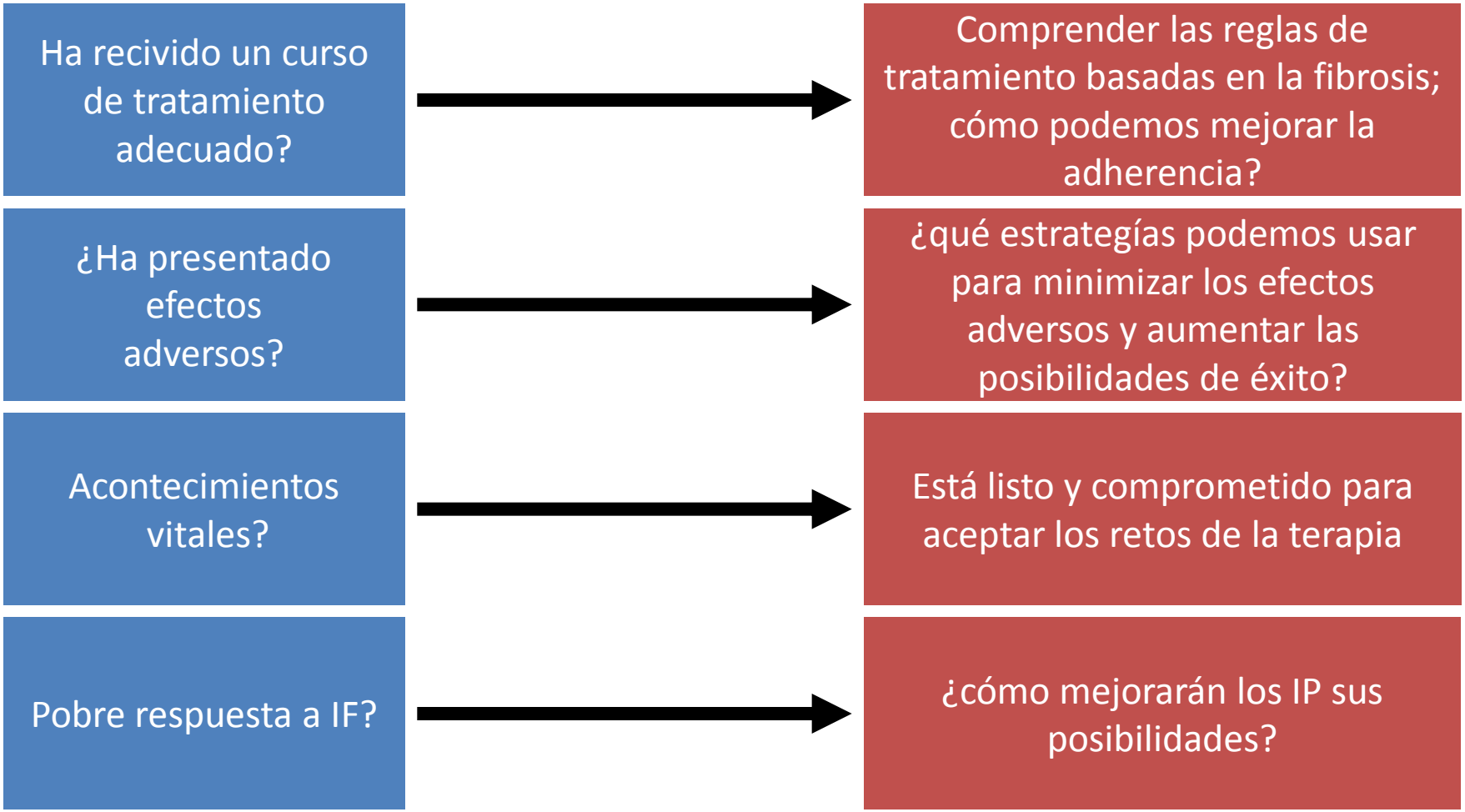
¿Está nuestro paciente preparado para el tratamiento?

Reyes Pascual

Servicio de Medicina Interna

Unidad de Enfermedades Infecciosas

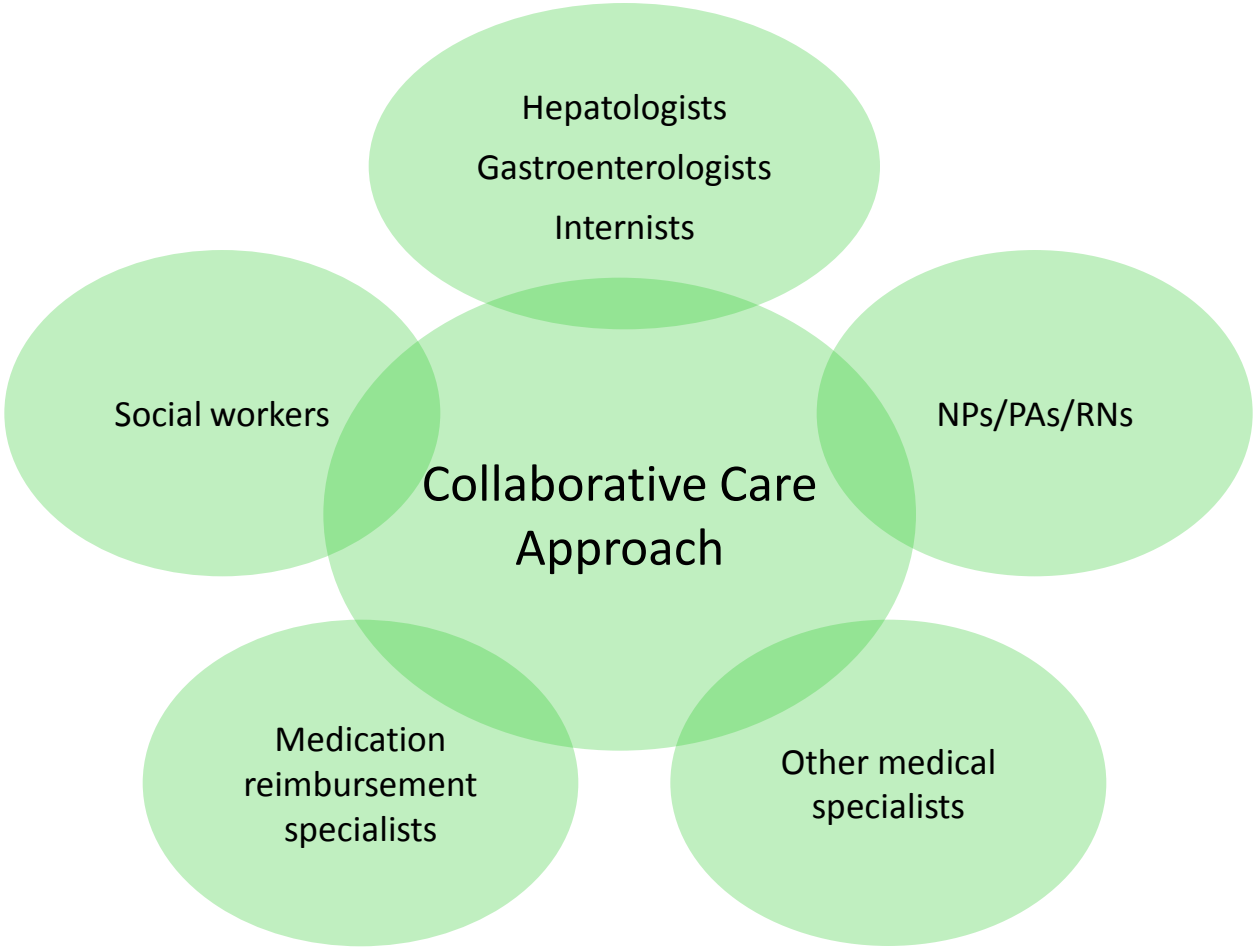
¿Porqué falló el tratamiento previo?



