

Trends in Cause-Specific Mortality in HIV-HCV Co-infected Patients in Canada (2003-2016): Early Impact of HCV Therapy



Nadine Kronfli¹, Sahir Rai Bhatnagar², Mark Hull³, Erica Moodie², Curtis Cooper⁴, Neora Pick⁵, Sharon Walmsley⁶, Marie-Louise Vachon⁷, Valerie Martel-Leferrerie⁸, John Gill⁹ and Marina B. Klein¹, on behalf of the Canadian Co-Infection Cohort Investigators

¹McGill University Health Centre, Montreal, Quebec, Canada ; ²Department of Epidemiology, Biostatistics & Occupational Health, McGill University, Montreal, Quebec, Canada ; ³Department of Medicine, University of British Columbia, Vancouver, British Columbia, Canada ; ⁴Ottawa Hospital Research Institute, Ottawa, Ontario, Canada ; ⁵Oak Tree Clinic, BC Women's Hospital and Health Centre, Vancouver, British Columbia, Canada ; ⁶Toronto General Hospital Research Institute, Toronto, Ontario, Canada ; ⁷Centre Hospitalier de l'Université Laval, Quebec, Quebec, Canada ; ⁸Department of Medicine, University of Calgary, Calgary, Alberta, Canada

Background

- With the use of cART, AIDS-related mortality has declined, resulting in the emergence of HCV as an important cause of morbidity and mortality.
- ~ 20-25% of mortality in HIV-HCV co-infection is secondary to liver disease-related deaths.
- With the introduction of oral direct-acting antivirals (DAAs), and their associated high SVR rates, liver disease-related deaths have declined in HIV-HCV co-infection.
- Determining which modifiable factors may contribute to excess mortality in HIV-HCV co-infection will help address the potentially preventable causes of death.
- Accounting for competing causes of death is necessary given the high risk from lifestyle exposures primarily related to risks associated with IDU seen in HIV-HCV co-infection.
- Study objectives:**
 - To examine cause-specific mortality among HIV-HCV co-infected patients.
 - To evaluate changes in cause-specific mortality before and after the increase in treatment uptake among HIV-HCV co-infected patients.

Methods

- The Canadian Co-infection Cohort (CTN 222) is a prospective multicentre cohort study of 1,693 HIV-HCV co-infected patients from 18 sites in Canada.
- Primary outcome:** Cause of death (Coding of Cause of Death in HIV (CoDE) Protocol).
- Linkage to provincial vital statistics available for 68% of participants.
- Deaths were classified into **5 categories: ESLD, Smoking-related causes, Drug overdose, Other and Unknown.**
- All cause and cause-specific event rates per 1000 person years (PY) were estimated using Poisson regression stratified by:
 - Time:** Early (04/01/03 - 12/31/08) and Late (01/01/09 - 07/31/16).
 - Age:** 20-49 and ≥ 50 .
- To account for competing risks, a **competing risks survival model** was used to estimate the cause-specific hazard ratios (HR) and 95% CIs of time and age groups on causes of death.
- Cause-specific **cumulative incidence functions** (CIFs) from the cause-specific HRs were computed.

