4.1. WHO to test HBV?

Decision-making tables – PICO 1

What is the impact, cost, and cost–effectiveness of different HBV testing approaches and scenarios?

Population:

1. *Risk-based screening in different high-risk populations:* Injecting drug users (IDUs), men who have sex with men (MSM), immigrants, recipients of blood transfusion and blood products, sex workers, and health-care workers (HCW), HIV-infected persons
2. *General population* (excluding blood donors) or selected subpopulations of general population (women during pregnancy, those with raised alanine aminotransferase [ALT], Infants, schoolchildren and adolescents)
3. *Other approaches:* Birth cohort screening (based on different age cut-offs, born between 1945–1960 or 1965 or 1970).
4. *One off screening* vs repeat screening every five years

Intervention: Testing strategies for HBV in different populations (risk based and general population and birth cohort); and at different prevalence thresholds

Comparator: No testing or current practice or comparison of different testing strategies

Outcomes: Benefits, harms and costs, and cost–effectiveness with different screening strategies for different target populations

Individual patient outcomes: No. of cases detected, overall mortality, liver-related mortality, cirrhosis, end-stage liver disease, rate of hospitalizations, serious adverse events, quality of life

Prevention: New infections (mother to child, horizontal [IDUs needle sharing and sexual; and sexual, esp MSM])

Cost–effectiveness: Cost and incremental cost per case diagnosed; cost and incremental cost per case screened and treated; cost and incremental cost per life saved; cost and incremental cost per infections averted; quality-adjusted life years (QALYs) gained

Background:

Epidemiology:

Chronic hepatitis B (CHB) – defined as persistence of hepatitis B surface antigen (HBsAg) for six months or more – is a major public health problem. Worldwide, there are an estimated 250 million chronically infected persons, particularly in low- and middle-income countries (LMICs). Universal hepatitis B immunization programmes that target infants, with the first dose at birth, have been highly effective in reducing the incidence and prevalence of hepatitis B in many endemic countries. However, these programmes will not have an impact on HBV-related deaths until several decades after their introduction.

The major complications of CHB are cirrhosis and hepatocellular carcinoma (HCC). Between 20% and 30% of those who become chronically infected will develop these complications, and an estimated 650 000 people will die annually due to CHB.

The risk of developing chronic HBV infection decreases with age at infection, from about 90% when infected perinatally up to 6 months of age to 20–60% between the ages of 6 months and 5 years. Of those who acquire HBV as children 25% will develop primary liver cancer or cirrhosis as adults.

Routes of transmission worldwide: In sub-Saharan Africa and east Asia, transmission predominantly occurs in infants and children by th eperinatal and horizontal routes (i.e. resulting from close contact that is not parenteral, perinatal, or sexual in nature) whereas in more industrialized countries, rates of new infection and acute disease are highest among young adults and transmission predominantly occurs via Injecting drug use and other high-risk behaviours. Worldwide, the majority of infections are acquired at birth or in early childhood.

Low rates of diagnosis: The majority of people are unaware of their HBV infection, and therefore often present with advanced disease. At present, there is a massive burden of undiagnosed and untreated hepatitis B and C, with 40–85% of infected persons undiagnosed, but varies greatly by setting. By contrast, the estimated awareness of status among people living with HIV (PLHIV) is within 40%–60% range for two thirds of countries, but varies significantly (CHAI, UNAIDS Info).

- Based on still limited studies, overall <15% of the estimated 180 million who are chronically infected with HCV are aware of their diagnosis, based on data from higher-income setting – United States, Europe and China.
- And from a survey in the US, a similar proportion of those with chronic HBV infection are aware of their diagnosis.
- The proportion in low-income settings is even higher, with only a tiny fraction diagnosed and aware.

Reasons for low uptake of testing are multifactorial, and include lack of awareness at all levels, lack of clear guidelines, competing health-care priorities, limited health-care budgets and political will.

This leads to many people remaining undiagnosed until the later stages of the disease, when prognosis is poor.

In addition to the very low access to and uptake of testing, there is also further attrition in the care cascade with very poor linkage to care and therefore treatment, among those who test positive.

Hepatitis B and C testing and diagnosis are at the core of entry to both the prevention and treatment cascade.

- Testing is required to *identify those with are positive*, linking them with care, counselling them on measures to reduce transmission to others then assessing who needs treatment, initiating treatment, achieving treatment response (sustained virological response [SVR] for hepatitis C) or long-term viral suppression for HBV and retaining in care for HBV.
- Hepatitis testing is also needed to *identify those who are negative*, to provide hepatitis B vaccination, and the opportunity to implement individual or facility-level prevention measures, counsel to reduce risk behaviours, or institute facility-level prevention measures on measures to acquisition.

There are three key approaches to screening:

1. **Population- or community-based screening (including antenatal).** This means that all members of the population have access to the screening programme under consideration. It may also include home-based testing (house to house); campaigns (e.g. HTC plus – malaria, safe water, noncommunicable diseases e.g. diabetes and hypertension); outreach (mobile) in general and key populations; workplaces and schools; and health-care facility0based screening.
2. **Health-care facilities.** Testing could also be offered in special dedicated clinics, e.g. HIV, STI clinics. Screening at health-care facilities may include primary care settings, inpatient and outpatient settings, and may involve screening on the basis of clinical presentation or focus on only those with abnormal liver function tests, abnormal ultrasound scan, family history of liver disease or other clinical suspicion of liver function test.
3. **Targeted risk factor-based screening.** This refers to screening of specific groups including key populations, who are generally at higher risk of being infected than the general population. This includes people who inject drugs (PWID), people in prisons and other closed settings, migrant populations, some indigenous populations, MSM and sex workers, but may also include health-care workers. People attending services providing care and treatment for viral hepatitis or HIV can be encouraged to bring their partners to be tested.
4. **Birth cohort screening** for HBV and HCV.

Existing guidelines: what are countries doing?

1. Most countries have based their list of high-risk groups as defined by the Centers for Disease Control and Prevention (CDC), and are largely based on known modes of transmission. Generally they include recommendations for three main screening approaches: (Apata, MMWR Morb Mortal Wkly Rep. 2014;63:613–19; Weinbaum, Hepatology. 2009;49:S35–S44; Han, Vaccine.

2013;31 Suppl 9:J36–J42)

- Population-based screening that includes antenatal clinic screening
- Screen those with high-risk behaviours, exposures and other conditions
  - Family members and household contacts of hepatitis B patients
  - MSM
  - PWID
  - HIV-positive patients
  - Patients on immunosuppression or chemotherapy
  - Persons with liver disease of unclear etiology
  - Health-care workers.
- Birth cohort for HCV screening in US and Japan.

2. At present, there is no universally accepted recommended screening programme. There is widespread testing of blood donors (but not necessarily universal), and widespread antenatal screening and infant vaccination in Asia. In addition, there is a risk factor-based testing in high-risk groups in Asia (PWID, liver disease, renal dialysis) and use of a birth cohort approach in the US and Japan.

Survey of guidelines (Surjo De)

Evidence: systematic reviews of prevalence of HbsAg

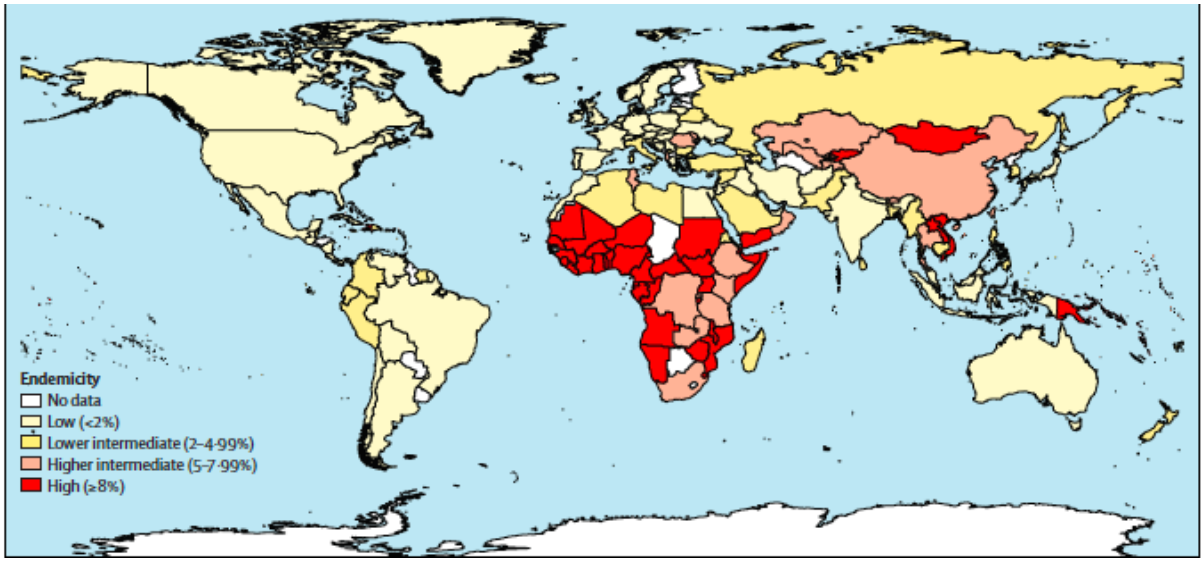
1. General population: systematic review (Ott, Lancet 2015)

161 countries included.

High endemicity (>5%): Most countries in Africa were of higher–intermediate endemicity (HBsAg prevalence 5–7·99%), or highly endemic for HBV (HBsAg prevalence ≥8%. The Western Pacific Region was also a high–intermediate endemicity region (5–7.99%), especially in the Pacific Island States such as the Solomon Islands.

Intermediate endemicity (2–5%): The Eastern Mediterranean Region was of lower–intermediate endemicity (2·00–4·99%), but Djibouti, Somalia and Sudan showed a higher prevalence of HBsAg than other countries in the region such as Iran.

Low endemicity: Countries in the Americas, such as Mexico, Guatemala, and the USA had mostly low endemicity levels (HBsAg prevalence <2%), ranging from 0.01% (95% CI 0.01–0.01) in the UK to 10.32% (8.56–12.38) in Kyrgyzstan. Overall, the South-East Asia Region had low endemicity levels but on country level, an HBsAg prevalence below 2% was only noted in India, Indonesia and Nepal.



Summary of prevalence across risk groups

General Population (Schweitzer et al. 2015)	PWID (Nelson et al. 2011)	MSM (Hope, et al. 2014 data is for European countries outside of the EU)	Sex Workers (Hope, et al. 2014 data is for European countries outside of the EU)	Migrants & Refugees (Rossi et al. 2012; Hanhe et al. 2013; Nilgun, 2011))	Prisoners	Pregnant Women (Hanhe et al, 2013; Nilgun, 2011))	HIV-infected persons (general population) (Easterbrook et al. 2015)	Healthcare Workers
East Asia and Pacific 5-7.99% South Asia Region 2-4% Central and Eastern Europe and Central Asia Region 2-4% North Africa and Middle East Region 2-4% Sub-Saharan Africa Region 5-7.99% Latin America	Southeast Asia and East Asia 2.9 - 19.5% South Asia 5.8 - 17.3% Central Asia 7.9% Eastern Europe 0.5-21.3% North Africa and Middle East region 0.0 - 18.5% Central Africa 3.8 - 9.0% Andean Latin America 2.3	Albania 18% Azerbaijan 4% Croatia 0.90% Georgia 10% Serbia (incl. Kosovo) 8.70% Turkey 3.60% Ukraine 9.80%	Azerbaijan 3.3% Bosnia 1.4% Serbia 18.3% Turkey 2.4%5 Ukraine 9.1%	East Asia and Pacific 11.3% South Asia Region 4.6% Central and Eastern Europe and Central Asia Region 5.8% North Africa and Middle East Region 2% Sub-Saharan Africa Region 10.3% Latin America and Caribbean Region 1.7% Europe 1.0-		Europe 0.1(Spain)-4.4% (Slovakia) Middle East 1% (Qatar) 2.9% (Lebanon)	East Africa 5-11% West, Central Africa 5-15% Latin America 0.6-2% South East Asia 1-2% Eastern Mediterranean 10%	Tanzania tertiary hospital 5.6-7% (Mueller et al. 2015) Uganda tertiary hospital 8.1% (Ziraba et al. 2010).

2. PWID: Systematic review ((*Nelson et al. 2011***))**

PWID are a key population who are at particularly high risk of HBV, HCV and HIV infection. In many high-income countries and some developing countries, ongoing HCV transmission is driven mainly by PWID populations. A review of global prevalence data from 77 countries estimated that exposure to HCV (anti-HCV positive) among PWID is estimated to be between 60% and 80% in 25 countries, and over 80% in 12 countries. Similarly, of 59 countries where data were available, prevalence of HBsAg

among PWID ranged from 5% to 10% in 21 countries and over 10% in 10 countries.
PWID data are global by 20 Global Burden of Disease regions
Southeast Asia and East Asia: 2.9–19.5%
South Asia: 5.8–17.3%
Central Asia: 7.9%
Eastern Europe: 0.5–21.3%
Central Africa: 3.8–9.0%
Andean Latin America: 2.3–8.6%

3. MSMs and sex workers: systematic review ((Hope et al. 2014)))

MSM can acquire HBV and HCV sexually. In many populations, there are higher rates of HBV infection among MSM, requiring targeted HBV screening and vaccination. MSM who are HIV positive are at significantly higher risk of acquiring HCV infection than HIV-negative MSM.

Sex workers are a key population who are at high risk of acquiring HBV and HCV infection. Multiple factors may contribute to this vulnerability, including unsafe working conditions, barriers to negotiating consistent condom use, and difficulties accessing health-care services.

MSM (12 countries), sex workers (5 countries)

Country	MSM	Sex workers
Albania	18%	
Azerbaijan	4%	3.3%
Croatia	0.9%	1.4% (Bosnia)
Georgia	10%	11.1%
Serbia (incl. Kosova)	8.7%	18.3%
Turkey	3.6%	2.4%
Ukraine	9.8%	9.1%

4. Migrants and refugees: systematic review (Rossi et al. 2012)
sub-Saharan Africa Region: 10.3%
East Asia and Pacific: 11.3%
Central and Eastern Europe and Central Asia Region: 5.8%

5. HIV-infected persons: systematic review (Easterbrook et al. 2015)
HIV/HBV (483 estimates from 75/193 (39%) countries

	Gen pop	PWID	MSM	Hetero	Pregnant
	Mid-point co-infection prevalence (Interquartile range) **Number of studies**				
East Africa	8% (6-11) **10**		9% **1**	6.5%(5-10) **10**	4% (2-5) 2
West, Central Africa	11% (6-15) **11**		22% **1**	12% (8-20.5) **32**	9% (0-13) **3**
South Africa			6.5% **1**	7% (5-20) **7**	5% (3-6) **2**
Latin America	1% (0.6-2) **3**	27% **1**	9% (6-11) **5**	3% (2-7) **4**	0.5% (0.5-1.8) **3**
North America		7% **1**	5% (5-6) **2**	17% **1**	
South East Asia	2% (1-2) **2**	18% (10-20) **10**	15% (10-19) **6**	9% (0-15) **10**	
Eastern Europe and CAR					
Europe		4% (3-7) **3**	5% (4-6) **9**	7% (2-11) **2**	
East Med	10% **1**	8% (4-44) **6**			
East Asia		9.5% (2.5-37) **4**	12% (10-13.5) **4**	5% (4-6%) **4**	
Western Pacific			4% (3-5) **6**		

HBsAg prevalence based on a total of 170 estimates in HIV-infected persons, based on population type (general population, PWID, MSM, heterosexual, and pregnant women) and by eleven geographical regions.

1. First, reflecting the epidemiology of HBV in Africa whereby the majority of HBV infections are acquired perinatally or in childhood, the prevalence among key populations of HIV-infected PWID and MSM is not substantially higher than the background rate in the general population or among heterosexuals, especially in Africa,
2. Only in the South-East Asia Region is there a higher prevalence in among PWID and MSM.

6. Prisoners

The prevalence of HBV in prisons is often significantly higher than in the general population. Globally, the prevalence of HIV, STIs, hepatitis B and C and tuberculosis in prison populations is estimated to be two to ten times higher than in the general population, and in some settings, 50 times higher. People in prisons and closed settings may be at particular risk for HBV, HCV and HIV infection for a number of reasons. Most commonly, this is due to sharing of needles and syringes and other injecting equipment; often because prevention hardware such as clean needles and syringes are not accessible to prisoners.

7. Indigenous populations: In some settings, indigenous populations are also disproportionately affected by viral hepatitis infection, along with a number of other health problems. Contributing factors to these disparities may include higher rates of injecting risk behaviours among indigenous people who inject drugs and higher rates of incarceration.

Epidemic scenarios

The broad categories of “generalized” and “concentrated” epidemics are not necessarily helpful in determining how best to prioritize hepatitis testing services. But some general principles apply.

Epidemic Scenarios			
	Definition	Disaggregation	Country Example
Generalised	High >8%		West Africa
	High Intermediate (5-7%)		China, Vietnam
	Low Intermediate (2-4%)		Turkey, Taiwan
	Low (<2%)		Brazil, Ukraine
	<1%		United Kingdom, France
Mixed	Generalised population prevalence, low intermediate (and potentially high intermediate), with a sizeable risk population	High	Greece
		High intermediate	Tanzania, Myanmar
		Low intermediate generalised	Iran, India
Concentrated	Generalised population prevalence <2% with high risk groups	Low (<2%) with risk groups	Italy, Russian Federation
		Low (<2 %) without risk group	
		PWID with >8% prevalence	Estonia, Bulgaria
		PWID with < 8% prevalence	Western Europe
		Countries with migrant populations with prevalence >5%	Canada, Netherlands

Recommendations

Guiding principles for hepatitis B and C testing:

1. Promotion of health equity and human rights in national hepatitis B and C testing so that: expanded testing and access is fair and equitable; priority for testing is on diagnosing the undiagnosed; identifying those in greatest need of treatment and those with ongoing risk of infection; and that testing is voluntary and care is provided in a supportive environment free of stigma and discrimination.

   This is critical as many of the affected population are those who are systematically excluded from access to testing, treatment and care, such as sex workers, injection drug users, men who have sex with men, and prisoners.
2. All persons who test positive for hepatitis B and C (in addition to HIV) should have access to and be linked to hepatitis care and treatment services.
3. Testing of key populations should be undertaken where possible in conjunction with other risk or harm-reduction services.

DRAFT recommendation(s): Existing recommendations on prisons, for sex workers and PWID on HBV vaccination

1. Prisons should have a comprehensive hepatitis programme, including the provision of free hepatitis B vaccination for all prisoners, free hepatitis A vaccination to those at risk, and other interventions to prevent, diagnose and treat hepatitis B and C equivalent to those available in the community (including condom, needle and syringe programmes and drug dependence treatment as needed).
2. Include sex workers as targets of catch-up hepatitis B immunization strategies in settings where infant immunization has not reached full coverage (*Source*: WHO, 2012).[36]

3. It is suggested to offer people who inject drugs the rapid hepatitis B vaccination regimen.

Summary and quality of evidence (*see SR_Who to screen_HBV modelling report* for references)

Summary of evidence base for different screening approaches

The evidence base for these different screening approaches remains very limited, and largely relies on observational data and modelling.

- There are descriptive data showing that targeted testing and community-based screening programme approaches can increase uptake of testing and detection of cases, but very limited data to show impact on patient important outcomes (Pollack, Health Aff (Millwood) 2011;30:1974–83; Bryce BD, Yartel AK. Am J Prev Med 2014;47:23341). Community-based: BFreeNYC screening program (~9000 people screened, 6 cases HCC + 22 end-stage liver failure diagnosed and managed)
- Lack of evidence and uncertainty as to whether risk-based targeted screening is reaching targeted populations.

Cost–effectiveness evidence summary: overview of report – summary of existing studies on cost–effectiveness of screening and treatment for HBV, with an analytic summary of key considerations.

- 32 studies all from high-income countries in settings with low HBV prevalence. No data on cost or cost–effectiveness of screening for HBV in LMICs was identified. Eight published studies, and one unpublished study (PROLIFICA screening study in Gambia) met inclusion criteria.
- Two studies evaluated HBV screening in the general population and seven studies in "high-risk" groups (all but one concerned screening in migrant or refugee populations). There was one previously published study in the USA and one forthcoming study in the Gambia, looking at the cost–effectiveness of offering screening and treatment to the general population.
- The studies used different methods of screening the "high-risk groups"

☐ High
☐ Moderate
☐ Low
☐ Very low

including, in the clinical setting (Wong, Rein), community outreach methods (Rein) and overseas screening (Jezwa). Various outcome measures were used, including cost per quality-adjusted life year (QALY) gained, cost per LY saved and cost per case screened. Many of the models were simulated using hypothetical cohorts.

- Overall, data show that offering screening to the general population with subsequent antiviral treatment strategy is cost–effective in HICs (Eckman), as well as LICs (Nayagam), even down to a population prevalence as low as 0.3% and 2%, respectively, in these studies.
- **PROLIFICA study of HBV community-based screening in Gambia:** the feasibility of large-scale screening and treatment in sub-Saharan Africa (SSA) has been demonstrated by the ongoing PROLIFICA (Prevention of Liver Fibrosis and Liver Cancer in Africa) study in West Africa (Lemoine et al., forthcoming). This implementation study has screened nearly 10 000 adults for HBsAg at the community level in the Gambia and Senegal using an active outreach method. This is followed by full clinical assessment of those found to be HBsAg positive and antiviral treatment if meeting eligibility criteria. A cost–effectiveness analysis of this community-based screen and treat strategy in the Gambia (Nayagam et al., forthcoming), compared to status quo, revealed an incremental cost–effectiveness ratio (ICER) of $705/LY gained (other outcome measures also calculated: $476/QALY gained or $575/DALY averted). The authors acknowledge that willingness to pay (WTP) thresholds levels, and their use, are highly debated in LMICs. However, it can be regarded as cost-effective if using the WHO WTP threshold of three times the country's GDP per capita to define a cost–effective intervention (3 times GDP per capita = $1460 in the Gambia). This is the only cost–effectiveness study of screening and treatment we have found in LMIC settings. Furthermore, it is furnished with real-life cost and effectiveness data from a large-scale screening and treatment intervention programme. Furthermore, screening also has benefits that extend beyond the person screened to also others, for example, prevention-of-mother to child transmission.

Conclusions: The data on the cost–effectiveness of screening for HBV is lacking, especially in LMICs. Difficult to draw conclusions regarding the best screening strategy, in terms of who to screen and where to screen, based on cost–effectiveness alone. Currently, there is not enough literature to make strong recommendations for screening based on cost–effectiveness arguments alone.

Relatively low screening costs, highly effective and relatively low-

cost antiviral therapy at generic price and a fraction of HBsAg-positive persons requiring antiviral therapy should help drive the cost–effectiveness of a test-and-treat strategy. However, this has to be balanced against long-term treatment and the fact that a high proportion with CHB will survive without treatment.

Limitations of comparing models/generalizability of results: WHO recommendations are primarily aimed for use in LMICs. All models were from HICs (except PROLIFICA); making generalizations of results from cost–effectiveness analyses between countries or regions with such differing health-care structures, costs, patient behaviours, disease prevalence profiles and willingness-to-pay thresholds can be misleading.

Key determinants of testing approach for countries (from cost–effectiveness review):

HBsAg prevalence:

HBsAg prevalence had a relatively small influence on cost–effectiveness in most of the studies. General population screening was found to remain cost–effective (i.e. ICER below the respective WTH threshold) down to HBsAg prevalence of 0.3% in the USA (Eckman) and 2% in the Gambia (PROLIFICA).

Costs:

Cost components that need to be considered in economic evaluations of screening and treatment for HBV include costs of screening, diagnostics, monitoring and drugs. This should involve both the cost of consumables, as well as other costs, including human resource costs (which are included to various extents between different studies). A key driver of cost–effectiveness of a screen-and-treat strategy reported in some studies is the cost of antiviral drug (Rossi, Hutton, PROLIFICA). Screening costs varied between the studies, and were only found to be drivers of cost–effectiveness in the Wong and PROLIFICA studies.

Linkage to care and adherence:

Adherence to treatment and linkage to care were reported as key drivers of cost–effectiveness in several studies (Rossi, Veld). In the PROLIFICA study, variation in treatment adherence was also a key driver of cost-effectiveness.

Uptake of screening is not reported to be a key driver of ICER in the studies; however, this does not imply that high participation levels in screening is not important, as when considering health impact alone, increasing uptake

is key. The implication of this result is that it is likely to be worthwhile performing screening and treatment, even if participation in screening is assumed to be low. This could be because screening costs are low, relative to the costs and health benefits of treatment for those who are infected. **Distribution of patients between different disease states** The proportion of people who would benefit from treatment in a population will guide cost–effectiveness, but by how much is difficult to quantify based on current evidence, and needs further research.	
Risks/benefits **Community-based testing (outreach, mobile or venue-based)** **Benefits** • Leads to earlier diagnosis and access to treatment before development of cirrhosis • Worldwide, the majority of infections are acquired at birth or in early childhood, and there is therefore generalized high prevalence throughout population, which requires population-based testing approaches. • Highly acceptable with index partner testing, home-based and mobile outreach for HIV • Generally good uptake • Way of accessing missing populations, such as men, key populations and young women who are not pregnant • Community-based testing is a critical approach for reaching people from key populations and vulnerable populations who are unlikely to go to a facility, particularly those who are asymptomatic. **Risks** • May lead to lower-than-expected positivity rates with home-based testing, testing within campaigns, key population outreach and testing of index partners. • Suboptimal linkage to care is highly variable and may be problematic. • Unit costs may be higher, but may be cost–effective. **Provider-initiated testing and counselling (PITC) in health-care facilities** **Benefits** • 89/117 low- or middle-income countries recommend HIV PITC in all patient encounters	☐ Benefits clearly outweigh harms ☐ Benefits and harms are balanced ☐ Potential harms clearly outweigh potential benefits *Are the desirable anticipated effects large?* ☐ No ☐ Probably ☐ Uncertain ☐ Yes ☐ Varies

- High HIV PITC acceptance in antenatal care (ANC) and TB settings
- Introduction of PITC increased paediatric HIV testing
- Many clinical settings in generalized epidemic settings not offering hepatitis testing – e.g. STI clinics, primary care, and so many missed opportunities for HBV diagnosis in health-care facilities.

Key and other populations targeted testing

Benefits

- Key populations are disproportionately affected by hepatitis in all regions.
- Key populations are less likely to have received HBV vaccination and offer of HBV testing will facilitate higher rates of completion of vaccination.

Partner testing

Benefits

- Participating in couples and partner HBV testing has a number of benefits. These include adoption of prevention strategies by the couple (for example, condom use, safe injecting practices) and promotion of linkage to and retention in appropriate health-care services.
- Also applies to opportunistically offering HBV testing and vaccination to family members and other close household contacts of people diagnosed with CHB re access to vaccination and care.
- Couples and partner testing helps more people know their HBV and/or HCV status, particularly men, who in generalized epidemic settings may be less likely to test than women.
- Partners: <5% of people currently HIV test with their partners and similar low rates for HBV. Note: HIV serodiscordance is common (half to two thirds of HIV-positive adults with a co-habiting relationship have an HIV-negative partner
- Offering **partner testing** for persons with HBV and HCV – highest possible yield. Although risk of infection may be low, a negative test in the partner provides reassurance and the opportunity to provide counselling on reducing future risk including vaccination.

Risks

- People may be reluctant to admit risk behaviours, or may be unaware they are at risk, and so a screening approach that relies on history may miss a substantial proportion of cases.

Acceptability, values and preferences **PITC** • High HIV PITC acceptance in ANC and TB settings **Partner testing** • Offering partner testing for persons with HBV and HCV – highest possible yield • Need to overcome reluctance to provide partner testing/index partner testing **Community-based testing** • Community-based testing services would need to be made available in settings acceptable and convenient to people from key populations and vulnerable populations. • Services need to be convenient and available, through flexible opening hours and/or walk-in or same-day appointments. • Involving affected populations, including adolescents in design, delivery and evaluation of testing services is necessary to ensure that these programmes address their need. • Need to address concerns that older relatives, neighbours or family friends will see them attending viral hepatitis/HIV services, including testing services.	☐ No major variability ☐ Major variability Is the option acceptable to key stakeholders? ☐ No ☐ Probably ☐ Uncertain ☐ Yes ☐ Varies
Equity, ethics and human right implications *Will recommendation raise questions around equity?* • As for all testing services, programmes for key populations need to emphasize WHO's "5 Cs" – particularly consent, confidentiality and connection to comprehensive prevention, care and treatment. • The use of community-based and hepatitis B and C rapid testing can increase the likelihood of some key populations, such as prisoners, receiving their results. • Testing in certain populations, such as in prisons may increase the chances of stigmatization. *Are there ethical implications to this recommendation?* • No major concerns.	☐ Less equitable ☐ More equitable
Resource use and financial implications	

Resource use (see parameter matrix for sample HIV testing programme costs) Estimating the costs associated with a given hepatitis testing approach can be challenging. Costs for similar hepatitis testing may differ significantly between countries and by programme type within a country. Differences in programme costs may be due to general cost differences between countries, in what specific services are provided (referral to clinic for those testing hepatitis-positive vs enhanced linkage support), cadre of staff employed (nurses vs community health workers), the ease of reaching different populations, the capacity of the health system, and the level of HIV testing coverage. **Standardized approach to costing of hepatitis testing:** A common approach to estimating costs involves identifying and estimating costs incurred by the health-care provider within the following broad categories: • personnel (for example, health-care providers at facilities, counsellors, other paid programme staff, volunteers); • recurrent costs (for example, HIV test kits and commodities, printed materials, office supplies); • capital expenses, often amortized over their useful life and discounted annually at 3% (for example, office space, transportation, equipment); **Materials:** • Cost of testing kits, buffer/reagents • Cost of sterile lancets, pipettes, gloves, sharps-bins or other method of disposal of used-kits • Cost of automated reading machine, if applicable • Quality-control reagents, if applicable (some kits are supplied with positive and negative controls) **Training and supervision:** • Cost of training testing providers and appropriate assessment, validation and revalidation of their skills • From included studies, excellent robust specificity of all tests is reassuring in terms of ensuring cost–effective initiation of algorithms for further investigation and treatment. • If being utilized at the point of care, it will be the responsibility of the testing provider to record and report the result appropriately. **Other:**	*Are the resources required small?* ☐ No ☐ Probably ☐ Uncertain ☐ Yes ☐ Varies

- Creation of a database into which results obtained by POC can be recorded
- Linkage to care, e.g. antenatal clinics.

Possible test procurement cost:

Test	Cost (US$) per test	Source
RDT	0.3–0.95 (procurement cost)	WHO database
EIA	0.4–2.8 (procurement cost)	WHO database

Costs

In the PROLIFICA study, despite an active community-based screening campaign, screening costs were low ($7.43 per person offered screening) and the intervention remained cost–effective even if there was a 3-fold increase in screening costs. The Rein study in USA reported costs per person screened between $40 and $280, with the higher costs representing the more active outreach strategies.

