



# Consensus recommendation on treatment of acute HCV in HIV+ people, ideas for trials

**HEPDART 2011**, Frontiers in drug development for viral hepatitis,  
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## **Acute hepatitis C in HIV-infected individuals: recommendations from the European AIDS Treatment Network (NEAT) consensus conference**

**The European AIDS Treatment Network (NEAT) Acute Hepatitis C  
Infection Consensus Panel**

*AIDS* 2011, 25:399–409

# Grading of Evidence, definition consensus

Strength of Recommendation	
Grade A	Strong – good evidence to support a statement
Grade B	Moderate – moderate evidence to support a statement
Grade C	Optional – poor evidence to support a statement
Quality of Evidence	
Level I	Evidence from at least one randomized controlled study
Level II	Evidence from at least one well-designed non-randomized study; one or more cohort or case-controlled studies; or from dramatic results of uncontrolled studies
Level III	Evidence from expert opinion only

**Consensus was reached if 80% or more of attendees were in favor of a statement**

# Acute HCV in HIV

- **When to treat**
- **How to treat**
- **Future trials**

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# Natural Course AHC in HIV-positive *C.NEAT Cohort, 92 untreated patients*

- Week 4 HCV-RNA may be predictive for negative HCV-RNA at week 24 (=spontaneous clearance)
- Sensitivity analysis classifying missing = failure reduced NPV of a pRVC to 78%

**pRVC** partial rapid virological control

*2 log drop of HCV-RNA at week 4*

**cRVC** complete rapid virological control

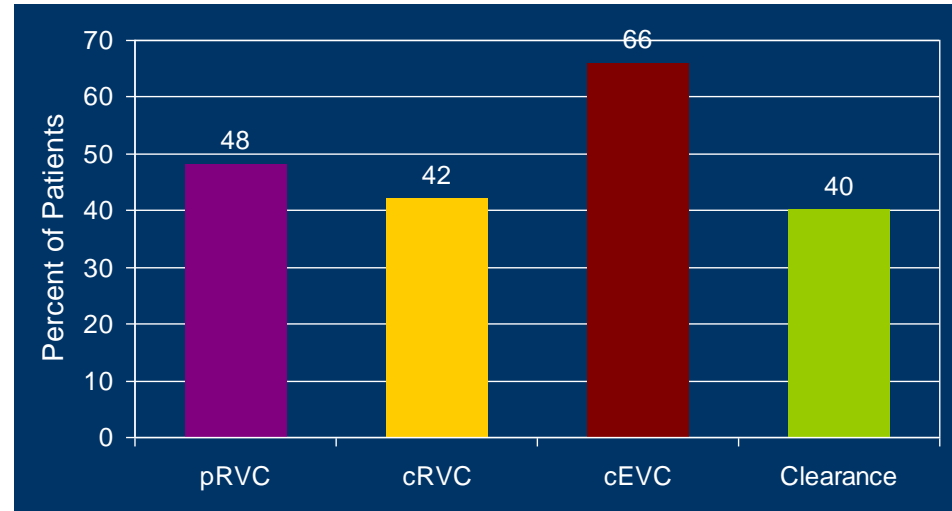
*HCV-RNA < 600 IU/ml at week 4*

**cEVC** complete early virological control

*HCV-RNA < 600 IU/ml at week 12*

**Clearance**

*HCV-RNA < 600 IU/ml week 24*



	Clearance	chronic HCV	predictive value
<b>pRVC</b>	22	3	PPV 88%
<b>no pRVC</b>	4	23	NPV 85%
<b>cEVC</b>	32	4	PPV 89%
<b>no cEVC</b>	2	23	NPV 92%

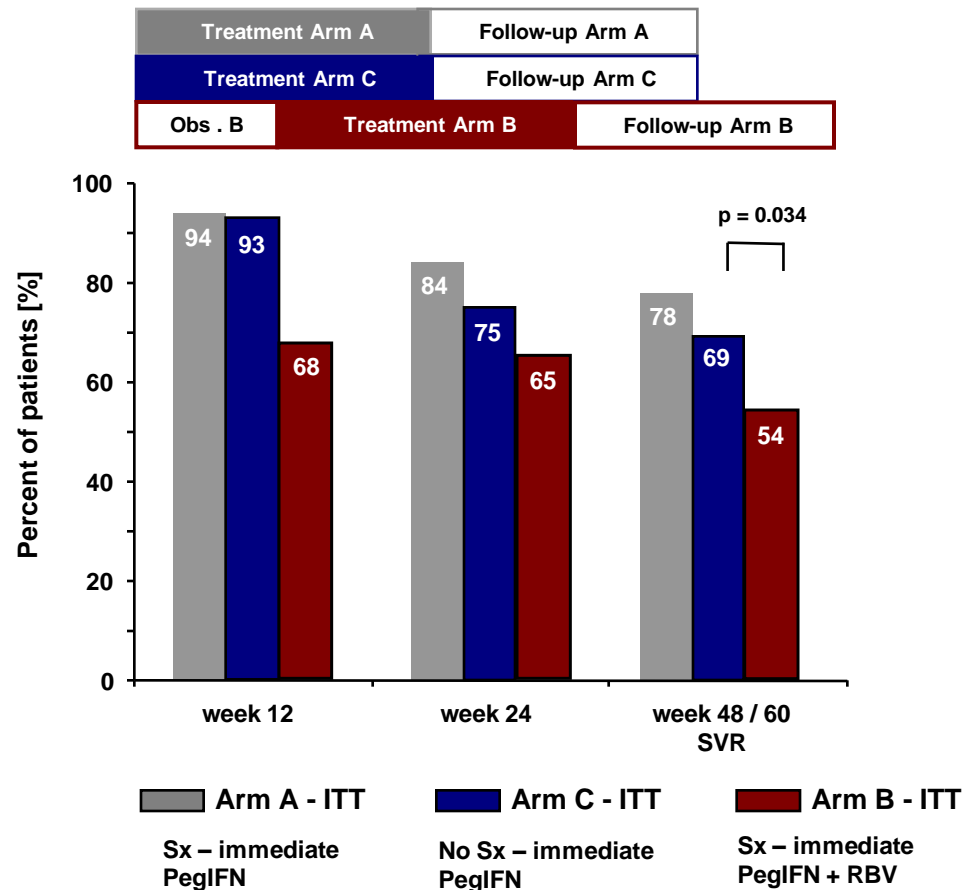
# When is the best time to treat?

