WORLD HEALTH ORGANIZATION
EUROPE

6 Management of Hepatitis C and HIV Coinfection

Clinical Protocol for the WHO European Region

Contents

I. Epidemiology and natural history of HCV in HIV infection

In Europe, the prevalence of hepatitis C virus (HCV) infection in HIV-infected patients is particularly high – and still rising, in contrast to the rest of the world. Yet only a minority of HCV/HIV-coinfected patients are treated for their hepatitis. The compounding effect of coinfection makes the care for these patients a major challenge.

In the pre-HAART era, the late consequences of HCV-related chronic liver disease in coinfected individuals were overshadowed by AIDS mortality connected with severe immune deficiency. With the development of HAART, morbidity and mortality among HIV-infected patients have decreased significantly. The consequences of liver-related disease associated with chronic HCV infection are now far more worrying. End-stage liver disease (ESLD) is now the predominant cause of death in patients coinfected by HCV and HIV, as well as in hepatitis B virus (HBV)/HIV-coinfected patients *(1)*, despite the availability of treatments with proven efficacy *(2–5)*. Most patients are, however, not treated, underscoring the need for treatment guidelines. Efforts must also be made, via multidisciplinary health-care services, to increase the applicability and availability of treatment, especially in more vulnerable populations, including but not limited to migrants, injecting drug users (IDUs), prisoners, people with psychiatric illnesses and people who consume too much alcohol.

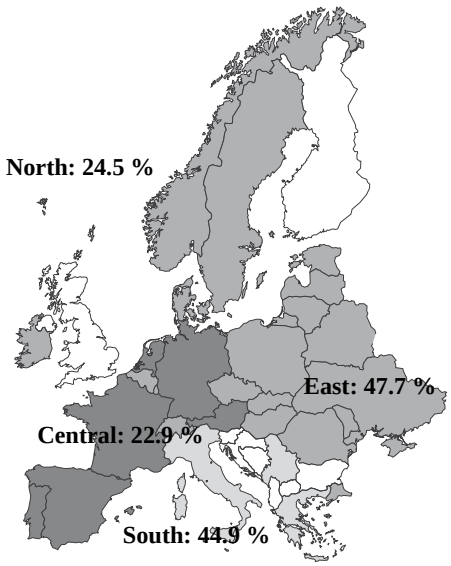
1. Prevalence, risk factors and transmission

Worldwide about 180 million people are chronic carriers of HCV. Overlapping routes of transmission for HCV and HIV result in a high frequency of coinfection in Europe.

1.1. Prevalence of HCV in HIV infection

The prevalence of HCV infection in individuals infected with HIV in the WHO European Region is very high, averaging 40% and reaching 50–90% in urban areas. Data from a EuroSIDA study (see Fig. 1) shows the prevalence is higher in the eastern (47.7%) and southern (44.9%) EuroSIDA regions than in the northern (24.5%) EuroSIDA region, due to the high rates of injecting drug use in the two former regions *(6)*.

Fig. 1. Prevalence of HCV in HIV-infected patients in Europe

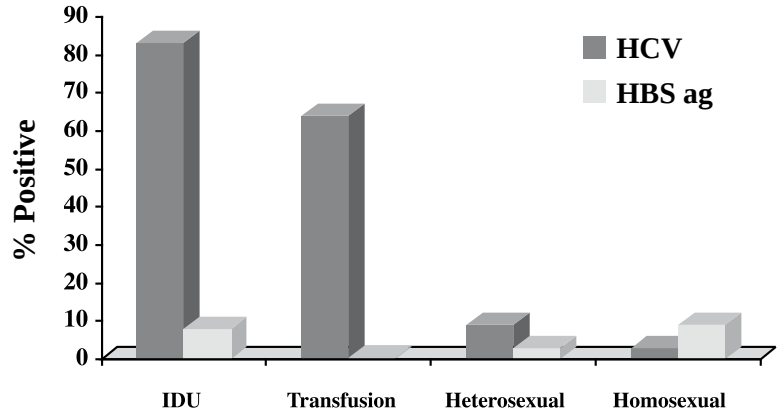


Source: Rockstroh et al. *(7)*.

The prevalence of HCV antibodies also varies widely among HIV transmission groups, ranging from 7–8% in men who have sex with men to 60–70% in haemophiliacs and 80–90% in IDUs, the most important group (see Fig. 2) *(8–12)*. HCV is easily transmitted among IDUs, which makes it difficult to prevent. IDU transmission occurs in several ways:

- sharing needles and syringes
- sharing auxiliary paraphernalia, such as cookers, straws, swabs, tourniquets and cotton
- sharing drug doses from a common syringe
- accidental needle-sticks.

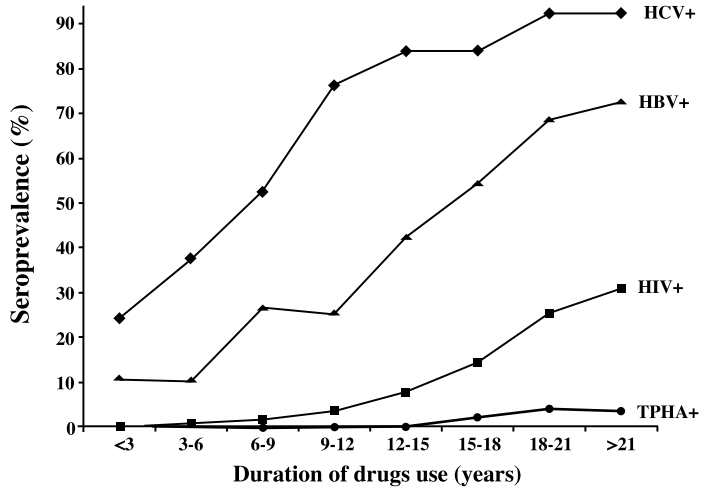
Fig. 2. Prevalence of HCV antibodies in different transmission groups



Source: Alter *(13)*.

The prevalence of HCV among IDUs increases with the duration of injection, as shown in Fig. 3.

Fig. 3. Prevalence of HCV among IDUs in relation to injecting history



Source: Quaglio et al. *(14)*.

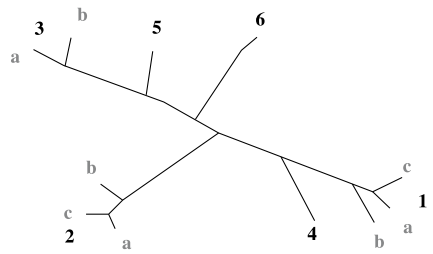
1.2. Primary modes of transmission

The primary modes of transmission for HCV are parenteral and vertical (from mother to child); it is rarely transmitted sexually. In Europe, the most common route of transmission occurs via injecting drug use. Although sexual transmission of HCV occurs in <1% *(15)* of monogamous couples, there have been increasing reports of sexual transmission between men who have sex with men (MSM) *(16)*. Household contact with an HCV-infected person has been associated with an average non-sexual transmission rate of 4% (0–11%) *(17)*. Other risk factors for transmission of HCV include tattooing and accidental needle-sticks in medical settings *(18)*.

1.3. Genotypes

HCV exhibits a high genetic heterogeneity around the world, with six different clades or genotypes being distinguished and differing as much as 30% in their genome (see Fig. 4). Furthermore, phylogenetic analyses can also distinguish subtypes and isolates within a particular type.

Fig. 4. Phylogenetic tree of HCV genotypes and subtypes

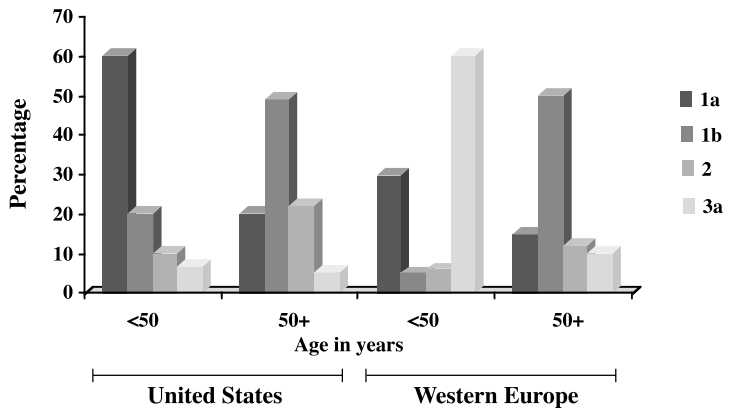


Source: Francisus *(19)*.

From an epidemiological point of view, infection with genotypes 3 and 4 is more prevalent in IDUs and HIV-coinfected patients than in monoinfected patients. Acute genotype 4 infection has recently been found among MSM *(16)*.

The distribution of genotypes may differ from one region of the world to another. As genotypes have differed in their sensitivity to the standard treatment since 2005 – pegylated interferon (PEG-IFN) and ribavirin (RBV) – it is important to know the genotype of each patient and the distribution of the genotypes in each country.

Fig. 5. Prevalence of genotypes 1–3 in the United States and western Europe



Source: Simmonds et al., Zeuzem S et al. *(20, 21)*.

2. Access of coinfected patients to hepatitis C treatment

Low percentages (0–23%) of coinfected patients have access to hepatitis C treatment *(22)*. There may be several reasons for this:

- The efficacy of PEG-IFN and RBV in treating coinfected patients was only published in 2004, and these drugs are not widely available.
- A great number of patients who continue active drug use do not have access to substitution treatment and/or ART.
- Many countries lack guidelines for diagnosis and treatment.
- Evaluation of the severity of HCV disease and treatment requires high technology and skills.
- Neuropsychological side-effects and toxicity are frequent during HCV treatment.
- Treatment is very costly.

3. Reciprocal influences of HIV and HCV

3.1. Impact of HIV infection on HCV disease progression

- Several studies have demonstrated that patients coinfected with HCV and HIV have more rapid fibrosis progression than monoinfected patients, even after taking into account age, sex and alcohol consumption *(23)*.
- People with HCV/HIV coinfection may have quantitative and/or qualitative deficiency in their immune responses to HCV. HIV accelerates the course of HCV-associated liver disease, particularly in patients who are more severely immune deficient, by increasing:
  - the HCV viraemia level from two- to eightfold, resulting in a significant decrease in spontaneous recovery from acute hepatitis *(24)*;
  - the risk of mother-to-child and sexual transmission (from averages of 6% to 20% and from 0% to 3%, respectively); and
  - rates of liver fibrosis (two- to fivefold), cirrhosis, decompensation, hepatocellular carcinoma (HCC) and liver-related mortality *(25)*.
- Liver disease is the leading cause of morbidity and mortality in HCV/HIV-coinfected patients in some parts of Europe, despite the suggestion that HAART, especially protease inhibitors, may decrease the severity of liver disease and the related mortality *(1)*.
- Comorbidities with hepatic consequences (drug hepatotoxicity, HBV, steatosis, alcohol or drug abuse) are frequent in coinfected patients and may increase the rate of complications associated with HCV-related liver disease. Patients with CD4 <200 cells/mm^3 are those most likely to progress to severe liver disease *(6, 23, 25, 26)*. For example, HIV-infected patients with CD4 <200 cells/mm^3 who drink more than 50 g of alcohol daily have a median expected time to cirrhosis of 16 years, versus 36 years for HIV-infected patients with CD4 >200 cells/mm^3 who drink 50 g or less of alcohol daily *(26)*.
- Spontaneous clearance of HCV is significantly lower in HIV-infected patients than in immunocompetent patients with acute hepatitis. As HCV ribonucleic acid (RNA) might become temporarily undetectable during the acute phase of HCV infection, clearance must be confirmed with a sensitive qualitative HCV RNA assay on at least two occasions six months apart *(27, 28)*.
- In profoundly immunosuppressed patients, HCV serology has occasionally been found to be falsely negative despite HCV chronic infection.[1] Such false negatives have become very rare due to the high sensitivity of third-generation serology *(27, 28)*.

[1] HCV RNA testing should, therefore, be performed in people at risk, such as IDUs and MSM, and in others who may be profoundly immunosuppressed and present unexplained ALT elevation despite negative HCV serology.

