



Patient With HCV: Managing Side Effects of Antiviral Therapy

Educational Objectives

- ◆ Describe strategies for treatment of chronic HCV infection
- ◆ Discuss HCV treatment strategies for patients with hyperglycemia
- ◆ Discuss the diagnosis and management of interferon–induced thyroidosis

Patient D.S.

- ◆ 43-year-old Hispanic woman is referred to you by her primary care physician who found elevated liver enzymes on routine follow-up for statin use
- ◆ Previous medical history: hiatal hernia; GERD; obesity; dyslipidemia; intermittent hyperglycemia
- ◆ Medications: esomeprazole; atorvastatin
- ◆ Family history: noncontributory
- ◆ Social history: social ETOH (3 to 4 drinks per month), occasional smoker
- ◆ No known drug allergies

Patient D.S. (cont)

- ◆ LABS: HCV Ab+; genotype 1a; HCV RNA 624,000 IU/mL; AFP 12; ALT 82; AST 114; TP 7.4; Alb 4.0; AP 96; ferritin 180; ANA–; Hgb 13.3; HCT 42; WBC 7; Plt 210
 - TFTs and metabolic panel are normal with the exception of nonfasting serum glucose of 130 mg/dL (normal range=126–140 mg/dL)
 - HIV and Hep B serologies are negative
 - Ultrasound of the abdomen → mild hepatomegaly; no ascites and no hepatoma

Patient D.S. (cont)

- ◆ PE: BP 110/70; P 64; RR 14; temp 97°F; weight 175 lbs; height 5'3"; BMI 31.0
 - Otherwise unremarkable

Question 1

What would you do first?

- A. Liver biopsy
- B. Evaluate history of hyperglycemia
- C. A and B
- D. None of the above

Answer to Question 1

Answer—C

- ◆ Schedule liver biopsy
- ◆ Order fasting glucose, fasting insulin, and HbA_{1c}

Liver Biopsy

- ◆ Liver biopsy is recommended when results will influence whether treatment is recommended
- ◆ After weighing the risks and benefits of treatment, most clinicians obtain a liver biopsy in patients with HCV genotype 1
- ◆ Patients with HCV genotypes 2 and 3 have a high likelihood of response and in many cases can be treated without a liver biopsy

Patient D.S. (cont)

- ◆ Liver biopsy obtained (Metavir)
 - Grade 2 (scale 0–4) inflammation
 - Stage 2-3 (scale 0–4) fibrosis and portal–portal septae
 - Moderate steatosis
- ◆ Metabolic
 - Fasting glucose=100 mg/dL (70–115 mg/dL)
 - Fasting insulin=26 μ U/mL (5–25 μ U/mL)
 - HbA_{1c}=6.8% (5.2%–7.5%)
 - HOMA: 3.4 (normal <2)

Question 2

What would you do next?

- A. Recommend a regimen of exercise and weight loss
- B. Consider starting metformin
- C. Start treatment of hepatitis C
- D. All of the above

Answer to Question 2

Answer—D

- A. Begin therapy for hepatitis C
- B. Initiate behavioral and pharmacologic interventions to address insulin resistance

Predictors of Response



Viral Factors

- Genotype
- Viral load

Social Factors

- Adherence
- Mental health
- Substance use



Host Factors

- Age
- Sex
- Ethnicity/race
- Cirrhosis
- Coinfection
- Fe overload
- Insulin resistance
- Steatosis
- Weight

HCV Therapy: Current Recommendations

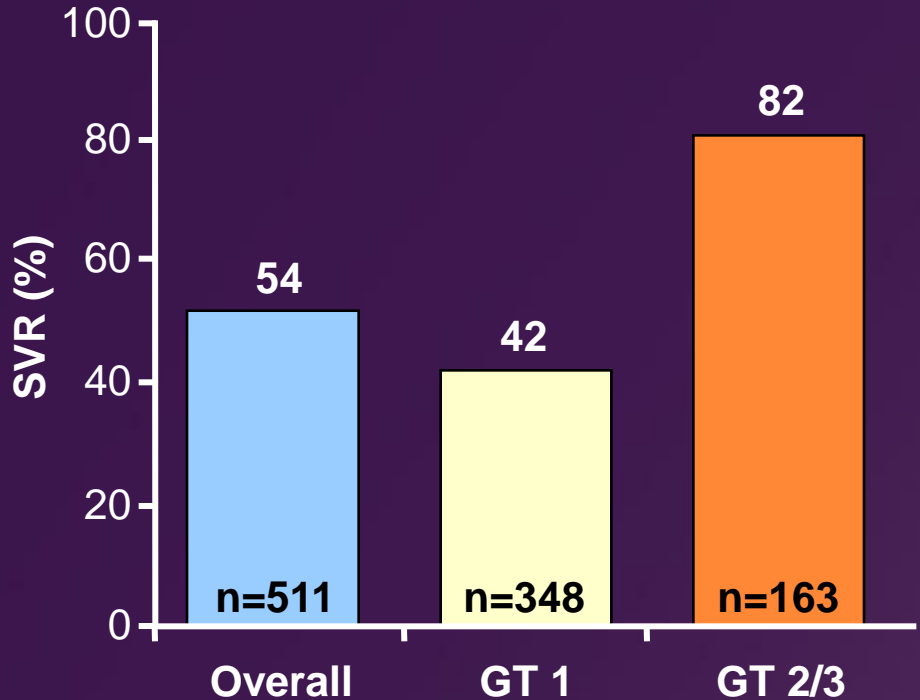
Genotype	Agent	RBV Dose* (mg/day)	Duration
1	Peg-IFN	800–1400	48 weeks
4	Peg-IFN	800–1400	48 weeks
2	Peg-IFN	800–1400	24 weeks
3	Peg-IFN	800–1400	24 weeks

* Product labeling combination dosage recommendations

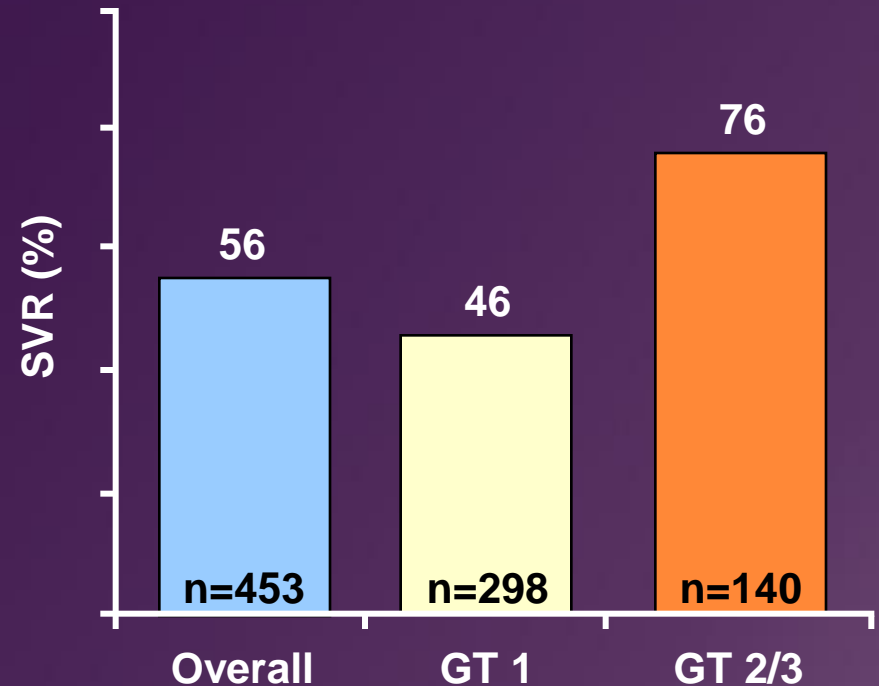
- Peg-IFN alfa-2a plus RBV 800 mg (GT2/3) and 1000–1200 mg for GT1/4) based on weight
- Peg-IFN alfa-2b plus RBV 800–1400 mg for all GT
- ◆ Some clinicians are dosing RBV at 13–15 mcg/kg/day regardless of genotype

