FIND

Because diagnosis matters

Diagnostics for hepatitis C: what do we have

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World Hepatitis Alliance on-line workshop

FIND is a global non-profit driving diagnostic innovation to combat major diseases affecting the world's poorest populations

- WHO Collaborating Centre for Laboratory Strengthening & Diagnostic Technology Evaluation
- WHO SAGE-IVD member
- ISO-certified quality management system for IVD clinical trials

ANTIMICROBIAL RESISTANCE	HEPATITIS C & HIV	MALARIA & FEVER
NEGLECTED TROPICAL DISEASES	PANDEMIC PREPAREDNESS	TUBERCULOSIS

We address market failure by partnering to develop and deliver diagnostic solutions to LMICs

In-vitro diagnostics (IVD)

What is an in-vitro diagnostic?

- "**In-vitro diagnostics** are tests done on samples such as blood or tissue that have been taken from the human body. **In-vitro diagnostics** can detect diseases or other conditions, and can be used to monitor a person's overall health to help cure, treat, or prevent diseases"[1]

In-vitro means:

- happening outside the body

[1] https://www.fda.gov/medical-devices/products-and-medical-procedures/vitro-diagnostics

Sensitivity and Specificity

- Sensitivity
  - What percentage of the time a test correctly will diagnose someone **with the** disease **who has the disease**
- Specificity
  - What percentage of the time a test correctly will diagnose the person **as not having** the disease **who does not have the disease**

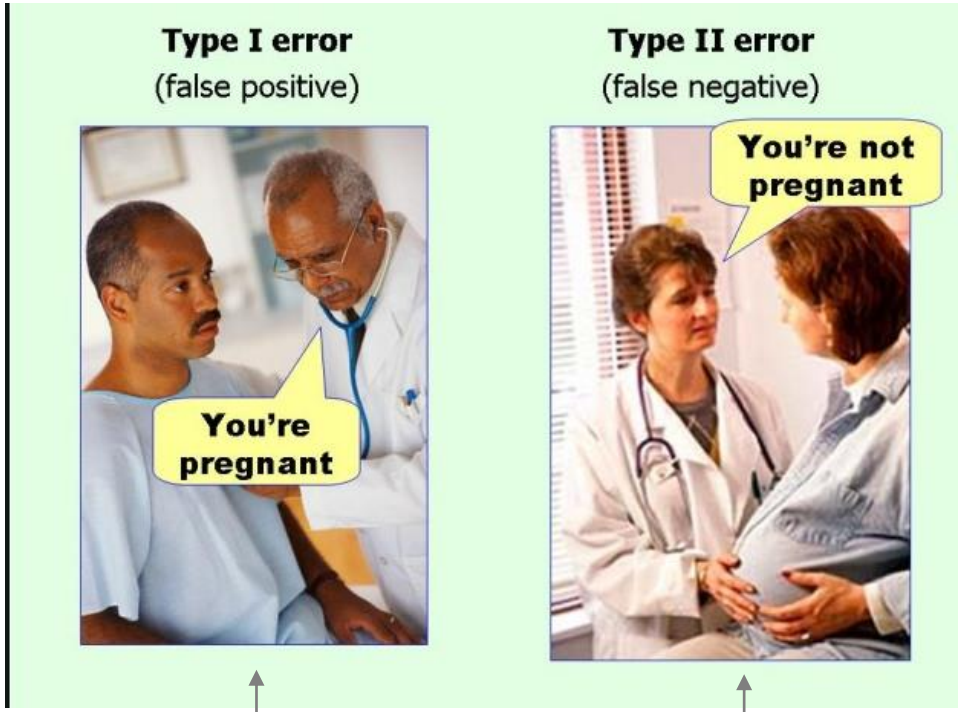


Image from: https://effectsizefaq.com/2010/05/31/i-always-get-confused-about-type-i-and-ii-errors-can-you-show-me-something-to-help-me-remember-the-difference/

Regulatory bodies governing IVD quality

Why are regulatory authorities needed?

- There are several components that go into ensuring that the diagnostic being used is giving correct results
- For today's session will focus on one aspect; stringent regulatory authority (SRA)/ WHO Prequalification
- SRA is a regulatory body that ensures that a diagnostic is quality assured;
  - basically that the diagnostic does what it says it will do; it will correctly identify a specific disease in the sensitivity and specificity ranges as stated by the manufacturer
  - that the manufacturing facility and process is uniform so as to produce diagnostics of a consistent standard

Different types of regulatory authorities

Global

- WHO Prequalification (often times called WHO “PQ”)
- Expert Review Panel for Diagnostics (ERPD)

Country/region specific (non-exhaustive)

- Australia, Therapeutic Goods Administration
- European Union, European Commission Directorate-General for Internal Market, Industry, Entrepreneurship and SMEs
- Japan, Pharmaceuticals and Medical Devices Agency and the Ministry of Health, Labour and Welfare
- United States of America, US Food and Drug Administration

WHO Prequalification and Expert Review Pannel

- WHO Prequalification (often times called WHO “PQ”)

  Why it is important: helps ensure quality of a diagnostic and if a diagnostic has WHO PQ then that specific make/model can be procured through UN and Global Fund

  Source: https://www.who.int/topics/prequalification/en/

  Where you can look up what diagnostics are currently WHO PQ’: https://www.who.int/diagnostics_laboratory/evaluations/191029_prequalified_product_list.pdf?ua=1

  Additional information on WHO Prequalification: https://www.who.int/diagnostics_laboratory/evaluations/en/

- Expert Review Panel for diagnostics (ERPD)

  Why it is important: Hosted by WHO, the expert review panel consists of independent experts that review diagnostics that have not yet gone through/are in the process of going through WHO PQ or SRA review. Diagnostics that are reviewed to be of a quality standard are eligible to be procured using Global Fund funds.

