

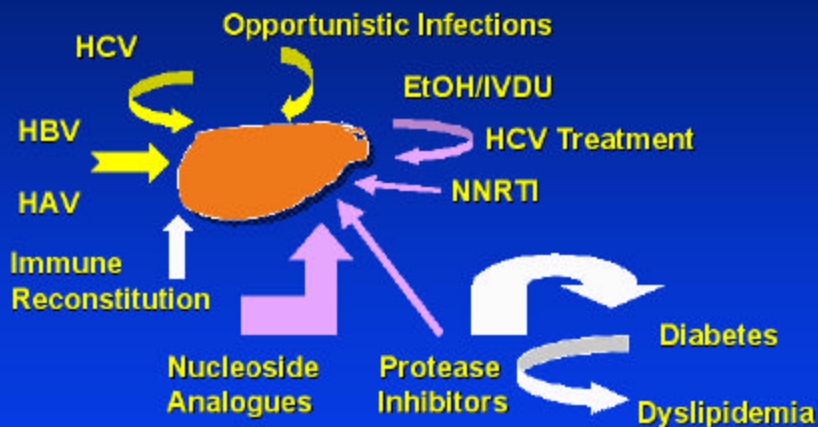
Treatment of HCV in HIV Disease: New Challenges, New Promise

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Department of Medicine
Professor of Medicine
Mt. Sinai School of Medicine
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P-1

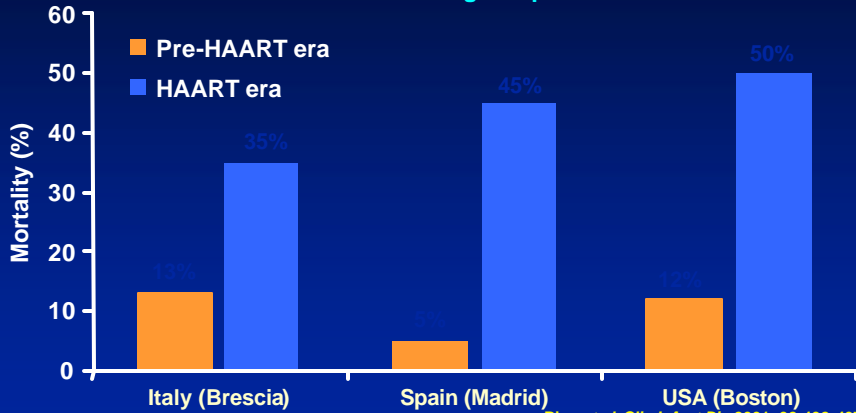
Factors Affecting the Liver in HIV



Slide courtesy of R. Berggren, MD.

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

Death from end-stage liver disease (ESLD) as a % of all deaths among HIV patients



Bica et al. *Clin Infect Dis* 2001; 32:492-497

Puoti et al. *JAIDS* 2000; 24:211-217

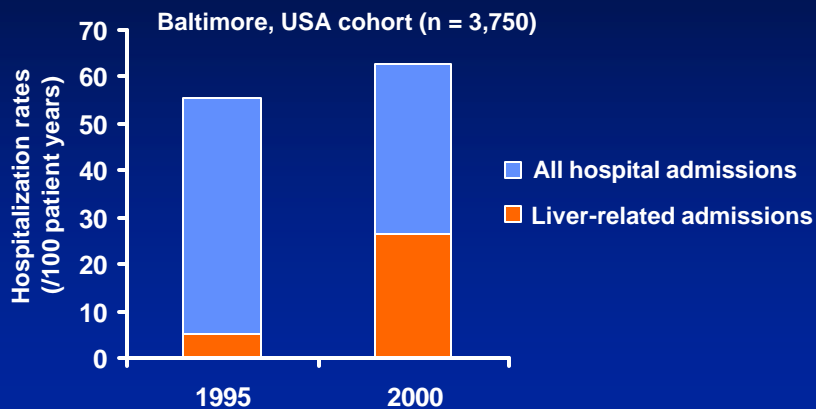
Soriano et al. *Eur J Epidemiol* 1999; 15:1-4

Soriano et al. *PRN Notebook* 2002; 7:10-15

Martin-Carbonero et al. *AIDS Res Human Retrovirus* 2001; 17:1467-1471

P-3

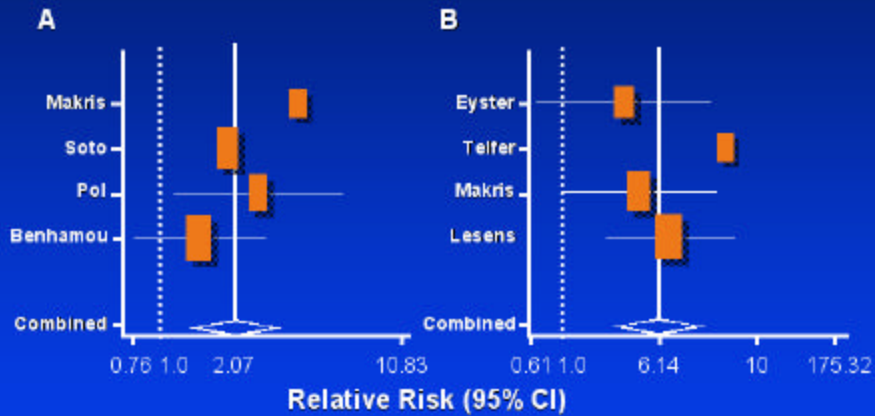
Liver-related Hospitalization Rates of HIV-HCV Coinfected Patients



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

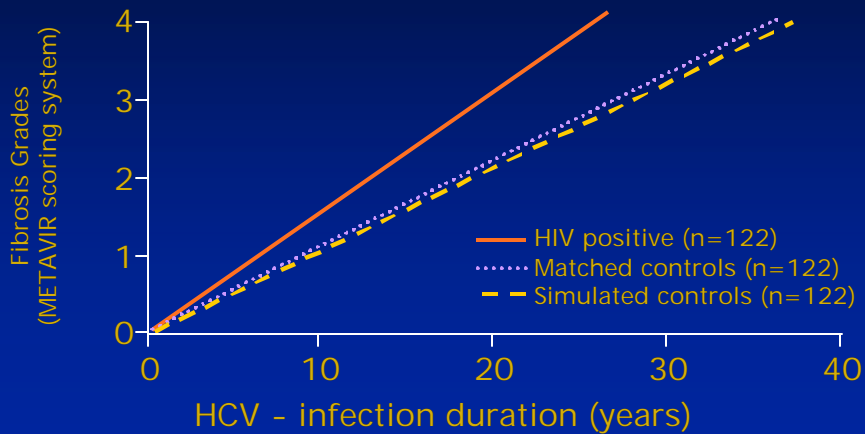
P-4

Increased Risk of Cirrhosis and ESLD in HIV/HCV-Coinfected Patients



Clin Infect Disease, Graham et al, The University of Chicago Press.

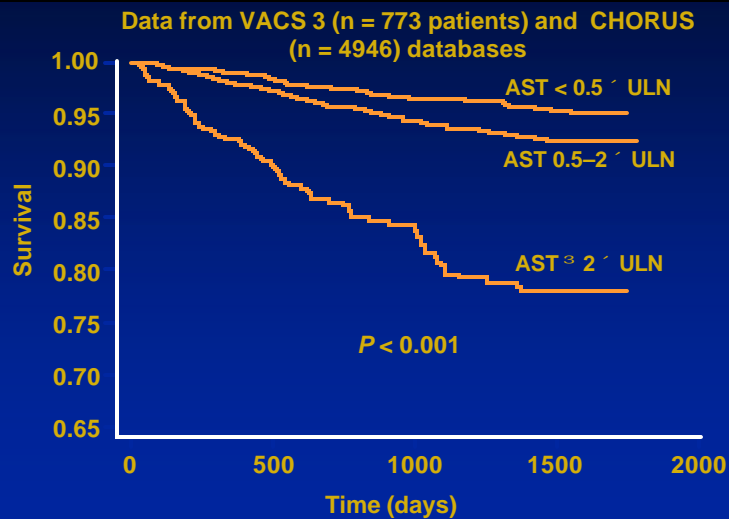
Liver Fibrosis Progression Rate



Benhamou Y. *Hepatology* 1999;30:1054

P-6

AST levels are associated with survival in HIV+ patients



Justice et al. XIV IAC 2002; poster no. 1058

P-7

Survival: Multivariable Analyses*

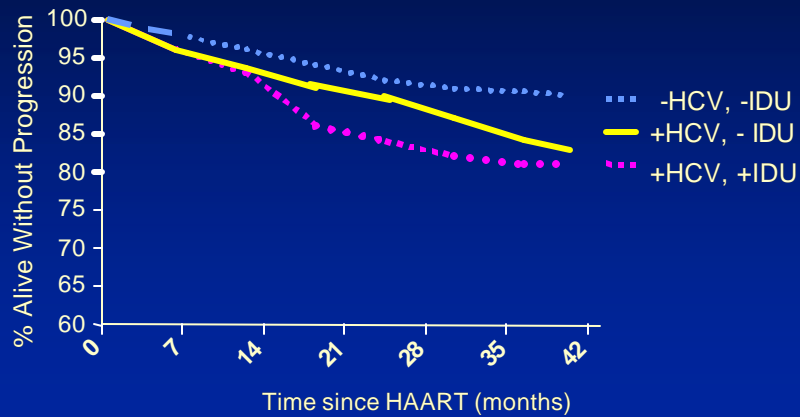
Variable	CHORUS		VACS 3	
	HR	p	HR	p
Hemoglobin	0.80	<0.001	0.75	<0.001
Hepatitis C	1.25	0.2	1.07	0.8
Chronic hepatitis B	0.84	0.2	0.82	0.7
AST/Top Normal	1.35	<0.001	1.47	0.001
ALT/Top Normal	0.83	0.005	0.61	0.04
SQRT (CD4)	0.91	<0.001	0.97	0.1
Log (HIV-1 RNA)	1.40	<0.001	1.54	<0.001
Age	1.04	<0.001	1.05	<0.001

*Proportional Hazards, C Statistic for Models: 0.83, 0.78 respectively.

