

A Portrait of HIV/HCV Coinfected Persons in Canada

Implications for Research and Treatment



Marina B Klein, MD, MSc, FRCP(C)

Associate Professor of Medicine

Division of Infectious Diseases/ Immunodeficiency

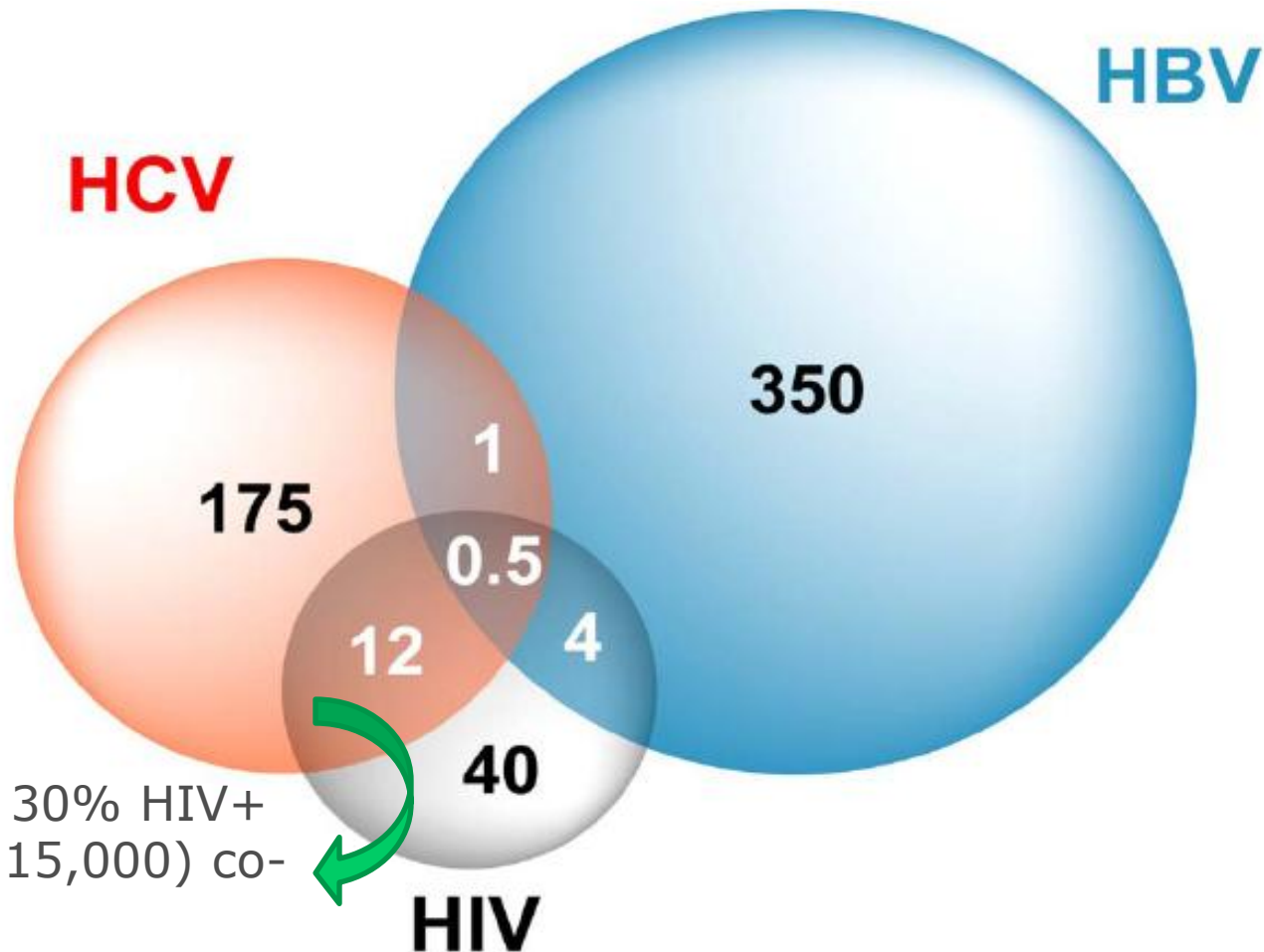
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Montréal, Canada

Context

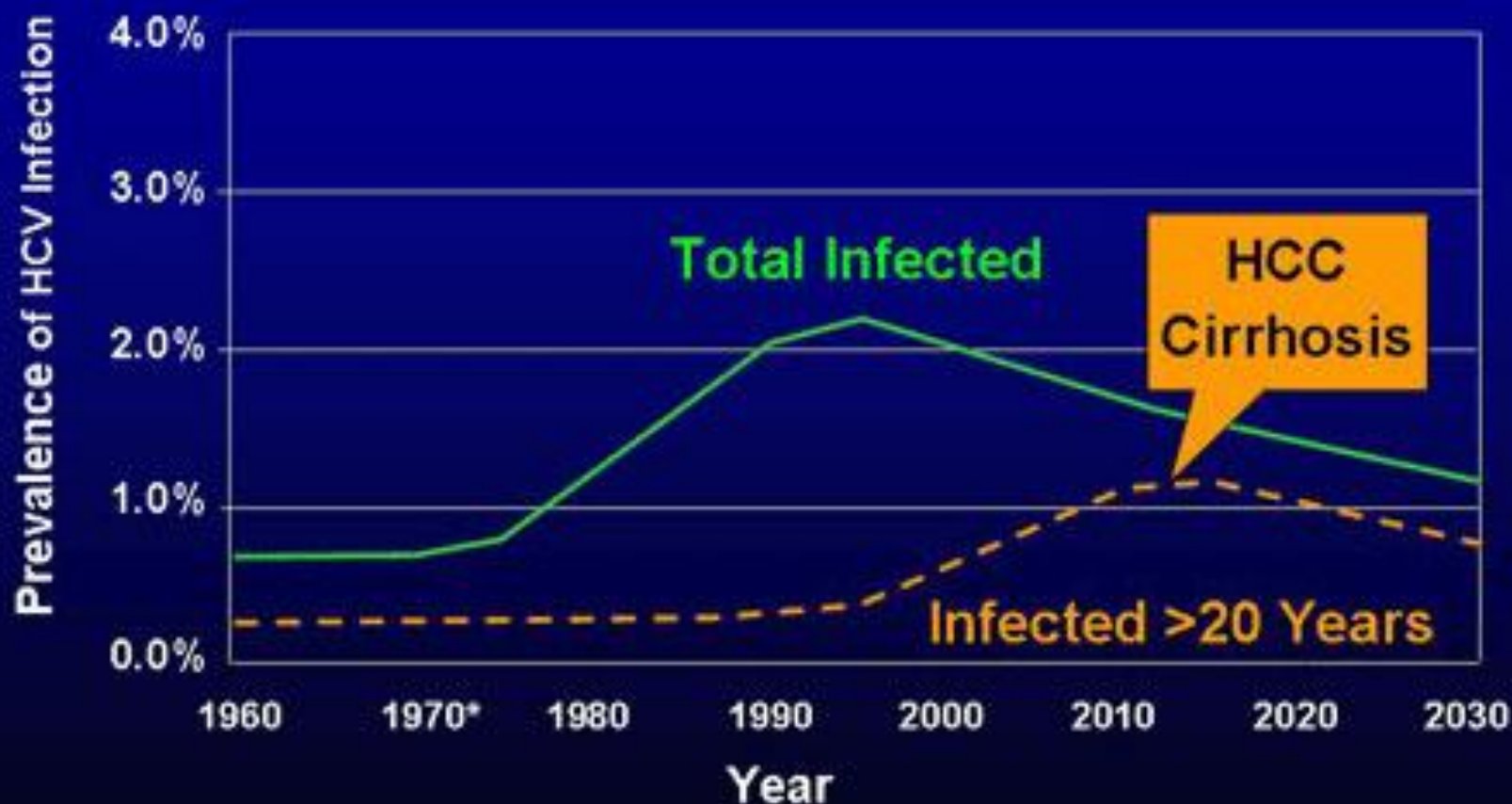


Estimated numbers of Co-infected persons (worldwide)



