INHSU 2016
Simplified HCV Diagnostics

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MSF Access Campaign

MSF AND HCV

MSF HCV Projects

- **Unitaid grant**: “Ensuring access to the HCV treatment revolution for HCV/HIV co-infected patients in Low and Middle Income Countries”

- **Sites** (Unitaid (co-infection) and MSF (mono-infection) funded):
  - **PWID**: **India, Kenya, Uzbekistan**
  - **Generalised**: **Myanmar** (incl PWID, GT6) **Mozambiqu**e (GT5, also HBV), **Pakistan, Cambodia** (GT6), **South Africa** (GT5)
  - (Increased demand for HCV treatment programmes within TB programmes in Eastern Europe)

- **Studies**:
  - Multi-centric longitudinal cohort to evaluate HCV treatment effectiveness in HIV co-infected people
  - Evaluation of the performance of HCV RDTs among HCV/HIV co-infected people
  - Cost-effectiveness (with Bristol University)

MSF HCV DAA Tx to date

- In MSF HIV programmes (different types of cohorts):

  HCV prevalence Asia/Middle East >> east/southern Africa

- **% RNA+**
  - **Nairobi** (Kibera): **0.04%**; **Mozambique** (Maputo): **1%**; **Uganda** (Mbarara): **0.07%**
  - **Cambodia** (Phnom Penh): **4%**; **India** (Manipur): **6.8%**; **Myanmar** (Yangon): **6.5%**; **Myanmar** (Dawei): **8%**
  - **Pakistan** (Karachi): **37%**; **Armenia** (Yerevan): **13%**

- **Actively treating:** India, Pakistan
- **Few treatments:** Kenya, Uganda
- **Recently started:** Uzbekistan, Cambodia
- **About to start:** Myanmar

- **DAAs: SOF + DAC generic and originator**
- In countries where there are patents, obliged to use originator or generics part of VL

Challenges for blood transfusion

- **Systematic screening of any donor or blood unit**
- Activities:
  - Main projects: **surgery, maternity, malaria**
  - Around 75,000 tests of donors per year
  - 100,000 units of blood, transfused per year
- **HCV RDT used (EIA lab platforms not available on site) → not intended use of Dx test but no choice**
- Problem of test specificity eg: Mali / Koutiala (**accuracy matters!**)
  - 2014: 14.6 % positive HCV serology – previous RDT
  - 2015: 2.5 % positive HCV serology – OraQuick HCV RDT

Example – Myanmar (Kachin State)

- **MSF 2016: >10,500 people on ART and growing**
- **MSF + AHRN: 280 stable on ART and taking methadone > 1 year**
- **Typical person:**
  - Migrant worker
  - Owns a motorbike
  - Searches for jade
  - Young
  - Male
  - **PWID, HIV, DR-TB, HCV**
- **Treatment:**
  - ART – MSF
  - HCV – no one (at the moment)
  - DR-TB – Myitkyina (9 hours away)
  - Methadone - AHRN

Example – India (Manipur)

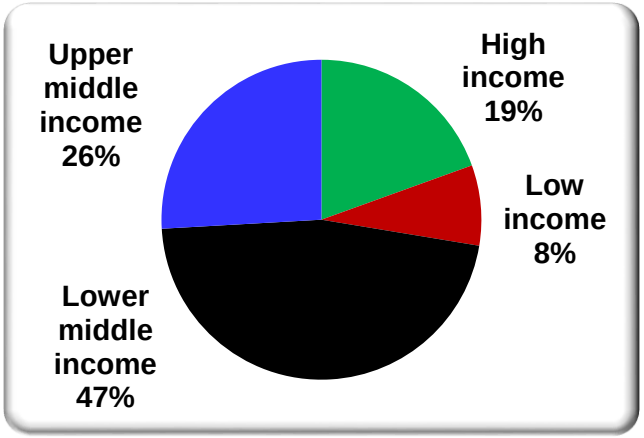
- **MSF 2016:** 1850 HIV patients under care with 1600 people receiving ART
- **HIV / HCV / TB / MDRTB** treatment
- Disclosure past or present **IDU within HIV** cohort:
  - Churachandpur: **65%**
  - Moreh: **20%**
- Churachandpur **HIV/HCV** co-infection:
  - Current IDU use: **31%**
  - Past IDU: **45%**
- **PWID** prevalence: **˜2%**
- **Prevalence** of HIV and HCV amongst **PWID** (Solomon et al. Burden of hepatitis C virus disease and access to hepatitis C virus services in people who inject drugs in India: a cross-sectional study *Lancet Infect Dis 2014*)
  - HIV mono-infection: **6.9%**
  - HCV mono-infection: **38%**
  - HIV / HCV co-infection: **21%**

HCV DX SIMPLIFICATION: (TYPE OF TESTS AND FREQUENCY OF TESTING)

Why simplified HCV Dx is important

˜70 million (56M – 90M) people are infected with **HCV** (**viraemic**), a 2016 **prevalence** of **1%** (0.8%-1.2%)

Source: Polaris Observatory http://www.polarisobservatory.com/)



- As there are few comprehensive screening programmes in LMICs, **few people know their status**
- The diagnostic package needed for IFN-based therapy was complex but can now be **drastically simplified with pan-genotypic, all oral DAA-based therapy**
- **Two current barriers to simplification: 1. no pan-genotypic regimen** in WHO guidelines, **2. eligibility criteria** still used (cost, minimal access to Tx, no FDC)

The current standard of HCV monitoring during HCV treatment with PEG-IFN-alpha

Source: EASL Clinical Practice Guidelines: 2013 revised version. Clinical practice guidelines to optimize the management of hepatitis C virus infection.

