# CASE 1:

- 55 year old man with HCV cirrhosis and HCC is listed for LT with exception points – currently at MELD 20, blood group O. He has no prior complications of cirrhosis. EGD: grade 1 varices. His MELD score based on laboratory tests is 10. He is infected with HCV genotype 1b and has an HCV RNA level of 1.3 million IUml. He has never been treated before. At this program the median MELD score at LT for blood group O patients is 27.

# What would you recommend regarding HCV treatment in this patient?

- Defer antiviral therapy until after transplantation as treatment pre-LT is too risky
- Treat with antiviral therapy for 12 weeks, and if no response – stop
- Treat with antiviral therapy and if no virologic response, continue up to time of LT to decrease likelihood of recurrence
- Treat with antiviral therapy and if response plan to defer LT to complete a full 48 week course.

# Strategies to treat HCV infection before LT

**Everson et al 2005**

**Low Accelerating Dose Regimen (LADR)**
**IFN plus RBV, start at low doses**

**SVR**

**LT**

**Treatment** | **Follow up** | **Follow up after LT**

**6-12 m.** | **6 months**

**Forns et al 2003**

**Short treatment Regimen**
**Daily IFN or Peg IFN plus RBV**
**Full doses**

**undetectable**

**LT**

**SVR**

**Treatment** | **Follow up after LT**

**3-4 m.** | **6 months**

# Strategies to treat HCV infection before LT

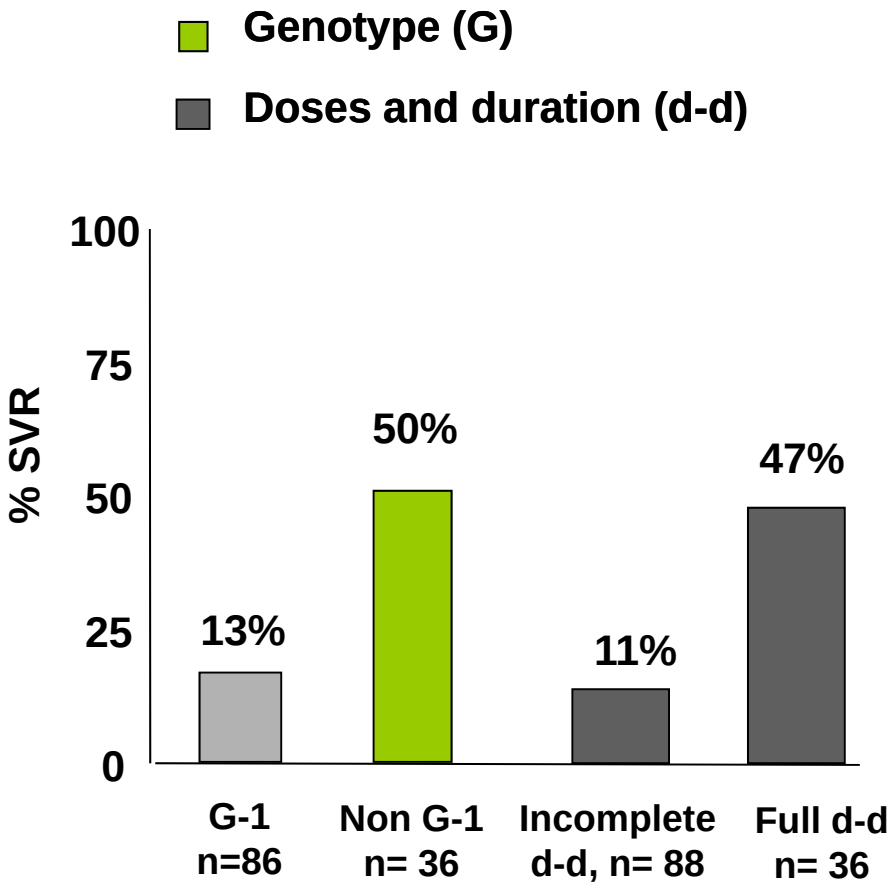
| | LADR<br>IFN + RBV (n=124) | Short treatment regimen<br>IFN/Peg-IFN + RBV (n=81) |
|---|---|---|
| Age | 58 (35-65) | 57 (33-66) |
| Male (n, %) | 81 (65%) | 59 (73%) |
| Child-Pugh | | |
| A | 56 (45%) | 38 (47%) |
| B | 45 (36%) | 34 (42%) |
| C | 23 (18%) | 9 (11%) |
| Genotype 1 | 86 (70%) | 65 (80%) |
| Viral load ($log_{10}$ IU/mL) | 26% (< *850.000 UImL*) | 5.7 (2-8.5) |
| Duration of therapy (months) | 6-12 | 3-4 |
| Underwent LT | 47 (38%) | 73 (90%) |
| EOTR | 57 (46%) | 24 (30%) |
| SVR | 27 (22%) | 16 (20%) |

*Everson et al, Hepatology 2005*

*Forns et al, J Hepatol. 2003*
*Carrión et al, J Hepatol 2009*

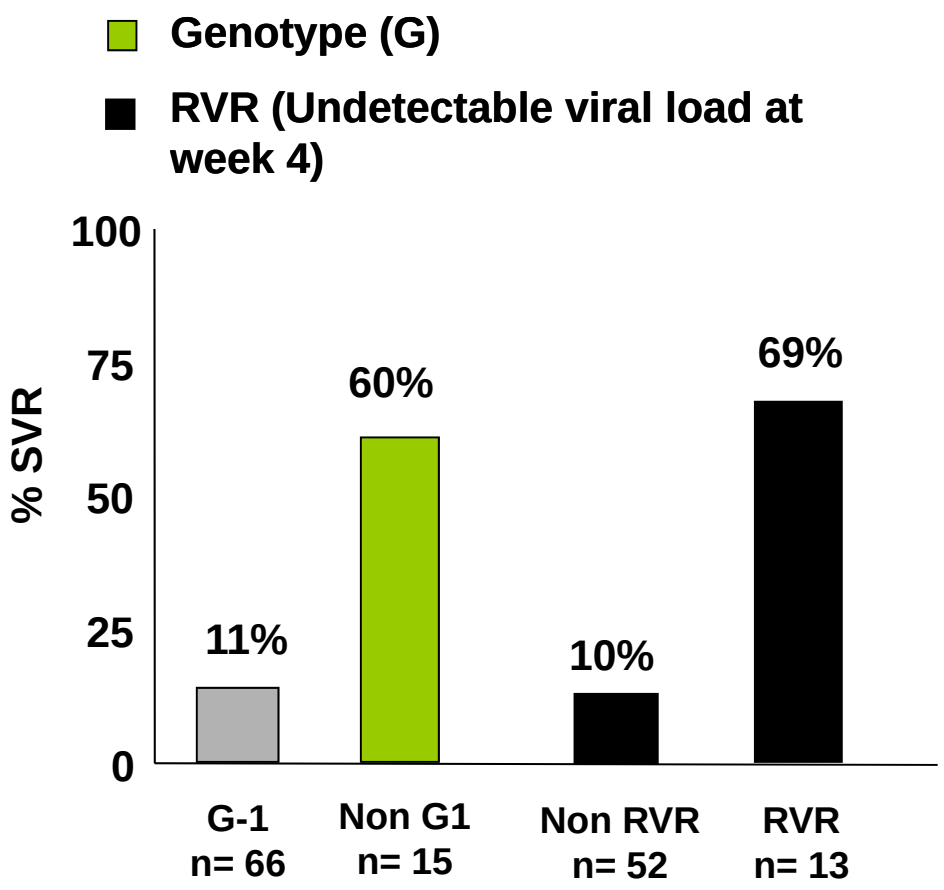
# Variables predicting virological response

