

HEP DART 2005

frontiers in drug development for viral hepatitis

HIV/HBV co-infection: new therapies

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New insights into HCV and HBV in HIV patients

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2005

Goals of Therapy

- Decrease viral replication
- Ameliorate symptoms
- Decrease inflammation
- Decrease progression to cirrhosis
- Decrease Hepatocellular carcinoma
- Improve survival life-time risk

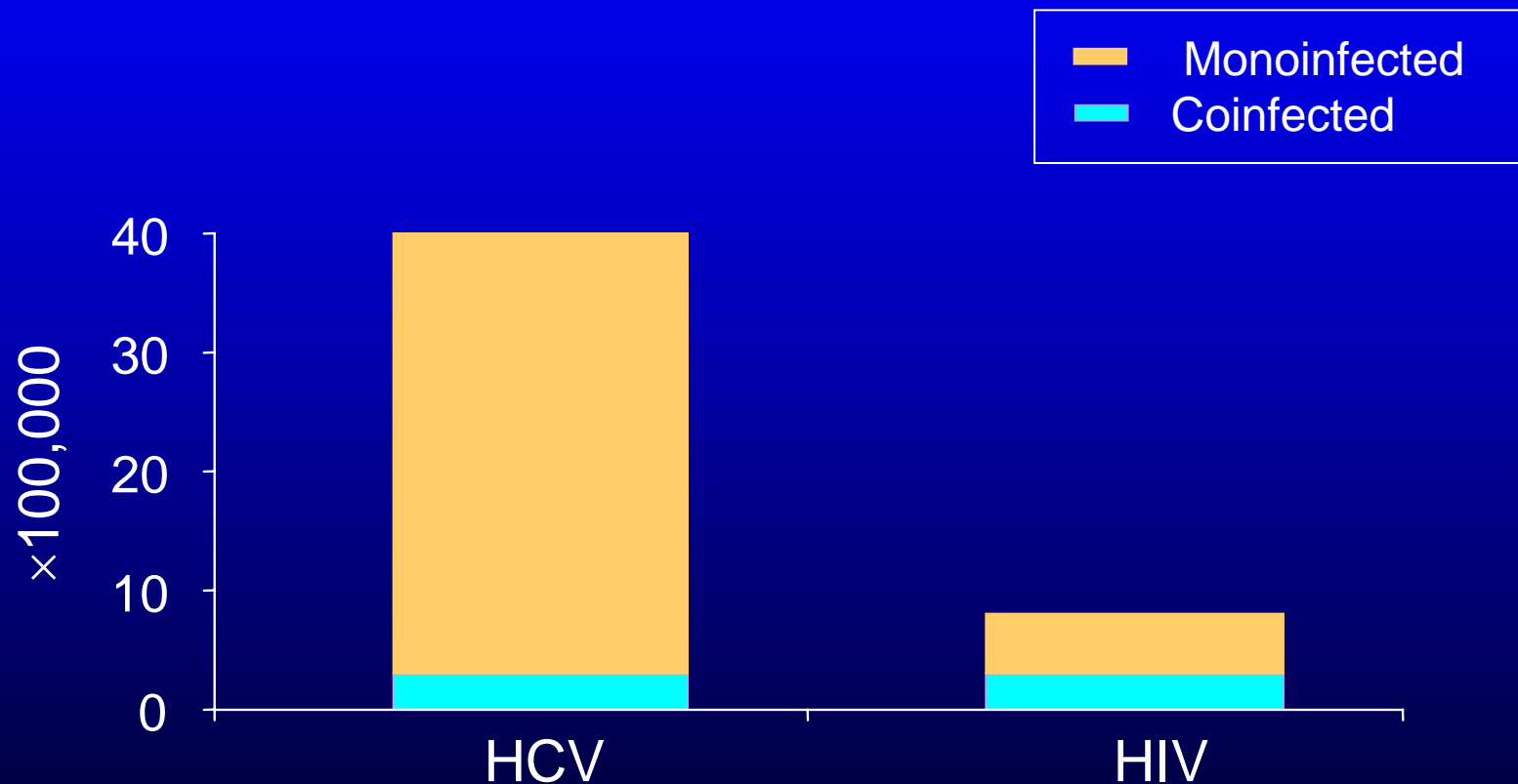
Comparison of HCV HIV

HCV

HIV

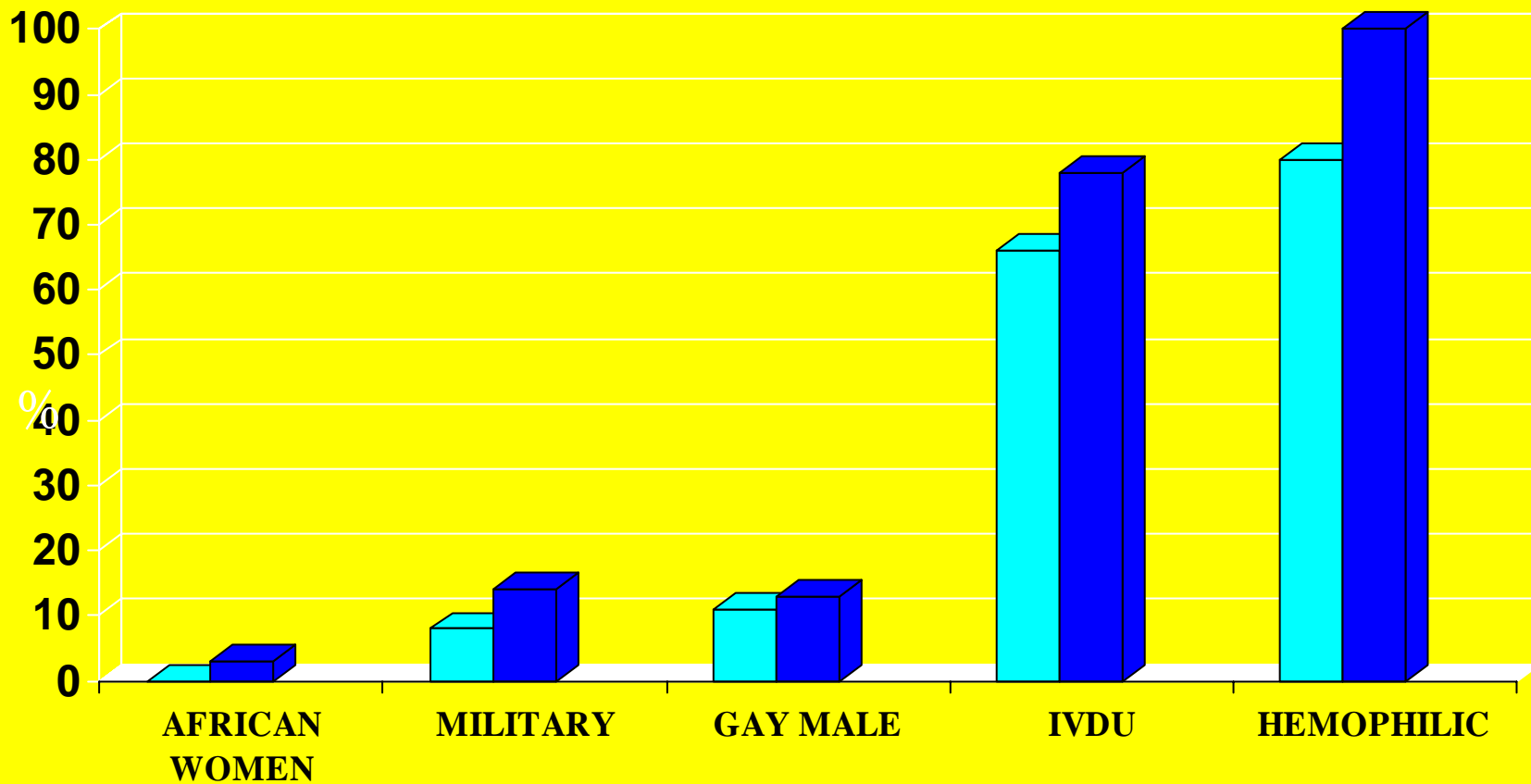
- | | | |
|---------------|----------------------------|------------------|
| • Virus | RNA +ss | RNA + ss |
| • Mutation | high 10^{11-12} | high 10^{9-10} |
| • Viral load | Not prognostic | Prognostic |
| • Goal | ↓inflammation
Avoid HCC | Remission |
| • Vaccine | No | No |
| • Latency | no | usual |
| • Integration | no | yes |
| • Curable | yes | no |

HIV/HCV Coinfection in US



HCV = hepatitis C virus; HIV = human immunodeficiency virus.
Slide courtesy of Dave Thomas, MD.
CDC. *MMWR*. 1998;47(RR-19):1-66.

HCV Antibody prevalence in HIV-infected subjects



Acute HCV in HIV MSM

- 11 cases in Bay Area
- Incidentally ↑ AST/ALT to severe liver dysfunction
- 10/11 CD4 > 250
- 5/11 recent STD
- 3 spontaneous lost HCV RNA
- 4/5 SVR after Peg IFN and RBV
- 3/6 untreated became chronic