- **Data mono-infected patients**
  - Despite delay of treatment for 12 weeks after onset of symptoms high treatment response rates were observed (SVR 80%)<sup>1</sup>
  - Patients with GT1-infections and high HCV-RNA *worse Outcome* comparing start at week 8 vs. 20<sup>2</sup> after diagnosis
    - week 8 SVR 75%, week 12 SVR 72%, week 20 SVR 42%
- **Data HIV co-infected patients – start of treatment after diagnosis**
  - French<sup>3</sup> cohort (n=23, 3 – 24 weeks), German<sup>4</sup> cohort (n=36, 0 – 24 weeks): no influence on Treatment *Outcome*

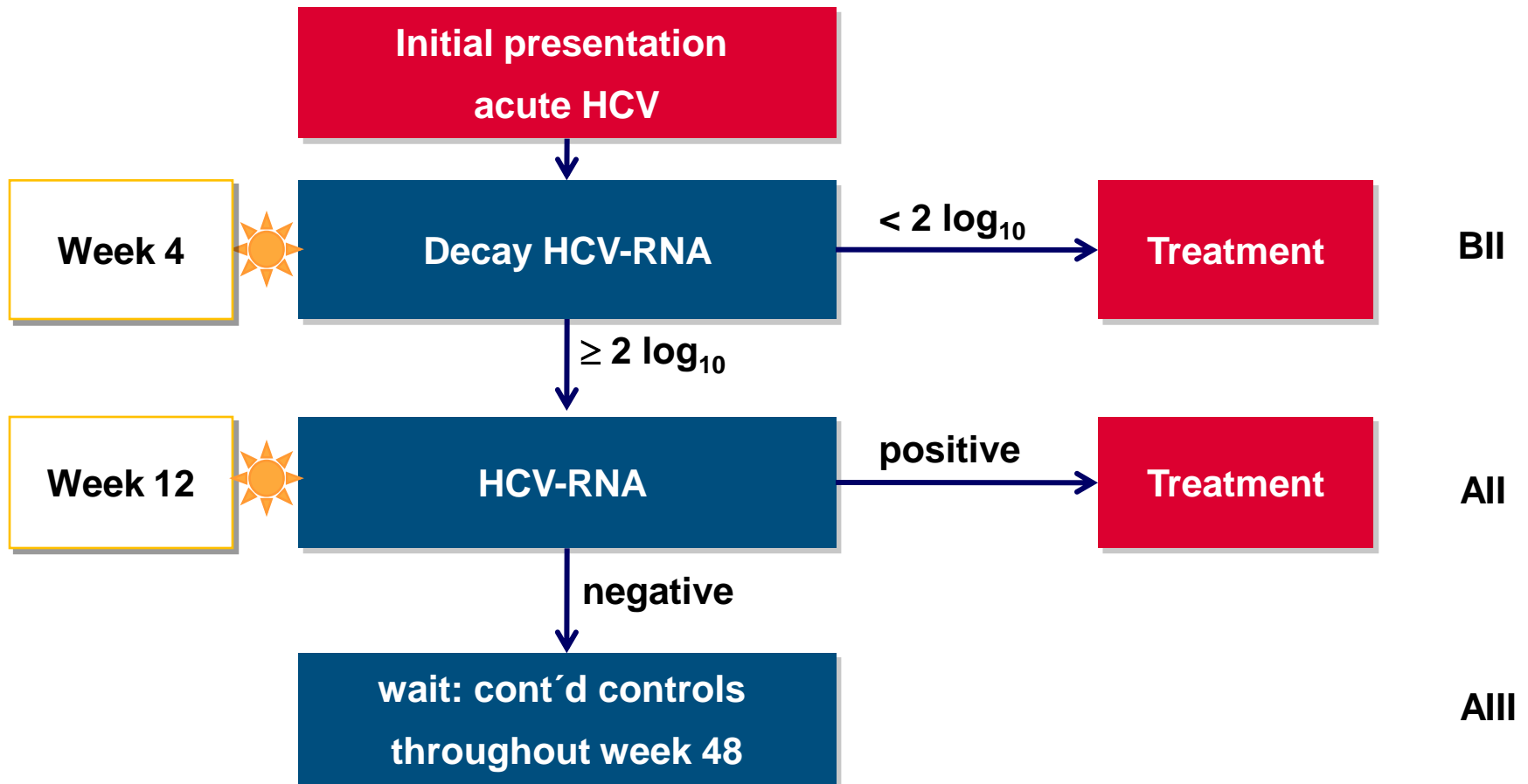
# When to treat acute HCV?

## *Monoinfected patients*

- Treatment schedule
  - Arm A: symptomatic AHC, immediate therapy
  - Arm B: symptomatic AHC, deferred therapy (if HCV-RNA positive at week 12 treat)
  - Arm C: asymptomatic AHC immediate therapy
- As-treated analysis no difference in SVR, all 12 patients in the late arm who completed therapy reached SVR
- CAVEAT: high drop-out rate in the watch and wait arm, ITT showed significantly poorer outcome 69 vs. 54% SVR



# Monitoring and initiation antiviral therapy



Testing of retrospective samples may be useful to assess duration of viral infection. In case of HCV infection durations greater than 12 weeks treatment initiation should occur if viable.

