Impact of viral hepatitis co-infection on mortality of HIV-positive individuals receiving antiretroviral therapy

J Gillis, C Cooper, A Cescon, M Smieja, J Raboud
and the OHTN Cohort Study Team

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OCS OHTN Cohort Study

UHN Toronto General Hospital

Conflict of Interest Disclosure

* None of the authors have a conflict of interest to declare.

Background

* HCV and HBV progression is exacerbated by HIV co-infection
  * Increased rate of progression to cirrhosis, end-stage liver disease, and hepatocellular carcinoma[1]
  * Overall, liver disease is the second leading cause of death in HIV positive individuals[2]
  * No consensus between studies examining impact of antiretroviral (ARV) therapy on HBV or HCV progression[2]
* In HIV viral hepatitis co-infection, an increase in hepatotoxicity may be related to ARVs
  * The majority of co-infected individuals tolerate ARV therapy well[2]
  * Often, hepatotoxicity is associated with progressed HCV/HBV disease[2]

[1] Koziel and Peters. *N Engl J Med* 2007, 356: 1445-1454; [2] Sulkowski. *J of Hepat* 2008, 48:353-367

Objectives

* Assess the impact of **co-infection with hepatitis B and/or C** on **all-cause mortality** in HIV-positive individuals treated with antiretroviral therapy

Ontario HIV Treatment Network Cohort Study (OCS)

* The OCS was initiated in 2005 and consists of:
  * New enrollees
  * Individuals who consented to continue enrollment from HOOD
* 11 active HIV care sites enroll participants
* 5644 participants were enrolled in the OCS as of September 2011
* In 2007, a questionnaire collecting socio-behavioural and demographic data was added
  * Previously, the HOOD questionnaire was administered
* Clinical and laboratory data are extracted from medical charts every 6 months or transferred electronically

Methods

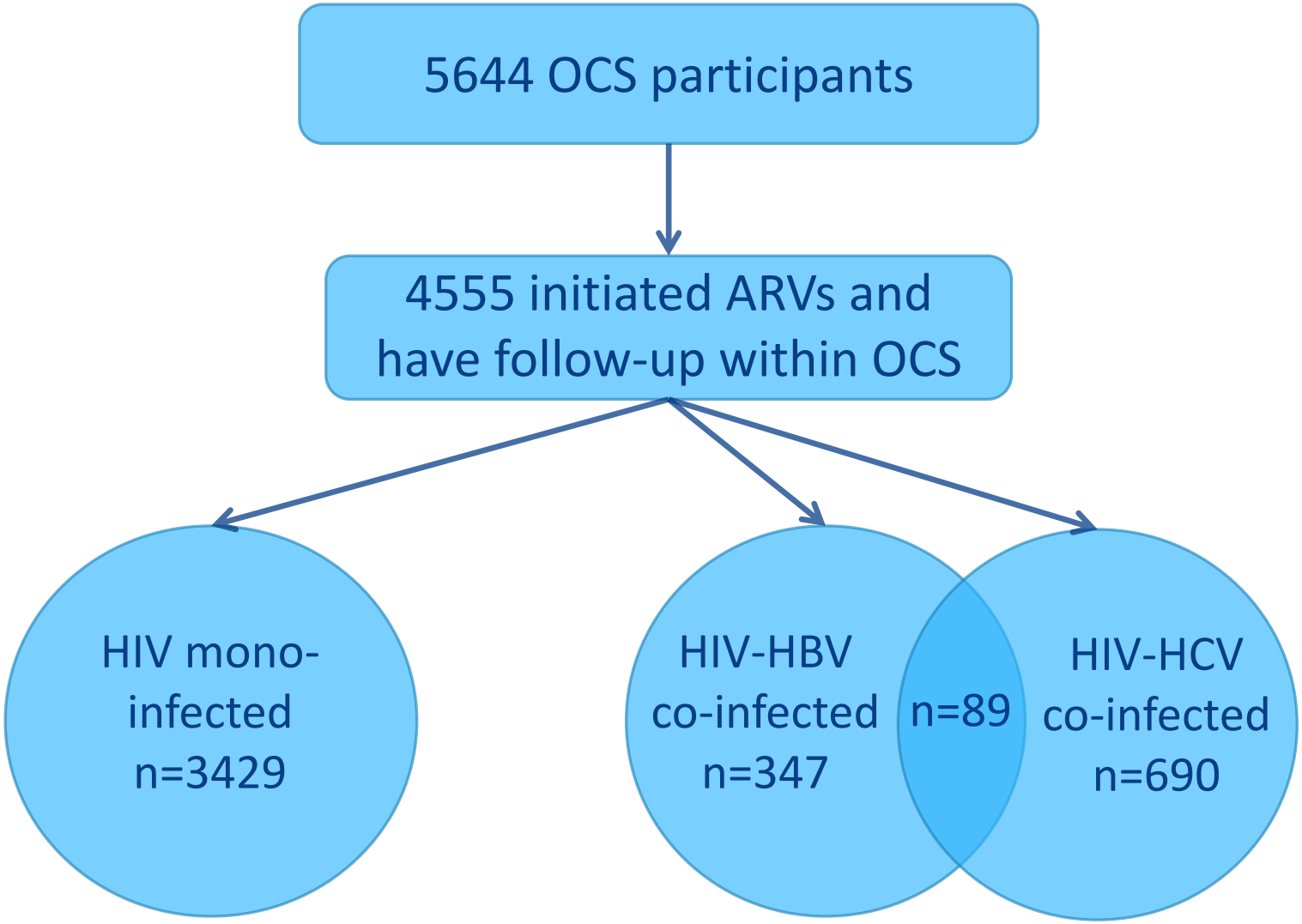
* **Inclusion criteria:** Participants from the OCS who have initiated antiretroviral (ARV) therapy
* **Classification:** HIV-HBV and HIV-HCV co-infection was identified from lab tests, diagnosis or adverse events
* **Comparison:** Baseline socio-demographic, behavioural, clinical, and psychosocial factors were compared by HIV mono-infection, HIV-HBV and HIV-HCV co-infection
  * Chi square or Fisher's exact test for categorical variables
  * Wilcoxon rank sum tests for continuous variables