SVR by Genotype

Peg-IFN alfa-2b 1.5 µg/kg/week
+ RBV 800 mg/day for 48 weeks¹

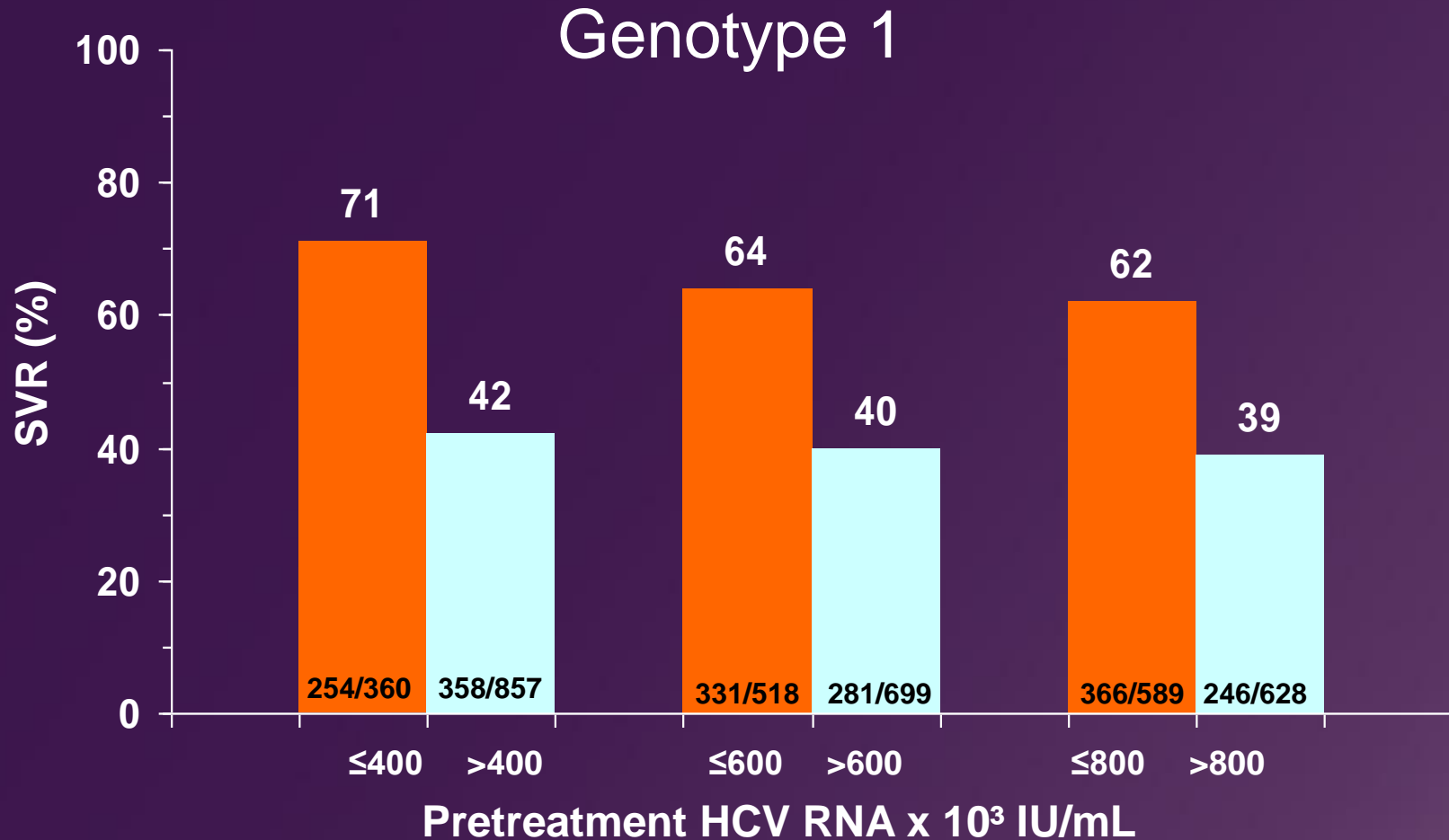


Peg-IFN alfa-2a 180 µg/week
+ weight-based RBV (1000 or
1200 mg/day) for 48 weeks²