  Source: https://www.theglobalfund.org/en/sourcing-management/quality-assurance/expert-review-panel/

  Where you can look up what diagnostics are currently have ERPD approval; https://www.theglobalfund.org/media/5878/psm_productshiv-who_list_en.pdf

Context is important

Each country has it's own land scape when it comes to diagnostic regulations

Some require in-country studies to be done on the tests

Others accept tests to be registered if already WHO PQ/FDA/CE or equivalent

WHO HCV testing algorithm

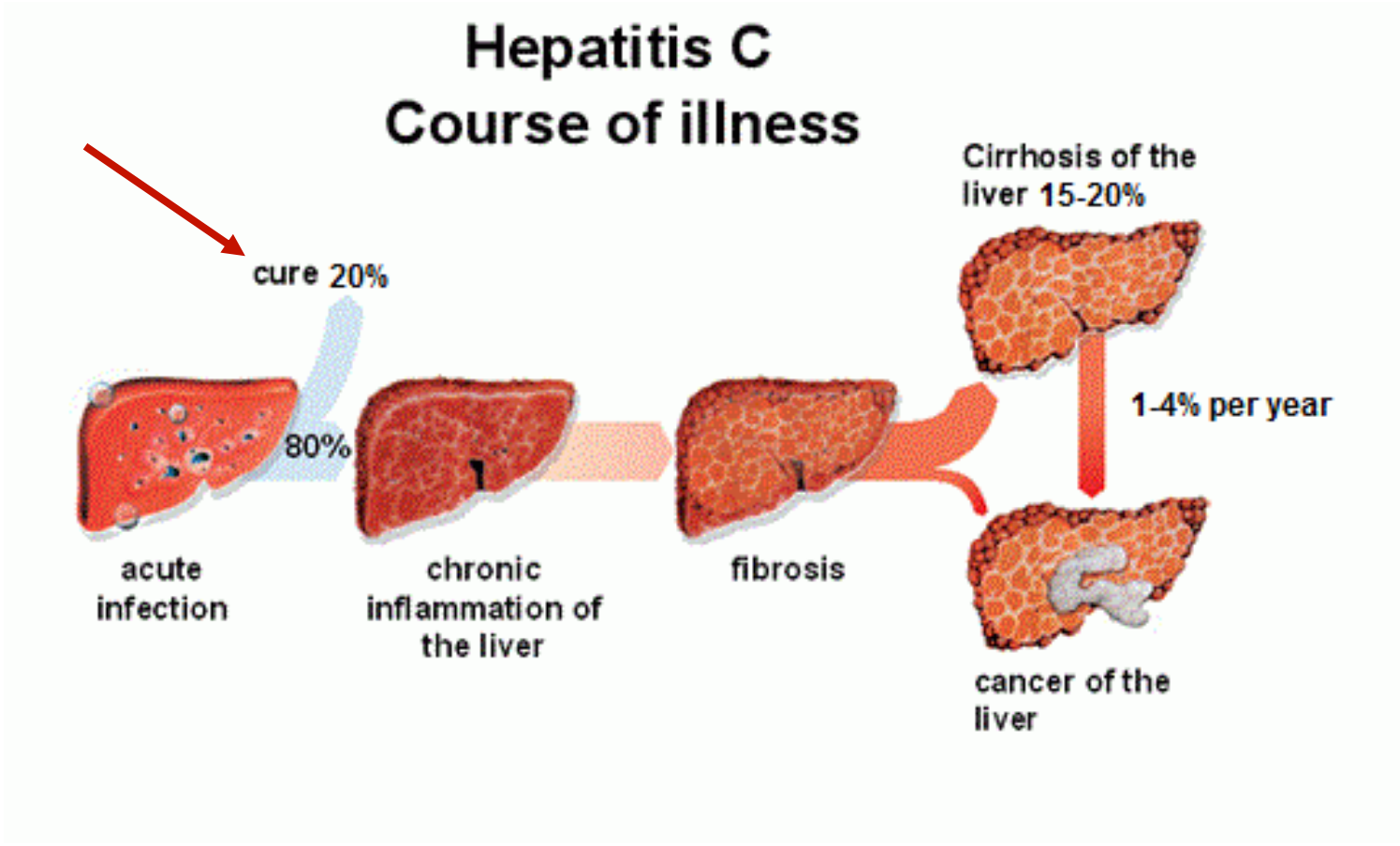
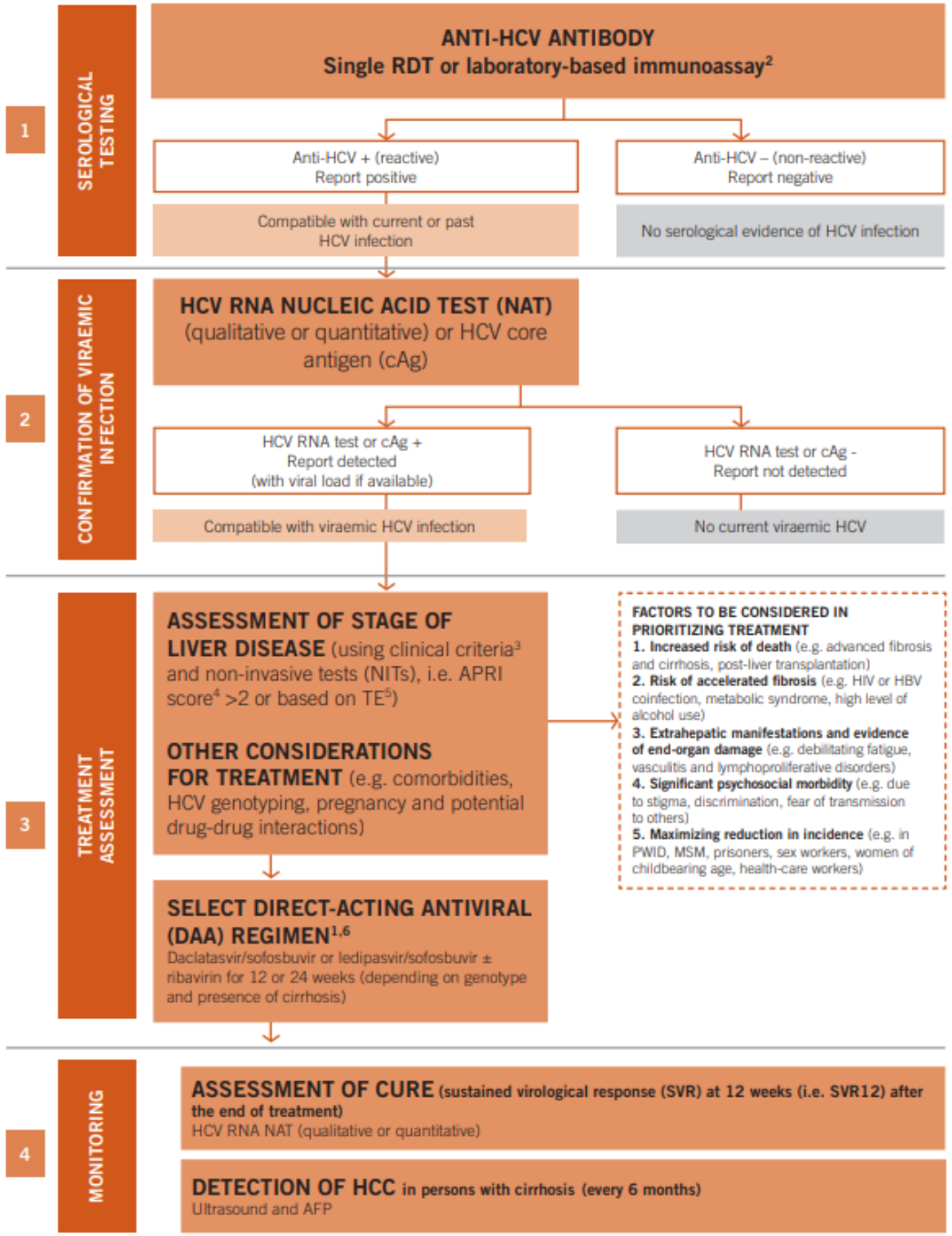


