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 surveillance approach to estimate HCV incidence requires screening for acute HCV infection—a stage of current infection where an individual is viremic 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 Zepetella, 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 who 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)
- (3) Ortho HCV Version 3.0 ELISA (Ortho Clinical Diagnostics)
- (4) Murex 4.0 ELISA (Abbott)

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, and 25 days from the binormal regression models fitted with a logit-cubic link function and log-log link function, respectively.

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

We estimated the mean duration of recent infection (MDRI) prior to 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 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 sensitive and cost-effective alternative to NAT.

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.

Conclusions

Our estimates regarding 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.

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

<table>
<thead>
<tr>
<th>Detection of Primary Infection</th>
<th>Detection of Seroconversion</th>
<th>No. Subjects (Samples) Identified as Ab Negative Post-Infection</th>
<th>MDRI [95% CI]</th>
<th>MDRI [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>RNA+</td>
<td>Anti-HCV Antibody</td>
<td>9 (35)</td>
<td>29 [24, 34]</td>
<td>30 [26, 35]</td>
</tr>
<tr>
<td>Ortho HCV 3.0 ELISA</td>
<td>Anti-HCV Antibody</td>
<td>43 (241)</td>
<td>39 [34, 45]</td>
<td>45 [36, 54]</td>
</tr>
<tr>
<td>Murex 4.0 ELISA</td>
<td>Anti-HCV Antibody</td>
<td>39 (208)</td>
<td>40 [37, 44]</td>
<td>41 [36, 46]</td>
</tr>
<tr>
<td>Ag/Ab Combo +</td>
<td>Anti-HCV Antibody</td>
<td>6 (23)</td>
<td>40 [37, 43]</td>
<td>41 [34, 47]</td>
</tr>
<tr>
<td>Murex 4.0 ELISA</td>
<td>Anti-HCV Antibody</td>
<td>32 (148)</td>
<td>41 [35, 49]</td>
<td>45 [30, 60]</td>
</tr>
<tr>
<td>Murex 4.0 ELISA</td>
<td>Anti-HCV Antibody</td>
<td>32 (149)</td>
<td>40 [29, 51]</td>
<td>45 [30, 70]</td>
</tr>
</tbody>
</table>

We used the manufacturer’s cutoff to determine positivity by each assay (i.e., tested in full at ratio >1.0).

We estimated the mean duration of recent infection (MDRI) prior to seroconversion for 6 testing algorithms. MDRI estimates were calculated by fitting binormal 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 refers since detection of an acute infection. We performed 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 R studio package in R (Kassanjee et al. 2012).