17TH ANNUAL CONFERENCE OF THE BRITISH HIV ASSOCIATION (BHIVA)

British HIV Association BHIVA

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Chelsea and Westminster Hospital, London

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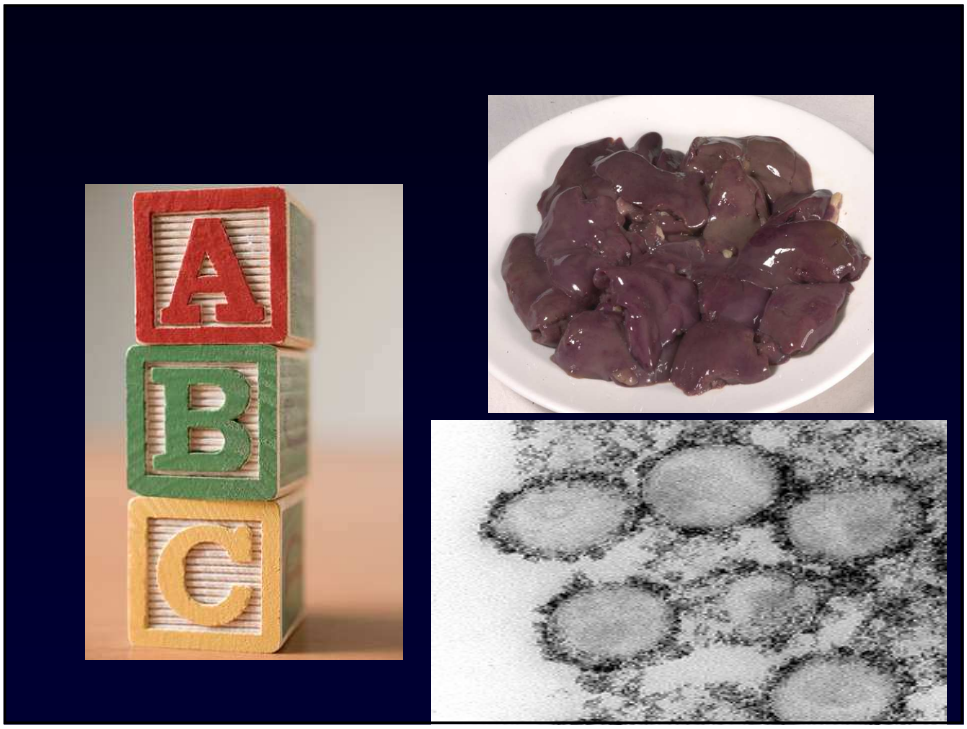
North Manchester General Hospital

6-8 April 2011, Bournemouth International Centre

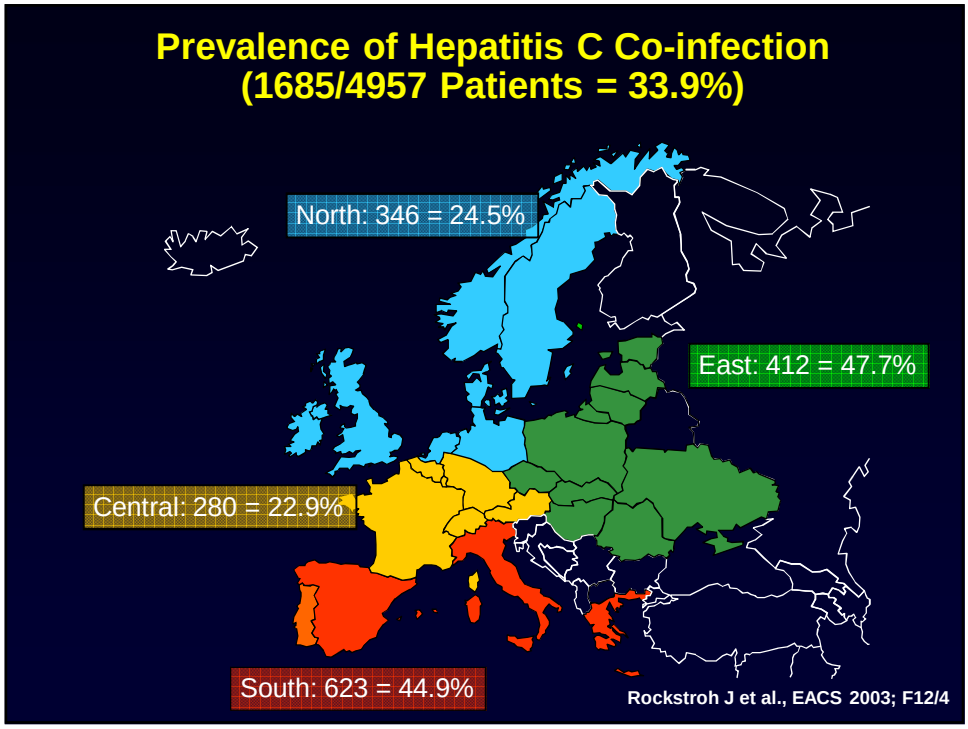


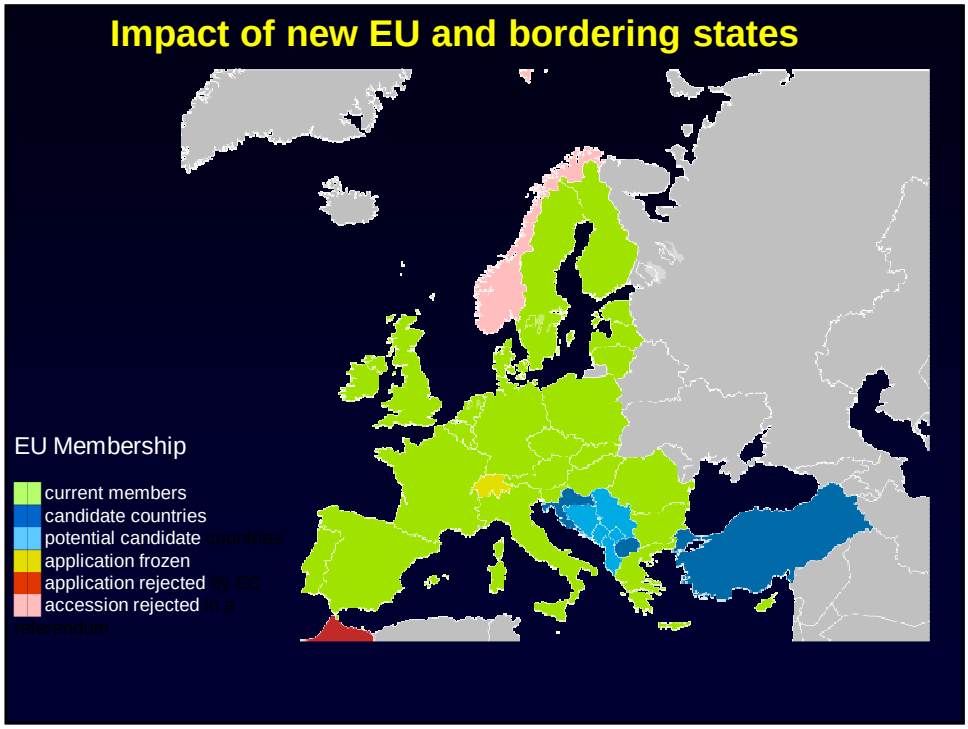
Vaccinate, Vaccinate, Vaccinate

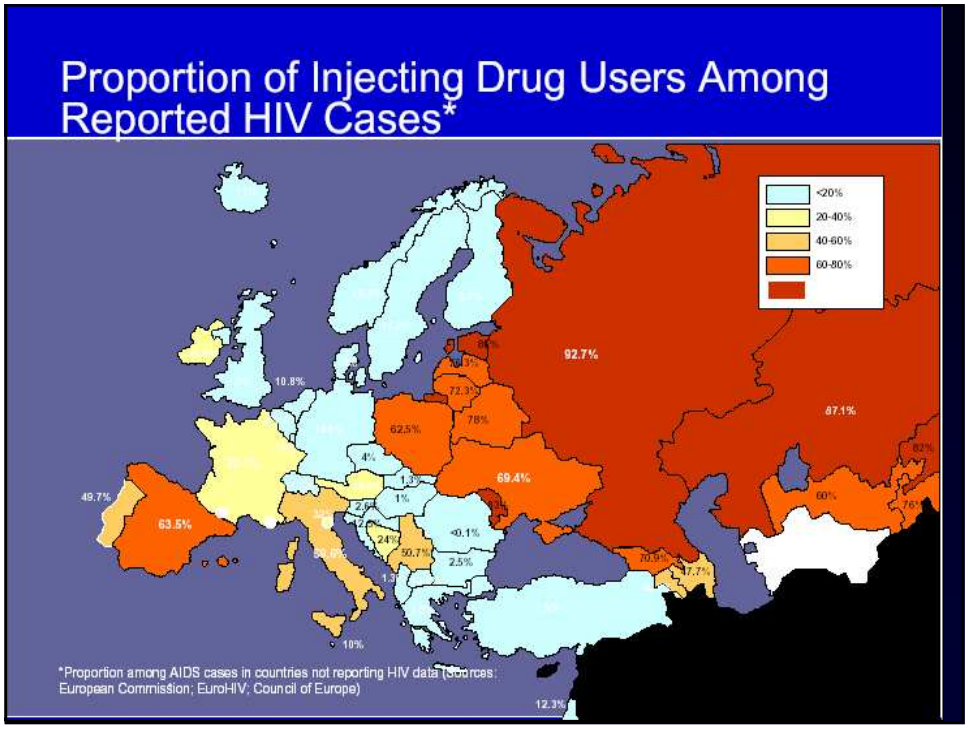
Why We Need New Drugs for Hepatitis C Now

- Increasing prevalence

People die


Prevalence of Hepatitis C Co-infection
(1685/4957 Patients = 33.9%)
North: 346 = 24.5%
East: 412 = 47.7%
Central: 280 = 22.9%
South: 623 = 44.9%
Rockstroh J et al., EACS 2003; F12/4


Impact of new EU and bordering states
EU Membership
current members
candidate countries
potential candidate countries
application frozen
application rejected by EC
accession rejected in a referendum


Proportion of Injecting Drug Users Among Reported HIV Cases*
<20%
20-40%
40-60%
60-80%
92.7%
87.1%
69.4%
62.5%
78%
72.3%
10.8%
49.7%
63.5%
4%
1%
2%
24%
50.7%
<0.1%
2.5%
70.9%
17.7%
10%
12.3%
*Proportion among AIDS cases in countries not reporting HIV data (Sources: European Commission; EuroHIV; Council of Europe)


Protect Yourself and Others
Reports from Europe and more recently New York and San Francisco suggest that hepatitis C transmission through sexual activity is occurring among gay and other men who have sex with men.
This information is provided by the Hepatitis C Support Project / HCV Advocate and Project Inform.
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A special thanks to Matt Sharp who convened the discussion that produced the document
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Dana Van Gorder
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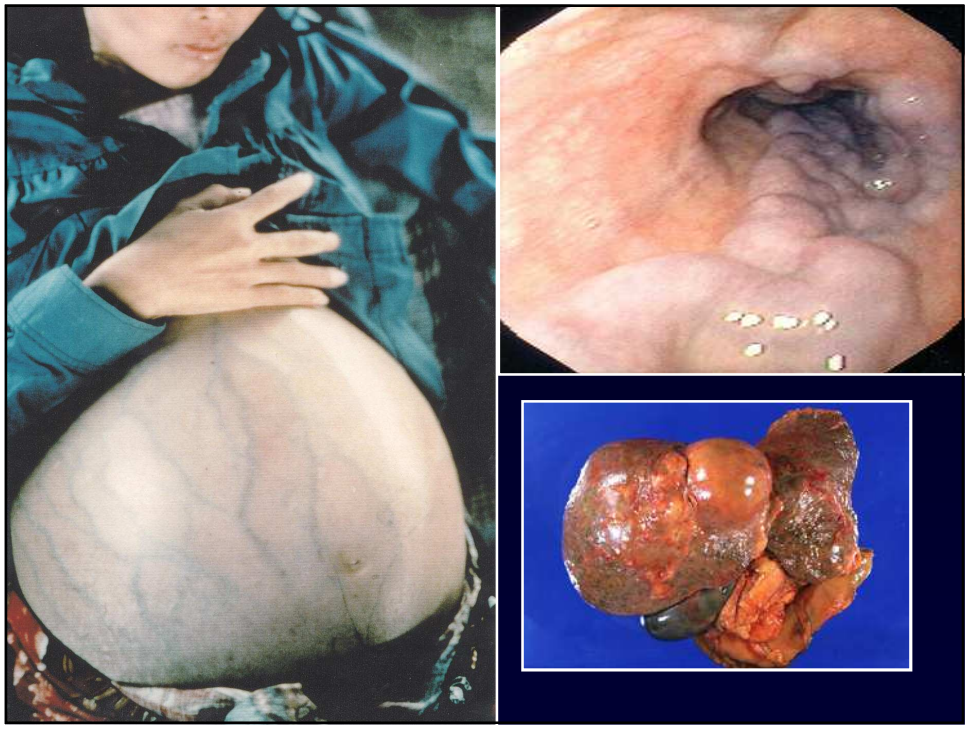
HCV ADVOCATE
INFORM
Gay Men and Hepatitis C
Useful Facts

Why We Need New Drugs for Hepatitis C Now

- Increasing prevalence
- More Rapid Progression of disease

People die

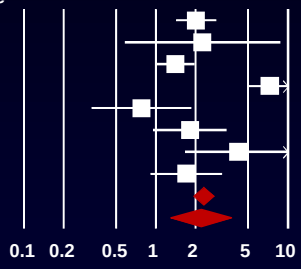


Rate ratio of Cirrhosis between HIV/HCV and HCV: HAART era

Model	Study name	N	Risk ratio	Lower limit	Upper limit	Z-Value	p-Value
	Verma, 2006a	381	2.015	1.421	2.858	3.928	0.000
	Di Martino, 2001	160	2.245	0.581	8.683	1.172	0.241
	Brau, 2006	656	1.404	1.010	1.951	2.019	0.044
	Gaslightwala & Bini, 2006	708	7.289	4.938	10.760	9.998	0.000
	Monto, 2005	464	0.778	0.327	1.854	-0.566	0.572
	Mohsen, 2003	208	1.814	0.958	3.434	1.830	0.067
	Martinez-Sierra, 2003	188	4.195	1.665	10.567	3.042	0.002
	Macias, 2005	234	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

