

Management and treatment of hepatitis C virus in patients with HIV and hepatitis C virus coinfection: A practical guide for health care professionals

Pierre Côté MD^{1,2*}, Jean-Guy Baril MD^{1,2,3*}, Marie-Nicole Hébert MURb^{3*}, Marina Klein MD FRCPC⁴, Richard Lalonde MD FRCPC^{4*}, Marc Poliquin MD FRCPC², Danielle Rouleau MD MSc FRCPC^{2*}, Rachel Therrien MSc BPharm^{2*}, Sylvie Vézina MD^{2,5}, Bernard Willems MD FRCPC², Harold Dion MD^{5,6*}, Patrice Junod MD^{2*}, Normand Lapointe MD^{7*}, Dominic Lévesque RN^{8*}, Lyse Pinault^{9*}, Cécile Tremblay MD FRCPC^{2*}, Benoît Trottier MD^{2,5*}, Sylvie Trottier MD MSc FRCPC^{10*}, Chris Tsoukas CM MD FRCPC^{4*}, Alain Piché MD^{11*}

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Concomitant HIV and hepatitis C virus (HCV) is a common yet complex coinfection. The present document is a practical guide for treating HCV infection in people coinfecting with HIV. Effective antiretroviral therapies have prolonged survival rates for HIV-infected people over the past decade, which have made latent complications of HCV major causes of morbidity and mortality in these patients. Advances in the treatment of HCV (eg, combined pegylated interferon and ribavirin) offer the possibility of eradicating HCV infection in coinfecting persons. The treatment of HCV must be considered in all cases. Intensive management of the adverse effects of HCV treatment is one of the factors for the success of these therapies. HCV eradication is predicted to decrease the mortality associated with coinfection and reduce the toxicity of HIV treatment.

Key Words: Antiretrovirals; Coinfection; Hepatitis C virus; HIV; Practical guide

Concomitant HIV and hepatitis C virus (HCV) infection is a complex and frequent problem. The increased survival rates since 1996 for HIV-infected people following highly active antiretroviral therapy have led to latent complications of HCV becoming major causes of morbidity and mortality in people living with HIV. Interactions with respect to pathogenesis, complexity of clinical management and treatment of HCV and/or HIV are a challenge for clinicians and the health care system. The present document is a practical guide for treating HCV infection in people coinfecting with HIV. It promotes optimal follow-up and comprehensive case management by multidisciplinary teams.

The current practical guide was developed by the Comité consultatif sur la prise en charge des personnes vivant avec le

La prise en charge et le traitement du virus de l'hépatite C chez des patients co-infectés par le VIH et le virus de l'hépatite C : Guide pratique pour les professionnels de la santé

La co-infection par le VIH et le virus de l'hépatite C (VHC) est courante, mais complexe. Le présent document se veut un guide pratique pour le traitement de l'infection par le VHC chez les personnes co-infectées par le VIH. Des thérapies antirétrovirales efficaces ont prolongé les taux de survie des personnes infectées par le VIH depuis dix ans, ce qui fait des complications latentes du VHC des causes importantes de morbidité et de mortalité chez ces patients. Les progrès dans le traitement du VHC (p. ex., PEG-interféron associé à la ribavirine) offrent la possibilité d'éradiquer l'infection par le VHC chez les personnes co-infectées. Il faut envisager le traitement du VHC dans tous les cas. La prise en charge intensive des effets indésirables du traitement du VHC fait partie des facteurs de réussite de ces thérapies. L'éradication du VHC devrait réduire la mortalité associée à la co-infection ainsi que la toxicité du traitement du VIH.

VIH (Consultant Committee). This Quebec-based panel includes members with extensive experience in the care of HIV patients. They are mandated by the Ministère de la Santé et des Services sociaux (Ministry of Health and Social Services) to establish clinical guidelines on the management and treatment of persons living with HIV. A subgroup of the panel, in conjunction with HCV experts, was formed to develop the present practical guide to provide guidance to health care providers on the treatment of HCV in the setting of HIV-HCV coinfection. These recommendations are based on the current standard of care in treatment, published clinical guidelines, literature review and extensive clinical expertise by the members of the panel. Recommendations were obtained by consensus, and a medical writing subcommittee was established.

¹Clinique médicale du Quartier Latin; ²Centre hospitalier de l'université de Montréal; ³Service de lutte contre les infections transmissibles sexuellement et par le sang, Ministère de la Santé et des Services sociaux; ⁴Centre universitaire de santé McGill; ⁵Clinique médicale l'Actuel; ⁶Collège québécois des médecins de famille (Quebec College of Family Physicians); ⁷Hôpital Sainte-Justine, Centre maternel et infantile sur le sida; ⁸Comité des personnes atteintes du VIH du Québec (CPAVIH); ⁹Coalition des organismes communautaires québécois de lutte contre le sida (COCQ-sida), Montréal; ¹⁰Centre hospitalier universitaire de Québec, Sainte-Foy; ¹¹Centre hospitalier universitaire de Sherbrooke, Sherbrooke, Québec

*Members of the Comité consultatif sur la prise en charge clinique des personnes vivant avec le VIH

Correspondence and reprints: Dr Pierre Côté, Clinique médicale du Quartier Latin, 905, boul René-Lévesque Est, Montréal, Québec H2L 5B1.

Telephone 514-285-5500, fax 514-285-2226, e-mail info@quartier-latin.ca

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TABLE 1
Risk of transmission in the absence of treatment or postexposure prophylaxis

Event	HIV	HCV (reference)
High-risk sexual exposure	0.5%–3%	Rare; 3% if coinfecting (2)
Percutaneous exposure (small amounts)	0.3%	1.8% (3)
Vertical transmission	20%–30%	2% to 5%; up to 36% if coinfecting (9,12,16)

HCV Hepatitis C virus

The document was then reviewed and endorsed by the Consultant Committee. These recommendations are not intended to be a formal review of the published literature or to supersede the judgment of clinicians who are knowledgeable in the care of HIV-HCV coinfecting persons. This is an evolving science; the availability of new clinical data with existing agents and the availability of new therapeutic options periodically change treatment options and preferences.

