Moderne Therapie der HIV/HCV-Koinfektion

Fortbildung Arbeitskreis AIDS, Berlin,

Mittwoch 17. Oktober 2012

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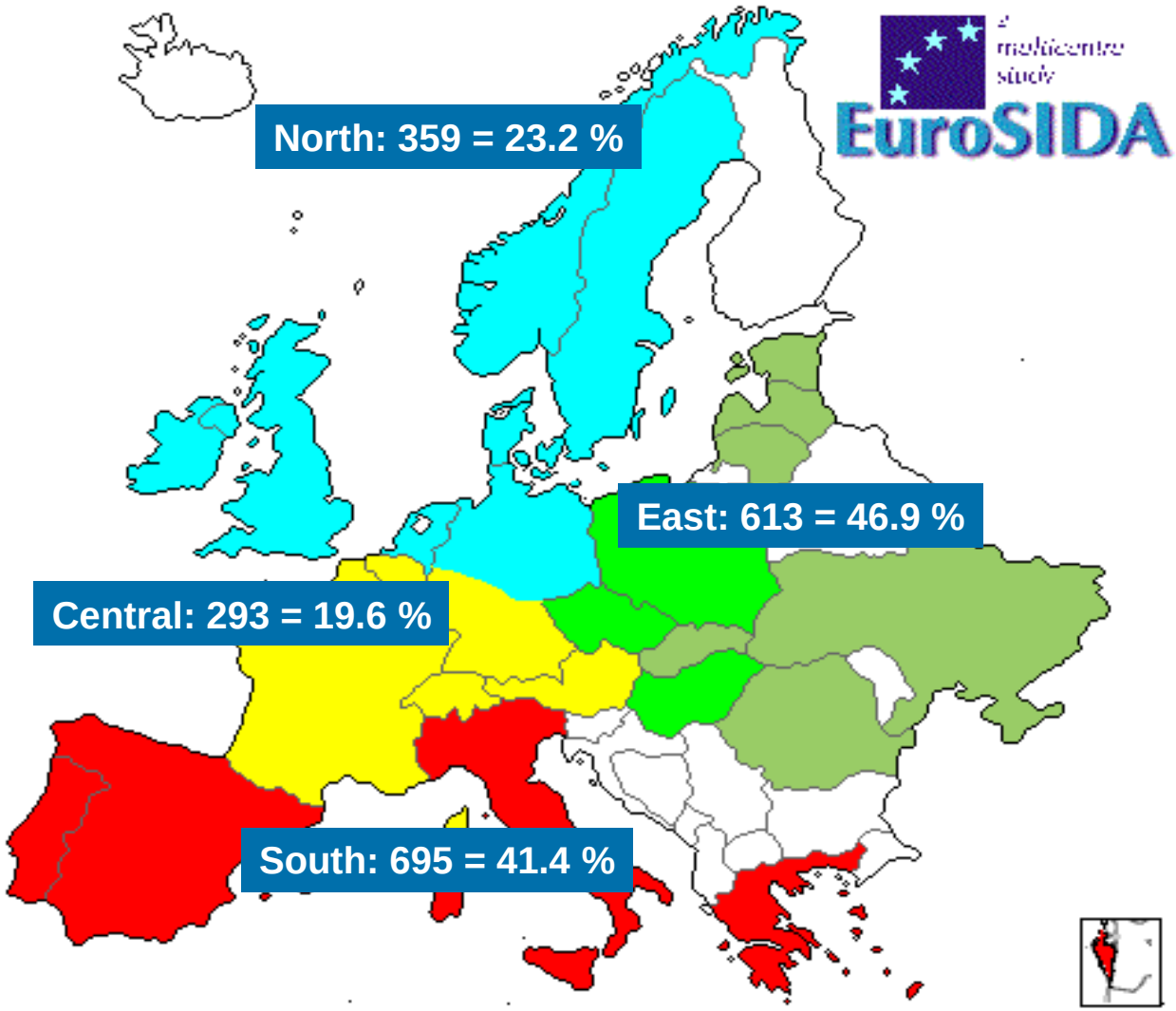
Medizinische Klinik I

Universitätsklinikum Bonn

Prevalence of hepatitis C in the HIV population (1960/5957 patients = 33%)

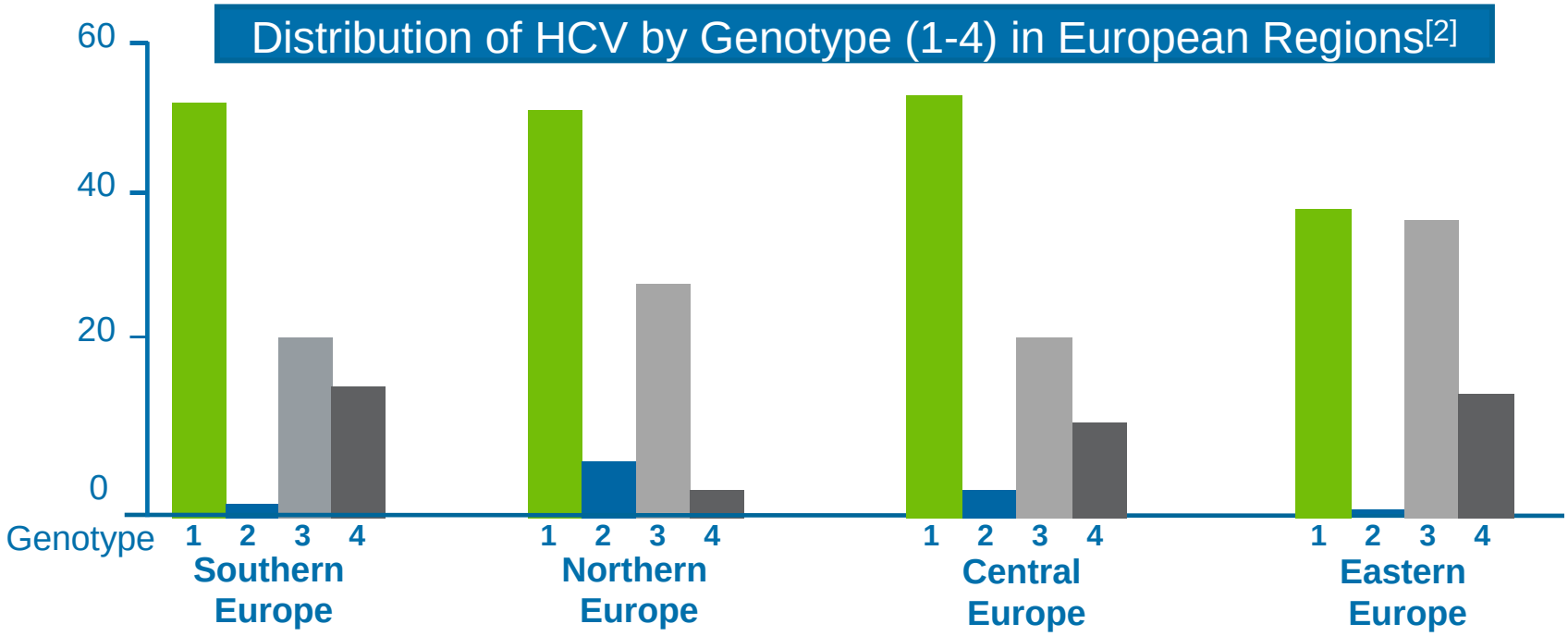


Regions:
South
Central
North
East

Rockstroh et al. J Inf Dis 2005;192:992–1002

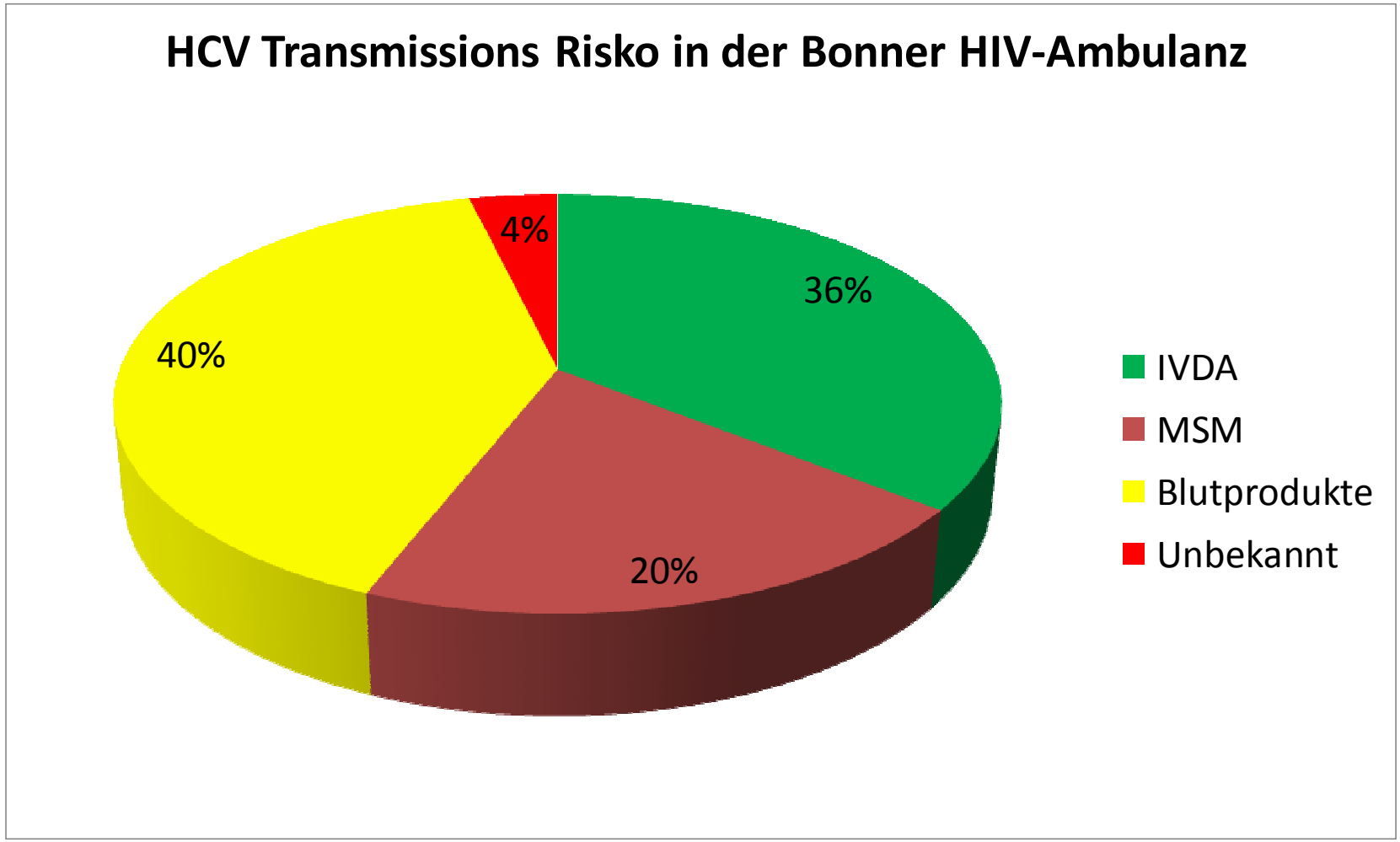
HCV Coinfection in EuroSIDA

- Prevalence of HCV seropositivity in EuroSIDA is 33%[1]
- Of 1940 HCV Ab+ patients, 77% were serum HCV RNA-positive (95% CI: 75% to 79%)[2]



1. Rockstroh J, et al. J Infect Dis. 2005;192:99-1002. 2. Soriano V, et al. J Infect Dis. 2008;198:1337-1344.

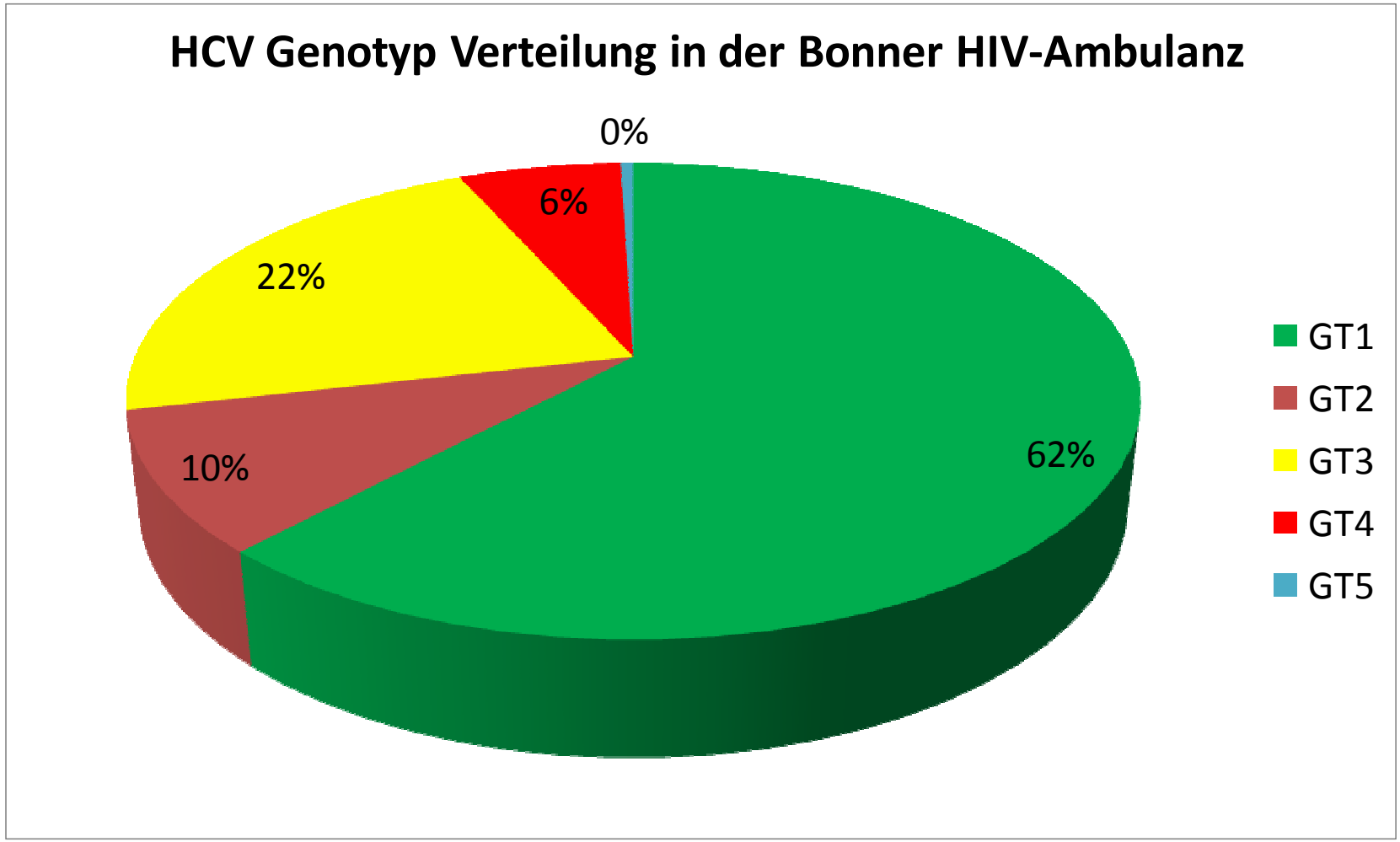
HCV Transmissionsgruppen n=373



Bislang dokumentierte HCV Therapie: 117/373 (31.4%)

