The dollars of HCV: pay now or pay later

Dan Smyth, MD, FRCPC

AMMI CACMID April 18th,2015

Disclosures:

In the past two years I have participated in research[1] or received consultation/speaking fees[2] from:

- Abbvie[1, 2]
- Gilead[2]
- Merck[1, 2]

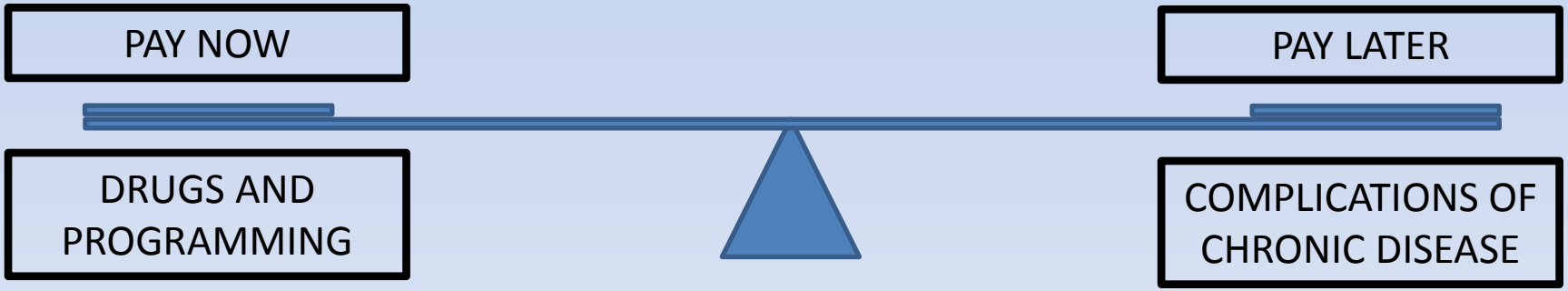
Objectives

(1) To review the health economic impact of untreated HCV

(2) To review the potential economic impact of increased treatment using novel HCV regimens.

(3) To discuss optimal models of care designed to evaluate clinical, epidemiologic, and economic impact in Atlantic Canada.

- The premise:
  - That highly effective therapies for HCV while expensive offset significant (and greater) downstream costs related to complications of chronic untreated infection in Canada.
  - That highly effective and well tolerated therapies represent a unique opportunity to access marginalized populations, which will ultimately achieve significant downstream savings through reduced transmission.



Poll the audience

HCV: Pay now or pay later?

(1) Treat everyone now to prevent complications and incident infections.

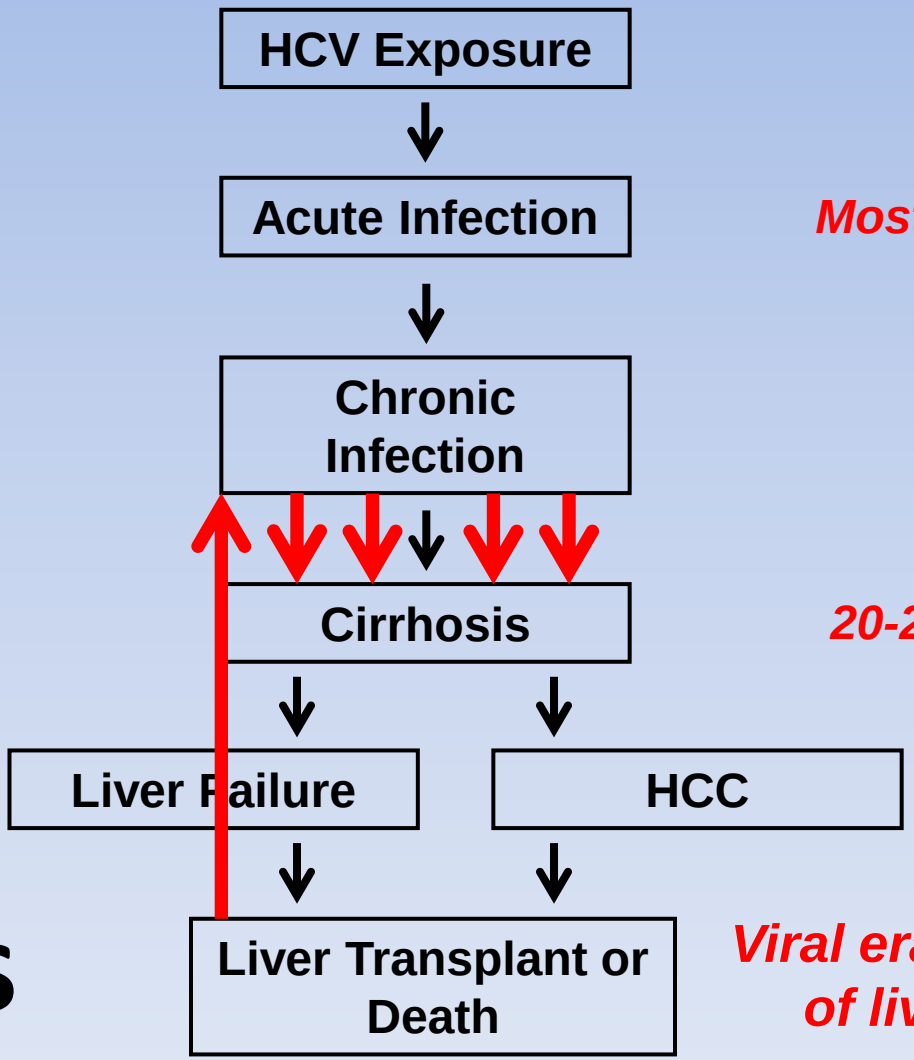
(2) Partial treatment access with Fibrosis restriction (F2).

(3) Focus on the sickest first then expand access to everyone.

(4) Treatment costs way to much, focus on prevention for now and pay later when complications occur.

(5) Give me a little more information and ask me again in 25 min.

Natural History of HCV Infection



$

$$

$$$

$$$$

Most Asymptomatic

20-25% of patients

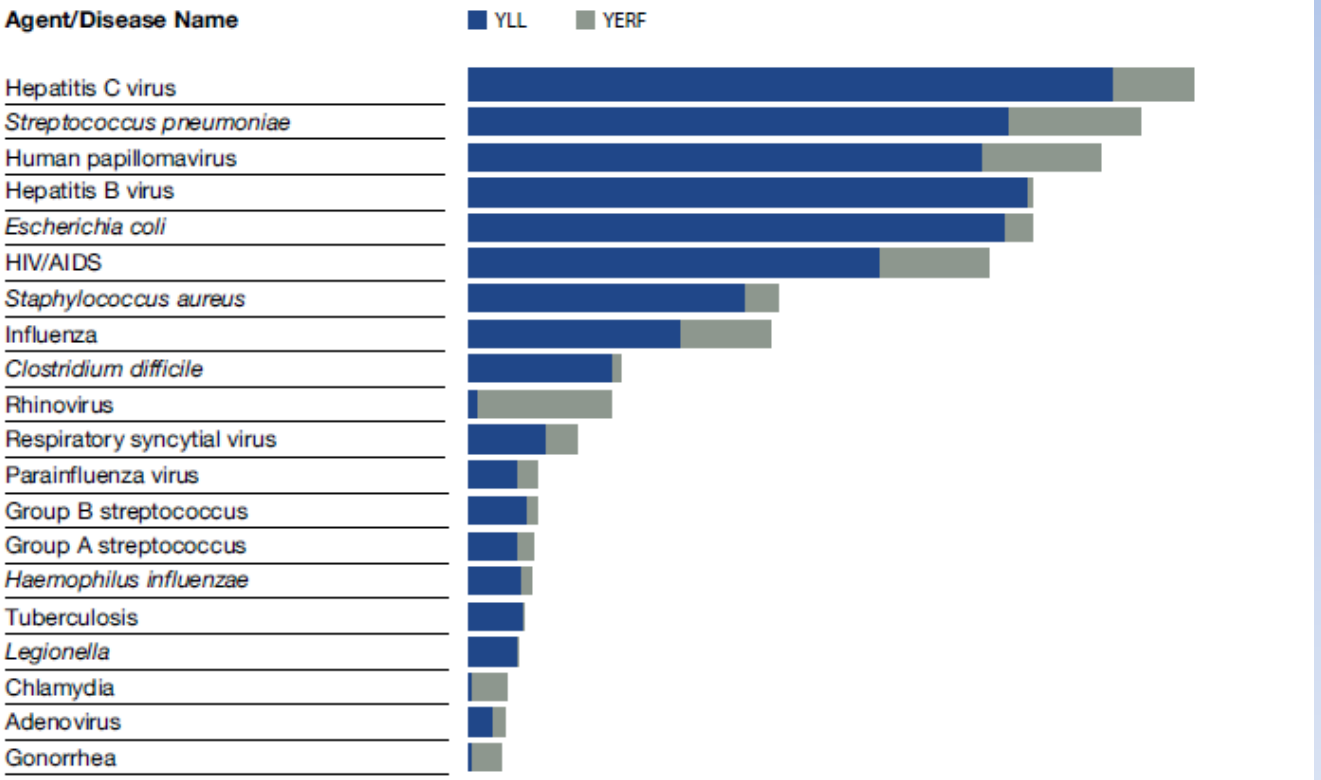
1-4%/year

Viral eradication stops progression of liver disease and improves clinical outcomes

Hepatitis C, of all infectious diseases, is responsible for highest increase in premature mortality.

