Pipeline Report » 2019

HCV Diagnostics

TAG
Treatment Action Group

Off Track with HCV Diagnosis Targets: Leaving People Undiagnosed and Untreated[1]

By Bryn Gay

The roll out of generic, pangenotypic DAAs has increased, national elimination plans have emerged, and WHO guidelines simplify the diagnostics algorithm and models of care, yet there is unfinished business to remove the complicated, interrelated barriers to HCV testing. The significant progress that has been made to increase treatment and linkage to care among people with hepatitis C will be hampered if we do not invest in outreach, prevention, and point-of-care (POC) testing services, particularly for overlooked and under-served communities, including people who inject drugs. Meeting global diagnosis targets determines whether we meet the other elimination targets.

It's been over five years since the launch of sofosbuvir and only 5 of the 71 million people living with chronic HCV have been treated with direct-acting antivirals (DAAs) globally—we are leaving the vast majority of people behind, undiagnosed and untreated. Global targets indicate major gaps in testing, treatment, and harm reduction coverage, except for a handful of countries, according to 2020 targets, let alone for elimination by 2030. In 2017, 13.1 million (or 19%) of the targeted 30% of people with HCV were diagnosed. High patient out-of pocket costs, insufficient lab capacity, centralized testing services, limited trained staff, and stigma and discrimination experienced by people living with HIV/HCV are among myriad barriers to scaling up diagnoses. Investing in viral hepatitis also remains dismal: only 8% (or US$500 million) of the funding needed in low- and middle-income countries (LMICs) is available.

But more affordable, effective, easy-to-use, high quality, point-of-care diagnostics options are becoming available or in the pipeline, which could further help with the decentralization of screening and confirmatory testing. HCV self-tests, supported with telehealth and counseling, could potentially diagnose and link people who face stigma and discrimination to care. Combination tests for HIV, HBV, and HCV could provide simpler antibody testing for healthcare professionals and people at higher risk to the viruses, such as men who have sex with men and people who inject drugs. Combination tests can also link people at higher risk to care. Open-licensed, polyvalent platforms that allow different manufacturers of tests for various diseases to implement them on the same instrument could align with a more integrated service delivery approach and bring down diagnostics costs. New research provides guidance to manufacturers of point-of-care HCV diagnostics on the optimal limit of active viremic detection as close to 1,318 IU/mL. This threshold would detect 97% of active infections and minimize false negatives.

Genotyping may no longer be necessary in most cases, but for treatment-experienced patients or countries without affordable access to pangenotypic DAAs, there are several genotype testing options. Dried blood spot sample collection at points of care could enable viral load testing among patients in rural and remote settings, through remote sample transport and quicker return for the results, while requiring minimal training for collecting, storing, and transporting samples. Compared to other methods (plasma,

whole blood), DBS has lower costs, despite a more expensive sample collection process. This may be attributed to lower costs for sample storage and transportation. The global forecast for DBS sampling is 9 million of the total 28 million viral load tests needed until 2021, yet estimated global demand is only about 1.7 million tests.

Core antigen remains an important opportunity for large-scale screening campaigns for active HCV infection and for scaling up diagnoses in resource-limited contexts; however, its implementation is fairly poor. The estimated demand for core antigen testing—whether it can confirm SVR, detect reinfection, or be developed for point-of-care settings—continues to be explored. Advocacy points for different stakeholders to accelerate affordable access to simpler HCV testing and the developments in diagnostics products are highlighted below. See *Pipeline Report 2018* for previous developments.

