18th Annual Conference of the British HIV Association (BHIVA)

Dr Mark Nelson

Chelsea and Westminster Hospital, London

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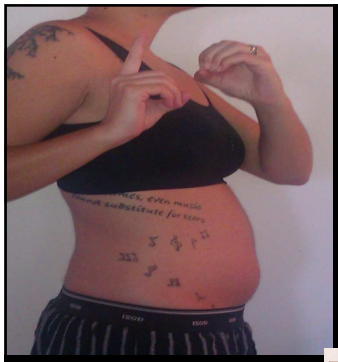
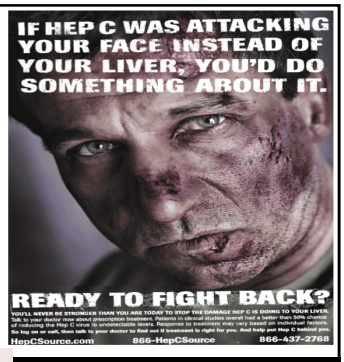
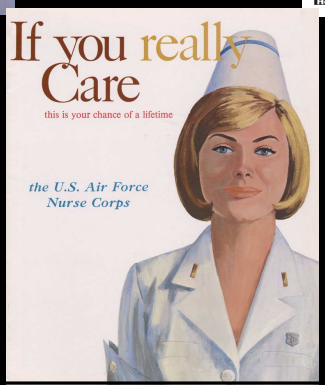
COMPETING INTEREST OF FINANCIAL VALUE ≥ £1,000:	
Speaker Name	**Statement**
Dr Mark Nelson:	Dr Nelson has received educational grants, research support and honoraria from the following companies involved in hepatitis and HIV: MSD, Gilead, ViiV, Abbott, BMS, Idenix, Pfizer, Tibotec, BI in the last 12 months
Date	**April 2012**

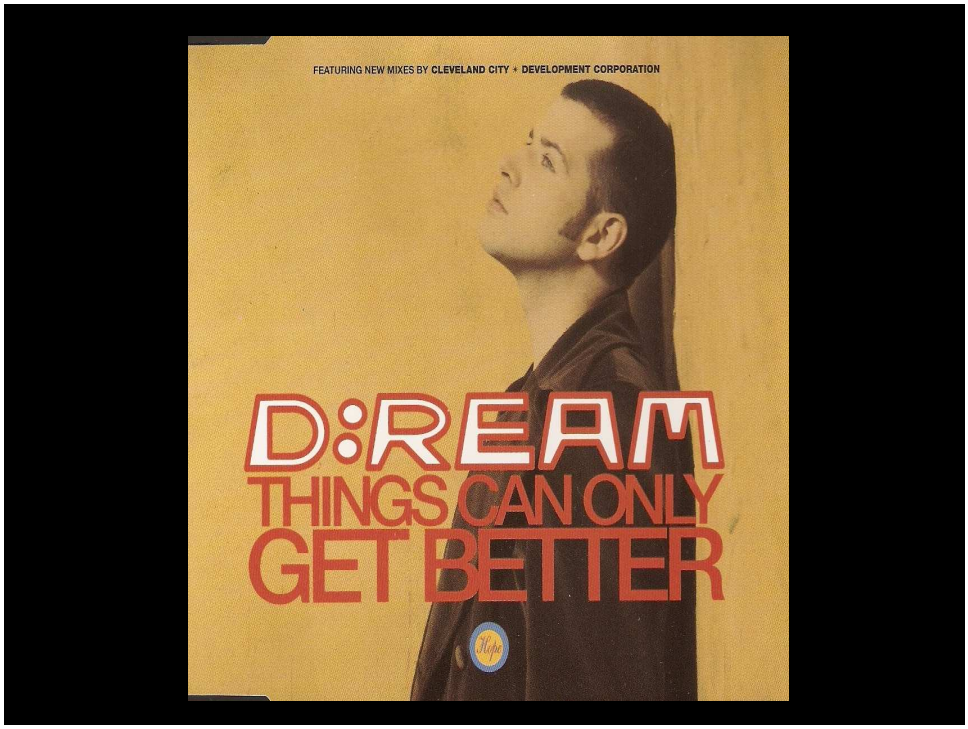
18-20 April 2012, The International Convention Centre, Birmingham



Treat Now


IF HEP C WAS ATTACKING YOUR FACE INSTEAD OF YOUR LIVER, YOU'D DO SOMETHING ABOUT IT.
READY TO FIGHT BACK?
HepCSource.com
866-HepCSource
866-437-2768


If you really Care
this is your chance of a lifetime
the U.S. Air Force
Nurse Corps


FEATURING NEW MIXES BY CLEVELAND CITY + DEVELOPMENT CORPORATION
D:REAM
THINGS CAN ONLY
GET BETTER

Chronic hepatitis C
routes of transmission

Primary HCV in HIV+ MSM: Initial Epidemic Reports

Browne 2004
Gilleece 2005

Ghosn 2004
Gambotti 2005

Götz 2005

Vogel 2005

Primary HCV in HIV+ MSM: Further Epidemic Reports

Luetkemeyer 2006
Fierer 2008

Matthews 2007

Primary HCV in HIV+ MSM: Further Epidemic Reports

Bottieau 2010

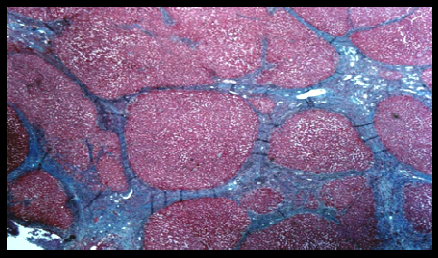
Barfod 2011

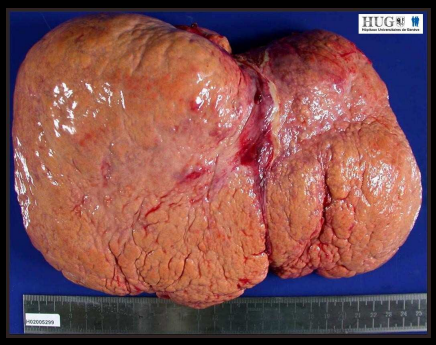
Montoya 2011

Fibrosis During Primary HCV Infection in HIV+ Men

- Antwerp, Belgium 2001 through April 2010
- 37 patients had liver biopsy, median 7 months (range: 3–36 months) after diagnosis of HCV infection:
- 22/37 (59%) had stage 2 or 3 fibrosis

Bottieau Eurosurv 2010



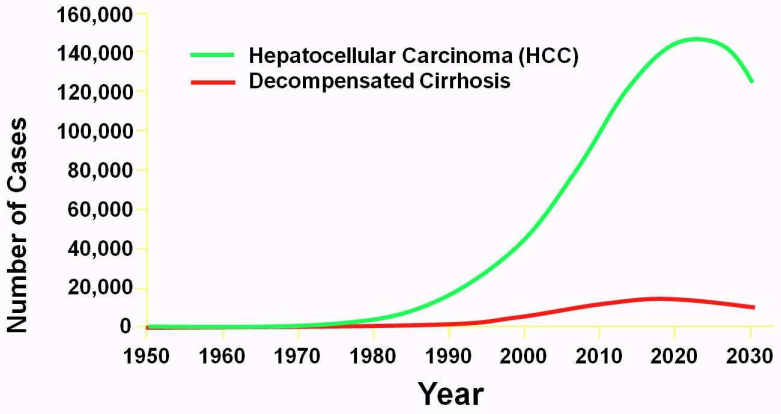

HUG


CORROSUS
ALCOHOLIC
DEATH
NOISE

ICVH 2012 INTERNATIONAL CONFERENCE ON VIRAL HEPATITIS

Projected Prevalence of Chronic HCV, Cirrhosis, and Complications

Projected Number of Patients With Decompensated Cirrhosis and Hepatocellular Carcinoma



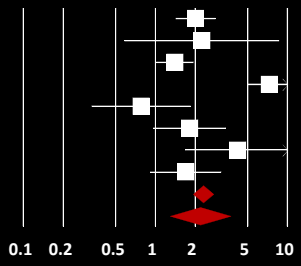
Davis GL, et al. *Gastroenterology.* 2010;138(2):513-521 e516.