¿Tenemos una idea clara de la histología/fibrosis e historial de tratamientos previos?

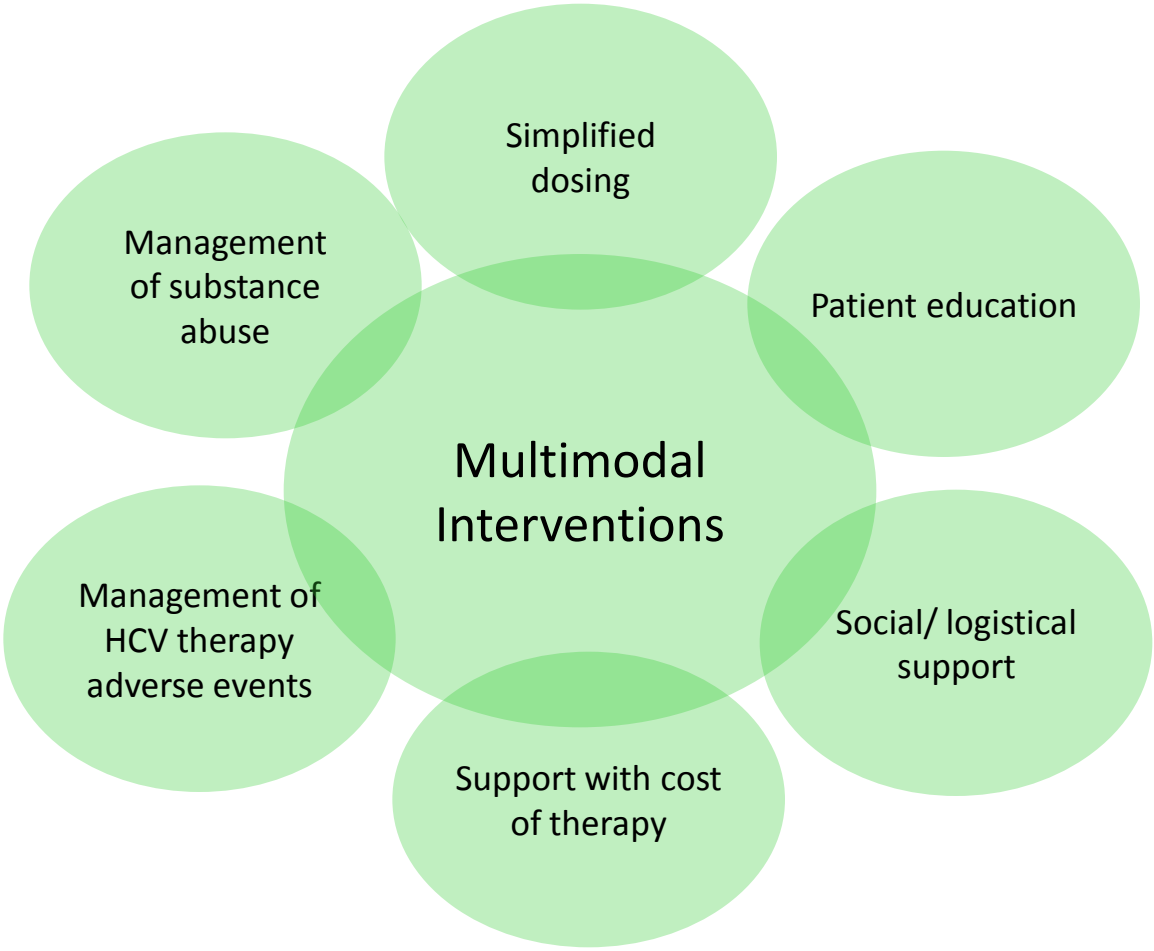
- How should histology be staged for PI therapy?
- When should patients be rebiopsied?
- How can noninvasive approaches be useful?
- What information is needed to have sufficient evidence of previous treatment course?
- How should patients previously treated with standard (not pegylated) IFN be classified?
- What is the approach when the previous response pattern is unclear?

Optimizing Adherence: A Collaborative Care Approach



Yozviak JL, et al. 2011 International Conference on Viral Hepatitis. Abstract 70752.
Gujral H, et al. Cleve Clin J Med. 2004;71(suppl 3):S33-S37.

Optimizing Adherence: A Multimodal Approach



Liu SS, et al. J Clin Gastroenterol. 2010;44:e178-e185. Cacoub P, et al. World J Gastroenterol. 2008;14:6195-6203. Ghany MG, et al. Hepatology. 2009;49:1335-1374. Gujral H, et al. Cleve Clin J Med. 2004;71:S33-S37. Alam I, et al. Aliment Pharmacol Ther. 2010;32:535-542.

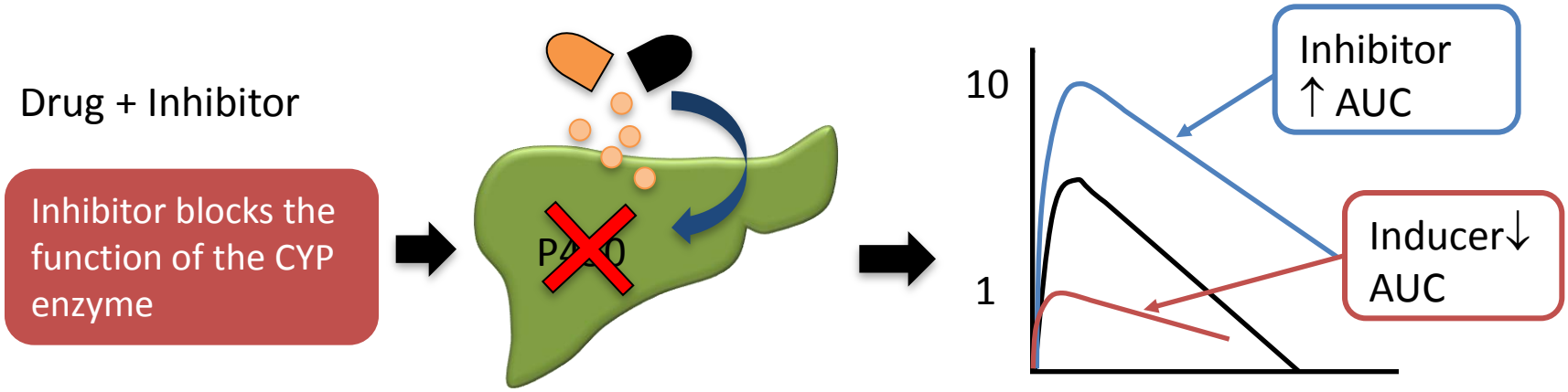
Patient Education Is the Foundation of HCV Management

