Overview of HCV and Strategies to Treat HCV Among Patients With Substance Use Disorders

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Program Overview

- **Basic principles of viral hepatitis liver disease and treatment approaches in 2012**
- Epidemiology considerations and significance of liver disease and hepatitis in HIV
- Special consideration for HCV-infected persons with substance use disorders

The Hepatitis C Epidemic

- Worldwide prevalence of chronic HCV: 170 million
- Most patients with HCV are asymptomatic until irreversible liver damage occurs
- Diagnosis depends on high index of suspicion and proper screening
- Screening recommended for:
  - IDUs
  - Blood transfusion
  - Tattoos (high risk settings)
  - Diaylysis patients
  - Birth cohort (US)

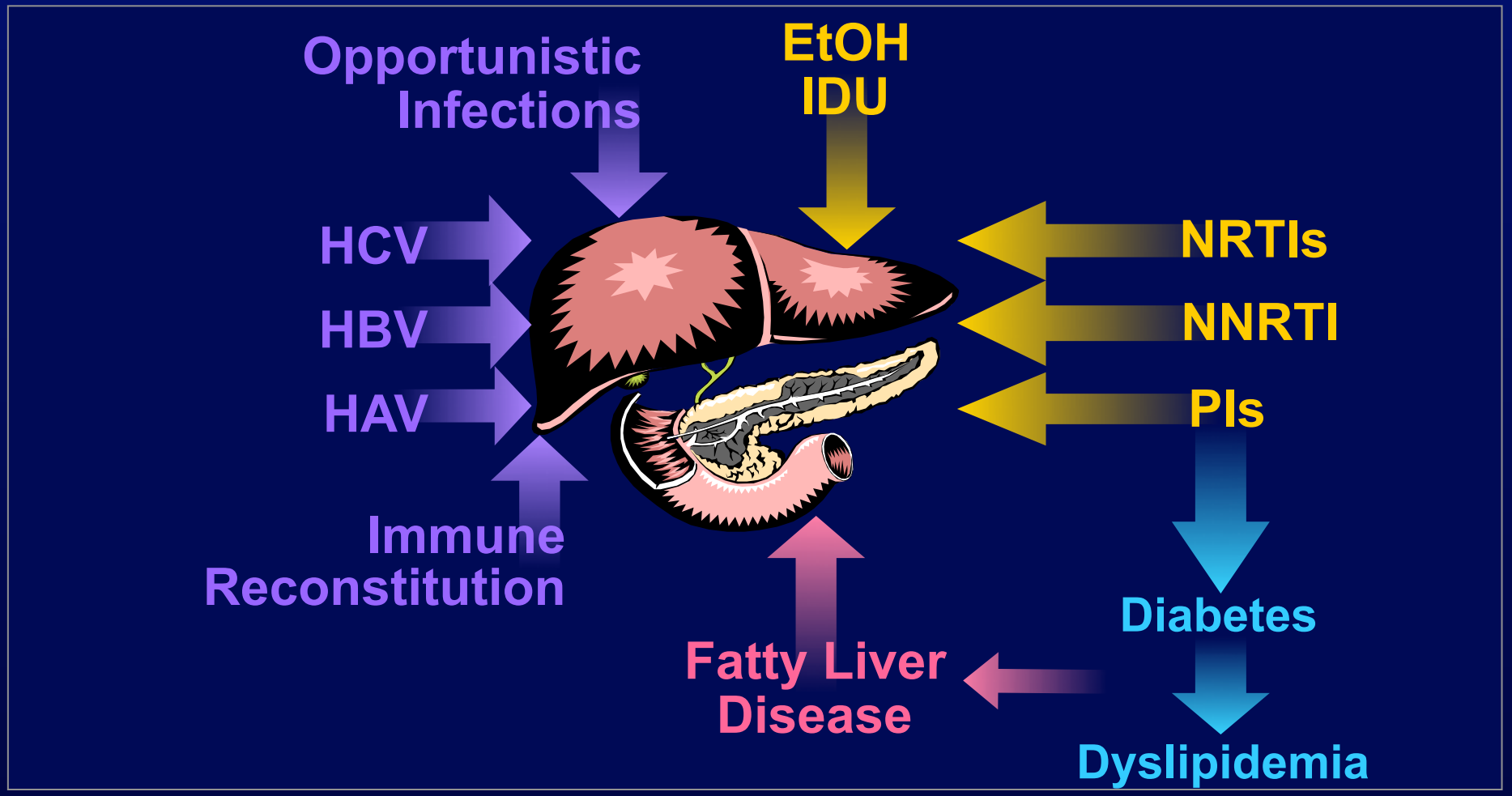
World Health Organization hepatitis C fact sheet 2011; Ghany MG, et al. Hepatology. 2009;49:1-40.

Basic Principles

- Hepatic fibrosis is not reliably diagnosed by ultrasound or other imaging modalities
- Liver fibrosis rates are not predictable or linear
- Progression from compensated cirrhosis to decompensated liver disease occurs in 5% of patients per year
- Hepatocellular carcinoma develops in 1% to 2% of patients with hepatitis-related cirrhosis each year

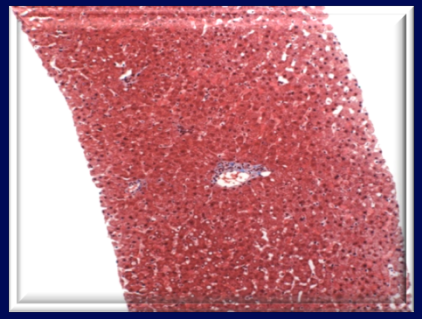
Sherman KE. *Top HIV Med.* 2011;19:121-125.

Causes of Liver Disease in HIV Infection

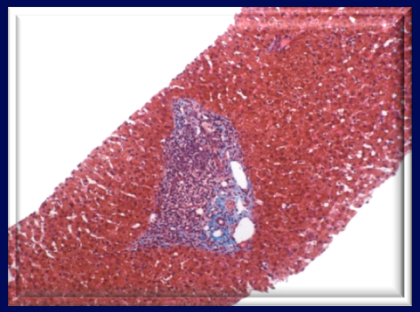


Progression of Fibrosis in Viral Hepatitis on Biopsy (Metavir)

No Fibrosis

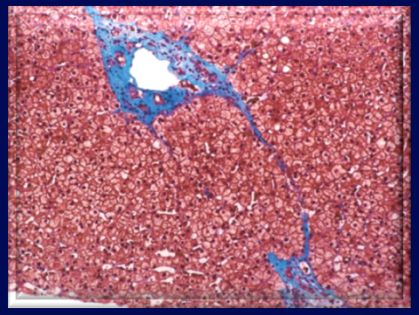


Stage 1



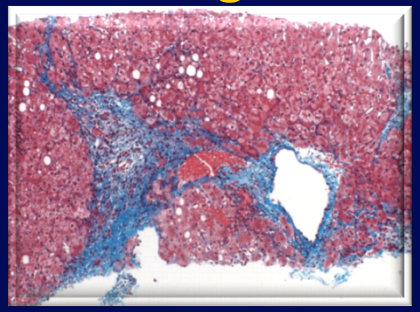
Fibrous expansion of some portal areas

Stage 2



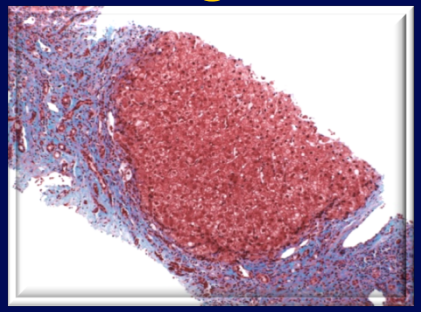
Fibrous expansion of most portal areas with occasional portal to portal bridging

Stage 3



Fibrous expansion of portal areas with marked bridging (portal-to-portal and portal-to-central)