Rate ratio of Cirrhosis between HIV/HCV and HCV: HAART era

Model	Study name	Risk ratio	Lower limit	Upper limit	Z-Value	p-Value
	Verma, 2006a	2.015	1.421	2.858	3.928	0.000
	Di Martino, 2001	2.245	0.581	8.683	1.172	0.241
	Brau, 2006	1.404	1.010	1.951	2.019	0.044
	Gaslightwala & Bini, 2006	7.289	4.938	10.760	9.998	0.000
	Monto, 2005	0.778	0.327	1.854	-0.566	0.572
	Mohsen, 2003	1.814	0.958	3.434	1.830	0.067
	Martinez-Sierra, 2003	4.195	1.665	10.567	3.042	0.002
	Macias, 2005	1.698	0.911	3.165	1.666	0.096
Fixed		2.290	1.919	2.732	9.197	0.000
Random		2.181	1.285	3.703	2.887	0.004

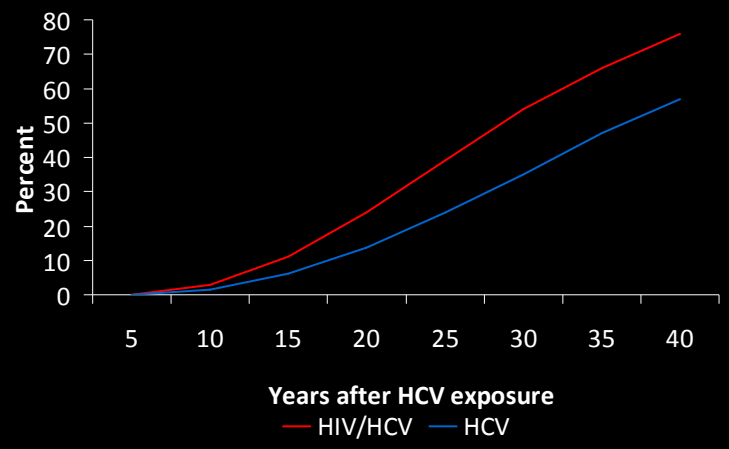
Statistics for each study

Risk ratio and 95% CI

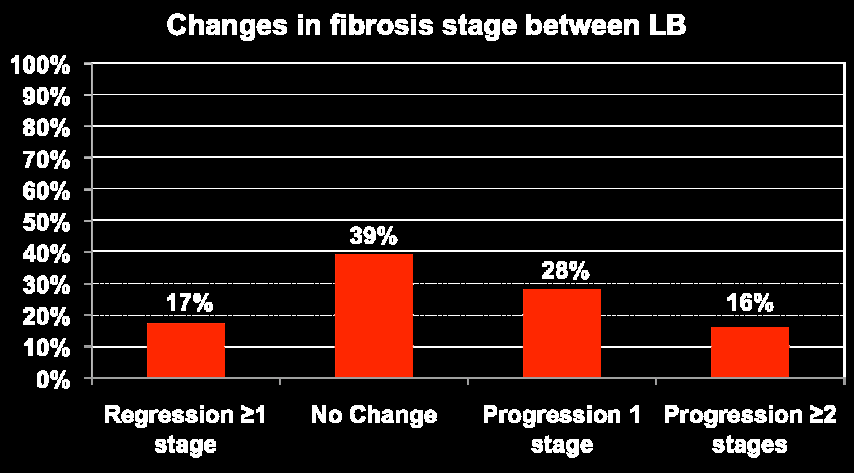


Meta-Analysis

Results: Cumulative probability of cirrhosis



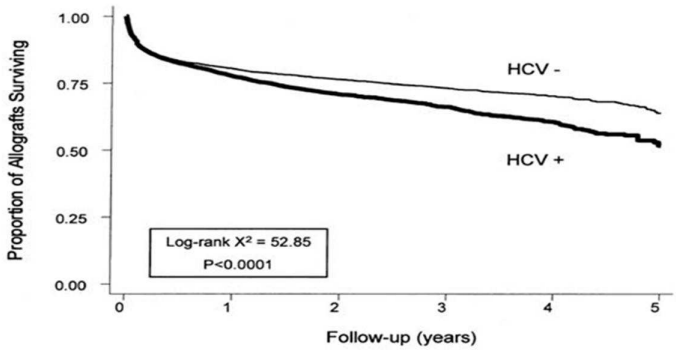
RESULTS (III)



Median (Q1-Q3) time between LB: 3.3 (2-5.2) years

Outcome of Hepatitis C Recurrence

Impact of Hepatitis C Recurrence in patient and graft survival

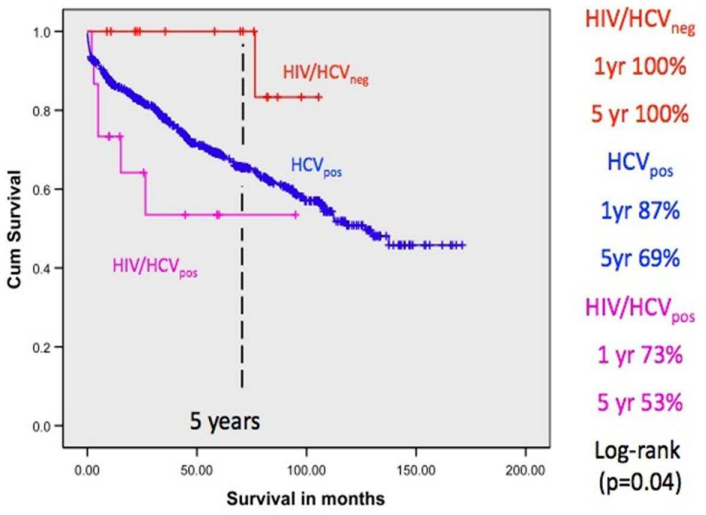


No. at Risk						
HCV+	4805	3040	1922	1111	502	97
HCV-	6986	4755	3300	2080	984	211

Forman et al , Gastro 2002

Kings data 'prohibitive survival for HIV/HCV post LT?'

