LABLINK MEDICAL LABORATORY TESTING ALGORITHM FOR THE DIAGNOSIS OF HCV

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1. Introduction

1.1 Epidemiology of hepatitis C infection

Recent analyses of the global prevalence of HCV indicate that there may be fewer persons living with hepatitis C infection than previously estimated. A recent systematic review estimated that 110 million persons have a history of HCV infection (i.e. are HCV-antibody positive) and 80 million have a chronic viraemic infection. Regions estimated to have a high prevalence in the general population (>3.5%) are Central and East Asia, and North Africa/Middle East; those with a moderate prevalence (1.5–3.5%) include South and South-East Asia, Sub-Saharan Africa, Latin America (Andean, central, and southern regions), the Caribbean, Oceania, Australasia, and central, eastern and western Europe; whereas low-prevalence (<1.5%) regions include Asia–Pacific, Latin America, and North America. Updated estimates in Africa show an HCV prevalence of 2.98%, with a higher prevalence observed in West Africa and lower in south-east Africa.

Despite the declining incidence, a large number of persons who were infected 30–60 years ago are now dying from HCV-related cirrhosis and liver cancer, as these complications often take decades to develop. According to estimates from the Global Burden of Disease study, the number of deaths due to hepatitis C increased from 333 000 in 1990 to 499 000 in 2010 and 704 000 in 2013, and this increase is projected to continue for several more decades unless treatment is scaled up considerably.

HIV and HCV have common routes of transmission, and persons with HIV infection, in particular PWID and MSM, are at increased risk of HCV infection. In a recent comprehensive systematic review, it is estimated that, globally, 2.3 million persons are coinfected with these two viruses, of whom 1.2 million (interquartile range [IQR] 0.9–1.4 million) are PWID. With the widespread use of antiretroviral therapy (ART), which reduces the risk of HIV-associated opportunistic infections, HCV-related liver disease has started to overtake AIDS-defining illnesses as a leading cause of death among people living with HIV in some high-income countries (HICs).

1.2 Transmission of HCV Infection

There are four main routes of transmission: healthcare-associated transmission, injecting drug use, mother-to-child transmission (MTCT), and sexual transmission. In LMICs, infection with HCV is most commonly associated with unsafe injection practices, and invasive procedures in health-care facilities with inadequate infection control practices, such as renal dialysis and unscreened (or inadequately screened) blood transfusions. Persons who received untested blood products prior to the introduction of screening of blood for HCV in (HICs) are also at risk, and WHO reports suggest that there are still 39 countries that do not routinely screen blood transfusions for bloodborne viruses. In middle- and high-income countries, most HCV infections occur among people who use unsterile equipment to inject drugs. PWID have a high global prevalence of infection at around 67%. Of the estimated 16 million people in 148 countries who actively inject drugs, 10 million have serological evidence of HCV infection. There is a moderate risk of MTCT of HCV which is higher in HIV-coinfected mothers (10–20%). The risk of sexual transmission of HCV is also greater in HIV-positive persons, particularly MSM, but is low among HIV-uninfected heterosexual couples and MSM. Other routes of bloodborne transmission include the acquisition by health-care workers, cosmetic procedures (such as tattooing and body piercing), scarification and circumcision, and intranasal drug use.

1.3 HCV Structure and Genome

HCV is an enveloped single-stranded RNA virus contain an icosahedral protein capsid. The outer envelope has a lipid structure anchoring two glycoproteins E1 and E2. The linear RNA strand is composing approximately 9600 bases coding for unique precursor polyprotein. Proteases coming from the virus NS2 and NS3 and the cell itself cleave this polyprotein into two categories of viral protein. Structural protein including the capsid C protein, and the envelope E1 and E2 and non-structural protein NS. The non-structural proteins include protease NS2, serine protease NS3, a cofactor for NS3 activity call NS4A, a regulator protein NS5A and RNA dependant RNA polymerase NS5B. HCV is transmitted mainly through blood and reaches the liver via the bloodstream. The virus circulates as the so-called lipo-viral-particles associated with components of low-density and very low-density lipoproteins. The viral envelope glycoproteins are localized on the surface, whereas the nucleocapsid is located within the hydrophobic interior of the lipo-viral-particle. The nucleocapsid is formed of core proteins interacting with the viral RNA genome.

