Measures of hepatitis C (HCV) incidence in the era of HCV prevention

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INTRODUCTION

- The new Directly Acting Antivirals (DAAs) have the potential to transform the treatment of hepatitis C (HCV) and so the prevention landscape
- Measuring changes in HCV incidence is important for assessing the impact of interventions, including the use of DAAs in treatment as prevention (TasP), to prevent and control HCV.
- In this study we compare utility of two incidence estimates from cross-sectional studies use biological markers:-
  a) **Anti-HCV avidity ("avidity")**: weak avidity among individuals *positive* for HCV antibody (and HCV RNA present)[1]
  b) **HCV RNA ("RNA")**: HCV RNA among individuals *negative* for HCV antibody[2]

METHODS

Persons who inject drugs (PWID) have been recruited into a voluntary unlinked-anonymous monitoring system in the UK (except Scotland) since 1990 [3, 4]. Participants in this national multi-site survey provide a dried-blood spot (DBS) sample and self-complete a short behavioural questionnaire.

Participants from 2011-13 who reported injecting in the preceding year were eligible for inclusion in this study. Participants were included in the analysis if they were either anti-HCV negative or had one of the two recent infection markers. Those HIV positive were excluded (n=25).

The DBS samples are tested for antibodies to HIV, hepatitis B and hepatitis C. Two methods were used to identify recent infections with hepatitis C: anti-HCV avidity testing of the anti-HCV positive samples, and RNA testing of the anti-HCV negative samples. The two markers were used separately and in combination to estimate HCV incidence.

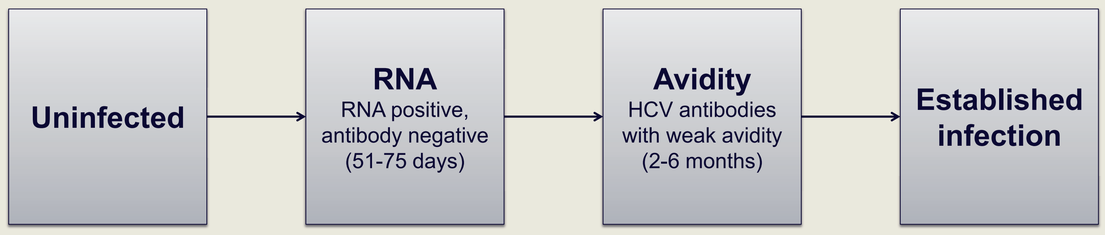
Factors associated with recent hepatitis C infection by both markers (avidity and RNA) separately and in combination were explored using multivariate logistic regression.

Power calculations were conducted to determine what reductions in incidence could be detected based on each marker of recent infection, or in combination.

MARKERS OF HCV INCIDENCE

- In early infection with HCV, RNA alone is detected before seroconversion and development of HCV antibodies. After seroconversion, in early infection, there is weak avidity. Once infection is established, avidity strengthens. Therefore, infection status can be classified according to presence of RNA, antibody status, and avidity of the antibody (figure 1). However, avidity can remain weak in those infected with HIV or other chronic infections.

Figure 1: Classification of infection status according to RNA and avidity



Average durations for remaining in infection state ("window periods") are shown in parenthesis.

- There are limitations of each method, including duration and variability of the window periods (table 1)

Table 1: Properties of "avidity" and "RNA" for measuring HCV incidence

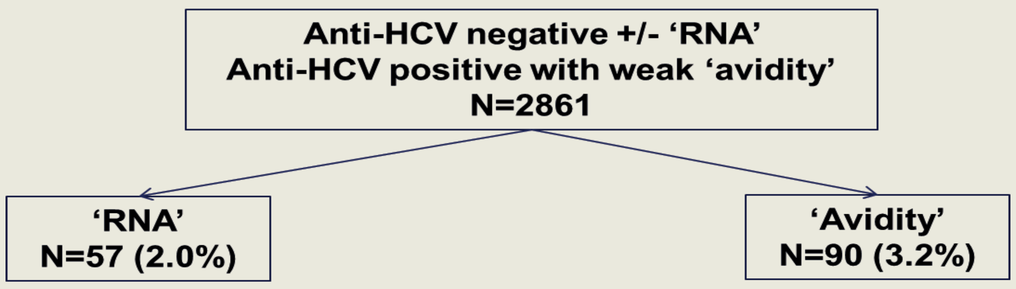
	Avidity	RNA
Window period	Long (2-6 months)	Shorter (51-75 days)
Cost	Lower	Higher
Hepatitis C incidence required	Slightly lower	High
Sample size required	Slightly smaller sample size	Large sample size
False positive	Yes (some chronically infected have weak avidity, HIV positive)	No

RESULTS

Hepatitis C incidence estimates (figure 2)

- Between 2011-13, 2,816 HIV negative PWIDs were either anti-HCV negative or had one of the two recent infection markers.
- 57 (2.0%) were HCV RNA positive and anti-HCV negative ("RNA"), and 90 (3.2%) had weak anti-HCV avidity with HCV RNA present ("avidity")
- Pooled estimated incidence was 12.3 per 100py (95% credible interval 8.8-17.0) with no significant difference compared to avidity alone (p=0.865) or RNA-only (p=0.691).
- The window period was driven by that for the RNA approach

Figure 2: Summary of hepatitis C incidence estimates



Sample characteristics by biological marker of recent infection

- Recent infections were more common among those who reported injecting crack and sharing injecting equipment
- The two markers had similar distributions of risk factors and demographic characteristics

Detecting changes in incidence

- Power calculations suggest that in a survey recruiting 1,000 participants without established HCV infection annually, where 5% have one of the two markers of recent infection at baseline (2% RNA, 3% avidity), the power of the study to detect the following reductions in incidence over a 5-year period would be as outlined in table 2:

Table 2: Power of 1,000 participant per year study to detect changes in incidence

Incidence (baseline 5%)	Power with RNA only	Power with avidity only	Power with combined estimate
1.67% (third)	25%	38%	57%
2.5% (half)	53%	75%	93%
3.33% (two thirds)	87%	97%	100%

- RNA or avidity alone as markers of incidence can detect a reduction in incidence to half or more with a power of ≤75%, increasing with a combined estimate.

Limitations

- Due to uncertainty in the window period for weak avidity, the combined model for incidence relied largely on RNA data.
- Long-term chronic infection may eventually weaken avidity (false positives)
- Other markers of recent infection (e.g. antigen) were not explored in this study

Key Points

- Measures of recent and current hepatitis C infection are important to monitor hepatitis C incidence, chronic prevalence and reinfection
- RNA and avidity provide similar HCV incidence estimates in higher HCV prevalence settings
- RNA is limited by its short window period; avidity is limited by uncertainty about its longer window period
- Where HCV incidence is high, one marker may provide an accurate incidence estimate
- In the context of falling incidence (e.g. due to TasP), use in combination may be required

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