

Dr Ranjababu Kulasegaram

St Thomas' Hospital, London

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

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St Thomas' Hospital, London

COMPETING INTEREST OF FINANCIAL VALUE > £1,000:	
Speaker Name	Statement
Dr Ranjababu Kulasegaram:	Dr Ranjababu Kulasegaram has received grants, travel sponsorship and or research support from ViiV, MSD, Abbott, Gilead, BMS and Janssen. He has also undertaken speaker / advisory board / consultancy work for MSD, ViiV, Abbott, BMS, Janssen and Gilead
Date	April 2012

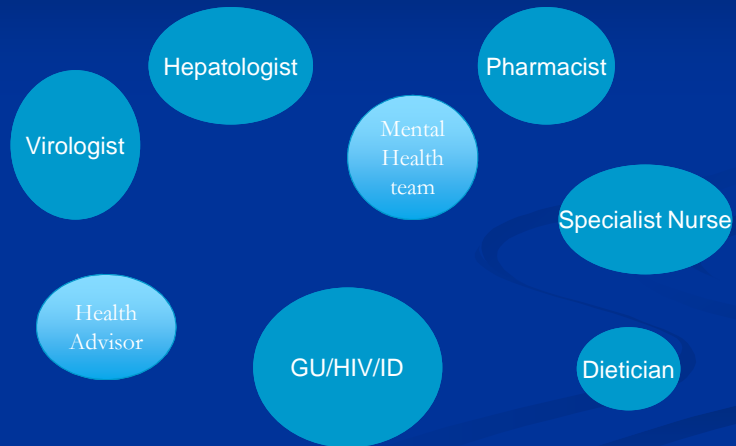
18-20 April 2012, The International Convention Centre, Birmingham

The role of HIV Physician in managing HIV-HCV co- infection

Dr Ranjababu (Babu) Kulasegaram
Guy's & St. Thomas' NHS Foundation
Trust , London UK

“Hepatitis C is the new HIV”

Team involved in HIV-HCV co-infection patient care



Please vote by raising your hand

Who plays the key role in managing patients with HIV/HCV co infection?

Hepatologist

GU/HIV/ID

Results

Hepatologist

10%

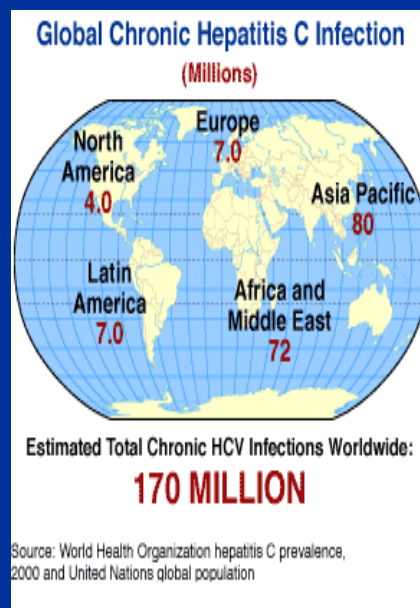
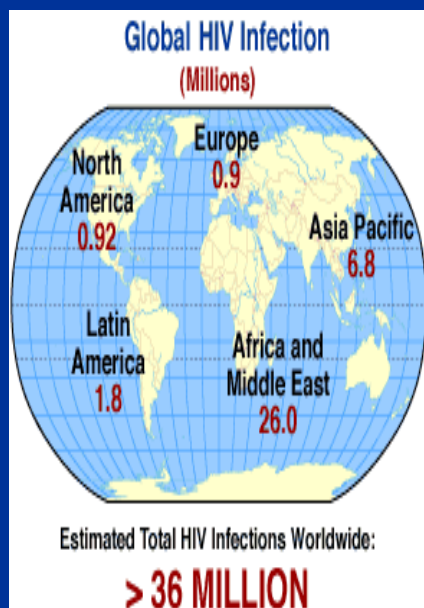
GU/HIV/ID

90%

HIV groups have much to teach hepatitis doctors about better diagnosis and treatment

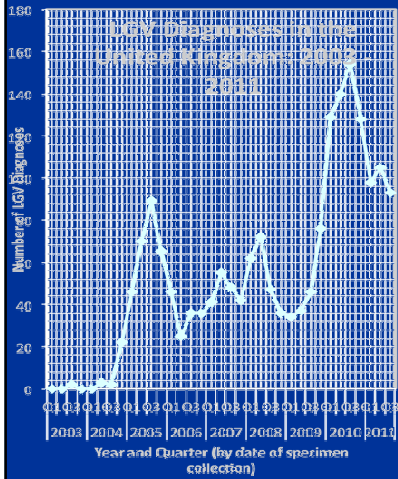
[BMJ](#). 2012 Feb 20;344:e1266. doi: 0.1136/bmj.e1266

[Parry J](#)



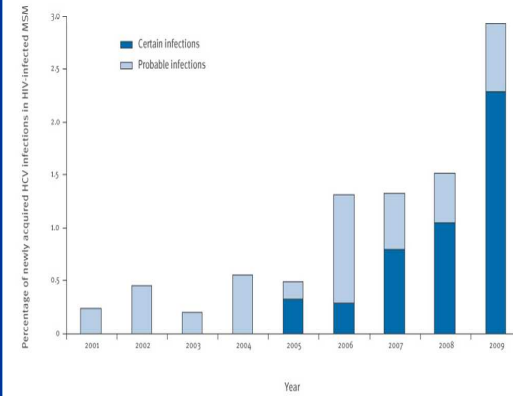
LGV

N = 1993 cases since 2003



FIGURE

Annual incidence of episodes of newly acquired HCV infection among HIV-infected men who have sex with men, Antwerp, Belgium, 2001–2009 (n=69)



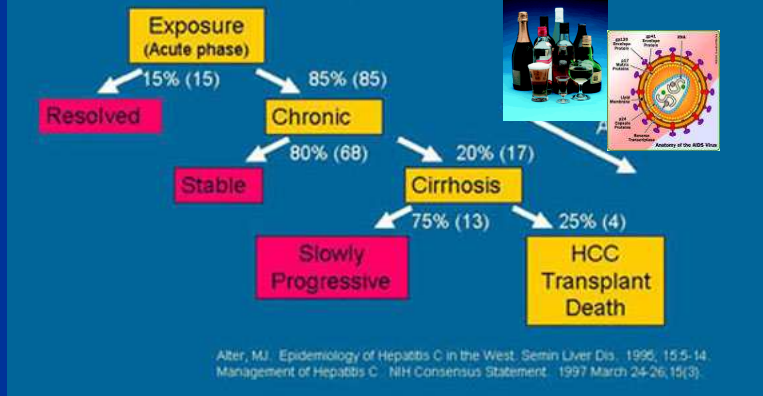
* Followed from 2001 to 2009 at the HIV/STI reference clinic of the Institute of Tropical Medicine of Antwerp, Belgium.