## Low accelerating dose regimen



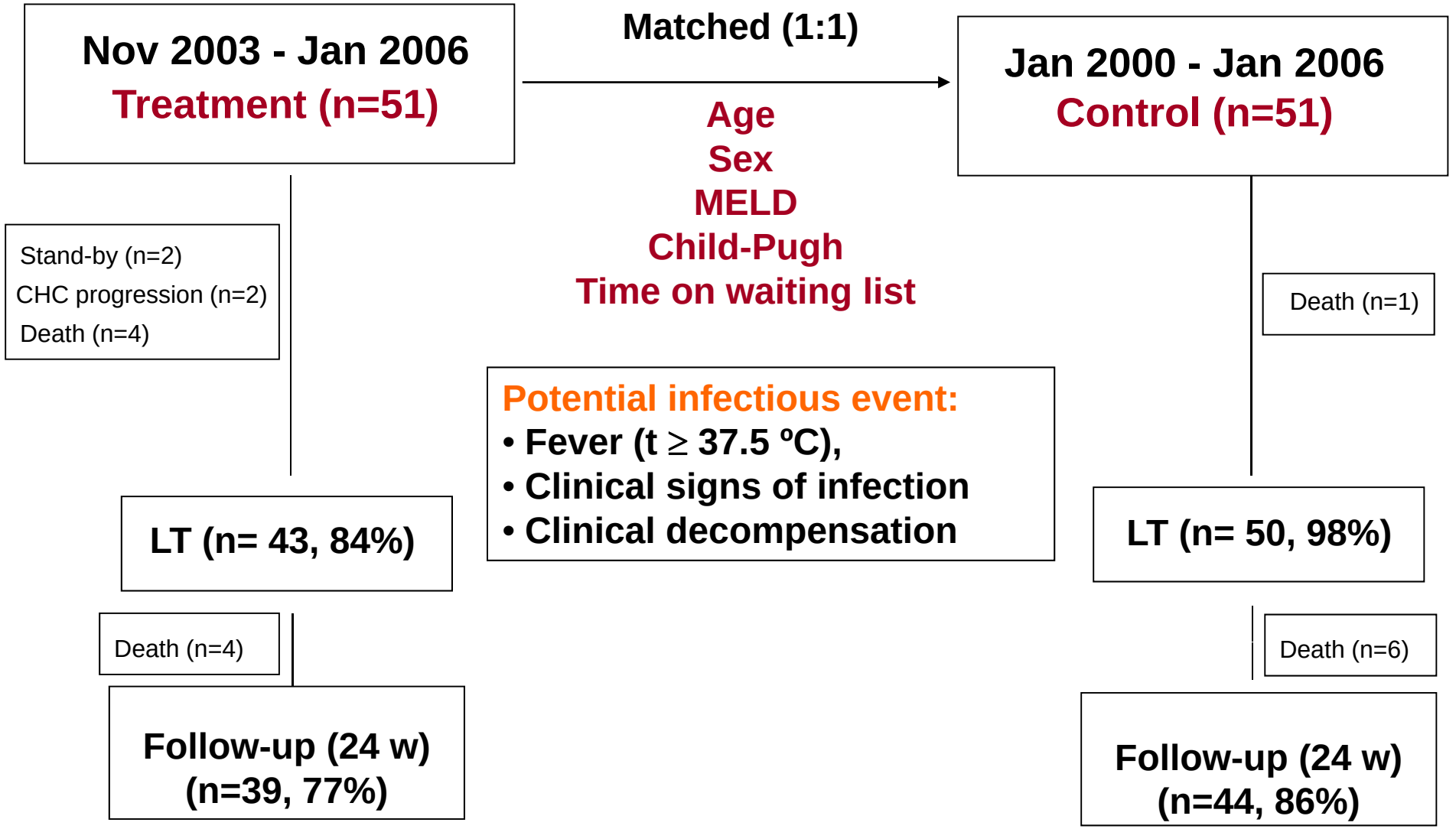

*Everson et al, Hepatology 2005*

## Short treatment course




*Forns et al, J Hepatol. 2003*
*Carrión et al, J Hepatol 2009*

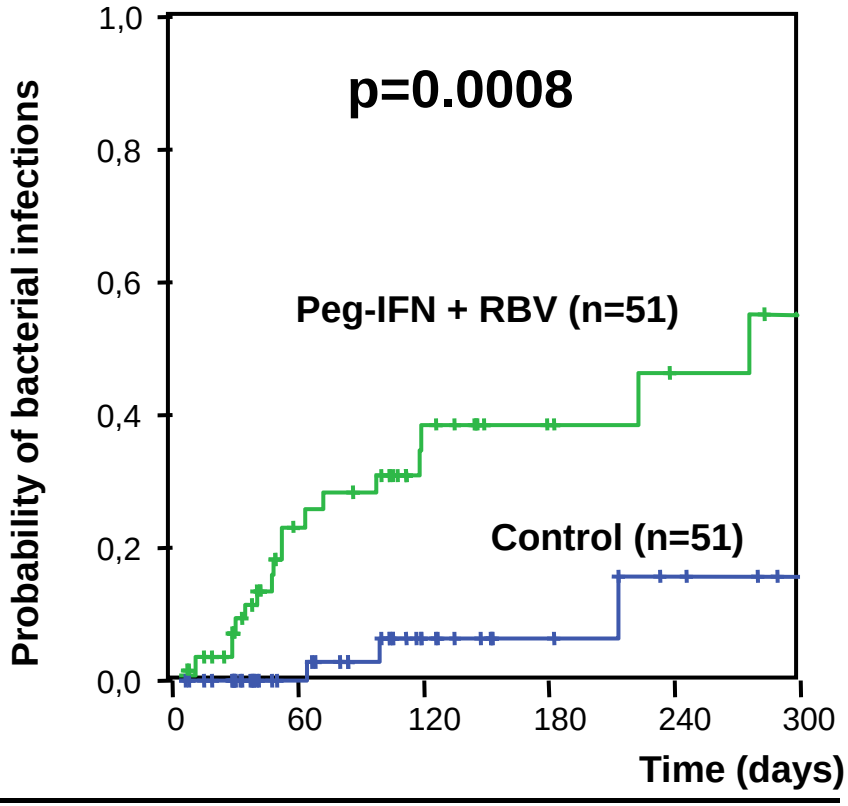
# Adverse events due to antiviral therapy




*Carrion et al, J. Hepatol. 2009*

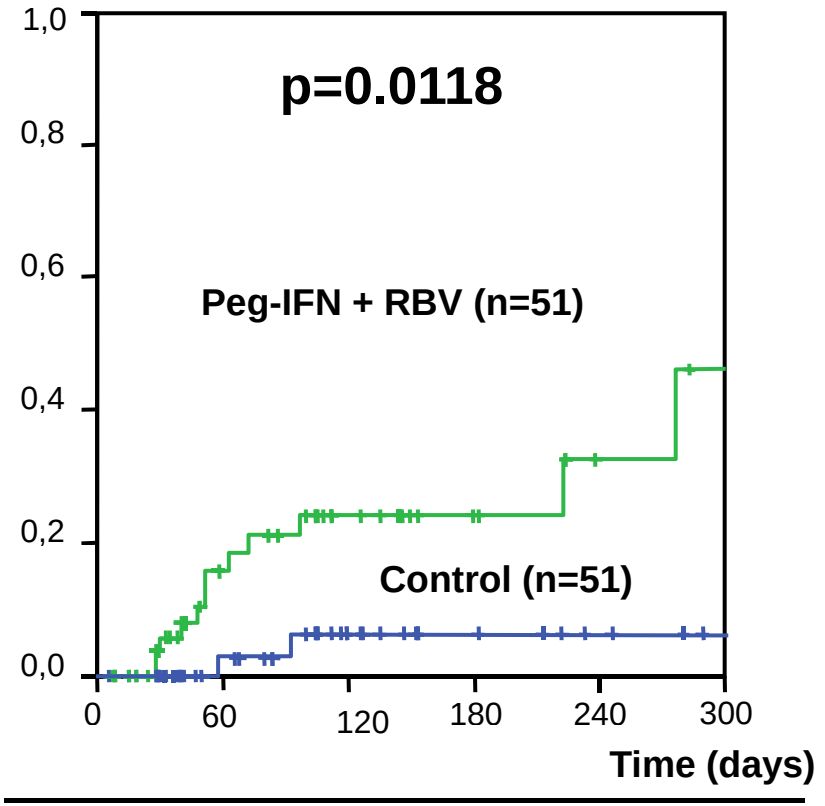
# Adverse events due to antiviral therapy: bacterial infections

## Bacterial infections (n=102)




| | | | | | | |
|---|---|---|---|---|---|---|
| Treated | 51 | 30 | 16 | 9 | 6 | 4 |
| Control | 51 | 34 | 18 | 11 | 7 | 4 |

## SBP/ SB (n=102)

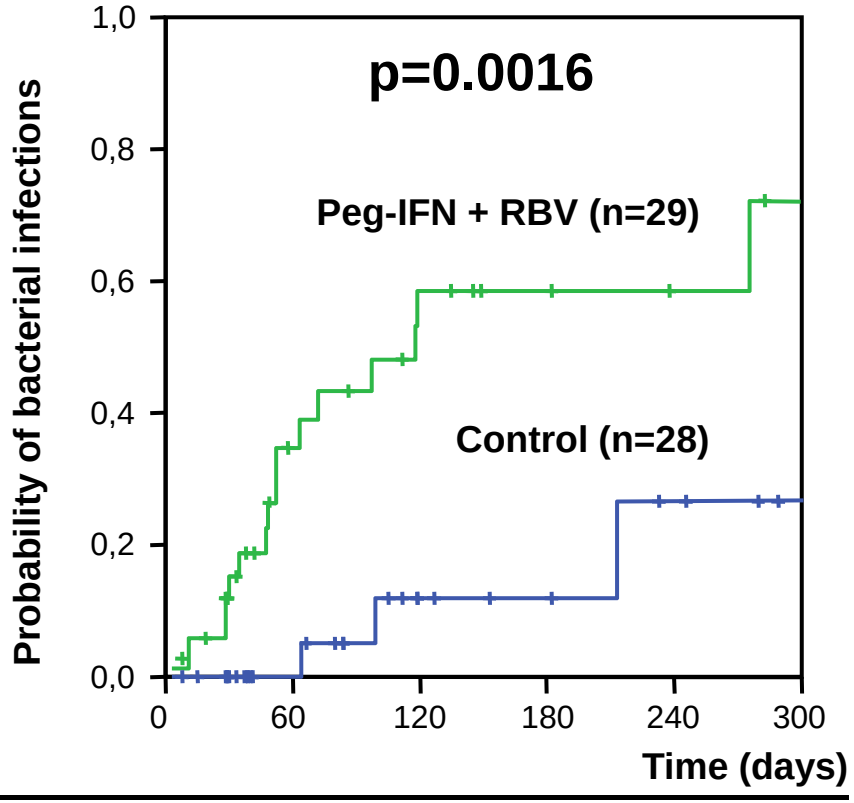



| | | | | | | |
|---|---|---|---|---|---|---|
| | 51 | 31 | 18 | 10 | 5 | 3 |
| | 51 | 34 | 18 | 11 | 7 | 4 |

*Carrion et al, J. Hepatol. 2009*

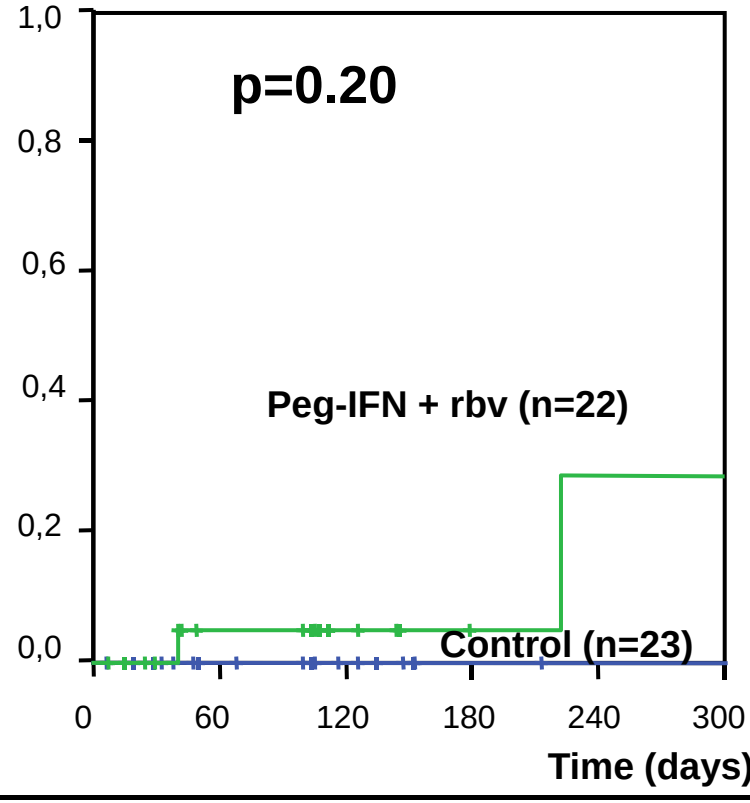
# Adverse events due to antiviral therapy: bacterial infections

