HCV/HIV among People who Inject Drugs

What Issues Remain?

INSHU 2017

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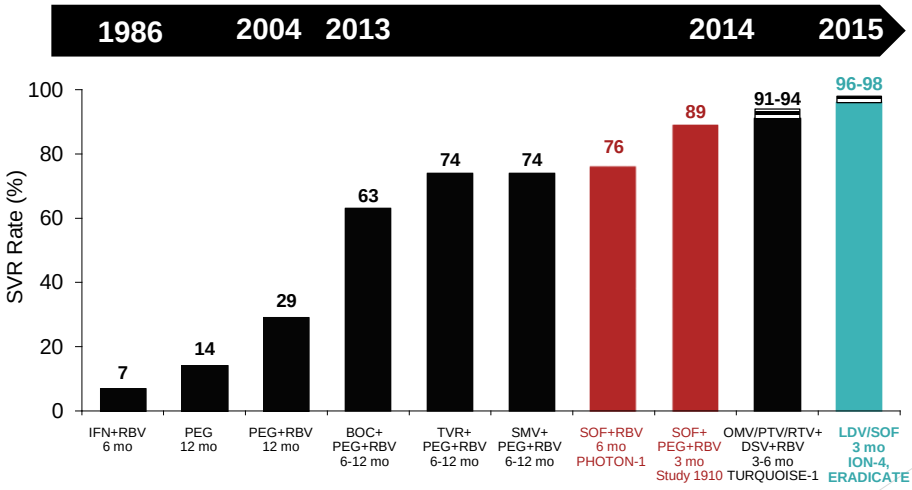
- Research grants for investigator initiated trials: ViiV, Merck
- Consulting fees: ViiV, BMS, Merck, Gilead

What issues DON'T Remain

Efficacy of treatment

The Hepatitis C Treatment Revolution



2015 AASLD/IDSA Guidance: "HIV/HCV co-infection should receive the same treatment as recommended for HCV mono-infection"

Dieterich D et al. CROI 2014; P#24; Rodriguez-Torres M et al. IDWeek 2013; P#714; Sulkowski M et al. Lancet Infect Dis 2013;13:597-605; Sulkowski M et al. Ann Intern Med 2013;159:86-96; Sulkowski M et al Lancet 2014;314:653-61; Sulkowski M et al. AIDS 2014; P#104 LB; Torriani FJ, et al. N Engl J Med 2004;351:438-50; AASLD/IDSA/IAS-USA. Recommendations for testing, managing, and treating hepatitis C. http://www.hcvguidelines.org. Accessed January 15, 2015

Next Generation Direct-Acting Antivirals

Glecaprevir
(formerly ABT-493)
pangenotypic NS3/4A protease inhibitor

Coformulated: G/P

Pibrentasvir
(formerly ABT-530)
pangenotypic NS5A inhibitor

In vitro:[1,2]
- High barrier to resistance
- Potent against common NS3 polymorphisms (e.g., positions 80, 155, and 168) and NS5A polymorphisms (e.g., positions 28, 30, 31 and 93)
- Synergistic antiviral activity

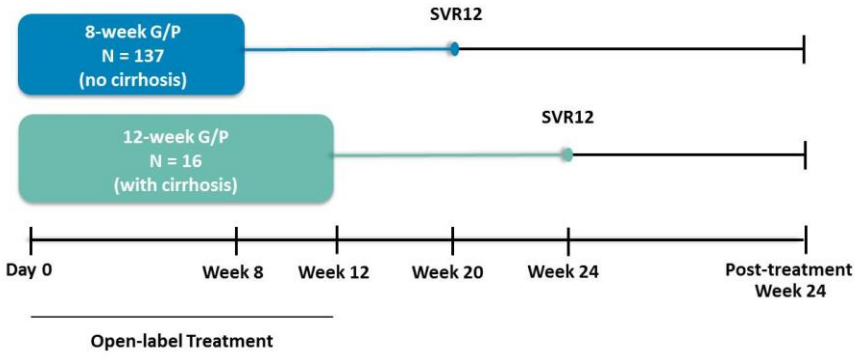
Clinical PK & metabolism:
- Once-daily oral dosing with food
- Minimal metabolism and primary biliary excretion
- Negligible renal excretion (<1%)

G/P is co-formulated and dosed once daily as three 100 mg/40 mg pills for a total dose of 300 mg/120 mg
Glecaprevir was identified by AbbVie and Enanta.

1. Ng TI, et al. *Antimicrobial Agents and Chemotherapy;* 2017 . 2. Ng TI, et al. Abstract 636. CROI, 2014

EXPEDITION-2 Study Design

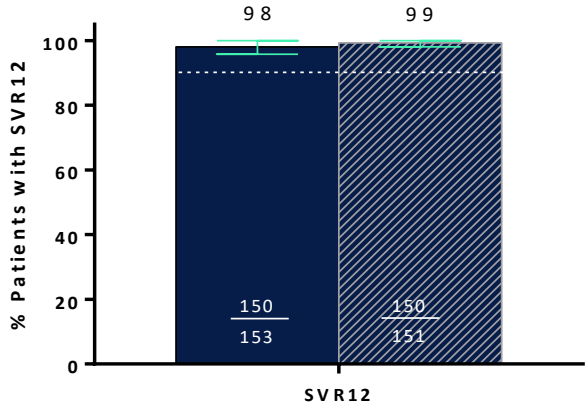
A phase 3, multicenter global study evaluating 8- or 12-week treatment with G/P in HCV/HIV-1 co-infected adults without or with compensated cirrhosis, respectively



Patients were enrolled in Australia, Belarus, France, Germany, Poland, Puerto Rico, Russian Federation, United Kingdom and United States

G/P is co-formulated and dosed once daily as three 100 mg/40 mg pills for a total dose of 300 mg/120 mg.