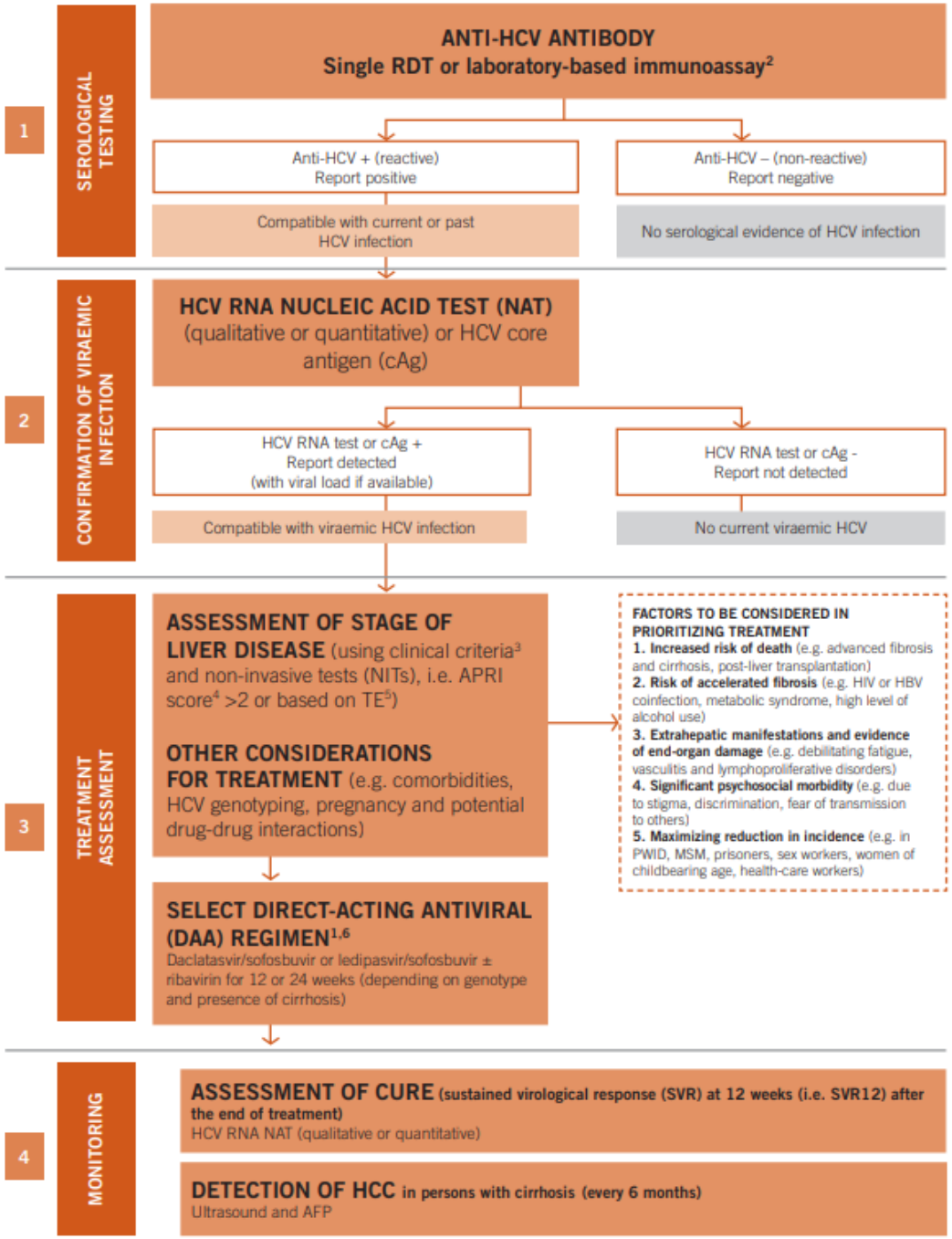
Image from: DECODE http://dgrc.com.np/hepatitis-c/

WHO HCV Testing guidelines; https://apps.who.int/iris/bitstream/handle/10665/254621/9789241549981-eng.pdf?sequence=1



1. Single test for 'screening'
2. Prompt blood draw for test to see if the person has viremia
3. Determine liver staging using non-invasive tests
   - Treat all with pangenotypic regimens
4. One test of cure at 12 weeks after completion of treatment

Serological testing for HCV



1

Single assay: laboratory testing (EIA/CIA) or quality-assured RDT

Serological tests (also called serological assays), tests that screen for HCV

Serological assays:

- Assays that detect the presence of either antigens or antibodies, typically in serum or plasma but also in capillary/venous whole blood and oral fluid. These include rapid diagnostic tests (RDTs), and laboratory-based immunoassays, e.g. enzyme immunoassays (EIAs)

Rapid diagnostic test (RDT)

- Immunoassays that detect antigen or antibodies and can give a result in less than 30 minutes.

