Managing the Treatment of HCV/HIV Coinfection

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Overview of talk

- HCV/HIV Epidemiology
- Increased Mortality in HIV due to liver disease
- Influence of HIV on HCV-related liver disease
- HCV treatment in persons with HIV
    - Barriers
    - Side effects
    - Neuropsychiatric Context
    - Efficacy
    - New Developments
- Adherence to HCV treatment
- Research Agenda

HIV + HCV coinfection
Epidemiology

HCV within HIV+ pts:

Depends on mode of transmission of HIV itself:

IDU	91 %
blood transfusion	71 %
sexual transmission	7.1 %

Saillour F et al., Brit Med J, 1996

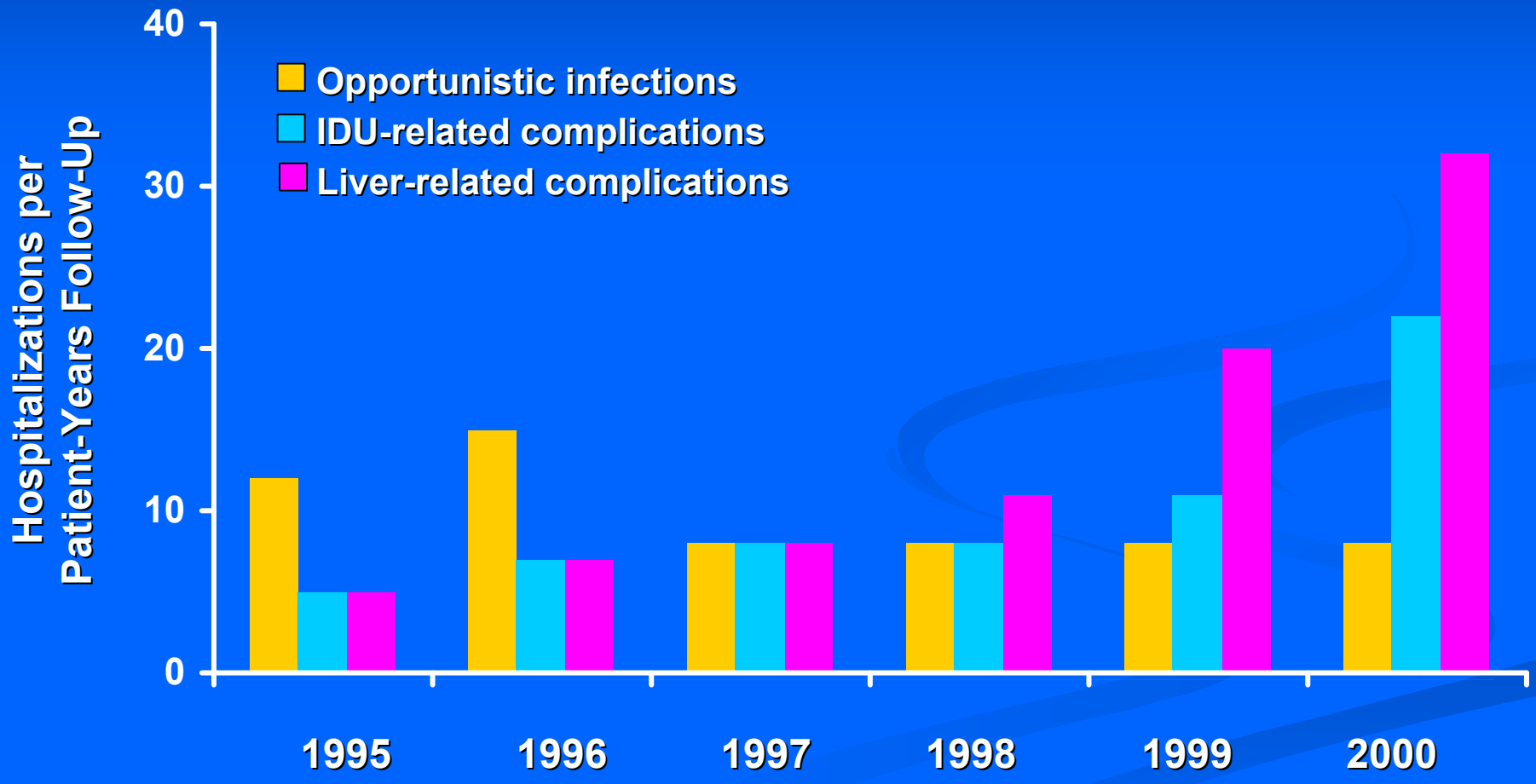
HIV within HCV+ pts:

US veterans in NYC metro area **24.8 %**

NYC vs. suburbs 28.9% vs. 7.8% (p=0.003)

