Hepatitis C Virus (HCV) Epidemiology, Diagnosis and access to treatment in a UK Cohort

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Introduction

The WHO estimates that 71 million people worldwide have chronic HCV infection with 0.4 million people dying each year from their infection [1,2]. Up to 85% of infected patients may be unaware of their infection, and a minority of those diagnosed receive treatment [3].

Diagnosis of HCV is based on a 3-fold approach to testing:

1. Detection of HCV IgG by ELISA (no discrimination between active and previous infection)
2. Detection of HCV core antigen (HCV-Ag. Diagnostic of active infection and improved specificity compared to HCV-Ab)
3. Detection of HCV RNA by PCR (gold standard, but not financially viable in resource poor settings)

Up until 2014, detection of HCV-Ab was widely used to estimate seroprevalence. However this method detects cleared infection, has inter-assay variability and false positive results associated with various factors [4,5] (including ethnicity [6,7], ESR[4], auto-antibodies [8] and prosthetic devices [9]). There has been a move towards using HCV-Ag and/or HCV PCR to accurately determine population prevalence although there are doubts as to the sensitivity of HCV-Ag as a primary screening tool and WHO guidelines still recommend HCV-Ab as first line [1].

Here we set out to look at the performance of several diagnostic tools in a UK tertiary referral hospital. We reviewed the performance of the local HCV testing protocol in 2 different time periods:

- When HCV antibody screening alone was available
- After the combined Ab/Ag test was introduced

We collated these results alongside HCV RNA detection to describe the local epidemiology, and reviewed the proportion of individuals with a diagnosis of HCV who are referred onto hepatology services and attend for treatment. This is part of an ongoing local effort on HCV surveillance and treatment [10,11].

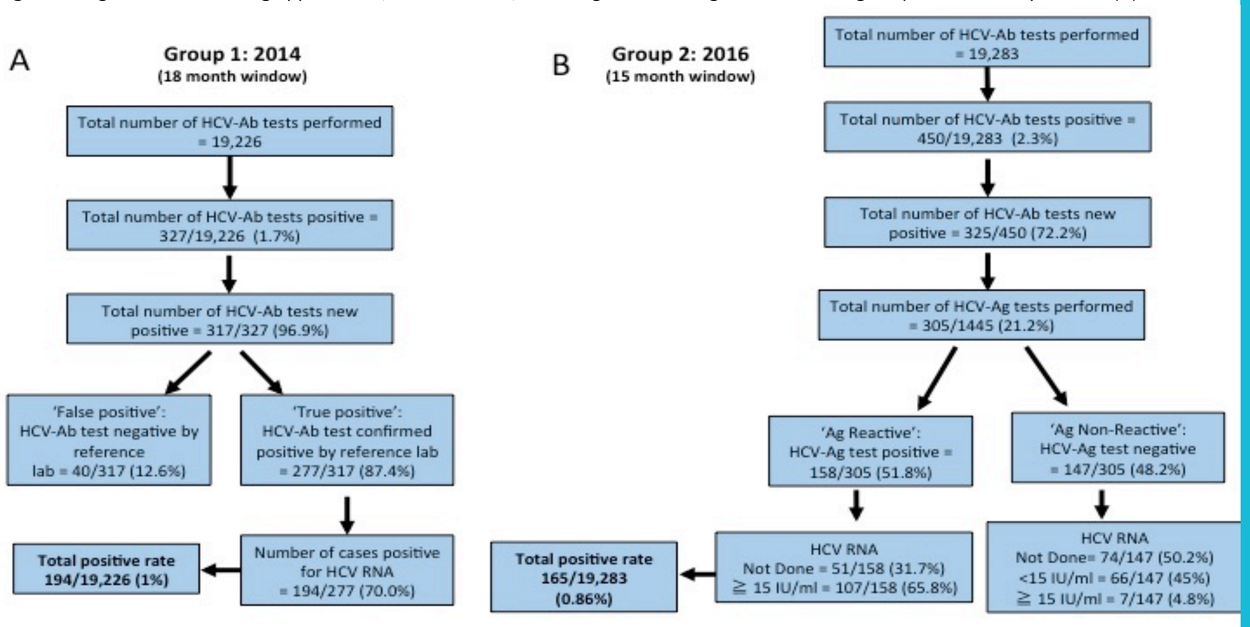
Methods

The laboratory involved handles samples from a wide community as well as four hospital inpatient sites. We retrospectively looked at all HCV screening tests performed within two time intervals in which different diagnostic algorithms were operating (figure 1):