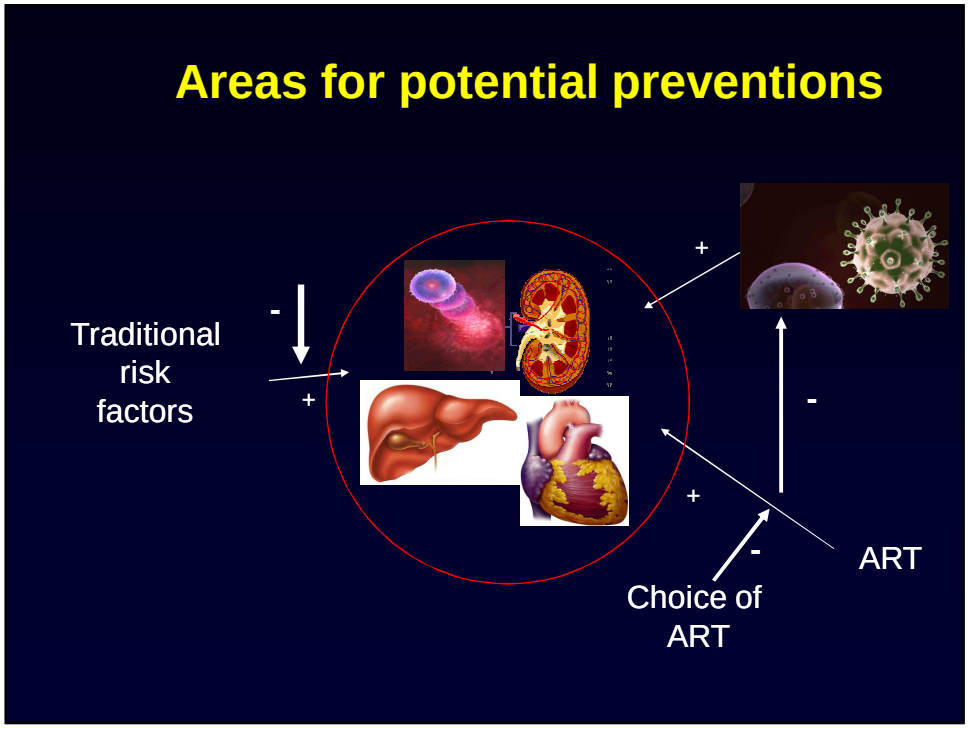
Risk ratio and 95% CI

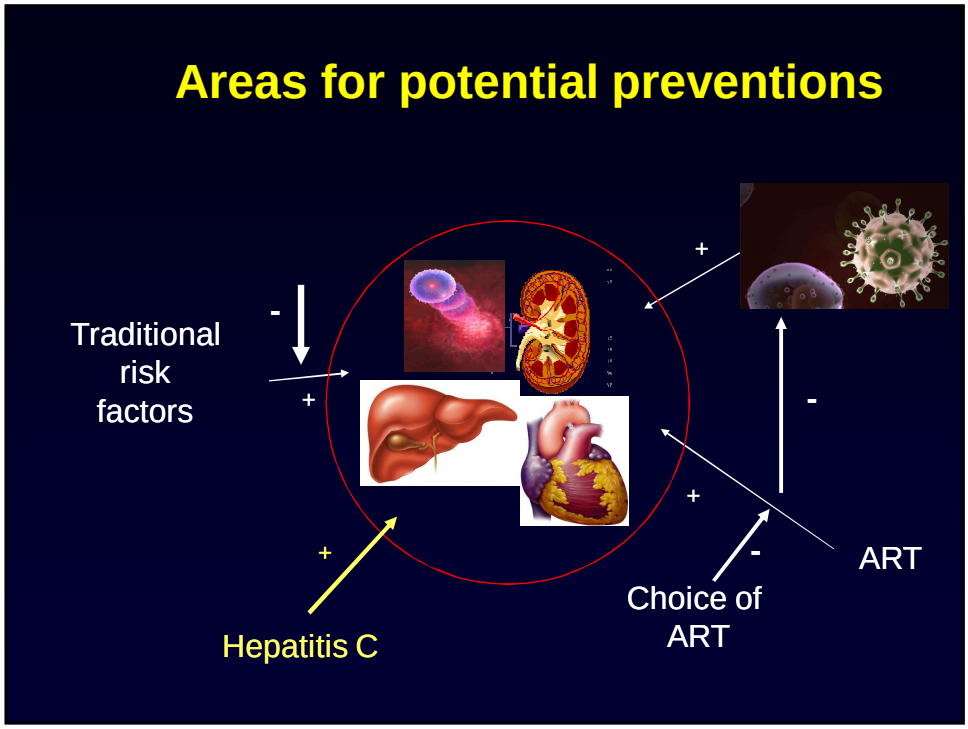


Meta-Analysis

Why We Need New Drugs for Hepatitis C Now

- Increasing prevalence
- More Rapid Progression of disease
- Increase in now known HIV related comorbidities


Areas for potential preventions
Traditional risk factors
-
+
+
-
+
-
ART
Choice of ART

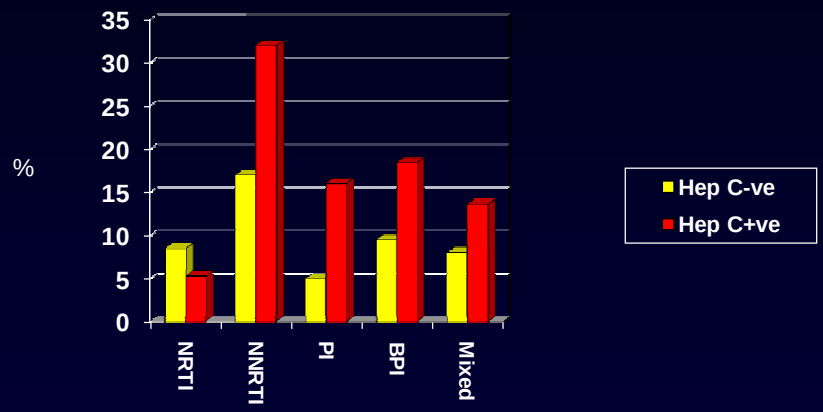

Areas for potential preventions
Traditional risk factors
-
+
+
-
+
-
+
ART
Choice of ART
Hepatitis C

Why We Need New Drugs for Hepatitis C Now

- Increasing prevalence
- More Rapid Progression of disease
- Increase in now known HIV related comorbidities
- Increase in HAART toxicity

People die

Incidence of Grade 2 or Above Liver Enzyme Elevation



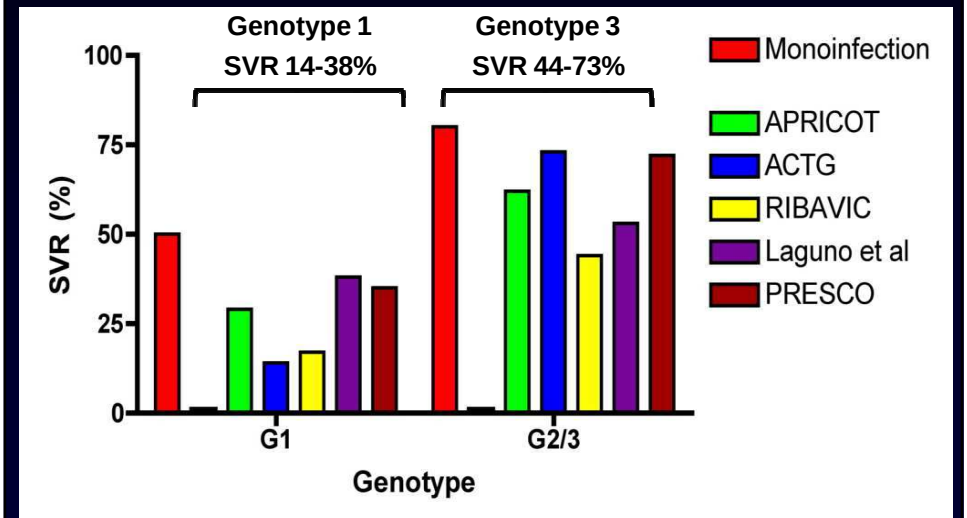
Benhamou Y,. Program and abstracts of the 13th Conference on Retroviruses and Opportunistic Infections; February 5-8, 2006; Denver, Colorado. Abstract 88.

Why We Need New Drugs for Hepatitis C Now

- Increasing prevalence
- More Rapid Progression of disease
- Increase in now known HIV related comorbidities
- Increase in HAART toxicity
- Treatment suboptimal

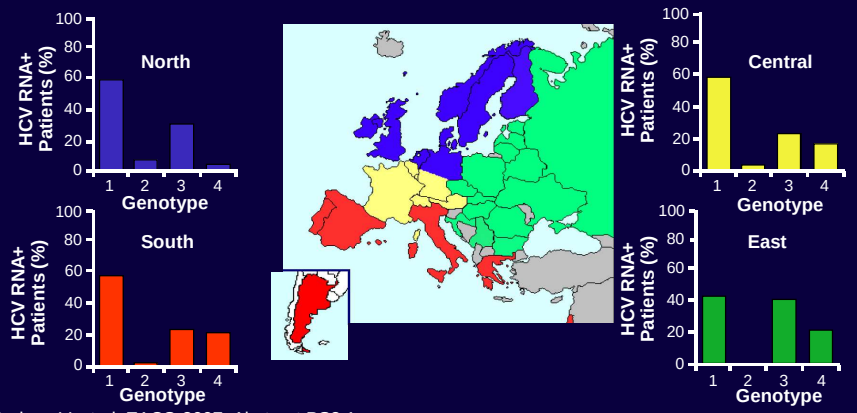
People die

HCV/HIV TREATMENT OUTCOMES



EuroSIDA: Prevalence and Genotype of HCV Across Europe

- 2263 HCV antibody positive patients in EuroSIDA (N = 14,282)
  - 74% positive for serum HCV RNA (95% CI: 71% to 78%)



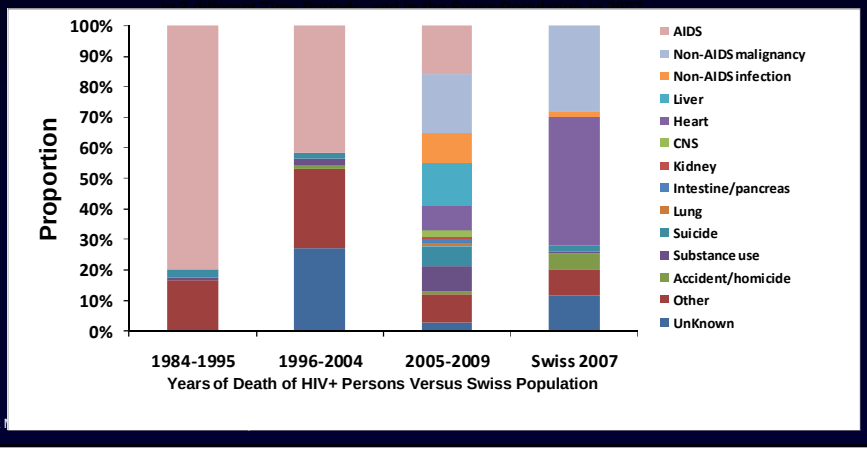
Soriano V, et al. EACS 2007. Abstract PS8.1.

Why We Need New Drugs for Hepatitis C Now

- Increasing prevalence
- More Rapid Progression of disease
- Increase in now known HIV related comorbidities
- Increase in HAART toxicity
- Treatment suboptimal
- People die

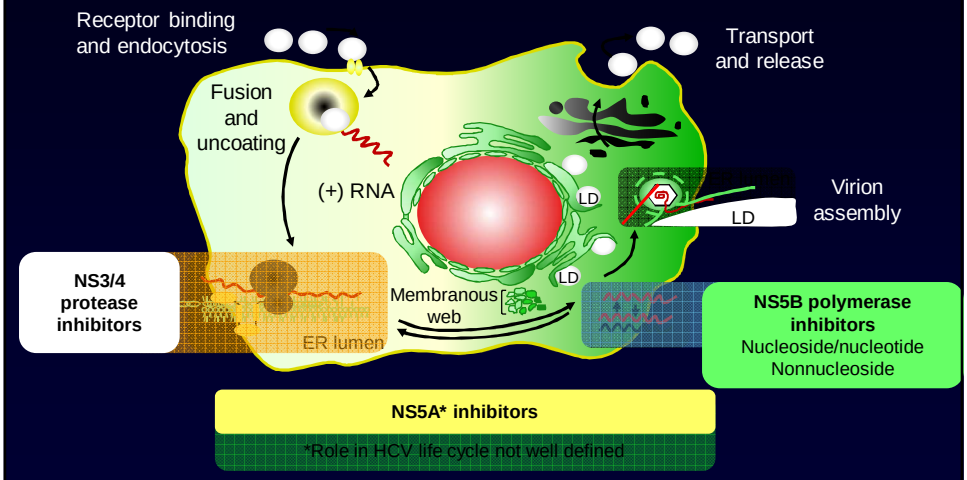
Changing Patterns of the Causes of Death in a Swiss Cohort (SHCS)

- SHCS is a prospective observational cohort
- Characteristics of participants that died from 2005-2009
- 459 deaths/9,053 participants (5.1%)



