Hepatitis C: transitioning to highly effective therapies

Dan Smyth, MD, FRCPC

September 24th,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]

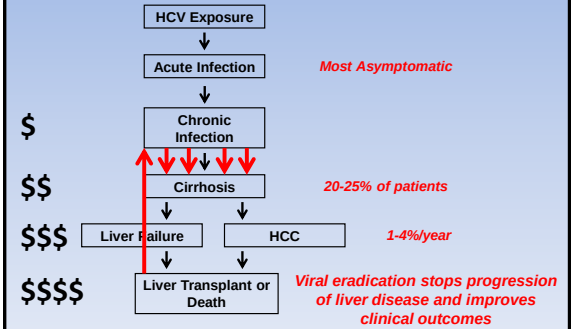
Objectives

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

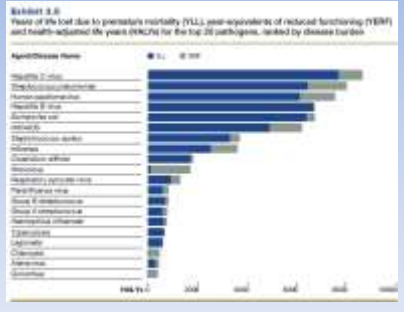
(2) To review the potential impact of increased treatment using novel HCV regimens.

(3) To discuss optimal models of care designed to evaluate the clinical, epidemiologic, and economic impact of HCV treatment.

Natural History of HCV Infection

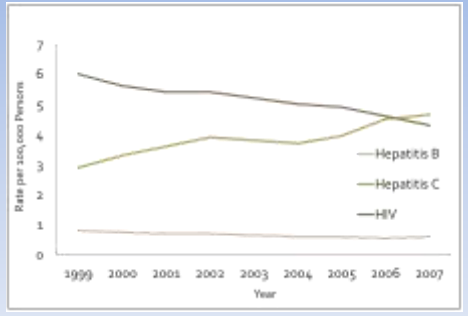


Hepatitis C, of all infectious diseases, is responsible for highest increase in premature mortality.



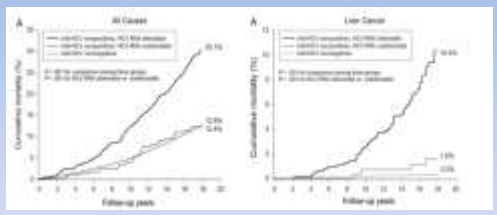
Ontario Agency for Health Promotion and Protection, 2010

HCV related mortality now exceeds that of HIV



Ly et al. Ann Intern Med 2012

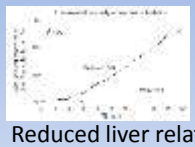
Hepatitis C Medical Burden:

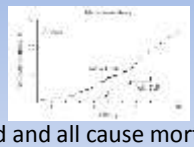


HCV increases all cause mortality.

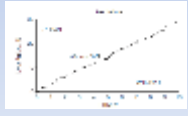
Lee MH et al. J Infect Dis. 2012

Attainment of SVR associated with:





Reduced liver related and all cause mortality.



Reduced HCC and liver failure.

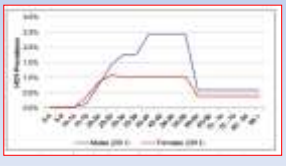
Van der Meer. JAMA 2012

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

Median Follow up 10 years

Purevsambuu. EASL 2014 Abstract 0125

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

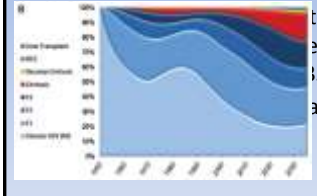
2013-2030 Predictions

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%

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5.
atment

- Chronic infection
  - 75% 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

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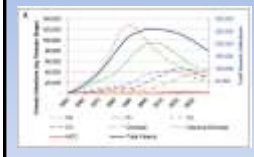