## Bacterial infections
## Ch-P B or C score (n=57)




| | | | | | | |
|---|---|---|---|---|---|---|
| Treated | 29 | 15 | 8 | 5 | 3 | 1 |
| Control | 28 | 19 | 8 | 7 | 4 | 1 |

## Bacterial infections
## Ch-P A score (n=45)

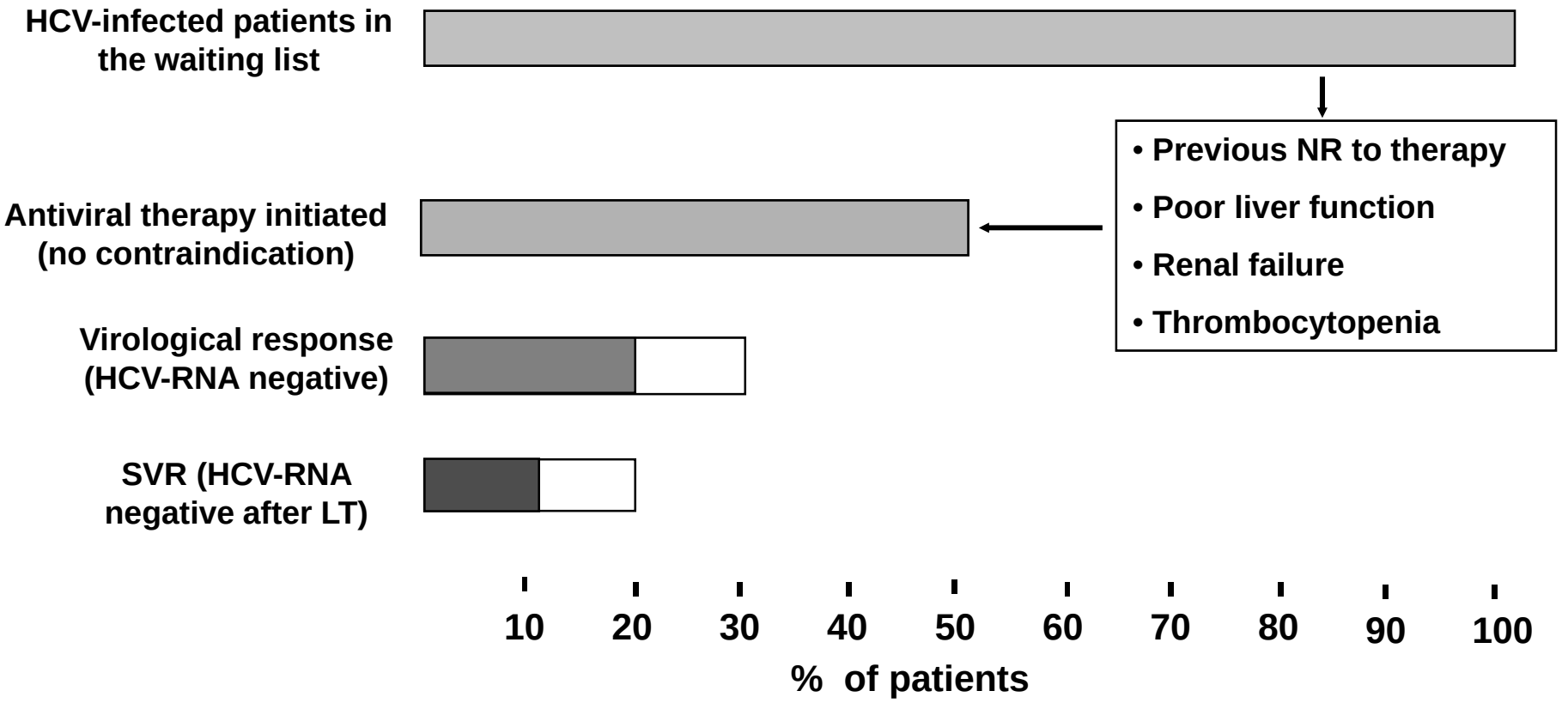



| | | | | | | |
|---|---|---|---|---|---|---|
| | 22 | 15 | 8 | 4 | 3 | 3 |
| | 23 | 15 | 9 | 4 | 3 | 3 |

*Carrion et al, J. Hepatol. 2009*

# Applicability of antiviral treatment before LT

## Antiviral therapy with Pegylated interferon alfa-2a plus ribavirin




*Forns et al, J Hepatol. 2003*

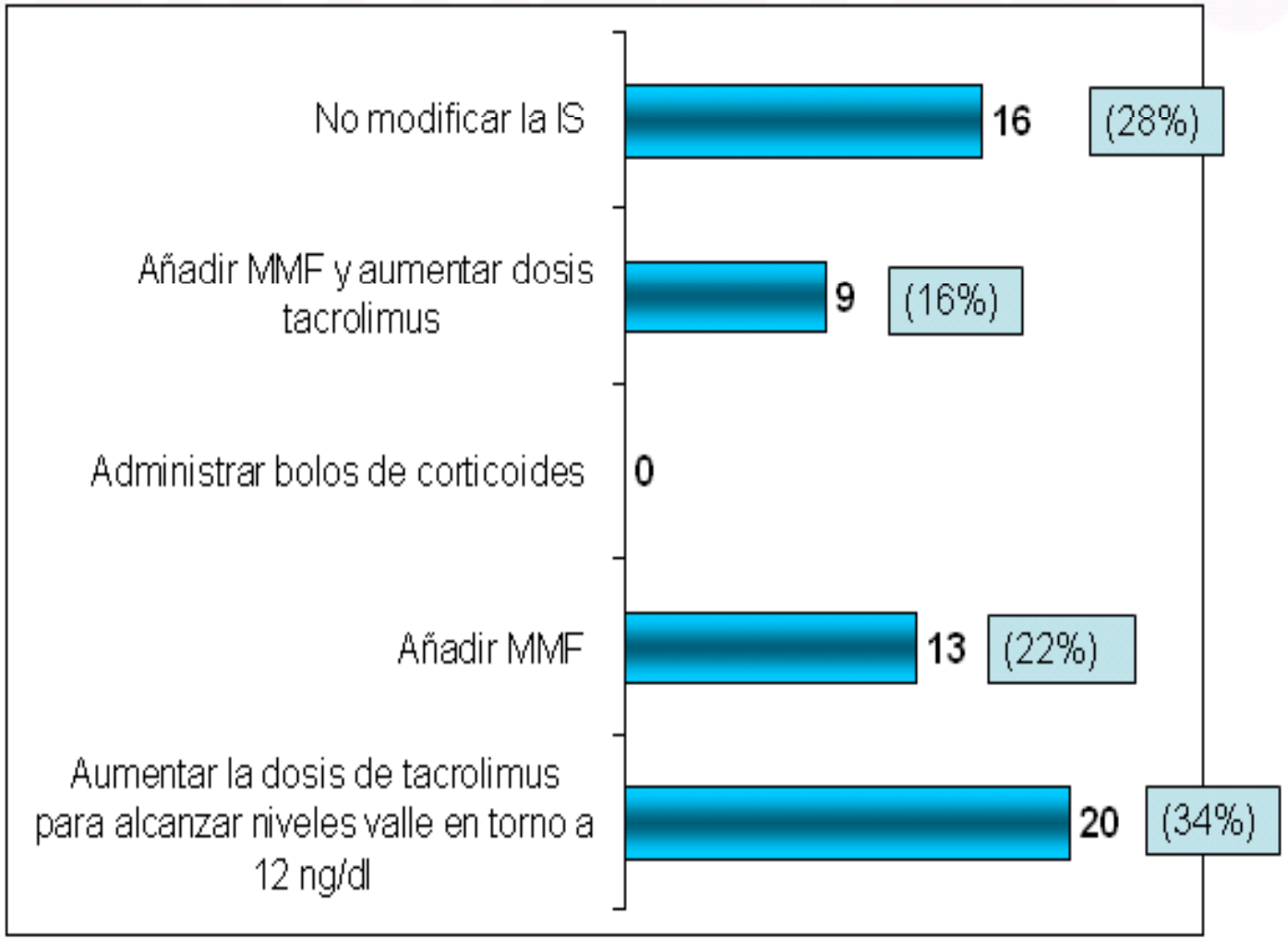
*Carrión et al, J Hepatol 2009*

# Case 2:

- 57 years old man. Liver transplantation for HCV genotype 1a- cirrhosis. Child-Pugh C10, Meld 22. Naïve for antiviral therapy.
- Donor: 70 years old man, no steatosis, normal liver enzymes, cause of death: CVA, 72 h. in the ICU.
- Induction IS: Tac + P. No problems during the early post-transplant period.
- One month post-transplant, increase of transaminases, GGT and alkaline phosph (about twice the uln). A liver biopsy shows changes compatible with mild rejection together with acute lobular hepatitis.
- Tac trough levels: 9-10 ng/dl. Normal kidney function. Prednisone dose: 15 mg /d.

