

Natural History and Pathogenesis of Hepatitis C in HIV-Infected Persons

David L. Thomas, MD

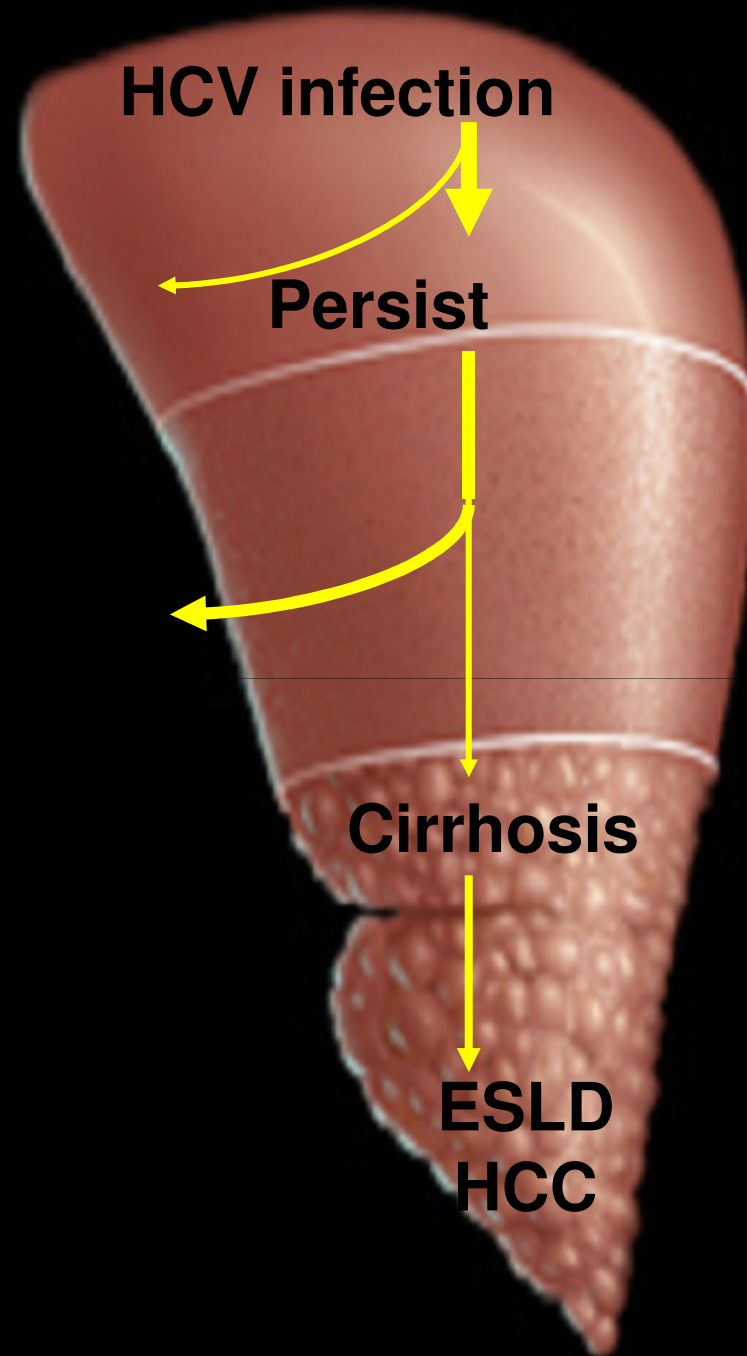
HIV/HCV IDU Studies Baltimore

- ALIVE cohort:
 - David Vlahov
 - Ken Nelson
 - Steffanie Strathdee
 - Shruti Mehta
 - Greg Kirk
 - Jacquie Astemborski
- Immunology/Chimp:
 - Andrea Cox
 - Stuart Ray
 - Kim Dowd
 - Dale Netski
- NIDA
 - K Davenny
 - J Khalsa
- Virologic testing:
 - Stuart Ray

