New Diagnostics for Advancing Hepatitis C Elimination

Jordan J. Feld MD MPH

Toronto Centre for Liver Disease
Sandra Rotman Centre for Global Health
University of Toronto
Disclosures

- **Research:** Abbvie, Cepheid, Eiger, Enanta, Gilead, Janssen

- **Consulting:** Abbvie, Antios, Arbutus, Bluejay, Gilead, GSK, Janssen
Learning Objectives

1. Recognize the importance of the diagnostic cascade in reaching HCV elimination goals, including the limitations of current tools
2. Appreciate the range of diagnostic options for HCV infection with a focus on newer technologies
3. Understand how to optimize the use of new HCV diagnostics by matching the test to the setting
Outline

• Why are new diagnostics important?
• What new(er) options are available?
• Using our current tests better
  – The test
  – The setting
  – Matching the test to the setting
Eye on the prize: Viral hepatitis elimination

- Eliminate viral hepatitis as a major public health threat by 2030
- Calling on all countries to develop national action plans
What do we mean by elimination?
What do we mean by elimination?

<table>
<thead>
<tr>
<th>Eradication</th>
<th>Elimination</th>
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</thead>
<tbody>
<tr>
<td>• Decrease <em>global</em> prevalence to 0 cases</td>
<td>• Decrease in <em>regional/national</em> prevalence to below a threshold to <em>limit impact as a public health problem</em></td>
</tr>
<tr>
<td>• No ongoing surveillance or control efforts required</td>
<td>• Ongoing surveillance and control required</td>
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Likely impossible without a vaccine (among other things!)

Challenging but feasible with the right tools

To reach these endpoints → we need to diagnose & treat a lot of people
But... new infections outpacing cures

Worldwide, 68.5 million HCV infected in 2017 (-1.8%)

- 1.6 million new HCV infections
- 1.5 million cures
- 350,000 HCV related deaths
- 1.04 million non-HCV related deaths

Despite massive treatment uptake... very limited overall effect
Lots of work to do!

- By end of 2019 – 9.4 M people treated but only 21% diagnosed globally!
- 1.5 (1.3-1.8) M new infections in 2019!
Costs have come way down

- Availability of generics in many countries makes treatment affordable...
- Diagnostics often cost more than the drugs!

Estimate $6 billion annually required to reach elimination goals

WHO Global Progress Report HIV, Hepatitis and STIs 2021
People assumed with no IFN, no drop-offs in cascade of care

Reminder in EMR → 92,012 visits → 16,772 (18%) tested → 715 Ab + (4.2%)

Even with effective treatment, major gaps in cascade of care!

Consistent problems:
- No HCV RNA after Ab
- No initial clinic visit

DAAs only help here

Left side of the cascade actually more important

Mera MMWR 2016
HCV diagnosis needs simplification

Step 1
See the doctor

Step 2
To the lab for HCV Ab

Step 3
See the doctor for result

Step 4
To the lab for HCV RNA

Step 5
See the doctor for result

Step 6
Start DAA therapy (may be additional steps: fibrosis assessment, approvals etc)

Loss to F/U

Lots of places to ‘get lost’…particularly if HCV not a priority & COVID made it worse!
Diagnosis: A preferred paradigm

Finger Prick → Anti-HCV POCT (5-20 min) → POC HCV RNA (60 min) → Exclude cirrhosis → Start treatment

Diagnosed and on treatment in < 2 hours...but could be even better!

Grebely/Feld Exp Rev Mol Diag 2017
COVID-19 affects all aspects of the cascade

At risk for HCV

- Reduced testing
- Access to labs

Prevention Strategies
- Reduced harm reduction
- Increased use

Post-treatment outcomes
- Postpone follow up care

Long-term Follow-up
- Deferral of treatment

Adapted Janjua et al eBiomed 2016
Impacts of COVID-19 Pandemic on HCV Testing in Ontario

- Significant declines with each wave
- Rebound to below pre-pandemic levels
Challenge yes…derail no

Opportunities

• Public Health Approach to infectious disease ‘accepted’
• Coordinated responses were put in place quickly...and they worked!
• Telemedicine advanced dramatically – perfect with simplified treatment
• Vaccine development and rollout...
• Testing opportunities Increased testing capacity central labs

