Incidence and risk of cardiovascular disease among antiretroviral-treated HIV-HCV and HIV-HBV co-infected patients

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OCS OHTN Cohort Study

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Conflict of Interest Disclosure

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

Background

* Increased risk of cardiovascular disease (CVD) in HIV infection[1]
  * Contributing factors: CVD risk factors common in HIV, HIV itself and use of antiretroviral (ARV) medications
* HCV co-infection may perturb the interaction between HIV and ARV therapy through:
  * Alteration of metabolic milieu[2,3]
  * Delayed immune reconstitution; prolonged pro-inflammatory state[4]
* Few studies have explored the impact of HBV co-infection on CVD
* There is a lack of consensus regarding the impact of viral hepatitis co-infection in HIV on CVD risk

[1] Dolan et al. *JAIDS* 2005, 39(1):44-45; [2] Kamin and Grinspoon. *AIDS* 2005, 19:641-652; [3] Cooper et al. *AIDS* 2007, 21(1):71-76; [4] Greub et al. *Lancet* 2000, 356(9307): 1708-1713

Objective

* Assess the impact of **co-infection with hepatitis B and/or C** on incidence and risk of **new cardiovascular disease** in HIV-positive individuals receiving ARV therapy

* **Cardiovascular disease** is defined as any of:
  * **Coronary artery disease**
  * **Myocardial infarction**
  * **Congestive heart failure**
  * **Cerebrovascular accident/stroke**
  * **Sudden cardiac death**

Methods

* **Inclusion criteria:**
  * Participants from the OHTN Cohort Study (OCS)
  * Had initiated antiretroviral therapy
  * No prior CVD
* **Classification:** HIV-HBV and HIV-HCV co-infection was identified from
  * lab tests
  * Diagnoses/adverse events