1.4 Life Cycle of HCV

HCV replicates in the hepatocytes of the liver and circulates throughout the body. Entry of the virus into hepatocytes occurs through the interaction of the viral envelope with receptors on the surface of the host cell. Once the viral particle reaches the hepatocyte surface, it interacts first with the glycosaminoglycans and syndecans, follows by binding to more specific receptors including the scavenger receptor B1 and the tetraspanin protein CD81. The viral particle complexed with these entry particles reaches a tight junction and engages its further interaction with claudin-1 (CLDN1) and occludin. The viral particle subsequently enters the cell via receptor- and clathrin-mediated endocytosis. After its release into the cytosol, the clathrin-coated vesicle interacts with the motor protein dynein. Dynein transport the vesicle by walking along microtubules to reach the endoplasmic reticulum area.

Acidification of the endosome lumen induces conformational changes of the viral envelope glycoproteins, which in turn interact with the endosomal membrane, leading to fusion of the viral and endosomal membranes. Membrane fusion is followed by uncoating of the nucleocapsid and the release of viral RNA genome into the cytosol. HCV utilize many of the host cell proteins and molecules in order to replicate. Binding and assembly of ribosome subunits on the viral RNA is the starting of HCV polyprotein translation. A signal sequence located in the beginning of the translated polyproteins allows the ribosome to be targeted to the translocon on the endoplasmic reticulum membrane. Translation can thereby proceed further giving rise to a polyprotein which is cleaved by cellular signal peptidases and by the viral proteases into 10 mature proteins.

The structural proteins which make up the viral particle comprise a core and the envelope glycoproteins E1 and E2. p7 and NS2 support viral particle production while not being incorporated into the particle. The replicase component NS3-4A, NS4B, NS5A and NS5B, are sufficient to support viral RNA replication. HCV replicase proteins in concert with host factors, induce rearrangement of the ER membrane, including the formation of double-membrane vesicles. These vesicles cluster to form the membranous web, which represents the site of HCV RNA replication.

Viral RNA synthesis is catalyzed by the RNA-dependant RNA polymerase activity of NS5B, which acts in concert with other viral non-structural proteins, as well as several host factors. After synthesis of a negative-strand RNA intermediate multiple positive-strand progeny RNAs are generated from this template and are either use for translation and replication or packaged into nucleocapsid particles. The latter process is thought to be initiated on the surface of lipid droplets that are targeted by the core protein. It is assumed that a network of NS5A delivers the viral RNA to core proteins for assembly into nucleocapsids. Nucleocapsids formed at the ER-derived membranes, where E1 and E2 accumulate in conjunction with p7, NS2, and host factors including apolipoprotein E.

The viral envelope glycoproteins are acquired by budding, a process which appears to be linked to the very low-density lipoprotein machinery. Newly synthesized virus particles are thought to be transported to the cell surface in export vesicles via the cellular secretory pathway. Finally, they are released from the cell by exocytosis to reach the bloodstream.

1.5 Natural history of HCV infection

Hepatitis C virus causes both acute and chronic infection. Acute HCV infection is defined as the presence of certain markers of HCV infection within six months of exposure to an infection with HCV and is characterized by the appearance of HCV RNA, HCV core antigen (p22 Ag), and subsequently HCV antibodies, which may or may not be associated with viral clearance. Antibodies to HCV develop as part of acute infection and persist throughout life. Acute infection is usually clinically silent and is only very rarely associated with a life-threatening disease. Spontaneous clearance of acute HCV infection generally occurs within six months of infection in 15–45% of infected individuals in the absence of treatment, but this varies by region and population. Antibodies to HCV develop as part of acute infection and persist throughout life. Almost all the remaining 55–85% of persons who do not clear HCV within six months are defined as having chronic HCV infection. Left untreated, chronic HCV infection can cause liver cirrhosis, liver failure and HCC. Of those with chronic HCV infection, the risk of cirrhosis of the liver is 15–30% within 20 years. The risk of HCC in persons with cirrhosis is approximately 2–4% per year. Clearance of infection, whether spontaneous or as a result of antiviral treatment, does not provide lasting protection from reinfection.

2. Audience

These recommendations describe the types and sequence of laboratory assays used to make the laboratory diagnosis of acute HCV infection, chronic HCV infection, as well as monitoring patient on Anti-Viral therapy using HCV RNA viral load assay. They are intended for use by Lablink Medical Laboratory and Network of Lablink Medical Laboratories.