Justice et al. Barcelona 2002

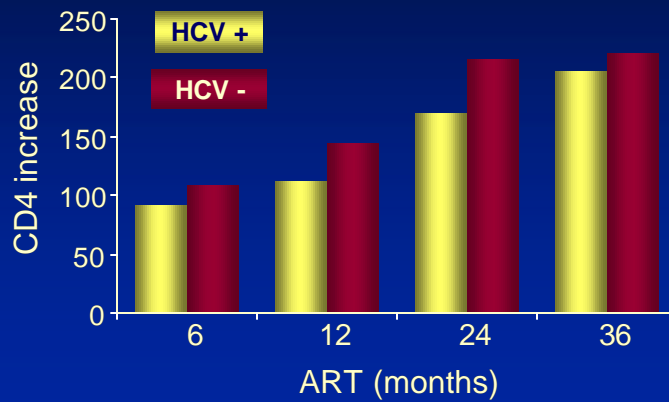
P-8

Outcomes After HAART According to HCV Status and IDU: Swiss HIV Cohort



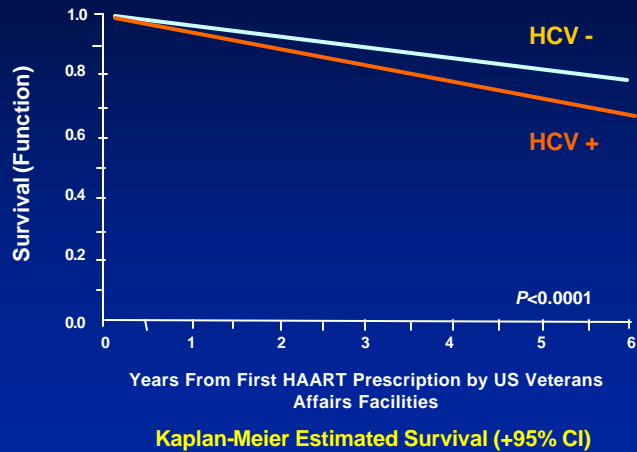
Greub G, et al. Lancet. 2000;356:1800.

Suppressed CD4 Lymphocyte Responses in HIV/HCV Co-infected Persons



Greub G, et al. Lancet. 2000;356:1800.

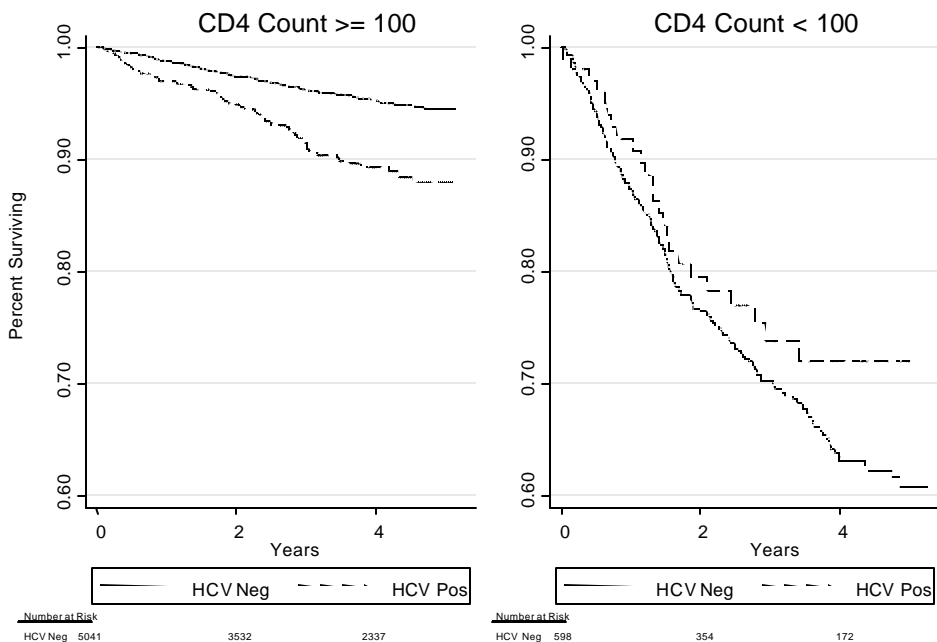
Mortality of HIV-HCV Coinfected US Veterans on HAART (cont'd)

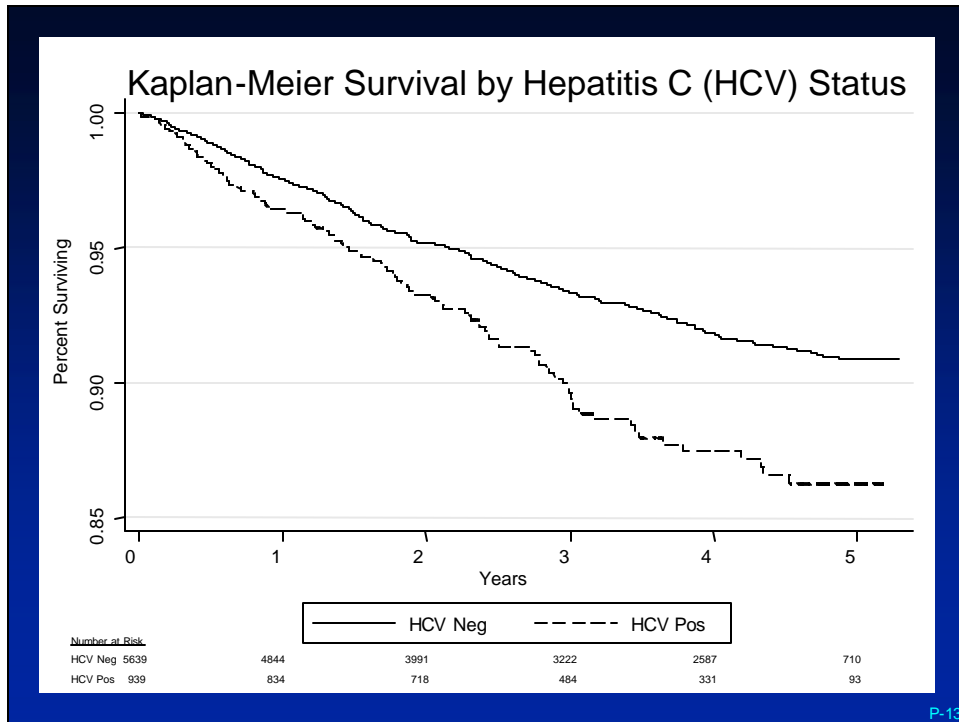


Backus L, et al. 11th CROI, 2004; Abs.800.

P-11

Kaplan Meier Survival by Hepatitis C (HCV) Status



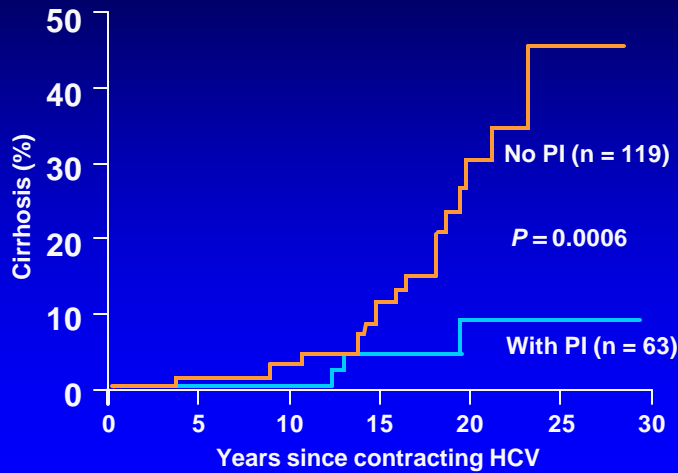


Increase in CD4 Lymphocyte Count Following HCV Clearance in a Cohort of HIV/HCV Infected Pts.