## What would you recommend at this point?

- No modification of immunosuppression
- Add MMF and increase Tac doses
- Add steroid bolus
- Add MMF
- Increase Tac levels to about 12 ng/dl

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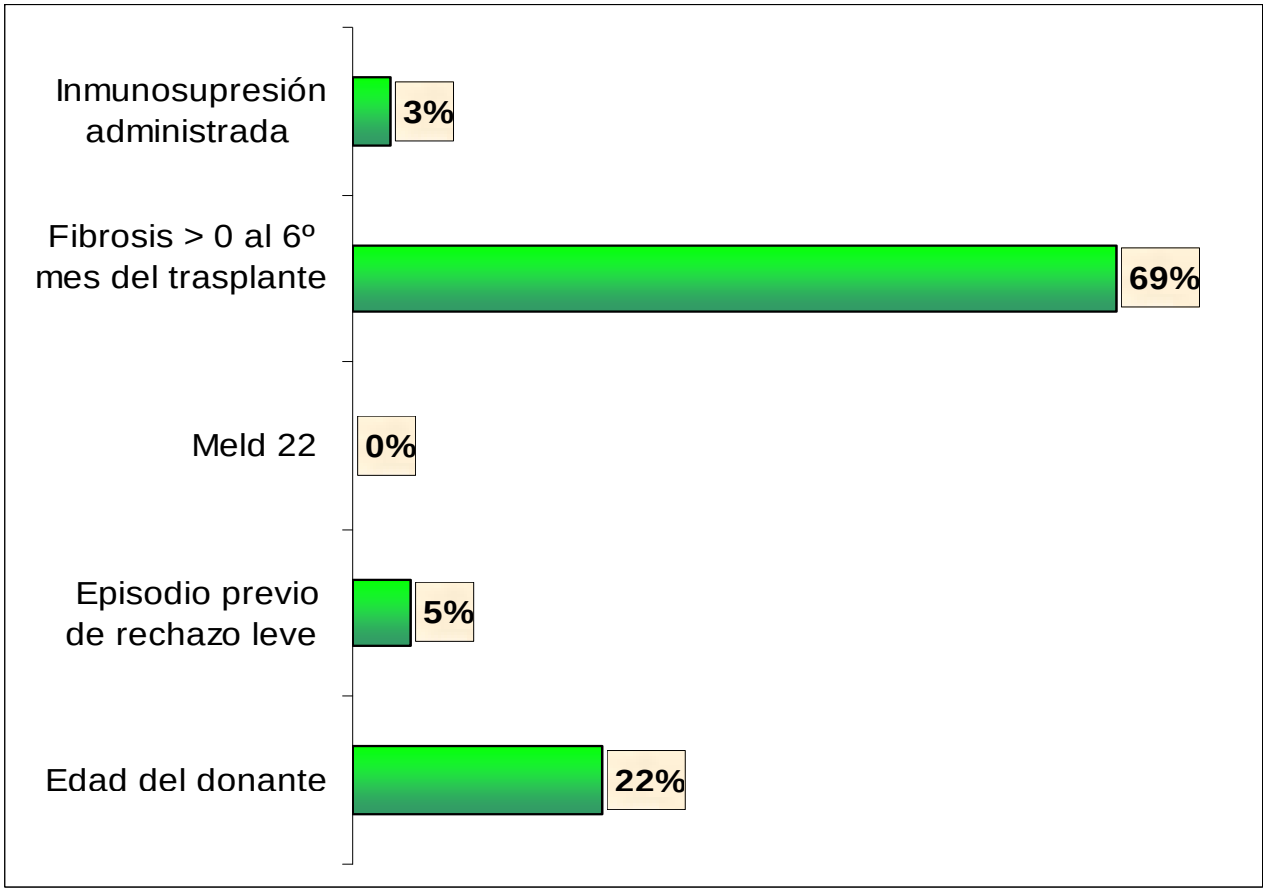
- A couple of months later, transaminase levels were AST 49 UI, ALT 67 UI, GGT 72 UI while the remainder parameters were within normal range.
- Prednisone dose was reduced progressively to 5 mg/day with Tac levels at 3 months around 7-8 ng/dl.
- On the fifth post-operative month, a new increase in transaminases occurred to 4 times the uln, together with an increase in Bil and AP.
- A new liver biopsy showed signs compatible with recurrent chronic hepatitis with moderate necroinflammation and portal fibrosis (1-2 / 6 Ishack score).

## What do you consider more worrisome regarding the course of recurrent hepatitis C?

- The immunosuppression that the patient has received
- Having fibrosis > 0 at 6 months post-transplantation
- Meld 22 at transplantation
- Prior episode of untreated mild rejection
- Donor age

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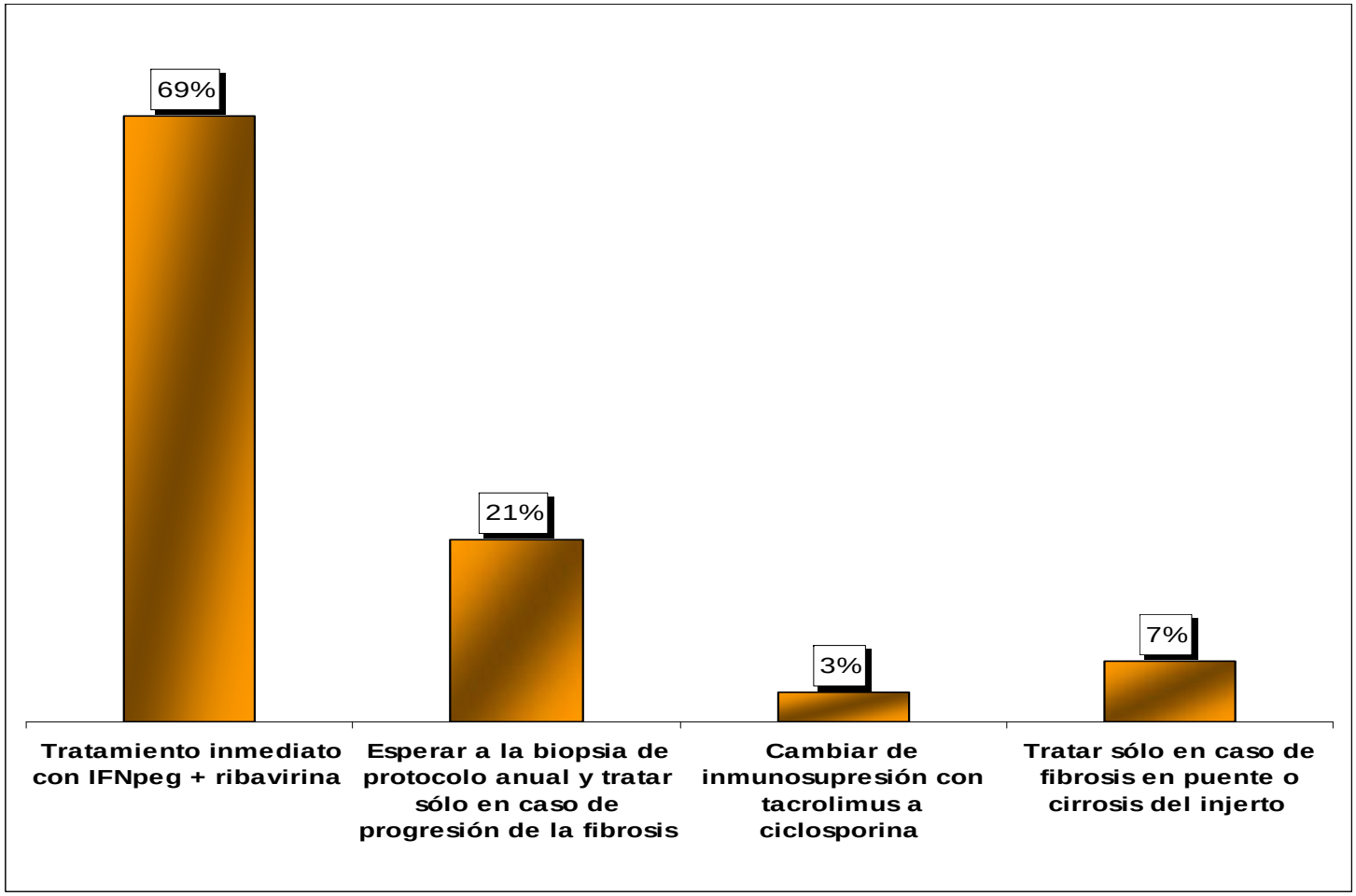
# What would you recommend in this patient?

- Start antiviral therapy with pegIFN and ribavirin
- Wait for the one-year protocol liver biopsy and only treat in case of fibrosis progression
- Treat only in case of fibrosing cholestatic hepatitis or graft cirrhosis
- Modify immunosuppression: change from Tac to CsA

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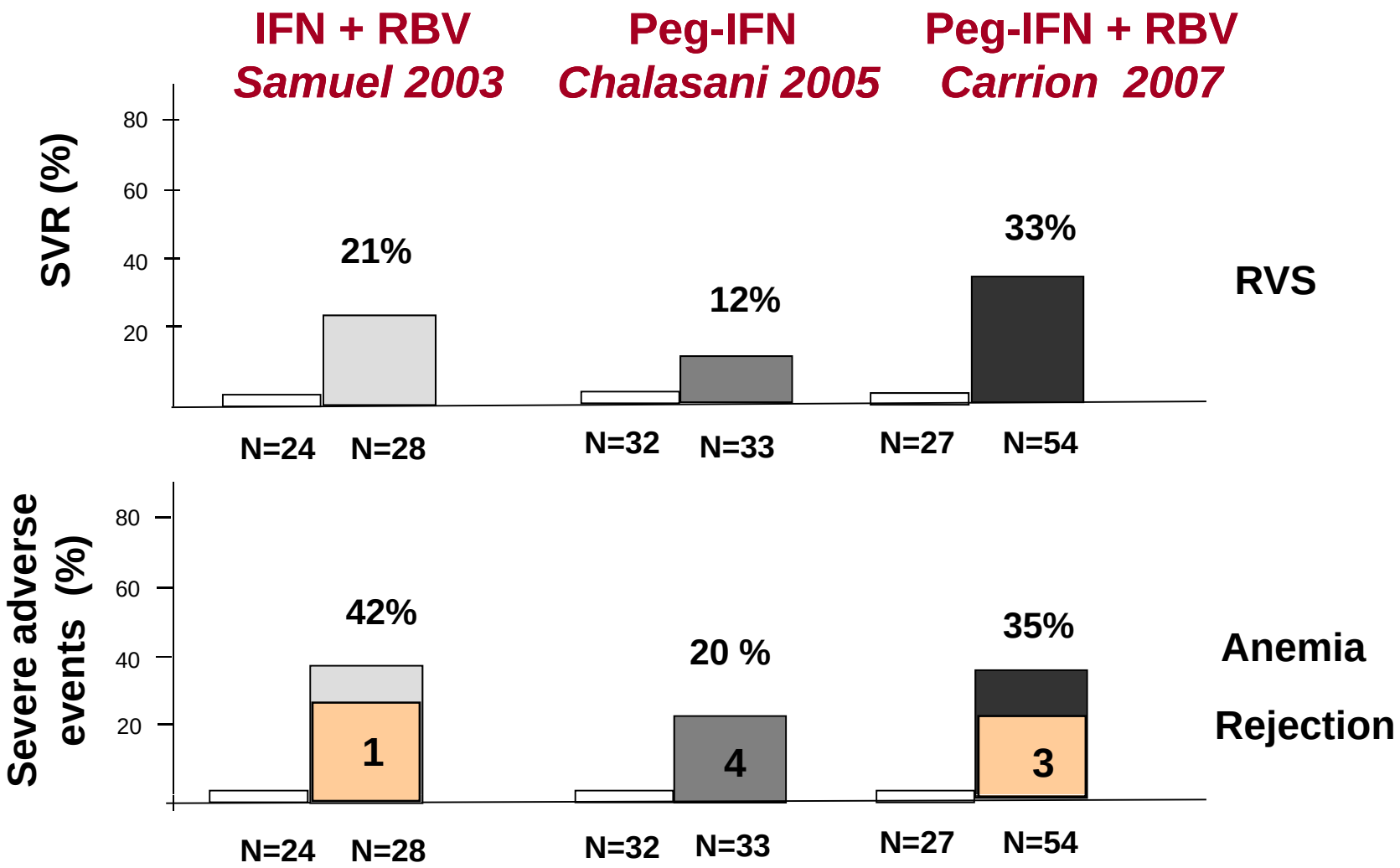
# Post-transplant HCV Treatment with pegIFN + ribavirin

