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MAJOR ARTICLE

Assessing Molecular Point-of-Care Testing and Dried Blood Spot for Hepatitis C Virus Screening in People Who Inject Drugs

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Background. Injecting drug use is a major driver of hepatitis C virus (HCV) spread worldwide, and the World Health Organization (WHO) has identified people who inject drugs (PWID) as a key population to target for HCV screening and care. Point-of-care (POC) hepatitis C tests and dried blood spot (DBS) sampling offer benefits for the management of patients with HCV infection by increasing HCV testing and linkage to care in different nonclinical settings. The aims of this prospective study were to evaluate the feasibility and the acceptability of use HCV ribonucleic acid (RNA) POC and fingerstick DBS testing in social-medical risk-reduction centers and to describe the cascade of care among PWID in France.

Methods. Between June 2018 and February 2019, 89 consecutive HCV-seropositive PWID attending 2 drug treatment services and 1 supervised consumption room in inner Paris were invited to participate in further evaluation, undergoing a clinical review with a liver assessment and blood tests including fingerstick capillary whole blood POC HCV RNA testing and fingerstick DBS sampling.

Results. Of the 89 participants enrolled, HCV RNA was detected in 34 (38.6%) participants. Fingerstick whole blood POC RNA testing and HCV RNA detection from DBS sample were feasible and acceptable among PWID with no major difference in terms of HCV RNA detection rate. Overall, 16 participants received pan-genotypic antiviral treatment. The proportion of PWID with sustained virologic response at 12 weeks was 81.2%, with data for 3 patients still pending.

Conclusions. One-step screening strategy based on the detection of HCV RNA would engage people in care for treatment scale-up and HCV elimination.

Keywords. dried blood spot; HCV RNA screening; hepatitis C; people who inject drugs; point of care test.

Hepatitis C virus (HCV) infection is a major public health issue with an estimated 71 million people chronically infected worldwide and over 400 000 annual HCV-related deaths [1, 2]. Injecting drug use through sharing of injection equipment is a major driver of HCV spread worldwide. The World Health Organization (WHO) has identified people who inject drugs (PWID) as a key population to target for HCV screening and care [3]. In France, as in many high-income countries, PWID account for the majority of the HCV burden and transmission. The prevalence of active HCV infection among PWID is estimated to be 40% in Western Europe and 48% in France [4]. International clinical guidelines recommend direct-acting antiviral (DAA) treatment for all patients with HCV. The majority of PWID receiving or not receiving opioid agonist therapy (OAT) and undergoing HCV DAA treatment achieve cure [5]. The 2-step process of HCV diagnosis using an initial HCV antibody test (relatively low cost and indicative of HCV exposure) followed by confirmatory HCV ribonucleic acid (RNA) testing (relatively high cost), poor venous access, discrimination faced by PWID in traditional healthcare setting, and lack of the health insurance coverage are major barriers to PWID entering and progressing along the cascade of care from initial test to cure [6, 7].

Recent developments, including rapid point-of-care (POC) HCV antibody, POC HCV RNA, core antigen-based alternatives for the detection of active infection, and dried blood spot (DBS) for blood collection provide promise in the diagnostic field. Point-of-care tests offer benefits for the management of patients with HCV infection by shortening the time to results and by making the test available close to the site of patient care. Molecular POC assays that are able to detect and quantify HCV RNA in less than 1 hour with the

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simplicity and ease of use are now available. The new Xpert HCV Viral Load Fingerstick ([Xpert HCV VL FS] Cepheid, Sunnyvale, CA) assay has significant advantages over classic molecular tests because it requires shorter processing time for plasma or serum separation and diagnosis and increases the potential to reach diagnosis within a single visit [8, 9]. A single visit diagnosis will be the norm in most settings such as drug and alcohol treatment services, prisons, needle and syringe programs, supervised drug consumption rooms, and community-based mobile outreach services. Although none of the commercial HCV RNA assays is approved for use of whole blood recovered from DBS, the WHO guidelines on hepatitis B and C testing recommend the use of DBS in specific settings in high-income countries as well as in low- or middle incomes countries to facilitate access to HCV diagnosis and care [10].

This prospective real-life study aimed to evaluate the feasibility and the acceptability of the on-site POC capillary whole blood collection for HCV RNA detection and fingerstick DBS testing in social-medical risk-reduction centers and to describe the cascade of care among PWID in Paris.