3. Scope

The scope of this guidelines is to provide a testing strategy for the diagnosis of acute and chronic HCV infection, as well as treatment monitoring. These recommendations are intended for testing of serum or plasma specimens from adults, and children more than 18 months of age. These recommendations do not address methods or strategies for screening blood or organ donors for HCV infection.

4. Diagnostics testing for hepatitis C infection

Serological assays are typically used as the first line of the testing strategy to screen for exposure to a virus because of their relatively low cost (compared to NAT) and are therefore used to rule in all individuals who might potentially be infected with HCV. Serological assays detect the host immune response (antibodies to HCV) or a viral antigen (HCVcAg). They are based on the immunoassay principle and are available in the form of rapid diagnostic tests (RDTs) or laboratory-based enzyme immunoassays (EIAs), chemiluminescence immunoassays (CLIAs) and electrochemiluminescence immunoassays (ECLs). In contrast, NAT technologies are typically used to detect the presence of the virus, determine if the infection is active and if the individual would benefit from antiviral treatment. NAT technologies are also used to determine when antiviral treatment should be discontinued (due to non-response or resistance) or to confirm virological cure (HCV).

4.1 Serological Assay

a. Laboratory-based Immunoassay

Most laboratory-based serological immunoassays (EIAs, CLIAs and ECLs) detect antibodies, antigens or a combination of both and differ only in the mode of detection of immune complexes formed. A cut-off value, usually determined by the manufacturer of the assay, specifies the point at which the results are considered to be reactive, and therefore, EIA results are generally reported as optical density divided by the assay cut-off (OD/CO) values. These types of assays are best suited for and most cost-effective to perform in settings with a high throughput of specimens (in excess of 40 per day). They are meant for laboratory- or facility-based testing rather than for use in the community, where infrastructure (electricity, cold storage, climate-controlled rooms) and skilled staff are consistently available, as cold-chain storage of test kits and the use of precision pipettes are usually required. These assays are typically used only with serum or plasma specimens, and therefore require phlebotomy to collect an appropriate specimen.

These assays may be performed either manually or on non-dedicated automated assay or specifically dedicated automated systems. Simple immunoanalysers automate a number of the processes and as such requires less hands-on time than a manually run EIA. They can therefore be used in a range of different situations from high-throughput laboratories for the screening of large numbers of samples with full automation, to medium-sized laboratories with semi-automation, to small laboratories, such as those in remote areas, which conduct a small number of tests manually.

b. Confirmatory assay

For anti-HCV – line immunoassays or immunoblots are serological techniques to confirm the presence of antibodies to HCV that have already been detected by other serological assays. The use of confirmatory assays should be able to provide a definitive result, although these assays are more expensive than other assays and are prone to high rates of indeterminate results. These assays only confirm serostatus and cannot be used to diagnose viraemic active HCV infection.

4.2 Nucleic Acid testing Technologies

These assays detect the presence of viral nucleic acid – RNA – through targeting a specific segment of the virus, which is then amplified. The amplification step enables the detection of low levels of the virus in the original specimen, which might not otherwise have been detectable. Laboratory-based technologies for NAT require sophisticated equipment, rigorous laboratory conditions and specimen collection, and highly trained staff who can perform precision steps and avoid contamination. Not all NAT technologies detect all genotypes or subtypes equally well unless they are optimized to do so. Newly developed NAT technologies that are simpler and more robust are intended for use at or near the point of care and may avoid some of the logistical and technical disadvantages of laboratory-based NAT technologies. In addition to NAT assays that target a single virus, multiplex NAT screening assays have been developed, which can detect DNA or RNA from multiple viruses simultaneously.