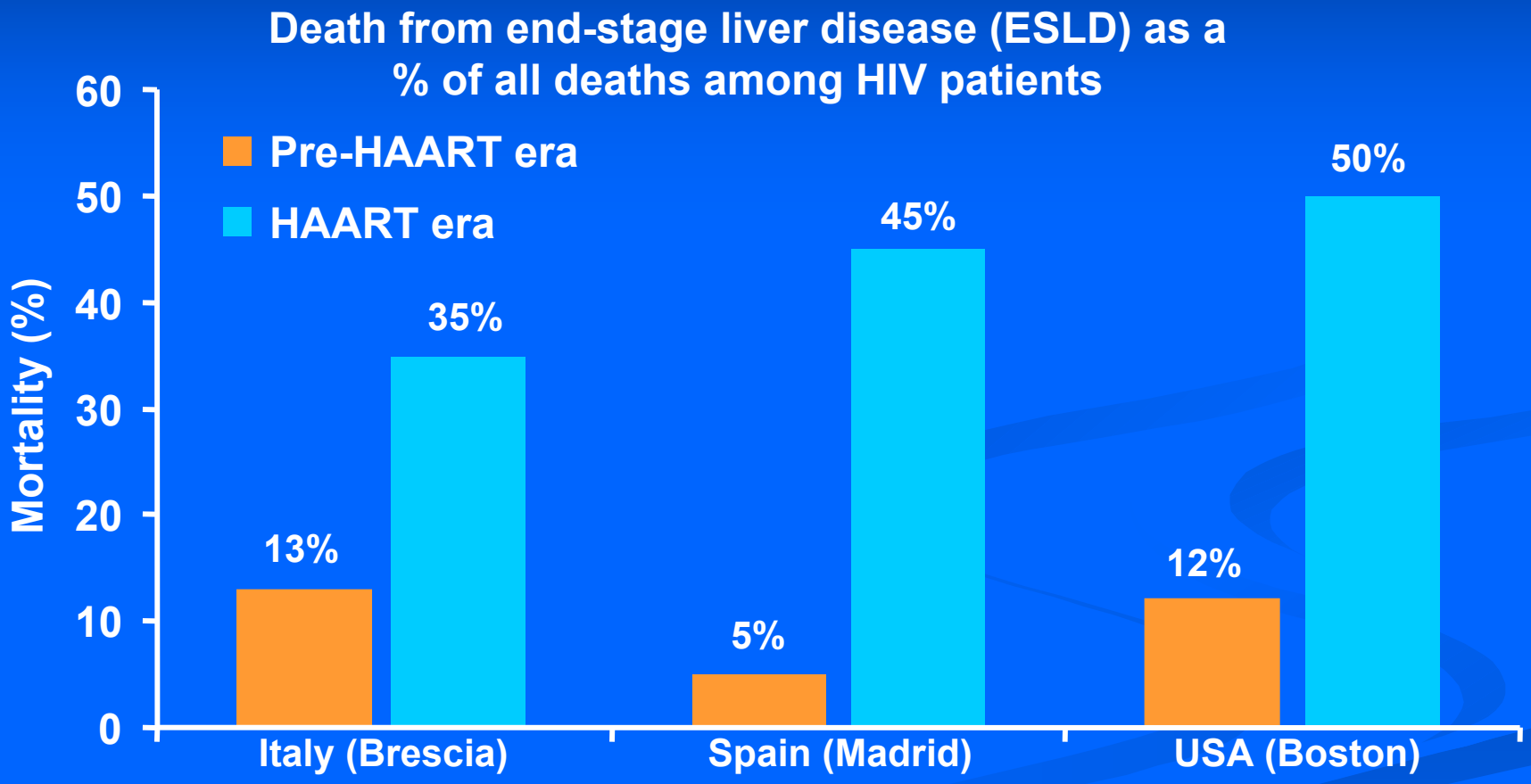
Bräu et al., Am J Gastroenterol, 2002

Hospital Admissions for Liver Complications Increased 5-Fold (1995–2000)



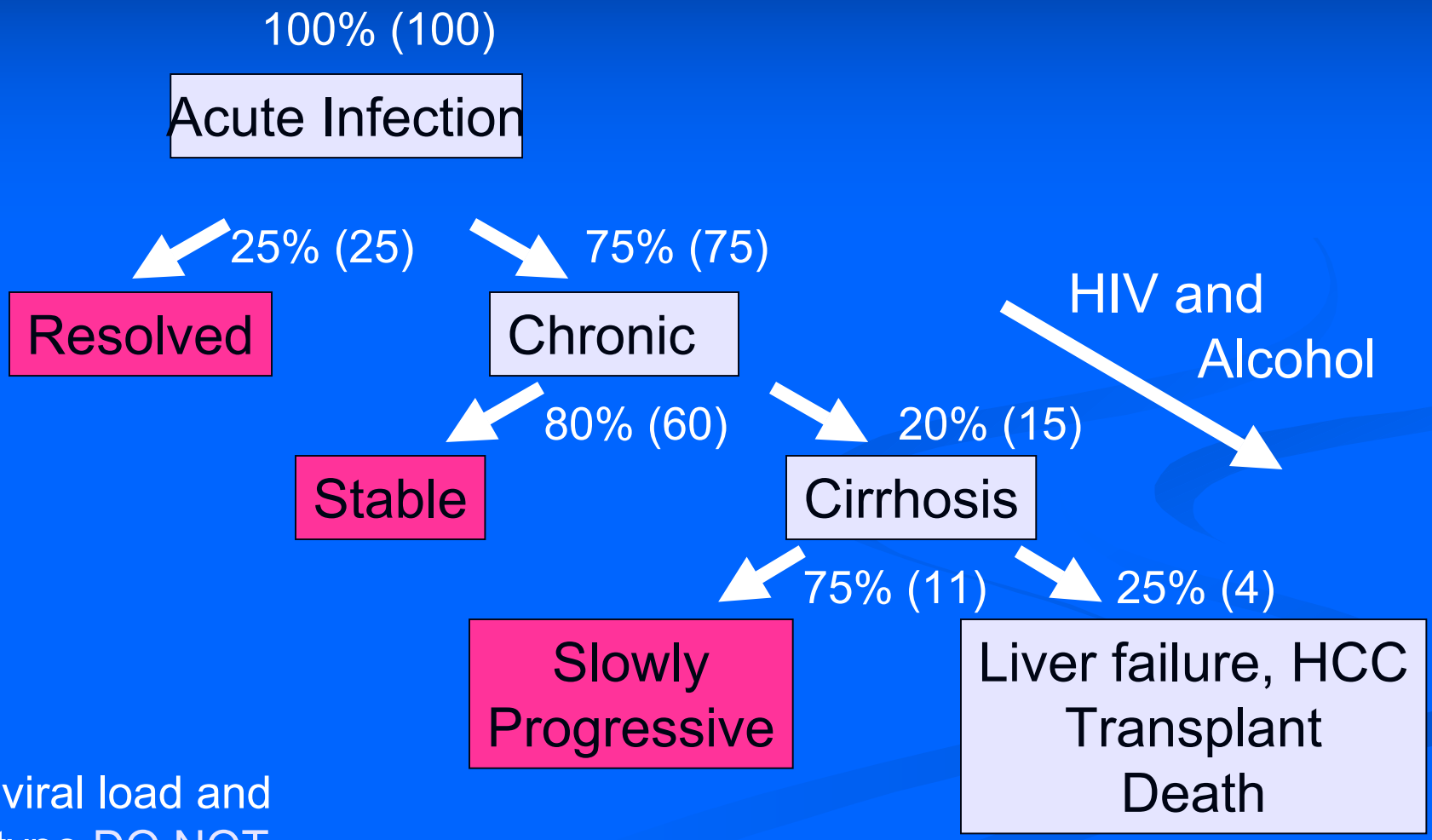
Gebo KA, et al. *JAIDS.* 2003;34:165-173.