Hepatitis C Natural History

Recovery

Silent infection



HCV infection

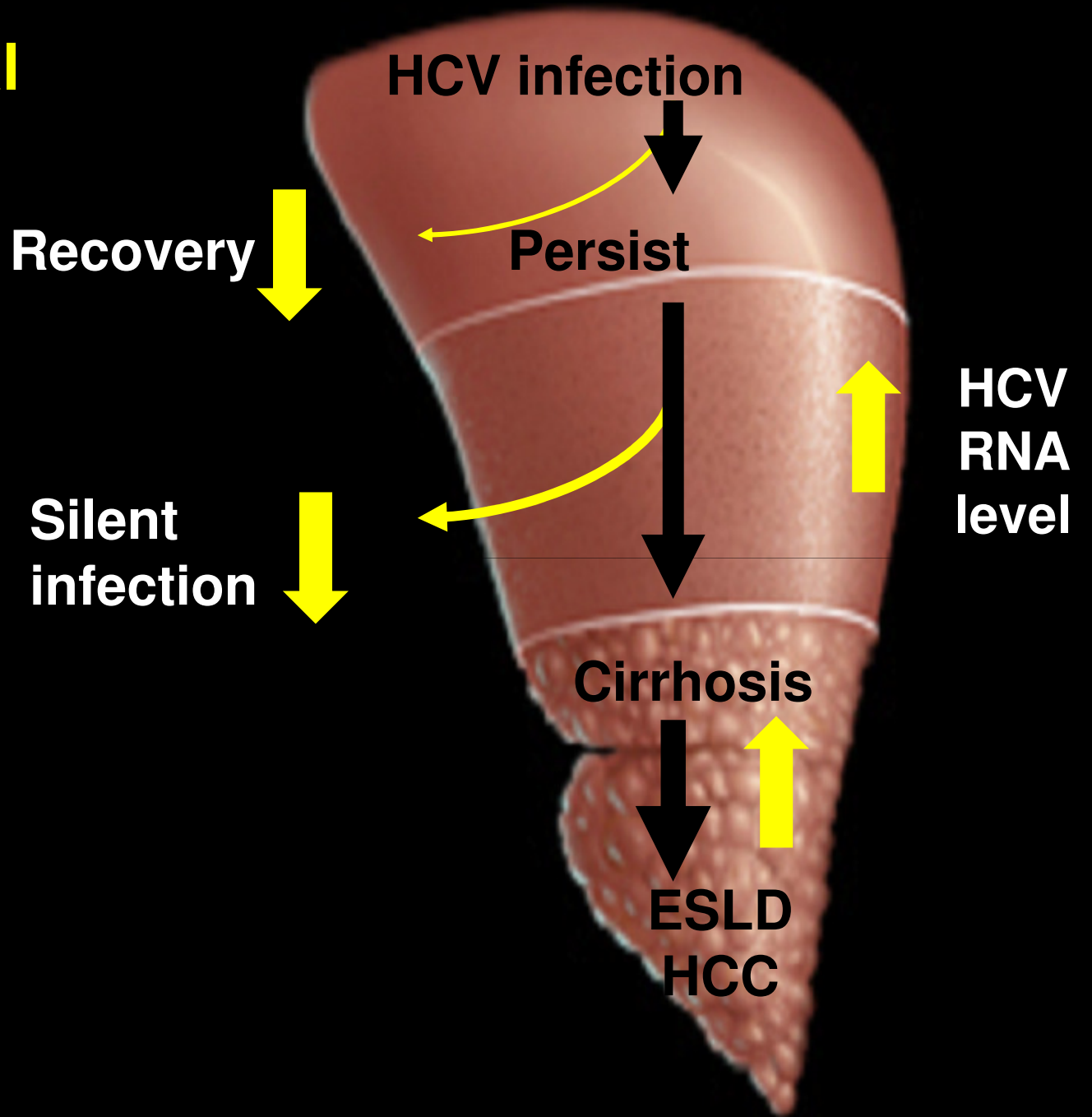
Persist

Cirrhosis

ESLD
HCC

Hepatitis C Natural History

HIV makes all stages worse



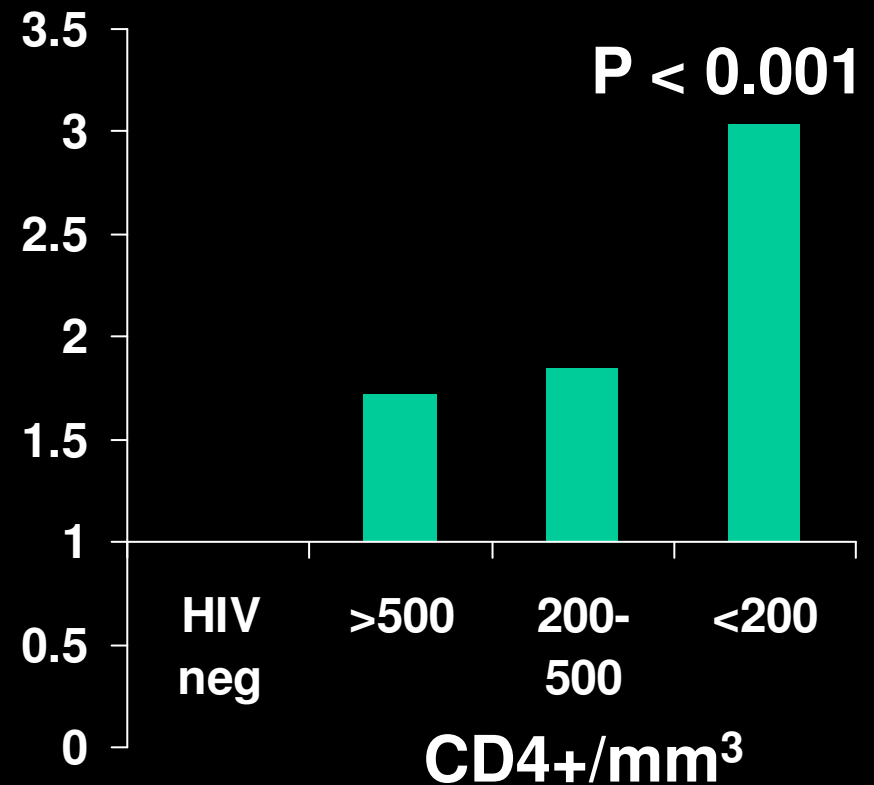
HCV Clearance is Lower in HIV-infected Baltimore IDUs

- Cohort recruited 1989
- 1667 HCV antibody +
- Clearance, N=95
 - HCV RNA <50 c/ml X2
- Persistence, N=722
- *OR versus HIV neg, adjusted for HBsAg, age, and race.

