

CIHR Canadian HIV Trials Network Coinfection and Concurrent Diseases Core: Canadian guidelines for management and treatment of HIV/hepatitis C coinfection in adults

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BACKGROUND: Hepatitis C virus (HCV) coinfection occurs in 20% to 30% of Canadians living with HIV, and is responsible for a heavy burden of morbidity and mortality. HIV-HCV management is more complex due to the accelerated progression of liver disease, the timing and nature of antiretroviral and HCV therapy, mental health and addictions management, socioeconomic obstacles and drug-drug interactions between new HCV direct-acting antiviral therapies and antiretroviral regimens.

OBJECTIVE: To develop national standards for the management of HCV-HIV coinfection in adults in the Canadian context.

METHODS: A panel with specific clinical expertise in HIV-HCV co-infection was convened by The CIHR HIV Trials Network to review

current literature, existing guidelines and protocols. Following broad solicitation for input, consensus recommendations were approved by the working group, and were characterized using a Class (benefit versus harm) and Level (strength of certainty) quality-of-evidence scale.

RESULTS: All HIV-HCV coinfection individuals should be assessed for HCV therapy. Individuals unable to initiate HCV therapy should initiate antiretroviral therapy to slow liver disease progression. Standard of care for genotype 1 is pegylated interferon and weight-based ribavirin dosing plus an HCV protease inhibitor; traditional dual therapy for 24 weeks (for genotype 2/3 with virological clearance at week 4); or 48 weeks (for genotypes 2-6). Therapy deferral for individuals with mild liver disease may be considered. HIV should not be considered a barrier to liver transplantation in coinfection patients.

DISCUSSION: Recommendations may not supersede individual clinical judgement.

Key Words: Antivirals; Direct-acting antivirals; HCV; HIV; Pharmacokinetics

PROCESS STATEMENT

The concept for the HIV-HCV coinfection guidelines was originated and developed by CC, MK and MH, with CIHR Canadian HIV Trials Network (CTN) and Canadian Association for HIV Research (CAHR) support. All authors contributed to the literature review, writing, editing and final approval (April 2013) of the document. External input was obtained from academic and community-based stakeholder organizations and individuals by a CIHR CTN/CAHR lead online posting of the draft guidelines (March and April 2013) and a CIHR Meeting, Planning and Dissemination Grant-supported HIV-HCV Co-Infection Guidelines Symposium, held April 12, 2013, during the 22nd Annual CAHR Conference (Vancouver, British Columbia).

INTRODUCTION

Continued improvements in combination antiretroviral therapy (ART) have resulted in sustained gains in projected life expectancy for HIV-infected individuals (1). Long-term management of HIV now increasingly requires assessment and appropriate interventions for comorbid conditions that may impact long-term morbidity and mortality to a greater extent than HIV infection itself. Mortality secondary to chronic hepatitis C virus (HCV) infection has now surpassed that of HIV in the United States (2) in general, and is a cause of

significant mortality in coinfection individuals in the ART era (3). Management of HIV-HCV coinfection individuals is more complex relative to HIV mono-infected patients, with issues related to accelerated progression of liver disease, timing and nature of ART and HCV therapy, addictions management and, with the advent of direct-acting antiviral agents (DAAs) for HCV therapy, increasing potential for clinically significant drug-drug interactions with ART regimens. To develop national standards for the management of coinfection individuals, the CIHR Canadian HIV Trials Network convened a panel of physicians and pharmacists with specific expertise in HIV-HCV coinfection, who were tasked with reviewing current literature, existing guidelines and protocols, and adapting them to a Canadian context. The present document reflects the consensus recommendations of this panel and was approved by the committee at large. In an effort to characterize the quality of evidence supporting these recommendations, a Class (reflecting benefit versus harm) and Level (assessing strength of certainty) of evidence scale was used. This system was used for recent Canadian Association for the Study of the Liver guidelines for HCV and HBV management (4,5) (Table 1). These recommendations are intended to aid clinicians in the management of the coinfection patient but may not supersede individual clinical judgement. A summary of these recommendations can be found on page 231.

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TABLE 1
Grading system for recommendations

Class/Grade	Classification description
Class of evidence	
Class 1	Conditions for which there is evidence and/or general agreement that a given diagnostic evaluation procedure or treatment is beneficial, useful and effective
Class 2	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a diagnostic evaluation, procedure or treatment
Class 2a	Weight of evidence/opinion is in favour of usefulness/efficacy
Class 2b	Usefulness/efficacy is less well established by evidence/opinion
Class 3	Conditions for which there is evidence and/or general agreement that a diagnostic evaluation, procedure or treatment is not useful/effective and in some cases may be harmful
Grade of evidence	
Level A	Data derived from multiple randomized clinical trials or meta-analyses
Level B	Data derived from a single randomized trial, or nonrandomized studies
Level C	Only consensus opinions of experts, case studies or standard of care