- 26 patients compared SVR's vs Non Responders(NR)
- Observation period 76 weeks
- HIV <400 in 54% of SVR vs 47% of NR's
- Median Change in CD4 was +65 cells in SVR's vs. NR's (-207 to +258) -83 cells
- P< 0.018 independent of HIV control
 - Uriel A, Guitierrez J Reichenberg A and Dieterich D Hepatology Oct 2003 Abstract

PI-based HAART has been predicted to slow rate of HCV progression

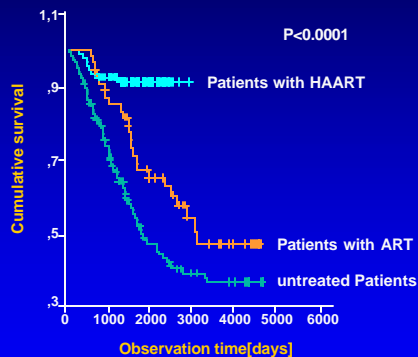
Cirrhosis rate modelled in 182 HIV-HCV co-infected patients



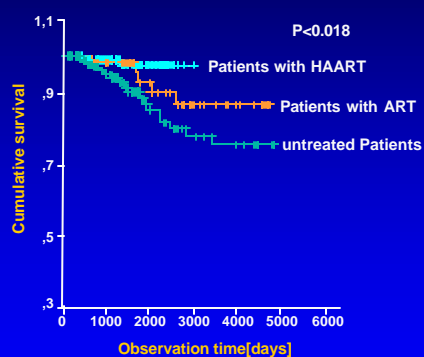
Benhamou *et al. Hepatology* 2001; 34:283–287

Kaplan Meier Analysis of Overall and Liver-related Mortality

A) Overall-Mortality



A) Liver-related-Mortality



Patients under observation:

HAART-group:	93	79	33	-	-	-
ART-group:	55	46	30	15	9	1
Untreated-group:	137	94	49	37	32	27

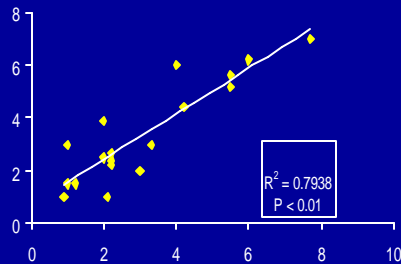
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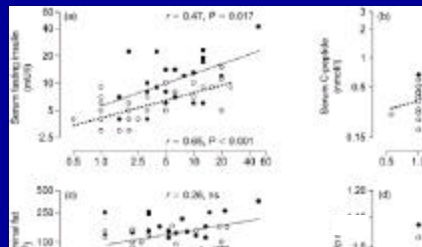
Qurishi N *et al., Lancet* 2003;362:1708-1713

FAT IN THE WRONG PLACES AND INSULIN RESISTANCE

HOMA-IR



% Intramuscular
fat in HIV+ men
(Sakkas, unpubl,
2003)



Liver (Sutinen AIDS 2002):

- ◆ Significantly higher % liver fat in HIV+ LD vs. HIV+ no LD and HIV-
- ◆ Severity of insulin resistance related to liver fat but not VAT

P-17

Blood lactate as a predictor of outcome in paracetamol-induced acute liver failure

- Retrospective review of 103 patients
- Prospective review of 107 patients
- Median Lactate: Deaths 8.5
- Median Lactate: Survivors 1.4
- Arterial Lactate effectively predicts death from liver failure
 - Bernal, Lancet 2002 359: 558-63

P-18

RIBAVIC - ANRS HC02

mitochondrial toxicity event » (MTE)

- 6 acute pancreatitis (one with hyperlactatemia)
- 7 hyperlactatemia (hospitalization)
- 4 suspicions of hyperlactatemia
- Association with Didanosine treatment*

ddI	d4T	% with MTE
yes	yes	24% (12/50)
yes	no	7% (3/30)
no	yes	0% (0/114)
no	no	2% (2/98)

Odds-ratio for ddi = 23 [95% CI : 5-105]

P-19

APRICOT

Final Results:

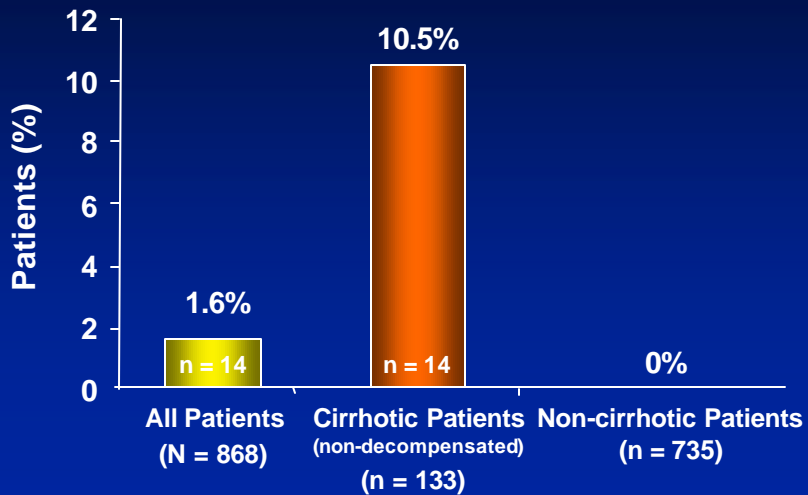
CROI

February 2004



P-20

Occurrence of Hepatic Decompensation



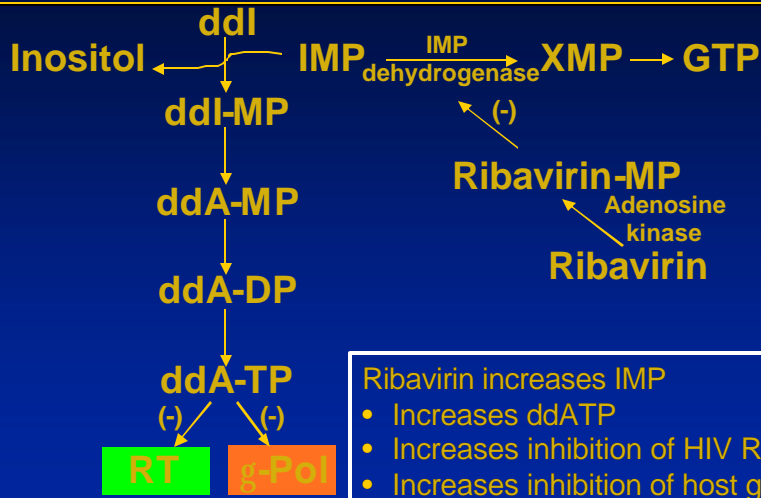
P-21

Risk Factors

- Total bilirubin \bar{Y} (OR 1.12, $P < 0.001$)
- Alkaline phosphatase \bar{Y} (OR 1.02, $P < 0.001$)
- Albumin β (OR 0.83, $P < 0.002$)
- Platelets β (OR 0.96, $P < 0.001$)
- Hemoglobin β (OR 0.53, $P = 0.001$)
- **Didanosine treatment (OR 4.06, $P = 0.03$)**
- Lamivudine treatment (OR 0.30, $P = 0.04$)
- PT INR, efavirenz, saquinavir and non-nucleoside inhibitor treatments ($P < 0.20$)

P-22

Ribavirin and ddl Anabolism

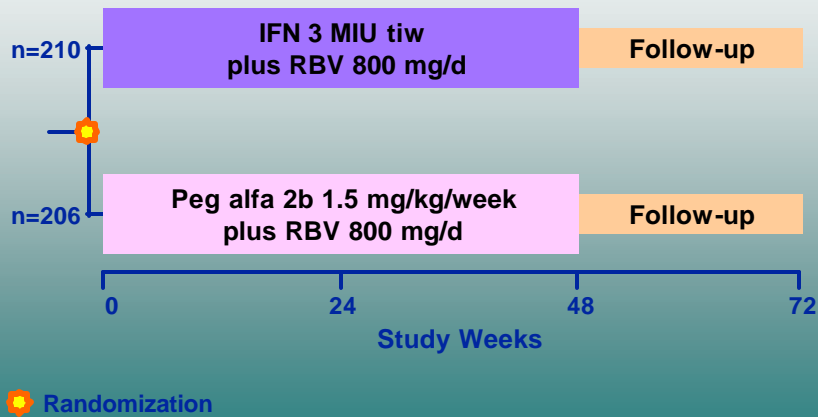


P-23

Therapy with IFN α + Ribavirin in HCV-treatment naive HIV/HCV co-infected patients

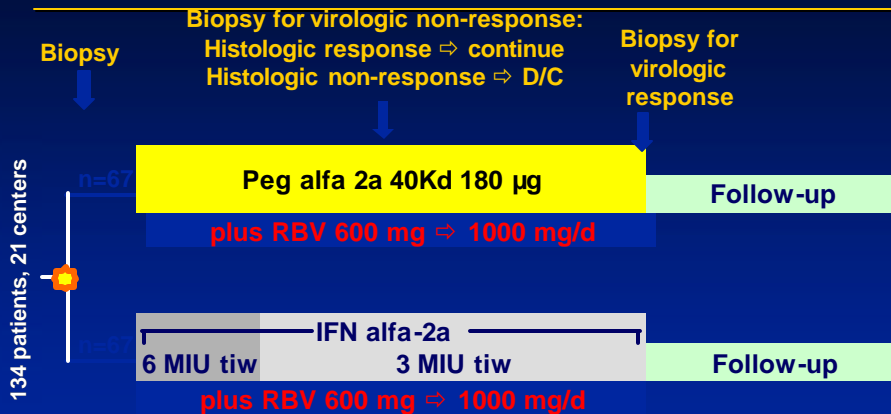
Author	End of Treatment response	Sustained response	Treatment discontinuation: due to AE
Landau 2000	24/60 (40%)	16/60 (26%)	9/60 (15%)
Sauleda 2000	n.a.	6/19 (31%)	0/19 (0%)
Bochet 2001	9/30 (30%)	6/30 (20%)	n.a.
Nasti 2001	5/17 (31%)	3/17 (19%)	1/17 (6%)
Rockstroh 2001	3/23 (13%)	3/23 (13%)	6/23 (26%)
Total	34/130 (26%)	34/149 (23%)	16/119 (14%)

Peg alfa2b/RBV vs IFN/RBV in HIV/HCV Co-Infection (RIBAVIC Study)