- HCV transmission
  - Review CDC recommendations including sexual transmission
- Avoid pregnancy during and for 6 mos after RBV-based therapy
- Liver healthy lifestyle
  - Achieve and/or maintain a normal BMI
  - Avoid alcohol
  - Coffee? Milk thistle?
- HCV natural history
- Drug–drug interactions with HCV PIs
  - Careful medication history

Considerar interacciones

Preparation for Treatment: Evaluation of Drug–Drug Interactions

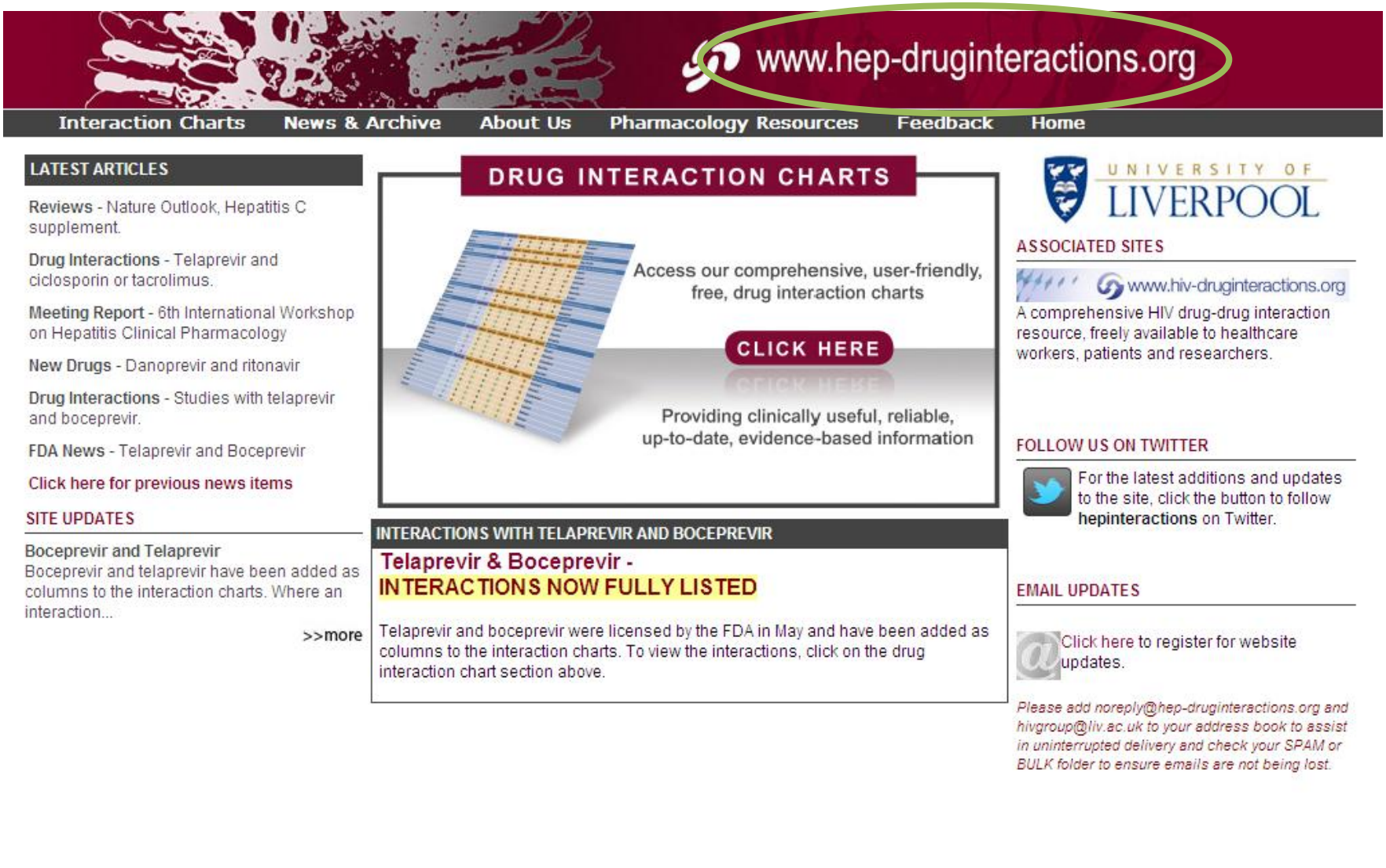
- Boceprevir and telaprevir are CYP3A4 inhibitors
- Drug interactions may affect blood levels of either HCV PI or a coadministered drug



- Caution is needed with ALL coadministered medications
  - Review FDA-approved label information for interaction lists
  - Reconcile patient medication list
  - Patient needs to communicate new medications started by other healthcare providers

Back D. 2011 International Workshop on HIV & Hepatitis Coinfection. Lecture.

Helpful Drug–Drug Interaction Resource



Key Drug–Drug Interactions: Antidepressants

Drug(s) With Interaction	PI Involved	Effect on Concentration of PI or Concomitant Drug
St John's wort	BOC or TVR	**CONTRAINDICATED:** ▪ May lead to loss of virologic response (↓ concentrations of PIs)
Trazodone	BOC or TVR	**↑ trazodone:** ▪ Dizziness, hypotension, and syncope ▪ **Use with caution; consider lower doses of trazodone**
Escitalopram	BOC or TVR	**↔ telaprevir, ↓ escitalopram:** ▪ **Closely monitor; dose of escitalopram may need to be adjusted**

Boceprevir [package insert]. July 2012. Telaprevir [package insert]. October 2012.

Key Drug–Drug Interactions: Statins

Drug(s) With Interaction	PI Involved	Effect on Concentration of PI or Concomitant Drug
Atorvastatin	BOC	↑ **atorvastatin:** ▪ **Use lowest effective dose;** max dose of 40 mg/day
Atorvastatin	TVR	↑ **atorvastatin:** ▪ **Avoid coadministration**
Lovastatin, simvastatin	BOC or TVR	**CONTRAINDICATED:** ▪ Potential for myopathy including rhabdomyolysis
Pravastatin	BOC	↑ **pravastatin:** ▪ May coadminister but **close monitoring required**
Rosuvastatin	BOC or TVR	No known concerns

Boceprevir [package insert]. July 2012. Telaprevir [package insert]. October 2012.