EPIDEMIOLOGY

It is estimated that approximately 20% of HIV-infected people in Canada are coinfecting by HCV (1). The two viruses have certain common modes of transmission. HCV is approximately 10 times more transmissible than HIV by percutaneous exposure to contaminated needles (2). Transmission of one or the other is frequent in cases of transfusion or use of coagulation factors, as evidenced by the high rate of coinfection in hemophiliacs before the universal implementation of blood donor screening (3,4). The risk of HIV transmission following a single, high-risk, unprotected incident of sexual contact has been estimated to be 0.5% to 3% (5). HCV sexual transmission is rare (6,7). Vertical transmission of HIV from mother to child in the absence of antiretroviral therapy has been found to occur in approximately 20% to 30% of cases (2,8). Vertical HCV transmission is rare (2% to 5%) in mothers with HCV alone (2), but has been found to occur in up to 36% of mothers with HIV-HCV coinfection (9,10). HIV-HCV coinfection also increases the risk of sexual transmission of HCV (2,7,11), particularly in homosexual men (10,12). Transmission rates are shown in Table 1 (13). The number of HCV carriers in Canada has been estimated to be 250,000 (1). In studies examining injection drug users (IDUs) in two Canadian cities before 1999, the annual incidence of HCV was reported to be 26% in Vancouver and 27% in Montreal. The prevalence of HCV among IDUs in those two cities was 85% and 70%, respectively (14). In 2003, it was estimated that approximately 14.7% of Quebec IDUs were infected by HIV (15) and other, American, data (7) showed that 85% of persons infected with HIV through injection drug use were also infected by HCV.

NATURAL HISTORY OF HIV-HCV COINFECTION

The independent natural histories of HIV and HCV has been reported in detail elsewhere (2,16-27). These natural histories can be significantly changed in the presence of coinfection.

HIV infection has a significant effect on the evolution of HCV. HIV increases the frequency of persistence of HCV after infection (27,28). Spontaneous clearance of HCV only occurs in 5% to 10% of HIV-positive people. HIV infection can also be

associated with an increase in the HCV viral load (2), which can result in a decreased response to eradication treatments (2).

HIV has been associated with a faster progression toward cirrhosis (29), hepatic decompensation and, in some cases, hepatocellular carcinoma (30). Median progression for the development of cirrhosis in people with HCV-HIV coinfection can occur up to 10 years earlier than in those with HCV infection alone. A 1997 cross-sectional study (30) comparing the results of liver biopsies showed a median interval to cirrhosis of 6.9 years in coinfecting people, compared with 23.2 years in monoinfecting people. A more severe immunodeficiency (CD4 count less than 200 cells/ μ L) (31), consumption of more than 50 g of alcohol per day (equivalent to 3.6 standard drinks [where one standard drink equals one beer, one glass of wine, one aperitif or one hard liquor]) (31,32) and being older than 20 years of age at the time of HCV infection are independent aggravating factors in coinfection. The effect of HIV antiretroviral therapy on the evolution of HCV is not known (33), but some cases of decreased inflammation and fibrosis have been reported (31).

The influence of HCV infection on the natural history of HIV infection is less significant. Different cohorts have produced discordant findings, which can be explained by the selection bias of populations with negative prognostic factors for HIV, including alcohol and substance abuse, poor nutritional status and low adherence with antiretroviral treatment. Antiretroviral hepatotoxicity may be increased in the presence of HCV (34) and has been reported to result in more frequent treatment interruptions in coinfecting patients (35). A recent Canadian study (36) has shown that HCV seropositivity is an independent predictor of mortality, especially death related to HIV infection.

LABORATORY TESTS AND THEIR INTERPRETATION

Diagnosis of coinfection

HCV infection is diagnosed using a serological test for anti-HCV. However, a positive anti-HCV test does not distinguish between the majority of patients with chronic infection and a minority of those who have spontaneously cleared the virus. Hence, a positive anti-HCV test should be confirmed by a qualitative HCV RNA polymerase chain reaction test. All HIV-infected people should be screened for HCV infection. At HIV diagnosis, HCV testing should be repeated for those who were initially HCV seronegative based on risk factors and clinical manifestations.

In immunocompromised people, HCV infection can be present despite a negative HCV antibody test (3% to 7% of cases) (37,38). Qualitative HCV RNA testing is recommended in HIV-positive people, along with a negative HCV antibody test, to detect serologically negative HCV infections in people with a sustained increase in liver enzymes or with risk factors for HCV (eg, IDUs and pre-1990 transfusion recipients).

HIV infection is diagnosed using a serological test for anti-HIV. Note that HIV viral load is not a screening test for HIV infection. HCV-infected people should be screened for HIV infection, particularly when a treatment for HCV infection is being considered.

ASSESSMENT OF COINFECTIONED PATIENTS

The baseline assessment and follow-up for HIV includes CD4 lymphocyte quantitation and HIV viral load testing. HIV plasma viral load testing and CD4 lymphocyte quantitation

TABLE 2
The METAVIR scoring system taking into account inflammatory activity and fibrosis

Activity	Grade	Fibrosis	Stage
No activity	A0	No fibrosis	F0
Minimal activity	A1	Portal fibrosis without septa	F1
Moderate activity	A2	Portal fibrosis and some septa	F2
Severe activity	A3	Septal fibrosis without cirrhosis	F3
		Cirrhosis	F4

Histology activity index – Knodell scoring system*

Periportal ± bridging necrosis	Score	Intralobular degeneration and focal necrosis	Score	Portal inflammation	Score	Fibrosis	Score
None	0	None	0	No portal inflammation	0	No fibrosis	0
Mild piecemeal necrosis	1	Mild (acidophilic bodies, ballooning degeneration and/or scattered foci of hepatocellular necrosis in 1/3 of lobules or nodules)	1	Mild (sprinkling of inflammatory cells in <1/3 of portal tracts)		Fibrous portal expansion	1
Moderate piecemeal necrosis (involves <50% of the circumference of most portal tracts)	3	Moderate (involvement of 1/3–2/3 of lobules or nodules)	3	Moderate (increased inflammatory cells in 1/3–2/3 of portal tracts)	3	Bridging fibrosis (portal-portal or portal-central linkage)	3
Marked piecemeal necrosis (involves >50% of the circumference of most portal tracts)	4	Marked (involvement of >2/3 of lobules or nodules)	4	Marked (dense packing of inflammatory cells in >2/3 of portal tracts)	4	Cirrhosis	4
Moderate piecemeal necrosis plus bridging necrosis	5						
Marked piecemeal necrosis plus bridging necrosis	6						
Multilobular necrosis	10						

*Total hepatic histology activity index (Knodell score) = $\times/22$. Data from references 44 and 45

should be performed at the time of HIV diagnosis and every three to six months thereafter in untreated people. Recommendations for HIV monitoring, treatment and patient management are extensively covered in the literature (39-41).

