Chronic hepatitis C: new treatments

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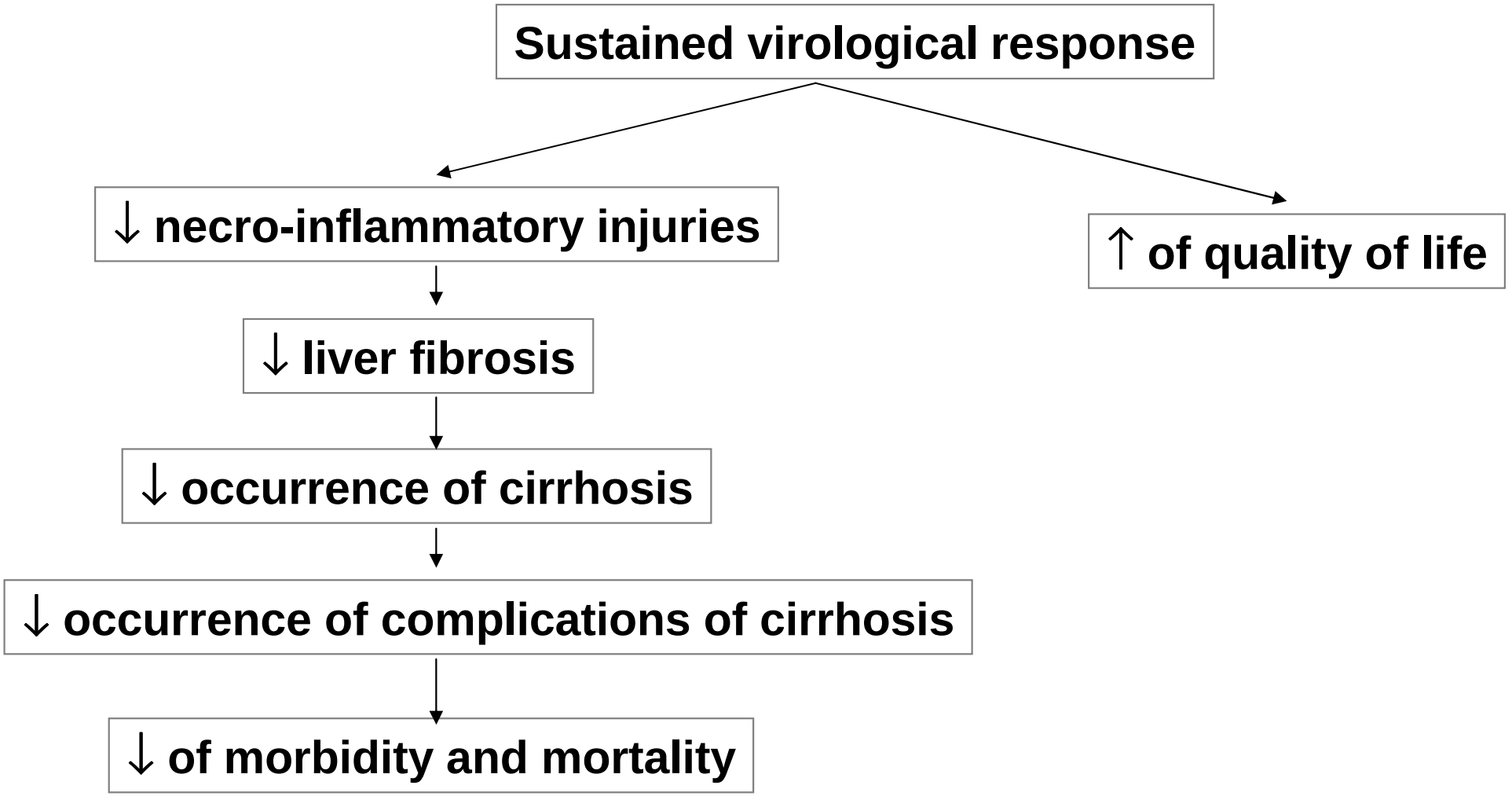
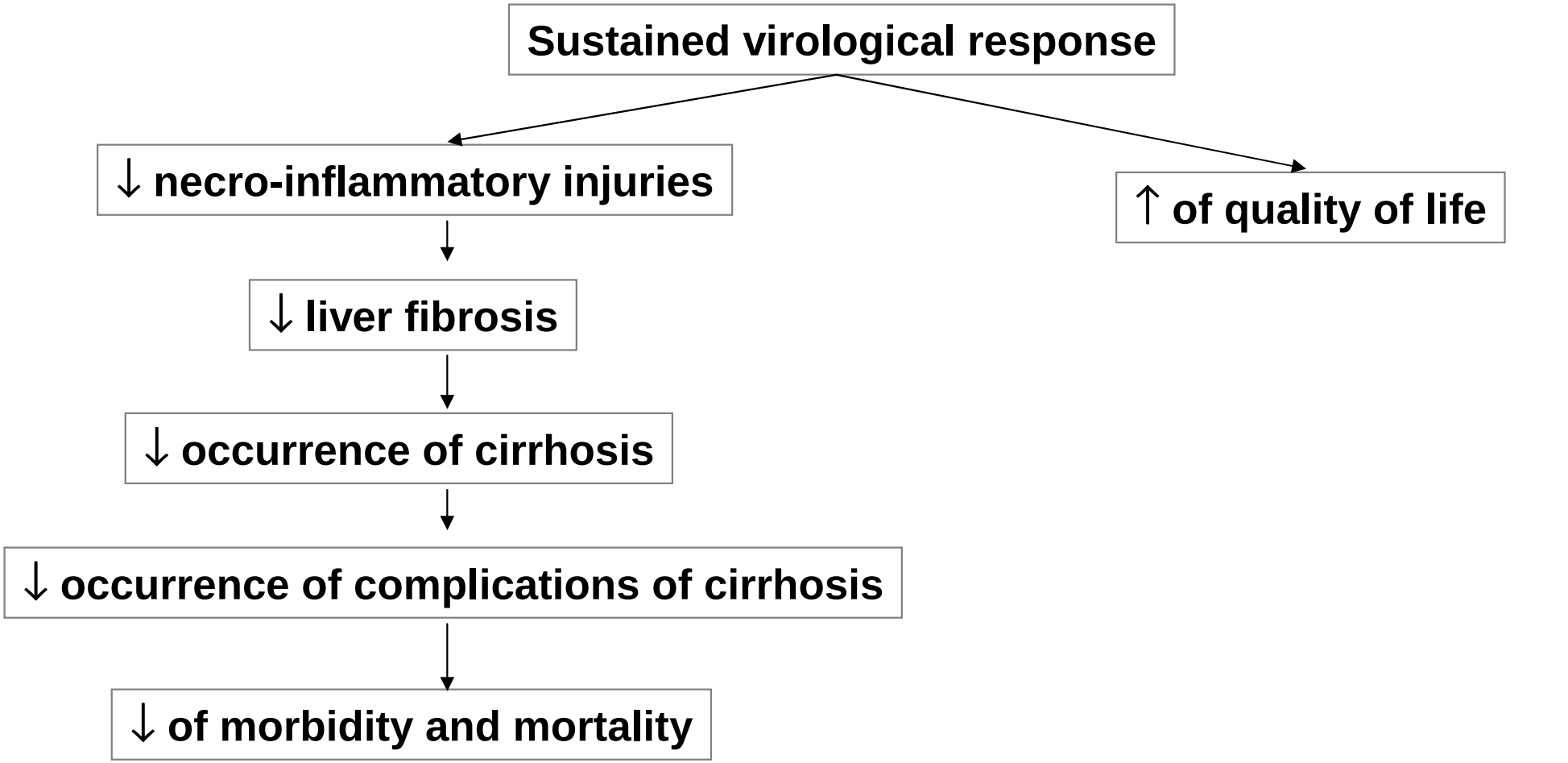
Objectives of the treatment