## Observational database

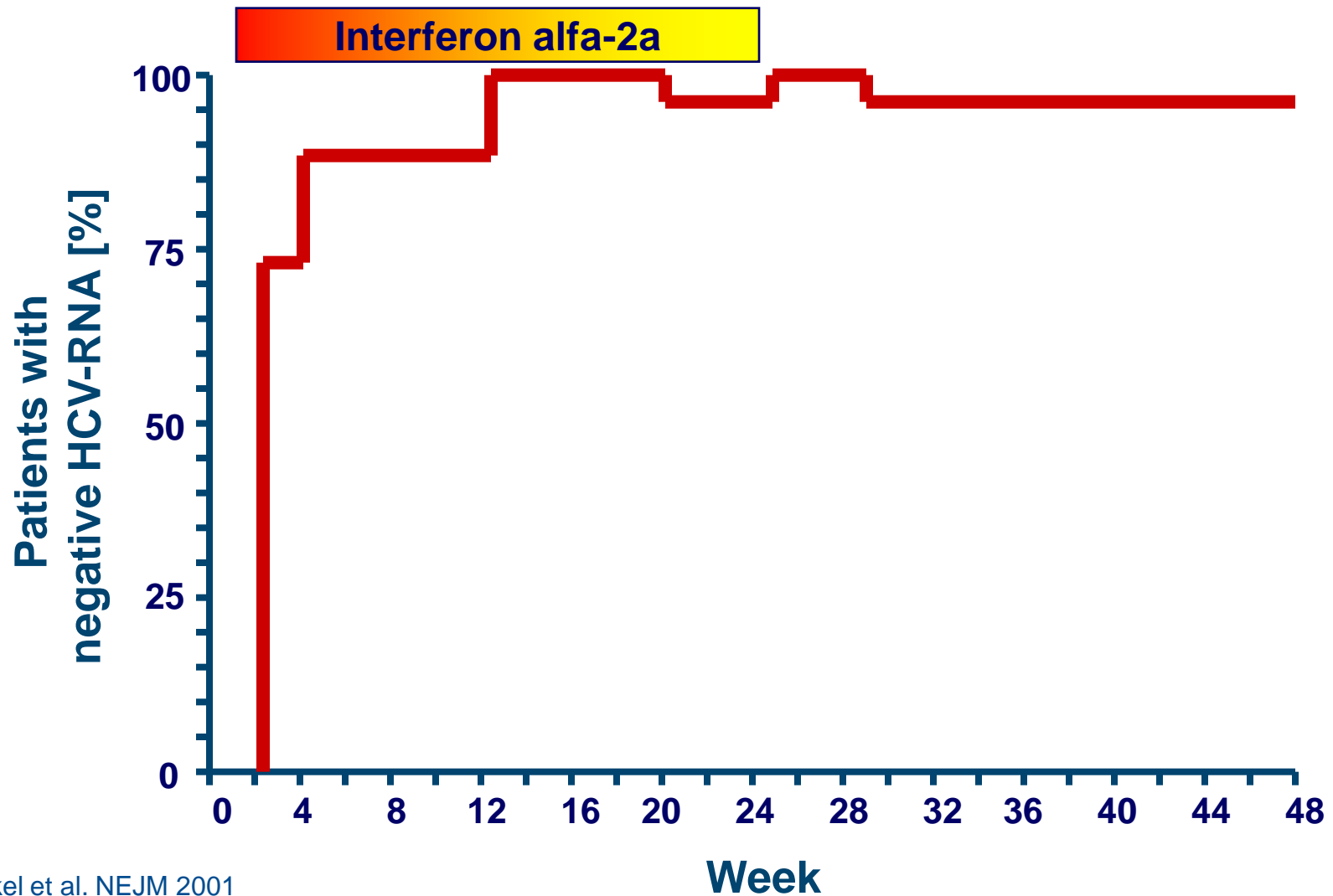


# Acute HCV in HIV

- **When to treat**
- **How to treat**
- **Future trials**

# High efficacy of IFN mono

*HIV- patients*



# How to treat acute HCV in HIV+

## Current data

- **National pilot studies<sup>1-3</sup> – similar protocols**
  - Pegylated Interferon + / - Ribavirin
  - Duration: 24 Weeks
  - **Sustained virological response (SVR): 60 - 70%**
- **Problems:**
  - no randomized trials
  - small patient samples



# Treatment Regimen

Study	Number treated (n)	Treatment	Treatment duration (weeks)	SVR [n (%)]
New York [11]	15	Peg-IFN 2a + RBV 1000–1200mg	24–48	8 (80)
San Francisco [12]	4	Peg-IFN 2a + RBV 1000mg	24–48	2/3 (87)
Australia [13]	22	Peg-IFN 2a + RBV	24	16 (73)
London [23]	27	Peg-IFN 2a+ RBV 800–1200mg	24	16 (59)
Germany [34]	36	Peg-IFN 2a/2b + RBV 800–1200mg (n=22)/no RBV (n=14)	24–48	22 (81)
Paris [35]	20	Peg-IFN 2a + RBV 800mg	24–36	13 (85)
Paris [36]	14	Peg-IFN 2a + ribavirin 80	24	10 (71)
Moscow [37]	17	Peg-IFN 2b + RBV 800–100mg	24	9 (53)
Paris [38]	10	Standard-IFN 9/10 + RBV 2/10	24	0 (0)
Dijon [50]	40	Peg-IFN 2a/2b + RBV 800–1200mg (n=38)/no RBV (n=2)	24–48	32/39 (82)

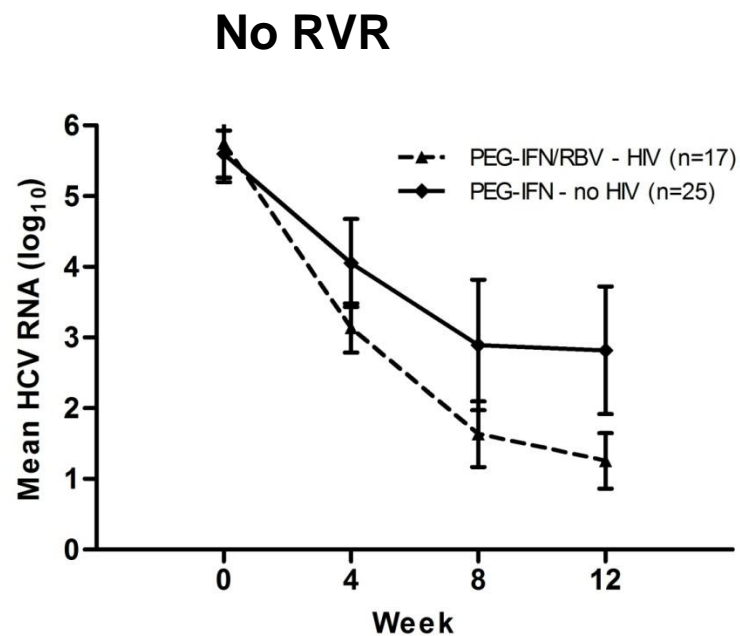
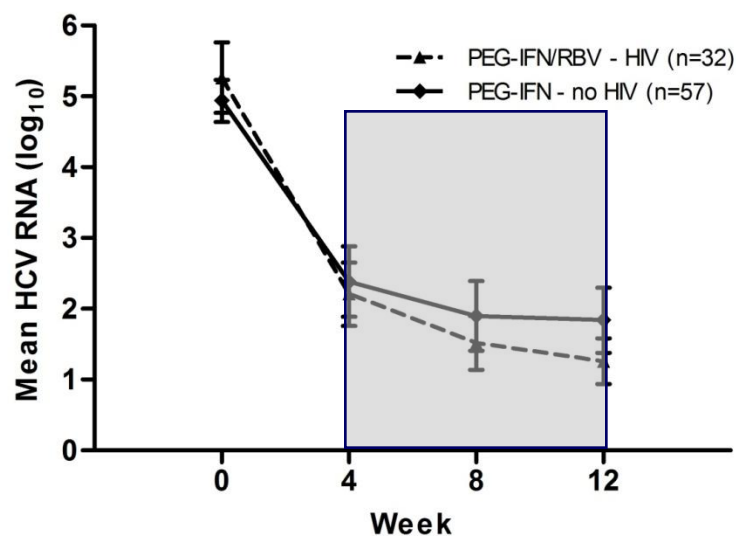
Peg-IFN, pegylated interferon; RBV, ribavirin; SVR, sustained virological response

