#  Standard Operating Procedures forManagement of Hepatitis C Infection

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# Standard Operating Procedures for:Management of Hepatitis C Infection

## PURPOSE

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| This standard operating procedure (SOP) is a guideline for the clinical management of Hepatitis C virus (HCV) infection for participants in the endTB clinical trials. |

## SCOPE

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| This SOP is developed for trained healthcare workers who are managing the treatment of participants in the endTB clinical trials. |

## RESPONSIBLE FUNCTIONS

|  |  |
| --- | --- |
| **Function** | **Activities** |
| **Site Principal Investigator (Site PI)** | * Accountable for patient eligibility
* Support the delegated Site CI in determining the eligibility of the participants for HCV treatment, performing and interpreting diagnostics, and providing HCV treatment
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| **Site Principal Investigator (Site PI) and/or Site Co Investigator** **(Site CI)**  | * Determine the eligibility of the participants for HCV treatment, perform and interpret diagnostics, and provide HCV treatment
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| **Clinical Advisory Committee (CAC)** | * Provides advice regarding doubtful cases to clinical staff as specified in SOP SP-024-CT Modus Operandi and Communication with the CAC
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## DEFINITIONS and ABBREVIATIONS

**APRI score:** Aspartate aminotransferase to platelet ratio index score.

**AST:** Aspartate aminotransferase.

**Clinical Advisory Committee (CAC):** The CAC is composed of both internal and external clinical experts representing various disciplines and specialties. It serves as an advisory body to endTB site investigators by providing consultation regarding subject eligibility, case management, medical monitoring, and permanent treatment discontinuation.

**HBV:** Hepatitis B virus.

**HCV:** Hepatitis C virus.

**HIV:** Human immunodeficiency virus.

## PROCEDURE

### Diagnosis of chronic Hepatitis C

Serological testing for HCV antibodies should be performed routinely for all subjects screened for the endTB clinical trials, in the absence of documentation of a recent test. All subjects with a positive anti-HCV antibody test should undergo a confirmation test with a quantitative or qualitative HCV RNA nucleic acid test.

Serological testing for HCV antibodies test may be false negative in severely immunosuppressed patients, for instance patients with advanced HIV disease (low CD4 levels), and during acute HCV infection. In such patients, in the presence of unexplained high levels of ALT and a negative serological test for HCV antibodies, a quantitative or qualitative HCV RNA nucleic acid test should be considered.

#### HCV genotype

The currently recommended treatment for HCV infection is pan-genotypic, i.e., it works on all six most common HCV genotypes. Therefore, performing HCV genotype testing before treatment start is not mandatory. However, if available, HCV genotype testing should be performed in patients with liver cirrhosis to guide the duration of treatment.

#### Diagnosis of relevant comorbidities

Serological testing for HBV and HIV should be performed routinely for all subjects screened for the endTB clinical trials, in the absence of documentation of a recent test. The presence of these co-infections can influence HCV treatment.

#### Pregnancy

There is still not definite evidence of the safety of direct acting antivirals (DAA) during pregnancy, although so far these drugs appear to be safer than older treatments like interferon alpha and ribavirin. HCV treatment in pregnant MDR-TB/HCV co-infected patients can usually be postponed to after the delivery, in consultation with the CAC.

### Clinical and instrumental eligibility assessment

All patients with confirmed HCV infection (positive HCV RNA nucleic acid test) should undergo a thorough clinical and instrumental assessment. Eligibility for treatment for HCV will then be assessed.

#### Clinical assessment

The **Site CI** should perform a physical examination and a review of previous medical history, with specific attention for signs/symptoms of cirrhosis and decompensated cirrhosis, in particular:

Hepatic encephalopathy;

* Ascites;
* Liver and spleen palpation and detection of masses;
* History of upper gastrointestinal bleeding;
* Signs of severe fibrosis with portal hypertension;
* Jaundice;
* Peripheral stigmata of liver disease (telangiectasias, palmar erythema, gynecomastia, etc.).

#### Instrumental assessments

Multiple non-invasive instrumental tests are available for staging liver disease. If available, both elastography and a biomarker evaluation (i.e., APRI score) are recommended in all HCV-positive patients.