| | N patients | N studies | Years | SVR | SVR G1 |
|---|---|---|---|---|---|
| Wang , 2006 | 587 (11-86/st) | 16 | 1980-2005 | 27% | |
| Berenguer, 2008 | 611 (12-61/st) | 19 | 2002-2006 | 30.2% | 28.7% |
| Xirouchakis, 2008 | 264 (13-54/st) | 6 | 1999-2008 | 31% | |

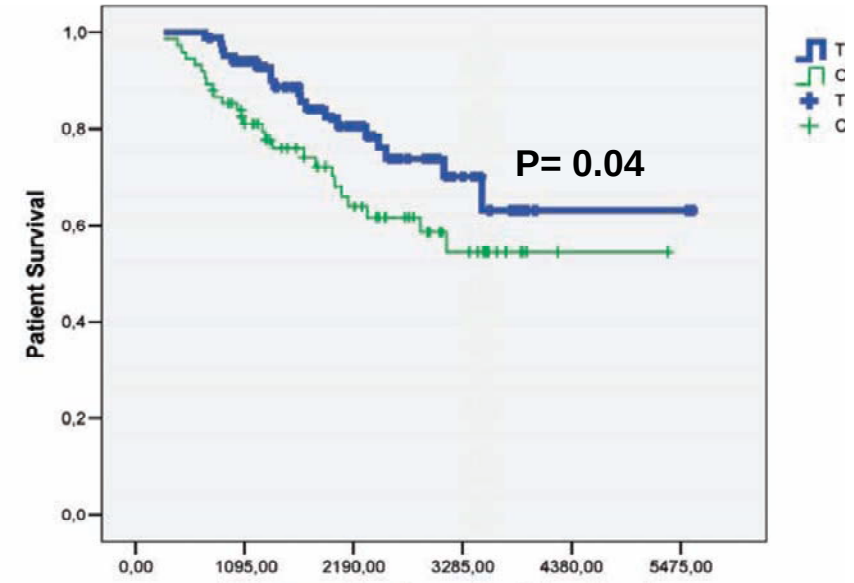
# Delayed therapy after LT: Chronic Hepatitis



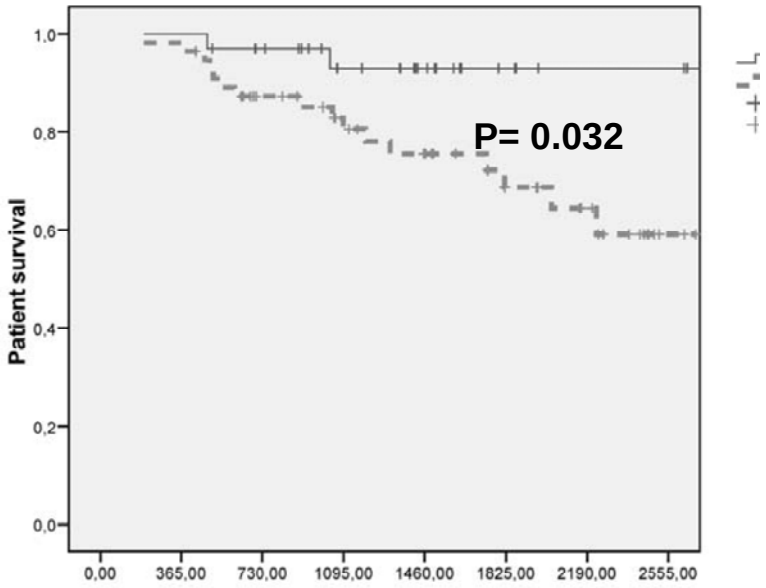
# Beneficial effect of antiviral therapy

## Antiviral Therapy after LT reduces clinical decompensation and mortality

**Patient survival in treated vs controls**




**Patient survival in SVR (n=33) vs NR (n= 56)**




*Berenguer et al., Am J Transpl 2008*

# Factors associated with SVR

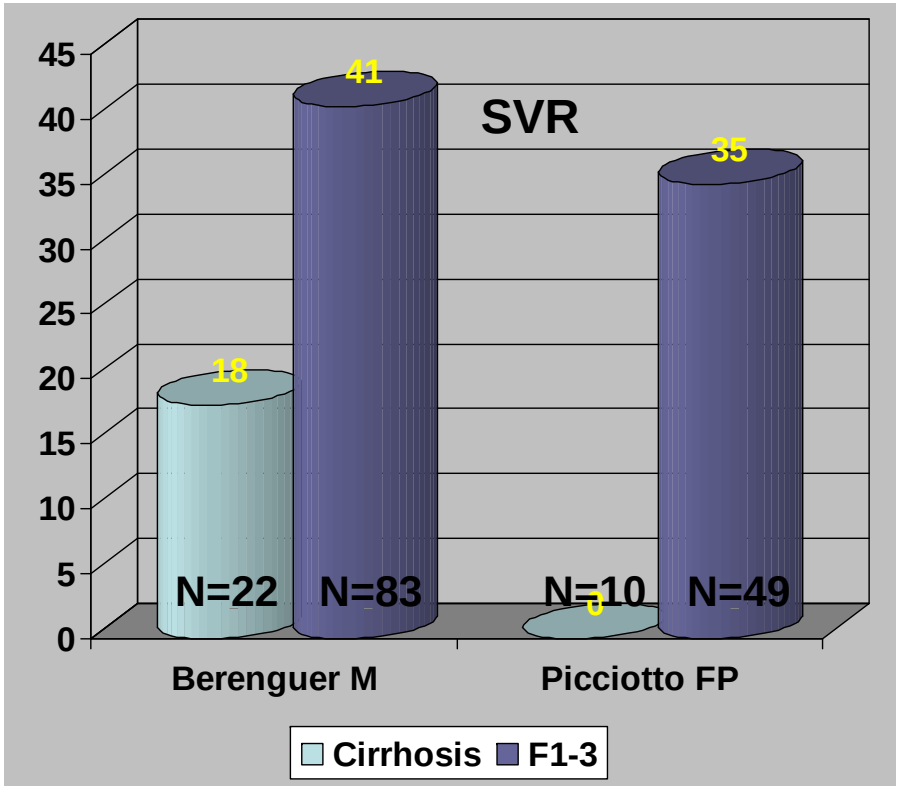
| | n | Studies | Years | SVR | Factors |
|---|---|---|---|---|---|
| **IFN + RBV** | | | | | |
| Wang (AJT, 2006) | 689 | 24 | 1980-2005 | 24% | - non-1 Genotype<br>- Naive |
| **Peg-IFN + RBV** | | | | | |
| Wang (AJT, 2006) | 587 | 16 | 1980-2005 | 27% | - non-1 Genotype<br>- Naive |
| Berenguer (JH, 2008) | 611 | 22 | 2002-2006 | 30% | - EVR<br>- Genotype-2<br>- Adherence<br>- Low VL |
| **RCT** | | | | | |
| Xirouchakis (Cochrane, 2009) | 242 | 6 | 1999-2008 | 31% | - 80/80/80 |