# PegIFN mono vs. PegIFN + RBV

*observational cohort data n = 111*

	no SVR n = 42	SVR n = 69	SVR-rate	p-Value
RBV 1000 - 1200 mg	27 (64%)	49 (71%)	64%	0.30
RBV 600 - 800 mg	11 (26%)	10 (14%)	48%	
no RBV	4 (10%)	10 (14%)	71%	

# Ribavirin improves HCV RNA decay kinetics



	PEG	PEG/RB V	P
Mean HCV RNA log <sub>10</sub> decline wk 4	2.56	2.97	0.241
Mean HCV RNA log <sub>10</sub> decline wk 8	3.11	3.91	0.041
Mean HCV RNA log <sub>10</sub> decline wk 12	3.10	3.95	0.025
HCV < 10 IU/ml at wk 12	76%	90%	0.150
SVR	63%	75%	0.347

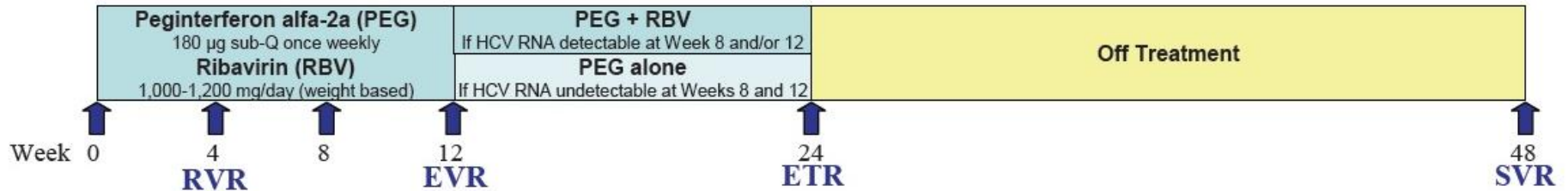
	PEG	PEG/RBV	P
Mean slope BL- wk 4	0.39	0.65	0.024
Mean slope Wk 4 -12	0.16	0.24	0.034

## **Pegylated interferon- $\alpha$ monotherapy leads to low response rates in HIV-infected patients with acute hepatitis C.**

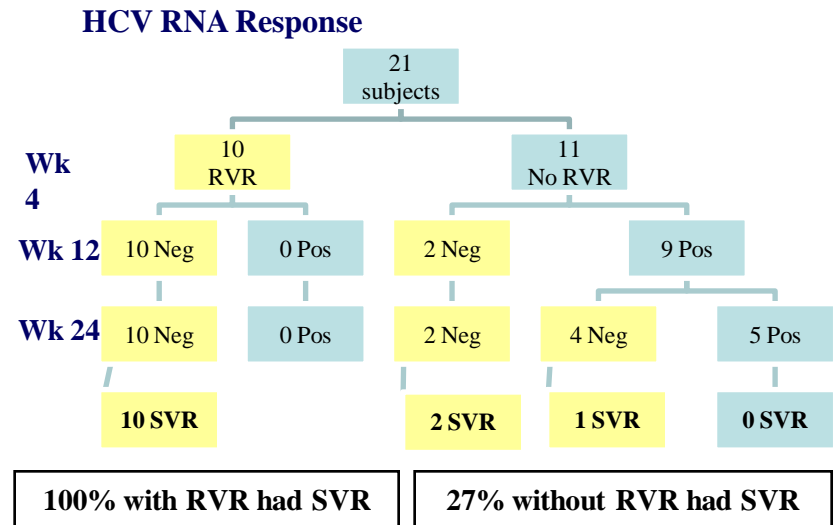
- **METHODS:** A total of 23 HIV-infected patients were prospectively diagnosed with acute HCV and treated with PEG-IFN- $\alpha$ 2a monotherapy (180  $\mu$ g/week) for 24 or 48 weeks. Add-on ribavirin was allowed from week 4 of therapy onwards.
- **RESULTS:** 19 patients (13 genotype 1 and 6 genotype 4) received treatment with PEG-IFN- $\alpha$  monotherapy (3 with add-on ribavirin) resulting in a rapid virological response
- A SVR was reached in 7 (37%) patients, whereas 9 (47%) patients were null-responders to treatment (that is,  $<2 \log_{10}$  drop in HCV RNA at week 12 ).