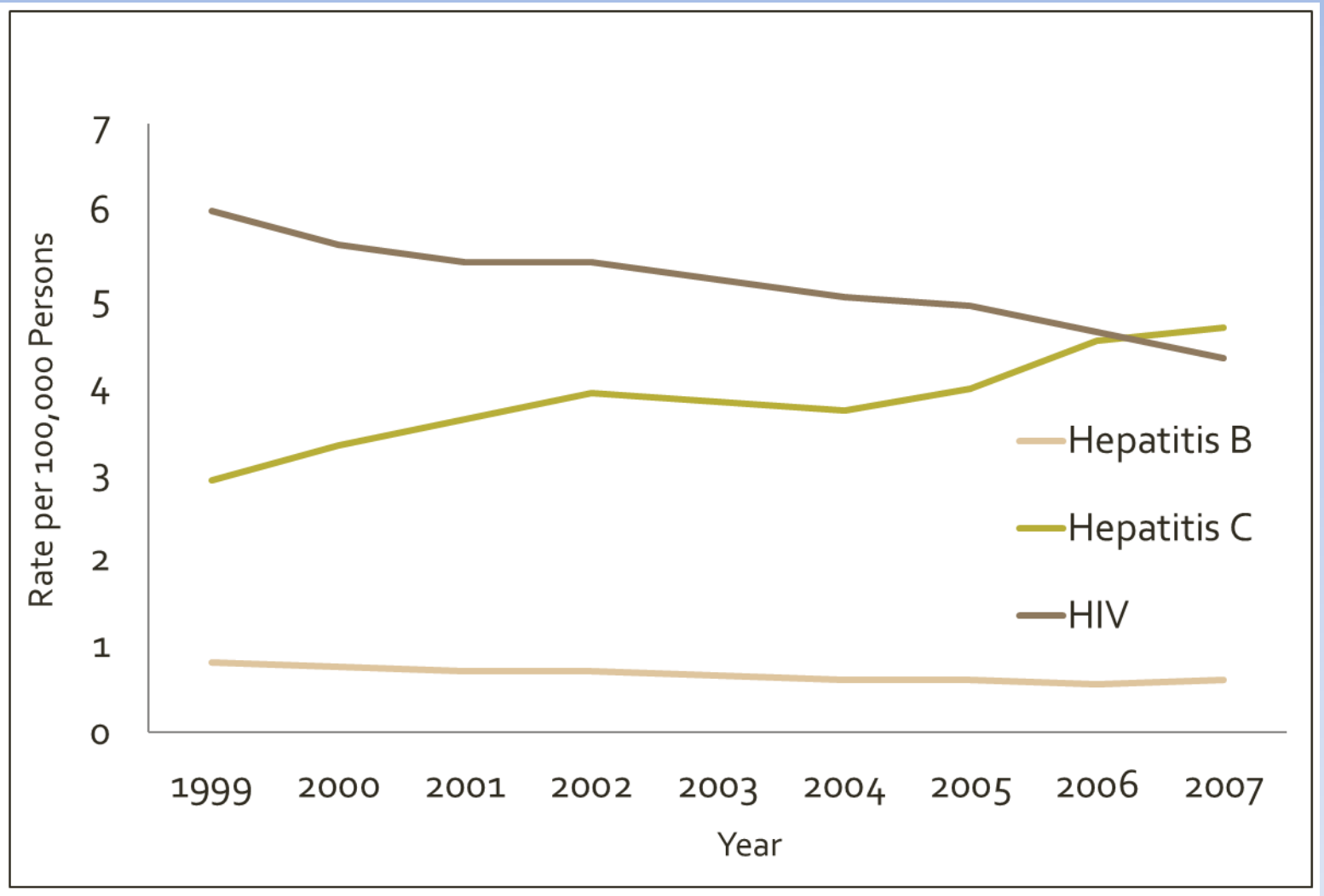
Exhibit 3.5

Years of life lost due to premature mortality (YLL), year-equivalents of reduced functioning (YERF) and health-adjusted life years (HALYs) for the top 20 pathogens, ranked by disease burden



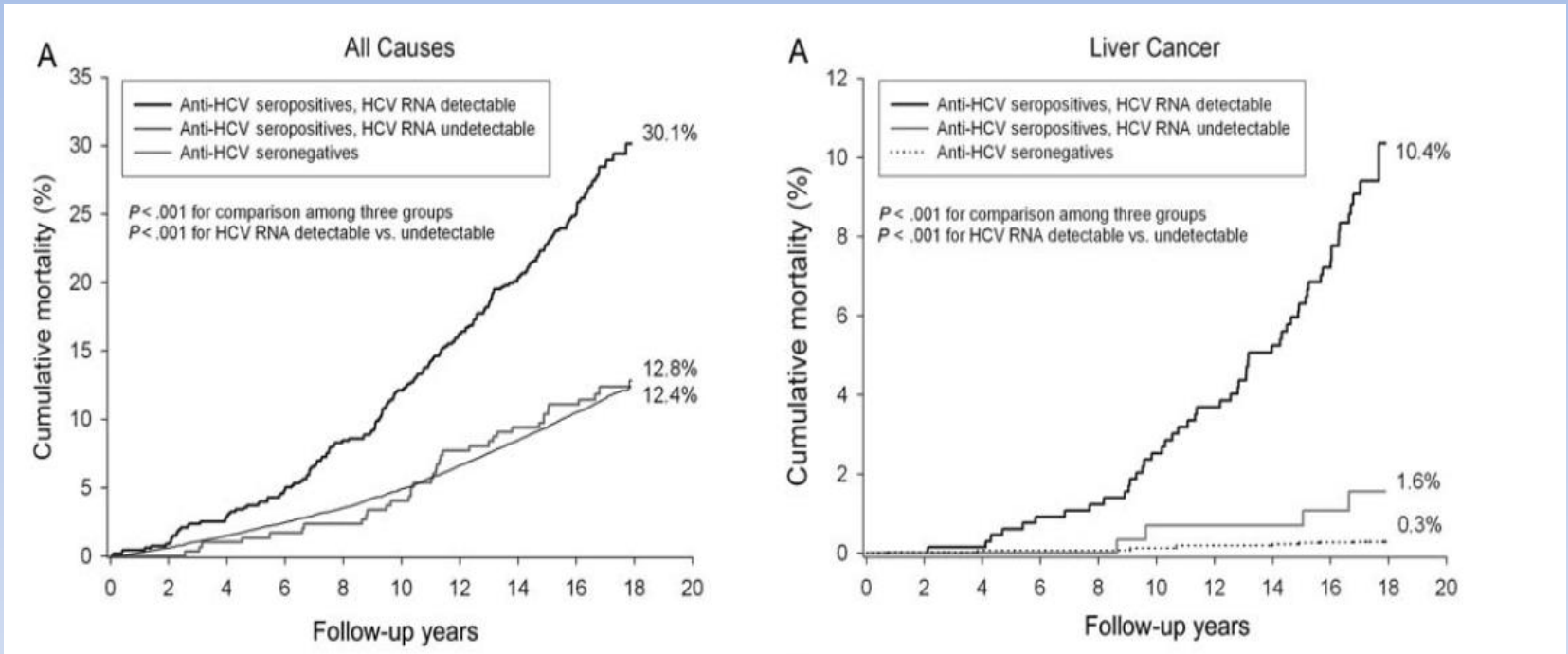
Ontario Agency for Health Promotion and Protection, 2010

HCV related mortality now exceeds that of HIV



Ly et al, Ann Intern Med 2012

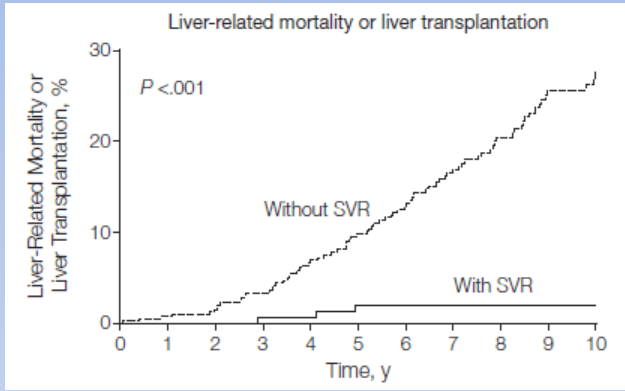
Hepatitis C Medical Burden:

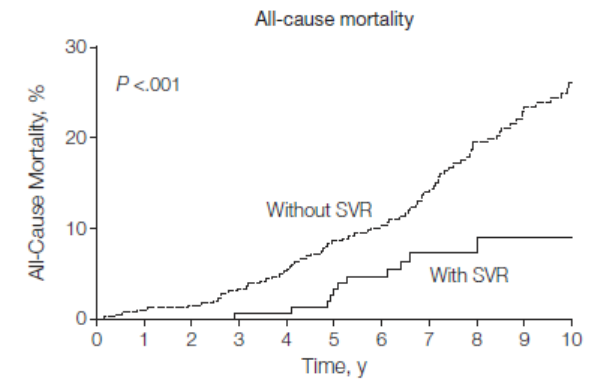


HCV increases all cause mortality.

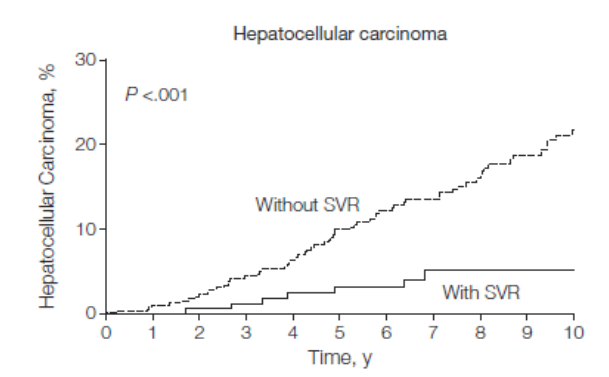
Lee MH et al. J Infect Dis, 2012

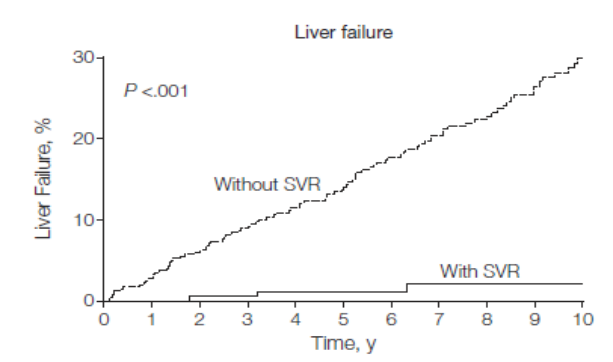
Attainment of SVR associated with:





Reduced liver related and all cause mortality.

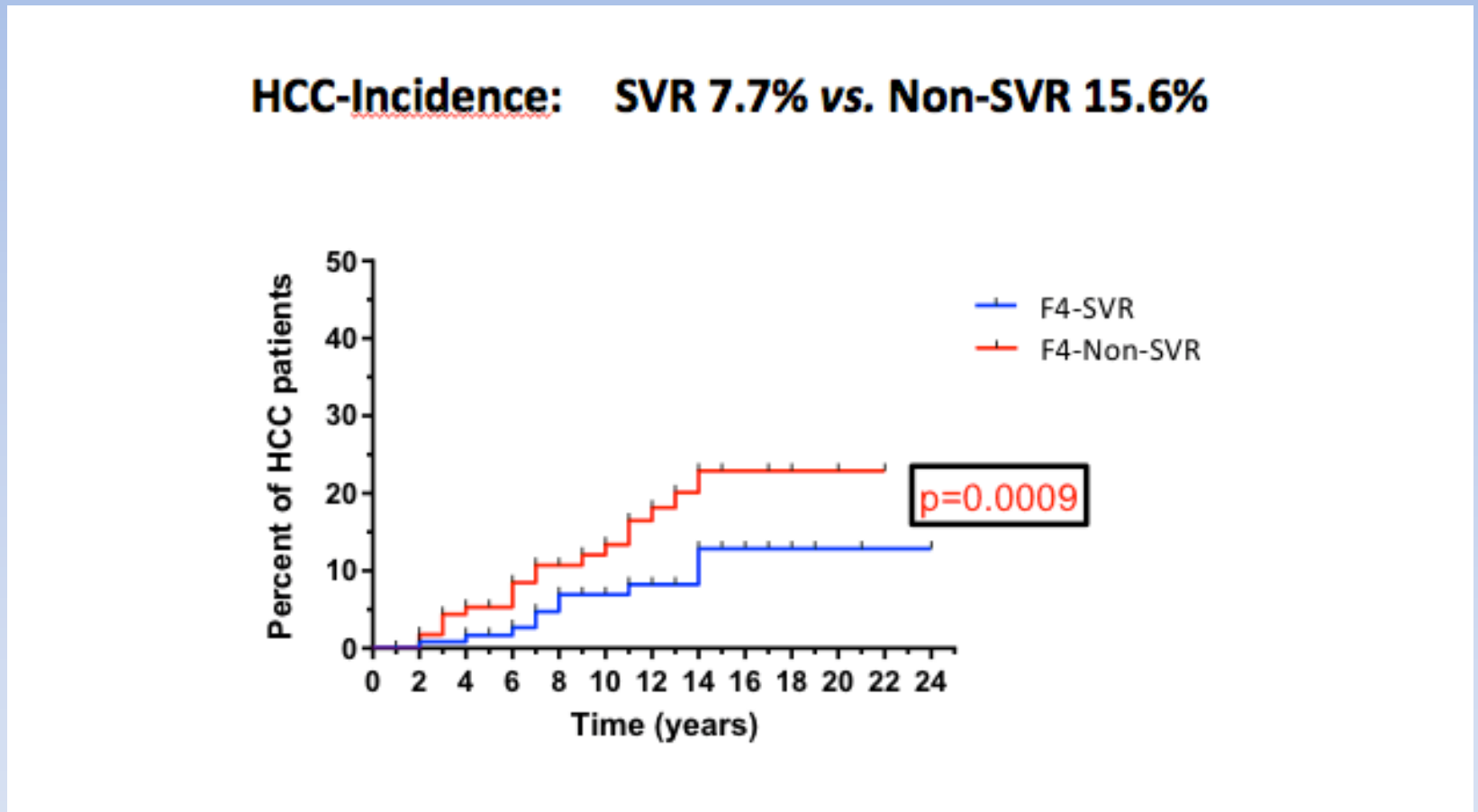




Reduced HCC and liver failure.