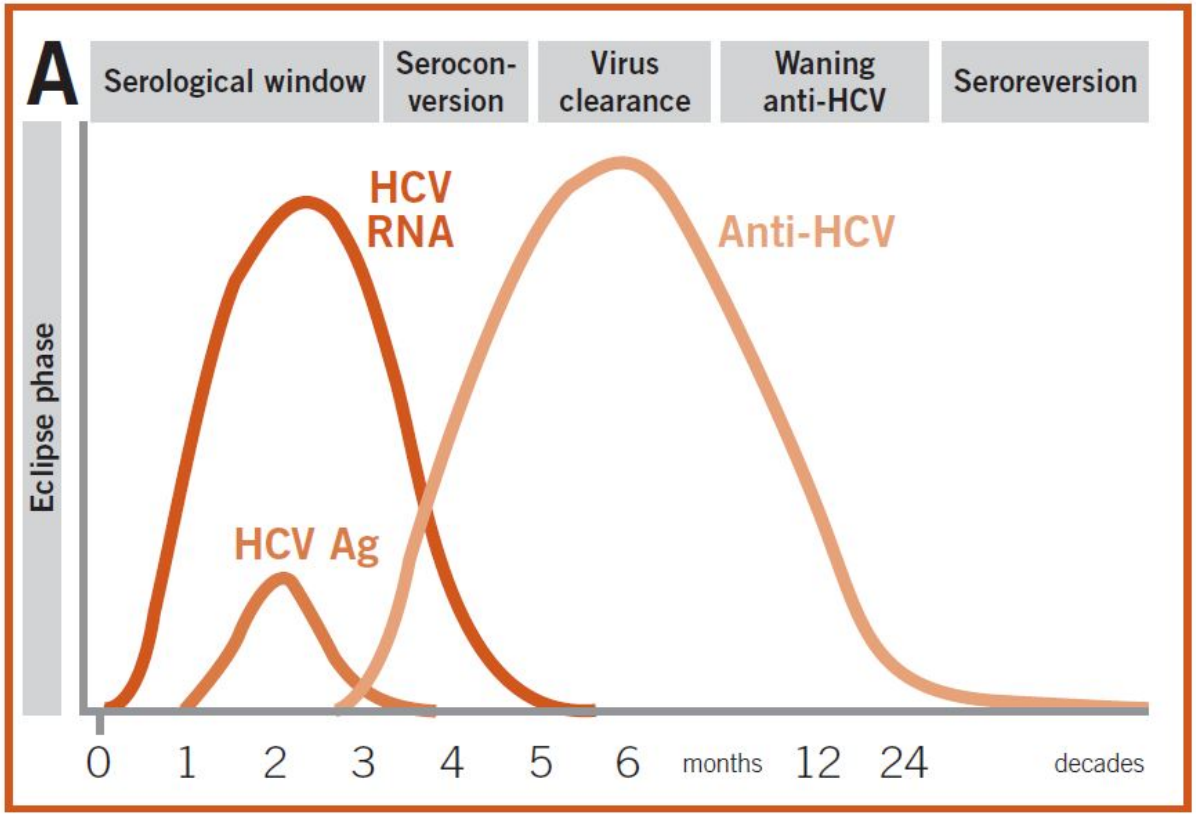
5. Time course of serological markers for HCV infection

The exact time course of virological and immunological markers of HCV infection is not well defined, particularly during the first months of infection, due to differences in each host (patient) immune response, specific properties of the infecting virus, and sensitivity of assays used to determine the appearance of HCV markers. As illustrated in Fig. 5.2, following an initial eclipse phase of 1–2 weeks when no virological or serological markers of infection may be detected, the natural course of HCV infection is characterized by the appearance of HCV RNA, then HCV core p22 Ag in the absence of an antibody response for a further 6–10 weeks. During this serological window, it has been shown that free (i.e. not complexed with antibody) HCV core antigen (HCVcAg) can be detected in a proportion of individuals.