# Is ribavirin useful?

## 21 HIV+ Patients with acute HCV



- Median duration to start of therapy 87 days (Range 40 – 163)
- 12 weeks pegylated pegIFN alfa-2a + 1000 / 1200 mg RBV
- If HCV-RNA week 8 or 12 negative, stop RBV
- 13 patients stopped RBV week 12 – no rebound until end-of treatment
- SVR overall 62%



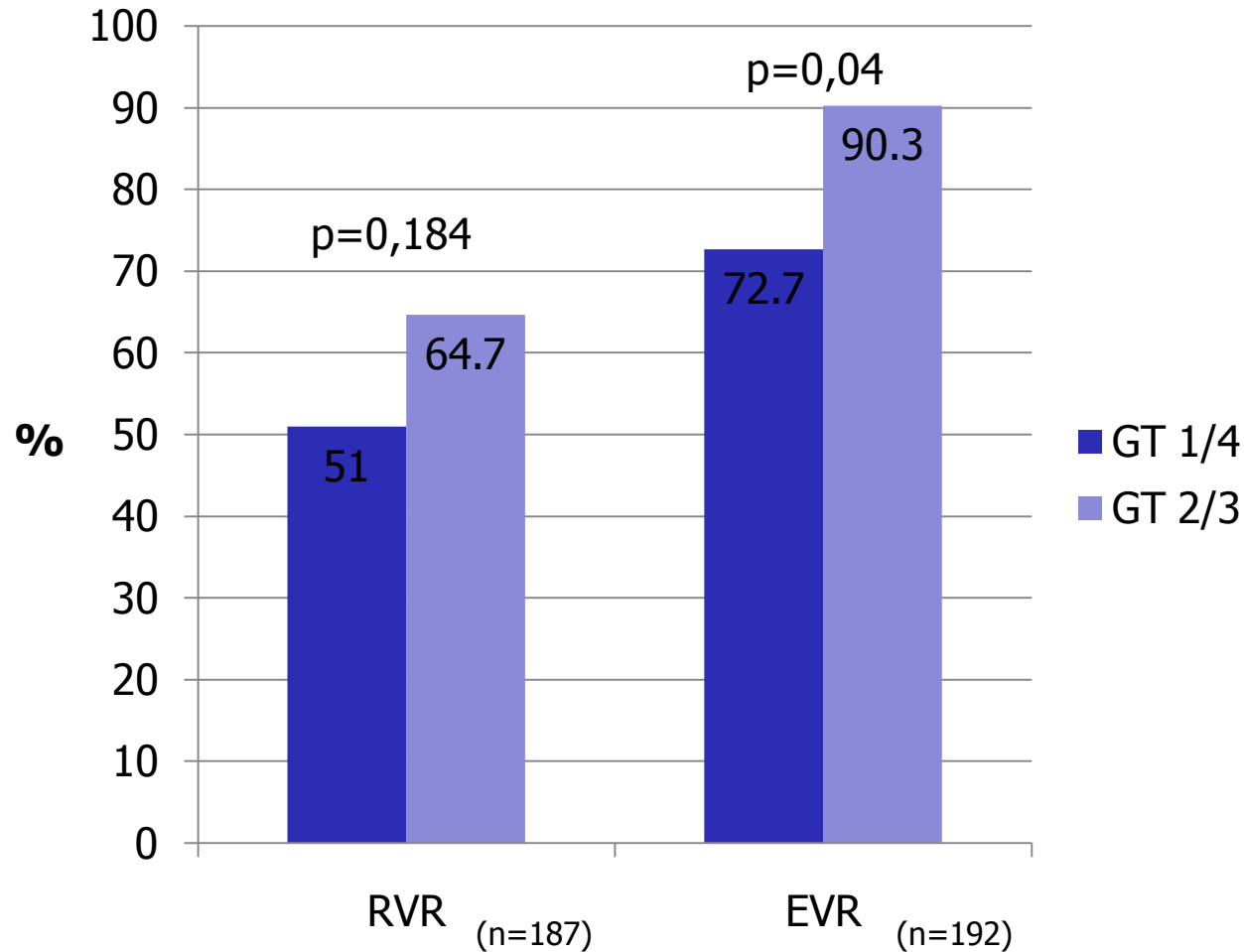
# RVR, EVR and SVR

## *European Collaborative, n=111*

### RVR and EVR may help to guide treatment duration

- Patients with RVR reached SVR in 93%
- Patients who were still HCV-RNA positive at week 12 reached SVR in 9% of cases
- Virological response may help to guide treatment duration

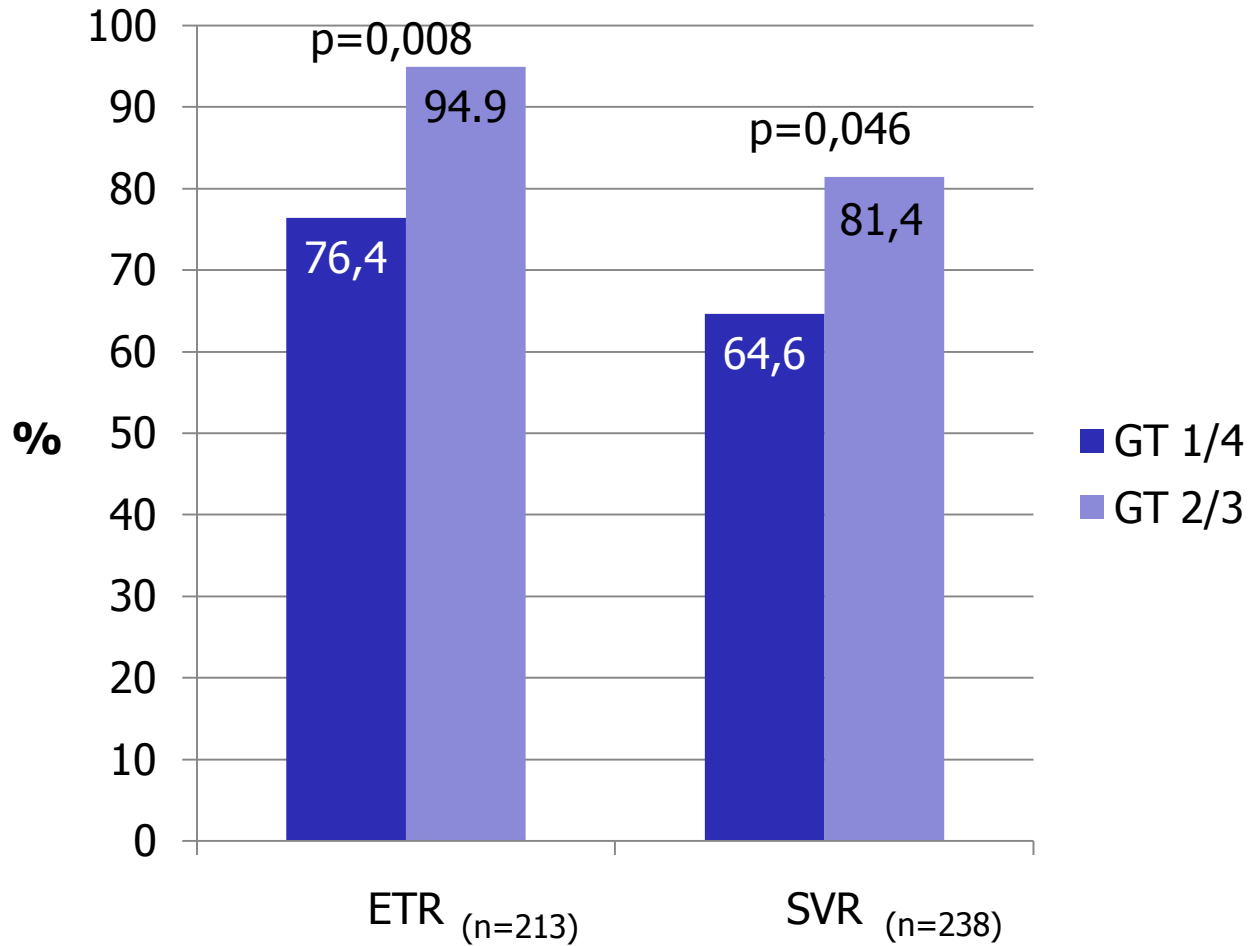
RVR and EVR – predictors for SVR			
	SVR	no SVR	PPV / NPV
RVR	39	3	<u>PPV: 93%</u>
no RVR	30	39	NPV: 57%
EVR	66	12	PPV: 85%
no EVR	3	30	<u>NPV: 91%</u>