Feasibility and constraints to implementation

Are any major barriers expected for the implementation of this recommendation?

The feasibility of large-scale screening and treatment in sub-Saharan Africa (SSA) has been demonstrated by the ongoing PROLIFICA (Prevention of liver fibrosis and liver cancer in Africa) study in West Africa (Lemoine et al., forthcoming). This implementation study has screened nearly 10 000 adults for HBsAg at the community level in the Gambia and Senegal using an active outreach method. This is followed by full clinical assessment of those found to HBsAg positive and antiviral treatment if meeting eligibility criteria.

A cost–effectiveness analysis of this community-based screen and treat strategy in the Gambia (Nayagam et al., forthcoming), compared to status quo, revealed an ICER of $705/LY gained (other outcome measures also calculated: $476/QALY gained or $575/disability-adjusted life year [DALY] averted). They authors acknowledge that WTP thresholds levels, and their use, are highly debated in LMICs. However, it can be regarded as cost–effective if using the WHO WTP threshold of three times the country's GDP per ca–ita to define a cost-effective intervention (3 times GDP per capita = $1460 in the Gambia). This is the only cost–effectiveness study of screening and treatment we have found in LMIC settings.

Couples and partners

Is the option feasible to implement?

☐ No
☐ Probably
☐ Uncertain
☐ Yes
☐ Varies

HIV testing for couples and partners has been conducted in various settings, including ANC and community-based TB services, through ART services and during premarital health visits. Couples and partner HIV testing for the partners of women attending ANC, in particular, is a focus in the 21 priority eMTCT countries. These countries are all highly endemic for HBV, and this provides a unique opportunity to integrate concurrent HBV testing for partners of women with CHB, or chronic HCV infection if risk factors are present.	

Relevance to different settings/populations

Will this recommendation be most relevant for particular settings (e.g. endemicity)?

Adolescents

In high HBV-prevalence settings there are two groups of adolescents (that is, people 10–19 years of age) who may need access to HBV testing: (1) undiagnosed adolescents who were exposed perinatally or in early childhood and; (2) adolescents who acquire HBV sexually (through early sex, sex with multiple partners or sex with a person with CHB), or through injecting drug use. Perinatally infected adolescents urgently need to be diagnosed so that they can be linked to HBV monitoring and care and start antiviral treatment if and when this is clinically indicated. In many highly endemic HBV settings, there are a significant number of undiagnosed perinatally infected adolescents. Perinatally exposed adolescents who do not have evidence of CHB need to be vaccinated if this has not yet been done. In many countries, adolescents and young adults may have missed out on HBV vaccination depending on the timing of introduction of universal infant vaccination.

Children

Universal HBV immunization, including a vaccine birth dose within 24 hours after birth, is key to preventing MTCT of HBV, but many countries have not been able to implement this crucial intervention, due to economic and logistic constraints.

Most infants whose mothers have been diagnosed with HBV or HCV should be followed-up and routinely offered EID, and those diagnosed with either with should be regularly monitored for signs of liver disease so that treatment can be offered when necessary. However, some infants are lost to follow-up, so additional pediatric case finding is important. This can be achieved through the routine offer of PITC in health facilities, particularly in high prevalence settings, and also through testing the family members of index cases where appropriate.

HBV testing services for infants should be implemented with the aim of identifying as many HBV-infected infants as early as possible. Although a conservative approach to treatment is usually indicated, children born to HBV-infected mothers should be screened early so that monitoring for progression of liver disease can be organized and so that testing and vaccination of household contacts can be carried out.

In high-prevalence settings: HBV and HCV testing of mothers and infants should be routinely

available through a variety of services – child health services, immunization clinics, under-5 clinics, malnutrition services, well-child services and services for hospitalized and all sick children, TB clinics, and services for orphans and vulnerable children.

Testing the family members of index cases

Gaps in HBV testing and in documenting the HBV status of children of HBV-positive parents constitute significant missed opportunities. These gaps can be closed by following up the families of cases identified in ANC or facilities offering HBV testing. In all settings all children with an HBV-positive parent or close household contact should be tested for HBV as a priority.

Rationale for recommendation:

Strength of recommendation

Implementation considerations

- As for all testing services, programmes for key populations need to emphasize WHO's "5 Cs" – particularly consent, confidentiality and connection to comprehensive prevention, care and treatment.
- Need to overcome reluctance to provide partner testing/index partner testing
- Make use of lay providers/peer testing for outreach especially among key populations
- Viral hepatitis testing for key populations needs to be delivered alongside other key primary prevention interventions.
- Accessibility and coverage of testing would need to be high to have an impact on the prevalence of HBV among PWID and other key populations. Offering DBS testing for HCV to PWID attending drug treatment programmes increased uptake of testing services.

Research gaps

- Further research and large scale-implementation studies should be performed to evaluate this further in other high-endemic, low-income settings.
- What proportion of HBV- or HCV-positive cases will be missed by a testing policy based on screening for at risk behaviours and exposures?
- Evaluation of different testing approaches in terms of cost, impact and cost–effectiveness and evaluation of key drivers in a range of different settings.

4.2. Who to test HCV

Decision-making tables – PICO 2

What is the impact, cost and cost–effectiveness of different HCV testing approaches and scenarios?

Topic for analysis: who to screen?

Population:

1. Risk-based screening in different high-risk populations

Injecting drug users (IDUs), men who have sex with men (MSM), immigrants, recipients of blood transfusion and blood products, sex workers, and health-care workers (HCW), HIV-infected persons

2. General population (excluding blood donors) or selected subpopulations of general population (women during pregnancy, those with raised alanine aminotransferase (ALT), infants, schoolchildren and adolescents)

3. Other approaches: Birth cohort screening (based on different age cut-offs; born between 1945–1960 or 1965 or 1970)

4. One-off screening vs repeat screening every five years.

Intervention: Testing strategies for HBV in different populations (risk-based and general population and birth cohort); and at different prevalence thresholds

Comparator: No testing or current practice or comparison of different testing strategies

Outcomes: Benefits, harms and costs, and cost–effectiveness with different screening strategies for different target populations

Individual patient outcomes: Number of cases detected, overall mortality, liver-related mortality, cirrhosis, end-stage liver disease, rate of hospitalizations, serious adverse events, quality of life

Prevention: New infections (mother to child, horizontal (IDUs needle sharing and sexual; and sexual, especially MSM)

Cost–effectiveness: Cost and incremental cost per case diagnosed; cost and incremental cost per case screened and treated; cost and incremental cost per life saved; cost and incremental cost per infections averted; quality-adjusted life-years (QALYs) gained

Background:

Hepatitis C virus (HCV) is a global public health burden and major cause of morbidity and mortality including liver failure and hepatocellular carcinoma. Current global HCV seroprevalence is estimated to be 2.8%, or >185 million infected individuals worldwide.

Routes of transmission: In many countries, HBV, HCV and HIV transmission occurs predominantly in high-risk key populations, often via common routes of transmission. Key populations include people who inject drugs (PWID), people in prisons and other closed settings, some mobile populations, some indigenous populations, MSM and sex workers. PWID are a key population who are at particularly high risk of HCV infection. In many high-income countries and some developing countries, ongoing HCV transmission is driven mainly by PWID populations.

The advent of high-efficacy, low duration therapy, however, generates prioritization for testing for HCV infection, linking infected patients to care, and curing HCV before patients begin to experience the consequences of cirrhosis and end-stage liver disease.

Low rates of diagnosis and linkage to care: The majority of people are unaware of their HCV infection, and therefore often present with advanced disease. Based on still limited studies, overall <15% of the estimated 180 million who are chronically infected with HCV are aware of their diagnosis, based on data from higher-income settings – United States, Europe and China.

In addition to the very low access to and uptake of testing, there is also further attrition on the care cascade with very poor linkage to care and therefore treatment, among those who test positive.

Hepatitis B and C testing and diagnosis are at the core of entry to both the prevention and treatment cascade. Testing is required to *identify those with are positive*, linking them with care, counselling them on measures to reduce transmission to others then assessing who needs treatment, initiating treatment, achieving treatment response (sustained virological response [SVR] for hepatitis C). Hepatitis testing is also needed to *identify those who are negative*, to provide hepatitis B vaccination, and the opportunity to implement individual or facility level prevention measures counsel to reduce risk behaviours.

There are three key approaches to HCV screening

1. Targeted risk factor-based screening. This refers to screening of specific groups including key populations, who are generally at higher risk of being infected than the general population. This includes PWID, people in prisons and other closed settings, migrant populations, some indigenous populations, MSM and sex workers, but may also include health-care workers. People attending services providing care and treatment for viral hepatitis or HIV can be encouraged to bring their partners to be tested.

   This involves screening those with high-risk behaviours, exposures and other conditions.

Most countries have based their list of high-risk groups as defined by the Centers for Disease Control and Prevention (CDC), and are largely based on known modes of transmission.

i. Family members and household contacts of hepatitis B patients
ii. MSM
iii. PWID
iv. HIV-positive patients
v. Patients on immunosuppression or chemotherapy
vi. Persons with liver disease of unclear etiology
vii. Health-care workers.

2. **Birth cohort screening** for HBV and HCV
3. **Population or community-based screening (including antenatal).** Routine general population screening: i.e. testing among the general population without attempt to identify high-risk behaviours or characteristics ("routine testing"). This means that all members of the population have access to the screening programme under consideration. It may also include home-based testing (house to house); campaigns (e.g. HTC plus – malaria, safe water, non-communicable diseases (diabetes and hypertension); outreach (mobile) in general and key populations; workplaces and schools; and health-care facility-based screening.
4. **Health-care facilities.** Testing could also be offered in special dedicated clinics, e.g. HIV, STI clinics. Screening at health-care facilities may include primary care settings, inpatient and outpatient settings, and may involve screening on the basis of clinical presentation or focus on only those with abnormal liver function tests, abnormal ultrasound scan, family history of liver disease or other clinical suspicion of liver function test.

   Persons in whom there is clinical suspicion of viral hepatitis: even when risk factors for HBV and/or HCV are not present, screening is indicated wherever there is clinical suspicion of viral hepatitis infection. This may occur, for example, where there is existing liver disease, including liver cirrhosis or hepatocellular carcinoma, or where there is unexplained liver disease including abnormal liver function tests.

Existing guidelines: what are countries doing?

The main approach to HCV testing is a targeted risk factor-based testing for those with high-risk behaviours, exposures and other conditions, e.g. (PWID, liver disease, renal dialysis) and use of a birth cohort approach in the US and Japan. At present, no country guidelines recommend routine testing for all individuals regardless of demographics or specific behavioural risk.

1. Screen those with high-risk behaviours, exposures and other conditions. Most countries have based their list of high-risk groups as defined by CDC, and are largely based on known modes of transmission.

   i. Family members and household contacts of hepatitis B patients
   ii. MSM
   iii. PWID

iv. HIV-positive patients
v. Patients on immunosuppression or chemotherapy
vi. Persons with liver disease of unclear etiology
vii. Health-care workers.

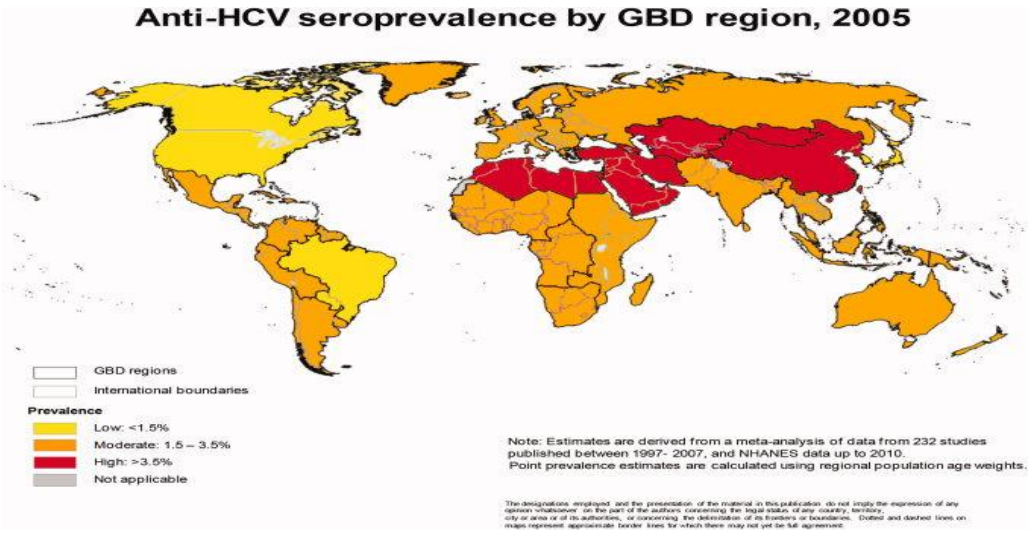
Survey of guidelines (Surjo De)

Global prevalence of hepatitis C virus

General population (Hanafiah et al. 2013)	PWID (Nelson et al. 2011)	MSM (Hope, et al. 2014 – data is for European countries outside of the EU)	Sex workers (Hope, et al. 2014 – data is for European countries outside of the EU)	Migrants and refugees (Hanhe et al. 2013)	Prisoners (Larney et al. 2013)	Pregnant women (Hanhe et al., 2013)	HIV-infected persons	Health-care workers
Southeast Asia 2% East Asia 3.7% Oceana 2.6% South Asia 3.4% Central Asia 3.8% Central Europe 2.4% Eastern Europe 2.9% North Africa and Middle East region 3.6% Central Africa 2.3% East Africa 2% Southern Africa 2.1% West Africa 2.8% Andean Latin America 2% Central Latin America 1.6% Southern Latin America 1.6% Tropical Latin America 1.2% Caribbean 2.1% Asia Pacific High income 1.4% Australasia 2.7% Western Europe 2.4%	Southeast Asia and East Asia 41–89.8% South Asia 36.0– 87.3% Central Asia 51.7–61.3 % Eastern Europe 22.6–90.5% North Africa and Middle East region 28.–67.6% West Africa 22.2 - 97.3% Andean Latin America 9.8 – 97.4% Australasia 51.9-54.6 % Western Europe 20.7 – 86.2%	Azerbaijan 14% Bosnia 12% Croatia 3% Georgia 16% Kazakhstan 4.20% Kyrgyzstan 1.20% Republic of Moldova 11% Russian Federation 2.30% Ukraine 20%	Azerbaijan 9.30% Bosnia and Herzegovina 4.30% Croatia 4% Kazakhstan 11% Kyrgyzstan 3.9–28% Republic of Moldova 13% Russian Federation 14–40% Serbia 3.30% Tajikistan 6.30% Turkey 2. 40% Ukraine 32% Uzbekistan 11–12.8%	Europe 0–23.4% (Hungary)	SSA 7–26% Western Europe 26–34% Eastern Europe 14–31% Latin America 8–19% Australasia 28–43% North America 24–34% South Asia 4–11% Middle East and North Africa 1–5% East and SE Asia 13–38% Central Asia 32–43% Extrapolated global 23–29%	Europe 0 (Slovakia) –1.7% (Italy)		United States Hospital workers 1% (Alter, 1997) Egypt National Liver Institute HCWs 16.8% (Adelwahab et al. 2013)

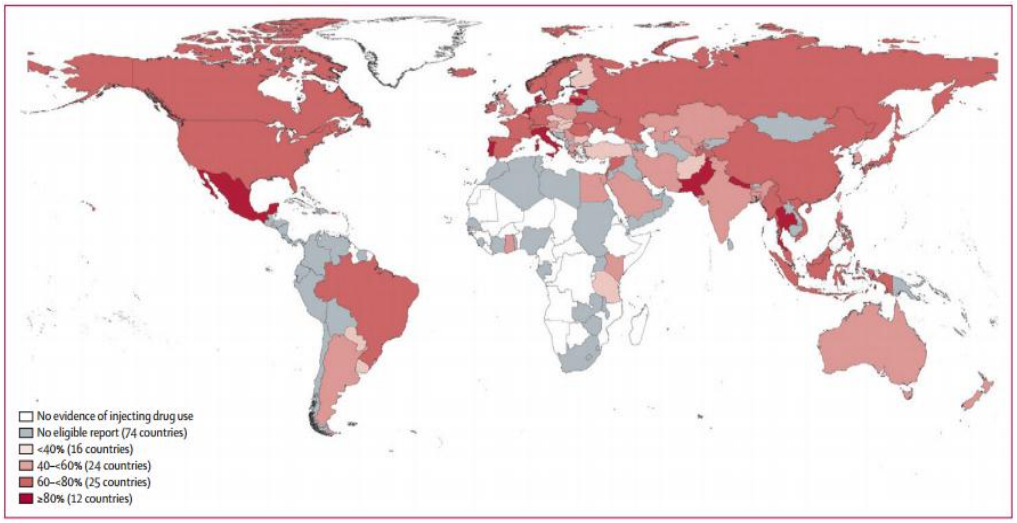
North America High Income 1.3%								

Global epidemiology of hepatitis C virus infection: new estimates of age ‐ specific antibody to HCV seroprevalence (Hanafiah, 2013)



Prevalence of hepatitis C antibodies in injecting drug users

A review of global prevalence data from 77 countries estimated that exposure to HCV (anti-HCV positive) among PWID is estimated to be between 60% and 80% in 25 countries and over 80% in 12 countries.



MSM

MSM can acquire HBV and HCV sexually. MSM who are HIV positive are at significantly higher risk of

acquiring HCV infection than HIV negative MSM. Incidence rates of sexually acquired HCV among MSM have been rising in several industrialized countries since 2000, and outbreaks have been described in some less industrialized nations.

Systematic review of HCV prevalence in HIV-infected persons (Platt et al. 2015).

Coinfection estimates were identified for 78 of the 194 countries (40%). There were 760 HIV/HCV coinfection prevalence estimates. Findings suggest that globally HCV/HIV coinfection is 1.9% (IQR = 0·4–6·6%) among general population samples, 7% (IQR = 2·6–11·1%) among people living with HIV (PLHIV) who are pregnant or where heterosexual transmission is reported, 6.2% (IQR = 3·3–13·5%) among men who have sex with men (MSM) and 83% (IQR = 55·2–94·1%) among people who inject drugs (PWID). Odds of HCV infection are 11 times higher in the presence of HIV infection, but varied by risk group. The global estimate of HCV coinfections among PLHIV is 3.2 million (IQR = 1.4–4.3 million) of whom 1.2 million (IQR = 0.9–1.4 million) are PWID

	Mid-point co-infection prevalence (Interquartile range) **Number of studies**				
	Gen pop	**PWID**	**MSM**	**Hetero**	**Pregnant**
East Africa	1.3% (0-4.9) **5**	71 % (42-99) **2**	20%(1-38) **2**	4% (3-9) **10**	0.6% (0.1-5) **3**
Cental and West Africa	5 % (2-12) **9**		8% **1**	8% (4-12.4) **19**	10.1 (5-16) **4**
South Africa			2% **1**	0.5% (0-1) **3**	
Latin America	7% (0.8-16.1) **3**	82% (52-88) **4**	4% (0-16) **6**	11% (8-15) **2**	10% (5-18) **4**
North America		84 (41-89) **25**	13 (8-15) **16**	12 (9-25) **9**	4% **1**
South East Asia	5% (3-29) **7**	90 (86-97) **18**	6% (5-8) **5**	5% (1.5-7) **5**	
Eastern Europe and Central Asia		82% (68-95) **8**			
Europe	6% (0.3-30) **3**	82% (53-91) **41**	8% (4-17) **40**	11% (4-23) **11**	3% **1**
East Med	1% **1**	81% (74-89) **7**			
East Asia		96% (80-98) **15**	4% (2-9) **3**	51% (6-89) **7**	
Western Pacific			9% (7-10) **4**		

We compared the prevalence of HCV among 105 samples of HIV-positive and -negative population groups (general population, PWID, MSM, sex workers, prison inmates and high-risk populations). This is summarized in Figure 4 and in the online table. Overall, there was a 12-fold (95% CI 11·2–11·8) increased odds for HCV positivity across all population groups among HIV-positive compared to HIV-negative persons. Odds of HCV were highest among HIV-positive prison inmates (OR=16·5 95% CI 15·9–17·1) and other high-risk populations (OR = 11·7 95% CI 11·0–12·4), PWID (OR = 5·1 95% CI 4·7–5·5), followed by MSM (OR = 3·8 95% CI 3·1–4·5) and general population samples (OR = 3·7 95% CI 3·3–4·3) and sex workers (OR = 2·5 95% CI 2·0–3·2).

Epidemic scenarios hepatitis C virus

Generally, HCV epidemics around the world are heterogeneous and represent mixtures of three core

epidemic components:

1. *Infection related to high-risk behaviours:* In essentially every geographical region, the highest prevalence of HCV infection is among persons who use injection drugs (PWID). The prevalence of injection drug use differs between countries and regions, but within those who do inject drugs, HCV prevalence is nearly universally high. Commercial sex workers and prisoners also have increased prevalence (presumably related to both drug use and perhaps sexual transmission) as do men who have sex with men, especially those who are HIV infected. In many cohorts of PWID in North America, Europe and Asia, HCV prevalence ranges from 30% to 75%.
2. *Infection related to past generalized exposures that have since been identified and removed:* this epidemic pattern, in which there is a high prevalence of HCV within a given age group, is commonly referred to as a "birth cohort epidemic." While typically identified as being the infection pattern in North America and Europe, many nations have some element of birth cohort epidemics with their unique HCV epidemiology (Table 1). Birth cohort epidemics reflect an HCV exposure source that was once present and to which a large portion of the population was exposed, but that has since been identified and removed. For example, before it was identified and sequenced, HCV infected the blood supply of many countries in all regions of the world. When the blood supply began to be screened for the presence of HCV, the exposure was removed. As a result, the incidence of HCV fell dramatically among the general population, but there remains a burden of prevalent, chronic HCV among patients who were alive and likely to get a blood transfusion during the time that HCV existed in the blood supply.
3. *Generalized population epidemic:* This pattern is related to a widespread exposure, often iatrogenic, that results in high prevalence (8–10%) across essentially all age groups. Note that the primary difference between a "birth cohort" pattern and a generalized pattern of infection is the duration of time that the generalized exposure existed and whether it has been removed or mitigated. An example of a generalized exposure is the common use of reusable hypodermic syringes and needles in medical settings without adequate sterilization between uses.

Few epidemics fall into one of the above three categories. Rather, most are mixed, and represent some combination of all components (Table).

Epidemic scenarios			1.1.2
	Definition	**Disaggregation**	**Country example**
Generalized	High (>5%)	With birth cohort	Egypt, Pakistan
		Without birth cohort	1.1.3
	High intermediate (3–5%)	With birth cohort	Congo, Ukraine
		Without birth cohort	1.1.4
	Low intermediate (2–3%)	With birth cohort	Cote d'Ivoire, Thailand
		Without birth cohort	1.1.5

Mixed	Generalized population prevalence, low, moderate or high with a sizeable risk population (PWID)	High generalized	Uzbekistan
		High intermediate generalized	Taiwan
		Low intermediate generalized	Syria, Hong Kong
		Low (1–2%) with PWID	Mexico, Switzerland
		Low (1–2 %) without PWID	The Gambia, Singapore
		To check (UNDOC % of population)	1.1.6
Concentrated	Generalized population prevalence <1% with high-risk groups		United Kingdom, Turkey

Extra risk classification	**Country example**
Unsafe blood transfusions prior to 1990	Brazil, Portugal

Draft recommendation(s):

Existing recommendations (*Source:* WHO, 2014[9])

1. **Risk-based:** It is recommended that HCV serology testing be offered to individuals who are part of a population with high HCV seroprevalence or who have a history of HCV risk exposure/behaviour. These include:

- Persons who inject drugs (PWID)
- Persons with HIV infection (HIV-positive men who have sex with men)
- Prisoners and persons previously incarcerated
- Persons who have had tattoos, body piercing or scarification procedures where infection control is not guaranteed
- Children born to mothers infected with HCV
- Close contacts of persons infected with HCV
- Persons who have used intranasal drugs
- Persons from a country with intermediate or high prevalence (2% or greater) of hepatitis C
- Persons who have received medical or dental interventions in health-care settings where infection control is not guaranteed
- Persons who have received blood transfusions prior to the time when HCV serologic testing of blood donors was initiated or in countries where HCV serologic testing of blood donations is not routinely performed.

2. **General population and birth cohort:** It is recommended that in settings with a high HCV seroprevalence (>8%) in the general population, testing be offered, especially at least once, to persons born between 1945 and 1955.

Existing WHO recommendations

HIV testing services should be routinely offered to all key populations in the community, closed settings such as prisons, and clinical settings.

PWID: WHO recommends delivery of a comprehensive package of nine evidence-based interventions for HIV prevention, treatment and care for PWID, all of which are also directly relevant to prevention, treatment and care for HBV and HCV, and one of which is specific to viral hepatitis testing (vaccination, diagnosis and treatment of viral hepatitis, see Box).

The nine interventions in the comprehensive package for HIV prevention, treatment and care for people who inject drugs

1. Needle and syringe programmes
2. Opioid substitution therapy and other drug dependence treatment
3. HIV testing and counselling
4. Antiretroviral therapy
5. Prevention and treatment of sexually transmitted infections
6. Condom programmes for people who inject drugs and their sexual partners
7. Targeted information, education and communication for people who inject drugs and their sexual partners
8. Vaccination, diagnosis and treatment of viral hepatitis
9. Prevention, diagnosis and treatment of tuberculosis.

Source: WHO, UNODC, UNAIDS,

Sex workers

WHO outlines a comprehensive set of interventions and approaches, both to promote enabling environments and to provide prevention, testing, care and treatment, in relation to HIV and STI programming for sex workers (see Box). These recommendations are directly relevant to the response to viral hepatitis among sex worker populations. Essential interventions include enabling sex workers to access and consistently use condoms, access prevention and care, treatment and support services, diagnosis and treatment of important comorbid conditions such as for TB (particularly in HIV endemic settings, incarcerated persons, PWID and sex workers living in exposed to poor cramped working and living conditions), other STIs, and access to harm reduction services for sex workers who inject drugs.

Importantly, as sex workers are a key population highly affected by the HBV epidemic, particularly in settings where vaccine coverage is suboptimal, and at high risk for HCV if they inject drugs, they must have access to hepatitis testing services (HepTS), repeat viral hepatitis testing, and partner and family testing wherever appropriate. The offer of HIV testing services (HTS) should be offered alongside HepTS, and HepTS can be integrated into HTS wherever possible. Delivery of HepTS should be informed by recommendations for the delivery of HTS. A variety of settings may be

appropriate in which to implement testing services, including health-care settings as well as community settings, and via multiple different approaches. Outreach peer-led testing is likely to be particularly effective and acceptable in many sex worker populations.

Good practice recommendations

1. All countries should work toward decriminalization of sex work and elimination of the unjust application of non-criminal laws and regulations against sex workers.
2. Governments should establish antidiscrimination and other rights-respecting laws to protect against discrimination and violence and other violations of rights faced by sex workers in order to realize their human rights and reduce their vulnerability to HIV infection and the impact of AIDS. Antidiscrimination laws and regulations should guarantee sex workers' right to health and financial services.
3. Health services should be made available, accessible and acceptable to sex workers based on the principles of avoidance of stigma, non-discrimination and the right to health.
4. Violence against sex workers is a risk factor for HIV and must be prevented and addressed in partnership with sex workers and sex worker-led organizations.

Evidence-based recommendations

1. Offer a package of interventions to enhance community empowerment among sex workers.
2. Promote correct and consistent condom use among sex workers and their clients.
3. Offer periodic screening for asymptomatic STIs to female sex workers.
4. Offer female sex workers, in settings with high prevalence and limited clinical services, periodic presumptive treatment for asymptomatic STIs.
5. Offer voluntary HIV testing and counselling to sex workers.
6. Use the current WHO recommendations on the use of antiretroviral therapy for HIV positive general populations for sex workers.
7. Use the current WHO recommendations on harm reduction for sex workers who inject drugs (in particular needle and syringe programme and opioid substitution therapy).
8. Include sex workers as targets of catch-up hepatitis B immunization strategies in settings where infant immunization has not reached full coverage.

Source: WHO, 2012

Prisons

Key WHO recommendations around testing services for people in prisons and closed settings have, to date, mostly focused on HIV prevention, testing and treatment. In 2013, UNODC and partners developed a comprehensive package of 15 key interventions for HIV prevention and treatment in prisons and other closed settings. Due to common transmission routes, these recommendations are equally applicable to viral hepatitis, and HBV vaccination and diagnosis and treatment of viral hepatitis is one of the specific recommendations (see box). This recommendation stipulates that

"prisons should have a comprehensive hepatitis programme, including the provision of free hepatitis B vaccination for all prisoners, free hepatitis A vaccination to those at risk, and other interventions to prevent, diagnose and treat hepatitis B and C equivalent to those available in the community (including condom, needle and syringe programmes and drug dependence treatment as needed)."

Existing recommendations

1. Information, education and communication
2. Condom programmes
3. Prevention of sexual violence
4. Drug dependence treatment, including opioid substitution therapy
5. Needle and syringe programmes
6. Prevention of transmission through medical or dental services
7. Prevention of transmission through tattooing, piercing and other forms of skin penetration
8. Post-exposure prophylaxis
9. HIV testing and counselling
10. HIV treatment, care and support
11. Prevention, diagnosis and treatment of tuberculosis
12. Prevention of mother-to-child transmission of HIV
13. Prevention and treatment of sexually transmitted infections
14. Vaccination, diagnosis and treatment of viral hepatitis
15. Protecting staff from occupational hazards

Source: WHO, 2013

Recommendations and principles surrounding HIV testing in prisons apply equally to HBV and HCV testing in prisons (see box).

Existing recommendations

- It is important to guard against negative consequences of testing in prisons – for example, segregation of prisoners – and to respect confidentiality.
- It is also important that people who test positive have access and are linked to HIV care and treatment services.
- HIV testing and counselling should be voluntary.
- The use of HIV rapid testing can increase the likelihood of prisoners receiving their results.
- Testing in conjunction with other risk-reduction services such as the provision of condoms with lubricants and STI screening can increase the benefits of testing and counselling.

Source: WHO, 2014.

Summary and quality of evidence

Summary of evidence base for different screening approaches

Cost–effectiveness evidence summary: overview of report

☐ High
☐ Moderate
☐ Low
☐ Very low

Cost–effectiveness analyses of screening for HCV

1. **Gleue systematic search identified 19 studies.** Majority of studies evaluated the cost–effectiveness of screening for HCV in Europe or the US; one study was carried out in Japan and another one in Italy. Ten studies evaluated screening in the general population; eleven studies screening IDUs; three studies looked at recipients of blood transfusions; one study evaluated screening in women during pregnancy and a further study looked at HCWs. Studies evaluated a one-off screening intervention, with the exception of one study that analysed screening every five years. Comparators were either: no screening or the status quo or different strategies were compared with each other. Recent studies concentrated on birth cohort screening in the US, evaluating the cost–effectiveness of one-off screening for a cohort born between 1946 and 1970 and a cohort born between 1945 and 1965. HCV prevalence in this population was comparatively high. The initiation of a one-off screening intervention was assessed and compared with current risk-based screening interventions in these US studies.