Methods

Time to Event Analyses

* **Proportional hazards** models were used to estimate HR of mortality associated with co-infection with HCV and/or HBV
* **Complicating factor: left truncation**
  * OCS participants may have initiated ARVs prior to enrollment
  * Individuals must survive to enrollment to be part of the OCS, and thus are not at risk of death between ARV initiation and consent date

Results


5644 OCS participants
4555 initiated ARVs and have follow-up within OCS
HIV mono-infected n=3429
HIV-HBV co-infected n=347
n=89
HIV-HCV co-infected n=690

Demographics

	HIV (n=3429)	HIV-HBV (n=436)	HIV-HCV (n=779)	P-value HBV	P-value HCV
Age	37 (31-43)	36 (31-42)	37 (31-42)	0.66	0.31
Male	85%	**94%**	82%	<0.001	<0.001
HIV Risk Factor: MSM	73%	76%	39%	0.22	<0.001
IDU	5%	**17%**	**53%**	<0.001	<0.001
Endemic	14%	10%	4%	0.05	<0.001
Race: Caucasian	69%	71%	**74%**	0.72	<0.001
Black	7%	6%	14%		
Aboriginal	14%	12%	5%		
Other	10%	10%	6%		
Year of ARV Initiation	1997(1995-2004)	1997 (1994-2002)	1997 (1995-2003)	<0.001	0.05
1st Regimen: Non-HAART	45%	**51%**	**48%**	0.02	0.03
PI-Based	36%	31%	36%		
NNRTI-Based	18%	15%	14%		
Other HAART	1%	2%	2%		
Ever Smoker	62%	**71%**	**84%**	<0.001	<0.001