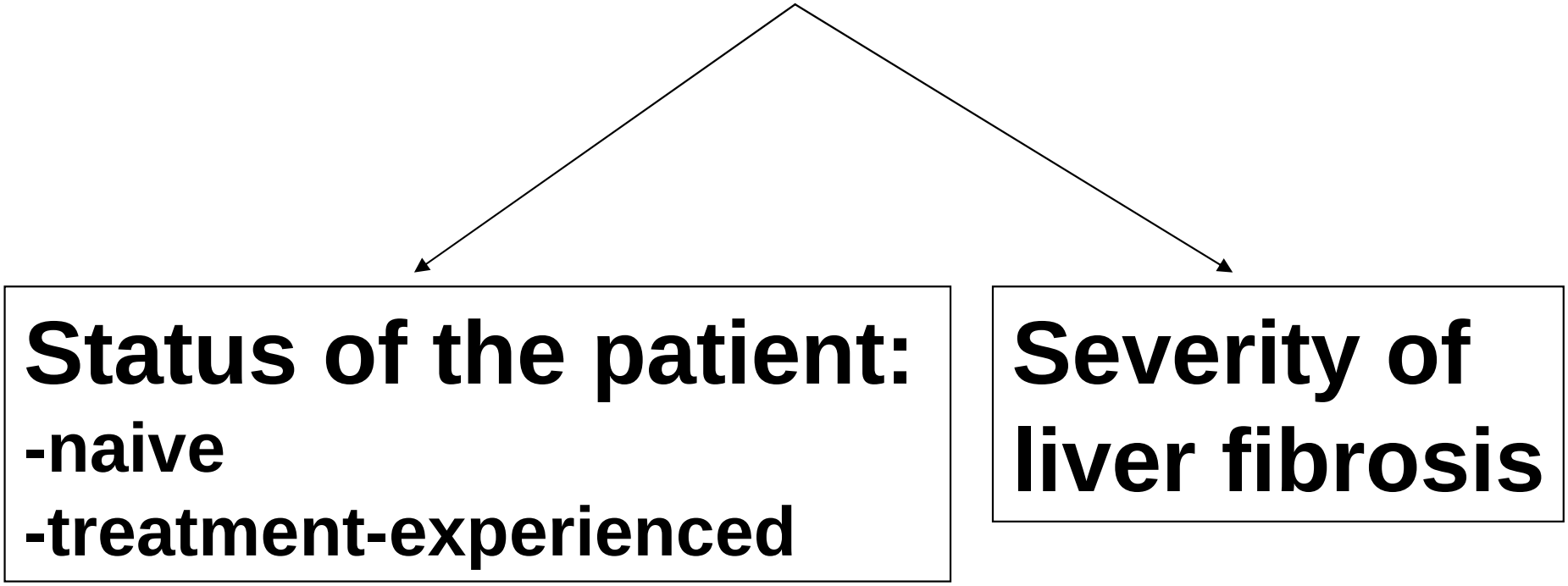
2 news friends

Telaprevir **Boceprevir**

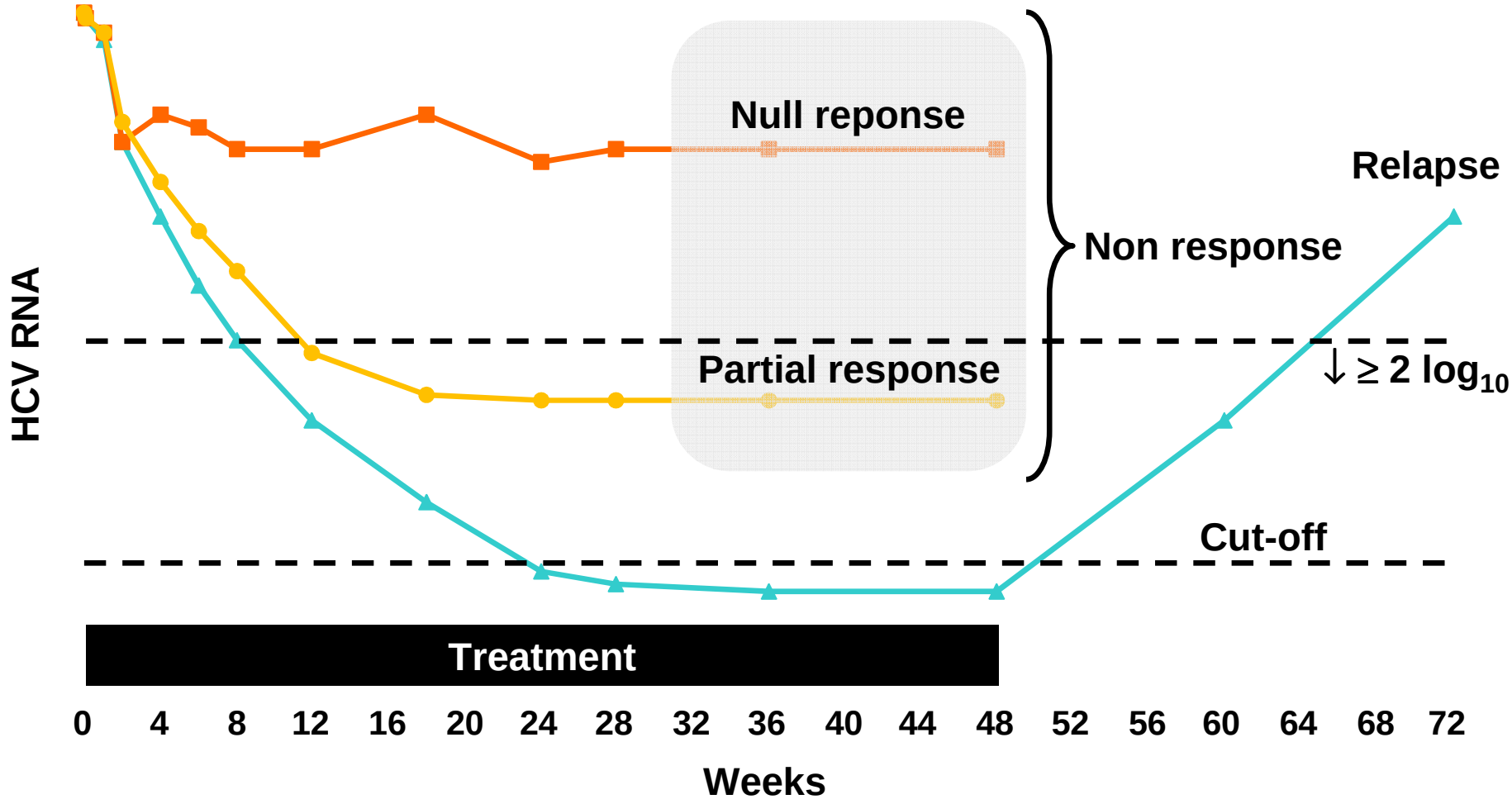


Who treat ?