METHODS

Study Design and Participants

Between June 2018 and February 2019, consecutive HCV-seropositive PWID attending 2 drug treatment centers and 1 supervised drug consumption room in inner Paris were invited to participate in further evaluation by undergoing a clinical review with a liver assessment and blood tests including fingerstick capillary whole blood POC HCV RNA testing and fingerstick DBS sampling. Inclusion criteria were age ≥18 years, positive for HCV antibodies, and a lifetime injection drug use, with either recent injecting drug use or current receipt of OAT. Exclusion criteria included current pregnancy.

Of the 90 individuals who agreed to participate, 89 were eligible and were invited to participate in further evaluation, whereas 1 (1.1%) participant reported no history of injecting drug use. Among eligible participants, 9 (10.1%) were recruited at Gaïa Paris and 61 (68.5%) at Aurore EGO Paris, respectively. The remaining 19 (21.4%) participants were recruited at supervised drug consumption room.

A questionnaire administered by trained staff collecting demographic characteristics, drug use history, self-reported HCV, and human immunodeficiency virus testing and previous treatment of HCV infection was used for data collection.

The prospective study was approved by the appropriate ethics committee. All patients gave oral informed consent. The present work was an ancillary study derived from the PARCOURS program (new patient pathways for better care of an HCV-infected, vulnerable population) [11].

Assessment of Liver Fibrosis

The fibrosis stage was assessed by means of transient elastography (FibroScan; Echosens, Paris, France). Fibrosis stages were defined by moderate fibrosis (FibroScan >7.0 to ≤9.5 kPa), severe fibrosis (FibroScan >9.5 to ≤12.5 kPa), and cirrhosis (FibroScan >12.5 kPa).

Laboratory Measurements

Whole blood HCV RNA levels were measured by the real-time PCR Xpert HCV VL FS assay according to the manufacturer's instructions. In brief, 100 µL capillary whole blood were collected into a minivette collection tube. Whole blood was then placed directly into the Xpert HCV VL FS cartridge and loaded into the GeneXpert instrument for onsite HCV RNA testing. The limit of detection is 40 IU/mL, and the lower limit of quantification is 100 IU/mL according to the assay manufacturer's product inserts.

Hepatitis C virus RNA levels were also measured on capillary whole blood specimens collected using the DBS technique. In brief, large drops of free-flowing blood were spotted onto the filter paper card (Whatman 930; GE Healthcare Europe, Freiburg, Germany) in 1 step to completely fill preprinted circles. A completed saturated circle contains approximately 50 µL blood. The filter paper was then placed onto a horizontal clean dry surface to air dry for at least 1 hour. Each dried DBS was then stored in an individually sealed plastic bag with a desiccant package at −80°C until analysis. A punched circle with a 12-mm diameter was eluted into 1.5 mL pre-extraction buffer (Cobas AmpliPrep/Cobas TaqMan [CAP/CTM] Specimen Pre-Extraction [SPEX] or lysis reagent) at 56°C with gentle agitation for 15–30 minutes and centrifuged at 36 220 ×*g* for 1 minute before use. A total of 650 µL or 1000 µL of pre-extraction supernatant was used to perform the CAP/CTM HCV, version 2 (Roche Molecular Systems, Pleasanton, CA) or the Xpert HCV VL assays, respectively.

The HCV genotype was determined by phylogenetic analysis of a portion of the nonstructural 5B gene encoding the RNA-dependent RNA polymerase from whole blood collected on DBS with an HCV RNA level ≥3 log IU/mL [12]. After extraction of viral RNA from 400 µL of the pre-extraction supernatant using the QIAsymphony DSP Virus/Pathogen kit (QIAGEN, Hilden, Germany), a nested polymerase chain reaction (PCR) was performed to amplify a 286-base pair fragment with primers Sn755, Asn1121, 5B-SI766, and 5B-ASI1110, as previously described [13]. The PCR products were sequenced by means of the Big-Dye Terminator v3.1 sequencing kit on the ABI 3100 sequencer (Applied Biosystems, Foster City, CA), according to the manufacturer's protocol. Phylogenetic analyses were performed using different prototype HCV genotype 1–8 sequences, with software from the Phylogeny Inference Package (PHYLIP), version 3.65.