#### Elastography

Liver stiffness is measured through a device called Fibroscan®, which consists of an ultrasound transducer probe mounted on the axis of a vibrator. Fibroscan examination is painless and rapid (< 5 minutes). It is performed with the patient fasting for at least 2 hours in the supine position, with the right arm tucked behind the head. The probe transducer is placed on the skin, between the rib bones at the level of the right lobe of the liver where a biopsy would be performed. The operator performs 10 valid acquisitions, and then Fibroscan software calculates the median value. The software itself determines whether each measurement is successful or not. Results are expressed in kiloPascals (kPa) and level of validity (> 75%).

The following thresholds are used to stage the level of liver fibrosis in HCV-infected patients:

* F0-F1 (≤ 7 kPa): no or minimal fibrosis;
* F2 (7,1-9.5 kPa): moderate fibrosis;
* F3 (9,6-13,9 kPa): severe fibrosis;
* F4 (≥ 14 kPa): cirrhosis.

Transient elastography values may be artificially increased by a number of factors, including acute liver inflammation (cytolysis), liver congestion (e.g., cardiac failure), a recent meal, amyloidosis and cholestasis; it may be less accurate in obese patients or when performed by inexperienced operators.

For a good quality Fibroscan exam:

* The patient must be fasting at least since 120 min before performing the Fibroscan;
* Unreliable readings are mostly seen in patients with obesity or ascites.

#### APRI score

Biomarker scores are other tools to assess liver fibrosis: they are less accurate than Fibroscan. However, if scores are above the threshold, they have good predictive value for advanced liver disease. It is recommended to use the aspartate aminotransferase (AST)-to-platelet ratio index (APRI) score, for which only platelets and AST are needed:

**APRI score = [{AST/AST\_ULN} x 100] / platelet count**
(where AST\_ULN = upper limit of normal for AST result)

Note: The units for AST and AST\_ULN are IU/L. The units for platelet count are 109/L. The value of AST\_ULN depends on the local laboratory values used as reference. The APRI score has been validated for the diagnosis of both significant fibrosis and cirrhosis.

Online calculators can be used (<https://www.mdcalc.com/ast-platelet-ratio-index-apri>); in alternative, free phone apps are available (MDCalc).

*Table 1: Low and high cut-off values and summary of sensitivity and specificity of APRI score (WHO HCV guidelines 2018, p34)*

|  |  |  |
| --- | --- | --- |
|  | **Low cut-off** | **High cut-off** |
| **Significant fibrosis****(METAVIR ≥F2)** | Cut-off value | 0,5 | 1,5 |
| Sensitivity(95% CI) | 82(77-86) | 39(32-47) |
| Specificity(95% CI) | 57(49-65) | 92(89-94) |
| **Cirrhosis****(METAVIR F4)** | Cut-off value | 1,0 | 2,0 |
| Sensitivity(95% CI) | 77(73-81) | 48(41-56) |
| Specificity(95% CI) | 78(74-81) | 94(91-95) |

For the purpose of assessing the patients for the presence of cirrhosis (METAVIR F4) it is recommended to use the low cut-off of the APRI score (1,0) in order to minimize the number of false negative results.

#### Evaluation of the severity of liver cirrhosis

In patients with a clinical suspicion of being affected by cirrhosis, based either on clinical presentation or on instrumental assessments (F4 in APRI score or Fibroscan), the severity of the cirrhosis should be classified as compensated or decompensated using the Child-Pugh score. The Child-Pugh score combines five clinical and biological markers of liver disease (platelets, albumin, INR/Quick Test, total bilirubin): each measure is scored 1-3, with 3 indicating most severe disease (Table 2).

*Table 2: Evaluation of Child-Pugh score:*

|  |  |  |  |
| --- | --- | --- | --- |
| Measure | 1 point | 2 points | 3 points |
| Total bilirubin, μmol/L (mg/dL) | < 34 (< 2) | 34-50 (2-3) | > 50 (> 3) |
| Serum albumin, g/L | > 35 | 28-35 | < 28 |
| INR | < 1.7 | 1.71-2.30 | > 2.30 |
| Ascites, grade (see below) | None | Mild | Moderate to Severe |
| Hepatic encephalopathy, West Haven criteria (see below) | None | Grade I-II (or suppressed with medication) | Grade III-IV (or refractory) |

***Grade of ascites:***

* Mild – only visible on ultrasound and CT;
* Moderate – detectable with flank bulging and shifting dullness;
* Severe – directly visible, confirmed with the fluid wave test.