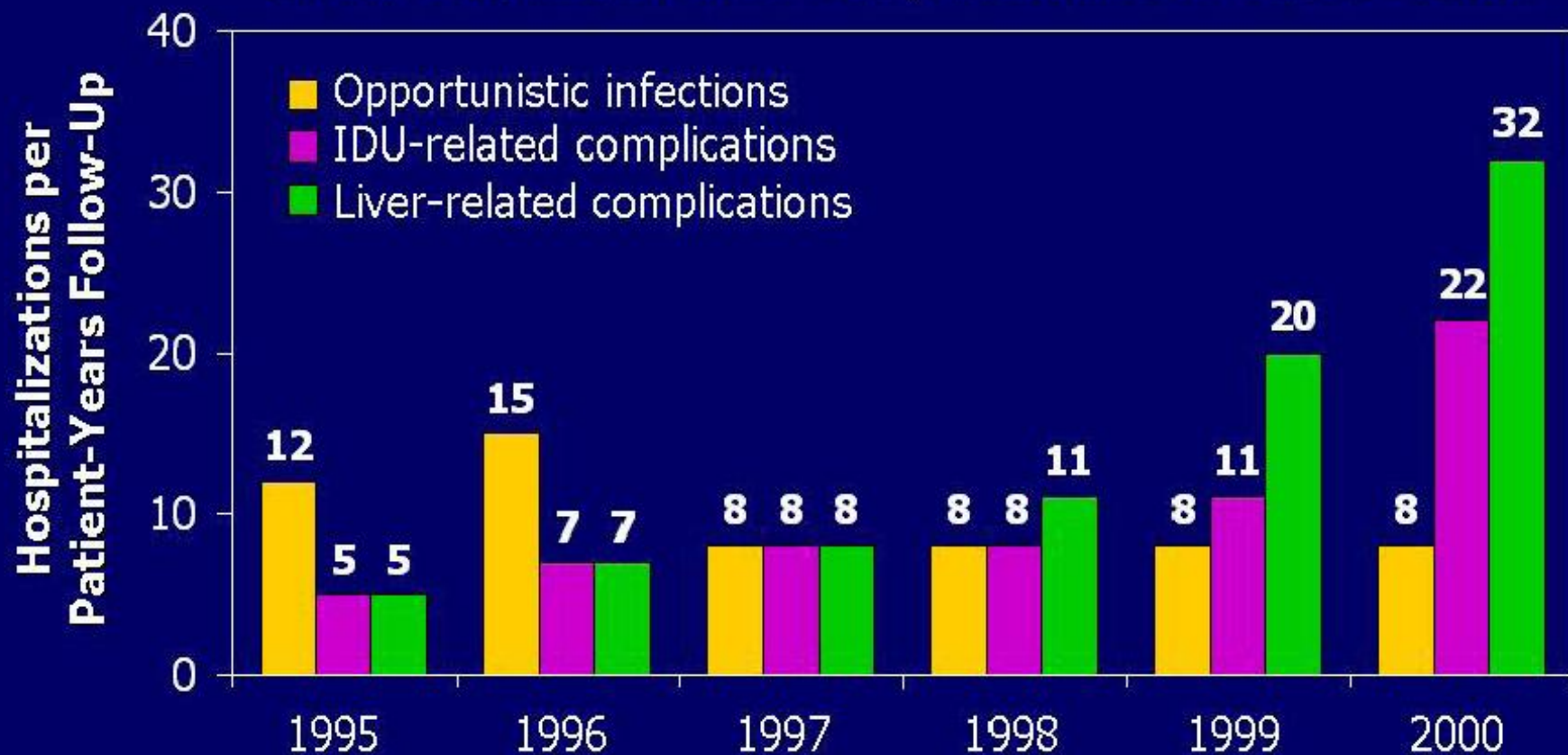
Canada: 30% HIV+
(est. 12-15,000) co-
infected

Predicted Future Prevalence of HCV in the United States



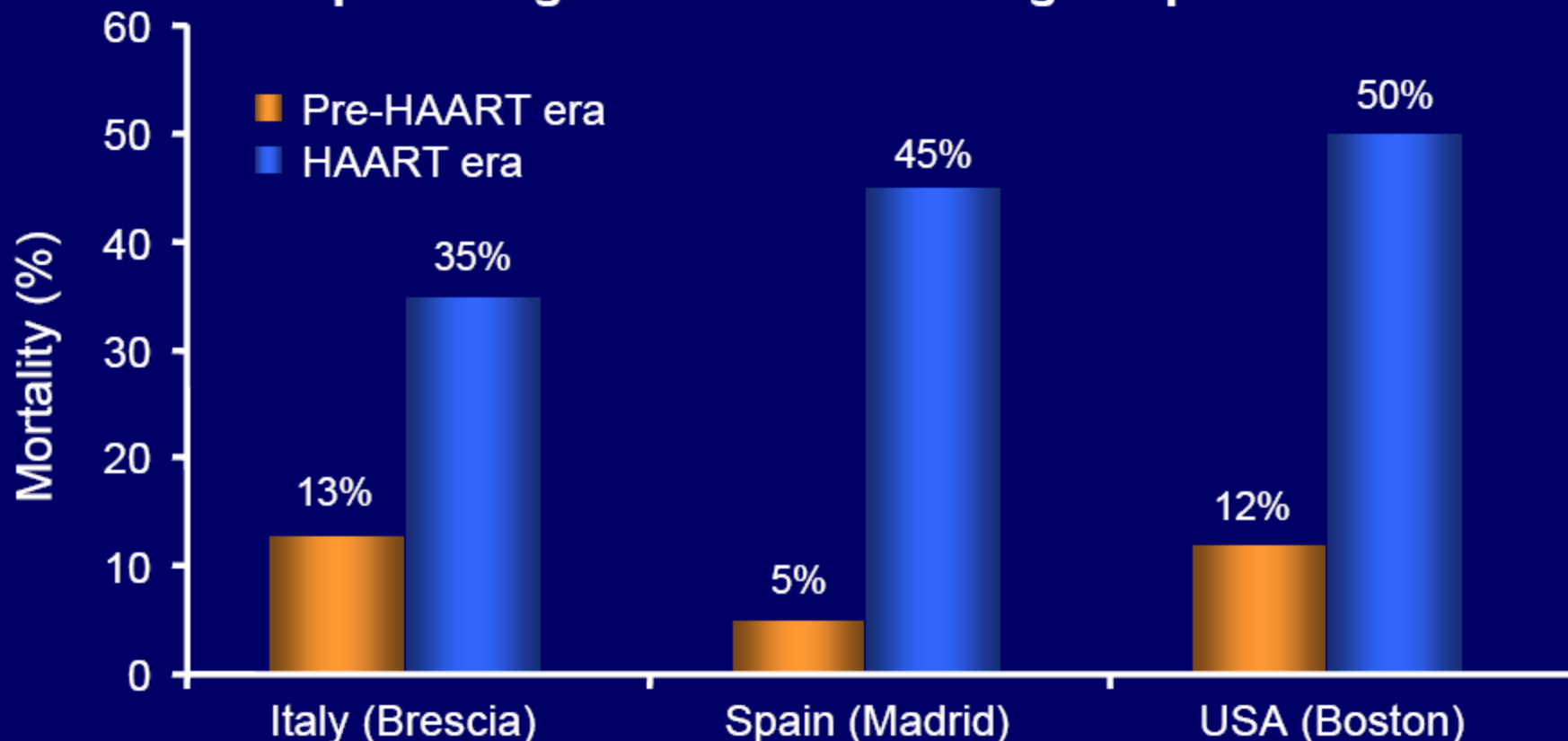
Hospital Admissions Amongst HIV Infected Patients