Bottieau et al. Eurosurveillance, 2010; 15, 39 (15), 30 September 2010

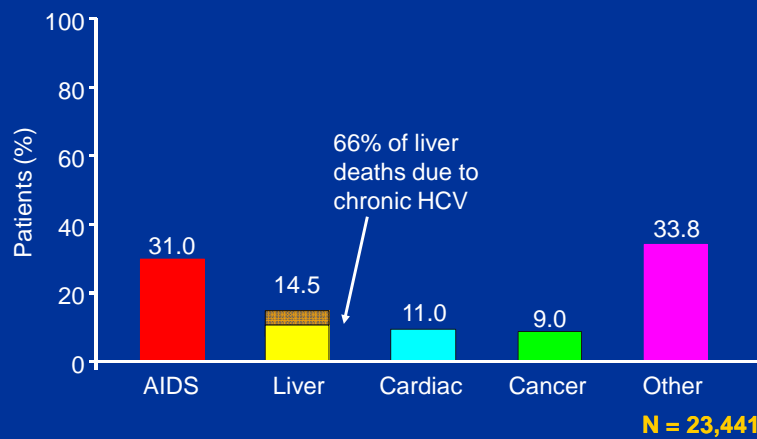
HIV

- HBV /HDV
- HCV
- HEV
- CMV
- HHV 8
- EBV
- HSV
- HZV
- HPV
- GBV
- Any others not yet identified

Natural History of HCV Infection



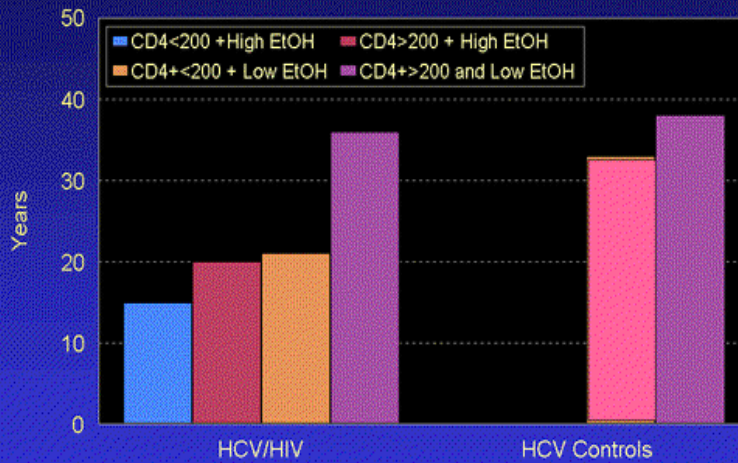
Causes of Death in 1246 HIV-Positive Pts Followed in the D:A:D Study



Sulkowski MS. J Hepatol. 2008;48:353-367. Weber R, et al. Arch Intern Med. 2006;166:1632-1641.

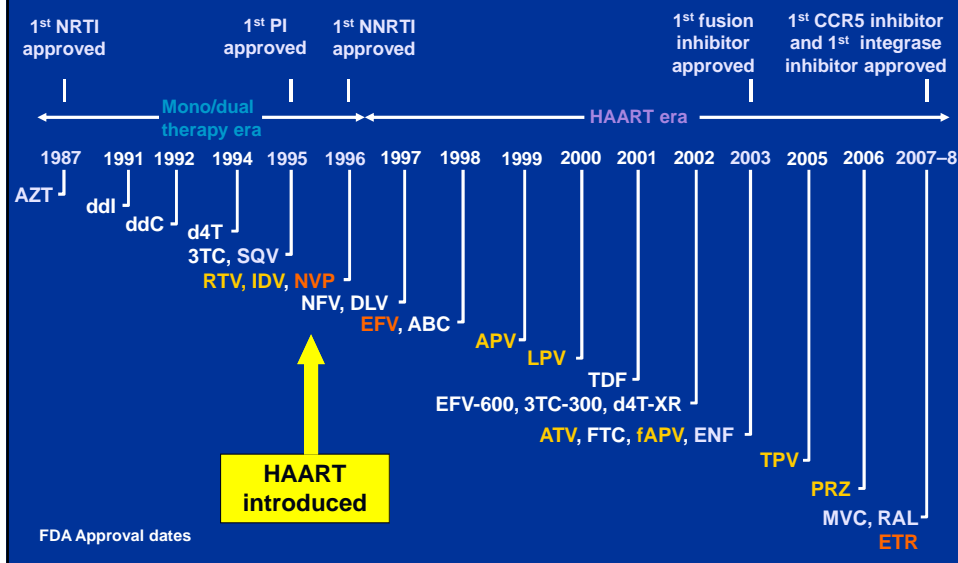
HCV/HIV COINFECTION

Median Time to Cirrhosis



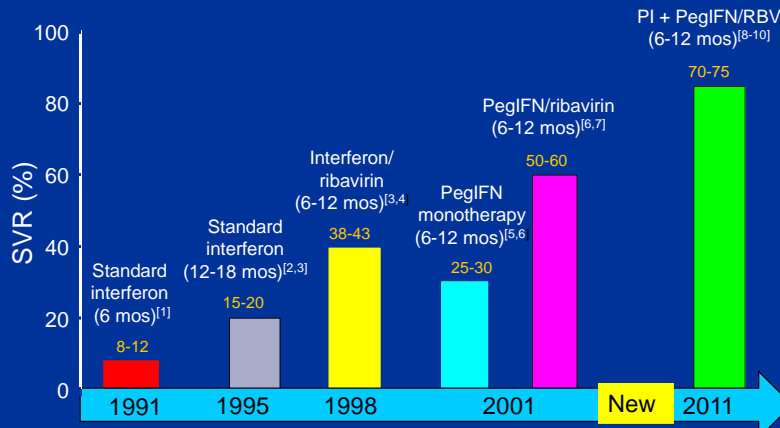
Benhamou et. al., HEPATOLOGY, 1999

Evolution of ARV therapy



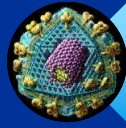
Treatment of Chronic Hepatitis C

New HIV



1. Carithers RL Jr., et al. Hepatology. 1997;26(3 suppl 1):83S-88S. 2. Zeuzem S, et al. NEJM. 2000;343:1666-1672. 3. Poynard T, et al. Lancet. 1998;352:1426-1432. 4. McHutchison JG, et al. NEJM. 1998;339:1485-1492. 5. Lindsay KL, et al. Hepatology. 2001;34:395-403. 6. Fried MW, et al. NEJM. 2002;347:975-982. 7. Manns MP, et al. Lancet. 2001;358:958-965. 8. Poordad F, et al. NEJM. 2011;364:1195-1206. 9. Jacobson IM, et al. NEJM. 2011;364:2405-2416. 10. Sherman KE, et al. NEJM. 2011;365:1014-1024