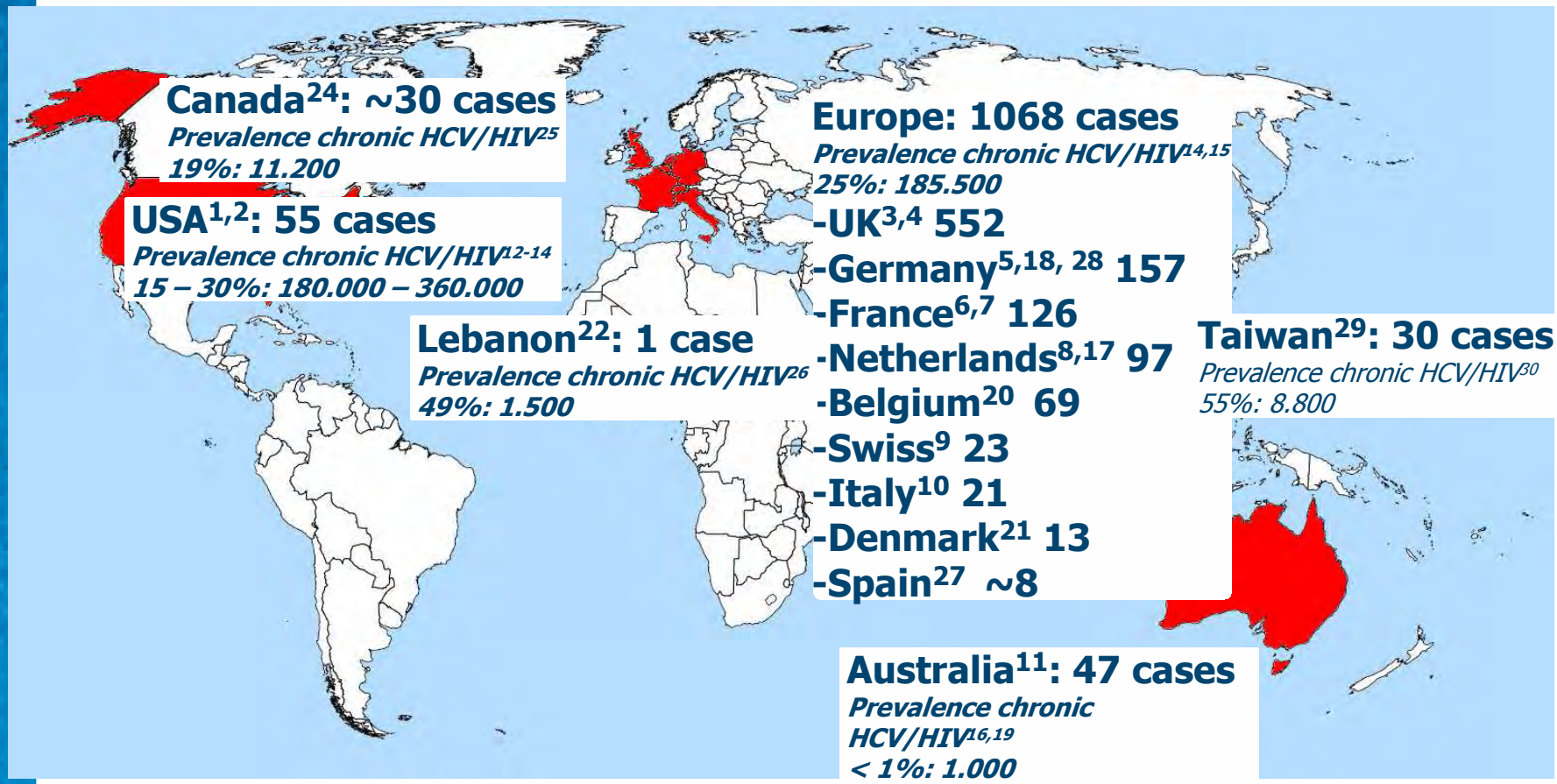
Boesecke C, persönliche Kommunikation

HCV Genotyp Verteilung an der Bonner HIV-Ambulanz n=210



Boesecke C, persönliche Kommunikation

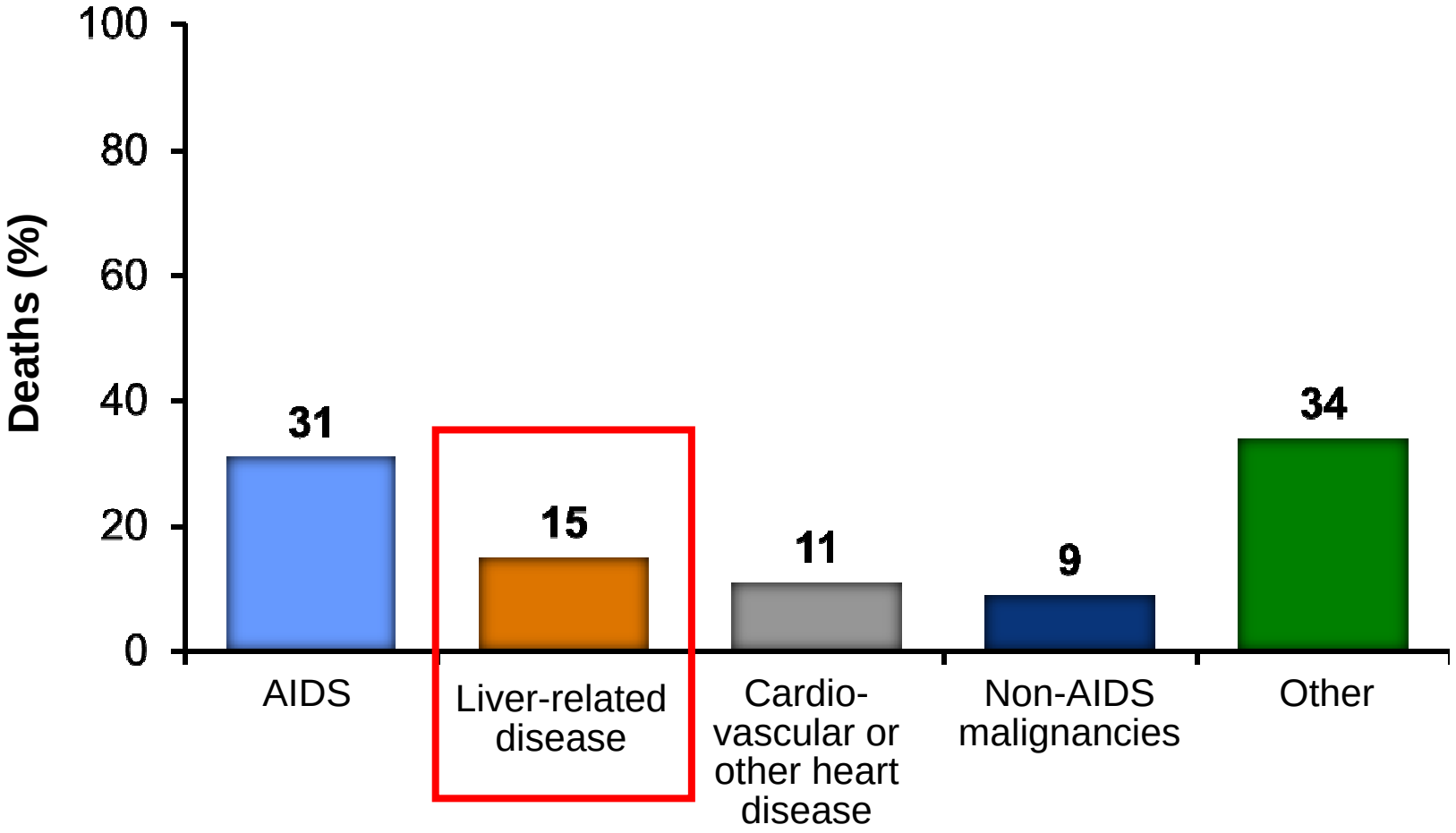
Acute HCV among HIV+ MSM



1.Luetkemeyer JAIDS 2006; 2.Cox Gastroenterology 2008; 3.Giraudon Sex Transm Infect 2008; 4.Ruf Eurosurveill 2008; 5. Vogel CID 2009; 6.Gambotti Euro Surveill 2005; 7.Morin Eur J Gastro Hepat 2010; 8.Urbanus AIDS 2009; 9.Rauch CID 2005; 10.Gallotta 4th Works. HIV & Hep. Coinf. 2008; 11.Matthews CID 2009; 12. Sherman CID 2002; 13: Backus JAIDS 2005; 14: UNAIDS Report 2008; 15: Soriano JID 2008; 16: Matthews CID 2011; 17: Arends Neth J Med 2011; 18: Neukam HIV Med 2011; 19: Pfafferott PLoS One 2011; 20: Bottieau Euro Surveill 2010; 21: Barfod Scand JID 2011; 22: Dionne-Odom Lancet Infect Dis 2009; 23: Taylor Gastroenterology 2009; 24: Hull personal conversation 2011; 25: Remis 1st Canadian HCV Conference 2001; 26: UNGASS Country progress Report 2010; 27: Soriano personal conversation 2011; 28: Boesecke 18th CROI Boston 2011 abstract #113

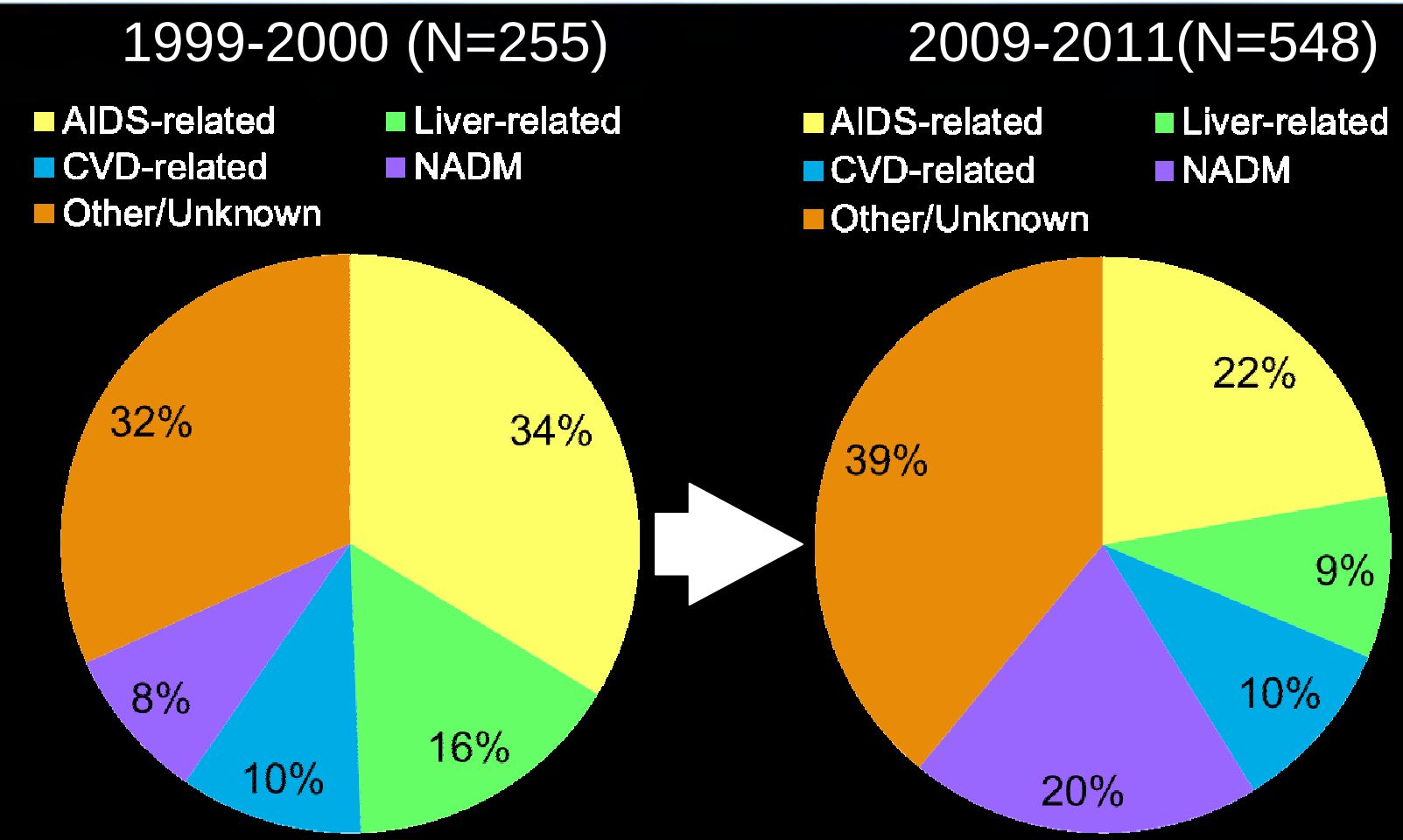
Main causes of death in HIV-infected patients (n=23,441)

15% of the 1246 deaths were related to liver disease



Weber R, et al. Arch Intern Med 2006;166:1632–41

Changes in Causes of Death Over Time



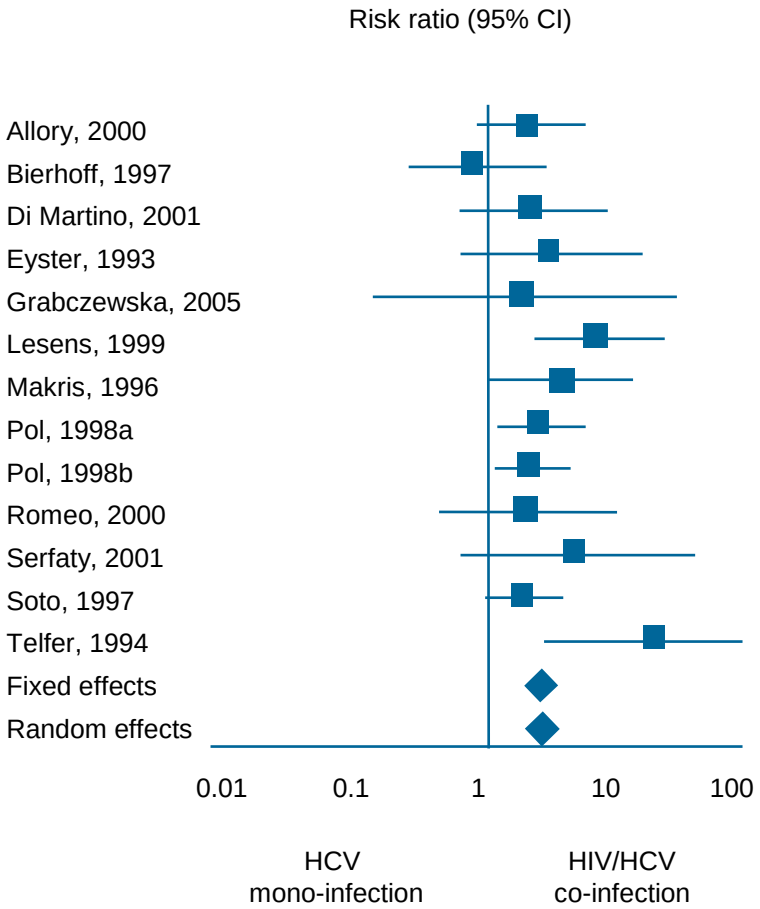
Death rate fell from 17.4 deaths per 1000 py in 1999-2000 to 8.3 deaths in 2009-2011

Weber R, et al. 19th IAC; Washington, DC; July 22-27, 2012; Abst. THAB03104.