2. **Targeted review of the literature** to determine the state of evidence about the cost–effectiveness of testing for HCV in different types of epidemics and among different risk groups. We provide a qualitative assessment of conclusions.

- Testing in high-risk groups such as PWID, MSM, prisoners, HIV-infected persons, and commercial sex workers is likely cost–effective. Testing in settings with a high prevalence of high-risk patients is almost certainly cost–effective in all locations. It is important, however, to ensure adequate follow up after diagnosis.
- The best approach to testing outside of high-risk risk groups depends a great deal on a country's unique HCV epidemiology. Most countries have at least some component of "birth cohort" epidemic, and "birth cohort" testing is likely cost–effective in most settings.
- In most epidemics, routine screening in the entire population is likely not to be cost–effective. The specific threshold at which a country should alter its approach to routine testing, however, is a

function of multiple factors and cannot be identified more generally.

This report does not represent the results of a full systematic review. It is meant to serve as a summary of existing studies on cost–effectiveness of screening and treatment for HCV, with an analytic summary of key considerations. Due to the lack of relevant literature from low- and middle-income countries (LMICs), existing studies from high-income countries (HICs) are described and their potential uses and limitations, when drawing conclusions are discussed.

Summary of findings and conclusions

- Testing in high-risk groups such as PWID, MSM, prisoners, HIV-infected persons, and commercial sex workers is likely cost–effective. Testing in settings with a high prevalence of high-risk patients is almost certainly cost–effective in all locations. It is important, however, to ensure adequate follow up after diagnosis.
- Persons who inject drugs: Multiple analyses in many geographical regions concur that routine testing for HCV in venues with a high prevalence of PWID is cost–effective, even when the studies assume very poor follow-up rates and limited access to therapy. Further, dynamic HCV transmission models suggest that aggressive diagnosis and treatment among current drug users could reduce the incidence of HCV – "cure as prevention". With typical prevalence estimates of 40%, but ranging as high as 75% in some cohorts, routine screening for HCV is almost certainly cost–effective.

1. *Men who have sex with men:* Men who have sex with men (MSM) are also at an increased risk of HCV incidence, particularly if they are also HIV-positive. Cost–effectiveness modelling has found testing using liver function tests in combination with HCV Ab testing to be cost–effective in the HIV-positive MSM population. The results of these studies are dependent on appropriate linkage to effective therapy and retention in care.
2. *Prisoners:* Prisons are likely to have a high HCV prevalence as the result of a high prevalence of PWID in prisons. A UK-based study, however, found that HCV case detection, using dried blood spot testing, was cost–effective, even when the model assumed low rates of HCV treatment initiation. A second study concurs that screening in prisons can be cost–effective, but this study concluded that targeting to screening to those prisoners with a history of injection drug use improves cost–effectiveness.

3. HIV-infected persons: Although nearly every guideline for HCV care recommends HCV screening at enrolment in care, there are no cost–effectiveness analyses that address the specific question of the cost–effectiveness of HCV testing at enrollment in HCV care. Because the prevalence of HCV is known to be high in HIV-infected persons, the pace of fibrosis progression in HIV/HCV-coinfected patients is high, and new therapies to treat HCV are effective in HIV/HCV coinfection, testing for HCV at enrolment in HCV is almost certainly cost–effective.
4. *Sex workers:* Because many sex workers are also PWID or non-injection drug users, the prevalence of HCV in this group is likely high. No studies were identified that address cost–effectiveness of HCV testing in sex workers, and therefore uncertain whether cost–effective to routinely screen all sex workers, compared to an approach that targets testing to sex workers who report a history of injection drug use.

- **Birth-cohort:** i.e. testing among easily identified age or demographic groups known to have high HCV prevalence ("birth-cohort testing"). Most countries have at least some component of "birth cohort" epidemic, and "birth cohort" testing is likely cost–effective in most settings**.** Whenever there is an easily identified demographic group that has high HCV prevalence (for example, all individuals born in a certain time period) it is likely cost–effective to routinely test for HCV within that cohort. Several cost–effectiveness studies in the US and in Portugal show that birth cohort testing was cost–effective.
- **Routine testing of the entire population:** Routine general population screening: testing among the general population without attempt to identify high-risk behaviours or characteristics ("routine testing"). The data about population screening typically come from HICs such as the US and UK, and such studies find that routine testing in the general population is not cost–effective. When compared to "birth cohort testing", however, universal testing resulted in worse outcomes and higher costs than the birth cohort approach. This analysis raises the spectre that in countries whose HCV epidemic is largely concentrated to a specific birth cohort or demographics group, attempting to identify cases by routine testing of the entire population can dilute the testing effort and result in fewer cases of HCV being identified. An older study, conducted in the UK, also found that although screening high-risk groups in primary care settings was cost–effective, extending screening beyond high-risk individuals was not.

Importantly, all of the above studies reflect the epidemiology of HCV in HICs. One recent paper explicitly studied the cost–effectiveness in Egypt of one-time, routine screening for HCV followed by treatment with either pegylated interferon and ribavirin (PEG-RBV) or PEG-RBV plus an HCV protease inhibitor. Given the very high prevalence of disease, screening was always cost–effective, and often cost-saving. **Drivers of cost–effectiveness** **HCV prevalence**: Screening provides increasing value as prevalence rises. In one U.S.-based study, screening was cost–effective (compared to no screening) at a US willingness-to-pay threshold down to a prevalence of 0.53%. In addition to the underlying prevalence of HCV infection, studies identified the **rate of progression from chronic HCV to cirrhosis** as an important factor together with levels of linkage to care and treatment that substantially influenced cost–effectiveness results.	
Risks/benefits **Targeted risk-based testing** **Benefits** • Key populations are disproportionately affected by hepatitis in all regions. • Key populations are less likely to have received HBV vaccination, and offer of HBV testing will facilitate higher rates of completion of vaccination. • *In HIV-infected persons:* Benefits of testing and treatment greatest in HIV-coinfected persons as they have more rapid progression of liver disease (HCV-associated liver disease in coinfected patients is emerging as a major cause of morbidity and mortality in HIV-infected persons) and risk of onward transmission than those without HIV infection. • Leads to earlier diagnosis and access to treatment before development of cirrhosis. • Some studies of PWID have shown that HCV testing and knowledge of serostatus results in reduction in injecting risk behaviours, including frequency of injecting and number of people injected with, in addition to other important risk behaviours, such as heavy alcohol consumption, and increases treatment uptake. • Modelling studies suggest that scaling up treatment with DAAs, across different prevalence settings, would have a major impact on the prevalence of HCV.	☐ Benefits clearly outweigh harms ☐ Benefits and harms are balanced ☐ Potential harms clearly outweigh potential benefits *Are the desirable anticipated effects large?* ☐ No ☐ Probably ☐ Uncertain ☐ Yes ☐ Varies

- HCV treatment outcomes among people who actively inject drugs have been found to be acceptable.
- Community-based testing is a critical approach for reaching people from key populations and vulnerable populations who are unlikely to go to a facility, particularly those who are asymptomatic.

Risks

- Challenging to identify and engage high-risk groups
- People may be reluctant to admit risk behaviours, or may be unaware they are at risk, and so a screening approach that relies on history may miss a substantial proportion of cases.
- Much high-risk behaviour is stigmatized and underreported.
- Health-care workers are not always skilled at identifying high-risk behaviours.
- Because HCV risk behaviours are stigmatized and underreported, trying to identify high-risk individuals is difficult and prone to under testing high-risk patients.
- For key populations, especially those whose behaviour is criminalized, testing services are sometimes misused in punitive or coercive ways. As a result, people from key populations avoid the health services that they need.
- In addition, stigma, discrimination, lack of confidentiality, coercion and fear of repercussions, as well as lack of appropriate health services, resources and supplies, prevent people from testing and, if positive, linking to care.
- Provider-initiated testing and counselling (PITC) among key populations and vulnerable populations is recommended, so long as it is not compulsory or coercive and it is linked to treatment and care.
- In many settings, and in spite of guidelines, service providers are often reluctant to offer antiviral treatment to PWID.

PITC in health-care facilities

Benefits

- 89/117 LMICs recommend HIV PITC in all patient encounters.
- High HIV PITC acceptance in antenatal care (ANC) and TB settings
- Introduction of PITC increased paediatric HIV testing
- Many clinical settings in generalized epidemic settings not offering hepatitis testing – e.g. STI clinics, primary care, and so many missed opportunities for HBV diagnosis in health care facilities.

Partner testing

Benefits

- Participating in couples and partner HBV testing has a number of benefits. These include adoption of prevention strategies by the couple (for example, condom use, safe injecting practices) and promotion of linkage to and retention in appropriate health-care services.
- Also applies to opportunistically offering HBV testing and vaccination to family members and other close household contacts of people diagnosed with CHB re access to vaccination and care.
- Couples and partner testing helps more people know their HBV and/or HCV status, particularly men, who in generalized epidemic settings may be less likely to test than women.
- Partners: <5% of people currently HIV test with their partners and similar low rates for HBV. Note: HIV serodiscordancy is common (half to two thirds of HIV-positive adults with cohabiting relationship have HIV-negative partner.
- Offering partner testing for persons with HBV and HCV – highest possible yield. Although risk of infection may be low, a negative test in the partner provides reassurance and the opportunity to provide counselling on reducing future risk, including vaccination.

Birth cohort testing

Benefits

- Being a member of a birth cohort is easily determined.
- Screening by age group is less stigmatizing.
- Targeting testing to birth cohorts is feasible and often cost–effective.
- In countries with a strong birth cohort dynamic, birth cohort screening is likely preferred.

Risks

- Feasibility and successful implementation of birth cohort screening not well established

Routine generalized testing

Benefits

- Leads to earlier diagnosis and access to treatment before development of cirrhosis

• Way of accessing missing populations, such as men, key populations and young women who are not pregnant • Community-based testing is a critical approach for reaching people from key populations and vulnerable populations who are unlikely to go to a facility, particularly those who are asymptomatic. **Risks** • When the HCV epidemic is concentrated to a specific age or risk group, routine generalized testing and screening may dilute the screening effort in the cohort with the highest prevalence of HCV and result in fewer cases of HCV identified and higher cost than "birth cohort testing." • If an epidemic is highly concentrated with a specific risk or demographic group, screening outside of that group can be inefficient and increase costs. • In most epidemics, routine screening in the entire population may not be cost–effective. • May lead to lower-than-expected positivity rates with home-based testing, testing within campaigns, key population outreach and testing of index partners. • Countries with high HCV prevalence across the entire population should implement routine screening, but • The specific threshold at which a country should alter its approach to routine testing, however, is a function of multiple factors and cannot be identified more generally. • Suboptimal linkage to care is highly variable and may be problematic	
Acceptability, values and preferences A values and preferences survey of implementers and users of hepatitis B and C testing services was carried out by FIND in September 2015. A total of 104 respondents from 43 (20 high-income, 23 low- and middle-income) countries. Relating to this PICO, • Respondents from LMICs identified following target populations as priority for hepatitis B and C testing: blood donors (>85% for B and C), children born to HCV-infected mothers (55% vs 75% for HBV), persons living with HIV (50% vs 65%), and pregnant women (40% vs 78%), MSM (25% vs 45% for HBV), sex workers (<10% for HCV and 45% for HBV), and prisoners (25% for HCV and HBV) and those chronically ill (around 25% for HCV and HBV%).	☐ No major variability ☐ Major variability Is the option acceptable to key stakeholders? ☐ No ☐ Probably ☐ Uncertain ☐ Yes ☐ Varies

• Population – wide screening was suggested by less than 10% for HCV and around 15% for HBV (30% of respondents), and in blood donors (22%) was less supported. **PITC** • There is generally high acceptance of testing in ANC settings **Partner testing** • Offering partner testing for persons with HBV and HCV – highest possible yield • Need to overcome reluctance to provide partner testing/index partner testing. **Targeted testing in drug treatment programmes, STI clinics, HIV clinics** • Routine HIV, hepatitis B and C testing in these clinic settings less stigmatizing	
Equity, ethics and human right implications *Will recommendation raise questions around equity?* • As for all testing services, programmes for key populations need to emphasize WHO's "5 Cs" – particularly consent, confidentiality and connection to comprehensive prevention, care and treatment. • The use of community-based and hepatitis B and C rapid testing can increase the likelihood of some key populations, such as prisoners receiving their results. • Testing in certain populations, such as in prisons may increase chance for stigmatization. *Are there ethical implications to this recommendation?* • No major concerns.	☐ Less equitable ☐ More equitable
Resource use and financial implications **Resource use (*see* parameter matrix for sample HIV testing programme costs)** Estimating the costs associated with a given hepatitis testing approach can be challenging. Costs for similar hepatitis testing may differ significantly between countries and by programme type within a country. Differences in	*1.1.9* *Are the resources required small?* ☐ No ☐ Probably ☐ Uncertain ☐ Yes ☐ Varies

programme costs may be due to general cost differences between countries, in what specific services are provided (referral to clinic for those testing hepatitis-positive vs enhanced linkage support), cadre of staff employed (nurses vs community health workers), the ease of reaching different populations, the capacity of the health system, and the level of HIV testing coverage. **Standardized approach to costing of hepatitis testing:** A common approach to estimating costs involves identifying and estimating costs incurred by the health-care provider within the following broad categories: • personnel (for example, health-care providers at facilities, counsellors, other paid programme staff, volunteers); • recurrent costs (for example, HIV test kits and commodities, printed materials, office supplies); • capital expenses, often amortized over their useful life and discounted annually at 3% (for example, office space, transportation, equipment); **Materials:** • Cost of testing kits, buffer/reagents • Cost of sterile lancets, pipettes, gloves, sharps-bins or other method of disposal of used kits • Cost of automated reading machine, if applicable • Quality-control reagents, if applicable (some kits are supplied with positive and negative controls) **Training and supervision:** • Cost of training testing providers and appropriate assessment, validation and revalidation of their skills • From included studies, excellent robust specificity of all tests is reassuring in terms of ensuring cost effective initiation of algorithms for further investigation and treatment. • If being utilized at the point of care, it will be the responsibility of the testing provider to record and report the result appropriately.	

- **Feasibility and constraints to implementation**

Are any major barriers expected for the implementation of this recommendation?

- As for all testing services, programmes for key populations need to emphasize WHO's "5 Cs" – particularly consent, confidentiality and connection to comprehensive prevention, care and treatment.
- Need to overcome reluctance to provide partner testing/index partner testing
- Make use of lay providers/peer testing for outreach especially among key populations
- Viral hepatitis testing for key populations needs to be delivered alongside other key primary prevention interventions.
- Accessibility and coverage of testing would need to be high to have an impact on the prevalence of HBV among PWID and other key populations. Offering dried blood spot (DBS) testing for HCV to PWID attending drug treatment programmes increased uptake of testing services.

Is the option feasible to implement?

☐ No
☐ Probably
☐ Uncertain
☐ Yes
☐ Varies

Relevance to different settings/populations

Will this recommendation be most relevant for particular settings (e.g. endemicity)?

Key populations

1. In all settings, a number of social and structural barriers exist to PWID being able to access testing, health-care and harm reduction services, including inadequate coverage and delivery of interventions, stigma and discrimination, high incarceration rates, unstable living conditions, comorbid health problems, poor health literacy and social difficulties. This results in inadequate uptake of prevention, testing, treatment and HBV vaccination,
2. Viral hepatitis testing and treatment for PWID must always be delivered alongside other evidence-based essential primary prevention interventions also. Studies have shown that the uptake of opioid substitution therapy (OST) and adequate needle–syringe programme (NSP) coverage, in isolation, have been shown to reduce the odds of acquiring HCV, but the combination of both interventions together had a much larger impact. Additionally, the high prevalence of comorbidities in populations of PWID, including viral hepatitis/HIV coinfection, TB, mental health problems and poly-drug use alongside social and economic predictors of poor health means that it is particularly important that comprehensive prevention, treatment, care and social services are integrated and accessible to this population.
3. In many settings, responses to viral hepatitis, with particular regard for the need to reach key populations, can be integrated in order to be most effective. When this is not possible, strong links among health services working with priority populations should be established and maintained. Additionally, integration of viral hepatitis testing and treatment with existing services for HIV diagnosis and care is likely to be effective and less resource intensive.

4. Community-based testing is a critical approach for reaching people from key populations and vulnerable populations who are unlikely to go to a facility, particularly those who are asymptomatic. To improve access to and uptake of HBV, HCV and HIV testing, community-based testing services should be made available in settings acceptable and convenient to people from key populations and vulnerable populations
5. Accessibility and coverage of viral hepatitis testing will need to be high to have an impact on the prevalence of HBV and HCV among PWID. In order to achieve this, approaches must be acceptable to PWID populations. For example, studies from the UK suggest that offering DBS testing for HCV to PWID attending substance misuse services may increase uptake of testing services.

Prisoners

Many prisons around the world have implemented viral hepatitis and HIV prevention programmes, including HepTS and HTS as part of a comprehensive package of interventions; however, they are often small in scale and lack the necessary combination of essential interventions, greatly reducing their effectiveness.

Access to testing and counselling for viral hepatitis and HIV which is voluntary in nature and easily accessible alongside access to prevention, care and treatment interventions must be urgently scaled up in prisons. Particular attention must go to providing accurate information, obtaining informed consent and maintaining confidentiality. Additionally, there are often major challenges to continuity of care within closed settings and between prisons and the community that need to be addressed.

Pregnant women

Although the risk of mother-to-child transmission (MTCT) of HCV is much lower than that of HBV, perinatal transmission of HCV does occur in 4–6% of births, and the risk is two to three times higher if the mother is coinfected with HIV. MTCT is the most common cause of HCV infection in young children. In some settings, such as in west sub-Saharan Africa, there is a relatively high prevalence of HCV among young children, which may be a result of the high prevalence of HIV/HCV coinfection in that region.

HCV risk factor information should be elicited from pregnant women, and if present, testing of pregnant women for HCV should also be considered alongside testing initiatives for HIV and HBV. There is currently no effective public health intervention to decrease the risk of MTCT of HCV. However, as DAAs become more widely available, they may have a potential role to play in preventing MTCT of HCV if found to be safe and effective for use in pregnancy. Diagnosis of women with HCV before pregnancy should be prioritized so that appropriate treatment and potential HCV clearance can be achieved.

Children

Consideration should be given to testing children born to HCV-infected mothers, particularly if the

mother is coinfected with HIV or has other risk factors for HCV infection, such as injecting drug use. Similar to HBV, the progression of HCV liver disease is usually slow in infected children, but early diagnosis is important to enable monitoring for liver disease and for linkage to appropriate care and treatment when necessary. As DAAs become more widely available, HCV testing in infants and children will become important to be able to offer curative treatment at an early stage before progression of liver disease.

Most infants whose mothers have been diagnosed with HBV or HCV should be followed up and routinely offered EID, and those diagnosed with either with should be regularly monitored for signs of liver disease so that treatment can be offered when necessary. However, some infants are lost to follow up, so additional paediatric case-finding is important. This can be achieved through the routine offer of PITC in health facilities, particularly in high-prevalence settings, and also through testing the family members of index cases where appropriate.

Integration of HBV and HCV testing into child health programmes

In high-prevalence settings: HBV and HCV testing of mothers and infants should be routinely available through a variety of services – child health services, immunization clinics, under-5 clinics, malnutrition services, well-child services and services for hospitalized and all sick children, TB clinics, and services for orphans and vulnerable children. For example, in Malawi it was reported that integrated testing for HIV-exposed infants at six weeks of age into routine postnatal, under-5 and immunization clinics was acceptable and feasible.

Potential viral hepatitis testing approaches to improve case-finding among infants and children

In all settings

- Offer early infant diagnosis for HBV- and HCV-exposed infants.
- Offer testing to all children and adolescents presenting with indicator conditions/signs and symptoms that suggest acute HBV or HCV, including anorexia, nausea, jaundice, right upper quadrant discomfort and abnormal liver function tests.
- Consider offering viral hepatitis testing to all children and adolescents attending HIV services, STI clinics and TB clinics.

In high-prevalence settings and for high-risk individuals

- Offer viral hepatitis testing or retesting to mothers or infants in immunization clinics or under-5 clinics. If mothers are not available for testing or refuse testing, infant testing is an acceptable alternative.
- Offer viral hepatitis testing to all children with parents or siblings receiving any HIV service (for example, PMTCT, ART) through home-based or facility-based HTS.
- Consider viral hepatitis testing in all children and adolescents attending paediatric inpatient health services.

Rationale for recommendation

. Strength of recommendation
. Implementation considerations
16. Research gaps • Large-scale implementation studies in range of different LMICs should be performed to evaluate different testing approaches and the extent to which providers can accurately identify and test high risk patients when employing a targeted approach or birth cohort approach, as well as estimate of linkage to HCV care and the HCV cascade. Terms of cost, impact and cost–effectiveness and evaluation of key drivers in a range of different high-endemic, low-income settings. • A formal cost–effectiveness analysis that compares “targeted” vs “birth cohort” vs “routine” testing requires estimates of the prevalence of high-risk behaviours, stratified by age, the prevalence of HCV among those with high- and low-risk behaviours, stratified by age, and the age structure of the population. This will need to be informed by cost of both HCV therapy in a country, as well as the costs associated with untreated HCV and end-stage liver disease. • What proportion of HCV-positive cases will be missed by a testing policy based on screening for at-risk behaviours and exposures?

4.3. How to test HBV

Decision-making tables – PICO 1

HBsAg testing: Among persons identified for hepatitis B testing, what is the diagnostic accuracy of available assays for detecting HBsAg (RDT, EIA)?

Topic for analysis: How to test

Population: Persons identified for HBV testing

Intervention: Rapid diagnostic test for HBsAg detection

Comparison: Enzyme immunoassays for HBsAg detection

Outcomes: Diagnostic accuracy (Sensitivity, Specificity, Positive predictive value, Negative predictive value, TN, TP, FN, and FP).

Background:

- The most important marker for the diagnosis of hepatitis B infection that may require treatment remains the detection of hepatitis B surface antigen (HBsAg).
- Chronic hepatitis B infection is defined by the detection of HBsAg on two occasions six months apart.
- However, after initial testing, further characterization of the individual's HBV infection is based on a sequential testing strategy of for other markers of HBV infection (supplementary testing) triggered by the detection of HBsAg in the first instance.

Immunoassays (laboratory-based)

- The most widely used HBsAg assays are laboratory-based immunoassays.
- This can be in the form of an enzyme immunoassay (EIA), chemiluminescence immunoassay (CLIA) or electrochemiluminescence immunoassay (ECL).
- These are best suited to settings with high throughput of specimens and where infrastructure (electricity, cold storage, climate-controlled rooms) and skilled staff are consistently available.
- Other simple assays such as agglutination assays are also available for detection of HBsAg but these generally require serum/plasma specimens and cold storage. The results of simple assays may be read visually.

Rapid diagnostic tests (RDTs) – performed in-laboratory or at the point-of-care

- Many laboratories in resource-limited settings may not have access to specialized equipment and

process few specimens, per day. Hence, individual tests, including rapid diagnostic tests (RDTs), may be more appropriate.

- RDTs for detection of HBsAg come in immunofiltration (flow through) and immunochromatographic (lateral flow) formats.
- In general, RDTs do not require cold storage and may be tested using capillary (finger-stick) whole blood.
- The manufacturer's instructions for use should always be followed. The results of RDTs are read visually.
- RDTs may be deliverable at the point of care (POC).
- The expansion of their use depends on their performance and operational characteristics in the setting of intended use, ultimately with the aim being to reach resource-limited settings and offer cost-efficient testing services as an alternative to assays that require specific laboratory infrastructure and staff skills to perform.

The selection of EIA or RDTs should not be mutually exclusive. Choice of appropriate technology can be complex but can usually be distilled down to three main factors: performance, cost and accessibility. There are inevitably trade-offs, based not only on disease prevalence and the health-care infrastructure, but also on technical, socioeconomic, cultural, behavioural considerations.

DRAFT recommendation(s):

Summary pooled diagnostic accuracy of rapid HBsAg assays stratified by study, patient, index and reference test

□ High
□ Moderate
□ Low
□ Very low

	Sub-analysis	Pooled clinical accuracy			Likelihood ratios (REM)		Heterogeneity (Tau-squared)	
		n	*Sen (95% CI)*	*Spec (95% CI)*	*LR^+ (95%CI)*	*LR^- (95% CI)*	*PLR*	*NLR*
Study	*Pre 2005*	19	96.9 (96.0–97.7)	99.7 (99.6–99.8)	266 (106–665)	0.056 (0.033–0.095)	2.72	0.91
	Post 2005	44	86.4 (85.2–87.5)	99.4 (99.2–99.5)	84.6 (43.6–165)	0.126 (0.087–0.183)	4.10	1.27
	Case–control	21	96.7 (96.0–	99.3 (99.0–	105 (48.0–	0.028 (0.010–	2.23	4.86

			97.3)	99.5)	230)	0.076)		
Patient	*Blood donors*	19	91.6 (90.1–92.9)	99.5 (99.3–99.7)	89.2 (32.8–243)	0.106 (0.055–0.204)	3.82	1.86
	HIV+	6	72.3 (67.9 – 76.4)	99.8 (99.5–99.9)	193 (77.4–497)	0.29 (0.22–0.38)	0.384	0.0059
	HIV–	4	92.6 (89.8–94.8)	99.6 (99.0–99.9)	79.5 (11.6–545)	0.08 (0.05–0.13)	2.97	0.080
Index Test	*Whole blood*	11	91.7 (89.1–93.9)	99.9 (99.8–99.9)	347 (158–762)	0.089 (0.058–0.136)	0.81	0.24
	Determine	12	90.8 (88.9–92.4)	99.1 (98.9–99.4)	239 (17.1–33300)	0.077 (0.035–0.168)	20.2	1.56
	BinaxNOW	6	97.6 (96.2–98.6)	100 (99.7–100)	221 (36.1–1350)	0.045 (0.016–0.128)	3.53	1.20
	VIKIA	3	82.5 (77.5–86.7)	99.9 (99.8–100)	1070 (376–3060)	0.108 (0.026–0.458)	<0.005	1.472
	Serodia	3	82.5 (77.5–86.7)	99.9 (99.8–100)	285 (71.4–1140)	0.045 (0.029–0.069)	<0.005	<0.005
Reference Test	*CMIA*	9	80.4 (77.9–82.6)	99.0 (99.6–99.3)	58.5 (31.3–109)	0.141 (0.074–0.268)	0.44	0.73

EIA: enzyme immunoassay; RDT: rapid diagnostic test; CI: confidence interval; *with EIA reference

Quality of evidence

*Refer GRADE table in footnote

Conclusions:

- Rapid diagnostic tests, including those performed on whole blood specimens, have good clinical sensitivity and excellent clinical specificity compared to the reference standard (laboratory-based EIA for HBsAg detection). Improvement in both clinical and analytical sensitivity could potentially enhance their impact globally.
- Caution in HIV-positive individuals is important with significantly reduced clinical sensitivity compared to HIV-negative individuals

  Reassuring accuracy of whole blood specimens compared to plasma or serum specimens further facilitates use in the field.

Risks/benefits

□ Benefits clearly outweigh harms

Benefits **Advantages of testing by RDT compared to laboratory-exclusive EIAs** • Does not require capital investment in laboratory infrastructure, e.g. EIA plate washers, readers, incubators, analysers, cartridge or random-access analysers • Concurrent reduction in maintenance costs and reagents • May be deliverable at the point of care (POC). This may allow greater access to testing and eliminate need for mechanisms for transportation of specimens to the laboratory • If testing at POC, may reduce number of individuals "lost to follow up", i.e. never receive their test results • May be carried out by trained lay providers and health-care workers, in addition to trained laboratory scientists • Dedicated venepuncture may not be required. **Risks** Disadvantages of testing by RDT compared to laboratory-exclusive EIAs • Possible reduction in clinical sensitivity/specificity compared to laboratory-based methods. • RDTs appear to be less sensitive in HIV-positive individuals. • Higher cost per test after expense of laboratory infrastructure has been met. • User variability and subjectivity in reading of a visual assay, second reader suggested. • Performance characteristics may vary with environmental factors, e.g. heat, humidity, storage conditions. • Internal quality control measures may be inferior to standardised laboratory assays, e.g. lack of test kit controls, no specimen addition controls. • Although RDTs using capillary whole blood negate the need for venipuncture and maintenance of laboratory equipment, significant heterogeneity and sub-optimal clinical and analytical sensitivity must be considered. • Recording of results in a database which can be subsequently interrogated and audited as is the case with centralised laboratory testing may be compromised with testing at POC. This may impact on reporting and epidemiological surveillance of the burden of disease.	□ Benefits and harms are balanced □ Potential harms clearly outweigh potential benefits *Are the desirable anticipated effects large?* □ No □ Probably □ Uncertain □ Yes □ Varies
Acceptability, values and preferences A values and preferences survey of implementers and users of hepatitis B and	□ No major variability

C testing services was carried out by FIND in September 2015. A total of 104 respondents from 43 (20 high-income, 23 low- and middle-income) countries. Relating to this PICO, • 47% of respondents from low- and middle-income countries would prefer an RDT method of testing using capillary whole blood compared to dedicated venepuncture, even at the cost of reduced clinical sensitivity). • 50% of respondent would accept an assay with a minimal sensitivity of 95%, 43.5% would accept 98% and 4.3% would accept 90%. However, when the notion of cost was introduced, only 7% responded that 95% sensitivity would not be acceptable. • 77.3% of respondents preferred results of be available on the same day or sooner. Respondents commented that delay in individuals receiving results was likely to result in a loss to follow-up. **Community:** • Support for the most effective testing approach in order to impact on availability of testing, especially in resource-limited settings and remote areas and optimize access to at-risk groups. **Patients/caretakers:** • In the setting of HIV, use of RDTs has facilitated scaling up of testing services in terms of widening access to testing services. **Health-care workers:** • If RDTs are utilized at the POC, this will allow HCWs to carry out testing and organize follow up potentially in one consultation. There is a need for appropriate training of testing-providers and laboratory staff. • The intervention was considered likely to be acceptable to key stakeholders as the sensitivity and the specificity of RDT for screening of chronic HBV infections are comparable with EIAs.	□ Major variability Is the option acceptable to key stakeholders? □ No □ Probably □ Uncertain □ Yes □ Varies
Equity, ethics and human right implications *Will the recommendation raise questions around equity?* • No. The recommendation of the possibility of testing using RDT at POC offers new opportunities for enhancing screening, referral, and treatment for the individuals with chronic HBV infection especially in the resource-limited settings, thus will reduce transmission, morbidity and mortality associated with undetected and untreated HBV infection.	□ Less equitable □ More equitable

Are there ethical implications to this recommendation?