Thomas et al JAMA 2000

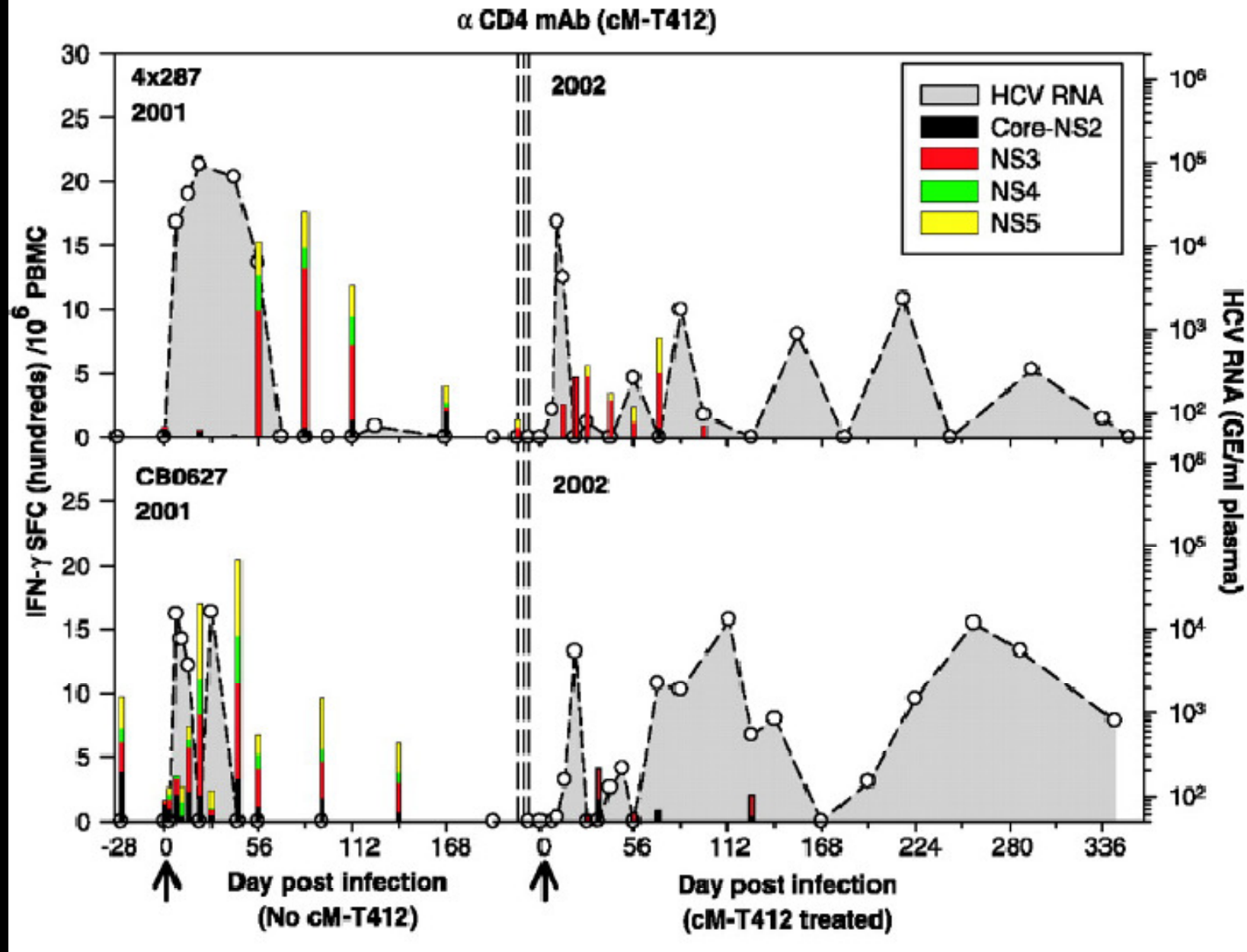
Villano Hepatology 1999

Odds of Persistence*



HIV Probably Increases HCV Persistence by Effects on CD4 Lymphocyte

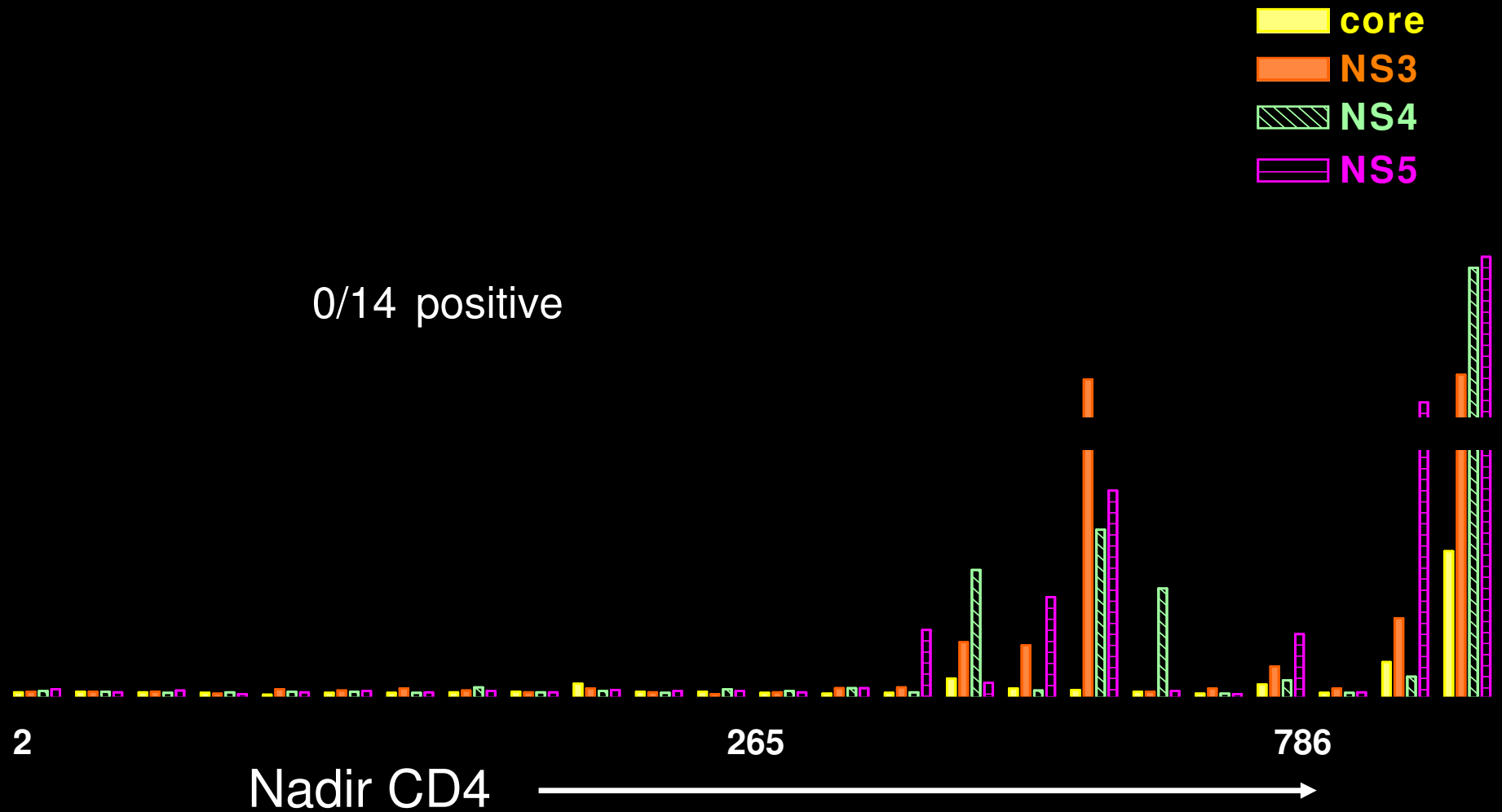
- **CD4 lymphocyte depletion of chimps associated with viral persistence on re-challenge**



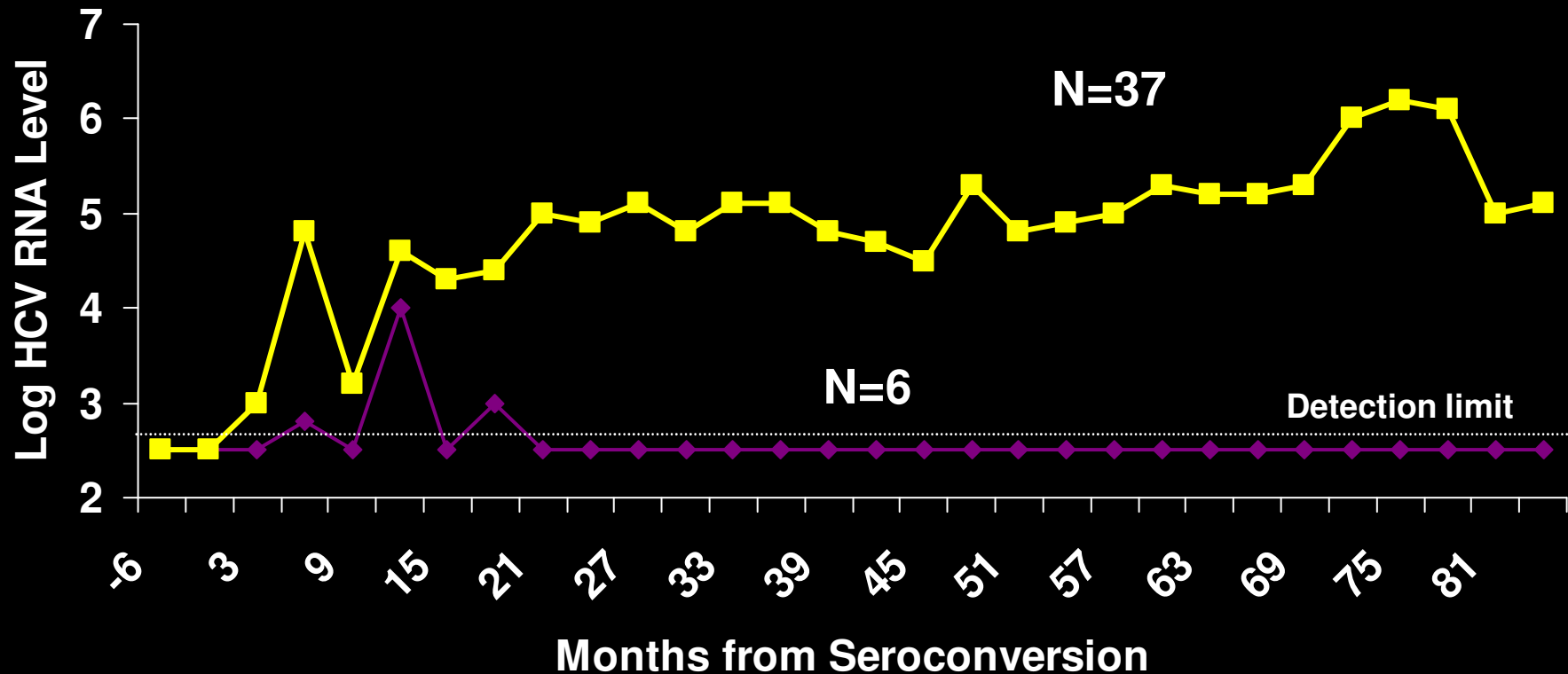
Initial infection

**Re-infection with CD4
depletion**

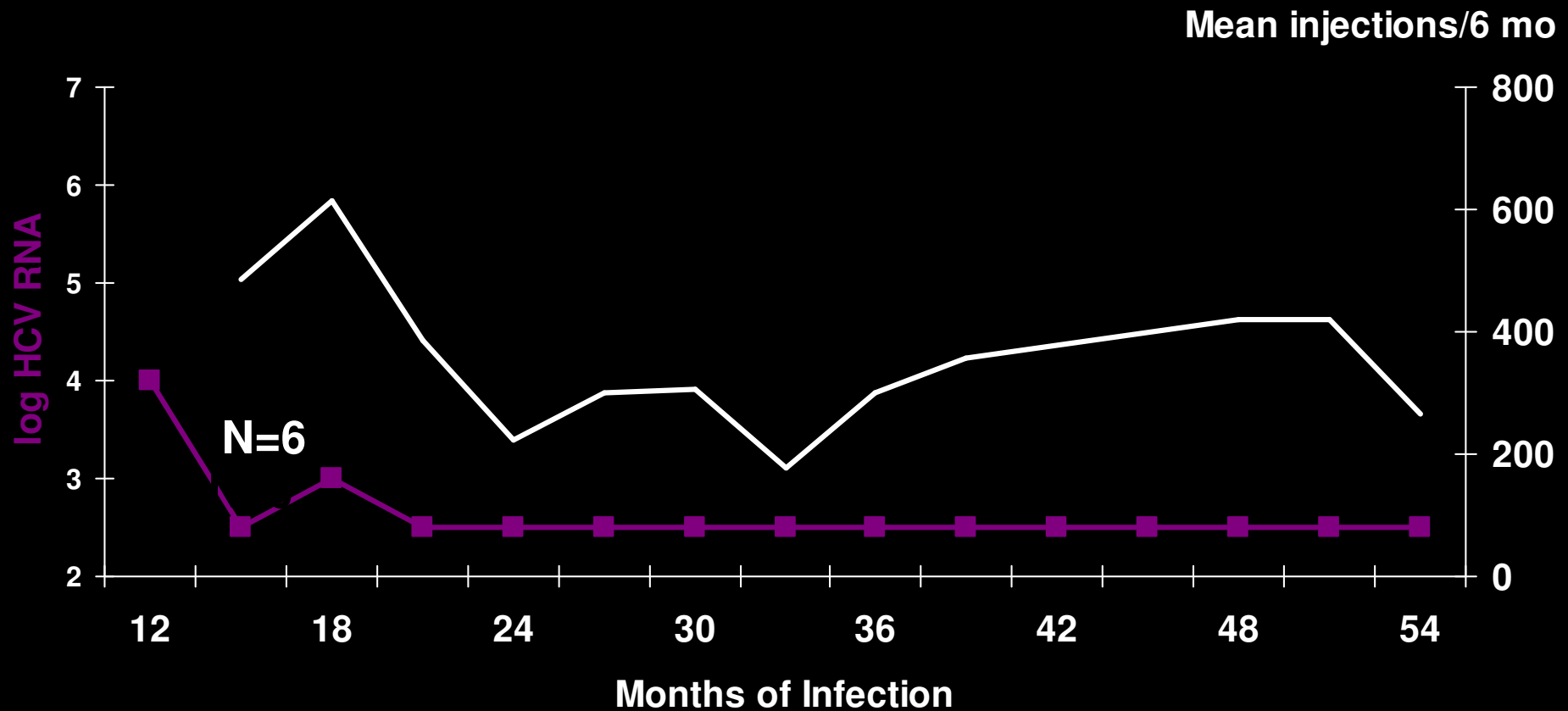
Low nadir CD4 counts associated with absence of HCV-specific responses