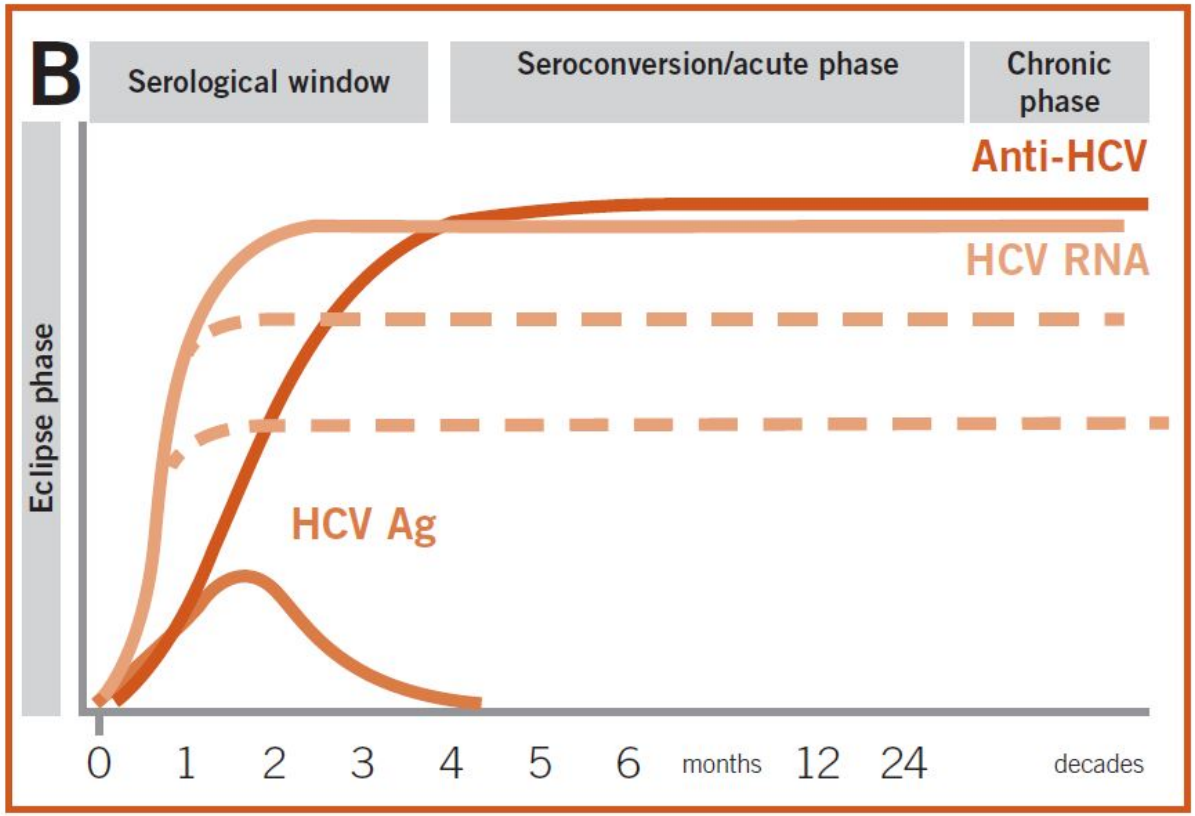
5.1 Window Period

Assays designed solely to detect antibodies to HCV inevitably have a window period of infectivity in early infection, during which antibodies may be undetectable. This window period can be shortened by utilizing assays that also include direct detection of HCVcAg (50–60 days). HCV RNA is typically not used to determine exposure to HCV, in spite of its short window period (1–2 weeks after the onset of acute infection) primarily because of cost. There are increasing reports of occult HCV infection, i.e. HCV RNA detectable in the absence of any serological markers (i.e. HCV seronegative) which may be due to underlying immunosuppression in, for example, HIV-infected populations.

5.2 Self-resolving HCV infection – Approximate time course of virological and immunological markers of HCV infection.



5.3 Chronic HCV infection – Approximate time course of virological and immunological markers of HCV infection.



6. Types of HCV assays available at Lablink Medical Laboratories as at 30th January 2018.

6.1 Screening Test

a. Anti-HCV – Anti-HCV II (3rd Generation) is an in-vitro diagnostic test for the qualitative detection of antibodies to hepatitis C virus in human serum and plasma. The electrochemiluminescence immunoassay (ECLIA) is intended for use on Elecsys and Cobas e immunoassay analyzers

6.2 Supplementary Test

a. HCV LIA – INNO-LIA HCV score is a 3rd generation line immunoassay which incorporates HCV antigens derived from the core region, the E2 hypervariable region (HVR), the NS3 helicase region, the NS4A, NS4B, and NS5A regions. In anti-HCV positive (Equivocal/ Weak Reactive/ Reactive) individuals who test negative for HCV RNA, use of HCV LIA may be considered for distinction between true HCV exposure and biological false positivity.

b. HCV Viral Load – The Xpert® HCV Viral Load assay, perform on GeneXpert® instrument systems, is designed for rapid quantitation of HCV RNA virus in human serum or plasma (EDTA) from HCV infected individuals. The test utilizes automated reverse transcriptase polymerase chain reaction (RT-PCR) using fluorescence to detect the RNA of interest for the quantification of HCV. The Xpert® HCV Viral Load Assay quantifies HCV genotypes 1-6 over the range of 10 to 100, 000, 000 IU/mL. Results from the Xpert® HCV Viral Load Assay can be used to confirm and to supplement the diagnosis of HCV infection in anti-HCV positive (Equivocal/ Weak Reactive/ Reactive) individuals.