Results

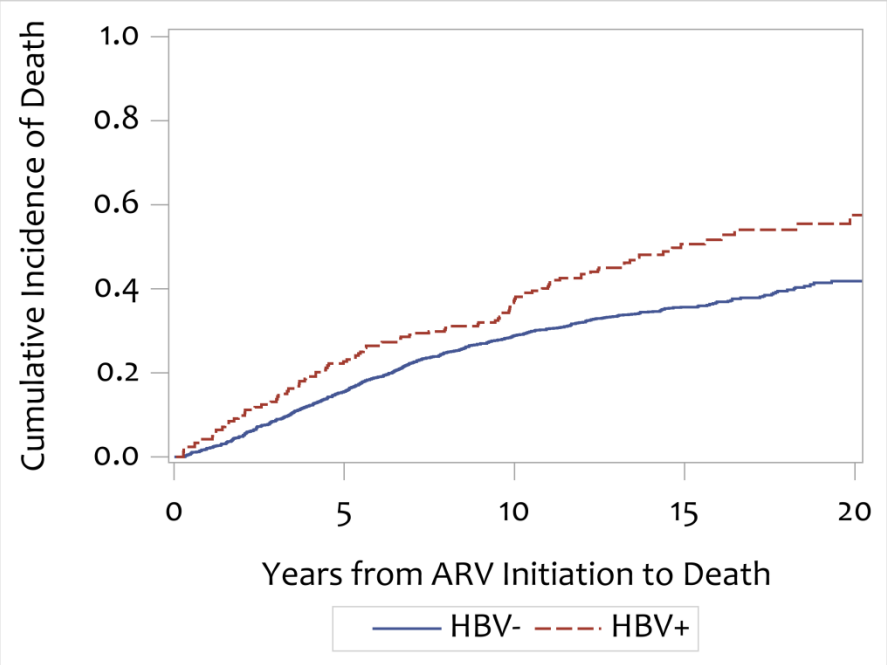


Figure 1. Cumulative incidence of death by HBV co-infection

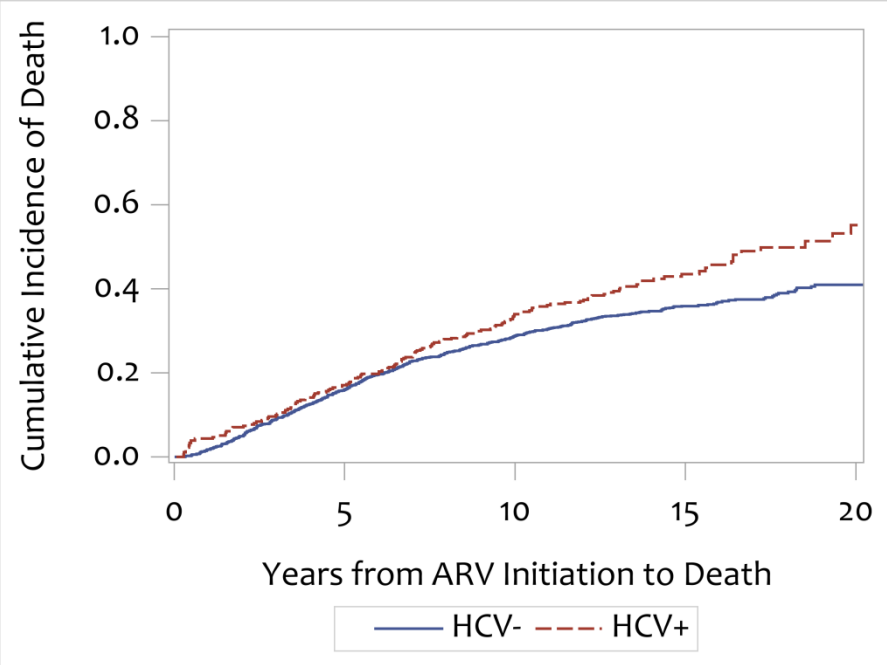


Figure 2. Cumulative incidence of death by HCV co-infection

* The estimated mortality at 5 and 10 years is:
  * 15% and 27% for HIV mono-infected
  * 21% and 35% for HIV-HBV co-infected
  * 16% and 31% for HIV-HCV co-infected

Survival Analysis

	Univariate Models		Multivariable Model	
	Hazard Ratio	P-value	Hazard Ratio	P-value
HBV	**1.48**	**<0.001**	**1.35**	**0.02**
HCV	**1.26**	**0.01**	**1.31**	**0.04**
Race: Caucasian	REF	--	REF	--
Aboriginal	**0.59**	<0.01	**0.64**	0.02
Black	**0.40**	<0.0001	**0.60**	0.02
Other	**0.53**	<0.001	**0.66**	0.04
Baseline Regimen: Non-HAART	REF	--	REF	--
PI-Based	**0.38**	<0.0001	0.83	0.12
NNRTI-Based	**0.22**	<0.0001	0.66	0.07
Other HAART	**0.15**	<0.01	0.43	0.23
Time-dependent CD4: >500 cells/mm^3	REF	--	REF	--
350-500 cells/mm^3	1.23	0.29	1.08	0.71
200-350 cells/mm^3	**2.59**	<0.0001	**2.07**	<0.0001
<200 cells/mm^3	**16.91**	<0.0001	**10.18**	<0.0001
Time-dependent Uncontrolled Viral Load	**4.13**	<0.0001	**1.64**	<0.0001

*Multivariable model adjusted for presumed confounders: age, sex, smoking status and injection drug use as HIV risk factor

Limitations

* **HCV definition**
  * Classification based on antibody tests may include false positives
  * Those who cleared HCV spontaneously or via treatment are considered positive for entire study period
  * May have recall bias for medical histories of HCV infection
* Cause of death data is incomplete
  * Unable to explore differences in cause of death by co-infection
* Incomplete covariate data:
  * No BMI, family history or cholesterol data
  * Incomplete alcohol and substance use data

Conclusion

* Despite use of ARVs, all-cause mortality is increased in both hepatitis B and C co-infection with HIV
* Revision of HCV definition may result in greater association of HCV co-infection and mortality
  * Exclude false positive anti-HCV antibody results and diagnoses unconfirmed with laboratory results

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OCS Study Team

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Ahmed M Bayoumi
Jeffrey Cohen
Fred Crouzat
Kevin Gough
Mona Loutfy
Janet Raboud
Edward Ralph
Irving E Salit
Marek Smieja
Ann N Burchell (Co-PI)
John Cairney
Curtis Cooper
Sandra Gardner
Don Kilby
Nicole Mittmann
Anita Rachlis
Sergio Rueda
Roger Sandre
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Munim Saeed