Adapted from references 5, 211 and 212

TABLE 2
Modelling of HIV-hepatitis C virus (HCV) coinfection according to exposure category

	HIV infection, n	HIV-HCV coinfection, n (%)	Proportion in Canada, %
Men who have sex with men	31,300	1316 (4.2)	10.0
Men who have sex with men-injection drug users	2030	1665 (82.0)	12.7
Injection drug users	11,180	9279 (83.0)	70.7
HIV-endemic	9250	139 (1.5)	1.1
Heterosexual	10,710	278 (2.6)	2.1
Other*	500	450 (90.0)	3.4
Total	65,000	13,127 (20.2)	100.0

*Data from reference 13. *Other exposures include individuals infected by clotting factors and blood transfusions*

I. EPIDEMIOLOGY OF HIV AND HCV COINFECTION

Epidemiology

In the 30 years since HIV was identified, tremendous progress has been made in its treatment. Once universally fatal, characterized by AIDS-related opportunistic infections and malignancies, effective combination therapies have rendered HIV infection a manageable chronic condition in developed countries (6). HIV-infected individuals are now surviving for decades after acquiring the infection (7), resulting in comorbidities, such as HCV coinfection, now emerging as significant health problems for HIV-infected individuals. In fact, end-stage liver disease (ESLD) due to HCV is now a primary cause of morbidity and mortality in HIV-infected individuals (8), including in Canada (9).

HCV infection is recognized as one of the fastest-growing health problems facing industrialized countries, with an estimated 170 million individuals (10,11) and 250,000 Canadians infected (0.8% to 1.8% of the population) (12). In 2008, 13,127 individuals (20% of the HIV-infected population) were estimated to be coinfecting in Canada (Table 2), with significant geographical variations (13). Currently, injection drug use (IDU) is the primary mode of HCV transmission (responsible for approximately 80% of infections) and is an important risk factor for HIV infection, accounting for an estimated 17% of new HIV infections in 2008 (14). Although the proportion of new HIV infections attributable to IDU has been in decline over the past decade among men, an increasing trend among women has been observed since 2003. In sentinel sites in Quebec and Ontario, HIV seroprevalence among the injection drug user population peaked at 18.6% in 2003. From 2003 to June 2008, the prevalence of HCV infection was 63%, and the overall proportion of those coinfecting with HIV and HCV was 13% (15).

Women, youth and Aboriginal injection drug user populations are particularly at risk for coinfection because of shared vulnerabilities. Aboriginal people comprised 3.8% of the Canadian population in 2006 but 8% of HIV infections (16). HIV diagnosis among Aboriginal women was 14 times more common than among non-Aboriginal women in 1999 to 2003, and the gap increased to almost 20 times the

nonindigenous rate in 2004 to 2008. High rates of IDU are resulting in parallel increases in HCV coinfection. The highest rates of these new HIV diagnoses are in Saskatchewan, 75% of which are associated with IDU; consequently, HCV coinfection rates approach 90% (17). Aboriginal women <30 years of age account for a disproportionate number of all new HIV-positive patients in the province. In Vancouver (British Columbia), between 1996 to 2005, the Aboriginal injection drug user population was found to have a significantly elevated baseline prevalence of HIV infection compared with those of other ethnicities (25.1% versus 16.0%) (18).

Another important at-risk population are individuals incarcerated in correctional facilities. The elevated prevalence of HIV and HCV infections among inmates has been closely linked to IDU and the sharing of injection equipment. Reports have shown that 30% to 50% of Canadian inmates have a history of IDU. For example, in Ontario in 2007, the prevalence of HCV infection was found to be 15.9% among men, 30.2% among women and 54.7% among injection drug users remanded in provincial facilities. The prevalence of HCV-HIV coinfection was 1.2% among men and 1.5% among women. It was highest among older inmates and injection drug users (19). In federal penitentiaries, 31% of those who had ever been tested for HCV reported being positive. Aboriginal women reported the highest rate (49%), more than 50% higher than the rates among non-Aboriginal women (30%) and all men (30.8%) (20). The considerable movement between correctional populations both within and outside the correctional system presents numerous opportunities for HIV and HCV transmission.

Acquisition of HCV is rapid following initiation of IDU and of injecting paraphernalia (21,22). In addition, noninjection smoking paraphernalia has been implicated in HCV transmission (23). Given the risk of HCV morbidity and the high costs of treating HCV among injection drug users (see 'Economic impact'), evidence-based harm-reduction strategies should be implemented (23-26). Given the high rate of ongoing drug use during periods of incarceration, often associated with elevated risks of needle sharing, harm-reduction strategies for incarcerated individuals should also be considered (27-29).