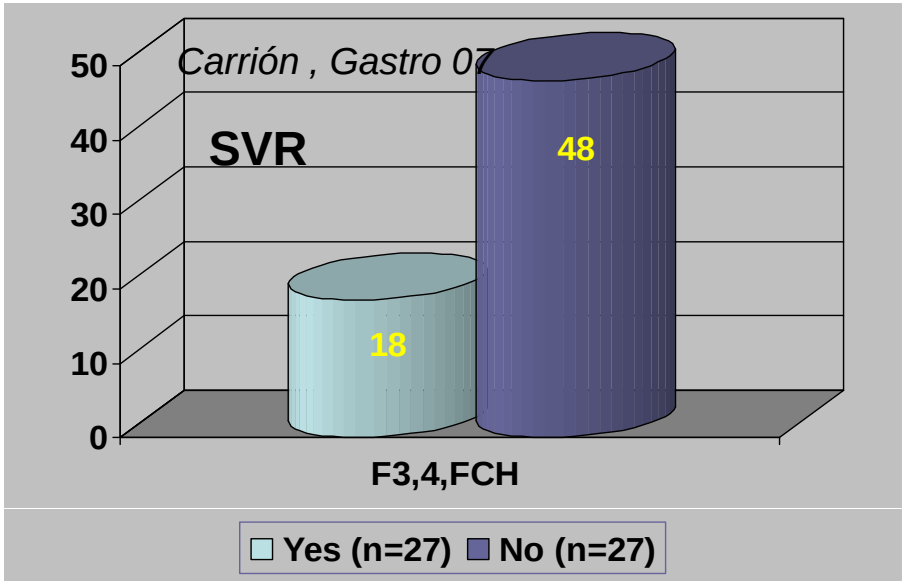
# CNI and antiviral response

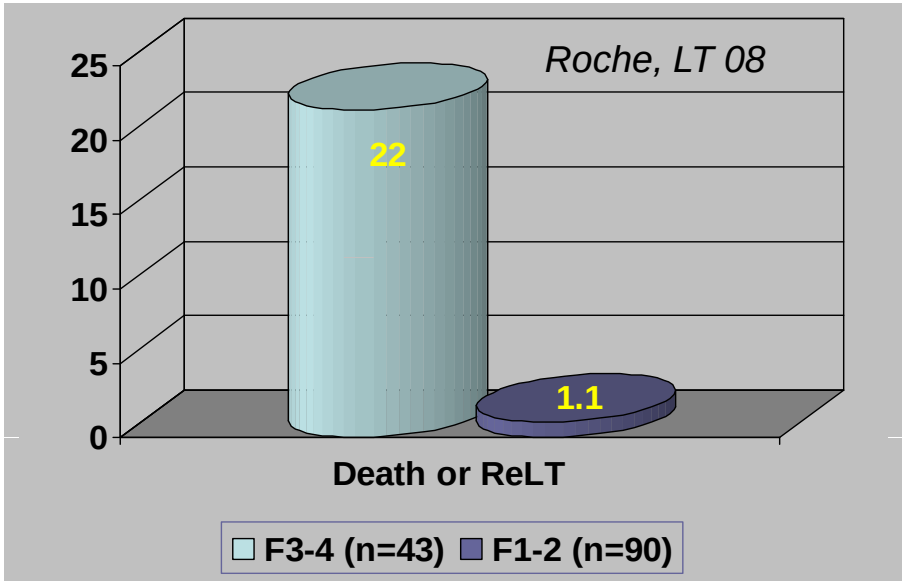
| Author | CsA/Tac (N) | SVR CsA | SVR Tac | Multivariate analysis |
|---|---|---|---|---|
| **Dumortier** | 3/17 | 2/3 (67%) | 9/17 (53%) | Univariate:G, treatment duration, EVR |
| **Babatin** | 7/3 | 1/7 (14%) | 1/3 (33%) | - |
| **Biselli** | 11/9 | 6/11 (54%) | 3/ 9 (33%) | Univariate: RVR |
| **Berenguer** | 15/21 | 11/15 (73%) | 11/21 (52%) | EVR |
| **Oton** | 18/34 | 5/18 (28%) | 19/34 (56%) | Viremia, RVR, EVR, 2-4 yrs post-LT |
| **Fernandez** | 12/35 | 2/12 (17%) | 9/35 (26%) | Univariate:viremia, EVR, 80x80x80,GGT |
| **Picciotto** | 33/28 | 10/33 (30%) | 7/28 (25%) | G2, pegIFN dose |
| **Carrion** | 22/29 | 10/22 (45%) | 8/29 (27%) | EVR |
| **Hanouneh** | 9/37 | 4/9 (44%) | 11/37 (30%) | Univariate:G, viremia, RVR, EVR |
| **Cescon** | 37/62 | 16/37 (43%) | 9/62 (14%) | Donor age, G, **CsA** |
| **Selzner** | 80/92 | 46/80 (57%) | 40/92 (43%) | G, **CsA**, HAI, donor age |
| **Berenguer** | 42/65 | 16/42 (38%) | 23/65 (35%) | EVR, donor age |
| **Roche** | 77/56 | 29/77 (38%) | 22/56 (39%) | Viremia, G, treatment duration |
| **RevistTC** | 123/287 | 59/123 (48%) | 106/287 (37%) | Viremia, **CsA**, duration, G,donor age |
| **Firpi** | **18/20** | **7/18 (39%)** | **7/20 (35%)** | **Randomization: CsA vs Tac** |
| **TOTAL** | 507/795 | 224 /507 (44%) | 285 /795 (36%) | |

# Treatment of recurrent hepatitis C

## MILD VS ADVANCED FIBROSIS




*Berenguer M, LT 2009; Picciotto, J Hepatol 2007*

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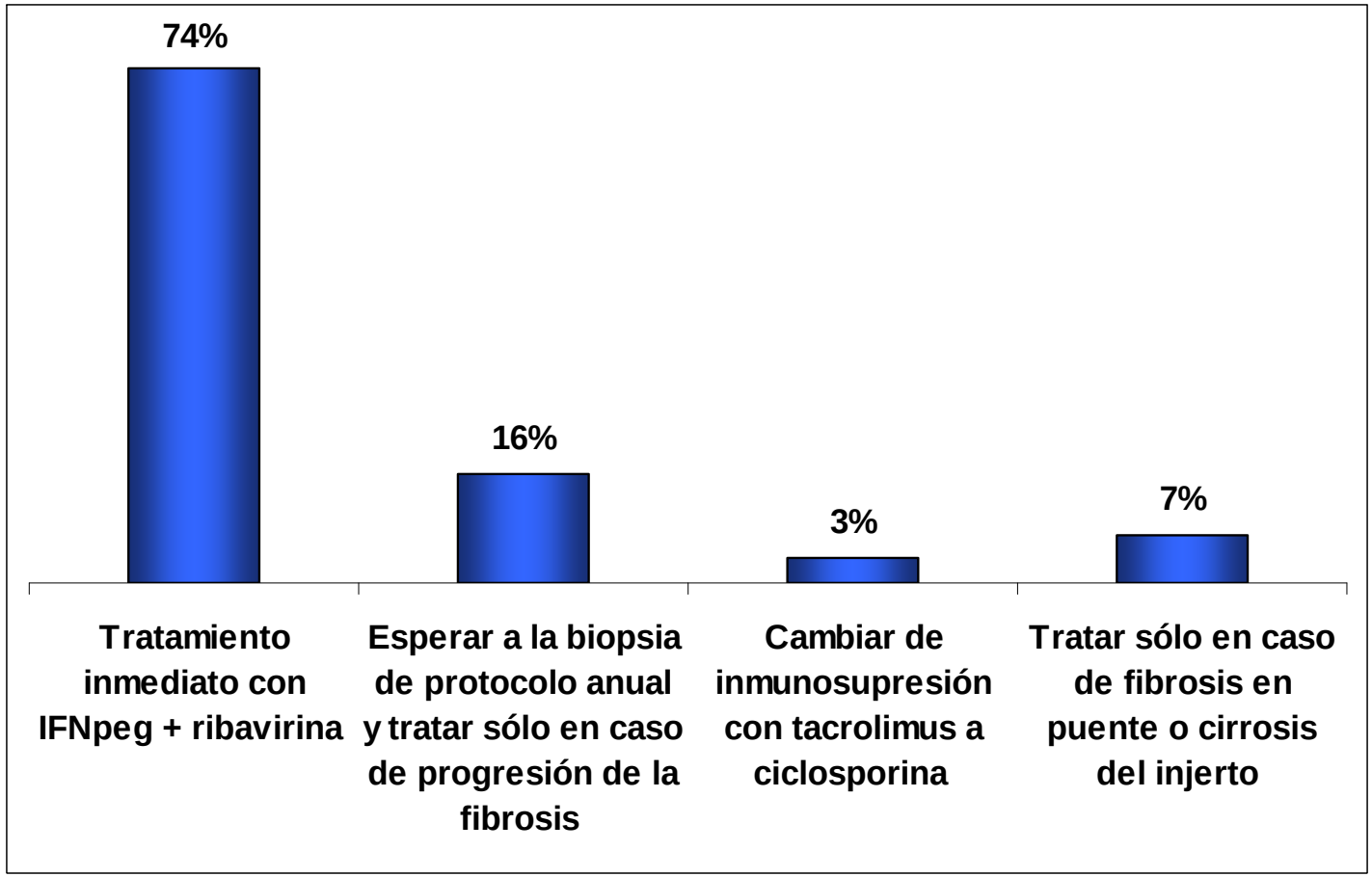
# If the infecting genotype had been 2 or 3 instead of 1, what would have been your strategy ?

- Start antiviral therapy with pegIFN and ribavirin
- Wait for the one-year protocol liver biopsy and only treat in case of fibrosis progression
- Treat only in case of fibrosing cholestatic hepatitis or graft cirrhosis
- Modify immunosuppression: change from Tac to CsA