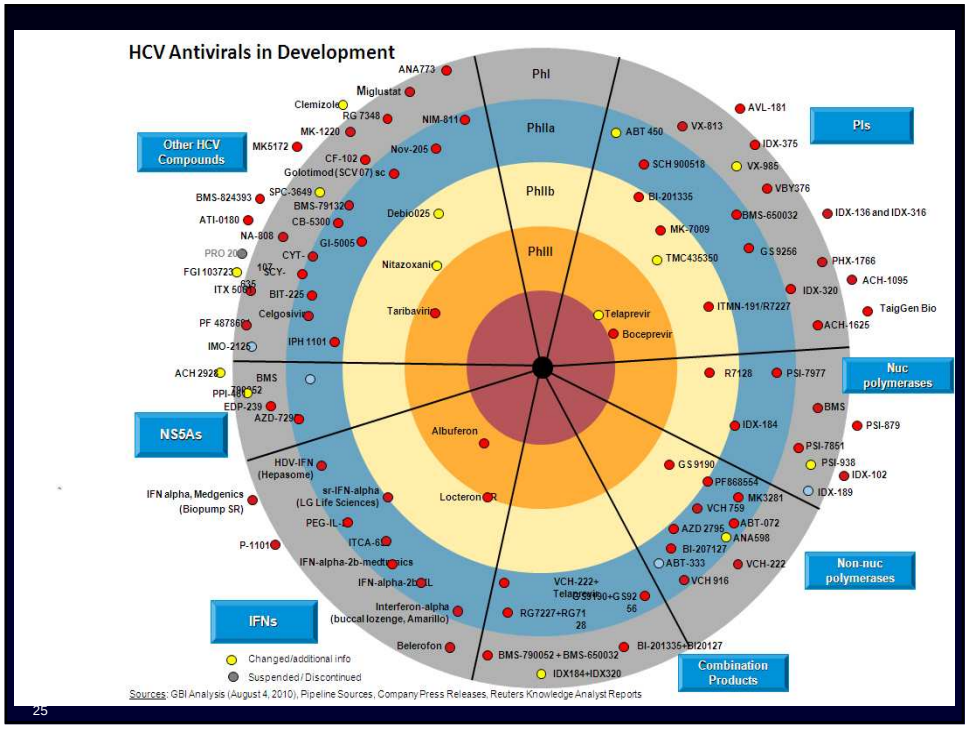
Ruppik M

HCV Life Cycle and DAA Targets

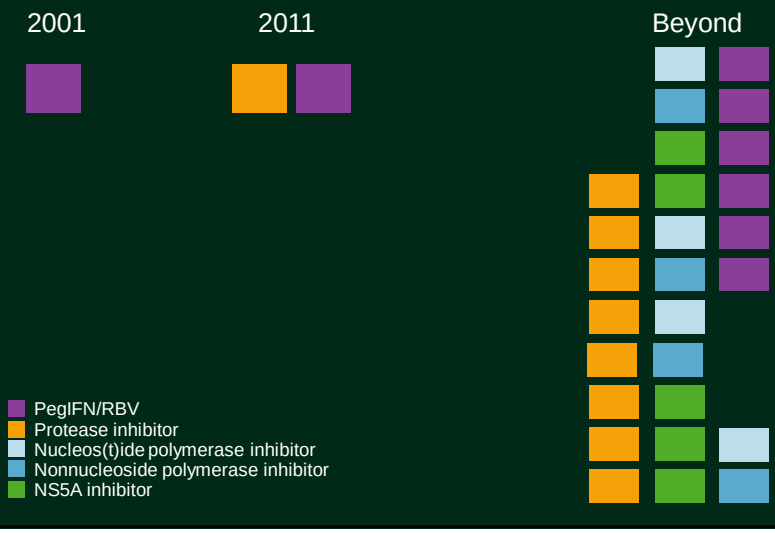


Adapted from Manns MP, et al. Nat Rev Drug Discov. 2007;6:991-1000.

ZEUZEUM



Evolution of Hepatitis C Therapy



Boceprevir and Telaprevir

- Boceprevir, a potent inhibitor of HCV NS3/4A protease
- Telaprevir, a potent inhibitor of HCV NS3/4A protease
- Both being tested in combination with standard-of-care pegIFN alfa-2/RBV in phase III studies in chronic HCV infection

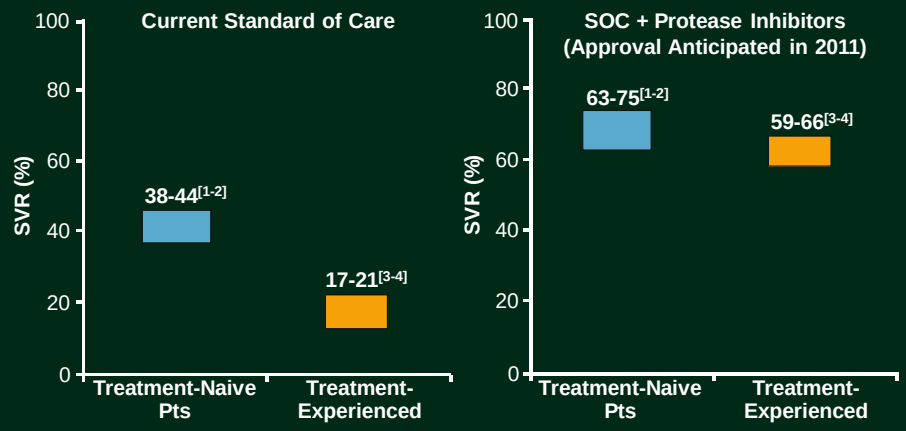
Boceprevir

- SPRINT-2: naive GT1 patients
- RESPOND-2: nonresponder GT1 patients (partial responders and relapsers)

Telaprevir

- ADVANCE: naive GT1 patients
- ILLUMINATE: response-guided therapy in naive GT1 paitents
- REALIZE: nonresponder GT1 patients (null responders, partial responders, relapsers)

SVR Rates With BOC and TPV in GT1 Treatment-Naive and -Experienced Pts



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.

Activity of DAAs by HCV Genotype

Agent	Potential Activity
Protease Inhibitors	
Boceprevir[1,2]	1, 2
Telaprevir[3,4]	1, 2
BI 201335[5]	1, 2?
Danoprevir[6]	1, 2?
MK-5172[7]	1-6
TMC435[8]	1, 2, 4, 5, 6
Vaniprevir[9]	1, 2?

1. Poordad F, et al. AASLD 2010. Abstract LB-4. 2. Pawlotsky JM, et al. Gastroenterology. 2011[epub ahead of print]. Abstract 820. 3. Jacobson IM, et al. AASLD 2010. Abstract 211. 4. Foster G, et al. EASL 2010. Abstract 57. 5. Sulkowski M, et al. EASL 2010. Abstract 1190. 6. Terrault N, et al. AASLD 2010. Abstract 32. 7. Petry A, et al. AASLD 2010. Abstract 807. 8. Fried M, et al. AASLD 2010. Abstract LB-5. 9. Manns MP, et al. AASLD 2010. Abstract 82.

Common AEs of DAAs in Current Trials in Naive Pts

Agent	AEs More Frequent in Experimental Arm vs PR	Discontinuations due to AEs, % (Wk)
Boceprevir[1]	Anemia, dysgeusia	14 (48)
Telaprevir[2]	Rash, anemia, pruritus, nausea	10 (48)
ANA598[3]	Rash incidence and severity increased with 400-mg dose	2 (12)
BI 201335[4]	Gastrointestinal events, jaundice, and rash*	5 (12)
BMS-790052[5]	None reported	8 (12)
Danoprevir[6]	ALT elevation, neutropenia, nausea diarrhea	4 (12)
Filibuvir[7]	None reported	0 (4)
RG7128[8]	None reported	2 (12)
TMC435[9]	Mild bilirubin increases in first 2 wks of therapy	7 (24)
Vaniprevir[10]	Vomiting with 600-mg dose	0 (6)

*Higher in BID dosing than QD.

1. Poordad F, et al. AASLD 2010. Abstract LB-4. 2. Jacobson IM, et al. AASLD 2010. Abstract 211. 3.Lawitz E, et al. AASLD 2010. Abstract 31. 4. Sulkowski M, et al. EASL 2010. Abstract 1190. 5. Pol S, et al. EASL 2010. Abstract 1189. 6. Terrault N, et al. AASLD 2010. Abstract 32. 7. Jacobson I, et al. EASL 2010. Abstract 2088. 8. Jensen DM, et al. AASLD 2010. Abstract 81. 9. Fried M, et al. AASLD 2010. Abstract LB-5. 10. Manns MP, et al. AASLD 2010. Abstract 82.

Dosing Frequency of DAAs (All Plus PegIFN/RBV) in Current Trials in Naive Pts

QD	BID	TID
BI 201335	BI 201335	Boceprevir
BMS-790052	Telaprevir	Telaprevir
TMC435	Danoprevir*	Danoprevir
	Vaniprevir	
	ANA598	
	RG7128	
	Filibuvir	

*With RTV boosting.

Cross-Resistance and Persistence of Mutations With Protease Inhibitors

- Geometry of active site increases potential for cross-resistance among NS3 protease inhibitors
- Hallmark resistance mutations A156V/T, R155K/T confer cross-resistance
  - Other: D168V/E/T
- Ongoing studies into persistence of resistance
  - Boceprevir mutations can persist at least 3 yrs after exposure
  - However, telaprevir resistance mutations undetectable 2 yrs after treatment discontinuation in 89% of patients in EXTEND study[2]

1. Wyles DL. Top HIV Med. 2010;18:132-136. 2. Zeuzem S, et al. AASLD 2010. Abstract 227.

Similarities and Differences in Phase III Studies of TVR and BOC in GT1 Naive Pts

Parameter	TVR[1]	BOC[2]
PR lead-in?	No	Yes: 4 wks
PegIFN alfa formulation	2a	2b
PI dosing requirements	TID; administer with fatty meal	TID
Duration of PI triple therapy	8-12 wks followed by 12-40 wks PR	24-44 wks after 4 wks PR lead-in
Qualification for shortened therapy (response guided)	Undetectable HCV RNA until Wk 12 of triple therapy	Undetectable HCV RNA until Wk 24 of triple therapy
Qualified for shortened therapy, %	58 (24 wks)	44 (28 wks)
SVR, %	69-75	63-66
Relapse, %	9	9
Adverse events more frequent in PI arms	Rash, anemia, pruritus, nausea	Anemia, dysgeusia

1. Jacobson IM, et al. AASLD 2010. Abstract 211. 2. Poordad F, et al. AASLD 2010. Abstract LB-4.

Future Generations: Direct-Acting Antivirals for Hepatitis C
clinicaloptions.com/hepatitis

Activity of Other Protease Inhibitors Combined With PR in Phase II Studies

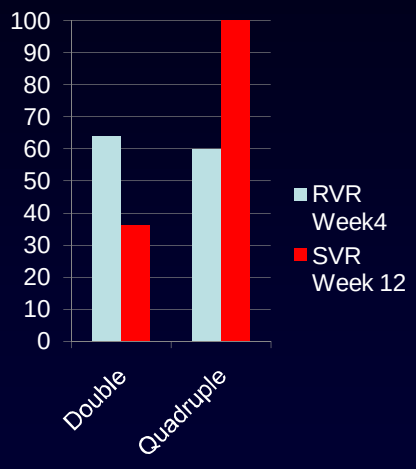
Protease Inhibitor	Trial, Phase	Patients Meeting Efficacy Measure, % (SOC)
BI 201335[1]	SILEN-C2, II	RVR: 62-69 (NR) EVR: 54-59 (NR)
Danoprevir (RG7227)[2]	ATLAS, II	RVR: 73-86 (7) cEVR: 88-92 (43)
TMC435[3]	PILLAR, IIb	SVR4: 91-93 (NR) SVR12: 88-97 (NR)
Vaniprevir (MK-7009)[4]	Protocol 007, IIa	RVR: 67-84 (5)* cEVR: 74-85 (47)* SVR: 61-84 (63)

*Significant difference.

1. Sulkowski M, et al. EASL 2010. Abstract 1190. 2. Terrault N, et al. AASLD 2010. Abstract 32.
3. Fried M, et al. AASLD 2010. Abstract LB-5. 4. Manns MP, et al. AASLD 2010. Abstract 82.

Quadruple Therapy with BMS-790052, BMS-650032 and PEG/RBV

- 21 null responders
- All genotype 1
- 19 unfavourable IL28B genotype
- Randomized to therapy with BMS- 790052 (NS5A inhibitor) and BMS-650032 (NS3 protease inhibitor) alone or with PEG/rbv for 24 weeks



Pros and Cons of Treating vs Deferring Therapy Once PIs Are Available

Treat

- Protease inhibitors substantially increase chance of SVR
- Successful treatment may arrest progression of liver disease (including potential for cirrhosis, HCC, etc)
- Many patients already "warehoused" awaiting DAAs, but when is the right time to exit the warehouse?

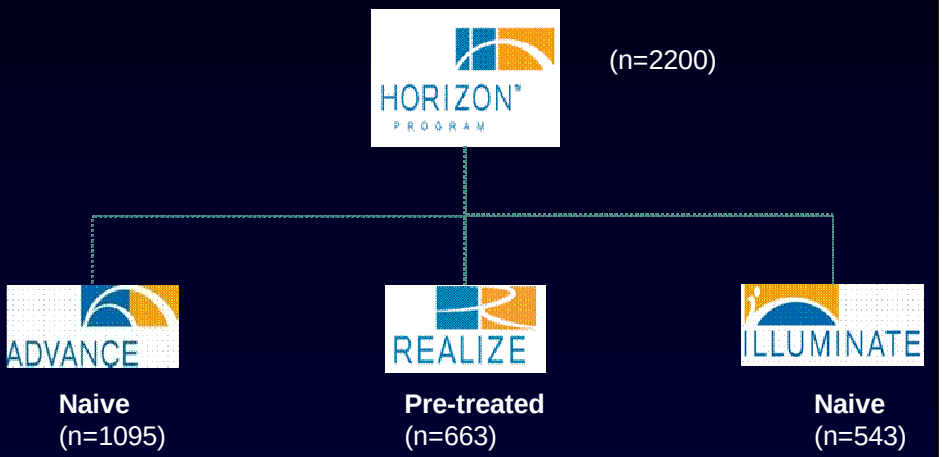
Defer

- Current regimens complex, challenging adverse events
- Potential for better treatment options in future, eg, better response rates, fewer adverse events, shorter duration
- Risk of resistance if therapy fails; impact on future options?