Survival rates between HIV/HCV_{neg} HCV_{pos} and HIV/HCV_{pos} patients in UK



HIV/HCV_{neg}

1yr 100%

5 yr 100%

HCV_{pos}

1yr 87%

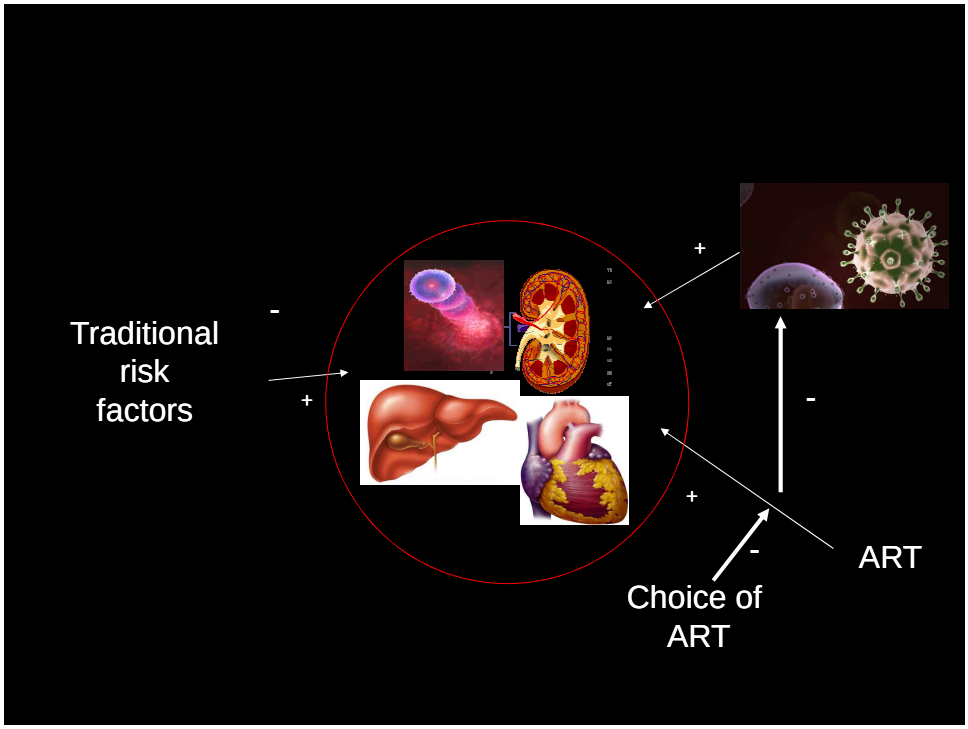
5yr 69%