Advocacy points

For companies:

- Reduce the prices of tests regardless of volumes so that they are more in line with the cost of goods, and have savings reflected by iterative decreases in list prices (e.g., savings from royalty expiration, increased manufacturing efficiencies, increased volumes).
- Divulge transparent and disaggregated pricing on the total costs of diagnostics. Pricing should be transparent along the value chain.
- Minimize and ensure transparency of service/maintenance costs for instrument-based platforms to better inform procurement and health program costs in LMICs.
- Make maintenance-free, POC platforms!
- Offer different types of procurement contracts (e.g., reagent rental or price per test, with bundled pricing across disease areas), which may be better suited for countries. Pooled procurement should be facilitated either globally or regionally to improve negotiations and to take advantage of higher volumes.
- Develop and validate DBS protocols and submit them for in vitro diagnostics (IVD) stringent regulatory authority approval so that DBS is a manufacturer-recommended sample type.
- Prioritize and register professional use antibody tests with less invasive sampling procedures (oral, capillary blood) for self-testing.
- Prioritize the development of POC ribonucleic acid (RNA) test and POC HCV core antigen (cAg) with acceptable diagnostic accuracy (sensitivity/specificity), and promote operational research of these technologies as soon as possible to understand their advantages/disadvantages when used in routine settings and in resource-limited countries.

- Develop probes to identify people with genotype subtypes that can help with adjusting treatment regimens.
- Evaluate the performance of RDTs and EIAs in adolescents and children (for testing after 18 months old, once maternal antibodies may have cleared).
- Validate non-invasive tests for assessing liver disease in children.
- Cepheid should disclose the public investments that were made to develop GeneXpert; this significant public contribution should be reflected in the prices of their platforms and cartridges. Roche should expand its Diagnostic Access Initiatives for HIV viral load testing and early infant diagnosis to HCV Viral Load. Other companies, including Abbott, Biocentric, bioMérieux, Hologic, and Qiagen should offer similar diagnostics access initiatives and offer pricing regardless of volume for both standard purchase and reagent rentals.
- Include community and civil society organizations in the design, research, and implementation of diagnostics, which could address affordability, simplicity, and community-friendly testing settings.

For World Health Organization:

- Facilitate the pre-qualification process for open platforms, which already have other quality certifications (such as from the US Food and Drug Administration, CE-IVD marking, ISO 13485:2003 standard, etc).

For governments and implementing partners:

- Use pangenotypic DAAs to simplify the diagnostics algorithm and increase patients' linkage and retention in care.
- Promote the integration of HCV assays on polyvalent, open platforms, which enables cost-sharing of operational costs across programs and facilitates price negotiations with the manufacturer by bundling items that aid in bulk purchasing and ease distribution. The Global Fund to Fight AIDS, TB and Malaria (GFATM) provides the option for countries to purchase open platforms, reagents for HIV, TB and malaria, and consumables through the procurement platform, WAMBO. Countries should purchase polyvalent, open diagnostics platforms.
- Facilitate the integration of diagnostic services and move away from vertical disease specific management models.
- Standardize and harmonize regulatory requirements for the in-country registration process for in vitro diagnostics (IVDs) and establish fast-

track procedures for quality-assured (i.e. stringent-regulatory approved, WHO prequalified [PQ]) diagnostics products from the WHO Essential Diagnostics List.

- Establish national external quality assurance schemes for facilities and services performing HCV screening and/or confirmatory testing (through external collaboration or internal development).
- French public research institutions, Public Hospitals of Paris (AP-HP) and *Institut National de la Santé et de la Recherche* (INSERM) should revoke the exclusive licensing to BioPredictive, the test results analysis system needed for analyzing liver disease assessment by Fibrotest, to allow open licenses and the transfer of technology (for the software used in the analysis of samples) to other firms.
- French public research institutions, INSERM and *Ecole Supérieure de Physique* et de *Chimie Industrielles de la ville de Paris* (ESPCI) which funded the company, Echosens, to develop the liver disease assessment technology, FibroScan, should work to facilitate technology transfer to other countries and firms.
- Demand companies to divulge transparent and disaggregated pricing on the total costs of diagnostics, and/or demand all-inclusive pricing in the *ex works* price.
- Ensure increased volumes of patients screened and tested, bundled procurement, competition and diverse distributor options to bring down diagnostics prices in countries.
- Minimize the layers of distribution; ensure transparency and accountability along the global and domestic supply chains to reduce costs; and exclude taxes on public goods.
- Utilize diagnostics to support surveillance studies to understand countries' local epidemics, monitor impact, and adapt testing strategies. When feasible, prioritize surveys across infectious diseases for efficient use of resources.
- Consider renewing antibody screening campaigns if previously conducted using older, less specific, non-PQ/non-CE-IVD marked tests.