Stage 4

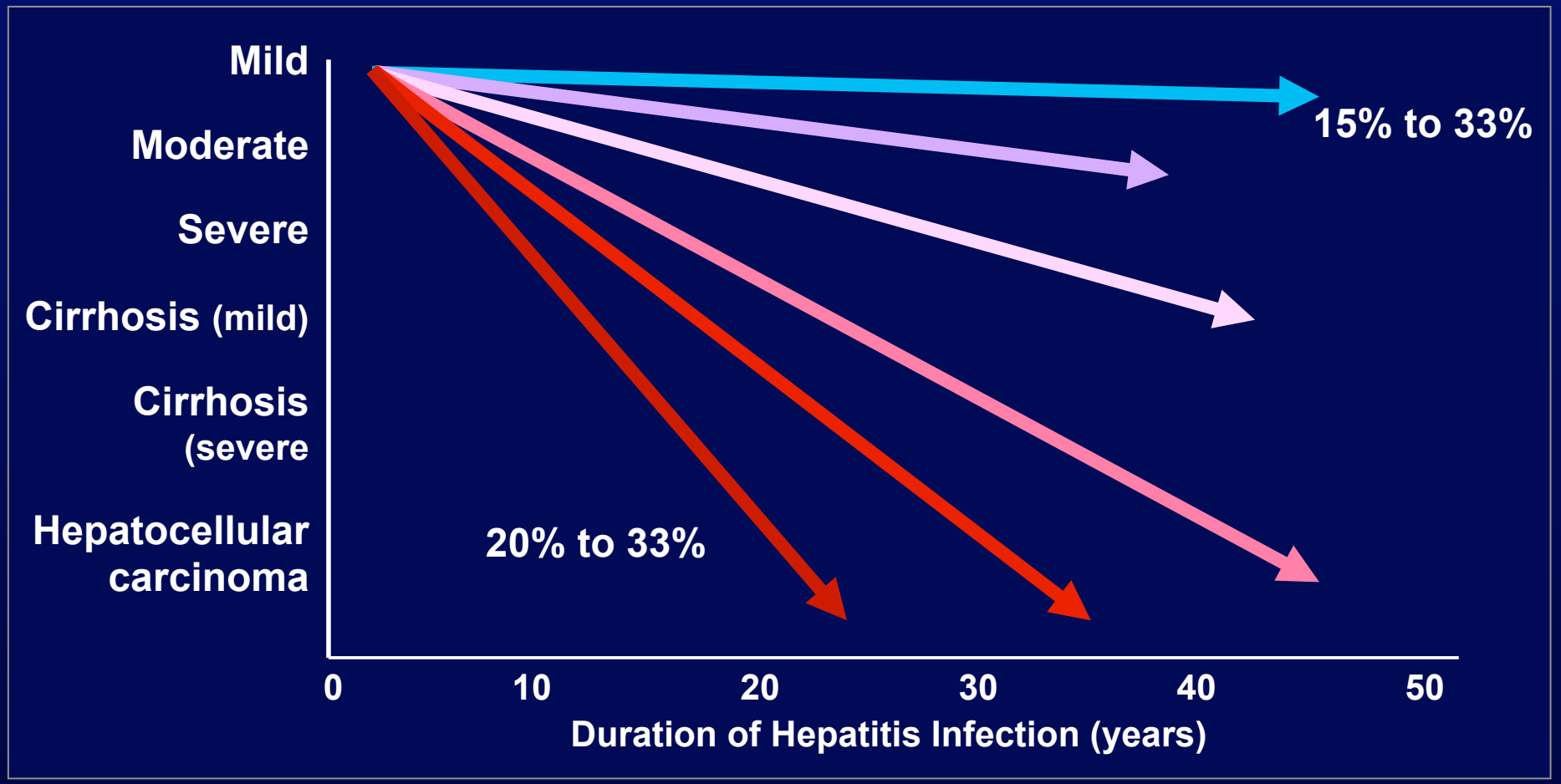


Cirrhosis

Cirrhotic Liver

Faria SC, et al. *Radiographics.* 2009;29:1615-1635. Adapted from Everson GT.

Fibrotic Progression in Viral Hepatitis



Afdhal NH. *Semin Liver Dis.* 2004:24(suupl 2):3-8.

Risk Factors for Progress Fibrosis in HCV Mono-Infected Patients

Modifiable

- Alcohol excess (>50 gm/day)
- Daily marijuana use
- Metabolic syndrome (↑ BMI, obesity, insulin resistance)
- Longer duration of infection
- Age >40 years at time of infection
- Male gender, post-menopausal women
- Coinfections: HBV, HIV, Schistosomiasis
- Organ transplantation

Poynard, Lancet, 1997
Mathurin, Hepatology, 1998
Benhamou, Hepatology, 1999
Kamal, Hepatology, 2006
Asselah, Gut, 2006
Ishida, J Clin Gastro Hep, 2008

HCV Treatment Goals (2012)

Viral Eradication (SVR)

- **Sustained loss of HCV RNA 6 months post-Rx**

Prevention of Disease Progression

- **Normalization of LFTs**
- **Improved HRQoL**
- **Improved liver histology**
- **Decreased cirrhosis**
- **Decreased HCC**
- **Improved survival**

HCV Treatment Expectations (2012)

GT	Medication Regimen	Duration	SVR
1	PEG+RBV+Telapravir	24-48 wks (RGT)	75%
	PEG+RBV+Bocepravir	24-48 wks (RGT)	68%
2	PEG+RBV	24-48 wks (RGT)	75%
3	PEG+RBV	24-48 wks (RGT)	66%
4	PEG+RBV	48 wks	(~55%)
5	PEG+RBV	48 wks	55%
6	PEG+RBV	48 wks	70%

Poordad, NEJM, 2011; Jacobson, NEJM, 2011; Shiffman, NEJM, 2007; Khattab, 2011; D'Heygere, Med Virol, 2011, Lam, Hepatology, 2010