Viremia Patterns After HCV Infection: Aggregate HCV RNA Levels in 43 Seroconverters



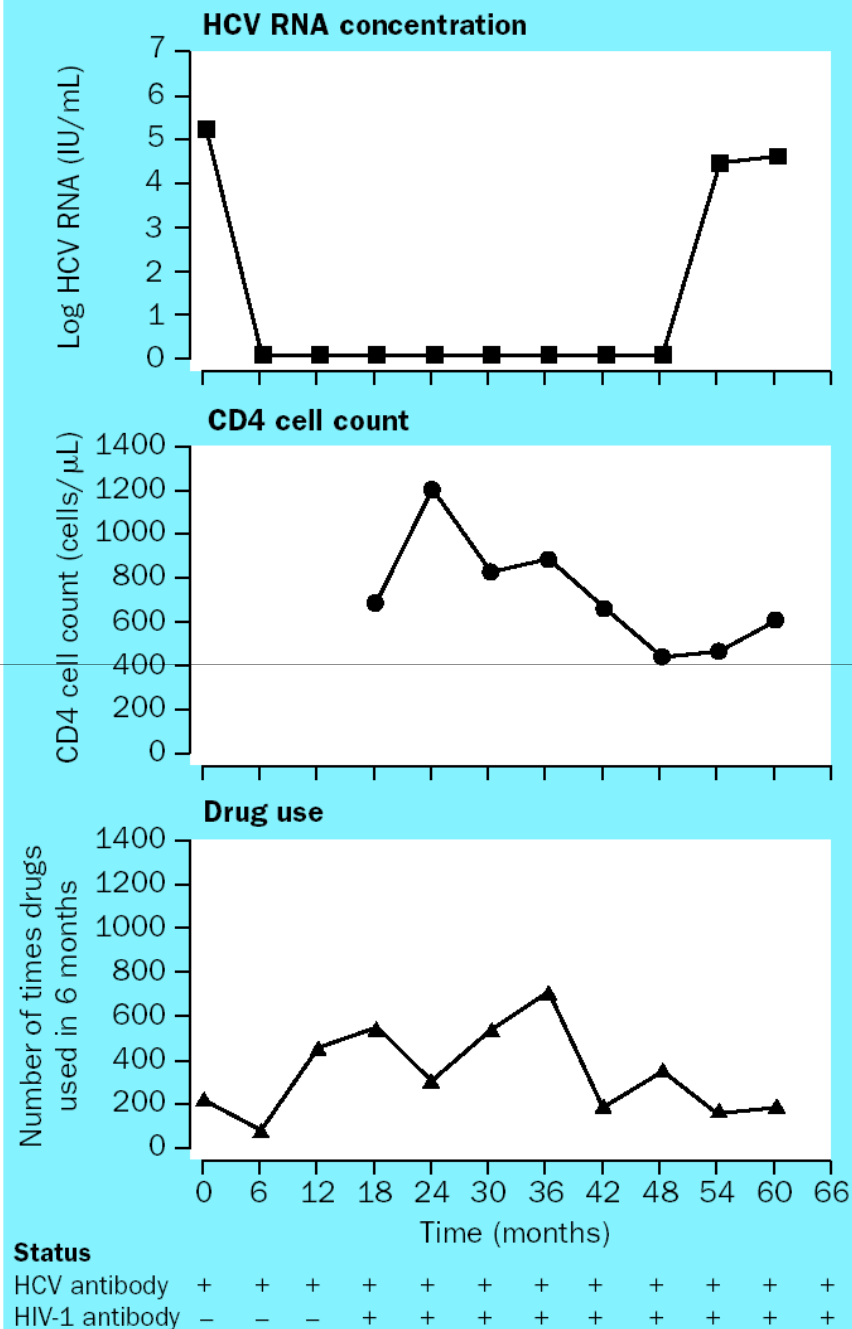
Six IDUs Who Cleared HCV Are Continually Exposed But Not Infected



Effect of HIV on HCV Persistence in an Active IDU

- 95 HCV AB +, RNA neg X2
- Persistence on reinfection >6 fold more likely if HIV pos

