Time-dependent bias related to Hepatitis C classification in a cohort of HIV-positive individuals

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Outline

* Description of Motivating Study
  * Viral hepatitis co-infection in HIV
  * Cardiovascular disease and mortality related to co-infection
  * Historical Hepatitis C classification in studies of HIV-positive individuals
  * Changing opinions and current findings

* Description of Time-dependent Bias and Misclassification
  * Statistical considerations related to time-dependent bias and misclassification
  * Examples of situations in which time-dependent bias arises

* Impact of Time-dependent Bias on Estimation of Mortality
**Background:**

* Viral hepatitis co-infection is common in HIV
  * 30% **hepatitis C virus** (HCV) and 10% **hepatitis B virus** (HBV) co-infected
* Treatment of HIV infection successful; focus shifting to co-morbidities
* Prevalence of cardiovascular disease in HIV-positive individuals higher than in HIV-negative individuals
  * Increased risk may be due to: **virus/infection** itself, **medications** or **higher rates of traditional risk factors for CVD**
* Impact of viral hepatitis co-infection on CVD is unknown
  * Potential increased risk due to: **insulin resistance**, **higher rates of type 2 diabetes**, **pro-inflammatory state** in these individuals
  * Potential decreased risk due to: **positive impact on lipid profiles**

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Motivating Study

* Background cont’d:
  * Mortality is increased in HIV-viral hepatitis co-infected individuals
    * **HCV** and **HBV progression** is **exacerbated** by HIV co-infection
    * Increased rate of progression to cirrhosis, end-stage liver disease, and hepatocellular carcinoma\(^1\)
    * **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\(^2\)
    * **ARVs** may **increase risk** due to further burden the liver and hepatotoxicity
    * The **majority** of co-infected individuals **tolerate ARV therapy** well\(^2\)
    * Any increased risk and hepatotoxicity is often associated with progressed HCV/HBV disease\(^2\)
    * But, **therapy** also **limits pro-inflammatory state** thereby **decreasing risk**

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Objective:

* Assess the risk imposed by viral hepatitis co-infection on mortality and cardiovascular disease in HIV-positive individuals receiving antiretroviral therapy

Cohort: The Ontario HIV Treatment Network Cohort Study (OCS)

* Initiated in 2005 and consists of new enrollees and 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
Historically, studies of the risk posed by hepatitis C virus co-infection in HIV often classify individuals ever testing positive for HCV as positive for their entire follow-up, assuming:

- HCV acquisition antedates that of HIV
  - HCV is more infectious than HIV through blood contact
- HCV clearance is rare in HIV-positive individuals
  - Treatment with interferon and ribavirin were often contraindicated and treatment course was arduous

Classification is also complicated by evolution of diagnostic testing

- Guidelines previously limited screening for HCV to those considered at high risk, i.e. injection drug users
- HCV RNA confirmatory testing only became available in 2000
1. Increasing **incidence** of HCV infection in HIV+ MSM
   * HCV incidence of 5.1 per 1000 person years (pys) in HIV-positive MSM without history of IDU\(^1\)
   * HCV incidence increased 18-fold, to 4.09 per 100 pys in 2011, in MSM enrolled in the Swiss Cohort between 1998 and 2011\(^2\)

2. Spontaneous and treatment related **clearance**
   * 5-10% spontaneously\(^3\); 45-55% of whom *complete* treatment\(^4\)

3. **Accuracy** and **access** to diagnostic testing
   * Guidelines for HCV testing in HIV-positive individuals have evolved
   * Accuracy of testing has improved; early tests prone to false positives\(^5\)
   * False negatives can occur in highly immune compromised individuals\(^5\)

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Demonstrate the complexity of HCV classification in a cohort study, exploring:

1. New incidence of HCV infection after ARV initiation
2. Rate of spontaneous or treatment-related clearance
3. Impact of calendar period and censoring on HCV testing
Inclusion criteria:
- Participants from the OHTN Cohort Study (OCS) who had initiated antiretroviral therapy

Classification:
- HCV co-infection identified from anti-HCV antibody (Ab) and HCV RNA (RNA) laboratory tests through linkage with Public Health Ontario Laboratories (PHOL)
- Seroconversion during follow-up: negative antibody results prior to positive antibody or RNA test
- Clearance of virus: negative RNA test results after positive antibody or RNA tests
- Percentage of individuals with antibody and RNA testing was examined over follow-up by calendar year of therapy initiation
1. Seroconversion
   * 79 (11%) had negative Ab results prior to first positive Ab or RNA

