

# Breaking Down Barriers to Care in Hepatitis C Virus Infection

Mark Thursz<sup>1</sup> and Karine Lacombe<sup>2,3</sup>

<sup>1</sup>Division of Digestive Disease, Imperial College, London, United Kingdom; <sup>2</sup>Department of Infectious Diseases and Tropical Medicine, Saint-Antoine Hospital, AP-HP, and <sup>3</sup>Sorbonne Universités, UPMC University Paris 06, UMR\_S 1136, Institut Pierre Louis d'Epidémiologie et de Santé Publique, France

(See the major article by Soulier et al on pages 1087–95.)

**Keywords.** dried blood spot; HCV; viral load; resource limited countries; people who inject drugs (PWID).

The Global Burden of Disease study revealed that both cirrhosis and liver cancer were among the top 20 causes for mortality, but when these 2 forms of end-stage liver disease are taken together, liver disease moves into the top 10, with levels of mortality and morbidity similar to those exerted by human immunodeficiency virus (HIV) infection, tuberculosis, and malaria [1, 2]. On a global scale, the majority of liver-related mortality is attributable to viral hepatitis due to chronic hepatitis C virus (HCV) and chronic hepatitis B virus (HBV) infections. According to recent estimates from the World Health Organization, 170 million people worldwide are chronically infected with HCV [3]. However, the distribution of infection is heterogeneous, with the majority of infected people living in low-income or low-middle-income countries (LMICs).

Over the last 5 years, we have witnessed a therapeutic transformation for HCV infection, wherein treatment efficacy, tolerability, and durations have all sub-

stantially improved. The mainstay of treatment for the last 20 years has been pegylated interferon and ribavirin, which delivered a 50% chance of cure after 48 weeks of treatment, accompanied by myriad side effects. In contrast, >95% of non-cirrhotic patients with HCV genotype 1 infection (including those coinfecting with HIV) can now reasonably expect cure after a 12-week regimen, without any side effects, mostly with interferon- and ribavirin-free combinations [4, 5]. However, access to the new all-oral antiviral treatment regimens is limited, and the cost of the drugs is not the only barrier.

Despite the high prevalence and burden of disease, there are very few programs or facilities in resource-limited settings to screen and manage viral hepatitis infections [6]. Management of hepatitis C requires access to virologic diagnostic assays, tools to assess disease stage, and skilled physicians to coordinate care and effective drugs. Virology laboratories in LMICs are rare and frequently are centralized. Although many laboratories have the facilities to perform molecular diagnostic assays, including real-time polymerase chain reaction assays, the cost of the tests, invariably borne directly by the patient, are substantially higher than costs in Europe and North America. An additional barrier to access viral diagnostic tests is that, for collection of blood specimens, patients must travel to a clinic close to the laboratory, because of lack of phlebotomy facilities and logistical issues with sample transportation.

A practical solution to the problem of blood sample collection and transport is the use of capillary samples collected on filter paper as dried blood spots (DBS). Until now, however, uncertainty has persisted over the sensitivity and specificity of diagnostic tests of DBS for HCV. The article by Soulier et al in this issue of *The Journal of Infectious Diseases* directly and positively addresses this issue [7]. Using parallel venous blood samples collected conventionally and as DBS, Soulier et al demonstrated high sensitivity and specificity for anti-HCV antibody tests and for HCV load tests, using both the Abbott m2000 platform and the Roche Cobas Ampliprep/Cobas TaqMan HCV system, version 2. However, the sensitivity of HCV core antigen detection on DBS was unacceptably low, which is disappointing because the assay is performed on the ubiquitous Architect platform and is approximately 30% cheaper than real-time PCR for the detection of viremia [8]. As point-of-care tests are being developed that focus on HCV core antigen quantification as a surrogate marker of HCV replication in LMICs, it is essential to perform more research on the use of DBS for this specific diagnostic test. Extraction of HCV RNA from DBS appears to be effective, using methods that would readily transfer to laboratory facilities in LMICs.

DBS sampling has been widely used in sub-Saharan Africa for diagnosing infectious diseases, monitoring HIV infection, and for epidemiological surveillance.

Received and accepted 12 August 2015; published online 2 September 2015.

Correspondence: M. Thursz, Division of Digestive Disease, Imperial College, Norfolk Pl, London W2 1NY, UK (m.thursz@imperial.ac.uk).

**The Journal of Infectious Diseases**® 2016;213:1055–6  
 © The Author 2015. Published by Oxford University Press for the Infectious Diseases Society of America. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (<http://creativecommons.org/licenses/by-nc-nd/4.0/>), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, contact journals.permissions@oup.com. DOI: 10.1093/infdis/jiv427

Previous studies of anti-HCV antibody serologic assays of DBS have shown good sensitivity and specificity, but there are very few data on testing for viremia. Tuailleon et al compared DBS to venous samples for measurement of HCV viremia, using the Cobas Taqman assay, and found a good correlation of viral loads, but the absolute values were an average of 2.27 log IU/mL lower in DBS [9]. In the current study, viral loads were 1.60–1.75 log IU/mL lower in DBS.

