HepHIV 2019
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Testing as part of HCV elimination strategies: Finding the missing millions

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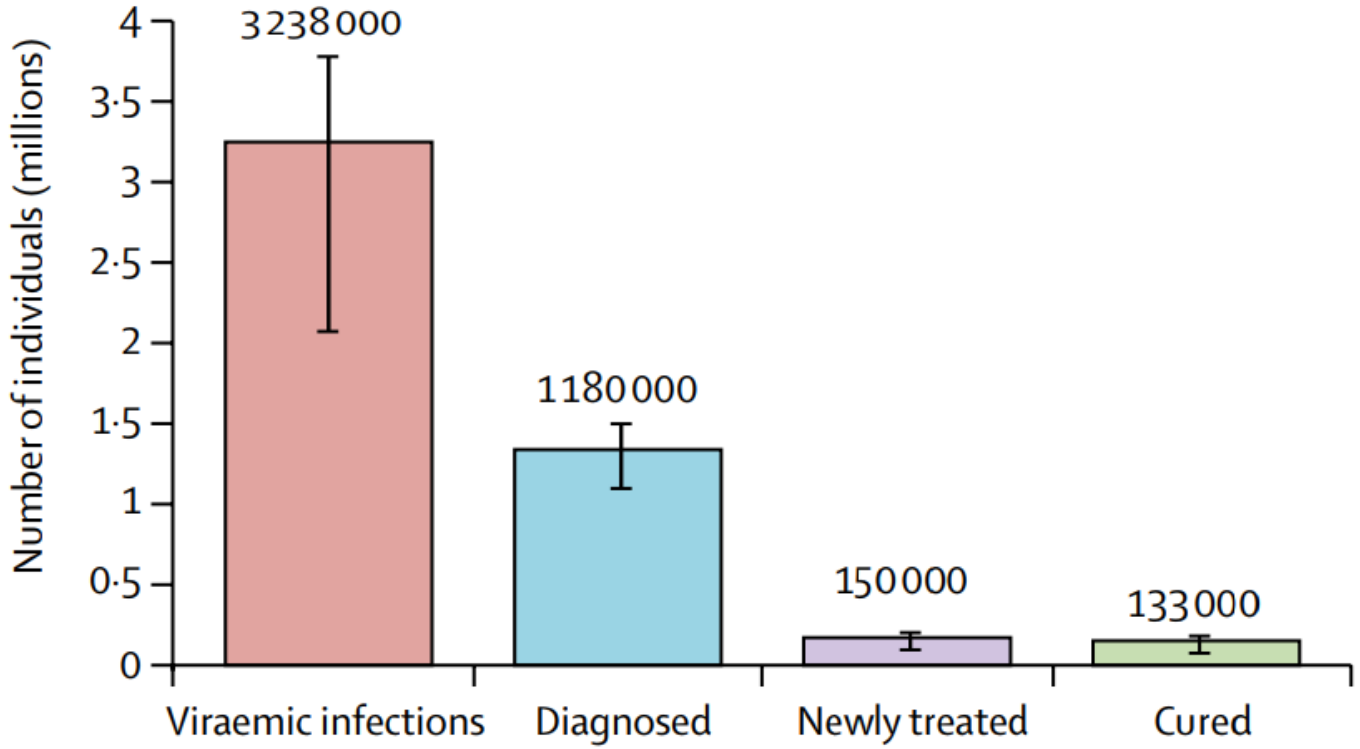
The HCV continuum of care in Europe (2015)



Lancet Gastroenterol Hepatol 2017;2:325-336

Testing: a mainstay of the EASL HCV elimination strategy

- ***Rapid point-of-care tests*** (including for viremia) should be implemented
- Screening should include HIV and hepatitis B virus
- Priority should be given to persons engaging in high-risk practices
- Screening strategies other than risk-based should be evaluated at the single country level, supported by cost-effectiveness and feasibility analyses
- Countries should avoid late presentation and diagnosis by fostering decentralized testing (addiction services, prisons, communities)

EASL Policy Statement on HCV elimination (in preparation)

How to test: the HCV diagnosis involves two steps

Screening for HCV infection is presently based on the detection of

anti-HCV antibodies

Rapid diagnostic tests (RDTs) using serum, plasma, fingerstick whole blood or crevicular fluid (saliva) can be used instead of classical EIA to facilitate anti-HCV antibody screening and improve access to care

Whole blood sampled on ***dried blood spots*** can be used as an alternative to serum or plasma obtained by venepuncture

Active infection is confirmed by

serum HCV RNA or HCV Ag detection

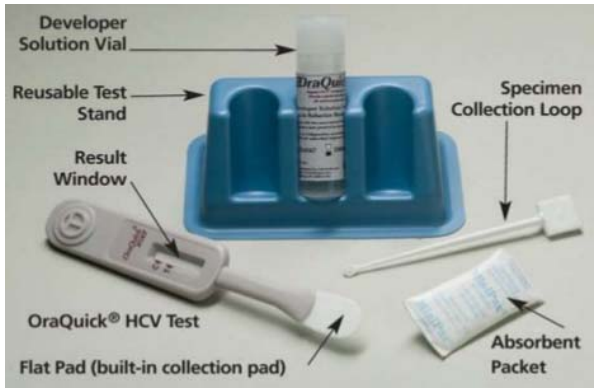
EASL Recommendations on Treatment of Hepatitis C 2018. J Hepatol 2018;69:461-511