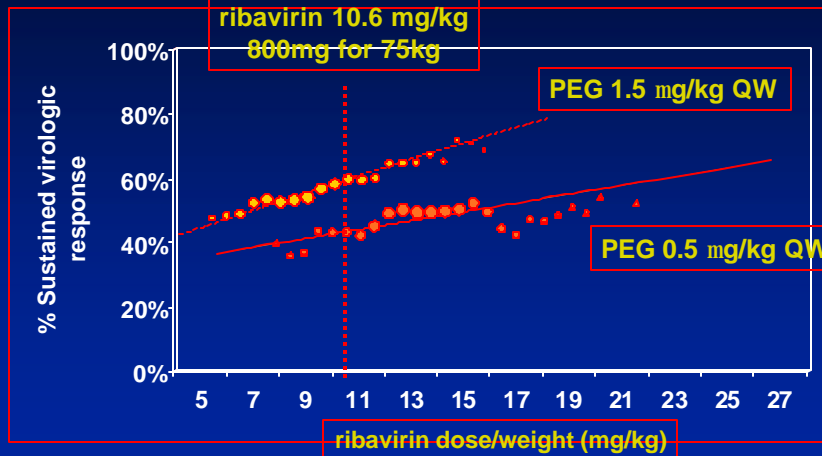
Pol et al et al, EASL 2003, oral

AACTG A5071: Study Design



P-26

Effect of ribavirin dose mg/kg on virologic response (Secondary logistic regression analysis)

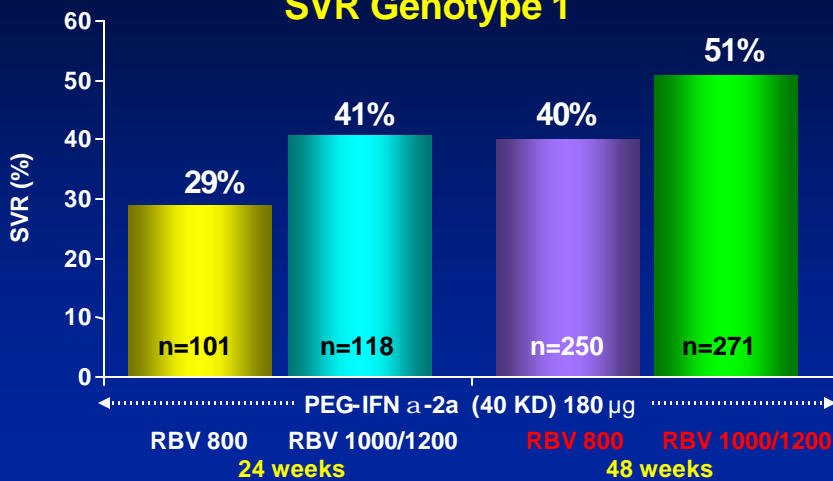


Manns et al., Lancet 2001

P-27

PEG-IFN α -2a (40 KD) + RBV NV 15942 (Hadziyannis) Trial

SVR Genotype 1

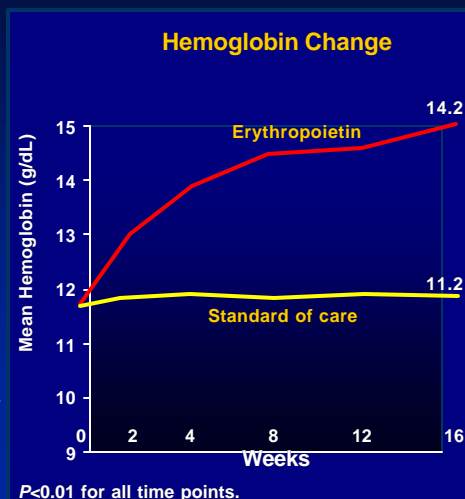


Hadziyannis SJ et al. *J Hepatol* 2002;36(S1):p3.

P-28

Correction of Ribavirin-Induced Anemia With Erythropoietin

- Open-label trial
 - 64 HCV-monoinfected patients
 - HCV regimen
 - Standard interferon plus ribavirin
- To treat anemia, patients were randomized to receive either:
 - Erythropoietin (n=36)
 - 40,000 U subcutaneously once weekly
 - Standard of care (n=28)
 - Nonpharmacologic management

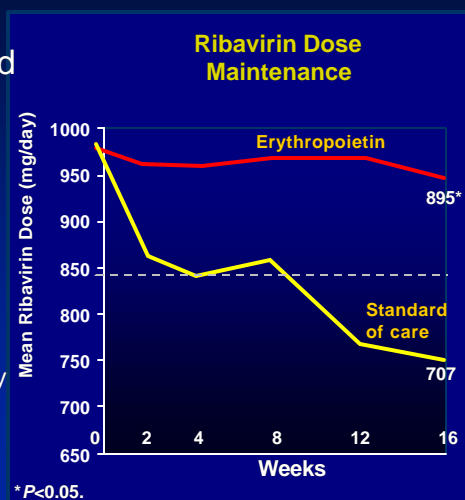


Dieterich DT, et al. *Am J Gastroenterol.* 2003;98:2491-2499.

P-29

Erythropoietin: Maintenance of Ribavirin Dosing in HCV-Monoinfected Patients

- Open-label trial
 - 64 HCV-monoinfected patients
 - HCV regimen
 - Standard interferon plus ribavirin
- To treat anemia, patients were randomized to receive either:
 - Erythropoietin (n=36)
 - 40,000 U subcutaneously once weekly
 - Standard of care (n=28)
 - Nonpharmacologic management

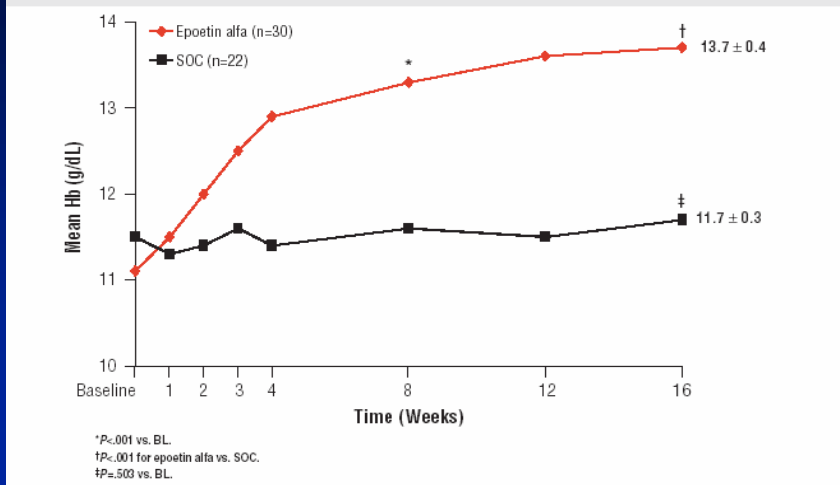


Dieterich DT, et al. *Am J Gastroenterol.* 2003;98:2491-2499.

P-30

Hematologic Response

Figure 1. Hemoglobin levels by treatment group.

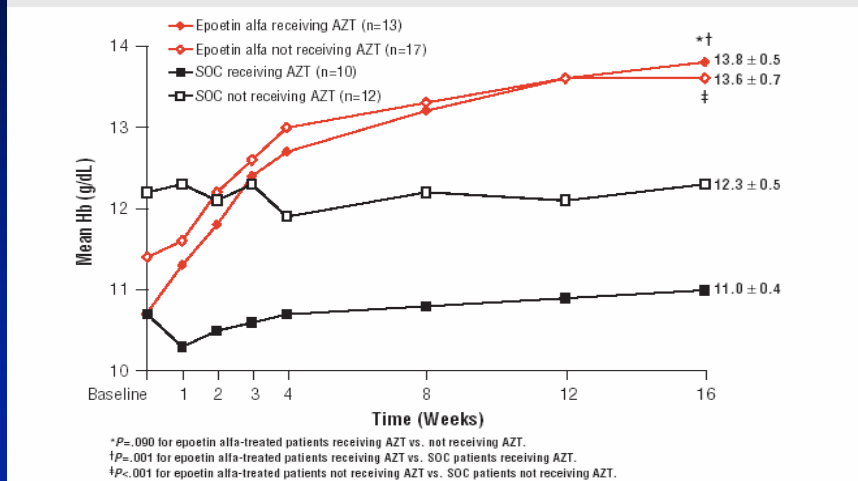


Dieterich D, et al. CROI/2004

P-31

Hematologic Response: AZT vs. no AZT

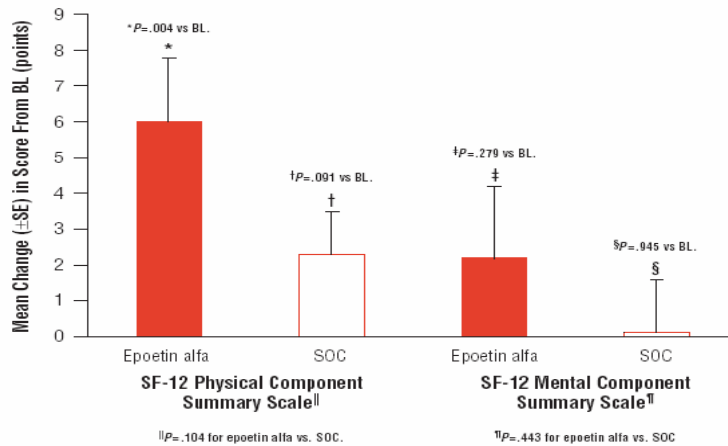
Figure 2. Hemoglobin levels by treatment group in patients receiving or not receiving zidovudine (AZT).