Counselling regarding the risk of acquiring HIV in HCV mono-infected individuals should be undertaken at the time of original diagnosis because subsequent HIV infection may occur if risk behaviours continue (30). All HCV-infected individuals should undergo baseline HIV testing, with repeat testing recommended for those with ongoing risk behaviours for HIV transmission.

Sexual transmission of HCV

Sexual transmission of HCV among heterosexuals is rare, estimated to be one in 190,000 episodes of intercourse (31). In contrast, acute HCV infection from sexual transmission has been increasingly observed in HIV-positive men who have sex with men (MSM) (32-34), in whom HCV prevalence now ranges from 4% to 20% (32,35). In 2008, in Canada, it was estimated that 1316 MSM were coinfecting. In a recent systematic review, HIV-positive MSM had rates of acute HCV infection that were 3.2 times higher (0.537 per 100 person-years) than those of HIV-negative MSM (0.166 per 100 person-years), which is closer to that in the general population and clearly supports routine screening for this population (36). The reasons why MSM may be at increased risk for acquiring HCV has not been fully determined, nor is it clear whether HIV itself enhances either susceptibility or transmission of HCV. Unreported IDU, as well as serosorting, whereby unprotected anal sex occurs only with partners of the same HIV status as their own (37), may be contributory. Factors to be considered in the HIV-positive MSM population include: sexual practices that may lead to transmission through blood contact or concomitant sexually transmitted infections (genital ulcer disease) that may increase susceptibility of transmission rates (38,39); and higher HCV viral loads in the context of HIV and HCV coinfection (38). Transmission networks appear to be quite important in most of the recent reports of acute HCV among HIV-positive MSM, raising the possibility that certain viral strains play a role (40). The European AIDS Treatment Network (NEAT) Consensus Panel on acute HCV in MSM has previously recommended consideration of screening MSM at risk for acute HCV with testing of liver enzyme levels every six months, and HCV antibody testing annually. For those with ongoing IDU or recent sexually transmitted infection, screening every three months was recommended by the NEAT panel (41). A recent cost-effectiveness analysis of screening options to detect acute HCV among MSM concluded that the strategy of liver enzyme testing every six months in combination with annual HCV screening was cost effective in communities with incidence <1.25 per 100 person-years, while screening using liver enzyme levels every three months was optimal in communities with higher incidence (42).

RECOMMENDATION

1. All HIV-positive individuals should undergo screening for HCV antibodies when first evaluated. Screening should be repeated periodically – at least annually, particularly for high-risk individuals initially found to be negative (such as active injection drug users, Aboriginal peoples and individuals who are/have been incarcerated). HIV-positive MSM should undergo screening for HCV antibodies annually in combination with testing of liver enzyme levels every six months if sexually active with high-risk behaviours, and repeat HCV antibody testing (with consideration of additional HCV RNA testing) should be performed whenever unexplained elevations in liver enzyme levels are noted (Class 2a, Level C).
2. Identification of HCV coinfection in HIV provides opportunities for prevention of transmission, risk reduction, counselling, and linkage to care and harm-reduction services (Class 1, Level C).

Coinfected individuals are highly vulnerable in a number of ways that impact health, access to care and treatment. This can be illustrated with data from the Canadian Coinfection Cohort (CCC) study (CTN222), a CIHR-funded prospective cohort that follows 1010 individuals with HIV-HCV coinfection (www.cocostudy.ca) (43). Participants experience very high rates of social instability and poverty. Aboriginal peoples

are disproportionately represented in the cohort: 15% of the cohort overall and 33% in British Columbia self-identified as Aboriginal; a very high proportion of these were women (62%). Overall, 458 (57%) had been previously incarcerated (78% of Aboriginal peoples versus 53% of non-Aboriginal peoples) and 44% reported a psychiatric diagnosis. There are very high rates of past and current (past six months) substance use among participants, with 81% reporting a history of IDU (38% were currently injecting; 23% sharing needles); 50% were current alcohol drinkers (31% reported binge/hazardous drinking, defined as >6 drinks/day) and 77% currently smoked cigarettes (43).

Distribution of HCV genotypes in Canada

The most important predictor of treatment response has been HCV genotype, with more favourable responses to standard pegylated interferon and ribavirin apparent among genotypes 2 and 3, and lower response rates among genotypes 1 and 4. In Canada, 62% of HCV infections are genotype 1. Among injection drug users, genotypes 1 and 3 are most common. Genotypes 2a and 5 are more frequent among patients previously exposed to multiple injections, surgery or transfusions, and genotype 4 is more frequent among African immigrants. The existence of several genotypes in Canada despite the low prevalence of HCV reflects the diversity of the population and active immigration (44). Several recent global outbreaks of HCV among HIV-positive MSM have been attributed to genotype 4 infections (45).