	Pre-treatment	Baseline	Week 4	Week 12	End of treatment (week 24)	SVR12	SVR24
Antibody screening	x						
Virological confirmation	x						
Liver staging		x					
IL-28B		x					
Genotype		x					
Viral load		x	x	x	x	x	x
Complete blood count with differential		x	x	x			x
Thyroid stimulating hormone		x	x	x			
Clinical chemistry and haematology		x	x	x			x
Alpha-fetoprotein		x					
Lipids panel		x					

The proposed standard of diagnostic monitoring with an ideal, all oral, pan-genotypic regimen

	Pre-treatment	Baseline	Week 4	End of treatment (week 12)	SVR12
HCV core antigen or RNA (qualitative)	x				x
Alanine transaminase		x	x	x	
Creatinine		x	x	x	
Haemaglobin		x	x	x	

Source: Cohn J, Roberts T, Amorosa V, et al. Simplified diagnostic monitoring for Hepatitis C, in the era of Direct Acting Antiviral treatment. Curr Opin HIV AIDS. 2015;10:369–373.

TABLE 8.4 Framework for the frequency of monitoring patients undergoing HCV therapy based on type of regimen

Time	DAA alone			DAA + ribavirin			DAA + pegylated interferon + ribavirin			
	FBC, renal, liver function	Adherence, side-effects	HCV RNA	FBC, renal, liver functions	Adherence, side-effects	HCV RNA	FBC, creatinine, ALT	Thyroid function	Adherence, side-effects	HCV RNA
Baseline	X		X	X		X	X	X		X
Week 1				X	X		X		X	
Week 2				X	X		X		X	
Week 4	X	X		X	X		X		X	
Week 8				X	X		X		X	
Week 12				X	X		X	X	X	
Week 12 after end of treatment			X	X		X	X	X		X
Week 24 after end of treatment										X

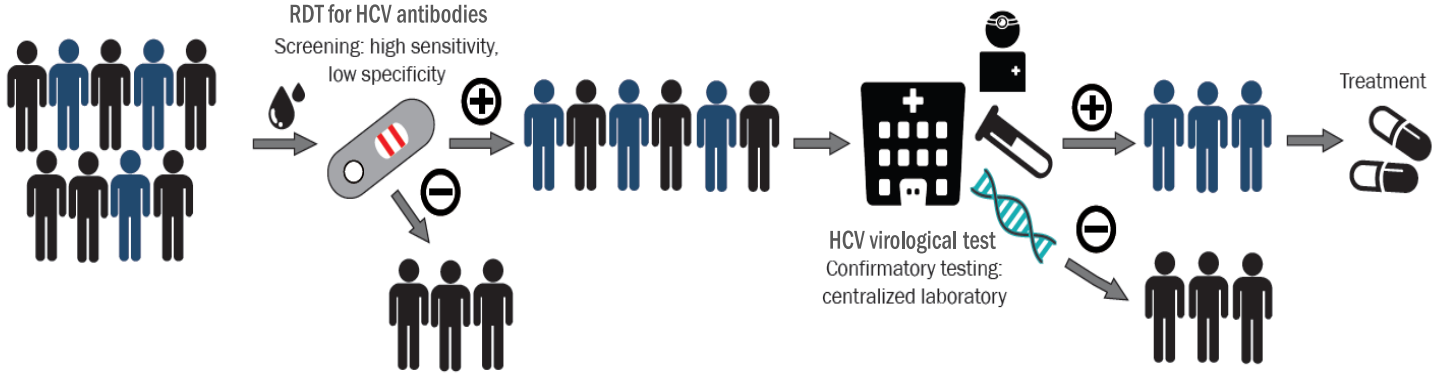
ALT: alanine aminotrar [illegible] direct-acting antiviral; FBC: full blood count

Source: WHO Guidelines for the screening, care and treatment of persons with chronic HCV infection 2016