Telapravir

People die

Telaprevir
Phase III program HCV Genotype 1 MONOINFECTED



38

Telaprevir: An Orally-Available HCV Protease Inhibitor

- Telaprevir (TVR) is a selective inhibitor of NS3/4A HCV serine protease
- In genotype 1 mono-infected patients, telaprevir with peginterferon alfa-2a/ribavirin (T/PR) led to substantial improvements in SVR in phase 3 studies[1-4]:
  - **Treatment-naïve patients (ADVANCE trial, N=1088)[1],**
    - **69-75% vs 44% in control**
    - **12w >8w**
    - **24w fine if RVR**

[1]Jacobson et al 2010, Hepatology 52(Suppl 4)427A, [2]Sherman et al 2010, Hepatology 52(Suppl 4)401A-402A, [3]Foster et al 2011 Hepatology Int 52(Suppl.1):14, [4]Sherman et al. CROI 2011, Poster 957, [5]Van Heeswik et al. CROI 2011, Abstract 146LB

Debating Key Concepts in HCV Management With New HCV Therapies
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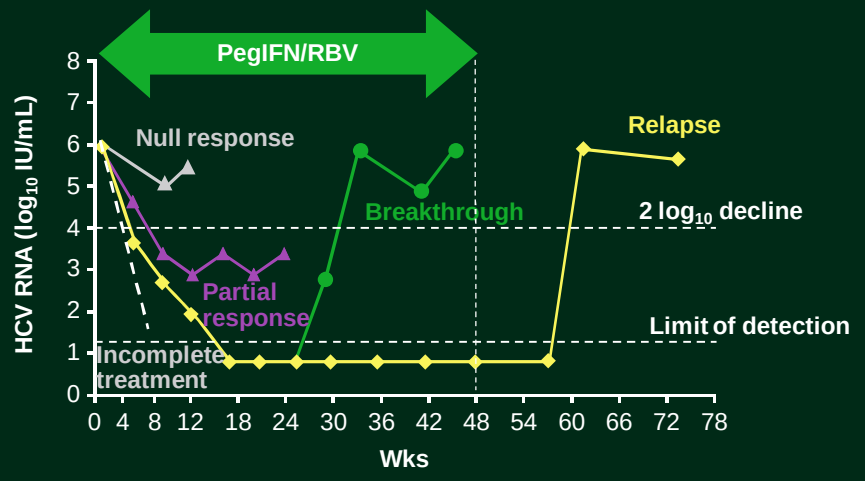
CLINICAL CARE OPTIONS HEPATITIS

Suboptimal Virologic Responses



McHutchison JG, et al. N Engl J Med. 2009;361:580-593.

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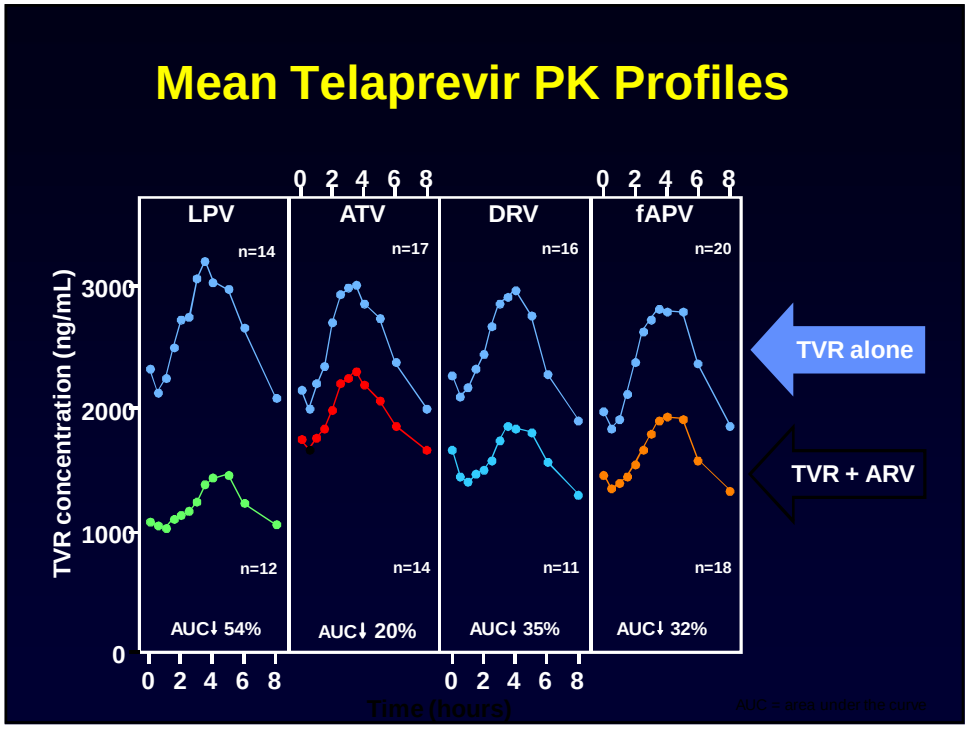
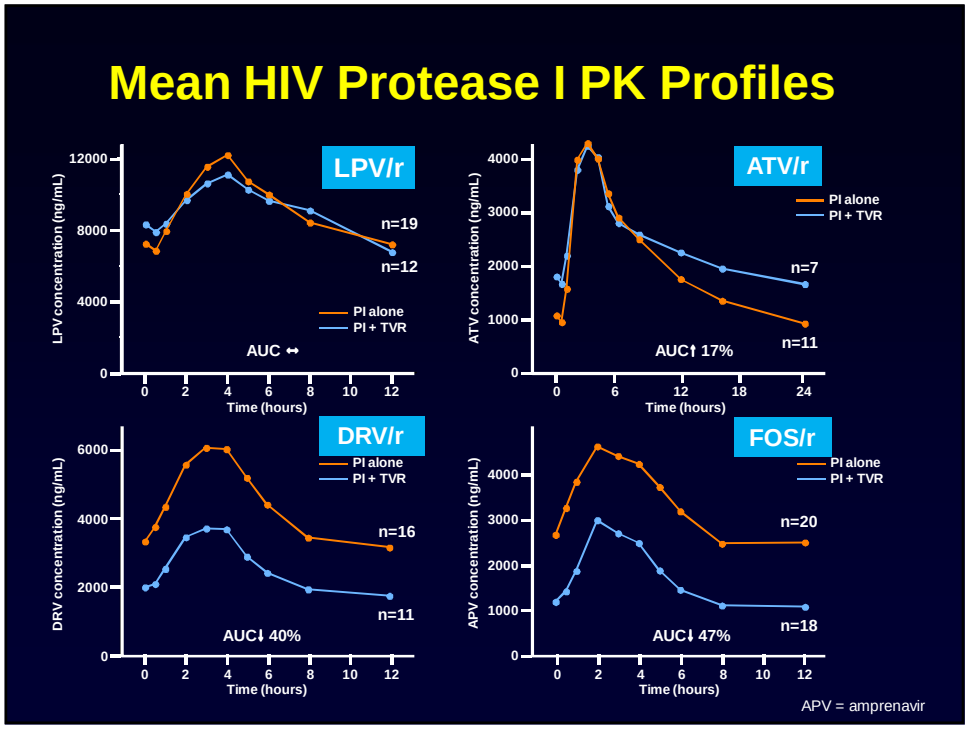
- In genotype 1 mono-infected patients, telaprevir with peginterferon alfa-2a/ribavirin (T/PR) led to substantial improvements in SVR in phase 3 studies[1-4]:
  - Treatment-naïve patients (ADVANCE trial, N=1088)[1,]
    - 69-75% vs 44% in control
  - **Treatment-experienced patients (REALIZE trial, N=662)[3]: PROVE 3**
    - **31% vs 5% in control (prior null responders)**
    - **57% vs 15% in control (prior partial responders)**
    - **86% vs 24% in control (prior relapsers)**
    - **RBV essential**

[1]Jacobson et al 2010, Hepatology 52(Suppl 4)427A, [2]Sherman et al 2010, Hepatology 52(Suppl 4)401A-402A, [3]Foster et al 2011 Hepatology Int 52(Suppl.1):1-4, [4]Sherman et al. CROI 2011, Poster 957, [5]Van Heeswik et al. CROI 2011, Abstract 146LB

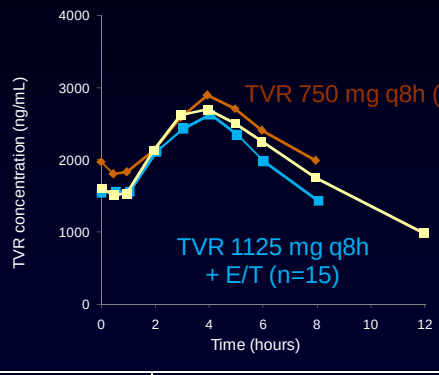
LOOKING AT CO-INFECTED Telapravir

- PK studies
- Pilot studies:
  - Off ARV high CD4
  - On ARV high CD4 undetectable viral load


Mean Telaprevir PK Profiles
LPV
ATV
DRV
fAPV
n=14
n=17
n=16
n=20
n=12
n=14
n=11
n=18
AUC↓ 54%
AUC↓ 20%
AUC↓ 35%
AUC↓ 32%
TVR concentration (ng/mL)
Time (hours)
TVR alone
TVR + ARV
AUC = area under the curve


Mean HIV Protease I PK Profiles
LPV/r
n=19
n=12
PI alone
PI + TVR
AUC ↔
LPV concentration (ng/mL)
ATV/r
n=7
n=11
AUC↑ 17%
ATV concentration (ng/mL)
DRV/r
n=16
n=11
AUC↓ 40%
DRV concentration (ng/mL)
FOS/r
n=20
n=18
AUC↓ 47%
APV concentration (ng/mL)
Time (hours)
APV = amprenavir

Mean TVR PK profiles with EFV

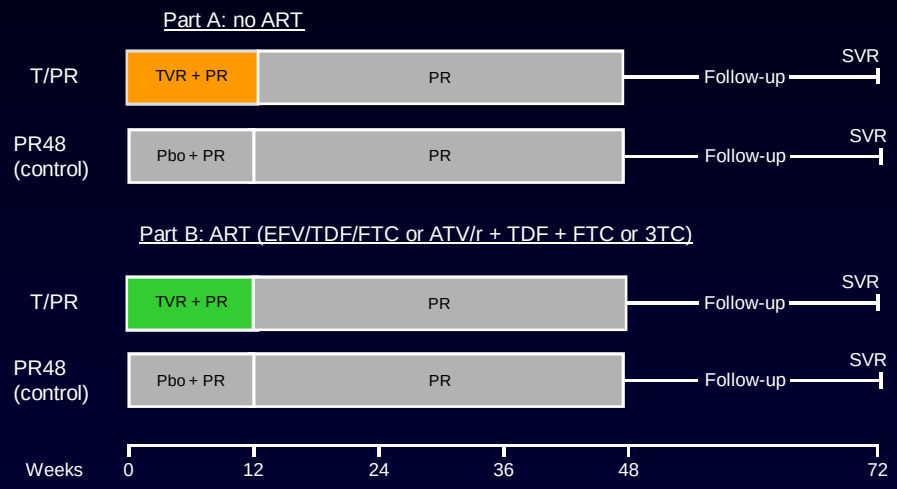


No effect of TVR on EFV

TVR dose	Effect of EFV/TDF on TVR		
	C_{min}	C_{max}	AUC_{8h}
1125 mg q8h	0.75 (0.66–0.86)	0.86 (0.76–0.97)	0.82 (0.73–0.92)
1500 mg q12h	0.52 (0.42–0.64)	0.97 (0.88–1.06)	0.80 (0.73–0.88)*

*Average steady state plasma concentration ($Css_{average}$)

Study Design



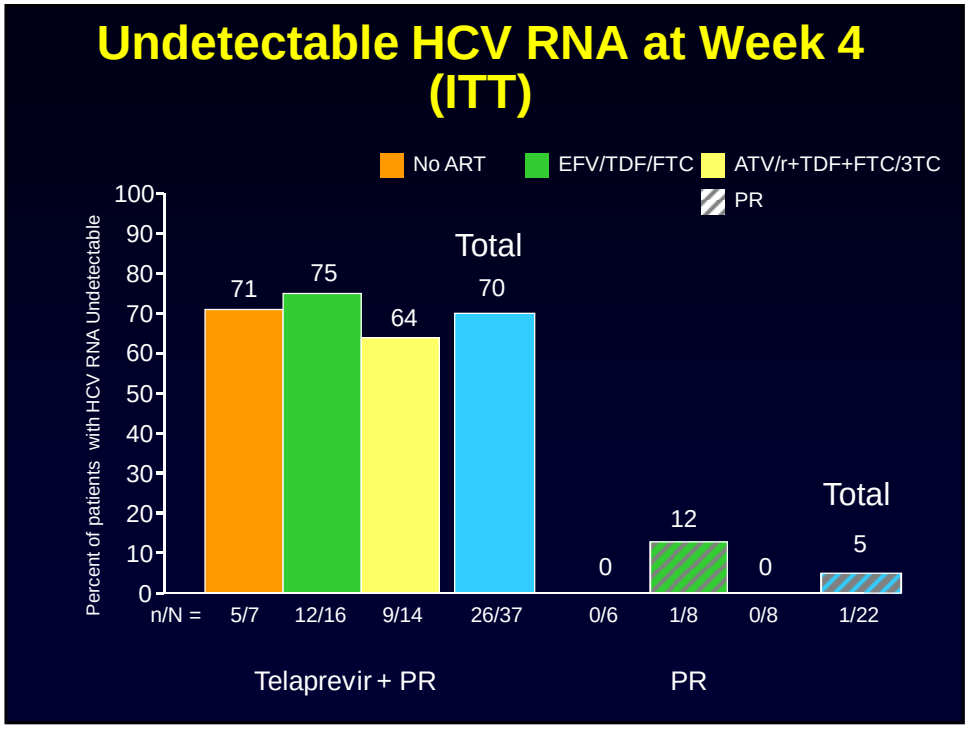
(EFV)=efavirenz; (TDF)=tenofovir; (FTC)=emtricitabine; (ATV/r)=ritonavir-boosted atazanavir; (3TC)=lamivudine;
(T) TVR=telaprevir 750 mg q8h or 1125 mg q8h (with EFV); Pbo=Placebo; (P) Peg-IFN=pegylated interferon alfa-2a (40 kD) 180 µg/wk; (R) RBV=ribavirin 800 mg/day or weight-based (1000 mg/day if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