***West Haven Criteria of hepatic encephalopathy:***

* **Grade I** – Trivial lack of awareness; euphoria or anxiety; shortened attention span; impaired performance of addition or subtraction;
* **Grade II** – Lethargy or apathy; minimal disorientation for time or place; subtle personality change; inappropriate behaviour;
* **Grade III** – Somnolence to semi-stupor but responsive to verbal stimuli; confusion; gross disorientation;
* **Grade IV** – Coma (unresponsive to verbal or noxious stimuli).

*Table 3: Interpretation of Child-Pugh score results:*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Points | Class | Type of cirrhosis | One-year survival | Two-year survival |
| 5-6 | A | Compensated cirrhosis | 100% | 85% |
| 7-9 | B | Decompensated cirrhosis | 81% | 57% |
| 10-15 | C | 45% | 35% |

### HCV treatment

#### Eligibility for HCV treatment

All patients with HCV infection should be assessed for eligibility for HCV treatment.

It is currently recommended that all patients with HCV infection without cirrhosis and with compensated cirrhosis (Child-Pugh class A) receive HCV treatment. This recommendation may be even stronger in subjects affected by drug-resistant tuberculosis, where the HCV infection can lead to increased toxicity associated with the anti-tuberculosis treatment.

Patients with decompensated cirrhosis (Child-Pugh class B and C) should be evaluated for treatment on a case-by-case basis. Benefits of treatment are reduced because of the limited reversion of advanced hepatic damage and in particular if liver transplant is unavailable; complications of both treatment and HCV infection are more likely (liver failure, possible renal impairment, higher chances of complications with probably lower chances of sustained virologic response). The indication for HCV treatment for these patients should be discussed with the CAC.

#### Choice of treatment and treatment duration

The choice of the HCV treatment regimen is different depending on whether HCV genotype is available, and on the prevalence of HCV genotype 3 (see Appendix 1).

1. If the HCV genotype is available:
* The recommended treatment for 1) patients without cirrhosis and 2) patients with compensated cirrhosis (Child-Pugh class A) and HCV genotype 1,2,4,5, and 6, is the association of Sofosbuvir 400 mg 1 capsule/day and Daclatasvir 60 mg 1 capsule/day taken with or without food for a duration of 12 weeks.
* The recommended treatment for patients with compensated cirrhosis (Child-Pugh class A) and HCV genotype 3 is the association of Sofosbuvir 400 mg 1 capsule/day and Daclatasvir 60 mg 1 capsule/day taken with or without food for a duration of 24 weeks.
1. If the HCV genotype is not available and HCV genotype 3 prevalence is estimated at < 5%:
* The recommended treatment for patients without cirrhosis and patients with compensated cirrhosis (Child-Pugh class A) is the association of Sofosbuvir 400 mg 1 capsule/day and Daclatasvir 60 mg 1 capsule/day taken with or without food for a duration of 12 weeks.
1. If the HCV genotype is not available and HCV genotype 3 prevalence is estimated at ≥ 5%, or if the prevalence is unknown:
* The recommended treatment for patients without cirrhosis is the association of Sofosbuvir 400 mg 1 capsule/day and Daclatasvir 60 mg 1 capsule/day taken with or without food for a duration of 12 weeks;
* The recommended treatment for patients with compensated cirrhosis (Child-Pugh class A) is the association of Sofosbuvir 400 mg 1 capsule/day and Daclatasvir 60 mg 1 capsule/day (or 30 mg 2 capsules/day) taken with or without food for a duration of 24 weeks.

#### Timing of HCV treatment

The best timing of HCV treatment in patients receiving MDR-TB treatment is unclear. It is generally recommended to start HCV treatment after 2-4 weeks after MDR-TB treatment start.