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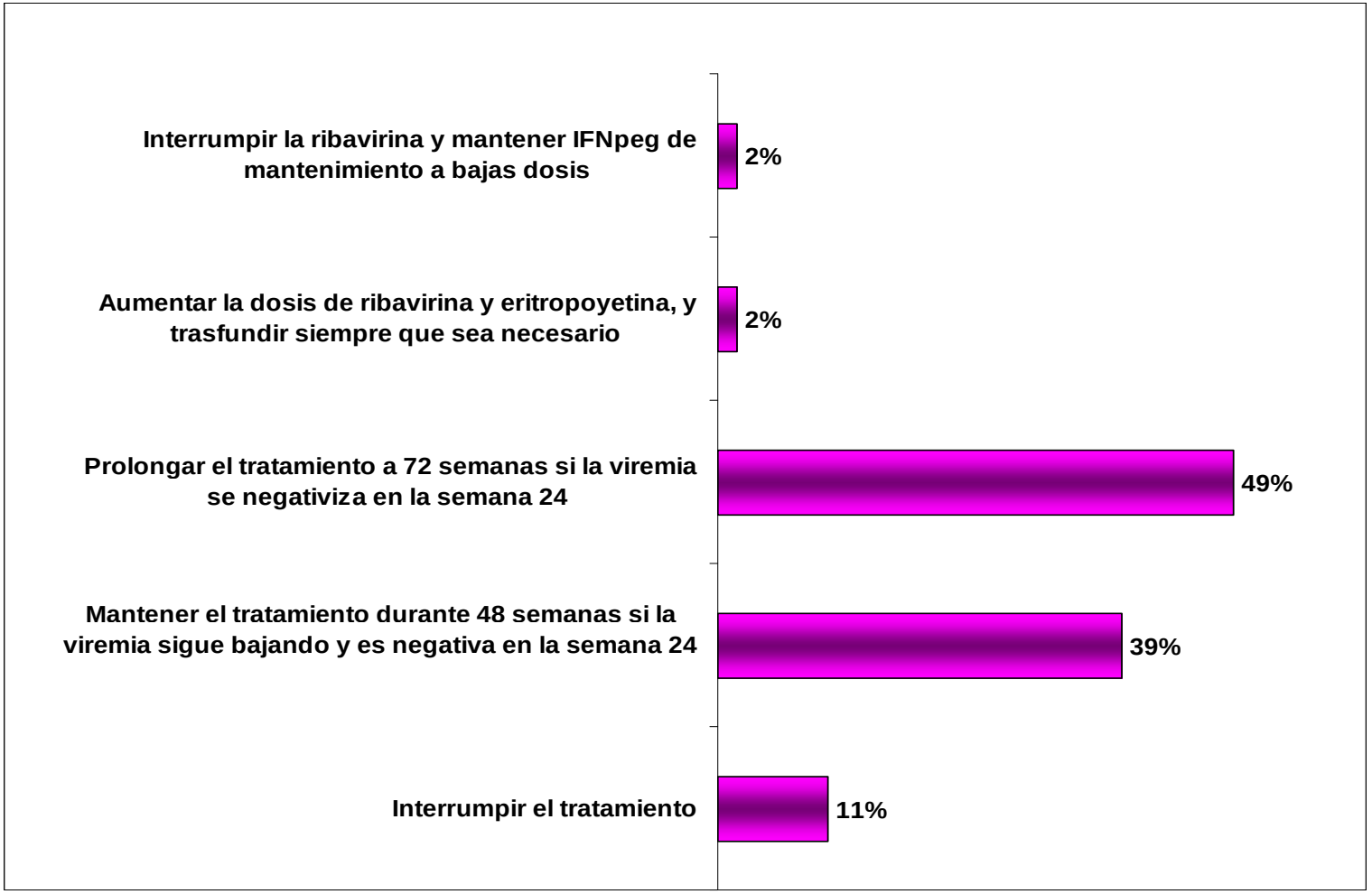
# Follow up 2

- In this case, the patient was not treated with antivirals at 6 months post-transplantation, and a new liver biopsy was performed at one year post-transplantation (protocol liver biopsy) which showed fibrosis 3 / 6 and severe necro-inflammation. Treatment was then initiated with IFNpeg + ribavirin at full doses (weight-based RBV doses). Viral load: 1.375.000 UI/ml. Weight: 82 kg, Heigth: 1.75 m. Tac levels: 5 ng/ml. Blodd tests: creatinine 1.4 mg/dl; AST 68 UI, ALT 99 UI, GGT: 55 UI, total Bil 1.5 mg/dl; Hgb 14.5; Leuc: 4.500; Platelets: 98.000.
- One month post-treatment, EPO was added (40.000 IU sc/wk) and riba was reduced to 800 mg/day due to anemia (Hgb 8 g/dl, leuc: 2.200; Plat: 65.000).
- At week 12, transaminases were within normal range and viral load had decreased to 103.000 UI/ml.

## What would you recommend at this time point?

- Stop RBV and continue with maintenance low dose pegIFN
- Increase RBV and EPO doses and transfuse whenever needed
- Continue therapy to 72 weeks if viremia is undetectable at week 24
- Continue therapy to 48 additional weeks after HCV RNA undetectability.
- Stop therapy

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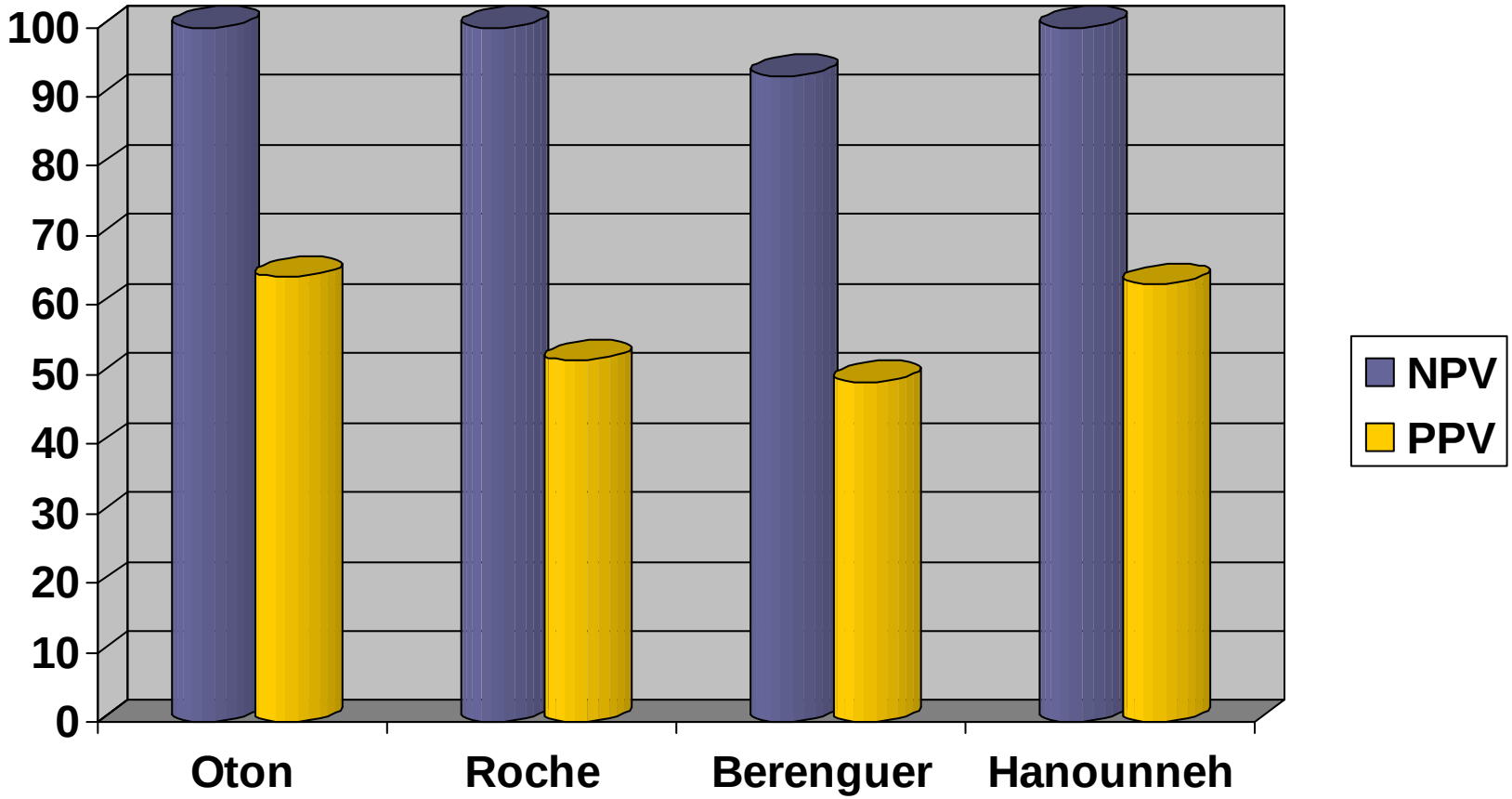
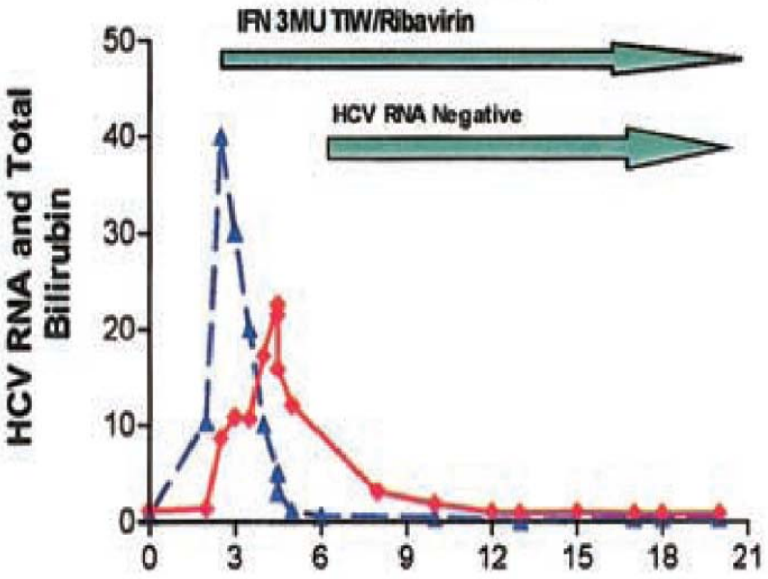
# Lack of EVR predicts NR



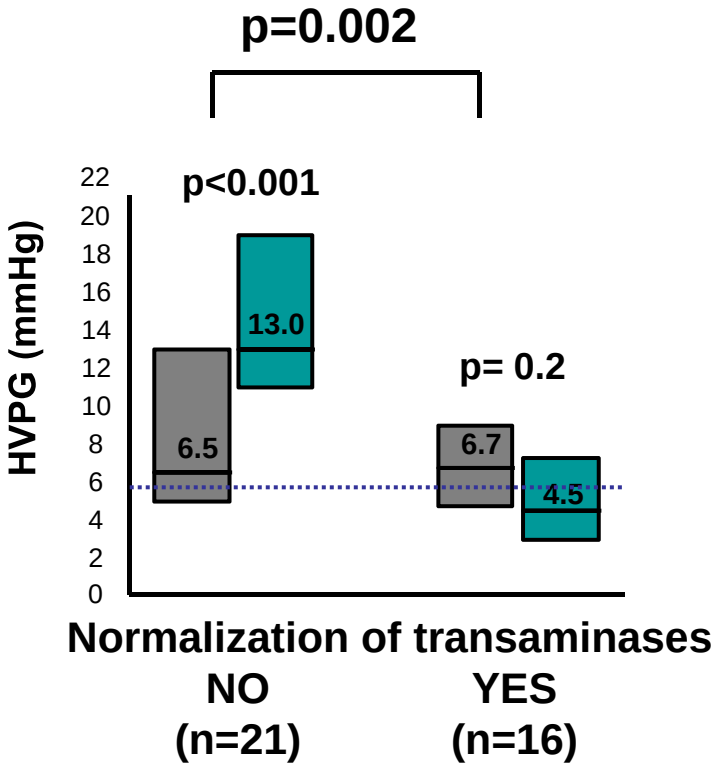
# Longer treatment regimens in cholestatic recurrence