Efficacy

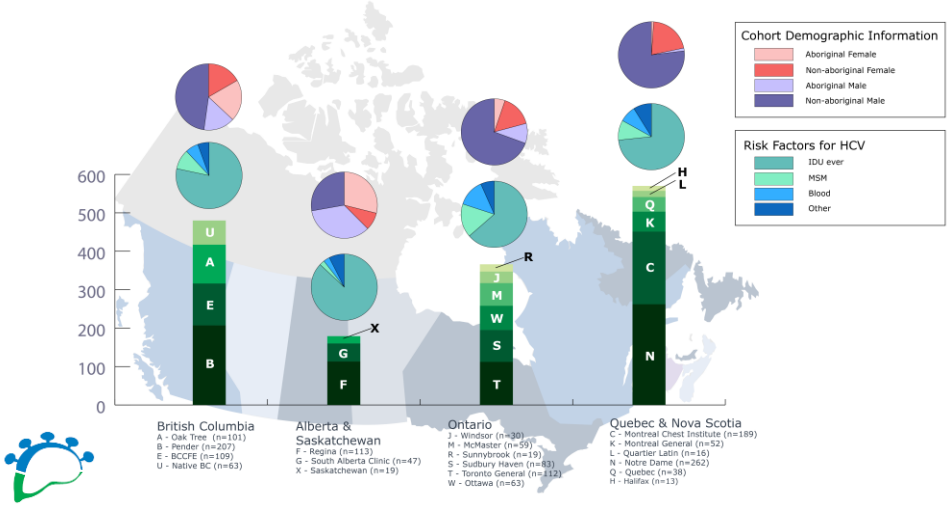


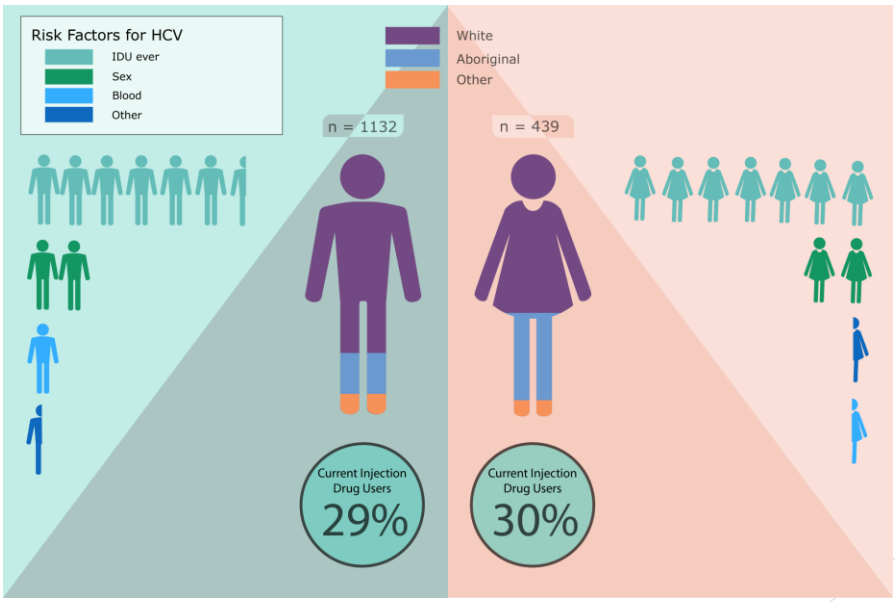
Breakthrough	1
Relapse	0
Missing Data	1*
Discontinued	1

- One patient with GT3 infection and cirrhosis had on-treatment virologic failure at week 8; the patient was 85% compliant with treatment
- Tx combined with integrase inhibitors, ripilvirine, boosted darunavir and lopinavir (in non-cirrhotics)

*Patient returned at post-treatment week 24 and had achieved SVR

The Canadian Coinfection Cohort 2003-2016 (n=1695)





Clinical Trials in Co-infection

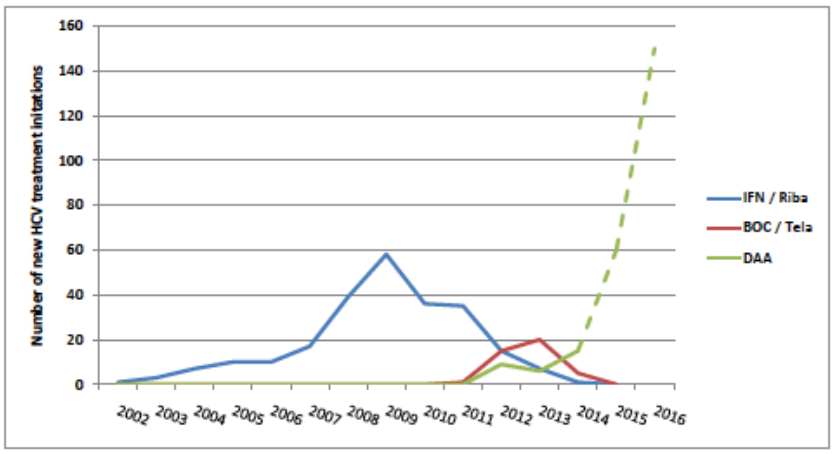
Phase 3 Trials evaluating 2nd generation DAAs in co-infected individuals

Simeprevir,
Sofosbuvir,
Ledipasvir,
Ombitasvir, paritaprevir/ritonavir and dasabuvir (3D)
Daclatasvir

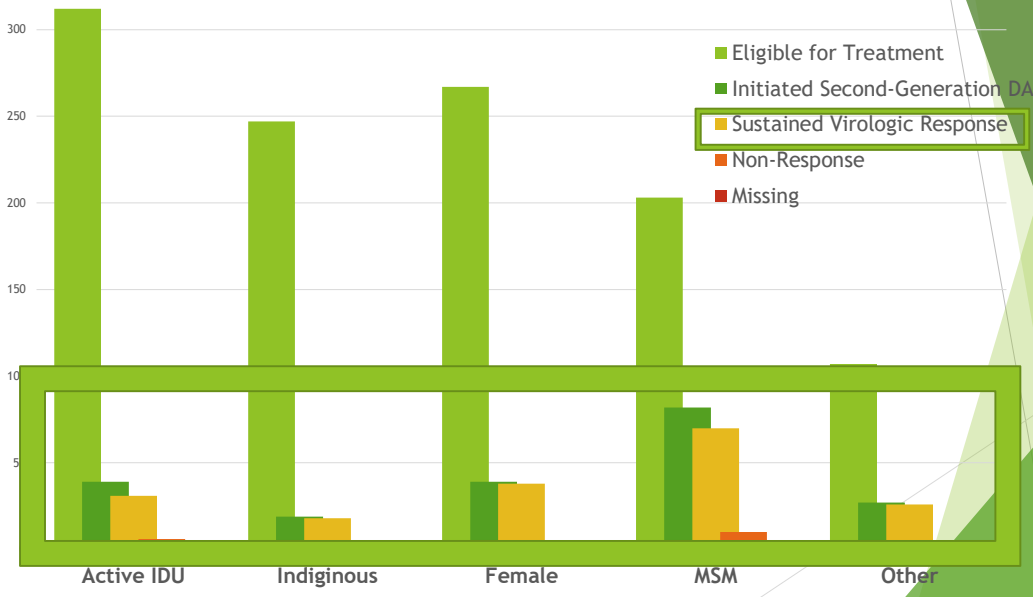
Using PubMed & clinicaltrials.gov
As of September 2015

Saeed et al, *Clin Inf Dis*, 2016

Rapid scale up of HCV treatment since DAAs



Real world SVR rates excellent across risk groups



What issues do remain?

Co-management and DRUG-DRUG interactions

Challenges of dual infection

1. Complicating comorbid medical and mental health conditions
2. Lower access to HIV and HCV care
3. Lower adherence to therapy
4. Medication side effects and toxicities
5. Concomitant substance use treatment
6. Drug interactions

Therapeutic failure generally correlates with the degree that drug use disrupts daily activities rather than with drug use per se

Drug-Drug Interactions: DAAs

		Hepatitis C directly acting antivirals									
	Proportion of patients	BOC	DCV	LED/SOF	OBV/PTVr	OBV/PTVr + DSV	SMV	SOF	TVR	Peg IFN	RBV
HIV nucleosides/nucleotides reverse transcriptase inhibitors											
ABC	23.0%										
ddI	0.9%										
FTC	59.3%										
LAM	27.0%										
TDF	64.0%										
ZDV	4.8%										
HIV non nucleosides/nucleotides reverse transcriptase inhibitors											
EFV	10.3%										
ETV	8.1%										
NVP	5.5%										
RPV	1.7%										
HIV entry/integrase inhibitors											
DLG	0.2%										
EVGc	0.0%										
MRV	3.3%										
RAL	26.9%										
HIV protease inhibitors											
ATV/	20.1%										
DRVr	24.0%										
fAPV	4.7%										
IDVr	0.3%										
LPVr	9.6%										
SQVr	1.3%										
TPVr	0.2%										
Contraindicated administration		0.0%	0.0%	0.2%	34.4%	34.4%	78.8%	0.2%	0.0%	4.8%	5.6%
Potential interaction		82.3%	49.4%	67.6%	52.2%	52.2%	0.0%	0%	98%	91.6%	92.4%
No clinically significant interaction		17.7%	50.6%	32.2%	13.4%	13.4%	21.2%	99.8%	2.0%	3.5%	2.0%