5 Fold Increase In Liver Complications From 1995 - 2000



Liver Disease Is a Major Cause of Death in the ART Era

Death from end-stage liver disease (ESLD) as a percentage of all deaths among HIV patients



Bica I et al. *Clin Infect Dis*. 2001;32:492-497.

Puoti M et al. *J Acquir Immune Defic Syndr*. 2000;24:211-217.

Soriano V et al. *Eur J Epidemiol*. 1999;15:1-4.

Soriano V et al. *PRN Notebook*. 2002;7:10-15.

Martin-Carbonero L et al. *AIDS Res Human Retrovirus*. 2001;17:1467-1471.

HIV-HCV Co-infection

- HCV behaves like an opportunistic infection in HIV infected individuals
 - Increased incidence of chronic HCV in those with HIV
 - Accelerated natural history of HCV in those with HIV

- Major clinical impacts of HIV on HCV include:
 - Increased rate of viral persistence
 - Higher hepatitis C viral load
 - Higher transmission rates
 - Reduced response to HCV therapy
 - Increased risk of severe liver disease

- ART has led to a decline in morbidity and mortality from nearly all illnesses among those with HIV, with **liver disease** being a notable exception and thus now is a leading cause of morbidity/death in HIV-HCV co-infected



The Canadian Co-Infection Cohort Study: Stemming the epidemic of liver related morbidity and mortality in HIV-HCV co-infection: Is ART enough?

CTN 222



Marina Klein MD M.Sc
McGill University Health Centre

Objectives

- Determine the effect of ART on liver disease progression in people co-infected with HIV and HCV.
 - Evaluate the effect of ART on progression to end-stage liver disease (ESLD)
 - Identify factors that contribute to liver disease progression in HIV-HCV co-infection
 - Examine effects of alcohol and drug use on liver disease progression
 - Examine the rates of chronic toxicities, specifically hepatic steatosis and insulin resistance, according to ART use
 - Establish a tissue bank of peripheral blood mononuclear cells (PBMC), plasma, serum and liver tissue for additional research questions concerned with immune function, viral dynamics, and mechanisms of fibrosis.



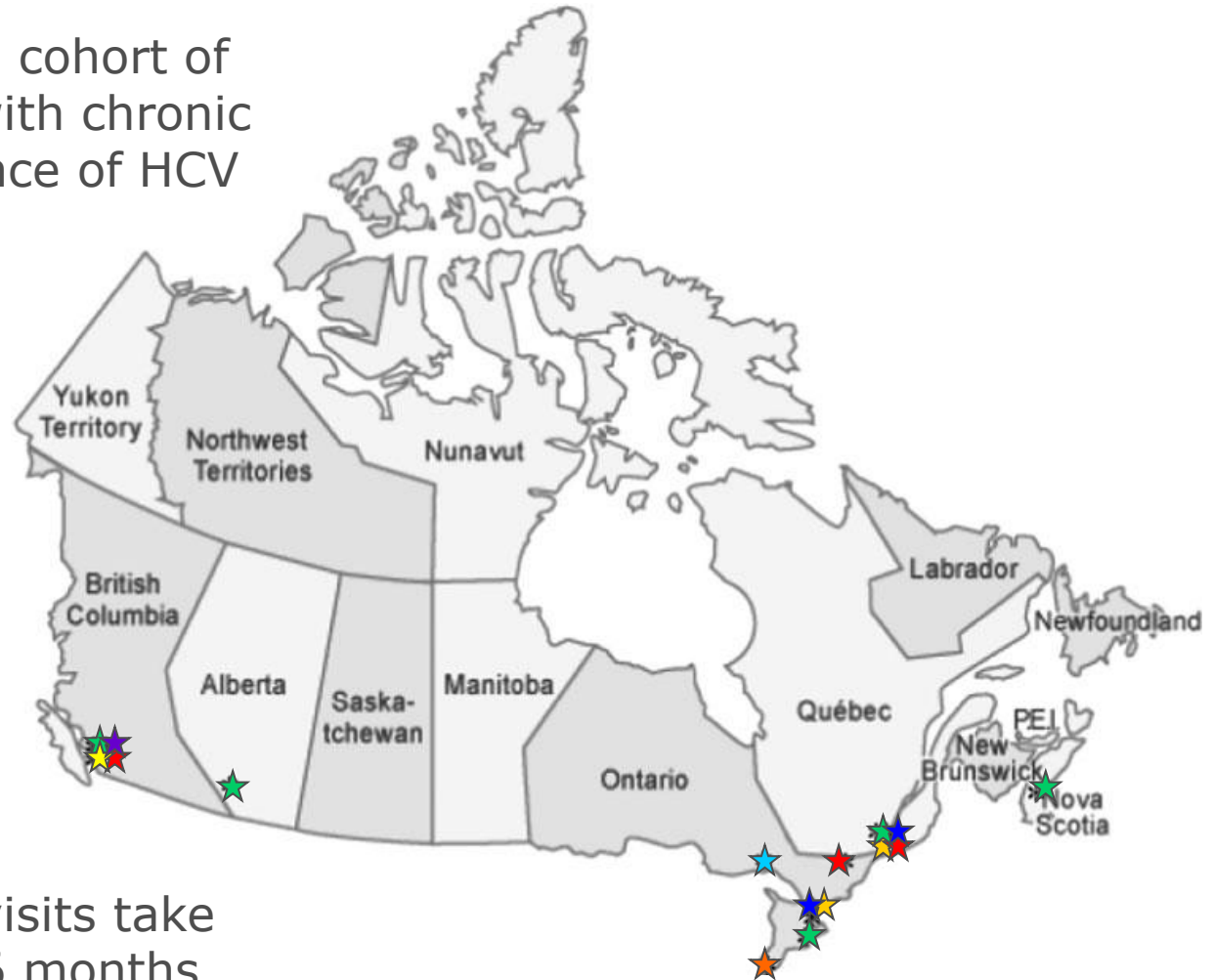
Study Setting: The Canadian Co-infection Cohort

- Multi-site prospective cohort of HIV-infected persons with chronic HCV infection or evidence of HCV exposure

- Between 2003 and the end of 2009, 966 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