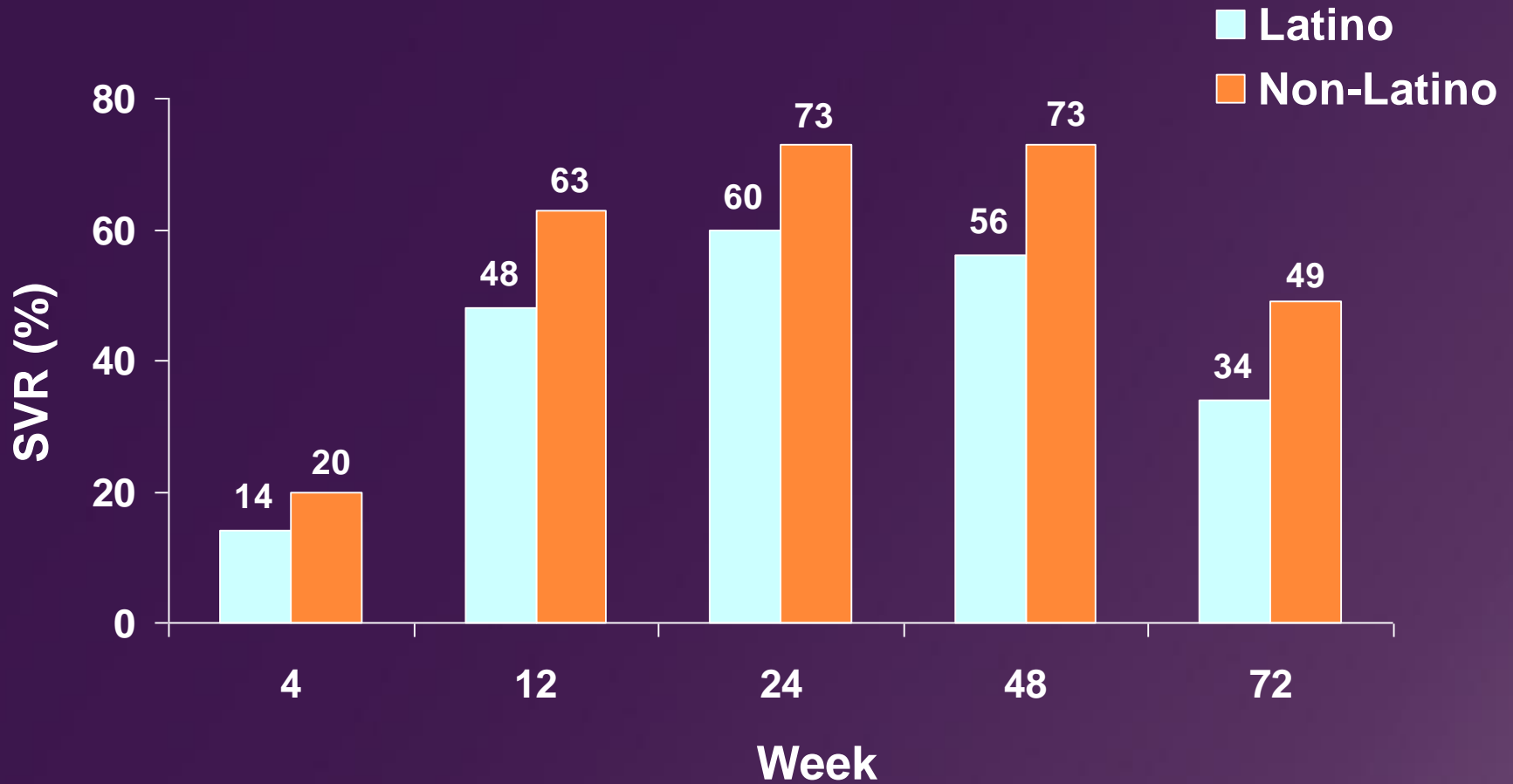


1. Manns M et al. *Lancet*. 2001;358:958-965.
2. Fried MW et al. *N Engl J Med*. 2002;347:975-982.

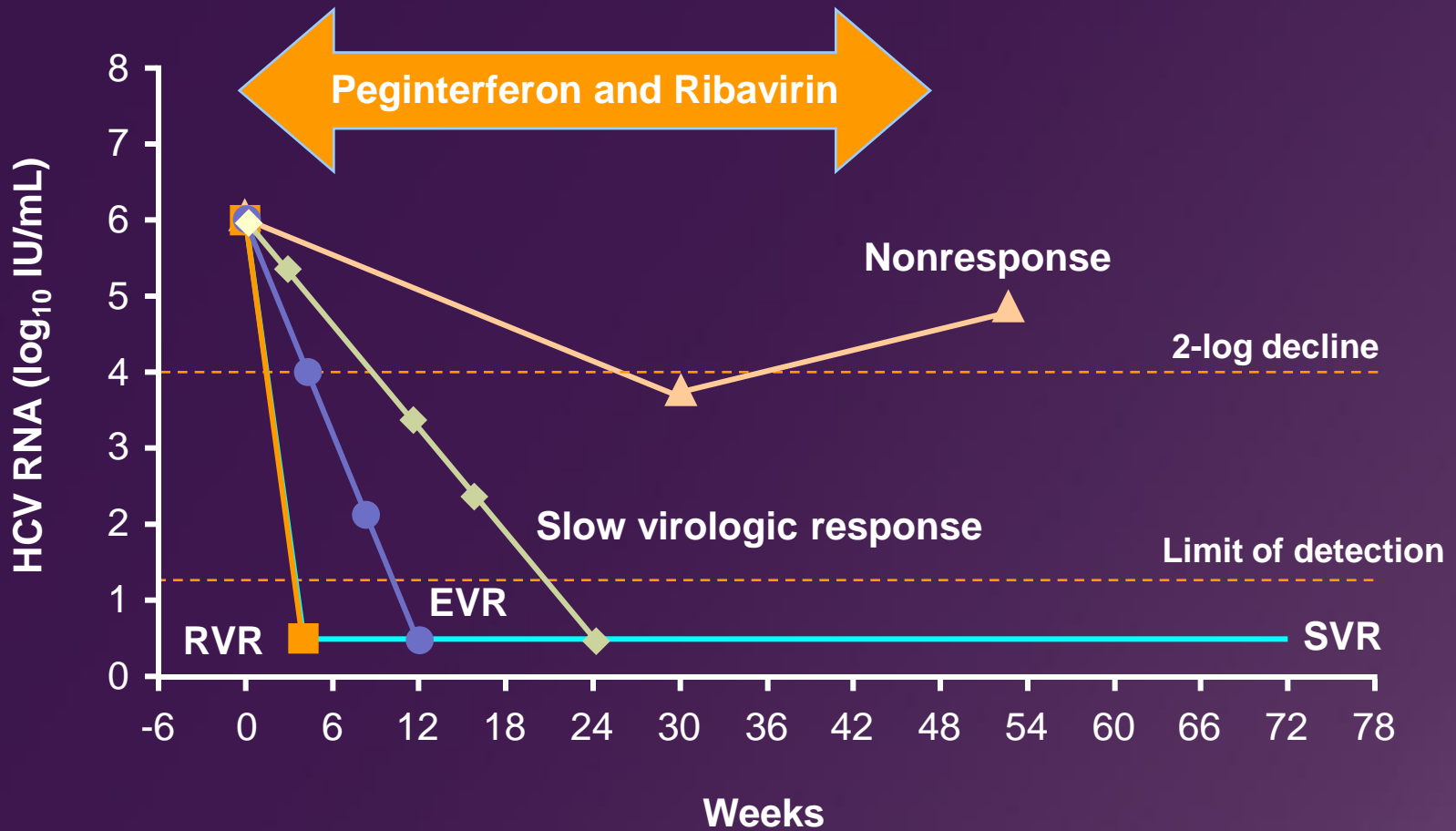
SVR by Viral Load



LATINO Study



Virologic Response



Virologic Response

Response	Definition
Rapid Virologic Response (RVR)	HCV RNA-negative at 4 weeks as defined by HCV RNA <50 IU/mL
Early Virologic Response (EVR)	HCV RNA-negative or $>2\text{-log}_{10}$ drop at week 12
Complete EVR (cEVR)	No RVR but HCV RNA-negative (<50 IU/mL) at week 12
Partial EVR (pEVR)	No RVR and detectable but $\geq 2\text{-log}_{10}$ drop in HCV RNA at week 12
Slow Responder	$\geq 2\text{-log}_{10}$ drop in HCV-RNA at week 12 but not HCV RNA-negative until week 24
Partial Responder	$>2\text{-log}_{10}$ drop in HCV-RNA at week 12 but HCV RNA-positive at week 24
Sustained Virologic Response (SVR)	HCV RNA-negative 24 weeks after end of treatment
Relapse	HCV RNA-negative at end of treatment but HCV RNA-positive after treatment stopped

Patient D.S. (cont)