For donors:

- Invest and prioritize development of POC ribonucleic acid (RNA) test and POC HCV core antigen (cAg) with acceptable diagnostic accuracy (sensitivity/specificity), and promote operational research of these technologies as soon as possible to understand their advantages/ disadvantages when used in routine settings and in resource-limited countries.

- Include hepatitis C test instruments, reagents, and commodities, along with ongoing reagent, commodity, service and maintenance and training costs in diagnostics procurement budgets.

- Facilitate the integration of disease-specific programs by promoting the sharing of multiplexed platforms across different programs and offer cross-disease instead of vertical funding.

- Central procurement platforms, such as Global Fund's WAMBO and the Global Drug Facility, should cover diseases beyond HIV, TB and malaria, at minimum for HIV coinfection, to enable countries to procure reagents at the same price points as in these programs, or at least have transparent price information available via these platforms to improve domestic procurement negotiations.

- Utilize good practices for procurement which include centralized or pooled procurement (i.e., globally or regionally via pooled procurement mechanisms); that use competitive tender processes which deliver the total package required to perform testing in countries; allow split tenders to create the number of suppliers and to incentivize suppliers to improve services; and put long-term agreements in place that can guarantee a stable price but flexible test quantities according to changing forecasts and needs across diseases.

TABLE 1. HCV Diagnostics Pipeline: Products with New Published Data or Regulatory Updates Since July 2018

Assay	Sample/ Setting	Company	Regulatory Status	Price (*ex works* or free carrier)
ANTIBODY ASSAYS – SCREENING				
Fortune Assay	**Oral fluid POC**	**Fortune Bioscience Co., Ltd (China)**	**TK**	**TK**
▪ One independent evaluation study performed. Evaluated against 2 serum (InTec anti-HCV, Kehua lab-based immunoassay) and 1 oral assay (OraQuick). Positive anti-HCV results were genotyped. ▪ Performance compared to Intec and Kehua serum assays: Sensitivity: 93.11% (95% CI 90.00, 95.49) (below WHO requirements, which should be above 97% for RDT and above 98% for EIA), specificity: 98.48% (95% CI 97.23, 99.27), accuracy: 96.58% (95% CI 95.46, 97.69). ▪ n=1,022 (348 anti-HCV positive; 674 anti-HCV negative); males: 546, females: 476, average age: 46.3 years. ▪ Consistency with OraQuick comparison oral assay was 96.35% (10 results were inconsistent). ▪ Turnaround time = 10-15 min lateral flow. In comparison to OraQuick, the Fortune assay has shorter turnaround time. ▪ Fortune assay demonstrated a 97.46% (115/118) positivity among patients with active viremia; 3 patients were not detected by the Fortune assay. ▪ 350 results for genotype sensitivity: Sensitivity of the Fortune assay among genotypes 1, 2 and non-1/2 genotype was 93.39% (212/227), 91.55% (65/71) and 92.31% (48/52), respectively. ▪ Did not assess GT 4 and 5 sensitivity (prevalent in MENA and Africa regions), and could not identify genotype subtypes. ▪ Presence of HBV antibodies could be a potential factor for giving false positives; more research is required to understand other factors that interfere with the oral assay results. ▪ Further evaluation and improvement for sensitivity is needed.				
HCV Self-Test[2]	**Oral fluid, capillary blood POC; harm reduction settings, at home**	**OraSure (USA)**	**Expected Q2 2020[3]**	**Target: <US$4 per test[4]**
▪ There is no HCV self-test currently on the market. An HCV self-test would not be helpful if treatment and care is not accessible, or if there is no counselling component. For highly stigmatized communities HCV self tests may provide the confidentiality and telehealth support needed to encourage people to get tested. ▪ FIND and WHO are conducting pilot observational studies together in different countries to assess the usability and acceptability of HCV self-testing.				