Liver disease is a major cause of death in the ART era



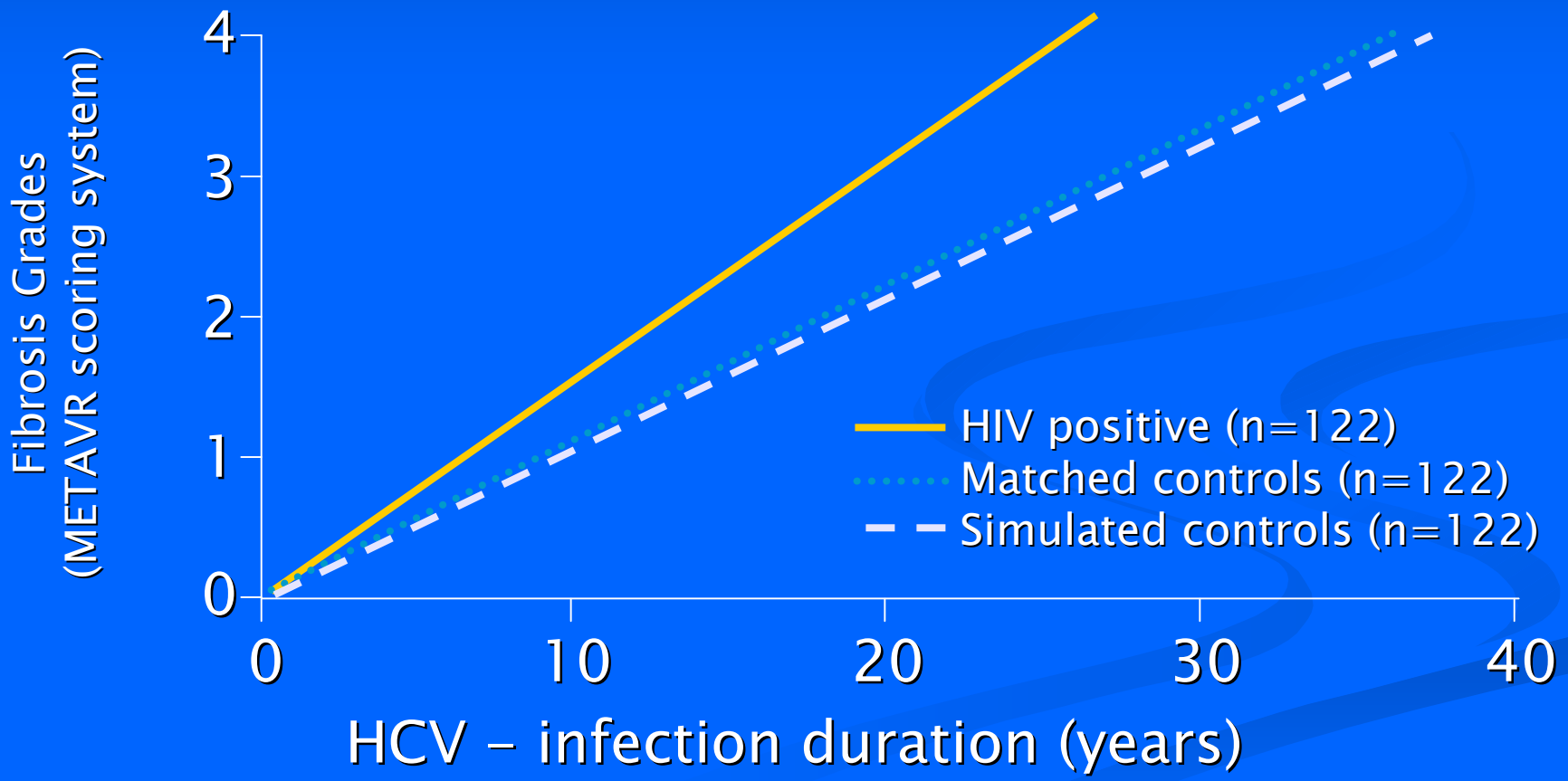
Bica *et al. Clin Infect Dis* 2001; 32:492–497
Puoti *et al. JAIDS* 2000; 24:211–217
Soriano *et al. Eur J Epidemiol* 1999; 15:1–4
Soriano *et al. PRN Notebook* 2002; 7:10–15
Martin-Carbonero *et al. AIDS Res Human Retrovirus* 2001; 17:1467–1471

Natural History of HCV Infection



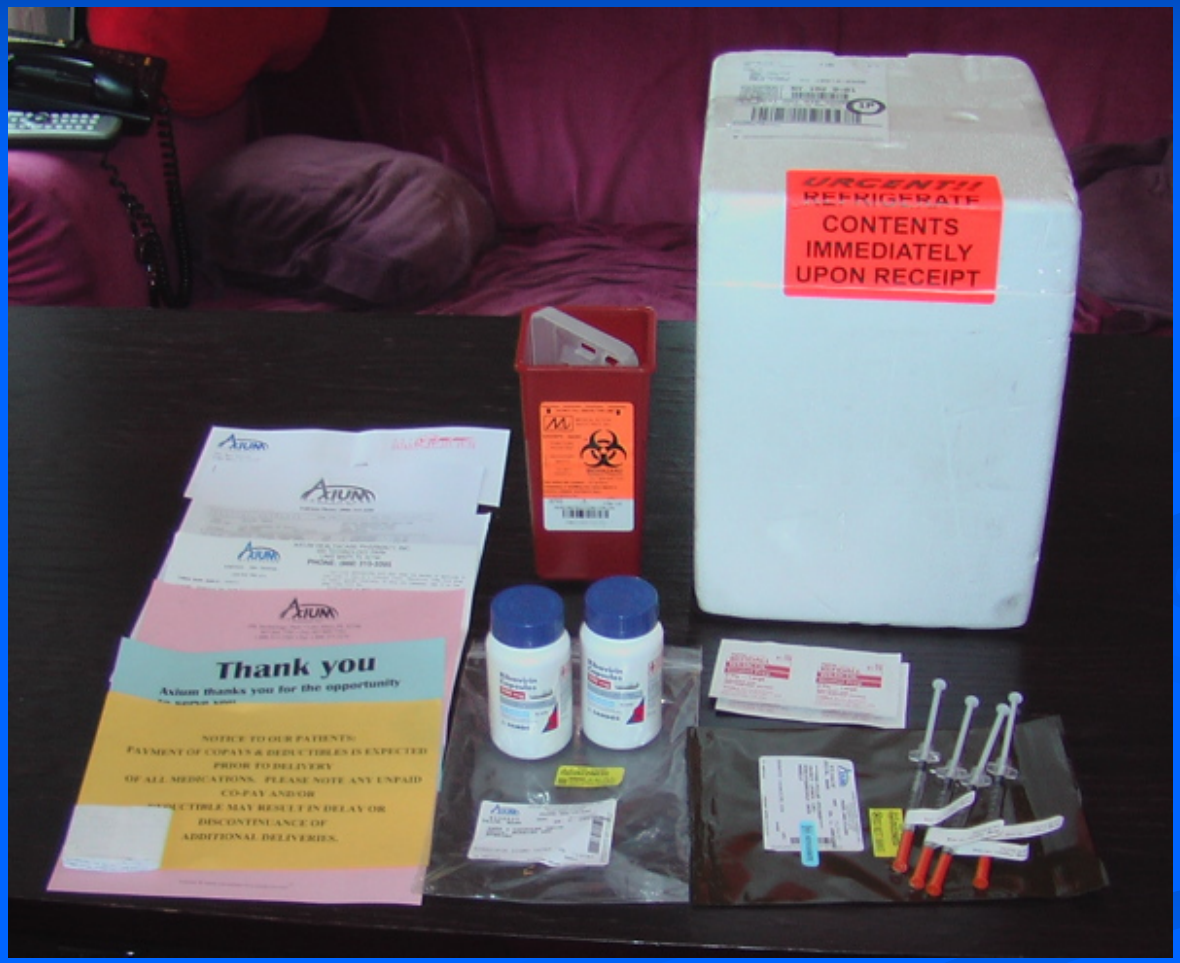
HCV viral load and genotype DO NOT influence progression