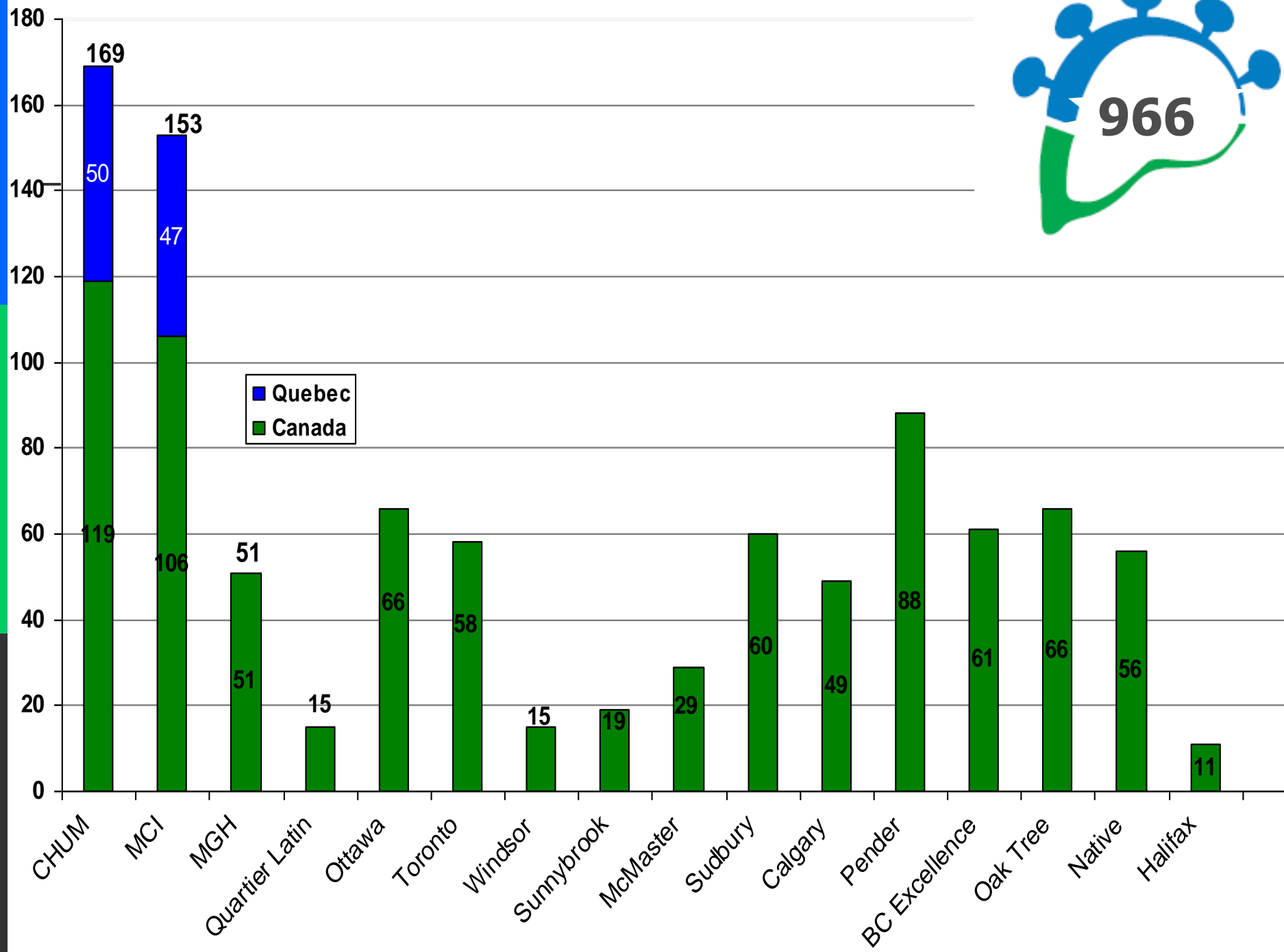


Table 1. Recruitment statistics for sites participating in the CCC

Site	Province	PI	Approximate number of HIV/HCV patients followed	Number recruited as of May 2010
Montreal Chest Institute	QC	M.B. Klein	170	156
CHUM	QC	D. Rouleau	200	169
Montreal General Hospital	QC	J. Cox	65	51
Clinique du Quartier Latin	QC	P. Cote	100	15
Pender Clinic	BC	B. Conway	200	92
BC Centre for Excellence	BC	J. Montaner	200	62
Native Health	BC	M. Tyndall	200	64
Oak Tree Clinic	BC	N. Pick	80	68
Calgary	AB	J. Gill	80	49
Sudbury	ON	R. Sandre	80	60
Hamilton	ON	H. Shariq	100	29
Toronto	ON	S. Walmsley	100	60
Windsor	ON	J. Cohen	40	15
Ottawa	ON	C. Cooper	200	66
Sunnybrooke	ON	A. Rachlis	55	20
Halifax	NS	D. Haase	60	11
Total	16		1930	987

CHUM; Centre Hospitalier de l'Université de Montréal, QC; Quebec, BC; British Columbia, AB; Alberta, ON; Ontario, NS; Nova Scotia