Assay	Sample/ Setting	Company	Regulatory Status	Price (*ex works* or free carrier)
HIV/HCV/HBsAg Triplex Combo RDT	**50 µl Whole blood (venipuncture or fingerstick), 25 µl serum/plasma** **POC; hospitals; clinical settings**	**Biotest Biotech Inc., (China)**	**TK**	**TK**

- Several combination assays are already on the market, but they do not have stringent regulatory approval, the accuracy is still unclear, and they are not well implemented in countries.
- One example of triple combination test showed high sensitivity and specificity, in accordance with WHO recommendations, with HIV Ab: sensitivity ≥ 99% and specificity≥ 98%; HCV Ab: sensitivity ≥ 98% and specificity ≥97%; HBsAg: sensitivity = 100% and specificity ≥ 98%.
- n = 250 HIV-1 positive patients; n = 110 HIV-2 positive patients; n= 250 anti-HCV positive patients; n= 250 HBV surface antigen positive patients; n= 250 patients who were sera-negative for HIV/HCV/HBsAg in Côte d'Ivoire. 187 patients were HCV RNA positive; 63 patients had cleared the virus. No one was coinfected with HIV/HBV/HCV.
- Detects HIV-1, HIV-2, anti-HCV, and HBV surface antigen in <15 min.
- For HBsAg detection, LoD: 2.38 ± 0.63 IU/ml.
- Combination tests help with simplifying diagnosis, requiring minimal training, fewer finger-sticks, fewer samples and tests, which can reduce costs. They can improve patient flow and clinical care, with fewer clinic visits. Combo tests help with linking higher risk groups and people in remote settings to care.

Rapid Anti-HCV assay	**10 µl, Whole blood, serum, plasma** **POC; lab**	**InTec Products Inc (China)**	**CE-IVD, WHO PQ in 2019**	**40 tests per kit; estimates[5] US$0.25-0.50 per test with some markups/import taxes**

- Results in 15-20 min.
- Sensitivity: 100%, specificity: 97.98%.
- Provides an additional antibody assay for large-scale screening campaigns in LMICs, in which lab-based testing is not widely accessible.

HCV-WES enzyme immunoassay	**Serum, plasma** **Lab; clinical settings**	**Protein Simple (USA)**	**Regulatory approval pending**	**Estimates 1/3 the cost of INNO-LIA (for the initial instrument cost)**

- One Study has researched a supplemental anti-HCV confirmatory test for screening in the US, because INNO-LIA is not approved, which could be useful for surveillance/population prevalence estimates in the absence of HCV RNA testing. However, instead of anti-HCV confirmatory, WHO recommends RDT or EIA for anti-HCV, then HCV RNA for confirming diagnosis.
- Detection process involves cross-linking anti-HCV antibodies (in serum or plasma) to the HCV antigen. Compass software (Protein Simple) measures when this signal is higher and records different peaks and bands. HCV antibody is positive if 42kDa band is detected, regardless of band intensity value.
- n=275 well-characterized samples. Only 30 anti-HCV-negative samples tested for specificity; sensitivity tested with 40 anti-HCV-positive/RNA-positive serum/plasma samples: HCV-WES EIA confirmed 38 (95%) as positive, and INNO-LOA (reference assay) confirmed 39 (97.5%) as positive.
- Specificity: 100%; sensitivity: 95% (below WHO requirements, which should be above 97% for RDT and above 98% for EIA). Low sensitivity brings into question the usefulness of this test.
- Turnaround time = 30-60 min to prepare samples then 3-hour run; less than INNO-LIA (>1 day).
- High replicability; automation could reduce human error and save time. Results in digital format with simple read out of positive or negative results.