The effect of HIV on the natural history of HCV

In HCV monoinfection without concurrent excess alcohol consumption, it generally takes a minimum of 20 to 30 years for HCV to cause significant liver disease such as cirrhosis, decompensated cirrhosis and/or liver cancer (46). HIV infection exerts a negative impact on this time course. Coinfected individuals progress more rapidly to liver fibrosis, cirrhosis and ESLD compared with those infected with HCV alone (47-50). In a meta-analysis, the RR for cirrhosis was 2.49 (95% CI 1.81 to 3.42) in ART-untreated and 1.72 (95% CI 1.06 to 2.80) in ART-treated coinfecting versus monoinfected individuals (50). Once cirrhosis develops, there is also a dramatic sixfold acceleration to decompensation and death (47). Fibrosis rates in HIV-infected MSM acquiring acute HCV while on ART have also been shown to be surprisingly rapid, suggesting an accelerated course of HCV despite effective HIV control (51). This more rapid course is driving, in large measure, the increased liver-related mortality that has been observed worldwide in developed countries in the post-ART era. In a large HIV cohort collaboration (the Data Collection on Adverse events of Anti-HIV Drugs [D:A:D] study), liver-related deaths (14% overall) were second only to AIDS and were associated with coinfection (3). The proportion of deaths from ESLD among HIV-infected individuals in France increased from 1.5% in 1995 to 17% in 2005 (52); 80% of these were attributable, in part, to HCV coinfection (53). In the CCC, very high progression rates of fibrosis and the occurrence of clinical ESLD events have been observed – rates approximately six times higher than those reported in HCV mono-infected populations with similar duration of infection. Indeed, ESLD has emerged as the primary cause of death among cohort participants. While alarming, these data may actually be an underestimation of the true burden of disease in this population given that this cohort only includes patients seeking and following regular care.

Coinfected individuals are at risk for the development of hepatocellular carcinoma (HCC). Population-based assessments have demonstrated increased incidence among coinfecting patients in some studies (1.32 per 1000 person-years compared with 0.20 per 1000 person-years in HIV mono-infected patients) (54) but not others (55), and incidence may be increasing over time (56). Development of HCC occurs at a younger age in coinfecting patients, and may be associated with degree of immune suppression in some studies (57,58).

Health economic impact

Among infectious diseases, HCV is associated with the largest burden of disease, both because of the frequency of the infection and its consequences (59). HCV infection has become the primary indication for liver

TABLE 3
Current recommendations in international guidelines for HIV treatment initiation in hepatitis C virus (HCV) coinfecting individuals

Guidelines, year (reference)	HCV coinfection	Class/Grade of evidence
IAS-USA Guidelines, 2012 (66)	ART regardless of CD4 cell count	BIIa
US DHHS Guidelines, 2012 (67)	ART regardless of CD4 cell count	BII
British HIV Association Guidelines, 2012 (68)	ART if CD4 count <500 cells/ μ L	IC
European AIDS Clinical Society Guidelines, 2012 (69)	ART if CD4 count <500 cells/ μ L; \geq 500 cells/ μ L: consider ART if HCV therapy not feasible	

ART Antiretroviral therapy; IAS-USA International Antiviral Society – United States; US DHHA United States Department of Health and Human Services

transplantation in the developed world. It has been estimated that the costs of treating the chronic sequelae of HCV among injection drug users in Canada will rise to \$210 million annually by 2026 (60). Strategies to reduce HCV transmission in high-risk groups such as injection drug users should, therefore, be considered (Section I).

II. MANAGING HIV IN THE SETTING OF COINFECTION

The management of HIV infection in the context of coinfection requires consideration of several factors:

- Effect of ART on the natural history of liver disease;
- Timing of initiation of ART;
- Risk of hepatotoxicity when ART is initiated;
- Potential for drug-drug interactions when undertaking HCV therapy;
- Adherence to ART and HCV therapy, particularly among those with active addiction concerns; and
- Selection of regimens with decreased risk for similar adverse events to those associated with HCV therapy.

Effects of ART on HCV natural history and timing of ART initiation

Coinfected individuals experience faster progression of HCV disease, with higher risk of ESLD, particularly when both HIV and HCV remain untreated (47,49). In an analysis of coinfecting individuals in the pre-ART era, the mean time from infection to cirrhosis was as short as 6.9 years compared with 23.2 years in monoinfected patients (49). Subsequent data have suggested that initiation of ART may serve to slow the rate of fibrosis progression and, hence, delay the onset of ESLD. Brau et al (61) conducted a retrospective analysis of 656 HCV patients (274 coinfecting with HIV) and determined a fibrosis progression rate as biopsy-determined fibrosis score/duration of HCV infection. Fibrosis progression rates were highest in HIV-infected individuals with detectable HIV plasma viral load but were similarly reduced in HIV-infected individuals with suppressed viral load and in HCV monoinfected patients. Other analyses have shown similar protective effects of longer duration of ART therapy and reduced biopsy-proven fibrosis (62).