Dieterich D, et al. CROI/2004

Health-Related Quality of Life Changes

Figure 3. Health-related quality-of-life changes by treatment group.



Dieterich D, et al. CROI 2004

P-33

RIBAVIC

PEG-2b 1.5 µg/kg
RBV 800 mg/d
n=205

IFN-2b 3 MU
+RBV 800 mg/d
n=207

SVR

GT 1 (58%)
GT 2+3 + others

27%

16%
43%

19%

5%
41%

p=0.03

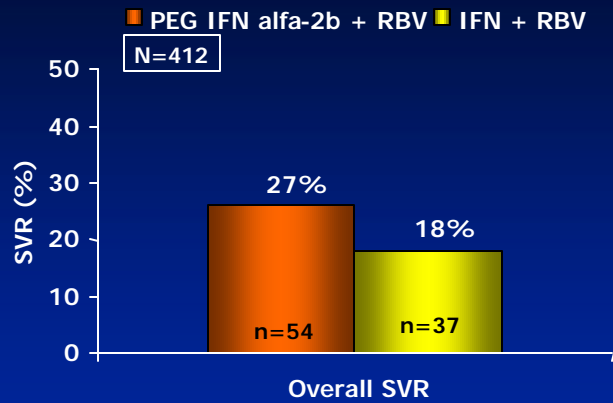
p=0.01
p=NS

Sep-2002 data

Treatment D/C:		34%	
Severe Adverse Events		24%	
Hospitalizations		5.7%	n=20
Hosp. with Lactic Acidosis	1.9%	n= 8	(8/8 on ddl, 7/8 on d4T)

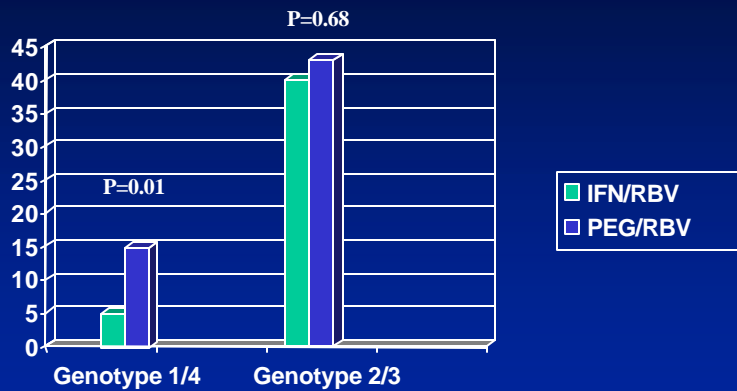
Peronne C11thCROI, Feb-2004

RIBAVIC SVR Rates



P-35

RIBAVIC: SVR by Genotype



Perronne C, et al. 11th CROI, 2004; Abs.117LB.

P-36

ACTG 5071: Baseline Characteristics

	IFN/RBV (n=67)	PEG-IFN/RBV (n= 66)
Male	85%	79%
Caucasian/AA	46%/34%	50%/32%
Age, median	44	45
CD4, median	444	492
HIV-1 RNA <50	60%	61%
Any ART	87%	85%
HCV Genotype 1	78%	77%
Log ₁₀ HCV RNA	6.2	6.2
% cirrhosis	9%	11%

Chung R, et al. 11th CROI, 2004; Abs.110.

P-37

ACTG 5071

(N=133)

	PEG-2a 180 µg + RBV 600 → 1000 n=66	IFN-2b 6→3 MU + RBV 600 → 1000 n=67	
Sustained viral response (all)	27%	12%	p<0.05
GT 1	14%	6%	p=NS
GT 2+3 + others	73%	33%	p=0.07
Treatment D/C	12%	12%	p=NS
Grade 4 AEs (mostly lab) p=0.0012	17%	4%	

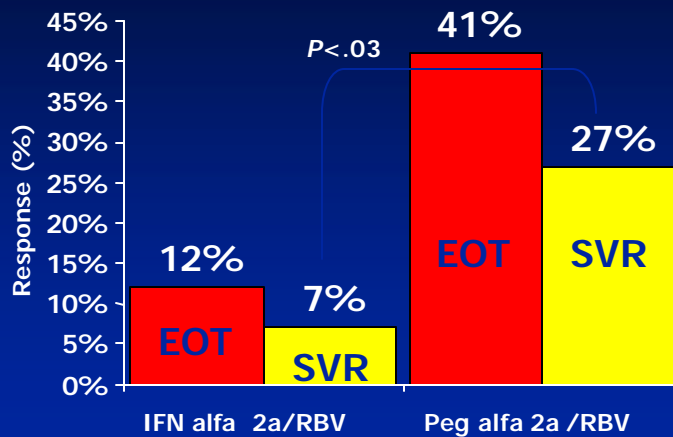
Week 12 EVR

NPV=100%

Chung RT, 11th CROI, Feb-2004

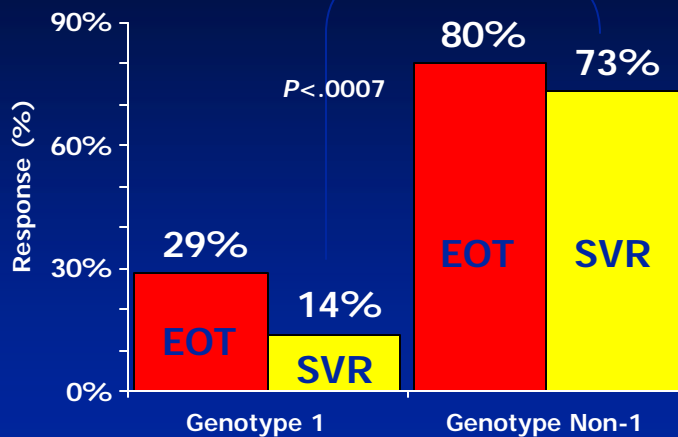
P-38

ACTG 5071 Results (Overall)



P-39

ACTG 5071: Peg alfa 2a 40Kd /RBV Arm By Genotype



P-40

ACTG 5071: Predictors of SVR

Variable	Univariate	Multivariate	OR
PEG/RBV	0.03	0.008	4.76
Genotype non-1	<0.001	<0.001	15.8
No previous IDU	0.04	0.009	0.48
Base HIV VL >50	0.046	0.023	3.55

Chung R, et al. 11th CROI, 2004; Abs.110.

P-41

Conclusions ACTG 5071

- Peg alfa 2a + RBV is superior to IFN + RBV in the treatment of chronic HCV in HIV-coinfected persons and is well tolerated without adverse effect on HIV disease
- The marked genotype discrepancy in SVR indicates that strategies to improve outcome in genotype 1 HCV are needed
- These regimens may provide clinical benefit even in the absence of virologic clearance
 - Histologic response observed in 36% of NR
 - Histologic response observed in 52% of VR who underwent biopsy

P-42

Demographics PEG-IFN Treatment Groups

	RIBAVIC ANRS HC02 n=206	AACTG A 5071 n=67	APRICOT n=525
Male	77%	79%	81%
Caucas. / AA	n.a.	49% / 33%	81% / n.a.
Age [years]	39.4	45	40
CD4 [/ μ L]	525 (mean)	500 (median)	477 (median)
HIV-1-RNA on ART	70% <400 c/mL 82%	58% <500 c/mL 87%	<50 c/mL (median) 85%
HCV-RNA	n.a.	6.2 \pm 0.4 log ₁₀ IU/mL	8.7x10 ⁶ c/mL
HCV G1	52%	78%	59.3%
ALT abnorm.	85%	66%	88%
Cirrhosis	15%	10%	16.8%

P-43

HIV/HCV Co-infection Study

**AIDS
PEGASYS®
Ribavirin
International
CO-Infection
Trial**



P-44

Patients Randomized/Country

868 Patients at 95 Centers in 19 Countries

	Argentina	27		Italy	85
	Australia	40		Netherlands	2
	Austria	9		Norway	5
	Belgium	18		Portugal	29
	Brazil	46		Spain	158
	Canada	33		Sweden	9
	Denmark	6		Switzerland	15
	France	39		UK	30
	Germany	37		US	278
				Mexico	2

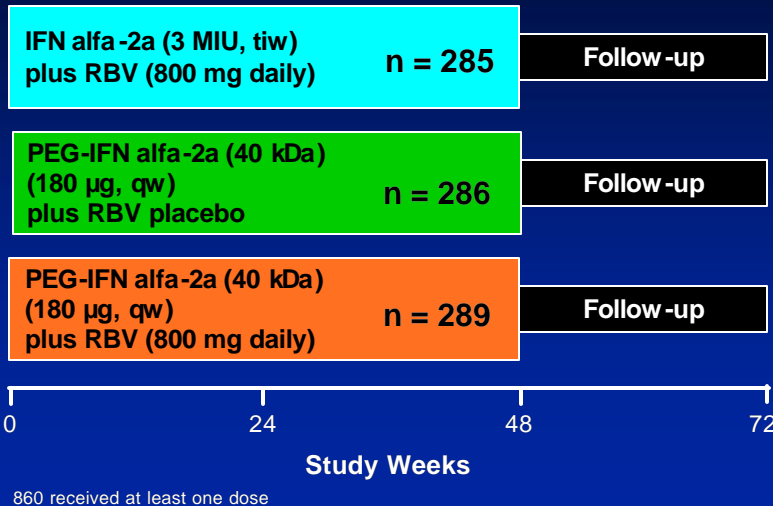
P-45

APRICOT Study Group

Alaeus, A.	Coelho, H.S.	Hirschel, B.	Molina, J-M.	Rosado-Santos, H.
Allworth, A.	Cooper, D.	Hoepelman, I.M.	Montaner, J.	Rouleau, D.
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Cassetti, I.	Greiger, P.	Mazzotta, F.	Rockstroh, J.	Torres-Ibarra, R.
Clotet, B.	Guardiola, J.	McGovern, B.	Rodriguez, A.	Torriani, F.
Clumeck, N.	Guzman, E.	Meynard, J-L.	Rodriguez-Torres, M.	Trepo, C.