NS3/4A Protease Inhibitors	NS5B Polymerase Inhibitors		NS5A Inhibitors	Cyclophilin A Inhibitors
	Nucleos(t)ide Analogue	Non- nucleos(t)ide		
<ul style="list-style-type: none"> High efficacy Low genetic barrier to resistance Macrocyclic or linear Phase III: BI 201335, TMC435 	<ul style="list-style-type: none"> Mimic natural substrates of the polymerase Incorporated into RNA chain causing chain termination Broad genotypic coverage High genetic barrier to resistance Phase III: PSI-7977 	<ul style="list-style-type: none"> Bind to several different allosteric enzyme sites; results in conformational change Resistance more frequent than nuc Several agents in phase II 	<ul style="list-style-type: none"> NS5A has role in assembly of replication complex Mechanism of inhibition under study Phase III: Daclatasvir (BMS-790052) 	<ul style="list-style-type: none"> Supports HCV-specific RNA replication, protein expression Interacts with NS2, NS5A, NS5B May regulate polypeptide processing, viral assembly Phase III: Alisporivir



HIV Success – control / ?cure

HIV - VIRUS

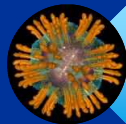
- HIV Viral load (assay)
- Resistance – Baseline / detectable / deep sequencing

Drug

- Side effects
- DDI

Patient

- Adherence (pill burden, frequency)
- Life style
- Timing – when to start / switch