Indication according to

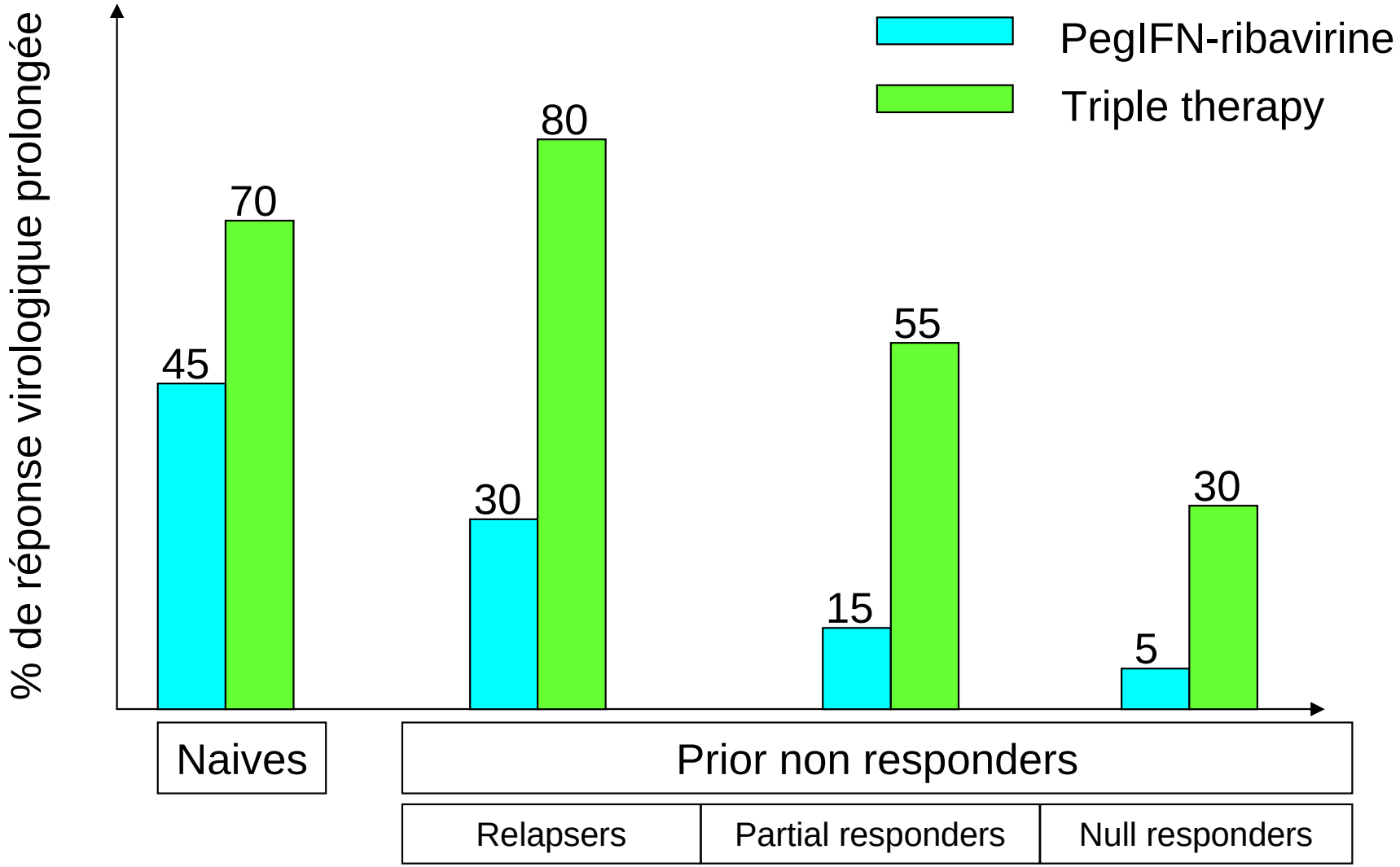


Definition of failure treatment



Adapté de Shiffman ML. Curr Gastroenterol Rep 2006;8:46–52

SVR according the status of the patient



Poordad F et al, N Engl J Med 2011
Bacon B et al, N Engl J Med 2011
Jacobson IM et al, N Engl J med 2011
Zeuzem S et al, N Engl J Med 2011

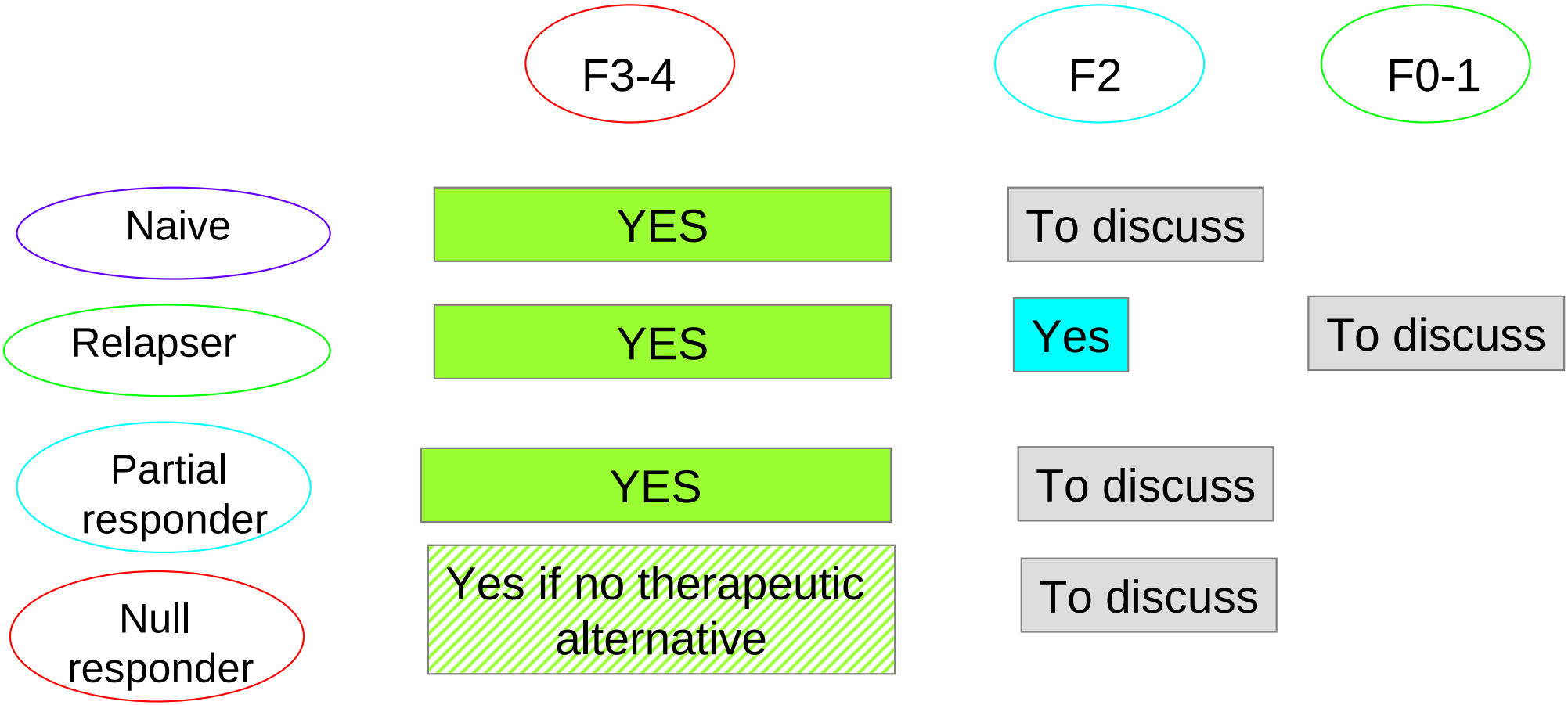
SVR according the status and the fibrosis

Approximative values

	Naive	Relapser	Partial responder	Null responder
F0-2	70-80%	70-85 %	50-70 %	30-40%
F3	50 %	70-85 %	40-55 %	35 %
F4	40-60 %	70-85 %	35 %	15 %

Poordad F et al, N Engl J Med 2011
Bacon B et al, N Engl J Med 2011
Jacobson IM et al, N Engl J med 2011
Zeuzem S et al, N Engl J Med 2011

Therapeutic indication (AFEF)