Results

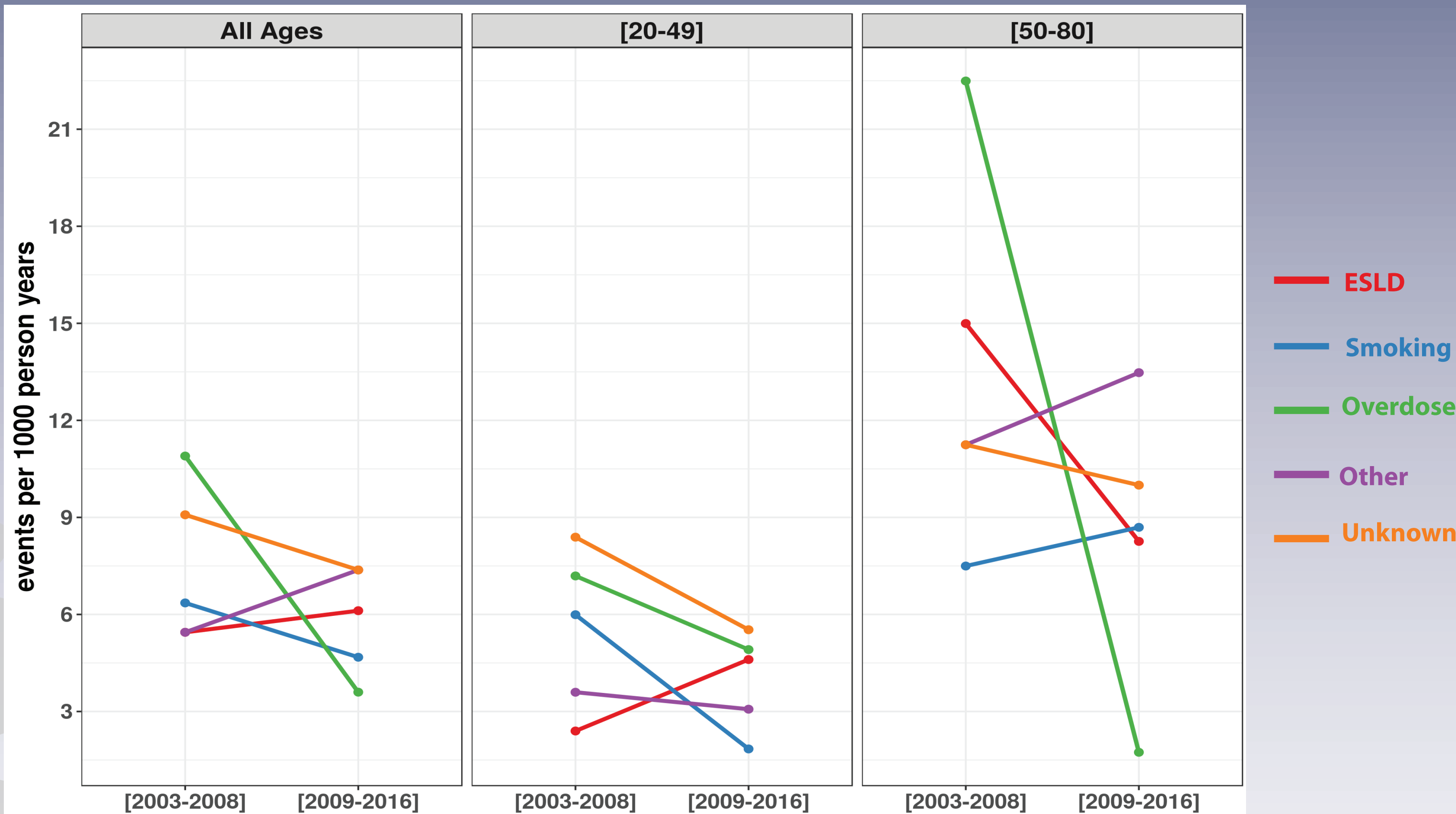
- 1477 participants included; median follow-up 4.1 [IQR 1.8-6.9] years.
- 203 (14%) patients died $\rightarrow$ Death rate 30.5 per 1000 person-years.
- Median age at death: 47 [IQR 43-54] years.

