Actualizacion de la terapia de la hepatitis C en pacientes coinfectados por VIH

VII Curso Avances en Infeccion VIH y Hepatitis Virales

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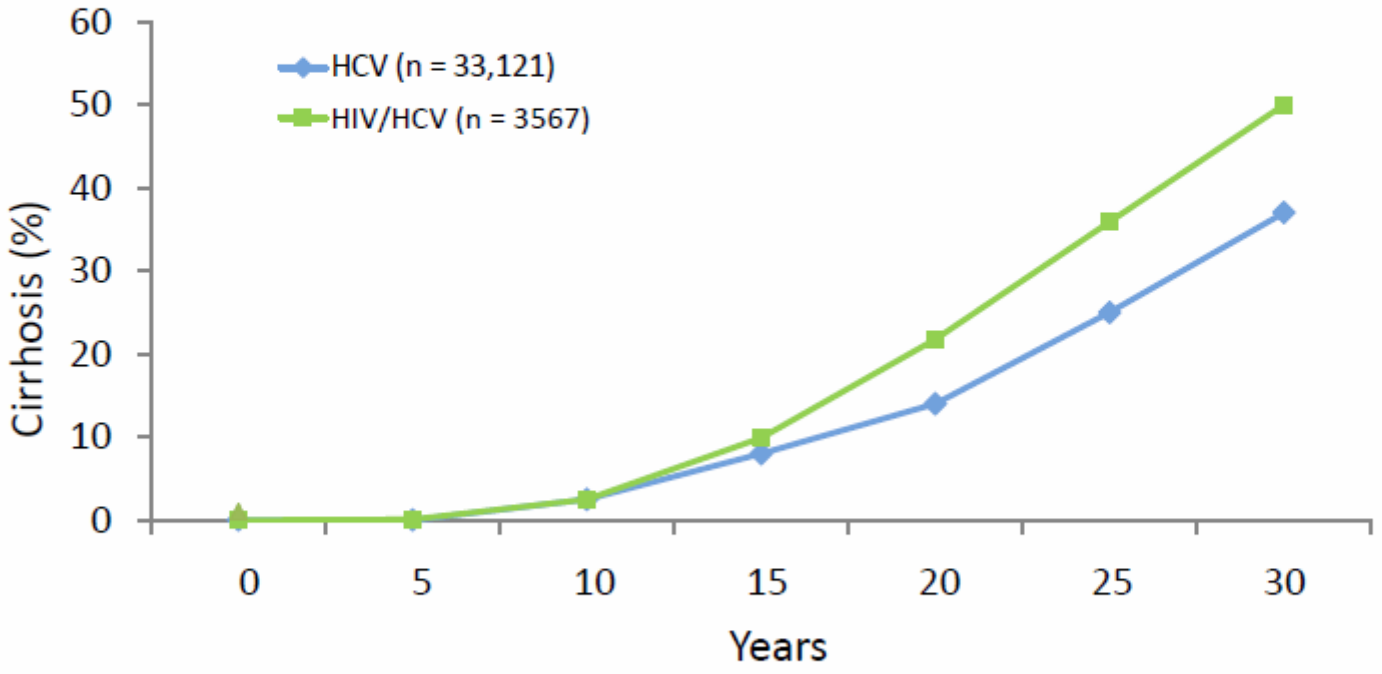
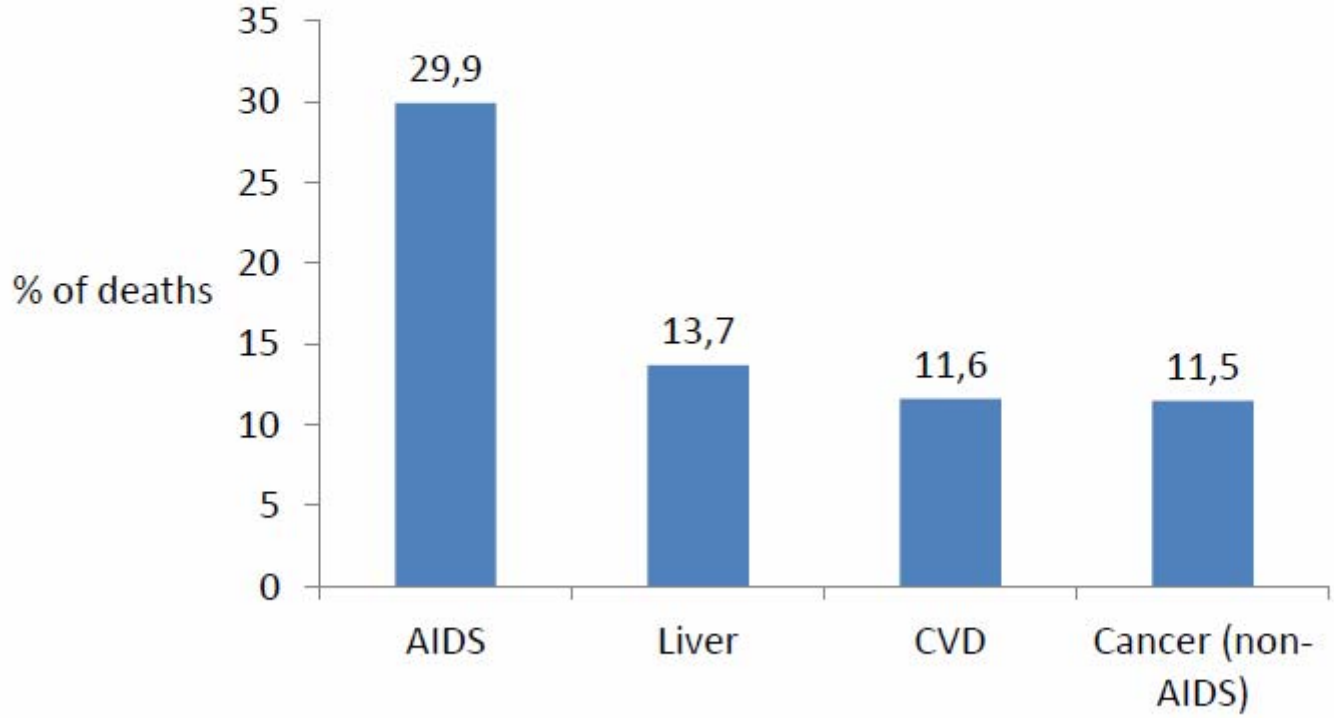
Impact of HIV on HCV-related Liver Disease Progression



Thein H-H et al. AIDS. 2008;22:1979-1991.
Thein H-H et al. Hepatology. 2008;48:418-431.

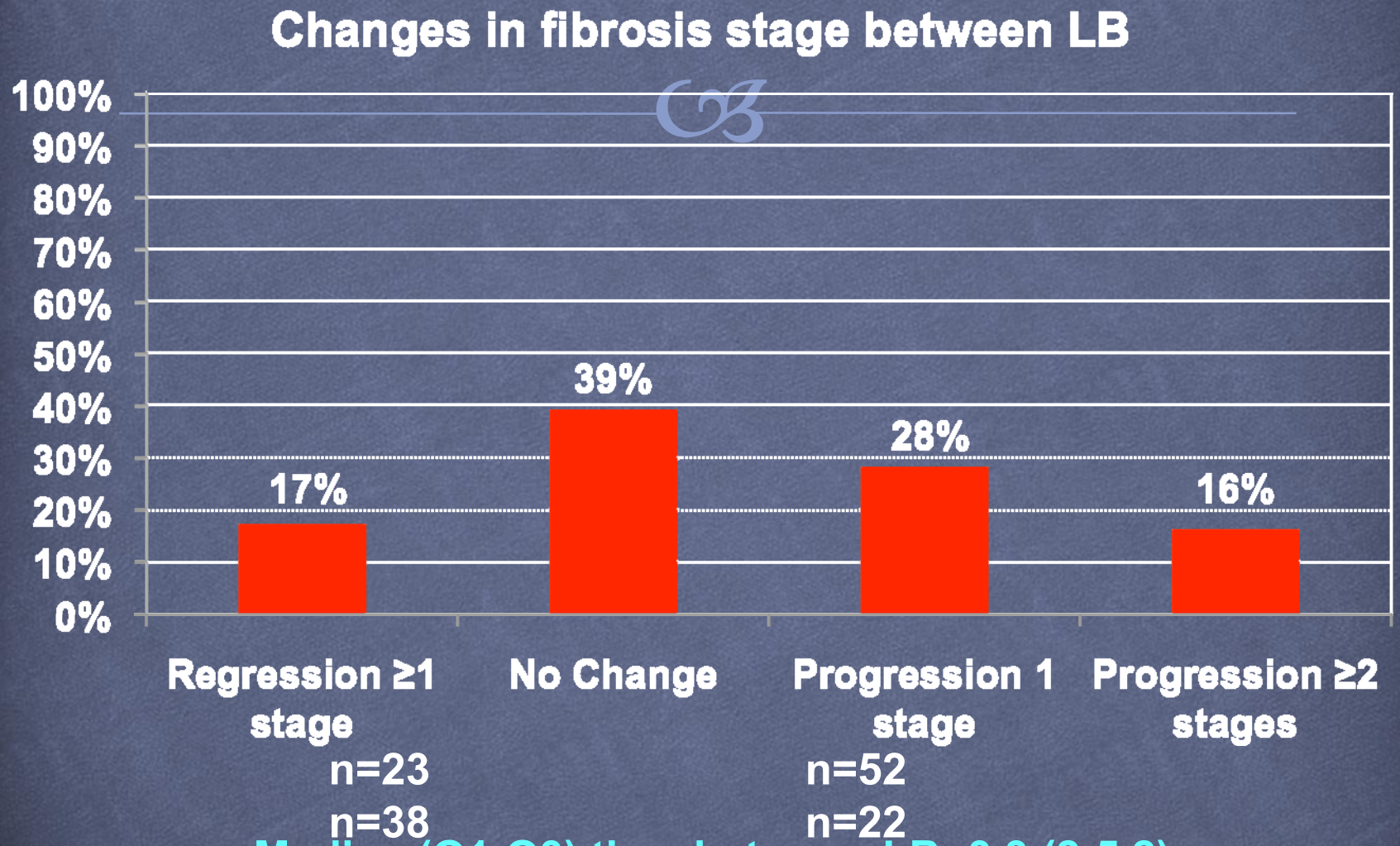
Liver disease is the second leading specific causes of death amongst HIV-positive individuals in the D:A:D study



AIDS. 2010 Jun 19;24(10):1537-48.

Fibrosis progression

Paired liver biopsy study (n=135)



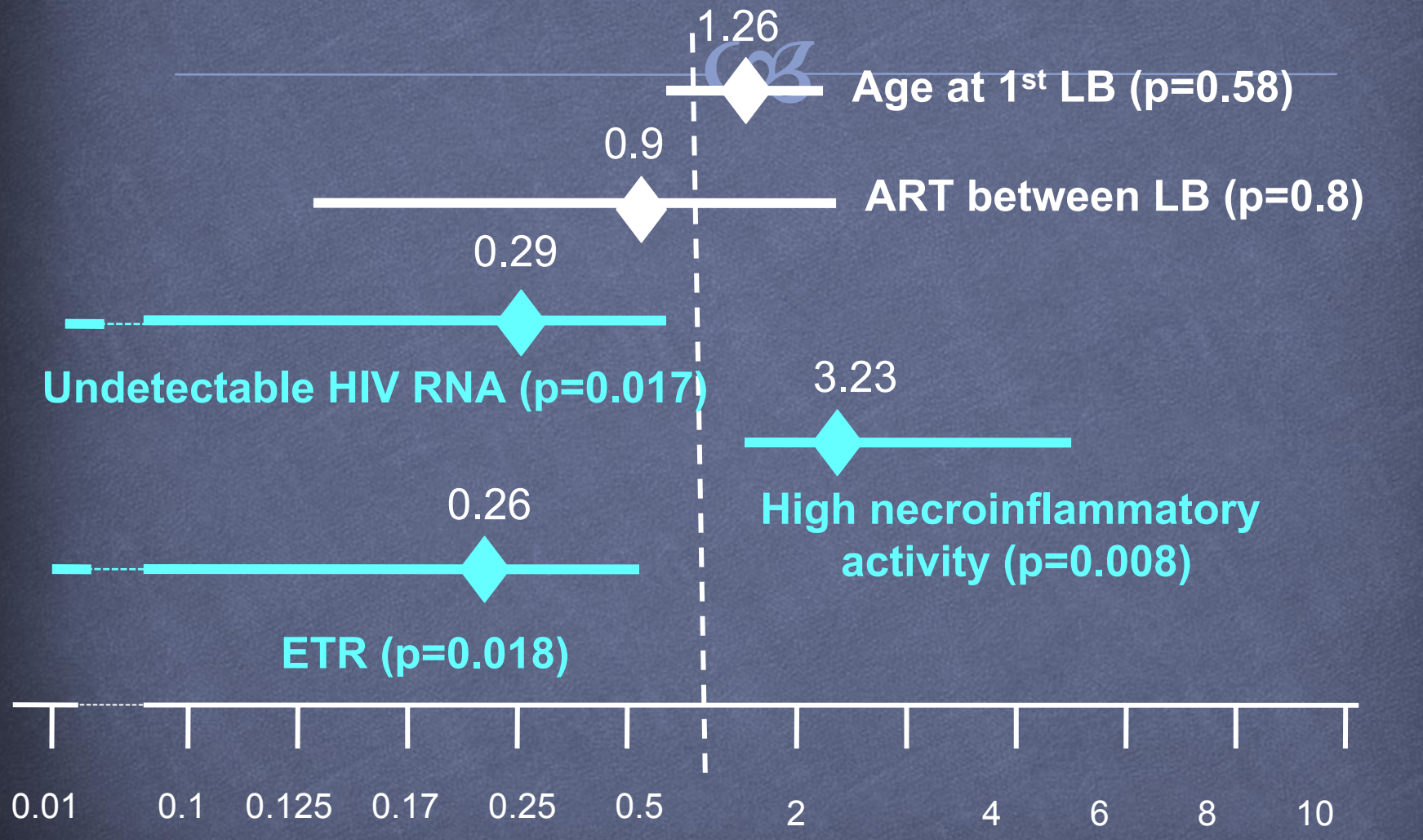
Median (Q1-Q3) time between LB: 3.3 (2-5.2) years

