HIV-Hepatitis C Virus Co-infection: An Evolving Epidemic

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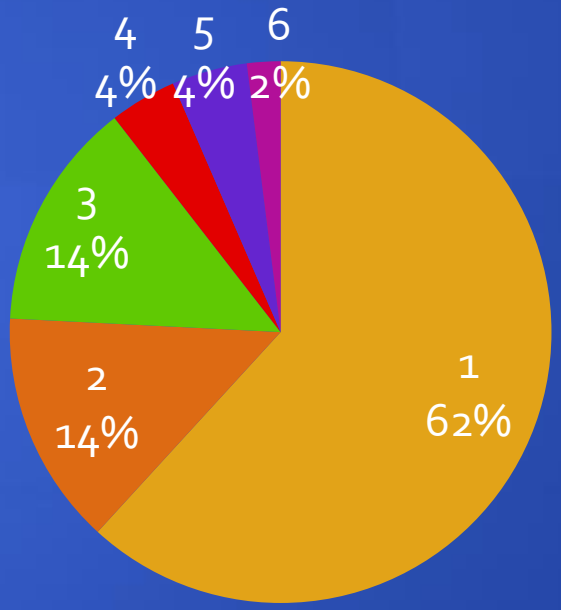
HCV Genotype

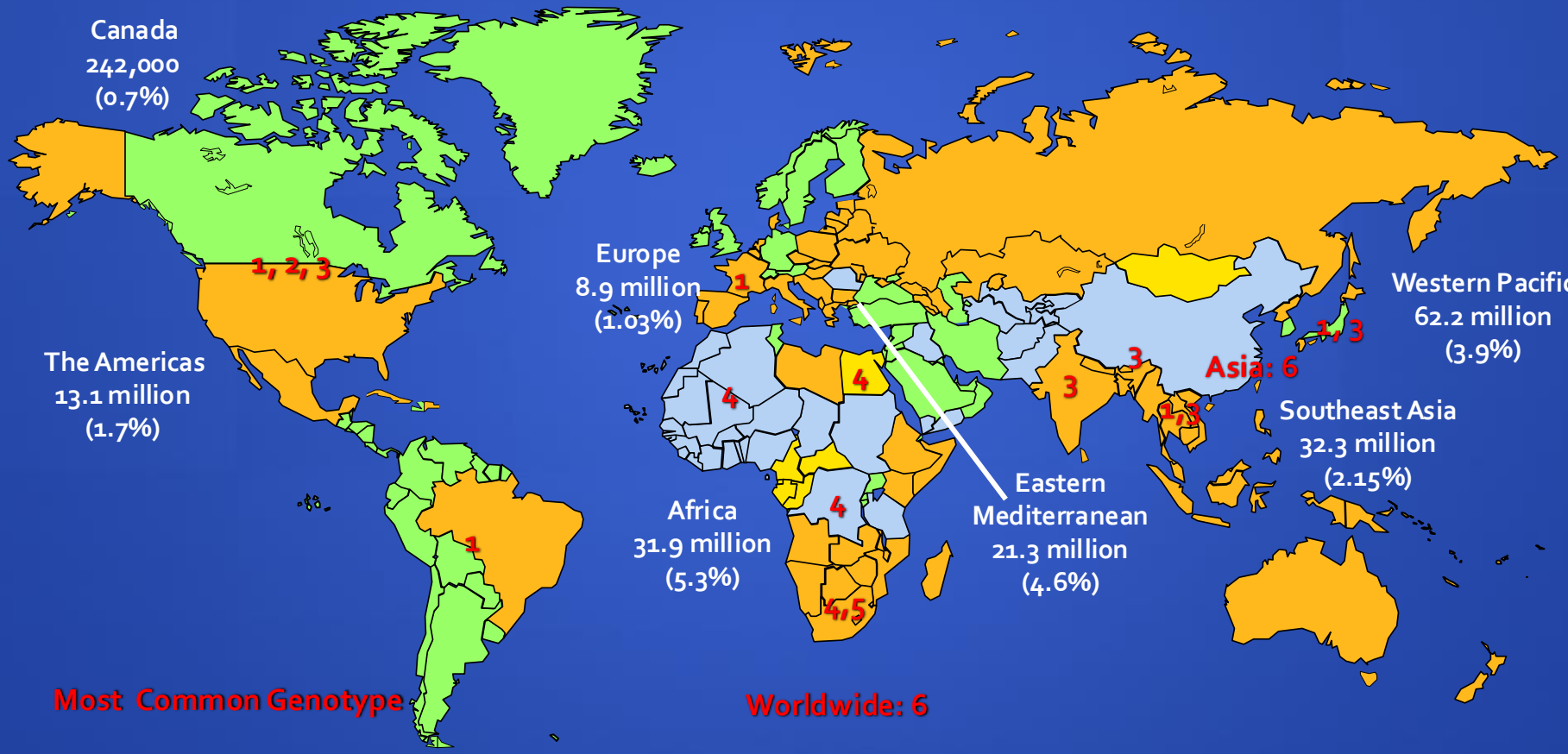
- Genotypes 1-6
  - 62% genotype 1 in Canada
  - 1, 3 more in IDUs
  - Genotypes 2a and 5 are more frequent in patients previously exposed to multiple injections, surgery, or transfusions
  - Type 4 more in African immigrants
  - Existence of several genotypes in Canada despite low prevalence of HCV reflects the diversity of the population and active immigration
- Most important predictor of IFN treatment response
- Does *not* predict amount of liver damage



Andonov A, Chaudhary RK. J Clin Microbiol ,1994.

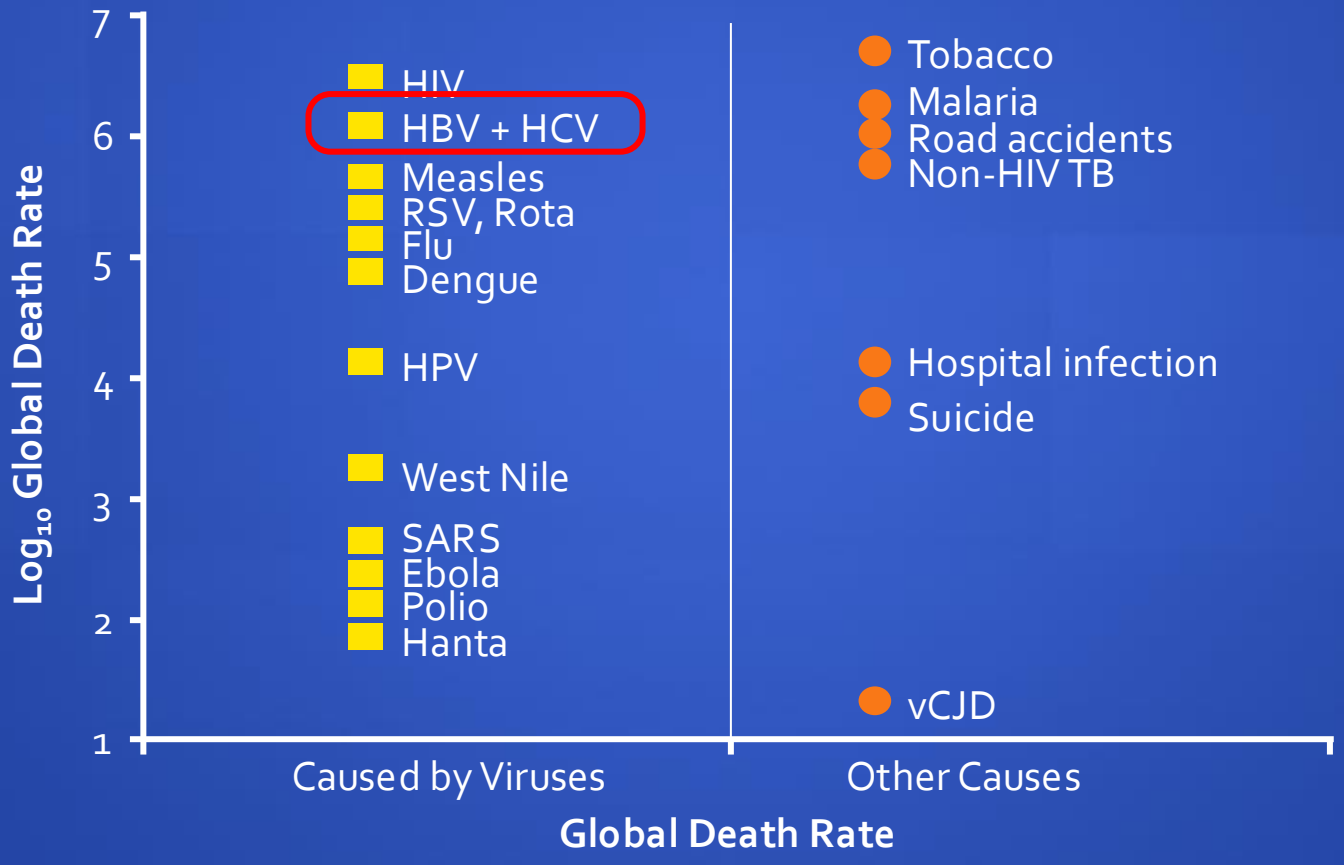
Hepatitis C: A Worldwide Epidemic

Estimated ~ 170 million (3.1%) globally (2003)

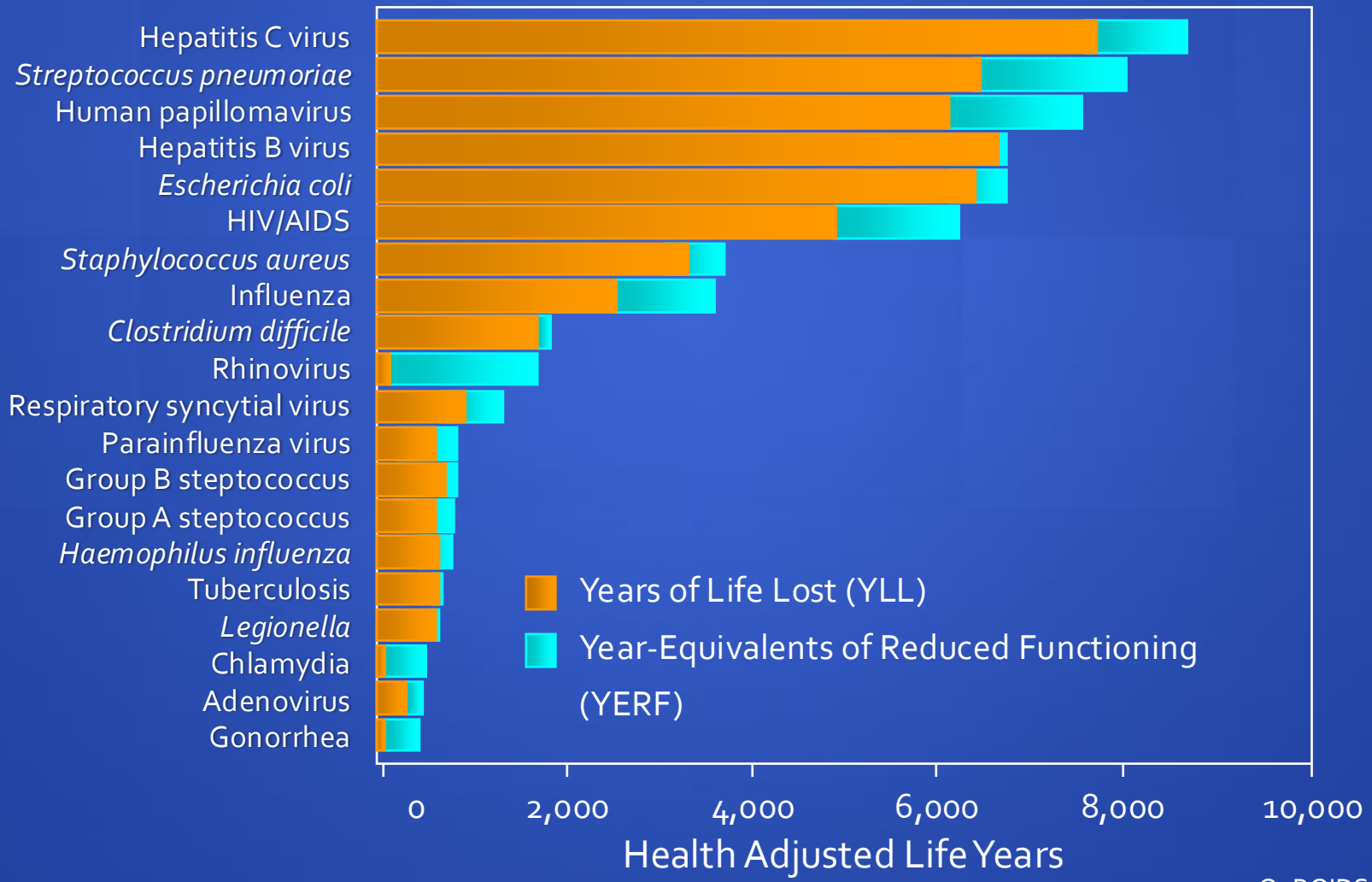


World Health Organization. Hepatitis C: global prevalence: update. 2003.
Farci P, et al. Semin Liver Dis. 2000. Wasley A, et al. Semin Liver Dis. 2000.
Remis, for the Public Health Agency of Canada. Modeling the Incidence and Prevalence of Hepatitis C Infection and its Sequelae in Canada, 2007. Unpublished data, 2009.

HCV: A Global Public Health Concern

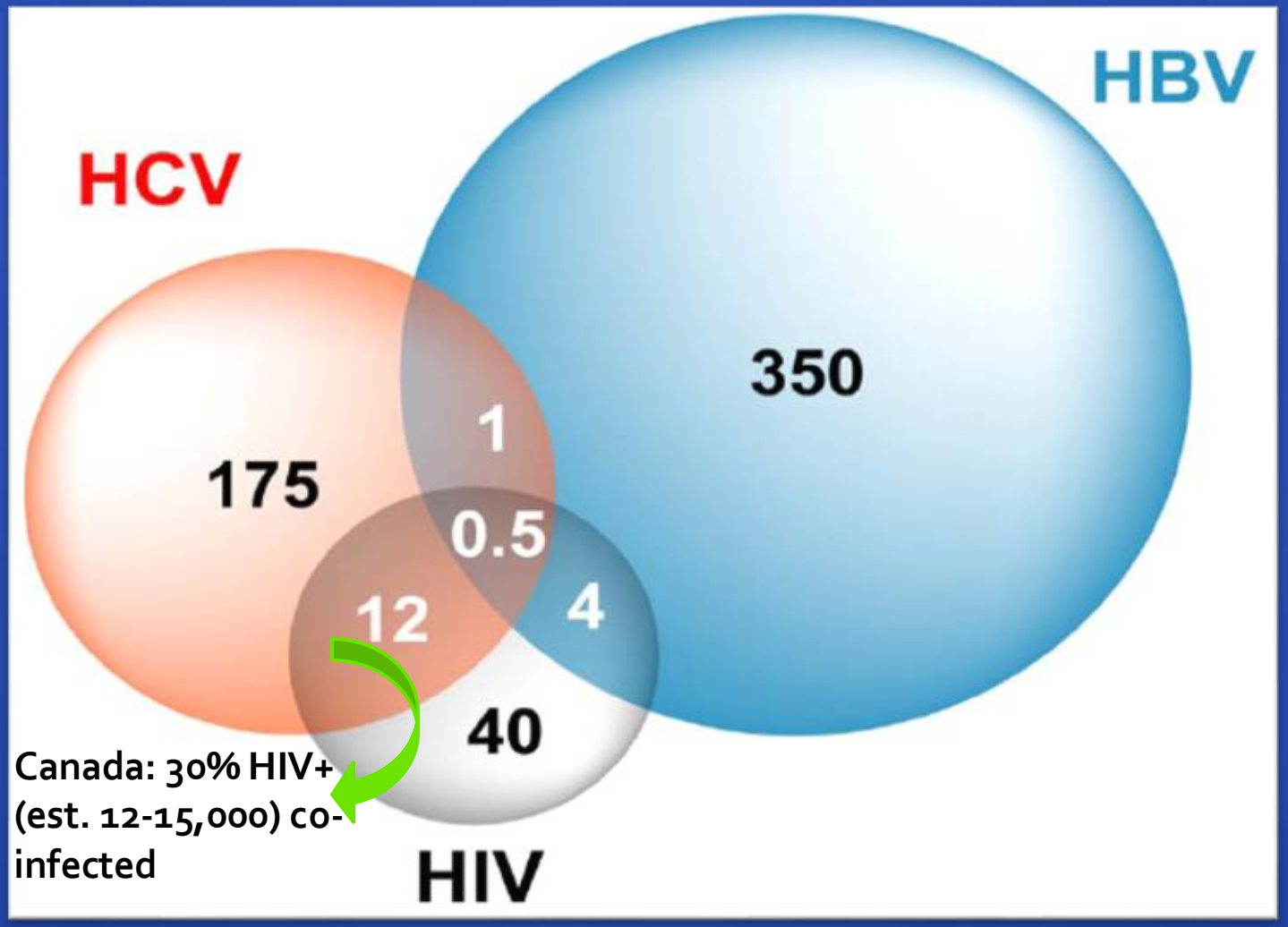


Morbidity and Mortality for the top 20 pathogens in ON, ranked by disease burden

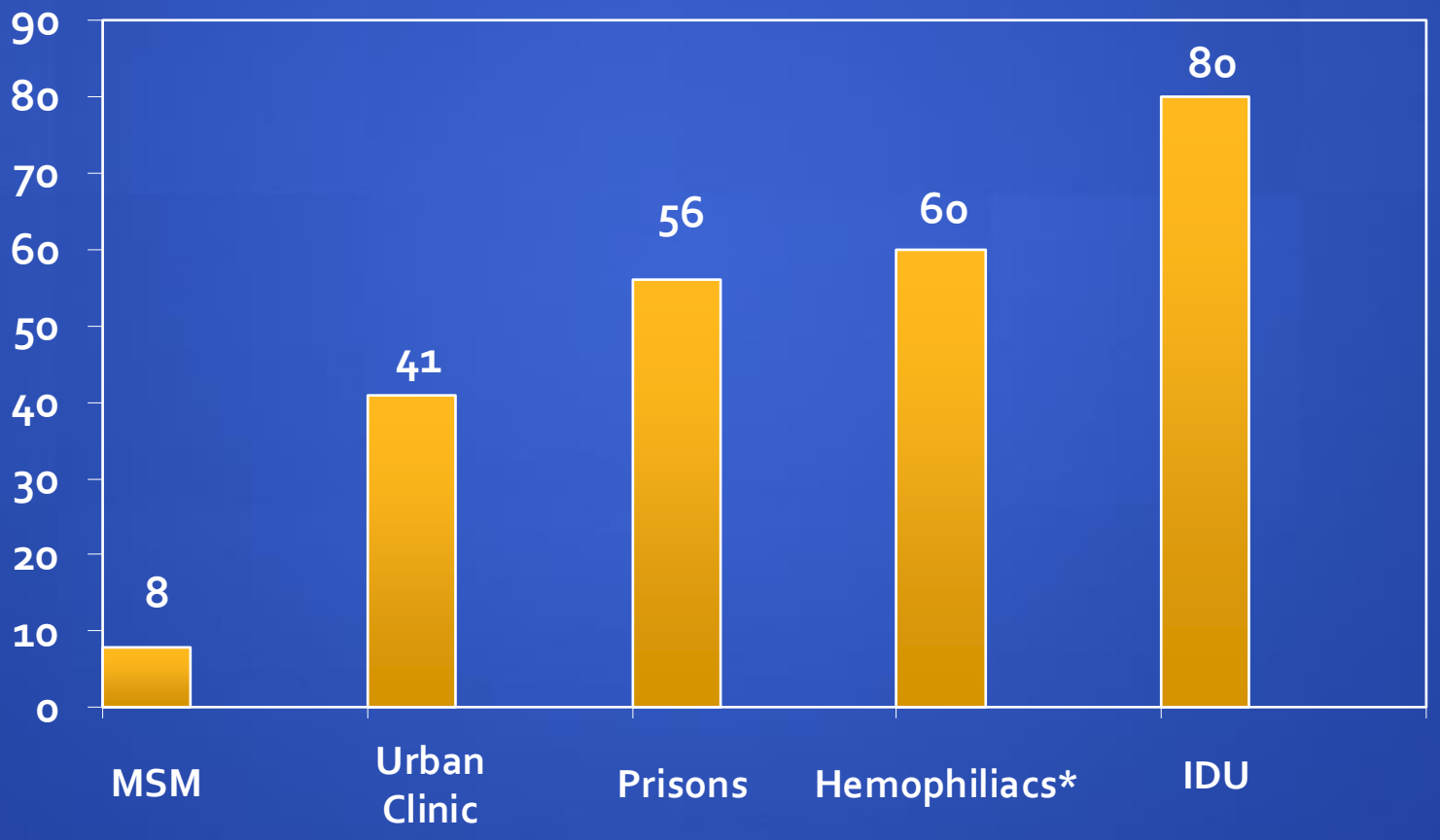


OnBOIDS, Dec 2010

Estimated numbers of Co-infected persons (worldwide)



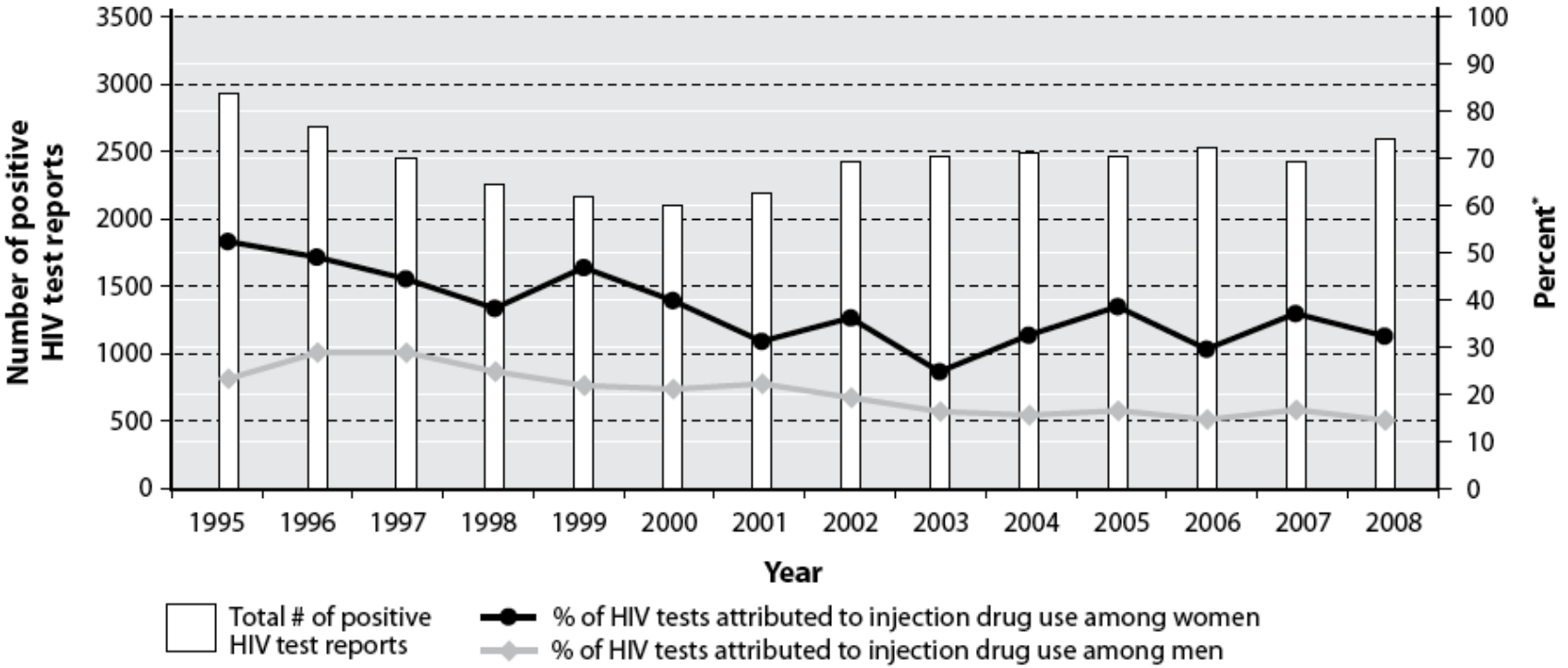
Prevalence of HCV among HIV seropositives



Remis R. Health Canada Report, 2001.