2. Clearance
   * 120 (16%) had negative RNA results after positive Ab or RNA

3. Access and Accuracy
   * Inadequate testing for 669 (15%) of 4555 eligible for analysis
     * 634 had no HCV laboratory results during follow-up; 31% died
     * 35 had only laboratory tests with missing dates or no results
   * Of the 3886 with results:
     * 34 (1%) had potential false positive Ab results
     * 61 (1.6%) had potential false negative Ab results
Figure 1. Percentage of individuals with anti-HCV, RNA or missing data during follow-up by year of ARV initiation.
Time-dependent Bias and Misclassification

- As we observed:
  - 11% of individuals seroconverted during follow-up
  - 16% cleared the HCV
  - Differential testing patterns were observed based on calendar period of therapy initiation

- As such, previous assumptions and treatment of HCV status as fixed over follow-up may contribute to time-dependent bias
  - The value of the covariate, obtained after baseline, is considered fixed throughout the entire follow-up period
  - The biased estimate of mortality for the adverse exposure will be less than the unbiased one\(^1\) when considered known from baseline

\(^1\) Beyersmann et al. *Statistics in Medicine* 2008; 27:6439-6454
Time-dependent Bias

- Treatment of any exposure or covariate measured during follow-up as fixed from the time origin of interest

- Examples:
  - Impact of hospital acquired infection on length of stay in hospital
  - Risk of mortality related to transplantation
  - Exposure to medications in preventing progression of disease

- Commonly found in clinical literature
  - 127 (19%) of the 682 surveyed studies evaluated a time-dependent factor unavailable at baseline
  - 23 of 38 evaluable studies would have drawn different conclusions had time-updated covariates had been used

Excess follow-up time will be incorrectly attributed to the exposure or covariate of interest

- Fixed:
- An individual tests positive during follow-up
  - Time-updated:
- An individual tests positive during follow-up and clears the virus
  - Time-updated:
- We are therefore inflating the risk set of those who are infected

Other considerations:
- Complicated further by differential potential for censoring and ascertainment of status/covariate value by exposure group

For the simplest case of non-differential misclassification, Beyersmann et al demonstrated that underestimation occurs via the Nelson-Aalen estimator:

\[ \sum_t \frac{\text{# in exposure group} \rightarrow \text{event at } t}{\text{# in exposure group just prior to } t} \]

The numerator does not change between the fixed and time-updated models at time, t

The denominator, however, will be larger for the exposed group when the fixed model is employed

Another way to think of it: Inflation of the risk set

1 Beyersmann et al. J Clin Epi 2008; 61:1216-1221
Time-dependent Bias

* Three scenarios:
  * Exposure has no impact
    
    \[
    \frac{\text{# in exposed group} \rightarrow \text{event at } t}{\text{# in exposed group just prior to } t} = \frac{\text{# in unexposed group} \rightarrow \text{event at } t}{\text{# in unexposed group just prior to } t}
    \]
  * Exposure has prolonging impact
    
    \[
    \frac{\text{# in exposed group} \rightarrow \text{event at } t}{\text{# in exposed group just prior to } t} < \frac{\text{# in unexposed group} \rightarrow \text{event at } t}{\text{# in unexposed group just prior to } t}
    \]
  * Exposure has accelerating impact
    
    \[
    \frac{\text{# in exposed group} \rightarrow \text{event at } t}{\text{# in exposed group just prior to } t} > \frac{\text{# in unexposed group} \rightarrow \text{event at } t}{\text{# in unexposed group just prior to } t}
    \]

* When treated as fixed, the left side of the equations will be smaller since denominator is increased

* We would observe attenuation of the accelerating impact and overestimation of the prolonging impact of exposure

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1 Beyersmann et al. *J Clin Epi* 2008; 61:1216-1221
More complicated, in practice:

- How do we treat these individuals never tested
- What about misclassification from false positive and negative results
  - These are more common in earlier era of follow-up

Misclassification can have more complex impact on bias

- If non-differential, simply compounds time-dependent bias
- If differential, either under or overestimation is possible
  - Depends on the true association of exposure on the event and degree of differential misclassification

We still hypothesize that using a fixed covariate for HCV status underestimates the risk imposed by co-infection on mortality

Use of a time-dependent variable should provide a more accurate idea, but need to continue exploring all angles of information bias
## Demographics