Macías et al. Hepatology 2009

Fibrosis progression

Odds of increasing ≥1 stage

Adjusted Odds Ratio (95% Confidence Interval)

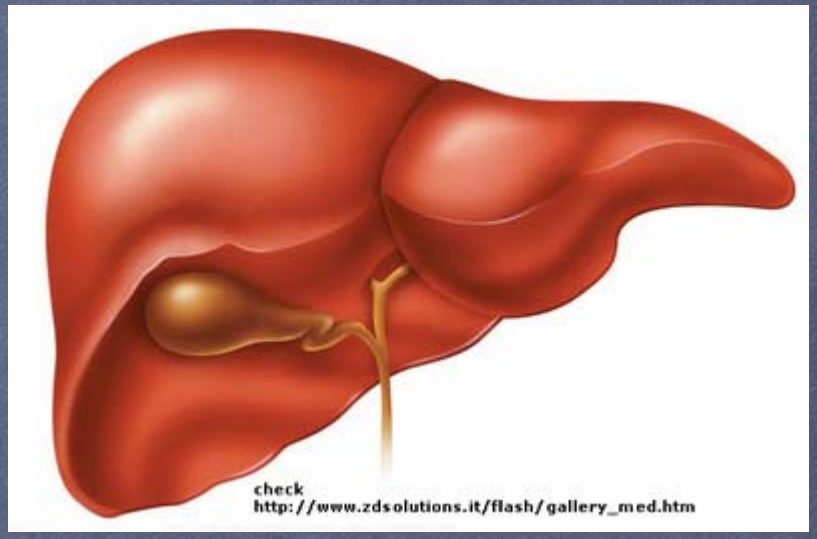


Macías et al. Hepatology 2009

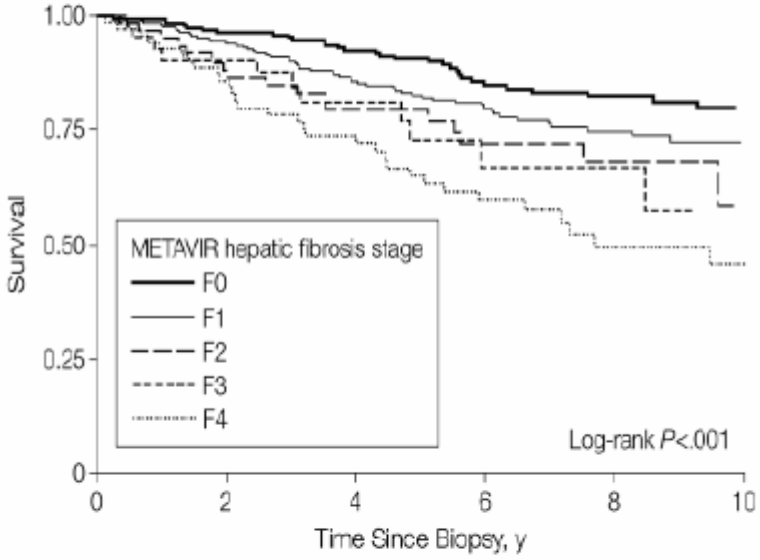
ART & liver fibrosis progression

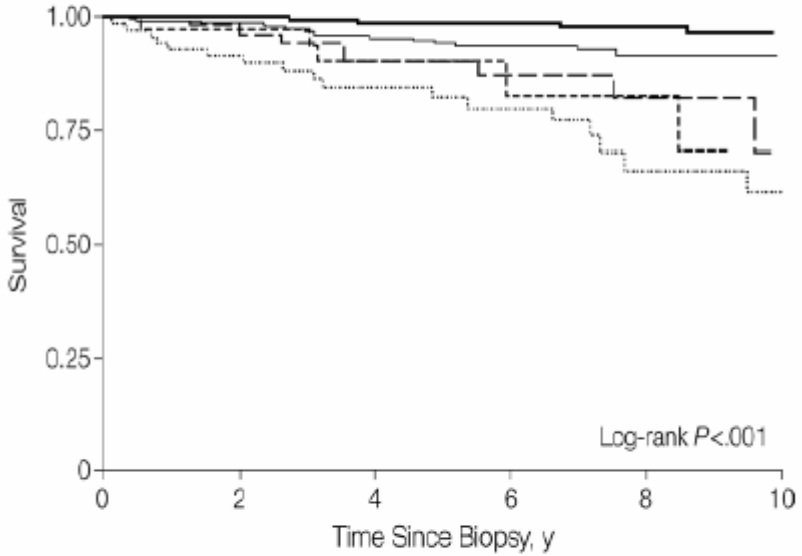
Start ART early in HIV/HCV-coinfected patients…

…but don't expect that fibrosis progression is stopped by ART.



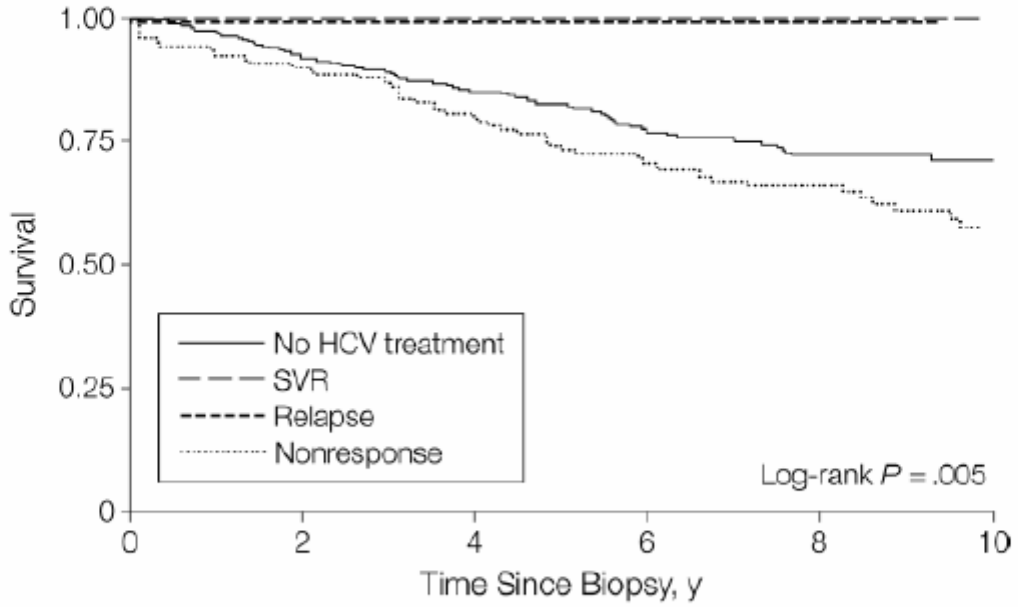
Time to death, ESLD or HCC among 638 HIV/HCV coinfected adults prospectively followed after liver biopsy





JAMA. July 25, 2012,308(4):370-378

HCV suppression during or eradication following treatment was associated with survival



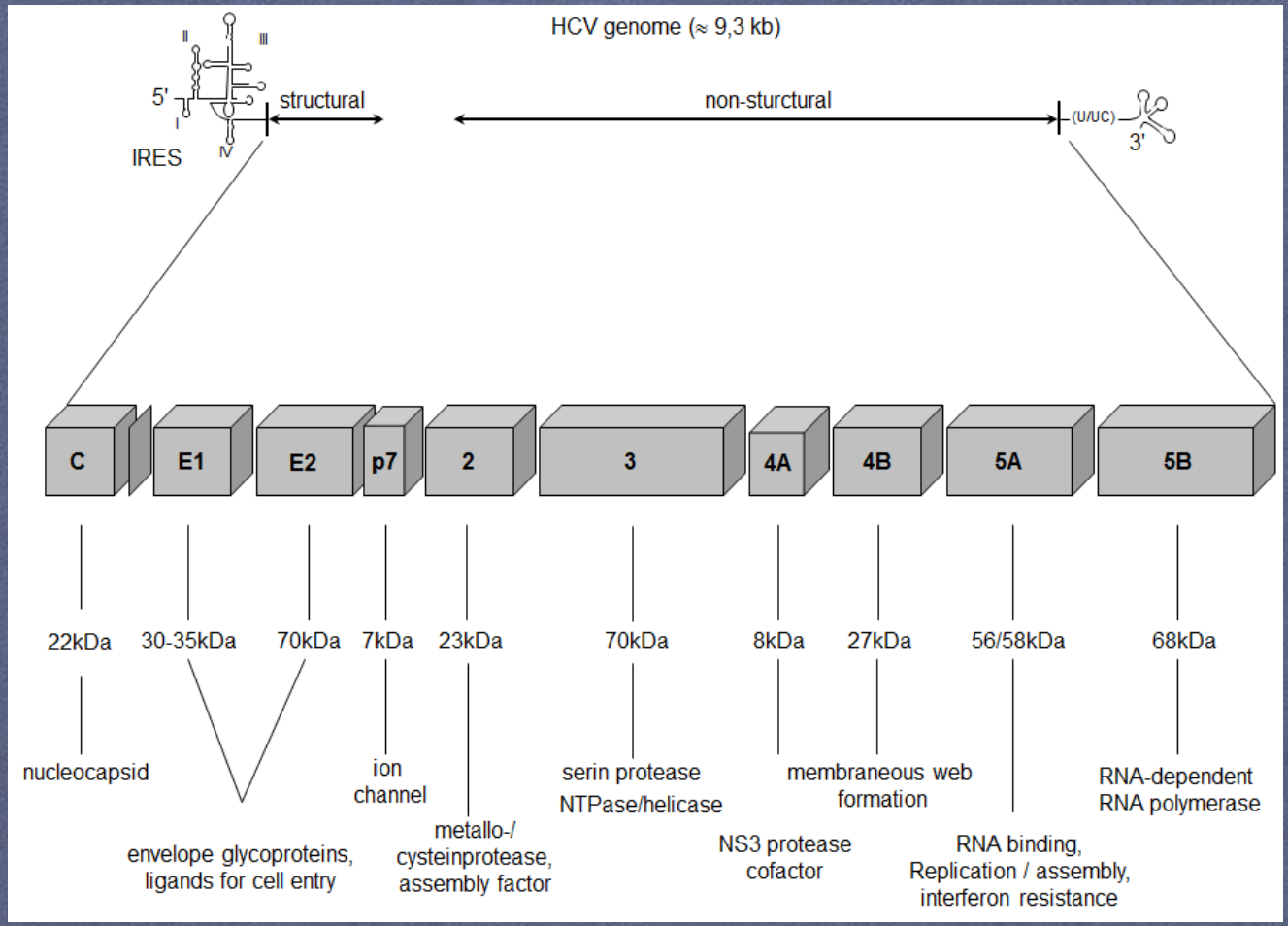
JAMA. July 25, 2012,308(4):370-378

PegIFN/RBV for HCV infection in HIV-coinfected patients

Study	Regimen	SVR (%) G1 or G4	SVR (%) G2 or G3	Take home observations
RIBAVIC[1] France (N = 412)	Peg-IFN α-2b RBV 800 mg	17	44	Low-dose RBV Toxicity with ddI + RBV Failure to suppress HCV RNA at week 4 <460,000 IU/mL → 100% NPV
Laguno et al[2] Spain (N =182)	Peg-IFN α-2b RBV 800 – 1200 mg	28	62	Weight-based RBV → higher SVR Short (24-week) therapy for genotype 2/3 not effective
ACTG A5071[3] USA (N = 133)	Peg-IFN α-2a RBV 600 - 1000 mg	14	73	Low-dose RBV Failure to achieve week 12 EVR → 100% NPV ZDV + RBV → more anemia
APRICOT[4] International (N = 868)	Peg-IFN α-2a RBV 800 mg	29	62	Low-dose RBV Decompensation with advanced fibrosis Genotype 1/High HCV RNA –18% SVR
PRESCO[5] Spain (N = 389)	Peg-IFN α-2a RBV 1000 – 1200 mg	35	72	Weight-based RBV → higher SVR No increase in anemia Long (72-week) therapy not well tolerated