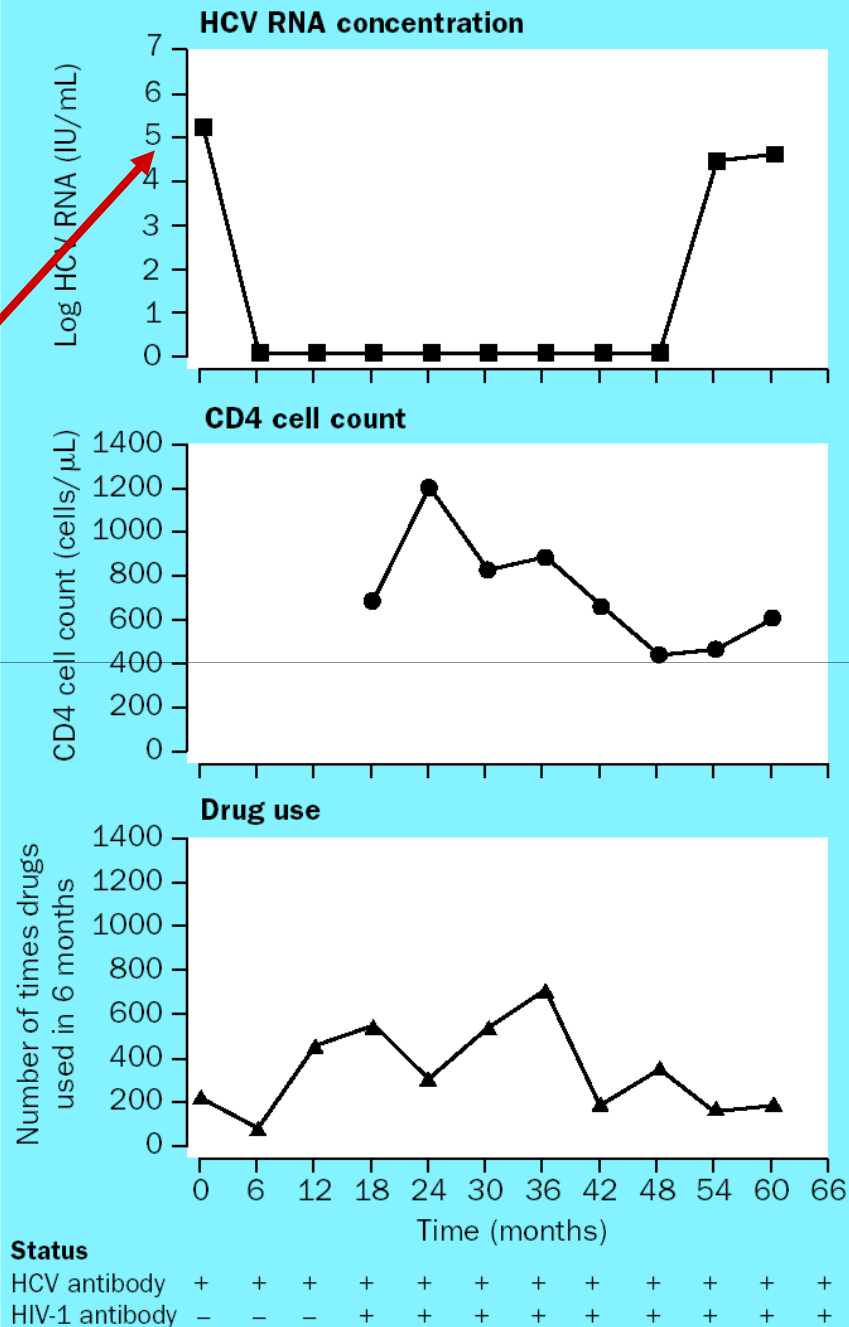
Mehta et al Lancet 2002



Effect of HIV on HCV Persistence in an Active IDU

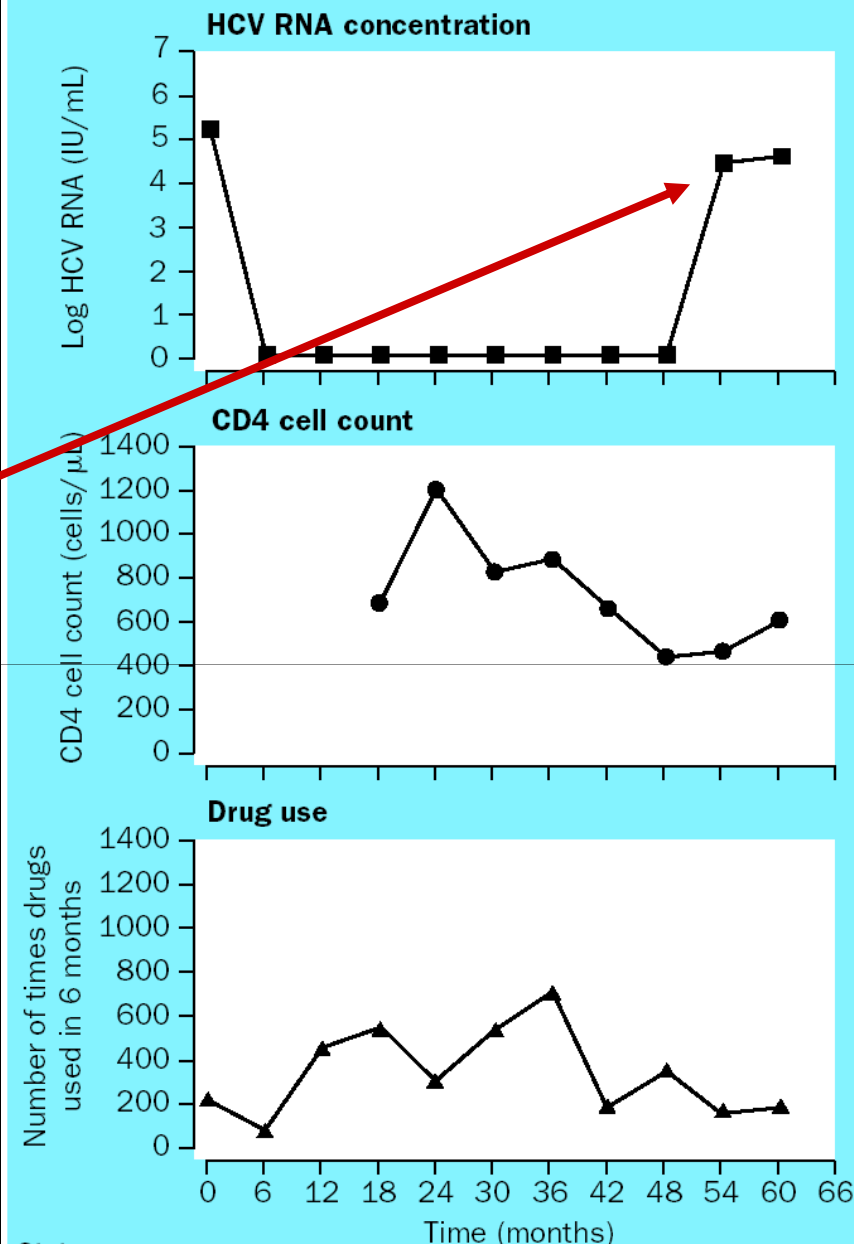
Initial HCV infection and clearance

Mehta Lancet 2002



Effect of HIV on HCV Persistence in an Active IDU

HCV persistence



Status

HCV antibody	+	+	+	+	+	+	+	+	+	+	+
HIV-1 antibody	-	-	-	+	+	+	+	+	+	+	+

Mehta Lancet 2002

How HIV Abrogates Immunologic Control of Acute HCV Infection Is Unknown

- **CD8+ T cell response is important¹**
- **Neutralizing antibodies are diminished by HIV-related CD4 lymphocyte depletion²**

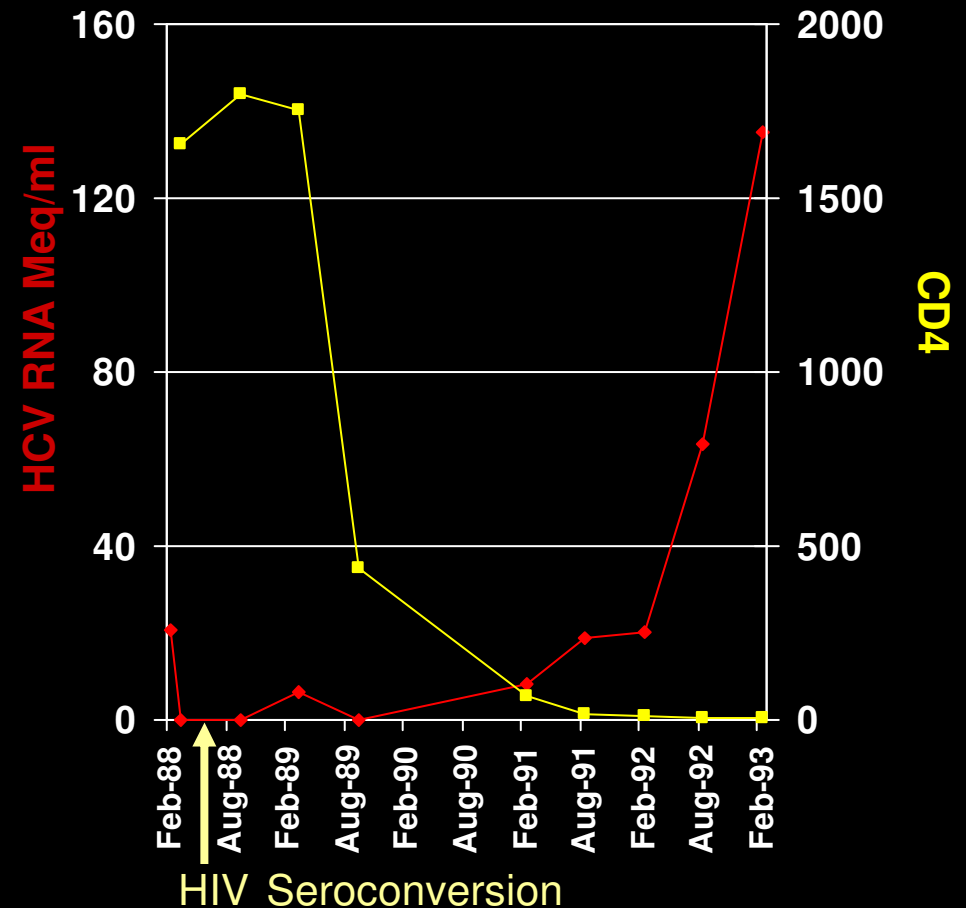
¹Cox Hepatol 2005; Cox J Exp Med 2005; ²Netski JID 2007;
Dowd Int HCV Meeting Glasgow 2007