HCV Success – SVR / cure

HCV - VIRUS

- HCV Viral load, genotype
- **Resistance**

Drug

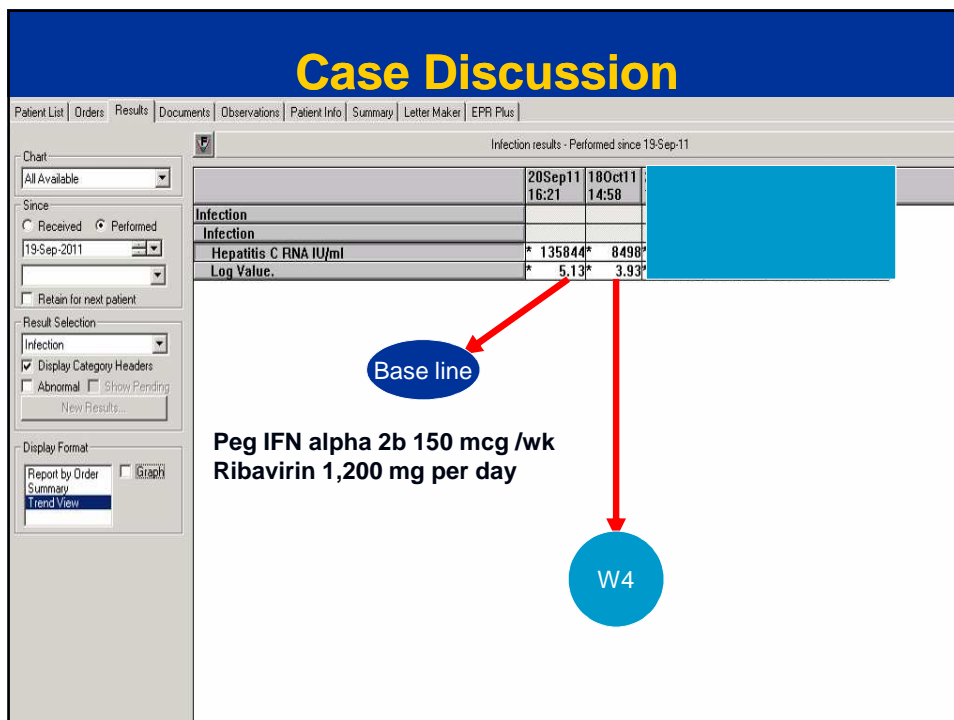
- Side effects
- DDI

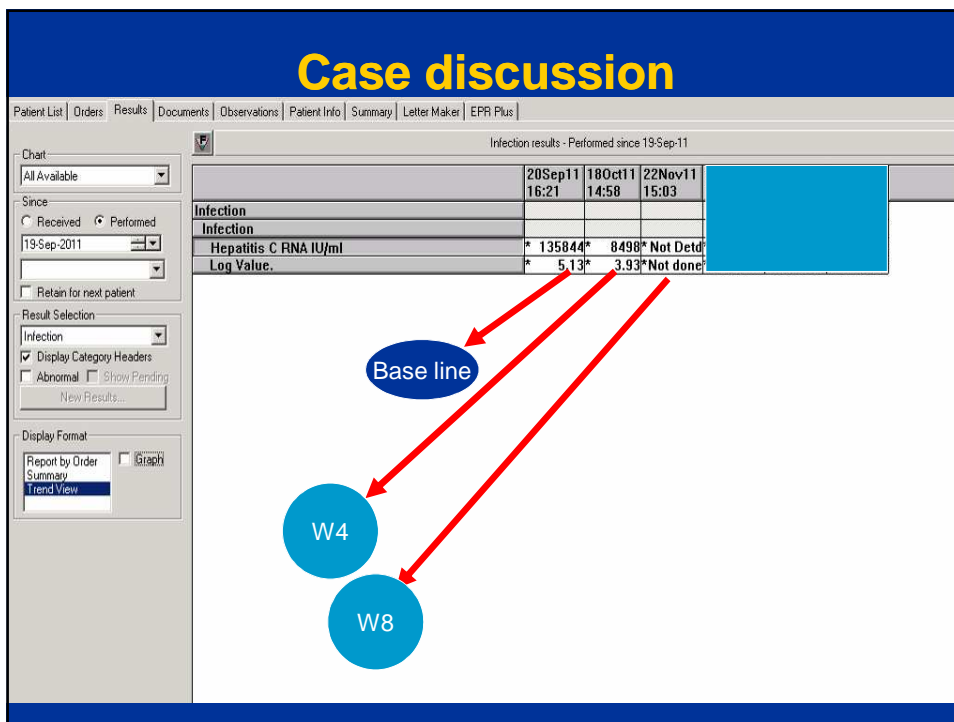
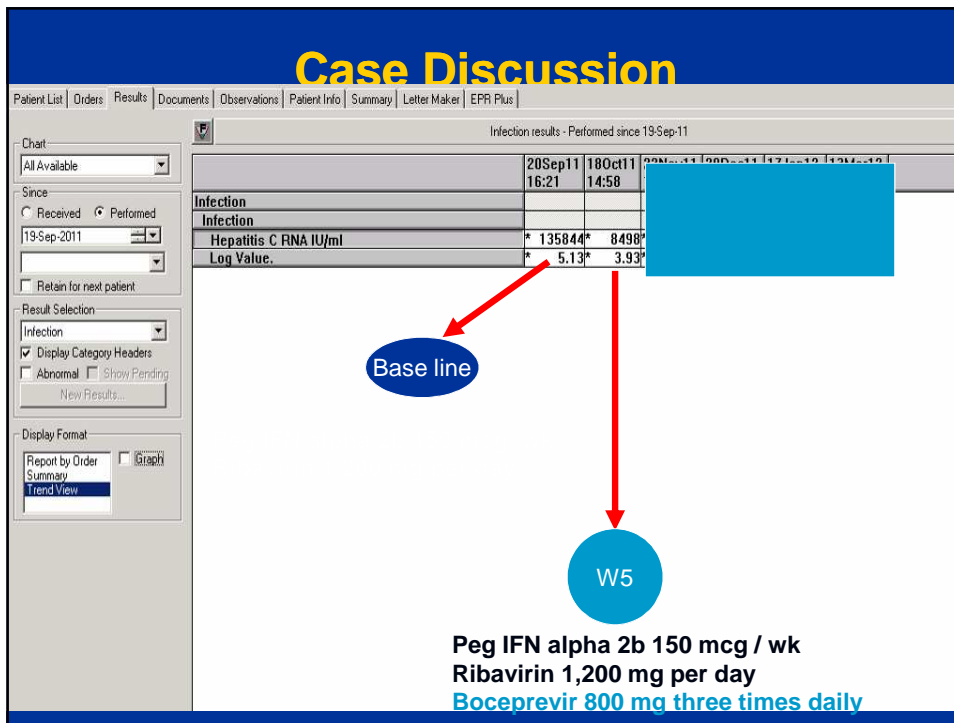
Patient

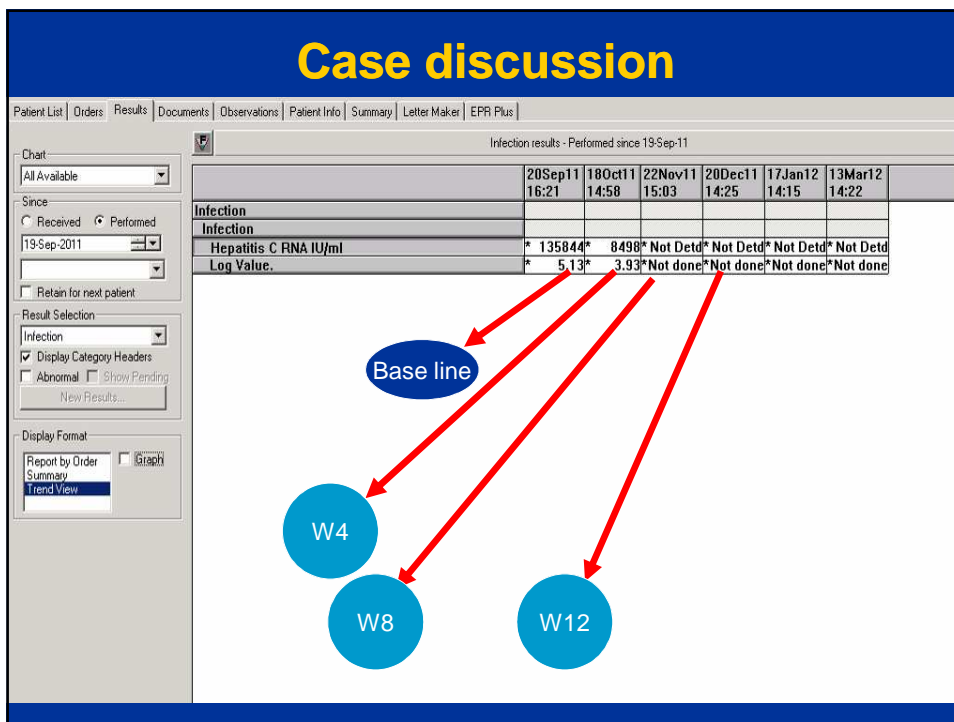
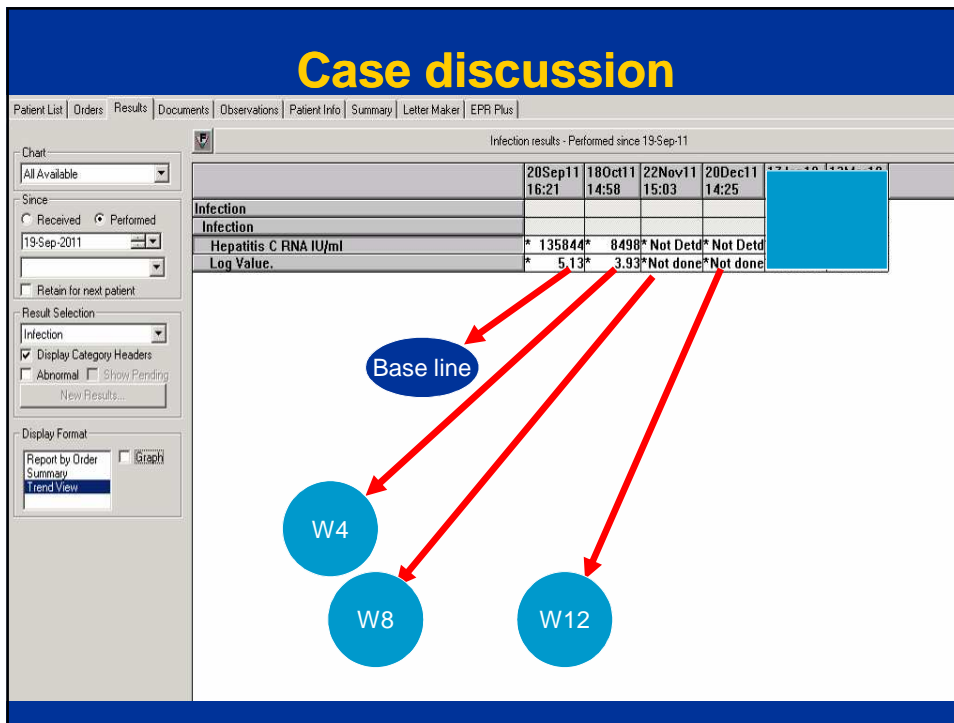
- Adherence (pill burden, frequency)
- When to treat? / Stop?