• Challenges for sure but we need to be planning now to regain momentum towards micro and ultimately macro elimination
• Try to leverage some opportunities that COVID presents – including diagnostics!
Current Tests

• Serum/plasma
  – HCV Antibody
  – HCV RNA
  – HCV genotype
  – APRI/FIB4

• Point-of-care (whole blood)
  – HCV Ab

• Unapproved tests
  – HCV core antigen
  – Dried blood spot collection

• Unapproved tests
  – Salivary fluid – HCV Ab
  – HCV RNA
Current Tests

• Serum/plasma
  – HCV Antibody
  – HCV RNA
  – HCV genotype (except in cirrhosis)
  – APRI/FIB4

• Point-of-care (whole blood)
  – HCV Ab

• Unapproved tests
  – HCV core antigen
  – Dried blood spot collection

• Unapproved tests
  – Salivary fluid – HCV Ab
  – HCV RNA
Reflex HCV RNA testing

RNA follow-up testing within 30 days of Ab+ result

Quest changes policy and tests all anti-HCV+ specimens

LabCorp – continues requirement for second specimen

Total tested: Quest 415,000; LabCorps 319,000

J Ward – CDC – unpublished data
Anti-HCV Reflex to Quantitative HCV RNA: Effect on Testing

• HCV RNA reflex testing of anti-HCV positive patients in Barcelona, Spain, 2015-2018
• Analysis of diagnostic tests performed by a central laboratory before and after implementing a reflex testing protocol

Reflex testing is very effective – increasingly but not universally available

Alternative to RNA

• Learning from COVID-19

• POC Antigen testing – confirm active infection
  – SARS-CoV-2 Ag tests – 5’ and $5/test! → cheap enough to skip Ab screen

• HCV Core Ag
  – Correlates well with HCV RNA but less sensitive
  – Lower sensitivity → LLOD ~3,000 IU/mL of HCV RNA
  – Can be done on the same sample as used for Ab test
  – Cheaper – 15-25% cost of HCV RNA (a bit arbitrary)
  – Fully automated (but requires central lab)
  – Will be difficult to make ‘POC’ – lysis of sample, dissociation from Abs and signal amplification for sensitivity all required…challenging!
HCV Core Ag performance

- Similar performance for Abbott Architect & Ortho ELISA-Ag but more Architect data
- **Specificity 98.9% & Sensitivity >93%** with good correlation if HCV RNA>3000 IU/mL
- Could not assess HIV & HBV co-infection (small n) or genotype
Does it matter?

- 62,000 samples from around the world
- Different genotypes
- HIV
- 97%>1000 IU/mL
- With current tests <1% miss rate, if increase threshold to 1000 IU/mL ~3% miss rate for chronic HCV

EASL now recommends HCV RNA with threshold of 1000 IU/mL

Freiman J Hep 2019, EASL HCV Clinical Practice Guidelines
Is 1000 IU/mL good enough?

• It depends a bit on the population

• For population screening...prevalence ~1-2%
  – Even with 97% sensitivity → Negative Predictive Value = 99.9%
  – Acceptable – particularly at the population level

• In high prevalence populations (eg. PWID – prevalence = 40%)
  – With 97% sensitivity → NPV 98%
  – Not perfect but pretty good
  – ’Acceptable’ if it would increase screening eg. simpler testing paradigm
  – Important to keep RNA as a back-up particularly if concerns eg. cirrhosis
Treatment monitoring & SVR assessment

Conclusions:
1. Core Ag effective for confirming viremia for screening/baseline
2. On-treatment and EOT monitoring had poor predictive value –
   - Core Ag & RNA similar but neither necessary
3. SVR12 – RNA may be preferred – 3 missed SVRs, 1 missed relapse
   Collectively: If RNA used only for SVR & Ab+/Ag- → avoid a high % of total HCV RNA tests

Issues with Core Ag

- Sensitivity good but probably not good enough (yet!)
- Particularly given that false negatives more likely in those we cannot miss (cirrhosis, HIV, G3)
- Performs less well for confirmation of SVR – false + and false -
- Not PoC – significant technical challenges

- For now...as a sole test, only option would be Combined Ag/Ab test with HCV RNA done for Ab+/Ag- → would reduce HCV RNA testing but not a panacea...
- But – an improved Core Ag test – sensitivity/PoC could be a major step forward
Not just the test, but the collection method
Dried Blood Spot (DBS) Testing