In addition to HIV-specific biological parameters, monitoring of a coinfecting individual can include many other laboratory and imaging tests as determined on a case-by-case basis.

Patients with clinical signs of liver failure or cirrhosis can be classified into stage A, B or C using the Child-Pugh scale, which considers biochemical markers, as well as the presence or absence of ascites or encephalopathy. A score from 1 to 3 is attributed to each of the parameters, and the total determines the Child-Pugh stage (42). The stage determines the five-year survival prognosis: 80% for stage A, 50% for stage B and 20% for stage C. Clinicians should be aware that the Child-Pugh score may be artificially high in HIV-infected patients receiving atazanavir- or indinavir-containing regimens. These patients may have increased total serum bilirubin levels on the basis of impaired glucuronidation, which is not indicative of liver disease.

If the coinfecting patient can potentially be treated for HCV (see indications and contraindications below), the assessment should be more thorough and should include:

- HCV genotyping, which provides an indication of the sensitivity to treatment. (There are at least six HCV genotypes [43]. Genotype 1 is the most frequent in Canada.)
- Liver biopsy. The findings of a liver biopsy are interpreted based on semiquantitative criteria of the degree of inflammatory activity, hepatocellular necrosis and fibrosis.

There are at least four histological scores for inflammation and fibrosis – the METAVIR, the Knodell, the Ishak and the Scheuer scores are the most used (44,45). Table 2 shows an example of the METAVIR and the Knodell scoring systems. Interpretation of biopsy findings must be discussed with a HCV treatment specialist. Note that a liver biopsy is useful but not essential to the decision of whether to treat; its indication is controversial, particularly in the presence of a recent infection or an HCV genotype 2 or 3 infection. The higher rate of efficacy in treating HCV of these two genotypes makes the decision of whether to treat less dependent on biopsy results.

Warning signs of liver disease

Assessment by an expert is recommended when the following warning signs are present:

- Persistent increase in aspartate aminotransferase levels or alanine aminotransferase (ALT) levels to more than 10 times the upper limit of normal;
- Signs of liver failure (spider angioma in the cava territory, palmar erythema, jaundice, hepatic encephalopathy, white nails, clubbing and ascites);
- Signs of portal hypertension (gastrointestinal bleeding, splenomegaly, abdominal portal systemic collateral venous circulation and ascites); and
- Signs of cirrhosis decompensation (jaundice, ascites and hepatic encephalopathy).

Patients with biopsy-proven cirrhosis should be monitored more closely.

TABLE 3
Monitoring tests

Frequency	Workup for HCV	Additional workup in case of proven or suspected cirrhosis	Additional workup specific to HIV
Baseline	CBC, AST, ALT, alkaline phosphatase, bilirubin, GGT, albumin, creatinine, INR, HCV RNA, HBsAg, anti-HBs, anti-HBc, IgG, liver biopsy, alpha-fetoprotein, liver ultrasound	Gastroscopy	CD4 lymphocyte quantitation, HIV viral load, HIV genotyping testing for antiretroviral resistance
Every 3 to 6 months	CBC, AST, ALT, alkaline phosphatase, bilirubin, GGT, albumin, creatinine, INR	Alpha-fetoprotein	CD4 lymphocyte quantitation, HIV viral load
Every 6 months		Alpha-fetoprotein, liver ultrasound (can be performed more often if alpha-fetoproteins increase)	
Every 2 to 5 years		Liver biopsy	Gastroscopy

Repeat every month for the first three months after starting anti-HIV therapy in coinfecting patients. ALT Alanine aminotransferase; AST Aspartate aminotransferase; CBC Complete blood count; GGT Gamma-glutamyl transferase; HBc Hepatitis B core; HBsAg Hepatitis B surface antigen; IgG Immunoglobulin G; INR International normalized ratio

Lifestyle recommendations

Screening for alcohol problems is extremely important, with the goal being complete abstinence. Alcohol consumption should be minimized and should not exceed 50 g/day. Another lifestyle issue to consider is the degree of adherence to anti-retroviral treatment; steps should be taken to optimize adherence. Steps should also be taken to prevent HCV reinfections because prior infection does not confer protective immunity. Finally, it is imperative to provide weight maintenance counselling, because weight gain can lead to faster development of fibrosis in the presence of fatty liver (46).

Assessment of psychological and social stability

The psychological and social assessment and case management of coinfecting patients involves several important aspects. First, these patients should all undergo screening for mental health problems, because untreated psychosis and depression with suicidal ideation are contraindications to interferon (IFN) treatment, and a history of severe depression can sometimes be a relative contraindication for treatment.

Addictions are also a key consideration; one should aim for psychological and social stabilization, which, in cases of active addiction, can be assessed via the following elements:

- Having stable lodging;
- Being able to cooperate in a context of care;
- Keeping appointments and taking medication as prescribed;
- Having access to drug insurance and providing for essential needs – food, hygiene and transportation;

- Evaluating, informing and involving the support network with respect to side effects of medications;
- Promoting awareness of friends and family as to the impact of treatment; and
- Assessing the patient's motivation to follow the treatment program.

Vaccination

People with HCV-HIV coinfection should be protected against other viral or bacterial infections. Of particular importance are hepatitis B virus, hepatitis A virus, influenza and pneumococcus (27,47-50). Clinicians should note that the immunogenicity of most vaccines is reduced in the HIV-infected population. Serological testing should be performed first to identify the presence of pre-existing antibody and/or those who are susceptible. However, vaccination should not be delayed when exposure can be predicted, particularly in IDUs.

