Poster # 515

# Duration of Acute Hepatitis C Infection and Implications for Incidence Estimation

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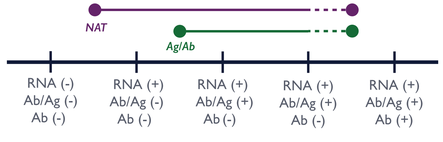
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## BACKGROUND

- The World Health Organization has set an ambitious global target to reduce the incidence of hepatitis C virus (HCV) infection by 90% by 2030. Thus, accurate, reliable, and feasible methods to estimate HCV incidence are urgently needed to monitor the epidemic.
- One surveillence approach to estimate HCV incidence requires screening for acute HCV infection—a stage of recent infection where an individual is virologically positive but IgG antibody (Ab) negative. The duration of this pre-seroconversion window period may vary by the method used to detect primary viral infection and subsequent IgG Ab seroconversion.
- We estimated the duration of acute HCV infection using various assay algorithms, and compared their utility to precisely estimate the incidence of HCV infection in hypothetical scenarios.

## METHODS

- Data on commercially available HCV seroconversion panels were abstracted from online publications by Zeptometrix, Inc. (Buffalo, NY) and Seracare Life Sciences (Milford, MA). All data were stripped of personal identifiers. Serial serum/plasma specimens were collected from repeat blood donors in the U.S. who were closely monitored for HCV infection and IgG Ab seroconversion by multiple assays. Only persons that were HCV RNA negative and HCV IgG Ab negative at enrollment were eligible.
- The estimated date of detectable infection was determined using:
  (1) HCV RNA positivity (nucleic acid testing [NAT] by any assay)
  (2) Murex HCV Ag/Ab Combo Assay (*Abbott*)
- The estimated date of detectable seroconversion was determined using:
  (1) Architect Anti-HCV Assay (*Abbott*)
  (2) Ortho HCV Version 3.0 ELISA (*Ortho Clinical Diagnostics*)
  (3) Murex 4.0 ELISA (*Abbott*)




- We estimated the mean duration of recent infection (MDRI) prior to seroconversion for 6 testing algorithms. MDRI estimates were calculated by fitting binomial regression models to the probability of testing "acute" (i.e., RNA+/Ab-) with a logit link on a polynomial in t of the 3rd degree, (t = time since detection of primary infection). We also repeated this analysis using a log-log link on log(t). To account for multiple samples contributed by the same donor, 95% CI were estimated using subject-level bootstrapping (resampling 1,000 replicates). Statistical analyses were performed using the *inctools* package in R [Kassanjee et al. (2012) *Epidemiology*].

## RESULTS

### *SAMPLE POPULATION*

- Laboratory data were abstracted from 82 repeat donors (754 visits). We excluded 23 donors who were HCV RNA positive at baseline, 12 donors who remained HCV RNA negative during observation, and 4 donors whose interval to estimate the initial infection date was >30 days.
- The analytic population consisted of 43 acute infections (Table 1). Subjects contributed a median of 11 (IQR, 8-13) person-visits. The median time between study visits was 4 days (IQR, 2-5).
- There were 32 subjects that were also tested by the Murex HCV Ag/Ab Combo assay in addition to NAT. The number of individuals and samples tested by the three assays used to detect seroconversion varied (Table 1). There were a limited number of subjects tested by the Ortho HCV 3.0 ELISA, so these data should be interpreted with caution.
- The average time spent in the RNA+/Ab- stage prior to positivity by the Murex HCV Ag/Ab Combo assay was estimated to be 18 days and 25 days from the binomial regression models fitted with a logit-cubic link function and log-log link function, respectively.

### *MEAN DURATION OF RECENT (ACUTE) INFECTION*

- When examining all available data, MDRI point estimates ranged from 29 to 41 days when using the gold standard NAT to assess the date of initial infection. Similar estimates (26-45 days) were obtained when using the Murex HCV Ag/Ab Combo assay to assess the date of initial infection (Table 1).
- When examining subjects tested by all assays (except Ortho), the MDRI point estimates and 95% confidence intervals were equivalent between the Architect Anti-HCV assay & Murex 4.0 ELISA (40-45 days). This sensitivity analaysis again demonstrates the similar MDRI estimates between NAT and the Murex HCV Ag/Ab Combo assay (Table 2).
- There was minimal variation in the point estimates and lower-bound 95% confidence interval estimates between the two analytic methods employed to estimate the MDRI (logit-cubic vs. log-log functional form) however, there were convergence issues for some analyses (Tables 1, 2).
- There were large confidence intervals for almost all estimates, which is likely due to underpowered calculations (Tables 1, 2).