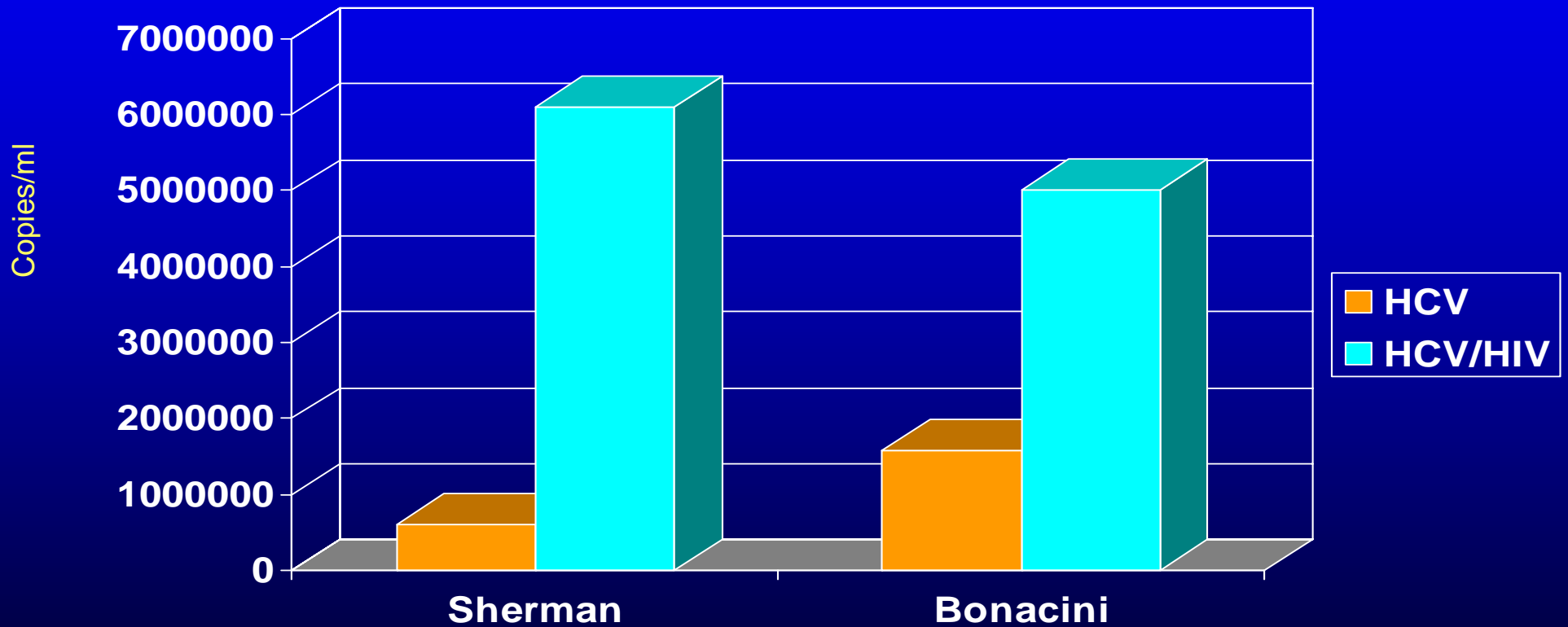
Acute HCV in HIV

- 210 subjects in London
- Case control questionnaire
- 64% on ART, mean CD4 552
- 88% genotype 1-
 - 78 had genotype 1a; 5 clusters largest 43 pts
 - 1b in 7 same cluster
 - 3a 4/6 same cluster
- 30% syphilis in last year

Acute HCV in HIV

	Cases	controls
• IDA last year	17%	6%
• Dating internet	50	5
• Median # partners	30	10
• One night stand	20	8
• Group sex	88%	52%
• Use of party drugs	92%	62%
• STD	92%	78%