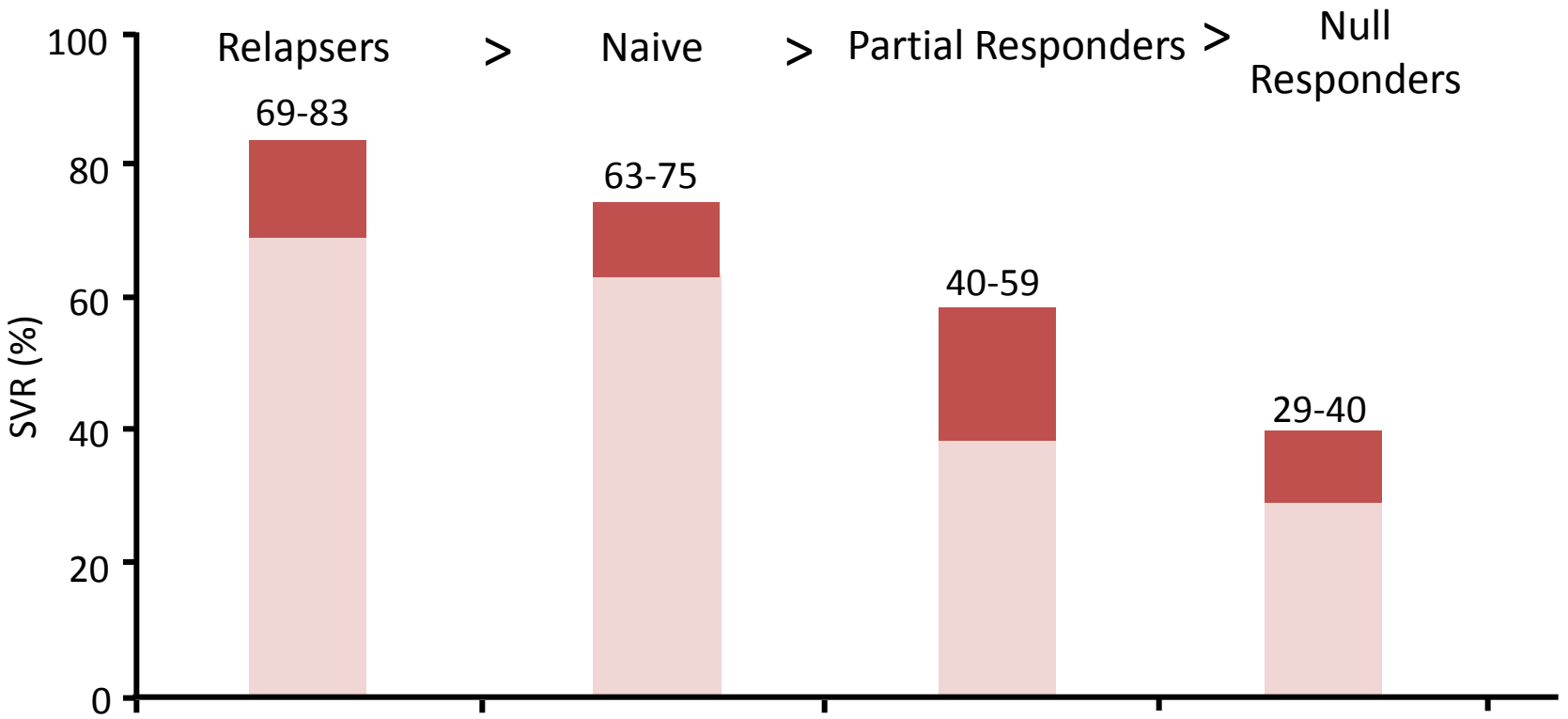
Control de la natalidad y el embarazo durante la terapia triple para el VHC

- La triple terapia con ribavirina está contraindicada en mujeres embarazadas y los hombres cuyas parejas están embarazadas
- Las interacciones medicamentosas con inhibidores de la proteasa del VHC puede disminuir el AUC de anticonceptivos orales, dando lugar a disminución de la eficacia
- Los anticonceptivos hormonales sistémicos no deben ser considerados como un método efectivo de anticoncepción

- **Se deben utilizar 2 métodos alternativos de anticoncepción (métodos de barrera o DIU) durante el tratamiento y durante 6 meses después, las píldoras anticonceptivas no deben suspenderse**

Boceprevir [package insert]. July 2012. Telaprevir [package insert]. October 2012.

SVR Rates With BOC or TVR + PR According to Treatment History



Poordad F, et al. N Engl J Med. 2011;364:1195-1206. Jacobson IM, et al. N Engl J Med. 2011;364: 2405-2416. Bacon BR, et al. N Engl J Med. 2011;364:1207-1217. Zeuzem S, et al. N Engl J Med. 2011;364: 2417-2428. Bronowicki JP, et al. EASL 2012. Abstract 11.