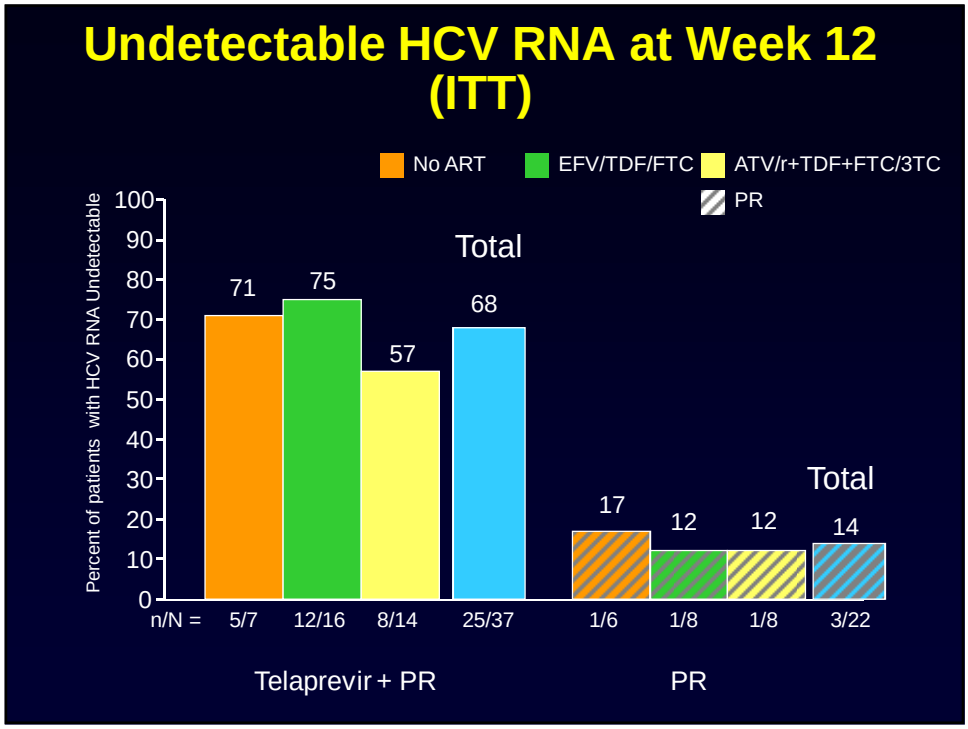
Principal Eligibility Criteria

- Male and female patients, 18 to 65 years of age with treatment-naïve for HCV
  - Mainly young white men
- Liver biopsy within 1 year; compensated cirrhosis permitted
- Part A: up to 20 patients not receiving ART, with CD4 count ≥500 cells/mm^3, and HIV RNA ≤100,000 copies/mL
  - Median CD4 600, viral load <10,000
- Part B: up to 48 patients receiving a stable ART regimen
  - TDF/EFV/FTC, or ATV/r with TDF and FTC or 3TC, with CD4 count ≥300 cells/mm^3, and HIV RNA ≤50 copies/mL
  - Median CD4 500, viral load <50

Methods

- Interim analysis based on 59 of 60 patients who received at least 1 dose of study drugs; 41/59 patients had reached week 12 at time of analysis
  - 13 patients from Part A
  - 46 patients from Part B
    - 24 patients received TDF/EFV/FTC and,
    - 22 patients received ATV/r + TDF + FTC or 3TC
- HIV RNA and CD4: Week 4, 8, 12 during TVR/Pbo
- HCV RNA: Day 1, 2,4, and week 1, 2, 3, 4, 8 and 12 during TVR/Pbo during TVR/Pbo dosing
- Proportion of patients with HCV RNA undetectable at week 4 and 12


Undetectable HCV RNA at Week 4 (ITT)
No ART
EFV/TDF/FTC
ATV/r+TDF+FTC/3TC
PR
Percent of patients with HCV RNA Undetectable
100
90
80
70
60
50
40
30
20
10
0
Total
71
75
64
70
0
12
0
Total
5
n/N =
5/7
12/16
9/14
26/37
0/6
1/8
0/8
1/22
Telaprevir + PR
PR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Percent of patients with HCV RNA Undetectable
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0
Total
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75
57
68
17
12
12
Total
14
n/N =
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Telaprevir + PR
PR

HCV Virological Failure

- 2 telaprevir patients experienced viral breakthrough*:
  - 1 patient at week 4 (receiving ATV/r + TDF + FTC)
  - 1 patient at week 8 (receiving EFV/TDF/FTC)
- 4 patients discontinued treatment due to stopping rules:
  - 1 telaprevir patient (receiving EFV/TDF/FTC) at week 8
  - 3 placebo patients
- HCV sequencing has not been performed yet

*defined as HCV RNA >100 IU/mL after HCV RNA undetectable or a 1 $\log_{10}$ increase from nadir

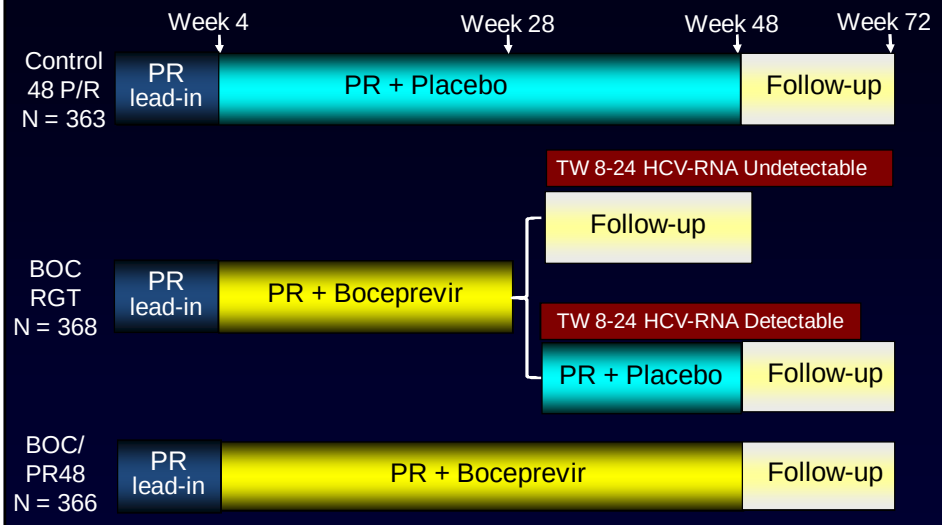
Access

- Nil at present
- Named patient programme excludes HIV
- Separate HIV programme access programme is planned
- Advisory board planned to discuss access programme in Europe planned for coinfection meeting

Boceprevir
GT 1 MONOINFECTED

NAÏVE	NON-RESPONDERS
SPRINT – 2 N = >900	RESPOND – 2 N = >400

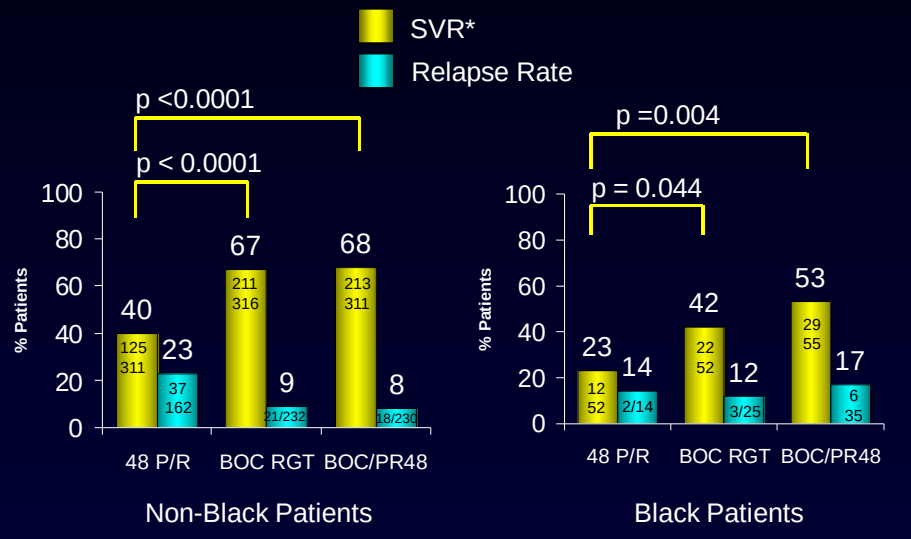
SPRINT 2: Study Design



Peginterferon (P) administered subcutaneously at 1.5 µg/kg once weekly, plus ribavirin (R) using weight based dosing of 600-1400 mg/day in a divided daily dose

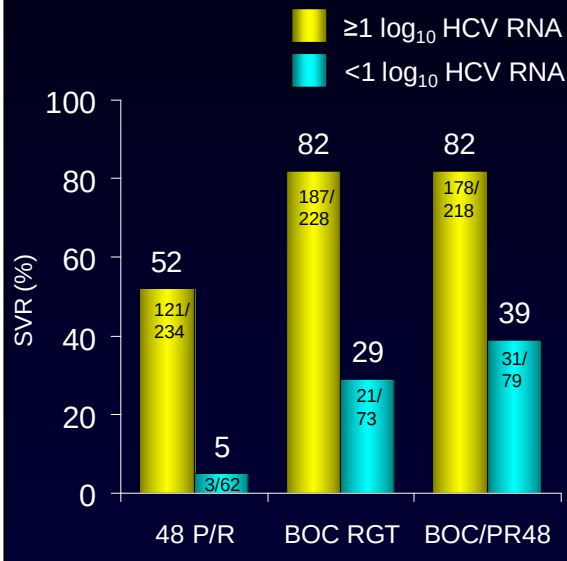
Boceprevir dose of 800 mg thrice daily

SPRINT 2: SVR and Relapse Rates (ITT)



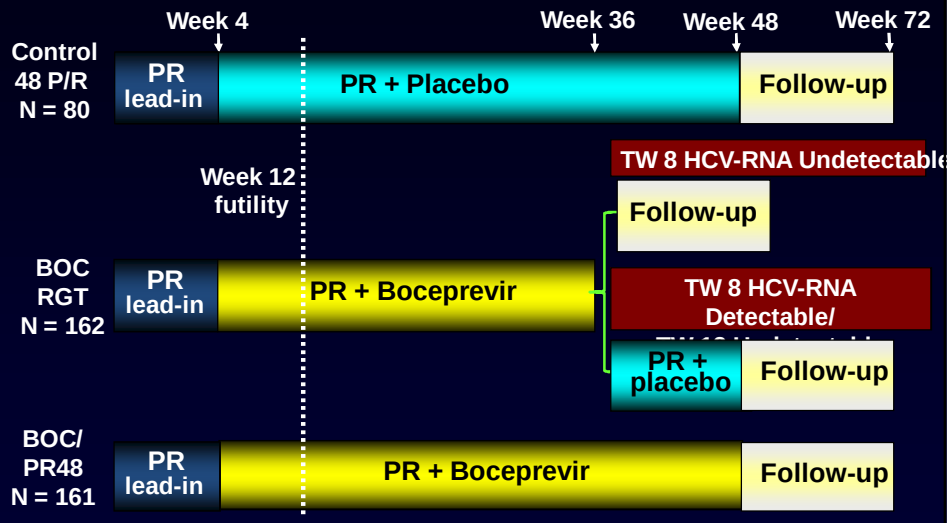
*SVR was defined as undetectable HCV RNA at the end of the follow-up period. The 12-week post-treatment HCV RNA level was used if the 24-week post-treatment level was missing (as specified in the protocol). A sensitivity analysis was performed counting only patients with undetectable HCV RNA documented at 24 weeks post-treatment and the SVR rates for Arms 1, 2 and 3 in Cohort 1 were 39% (122/311), 66% (207/316) and 68% (210/311), respectively and in Cohort 2 were 21% (11/52), 42% (22/52) and 51% (28/55), respectively.

SVR Based on Week 4 PR Lead-In in Non-Black Patients



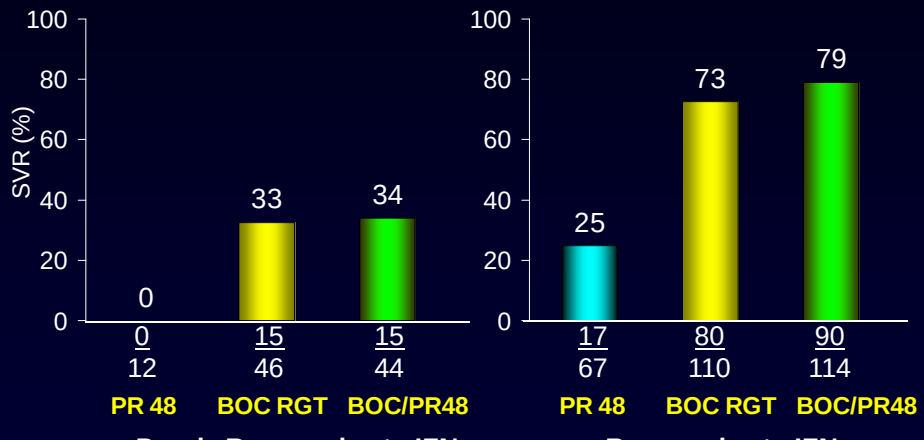
* Boceprevir resistance-associated variants determined with population sequencing

Respond 2 Study Arms and Dosing Regimen

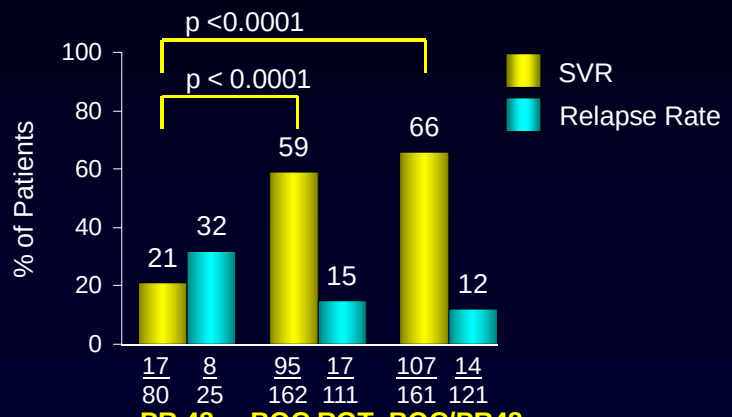


HCV-RNA measured by the Cobas TaqMan assay (Roche). Patients with detectable HCV-RNA (LLD=9.3 IU/mL) at week 12 were considered treatment failures.
Peginterferon (P) administered subcutaneously at 1.5 µg/kg once weekly, plus Ribavirin (R) using weight based dosing of 600-1400 mg/day in a divided daily dose
Boceprevir dose of 800 mg thrice daily

SVR by Week 4 PR Lead-In Response



RESPOND-2 SVR and Relapse Rates
Intention to treat population



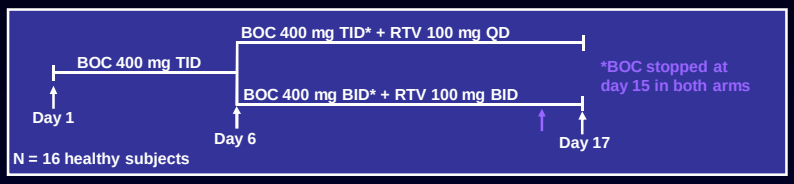
SVR rates in BOC RGT and BOC/PR48 arm not statistically different (OR, 1.4; 95% CI [0.9, 2.2])

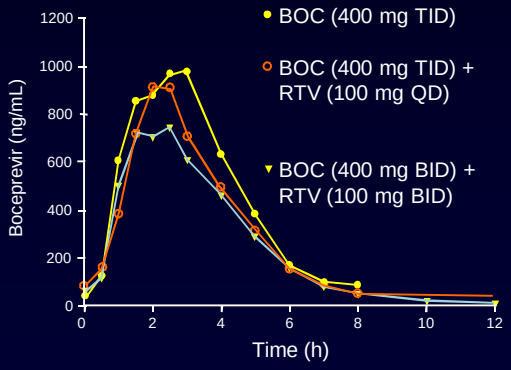
12-week HCV RNA level used if 24-week post-treatment level was missing. A sensitivity analysis where missing data was considered as non-responder, SVR rates for Arms 1, 2 and 3 were 21% (17/80), 58% (94/162) and 66% (106/161), respectively.