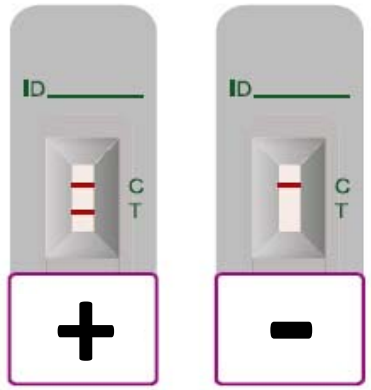
Anti-HCV Rapid Diagnostic Test: the OraQuick™

- Simple, non-instrumented, rapid (20 min), point-of-care test developed by OraSure Technologies Inc. (Bethlehem, PA, USA)
- Can be used on serum, whole venous blood, fingerstick blood or crevicular fluid
- Sensitivity is 97.8-99.2% (saliva), 100% (serum), specificity is 100%

LEE *et al,* J Virol Methods. 2011;172:27–31; CHA *et al,* Ann Lab Med 2013;33:184-9

- Licensed by FDA for use on whole blood (2010) or fingerstick blood (2011)
- WHO prequalified





http://www.who.int/diagnostics_laboratory/evaluations/pq-list/hcv/170301_final_pq_report_PQDx_0244_055_00.pdf?ua=1

Performance of HCV RDTs: a meta-analysis

(N=18 studies [1994-2001]; 4,126 whole blood (venous and capillary) and 4,259 saliva specimens)

Specimen	Specificity	Sensitivity
Whole blood	99.5%	98.9%
Saliva	98.2%	97.1%

SHIVKUMAR *et al,* Ann Intern Med 2012;157:558-66

Performance of anti-HCV rapid diagnostic test kits

Anti-HCV rapid diagnostic test kits	Panel	Sensitivity (95% CI)	Specificity (95% CI)
Alere Truline (Product code: 11304191030)	Indian	100% (96.9%-100%)	100% (98.5%-100%)
	US-CDC	97.5% (86.5%-99.9%)	100% (94%-100%)
	Overall	99.4% (96.6%-99.9%)	100% (98.8%-100%)
Flaviscreen (Product code: 402170050)	Indian	88.3% (81.2%-93.5%)	100% (98.5%-100%)
	US-CDC	80% (64.4%-90.9%)	100% (94%-100%)
	Overall	86.3% (79.9%-91.2%)	100% (98.8%-100%)
Advanced Quality (Product code: ITP01151-TC40)	Indian	95.8% (90.5%-98.6%)	100% (98.5%-100%)
	US-CDC	97.5% (86.8%-99.9%)	100% (94%-100%)
	Overall	96.3% (91.9%-98.6%)	100% (98.8%-100%)
SD Bioline (Product code: 02FK10)	Indian	100% (96.9%-100%)	100% (98.5%-100%)
	US-CDC	97.4% (86.5%-99.9%)	100% (94%-100%)
	Overall	99.4% (96.6%-99.9%)	100% (98.8%-100%)
OraQuick (Product code: 0006656483)	Indian	100% (96.9%-100%)	100% (98.5%-100%)
	US-CDC	97.4% (86.5%-99.9%)	100% (94%-100%)
	Overall	99.4% (96.6%-99.9%)	100% (98.8%-100%)

MANE *et al,* PLoS One 2019 Jan 17;14:e0210556

Whom to test: screening strategies

Risk-based

- Efficient where infection is mostly restricted to high-risk settings (e.g. Iceland)

Birth cohort

- Requires robust epidemiological data
- Should allow identifying a substantial proportion of those infected
- May be cost-effective in most patients' subgroups (depends on drug prices)

REIN *et al,* Ann Intern Med 2012; SMITH *et al,* MMWR Recomm Rep 2012

- May fail to identify older patients, at higher risk of advanced fibrosis due to long duration of infection

General population

- Requires the largest financial commitment
- Cost-effective if coupled to treatment with discounted DAA

YOUNOSSI *et al,* Liver Int 2017; RATTAY *et al,* Gastroenterology 2017

- Requires the set-up of a national registry

HCV cascade of care in the OST setting (Aargau, Switzerland)