Rationale for Treating HCV Infection

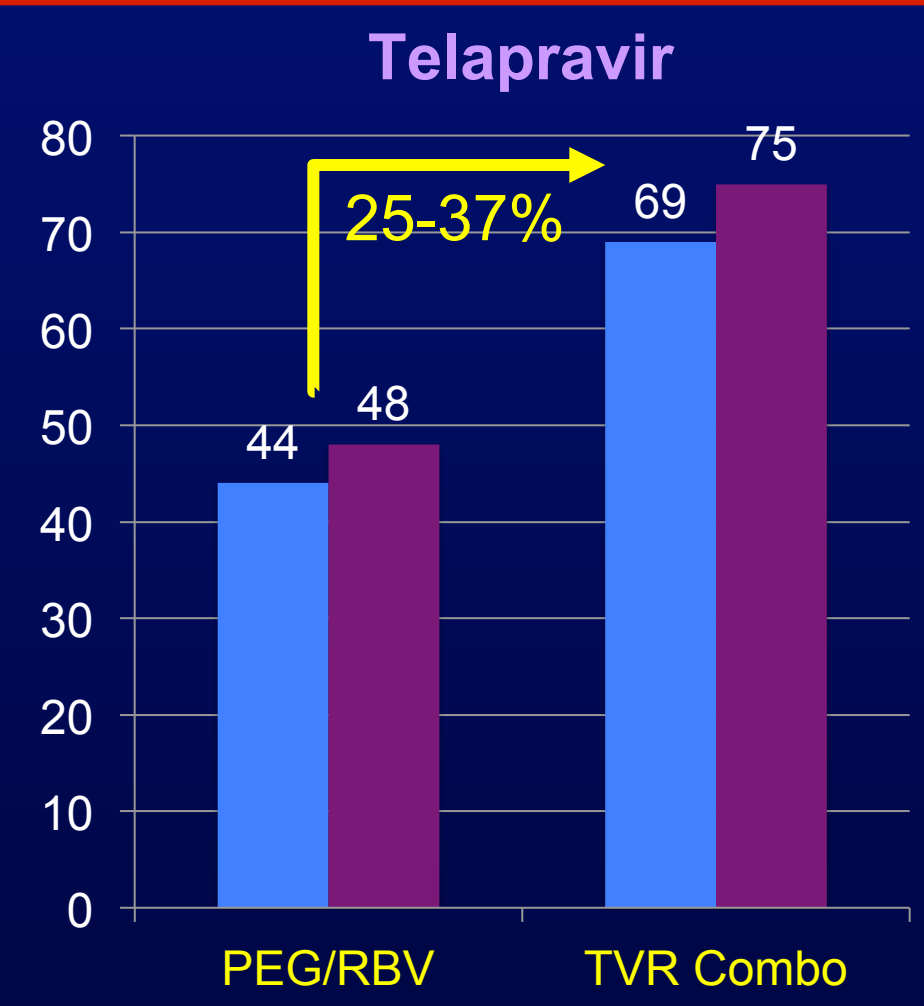
Favor

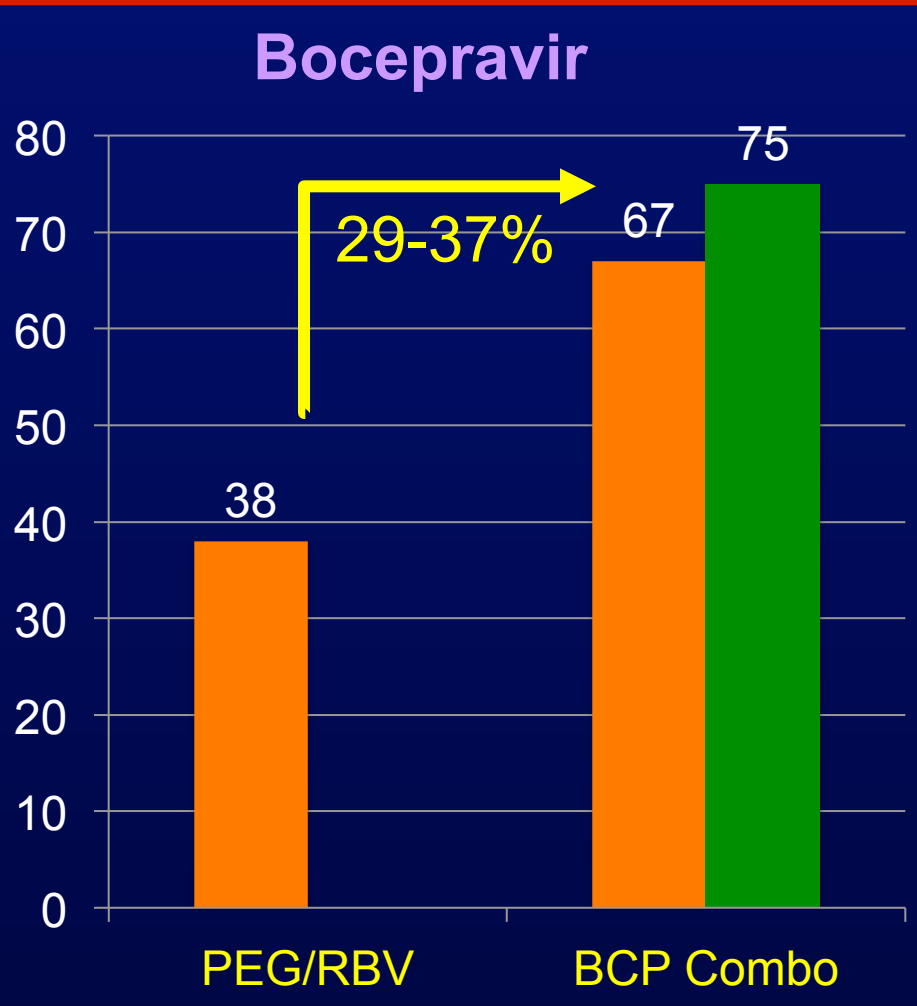
- Increased ability to ‘cure’ GT1
- Reduce disease progression to ESLD, cirrhosis and HCC
- Improve tolerability to other medications (e.g. ART)
- Decrease pool of HCV-infected persons

Against

- Poor tolerability
- Many often not treatment candidates
- Drug interactions
- Low physician comfort level
- Decreased response in HIV/HCV coinfected persons

SVR in GT1 Treatment Naïve Patients Receiving PI-containing Rx





Jacobson IM, NEJM, 2011

Poordad F, NEJM, 2011

Futility Rules for PI-Based Therapy in Treatment-Naïve Patients

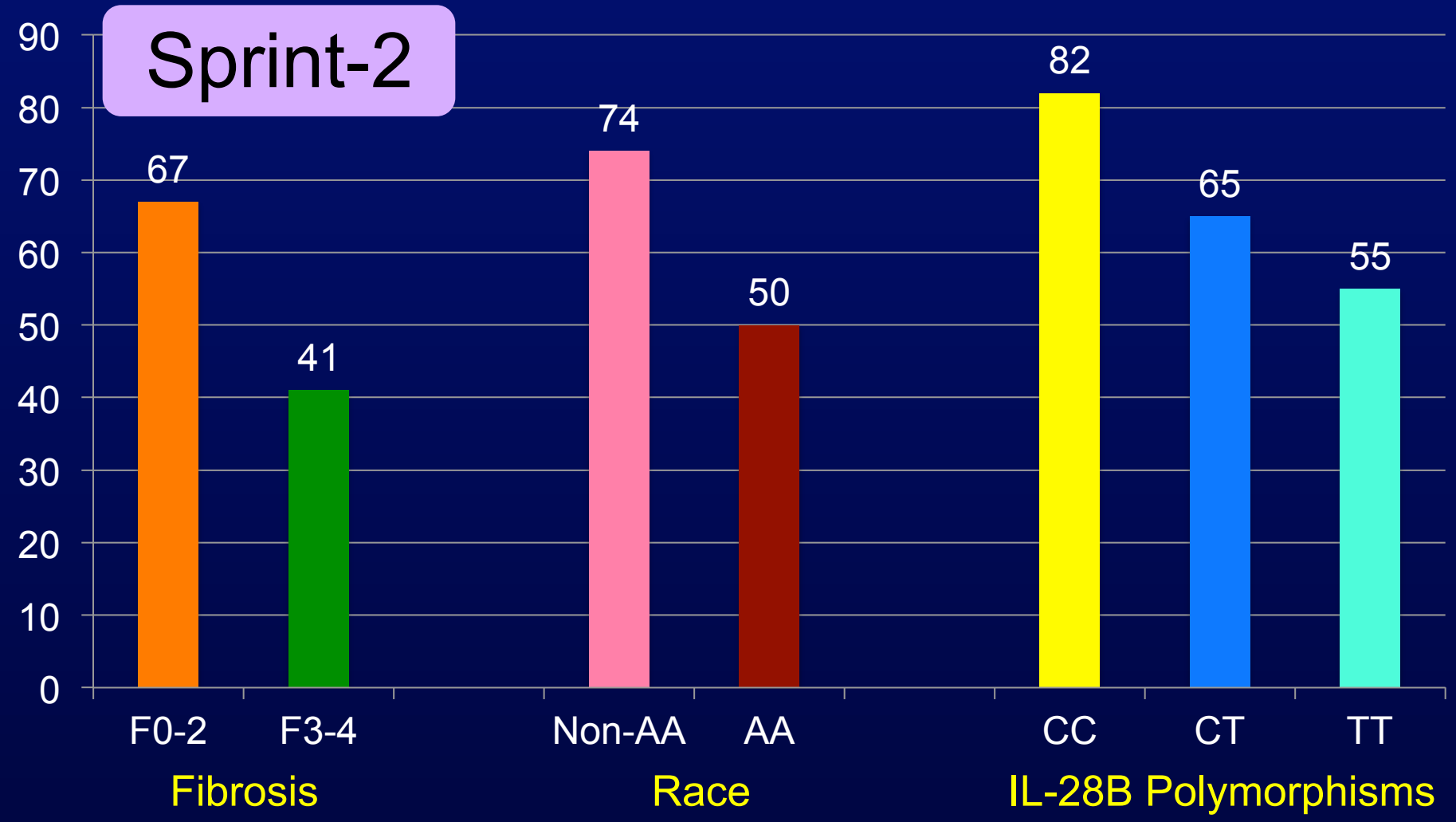
- Recommendation: All therapy should be discontinued in patients with the following:

Boceprevir		
Time Point	**Criteria**	**Action**
Wk 12	HCV RNA ≥ 100 IU/mL	Discontinue all therapy
Wk 24	HCV RNA detectable	Discontinue all therapy

Telaprevir		
Time Point	**Criteria**	**Action**
Wk 4 or 12	HCV RNA > 1000 IU/mL	Discontinue all therapy
Wk 24	HCV RNA detectable	Discontinue pegIFN/RBV

Assay should have a lower limit of HCV RNA quantification of ≤ 25 IU/mL and a limit of HCV RNA detection of approximately 10-15 IU/mL.

Key Host and Viral Factors Affecting SVR Rates in HCV Mono-Infection



Poordad F, NEJM, 2011; Bruno S, EASL 2011, Abstract 195

Adverse Events with PI-Based Treatment Compared to PEG/RBV Alone

- **Boceprevir**
  - Anemia (50% v 30%)
    - Managed with RBV reduction or Epo in 43%
  - Neutropenia (25% v 19%)
  - Dysgeusia (35% v 16%)
- **Telaprevir**
  - Rash (56% v 34%)
    - Severe rash in 4%; discontinuation in 6% (SJS-3; DRESS-11)
    - Most occurred in first 4 weeks, but may happen anytime
  - Anemia (36% v 17%)
  - Anorectal events (29% v 7%)

Key Elements of PI-Combination Rx

Similarities

- RGT: EVR determines Rx duration
- Futility rules used to minimize resistance
- Extended treatment in cirrhotics