IDU and HIV

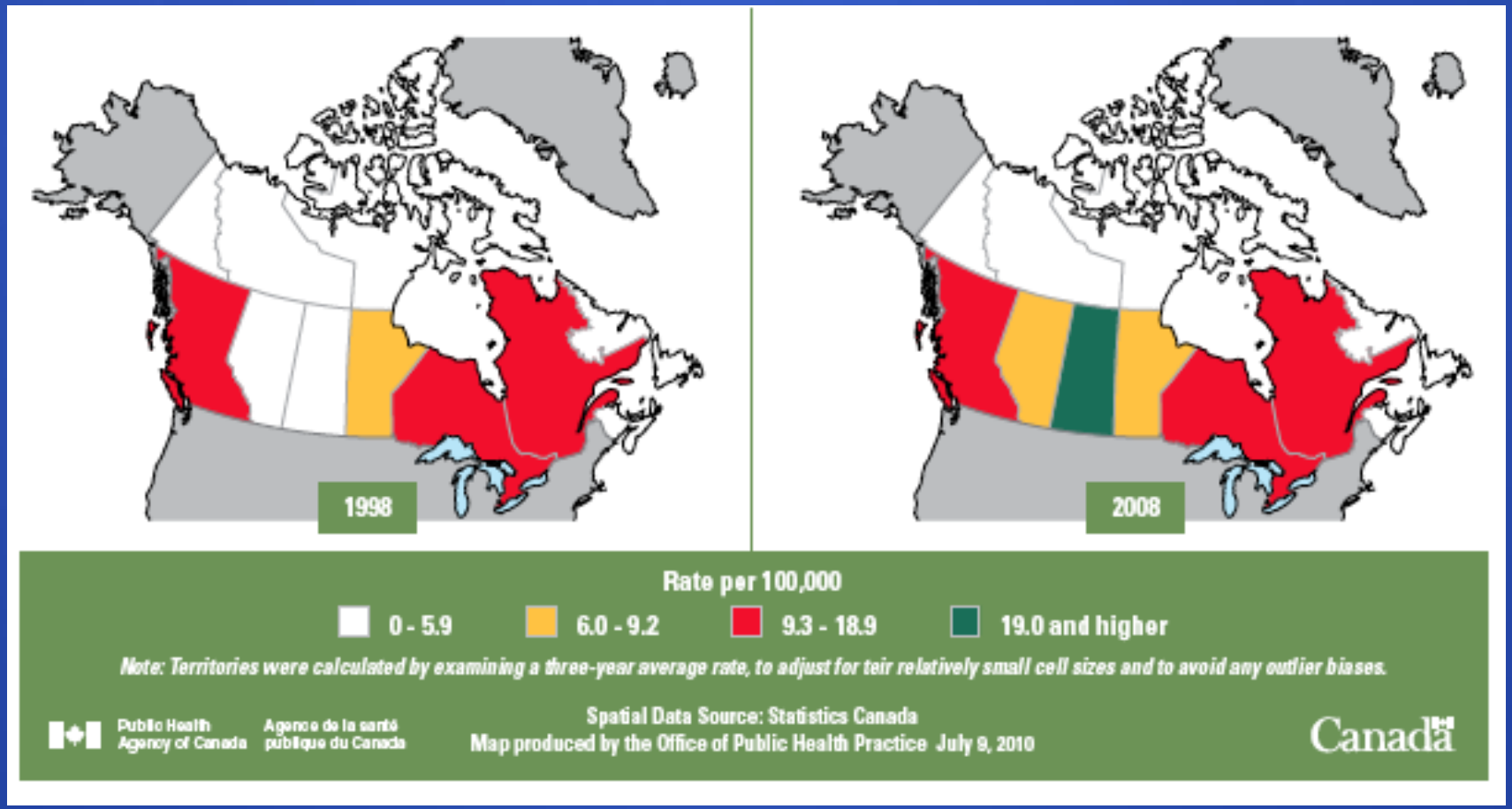
Figure 1. Total number of positive HIV test reports and proportion attributed to injection drug use in Canada, by sex, 1995-2008



Public Health Agency of Canada, 2010

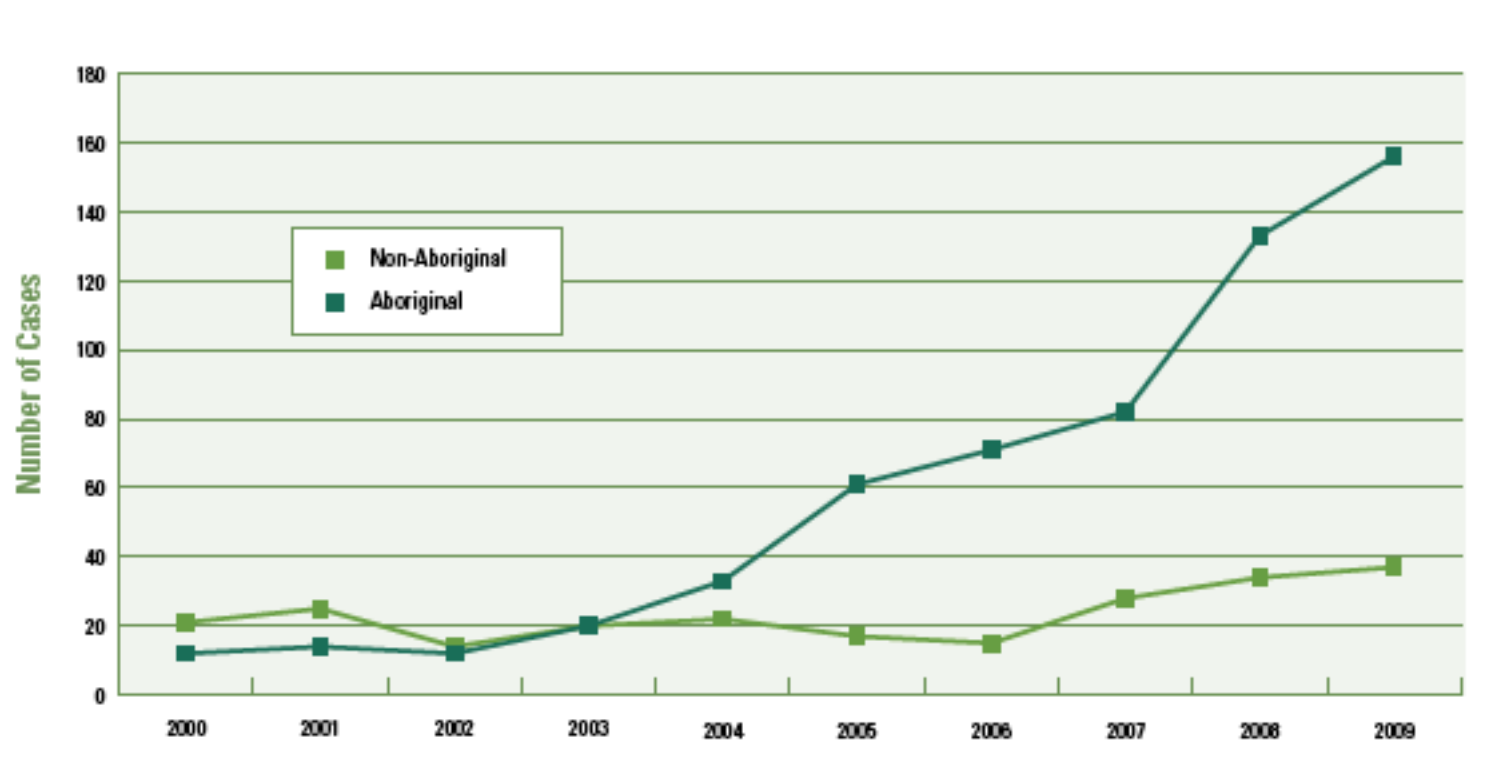
HIV Infection: Recent Trends

Rate (per 100,00 population) of Diagnoses of HIV Infection in Canada, 1998 and 2008 (both sexes, ages >= 15)



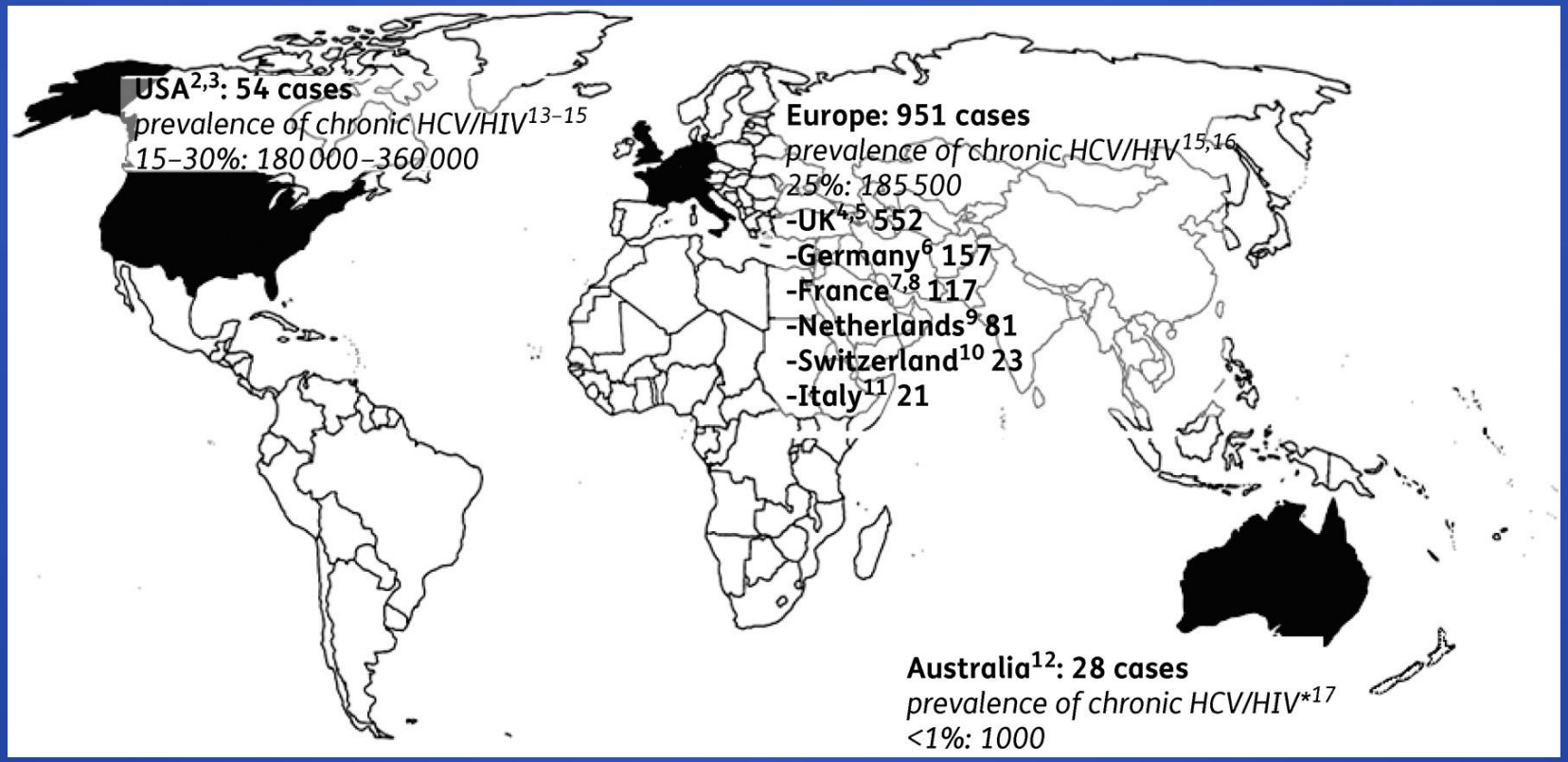
Diagnosis of HIV Infection in Canada, 1998 and 2008
Source: ©Statistics Canada & PHAC/Office of Public Health Practice, July 2010

Saskatchewan: An Emerging Epidemic



HIV Cases by Selected Self-reported Ethnicity in Saskatchewan, 2000 to 2009
Ministry on Health-PHB, 2010

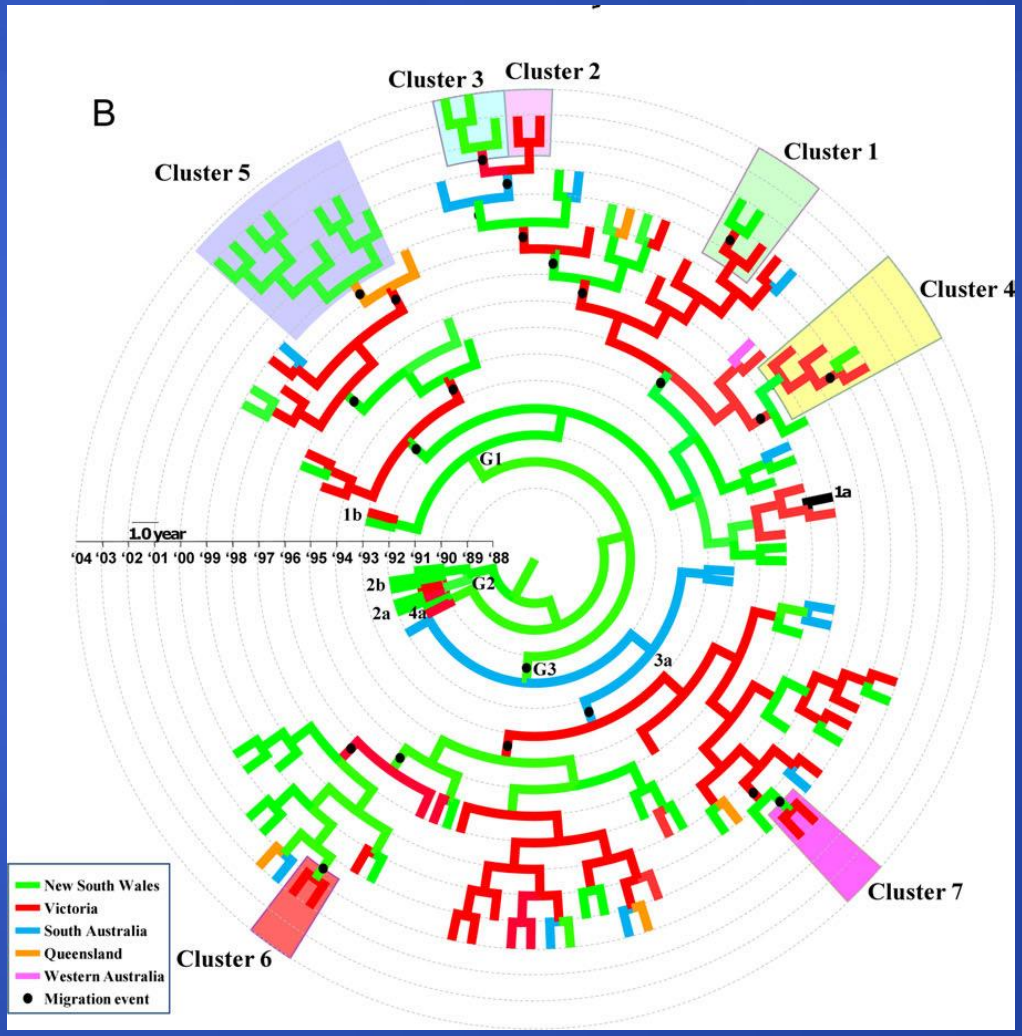
Reported cases of acute HCV infections among HIV-positive men who have sex with men and prevalence of chronic HCV/HIV infection.



Vogel, Rockstroh. *J Antimicrob Chemother*, 2010

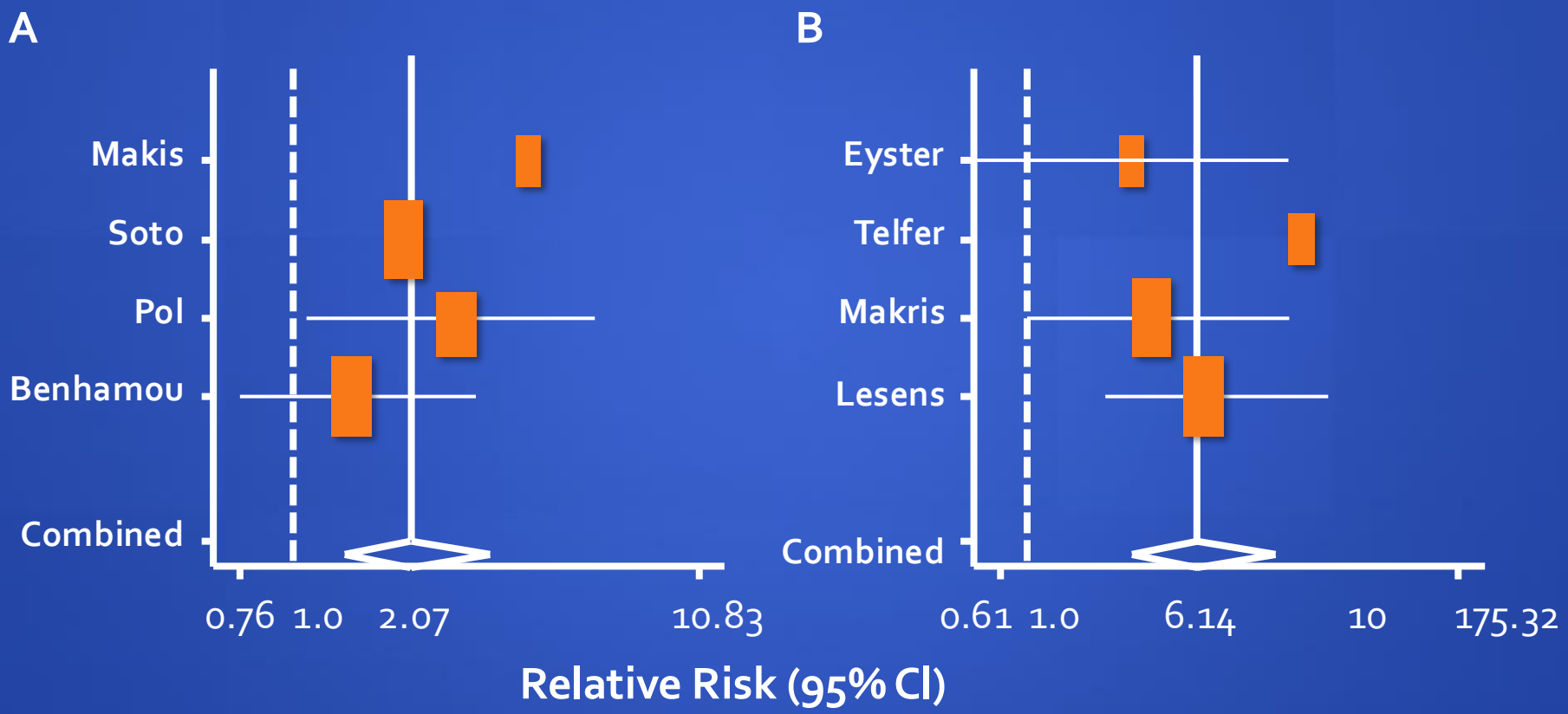
Acute HCV: Importance of Transmission networks

- IDU in 73%
- Sexual transmission in 18% of whom 92% were HIV+.



Matthews. *Clin Inf Dis*, 2011

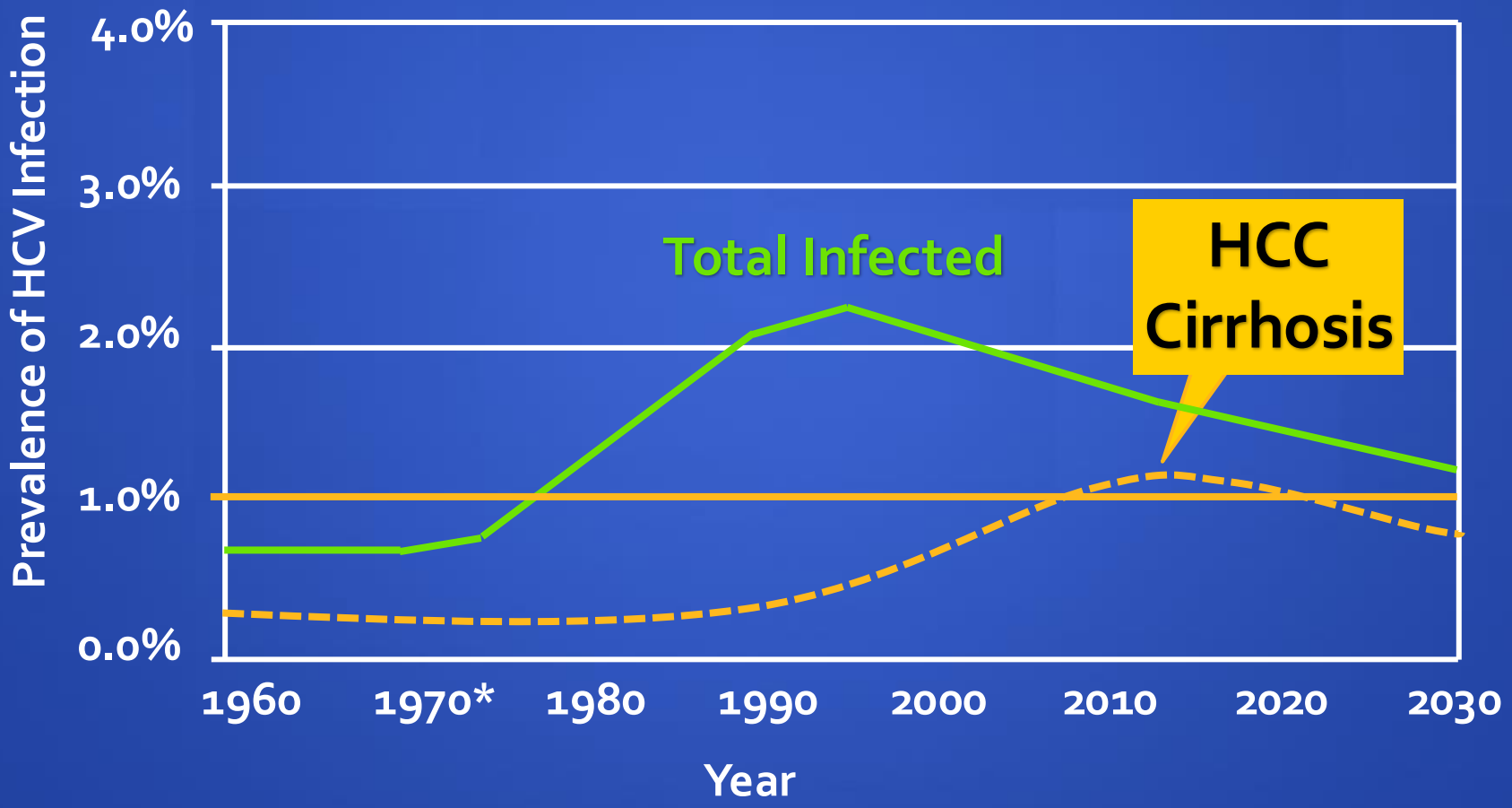
Increased Risk of Cirrhosis and ESLD in HIV/HCV-Coinfected Patients



RR of for end-stage liver disease: 2.92 (95% CI, 1.70-5.01).

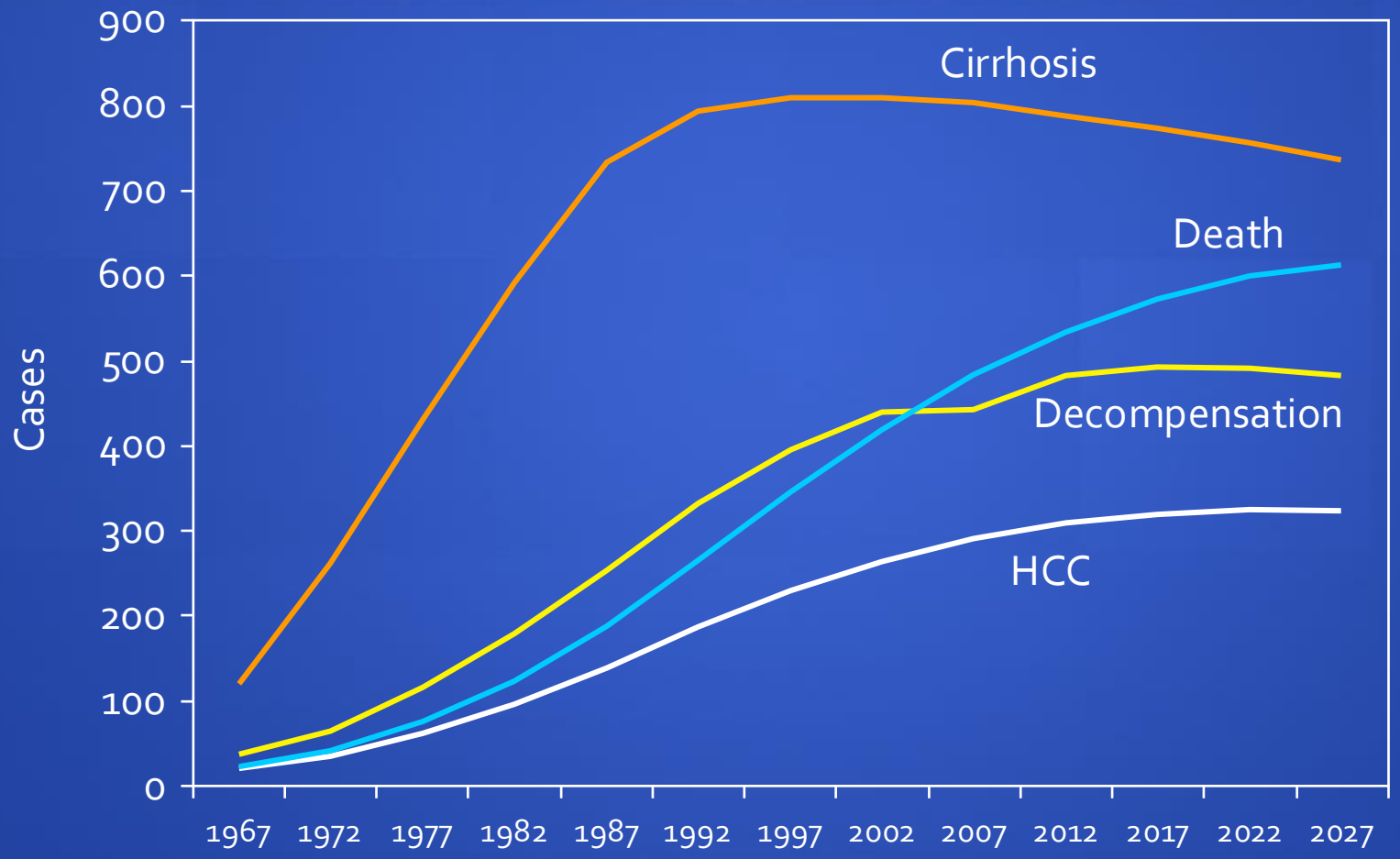
Graham et al. *Clin Infect Dis*, 2001

Predicted Future Prevalence of HCV in the United States



Armstrong et al. *Hepatology*, 2000

Projected liver-related outcomes: Population 242,521

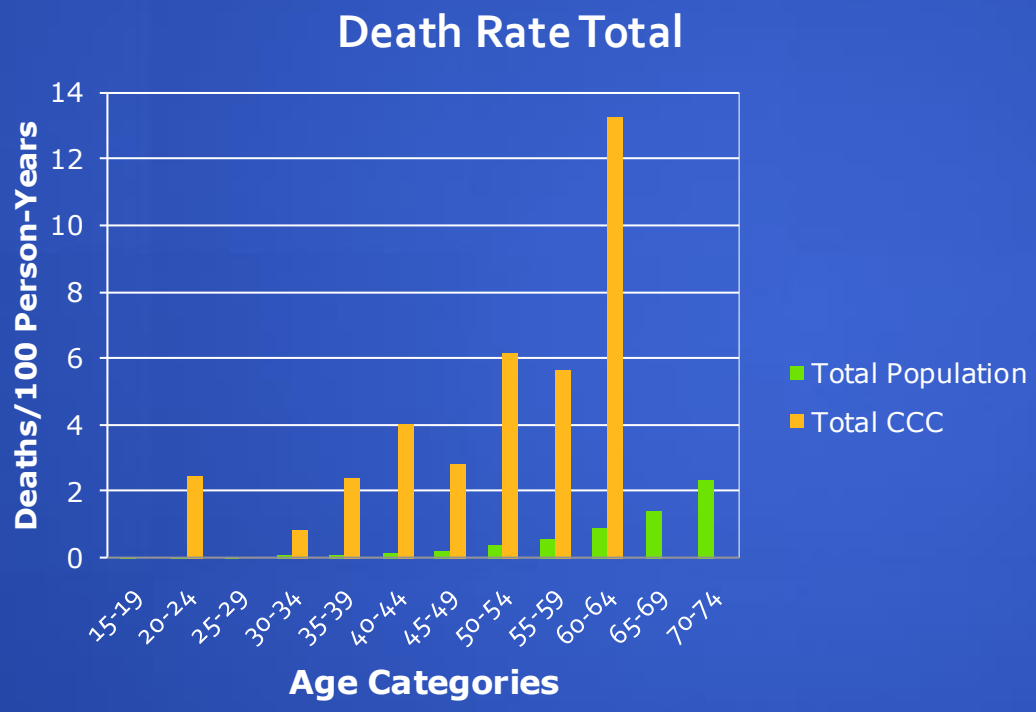


Remis R. *Public Health Agency of Canada*, 2007

Study Setting: The Canadian Co-infection Cohort

- Multi-site prospective cohort of HIV-infected persons with chronic HCV infection or evidence of HCV exposure
- Between 2003 and the end of 2012, 1020 persons were enrolled from 16 sites
- Participants fill out a questionnaire and provide blood for laboratory analysis
- Follow-up visits take place every 6 months

Mortality in the Canadian Co-infection Cohort Study



Cause of death	N	%
ESLD	18	29
OVERDOSE	15	24
CANCER	6	10
AIDS	3	5
OTHERS (infections/trauma)	9	15
UNKNOWN	11	18
Total	62	100

SMR: 17.08 (95% CI; 12.83, 21.34)

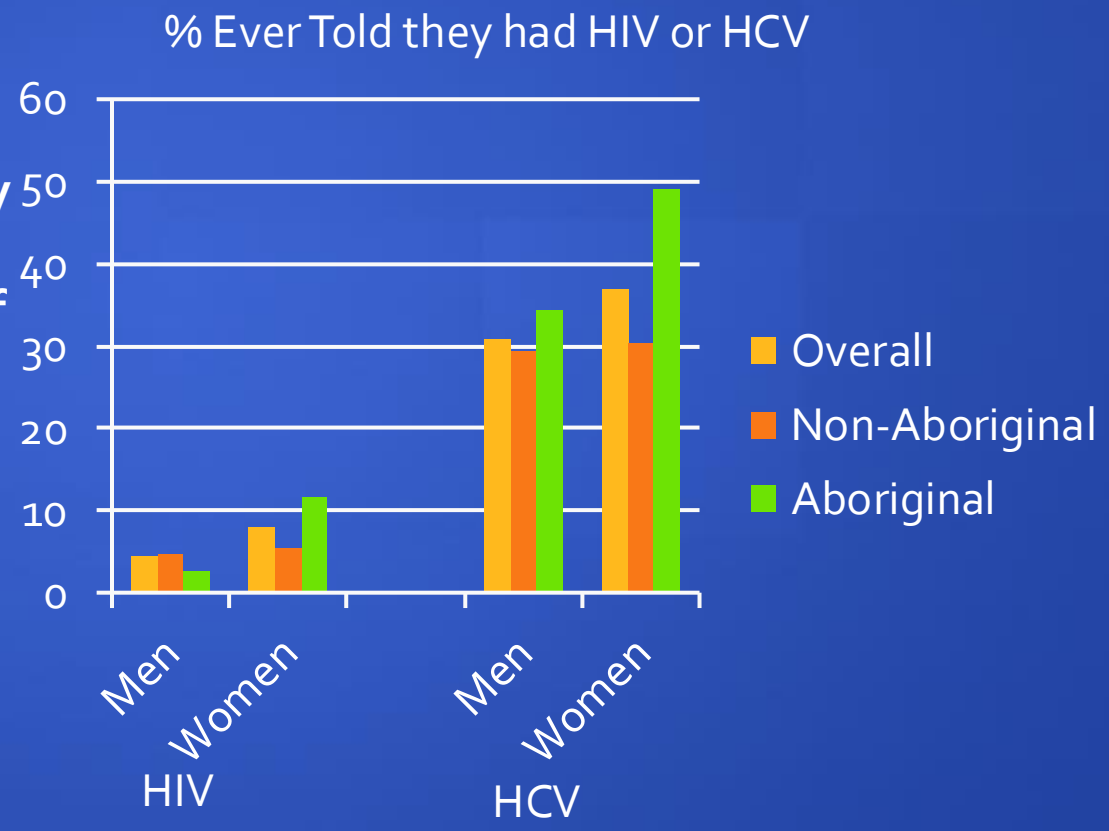
Klein. *HIV Medicine*, 2012

How to reduce burden of HCV in HIV infected persons?