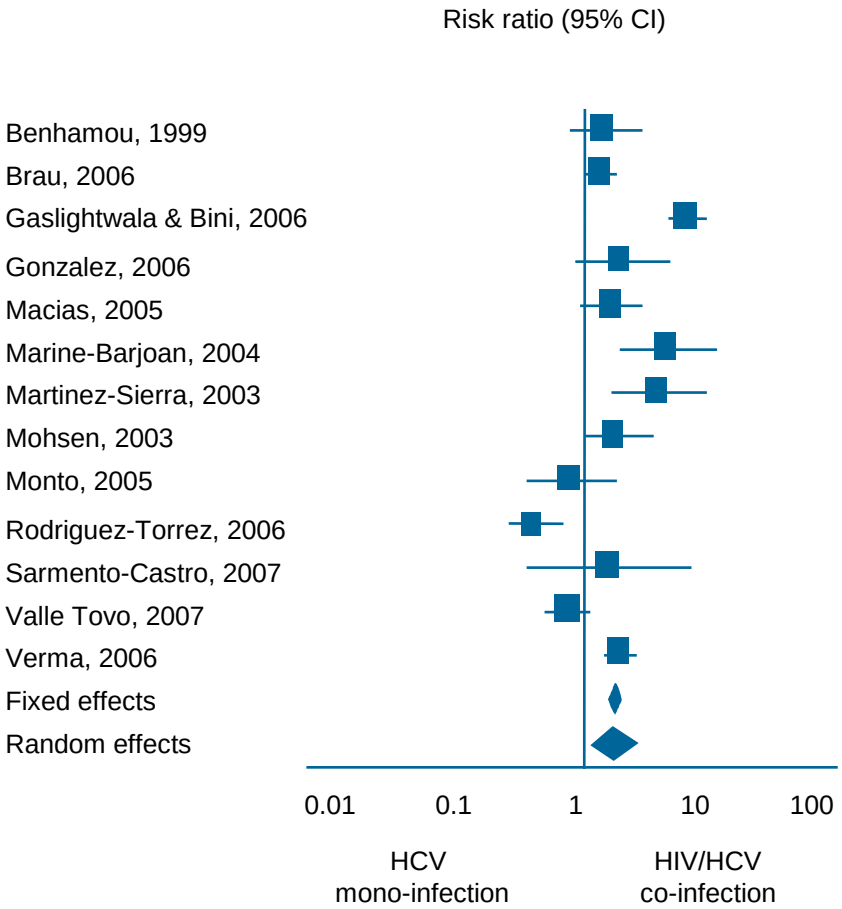
Has the outcome of liver disease in HIV/HCV co-infected patients become similar to that in HCV mono-infection?

Meta-analysis of 26 studies

No HAART



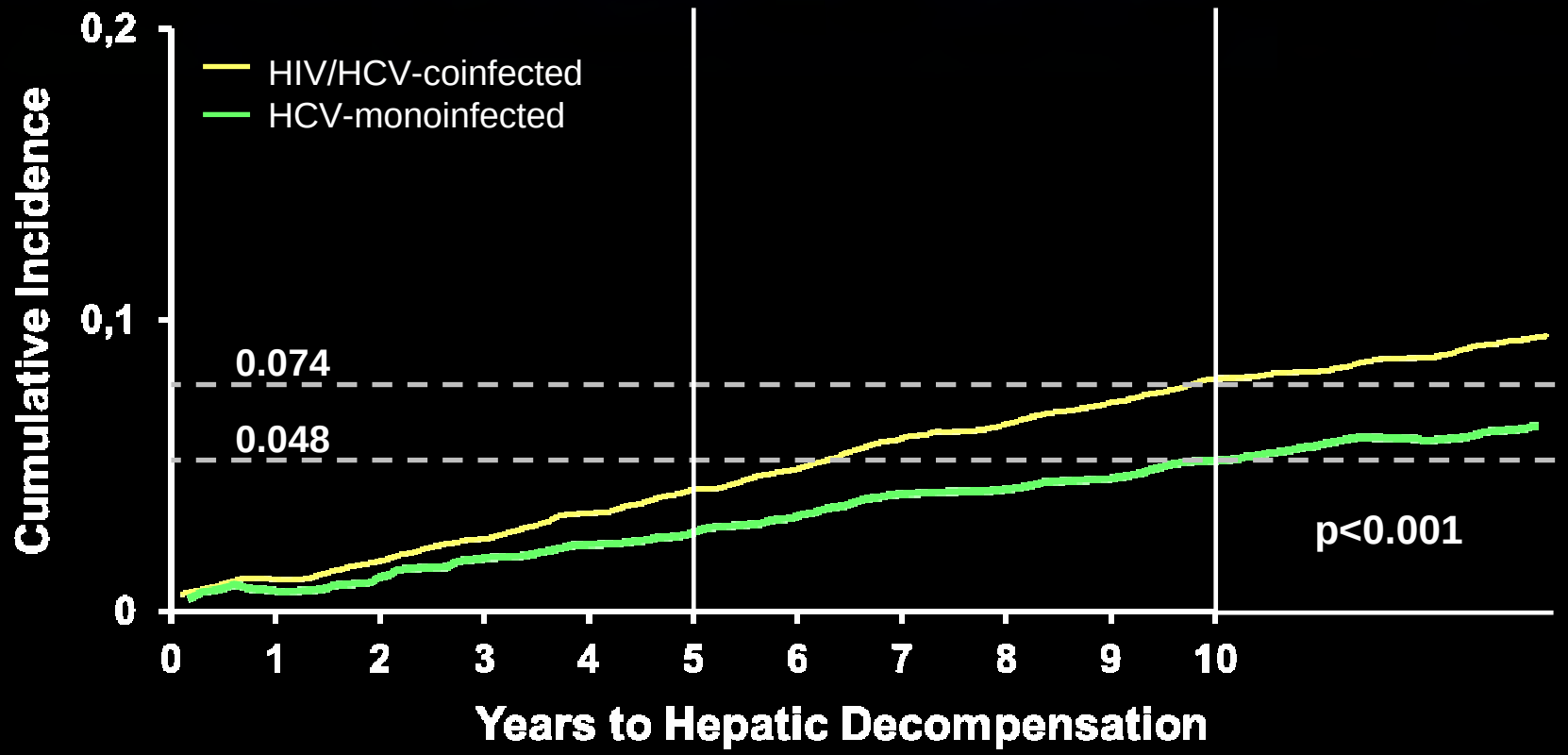
HAART



HAART: highly active antiretroviral therapy

Deng L, et al. World J Gastroenterol 2009;15:996–1003

Standardized Cumulative Incidence of Hepatic Decompensation



Hepatic decompensation risk 83% higher in the coinfected group (aHR 1.83, 95% confidence interval [CI] 1.54 to 2.18)

Lo Re V, et al. 19th IAC; Washington, DC; July 22-27, 2012; Abst. WEAB0102.

EACS Guidelines: When to Start

- Initiation of ART
  - ART is always recommended if CD4 count <350 cells/mm3
  - Serodiscordant couples: Early ART should be considered and actively discussed

Condition	Current CD4 + lymphocyte count[I, II, III]	
	350-500	>500
Asymptomatic HIV infection	C	D
Symptomatic HIV disease (CDC B or C conditions) incl. tuberculosis	R	R
Primary HIV infection	C	C
Pregnancy (before third trimester)	R	R
Conditions (likely or possibly) associated with HIV, other than CDC stage B or C disease:		
HIV-associated kidney disease	R	R
HIV-associated neurocognitive impairment	R	R
Hodgkin's lymphoma	R	R
HPV-associated cancers	R	R
Other non-AIDS-defining cancers requiring chemo- and/or radiotherapy	C	C
Autoimmune disease — otherwise unexplained	C	C
High risk for CVD(>20% estimated 10 yr risk) or history of CVD	C	C
Chronic viral hepatitis		
HBV requiring anti-HBV treatment	R	R
HBV not requiring anti-HBV treatment	C/R [IV]	D
HCV for which anti-HCV treatment is being considered or given	R [V]	D [VI]
HCV for which anti-HCV treatment not feasible	R	C

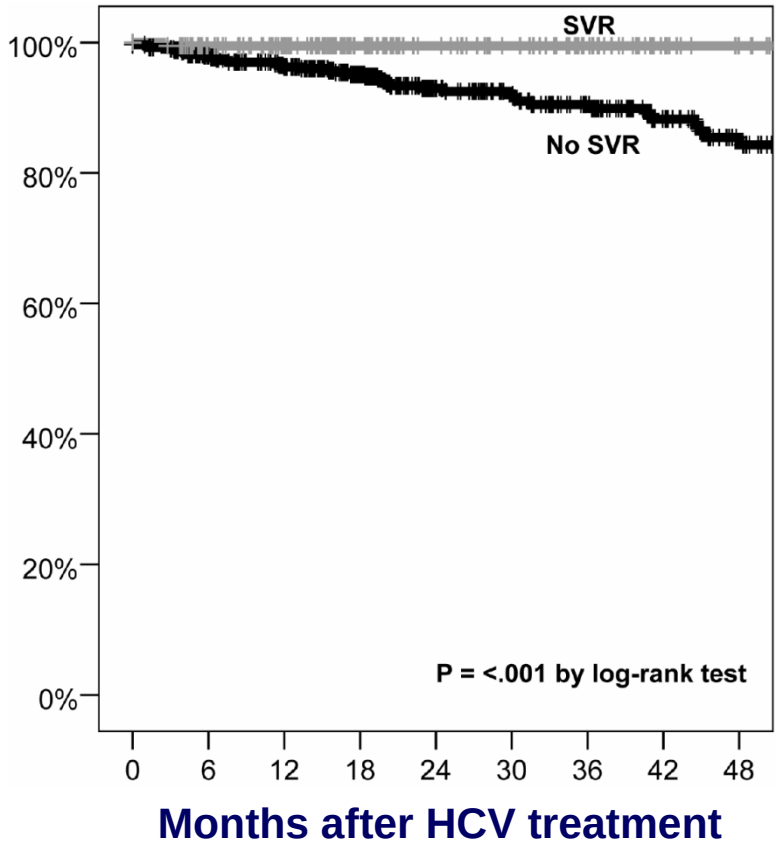
www.eacs.eu. (October 2011)

C = CONSIDER. D = DEFER. R = RECOMMENDED

HCV Infection Can Be Cured

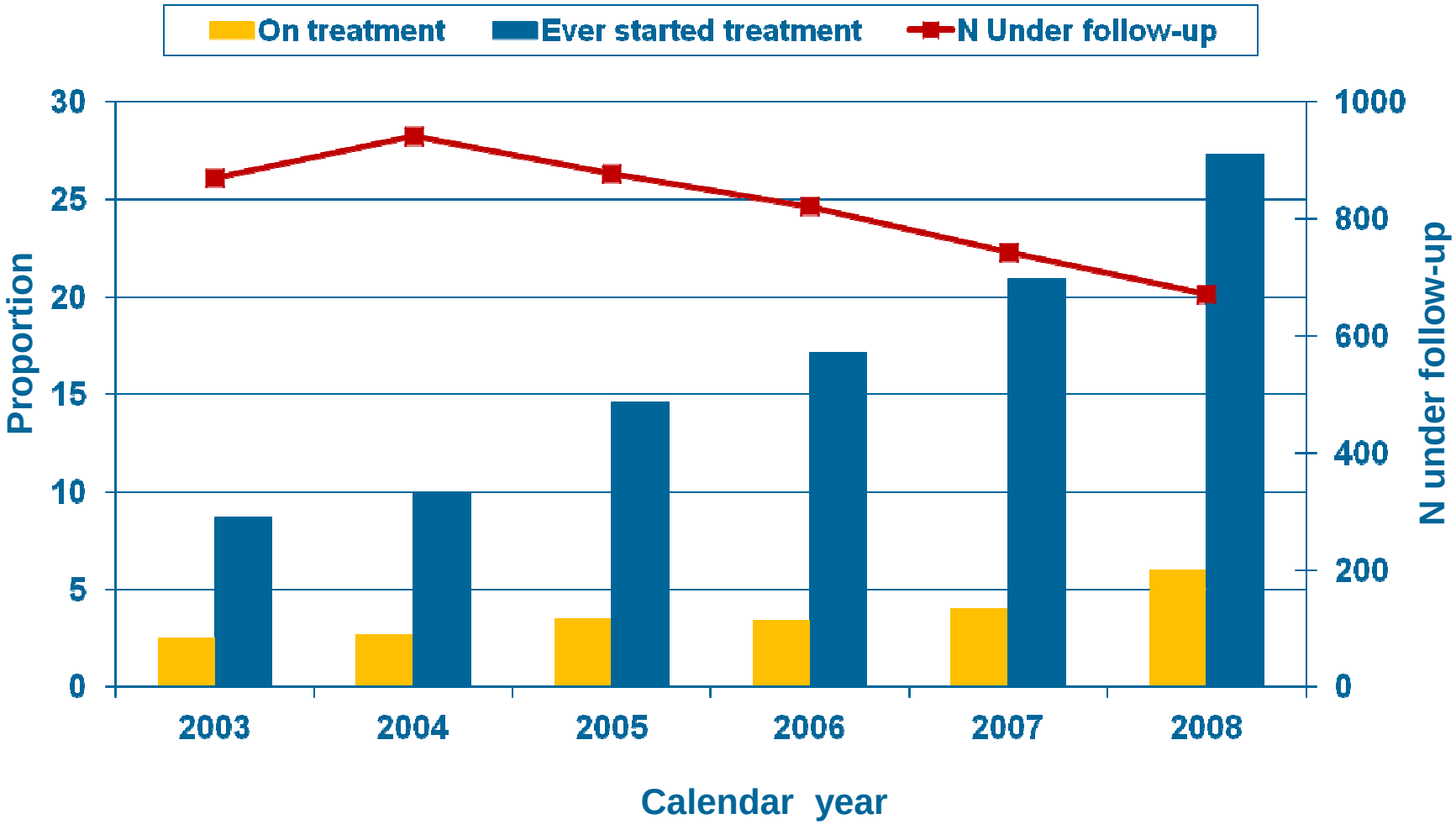
- Testing and counseling
- Treatment of chronic infection
  - Sustained virologic response is possible[1]
  - Sustained virologic response is durable[2]
  - Sustained virologic response prevents death[3]