P-46

APRICOT Study Design



P-47

APRICOT Study Design

- PEG-IFN alfa-2a combination therapy blinded (RBV vs placebo)
- Stratified
 - Genotype 1 vs non-1
 - CD4⁺ 100 to <200/µL vs ≥200/µL
 - ART vs no ART
 - Cirrhotic vs non-cirrhotic
 - Geographic region

P-48

Key Inclusion Criteria

- HCV criteria
 - Naive to IFN and ribavirin
 - HCV antibody positive
 - Quantifiable HCV RNA (Amplicor™ MONITOR)
 - Elevated serum ALT
 - Liver biopsy (≤ 15 months) consistent with HCV infection
 - Non-cirrhotic or cirrhotic
 - If cirrhotic, Child-Pugh Grade A

P-49

Key Inclusion Criteria

- HIV criteria
 - HIV antibody or quantifiable HIV RNA
 - CD4⁺ cell count
 - $\geq 200/\mu\text{L}$ or
 - $\geq 100/\mu\text{L}$ to $< 200/\mu\text{L}$ with < 5000 copies/mL HIV RNA
 - Stable HIV disease with or without antiretroviral treatment

P-50

Key Exclusion Criteria

- Decompensated liver disease
- Other chronic liver disease
- Active HIV-related opportunistic infections
- Significant medical conditions
 - Psychiatric/neurological
 - Pulmonary
 - Cardiac
 - Thyroid/immunologically-mediated disease
 - Retinopathy
- Pregnancy/male partners of pregnant women

P-51

Primary Efficacy Endpoint

Sustained Virologic Response (SVR) –

Undetectable serum HCV RNA*
at end of 24-week treatment-free follow-up
(week 72)

*Amplicor™ HCV test v2.0, sensitivity <50 IU/mL

P-52

Baseline Characteristics

	IFN alfa -2a + RBV (n = 285)	PEG-IFN alfa -2a (40 kDa) + Placebo (n = 286)	PEG-IFN alfa -2a (40 kDa) + RBV (n = 289)
Male gender (%)	81	82	80
Race (% Caucasian)	78	79	80
Age (years)	40	40	40
Body Mass Index (kg/m ²)	25	25	24
Qualifying ALT (IU/L)	87	88	85
Cirrhotic (%)	16	16	15
Mode of Infection – IVDU (%)	71	62	62

P-53

Baseline Characteristics: HCV Disease Status

	IFN alfa -2a + RBV (n = 285)	PEG-IFN alfa -2a (40 kDa) + Placebo (n = 286)	PEG-IFN alfa -2a (40 kDa) + RBV (n = 289)
HCV RNA (IU/mL x 10 ⁶)			
Mean	5.2	6.3	5.6
HCV Genotype (%)			
Type 1	60	61	61
Type non-1	40	38	38
2	5	6	4
3	26	26	28
4	8	7	6
Other	<1	<1	<1

P-54

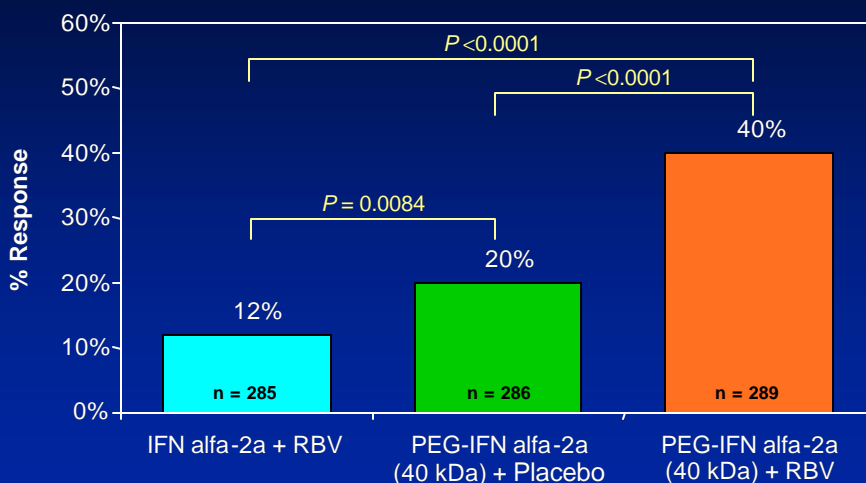
Baseline Characteristics: HIV Disease Status

	IFN alfa-2a + RBV (n = 285)	PEG-IFN alfa-2a (40 kDa) + Placebo (n = 286)	PEG-IFN alfa-2a (40 kDa) + RBV (n = 289)
ART* (%)	84	85	84
HIV RNA			
Log ₁₀ copies/mL (mean ± SD)	2.3 ± 1.0	2.4 ± 1.0	2.3 ± 1.0
<50 copies/mL (%)	60	60	60
CD4 ⁺ counts (cells/μL)			
Mean	542	530	520
<200 (%)	7	5	6

* Any treatment used as antiretroviral therapy

P-55

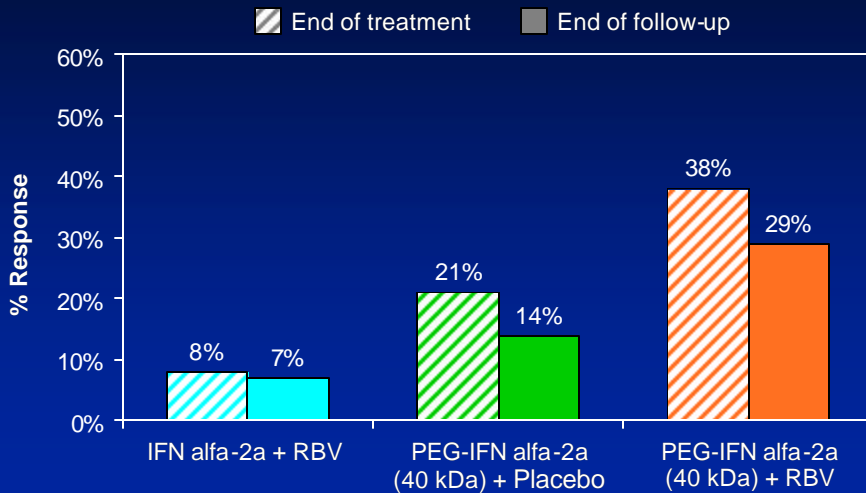
Sustained Virologic Response*



* Defined as <50 IU/mL HCV RNA at week 72; ITT

P-56

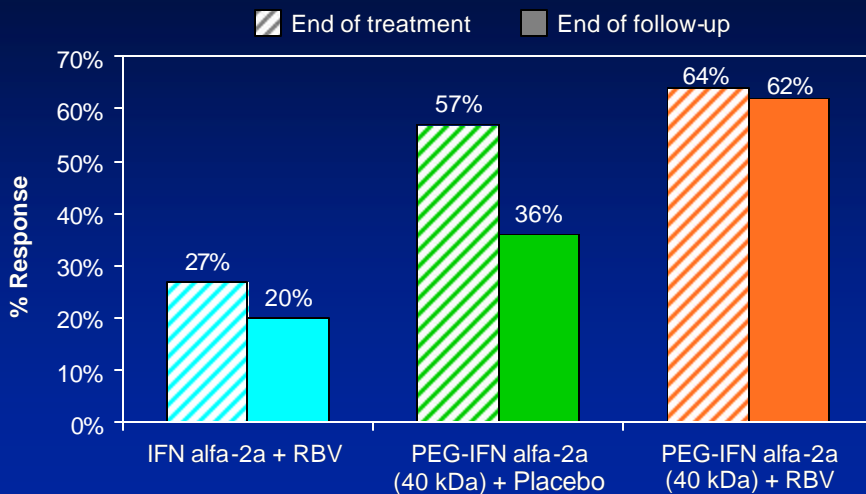
Virologic Response* – End of Treatment vs End of Follow-up (Genotype 1)



* Defined as <50 IU/mL HCV RNA

P-57

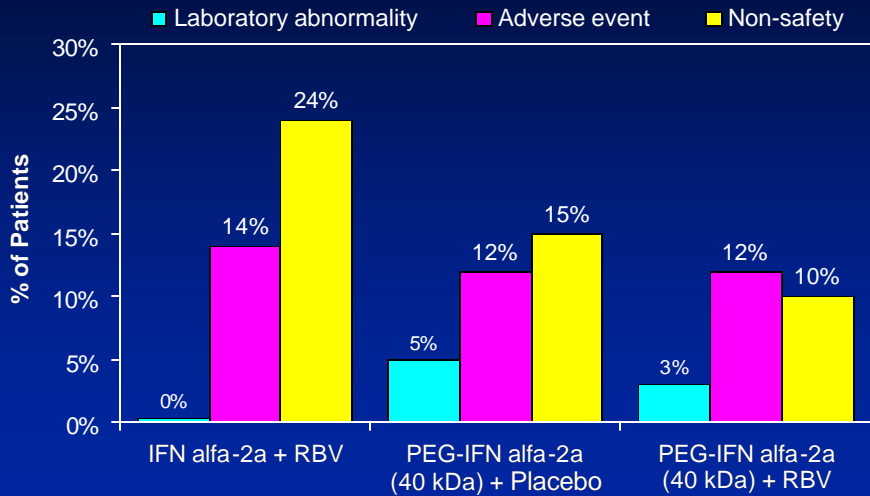
Virologic Response* – End of Treatment vs End of Follow-up (Genotype 2 and 3)