238 HIV-infected male patients from 4 European countries (UK, France, Germany, Austria) with diagnosed acute HCV infection were treated early with pegylated interferon (pegIFN) and ribavirin (RBV) (n=207) or pegylated interferon alone (n=31), followed prospectively since 2002 and evaluated for SVR.

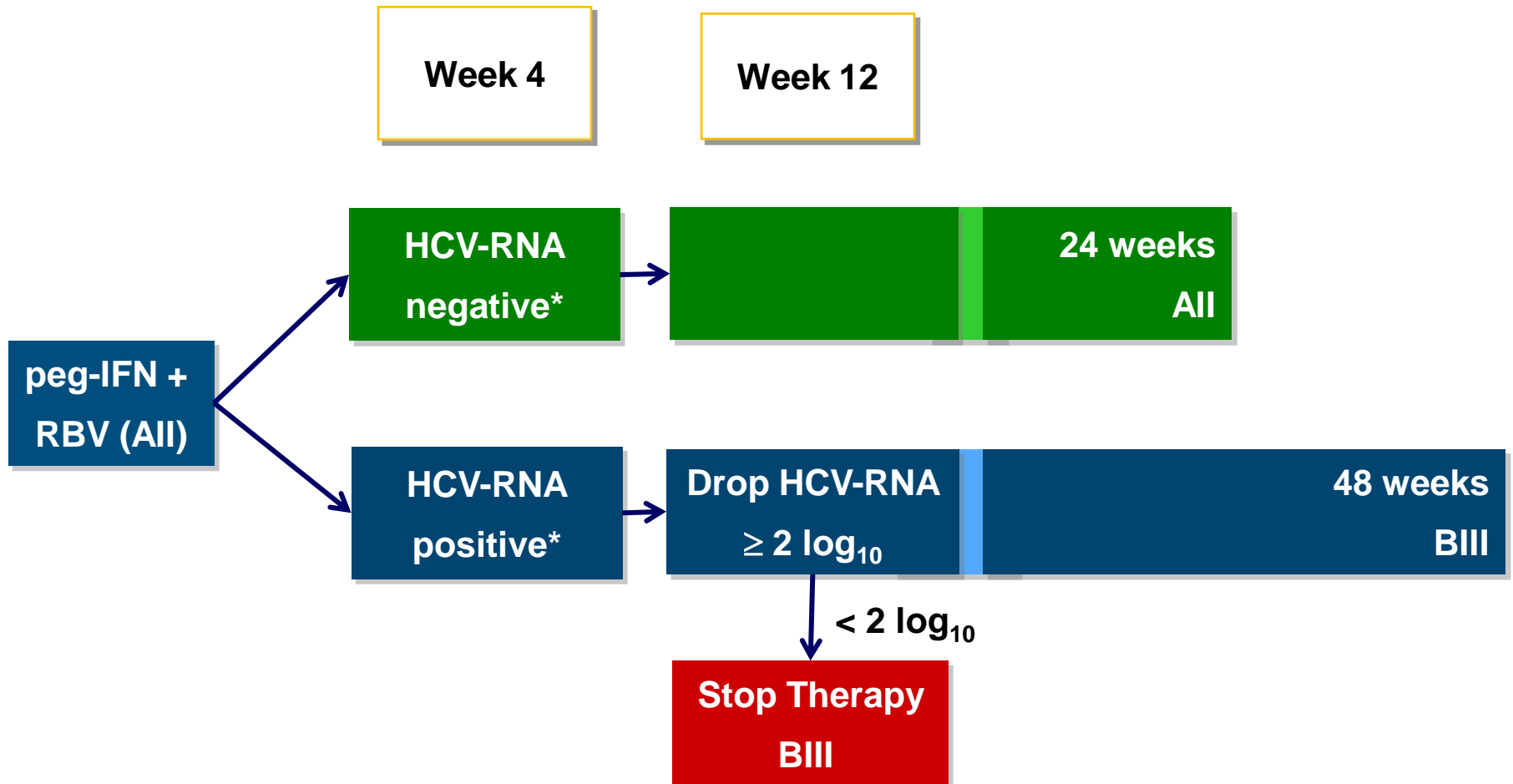
In 85% of cases (175/207) weight-adapted dosage of ribavirin (wt ≤75kg: 1000mg; wt >75kg: 1200mg/d) was used.

