

# Clinical Management of Co-Infected Patients

*HIV/HBV and HIV/HCV*

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# HIV HBV HCV

- **Shared routes of transmission**
  - Sex
  - Contaminated needles and blood products
  - Maternal-Fetal
- **Overlapping drug activity**
  - Lamivudine
  - Tenofovir
  - Adefovir
  - Emtracitabine
  - Interferon
- **Intervirus effects**
  - HBV and HCV more aggressive with HIV
- **Chronic infection rates**
  - HIV 100%
  - HCV 80%
  - HBV 5-10%
- **Non-Overlapping drugs**
  - Entecavir, telbivudine
  - VX-950, NM283
- **Variable resistance rates**
  - All monotherapy-resistance
  - Lamivudine
  - Tenofovir
- **Vaccination**
  - Less effective for HBV when HIV present

# Commonalities: HIV HBV HCV

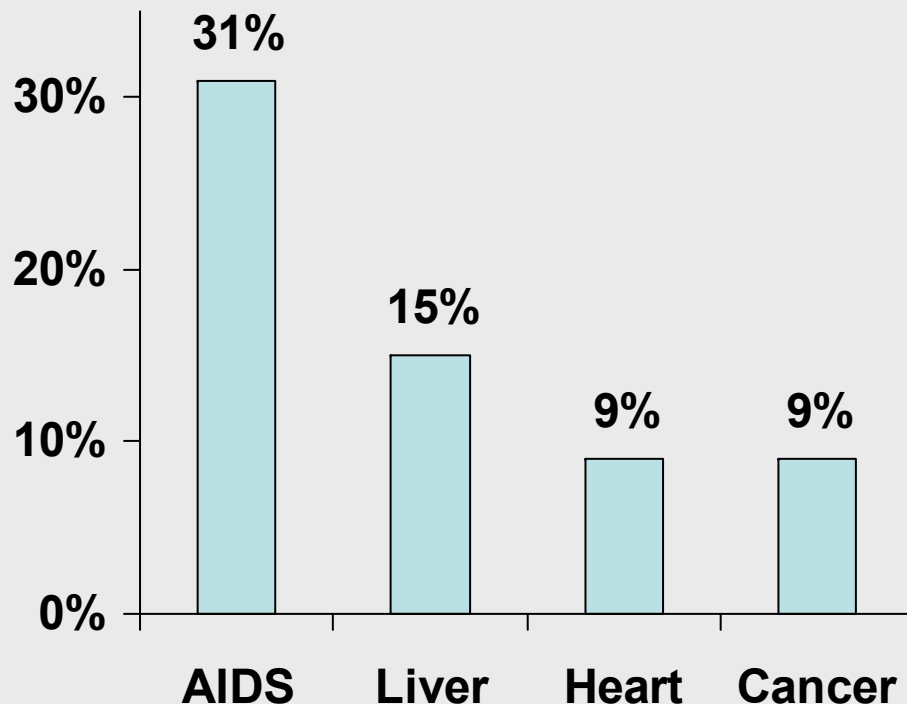
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- Routes of transmission are shared
- All are very dynamic
- Treatment is complicated and prolonged
- Co-infection treatment is even more complicated
- *Dead* viruses don't mutate
- *Dead* viruses aren't associated with disease progression
- *Dead* viruses are good

# Causes of Death Among HIV+ Persons with Access to ARVs

23,441 HIV+ Patients

D.A.D: Cause of Death



Multivariate model for liver death:

HCV 6.7 (3.9 – 11.2)

HBV 3.7 (2.4 – 5.9)

Low CD4 1.23 (1.2 - 1.3)

IDU 2.0 (1.2 – 3.4)

Older age 1.3 (1.2 – 1.5)

# Management Difficulties in Co-Infected Patients

- HIV + HBV
  - Drugs overlap
  - Combination therapy recommended
    - Based on very little data, if any
  - Relatively easy
- HIV + HCV
  - Drugs don't overlap
  - IFN + RBV very poorly tolerated
  - Very difficult
- HIV + HBV + HCV
  - Very rare

# Treatment Management Issues

## HIV + HBV

- Who gets treated
  - HIV
  - HBV
  - HIV/HBV
- What treatment
  - IFN?
  - HIV/HBV drug
    - Lam, FTC, TDF
  - HBV drug
    - Telbivudine, entecavir, adefovir (low dose)

# Recently Reported Guidelines for Management of HBV-HIV Coinfection

- Consensus conference on chronic viral hepatitis and HIV infection: updated Spanish recommendations- May 2003 (published *J Viral Hep.* 2004.)
- CDC, NIH, DHHS- *MMWR* December 2004
- First European Consensus Conference on the Treatment of Chronic Hepatitis B and C in HIV Coinfected Patients- March 2005 (published *Journal of Hepatol.* 2005.)
- Care of patients with chronic hepatitis B and HIV co-infection: recommendations from an HIV-HBV international panel. October 2004 (published *AIDS.* 2005.)
- DHHS Guidelines for the treatment of adults with HIV Infection. May 4, 2006.

# Types of HBV/HIV-infected Patients

1. Needs HBV treatment – doesn't need HIV treatment
2. Needs HBV and HIV treatment – lamivudine naïve
  1. Who goes first? Simultaneous?
  2. Many overlapping drugs
3. Needs HBV and HIV treatment – lamivudine experienced
  1. Can you stop a drug failing one virus?

# Who to Treat

Spanish

Elevated transaminase levels AND  
Detectable HBV DNA

CDC, NIH

Actively replicating virus (HBeAg or HBV DNA  $>10^5$   
cop/ml) AND  
Liver disease (elevated ALT or histology)

European

HBV DNA  $>10^5$  cp/ml in HBeAg+ or  $>10^4$  cp/ml in HBeAg-  
AND  
Liver disease (elevated ALT or histology)  
Cirrhosis

International  
panel

No strict recommendations. Individualize and consider  
need for HIV therapy.

DHHS

Treat all HIV/HBV patients with 2 active hepatitis B drugs.

# What to Treat with: *HIV Treatment not Indicated*

Spanish	CDC, NIH	European	International panel
PEG-IFN ADV	PEG-IFN* ADV	CD4 $\geq$ 500: PEG-IFN or ADV CD4 <500: HAART incl TDF+LAM/FTC	HBeAg+: IFN HBeAg-: ADV

NOTE: Entecavir and telbivudine were not yet approved when these were published.

\*Cannot use in decompensated liver disease.

