Incidence Rates and Risk Factors for Severe Bacterial Infections in HIV/HCV Co-infected Patients

Rollet-Kurhajec KC[1], Gill J[2], Cooper C[3], Hull M[4], Cox J[5], Conway B[6], Pick N[7], Vachon M-L[8], Klein MB[1]
for the Canadian Co-infection Cohort Study Investigators

[1]Division of Infectious Diseases and Chronic Viral Illness Service (CVIS), McGill University Health Centre, Montreal, QC, Canada; [2]Southern Alberta HIV Clinic, Calgary, AB, Canada; [3]The Ottawa Hospital Research Institute, Ottawa, ON, Canada; [4]BC Centre for Excellence in HIV/AIDS, Vancouver, BC, Canada; [5]Montréal General Hospital, Montréal, QC Canada; [6]Vancouver Infectious Diseases Research and Care Centre, Vancouver, BC, Canada; [7]Oak Tree Clinic, Children's and Women's Health Centre of British Columbia, University of British Columbia, Vancouver, BC, Canada; [8]Centre Hospitalier Universitaire de Québec, Québec, QC, Canada.

Marina B Klein, MD, MSc., FRCP
Montreal Chest Institute
3650 St-Urbain, Suite J-9
Montreal, Quebec, H2X 2P4
marina.klein@mcgill.ca
Phone: +1 (514) 843-2090
Fax: +1 (514) 843-2092

Visit out website:
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Abstract

BACKGROUND: HIV/HCV co-infection is placing an increasing burden on the health care system. Due to comorbidities and more rapid progression of liver disease associated with co-infection, infectious complications may contribute to excess morbidity. We measured the incidence and identified predictors of severe bacterial infections requiring health service use or leading to death among HIV/HCV co-infected patients.

METHODS: Data were analyzed from a Canadian multicentre prospective cohort of 1151 HIV/HCV co-infected patients with at least 2 consecutive visits between 2003-13. Every 6 months, patients self-reported reasons for walk-in clinic and emergency room visits and overnight hospitalizations. Causes of death were available from detailed case reports and linkage to vital statistics. The primary outcome was a first episode of severe bacterial infection (overall). We also examined specific subgroups: pneumonia, invasive bacterial infections [osteomyelitis, endocarditis, peritonitis, pyelonephritis, bacteremia, meningitis, septic arthritis] and skin and soft tissue (SST) infections. We used multivariate discrete-time proportional hazards models adjusted for age, sex, baseline BMI (as a marker for risk of insulin resistance) and hemoglobin and time-updated intravenous drug use (IDU), cigarette smoking, CD4 cell count, HIVRNA and APRI (≥1.5=significant fibrosis).

RESULTS: At baseline, median age was 45 years, 26% were female, 16% Aboriginal, 35% active IDU, 76% smoked cigarettes and median BMI was 24. Median CD4 was 440 cells/μL and 81% were on cART. During 2063 person-years (PY) of follow-up, 113(13%) patients reported any severe bacterial infection [IR=5.5/100 PY; 95% CI, 4.5-6.5]. 61(7%) developed at least one episode of pneumonia [IR=2.9; 2.1-3.6], 26(3%) invasive infection [IR=1.2; 0.7-1.6], and 37(4%) SST infection [IR=1.7; 1.2-2.2]. Of 133 deaths, 13(10%) were attributable to infection. Factors associated with severe bacterial infections are shown in the table below. Inclusion of HCV therapy in the models had no effect on the results.

CONCLUSIONS: Severe bacterial infections represent common causes of death and health service use among HIV/HCV co-infected patients. Risk for these infections is driven primarily by low CD4 and IDU rather than stage of liver disease. Insulin resistance and anemia may also be contributory. Efforts to address comorbidities and improve ART uptake and adherence in this population are warranted to limit the burden of severe infections.