Differences

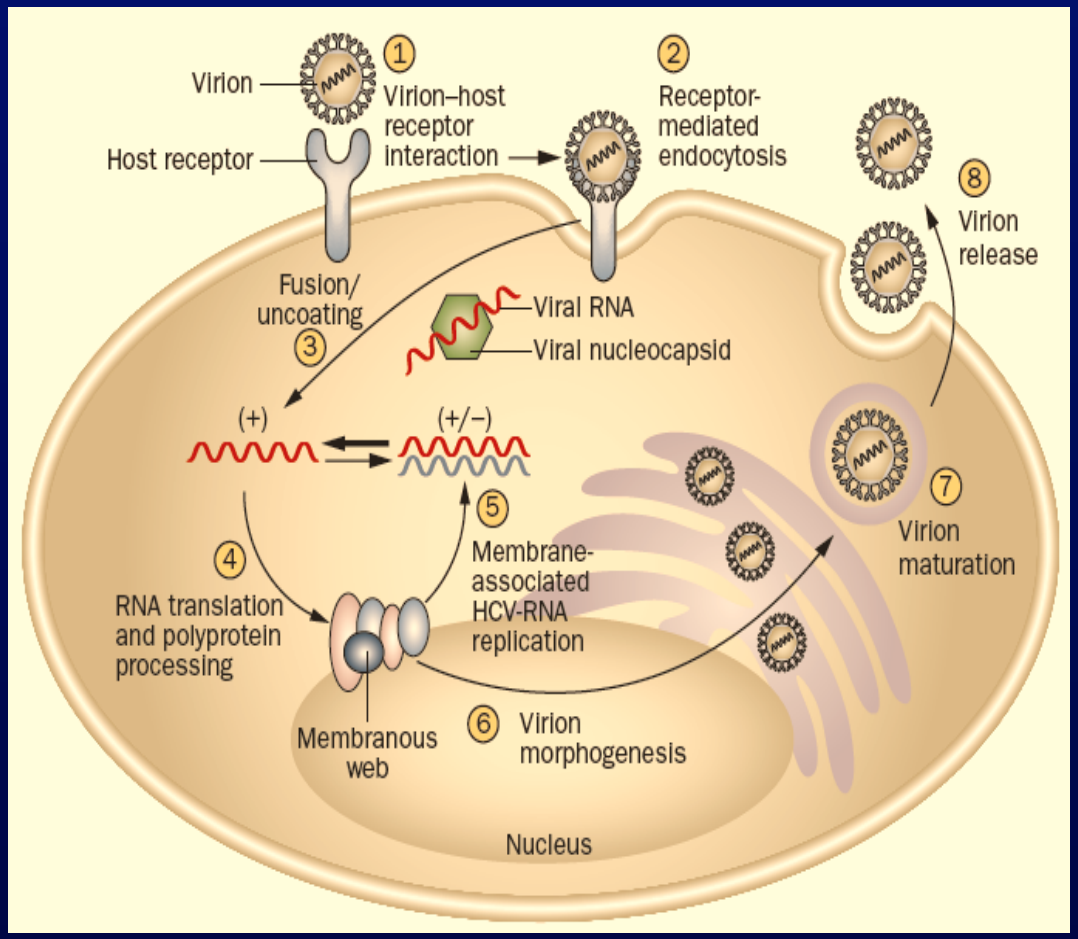
- Lead-in with BCP; none with TLV
- Duration of triple vs dual therapy
- Rules for RGT and futility differ
- Potential for twice-daily Rx for TLV

Treatment of GT1 HCV Infection Using PI-Based Therapy Summary

- SVR rates superior to PEG/RBV, but several subtypes with suboptimal response
  - ~15% lower if cirrhotic, AA or unfavorable IL-B28
  - Prior partial or null response to PEG/RBV (SVR is ≤50% when treated with PI combo)
- RGT offers shorter treatment duration for ~50-60% of patients
  - EVR is highly predictive of SVR
  - Lead-in with PEG/RBV identified less responsive patient
  - Cirrhotics not eligible for shortened treatment

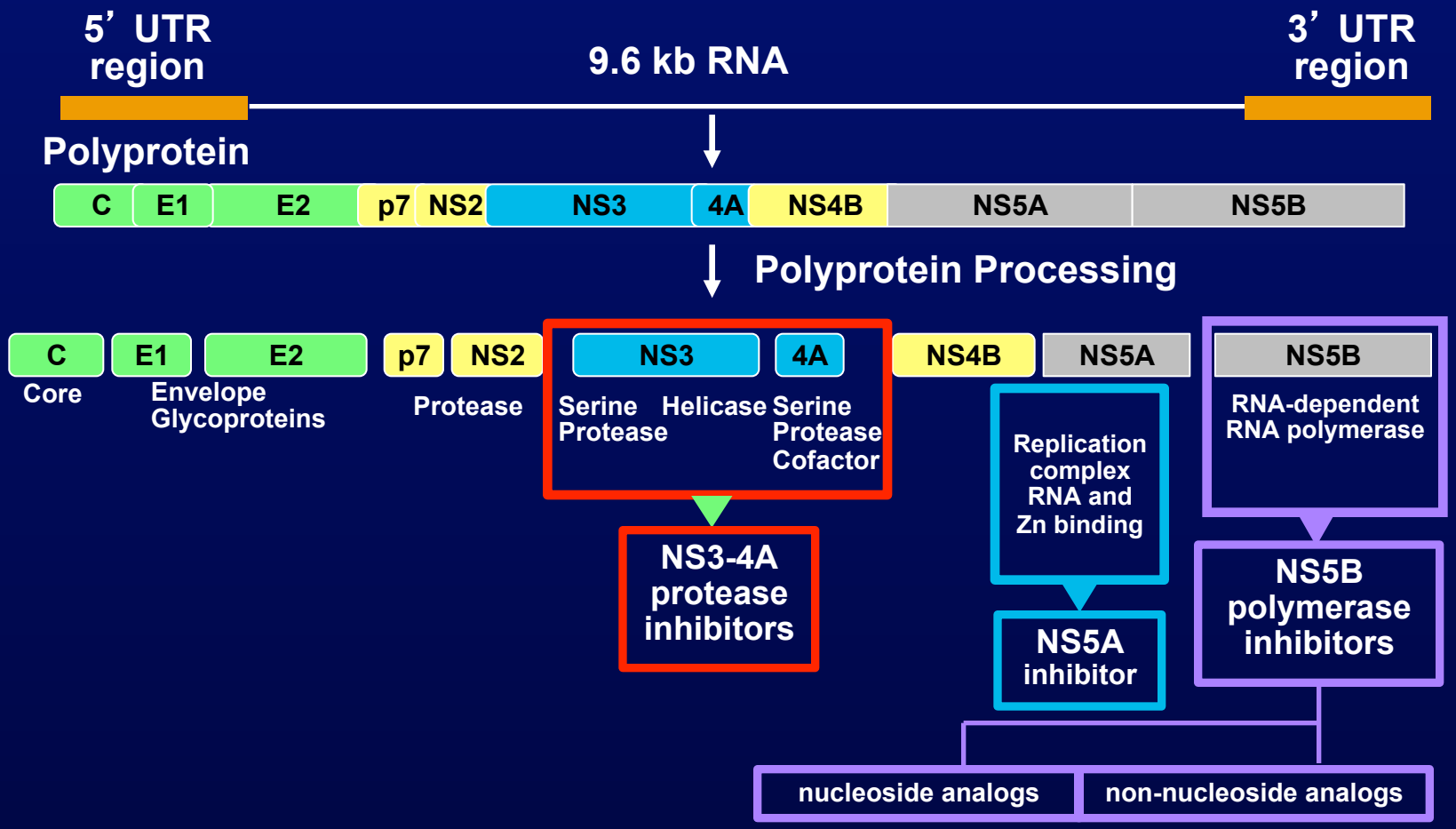
HCV Life Cycle and Targets for STAT-C/DAAs

- **Prevent viral entry**
  - Polyclonal and monoclonal antibodies
- **Prevent translation of viral RNA**
  - NS3/4 protease inhibitors
- **Inhibit HCV-RNA polymerase**
  - Nucleoside analogue NS5B polymerase inhibitors
  - Non-nucleoside analogue NS5B polymerase inhibitors
  - Replication complex inhibitor
  - Cyclophilin B inhibitors
- **Viral assembly/release**
  - Glucosidase inhibitor