No clinically significant interaction expected

Potential interaction – may require close monitoring, alteration of drug dosage or timing of administration

These drugs should not be coadministered

See also
http://www.hep-druginteractions.org/

http://www.hcvdruginfo.ca/downloads/DAA-ARV%20int%20table_summary.pdf

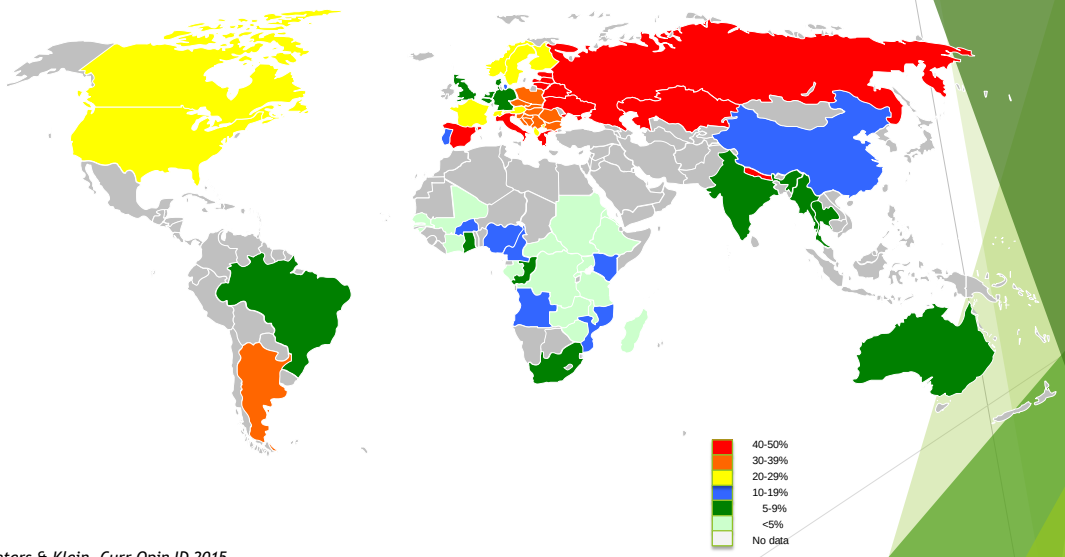
DRUG-DRUG interactions: Street drugs & OST

- **MDMA, GHB, ketamine, and methamphetamine** all have the potential to interact with ARV agents because all are metabolized by the CYP450 system
  - Overdoses secondary to interactions between MDMA or GHB and PI-based ART have been reported
- Because of its opioid-induced effects on gastric emptying and the metabolism of CYP450 isoenzymes 2B6, 3A4, and 2D6, pharmacologic effects and interactions between **methadone** with ARV agents may commonly occur
  - may diminish the effectiveness of either or both therapies by causing opioid withdrawal or overdose, increased methadone toxicity, and/or decreased ARV efficacy but **no major issues with DAAs**
- Limited information is currently available about interactions between **buprenorphine** and ARV agents and appears safe with DAAs
- **Naltrexone** not expected to have major interactions

What issues do remain?

It's a matter of risks and vulnerabilities

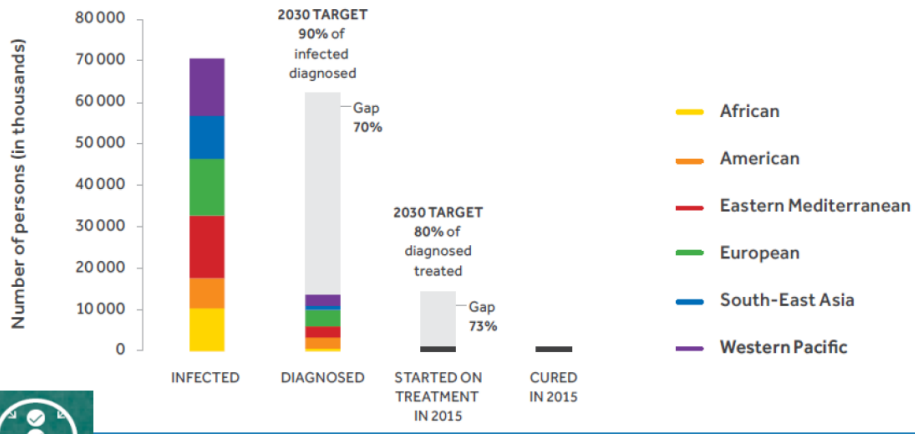
Global prevalence of HCV in HIV+ persons