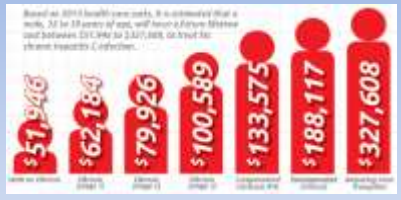
Estimated future lifetime cost according to disease state for men 35 to 39 years of age with hepatitis C virus infection in 2013

	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	188,770
Diuretic-refractory ascites	220,330
Variceal hemorrhage	189,200
Hepatic encephalopathy	133,500
Hepatocellular carcinoma	42,375
Liver transplant	327,600

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

Myers et al. Can J Gastroenterol Hepatol. 2014

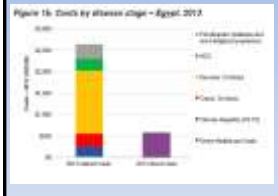
Hepatitis C: Significant Burden of Disease[1,2]



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).

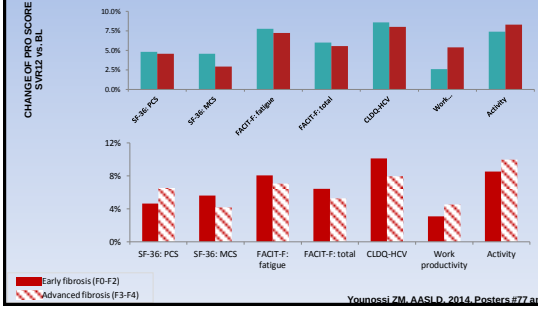
Indirect cost: $ 2, 575 M (2013 USD).

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.

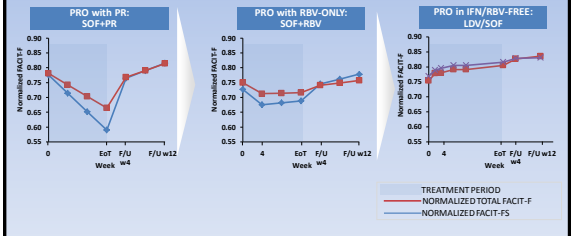
Waked et al. 2014

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



Younossi ZM. AASLD. 2014. Posters #77 and1445

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

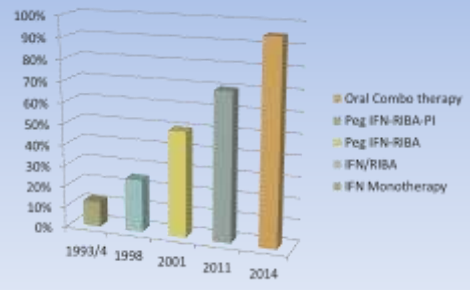


Younossi ZM. AASLD. 2014. Poster #77

Treatment:

Pawlotsky, 4/22/12, Barcelona

Treatment Evolution:



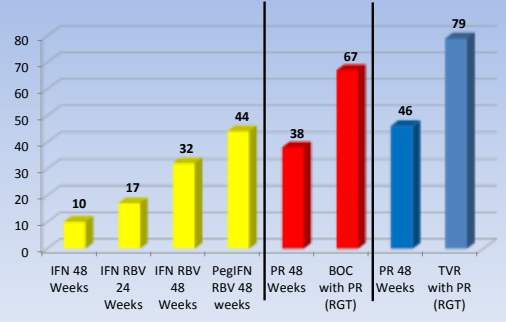
Sustained Virologic Response (SVR) in the IFN era

Genotype	Treatment duration (weeks)	SVR (%)
1	48	45
2	24	80
3	24	70
4	48	60

History:

- 2001: PEG-IFN and RBV therapy.
- Summer 2011: Health Canada approves BOC/TVR for G1 treatment (with PR).
- Nov 2013: Health Canada approves Simeprevir for G1 treatment (with PR).
- Dec 2013: Health Canada approval of Sofosbuvir (SOF):
  - With PR for GT1 and 4
  - With RBV alone for G2 and G3 = IFN FREE!!