Enzyme immunoassay (EIA)

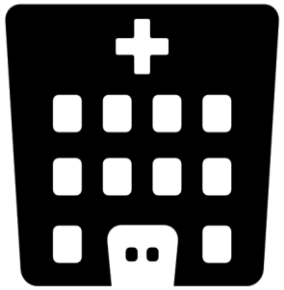
- Immunoassays that detect antigen or antibodies

Screening for HCV

Centralized settings

Dried Blood Spots

Decentralized settings



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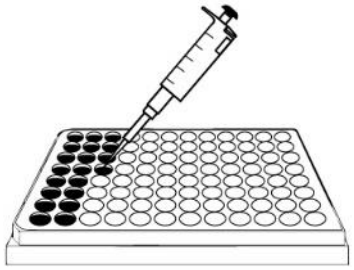
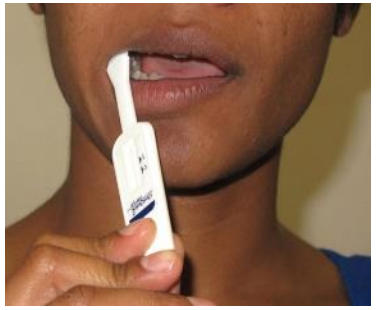




EIA

CIA

RDT
(blood-based)

RDT
(oral fluid-based)

Settings: well-equipped lab

Operator: qualified lab technician

Specimen type: plasma, serum

Turnaround time: >2 hours

Settings: primary facility

Operator: trained healthcare worker

Specimen type: capillary blood, oral fluid

Turnaround time: 5-20 min

Hepatitis C antibody Rapid Diagnostic Test (RDT) that are WHO PQ'd

Product name	Manufacturer	Performance*	Sample type	WHO PQ?	Stringent Regulatory Authority	List (USD)
Rapid Anti-HCV Test	InTec PRODUCTS, INC	Sens: 99.2% Spec: 99.1% in mono-infected Sens: 91.7% Spec: 99.2% in HIV-co-infected	Serum/Plasma /Whole Blood	Yes	RoW	1.6 to 2.4
SD BIOLINE HCV	Standard Diagnostics, Inc.	Sens: 99.5% Spec: 99.6% in mono-infected Sens: 88.6% Spec: 99.7% in HIV-co-infected	Serum/Plasma /Whole Blood	Yes	RoW	1 to 2.4
OraQuick® HCV Rapid Antibody Test Kit	OraSure Technologies, Inc.	Sens: 99.5% Spec: 99.6% in mono-infected Sens: 89.4% Spec: 99.4% in HIV-co-infected	Serum/Plasma /Whole Blood/Body Fluids	Yes	CE mark	8 (MSF Access price) 14 (on US market)
First Response® HCV Card Test	Premier Medical Corporation Pvt. Ltd., Nani Daman, India	Sens: 99.5% Spec: 100% in mono-infected Sens: 90.5% Spec: 99.7% in HIV-co-infected	Serum/Plasma /Whole Blood	No-ERPD	CE mark	.60 to 1

* FIND 2019, publication forthcoming

HCV EIA, WHO PQ'd

Product name	Manufacturer	Sample type	WHO PQ?	Stringent Regulatory Authority
ARCHITECT HCV Ag assay**	Denka Seiken Co., LTD, Kagamida Factory	Serum/Plasma	Yes	CE mark
INNOTEST HCV Ab IV	Fujirebio Europe NV	Serum/Plasma	Yes	CE mark
INNO-LIA HCV Score	Fujirebio Europe NV	Serum/Plasma	Yes	CE mark
Murex anti-HCV (version 4.0)	DiaSorin South Africa (Pty) Ltd.	Serum/Plasma	Yes	RoW
*Bioelisa HCV 4.0	Biokit S.A.	Serum/Plasma	Yes	CE mark

** ARCHITECT HCV Ag assay can be used for confirmation of viraemia, the other tests on this list can be used to determine presence of HCV antibodies

Self-testing (serology)

HCV self-testing

Currently available data on HCV self-testing is very limited

- One published report investigates acceptability of HCV self-testing among persons who inject drugs in the UK (Guise et al. 2018).
  - The study showed potential acceptability but also revealed multiple concerns associated with self-testing, primarily poor access to confirmatory testing and care.

- Another published study by Kimble and colleagues (2019) assessed the performance of OraQuick® HCV Rapid Antibody Test (Orasure Technologies, Inc., Bethlehem, PA) on oral fluid specimens when used by patients for self-testing.
  - The study included 95 participants and showed 88.4% sensitivity and 100% specificity of the test when used for self-testing compared to manufacturer-reported 98.1% and 99.6% when used by a professional healthcare provider (http://orc.orasure.com/default.aspx?pageid=1475).
  - Participants found testing procedure easy but reported some difficulties in interpreting test results. It is important to note that in this study graphical instructions for use were not provided by a test manufacturer but developed by the study team.

HCV self-testing: pilot feasibility study

A project funded by Unitaid
Innovation in Global Health

- Objectives: determine acceptability and usability of HCV self-testing
- Several countries in different geographic regions:

Country	Settings	Population	Status
Egypt	District hospital (ALPC)	General population	Completed
China	CBO	MSM	Ongoing
Kenya	CBO	PWID	In preparation
Georgia	Harm reduction centers, PreP clinics	PWID, MSM	In preparation
Vietnam	CBO	PWID, MSM	In preparation

- 100-200 participants per site
- OraSure HCV Rapid diagnostic test adapted by the manufacturer for self-testing (research use only)

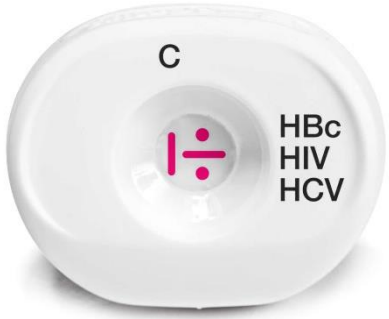
Combo testing (serology)

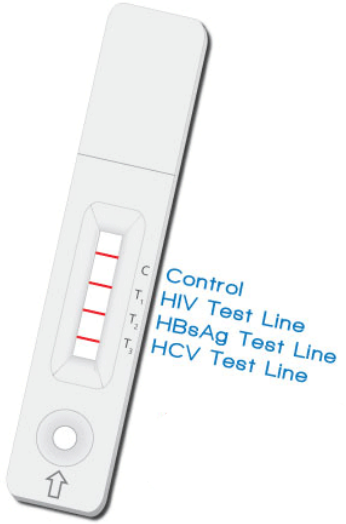
Multiplex serology testing (combo tests)

6.4.2 Integrating the diagnosis of hepatitis with diagnostic platforms and laboratory services used for other infections

Combination integrated multidisease serological tests

The use of combination integrated blood- or oral-based multidisease assays allow for integrated testing of HIV, HBV and HCV. Using a single specimen improves the efficiency of testing programmes, especially in populations with a high prevalence of HIV/HCV or HBV/HCV coinfection. While not yet fully validated, preliminary results of these combination assays appear promising *(160)*.