Assay	Sample/ Setting	Company	Regulatory Status	Price (*ex works* or free carrier)
RNA ASSAYS – CONFIRMATORY AND TEST OF CURE				
BLINK ONE cartridge[6]	**Whole blood** **POC**	**BLINK Diagnostics (Germany)**	**Early prototype**	**TK**
▪ This portable, multi-plexing platform has a cartridge which is made accessible to any manufacturer to develop their own assays for various diseases. This platform can be used for other molecular diagnostics, not just RNA. ▪ BLINK uses an open-licensing business model so that any developer could develop their assays for diagnosing a range of infectious diseases, including HCV, and "rent" the platform to run the tests in a short turnaround time. ▪ HCV results in <20 min. ▪ Introduces analyte-specific probes, which contain all reagents freeze-dried into a single pellet, to amplify the specific target being tested. Liquid reagents can be added. The developer using the system would add target-specific primers and probes, according to defined position on the ONE cartridge. BLINK's software then can modify the assay according to these specifications. ▪ Developed reagents, BLINK Beads, which combine several roles into one unit. Each particle is encoded and color-coded for easier particle identification.				
Genedrive® HCV RNA	**30 µL Plasma** **POC**	**Genedrive (UK)**	**CE-IVD in 2017; WHO PQ (under review)**	**US$ 5000 per device; US$25-35 per test**
▪ Genedrive showed 98.6% sensitivity (95% CI 96.9% to 99.5%) and 100% specificity (95% CI 99.3% to 100%); yet less sensitive than Xpert. ▪ Requires two precise pipetting steps, with a 90-minute turnaround time, possible for task-shifting, requires reliable electricity and connectivity which may not be available in some LMICs. ▪ Accuracy for all genotypes; limit of detection of 2362 IU/mL. ▪ Possible use for testing in pharmacy settings for people using OST (REACH HCV study underway in Q2 2019). ▪ Single-use inputs/consummables, which require consistent biowaste disposal.				
TrueNAT HCV PCR	**250 µL Whole blood, 500 µL Plasma** **POC**	**Molbio (India)**	**Expected Q4 2019[7]**	**US$9,000 per instrument; US$15-20 per test (early estimates price is lower than Genedrive[8])**
▪ The polyvalent, two-step, portable RNA confirmatory platform weighs <3kg. ▪ Battery-operated with 8-hour battery life, overnight battery recharging (≈ 4 hours). ▪ Runs 15 samples at a time then re-charge device; turnaround time = <1 hour. ▪ Sensitivity: 100%; specificity: 100%. ▪ LoD: 216 IU/mL; manufacturer needs to evaluate assay for determining SVR. ▪ Half-day training required; automatic results on touchscreen; Bluetooth wireless connectivity. ▪ Single-use inputs/consummables, which require consistent biowaste disposal.				
Alinity m HCV assay	**Plasma, serum** **Lab, clinical**	**Abbott (USA)**	**CE-IVD; WHO PQ (under review)**	**US$50 per test**
▪ A real-time quantitative PCR assay that uses one-step; to diagnose all genotypes. ▪ Simplified monitoring viral load/adherence method using specific hybridization probes, to be combined with simple RNA extraction. ▪ Sensitivity: 100%; Specificity: 100%; similar efficacy in comparison to Cobas. ▪ AmpliPrep/Cobas TaqMan® HCV Test, v2.0 Quantitative assay (reference assay) (also seen in Morocco study: Figure 3B). ▪ LoD: plasma: 5.11 IU/mL (95% CI 3.92 to 8.46 IU/mL); serum: 5.11 IU/mL (95% CI 4.16 to 7.47 IU/mL). ▪ Need to ensure correct storage to achieve sensitivity.				