Initiation of ART has also been shown to reduce liver-related mortality in coinfecting patients. In a cohort of 285 coinfecting patients initiating either limited ART (n=55) or full ART (n=93), or remaining untreated between 1990 and 2002, liver-related mortality rates were lowest in those receiving ART (0.45 per 100 person-years) or dual therapy (0.69 per 100 person-years), and highest in those who received no therapy (1.70 per 100 person-years) (63). In a cohort of 472 HIV-infected patients (256 of whom were coinfecting with HCV), 41% of overall mortality was due to liver-related deaths and, in Cox regression analysis, receipt of zero to two antiretroviral agents compared with ART was associated with an RR of 2.9 (95% CI 1.3 to 6.7) for liver-related mortality (64). Overall evidence derived from these and other cohort studies supports ART-related decreases in fibrosis progression and potential reduction in liver-related mortality (65).

These data have been incorporated into current treatment guidelines for HIV-infected individuals, in which underlying HCV coinfection is recognized to be a potential reason to consider early initiation of ART at relatively high CD4 cell counts (Table 3) (66-69). The

International Antiviral Society-USA and US Department of Health and Human Services guidelines recommend initiation of ART regardless of CD4 cell count, whereas the British and European guidelines recommend initiation of ART in individuals with CD4 cell count <500 cells/ μ L (compared with <350 cells/ μ L for a general treatment initiation threshold) (68,69).

In all circumstances with CD4 cell counts \geq 500 cells/ μ L, it may be ideal to consider initiating HCV therapy first to avoid potential drug-drug interactions (see below), decrease risk of ART-related hepatotoxicity (70) and, potentially, improve HCV therapy outcome with high baseline CD4 cell count. If HCV therapy is not considered to be imminent or feasible due to competing comorbid conditions, ART initiation at CD4 counts \geq 500 cells/ μ L should be considered.

RECOMMENDATIONS

3. Initiation of ART may serve to slow progression of liver disease in coinfecting patients. Early initiation of ART is recommended for all individuals with CD4 cell count <500 cells/ μ L (Class 1, Level B).
4. Initiation of ART in individuals with CD4 cell count \geq 500 cells/ μ L can be considered if initiation of HCV therapy is not believed to be an option (Class 2a, Level B) in patients who have undergone thorough assessment of barriers to ART adherence and counselling regarding the long-term nature of ART.

ART and accelerated hepatic fibrosis

A direct causative association between ART and fibrosis progression in coinfecting patients has not been well established and may be subject to additional confounders when assessed in terms of underlying alcohol or substance use, differing classes of antiretroviral agents and the potential beneficial effects on hepatic disease progression associated with initiation of ART, as described above. Nevertheless, a potential association between ART and fibrosis progression has been observed in some studies (71,72). Further evaluation of this potential interaction is required.

ART and risk of hepatotoxicity in coinfecting individuals

Hepatotoxicity is usually defined using the AIDS Clinical Trial Group grading system, with grade 3 (alanine aminotransferase [ALT] elevations $>5 \times$ the upper limit of normal [ULN] range in individuals with normal values at baseline) considered to be a standard for more severe disease. Some experts have proposed an additional classification, with grade 3 elevation considered to be $>3.5 \times$ ULN when baseline values are abnormal (73). Overall, the incidence of hepatotoxicity in observational studies ranges from 2% to 18% (74), and the presence of HCV coinfection increases the risk by at least two- to five-fold (75-78). Studies performed in the early ART era revealed increased risk of hepatotoxicity among coinfecting individuals initiating ART containing the early protease inhibitors (PIs), particularly high-dose ritonavir (73,78,79), although other antiretrovirals with known hepatotoxicity profiles, such as the non-nucleoside reverse-transcriptase inhibitor (NNRTI) nevirapine, have also been implicated (80).

Tolerability of current first- and second-line NNRTI and PI agents in coinfecting patients has been assessed in post hoc analysis of phase II and III randomized clinical trials, including newer agents such as raltegravir (81), rilpivirine (82), etravirine (83) and darunavir (84),

although relatively small numbers of coinfecting individuals were included in the latter. Presently, there is limited information regarding use of the new boosted integrase inhibitor elvitegravir/cobicistat in coinfecting patients, because HCV coinfection was identified in 5% of individuals randomly assigned to this combination in trials comparing it with both efavirenz or atazanavir/ritonavir (85,86). Nonetheless, no significant hepatotoxicity was noted.

Risk of antiretroviral-related hepatotoxicity has been associated with degree of underlying liver fibrosis. In a prospective study involving 107 patients with biopsy-confirmed fibrosis ranging from F0 to F4, the overall incidence of hepatotoxicity was 5.1 events per 100 person-years. However, the incidence among those with F3/4 fibrosis was 38% compared with 15% among those with F1/2 fibrosis (RR 2.75 [95% CI 1.08 to 6.97]) (87). In some studies, infection with HCV genotype 3 has also been associated with increased risk for hepatotoxicity (88,89).