Case discussion: 49yr man

- Hepatitis C genotype 1a
- 1997 Non-responder to IFN monotherapy
- 2003 48 weeks with Peg IFN + RBV – relapsed
- Liver biopsy 2006 stage 1/6 fibrosis
- Liver biopsy 2010 stage 4/6 fibrosis
- FibroScan March 2010 median stiffness 8.5kPa
- 2011







HCV, GT 1b, Caucasian male, 50yr

Rx Start	Week 4	Week 12	Week 24
26/11/10	23/12/10	18/02/11	11/05/11
2585126	254579	19291	299865
Log 6.41	Log 5.41	Log 4.29	Log 5.48

Rx
Peginterferon 2b 120mcg/week
Ribavirin 1000mg/day

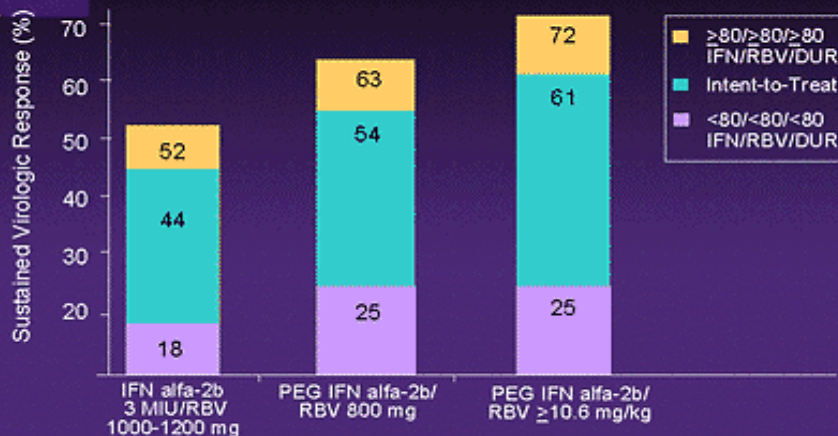
Rx Start	Week 4
19/03/12	16/04/12
3559537	Not detected
Log 6.55	

Rx
Peginterferon 2a 180mcg/week
Ribavirin 600mg BD
Telaprevir 750mg TSD

July 2011
Liver biopsy
3/6 – 6/18
IL28B – TG/CT



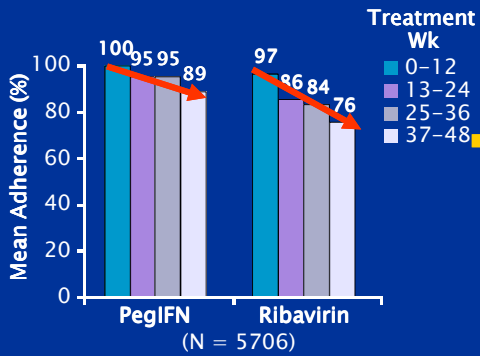
Adherence to Therapy An Outcome Predictor



DUR = duration; IFN = interferon; MIU = million international units; QD = once a day;
RBV = ribavirin; TIV = three times a week.
McHutchison et al. *Gastroenterology*. 2002;123:1061-1069.

Current standard of care is complex

- Adherence to pegIFN/RBV therapy decreases over time
- BOC TID: 12 pills/day
- TVR TID: 6 pills/day
- RBV BID: 4-6 pills/day
- PegIFN: QW injection



■ Increased risks with nonadherence to triple therapy include potential for resistance

Lo Re V 3rd, et al. Ann Intern Med. 2011;155:353-360.

Case presentation 2

All Available	06Sep11 15:13
Since	
<input type="radio"/> Received <input checked="" type="radio"/> Performed	
10-Apr-2011	
One year ago	
<input type="checkbox"/> Retain for next patient	
Result Selection	
Infection	
<input checked="" type="checkbox"/> Display Category Headers	
<input type="checkbox"/> Abnormal <input type="checkbox"/> Show Pending	
New Results...	

Infection	
Infection	
Hepatitis C RNA IU/ml	*4358006*
Log Value.	* 6.64*

Base line

Case presentation 2

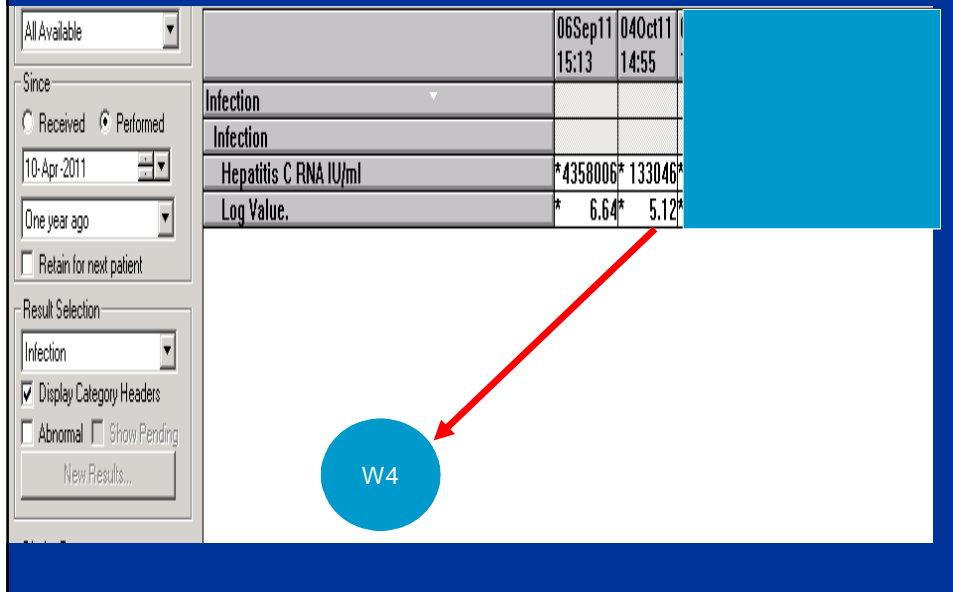
All Available

Since
 Received Performed
10-Apr-2011
One year ago
 Retain for next patient

Result Selection
Infection
 Display Category Headers
 Abnormal Show Pending
New Results...