Assay	Sample/ Setting	Company	Regulatory Status	Price (*ex works* or free carrier)
Aptima HCV Quant	**Plasma, serum** **Lab**	**Hologic (USA)**	**CE-IVD; FDA approved**	**US$10-15 per test; US$12 all-inclusive price for HCV VL[9]**
▪ Quantitates patient's HCV RNA to assess achievement of SVR/test of cure. ▪ Under-quantifies GT 3; clinicians need to know that different VL assays run on different platforms may show different results before deciding on treatment options. ▪ An off-label study showed this test using DBS is a good alternative to plasma for PWID. ▪ n=107, compared venous and DBS samples: ▪ For plasma (compared with Roche CAP/CTM), 78% of samples (n=83) had detectable HCV RNA. For comparison, sensitivity for HCV RNA detection in DBS using a quantitative threshold of ≥15 IU/mL in plasma: 95.1% (95% CI: 88%–98.7%) and specificity: 96.0% (95% CI: 79.7%–99.9%). ▪ Aptima assay using DBS, sensitivity: 96.4% (95% CI: 89.8–99.3%) and specificity: 95.8% (95% CI: 78.8–99.9%). Used a quantitative threshold of ≥1000 IU/mL, sensitivity: 100% (95% CI: 95.3–100%) and specificity: 100% (95% CI: 88.4–100%). ▪ Overall, Aptima assay using DBS showed good sensitivity and specificity compared to plasma, with a threshold of ≥1000 IU/mL.				
Biocentric Generic HCV PCR assay	**Plasma, serum** **Lab, clinical settings, research labs**	**Biocentric Generic, Montpellier University Hospital (France) and Medical Laboratory, Institut Pasteur (Cambodia)**	**CE-IVD**	**US$23 per test** **US$13.50-17 (€12-15) per test (updated price expected by end-2019)[10]**
▪ RNA confirmation test used on open-licensed PCR platform could be more affordable than other platforms. ▪ Study evaluated and showed good performance, compared with Roche Cobas AmpliPrep/Cobas TaqMan HCV RNA assay (n=141, France; n=185, Cambodia). ▪ LoD: ranging from 50 HCV RNA IU/ml to 300 HCV RNA IU/ml. ▪ Specificity: 100% (CI: 92.5–100); sensitivity: 98.7% (CI: 92.3–99.9) in France. ▪ Specificity: 100% (CI: 95.5–100); sensitivity: 100% (CI: 94.4–100%) in Cambodia. ▪ Showed good agreement between the two Biocentric Generic and Cobas TaqMan assays, including GT 6, which is predominant in Cambodia. ▪ Biocentric's open platforms are available in 20 countries, and only in public sector facilities.[11]				
Cobas® 6800/8800 systems (Cobas HCV RNA)	**500 µL Plasma, or 200 µL serum** **Lab, high volume clinical settings**	**Roche (Switzerland)**	**CE-IVD, FDA-approved**	**US$340,000-US$475,000 per instrument (depending on instrument and volume); US$35-45 per test**
▪ Both systems show high sensitivity, specificity, and accuracy for viral load monitoring and to determine SVR12. ▪ Has medium (6800 system) and high (8800 system) throughput testing (384 and 960 tests, respectively, per 8 hour shift. ▪ Time to results: first 96 results < 3.5 hours, every 90 min for 96 more results (Cobas 6800 System); first 96 results < 3.5 hours, every 30 min for 96 more results (Cobas 8800 System). ▪ Study: Cobas 6800: n=233; Cobas 8800: n=229 of 233. HCV RNA ≥ 25 IU/mL was active infection. ▪ Specificity: Cobas 6800: 99.6%; Cobas 8800: 100% (patients were HCV-negative with non-HCV related liver disease). ▪ The limit of detection was determined as: 12.0 IU/mL in plasma and 13.7 IU/mL in serum for all GT 1-6 on both systems. Broad measurable range: 15 − ~1.0E + 08 IU/mL.				

Assay	Sample/ Setting	Company	Regulatory Status	Price (*ex works* or free carrier)
cobas® Plasma Separation Card	**Whole blood, plasma** **Lab**	**Roche (Switzerland)**	**CE-IVD (for HIV); Not FDA-approved**	**TK**
▪ Registered for HIV RNA testing for confirming positive HIV results by measuring baseline levels or to monitor ART, but technology could be developed for HBV, HCV, other diseases. ▪ Can courier/transport sample up to 28 days at 18-45°C and with up to 85% humidity; good diagnostic solution for rural and remote settings.				
RealTime HCV Viral Load	**0.5 mL Plasma, 0.2 mL serum DBS (fingerstick)** **Lab**	**Abbott (USA)**	**CE-IVD (for HIV DBS and HCV RNA plasma and serum only); WHO PQ (under review)**	**US$11-23 per test; Global Fund price varies according to test volume/term commitment**