Inevitably, the sensitivity of viral load detection and measurement at the lower end of the dynamic range (ie, <1.75 log IU/mL) for DBS will not be as good as that for conventional plasma or serum samples. This should not significantly compromise the use of DBS-based testing in untreated patients: because viral loads in such individuals are typically higher than levels in treated patients, the sensitivity is not affected. The lack of sensitivity at lower levels of viremia may limit the use of DBS for monitoring during treatment, which has been an important component of HCV therapy in the interferon era, but is unlikely to be as important in the new era of direct-acting antivirals, during which dynamic monitoring of viral load has no proven benefit [10]. Indeed, the few patients who experience virological relapse during or after direct-acting antiviral-based treatment do so with high viral loads, well above the limit of detection in DBS. Therefore, the evaluation of virological success rates should not be hampered by the detection threshold.

To surmount the logistical barriers found in LMICs, it is essential that DBS remain stable at room temperature. In the study by Soulier et al, viral loads in DBS stored at room temperature for 19 months remained virtually identical to those in DBS stored at –80°C. In contrast, Tuailleon et al found that viral loads in

DBS deteriorated after specimens were stored for 7 days at room temperature [9]. The stability of viral loads in DBS stored at room temperature is a vital characteristic for deployment of DBS testing in the field and needs to be confirmed in light of these inconsistent findings.

Of note, the value of DBS testing for HCV extends beyond LMICs. Because the routes of transmission of HCV in developed countries include injection drug use and, among men who have sex with men, violent anal sex, the use of DBS may become an invaluable tool for HCV testing in treatment centers for illicit drug [11] and alcohol use, in sexual health clinics, and in prisons, where the risk of acute infection and the prevalence of chronic infection are high. In these environments, access to phlebotomy and frequent problems with venous access make it difficult to rely on conventional venous blood testing, and recent publications indicate that the uptake of HCV testing has been increased by the use of DBS.

Although DBS were useful for estimating viral load, viral genotyping could only be achieved for 84.5% of samples in the study by Soulier et al study, and it would be reasonable to expect lower rates of successful genotyping in the real world. Does this matter? Probably not. Currently, sofosbuvir-based regimens can be considered to have pangenotypic coverage, albeit with slightly less efficacy against HCV genotype 3. Admittedly, the Abbvie regimen (ombitasvir/paritaprevir/ritonavir and dasabuvir) is only effective against HCV genotypes 1 and 4. Nevertheless, future all-oral regimens are expected to be pangenotypic, making the requirement for genotype testing obsolete.

With limited reservations, DBS collection provides a solution to one of the practical barriers to HCV treatment access in LMICs. Simplification of drug

regimens and pangenotypic antiviral drugs should reduce the level of clinical expertise required to deploy therapy. Generic pricing agreements for HCV drugs are already being negotiated. Perhaps it is time for optimism around access to HCV treatment.

## Note

**Potential conflict of interest.** M. T. has received personal fees from Abbott Laboratories outside of the submitted work. K. L. has received personal fees and nonfinancial support from BMS, Gilead, MSD, and ViiV and personal fees from Abbvie, all outside of the submitted work. Both 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.

## References

1. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* **2012**; 380:2095–128.
2. Cooke GS, Lemoine M, Thursz M, et al. Viral hepatitis and the Global Burden of Disease: a need to regroup. *J Viral Hepat* **2013**; 20:600–1.
3. Mohd Hanafiah K, Groeger J, Flaxman AD, Wiersma ST. Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence. *Hepatology* **2013**; 57:1333–42.
4. Afdhal N, Zeuzem S, Kwo P, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. *N Engl J Med* **2014**; 370:1889–98.
5. Ferenci P, Bernstein D, Lalezari J, et al. ABT-450/ropegitavir and dasabuvir with or without ribavirin for HCV. *N Engl J Med* **2014**; 370:1983–92.
6. Lemoine M, Thursz M. Viral hepatitis: Scaling up HCV treatment in resource-limited countries. *Nat Rev Gastroenterol Hepatol* **2015**; 12:193–4.
7. Soulier A, Poiteau L, Rosa I, et al. Dried blood spots: a tool to ensure broad access to hepatitis C screening, diagnosis and treatment monitoring. *J Infect Dis* **2016**; 213:1087–95.
8. Mederacke I, Wedemeyer H, Ciesek S, et al. Performance and clinical utility of a novel fully automated quantitative HCV-core antigen assay. *J Clin Virol* **2009**; 46:210–5.
9. Tuailleon E, Mondain AM, Meroueh F, et al. Dried blood spot for hepatitis C virus serology and molecular testing. *Hepatology* **2010**; 51:752–8.
10. Sidharthan S, Kohli A, Sims Z, et al. Utility of hepatitis C viral load monitoring on direct-acting antiviral therapy. *Clin Infect Dis* **2015**; 60:1743–51.
11. McLeod A, Weir A, Aitken C, et al. Rise in testing and diagnosis associated with Scotland's Action Plan on Hepatitis C and introduction of dried blood spot testing. *J Epidemiol Community Health* **2014**; 68:1182–8.