**Pros:**
- No blood draw (screening drives, PWID)
- Peer testing
- Easy storage → mail to lab
- No need for 2nd visit for confirmatory RNA test

**Cons:**
- Smaller volume – may need multiple pricks – better with capillary
- Lower HCV RNA titre
- No immediate result
HCV RNA off DBS

- Predictably **lower HCV RNA titre** - ~1.5-2 log IU/mL
- Rarely goes from positive to negative – particularly for diagnosis

CAP/CTM (Roche)

m2000 (Abbott)

Soulier JID 2016
Core Ag: DBS vs serum

Useful as a qualitative but not quantitative test off DBS
Does DBS handling matter?

Assessed Ab, core Ag and HCV RNA off DBS samples with improper handling:
- Unfrozen (4C/RT), heated (37C), hot/cold

<table>
<thead>
<tr>
<th></th>
<th>-80°C</th>
<th>+4°C</th>
<th>RT</th>
<th>+37°C</th>
<th>Hot/Cold</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ab</strong></td>
<td>93/93 (100%)</td>
<td>91/91 (100%)</td>
<td>89/89 (100%)</td>
<td>91/91 (100%)</td>
<td>89/89 (100%)</td>
</tr>
<tr>
<td><strong>Core Ag</strong> (2 spots)</td>
<td>86/94 (91%)</td>
<td>84/90 (93%)</td>
<td>79/89 (89%)</td>
<td>83/91 (92%)</td>
<td>80/89 (90%)</td>
</tr>
<tr>
<td><strong>HCV RNA</strong> (2 spots)</td>
<td>66/66 (100%)</td>
<td>72/74 (97%)</td>
<td>75/75 (100%)</td>
<td>74/75 (99%)</td>
<td>67/67 (100%)</td>
</tr>
</tbody>
</table>

- Previous study – core Ag off DBS sensitivity of 65% - 1 spot
- Increases to ~90% with 2 spots – no effect of handling conditions
DBS in remote settings

- High burden of HCV in Canadian Indigenous populations
- Very remote communities → no road access
- Very limited resources

- **HCV Screening**
  - Community leaders (Chief & council) support
  - **Peer screeners → DBS**
  - Peer & RN counseling
  - Screen >1/3 adult pop’n 3d

- **Linkage to care**
  - Local MD/RN – treatment with ECHO model
  - OST clinics
Lac Seul and Kitchenuhmaykoosib Inninuwug leading the way

Smookler Can Liver Journ 2022
But still not point of care…
Rapid antibody tests

- Meta-analysis
- >13,000 individuals included in 18 studies (11 in LMIC) between 1992 and 2012

<table>
<thead>
<tr>
<th>Specimen</th>
<th>Specificity</th>
<th>Sensitivity</th>
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<tbody>
<tr>
<td>Whole blood POCTs</td>
<td>99.5%</td>
<td>98.9%</td>
</tr>
<tr>
<td>Serum &amp; Plasma POCTs</td>
<td>99.7%</td>
<td>98.9%</td>
</tr>
<tr>
<td>Serum &amp; Plasma RDTs</td>
<td>98.6%</td>
<td>98.4%</td>
</tr>
<tr>
<td>Saliva POCTs</td>
<td>98.2%</td>
<td>97.1%</td>
</tr>
</tbody>
</table>

**Other issues:** Co-infection, accuracy across genotypes
Oral Fluid (saliva)

OraQuick test crevicular fluid – 513 patients – **Specificity 100%, Sensitivity 97.6%**

- 8 False negatives – 6 CHC, 2 resolved

- Despite excellent performance – **not FDA approved** but approved in UK & Europe
- Significant advantages for screening in certain settings

Chevaliez Clin Micro Infect 2016
Making OraQuick quicker

Can we take advantage of the fact that Ab titers wane with time?