Successful HCV therapy has been associated with potential decrease in risk for subsequent antiretroviral-related hepatotoxicity (70). In a cohort of 132 coinfecting patients, sustained virological response (SVR) following HCV therapy was achieved in 33% of individuals. The yearly incidence rate of antiretroviral hepatotoxicity among those with SVR was 3.1% versus 12.9% among those without SVR (70).

Presently, no specific antiretroviral regimen can be preferentially recommended for use in coinfecting patients. However, certain regimens may need to be used cautiously in the setting of advanced liver disease. Close monitoring is required, and dosage adjustments or alterations of combination ART may be required if hepatic decompensation occurs (67). Certain antiretroviral agents must be avoided altogether due to drug-drug interactions when HCV therapy containing HCV PIs is being initiated (see 'Drug-drug interaction' section).

RECOMMENDATIONS

- Current first- and second-line ART regimens should be initiated as per current guidelines because they are effective and well-tolerated in coinfecting patients (Class 1, Level A).
- HCV therapy should be considered before ART initiation in individuals with early HIV disease as a potential means of decreasing risk of antiretroviral-related hepatotoxicity and to avoid risk of drug interactions between ART and HCV therapies (Class 2a, Level C).

III. BASELINE EVALUATION AND MANAGEMENT OF HCV IN COINFECTING PATIENTS

Baseline evaluation and monitoring of coinfecting patients is similar to that of mono-infected patients and should focus on determination of degree of liver disease/hepatic fibrosis as a prelude to consideration of HCV therapy (Table 4). Additional monitoring is required for patients with underlying cirrhosis, and steps to prevent additional viral hepatitis infections should be considered.

Diagnosis

In Canada, as many as 25% to 30% of HIV-HCV coinfecting individuals are estimated to be unaware of their infection. Thus, there is a clear need to increase testing. Identification of HIV-HCV coinfection provides opportunities for prevention of transmission, risk reduction, counselling, and linkage to care and harm-reduction services.

All HIV-infected patients should be screened for HCV coinfection using serological testing. In individuals with significant immune compromise, the HCV antibody may occasionally be falsely negative, and consideration should be given to directly testing for the presence of HCV RNA (90).

The frequency of testing for HCV infection should depend on ongoing risk behaviours (Section I). Detection of HCV antibody does not determine active infection. The presence of HCV RNA should be confirmed to rule out spontaneous clearance using qualitative or quantitative polymerase chain reaction. In the EuroSIDA cohort, 23% of anti-HCV-positive individuals tested HCV RNA negative (91).

TABLE 4
Baseline assessment of coinfecting patients

	Test	Comment
Viral hepatitis screens	HCV antibody	
	Quantitative HCV RNA	
	HCV genotype	
	Hepatitis B surface antigen	Chronic HBV infection
	Hepatitis B surface antibody	Immunity to HBV
	Hepatitis B core antibody	
Liver-related	Hepatitis A immunoglobulin G	Indicates need for HAV vaccine
	Complete blood count	Thrombocytopenia may indicate advanced liver disease
	Alanine aminotransferase; aspartate aminotransferase; alkaline phosphatase; gamma-glutamyltransferase	
	Albumin, international normalized ratio, total bilirubin	Abnormalities suggest advanced liver disease
	Ultrasound	
	Screens for other chronic conditions of liver disease	
	Alpha-1-antitrypsin	Alpha-1-antitrypsin deficiency
	Antinuclear antibody, anti-smooth muscle antibody	Autoimmune hepatitis
	Antimitochondrial antibody	Primary biliary cirrhosis
	Ceruloplasmin	Wilson disease
Ferritin, iron studies	Hemochromatosis	
Immunoglobulins A, G and M	Autoimmune hepatitis, primary biliary cirrhosis, alcoholic liver disease	

HAV Hepatitis A virus; HBV Hepatitis B virus; HCV Hepatitis C virus

Individuals with positive HCV RNA tests should undergo determination of HCV genotype as an initial step of determining the nature of subsequent HCV therapy (Section IV).

Individuals with baseline negative HCV RNA should be considered for repeat testing to confirm the absence of chronic infection at least once, especially if ALT is elevated.

RECOMMENDATIONS

- Patients with confirmed HCV antibody should be evaluated using HCV RNA polymerase chain reaction (Class 1, Level C).
- Individuals with positive HCV RNA tests should undergo HCV genotyping (Class 1, Level C).
- Individuals with negative HCV RNA tests should undergo repeat testing at least once to confirm spontaneous clearance if liver enzyme levels are elevated (Class 1, Level C).