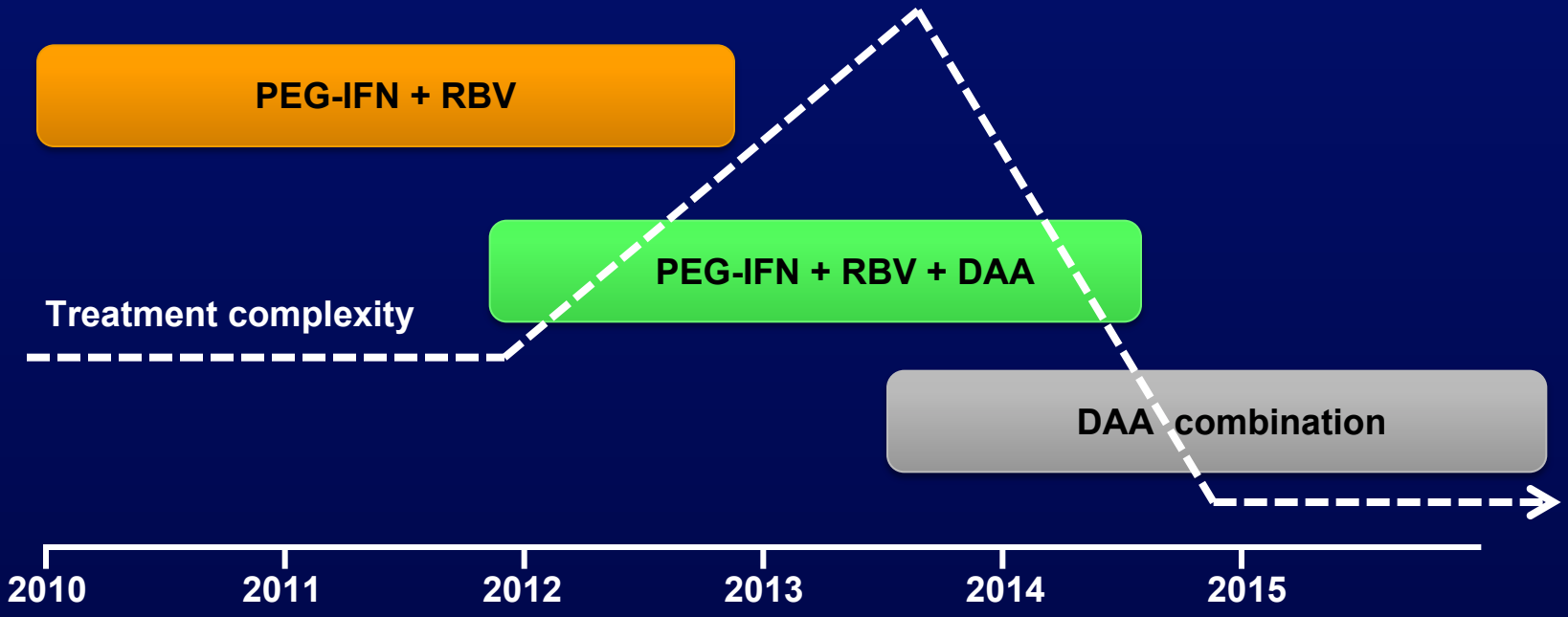
Pereira AA, et al. *Nat Rev Gastroenterol Hepatol.* 2009;6:403-411.

Multiple Direct Antiviral Targets



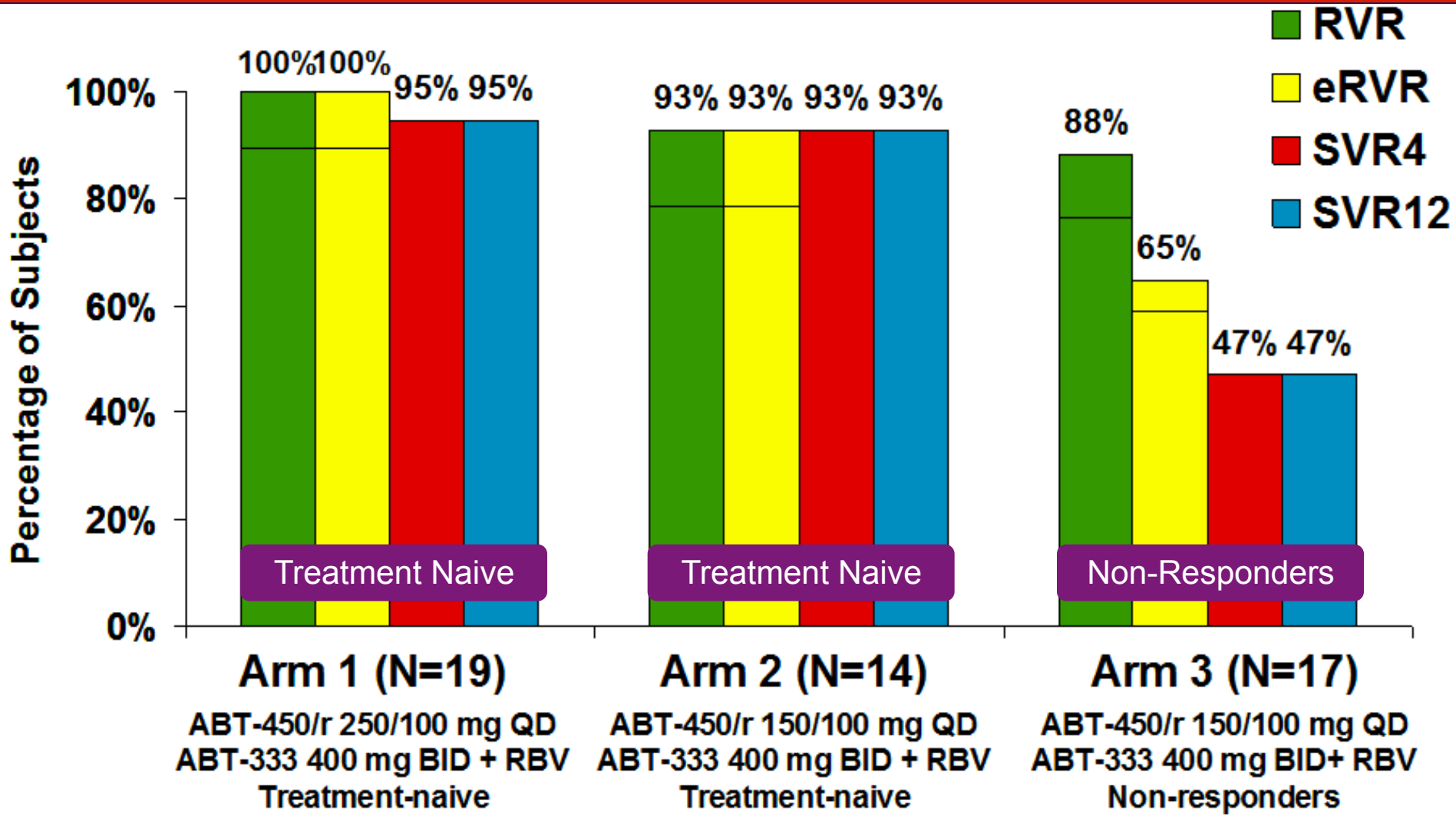
Terrault N, 19th IAC; Washington, DC; July 22-27, 2012; Abst. WEAB0104.

DAA Development Timeline



Dore G, 19th IAC; Washington, DC; July 22-27, 2012; Abst. THSS0202; Dore GJ. Med J Aust 2012; 196:629-632

GT1: PEG-Free Therapy
Boosted PI + NN Pol Inhibitor + RBV



Poordad, EASL, 2012

Considerations About Whether to Treat Now or Wait for New Therapies

- **Likelihood of response and risk of waiting**
  - Stage of fibrosis
  - Prior treatment history
    - Partial and null responders need better medications
- **Tolerability of PEG/RBV**
  - If previously treated, why was it stopped
  - Cirrhotics require 48 weeks – more risk of side side effects, especially cytopenias
- **Practical issues**
  - Insurance status & co-pays
  - Social support
- **Public health – secondary prevention**

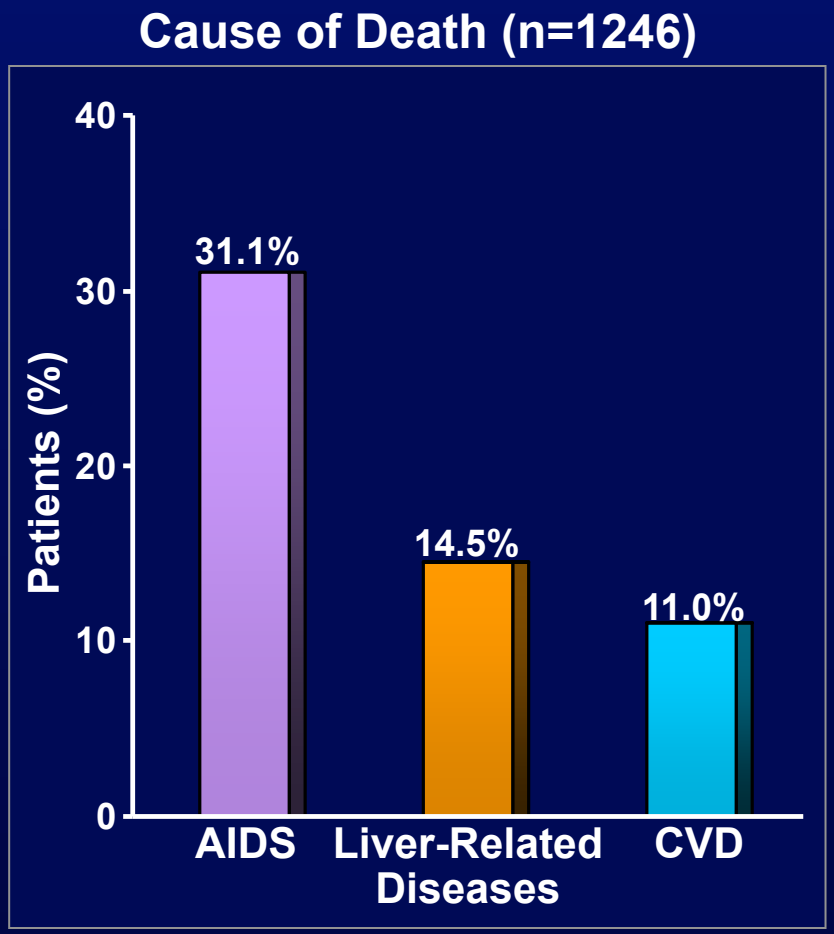
Altice, personal opinion, 2012

Program Overview

- Basic principles of viral hepatitis liver disease
- **Epidemiology considerations and significance of liver disease and hepatitis in HIV**
- Special consideration for HCV-infected persons with substance use disorders