Results



Baseline Cohort Characteristics

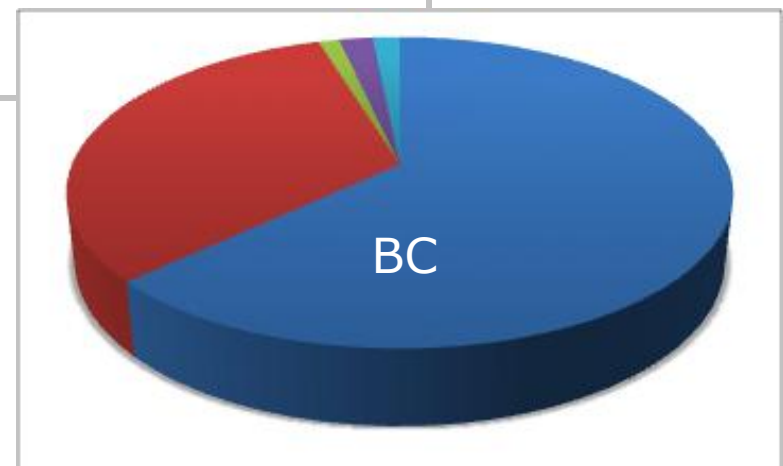
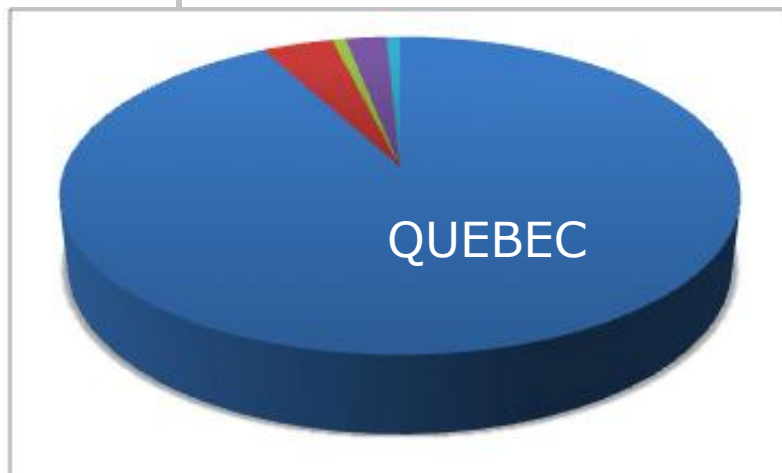
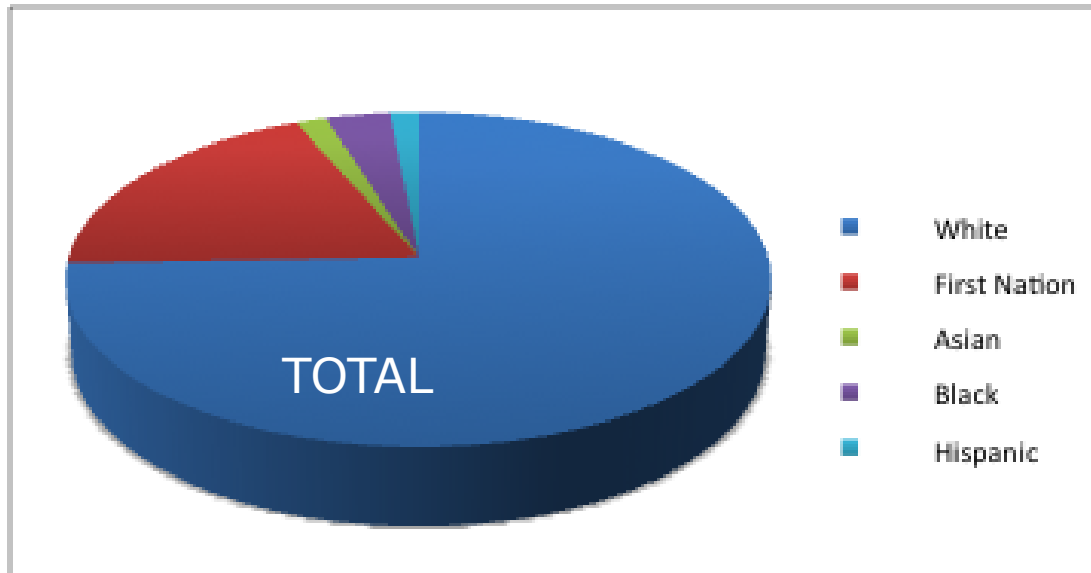
- 993 participants analyzed and followed for a median of 1.4 years (0.3-7.0 years)
- Only 3% lost to follow-up
- Majority are male (73%) between the ages of 19-68 years old and born in Canada
- At baseline, 38% reported active IDU; 81% have a history of IDU
- Median CD4 cell count: 374 cells/ μ L
- 80% were on ART
- 55% undetectable HIV RNA



Baseline Characteristics: Sociodemographics

	TOTAL	QUEBEC	BC	ALBERTA	ONTARIO	NOVA SCOTIA
# of patients	933	375	259	47	241	11
Median follow-up (in years)*	1.4(0.30, 7.0)	2.7 (0.4, 7.0)	0.8(0.3, 5.7)	2.0 (0.5, 3.0)	1.1 (0.3, 6.0)	1.2 (0.8, 2.0)
Gender (%)						
Male	73	79	59	68	79	82
Female	26	20	39	30	21	18
Transgender	1	1	2	2	0	0
Median age (in years)*	45 (19, 76)	44 (19, 70)	45(24, 71)	45(20, 70.00)	47(24, 76)	49(35, 60)
Born in Canada (%)	86	80	92	92	84	100
Greater than high school education (%)	26	22	23	26	36	36
Gross monthly income >\$1500 (%)	24	14	23	40	35	60
Marital status (%)						
Single	66	77	60	57	60	45
Married/Common-law	20	12	22	26	27	45
Widow	4	3	5	4	5	9
Divorced	10	7	13	13	9	0
Orientation (%)						
Heterosexual	75	77	80	76	67	80
Homosexual	18	16	13	15	28	20
Bisexual	7	7	7	9	5	0

Ethnicity



Risk Behaviours and Exposures

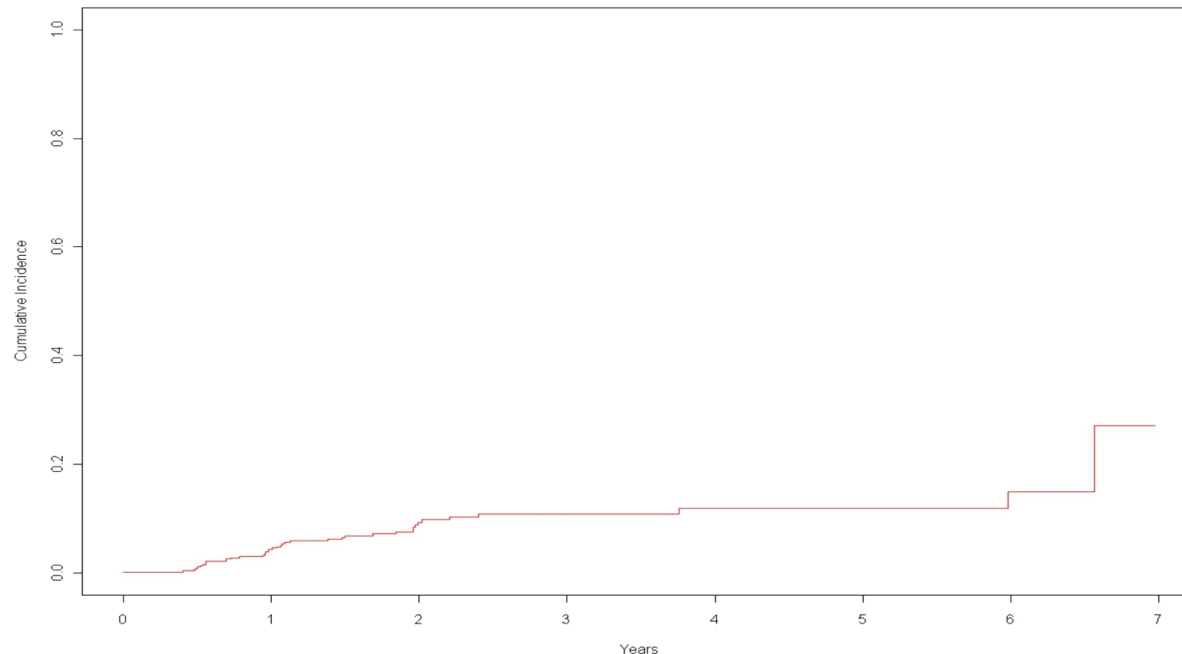
	TOTAL	QC	BC	AB	ON	NS
History of IDU (%)	81	83	90	87	67	73
Median # of years since first IDU	19 (1, 62)	18 (1, 46)	18 (1, 60)	19 (1, 42)	21(1, 48)	25 (2, 42)
Active IDU within 6 months (%)	34	39	46	9	20	18
Needle sharing ever ¹ (%)	76	84	74	63	66	88
Equipment sharing ever ¹ (%)	74	73	76	67	74	88
Used clean needles services ever	79	85	82	85	63	63
Snort ever (%)	82	85	87	87	73	64
Ever used therapy programs (%)	60	61	68	61	49	70
Current alcohol use (%)	49	59	35	34	52	64
Binge drinking >6 drinks ³ (%)	16	19	15	0	16	0
Current smoking (%)	78	82	82	81	68	80
Smoke pot (%)	53	56	50	32	97	70
History of sexwork or use (%)	47	51	54	51	32	45
Ever been in jail (%)	57	42	74	78	58	60
Tattoo (%)	53	51	59	53	50	29
Bodypiercing (%)	47	38	56	57	51	60

Health Status/Interventions

Median APRI*	0.60 (0.12, 49.52)
Liver biopsy ever (%)	21.33
Fibrosis¹ (%)	20.27
Steatosis¹ (%)	42.54
Abdominal US (%)	35.29
Hepatitis A (%)	9.20
Vaccinated for Hepatitis A (%)	51.58
Hepatitis B (%)	22.12
Vaccinated for Hepatitis B (%)	53.23
AIDS diagnoses (%)	31.77
esld (%)	10.90

17% treated for HCV at baseline; another 16% during follow-up

Cumulative incidence of first ESLD



Among 843 patients without ESLD at baseline, 44 (5%) participants developed ESLD during follow-up (3.6/100 person-years; 95% CI, 2.54 to 4.67).