3.2. Impact of HCV infection on HIV disease progression

HCV has little or no effect on the response to ART or on immunological, virological or HIV-related clinical disease progression. Although HCV antibodies per se do not influence progression, infection with certain multiple genotypes might do so *(29)*.

Extended follow-up in various studies indicate that patients on HAART do not have any major differences in HIV-related mortality from HCV/HIV-coinfected patients or those infected with HIV alone, particularly if ART is given *(6)*. There is, however, an increased risk for liver disease-related morbidity and mortality in hepatitis-coinfected HIV, as well as more hepatotoxicity under ART regimens *(30)*.

II. Identification of HCV/HIV

1. Assessment of HCV risk and diagnosis of hepatitis C in HIV-infected patients

1.1. Initial laboratory assessment of HCV status

1.1.1. Step 1: All HIV-infected patients should be tested for HCV antibodies.

- For patients with acute HCV infection, it is important to bear in mind that antibodies may not be detectable for three to eight weeks following initial HCV infection. Retesting is not necessary if the infection was transmitted heterosexually and in the absence of other risky behaviour. For others who continue to run the risk of infection, such as active IDUs or MSM with multiple partners, testing is recommended every one to two years *(31)*.
- The presence of HCV antibodies is indicative of past or present infection. Antibodies persist indefinitely, in chronically infected patients but the antibody titres may decrease (and even disappear) in patients who clear HCV (either spontaneously or after antiviral treatment).
- HIV infection can impair antibody responses to HCV infection *(27)*, so a second- or third- generation enzyme immunoassay (EIA) for HCV antibodies should be used in coinfected individuals.
- In HCV antibody-negative HIV patients with profound immunosuppression, HCV RNA determination is recommended when there are liver test abnormalities or clinical suspicion of liver disease.

1.1.2. Step 2: When testing for HCV antibodies is positive, detection of HCV RNA should be performed to confirm or exclude active replication.

- HCV RNA can be detected as soon as a few days after infection.
- HCV RNA can be detected by PCR (polymerase chain reaction) or by TMA (transcription-mediated amplification).
- Persistence of HCV RNA more than six months after initial infection confirms chronic hepatitis C *(27, 31)*.
- Determination of HCV RNA can be done through qualitative or quantitative assays.
  - A qualitative assay is enough for diagnostic purposes.
  - A quantitative assay (viral load) is important for assessment of patients who will receive HCV treatment.
- High pretreatment HCV RNA levels are associated with lower rates of sustained virological response (SVR); the cut-off is generally 800 000 copies/ml (IU/ml) *(32)*. SVR rates may reach 60% in persons with either a genotype other than 1 or 4, or genotype 1 HCV infection with an HCV RNA level ≤800 000 IU/ml after 48 weeks of PEG-IFN and RBV treatment, as opposed to only 18% for those with genotype 1 and an HCV RNA level >800 000 IU/ml. *(2–5, 32)*.
- It is important to consider that viral load is higher (0.5–1 log on average) in HCV/HIV-coinfected individuals than in those who are monoinfected. This may also account for higher HCV transmission to children born to coinfected mothers. Therefore, assays with a wide dynamic range may represent an advantage.

1.1.3. Step 3: Use HCV genotype determination in predicting treatment response.

Distribution of genotypes differs between HCV-monoinfected and coinfected patients, as illustrated in Table 1.

Table 1.	Distribution of genotypes by monoinfection and coinfection, in %			
	Genotype 1	**Genotype 2**	**Genotype 3**	**Genotype 4**
Monoinfected	65	12	19	3
Coinfected	60	5	28	8

Source: Fried et al., Tottiani et al. *(33, 34)*.

- Infections with more than one HCV genotype appear to be more often (>5%) in patients coinfected with HCV and HIV, particularly IDUs and haemophiliacs *(29, 35)*.
- HCV genotype plays a predominant role as a predictor of SVR in HIV-infected patients, as it has been found in all studies of people without HIV infection.
  - For genotypes other than 1 or 4, SVR rates are generally high, ranging from 73% in the ACTG 5071 study *(4)* to 62% in the APRICOT study *(3)*, 53% in the Barcelona study *(5)* and 44% in the RIBAVIC study *(2)*.
  - For genotype 1, SVR rates range from 29% in APRICOT *(3)* to 17% in RIBAVIC *(2)* and 14% in ACTG 507 *(4)*, while Barcelona reported a 38% SVR rate for those with genotype 1 or 4 *(5)*.

For more information about laboratory assays for HCV, please see Annex 1.

1.2. Evaluation of HCV disease severity

- Evaluation of HCV disease severity should include attempting to define the duration of the infection. The date of infection is usually defined as the first date of risk exposure to HCV infection (first drug injection date, etc.).
- For decisions regarding treatment, the focus of the evaluation should be on chronic liver disease, comorbidities and co-conditions.

1.2.1. Clinical evaluation of liver disease

Clinical signs of cirrhosis are:
- stellar angiomas
- dysmorphic liver
- digital hippocratism (clubbing of the fingers)
- collateral abdominal circulation
- signs of hepatic decompensation (ascites, icterus, encephalopathy, etc.).

1.2.2. Biochemical parameters

Biochemical tests to be performed are:
- transaminases (ALT, AST)[2, 3]
- gamma glutamyl transpeptidase (GGT) (may increase in case of cirrhosis)
- alcalines phosphatases (to establish another possible cause of hepatic disease)
- bilirubine
- albumin
- prothrombin time.

[2] Alanine aminotransferase (ALT) levels do not necessarily reflect the stage of fibrosis, especially in HCV/HIV-coinfected patients. A normal ALT level alone should not be grounds to defer treatment. A biopsy in this situation can help to make a more informed decision. In the RIBAVIC study, baseline ALT >3 times the upper limit of normal was a predictor of higher SVR.
[3] Asparate aminotransferase (AST) levels should be controlled when performing the initial complete hepatic evaluation to eliminate other causes of hepatic disease; for example, in cases of alcoholic intoxication there may be an increase in AST and GGT.

1.2.3. Child-Pugzh score

The Child-Pugh Score, combining clinical symptoms and biological tests (Table 2), is useful for grading the severity of ESLD and should be performed in all patients with cirrhosis *(36)*.

Table 2. Child-Pugh classification

Clinical and biochemical parameters	Points		
	1	2	3
Bilirubin	<2 mg/dl (<34 μmol/l)	2–3 mg/dl (34–50 μmol/l)	>3 mg/dl (>50 μmol/l)
Albumin	>3.5 g/dl	2.8–3.5 g/dl	<2.8 g/dl
Ascites	Absent	Moderate[a]	Severe/ refractory[b]
Encephalopathy	Absent	Moderate (stage I–II)	Severe (stage III–IV)
Prothrombin time[c]	>60%	40–60%	<40%

[a] Controlled medically.
[b] poorly controlled.
[c] now replaced in some European countries by international normalized ratio (INR with the following Child-Pugh values: INR <1.70 = 1 point; 1.71–2.20 = 2 points; >2.20 = 3 points.
Source: Pugh et al. *(36)*.

Interpretation of the Child-Pugh classification:
- Class A (5–6 points) – compensated cirrhosis
- Class B (7–9 points) – compensated cirrhosis
- Class C (10–15 points) - decompensated cirrhosis

1.2.4. Ultrasound

Ultrasound (Doppler if possible) examination of the liver can reveal:
- cirrhosis: dysmorphy of the liver
- steatosis: hyperechogenic liver
- possibly early HCC: nodular unique or, rarely, multiple lesions.

1.2.5. Histological evaluation

Liver biopsy is the standard procedure for evaluation of the severity of liver disease (see Table 3 for indications). It is especially important for patients with a suspected low chance of SVR (genotype 1 with a high viral load) or excess risk of severe side-effects, and allows evaluating:
- the degree of fibrosis and necroinflammatory activity
- the presence of comorbidities (steatosis, drug toxicity, alcohol related lesions, HBV).

Table 3. Indications for liver biopsy in HCV/HIV-coinfected patients

Indications for biopsy	Biopsy not required
Genotype 1 or 4 with high HCV viral load (>800 000 IU/ml)	Genotype 2 and 3
Presence of comorbidities: - excessive alcohol consumption - coinfection with HBV and/or hepatitis delta virus - suspicion of medication-associated hepatotoxicity	Genotype 1 (and probably 4) with low HCV load (≤800 000 IU/ml) Clinical signs of cirrhosis

Biopsies must be performed by trained physicians, as significant complications may occur in 1/200 patients. They should be read by specialized anatomopathologists, as subtle differences may change

the classification of the severity of the disease. These limitations impede generalized biopsies for all HCV-infected patients (see section II.1.2.7 below for clinical situations not requiring liver biopsy). Activity and fibrosis are two major histological features of chronic hepatitis C that are included in proposed classifications, such as Ishak, Metavir and Knodell, that allow improved consistency in interpretation of hepatic fibrosis with a somewhat weaker reproducibility for hepatic inflammation grade *(37, 38)*. See Table 4.

Table 4. Metavir classification: activity and fibrosis scoring

Activity score (A)		Lobular necrosis		
		Absent (0)	**Moderate (1)**	**Severe (2)**
Parcellar necrosis	**Absent (0)**	A0	A1	A2
	Minimal (1)	A1	A1	A2
	Moderate (2)	A2	A2	A3
	Severe (3)	A3	A3	A3

A0 = no histological activity; A1 = minimal activity; A2 = moderate activity; A3 = severe activity.

Table 4a.

Fibrosis score (F)
F0: absence of portal fibrosis
F1: stellar portal fibrosis with no septa
F2: portal fibrosis with some septa
F3: many septa but no cirrhosis
F4: cirrhosis

Source: Simmonds et al. *(20)*.

This system assesses histological lesions in chronic hepatitis C using two separate scores, one for necroinflammatory grade (A for Activity) and another for the stage of fibrosis (F). The fibrosis stage and inflammatory grade are correlated, but for approximately one third of patients there is discordance. In lower grades of liver fibrosis (F0–F1), regardless of HCV genotype, treatment can be deferred. See Table 4a.

1.2.6. Non-invasive markers of liver fibrosis

Non-invasive tools for assessing liver fibrosis, such as those based on serum markers (for example, FibroTest™) or image technique (for example, FibroScan™) are available. Several non-invasive methods to evaluate inflammation and fibrosis have been developed for monoinfected patients and include serological tests combining serum fibrosis markers. They are used to distinguish Metavir fibrosis stages 0–2 from stages 3 and 4. The tests are quite reliable, are better accepted by patients than biopsies and could potentially save approximately 50% of patients from being biopsied.

Recently, alternatives to biopsies have become available for coinfected patients *(39)*, including a combination of biochemical tests indicating the degree of liver inflammation and fibrosis, such as the Forns index which has been recently validated for HIV/HCV-coinfected patients *(40)*, and an elastometric method reflecting the degree of fibrosis (see Annex 2) *(41, 42)*.

1.2.7. Clinical situations not requiring histological evaluation

The First European Consensus Conference on the Treatment of Hepatitis in HIV-Infected Patients did not mandate biopsy in cases where treatment is already indicated *(43)*. Treatment without biopsy or other liver assessment is recommended in the following situations:

- infection with HCV genotype 2 or 3;
- infection with HCV genotype 1 with a low viral load; and
- absence of major contraindications and patient willingness to undergo treatment, in which case the SVR will be on the order of 40–60% *(2–5)*.

Given the limitations of biopsy and the faster progression of fibrosis in HCV/HIV patients, treatment should still be offered when candidates for biopsy decline it or lack access to it.

1.3. Evaluation of comorbidities and co-conditions

1.3.1. Psychiatric disorders

- An initial evaluation of psychiatric disorders should be performed, as treatment with IFN can reveal and worsen depression. Treatment for hepatitis C should therefore be deferred in patients with moderate to severe depression until the condition improves. Prophylactic treatment with psychiatric drugs may be advisable and treatment may be feasible thereafter.
- In patients with mild psychiatric illness, treatment for hepatitis C should not be deferred and counselling and/or antidepressant medication should be offered along with HCV treatment.