Survival after HCV treatment for 493 with no SVR and 218 with SVR



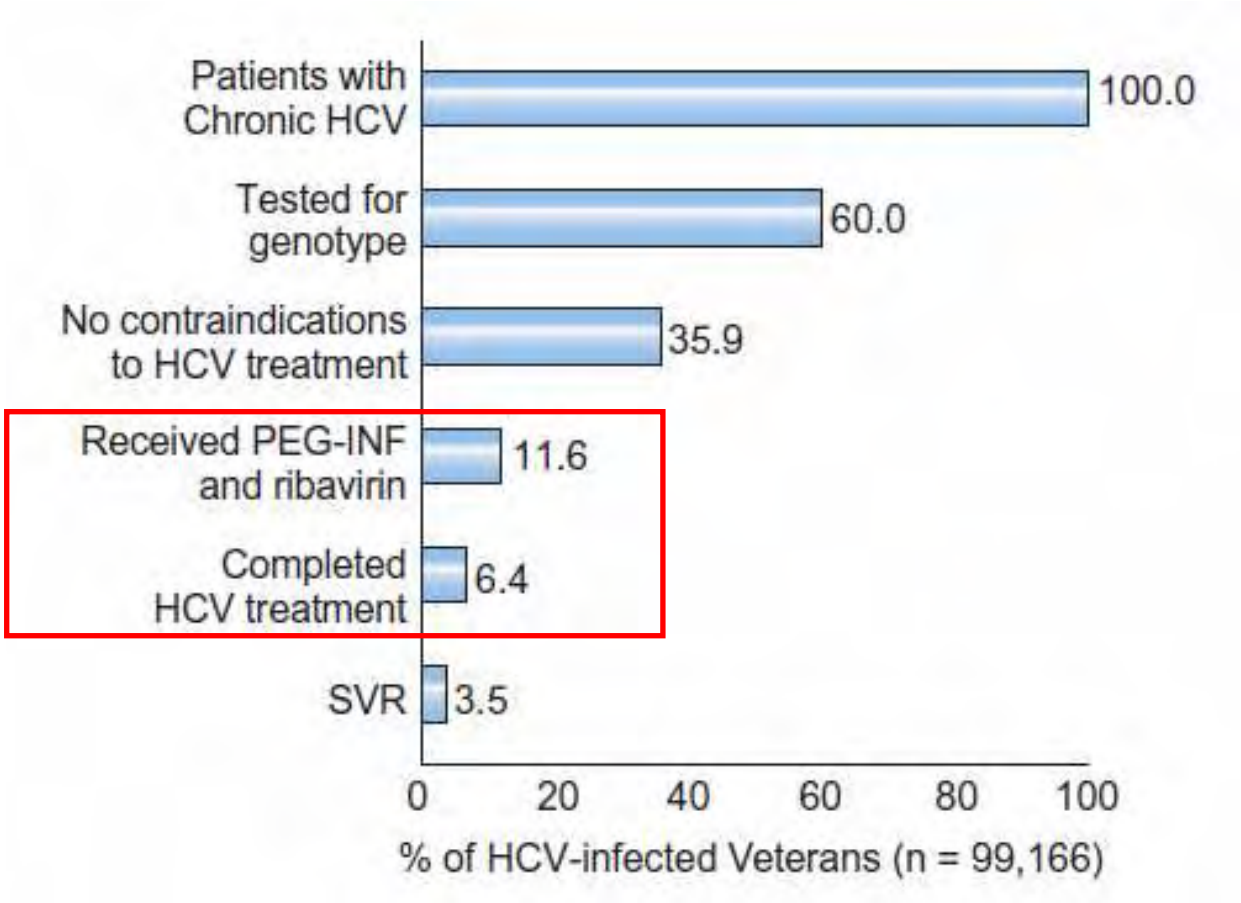
1. Torriani FJ, et al. New Engl J Med. 2004;351:438-450. 2. Soriano V, et al. Antivir Ther. 2004;9:987-992.
3. Berenguer J, et al. Hepatology. 2009;50:407-413.

Current and Cumulative Exposure to HCV Treatment



Mocroft A, et al. EACS Conference 2009. Abstract PS2/3.

Low Rates of Treatment Initiation and Completion of HCV Therapy in US VA System



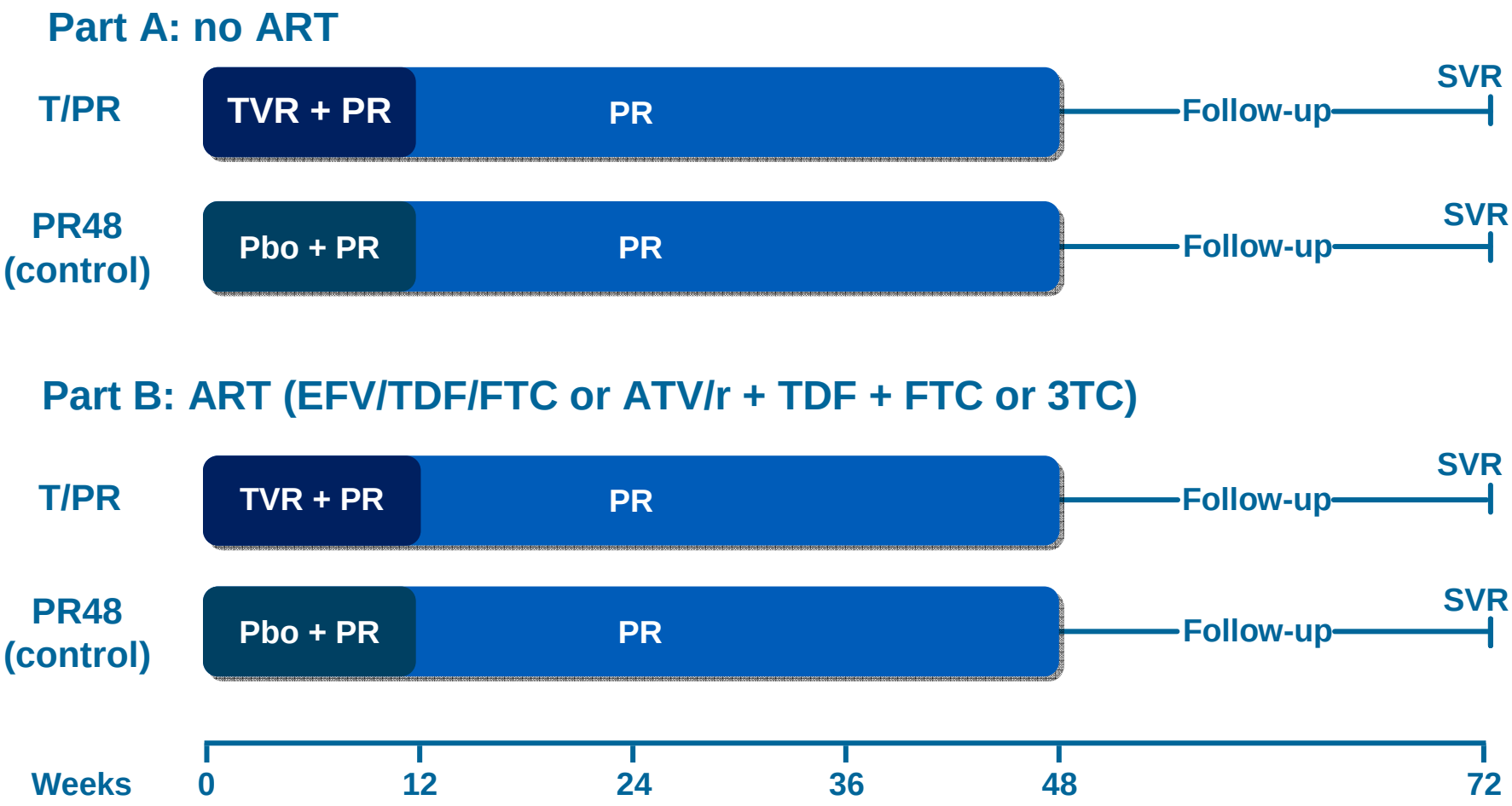
- Among individuals not receiving HIV coinfection cited as the reason for 6.3%

Kramer JR, et al. J Hepatol. 2012;56:320-325.

New HCV agents on the horizon: What are the possible challenges?

- Higher HCV viral loads in HIV/HCV co-infection
  - Lower probability of EVR
  - Higher risk for resistance development
- Drug-drug interactions between HCV drugs and the new oral HCV agents
- Overlapping drug toxicities

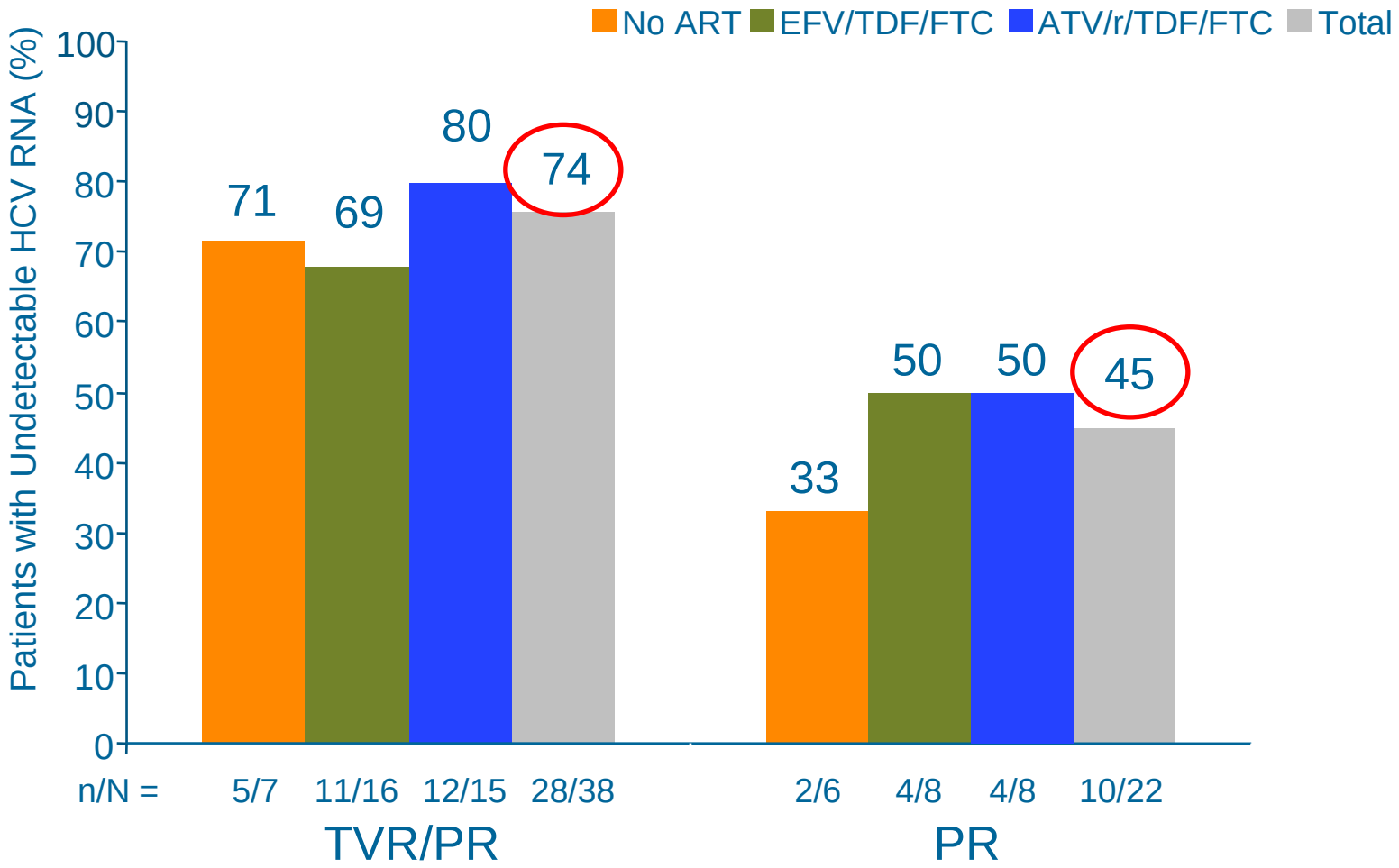
Study 110: Telaprevir in HIV/HCV co-infected patients



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

PR – Pegylated interferon/ribavirin,
TVR – Telaprevir,SVR – Sustained virologic response

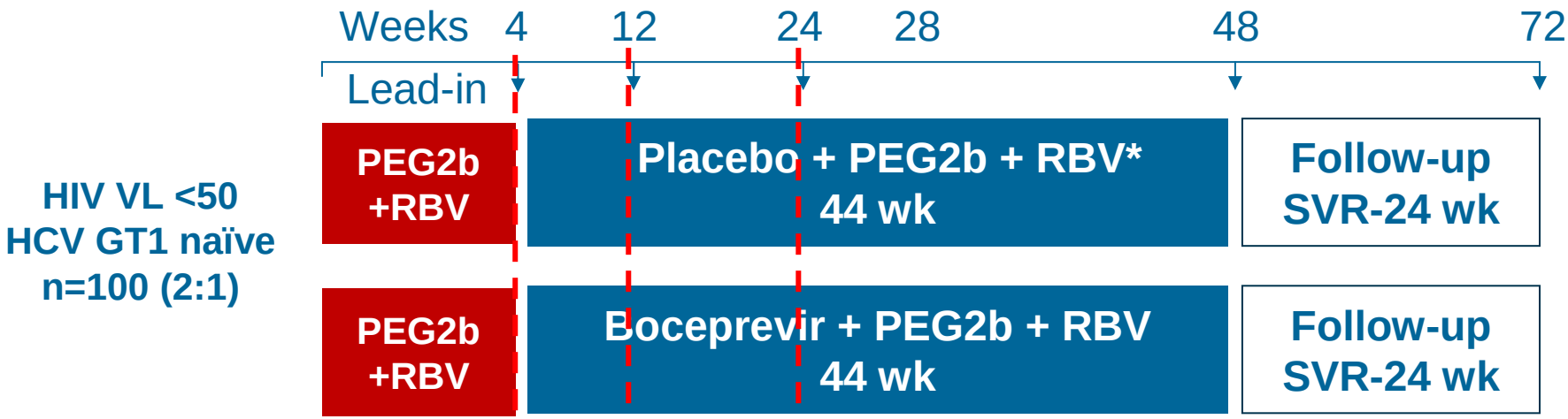
Study 110: SVR Rates
12 Weeks Post-Treatment (SVR12)