HIV + HCV coinfection:
Liver Fibrosis Progression Rate

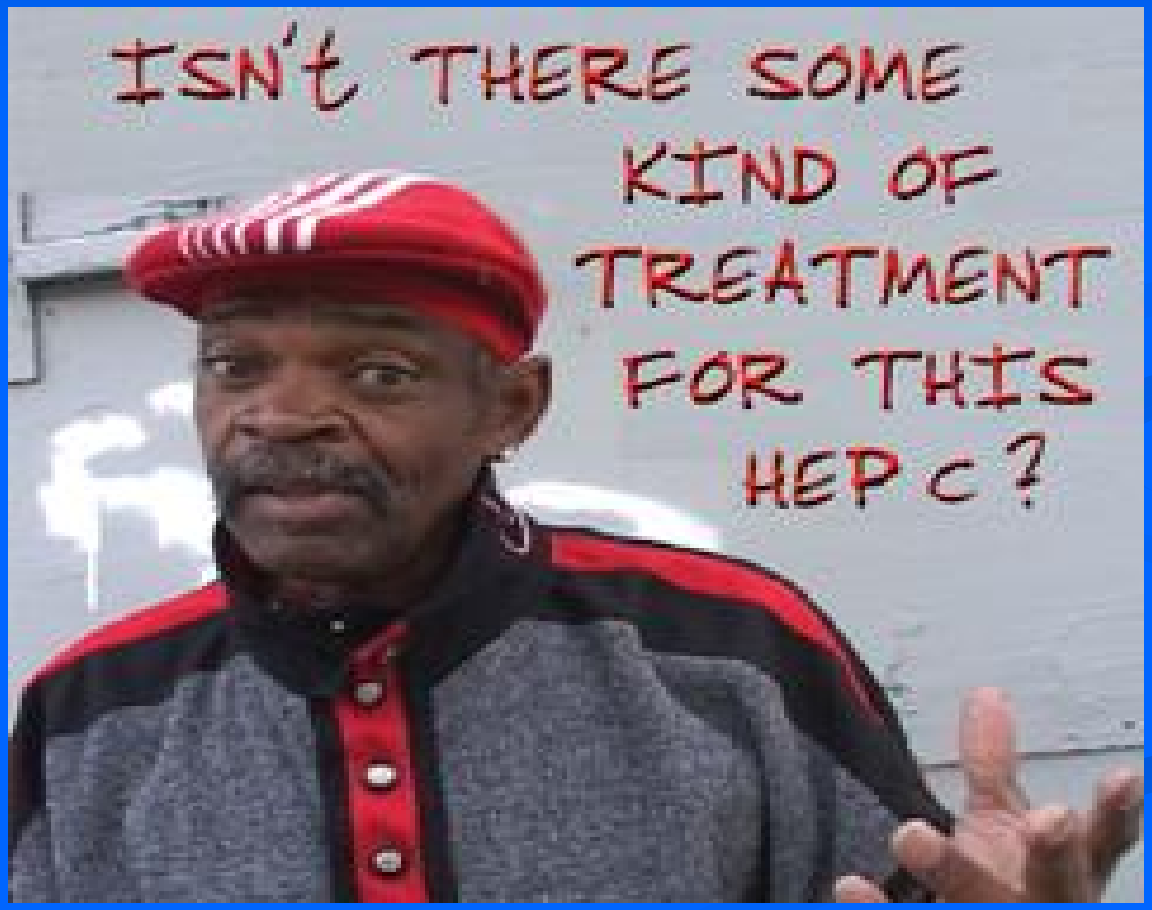


Benhamou Y, Hepatology, Oct 1999

Pegylated Interferon/Ribavirin



Patients Need Information & Myths Dispelled



Psychiatric Barriers to Care: Low Rates of Referral/Treatment of HCV

Providers are hesitant to refer and treat HCV in patients (particularly co-infected patients) for many reasons:

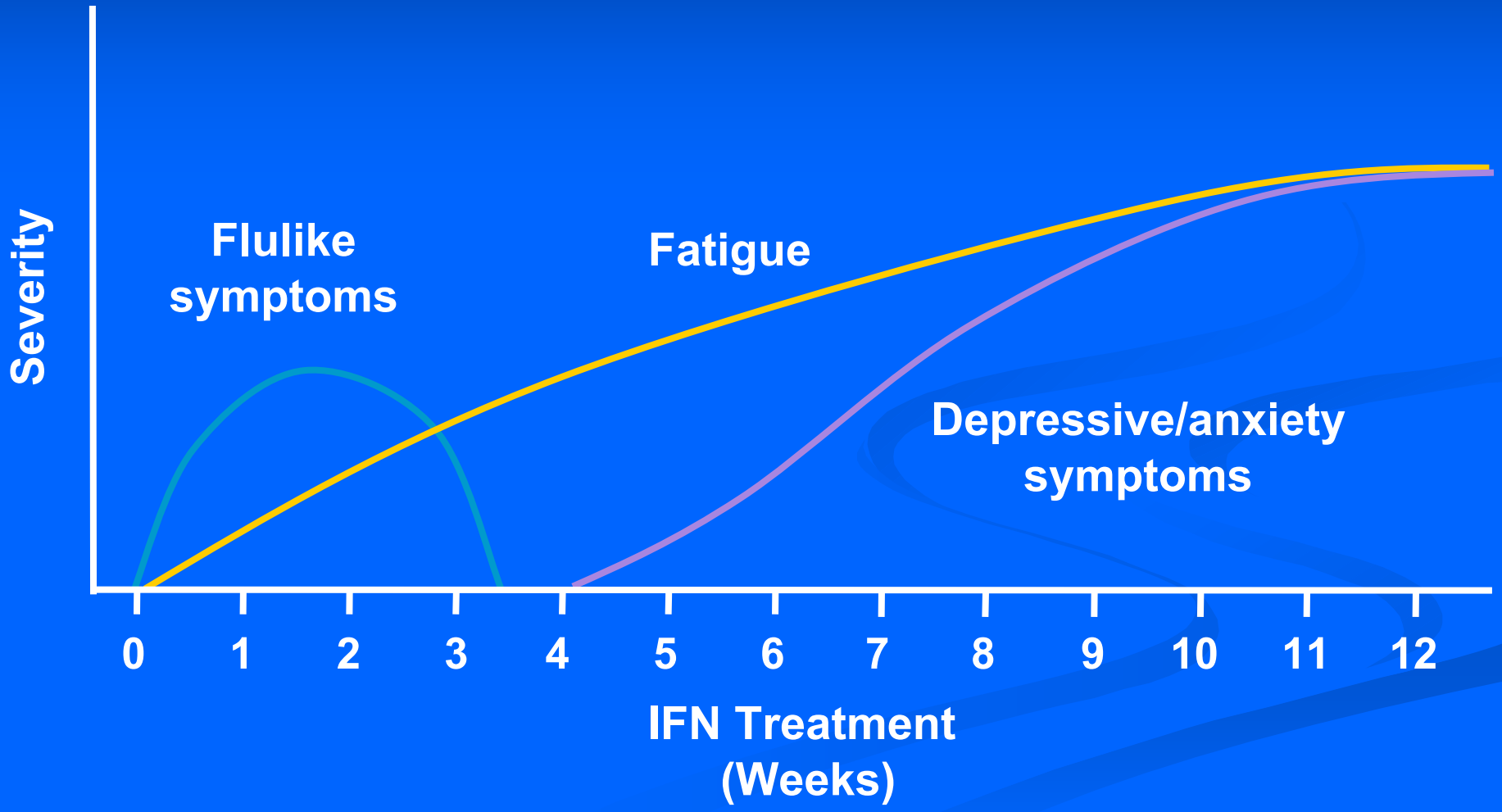
- Current/History of depression/psychiatric illness
- Current/History of Substance use problems
- Cognitive impairment
- Suspected poor adherence
- High burden of treatment side effects
- HCV treatment is immunosuppressive
- Low likelihood of treatment success