- All viremic patients positive within 5 minutes (clinic + real-world validation cohort)
  - if negative, not viremic (reduces number of RNA tests that need to be done)
  - if positive immediate RNA by DBS/venipuncture or POC RNA
- Only need to engage for 5 minutes *(we lost 18% waiting for 20’ and 0.6% waiting 5’!)*

Sensitivity: 100%
Specificity: 38.3
(95% CI 0.98-1.00)
(95% CI 0.32-0.42)

PPV 66.8%
(95% CI 0.62-0.72)

NPV 100.0%
(95% CI 0.95-1.00)

Smookler Clin Gastro Hep 2021
Rapid RNA test – almost PoC

- Serum/plasma sample (1mL)
- Cartridge to reader
- ~100 mins

- Relatively easy-to-use rapid HCV RNA test – platform present in many LMIC
- Broad diagnostic range – 10-10e7 IU/mL, all genotypes → 60’ to result
- High correlation with standard PCR assays – analytical performance r=0.99
- Real-world performance very good (but not FDA approved!)
  - Venipuncture - Sens 100%, Spec 99.1%
  - Finger-prick – Sens 95.5%, Spec 98.1%
- Other similar assays in development

McHugh J Clin Micro 2017, Grebely Lancet Gastro Hep 2017
Can we improve on current tests?

ETHOS cohort Australia → 325 HCV RNA detectable, 1061 undetectable

Time to positivity correlates with VL

Positive results can be obtained relatively rapidly (median 32’)...but 57’ for negative result

Grebely JID 2020
Newer assays for PoC Viremia – RNA or Core Ag

- Strategies to decrease turnaround time – goal of 20-30 minutes
- Decrease price
  - Feasible to screen for viremia at population level

- DASL – ~40 minutes, sensitivity ~1000 IU/mL
- CRISPR-CAS13a
  - Specific detection
  - Trans cleavage → visual signal
  - Cheap, fast, sensitive
  - Done for COVID

Safari Vir Res 2021, Ackerman Nature 2020, Zaoor CLM 2022
A preferred paradigm

Finger Prick → POC Test of Viremia → Exclude cirrhosis → Start treatment

Immediate diagnosis – same day start – key for certain populations

Grebely/Feld Exp Rev Mol Diag 2017
Beyond the virus

• Fibrosis assessment
  – Critical to identify cirrhosis
  – Simple tools – FIB4 and APRI score
    • Require only ALT, AST and platelet count

  – **POC ALT + AST + Platelet** (or transient elastography if you have it)

\[
\text{FIB4} = \frac{\text{Age (years)} \times \text{AST (U/L)}}{\text{Platelet count (10}^9/\text{L}) \times \sqrt{\text{ALT}}}
\]

\[
\text{APRI} = \frac{\text{AST(U/L)} \div \text{ULN} \times 100}{\text{Platelet count (10}^9/\text{L})}
\]

Some technical challenges but can be overcome → would be very useful
A preferred paradigm

Finger Prick → POC Test of Viremia → Exclude cirrhosis → Start treatment

Immediate diagnosis – same day start – key for certain populations

Grebely/Feld Exp Rev Mol Diag 2017
This is what it could look like

Finger Prick

Anti-HCV POCT

POC HCV RNA/Ag

POC APRI/FIB4/TE

Exclude cirrhosis

<15 min

<15 min

<15 min

Start treatment

Diagnosed, assessed and ready to start in 30 minutes or less with only a finger prick!
Cost is a major consideration (as always)

- In theory…could skip Ab testing already
- Main barrier is cost – even more so in LMIC!
- PCR platform will always be fairly expensive…likely cost-prohibitive except in very high prevalence settings (e.g. SIS)…
- Newer technologies – core Ag (if PoC and more sensitive), COVID-19 approaches (and volumes)…could bring price down ‘low enough’

Just as understanding the threshold for sensitivity (e.g. 1000 IU/mL) is important…**critical to understand the cost to make this feasible**
But until we have better tools...let’s use what we have well
Opportunistic screening

Screen when you have the chance
- Emergency Rooms
- Hospital Inpatients
- Substance use treatment

You mean you’re not a herpetologist?
Match the test to the situation

• Considerations
  – **Population** – likelihood of follow-up, prevalence of HCV
  – **Sample type** – need for phlebotomy vs finger-prick (vs saliva)
  – **Urgency for treatment** – need for PoC
  – **Geography** – access to care provider – self-collection (DBS)
  – **Cost** – test type, prevalence

• Was done fairly well for COVID-19
  – RDT vs PCR used fairly effectively – need to consider a public health approach - balance individual vs population…
  – **Elimination requires a public health approach**