Consejos pretratamiento

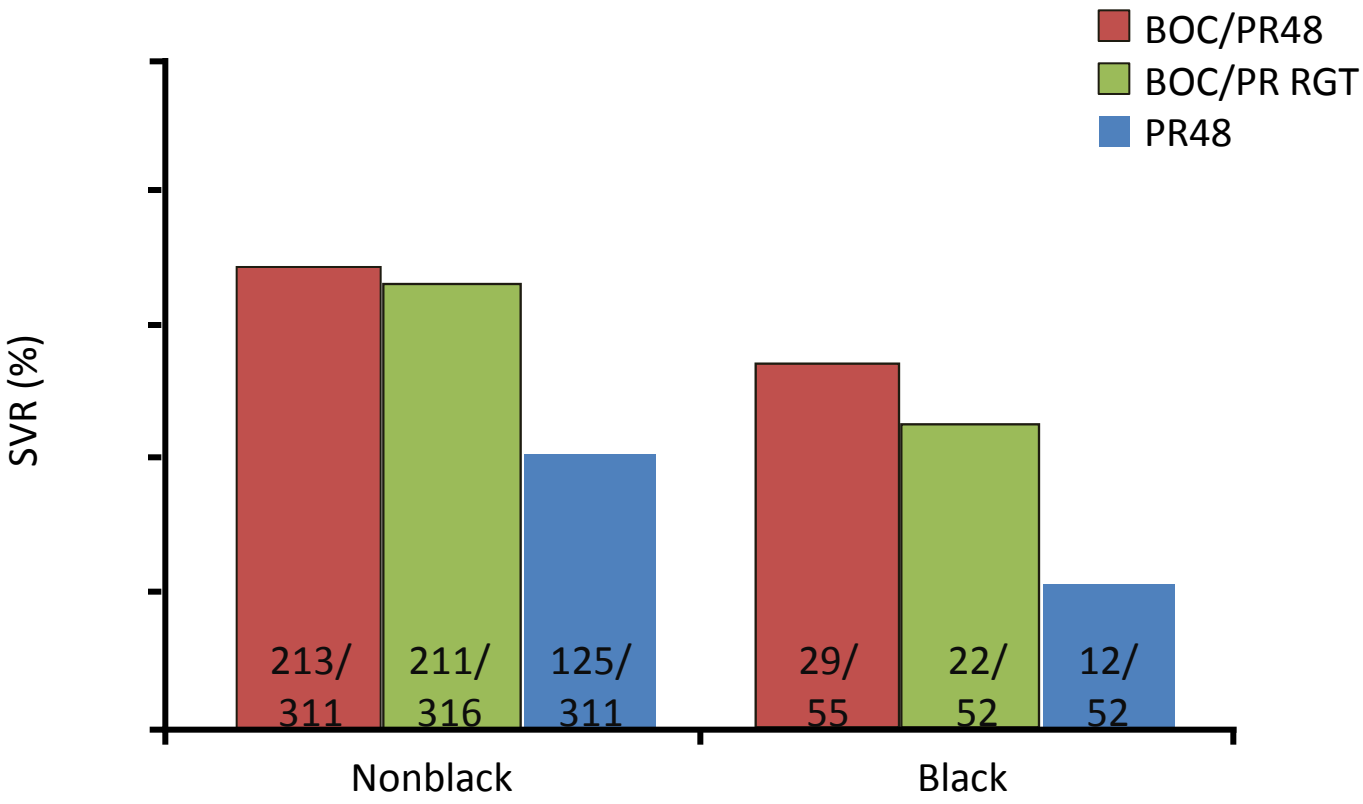
Tasa de RVS por estadio de Fibrosis con Boceprevir or Telaprevir

Fibrosis Stage	SVR Rate (Phase III Trials), %
Treatment-naive patients (TVR and BOC)[1,2]	
Stage 0/1/2	67-78
Stage 3/4	41-62
Treatment-experienced patients	
Stage 0/1/2 (BOC)[3]	66
Stage 3/4 (BOC)[3]	44
Relapser (TVR)[4]	
▪ No/minimal/portal	86
▪ Bridging	85
▪ Cirrhosis	84
Partial responder (TVR)[4]	
▪ No/minimal/portal	72
▪ Bridging	56
▪ Cirrhosis	34
Null responder (TVR)[4]	
▪ No/minimal/portal	41
▪ Bridging	39
▪ Cirrhosis	14

1. Jacobson IM, et al. N Engl J Med. 2011;364:2405-2416. 2. Poordad F, et al. N Engl J Med. 2011;364:1195-1206.
3. Bacon BR, et al. N Engl J Med. 2011;364:1207-1217. 4. Zeuzem S, et al. EASL 2011. Abstract 5.

RVS en relación a la raza

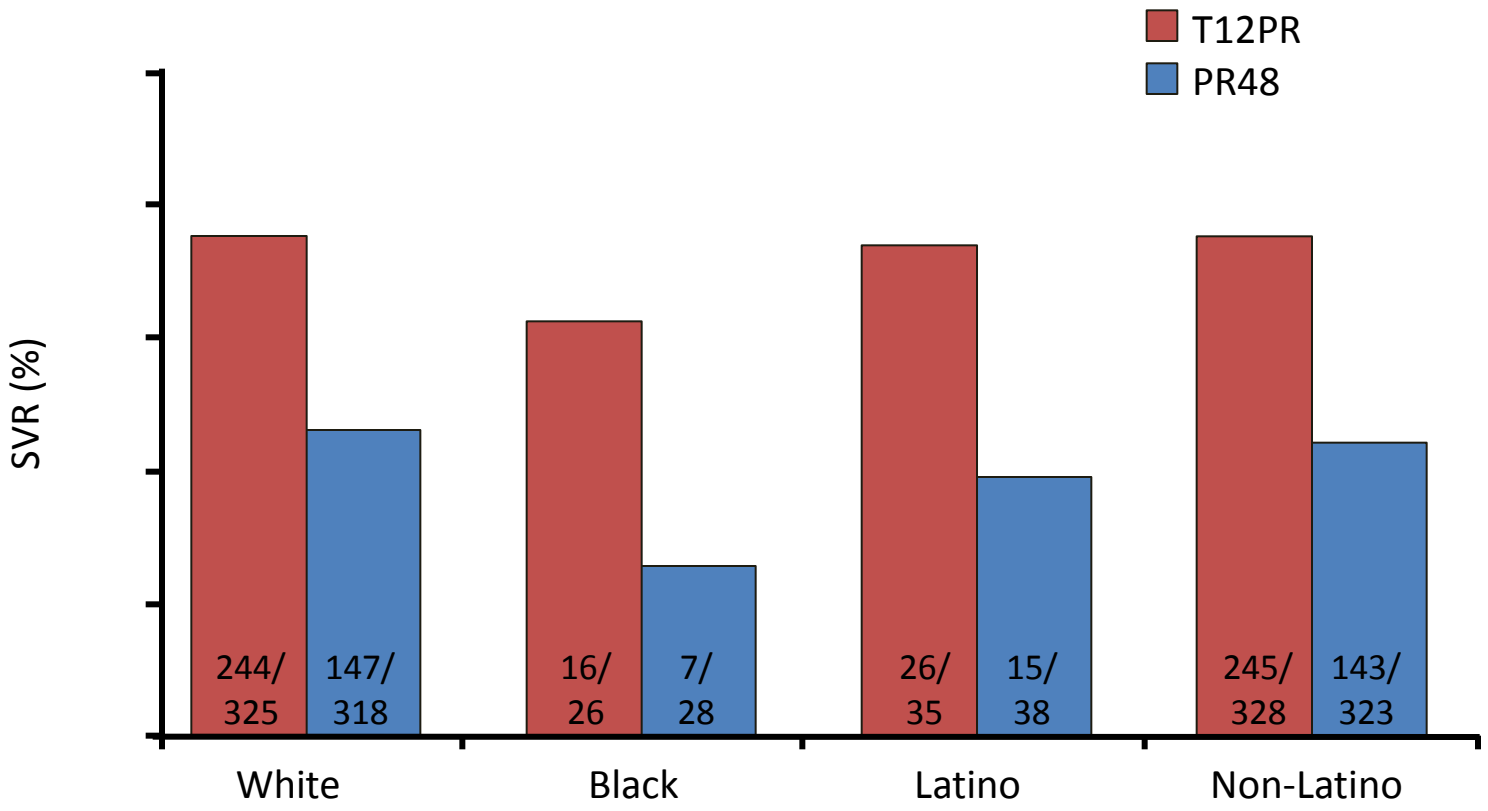
SPRINT-2 (BOC): Naive Patients With Genotype 1 HCV



Poordad F, et al. N Engl J Med. 2011;364:1195-1206.