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

BOC + PEG/RBV for HCV/HIV co-infection (interim analysis)

Phase II, BOC-double-blinded 800mg TID, PEG2b 1.5µg/kg QW/RBV WB



- Futility rules: W12: <2 $\log_{10}$ decline; W24: HCV RNA ≥ LLOQ
- BL characteristics were well balanced, but cirrhosis: 1-control, 4-BOC

BOC – Boceprevir, PEG/RBV – Pegylated interferon/ribavirin, LLOQ – Lower limit of quantification

Boceprevir: Use of antiretroviral therapy

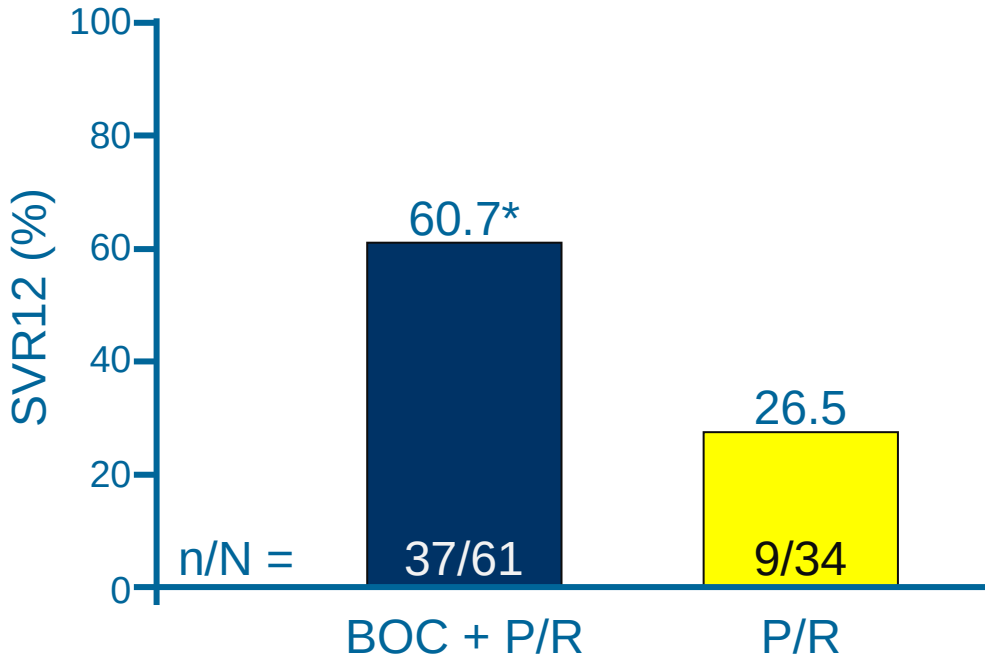
	PR	B/PR
Any*	34 (100)	64 (100)
HIV Protease Inhibitors†	31 (91)	54 (84)
ATV/r Lopinavir/r Darunavir/r	13 (38) 10 (29) 7 (21)	20 (31) 16 (25) 12 (19)
NRTIs††	33 (97)	60 (94)
Integrase Inhibitors	4 (12)	11 (17)
CCR5 antagonists	1 (3)	1 (2)

* To maintain blinding in this continuing study, data is only shown where at least 1 patient in each treatment group is represented.
† HIV PIs included ATVr, DRV/r, LPV/r, fAMP/r, SAQ/r
† † NRTIs included TDF, ABC, 3TC, FTC

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.

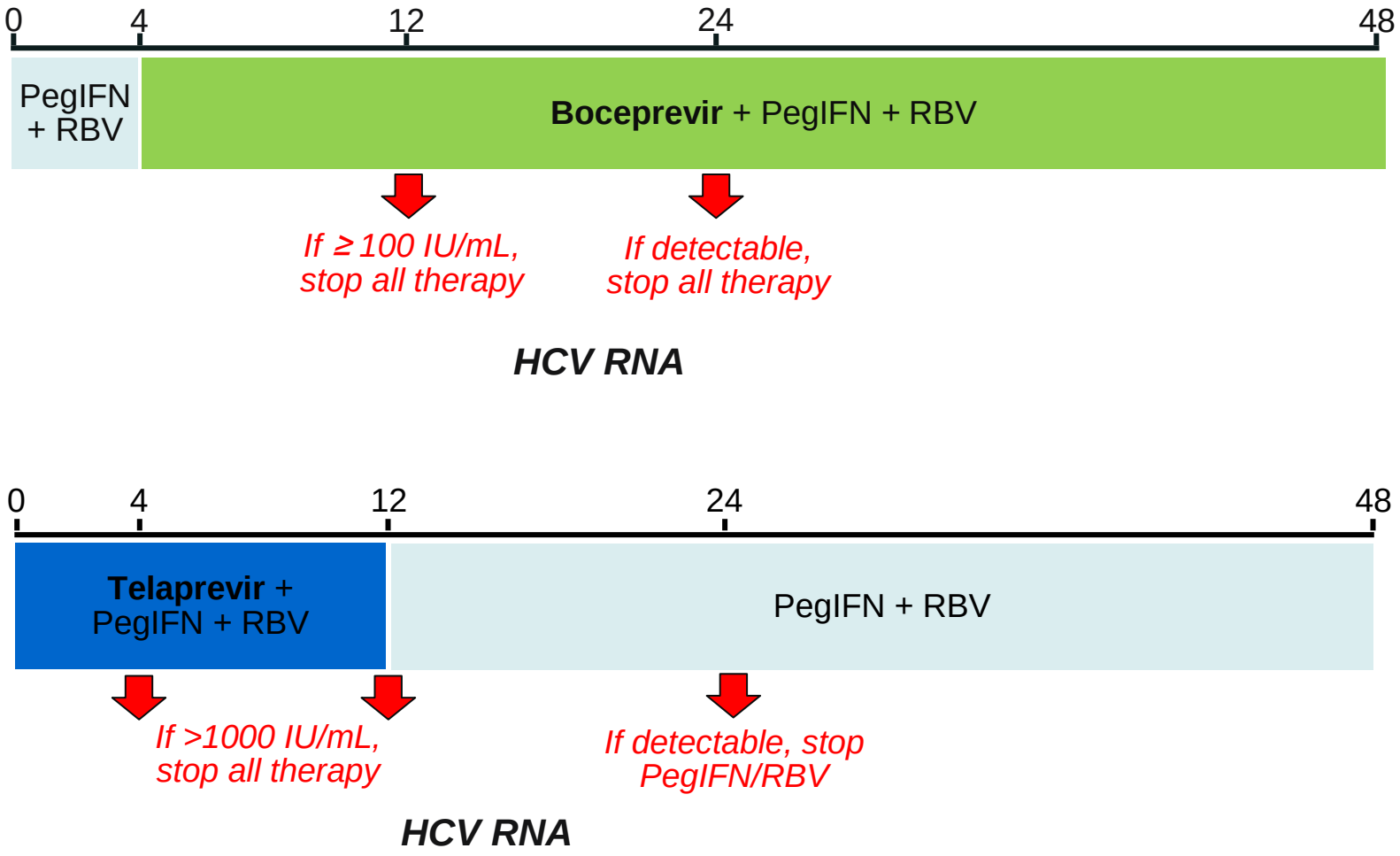
Sulkowski M, et al.; 19th CROI; Seattle, WA, 2012. Abst. 47

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%, respectively**
- **HIV Breakthroughs were observed in 3/64 patients in the BOC group and 4/34 patients in the control group**

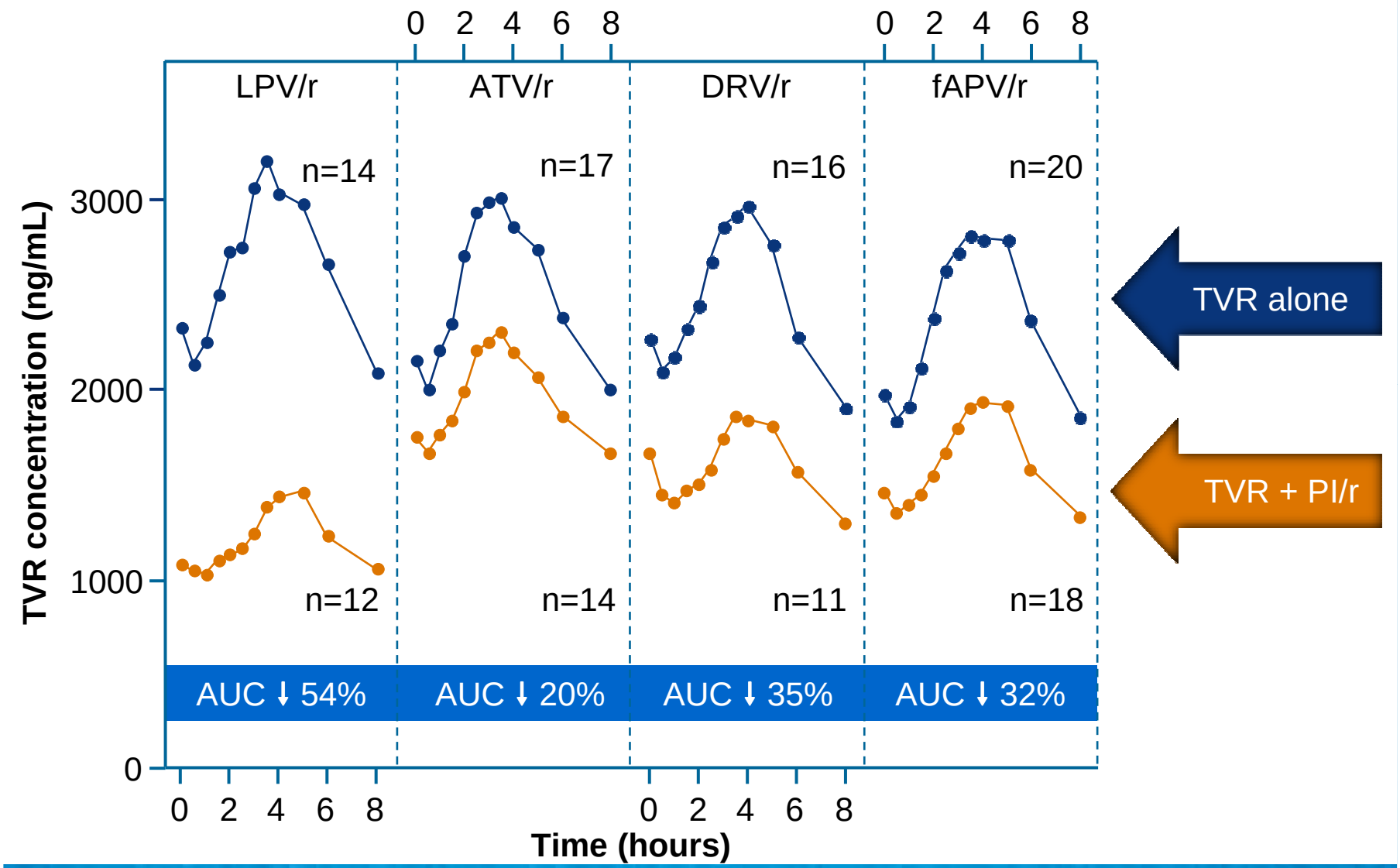
1. Dieterich DT, et al. CROI 2012. Abstract 46.
2. Mallolas J, et al. EASL 2012. Abstract 50.

Use of HCV Therapies in HIV-coinfected Individuals



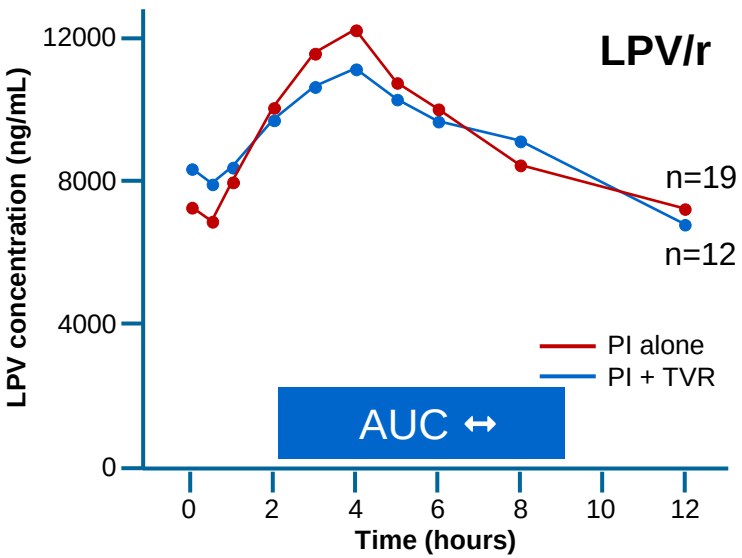
Boceprevir PI. Telaprevir PI.