Methods

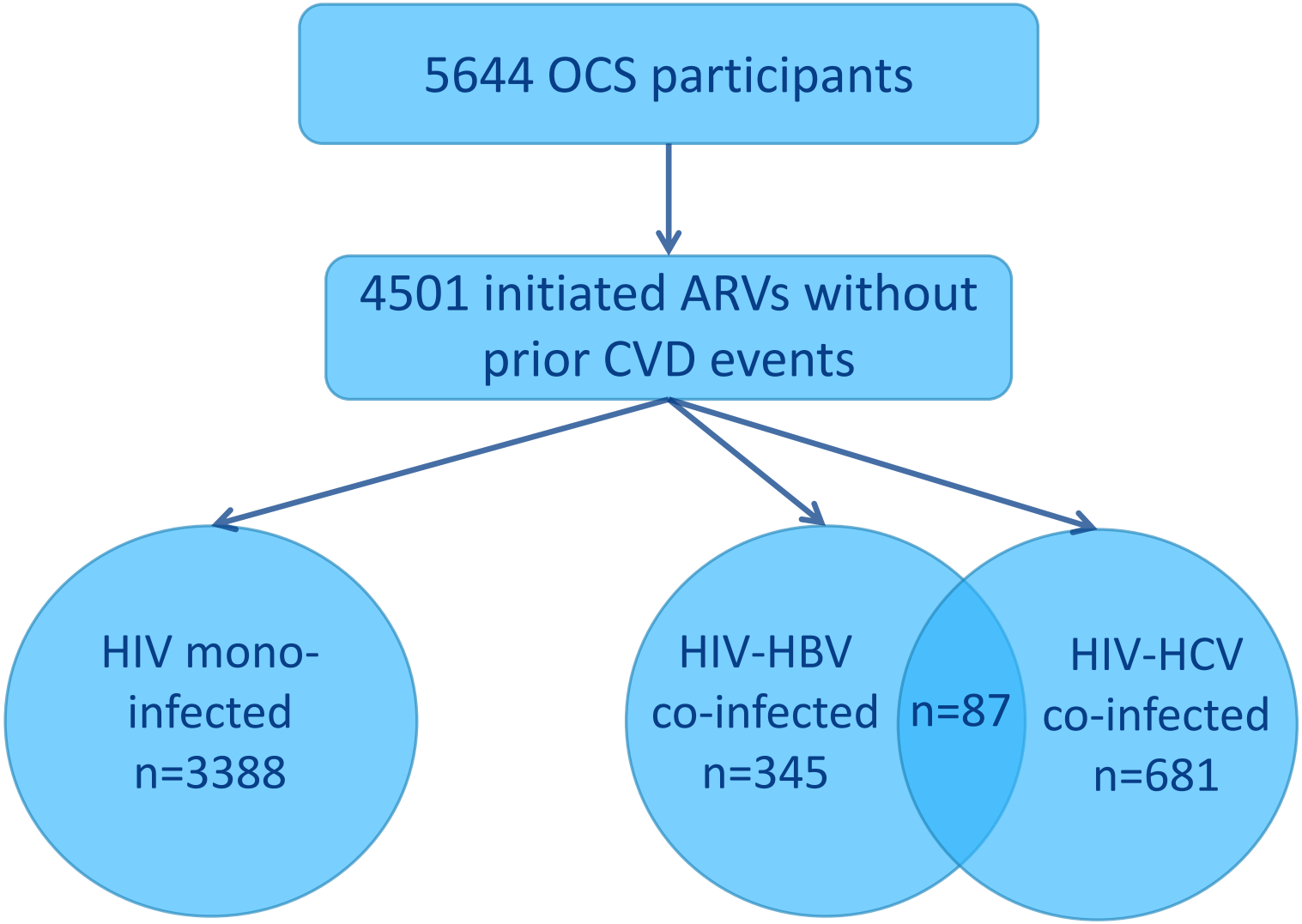
Time to event analyses

* **Outcome of interest:** Time from ARV initiation to CVD event
* **Complicating factor:**
  * Death may obscure the observance of CVD events
  * Do not want to treat deaths as censored observations
  * Mortality varies by HBV and HCV co-infection
* **Competing risks methodology**
  * Partitions the probability of CVD or death, into the probability for each type of event
  * **Semi-competing risks** as CVD does not obscure observation of death
  * **Cumulative incidence function (CIF)** plots and **Fine and Gray** models were used to assess the impact of HBV and HCV on CVD

Left Truncation

* Participants may have initiated ARVs before enrollment into the OCS
  * Participants can not be at risk for death between ARV initiation and enrollment
* CVD events may have occurred between ARV initiation and enrollment
  * Some data collected through medical histories
  * Amount of data varies by calendar year and site
  * Only observed in participants who survived to enrolment.

Results


5644 OCS participants
4501 initiated ARVs without prior CVD events
HIV mono-infected n=3388
HIV-HBV co-infected n=345
n=87
HIV-HCV co-infected n=681

Demographics

	HIV (n=3388)	HIV-HBV (n=432)	HIV-HCV (n=768)	P-value HBV	P-value HCV
Age	36 (31-43)	36 (31-42)	36 (31-42)	0.64	0.27
Male	85%	**94%**	81%	<0.0001	0.02
HIV Risk Factor: MSM	73%	76%	39%	0.26	<0.0001
IDU	5%	**18%**	**53%**	<0.0001	<0.0001
Endemic	14%	10%	4%	0.06	<0.0001
Race: Caucasian	69%	71%	74%	0.72	<0.0001
Black	14%	12%	5%		
Aboriginal	7%	6%	14%		
Other	10%	10%	6%		
Year of ARV Initiation	1997 (1995-2004)	1997 (1994-2002)	1997 (1995-2003)	<0.001	0.05
Baseline Smoking Status: Non-Smoker	38%	29%	16%	<0.01	<0.0001
Past Smoker	14%	12%	8%		
Smoker	49%	**59%**	**76%**		