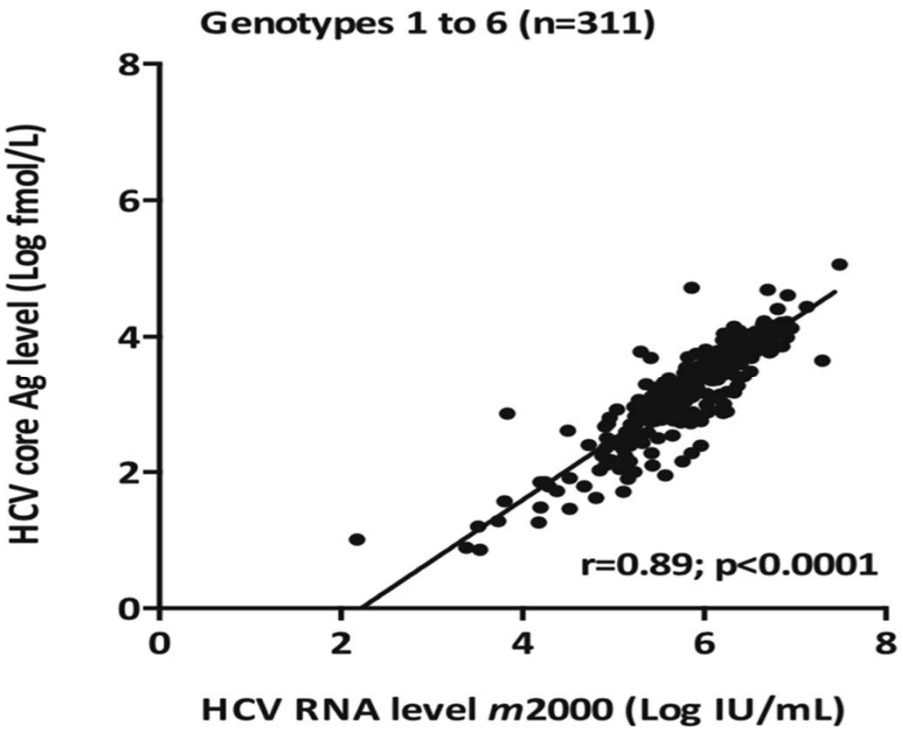
- Questionnaires sent to 161 physicians treating 631 OST patients
- Among the only 205 (32.5%) patients recruited (as of July 2015):
  - ***49 (24%) had never been screened for HCV***
  - 18/95 (19%) of those anti-HCV+ had never been tested for HCV RNA
  - 12/61 (20%) with chronic hepatitis C had never been genotyped
  - 32/61 (53%) had never undergone a liver biopsy
  - 33/61 (54%) had never been treated for HCV, and those treated had never received DAA (even though available since August 2014)

BREGENZER *et al,* Swiss Med Wkly 2017;147:w14544

Why testing for anti-HCV is not the ultimate solution

- **It requires confirmation of ongoing infection by testing for HCV-Ag or HCV RNA**
- **It requires linkage to specialized care**
- **Both steps decrease the retention in care**

Relationship between HCV Core Ag and HCV RNA Levels



- Analytical sensitivity corresponding to ~500-3000 IU/mL of HCV RNA
- Rare false negatives (core Ag-negative, HCV RNA-positive)

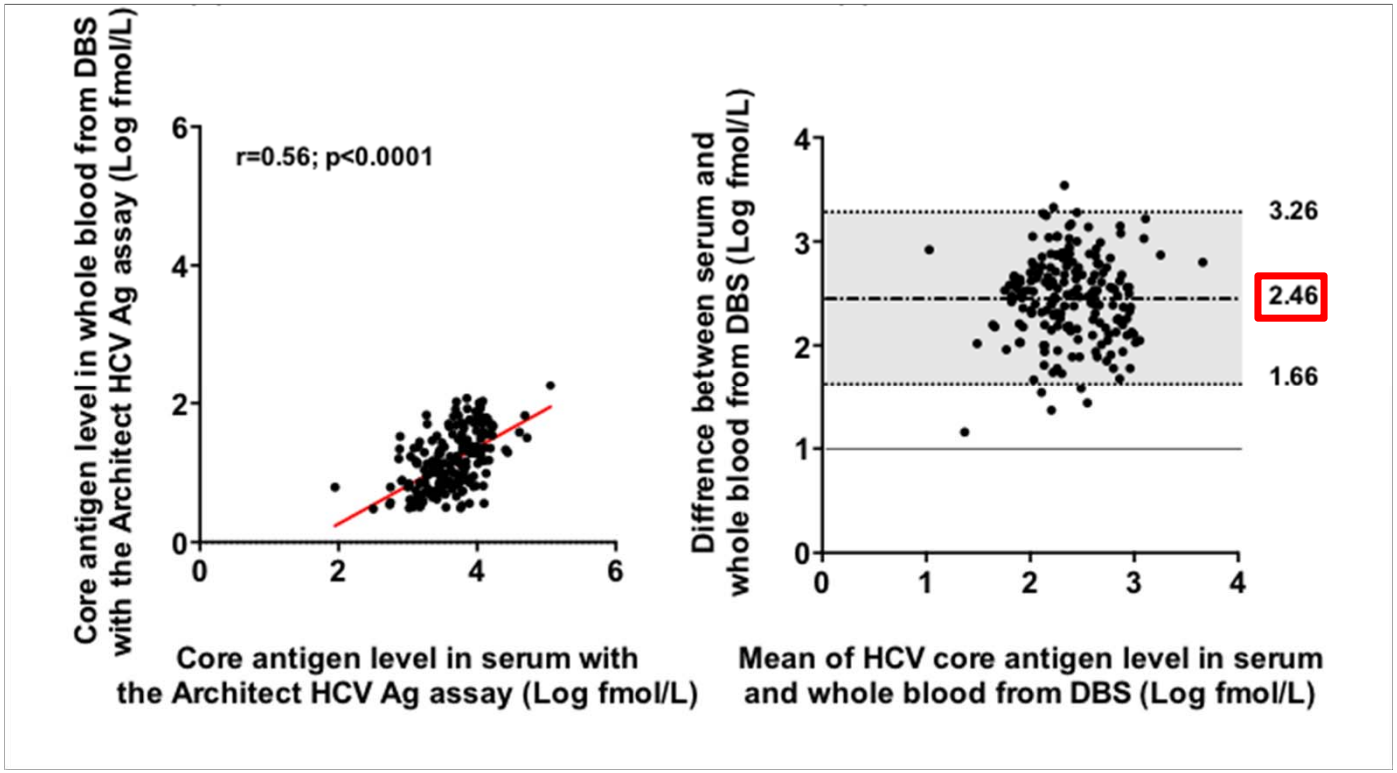
CHEVALIEZ *et al,* J Clin Virol 2014;61:145-8