SVR in GT1 with BOC and TVR



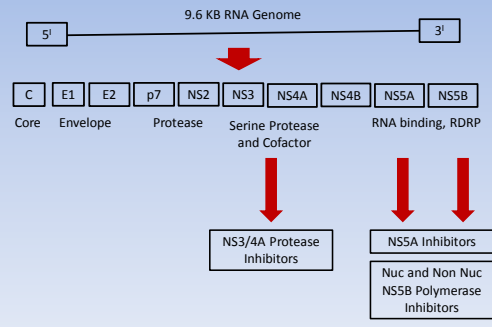
Poordad, NEJM 2011; Jacobson, NEJM 2011

Real world experience and cost

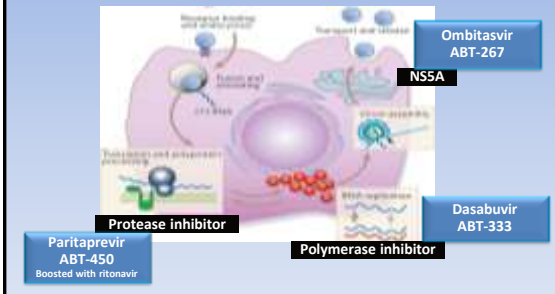
- TVR: registration trials 64-75% SVR
- Real world experience: HCV TARGET[1], 90 centers, > 2000 patients, **overall SVR 54%**, 90% with AE leading to treatment change, serious AE in >10%.
- Real world median cost of SVR in 147 patients 189,338 (2012 USD), with close to 10% of cost spent on AE management[2].

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

The HCV DAA Explosion:



Ombitasvir/paritaprevir/ritonavir and dasabuvir

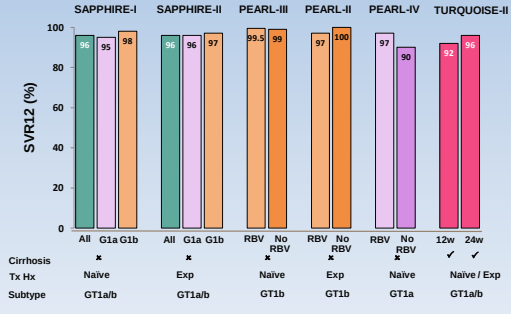


Phase 3 Program – Evaluation in Broad Range of GT1 Patient Populations, with and without RBV

Study	Population	Regimen	N
M11-646 (SAPPHIRE-I)	GT1, non-cirrhotic, treatment-naive	3-DAA + RBV vs placebo for 12 weeks	631
M13-098 (SAPPHIRE-II)	GT1, non-cirrhotic, treatment-experienced	3-DAA + RBV vs placebo for 12 weeks	394
M13-099 (TURQUOISE-II)	GT1, treatment-naive and treatment-experienced, with compensated cirrhosis (Child-Pugh A)	3-DAA + RBV for 12 weeks vs 24 weeks	380
M13-389 (PEARL-II)	GT1b, non-cirrhotic, treatment-experienced	3-DAA + RBV vs 3-DAA for 12 weeks	179
M13-961 (PEARL-III)	GT1b, non-cirrhotic, treatment-naive	3-DAA + RBV vs 3-DAA for 12 weeks	419
M14-002 (PEARL-IV)	GT1a, non-cirrhotic, treatment-naive	3-DAA + RBV vs 3-DAA for 12 weeks	305