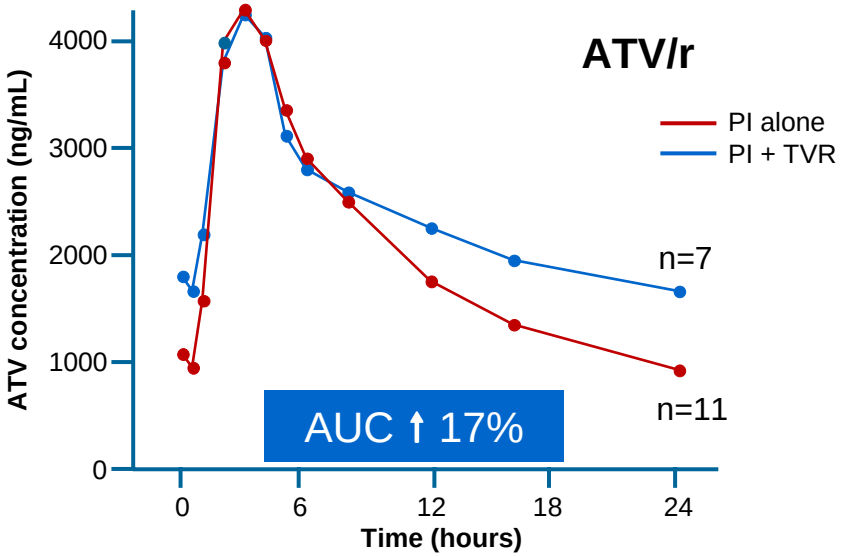
Telaprevir Exposure Decreased With HIV PIs

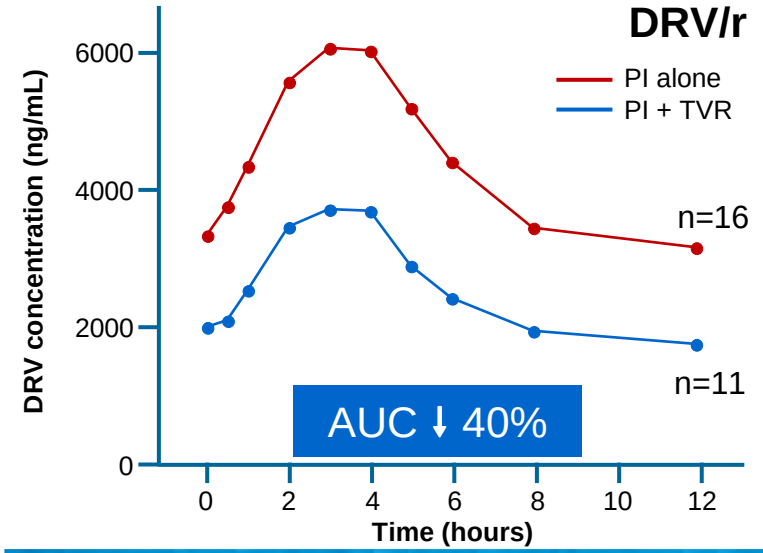


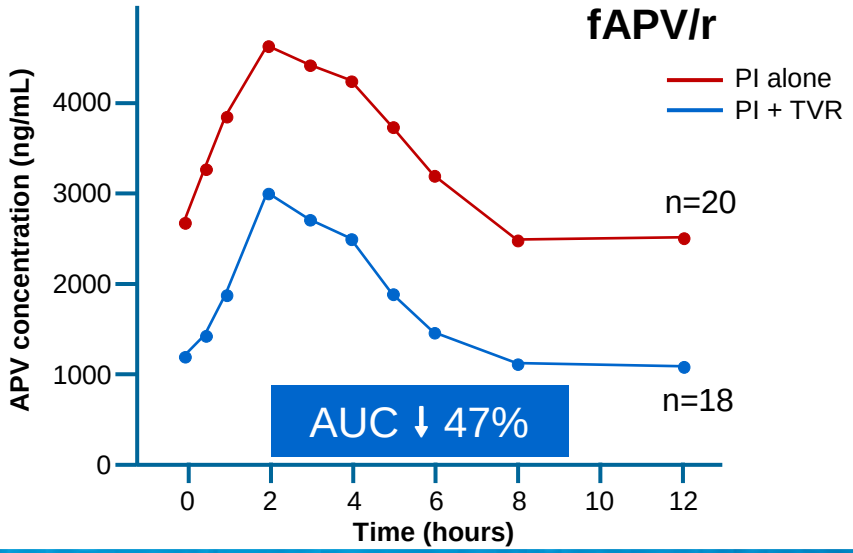
van Heeswijk R, et al. CROI 2011. Abstract 119.

Variable Effect of Telaprevir on HIV PI Exposure









van Heeswijk R, et al. CROI 2011. Abstract 119.

No dose adjustment of raltegravir required in presence of telaprevir

Treatment A: TVR for 6 days with single dose on Day 7

TVR 750 mg q8h

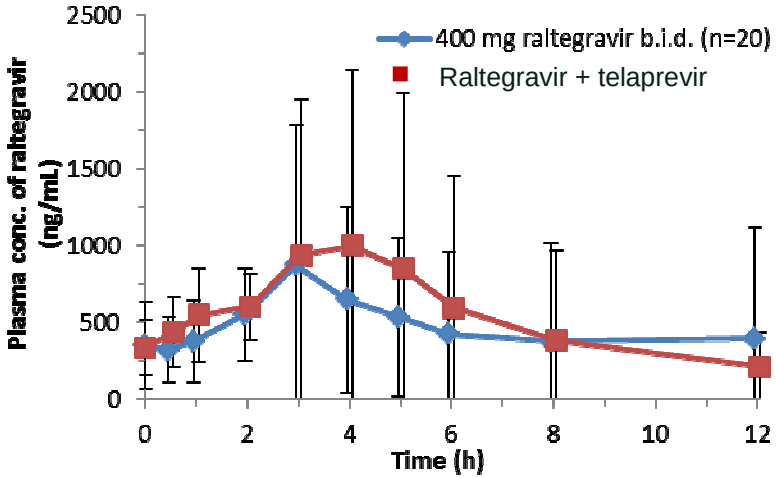
PK

Treatment B: RAL for 10 days, TVR from days 5 to 10 with single doses on Day 11

RAL 400 mg bid

TVR 750 mg q8h

PK PK



➢ **Raltegravir AUC increased by 31%**

Telaprevir: Drug-Drug Interactions With ARVs

HIV Antiretroviral	Recommendation
Studies completed	
Atazanavir/r	Clinical and laboratory monitoring for hyperbilirubinaemia is recommended
Darunavir/r Fosamprenavir/r Lopinavir/r	Coadministration not recommended
Efavirenz	TVR dose increase necessary (1125 mg q8h)
Raltegravir	No dose adjustment required
Etravirine and rilpivirine	No dose adjustment required
Tenofovir	Increased clinical and laboratory monitoring is warranted
Studies not completed	
Abacavir; zidovudine	An effect of telaprevir on UDP-glucuronyltransferases cannot be ruled out and may affect plasma concentrations of abacavir or zidovudine (not studied)

UDP, glucuronosyltransferase: uridine 5'-diphospho-glucuronosyltransferase.

Telaprevir EU SmPC.

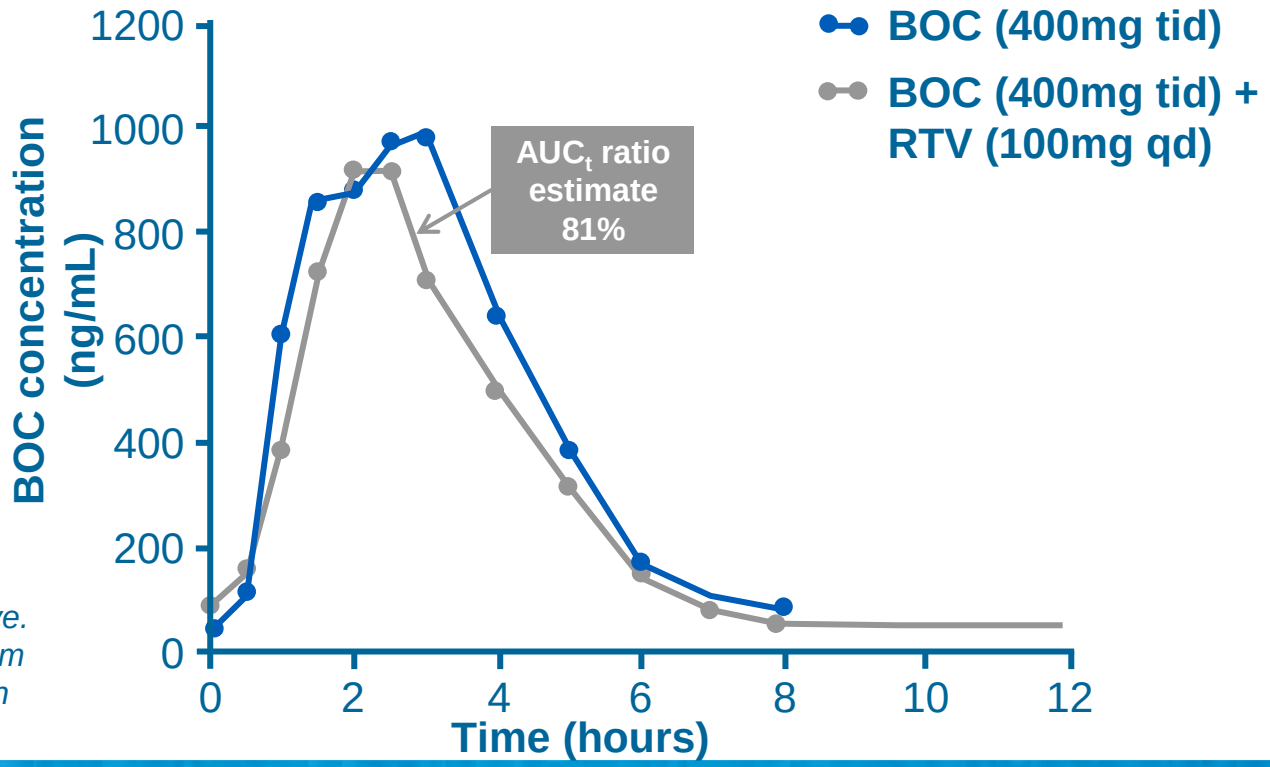
Boceprevir + Ritonavir: No Pharmacoenhancement

N=16 healthy volunteers†

BOC 400mg tid → BOC 400mg tid* + RTV 100mg qd

***BOC stopped at Day 15**

Day 1 — 6 — 17



AUC, area under the curve.
† Number includes pts from a third BID arm not shown here

Modified from Kassera C et al, CROI 2011. Abstract 118.

Effect of ATV/r, LPV/r and DRV/r Coadministration on Boceprevir PK

Coadministered Drug	Ratio Estimate of Coadministered Drug (In Combination Vs Boceprevir Alone) GMR (90% CI)		
	AUC_{τ}	C_{max}	C_{min}
Atazanavir	0.95 (0.87, 1.05)	0.93 (0.80, 1.08)	0.82 (0.68, 0.98)
Lopinavir	0.55 (0.49, 0.61)	0.50 (0.45, 0.55)	0.43 (0.36, 0.53)
Darunavir	0.68 (0.65, 0.72)	0.75 (0.67, 0.85)	0.65 (0.56, 0.76)

- Co-administration with ATV/r does not alter boceprevir AUCτ, but coadministration with LPV/r and DRV/r decreases boceprevir AUCτ 45% and 32%, respectively

GMR, geometric least squares mean ratio.

Hulskotte E, et al. CROI 2012. Abstract 771LB.

Effect of Boceprevir Coadministration on PK of Ritonavir-Boosted ATV, LPV and DRV

Coadministered Drug	Ratio Estimate of Coadministered Drug (In Combination Vs Alone) GMR (90% CI)		
	$AUC_{0\text{-last}}$	C_{max}	C_{min}
Atazanavir	0.65 (0.55, 0.78)	0.75 (0.64, 0.88)	0.51 (0.44, 0.61)
Lopinavir	0.66 (0.60, 0.72)	0.70 (0.65, 0.77)	0.57 (0.49, 0.65)
Darunavir	0.56 (0.51, 0.61)	0.64 (0.58, 0.71)	0.41 (0.38, 0.45)

- Boceprevir coadministration reduces the exposure of ATV, LPV, and DRV by 35%, 34%, and 44%, respectively, and reduces trough concentrations 49%, 43%, and 59%, respectively.
- Mean ATV C_{min} decreased from 693 ng/mL to 357 ng/mL; mean LPV C_{min} decreased from 6,730 ng/mL to 3,805 ng/mL; mean DRV C_{min} decreased from 3,220 ng/mL to 1,321 ng/mL.

GMR, geometric least squares mean ratio.

Hulskotte E, et al. CROI 2012. Abstract 771LB.

Boceprevir Exposure is Decreased by Efavirenz

	Treatment	LSmean*	Ratio estimate, % (90% CI)
BOC AUC_{0-8h}, ng•h/mL	BOC	6913	81 (75–89)
	BOC + EFV	5630	
EFV AUC_{0-24h}, ng•h/mL	EFV	78667	120 (115–126)
	EFV + BOC	94655	

The clinical outcome of this observed reduction of boceprevir trough concentrations has not been directly assessed

SD, single dose.

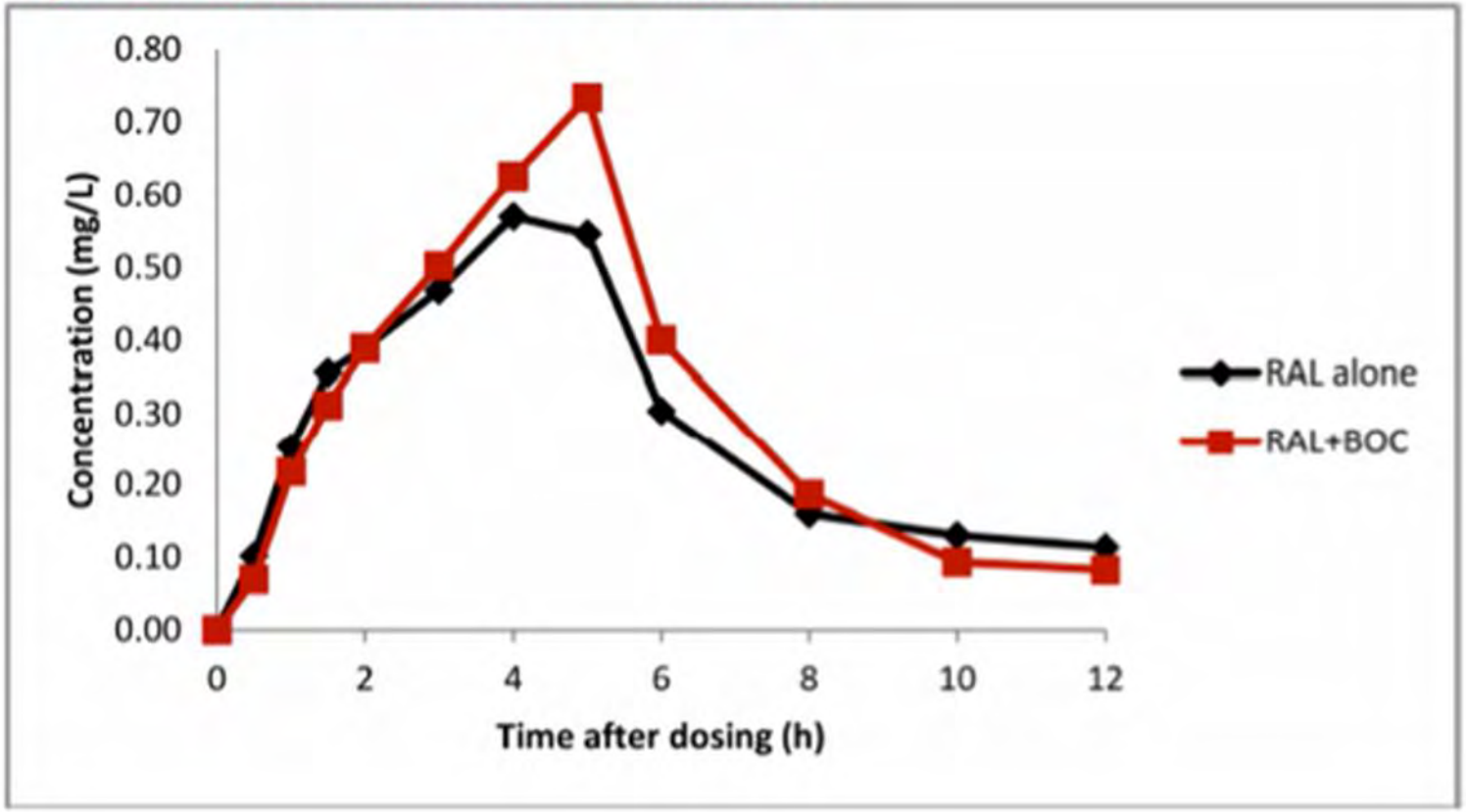
*Model-based (least squares) geometric mean, ANOVA extracting the effects due to treatment and volunteer.