* Defined as <50 IU/mL HCV RNA

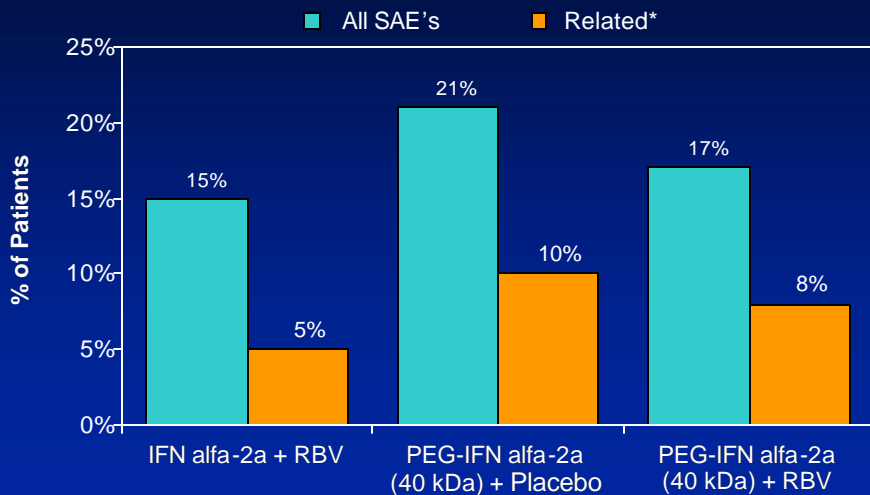
P-58

Withdrawal from Treatment



P-59

Patients with Serious Adverse Events



* Possibly or probably related

P-60

Adverse Events ³20%*

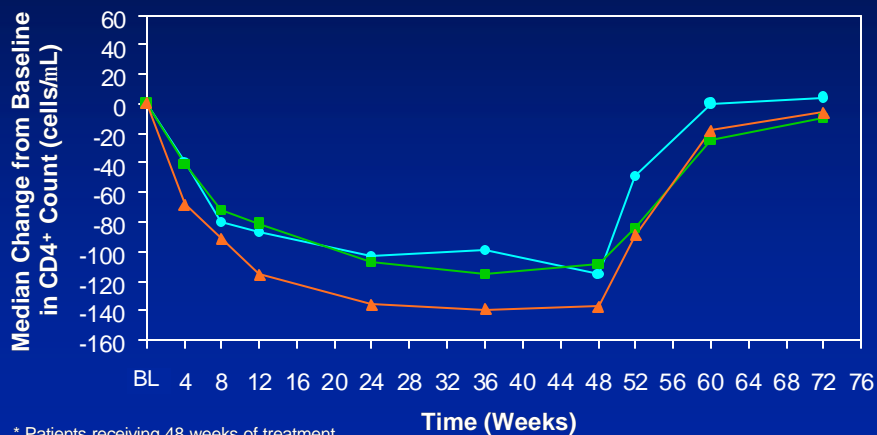
	IFN alfa-2a + RBV (n = 285)	PEG-IFN alfa-2a (40 kDa) + Placebo (n = 286)	PEG-IFN alfa-2a (40 kDa) + RBV (n = 288)
Fatigue	36%	36%	40%
Pyrexia	32%	35%	41%
Headache	34%	29%	35%
Myalgia	27%	29%	32%
Nausea	19%	19%	22%
Insomnia	23%	16%	19%
Asthenia	23%	20%	26%
Depression	20%	16%	20%

* Possibly or probably related

P-61

Median Change from Baseline in CD4⁺ Counts*

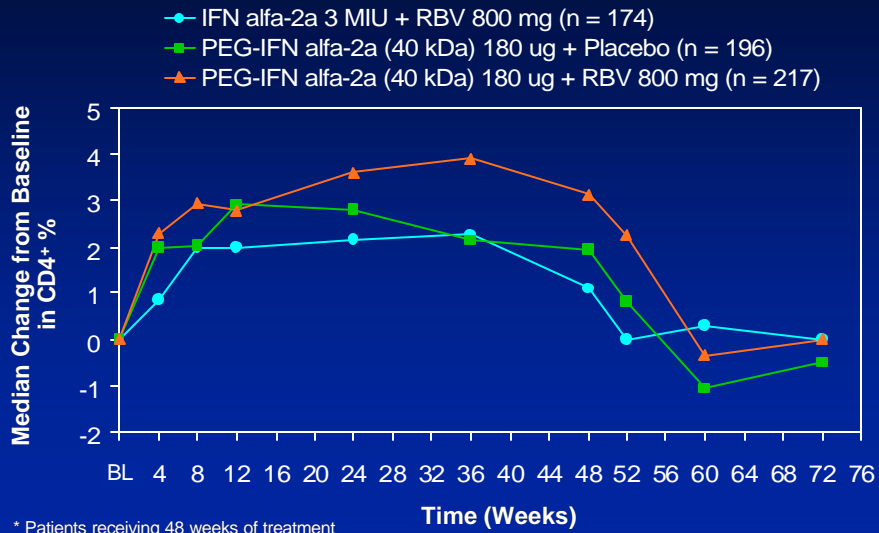
- IFN alfa-2a 3 MIU + RBV 800 mg (n = 174)
- PEG-IFN alfa-2a (40 kDa) 180 ug + Placebo (n = 196)
- ▲— PEG-IFN alfa-2a (40 kDa) 180 ug + RBV 800 mg (n = 217)



* Patients receiving 48 weeks of treatment

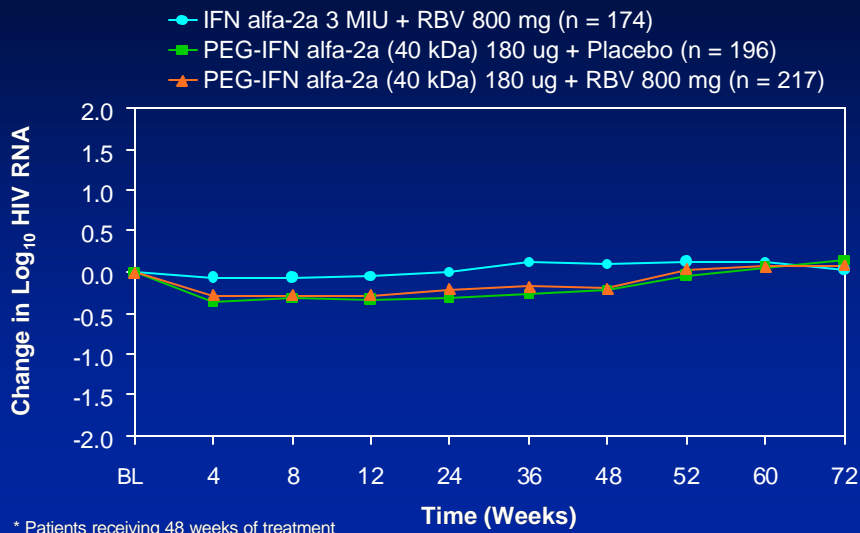
P-62

Median Change from Baseline in CD4+ %*



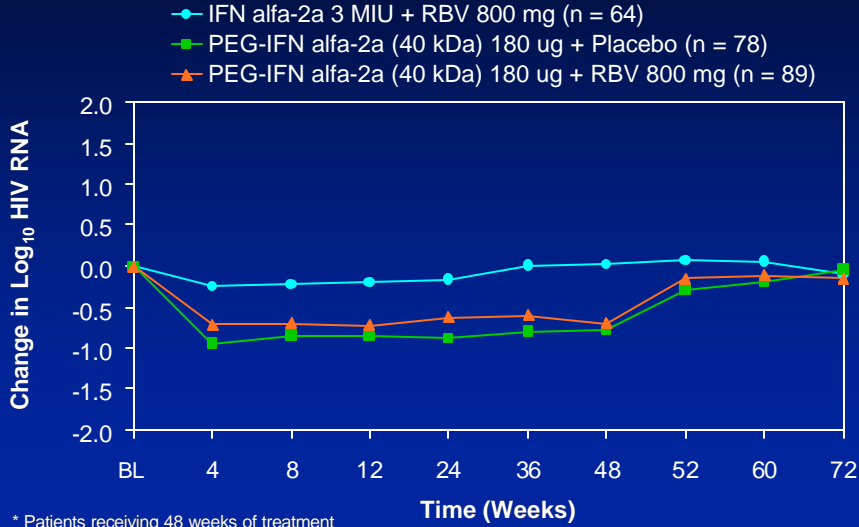
P-63

Mean Change from Baseline in HIV RNA: All Patients Treated*



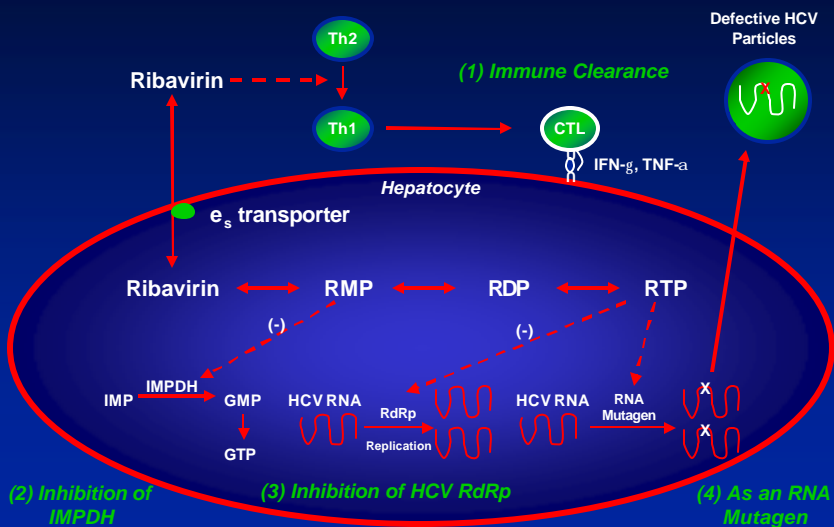
P-64

Mean Change from Baseline in HIV RNA: Patients with Detectable HIV RNA at Baseline*