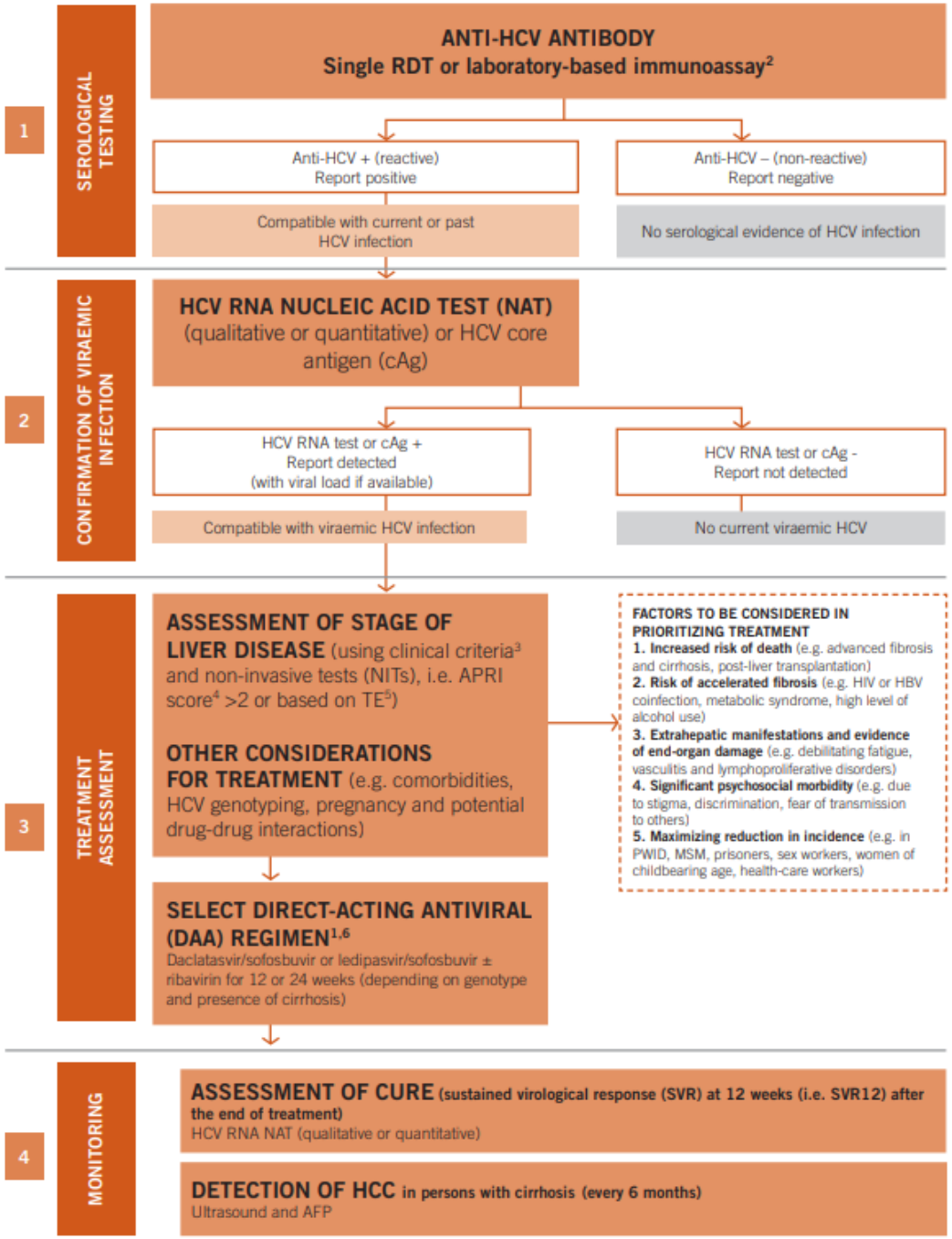


Multiplex serology testing (combo tests)

Test	Manufacturer	Detection			Regulatory status (SRA)
		HBV	HCV	HIV	
Detect 3 HIV/HCV/HBV combo kit	Artron Laboratories (Canada)	X	X	X	CE (plasma, serum)
Triplex HIV, HCV, HBsAg	Biosynex (France)	X	X	X	NA
Hep B, Hep C, HIV Combination Rapid Test	Maternova (US)	X	X	X	NA
Multiplo HBc/HIV/HCV	MedMira (Canada)	X	X	X	RUO
HBsAg/HCV Ab Rapid Test	Spectrum Diagnostics (Egypt)	X	X		NA
Rapid HBsAg/HCV/HIV/Syphlis Combo	Euro Genomas (Lithuania)	X	X	X	CE
OnSite HBsAg/HCV Ab Rapid Test	CTK Biotech (US)	X	X		NA
COMBIQUIC HIV/HCV	Qualpro Diagnostics (India)		X	X	NA
TriQuick HIV/HCV/HCV	Genlantis Diagnostics	X	X	X	NA

Field validation is needed to assess diagnostic accuracy of these tests

Diagnosis of hepatitis C virus: confirmation of active infection



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Prompt or reflex HCV RNA or HCV core Ag testing

Confirmation of viremia for HCV

Centralized settings

Dried Blood Spots

Decentralized settings

Currently off-label;

needs field validation

HCV RNA

HCV core antigen test

HCV RNA

In development:

HCV core antigen RDT

Settings: well-equipped lab

Operator: qualified lab technician

Specimen type: plasma, serum

Turnaround time: >5 hours

Settings: district hospitals

Operator: trained healthcare worker

Specimen type: capillary blood/plasma

Turnaround time: 60-90 min

Each conventional molecular instrument possesses unique features, which need to be considered when defining the optimal device mix within a Lab Network

Instrument	Cobas 4800-6800-8800	CAP/CTM 96	m2000sp	Panther
Supplier	Roche	Roche	Abbott	Hologic
				
Assays	HIV (EID;VL);HPV;HCV; HBV; TB	HIV (EID;VL);HCV; HBV; TB	HIV (EID;VL);TB; HPV; HCV; HBV	HIV (EID; VL); HPV; HCV; HBV
HIV sample types	DBS; Plasma; PSC (VL)	DBS; Plasma	DBS; Plasma	DBS (VL) ; Plasma
HCV sample types	Plasma (PSC and DBS in the pipeline)	Plasma	Serum; Plasma (DBS in the pipeline)	Serum; Plasma (DBS in the pipeline)
Infrastructure Requirements				
Space requirements	1.8 m^2- 5.5 m^2, Fixed	3 m^2, Fixed	3.15. m^2, Fixed	1 m^2, Moveable
Human resources	1-2 FTEs/machine	1-2 FTEs/machine	1-2 FTEs/machine	1 FTE/<4 machines
Workflow Requirements				
Workflow	Batch	Batch	Batch	Random access
Throughput (8hr)	192-960	168	96	320
Time to first result (hr)	< 3.5	~5.5	~5.5	< 3.5