# What to Treat with: *HIV Treatment Indicated and LAM-Naïve*

Spanish	CDC, NIH	European	International panel
LAM TDF LAM/TDF	LAM* (preferably with ADV or TDF)  TDF (with LAM* until more known about TDF-R)	HBV DNA > 10 <sup>5</sup> cp/ml: HAART with 2 anti-HBV drugs  HBV DNA <10 <sup>4</sup> cp/ml: HAART of choice (optional if active against HBV)	LAM or FTC plus TDF

\*Can substitute emtricitabine for LAM.

# What to Treat with: *HIV Treatment Indicated and LAM- experienced*

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**Spanish**

**CDC, NIH**

**European**

**International  
panel**

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Not  
discussed

ADV  
TDF

TDF

Not discussed

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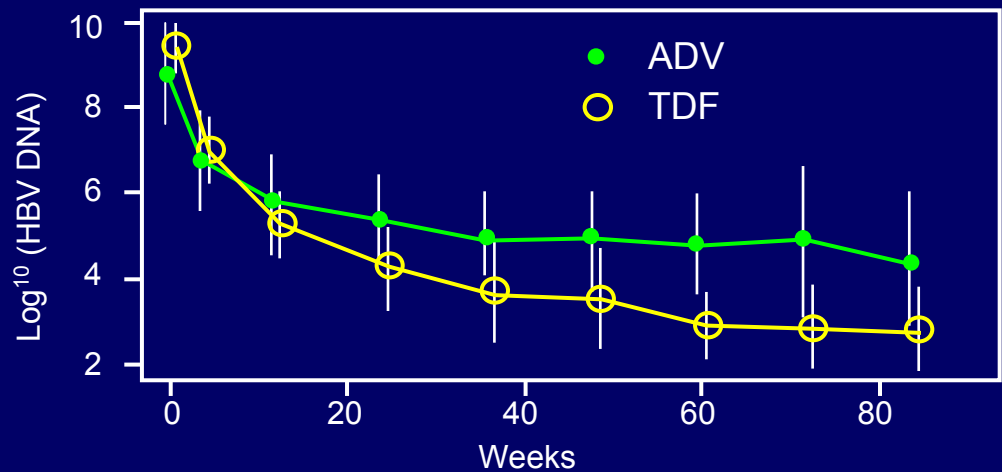
# ACTG A5127: TDF vs Adefovir for HBV in HIV Coinfection

- Double-blind, placebo-controlled study of ADF (10 mg) vs TDF (300 mg)
- Patients on stable HAART;  $n=52$
- HBV DNA  $>100,000$  c/mL
- HIV RNA  $<10,000$  c/mL
- Early termination when endpoints met

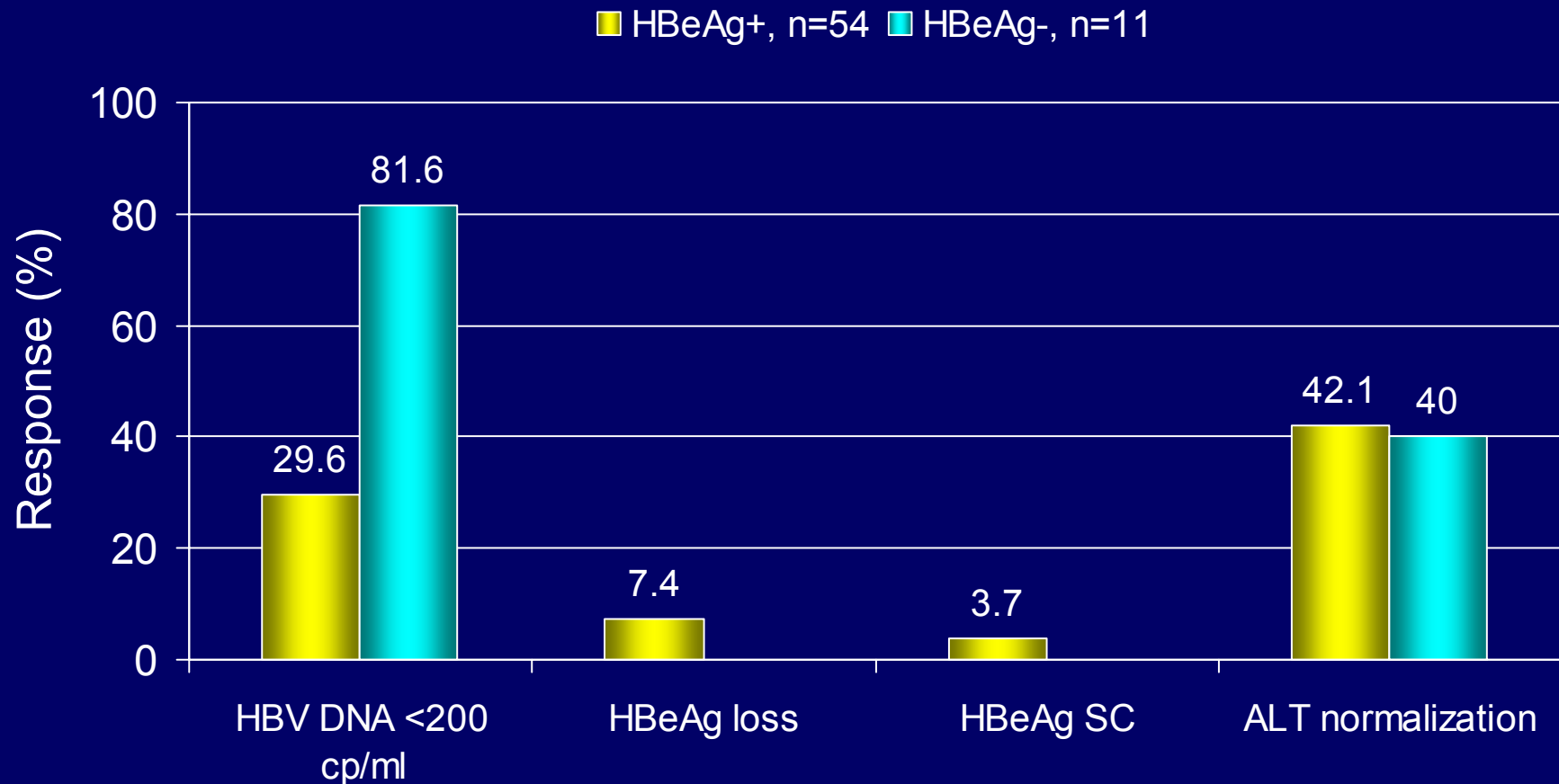
Serum HBV DNA DAVG<sub>48</sub> (log<sub>10</sub> c/mL)