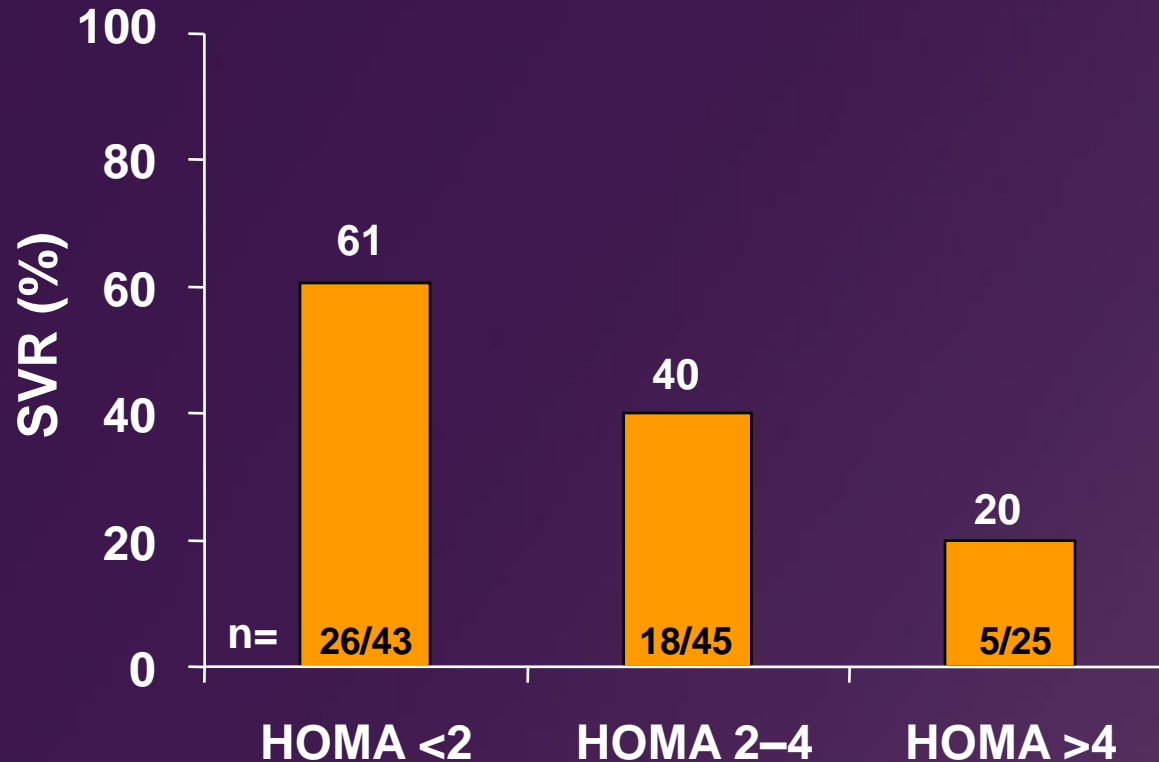
- ◆ Patient is counseled on diet and exercise
- ◆ She begins metformin 500 mg twice daily
- ◆ Two months later, she has lost 5 lbs
- ◆ She is started on Peg-IFN alfa-2a 180 µg/week and RBV 1200 mg/day

Insulin Resistance and HCV

- ◆ Insulin resistance, diabetes, and steatosis are associated with decreased SVR¹
- ◆ Insulin resistance and diabetes are associated with increased risk of advanced fibrosis²
- ◆ Thiazolidinediones or metformin may improve glucose tolerance and steatosis in patients with HCV^{3,4}

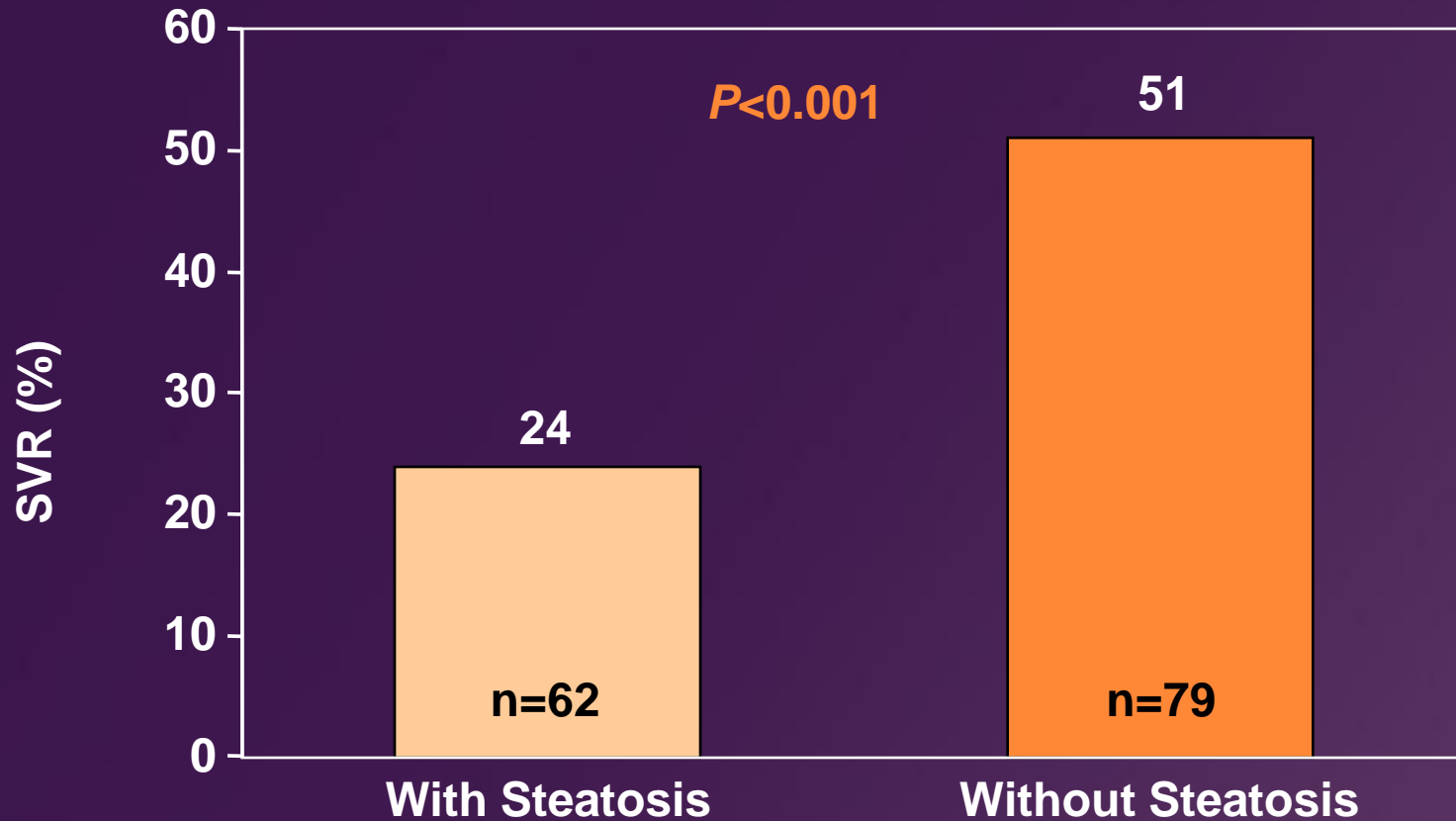
1. Poynard T et al. *Hepatology*. 2003;38:75-85.
2. Petta S et al. *Am J Gastroenterol*. 2008;103:1136-1144.
3. Belfort R et al. *N Eng J Med*. 2006;355:2297-2307.
4. Harrison SA. *J Clin Gastroenterol*. 2006;40:68-76.