Don’t let perfect get in the way of very very good
Matching the test to the setting

- **Current model** (Ab then RNA or Ab reflex RNA)
  - Boomer/all adult screening, prenatal (?), OAT clinics (?) → Reliable F/U
- **PoC Ab + PoC RNA/DBS**
  - Screening drives/outreach, prison, inpatient screening
- **PoC saliva + PoC RNA/DBS**
  - Screening drives, opportunistic screening (ER, prison) – where blood/sharps or time is an issue (accept lower sensitivity of saliva)
- **PoC RNA (or Core Ag)**
  - Very high prevalence population – active PWID (SIS), prison (?), OAT (?)
- **DBS**
  - Rural remote (no lab), hard-to-reach, self-collection, time issues (ER)
PoC not suitable for all settings

No impact to ER flow
No cost to the department

Rapid testing is not always ‘rapid’ – pre and post-test counseling + linkage
ER Screening key

- ER screening very effective for dx – but problems with linkage
- Shown to be cost-effective
  - Birth Cohort ICER
    - $17,287-$25,584 / QALY
  - General population screening
    - $15,862-$19,733 / QALY
- Assuming only 50% linkage!
- Other opportunistic screening likely helpful e.g. hospital admission, outreach – bring screening to people

We need to find people, diagnose them and link them to care

Mendlowitz J Viral Hep 2020
In the right setting…RNA can be your first test

Pilot program
- Offering HCV testing in SIS in Toronto
  - Xpert HCV RNA at entry
  - 52 (42%) positive
  - DBS for confirmation (+ Ab)
- Immediate result → 53% Linkage to care and treated
- Similar program Melbourne
  - Prevalence 28%
  - Of whom 89% treated
  - Including 13 on day of positive test!

Lettner INHSU 2021, Maclsaac INHSU 2021
HCV Prevalence Among People with Mental Illness

- Huge burden
- Very minimal focus in elimination efforts
INSPIRE - All patients admitted to acute psychiatry ward at CAMH

Ab Screen - Orasure + HCV RNA Xpert

- Treat in Psychiatric setting by hospitalist
- Refer to hepatology

• Who needs hepatologists??
• Expect higher uptake and completion with referral
Opportunism: HCV screening during COVID-19 vaccination

- COVID-19 & HCV → similar populations
- Limited interaction with healthcare system
- **Vaccination may be an opportunity**

- 20’ minute observation period post-vaccine
  - 5-minute rule POC
  - DBS for RNA...no phlebotomy
- We have started with vaccination at Centre for Addiction & Mental Health
- Very good uptake ~2000/m with good linkage to care

Vanderhoff AASLD 2021
HCV Testing at Psychiatry Hospital-based Vaccine Clinic
HCV Testing at Mobile Vaccine Clinic
HCV Testing in a COVID Vaccine Clinic

- **5’ rule** - 2304/2317 (99.4%) stayed for results
- **20’ rule** - 282/1582 (18.5%) left early

CAMH patients – 2.6%
Staff – 1.0%
Declined to answer – 21%

<table>
<thead>
<tr>
<th>Doses Given</th>
<th>Approach</th>
<th>HCV POCT</th>
<th>213/day (32-488)</th>
<th>11923</th>
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- **89% first test**
- **99.5% stayed for 5-minute result**
DBS Self collection

- Has been evaluated in HIV & SARS-CoV-2
- High acceptability, comfort and performance

Valentine-Graves PLoS One 2020, Takano BMC ID 2018
Everyone wants to know their COVID Ab status right?

- Protocol of self-collection of Dried Blood Spot
- Test for COVID, HCV and HBV in known positives and family practice
Summary

- Diagnostics are a critical tool for HCV elimination – have not kept pace with therapeutics
- Critical to match the testing paradigm to the clinical situation
  - Time to diagnosis is *not always* the biggest issue
  - Don’t let perfect get in the way of very good (e.g. saliva Ab testing)
  - Using our current tests more efficiently would help – e.g. the 5’ rule
  - Need to focus on a public health approach to testing
- PoC tests (Ab and RNA) need to be faster & whole blood – true PoC <5’
- Hopefully the rapid innovation for COVID-19 will spill over to HCV and achieve a single test cost-efficient diagnosis!