Peters & Klein, Curr Opin ID 2015

HCV – 20% diagnosed, yet major Tx gap; cost reductions < $ 150 / cure

HCV

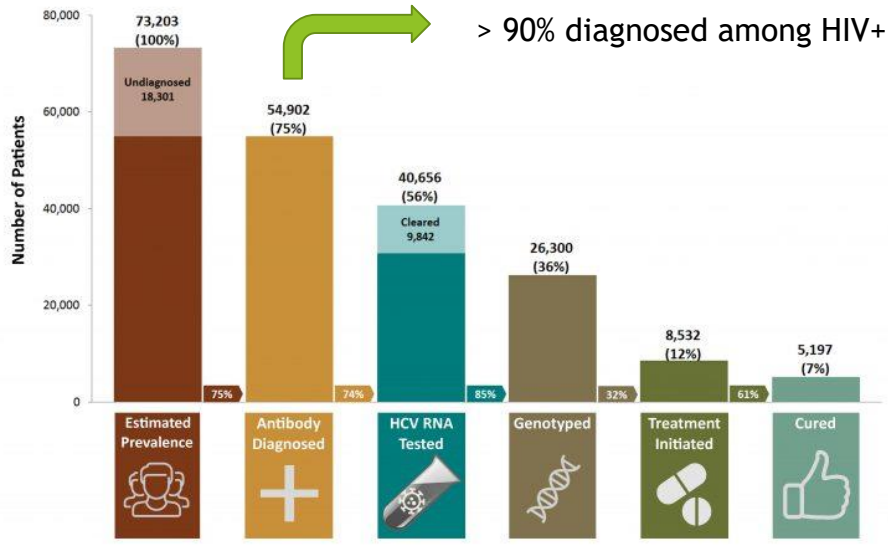


Sources – WHO, work conducted by Center for Disease Analysis

World Health Organization

Gottfried Hirnschall

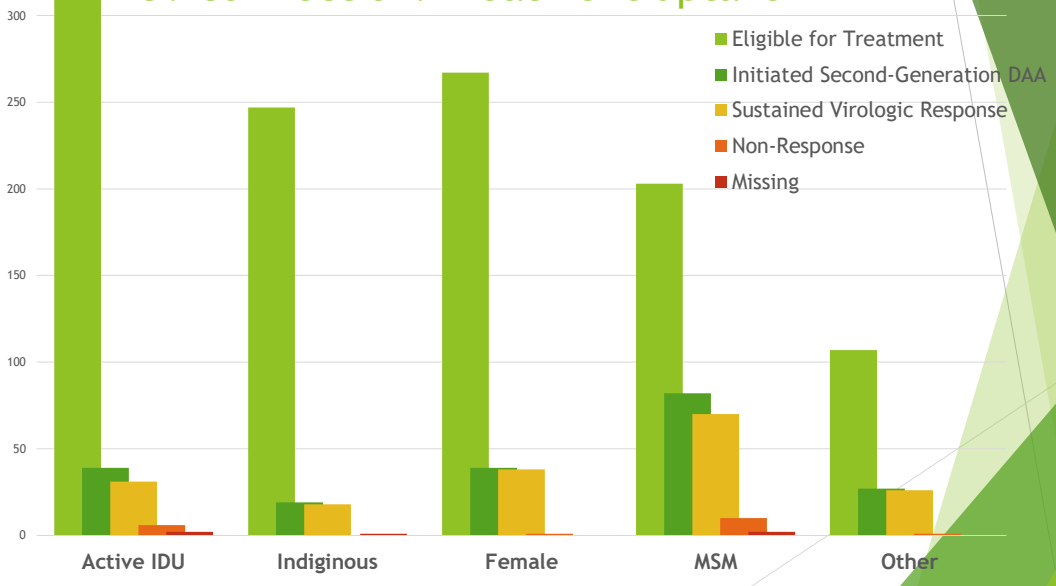
HCV Care Cascade Canada



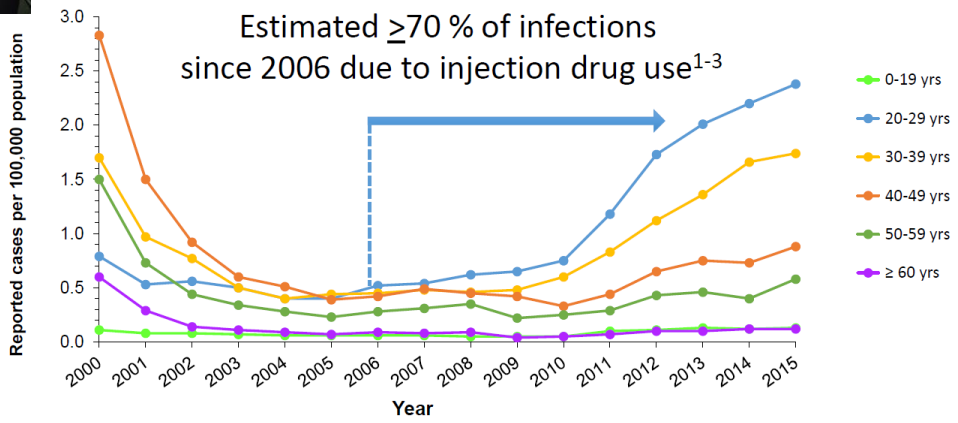
> 90% diagnosed among HIV+

BC HTC British Columbia Hepatitis Testers Cohort

Main barrier to HCV elimination in HIV-HCV coinfection: Treatment uptake



Incidence of Acute Hepatitis C, By Age Group — United States National Notifiable Diseases Surveillance System, 2000-2014



1. Zibbell, 2015, MMWR; 64(17): 453-8. 2. Suryaprasad, 2014, Clin Infect Dis; 59(10):1411-9. 3. CDC, 2014; Viral hepatitis surveillance -- United States, 2013.

John Brooks CDC

Injection of prescription opioids: a significant threat to HIV and HCV prevention among PWID

Association between frequent injection (≥120/month) and drugs injected in the month prior to interview (N=2829 visits).

Drugs category	No.	%	Crude PR	Adjusted[a] PR (95% CI)	
Crack/cocaine ± other drugs[b]	1008	35.6	Ref	Ref	
Prescription opioids only	422	14.9	2.93	2.84 (2.14-3.77)	**
Prescription opioids + heroin/speedball, crack/cocaine or other drugs[b]	1176	41.6	4.13	3.73 (2.94-4.73)	**
Heroin/speedball ± crack/cocaine or other drugs[b]	207	7.3	1.74	1.73 (1.20-2.50)	*
Other drugs[b] only	16	0.6	0.55	0.51 (0.07-3.48)	

Abreviations: PR: prevalence ratio; CI, confidence interval; Ref, reference.
** p<0.0001; * p<0.01.
[a] PR adjusted for age, gender, homelessness, income and smoking crack in the six months prior to interview, N=2770 visits (59 missing values).
[b] Other drugs: amphetamine-type stimulants, benzodiazepines, ketamine, etc.

E. Roy[1,2], P. Leclerc[3], C. Morissette[3], C. Blanchette[4], K. Blouin[5], N. Arruda[1], M. Alary[4], IAS 2017

An emerging epidemic

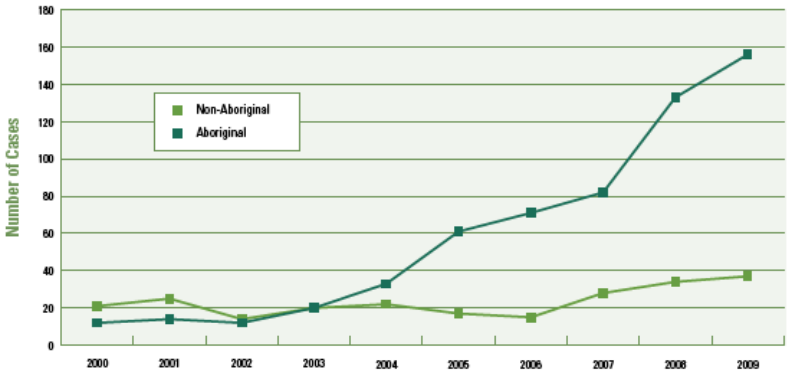
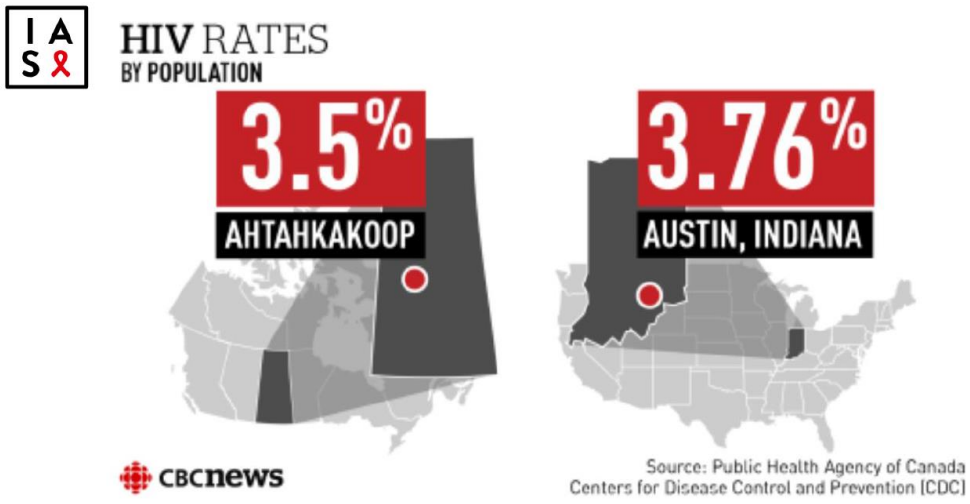