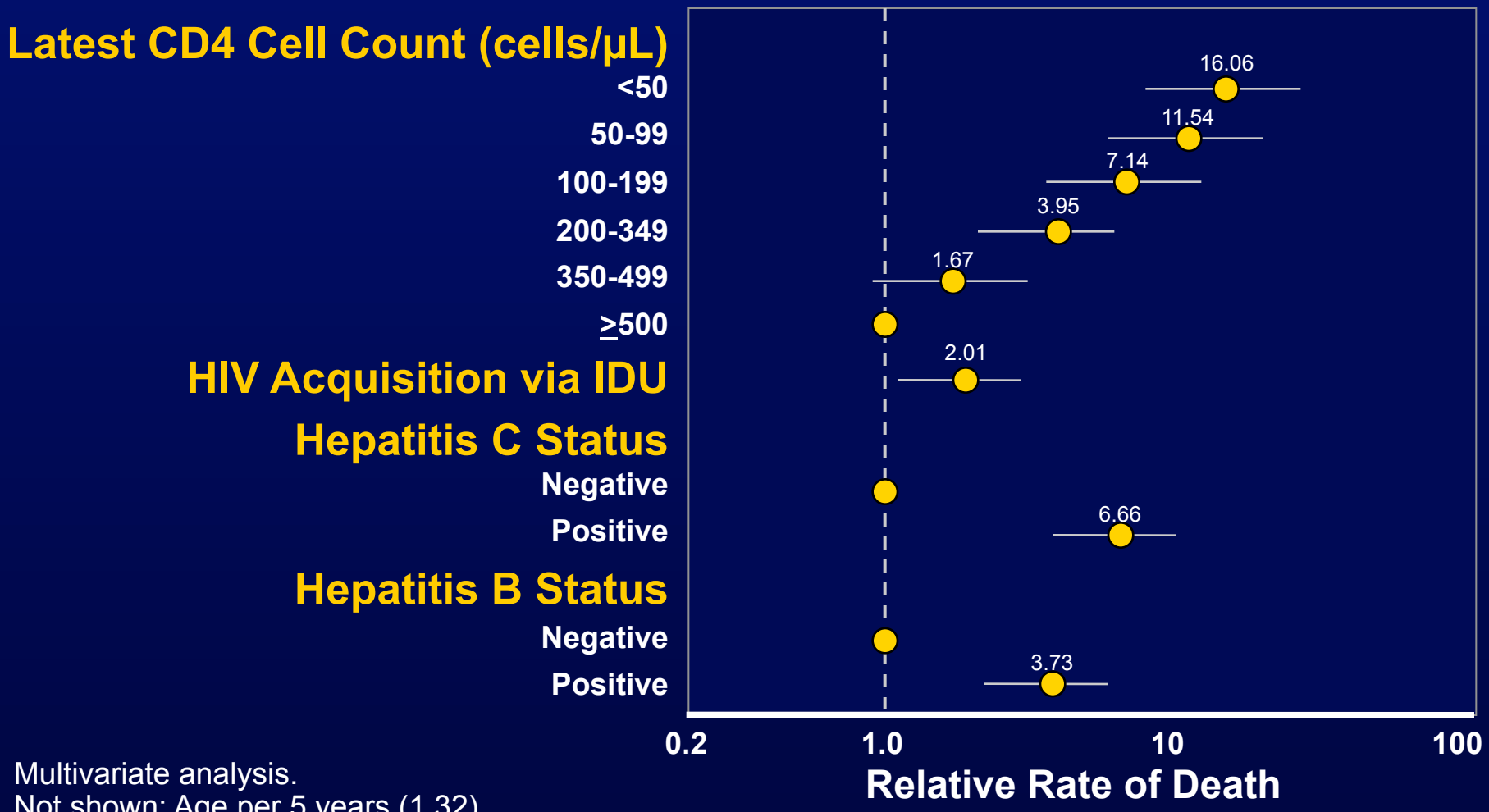
Liver Disease is the Second Leading Cause of Death in HIV-Infected Patients (1999-2004)

- D:A:D study (n=23,441)
  - Median follow-up: 3.5 years
- Baseline characteristics
  - Nadir CD4: 200 cells/μL
  - Previous AIDS: 26.5%
  - HCV positive: 22.5%
  - Active HBV infection: 6.8%
    - Inactive HBV infection: 21.4%
  - Receiving combination antiretroviral therapy: 88.7%
- Mortality
  - Total: 5.3%
  - Incidence: 1.62 per 100 person-years
  - Median age: 44 years



Weber R, et al. *Arch Intern Med.* 2006;166:1632-1641.

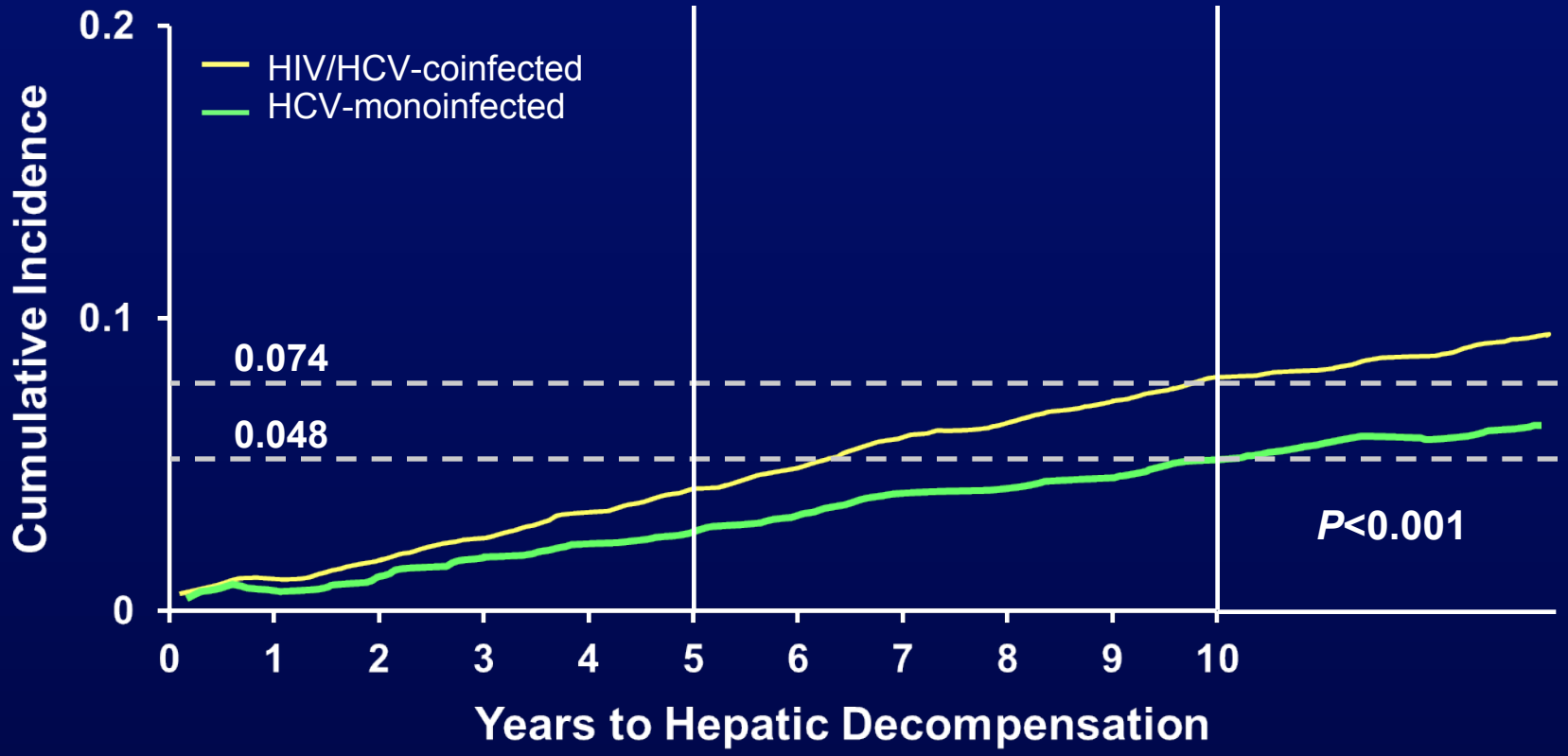
Independent Predictors of Liver-Related Death



Multivariate analysis.
Not shown: Age per 5 years (1.32).