1.3.2. Alcohol abuse

- Assessment of alcohol intake is an important part of evaluation (please see Annex 3).
- Heavy alcohol intake (50 g/day or more) contributes to fibrosis of the liver, which can be identified by biopsy in HCV patients independently of other predictors. This intake is equivalent to five or more drinks per day, in which a drink = 10 g of alcohol, for example 330 ml (12 oz) of beer, 150 ml (5 oz) of wine or 38 ml (1.25 oz) of hard alcohol.
- There is evidence of synergistic interaction between alcohol consumption ≥80 ml/day and chronic HBV or HCV infection *(44)*. Continued alcohol consumption increases HCV replication, accelerates fibrogenesis and liver disease progression in hepatitis B and C and diminishes the response and adherence to treatment (especially if consumption is >50 g/day).
- Active alcohol intake is considered a relative contraindication for IFN-based treatment, due to the documented non-compliance of heavy drinkers in medical therapies, combined with the side-effects that otherwise affect compliance *(45)*.
- Psychological, social and medical support should be offered to reduce alcohol intake to <10 g/day or stop it altogether.

1.3.3. Drug use

- Treatment of patients on opioid substitution therapy should not be deferred.
- Initiation of HCV treatment in active drug users should be considered on a case-by-case basis. (Please refer to Protocol 5, *HIV/AIDS treatment and care for injecting drug users*.)
- Medical, psychological and social support from a multidisciplinary team should be provided for these patients.

1.3.4. Other comorbidities and co-conditions

Testing of comorbidities should include a comprehensive history with a particular focus on factors associated with more progressive liver injury. Analysis can include:

- testing for viral liver diseases[4]
- testing for tuberculosis (TB) and sexually transmitted infections (STIs) that need treatment before HCV treatment begins.[5]

When a treatment has been decided, other tests are needed:

- thyroid-stimulating hormone (TSH) dosage;
- dosage of antiperoxydase, antinuclear, anti-smooth muscle, anti-liver-kidney microsome antibody (LKM1);
- creatininaemia;
- proteinuria ;
- glycaemia;
- ferritinaemia;
- electrocardiogram (ECG, to detect coronary disease that could decompensate after treatment-induced anaemia);
- a pregnancy test.[6]

[4] For HBV and HAV please refer to Protocol 7, Management of hepatitis B and HIV coinfection.

[5] See Protocol 4, *Management of tuberculosis and HIV coinfection,* and the European STD Guidelines *(46).*

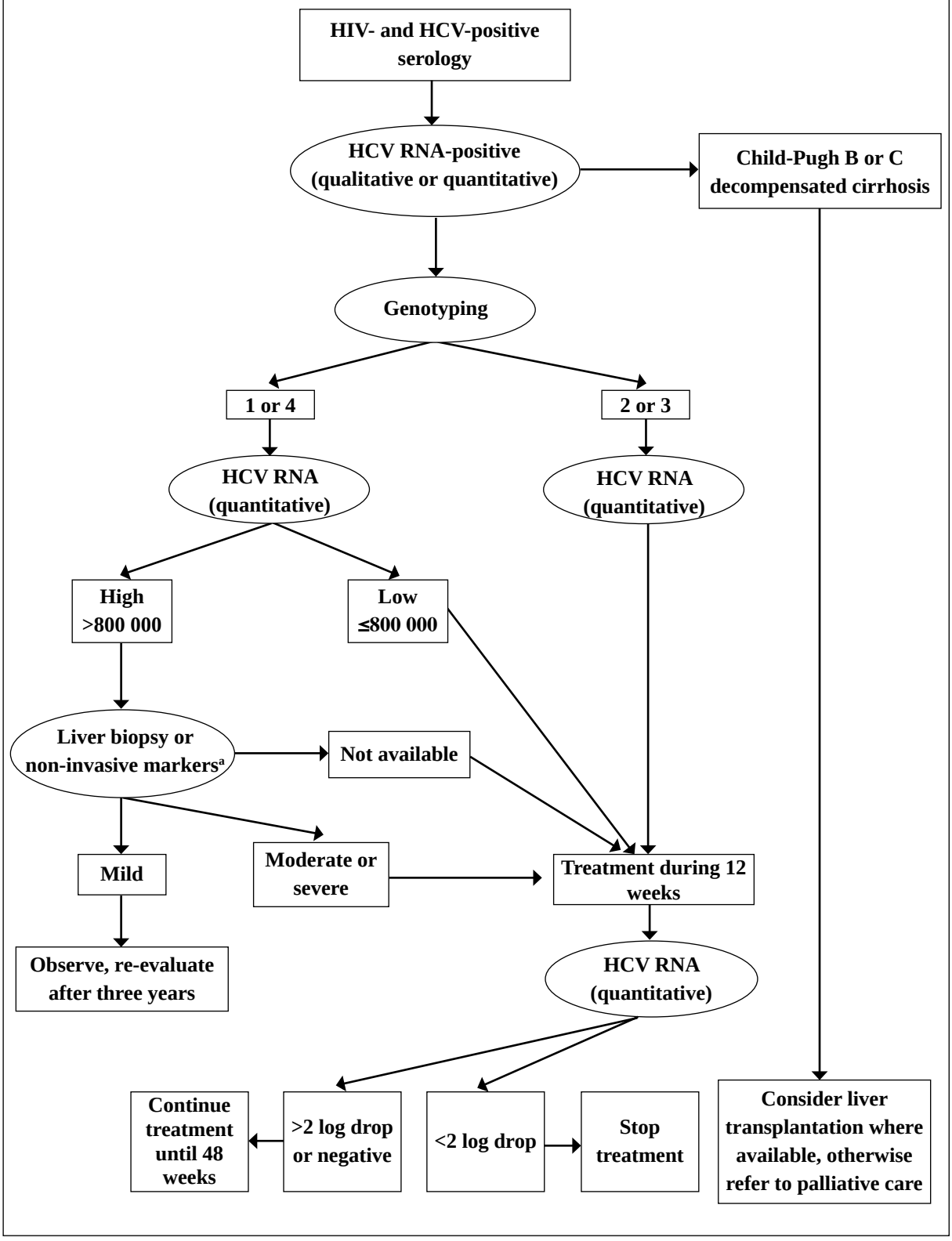
[6] It should be explained that because RBV is teratogenic and contraindicated during pregnancy, procreation should be avoided during treatment and six months after, and that due to higher levels of HCV viraemia in coinfected women, approximately 20% transmit HCV to their offspring, versus 7–8% in those monoinfected with hepatitis C (47).

1.4. Evaluation and treatment algorithms for hepatitis C

1.4.1. Algorithm 1

This algorithm is preferred and focuses on genotyping.

Fig. 6. Algorithm 1



[a] FibroScan (image technique), Fibro Test (serum fibromarkers)

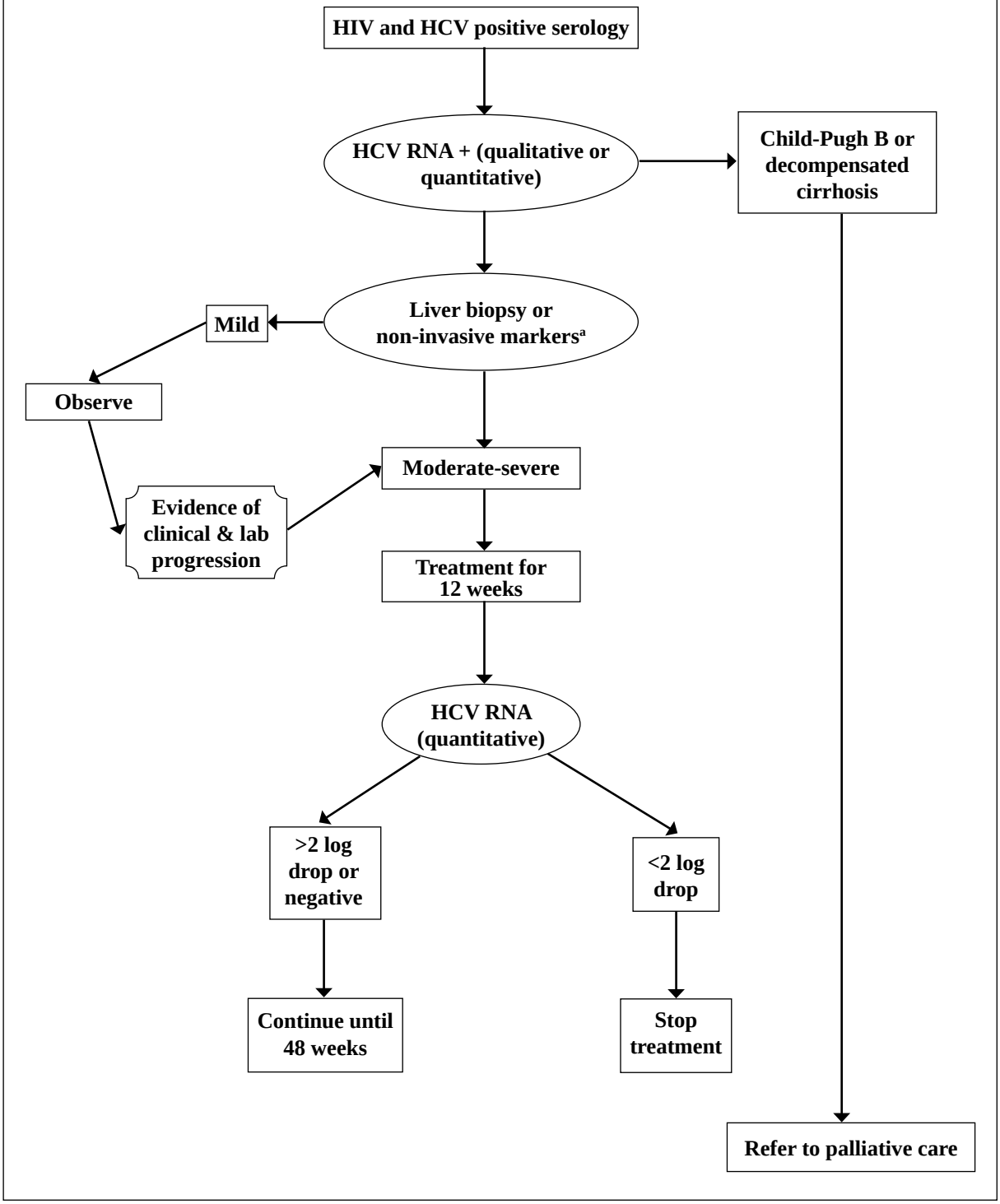
In Algorithm 1, the decision to treat lies mainly upon the HCV genotype determination and HCV quantification. Liver biopsy is limited to patients with genotype 1, high viral load and low response to PEG-IFN and RBV.

- Subsequent to an HCV/HIV positive serology, qualitative HCV RNA detection should be undertaken to confirm the chronicity of hepatitis.
- In case of positive HCV RNA, a genotyping should be performed.
- In case of genotype 2 or 3, more frequently found in IDUs, treatment should be proposed for all patients without liver biopsy where there is no contraindication (please see contraindications in section III.2.3).
- In case of genotype 1, the patient should have a quantification of HCV RNA, since responses are related to viral load. This test should be available everywhere HIV viral load is performed.
- In the absence of local testing possibilities, the patient should be referred to a specialist, or a sample should be collected at the district level and a genotyping test done centrally.
    - When viral load is low (≤800 000 IU/ml), treatment of genotype 1 is recommended without a liver biopsy.
    - When viral load is high (>800 000 IU/ml), an assessment of liver fibrosis by biopsy is recommended to differentiate patients with severe liver disease.
- A fibrosis score of F2–F4 indicates a need for *immediate* treatment.
- Mild liver disease (F0, F1) indicates that treatment should be delayed due to the low chances of SVR.
- Follow-up treatment should rely on HCV RNA quantification at week 12, and then HCV RNA qualitative detection at weeks 24 and 48.
    - At week 12, if the drop of viral load is less than 2 log, the treatment should be stopped because the chance of success does not exceed 1–2% regardless of genotype. Otherwise, the treatment should be continued.
    - Additional qualitative tests should be performed at week 24 and treatment should be stopped if HCV viral load is detectable; otherwise, treatment should be pursued until week 48 and treatment efficacy checked with a qualitative test at this time.
    - At week 72, HCV RNA detection should confirm or disprove a sustained virological response.
- Patients with cirrhosis should also be referred to a specialist for initial evaluation of their cirrhosis.