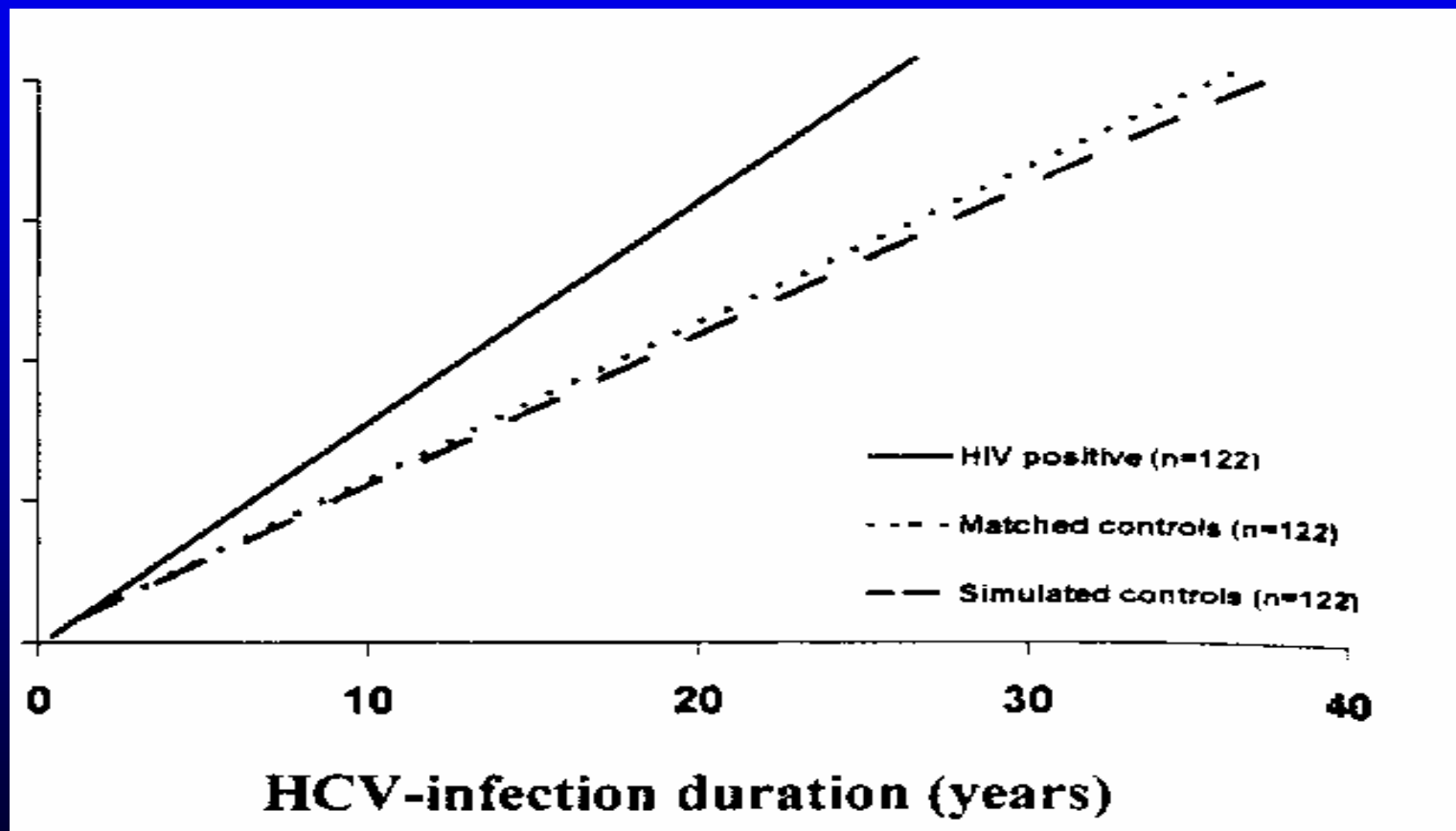
HCV VIRAL LOAD



Sherman et. al, CID, 2002

Bonacini et. al., J VIRAL HEP, 1999

FIBROTIC PROGRESSION IN COINFECTED PATIENTS



FACTORS ASSOCIATED WITH FIBROTIC PROGRESSION IN HIV-INFECTED PATIENTS

- Alcohol > 50 gms/day
- CD4+ < 200 cell/mm³
- Age at Time of HCV Infection (>20)
- No Protease Inhibitor Therapy

HCV-HIV Coinfection

- HCV a significant cause of morbidity and mortality in HIV cohort
- IFN and ribavirin-based therapies produce modest response rates in coinfection
- Treatment is associated with toxicities, higher in coinfecting patients (10-29% premature D/C rate)- lower with psych and growth factor support
- PEG-IFN and ribavirin are now standard of care in HCV and HIV

Why Treat HCV/HIV Coinfection?

In favor

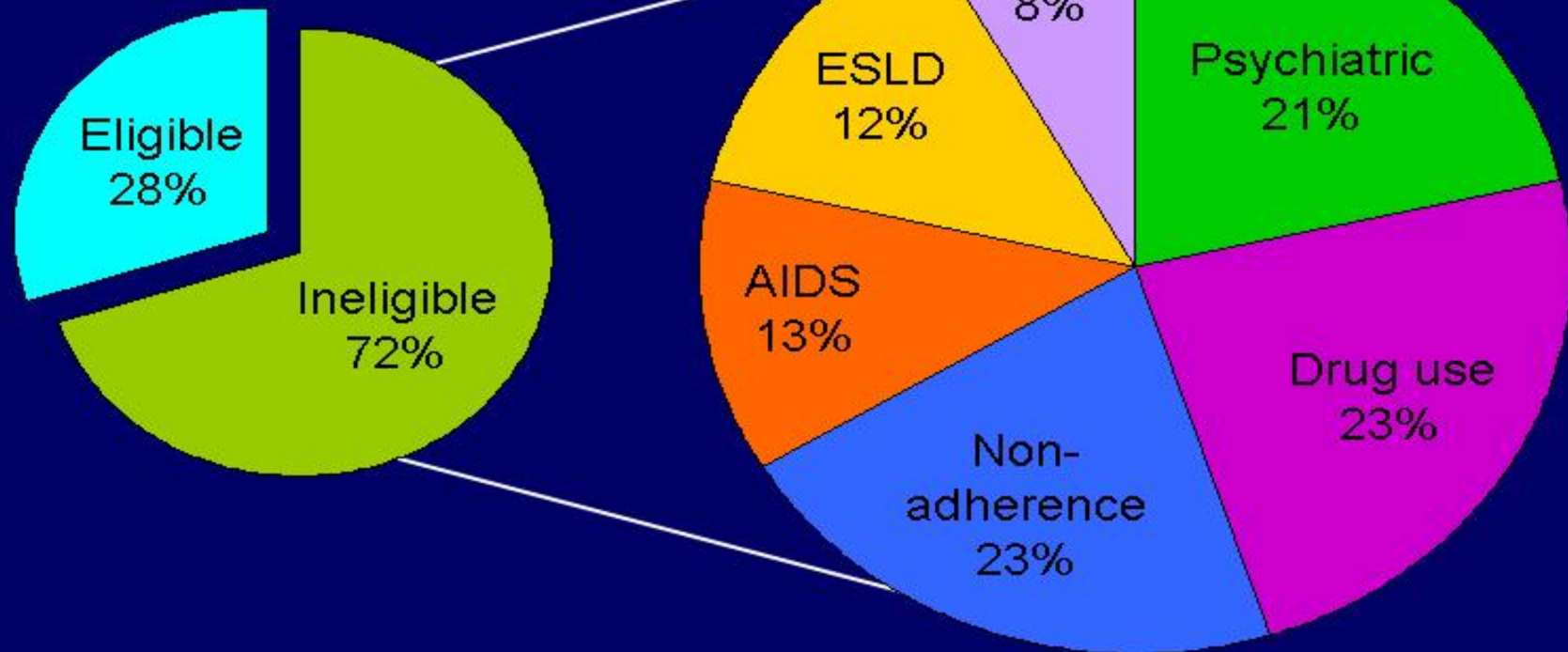
- HIV HCV have increased Rate of Progression
- Increased Liver Associated Morbidity
- SVR Occurs with PEG-IFN/Riba Treatment
- May Improve Ability to Give HAART

Against

- Poor Tolerability
- Patients often Not Treatment Candidates
- Decreased Response Rates Compared to HCV Monoinfected
- Drug Interactions
- Clinician Comfort Level Low