RVS en relación a la raza

ADVANCE (TVR): Naive Patients With Genotype 1 HCV



Jacobson IM, et al. N Engl J Med. 2011;364:2405-2416.

Importancia del subtipo del VHC en la terapia basada en inhibidor de la proteasa

- En ensayos clínicos en pacientes naive, el genotipo **1a** responde numéricamente menos que el genotipo 1b[1,2]
  - 59% to 71% vs 66% to 79%
- La prevalencia de variante de resistencia asociadas puede explicar las diferencias en la RVA[3]
  - Las tasas de resistencia asociada a variantes son mayores en genotipo 1a

1. Poordad F, et al. N Engl J Med. 2011;364:1195-1206. 2. Jacobson IM, et al. N Engl J Med. 2011;364:2405-2416. 3. Brass CA, et al. EASL 2011. Abstract 1194.

IL28B como predictor de RVS con IP

- *IL28B* permanece como predictor de respuesta a IFN
  - Puede predecir la probabilidad de RVS en pacientes naive
  - Puede predecir la probabilidad de acortar el tratamiento en pacientes naive
    - Los pacientes CC tienen mayor probabilidad de ser candidatos a cursos de tratamiento más cortos
- Es útil en fracasos previos al tratamiento donde la respuesta previa no está bien caracterizada

Jacobson IM, et al. EASL 2011. Abstract 1369. Poordad F, et al. Gastroenterology. 2012;143:608-618.

El uso de predictores para decidir tratar o esperar: cuestiones actuales

Long treatment duration

- At least 24 wks for genotype 1 HCV
- Suboptimal results for non-RVR patients after 48 wks of treatment

Challenging safety profile

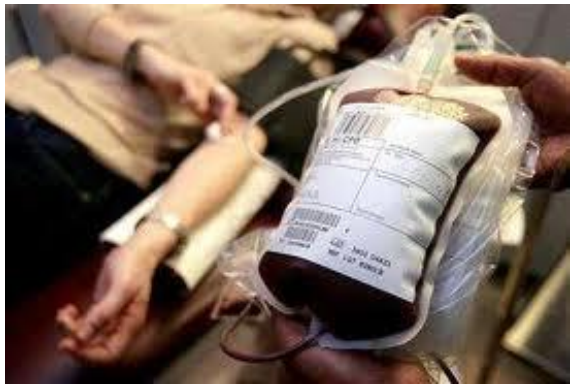
- Several IFN-related adverse effects
- New PIs: anemia, rash, etc

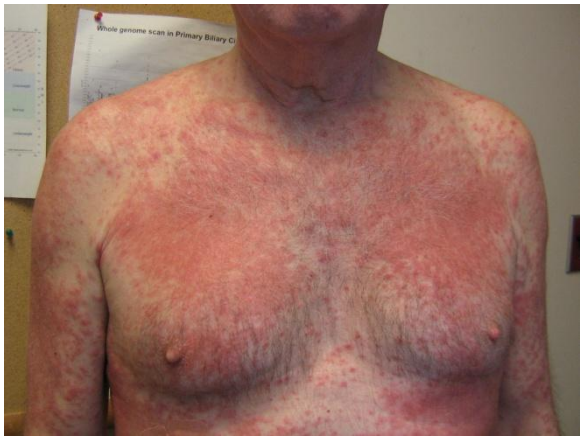
Low efficacy in certain patients

- History of null response
- *IL28B:* TT
- Liver cirrhosis

Efectos adversos

Efectos adversos





Esquema

- Sucesos adversos
  - Ensayos clínicos en fase III vs práctica clínica
- Consejos pretratamiento
- Anemia
- Trombocitopenia
- Rash

Efectos adversos con triple terapia de VHC

- **Treatment-naive, GT1 protease inhibitor phase III trials**
- **IFN adverse events are a dominant feature**

Adverse Event, %	Boceprevir RGT (N = 368)	Placebo (N = 363)	ADVANCE T12PR (N = 363)	Placebo (N = 361)
Fatigue	53	60	57	57
Headache	46	42	41	39
Nausea	48	42	43	31
Diarrhea	22	22	28	22
Pyrexia	33	33	26	24
Chills	36	28	13	15
Insomnia	32	33	32	31

Jacobson IM, et al. N Engl J Med. 2011;364:2405-2416. Poordad F, et al. N Engl J Med. 2011;364:1195-1206.

Efectos adversos graves asociados con el tratamiento con Boceprevir o Telaprevir

Outcome, %	Boceprevir RGT (N = 368)	Placebo (N = 363)	ADVANCE T12PR (N = 363)	Placebo (N = 361)
Serious adverse events	11	9	9	7
▪ Anemia	1.0	0.3	2.0	1.0
Premature discontinuation	12	16	10	7
Death	0.3	1.0	0.6	0.3

Boceprevir: 2 deaths felt related to medications; both suicides due to pegIFN.
Telaprevir: 2 suicide events; 1 T12PR patient died of liver disease after treatment ended.

Jacobson IM, et al. N Engl J Med. 2011;364:2405-2416. Poordad F, et al. N Engl J Med. 2011;364:1195-1206.

Resultados en la práctica clínica: CUPIC Study of the French Early Access Program

- Patients received 1 of the following
  - Boceprevir-based therapy*
  - Telaprevir-based therapy†
- Patients had compensated cirrhosis and were previous nonresponders
- Wk 16 interim analysis
  - 497 patients

*4-wk pegIFN 1.5 µg/kg/wk + RBV 800-1400 mg/day lead-in and then boceprevir 800 mg TID + pegIFN/RBV for 44 wks.

†Telaprevir 750 mg TID + pegIFN 180 µg/wk + RBV 1000-1200 mg/day for 12 wks and then pegIFN/RBV for 36 wks.

Hezode C, et al. AASLD 2012. Abstract 51.

Resultados en la práctica clínica: CUPIC Study of the French Early Access Program

Outcome, %	Telaprevir (N = 292)	Boceprevir (N = 205)
Serious adverse event	45	33
Premature discontinuation	23	26
Hepatic decompensation	2	3
Death*	3	1
Infection (grade 3 or 4)	7	2

*Causes of death: septicemia, septic shock, pneumopathy (2), endocarditis, esophageal varices bleeding.

- Why are the results different from phase III trials?
  - Higher risk in cirrhotic patients?
  - Study population healthier in phase III trials?
  - Is the population truly compensated cirrhosis?

Hezode C, et al. AASLD 2012. Abstract 51.