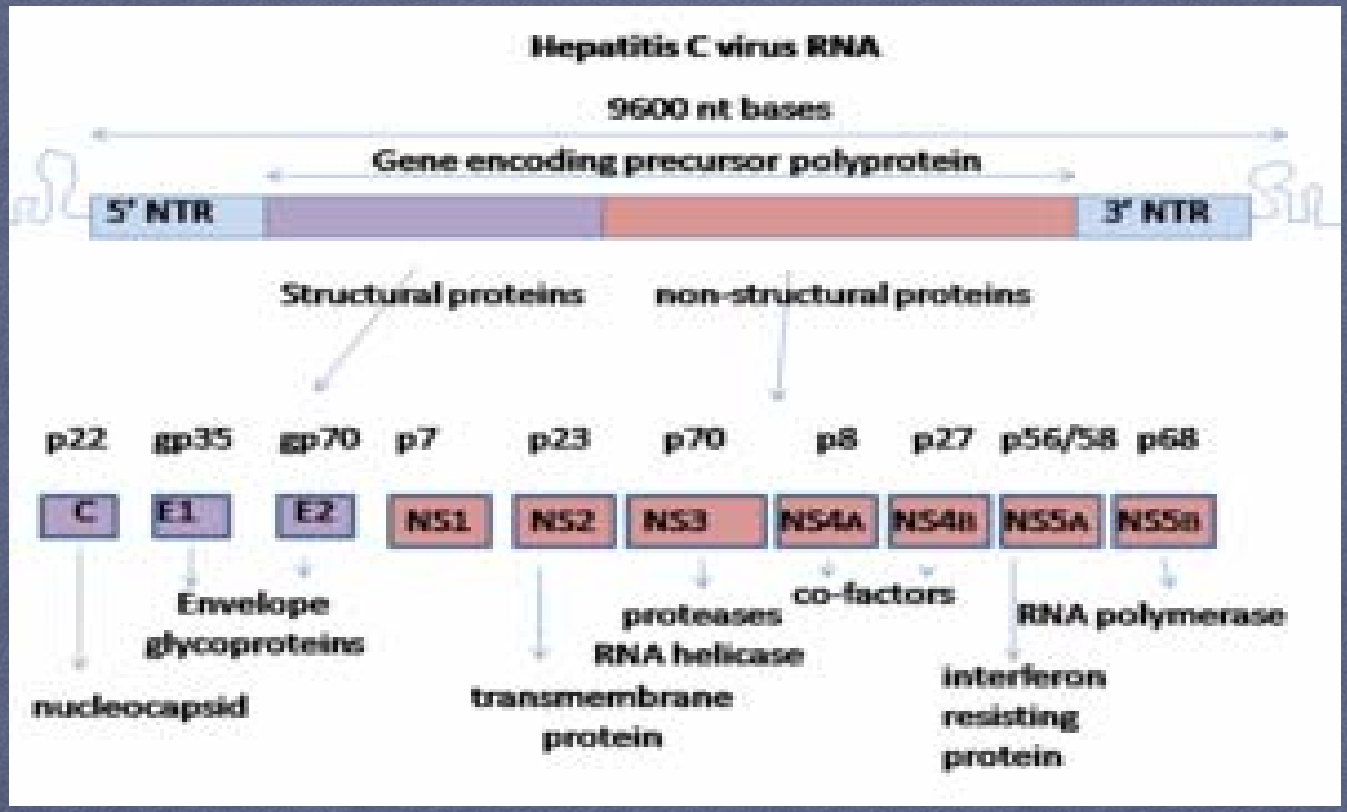
Response to treatment in G1 with P/R

Genomic Organization of HCV

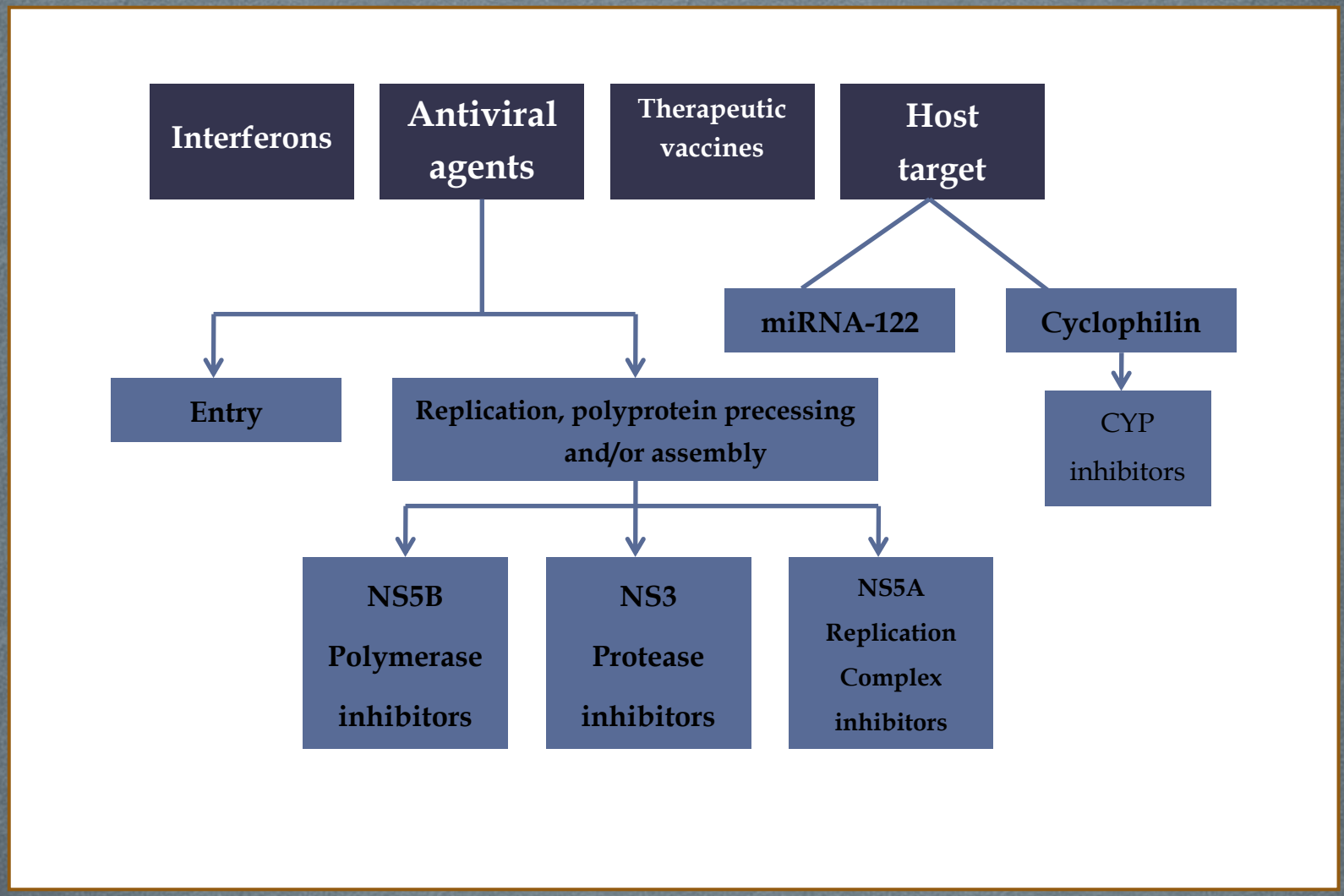


Adapted from Lange, Sarrazin. Hepatology 2012; 239-61

Genomic Organization of HCV



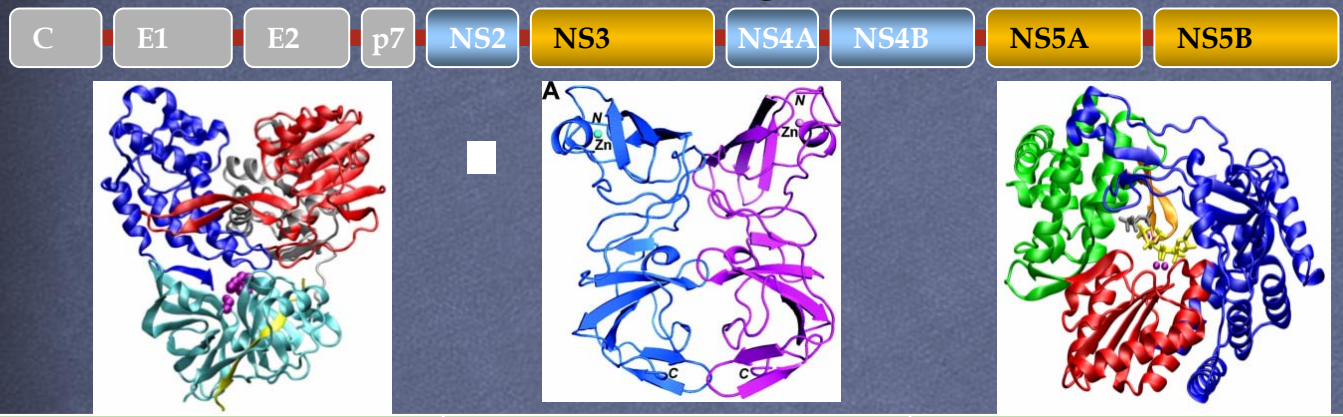
Classes of New Agents for the Treatment of HCV



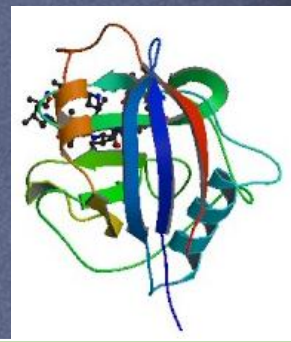
(Adapted from Nelson DR. 2012 Annual Update. CCO)

Understanding of HCV life cycle revealed several potential innovative drug targets

Viral targets



Host targets



NS3	NS5A	NS5B	Cyclophilin A
The NS3/4A serine protease is essential for post-translational processing of HCV polyproteins[1]	Multifunctional membrane-associated phosphoprotein essential component of the HCV-RNA replication complex[2,3]	NS5B is an HCV-specific, RNA-dependent RNA polymerase[1]	Host protein involved in HCV replication through interaction with NS5A and the HCV polymerase[4]
Boceprevir **Telaprevir** ABT-450/r, ACH-1625 Asunaprevir, TMC-435 (Simeprevir), BI-201335 Danoprevir/r, GS-9451 MK-5172	Daclatasvir GS-5885 ABT-267 PPI-668	<u>Nucleos(t)ide analogue</u> GS-7977, Mericitabine, IDX-184* <u>Non-nucleoside analogue</u> BI-207127, ABT-333 ABT-072, BMS-791325 Tegobuvir, Setrobuvir VX-222, Filibuvir	Alisporivir** SCY-635

*On clinical hold, Idenix press release; **On clinical hold, Novartis press release

Adapted from 1. Pawlotsky JM, et al. *Gastroenterology* 2007;132:1979–98; 2. Tellinghuisen TL, et al. *Nature* 2005;435:374–9; 3. Gish R & Meanwell NA. *Clin Liver Dis*. 2011;15:627–39; 4. Coelmont L, et al. *PLoS One* 2010;5:e13678

Phase 2 studies of HCV PI + PR

	Telaprevir	Boceprevir
Number	TVR, 38; Control, 22	BOC, 64; Control, 34
HCV population	Naïve, genotype 1	Naïve, genotype 1
HIV population	CD4 ≥500; HIV ≤100,000 c/mL CD4 ≥ 300; HIV ≤50 c/mL	CD4 ≥ 200 cells/mm^3 HIV RNA <50 c/mL
ART	None (n=7) EFV (n=16) or ATV/r (n=15) + TDF/FTC	No NNRTIs ATV/r, (n=20); DVR/r (n=16); DRV/r (n=12); RAL(n=11)
HCV regimen	TLV 750 mg Q8H or 1125 mg Q8H (if EFV co-admin) + pegIFN-2a + RBV 800 mg/day	BOC 800 mg Q8H + pegIFN-2b + weight based RBV (600–1400 mg/day)
Lead-in	No	Yes
Duration of PI	12 weeks	44 weeks
Duration of PR	48 weeks	48 weeks

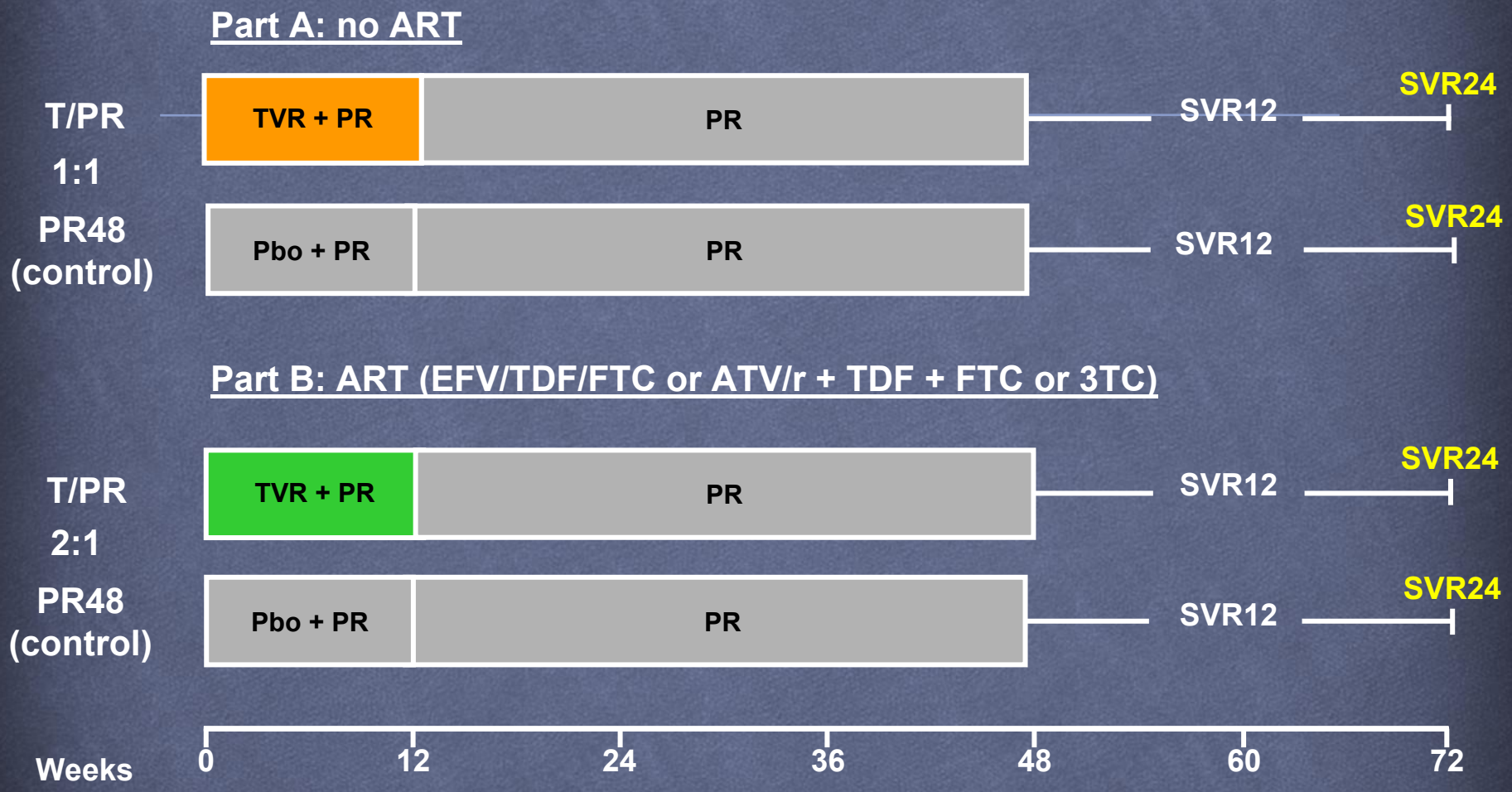
Telaprevir in Combination with Peginterferon Alfa-2a/Ribavirin in HCV/HIV Co-infected Patients: SVR24 Final Study Results

