Perspectives on requirements for laboratory tests for HCV therapy

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New HCV /HIV epidemiological data. Center for Disease Analysis 2013 (1)
1. HCV testing

• “It is recommended that HCV serology testing be offered to individuals, who are part of a population with high HCV prevalence or who have a history of HCV risk exposure/behaviour.”
• At country level: ensure access to HCV screening and diagnostic:
  – Ensure availability of reliable and affordable HCV screening tests
  – Elaborate screening strategies for vulnerable groups without discrimination
• At WHO level:
  – timely validation and pre-qualification of HCV rapid diagnostic tests for RLS, including for HIV-HCV co-infected people.
  – Guidance for screening strategies, including prioritization for screening and vulnerable groups
Access to HCV testing: game-changer

Globally, 59% of the world’s population has no access to hepatitis C diagnosis.

• These findings correlate with the wealth of the country: Dx using serology is available in 53% of lower middle income countries, and 11% of low income countries (WHA report 2010).

MSF RDT (rapid diagnostic test) procurement:

Before:

• HCV Scan (EY laboratories) sensibility: 100%, specificity: 93.7% (WHO 2001)
• HCV Spot (MP Medicals)

Average price 1-4 EUR per test.

Now:

⇒ New line OraQuick (Orasure, USA): Best and most up to date performance but 10-12x more expensive than other RDTs. (14 euros/test) (sensibility: 99.2%, specificity: 99.8% (Lee 2010) Can be done on whole blood (e.g. finger prick) or oral fluid. (MSF HCV landscape analysis 2014)

Requirements for a point-of-care RDT for HCV infection in resource-limited settings

- Close to 100% sensitivity and a high negative predictive value.
- Simple procedure
- No cold chain requirement
- No additional equipment
- WHO prequalified, CE marked, or FDA approved (as class I/A product)
- Good manufacturing practice
- Low cost
- No interaction with other co-morbidities (especially HIV/AIDS)
MSF UNITAID HIV-HCV grant
HCV public health problem, prevalence HCV –HIV co-infection

• 52.3% HCV-HIV co-infected patients in NE India
• 67.2% in IDU in Iran
• 10.3% in Nairobi, Kenya
• 15.7% in Mozambique
• 29% in North Myanmar
• 53.3% among IDU in Ukraine
2. diagnostic

• “It is suggested that nucleic acid testing for HCV RNA be performed directly following a positive HCV antibody test to establish the diagnosis of chronic HCV infection, in addition to HCV RNA testing as part of the assessment for receiving treatment for HCV”.

• At country level:
  – ensure access to affordable and reliable HCV viral load testing (laboratory-based and point of care) and genotyping.
  – Establish a network of laboratories that have an internal quality control system and participate in an external quality assurance program.
  – Train treaters/physicians about diagnostic and management of viral hepatitis.

• At WHO level:
  – Validate and pre-qualify of HCV viral load and genotyping for RLS.
  – Promote availability of multi-analytic platforms for molecular diagnostics and use existing facilities available for HIV.
  – Establish a target product profile for point of care hepatitis C viral load testing.
  – Develop simplified screening-diagnostic-monitoring algorithms for RLS.
HCV confirmation test: Detection of HCV RNA

• HCV PCR is the most common method to detect viral RNA. It is also used to quantify the virus for treatment monitoring purpose. Usually: Abbott, Roche, Siemens quantitative VL.

• HCV PCR is hardly accessible and costs >=100 USD per test.

• We need affordable:
  – POC HCV Viral load: pipeline Wave 80, Alere, Cepheid, IQuum, Daktari.
  – Flexible PCR platforms (Multitest: HBV-HIV-HCV) like Sacace generic open platform test, or Qiagen. (MSF HCV landscape analysis)
Table 1: Key requirements for viral load test specification for resource-poor settings

**ASSAY CHARACTERISTICS**

<table>
<thead>
<tr>
<th>Assay characteristics</th>
<th>Centralized, laboratory based</th>
<th>Decentralized, point-of-care based test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample collection method</td>
<td>Plasma, dry blood spot</td>
<td>Fingerstick, heelstick</td>
</tr>
<tr>
<td>Sample volume</td>
<td>Plasma: 200-1000uL; Dry blood spot: ≤100uL per spot</td>
<td>≤100uL</td>
</tr>
<tr>
<td>Sample preparation</td>
<td>Simple nucleic acid extraction method; no possibility of contamination; preferably automated</td>
<td>Simple, automated, electricity-free (can be battery operated) nucleic acid extraction method, preferably integrated into point-of-care amplification device</td>
</tr>
<tr>
<td>Consumables per result</td>
<td>Minimal; open access to consumables</td>
<td>Minimal – for example, 1 lancet, 1 capillary collection tube, 1 disposable cartridge</td>
</tr>
<tr>
<td>Reagent characteristics</td>
<td>Lyophilised reagents; no cold storage necessary; stable to 40°C for ≤18 months</td>
<td>Lyophilised reagent embedded on cartridge; no cold storage necessary; stable to 40°C for ≤18 months, with tolerance for temperature spikes up to 50°C; can tolerate temperatures below 0°C</td>
</tr>
</tbody>
</table>
Table 2: Key requirements for viral load test specification for resource-poor settings