Common Side Effects of HCV Therapy

- Fatigue and weakness(65-66%)
- Headaches (43-62%)
- Body, muscle, joint aches (40-56%)
- Irritibility, anxiety (33-47%)
- Insomnia (30-40%)
- Neutropenia (26-27%)
- Loss of appetite (24-32%)
- Anemia (22%)
- Depression (20-31%)
- Concentration Problems (10-17%)

Aggressive side-effect management involves addition of other medications (e.g., antidepressants) potentially including other injectable medications (e.g., Procrit)

Time Course of IFN Side Effects



KR Reddy, MD, HIV-HCV co-infection preceptorship programme, New York, 19-20 May 2005

HCV Neuropsychiatric Context

- There are high rates of current/past psychiatric and substance use disorders (IDU) in the population of HIV/HCV coinfected persons medically eligible for HCV treatment

- PEG-IFN/RBV causes neuropsychiatric symptoms (depression, anxiety, emotional lability, irritability, insomnia) in a high percentage of treated patients and can result in dose reductions and early treatment discontinuation.

Pre-HCV treatment psychiatric management

- All patients are referred for psychiatric evaluation of current functioning prior to beginning HCV treatment
- If no current symptoms/disorders, monitor closely (no empirical evidence for antidepressant prophylaxis) – follow-up with evaluator by week 2 of treatment
- If current symptoms/disorders, treat and stabilize prior to beginning HCV treatment; montior closely during treatment

Current HCV Treatment

- High rates of dose reductions (43% RBV; 27% IFN) and early treatment discontinuation (15-50%) due to toxicity of side effects
- Goal is eradication of HCV = Sustained Virologic Response (SVR): Undetectable HCV viral load 6 months after the completion of HCV treatment

HCV Treatment Efficacy

Immunologic impairment caused by HIV may explain lower rates of SVR in co-infection clinical trials compared to HCV monoinfection

Lower rates seen in clinical settings

Rates of SVR are affected by genotype, race, HCV viral load and stage of liver disease prior to treatment initiation, HIV co-infection, degree of immune suppression in co-infected patients

Treatment efficacy is limited by dose reductions and early treatment discontinuation due to side effects

Is patient adherence also playing a role in poor outcome?

Definition of On-treatment Virologic Responses

- **RVR** (Rapid Viral Response: undetectable HCV RNA at week 4)
- **cEVR** (complete Early Viral Response: no RVR but undetectable HCV RNA at week 12)
- **pEVR** (partial Early Viral Response: no RVR and detectable HCV RNA but a >2 log10 drop at week 12)

Summary of Results From Coinfection Trials

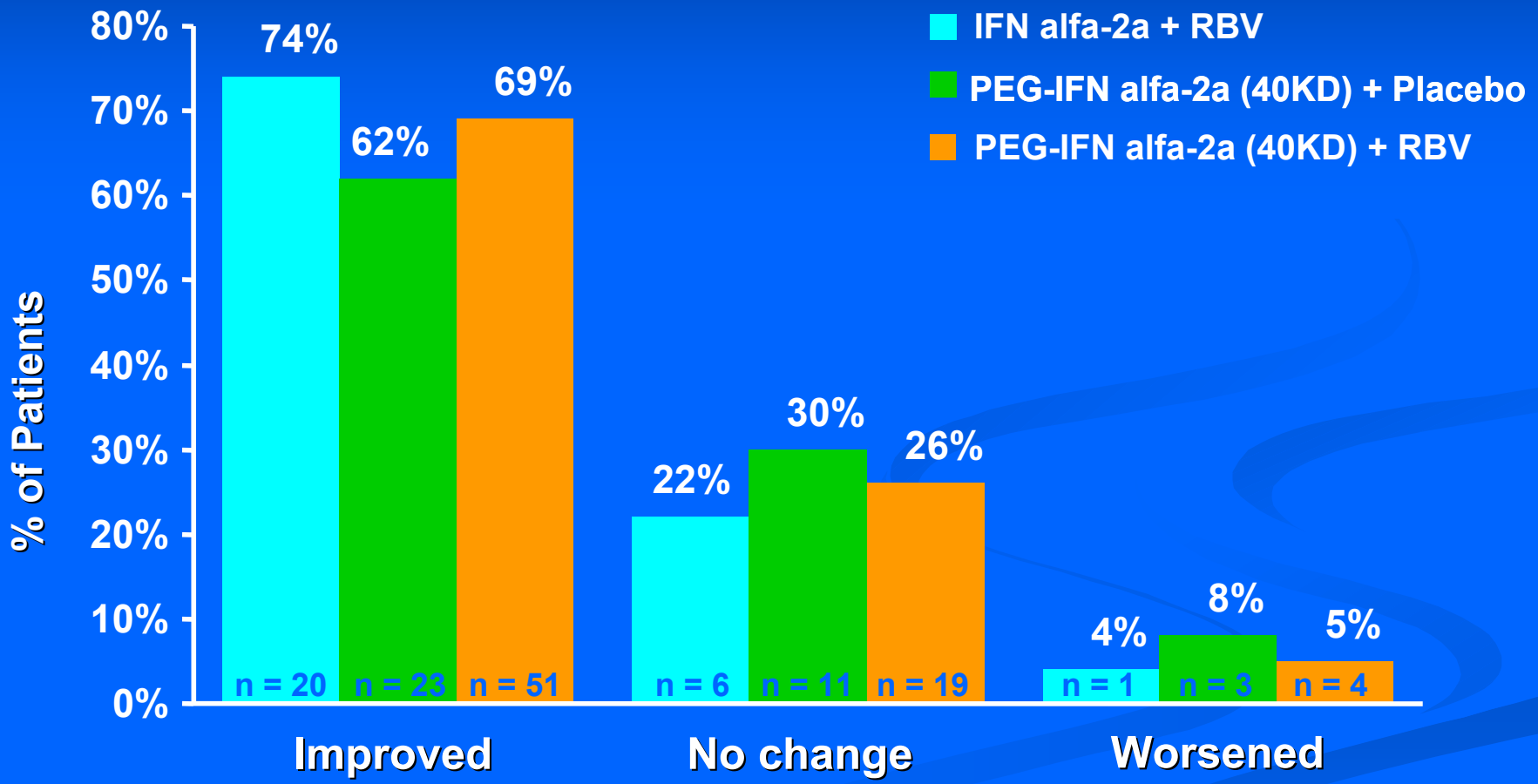
Study	N	Treatment	SVR (%)		
			All	GT 1	GT non-1
RIBAVIC	412	PEG IFN α-2b + RBV 800	27	17*	44
		IFN α-2b + RBV 800	20	6	43
ACTG	133	PEG IFN α 2a + RBV 600	27	14	73
		IFN α -2a + RBV 600	12	6	33
APRICOT	860	PEG IFN α 2a + RBV 800	40	29	62
		IFN α -2a + RBV 800	12	7	20
LAGUNO	93	PEG IFN α-2b + W/B RBV	44	38	53
		IFN α-2b + W/B RBV	21	7	47
PRESCO	389	PEG IFN α-2a + W/B RBV	50	36	72
		G1 48 w 31 72w 52			
		G2 24 w 67 48w 82			