Barrier to HCV Treatment in an Urban HCV/HIV Clinic

149 HIV/HCV-infected patients



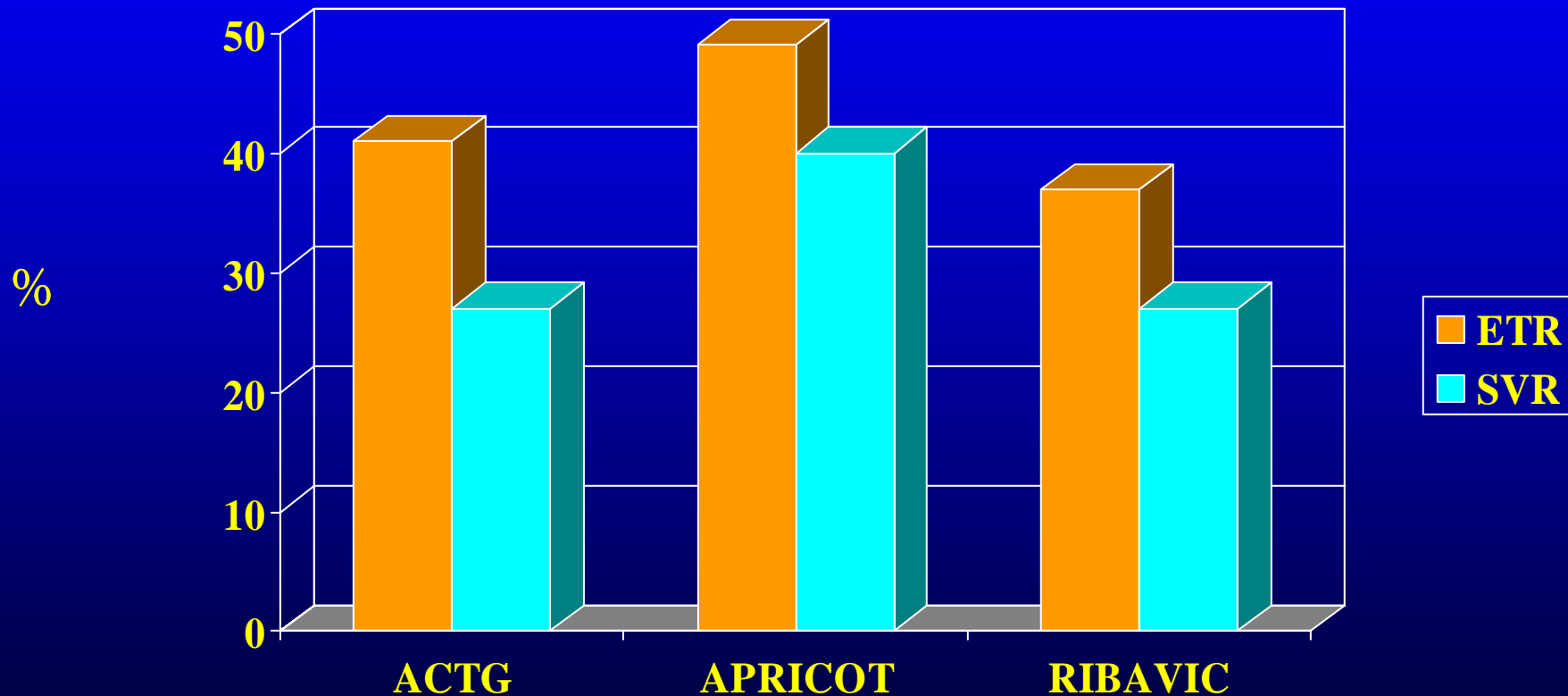
ESLD, end stage liver disease.

Fleming et al. *Clin Infect Dis*. 2003;36:97-100.

Randomized PEG-IFN Trials HCV/HIV

- ACTG 5071/5091s
- APRICOT
- RIBAVIC
- Other Single Center Clinical Trials
- Presco- RBV weight based dosing ongoing