1.4.2. Algorithm 2

This algorithm is an alternative, focusing on liver biopsy and other tools in the absence of genotyping.

Fig. 7. Algorithm 2



[a] FibroScan (image technique), Fibro Test (serum fibromarkers).

2. Assessment of HIV risk and diagnosis of HIV/AIDS in HCV patients

All patients with HCV should be offered HIV testing and counselling because the two viruses share transmission routes and because HIV exacerbates the development of HCV. Health-care providers should explain the reasons for offering the test to patients and its importance in proper clinical management. However, patients have the right to opt out.

Initial assessment of HIV status should include:

- HIV pretest counselling;
- serological testing (typically enzyme-linked immunosorbent assay (ELISA) and/or rapid tests) for HIV antibodies, followed by a western blot confirmatory test if positive; and
- post-test counselling, including information on reducing risky behaviour, regardless of whether the HIV results were positive or negative.

Further clinical evaluation of HIV-infected patients is required to develop a strategy of clinical management. It should include:

- checking symptoms
- a physical examination
- evaluation of mental health and preparedness for treatment
- a routine laboratory assessment
- a CD4 lymphocyte count to determine the severity of immunodeficiency
- viral load testing if available
- pregnancy testing if indicated
- testing for comorbidities, including hepatitis B, TB and psychiatric disorders
- other tests as indicated by the patient's condition.

Table 5. Initial and pre-therapeutic evaluation for HCV/HIV-coinfected patients

	Tests	Initial evaluation	Pre-therapeutic evaluation
HCV disease	- qualitative HCV RNA	+	
	- transaminases (ALT, AST), GGT, alkaline phosphatases, bilirubin, albumin, prothrombintime	+	
	- HCV genotype		+
	- quantitative HCV RNA		+
	- ultrasound examination of the liver	+	
	- histological evaluation, non-invasive markers		+
HIV[a]	- CD4 cell count	+	
	- HIV RNA	+	
	- present antiretroviral regimen		+
Comorbidities and co-conditions	- HBV serology	+	
	- HAV serology	+	
	- TB diagnosis	+	
	- TSH dosage		+
	- auto-antibodies		+
	- creatininaemia, proteinuria		+
	- glycaemia		+
	- ferritinaemia		+
	- quantification of alcohol consumption	+	
	- drug consumption	+	
	- pregnancy test		+
	- ECG (if >50 years old or known cardiopathy)		+
	- psychiatric consultation if previous psychiatric history		+

[a] For more information refer to section on initial patient evaluation in Protocol 1, *Patient evaluation and antiretroviral treatment for adults and adolescents.*

III. Clinical management of HCV/HIV patients

The key issue in the clinical management of HCV/HIV-coinfected patients is the treatment decision for each condition and when to initiate it. By the end of the laboratory and clinical assessment of patients with HCV/HIV coinfection, patients can be split into four categories:

1. patients not requiring hepatitis C or HIV/AIDS treatment
2. patients requiring only hepatitis C treatment
3. patients requiring only HIV/AIDS treatment
4. patients requiring both hepatitis C and HIV/AIDS treatment.

1. Coinfected patients not requiring any treatment

Coinfected patients not requiring any treatment meet the following criteria:

- CD4 count >350 cells/mm^3 and absence of HIV-related symptoms, and
- HCV antibodies, but absence of HCV RNA replication.[7]
- Coinfected patients *not* needing treatment should be monitored every six months (clinical follow-up, liver function tests) and every three years for histological liver lesions (using alternatives to liver biopsies).

2. Coinfected patients requiring only HCV treatment

Coinfected patients requiring only HCV treatment meet the following conditions:

- CD4 count >350 cells/mm^3 and absence of HIV-related symptoms, and
- active or chronic hepatitis C.[8]

HCV treatment offers the possibility of eradicating HCV within a defined treatment period. In the following situations, where the benefits outweigh the risks, there are two main reasons to consider all HCV/HIV-coinfected patients for HCV treatment:

- The liver disease progresses more rapidly to end-stage complications and at earlier ages than in HCV-monoinfected patients.
- Patients are at higher risk for developing hepatotoxicity following the initiation of ART than HIV-monoinfected patients. Efficient HCV treatment will hence facilitate the subsequent management of ART.

2.1. Indications for HCV treatment

- Genotype 2 or 3 regardless of HCV viral load or histology
- Genotype 1, viral load ≤800 000 IU/ml regardless of histology
- Genotype 1 or 4, viral load >800 000 IU/ml and moderate or severe fibrosis

2.2. Predictors of sustained virological response probability

Several baseline parameters can predict a greater likelihood of achieving an SVR *(32)*:

- infection with genotype 2 or 3
- viral load ≤800 000 IU/ml
- absence of cirrhosis
- age <40 years
- ALT levels >3 x upper limit of normal.

[7] Some patients may have HCV RNA but harbour genotype 1 or 4 and a mild disease. In such cases, treatment is not recommended; regular yearly monitoring is the recommended option, with an assessment for liver fibrosis after three years.
[8] For patients with evidence of advanced liver fibrosis, HCV treatment should be a priority.

2.3. Contraindications for hepatitis C treatment

The following contraindications for treatment of hepatitis C should be borne in mind:

- pregnancy, because of risk of IFN and RBV[9,10]
- cardiopathy, such as ischaemic disease and cardiac insufficiency
- psychiatric disorders or history of same
- active alcohol intake (>50 g/day)
- decompensated cirrhosis (Child-Pugh C).[11]

2.4. Treatment of acute hepatitis C

- Treatment of acute hepatitis C may reduce the risk of chronicity *(51)*. Therefore, if serum HCV RNA is not eliminated spontaneously within three months of the disease onset (clinically and/or laboratory documented), treatment with PEG-IFN is recommended for six months *(51)*.
- The use of combination treatment in this population remains a field of research.

2.5. Treatment of chronic hepatitis C (doses and schedules)

All patients should receive a combination of PEG-IFN α2a or α2b and RBV. The standard dose for PEG-IFN α2a is 180 μg once weekly (QW), and for PEG-IFN α2b it is 1.5 μg/kg body weight QW *(2–5)*.

The dose of RBV is critical. Although clinical trials in HIV/HCV-coinfected patients have used a fixed dose of 800 mg per day [400 mg twice daily (BID)] for all genotypes, studies from HCV-monoinfected patients support the use of 1000 mg to 1200 mg RBV per day (in 2 doses) for treatment of infections with genotypes 1 and 4, and 800 mg RBV per day (400 mg BID) for genotypes 2 and 3 *(49)*.

The current recommendations are as follows:

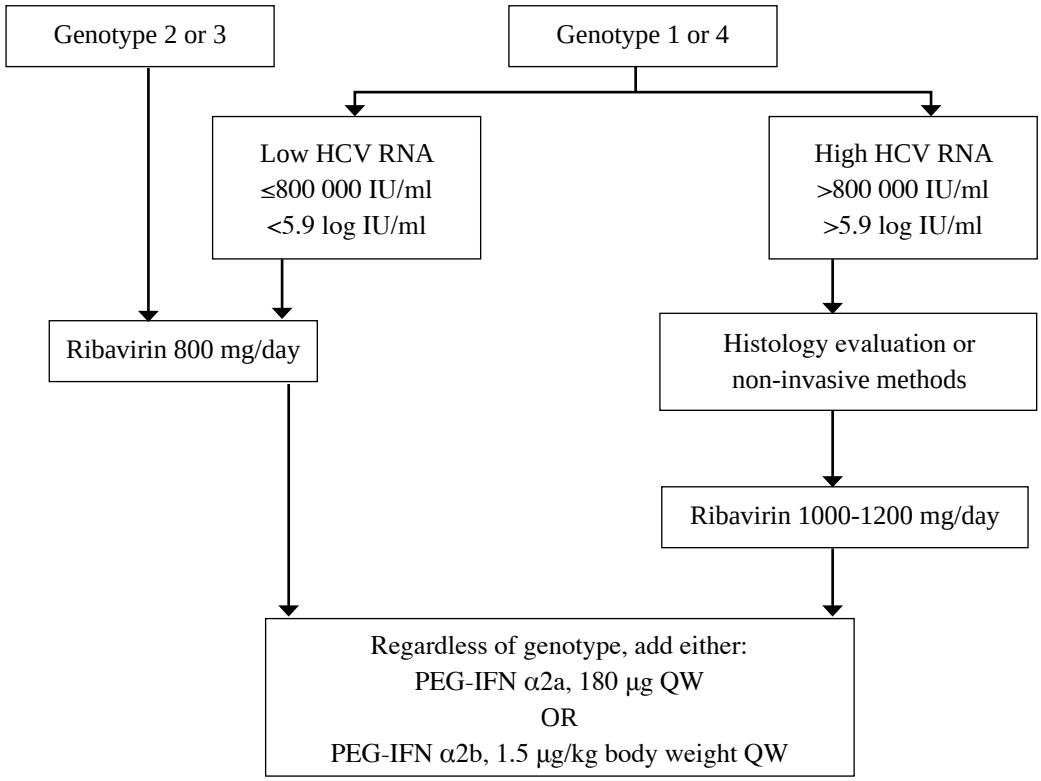
- for HCV/HIV-coinfected patients with genotype 1 or 4, an initial RBV dose of 1000–1200 mg once daily (OD);
- for HCV/HIV-coinfected patients with genotype 2 or 3, 800 mg OD *(43)*.

[9] Limited data suggest IFN does not have any effect on the embryo or foetus.

[10] RBV is teratogenic (causes birth defects) in multiple animal species and its use during pregnancy is contraindicated *(48)*. Since RBV may cause abnormalities in sperm, men taking it should wait six months after discontinuing use before attempting to impregnate a woman.

[11] IFN is very badly tolerated in these patients *(49)*; however, after regression of the decompensation, treatment may sometimes be initiated *(50)* and liver transplantation should be the primary treatment option for such patients.

Fig. 8. Therapeutic algorithm for HCV treatment in HIV-infected patients



Source: Alberti et al., Sulkowski *(43,52)*

2.6. Treatment duration

Regardless of genotype, the expected duration of treatment in coinfected patients should be 48 weeks. However, depending on HCV RNA levels at week 12, treatment may be interrupted earlier (refer to Algorithms 1 and 2 in section II.1.4 above) *(43)*.

Genotype 2 and 3 patients treated for six months have significantly higher relapse rates than those treated for one year *(5, 53)*. Therefore, all HCV/HIV-coinfected patients should be treated for one year. HCV genotype can be used as a predictor of response but not as a basis for modifying treatment duration, as with immunocompetent patients.

3. Coinfected patients requiring only HIV/AIDS treatment

Coinfected patients requiring only HIV/AIDS treatment satisfy at least one condition in each of the following bullet points

- CD4 count ≤350 cells/mm^3 in symptomatic patients or patients with viral load >100 000 copies/ml, *or* CD4 count ≤200 cells/mm^3 irrespective of symptoms;
  and
- HCV antibodies but no HCV RNA replication, or hepatitis C with contraindications to treatment (in the knowledge that they may be transient – see section III.2.3 on contraindictions).

3.1. Initiation of HAART

Initiation of ART in HCV/HIV-coinfected patients should follow the current recommendations for HIV-monoinfected patients *(54)*. (For further details, please refer to Protocol 1, *Patient evaluation and antiretroviral treatment for adults and adolescents.*) (see Table 6)

Table 6. Recommendations for initiating HAART in HCV/HIV-coinfected patients

CD4 cell count	Recommendations
CD4 <200 cells/mm^3	Antiretroviral treatment
CD4 200–350 cells/ mm^3 or VL > 100 000 copies/ml	Antiretroviral treatment should be considered when there is a high viral load, a rapid decline in CD4 count or the presence of symptomatic HIV disease. It should be started before the CD4 count falls to <200 cells/mm^3.