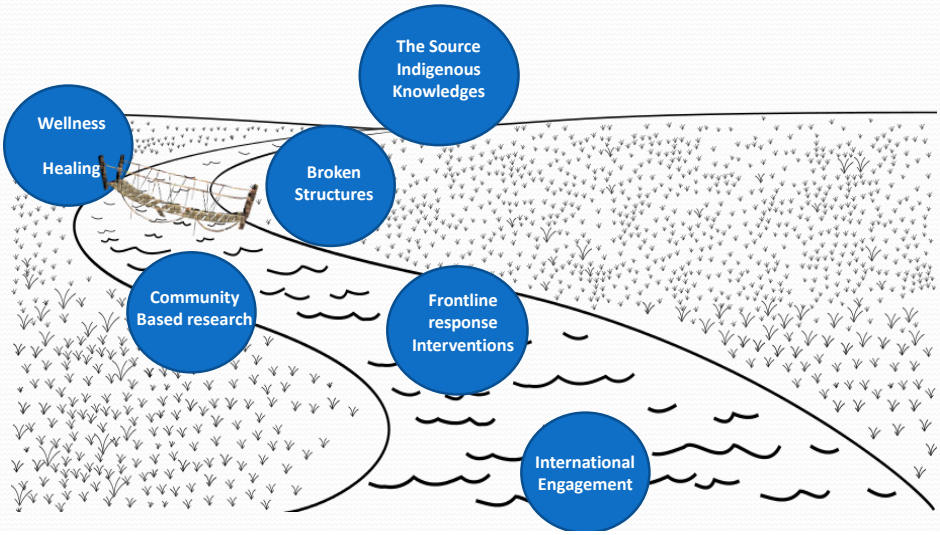
Figure 4: HIV Cases by Selected Self-reported Ethnicity in Saskatchewan, 2000 to 2009. *Reference: Ministry of Health-PHB, 2010.*



John Brooks CDC

www.iasociety.org

River Journey



Barriers to HCV Treatment

Structural Barriers

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

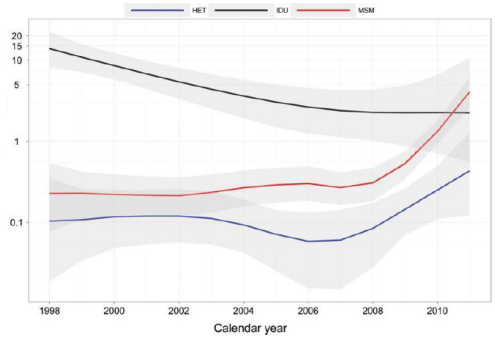
Provider Barriers

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

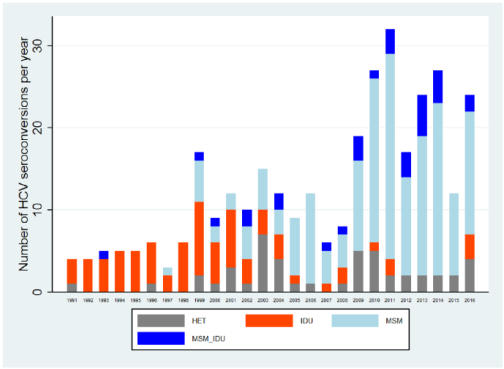
Patient Barriers

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

Hepatitis C virus infection incidence rates by transmission group



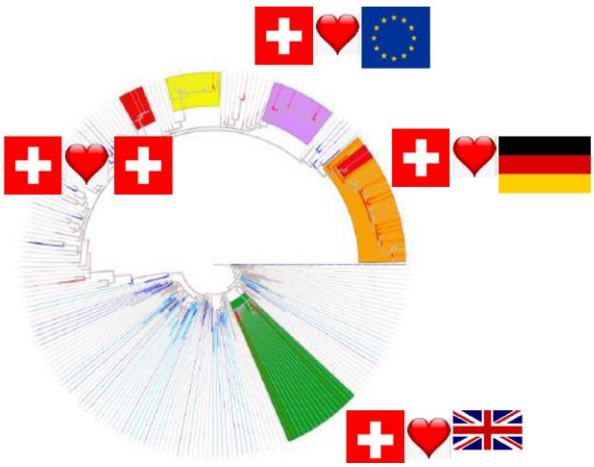
Wandeler G et al. Clin Infect Dis. 2012

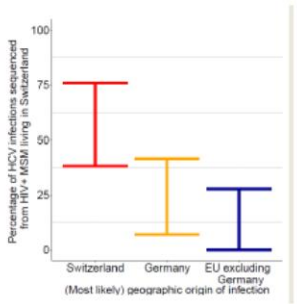


Updated from Wandeler G et al. SMW 2015

Andri Rauch, SHCS

The international love life of the Swiss





Salazar-Vizcaya et al. IWHOD 2017

Andri Rauch, SHCS

Morbidity and mortality rates from HCV infection in HIV co-infected patients are increasing[1]

7% of HIV infected gay men in London are also infected with HCV[2]

There are more co-infected gay men than co-infected IV drug users[2]

Approximately **92%** of HCV/HIV co-infections were in gay men located across London, Manchester & South East England in **2011**[2]

There is currently no national strategic approach to prevent HCV infections in gay men in the UK[2]

It is estimated that around **25%** of all European HIV patients have concomitant (HCV) co-infection[1]

Co-infection with HIV and HCV complicates each disease[2]

A significant proportion of HIV positive gay men who are successfully treated for HCV are rapidly re-infected with the virus[2] with the two-year re-infection rate at a North London hospital at 40%.[2]

At Chelsea & Westminster Hospital NHS Foundation Trust, which hosts robust ChemSex referral and support services, the reinfection rate is 25%.[3]

The main factors that have influenced and define ChemSex behaviour have been:

The increased availability and use of three recreational drugs by MSM in London, including crystal methamphetamine, mephedrone

Increased injecting use of crystal methamphetamine and mephedrone by MSM. Traditionally, MSM have preferred drugs like ecstasy and

The use of smartphone Apps and online 'hooking-up' sites to seek sexual activity as well as procuring drugs. While some

PrEP
Condomless sex

Dean Street MSMChemSex Presentations (>500) Key learnings:

- Good understanding about HIV transmission risks, prevention strategies and comfort with disclosure of serostatus, viral load
- Serosorting common
- **HCV however much more stigmatizing**, less likely to be disclosed and common reason for rejection online
- Reluctance to disclose high risk practices and drug use
- **"Naïve" injection practices**

Terms to be familiar with:

Slang, street names, colloquial terms	Definition
Tina/Meth/Ice/Crystal	Crystal methamphetamine, which can be injected, smoked, snorted or booty bumped
Meph/Meow Meow/Drone	Mephedrone, which can be snorted, injected, swallowed or booty bumped
G/Gina	GHB/GBL, taken orally (a liquid)
Slamming/slammed/to slam	Injecting/injected/to inject
Barebacking	Condom-less anal intercourse
Booty-bumping	To squirt diluted drug into the anus
Bender	Episode of drug use
Chems	Recreational drugs

Associated with

Extended sex for many hours/several days.