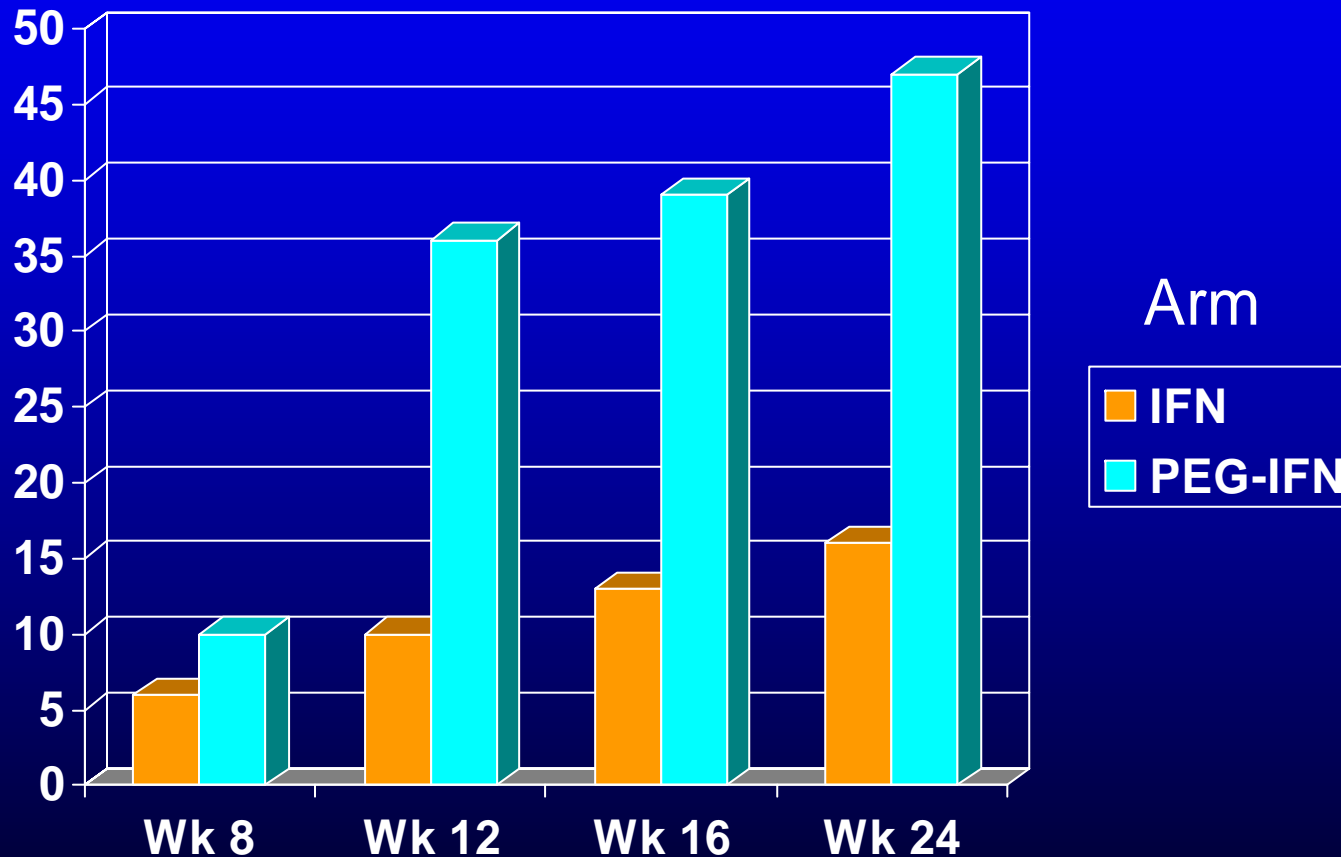
PEG-IFN VIROLOGIC RESPONSE RATES



Chung et. al., 2004 NEJM
Torriani et. al., 2004 NEJM
Carrat et. al., 2004 JAMA

HCV RNA status over time: ACTG 5071

% of subjects with undetectable HCV RNA



Early virologic response has 100% negative predictive value

Week 12
(N = 106)



2 log₁₀ drop
or neg HCV RNA

Yes

n = 43
(41%)

SVR

n = 22
(51%)

No SVR

n = 21
(49%)

No

n = 63
(59%)

SVR

n = 0
(0%)