#### Treatment monitoring

The advised treatment monitoring schedule is summarised in Table 4. In addition, if available and if curative treatment is potentially accessible for the patient, patients with cirrhosis (F4) should have a follow-up ultrasound every 6 months to check for the emergence of hepatocellular cancer, which if diagnosed early has good chances of treatment.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Examination** | **Baseline** | **W4** | **W12** | **W24** | **12 weeks after end of treatment** |
| Clinical Evaluation | X | x |  | X | X |
| Creatinine  | x |  |  |  |  |
| ALT, AST | X | X |  |  | X |
| Haemoglobin  | X | X2 | X |  |  |
| Platelets1 | X |  | X1 | X1 |  |
| INR or PT1 | X |  | X1 | X1 |  |
| Bilirubin total1 | X |  | X1 | X1 |  |
| Albumin1 | X |  | X1 | X1 |  |
| HCV-RNA (quantitative/qualitative) | X |  |  |  | X |
| HCV Genotype | X |  |  |  |  |
| Fibroscan | X |  |  |  |  |
| Liver Ultrasound and alpha-fetoprotein (AFP)1  | X |  |  |  |  |
| Gastroscopy3  | X |  |  |  |  |

*1 if patients are F4*

*2 if ribavirin treatment: but we do not propose to associate ribavirin, so I think you can delete this at least for HCV monitoring maybe you need for MDR-TB*

*3 In patients F4 with fibrosis > 20 kPa and platelets < 150000/µL*

#### Drug-drug interactions

There is no known interaction between Sofosbuvir/Daclatasvir and second-line anti-tuberculosis drugs, including new (bedaquiline, delamanid) and repurposed drugs (linezolid, clofazimine, carbapenems).

The following drug-drug interactions should be taken into account when Sofosbuvir/Daclatasvir are used:

* Co-administration with drugs that strongly induce CYP3A4 and P-glycoprotein and thus reduce DAA exposure is contraindicated: anticonvulsants (carbamazepine, phenytoin, oxcarbazepine, phenobarbital), antimycobacterials (rifampicin, rifabutin, rifapentine), systemic dexamethasone, and St John’s wort.
* Co-administration of rifaximin: Daclatasvir may increase the blood levels and effects of rifaximin; therefore, this association should be avoided if possible.
* Concomitant use with antiretrovirals:
	+ Co-administration with efavirenz or nevirapine: the dose of Daclatasvir should be increased to 90 mg once daily;
	+ Co-administration with atazanavir/ritonavir and cobicistat-containing regimens: the dose of Daclatasvir should be reduced to 30 mg once daily;
	+ No dose change is recommended in case of co-administration with darunavir/ritonavir or lopinavir/ritonavir;
	+ There is no known drug interaction with tenofovir, emtricitabine, abacavir, lamivudine, zidovudine, stavudine, rilpivirine, raltegravir, dolutegravir, or maraviroc.
* Co-administration with clarithromycin, telithromycin, erythromycin, ketoconazole, itraconazole, posaconazole, and voriconazole: the dose of Daclatasvir should be reduced to 30 mg once daily;
* All Sofosbuvir-based regimens are contraindicated in patients who are being treated with amiodarone because of the risk of life-threatening arrhythmias;
* Due to Daclatasvir inhibiting some transport proteins, monitoring is required with dabigatran and digoxin and other P-glycoprotein substrates.

#### Special situations

HCV treatment in these specific situations should be discussed with the CAC.

* **Renal insufficiency:**

Currently, Sofosbuvir is contraindicated if creatinine clearance is < 30ml/min: however, there is accumulating evidence on safe use of Sofosbuvir based regimen in this category of patients.

* **Patients with decompensated cirrhosis:**

In patients with decompensated cirrhosis (Child-Pugh B and
C), sustained virologic response doesn't always prevent liver disease progression and liver related death. In addition, a proportion of patients with decompensated liver disease may deteriorate on treatment and currently there are no predictors to identify this subgroup. Therefore, treatment of persons with decompensated cirrhosis ideally takes place in centres with the expertise to manage complications and where access to liver transplantation is available.Most deaths among those receiving DAA therapy relate to the severity of underlying liver disease. The predictors of improvement or decline have not been clearly identified, though patients with a Model for End-Stage Liver Disease (MELD) score >20 or severe portal hypertension complications may be less likely to improve and might be better served by transplantation than treatment. If indicated, treatment may include Sofosbuvir and Daclatasvir for a duration of 24 weeks.

* **Patients who failed a previous treatment containing DAAs:**

Treatment outcome of patients receiving DAAs is generally excellent across the different HCV genotypes. For patients who do not achieve Sustained Virologic Response at 12 weeks after the end of treatment, the alternatives are limited. The HCV RNA nucleid acid test should be repeated before starting a new regimen as spontaneous clearance few months after the first treatment may occur. Expert advice should be sought to evaluate the best option for these patients.The association of Sofosbuvir, Velpatasvir, and Voxilaprevir is an approved pan-genotypic treatment for use in HCV-infected persons who previously failed a DAA regimen. However, Voxilaprevir cannot be used in patients with decompensated cirrhosis.