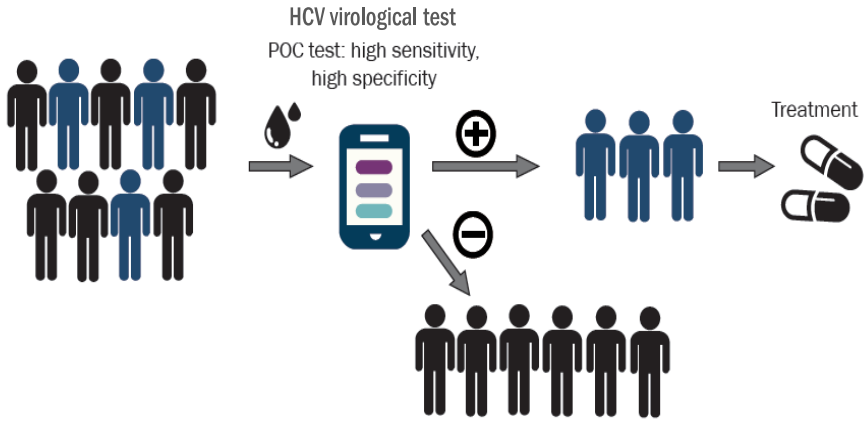
One vs two step Dx strategy

(depending on prevalence, cost, ease-of-use, LTFU etc)

TWO-STEP DIAGNOSIS



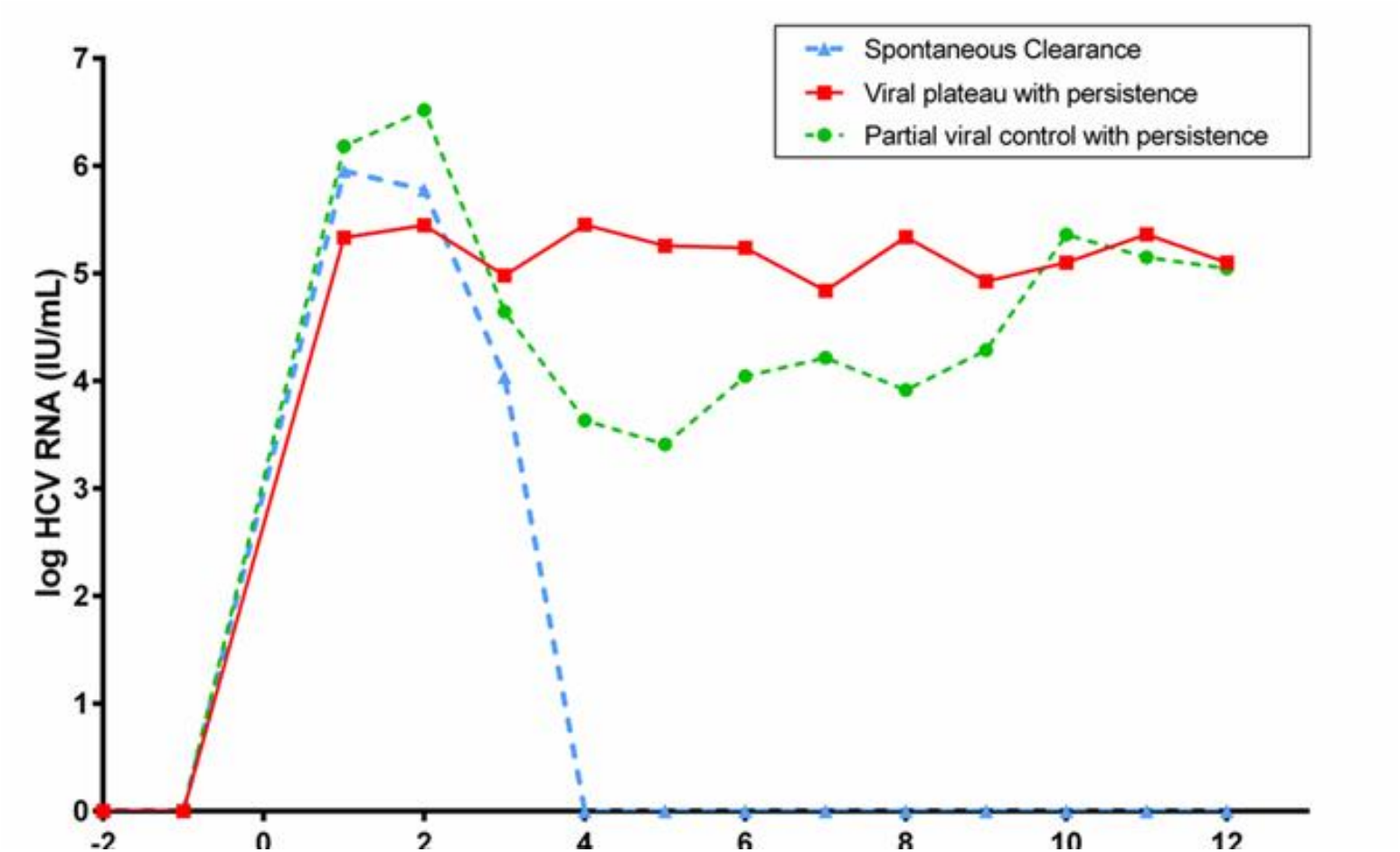
ONE-STEP DIAGNOSIS



Source: FIND

Sensitivity - What is good enough?

