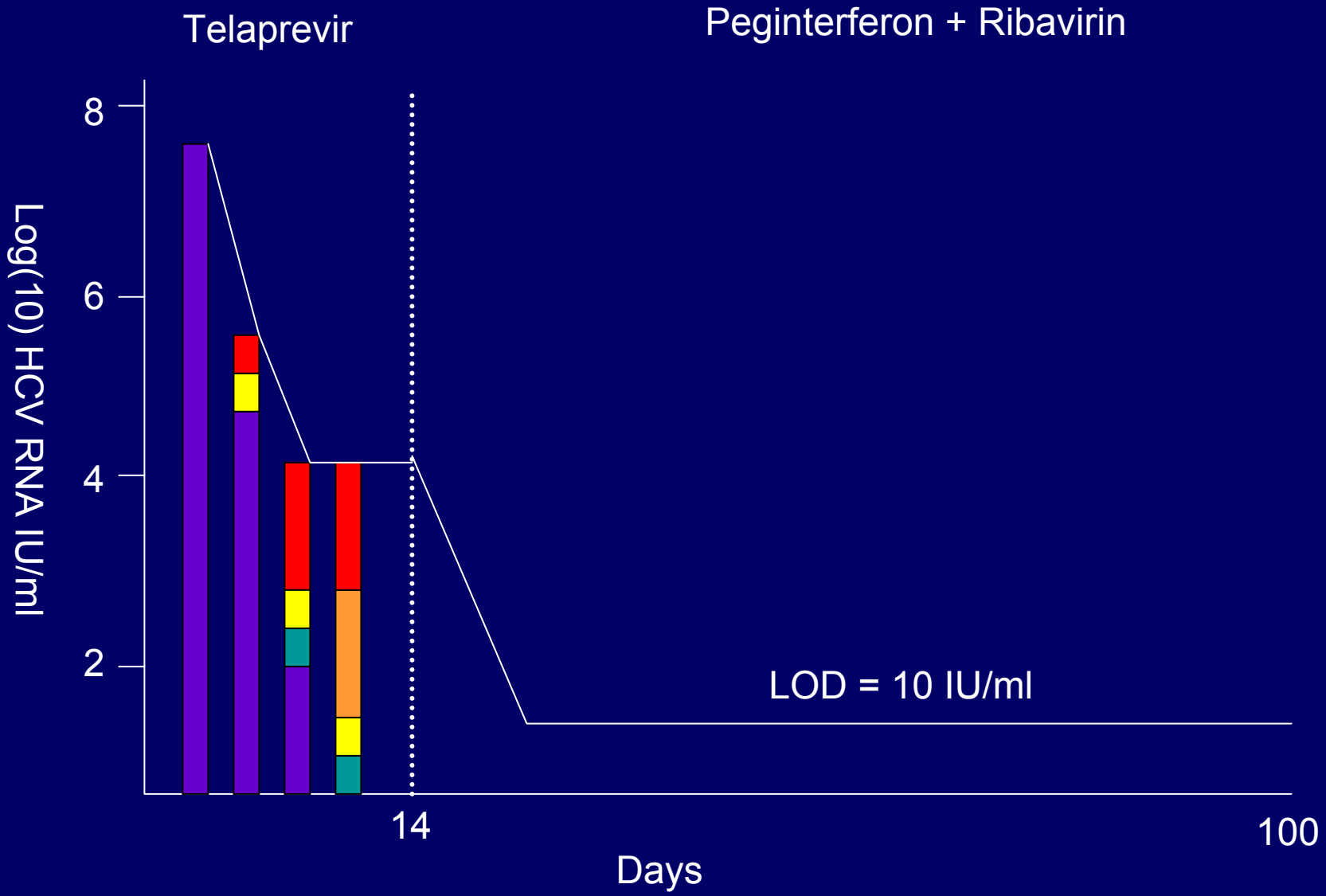
Reesink H et al. EASL. April 26-30, 2006.
Vienna, Austria. Abstract 737.