	<i>n</i>	ADF	TDF	Diff	Lower CI
ITT	52	-3.12	-4.03	0.91	-0.498
Mod. ITT	47	-3.35	-4.46	1.11	-0.090
AT	41	-3.48	-4.76	1.28	0.180

Mean change in HBV DNA from BL



# Cohort Study of 12 Months of Tenofovir in HIV-infected Persons with LAM-R HBV



# Cross-resistance of Drug-Resistant HBV

HBV	Lamivudine LAM <sup>1</sup> Fold Resistance	Adefovir PMEA <sup>2</sup> Fold Resistance	Clevudine L-FMAU <sup>1,3</sup> Fold Resistance	Telbivudine L-dT <sup>4</sup> Fold Resistance	Entecavir ETV <sup>4,5</sup> Fold Resistance
Wild-type	1	1	1	1	1
L180M	1.7	0.5	>120	12	1
M204I	>106	0.7	>120	236	30
L180M+ M204V	>105	0.2	>120	133	30
A181T/V	2-6	1-5	NA	NA	NA
N236T	3-8	7-10	4.7	2.4	0.67
I169T/M250V	>1,000	1.0	NA	>100	>1,000
T184G/S202I	>1,000	2.0	NA	>1,000	>1,000

1. Chin et al. *AAC*. 2001;45:2495.
2. Angus et al. *Gastroenterology*. 2004;125:297.
3. Ono-Nita et al. *AAC*. 2002;46:2602.
4. Levine et al. *AAC*. 2002;46:2525.
5. Tenny et al. *AAC*. 2004 (in press).

# Combination Therapy

	LAM-naïve			LAM-experienced		
24 weeks	TDF N=10	LAM N=11	TDF/LAM N=6	TDF N=12	LAM N=9	TDF/LAM N=11
$\Delta$ HBV DNA (log cp/ml)	-4.66	-3.31	<b>-5.03</b>	<b>-3.41</b>	-0.82	<b>-3.93</b>
HBV DNA <400 cp/ml (%) (ITT)	40	36.4	50	16.7	0	36.4
ALT normalization (%)(ITT)	30	63.6	50	25	0	36.4

Yellow indicates  $P < 0.05$  compared to LAM group.

# Strategies to Treat HBV and not HIV

- Use agents that are not active against HIV to prevent development of drug-resistant HIV
- Pegylated-interferon-alfa
  - HBeAg+, genotype A, elevated ALT
- Entecavir
- Telbivudine
- Adefovir (?)
- ?combination entecavir+ adefovir

# Strategies to Treat HBV and HIV: LAM Naïve

- All of the following should be used with full HAART
  - First line: TDF plus LAM/FTC (emtricitabine)
  - Other considerations
    - Entecavir/telbivudine plus TDF
    - PEG-IFN
  - *Avoid: LAM, FTC or TDF as only HBV active agent*

# Strategies to Treat HBV and HIV: LAM Experienced

- All of the following should be used with full HAART
  - First line: Add TDF to LAM
  - Other considerations
    - Entecavir 1.0 mg- resistance occurs in presence of LAM-R
    - Add ADV
    - Add telbivudine

# Summary HIV/HBV Infection

- Treatment of HBV should be considered in HIV co-infected persons
- Resistance occurs to single agent therapy but rates vary
  - Cross-resistance also occurs
  - Use 2 HBV drugs upfront (DHHS Guidelines)
- Treatment plan is individualized based on need for HIV treatment and prior LAM therapy
  - HIV clinicians avoid ADF
- More potent agents are needed
- Combination therapy recommended but it still needs further investigation although it is already in the DHHS Guidelines

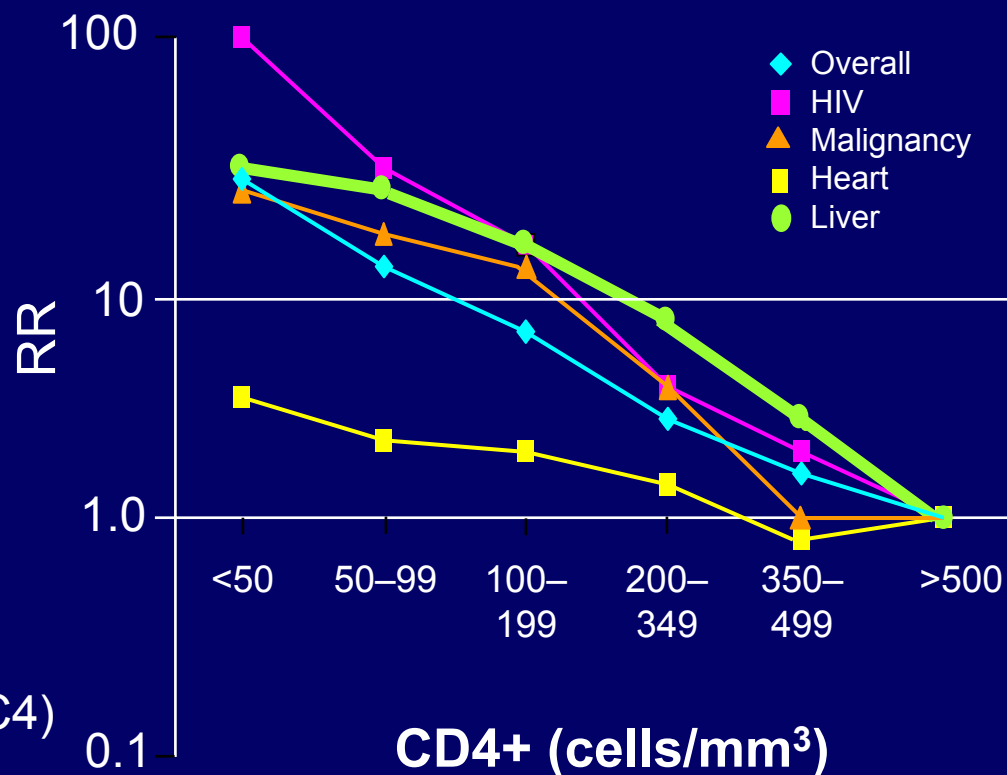
# HIV/HCV Coinfection

- ~30% HIV-infected are coinfecting with HCV
- HIV accelerates HCV disease
- HCV infection influence on HIV
  - ARV-associated hepatotoxicity
  - Response to ARV therapy
  - Natural history of HIV disease
  - Extrahepatic manifestations