1. Modified from Kassera C, et al. CROI 2011. Abstract 118. 2. Boceprevir EU SmPC.

No need for raltegravir dose changes in combination with Boceprevir

universitäts klinikum bonn

Figure 1: RAL plasma concentration vs. time curves



De Kanter et al, CROI 2012 Abstract 772LB

Boceprevir: DDIs with HIV antiretrovirals

HIV antiretroviral	Recommendation
Studies completed	
Atazanavir/r	In general not recommended; EMEA says can be considered on a case-by-case basis if patient has no prior HIV drug resistance and is suppressed
Darunavir/r Fosamprenavir/r Lopinavir/r	Not recommended
Efavirenz	Not recommended
Etravirine	No dose adjustment required
Raltegravir	No dose adjustment required

DDI –Drug-drug interactions

Hulskotte E et al., 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 771LB
De Kanter C et al., 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 772LB
FDA Safety Announcement, dated 08 Feb 2012
EMA press release, dated 17 Feb 2012
Merck "Dear Health Care Provider" letter, dated 06 Feb 2012
Hammond K, et al. IWCPHIV 2012. Abstract O_15

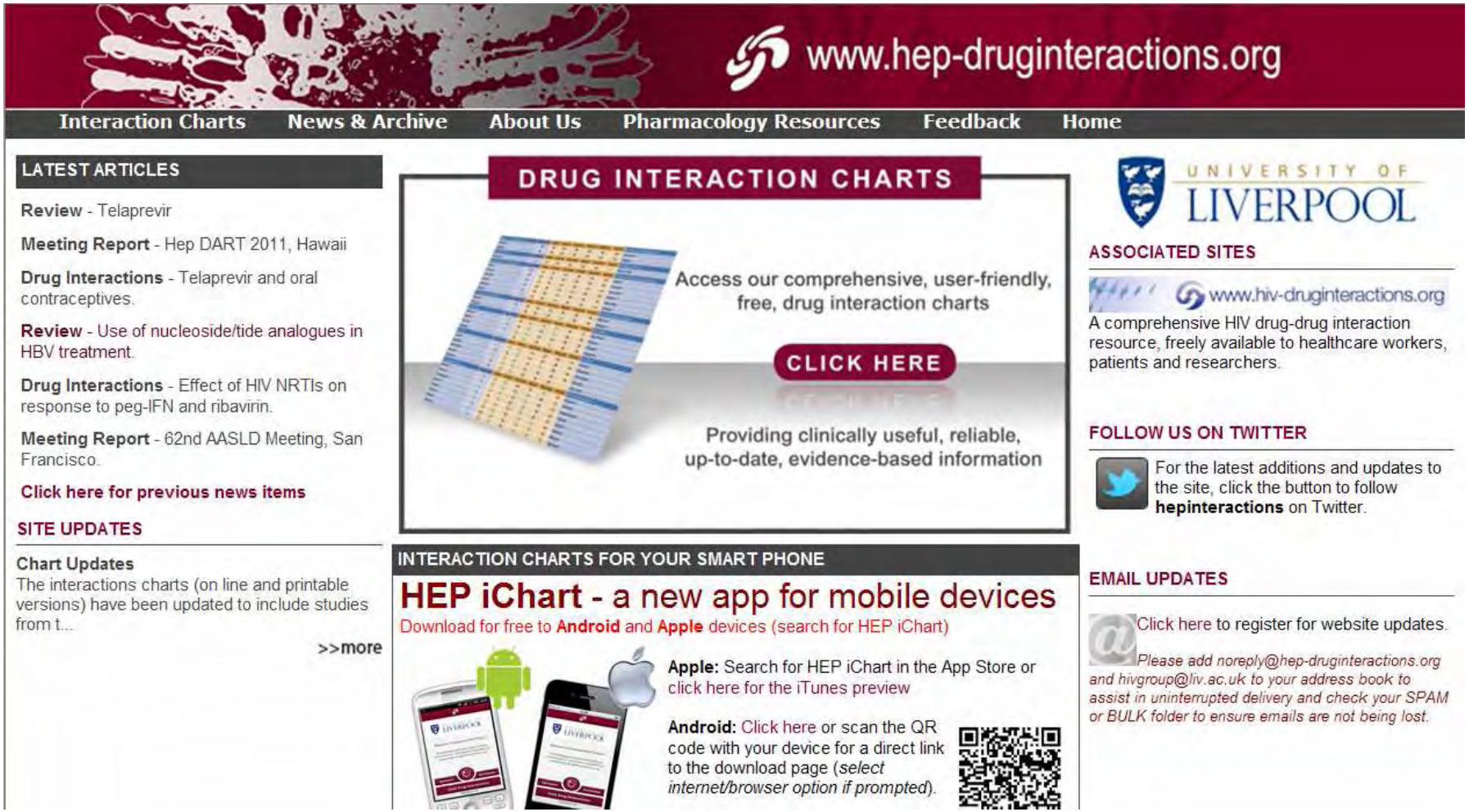
Correspondence

AIDS 2012, 26:000–000

HIV protease inhibitors in combination with boceprevir: are drug–drug interactions the same for all patients?

Carolynne Schwarze-Zander and Jürgen K. Rockstroh,
Department of Internal Medicine I, University Hospital Bonn, Bonn, Germany.

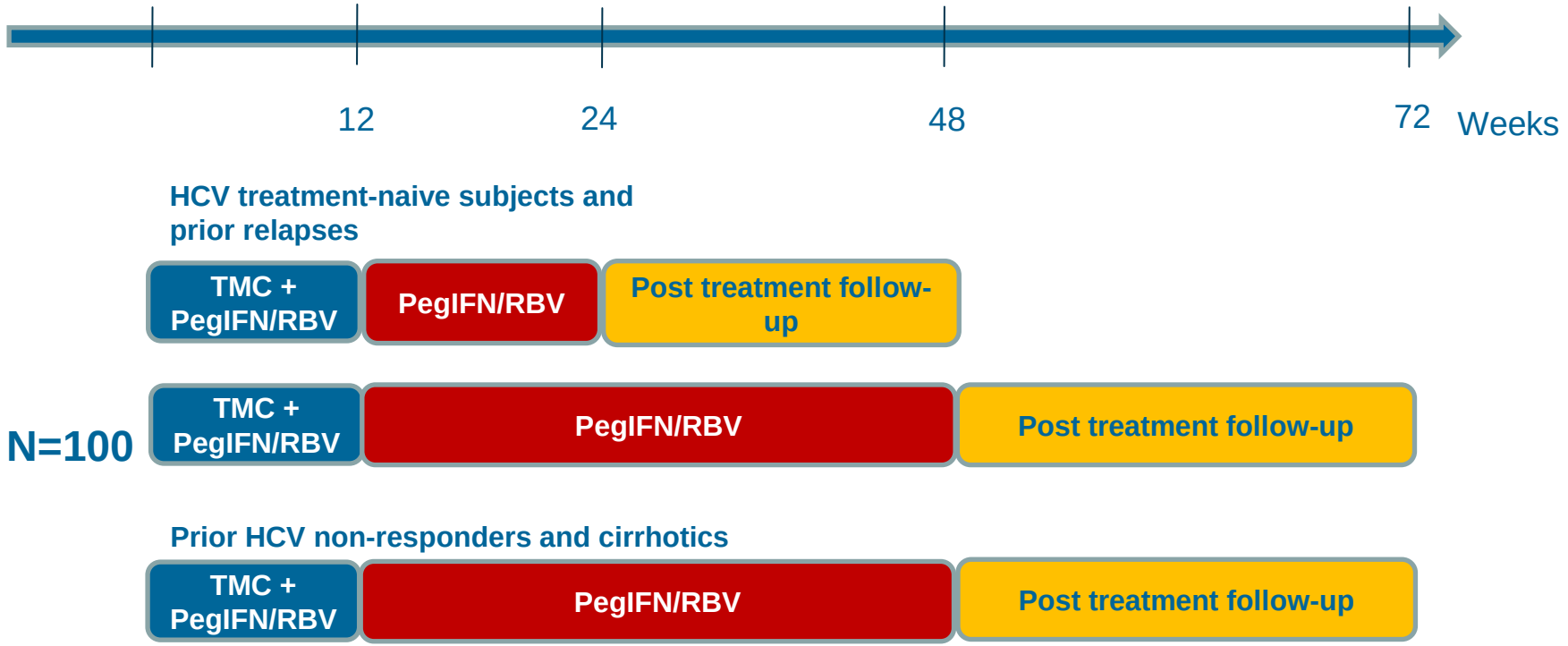
Management Issues with Comedications



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

- With first pilot studies in HIV/HCV-coinfected subjects demonstrating significant higher SVR12 rates with triple 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.
- Although shorter treatment durations of triple therapy have been demonstrated to be very efficacious in HCV monoinfected subjects with rapid virological response this data so far is not available for HIV/HCV coinfected subjects.

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



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

http://clinicaltrials.gov/ct2/show/NCT01479868

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

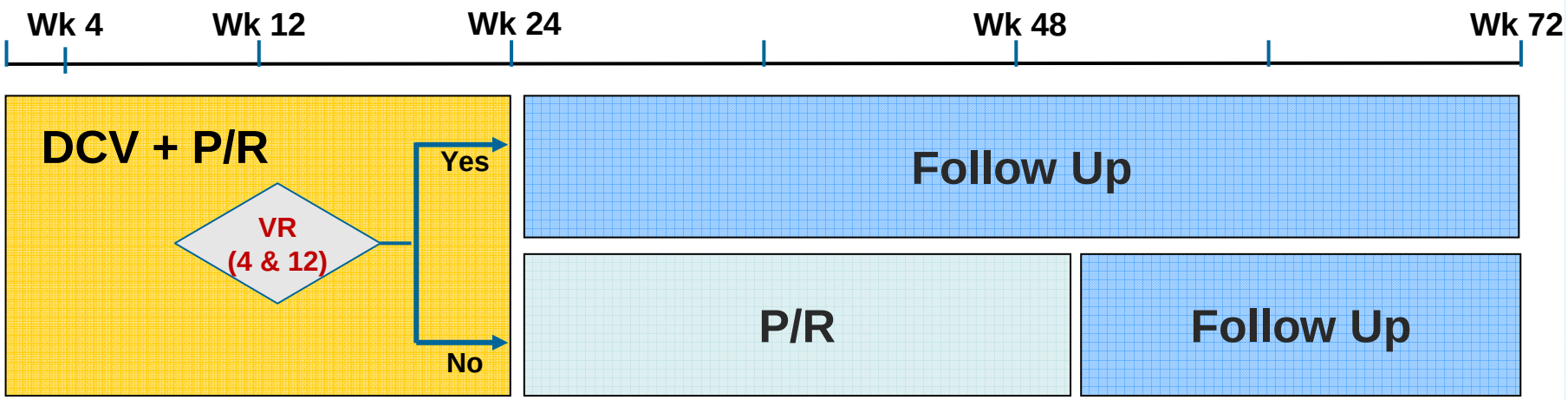
- Raltegravir, Tenofovir/Emitricitabine
- DRV/RTV, ATZ/RTV (limited n)
- Efavirenz
- Maraviroc
- Abacavir, Lamivudine

Additional information

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

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

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



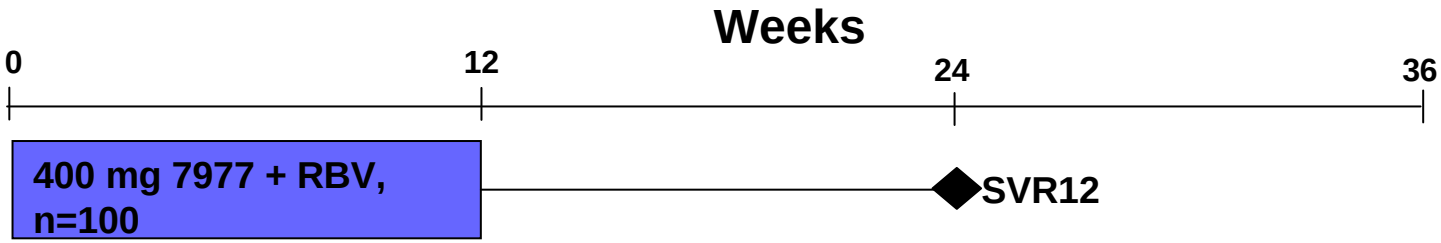
Response Guided Treatment (RGT)

- 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

http://clinicaltrials.gov/ct2/show/NCT01471574

334-0123: GT- 2/3 HIV/HCV Coinfected Treatment Naïve and Experienced Subjects



- 115 GT- 2/3 Treatment Naïve and Experienced Subjects
- Planned study start in July 2012 (US only)
- HIV treatment status
  - Stable approved ART with CD4 > 200cells/mm3 or
  - No ART with CD4 > 500cells/mm3 (Up to 10%)
  - FTC/TDF, DRV/r, RAL and RPV allowed for ARV regimens
- Optimized ART for 8 weeks prior to screening
- Up to 20% compensated cirrhotics
- GT 1 arm to follow pending evolving data