6.2 Monitoring Test

a. HCV Viral Load – The Xpert® HCV Viral Load assay, perform on GeneXpert® instrument systems, is designed for rapid quantitation of HCV RNA virus in human serum or plasma (EDTA) from HCV infected individuals. The test utilizes automated reverse transcriptase polymerase chain reaction (RT-PCR) using fluorescence to detect the RNA of interest for the quantification of HCV. The Xpert® HCV Viral Load Assay quantifies HCV genotypes 1-6 over the range of 10 to 100, 000, 000 IU/mL. The Xpert® HCV RNA Viral Load Assay can be used as an aid in the management of HCV infected patients undergoing anti-viral therapy. The test measures HCV RNA levels at

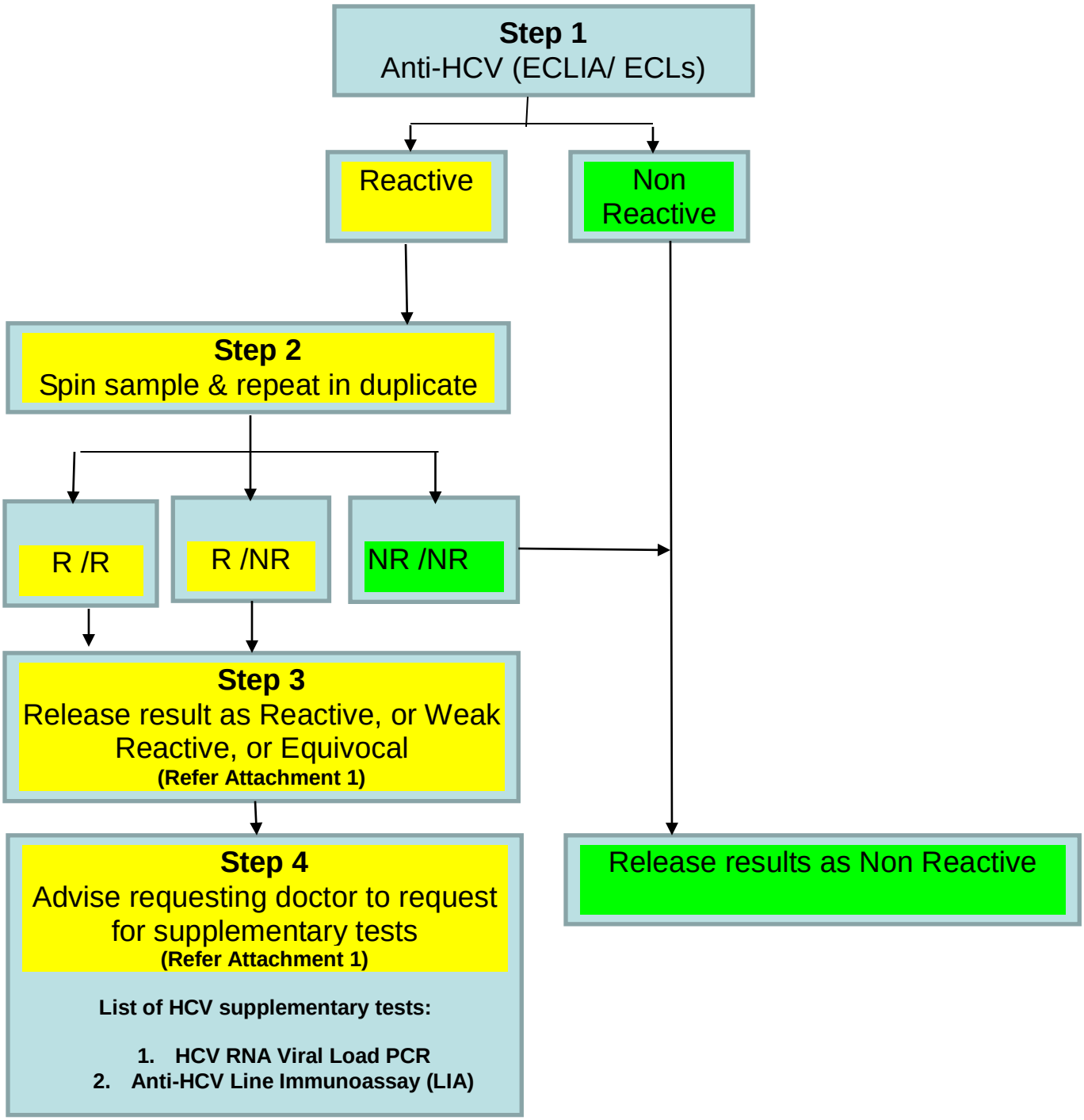
baseline, and during treatment, and can be utilized to predict sustained (SVR) and non-sustained (NSVR) virological responses to HCV therapy.