Dried blood spot (DBS)

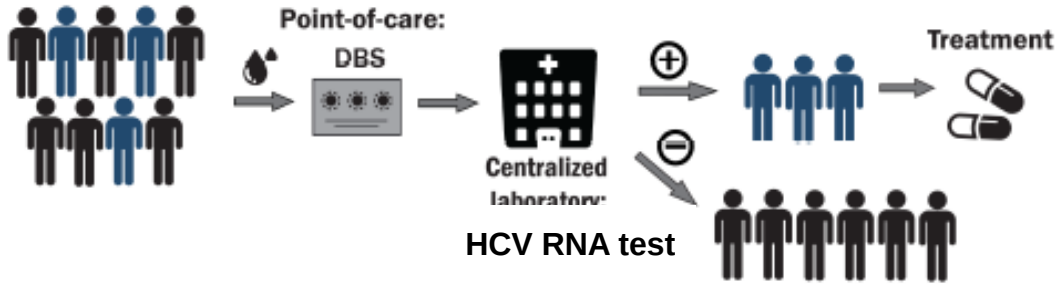
Validation of DBS sampling

A project funded by Unitaid
Innovation in Global Health

DBS sampling for HCV RNA test

Aim: provide HCV diagnostics in the settings with no access to laboratory infrastructure

Concept:



FIND study: multicenter diagnostics accuracy study to obtain evidence of the performance of HCV RNA tests from DBS/PSC (with the intention of data to be included to companies' regulatory dossiers)

- real-life conditions: RT transport and storage of DBS and PSC samples
- DBS and PSC processing using manufacturers' protocols
  - Abbott M2000
  - Roche cobas® 4800 and 6800 (PSC and DBS)
  - Hologic Panther

Study sites:

- Georgia
- Greece
- Cameroon
- Rwanda
- Australia (NRL – central testing)

Sample size: 415 HCV RNA positives, 415 HCV RNA negatives
Timeline: Q1 2019 – Q3 2019

Point of Care (POC) and near POC

Near-POC HCV RNA assays available on the market

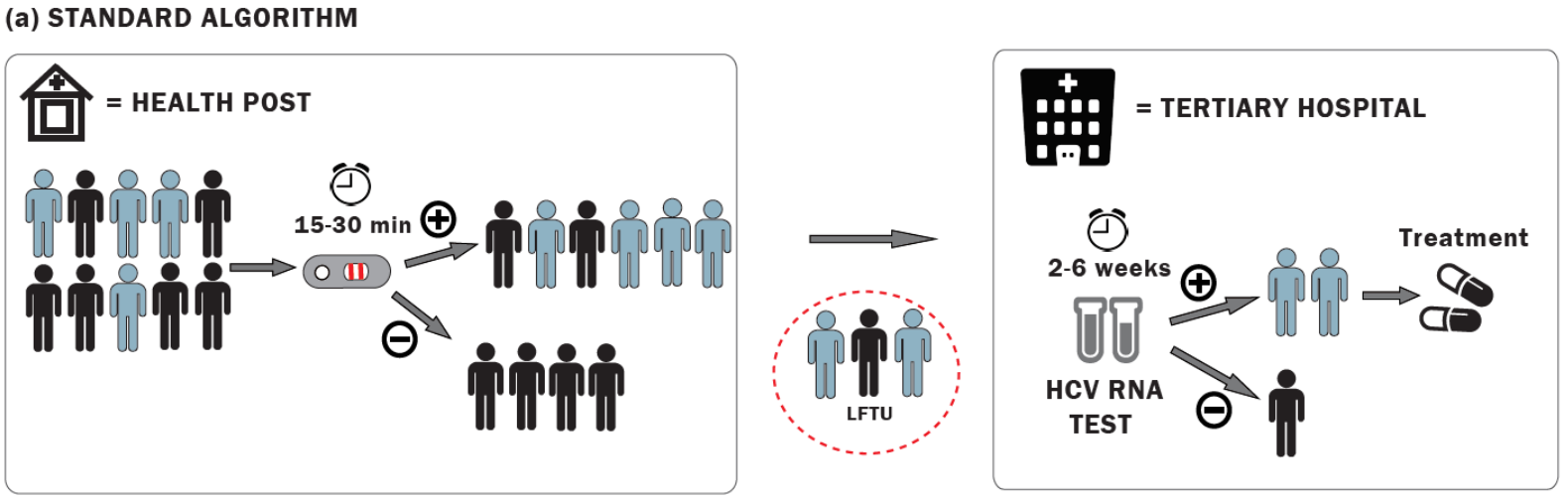
PLATFORM	Xpert HCV VL assay	Xpert HCV Fingerstick VL assay	GeneDrive HCV ID assay
			
SAMPLE TYPE	Plasma	Capillary blood	Plasma
SENSITIVITY	99%	98%	98%
SPECIFICITY	100%	100%	100%
SAMPLE PREPARATION	Integrated	Integrated	Off-board (several pipetting steps)
TIME TO RESULT	110 min	60 min	~120 min
REGULATORY STATUS	CE-IVD, WHO PQ	CE-IVD	CE-IVD
POWER SUPPLY	Need electricity supply		Need electricity supply
DATA ANALYSIS	PC		Integrated
TEST MENU	TB, HIV, HBV and many others		TB in development
TEST COST	US$ 14.95 ex works		Not disclosed
INSTRUMENT COST	US$ 17,500		Not disclosed