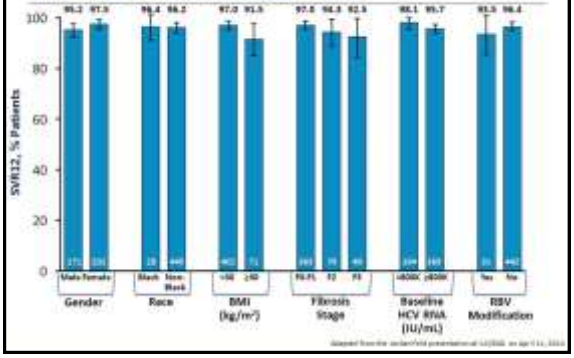
1. Feld JJ, *et al. New Engl J Med* 2014; online DOI: 10.1056/NEJMoa1315722; 2. Zeuzem S, *et al. New Engl J Med* 2014; online DOI: 10.1056/NEJMoa1401561; 3. Poordad F, *et al. N Engl J Med* 2014. Online DOI:10.1056/NEJMoa1402869; 4. AbbVie press release 2014 [Accessed 28-04-2014]; 5. Ferenci P, *et al. EASL* 2014. Abstract 1299 LJ

Phase 3 Program Clinical Data: Efficacy (SVR12)



1.Feld *NEJM* 2014; 2. Zeuzem *NEJM;* 2014; 3. Andreone DDW 2014; 4.Ferenci *NEJM* 2014; 5.Ferenci *NEJM* 2014; 6. Poordad *NEJM* 2014.

SAPPHIRE-I: ITT SVR12 Rates in Subpopulations

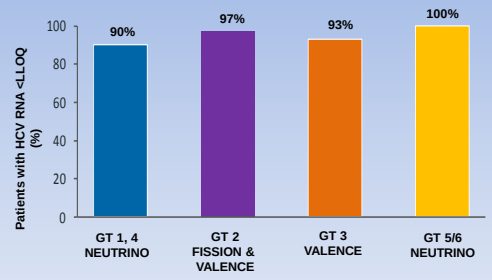


Phase 3 Program Clinical data: safety

Study	Population	Regimen	D/C due to AEs
M11-646 (SAPPHIRE-I)	GT1, non-cirrhotic, treatment-naive	3-DAA + RBV vs placebo for 12 weeks	1%
M13-098 (SAPPHIRE-II)	GT1, non-cirrhotic, treatment-experienced	3-DAA + RBV vs placebo for 12 weeks	1%
M13-099 (TURQUOISE-II)	GT1, treatment-naive and treatment-experienced, with compensated cirrhosis (Child-Pugh A)	3-DAA + RBV for 12 weeks vs 24 weeks	12 weeks: 2% 24 weeks: 2%
M13-389 (PEARL-II)	GT1b, non-cirrhotic, treatment-experienced	3-DAA + RBV vs 3-DAA for 12 weeks	3-DAA: 0% 3-DAA + RBV: 2%
M13-961 (PEARL-III)	GT1b, non-cirrhotic, treatment-naive	3-DAA + RBV vs 3-DAA for 12 weeks	3-DAA: 0% 3-DAA + RBV: 0%
M14-002 (PEARL-IV)	GT1a, non-cirrhotic, treatment-naive	3-DAA + RBV vs 3-DAA for 12 weeks	3-DAA: 1% 3-DAA + RBV: 0%

Feld JJ, *et al. New Engl J Med* 2014; online DOI: 10.1056/NEJMoa1315722; Zeuzem S, *et al. New Engl J Med* 2014; online DOI: 10.1056/NEJMoa1401561;

Sofosbuvir SVR 12 Across Treatment-Naïve Genotypes 1, 2, 3, 4, 5, 6



Lawitz E, et al. *N Engl J Med.* 2013 May 16
Lawitz E, et al. APASL 2013. Singapore. Oral #LB-02
Zeuzem S, et al. AASLD 2013. Washington, DC. #1085

Ledipasvir/Sofosbuvir Background:

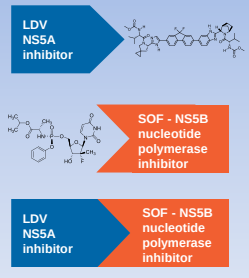
- LDV/SOF:
  - Health Canada NOC October 16th, 2014.