7. Specimen types used for HCV testing

7.1 Serum : freshly collected whole blood is allowed to coagulate, and the serum fraction is collected away from the clotted red blood cells.

7.2 Plasma : freshly collected wholeblood is added to the recommended anticoagulant, such as EDTA, heparin, or citrate. After centrifugation, the plasma is separated. Use only anticoagulant validated by the assay manufacturer.

8.0 Lablink Medical Laboratory HCV Testing Algorithms



Role of supplementary tests:

1. Confirmation of viraemic status
2. Additional testing to support inconclusive results eg. Equivocal and Weak Reactive ECLIA/ ECLs results.

9.0 Recommended supplementary assays for confirmation of HCV viraemic status and additional tests to support inconclusive results, eg. Equivocal and Weak Reactive ECLIA/ ECLs.

Range COI (ECLIA)	Result	Recommended supplementary assays for confirmation of HCV viraemic status and additional tests to support inconclusive results.
< 0.9	Non Reactive	Not Applicable. Note: If recent exposure is suspected; test for HCV RNA Viral Load Assay
0.9 – 10.0	Equivocal	Assays for confirmation of HCV infection: 1. HCV RNA Viral Load Assay[a, b] 2. Anti-HCV LIA[b] Note: In haemodialysis patient, firstly, establish the status of HCV by using ECLIA, HCV RNA Viral Load Assay & Anti-HCV LIA. Then assess the status by monitoring COI on subsequent ECLIA testing. If on follow-up, COI value showed significant increment from baseline; assess the status again using HCV RNA Viral Load Assay and Anti-HCV LIA.
10.1 – 15.0	Weak Reactive	Assays for confirmation of HCV infection: 1. HCV RNA Viral Load Assay[a, b] 2. Anti-HCV LIA[b] Note: In haemodialysis patient, firstly, establish the status of HCV by using ECLIA, HCV RNA Viral Load Assay & Anti-HCV LIA. Then assess the status by monitoring COI on subsequent ECLIA testing. If on follow-up, COI value showed significant increment from baseline; assess the status again using HCV RNA Viral Load Assay and Anti-HCV LIA.
> 15.0	Reactive	Assays for confirmation of HCV infection and status of infection: 1. HCV RNA Viral Load Assay

[a]Confirmation of HCV viraemic status

[b]Supplementary tests to support inconclusive ECLIA/ ECLs results.

10. Detail list of tests for the diagnosis of HCV available at Lablink Medical Laboratory as at 30th of January 2018.

No.	Test / Objective	Specimen	Container	Transportation Requirement	Method	Note
9.1	**Test:** Anti-HCV	Venous Blood (Serum and Plasma)	Plain Tube or Plain Tube with Serum Separator. OR Li-heparin tube OR EDTA tube OR Li- heparin with plasma separator	4 weeks at 2–8 °C 7 days at 25 °C 3 month at -20°C (frozen 5 times only)	Electrochemilumi nescence Enzyme Immunoassay – ECLIA	**Note 1:** Anti-HCV antibody tests are used alone or in combination with other tests (e.g. HCV-RNA) to detect an infection with hepatitis C virus and to identify blood and blood products of individuals infected with HCV. The Elecsys Anti-HCV II assay is a third-generation test. The Elecsys Anti-HCV II assay uses peptides and recombinant antigens representing core, NS3 and NS4 proteins for the determination of anti-HCV antibodies.