More extreme sexual practices/traumatic sex

Multiple partners

Extreme sexual disinhibition/extreme sexual focus

Unpredictable drug interactions (eg; GBL & alcohol)

Increased injecting use amongst an injecting-naïve population; BBV risks & injecting-related harms

Poor condom use

Poor ARV adherence*

Frequent STI's (including a current Shigella outbreak), HIV infections, HCV infection/repeated re-infections

Multipile and repeated use of PEP

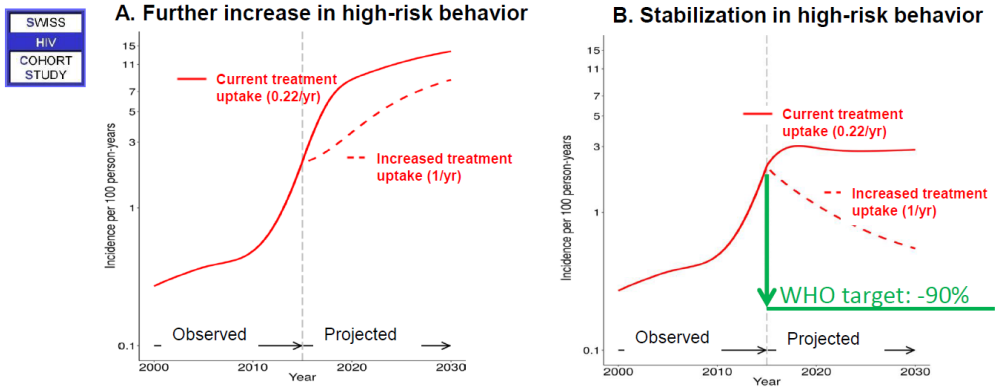
Psychosis/ physical dependence/ overdoses

Stuart D and Collins S, Methmephangee - ChemSex vs recreational drug use: a proposed definition for health workers. HIV Treatment Bulletin, Volume 16 Number 5/6, May/June 2015. Published online ahead of press.

What issues do remain?

Implications for elimination

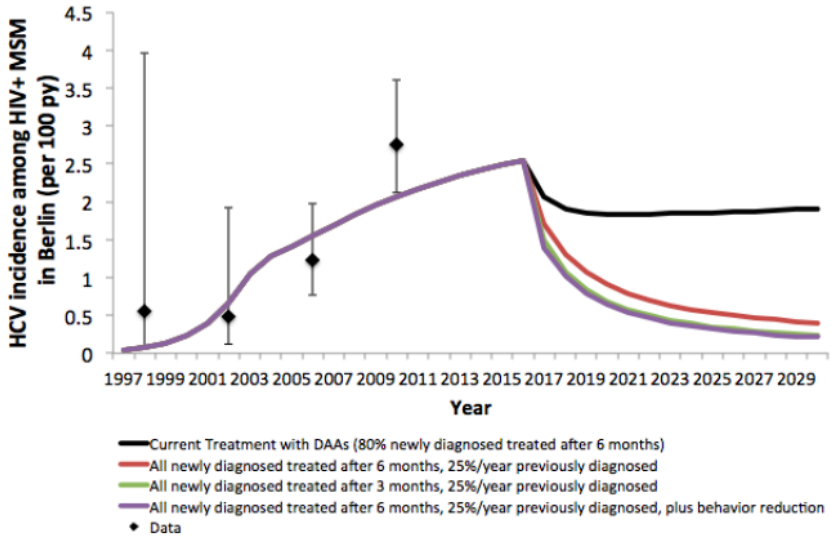
Risk behavior and treatment-as-prevention



Salazar-Vizcaya et al. Hepatology 2016

Andri Rauch, SHCS

BERLIN: INCREASING INCIDENCE AND HIGH TESTING/TREATMENT, NEED ACUTE TREAMENT OR BEHAVIOR CHANGE



Difficult to reverse increasing incidence with existing high testing/treatment rates.

Requires:

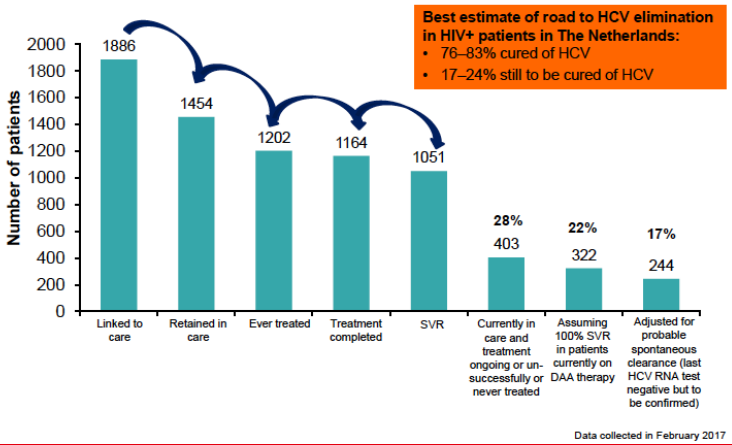
- All newly diagnosed treated within 3 months (licensing for acute treatment), or
- All newly diagnosed treated within 6 months plus 10% risk behavior reduction

← 90% reduction

Martin NK and Ingiliz P, preliminary work

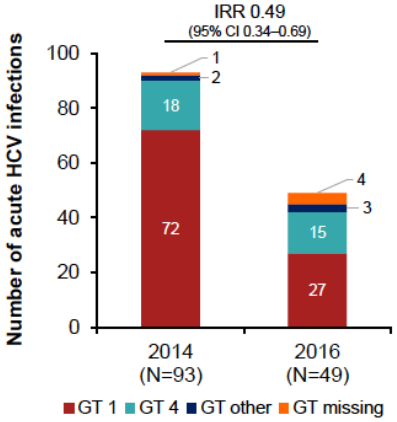
The Dutch experience

HCV care cascade in HIV+ patients in The Netherlands (MSM and non-MSM)



Data collected in February 2017

Acute HCV infections in 2014 and 2016



B.JA Rijnders, IAS Coinfection meeting 2017

Discussion

Acute HCV problem is still far from being 'eliminated' !

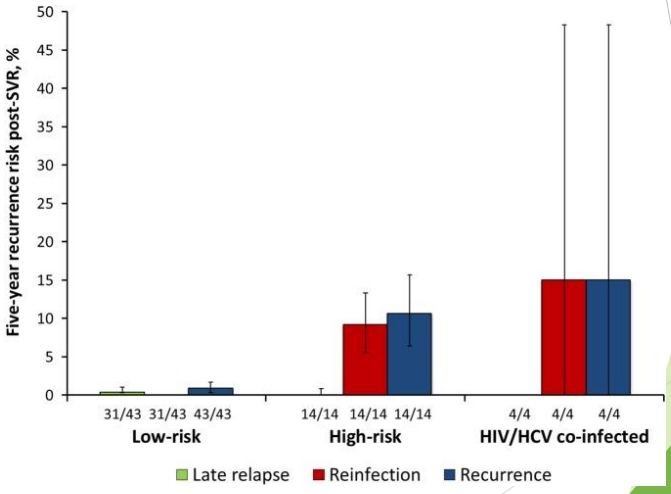
Reduction seems to stabilise in 2017 (IRR 0.5 in jan-apr 2017)

- Cross-border and cross continent transmission
  - Most new infections in Amsterdam area
- Undiagnosed HCV among HIV+ MSM: even in resource-rich setting
- Undiagnosed HCV among HIV- MSM: pool for re-introduction in HIV+
  - 4.8% prevalence of chronic HCV at time of PrEP initiation in Amsterdam(*)
  - N=13 HIV- patients with acute HCV in DAHHS-2 centres in 2016 !
  - N=8/13 were using PREP at time of HCV infection
- DAAs unapproved for acute HCV => ongoing transmission during wait

DAAs for all HIV+ patients with chronic HCV will not suffice to 'eliminate' HCV

(*) E Hoorenburg et al. AIDS 2017

Are co-infected at increased risk of reinfection?