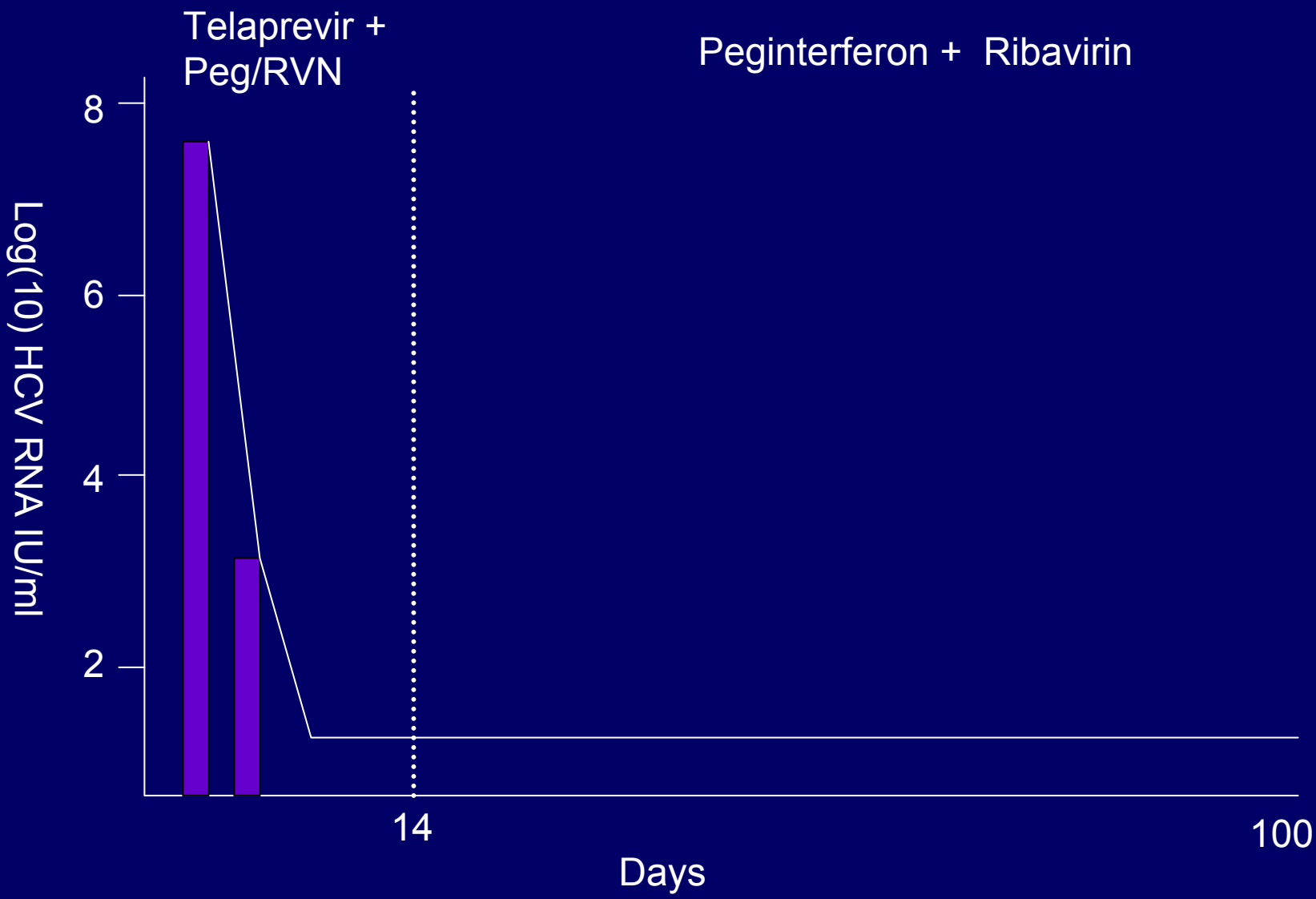
Slide courtesy Roche Medical Affairs

Phenotypic Characterization of Telaprevir-Resistant Variants

- Highly sensitive clonal method
  - Detect 5% frequency of variants
  - Performed at days 4, 8, 12, 14
  - 80 sequences/patient/time point

Adapted from Kieffer T, et al. 2006 AASLD, Boston, #92


Telaprevir
Peginterferon + Ribavirin
8
6
4
2
Log(10) HCV RNA IU/ml
LOD = 10 IU/ml
14
100
Days



Adapted from Kieffer T, et al. 2006 AASLD, Boston, #92

Liver Transplantation

- Similar survival post-txp b/t HIV+ and HIV- pts transplanted for Hep C
  - 12 mo survival: 87% vs. 87%
  - 24 mo survival: 73% vs. 82%
  - UCSF experience: 15/21 alive w/ mean f/u 33 mos
- No significant HIV clinical, virologic or immunologic disease progression in post-txp patients
- Drug interactions w/ HAART and immunosuppressants
- Criteria for eval: CD4>200, HIVL <400, no active OI
  - REFER EARLY, MELD score doesn't predict well
- UCSF

Rockstroh and Spengler. Lancet Inf Dis 2004; 437-44
VA Guidelines. Am J Gastroenterol 2005; 2338-54
Stock P. AASLD Oral Presentation 2006.