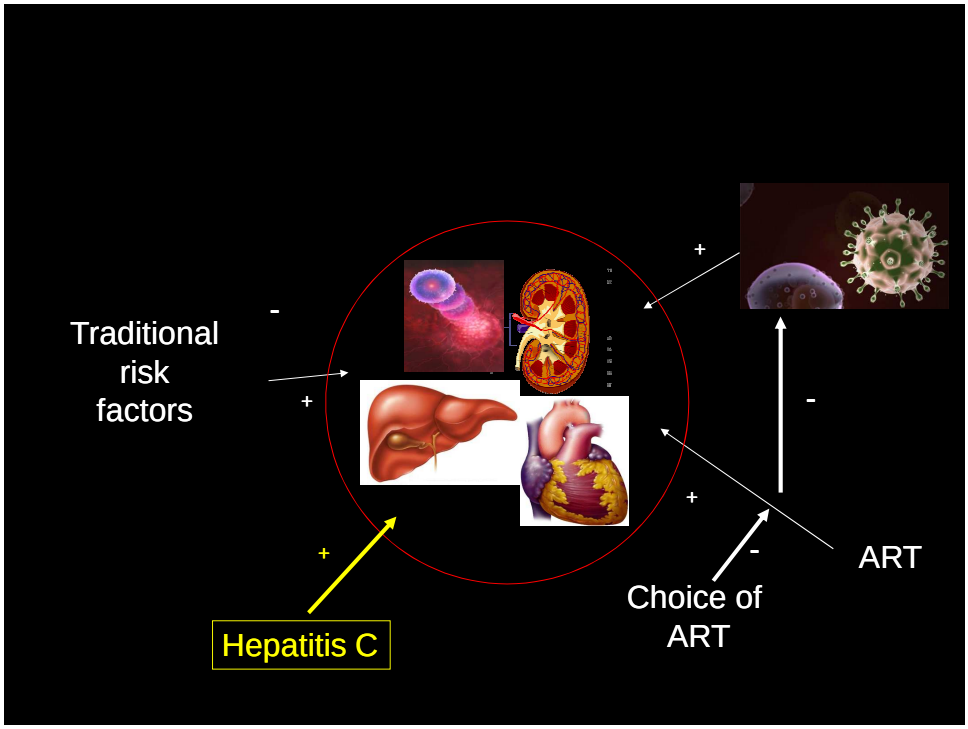
HIV/HCV_{pos}

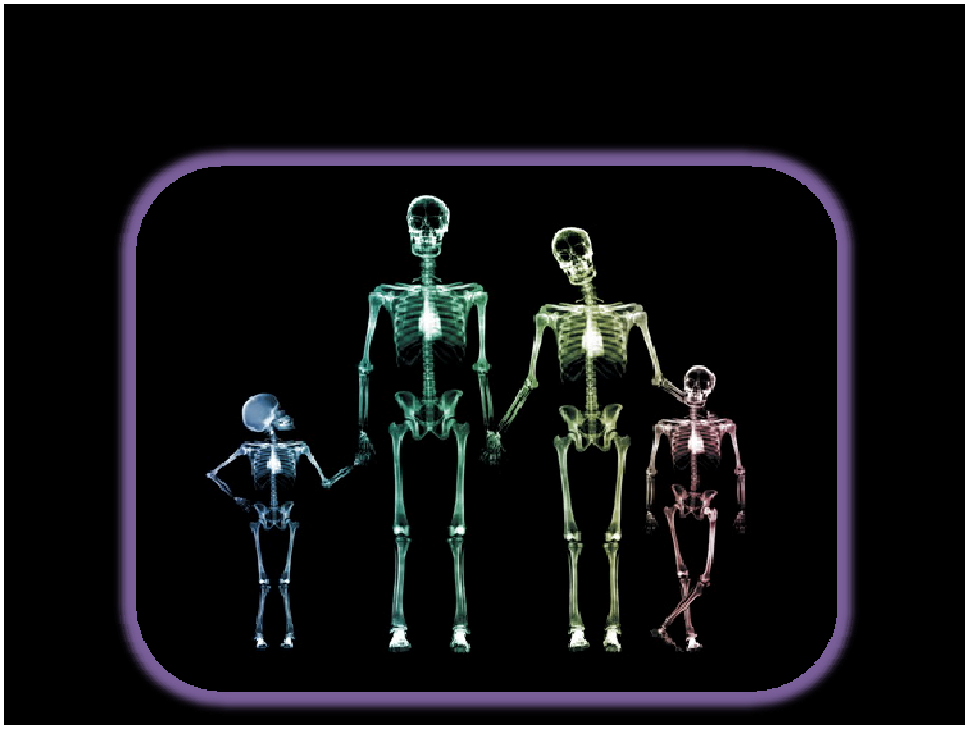
1 yr 73%

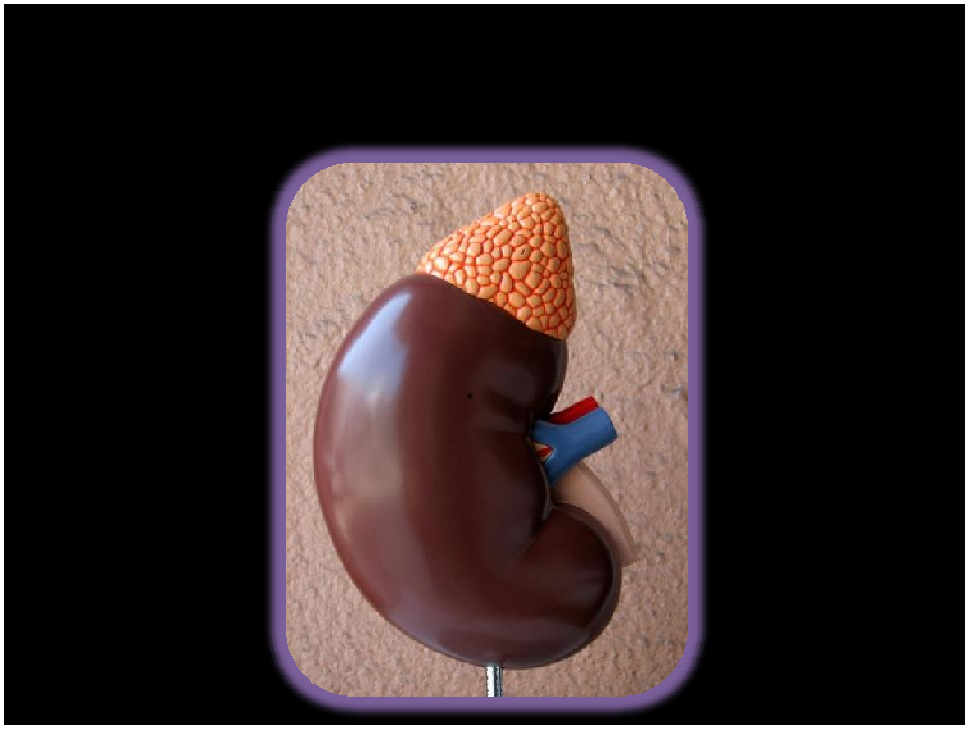
5 yr 53%

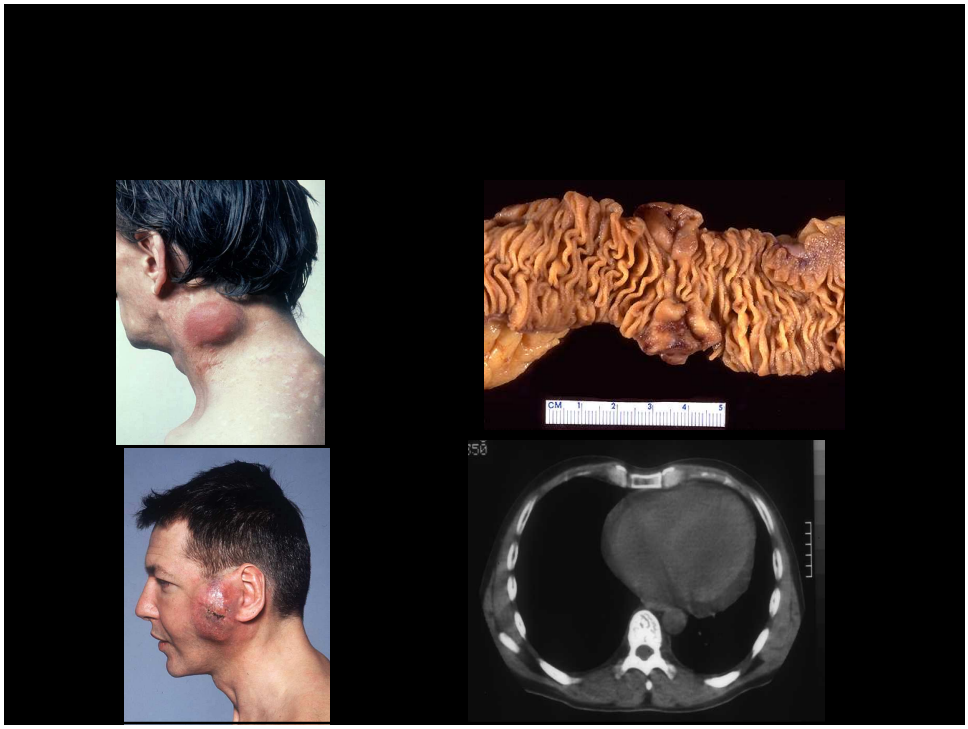
Log-rank (p=0.04)