**TABLE 1. Mean Duration of Recent Infection (MDRI) Among All Available Data.**

| Detection of Primary Infection | Detection of Seroconversion | No. Subjects (Samples) Evaluated Post -Infection | No. Subjects (Samples) Identified as Ab Negative Post-Infection | MDRI [95% CI] (logit - cubic) | MDRI [95% CI] (log -log) |
|---|---|---|---|---|---|
| RNA+ | Ortho HCV 3.0 ELISA | 9 (52) | 9 (39) | 29 [28, 62] | 31 [30, 35] |
| | Architect Anti -HCV Assay | 43 (241) | 43 (221) | 39 [34, 53] | 45 [36, 74] |
| | Murex 4.0 ELISA | 39 (224) | 39 (208) | 40 [37, 87] | 41 [36, 64] |
| Ag/Ab Combo + | Ortho HCV 3.0 ELISA | 6 (36) | 6 (23) | --- | 26 [20, 35] |
| | Architect Anti -HCV Assay | 32 (165) | 32 (148) | --- | 45 [29, 73] |
| | Murex 4.0 ELISA | 32 (165) | 32 (149) | --- | 45 [28, 70] |

*We used the manufacturer's cut-offs to determine positivity by each assay (i.e., signal to cut-off ratio >1.0).*

**TABLE 2. Mean Duration of Recent Infection (MDRI) Among Subjects Tested By All Assays** *(Complete-Case Sensitivity Analysis)*.

| Detection of Primary Infection | Detection of Seroconversion | No. Subjects (Samples) Evaluated Post-Infection | No. Subjects (Samples) Identified as Ab Negative Post-Infection | MDRI [95% CI] (logit - cubic) | MDRI [95% CI] (log -log) |
|---|---|---|---|---|---|
| RNA+ | Architect Anti-HCV Assay | 39 (224) | 39 (207) | 40 [34, 84] | 41 [35, 62] |
| | Murex 4.0 ELISA | 39 (224) | 39 (208) | 40 [35, 84] | 42 [36, 60] |
| Ag/Ab Combo + | Architect Anti-HCV Assay | 32 (165) | 32(148) | --- | 45 [29, 73] |
| | Murex 4.0 ELISA | 32 (165) | 32(149) | --- | 45 [28, 70] |

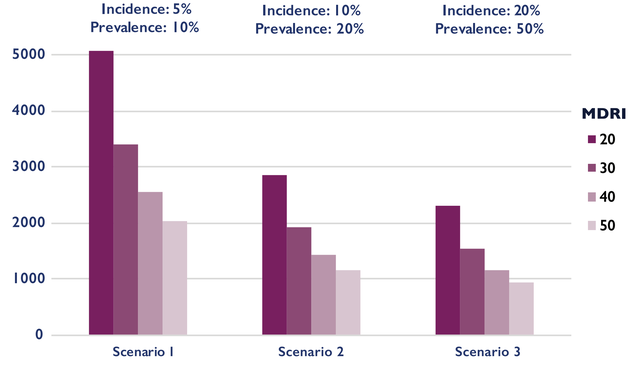



**FIGURE 1. Sample Sizes Necessary to Estimate HCV Incidence in Various Hypothetical Scenarios** (*Relative Standard Error <30%*).

## CONCLUSIONS

- Our estimates regarding the the pre-seroconversion window period of acute hepatitis C infection are in agreement with the published literature (~45 days), including previous estimates calculated among PWID.
- We found fairly consistent MDRI point estimates with overlapping confidence intervals between assays; however, the width of the the confidence intervals suggest further evaluation is needed. Use of a combo Ag/Ab assay to identify acute infections among HCV seronegative populations may be a more feasible and cost-effective alternative to NAT.
- While screening for acute HCV infection (pre-seroconversion) alone requires large sample sizes to estimate incidence, it could extend the window period of identifying new HCV infections when combined with biomarkers of "recent" infection post-seroconversion.
- Efforts need to be made to optimize methods for cross-sectional HCV incidence estimation as this may yield a more sensitive and powerful strategy to actively monitor the progress toward HCV elimination.

## ACKNOWLEDGEMENTS

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