- Testing
  - Estimates that in US only 30% of chronic HCV are aware of their infection;
  - Among HIV infected persons this is probably much lower as routine screening for HCV is recommended
- Harm reduction, counselling and services
- Safe injection and infection control practices
- Need to increase general knowledge among patients and physicians and referral to HCV care and services as HCV is often not prioritized
- Treatment
  - Clear evidence that successful HCV treatment leads to reduced disease burden (e.g. Reduces rates of cirrhosis, ESLD and HCC)
  - ? Treatment as prevention

High Rates among incarcerated Populations

- Among those ever tested for HCV, 31% reported being positive
- This self-reported rate of HCV infection is approximately 39 times greater than the rate of 0.7% in the Canadian population
- Aboriginal women reported the highest rate: 49%, more than 50% greater than the rates among non-Aboriginal women (30%) and all men (30.8%)



A minority of co-infected patients initiate treatment

US:

Overall only 20% initiate treatment in the HOPS cohort

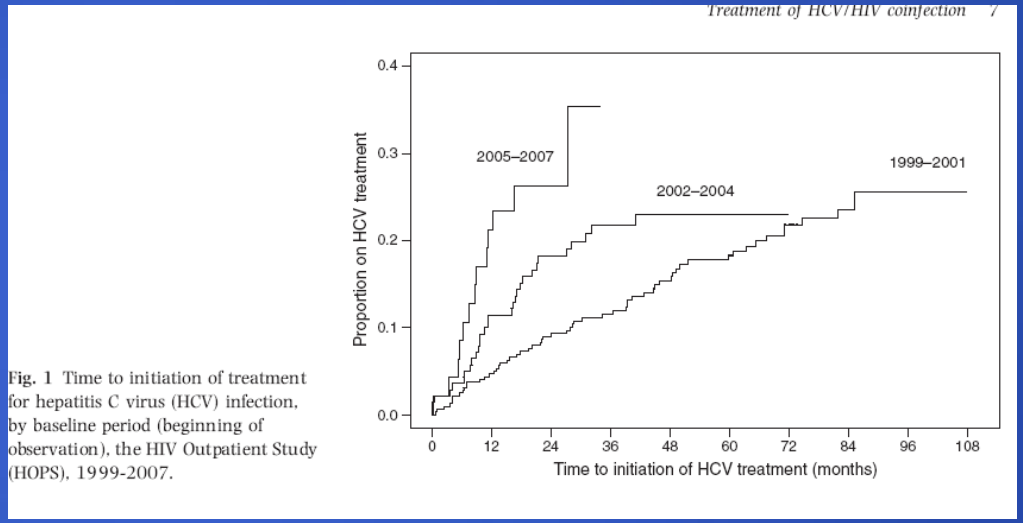


Fig. 1 Time to initiation of treatment for hepatitis C virus (HCV) infection, by baseline period (beginning of observation), the HIV Outpatient Study (HOPS), 1999-2007.

Canada:

- 1.1% (15 of 1360) initiated treatment for HCV from January 2000 to December 2004 in a BC inner city cohort (Grebely, *J Viral Hepatitis*, 2009)
- Canadian Co-infection Cohort: 16% already treated at baseline and 13% initiate follow-up (total: 29% in 2010)

HIV-HCV Epidemiology: Summary

- Co-infection infection occurs worldwide
- In Canada, HCV is strongly associated with IDU and the correctional system especially in aboriginals
- Newly identified risk among high risk MSM especially HIV+
- Looming epidemic of ESLD and liver related death
- Reducing the burden of HCV related morbidity and mortality will require enhanced testing, referral for evaluation and HCV treatment initiation

Management of HIV infection in HIV/HCV co-infected patients

Mark Hull, MD, MHSc, FRCPC
Division of AIDS
University of British Columbia

Objectives

- Review the effects of antiretroviral therapy (cART) on HCV natural history
- ART regimen choice in co-infected patients:
  - Risk of hepatotoxicity
  - Amelioration of hepatic fibrosis
  - Drug-drug interactions with HCV therapy

Introduction

- HIV co-infection negatively affects HCV disease progression:
  - Decreased rates of spontaneous clearance in those with pre-existing HIV
    - ~10% will clear acute infection
  - Higher HCV viral loads, regardless of genotype
    - Impacts treatment response to pegylated interferon and ribavirin dual combination regimens

Thomas et al. JAMA 2000.
Sherman et al. J Clin Microbiol,1993.

Introduction

- HIV co-infection negatively affects HCV disease progression:
- Faster progression to cirrhosis in individuals with untreated HIV infection
  - Mean estimated interval to cirrhosis as short as 6.9 yrs vs. 23.2 yrs
- This translates into higher risk of complications
  - Meta-analysis of 8 studies found co-infection had increased risk of 6.14 for decompensated liver disease

Soto et al. J Hepatol, 1997.
Graham et al. CID, 2001.

Introduction

- Management of HIV infection requires consideration of :
- 1. Effects of antiretroviral therapy (ART) on HCV disease progression
  - Early initiation of ART may be necessary
- 2. Optimizing ART regimen selection
  - Risk of hepatotoxicity
  - Potential effects on fibrosis progression
  - Drug-drug interactions with HCV therapeutic agents

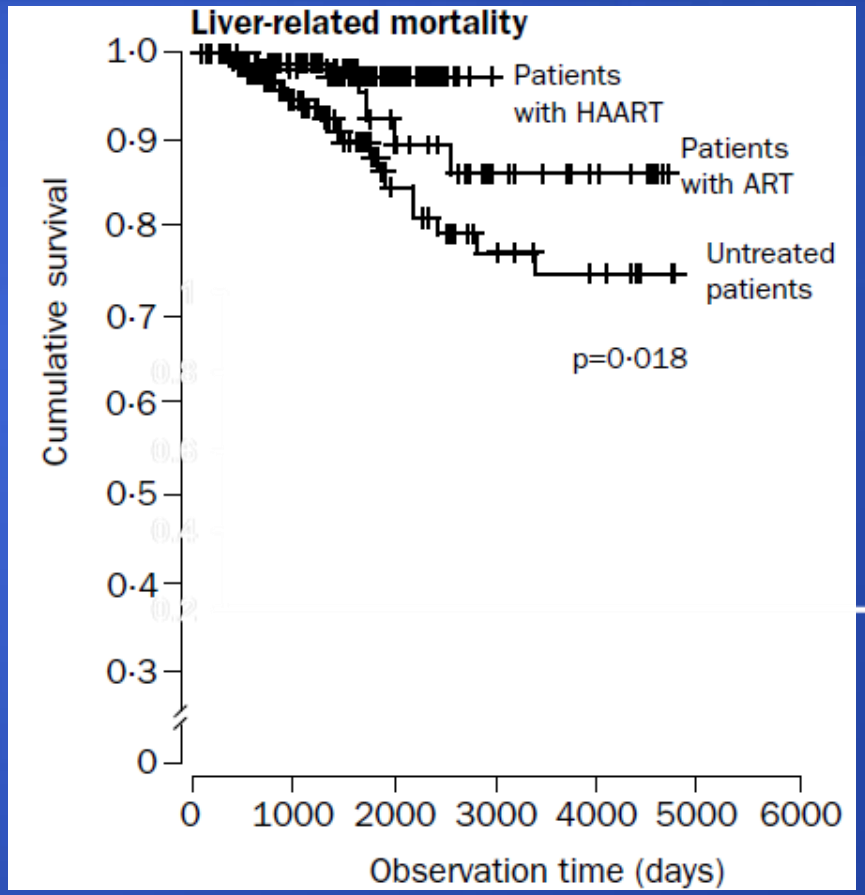
Effects of cART on HCV disease progression

- Control of HIV viremia may lead to slower rates of fibrosis progression
  - Co-infected individuals undergoing liver biopsy with HIV viral load (pVL) >400 copies/mL had faster fibrosis progression rates than those with pVL <400 copies/mL
  - Duration of cART-related pVL suppression associated with decreased hepatic fibrosis

Brau et al. J Hepatol, 2006.
Tural et al. J Viral Hepatitis, 2003.

cART decreases HCV liver-related mortality

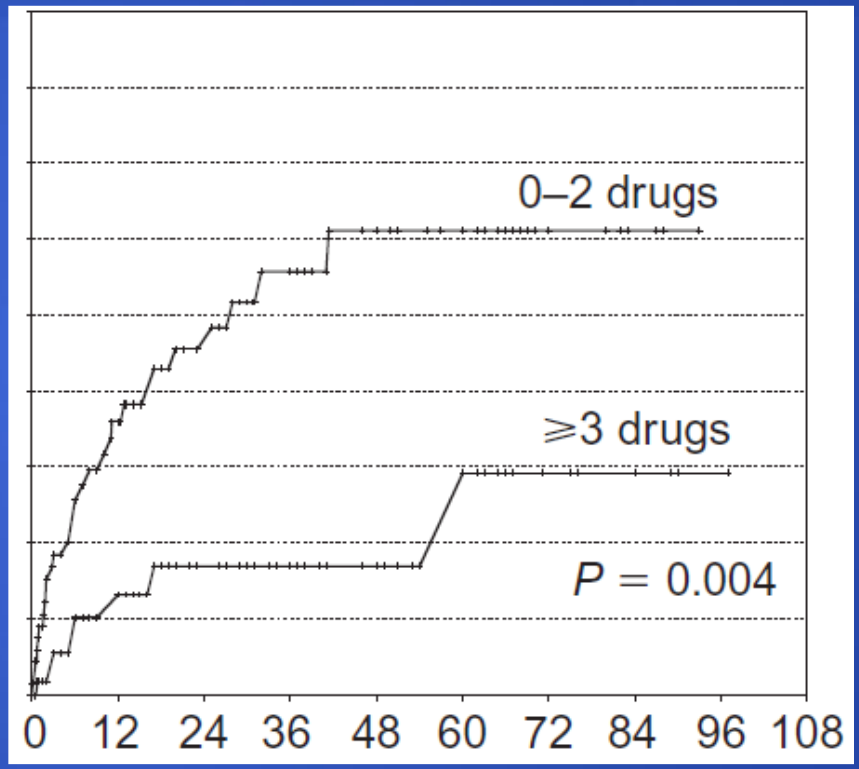
- Bonn cohort (1990-2002)
  - 285 HIV-HCV co-infected patients
  - 93 received cART (HAART), 55 dual nucleosides (ART) and 137 received no ARVs
  - Liver-related mortality rates per 100 person-years
  - cART: 0.45
  - Dual therapy: 0.69
  - No therapy: 1.70



Qurishi et al. Lancet 2003.

cART decreases liver-related mortality

- Prospective cohort of 472 HIV-infected patients
  - 72 HBV+, 256 HCV+
  - 8343 patient-months of followup
  - 41% of overall mortality due to liver-related deaths
- Use of 0-2 ART agents vs. cART associated with liver-related mortality (Relative Risk 2.9, 95% CI 1.3 – 6.7)

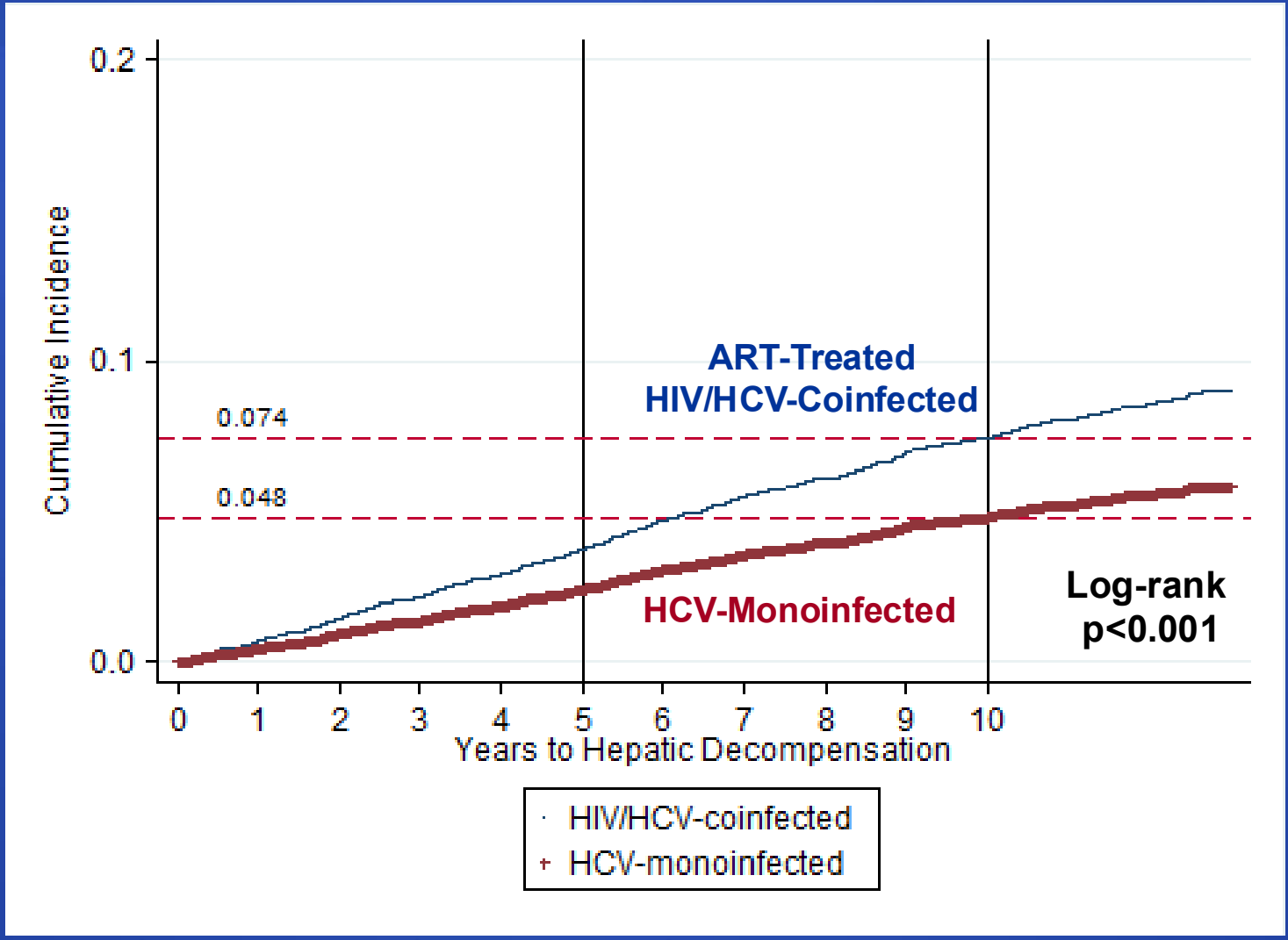


Multivariate analysis of factors associated with liver mortality: protective effect of cART

Bonacini et al. AIDS, 2004.

	IAS-USA Guidelines 2012	US DHHS Guidelines 2012	British HIV Association Guidelines 2012	European AIDS Clinical Society Guidelines 2012
HCV co-infection	ART regardless of CD_4 cell count	ART regardless of CD_4 cell count	ART if CD_4 < 500 cells/mL	ART if CD_4 < 500 cells/mL >500 – consider if HCV therapy not feasible
Grade of evidence	BIIa	BII	IC	

Incidence of Hepatic Decompensation despite cART



* Based on competing risk regression analysis.

Lo Re. IAS 2012. Abstract WEAB0102

Antiretroviral therapy-related hepatotoxicity

- Initiation of cART is associated with increased risk of hepatotoxicity in co-infected individuals.
  - The incidence of Grade 3 or 4 hepatotoxicity has been estimated to be between 2-18% in observational studies
  - Additional risk factors include alcohol or substance use, older age and in some studies genotype 3 HCV

Nunez. Hepatology, 2010.
Nunez et al. JAIDS, 2002.

Mechanisms of liver toxicity

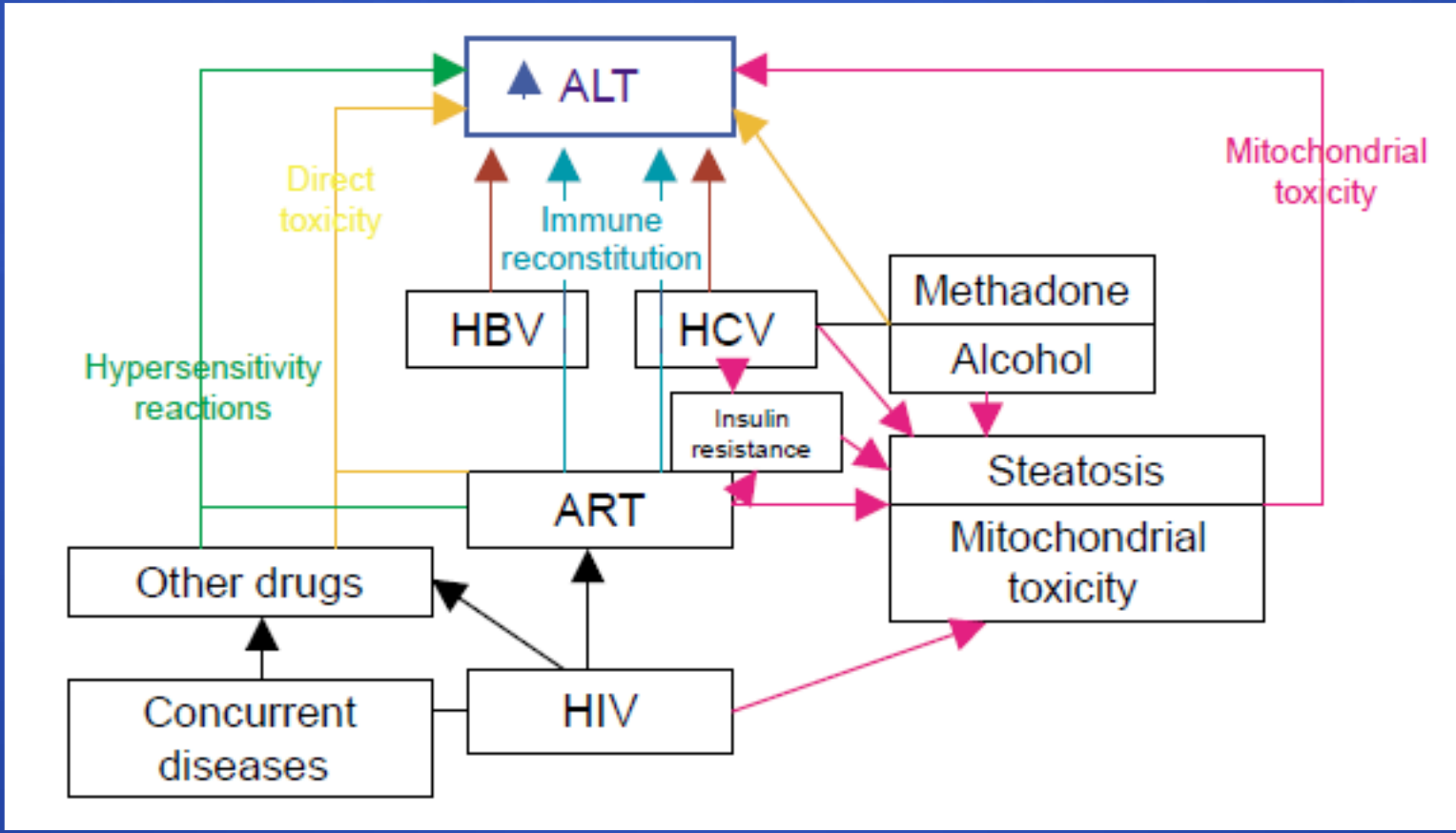


Figure from Nunez. J Hepatology, 2006.

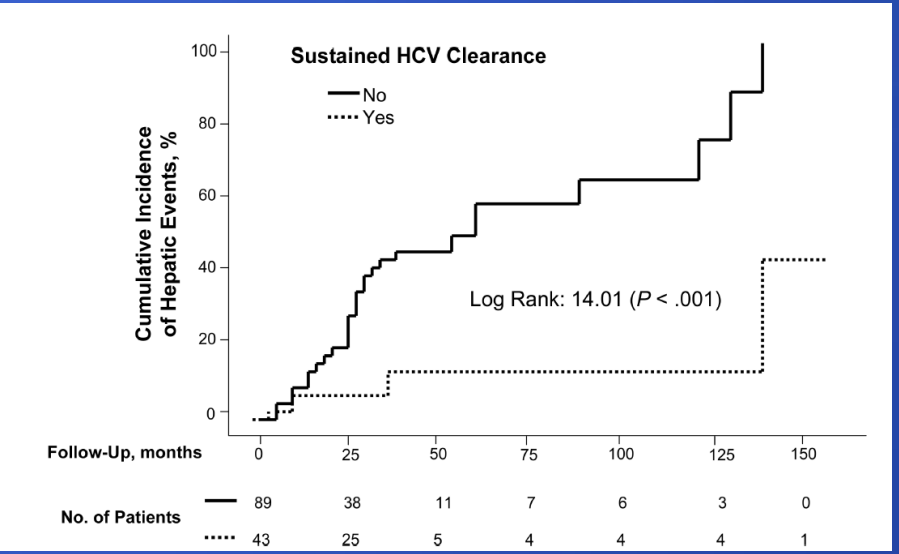
Antiretroviral therapy-related hepatotoxicity

- Most reports of hepatotoxicity originate in the early cART era (1996-2002)
- Early protease inhibitors associated with risk of hepatotoxicity
  - In particular high-dose ritonavir
- Nevirapine > efavirenz

Sulkowski et al. JAMA, 2000.
Aceti et al. JAIDS, 2002.
Sulkowski et al. Hepatology, 2002.
Martin-Carbonero et al. HIV Clin Trials, 2003.

Antiretroviral therapy-related hepatotoxicity

- Successful HCV therapy associated with decreased risk of subsequent ART hepatotoxicity
- Cohort of 132 co-infected individuals
- 33% achieved SVR
- Lower yearly incidence of hepatotoxicity in those with SVR (3.1% vs. 12.9%)



Labarga et al. JID, 2007.

Current antiretroviral regimens in co-infected patients

- Current first and second line regimens appear well-tolerated in HCV co-infected patients
  - Atazanavir/ritonavir
  - Raltegravir
  - Rilpivirine
  - Etravirine
  - Darunavir/ritonavir

Absalon et al. J Int AIDS Soc, 2008.
Rockstroh et al. ICAAC, 2012 Abstract 1297.
Nelson et al. JAC, 2012.
Clotet et al. JAC, 2010.
Rachlis et al. HIV Clin Trials, 2007.

cART and HCV therapy

- DDI:
  - increased risk of mitochondrial toxicity
  - Increased risk of hepatic decompensation if cirrhotic
- D4T:
  - increased risks of mitochondrial toxicity/lactic acidosis while on ribavirin
- AZT:
  - increased risk of anemia
  - Concomitant need for ribavirin dose reduction
  - Decreased SVR

Alvarez et al. J Viral Hepatitis, 2006.
Fleischer et al. Clin Infect Dis, 2004.
Bani-Sadr et al. J Infect Dis, 2008.

cART and HCV therapy

- Abacavir: ? interaction with ribavirin with lower HCV SVR
  - Retrospective review of the RIBAVIC trial: OR 4.92 (95% CI 1.50-16.06) for lower EVR
  - Not seen in analyses of SVR in a cohort treated with weight-based dosing

Bani-Sadr et al. JAIDS, 2007.
Laufer et al. Antiviral Therapy, 2008.

cART and HCV PI interactions

ARV	Telaprevir	Boceprevir
Raltegravir	↔	↔
Efavirenz	↓ Telaprevir AUC Needs dose of 1125mg q8hr	↓ 20% BOC AUC/Cmin
Atazanavir/r	↓ 20% TPV AUC ↑17% ATV AUC	↓35% ATV AUC
Lopinavir/r	↓54% TPV AUC	↓45% BOC AUC ↓34% LPV AUC
Darunavir/r	↓ 35% TPV AUC ↓40% DRV AUC	↓32% BOC AUC ↓44% DRV AUC

Novel considerations for cART choice in co-infection

- Potential decrease in fibrosis progression with switch from PI to raltegravir
  - Ongoing clinical trial
    - ClinicalTrials.gov identifier: NCT01231685
- Maraviroc may modulate chemokine pathways associated with fibrosis
  - Preliminary studies underway

Macias et al. Eur J Clin Microbiol Infect Dis, 2012.
Nasta et al. IAS, 2010 Abstract WEAB0105

Conclusions

- Untreated HIV infection is associated with rapid progression of hepatic fibrosis and cirrhosis risk.
- Initiating cART may slow progression of hepatic disease
  - But increased risk for hepatic disease remains higher than mono-infected patients
- Current guidelines support early cART initiation in HIV/HCV patients
  - In those with CD_4 count >500 strong consideration should be given to HCV therapy prior to cART

Conclusions

- cART use may increase risk of hepatoxicity
  - Prior successful HCV therapy lowers this risk
- Selection of cART regimen should take into account future HCV therapy and risk of drug-drug interactions

Management of HCV in Co-Infected Patients

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Centre Hospitalier Universitaire de Québec

Management of HCV in Co-Infected Patients

- Prevention and counselling
- Baseline laboratory testing
- All patients should be considered for HCV treatment
- Treatment recommendations for HCV genotype 1 infection
- Monitoring during therapy
- Side effect management
- Resistance issues

Prevention and Counselling: What patients should be told

- Avoid alcohol
- Maintain healthy diet and weight
- Use precautions to prevent transmission of HCV (and HIV) to others and reinfection
- Get vaccinated against hepatitis A virus (HAV) and hepatitis B virus (HBV) if susceptible
- Give a complete list of medications, vitamins, supplements and herbs you are currently taking to your doctor

Baseline Laboratory Testing

- Virological tests to confirm and type HCV infection
  - Anti-HCV
  - HCV RNA
  - HCV genotype
- Baseline blood tests
  - CBC with differential
  - CD4/CD8 counts
  - Liver enzymes and function tests (ALT, AST, ALP, GGT, Tot and direct bili, albumin, INR)
  - Glucose and insulin, creatinine
  - AFP
- Liver Imaging
  - Abdominal ultrasound
- Liver fibrosis assessment
  - FibroScan
  - Biomarker panel
  - Liver biopsy
- Other
  - Screen for HBV and HAV immunity
  - Tests to exclude other liver disease
  - Tests to diagnose extrahepatic manifestations of HCV
  - IL28B

FibroScan® and serum biomarkers for fibrosis assessment

- FibroScan ® (transient elastography)
  - Health Canada-approved
  - Non-invasive
  - Fast
  - Can be done during first patient's visit
  - High sensitivity to exclude cirrhosis
  - Validated in HIV/HCV co-infected patients
- Serum biomarkers
  - APRI
  - FIB-4
  - Forns index
  - others

Liver biopsy is helpful when there is discordant or indeterminate results with non-invasive techniques and to diagnose other causes of liver disease.