Mark S. Sulkowski[1], Kenneth E. Sherman[2], Vincent Soriano[3], Jürgen K. Rockstroh[4], Douglas T. Dieterich[5], Pierre-Marie Girard[6], Mohammad Bsharat[7], Joshua Henshaw[7], Raymond A. Rubin[7], Varun Garg[7], Nathalie Adda[7]

On behalf of the Study 110 Team

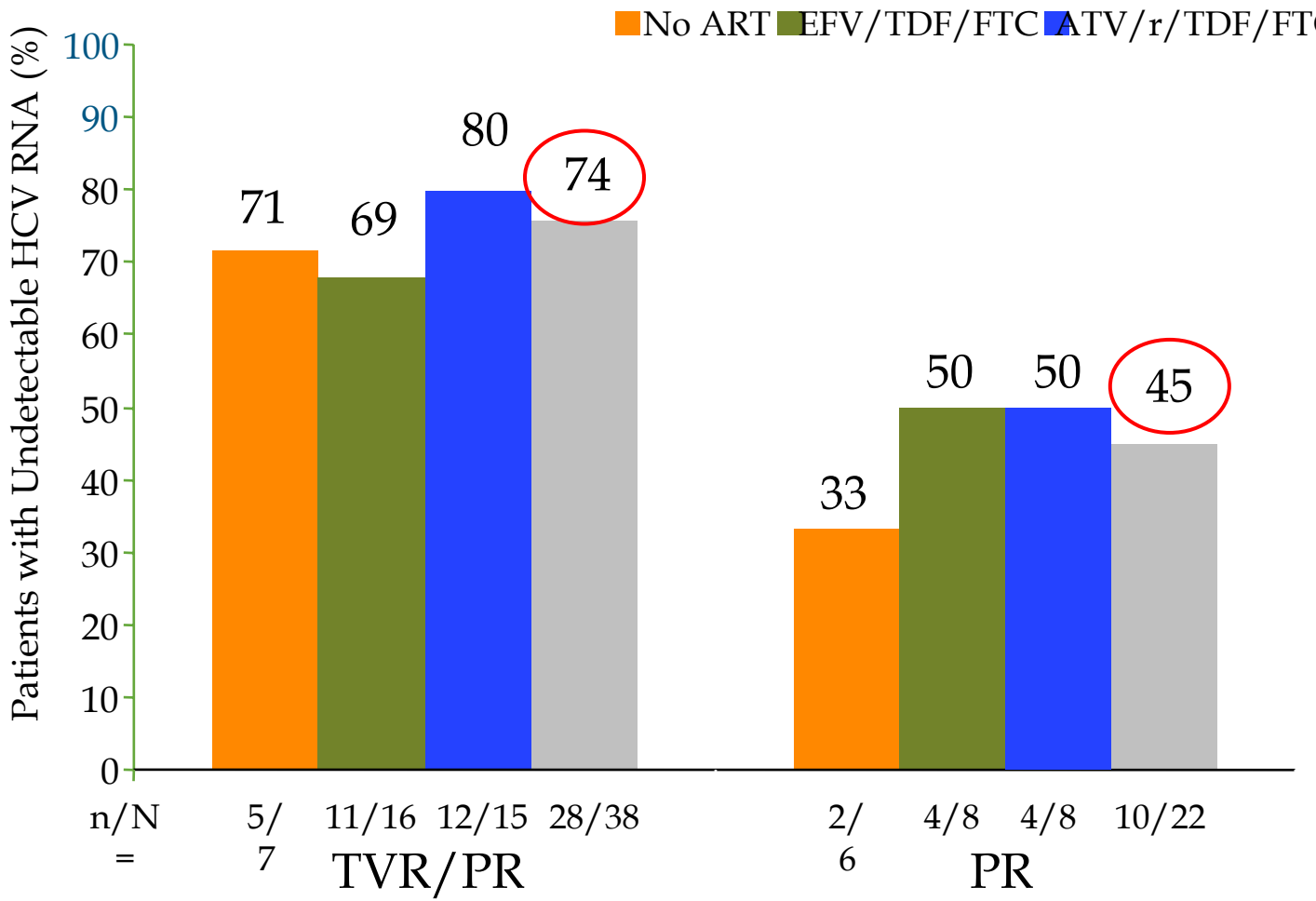
[1]Johns Hopkins University School of Medicine, Baltimore, MD, United States, [2]University of Cincinnati College of Medicine, Cincinnati, OH, United States, [3]Hospital Carlos III, Madrid, Spain, [4]University of Bonn, Bonn, Germany, [5]Mount Sinai School of Medicine, New York, NY, United States, [6]Hôpital St Antoine, Paris, France, and [7]Vertex Pharmaceuticals Incorporated, Cambridge, MA, United States.

Study 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).

Study 110: SVR Rates
12 Weeks Post-Treatment (SVR24)



Dieterich DT, et al. CROI 2012. Abstract 46.

Most Common Adverse Events in >15% Patients: TVR Treatment Phase (Weeks 1-12)*

N (%)	T/PR N=38	PR N=22
Fatigue	15 (39)	9 (41)
Pruritus	**13 (34)**	**1 (5)**
Headache	**13 (34)**	**5 (23)**
Nausea	**12 (32)**	**4 (18)**
Rash†	**11 (29)**	**4 (18)**
Diarrhea	8 (21)	3 (14)
Dizziness	**8 (21)**	**2 (9)**
Pyrexia	7 (18)	2 (9)
Depression	6 (16)	2 (9)
Anemia†	5 (13)	4 (18)
Vomiting	6 (16)	2 (9)
Myalgia	**5 (13)**	**5 (23)**
Chills	5 (13)	4 (18)
Insomnia	5 (13)	4 (18)

*events highlighted in yellow occurred >10% difference between T/PR group vs PR. †Rash and anemia were defined using a group of related search terms in which the event of highest severity was scored.

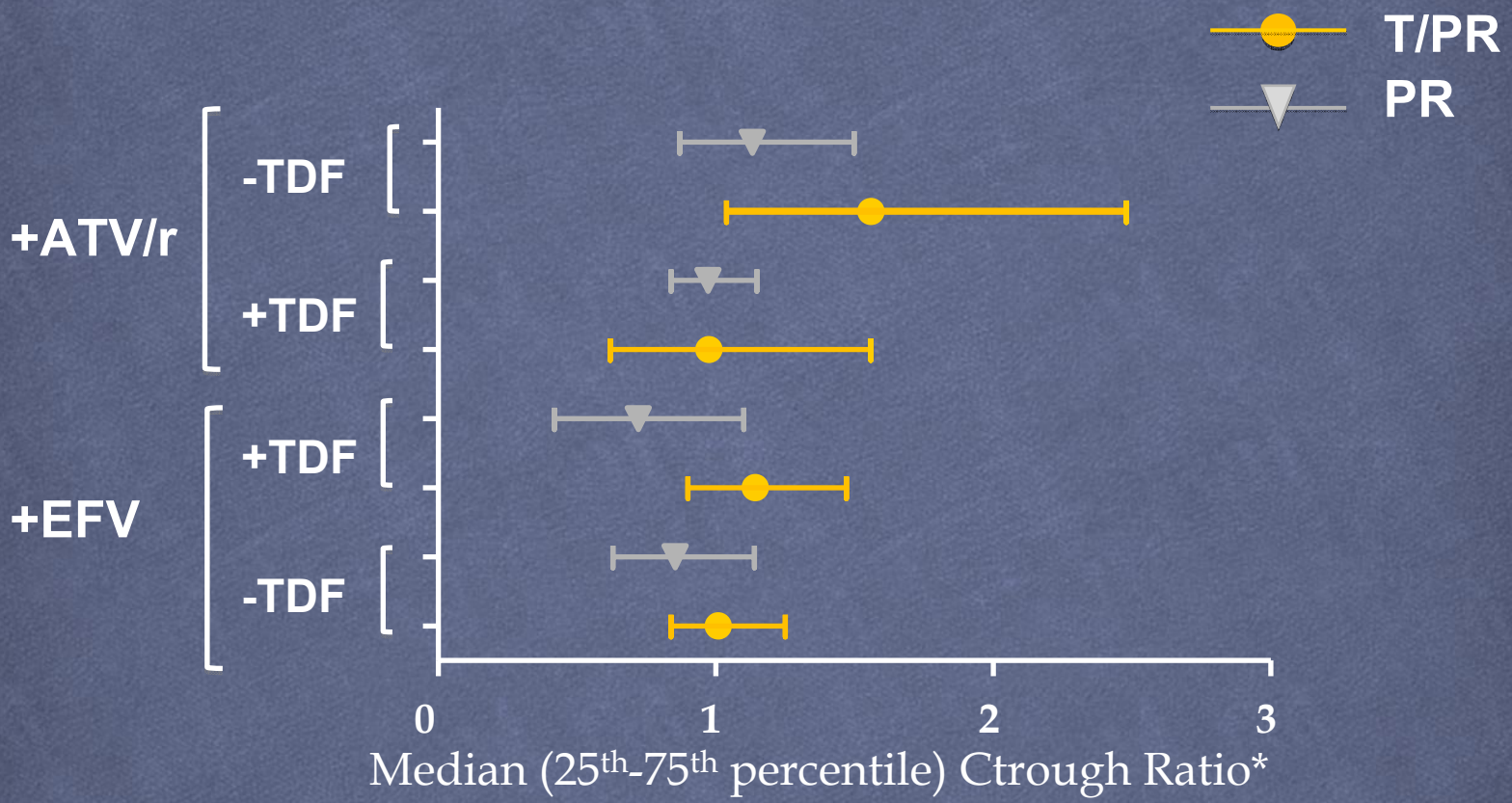
Events of Special Interest: Overall Treatment Phase

Adverse Events, n (%)	T/PR N=38	PR N=22
Severe rash*	0 (0)	0 (0)
Mild or moderate rash*	13 (34)	5 (23)
Any anemia (hemoglobin <10 g/dL)	7 (18)	4 (18)
Severe anemia (hemoglobin 7.0-8.9 g/dL or decrease from baseline ≥4.5 g/dL)*	1 (3)	1 (5)
Use of erythropoietin stimulating agent	3 (8)	1 (5)
Blood transfusions	4 (11)	1 (5)
Discontinuation due to AE	3 (8)	0 (0)

*If a patient had multiple events, the event with highest severity was counted

- No HIV breakthrough; CD4 counts declined in T/PR and PR groups; CD4% unchanged

Pharmacokinetics of ART Similar Among T/PR and PR Groups



ATV/r: N=7 PR, N=14 for T/PR

EFV: N =8 PR, N=15 for T/PR

- C_{trough} ratio = arithmetic mean of predose concentrations on Weeks 1, 2, 4, and 12 (mean C_{trough} during TVR or placebo exposure)/predose concentration on Day -1 for individual patients (C_{trough} before TVR or placebo exposure).