Van der Meer, JAMA 2012

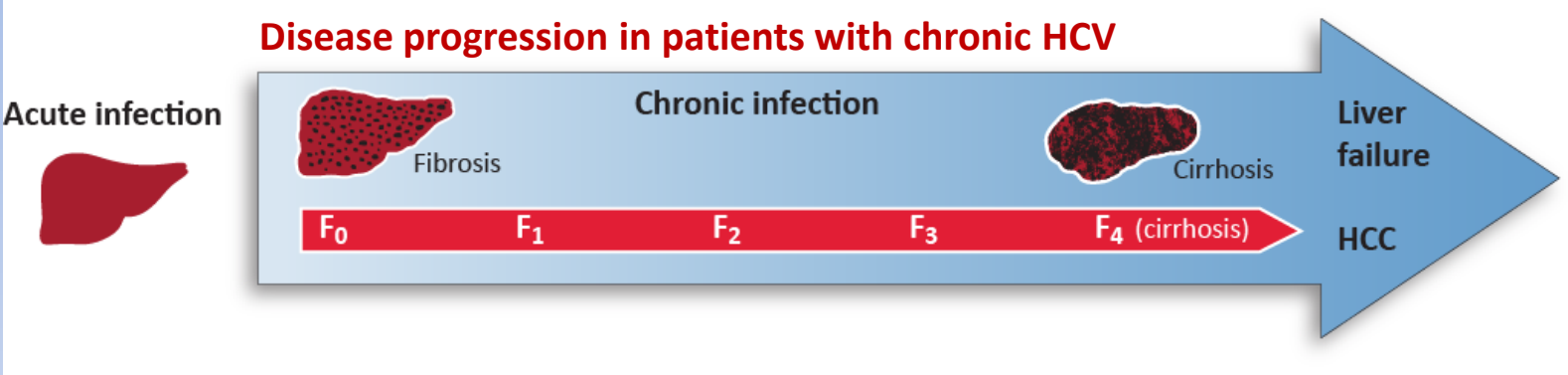
HCC Incidence over time in F4 patients according to SVR status.



Median Follow up 10 years

Purevsambu, EASL 2014 Abstract 0125

Disease Progression and Comorbidities



Morbidities associated with chronic HCV infection[1,2]

PAY NOW

- Cirrhosis
- End stage liver disease
- Hepatocellular carcinoma
- Liver transplantation

DRUGS AND PROGRAMMING

Major co-morbidities associated with chronic HCV infection[3]

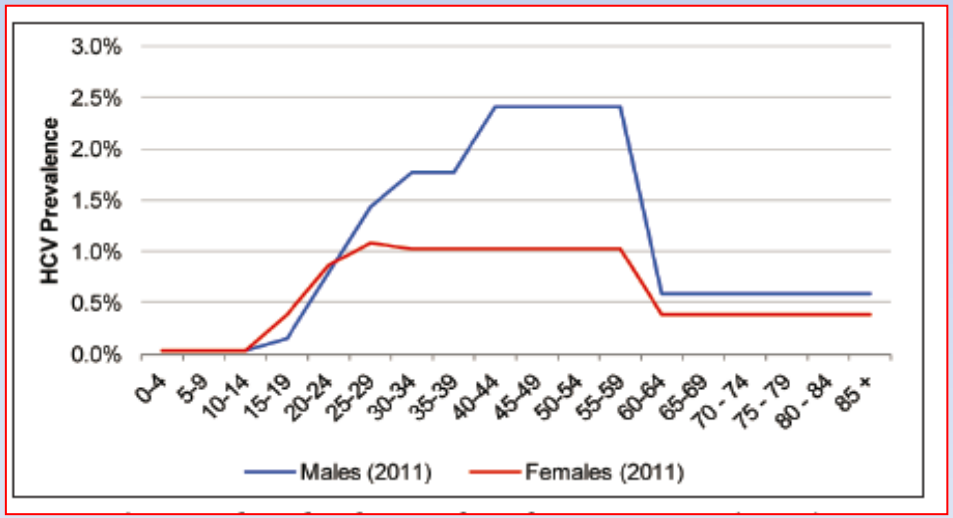
PAY LATER

- Coronary artery disease
- Diabetes

COMPLICATIONS OF CHRONIC DISEASE

1. O'Leary 2008; 2. Perz 2006; 3. White 2008

The coming Wave of Liver Disease



- Driven largely by chronically infected baby boomer population.
- HCV leading cause of hepatic adverse outcome including liver transplantation in North America.
- Curative well tolerated therapies will increase treatment demand and require global management plan with stratified access.

O'Leary et al, Gastroenterology ,2008; Myers et al, CJGH, 2014

2013-2030 Predictions

45% ↑
Liver cirrhosis

90% ↑
Liver related death

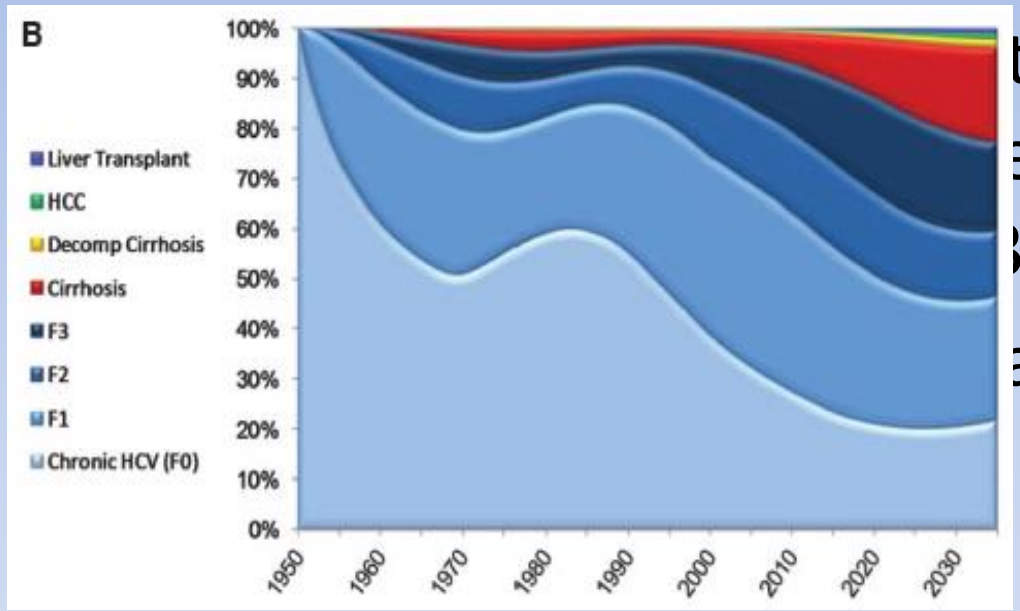
35% ↑
Decompensated cirrhosis

120% ↑
Hepatocellular carcinoma

Sherman, M. (2013). Liver disease in Canada a crisis in the making. *Canadian Liver Foundation*

ORIGINAL ARTICLE

Burden of disease and cost of chronic hepatitis C virus infection in Canada



Versus 2013, increase in compensated cirrhosis, decompensated cirrhosis, HCC and liver related deaths 89%, 80%, 205%, and 160%

tem dynamic framework
eled disease progression
35.
atment.

- Assumptions made:
  - 70% of infected population diagnosed.
  - 77% viremic.
  - Modeled IFN/RBV treatment using historical data and treatment dispensing in Canada.

- Peak comp/decompensated cirrhosis in 2031 (36,210/3380 cases).
- Peak HCC 2035 at 2220 cases.
- Peak mortality 2034.
- 32,460 deaths 2013-2035 from liver related causes.

Myers et al, Can J Gastroenterol Hepatol, 2014

Average annual all-cause healthcare costs are increased with HCV (US):

Patient Population	Mean per person annual healthcare cost (2010 USD[2])
HCV uninfected[1]	**9979**
HCV+, non-cirrhotic[2]	**17,277**
HCV+, compensated cirrhotic[2]	**22,752**
HCV+, ESLD[2]	**59,995**
HCV+, HCC[2]	**112,537**
HCV+, OLT[2]	**145,045**

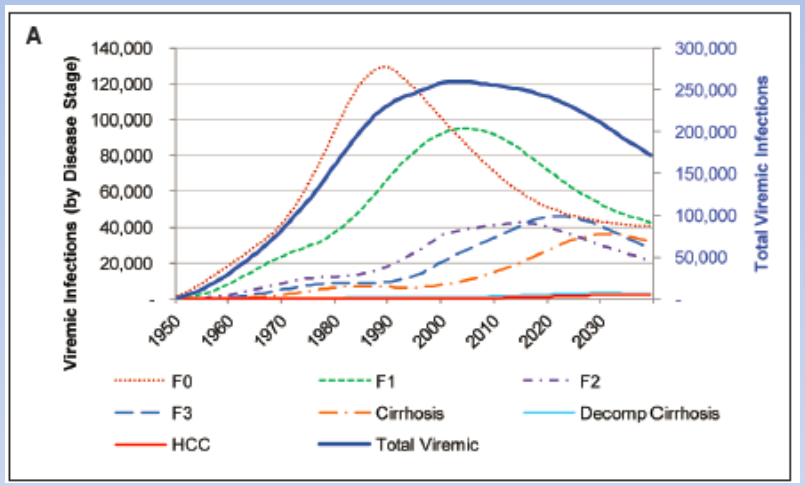
US Insurance claims data > 50,000 persons 2002-2010

Cost 247% higher with ESLD versus non cirrhotic independent of age or other comorbidities (>93% ambulatory, inpatient, and pharmacy).

