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

British HIV Association
BHIVA

Dr Sanjay Bhagani

Royal Free Hospital, London

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

This house believes that patients with HIV/HCV co-infection should be treated with Peg-IFN containing triple therapy regimens rather than wait for IFN-free therapy

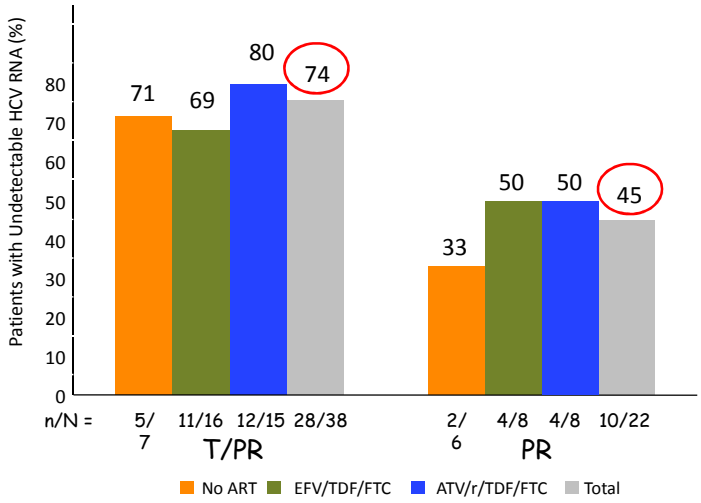
NO!!!!!

Sanjay Bhagani
Royal Free London & UCL

UCL

Royal Free Hampstead NHS
NHS Trust

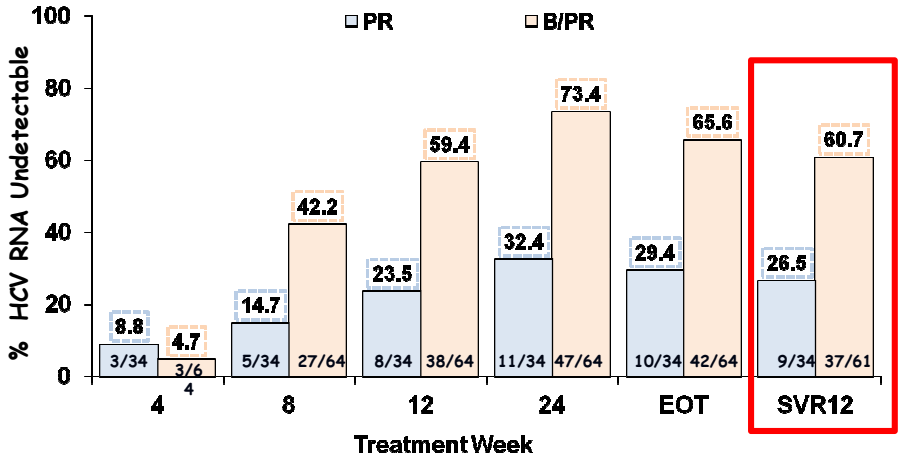
Study 110: SVR Rates
12 Weeks Post-Treatment (SVR12)



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

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.

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

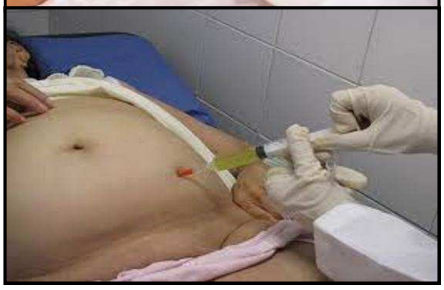
Let's examine this in the real-world context….

- Study 110 – 3 patients F3/F4 fibrosis
- BOC study – 6 patients F4 fibrosis

- TVR – 2 tablets tds with fatty food
- BOC – 4 tablets tds
- 48 weeks of therapy in total

- Significant drug-drug interactions…
  BOC – EFV and all boosted PIs
  TVR – EFV (increased dose), all boosted PIs except ATV/r
  BI 201335 – All boosted-PIs except Darunavir/r
  TMC435 – No data with boosted PIs

Interferon is evil…then add the significant side-effects of the third regimen….



- BOC – anaemia
- TVR – anaemia, rash, ano-rectal pain…
- TMC435 – hyperbilirubinaemia
- BI201335 – sun hypersensitivity, hyperbilirubinaemia

- Significant side-effects…….
  TVR – 45% discontinued Rx
  BOC – 38% discontinued Rx

- 35-50% SAEs in the French EAP for BOC/TVR +PegIFN/Riba in patients with cirrhosis (EASL 2012)

So who will be able to have PI-based triple therapy with significant SVRs

Who needs treatment?

- Fibrosis

  F0/1 F2 F3 F4

- Genotype

  1 2/3 4

- Prior Rx with PegIFN/Ribavirin

  Naive Partial Relapse Null

Who needs treatment as a matter of priority?

- Fibrosis

  F0/1 F2 **F3 F4**

- Genotype

  1 2/3 4

- Prior Rx with PegIFN/Ribavirin

  Naive Partial Relapse Null

Who will currently available triple therapy be effective for?