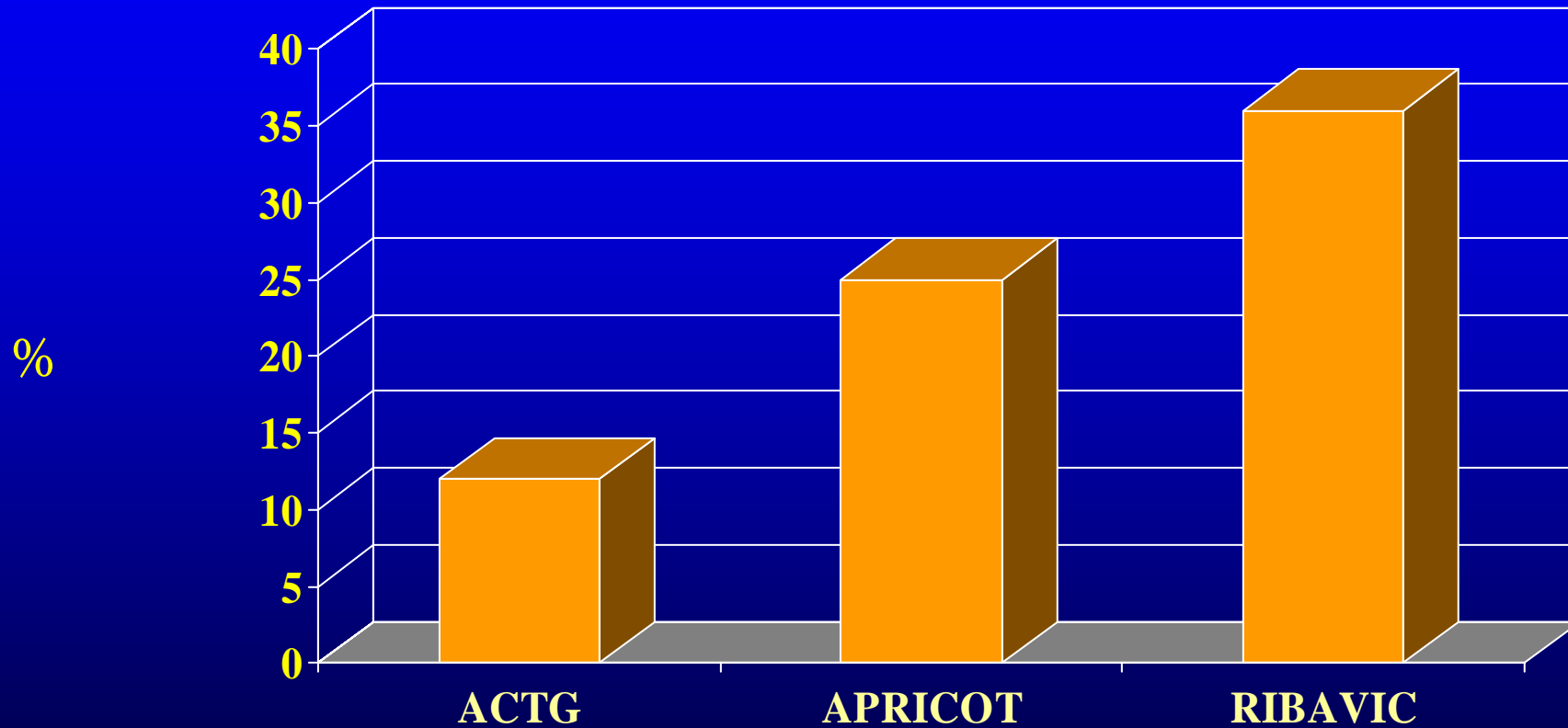
No SVR

n = 63
(100%)

	Apricot	5071	Ribaviric
•Type IFN	Peg40	Peg 40kd	Peg12kd
•Ribavirin	800	escalating	800mg
•Geno 1	60%	77%	58% (4)
•Stage 3 /4	16%	11%(4)	39%
•HCV RNA	same		
•Caucasian	80%	50%	?
•SVR overall	40%	27%	27%
•SVR geno 1	29%	14%	17%
•SVR geno 2/3	62%	73%	

Chung NEJM 2004; Torriani NEJM 2004; Carrat JAMA 2004)

PATIENT DROP-OUT



Chung et. al., 2004 NEJM
Torriani et. al., 2004 NEJM
Carrat et. al., 2004 JAMA

Pancreatitis on DDI; decompensation in cirrhotics;
Anemia and ddi;

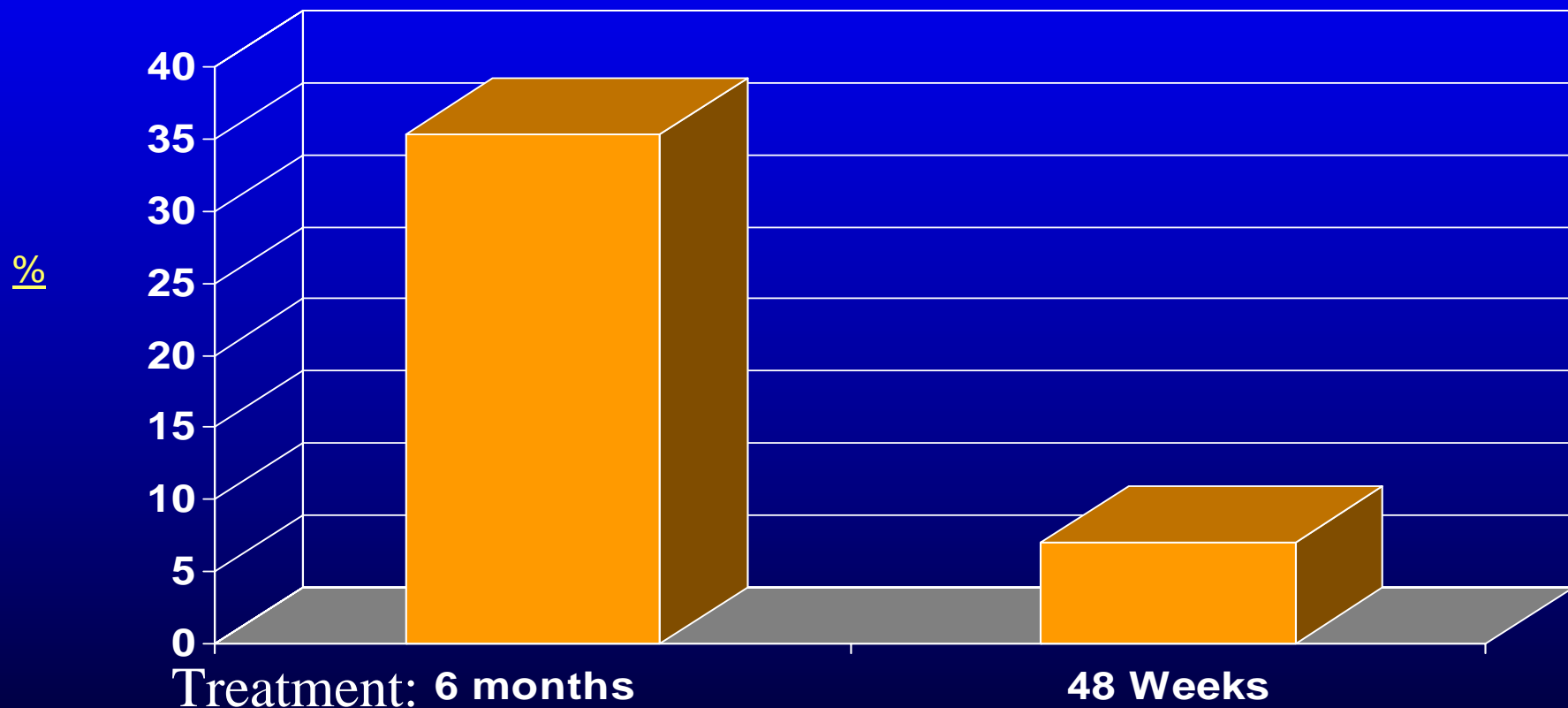
Virologic non-responders experienced histologic response