HIV Adversely Affects Hepatitis C Natural History

- **Viral persistence**
- **HCV RNA abundance (load)**

HCV RNA Levels Increase After HIV Seroconversion

- Sherman et al J Clin Micro 1993; Eyster et al Blood 1994
- 27 HCV pos with HIV SC
- HCV RNA increased 0.6 logs after HIV SC
- CD4 decline and time associated with HCV RNA increase

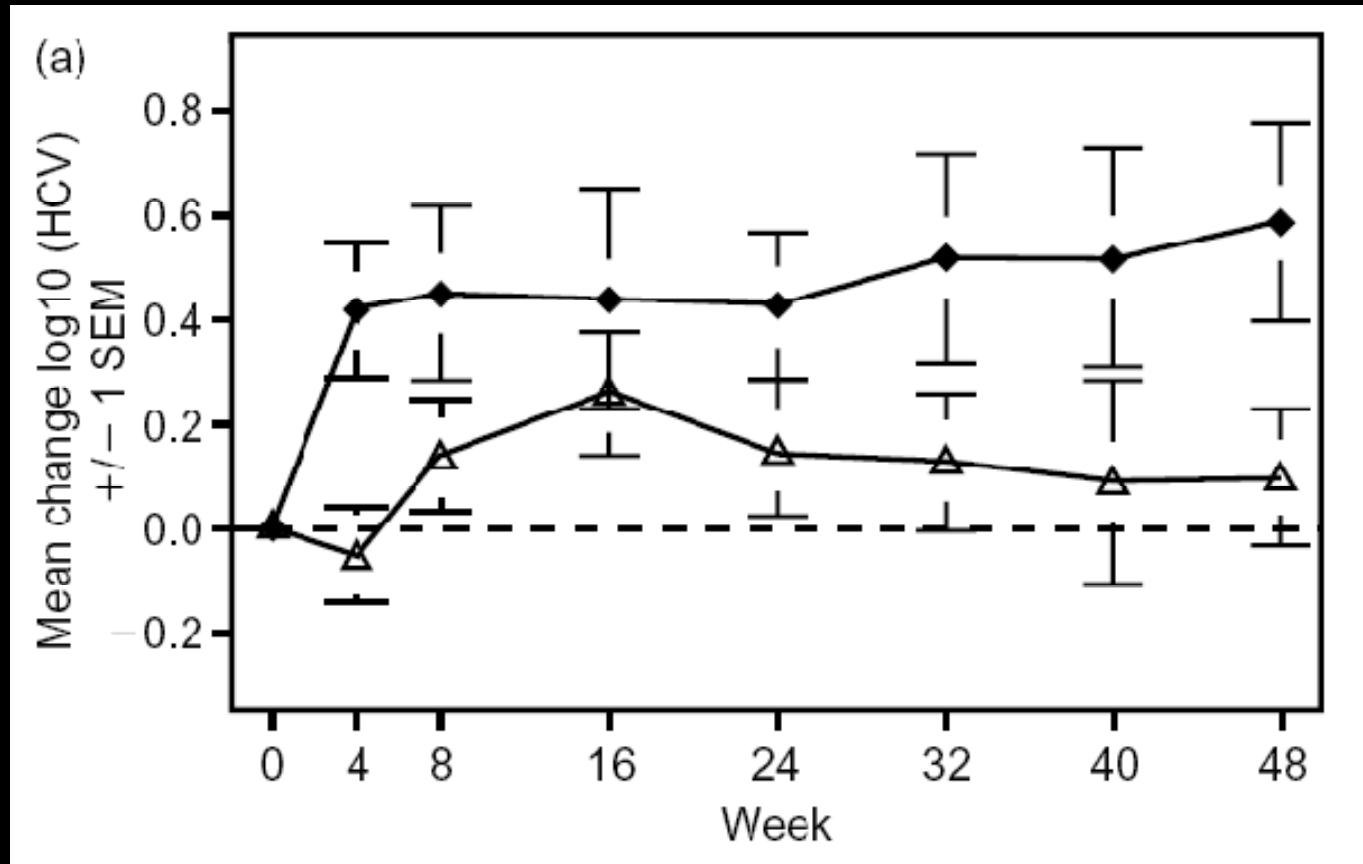


Thomas 1996 JID

How HIV increases HCV Abundance Is Not Known

- **CD4 lymphocyte depletion contributes but is not necessary**
- **HAART therapy actually increases HCV RNA level (in those with CD4 lymphocyte < 350/mm³)**
 - ? Immune activation

Increase HCV RNA After ART



CD4 < 350/mm³

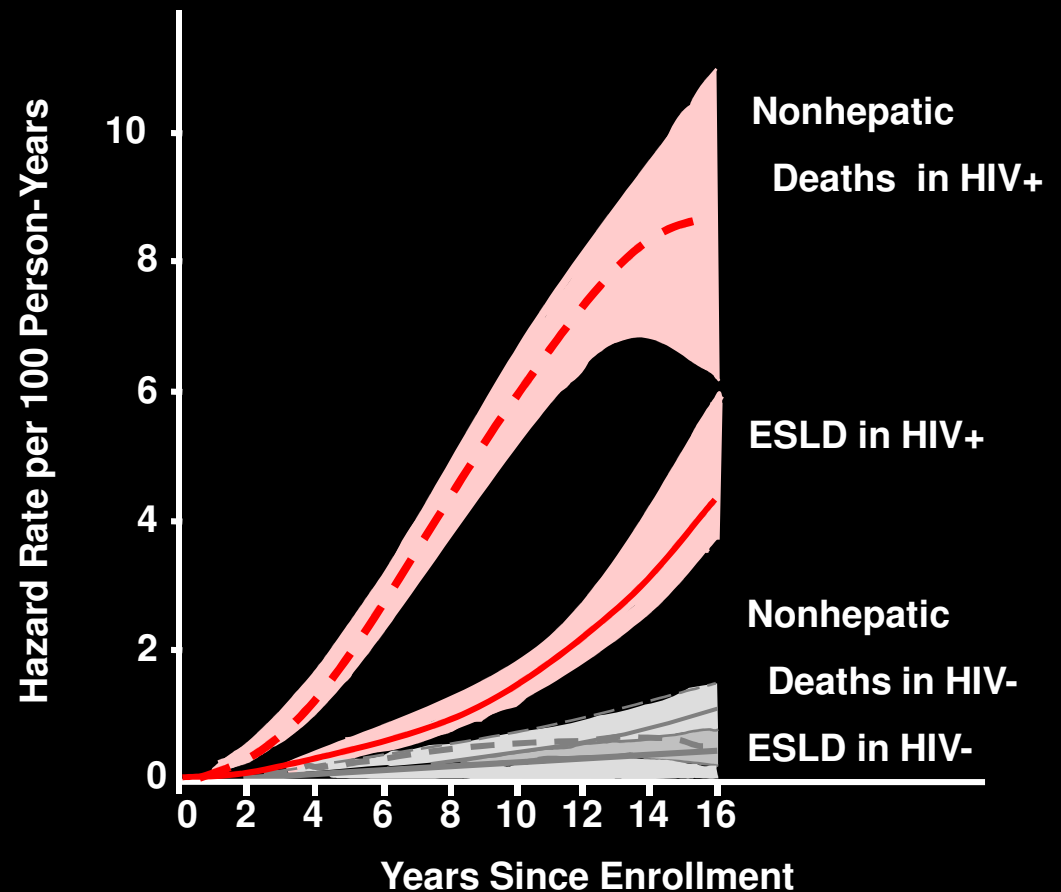
CD4 > 350/mm³

HIV Adversely Affects Hepatitis C Natural History

- **Viral persistence**
- **HCV RNA abundance (load)**
- **Cirrhosis or end stage liver disease**