Weber R, et al. *Arch Intern Med.* 2006;166:1632-1641.

Standardized Cumulative Incidence of Hepatic Decompensation



Hepatic decompensation risk 83% higher in the coinfected group (aHR 1.83, 95% confidence interval [CI] 1.54 to 2.18)

Lo Re V, et al. 19th IAC; Washington, DC; July 22-27, 2012; Abst. WEAB0102.

Summary of Findings for PI-based Treatment for HIV/HCV Co-Infection

- Improved efficacy ➔ 30% over PEG/RBV
  - Similar to HCV monoinfected
  - Tolerability similar to monoinfected
- BUT …….
  - Only applicable to GT1, treatment-naïve patients
  - Still requires 48 weeks of treatment
  - Limited number of ART regimens studied
  - May use either if on no ART or RAL+2NRTIs
  - Use TLV if on ATV/r+2NRTIs
  - Use increased TLV 1125 Q8h if on EFV+2NRTIs

Increased Potential for Pharmacokinetic Drug Interactions

- Telaprevir
  - CYP3A4 and P-gp substrate
  - Non-cytochrome P450 metabolism as well
  - CYP3A4 inhibitor
- Boceprevir
  - Aldoketoreductase (AKR) and CYP3A4/5 substrate
  - CYP3A4 and P-gp inhibitor
- HIV PIs or NNRTIs, statins, antiarrhythmics, others

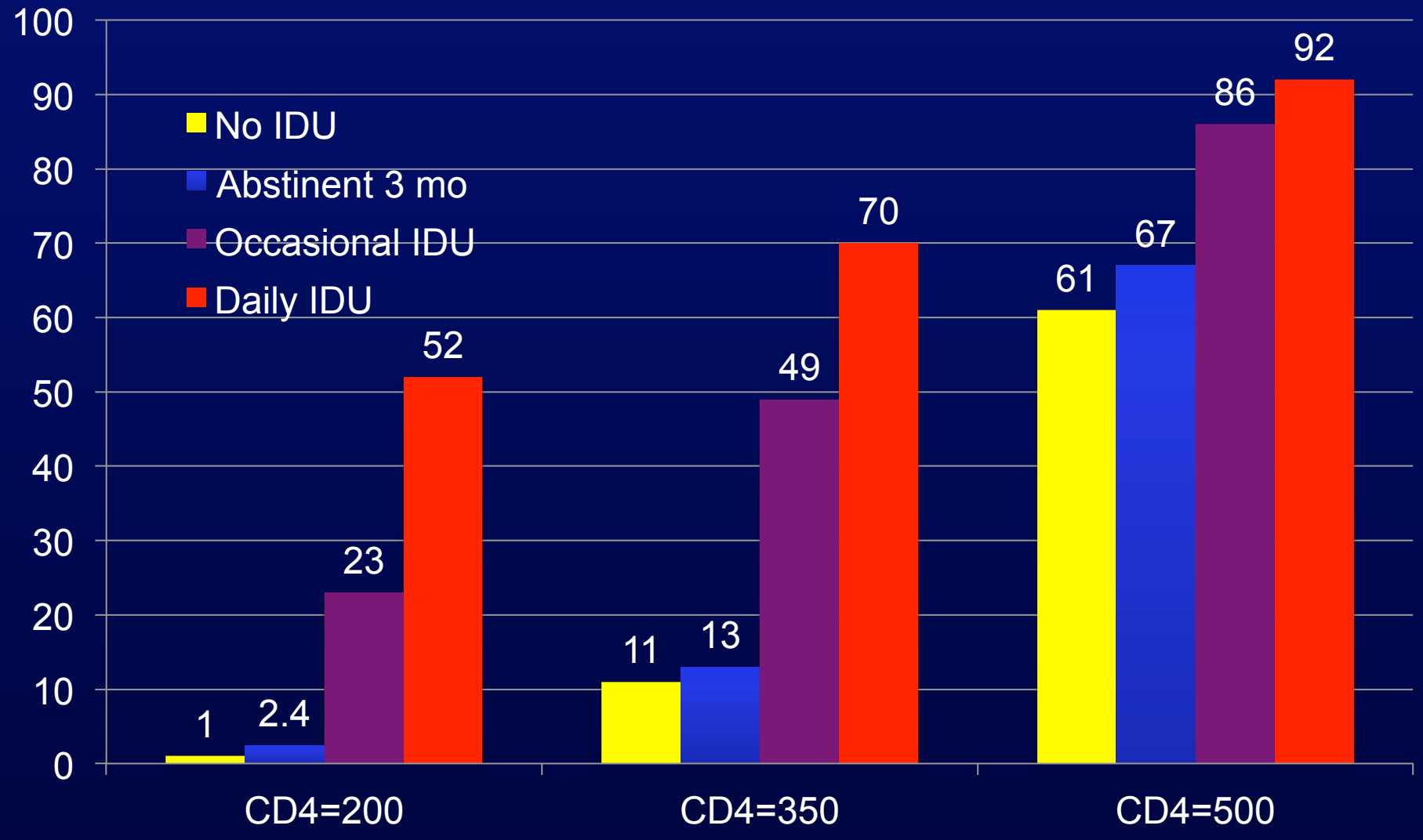
Program Overview

- Basic principles of viral hepatitis liver disease
- Epidemiology considerations and significance of liver disease and hepatitis in HIV
- **Special consideration for HCV-infected persons with substance use disorders**

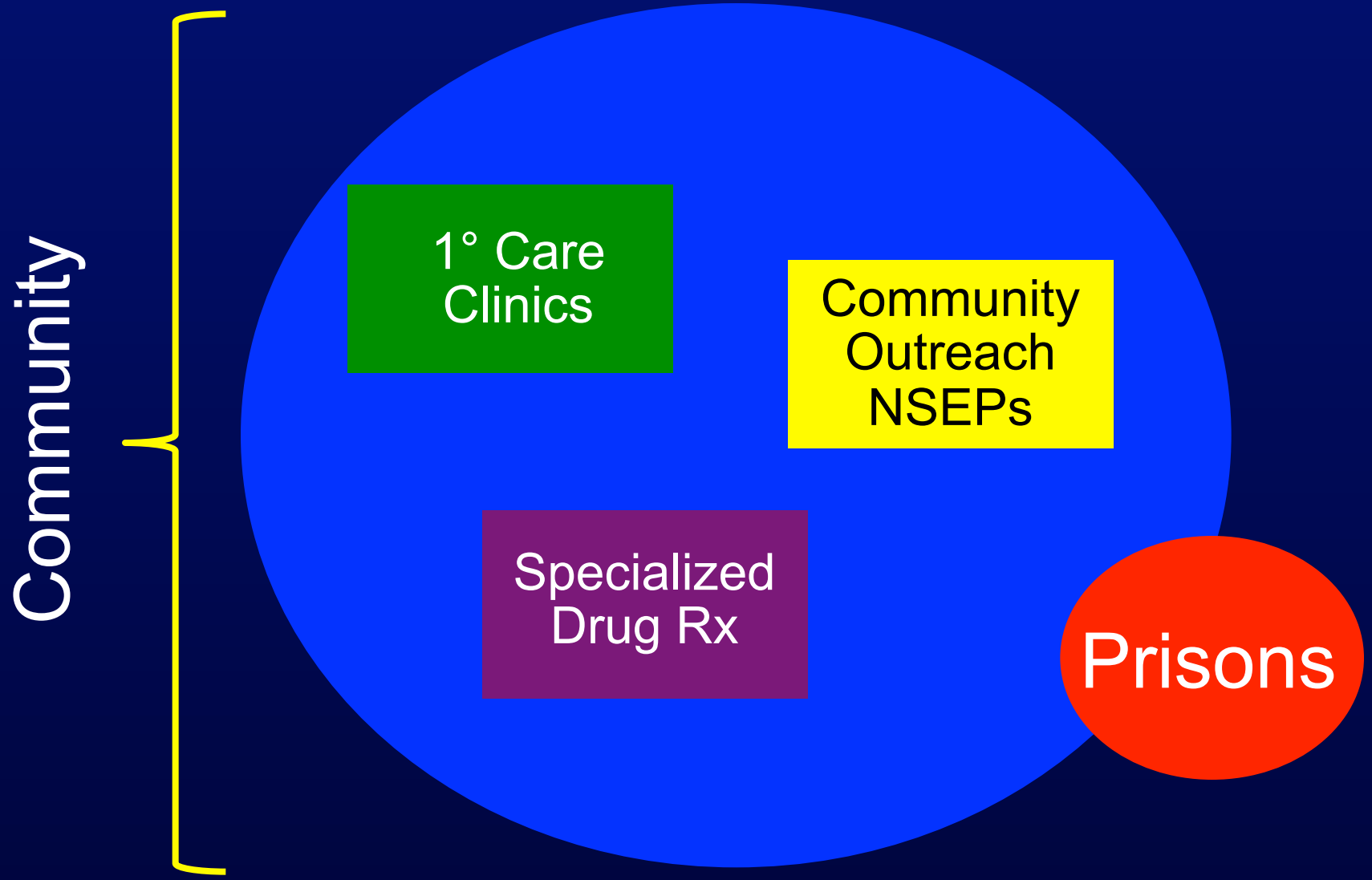
Treating HCV Among Drug & Alcohol Users

- Can reduce treatment duration
- Relatively few drug interactions
- Providers, however, unlikely to treat
- Many substance use disorders can be effectively treated with medication-assisted therapy
  - Opioids (methadone, buprenorphine, XR-NTX)
  - Alcohol (XR-NTX, acamprosate)
- Creative delivery of health services may be needed to overcome existing obstacles