Population	Duration	Dose
TN GT 1 Non cirrhotic	12* weeks	LDV 90mg/SOF 400 mg PO OD
TN GT1 cirrhotic	12 weeks	
TE GT1 non cirrhotic	12 weeks	
TE GT1 cirrhotic	24 weeks	

* Can consider for 8 weeks in treatment naïve non cirrhotic with pre treatment HCV RNA < 6 million IU/mL

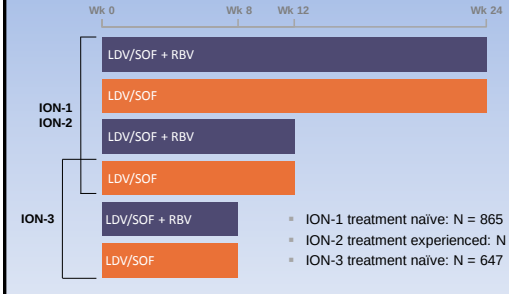
Ledipasvir/Sofosbuvir:

- **Ledipasvir**
  - Picomolar potency against HCV GT 1a and 1b[1]
  - Effective against NS5B RAV S282T[2]
  - Once-daily, oral, 90 mg
- **Sofosbuvir**
  - Potent antiviral activity against HCV GT 1–6
  - High barrier to resistance
  - Once-daily, oral, 400-mg tablet
- **Ledipasvir/Sofosbuvir STR**
  - Once-daily, oral fixed-dose (90/400 mg) combination tablet
  - No food effect
  - >2000 patients treated



1. Lawitz E, et al. EASL 2011, poster 1219. 2. Chang G, et al. EASL 2013, poster 1172

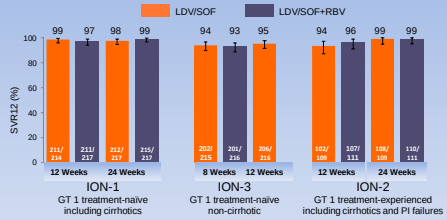
LDV/SOF Phase 3 Program (ION-1, ION-2, ION-3)



- ION-1 treatment naïve: N = 865
- ION-2 treatment experienced: N = 440
- ION-3 treatment naïve: N = 647

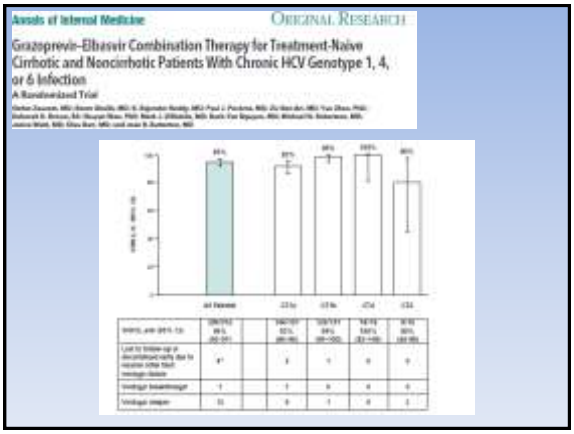
N=1952 total patients

ION Phase 3 Program (ION-1, ION-2, ION-3) Efficacy Summary



- 97% (1886/1952) overall SVR rate
- 3% (66/1952) did not achieve SVR
  - 1.4% (28) LTFU
  - 0.1% (2) virologic breakthrough (both due to non-adherence)
  - 1.8% (36) relapsed. Patients may be rolled over to a retreatment study