NR	IFN/RBV n=57	PEG/RBV n=37
Wk 24 Bx obtained	45	26
Histologic response	16 (36%)	9 (35%)
Median log ₁₀ HCV RNA change, Histologic Responder		
ΔHCV RNA, W0-24	-0.61	-1.01
Median log ₁₀ HCV RNA change, Histologic Non-Responder		
ΔHCV RNA, W0-24	-0.58	-0.71

Summary

- PEG IFN α -2a + RBV is superior to IFN α -2a + RBV in achieving SVR in HCV/HIV coinfection
- SVR rates for HCV gt 1 are lower than seen in HCV mono-infection
- Independent predictors of SVR were PEG/R, genotype, detectable baseline HIV RNA, absence of IDU
- Early virologic response ($>2 \log_{10}$ HCV RNA drop) has 100% negative predictive value for SVR
- Both treatments improved liver histology in more than half the virologic responders and a third of non-responders

Relapse Rates in HCV/HIV Genotype 2,3

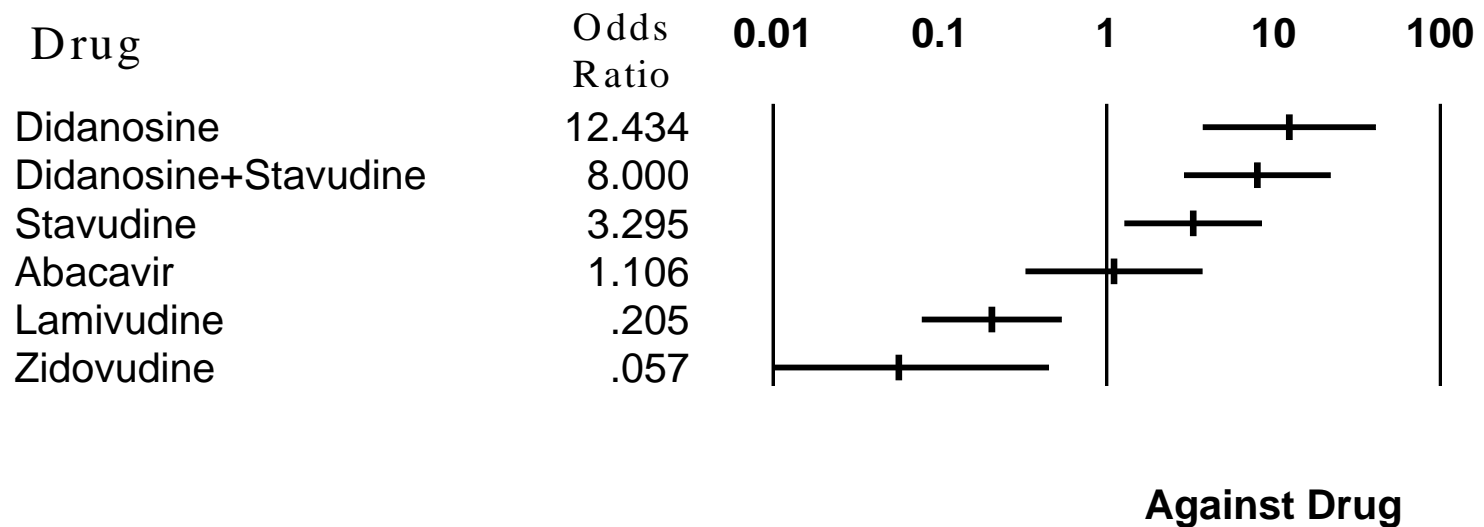


Relapse Rates for HCV/HIV coinfecting patients treated with 6 months or 48 weeks with Peg-IFN + Riba

Soriano et. al., 2004, AIDS Research and Human Retroviruses

Chung et. al., 2004, NEJM

RIBAVIRIN-NRTI MITOCHONDRIAL TOXICITY



Predictors of Response to therapy

	GOOD	POOR
• Genotype	2/3	1
• sex	female	male
• age	<40	>40
• viral load	<2x10 ⁶	>2x10 ⁶
• fibrosis	no	Cirrhosis
• kinetics	fast	Slow
• Alcohol	none	>50 g/d
• HIV	-	+
• BMI	Low	High

IFN in HCV HIV

Depends upon a number of factors including

- **Virus** Genotype, HCV RNA
 HIV status
- **Host** Race, age, weight
- **Drug** Adherence, ribavirin dosing

Summary

Strategies must focus on optimizing outcome in genotype 1

- Ribavirin dosing- Presco trial
- Use of EVR tool- earlier assessment
- Duration of Rx
- Use of HAART to boost SVR- ACTG 5184
- Maintenance approaches for NR- ACTG 5178

HIV HCV- Summary

- Biopsy if compensated liver disease
- Treat if compensated HIV and liver disease
- Support side effects aggressively
- Continue Rx through abnormal ALT
- Promote adherence
- Screen for HCC with AFP and ultrasound
- Watch for drug interactions and toxicities
- Watch for acute HCV, esp in MSM patients
- Customize therapy- 1 y for genotype 2/3
?longer, higher induction for genotype 1