Group 1 (Jan 2013 - June 2014)
Samples screened for HCV Ab only using an automated immunoassay. Positive results were sent to the reference laboratory for confirmation using two further ELISA tests, and those confirmed positive were then tested for HCV RNA.

Group 2 (Jan 2015 - March 2016)
HCV diagnosis using combination of HCV Ab/Ag testing. HCV Ag positives were classed as those in range 10-20,000 fmol/L.

Figure 1: Algorithms describing approach to, and results of, HCV diagnostic testing in a UK teaching hospital laboratory in 2014 (A) and 2016



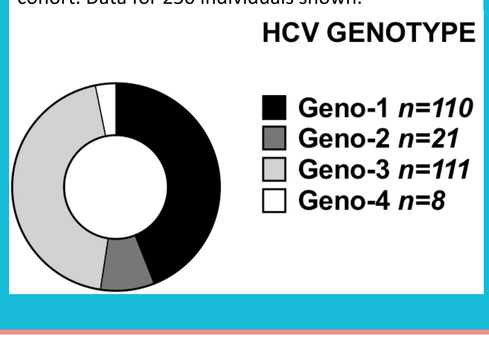
Results

38,510 HCV tests were done during the two intervals with 359 new active HCV infections identified and confirmed (0.9%). Characteristics of individuals with new infection are shown in table 1.
HCV genotype was available in 70% new diagnoses, with geno-1 and 3 accounting for the majority (figure 2), in keeping with overall genotype distribution in Europe and PHE data [12,13].

Table 1: Characteristics of individuals with active HCV infection in a UK teaching hospital in two time windows between 2014 and 2016

	Group 1 (2014)	Group 2 (2016)	Group 1 + Group 2 (2014-2016)
Total number confirmed positive for active HCV infection	194	165	359
Number male (% of positive tests)	167 (86.1%)	137 (83.0%)	304 (84.7%)
Age in years (median and IQR)	39 (31-49)	37 (30-44)	37 (31-48)
Location			
- Prison	63 (32.5%)	66 (40.7%)	129 (36.2%)
- Hospital in-patient	15 (7.7%)	13 (8%)	28 (7.9%)
- Hospital out-patient / primary care	90 (46.4%)	64 (38.8%)	154 (42.9%)
- Sexual health clinic	16 (8.2%)	13 (7.9%)	29 (8.1%)
- Occupational health	2 (1%)	1 (0.6%)	3 (0.8%)
	8 (4.2%)	8 (4.8%)	16 (4.5%)
Ethnic origin			
- Black	7 (3.6%)	1 (0.6%)	8 (2.2%)
- Asian	18 (9.3%)	7 (4.2%)	25 (7.0%)
- European	149 (76.8%)	97 (60.7%)	246 (69.4%)
	20 (10.3%)	57 (34.5%)	77 (21.4%)

Figure 2: Distribution of HCV genotypes in a UK cohort. Data for 250 individuals shown.



HCV-Ab test outcomes and performance

In the earlier testing group (group 1) 277 of 317 positive HCV-Ab tests were positive on repeat testing giving a PPV of 87.4% for our in-house test when compared to the regionally accepted standard. We found African ethnicity was significantly associated with a false positive Ab test (p=0.0004) but age >60 yrs and gender were not. Prison location was associated with a true positive Ab test.