Background

- With aging of the HIV population and a decrease in opportunistic infections, other comorbid conditions such as bacterial infections have become increasingly common among HIV-infected patients including those who maintain virologic suppression.
- Several studies in HIV mono-infection have demonstrated that parameters related to HIV disease (low CD4 count and uncontrolled HIV viral load) may play a role in the occurrence of non-AIDS defining infections.
- Non-AIDS disease risk may be increased by co-infection with hepatitis C virus (HCV).
- IDU and smoking (of both cigarette and illicit drugs) have been reported for HIV-infected persons as factors associated with an increased risk of developing bacterial infection.
- In the general population, overweight and obese persons were found to be more vulnerable to respiratory, invasive and skin bacterial infection via impaired immune response or development of Type 2 Diabetes.

OBJECTIVE: 1) To measure the incidence rates and identified predictors of severe bacterial infections requiring health services use or leading to death and;
2) To identify modifiable risk factors that could help prevent serious bacterial infections among co-infected patients.

Study Settings & Population

- The Canadian Co-Infection Cohort (CCC):
  - Prospective multi-centre cohort of HIV/HCV co-infected individuals (n=1151) recruited from 18 centers across Canada from 2003-2013, representing 20% of the co-infected population under care. Data and samples are collected at visits every 6 months. Causes of death are available from detailed case reports and linkage to vital statistics.
  - Cohort eligibility criteria: 1) over 16 years old; 2) documented HIV infection; 3) evidence of HCV infection.

Methods

- **Inclusion criteria**: All patients with at least 2 consecutive visits between 2003-2013.
- **Follow-up**: Patients were followed until their first outcome occurrence or last study visit.
- **Outcome:** The primary outcome was a first episode of severe bacterial infection (overall). We also looked at specific subgroups as followed:
  - **Invasive infection**: osteomyelitis, endocarditis, peritonitis, pyelonephritis, bacteremia, meningitis, septic arthritis.
  - **Skin and soft tissue (SST) infection**: cellulitis, MRSA, infected limb.
  - **Pneumonia**

Outcomes were identified from the free text description of reasons for emergency room visit, overnight hospital stay and walk-in clinic visit self-reported by patients at each visit in the questionnaire as well as from the standardized code of death case report form (CRF) used by the CCC sites that capture patient information near the time of death and precisely describe the causes of death.

- **Analysis:**
  - Incidence rates for each outcome were estimated by dividing the number of participants developing the outcome by the number of person-years at risk, and expressed in cases per 100 person-years (PY) of follow-up. Poisson count models were used to calculate confidence intervals (CI) for incidence rates.
  - Mortality rate from infection and cause of death were summarized.
  - We used multivariate discrete-time proportional hazards models, with robust standard errors to allow for repeated measures within individuals. Models were adjusted for age, sex, baseline BMI (as a marker for risk of insulin resistance) and hemoglobin and time-updated intravenous drug use (IDU), cigarette smoking, CD4 cell count, HIVRNA and APRI (≥1.5=significant fibrosis).
- **Software**: All analyses were conducted using Stata v11.2 (College Station, TX: StataCorp LP. 2009).

Limitations

- A major limitation in this study was that we could only use self-reported (not physician-diagnosed) episode of bacterial infection. In the future we will attempt to link those self-reported diagnosis data with provincial medical databases.
- We were unable to control for influenza /pneumococcal vaccinations.

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Results

Table 1. Sociodemographic and clinical characteristics of HIV-HCV co-infected patients at cohort entry by selected outcomes (2003-2012).