Patterns of HCV RNA levels in individuals with well-characterized acute HCV infection in the InC3 study
(total n = 162); source: Hajarizadeh PLOS one 2015



Sensitivity - What is good enough?

- **~ 95% of individuals have HCV RNA >10,000 IU/mL in chronic infection**
  (Source: Hajarizadeh PLOS one 2015; Hajarizadeh J Med Virol 2014; Glynn Transfusion 2005)
- Subset of patients with persistent infection have **partial viral control** and drop to at least **>1,000 IU/mL** temporarily (several months) but then go back to a viral load **>100,000 IU/mL** between months 10 and 12
- Therefore unlikely to need very sensitive tests because **clinically relevant sensitivity is >1,000 IU/mL**, which means testing using small blood volumes (e.g. fingerstick blood) or core antigen is much more feasible
- E.g. Abbott Architect HCV Ag assay: LOD 3fmol/L (sensitivity of 1000-3000 IU/mL)

- **BUT current guidelines (e.g. EASL, AASLD) recommend <25 IU/mL analytical sensitivity → needs revising for appropriate clinical sensitivity so that POC and core Ag tests can be used**
- Awaiting systematic review of the evidence to confirm acceptable sensitivity for diagnosis and SVR12
- Hopefully same qualitative test can be used for Dx and SVR12

Systematic review: core Ag detection for the diagnosis of HCV

- Freiman et al Hepatitis C Core Antigen Testing for Diagnosis of Hepatitis C Virus Infection, Ann Intern Med. doi:10.7326/M16-0065

- HCV core Ag assays can perform with **high sensitivity** (>90%) and **specificity** (>98%) **compared with RNA assays**
- HCV core Ag can conceivably reach a lower cost (based on cost of goods analysis); <10USD
- **Access**:
  - POC suitability versus centralized testing: possibly equal for both RNA/core Ag tests
  - DBS for core Ag: Lamoury et al (Kirby Institute) will present on good accuracy of core Ag DBS at the 10th Australian Viral Hepatitis Conference
- **Well-performing core Ag tests could serve as a replacement for RNA for HCV detection, particularly if they are more accessible and affordable than RNA tests**

Systematic reviews:
Accuracy of DBS compared to venous blood samples

- **HCV Ab**:
  - Sensitivity 98% (CI95% 94-99)
  - Specificity 99% (CI95% 97-100)
  - Positive likelihood ratio 171
  - Negative likelihood ratio 0.02
- **HBV sAg**:
  - Sensitivity 96.6% (CI95% 92-98.6)
  - Specificity 99.9% (CI95% 97.6-100)
  - Positive likelihood ratio 49.16
  - Negative likelihood ratio 0.06

- **HCV RNA**:
  - Sensitivity 96.0% (CI95% 93.4-97.6)
  - Specificity 97.7% (CI95% 94.7-99.0)
  - Positive likelihood ratio 171
  - Negative likelihood ratio 0.02
- **HBV DNA**:
  - Sensitivity 96% (CI95% 90-98)
  - Specificity 99% (CI95% 54-100)
  - Positive likelihood ratio 304
  - Negative likelihood ratio 0.04

- To **mimick real world conditions**, further info is needed when DBS are stored outside of the cold chain under conditions of higher temperatures and humidity and for up to 1 month
- **Manufacturers should validate DBS** as a sample type, provide protocols to end-users and submit for WHO PQ and regulatory approval

Source: Lange et al, ESCMID & unpublished

Overview of the programmatic experience of using DBS

- **DBS used by associations**:
  - "Hepatitis C Trust" in UK
  - le "Réseau Hépatites LR" in France
  - by community pharmacists in UK
- **France: cited and discussed but not recommended**
  - "CheckPoint-Paris from the Kiosque" is a VCT service in France that has offered rapid tests for screening and DBS for confirmation since 2010
  - guidelines from the "Haute Autorité Sanitaire" and AFEF-ANRS underlined that DBS tests have good performance and are an alternative to venous blood tests
  - ANRS: DBS frequently used for research studies
- **UK (NICE public health guidance): recommended to promote and offer testing to people at increased risk of infection**
  - Prison services and drug services
  - People with poor venous access / no phlebotomy services
  - Consider extending pilot programmes (pharmacists providing DBS)
  - **In Scotland, 19% of new HCV diagnoses during 2011-2013 were made in specialist drug service where DBS testing has been introduced**

Source: Edouard Tuaillon (Montpellier University)

HCV TESTS AVAILABLE

Serological antibody screening tests

- **Only one known strictly regulatory approved RDT for HCV: OraQuick HCV Rapid Antibody Test**
  - Good performance
  - At least USD10 in developing countries
  - MSF get the lowest price at <USD8
  - FDA approved: fingerstick whole blood
  - CE marked: oral fluid, serum, plasma and fingerstick whole blood
  - Oral fluid test useful for self-testing
  - Manufactured in the US so freight can significantly increase cost
  - Awaiting approval of other RDTs by WHO prequalification
  - Only EIAs (lab-based) have WHO PQ so far:

    http://www.who.int/diagnostics_laboratory/evaluations/PQ_list/en/
  - Donors and large procurers e.g. GFATM, PEPFAR have strict quality stds for procurement eligibility but HCV is largely domestically funded so countries often make a choice on price, not quality = no incentive for manufacturers to invest in better quality tests