Age	2003-2008	2009-2016
20-49	27 (IQR 13, 57)	20 (IQR 13, 31)
50-80	67 (IQR 30, 152)	42 (IQR 30, 60)

Table 1 Patient characteristics at cohort entry	
At Cohort Entry	Total (n=1477)
Age	45 (IQR 39, 51)
History of IDU	1186 (80%)
Active IDU	515 (35%)
History ETOH use	640 (49%)
Current ETOH use	763 (52%)
History of smoking	1336 (91%)
Current smoker	1094 (75%)
CD4+ cell count	396 (IQR 250, 570)
On cART	1234 (84%)
HIV RNA < 50 copies/ml	926 (64%)
Duration HCV infection	18 (IQR 10, 26)
HCV RNA positive	1188 (86%)
HCV Treatment naïve	1195 (81%)
APRI > 1.5	291 (21%)
Prior ESLD diagnosis	133 (9%)

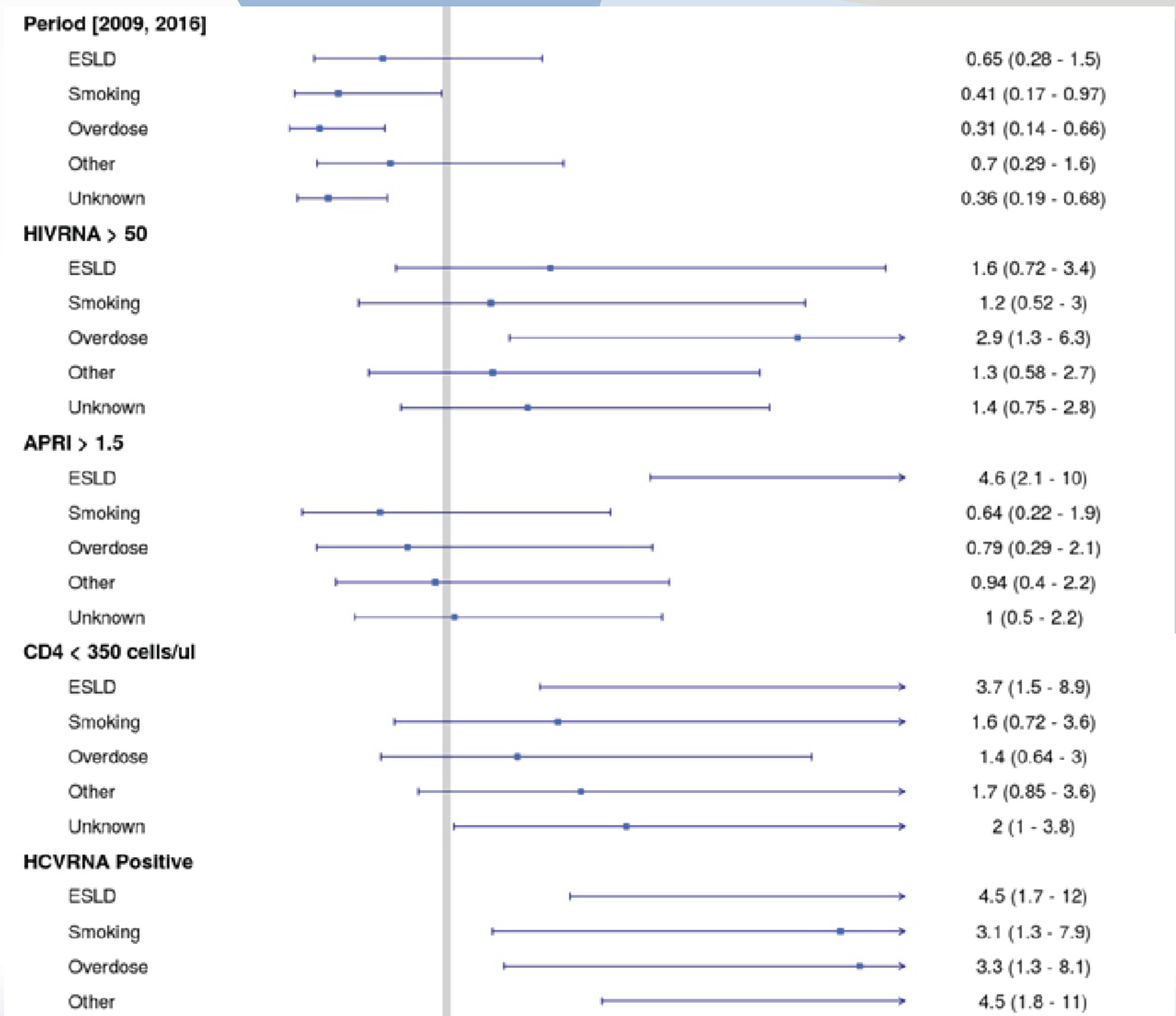
Table 2 Patient characteristics at death		
At Last Visit	Dead (n=203)	Alive (n=1274)
Active IDU	59 (29%)	340 (27%)
Current ETOH use	95 (47%)	702 (56%)
Current smoker	160 (80%)	898 (71%)
CD4+ cell count	319 (IQR 169, 520)	480 (IQR 302, 680)
On cART	180 (89%)	1155 (91%)
HIV RNA < 50 copies/ml	123 (65%)	988 (80%)
Duration HCV infection	21.5 (IQR 14, 28)	17.5 (IQR 9.5, 25)
HCV RNA positive	115 (82%)	537 (65%)
HCV treatment naïve	154 (76%)	737 (58%)
APRI > 1.5	60 (32%)	182 (15%)
Prior ESLD diagnosis	28 (14%)	52 (4.1%)