- No major concerns.

Resource use and financial implications

Materials:

- Cost of test kits
- Cost of sterile lancets, alcohol swabs, gloves, sharps bins or other method of disposal of used kits
- Cost of automated RDT readers, if applicable
- Quality control reagents, if applicable (some kits are supplied with positive and negative test kit controls).

Training and supervision:

- Cost of training testing providers and appropriate competency assessment, certification and re-certification of their skills
- From included studies, excellent clinical specificity of all assay formats is reassuring in terms of ensuring cost effective initiation of testing strategies for further investigation and treatment.
- If being utilized at the point-of-care, it will be the responsibility of the testing provider to record and report the result appropriately.

Other:

- Creation of a database into which results obtained by POC can be recorded
- Linkage to care, e.g. antenatal clinics

Possible test procurement cost:

Test	Cost (US$) per test	Source
RDT	0.3–0.95 (procurement cost)	WHO database
EIA	0.4–2.8 (procurement cost)	WHO database

Are the resources required small?

□ No
□ Probably
□ Uncertain
□ Yes
□ Varies

Feasibility and constraints to implementation *Are any major barriers expected for the implementation of this recommendation?* • High-throughput EIAs require certain laboratory infrastructure and equipment with precision and expertise required in its operation. • Delivery of RDTs requires appropriate training of test providers in performing and reading of the test result, storage of materials and recording and reporting of the status. Decentralisation of testing puts tremendous stress on already fragile health systems in terms of training needs, supply chain management, quality assurance, and monitoring and evaluation of effectiveness and impact. External quality assessment of quality of tests and testing possible but challenging when the need for proficiency panels is increased from a few laboratories to hundreds and possibly thousands of POC sites. **Feasibility survey report to be presented at meeting.**	1.1.10 *Is the option feasible to implement?* □ No □ Probably □ Uncertain □ Yes □ Varies

Relevance to different settings/populations

Will this recommendation be most relevant for particular settings (e.g. endemicity)?

- The introduction of HBsAg testing using RDTs will be most relevant in settings where there is poor access to existing laboratory testing-services, either access to centralised laboratory testing or lack of testing-infrastructure in existing laboratories.
- Delivery of RDTs at the point-of-care in remote or resource-limited settings, e.g. HBsAg testing in antenatal clinics may significantly affect the future burden of disease.
- Useful for testing of both symptomatic and asymptomatic individuals.
- It will be most relevant to key affected populations who may be at risk of infection but who may be reluctant to or have poor access to health-care services, such as individuals who attend drug-rehabilitation clinics or prisoners. These individuals require screening, may require treatment if infected or vaccination if not currently infected.
- It will be less relevant in individuals who have good access to health care and in settings where laboratory testing for hepatitis B is already well established.

Rationale for recommendation:

Strength of recommendation
Implementation considerations • Symptomatic vs asymptomatic individuals; in a symptomatic individual, you may not need such good analytical sensitivity than when screening an asymptomatic individual.
Research gaps • Impact of using RDTs for HBsAg at the point-of-care on delivery and implementation of testing services.

GRADE Summary of findings

Question: Should RDTs be used to diagnose HBsAg in HIV-negative individuals?

Sensitivity	0.88 to 0.95
Specificity	0.93 to 1.00

Prevalences	5%	20%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease quality of evidence					Effect per 1000 patients/year		Test accuracy QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 5%	pre-test probability of 20%	
True positives (patients with HBsAg)	4 studies 997 patients	cross-sectional (cohort type accuracy study)	serious [1]	not serious [2]	serious [3]	serious [4]	none	44 to 48	176 to 190	⊕◯◯◯ VERY LOW [1 2 3 4]
False negatives (patients incorrectly classified as not having HBsAg)								2 to 6	10 to 24	
True negatives (patients without HBsAg)	4 studies 997 patients	cross-sectional (cohort type accuracy study)	serious [1]	not serious [2]	serious [3]	not serious [5]	none	884 to 950	744 to 800	⊕⊕◯◯ LOW [1 2 3 5]
False positives (patients incorrectly classified as having HBsAg)								0 to 66	0 to 56	

1. Downgraded by one for risk of bias: all studies were prospective cohort studies *(1)*, although one was assessed as high risk of bias because patients were pre-selected based from known chronic hepatitis B patients.
2. Although study was not specifically designed in HIV-negative patients, clear testing and results were included
3. Downgraded by one for inconsistency: unexplained heterogeneity may arise from differences between studies in specimen condition (serum, whole blood), specimen processing (field vs laboratory), reference tests (CMIA; EIA on dried blood spots) and study population (e.g. known chronic hepatitis B patients, general community screen)
4. Downgraded by one for imprecision: confidence intervals extend below 90% accuracy, with tau-squared for PLR >1 (indicating substantial heterogeneity)

Question: Should RDTs be used to diagnose HBsAg in HIV-positive individuals?

Sensitivity	0.72 (95% CI: 0.68–0.76)
Specificity	1.00 (95% CI: 0.99–1.00)

Prevalence	5%	20%

Outcome	No. of studies (No of patients)	Study design	Factors that may decrease quality of evidence					Effect per 1000 patients/year		Test accuracy QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 5%	pre-test probability of 20%	2
True positives (patients with HBsAg)	5 studies 2566 patients	cross-sectional (cohort type accuracy study)	serious[1]	not serious[2]	serious[3]	serious[4]	none	36 (34–38)	145 (136–153)	⊕◯◯◯ Very low[1–4]
False negatives (patients incorrectly classified as not having HBsAg)								14 (12–16)	55 (47–64)	
True negatives (patients without HBsAg)	5 studies 2566 patients	cross-sectional (cohort type accuracy study)	serious[1]	not serious[2]	not serious[5]	not serious[6]	none	948 (945–949)	798 (796–799)	⊕⊕⊕◯ Moderate[1–2, 5–6]
False positives (patients incorrectly classified as having HBsAg)								2 (1– 5)	2 (1–4)	

1. Downgraded for one for risk of bias: all studies were prospective cohort studies of consecutive patients. Studies used different specimens (serum, 2; capillary whole blood, 1; venous whole blood, 1), reference standards (CMIA, EIA confirmed by neutralization), and had patients with different ART status (four studies ART naive).
2. Not downgraded for indirectness: all studies performed in cohorts of consecutive patients in Tanzania *(2)*, Ghana *(3)*, Malawi *(4)*, South Africa *(5)* and Bissau *(6)*.

3. Downgraded by one for inconsistency with sensitivities ranging from 62% to 100%: unexplained heterogeneity may arise from differences between studies in specimen type, specimen processing and study population. Two studies had very high sensitivities (100%, 96%) while the remainder *(3,5,6)* had low sensitivities (range 62–70%). Tau-squared <1 for studies
4. Downgraded by one for imprecision: confidence intervals 67.9–76.4%. Two studies had very high sensitivities (100%, 96%) while the remainder *(3,5,6)* had low sensitivities (range 62–70%).
5. Not downgraded for inconsistency: specificities ranged from 99% to 100%, with tau-squared <1
6. Not downgraded for imprecision: narrow confidence interval

Question: Should Determine HBsAg be used to diagnose HBsAg in a global setting?

Sensitivity	0.91 (95% CI: 0.89–0.92)
Specificity	0.99 (95% CI: 0.99–0.99)

Prevalences	5%	20%

Outcome	No. of studies (No. of patients)	Study design	Factors that may decrease quality of evidence					Effect per 1000 patients/year		Test accuracy QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 5%	pre-test probability of 20%	
True positives (patients with HBsAg)	12 studies 7552 patients	cohort and case–control type studies [1]	serious	not serious	very serious[2]	not serious	none	45 (44–46)	182 (178–185)	⊕◯◯◯ Very low[2]
False negatives (patients incorrectly classified as not having HBsAg)								5 (4–6)	18 (15–22)	
True negatives (patients without HBsAg)	12 studies 7552 patients	cohort and case–control type studies	serious	not serious	serious[3]	not serious	none	941 (940–944)	793 (791–795)	⊕⊕◯◯ Low[3]
False positives								9 (6–10)	7 (5–9)	

Outcome	No. of studies (No. of patients)	Study design	Factors that may decrease quality of evidence					Effect per 1000 patients/year		Test accuracy QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 5%	pre-test probability of 20%	
(patients incorrectly classified as having HBsAg)										

1. Lin *(7)*, Lien *(8)* and Randrianna *(9)* used a case–control design.
2. Significant heterogeneity across studies for sensitivity; tau-squared 20.2.
3. Heterogeneity exists, but with lower clinical impact; tau-squared 1.56.

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4.4. How to test HCV

Decision-making tables – PICO 2

To ascertain exposure to HCV through anti-HCV testing: Among individuals identified for hepatitis C testing, what is the diagnostic accuracy of available assays for detecting anti-HCV (RDT, EIA)?

1. Topic for analysis: How to test

Population: Individuals identified for HCV testing to ascertain exposure to HCV

Intervention: Rapid diagnostic tests and enzyme immunoassays for detection of antibodies to HCV

Comparison:

1. Nucleic acid testing (NAT)
2. EIA and immunoblot
3. EIA only

Outcomes: Diagnostic accuracy (Sensitivity, Specificity, Positive predictive value, Negative predictive value, TN, TP, FN and FP).

2. Background:

- Screening for exposure to hepatitis C virus (HCV) is dependent on assays that detect antibodies to HCV (anti-HCV) in the first instance.
- Once antibody status is confirmed, the individual should undergo supplementary testing for active HCV infection using an assay designed to detect viral replication, such as HCV RNA or core antigen (HCV cAg).
- Assays designed solely to detect antibodies to viral antigens will inevitably have a "window period" of infectivity in early infection in an individual who has been recently infected whose infection will not be detected by a given serological assay. This diagnostic window period can be shortened by direct detection of viral antigen or nucleic acid.
- The improvements in assay performance over time, in particular the EIAs, have been termed as "generations" of the assays. **(see footnote)*
- It is important to note that the latest generation of assays designed to detect anti-HCV also are combined with cAg in order in increase seroconversion sensitivity of the assay, but these "4th generation" or "combination" assays should not be used to differentiate exposure from chronic infection.

- Note that sensitivity of antibody-only assays may be reduced if the patient is immunocompromised, e.g. HIV, immunosuppressive therapy, renal dialysis.

Immunoassays (laboratory-based)

- The most widely used anti-HCV assays are laboratory-based immunoassays.
- They detect antibodies to core and non-structural antigens. In the case of 4th generation assays, the assay combines detection of antibodies to HCV along with detection of hepatitis C core (P22 Ag) antigen directly.
- These can be in the form of an enzyme immunoassay (EIA), chemiluminescence immunoassay (CLIA), electrochemiluminescence immunoassay (ECL) or recombinant immunoblot assay.
- These are best suited to settings with high throughput of specimens and where infrastructure (electricity, cold storage, climate-controlled rooms) and skilled staff are consistently available.

Rapid diagnostic tests (RDTs)

- Many laboratories in resource-limited settings may not have access to this specialized equipment and process fewer specimens, per day. Hence, individual tests, including rapid diagnostic tests (RDTs), may be more appropriate.
- RDTs for detection of anti-HCV are simple to perform and do not require instrumentation, they come in immunofiltration (flow through) and immunochromatographic (lateral flow) formats and may be read visually.
- In general, RDTs do not require cold storage and may be tested using capillary (fingerstick) whole blood or oral fluid. However, the manufacturer's instructions for use should always be followed.
- RDTs may be deliverable at the point of care (POC).
- The expansion of their use depends on their performance and operational characteristics in the setting of intended use, ultimately with the aim being to reach resource-limited settings and offer cost-efficient testing services as an alternative to assays that require specific laboratory infrastructure and staff skills to perform.

*** Summary of assay "generations"**

1st generation assays:

- Detection of antibodies to NS4 antigen only
- Becomes detectable 12–26 weeks after exposure
- High false-positive rate, i.e. poor positive-predictive value in low-prevalence populations.

2nd generation assays:

- Detects antibodies to NS3, NS4 and core antigen
- Decreased window period of infectivity to 10–24 weeks.

3rd generation assays:

- Detects antibodies to NS3, NS4, NS5 and core antigen
- Further decreased window period of infectivity.

4th generation assays A.K.A. combination assays:

- Combination of detection of circulating antibodies to viral antigens as above, but also addition of monoclonal antibodies to detect hepatitis C antigens (P22 Ag) directly.
- Immunoassays solely for the detection of HCV core antigen were developed initially to close the diagnostic window in seronegative infection and subsequently for the detection of antigenaemia in the presence of antibody.

3. Draft recommendation(s):

4. Summary and quality of evidence

□ High
□ Moderate
□ Low
□ Very low

<u>Systematic review report</u>

A systematic review was commissioned in order to assess this PICO question (*see* SR PICO 2). The purpose of this review was to determine the sensitivity and specificity of assays used to detect hepatitis C antibody using multiple specimen types, including serum, whole blood and oral fluid.

Summary of the evidence

Method: A literature search was conducted focused on hepatitis C, diagnostic tests, and diagnostic accuracy. Studies were included if they evaluated an assay to determine the sensitivity and specificity of a single hepatitis C antibody (HCVAb) test among humans. Two reviewers performed a quality assessment of the studies and extracted data for estimating test accuracy.

Results:

A total of 52 studies were included, evaluating 30 RDT devices of varying generation of assay.

- **RDTs vs EIA only:**
  Pooled clinical sensitivity and specificity were 0.98 and 1.00, respectively.
- **RDTs vs EIA, immunoblot and NAT:**
  Pooled clinical sensitivity and specificity were 0.96 and 1.00, respectively.
- **RDTs vs NAT or immunoblot:**
  Pooled clinical sensitivity and specificity were 0.93 and 0.98, respectively.
- **RDTs vs Ag/Ab combination assay:**
  Pooled clinical sensitivity and specificity were 0.86 and 0.99, respectively.
- **RDTs on oral fluid compared to a serological reference standard using serum/plasma:**
  Pooled clinical sensitivity and clinical specificity were 0.94 and 1.00, respectively.
- Results were comparable across general populations, hospital patients and key populations.

Pooled diagnostic accuracy for HCV antibody tests

Pooled test accuracy for different tests (52 research studies).

Comparison (number of studies)	**Pooled SE**	**95%CI**		**Tau-square *P*-value for hetero-geneity**	**Pooled SP**	**95% CI**		**Tau-square *P*-value for hetero-geneity**
RDT versus EIA only (*n* = 5)	0.99	0.98	1.00	<0.001	1.00	1.00	1.00	<0.001
RDT versus NAT or Immunoblot (*n* = 13)	0.93	0.91	0.95	<0.001	0.98	0.97	0.99	<0.001
RDT versus EIA, NAT or Immunoblot (*n* = 14)	0.97	0.96	0.98	<0.001	1.00	1.00	1.00	<0.001
Oral RDT versus blood reference (*n* = 12)	0.94	0.93	0.96	<0.001	1.00	1.00	1.00	<0.001
Sample type								
Blood samples *(n* = 45)	0.98	0.97	0.98	<0.001	0.98	0.98	0.99	1.1.11
Oral samples (*n* = 12)	0.94	0.93	0.96	<0.001	1.00	1.00	1.00	<0.001
Source population								
General screening (*n* = 17)	0.95	0.94	0.96	<0.001	0.99	0.98	0.99	<0.001
Key population (*n* = 19)	0.97	0.96	0.98	<0.001	0.94	0.94	0.95	<0.001
Hospital patients (n = 16)	0.97	0.96	0.98	<0.001	1.00	1.00	1.00	<0.001
Antibody and Antigen Combo testing (*n*=6)	0.86	0.79	0.94	<0.001	0.99	0.98	1.00	<0.001
Oral kits brand								
OraQuick (n = 8)	0.98	0.97	0.99	<0.001	1.00	1.00	1.00	<0.001

Other brands (n = 6)	0.88	0.84	0.92	<0.001	0.99	0.99	1.00	<0.001

SE: sensitivity; SP: specificity; CI: confidential interval; RDT: rapid diagnostic test; EIA: enzyme immunoassay; NAT: nucleic acid testing

Note:*

[#] Studies conducted across these regions were not included here.

Conclusions:

- Rapid diagnostic tests, including RDTs for oral fluid, have excellent sensitivity and specificity compared to laboratory-based methods, across different populations for detection of antibodies to HCV. This suggests that RDTs can be used to test for HCV antibody.
- Sensitivity/specificity was less for RDTs for anti-HCV compared to newer combination antibody/antigen assays.

Issues raised from the review:

- The comparison of RDT versus immunoblot would include HCV-cleared person: HCV Ab^{+} but HCV RNA^{-}.
- Publication bias, as studies with poor test performance were less likely to be published, lead to exaggerated estimates of the accuracy.

Quality of evidence

*Refer GRADE table in footnote

5. Risks/benefits

Benefits

Advantages of testing by RDT compared to laboratory-exclusive EIAs

- Does not require capital investment in laboratory infrastructure, e.g. EIA washers, readers, incubators, analysers, cartridge or random-access analysers
- Concurrent reduction in maintenance costs and reagents
- May be deliverable at the point of care (POC). This may allow greater access to testing and eliminate need for mechanisms for transportation of specimens to the laboratory
- If testing at POC, may reduce number of individuals "lost to follow-up", i.e. never receive their test results
- May be carried out by trained lay-providers and health-care workers, in addition to trained laboratory scientists
- Dedicated venepuncture may not be required as some assays are validated

□ Benefits clearly outweigh harms
□ Benefits and harms are balanced
□ Potential harms clearly outweigh potential benefits

Are the desirable anticipated effects large?

for capillary whole blood or oral fluid. • Rapid diagnostic tests (RDTs) have potential for scaling up access to hepatitis B testing, particularly for key populations. **Risks** Disadvantages of testing by RDTs compared to laboratory-exclusive EIAs • Increased cost per test after expense of laboratory infrastructure has been met • User variability and subjectivity in reading the visual assay, suggest second reader • Performance characteristics may vary with environmental factors, e.g. heat, humidity, storage conditions. • Internal quality control measures may be inferior to standardized laboratory assays, e.g. lack of test kit controls, no specimen addition controls. • Performance characteristics may vary in certain individuals, e.g. HIV infection, immunosuppressed – lower sensitivity of anti-HCV compared to NAT testing. • Recording of results in a database which can be subsequently interrogated and audited as is the case with centralized laboratory testing may be compromised with testing at POC. This may impact on reporting and epidemiological surveillance of the burden of disease.	□ No □ Probably □ Uncertain □ Yes □ Varies
6. Acceptability, values and preferences A values and preferences survey of implementers and users of hepatitis B and C testing services was carried out by FIND in September 2015. A total of 104 respondents from 43 (20 high-income, 23 low- and middle-income) countries participated. Relating to this PICO, • 47% of respondents from low- and middle-income countries would prefer an RDT method of testing, even at the cost of reduced sensitivity). **Community:** • Support for the most effective testing approach in order to impact on availability of testing, especially in resource-limited and remote areas and optimize access to at-risk groups. **Patients/caretakers:** • In the setting of HIV, use of RDTs has facilitated scaling up of testing services in terms of widening access to testing services. **Health-care workers:** • If RDTs are utilized at POC, this will allow HCWs to carry out testing and	□ No major variability □ Major variability Is the option acceptable to key stakeholders? □ No □ Probably □ Uncertain □ Yes □ Varies

organize follow up potentially in one consultation. There is a need for appropriate training of testing providers and laboratory staff. • Appropriate pre- and post-test counselling was mentioned in the values and preferences survey, which suggested that in low- and middle-income countries, not all individuals were being offered this service. • 47% of respondents (*n* = 23) preferred POC testing using capillary whole blood even at the expense of clinical sensitivity. • The intervention was considered likely to be acceptable to key stakeholders as clinical sensitivity and clinical specificity of RDTs for ascertaining HCV exposure are comparable with EIAs.	
7. Equity, ethics and human right implications *Will the recommendation raise questions around equity?* • No. The recommendation of the possibility of testing using RDTs offers new opportunities for enhancing screening, referral, and treatment for the individuals with chronic HCV infection especially in the resource-limited settings, thus will reduce transmission, morbidity and mortality associated with undetected and untreated HCV infection. *Are there ethical implications to this recommendation?* • No major concerns.	□ Less equitable □ More equitable
Resource use and financial implications **Materials:** • Cost of test kits • Cost of sterile lancets, alcohol swabs, gloves, sharps-bins or other method of disposal of used-kits • Cost of automated RDT readers, if applicable • Quality control reagents, if applicable (some kits are supplied with positive and negative test kit controls) **Training and supervision:** • Cost of training testing providers and appropriate competency assessment, certification and re-certification of their skills • From included studies, excellent specificity of all assays is reassuring in	*Are the resources required small?* □ No □ Probably □ Uncertain □ Yes □ Varies

terms of ensuring cost–effective initiation of algorithms for further investigation and treatment.

Other:

- Creation of a database into which results obtained by POC can be recorded
- Linkage to care, e.g. antenatal clinics

Possible test-procurement costs:

RDTs	Cost (US$) per test	Source
	0.50–1.70 (>10 for oral fluid)	MSF, WHO database
Laboratory-based assays		
HCV EIA	2.60–4.30 (procurement costs)	WHO database
HCV RNA	~20	

8. Feasibility and constraints to implementation

Are any major barriers expected for the implementation of this recommendation?

- High-throughput EIAs require extensive laboratory infrastructure and equipment with staff expertise in its operation. Batching can lead to long delays before results are available.
- Delivery of RDTs requires appropriate training of test providers in performing and reading of the test result, storage of materials and recording and reporting of status.
- Decentralization of testing puts tremendous stress on already fragile health systems in terms of training needs, supply chain management, quality assurance, and monitoring and evaluation of effectiveness and impact. External quality assessment of quality of tests and testing possible but challenging when the need for proficiency panels is increased from a few laboratories to hundreds and possibly thousands of POC sites.

Feasibility survey report to be presented at meeting.

Is the option feasible to implement?

□ No
□ Probably
□ Uncertain
□ Yes
□ Varies

9. Relevance to different settings/populations

Will this recommendation be most relevant for particular settings (e.g. endemicity)?

- This recommendation of the introduction of RDTs will be most relevant in settings where there is poor provision of laboratory testing-services, either access to centralized laboratory testing or lack of testing infrastructure in existing laboratories.
- Delivery of RDTs at the POC will have relevance more in remote or resource-limited settings,

compared to settings where there is good access to health care and established screening programmes.

- It will be most relevant to groups of patients at risk of infection but who may be reluctant to or have poor access to health-care services, such as individuals who attend drug-rehabilitation clinics or closed settings such as prisoners. These individuals require screening and may require assessment and treatment if found to be infected.
- It will be less relevant in individuals who have good access to health care and in settings where laboratory testing for hepatitis C is already well established.

10. Rationale for recommendation:

11. Strength of recommendation

12. Implementation considerations

13. Research Gaps

- Impact of testing at POC using RDTs to rule out/rule in HCV exposure on HCV-associated morbidity and mortality and onward transmission testing and treatment programmes.

GRADE Summary of findings

Table: Strength of evidence for diagnostic accuracy

	Unit of analysis	Type of samples	Studies, *n*	Risk of bias	Consistency	Directness	Precision	# of samples	Strength of evidence	Sen (95% CI)	Sp (95% CI)	Pretest probability (%)	Positive LR (95% CI)	PPV	Negative LR (95% CI)	NPV	Strength evidence
RDT versus EIA, or immunoblot	General population, hospital patients, blood donors, injection drug users and other high-risk populations	Oral fluid, serum or plasma	14	Mod	Se: Inconsistent	Indirect	Precise	42,239	Se: Mod	0.97 (0.0.96 –0.98)	1.00 (1.00 –1.00)	0.05	372.92 (267.56 –574.12)	0.95	0.03 (0.02 –0.04)	1.00	
					Sp: Consistent				Sp: Mod								
Oral RDT versus blood reference	General population, hospital patients, blood donors, injection drug users and other high-risk populations	Oral fluid, serum or plasma	12	Mod	Se: Inconsistent	Indirect	Precise	14,547	Se: Mod	0.94 (0.93 –0.96)	1.00 (1.00 –1.00)	0.05	314.5 (202.02 –684.07)	0.94	0.06 (0.04 –0.07)	1.00	
					Sp: Consistent				Sp: Mod								

Mod: Moderate; Sen: sensitivity; Sp: specific

4.5. How to test - testing strategy HBV

Decision-making tables – PICO 3

Testing strategy to diagnose chronic HBV infection through detection of HBsAg: Among individuals identified for hepatitis B testing, what is the best testing strategy (diagnostic accuracy and other outcomes) for detection of HBsAg? (One-assay versus two-assay strategy)

1. Topic for analysis: How to test

Population: Persons identified for HBV testing

Intervention: One-assay testing strategy; one HBsAg assay

Comparison: Two-assay testing strategy; two different HBsAg assays

Outcomes: Diagnostic accuracy (Sensitivity, Specificity, Positive predictive value, Negative predictive value, TN, TP, FN, and FP).

Background:

HIGH CONCERN HIV	MODERATE HBV	LOW HCV
Lifelong ARVs initiated on basis of serologic test alone Major implications to false positive results	Initiation of lifelong TDF would usually require HBV DNA or presence of cirrhosis	Initiation of DAAs would always require confirmation of ACTIVE infection with HCV NAT or Ag

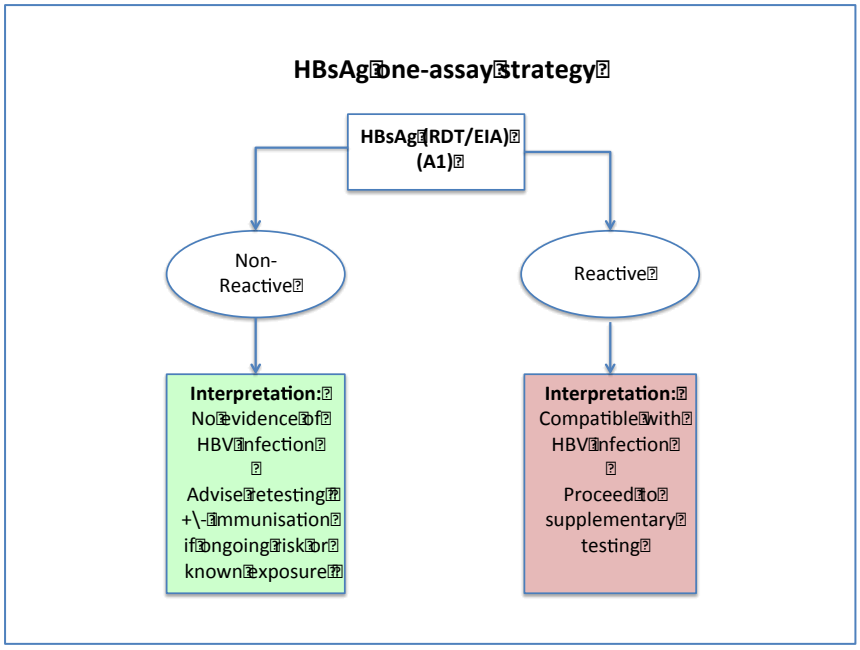
- The most important marker for the diagnosis of chronic hepatitis B infection that may require treatment remains the detection of hepatitis B surface antigen (HBsAg).
- Although the case definition of chronic hepatitis B is the detection of HBsAg twice six months apart, if facilities exist, after an initial positive result, supplementary testing can be undertaken in order to facilitate entry into a care pathway.
- HBsAg will be detectable in the blood if there is current hepatitis B infection. Confirmation of the specificity of a reactive HBsAg first-line test result is usually carried out by either;
  i) repeating the HBsAg testing in a different assay of similar sensitivity, or
  ii) performing a neutralization test using a specific anti-HBs-containing reagent in the same first-line assay after appropriate dilution of the specimen under test. Specificity is confirmed when this reagent abolishes reactivity in the assay.
- This PICO question addresses the issue of whether a positive result from a single HBsAg assay has sufficient specificity in order to proceed to supplementary testing and/or entry into a care pathway, or whether confirmatory testing on the same specimen with a different HBsAg assay

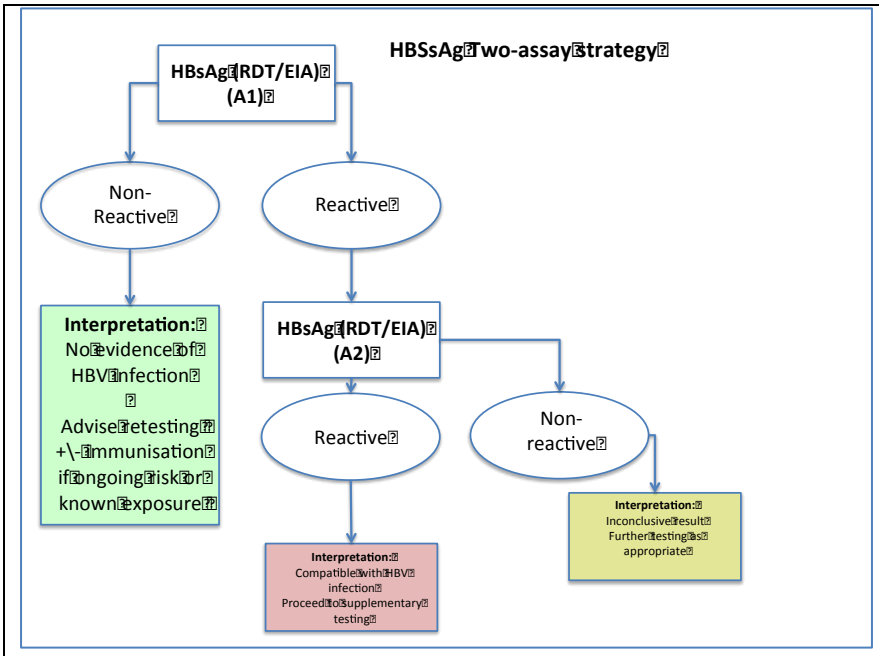
(or neutralization), performed sequentially after the first assay is required.