MONITORING OF COINFECTED PERSONS

In Canada, more than 70% of HCV-infected people have a history of injection drug use (14). Although it would be appropriate to treat many of these patients for HIV and/or HCV, in actual fact, only a few are treated particularly for HCV.

Active consumption of illicit psychotropic substances for recreational use can lower the chances of responding to treatment, because adherence is often reduced. Drug or alcohol consumption should not, however, be an absolute contraindication to treatment. The decision to initiate treatment should be made on an individual basis.

Adverse or toxic effects should be minimized, and drug interactions should be avoided if possible. Physical, psychological and social needs also have to be met, not only at the beginning, but throughout treatment.

The monitoring of a coinfecting person is complex. Several tests are indicated for the optimal monitoring of patients with HCV and those with HCV-HIV coinfection. Table 3 shows these tests and their optimal frequency.

Optimal monitoring is achieved when there is access to a multidisciplinary health team with experience in considering HIV, HCV, addiction, mental health, nutrition, and psychological and social aspects.

WHICH INFECTION TO TREAT FIRST

It is not recommended to begin HIV and HCV treatments simultaneously due to their complexity and overlapping drug toxicities. Clinical experience has shown that adherence is better when treatments are introduced separately. The efficacy of and tolerance to a single treatment should be determined before beginning another.

Ideally, treatment of HCV should be initiated before anti-HIV treatment to decrease the risk of hepatotoxicity of anti-HIV medication, to decrease the potential risks of hepatic decompensation during immune reconstitution syndrome, and to avoid overlapping drug toxicity between anti-HIV and HCV treatments.

HCV treatment should be initiated before HIV therapy when the HIV infection is stable and does not require immediate therapeutic intervention. This is usually the case when the CD4 cell count is higher than 350 cells/ μ L.

Treating HIV first is clearly indicated when the CD4 lymphocyte count is very low (less than 200 cells/ μ L). In some

cases, however, when CD4 counts are between 200 cells/ μ L and 350 cells/ μ L, antiretroviral treatment can be delayed, particularly in the absence of opportunistic infections or markers of rapid progression (elevated viral load or clinical symptoms). The caregiving team needs to evaluate the risks and benefits of treating HIV or HCV first on a case-by-case basis.

TREATMENT OF HCV

The relevance of treating HCV should be considered for each coinfecting patient. The decision of whether to treat must be made on an individual basis, considering the risk of progression of liver disease, the possibility of response to treatment, the risk of side effects, and the patient's condition and motivation (51).

When the decision to treat is taken, additional tests are called for to assess response to treatment and side effects, including quantitative HCV RNA and HCV genotype.

HCV treatment is contraindicated in certain cases. Absolute contraindications include (52,53):

- Pregnancy, breastfeeding or the inability to use an effective means of contraception;
- Hypersensitivity to IFNs, ribavirin (RBV) or excipients in the medication;
- Active autoimmune disease, such as uncontrolled thyroid diseases or autoimmune hepatitis;
- Kidney failure with a creatinine clearance of less than 50 mL/min (in these cases, pegylated [PEG] IFN- α -2a-based treatment without RBV can be considered with dose reduction if the creatinine clearance is less than 20 mL/min); and
- Decompensated liver disease.

Relative contraindications include:

- Problems with taking medication and keeping medical appointments;
- Major uncontrolled depression and repeated suicide attempts – a psychological evaluation is necessary to assess suicide risk;
- An uncontrolled psychotic state – if the psychosis is stable, HCV treatment may be undertaken if there is appropriate follow-up;
- Severe coronary and valvular heart disease;
- Uncontrolled epilepsy;
- Retinopathy;
- Platelet count less than $50,000 \times 10^9/L$;
- Neutropenia less than $750 \times 10^9/L$;
- Severe anemia – hemoglobin (Hb) level lower than 100 g/L; and
- CD4 count less than 200 cells/ μ L.

To consider a treatment for HCV, liver biopsy is highly desirable (2). It should show significant damage – for example, a METAVIR score of F2 or higher, or equivalent (Table 2). Studies have shown that anti-HCV therapy treatment response is reduced in the presence of hepatic cirrhosis (54). Some authors believe that due to the prognosis of HCV in coinfection, treatment can be justified even in patients with little histological damage (55). The patient's refusal to undergo a biopsy is not in itself a contraindication to treatment. This is

TABLE 4
Pegasys RBV* (pegylated interferon alpha-2a) and COPEGUS† (ribavirin) doses

Genotype	Pegasys dose weekly	Ribavirin dose daily
1 or 4	180 μ g	Weight <75 kg = 1000 mg/day Weight \geq 75 kg = 1200 mg/day
2 or 3	180 μ g	800 mg (regardless of weight)

*Hoffmann-La Roche Ltd, Canada; †Hoffmann-La Roche Inc, USA

Pegetron* (pegylated interferon-alpha-2b) and ribavirin doses

Weight (kg)	Pegetron RediPen* or vial strength to use	Amount of Pegetron to administer weekly (μ g)	Volume of Pegetron to administer weekly (mL)	Ribavirin dose to administer daily (mg)
<40	50 μ g/0.5 mL	50	0.5	800
40–<50	80 μ g/0.5 mL	64	0.4	800
50–<64	80 μ g/0.5 mL	80	0.5	800
64–<75	120 μ g/0.5 mL	96	0.4	1000
75–<85	120 μ g/0.5 mL	120	0.5	1000
\geq 85	150 μ g/0.5 mL	150	0.5	1200

*Schering-Plough Canada Inc

even truer for patients with a genotype 2 or 3 HCV infection because of the good response rate in these cases.

In cases of acute HCV infection (less than six months), studies (56) have reported very high response rates for mono-infection (98%). There are little similar published data for coinfection (57,58). However, in the presence of acute HCV infection and when not contraindicated, treatment should be initiated quickly, without a liver biopsy, as soon as possible following the 12-week postdiagnosis period (symptoms or viremia outbreak). Chances of spontaneous disappearance of HCV infection are low after 12 weeks.