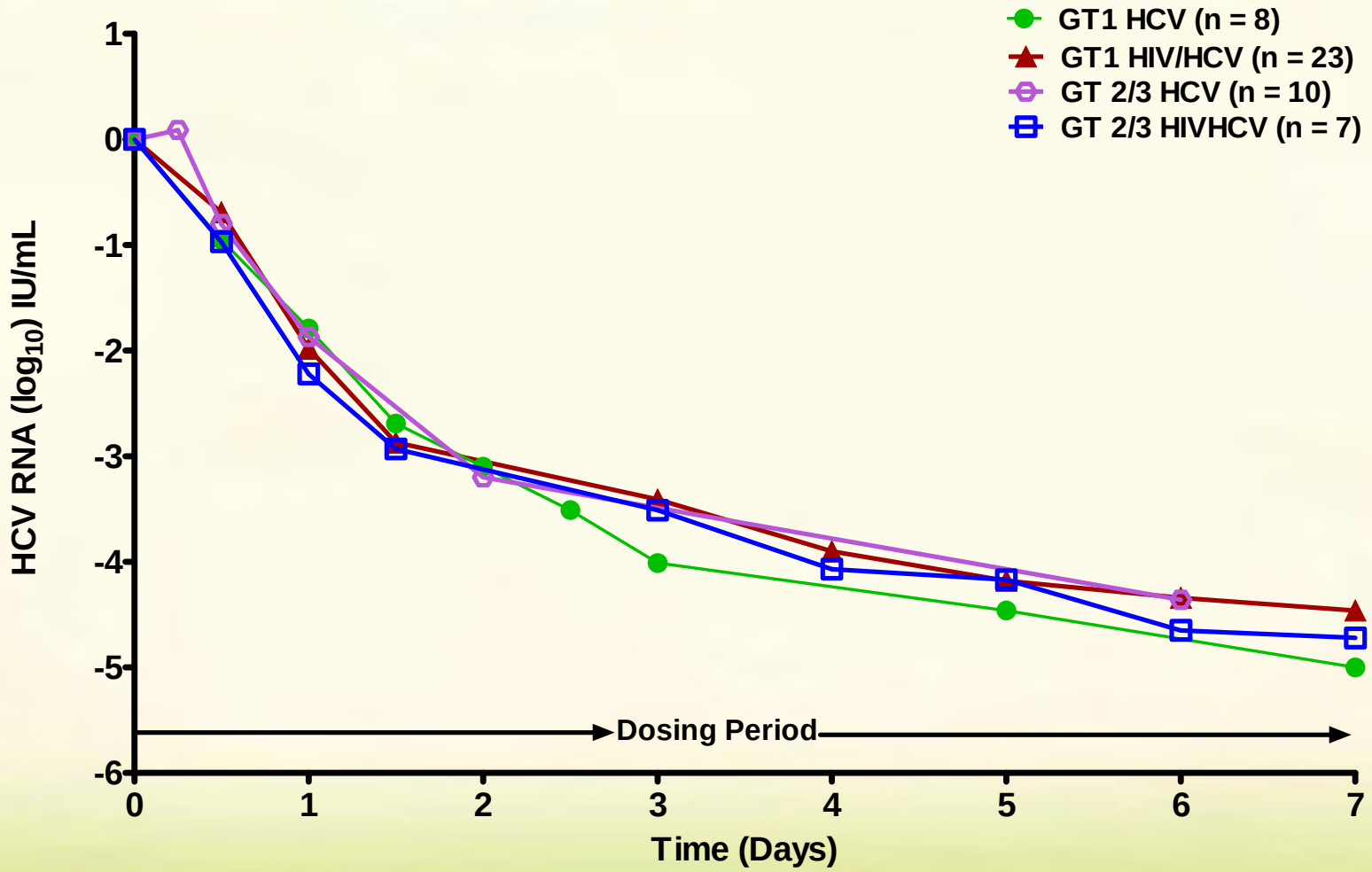
GILEAD

Study Objectives

- Evaluate the early HCV viral kinetics of Sofosbuvir (SOF; GS-7977) in HIV/HCV coinfected subjects
- Assess the safety and tolerability of SOF 400 mg QD × 7 days in combination with ARV regimens
- Evaluate the impact of SOF on HIV RNA and CD4%
- Evaluate drug-drug interactions between SOF and ARV regimens

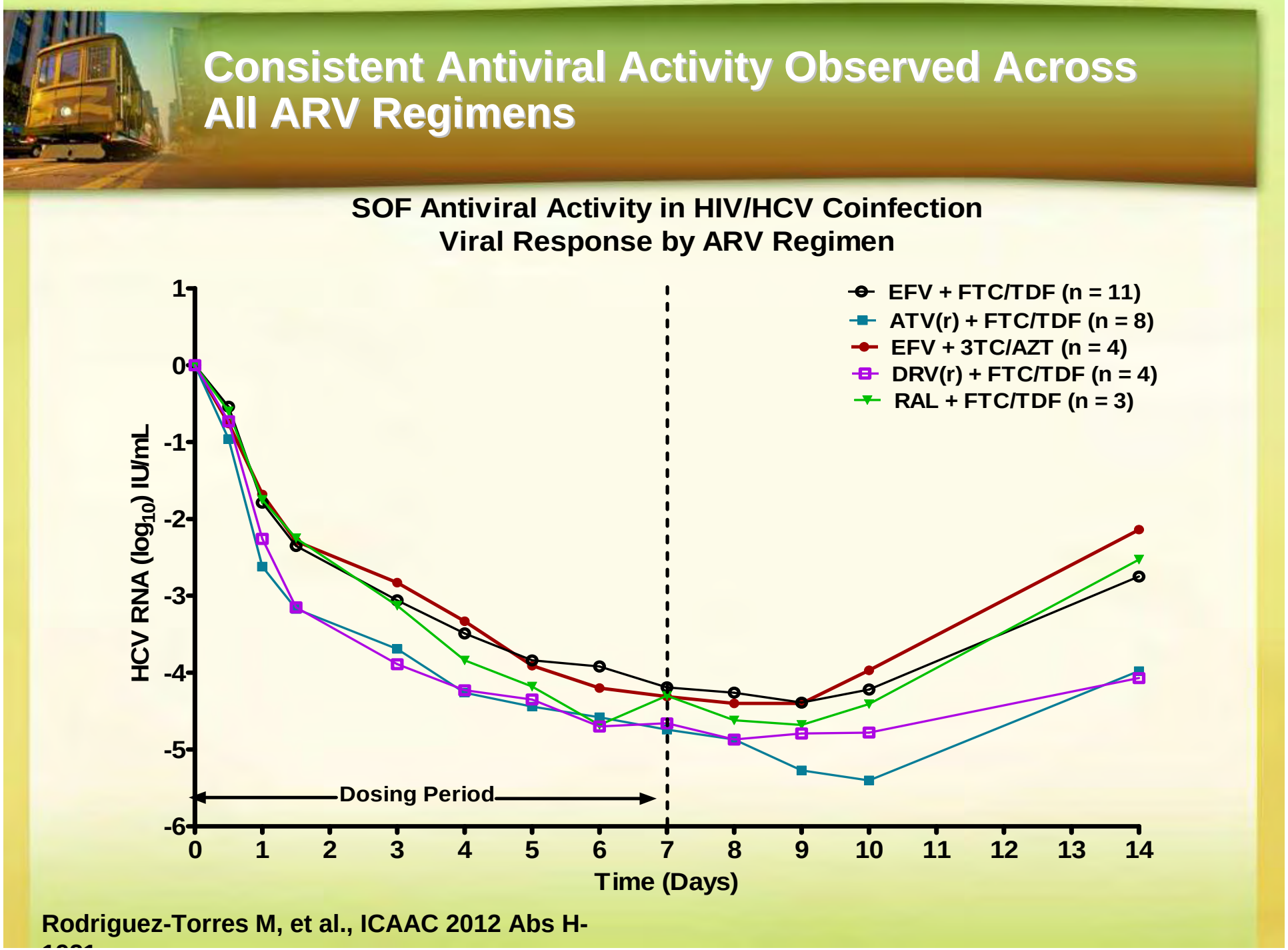
Rodriguez-Torres M, et al., ICAAC 2012 Abs H-1921a

Similar Early Viral Kinetics in Monoinfection and Coinfection



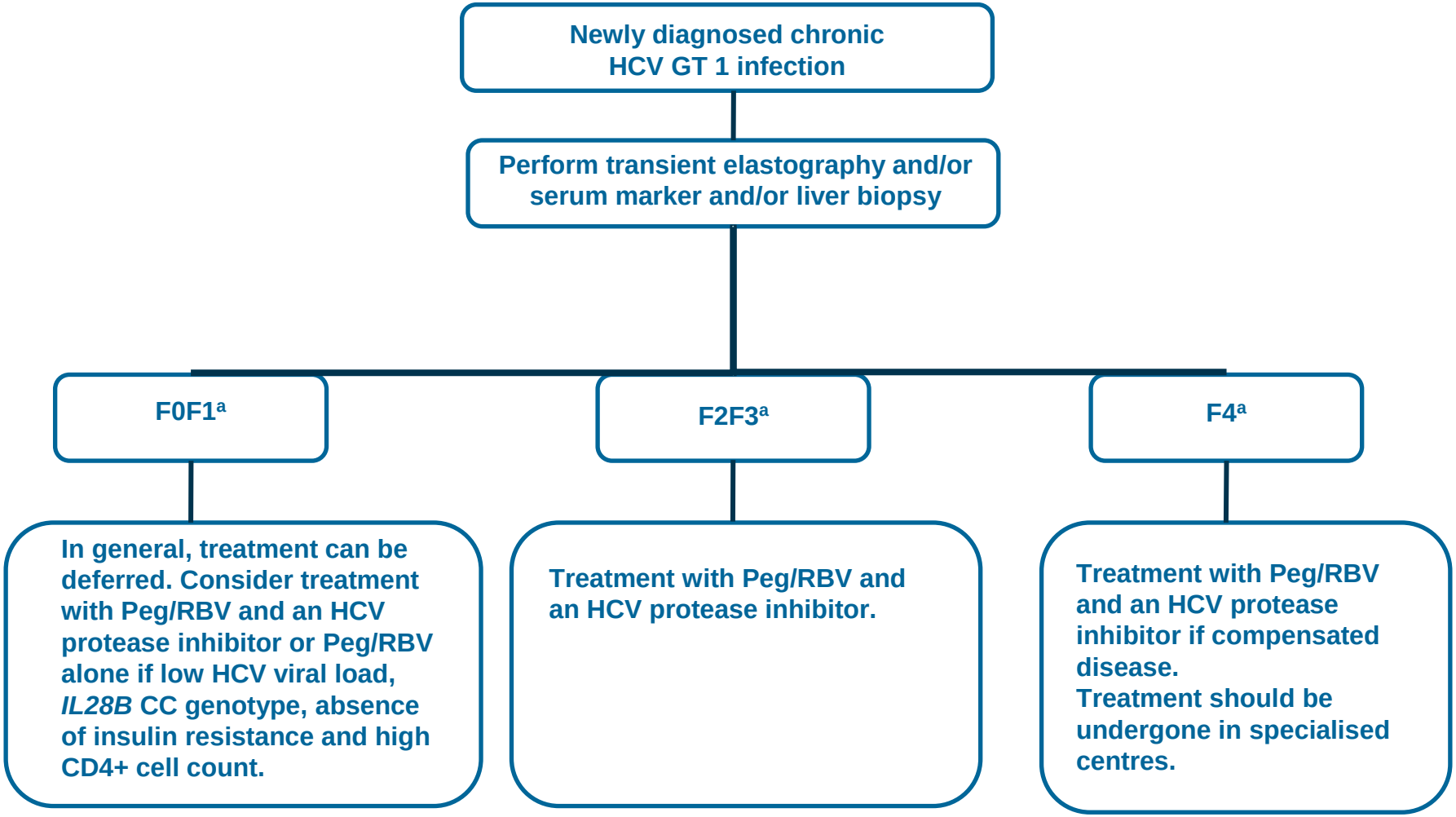
Lawitz E, et al. EASL 2012; Gane E, et al. AASLD 2011; Rodriguez-Torres M, et al., ICAAC 2012 Abs H-1921a

Consistent Antiviral Activity Observed Across All ARV Regimens



Rodriguez-Torres M, et al., ICAAC 2012 Abs H-

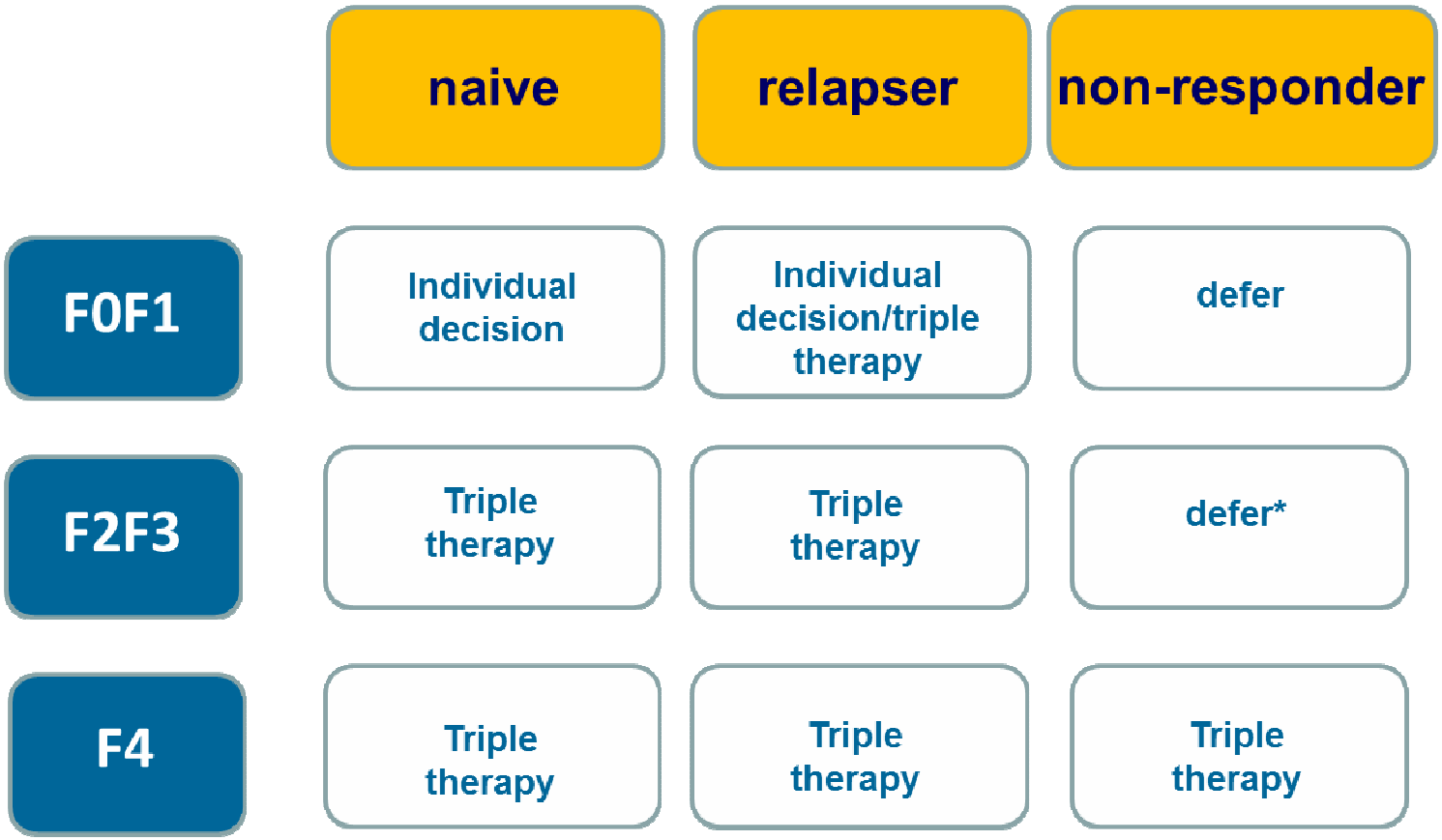
Management of Newly Diagnosed HIV/HCV Coinfected Genotype 1 Patients



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

Ingiliz P, Rockstroh. J. Liver International 2012

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



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

Ingiliz P, Rockstroh. J. Liver International 2012

Summary

- HCV/HIV-coinfected patients show a faster progression to cirrhosis and increased liver-related mortality compared with HCV monoinfection
- HCV treatment options need to be evaluated and discussed with the patient
- HAART should not be withheld in coinfected patients, and needs to be adapted to concomitant HCV therapy
- HCV treatment decisions need to be based on fibrosis stage, likelihood of treatment response, and previous response to IFN/RBV-based therapies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