All individuals should also undergo screening for hepatitis A immunity (hepatitis A immunoglobulin G) and for hepatitis B (hepatitis B surface antigen, hepatitis B surface antibody and hepatitis B core antibody), and should be vaccinated if nonimmune or assessed for therapy if chronically infected with hepatitis B.

RECOMMENDATIONS

- All patients should undergo screening for hepatitis A and B, and should be offered vaccination if nonimmune (Class 1, Level C).

Clinical assessment

A detailed history and physical examination focused on signs and symptoms of liver disease is required. Features of advanced liver disease may include ascites, bulging flanks, peripheral edema, history of gastrointestinal bleeding and jaundice. Examination for splenomegaly,

ascites, gynecomastia, spider nevi and other manifestations of ESLD should be performed.

Laboratory monitoring

Monitoring of complete blood count, liver enzyme panel including ALT and aspartate aminotransferase (AST), and markers of synthetic function (international normalized ratio, albumin and bilirubin) should be performed at baseline and can be monitored as a component of routine (every three to four months) laboratory testing in individuals undergoing ART. Testing should be performed at least twice per year in individuals not yet requiring antiretroviral therapy because HCV disease activity may prompt earlier consideration of ART (Section III).

Thrombocytopenia may be a marker of hypersplenism and advanced liver disease. Derangements in synthetic function also suggest advanced disease. Caution should be used when interpreting elevated bilirubin levels in patients receiving atazanavir-based regimens because atazanavir is associated with unconjugated hyperbilirubinemia, but elevated conjugated bilirubin indicates liver disease. Similarly, discordance between the absolute CD4 cell count and CD4 percentage (higher CD4 percentage than expected for the corresponding absolute value) in coinfecting individuals may also suggest advanced disease. Among individuals enrolled in the CCC, 31% had evidence of high discordance, which was associated with markers of ESLD (92). CD4 discordance has also been shown to correspond with advanced liver disease when assessed using transient elastography (TE) (93).

Additional baseline screening for other causes of chronic liver disease can be considered, including investigations for hemochromatosis (iron binding capacity with genetic testing if iron saturation exceeds 0.60), autoimmune hepatitis (including primary biliary cirrhosis where appropriate – antinuclear antibody, antismooth muscle antibody, anti-mitochondrial antibody and immunoglobulin levels), Wilson disease (ceruloplasmin) and alpha-1-antitrypsin deficiency. Attention to alcohol consumption is essential given the negative influence alcohol has on fibrosis progression.

RECOMMENDATIONS

11. Patients should be evaluated for other conditions that may result in or aggravate chronic liver disease (Table 4) (Class 1, Level C).
12. All patients should be counselled regarding alcohol reduction/abstinence (Class 1, Level C).

Ultrasound of the liver at baseline should also be considered, and should be performed whenever thrombocytopenia is present.

Although liver enzyme elevations have traditionally been believed to reflect disease activity, it is now evident that HCV-infected individuals may develop fibrosis, and even cirrhosis, without significant elevations in liver enzyme levels. In a retrospective review of 326 liver biopsies performed in coinfecting individuals between 1997 and 2003 at a European centre, approximately 25% of individuals with persistently normal ALT values were found to have at least stage 2 fibrosis (94). As such, ALT criteria alone should not determine treatment initiation in coinfecting patients.

Role of liver biopsy

Liver biopsy has traditionally been regarded to be the gold standard of investigation for HCV-related disease progression in North America (95). The liver biopsy assesses both the degree of inflammatory activity and fibrosis, and may also reveal an alternative etiology of liver damage. Nonetheless, liver biopsies are invasive and difficult to repeat, often resulting in limited sample size and selection bias; therefore, they are, at best, an imperfect gold standard. In addition, results may be affected by tissue sampling and interpretation error (96). Results of the liver biopsy influence decisions regarding initiation of HCV therapy, with biopsy findings of more advanced fibrosis leading to more urgent initiation and minimal fibrosis scores potentially allowing for

treatment deferral. However, a liver biopsy should not be considered mandatory for all individuals being considered for therapy, and decisions regarding biopsy should be conducted on a case-by-case basis. In circumstances in which the biopsy has led to a deferral of therapy, repeat biopsy in three years (compared with four to five years for mono-infected patients [97]) or evaluation of fibrosis using a non-invasive modality (see below) should be considered given concerns for progressive liver disease in coinfecting patients.