LOOKING AT CO-INFECTED
Boceprevir

- PK studies
- Pilot studies:

Ritonavir



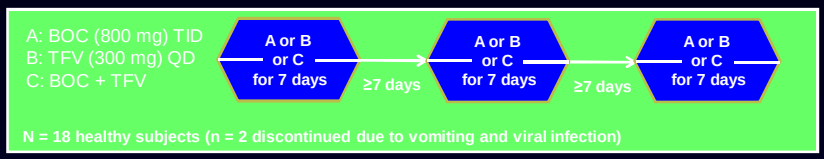


BOC + RTV (100 mg QD) vs BOC
$AUC_{(T)}$ ratio estimate
81% (90% CI: 73–91)
C_{max} R.E.
73% (90% CI: 57–93)

BOC + RTV (100 mg BID) vs BOC
$AUC_{(T)}$ ratio estimate
82% (90% CI: 75–88)
C_{max} R.E.
x% (90% CI: y–z)

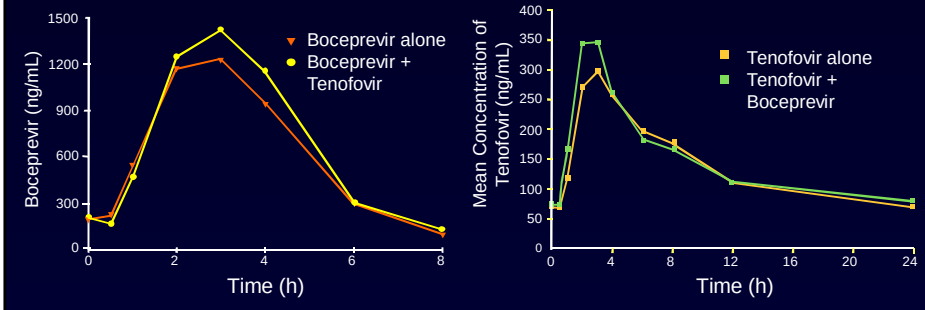
$AUC_{(T)}$, area under the plasma concentration versus time curve from time 0 dosing interval; BID, two time a day; BOC, boceprevir; CI, confidence interval; RTV, ritonavir; TID, three times a day.

Tenofovir



BOC vs BOC + TFV
$AUC_{(0\text{-}8h)}$ ratio estimate 108% (90% CI: 102–114)
C_{max} R.E. 105% (90%CI: 98–112)

TFV vs TFV + BOC
$AUC_{(0\text{-}8h)}$ ratio estimate 105% (90% CI: 101–109)
C_{max} R.E. 132% (90% CI: 119–145)



$AUC_{(0\text{-}8\ h)}$, area under the plasma concentration-time curve from 0 to 8 hours; BOC, boceprevir; CI, confidence interval; QD, once daily; TFV, tenofovir; TID, three times a day.

Efavirenz

Days 1–5: BOC 800 mg TID
Day 6: BOC 800 mg single dose

Washout ≥7 days

Days 1–10:
•EFV 600 mg QD

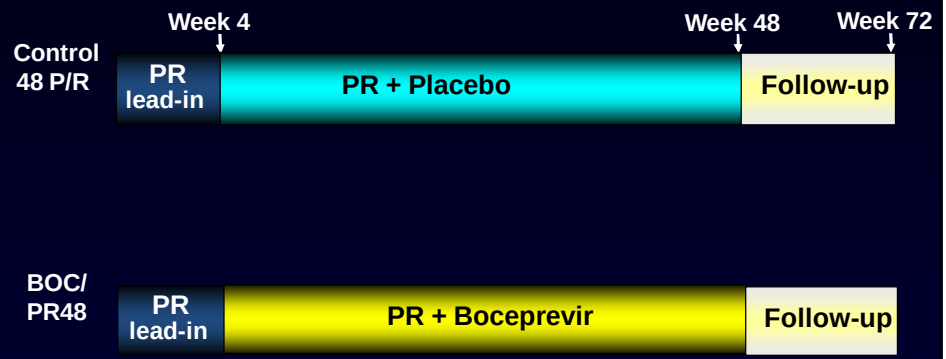
Days 11–15: BOC 800 mg TID
Day 16: BOC 800 mg single dose
Days 11–16: EFV 600 mg QD

N = 12 healthy volunteers

	Treatment	LS Mean[a]	Ratio Estimate, % (90% CI)
Effect of EFV (600 mg QD) on BOC (800 mg TID)			
C_{max} (ng/mL)	BOC	2038	92 (78–108)
	BOC + EFV	1871	
$AUC_{(0\text{-}8h)}$ (ng·h/mL)	BOC	6913	81 (75–89)
	BOC + EFV	5630	
C_{min} (ng/mL)	BOC	94.4	56 (42–74)
	BOC + EFV	52.5	
Effect of BOC (800 mg TID) on EFV (600 mg QD)			
C_{max} (ng/mL)	EFV	4573	111 (102–120)
	EFV + BOC	5077	
$AUC_{(0\text{-}24h)}$ (ng·h/mL)	EFV	78667	120 (115–126)
	EFV + BOC	94655	

[a]Model-based (least squares) geometric mean; ANOVA extracting the effects due to treatment and subject.
AUC, area under the plasma concentration-time curve; BOC, boceprevir; CI, confidence interval; C_{max}, maximum observed plasma concentration; C_{min}, minimum observed plasma concentration; EFV, efavirenz; LS, least squares; QD, once daily; TID, three times a day.

A Phase 2b, Safety and Efficacy Study of Boceprevir in Patients Coinfected With HIV and Hepatitis C



Boceprevir dose of 800 mg thrice daily

Access

- Named patient programme
- Previously failed PEG/rbv (min 12 weeks)
- Documented bridging fibrosis or cirrhosis
- Haemoglobin > 12g/dl (female), 13g/dl (male); neutrophils >1500 mm; platelets > 100 mm
- HIV IS NOT AN EXCLUSION

Other Compounds and Access in UK

- BI 201335 : Trial to commence Q3 2011
- TMC 235 : Site selection underway
- BMS Compounds : Country selection underway

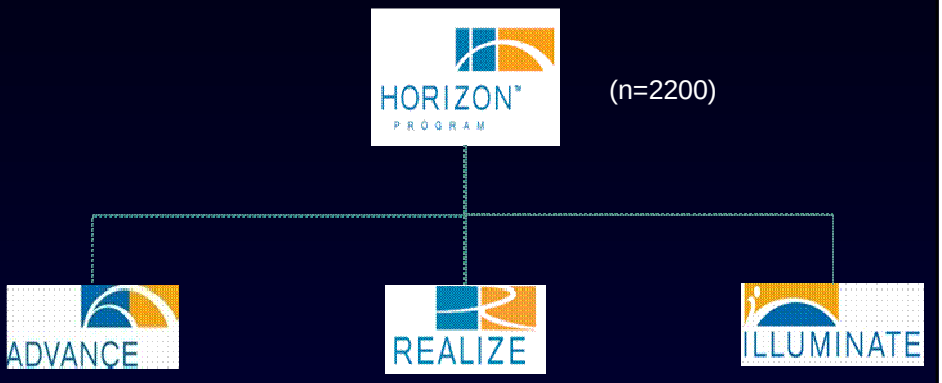
Questions

- Both MSD and Janssen wish their drugs to be appropiately used in the HIV population
- Who should have access- HIV physician,hepatologist or both?
- Can BHIVA help in the process eg advice on use or specific guidelines, monitoring use, regulating use, collecting data on efficacy and toxicity?

Telapravir

People die

Telaprevir
Phase III program HCV Genotype 1



Naive
(n=1095)

Pre-treated
(n=663)

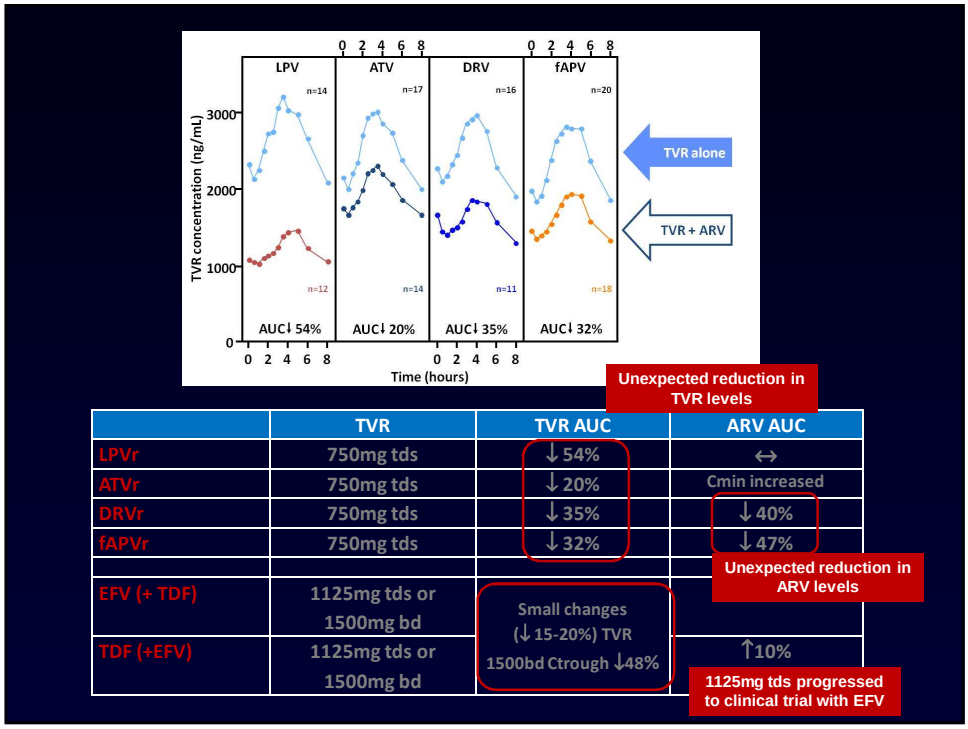
Naive
(n=543)

69

Telaprevir: An Orally-Available HCV Protease Inhibitor

- Telaprevir (TVR) is a selective inhibitor of NS3/4A HCV serine protease
- In genotype 1 mono-infected patients, telaprevir with peginterferon alfa-2a/ribavirin (T/PR) led to substantial improvements in SVR in phase 3 studies[1-4]:
  - Treatment-naïve patients (ADVANCE trial, N=1088)[1,]
    - 69-75% vs 44% in control
  - Treatment-experienced patients (REALIZE trial, N=662)[3]:
    - 31% vs 5% in control (prior null responders)
    - 57% vs 15% in control (prior partial responders)
    - 86% vs 24% in control (prior relapsers)

[1]Jacobson et al 2010, Hepatology 52(Suppl 4)427A; [2]Sherman et al 2010, Hepatology 52(Suppl 4)401A;402A; [3]Foster et al 2011 Hepatology Int 52(Suppl.1) 1-4; [4]Sherman et al. CROI 2011, Poster 957; [5]Van Heeswik et al. CROI 2011, Abstract 146LB



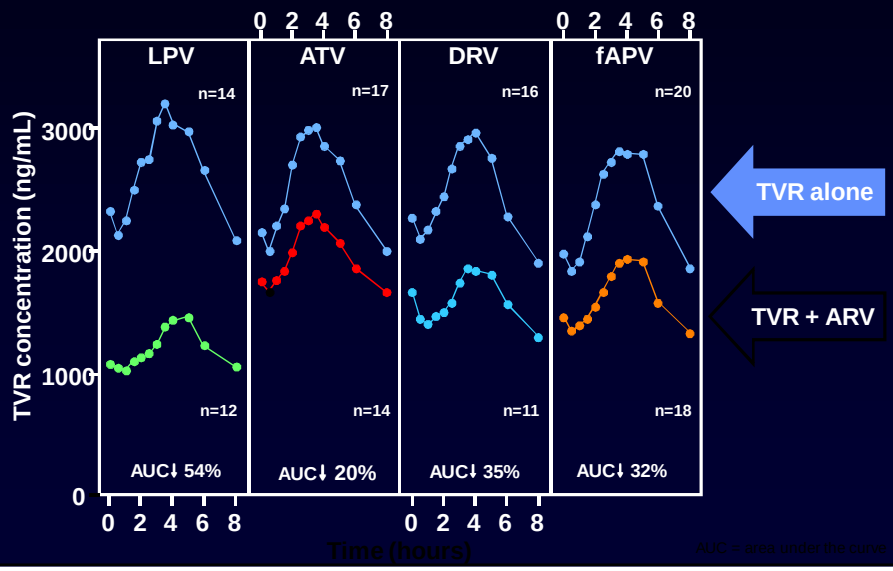
Unexpected reduction in TVR levels

	TVR	TVR AUC	ARV AUC
LPVr	750mg tds	↓54%	↔
ATVr	750mg tds	↓20%	Cmin increased
DRVr	750mg tds	↓35%	↓40%
fAPVr	750mg tds	↓32%	↓47%
EFV (+ TDF)	1125mg tds or 1500mg bd	Small changes (↓15-20%) TVR 1500bd Ctrough ↓48%	
TDF (+EFV)	1125mg tds or 1500mg bd		↑10%