* **HIV-infected patients:**

Overall, treatment outcomes of HCV treatment in HIV-positive patients are as good as in HIV-negative patients. However, caution should be observed drug-drug interactions between DAAs and antiretrovirals.

* **HBV-infected patients:**

Although rare, there is a potential risk of HBV reactivation during HCV treatment with DAAs. Generally, HBsAg-positive patients should be treated concomitantly for both HBV and HCV. HBV treatment, e.g. with Tenofovir disoproxil fumarate (TDF), should be continued for life if feasible or at least up to 3 months after the end of HCV treatment.

For HBsAg-negative patients, no follow-up is needed.

#### Treatment outcomes

An undetectable HCV viral load (< 15 IU/ml) at 12 weeks after the end of treatment is defined as a **Sustained Virologic Response**, which corresponds to clinical cure.

A detectable viral load at 12 weeks after end of treatment is a **treatment failure** or a reinfection.

However, if the viral load is low, repeat the HCV viral load 12 weeks later (24 weeks after the end of treatment), as late clearance can happen. If the viral load is still above 1000 IU/ml, the treatment failure is confirmed.

### Other investigations and comorbidities

* **Spontaneous bacterial peritonitis prophylaxis:** Spontaneous bacterial peritonitis (SBP) is the development of a bacterial infection in the peritoneum, occurring almost exclusively in patients with liver cirrhosis and ascites. In patients with previous episodes of SBP, or in those with risk factors for SBP, an antibiotic prophylaxis might be needed. The most used antibiotics are fluoroquinolones (ciprofloxacin or norfloxacin) or trimethoprim/sulfamethoxazole. In case SBP prophylaxis is needed for endTB trial participants, the following is advised:
	+ If the patient is already receiving a fluoroquinolone (levofloxacin or moxifloxacin) as part of the endTB trial regimen (either in experimental or control arm), no additional prophylaxis will be needed;
	+ If the patient is not receiving a fluoroquinolone as part of the endTB trial regimen, the recommended prophylaxis is trimethoprim/sulfamethoxazole.
* **Hepatic encephalopathy:** Hepatic encephalopathy (HE) encompasses a spectrum of neuropsychiatric abnormalities affecting patients with severe liver dysfunction. The pharmacologic treatment of HE usually includes lactulose, rifaximin, or both. However, daclatasvir may increase the blood levels and effects of rifaximin. Therefore, if the patient is receiving daclatasvir, the preferred option for the prevention of HE should be lactulose.
* **Hepatitis B and D:** If the patient is HBsAg-positive: if possible, test for Hepatitis D virus co-infection. Consider specific HBV treatment, in addition to HCV treatment.
* **Anti-HEV:** Screening for chronic HEV infection (with HEV PCR) will be considered only for selected patients with persistent evidence of liver damage (persistently high ALT, symptoms of chronic active hepatitis, episodes of hepatitis flare) in spite of response to HCV treatment.
* **Abdominal ultrasound and alpha-fetoprotein (AFP):** If available, abdominal ultrasound and serum AFP are recommended to screen for hepatocellular carcinoma (HCC), even after HCV cure for patients in Stage F3-F4. Patients with HCC are not eligible for HCV treatment. However, if ultrasound is not available, treating with DAAs a patient with an undiagnosed HCC will not worsen the patient survival prognosis.
* **Gastroscopy:** If available, gastroscopyshould be proposed in cirrhotic patients at high risk of bleeding, including those with Fibroscan > 20 kPa and platelets < 150,000/µL, or with history of upper gastrointestinal bleeding. The presence of oesophageal varices of grade ≥ 2 with no bleeding is an indication to prescribe a beta-blocker to prevent rupture of the varices. If lifelong treatment with beta-blockers is contraindicated, ligature of the varices can be an alternative.

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## SUPPORTING DOCUMENTS

* SOP SP-024-CT Modus Operandi and Communication with the CAC (endTB Site Study Documents)

## APPENDIX

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| **Number** | **Title** |
| A1 | SP-033-CT\_A1\_Diagnostic and therapeutic Hepatitis C virus infection algorithm  |