Insulin Resistance and Virologic Response in Patients With Genotype 1



159 consecutive patients treated with Peg-IFN alfa-2a plus RBV or Peg-IFN alfa-2b plus RBV

Impact of Steatosis on SVR



Genotypes 1, 4, 5, and 6; high viral load

Patient D.S. (cont)

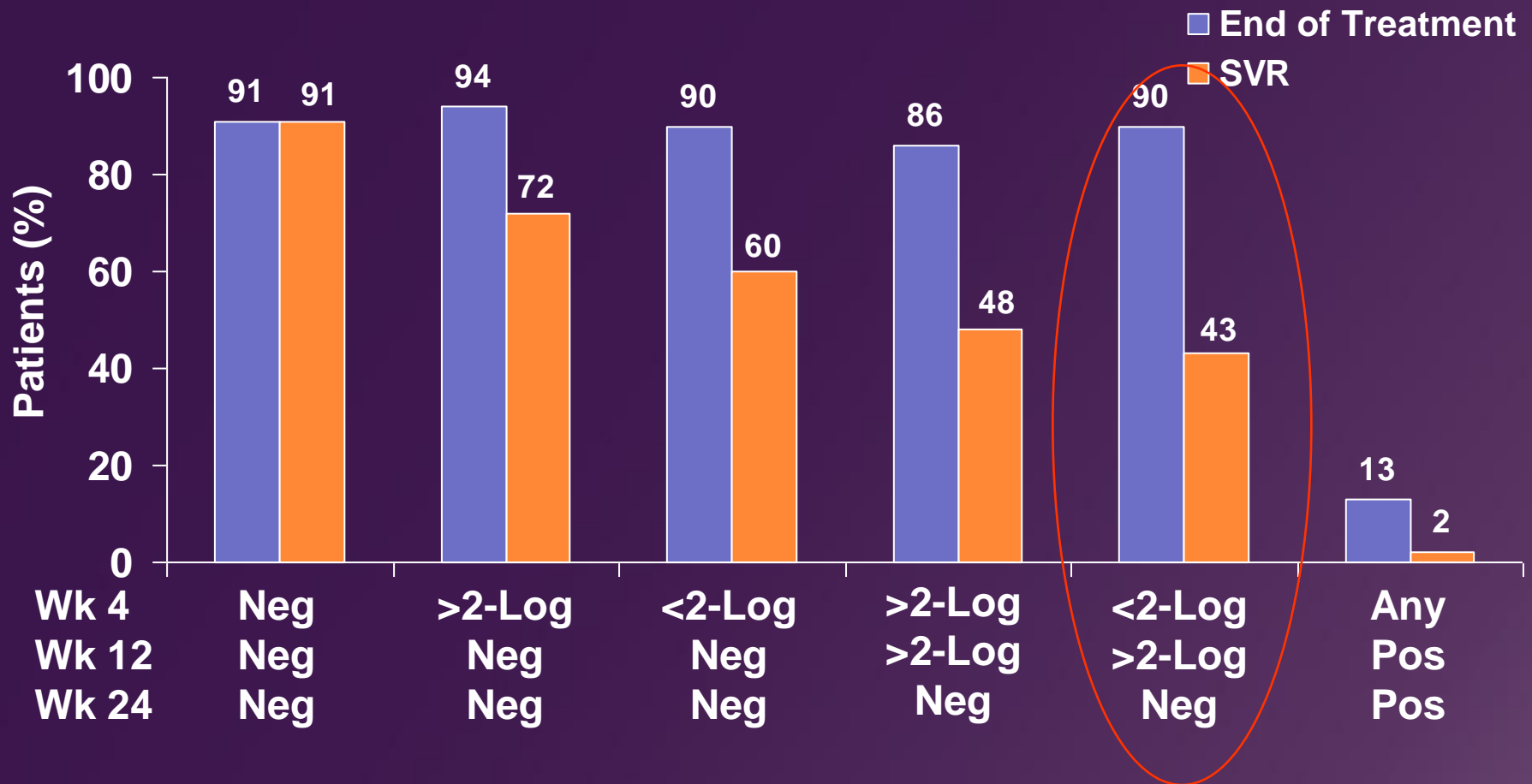
◆ Week 24

- Baseline: HCV RNA: 624,000 IU/mL (5.8 log₁₀)
- Week 4: HCV RNA: 40,000 IU/mL (4.6 log₁₀)
- Week 12: 2000 IU/mL (3.3 log₁₀)
- Week 24: HCV RNA undetectable

◆ Partial early virologic response

- No RVR
- >2-log₁₀ drop at week 12

Viral Kinetics and Outcome: Importance of Rapid Virologic Response



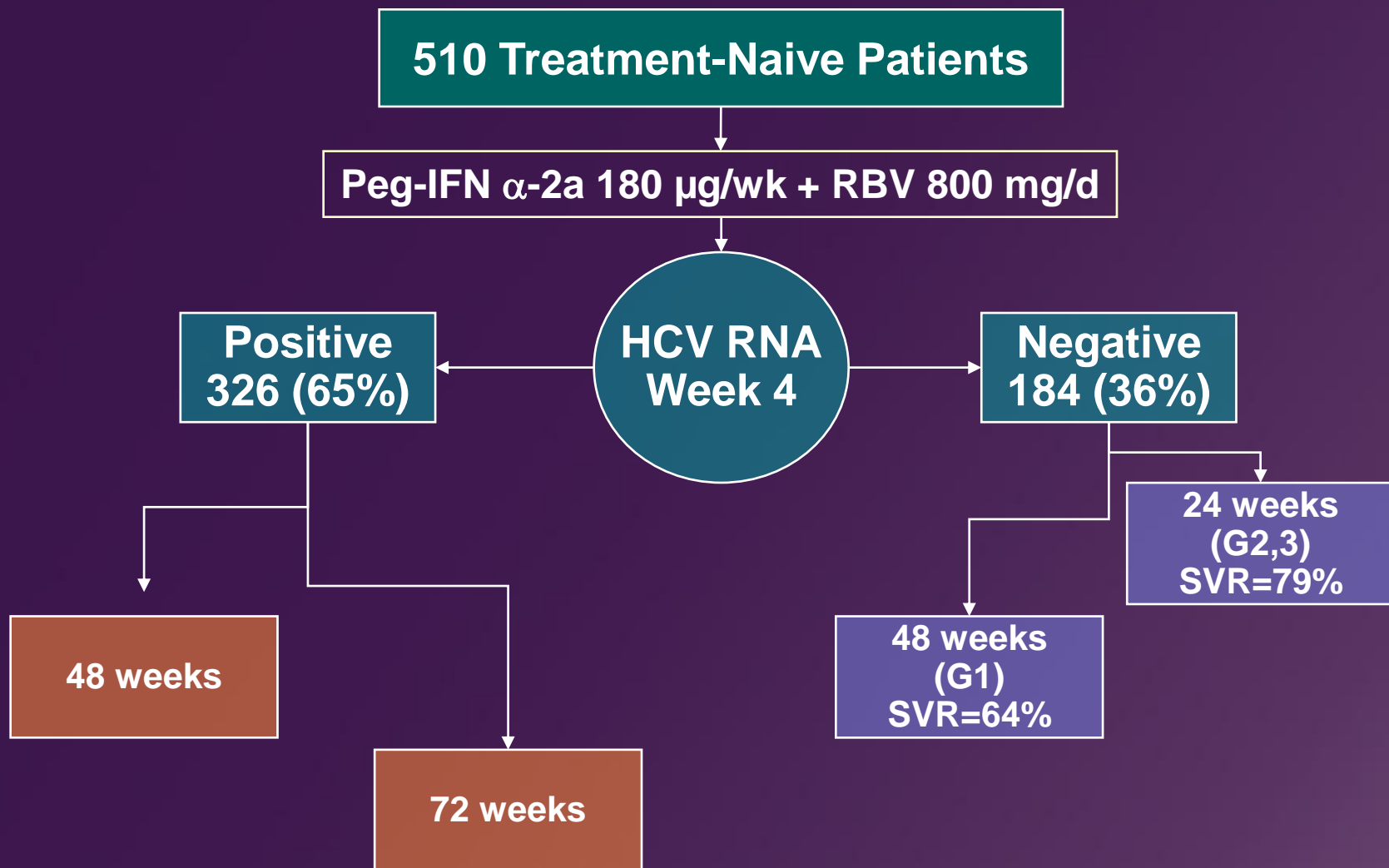
Virologic response (VR)=neg or >2-log decrease; VR at 4 weeks=rapid (RVR); VR at 12 weeks=early (EVR).