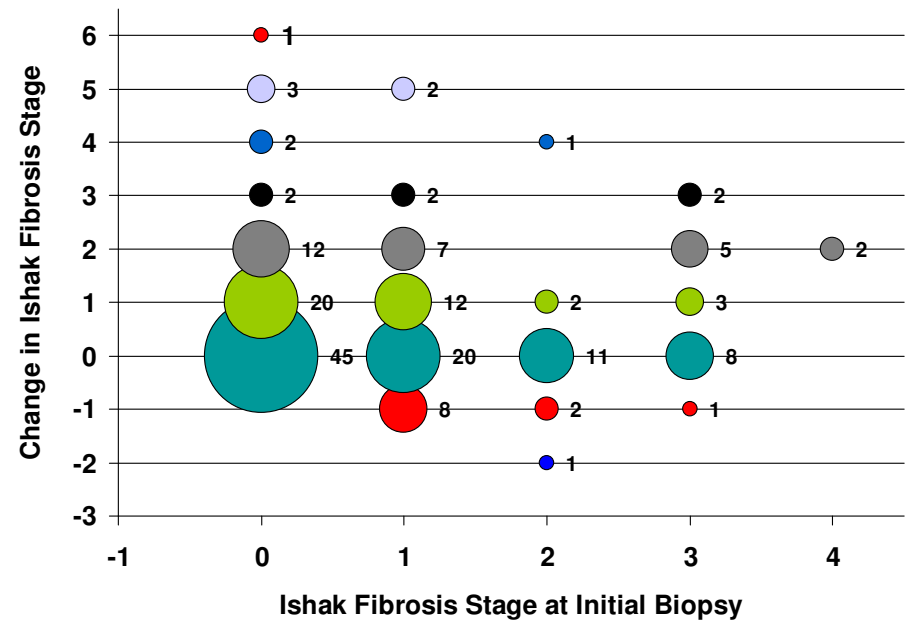
Increased ESLD and Nonhepatic Deaths Among HIV-HCV Infected MHCS Participants

- 1816 HCV-infected hemophiliacs followed 16 years
- 624 HIV neg; 1192 HIV pos
- 135 HBsAg pos



Rapid Progression of Liver Disease in HIV/HCV-coinfected Persons*

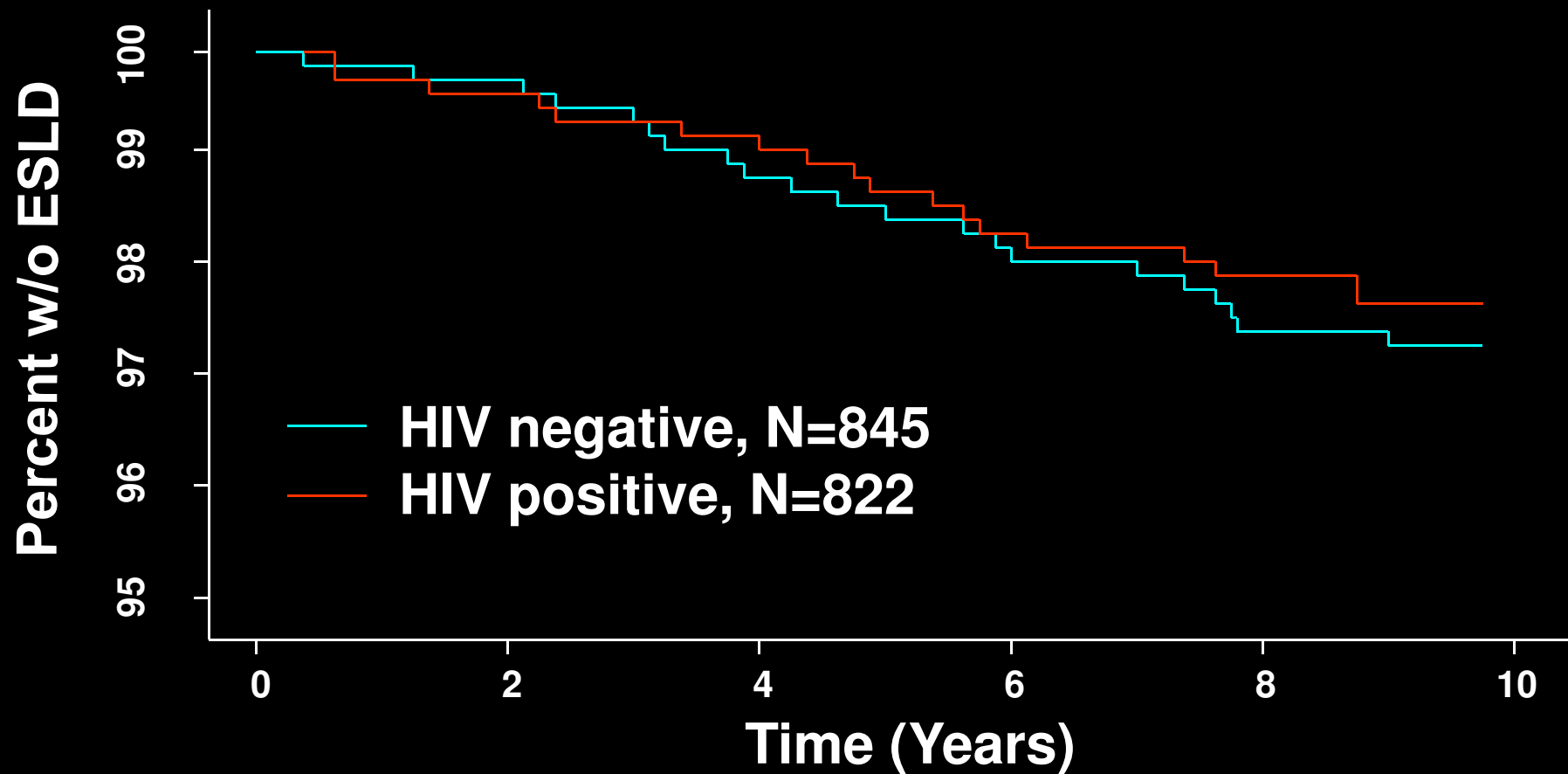
- 175 HIV/HCV coinfected persons biopsied twice, median 2.9 yrs
- 41 (24%) had ≥ 2 pt increase



Liver Disease Progression in IDUs not As Strongly Associated with HIV

- **119 IDUs paired biopsies over 4.2 years**
 - **21% had at least 2 (Ishak) point increase**
 - **No difference in HIV pos versus negative**
- **Competing mortality, pre- or off-ART**
- **Recent data shows greater cirrhosis but effect less than hemophilia populations**

ESLD among HCV infected IDUs*



* JAMA 2000;284:450

HIV increases Risk of Cirrhosis among HIV infected IDUs

Mechanism for Effect of HIV on Liver Fibrosis Progression is not Known

- **Direct viral interaction is not likely**
- **Diminishes quasispecies diversity probably reflecting reduced immunity¹**
- **Increased STAT1 activation and Fas ligand expression associated with HIV²**
- **Increased TGF beta associated with HIV³**

¹Mao J Virol 2001; Qin Blood 2005; Shuhart JID 2006;

Balusubramanian J Inf Dis 2006; ²Blackard J Interferon Cyt Res 2007

Microbial Translocation and Markers of HIV and HCV Pathogenesis

- **Brenchley et al linked microbial translocation markers (LPS, sCD14, LPS binding protein, and IgM endocore AB) to HIV-related immune activation (Nat Med 2006)**
- **Microbial translocation is a mechanism for alcohol related liver disease**
- **88 HCV infected (29 HIV/HCV coinfectd) subjects with minimal fibrosis (n=65) or cirrhosis (n=23)**
- **HIV strongly associated with all 4 markers**

Association of Microbial Translocation with Cirrhosis and HIV infection

Variable	OR	95% CI	p-value
age \geq 47	16.49	4.53 – 59.96	<0.0001
Ips 10-64	9.99	2.08 – 47.89	0.0040
Ips \geq 65	17.90	4.07 – 78.70	0.0001

Association of Microbial Translocation with Cirrhosis and HIV infection

Variable	OR	95% CI	p-value
age \geq 47	16.06	5.00 – 51.97	<0.0001
cd4 $<$ 350	5.51	1.31 – 23.17	0.0198
cd4 \geq 350	3.23	0.71 – 14.77	0.1308