EFV = efavirenz-based ART regimen; ATV = atazanavir/ritonavir-based ART regimen; TDF = tenofovir

Summary and Conclusions

- Higher SVR24 rates were observed in chronic genotype 1 HCV/HIV co-infected patients treated with telaprevir combination treatment
  - **T/PR 74%**
  - PR 45%
- Drug interactions with Telaprevir and select ART were not clinically meaningful
  - Increased dose of telaprevir with efavirenz compensated for CYP3A induction
  - Telaprevir did not substantially modify ART exposure
  - No HIV breakthroughs in patients on ART
- Overall safety and tolerability profile was comparable to that previously observed in chronic genotype 1 HCV mono-infected patients

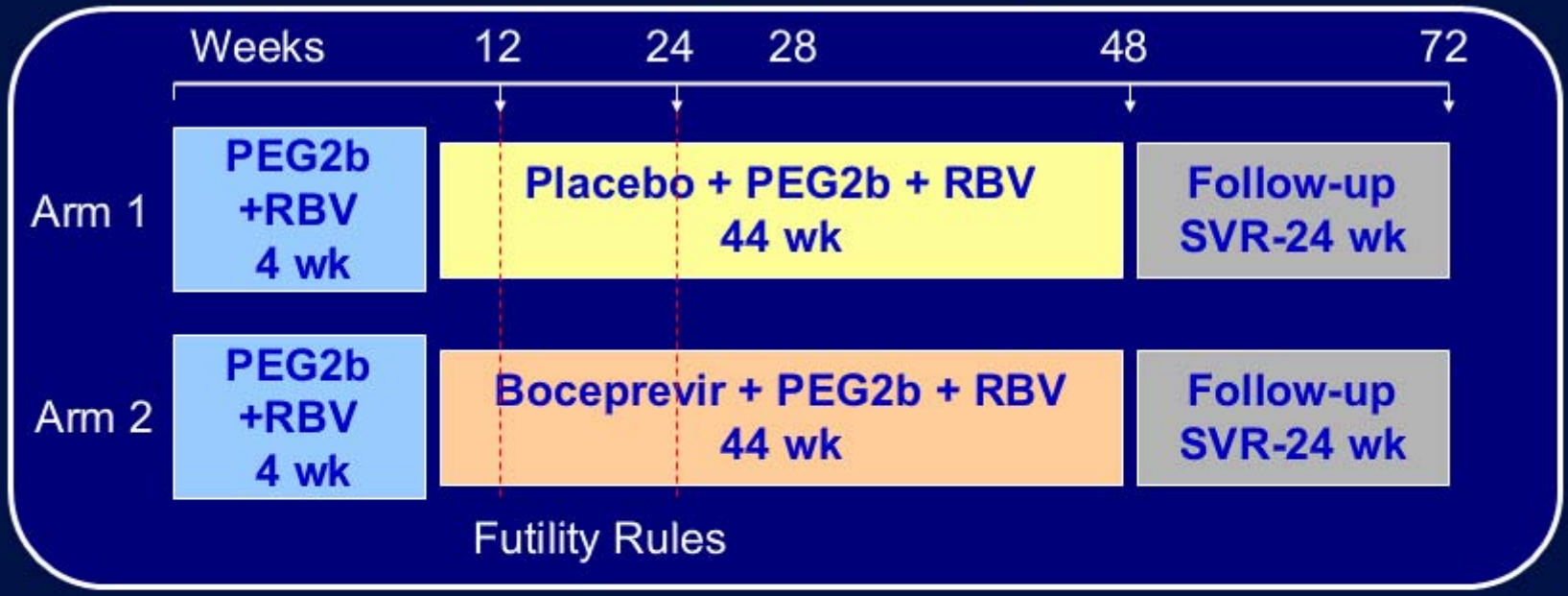
Boceprevir Plus Peginterferon/Ribavirin for the Treatment of HCV/HIV Co-Infected Patients.

M Sulkowski[1], S Pol[2], C Cooper[3], H Fainboim[4], J Slim[5], A Rivero[6], S Thompson[7], W Greaves[7], J Wahl[7], J Mallolas[8]

[1]John Hopkins University School of Medicine, Baltimore, MD; [2]Hopital Cochin, Paris, France; [3]The Ottawa Hospital, Ottawa, ON, Canada; [4]F. J. Muñiz Hospital De Infecciosas, Buenos Aires, Argentina; [5]Saint Michael's Medical Center, Newark, NJ; [6]Hospital Universitario Reina Sofia, Córdoba, Spain; [7]Merck Sharp & Dohme, Whitehouse Station, NJ; [8]Hospital Clinic i Provincial Barcelona, Spain

Sulkowski MS, et al. Presented at IDSA October 20 - 23, 2011, Boston MA

Study Design



- Two-arm study, double-blinded for BOC, open-label for PEG2b/RBV
  - 1:2 randomization (control: experimental)
  - 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 subjects with HCV-RNA ≥ LLQ at TW 24 were offered open-label PEG2b/RBV+BOC via a cross-over arm

Study Eligibility

- Key inclusion criteria
  - Male/female patients, 18 to 65 years of age
  - Chronic HCV Genotype 1/HIV-1 co-infected patients
  - Previously untreated for HCV
  - Liver biopsy within 2 years unless prior cirrhosis
  - CD4 ≥200 cells/mm^3, HIV RNA <50 copies/mL
- Key exclusion criteria
  - Decompensated cirrhosis or coinfection with HBV
  - Use of zidovudine (AZT), didanosine (ddI), stavudine (d4T), efavirenz, etravirine, or nevirapine

Study Methods

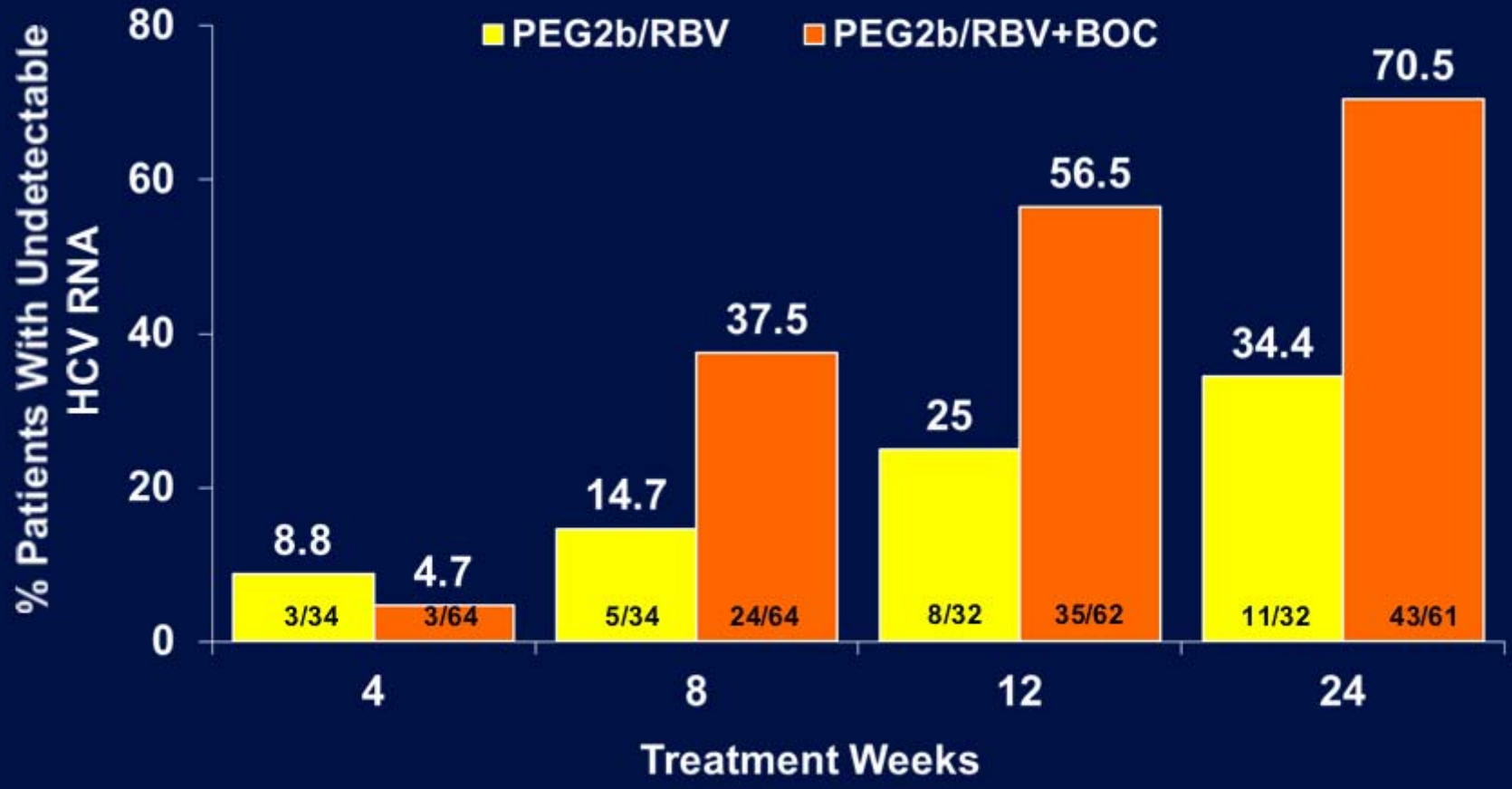
- Interim analysis of 98 patients (PEG2b/RBV Control [n=34]; PEG2b/RBV+BOC [n=64]) who received ≥1 dose of BOC
  - >90% patients had reached TW 24 or had discontinued at the time of analysis
- Assessments
  - HIV RNA and CD4: TW 4, 12, 24
  - HCV RNA: TW 4, 8, 12, 24
  - Proportion with HCV undetectable at TW 4, 8, 12, 24

Demographics and Baseline Characteristics

	PEG2b/RBV (N=34)	PEG2b/RBV+BOC (N=64)
Mean age (years)	45 (9.8)	43 (8.3)
Male, n (%)	22 (65)	46 (72)
Race, n (%)		
Non-White	6 (18)	12 (19)
White	28 (82)	52 (81)
BMI – mean (SD)	26 (5)	25 (5)
Cirrhosis, n (%)	1 (3)	4 (6)
HCV genotype subtype, n (%)*		
1a	22 (65)	42 (66)
1b	10 (29)	15 (23)
HCV RNA Level >800,000 IU/mL, n (%)	30 (88)	56 (88)
HIV RNA <50 copies/mL, n (%)	33 (97)	62 (97)
CD4 count (cells/mm^3), median (range)	585 (187-1258)	577 (230-1539)

*Subtyping not reported for 9 subjects with Genotype 1.

Virologic Response Over Time (% HCV RNA Undetectable)



Summary of Safety

	PEG2b/RBV (N = 34)	PEG2b/RBV + BOC (N = 64)
Days on study, median	166	211
Any AE, n (%)	34 (100)	63 (98)
Serious AEs, n (%)	7 (21%)	5 (8%)
Treatment-related Treatment-emergent AEs, n (%)	34 (100%)	61 (95%)
Study Discontinuation Due to an AE, n (%)	3 (9%)	9 (14%)
Any Drug Modification Due to an AE, n (%)	7 (21%)	12 (19%)

Most Common Adverse Events With a Difference of ≥10% Between Groups*

	PEG2b/RBV (N=34)	PEG2b/RBV + BOC (N=64)
Days on study, median	166	211
Neutropenia, n (%)	3%	13%
Dysgeusia, n (%)	15%	25%
Vomiting, n (%)	15%	25%
Pyrexia, n (%)	21%	34%
Headache, n (%)	12%	28%
Decreased Appetite, n (%)	18%	30%

*A difference of ≥10% for patients receiving PEG2b/RBV+BOC when compared with PEG2b/RBV.

Hematologic Adverse Events

	PEG2b/RBV	PEG2b/RBV + BOC
Anemia		
SAEs, %	6	2
AEs leading to discontinuation, %	3	2
Grade 2 (8.0 to <9.5 g/dL), %	21	16
Grade 3 (6.5 to <8.0 g/dL), %	3	5
Erythropoietin use, % (n)	21 (7)	27 (17)
Transfusions, % (n)	6 (2)	6 (4)

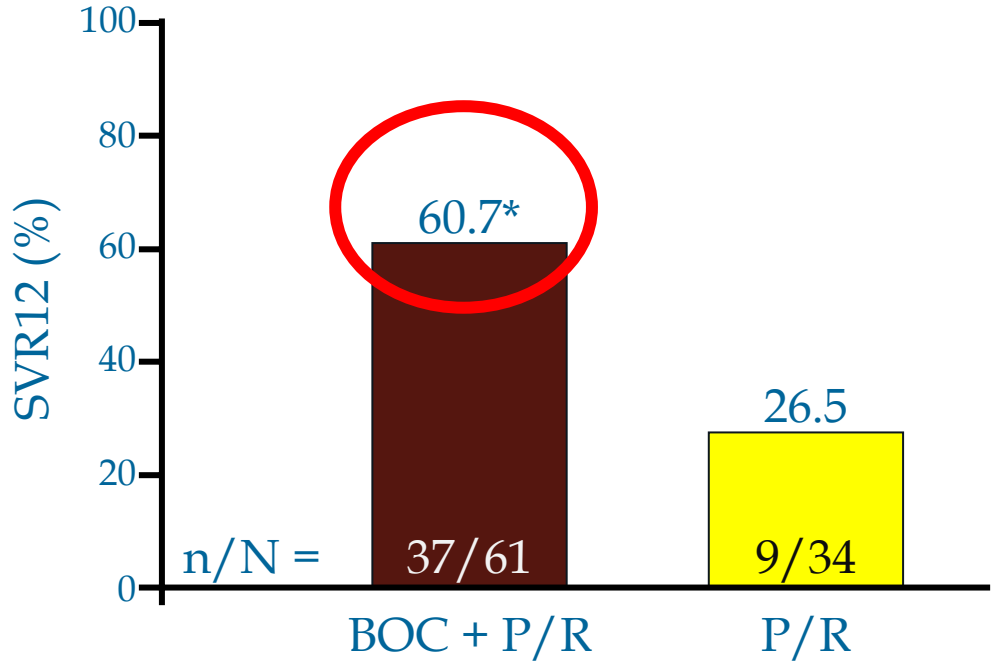
Interim Analysis Summary

- In HCV-HIV co-infected patients who were previously untreated had higher on-treatment rates of HCV response:
  - At TW24, 70.5% of pts on PR +BOC had undetectable HCV RNA vs. 34.4% of pts on PR
- Preliminary safety data of PEG2b/RBV+BOC in co-infected patients showed a profile consistent with that observed in mono-infected patients.
- There were no unexpected trends in CD4 counts or HIV RNA level
- Further studies of PR + BOC are planned

Interim Analysis: SVR Rates 12 Weeks Post-Treatment (SVR12)

Interim efficacy analysis

- 3 BOC pts had not yet reached SVR12 time point



*3 patients with missing data achieved SVR4.