SVR With 72 Weeks of Treatment in Patients With G1 Who Are Slow Responders

- ◆ Peg-IFN alfa-2b 1.5 µg/kg/wk + RBV 800–1400 mg/day
- ◆ HCV RNA-positive at wk 12 but HCV RNA-negative at wk 24 (n=101 slow responders)
- ◆ Continued treatment through wks 48 vs 72
- ◆ Baseline characteristics
 - 48% black
 - 78% high HCV RNA
 - 26% F3/4 fibrosis

Response (%)	48 Wks	72 Wks	P Value
ETR	45	48	NS
SVR	18	38	0.03
Relapse	59	20	0.004

Extended Duration of Therapy: TeraViC-4



Question 3

What would you recommend for duration of therapy based on the patient's virologic response?

- A. Discontinue antiviral therapy
- B. Continue to 48 weeks
- C. Treat for 72 weeks
- D. None of the above

Answer to Question 3

Answer—C

- ◆ Continue treatment
 - HCV RNA is undetectable at 24 weeks
 - Treatment is continued for 48 additional weeks for a total of 72 weeks
 - Consider extending duration of therapy in genotype 1 patients who are slow responders

Patient D.S. (cont)

- ◆ Week 24
- ◆ Patient reports irritability; weight loss despite appetite; and occasional diplopia
- ◆ Physical exam reveals tachycardia (HR 112) and temperature of 99.2°F
- ◆ Abnormal laboratory result
 - TSH=0.03 μ IU/mL

Question 4

What is the diagnosis?

- A. Generalized anxiety
- B. Hypothyroidism
- C. Graves'-like disease
- D. Subclinical hyperthyroidism
- E. None of the above

Answer to Question 4

Answer—C

- ◆ Decreased TSH and clinical signs and symptoms are consistent with Graves'-like hyperthyroidism, which can sometimes be an adverse effect of treatment with IFN-alfa

Interferon–induced Thyroid Dysfunction: Spectrum of Disease

- ◆ **Thyroid antibodies**
 - Most common is presence of antibodies without clinical disease
 - 5%–10% of patients are positive for TPO-Ab, Tg-Ab, or both; can be de novo or exacerbation of pre-existing condition
- ◆ **Hashimoto's thyroiditis**
 - Thyroid antibodies with clinical hypothyroidism
- ◆ **Graves'-like thyroiditis**
 - Clinical hyperthyroidism and TSHR-Ab
 - Some develop Graves' ophthalmopathy

TPO-Ab=thyroid peroxidase antibody; Tg-Ab=thyroglobulin antibody; TSHR-Ab=TSH receptor antibody

Interferon–induced Thyroid Dysfunction: Diagnosis and Management

Disorder	Diagnosis	Treatment	Antiviral Therapy
Hypothyroidism	↑TSH, ↓FT ₄ , ↓FT ₃ ,	T ₄	◆ Continue
Graves'-like Disease	↓TSH, ↑FT ₄ , ↑FT ₃ , ↑RAIU, TSHRAb+	Antithyroid drugs (mild) Radioiodine (severe)	◆ Continue if mild ◆ Withdraw if severe until function normalizes, then resume
Destructive thyroiditis	↓TSH, ↑FT ₄ , ↑FT ₃ , ↓RAIU,	Beta blockers	◆ Continue if controlled ◆ Withdraw if severe or uncontrolled

FT₃=free T₃; FT₄=free T₄; TSH=thyroid stimulating hormone; RAIU=radioiodine uptake; TSHRAb=TSH receptor antibody

Question 5

What would be your next step(s):

- A. Radioiodine uptake scan
- B. Additional labs: FT3 and FT4; Tg-Ab; TPO-Ab
- C. Refer to endocrinology
- D. Orbital CT or MRI
- E. All of the above
- F. A, B, and C

Answer to Question 5

Answer—F

- ◆ FT₃ and FT₄ will help to confirm the diagnosis of hyperthyroidism and provide a baseline for treatment
- ◆ Radioiodine uptake scan is helpful to confirm the diagnosis and differentiate Graves' disease from destructive thyroiditis
- ◆ Elevations in Tg-Ab and TPO-Ab are consistent with IFN–induced hyperthyroidism and suggest a higher risk of clinical thyroid dysfunction
- ◆ This patient did not have pronounced exophthalmia or orbital edema, so it may not be necessary to perform a scan

Question 6

What would be your next step?

- A. Discontinue antiviral therapy
- B. Reduce the doses of Peg-IFN and ribavirin
- C. Begin methimazole
- D. Begin corticosteroids
- E. A and B
- F. C and D