Association of Microbial Translocation with Cirrhosis and HIV infection

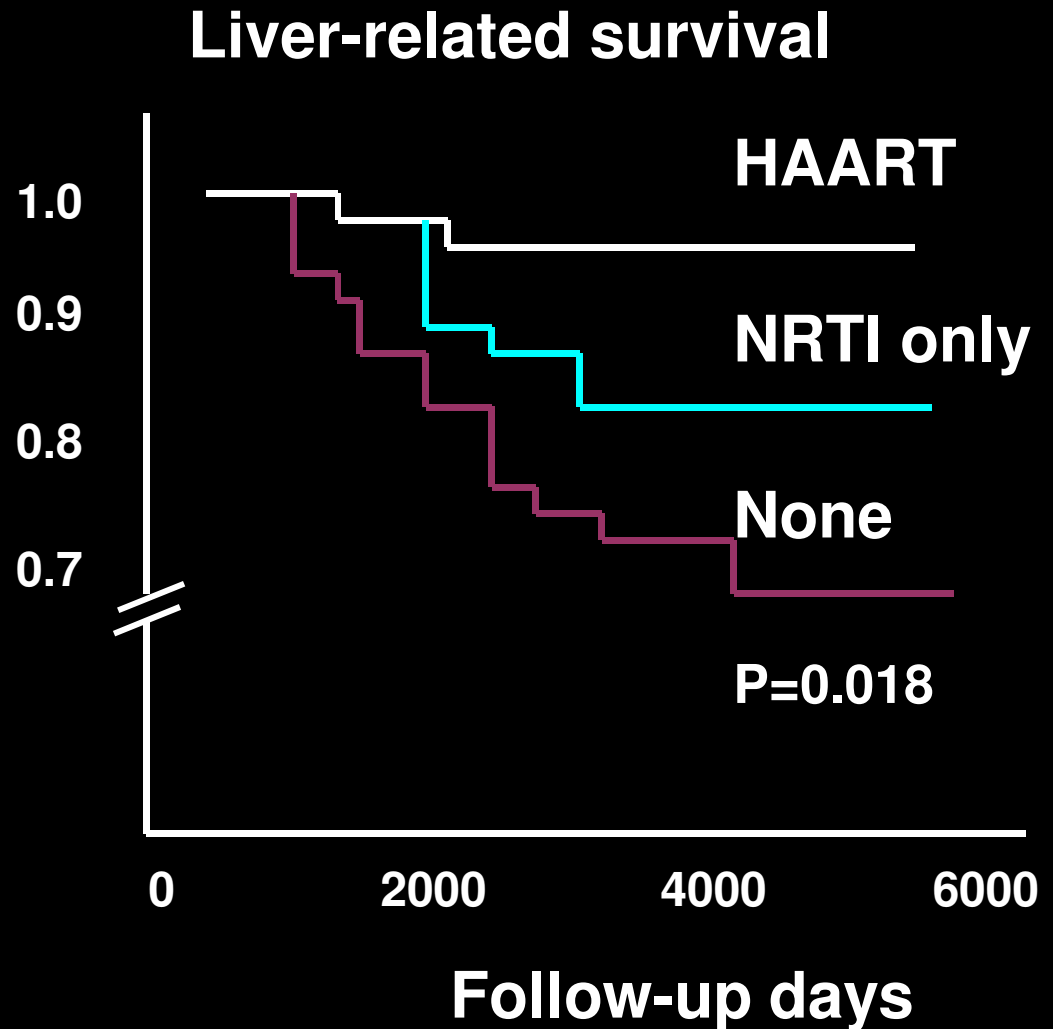
Variable	OR	95% CI	p-value
age \geq 47	20.62	4.94 – 86.11	<0.0001
Ips 10-64	11.35	2.15 – 59.94	0.0042
Ips \geq 65	14.66	3.25 – 66.13	0.0005
cd4 $<$ 350	4.54	0.98 – 21.15	0.0539
cd4 \geq 350	2.06	0.36 – 11.68	0.4148

Might early ART use lead to lower rates of liver disease?

- **Yes**
 - Marked reduction in viral replication
 - Restores CD4 lymphocyte count and some functions
- **No**
 - ART increases liver enzymes (fat)
 - ART increases peripheral CD4 lymphocyte but NOT in gut and some other tissues
 - ART increases HCV RNA level
 - May not restore meaningful immunity

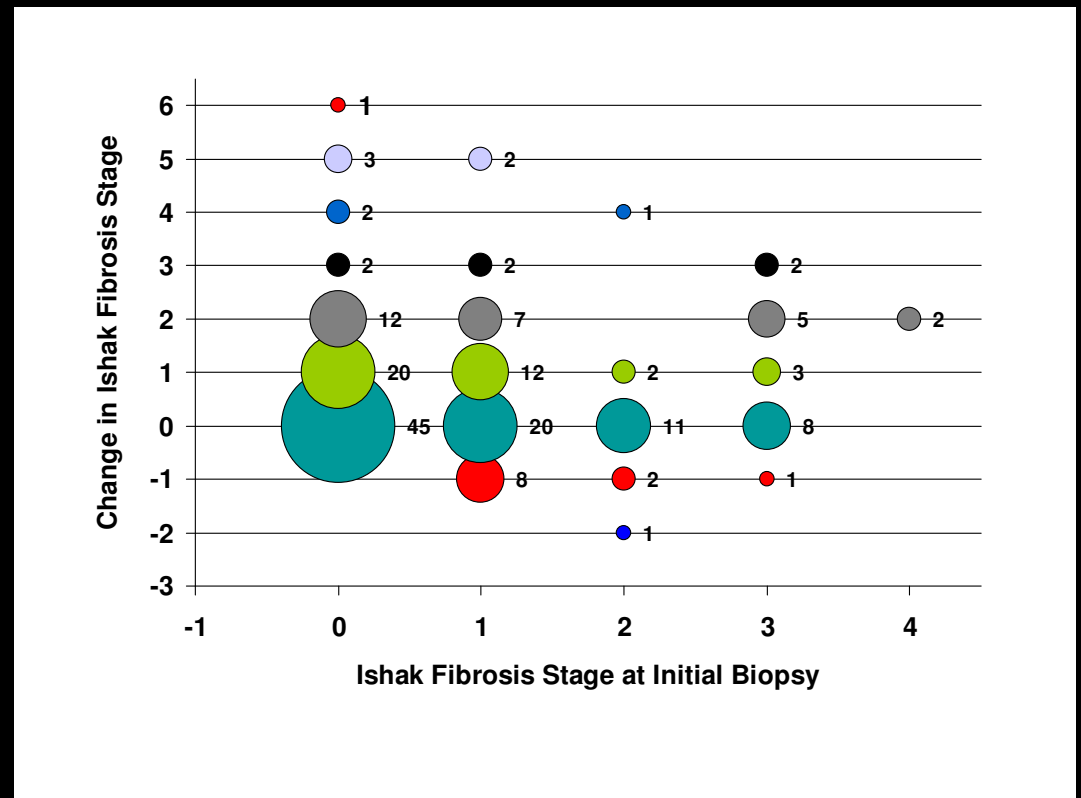
Lower Liver-Related Mortality In Patients Taking HAART

- HIV/HCV patients from 1990 to 2002
 - 93 HAART
 - 53 NRTI
 - 137 no treatment
 - ~80% hemophilia
 - ~5% HBsAg



Three Year Predictive Value of Liver Biopsy Represents Error and Natural History

- 175 HIV/HCV coinfecting persons biopsied twice, median 2.9 yrs
- 41 (24%) had ≥ 2 pt increase
- No differences detected in time on ART before Bx1, HIV RNA or CD4 lymphocyte between Bxs
- Kupffer cells and CD4 lymphocyte nadir



Summary

- **HIV adversely affects natural history of HCV infection**
- **CD4 lymphocyte depletion is important**
- **Mechanisms poorly understood**
- **ART does not appear to substantially reverse in short term**