3.2. Considerations in choosing a HAART regimen

In HCV/HIV-coinfected patients, the selection of an adequate first-line regimen should take into account major concerns and potential problems:

- adherence (a once-daily regimen should be favoured);
- hepatotoxicity of non-nucleoside reverse transcriptase inhibitors (NNRTIs) (acute, such as with nevirapine (NVP));
- drug interaction: didanosine (ddI) and zidovudine (ZDV) with RBV, efavirenz (EFV) and PEG-IFN (severe depression);
- use of opioid substitution therapy (OST): pharmacokinetic interaction between NNRTIs and methadone or buprenorphine (dose adjustments);
- coexistent medical/psychiatric conditions; and
- the same concerns as in monoinfection: potency, maintenance of future options, cost and availability.

3.3. First-line HAART regimens

Table 7. Treatment Regimens for first-line HAART in HCV/HIV-coinfected patients

	ARV drug classes	HAART regimens
Preferred first line	2 NRTIs + 1 NNRTI	ZDV[a] or d4T ↘ ↗ EFV[b] 3TC or FTC[c] ABC or TDF ↗ ↘ NVP[b]
Alternative first line	3 NRTIs	ZDV[a] ↘ ↗ ABC[d] 3TC or FTC[c] d4T ↗ ↘ TDF

[a] ZDV is not an absolute contraindication if a patient is on RBV, but haemoglobin (Hb) levels should be closely monitored.
[b] EFV has been considered the preferred NNRTI option, but NVP can be considered for patients without evidence of hepatic dysfunction, with close monitoring. However, it should be avoided in HIV-infected patients if CD4 is >400 cells/mm^3 (>250 mm^3 in women) *(55)*.
[c] Emtricitabine (FTC) is equivalent to 3TC. FTC is available together with TDF, and 3TC together with ABC as fixed-dose combination (FDCs).
[d] ZDV/3TC/ABC regimen is available as an FDC.

- In case of severe toxicity and side-effects in first-line antiretrivorals (ARVs), substituting another ARV with a different toxicity profile within the front-line regimens is recommended.
- Switching to second-line ARV regimens is recommended in the absence of immunological or virological response to ART, as measured by CD4 cell count and viral load. (Please refer to Protocol 1, *Patient evaluation and antiretroviral treatment for adults and adolescents* for further details).

3.4. Second-line HAART regimens

For second-line HAART, WHO recommends selecting three different drugs containing at least one new pharmacological class.

- The best options are regimens with a boosted protease inhibitor (PI) as the key drug, together with two nucleosides if a classical approach of 2 NRTIs + 1 NNRTI was the first-line treatment.
- In case of a simplified first choice with 3 NRTIs, the second-line should use a boosted PI + 1 NNRTI and/or 1 NRTI.

Among second-line NRTIs, those with better resistant profiles, such as ddI, ABC and TDF, should be given preference.

- The combination d4T+ddI has to be avoided due to the risk of mitochondrial toxity, leading to hepatic steatosis and potentially enhancing fibrosis *(56)*.
- TDF/ddi is also contraindicated due to negative pharmacological interactions.

Table 8. Treatment regimens for second-line HAART in HIV/HCV-coinfected patients

	ARV drug classes	HAART regimens
Preferred second line	2 NRTIs + 1 boosted PI	ABC + TDF or ABC + ddI[a] + LPV/r or SQV/r or ATZ/r[b]
Alternative second line	1 NNRTI +/- 1 NRTI + 1 boosted PI or double PI	ABC ↘ ↗ TDF EFV ➔ LPV/r SQV/r ATZ/r[b] or LPV/r + EFV or LPV/r + SQV

[a] A ddI dose in combination with TDF should be adjusted to less than 4.1 mg/kg per day so as not to compromise immune recovery. It is contraindicated in patients with cirrhosis and under RBV treatment, and should be used with caution in patients with less severe liver disease.
[b] Unboosted ATZ or NFV can be used in absence of a cold chain.

4. Coinfected patients requiring both HCV and HIV/AIDS treatment

Coinfected patients requiring both HCV and HIV/AIDS treatment meet the following criteria:

- CD4 count ≤350 cells/mm^3 in symptomatic patients or patients with viral load >100 000 copies/ml, or CD4 count ≤200 cells/mm^3 irrespective of symptoms; and
- acute or chronic hepatitis C.[12]

4.1. Strategy for initiation of treatment

See Table 9 below.

- If a coinfected patient has severe immunodeficiency (CD4 count <200 cells/mm^3), the CD4 count should be improved using HAART before commencing HCV treatment.
- If CD4 is between 200 and 350 cells/mm^3, HCV treatment should be offered first in order to avoid interactions between HAART and anti-HCV drugs and facilitate adherence. After HCV treatment is finished (12 months), HAART should be initiated.
- Patients, who need or are receiving HAART, should be in stable treatment (adherence to treatment, absence of side-effects, CD4 >200 cells/mm^3) for a few months before starting HCV treatment. HAART should be continued during HCV treatment but ddI, ZDV or d4T should be changed for other drugs (ABC, TDF, etc.) before initiating RBV.

[12] For patients with evidence of advanced liver fibrosis, HCV treatment should be a priority.

- In some cases (if CD4 nadir has never been <200 cells/mm^3), interruption of HAART during HCV treatment is feasible if the patient asks for it. In this case, the original regimen is usually reintroduced after the end of HCV treatment or in case the CD4 count drops <200 cells/mm^3 during the treatment.
- Patients with a low baseline CD4 count (<200 cells/mm^3) may tolerate HCV treatment less well and may be at higher risk for developing opportunistic infections, since IFN treatment is often associated with loss of CD4 cells in the bloodstream, although the CD4 percentage is conserved *(2–5)*.

Table 9. Algorithm for initiation of hepatitis C treatment and HAART in HCV/HIV-coinfected patients

Patients	HAART		HCV treatment
Untreated	**No indication for ARV** CD4 >350 cells/mm^3	⇨	Treat HCV first
	ARV initiation indicated CD4 200–350 cells/mm^3		Treat HCV first, then initiate HAART
	CD4 <200 cells/mm^3	⇨	Initiate HAART, wait until stable, and regimen is well tolerated, then treat HCV
ARV-treated	Replace ddI and ZDV if on alternative options. It is possible to interrupt HAART until the end of HCV treatment (if CD4 nadir was never <200 cells/mm^3, and patient asks for it).		Treat HCV if CD4 > 200 cells/mm^3.

4.2. Considerations of ARVs when treating both HCV and HIV infections

4.2.1 Zidovudine (ZDV)

ZDV, when taken concomitantly with RBV, is associated with an increased frequency of anaemia, but not severe neutropenia. When alternative options are available, ZDV should be replaced by another NRTI during HCV treatment.

4.2.2 Didanosine (ddI)

Didanosine used in association with RBV was shown to be associated with a markedly increased risk of lactic acidosis, pancreatitis (57, 58) and an unexpected number of hepatic decompensations in patients with cirrhosis (59). It is consequently contraindicated in patients with cirrhosis and should be used with caution in patients with less severe liver disease during PEG-IFN + RBV combination treatment.

4.2.3 Efavirenz (EFV)

EFV and PEG-IFN can be co-prescribed but must not be initiated simultaneously, as both drugs can induce psychiatric troubles. If EFV is well tolerated then IFN can be added.

4.2.4 Protease inhibitors (PIs)

A potential negative impact of PI use on SVR in patients with HCV/HIV coinfection treated with PEG-IFN + RBV has been suggested in a subgroup analysis of a single study (25). As there is no solid evidence regarding this possible negative impact of PI use on SVR, PIs cannot be excluded from recommended ARVs for HCV/HIV patients. However, more research is needed to obtain better evidence.

4.3. Hepatotoxicity of ARV drugs

HAART is associated with a higher risk of hepatotoxicity (defined as at least two fold ALT/AST increase above upper limit of normal (ULN)) in HCV/HIV-coinfected patients than in HIV-monoinfected patients *(30, 60–64)*. However, the incidence and risk factors for liver enzyme elevations in large cohorts of HCV/HIV-coinfected patients are not well defined. In several studies, however, independent risk factors for hepatotoxicity have been identified *(30, 60–64)*:

- previous liver transaminase elevations to a grade ≥ III
- higher baseline alanine amino-transferase values
- viral coinfection
- high plasma drug levels
- degree of immune damage *(64)*.

Hepatotoxicity has been associated with all currently used ARV drugs, but existing studies fail to demonstrate a consistent association between particular drugs or drug classes and the development of subsequent hepatotoxicity. Comparison of HAART regimens (single-PI, multiple-PI and NNRTI-based) has given inconsistent results for liver-tolerability in cohorts in which HCV/HIV-coinfected patients are underrepresented.

- Acute hepatotoxicity: in a single cohort study involving HCV positive and negative patients, the use of NVF within 12 weeks of initiating treatment and the use of full-dose ritonavir (RTV) (600 mg BID) have been implicated *(62)*. But most liver enzyme elevation events are sub-clinical and usually reverse spontaneously. NVP is not contraindicated in all HCV/HIV-coinfected subjects, but should be closely monitored when used in asymptomatic patients. A majority of experts recommend avoiding its use in patients with evidence of liver dysfunction.
- Chronic hepatotoxicity: the prolonged use of nucleoside analogue reverse transcriptase inhibitors (especially of those having a strong affinity for mitochondrial deoxyribonucleic acid (DNA) polymerase, such as ddI and d4T) exposes treated patients to a risk of chronic mitochondrial toxicity, whose target, among other organs, is the liver. This toxicity, possibly exacerbated in some patients by the specific chronic toxicity of PIs on the liver, may lead to hepatic steatosis and worsen pre-existing fibrosis.

4.4. ARV dose adjustment in patients with cirrhosis

- Like a majority of drugs metabolized in the liver, antiretroviral agents such as PIs and NNRTIs are metabolized with difficulty in patients with cirrhosis *(65, 66)*.
- Although the relationship between high plasma concentrations and toxicity is not constant for all antiretroviral agents, it has been clearly demonstrated for certain PIs, such as NFV, LPV and amprenavir (APV), and NNRTIs such as EFV *(67–70)*.
- Of the NRTIs, only ZDV and ABC are metabolized by liver enzymes other than cytochrome P450 (CYP) *(65, 66)*. Consequently, use of PIs, NNRTIs, ZDV or ABC in patients with liver-decompensated cirrhosis requires dosage adjustment in order to avoid a risk of drug accumulation. However, little specific guidance has been established to precisely adapt ARV dosages in patients with cirrhosis.

Table 10. Recommendations for antiretroviral dosage adjustment in patients with ESLD

ARV	Main metabolism pathway	Pharmacokinetic in ESLD	Adjustment recommendation
NRTI			
Zidovudine	80% liver glucuronidation and <5% renal elimination	Accumulation and increased risk of haematological toxicity	Dosage adjustment may be useful but no specific recommendations. Clinical monitoring and decreased daily dose in case of intolerance (anaemia).
Lamivudine	80% renal elimination	Not affected	No change
Emtricitabine	80% renal elimination	No data	No change
Stavudine	80% renal elimination	Not affected	Avoid due to high risk of hepatic steatosis.
Didanosine	50% renal elimination	No data	Avoid due to high risk of hepatic steatosis and pancreatitis.
Tenofovir	80% renal elimination	Not affected	No change
Abacavir	Liver glucuronidation; <5% renal elimination	Accumulation	Avoid.
NNRTI			
Nevirapine	Liver (CYP enzymes)	Reduced clearance	Avoid due to the risk of severe hepatotoxicity (grade 3 or 4).
Efavirenz	Liver (CYP enzymes)	Reduced clearance Little information	Careful monitoring of CNS side-effects if elevated transaminases. Drug monitoring if available.
PI			
Nelfinavir	Liver (CYP enzymes)	Reduced clearance	Drug monitoring
Indinavir	Liver (CYP enzymes)	Sparse data	Drug monitoring. If not available, dosage has to be reduced at least to: - 600 mg three times daily without RTV; or - 600 mg + 100 mg RTV BID.
Saquinavir	Liver (CYP enzymes)	No data	Drug monitoring
Lopinavir/r	Liver (CYP enzymes)	Altered	Drug monitoring
Atazanavir	Liver (CYP enzymes)	Altered	Decrease by 50%.
Amprenavir	Liver (CYP enzymes)	Altered	Decrease the dose: - to 450 mg BID if Child-Pugh A - to 300 mg BID if Child-Pugh B–C.
Fosamprenavir	Liver (CYP enzymes)	Altered	Contraindicated if severe liver disease

Source: Wyles & Gerber, Salmon & Taburet *(65, 66)*.