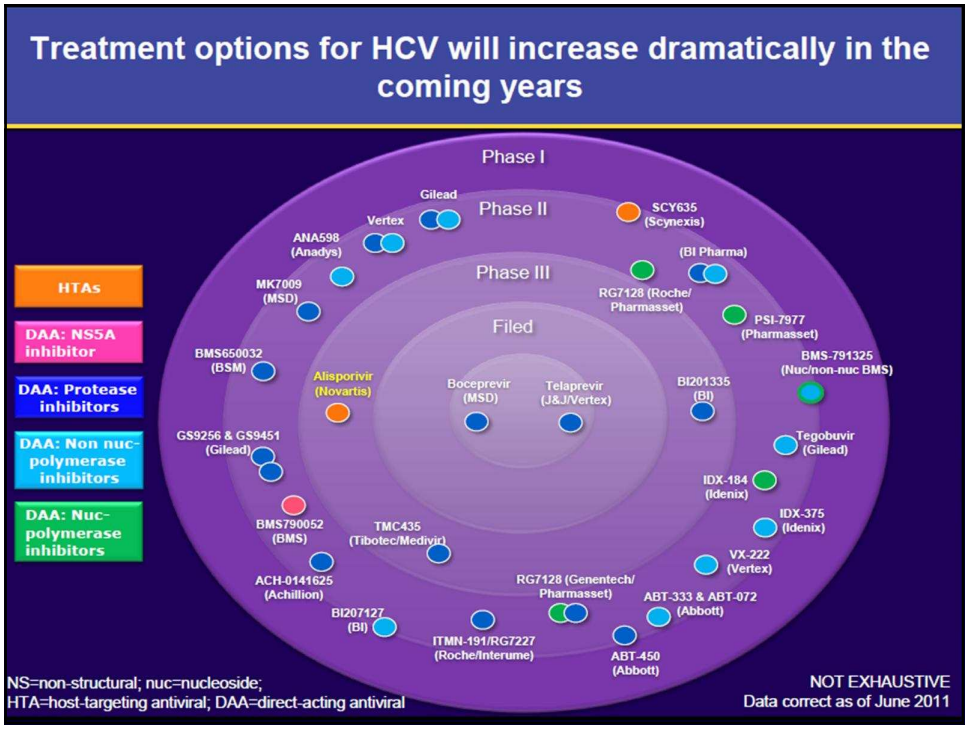

Traditional risk factors
-
+
+
-
+
-
ART
Choice of ART

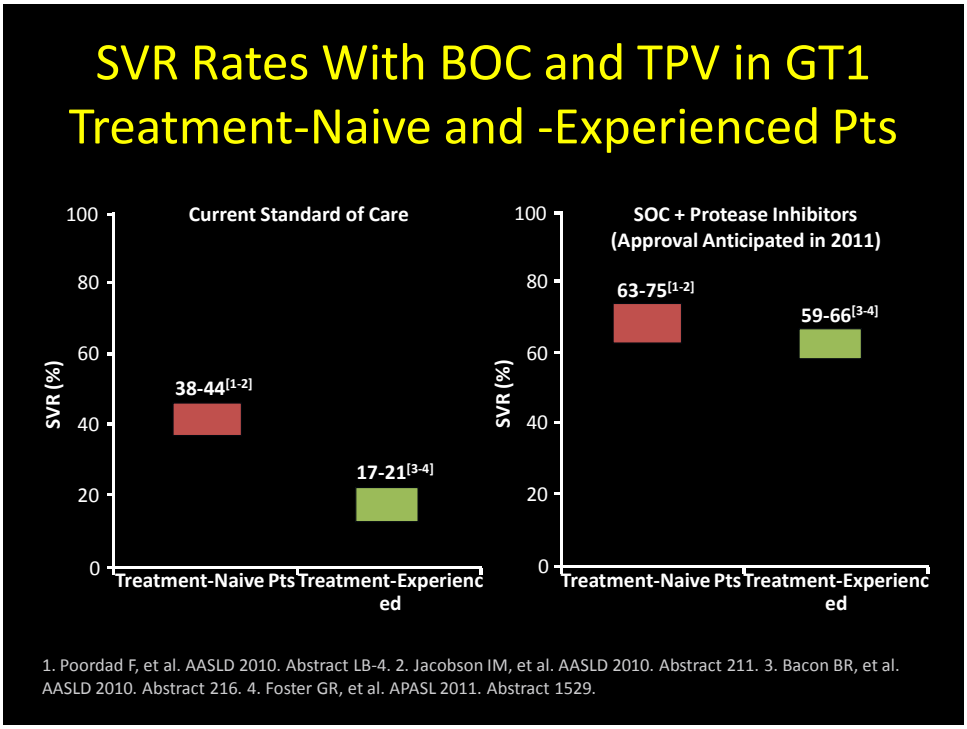

Traditional risk factors
-
+
+
-
+
-
ART
Choice of ART
+
Hepatitis C



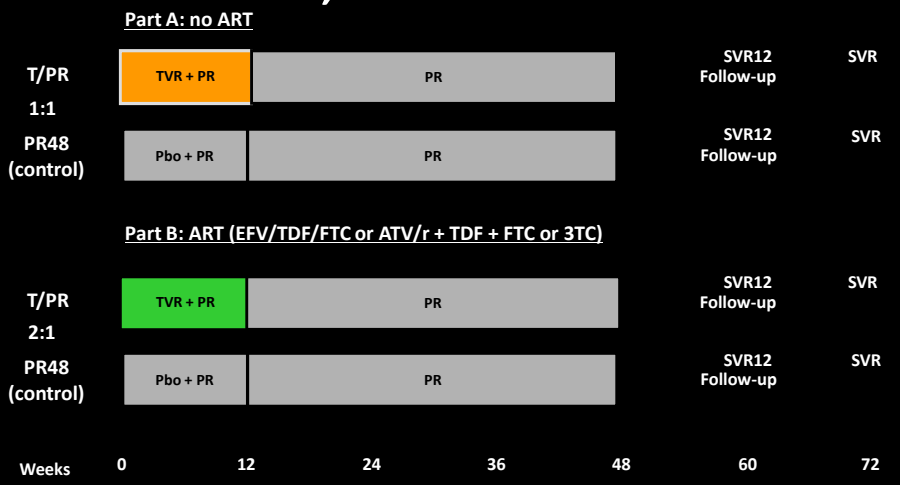





Treatment options for HCV will increase dramatically in the coming years
Phase I
Phase II
Phase III
Filed
HTAs
DAA: NS5A inhibitor
DAA: Protease inhibitors
DAA: Non nuc-polymerase inhibitors
DAA: Nuc-polymerase inhibitors
Gilead
Vertex
ANA598 (Anadys)
MK7009 (MSD)
BMS650032 (BSM)
Alisporivir (Novartis)
GS9256 & GS9451 (Gilead)
BMS790052 (BMS)
ACH-0141625 (Achillion)
BI207127 (BI)
ITMN-191/RG7227 (Roche/Interume)
Boceprevir (MSD)
Telaprevir (J&J/Vertex)
RG7128 (Genentech/ Pharmasset)
ABT-450 (Abbott)
TMC435 (Tibotec/Mediviri)
ABT-333 & ABT-072 (Abbott)
SCY635 (Scynexis)
(BI Pharma)
RG7128 (Roche/ Pharmasset)
PSI-7977 (Pharmasset)
BI201335 (BI)
BMS-791325 (Nuc/non-nuc BMS)
Tegobuvir (Gilead)
IDX-184 (Idenix)
IDX-375 (Idenix)
VX-222 (Vertex)
NS=non-structural; nuc=nucleoside;
HTA=host-targeting antiviral; DAA=direct-acting antiviral
NOT EXHAUSTIVE
Data correct as of June 2011

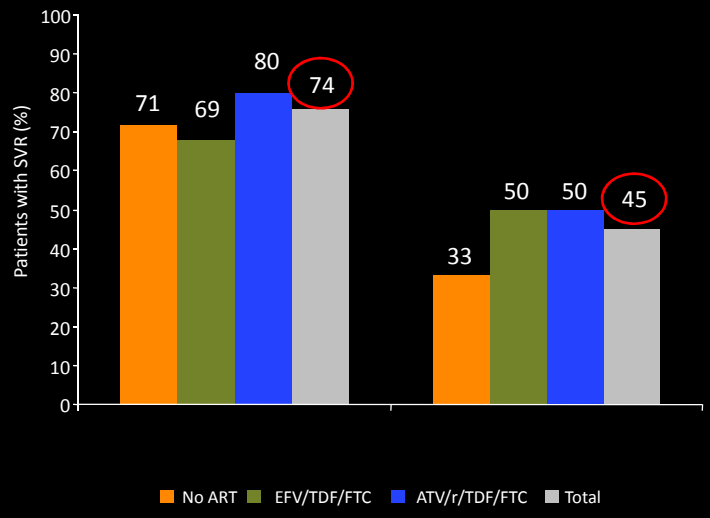

SVR Rates With BOC and TPV in GT1 Treatment-Naive and -Experienced Pts
Current Standard of Care
SVR (%)
100
80
60
40
20
0
38-44[1-2]
17-21[3-4]
Treatment-Naive Pts
Treatment-Experienced
SOC + Protease Inhibitors (Approval Anticipated in 2011)
63-75[1-2]
59-66[3-4]
1. Poordad F, et al. AASLD 2010. Abstract LB-4. 2. Jacobson IM, et al. AASLD 2010. Abstract 211. 3. Bacon BR, et al. AASLD 2010. Abstract 216. 4. Foster GR, et al. APASL 2011. Abstract 1529.