	06Sep11 15:13	04Oct11 14:55
Infection		
Infection		
Hepatitis C RNA IU/ml	*4358006*	133046*
Log Value.	* 6.64*	5.12*

W4



Case presentation 2

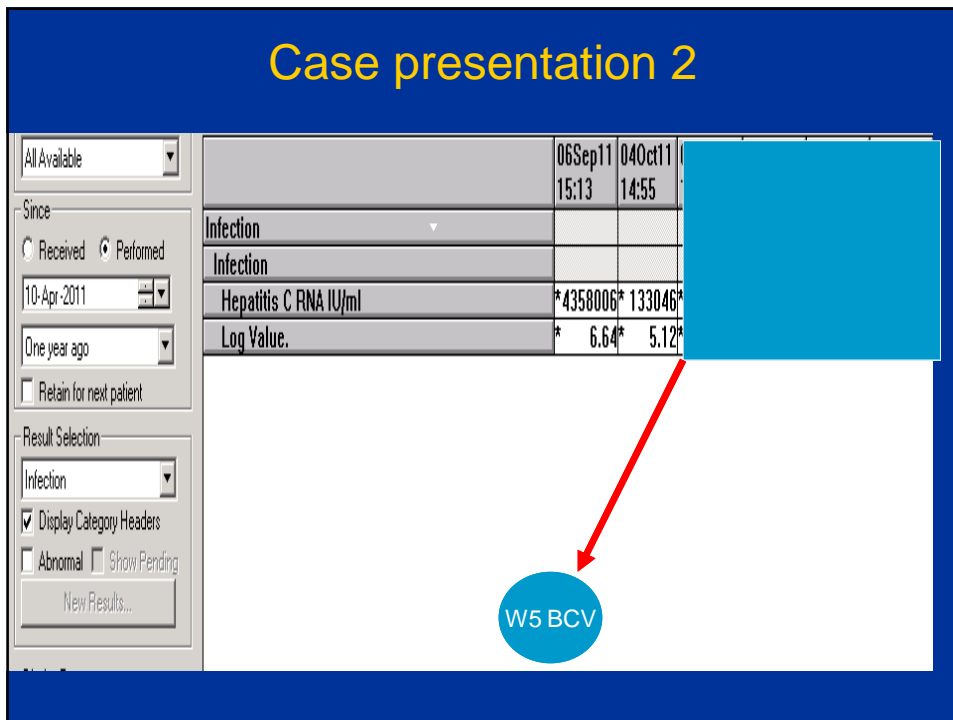
All Available

Since
 Received Performed
10-Apr-2011
One year ago
 Retain for next patient

Result Selection
Infection
 Display Category Headers
 Abnormal Show Pending
New Results...

	06Sep11 15:13	04Oct11 14:55
Infection		
Infection		
Hepatitis C RNA IU/ml	*4358006*	133046*
Log Value.	* 6.64*	5.12*

W5 BCV



Case presentation 2

	06Sep11 15:13	04Oct11 14:55	07Nov11 13:57	
Infection				
Hepatitis C RNA IU/ml	*4358006*	133046*	249*	
Log Value.	* 6.64*	5.12*	2.40*	

W8

Case presentation 2

	06Sep11 15:13	04Oct11 14:55	07Nov11 13:57	05Dec11 16:14	
Infection					
Hepatitis C RNA IU/ml	*4358006*	133046*	249*	35*	
Log Value.	* 6.64*	5.12*	2.40*	1.54*	

W12

Since
 Received Performed

Retain for next patient

Result Selection

Display Category Headers
 Abnormal Show Pending

	06Sep11 15:13	04Oct11 14:55	07Nov11 13:57	05Dec11 16:14	20Feb12 14:13
Infection					
Hepatitis C RNA IU/ml	*4358006*	133046*	249*	35*	9824*
Log Value.	*6.64*	5.12*	2.40*	1.54*	3.99*

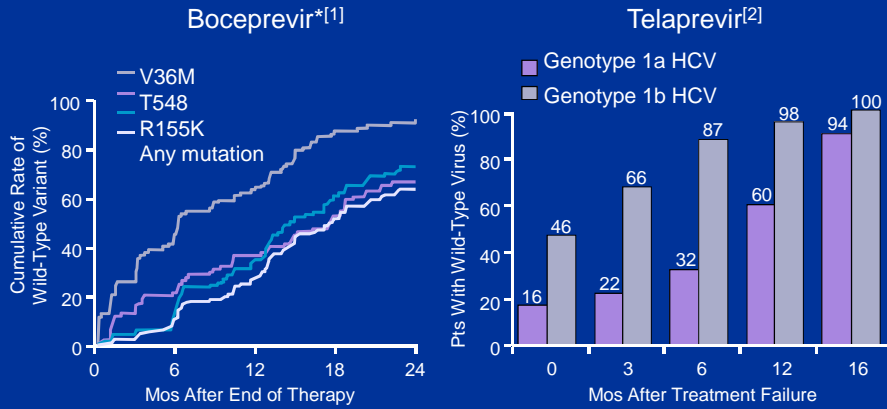
Treatment-Emergent Substitutions During PI-Based Therapy

- Pooled analyses of subjects who had on-treatment failure or relapse during clinical trials with boceprevir or telaprevir
 - Patterns of treatment-emergent substitutions varied by subtype 1a vs 1b

HCV Genotype 1 Subtype	Treatment-Emergent Substitutions	
	Telaprevir ^[1]	Boceprevir ^[2]
1a	V36M R155K Combination of V36M and R155K	V36M T54S R155K
1b	V36A T54A/S A156S/T	T54A/S V55A A156S I/V170A

1. Telaprevir [package insert], May 2011. 2. Boceprevir [package insert], May 2011.

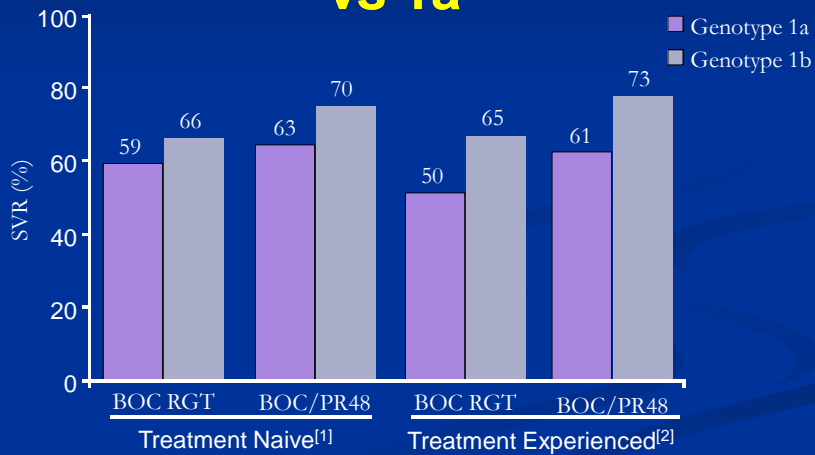
Loss of Detectable Resistance in Patients Stopping BOC or TVR + PegIFN/RBV



*Data from phase II studies.