4.4.1 Recommendations

- In the absence of specific recommendations, the full dose of ARVs is usually prescribed in patients with compensated cirrhosis.
- If therapeutic drug monitoring is available, residual drug concentrations of ARVs should be measured at the first monitoring visit in order to adjust dosages.
- In cases of decompensated cirrhosis where drug monitoring is not available, one should:
  - avoid NNRTIs
  - reduce the daily dosage of ZDV and ABC
  - reduce the daily dose of most PIs (precise data are lacking).

5. Clinical monitoring

HCV/HIV coinfected patients should be carefully monitored during treatment. For monitoring of patients receiving ART please refer to Protocol 1, *Patient evaluation and antiretroviral treatment for adults and adolescents.*

Patients treated for HCV should be followed monthly for clinical evaluation of treatment tolerance. The tests to be regularly performed are shown in Table 11.

Table 11. Monitoring during treatment

		Before treatment	W4	W8	W12	W16	W20	W24	W28	W32	W34	W36	W48	W72
Tolerance	Blood count and platelets*		W1 W2 W4	X	X	X	X	X	X	X	X	X	X	X
	CD4			X	X			X	X	X	X	X	X	X
	TSH				X			X			X			
Efficacy	Quantitative HCV viral load	X			X									
	Qualitative HCV RNA							X					X	X

Note: W=week
* Blood and platelets counts should also occur during weeks 1 and 2.

5.1. Virological response monitoring

See Table 11 above.

The virological response should be monitored by serum HCV RNA quantification before initiation of treatment and 12 weeks after starting treatment using the same sensitive test with a lower detection limit of 50 IU/ml:

- For patients with at least a 2 log reduction in viral load at week 12 – defined as an early virological response (EVR) – treatment should be continued.
- If a 2 log reduction in viral load is not achieved at week 12, treatment should be stopped, because the negative predictive value of achieving SVR is 99–100%. This rule is applicable to all genotypes.

The log rule at week 12 in coinfected patients is of great relevance to optimizing treatment. It encourages treatment of all candidates in the absence of contraindication, given that treatment can be stopped after 12 weeks if there is no chance of a cure.

After week 12, assessment should be made by a qualitative HCV RNA test, as follows:

- Week 24: for patients remaining positive for serum HCV RNA at week 24 (negative predictive value for achieving SVR is 100%), treatment should be discontinued.
- Week 48 marks the end of treatment response.
- Week 72: after six months off treatment, negative HCV RNA indicates an SVR. Recurrence of HCV infection thereafter is very rare.
- A new assessment might also be useful 12–24 months after the end of treatment.

5.2. Histological response monitoring

A new liver biopsy is not indicated except in patients with no SVR, for whom the result of liver biopsy could modify HCV treatment.

5.3. Tolerance monitoring

See Table 11 above.

A full blood count as well as transaminases and bilirubin tests should be performed in weeks 1, 2 and 4, and thereafter on a monthly basis. CD4 cell count should be monitored monthly. Additional laboratory tests can then be carried out at the physician's discretion and should include assessment of thyroid-stimulating hormone (TSH) at least every three months.

5.4. Management of toxicity and side-effects of PEG-IFN + RBV treatment

Side-effects of PEG-IFN and RBV occur in a majority of patients and may be severe *(2–5, 71)*. Effort should be made to keep patients on the optimal dose of PEG-IFN plus RBV and to proactively manage side-effects of treatment. It is important to maintain the optimal doses of RBV and PEG-IFN during treatment, especially during the first 12 weeks. The use of erytropoetin may make it possible to avoid decreasing RBV dosage *(72)*. However, if severe side-effects or laboratory abnormalities develop during treatment and no growth factor is available, the dosages of each product have to be modified until the reactions disappear, as described in section 5.4.2 below.

5.4.1. Anaemia and neutropenia

- Anaemia (<10 g/dl) is reported in up to 30% of patients receiving PEG-IFN + RBV and has been shown to impair quality of life *(2–5, 71)*.
- Anaemia increases with the concomitant use of ZDV and a lower baseline haemoglobin.
- ZDV should be replaced in patients with ART alternatives.
- Neutropenia (<1000 cells/mm^3) is observed in up to 50% of patients, but serious bacterial infections seem infrequent *(2–5, 71)*.

5.4.2. Dose adjustment of PEG-IFN and RBV

Table 12. Dose adjustment for side-effects and toxicity

	Reduce RBV to 600 mg	Withhold RBV	Reduce PEG-IFN by 70%, 50%, 25%	Withhold PEG-IFN	Discontinue combination
Absolute neutrophil count			<750/mm^3	<500/mm^3	
Platelet count			25 000–50 000/mm^3		<25 000/mm^3
Haemoglobin					
- no cardiac disease	8.5–10.0 g/dl	<8.5 g/dl			
- stable cardiac disease	decrease of ≥2 g/dl during any four weeks	<12 g/dl despite four weeks at reduced dose			

Source: European Medicine Agency *(73, 74)*.

- RBV should be reduced to 600 mg/daily (200 mg in the morning and 400 mg in the evening) if either of the following applies:
  - the haemoglobin of a patient without significant cardiovascular disease falls to <10 g/dl and ≥8.5 g/dl; or
  - the haemoglobin of a patient with stable cardiovascular disease fall by ≥2 g/dl during any four weeks of treatment (a return to the original dosage is not recommended).
- RBV should be discontinued if either of the following applies.
  - The haemoglobin of a patient without significant cardiovascular disease falls to <8.5 g/dl.
  - A patient with stable cardiovascular disease maintains a haemoglobin value <12 g/dl despite four weeks on a reduced dose.

If the abnormality is reversed, RBV may be restarted at 600 mg daily, and be increased to 800 mg daily at the discretion of the treating physician (a return to the original dosage is not recommended).

- In case of RBV intolerance, PEG-IFN monotreatment should be continued.
- Dose reduction of PEG-IFN is recommended if the neutrophil count is <750/mm^3 as described in Table 12 *(53)*. For patients with an absolute neutrophil count <500/mm^3 treatment should be suspended until values return to >1000/mm^3. Treatment should be reinstituted at 50% of the dose and the neutrophil count monitored.
- A 50% dose reduction is recommended if the platelet count is <50 000/mm^3. Cessation of treatment is recommended when platelet count decreases to levels <25 000/mm^3.

5.4.3. Influenza-like symptoms

- Paracetamol (possibly combined with non-steroidal anti-inflammatory drugs) should be used for influenza-like syndrome, particularly before injection of PEG-IFN.
- Low platelets are a relative contraindication for the use of acetylsalicylic acid, diclofenac or ibuprofen, because of the inhibition of platelet aggregation.
- Dose adjustment may be required in case of severe side-effects despite symptomatic treatment. An initial dose reduction to 75% or 50% of the dose is generally adequate.

5.4.4. Nausea

Nausea can be reduced with metoclopramide 10 mg three times daily (TID).

5.4.5. Depression

- Depressive mood changes are frequent and should be managed proactively with symptomatic treatment. In patients with a history of neurotic or minor depression, initiation of treatment with antidepressants before starting IFN-based treatment should be considered. Antidepressants are frequently needed for clinically-relevant depression. Use the following dosages:
  - selective serotonin reuptake inhibitors such as citaprolamin, paroxetin and tricyclic at initial dosages of 20 mg/day; and
  - antidepressants such as doxepine at an initial dosage of 50 mg/day.
- Consultation with an experienced psychiatrist for the establishment of a standardized treatment procedure is recommended.
- In patients with pre-existing depressive mood disorders or other profound neurotic disorders, initiation of specific psychiatric medication is recommended to reduce the destabilizing effect of IFN-based treatment.
- In patients with a history of hospitalization due to major depression or psychosis, IFN-based treatment is generally contraindicated. In large controlled studies the incidence of attempted or completed suicides, psychosis and major depression is <1% *(2–5, 71)*. The choice of treatment strategy should be made in consultation with a psychiatrist.
- In patients with a history of injecting drug use, benzodiazepines should be avoided because of their potential to induce addiction.

5.4.6. Dysthyroidism

IFN-induced dysthyroidism occurs in 7% of patients, but does not require treatment interruption.

- Thyroid hormone substitution is used in case of hypothyroidism.
- Beta-blockers are useful to relieve symptoms of hyperthyroidism *(75)*.

5.5. Management of treatment adherence

Even among patients who are appropriate candidates for treatment with IFN, acceptance of treatment is low in HCV/HIV-coinfected populations, predominantly due to treatment side-effects and toxicity. However, a proportion of patients who initially decline IFN treatment accept it after education and peer support programmes to facilitate successful treatment. Patients may continue to

work if necessary, with possible working time adjustments to accommodate for treatment and drug reactions.

Counselling is essential to increasing adherence. Physicians should:
- listen to patients' complaints
- teach them to recognize and manage side-effects
- discuss ways to improve compliance.

A team approach to patient care and management is an effective strategy for increasing adherence. The team should include physicians, nurses, psychiatrists where relevant and social workers or other care providers.

Initiatives that have proven effective include directly observed treatment, patient discussion groups, patient manuals, hotlines and psychological support. For further information on adherence please refer to Protocol 5, *HIV/AIDS treatment and care for injecting drug users,* and Protocol 1, *Patient evaluation and antiretroviral treatment for adults and adolescents.*

5.6. Management of non-responders

Non-response can be observed in any HCV treatment, ranging from "no viral decline during treatment" to "end-of-treatment virological response and subsequent virological relapse". The decision to treat patients again with PEG-IFN plus RBV should be based on:
- type of response
- toleration of the previous treatment
- extent of liver damage
- HCV genotype.

If the therapeutic aim in treating patients with biopsy-proven advanced fibrosis/cirrhosis is to delay or prevent disease progression in non-responders at week 12 and/or week 24, continuation with PEG-IFN monotreatment can be considered, since a histological response was observed in about 35% of non-responders who received PEG-IFN + RBV in four pivotal trials *(2–5)*. However, data on dose, duration and clinical benefits of such maintenance treatment are very scarce in HCV/HIV-coinfected patients, and further research is needed.

5.7. Management of end-stage liver disease (ESLD)[13]

5.7.1. Testing for hepatocellular carcinoma (HCC)

Cirrhotic patients should be screened for HCC at four-to-six-month intervals using ultrasonography and measurement of alfa-fetoprotein levels *(43)*. It has been found that HCC occurs more rapidly and is more aggressive in patients with HIV infection *(76)*. Patients whose test results are abnormal should be followed up at referral centres for diagnosis, staging and treatment, which is only available for early-stage HCC *(77)*.

5.7.2. Testing for oesophageal varices

Annual endoscopy, including the investigation of oesophageal varices in the gastric fundus, is recommended *(43)*. In the presence of significant oesophageal varices, a prevention of bleeding by non-cardioselective beta-blockers (associated with variceal ligation in case of > grade 2 varices) is recommended *(78)*. The most frequently prescribed drug is propanolol at a dosage varying from 40 to 160 mg/day in order to obtain a blocking effect (cardiac pulse reduction of 30%).

[13] For further details on ESLD, please see Annex 4.

5.8. Drug–drug interactions

5.8.1. Interactions between HIV drugs and HCV drugs

Interactions of ARV agents and anti-HCV drugs must be taken into account, as they partially explain the high rate of side-effects in HCV/HIV-coinfected patients treated for HCV.