- Pre-seroconversion panel: 100% sensitivity
- Post-seroconversion panel: sensitivity 94.3%

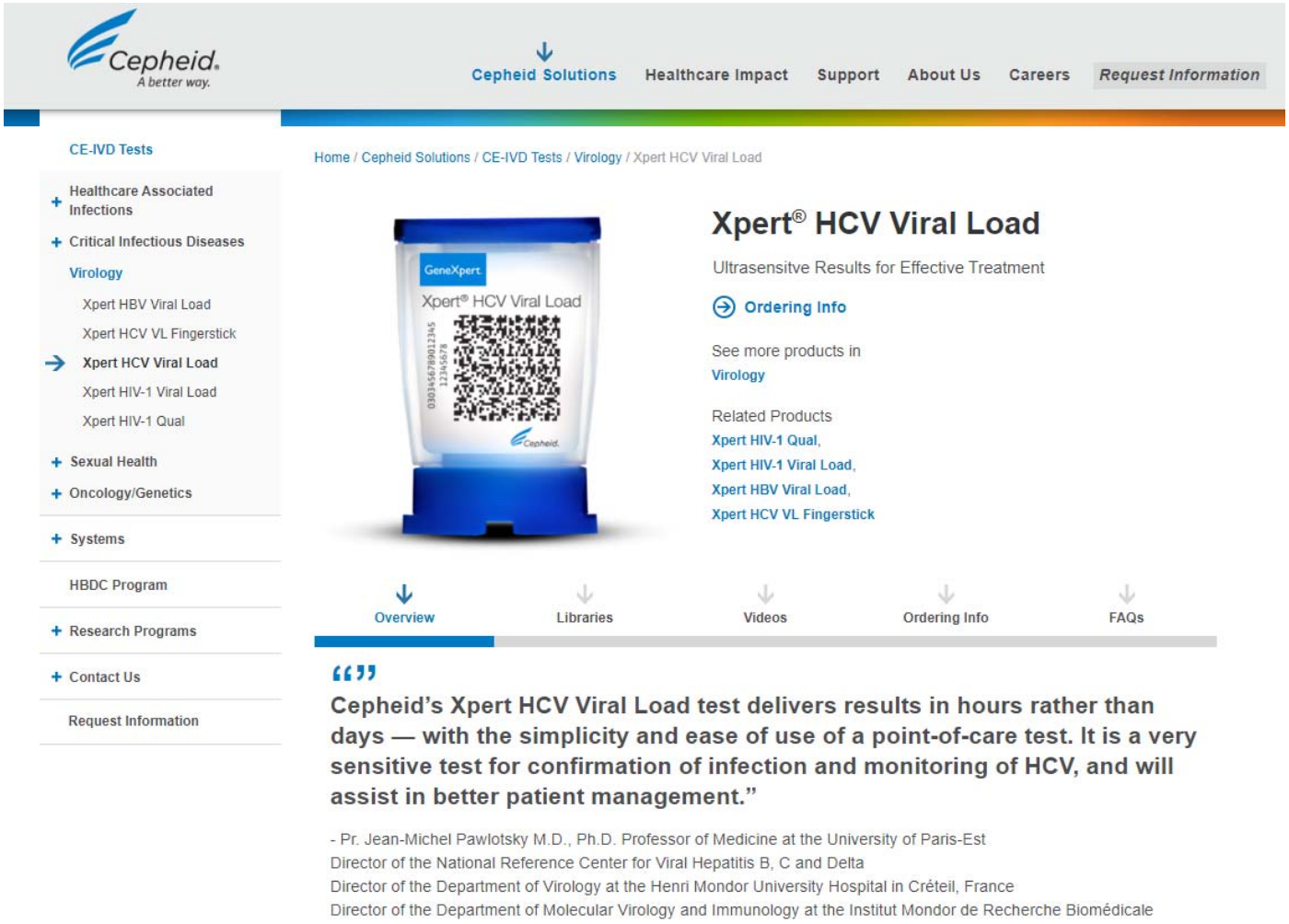
MIXSON-HAYDEN *et al,* J Clin Virol 2015;66:15-8

Recommended by EASL !