Study 110 Design: Randomized, Double-blind, Placebo-controlled Trial

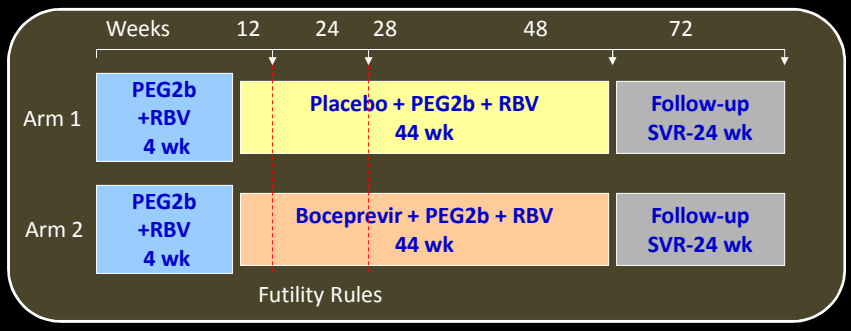


(EFV)=efavirenz; (TDF)=tenofovir; (FTC)=emtricitabine; (ATV/r)=ritonavir-boosted atazanavir; (3TC)=lamivudine;
(T) TVR=telaprevir 750 mg q8h or 1125 mg q8h (with EFV); Pbo=Placebo; (P) Peg-IFN=pegylated interferon alfa-2a (40 kD) 180 µg/wk; (R) RBV=ribavirin 800 mg/day or weight-based (1000 mg/day if weight <75 kg, 1200 mg/day for if weight ≥75 kg; France, Germany, n=5 patients)
Roche COBAS® TaqMan® HCV test v2.0, LLOQ of 25 IU/mL, LOD of <10 IU/mL

SVR Rates 12 Weeks Post-Treatment (SVR12*)



Study Design

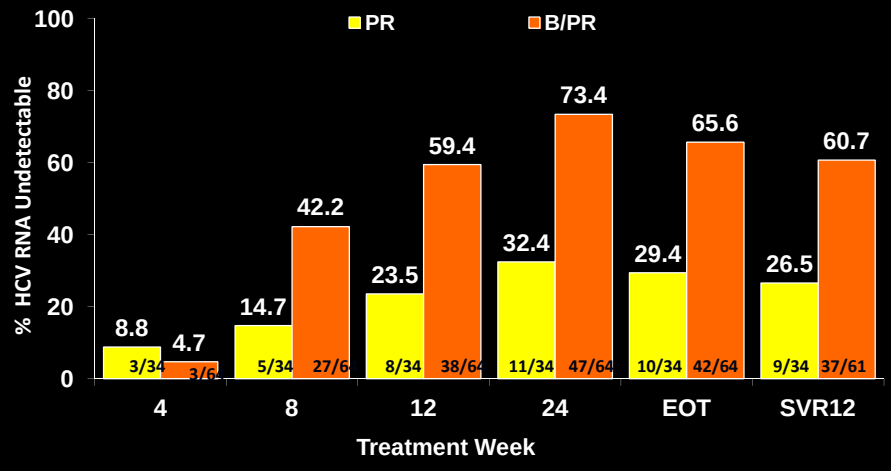


- Two-arm study, double-blinded for BOC, open-label for PEG2b/RBV
  - 2:1 randomization (experimental: control)
  - Boceprevir dose 800 mg TID
- 4-week lead-in with PEG2b/RBV for all patients
  - PEG-2b 1.5 µg/kg QW; RBV 600-1400 mg/day divided BID
- Control arm patients with HCV-RNA ≥ LLOQ at TW 24 were offered open-label PEG2b/RBV+BOC via a crossover arm

29

29

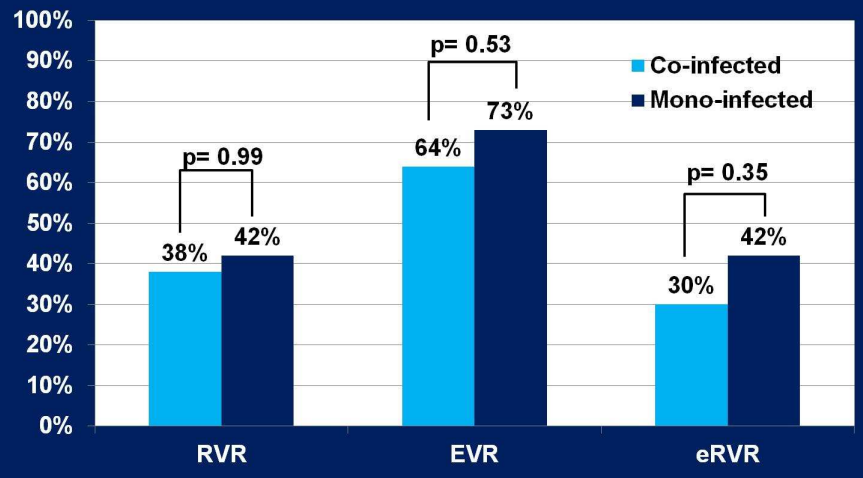
Virologic Response Over Time†



† Three patients undetectable at FW4 have not yet reached FW12 and were not included in SVR12 analysis.

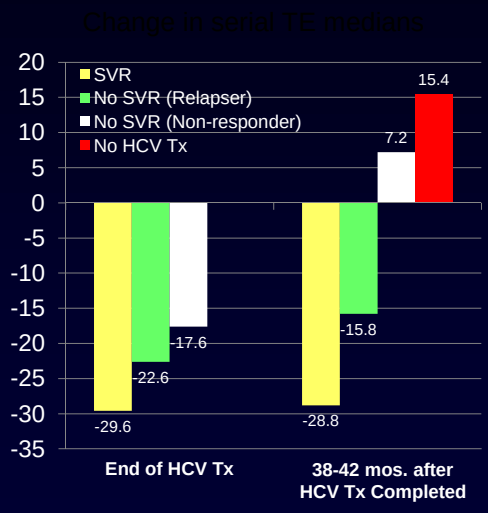
Sulkowski M et al., 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 47

Virological responses



Liver Fibrosis in HIV/HCV After HCV Treatment

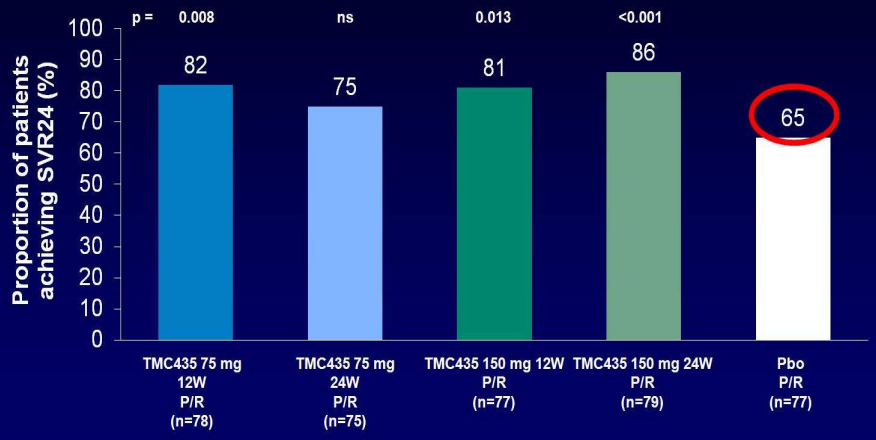
- Study assessing liver fibrosis (LF) over time in 328 HIV/HCV patients on ART
  - 210 received HCV Tx: 80 SVR, 130 No SVR (49 Relapse, 81 non-responders)
- LF assessments
  - Baseline: Liver Bx or elastometry (TE)
  - Over time: TE, biochemical indices
- Results:
  - Decreased LF during HCV Tx in all patients receiving Tx
    - 28.5% improved > than 1 stage
  - Sustained decrease in LF only in patients with SVR and relapsers



Carton JA, et al. 51st ICAAC; Chicago, IL; September 17-20, 2011; Abst. H3-812 and H3-813.