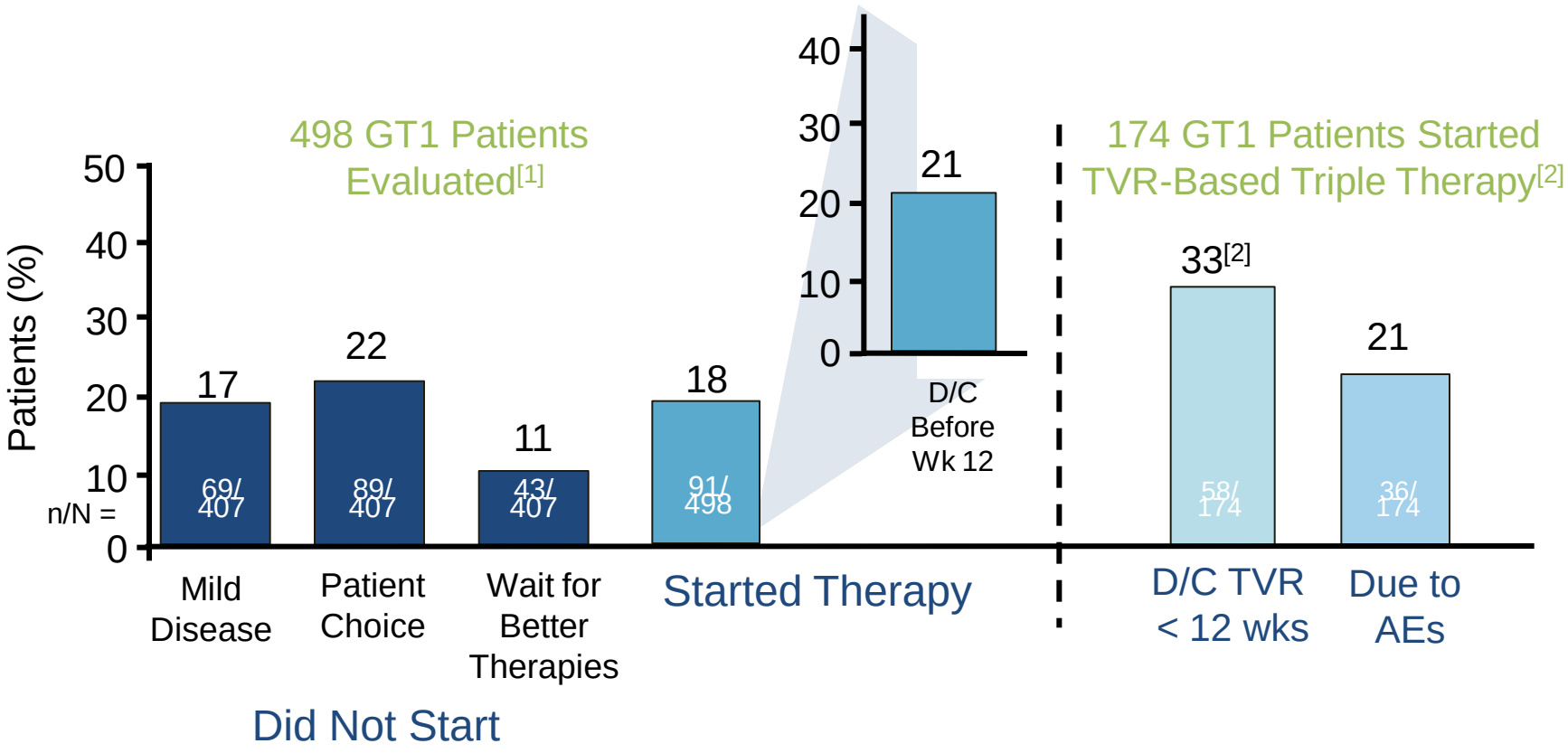
Preliminary Real-World Safety Findings: CUPIC—PIs in Patients With Cirrhosis

Safety Outcome, n (%)	TVR-Based Treatment (n = 292)	BOC-Based Treatment (n = 205)
Serious AEs	**132 (45.2)**	**67 (32.7)**
Premature discontinuation	66 (22.6)	54 (26.3)
▪ From serious AEs	43 (14.7)	15 (7.3)
Death*	**5 (2.6)**	**1 (0.5)**
Infection (grade 3/4)	**19 (6.5)**	**5 (2.4)**
Rash		
▪ Grade 3/SCAR	14 (4.8)	0
Hepatic decompensation	6 (2.0)	6 (2.9)
Blood transfusions	**47 (16.1)**	**13 (6.3)**

*Causes of death in patients treated with TVR: septicemia, septic shock, pneumopathy, esophageal varices bleeding, endocarditis; causes of death in patients treated with BOC: pneumopathy.

Hezode C, et al. EASL 2012. Abstract 8.

Higher Discontinuation Rates in Real-World Settings Than in Clinical Trials



1. Chen EY, et al. AASLD 2012. Abstract 133. 2. Bichoupan K, et al. AASLD 2012. Abstract 1755.

Resultados en la práctica clínica: Estudios retrospectivos en USA

- Data from medical records review and included patients with genotype 1 HCV infection[1,2]

- 2 centers in Dallas and Miami with 12-wk follow-up[1]
- Exclusions: transplantation, dialysis, or HIV coinfected
- Of 498 patients identified
  - 18% began triple therapy
  - 21% discontinued triple therapy before Wk 12

- Mount Sinai Medical Center and Montefiore with 12-wk follow-up[2]
- Of 174 patients who initiated TVR-based triple therapy
  - 33% discontinued TVR prematurely
  - 21% discontinued treatment due to adverse events

1. Chen EY, et al. AASLD 2012. Abstract 133. 2. Bichoupan K, et al. AASLD 2012. Abstract 1755.

Manejo de los pacientes con cirrosis: Consideraciones antes del tratamiento

- Assessment for portal hypertension and HCC[1]
  - Upper endoscopy
  - Imaging
- Transplantation eligibility evaluation for patients
  - Child-Turcotte-Pugh class B/C[2]
  - Features of portal hypertension[2]
  - MELD score to predict early mortality[1]
- Use of lead-in prior to the addition of a protease inhibitor?

1. Bruix J, et al. AASLD practice guidelines: management of hepatocellular carcinoma. July 2010.
2. Ghany M, et al. AASLD practice guidelines: diagnosis, management, and treatment of hepatitis C: an update. April 2009.

