New virological tools for screening, diagnosis and monitoring of hepatitis B and C in resource-limited settings.

Original reference: Chevaliez S, Pawlotsky JM. J Hepatol. 2018 May 22. pii: S0168-8278(18)32063-4. doi: 10.1016/j.jhep.2018.05.017. [Epub ahead of print] Review.

Summary:

This review analyses how diagnosis and linkage to care of HBV and HCV infections can be promoted in two particular settings: low and middle income countries (LMIC) and vulnerable areas of high income countries. Two strategies are described to reach this objective: point-of-care (POC) techniques and testing of dried blood spot (DBS) samples.

POC tests must meet WHO ASSURED criteria allowing a patient centered approach able to give an immediate result. A number of POC tests for HBV diagnosis have been developed through HBsAg detection, with an average sensitivity and specificity of 90% and 99%, respectively. However, sensitivity decreases to 72% among HIV infected individuals.

Table. Performance of HBV and HCV POC tests (adapted from Chevaliez & Pawlotsky, 2018).

POC Test	Matrices	Pooled sensitivity (95% CI)	Pooled specificity (95% CI)	Positive Likelihood ratio (95% CI)	Negative Likelihood ratio (95% CI)
Determine® HBsAg	Plasma, serum	90,8 (88,9-92,4)	99,1 (98,9-99-4)	239,2 (17,1-33339,4)	0,077 (0,035-0,168)
VIKIA® HBsAg	Plasma, serum	82,5 (77,5-86,7)	99,9 (99,8-100)	1072,3 (376,1-3057,2)	0,108 (0,026-0,458)
OraQuick® HCV rapid Ab test	Whole blood, plasma	99,5 (98,9-99,8)	99,8 (99,6-99,9)	445,8 (269,0-739,0)	0,004 (0,002-0,006)
	Oral Fluid	95,9 (92,1-97,9)	99,4 (98,1-99,8)	148,0 (47,9-456,9)	0,037 (0,020-0,067)
SD Bioline HCV	Serum	93,5 (73,2-98,7)	99,5 (97,7-99,9)	186,4 (37,8-919,5)	0,038 (0,004-0,402)

For HCV antibody testing, data from a meta-analysis gave a pooled sensitivity of 98% and 94%, when whole blood or oral fluid were assessed, respectively. HCV testing using POC test was associated also with false negative results among HIV-coinfected patients.

Considering molecular POC tests, no HBV methods are available and a few HCV methods are cited with sensitivities close to 100%: HCV Xpert® and Genedrive®, currently marketed, together with Alere q®, under development.

Whole blood collected by DBS can be shipped as non-hazardous material and allow processing at distant laboratories with available state-of-the-art serological and molecular technology. However, results are not immediate

and require two patient visits. HBV markers (HBs Ag and HBV DNA) have been studied from DBS with reported sensitivity of 98% and 95%, respectively. HBV DNA quantification and genotyping can be performed from DBS. Anti-HCV antibodies can be detected from DBS through conventional or POC immunoassays with sensitivity ranging 98,6-100%, and specificity 100%. HCV RNA can be successfully detected when viral load is greater than 500 IU/mL, keeping with the EASL acceptance of a limit of detection lower than 1000 IU/mL for HCV RNA assessment, and sequencing can be performed when viral load is above 3000 IU/mL. However, HCV antigen detection is suboptimal when studied in DBS samples (65% sensitivity).

The authors conclude that decision algorithms are required by combination of technological advances and innovative strategies to carry out appropriate interventions in resource-limited settings.

Comments:

An eventual eradication of HCV still requires to identify those non-diagnosed viremic patients and a correct surveillance of reinfections as only 36% of individuals in the EU have been diagnosed.

Linkage to care must be a priority so that effective treatment can be initiated promptly. Therefore, reducing the necessary steps until therapy is started will lower the number of patients lost to follow-up.

In locations where laboratory testing is available, conventional immunoassays and molecular analysis are preferred, however rapid tests such

as POC are an easy strategy to screen large populations for HBV and HCV, although they still lack an optimal sensitivity. Samples collected with DBS allow an expanded access to screening, diagnosis and genotyping using fingerstick whole blood. Both people from LMIC and marginalized populations of high income countries could benefit from these strategies to get an impact on transmission and disease progression.

HBV infection can be studied through HBsAg POC tests, but there are important differences among methods and only Alere Determine® HBsAg reaches 90% sensitivity. Additional HBV serological markers can be explored also through rapid tests. However, POC molecular methods must be developed to monitor HBV infection, particularly necessary when HBeAg is non-detectable. At this moment, follow-up in LMIC could be performed using DBS samples.

Unlike HIV or HBV, HCV screening relies on antibody detection only. A number of different POC methods have been marketed but those performed with whole blood are more reliable, as the lower level of antibodies in oral fluid leads to a reduced sensitivity. The key factor of HCV infection is to get to know those individuals who could benefit from antiviral treatment. No HCV antigen POC test is available, although a new assay (Daktari Diagnostics) is undergoing clinical evaluation to investigate suitability among HIV-HBV coinfected patients and detection of HCV genotype 3, 4, 5 and 6, as false negative results may occur. Therefore, viremic patients can be detected today only by HCV RNA investigation, at a substantial higher price. DBS has demonstrated to be a reliable sample to carry out HCV RNA detection and characterization with a

moderate cost, therefore, this specimen can be preferred to study viremia and genotype in LMIC and areas where no laboratory facilities are available.

To summarize, a screening approach based on POC testing for HBsAg and anti-HCV antibodies, followed by DBS sampling for additional serological and molecular analysis can be valuable and cost-effective.

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