No.	Test	Specimen	Container	Transportation Requirement	Method	Note
9.2	**Test:** HCV Line-Immunoassay (LIA)	Venous blood (Serum or plasma)	Plain Tube or Plain Tube with Serum Separator. OR EDTA Tube or EDTA Tube with Plasma Separator. OR Citrate tube OR Heparin tube	7 days at 2-8 °C >7 days at -20°C (frozen 3 times only)	Line Immunoassay (LIA)	**Note 1:** INNO-LIA™ HCV Score detects antibodies against: the Core region (C1, C2), the Envelop region (E2), the replication region (NS3, NS4, NS5)

No.	Test	Specimen & Container	Transportation Requirement	Method	Note
10.4	**Test:** Rapid Xpert® HCV Viral Load PCR	Specimens: **Plasma:** Sterile EDTA / EDTA-PPT collection tube (min volume 2.5 mL) **Serum:** Plain tube with serum separator (min volume 2.5 mL)	At 2–8 °C for up to 72 hours, prior to preparing and testing the specimen.	Reverse Transcriptase Real Time PCR (RT-PCR)	**Note 1** For treatment monitoring and can be use as a supplementary test for confirmation of HCV infection.

11.0 How to interpret HCV results

11.1 How to report non-reactive HCV result?

Run 1	Run 2	Run 3	Result	Comments
NR (<0.9)	NA	NA	Non-Reactive	If recent HCV exposure is suspected, please test using HCV RNA Viral Load PCR assay.
R (Eq) (0.9 - 10)	NR (<0.9)	NR (<0.9)	Non-Reactive	If recent HCV exposure is suspected, please test using HCV RNA Viral Load PCR assay.
R (WR) (10.1 – 15.0)	NR (<0.9)	NR (<0.9)	Non-Reactive	If recent HCV exposure is suspected, please test using HCV RNA Viral Load PCR assay.

NOTE: Refer Lablink Medical Laboratory HCV testing algorithm, page 15: NR – Non-Reactive; Eq – Equivocal; WR – Weak Reactive; NA – Not Applicable.

11.2 How to report equivocal HCV result?

Run 1	Run 2	Run 3	Result	Comments
EQ (0.9-10.0)	EQ (0.9-10.0)	EQ (0.9-10.0)	Equivocal (EQ)	Most likely biological false positive result in the absence of risk factors. If recent high-risk exposure is suspected, the result may indicate an early infection. Kindly sent a repeat specimen for confirmation of HCV status, if clinically indicated. Assays for HCV confirmation include; 1. HCV RNA Viral Load PCR Assay, and or 2. HCV Line Immunoassay Note: Note: Equivocal results are common in haemodialysis patients. It is recommended to establish the status of HCV by using all HCV assays which include ECLIA, HCV Viral Load RNA PCR & HCV LIA. Future assessment of HCV status can be performed by monitoring COI value of Anti-HCV ECLIA on subsequent testing. If follow-up COI value showed significant increment from baseline; assess the status again by using HCV RNA PCR and HCV LIA.

NOTE: Refer Lablink Medical Laboratory HCV testing algorithm, page 15.

11.3 How to interpret weak reactive HCV result?

Run 1	Run 2	Run 3	Result	Comments
WR (10.1-15.0)	WR (10.1- 15.0)	WR (10.1-15.0)	Weakly Reactive (WR)	Most likely biological false positive result in the absence of risk factors. If recent high-risk exposure is suspected, the result may indicate an early infection. Kindly sent a repeat specimen for confirmation of HCV status, if clinically indicated. Assays for HCV confirmation include; 1. HCV RNA Viral Load PCR Assay, and or 2. HCV Line Immunoassay Note: Note: Equivocal results are common in haemodialysis patients. It is recommended to establish the status of HCV by using all HCV assays which include ECLIA, HCV Viral Load RNA PCR & HCV LIA. Future assessment of HCV status can be performed by monitoring COI value of Anti-HCV ECLIA on subsequent testing. If follow-up COI value showed significant increment from baseline; assess the status again by using HCV RNA PCR and HCV LIA.

NOTE: Refer Lablink Medical Laboratory HCV testing algorithm, page 15.

11.4 How to interpret reactive HCV results?

Run 1	Run 2	Run 3	Result	Comments
R (>15.0)	R (>15.0)	R (>15.0)	Reactive (R)	A repeatedly reactive result is consistent with current HCV infection, or past HCV infection that has been resolved. Kindly test for HCV RNA Viral Load Assay to determine the current status of infection.

NOTE: Refer Lablink Medical Laboratory HCV testing algorithm, page 15.

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