Treatment of HCV infection

The most effective known treatment for HCV is PEG IFN with RBV. There are two formulations marketed in Canada.

1) Pegasys RBV (Hoffmann-La Roche Ltd, Canada): It consists of PEG IFN- α -2a at a fixed dose of 180 μ g, once a week, associated with RBV. For genotype 1 or 4, RBV is given at a daily weight-adapted dose of 1000 mg for people weighing less than 75 kg and 1200 mg for people weighing 75 kg or more. For genotype 2 or 3, the dose of RBV is 800 mg (regardless of weight) (Table 4) (52).

2) Pegetron (Schering-Plough Canada Inc): It consists of PEG IFN α -2b administered in variable doses based on weight 1.5 μ g/kg (as a subcutaneous injection once a week), with a variable oral dose of between 800 mg/day and 1200 mg/day of RBV based on weight (Table 4) (53).

There are no comparative studies showing whether one of the PEG IFN/RBV formulations available is more effective than the other for coinfection. In December 2005, Health Canada approved Pegasys RBV formulation for use in HIV-HCV coinfecting patients with a RBV dose of 800 mg (52). However, clinical studies following pivotal trials have demonstrated superior results with increased doses of RBV. RBV doses of between 1000 mg/day and 1200 mg/day (based on weight) as used in monotherapy are, therefore, recommended when tolerated (51,59,60).

TABLE 5
Summary of sustained virological response in arms treated with pegylated interferon-alpha (PEG IFN- α) + ribavirin (RBV) in HIV-hepatitis C virus (HCV) coinfecting patients compared with HCV monoinfected patients

Study (reference)	Treatment population	n	RBV dose (mg)		Length of treatment (weeks)	Genotype 1 response (%)	Genotype 2 + 3 response (%)
			PEG	IFN			
CLINIVIC, Laguno et al (60) [†]	Coinfected	52	800/1200	α -2b	48	38*	53
RIBAVIC-ANRS (61)	Coinfected	412	800	α -2b	48	17	44
APRICOT (54)	Coinfected	289	800	α -2a	48	29	62
ACTGA5071 (62)	Coinfected	67	600/1000	α -2a	48	14	73
Hadziyannis et al (63)	Monoinfected	361	800	α -2a	48	41	79
	Monoinfected	436	1000/1200	α -2a	48	52	80
Fried et al (87)	Monoinfected	1121	1000/1200	α -2a	48	46	76
Manns et al (88)	Monoinfected	1530	1000/1200	α -2b	48	42	82

*Genotype 1 and genotype 4 patients combined. ACTG AIDS Clinical Trial Group; APRICOT AIDS Pegasys Ribavirin International Co-infection Trial; ANRS Agence nationale de recherches sur le sida

Studies (54,60-62) have shown that response to HCV treatment is reduced in coinfecting patients. HCV is treated for 48 weeks, regardless of genotype, in the setting of coinfection. For mono-infection, the duration of treatment depends on the genotype. Genotype 2 or 3 is treated for 24 weeks and genotype 1 or 4 is treated for 48 weeks.

HOW TO EVALUATE THE RESPONSE TO TREATMENT

Response to treatment is evaluated at different follow-up stages:

- Early virological response (EVR) – negative qualitative HCV RNA test or two-log₁₀ decrease at 12 weeks in quantitative HCV RNA, followed by a negative qualitative HCV RNA test at week 24 (54);
- End-of-treatment virological response (ETR) – negative qualitative HCV RNA test at 48 weeks; and
- Sustained virological response (SVR) – negative qualitative HCV RNA test 24 weeks after the end of treatment (week 72) and sustained normal liver enzyme values.

HCV treatment efficacy is reduced in the presence of coinfection. Recent studies (54,60-62) have compared coinfecting patient treatment efficacy with that of mono-infected patients (Table 5) (54,62,63). In coinfecting patients, HCV treatment efficacy varies between 14% and 38% for genotype 1, compared with between 41% and 52% in mono-infections. For genotypes 2 and 3, efficacy is between 44% and 73%, compared with approximately 80% in mono-infected patients.

Treatment efficacy and indication to continue treatment for 48 weeks with PEG IFN plus RBV are evaluated as a function of kinetic viral response (HCV viral clearance) at 12 weeks. Before starting treatment, quantitative (viral load) testing of HCV

RNA must be performed. After 12 weeks of treatment, HCV RNA qualitative and quantitative testing must be repeated. Quantitative RNA testing is only to be performed if qualitative RNA is positive.

A negative qualitative HCV RNA at week 12 or a minimal two-log decrease in HCV RNA from initiation of anti-HCV therapy is required to continue treatment (54). If qualitative polymerase chain reaction is still positive at week 12, a quantitative HCV RNA viral load test should be performed. If the quantitative viral load shows a two-log decrease (100 times) compared with baseline, treatment should be continued and a qualitative HCV RNA test should be performed at week 24 to ensure that results are negative (54). If the quantitative HCV RNA viral load has not decreased by more than two-log, treatment should be discontinued. The probability of virological response in these cases is less than 2% (54).

HCV relapse is defined by a repositivation of qualitative HCV RNA at week 72 in the absence of clinical factors indicative of possible reinfection.

PROPOSED MONITORING AT THE BEGINNING OF AND DURING TREATMENT

An electrocardiogram should be performed in patients older than 50 years of age or in those with risk factors for arteriosclerotic heart disease. A chest x-ray and a tuberculin skin test (baseline purified protein derivative) should be performed in all patients who have not previously had these tests completed as part of their baseline HIV assessment. In general, medical visits should be scheduled for every 15 days for the first two months and every month thereafter. Frequency and monitoring are suggestions and can be adapted on a case-by-case basis. At the first visit, the patient should undergo a CD4/CD8 profile and HIV viral load test. At each visit, a complete blood count (CBC) should be performed, and electrolyte, glucose, creatinine, bicarbonate, aspartate aminotransferase, ALT, alkaline phosphatase, gamma-glutamyl transferase, bilirubin, albumin, amylase and uric acid levels should be measured. Once a month, a CD4/CD8 profile and a urinalysis should be performed. Also, venous lactic acid should be measured in the presence of symptoms of lactic acidosis or lowered bicarbonates. Once every three months, thyroid-stimulating hormone, HIV viral load and amylase should be measured and a fasting lipid profile should be obtained. Table 6 shows a representation of an optimal monitoring regimen.