- RBV competes for phosphorylation with thymidine and cytosine analogues such as ZDV and d4T *(79, 80)*. However, in controlled trials, no effect of RBV on the efficacy of the ARV combination treatment has been observed *(81)*.
- IFN has a moderate antiretroviral effect which may compensate for the effect of RBV on the efficacy of the ART regimen *(82)*.
- In contrast, the phosphorylation of ddI is increased by RBV *(83–87)*, which may explain some side-effects observed in co-administration *(56–58)*.

5.8.2. Interactions among recreational drugs, OST, anti-HCV drugs and ARVs

- No finding of interaction between opioids and anti-HCV drugs has been published.
- All PIs and NNRTIs are substrates and potent inhibitors or inducers of the cytochrome P450 system. Many classes of recreational drugs, including benzodiazepines, amphetamines and opioids, are also metabolized by the liver and can potentially interact with antiretrovirals. Overdoses as a secondary reaction to interactions between the amphetamine-type stimulants (MDMA) and PIs, particularly RTV, have been reported.
- ARVs that are CYP3A4 inducers (NVP, EFV and PIs) can decrease the level of methadone, causing withdrawal symptoms and increasing the risk of relapse into heroin abuse.
- An opiate metabolism can be inhibited or induced by concomitant PIs, so patients should be monitored for signs of toxicity. Withdrawal symptoms generally occur within 4–10 days of ART initiation. Withdrawals should be monitored clinically and dose increases of 10 mg increments from days 8–10 should manage the problem.

5.9. Hepatotoxicity of TB drugs in chronic HCV infection

- The rate of hepatotoxicity is significantly higher in TB patients with HCV or HBV coinfection (59%) than without coinfection (24%) *(88)*.
- Commonly used anti-TB drugs, such as isoniazid, rifampicin, pyrazinamide and ethambutol, are all hepatotoxic.
- Pyrazinamide is the most hepatotoxic and should be avoided in TB patients with severe chronic liver disease *(89)*.
- It is not necessary to adapt doses of anti-TB drugs in hepatic insufficiency.
- In decompensated liver disease, a regimen without pyrazinamide should be used.
- Streptomycin, ethambutol, and a reserve drug such as fluoroquinolone can be used if treatment is necessary in patients with fulminant liver disease. Consultation by a specialist is required.
- Alternative anti-TB drugs with lower hepatotoxicity (rifabutin, amikacin, ofloxacin, levofloxacin, etc.) might be used in cases of severe liver dysfunction, The treatment of these special cases should be decided in consultation with an acknowledged expert.
- Hepatotoxicity occurrence justifies a monthly monitoring of liver functions.

IV. Suggested minimum data to be collected at the clinical level

The suggested minimum data to be collected is important in the development of key indicators on access to treatment and its success. Such indicators assist managers in decision-making on ways to strengthen and expand these services to all those in need.

The following data should be collected at each clinical facility on a regular basis (e.g. monthly, quarterly or semi-annually):

- number of HIV patients ("seen for care" – this will be the denominator for the data below);
- number of HIV patients coinfected with HCV;
- number of HCV/HIV-coinfected patients with chronic hepatitis C;
- number of HCV/HIV-coinfected patients with chronic hepatitis C receiving:
  - only HCV treatment
  - only ART
  - both treatments; and
- number of HCV/HIV-coinfected patients who have died (in a given period) including cause of death (e.g. liver-related deaths, HIV/AIDS related mortality or non-HIV/AIDS related mortality such as accident, overdose or suicide).

Annex 1. Laboratory assays for HCV *(31)*

Detection of HCV antibodies

Detection of HCV antibodies is the first step in screening patients for suspected HCV infection. Currently available assays are highly sensitive, and specific HCV antibodies are detected with enzyme immunoassays (EIA). These assays detect mixtures of antibodies directed against various HCV epitopes located in HCV proteins: core, NS3, NS4 and, in third-generation tests, NS5 *(1, 6)*. The specificity and sensitivity of currently available EIAs for HCV antibodies are greater than 99% in immunocompetent patients with active viral replication (presence of HCV RNA). For patients with acute HCV infection, it is important to bear in mind that antibodies may not be detectable for three to eight weeks following initial infection.

The presence of HCV antibodies is indicative of past or present infection. Antibodies persist indefinitely in chronically infected patients, but antibody titres may decrease or even disappear in patients who clear HCV either spontaneously or after ART.

Different types of assays and immunoblot tests, were used in the past to confirm positive EIAs results in low-risk populations, such as in healthy blood donors. The excellent performance of currently available EIAs and the general availability of HCV RNA testing make these assays outdated. In blood banks, nucleic acid testing (NAT) has recently been implemented. With NAT, the presence of HCV RNA is analyzed in small blood pools and, if a viral genome is detected, an individual analysis of the implicated blood samples is performed. With the addition of NAT, the risk of HCV transmission has been reduced to around 1/1 000 000 donations.

Qualitative detection of HCV RNA

HCV RNA can be detected as soon as a few days after infection. In general, qualitative assays to detect HCV RNA are more sensitive than most currently available quantitative assays. However, the latest quantitative methods are very sensitive and in the future could become the universally used methods.

The qualitative detection procedure begins with RNA extraction from clinical samples. In most centres RNA extraction has become fully automated, increasing its reproducibility. Thereafter, the target is amplified, either by PCR or TMA.

There are currently two commercially available qualitative assays to detect HCV RNA: one PCR-based assay (Cobas Amplicor HCV v. 2.0, Roche) with a sensitivity of 50 IU/ml and one TMA assay (Versant HCV RNA qualitative assay, Bayer) with a sensitivity of 5–10 IU/ml. The specificity of both assays is close to 100%.

Quantification of HCV RNA

In individuals who become chronically infected, HCV RNA levels are relatively stable over time *(90)*. HCV RNA quantification can be obtained by two techniques.

1. PCR assays
Quantification is based on amplification of the viral template with a known amount of synthetic RNA standard added to each reaction. The relative amounts of amplified viral template and standard amplicons are measured at the end of the PCR reaction. More recently, "real time" PCR has been developed, with many advantages such as simplicity, rapidity, wider linear range of HCV RNA concentrations and minor risk of contamination. Real-time PCR is already replacing conventional PCR assays.

2. DNA assay
Another approach to quantifying HCV RNA is signal amplification, in which viral genomes are released from the virions and hybridized in solution using target probes. The HCV RNA with target probes are

then captured onto microwell plates. Additional target probes bind the viral RNA to branched-DNA amplifier molecules. The signal is amplified by hybridization of oligonucleotide probes conjugated with alkaline phosphatase for detection and quantification of the HCV RNA.

Determination of HCV genotype *(91)*

Two methods can be used to determine HCV genotype:

1. RT-PCR assay, based on analysis of the 5' untranslated region of the HCV genome is the most commonly used method. Typing errors are rare but can occur between genotype 1 and some isolates of genotype 4; sub-typing errors might occur in 15–20% of cases. These errors can be explained by the high degree of nucleotide conservation within this region.

2. Serology: determination of HCV genotype can also be performed by detecting type-specific antibodies. Several antigenic determinants have been identified after epitope mapping of the NS4 and core proteins of HCV. These epitopes have been used to develop a competitive EIA (Murex HCV EIA) and an immunoblot assay (RIBA, Chiron Corp).

There are studies demonstrating a lower performance of tests aimed at detecting HCV antibodies in HIV-infected patients, as well as cases of HCV antibody seroconversion coinciding with the administration of HAART (probably due to immune restoration). However, latest generation HCV antibody EIAs have incorporated multiple HCV antigens and are very sensitive in HIV-infected patients. Recently, sera from 559 HIV-infected and 944 HIV-negative IDUs were tested both for HCV antibodies using a third-generation assay and for HCV RNA using a commercially available test. Of the HIV-infected individuals, 547 (97.8%) had detectable HCV antibodies, and only one HCV antibody-negative patient had detectable HCV RNA *(27, 28)*. The figure was similar for HIV-negative patients, indicating that HCV antibody screening using latest generation assays is reliable in coinfected patients.

Annex 2. Alternative biochemical tests to assess hepatic fibrosis

Table 13. Initial reports from all major serum assays

	No. of patients	Serum markers	Significant fibrosis	Auro (95% CI)	Cut-off	Sensitivity	Specificity	PPV[a]	NPV[b]	Comments
Indirect assays										
Wai et al. *(92)*	192	APRI (AST, platelets)	Ishak ≥3	0.88 (0.80–0.96)	≤ 1.5	41%	95%	88%	64%	Simple index; accurately predicts significant fibrosis and cirrhosis
Forns et al. *(93)*	476	Forns Index (age, GGT, cholesterol, platelet count)	Metavir ≥2	0.86	<4.2	94%	51%	40%	96%	Approx. half of those with insignificant fibrosis detected;. use of cholesterol a confounding variable
Ziol at el. *(94)*	327	FibroScan™ (hepatic elastography)	Metavir ≥2	0.79 (0.73–0.84)	>8.7	56%	91%	88%	56%	Excellent for the detection of cirrhosis; continuous variable strength
Imbert-Bismut et al. *(95)*	134	FibroTest™ (α2 macroglobulin, α2 globulin, .γglobulin, apolipoprotein A1, GGT and total bilirubin)	Metavir ≥2	0.87 (SD 0.34)	0.30	87%	59%	63%	85%	False positives with inflammation and haemolysis; large validated data reported
Castera et al. *(96)*	183	Combined FibroScan and FibroTest	Metavir ≥2	0.88 (0.82–0.92)		NA	NA	NA	NA	Combined score appears to enhance efficacy
Direct assays										
Patel et al. *(97)*	402	Fibrospect hyaluronic acid, tissue inhibitor of metalloproteinase 1 (TIMP-1) and alfa2-macro-globulin	Metavir ≥2	0.831	0.36	77%	73%	74%	76%	No indeterminate score across all stages
Kelleher et al. *(98)*	95	SHASTA (hyaluronic acid, AST & albumin)	Ishak ≥3	0.87	0.30	88%	72%	55%	94%	Detection of early fibrosis in HCV/HIV-coinfected patients
Rosenberg et al. *(99)*	1021	ELF (Propeptide III collagen, TIMP 1, HA)	Scheuer 3 or 4	0.80 (0.76–0.85)	0.102	90.5%	41%	99%	92%	Validated for multiple etiologies; high reproducibility and automated processing strength

[a] PPV: positive predictive value.
[b] NPV: negative predictive value.

Annex 3. Alcohol screening questionnaires

The following is an overview of the most used and well-established alcohol screening questionnaires.

CAGE Test

CAGE *(100)* is an acronym of the four questions:
1. Have you ever felt you ought to **C**ut down on your drinking? (yes/no)
2. Have people **A**nnoyed you by criticizing your drinking? (yes/no)
3. Have you ever felt bad or **G**uilty about your drinking? (yes/no)
4. Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover (**E**ye-opener)? (yes/no)

Item responses are scored 0 or 1, with a higher score an indication of alcohol problems. A total score of 2 or greater is considered clinically significant.

AUDIT Test

The AUDIT Test *(101)* was developed as a simple method of screening for excessive drinking, alcohol dependence and harmful drinking (see Table 14 below). It has the following advantages:
- cross-national standardization, the only screening test designed for international use;
- identifies hazardous and harmful alcohol use, as well as possible dependence;
- it is brief, rapid and flexible;
- designed for primary health-care workers; and
- focuses on recent alcohol use.

A score of 8 in men and 7 in women indicates a strong likelihood of hazardous or harmful alcohol consumption. A score of 13 or more is suggestive of alcohol-related harm.