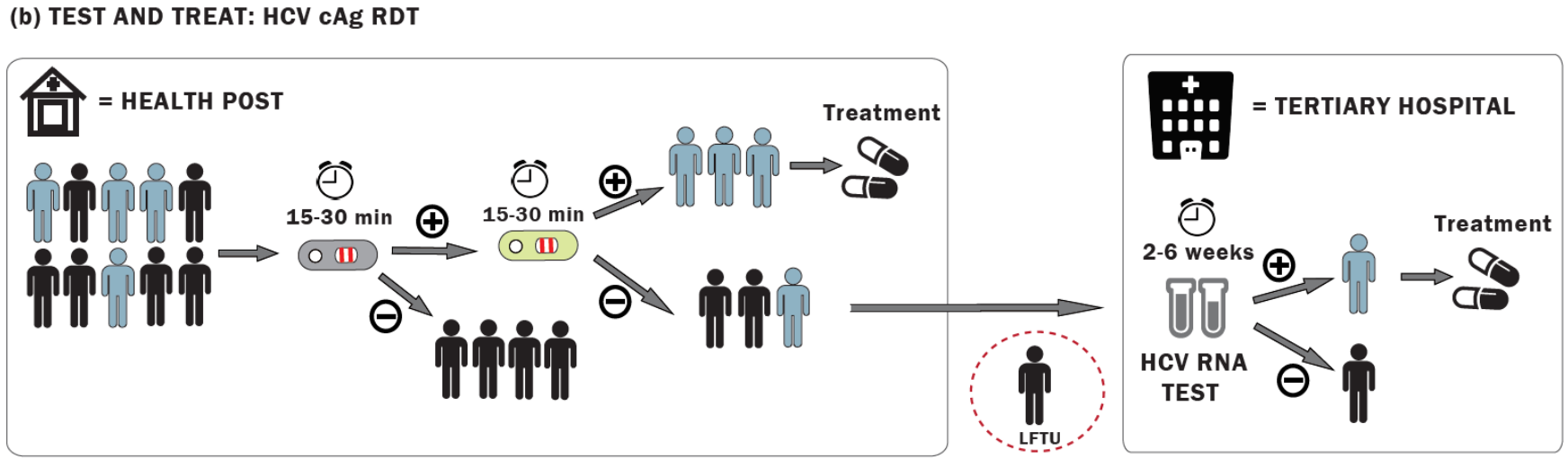
cAg RDT

HCV core Ag RDT concept

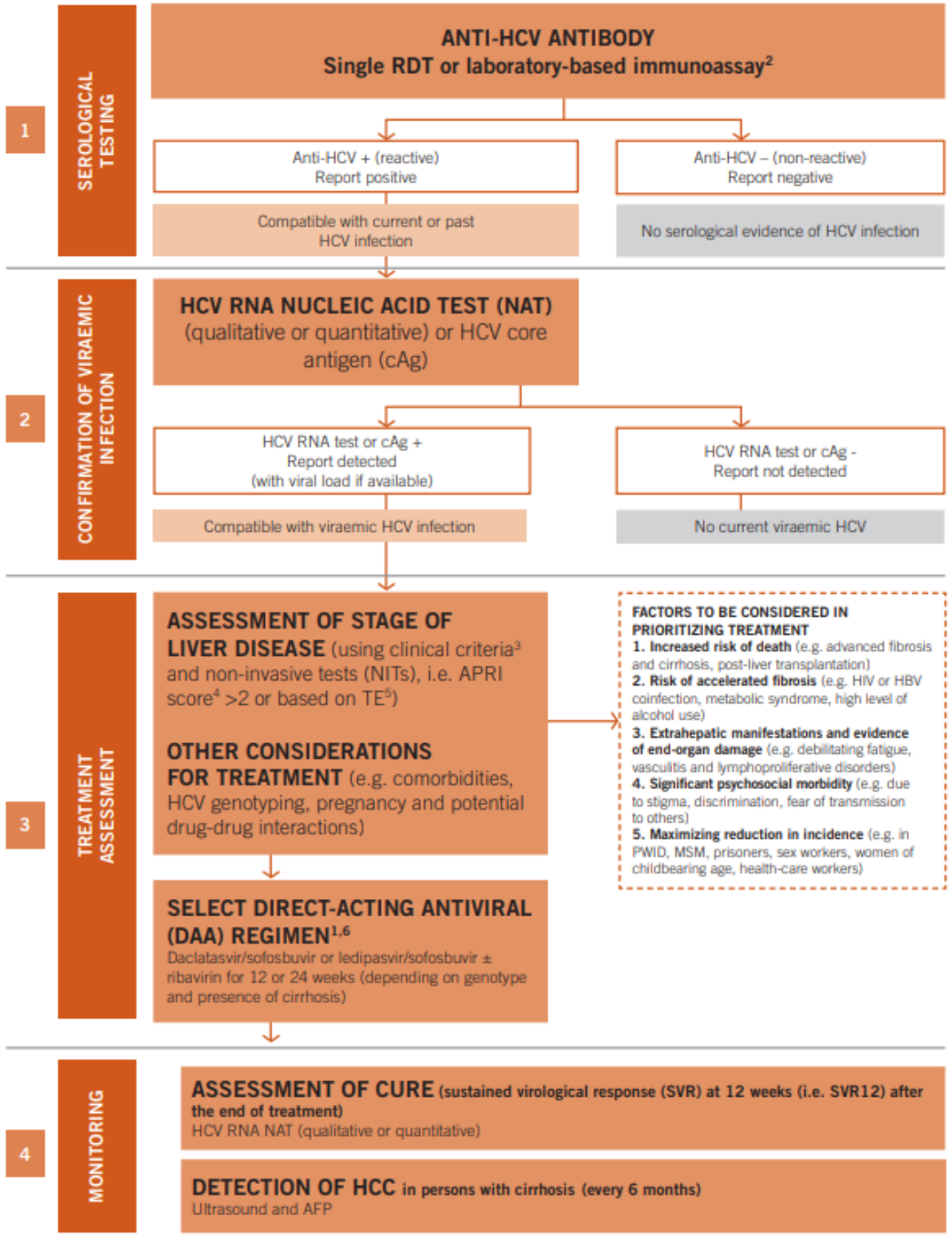
Main technical challenge: high analytical sensitivity requirements unlikely to be met in RDT format

HCV core Ag RDT will have 75-85% clinical sensitivity, but impact will likely outweigh suboptimal sensitivity