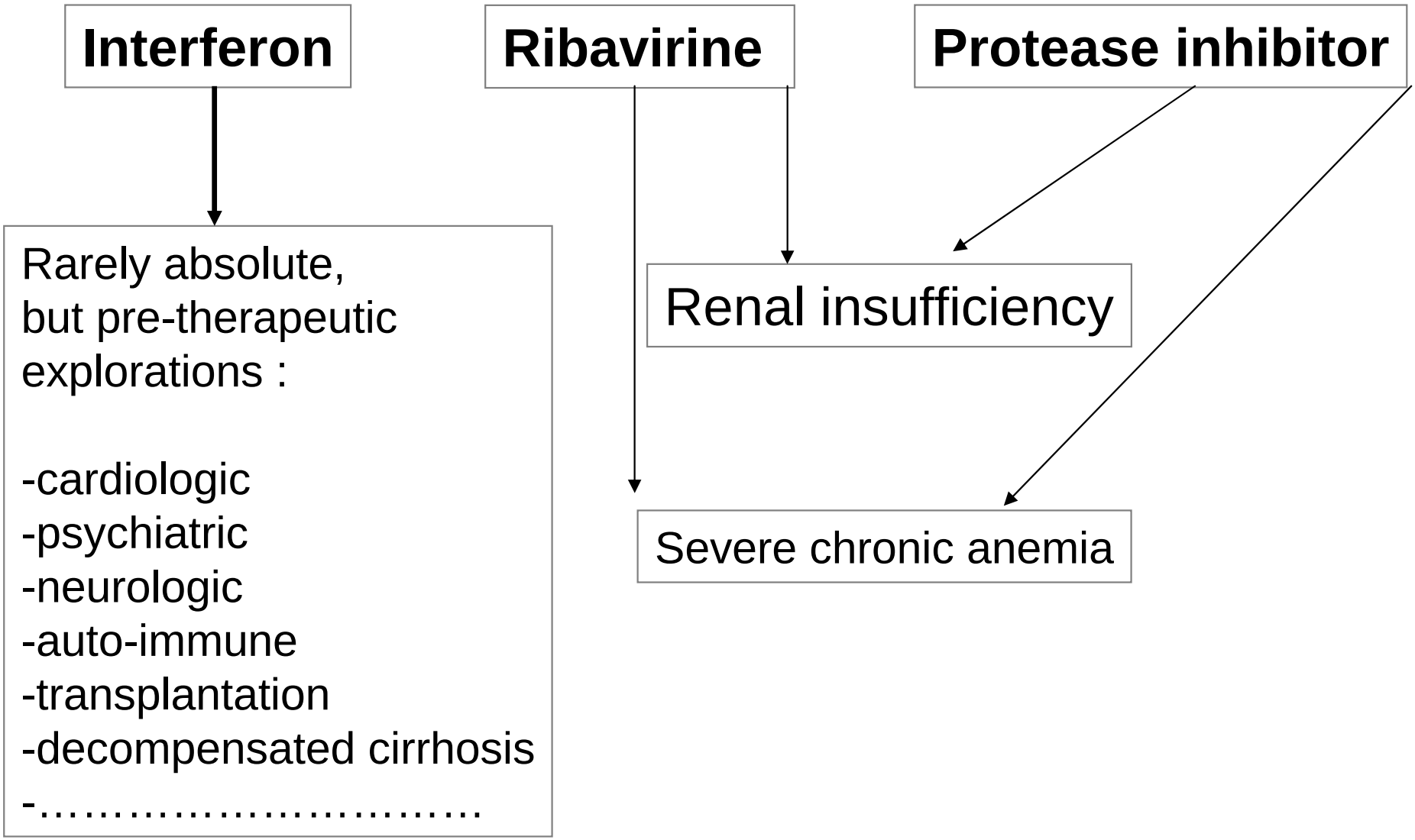
According the risk factors of fibrosis:
NAFLD, HIV or HBV co-infections, alcohol consumption

How to treat ?
Before the treatment

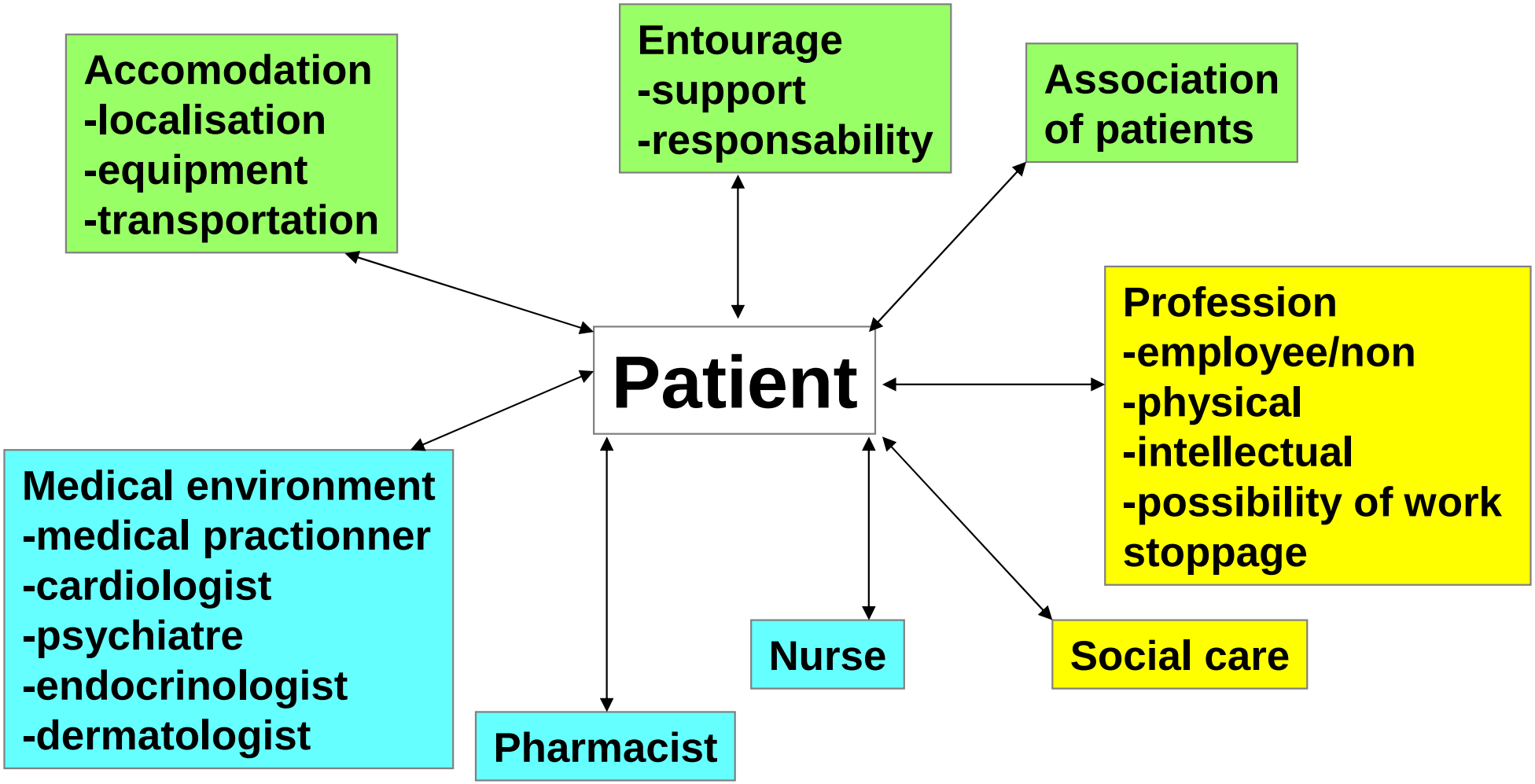
- 1. Check the therapeutic indication
- 2. Check the absence of contra-indication
- 3. Global evaluation of the patient
- 4. Interactions with other treatments
- 5. Contraception
- 6. Education ++++++++++