Answer to Question 6

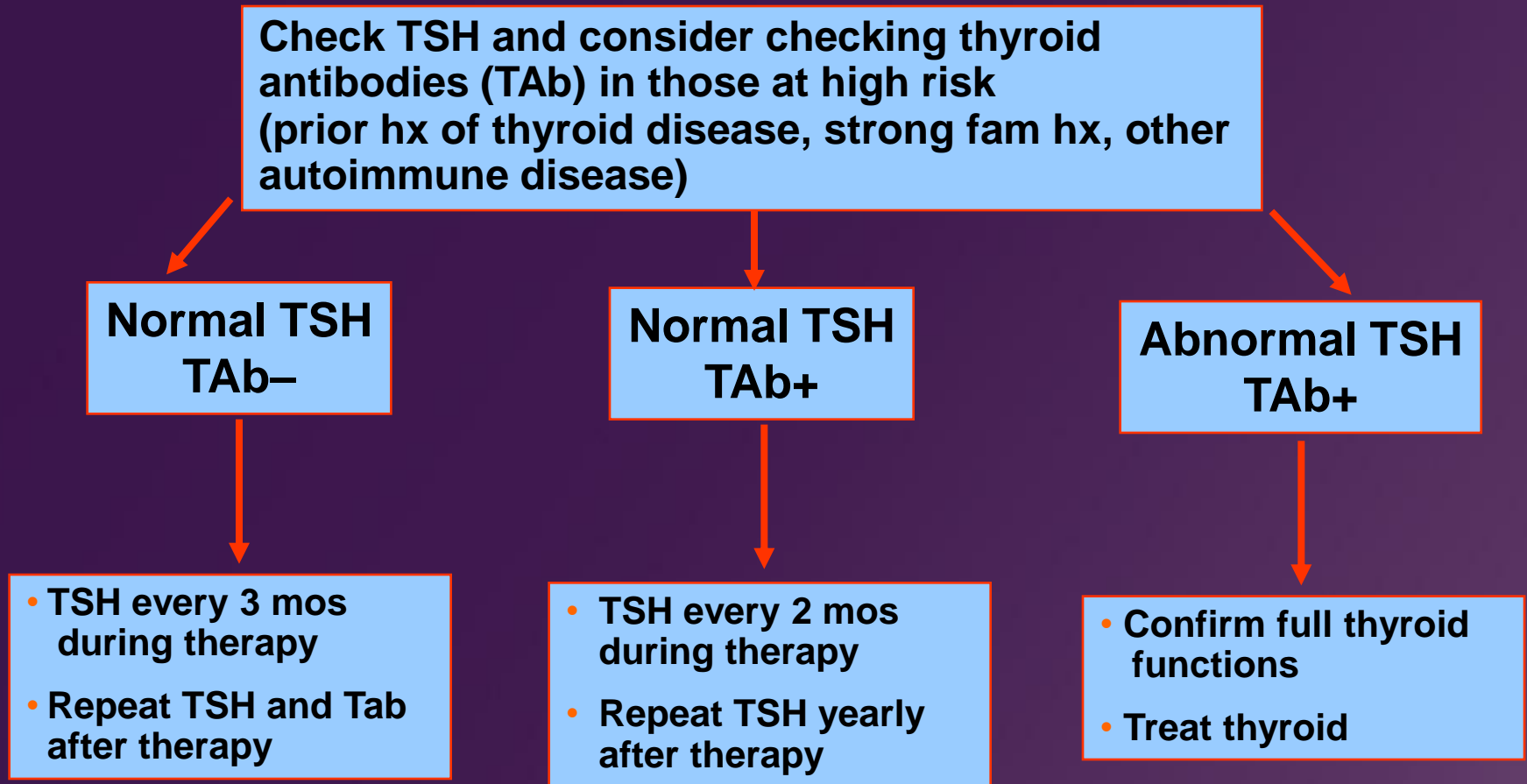
Answer—C

- ◆ Mild-to-moderate IFN–induced thyroiditis is usually limited and responds to antithyroid treatment
- ◆ Corticosteroids, although helpful in subacute thyroiditis, are not generally used in patients with hepatitis C
- ◆ Patients receiving antithyroid therapies may become hypothyroid and require replacement therapy

Therapies for Hyperthyroidism

- ◆ Mild-to-moderate
 - Antithyroid drugs
 - Methimazole 0.4 mg/kg/day
 - Propylthiouracil 300–400 mg every 8 hours
 - Infrequently associated with risk of hepatotoxicity
- ◆ If disease is severe, may consult with endocrinologist to consider withdrawal of Peg-IFN/RBV
 - Generally can be resumed on return to normal thyroid function
 - Rechallenge with Peg-IFN may infrequently result in recurrence of hyperthyroidism, sometimes severe
 - Patients should be monitored

Summary: Initiating HCV Therapy



Summary: Abnormal Thyroid Function

Hyperthyroidism

Test TAbS, thyroid scan

Graves' Disease

Destructive Thyroiditis

- Standard therapy
 - Antithyroid agent (mild)
 - Radioiodine or surgery (severe)
- Consider d/c HCV therapy

- Beta blockers
- Consider d/c HCV therapy

Hypothyroidism

Abnormal TSH
TAb+

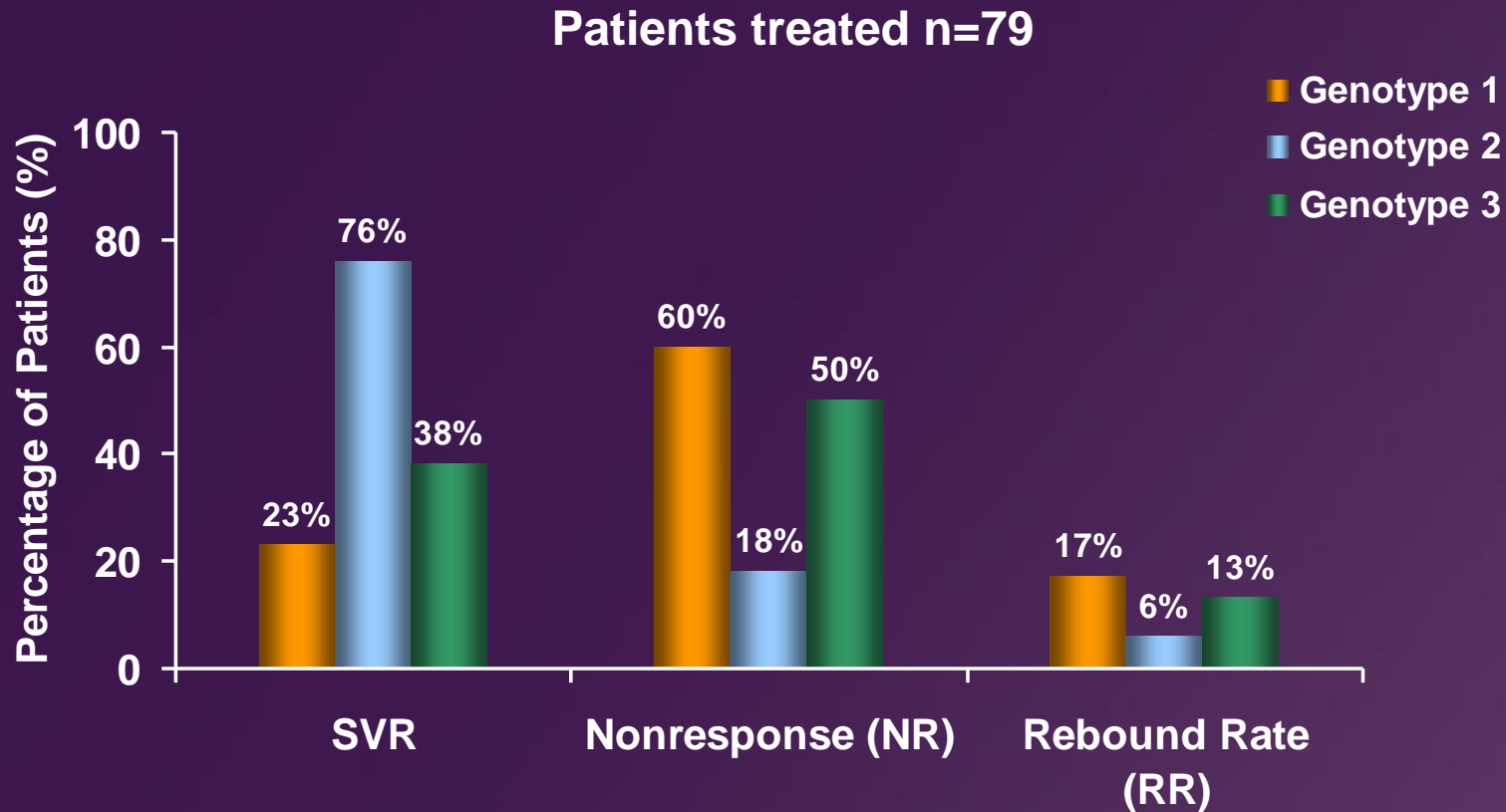
- Thyroid hormone replacement
- Continue HCV therapy
- Monitor thyroid functions every 2 months