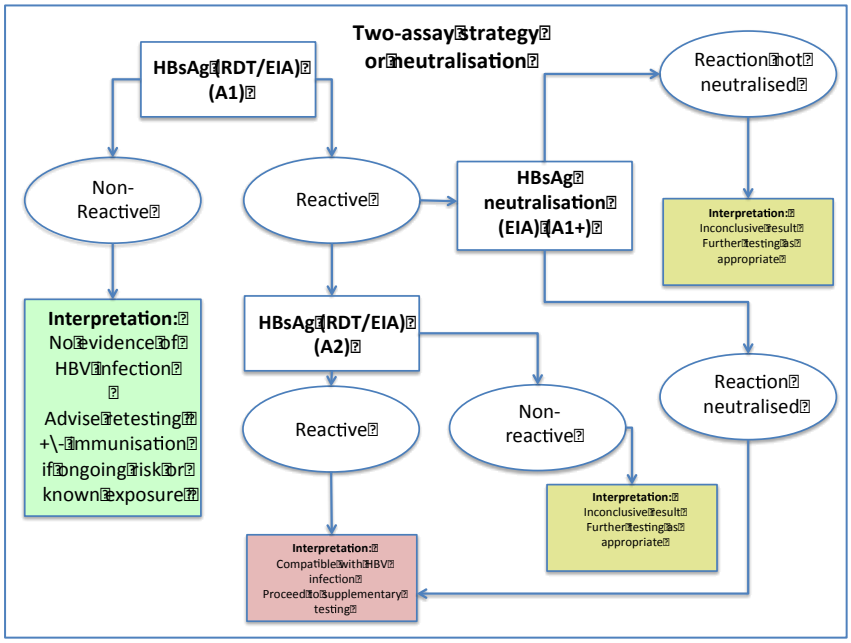
Testing strategies:

- WHO recommends standardized testing strategies to maximize the accuracy of hepatitis B and C testing while minimizing cost and increasing simplicity.
- A testing strategy describes a testing sequence for a specific testing objective, taking into consideration the presumed prevalence of the analyte to be tested in the population. In both high and low prevalence settings, more than one assay may be required.
  See footnote for further detailed explanation of the one- and two-assay strategies.

Figs 1–3: Possible testing strategies for detecting HBsAg







Since the decision for PICO 3 critically depends on whether currently available tests for detecting HBsAg show acceptable sensitivity and specificity, the following conclusions from PICO 1 should be considered:

- Overall compared to an EIA reference, RDTs had pooled clinical sensitivity 90% (95% CI: 89, 91) and clinical specificity 100% (95% CI: 99, 100).
- RDTs were more accurate among HIV-negative patients, with pooled clinical sensitivity of 93% (95% CI: 90, 95), and pooled clinical specificity of 100% (95% CI: 99, 100) compared to results in HIV-positive patients in whom RDTs are 72% sensitive (95% CI: 68, 76) and 100% specific (95% CI: 100, 100) compared to an EIA reference.
- Results for capillary whole blood specimens were comparable to serum and less heterogeneous.

The two-test strategy involves the use of a more sensitive test as the screening test and a second test that is more specific to reduce false-positive results. Since the review in PICO 1 showed that HBsAg serological assays have excellent specificity, then there is no need for the use of another test if a simple testing strategy is desired.

2. DRAFT recommendation(s):

Summary and quality of evidence

Systematic review

- A systematic review by the London School of Hygiene and Tropical Medicine (LSHTM) was commissioned to assess this PICO question.

Summary of results

- No studies directly compared diagnostic accuracy, cost, cost-effectiveness of one- vs two-assay HBsAg testing strategies.
- The reviewers found four documents that demonstrated a strategy for hepatitis B testing.
- The Public Health England UK standard for microbiology investigation (SMI) (under review) suggested that either neutralization or repeat testing of the same specimen with a different HBsAg assay would be acceptable, but did not directly quote any evidence for this.
- The Australian "National Testing Policy for hepatitis B" suggested that HBsAg be confirmed with neutralization but also anti-HBc and anti-HBs should be assessed in order to form a profile and suggested management, e.g. immunization.
- Fan et al. (2014) used a decision-tree model of sequential HBeAg and HBV-DNA in a cohort of pregnant women in order to calculate cost-effectiveness.

□ High
□ Moderate
□ Low
□ Very low

Conclusions • Diagnosis of HBV is very complex and there may not be 1–2 simple algorithms that will cover all settings. **Quality of evidence** • Study quality was not evaluated using the QUADAS-2 tool and the STARD checklist, as it was not applicable. • None of the studies met inclusion criteria. **GRADE Summary of findings** Not applicable as no studies met the inclusion criteria for the systematic review. • All PICOs related to HBV will need to be looked at together in order to try and answer PICO 3. **<u>Modelling studies of one-assay vs two-assay strategies</u>** *To be added at meeting.*	
3. Risks/benefits **Benefits** • The intervention of testing using a single HBsAg assay would simplify the process of testing. • Sensitivity, i.e. detecting those individuals with HBV infection should not be compromised with a one-assay strategy. This will identify those who require further assessment and possible treatment. • Cost of overall testing may be reduced. • May allow more rapid reporting of the result, so that the patient can be appropriately followed up for further assessment, vaccination or given health protection advice, e.g. measures to reduce onward transmission. **Risks** • Possible reduced positive predictive value of a single test result on one	□ Benefits clearly outweigh harms □ Benefits and harms are balanced □ Potential harms clearly outweigh potential benefits *Are the desirable anticipated effects large?* □ No □ Probably □ Uncertain □ Yes □ Varies

assay may lead to more false-positives and associated anxiety and cost associated with follow up, before the correct diagnosis is ultimately made. This is especially relevant in low-prevalence settings at which even a test of 99% specificity may yield more false-positive than true-positive results. • If analytical or clinical sensitivity of the first-line assay is lower than the combination of two different assays, this may result in more false-negatives, resulting in individuals not referred for the appropriate further assessment and potential ongoing transmission • The recommendation of confirmation with neutralization is reliant on adequate facilities being available. If performed incorrectly, may result in indeterminate results, leading to increased cost of further testing.	
4. Acceptability, values and preferences **Community/patients/caretakers** • Patients require a simple and rapid testing strategy, yet one that is acceptably accurate for the purpose of testing **Health-care workers** • HCWs will need to understand the strengths and limitations of any given testing strategy and appropriately counsel patients who are screened. • HCWs will need to appropriately act on results, either positive and negative. • If performing testing at POC, HCWs need to be adequately trained in the use of RDTs and record/report results appropriately. **Other** • Laboratory staff need to be appropriately trained in performance of the various assays according to the manufacturers' instructions for use, especially if HBsAg neutralization is being utilized	□ No major variability □ Major variability Is the option acceptable to key stakeholders? □ No □ Probably □ Uncertain □ Yes □ Varies
Equity, ethics and human right implications *Will recommendation raise questions around equity?* • Yes, availability of HBsAg neutralization assays or other supplementary testing, such as nucleic acid testing and/or further hepatitis B markers with be more available in settings with established hepatitis B testing	□ Less equitable □ More equitable

facilities.

- However, note that where an RDT for HBsAg is used and no neutralization reagents are available, confirmation of an acute or chronic infection for diagnostic purposes may be concluded by repeat testing for HBsAg after a period of time. Consecutive reports of HBsAg-positive status twice at least 6 months apart will confirm a diagnosis of chronic HBV infection.

Are there ethical implications to this recommendation?

- The ethical implication of recommending a strategy with possible suboptimal PPV.

5. Resource use and financial implications

Diagnostics/laboratory monitoring

- Cost of a one-test vs two-test strategy will be less due to fewer tests being used.

Assay format	Indicative cost (US$) per test	Source
RDT	0.30–0.95 (procurement cost)	WHO database
EIA	0.40–2.80 (procurement cost)	WHO database

Training and supervision

- Appropriate training for laboratory staff and health-care workers delivering testing services at the point of care.

Are the resources required small?

□ No
□ Probably
□ Uncertain
□ Yes
□ Varies

6. Feasibility and constraints to implementation

Are any major barriers expected for the implementation of this recommendation?

- Procurement of appropriate test kits meeting required sensitivity/specificity/analytical sensitivity

Is the option feasible to implement?

□ No
□ Probably

• Delivery of testing services to remote/resource-limited settings **<u>Feasibility survey report to be presented at meeting.</u>**	□ Uncertain □ Yes □ Varies

7. Relevance to different settings/populations

Will this recommendation be most relevant for particular settings (e.g. endemicity)?

- This recommendation will be most relevant in settings that do not have established hepatitis B testing programmes and of less relevance where laboratory testing for hepatitis B is already well established.

8. Rationale for recommendation:

9. Strength of recommendation

10. Implementation considerations

11. Research gaps

- Impact of a one- vs two-step testing strategy on hepatitis B testing programmes
- Cost-effectiveness studies of one- versus two-assay or neutralization testing strategies

Footnote: Explanation of one- and two-assay strategies and PPV and NPV calculation method based on prevalence

One-assay strategy

- A single test is performed. If the test result is reactive, an "HBsAg positive" status is reported, with need for complementary testing and follow-up HBsAg testing in 6 months to diagnose chronic infection recommended.
- If the initial test result is non-reactive, an "HBsAg negative" status is reported.
- This strategy efficiently identifies most uninfected individuals and rules out chronic HBV infection; it identifies those likely to be infected and in need of additional testing.

- It is a suitable testing strategy for resource-limited settings because only a single test or one assay is performed as long as an assay that meets high standards for analytical and clinical sensitivity and clinical specificity is used.
- Limitations of this approach are that a small percentage of test results may be false positive, so appropriate procedures to follow up individuals need to be in place.

Two-assay strategy

- The test results of two different assays are used sequentially (i.e. not in parallel), to increase the positive predictive value of the overall test strategy.
- If the test result on the first-line assay is non-reactive, an "HBsAg negative" result is reported. However, if the test result on the first-line assay is reactive, a second test with an assay from a different manufacturer is performed.
- If both test results are reactive, the status is reported as: "HBsAg positive" with need for supplementary testing and follow-up HBsAg testing in 6 months to diagnose chronic infection recommended." If the test result on the second-line assay is non-reactive, the result is reported as "HBsAg inconclusive; requires additional testing."
- This strategy efficiently identifies most uninfected individuals and more definitively rules out chronic HBV infection than a one-assay testing strategy. It improves the positive predictive value when the test results of two different assays are both reactive. It can be used by non-laboratory staff, provided that adequate quality assurance standards are in place.
- The two-assay strategy may produce a small number of false-positive results (particularly in low-prevalence settings); some persons with recent HBV infection may receive false-negative results, which will depend on the analytical sensitivity of the assays used.

Worked example to illustrate the effect of prevalence on predictive values for the two different testing strategies

Assuming the following assay performance characteristics:

- If Assay 1 has sensitivity of 99% and specificity of 98%.
- If Assay 2 has sensitivity of 99.4 and specificity of 99.5%.

	Prevalence of analyte		
	0.1%	1%	10%
Positive predictive values			
Assay 1	4.7%	33.3%	84.6%
Assay 1 + Assay 2 (serial)	90.7%	99%	99.9%
Negative predictive values			
Assay 1	99.9%	99.99%	99.99%

Using the following equation for PPV and NPV that incorporates prevalence more correctly,

$$\mathrm{PPV} = \frac{\text{sensitivity} \times \text{prevalence}}{\text{sensitivity} \times \text{prevalence} + (1 - \text{specificity}) \times (1 - \text{prevalence})}$$

$$\mathrm{NPV} = \frac{\text{specificity} \times (1 - \text{prevalence})}{(1 - \text{sensitivity}) \times \text{prevalence} + \text{specificity} \times (1 - \text{prevalence})}$$

Reference: Altman DG, Bland JM. Diagnostic tests 2: predictive values. BMJ. 1994 Jul 9; 309(6947): 102. Available at: https://www.ncbi.nlm.nih.gov/pmc/ articles/PMC2540558 /pdf/bmj00448-0038a.pdf

4.6. How to test - testing strategy HCV

Decision-making tables – PICO 4

Testing strategy to ascertain exposure to HCV: Among persons identified for hepatitis C testing, what is the best testing strategy (diagnostic accuracy and other outcomes) for detection of antibodies to HCV? (One-assay versus two-assay strategy)

1. Topic for analysis: How to treat

Population: Persons identified for hepatitis C virus (HCV) testing

Intervention: One-assay testing strategy; one HCV serological assay

Comparison: Two-assay testing; two different HCV serological assays

Outcomes: Diagnostic accuracy (Sensitivity, specificity, positive predictive value, Negative predictive value, TN, TP, FN, and FP).

2. Background:

HIGH CONCERN HIV	MODERATE HBV	LOW HCV
Lifelong ARVs initiated on basis of serologic test alone Major implications to false positive results	Initiation of lifelong TDF would usually require HBV DNA or presence of cirrhosis	Initiation of DAAs would always require confirmation of ACTIVE infection with HCV NAT or Ag

- WHO recommends standardized testing strategies to maximize accuracy while minimizing cost and increasing simplicity.
- A testing strategy describes a testing sequence for a specific testing objective, taking into consideration the presumed prevalence of the analyte to be tested in the population. In both high- and low-prevalence settings, more than one serological assay may be required to establish exposure to HCV.
- Screening for exposure to HCV is dependent on assays that detect antibodies to HCV (anti-HCV) in the first instance. Once antibody status is confirmed, the patient will undergo supplementary testing for active HCV infection using an assay designed to detect viral replication, such as HCV RNA or core antigen (HCV cAg).
- It is important to note that the latest generation of assays designed to detect anti-HCV also are combined with cAg in order in increase sensitivity of the assay, but these "combo" assays should not be used to differentiate HCV exposure from active HCV infection.
- The question this PICO aims to address is whether one or two serological assays (anti-HCV or HCV Ag/Ab combo assays) performed sequentially are required in terms of specificity and positive predictive value in order to proceed to supplementary testing.

See footnotes for explanation of one-test and two-test strategies.

Figs 1–4: Possible testing strategies for detection of anti-HCV and diagnosis of active HCV infection

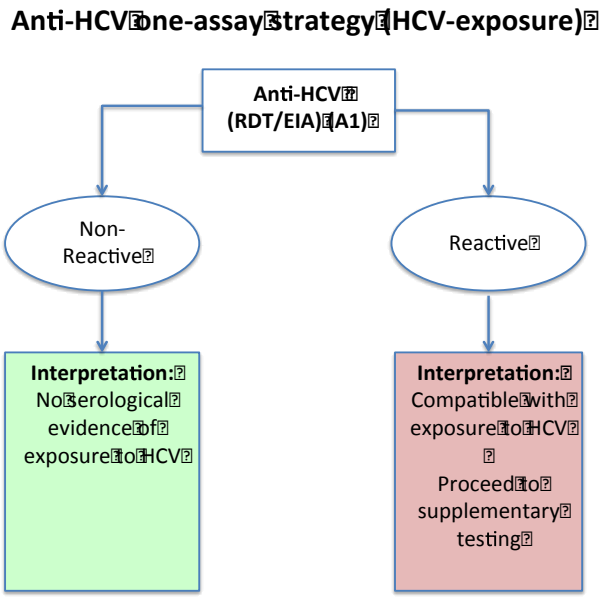


Fig. 1. One-assay testing strategy for exposure to HCV (detection of anti-HCV)

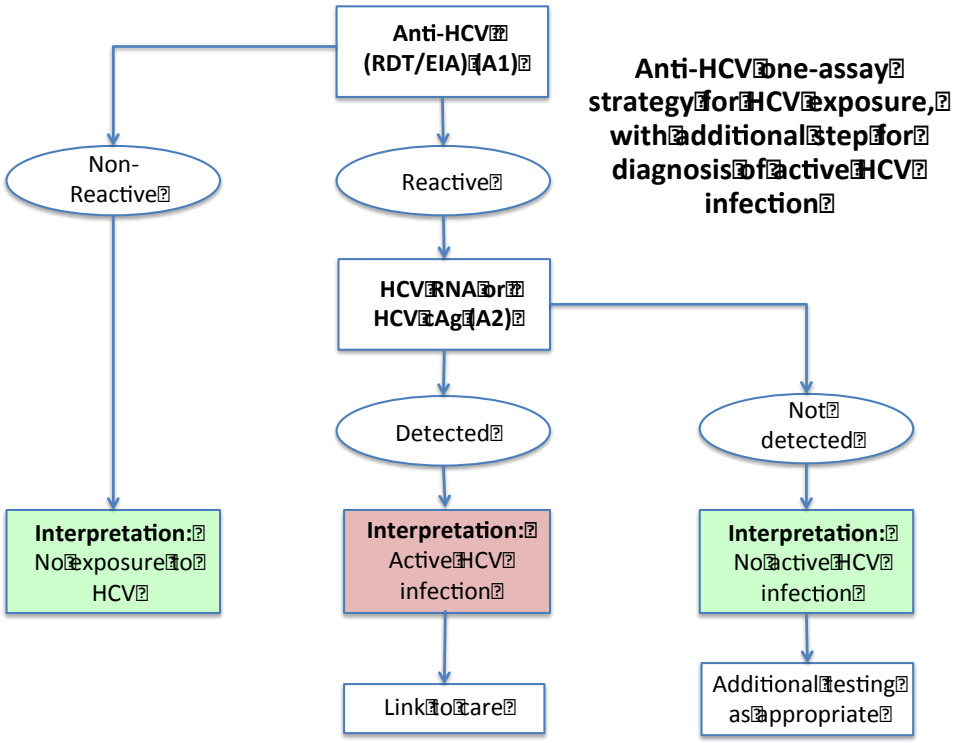


Fig. 2. One-assay testing strategy for diagnosis of HCV (detection of anti-HCV, followed by HCV RNA/core Ag)

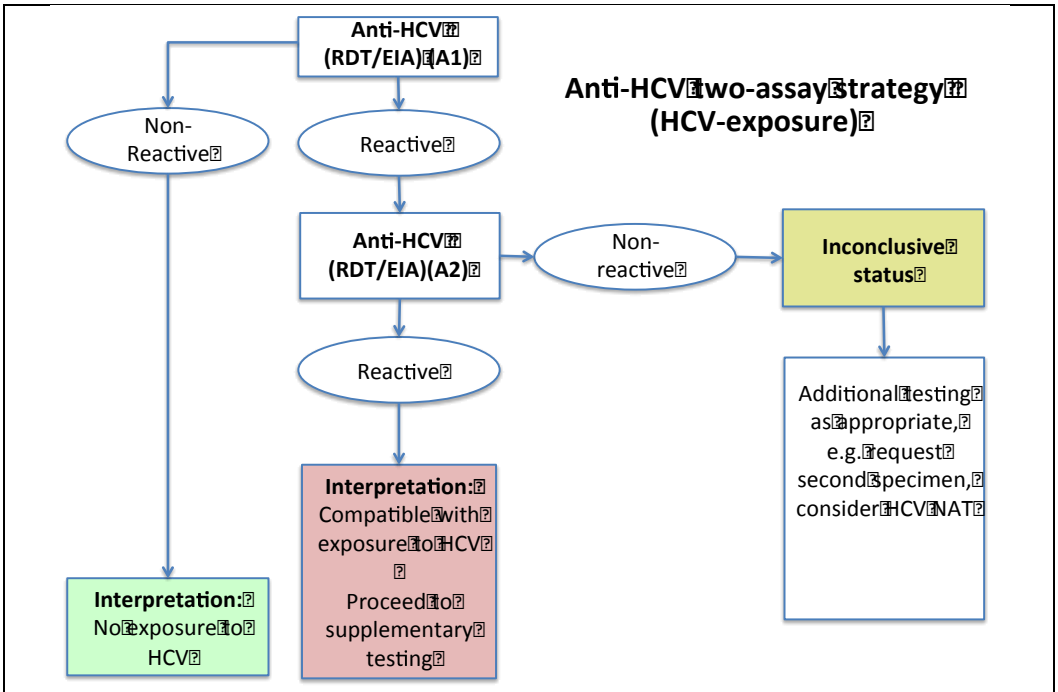


Fig. 3. Two-assay testing strategy for exposure to HCV (detection of anti-HCV)

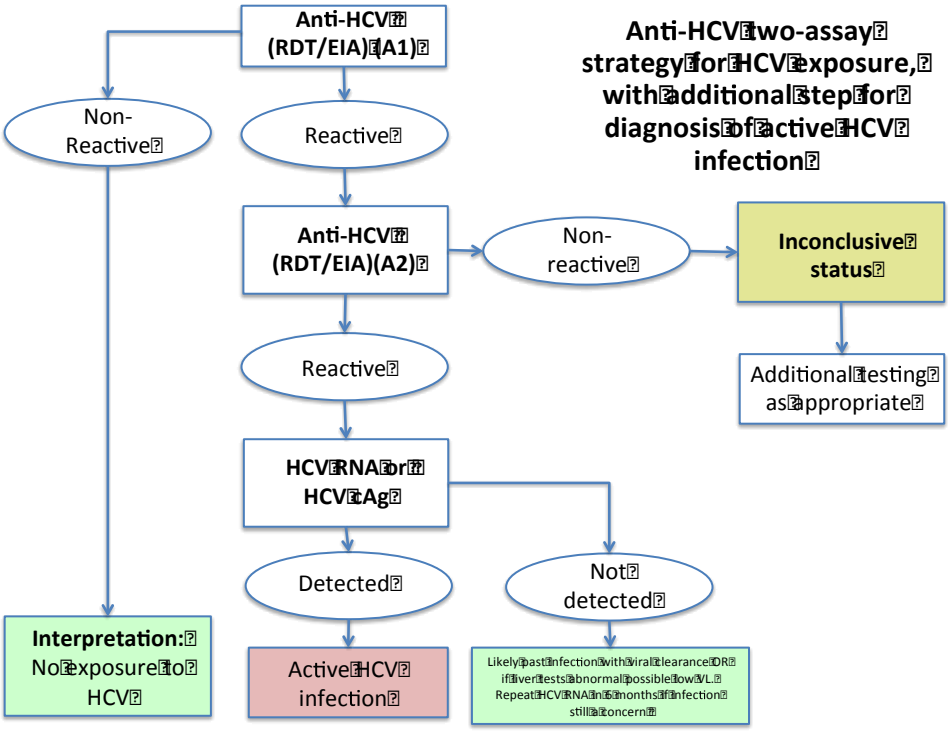


Fig. 4. Two-assay testing strategy for diagnosis of HCV (detection of anti-HCV, followed by HCV RNA/core Ag)

3. Draft recommendation(s):

4. Summary and quality of evidence

□ High
□ Moderate
□ Low
□ Very low

Systematic review:

A systematic review was commissioned in order to assess this PICO question. The purpose of this review was to determine from the published literature the evidence for a one-assay strategy for one-assay testing compared to two assays (sequential), before testing to diagnose active HCV infection is undertaken.

Summary of results

No study compared the diagnostic accuracy, cost, or cost-effectiveness of one- versus two-assay testing strategies for HCV exposure.

The result of the PICO 2 review showed that the overall pooled clinical sensitivity and clinical specificity for HCVAb RDT versus EIA were 0.98 (95% CI 0.98–1.00) and 1.00 (95% CI 1.00–1.00). The overall pooled clinical sensitivity and clinical specificity for RDTs that use oral fluid compared to a serological reference standard using serum/plasma were 0.94 (95% CI 0.93–0.96) and 1.00 (95% CI 1.00–1.00).

See footnote for tables illustrating the impact of prevalence and one- versus two-assay strategies on PPV.

Quality of evidence

- Study quality was not evaluated using the QUADAS-2 tool and the STARD checklist, as it was not applicable.
- None of the studies met inclusion criteria.

GRADE Summary of findings

Not applicable as no studies met the inclusion criteria for the systematic review.

Predictive modelling analysis: (Parry, Public Health England)

- There is a strong influence of prevalence and assay specificity on positive predictive value (PPV).
- At high prevalence, the use of a highly specific single screening test yields a PPV in excess of 0.99, and the ratio of true-positive (TP):false-positive (FP) results is high (164).
- At the lowest prevalence (e.g. 0.4%), PPV might be expected to fall below 0.5, yielding more false-positive diagnoses than true ones, particularly if the test specificity falls below 0.995.
- Even in middling prevalence, the PPV will struggle to exceed 0.9 should the specificity performance of the test employed fall below 0.99.
- The negative predictive value (NPV) is generally high except in high-prevalence populations (e.g. 45%) when a test with relatively poor sensitivity (<99%) is employed.

• In all but the highest population prevalence, the use of less sensitive test kits in the two-test strategy had only a modest impact on NPVs. In all but the highest prevalence, the calculations demonstrate the potential for substantial gains in diagnostic accuracy in return for a modest investment in a second, independent, test kit to be applied to initially reactive individuals. • For example, taking a model population of 100 000 with an anti-HCV prevalence of 2%, the PPV of an algorithm employing two independent test kits with modest sensitivities and specificities of 0.98 is improved from 0.500 to 0.980 in return for the supplementary use of <4000 of Test Kit B. **<u>Predictive modelling analysis: (Linas, Boston University)</u>** *To be added at meeting*	
5. Risks/benefits **Benefits** • The intervention of testing using a single test on one anti-HCV/core Ag assay will simplify the process of testing. • Cost of overall testing may be reduced. • May allow more rapid reporting of the result, so that the patient can be appropriately followed up for further assessment or given health protection advice. **Risks** • Possible reduced PPV of a single test on one assay may lead to more false-positives, especially in low-prevalence settings, with associated anxiety and cost associated with follow-up testing or treatment.	□ Benefits clearly outweigh harms □ Benefits and harms are balanced □ Potential harms clearly outweigh potential benefits *Are the desirable anticipated effects large?* □ No □ Probably □ Uncertain □ Yes □ Varies

6. Acceptability, values and preferences A values and preferences survey of implementers and users of hepatitis B and C testing services was carried out by FIND in September 2015. A total of 104 respondents from 43 (20 high-income, 23 low- and middle-income) countries participated. Relating to this PICO, • 50% of respondents to the values and preference survey from low- and middle-income settings (*n* = 23) preferred a one-assay screening strategy before confirmatory testing (compared to a one-assay strategy for diagnosis of HCV active infection). **Patients/caretakers** • Patients require a simple and rapid testing strategy, yet one that is acceptably accurate for the purpose of testing. **Health-care workers** • HCWs will need to understand the strengths and limitations of any given testing strategy and appropriately counsel patients who are screened. • HCWs will need to appropriately act on results, either positive or negative. **Other** • Laboratory staff needs to be appropriately trained in performance of the various assays according to the manufacturers' instructions for use.	□ No major variability □ Major variability Is the option acceptable to key stakeholders? □ No □ Probably □ Uncertain □ Yes □ Varies
Equity, ethics and human right implications *Will recommendation raise questions around equity?* • Yes, availability of HCV RNA NAT assays or other supplemental testing, such as core antigen testing, will be more easily available in settings with established hepatitis C testing facilities. *Are there ethical implications to this recommendation?*	□ Less equitable □ More equitable

7. Resource use and financial implications

Are the resources required small?

□ No
□ Probably
□ Uncertain
□ Yes
□ Varies

Diagnostics/Laboratory monitoring

- Cost of a one-test vs two-assay strategy will be less due to fewer tests being used but the positive predictive value is higher and therefore the status will be more accurately assigned.

Assay format	Indicative cost (US$) per test	Source
RDTs	0.50–2.00 (10 for oral fluid RDTs)	MSF, WHO
EIA	0.50–1.70	WHO
HCV Ag	25–50	MSF
Quantitative NAT for HCV RNA	10–45	MSF, UNITAID
Qualitative NAT for HCV RNA)	43–51	UNITAID

8. Feasibility and constraints to implementation

Are any major barriers expected for the implementation of this recommendation?

Is the option feasible to implement?

□ No
□ Probably
□ Uncertain
□ Yes
□ Varies

- None, provided there is internal and country commitment to HCV testing
- Regional and country variability in access to treatment and procurement of testing equipment and services
- With regard to any diagnostic assay, availability of a local laboratory, which is able to procure the testing platform and reagents required for testing.

Feasibility survey report to be presented at meeting

9. Relevance to different settings/populations

Will this recommendation be most relevant for particular settings (e.g. endemicity)?

10. Rationale for recommendation:
11. Strength of recommendation
12. Implementation considerations
13. Research gaps • Development/implementation projects evaluating use of HCV core antigen as a one-stop diagnostic test • Impact of one-test vs two-test screening on hepatitis C testing services

GRADE Summary of findings

Footnote: Explanation of one- and two-assay strategies

One-assay testing strategy

- A single test is performed. If the test result is reactive, an "anti-HCV positive" status is reported. A specimen should be collected for supplemental laboratory testing to pursue the testing algorithm. If the initial test is non-reactive, an "anti-HCV negative" status is reported.
- This testing strategy efficiently identifies most uninfected individuals, it identifies those likely to be infected and in need of additional testing.
- It is suitable for resource-limited settings because one single test on one assay is performed as long as the assay used has high clinical sensitivity and clinical specificity. Limitations of this approach are that a small percentage of test results may be false positive, so appropriate procedures to follow up individuals need to be in place.

Two-assay testing strategy

- The test results of two different assays are used sequentially (i.e. not in parallel), to improve the positive predictive value of overall testing strategy.
- If the test result for the first-line assay is non-reactive, an "anti-HCV negative" status is reported.
- If the test result for the first-line assay is reactive, a second test performed on an assay from a different manufacturer is performed.
- If both test results are reactive, the result is reported as: "anti-HCV positive for further diagnostic testing." If the test result of the second-line assay is non-reactive, the result is reported as "anti-HCV inconclusive; requires additional testing".
- This testing strategy efficiently identifies most uninfected individuals and more definitively rules out exposure to HCV than a one-assay testing strategy. It improves the positive predictive value when the test results for two different assays are both reactive. It can be used by non-laboratory staff, provided that adequate quality assurance measures are in place.