Explanations to the patient and the family

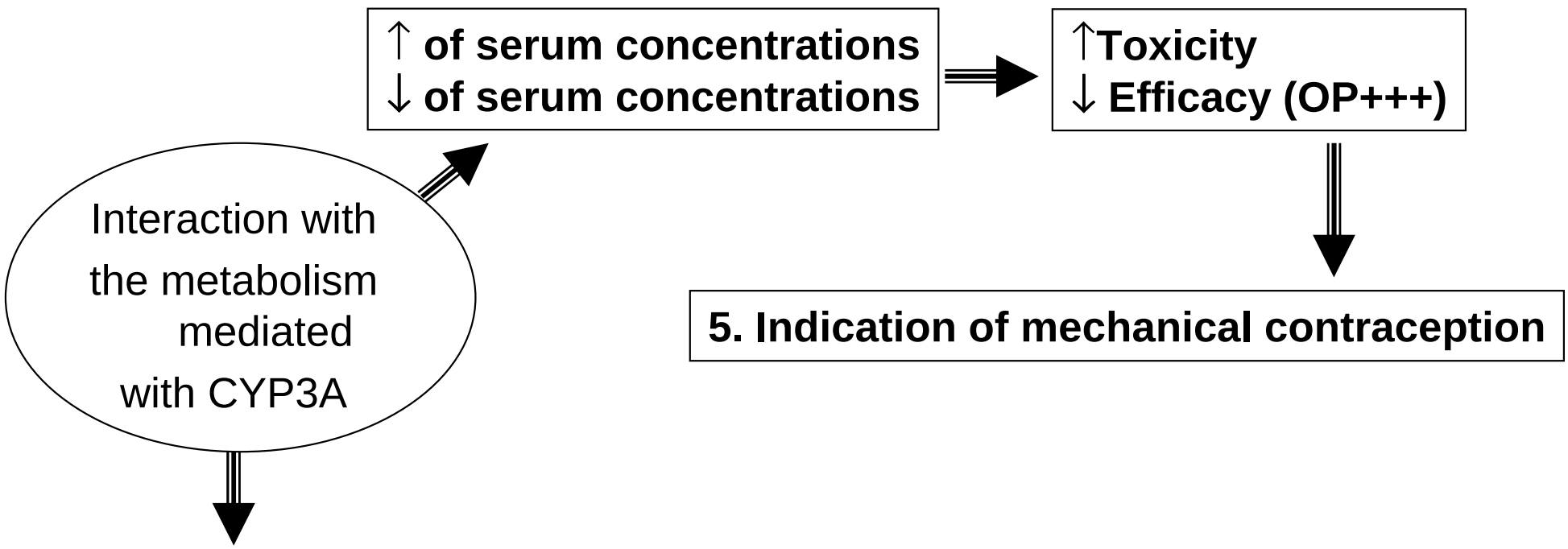
2. Check the absence of contra-indication



3. Global evaluation of the patient



4. Check the drug interactions



Listing of treatments before and after the treatment

- www.druginteractions.org
- www.pharmacoclin.ch

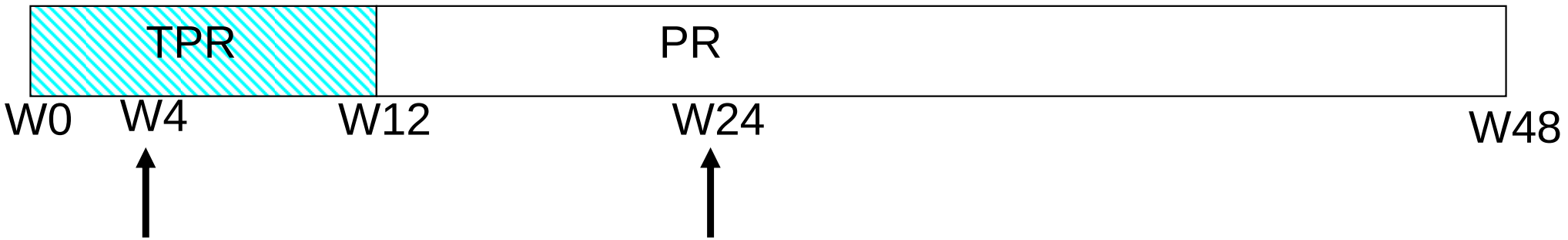
How to treat ?
During the treatment

1. Therapeutic schedule
2. Snack associated with protease inhibitors
3. Follow-up
4. Management of adverse effects

Therapeutic regimen with telaprevir

Optimal duration of the treatment :
-24 weeks in naives, relapsers, non cirrhotic patients, with eRVR
-48 weeks in others

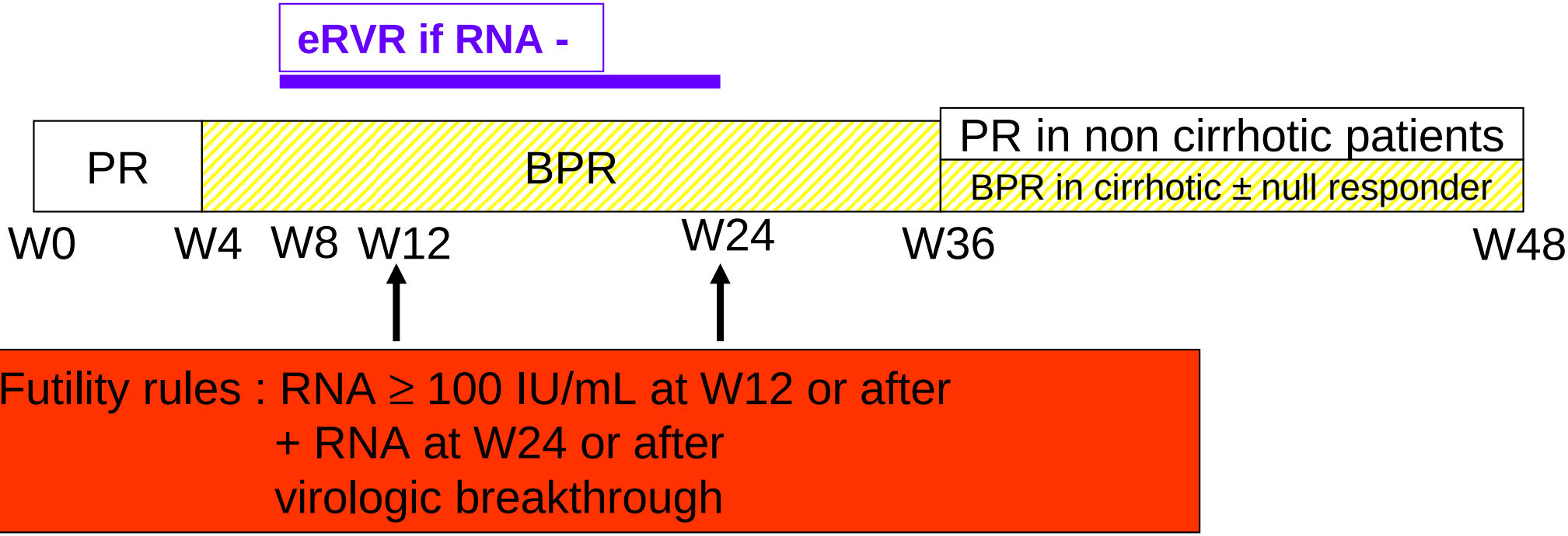
eRVR
If RNA -



Futility rules : RNA > 1000 IU/mL at W4 or after
+ RNA at W24 or after
virologic breakthrough

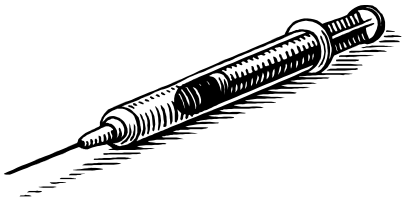
Therapeutic regimen with boceprevir

Optimal duration of treatment :
-28 weeks in naive, non cirrhotic patients with eRVR
-48 weeks in others



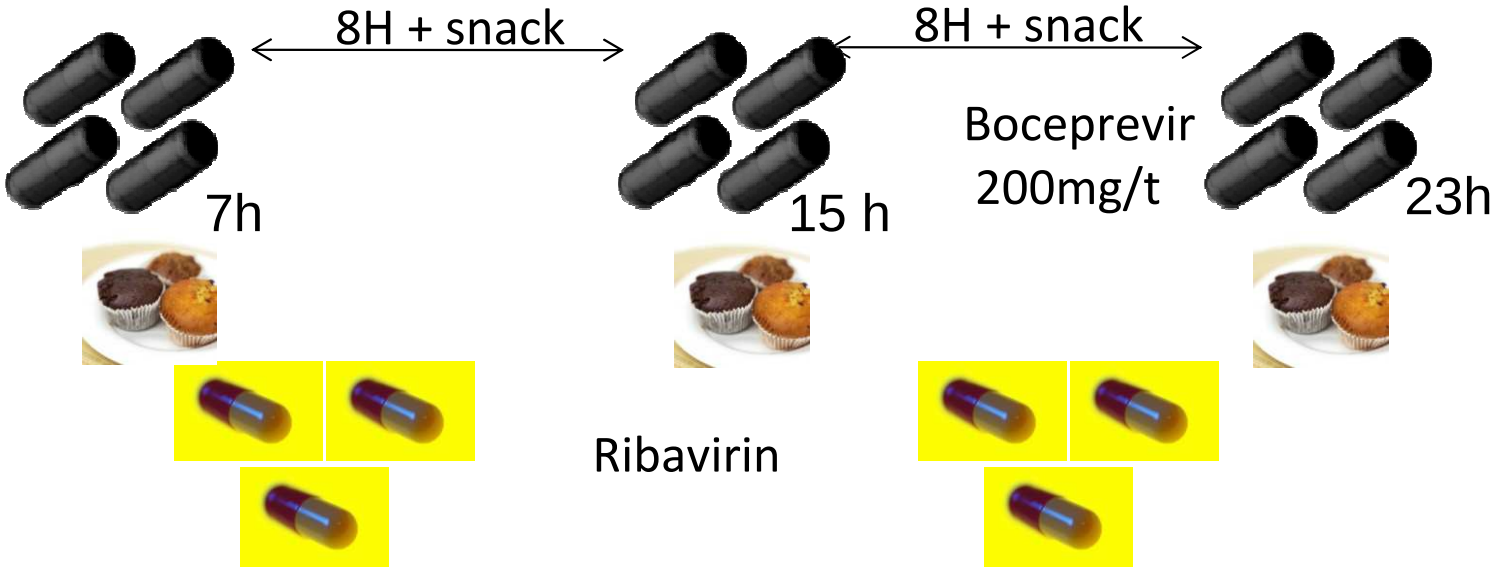
Futility rules : RNA ≥ 100 IU/mL at W12 or after
+ RNA at W24 or after
virologic breakthrough