PRESCO Trial in HCV/HIV Coinfection: Safety Events and Withdrawals

- The most common adverse events were depression or psychiatric illness and weight loss followed by hematologic events and asthenia
- Treatment discontinuations
  - 66 patients (17%) for virologic failure at week 24
  - 33 patients (8.5%) for severe adverse advents
  - 108 patients (30%) for side-effects, lost to follow-up or voluntary withdrawal
- Patients with G1/4 receiving extended duration had the highest withdrawal rate
- Pegasys or ribavirin dose modified in 116 patients (29.8%)

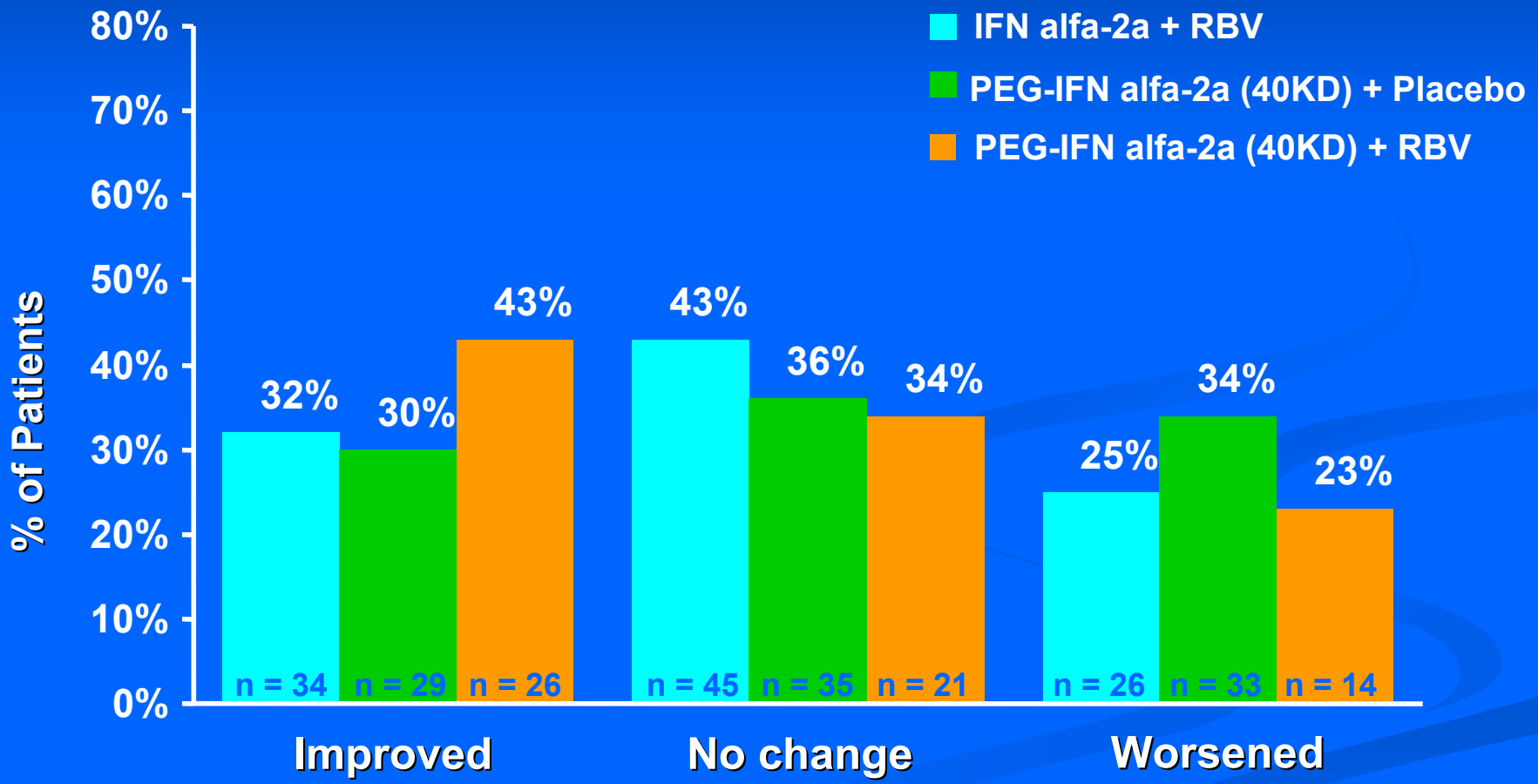
Nuñez M, et al. AASLD. Oct. 27-31, 2006. Boston, MA. Poster 365.

Histological Response in Patients with an SVR



No Change = Change of +1, -1 or 0 in HAI score;
Worsening = ≥2-point increase in HAI score