	Overall infection (N=113)	Invasive (N= 26)	SST (N= 37)	Pneumonia (N= 61)
Age (years), median (IQR)	44 (43, 45)	44 (43, 45)	44 (43, 46)	44 (43, 45)
Female sex, No. (%)	30 (27)	7 (27)	11 (30)	16 (26)
Aboriginal, No. (%)	20 (18)	5 (19)	9 (24)	9 (15)
Greater than high school education, No. (%)	26 (23)	8 (31)	10 (27)	11 (18)
Gross monthly income >$1500, No. (%)	20 (18)	3 (12)	8 (22)	12 (20)
Homeless or live in shelter, No. (%)	12 (11)	1 (4)	5 (14)	8 (13)
Current alcohol use, No. (%)	48 (42)	10 (38)	19 (51)	24 (39)
Active IDU, No. (%)	43 (38)	12 (46)	15 (41)	22 (36)
Current cigarette smoker, No. (%)	89 (79)	22 (85)	26 (70)	49 (80)
Time since HIV diagnosis (years), median (IQR)	11 (10, 12)	10 (9, 12)	11 (10, 12)	11 (10, 12)
Duration HCV infection (years), median (IQR)	19 (18, 20)	19 (18, 20)	18 (17, 20)	19 (18, 20)
CD4 count (cells/μL), median (IQR)	290 (198, 473)	380 (272, 541)	295 (240, 433)	240 (140, 400)
<200 cells/μL, No. (%)	28 (25)	3 (12)	6 (17)	22 (36)
200-349 cells/μL, No. (%)	36 (32)	9 (35)	13 (36)	19 (31)
350-499 cells/μL, No. (%)	22 (20)	3 (12)	10 (28)	9 (15)
≥500 cells/μL, No. (%)	26 (23)	11 (42)	7 (19)	11 (18)
HIVRNA load (log10 copies/mL), median (IQR)	1.7 (1.6, 2.2)	1.7 (1.7, 3.9)	1.7 (1.6, 3.1)	2.1 (1.7, 4.2)
HIVRNA load ≤50 copies/mL, No. (%)	59 (53)	14 (54)	24 (65)	27 (45)
On cART, No. (%)	91 (81)	17 (65)	28 (76)	52 (85)
Prior AIDS diagnosis, No. (%)	32 (28)	4 (15)	10 (27)	21 (34)
APRI ≥1.5 (fibrosis), No. (%)	20 (18)	6 (23)	10 (27)	7 (11)
HCV treatment naïve, No. (%)	93 (82)	21 (81)	32 (86)	49 (80)
HCV genotype (1 & 4), No. (%)	69 (77)	19 (83)	25 (83)	34 (71)
History of diabetes mellitus, No. (%)	5 (5)	0	3 (8)	3 (5)
Hemoglobin level (g/L), median (IQR)	138 (127, 150)	138 (131, 143)	139 (123, 153)	139 (124, 149)
Current BMI, median (IQR)	25 (21, 28)	22 (20, 27)	26 (23, 28)	24 (21, 26)

Tables Legend:

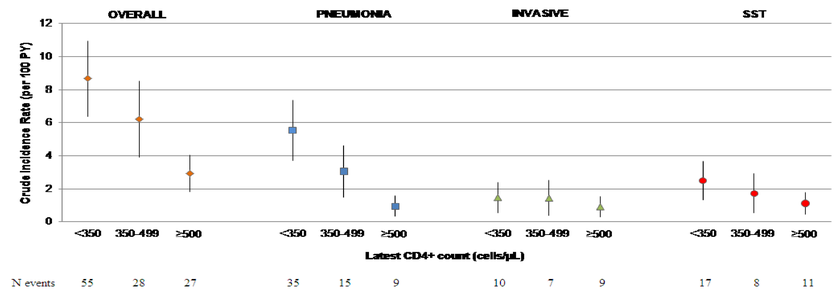
HIV – human immunodeficiency virus;
HCV – Hepatitis C virus;
IDU – injection drug use;
cART – current antiretroviral therapy;
APRI – aspartate aminotrasferase (AST) to platelet ratio calculated as: [100 x (AST / upper limit of normal)]/ platelet count ;
BMI – Body mass index calculated as: weight (kg) divided by height squared (m^2);
IQR – interquartile range;
PY FU– person years of follow-up;
aHR – adjusted hazard ratio.

- Of the 1151 patients enrolled in the cohort, median age was 44 years, 26% were female, 35% active IDU, 76% smoked cigarettes and median BMI was 24. Median CD4 cell count was 380 cells/μL, 61% had an undetectable HIVRNA and 81% of patients were on cART.
- The majority of patient remains naïve to HCV therapy.
- Patients self-reporting pneumonia appeared strongly immuno-compromised at cohort entry.