All patients with HIV/HCV co-infection should be considered for HCV therapy

- HCV PI in association with pegIFN and RBV has been approved for treatment of genotype 1 HCV mono-infection
- Safety and efficacy in HIV-infected patients are largely unproven and regulatory approval is pending, but preliminary data are encouraging
  - Decisions to use or withhold HCV PIs in HIV/HCV co-infected persons depend on multiple considerations
- Contraindications to pegIFN and RBV therapy apply with the use of HCV PI

Considerations prior to decision to use or withold HCV treatment

- HCV eradication is associated with decreased morbidity and mortality
  - Liver fibrosis progresses more rapidly in HIV co-infected patients
  - Priority is given to patients with advanced fibrosis and cirrhosis
- Higher success rates are achieved in patients with positive predictors of SVR
  - Consider treating patients with IL28B CC genotype, low viral load (<400 000 IU/ml), naïve or prior relapsers, even if no or low fibrosis stage
- Patient's motivation
  - Now may be a good time to treat for some patients (e.g. young woman with mild fibrosis who wishes to become pregnant in the future)
- Well-controlled HIV is desired before starting HCV treatment
  - Patients with well-controlled HIV respond better to HCV treatment and higher CD_4 counts facilitate management during HCV treatment. For patients with low CD_4 counts (<200 cells/mm^3), if possible, ART should be initiated and HCV treatment delayed until HIV RNA is undetectable and CD_4 counts have increased
- Drug-drug interactions between HCV PIs and ART should be assessed: overall limited data available
- Liver transplantation is not widely available and not highly successful in HIV co-infected
- Poor side effect profile associated with HCV PIs and new anti-HCV drugs are being developed

Treatment Options for HCV Genotype 1 Patients co-infected with HIV: DHHS Guidelines

Recommendations on use of boceprevir or telaprevir in HIV/HCV genotype 1 co-infected patients

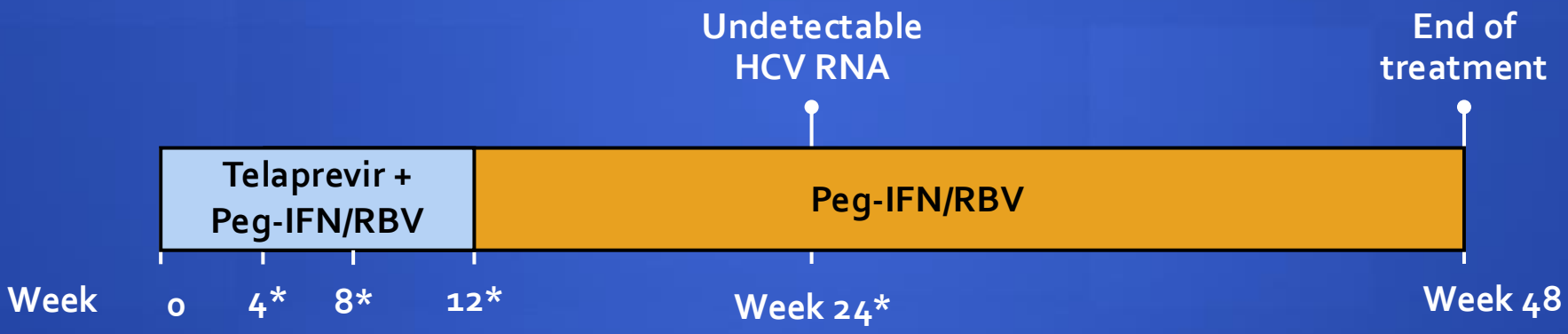
Patient Group	Recommendation*
Patients not on ART	Use either boceprevir or telaprevir
Patients receiving RAL + 2 NRTIs	Use either boceprevir or telaprevir
Patients receiving ATV/r + 2 NRTIs	Use telaprevir at the standard dose. Do not use boceprevir.
Patients receiving EFV + 2 NRTIs	Use telaprevir at increased dose of 1,125 mg every 7-9 hours. Do not use boceprevir.

*These recommendations may be modified as new drug interaction and clinical trial information become available.

DHHS Guidelines, 2012.

Proposed treatment algorithm: telaprevir in patients with HIV/HCV co-infection

Until more data are available, a 48 week treatment duration is recommended for all HIV infected patients using week 4, 12 and 24 futility rule time points, without RGT.



Peg-IFN : peginterferon; RBV : ribavirine; RGT: response-guided therapy

* Stop treatment at these timepoints because of futility in patients with HCV RNA > 1000 IU/mL at week 4 or 12 or a detectable HCV RNA at week 24.

Proposed treatment algorithm: boceprevir in patients with HIV/HCV co-infection

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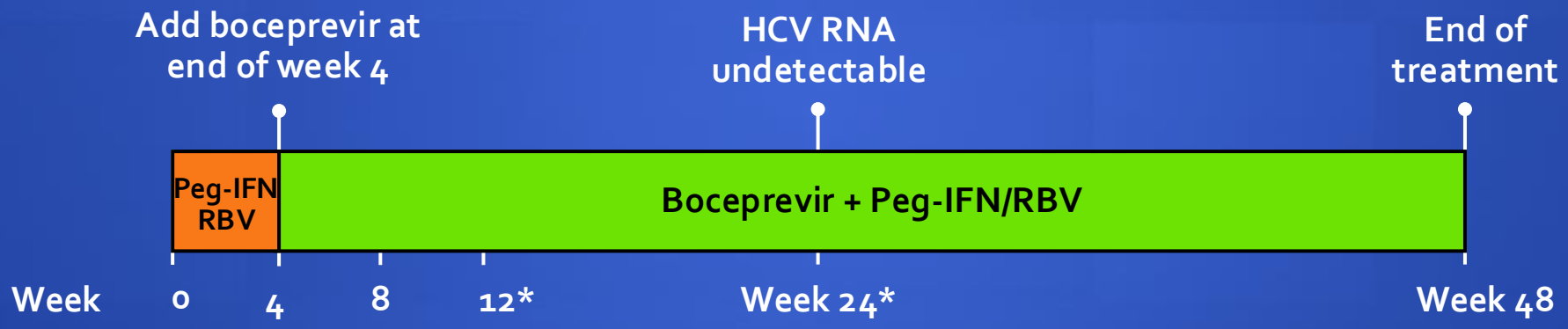


Peg-IFN : peginterferon; RBV : ribavirine; RGT: response-guided therapy

* Stop treatment at these time points because of futility in patients with HCV RNA >100 IU/ml at week 12 or a detectable HCV RNA at week 24.

Monitoring during HCV treatment

What to monitor

- HCV RNA, quantitative
- HCV RNA, qualitative
- Other laboratory tests
  - CBC with differential, liver panel, biochemistry, TSH, CD_4 cell count, HIV viral load, and AFP if cirrhotic

When to monitor

Telaprevir: Week 0,4,8, and 12
Boceprevir: Week 0 and 12

Telaprevir: Week 24 and 48
Boceprevir: Week 24 and 48

CBC weekly for the first 4 weeks of PI use, every other week until week 12 and every month thereafter. Use clinical judgement. Liver panel, CD_4 count, . biochemistry and TSH monthly.
HIV load every 4-12 weeks, AFP every 6 months if cirrhotic.

Testing during HCV treatment with telaprevir of HIV co-infected patients

Week Test	0	1-3	4	6	8	10	12	16	20	24	28-44	48
HCV RNA quant	X		X				X					
HCV RNA qual										X		X
CBC	X	X	X	X	X	X	X	X	X	X	X	X
CD4+	X		X		X		X			X	36	X
HIV RNA	X		X				X			X	36	X
Liver + bio	X		X		X		X	X	X	X	X	X
TSH	X		X		X		X	X	X	X	X	X
AFP	X									X		X

Testing during HCV treatment with boceprevir of HIV co-infected patients

Week Test	0	2	4	5-7	8	10	12	16	20	24	28-44	48
HCV RNA quant	X						X					
HCV RNA qual										X		X
CBC	X	X	X	X	X	X	X	X	X	X	X	X
CD4+	X		X		X		X			X	36	X
HIV RNA	X		X				X			X	36	X
Liver + bio	X		X		X		X	X	X	X	X	X
TSH	X		X		X		X	X	X	X	X	X
AFP	X									X		X

Side effect management

- The most frequent adverse events reported in the clinical trials are
  - Telaprevir: Rash, pruritus, anemia and ano-rectal discomfort
  - Boceprevir: Anemia and dysgueusia
- Same side effect management in co-infected as in HCV mono-infected
  - Anemia can be severe and develop rapidly
  - Ribavirin dose reduction in HCV mono-infection does not impact SVR rates

HCV Protease Inhibitors and resistance

Higher HCV viral load in HIV/HCV co-infected patients suggests higher risk for resistance development

- Patient adherence to q7-9 hours schedule of boceprevir and telaprevir
- Strict adherence to futility rules
- Boceprevir and telaprevir have the same resistance pattern. Patients who fail HCV PI therapy should not be retreated with the same or the other protease inhibitor
- Not every patient needs to be treated right away: treatment can be deferred in those with no or mild fibrosis or unmotivated patients
  - Other anti-HCV treatment classes are being evaluated in clinical trials that will be active against PI failures

Summary: Management of HCV in co-infected patients

- Baseline blood, imaging and fibrosis assessment is important to characterize HCV infection and plan HCV treatment
- PegIFN/RBV combination has low efficacy but SVR significantly increases outcomes
- Hepatitis C protease inhibitors in combination with PegIFN/RBV increase SVR
  - Phase II and III trials under way
  - Significant drug-drug interactions with ART

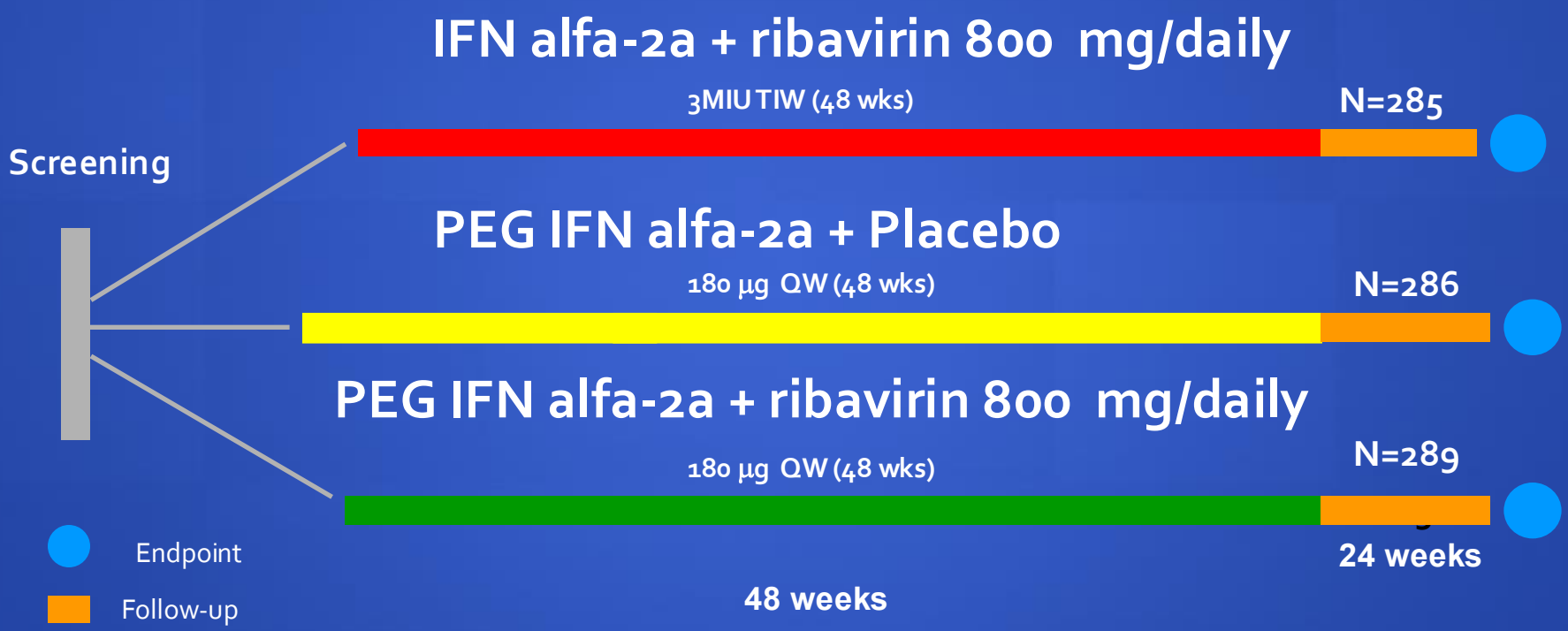
HCV Therapy: Direct Acting Antiviral Agents in Co-Infected Individuals

Curtis Cooper, MD, FRCPC
Faculty of Medicine, Division of Infectious Diseases
University of Ottawa

Key Peg-Interferon and Ribavirin Studies in HIV-HCV Co-Infection

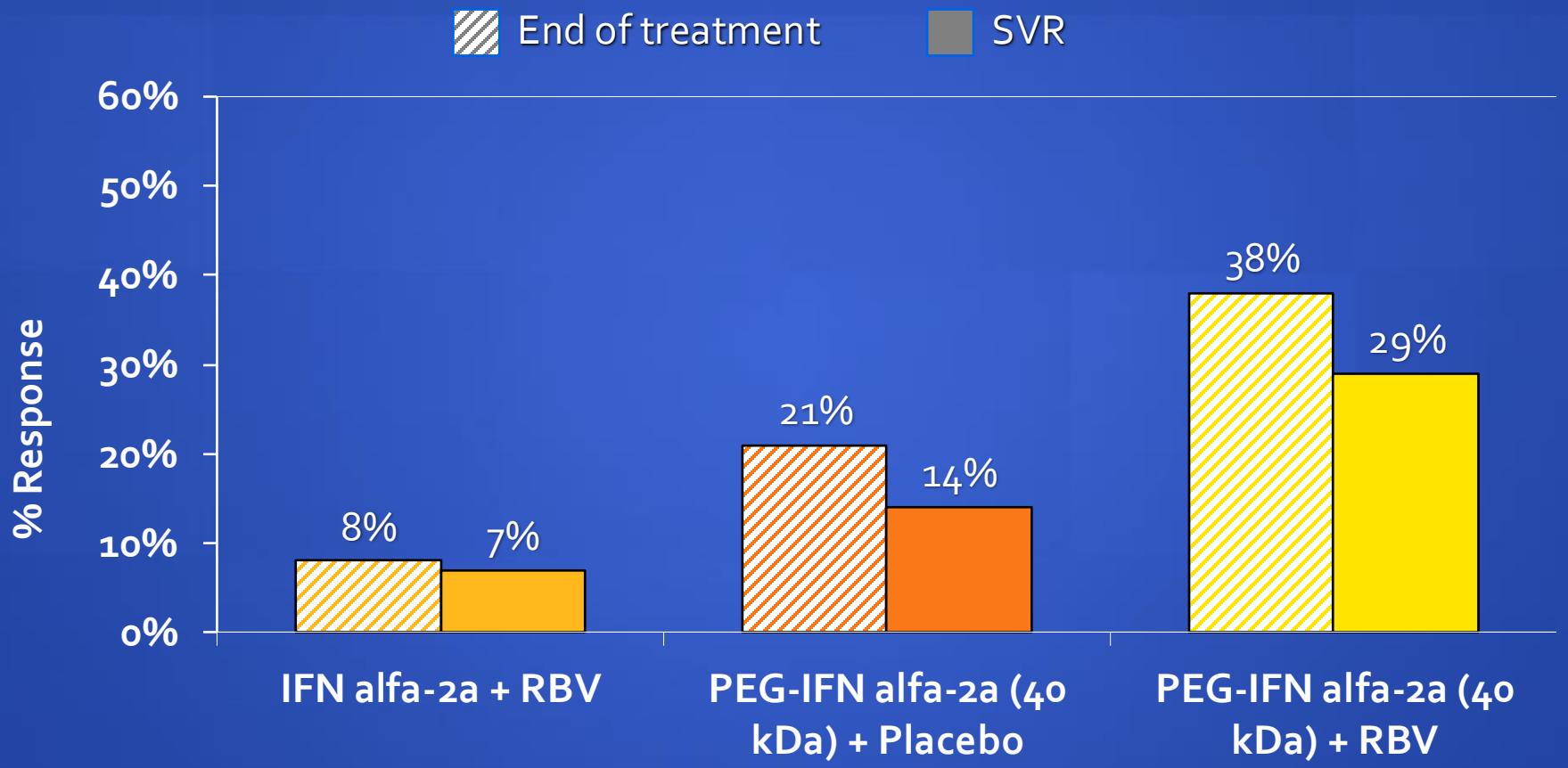
- APRICOT (Dietrich et al.)
  - 95 centers, 19 countries (Canada 33 patients)
  - Academic based
- RIBAVIC (Perrone et al.)
  - ANRS (French National Study Group)
  - Community based
- ACTG 5071 (Chung et al.)
  - US Cooperative group
  - 21 US community based sites

APRICOT (Dietrich)



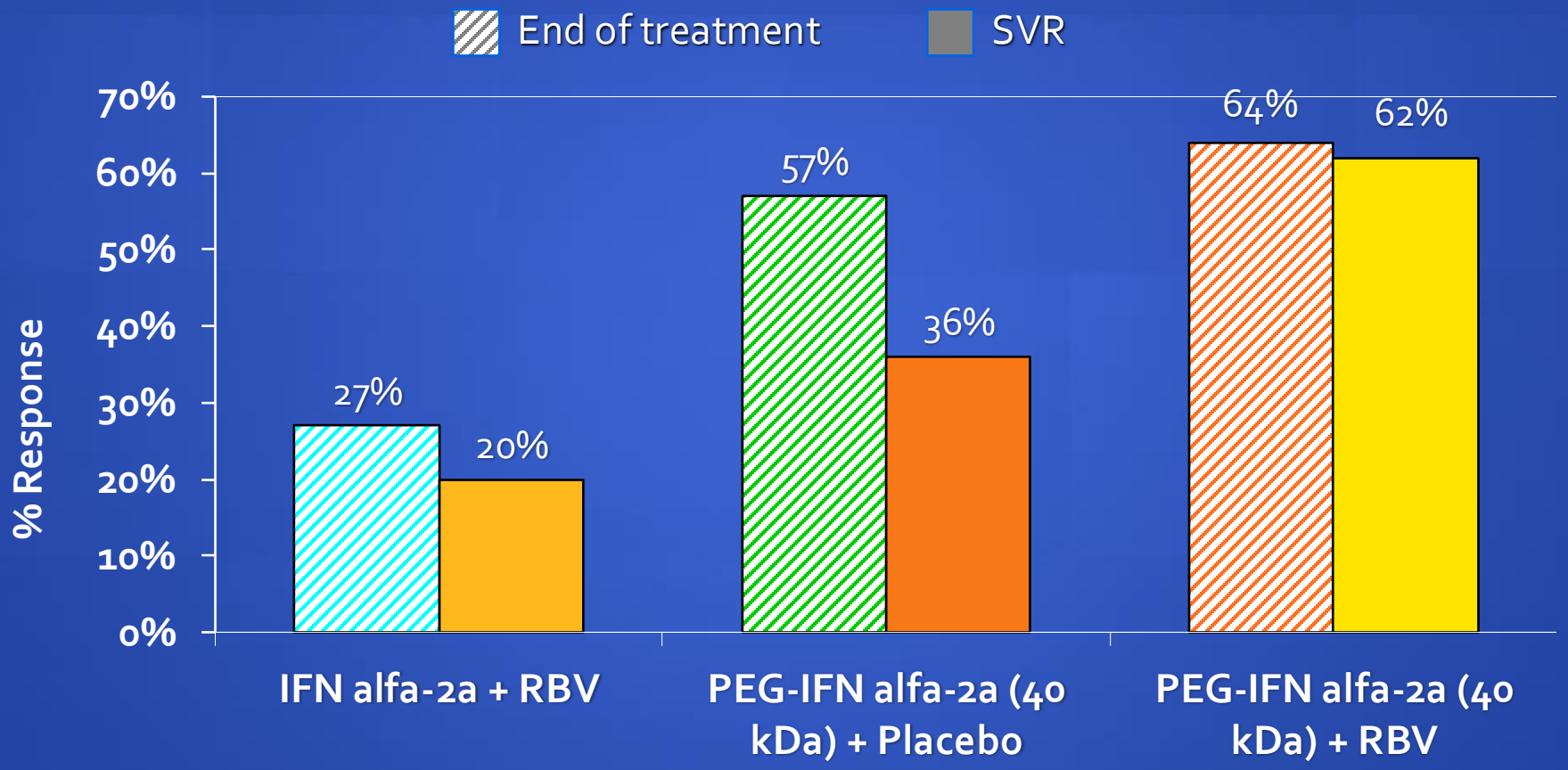
Primary endpoint: loss of serum HCV-RNA 24 weeks post-treatment.

Virologic Response* – End of Treatment vs End of Follow-up (Genotype 1)



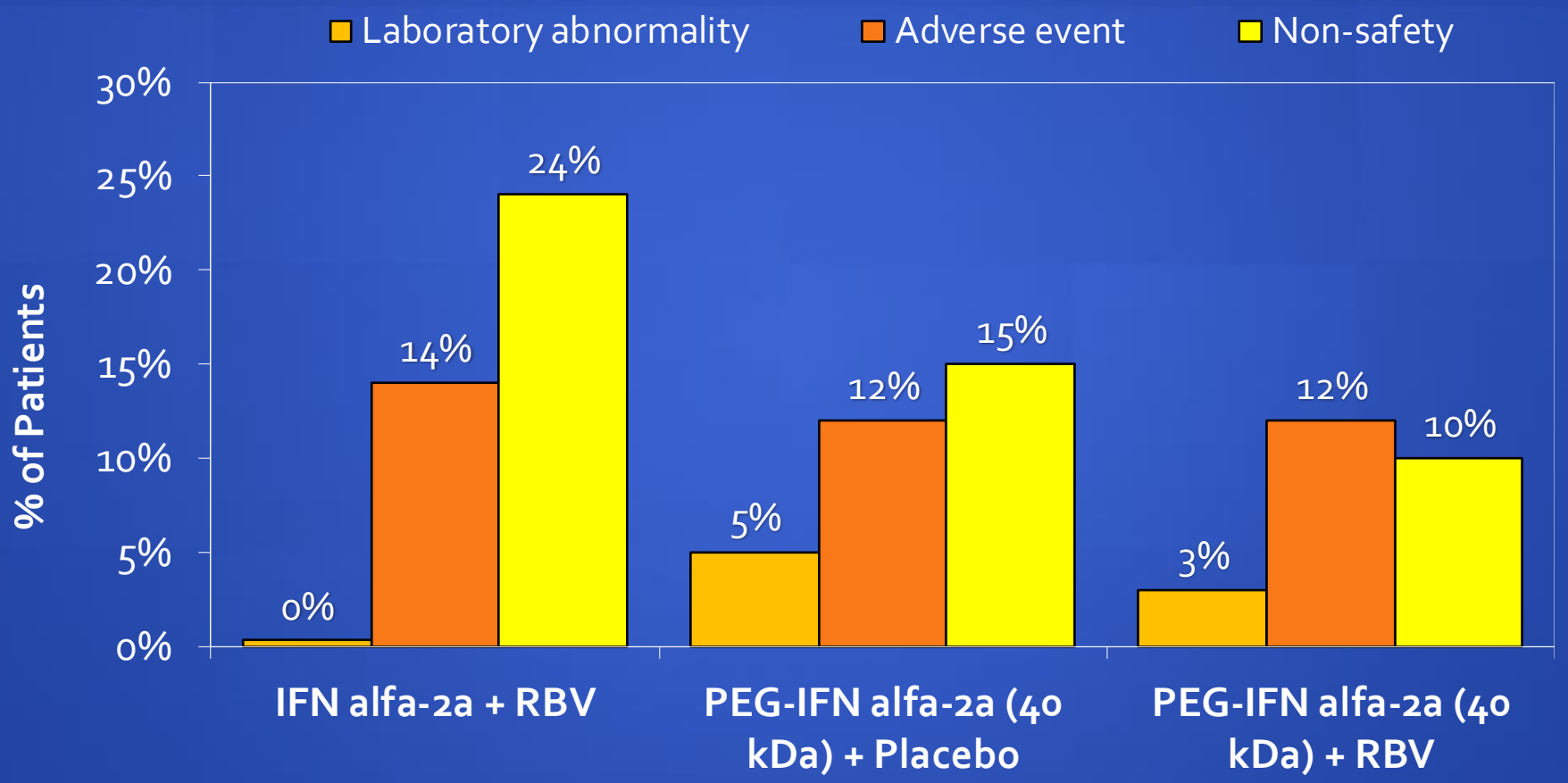
* Defined as <50 IU/mL HCV RNA

Virologic Response* – End of Treatment vs End of Follow-up (Genotype 2 and 3)

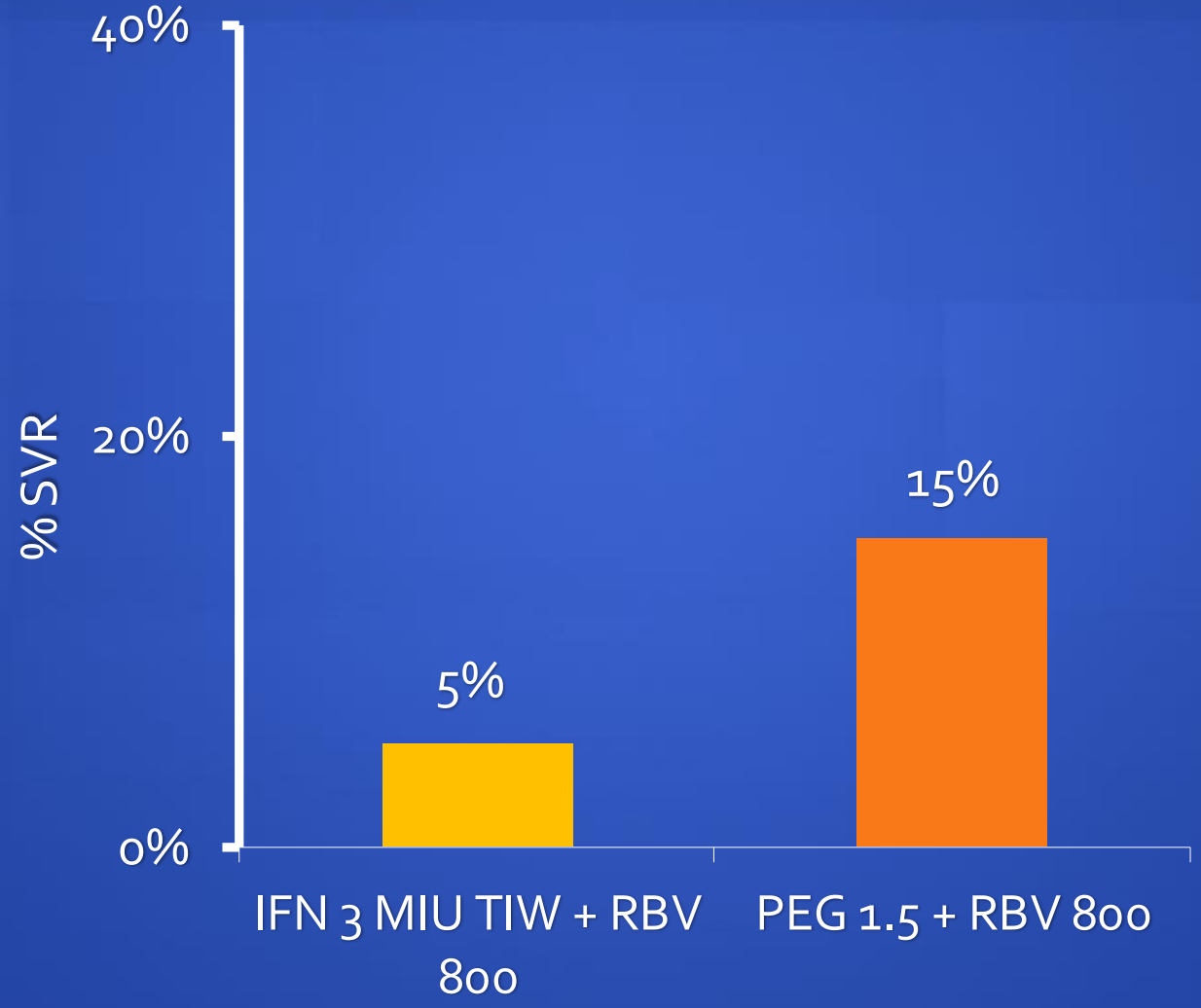


* Defined as <50 IU/mL HCV RNA

Withdrawal from Treatment



RIBAVIC:
ITT SVR Genotype 1



RIBAVIC: Safety

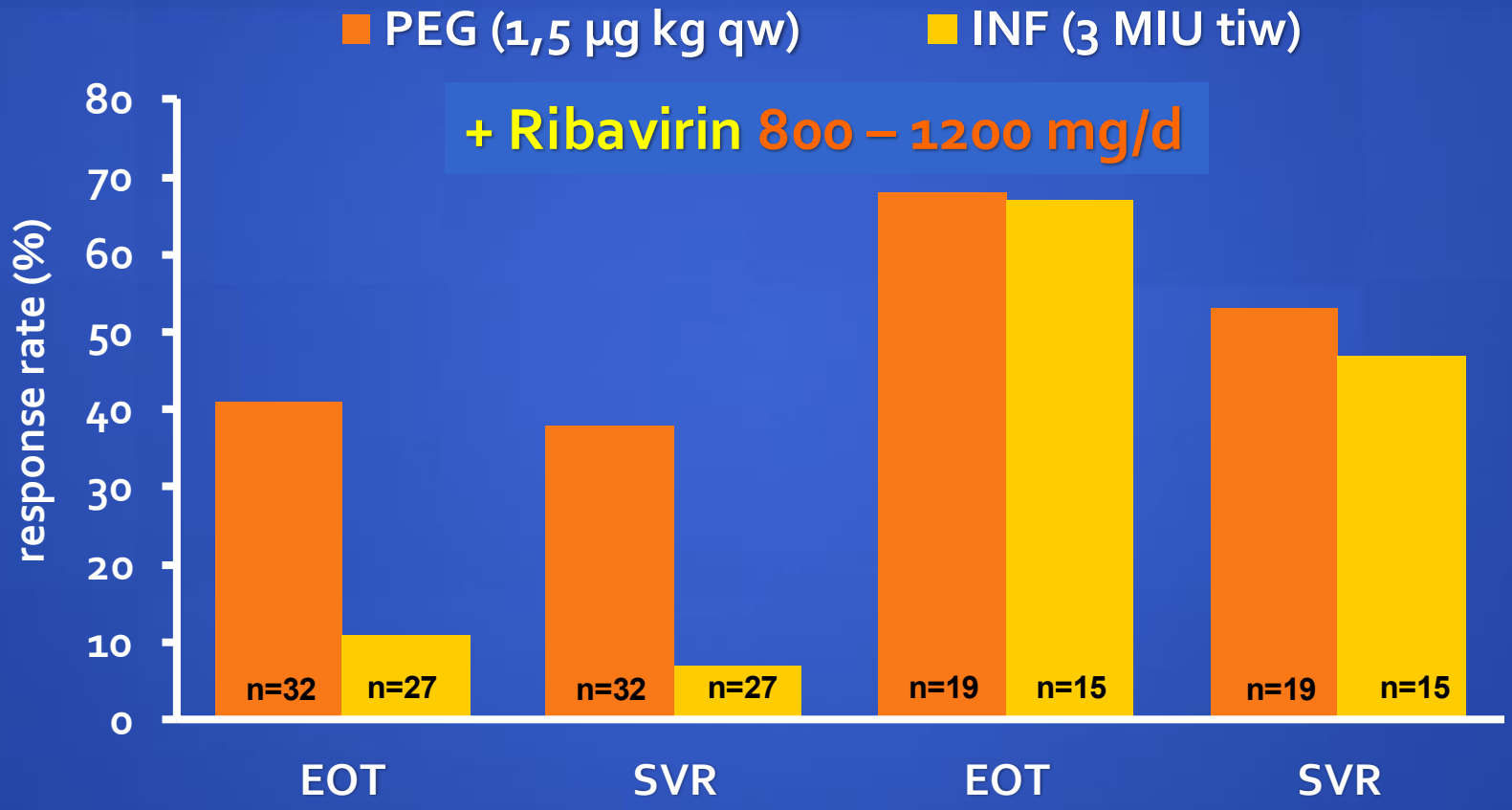
Treatment Discontinuation:

	IFN + RBV	PEG + RBV
Discontinuation	35% (n=72)	38% (n=77)

SAE:

	IFN + RBV	PEG + RBV
SAE	31% (n=64)	31% (n=63)

Improved Outcomes with Increased Ribavirin Dosing
Peginterferon α-2b vs. Interferon α-2b



HCV-genotype 1 or 4

EOT: p=0.033

SVR: p=0.007

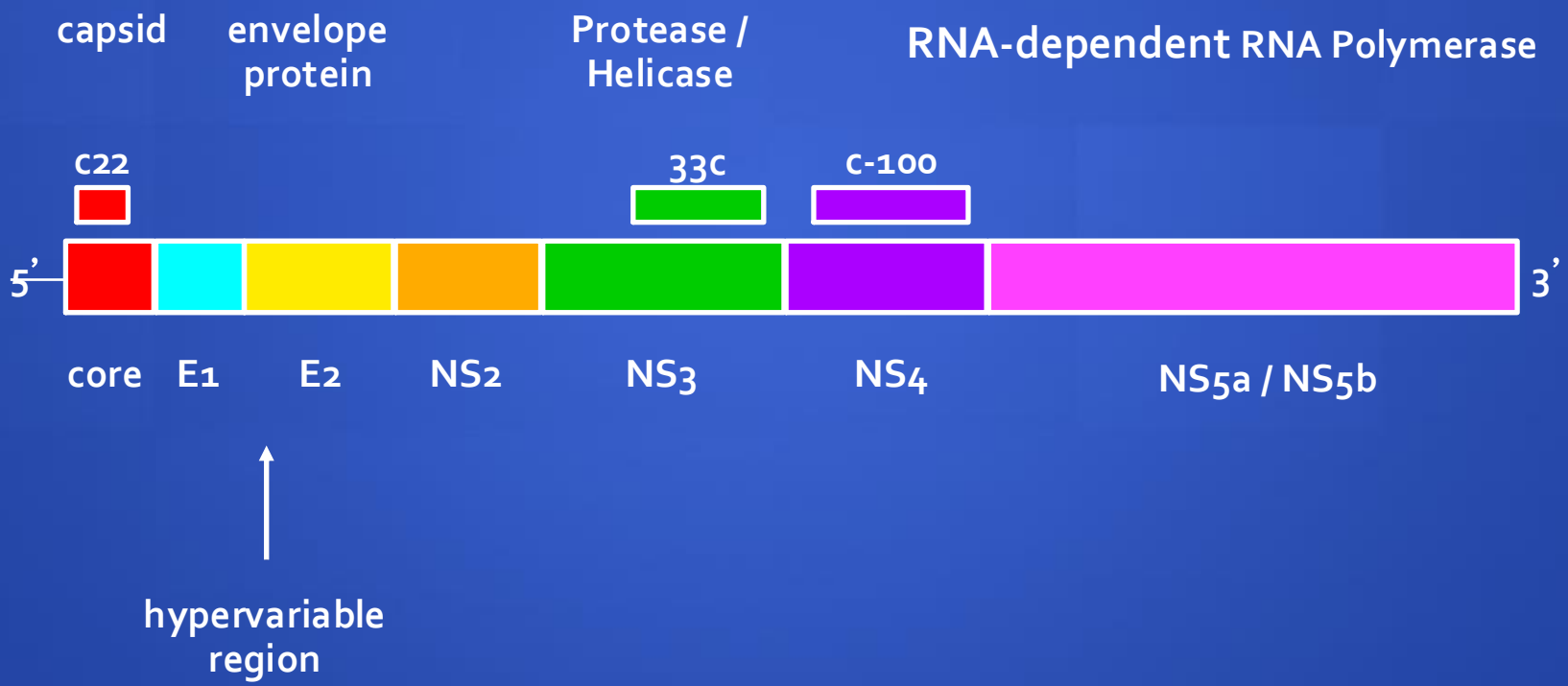
HCV-genotype 2 or 3

EOT: p=0.914

SVR: p=0.730

Laguno et al. AIDS, 2004.

Can Outcomes be Improved with the Addition of Protease Inhibitors and Other Direct Acting Antivirals?



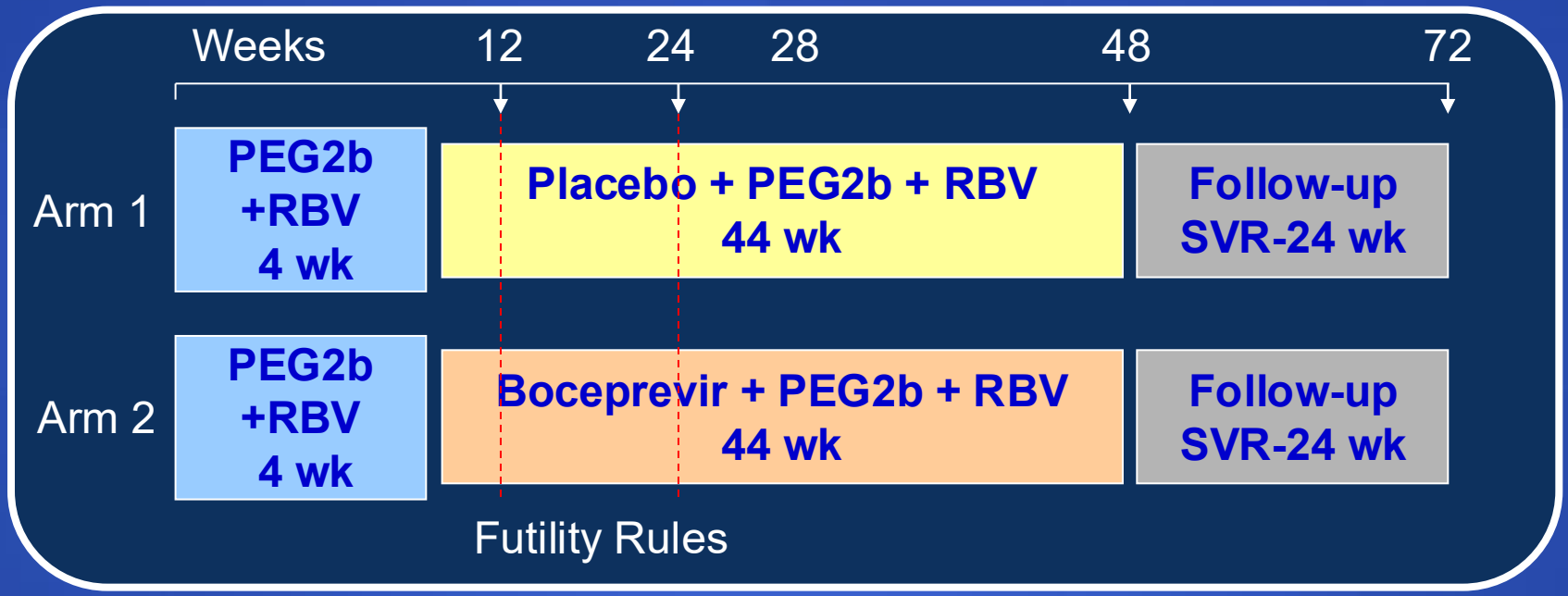
Boceprevir and Telaprevir

- Approved and funded HCV protease inhibitors for HCV genotype 1 mono-infection based on substantial improvement in SVR for treatment naïve, relapses, partial responders and null responders
- Used in combination with peginterferon alfa-2/ ribavirin

Key Phase III HCV-Mono-Infection Studies

- Boceprevir
  - SPRINT-2: naive GT1 patients
  - RESPOND-2: nonresponder GT1 patients
- Telaprevir
  - ADVANCE: naive GT1 patients
  - ILLUMINATE: response-guided therapy in naive GT1 patients

Boceprevir Plus Peginterferon/Ribavirin for the Treatment of HCV/HIV Co-Infected Patients



- Two-arm study, double-blinded for BOC, open-label for PEG2b/RBV
  - 2:1 randomization (experimental: control)
  - Boceprevir dose 800 mg TID
- 4-week lead-in with PEG2b/RBV for all patients
  - PEG-2b 1.5 µg/kg QW; RBV 600-1400 mg/day divided BID
- Control arm patients with HCV-RNA ≥ LLOQ at TW 24 were offered open-label PEG2b/RBV+BOC via a crossover arm

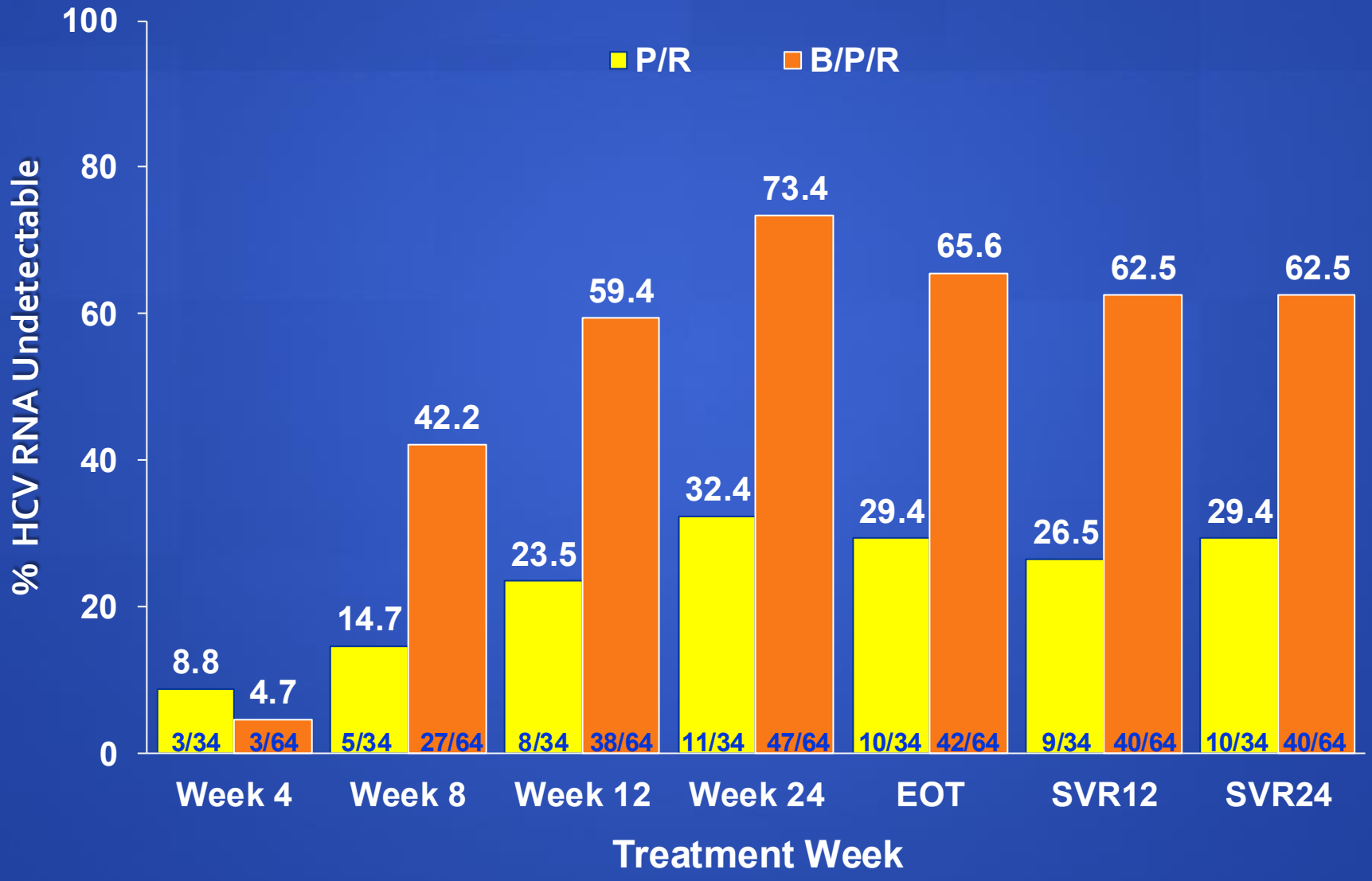
Demographics and Baseline Characteristics

	PR (N=34)	B/PR (N=64)
Age (years), mean (SD)	45 (9.8)	43 (8.3)
Male, n (%)	22 (65)	46 (72)
Race, n (%)		
White	28 (82)	52 (81)
Non-white	6 (18)	12 (19)
Body mass index, mean (SD)	26 (4)	25 (4)
Cirrhosis, n (%)	1 (3)	4 (6)
HCV genotype subtype, n (%)*		
1a	22 (65)	42 (66)
1b	10 (29)	15 (23)
HCV RNA level >800,000 IU/mL, n (%)	30 (88)	56 (88)
HIV RNA <50 copies/mL, n (%)	33 (97)	62 (97)
CD_4 count (cells/mm^3), median (range)	586 (187-1258)	577 (230-1539)

*Subtyping not reported for 9 patients with Genotype 1.

CROI 2012- Abstract # Q-175

Virologic Response Over Time



Updated from Sulkowski. Lancet ID. 2013 Jul;13(7):597-605.

Most Common Adverse Events With a Difference of ≥10% Between Groups

	PR (N=34)	B/PR (N=64)
Anemia	26%	41%
Pyrexia	21%	36%
Asthenia	24%	34%
Decreased appetite	18%	34%
Diarrhea	18%	28%
Dysgeusia	15%	28%
Vomiting	15%	28%
Flu-like illness	38%	25%
Neutropenia	6%	19%

CROI 2012- Abstract # Q-175

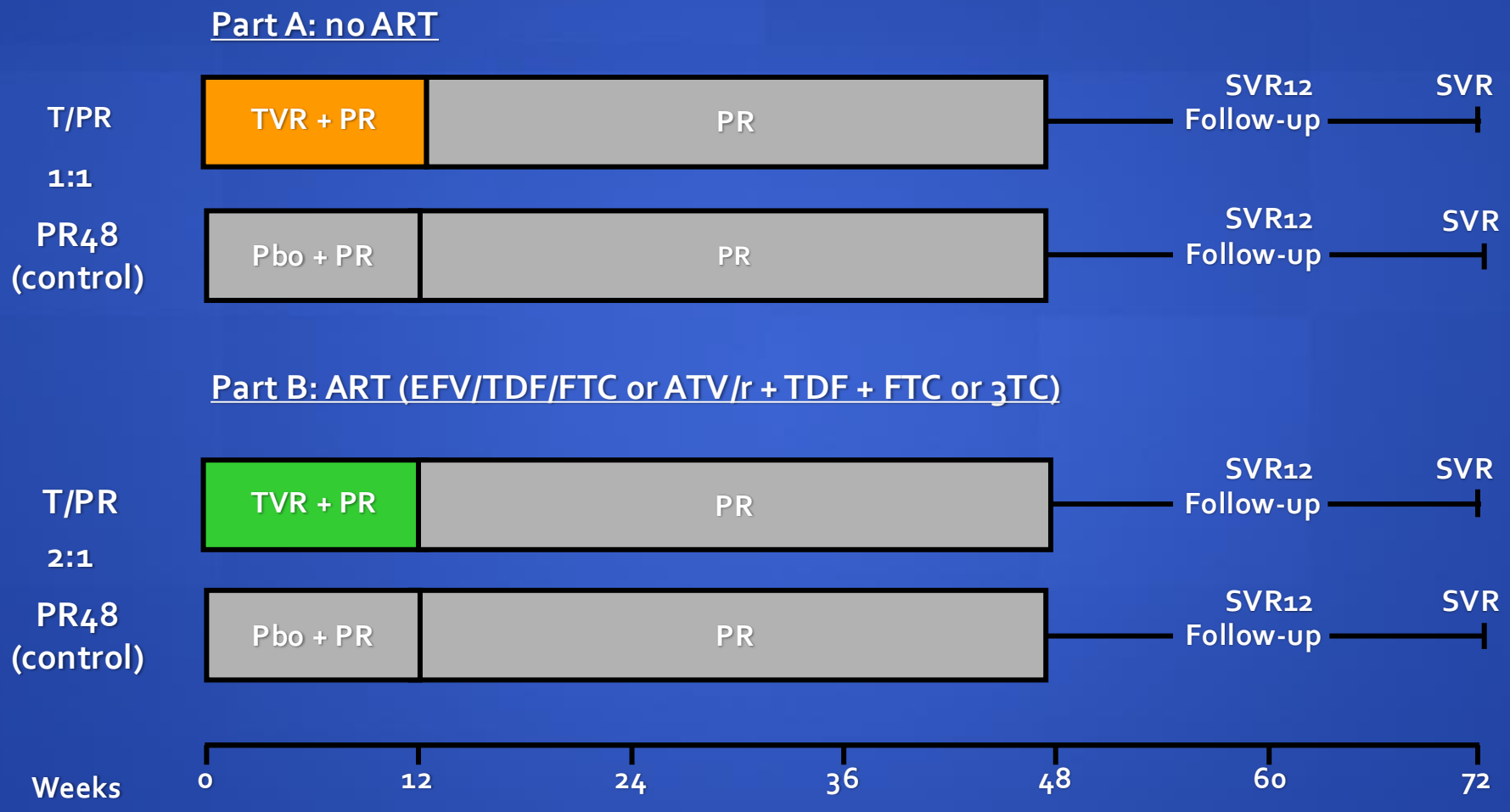
Analysis Summary

- HCV-HIV co-infected HCV treatment naïve patients had high rates of HCV response on BOC
  - SVR-24: 62.5% of patients on B/PR vs. 29.4% of patients on PR

- Preliminary safety data of B/PR in co-infected patients showed a profile consistent with that observed in mono-infected patients

Updated from Sulkowski. Lancet ID. 2013 Jul;13(7):597-605.

Telaprevir in Combination with Peginterferon Alfa-2a/Ribavirin in HCV/HIV Co-infected Patients: SVR24 Analysis



(EFV)=efavirenz; (TDF)=tenofovir; (FTC)=emtricitabine; (ATV/r)=ritonavir-boosted atazanavir; (3TC)=lamivudine;
(T) TVR=telaprevir 750 mg q8h or 1125 mg q8h (with EFV); Pbo=Placebo; (P) Peg-IFN=pegylated interferon alfa-2a (40 kD) 180 µg/wk; (R) RBV=ribavirin 800 mg/day or weight-based (1000 mg/day if weight <75 kg, 1200 mg/day for if weight ≥75 kg; France, Germany, n=5 patients)
Roche COBAS® TaqMan® HCV test v2.0, LLOQ of 25 IU/mL, LOD of <10 IU/mL

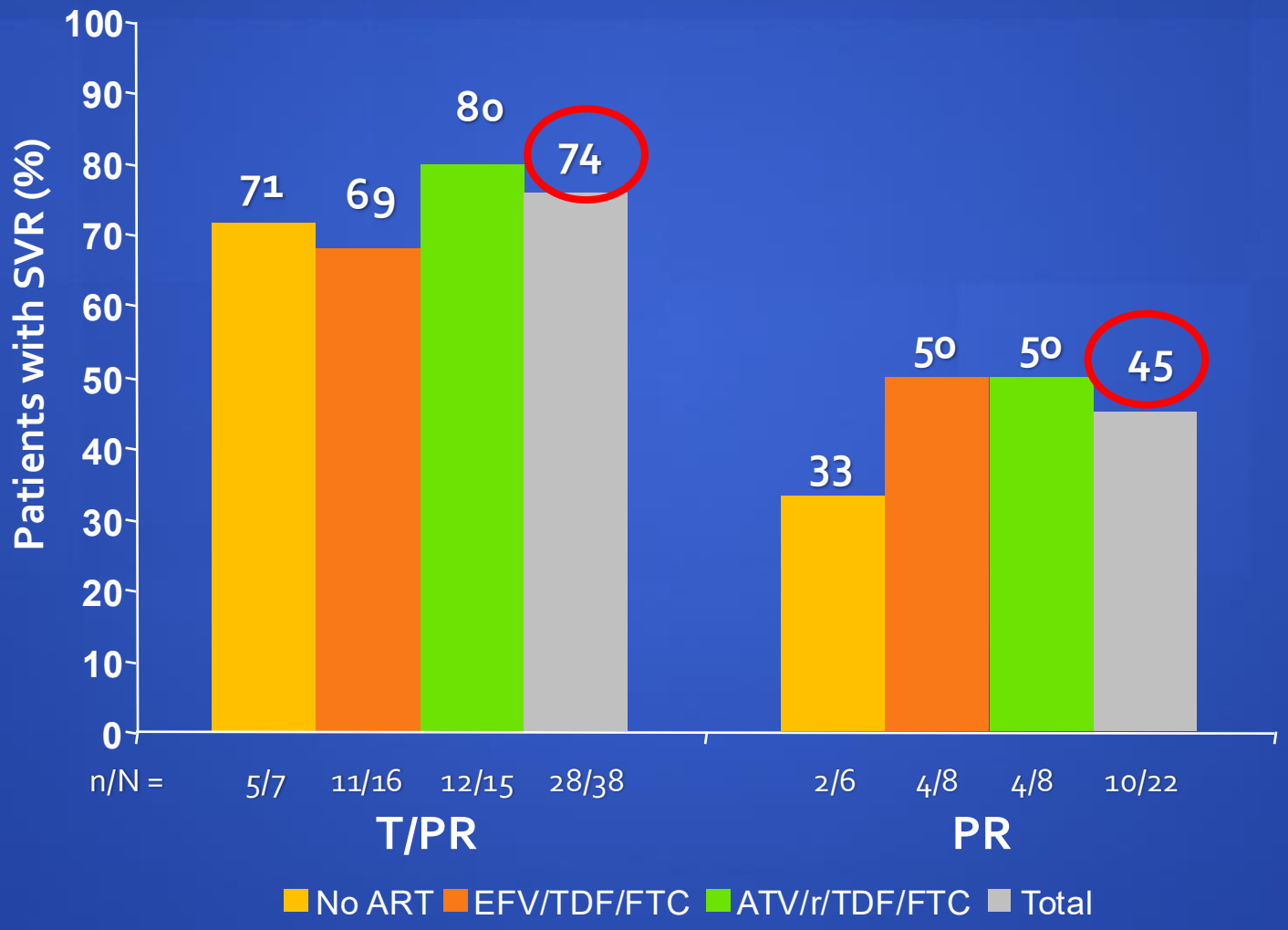
Updated from CROI 2012

Patient Demographics and Baseline Characteristics

	Part A		Part B			
	No ART		EFV/TDF/FTC		ATV/r + TDF + FTC or 3TC	
	T/PR N=7	PR N=6	T/PR N=16	PR N=8	T/PR N=15	PR N=8
Gender, n (%): Male	6 (86)	4 (67)	16 (100)	7 (88)	13 (87)	7 (88)
Caucasian†, n(%) Black/African American, n(%)	2 (29) 4 (57)	3 (50) 3 (50)	12 (75) 3 (19)	5 (62) 3 (38)	13 (87) 2 (13)	7 (88) 1 (12)
Ethnicity†: Hispanic, n (%)	3 (43)	2 (33)	5 (31)	1 (12)	3 (21)	3 (38)
Age, median years (range)	39 (34-50)	48 (42-65)	48 (31-57)	47 (31-53)	52 (36-59)	39 (26-53)
BMI, median kg/m² (range)	29 (22-37)	31 (26-37)	24 (21-32)	23 (19-28)	24 (23-33)	25 (22-30)
HCV RNA ≥ 800,000 IU/mL**, n (%)	7 (100)	5 (83)	13 (81)	7 (88)	12 (80)	7 (88)
HCV Genotype Subtype*, n (%) 1a 1b Other	 3 (43) 4 (57) 0 (0)	 3 (50) 2 (33) 1 (17)	 12 (75) 4 (25) 0 (0)	 6 (75) 1 (12) 1 (12)	 12 (80) 3 (20) 0 (0)	 5 (62) 3 (38) 0 (0)
Bridging Fibrosis, n(%) Cirrhosis, n (%)	1 (14) 0 (0)	0 (0) 0 (0)	2 (12) 2 (12)	1 (12) 0 (0)	0 (0) 0 (0)	1 (12) 0 (0)
HIV RNA median copies/mL (range)	1495 (193-53,450)	267 (25-21,950)	25 (25-25)	25 (25-25)	25 (25-25)	25 (25-25)
CD4+ median cells/mm³ (range)	604 (496-759)	672 (518-1189)	533 (299-984)	514 (323-1034)	514 (254-874)	535 (302-772)

†Race and ethnicity were self-reported
*5'NC InnoLipa line probe assay
**Roche COBAS® TaqMan® HCV test v2.0, LLOQ of 25 IU/mL and LLOD of 10-15 IU/mL

SVR Rates 24 Weeks Post-Treatment (SVR24*)



*Patient was defined as SVR24 if HCV RNA was < LLOQ in the visit window

Updated from Sulkowski. Ann Intern Med. 2013 Jul 16;159(2):86-96.