Slide 51

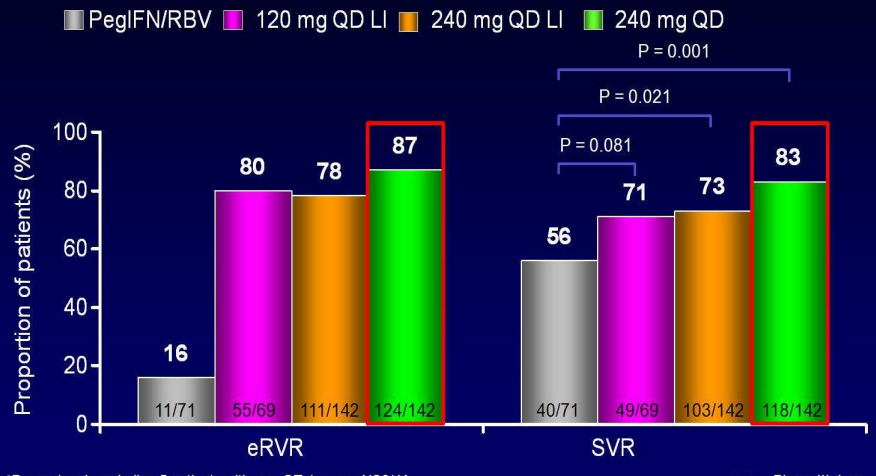
PILLAR Study: TMC 435 SVR24 (ITT)



HCV RNA assay: Roche COBAS TaqMan HCV assay v2; significant difference versus placebo control (closed testing procedure); ITT, intent-to-treat; P/R, peginterferon α-2a + ribavirin; SVR24, HCV RNA <25 IU/mL undetectable 24 weeks after planned end of treatment; W, Week

Slide 52

Silen C 1 Virologic response BI 1335



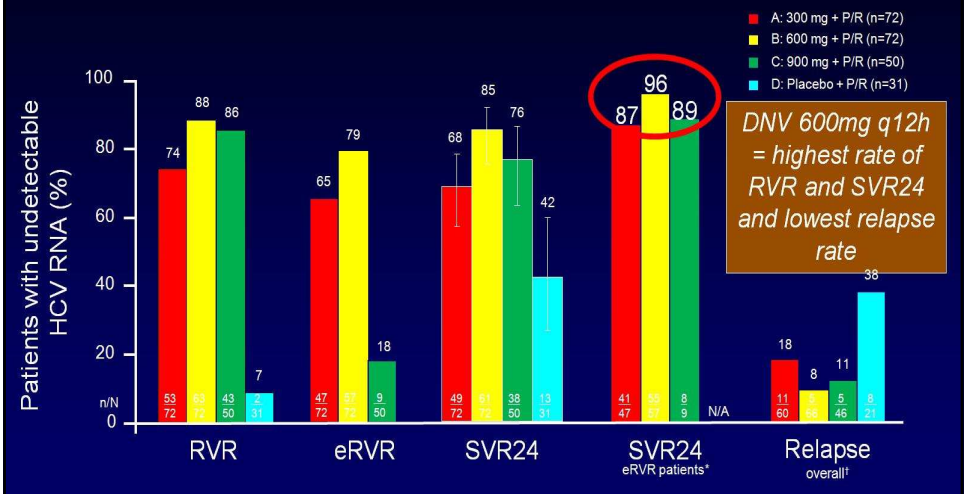
[a]Per protocol: excluding 5 patients with non-GT-1 as per NS3/4A sequencing; eRVR: HCV RNA < 25 IU/mL at Week 4 and undetected at Weeks 8 to 20; SVR, sustained virologic response

Phase III dose

Sulkowski MS, et al. EASL 2011. Abstract 60

Slide 53

Atlas Efficacy: Achievement of HCV RNA <15 IU/mL



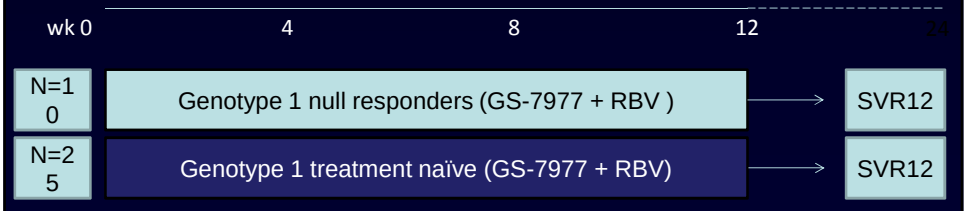
DNV 600mg q12h = highest rate of RVR and SVR24 and lowest relapse rate

* From a subset of patients who achieved extended RVR in the DNV-treated arms.

† Among patients with EOT response and at least one post-treatment HCV RNA assessment.

ELECTRON Study Design for HCV Genotype 1

- To evaluate the antiviral activity of 12 WEEKS Gs-7977 + RBV in genotype 1 patients who were either:
  - Prior null responders (<2 log10 reduction in HCV RNA at week 12 of a Peg/RBV regimen
  - Treatment naïve



- RBV dosing in all armas, independent of HCV genotype, was 1000mg for patients <75kg and 1000mg for those ≥75kg

Gane M et al., 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 54LB

100% Genotype 1 Prior Null Responders and Treatment Naïve Patients Achieved RVR

	Genotype 1 Null Responders (N=10)		Genotype 1 Treatment-naïve (N=25)		Genotype 2/3 Treatment-naïve (N=10)	
	n/N	% <LOD	n/N	% <LOD	n/N	% <LOD
Week 1	1/10	10	7/25	28	2/10	20
Week 2	7/10	70	17/24	71	10/10	80
Week 4	10/10	100	25/25	100	10/10	100

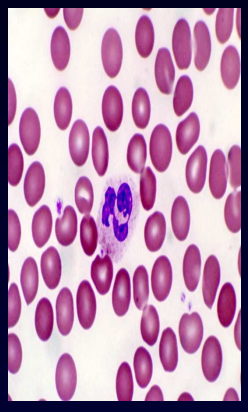
100% Genotype 1 Prior Null Responders Had HCV RNA <LOD at End of Treatment

	Genotype 1 Null Responders (N=10)		Genotype 1 Treatment-naïve (N=25)		Genotype 2/3 Treatment-naïve (N=10)	
	n/N	% <LOD	n/N	% <LOD	n/N	% <LOD
Week 1	1/10	10	7/25	28	2/10	20
Week 2	7/10	70	17/24	71	10/10	80
Week 4	10/10	100	25/25	100	10/10	100
Week 10	9/9	100	25/25	100	10/10	100
Week 11	9/9	100	16/16	100	10/10	100
Week 12	9/9	100	6/6	100	10/10	100

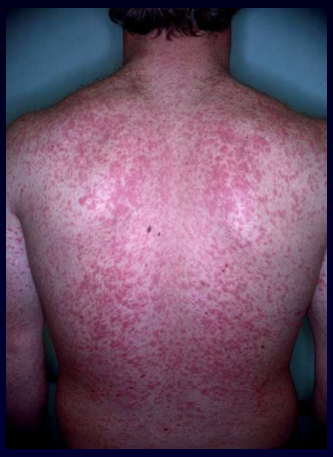
Electron

	Genotype 1 Null Responders (N=10)		Genotype 1 Treatment-naïve (N=25)		Genotype 2/3 Treatment-naïve (N=10)	
	n/N	% <LOD	n/N	% <LOD	n/N	% <LOD
Week 1	1/10	10	7/25	28	2/10	20
Week 2	7/10	70	17/24	71	10/10	80
Week 4	10/10	100	25/25	100	10/10	100
Week 10	9/9	100	25/25	100	10/10	100
Week 11	9/9	100	16/16	100	10/10	100
Week 12	9/9	100	6/6	100	10/10	100
SVR 4	1/9	11	--	--	10/10	100