Dosages during triple therapy



PegIFN α-2a, 180 µg /week + Copegus 1-1,2 g/d

PegIFN α-2b, 1,5 µg/kg/week + Rebetol 0,8-1,4 g/d



From 11 to 18 tablets/day

Adverse events during triple therapy

= those of the dual therapy

Anemia

Cutaneous adverse events

Dysgueusia

- « bland » foods
-fractionate the feed
-metoclopramide if needed
-compliance of snacks

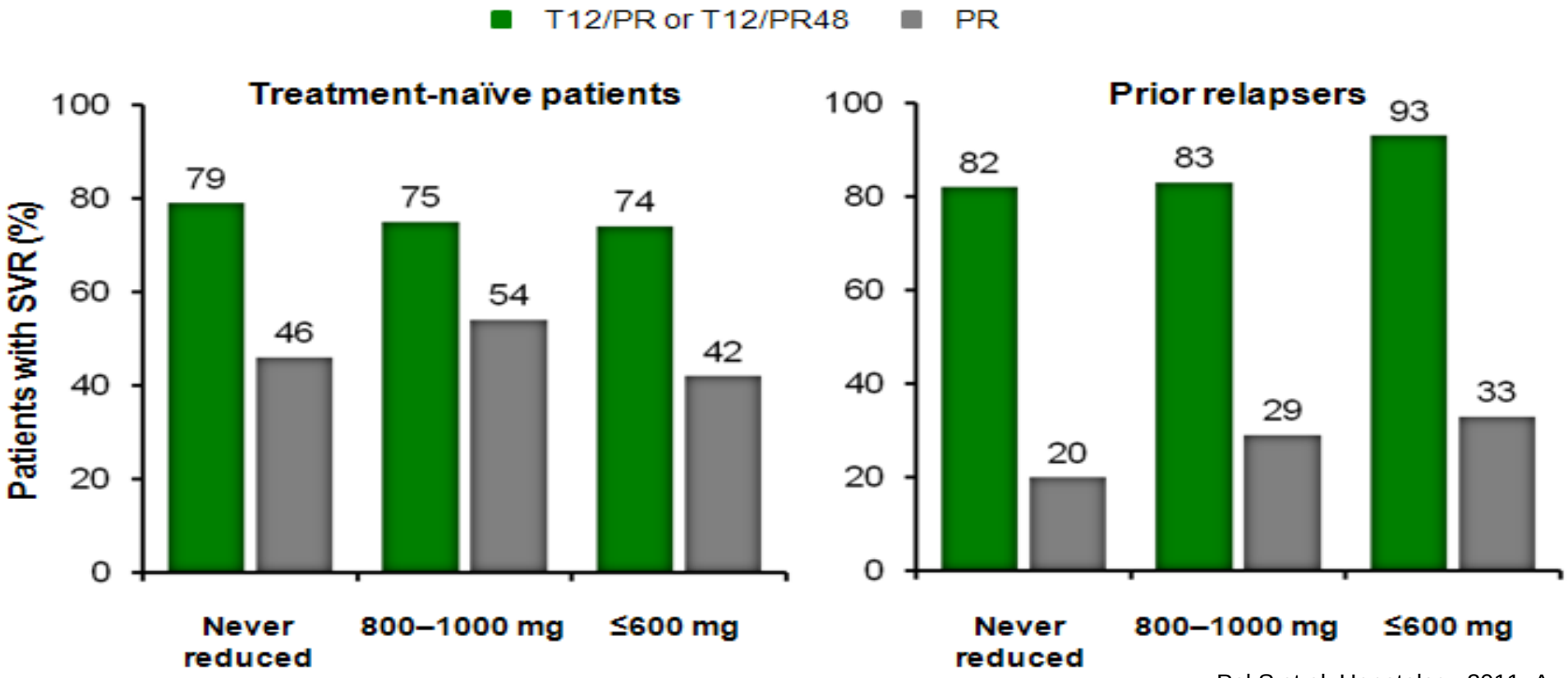
Anemia : SVR and decrease of ribavirin dosage

Mécanisme mixte (central et périphérique)

Anémie plus précoce et profonde

EPO moins efficace

↓ de la posologie de ribavirine par paliers de 200 mg (posologie minimum ?)



Pol S et al, Hepatology 2011; A

Management of cutaneous adverse effects with telaprevir

Emollient 2/day, one week before telaprevir

Grade 1 : < 30 % of total body area
Grade 2 : 30 to 50 % (diffus) without mucous membrane ulceration

90 %

→ Specialized consultation : emollients, topic corticoïds and follow-up < 1 week
Discontinuation of telaprevir if no improvement

Grade 3 : > 50 % of total body area
or including mucosal erosions
or epidermal detachement
or purpura or presence of fever
or high level liver

Grade 4 : SCAR
Generalized bullous eruption,
Stevens-Johnson,
Lyell syndrom,
Toxic epidermal necrolysis
Dress

→ Hospitalisation
Discontinuation of telaprevir

Follow-up during the triple therapy

Week	0	1	2	3	4	5	6	7	8	10	12	16 20	24	28 32	36	40 44	48
HCV RNA	x		T		x		B		X	X	X	X	X	X	X	X	X
Blood count	X	T	X	T	X	B	X	B	X	X	X	X	X	X	X	X	X
AST, ALT, GGT	X				X				X		X	X	X	X	X	X	X
Bilirubine, P Alc, TSH, fasting serum glucose, creatinin	X										X		X		X		X

B = boceprevir et T = telaprevir

HCV RNA 12 and 24 weeks after the discontinuation of therapy
Sustained Virologic Response = undetectable HCV RNA at 12 weeks