# Risk of Death in HIV-Infected (D:A:D Study)

- Cohort study of >23,000 patients in Europe, Australia, and the USA
- 1,248 (5.3%) deaths 2000–2004 (1.6/100 person-years)
  - Of these, 82% on ART
- Leading causes of death
  - AIDS (30%)
  - Liver disease (14%)
  - Heart disease (9%)
  - Malignancy (8%)
- Predictors of liver-related death:
  - Age (RR: 1.3 per 5 years older)
  - IDU (RR: 2 vs MSM)
  - CD4+ (RR: 1.23 per halving of C4)
  - **Anti-HCV+ (RR: 6.7)**
  - HBsAg+ (RR: 3.7)

RR of death according to immune function and specific cause



# Major Issues in HCV/HIV Co-Infected Patients

- Difficult patients
- Difficult drugs
- Difficult Drug-Drug Interactions
- Genotype and race
- Biopsies
- Sequencing strategies unknown
- Management of non-responders

# Coinfected Patients have Significant Comorbidities

*HIV-infected Veterans with and without HCV*

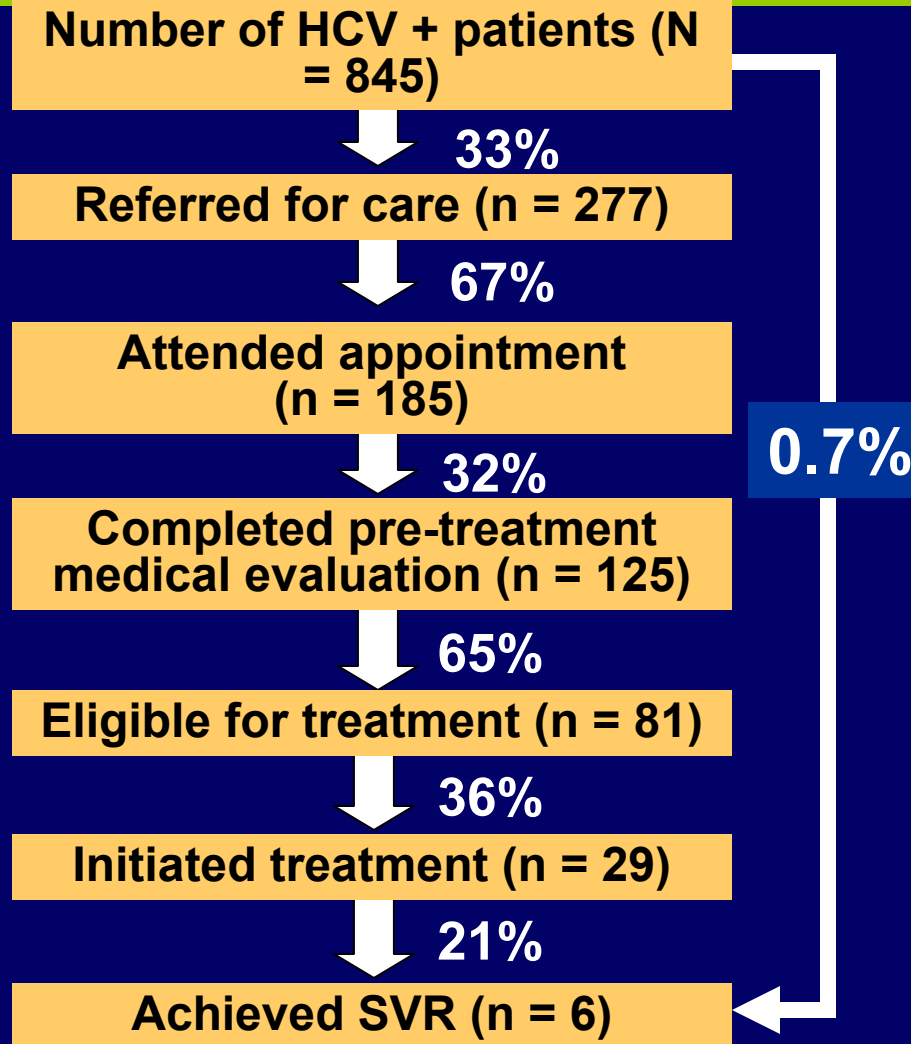
	HIV	HIV/HCV
Drug disorder	22%	58%
Alcohol disorder	24%	56%
Depression	28%	43%
Bipolar	6%	12%
Anemia	19%	27%
COPD	17%	21%
Hypertension	37%	42%

# Interferon/Ribavirin is the cornerstone of HCV therapy in HIV-Infection

- Ribavirin
  - interaction with zidovudine and other NRTIs
  - Teratogenic
  - Bone marrow toxicity
- Interferon
  - Decrease in CD4 counts, but not CD4%
  - Depression
  - Nausea, fatigue, malaise, alopecia
  - Injection
  - expensive
- Side effects in virtually 100% of patients

# Barriers to HCV Care

Johns Hopkins HIV Clinic (1998-2003)



## Referral associated with:

- ↑ALT levels
- Undetectable HIV RNA
- CD4+ > 350 cell/mm<sup>3</sup>
- Receiving care for psychiatric condition
- No active drug use

Mehta et al. CROI. Denver, CO. February 5-8, 2006. Abstract 884.