1. McAdam-Marx, J Manag Care Pharm, 2011; 2. Gordon et al, Hepatology, 2012

ORIGINAL ARTICLE

Burden of disease and cost of chronic hepatitis C virus infection in Canada



Estimated future lifetime cost according to disease state for men 35 to 39 years of age with hepatitis C virus infection in 2013

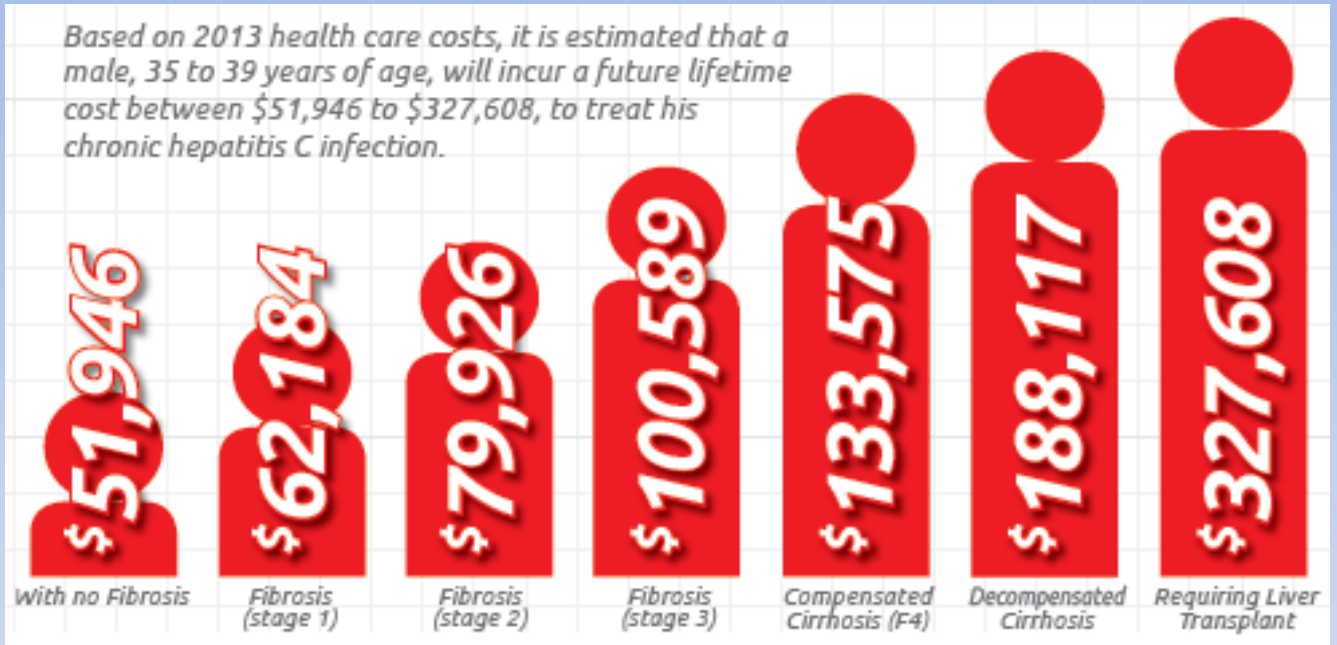
	Cost in 2013, $CAD
Chronic hepatitis C virus infection (F0)	51,946
F1	62,184
F2	79,926
F3	100,589
Compensated cirrhosis (F4)	133,575
Diuretic-sensitive ascites	196,770
Diuretic-refractory ascites	139,330
Variceal hemorrhage	189,398
Hepatic encephalopathy	133,505
Hepatocellular carcinoma	42,376
Liver transplant	327,608

F Fibrosis stage

Prevalence of HCV decreases while cost increases due to treatment of late complications.

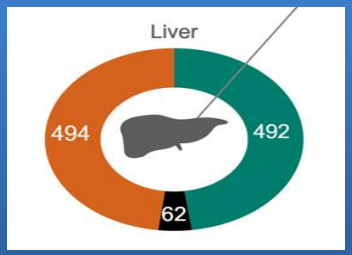
Myers et al, Can J Gastroenterol Hepatol, 2014

Hepatitis C: Significant Burden of Disease[1,2]



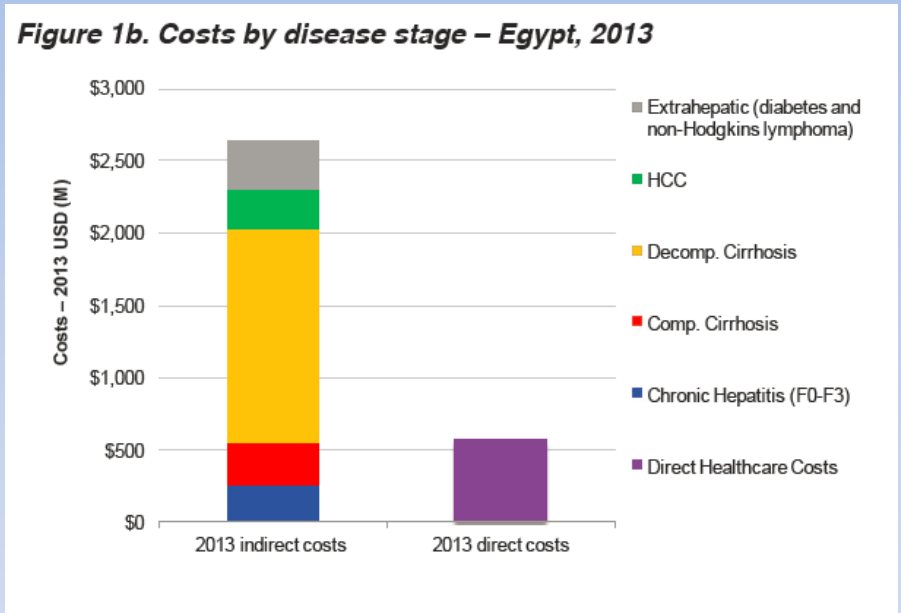
Hepatitis C is the main cause of liver transplantation. In 2012:

- **494 people received liver transplants**
- **492 people remained on the transplant list**
- **62 people died waiting for a transplant[4]**



1. Mühlberger et al 2009; 2. Gordon et al 2012: 3Myers et al. 2014; 4. Transplantation data from Canadian Institutes for Health Information, 2013.

Indirect costs exceed direct medical costs



Direct healthcare cost: $561 M (2013 USD).

Indirect cost: $ 2, 575 M (2013 USD).

Total 3.1 Billion (1.4% GDP).

- **Egypt:**
  - Anti-HCV seroprevalance 14.7% 2008.
  - Modelling of direct/indirect costs 2013.
  - Direct costs for each disease state from national government hospital.
  - Indirect costs by WHO DALY template.
    - YLD from chronic cirrhosis (F0-F3), compensated cirrhosis, HCC and EHM (DM, NHL).
    - YLL due to decompensated cirrhosis, HCC, and EHM.

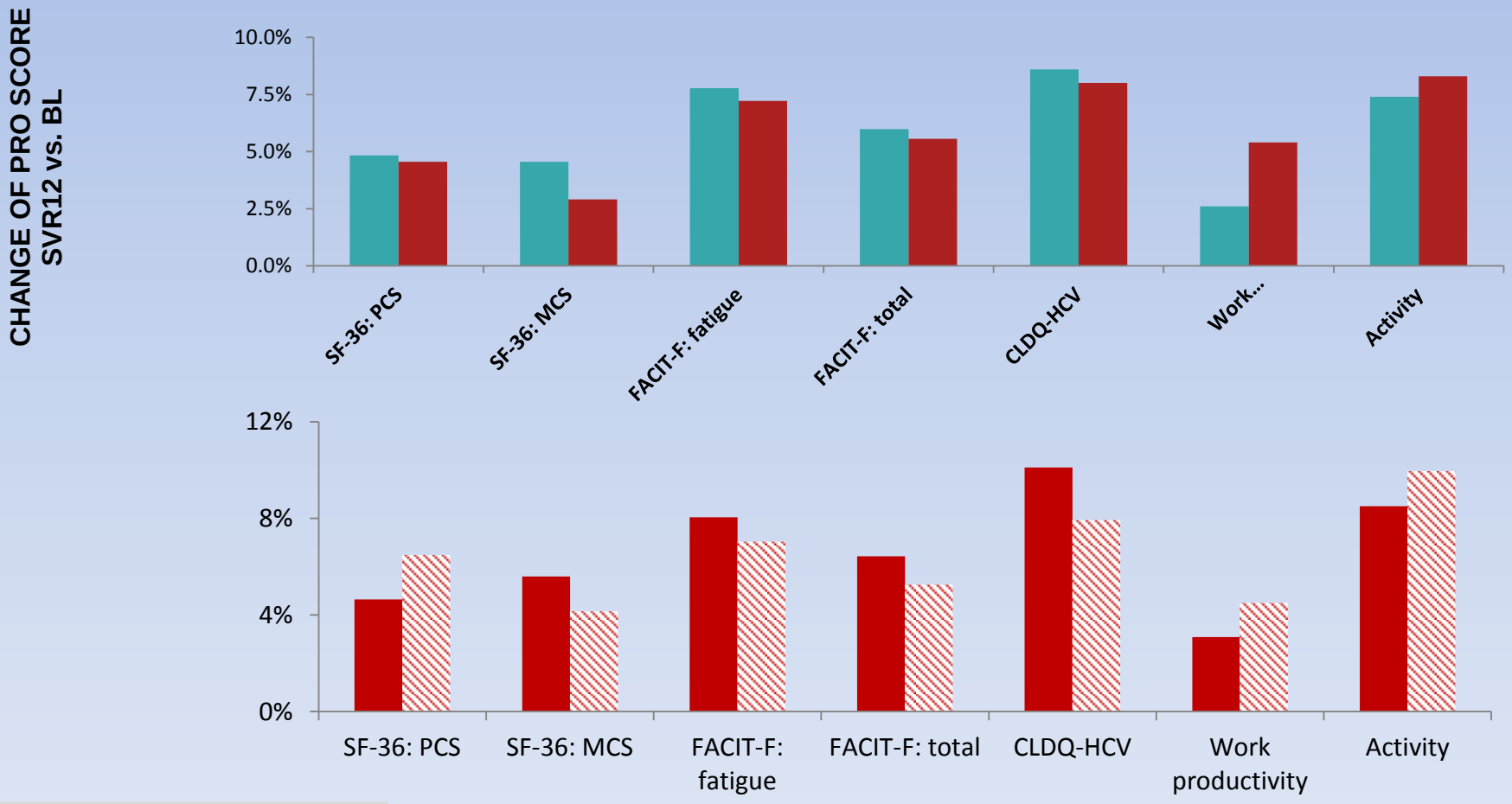
Waked et al, 2014.

SVR12 = improved Quality of Life (QOL) and Patient reported Outcomes (PRO)

Study/Regimen	Measurement	Outcome	Comments
VALENCE (SOF/RBV)[1]	SF-36, FACIT-F, CLDQ-HCV, WPAI-SHP	**SVR12 = improved general health, fatigue, emotional well being, SF-36 physical component summary**	Additional 12w of therapy did not affect PRO.
SOF containing regimes (NEUTRINO, FUSION)[2]	SF-36, FACIT-F, CLDQ-HCV	**SVR12 = improved fatigue using all measurements (P < 0.0001.)**	
QUEST 1/2, PROMISE (SMV/PR)[3]	FSS, WPAI-HCV, EQ-5D	**Versus PR alone reduced fatigue, depression, impairment of daily activities and work productivity, QOL.**	
Aviator (3D)[4]	SF-36, EQ-5D, HCV-PRO	**Minimal PRO impact during treatment, all PRO's improved over baseline at post treatment week 24**	