HCV Core Antigen from Dried Blood Spot



SOULIER *et al,* J Infect Dis 2016;213:1087-95

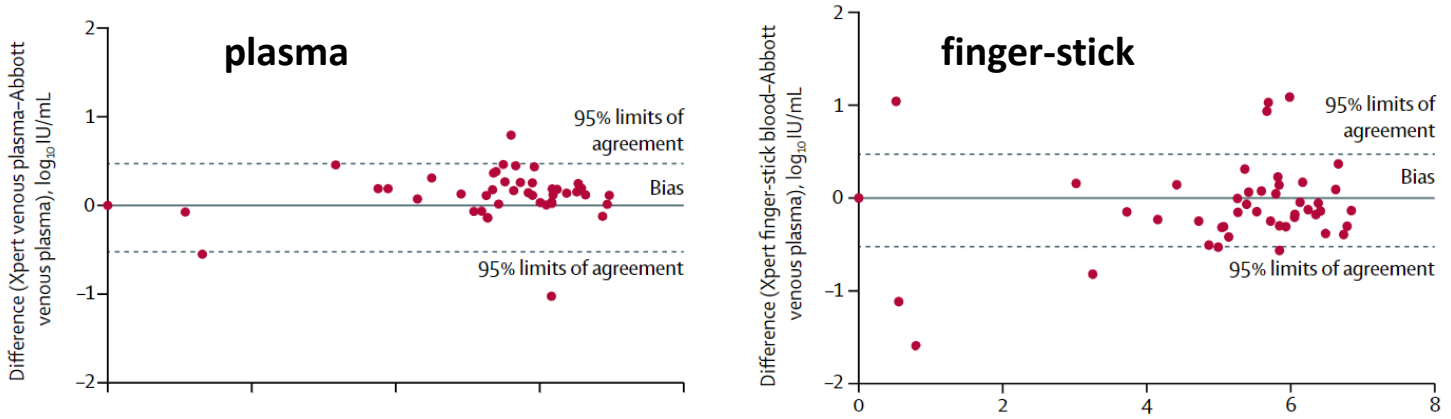


LOD 4.0 UI/mL (plasma)
LOD 6.1 UI/mL (serum)
No requirements for strict PCR room settings
1-min hands-on
90-min hands off
345 viral load results/8 h

POC Xpert assay (Cepheid) detects HCV RNA on a finger-stick sample

(LiveRLife open observational cohort study)

- 100 µl of capillary whole blood, ~90 min hands-off processing time
- 150 individuals tested, 45 with HCV RNA detectable in plasma by Abbott RealTime



	Specificity	Sensitivity
Plasma	**99.1%**	**100%**
Fingerstick capillary whole blood	**98.1%**	**95.5%**