Adverse effects of PEG IFN and RBV treatment

There are many common side effects of PEG IFN and RBV treatment. General symptoms include flu-like symptoms characterized by discomfort, joint pain, headaches, fever, weight loss and alopecia. Psychiatric and neurological symptoms can include irritability, anxiety, insomnia, depression and psychosis; there can also be convulsions, ototoxicity, neuropathy and altered vision (for symptoms that suggest retinal alteration, refer for urgent ophthalmology consultation).

Cutaneous symptoms are also common, such as eruptions, pruritus, dryness and local inflammation at the injection site. Many patients experience gastrointestinal symptoms such as anorexia, nausea, diarrhea, abdominal cramps and pancreatitis. Hematological effects include neutropenia, thrombocytopenia and anemia. Cardiovascular or pulmonary complications may also arise such as hypotension, arrhythmia, myocardial infarction, cardiomyopathy or pulmonary edema. Finally, there

are several autoimmune or renal adverse effects associated with PEG IFN and RBV treatment, such as thyroid dysfunction, vasculitis, arthritis, proteinuria and electrolyte imbalance.

Complications associated with treatment of HCV in coinfection and their management

1. Flu-like symptoms: Acetaminophen can be used up to a maximum dose of 1000 mg orally, four times a day, as needed. Other options include hydration and nonsteroidal anti-inflammatory drugs.
2. Insomnia: Oxazepam, temazepam or lorazepam can be used as needed. Other benzodiazepines are metabolized in the liver and can have interactions with HIV protease inhibitors.
3. Rash: 10 mg to 25 mg of hydroxyzine taken orally, three times daily, can be used as needed. This medication also has a sedating effect that can be helpful at bedtime.
4. Depression: If depression develops during PEG IFN plus RBV treatment, the usual therapeutic options can be used. A psychiatric assessment is always preferable, with a joint follow-up during treatment if possible. HCV treatment should be discontinued in cases of de novo psychosis, hallucinations, significant paranoia, suicide attempts or ideation, and an emergency psychiatric opinion should be obtained. Antidepressants are often helpful or necessary. It is best to avoid bupropion.
5. Hematological impact: Interventions should be based on individual product monographs with respect to hematological complications and dose adjustments.

In general, the following interventions are recommended. Furthermore, adjustments may vary on a case-by-case basis, based on the individual treating physician's experience:

- 5a. Thrombocytopenia (less than $50,000 \times 10^9/L$): This mainly appears at the beginning of treatment. PEG IFN dosage may be reduced by 25% to 50%, and a CBC should be performed every 15 days. Treatment should be discontinued if thrombocytopenia does not improve despite reduced doses, if there are hemorrhagic complications or if the platelet count is less than $20,000 \times 10^9/L$.
- 5b. Neutropenia: If the neutrophil count drops to less than $750 \times 10^9/L$, PEG IFN dosage may be reduced by 25% to 50% and the neutrophil count should be retested every seven to 15 days. If the neutrophil count is less than $500 \times 10^9/L$, options are to reduce the dose of PEG, discontinue treatment or administer granulocyte-colony stimulating factor – filgrastim (Neupogen, Amgen Canada Inc), 5 µg/kg, subcutaneously, two or three times per week.
- 5c. Anemia: The combination of azidothymidine (AZT) (64) and RBV increases the risk of developing anemia. RBV in association with tenofovir or abacavir is better tolerated. These latter options reduce hematological toxicity caused by RBV and allow for optimal dosing for successful therapy. If anemia is present from the start, AZT can be replaced with another nucleoside reverse transcriptase inhibitor (NRTI) such as abacavir or tenofovir when possible (absence of resistance or intolerance), before the start of HCV treatment.
In patients who develop anemia during treatment, the following can be considered on a case-by-case basis,

TABLE 6
Monitoring of coinfecting patients before and during treatment of hepatitis C virus (HCV) infection

Test	Start	2	4	6	8	10	12	16	20	24	28	32	34	36	40	44	48	60	72	
ECG	•																			
Chest x-ray	•																			
Qualitative HCV RNA	•						•				•*								•	•†
Quantitative HCV RNA	•						•‡													
CD4/CD8	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
HIV RNA	•						•				•				•				•	•
CBC	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Electrolytes	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Glucose	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Creatinine	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Bicarbonates	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
AST/ALT	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
ALKP/GGT	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Bilirubin	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Albumin	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Amylase	•						•				•				•				•	•
Chol/TGs	•						•				•				•				•	•
Lactic acid	Do this test if bicarbonates are low or in presence of symptoms																			
TSH	•						•				•				•					
Urinalysis	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Pregnancy test§	•																			

*Must be performed if qualitative HCV RNA is positive at week 12 and if there was a two-log₁₀ drop in quantitative HCV RNA at week 12 to determine whether treatment must be continued; †Must be performed if qualitative HCV RNA is negative at week 48 to confirm sustained response; ‡Must be performed if qualitative HCV RNA is positive at week 12; §Ensure proper contraception is used while under treatment. ALKP Alkaline phosphatase; ALT Alanine aminotransferase; AST Aspartate aminotransferase; CBC Complete blood count; Chol/TG Cholesterol/triglycerides; ECG Electrocardiogram; GGT Gamma-glutamyl transferase; TSH Thyroid-stimulating hormone

taking into consideration the baseline Hb level, the rate of fall, and the presence or absence of symptoms:

- Switch AZT for another NRTI.
- In patients with stable cardiac disease or chronic obstructive pulmonary disease, if the drop in Hb level is greater than 20 g/L or if the Hb level drops below 100 g/L in any patient, the RBV dose should be reduced in 200 mg increments (one capsule) and CBC should be monitored every seven to 14 days. RBV dose can be reduced in this way, to a minimum of 600 mg/day.
- If the Hb level falls below 85 g/L despite AZT discontinuation, RBV dose reduction, and/or use of recombinant erythropoietin (Eprex, Janssen-Ortho Inc, Canada) or darbepoetin (Aranesp, Amgen Canada Inc), RBV should be discontinued.
- In the absence of response or if the anemia gets worse, other causes of anemia must be investigated (bleeding or bone marrow involvement), and recombinant erythropoietin can be administered subcutaneously two to three times a week (50 U/kg to 100 U/kg) to a maximum of 40,000 U/kg per week. Some authors recommend usage of recombinant erythropoietin before reducing the RBV dose to increase the chance of successful HCV treatment (64,65).