There may be other CE marked tests but this has been difficult to confirm as no database exists

Point-of-care virological tests (HCV RNA)

SUPPLIER	CD4	HIV EID	HIV VL	HCV VL
Alere	Pima Analyser			
BD	FACSPresto			
Millipore	Muse Auto CD4/CD4% system			
Omega Diagnostics	Visitect CD4			
Sysmex Partec	CyFlow miniPOC			
Alere		q HIV 1/2 Detect		
Cepheid		Xpert HIV-1 qual	Xpert HIV-1 Viral Load	Xpert HCV Viral Load
Diagnostics for the Real World		SAMBA HIV-1 Qual Test SAMBA II HIV-1 Qual Whole Blood Test	SAMBA HIV-1 Semi Q Test SAMBA II HIV-1 Semi Q Plasma Test	
Molbio Diagnostics			Truelab/Truenat HIV	Truelab/Truenat HCV
Northwestern Global Health Foundation / Quidel		LYNX HIV p24 Antigen Test	Savanna Quantitative RealTime HIV-1 Assay	

Not yet available

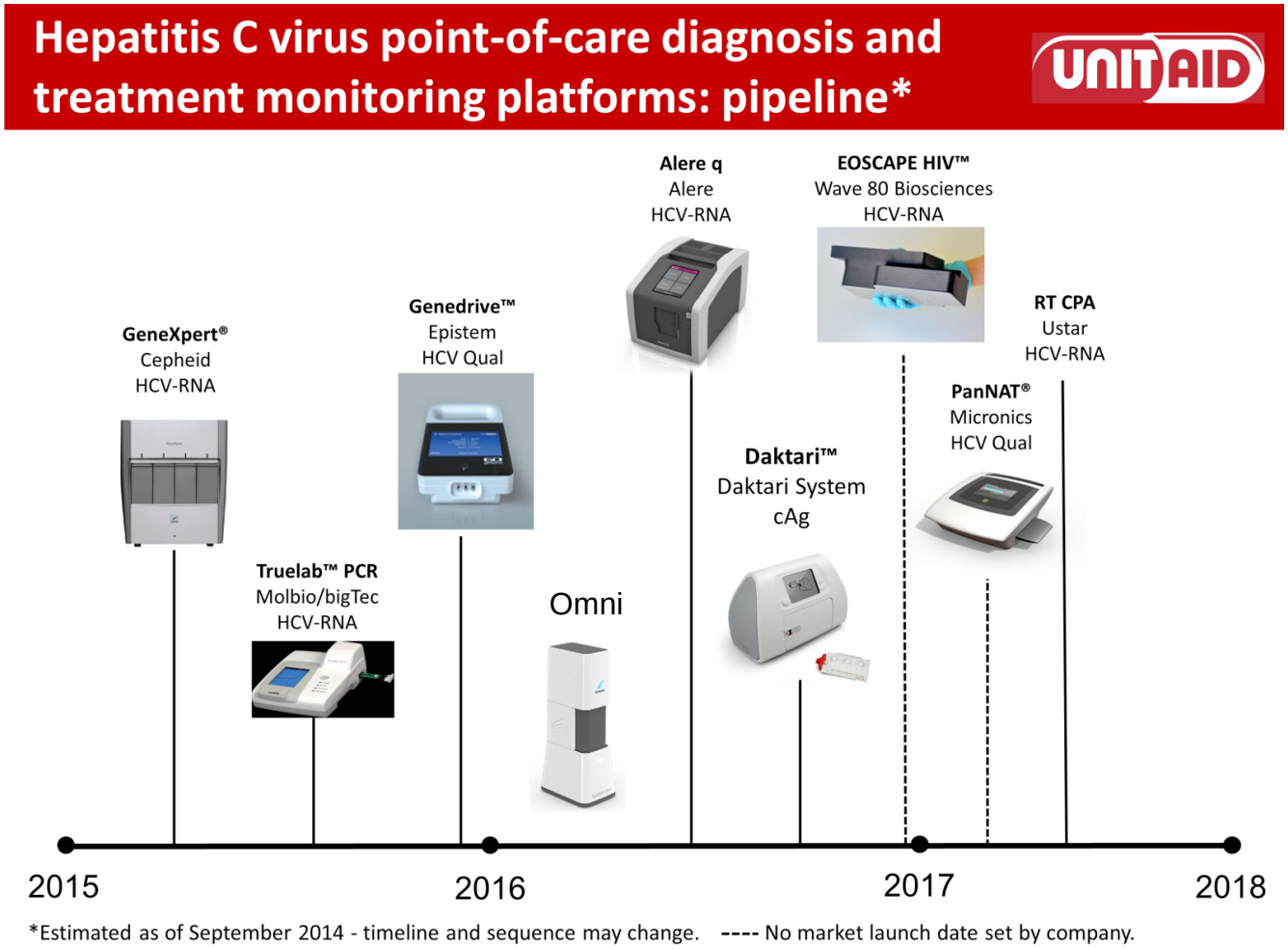
Source: http://msfaccess.org/HIV-HCV-diagnostic-product-guide-2015