P-65

Ribavirin Mechanism of Action



Lau et al. Hepatology, 2002; 35: 1002-1009

P-66

Patient Population

	Peg alfa 2a Placebo (N = 31)	Peg alfa 2a Ribavirin (N = 25)
Male; female	28; 3	19; 6
Mean age (range)	42 (23-61)	41 (21-54)
Mean BMI (kg/m ²)	26.3 ± 5.1	24.6 ± 4.3
Number (%) receiving:		
● Lamivudine	30 (97)	25 (100)
● Stavudine	17 (55)	15 (60)
● Zidovudine	14 (45)	10 (40)
● Didanosine	1 (3)	1 (4)
● Protease inhibitors	19 (61)	13 (52)
● NNRTIs	10 (32)	12 (48)

P-67

Ribavirin Pharmacokinetics: Comparison With Historic Data

Parameter	APRICOT Participants (Wk 8-12)	HCV Monoinfection (Wk 12)
Ribavirin Dose (mg/day)	800	1000 or 1200
AUC ₀₋₁₂ (ng•hr/mL)	23476 ± 9983	26361 ± 7520
C _{max} (ng/mL)	2771 ± 1653	2840 ± 834

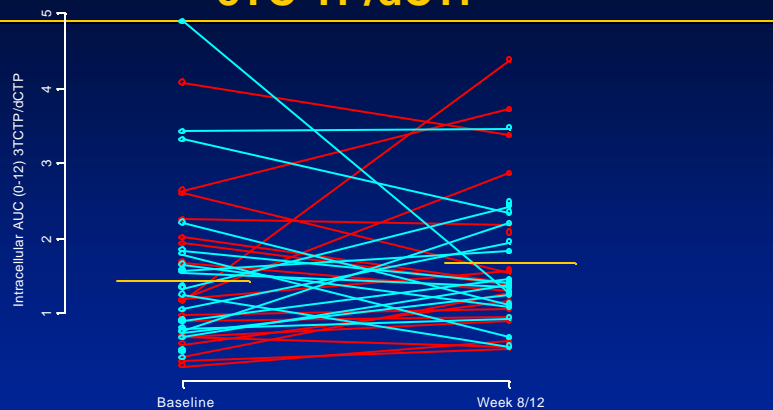
P-68

Effect of Ribavirin on Endogenous Nucleoside Triphosphates Pools

Intracellular AUC _{0-12h}	Treatment	N	Week 12 Least Squares Mean (a)	Difference of Least Squares Means (b)	95% Confidence Interval for Difference
Deoxythymidine TP	Ribavirin	18	3.753	0.761	-0.38, 1.90
	Placebo	19	2.991		
Deoxycytidine TP	Ribavirin	18	5.882	-0.119	-1.77, 1.53
	Placebo	18	6.001		

P-69

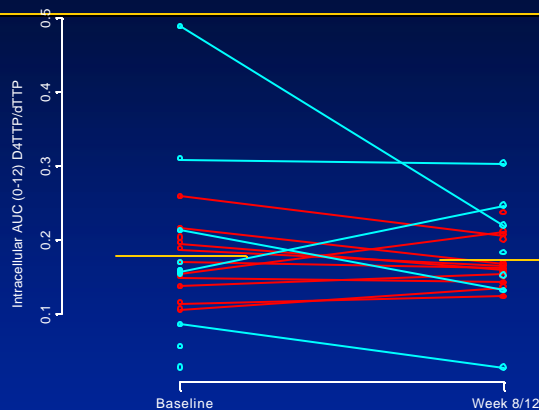
Individual Intracellular AUC₀₋₁₂ Ratio of 3TC-TP/dCTP



AUC _{0-12h} Ratio	Treatment	Week 12 LSM	Difference in LSM (95% CI)
3TC-TP/dCTP	Ribavirin	1.783	0.274 (-0.37, 0.91)
	Placebo	1.509	

P-70

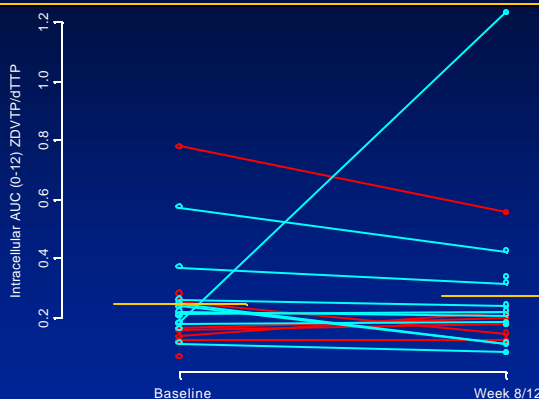
Individual Intracellular AUC₀₋₁₂ Ratio of d4T-TP/dTTP



AUC _{0-12h} Ratio	Treatment	Week 12 LSM	Difference in LSM (95% CI)
d4T-TP/dTTP	Ribavirin	0.173	0.009 (-0.06, 0.08)
	Placebo	0.164	

P-71

Individual Intracellular AUC₀₋₁₂ Ratio of ZDV-TP/dTTP



AUC _{0-12h} Ratio	Treatment	Week 12 LSM	Difference in LSM (95% CI)
ZDV-TP/dTTP	Ribavirin	0.235	-0.081 (-0.4, 0.24)
	Placebo	0.316	

P-72

Summary

In patients with HCV/HIV co-infection:

- Ribavirin appears not to perturb the intracellular metabolism of lamivudine, stavudine or zidovudine or their corresponding endogenous nucleoside triphosphates
- Ribavirin appears not to modify the plasma concentration-time profile of lamivudine, stavudine or zidovudine

P-73

Summary

- SVR was significantly higher for PEG-IFN alfa-2a (40 kDa) + RBV compared to conventional combination therapy
 - Overall: 40% vs 12%; $P < 0.0001$
 - Genotype 1: 29% vs 7%
 - Genotype 2/3: 62% vs 20%
- Adverse event profile of PEG-IFN alfa-2a (40kDa) + RBV is generally similar to IFN + RBV therapy
- Only 15% of patients discontinued for adverse events or laboratory abnormalities

P-74

Conclusion

- APRICOT is the largest and the only international registration study in HIV/HCV co-infection
- HCV therapy did not negatively impact control of HIV
- 40% SVR is the highest of any reported study in HIV/HCV co-infection

P-75

Survival in HIV-Infected Liver Transplants

- 23 HIV+ compared to 11,453 in UNOS data
- Age 47, 19M 4F, 14 HCV, 10 HBV 3 FHF: 1 HBV, 1 HCV and 1 NVP toxicity ALT 82
- MELD 15! CD4 200 HIV 400-179,000
- Post Trx 14 PI, 5 NNRTI, 4 NRTI CD4 281
 - HIV 400-9600, 6 ART toxicity, 4 HCV, 2 non-HCV
 - 12 month survival 90.9%
 - 12 month survival UNOS 87.6%
 - HCV risk higher but same as in HIV-
 - 5 now dead 1 NLF d/c'd 4 HCV related
 - Delay HCV treatment past first few weeks

Ragni M, et al CROI 2003 Boston Abstract 153

P-76

Nelfinavir: interaction with tacrolimus

- Mean 38-fold tacrolimus dose reduction for patients taking nelfinavir compared to placebo
- Mean dose for patients (n = 5) on nelfinavir: 0.26mg/d
- Frequent drug level monitoring and great caution are necessary when introducing or withdrawing HAART in HIV-positive organ transplant recipients

Jain et al. *Liver Transpl.* 2002;8:841-845

P-77

Kidney and Liver Transplantation in HIV-Infected Patients at 16 U.S. Transplant Centers

- Prospective, multi-center cohort study of 275 HIV+ patients who receive transplants and are followed for 2 to 5 years at 16 transplant centers.
- 150 kidney and 125 liver recipients
- Central hypothesis: HIV+ liver and kidney transplant recipients will have patient and graft survival rates comparable to other patient groups without HIV infection that are currently considered acceptable transplant candidates

P-78

CONCLUSIONS

- HCV is a major, if not **the** major cause of morbidity and mortality in HIV+ patients today
- Successful treatment of HCV (cure) in HIV+ patients is possible and even likely with pegylated interferon and ribavirin
- Side effects can be effectively managed to ensure treatment success
- Liver (and kidney) transplant is possible and is being investigated in HIV+ patients