GREBELY *et al,* Lancet Gastroenterol Hepatol 2017;2:514-20

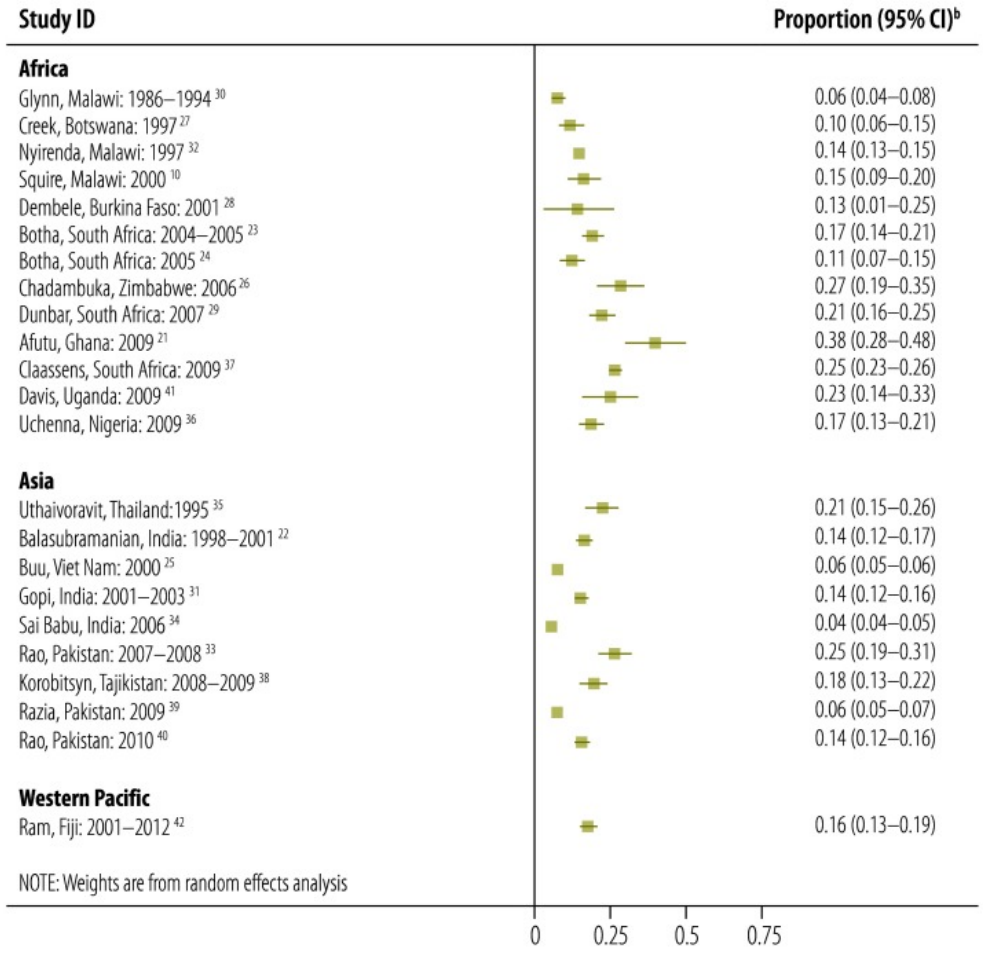
The future

The ideal HCV management of the future: simplification

- Should not require referral hospitals (**decentralization**)
- Should not require refrigeration of samples and/or reagents
- Should rely on **task shifting** to mid-level, specially trained providers
- **Same-day** diagnosis and treatment delivery, to ensure retention in care
- Should not miss subgroups with clinically significant complications (cirrhosis, HCC, extrahepatic manifestations)

Centralized lab diagnostics is responsible for pre-treatment loss to FU

A meta-analysis on tuberculosis



n=34,706 smear- or culture-positive TB patients from 14 low- or lower-middle-income or high-burden countries

4-38% pre-treatment loss to FU

MACPHERSON *et al,* Bull World Health Organ 2014;92:126-38

Starting treatment the same day as the diagnosis is possible

A lesson learned from the HIV field

PLOS | MEDICINE

RESEARCH ARTICLE

Initiating Antiretroviral Therapy for HIV at a Patient's First Clinic Visit: The RapIT Randomized Controlled Trial

Sydney Rosen[1,2]*, Mhairi Maskew[2], Matthew P. Fox[2,3], Cynthia Nyoni[2], Constance Mongwenyana[2], Given Malete[2], Ian Sanne[2], Dorah Bokaba[4], Celeste Sauls[2], Julia Rohr[1], Lawrence Long[2]

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OPEN ACCESS

Citation: Rosen S, Maskew M, Fox MP, Nyoni C, Mongwenyana C, Malete G, et al. (2016) Initiating Antiretroviral Therapy for HIV at a Patient's First Clinic Visit: The RapIT Randomized Controlled Trial. PLoS Med 13(5): e1002015. doi:10.1371/journal.pmed.1002015

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Data Availability Statement: Data will be made publicly available in the Dryad repository (http://www.datadryad.org/) after the protocol has been closed (anticipated closure June 2018). Until then, data will remain under the supervision of the University of the Witwatersrand Human Research Ethics Committee (HREC). Requests should be sent to the HREC Research Administrator at: https://www.wits.ac.za/research/about-our-research/ethics-and-research-integrity/human-research-ethics-committee-medical/.

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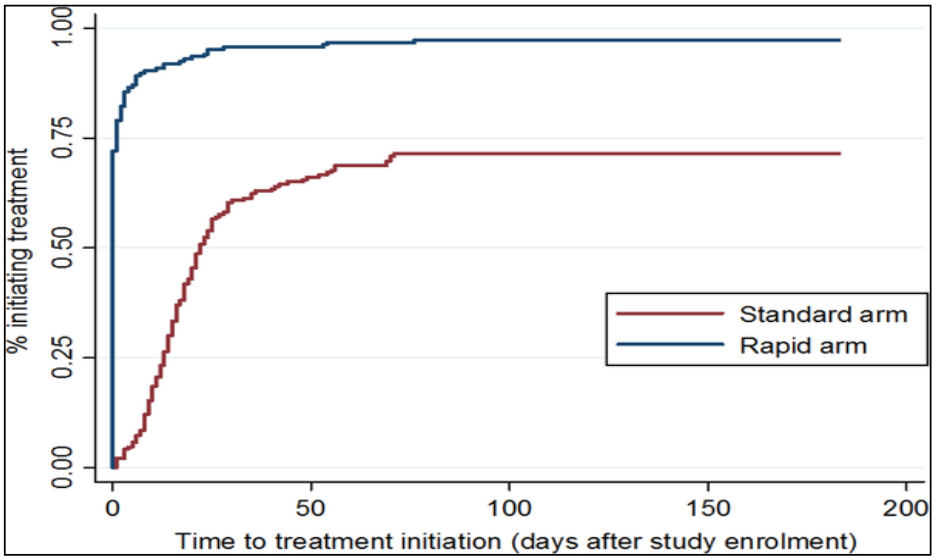
Abstract

Background

High rates of patient attrition from care between HIV testing and antiretroviral therapy (ART) initiation have been documented in sub-Saharan Africa, contributing to persistently low CD4 cell counts at treatment initiation. One reason for this is that starting ART in many countries is a lengthy and burdensome process, imposing long waits and multiple clinic visits on patients. We estimated the effect on uptake of ART and viral suppression of an accelerated initiation algorithm that allowed treatment-eligible patients to be dispensed their first supply of antiretroviral medications on the day of their first HIV-related clinic visit.