Mallolas J, et al. EASL 2012. Abstract 50.

HIV Breakthroughs in B/PR Group

- Overall, 7 patients had HIV breakthrough (>50 copies HIV RNA at 2 consecutive visits): 3/64 randomized to B/PR, and 4/34 to PR

	HIV RNA (copies/mL)						
Regimen	BL	TW4	TW12	TW24	TW36	EOT	FW4
ATV/r	<50	<50	---	659	---	53	2990
†LPV/r	<50	<50	<50	55	59	67	68
ATV/r	<50	<50	<50	<50	243	---	7870

ATV/r, atazanavir/ritonavir; LPV/r, lopinavir/ritonavir
†The only subject to change ART. LPV/r changed to ATV/r at TW42; ATV/r to DRV/r at FW24.

Sulkowski M, et al.; 19th CROI; Seattle, WA, 2012. Abst. 47

Tolerability and safety: first signals from pilot trials

- 34% and 23% of T/PR and PR patients, respectively had rash; no severe rashes were reported in either group
- Preliminary safety data of B/PR in co-infected patients showed a profile consistent with that observed in mono-infected patients (anemia 41% vs 26%); anemia rate in the T/PR arm and PR arm was 18% in both groups.
- HIV Breakthroughs were observed in 3/64 patients in the BOC group and 4/34 patients in the control group

1. Dieterich DT, et al. CROI 2012. Abstract 46.
2. Mallolas J, et al. EASL 2012. Abstract 50.

AASLD recommendation for HCV treatment in HIV-infected patients (2011)

"Pharmacokinetic interactions have particular implications in HIV-coinfected, where drug–drug interactions will complicate treatment paradigms, so that any use of BOC or TVR in transplant or HIV coinfected populations of patients with HCV should be done with caution and under close clinical monitoring"

Ghany et al. HEPATOLOGY, October 2011

DDIs with Telaprevir or Boceprevir

		TVR	BOC
IP/r	**DRV/r**		
	LPV/r		
	ATV/r	Recomendada monitorização clinica e laboratorial da hiperbilirrubinemia	
	fAPV/r		
NNRTI	**EFV**	TVR: 1125mg TID	
	ETR		TBD
	RPV		TBD
Inib.Integrase	**RAL**		
NRTI	**TDF**		
	AZT, ABC	UDP-Não pode ser posto de parte efeito de TVR nas glucuroniltransferases, que podem afectar as concentrações plasmáticas de ABC ou AZT	

Não recomendado | Precaução | Pode ser co-administrado

*Co-administração de atazanavir/ritonavir com boceprevir resultou numa diminuição da exposição a atazanavir, o que pode estar associado com diminuição da eficácia e perda do controlo do VIH. Esta co-administração pode ser avaliada caso-a-caso se for considerado necessário, em doentes com carga virica VIH suprimida e com estirpes de VIH sem suspeita de resistências para regime (ARV). Necessário aumentar monitorização clínica e laboratorial para supressão de VIH.

RCM Incivo ; RCM Victrelis; De Kanter et al. Poster,19th CROI, 2012 Seattle;Ouwerkerk-Mahadevan et al. Abstract 19th CROI, 2012, Seattle

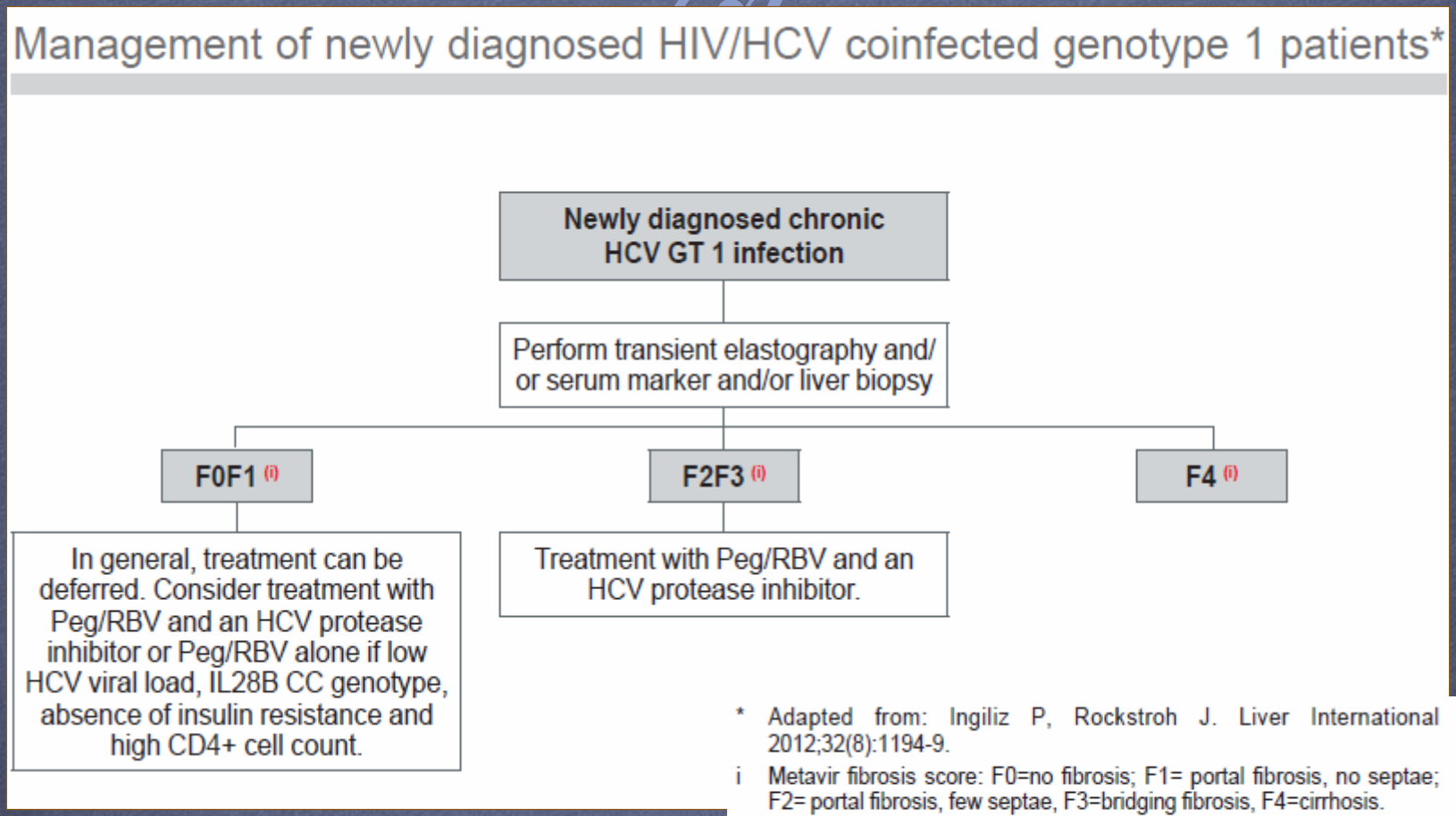
New Treatment Options for HIV/HCV Genotype 1 Patients: EACS Guidelines

- EACS guidelines include the option to treat HIV/HCV GT 1 coinfected patients with telaprevir*[1]
- Updated guidelines will also include option to treat with boceprevir as interim results became available

*With efavirenz, telaprevir dose should be increased to 1150mg every 8 hours. Data on coadministration of telaprevir with raltegravir is anticipated, but clinicians are advised to check www.hep-druginteractions.com for further information.

1. EACS Guidelines. October 2011. Version 6.0

HIV/HCV coinfection



EACS guidelines. November 2012

HIV/HCV coinfection

Management of HIV-HCV coinfected genotype-1 patients according to fibrosis stage and prior treatment outcome*

	Naive	Relapser	Non-responder
F0F1	Individual decision	Individual decision/triple therapy	Defer
F2F3	Triple therapy	Triple therapy	Defer (ii)
F4	Triple therapy	Triple therapy	Triple therapy

* Adapted from: Ingiliz P, Rockstroh J. Liver International 2012;32(8):1194-9.

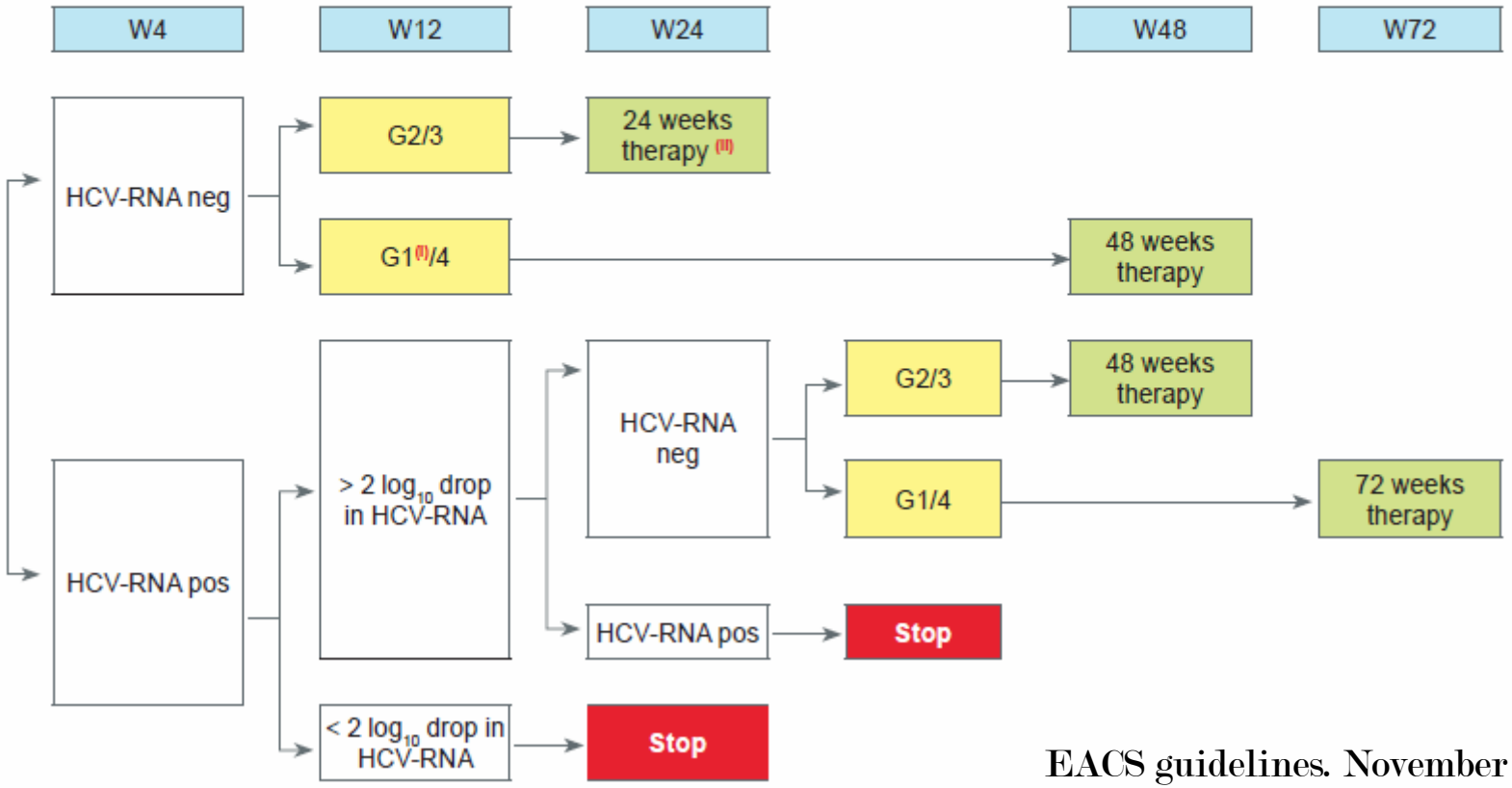
i Metavir fibrosis score: F0=no fibrosis; F1= portal fibrosis, no septae; F2= portal fibrosis, few septae, F3=bridging fibrosis, F4=cirrhosis.

ii Monitor fibrosis stage annually, preferably with two established methods. Treat with triple therapy, if rapid progression.