88 of 711 with APRI <1.5 (13%) developed an APRI score ≥ 1.5 during follow-up (9.5/100 person-years; 95% CI, 8.5 to 12.7);



Univariate and multivariate Cox proportional hazards regression

Variable	Univariate HR (95% CI)	Multivariate HR (95% CI)
Age (per 5 yr increase)	1.07 (0.91, 1.24)	1.07 (0.95, 1.21)
Female gender	1.06 (0.58, 1.95)	1.28 (0.71, 2.30)
Active IDU	0.83 (0.46, 1.49)	n/a
Active alcohol consumption	1.37 (0.79, 2.39)	n/a
Duration of HIV infection (per 5 yr increase)	1.09 (0.92, 1.31)	n/a
Duration of HCV infection (per 5 yr increase)	1.03 (0.91, 1.15)	n/a
Interruption of ART	2.75 (1.26, 5.98)	2.52 (1.20, 5.28)
Previously treated for HCV	1.53 (0.74, 3.16)	n/a
Nadir CD4+ T cell count (per 50 cell/uL increase)	0.98 (0.91, 1.05)	n/a
Highest HIV viral load (log copies/ml)	1.09 (0.87, 1.38)	n/a
Time-updated CD4+ T cell count	0.92 (0.86, 0.995)	0.95 (0.88, 1.00)
Time-updated HIV viral load	1.22 (1.02, 1.47)	1.13 (0.91, 1.41)
Baseline APRI < 0.5	1	1
Baseline APRI 0.5 to 0.99	2.89 (1.40, 5.94)	3.02 (1.49, 6.12)
Baseline APRI 1.0 to 1.49	7.86 (3.73, 16.6)	7.80 (3.75, 16.2)
HbsAg+	0.71 (0.10, 5.21)	n/a

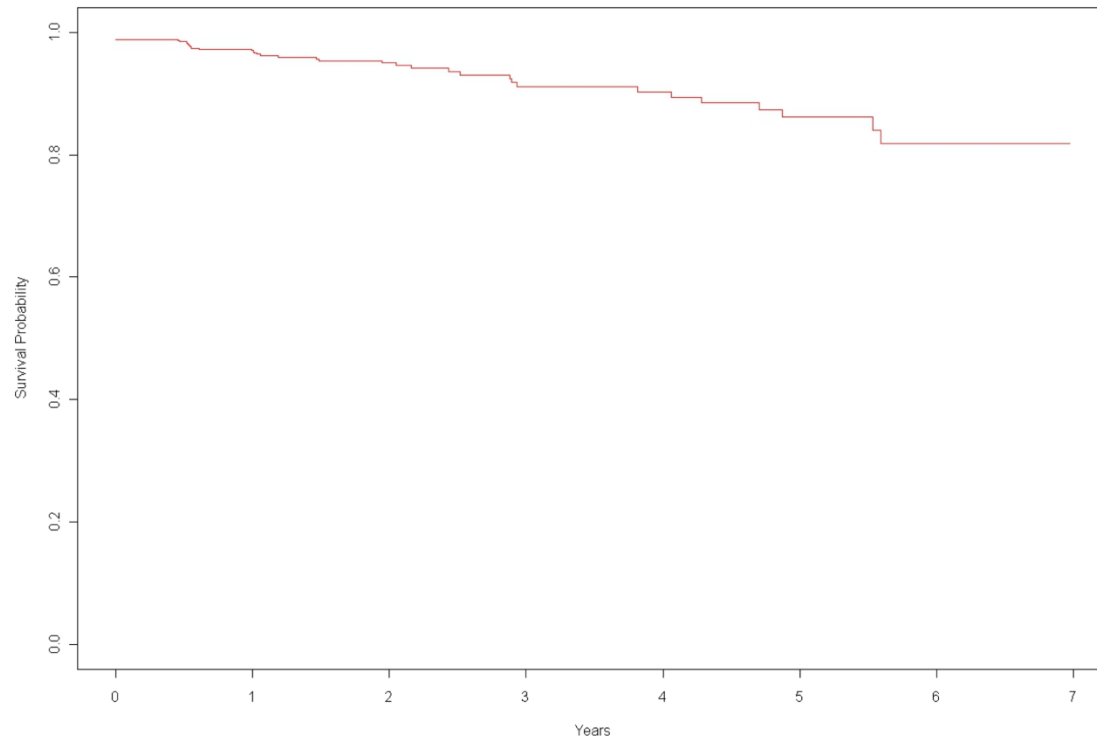


Implications

- ❑ Some of the liver disease progression in HIV/HCV co-infected patients may be due to the consequences of ART interruption and associated inflammation
- ❑ Patients may still wish to/have to discontinue treatment for a number of reasons so strategies to increase continuous ART exposure needed
- ❑ Plan to investigate the role of inflammation using stored samples/pair with fibrosis studies



Survival



Known causes of death were: ESLD (34%), drug overdose (25%), AIDS defining illnesses (18%), and cardiovascular disease (5%).