- The two-assay testing strategy may still produce a small number of false-positive results (particularly in low-prevalence settings); some persons with recent exposure may receive false-negative results which will depend on the analytical sensitivity of the assays used

Modelling tables:

Table 1: Outcomes for single-test strategy based on typical estimates of test accuracy

Anti-HCV Prevalence: 45%		Population		100,000								
Test A		Test B										
Sens	Spec	Sens	Spec	True Positives	False Negatives	False Positives	True negatives	Total Tests	PPV	NPV	Ratio of TP:FP	Overall sens.	Overall spec.
1.000	0.995	n/a	n/a	45,000	0	275	54,725	100,000	0.994	1.000	164	1.000	0.995
0.995	0.995	n/a	n/a	44,775	225	275	54,725	100,000	0.994	0.996	163	0.995	0.995
0.995	0.980	n/a	n/a	44,775	225	1,100	53,900	100,000	0.976	0.996	41	0.995	0.980
0.980	0.980	n/a	n/a	44,100	900	1,100	53,900	100,000	0.976	0.984	40	0.980	0.980

Anti-HCV Prevalence: 10%		Population		100,000								
Test A		Test B										
Sens	Spec	Sens	Spec	True Positives	False Negatives	False Positives	True negatives	Total Tests	PPV	NPV	Ratio of TP:FP	Overall sens.	Overall spec.
1.000	0.995	n/a	n/a	10,000	0	450	89,550	100,000	0.957	1.000	22	1.000	0.995
0.995	0.995	n/a	n/a	9,950	50	450	89,550	100,000	0.957	0.999	22	0.995	0.995
0.995	0.980	n/a	n/a	9,950	50	1,800	88,200	100,000	0.847	0.999	5.5	0.995	0.980
0.980	0.980	n/a	n/a	9,800	200	1,800	88,200	100,000	0.845	0.998	5.4	0.980	0.980

Anti-HCV Prevalence: 2%		Population		100,000								
Test A		Test B										
Sens	Spec	Sens	Spec	True Positives	False Negatives	False Positives	True negatives	Total Tests	PPV	NPV	Ratio of TP:FP	Overall sens.	Overall spec.
1.000	0.995	n/a	n/a	2,000	0	490	97,510	100,000	0.803	1.000	4.1	1.000	0.995
0.995	0.995	n/a	n/a	1,990	10	490	97,510	100,000	0.802	1.000	4.1	0.995	0.995
0.995	0.980	n/a	n/a	1,990	10	1,960	96,040	100,000	0.504	1.000	1.0	0.995	0.980
0.980	0.980	n/a	n/a	1,960	40	1,960	96,040	100,000	0.500	1.000	1.0	0.980	0.980

Anti-HCV Prevalence: 0.4%		Population		100,000								
Test A		Test B										
Sens	Spec	Sens	Spec	True Positives	False Negatives	False Positives	True negatives	Total Tests	PPV	NPV	Ratio of TP:FP	Overall sens.	Overall spec.
1.000	0.995	n/a	n/a	400	0	498	99,102	100,000	0.445	1.000	0.8	1.000	0.995
0.995	0.995	n/a	n/a	398	2	498	99,102	100,000	0.444	1.000	0.8	0.995	0.995
0.995	0.980	n/a	n/a	398	2	1,992	97,608	100,000	0.167	1.000	0.2	0.995	0.980
0.980	0.980	n/a	n/a	392	8	1,992	97,608	100,000	0.164	1.000	0.2	0.980	0.980

Table 2: Outcomes for two-test strategy based on typical estimates of test accuracy (see Fig. 4)

Anti-HCV Prevalence: 45%		Population		100,000								
Test Kit A		Test Kit B										
Sens	Spec	Sens	Spec	True Positives	False Negatives	False Positives	True negatives	Total Tests	PPV	NPV	Ratio of TP:FP	Overall sens.	Overall spec.
1.000	0.995	1.000	0.995	45,000	0	1	54,999	145,275	1.000	1.000	32,727	1.000	1.000
1.000	0.995	0.980	0.980	44,100	900	6	54,995	145,275	1.000	0.984	8,018	0.980	1.000
0.980	0.980	1.000	0.995	44,100	900	6	54,995	145,200	1.000	0.984	8,018	0.980	1.000
0.980	0.980	0.980	0.980	43,218	1,782	22	54,978	145,200	0.999	0.969	1,964	0.960	1.000

Anti-HCV Prevalence: 10%		Population		100,000								
Test Kit A		Test Kit B										
Sens	Spec	Sens	Spec	True Positives	False Negatives	False Positives	True negatives	Total Tests	PPV	NPV	Ratio of TP:FP	Overall sens.	Overall spec.
1.000	0.995	1.000	0.995	10,000	0	2	89,998	110,450	1.000	1.000	4,444	1.000	1.000
1.000	0.995	0.980	0.980	9,800	200	9	89,991	110,450	0.999	0.998	1,089	0.980	1.000
0.980	0.980	1.000	0.995	9,800	200	9	89,991	111,600	0.999	0.998	1,089	0.980	1.000
0.980	0.980	0.980	0.980	9,604	396	36	89,964	111,600	0.996	0.996	267	0.960	1.000

Anti-HCV Prevalence: 2%		Population		100,000								
Test Kit A		Test Kit B										
Sens	Spec	Sens	Spec	True Positives	False Negatives	False Positives	True negatives	Total Tests	PPV	NPV	Ratio of TP:FP	Overall sens.	Overall spec.
1.000	0.995	1.000	0.995	2,000	0	2	97,998	102,490	0.999	1.000	816	1.000	1.000
1.000	0.995	0.980	0.980	1,960	40	10	97,990	102,490	0.995	1.000	200	0.980	1.000
0.980	0.980	1.000	0.995	1,960	40	10	97,990	103,920	0.995	1.000	200	0.980	1.000
0.980	0.980	0.980	0.980	1,921	79	39	97,961	103,920	0.980	0.999	49	0.960	1.000

Anti-HCV Prevalence: 0.4%		Population		100,000								
Test Kit A		Test Kit B										
Sens	Spec	Sens	Spec	True Positives	False Negatives	False Positives	True negatives	Total Tests	PPV	NPV	Ratio of TP:FP	Overall sens.	Overall spec.
1.000	0.995	1.000	0.995	400	0	2	99,598	100,898	0.994	1.000	161	1.000	1.000
1.000	0.995	0.980	0.980	392	8	10	99,590	100,898	0.975	1.000	39	0.980	1.000
0.980	0.980	1.000	0.995	392	8	10	99,590	102,384	0.975	1.000	39	0.980	1.000
0.980	0.980	0.980	0.980	384	16	40	99,560	102,384	0.906	1.000	10	0.960	1.000

4.7. How to test – confirmation of viraemia HCV

Decision-making tables – PICO 5a

Testing strategy for diagnosis of HCV active infection: Among individuals with confirmed exposure to HCV (HCV Ab positive), what is best testing strategy (diagnostic accuracy and other outcomes); comparing HCV core antigen versus NAT for HCV RNA to diagnose active HCV infection?

Decision-making tables – PICO 6

Testing strategy for diagnosis of HCV active infection (quantitative or qualitative NAT): Among individuals with confirmed exposure to HCV (Ab positive), what is the diagnostic test accuracy of qualitative NAT methods versus quantitative NAT methods to diagnose active HCV infection?

1. Topic for analysis: How to test

PICO 5a

Population: Individuals with detectable HCV RNA with or without confirmed exposure to HCV (HCV seropositivity)

Intervention: HCV core antigen

Comparison: HCV RNA NAT

Outcomes: Diagnostic accuracy (Sensitivity, Specificity, Positive predictive value, Negative predictive value, TN, TP, FN, and FP).

PICO 6

Population: Persons with confirmed exposure to HCV (HCV seropositivity)

Intervention: Qualitative HCV RNA NAT

Comparison: Quantitative HCV RNA NAT

Outcomes: Diagnostic accuracy (Sensitivity, Specificity, Positive predictive value, Negative predictive value, TN, TP, FN, and FP).

2. Background:

- Determination of exposure to HCV through detection of antibodies to HCV (anti-HCV) is a commonly used first-line diagnostic tool to identify those who are infected with HCV who might benefit from antiviral treatment, yet diagnosis of active HCV infection requires evidence of active viral replication, traditionally ascertained by the detection of HCV ribonucleic acid (RNA) by nucleic acid testing (NAT).
- Detection of HCV RNA may also be used as the preferred first-line investigation in individuals who may be persistently seronegative due to underlying immunosuppression, e.g. poorly-controlled HIV infection, renal dialysis.
- Qualitative NAT for HCV allows for detection of the virus as well as evidence of the level of HCV RNA circulating in the peripheral blood falling below a clinically relevant threshold, i.e. a qualitative measurement.

- Assays to detect HCV-RNA have been developed for the near point-of-care (POC) setting.
- NAT assays can be very sensitive and specific but more costly than serological methods such as HCV core antigen testing, and require sophisticated laboratory equipment and therefore skilled staff.
- HCV core antigen (HCVcAg) testing was developed as an alternative to NAT for the diagnosis of active HCV infection. HCV nucleocapsid peptides 22 (p22) are released into plasma during viral assembly and can be detected throughout the course of HCV infection. There are also several assays that have been commercialized for stand-alone detection of HCV cAg as a replacement to NAT.
- Furthermore, HCV cAg is detectable earlier than antibodies and therefore detection of HCV cAg has also been applied as an additional analyte for serological assays for use to ascertain exposure to HCV as a combination HCV Ag/Ab (4th generation) assay. The addition of cAg in combination was intended to increase sensitivity of the assay in early infection. Although the output may be interrogated in order to ascertain whether antigen, antibody or both were detected, the purpose of the assays is not to differentiate seropositivity from active infection.
- Both HCV cAg and HCV RNA (either qualitative or quantitative detection) have been shown to have clinical utility for the detection of active HCV infection though there is scarce research comparing the HCVcAg, and qualitative and quantitative NAT for this purpose.

3. Draft recommendation(s):

- **Summary and quality of evidence**

□ High
□ Moderate
□ Low
□ Very low

1. Distribution of viraemia in persistent infection:

A threshold of >10 000 IU/mL will capture 95% of persistent infections (except, temporarily, for a minority of those with partial viral control) between 5 and 12 months post infection.

In 95% of cases of hepatitis C infections:

- Those with persistent infection and viral plateau will have a viral load (VL) >100 000 IU/mL at month 5 and remain at least >10 000 IU/mL between months 5 and 12.
- Those with persistent infection but partial viral control will also have >100 000 IU/mL at month 5 and remain having a VL at least >1000 IU/mL temporarily, going back to a viral load >100 000 IU/mL between months 10 and 12.
- Between 2 and 3–4 months after infection, acute infection (giving VLs up to >100

000 IU/mL) may be captured that would spontaneously resolve but would likely be antibody negative.

Publications are:

Hajarizadeh B, Grady B, Page K, Kim AY, McGovern BH, Cox AL et al. Patterns of hepatitis C RNA levels during acute infection: the C3 study. PLOS One. 2015;10 (4):e 0122232.

Hajarizadeh B, Grebely J, Applegate T, Matthews GV, Amin J, Petoumenos K et al. J Med Virol. 2014;86 (10):1722–9.

Glynn SA, Wright DJ, Kleinman SH, Hirschkorn D, Tu Y, Heldebrant C et al. Transfusion. 2005;45 (6):994–1002.

2. Systematic reviews of the evidence:

Two systematic reviews were commissioned to address the above PICO questions. These aimed to summarize (1) the diagnostic accuracy of HCV cAg testing (PICO 5a), (2) the diagnostic accuracy of qualitative versus quantitative RNA for diagnosis of active HCV infection (PICO 6).

Summary of results of HCV cAg review

Diagnostic accuracy of HCV cAg for diagnosis of active infection (Fig. 1)

- 7 assays utilizing HCV core antigen were assessed. Note that two of these were HCV antigen/antibody combination assays and not designed to differentiate active infection from seropositivity, but are included as the antigen/antibody components of the assays were reported separately.

			Effect Accuracy (95% CI)		Effect LR	
Index test	***n*** **(samples)**	**Unit of analysis**	**Sensitivity**	**Specificity**	**Positive LR**	**Negative LR**
Abbott ARCHITECT	20 (11,820)	Sample	93.4% (88.7, 96.2)	98.7% (96.9, 99.4)	71.8 (28.6, 160.3)	0.07 (0.04, 0.12)

HCV Ag Assay						
Ortho ELISA-Ag	5 (1,177)	Sample	93.2% (81.6, 97.7)	99.2% (87.9, 99.9)	116.5 (6.7, 977)	0.06 (0.02, 0.07)
Bio-RAD Monolisa HCV Ag-Ab ULTRA	5 (525)	Sample	28.6–95%*	94.9% (89.9, 99.8)**	NA	NA
EIKEN Lumispot HCV Ag	2 (235)	Sample	97.5–98.1%*	ND	NA	NA
Fujirebio Lumipulse Ortho HCV Ag	1 (80)	Sample	95% (90.2, 99.8)**	ND	NA	NA
Hunan Jynda HCV Core Ag ELISA	4 (524)	Sample	59.5% (46, 71.7)	82.9% (58.6, 94.3)	3.5 (1.1, 12.6)	0.28 (0.2, 0.3)
DiaSorin S.A. Murex Ag/Ab EIA	4 (730)	Sample	50–100%*	83.8–100%*	NA	NA

n: study number, CI: confidence interval; LR: likelihood ratio; ND: no data, NA: not applicable — if sensitivity and specificity results were not available from meta-analysis, likelihood ratios were not calculated.

* Meta-analysis not possible. Range of results seen across studies reported.

**Result from one study only.

<u>Limits of detection of HCV cAg assays</u>

- The limit of detection for the most evaluated and best performing assay (Abbott Architect) is 3 fmol/L HCV cAg or 0.06 pg/mL, which equals to a limit of detection of about ~1000–3000 IU/mL with a NAT.

Impact of findings in different prevalence settings (for assays where a meta-analysis was possible) (Fig. 2)

Outcome	Effect per 1000 patients with presumed HCV for varying prevalence settings comparing HCV core Ag against HCV RNA		
	Prevalence 2%*	**Prevalence 10%***	**Prevalence 30%***
Abbott ARCHITECT HCV Ag Assay			
TP	19 (18, 19)	93 (89, 96)	279 (267,288)
TN	967 (951, 974)	888 (873, 895)	691 (697, 696)
FP	13 (6, 29)	12 (5, 27)	9 (4, 21)
FN	1 (1, 2)	7 (4, 11)	21 (12, 33)
Ortho ELISA-Ag			
TP	19 (16, 20)	93 (82, 98)	279 (246, 294)
TN	970 (862,980)	891 (792, 900)	693 (616, 700)
FP	10 (0, 118)	9 (0, 108)	7 (0, 84)
FN	1 (0,4)	7 (2, 18)	21 (6, 54)
Hunan Jynda HCV Core Ag ELISA			
TP	12 (9, 14)	60 (46, 72)	179 (138, 216)
TN	813 (578, 921)	747 (531, 846)	581 (413, 658)
FP	167 (59, 402)	153 (54, 369)	119 (42, 287)
FN	8 (6, 11)	41 (28, 54)	122 (84, 162)

TR: true positives (individuals with active HCV); TN: true negatives (individuals without active HCV); FP: false positives (individuals incorrectly classified as having active HCV); FN: false negatives (individuals incorrectly classified as not having active HCV)

*Numbers in parentheses consider 95% confidence interval of accuracy estimate.

Limits of detection of hepatitis C NAT assays

This systematic review shows that for diagnosis of active HCV infection, the lower limit of detection of most commercial qualitative assays was in the 10–15 IU/mL range measured against a WHO standard, whereas the lower limit of detection for quantitative assays is at 600–1100 IU/mL.

Additional information:

Newer quantitative viral load assays report limits of detection similar to qualitative viral load but might not quantitate results at that level.

NAT are in the pipeline for detection on capillary whole blood. Furthermore, detection from dried blood spot is also promoted to increase access. For both those strategies, the limit of detection is likely to be substantially higher (e.g. in the range of 2000 IU/mL) than for existing assays (because of volume tested and technical feasibility).

Fig. 3: Limit of detection of qualitative vs quantitative NAT

	Limits of detection							
Study	**Qualitative NAT (IU/mL)**				**Quantitative NAT (IU/mL)**			
Lee 2000	COBAS AMPLICOR™ HCV Test v2.0 assay. *Roche*	15	25	>50	AMPLICOR HCV test, v 2.0. *Roche*	300	600	1100
		95%	95%	100%		57%	95%	100%
Sarrazin 2008	CAP/CTM *Roche*	100%	–	–				
	RealTime HCV assay *Abbott*	87%						

Lee SC, Antony A, Lee N, Leibow J, Yang JQ, Soveiro S et al. Improved version 2.0 qualitative and quantitative AMPLICOR reverse transcription-PCR tests for hepatitis C virus RNA: calibration to international units, enhanced genotype reactivity, and performance characteristics. J Clin Microbiol. 2000;38 (11):4171–9.

Sarrazin C, Dragan A, Gartner BC, Forman MS, Traver S, Zeuzem S et al. Evaluation of an automated, highly sensitive, real-time PCR-based assay (COBAS Ampliprep/COBAS TaqMan) for quantification of HCV RNA. J Clin Virol. 2008;43 (2):162–8.

Conclusions:

- HCV core Ag assays can have high sensitivity (up to 93.4% for certain commercialized assays), high specificity, and good correlation with HCV RNA to a detection limit of roughly 1000–3000 IU/mL.
- NAT on plasma and serum are able to achieve higher sensitivity than cAg. Qualitative assays from published data are more sensitive than quantitative assays. This might not be the case for newer assays.

Quality of evidence

*Refer GRADE table in footnote

Predictive modelling (Linas, Boston University)

To be added at meeting

4. Risks/benefits **<u>cAG vs NAT</u>** **Benefits** • HCV cAg testing by immunoassay format has the potential to be less costly given that the cost of goods is lower. • Also HCV cAg is more stable and thus does not require a cold chain. • Further assessment and treatment may be administered more promptly to individuals when diagnosis of active HCV infection is undertaken in a more decentralized manner. There are both HCV cAG and NAT tests in the pipeline that might be possible on capillary blood at the point of care. However, current cAg immunoassays still require sophisticated laboratory equipment, electricity and therefore skilled staff to operate, while there are already some NAT assays available that can be done near the patient (however, still require plasma). • HCV cAg assay can conceivably be used in a one-step testing strategy (i.e. without an antibody test) particularly in high-prevalence settings. With such a strategy, patients can be identified earlier in their infection (than with antibody testing), results may be available faster to the patient and provider, resulting in less loss to follow up and faster treatment initiation. **Risks** • The patient with low-level viraemia (<3000 IU/mL) could be missed with HCV cAg assays or HCV RNA NAT with lower sensitivity. The clinical implications for the individual person and on a population level are not well understood. However, if the test does reach more patients (e.g. because it can be done on capillary blood or is less costly), then this risk might be outweighed by the benefits. • Although data exist on the utility of HCV cAg in seronegative individuals, no studies examined the use of HCV cAg and HCV RNA NAT in diagnosing HCV infection in key affected populations, in a one-step testing strategy rather than using an antibody assay. Such a strategy would only be cost–effective in certain high-prevalence settings. **Qual versus Quant NAT** **Benefits** • Qualitative NATs generally are more or at least as sensitive than quantitative assays.	□ Benefits clearly outweigh harms □ Benefits and harms are balanced □ Potential harms clearly outweigh potential benefits *Are the desirable anticipated effects large?* □ No □ Probably □ Uncertain □ Yes □ Varies

• The cost of a qualitative NAT assay may be lower than that of a quantitative assay. **Risk** • Recent publications suggest that monitoring for HCV will not be necessary with direct-acting antivirals (DAA) (as viral load at EVR is not predictive of cure). Therefore, quantitation at baseline will not be necessary. This is currently not yet widely confirmed or reflected in guidelines.	
5. Acceptability, values and preferences A values and preferences survey of implementers and users of hepatitis B and C testing services was carried out by FIND in September 2015. A total of 104 respondents from 43 (20 high-income, 23 low- and middle-income) countries. Relating to this PICO, • As assay (platform) for detection of HCV cAg is currently available in India, Indonesia, Macedonia, Viet Nam, Turkey (although the representativeness of these data are limited). The platform is available in South Africa but not currently being used for HCV cAg detection. • 50% found a diagnostic sensitivity of >95% acceptable, particularly if the test cost is lower, therefore increasing access to testing (respondents felt that then the test cost should be less than US$ 10 (83%) with a sensitivity of 95%. For a test with a sensitivity of 98%, forty-one per cent of respondents would accept a cost of US$ 11–20). • Free text comments suggested that HCV cAg was easier to do. • A larger number of respondents felt that the cost of testing for HCV RNA by NAT was considered more of a barrier than that of HCV cAg. • 47% of respondents in low- and middle-income countries favoured a decentralized test and a test on capillary blood even at the cost of sensitivity. • Also, 50% of patients preferred a test result in <2 hours (which could only be achieved at the point of care) while 27% found a result on the same day acceptable. **Patient:** • Patients at risk of progressive liver disease will benefit from reduced disease progression and related mortality and morbidity, if treatment is provided as a result of wider access to testing programmes.	□ No major variability □ Major variability Is the option acceptable to key stakeholder? □ No □ Probably □ Uncertain □ Yes □ Varies

Community: • To identify the individuals who require assessment and treatment would be an effective use of resources. • As testing and treatment programmes are scaled up, the numbers developing progressive disease and serious outcomes (HCC and complications of advanced liver disease), premature morbidity and mortality within the community will be reduced, and so also the burden of disease to societies where the disease is most prevalent. **Health-care workers:** • Appropriate use of resources to channel treatment to patients with higher risk of complications in the medium- and short term • Will require training in the use of testing equipment if being used in the near-POC setting • Appropriate reporting and recording of results. **Laboratory:** • Will require training for HCV cAg test: careful sample processing is necessary for HCV cAg assay to lyse viral particles, expose antigen and dissociate antibody from antigen and optimize the detection for HCV cAg.	
6. Equity, ethics and human right implications *Will the recommendation raise questions around equity?* • Equity will improve as a result of decreased cost and increased decentralization of testing; however, still improvement of access to testing facilities is necessary. • Regional and country variability in access to treatment. *Are there ethical implications to this recommendation?* • Ethical consideration for the possibility that WHO could recommend a testing strategy.	□ Less equitable □ More equitable
7. Resource use and financial implications **Input from modelling team**	*Are the resources required*

Materials/equipment:

- Cost of testing platform and reagents
- Other laboratory consumables

Training and supervision:

- Appropriate training of laboratory staff
- Quality control programmes
- If using near-POC assays, appropriate training of testing providers.

Other:

- Cost of transportation of specimens to the laboratory

Possible procurement costs (Fig. 4):

EXW / FCA PRICING FROM MSF PRODUCT GUIDE "PUTTING HIV AND HCV TO THE TEST"
***or UNITAID Hepatitis C Diagnostics Technology Landscape 1st Edition**

Lab-based tests	Cost for HCV (USD)	Polyvalency
Abbott Architect core Ag	$25-30	Extensive test menu including anti-HCV, anti-HBsAg
Abbott m2000 VL & GT	$13-35 each	Bundled pricing: HIV VL & EID, MTB, HCV, HBV, HPV, CT/NG Also: HCV GT, CMV, MTB RIF/INH
Biocentric VL	$23	HIV-2, MTB + resistance, HBV
Hologic Aptima VL	Awaiting launch	CT/NG, T. vaginalis, HPV Others in development incl HBV
Qiagen artus VL	$16-45	HBV, CMV, EBV, BKV, VZV, HSV, CT, MTB, C. Diff, VanR, GBS
Qiagen careHCV VL	$22 (China)*	-
Roche CAP/CTM qual & VL	$36-38*	CMV, B*5701, CT, MTB, HBV Global Access Program HIV VL & EID: $9.40
Roche GT (LPA)	$43-51*	-
Sacace VL & GT	>$20	Extensive test menu incl HIV & HBV
Siemens VL & GT (LPA)	$72-100 & $132-350	-

Cepheid: <20 NAT. With volume-based pricing down to~15

Note that new POC or near-POC assay platforms for HCV RNA are in development. See figures at the end of the table.

small?

□ No
□ Probably
□ Uncertain
□ Yes
□ Varies

Feasibility and constraints to implementation *Are any major barriers expected for the implementation of this recommendation?* • None, provided there is internal and country commitment to HCV testing. • Regional and country variability in access to treatment and procurement of testing equipment and services • With regard to any diagnostic assay, availability of a local laboratory, which is able to procure the testing platform and reagents required for testing. **Feasibility survey report to be presented at meeting.**	*Is the option feasible to implement?* □ No □ Probably □ Uncertain □ Yes □ Varies

8. Relevance to different settings/populations

Will this recommendation be most relevant for particular settings (e.g. endemicity)?

- Currently available HCV cAg testing will be more relevant to populations that presently rely on centralized laboratory testing for HCV RNA for confirmation of status.
- One-step strategies for testing with HCV cAg or NAT may be cost-effective only in high-prevalence settings.
- The recommendations are less likely to be relevant in high-income settings where there is already access to established hepatitis C testing and treatment programmes.

9. Rationale for recommendation:

10. Strength of recommendation

11. Implementation considerations

- Optimize test for asymptomatic patients in primary-care settings or in the community where the HCV endemic is high.

12. Research gaps

- Development/implementation projects evaluating use of HCV core antigen or HCV RNA as a one-step diagnostic strategy.
- Surveillance data: how many patients are missed by assays that have limits of detection of 2000 IU.
- Outcomes of patients with low viral loads
- More information on patients with high viral loads and negative HCV cAg to inform the

optimization of antigen detection.

- The kinetics of HCVcAg with treatment needs to be evaluated further, particularly in the context of new DAA regimens.
- More rigorous assessment of covariates in accuracy studies is required, such as HIV or HBV coinfection or genotype (particularly genotypes 5 and 6 where there are limited data).
- Development of muliplex instrument with other disease diagnosis with HIV, HBV, and TB at health centre.

GRADE Summary of findings

Table: Strength of evidence for diagnostic accuracy

SR outcome: diagnostic accuracy				**Quality**				**Strength of evidence**
Index Test	**Outcome Measure**	**# Studies (# samples)**	**Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	
Abbott ARCHITECT HCV Ag Assay	Sensitivity	30 (12 788)	Cohort and cross-sectional	Low[1]	Low[2]	Moderate[3] (–1)	Low[4]	Moderate ⊕⊕⊕◯
	Specificity	20 (11 820)	Cohort and cross-sectional	Low[1]	Low[2]	Moderate[3] (–1)	Low[4]	Moderate ⊕⊕⊕◯
Ortho ELISA-Ag	Sensitivity	6 (1 423)	Cohort and cross-sectional	High[1] (–2)	Moderate[2] (–1)	Moderate[3] (–1)	Low[4]	Very low ⊕◯◯◯
	Specificity	5 (1 177)	Cohort and cross-sectional	High[1] (–2)	Moderate[2] (–1)	Moderate[3] (–1)	Low[4]	Very low ⊕◯◯◯
Bio-RAD Monolisa HCV Ag-Ab ULTRA:	Sensitivity	5 (525)	Cohort and cross-sectional	Low[1]	High[2] (–2)	Moderate[3] (–1)	Low[4]	Very low ⊕◯◯◯

Sensitivity	Specificity	1 (337)	Cross-sectional	Moderate[1] (–1)	NA[2] (–1)	Moderate[3] (–1)	NA[4]	Very low ⊕◯◯◯
EIKEN Lumispot HCV Ag: Sensitivity	Sensitivity	2 (235)	Cross-sectional	Moderate[1] (–1)	Low[2]	Moderate[3] (–1)	Low[4]	Low ⊕⊕◯◯
	Specificity	0	NA	NA	NA	NA	NA	NA
Fujirebio Lumipulse Ortho HCV Ag: Sensitivity	Sensitivity	1 (80)	Cross-sectional	Moderate[1] (–1)	NA[2] (–1)	Moderate[3] (–1)	NA[4]	Very low ⊕◯◯◯
	Specificity	0	NA	NA	NA	NA	NA	NA
Hunan Jynda HCV Core Ag ELISA	Sensitivity	4 (524)	Cohort and cross-sectional	Moderate[1] (–1)	High[2] (–2)	Moderate[3] (–1)	Low[4]	Very low ⊕◯◯◯
	Specificity	4 (524)	Cohort and cross-sectional	Moderate[1] (–1)	High[2] (–2)	Moderate[3] (–1)	Low[4]	Very low ⊕◯◯◯
DiaSorin S.A. Murex Ag/Ab EIA	Sensitivity	4 (770)	Cohort and cross-sectional	Low[1]	High[2] (–2)	Moderate[3] (–1)	None[4]	Very low ⊕◯◯◯
	Specificity	3	Cohort	Low[1]	Moderate[2]	Moderate[3]	Low[4]	Low

		(658)			(–1)	(–1)		⊕⊕◯◯

NA: not applicable

Footnotes:

For each index test, quality of evidence started high when there were several high-quality observational studies (prospective cohort studies, cross-sectional studies with direct comparison of index test results with a reference standard). We then downgraded one point when there was moderate concern identified and two points when a there was a high concern identified in any of the four factors that may decrease the quality of evidence: risk of bias, inconsistency, indirectness, and imprecision.

[1] We used QUADAS-2 to assess risk of bias.

- For ARCHITECT, in half of the studies it was unclear how participants were selected and one study used only healthy blood donors, however, the data from all studies are consistent and unclear selection does not appear to cause bias thus we did not downgrade.
- For the Ortho ELISA, two studies of five used convenience enrolment for participant selection, and one enrolled only healthy blood donors thus we downgraded 2 points.
- For the Monolisa, four of five studies had unclear patient selection. For one it was unclear if the index and reference tests were performed within 30 days. Given that there were no high-risk concerns for bias we did not downgrade. For specificity, there was only one study with data that had unclear participant selection, thus we downgraded one point as there were no data from studies with random or consecutive selection to compare to and identify possible selection bias (as was possible with the ARCHITECT).
- For the Lumispot, both studies had unclear patient selection. As there were no data from studies with random or consecutive selection to compare, we downgraded one point.
- The Lumipulse only included one study with unclear participant selection and was downgraded one point.
- The Hunan Jynda had one of four studies with unclear participant selection, one in only healthy blood donors, and one for which it was unclear whether the index and reference were performed within 30 days. As the use of only healthy blood donors was considered a high-risk category, in combination with the other unclear factors, we downgraded one point.
- For the Murex test, three of four studies had unclear participant selection but no other high-risk concerns for bias and thus we did not downgrade.

[2] Unexplained heterogeneity in the remaining studies may be related to covariates that could not be adjusted for in meta-regression due to limited data (HIV and HBV coinfections, HCV genotype). Additionally, not all studies identified HCV antibody status or stratified by acute and chronic infection thus variability of HCV replication could contribute to higher false-negative HCV cAg.

- There was little heterogeneity noted in the ARCHITECT studies thus we did not downgrade.
- For the Ortho ELISA, there was moderate heterogeneity with largely one outlier study, thus we downgraded 1 point.
- For the Monolisa sensitivity outcome, heterogeneity between studies precluded meta-analysis and thus we downgraded 2 points. For specificity, there is only 1 study and we cannot assess heterogeneity and downgraded 1 point.
- For the Murex sensitivity outcome there was too much heterogeneity to pool the data, and thus we downgraded 2 points. For specificity, there were not enough studies to perform meta-analysis and heterogeneity could not be formally assessed; however, there is a broad range among results and thus we downgraded one point.
- The EIKEN Lumispot was only used in 2 studies. Sensitivity was similar in both studies suggesting little heterogeneity, thus we did not downgrade.
- For the Fujirebio Lumipulse, there is only 1 study and we cannot assess heterogeneity and downgrade 1 point.

[3] All studies were performed in reference laboratories, and the majorities were in high- and middle-income countries. Thus the patient population, the viral population tested (e.g. genotype distribution), and the test users are not representative of the limited-resource settings for which these guidelines are envisioned. All were downgraded 1 point.

[4] We considered imprecision as present when the pooled confidence intervals were >10% and when there were fewer than 250 samples in the analysis. As such, we downgraded the Ortho ELISA, and Hunan Jynda one point for wide confidence intervals, and downgraded the Lumispot one point for small sample size. Additionally, imprecision could not be graded for the Monolisa specificity outcome, and the Lumipulse test as these only included one study.