EACS guidelines. November 2012

HIV/HCV coinfection

Proposed optimal duration of dual HCV therapy in HCV/HIV coinfected patients not eligible for triple therapy including direct acting antivirals against HCV



EACS guidelines. November 2012

HIV/HCV coinfection

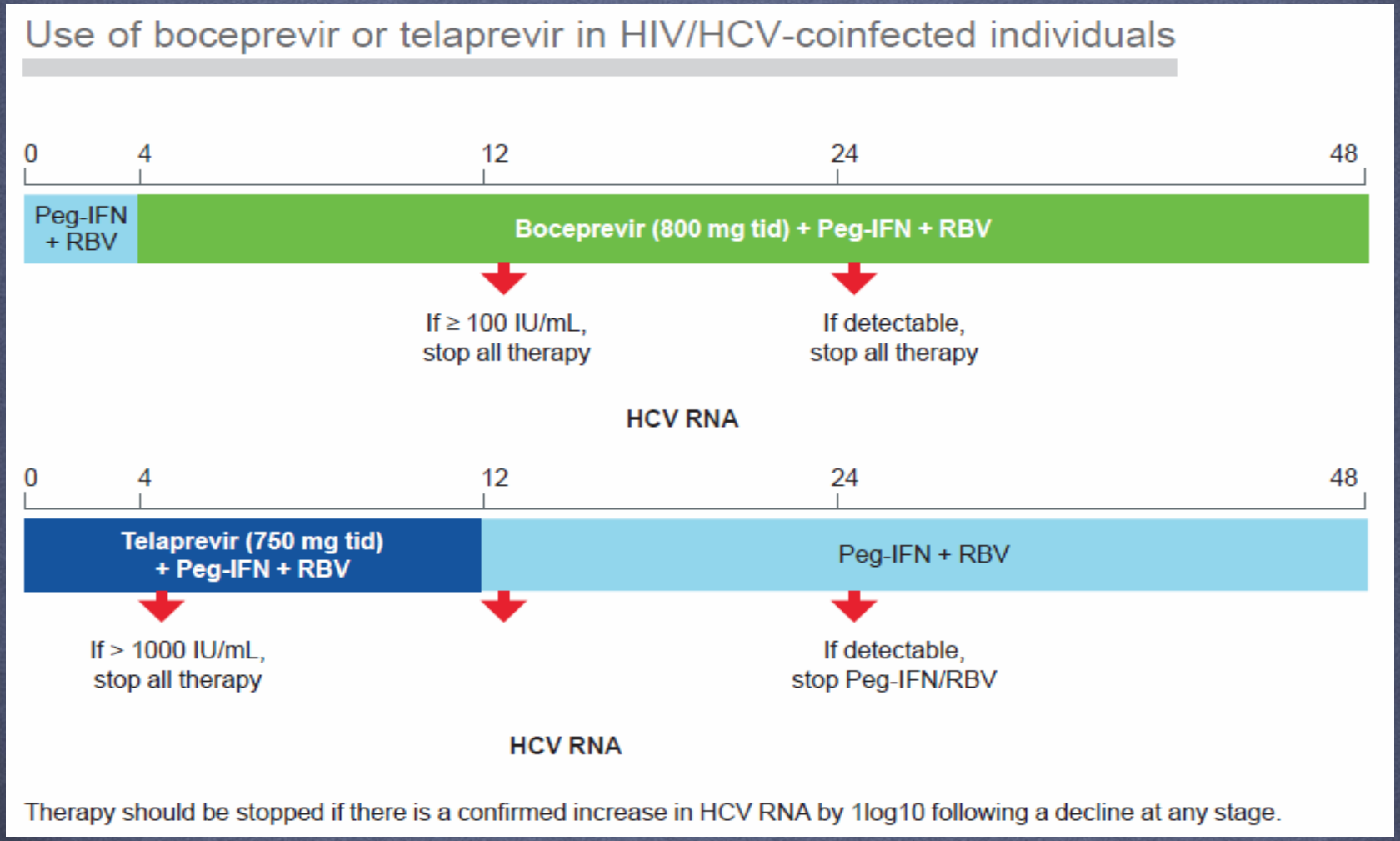
therapy compared to dual therapy, HCV protease inhibitor based therapy with either boceprevir or telaprevir is now the new standard of treatment in HCV genotype 1 infection in HIV-infected individuals where available. Tel-

48 weeks. Due to drug-drug interactions, telaprevir can currently only be safely combined with boosted atazanavir, raltegravir, rilpivirine, etravirine or efavirenz (with EFV, telaprevir doses need to be increased to 1125 mg every 8 hours) in combination with tenofovir or abacavir and FTC or 3TC (please also check www.hep-drugin-

subjects. Due to drug-drug interactions, boceprevir can only be currently safely combined with raltegravir or etravirine in combination with tenofovir or abacavir and FTC or 3TC. The EMEA has also suggested considering boceprevir in combination with boosted atazanavir in patients with no previous HIV treatment failure and no drug resistance who have suppressed HIV-RNA when starting HCV therapy as boceprevir exposure is not impacted by concomitant boosted atazanavir whereas atazanavir AUC decreased significantly but trough levels remained above the recommended IC90 in all patients.

EACS guidelines. November 2012

HIV/HCV coinfection



EACS guidelines. November 2012

No or Minimal Hepatic Fibrosis

- Genotype 2 or 3 or 4, consider PegIFN/RBV
- Genotype 1, IL28B CC, consider PegIFN/RBV
- Other patients
  - Treat with antiretroviral therapy (even high CD4)
  - No alcohol
  - Achieve or maintain a normal BMI
  - Defer HCV therapy pending more effective DAA regimens

Moderate to Severe Hepatic Fibrosis

- Genotype 2 or 3 or 4, treat with PegIFN/RBV
- Genotype 1
  - If available, data support the cautious use of telaprevir or boceprevir + PegIFN/RBV R in carefully selected patients based on ARV regimens and ability to tolerate therapy
  - Cost is major factor in use of HCV PIs

Investigational HCV Regimens

Regimens with one DAA + PEG-IFN alfa/RBV

- ABT-072, -333 (NNIs)
- Mericitabine (NI)
- GS-7977 (NI)
- Tegobuvir (NNI)
- ABT-450 (PI)
- BI201335 (PI)
- Daclatasvir (NS5A)
- Asunaprevir(PI)
- Danoprevir (PI)
- TMC-435 (PI)
- Alisporivir (Cyp)

Regimens with two DAAs (± PEG-IFN alfa and/or RBV)

- GS-9526 (PI) + tegobuvir
- Daclatasvir + Asunaprevir
- VX-222 (NNI) + telaprevir

IFN-free regimens

- GS-7977 + RBV
- Daclatasvir + GS-7977
- Daclatasvir + Asunaprevir ± RBV
- ABT-450/r + ABT-072 + RBV
- ABT-450/r + ABT-333 + RBV
- BI-201335 + BI-207127 ± RBV
- Mericitabine + Danoprevir/r + RBV
- GS-5885 + GS-9451 + Tegobuvir + RBV
- Alisporivir ± RBV

NNI = non-nucleoside NS5B inhibitor, NI = nucleoside NS5B inhibitor,
PI = protease inhibitor, RBV = ribavirin, NS5A = replication complex inhibitor
Cyp= cyclophilin inhibitor, r= ritonavir

EASL 2012 program
http://www2.kenes.com/liver-congress/Pages/Home.aspx

Phase III Clinical Trials in Coinfected Patients

Phase 3			
Drug Name	**Drug Category**	**Company**	**Updated**
BI201335	Protease Inhibitor	Boehringer Ingelheim Pharma	Nov 7, 2011
BMS-790052	NS5a Inhibitor	Bristol-Myers Squibb	Jan 18, 2012
Boceprevir	Protease Inhibitor	Merck	Jan 18, 2012
Telaprevir	Protease Inhibitor	Vertex / Tibotec	Mar 6, 2011
TMC435 (Simeprevir)	Protease Inhibitor	Tibotec	Jan 18, 2012
Telaprevir	Protease Inhibitor	Vertex / Tibotec	Nov 7, 2011

(Adapt from HCV Advocate)

DAA Profiles

	DAA				
	NS3[1]	NS3[2]	NS5A	nuc NS5B	non-nuc NS5B
Resistance profile	🔴	🟡	🟡	🟢	🔴
Pan-genotypic efficacy	🔴	🟡	🟡	🟢	🟡
Efficacy	🟡	🟢	🟢	🟢	🟡
Adverse events	🔴	🟢	🟡	🟡	🟡
Drug –drug interactions	🔴	🟡	🟡	🟢	🟡

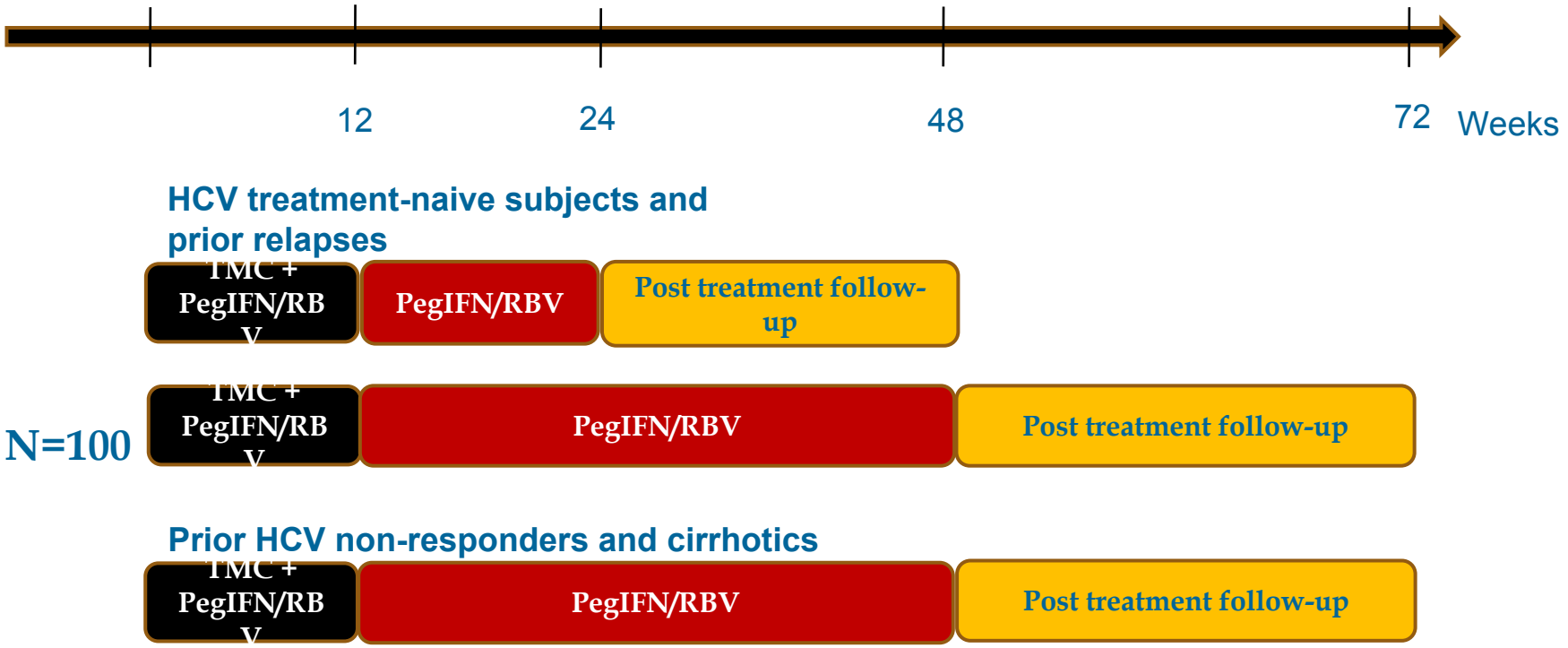
🟢 Good profile 🟡 Average profile 🔴 Least favorable profile

1: 1st generation
2: 2nd generation

Clinical Trials of Novel DAAs for HCV Treatment in HIV-infected Patients

- Simeprevir (PI) once daily + PegIFN/RBV
- Faldaprevir (PI) once daily + PegIFN/RBV
- Daclatasvir (NS5A) once daily + PegIFN/RBV
- Sofosbuvir (nucleotide analogue polymerase inhibitor) once daily + RBV
  - Genotype 2 or 3 – 12 weeks
  - Genotype 1 – 24 weeks

Study C212 TMC-435 (Simeprevir-PI): Open-label, Single-arm Study in HIV/HCV Coinfection



Simeprevir -150 mg QD

Allowed ART: 3TC, FTC, TDF, ABC, rilpivirine, maraviroc, raltegravir and T20

BI 201335 +PegIFN/RBV in HIV/HCV co-infected patients 1220.19 study

BI 201335

- 120mg QD and 240mg QD
- 12- and 24 weeks

PegIFN/RBV

- 24 weeks and 48 weeks
- Tests response guided-therapy
  - HCV RNA < 25 U/ml at week 4 and ≤ 25 U/ml undetectable at week 8, early treatment success