Events of Special Interest: Overall Treatment Phase

	T/PR N=38 n (%)	PR N=22 n/N (%)
Severe rash	0 (0)	0 (0)
Mild and moderate rash	13 (34)	5 (23)
Anemia	7 (18)	4 (18)
Grade 3 hemoglobin shifts* (7.0-8.9 g/dL)	11 (29)	5 (23)
Use of erythropoietin stimulating agent	3 (8)	1 (5)
Blood transfusions	4 (11)	1 (5)

- CD_4 counts declined in both T/PR and PR groups; CD_4% remained unchanged

*DAIDS HIV-negative scale

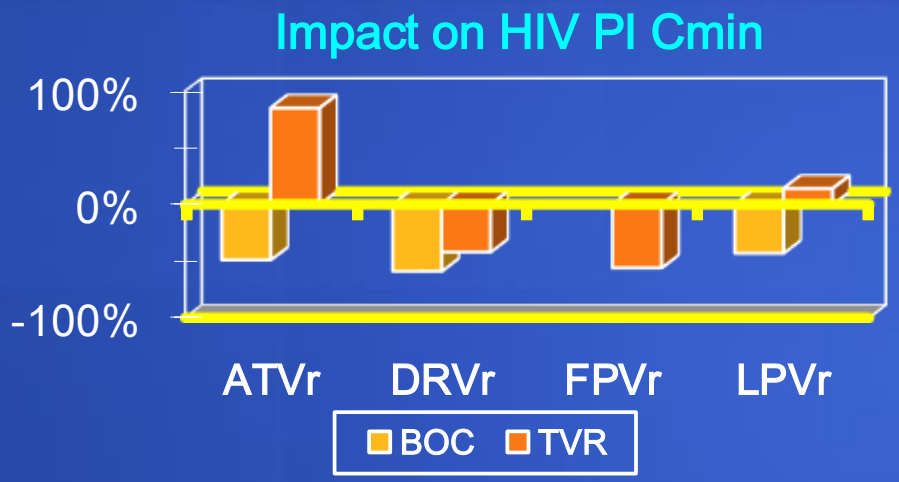
Conclusions

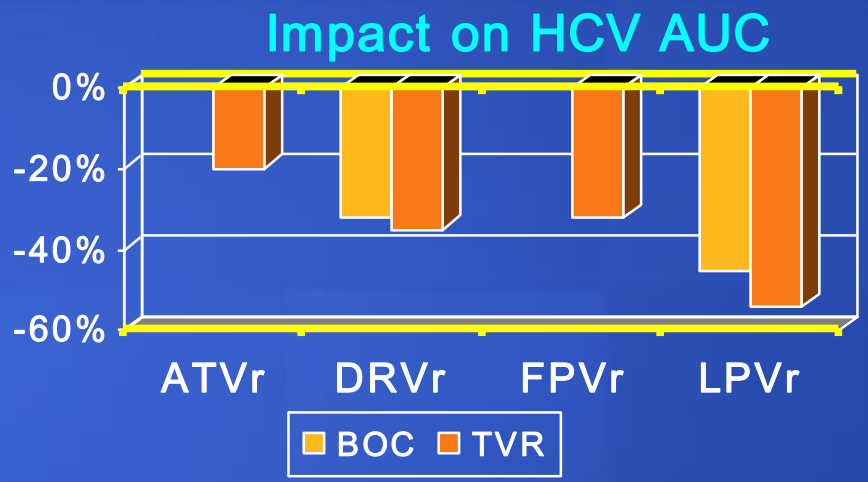
- Higher SVR24 rates were observed in chronic genotype 1 HCV/HIV co-infected patients treated with telaprevir combination treatment
  - T/PR 74%
  - PR 45%
- In patients treated with telaprevir combination treatment, overall safety and tolerability profile was comparable to that previously observed in chronic genotype 1 HCV mono-infected patients

Updated from Sulkowski. Ann Intern Med. 2013 Jul 16;159(2):86-96.

Interactions Between HCV and HIV PIs

Summary of Healthy Volunteer Studies



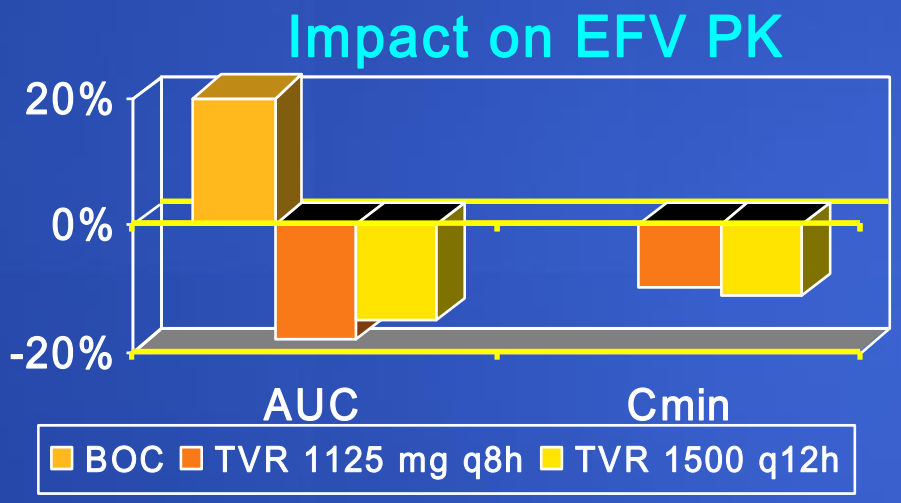


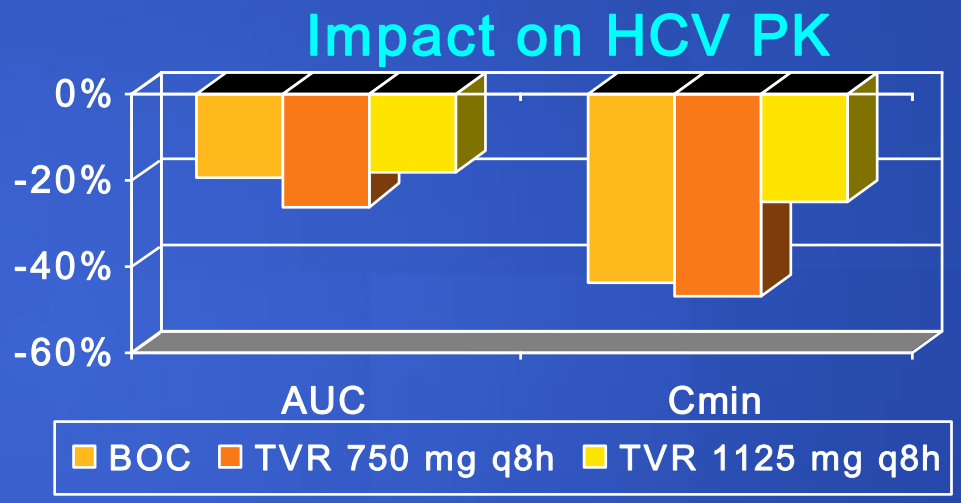
- **Dosing recommendations:**
  - **<u>Boceprevir:</u> coadministration with ritonavir-boosted PIs is not recommended**
  - **<u>Telaprevir</u>: do not administer with DRVr, FPVr or LPVr; ongoing evaluation with ATVr**

van Heeswijk et al. CROI 2011, #119. Hulskotte et al. CROI 2012, #771LB

Interactions Between HCV DAA & EFV

Summary of Healthy Volunteer Studies





- Dosing recommendations:
  - Boceprevir: co-administration EFV is not recommended
  - Telaprevir: use 1125 mg TID with EFV

van Heeswijk et al. CROI 2011, #119. Garg et al. 6th HCV PK Wksp 2011, #PK_13. Victrelis Monograph 2011

Statement

- The addition of DAA to IFN-based HCV antiviral therapy produces a substantial improvement in SVR with minimal increased sides effects
- Development of other Direct Acting Antivirals holds promise for additional advances in HIV-HCV co-infection treatment

Drug Interactions with Directly Acting Antivirals for HCV

Overview and Challenges in HIV/HCV Co-Infection

Alice Tseng, Pharm.D., FCSHP, AAHIVP
Toronto General Hospital
Faculty of Pharmacy
University of Toronto

Outline

- Understand how the pharmacology of DAAs contribute to drug interactions
- Highlight important HCV drug interactions
- Outline a strategy for identifying and managing drug interactions
- Identify pertinent HCV drug interaction resources

Boceprevir and Telaprevir Pharmacology

	Boceprevir	Telaprevir
Dosing	800 mg q8h with food	750 mg q8h with food (20 g fat)
Substrate	CYP3A4, P-gp, AKR	CYP3A4, Pgp
Inhibitor	3A4, P-gp	3A4, P-gp, renal transporters (?)
Inducer	No inducing effects in vitro (in vivo?)	

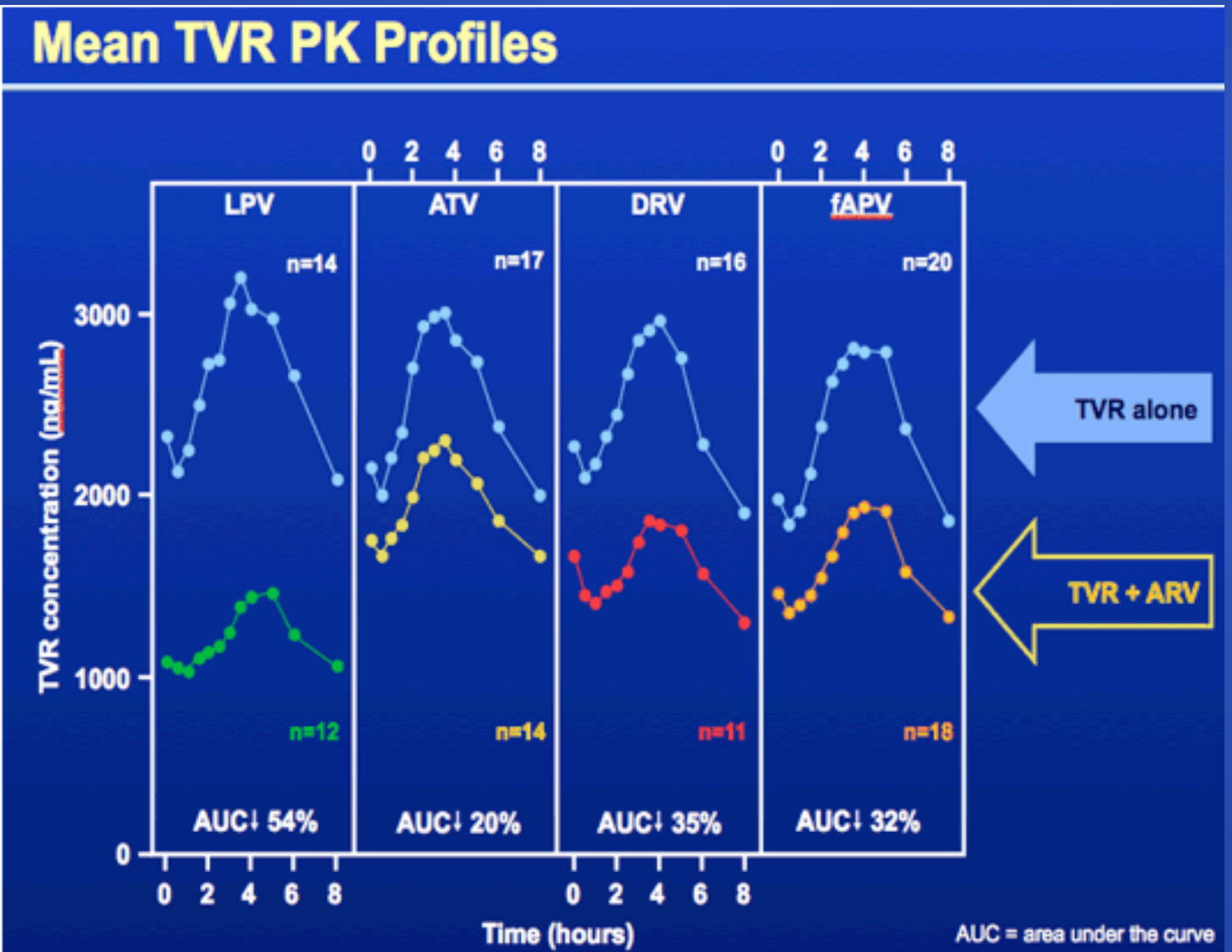
potential for interactions with other drugs

- can be clinically significant
- sometimes unpredictable

Interactions Between HCV & HIV Medications

- Multiple challenges in treating HIV/HCV co-infected patients
- Additive toxicities:
  - anemia: ribavirin, zidovudine, DAAs
  - CNS effects: interferon, efavirenz
- Altered concentrations of ARVs and/or DAAs:
  - ↑ risk of toxicity
  - ↓ efficacy, potential development of resistance (HIV and/or HCV)

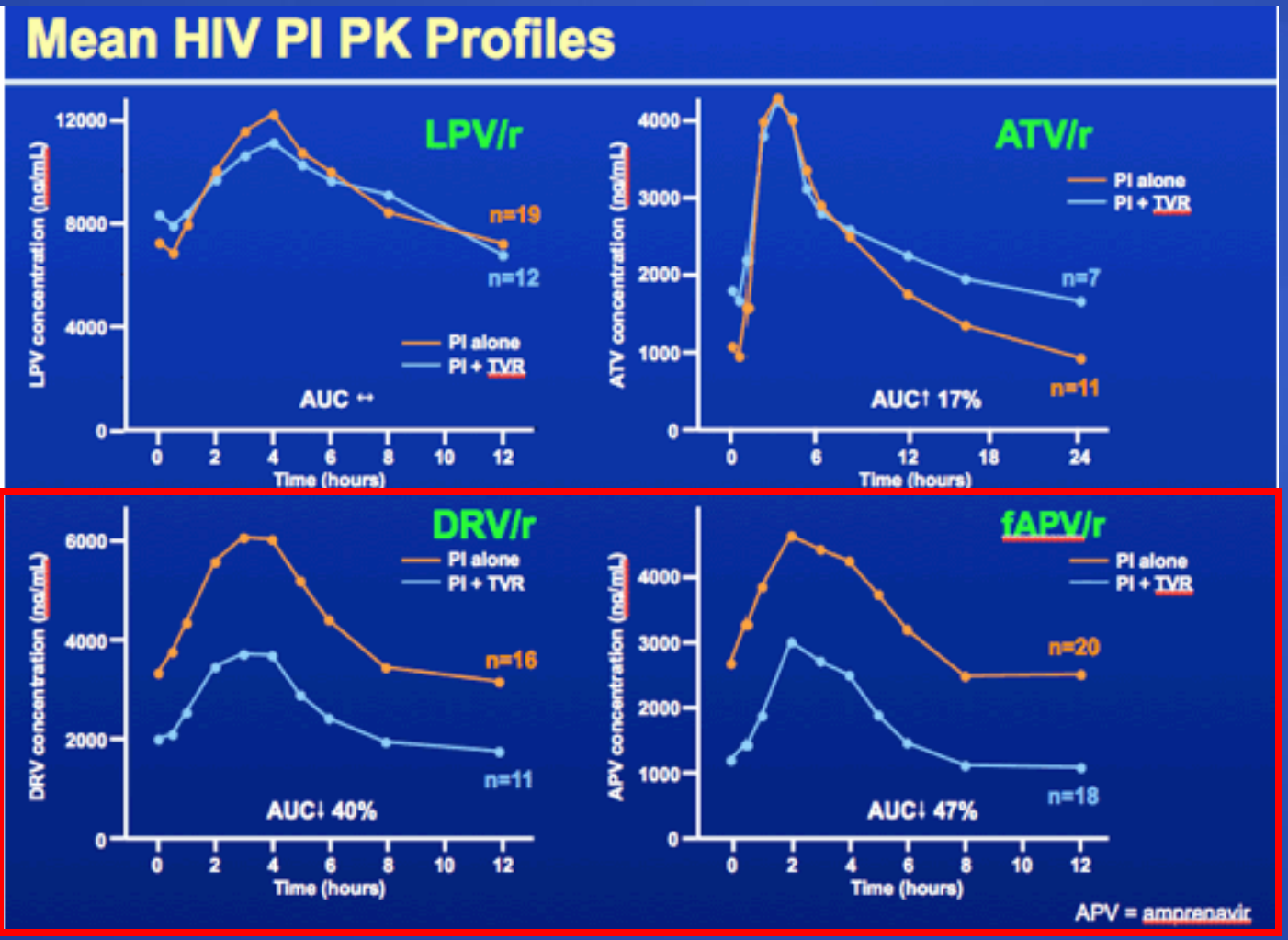
Telaprevir 750 mg q8h plus Boosted PIs in Healthy Volunteers



- Telaprevir exposure ↓ with PI/r
  - AUC ↓ 20-54%
  - Cmin ↓ 15-52%

van Heeswijk et al. CROI 2011, #119

Telaprevir 750 mg q8h plus Boosted PIs in Healthy Volunteers



- Telaprevir had variable effect on PIs:
  - 40-47% ↓ AUC of DRVr, FPVr
  - n/c with ATVr, LPVr
- Appropriate doses not yet established

van Heeswijk et al. CROI 2011, #119

Two-Way Interaction between Boceprevir and Boosted PIs

- Interaction studies in healthy volunteers

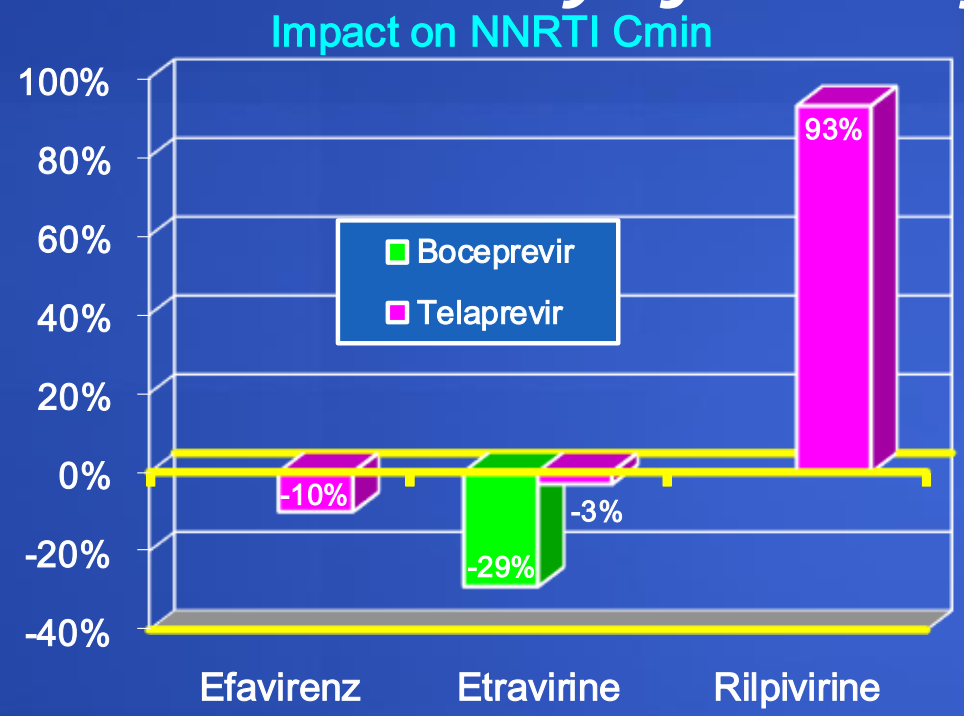
	PI Kinetics			*RTV AUC*	BOC AUC
	Ctrough	AUC	Cmax		
ATVr	↓ 49%	↓ 35%	↓ 25%	↓ 34%	-
DRVr	↓ 59%	↓ 44%	↓ 36%	↓ 27%	↓ 32%
LPVr	↓ 43%	↓ 34%	↓ 30%	↓ 22%	↓ 45%

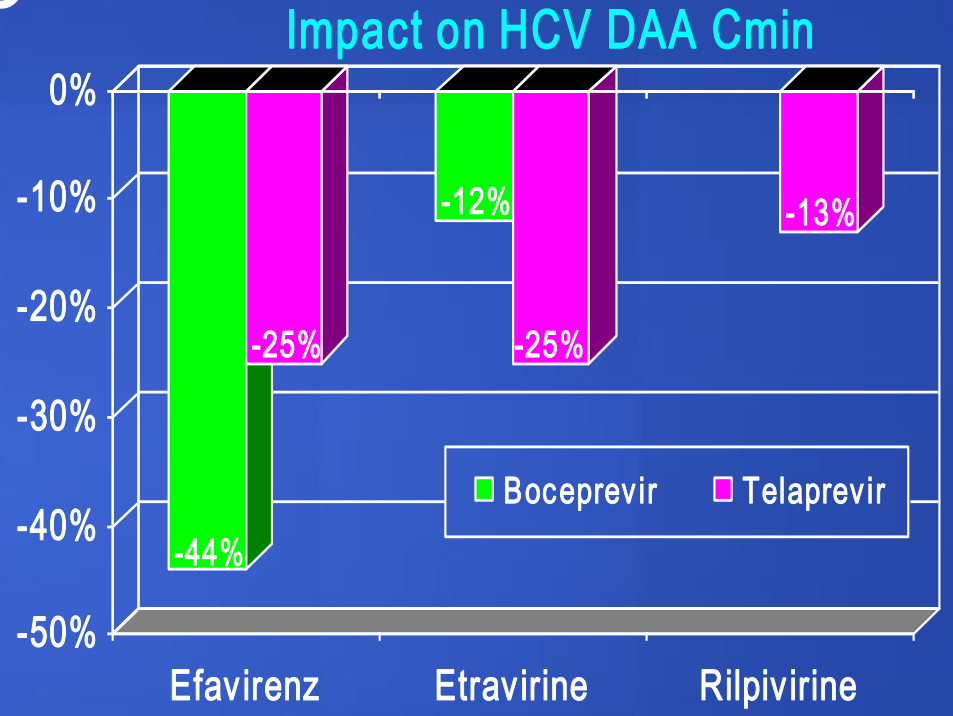
- Coadministration of boceprevir and ritonavir-boosted PIs is not recommended

Hulskotte et al. CROI 2012, #771LB

Interactions Between HCV DAA & NNRTIs

Summary of Healthy Volunteer Studies



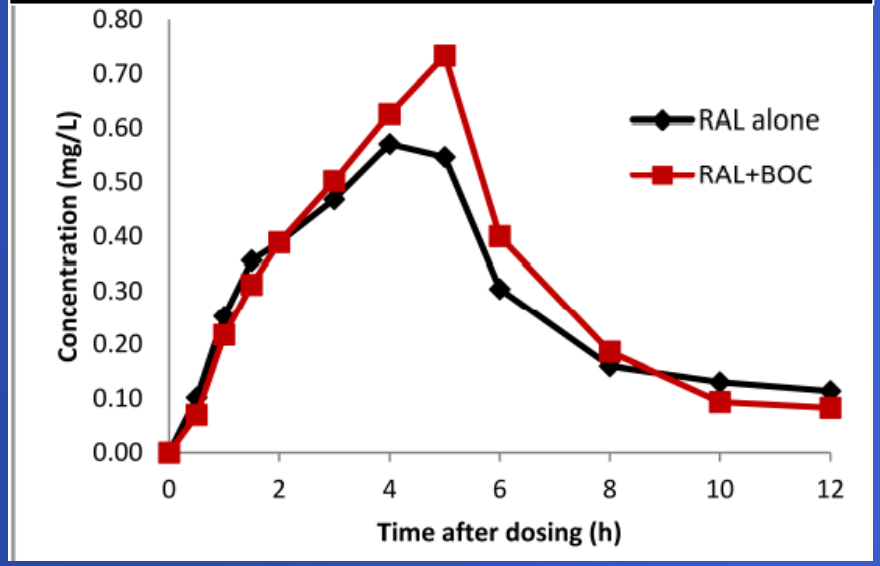


- **Dosing recommendations on using HIV non-nucleoside reverse transcriptase inhibitors (NNRTIs) with HCV directly acting antivirals:**
  - **Efavirenz: avoid with boceprevir, use 1125 mg TID telaprevir**
  - **Etravirine: ? with boceprevir, OK with telaprevir**
  - **Rilpivirine: OK with telaprevir**

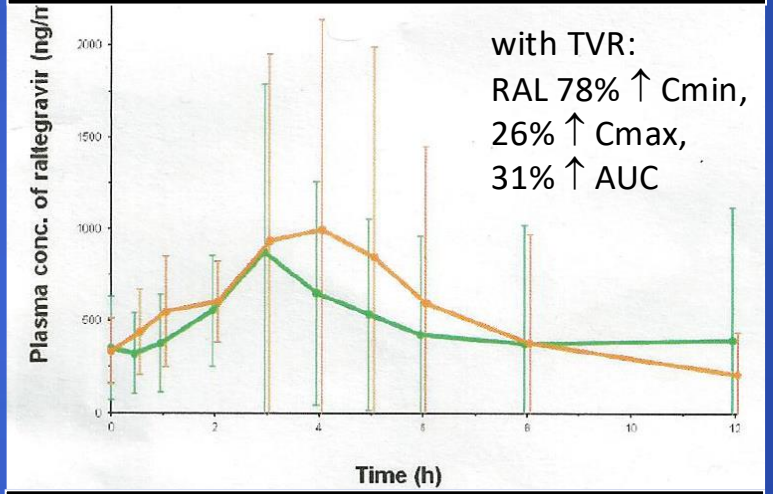
van Heeswijk et al. CROI 2011, #119. Garg et al. 6th HCV PK Wksp 2011, #PK_13.
Victrelis Monograph 2011. Hammond et al. IWCPHT 2012 O-15. Kakuda et al. IWCPHT 2012 O_18

No Clinically Significant Interaction with Raltegravir and Boceprevir or Telaprevir

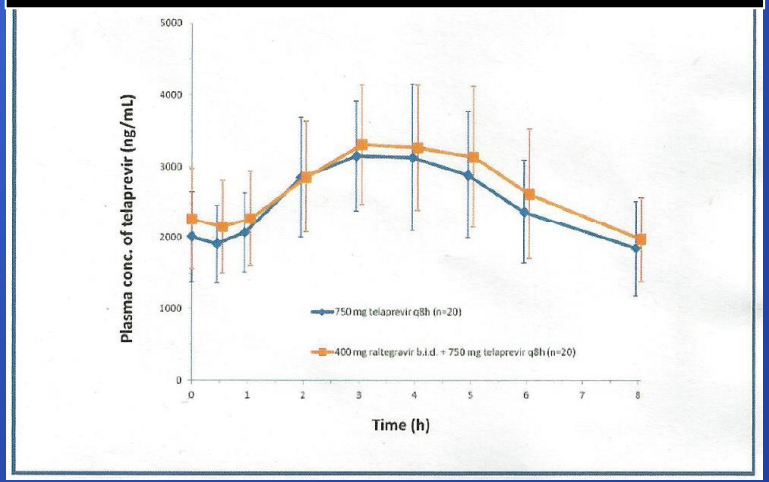
Mean Raltegravir PK +/- Boceprevir



Mean Raltegravir PK +/- Telaprevir



Mean Telaprevir PK +/- RAL



- In the presence of raltegravir, boceprevir exposures were similar to historical controls

de Kanter et al. CROI 2012, #772LB.

van Heeswijk et al. ICAAC 2011, #A1-1738a.