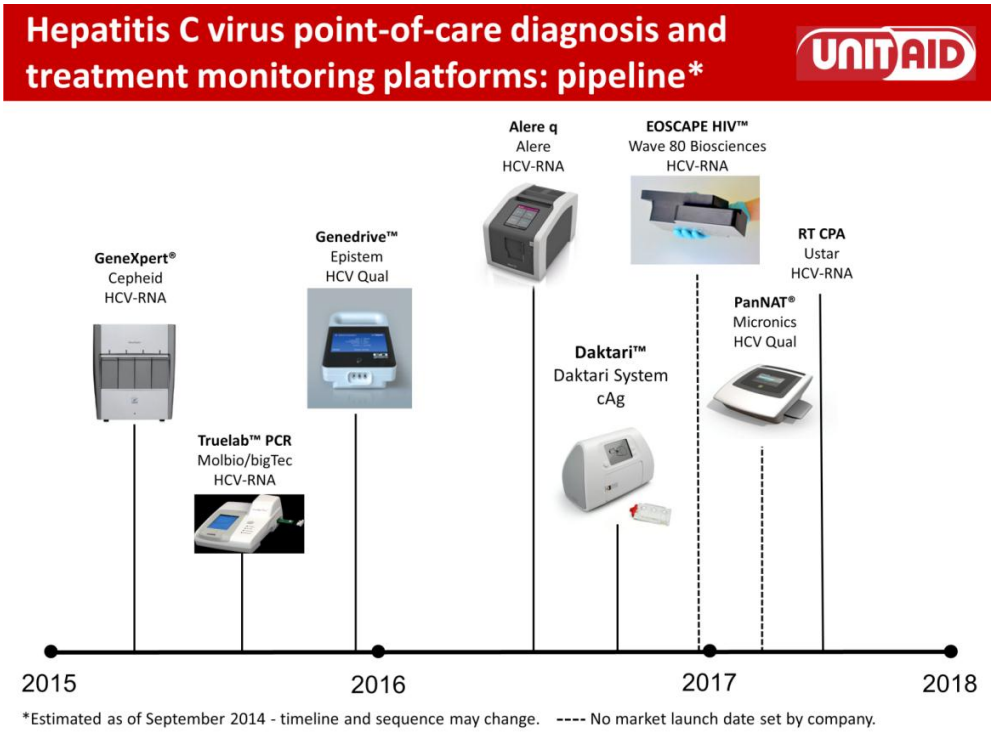
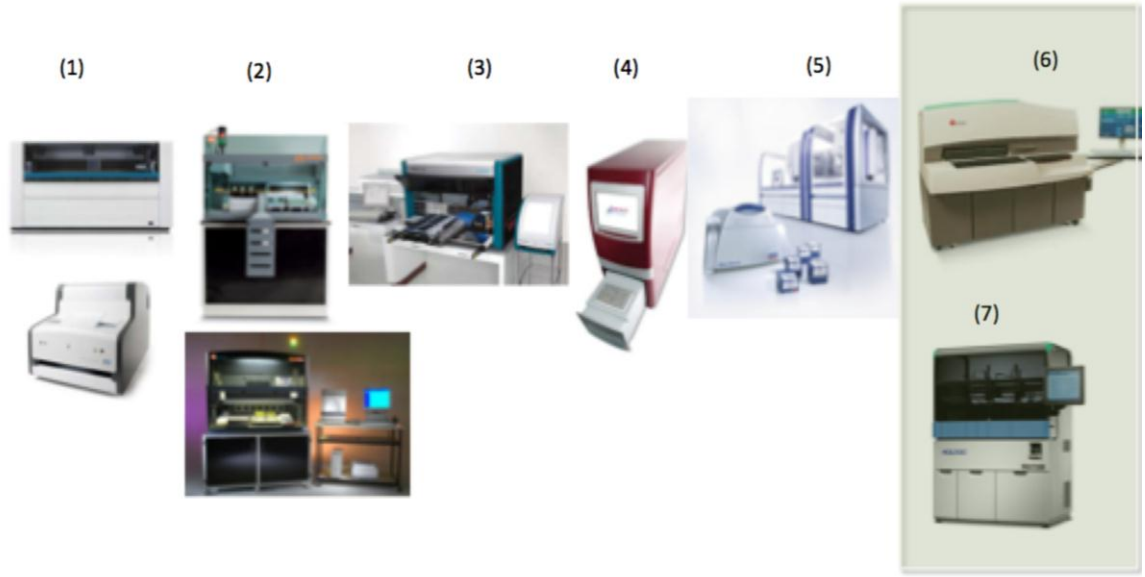


Fig. 1: POC HCV platforms available within the next 2 years

Fig. 2 and Table 2:

	Roche Molecular Systems (1)	Abbott Diagnostics (2)	Siemens Healthcare Diagnostics Inc. (3)	Sacace Biotechnologies (4)	QIAGEN (5)	Beckman Coulter (6)	Hologic Inc (7)
Qualitative	Roche COBAS AmpliPrep/COBAS TaqMan HCV Qualitative Test v.2						
Quantitative	Roche COBAS AmpliPrep/COBAS TaqMan HCV Quantitative Test v.2	Abbott RealTime HCV Assay	VERSANT HCV RNA 1.0 Assay (kPCR)	HCV Real-TM Quant Dx Assay	Artus HCV QS-RCQ Kit	VERIS MDx	RT-TMA Technology for the Panther® System
Lower limit of Detection	15 IU/mL	12 IU/mL –0.5 mL sample; 30 IU/mL –0.2 mL sample	15 IU/mL	13 IU/mL with 1 mL sample	35 IU/mL with automated extraction		
Sample type	Plasma or serum	Plasma or serum	Plasma or serum	Plasma	Plasma	Plasma, serum and culture	**Plasma**
Cost/test (US$)	36–38/43–51	13–35	72–100	>20	16–45		10–15
Price of instrument	80 000–100 000	248 000 (45 000 + 162 000 + 80 000)	Pricing for the assay and instrument is available from Siemens.	113 000 (95 000+18 645)	Pricing for the assay and instrument is available from Qiagen.	Pricing for the assay and instrument is available from Qiagen.	Pricing for the assay and instrument is available from Qiagen.
# Specimen/run	24 specimens in two hours, but it can process up to 72 samples at one time	96 samples at a time in about three hours of cycling time	89 samples per run with a total time to result of less than six hours	5–6 hours for a run of 24 samples	Continuous loading in batches of up to 24 samples plus internal controls	48 samples can be lined up on 12 racks. DNA tests is approximately 70 minutes and for RNA tests is 110 minutes	First reportable results available within three hours after loading samples and five results after every five minutes thereafter. Samples can be continuously loaded, with up to 120 samples on the Panther® System

Qualitative/Quantitative HCV RNA platforms currently available (1–5) and soon to be available (6–7)



4.8. Dried blot spots

Decision-making tables – PICO 7

Dried blood spots as sample collection method for serology/NAT for HBV/HCV: Among persons identified for (1) hepatitis B, or (2) hepatitis C testing, what is the diagnostic accuracy and impact of detecting HBsAg/HCV Ab or NAT from DBS samples versus venous samples?

1. Topic for analysis: How to test

Population:

- Samples for serology for HBV (HBsAg)
- Samples for serology for HCV (HCV Ab)
- Samples for HBV DNA
- Samples for HCV RNA

Intervention: Using dried blood spot (DBS) samples

Comparison: Using venous samples

Outcomes: Diagnostic accuracy (Sensitivity, specificity, positive predictive value, negative predictive value, TN, TP, FN, and FP)

2. Background:

In high-prevalence of hepatitis B virus (HBV) among low- and middle-income countries (LMICs) there is a need for improved HBV screening, especially in decentralized settings. And the entry of new all-oral direct acting antiviral therapy for hepatitis C provides an opportunity to scale up HCV care in LMICs and dramatically simplify diagnosis and monitoring.

In HIV, use of DBS has facilitated the diagnosis of HIV in children under 18 months and is a promising tool for HIV management in resource-limited settings (viral load monitoring is strongly recommended by WHO as the preferred ART monitoring test). While commercial rapid diagnostic tests (RDTs) exist for HBsAg and HCV antibody for HBV diagnosis and HCV screening, respectively, the use of DBS sent to centralized lab facilities for diagnosis or screening purposes may be useful in certain contexts where RDTs are not available or not feasible due to human resource, procurement, quality, regulatory or other constraints, particularly as they can be prepared from capillary blood, thus obviating the need for phlebotomy services.

Molecular tests for HBV DNA and HCV RNA must currently be performed in centralized facilities, where barriers to sample collection and transport, such as phlebotomy services, plasma separation

and cold chain, may make testing less feasible. One decentralized molecular platform for HCV RNA does exist but it too relies on plasma as a sample type. Thus DBS may be used in a similar way to HIV to facilitate diagnosis and monitoring in certain contexts.

Two main advantages of using DBS for HCV compared to HIV are that (1) there is no proviral DNA to overestimate the quantity of virus in the blood compared to plasma (although cell-associated RNA may still contribute) and (2) qualitative testing should suffice, both for diagnosis and measurement of SVR, as (i) viral load monitoring of DAA-based treatment is not useful and, (ii) since DAA therapy is non-toxic, a log drop calculation for treatment continuation at week 12 (EVR), as was the case for IFN-based therapy, is not needed.

In prioritizing the validation of serological testing on DBS versus NAT testing on DBS, depending on the context, they may be equally useful. If affordable, good-quality RDTs are available that can be performed off capillary blood then the impetus may be to prioritize that validation of NAT testing for HBV DNA and HCV RNA. However, if RDTs are not available then DBS testing may be equally important to increase access to serological testing, for example, for hard-to-reach populations and those with poor venous access. Equally, DBS may be useful where polyvalent screening for multiple diseases, such as HIV/HBV/HCV, is useful and where multiplex RDTs for this purpose are not available or more costly. Thus the choice and combination of test may be context specific whereby different programmes may opt for difference combinations of: (1) DBS serology + DBS NAT (remote settings), (2) RDT serology + DBS NAT (clinics, e.g. antental), or (3) EIA serology + plasma-based NAT (urban settings or more central hospitals).

See Feasibility section for current use of DBS.

3. Draft recommendation(s):

4. Summary and quality of evidence

Summary of results

□ High
□ Moderate
□ Low
□ Very low

7a: Meta-analysis for HBsAg

No. of included studies	10 (SR) 9 (meta-anal)
Total sample size	2481
Overall sensitivity	92.9% [86.2–96.5]
Overall specificity	99.0% [96.2–99.7]

Positive LR	92.9
Negative LR	0.072
Impact of cut-off	DBS LOD cut-off may be higher due to smaller sample volume (50 µL) but OD cut-off lower to maximize sensitivity (ROC curve needed to set cut-off) Std: SN 88% [74–95] SP 98.6% [89–100] High: SN 95.6% [91–98] SP 99.1% [97–100]
Impact of storage	Cold chain: SN 78.7% [70–85] SP 98.6% [68–100] ≥RT: SN 96.1% [92–98] SP 99.7% [98–100]
Impact of duration of storage	Accuracy not affected if RT –33°C for ≤15 d (1 study) or 63 d (another study)
Impact of assay	DBS provides good rule in test for diagnosing HBV but may not be able to rule out HBV in a minority of cases.

LR: likelihood ratio

7b: Meta-analysis for HCV Ab

No. of included studies	18 (SR) 14 (meta-anal)
Total sample size	6120
Overall sensitivity	98% [94–99]
Overall specificity	99% [97–100]
Positive LR	171
Negative LR	0.02
Impact of cut-off	None identified (varied widely, some used ROCs to set own cut-offs)
Impact of storage	–20°C = less variation compared to RT

Impact of duration of storage	Accuracy not affected if RT for ≤3 d (1 study) or ≤6 d (another study) or ≤60 d (another study)
Impact of assay	DBS provides good rule in and rule out test for screening for HCV.

7c: Meta-analysis for HBV DNA

No. of included studies	9 (SR) 7 (meta-anal)
Total sample size	905
Overall sensitivity	96% [91–98]
Overall specificity	100 [54–100]
Positive LR	287
Negative LR	0.04
Impact of threshold	LOD: 914 IU/mL (one study), 3000–4000 IU/mL (other studies) Clinical Tx threshold: 2000 IU/mL
Impact of storage	Not possible to calculate because all accuracy studies at –20°C.
Impact of duration of storage	No affect of accuracy if 4–37°C for ≤7 d (2 studies).
Impact of assay	DBS good to rule in HBV but may not rule out HBV in a minority of cases, particularly if viral loads are <3000 IU/mL.

7d: Meta-analysis for HCV RNA

No. of included studies	9 (SR & meta-anal)
Total sample size	1250
Overall sensitivity	96.0% [93.4–97.6]
Overall specificity	97.7% [94.7–99.0]
Positive LR	41.74
Negative LR	0.041
Impact of threshold	LOD: ≥150–250 IU/mL
Impact of storage	Better result at –20°C compared to RT; conflicting results re deterioration of sample at RT
Impact of duration of storage	Conflicting results re deterioration over time
Impact of assay	DBS good to rule in active HCV infection but may not rule out infection in a minority of cases with lower viral loads.

Quality of evidence

- Overall HBsAg: moderate (no significant indirectness, imprecision or inconsistency but significant risk of bias).
- Overall HCV Ag: moderate (no significant indirectness, imprecision or inconsistency but moderate risk of bias).
- Overall HBV DNA: low (no significant indirectness or imprecision but significant inconsistency and high risk of bias).
- Overall HCV RNA: moderate (no significant indirectness, imprecision or inconsistency but significant risk of bias).

*Refer GRADE table in footnote

5. Risks/Benefits

Benefits of DBS

□ Benefits clearly outweigh harms
□ Benefits and harms are balanced

- DBS is likely stable over time and maintains good accuracy in conditions with higher temperatures and with higher humidity.
- Lower biohazard, easier transport, no venepuncture needed
- Greater access to testing, especially for remote settings or specific programmes servicing key populations (people who inject drugs, prisoners, etc).

Risks of DBS

- Accuracy may be negatively affected when storing for prolonged durations (greater than 14 days) at higher temperatures (room temperature and above) and humidity.
- Use of DBS may require higher cut-offs to determine test positivity as DBS uses a small volume of blood, in order to maintain sensitivity, a higher cut-off may be required as compared to when using plasma samples. This may decrease the ability to rule out HBV/HCV in a minority of cases.
  DBS not regulatory approved as a sample type for HBsAg, HCV Ab, HBV DNA or HCV RNA testing.
- No guidance from manufacturers on use of commercial assays with DBS.
- The best type of filter paper to use is not known (but has been established for HIV DNA and RNA testing).
- Differences between capillary versus venous blood are not known (but has been established for HIV DNA and RNA testing with insignificant difference where training and proficiency testing are provided for capillary blood sampling).
- Most appropriate volume of capillary blood to be used (e.g. one versus more than one spot of 50 µL) is not known (but has been established for HIV DNA and RNA testing).
- Best types of commercial test kits to use with DBS are not known.

□ Potential harms clearly outweigh potential benefits

Are the desirable anticipated effects large?

□ No
□ Probably
□ Uncertain
□ Yes
□ Varies

6. Acceptability, values and preferences

1. Acceptable accuracy of DBS for testing HBsAg and HCV Ab as compared to use of plasma samples (as compared to WHO performance acceptance criteria):

HBsAg

	WHO EIA	WHO RDT	SR	Acceptable
Sensitivity	100	100	92	No
Specificity	≥98	≥98	99	Yes

□ No major variability
□ Major variability

Is the option acceptable

to key stakeholders?

□ No
□ Probably
□ Uncertain

EIA: enzyme immunoassays; SR: systematic review

□ Yes
□ Varies

HCV Ab

	WHO EIA	WHO RDT	SR	Acceptable
Sensitivity	100	≥98	98	Yes
Specificity	≥98	≥97	99	Yes

Accuracy is acceptable except for sensitivity of HBsAg testing, which may lead to a minority of cases being missed.

2. Acceptable accuracy of DBS for testing HBV DNA and HCV RNA as compared to use of plasma samples is not known because there are no WHO performance acceptance criteria. However accuracy should be measured in the context of clinical relevance, i.e.:

For HBV DNA:

1. Treatment thresholds of 2000 and 20 000 IU/mL
2. Ability to measure suppression in treatment monitoring (threshold not known but most people fail at viral loads >20 000 IU/mL).

For HCV RNA:

1. Confirming all those with chronic and active HCV infection (threshold not known but viral loads are generally high, with 95% of people having viral loads >1000 IU/mL if chronically infected and those with lower early viral loads more likely to clear infection).

Following new DAA therapy, confirming those with sustained virological response (SVR), whether at SVR 12/24 (threshold is not known but preliminary evidence suggests those failing therapy have higher viral loads).

7. Equity, ethics and human right implications

□ Less equitable
□ More equitable

Will the recommendation raise questions around equity?

DBS may allow more equitable access to testing.

Are there ethical implications to this recommendation? No.	
8. Resource use and financial implications • May reduce costs associated with sample collection, storage and transport. • May facilitate task shifting to lay workers to decrease human resource limitations.	*Are the resources required small?* □ No □ Probably □ Uncertain □ Yes □ Varies
9. Feasibility and constraints to implementation **10. Relevance to different settings/populations** *Are any major barriers expected for the implementation of this recommendation?* *Will this recommendation be most relevant for particular settings (e.g. endemicity)?* There is limited programmatic experience with the use of DBS for viral hepatitis testing, although this is well established for HIV DNA and RNA testing. 1. Studies are limited. 2. There are no current standards for test OD cut-offs for HBsAg or HCV Ab using DBS. 3. There is a dearth of studies that systematically examine the effects of storage and transport conditions on the accuracy of DBS. Hepatitis B and C testing using DBS have been used in several screening programmes in non-clinical settings and research studies. There is encouraging evidence from pilot schemes and where dried blood spot collection is used for hepatitis testing (detection of HBsAg and HCV Ab). DBS collection is view as an interesting alternative testing technology for peoples at increased risk of infection. For example, hepatitis testing using DBS is used by associations such as "Hepatitis C Trust" in the UK[1] or le "Réseau Hépatites LR" in France,[2] and by community pharmacists in the UK.[3] The "CheckPoint-Paris" from the "Kiosque", a	*Is the option feasible to implement?* □ No □ Probably □ Uncertain □ Yes □ Varies

voluntary counselling and testing service in France, offers rapid tests for screening and DBS for confirmation since 2010.[4] The National Institute for Health and Care Excellence (NICE) points out that DBS tests for hepatitis B and C can be useful in certain settings for people with poor venous access and where there may be no facilities or expertise to take venous blood samples.[3] The NICE recommends access to hepatitis B and C testing using DBS for prisoners and drug users.

In France, guidelines from the "Haute Autorité Sanitaire"[5] and AFEF-ANRS[6] underlined that DBS tests have good performance and are an alternative to venous blood tests. However, the absence of standardization limits the usefulness of DBS and thus there is no clear recommendation to expanded DBS testing.

Critically, as part of Scotland's Action Plan on HCV, "the introduction of DBS testing in the specialist drug services setting has had the greatest impact" in terms of increasing access to diagnosis.

References

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5. Haute Autorité Sanitaire, 2014. Place des tests rapides d'orientation diagnostique (TROD) dans la stratégie de dépistage de l'hépatite C (http://www.has-sante.fr/portail/upload/docs/application/pdf/2014-05/place_des_trod_dans_la_strategie_de_depistage_de_vhc-_rapport.pdf)
6. Prise en charge des personnes infectées par le virus de l'hépatite B ou de l'hépatite C (http://social-sante.gouv.fr/IMG/pdf/Rapport_Prise_en_charge_Hepatites_2014.pdf, accessed 06 June 2016).
7. Scotland's Action Plan on HCV. (http://www.inhsu.com/international-symposia.html.

11. Rationale for recommendation:

12. Strength of recommendation

13. Implementation considerations

- Regulatory approval for DBS as a sample type
- Where HR and phlebotomy services are lacking, training of lay workers to perform fingerprick DBS
- QA/QC; e-health/m-health to improve turnaround time of results
- Training clinicians to act on the result.

14. Research gaps

- Operational research to evaluate the accuracy of DBS using field specimens prepared and stored in real-life conditions will be needed.
- Validation of the use of DBS with commercially available HBsAg and HCV Ab tests and determining cut-off values with the use of ROC curves will be needed.
- The use of DBS for HCV RNA viral load measurement and of the rate of degradation of HCV RNA when stored in DBS at ambient temperatures and high humidity for different time periods will be needed as well as further study in HIV-coinfected patients and for use in treatment monitoring, specifically for measuring SVR 12/24 post DAA therapy.
- A systematic review on the LOD for HCV RNA testing on DBS that will serve to capture (1) everyone with chronic and active HCV infection, and (2) everyone failing DAA therapy at SVR12/24 (which will then inform the best time-point for SVR).
- A systematic review on the LOD for HBV DNA testing on DBS that will serve to capture (1) everyone who needs HBV treatment, and (2) everyone failing therapy.

GRADE Summary of findings for PICO7a

Number of studies	Type of study	Directness	Precision	Consistency	Risk of bias	Overall quality
Sensitivity 92.9% (95% CI 86.2–96.5)						
10 studies (370 HBsAg positive among 1516 samples)	Cross-sectional or cohort	No significant indirectness	No significant imprecision	Significant inconsistency (One paper reported lower sensitivity)	Significant risk of bias (patient enrolment not consecutive or random in some studies; pre-specified cut-off not used in	Moderate

					some studies)	
Specificity 99.9% (95% CI 97.6–100%)						
10 studies (370 HBsAg positive among 1516 samples)	Cross-sectional or cohort	No significant indirectness	No significant imprecision	No significant inconsistency	Significant risk of bias (patient enrolment not consecutive or random in some studies; pre-specified cut-off not used in some studies)	Moderate

DBS: dried blood spot

GRADE Summary of findings for PICO7b

Number of studies	Type of study	Directness	Precision	Consistency	Risk of bias	Overall quality
Sensitivity 98% (95% CI 93.0%–99.0%)						
14 studies (1549 HCV positive among 4304 samples)	Diagnostic accuracy	No significant indirectness	No significant imprecision	Significant inconsistency	Moderate risk of bias (patient enrolment only partly consecutive or random; several case–control studies)	Moderate
Specificity 99% (95% CI 97–100%)						
13 studies (2756 HCV positive among 4304 samples)	Diagnostic accuracy	No significant indirectness	No significant imprecision	Significant inconsistency	Moderate risk of bias (patient enrolment only partly consecutive or random; several case–control studies)	Moderate

GRADE Summary of Findings for PICO7c

Number of studies	Type of study	Directness	Precision	Consistency	Risk of bias	Overall quality
Sensitivity 98% (95% CI 92.0%–98.0%)						
7 studies (154 HBsAg positive among	Diagnostic accuracy	No significant indirectness	No significant imprecision	Significant inconsistency	High risk of bias (patient enrolment not consecutive or random in all studies;	Low

552 samples)					several case–control studies)	
Specificity 100% (95% CI 39–100%)						
4 studies (125 HBV DNA pos positive among 1648 samples)	Diagnostic accuracy	No significant indirectness	Significant imprecision with small sample size	Significant inconsistency	High risk of bias (patient enrolment not consecutive or random in all studies; several case control studies)	Low

GRADE Summary of findings for PICO7d

Number of studies	**Type of study**	**Directness**	**Precision**	**Consistency**	**Risk of bias**	**Overall quality**
Sensitivity of DBS for HCV VL: 96.0% (upper-lower bounds 93.4–97.6)						
9 studies 1335 samples	Cross-sectional, case–control or cohort	No significant indirectness	No significant imprecision	No significant inconsistency	Significant risk of bias (non-randomized or consecutive patient recruitment or case–control design)	Moderate
Specificity of DBS for HCV VL: 97.7% (upper-lower bounds 94.7–99.0)						
9 studies 1335 samples	Cross-sectional, case–control or cohort	No significant indirectness	No significant imprecision	No significant inconsistency	Significant risk of bias (non-randomized or consecutive patient recruitment or case–control design)	Moderate

4.9. Monitoring treatment response HCV

Decision-making tables – PICO 9

Monitoring for treatment response using HCV Ag testing in individuals with confirmed active HCV infection: Among individuals receiving antiviral treatment for HCV, what is the diagnostic accuracy of HCV core antigen versus NAT for HCV RNA qualitative detection (and/or) quantification to confirm successful treatment response with viral clearance?

Population: Patients receiving treatment for HCV

Intervention: HCV core antigen assay

Comparison: NAT for HCV RNA detection (and/or) quantification

Outcomes: Diagnostic accuracy (Sensitivity and specificity, TN, TP, FN, and FP)

1. **Background:**

- HCV core antigen (HCV cAg) testing was developed as an alternative to NAT for diagnosis of active HCV infection. HCV nucleocapsid peptides 22 (p22) are released into plasma during viral assembly and can be detected throughout the course of HCV infection.
- Detection of HCV viraemia is also important during treatment of chronic HCV infection.
- Current guidelines recommend verification of virological activity pre-treatment with the measurement of a baseline HCV RNA quantitative measurement (viral load) by NAT. For interferon-based treatments, HCV RNA viral load is assessed at week 4 of therapy for the "rapid viral response" (RVR) to help predict efficacy of therapy, and repeated at week 6 if elevated at week 4 to see further viral response and guide whether treatment should be continued.
- NAT for HCV RNA is performed again at week 12 (early viral response, EVR), at the end of treatment, and 12 and 24 weeks after therapy is completed to test for cure, "sustained viral response" (SVR).
- New, direct-acting antivirals (DAA) have made treatment for HCV much easier with oral rather than parenteral administration and shorter, more effective regimens that are likely to be easier to adhere to making access to affordable diagnostic and monitoring assays even more important. However, it is important to note that, ultimately, treatment monitoring may not be required with the routine use of DAAs.
- This PICO addresses the question of whether HCV cAg can be used as a tool for assessing response to treatment for HCV infection.

2. Draft recommendation(s):

3. Summary and quality of evidence

A systematic review (see SR_PICO 9) was commissioned to address the above PICO question. This aimed to examine the utility of HCV cAg monitoring for those on HCV treatment (PICO 9).

□ High
□ Moderate
□ Low
□ Very low

Summary of results

Sensitivity and specificity of Abbott ARCHITECT HCV cAg assay compared to HCV RNA assessed at baseline, at week 4 of interferon-based therapy (early viral response), and at week 24 after completion of treatment (sustained viral response)

		Baseline		**Early viral response (EVR)**		**Sustained viral response (SVR)**	
Author, Year	*N*	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**Sensitivity (95% CI)**	**Specificity (95% CI)**
Feng, 2014	32	100%	N/A	100%	88.9% (68.4%, 100%)	100%	100%
Loggi, 2013	35	100%	N/A	73.5% (58.7%, 88.4%)	100%	100%	94.1% (82.9%, 100%)
Moscato, 2010	23	N/A	N/A	100%	70% (41.6%, 98.4%)	N/A	N/A

N: number of subjects; HCV: hepatitis C virus, Ag: antigen, Se: sensitivity, Sp: specificity, CI: confidence interval, N/A: not applicable as cannot be calculated from study data

Sensitivity and specificity of HCV core antigen in prediction of sustained viral response (SVR) after initiation of interferon-based treatment

Author, Year	*N* (N to achieve SVR)	Index test	Timing of test after treatment start	Change in HCVcAg	Sensitivity	Specificity
Feng, 2014	32 (21)	Abbott ARCHITECT	6 days	Log 10	95.2%	70%
Loggi, 2013	90 (57)	Fujirebio Lumipulse	7 days	Absolute	79.4%	88.5%
Moscato, 2010	44 (10)	Fujirebio Lumipulse	7 days	Absolute	57.1%	93.3%

HCV: hepatitis C virus; *N*: number

Conclusions:

- HCV core Ag assays can have high sensitivity (up to 93.4% for certain commercialized assays), high specificity, and good correlation with HCV RNA to a detection limit of roughly 3000 IU/mL.
- The data on HCV core Ag for treatment monitoring and as a test of cure is too limited to reach reliable conclusions.

Quality of evidence

*Refer GRADE table in footnote

4. Risks/benefits

Benefits

- HCV cAg testing by immunoassay format has the potential to be less costly and less complicated to perform than HCV RNA by NAT. However, these immunoassays still require sophisticated laboratory equipment and therefore skilled staff to operate. Access to cold storage and constant electricity is required for the current types of assays available for HCV cAg testing.
- Results for patients on antiviral treatment being monitored for sustained viral response may be available more rapidly as a result of decentralized testing.

□ Benefits clearly outweigh harms
□ Benefits and harms are balanced
□ Potential harms clearly outweigh potential benefits

Are the desirable anticipated

Risks • Due to reduced analytical sensitivity and limited understanding of kinetics of HCV cAg compared to HCV RNA by NAT, individuals on antiviral treatment may be misclassified as responding to treatment, but may have persisting viraemia below the limits of detection of the assay.	*effects large?* □ No □ Probably □ Uncertain □ Yes □ Varies
5. Acceptability, values and preferences A values and preferences survey of implementers and users of hepatitis B and C testing services was carried out by FIND in September 2015. A total of 104 respondents from 43 (20 high-income, 23 low- and middle-income) countries participated. Relating to this PICO, • As assay (platform) for detection of HCV cAg is available in India, Indonesia, Former Yugoslav Republic of Macedonia, Viet Nam, Turkey. The platform is available in South Africa but not currently being used for HCV cAg detection. • Currently only 11% of respondents are using HCV cAg as a test of cure. • 44% of respondents preferred a 12-week follow up for testing after completion of therapy, while 19% and 15% preferred a 4- or 8-week follow up. • 47% of patients preferred to have the same test for monitoring and detection, ideally in decentralized settings. • Free text comments from respondents included concerns regarding the sensitivity and specificity of cAg, but that it was potentially easier to do. One comment stated that it could be acceptable if it increased access to treatment. • A larger number of respondents felt that the cost of testing for HCV RNA by NAT was considered more of a barrier than that of HCV cAg. • As stated previously, 47% of respondents in low- and middle-income countries would prefer testing at POC, even at the cost of sensitivity. **Patients:** • Patients at risk of progressive liver disease will benefit from reduced disease progression and related mortality and morbidity, if treatment is provided as a result of wider access to testing programmes. **Community:** • To identify the individuals who require assessment and treatment would be an effective use of resources. • As testing and treatment programmes are scaled up, the numbers developing	□ No major variability □ Major variability Is the option acceptable to key stakeholders? □ No □ Probably □ Uncertain □ Yes □ Varies

progressive disease and serious outcomes (HCC and complications of advanced liver disease), premature morbidity and mortality within the community will be reduced, and so also the burden of disease to societies where the disease is most prevalent. **Health-care workers:** • Appropriate use of resources to channel treatment to patients with higher risk of complication in the medium- and short term • Will require training in the use of testing equipment if being used in the near-POC setting • Appropriate reporting and recording of results. **Laboratory:** • Will require purchasing of the appropriate platform and reagents for the HBsAg detection assay Will require training for HCV cAg test: careful sample processing is necessary for HCV cAg assay to lyse viral particles, expose antigen and dissociate antibody from antigen and optimize the detection for HCVcAg.	
6. Equity, ethics and human right implications *Will the recommendation raise questions around equity?* • Equity will improve as a result of decentralization of testing, however, still improvement of access to the testing facilities is necessary. • Regional and country variability in access to treatment. *Are there ethical implications to this recommendation?* • Ethical consideration for the possibility that WHO could recommend a suboptimal testing strategy.	□ Less equitable □ More equitable
7. Resource use and financial implications **Materials/equipment:** • Cost of testing platform and reagents • Other laboratory consumables	*Are the resources required small?* □ No □ Probably □ Uncertain

Training and supervision:

- Appropriate training of laboratory staff
- Quality control programmes
- If using near-POC assays, appropriate training of testing providers.