Statistical Analysis

Descriptive results are presented as median with interquartile range for continuous data and number (percentage) for categorical data. Relationships between quantitative variables were studied by means of regression analysis. For better visualization of differences between the quantification assays, the Bland-Altman plot method was used. Comparisons between groups were made using the Kruskal-Wallis test or the Mann-Whitney *U* test. $P < .05$ were considered statistically significant. Results obtained for DBS specimens were not corrected for the hematocrit, as previously described [14].

RESULTS

Characteristics of Study Participants

Table 1 summarizes the characteristics of the 89 HCV-seropositive PWID included in the study. Among them, 84 were receiving OAT (including methadone, n = 54; buprenorphine, n = 6; unknown, n = 24), whereas 5 were not receiving OAT. The median age was 39 years, and the majority (89.9%) were male. Hepatitis C virus RNA was detected in 34 (38.6%) HCV-seropositive PWID. The most frequent HCV genotypes were 1a (45.4%) and 3a (36.4%) (Table 1). Eighteen of the 53 patients (33.3%) who had fibrosis assessment had significant fibrosis, and 6 (11.1%) had cirrhosis. Three of the 46 patients (6.5%) who had screening for hepatitis B surface antigen were coinfected with hepatitis B virus.

Hepatitis C Virus Ribonucleic Acid (HCV RNA) Screening Using Fingerstick Point-of-Care HCV RNA Testing or Dried Blood Spot Sampling

Among 89 participants enrolled between June 2018 and February 2019, all participants had a fingerstick whole blood sample available. Among those with a fingerstick whole blood samples (n = 89), 82 had Xpert HCV VL FS testing and 7 (7.9%) had no valid result (n = 6, errors due to low sample volume; n = 1, internal control being out of range). Among those enrolled (n = 89), 83 had a DBS sampling, whereas 6 (6.7%) had no DBS sample collected (n = 4, lack of DBS sampling; n = 1, loss of DBS by post office; n = 1, unawareness of the study).

Seventy-seven patients (86.5%) had paired fingerstick capillary whole blood for POC HCV RNA testing and fingerstick DBS sampling with interpretable results for a comparison. Hepatitis C virus RNA was not detected in 47 and 50 HCV-seropositive PWID by Xpert HCV VL FS testing and DBS sampling, respectively. In contrast, HCV RNA was detected in 30 and 27 HCV-seropositive PWID by Xpert HCV VL FS and DBS sampling, respectively. Hepatitis C virus RNA was not detected in 3 patients from whole blood collected on DBS compared with capillary whole blood Xpert VL FS assay including 1 patient with HCV RNA below the limit of quantification (<100 IU/mL), 1 patient with a low viral load (141 IU/mL), and 1 patient with a high viral load (39 811 IU/mL, ie, 4.6 log IU/mL). In the former patient, the absence of HCV RNA detection was due to the low volume of whole blood spotted onto the filter paper card (<50 µL). For all patients who were HCV RNA quantifiable, there were a good correlation (r = 0.96; $P < .0001$) (Figure 1A) and concordance (mean difference, 1.86 Log IU) (Figure 1B) in HCV RNA levels between fingerstick samples and whole blood collected on DBS. The median HCV RNA level was higher by Xpert HCV VL FS assay than by DBS sampling (5.5 Log IU [range, 2.1–6.6 Log IU] and 3.9 Log IU [range, 2.7–4.7 Log IU], respectively). Among people with detectable HCV RNA, 2.6% (n = 2) by Xpert HCV VL FS assay and 3.8% (n = 3) by DBS sampling had a result <1000 IU/mL or/disk, respectively.

Table 1. Characteristics of HCV-Seropositive PWID Undergoing Clinical Assessment (n = 89)

Age, years [median (range)]	39 (21–62)
Male sex [n (%)]	80 (89.9)
Positive HCV RNA [n (%)] (n = 88)	34 (38.6)
HCV genotype [n (%)] (n = 22)[a]	
1a	10 (45.4)
1b	3 (13.6)
3a	8 (36.4)
4a	1 (4.6)
Distribution of fibrosis stage according to LSM [n (%)] (n = 53)	
Moderate fibrosis	8 (14.8)
Severe fibrosis	4 (7.4)
Cirrhosis	6 (11.1)
Prior HCV treatment (n = 53)	28 (52.8)
HBsAg positive [n (%)] (n = 46)	3 (6.5)
HIV infection [n (%)] (n = 87)	2 (2.3)

Abbreviations: HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HIV, human immunodeficiency virus; LSM, liver stiffness measurement; PWID, people who inject drugs; RNA, ribonucleic acid.