Antiretroviral Treatment Options in HCV

	Boceprevir	Telaprevir
PIs	Avoid with PIr	Avoid DRVr, FPVr, LPVr
	Possible ATVr????	ATVr OK
NNRTIs	Avoid EFV	Dose ↑ with EFV
	Etravirine (?)	Etravirine OK
	No data	Rilpivirine OK
InSTIs	Raltegravir OK	
	Elvitegravir/cobicistat: no data (???)	
Maraviroc	No data *potential ↓/↑MVC; potential benefit on fibrosis?*	
NRTIs	Tenofovir OK	
	Avoid AZT (anemia)	

DAA Interactions with Other Drug Classes

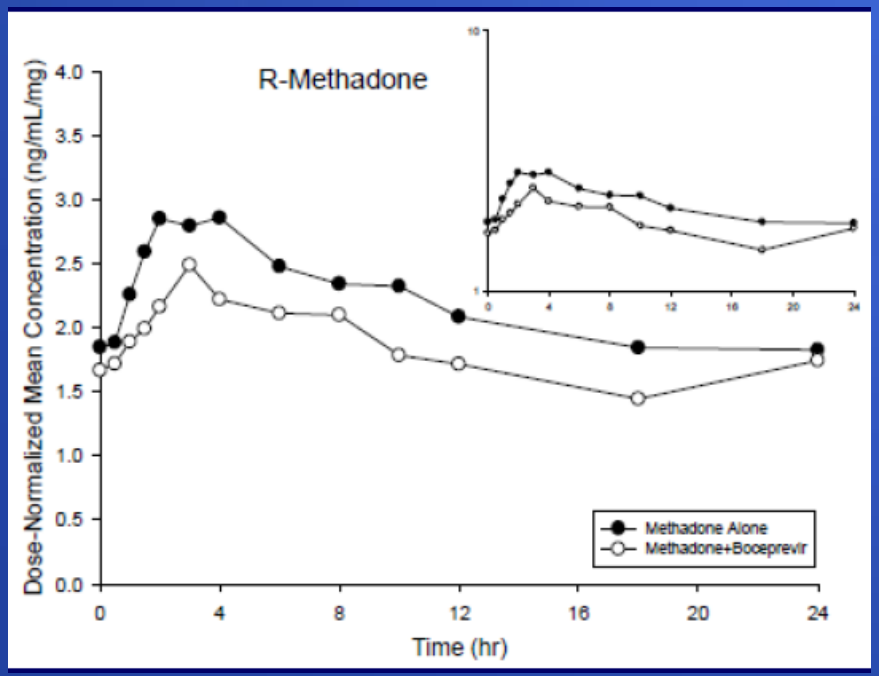
- Antidepressants
- Methadone
- Benzodiazepines
- Cardiovascular Drugs
- Transplant Drugs

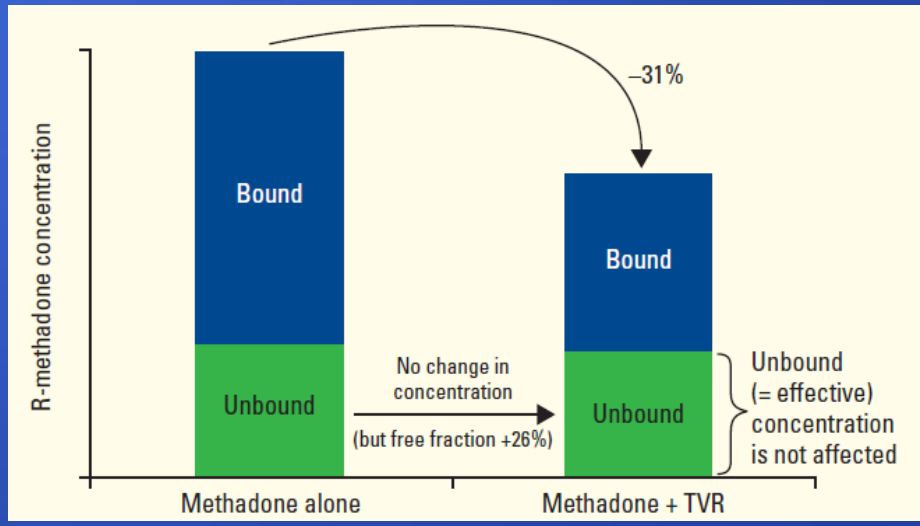
Treatment of Depression in HCV

- Patients with HCV may require antidepressant therapy
- Escitalopram is considered a first-line option
  - no interaction with boceprevir
  - 35% ↓ AUC with telaprevir, may need to titrate dose
- Agents which are partially metabolized via CYP3A4 may theoretically be ↑ by DAAs
  - e.g., desvenlafaxine, venlafaxine, sertraline, mirtazapine, imiprimine
  - combinations not studied, clinical significance unknown
- Low risk of interactions predicted with bupropion, tricyclic antidepressants, some SSRIs

Methadone Interactions

- Methadone is metabolized by CYP2B6, CYP2C19 & CYP3A, 85% protein bound; *R*-isomer is biologically active enantiomer
- <u>Boceprevir interaction</u>:
  - R-methadone AUC ↓ 16%, Cmax ↓ 10%; no withdrawal
- <u>Telaprevir interaction</u>:
  - R-methadone Cmin ↓ 31%, Cmax ↓ 21%, AUC ↓ 21%, but median unbound Cmin was unchanged, no withdrawal Sx





Hulskotte et al. 2012, Van Heeswijk et al. 2011.

Benzodiazepine Interactions

- Majority are substrates of CYP3A4
  - risk for prolonged/excessive sedation
- Oral midazolam & triazolam are contraindicated with boceprevir and telaprevir
  - 5 to 9-fold ↑ midazolam AUC with boceprevir or telaprevir
  - IV midazolam: consider ↓ dose, close monitoring for respiratory depression or prolonged sedation
- Other benzodiazepines: ↓ dose and monitor
- Consider using benzodiazepines that are glucuronidated: lorazepam, oxazepam, temazepam

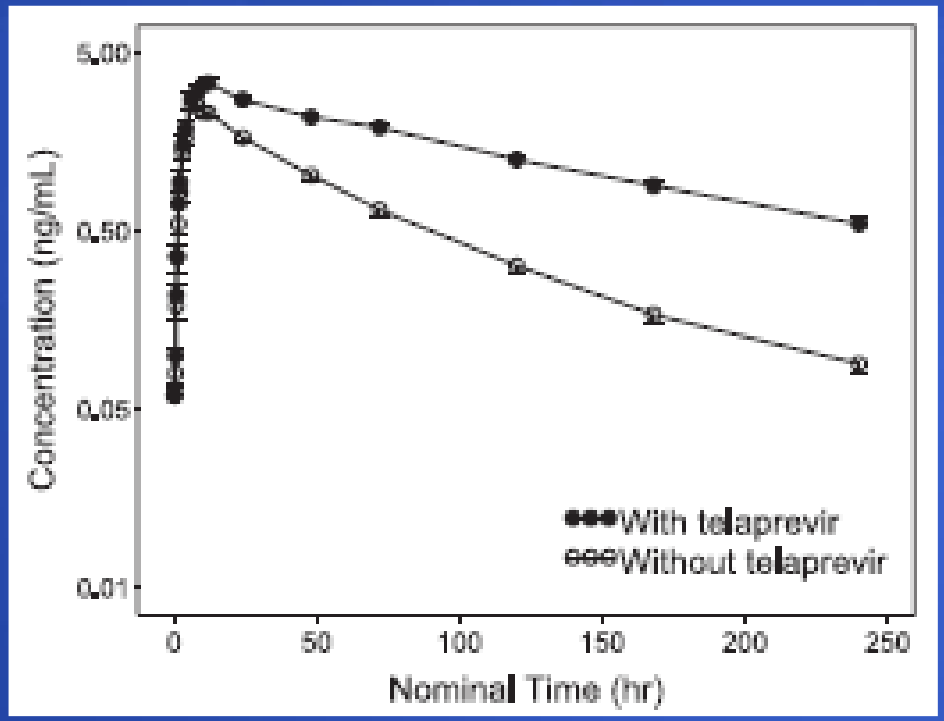
Using Statins with Boceprevir or Telaprevir

	Boceprevir	Telaprevir
Lovastatin, Simvastatin	CONTRAINDICATED	
Atorvastatin	May need to ↓ atorvastatin dose; do not exceed >20 mg/d	CONTRAINDICATED
Pravastatin	Start with recommended dose and monitor for toxicity.	Possible ↑ in statin; use with caution.
Rosuvastatin, Fluvastatin	Possible ↑ in statin; use with caution.	

- Use lowest statin dose and titrate slowly to response

Victrelis & Incivek Product Monographs, 2011; FDA HIV/AIDS Update, 2012.

Effect of Steady-State Telaprevir on the Pharmacokinetics of Amlodipine 5 mg



- amlodipine AUC ↑ 179%
- monitor for dose-related toxicity

Calcium channel blockers (CCBs)

- Amlodipine, diltiazem, felodipine, nifedipine, nicardapine, verapamil are CYP3A4 substrates
- Concentrations may be ↑ by boceprevir or telaprevir
- Use with caution, clinical monitoring
- Consider dose reduction

Lee et al. Antimicrob Agents Chemother 2011.

Interactions between DAAs and Transplant Drugs

- Cyclosporine & tacrolimus are CYP3A4 substrates; significant ↑↑ concentrations with DAAs:
  - cyclosporine: AUC ↑ 2.7-fold with boceprevir, ↑ 4.64-fold with telaprevir
  - tacrolimus: AUC ↑ 17.1-fold with boceprevir, ↑ 70.3-fold with telaprevir
- ↓ CsA and TAC dosing with telaprevir coadministration:
  - CsA: ↓ from 200 mg to 25 mg daily (n=7)
  - TAC: ↓ to 50% dose given weekly (n=7)

Hulskotte et al. HEP DART 2011, poster 123. Garg et al. Hepatology, 2011. Mantry et al. HEP DART 2011, #90. Kwo et al. EASL 2012, #202.

Drugs Contraindicated with Boceprevir and Telaprevir (1)

α1-adrenoreceptor antagonist	alfuzosin	hypotension, cardiac arrhythmia
antiarrhythmics	Quinidine, propafenone, amiodarone. Flecainide (TVR)	serious/life-threatening cardiac arrhythmia
antimycobacterials	Rifampin	Loss of virologic response
Ergot derivatives		Acute ergot toxicity
Herbal product	St. John's wort	Loss of virologic response
Statins	Lovastatin, simvastatin. Atorvastatin (TVR)	Myopathy including rhabdomyolysis
neuroleptic	Pimozide	serious/life-threatening cardiac arrhythmia

Victrelis & Incivek Product Monographs, 2011

Drugs Contraindicated with Boceprevir and Telaprevir (2)

PDE-5 inhibitor	sildenafil. tadalafil (BOC); vardenafil (TVR)	Visual abnormalities, hypotension, prolonged erection, syncope
Sedatives/ hypnotics	oral midazolam, triazolam	Increased sedation or respiratory depression
Other	cisapride, astemizole, terfenadine	serious/life-threatening cardiac arrhythmia
Anticonvulsants (BOC)	carbamazepine, phenytoin, phenobarbital	Loss of virologic response
OC (BOC)	drospirenone	hyperkalemia
Aldosterone antagonist (TVR)	eplerenone	hyperkalemia
Triptans (TVR)	eletriptan	Coronary artery vasospasm, MI, vent. tachycardia, VF

Victrelis & Incivek Product Monographs, 2011.

Summary

- Potential for numerous interactions between DAAs and ARVs, as well as agents prescribed by other providers
  - challenge in treating HIV/HCV coinfected patients, particularly in context of earlier cART initiation, aging population and management of comorbidities
- Steps to minimizing/managing interactions:
  - ensure medication records are up to date at each visit
  - utilize pertinent drug interaction resources to identify combinations of potential concern
  - consult with physicians & pharmacists with expertise in HIV and HCV
  - institute therapeutic plan with close monitoring

HIV & HCV
Drug Interaction Resources

- Interactions in HCV and HIV:
  - Kiser J et al. Hepatology 2012;55:1620-8.
  - Tseng & Foisy. Curr Infect Dis Rep 2012;14:67-82.

- Internet
  - Toronto General Hospital Immunodeficiency Clinic; www.hivclinic.ca, www.hcvdruginfo.ca
  - Liverpool Pharmacology Group; www.hep-druginteractions.org

Complicated cases

David Fletcher, MD
Department of Medicine
University of Toronto

CASE 1

- 54 yr/o man
- HIV positive 8 yrs ago
  - Tenofovir/FTC/RTV/Atazanavir x 4 yrs
  - Previously documented NNRTI resistance with Y181C, G190A,and mixed m184v/wt
  - CD4 320 HIV Viral Load<40

CASE 1

- Genotype 1a Hepatitis C biopsy proven cirrhosis
- Compensated and clinically stable
  - Previous therapy in 2009 with Peg IFN/1200mg RBV daily resulted in a null response by history from the patient

CASE 1

Patient is interested in a retrial of therapy for Hepatitis C with the new direct acting antiviral agents

- Would you offer treatment?
- Chance of cure?
- Which 3rd agent would you choose and why?
- Does patient's antiretroviral history play a role in 3rd agent choice?
- Is there a role for a 4 week lead in here regardless of agent chosen and if so…why?

CASE 1

It was decided to move forwards with Peg IFN/ 1200mg RBV/Telaprevir

- Is it necessary to change current ARVs?
- Would it be necessary to change ARVs if Boceprevir was chosen?…to what?

CASE 1

Peg IFN/1200mg RBV/Telaprevir…no lead in performed

- Week 0 HCVRNA 3.7 x 10e7
- Week 4 HCVRNA detectable but<12
- Would you continue?
- Are you concerned about the result?
- When would you do the next HCVRNA?

CASE 1

It was decided to continue with Peg IFN/1200mg RBV/Telaprevir and HCVRNA rechecked

- Week 0 HCVRNA 3.7 x 10e7
- Week 4 HCVRNA detectable but<12
- Week 6 HCVRNA <12
- Would you continue?

CASE 1

Peg IFN/1200mg RBV/Telaprevir

- Week 0 HB 140
- Week 2 HB 125
- Week 4 HB 109
- Week 6 HB 99…symptomatic
- How would you manage anemia?

CASE 1

Peg IFN/600mg RBV/Telaprevir

- Week 0 HCVRNA 3.7 x 10e7
- Week 4 HCVRNA detectable but<12
- Week 6 HCVRNA <12 HB 99 (symptoms)
- Week 8 HCVRNA <12 HB 98 (less symptomatic)
- What would you do?
- How would you further manage anemia

CASE 1

Peg IFN/600mg RBV/Telaprevir

- Week 0 HCVRNA 3.7 x 10e7
- Week 4 HCVRNA detectable but<12
- Week 6 HCVRNA <12
- Week 8 HCVRNA <12
- Week 12 HCVRNA detectable but <12 HB 103
- What would you do?
- When would you do your next HCVRNA?

CASE 1

Peg IFN/RBV re-increased to 1200mg

- Week 0 HCVRNA 3.7 x 10e7
- Week 4 HCVRNA detectable but <12
- Week 8 HCVRNA <12
- Week 12 HCVRNA detectable but <12
- Week 14 HCVRNA <12 HB 101
- What would you do?

CASE 1

Peg IFN/1200mg RBV

- Week 0 HCVRNA 3.7 x 10e7
- Week 4 HCVRNA detectable but<12
- Week 12 HCVRNA detectable but <12
- Week 14 HCVRNA <12 HB 101
- Week 24 HCVRNA <12 HB 105
- How much longer would you treat?
- When would you do your next HCVRNA?

CASE 1

Peg IFN/1200mg RBV

- Week 0 HCVRNA 3.7 x 10e7
- Week 4 HCVRNA detectable but <12
- Week 12 HCVRNA detectable but <12
- Week 24 HCVRNA <12
- Week 36 HCVRNA <12
- Week 48 HCVRNA <12
- Are we finished therapy?

CASE 1

An additional 24 weeks of PEG IFN/RBV (for a total of 72 weeks of therapy) was offered to the patient given the existence of cirrhosis and ?slow HCVRNA clearance as evidenced by a detectable HCVRNA at week 4 and 12

Week 12 and 24 HCVRNA post 72 weeks of therapy were undetectable!

CASE 2

- 52 yo man
- HIV positive 5 yrs ago
  - CAD with previous MI 3 yrs ago/Hypertensive/Hypothyroidism
- Tenofovir/FTC/Raltegravir x 4 yrs
  - CD4 700 HIV Viral Load<40

CASE 2

- Hypercholesterolemia and Hypertriglyceridemia on combination therapy with Atorvastatin 80mg/day and Fenofibrate 145mg/day
- Hypertension controlled on Amlodipine 10mg/day
- Hypothyroidism controlled on 0.125 mg L-Thyroxine

CASE 2

- Genotype 1a chronic hepatitis C
- Naïve to therapy
- F2-3/4 scarring
- Ready to start triple therapy with PEG IFN/RBV/Boceprevir
- Atorvastatin decreased to 40mg/day
- Baseline HCVRNA 1.66X10E6

CASE 2

- Week 0 HCVRNA 1.66x10E6
- Week 4 HCVRNA (lead in) 2.37X 10E2
- Week 8 HCVRNA <12
- At week 10 begins to feel tired/weak/constipated/muscle cramping
- TSH noted to be 18.91…L-T4 increased to 0.15mg/d in response

CASE 2

- At week 11 notes increasingly prominent myalgias, more predominant post interferon injection but lasting all week long as opposed to a few hrs post injection, along with increasing weakness
- Hb stable at 105g/l over last few weeks with RBV dose reduction to 600mg/d
- AST noted to be increasing while ALT has been normalizing over the last few weeks…also increasing swelling of ankles
  - ?Cause…Hepatic Decompensation?

CASE 2

- CK measured at 83,700
- BP noted to be low at 90/55 and swelling of ankles worsened now to mid calf…no ascites noted clinically
- Cause?

CASE 2

- Atorvastatin and Fenofibrate discontinued!!!
- CK fell over the next few weeks as did AST
- The symptomatic myalgias and weakness improved over the subsequent month
- Amlodipine discontinued…BP normalized to 130/80 and ankle swelling disappeared over the next month

Future Trials of Hepatitis C Therapy in the HIV Co-infected

Stephen D. Shafran, MD, FRCPC, FACP
Department of Medicine, Division of Infectious Diseases
University of Alberta

Ongoing Clinical Trials of HCV Therapy in the HIV Co-infected

- As of November 2012, the following regimens are under ongoing study:
- IFN-containing (only for HCV genotype 1)
  - PegIFNα-2a + RBV* + NS3 Protease Inhibitors
    - PegIFNα-2a + RBV + telaprevir
    - PegIFNα-2a + RBV + simeprevir
    - PegIFNα-2a + RBV + faldaprevir
  - PegIFNα-2a + RBV + NS5A Inhibitor
    - PegIFNα-2a + RBV + daclatasvir
- IFN-sparing (only for HCV genotypes 2 & 3)
  - Sofosbuvir (nucleotide polymerase inhibitor) + RBV

* RBV = ribavirin

www.clinicaltrials.gov

Two Ongoing Studies of PegIFNα-2a + RBV + Telaprevir in the HIV Co-Infected

Trial name	Vertex 115	INSIGHT
Trial identifier	NCT01467479	NCT01513941
Study design	Open-label	Open-label
No of subjects	160	150
HCV patient types	GT1 Naïve, relapsers, partial responders, null responders	
Telaprevir dosing*	1125 mg BID x 12 wk	750 mg TID x 12 wk
Study locations	USA, Canada, Spain, Germany	Europe, Australia, Brazil
Duration of PR	RGT (24 or 48 wk) in naives and relapsers; 48 wk in partials and nulls	
RBV dose	800 mg/d	
ART	Must be on suppressive ART	
Baseline CD_4	> 300 cells/mm^3	
Study status	Fully enrolled	Enrolling
SVR12 expected	Q3 2014	Q3 2014

* Telaprevir dosed 1125 mg TID in patients receiving efavirenz

www.clinicaltrials.gov

Ongoing Study of PegIFNα-2a + RBV + Simeprevir in the HIV Co-Infected

Trial name	C212
Trial identifier	NCT01479868
Study design	Open-label
No of subjects	107
HCV patient types	GT1 Naïve, relapsers, partial responders, null responders
Simeprevir dosing	150 mg QD x 12 wk
Study locations	USA, Europe, Canada
Duration of PR	RGT (24 or 48 wk) in naives and relapsers; 48 wk in partials/nulls/cirrhotics
RBV dose	800 mg/d
ART and CD4	CD4 > 300 on suppressive ART; or not on ART with CD4 > 500 and HIV RNA <100,000
Study status	Fully enrolled
SVR12 expected	Q4 2014

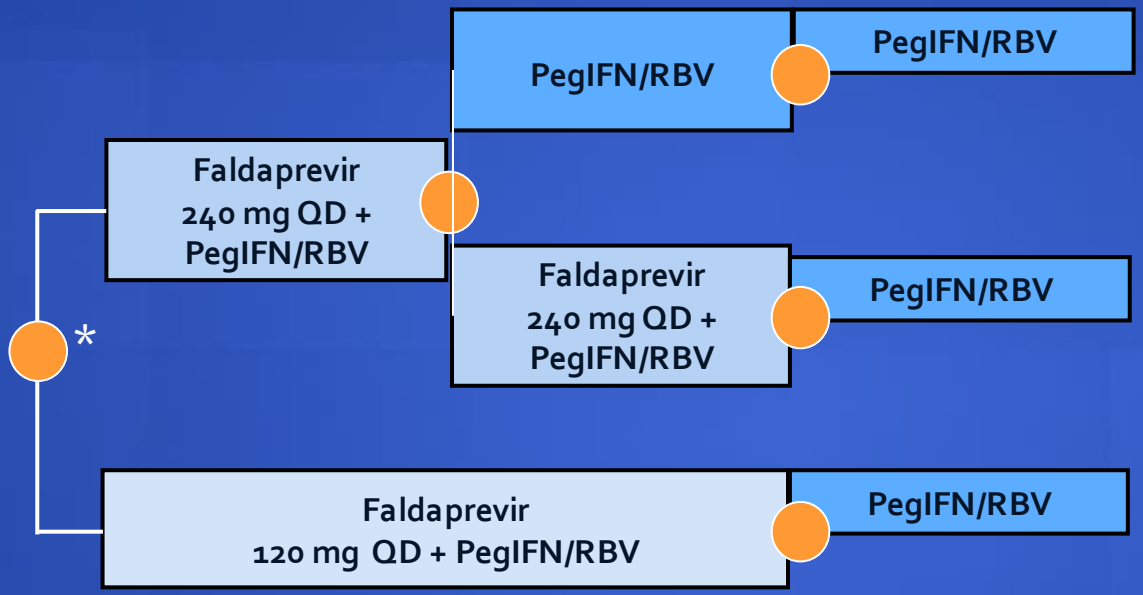
www.clinicaltrials.gov

Ongoing Study of PegIFNα-2a + RBV + Faldaprevir in the HIV Co-Infected

Trial name	STARTverso4
Trial identifier	NCT01399619
Study design	open-label with multiple randomizations
No of subjects	306
HCV patient types	GT1 Naïve, relapsers
Faldaprevir dosing	120 mg or 240 mg QD
Study locations	USA, Europe, Brazil
Duration of PR	RGT in naives and relapsers; 48 wk in partials/nulls/cirrhotics
RBV dose	1000/1200 mg/d
ART and CD4	CD4 > 300 on suppressive ART, OR not on ART with CD4 > 500 and pVL <100,000
Study status	Fully enrolled
SVR12 expected	Q4 2014

www.clinicaltrials.gov

PegIFNα-2a + RBV + Faldaprevir for HCV GT1 in HCV Treatment-Naïve and Relapser Patients with HIV Co-infection



Follow-up:
up to Week 120

Randomization (1:1)

Randomization (1:1)

ETS patients are re-randomized (1:1)
No ETS = 48 weeks PegIFN/RBV

ETS (early treatment response): HCV RNA <25 IU/mL, detectable or not at Week 4 and <25 IU/mL, undetectable at Week 8

* Patients directly assigned to the 240 mg dose group if receiving efavirenz and to the 120 mg dose group if receiving darunavir/ritonavir or atazanavir/ritonavir

Ongoing Study of PegIFNα-2a + RBV + Daclatasvir in the HIV Co-Infected

Trial name	COMMAND-HIV
Trial identifier	NCT01471574
Study design	open-label
No of subjects	300
HCV patient types	GT1 Naïve
Daclatasvir dosing	30 mg QD (ATZ/r, LPV/r or DRV/r), 60 mg QD (RAL, RIL or no ART) or 90 mg QD (EFV or NVP), all for 24 weeks
Study locations	USA, Europe, Brazil
Duration of PR	RGT (24 or 48 wks)
RBV dose	1000/1200 mg/d
ART and CD4	CD4 > 100 on suppressive ART, or not on ART with CD4 > 350
Study status	GT 1a capped. Still enrolling GT1b.
SVR12 expected	Q2 2014

www.clinicaltrials.gov

Ongoing Study of Sofosbuvir + RBV in the HIV Co-Infected

Trial name	
Trial identifier	NCT01667731
Study design	open-label
No of subjects	115
HCV patient types	GT 2 and 3 Naïve and PR failures
Sofosbuvir dosing	400 mg QD x 12 wk (naïve) or 24 wk (TF)
RBV dosing	1000/1200 mg/d x 12 wk (naïve) or 24 wks (TF)
Study locations	USA
ART and CD_4	CD_4 > 200 on suppressive ART, or not on ART with CD_4 > 500
Study status	Enrolling
SVR12 expected	Q1 2014

www.clinicaltrials.gov

Future Trials of Anti-HCV Therapy Anticipated in the HIV Co-infected

- Following completion of DDI studies identifying compatible ARVs, the following promising IFN-free anti-HCV regimens in the HCV-mono-infected *may* be tested in the HIV+ population:
  - Sofosbuvir + RBV (likely GT 2 and 3 only)
  - Sofosbuvir + NS5A inhibitor (likely pangenotypic)
    - SOF + GS-5885 fixed-dose combination (FDC)
    - SOF + Daclatasvir
  - NS3 + NNI + RBV (GT1 only)
    - Faldaprevr + BI-207127 + RBV in GT1b or GT1a/IL-28B CC
    - Telaprevir + VX-222 + RBV
  - NS3 + NNI + NS5A ± RBV
    - ABT-450/ABT-267/RTV (FDC) + ABT-333 ± RBV

HCV Infection in Marginalized Populations

Brian Conway, MD, FRCPC
Vancouver Infectious Diseases Centre (VIDC)

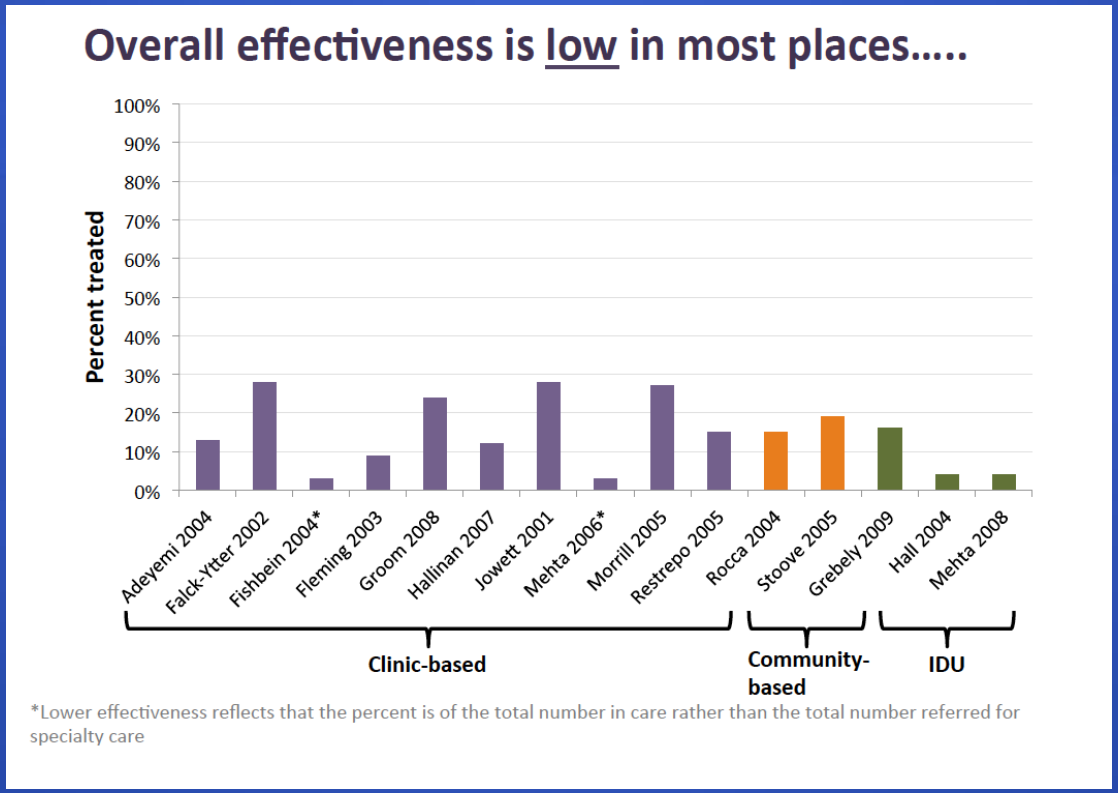
IDUs will drive the future HCV epidemic in Canada

- 300,000 HCV-infected Canadians, including over 180,000 IDUs (60% of prevalent cases)
- 14,000 new cases are diagnosed each year, including over 11,000 in IDUs (78% of incident cases)
- Traditional medical models (diagnosis-treatment-prognosis) will NOT apply to their engagement in care and successful implementation of successful antiviral therapy

Remis, *Health Canada*, 2004. Fischer et al. Can J Pub Health, 2006. Zou. Can J Pub Health, 2003.