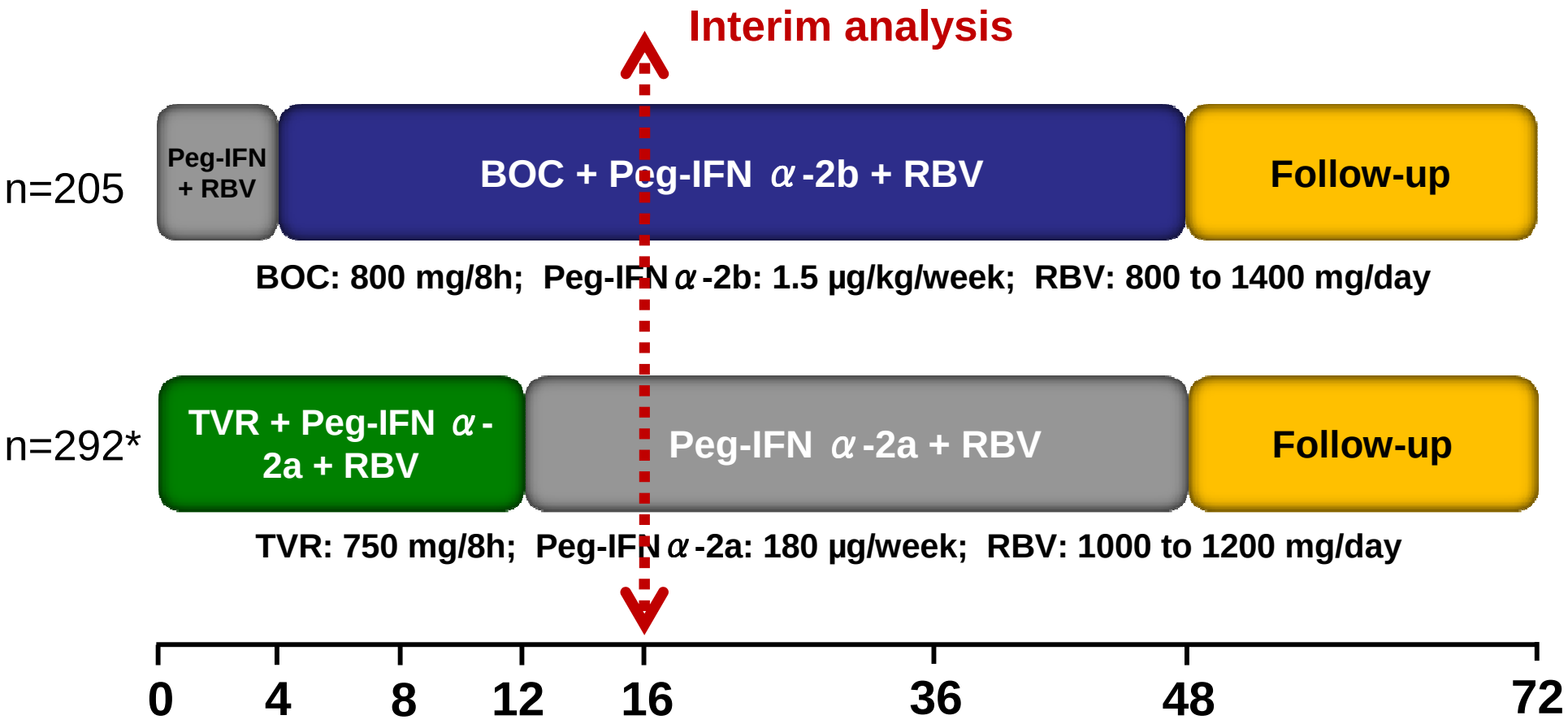
How to treat ?
After the treatment

Improvement of adverse events

Follow-up of cirrhotic patients after viral eradication

Follow-up of patients with treatment failure: fibrosis, therapeutic trial

CUPIC : Treatment regimen



*** 42 (14.4 %) TVR patients were treated with an initial lead-in phase**

http://www.afssaps.fr/var/afssaps_site/storage/original/application/4b8c53711bab9d8f7d4c3f947caa90f6.pdf
http://www.afssaps.fr/var/afssaps_site/storage/original/application/fa78af08e029caf9d82bcd9d3e77eb09.pdf

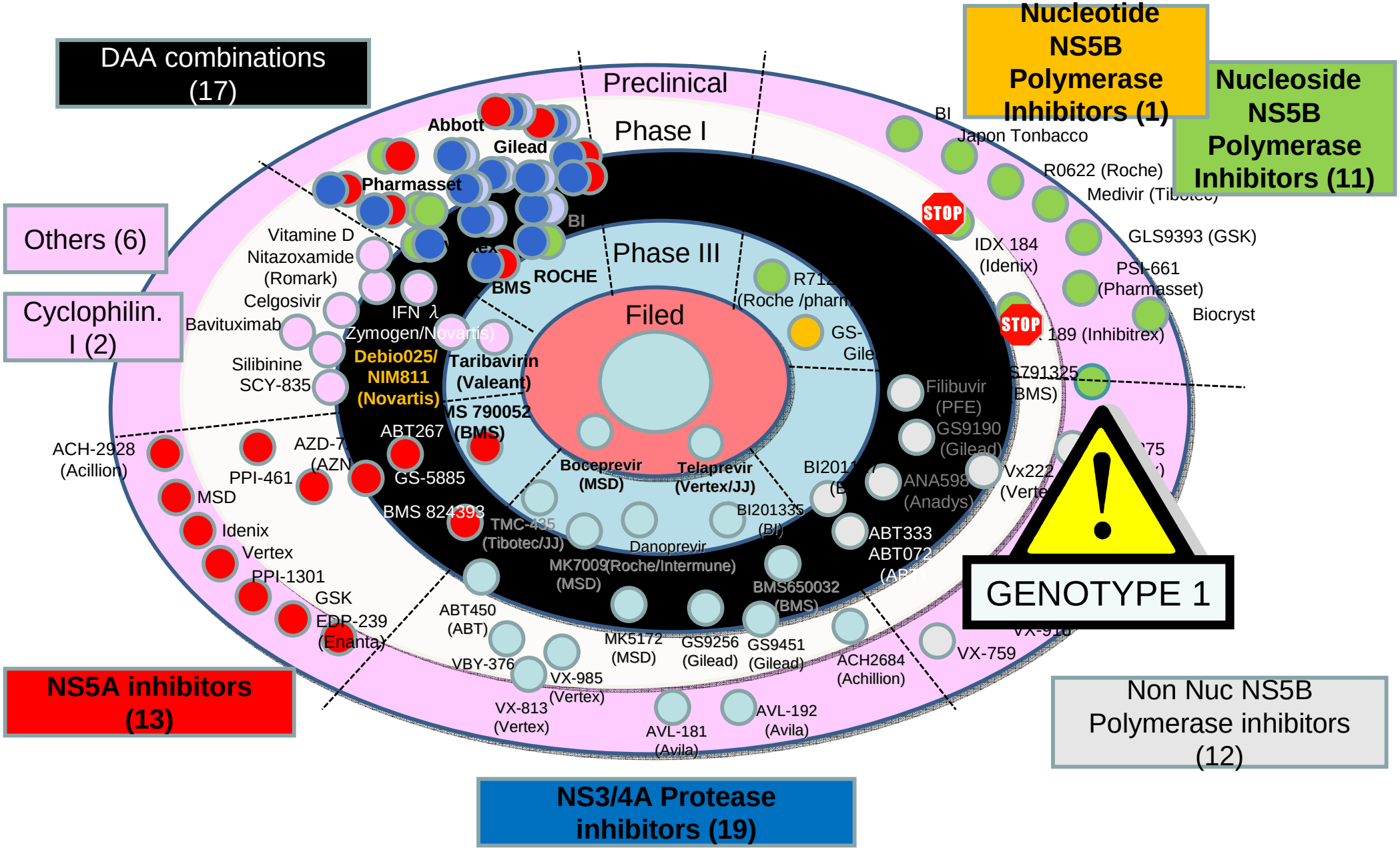
Risk of occurrence of death or severe complications