[a]The HCV genotype was not determined in 12 patients due to HCV RNA level ≤3 log IU/mL in 9 patients, insufficient volume (<50 µL) of whole blood spotted onto the filter paper card in 1 patient, and no dried blood spot sample collected in 2 patients.

Hepatitis C Virus Cascade of Care

Between June 2018 and February 2019, 89 HCV-seropositive PWID were successfully linked to further clinical and virological evaluations. Among PWID who were deemed to be HCV RNA positive, 7 had significant fibrosis and 2 patients had cirrhosis. Overall, 16 participants (47.1%) who were eligible received antiviral treatment, whereas the remaining 18 patients did not receive treatment for different reasons (Table 2). Thirteen (38.2%) participants were lost to follow-up. The DAA-containing regimens included glecaprevir and pibrentasvir for 8 or 12 weeks in 10 patients and sofosbuvir and velpatasvir with or without voxilaprevir in 6 patients for 12 weeks. The primary efficacy endpoint, sustained virologic response at 12 weeks, was achieved by 13 of 16 patients (81.2%), with data for 3 patients still pending. No patients discontinued treatment and no severe adverse events were reported. Figure 2 summarizes the HCV cascade of care.

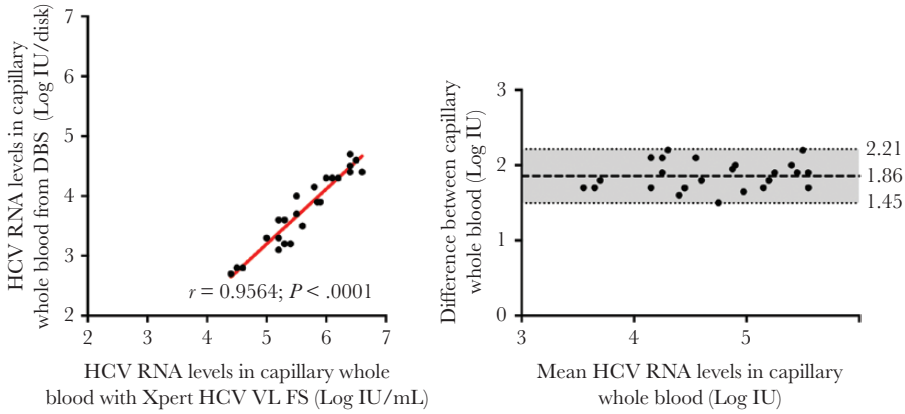

Figure 1. (A) Linear regression and (B) Bland-Altman plot analysis of hepatitis C virus (HCV) ribonucleic acid (RNA) levels measured by Xpert HCV Viral Load Fingerstick (Xpert HCV VL FS) assay and capillary whole blood collected on dried blood spot (DBS) in 29 paired specimens.

DISCUSSION

Reducing the burden of HCV infection among PWID will require targeted strategies focused on different stages of the HCV cascade of care [15]. Evidence-based interventions to improve testing, linkage to care, and treatment uptake among PWID are needed to reduce HCV mortality and morbidity among this population. A key step in the care cascade is a facilitating access to screening and diagnosis. The use of POC diagnostic testing and DBS sampling have now been recommended to simplify testing algorithms, increase diagnoses, and facilitate linkage to treatment in reducing visits. Compared with venipuncture, screening via affordable POC testing and fingerstick DBS testing are cost effective in PWID [16–18].