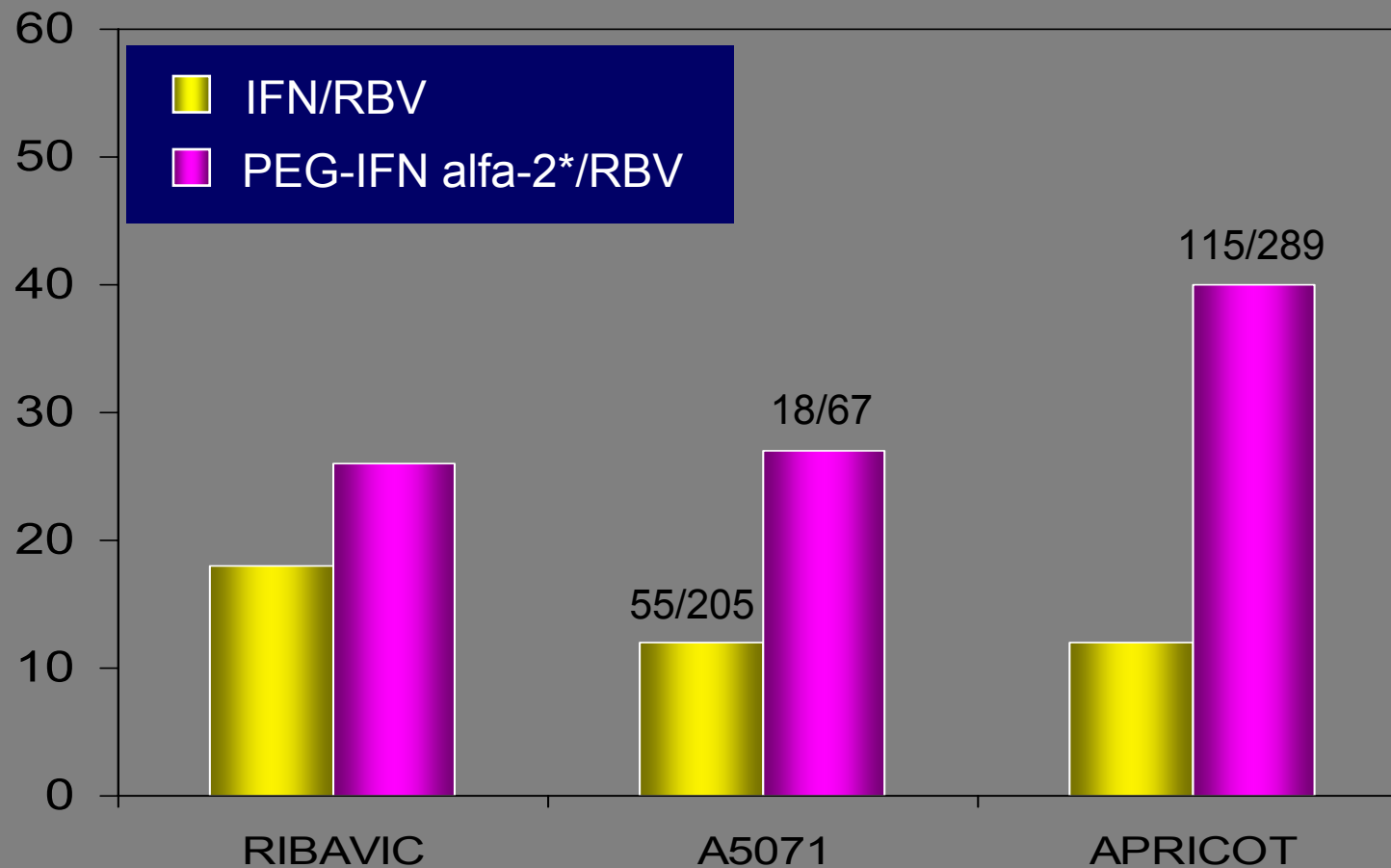
# Management of HIV/HCV Infection

- Guidelines mostly based upon Grade III evidence
  - Alberti A, et al. First European Consensus Conference. *J Hepatol.* 2005;42:615-624
  - Nelson M, et al. BHIV Coinfection Guideline Committee. *HIV Med.* 2005;Suppl 2:96-106
  - Soriano V, et al. HCV-HIV International Panel. *AIDS.* 2004;18:1-12.
- Requires multidisciplinary team of providers (doesn't exist if everyone gets treated)
  - HIV
  - HCV
  - Mental health
  - Addiction specialist

# HCV Treatment and Status of HIV Disease

- **Advanced and uncontrolled HIV Disease**
  - Little justification for HCV treatment
- **Stable HIV disease not requiring ARVs**
  - Candidate for HCV treatment with close monitoring
  - ACTG Study 5184
    - After 4 years of planning, 2 patients enrolled, study closed last week
- **Stable HIV disease on ARVs**
  - Good candidate (particularly if CD4 > 200 cells/uL)
  - Increased toxicity with ZDV and ddI
  - Potential decreased HIV activity with ZDV, d4T

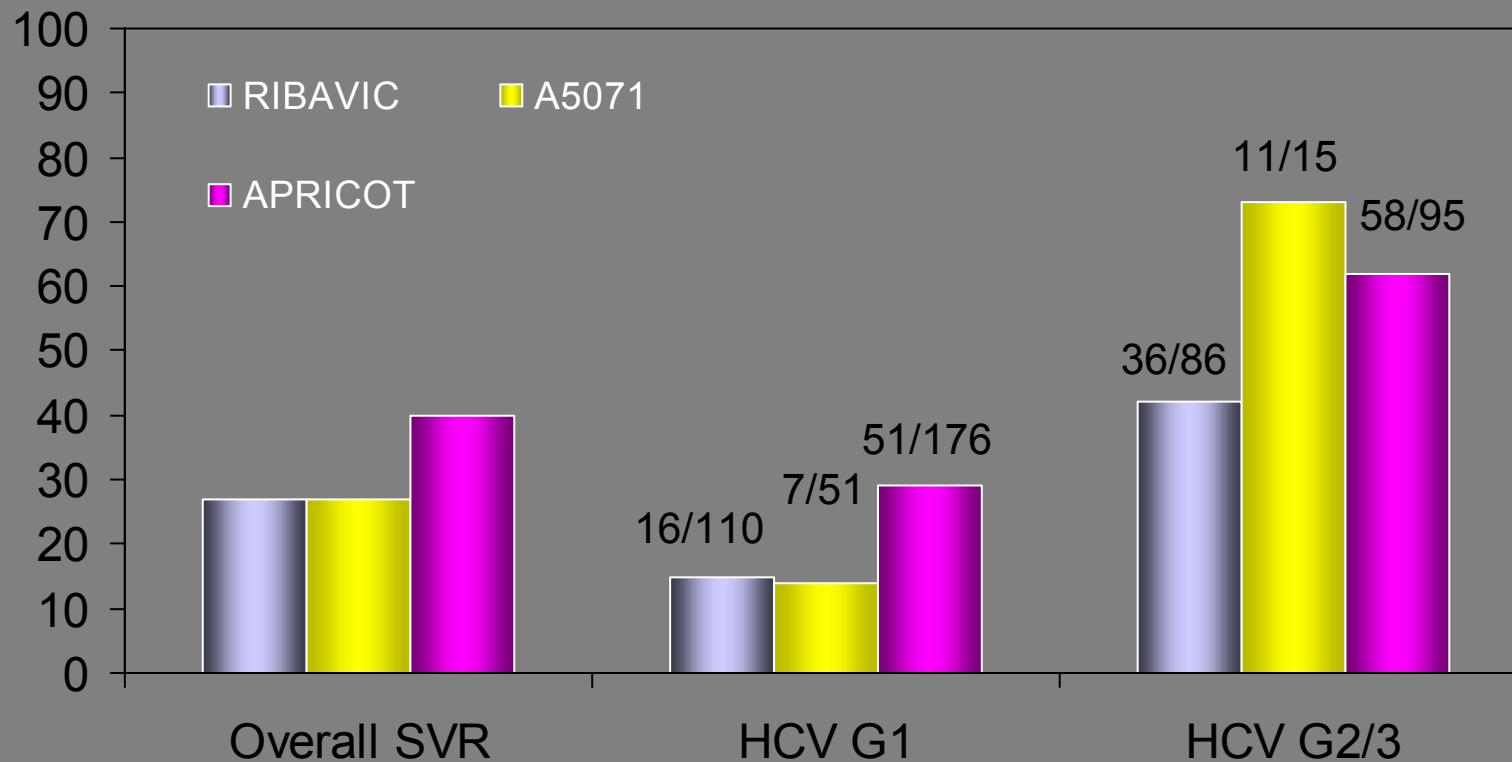
# Sustained Virologic Responses in HIV/HCV Trials with PEG IFN (ITT)