<table>
<thead>
<tr>
<th>Instrument characteristics</th>
<th>Centralised, laboratory based</th>
<th>Decentralised, point-of-care based test</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Power requirements</strong></td>
<td>AC and battery powered</td>
<td>AC, battery and solar powered (battery life should last ≥8 hours)</td>
</tr>
<tr>
<td><strong>Characteristics</strong></td>
<td>Open access to multiple different components, consumables and reagents; standardised operating procedure; basic laboratory required with single room technology and no risk of amplicon contamination; automated and as hands-free as possible</td>
<td>Single, closed system device; automated and integrated; small footprint bench-top or hand-held device; easily portable; able to withstand extreme environmental conditions (humidity, heat, cold, dust etc); able to function in a mobile, van-based clinic (for example, able to withstand rigorous movement)</td>
</tr>
<tr>
<td><strong>Cost of instrument</strong></td>
<td>All required instrumentation ≤USD$10,000 (for example, centrifuge, plate sealer, sample preparation instrument, thermocycler, etc)</td>
<td>Single device ≤USD$1000</td>
</tr>
</tbody>
</table>
Table 3: Key requirements for viral load test specification for resource-poor settings

**PERFORMANCE**

<table>
<thead>
<tr>
<th>Performance</th>
<th>Centralised, laboratory based</th>
<th>Decentralised, point-of-care based test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Technician / healthcare worker hands-on time</td>
<td>≤1 hour</td>
<td>≤10 minutes</td>
</tr>
<tr>
<td>Time to result</td>
<td>≤1 day</td>
<td>≤30 minutes</td>
</tr>
<tr>
<td>Analytic / diagnostic range</td>
<td>Quantitative; all HCV genotypes (1-6); ≥10-20 IU/mL</td>
<td>Quantitative; all HCV genotypes (1-6); ≥10-20 IU/mL</td>
</tr>
<tr>
<td>Training / level of skill</td>
<td>Low to medium level of technical training</td>
<td>Minimal basic training (≤ 2 days); 10th grade education; no precision pipetting required</td>
</tr>
</tbody>
</table>
**Table 4: Key requirements for viral load test specification for resource-poor settings**

**QUALITY & CONNECTIVITY**

<table>
<thead>
<tr>
<th>Quality</th>
<th>Approval from strict regulatory authority</th>
<th>Minimum: WHO prequalified; optional extra: CE marking and/or US-FDA approval, or approval from one of the other regulatory authorities belonging to the International Medical Device Regulators Forum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality assurance and quality control</td>
<td>Test has internal error / validation controls and negative, low positive and high positive controls; is compatible with external quality assurance / proficiency testing programmes</td>
<td></td>
</tr>
</tbody>
</table>

**CONNECTIVITY**

| Transcription and geo-positioning | For power-dependent instrument-based platforms, patient results and test errors should download to an encrypted server and/or be compatible with the national laboratory information management system; data should be geo-positioned to enable tracking of operators, quality and epidemiological information |
Global distribution of HCV genotypes

**Key**
- Red: Genotype 1
- Orange: Genotype 2
- Yellow: Genotype 3
- Cyan: Genotype 4
- Blue: Genotype 5
- Green: Genotype 6

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3. Genotyping & Fibrosis evaluation

• The required length of peg-IFN-ribavirin treatment, or oral treatments, and the expected outcome from treatment, is dependent on the HCV genotype.

• Tests, using a range of different technologies:
  – Abbott, Roche, Siemens tests
  – Sacace: generic open platform test (real time PCR)
  – Pipeline point-of-care test: Wave80

→ New oral drugs will allow for simplification, if we have access to pan-genotypic treatment then genotyping may not be needed

→ Liver fibrosis can be assessed at field level using Transient elastography: Fibroscan, or serum biomarkers like APRI (Lin ZH. Hepatol 2011) (WHO HCV Guidelines 2014).
Simplified HCV diagnostic strategies

• Oral fluid or whole blood finger prick HCV RDT + dry blood spots capillary blood for PCR HCV diagnostic confirmation performed das the same time but PCR done only if HCV screening is positive.
• Determiner how to use dry blood spots/ oral fluid vs capillary blood/detection thresholds.
• Determine if HCV core antigen has a role to play in the screening and treatment monitoring algorithm, as alternative to HCV PCR. HCV.
• The development of a HCV PCR network at countries level is crucial now, laboratory-based and as point of care, for decentralization and scaling-up.
• Genotyping remains necessary today, as it conditions treatment duration, and type of treatment. This may not always be the case.
• APRI and FIB4 are validated for liver fibrosis assessment in mono-infected people. For HIV co-infected people more evidence would be needed: Fibroscan.
**Treatment should be simple, highly effective, pan-genotypic, potent, at affordable cost, easy to take (MSF HCV landscape analysis 2014)**