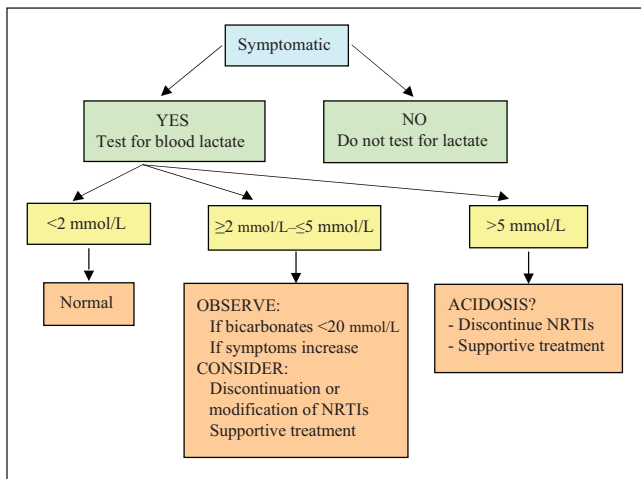


Figure 1) Investigation and treatment of hyperlactatemia. Adapted from reference 66. NRTIs Nucleoside reverse transcriptase inhibitors

6. If the CD4 count decreases to less than 200 cells/ μ L, prophylactic anti-*Pneumocystis jirovecii* (*carinii*) treatment must be initiated. The relative percentage of CD4 cells is not impacted much by HCV treatment, and the risk of developing an opportunistic infection is low. It is not clear whether IFN-driven decreases in CD4 count below 200 cells/ mm^3 , unassociated with a fall in CD4 percentage, are associated with any increase in opportunistic infections in general or in *P jirovecii* pneumonia in particular. Hence, it is not clear whether instituting *P jirovecii* pneumonia prophylaxis for such patients is essential. HCV treatment can be discontinued if opportunistic infections arise.
7. If the HIV viral load increases (rare occurrence), the patient's adherence to treatment must be checked and the merits of the following discussed with an HIV expert:
 - Observe only;
 - Introduce an antiretroviral treatment; and
 - Modify an antiretroviral treatment, if applicable.
8. Hypo- or hyperthyroidism: This complication does not usually require HCV treatment to be discontinued. Thyroxin substitution treatment is indicated in the presence of hypothyroidism. If hyperthyroidism is present, subacute thyroiditis, or more rarely, Graves disease, may be the cause. Diagnosis is made using a radioactive iodine scan and a thyroid-stimulating hormone receptor antibody test. Follow-up with an endocrinologist is recommended if required.
9. Lactic acidosis: Lactic acidosis is a rare complication of HIV treatments attributable to NRTI mitochondrial toxicity, resulting in depletion of mitochondrial DNA. Of 1000 people taking NRTIs, the frequency is approximately four to five people per year (66). Symptoms are nonspecific. Patients consult for significant general malaise, with lack of appetite, nausea, vomiting, weight loss, severe asthenia, dyspnea, cardiac arrhythmia and abdominal pain. These manifestations have been described mainly in women with fatty liver on stavudine, didanosine (ddI) or both (67,68). They result from the toxicity of medication on the mitochondria, which prevent these organelles from breaking down glucose via the usual metabolic pathways, resulting in excess production of lactic acid. The diagnosis is made in

the presence of metabolic acidosis and an increase in blood lactic acid levels to more than 5 mmol/L. In the presence of symptoms, an increase in lactic acidemia to between 2 mmol/L and 5 mmol/L points to the possibility of this diagnosis in certain cases (Figure 1) (66). It should be noted that increases in blood lactic acid levels are common. Between 15% and 35% of patients treated with NRTIs may present asymptomatic hyperlactatemia (66), which is not predictive of lactic acidosis arising later (69). When interpreting an elevated lactic acid level, the patient's symptoms, blood bicarbonate levels and, if required, arterial gas analysis results must be taken into account. Blood for lactic acid testing is drawn without a tourniquet and sent immediately to the laboratory on ice. Unless the diagnosis is probable or certain, and discontinuation of treatment is an emergency, an HIV expert should be consulted before modifying or stopping antiretroviral therapy. It is believed that RBV may potentiate the mitochondrial toxicity of certain NRTIs (65,70), which is why the concomitant administration of ddI is avoided and stavudine-based (d4T) therapies are used with caution. Routine lactate testing is not recommended because of complexities associated with specimen collection, as well as the sensitivity and specificity limits of this marker.

10. Acute pancreatitis: There is an increased risk of pancreatitis in patients receiving ddI and the combination of PEG IFN with RBV. Some hepatic decompensation episodes have occurred in cirrhotic patients receiving RBV and ddI (71); concomitant use of ddI was identified as a strong independent risk factor for hepatic decompensation in patients with HIV-HCV coinfection receiving anti-HCV treatment (71).
11. Hepatic decompensation: In case of evidence of hepatic decompensation, HCV treatment should be discontinued (52,53).

Hepatotoxicity, HCV and HIV antiretroviral agents

Most coinfecting patients present elevated ALT levels to a certain degree after starting anti-HIV treatment. As many as 12% of patients develop severe hepatotoxicity (ALT levels greater than 10 times the upper limit of normal) (34,72-74). Table 7 shows recommendations for the use of antiretrovirals in cases of hepatotoxicity.