Methods and Findings

RapIT (Rapid Initiation of Treatment) was an unblinded randomized controlled trial of single-visit ART initiation in two public sector clinics in South Africa, a primary health clinic (PHC) and a hospital-based HIV clinic. Adult (≥18 y old), non-pregnant patients receiving a positive HIV test or first treatment-eligible CD4 count were randomized to standard or rapid initiation. Patients in the rapid-initiation arm of the study ("rapid arm") received a point-of-care (POC) CD4 count if needed; those who were ART-eligible received a POC tuberculosis (TB) test if symptomatic, POC blood tests, physical exam, education, counseling, and antiretroviral (ARV) dispensing. Patients in the standard-initiation arm of the study ("standard arm") followed standard clinic procedures (three to five additional clinic visits over 2–4 wk prior to ARV dispensing). Follow up was by record review only. The primary outcome was viral suppression, defined as initiated, retained in care, and suppressed (≤400 copies/ml) within 10 mo of study enrollment. Secondary outcomes included initiation of ART ≤90 d of study enrollment, retention in care, time to ART initiation, patient-level predictors of primary



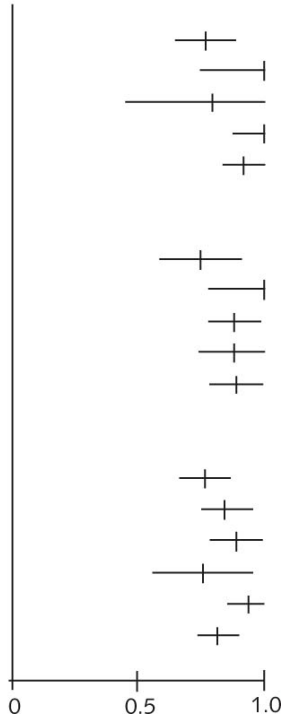
WHO recommendation (July 2017)

Consider same day start

Task shifting to community-based non-specialist providers

- Three hour education and training
- Overall SVR12 following sofosbuvir/ledipasvir was 87%
- No difference by provider type: Nurse Practitioners, 90%; Primary Care Physicians, 88%; Specialists, 85%

Provider	SVR Rate	Patients With SVR/ Total Patients, *n/N*
NPs		
NP 1	0.77	33/43
NP 2	1.00	12/12
NP 3	0.80	4/5
NP 4	1.00	30/30
NP 5	0.92	55/60
PCPs		
PCP 1	0.75	24/32
PCP 2	1.00	19/19
PCP 3	0.88	43/49
PCP 4	0.88	21/24
PCP 5	0.89	32/36
Specialists		
Specialist 1	0.77	47/61
Specialist 2	0.85	50/59
Specialist 3	0.89	34/38
Specialist 4	0.76	13/17
Specialist 5	0.94	35/37
Specialist 6	0.82	64/78



KATTAKUZHY et al, Ann Intern Med 2017

2005

2013

credit: nbcnews.com

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REPORTS | DIAGNOSTICS

A smartphone dongle for diagnosis of infectious diseases at the point of care

Tassaneewan Laksanasopin[1,*], Tiffany W. Guo[1,*], Samiksha Nayak[1], Archana A. Sridhara[1], Shi Xie[1], Owolabi O. Olowookere[1], Paolo Cadinu[1], Fanxing Meng[1], Natalie H. Chee[1], Jiyoon Kim[1], Curtis D. Chin[1], Elisaphane Munyazesa[2], Placidie Mugwaneza[3], Alex J. Rai[4], Veronicah Mugisha[2], Arnold R. Castro[5], David Steinmiller[6], Vincent Linder[6], Jessica E. Justman[7], Sabin Nsanzimana[3] and Samuel K. Sia[1,†]

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* These authors contributed equally to this work.