40 % of SAE
6 deaths

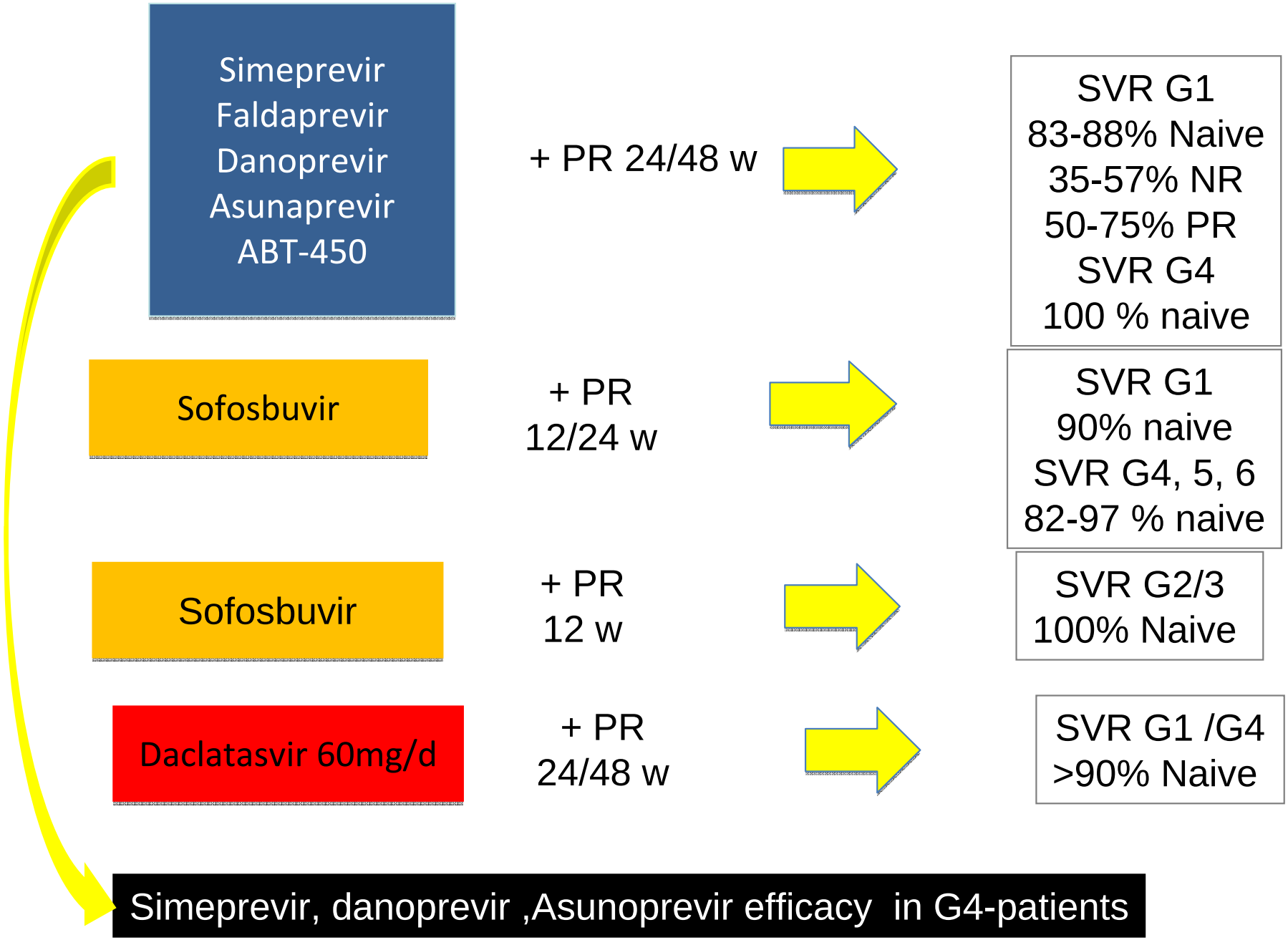
Predictors	Platelets count > 100,000/mm³	Platelets count ≤ 100,000/mm³
Albumin ≥35 g/L	(10/298) 3.4 %	(3/69) 4.3 %
Albumin <35 g/L	(2/28) 7.1 %	(15/34) 40.6 %

Hezode C et al, J Hepatol 2013, submitted

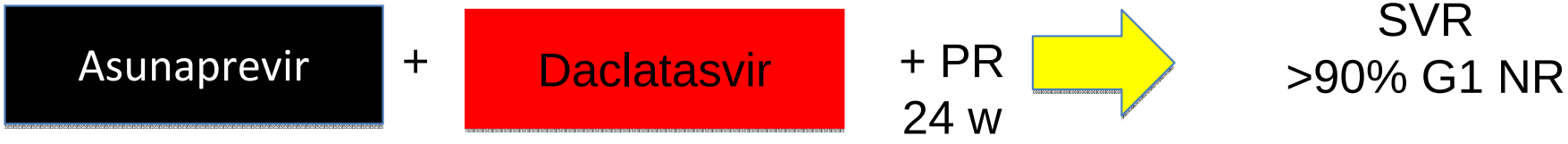
No future for HCV ?



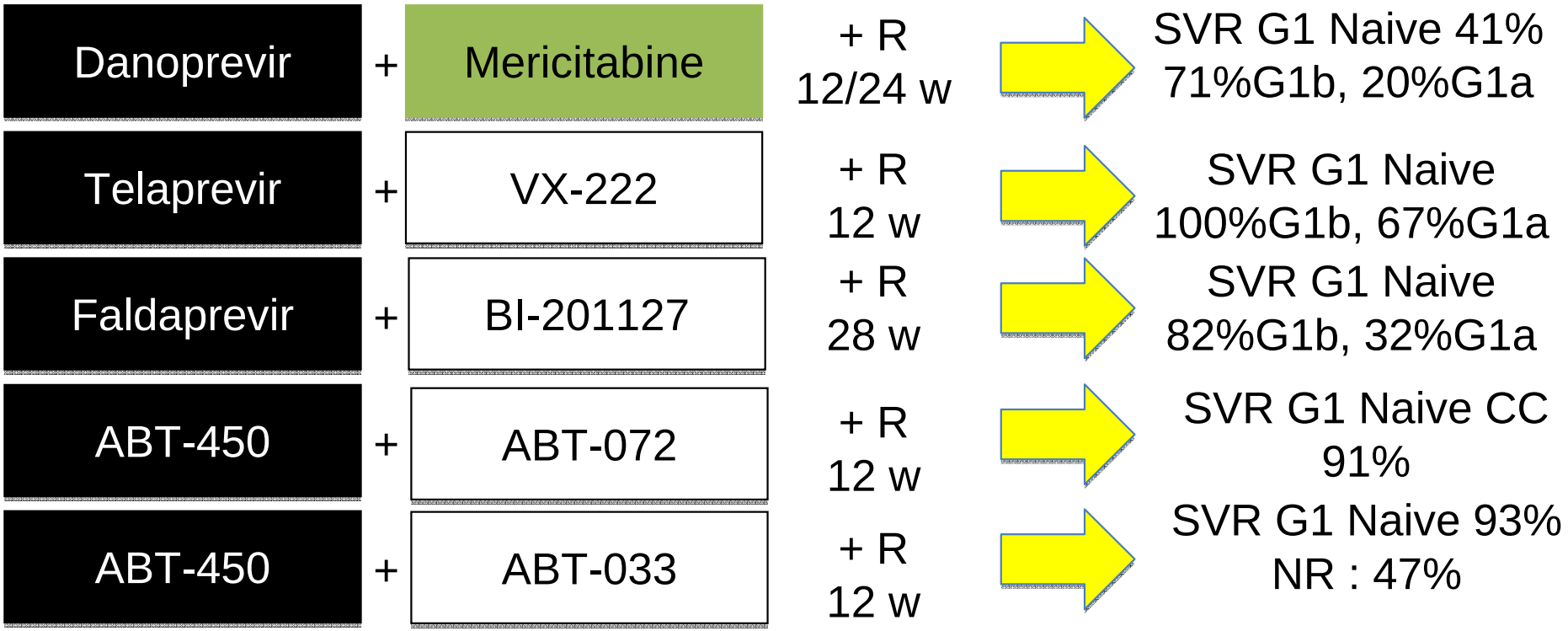
New combinations including +PR



News combinations in quadritherapy



Combinations without IFN



Combinations without IFN

Asunoprevir + Daclatasvir 24 w → SVR
91% G1b NR nul

Sofosbuvir + Daclatasvir 24 w → SVR
100% G1 Naive
100% G3 Naive

Sofosbuvir + R
12 w →

SVR G1	SVR G2/G3
88% Naive	100% Naive
11% NR	80% nr

ABT-450 + ABT-333 + ABT-267 + R
12 w → SVR
97% G1 Naive
93% G1 NR

Asunoprevir + Daclatasvir + BMS-791325 + 12-24 w → SVR
94% G1a/b

Conclusions

- The triple combination including 1° generation protease inhibitor allows obtaining a viral eradication in about 70 %, with a decrease of safety.
- The future combinations should:
  - improve the SVR, whatever the genotype
  - with a better safety, particularly with combinations without interferon
  - without drug interactions.
- These changes will modify the morbidity and the mortality due to chronic hepatitis C.