PROGRESSION TO:

- **Any bacterial infection**:
  - N= 113 (13%); PYFU: 2063
  - Rate= 5.5 (95% CI: 4.5, 6.5) per 100 PY
- **Invasive infection**:
  - N= 26 (3%); PYFU: 2201
  - Rate= 1.2 (95% CI: 0.7, 1.6) per 100 PY
- **SST infection**:
  - N= 37 (4%); PYFU: 2180
  - Rate= 1.7 (95% CI: 1.2, 2.2) per 100 PY
- **Pneumonia**:
  - N= 61 (7%); PYFU: 2134
  - Rate= 2.9 (95% CI: 2.1, 3.6) per 100 PY

Figure 1. Crude incidence rate of severe bacterial infection stratified by latest CD4 cell measurement.



- When stratified by most recent CD4 cell count the risk of bacterial infection gradually increased with declining immune response though the risk gradient is steeper for pneumonia.
- Overall, low CD4 count and low hemoglobin level were-associated with bacterial infection. IDU and BMI are strongly associated with SST infection. Pneumonia remains an important comorbidity associated with aging, lower CD4 counts and higher HIVRNA level.
- Of 133 deaths, 13 (10%) were from infection
  - Overall rate= 0.4 (95% CI: 0.2, 0.6) /100 PY.
  - Rate among patient who developed any type of infection: 2.51(95% CI: 1.5, 3.6) /100 PY.

Table 2. Multivariate discrete time proportional hazards models of factors associated with time to developing bacterial infection in follow-up (2003-2012).

	Overall (N= 113/904)		Invasive (N= 26/916)		SST (N= 37/914)		Pneumonia (N= 61/908)	
Independent Variables	aHR	95% CI	aHR	95% CI	aHR	95% CI	aHR	95% CI
Female sex	0.85	(0.49, 1.48)	0.64	(0.22, 1.85)	1.39	(0.63, 3.05)	0.84	(0.38, 1.88)
Aboriginal ethnicity	1.39	(0.78, 2.48)	1.40	(0.47, 4.13)	2.12	(0.97, 4.62)	0.88	(0.33, 2.37)
Baseline								
Age (per 5 years)	1.11	(0.96, 1.28)	0.92	(0.68, 1.26)	1.05	(0.82, 1.35)	1.23	(1.03, 1.48)
BMI (per 5 kg/m^2)	1.01	(0.85, 1.20)	0.96	(0.55, 1.67)	1.19	(1.00, 1.40)	0.91	(0.69, 1.19)
Hemoglobin (per 10 g/L)	0.83	(0.73, 0.95)	0.78	(0.63, 0.96)	0.88	(0.71, 1.09)	0.85	(0.70, 1.03)
Time-updated								
IDU	1.06	(0.65, 1.73)	1.80	(0.76, 4.27)	2.53	(1.15, 5.54)	0.55	(0.26, 1.15)
Cigarette consumption	1.17	(0.69, 2.00)	1.44	(0.41, 5.07)	0.63	(0.27, 1.47)	1.49	(0.72, 3.06)
CD4 count (per 100 cells/μL)	0.87	(0.79, 0.96)	1.00	(0.89, 1.12)	0.92	(0.80, 1.05)	0.77	(0.65, 0.92)
HIVRNA (per log10 copies/mL)	1.15	(0.94, 1.40)	1.07	(0.67, 1.70)	0.91	(0.62, 1.33)	1.27	(0.99, 1.62)
APRI ≥1.5	0.78	(0.47, 1.30)	0.79	(0.29, 2.18)	1.45	(0.64, 3.28)	0.69	(0.35, 1.35)

Note: Sample size varies by outcome as risk set of 2 consecutive visits were necessary for the analysis.

Conclusions

- Severe bacterial infections represent common causes of death and health service use among HIV/HCV co-infected patients in the late cART era.
- Risk for these infections is driven primarily by low CD4 and IDU rather than stage of liver disease. Insulin resistance and anemia may also be contributory.
- Further studies are needed to determine if immune depletion leads to more frequent bacterial infections and therefore if there is a risk-benefit of starting ART are higher CD4 cells count.
- Intervention aimed at timely initiation of ART and adherence as well as IDU cessation programs are warranted in this population to limit the burden of severe infections.