Figure 1 Unadjusted cause-specific event rates



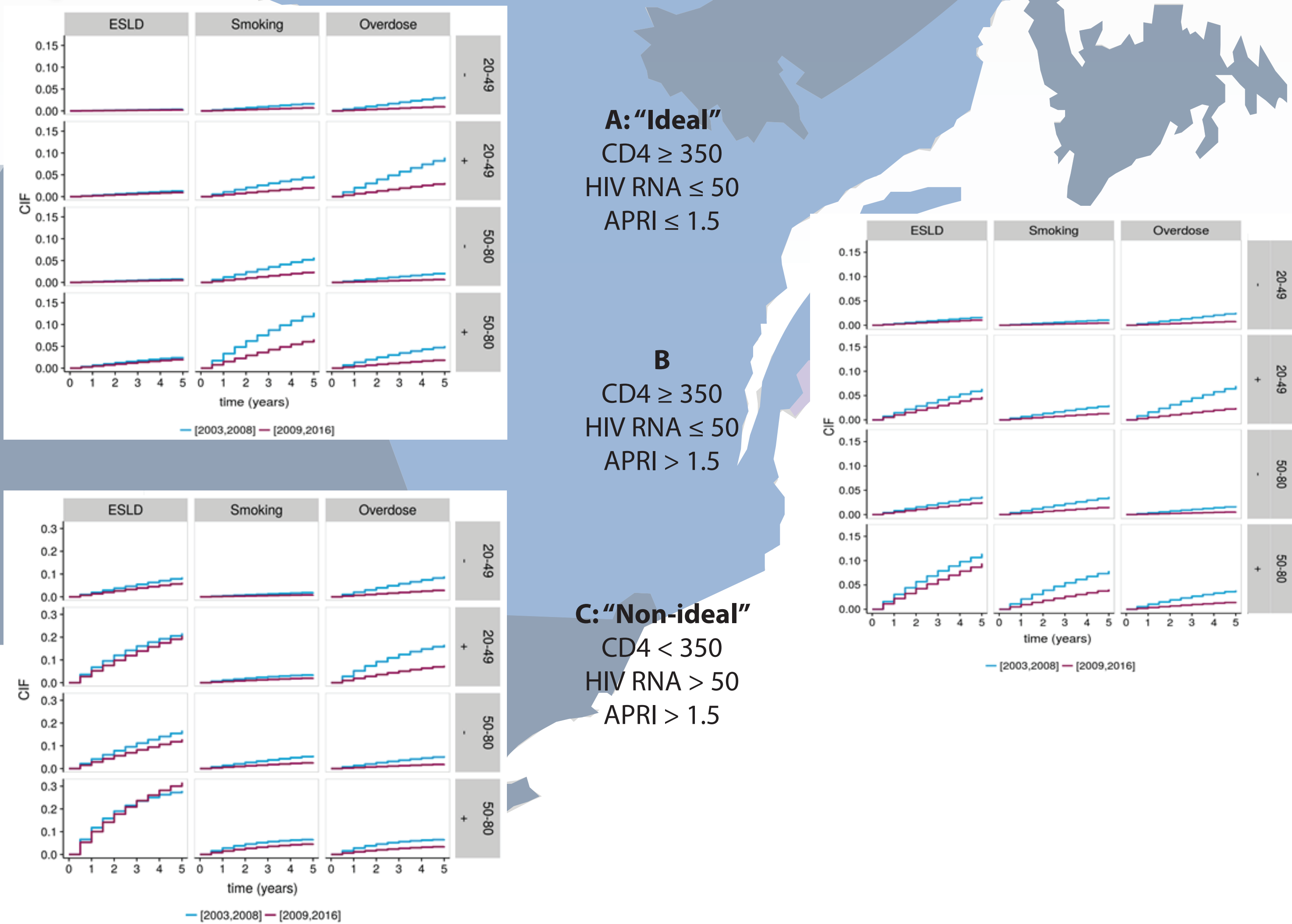
- Deaths due to ESLD do not appear to have decreased over time, but they were no longer the most common cause of death in the 2009-2016 time period in either age group.
- Smoking-related deaths accounted for the greatest proportion of deaths from 2009-2016.
- Drug overdose accounted for the greatest proportion of deaths among 20-49 year olds from 2009-2016.