Vierling JM, et al. EASL 2010. Abstract 2016. 2. Sullivan J, et al. EASL 2011. Abstract 8.

Higher SVR Rates With BOC in Patients With HCV Genotype 1b vs 1a



1. Poordad F, et al. N Engl J Med. 2011;364:1195-1206.
 2. Bacon BR, et al. N Engl J Med. 2011;364:1207-1217.

Futility Rules for BOC or TVR + PegIFN/RBV in Tx-Exp Patients

- Recommendation: All therapy should be discontinued in patients with the following:

BOC ^[1,2]		
Time Point	Criteria	Action
Wk 12	HCV RNA \geq 100 IU/mL	Discontinue all therapy
Wk 24	HCV RNA detectable	Discontinue all therapy

TVR ^[1,3]		
Time Point	Criteria	Action
Wk 4 or 12	HCV RNA > 1000 IU/mL	Discontinue all therapy
Wk 24	HCV RNA detectable	Discontinue pegIFN/RBV

Assay should have a lower limit of HCV RNA quantification of \leq 25 IU/mL and a limit of HCV RNA detection of approximately 10-15 IU/mL.

- Boceprevir [package insert]. May 2011.
- Ghany MG, et al. Hepatology. 2011;54:1433-1444.
- Telaprevir [package insert]. May 2011.

Coadministration of ARVs & HCV PIs

Telaprevir	Boceprevir
ARVs That Can Be Used^[1,2]	ARVs That Can Be Used^[3,4]
<ul style="list-style-type: none"> ATV/RTV EFV* TDF/FTC† RAL^[5] 	<ul style="list-style-type: none"> MVC NRTIs RAL
ARVs That Are Contraindicated/Not Recommended	
<ul style="list-style-type: none"> DRV/RTV FPV/RTV LPV/RTV 	<ul style="list-style-type: none"> EFV RTV-boosted PIs^[6]
ARVs for Which Data Are Lacking	
<ul style="list-style-type: none"> RPV EVG/COBI 	

*Increase TVR dose to 1125 mg q8.

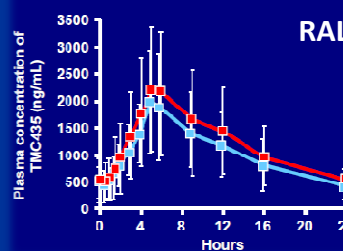
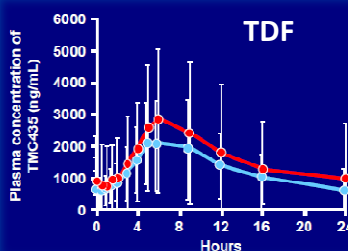
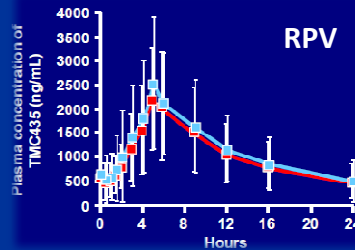
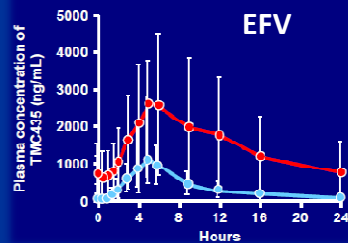
†Monitor for TDF toxicity.

1. Telaprevir [package insert]. 2011. 2. Sulkowski M, et al. CROI 2011. Abstract 146LB.

3. Boceprevir [package insert]. 2011. 4. Sulkowski M, et al. IDSA 2011. Abstract LB-37.

5. Van Heeswijk R, et al. ICAAC 2011. Abstract A-1738a. 6. Dear HCP letter 3 Feb 2012.

TMC 435 drug-drug interactions with ARV's



British HIV Association
BHIVA

Helpful Drug-Drug Interaction Resource

www.hep-druginteractions.org

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Meeting Report - 6th International Workshop on Hepatitis Clinical Pharmacology

New Drugs - Danoprevir and ritonavir

Drug Interactions - Studies with telaprevir and boceprevir.

FDA News - Telaprevir and Boceprevir

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SITE UPDATES

Boceprevir and Telaprevir
Boceprevir and telaprevir have been added as columns to the interaction charts. Where an interaction...

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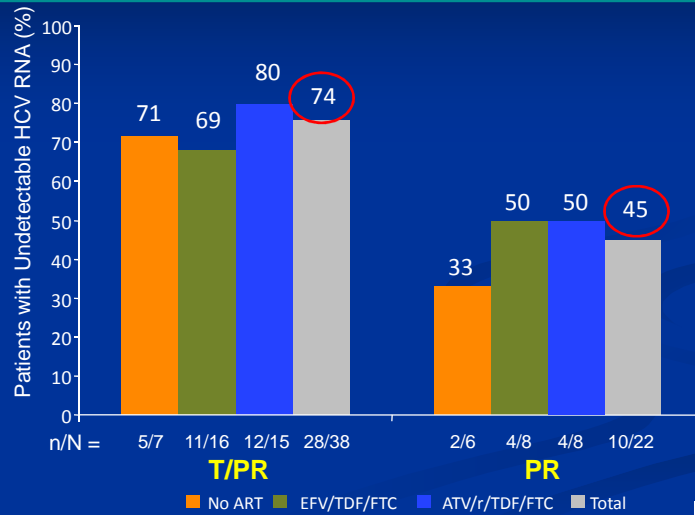
Please add notes@hep-druginteractions.org and hivgroup@liv.ac.uk to your address book to assist in uninterrupted delivery and check your SPAM or BULK folder to ensure emails are not being lost.