Histological Response in Patients without an SVR



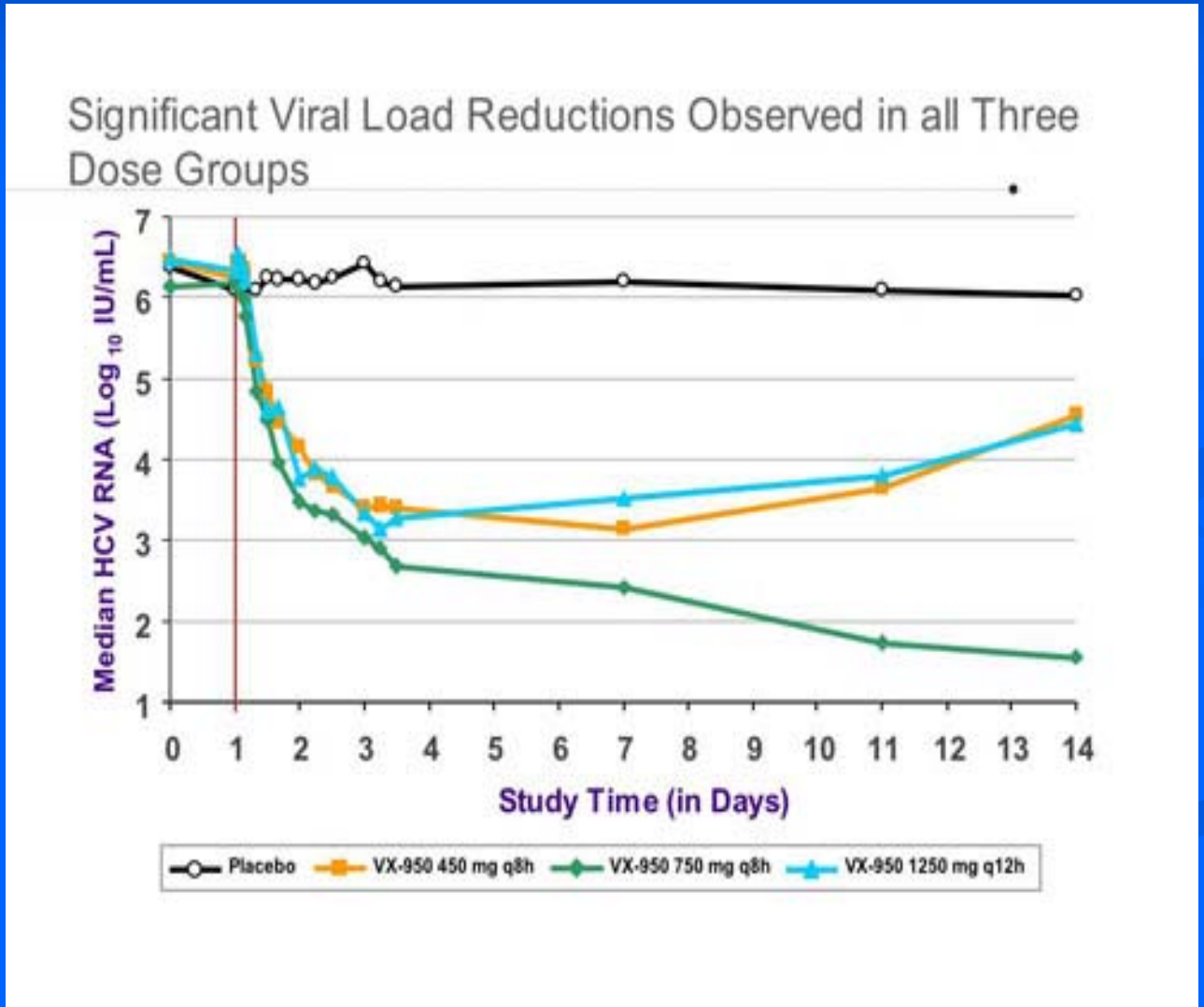
No Change = Change of +1, -1 or 0 in HAI score;
Worsening = ≥2-point increase in HAI score

Goals of STAT-C (Specifically Targeted Antiviral Therapy for HCV) therapy - Polymerase and Protease Viral Enzyme Inhibitors

- Multiple drugs and mechanisms of action
- Effective across a range of genoytypes
- Enhanced response
- Decreased duration
- Improved tolerability
- Diminished resistance
- Applicable to difficult-to-treat populations

John G. McHutchison, MD Revolutionizing the way we treat HCV: STAT-C
AASLD, Boston, October 28, 2006

Investigational HCV protease inhibitor: Telaprevir (VX-950, Vertex) given alone



The HCV Treatment Pipeline . . .

- Polymerase and Protease Enzyme Inhibitors
- Drug resistance has not been a problem in HCV therapy; it may become a problem with new generation treatment
- TID dosing with food will likely be required with some new agents (e.g., VX-950)
- The importance of adherence will likely increase in HCV treatment

Use of the Term 'Adherence' in HCV Research

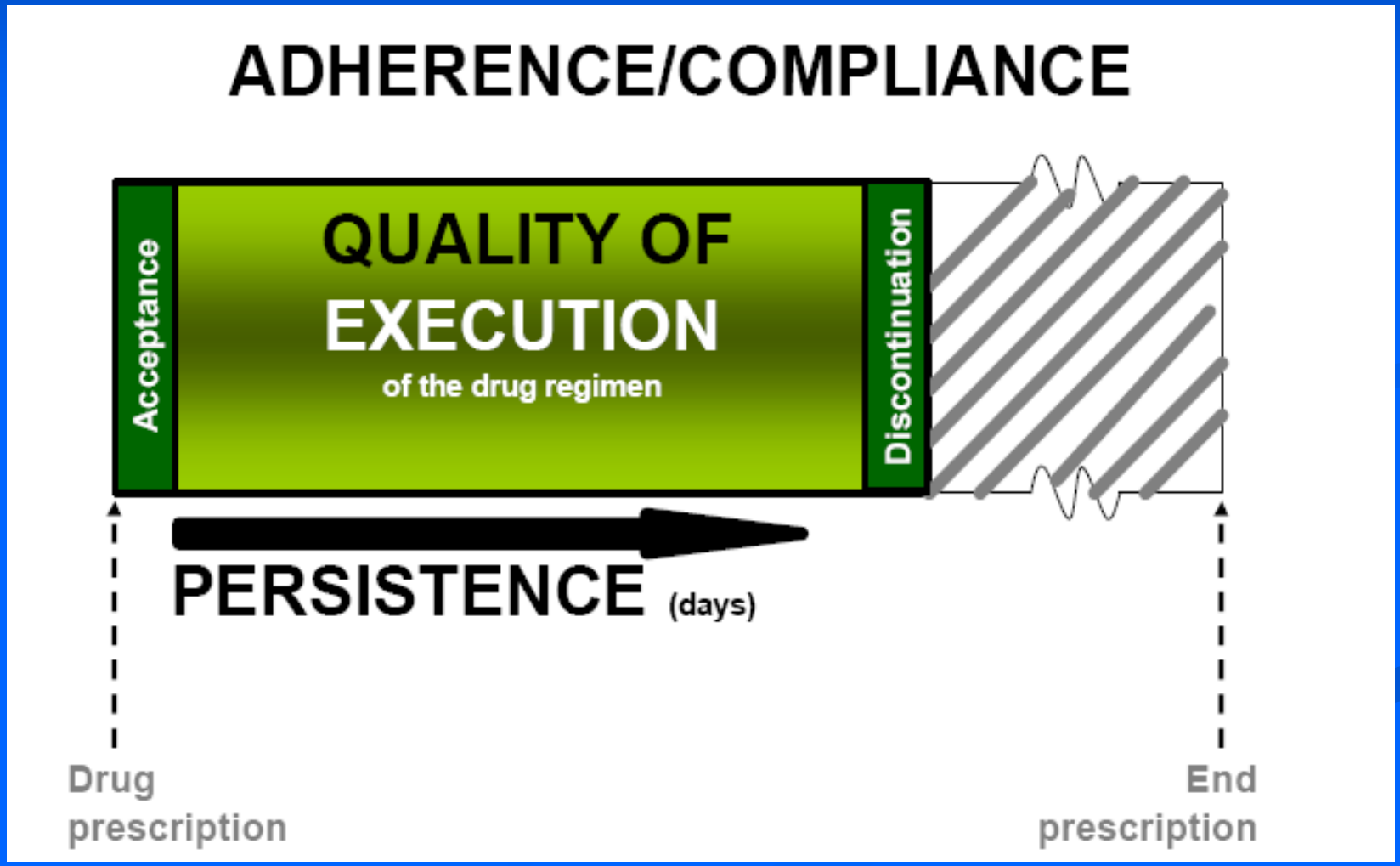
Provider-directed dose reductions

Early treatment discontinuation

ADHERENCE = TREATMENT EXPOSURE

ADHERENCE ≠ MISSED DOSES

Vrijens & Urquhart, 2005 Journal of Antimicrobial Chemotherapy



Adherence to HCV Therapy

- Persistence
- Quality of Execution
- Dose Reduction

HCV Treatment Exposure Predicts HCV Outcome in HCV Monoinfected Patients

The 80/80/80 rule:
the standard for patients to strive for in HCV treatment is continued prescription of at least 80% of the initially prescribed interferon dose and 80% of the initially prescribed ribavirin dose for at least 80% of the planned treatment duration