- Fibrosis

  F0/1 | F2 | F3 | F4

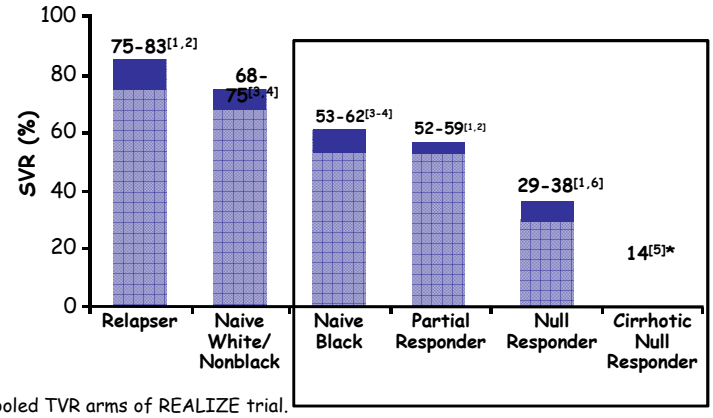
- Genotype

  1 | 2/3 | 4

- Prior Rx with PegIFN/Ribavirin

  Naive | Partial | Relapse | Null

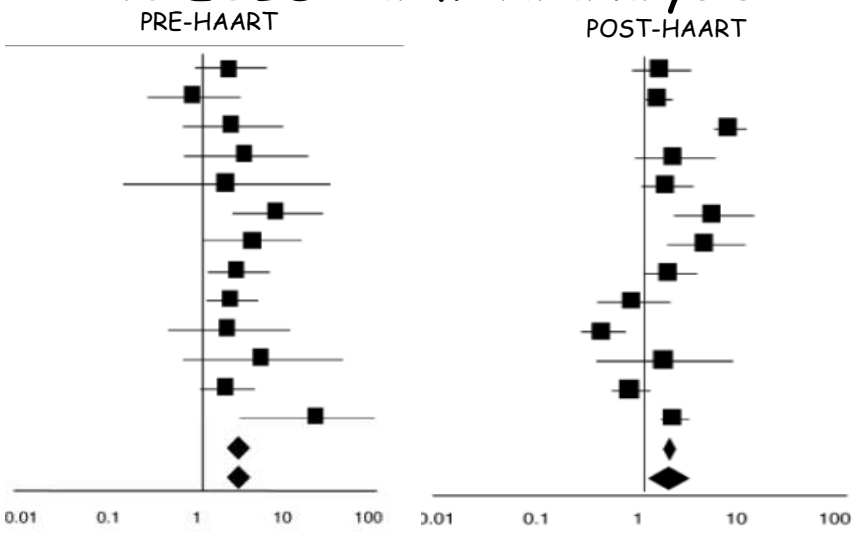
Telaprevir and Boceprevir SVR in GI mono-infected by patient type



*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.

Effect of HAART on progression to ESLD – a meta-analysis



Thien, H et al. AIDS 2008; 22: 1979-1991

So what's in the pipeline?

NS3/4A Protease Inhibitors	NS5B Polymerase Inhibitors		NS5A Inhibitors	Cyclophilin A Inhibitors
	Nucleos(t)ide Analogue	Non-nucleos(t)ide		
• High efficacy • Low genetic barrier to resistance • Macrocyclic or linear • Phase III: BI 201335, TMC435	• 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	• Bind to several different allosteric enzyme sites; results in conformational change • Resistance more frequent than nucs • Several agents in phase I/11	• NS5A has role in assembly of replication complex • Mechanism of inhibition under study • Phase III: Daclatasvir (BMS-790052)	▪ Supports HCV-specific RNA replication, protein expression ▪ Interacts with NS2, NS5A, NS5B ▪ May regulate polypeptide processing, viral assembly ▪ Phase III: Alisporivir

Is IFN-free therapy all a pipedream?

IFN-free pipeline

Drug 1	Drug 2	Drug 3	RBV
BI 201335	BI 207127	N/A	±
GS-7977	GS-938	N/A	±
ABT-450/ RTV	ABT-333 or ABT-072	N/A	+
GS-7977	Daclatasvir	N/A	±
GS-9256	Tegobuvir	N/A	±
GS-9451	GS-5885	± Tegobuvir	±
Asunaprevir	Daclatasvir	BMS-791325	N/A

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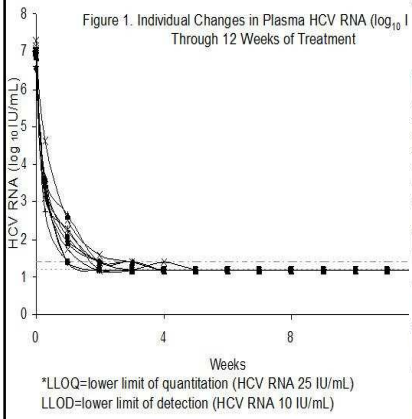

Table: Baseline Demographics and RVR, SVR_4, and SVR_{12} rates (Intent to Treat)