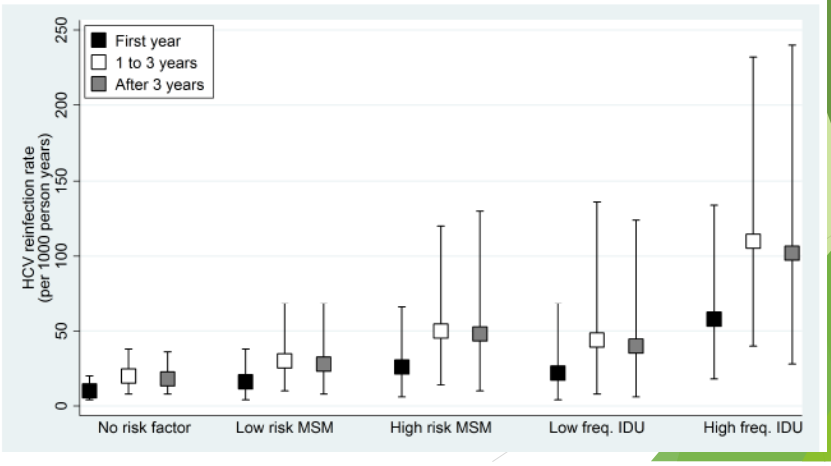


Simmons et al Clin Infect Dis. 2016 Mar 15; 62(6): 683–694.

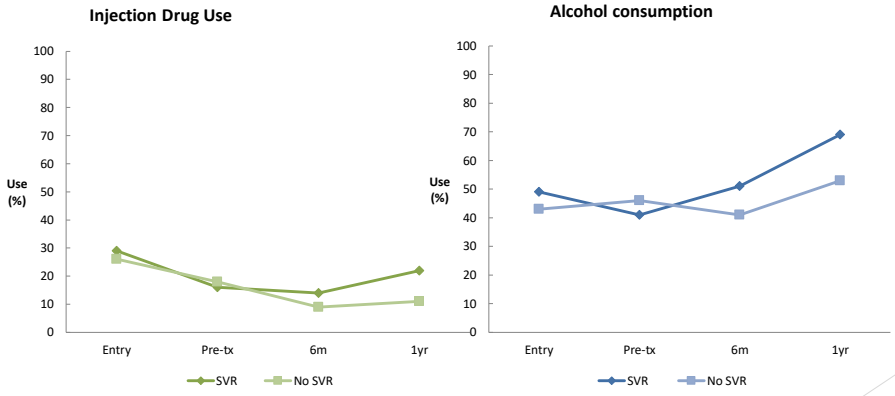
Clinical Infectious Diseases
MAJOR ARTICLE

Risk Factors for Hepatitis C Virus Reinfection After Sustained Virologic Response in Patients Coinfected With HIV

Jim Young,[1,2] Carmine Rossi,[1] John Gill,[3] Sharon Walmsley,[4,5] Curtis Cooper,[5,6] Joseph Cox,[1] Valerie Martel-Laferriere,[7] Brian Conway,[8] Neora Pick,[9] Marie-Louise Vachon,[10] and Marina B. Klein[1,5], for the Canadian Co-infection Cohort Investigators

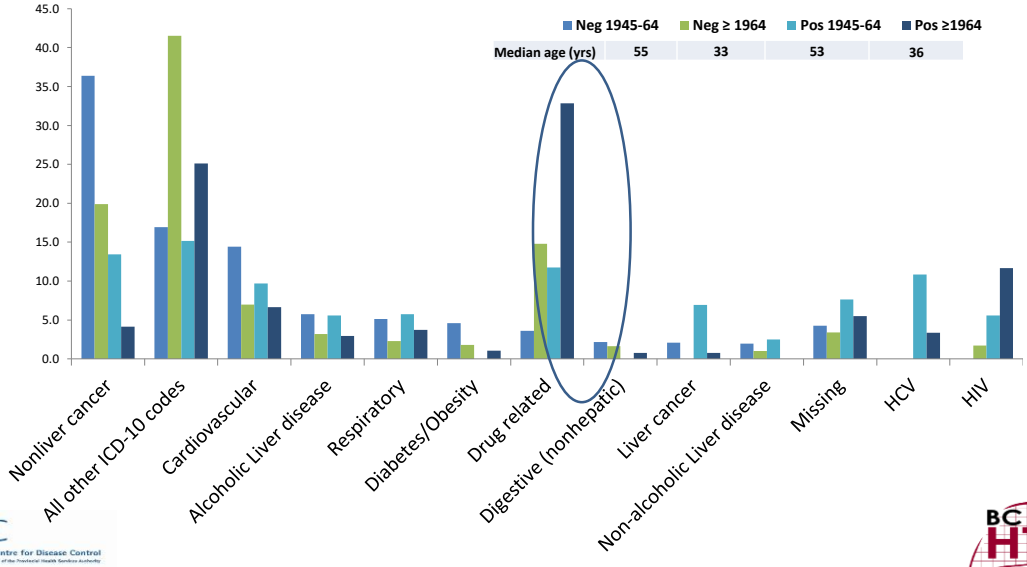


Risk behaviours after SVR



Man Wah Yeung et al HIV Clin Trials 2015

Mortality causes by birth cohort and HCV status



BC Centre for Disease Control

BC HTC British Columbia Hepatitis Testers Cohort

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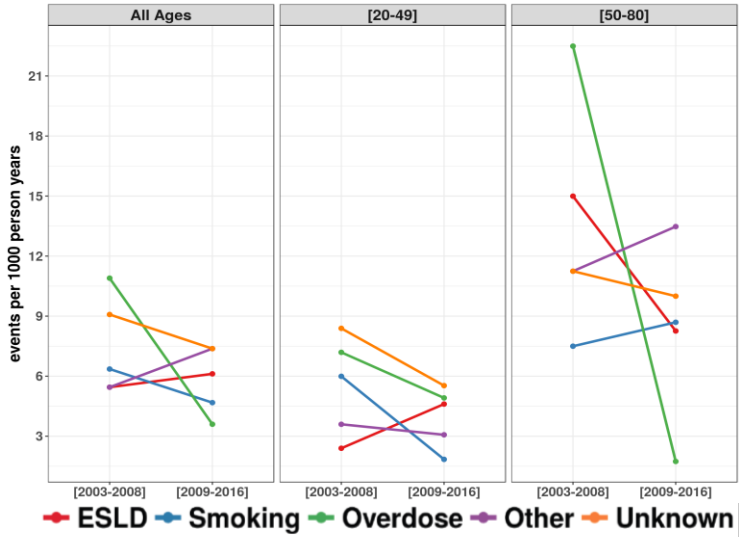
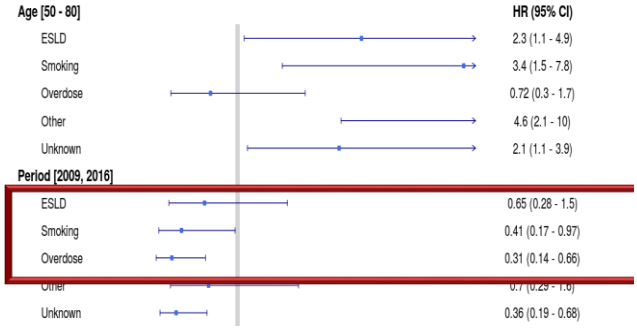
Do DAAs reduce mortality?