HCV Treatment Uptake Overall

Overall treatment uptake is low in most places…..



S. Mehta, with permission

Treatment Uptake in HIV-HCV Co-infection

	N	Cohort	HCV Treatment Uptake
Canada (Vancouver) (Grebely et al. J Viral Hep 2008)	1,361	Urban clinic of HCV & HIV/HCV co-infected patients	1.1%
United States (Baltimore) (Mehta et al. AIDS 2006)	845	Urban clinic of HIV/HCV co-infected patients	3.4%
Australia (NCHECR 2005)	2,500	Needle exchange	4.0%

NCHECR, 2003. Australia.
Grebely et al. J Hepatology, 2006.

Barriers to HCV Treatment

Structural Barriers

- Lack of infrastructure/multidisciplinary support
- Segregated services
- Provincial regulations
- Cost

Provider Barriers

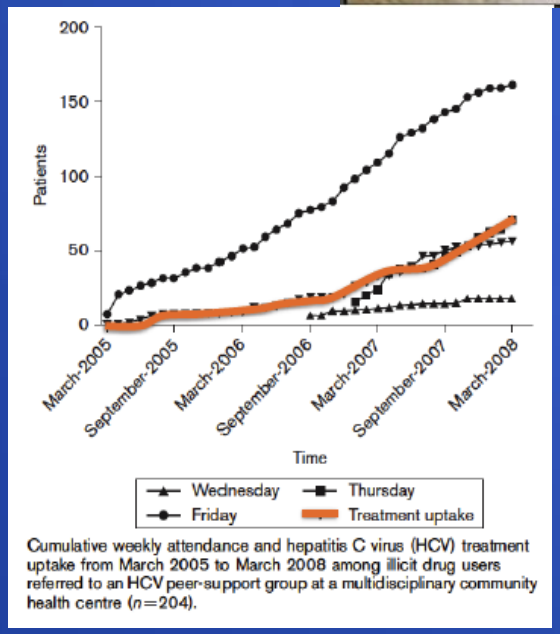
- Poor awareness/education
- Reticence to treat IDUs
- Lack of providers, especially in remote communities
- Focus on HIV

Patient Barriers

- Poor awareness/ education
- Lack of symptoms
- Competing health priorities (HIV, psychiatric)
- Competing social priorities (housing, substance use, financial)
- Fear of side effects

Example: Overcoming structural barriers:

Integrated care / co-location of HCV & Substance abuse treatment



Cumulative weekly attendance and hepatitis C virus (HCV) treatment uptake from March 2005 to March 2008 among illicit drug users referred to an HCV peer-support group at a multidisciplinary community health centre (n=204).

- Co-location of HCV care with methadone maintenance has been associated with favorable outcomes (One-stop shopping)
- Integrated services for HCV, addiction, mental health and psychosocial problems
- Some programs Incorporate peer educators
  - Peer educators are patients who have successfully completed HCV treatment
  - Peers lead support groups with medical providers
  - Provide support through all stages from HCV screening to treatment

Sylvestre 2007; Harris 2010; Litwin 2007; Edllin 2006; Grebely 2010. S. Mehta, with permission

Canadian situation

- 2007 Canadian consensus guideline reads: *An appropriately funded multidisciplinary effort is required to improve care strategies for HCV infected IDU. Antiviral therapy should be considered in selected patients in whom HCV related morbidity & mortality will become relevant.*
- BUT 80% of Canadian physicians specialized in treating viral hepatitis would not treat active drug users

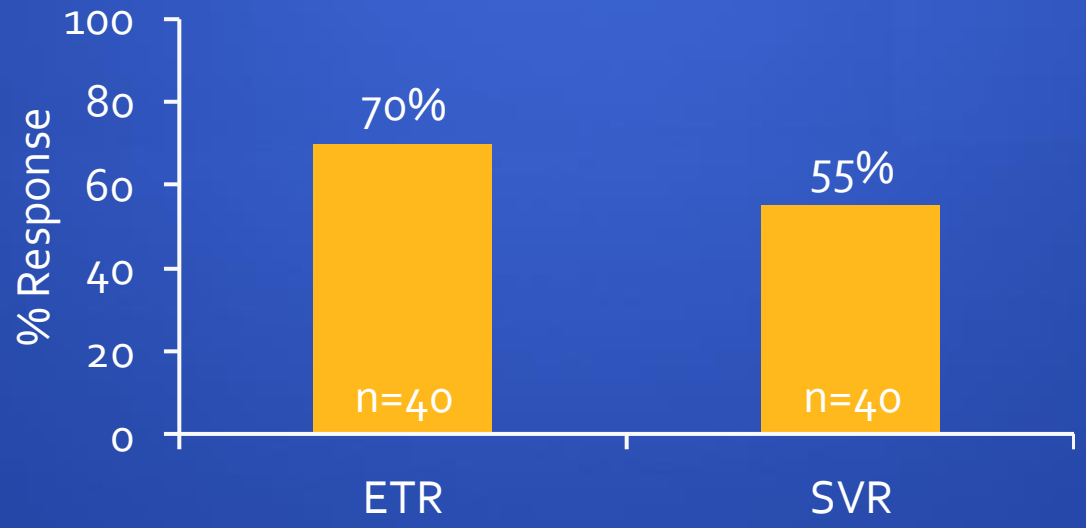
Myles et al. Can J Gastroenterology, 2011

Academic & Community Partnership Care Model

- In the community
- Community & Academic Partnership
- ONE STOP SHOP
- Multidisciplinary
  - Physicians (addiction & hepatology)
  - Nurses
  - Outreach workers
  - Research assistants
- Culture of research & excellence

Patient Characteristics and Response Rates

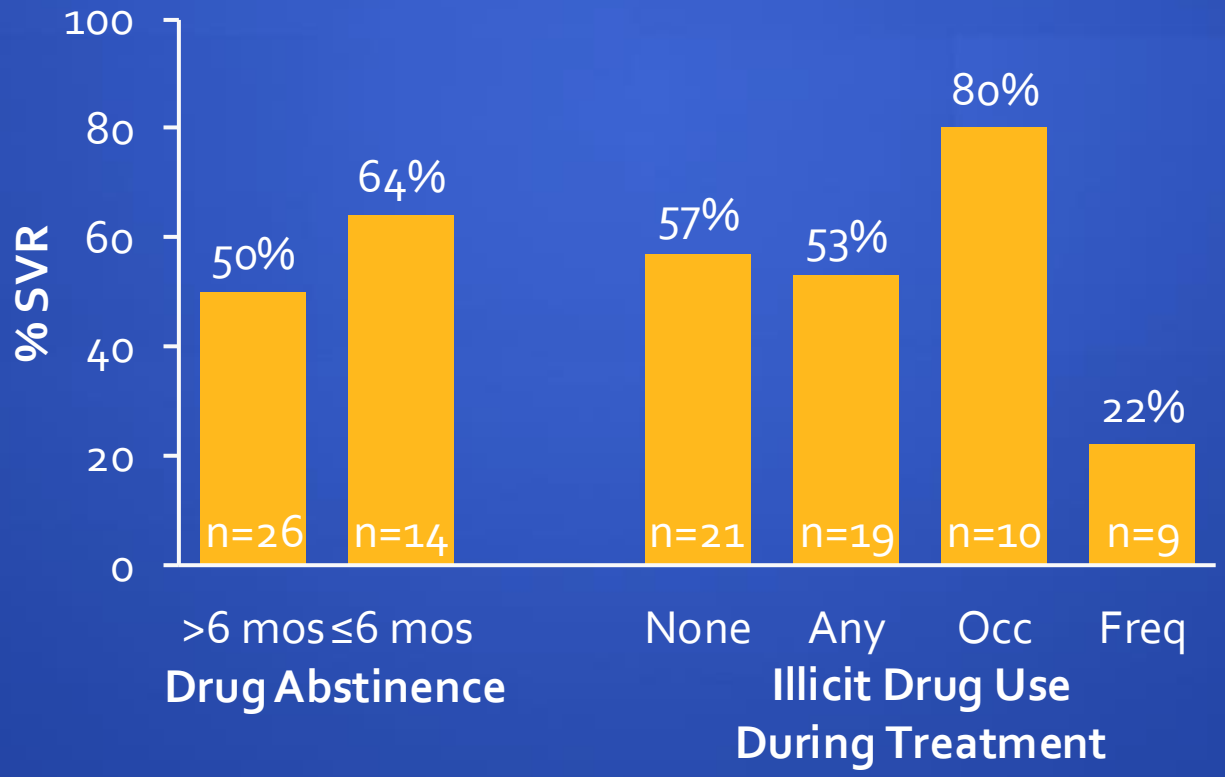
- Mean age 43, 83% male, 55% genotype 2/3
- Early discontinuation - 11 patients (28%)
- Treatment-limiting adverse events – 5 patients (13%)
  - nausea/vomiting, tinnitus, neutropenia, depression, anemia
- Illicit drug use – 6 patients (15%)



Grebely et al. J Gastroenterology and Hepatology, 2007.

Impact of Illicit Drug Use on Response

- 35% used illicit drugs in the last 6 months
- 48% used illicit drugs during treatment
- 10 (25%) used occasionally (monthly or once/twice)
- 9 (23%) used frequently (every day/every other day)



Grebely et al. J Gastroenterology and Hepatology, 2007.

Occurrence of Viremia in IDUs

Table 2. Occurrence of HCV Viremia in Participants Without Previous Infection Versus in Those With HCV Clearance

Characteristic	Previously Uninfected (HCV Ab−; n = 926), n (%)	HCV Clearance (HCV Ab+/HCV RNA−; n = 152), n (%)
Person-years of follow-up	2127	793
Median follow-up (years)	2.8	5.2
Occurrence of viremia	172/926 (18.6%)	14/152 (9.2%)
Incidence (/100 person-years, 95% CI)	8.1 (6.9-9.4)	1.8 (0.9-3.0)

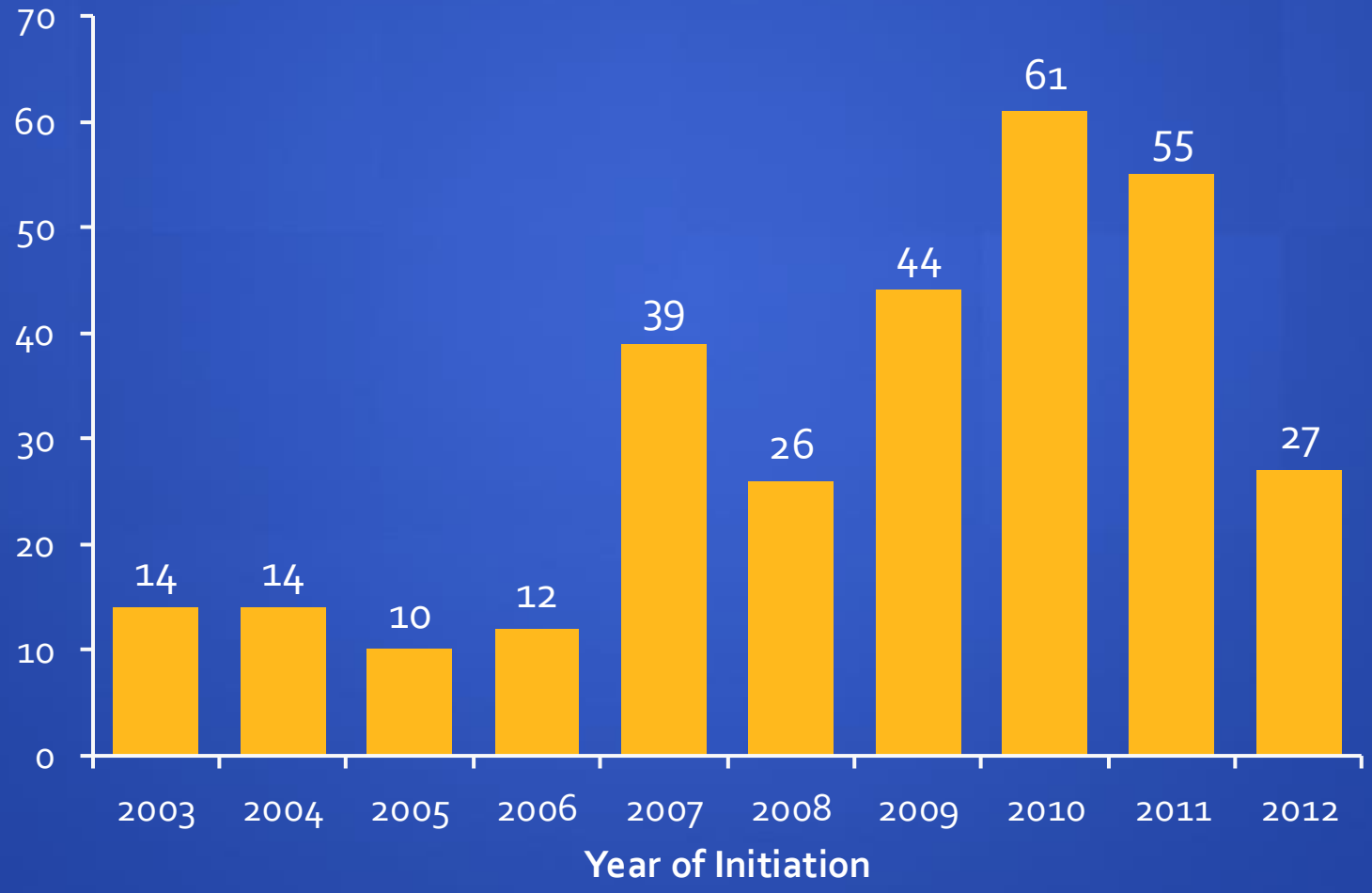
- After adjusting for potential confounders:
  - Individuals with viral clearance were 4 times less likely to develop infection than those infected for the first time
- THESE DATA MAY NOT (OR MAY) APPLY TO TREATMENT-INDUCED VIROLOGIC CLEARANCE

Grebely et al. Hepatology, 2006.

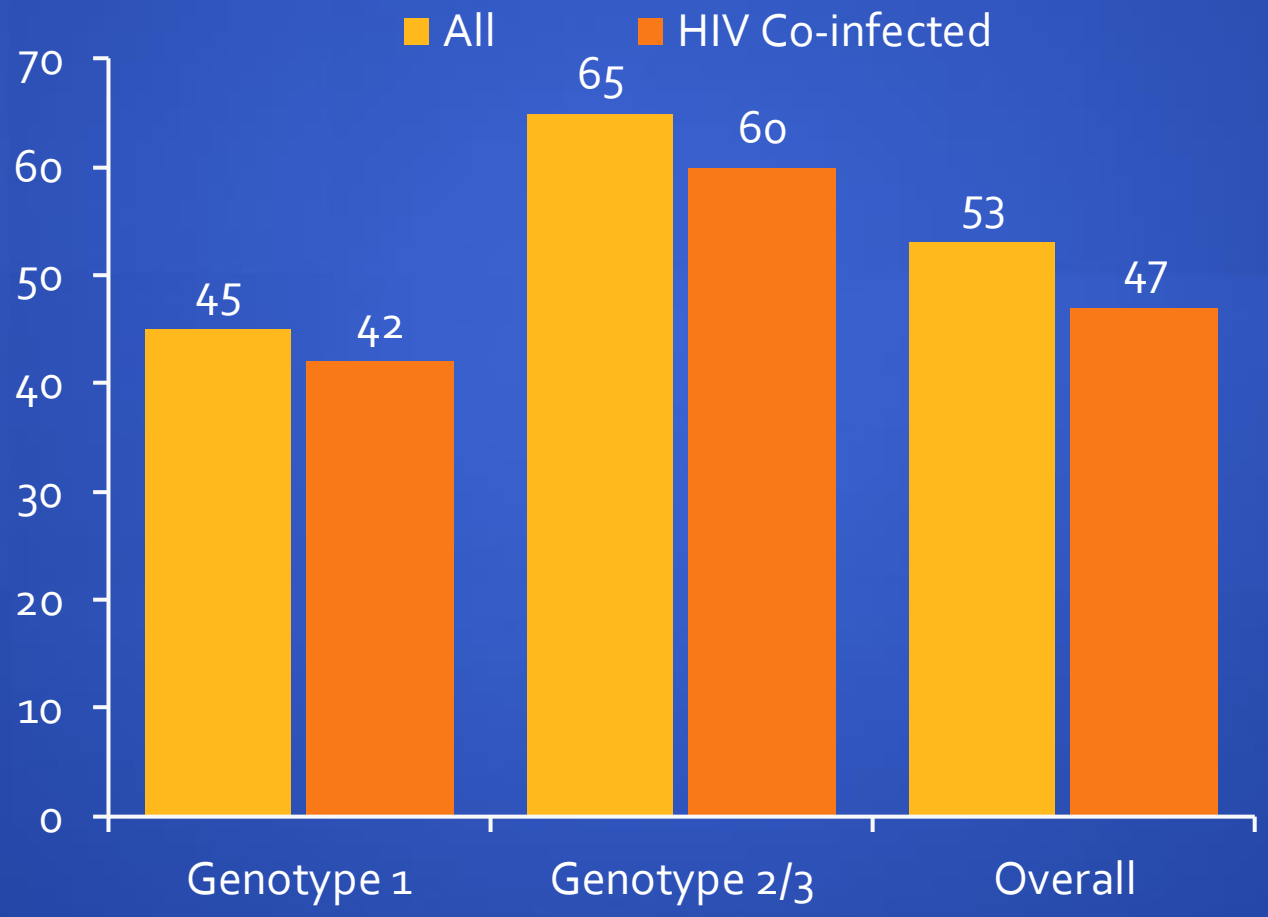
VIDC Baseline Characteristics

Characteristic	n (%)
Total treatment cases, (n)	302
Median Age in yrs (Range)	53 (34-70)
Female, n (%)	44 (15)
HIV co-infection, n (%)	43 (14)
HCV genotype, n (%)	
Genotype 1	189 (63)
Genotype 2/3	113 (37)
Treatment experience, n (%)	
Naïve	252 (83)
Experienced	50 (17)
Liver Cirrhosis, n (%)	33 (11)
History of recent IDU, n (%)	302 (100)
On methadone maintenance therapy, n (%)	211 (70)

Number of patients initiating treatment N=302



SVR rates in all treated and evaluable patients N=251



Treatment Discontinuation in all treated and evaluable patients; n=251

	Genotype 1 N=155	Genotype 2/3 N=96	Overall N=251
Completed Therapy	95 (61%)	72 (75%)	167 (67%)
Discontinued due to:	60 (39%)	24 (25%)	84 (33%)
• Lack of Response	37 (24%)	7 (7%)	44 (17%)
• Drug Toxicity	13 (8%)	14 (15%)	27 (11%)
• Non-adherence / drug relapse	10 (7%)	3 (3%)	13 (5%)

HCV Treatment Discontinuation Rates in IDUs vs. non-IDUs

- Lee et al. (Liver Int. 1270-77, 2012)
- 8853 courses of Peg-IFN-2a in non-IDUs
- 68.3% completion rate
- 10.3% discontinuation for toxicity

Conclusions

- HCV infection can be treated successfully in IDUs with response rates and patterns of treatment discontinuation similar to those seen in other populations, independent of HIV co-infection status.
- As reflected in the 2012 Canadian guidelines for the treatment of HCV infection, IDUs should be considered for HCV therapy when this is medically indicated, preferentially within the context of multidisciplinary community-based models for the delivery of health care where state-of-the-art expertise for the management of HCV infection is available.

EnTEnTE

- Engage: Take people who are not involved in their own health care and get them involved
- Test: Offer HCV testing in a setting favouring patient engagement
- Engage: Once a test result is available, use it to establish a long-term clinical relationship
- Treat: Optimize conditions to achieve SVR
- Engage: Towards a long-term solution to social inequality

THE (NEAR) FUTURE

- Test all marginalized populations for the presence of HCV infection
- Select "optimal" patients for HCV treatment NOW
- Continue to engage non-treated patients in ongoing models of care
- Seek & Treat models MUST be developed for HCV, with a realistic expectation of disease eradication in selected communities, given the increasing efficacy of available treatment modalities

HIV / HCV co-infection

Through the eyes of a co-infected hemophiliac

I.D.

History-The HCV Diagnosis

- More bad news delivered on the heels of an HIV diagnosis.
- I attend funerals for others I knew through the hemophilia clinic, lost to HIV.
- My physician is relieved that I take the news so well. It's the early 90's & my HIV is raging, CD_4 falling, & no treatment is offered. In this context I consider if an HCV infection will even matter? Surely HIV will take me before HCV gets a chance.
- I view treatment as pointless.

The Genetic Lottery

- My physician tells me little is known about predicting progression.
- I am told that approximately 20% clear the virus spontaneously & many live a full life unaware they carry the virus. Did I win the genetic lottery?
- Later I receive PCR and genotype information,…. Sorry, Type 1a & PCR pos, not a winner this time.

OPTIONS

- Do I stick my head in the sand and hope to be a slow or non-progressor?……I remember my previous genetic lottery result.
- Ifn + Rib as a combination arrives - I watch friends suffer and hear stories of very limited success. My HIV is not yet under control, & decide HCV treatment is not for me – at least not yet.
- I continue to wonder if my HCV diagnosis will really matter in the context of my HIV infection. I am told I could wait & choose to do so, but for how long?

Evolution

- HAART arrives & HIV treatment improves. My general health improves. My HIV is finally under control.
- My outlook on life changes from planning no more than 2 years ahead to looking 5years ahead but I'm afraid of another set back.
- I hear talk in the hemophilia community that friends are not dying from HIV anymore, HCV is now taking them.
- Another evolution in HCV treatment arrives - Peg IFN + Rib. The viral clearance numbers are better. Treatment now looks possible although the side effects seem daunting.
- I am told age is a determinant of success & I am approaching 40. My liver enzymes >3xULN, I take the chance.

Early Treatment - Peg Ifn Rib

- Treatment is required for a full year due to geno-type, it's now 2002 - I feel I can do this!
- I am unable to access a hepatologist but treatment is offered through my HIV doctor.
- Treatment costs are high but I still have private drug coverage – I feel lucky, but what about the others?
- I discuss side effects with my physician and he puts me at ease, assures me that not everyone experiences harsh effects to treatment – I am now ready!

Early Treatment – Initial Side Effects

- I take the first dose at the HIV clinic and become ill on the drive home. I crawl into bed. Sweats, chills, high fever, nausea, pounding head, lower back pain, they said flu like, but this is much more. What exactly did I sign on to?
- I panic, was I having an unexpected reaction? I want to call someone to ask if this is going to get worse but it's now after 5pm and no one is available to answer.

Early Treatment continues

- Difficult to eat & unable to enjoy the sun & heat during the summer. Thirsty, always thirsty – a small price to pay.
- Side effects remain strong for the first 6mos then gradually reduce. Weight loss, mood changes & depression seem the worst.
- Interim results are in & it looks like I will clear the virus – hooray!
- Many mornings my wife leaves for work while I remain on the bathroom floor – still thinking it will all be worth it.

What could have improved the treatment experience?

** Support **

- Having someone available by phone in the off hours if I had questions or needed help dealing with a side effect.
- Being connected to someone else that was previously successful for peer support.

After treatment – Peg ifn + Rib

- Treatment ends & my body weight comes back, with a vengeance, I will have to be careful now. It's a problem I actually welcome after experiencing HIV wasting.
- I still have trouble tolerating heat and sun – but it seems a small price to pay.
- My liver enzymes have fallen to almost normal levels, I feel good about the sacrifice.
- 6 mos out I am retested for HCV and find that the virus has returned. I no longer feel lucky.
- Other than longer terms of Peg-ifn treatment no other options are available. I am told I can afford to wait for newer treatments but there are none on the horizon.
- I continue attend the funerals for others I knew through the hemophilia clinic, now lost to HCV instead of HIV.

The Hepatologist

- A few years after treatment failure I am assigned a hepatologist.
- There are still no treatment options to offer other than more peg-ifn + Rib. He speaks of new treatment concepts using protease inhibitors that are far off but coming.
- Closer monitoring with Fibroscan and ultrasound begin.
- I am still sick, but now well documented.
- Results indicate I am one of the lucky ones that can wait for newer treatments to arrive.
- No clear strategy is offered for taking care of my liver in the interim other than advice to increase my coffee intake, avoid alcohol, be careful with my diet and try to exercise.
- I sympathize with my hepatologist for having so few tools to fight HCV and I am reminded again of the early days of HIV infection.

Where do affected persons go for information and support

- Our HIV Physicians & Hepatologists
- AIDS Service Organizations (CATIE is probably the best source)
- Canadian Hemophilia Society
- Provincial/Regional HepC organizations where available (i.e. HepCBC)
- The Internet
- The Canadian Liver foundation
- Other affected persons

The landscape today

Effective treatment may finally be just over the horizon – but for who?

- Fast Forward 10 years from my attempt at treatment with peg-ifn + Rib and HCV treatment is rapidly evolving, similar in many ways to the early days of HIV.
- From the patients perspective an alphabet soup of new medications are now making their way through the pipeline. The results look promising.
- We just need to hold on long enough.

Access to the latest available treatment

Telaprevir & Boceprevir

- Approved by Health Canada
- Doctors & most patients are aware of the improvement in viral clearance rates and there is good reason to be excited about this data.
- These new combinations provide increased rates of viral clearance but are still linked to a high degree of treatment side effects.
- Although the latest data is promising there remains a lack of trials in co-infected persons, and because of this treatments are not yet indicated for this group.

Are the people most in need getting access to the latest treatments?

- Access to Telaprevir & Boceprevir differs by Province, formularies are not uniform – What happened to Universal Health Care?
- For example Ontario provides access to Boceprevir only through the Exceptional Access Program but attaches a list of conditions to restrict use. The reality is that although the drug is available access is being rationed, especially for those most in need.
- Provincial governments should not get a free ride on heels of positive data for new treatment combinations by on one hand making them available through EAP & on the other rationing access through the use of limitations like "co-infected patients are not eligible".

Transplantation

- Livers are in short supply
- To a hemophiliac in need of a liver this is the holy grail. A successful liver transplant represents a win for all sides as it cures hemophilia and potentially reduces a significant cost burden to the system for factor replacement therapy going forward. Unfortunately this option remains only a mirage for not just HCV+ hemophiliacs but all co-infected patients.
- There remains a reluctance within transplant centres here in Canada to offer organs to people co-infected – social stigma?
- Co-infected persons have been known to die, unable to just get on the transplant list let alone receive a transplant – is this just?

What's different

- When compared to early advances in HIV treatment what appears different is an absence of strong patient and researcher based advocacy dedicated to HCV patients.
- While some exist, community based organizations dedicated to HCV are few and underfunded compared to HIV resulting in a void in care and support
- HIV ASO's provide information & have included some advocacy efforts due to the overlap of co-infected patients but is it enough?
- Only a small number of liver specialists exist in Canada, can patients get access to specialized care?
- No organization appears dedicated to pursuing HCV clinical research questions in Canada in the same way we handle HIV.

What's needed

- Improved access to the latest treatments, across all Provinces. Stop excluding those most in need.
- Research into developing treatment strategies to preserve the liver for patients currently in a holding pattern that need or want to wait for future treatments.
- Provide stable funding both Federally and Provincially for organizations supporting HCV infected persons. Delays in renewing funding agreements has put at risk the very existence of many organizations. PHAC has not lived up to the ongoing funding promise made by the Minister of Health in 2008.

What's needed (continued)

- Begin to provide access to transplants for co-infected patients here in Canada.
- Begin to explore the option of using livers from HIV infected donors in infected persons as a life saving measure here in Canada.
- Increase research focusing on the latest HCV treatments in co-infected populations as well as those previously experiencing treatment failure.
- Wider circulation of information and how to access clinical trials combined with encouragement and support for University and Industry research from government. Clinical trials in rural centres are needed.