▪ Registered for HCV viral load using plasma or serum; several off-label studies underway using DBS.
▪ MOVIDA-Hep study in Vietnam uses DBS in an off-label protocol, comparing Abbott m2000rt RealTime performance and turnaround time for DBS vs. standard protocols using plasma VL.
▪ Supports evidence for decentralized POC testing using DBS in resource-limited settings:
  ▪ One study (n=410) supported the use of DBS as a good alternative to plasma for RNA for people who are actively injecting drugs.
  ▪ Recruitment in 2019 for studies conducted by FIND using DBS on various platforms, including Abbott m2000; COBAS® AmpliPrep/COBAS TaqMan HCV Test from DBS; cobas® HCV for use on the cobas® 6800/8800 Systems from PSC and DBS; Aptima® HCV Quant Dx Assay from DBS.
▪ One 'research use only' study showed quantitative RNA results and compared plasma and DBS whole blood results on Abbott them2000sp and m2000rt systems:
  ▪ DBS panel: n=50 patients known to have positive RNA, with GT 1 A (n = 23), 2 (n = 5), 3 (n = 19), 4 (n = 1) and unknown GT (n = 2). Two false positives, likely due to patients having prior HCV infection.
  ▪ LoD: between 178 to 1779 IU/mL.
  ▪ Abbott 'research only' DBS protocol not as sensitive compared to plasma: 86% (95% CI: 73.76%–94.18%) increasing to 100% (CI: 91.59%–100%), when the viral load was >1000IU/mL. Yet it meets EASL recommendations that allow lower LoD of ≤1000 IU/mL for HCV RNA monitoring and linkage to care in LMICs and some HIC settings.
  ▪ Abbott 'research only' DBS protocol ran 35 min longer, but uses an automated method. Took 96 extractions during one assay run.				

Xpert® HCV Quantitative Viral Load assay	**Plasma, serum** **Lab; POC**	**Cepheid (USA)**	**CE-IVD; WHO PQ**	**US$17,000 per instrument; US$14.90 per test (for all virological tests in LMICs)**
▪ Field evaluation of Xpert® HCV assay for RNA quantification in GT 6 in Cambodia demonstrates high sensitivity of 100% (95% CI 99.2, 100) and specificity of 98.5% (95% CI 98.4, 99.9) compared with Roche Cobas Ampliprep-Cobas TaqMan® (reference assay). ▪ As a POC test it is easier to operate with fewer infrastructure requirements than central lab assay. There are some operational constraints such as the need for sufficient laboratory infrastructure, it is an expensive platform with costly cartridges for smaller, community clinics, and its waste management requires high temperature incinerators, which pose challenges for resource-limited settings. Further research for more affordable, environmentally-friendly POC PCR or cAg tests is needed.				

Assay	Sample/ Setting	Company	Regulatory Status	Price (ex works or free carrier)
Xpert® HCV VL FS assay	**100 µL, capillary blood, Fingerstick** **Tertiary POC: harm reduction settings**	**Cepheid (USA)**	**CE-IVD in 2018; Not FDA-approved**	**TK**

- The VL Fingerstick assay was a modified version of the HCV RNA assay.
- Xpert® HCV VL Fingerstick test for HCV RNA quantification demonstrates high sensitivity 100.0% (95% CI, 93.9%–100.0%) and specificity 100.0% (95% CI, 96.6%–100.0%), results <60 min.
- Potential as a screening tool for HCV RNA detection in high-prevalence settings, particularly in services for PWID and homeless populations.
- Major advance over Ab-based RDT tests.