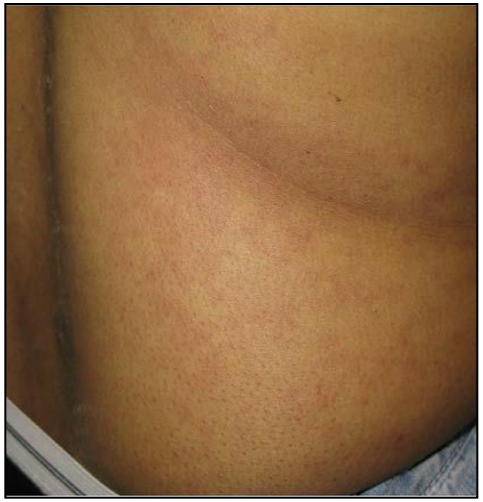
Manejo del rash

Consideraciones pretratamiento respecto al rash asociado a Telaprevir

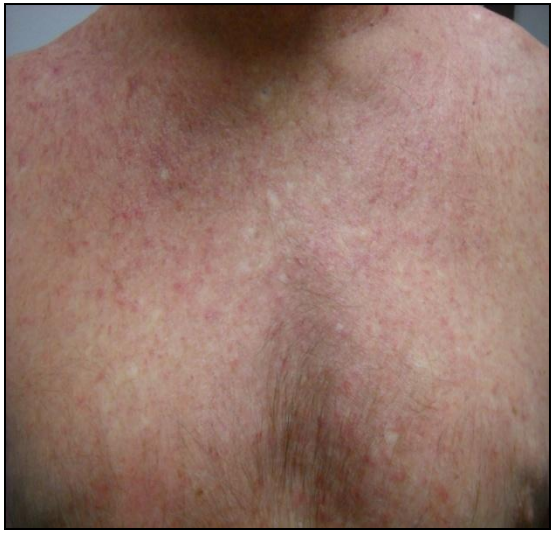
- Alertar al paciente del riesgo de rash (56% de los pacientes en ensayos en fase III)[1]
  - La mayoría de los casos fueros leves o moderados[1]
  - 4% rash grave[1]
  - Puede ocurrir en cualquier momento durante las 12 semanas de telaprevir[1]
- Buena higiene cutánea[2]
  - Cremas emolientes y lociones ricas en lípidos
  - Protectores solares, evitar la exposición prolongada al sol

1. TelaprevirOctober 2012. 2. Cacoub P, et al. J Heptol. 2012;56:455-463.

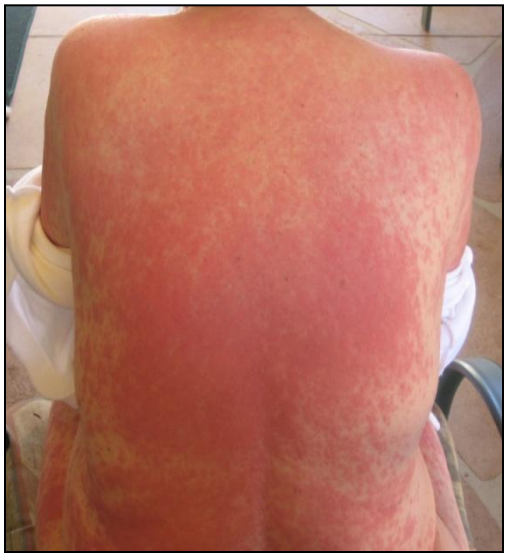
Grading of Telaprevir Rash



Mild (≤ 25% BSA)



Moderate (25% to 50% BSA)



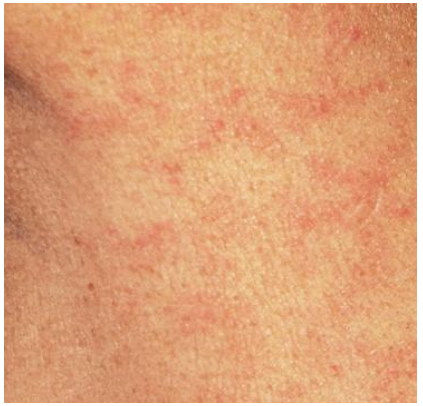
Severe (> 50% BSA)

US Food and Drug Administration. FDA briefing on boceprevir and telaprevir. May 2011.

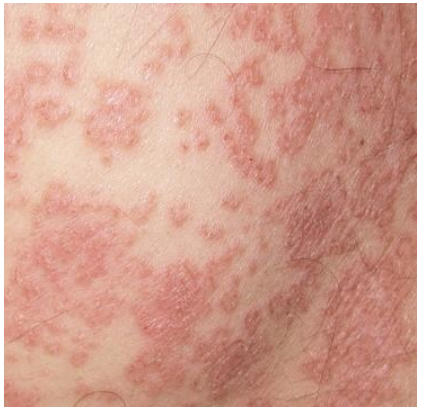
Management Recommendations for Mild or Moderate Rash Due to Telaprevir

- Monitor for systemic symptoms
- Continue all medicines
  - Do not dose reduce or discontinue TVR
- Watch for progression
- Continue good skin hygiene
- Consider topical steroids
  - Systemic steroids not recommended
- Consider oral antihistamines

Mild

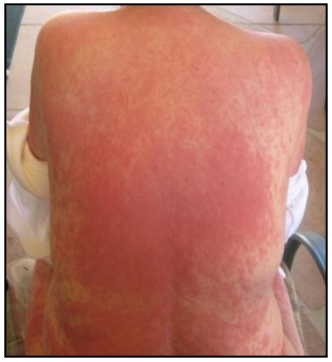


Moderate



Telaprevir [package insert]. October 2012.
Telaprevir: a guide to help you assess and manage rash. Accessed October 17, 2012.

Management Recommendations for Severe Rash Associated With Telaprevir



- Generalized rash involving either > 50% BSA or any of the following
  - Vesicles or bullae
  - Superficial ulceration of mucous membranes
  - Epidermal detachment
  - Atypical or typical target lesions
  - Palpable purpura, nonblanching erythema

- Recommendations
  - Discontinue telaprevir
    - If no better in 7 days (or early if indicated), discontinue RBV and/or pegIFN
    - Do not resume telaprevir
    - Remind patient that SVR is still possible
  - Good skin care practices
  - Oral antihistamines and/or topical corticosteroids
  - Consider referral to dermatologist

Cacoub P, et al. J Hepatol. 2012;56:455-463. Telaprevir [package insert]. October 2012.

Las reacciones cutáneas graves son raras pero posibles con Telaprevir

- En todos los pacientes con rash, monitorizar para
  - Síndrome de Stevens-Johnson
    - Fiebre, lesiones en diana, erosiones mucosas o ulceraciones
    - Eosinofilia en relación a fármacos y síntomas sistémicos (DRESS)
    - Fiebre, edema facial, afectación de órgano (nefritis, hepatitis)
    - La eosinofilia puede no estar presente
- **Suspender inmediatamente todos los fármacos**
- **Enviar de forma urgente para valoración.**

Telaprevir [package insert]. October 2012. Cacoub P, et al. J Hepatol. 2012;56:455-463.

Resumen

- Seleccionar bien a los pacientes.
- Considerar la posibilidad de respuesta
- Inteacciones y reacciones adversas muy frecuentes.
- Sopesar riesgos beneficios.
- La práctica clínica difiere de los ensayos clínicos.
- El objetivo es curar pero no siempre es posible…