Carrat F, et al. *JAMA*. 2004;292:2839-2848.  
Chung et al. *NEJM*. 2004;351:451-459.  
Torriani et al. *NEJM*. 2004;351:438-450.

PEG-IFN alfa-2a for APRICOT  
and A5071, -2b for RIBAVIC

# Sustained Virologic Responses to PEG IFN/RBV by HCV Genotype (ITT)



Carrat F, et al. *JAMA*. 2004;292:2839-2848.

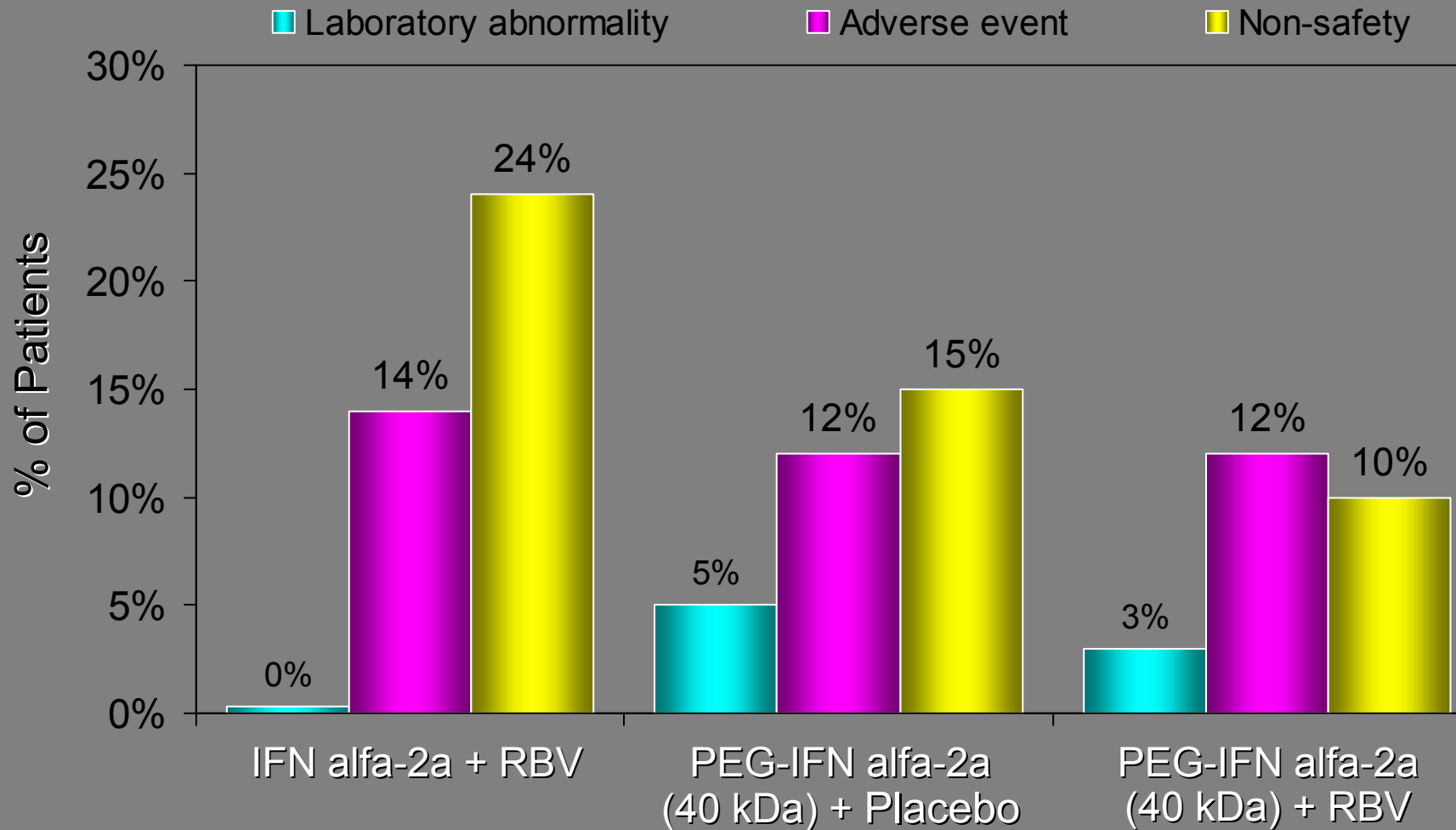
Chung et al. *NEJM*. 2004;351:451-459.

Torriani et al. *NEJM*. 2004;351:438-450.