This study shows that fingerstick whole blood RNA testing was feasible among PWID in France, which is consistent with previous studies conducted in other countries [19]. The rate of invalid results using the Xpert HCV VL FS was below 10%, meaning that decentralized testing using simple POC can be performed by staff without extensive clinical training. We also demonstrated the utility of a 1-step screening strategy based on the detection of HCV RNA from DBS sample. Indeed, a high degree of concordance for detection of active HCV infection from DBS compared with the Xpert HCV VL FS assay was observed. Hepatitis C virus RNA was not detected in only 3 patients including 2 patients with low-level viremia who were missed by a less sensitive test with a limit of detection of approximately 1000 IU/mL (3 log IU/mL) [20, 21]. Compared with venipuncture, HCV RNA detection using DBS sampling, which only requires capillary whole blood, is well adapted to PWID, for whom difficulties with venous access for blood collection are typically reported [22]. The absolute amount of HCV RNA should not be considered when quantification is performed on whole blood specimens, HCV RNA detection rather than quantification may reduce times for an HCV diagnosis and improve linkage to treatment [23]. In addition, HCV RNA detection using a qualitative assay with a lower limit of detection of <1000 IU/mL is sufficient for patients who undergo antiviral treatment [3].

Providing treatment in primary care is an essential component in engaging PWID in HCV treatment. Hepatitis C virus-infected PWID achieve high cure rates that are comparable to rates in non-PWID [5, 24, 25]. In addition, treatment uptake is generally improved in primary care compared with hospital-based specialist care [25]. Among PWID who were tested using whole blood collected by fingerstick, 38.6% had detectable HCV RNA and 47.1% received antiviral treatment. This is low compared with recent Australian data, which report that more than 50% of HCV-seropositive PWID from needle-syringe programs were HCV RNA detectable [9]. This is partly explained by the high rate of PWID who had previously benefitted from antiviral therapy (52.8%) and the low hepatitis C reinfection rate after DAA antiviral therapy among PWID on OAT [26, 27]. The large proportion of participants who were lost to follow up before initiation antiviral treatment highlights the need for the removal of prescriber-type restrictions for DAA therapies.

Limitations of our study include the small number of participants enrolled, which limits the generalizability of the findings. Recent injecting, defined as injecting in the prior

Table 2. Reasons for the Absence of Starting Antiviral Treatment

	Number of Patients (n = 18)
Lost of follow up	13
Death	1
Return to the country of origin	2
Lack of health insurance coverage	1
Denial of antiviral therapy	1

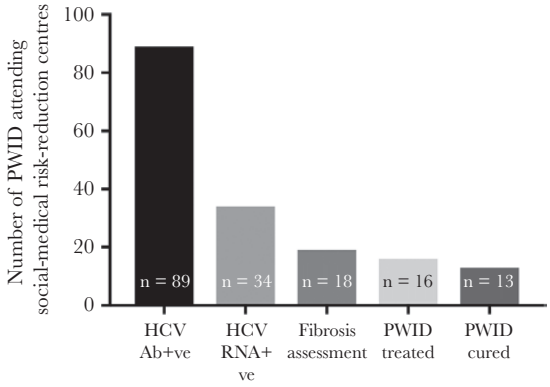

Figure 2. Hepatitis C virus (HCV) cascade of care for patient attending social-medical risk-reduction centers. Ab, antibody; PWID, people who inject drugs; RNA, ribonucleic acid.

6 months, is missing for most participants. Only 19 (42.7%) reported injecting drugs in the month before enrollment. No plasma or serum samples were collected to assess the performance of Xpert HCV VL FS and HCV RNA testing from DBS. However, a few recent studies showed satisfactory performance of these new tools compared with serum or plasma [8, 14, 22, 28]. Although our study focused on PWID in a high-income country, this model may also be applicable to people with geographical or cultural barriers to treatment in other settings, particularly in low- to middle-income countries where laboratory capacity is limited [28].

CONCLUSIONS

People who inject drugs is a key population to test and treat in order to achieve the WHO viral hepatitis elimination objectives of 90% reduction in HCV incidence, 65% reduction in HCV-related mortality, and 80% of patients receiving treatment by 2030. Strategies that engage priority populations, such as PWID, are crucial to engage people in care for treatment scale-up and HCV elimination. In France, simplified HCV care management, including the extension of treatment delivery to any pharmacies and the prescription of HCV treatment by nonspecialists in hepatology or infectious diseases, has now been implemented. The removal of prescriber-type restrictions for DAA therapies will elicit a massive opportunity to broaden access to HCV treatment, particularly in vulnerable populations.

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Potential conflicts of interest. S. C. has received a research grant from Gilead and has served as an advisor and/or speaker for Abbott, Cepheid, and Hologic. C. H. has served as a speaker for Abbott. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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