Not Prescribing ART to Drug Users



How to Increase Treatment of HCV



Integration into Specialty Drug Treatment Programs

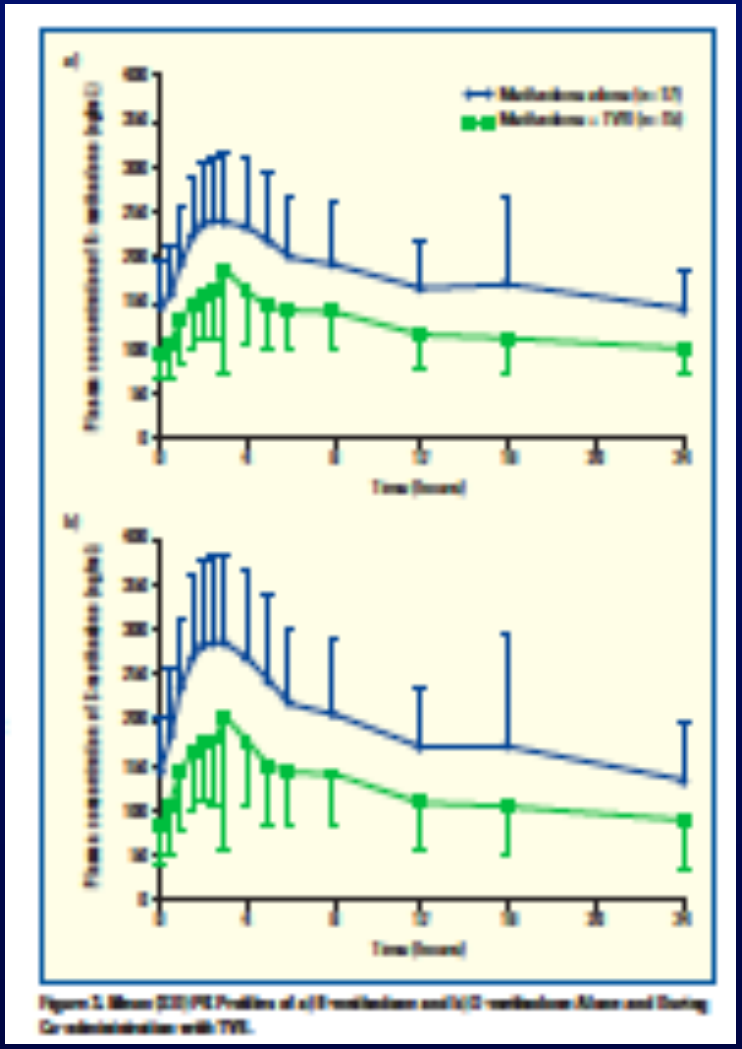
Developing a Modified Directly Observed Therapy Intervention for Hepatitis C Treatment in a Methadone Maintenance Program: Implications for Program Replication

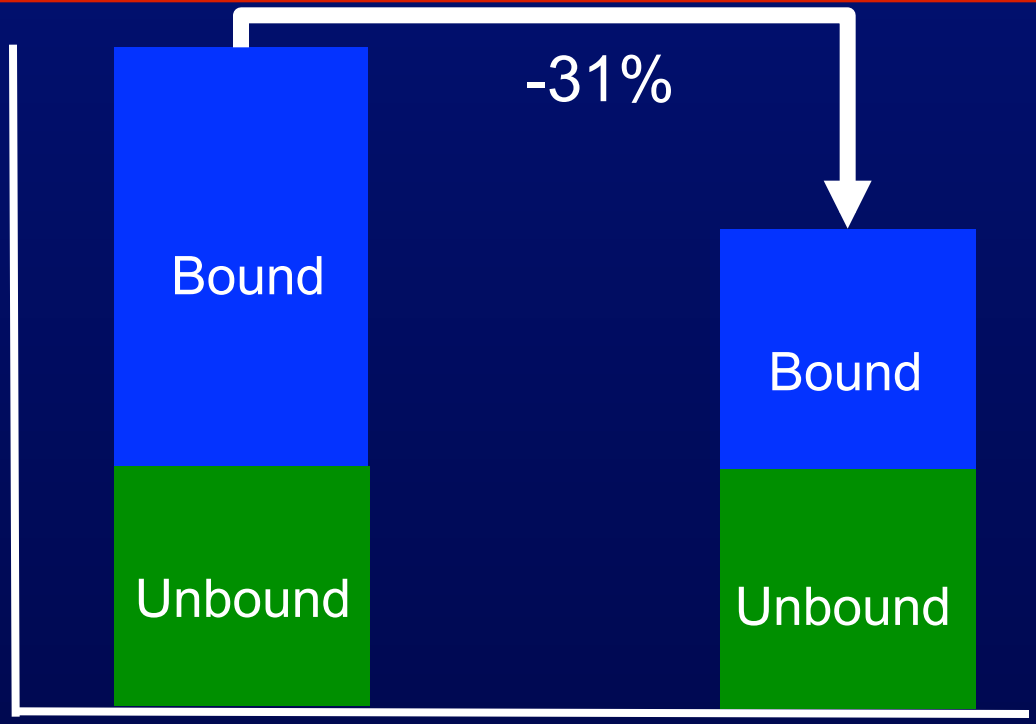
R. Douglas Bruce, M.D., M.A., M.Sc[1,2], Julie Eiserman, M.A.[1], Angela Acosta, B.S.[1], Ceilia Gote, APRN[3], Joseph K. Lim, M.D.[4], and Frederick L. Altice, M.D., M.A.[1,2]

- Supervised dosing enhances adherence
- Evidence for success in treating TB & HIV

	Integrated	Referral
Started Rx	100%	36.4%
EVR	83.3%	27.2%
SVR	50.0%	9.1%

Impact of Telaprevir on Methadone and Buprenorphine/NLX





- **No significant change in BPN/NLX AUC**
- **No clinical symptoms of opioid withdrawal for either**

Van Heeswijk, EASL, 2012, Abs 654
Luo, Antimicrob Agents Chemo, 2012

Project ECHO: Increasing Primary Care Treatment of HCV Infection

- Challenge: rural and non-specialists are unlikely to treat HCV
- Increased HCV screening, evaluation for Rx, self-efficacy and initiation of HCV treatment
- Weekly telemedicine clinical conferences with didactics, case presentations and discussions
- RCT of specialty HCV treatment versus ECHO:
  - SVR: 57.5% v 58.2%
  - SVR GT1: 45.8% v 49.7%
  - Serious adverse events: 13.7% v 6.9%

Arora, Hepatology, 2010
Arora, NEJM, 2011

HCV Treatment Outcomes in Prisons

- Prisons are structured settings to initiate and treat diseases
- Pilot study of HCV treatment outcomes
- SVR=51%
- Having depression and cirrhosis associated with no SVR

Table 3. Reasons for deferral of hepatitis C therapy.

Reason for deferral	No. (%) of patients (n = 70)
Patient's release was too soon	40 (57.1)
Normal liver function test results	8 (11.4)
Normal biopsy findings	7 (10.0)
Patient refused consent/change of facilities	2 (2.9)
Patient refused consent/other	5 (7.1)
Hepatic decompensation	2 (2.9)
Patient deemed to be noncompliant	1 (1.4)
Patient had uncontrolled HIV disease	3 (4.3)
Patient had uncontrolled diabetes	1 (1.4)
Unclear	1 (1.4)

Maru, CID, 2008

Medical Care

Drug Treatment

Mental Health

HIV Care

Case Management

Outreach

HCV Treatment

Summary

- Newer treatments have emerged that can “cure” HCV infection with shorter duration, but with increased complexity, cost and side effects
- Substance use disorders and psychiatric illnesses can be effectively treated with existing pharmacotherapies
- Innovative solutions are urgently needed if we intend to expand treatment and reduce negative health consequences to individuals and society