Conclusion

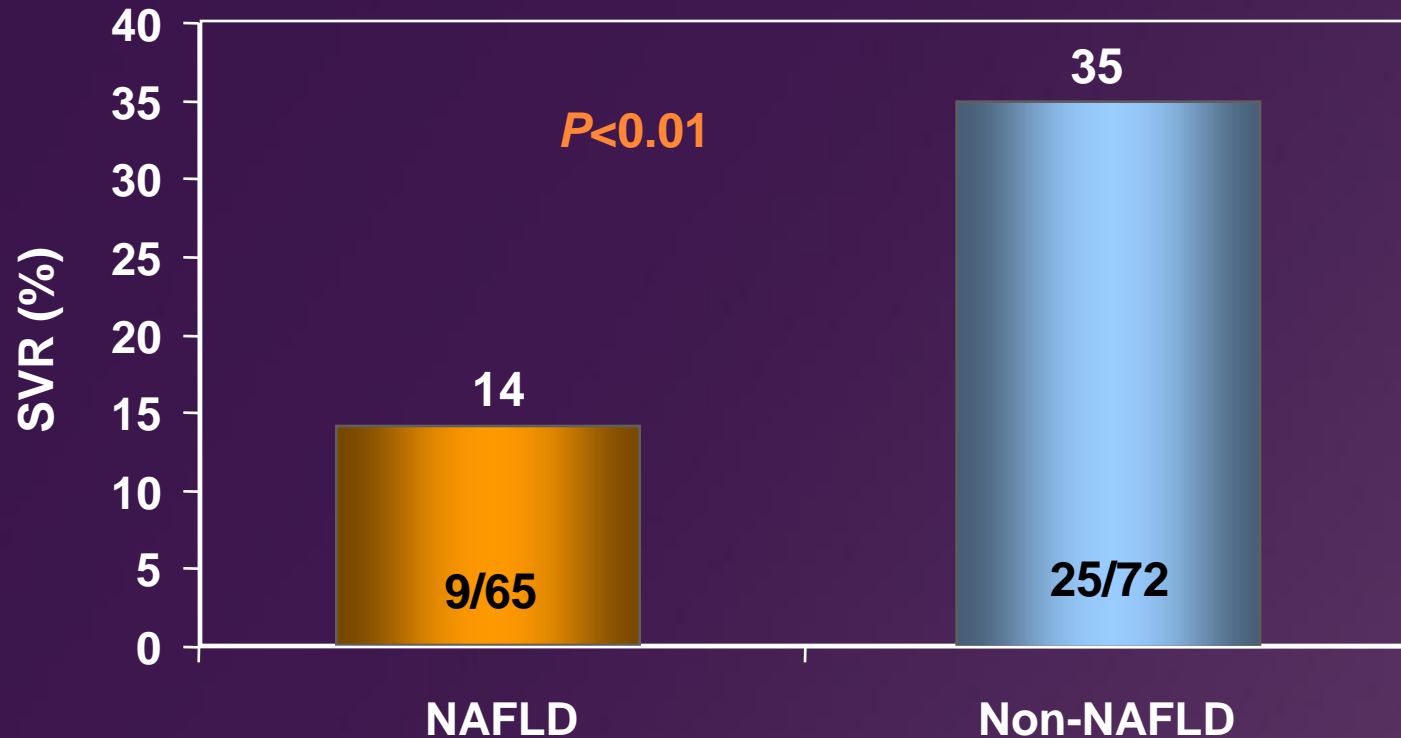
- ◆ Optimizing dosing and adherence throughout the treatment course is important
- ◆ Tailoring duration of therapy to virologic response should be considered for some patients
- ◆ Insulin resistance is associated with less SVR and should be managed in patients with chronic HCV infection
- ◆ Mild-to-moderate thyroid dysfunction is sometimes associated with therapy for HCV, can often be managed, and usually returns to normal after therapy

Additional Slides

Steatosis and Diabetes as a Predictor of Treatment Response in Latino-Americans

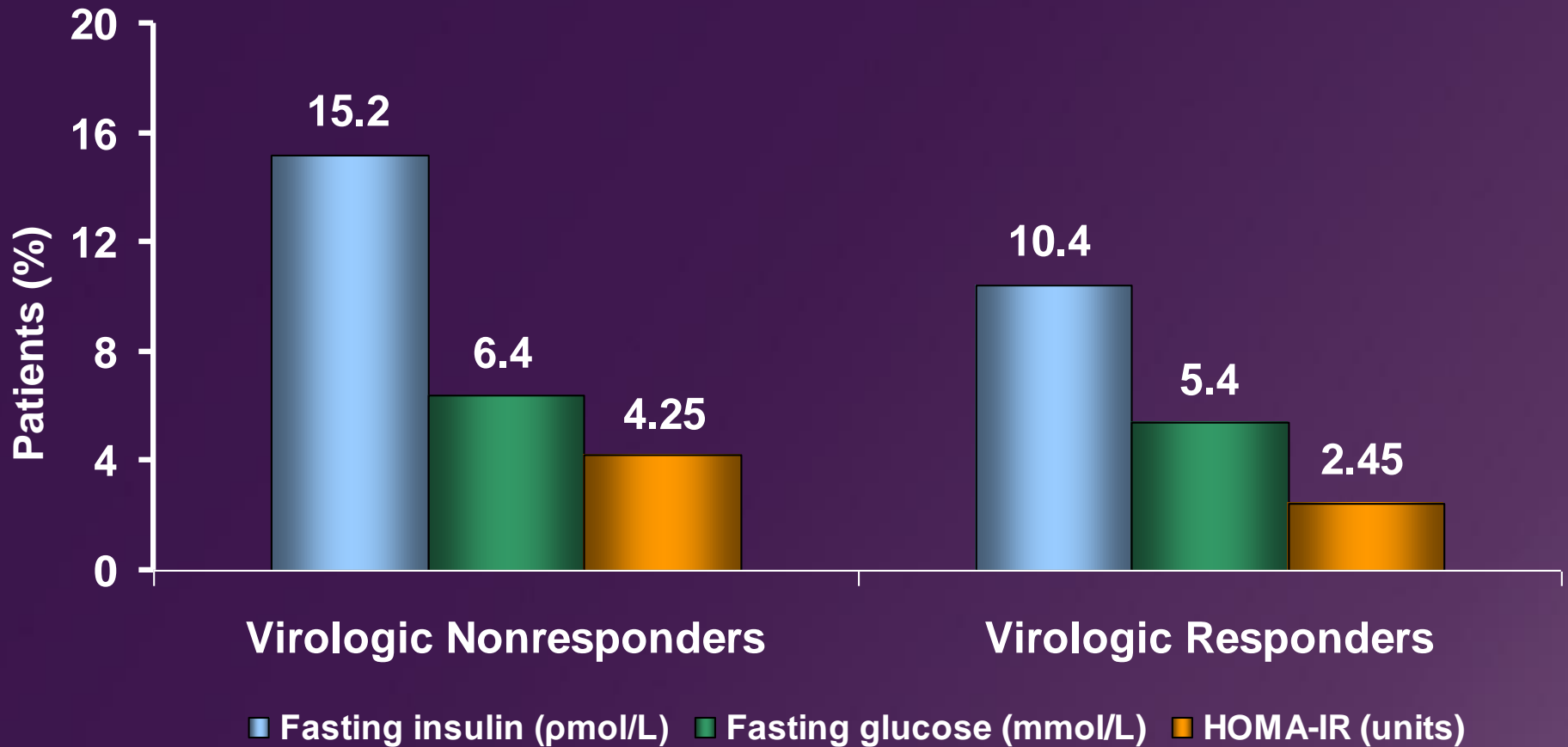


Impact of Coexisting NAFLD on Virologic Response to Anti-HCV Therapy



Metabolic Factors Associated With Virologic Response

Prospective analysis in 52 patients prior to HCV therapy



Decreased Response to Antiviral Therapy in HCV Patients With Coexistent Steatosis