# Predictors of HCV Response to PEG-IFN plus Ribavirin

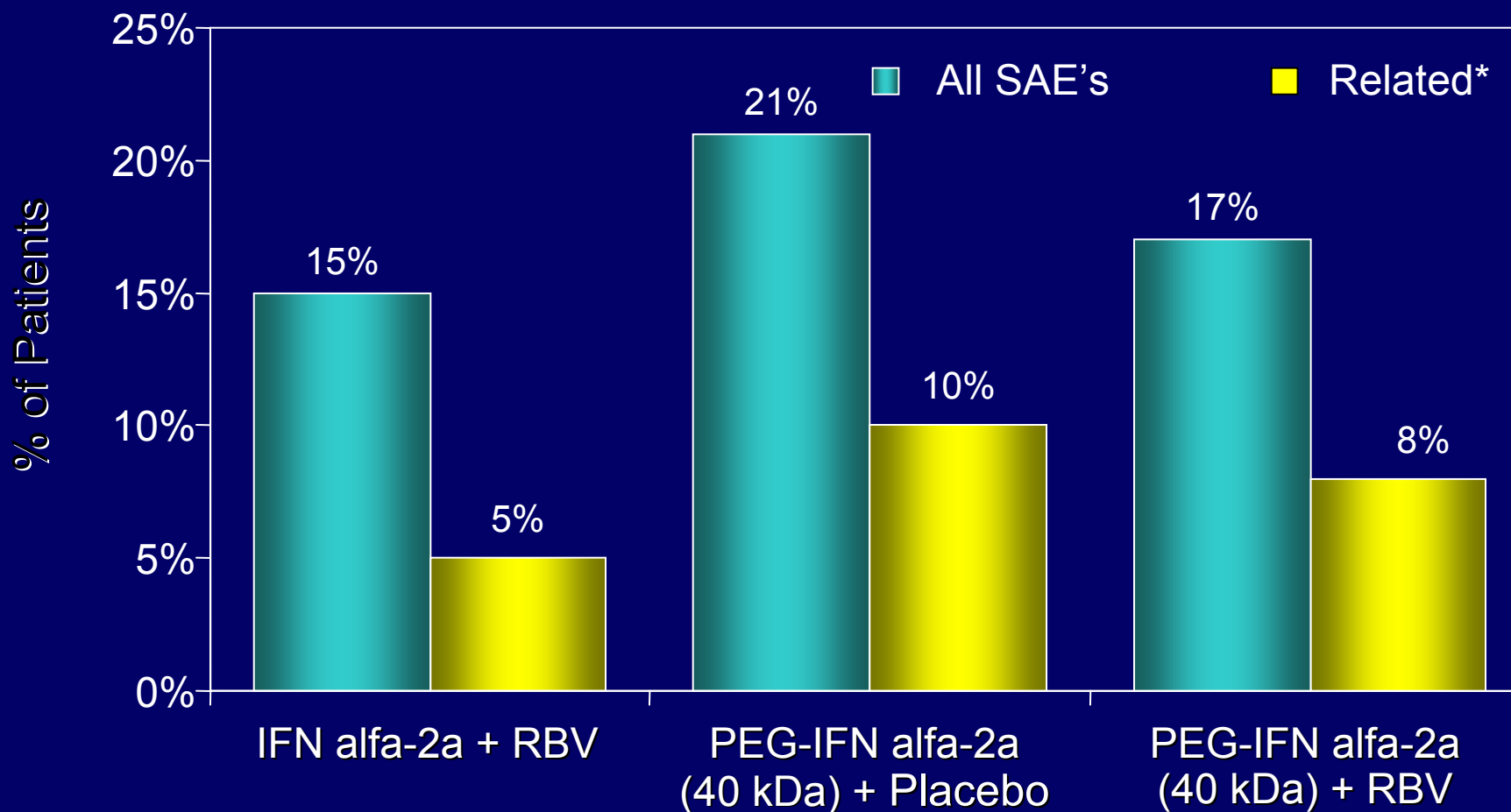
- **Virus**
  - Genotype
  - HCV RNA
  - HIV status
- **Drug**
  - Ribavirin dosing
  - Tolerability
  - Adherence
- **Host**
  - Race
  - Age
  - Weight
  - Genetics
  - Immune status

# Withdrawal from Treatment



Torriani et al. *NEJM*. 2004;351:438-450.

# Patients with Serious Adverse Events



\* Possibly or probably related

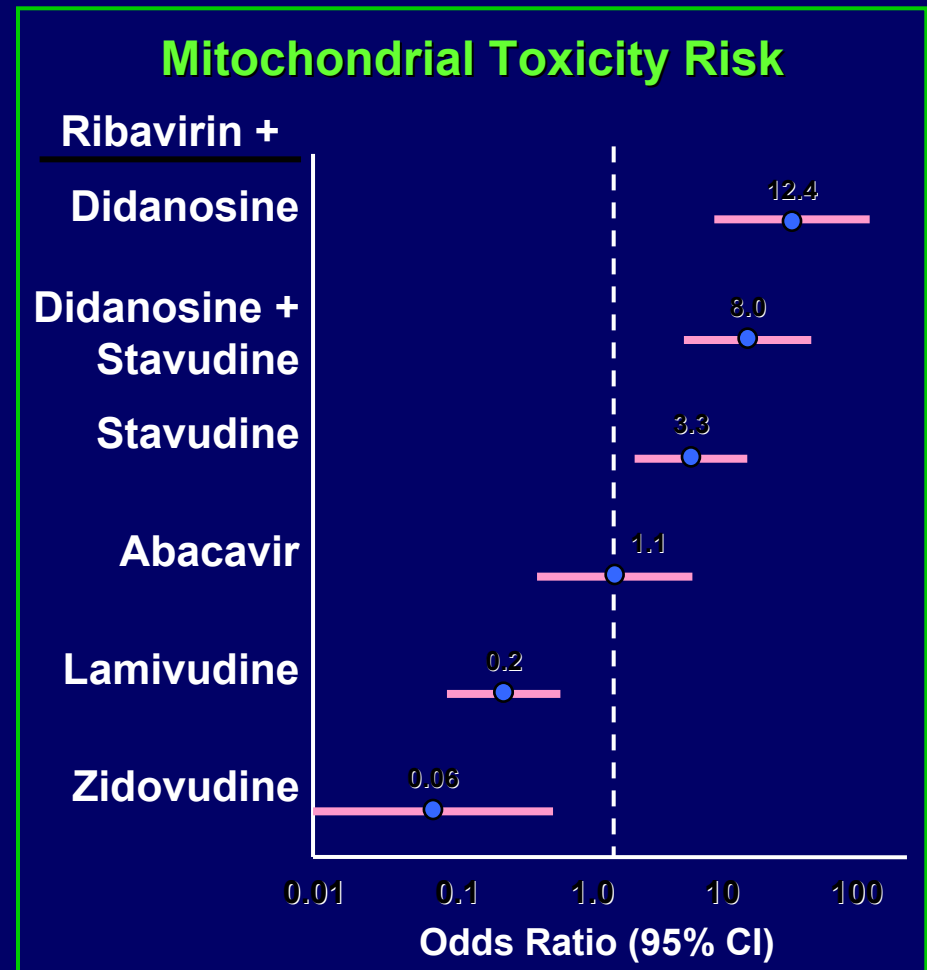
Carrat F, et al. *JAMA*. 2004;292:2839-2848.