1. Younossi, EASL 2014. 2. Younossi, EASL 2014. 3. Scott EASL 2014 Poster 1117. 4. Baran, AASLD 2013, Poster 1113

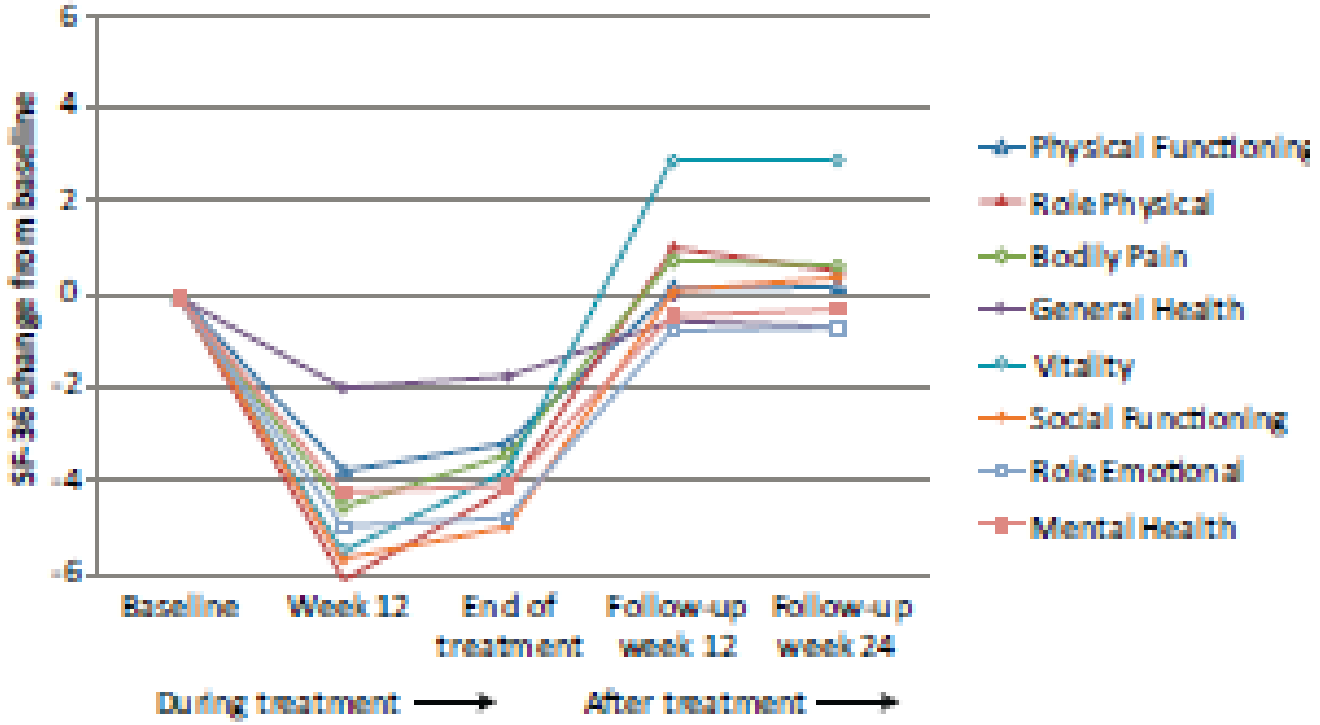
Indirect cost savings: SVR12 improves PRO and QOL even with advanced Fibrosis



Younossi ZM, AASLD, 2014, Posters #77 and1445

Indirect costs substantial with traditional therapy

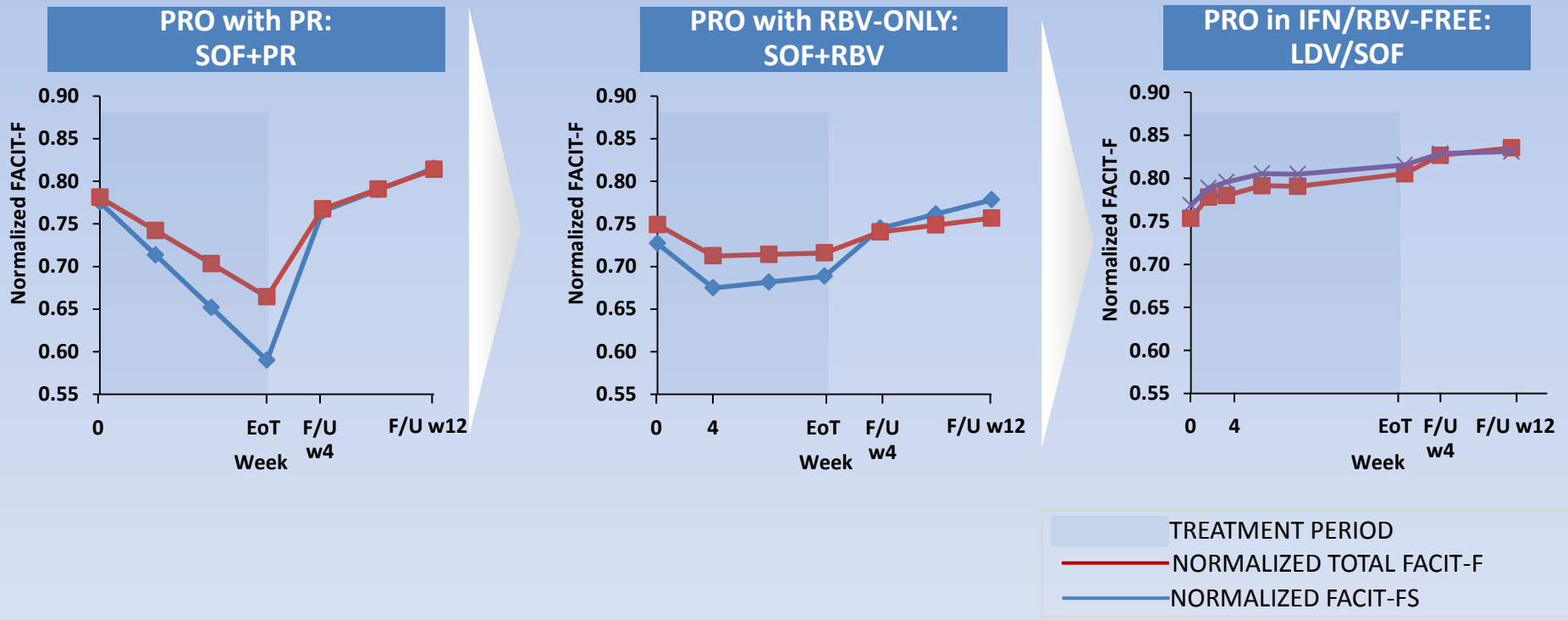
Figure 1: Mean HRQoL scores with IFN therapy: SF-36 response[10]



HRQoL = health-related quality of life; IFN = interferon α; SF = Short Form

Baran et al, AASLD 2013, adapted from McHutchinson et al, J Hepatol, 2001

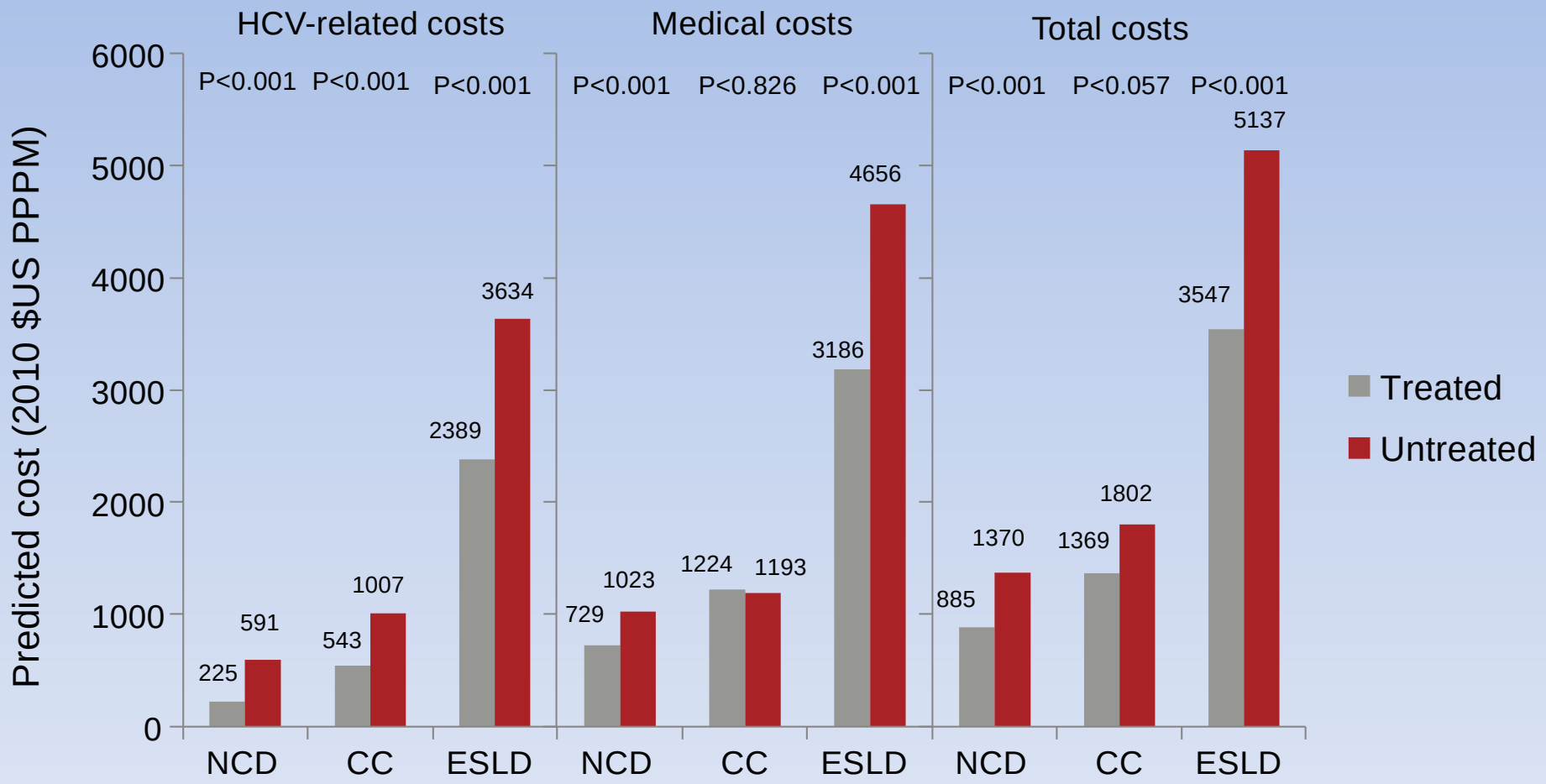
Indirect cost savings: new regimens improve PRO/QOL **on treatment**.



Younossi ZM, AASLD, 2014, Poster #77

- So lets start treating then. But these new drugs are pretty expensive?

Evaluation of Healthcare Costs in HCV Patients by Liver Disease Severity and Treatment Status



PPPM=per-patient-per-month; NCD=non-cirrhotic disease; CC=compensated cirrhosis; ESLD=end-stage liver disease
Covariates adjusted for in the analysis included age, sex, geographical region, index year, baseline comorbidities, and baseline treatment for HCV

Gordon et al. Aliment Pharmacol Ther 2013

Cost of treatment is increasing but cost per SVR is decreasing.

- Cost per SVR in cirrhotic patient, **direct drug cost** only (Canadian list prices).