	Arm 1: Treatment-naive ABT-450/r 250/100 mg + ABT-333 400 mg + RBV N=19	Arm 2: Treatment-naïve ABT-450/r 150/100 mg + ABT-333 400 mg + RBV N=14	Arm 3: Previous non-responders* ABT-450/r 150/100 mg + ABT-333 400 mg + RBV N=17
Baseline Demographics and Disease Characteristics			
Male, n (%)	10 (52.6)	14 (100)	11 (64.7)
White, n (%)	15 (78.9)	12 (85.7)	13 (76.5)
Age, Years, Mean ± SD	53.6 ± 9.78	50.9 ± 10.45	52.3 ± 9.03
BMI, kg/m², Mean ± SD	27.3 ± 3.84	24.6 ± 3.08	28.3 ± 5.11
HCV Genotype 1a, n (%)	17 (89.5)	11 (78.6)	16 (94.1)
IL28B CC Genotype, n (%)	10 (52.6)	5 (35.7)	0
Baseline HCV RNA, log_{10} IU/mL, Mean ± SD	6.25 ± 0.80	6.44 ± 1.15	6.93 ± 0.47
Virologic Results			
RVR: HCV RNA <25 IU/mL at Week 4, n (%)	19 (100)[a]	13 (92.9)[b]	15 (88.2)
SVR_4: HCV RNA <25 IU/mL 4 Weeks After End of Treatment, n (%)	18 (94.7)	13 (92.9)	8 (47.1%)[c,d]
SVR_{12}: HCV RNA <25 IU/mL 12 Weeks After End of Treatment, n (%)	18 (94.7)	13 (92.9)	8 (47.1%)

*6 subjects were null responders and 11 subjects failed to achieve undetectable HCV RNA at the end of treatment (partial responders). 3/6 null responders and 5/11 partial responders achieved SVR_{12}.
[a]1 subject discontinued due to ALT and AST elevation; [b]1 subject discontinued due to inability to comply with study drug regimen ; [c]6 subjects had viral breakthrough; [d]3 subjects relapsed

EASL 2012, IFN-Free Abbott studies. ABT-450/r + ABT-333 or ABT-072 + RBV 12 weeks for G1 patients. SVRs – >90%

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Drug 1	Drug 2	RBV	Comments	SVR
BI 201335	BI 207127	±	G1a non-CC G1b/1a-CC	68% 82%
ABT-450/ RTV	ABT-333	+	Naïve Null	94.7% 47.1%
GS-7977	Daclatasvir	±	97% <LLOD	
Asuneprevir	Daclatasvir	--	G1b Null	90%
Danoprevir/RTV	Merticitabine	+	SVR8	71%
GS-7977	N/A	+	G1 Naïve SVR4	88%

- BMS – Daclatasvir + Asunaprevir 24 weeks in G1b Null Responders – 90% SVR12
- GS/BMS – GS-7977 + Daclatasvir 24 weeks - G1/2/3 – 97% <LLOD after 12 weeks
- GS – Electron study, final results of SVR12, G1 12 weeks GS-7977 + Ribavirin
- Roche – INFORM-SVR – Danoprevir/R + Merticibine + Ribavirin 24 weeks – 71% SVR8

March 2012 – FDA 'pronounces' on IFN-free DAA studies

Phase 3 Considerations: Naives

- **Study "all comers"**
  - **Need to ensure that intolerant are not really nulls**
  - **Difficult (impossible) to randomize to an IFN-containing control**
- **INF-free regimens**
  - **Single arm/historical control depending on supporting Phase 2 data and likely only applicable for shorter term regimens (12 weeks or less)**
  - **NI vs. current SOC (whatever it is at the time)**
  - **Immediate vs. deferred PBO controlled**
- **Include a rescue strategy**
  - **May be challenging in IFN contraindicated**
- **Even if regimen is somewhat less effective, may be approvable if shorter duration, improved safety, and/or IFN-sparing**

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Phase 3 Considerations: Experienced

- **Need to maximize response**
  - **Limited options for retreatment of DAA failures**
- **IFN-free regimens**
  - **Historical control (until a regimen is approved)**
- **IFN-containing regimens**
  - **Nulls - Historical control**
  - **Partial responders - if Phase 2 data is robust, active control may not be necessary or feasible**

HIV/HCV Co-Infected

- Strongly encourage data at time of NDA submission
  - Drug-drug interaction with commonly used HIV drugs prior to dosing in co-infected
    - Need to understand how to use drugs together
  - Safety data
  - Efficacy data to assess SVR and Relapse
- To expand indication to co-infected
  - ~300 subjects treated with regimen
    - Trial design based on preliminary data and other available treatments
    - Endpoint SVR12
    - Safety evaluation includes loss of HIV efficacy

HCV Rx landscape – the future?

·pIFN + R + PI for Urgent Need
·pIFN + R (g3/g2 + acute HCV)

·Monitor frequently
·Early HAART
·Clinical Trials

IFN-alpha Historical therapy!

2011 2012 2013 2014 2015 2016 2017 2018

Use of IL28B
P/R lead-in phase
Response guided therapy

First line
1 or 2 DAA +/- R
2 or 3 DAAs

2nd Line
2DAAs + P+R

So, Dr Nelson…


A person who has committed a mistake and doesn't correct it is committing another mistake!
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