Table 14. AUDIT TEST

1. How often do you have a drink containing alcohol?				
(0) Never	(1) Monthly or less	(2) 2–4 times a month	(3) 2–3 times a week	(4) 4 or more times a week
2. How many drinks containing alcohol do you have on a typical day when you are drinking?				
(0) 1 or 2	(1) 3 or 4	(2) 5 or 6	(3) 7 to 9	(4) 10 or more
3. How often do you have six or more drinks on one occasion?				
(0) Never	(1) Less than monthly	(2) Monthly	(3) Weekly	(4) Daily or almost
4. How often during the past year have you found that you were not able to stop drinking once you had started?				
(0) Never	(1) Less than monthly	(2) Monthly	(3) Weekly	(4) Daily or almost
5. How often during the past year have you failed to do what was normally expected of you because of drinking?				
(0) Never	(1) Less than monthly	(2) Monthly	(3) Weekly	(4) Daily or almost
6. How often during the past year have you needed a first drink in the morning to get yourself going after a heavy drinking session?				
(0) Never	(1) Less than monthly	(2) Monthly	(3) Weekly	(4) Daily or almost
7. How often during the past year have you had a feeling of guilt or remorse after drinking?				
(0) Never	(1) Less than monthly	(2) Monthly	(3) Weekly	(4) Daily or almost
8. How often during the past year have you been unable to remember what happened the night before because you had been drinking?				
(0) Never	(1) Less than monthly	(2) Monthly	(3) Weekly	(4) Daily or almost
9. Have you or has someone else been injured as a result of your drinking?				
(0) No	(2) Yes, but not in the past year		(4) Yes, during the past year	
10. Has a relative or friend or a doctor or other health worker been concerned about your drinking or suggested you cut down?				
(0) No	(2) Yes, but not in the past year		(4) Yes, during the past year	

Source: Baber et al. *(101)*.

Annex 4. Management of end-stage liver disease

Hepatocellular carcinoma

As HIV-infected patients live longer, especially in industrialized countries where they have access to HAART, HCC may begin to emerge in those who would have otherwise have succumbed to complications from their primary HIV disease. For this reason, HCC is projected to become an increasingly significant clinical problem in the HIV populations *(76, 102–104)*.

Early diagnosis of HCC is particularly important in patients coinfected with HCV and HIV, because it is more aggressive and, in its advanced stages, incurable *(59)*. Prevention, therefore, becomes key to controlling the health-care burden of this disease.

The recommendations for HCC management developed in 2000 by the European Association for the Study of the Liver (EASL) *(105)* are being updated. Such recommendations might be problematic in view of the wide geographical variations in disease epidemiology and treatment availability. Guidelines for managing HCC arising in connection with HIV coinfection are lacking.

Early diagnosis

The 2000 EASL guidelines describe patient selection and surveillance intervals *(105)*. Patients with cirrhosis should be screened, if liver transplantation is feasible. A screening interval of every six months has been established to allow detection of tumours <3 cm in diameter. Patients whose screening results are abnormal should be followed up at referral centres for diagnosis and staging.

Ultrasonography and measurement of alpha-fetoprotein (AFP) levels, at six-month intervals, are the most commonly used methods to screen patients with cirrhosis for HCC *(77, 106)*. AFP values >400 ng/ml are considered diagnostic of HCC.

Treatment

Treatment for HCC is usually classified as curative or palliative *(77, 105)*. Curative treatment includes:

- surgical resection
- liver transplantation
- arterial embolization
- percutaneous ethanol injection in patients with small tumours who are not candidates for resection; a modest survival advantage has been shown for chemoembolization in randomized, controlled trials and one meta-analysis.

Most patients cannot undergo resection or liver transplantation because of underlying cirrhosis or advanced disease at diagnosis.

Early-stage HCC

A solitary tumour <5 cm, or up to 3 tumours <3 cm, in a patient with well-preserved liver function, constitutes early-stage HCC *(4, 8)*. Monoinfected patients can be successfully treated with curative therapies, although response rates and survival benefits are variable. Surgical resection and transplantation yield 5-year survival rates ranging from 60% to 70%. Recurrence, however, can be as high as 50% at 3 years and 70% at 5 years.

Percutaneous ethanol injection induces a complete response in about 80% of patients whose tumours are ≤3 cm. Response rates are lower with large or multinodal tumours *(105)*.

Advanced HCC

Most patients with HCC (approximately 50%) have advanced disease at diagnosis *(77, 105)*. Patients with advanced disease are candidates for loco-regional or systemic treatments rather than curative approaches *(4)*. Transarterial chemoembolization is the only palliative therapy that has been shown to improve survival, with careful patient selection.

Prevention and recurrence

HIV patients are likely to have other risk factors predisposing them to HCC, such as alcohol abuse and concurrent HBV infection. Among HIV patients, vaccination against HBV is strongly recommended. HCV/HIV-coinfected patients should receive treatment for chronic HCV infection using combination IFN and RBV.

Orthotopic liver transplantation

Orthotopic liver transplantation (OLT), where available, is the only therapeutic option for patients with end-stage liver disease. Accumulated experience in North America and Europe in the last five years indicates that three-year survival in selected HIV-infected recipients of liver transplants was similar to that of HIV-negative recipients *(107–110)*. HIV infection by itself is not, therefore, a contraindication for liver transplantation.

As the survival of HIV-infected patients with ESLD is shorter than that of non-HIV-infected patients, the OLT evaluation should be done after the first liver decompensation. The current selection criteria for HIV-positive transplant candidates include:

- no history of opportunistic infections or HIV-related neoplasms, except infections that can be efficaciously treated and prevented, such as TB, candidiasis or *Pneumocystis jirovecii* pneumonia (PCP);
- CD4 cell count >100 cells/mm^3; and
- plasma HIV viral load suppressible with antiretroviral treatment.

For drug users, a two-year abstinence from heroin and cocaine is also required, although patients in a methadone programme can be accepted.

The main problems in the post-transplant period are pharmacokinetic and pharmacodynamic interactions between ARVs and immunosuppressors, and the management of HCV infection relapse, one of the main causes of post-transplant mortality. Experience with PEG-IFN and RBV is scarce in this population.

Table 15. Three-year survival of patients with and without HIV-infection who had a liver transplant before and during the HAART period

Survival	Before HAART (<1996)	During HAART period (1996–2004)	
	HIV-infected patients (n = 32)	HIV-infected patients (n = 24)	Non-HIV-infected patients (UNOS) (n = 5225)
One year	69%	87%	87%
Two years	56%	73%	82%
Three years	44%	73%	79%

Source: Tzakis et al., Miró et al., Ragni et al., *(108–110)*.

Annex 5. Research needs and alternative treatments

Epidemiology

Studies on the epidemiology and the social impact of HCV in patients infected with HIV should be actively investigated, with a special emphasis on vulnerable populations.

HIV management

Studies addressing the optimal time in the course of chronic HIV infection to commence ART in HCV-coinfected patients should be initiated.

HCV management and physiopathology

- Studies to validate the utility of non-invasive methods of liver disease progression should be performed.
- Long-term follow-up studies of patients with and without SVR are strongly encouraged to determine late relapses, the duration of histological improvement and the effect of clinically relevant outcomes such as decompensation, HCC and death.
- Studies on pathophysiology, including extrahepatic viral reservoirs and the specific immune response to HCV, should be conducted.

Future directions for treatment

Research should also investigate:

- optimizing the response to existing treatments, such as higher doses of RBV or PEG-IFN
- treatment durations
- the utility of maintenance treatment
- the optimal regimen for delaying disease progression.

Higher doses of RBV

The optimal RBV dose for treatment of HCV genotype 1 and the potential benefits of prolonged treatment should be investigated. The optimal dose of RBV remains unclear. It is possible that higher SVR rates can be achieved by higher doses of RBV. In most of the published literature on HIV/HCV-coinfected patients, the RBV dose was 800 mg, in order to avoid anaemia, which was considered a greater problem in HIV-infected patients, especially those taking ZDV. However, in HIV-negative patients with genotype 1 HCV infection, it is clear that higher SVR rates are achieved with 1.0/1.2 g RBV (≤75 kg/>75 kg) than with 800 mg *(49)*. Thus, alternative strategies for HIV-infected patients need also to consider higher RBV doses. It is important to note that higher RBV doses appeared to be well tolerated in the Barcelona study *(5)*, where RBV was given by body weight as follows (per day): 800 mg, <60 kg; 1 g, 60–75 kg; and 1.2 g, >75 kg.

Higher doses of IFN

It is possible that higher SVR rates can be achieved by higher doses of IFN but this has not been investigated in HIV-infected patients.

Treatment duration

A shorter duration of treatment for patients with HCV genotypes 2 and 3 should be investigated.

In HIV-negative patients, SVR rates are the same for genotype 2 and 3 HCV infections if they are treated for 24 weeks instead of 48. However, analogous studies have not been reported for PLHIV *(5)*. Thus, studies emphasizing alternative dosing intervals are also needed for genotype 2 and 3 HCV infection before shorter regimens can be recommended. On the other hand, it might be useful to evaluate the usefulness of longer treatment duration for genotype 1 HCV infections with high viral loads.

IFN maintenance treatment

Studies on the use of maintenance treatment in patients with no SVR and with advanced liver disease are strongly recommended, including evaluation of the optimal dose and duration of treatment. Maintenance treatment is aimed at decreasing the incidence of ESLD without effecting SVR. The histologic response results of the ACTG 5071 study *(4)* described above provide a rationale for this approach. There are studies designed to test this hypothesis in both HIV-infected (SLAM-C) and HIV-uninfected people (HALT-C), but it remains undecided.

Acute HCV infection

The optimal treatment for acute HCV infection in HIV-infected patients should be investigated.

New treatments

As the current therapies are suboptimal in efficacy, tolerability and quality of life, the development of new drugs to improve these issues should be actively pursued.

Phase II and III trials of new drugs should be performed in HIV/HCV-coinfected patients as a priority due to the accelerated course of hepatitis infections in these populations.

There are many compounds under development, and some have progressed into Phase II clinical studies *(111)*:

- Viramidine (Valeant) is a prodrug of RBV that causes substantially less anaemia. In phase II studies, it was associated with less anaemia than RBV and SVR rates that were not inferior. Phase III studies are underway.
- Albuferon-alfa™ (Human Genome Sciences), is a fusion of albumin and IFN that prolongs IFN half-life.
- Interleukine-2 (IL-2) treatment has also been examined as a method to boost HCV antibody immune responses and enhance treatment responses. However, an early study in HIV/HCV-coinfected patients was associated with significant toxicity and provided no evidence of effectiveness *(10)*.
- NM283 (Idenix) interferes with the HCV polymerase and, in Phase II studies; its use was associated with a modest reduction in HCV RNA levels.
- VX 950 (Vertex) is an HCV protease inhibitor that is being examined in clinical trials.

The development of direct antivirals that block essential viral enzymes represents a straightforward approach to developing new agents to target HCV. Although all HCV enzymes are, in theory, equally appropriate for therapeutic intervention, the NS3–4A serine protease and the NS5B RNA polymerase have emerged as the most popular targets. A number of competitive inhibitors of the NS3 protease as well as nucleoside and non-nucleoside inhibitors of the NS5B polymerase are being developed. The efficacy shown by NS3 serine protease and the NS5B RNA-dependent RNA polymerase inhibitors in recent proof-of-concept clinical trials has validated the effort of finding clinical candidates and triggered a renewed interest in this area *(112)*.

Table 16. A sample of the drug pipeline for hepatitis C

Compound	Company	Clinical phase	Target	Mechanism of action
BILN 2061 (Ciluprevir)	Boehringer-Ingelheim	Phase II[a]	NS3–4A protease	Product-derived serine protease inhibitor
VX-950	Vertex/Mitsubishi	Phase Ib	NS3–4A protease	Serine protease reversible covalent inhibitor
NM283 (Valopicitabine)	Idenix/Novartis	Phase II	NS5B polymerase	Nucleoside analogue (chain terminator)
JTK-103	Japan Tobacco	Phase II	NS5B polymerase	Non-nucleoside allosteric inhibitor
HCV-796	ViroPharma/Wyeth	Phase Ia	NS5B polymerase	Non-nucleoside allosteric inhibitor
Host targets/immunomodulators				
Actilon (CpG-10101)	Coley Pharmaceutical Group	Phase Ib	Toll-like receptor-9	Immunomodulator
ANA245 (Isatoribine)	Anadys Pharmaceuticals	Phase Ib	Toll-like receptor-7	Immunomodulator
ANA975	Anadys Pharmaceuticals	Phase Ia	Toll-like receptor-7	Immunomodulator (prodrug of ANA245)

[a] Development has been halted due to cardiotoxicity in monkeys.
Source: Nunes et al. *(42)*.

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