Lab-based virological tests (HCV RNA and core antigen, GT)

SUPPLIER	HIV EID	HIV VL	HCV VL	HCV CORE ANTIGEN	HCV GENOTYPING
Abbott	RealTime HIV-1 Qualitative	RealTime HIV-1	RealTime HCV	ARCHITECT HCV Ag	RealTime HCV Genotype II
Biocentric	Generic HIV DNA Cell	Generic HIV Charge Virale	Generic HCV Charge Virale		
bioMérieux		NucliSENS EasyQ HIV-1			
Cavidi		ExaVir Load			
Hologic		Aptima HIV-1 Quant Dx Assay	Aptima HCV Quant Dx Assay		
Qiagen		artus HI Virus-1 RG RT-PCR artus HI Virus-1 QS-RGQ	artus HCV RG RT-PCR artus HCV QS-RGQ		
Roche Molecular Diagnostics	CAP/CTM HIV-1 Qualitative	CAP/CTM HIV-1	CAP/CTM HCV Qualitative and CAP/CTM HCV		cobas HCV GT
Sacace Biotechnologies		HIV Real-TM Quant Dx	HCV Real-TM Quant Dx		HCV Genotype Plus Real-TM
Siemens		VERSANT HIV-1 RNA Assay	VERSANT HCV RNA Assay		VERSANT HCV Genotype 2.0 Assay

Source: http://msfaccess.org/HIV-HCV-diagnostic-product-guide-2015

Point-of-care tests in the pipeline

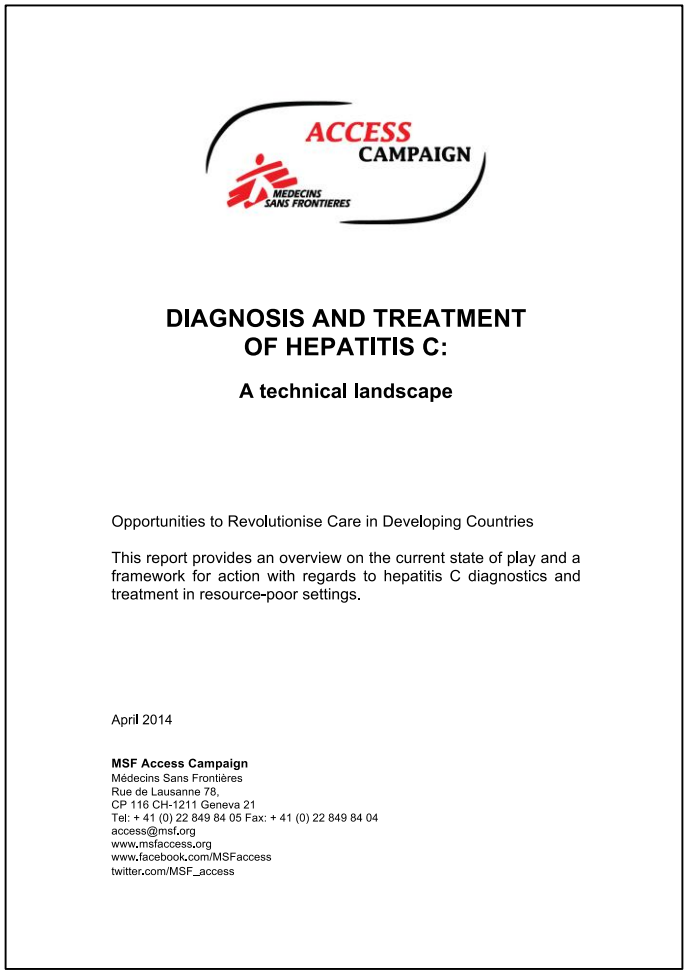


Source: http://unitaid.org/images/marketdynamics/publications/UNITAID-HCV_Diagnostic_Landscape-1st_edition.pdf

KEY RESOURCES

MSF Access Campaign Report

http://www.msfaccess.org/content/diagnosis-and-treatment-hepatitis-c-technical-landscape



ACCESS CAMPAIGN

MEDECINS SANS FRONTIERES

DIAGNOSIS AND TREATMENT OF HEPATITIS C:

A technical landscape

Opportunities to Revolutionise Care in Developing Countries

This report provides an overview on the current state of play and a framework for action with regards to hepatitis C diagnostics and treatment in resource-poor settings.