<table>
<thead>
<tr>
<th>Drug /combination</th>
<th>Overall Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir (SOF) ribavirin (RBV)</td>
<td>GT2, phase III 12 weeks SVR12: 93%</td>
</tr>
<tr>
<td>SOF RBV</td>
<td>GT3, phase III 24 weeks SVR12: 85%</td>
</tr>
<tr>
<td>SOF RBV</td>
<td>GT1 phase III 24 weeks SVR12: 76%</td>
</tr>
<tr>
<td>Peg-IFN +SOF+RBV</td>
<td>GT1 phase III 12 weeks SVR12: 90%</td>
</tr>
<tr>
<td>SOF + LDV(ledipasvir)</td>
<td>GT1 phase III 12 weeks SVR12: 97.7%</td>
</tr>
<tr>
<td>SOF+LDV</td>
<td>GT1 phase III 8 weeks SVR12: 94%</td>
</tr>
<tr>
<td>SOF+ LDV+GS 9669</td>
<td>GT1 phase II 6 weeks SVR12 95% (N=20)</td>
</tr>
<tr>
<td>SOF+LDV+GS 9451</td>
<td>GT1 phase II 6 weeks SVR12 100% (N=20)</td>
</tr>
</tbody>
</table>
### Update EASL 2014

<table>
<thead>
<tr>
<th>Drug/combo</th>
<th>Overall results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosburvir+ledipasvir HIV+HCV, N=50 (2: Osinusi A. EASL 2014)</td>
<td>GT1 no ART: SVR12: 10/10 GT1 on ART: SVR4: 21/21</td>
</tr>
</tbody>
</table>
The best components should be studied in combination and selected for market impact (MSF HCV landscape analysis 2014)

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<thead>
<tr>
<th>Drug /combination</th>
<th>Overall results</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOF+simpeprevir</td>
<td>GT 1 phase II 12 weeks SVR12 100% (n=14)</td>
</tr>
<tr>
<td>SOF+simpeprevir + RBV</td>
<td>SVR12 100% (n=12)</td>
</tr>
<tr>
<td>SOF+Daclatasvir (DCV) SOF+DCV+RBV</td>
<td>GT1 phase II 12 or 24 weeks SVR12 100% (n=14)</td>
</tr>
<tr>
<td></td>
<td>SVR12 95% (n=15)</td>
</tr>
<tr>
<td>SOF +DCV</td>
<td>GT1 Naïve SVR12 98%</td>
</tr>
<tr>
<td></td>
<td>GT1 Experienced SVR12 98%</td>
</tr>
<tr>
<td>SOF+DCV</td>
<td>GT2 SVR12 92% (n=26)</td>
</tr>
<tr>
<td>SOF+DCV</td>
<td>GT3 SVR12 89% (n=18)</td>
</tr>
<tr>
<td>DCV+asuneprevir+BMS 791325</td>
<td>GT1 phase II -12 or 24 weeks SVR12 94%</td>
</tr>
<tr>
<td>DCV 30mg+ simpeprevir (SMV)+/- RBV</td>
<td>GT1 SVR12= 75-85% in treatment naïve</td>
</tr>
<tr>
<td></td>
<td>SVR 12 = 65-95% in prior null responders</td>
</tr>
<tr>
<td>ABT 450/ +-ABT 267+-ABT333+-RBV</td>
<td>phase III, GT1, tt naïve, 12 weeks:</td>
</tr>
<tr>
<td></td>
<td>3 DAA+ RBV : SVR12: 99.5%, 3 DAA: SVR12: 99%</td>
</tr>
</tbody>
</table>
Treatment is prevention

• Simplified diagnostic & treatment may lead to:
  – Pro-active screening campaigns/ Higher uptake/adherence/completion
  – Integration, decentralization and scaling –up of HIV-HCV services, including vulnerable groups like injection drug users.
  – If the package of diagnosis and treatment can be largely available at affordable cost : < 500 usd...or even lower ...
Access to HBV treatment is discriminatory

If I don’t get HIV soon I am going to die
Prevalence of hepatitis B infection, adults 19-49 years, 2005

HBeAg Prevalence
- <2% = Low
- 2-4% = Low/intermediate
- 5-9% = High intermediate
- ≥10% = High
- Not applicable
HBV : key access issues

• HBV diagnostics, viral loads (polyvalent platforms and POC)
• Screening pregnant women for HIV, HBV, HCV, screening vulnerable groups including children
• Decision trees/who should be treated/when/how long/when to stop
• Tenofovir or lamivudine at end of pregnancy & delivery
• HBV birth dose immunization within 24 hours followed by EPI starting at 6 weeks
• Right to care for children and adolescents already infected with HBV
• Tenofovir registered for HBV mono-infection, improved generic competition, entecavir generic competition
• PMTCT & MCH pilot programs are needed
Conclusion: 500 million of people living with HBV and HCV are left behind

• It’s a matter of prioritization and political will.
• Civil societies, patients groups, care givers, are key players.
• Decriminalization and Universal access to care for the most vulnerable groups.
• Increasing the demand and decreasing the price of key diagnosis and treatments for HBV and HCV by creating:
  – Price competition, including generic competition
  – new market dynamics
  – new treatment paradigms.

• ➡ it’s time for action
MSF new report:
http://www.msfaccess.org/content/diagnosis-and-treatment-hepatitis-c-technical-landscape