Death Rate Total

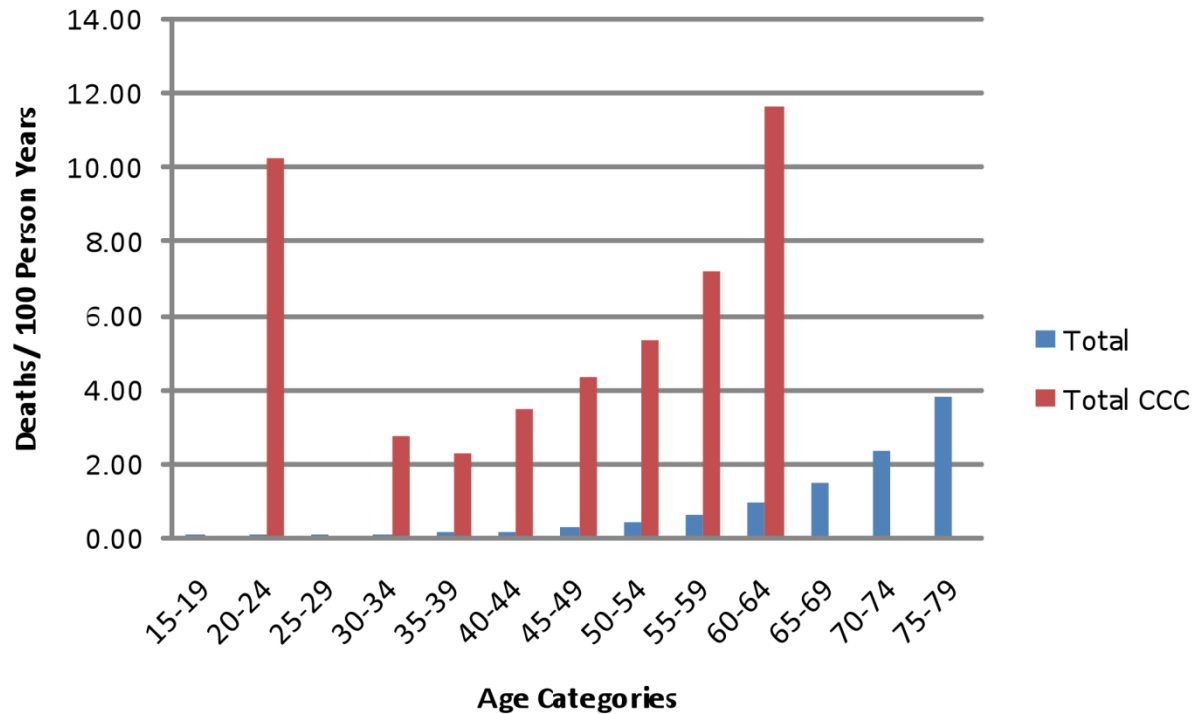


Table 2: Standardized Mortality Ratios by Age and Sex

	Female	Male	Total
Alberta	0	0	0
British Columbia	13.9647	8.503599	7.37059
Nova Scotia	0	0	0
Ontario	1.984648	33.45977	11.25554
Quebec	5.037817	67.90832	22.33837
CCC	5.085524	44.65988	17.55301

Impact of hepatitis C viral replication on CD4⁺ T-lymphocyte progression in HIV–HCV coinfection before and after antiretroviral therapy

Martin Potter, Adefowope Oduyeungbo, Hong Yang,
Sahar Saeed, Marina B. Klein, for the Canadian
Co-infection Cohort Study Investigators

1862 AIDS 2010, Vol 24 No 12

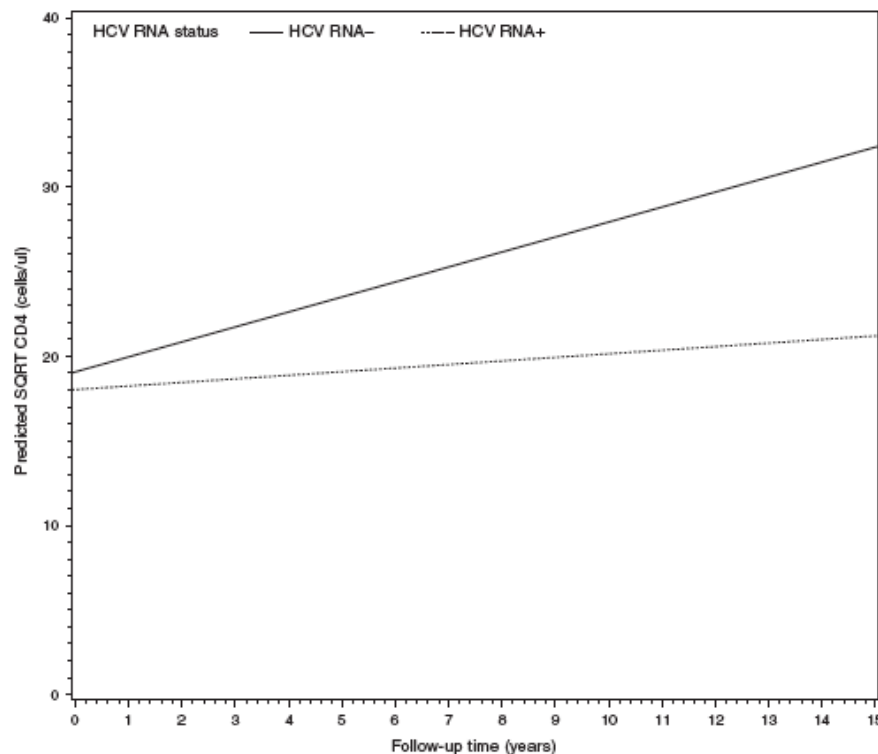


Fig. 1. CD4 T-lymphocyte changes (square root) after antiretroviral therapy according to presence of HCV RNA replication among HIV-infected patients. Solid line, spontaneous clearers of HCV infection (HCV RNA negative; $n=25$). Dashed line, chronically HCV infected (HCV RNA positive; $n=201$). Plots are based on predicted square root CD4⁺ T-lymphocyte changes from multivariable linear mixed effect models.

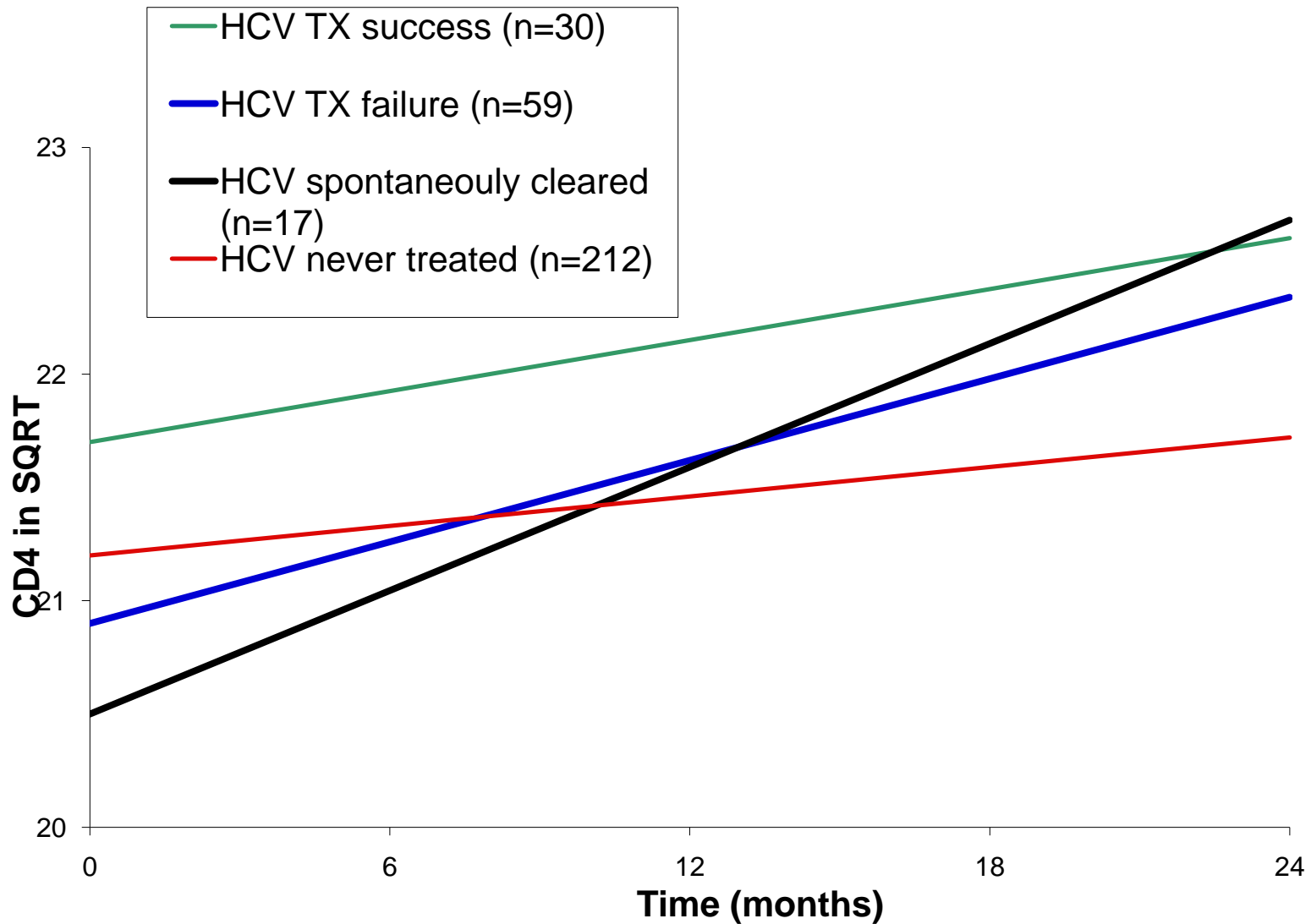
Table 3. Adjusted absolute CD4+ T-lymphocyte changes after antiretroviral therapy according to presence of HCV RNA replication among HIV-infected patients.