# ETR & SVR



	SVR n=161	no SVR n=77	Univariate p-value*	Multivariate p-value**	Multivariate Odds-Ratio (95% CI)**
<b>RVR [%] n=187</b>	<b>65,4</b>	<b>28,3</b>	<b>0,000</b>	<b>0,000</b>	<b>4,600 (2,336-9,059)</b>
GT 2/3 [%]	21,7	10,4	0,046	0,043	2,945 (1,034-8,385)
IL28B CC genotype [%] n=70	55,3	34,8	0,271		
Median baseline CD4-cells [/ $\mu$ l] (95% range)	484 (368-632)	433 (347-602)	0,164		
Baseline HIV-RNA <50cop/ml [%]	61,3	56,7	0,551		
Baseline HCV-RNA >800.000IU/ml [%]	44	58,1	0,069		
Median maximum ALT [U/l] (95% range)	398 (195-761)	325 (168-706)	0,227		
Hepatic symptoms [%]	27	22,4	0,523		
peg IFN/RBV [%]	85,7	88,3	0,714		
HAART [%]	67,7	63,6	0,559		

# Antiviral therapy of AHC



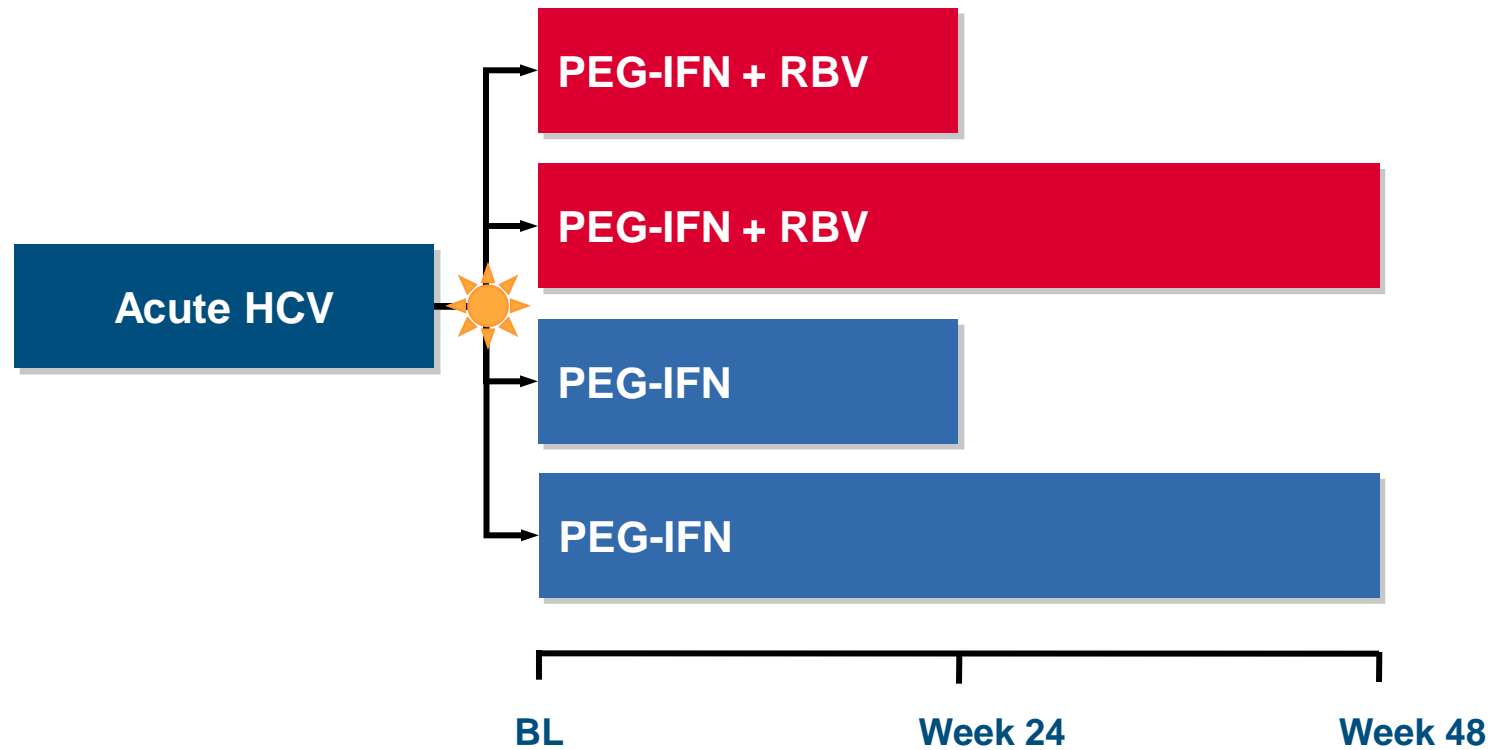
\*evidence based on using a 615 IU/ml cutoff to define negative HCV-RNA

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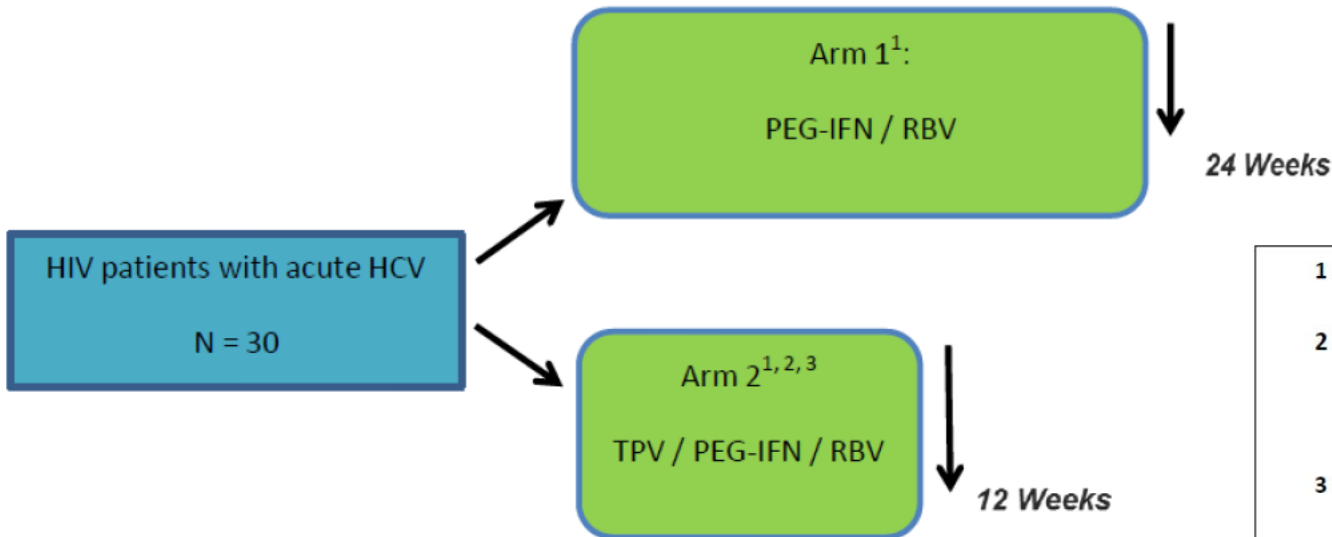
# NEAT 002