CORE ANTIGEN – CONFIRMATORY				
ARCHITECT HCV cAg assay	**Serum, DBS** **Lab**	**Abbott (USA)**	**CE-IVD; WHO PQ (under review)**	**US$8-23 (€7–20) per test**

- A retospective study analyzed samples from a HCV screening cohort (n=10 006), and treatment cohorts in Canada USA and Germany (n=219, which were mainly patients with cirrhosis [58%], GT 1 [66%], and treated with sofosbuvir-based regimens [64%]). Used Abbott's RealTime HCV RNA to compare results with ARCHITECT.
- Measured HCV cAg at baseline, weeks 4, 12, 24 of treatment, and end of treatment.
- False negatives associated with low viral load; cAg increases over time for patients with treatment failure; cAg could become positive after treatment ends.
- HCV RNA and cAg results were in agreement at week 24, suggesting cAg could be measured then and become part of one-step method to confirm cure. This is in line with EASL recommendations that cAg is only considered for SVR24.

GENOTYPING ASSAYS				
Versant® 61 HCV Genotype 2.0 (LiPA 2.0)	**Serum** **Lab**	**Abbott**	**TK**	**TK**

- 2k/1b chimeras present with GT 2, which can lead to <10% SVR12 with sofosbuvir/ribavirin, seen in Eastern European countries like Georgia.
- n=278 for genotyping, and n=230 used for study cohort, of which HCV GT 1 (n=53) and GT 2 (n=177); and n=48 patients with HCV 2/1 chimeric strains.
- Versant® identified 90% of GT 1 and 2 cases (43/48) and 65% of HCV 2/1 chimeric (31/48) cases. Not appropriate for detecting HCV 2/1 chimeric strains.

ABBREVIATIONS

Ab: Antibody

Ag: Antigen

ALT: Alanine aminotransferase

APRI: AST to Platelet Ratio Index

ART: Antiretroviral therapy

ARV: Antiretrovirals

cAg: Core antigen

CE: Conformité Européene/European Conformity

CI: Confidence interval

DAA: Direct-acting antivirals

DBS: Dried blood spot

FIB-4: Fibrosis-4 index

FS: Fingerstick

GFATM: Global Fund to Fight AIDS, TB and Malaria

GT: Genotype

HBsAg: Hepatitis B virus surface antigen

HCV: Hepatitis C virus

HIC: High-income countries

HPS/CTM: High Pure system/Cobas TaqMan version 2

IA: Immunoassay

IU/mL: International unit per milliliter

IVD: In vitro diagnostics

LoD: Limit of detection

LMICs: Low- and middle-income countries

MSM: Men who have sex with men

ND: No data

NPV: Negative predictive value (true negative HCV results)

OR: Odds ratio (odds of developing a disease like HCV)

OST: Opioid substitution therapy

POC: Point-of-care

PQ: Prequalification

PrEP: Pre-exposure prophylaxis

PPV: Positive predictive value (true positive HCV results)

PVL: Plasma viral load

PWID: People who use drugs

RDT: Rapid diagnostic test

RNA: Ribonucleic acid, or HCV RNA test

SVR: Sustained virological response

TK: To come

uL: unit of liquid volume equal to one millionth of a liter, or 1 mm3

VL: Viral load

WAMBO: Global Fund's procurement platform

WHO: World Health Organization

ENDNOTES

1. Thank you to Annette Gaudino, Elena Ivanova, Richard Jefferys, Pauline Londeix, Teri Roberts, and Jilian Sacks, whose comments and suggestions helped improve and clarify this section.
2. Ivanova E (FIND, Geneva). Personal communication with: Bryn Gay and Annette Gaudino (Treatment Action Group). 2019 February 20.
3. Ibid.
4. Ibid.
5. Freeman, James (GP2U Telehealth, Hobart, Tanzania). Personal communication with: hepC working group. 2019 June 9.
6. Ivanova E (FIND, Geneva). Personal communication with: Bryn Gay and Annette Gaudino (Treatment Action Group). 2019 February 20.
7. Ibid.
8. Ibid.
9. Fajardo E. Hepatitis diagnostics: Landscape, pipeline, priorities and market. Presentation at: Global Health Diagnostics; 2018 June 13; McGill University, Montreal, Canada.
10. Londeix P. Personal communication with: Bryn Gay (Treatment Action Group). 2019 June 19.
11. Ibid.

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TAG is a nonprofit, tax-exempt
501(c)(3) organization.
EIN 13-3624785