Other:

- Cost of transportation of specimens to the laboratory

Possible procurement costs:

Assay format	Indicative cost (US$) per test	Source
RDTs	0.50–2.00 (10 for oral fluid RDTs)	MSF, WHO
EIA	0.50–1.70	WHO
HCV Ag	25–50	MSF
Quantitative NAT for HCV RNA	10–45	MSF, UNITAID
Qualitative NAT for HCV RNA)	43–51	UNITAID

□ Yes
□ Varies

- **Feasibility and constraints to implementation**

Are any major barriers expected for the implementation of this recommendation?

- Regional and country variability in access to treatment and procurement of testing equipment and services
- With regard to HCV cAg, availability of a local laboratory, which is able to procure the testing platform and reagents required for testing.

Is the option feasible to implement?

□ No
□ Probably
□ Uncertain
□ Yes
□ Varies

8. Relevance to different settings/populations

Will this recommendation be most relevant for particular settings (e.g. endemicity)?

- HCV cAg testing will be more relevant to populations that presently rely on centralized laboratory testing for HCV RNA for confirmation of status.
- The recommendations are less likely to be relevant in high-income settings where there is already access to established hepatitis C testing and treatment programmes.

9. Rationale for recommendation:

10. Strength of recommendation

11. Implementation considerations

Optimize test for asymptomatic patients in primary-care settings or in the community where the HCV endemic is high.

12. Research gaps

- The kinetics of HCV cAg with treatment needs to be evaluated further, particularly in the context of new DAA regimens.
- More rigorous assessment of covariates is required in studies assessing HCV cAg or NATs for treatment monitoring or as a test of cure, such as HIV or HBV coinfection or genotype.
- Is treatment monitoring and/or confirmation of cure necessary with DAA regimens? If so, what would be the optimal timing of testing?
- When is the best time-point to test for cure with HCV core Ag?
- Development of muliplex instrument with other disease diagnosis such as HIV, HBV, and TB at health centre.
- HCVcAg assay to detect the variants of HCV.

GRADE Summary of findings

SR outcome 1: Diagnostic accuracy at SVR	1.1.16	1.1.17	1.1.18	Quality				Effect*	Strength of evidence
Index test	**Outcome measure**	**# Studies (# samples)**	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**1.1.19**	**1.1.20**
Abbott ARCHITECT HCVAg Assay	Sensitivity	2 (67)	RCT, cohort	Low[1]	Low[2] 1.1.21	Moderate[3] (–1)	Low[4] 1.1.22	100%*	Moderate ⊕⊕⊕◯
	Specificity	2 (67)	RCT, cohort	Low[1]	Moderate[2] (–1)	Moderate[3] (–1)	Low[4] 1.1.23	94–100%*	Low ⊕⊕◯◯

SR outcome 2: Predictive accuracy of SVR				Quality				Effect*	Strength of evidence
Index test	**Outcome measure**	**# Studies (# individuals)**	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**		
Abbott ARCHITECT HCV Ag Assay	Sensitivity	1 (23)	Cohort	Low[1]	NA[2] (–1)	Moderate[3] (–1)	NA[4]	95.2%**	Low ⊕⊕◯◯
	Specificity	1 (23)	Cohort	Low[1]	NA[2] (–1)	Moderate[3] (–1)	NA[4]	70%**	Low ⊕⊕◯◯
Fujirebio Lumipulse Ortho HCV Ag	Sensitivity	2 (134)	Cohort	Moderate[1] (–1)	Moderate[2] (–1)	Moderate[3] (–1)	Moderate[4] (–1)	57.1–79.4%*	Very low ⊕◯◯◯
	Specificity	2 (134)	Cohort	Moderate[1] (–1)	Moderate[2] (–1)	Moderate[3] (–1)	Moderate[4] (–1)	88.5–99.3%*	Very low ⊕◯◯◯

* Results reported are a range across studies or **individual result, NA: not applicable

References

1. Feng B, Yang RF, Xie Q, Shang J, Kong FY, Zhang HY et al. Hepatitis C virus core antigen, an earlier and stronger predictor on sustained virological response in patients with genotype 1 HCV infection. BMC Gastroenterol. 2014;14:47.
2. Loggi E, Cursaro C, Scuteri A, Grandini E, Panno AM, Galli s et al. Patterns of HCV-RNA and HCV core antigen in the early monitoring of standard treatment for chronic hepatitis C. J Clin Virol. 2013;56(3):207–11.
3. Moscato GA, Gianelli G, Grandi B, Pieri D, Marsi O, Guarducci I, Batini I et al. Quantitative determination of hepatitis C core antigen in therapy monitoring for chronic hepatitis C. Intervirology. 2011;54(2):61–5.

4.10. Intervention to promote linkage to care

Decision-making tables – PICO 10

Interventions to optimize uptake of hepatitis testing and linkage to care across the viral hepatitis treatment cascade

17. Topic for analysis

Population: Individuals living with chronic hepatitis B or C (diagnosed or undiagnosed) or providers caring for these patients

Intervention: Psychosocial or structural interventions delivered in conjunction with screening, care, or treatment of hepatitis

Comparison: Standard of care or no intervention

Outcomes: Retention and progression along the continuum of care

18. Background:

Globally, 250 million people are chronically infected with hepatitis B virus (HBV), and 80–140 million are infected with chronic hepatitis C virus (HCV). Viral hepatitis is now responsible for 1.45 million deaths every year and is the seventh leading cause of mortality worldwide. Chronic HBV and HCV are responsible for over 90% of these deaths. But therapeutic advances are rapidly changing clinical management of both HBV and HCV infection, especially HCV infection is increasingly curable.

Reaping the clinical benefits of novel HBV and HCV therapies will require a continuum of care that start with screening and ultimately reaches and sustains viral suppression (Fig. 1). Similar to the HIV continuum of care, each step of the HBV/HCV continuum of care necessarily requires all prior steps and must be maintained over time. Screening is the critical entry way into the continuum and allows positive individuals to proceed and negative individuals to receive vaccination in the case of HBV. However, several barriers to screening have been reported, such as lack of knowledge, awareness and/or denial, lack of access to the infrastructure where screening is available, cultural beliefs, financial conditions including health insurance status, fear of blood taking and stigmatization as a patient aspects, and lack and gaps of awareness of risk factors, knowledge, experience of patient management, lack of infrastructure for testing and lack of access to treatment centres as a health-care aspect. Interventions can enhance chronic viral hepatitis management as part of each step along the continuum of care, including screening, linkage to care, treatment uptake, adherence, and viral suppression.

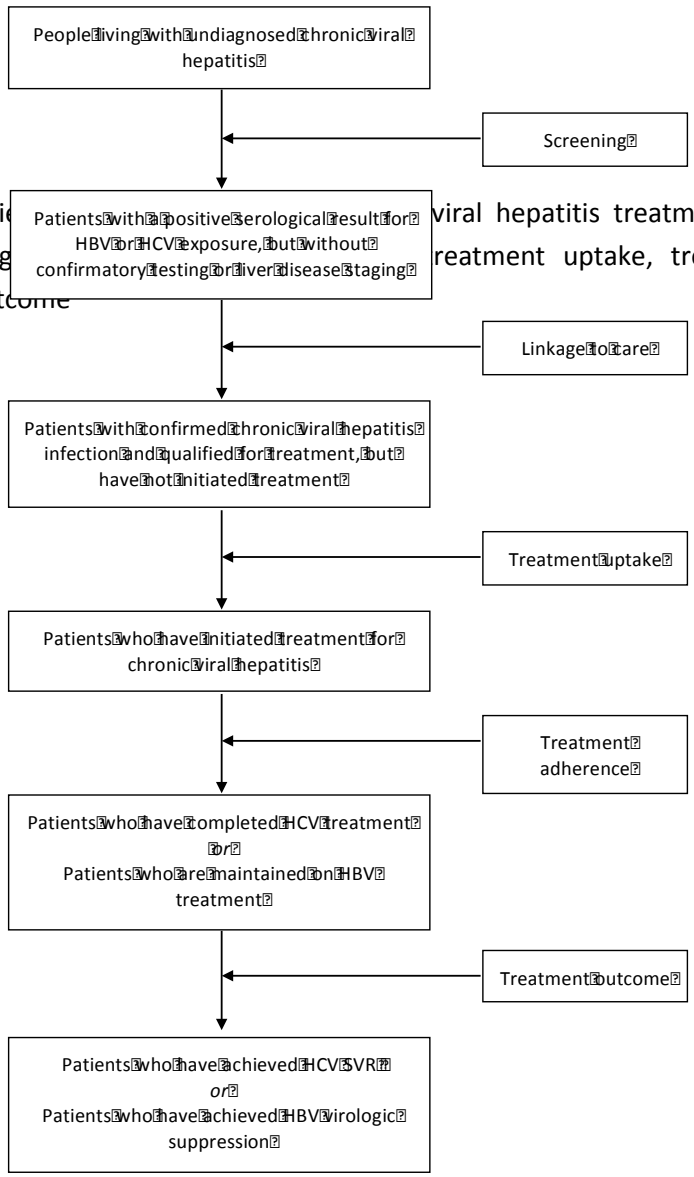


Fig. 1. Overvie viral hepatitis treatment continuum, including testing, linkag reatment uptake, treatment adherence, and treatment outcome

19. DRAFT recommendation(s):

20. Summary and quality of evidence

Summary of results

Evidence from the systematic review for linkage to care for HIV ARV GL 2015: among people living with HIV, what interventions facilitate linkage to care compared to standard of care? (PICO F.2.1)

Category	Summary	Quality
1. Counselling and support (*n* = 14)	Most interventions improved linkage to and engagement in care but not ART initiation	3 moderate, 6 low, 5 very low
2. Incentives (*n* = 4)	Mixed: one intervention worked, two did not	1 moderate, 2 low, 1 very low
3. Quality improvement (*n* = 7)	Most interventions increased outcomes targeted;	2 moderate, 5 very low

□ High
□ Moderate
□ Low
□ Very low

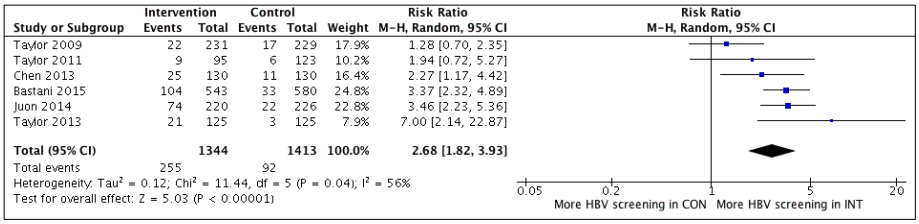
	interventions in category were multifaceted and incorporated interventions from other categories	

Evidence from the systematic review for linkage to care for hepatitis B and C testing GL:

We conducted a systematic review to identify interventions that improve the continuum of care in adults with chronic hepatitis B and C infection, quantify the effect size of these interventions, and recognize gaps in knowledge in interventional studies that target the chronic viral hepatitis continuum of care.

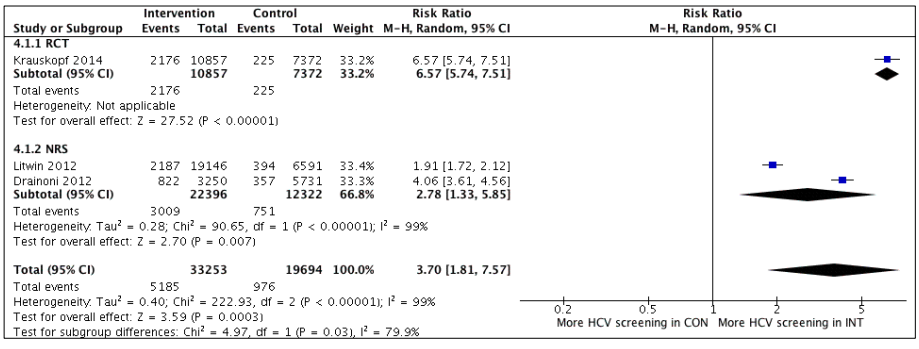
I. Meta-analyses for interventions to improve HBV screening

Single culturally tailored lay health worker educational session to improve HBV knowledge and promote testing vs no or unrelated educational session for self-reported HBV screening.



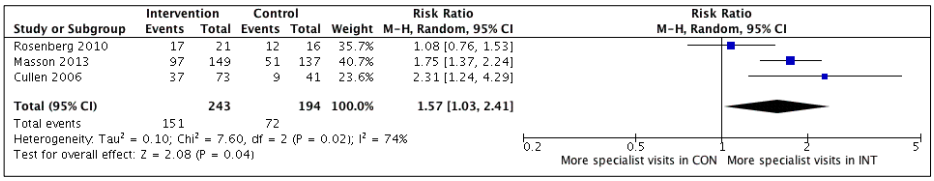
II. Meta-analyses for interventions to improve HCV screening

Clinician reminder to use HCV screening algorithm during clinical visit with or without supplementary provider education vs no clinician reminder for HCV screening.

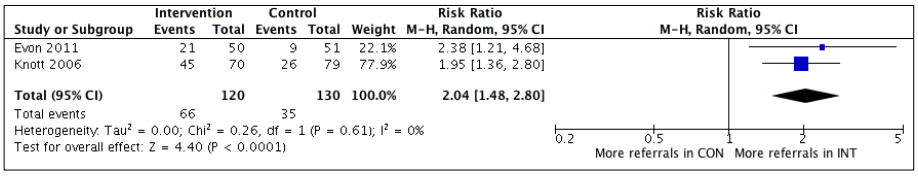


III. Meta-analyses for interventions to improve HCV linkage to care

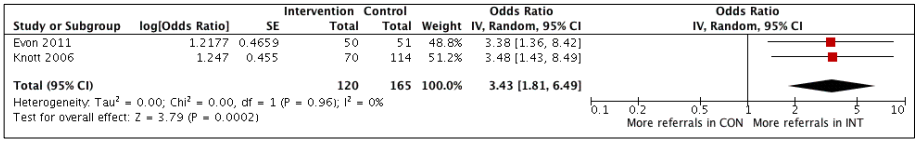
Facilitated referral and scheduling to specialist visit by staff at site of established care with or without supplementary HCV education and post-test counselling vs no facilitated referral for attendance at HCV specialist visit.



Individually tailored mental health counselling and motivational therapy for HCV^{+} patients with mental health and/or substance use comorbidities vs usual care for physician referral to initiate treatment.



Unadjusted results



Adjusted results

Results of educational interventions data from a systematic review:

For HBV

- Targeted population was HBV non-infected but at-risk individuals.
- Educational interventions increased: knowledge about the disease, HBsAg testing and HBV vaccination rates.

For HCV

- 50% of studies targeted HCV non-infected and the rest were HCV-infected individuals.
- Educational interventions increased: knowledge about the disease, the number of anti-HCVAb testing, willingness to undergo therapy, and treatment adherence.

Ref: Shah HA1, Abu-Amara M. Education provides significant benefits to patients with hepatitis B virus or hepatitis C virus infection: a systematic review. Clin Gastroenterol Hepatol. 2013;11(8):922–33. **Quality of evidence** *Refer GRADE table in footnote	
21. Risks/Benefits **Benefits of peer support, clinician reminder, and quality improvement initiatives/integration** • Increasing the rate for hepatitis B and C screening will increase the opportunity to link infected individuals to further hepatitis care and treatment. • The infected individuals will be offered health-protection advice to prevent disease progression and transmission. • Increase HCV treatment initiation, improve treatment completion, and increase SVR. **Risks** • Stigmatization by identifying HBV and/or HCV infection • Might be a challenge to differentially incentivize for receiving hepatitis care where poverty is prevalent and the rest of the population have limited access to health services in general. There are few studies on quality improvement initiatives/integration dealing with HBV.	□ Benefits clearly outweigh harms □ Benefits and harms are balanced □ Potential harms clearly outweigh potential benefits *Are the desirable anticipated effects large?* □ No □ Probably □ Uncertain □ Yes □ Varies
22. Acceptability, values and preferences **Counselling and peer support** • Counselling is recognized as standard of HIV-testing services and is also an essential intervention to support adherence. Although counselling for hepatitis testing services has not been established, simple educational interventions for lay health-care workers (HCWs) require little training, generate minimal costs, are highly feasible, and may substantially scale up HBV screening.	□ No major variability □ Major variability Is the option acceptable to key stakeholders?

Clinician reminder • HCWs will need to understand the strengths and limitations of appropriately counsel patients who are screened. • HCWs will need to aware the importance of reminder to enhance hepatitis screening during medical consultations. **Quality improvement initiatives/integration** • Coordinated mental health/substance abuse services within HCV service delivery will require new training and systems; however, linkage to initiation for HCV treatment, improved HCV treatment completion, and increased SVR will increase the rate of cure and prevent further HCV transmission.	□ No □ Probably □ Uncertain □ Yes □ Varies
23. Equity, ethics and human right implications **Counselling and peer support** *Will recommendation raise questions around equity?* • No. Increased rate for hepatitis B and C screening will increase equity to access for further hepatitis care and treatment, especially in resource-limited settings. *Are there ethical implications to this recommendation?* • No major concerns. **Clinician reminder** *Will recommendation raise questions around equity?* • No; increase in rate for hepatitis B and C screening will increase equity to access for further hepatitis care and treatment, especially in resource-limited settings. • Might be a challenge to differentially send clinician reminder to patients for receiving hepatitis care where poverty is prevalent and the rest of the population has limited access to health services in general. • Linkage to care of at-risk populations, e.g. antenatal clinics, tohose who attend drug-rehabilitation clinics, prisoners might be a challenge.	□ Less equitable □ More equitable

Are there ethical implications to this recommendation? • No major concerns. **Quality improvement initiatives/integration** *Will recommendation raise questions around equity?* • Some quality improvement initiatives may have a broader benefit for the health system. *Are there ethical implications to this recommendation?* • No major concerns.	
24. Resource use and financial implications **Counselling and peer support** • As testing and treatment programmes are scaled up, the numbers developing progressive disease and serious outcomes (HCC and complications of advanced liver disease), premature morbidity and mortality within the community will be reduced, and so also the burden of disease to societies where the disease is most prevalent. **Clinician reminder** • Creation of a new proper patient database in which the clinician reminder to prompt HCV testing require attention could be recorded might be costly; however, no extra cost is required to expand facility-based HCV screening in settings that have electronic records or analogous reminder systems. **Quality improvement initiatives/integration** • Variable and context specific, detailed costing of each intervention is not done	*Are the resources required small?* □ No □ Probably □ Uncertain □ Yes □ Varies
25. Feasibility and constraints to implementation *Are any major barriers expected for the implementation of this recommendation?* <u>Counselling and peer support and clinician reminder</u>	1.1.24 *Is the option feasible to implement?*

Feasible. • Simple educational intervention and clinician reminder, either electronic records or analogous reminder are highly feasible. <u>Quality improvement initiatives/integration</u> Feasible. • Coordinated mental health/substance abuse services within HCV service delivery will require involvement of stakeholders.	□ No □ Probably □ Uncertain □ Yes □ Varies
26. Relevance to different settings/populations *Will this recommendation be most relevant for particular settings (e.g. endemicity)?* • These recommendations will increase the opportunity of hepatitis screening and will be relevant to any circumstances.	
27. Rationale for recommendation:	
28. Strength of recommendation	
29. Implementation considerations • Establish linkages and referral pathways for the individuals infected with hepatitis viruses and suffering from mental health problems. • Ensure support from management and from service providers.	
30. Research gaps • Scientific implementation research, especially in low- and middle-income countries, is urgently needed to inform optimize chronic viral hepatitis service delivery systems. • Costing studies need to be performed.	

GRADE Summary of Findings

Evidence from the systematic review for linkage to care for HIV ARV GL 2015: interventions providing counselling and support (GRADE)

# (type) studies	Risk of:				N intervention (control)	Risk intervention (control)	Effect	Quality
	Bias	Inconsistency	Indirectness	Imprecision				
Linkage to care: trials								
1 (individual)	Not serious	Not serious	Not serious	Serious	200 (200)	0.67 (0.38)	RR 1.8 (1.4–2.1)	Moderate[1]
Linkage to care: observational								
7 (6 cohort, 1 other)	Serious	Not serious	Serious	Not serious	5271 (7195)*	0.81 (0.64)*	RR 1.25 (1.22–1.28)*	Very low[2]
Engagement in care: trials								
1 (individual)	Not serious	Not serious	Not serious	Not serious	188 (191)	0.92 (0.83)	pRR 1.1 (1.03–1.20)	Low[3]
Engagement in care: observational								
1 (Pre/post)	Serious	Serious	Serious	Not serious	1147 (1210)	0. 57 (0.45)	RR 1.28 (p<0.0001)	Low
ART initiation: trials								
2 (individual)	Not serious	Not serious	Not serious	Serious	806 (719)*	0.41 (0.43)*	RR 0.95 (0.84–1.07)*	Moderate[1]
PMTCT: trials								
1 (individual)	Not serious	Not serious	Not serious	Serious	197 (181)	0.64 (0.53)	aHR 1.39 (1.01–1.91)	Moderate[1]
PMTCT: observational								
1 (cohort)	Not serious	Not serious	Not serious	Serious	63 (332)	0.54 (0.25)	aOR 3.18 (1.76–5.73)	Low

Interventions offering incentives (GRADE)

# (type) studies	Risk of:				N intervention (control)	Risk intervention (control)	Effect	Quality
	Bias	Inconsistency	Indirectness	Imprecision				
Linkage to care: trials								
2 (1 individual, 1 cluster)	Not serious	Not serious	Not serious	Serious	60 (33)*	0.82 (0.48)*	RR 1.68 (1.16–2.44)*	Moderate[1]
Engagement in care: observational								
1 (cohort)	Serious	Not serious	Serious	Serious	100 (80)	0.94 (0.98)	2.00 (0.41–9.64)	Very low[1]

ART initiation: trials								
1 (individual)	Serious	Not serious	Not serious	Serious	60 (60)	0.45 (0.26)	aHR 2.93 (1.39–6.20)	Low[2]

Interventions introducing quality improvement (GRADE)

# (type) studies	Risk of:				N intervention (control)	Risk intervention (control)	Effect	Quality
	Bias	Inconsistency	Indirectness	Imprecision				
ART initiation: trials								
1 (1 cluster)	Not serious	Not serious	Not serious	Not serious	5390 (3862)	0.68 (0.62)	RR 1.24 (0.88–1.73)	Moderate[1]
Engagement in care: trials								
1 (1 cluster)	Not serious	Not serious	Not serious	Not serious	5390 (3862)	0.62 (0.58)	RR 1.1 (1.04–1.16)	High
PMTCT (ART initiation): observational								
3 (3 pre-post)	Serious	Not serious	Serious	Serious	619 (1296)*	0.36 (0.1)*	RR 3.48 (2.87– 4.22)*	Very low[3]
PMTCT (EID access): observational								
1 (1 pre-post)	Serious	Not serious	Serious	Serious	63 (332)	0.54 (0.25)	aOR 3.18 (1.76– 5.73)	Very low[2]
PMTCT (Receipt of AZT): trials								
1 (1 pre-post)	Serious	Not serious	Serious	Not serious	1258 (776)	0.87 (0.71)	RR 1.22 (1.16–1.28)	Very low[2]

Evidence from the systematic review for linkage to care for hepatitis B and C testing GL:

I. Meta-analyses for interventions to improve HBV screening

Quality assessment							No of patients		Effect		Quality
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Single LHW educational session**	**No or unrelated educational session**	**Relative (95% CI)**	**Absolute (95% CI)**	
HBV screening											
6	Randomized trials	Serious[1]	Not serious	Not serious[2]	Not serious[3]	None	255/1344 (19.0%)	92/1413 (6.5%)	RR 2.68 (1.82–3.93)	109 more per 1000 (from 53 more to 191 more)	⨁⨁⨁◯ Moderate
								6.6%		110 more per 1000 (from 54 more to 192 more)	

1. 6/6 studies are at high risk of detection bias because the outcome was self-reported HBV screening 6 months post intervention. 5/6 studies are at high risk of attrition bias because the ratio of participants with missing data to participants with HBV screening outcome was high (>1.0).
2. Although all included studies involved Asian immigrants in North America, this was not judged to be a significant enough difference in populations to downgrade because the intervention strategies are not exclusive to Asian immigrant populations.
3. The confidence interval is not wide. The OIS was calculated to be 222, and the pooled sample size exceeded the OIS. 3/6 included studies were cluster RCTs, none of which performed analyses that accounted for clustering. Consequently, this meta-analysis commits a unit-of-analysis error and produces over-precise results. Additionally, no ICC were reported in the included studies, so statistical methods could not be used to reduce the effective sample size of the cluster RCTs. Despite this limitation, it is unlikely proper adjustment for cluster design would significantly impact the precision of the pooled results.

II. Meta-analyses for interventions to improve HCV screening

Quality assessment							No. of patients		Effect		Quality
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Clinical testing reminder**	**No reminder**	**Relative (95% CI)**	**Absolute (95% CI)**	
HCV screening											
3	Other design[1]	Serious[2]	Serious[3]	Not serious	Serious[4]	None[5]	5185/33253 (15.6%)	976/19694 (5.0%)	**RR 3.70** (1.81–7.57)	134 more per 1000 (from 40 more to 326 more)	⊕◯◯◯ Very low
								6.0%		161 more per 1000 (from 48 more to 393 more)	

1. This meta-analysis includes 1 cluster RCT and 2 NRS.
2. Drainoni (2012) is at high risk of performance bias and did not employ methods to adjust for confounding potentially introduced by its non-randomized study design. Krauskopf (2014) did not report comparability of randomized clusters and therefore was at high risk of bias.
3. All included studies report a risk ratio >1.0. However, I^2 = 99%. The high degree of heterogeneity may be due to differences between HCV screening algorithms used in each intervention.
4. Although the pooled sample size exceeds the calculated OIS, the confidence interval is wide. Additionally, Krauskopf (2014) was a cluster RCT that did not account for clustering in its analysis. Consequently, this meta-analysis commits a unit-of-analysis error and produces over-precise results. No ICC was reported, so statistical methods could not be used to reduce the effective sample size of the cluster RCT.
5. All included studies report a risk ratio >2.0. However, the pooled results have not been upgraded for large effect because the non-randomized design of 2/3 studies introduces a significant possibility of confounding.

III. Meta-analyses for interventions to improve HCV linkage to care

Quality assessment							No. of patients		Effect		Quality
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Facilitated referral to specialist visit at site of established care**	**No facilitated referral**	**Relative (95% CI)**	**Absolute (95% CI)**	
Attended HCV specialist visit											
3	Randomized trials	Not serious[1]	Serious[2]	Not serious	Not serious[3]	None	151/243 (62.1%)	72/194 (37.1%)	**RR 1.57** (1.03–2.41)	212 more per 1000 (from 11 more to 523 more)	⨁⨁⨁◯ Moderate
								37.2%		212 more per 1000 (from 11 more to 525 more)	

1. Rosenberg (2010) relied on self-reported HCV status and self-reported attendance to an HCV specialist visit, putting the study at high risk of detection bias. However, because this study had a relatively small sample size it was not judged to put the entire meta-analysis at high risk of bias.
2. I^2 = 85%. This high degree of heterogeneity may be due to differences between the intensity of interventions in the included studies.
3. The confidence interval is not wide. The OIS was calculated to be 124, and the pooled sample size exceeded the OIS.

References

1. Drainoni ML, Litwin AH, Smith BD, Koppelman EA, McKee MD, Christiansen CL et al. Effectiveness of a risk screener in identifying hepatitis C virus in a primary care setting.Am J Public Health. 2012;102(11):e115–21.
2. Krauskopf K, Kil N, Sofianou A, Toribio W, Lyons J, Singer M et al. Evaluation of an electronic health record prompt for hepatitis c antibody screening of baby boomers in primary care – a cluster randomized control trial. J Gen Intern Med2014;29:S88–S89.
3. Rosenberg SD, Goldberg RW, Dixon LB, Wolford GL, Slade EP, HImelhoch S et al. Assessing the STIRR model of best practices for blood-borne infections of clients with severe mental illness. Psychiatr Serv. 2010;61(9):885–91.

Individually tailored mental health counselling and motivational therapy for HCV+ patients with mental health and/or substance use comorbidities vs usual care for physician referral to initiate treatment

Quality assessment							No. of patients		Effect		Quality
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Individually tailored mental health counselling and motivational therapy**	**Usual care**	**Relative (95% CI)**	**Absolute (95% CI)**	
Physician referral to initiate treatment											
2	Other design[1]	Serious[2]	Not serious	Not serious[3]	Not serious[4]	None	66/120 (55.0%)	35/130 (26.9%)	**RR 2.04** (1.48–2.80)	280 more per 1000 (from 129 more to 485 more)	⨁◯◯◯ Very low
								(25.3%)		263 more per 1000 (from 121 more to 455 more)	
Adjusted physician referral to initiate treatment											
2	Other design [1]	Serious [5]	Not serious	Not serious [3]	Serious[6]	None	–/120	–/165	**OR 3.43** (1.81–6.49)	0 fewer per 1000 (from 0 fewer to 0 fewer)	⨁◯◯◯ Very low

1. Evon (2011) is a RCT, while Knott (2006) is an NRS.
2. Knott (2006) is at high risk of detection bias because the outcome was subjective and determined by the physician overseeing treatment who was not blinded. Unadjusted results from Knott (2006) were used in this meta-analysis that did not employ methods to adjust for confounding potentially introduced by its non-randomized study design.
3. The decision to not downgrade for indirectness assumes guidelines are applied to other contexts where mental health or substance use comorbidities are also contraindications to recommending HCV+ patients for treatment.
4. The confidence interval is not wide. The OIS was calculated to be 94, and the pooled sample size exceeded the OIS. Knott (2006) is at high risk of detection bias because the outcome was subjective and determined by the physician overseeing treatment who was not blinded.
5. The confidence interval for the pooled adjusted outcomes is wide.

References

4. Evon DM, Simpson K, Kixmiller S, Galanko J, Dougherty K, Golin C et al. A randomized controlled trial of an integrated care intervention to increase eligibility for chronic hepatitis C treatment. Am J Gastroenterol. 2011;106(10):1777–86.
5. Knott A, Dieperink E, Willenbring ML, Heit S, Durfee JM, WIngert M et al. Integrated psychiatric/medical care in a chronic hepatitis C clinic: effect on antiviral treatment evaluation and outcomes. Am J Gastroenterol. 2006;101(10):2254–62.