Results

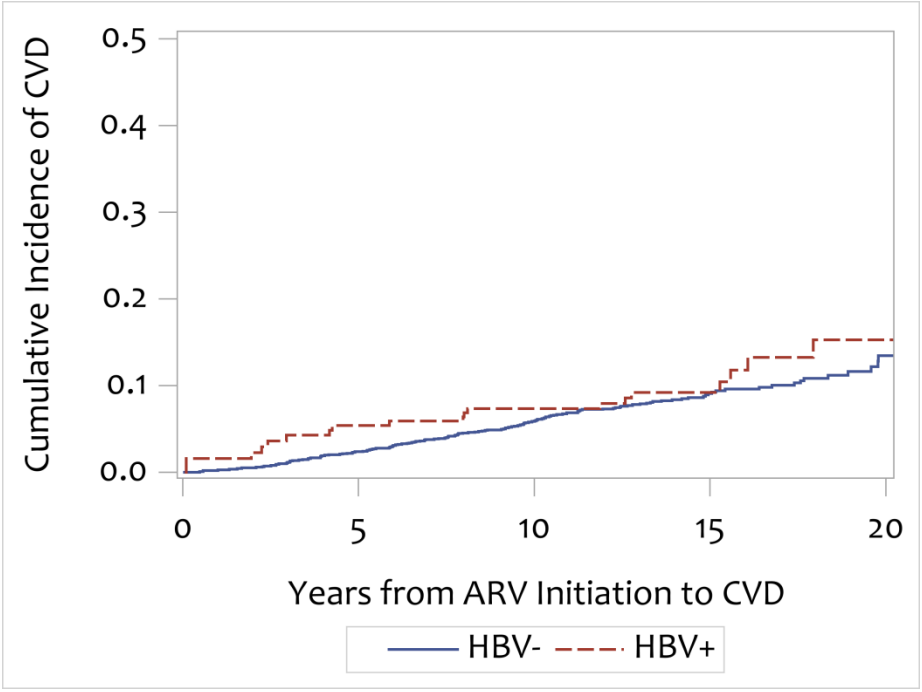


Figure 1. Cumulative incidence function plot of CVD by HBV

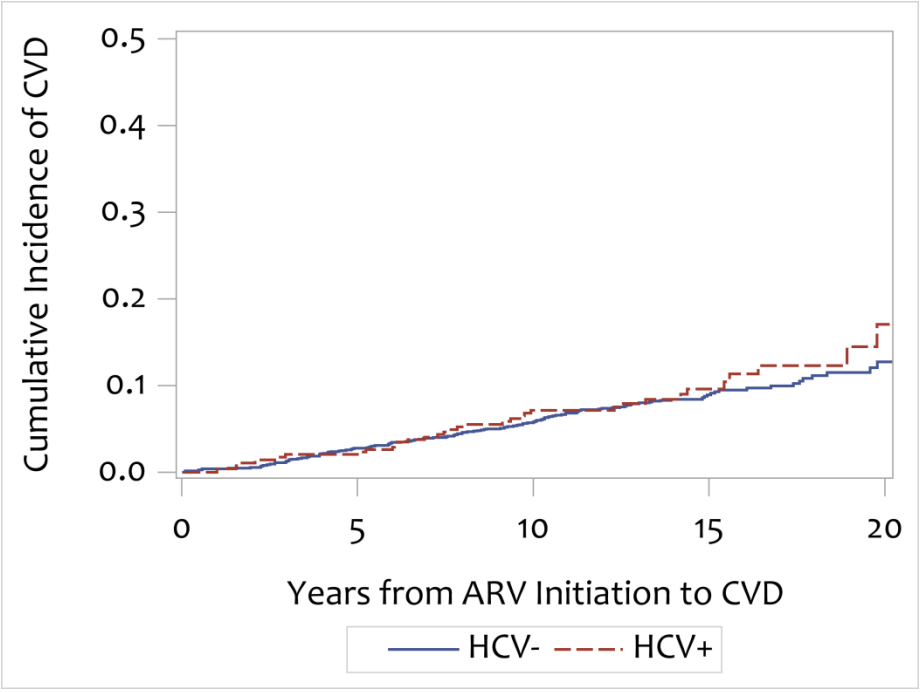


Figure 2. Cumulative incidence function plot of CVD by HCV

* Incidence per 10 years of follow-up:
  * HIV = 0.076
  * HIV-HBV = 0.087
  * HIV-HCV = 0.092

Survival Analysis

	Univariable Models		Multivariable Model	
	Hazard Ratio	P-value	Hazard Ratio	P-value
HBV	1.04	0.89	1.07	0.78
HCV	1.18	0.39	1.35	0.13
Age (per 10 years)	1.81	<0.0001	**1.98**	<0.0001
Baseline Smoking Status: Non-smoker	REF	--	REF	--
Past smoker	1.73	0.05	1.36	0.27
Smoker	1.63	0.02	**1.54**	0.04
Year of ARV Initiation: <1990	REF	--	REF	--
1990-1995	0.45	<0.01	**0.33**	<0.001
1995-2000	0.38	<0.01	**0.26**	<0.0001
2000-2005	0.28	<0.01	**0.17**	<0.0001
>2005	0.32	0.02	**0.22**	<0.01
Previous CVD related events	1.43	0.03	1.23	0.23
Weight (per 10 lbs)	1.03	0.26	1.04	0.17

* Multivariable model is also adjusted for sex and race.

Sensitivity Analysis

* Current definition of HCV positivity:
  * Any of: anti-HCV antibody positive, HCV RNA positive, chart diagnosis
    * Hazard ratio in multivariable left-truncated Fine and Gray model:

      1.35 (0.91, 2.00); p-value=0.13
* Sensitivity analyses with revised HCV definition:
  * (1) HCV RNA positive, or (2) anti-HCV antibody positive without ≥ 2 subsequent negative anti-HCV antibody results
    * Hazard ratio in multivariable left-truncated Fine and Gray model:

      1.46 (0.97, 2.20); p-value=0.07
  * Time-updated HCV status based upon both anti-HCV antibody and HCV RNA results
    * Hazard ratio in multivariable Fine and Gray model:

      1.48 (1.01, 2.15); p-value=0.04

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
* Naïve **left truncation** is inefficient
  * Lost 46 events that were captured via medical histories prior to enrollment in HOOD/OCS
* Incomplete covariate data:
  * No BMI, family history or cholesterol data
  * Incomplete alcohol, substance use, and cause of death data

Conclusion

* There may be elevated risk of CVD among individuals co-infected with HCV and HIV compared to HIV mono-infected patients

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