Regimen	Cost/regimen	SVR (%)	HCV drug cost/G1 SVR
PR 48 weeks + BOC 44 weeks	$66,200	55	66,200/0.55 = $120,364
PR 48 weeks + TVR 12 weeks	$55,000	62	55,000/0.62 = $88,710
PR + SOF 12 weeks	$60,000	80	60,000/0.80 = $75,000
SOF + LDV 12 weeks	$67,000	94	67,000/0.94 = $71,277
3D/RBV 12 weeks	$55,000	92	55,000/0.92 = $59,782

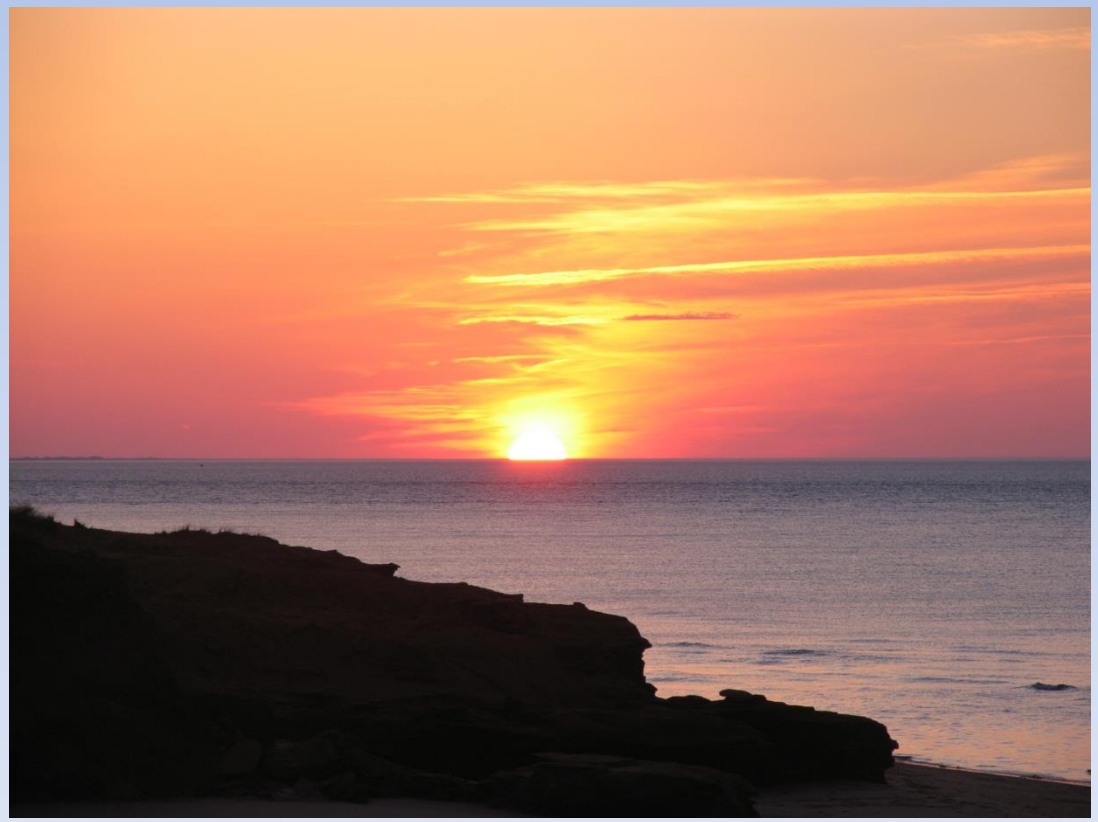
Modified from Shafran et al, CJGH, February 2015, with Poordad, NEJM, May 2014

Real world experience and cost

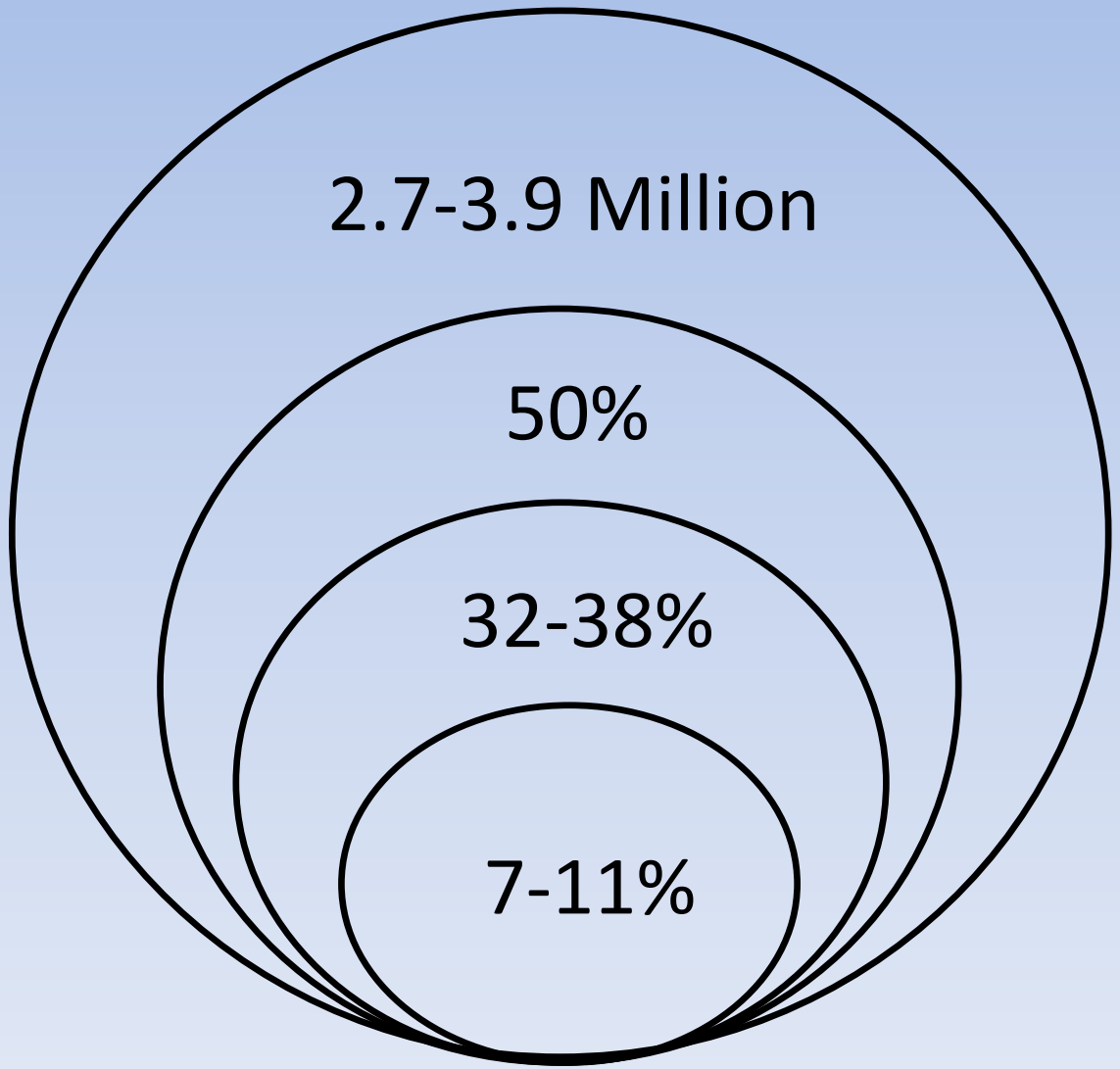
- TVR: registration trials 64-75% SVR
- Real world experience: HCV TARGET[1], 90 centers, > 2000 patients, **overall SVR 54%**, 90% with AE leading to treatment change, serious AE in >10%.
- Real world median cost of SVR in 147 patients 189,338 (2012 USD), with close to 10% of cost spent on AE management[2].

1. Gordon et al, J Hepatology, February 2015; 2. Bichoupan et al, Hepatology, October 2014

Program considerations



The treatment cascade: comprehensive HCV programming is essential



Asrani, Curr Gastroentrol Rep, 2014

Screening and Treatment are Cost-Effective in Canada

Age Group Screened	Strategy	ICER ($)	HCV Deaths Prevented (per 10,000 screened)
25-64			
	Screen and treat with PegIFN/RBV	38,117	9
	Screen and treat with DAA	34,783	18
45-64			
	Screen and treat with PegIFN/RBV	34,359	9
	Screen and treat with DAA	35,562	21

Wong W et al. CMAJ, Jan 2015

Defining ‘Highest’ or ‘High’ Priority HCV Patients for Treatment in the Chronic Hepatitis Cohort Study (CHeCS)

Retrospective study by CDC to identify how many patients in CHeCS database fall into the ‘Highest’ or ‘High’ Priority classification as defined by AASLD/IDSA treatment guidelines in the real-world

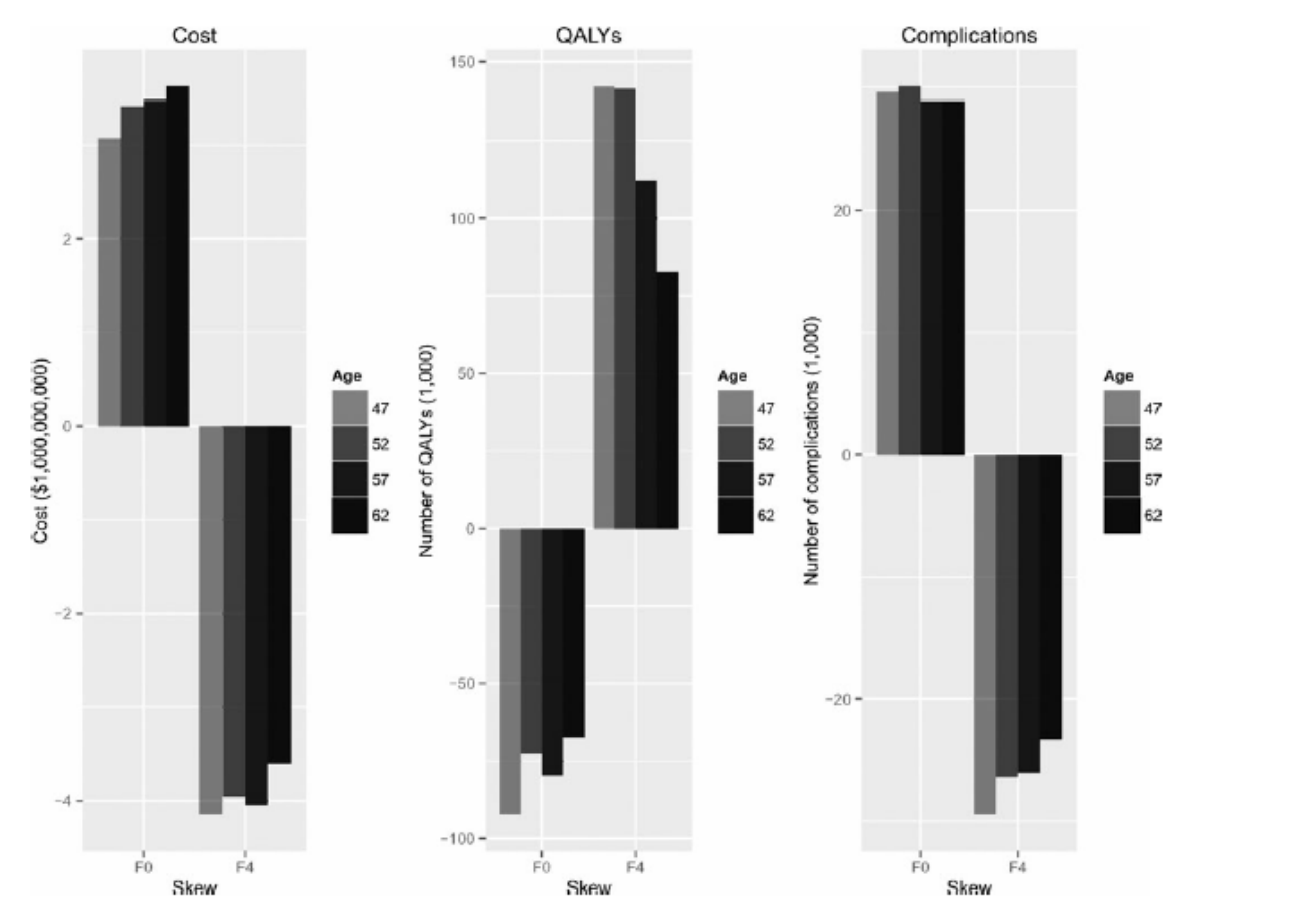
Patient Characteristics	
Patients Staged by Biopsy or FIB-4 Score (N=8,504)	% TOTAL
HIGHEST PRIORITY	**32.9**
F3 (biopsy staged F3 or higher or FIB-4 score ≥2.5)	30.0
Less than F3 with chronic kidney disease	2.9
HIGH PRIORITY	**28.9**
F2 (biopsy stage F2 of FIB-4 score ≥1.6 but <2.5)	22.7
Less than F2 with HIV co-infection	0.7
Less than F2 with HBV co-infection	0.2
Less than F2 with NASH	0.4
Less than F2 with Diabetes	4.9
NOT MEETING ‘HIGHEST OR HIGH’ PRIORITY CRITERIA	**38.1**

The majority of CHC patients in the USA fall within the ‘highest’ and ‘high’ treatment priority designation.