Boceprevir



Telaprevir

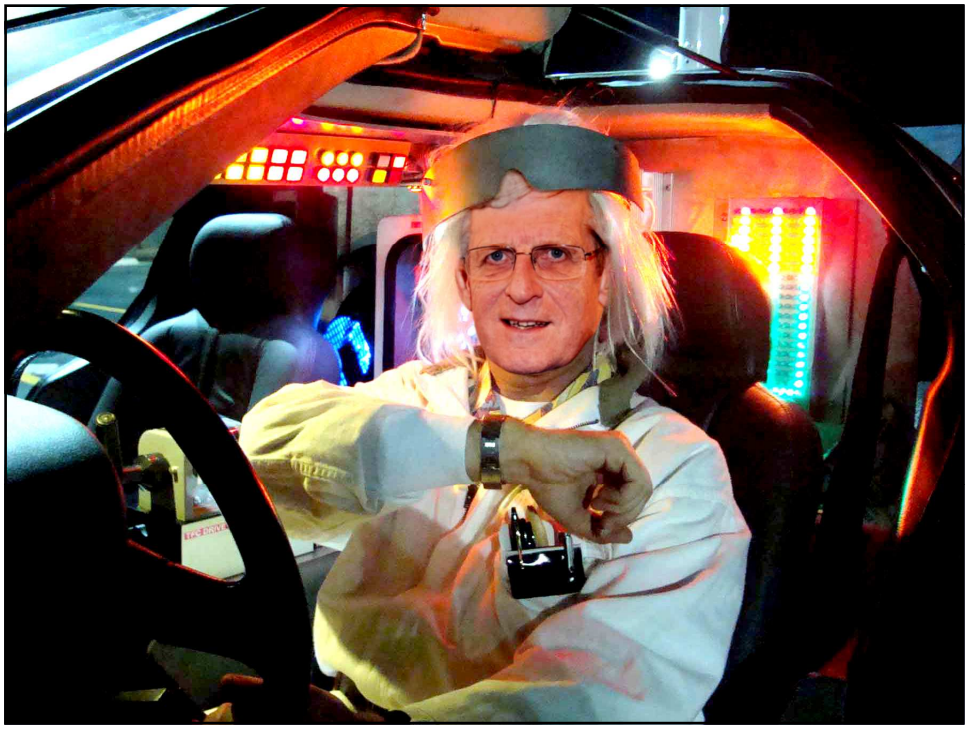

with or without food?

resistance?

side effects?

take together?

should I worry about pancreatitis?



Results

Patient	Gender	Response to previous therapy	Age
n1	M	Partial responder	41
n2	M	Relapser	65
n3	M	Null responder	48
n4	F	Partial responder	52
n5	M	Null responder	46

ARV Therapy

Patient	ARV combination	CD4 cells/mm^3 TW0	CD4 cells/mm^3 TW16	VL copies/ml TW0	VL copies/ml TW16
n1	RAL/TFV/FTC	368	202	<40	<40
n2	DRV/RTV/3TC/TFV	245	166	<40	<40
n3	DRV/RTV/TFV/FTC	742	562	<40	<40
n4	DRV/RTV/MVC/3TC	222	292	<40	<40
n5	TAZ/RTV/TFV/FTC*	688	351	<40	<40

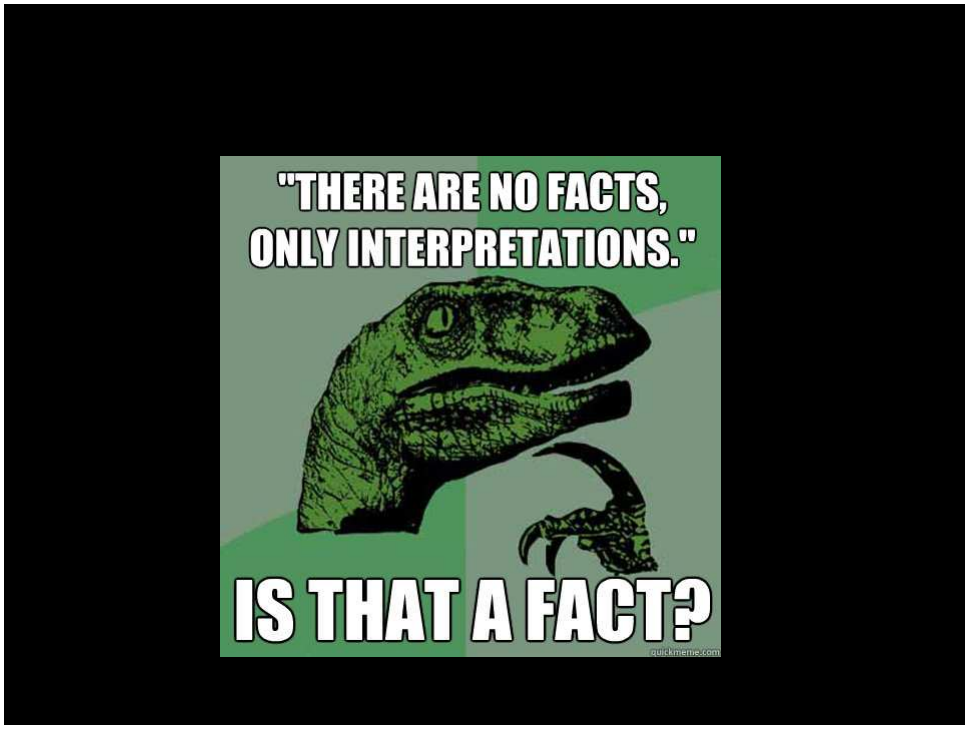
TW = treatment week

HCV PCR

Patient	HCV PCR (IU/ml) TW0	TW4	TW8	TW12	TW16
n1	3842790	85738	10172	<15	<15
n2	1947149	607039	<15	<15	<15
n3	117140	10088	<15	<15	<15
n4	9283263	5756	<15	<15	<15
n5	11190303	75634	<15	<15	<15

TW = treatment week

The facts



What the patients want from us

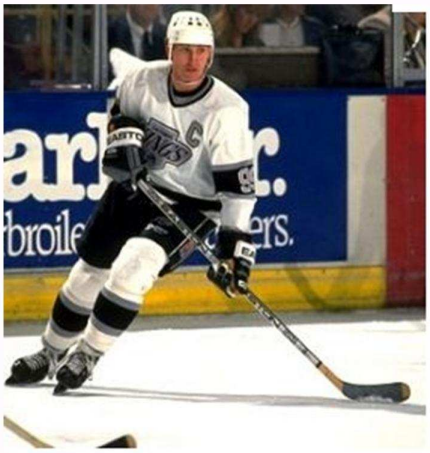
'Knowing is not enough, we must apply

Willing is not enough

we must do…'

Johann Wolfang von Goethe (1749-1832)

You miss a 100% of the shots you don't take …



Wayne Gretzky