Figure 2 Cause-specific hazard ratios



- After accounting for competing risks, there was a significant decreased risk of death from overdose and smoking-related causes from 2003-2008 to 2009-2016.
- ESLD also appeared to decrease from 2003-2008 to 2009-2016.
- Deaths due to ESLD were approximately 5-fold more likely with an APRI > 1.5 and a positive HCV RNA and over 3 times more likely with for those with a CD4 count < 350 cells/ μ l.
- The risk of death from all causes was higher in those with a positive HCV RNA at last visit.

Figure 3 Early and late period cause-specific CIFs



- For "ideal" patients without fibrosis (APRI ≤ 1.5), death due to ESLD was very unlikely even in the presence of a positive HCV RNA regardless of age. There was no change in death rates due to ESLD over time whereas deaths due to other causes decreased substantially (Figure 3A).
- In contrast, for patients whose HIV was well controlled, but who had advanced liver fibrosis (APRI > 1.5), deaths were primarily driven by ESLD, especially among those with detectable HCV RNA. In both age groups, ESLD deaths declined between 2009-2016 (Figure 3B).
- However, this benefit was lost if HIV was not well controlled (Figure 3C).

Limitations

- Although our cohort is highly generalizable to the HIV-HCV co-infected Canadian population in care, the results are not generalizable to HIV-HCV individuals who do not access care.
- Despite the use of standardized case report forms, 25% of causes of death were of unknown cause.
- Although linkage to provincial vital statistics (68% of participants) was performed for causes of death, we may have missed deaths among LTFTU.

Conclusions

- All cause mortality decreased in both age groups over time, but still remains high.
- Declining death rates were explained by a reduction in mortality from a variety of competing causes.
- No significant decrease in ESLD deaths overall; however, ESLD appears to be declining among 50-80 year olds – those who have been successfully treated.
- Immediate impact of HCV therapy will be most profound among those with advanced liver fibrosis.
- Unlikely to see any mortality benefit in short-term for individuals at low risk of ESLD, therefore targeting modifiable risk factors (substance abuse and tobacco smoking) will have the greatest impact.