Restricting treatment to only patients with advanced fibrosis will deprive a large percentage of patients from needed treatment.

Xu F, AASLD, 2014, LB-29

F4 prioritization decreases cost and liver complications



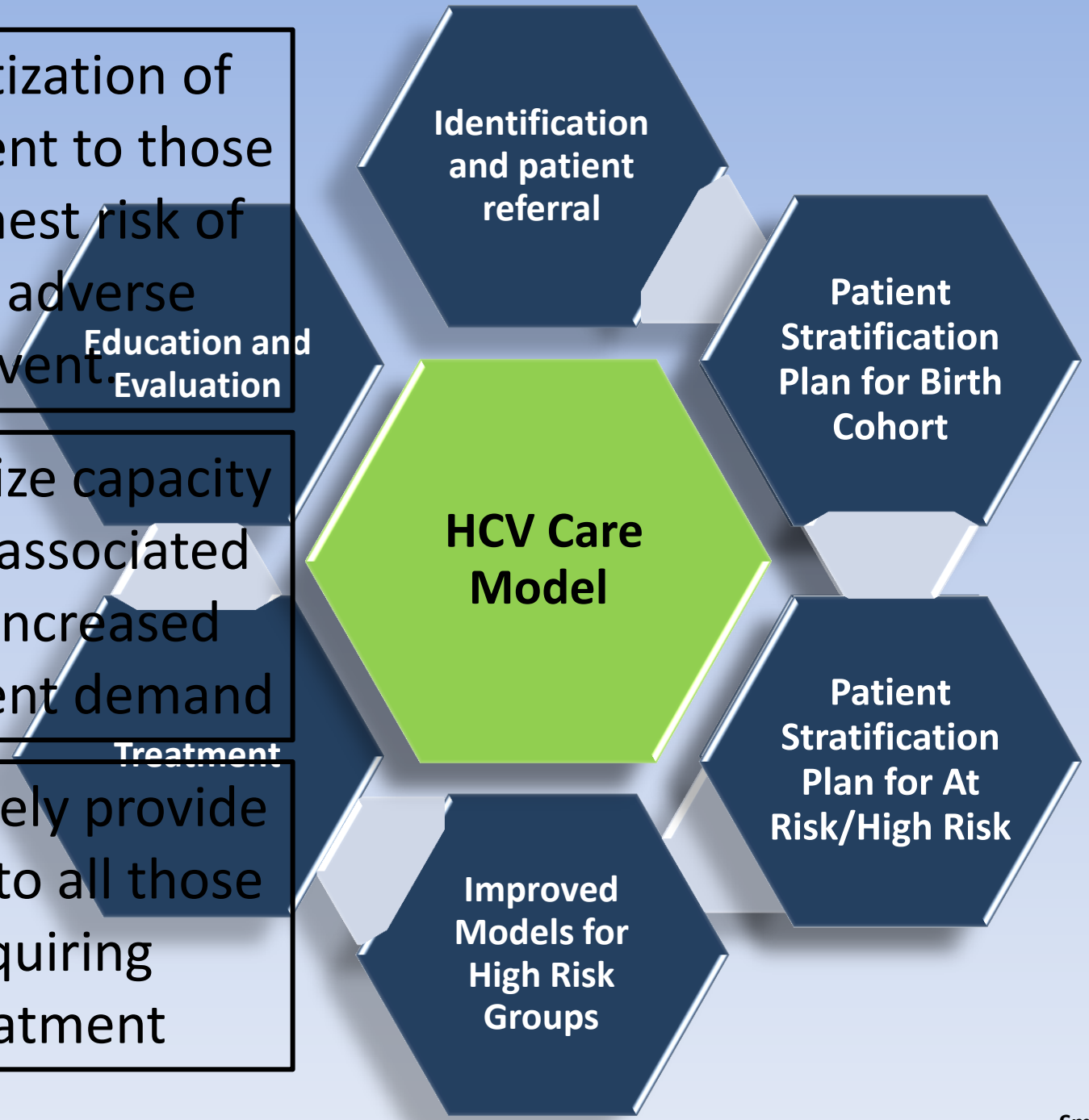
Markov HCV simulation model to model if phased fibrosis dependent treatment offers health economic value in screened baby boomers.

McEwan et al, Hepatology, 2013

Prioritization of treatment to those at highest risk of liver adverse event.

Recognize capacity issues associated with increased treatment demand

Ultimately provide access to all those requiring treatment



Smyth, CJGH, Nov 2014

Birth Cohort Stratification

Phase 1 (Short term, years 1-2, highest risk of hepatic adverse event or complication):
Cirrhosis with documented Fibrosis F3/F4.
Extra hepatic manifestation of chronic HCV infection.
HIV Positive
At discretion of HCV expert.
Phase 2 (incorporates lower risk patients):
Cirrhosis with documented Fibrosis F2/F3/F4.
Extra hepatic manifestation of chronic HCV infection.
Patient with HCV infection > 10 years.
At discretion of HCV expert.
Phase 3 (incorporates most patients):
All remaining patients at discretion of HCV expert.

Smyth, CJGH, Nov 2014

Targeting core transmitters

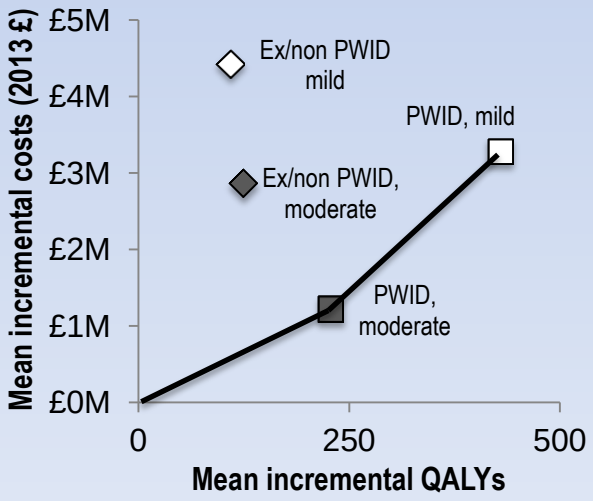
- Persons who inject drugs (PWID) account for 70-80% of incident infections in Canada.
- 50-80% will be seropositive after one year of IVDU.
- Estimated that average PWID will infect 20 persons, with majority of transmission event taking place in the first two years.
- 42.14% of opioid dependent persons in New Brunswick methadone maintenance clinic HCV+.

Davis, NEJM, 2001; Magiokinis, PLoS Cumput Biol, 2013; Manzer, 2012

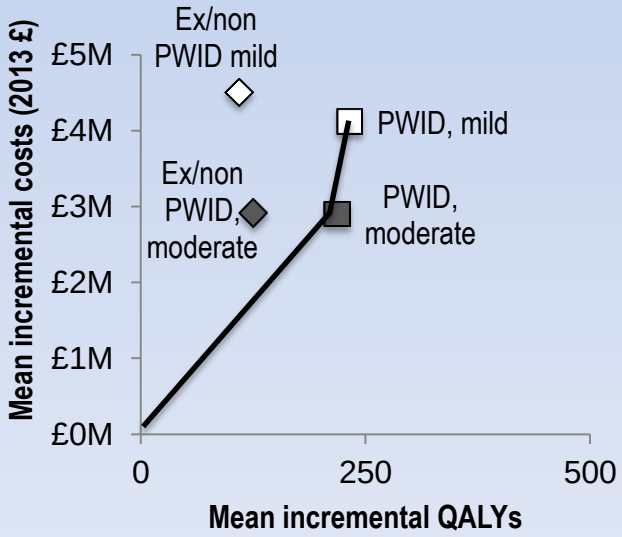
A Cost-Effectiveness Analysis for Prioritizing PWID / non-PWID Subpopulations for HCV Treatment

- HCV transmission and progression cost-effectiveness model to inform prioritization of HCV treatment; prioritizing cirrhotic patients was compared to prioritizing patients with IV drug use (PWID) and ex/non PWID with mild/moderate disease.
- In scenarios with low or medium HCV prevalence in PWID, it is cost-effective to prioritize treatment to PWID at earlier disease stages
  - These strategies likely prove to be cost-effective due to the substantial prevention benefits accrued by treating patients at an earlier stage of disease.

20% BASLINE CHC PREVALENCE AMONG PWID



40% BASLINE CHC PREVALENCE AMONG PWID



Martin NK, AASLD, 2014, #1752

RECAP model of care

- Centre for Research, Education and Clinical Care of At-Risk Populations (RECAP).
- Nurse practitioner-led, inter-professional model of care for patients who are HCV-positive or at-risk of HCV acquisition.
- After optimization of clinical, mental, and social status, and with consideration to other comorbidities, it is determined whether the patient is a candidate for HCV treatment.
- Saint John based demonstration of model to ensure clinical effectiveness with planned expansion to other areas in NB.