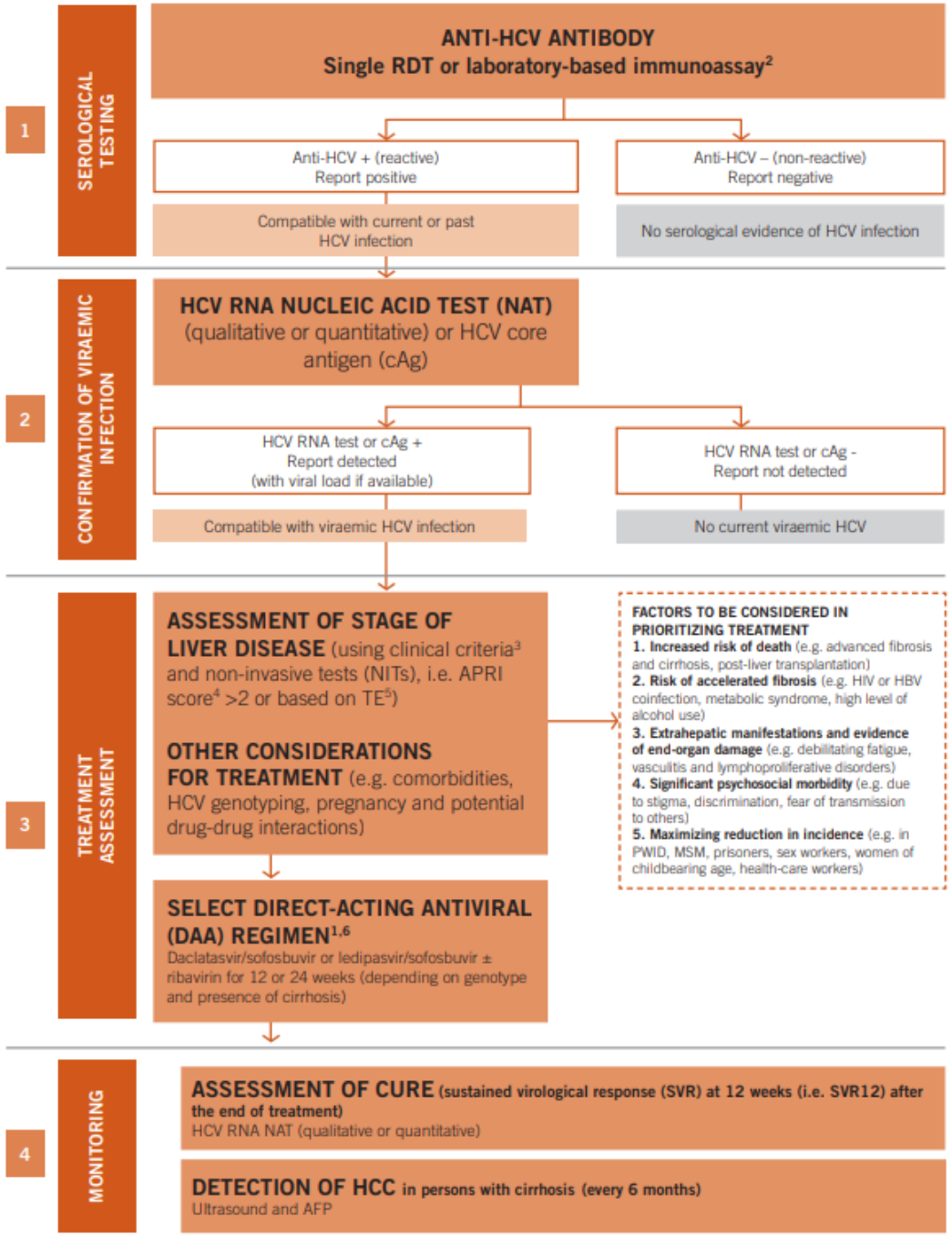
Liver staging



3 Assess and triage; Stage liver disease using NITs (APRI, FIB4, TE)

Existing liver staging options

Biochem	aspartate aminotransferase to platelet ratio index (APRI)	Uses blood test for a blood test to measure your aspartate aminotransferase (AST) and a platelet count	Machines needed to conduct the blood tests can usually be found at level 1 health centers. Is relatively inexpensive
	FIB4	Is a formula based on several laboratory tests: (Age x AST) / (Plts x (sqr (ALT))	
Fibroscan	Machine which can provide liver staging results		Machine is expensive Requires trained technician Is not widely available in all countries/contexts
Ultra sound	Can be used to provide liver staging results		While often machines are already in place for other services requires trained technician Wait times for ultrasound appointment can be long as other patient types may be prioritized (pregnant women)



4 One test of cure at 12 weeks after completion of treatment

HCV product pipeline

GeneDrive HCV test

2018

Q1 Q2 Q3 Q4

Xpert HCV FS (Cepheid)

2019

Q1 Q2 Q3 Q4

DBS HCV RNA
on Roche CAP/CTM
Abbott m2000
Hologic Panther

TrueNAT HCV (Molbio Dx)

HCV self-test

2020

Q1 Q2 Q3 Q4

SAMBA II HCV assay

2021

Q1 Q2 Q3 Q4

HCV cAg RDT

HCV test on BlinkOne (Blink Dx)

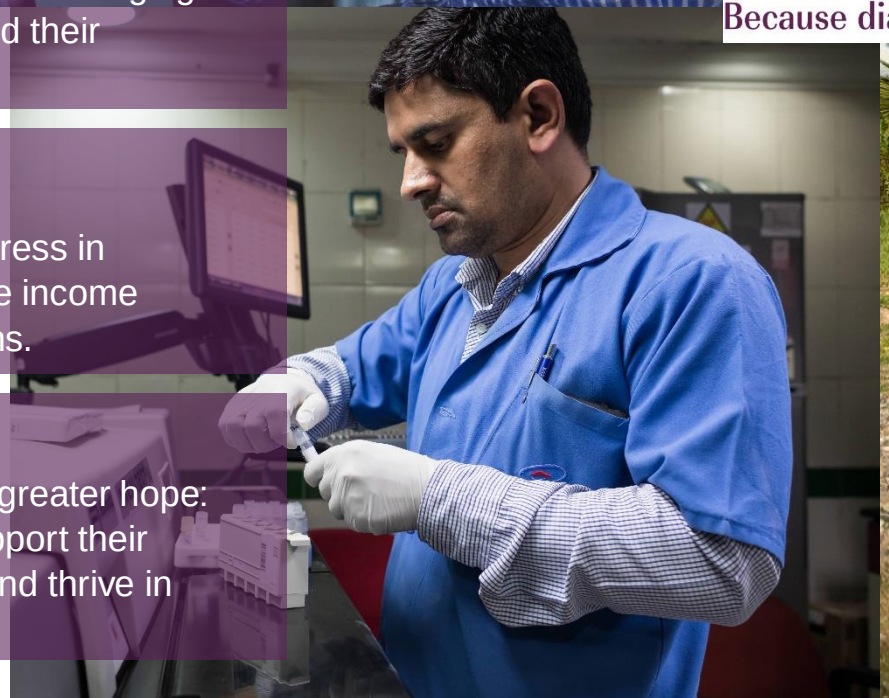
Thank you!

We believe

Simple, rapid, robust and affordable diagnostic solutions bring game-changing possibilities above and beyond their immediate benefit.

FIND

Because diagnosis matters



We believe

Our work can spark real progress in the health of lower and middle income countries and their populations.

We believe

With improved health comes greater hope: individuals empowered to support their families, revive businesses, and thrive in school.