Variable	HCV status			
	HCV RNA –		HCV RNA +	
	Regression estimate (95% CI)	P	Regression estimate (95% CI)	P
Change in CD4 T-lymphocyte count (cells/ μ l per year)*	26 (12–41)	0.0004	4 (–0.6 to 7)	0.10
Age (years)	–3 (–15 to 9)	0.66	–0.2 (–3 to 3)	0.91
Male	–18 (–23 to 19)	0.86	–55 (–112 to 9)	0.09
Injection drug use	–198 (–427 to 31)	0.09	–49 (–108 to 9)	0.10
Nadir CD4+ T-lymphocytes (SQRT cells/ μ l)	20 (6–35)	0.007	17 (14–22)	<0.0001
Cumulative duration on ART at baseline	24 (0.8–48)	0.04	12 (6–18)	0.0001
Time updated variables				
ART exposure	37 (–7 to 81)	0.10	47 (12–85)	0.009
HIV RNA (log 10 copies/ml)	–18 (–35 to –0.7)	0.04	–35 (–46 to –25)	<0.0001
CD8+ T-lymphocytes (SQRT cells/ μ l)	18 (15–19)	<0.0001	11 (10–13)	<0.0001

All models were adjusted for age, sex, calendar year, nadir CD4 cell count, injection drug use, time updated HIV RNA (log copies/ml) and time updated CD8+T-cells and for cumulative ART exposure (in years) at baseline and time updated ART exposure.

*CD4 progression rates were statistically significantly different between the two groups at 5% level (regression estimate for interaction: –23, 95% CI: –32, –12; $P < 0.001$).

Unadjusted CD4 progression rates (95% CI): HCV RNA negative: 38 (25, 52) cells/ μ l per year and HCV RNA positive: 7 (4, 11) cells/ μ l per year.



HCV Co-infection is associated with reduced renal function

Variable	Regression estimate in ml/min/1.73m ² (95% CI)	p-value
Decrease in CrCl among HIV/HCV co-infected patients (per year)	-4.35 (-7.07, -1.62)	
Decrease in CrCl among HIV mono-infected patients (per year)	-1.16 (-1.91, -0.41)	
Difference	-3.19 (-5.99, -0.39)	0.03
Covariates		
Black race	15.23 (12.07, 18.40)	< 0.01
Age (per year)	-0.95 (-1.09, -0.81)	< 0.01
Hypertension	-5.45 (-8.88, -2.01)	< 0.01
Exposure to atazanavir	-3.31 (-5.43, -1.18)	< 0.01
Exposure to tenofovir	-2.50 (-4.43, -0.56)	0.01
Female gender	-2.82 (-5.98, 0.34)	0.08
Weight (per Kg)	-0.06 (-0.14, 0.02)	0.12
Hepatitis B co-infection	-3.75 (-8.15, 0.64)	0.09
Baseline HIV duration (per year)	0.04 (-0.17, 0.26)	0.69

Models adjusted for: age, gender, black race, weight, baseline creatinine clearance, smoking status, time since HIV dx, CD4 count, HIV RNA level, AIDS, tenofovir exposure, atazanavir exposure, nephrotoxic drugs exposure, hepatitis B virus infection, end-stage liver disease, hypertension and diabetes

Challenges

- ❑ Co-infected persons face a number of challenges that impact their ability to engage in treatment for both HIV and especially for HCV
- ❑ High short-term rates of progression of fibrosis, ESLD and death due to liver disease and possibly other comorbidities
- ❑ Even some simple interventions and preventive measures such as vaccination, screening for HCC are low

Opportunities

- ▣ Rich data and sample collection and multi-disciplinary research team will permit a better understanding of factors associated with health outcomes in this population
- ▣ Large number of participants engaged in care in whom interventions can be developed and targeted
 - improving uptake of HCV treatment and preventive strategies
 - Following and diagnosing liver disease early
 - Targeting treatment (e.g. IL-28B)

Long term goals

- ❑ Investigate means of slowing liver disease progression rates in co-infection.
- ❑ In particular, we will evaluate of the role of HCV treatment in the evolution of liver disease with a particular emphasis on evaluating access to treatment, predictors of response and comparing responders vs. non- responders.
- ❑ Develop interventional studies through CTN aimed at slowing fibrosis progression in those for whom treatment has failed or is contraindicated
- ❑ The cohort will serve as a research network for additional questions important to understanding co-infection and related health outcomes.

Conclusions

- ▣ The CCC represents one of the largest multi-centre cohorts focused on HIV-HCV co-infection in the world.
- ▣ Long-term follow-up of this diverse cohort will permit the study of the impact of ART and HCV treatment on the natural history of liver disease while accounting for potential confounders such as socio-demographics, drug use and type of care received.

Website: www.cocostudy.ca



Canadian Co-infection Cohort

A Prospective Clinical Cohort of HIV and Hepatitis C Co-infected Patients

Français

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The Canadian Co-infection Cohort Study follows a group of HIV and hepatitis C (HCV) co-infected patients from 16 centers across Canada.

The cohort was established in 2002 initially at three University centers in Quebec with infrastructure funding from the FRSQ (pilot phase). Then in 2005, we received funding from CIHR to expand to an additional 13 sites across Canada.

The primary objective of this study is to determine the effect of HAART on liver disease progression in HCV-HIV co-infection. We now have enrolled 950 participants across Canada a unique cohort similar to no other cohorts' worldwide.

Participants are not required to take any special medications or change any of their behaviours, they are asked to complete a questionnaire every six months for five years. The questionnaires collect detailed information on demographics, drug and alcohol use, risk behaviours, smoking habits, quality of life measures and HIV and HCV treatment information. Blood samples are also collected and stored to perform viral, pathogenic and immunologic studies.

[Click here to view available positions](#)

Acknowledgments

- ❑ *Participants* in The Canadian Co-infection Cohort (CTN 222)
- ❑ *Co-Investigators*: Dr.'s Anita Rachlis, Brian Conway, Curtis Cooper, Danielle Rouleau, David Haase, David Wong, Erica Moodie, Jeff Cohen, Joe Cox, John Gill, Julio Montaner, Marianne Harris, Mark Hull, Mark Tyndall, Martin Potter, Neora Pick, Pierre Côté, Roger Sandre, Shariq Haider and Sharon Walmsley
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