SVR rates according to adherence and genotype

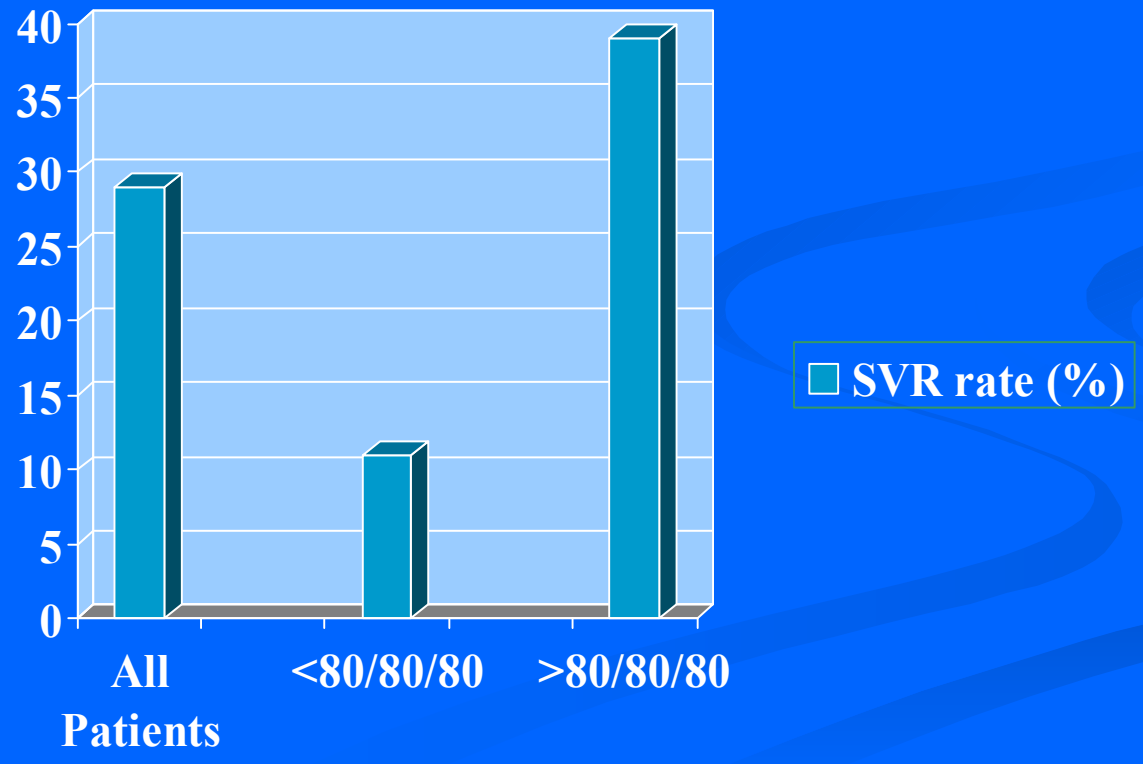
PEG-IFN/RBV	80/80/80	<80/<80/<80	*P*
all patients (48 wks)	191/305(63%)	61/118 (52%)	.04
genotype 1	105/206 (51%)	27/79 (34%)	.01
genotype 2/3	79/88 (90%)	34/48 (89%)	.96

McHutchison et al. Gastroenterology 2002; 123:1061-9

HCV Treatment Exposure Predicts HCV Outcome in HCV/HIV Co-infected Patients

ICAAC 2005 Milos Opravil for APRICOT

Genotype 1 patients only



First Published Study Reporting on Missed Doses in HCV Therapy

- Prospective observational study of 63 HIV/HCV patients treated with PEG-IFN/RBV (Barcelona, Spain)
- Fifteen subjects (24%) discontinued treatment (all but one by week 12).
- Self-reported adherence in last 2 weeks assessed at 12, 24, and 48 weeks: 98% or 99% at all time points
- Rates of ARV adherence were lower (52%-74%)

Fumaz et al. AIDS Care 2007; 19:1 38-145

Hepatitis C Patients' Self-reported Adherence to Pegylated Interferon and Ribavirin

In a sample of 180 patients on treatment for Hepatitis C (23% co-infected with HIV):
7% reported missing at least one injection of pegylated interferon in the last four weeks
21% reported missing at least one dose of ribavirin in the last 7 days

J. Weiss, L. Bhatti, D. Dieterich, Br. Edlin, D. Fishbein, M. Goetz, Ka. Yu, G. Wagner 2nd International Conference on HIV Adherence, March 2007

First Study of HCV Adherence with Multi-method Assessment

- 401 subjects enrolled in Virahep-C study
- Adherence measured by self-report and MEMS at weeks 4, 12, 24, 36, 48
- RBV assessed for past 4 days
- IFN assessed for past 4 weeks

Smith et al. Annals of Pharmacotherapy; 2007: 1116-1122


BREMERHAFEN.


Pegasys®
peginterferon alfa-2a
180 micrograms / 0.5 ml solution for injection
1 pre-filled syringe - 0.5 ml /
injection needle
Roche


Cat. No. BE-100
POST MEDICAL, INC.
BIOHAZARD

Percent of Sample Reporting 100% Adherence

Week:	4	12	24	36	48
RBV SELF	91%	85%	83%	76%	75%
RBV MEMS	74%	66%	62%	53%	43%
IFN SELF	98%	96%	96%	95%	97%
IFN MEMS	92%	86%	82%	84%	74%

Smith et al. Annals of Pharmacotherapy; 2007: 1116-1122

HIV/HCV Adherence Research Agenda

- Methodology to assess injection technique
- Adherence to self-injection vs. injection by others (former IVDU)
- Determine levels of adherence required to achieve SVR (might vary by genotype, HIV status, and for interferon and ribavirin)
- Develop adherence measure that assesses both patient dose reductions and missed doses
- Study adherence prospectively with assessment methods other than self-report

Further HIV/HCV research agenda

- Development of strategies to overcome patient and provider barriers to accessing HCV treatment
- Development of models to provide effective HCV treatment to medically-eligible co-infected patients with psychiatric and substance use disorders
- Evidence-based psychotropic management of co-infected patients pre and during HCV treatment
- Neuropsychiatric predictors of adherence, dose reduction, early treatment discontinuation, SVR
- Development of behavioral interventions to improve efficacy of HCV treatment

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