April 2014

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MSF Access Campaign Product Guide

(will be updated in 2017)

httwp://msfaccess.org/HIV-HCV-diagnostic-product-guide-2015

PUTTING HIV AND HCV TO THE TEST

A PRODUCT GUIDE FOR POINT-OF-CARE CD4 AND LABORATORY-BASED AND POINT-OF-CARE VIROLOGICAL HIV AND HCV TESTS

July 2015

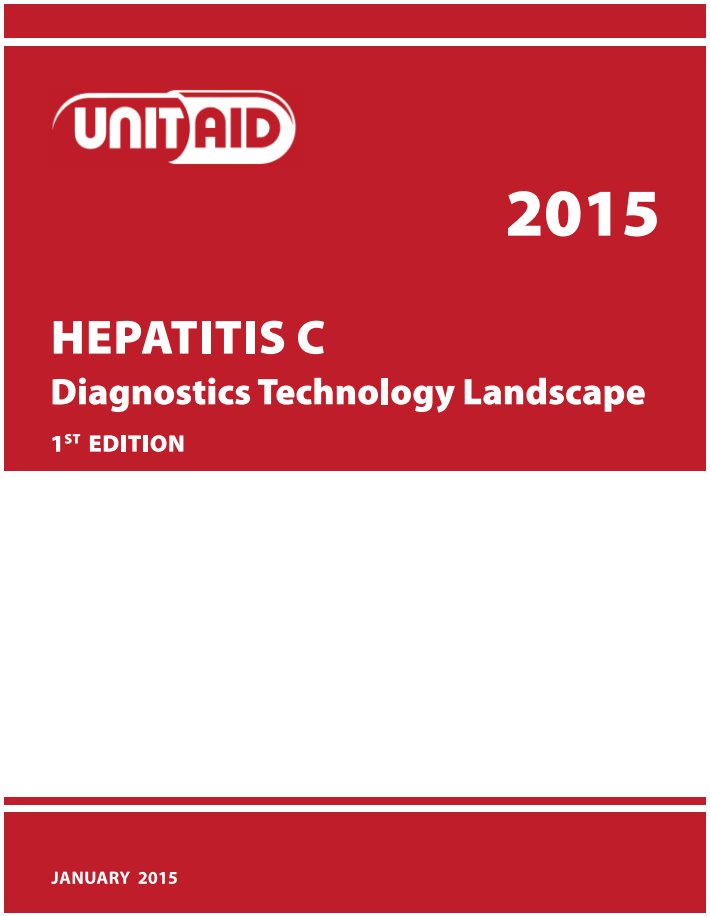
www.msfaccess.org

ACCESS CAMPAIGN
MEDECINS SANS FRONTIERES

Unitaid diagnostics landscape

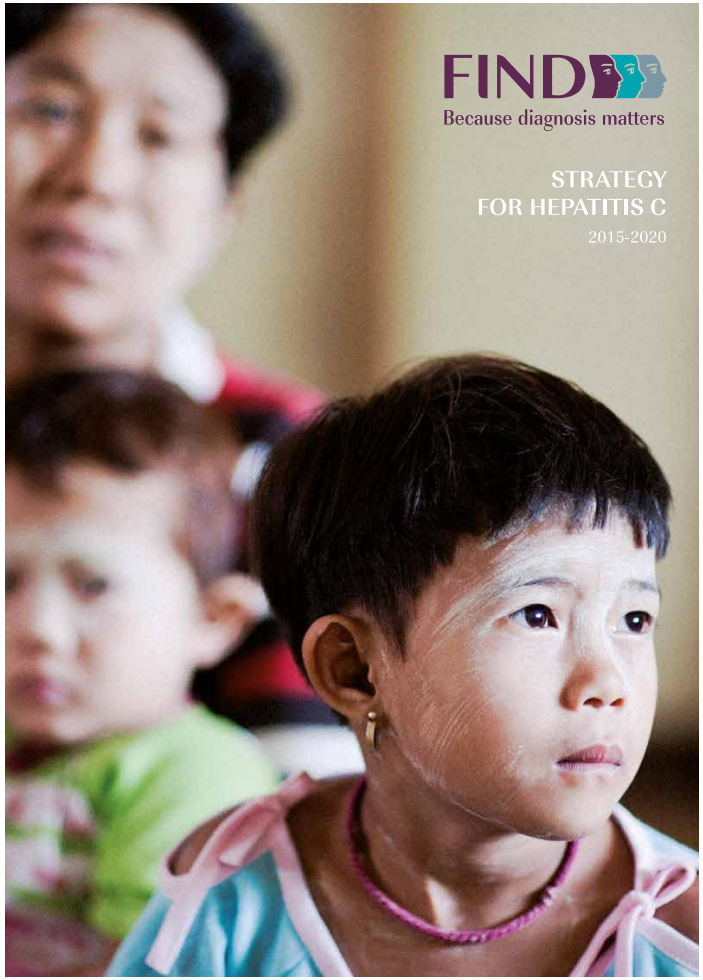
(updated periodically)

http://unitaid.org/images/marketdynamics/publications/UNITAID-HCV_Diagnostic_Landscape-1st_edition.pdf