R.E.C.A.P.
Centre for Research, Education & Clinical Care of At-Risk Populations

Populus

Inclusive registration of all treated patients

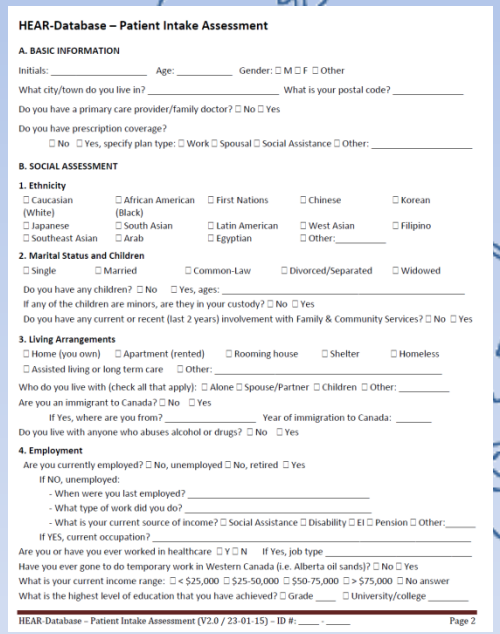
Voluntary evaluation/linkage to direct and indirect healthcare costs

Mechanism for outcomes measurement and program improvement

Populus

HEAR Database

(Hepatitis C Positive and At-Risk Prospective Patient Database)



HEAR-Database – Patient Intake Assessment

A. BASIC INFORMATION

Initials: _____ Age: _____ Gender: ☐ M ☐ F ☐ Other

What city/town do you live in? _____ What is your postal code? _____

Do you have a primary care provider/family doctor? ☐ No ☐ Yes

Do you have prescription coverage?
☐ No ☐ Yes, specify plan type: ☐ Work ☐ Spousal ☐ Social Assistance ☐ Other: _____

B. SOCIAL ASSESSMENT

1. Ethnicity

☐ Caucasian (White) ☐ African American (Black) ☐ First Nations ☐ Chinese ☐ Korean
☐ Japanese ☐ South Asian ☐ Latin American ☐ West Asian ☐ Filipino
☐ Southeast Asian ☐ Arab ☐ Egyptian ☐ Other:_____

2. Marital Status and Children

☐ Single ☐ Married ☐ Common-Law ☐ Divorced/Separated ☐ Widowed

Do you have any children? ☐ No ☐ Yes, ages: _____
If any of the children are minors, are they in your custody? ☐ No ☐ Yes
Do you have any current or recent (last 2 years) involvement with Family & Community Services? ☐ No ☐ Yes

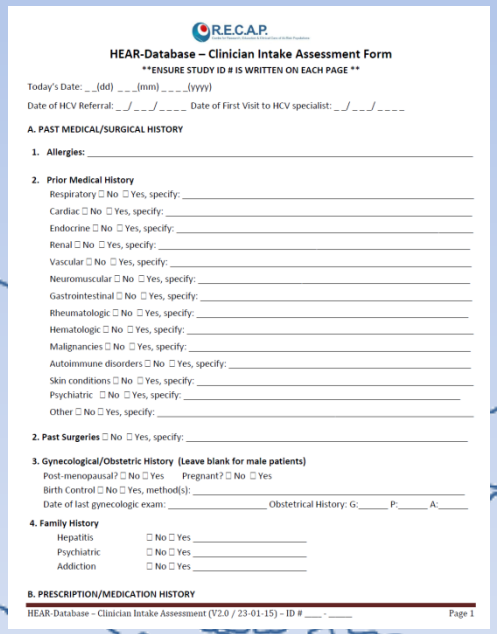
3. Living Arrangements

☐ Home (you own) ☐ Apartment (rented) ☐ Rooming house ☐ Shelter ☐ Homeless
☐ Assisted living or long term care ☐ Other: _____
Who do you live with (check all that apply): ☐ Alone ☐ Spouse/Partner ☐ Children ☐ Other: _____
Are you an immigrant to Canada? ☐ No ☐ Yes
If Yes, where are you from? _____ Year of immigration to Canada: _____
Do you live with anyone who abuses alcohol or drugs? ☐ No ☐ Yes

4. Employment

Are you currently employed? ☐ No, unemployed ☐ No, retired ☐ Yes
If NO, unemployed:
- When were you last employed? _____
- What type of work did you do? _____
- What is your current source of income? ☐ Social Assistance ☐ Disability ☐ EI ☐ Pension ☐ Other:_____

If YES, current occupation? _____
Are you or have you ever worked in healthcare ☐ Y ☐ N If Yes, job type _____
Have you ever gone to do temporary work in Western Canada (i.e. Alberta oil sands)? ☐ No ☐ Yes
What is your current income range: ☐ < $25,000 ☐ $25-50,000 ☐ $50-75,000 ☐ > $75,000 ☐ No answer
What is the highest level of education that you have achieved? ☐ Grade ____ ☐ University/college _____



R.E.C.A.P.

HEAR-Database – Clinician Intake Assessment Form

****ENSURE STUDY ID # IS WRITTEN ON EACH PAGE ****

Today's Date: _ _(dd) _ _ _(mm) _ _ _ _(yyyy)

Date of HCV Referral: _ _/ _ _ _/ _ _ _ _ Date of First Visit to HCV specialist: _ _/ _ _ _/ _ _ _ _

A. PAST MEDICAL/SURGICAL HISTORY

1. Allergies: _____

2. Prior Medical History

Respiratory ☐ No ☐ Yes, specify: _____
Cardiac ☐ No ☐ Yes, specify: _____
Endocrine ☐ No ☐ Yes, specify: _____
Renal ☐ No ☐ Yes, specify: _____
Vascular ☐ No ☐ Yes, specify: _____
Neuromuscular ☐ No ☐ Yes, specify: _____
Gastrointestinal ☐ No ☐ Yes, specify: _____
Rheumatologic ☐ No ☐ Yes, specify: _____
Hematologic ☐ No ☐ Yes, specify: _____
Malignancies ☐ No ☐ Yes, specify: _____
Autoimmune disorders ☐ No ☐ Yes, specify: _____
Skin conditions ☐ No ☐ Yes, specify: _____
Psychiatric ☐ No ☐ Yes, specify: _____
Other ☐ No ☐ Yes, specify: _____

2. Past Surgeries ☐ No ☐ Yes, specify: _____

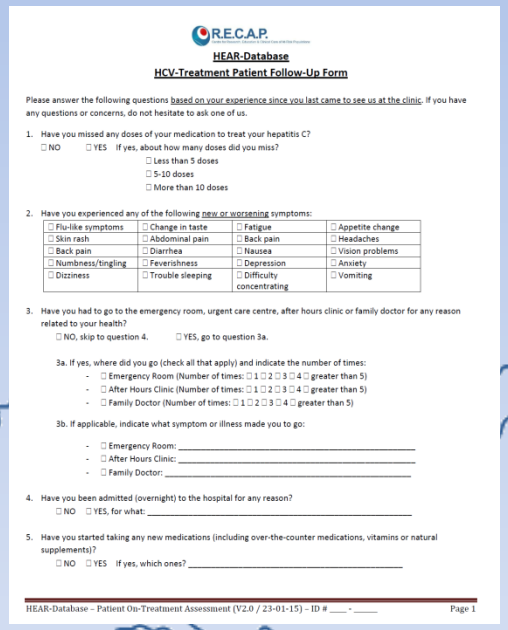
3. Gynecological/Obstetric History (Leave blank for male patients)

Post-menopausal? ☐ No ☐ Yes Pregnant? ☐ No ☐ Yes
Birth Control ☐ No ☐ Yes, method(s): _____
Date of last gynecologic exam: _____ Obstetrical History: G:_____ P:_____ A:_____

4. Family History

Hepatitis ☐ No ☐ Yes _____
Psychiatric ☐ No ☐ Yes _____
Addiction ☐ No ☐ Yes _____

B. PRESCRIPTION/MEDICATION HISTORY



R.E.C.A.P.

HEAR-Database

HCV-Treatment Patient Follow-Up Form

Please answer the following questions based on your experience since you last came to see us at the clinic. If you have any questions or concerns, do not hesitate to ask one of us.

1. Have you missed any doses of your medication to treat your hepatitis C?
☐ NO ☐ YES If yes, about how many doses did you miss?
☐ Less than 5 doses
☐ 5-10 doses
☐ More than 10 doses

2. Have you experienced any of the following new or worsening symptoms:

☐ Flu-like symptoms	☐ Change in taste	☐ Fatigue	☐ Appetite change
☐ Skin rash	☐ Abdominal pain	☐ Back pain	☐ Headaches
☐ Back pain	☐ Diarrhea	☐ Nausea	☐ Vision problems
☐ Numbness/tingling	☐ Feverishness	☐ Depression	☐ Anxiety
☐ Dizziness	☐ Trouble sleeping	☐ Difficulty concentrating	☐ Vomiting

3. Have you had to go to the emergency room, urgent care centre, after hours clinic or family doctor for any reason related to your health?
☐ NO, skip to question 4. ☐ YES, go to question 3a.

3a. If yes, where did you go (check all that apply) and indicate the number of times:
- ☐ Emergency Room (Number of times: ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ greater than 5)
- ☐ After Hours Clinic (Number of times: ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ greater than 5)
- ☐ Family Doctor (Number of times: ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ greater than 5)

3b. If applicable, indicate what symptom or illness made you to go:
- ☐ Emergency Room: _____
- ☐ After Hours Clinic: _____
- ☐ Family Doctor: _____

4. Have you been admitted (overnight) to the hospital for any reason?
☐ NO ☐ YES, for what: _____

5. Have you started taking any new medications (including over-the-counter medications, vitamins or natural supplements)?
☐ NO ☐ YES If yes, which ones? _____

Intake - Patient

Intake - Physician

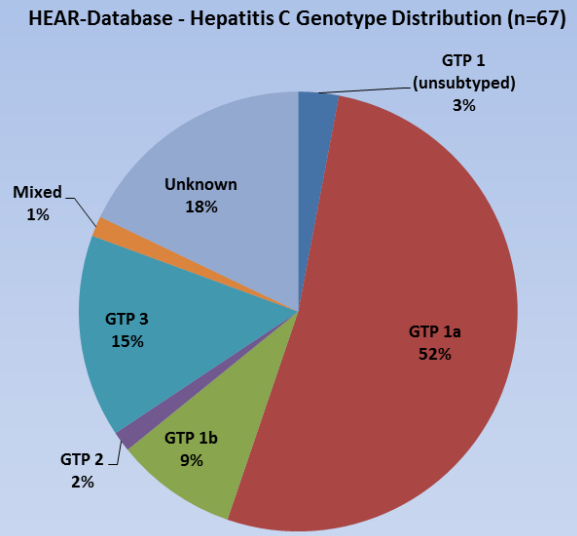
On/Post Treatment HEOR

Populus

HEAR Database

(Hepatitis C Positive and At-Risk Prospective Patient Database)

Demographic	
Male	63.0%
Median Age	37.0 years
Other Comorbidities	60.3%
No Primary Care Provider	44.8%



HCV-Risk Factor (Historical or Current)	
Intravenous Drug Use	62.1%
Shared Drug Paraphernalia	57.8%
High-Risk Sexual Activity	37.9%
Incarceration	60.3%
Tattoos/Piercing (Jail/Street)	40.5%

Areas requiring further research

- Prospective evaluation of health economic impact of new DAA's.
- Health economics of reinfection. Paying now and paying layer?
- High risk population feasibility studies including incarcerated persons, First Nations, and immigrants.

Summary

- While disease prevalence is decreasing, complications of untreated chronic HCV will increase over the next two decades, as will healthcare expenditure.
- Cost of therapy is increasing, however cost of an SVR is decreasing.
- Versus rigid “F” restriction, maximal economic impact can be attained through dynamic programming which initially targets those with more advanced liver disease and core transmitters.
- Patient registries and outcome measures in the context of new therapies are essential to gauge real world clinical and health economic experience.

Poll the audience

HCV: Pay now or pay later?

(1) Treat now to prevent complications and incident infections.

(2) Partial treatment access with Fibrosis restriction (F2)

(3) Focus on the sickest first then expand access to everyone.

(4) Treatment costs way to much, focus on prevention for now and pay later when complications occur.

(5) Still not sure. Have they refilled the giant vat of coffee yet?

- Thanks!
  - Dr. Duncan Webster
  - Stefanie Materniak
  - Dr. Lisa Barrett
  - Dr. Greg German
  - Dr. Natalie Wall
  - Dr. Mark MacMillan
  - Dr. Gordon Dow
  - Dr. Frank Schweiger
  - Dr. Lisa McKnight
  - Dr. Jeremy Beck
  - Dr. Connie Hoare
  - Dr. Meaghan O'Brien
  - Dr. Morris Sherman
  - Dr. Lamont Sweet
  - Dr. John Gill
  - Lise Dupuis
  - Lisa Frachette
  - Nigel Orfei and Populus team.

R.E.C.A.P.
Centre for Research, Education & Clinical Care of At-Risk Populations