Science Translational Medicine 04 Feb 2015:
Vol. 7, Issue 273, pp. 273re1
DOI: 10.1126/scitranslmed.aaa0056

Antibody assay: HIV, syphilis
2 μl of blood by fingerprick
Sensitivity 92%
Specificity 79-100%
15 minutes
1.6 mW per test
Audio jack powered
1.4 USD per triplex

SCIENTIFIC REPORTS

OPEN

Novel pH sensing semiconductor for point-of-care detection of HIV-1 viremia

Received: 16 March 2016
Accepted: 11 October 2016
Published: 10 November 2016

R. Gurrala[1], Z. Lang[2], L. Shepherd[2], D. Davidson[2], E. Harrison[2], M. McClure[1], S. Kaye[1], C. Toumazou[2,3] & G. S. Cooke[1]

The timely detection of viremia in HIV-infected patients receiving antiviral treatment is key to ensuring effective therapy and preventing the emergence of drug resistance. In high HIV burden settings, the cost and complexity of diagnostics limit their availability. We have developed a novel complementary metal-oxide semiconductor (CMOS) chip based, pH-mediated, point-of-care HIV-1 viral load monitoring assay that simultaneously amplifies and detects HIV-1 RNA. A novel low-buffer HIV-1 pH-LAMP (loop-mediated isothermal amplification) assay was optimised and incorporated into a pH sensitive CMOS chip. Screening of 991 clinical samples (164 on the chip) yielded a sensitivity of 95% (*in vitro*) and 88.8% (on-chip) at >1000 RNA copies/reaction across a broad spectrum of HIV-1 viral clades. Median time to detection was 20.8 minutes in samples with >1000 copies RNA. The sensitivity, specificity and reproducibility are close to that required to produce a point-of-care device which would be of benefit in resource poor regions, and could be performed on an USB stick or similar low power device.

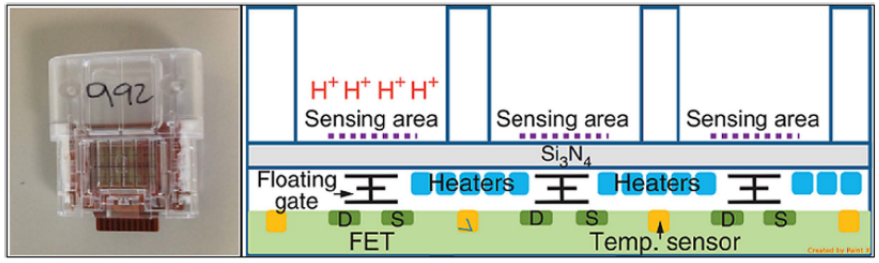

Figure 1. (a) Image of prototype chip for amplification and detection of nucleic acids compatible with a USB port. (b) Schematic of a chip. Each chamber functions independently, when the pH of the chamber changes the ISFET (ion sensitive field effect transistor) generates an electrical signal.

Loop-mediated isothermal amplification for HIV RNA
NO thermal cycling
95% sensitivity if HIV RNA >1000 copies/mL
100% specificity
12 samples per chip
30 min reaction
Powered by USB port

Scientific Reports 2016;6:36000

App-based ultrasound, ready when you are

Connect the Lumify transducer

Our innovation in portable ultrasound comes to your compatible device through a simple USB connection.

3D volumetric imaging,
shear wave elastography,
strain gauge imaging
all require significant processing capacity
not compatible with current smartphones
(for now, but the Moore's law says otherwise)

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March 26, 2018

Philips enhances point-of-care ultrasound with Reacts platform for remote collaboration and virtual training

- *Industry-first integrated tele-ultrasound solution breaks down barriers for care providers – from clinicians, teaching institutions, medical students and residents to EMS personnel, disaster relief organizations and hospitals with satellite clinics*
- *Enables remote collaboration and virtual training through face-to-face conversation along with simultaneous viewing of live ultrasound images and guided probe positioning*

Amsterdam, the Netherlands and Quebec, Canada – Royal Philips (NYSE: PHG, AEX: PHIA), a global leader in health technology, in partnership with Innovative Imaging Technologies (IIT), today announced an industry-first integrated tele-ultrasound solution based on Philips' Lumify portable ultrasound system and powered by IIT's Reacts collaborative platform. This innovation connects clinicians around the globe in real time by turning a compatible smart device into an integrated tele-ultrasound solution, combining two-way audio-visual calls with live ultrasound streaming. This innovation in point-of-care ultrasound brings endless possibilities to its users both inside and outside hospital walls.

With this intuitive, easy-to-use integrated system, clinicians can begin their Reacts session with a face-to-face conversation on their Lumify ultrasound system. Users can switch to the front-facing camera on their smart device to show the position of the probe. They can then share the Lumify ultrasound stream, so both parties are simultaneously viewing the live ultrasound image and probe positioning, while discussing and interacting at the same time. In addition to clinicians seeking virtual guidance, Philips Lumify with Reacts is a valuable tool for teaching institutions, medical students and residents, emergency medical service providers, disaster relief providers and hospitals with satellite clinics.

A mid-level healthcare worker in the community can call upon a specialist in a distant hospital to receive perspective and guidance, discussing the ultrasound exam using ***live streaming ultrasound as if they were in the same room***

www.usa.philips.com

What we have learned
from the HCV elimination national strategies in Europe

- Political will
- Timely and strong advocacy
- Partnership with the industry to reach price deals
- General population screening (financial incentives, penalties for inaction)
- National registries
- Extend the number of prescribers
- Decentralize diagnosis and treatment
- Simplify procedures