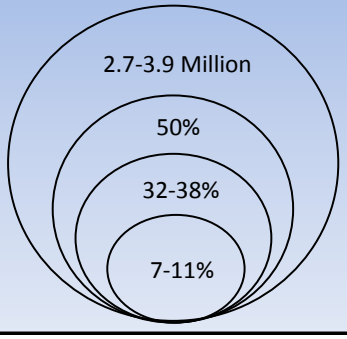
Afdhal N, et al. *N Engl J Med* 2014
Kowdley K, et al. *N Engl J Med* 2014
Afdhal N, et al. *N Engl J Med* 2014



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

Program considerations

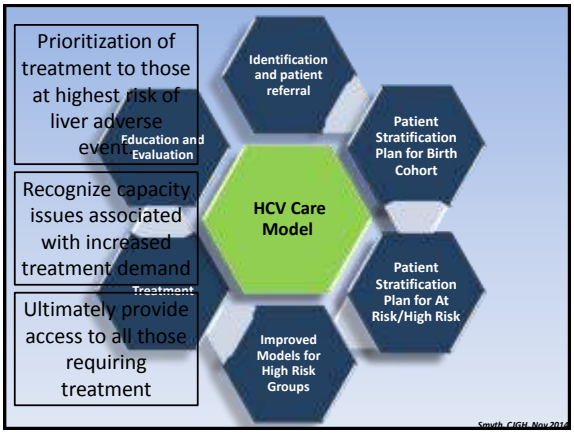
The treatment cascade: comprehensive HCV programming is essential



Asrani, Curr Gastroentrol Rep, 2014

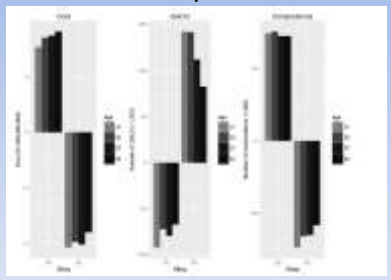
SPECIAL ARTICLE

Transitioning to highly effective therapies for the treatment of chronic hepatitis C virus infection: A policy statement and implementation guideline



Smyth, CJGH, Nov 2014

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

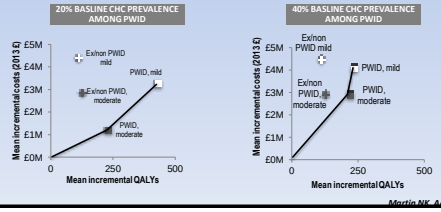
Targeting core transmitters

- 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; Magiorkinis. PLoS Comput 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.



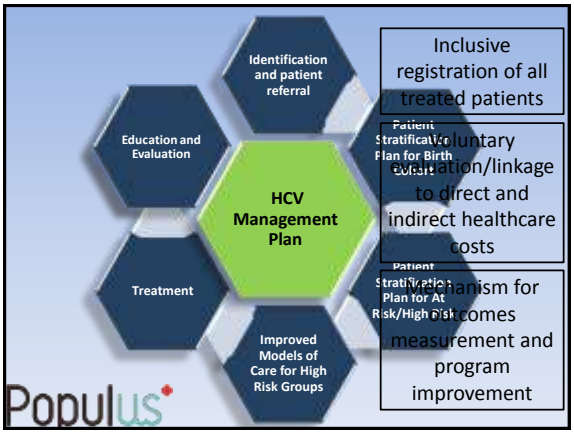
Martin NK. AASLD. 2014. #1752

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.

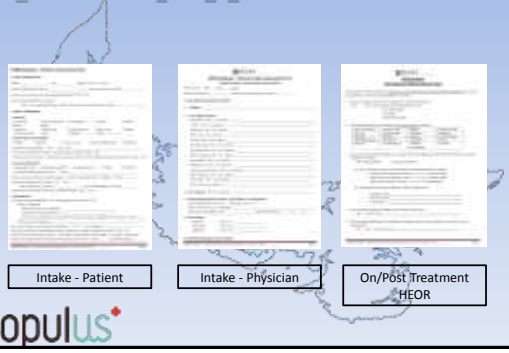
R.E.C.A.P.

Populus



HEAR Database

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



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.

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