INTERACTIONS WITH TELAPREVIR AND BOCEPREVIR

Telaprevir & Boceprevir - INTERACTIONS NOW FULLY LISTED

Telaprevir and boceprevir were licensed by the FDA in May and have been added as columns to the interaction charts. To view the interactions, click on the drug interaction chart section above.

Study 110: SVR Rates 12 Weeks Post-Treatment (SVR12)

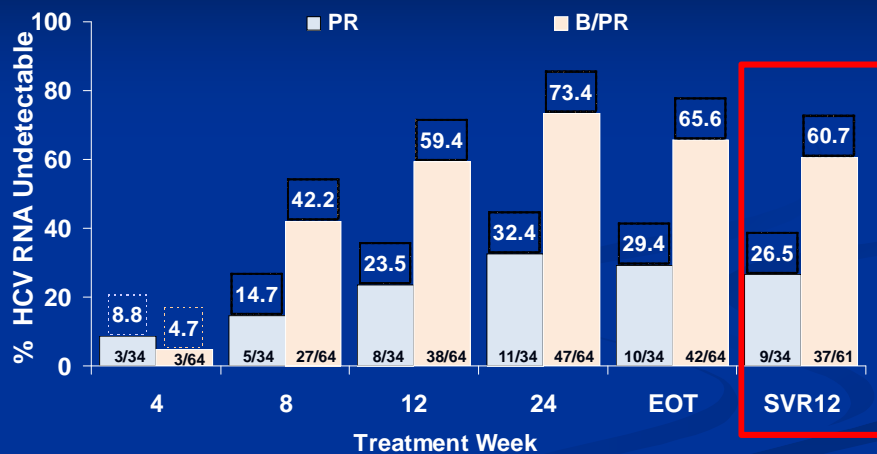


* Patient was defined as SVR12 if HCV RNA was < LLOQ in the visit window

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Dieterich D, et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 46

Virologic Response Over Time†- up to 12 Weeks Post-Treatment (SVR12)

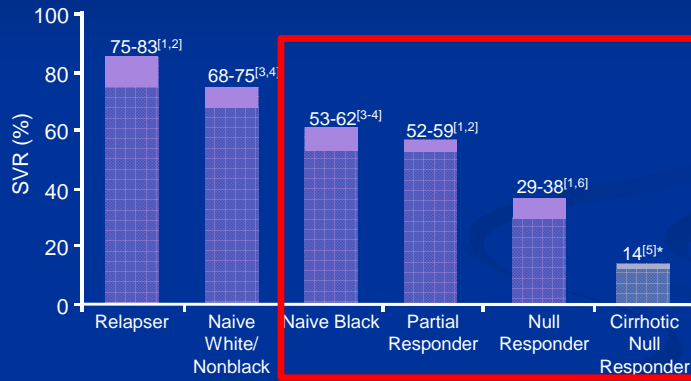


† Three patients undetectable at FW4 have not yet reached FW12 and were not included in SVR12 analysis.

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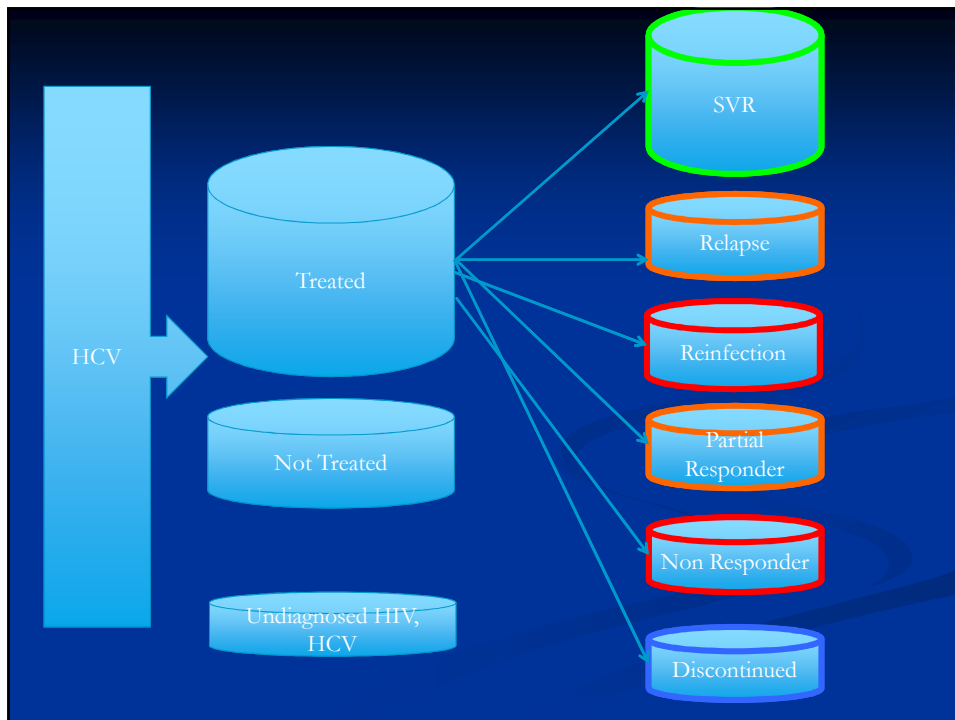
Sulkowski M et al., 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 47

Telaprevir and Boceprevir SVR by Patient Type



*Pooled TVR arms of REALIZE trial.

1. Zeuzem S, et al. N Engl J Med. 2011;364:2417-2428.
2. Bacon BR, et al. N Engl J Med. 2011;364:1207-1217.
3. Jacobson IM, et al. N Engl J Med. 2011;364:2405-2416.
4. Poordad F, et al. N Engl J Med. 2011;364:1195-1206.
5. Zeuzem S, et al. EASL 2011. Abstract 5.
6. Vierling JM, et al. AASLD 2011. Abstract 931.



Team involved in HIV-HCV co-infection patient care



HCV DAA Challenges

- DDI, ARV choices
- Adherence
- Resistance
- IL28B
- Liver fibrosis assessment
- Treat or delay – Debate
- Co morbidity management
- Advanced liver disease – co infection clinics
- Re infection / Prevention

Thank you

BHIVA AUTUMN CONFERENCE

including

CHIVA Parallel Sessions

4–5 October 2012

QUEEN ELIZABETH II CONFERENCE CENTRE
LONDON

preceded by

**Fifth Annual BHIVA Conference
for the Management of HIV/Hepatitis Co-infection**

Wednesday 3 October 2012
One Great George Street Conference Centre, London