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Ever HCV+ (n=735)</th>
<th>Only Tested HCV- (n=3151)</th>
<th>Never Tested (n=669)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>37</td>
<td>37</td>
<td>36</td>
</tr>
<tr>
<td>Male</td>
<td>81%</td>
<td>85%</td>
<td>89%</td>
</tr>
<tr>
<td>Risk Factor: MSM</td>
<td>38%</td>
<td>74%</td>
<td>75%</td>
</tr>
<tr>
<td>IDU</td>
<td>52%</td>
<td>5%</td>
<td>7%</td>
</tr>
<tr>
<td>Endemic</td>
<td>4%</td>
<td>14%</td>
<td>11%</td>
</tr>
<tr>
<td>Blood Products</td>
<td>18%</td>
<td>6%</td>
<td>5%</td>
</tr>
<tr>
<td>Heterosexual</td>
<td>37%</td>
<td>14%</td>
<td>14%</td>
</tr>
<tr>
<td>Race: Caucasian</td>
<td>74%</td>
<td>68%</td>
<td>75%</td>
</tr>
<tr>
<td>Black</td>
<td>5%</td>
<td>15%</td>
<td>12%</td>
</tr>
<tr>
<td>Aboriginal</td>
<td>15%</td>
<td>7%</td>
<td>6%</td>
</tr>
<tr>
<td>Other</td>
<td>6%</td>
<td>11%</td>
<td>7%</td>
</tr>
<tr>
<td>Year of ARV Initiation</td>
<td>1997</td>
<td>1998</td>
<td>1995</td>
</tr>
<tr>
<td>Category</td>
<td>HCV+</td>
<td>HCV-</td>
<td>Incidence</td>
</tr>
<tr>
<td>------------------------</td>
<td>------------</td>
<td>------------</td>
<td>-----------</td>
</tr>
<tr>
<td></td>
<td>Deaths (pyrs)</td>
<td>Deaths (pyrs)</td>
<td></td>
</tr>
<tr>
<td>Fixed Definition</td>
<td>139 (3646)</td>
<td>562 (18157)</td>
<td></td>
</tr>
<tr>
<td>Seroconversion</td>
<td>139 (3469)</td>
<td>562 (18334)</td>
<td></td>
</tr>
<tr>
<td>Clearance</td>
<td>132 (2936)</td>
<td>569 (18867)</td>
<td></td>
</tr>
<tr>
<td>Test after ARVs</td>
<td>132 (2499)</td>
<td>569 (19304)</td>
<td></td>
</tr>
<tr>
<td>False positive</td>
<td>128 (2200)</td>
<td>573 (19603)</td>
<td></td>
</tr>
<tr>
<td>False negative</td>
<td>143 (2517)</td>
<td>558 (19286)</td>
<td></td>
</tr>
<tr>
<td>No lab results</td>
<td>159 (2640)</td>
<td>542 (19163)</td>
<td></td>
</tr>
</tbody>
</table>
Table 3. Hazard ratios (95% confidence intervals) for HCV+ status from multivariable proportional hazards model of time to death.

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fixed</td>
<td>4555</td>
<td>1.38</td>
<td>(1.07, 1.77)</td>
</tr>
<tr>
<td>Time Updated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown Excluded</td>
<td>3886</td>
<td>2.03</td>
<td>(1.54, 2.67)</td>
</tr>
<tr>
<td>Unknown as HCV-</td>
<td>4555</td>
<td>1.98</td>
<td>(1.53, 2.57)</td>
</tr>
<tr>
<td>Unknown as Category</td>
<td>4555</td>
<td>1.94</td>
<td>(1.49, 2.53)</td>
</tr>
</tbody>
</table>

Models adjusted for age, sex, race, injection drug use, hepatitis B positivity, baseline smoking status, baseline regimen type, time-updated CD4 and viral load.
Future Work

* Bias associated with handling of unknown HCV status prior to confirmed laboratory tests
  * Consider use of imputation
* Addressing issues of false negatives
* Modeling time-dependent covariates in presence of competing risks and left-truncation
Conclusion

* Considerable time-dependent bias can be introduced when analysing HCV status as a fixed covariate
* This bias may be greater as cohorts observe increased incidence of HCV and clearance due to the use of more tolerable and effective HCV treatment
  1. Incidence of HCV
  2. Clearance due to the use of more tolerable and effective HCV treatment
* HCV status should be modeled as a time-dependent covariate, where possible, if incidence of HCV acquisition and clearance are non-trivial
We gratefully acknowledge all the people living with HIV who have volunteered to participate in the OHTN Cohort Study. We thank all interviewers, data collectors, research associates and coordinators, nurses and physicians who provide support for data collection and extraction.

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