FIND HCV Strategy

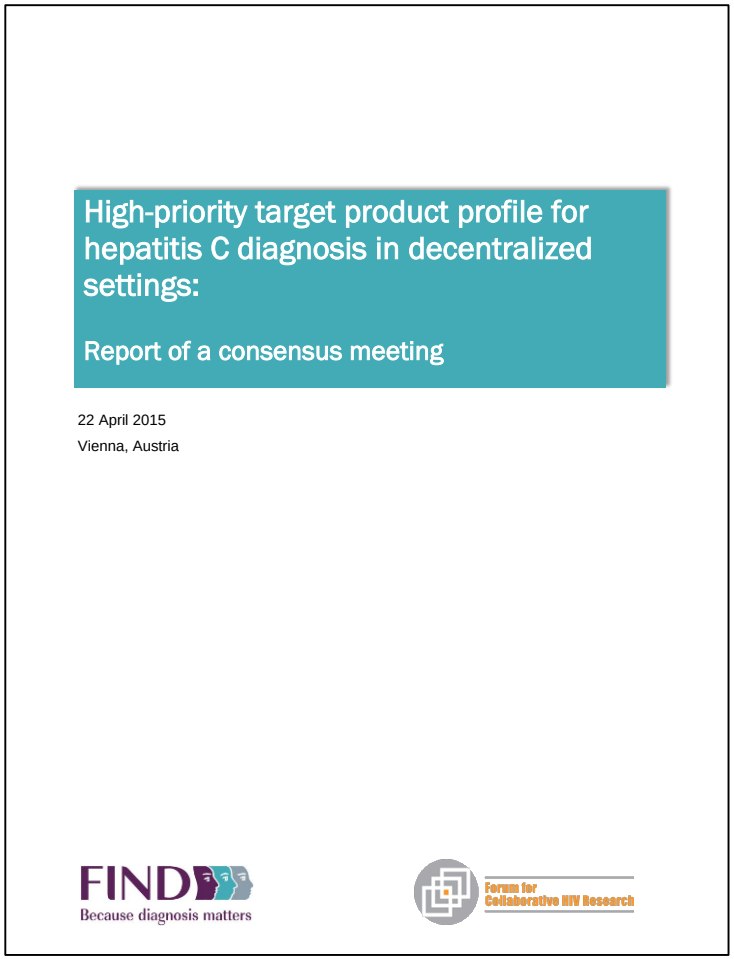
http://www.finddiagnostics.org/export/sites/default/resource-centre/reports_brochures/docs/FIND_strategies/FIND_HepatitisC_Strategy_21Nov14.pdf



FIND Target Product Profile

[High-priority target product profile for hepatitis C diagnosis in decentralized settings: Report of a consensus meeting]

http://www.finddiagnostics.org/programs/hepC/target-product-profile/



KEY ADVOCACY AREAS

Lessons Learnt

- **Delay in HCV screening** due to lack of in-country policy, guidelines and programmes
- **Unknown quality of serological screening** where counties use cheaper RDTs of unknown manufacturing quality and performance; **HIV co-infection** may cause false positives (polyclonal) and false negatives (immunosuppression)
- **DAAs are allowing for diagnostic simplification and decentralisation** but guidelines and models of care are still very conservative
- **Delay in access to DAA treatment in countries due to slow registration** and companies having no incentive to apply for WHO prequalification (no donor purchasing of drugs therefore no quality policy – same for Dx) means delay in implementing HCV programming overall
- **Reliance on external stakeholders and political will but no dedicated international funding available**; preferential pricing normally not extended to MICs, and LMICs are struggling to pay everything domestically, means manufacturers are not convinced of a viable market

Key messages

- **First WHO hepatitis testing guidelines will be released this year**
  - Encourage countries to take them up!
  - They include a public health approach to testing including high risk groups, RDTs, dried blood spots and uptake of testing, linkage to care and community-centric strategies
- **Lack of large donor funding for R&D and commodity purchasing**
  - Encourage large, classical donors to fund HCV (not just in the context of HIV co-infection)
  - Work on innovative domestic financing
  - Establish best policy for pharma funding/partnerships/donations to ensure sustainability
- **Lack of affordable quality assured HCV RDTs for screening**
  - Key requirements for a POC RDT for use in resource-limited settings are a test that is **accurate** (close to 100% sensitivity and high negative predictive value, and equally accurate in HCV/HIV co-infection)**; simple** (with minimal training requirements and no cold chain); **reliable** (WHO-prequalified, CE marked or FDA approved); and **cheap**, at <$2 per test
  - Increased procurement by large, classical donors will provide incentive for quality RDTs
  - Large procurers can also facilitate pooled procurement, increased volumes and competition for price reductions
  - Countries should strengthen their quality policies for diagnostics in general (tender systems should be based on quality and performance, not just price)
  - Ramping up of country HCV programmes will lead to price reductions due to increased volumes and competition
- **Advocacy**
  - Ramped up advocacy is needed for increased awareness for importance of HCV testing & funding

THANK YOU


HEPATITIS C TREATMENT:
149.75 MILLION PEOPLE
STILL WAITING...
Your number is
149.750.000