- Beware of Competing risks: How HCV and HCV treatment tie overall into drug user health?

Kronfli, IAS 2017

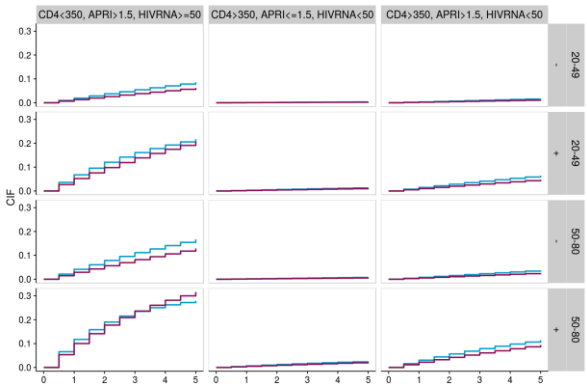
Early impact of DAAs in co-infection



APRI> 1.5 Poor HIV control

APRI < 1.5 Good HIV control

APRI > 1.5 Good HIV control



Kronfli IAS 2017 and submitted

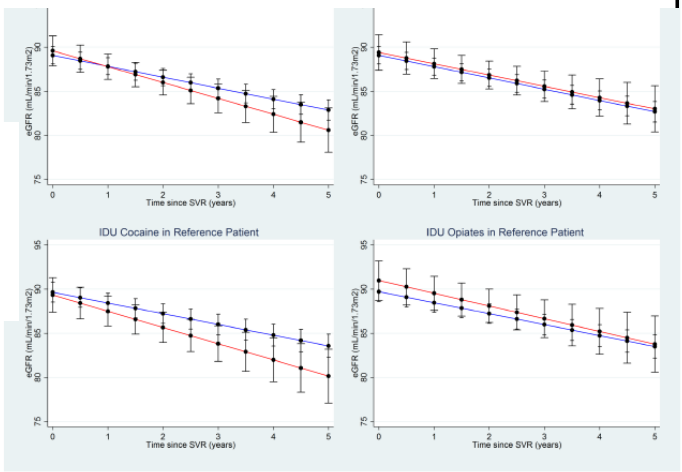
www.cocostudy.ca

Sustained virologic response (SVR) after hepatitis C virus (HCV) treatment does not lead to improved renal function in HIV/HCV coinfected patients

Carmine Rossi[1], Erica E. Moodie[1], Mark Hull[2], Valerie Martel-Lafferriere[3], Marie-Louise Vachon[4], Curtis Cooper[5], Neora Pick[6], Sharon Walmsley[7], and Marina B. Klein[8] **for the Canadian Co-infection Cohort Study Investigators**

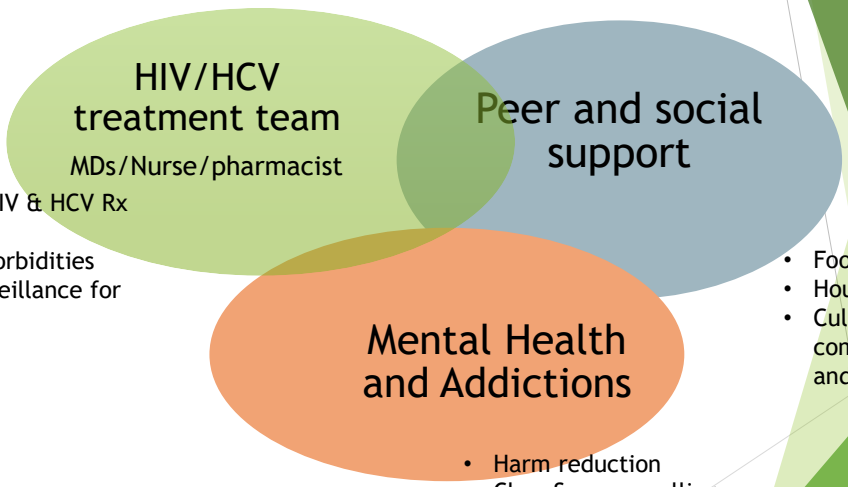
Table 2: Association between SVR and annual rates of change in eGFR in the PS-matched sample (n=996)

	ΔeGFR (mL/min/1.73m² per year) (95% Confidence Interval)
SVR	-1.21 (-1.69, -0.74)
Chronic Infection	-1.28 (-1.69, -0.86)
Difference	0.06 (-0.57, 0.69)



And finally ….what remains

Multidisciplinary Approach



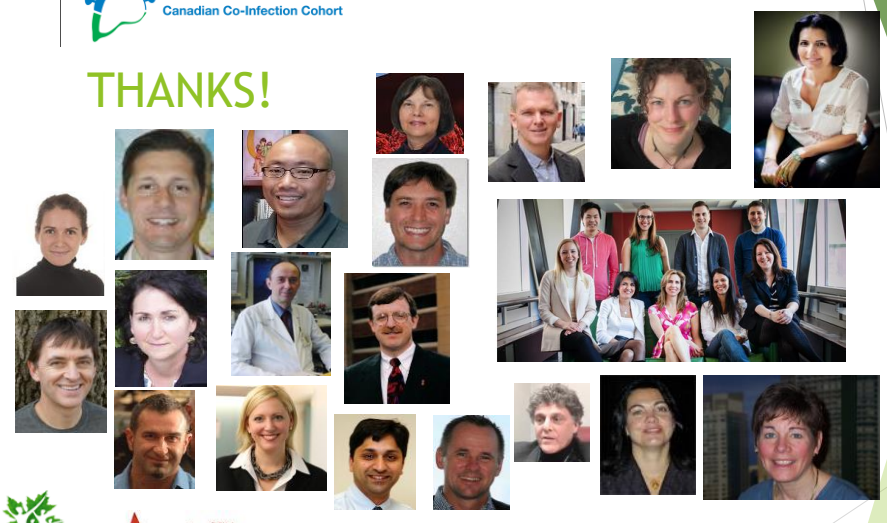
- Adherence HIV & HCV Rx
- Manage DDIs
- Manage comorbidities
- Ongoing surveillance for HCC

- Food security
- Housing
- Culturally competent care and supports

- Harm reduction
- ChemSex counselling
- Alcohol
- Smoking cessation

Canadian Co-Infection Cohort

THANKS!



CIHR IRSC

the CTN CIHR Canadian HIV Trials Network

Fonds de la recherche en santé Québec

CanHepC Canadian Network on Hepatitis C Réseau Canadien sur l'Hépatite C