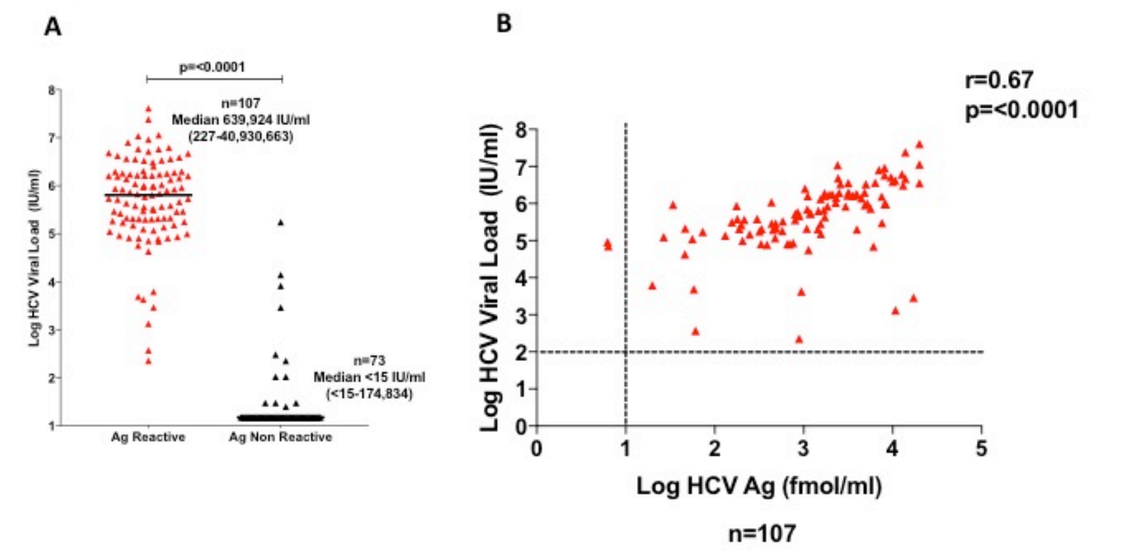
HCV-Ag test outcomes and performance

In the later testing group (group 2), the PPV of the combined use of HCV-Ab plus HCV-Ag test was 100% when compared to the gold standard test using HCV PCR.

We looked at the relationship between HCV-Ag and HCV RNA, and found there was a close positive correlation. This indicates HCV-Ag is a good surrogate of viraemia in the absence of access to a qPCR result (figure 3).

In a small number of cases the HCV-Ag test showed false negative results. There were no consistent features found to unify these misleading results.

Figure 3: Relationship between HCV Antigen test and quantitative PCR for HCV RNA viral load. (A) Range of HCV viral loads for samples testing HCV-Ag positive (n=107) and HCV-Ag negative (n=73). (B) Linear regression plot showing correlation between HCV-Ag and HCV-RNA for all samples testing HCV-Ag positive (n=108). Dashed lines represent threshold for detection for HCV RNA (15 IU/ml) and HCV-Ag (10 fmol/ml).



Referral to Hepatology and Treatment Attendance

Of the 359 patients with a new HCV diagnosis, only 117 (33%) attended a hepatology clinic appointment, 76 were treated (21%) and 48 had sustained viraemic remission (13%). This shows the loss of patients during the treatment pathway due to a multitude of factors.

Discussion

This study shows the large number of HCV requests processed in a UK teaching hospital laboratory. Overall 0.9% tests confirmed active HCV infection. There was a predominance in men and over one-third were from prison.

Our HCV-Ab test had PPV of 87% and performed worse in African populations. This illustrates how tests derived for Caucasian populations do not necessarily apply to other settings. Following our switch to combined HCV-Ab and HCV-Ag testing, PPV increased to 100%. Genotypes 1 and 3 predominate in keeping with national and international data.

Significance to Clinical Practice

Our results affirm the approach to diagnosis using HCV-Ag testing which could potentially replace a nucleic acid test for diagnosis or monitoring. PCR however remains the gold standard in both the UK and North America and is needed for genotyping to plan treatment.

The small proportion of diagnosed patients who subsequently attended clinic appointments and received treatment highlights the challenges for HCV elimination. Ensuring the prison population have access to specialist hepatology care seems particularly important given the high proportion of infected patients in prison.

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