Unexpected reduction in ARV levels

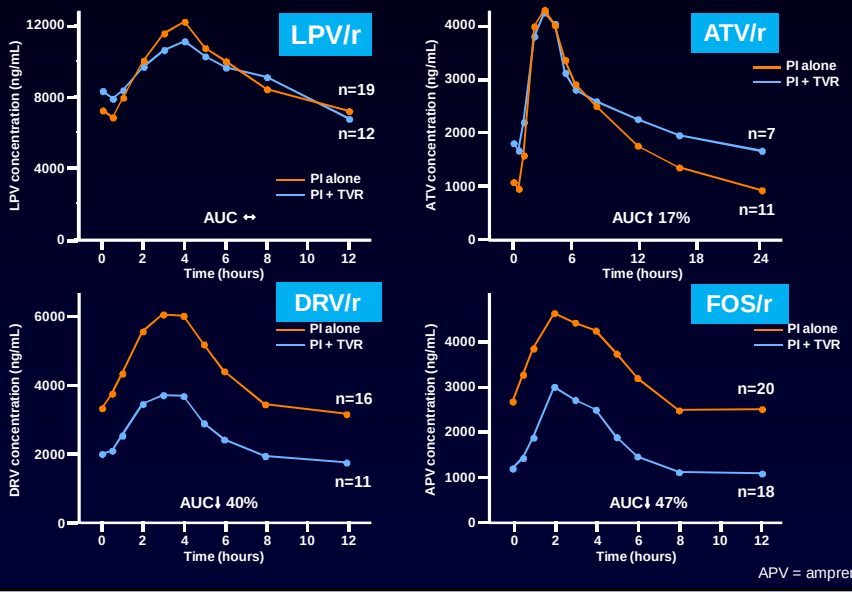
1125mg tds progressed to clinical trial with EFV

Mean TVR PK Profiles



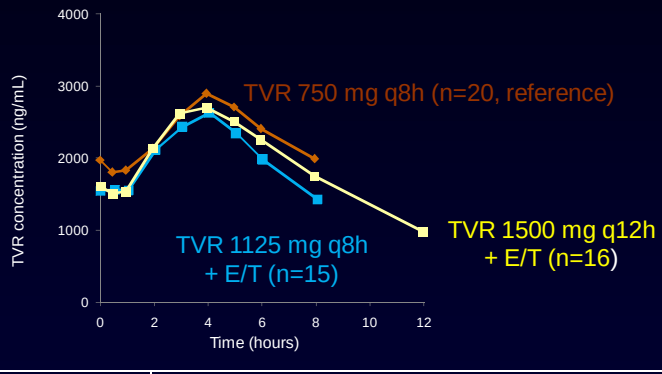
AUC = area under the curve

Mean HIV PI PK Profiles



APV = amprenavir

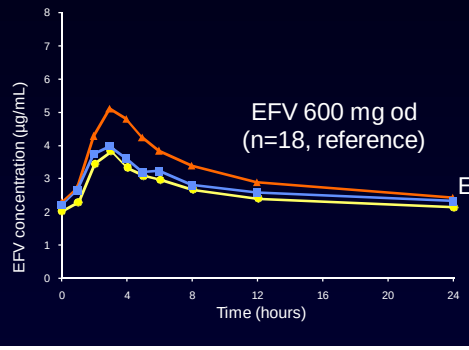
Mean TVR PK profiles and Statistics



TVR dose	Effect of EFV/TDF on TVR		
	C_{min}	C_{max}	AUC_{8h}
1125 mg q8h	0.75 (0.66–0.86)	0.86 (0.76–0.97)	0.82 (0.73–0.92)
1500 mg q12h	0.52 (0.42–0.64)	0.97 (0.88–1.06)	0.80 (0.73–0.88)*

*Average steady state plasma concentration ($Css_{average}$)

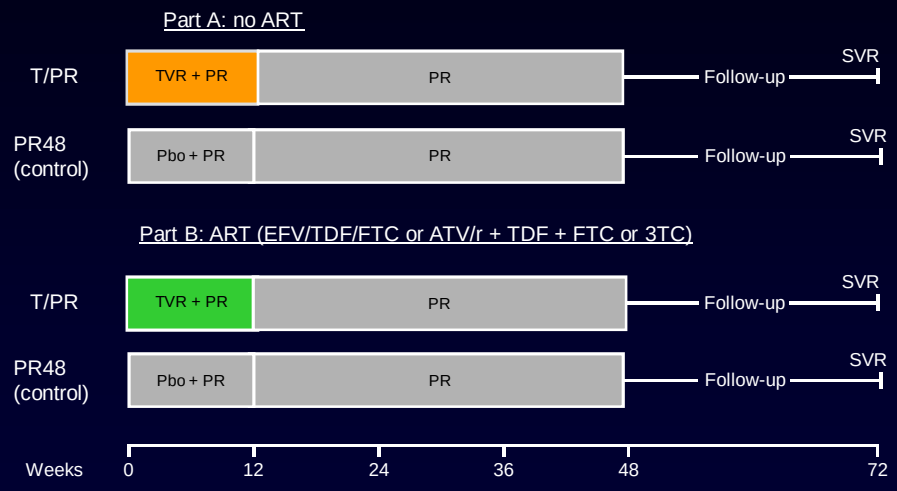
Mean EFV PK Profiles and Statistics



Effect of TVR on EFV

TVR dose	C_{min}	C_{max}	AUC_{24h}
1125 mg q8h	0.90 (0.81–1.01)	0.76 (0.68–0.85)	0.82 (0.74–0.90)
1500 mg q12h	0.89 (0.82–0.96)	0.80 (0.74–0.86)	0.85 (0.79–0.91)

Study Design



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Roche COBAS® TaqMan® HCV test v2.0, LLOQ of 25 IU/mL (pts with values below 25IU/mL were reported as <25 detectable or undetectable)

Principal Eligibility Criteria

- Male and female patients, 18 to 65 years of age with chronic HCV genotype 1/HIV-1 co-infection, and treatment-naïve for HCV
- Liver biopsy within 1 year; compensated cirrhosis permitted
- Part A: up to 20 patients not receiving ART, with CD4 count ≥500 cells/mm^3, and HIV RNA ≤100,000 copies/mL
- Part B: up to 48 patients receiving a stable ART regimen
  - TDF/EFV/FTC, or
  - ATV/r with TDF and FTC or 3TC, with CD4 count ≥300 cells/mm^3, and HIV RNA ≤50 copies/mL

Methods

- Interim analysis based on 59 of 60 patients who received at least 1 dose of study drugs; 41/59 patients had reached week 12 at time of analysis
  - 13 patients from Part A
  - 46 patients from Part B
    - 24 patients received TDF/EFV/FTC and,
    - 22 patients received ATV/r + TDF + FTC or 3TC
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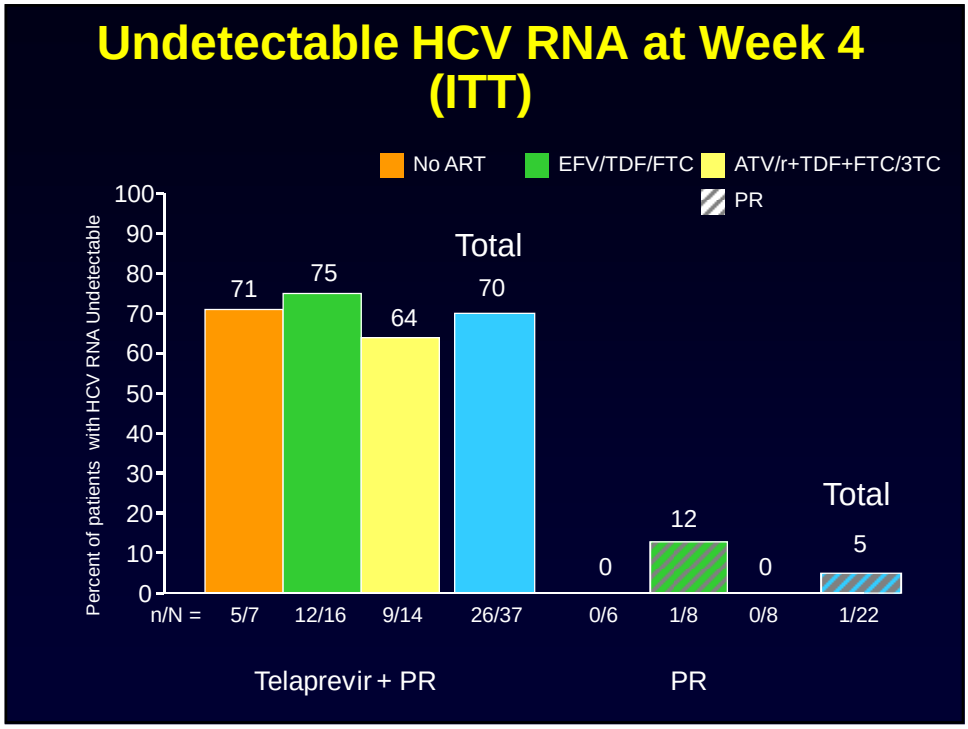
- Proportion of patients with HCV RNA undetectable at week 4 and 12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50
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30
20
10
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Total
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75
64
70
0
12
0
Total
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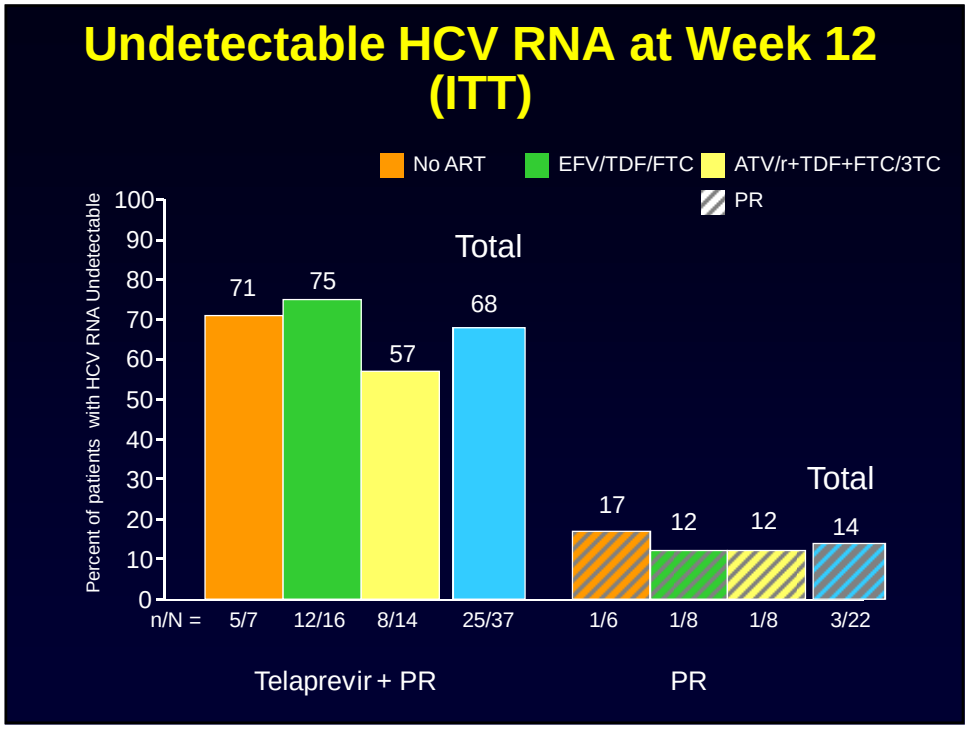
Telaprevir + PR
PR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30
20
10
0
Total
71
75
57
68
17
12
12
Total
14
n/N =
5/7
12/16
8/14
25/37
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1/8
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Telaprevir + PR
PR

HCV Virological Failure

- 2 telaprevir patients experienced viral breakthrough*:
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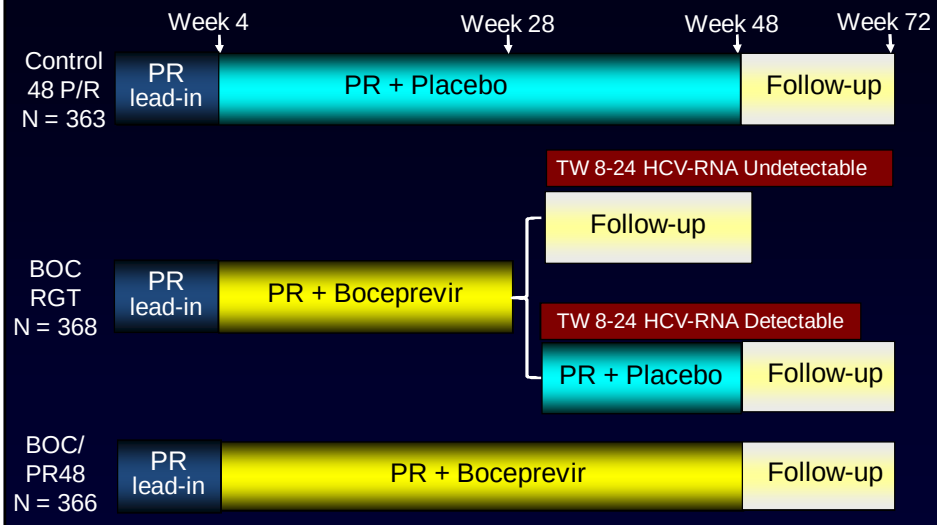
*defined as HCV RNA >100 IU/mL after HCV RNA undetectable or a 1 $\log_{10}$ increase from nadir

Access

- Nil at present
- Named patient programme excludes HIV
- Separate HIV programme access programme is planned
- Advisory board planned to discuss access programme in Europe planned for coinfection meeting