Intervention in cases of hepatotoxicity

It is essential, particularly in coinfecting patients, to carefully monitor liver function after introducing a new HIV antiretroviral agent (see complications below). Transaminases should be tested every month for the first three months and every three months thereafter. If ALT levels increase, other potential causes should be investigated, such as alcohol or cocaine use, acute or chronic hepatitis B, hepatitis A, opportunistic diseases or the hepatotoxicity of a concomitant medication. Interruption of HIV antiretroviral treatment may be required if there are symptoms or in cases of severe hepatitis. Reintroduction should be performed with caution due to the risk of hepatotoxicity recurring. Eradicating HCV virus before initiating HIV treatment can improve tolerance to antiretrovirals and should be considered in coinfecting people with a CD4 count higher than 350 cells/ μ L (2).

An algorithm for the management of hepatotoxicity is presented in Figure 2 (75).

TABLE 7
Antiretroviral dose adjustment in patients with hepatic insufficiency

Medication	Hepatic metabolism	Dose adjustment required in liver failure
Nucleoside/Nucleotide reverse transcriptase inhibitors		
Abacavir	Yes	No recommended in patients with moderate to severe impairment Child-Pugh score (dose): 5-6 (200 mg twice a day)
Zidovudine	Yes	No dosage adjustment
Lamivudine	No	No dosage adjustment
Didanosine	No	No dosage adjustment
Stavudine	No	No dosage adjustment
Emtricitabine	No	No dosage adjustment
Tenofovir	No	No dosage adjustment
Non-nucleoside reverse transcriptase inhibitors		
Delavirdine	Yes	No dosage adjustment; use with caution in patients with hepatic impairment
Efavirenz	Yes	No dosage adjustment; use with caution in patients with hepatic impairment
Nevirapine*	Yes	Avoid initiation in women with a CD4 count >250 cells/ μ L or in men with a CD4 count >400 cells/ μ L; if initiated, close monitoring is recommended (every 2 weeks for the first month, then monthly for 3 months, then every 3 months)
Protease inhibitors		
Atazanavir [†]	Yes	Child-Pugh score (dose): 7-9 (300 mg every day) >9 (not recommended)
Fosamprenavir	Yes	Child-Pugh score (dose): 5-8 (700 mg twice a day) 9-12 (not recommended)
Indinavir [†]	Yes	Mild to moderate hepatic insufficiency because of cirrhosis: 600 mg q8h
Nelfinavir	Yes	No dosage adjustment; use with caution in patients with hepatic impairment
Saquinavir	Yes	No dosage adjustment; use with caution in patients with hepatic impairment
Lopinavir/ritonavir	Yes	No dosage adjustment; use with caution in patients with hepatic impairment
Tipranavir	Yes	No dosage adjustment; use with caution in patients with hepatic impairment. TPV/RTV is contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh classes B and C)
Darunavir	Yes	No data with patients with hepatic impairment; use with caution in this population
Fusion inhibitors		
Enfuvirtide (T-20)	No	No dosage adjustment

*Reported cases of severe fulminant hepatitis and death – use not recommended in cases of liver failure; [†]Associated with unconjugated hyperbilirubinemia – refer to product monograph. q8h Every 8 h; TPV/RTV Tipranavir/ritonavir. Data from reference 79

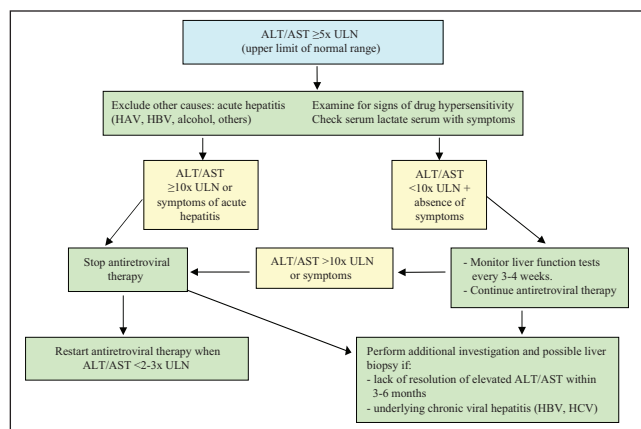


Figure 2) Clinical management of severe hepatotoxicity. Adapted from reference 75. ALT Alanine aminotransferase; AST Aspartate aminotransferase; HAV Hepatitis A virus; HBV Hepatitis B virus; HCV Hepatitis C virus; ULN Upper limit of normal

Antiretroviral metabolism

It has been shown that chronic liver disease can affect the pharmacokinetics of some anti-HIV agents. Increases in the plasma concentrations of most non-NRTIs and protease inhibitors have been reported with varying degrees of liver dysfunction (40,80-84). In some cases, these increases have been linked to toxicity (83). Therapeutic drug monitoring can possibly be helpful when available.

HIV medication to avoid while treating HCV

ddI is the only antiretroviral contraindicated during HCV treatment due to its increased toxicity in the presence of RBV. RBV has potentiated the antiretroviral effect of ddI in vitro and in animals by increasing the formation of the active triphosphate anabolite (ddATP). This observation raised the possibility that concomitant administration of RBV and ddI could increase the risk of adverse reactions to ddI (eg, peripheral neuropathy, pancreatitis and fatty liver accompanied by lactic acidosis). Increased frequency of pancreatitis and lactic acidosis has been observed with the coadministration of ddI and RBV (51,54,85,86).

The coadministration of zidovudine (AZT) and RBV has been associated with a greater risk of anemia (86). AZT is relatively contraindicated during the treatment of HCV; when used, it must be closely monitored. It is recommended that patients be switched to a nonzidovudine-containing regimen if at all possible.

The use of d4T with RBV increases the risk of lactic acidosis; particular attention should be paid to symptoms of hyperlactatemia or lactic acidosis (51,54).

CONCLUSIONS

Advances in the treatment of HCV using combined PEG IFN and RBV offer the possibility of eradicating HCV infection in coinfecting people. Due to the risk for hepatic morbidity associated with HCV infection in HIV-positive people, HCV eradication treatment must be considered in all cases in which there is no contraindication. Intensive management of the side effects of HCV treatment is one of the factors for the success of these therapies. HCV eradication is predicted to decrease the mortality associated with coinfection and reduce the toxicity of HIV treatment.

NOTES: Pegasys RBV is a trademark of Hoffmann-La Roche Ltd Canada, Pegatron is a trademark of Schering-Plough Canada Inc and Exprex is a trademark of Janssen-Ortho Inc, Canada.

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