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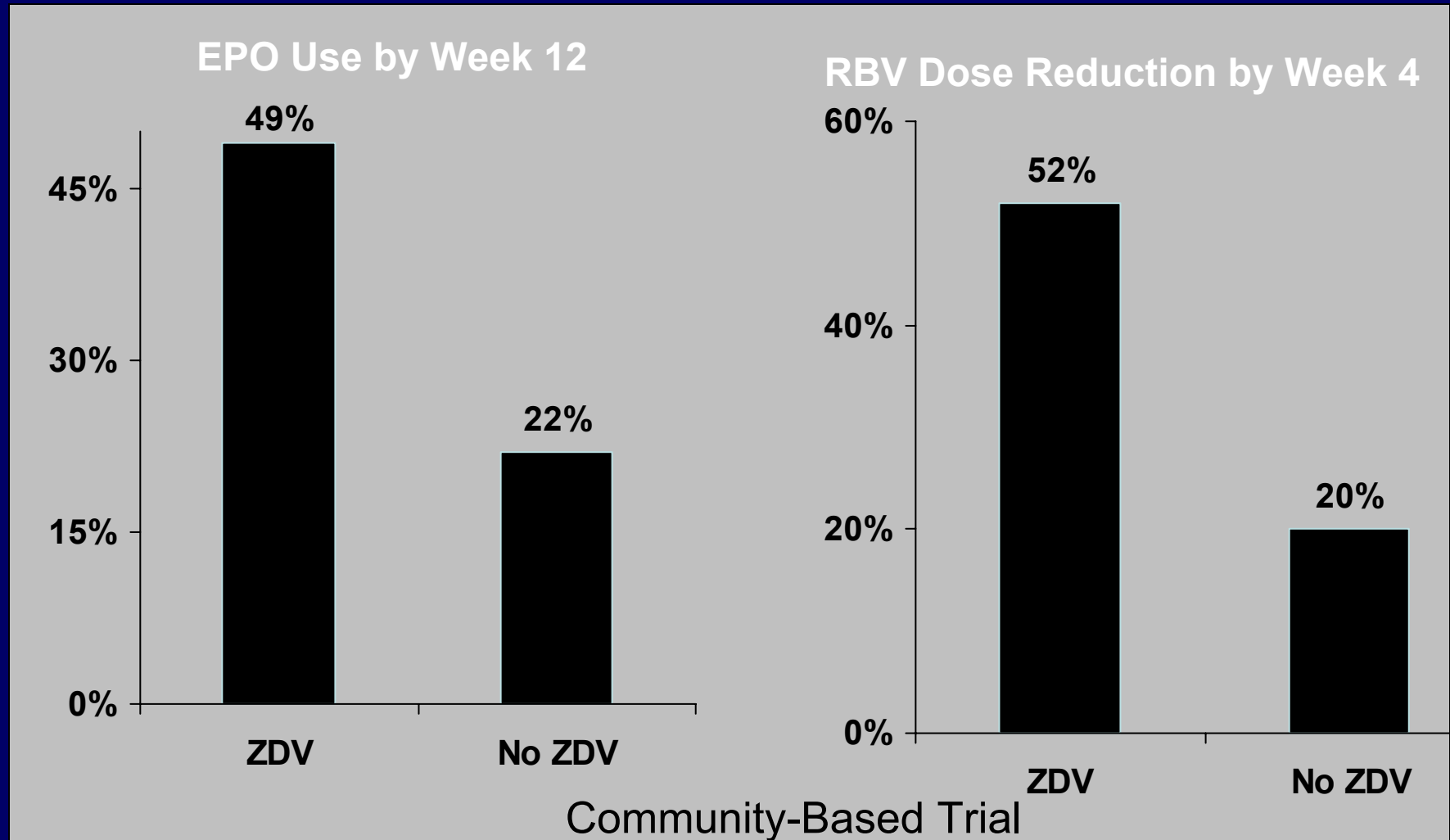
Torriani et al. *NEJM*. 2004;351:438-450.

# HAART and HCV Therapy: Didanosine

- US FDA Adverse Event Reporting System (2002)
  - Ribavirin + NRTIs
- 31 cases (58 adverse events) suggestive of mitochondrial toxicity
  - Pancreatitis and/or increased lipase (n=21)
  - Lactic acidosis (n=20)
  - Elevated LFTs (n=8)
  - Hepatic steatosis (n=6)
  - Elevated creatinine, neuropathy, multiorgan failure (n=1 each)



# HAART and HCV Therapy: Zidovudine



Alvarez D et al. Journal Viral Hepatitis. In press 2005.

# Initiating HCV Treatment

- Clinically evaluation
  - HIV disease (treat HCV first? HIV first? Simultaneous?)
  - Psychiatric
  - Substance use
  - Alcohol
- Pegylated interferon
  - $\alpha$ -2a (Pegasys<sup>TM</sup>, Roche)- 180 ug/wk SQ
  - $\alpha$ -2b (PegIntron<sup>TM</sup>, Schering-Plough)- 1.5 ug/Kg/wk
- Ribavirin
  - <75 Kg, 1000 mg/d
  - >75 Kg, 1200 mg/d
  - Possibly 800 mg/d if not genotype 1, 4 and HCV RNA <800,000 IU/mL

# Management of Non-responders

- No definitive strategy for management of these subjects
- There is data showing less inflammation even in non-responders
- Investigational strategies\*
  - Daily IFN-alpha
  - PEG-IFN induction
  - Low-dose PEG-IFN for years
  - **Investigational agents**
    - **Drug Drug interactions critical!**

\*Particularly in those with advanced fibrosis (e.g. bridging fibrosis or cirrhosis to delay decompensation and/or HCC).

# Decompensated Liver Disease

- Managed by hepatologist for portal HTN, coagulopathy, encephalopathy, ascites and HCC
- Not candidate for IFN-based therapy
- Referral to transplantation program
- Consideration for HIV-infected livers to be transplanted into HIV-HCV co-infected patients

# HIV HCV Conclusions

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- When to treat HCV, unclear
- IFN-ribavirin poorly tolerated in the highly selected patients offered it
- New drugs for HCV are very promising and have little overlap with HIV treatment
  - Small molecules
  - Potentially curable

# Acknowledgements

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- Nat Brown
- Rich Colonno
- Erik Daar
- Mike Otto
- Marion Peters
- Bruce Polsky
- Mark Sulkowsky
- Chloe Thio

# HIV DART™ 2006

FRONTIERS IN DRUG DEVELOPMENT  
FOR ANTIRETROVIRAL THERAPIES

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researchers, and basic scientists  
together to advance  
our knowledge of the  
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