Boceprevir

SPRINT 2: Study Design



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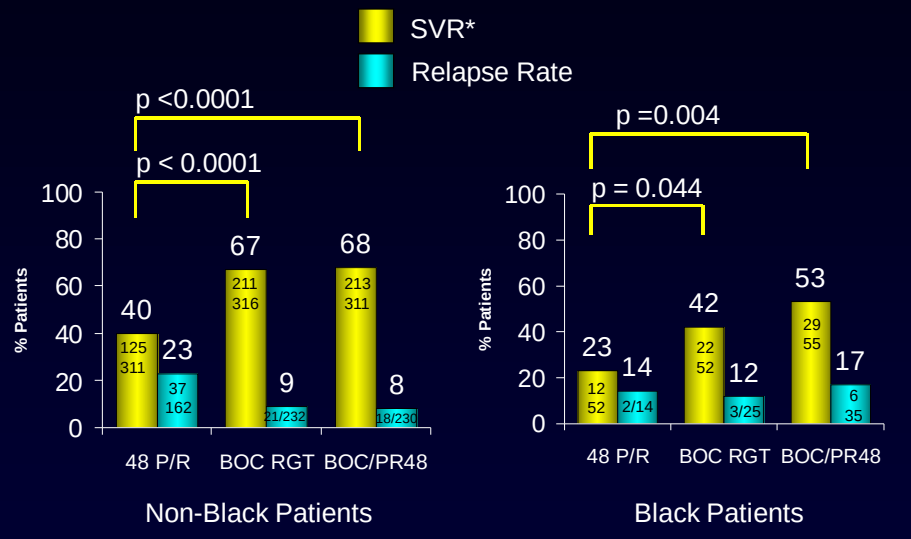
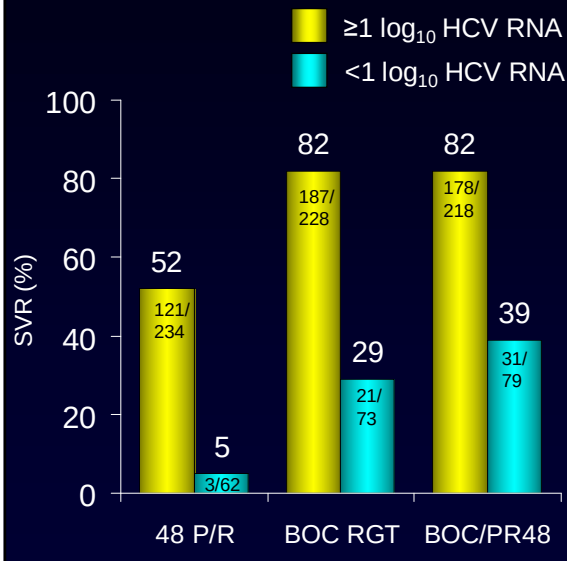
Boceprevir dose of 800 mg thrice daily

SPRINT 2: SVR and Relapse Rates (ITT)



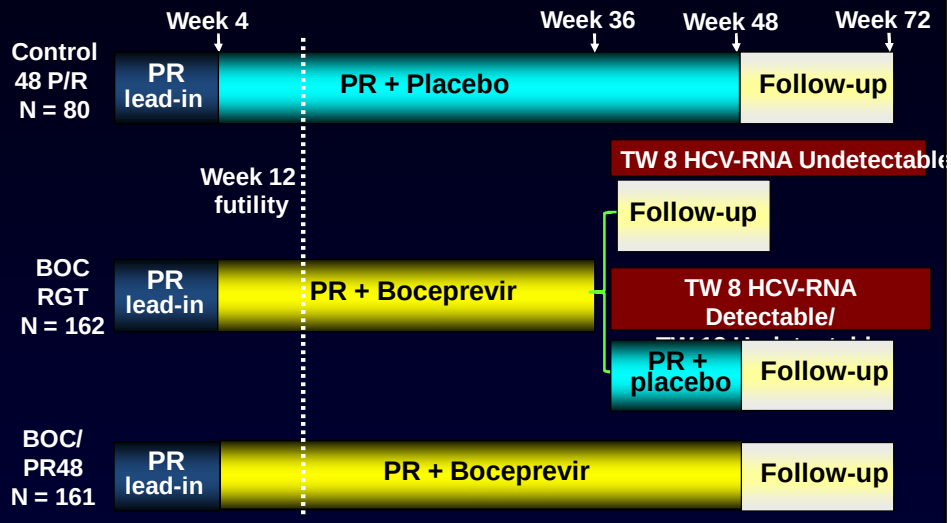
*SVR was defined as undetectable HCV RNA at the end of the follow-up period. The 12-week post-treatment HCV RNA level was used if the 24-week post-treatment level was missing (as specified in the protocol). A sensitivity analysis was performed counting only patients with undetectable HCV RNA documented at 24 weeks post-treatment and the SVR rates for Arms 1, 2 and 3 in Cohort 1 were 39% (122/311), 66% (207/316) and 68% (210/311), respectively and in Cohort 2 were 21% (11/52), 42% (22/52) and 51% (28/55), respectively.

SVR Based on Week 4 PR Lead-In in Non-Black Patients



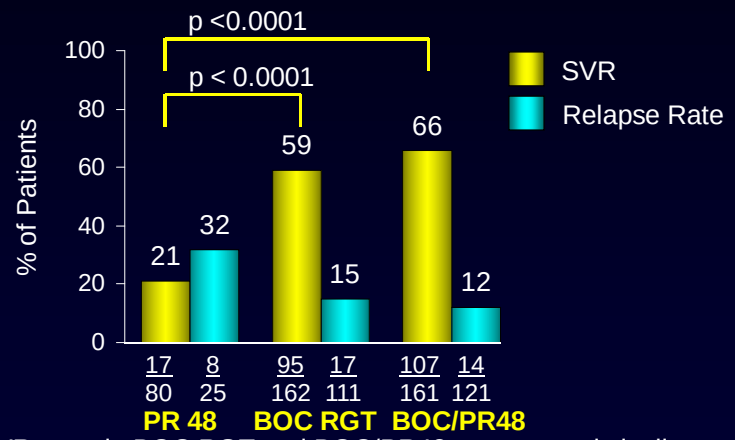
* Boceprevir resistance-associated variants determined with population sequencing

Respond 2 Study Arms and Dosing Regimen



HCV-RNA measured by the Cobas TaqMan assay (Roche). Patients with detectable HCV-RNA (LLD=9.3 IU/mL) at week 12 were considered treatment failures.
Peginterferon (P) administered subcutaneously at 1.5 µg/kg once weekly, plus Ribavirin (R) using weight based dosing of 600-1400 mg/day in a divided daily dose
Boceprevir dose of 800 mg thrice daily

RESPOND-2 SVR and Relapse Rates
Intention to treat population



SVR rates in BOC RGT and BOC/PR48 arm not statistically different (OR, 1.4; 95% CI [0.9, 2.2])

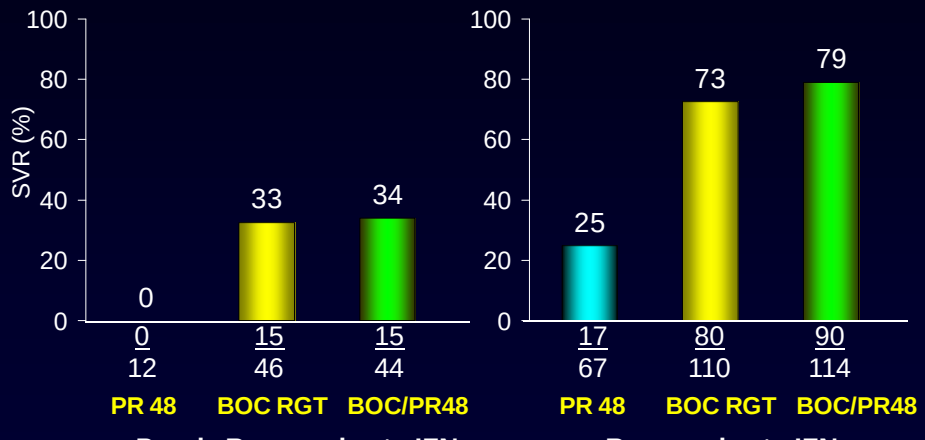
12-week HCV RNA level used if 24-week post-treatment level was missing. A sensitivity analysis where missing data was considered as non-responder, SVR rates for Arms 1, 2 and 3 were 21% (17/80), 58% (94/162) and 66% (106/161), respectively.

SVR by Historical Response Non-responders and Relapsers*

	Arm 1: 48 P/R N = 80	Arm 2: BOC RGT N = 162	Arm 3: BOC/PR48 N = 161
Non-responder – n/n (%)	2/29 (6.9)	23/57 (40.4)	30/58 (51.7)
Relapser – n/n (%)	15/51 (29.4)	72/105 (68.6)	77/103 (74.8)

*Non-responders had a decrease in plasma HCV-RNA of at least 2-$\log_{10}$ by week 12 of prior therapy but with detectable HCV-RNA throughout the course of therapy. Relapsers had undetectable HCV-RNA at end of prior therapy without subsequent attainment of a sustained virologic response.

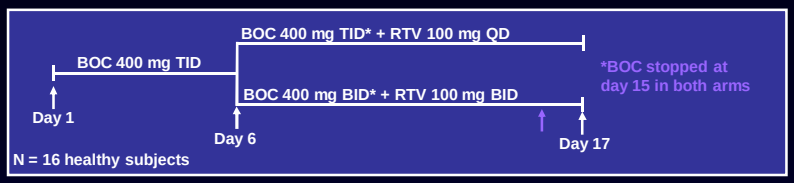
SVR by Week 4 PR Lead-In Response

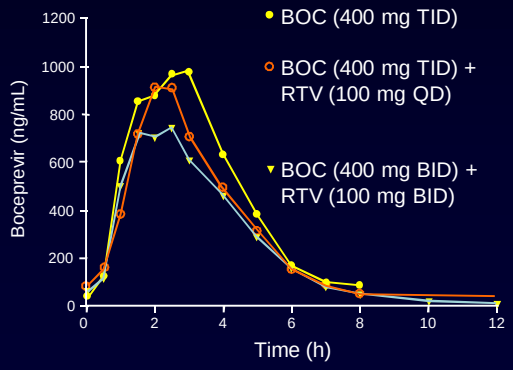


A Phase 2b, Safety and Efficacy Study of Boceprevir in Patients Coinfected With HIV and Hepatitis C

Boceprevir dose of 800 mg thrice daily

Ritonavir





BOC + RTV (100 mg QD) vs BOC
$AUC_{(T)}$ ratio estimate
81% (90% CI: 73–91)
C_{max} R.E.
73% (90% CI: 57–93)

BOC + RTV (100 mg BID) vs BOC
$AUC_{(T)}$ ratio estimate
82% (90% CI: 75–88)
C_{max} R.E.
x% (90% CI: y–z)

$AUC_{(T)}$, area under the plasma concentration versus time curve from time 0 dosing interval; BID, two time a day; BOC, boceprevir; CI, confidence interval; RTV, ritonavir; TID, three times a day.

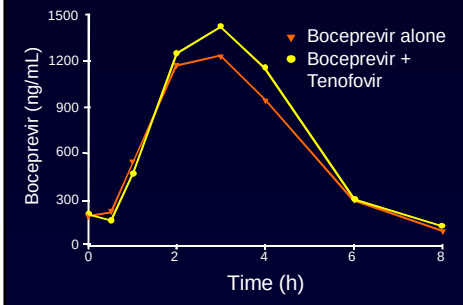
Tenofovir

A: BOC (800 mg) TID
B: TFV (300 mg) QD
C: BOC + TFV

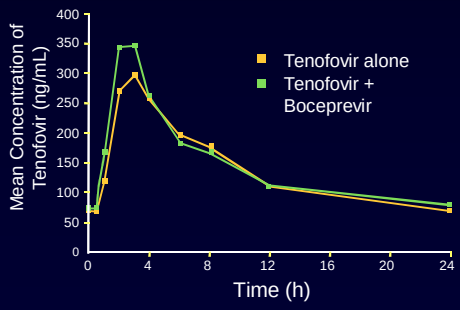
A or B or C for 7 days → ≥7 days → A or B or C for 7 days → ≥7 days → A or B or C for 7 days

N = 18 healthy subjects (n = 2 discontinued due to vomiting and viral infection)

BOC vs BOC + TFV
$AUC_{(0\text{-}8h)}$ ratio estimate 108% (90% CI: 102–114)
C_{max} R.E. 105% (90%CI: 98–112)



TFV vs TFV + BOC
$AUC_{(0\text{-}8h)}$ ratio estimate 105% (90% CI: 101–109)
C_{max} R.E. 132% (90% CI: 119–145)



$AUC_{(0\text{-}8\ h)}$, area under the plasma concentration-time curve from 0 to 8 hours; BOC, boceprevir; CI, confidence interval; QD, once daily; TFV, tenofovir; TID, three times a day.

Efavirenz

Days 1–5: BOC 800 mg TID
Day 6: BOC 800 mg single dose

N = 12 healthy volunteers

Washout ≥7 days

Days 1–10:
•EFV 600 mg QD

Days 11–15: BOC 800 mg TID
Day 16: BOC 800 mg single dose
Days 11–16: EFV 600 mg QD

	Treatment	LS Mean[a]	Ratio Estimate, % (90% CI)
Effect of EFV (600 mg QD) on BOC (800 mg TID)			
C_{max} (ng/mL)	BOC	2038	92 (78–108)
	BOC + EFV	1871	
$AUC_{(0\text{-}8h)}$ (ng·h/mL)	BOC	6913	81 (75–89)
	BOC + EFV	5630	
C_{min} (ng/mL)	BOC	94.4	56 (42–74)
	BOC + EFV	52.5	
Effect of BOC (800 mg TID) on EFV (600 mg QD)			
C_{max} (ng/mL)	EFV	4573	111 (102–120)
	EFV + BOC	5077	
$AUC_{(0\text{-}24h)}$ (ng·h/mL)	EFV	78667	120 (115–126)
	EFV + BOC	94655	

[a]Model-based (least squares) geometric mean; ANOVA extracting the effects due to treatment and subject.
AUC, area under the plasma concentration-time curve; BOC, boceprevir; CI, confidence interval; C_{max}, maximum observed plasma concentration; C_{min}, minimum observed plasma concentration; EFV, efavirenz; LS, least squares; QD, once daily; TID, three times a day.

Access

- Named patient programme
- Previously failed PEG/rbv (min 12 weeks)
- Documented bridging fibrosis or cirrhosis
- Haemoglobin > 12g/dl (female), 13g/dl (male); neutrophils >1500 mm; platelets > 100 mm
- HIV IS NOT AN EXCLUSION

Other Compounds and Access in UK

- BI 201335 : Trial to commence Q3 2011
- TMC 235 : Site selection underway
- BMS Compounds : Country selection underway

Questions

- Both MSD and Janssen wish their drugs to be appropiately used in the HIV population
- Who should have access- HIV physician,hepatologist or both?
- Can BHIVA help in the process eg advice on use or specific guidelines, monitoring use, regulating use, collecting data on efficacy and toxicity?