Start ???





# Clinical pilot trial



- 1 Patients who do not achieve an RVR will be treated for 48 weeks
- 2 Patients with a HCV RNA > 100 IU/ml at week 4 will be discontinued from Telaprevir and continued with PEG-IFN/RBV
- 3 The manufacturer of Telaprevir, Janssen, has committed to provide TPV medication free of charge for this pilot trial

# DARE C

## DAA based therapy for recently acquired hepatitis C

*Response-guided triple combination therapy with Telaprevir/PEG/RBV for the treatment of recently acquired hepatitis C infection*

A substudy of the Australian Trial in Acute Hepatitis C II (ATAHC II)

Genotype 1

Early chronic infection (estimated duration 6 -18 months)

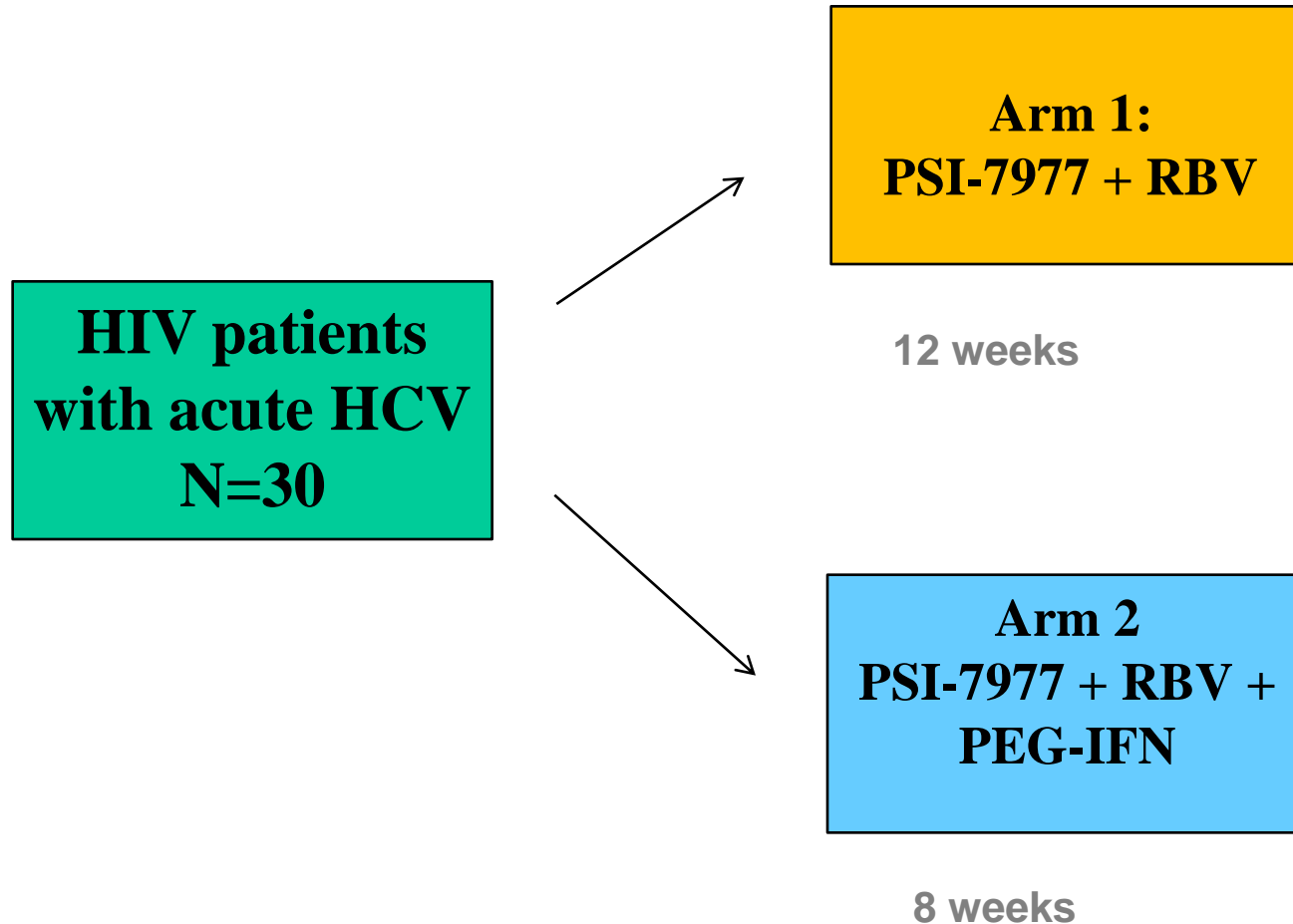
HIV negative

Duration of therapy based on time to 1<sup>st</sup> HCV RNA undetectable:

	<b>1<sup>st</sup> HCV RNA undetectable at:</b>	<b>Duration therapy with PEG/RBV</b>
<b>Group A</b>	<b>Week 2</b>	<b>8 weeks PEG/RBV/TPV</b>
<b>Group B</b>	<b>Week 4</b>	<b>12 weeks PEG/RBV/TPV</b>
<b>Group C</b>	<b>Week 8</b>	<b>12 weeks PEG/RBV/TPV + 12 weeks PEG/RBV</b>



# Clinical pilot trial



# NEAT Acute HCV Consensus Panel

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Christine Katlama  
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