## Beneficial effects maintaining antiviral treatment in patients with severe hepatitis C recurrence




*"Duration of antiviral therapy for cholestatic HCV recurrence may need to be indefinite"*

*Gopal and Rosen, LT2003*




*"These results should encourage the design of studies aimed at assessing the effect of longer treatment regimens (including maintenance therapy)"*

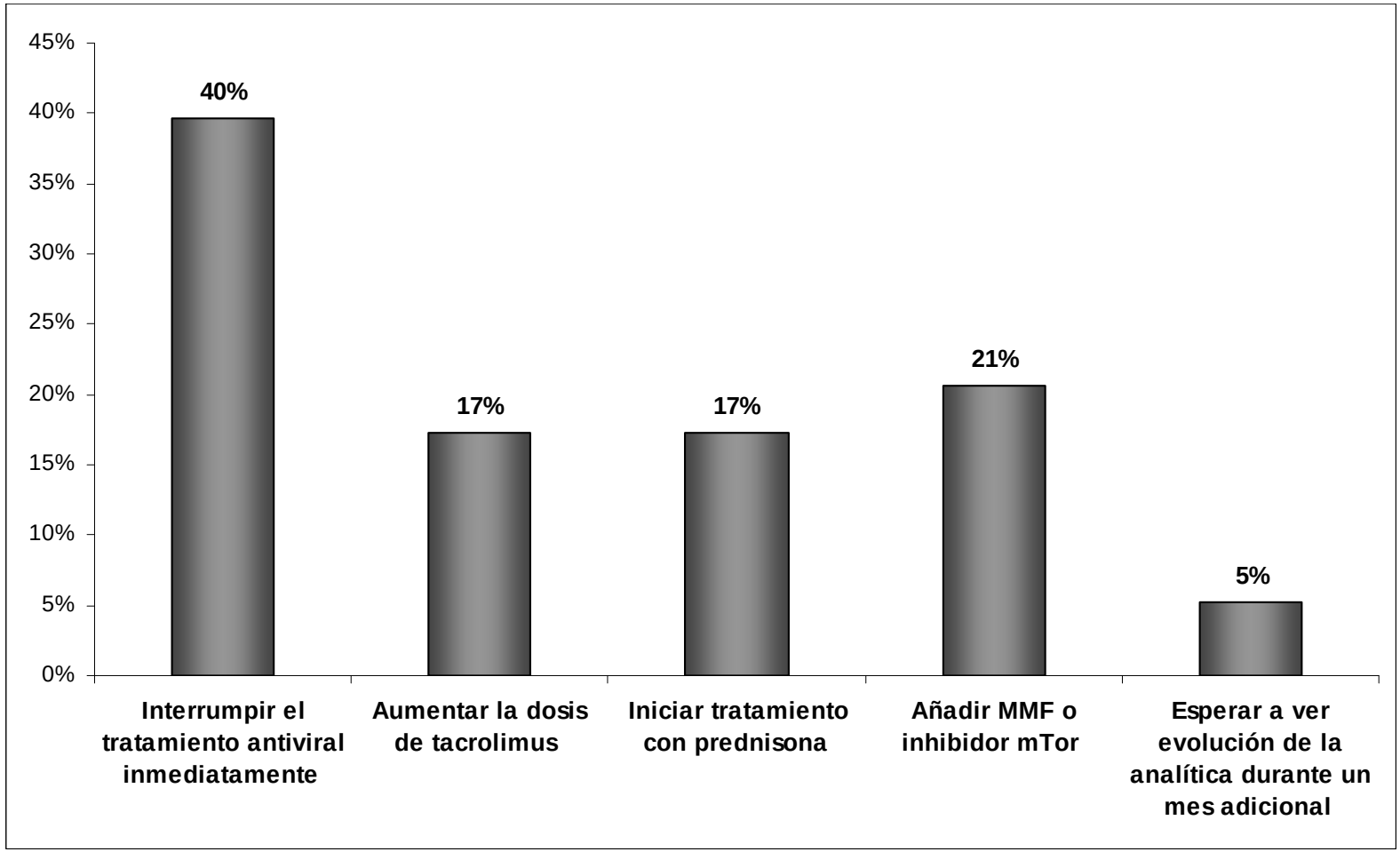
*Carrion et al. , Gastroenterology 2007*

# Follow-up 3

- Treatment was continued and at wk 24, liver enzymes were normal and HCV RNA was undetectable by RT-PCR. Tolerability to therapy was relatively good so that low doses of RBV (800 mg/d) + EPO were maintained throughout the remaining of treatment duration.
- At about week 30, an increase of transaminases, GGT, bilirubin and Alk Phosph was detected. A liver biopsy was performed which showed changes compatible with chronic hepatitis C with a rich mixed inflammatory infiltrate, rich in plasma cells in the portal tracts, with duct lesions and ductopenia < 30%, without endothelitis.
- Viral load continued to be negative.

# What would you recommend in this patient?

- Stop antiviral therapy immediately
- Increase Tac doses
- Start therapy with prednisone
- Add MMF or mTor inhibitor
- Wait to see the course of the disease for another 1 month

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# Adverse events associated with antiviral therapy

**Dose reduction**

- 74%, mostly due to hematologic toxicity
- EPO: 44%
- Filgastrim: 35%
- Transfusion: 7%

**Premature treatment discontinuation**

- 43%, mostly due to anemia

**Rejection**

- Incidence: 5-11%
- Mild rejection: 5%
- Chronic rejection:2-35%
- Risk factors: D/C RBV, CsA use, SVR

**“Allo-immune hepatitis”**

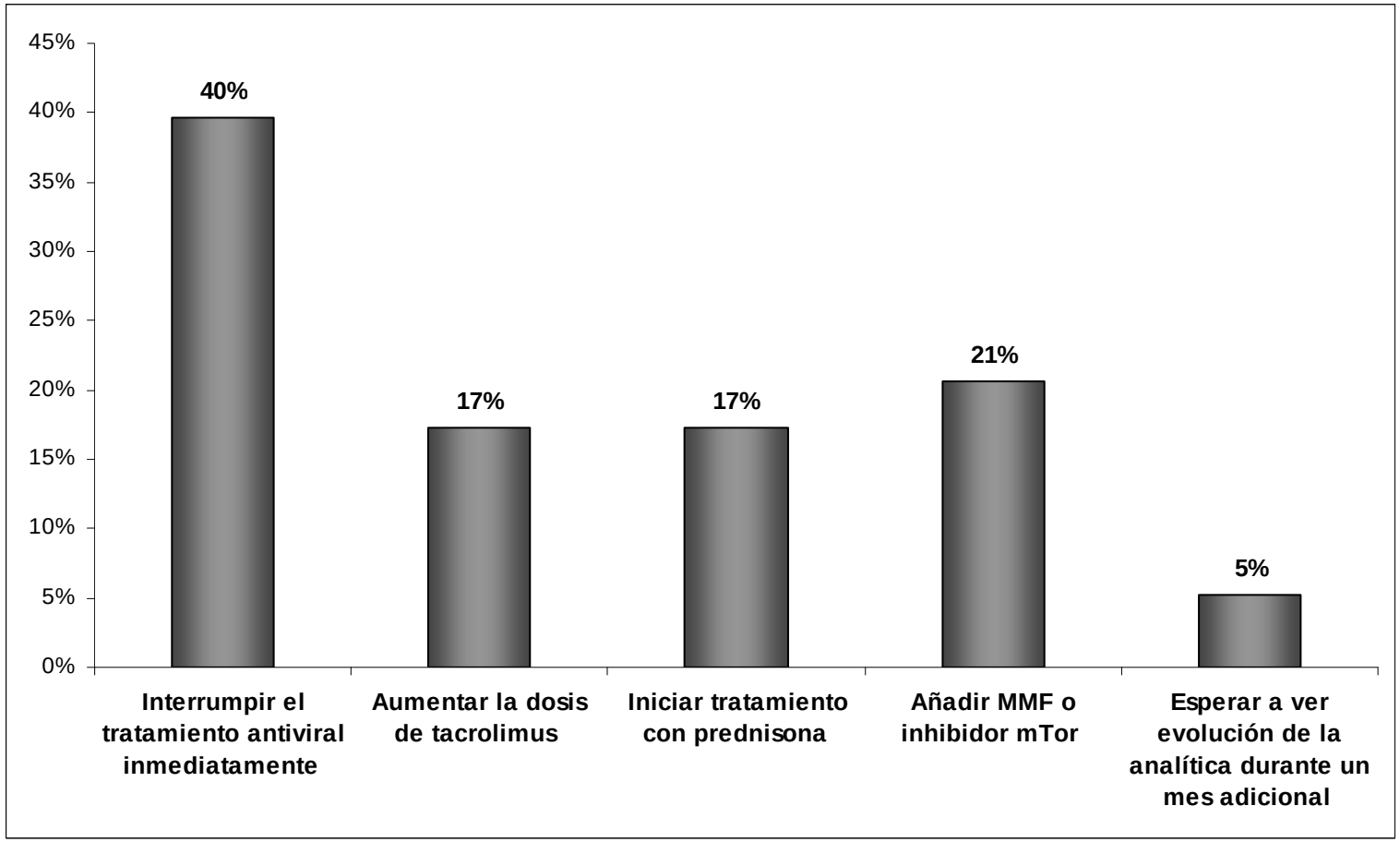
- Treatment was discontinued and IS was increased.

Outcome

- One month and a half following the discontinuation of antiviral therapy and the increase of baseline IS (increase of tac doses together with treatment with prednisone), viremia continued to be undetectable, but liver function tests worsened progressively, with significant cholestasis (Bil 10 mg/dl).

## What would you recommend at this time point?

- No modification of IS and no candidate for retransplantation
- Increase of IS adding MMF
- Retransplantation only if viremia continues to be undetectable during 4.5 additional months
- Immediate inclusion in the waiting list for retransplantation

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# Outcome

- The patient was retransplanted with good outcome following retransplantation and no viral recurrence.