Permitted ARVs

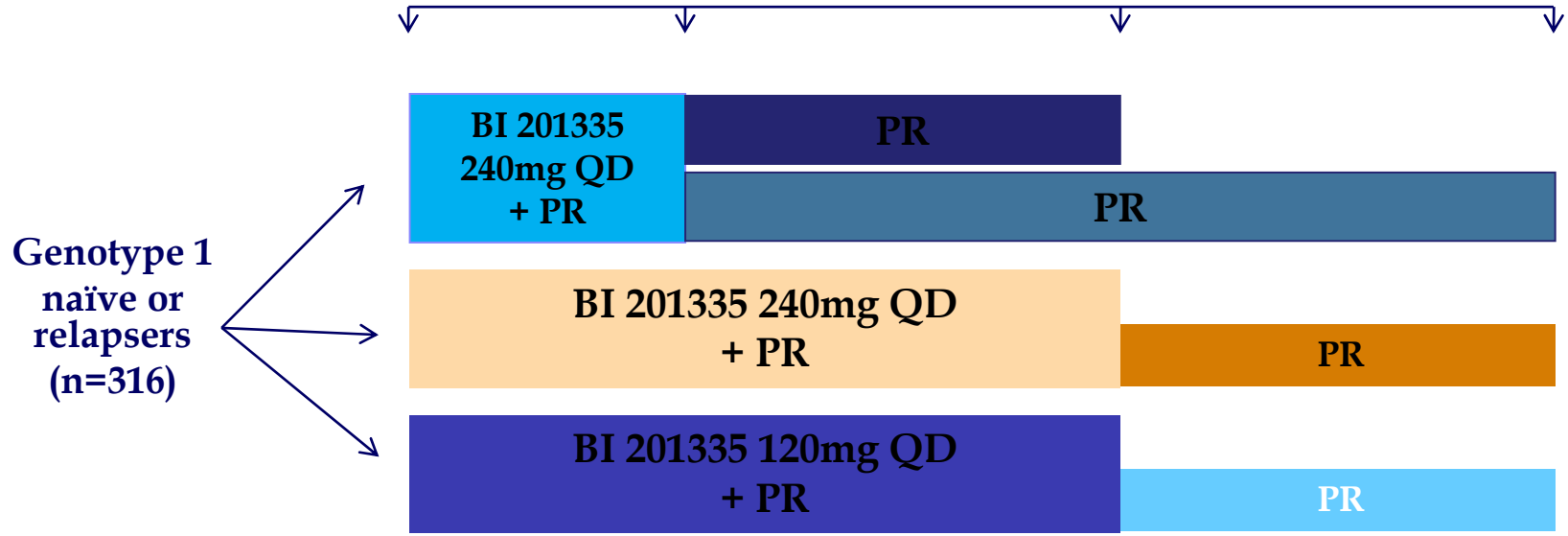
- Raltegravir, Tenofovir/Emitricitabine
- DRV/RTV, ATZ/RTV (limited n)
- Efavirenz
- Maraviroc
- Abacavir, Lamivudine

Additional information

HCV GT1
IFN-naive or relapser
N~ 300
Open label
Started in Q4 2011

http://clinicaltrials.gov/ct2/show/NCT01399619

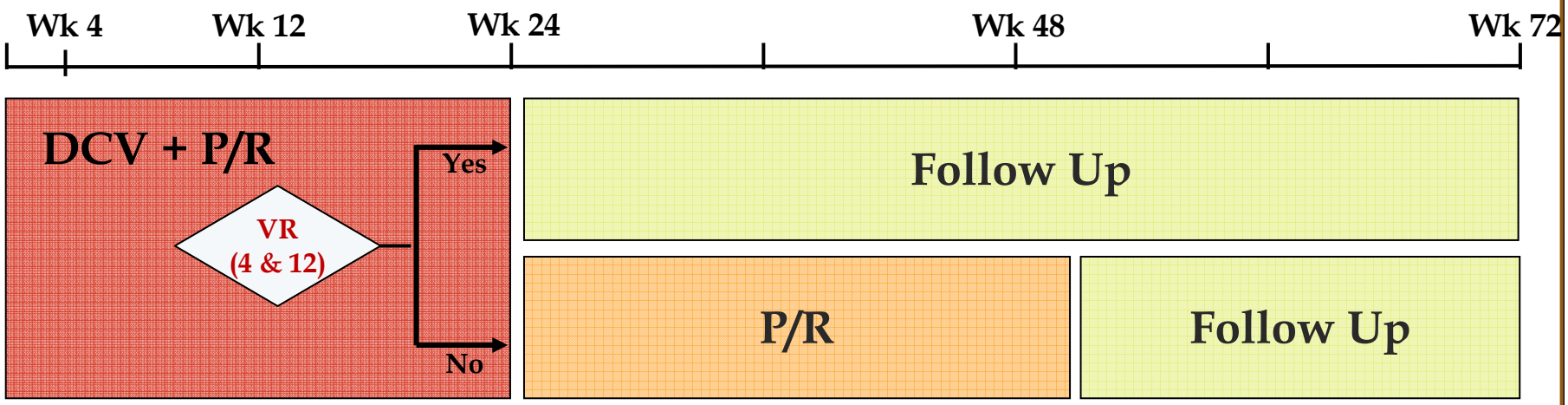
BI 201335 (Faldaprevir) IP + PegIFN + Ribavirin in naïve and relapsers coinfected patients



Aim: to evaluate efficacy and safety of BI 201335 for 12 or 24 weeks in combination with PegIFN/RBV for 24 – 48 weeks

Enrollment began in October 2011

COMMAND-HIV (AI444-043) BMS790052: Study Design & Duration



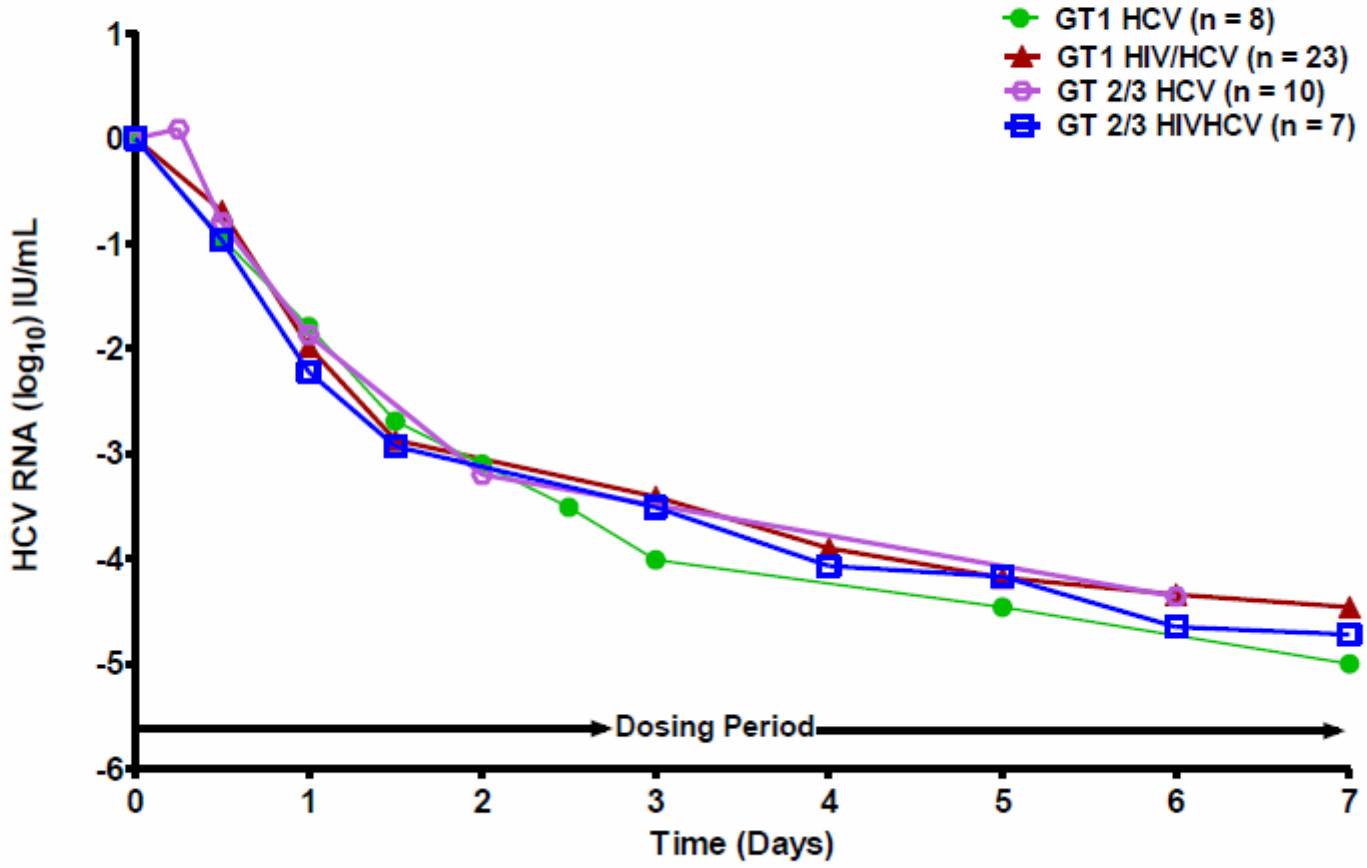
Response Guided Treatment (RGT)

- Subjects who achieve **Virologic Response (VR) at Wks 4 and 12** will complete 24 weeks of triple therapy
  - 48 weeks follow up after treatment
- Subjects not achieving VR at Wks 4 and 12 will receive 48 weeks total duration of therapy (additional 24 weeks P/R)
  - 24 weeks follow up after treatment

Therefore, the maximum duration of study for any subject completing treatment will be 72w

Sofosbuvir 400 mg daily for 7 days in Patients with HIV/HCV Coinfection

Viral kinetics according to HIV Coinfection and HCV genotype

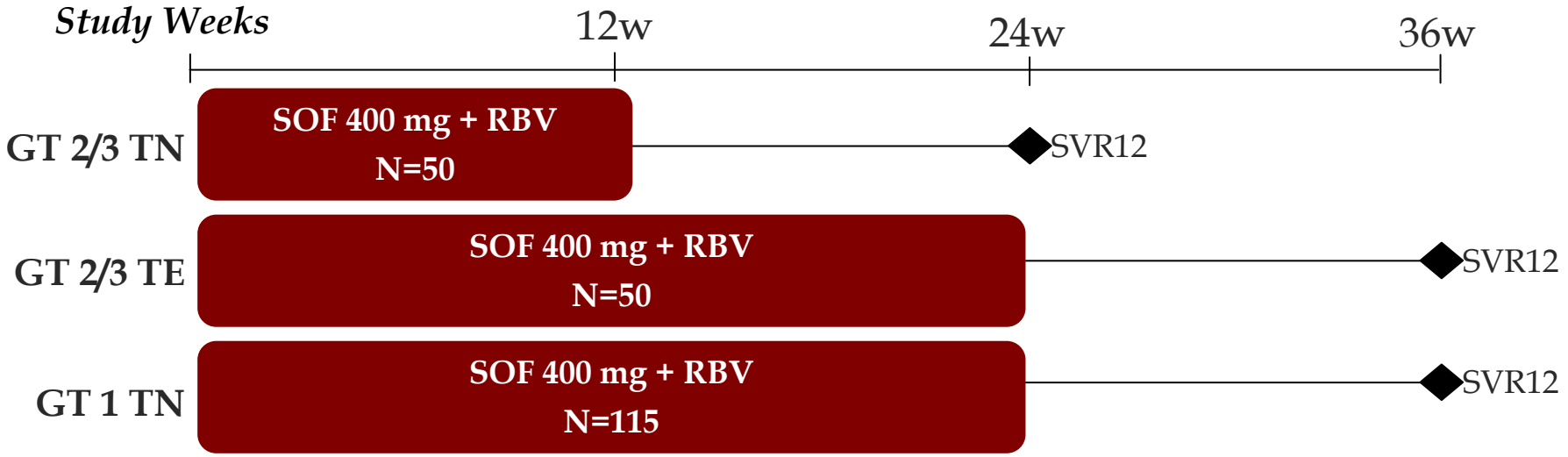


Lawitz E, et al. EASL 2012; Gane E, et al. AASLD 2011, Rodriguez-Torres et al. ICAAC 2012

Phase III: Sofosbuvir (SOF) Nuc HIV/HCV Co-infection

PHOTON-1 and 2

GT 1 treatment naïve (TN) and GT 2/3 TN and treatment experienced (TE) subjects



- Primary objective:
  - Determine efficacy of 12 weeks of treatment with SOF+RBV as measured by SVR12
  - Evaluate the safety and tolerability of Sofosbuvir

Clinicaltrials.gov NCT01667731

Enrolling

Overview: planned and ongoing clinical trials

	Telaprevir	Boceprevir
Clinical Trials	• INSIGHT (Janssen) • Study 115 (Vertex) • HPC3005 (Janssen) • ANRSHC26 (IIS: ANRS)	• Co-infection vs mono-infection (IIS: NIAID) • NIAID Phase III (IIS: NIAID) • ANRS pilot (IIS: ANRS)
DDIs Studies	• DDI with dolutegravir(ViiV) • DDI with maraviroc (ViiV)	• DDI with dolutegravir (ViiV) • DDI with maraviroc (ViiV)

DDI: drug-drug interaction; IIS: investigator-initiated study

Based on data available online at clinicaltrials.gov (accessed 25 May 2012)

Treatment of coinfected patients for the next 2 years

- ✓ Patients with HCV genotype 2 or 3 will receive PegIFN and ribavirin.
  - SVR arround 60-70%

- ✓ Patients with genotype 1 will be treated with triple therapy
  - SVR about 60-70% ?
  - Treatment mainly with PIs
  - More frequent adverse events
  - Interactions with several drugs

What we need in the future

- Easy dosing
- Better tolerability
- No interactions with other medication
- Pangenotypic responses
- High barrier to resistance

- Individualized regimens

HCV Therapy in the Future

Scenario I

One treatment regime
for <u>all</u> patients
<u>all</u> over the world

Scenario II

Small molecules for the western world or difficult to treat patients

and

IFN-based regime for developing countries or easy to treat patients

(adapt from M Manns, EASL 2012, Prage)

Future perspectives for the treatment of coinfected patients

- ✓ Treatment (all genotypes) with oral combinations
- ✓ SVR will be higher
- ✓ Transmission of HCV will be lower
- ✓ Reduction of cases of cirrhosis and decompensation
- ✓ Reduction of the number of transplants
- ✓ Cost savings
- ✓ Better quality of life
- ✓ Erradication of HCV infection

Muchas gracias!!