Noninvasive assessment of fibrosis – TE and laboratory markers

TE (Fibroscan, Echosens, France) is a noninvasive technique involving measuring liver stiffness (with scores measured in kPa) that serves as a marker of hepatic fibrosis (98). TE has been widely used in Europe and Canada for some time and was approved in the United States in April 2013. The Fibroscan received licensing approval in Canada in 2009. Use of TE for diagnosis of fibrosis has been established in a variety of chronic hepatic diseases, including HCV (99). Meta-analyses of TE compared with liver biopsy for the assessment of fibrosis have found relatively high concordance, with one meta-analysis finding that the mean area under the ROC curve for the diagnosis of significant fibrosis, severe fibrosis and cirrhosis were 0.84, 0.89 and 0.94, respectively (100). In another meta-analysis, the sensitivity and specificity for cut-offs for determining significant fibrosis were 71.9% and 82.4%, respectively, and were 84.4% and 94.6%, respectively, for cirrhosis (101).

TE has been validated in coinfecting patients. In a cohort of 169 Spanish patients undergoing liver biopsy, the sensitivity and specificity of TE was established (102). To diagnose significant liver fibrosis, a cut-off value of 7.2 kPa was associated with a positive predictive value of 88% and a negative predictive value of 75%. To diagnose cirrhosis, a cut-off value of 14.6 kPa was associated with a positive predictive value of 86% and a negative predictive value of 94% (102). Similarly, in an assessment of TE involving a North American cohort of injection drug users (the AIDS Linked to the IntraVenous Experience [ALIVE] cohort), including coinfecting patients, 79% to 83% of individuals were correctly identified as having significant fibrosis and cirrhosis when TE was compared with liver biopsy (103).

Fibroscan may be limited by body habitus (obesity may impair the ability of the probe to accurately assess the liver) and may be falsely elevated in circumstances of significant hepatic inflammation (98). Of note, development of probes dedicated for use in obese patients may improve diagnostic value (104).

Novel use of noninvasive laboratory markers may aid in the assessment of fibrosis in coinfecting patients. Use of the AST-to-platelet ratio index (APRI), calculated as $(\text{AST}/\text{ULN})/\text{platelet count} \times 10^9/\text{L} \times 100$, has been validated in a Canadian cohort of coinfecting patients (105,106) in which an APRI score >1.5 was 100% specific and 52% sensitive for significant fibrosis compared with the gold standard of liver biopsy.

Other formulae for assessing fibrosis include the Fib-4 score (age [years] \times AST [IU/L]/platelet count [expressed as platelets $\times 10^9/\text{L}$] \times (ALT^{1/2}[IU/L]) (107) and Fibrotest (LabCorp, USA) – a calculated algorithm of six serum tests (alpha-2-macroglobulin, apolipoprotein A1, haptoglobin, gamma-glutamyltransferase, ALT and bilirubin) and the age and sex of the patient (108,109). These methods lack sensitivity for diagnosing fibrosis compared with TE (110,111).

Interleukin-28B testing

Recent genome-wide association studies have identified a single nucleotide polymorphism located within the interleukin (IL) 28B gene that is associated with both spontaneous clearance and response to pegylated interferon and ribavirin therapy (112,113). Individuals who are homozygous for the CC allele have better outcomes compared with those with heterozygous CT or homozygous TT genotypes; however, the presence of a non-CC genotype does not rule out response to therapy. The role of IL28B polymorphisms in the era of DAAs has also not been well defined and, as such, routine testing to inform treatment decisions cannot be recommended at this time.

TABLE 5
Virological response definitions while undergoing hepatitis C virus (HCV) therapy

Definition	Time point	HCV RNA level	Comment
RVR	Week 4	Undetectable	RVR is highly predictive for SVR
EVR	Week 12	Undetectable: Complete EVR Detectable: Partial EVR (>2 log ₁₀ drop from baseline) Detectable: Null responder (<2 log ₁₀ drop from baseline)	Lack of EVR is highly predictive for not achieving SVR
Extended RVR	Week 4, 12	Undetectable	Highly predictive for achieving SVR with telaprevir-based therapy
Partial response	Week 24–48	Detectable	Treatment failure
End-of-treatment response	Week 48	Undetectable	
Relapser	Week 48–72	Detectable	Treatment failure
SVR – week 60 (SVR12)	Week 60	Undetectable	Predicts SVR24 in monoinfected patients
SVR – week 72 (SVR24)	Week 72	Undetectable	Treatment success

EVR Early virological response; RVR Rapid virological response; SVR Sustained virological response; SVR12/24 SVR after 12 or 24 weeks of follow-up

Monitoring of patients with cirrhosis

Patients with confirmed cirrhosis should undergo additional monitoring for the development of complications such as HCC. Surveillance screening with regular ultrasounds (every six months) with or without use of serum alpha fetoprotein should be undertaken, as is the case in HIV-negative individuals with cirrhosis. Referral to a gastroenterologist for consideration of endoscopy to screen and/or monitor esophageal varices may also be indicated.

Ongoing monitoring for HCC is also advised in patients with cirrhosis who have achieved SVR with HCV therapy because the risk related to underlying cirrhosis may persist.

RECOMMENDATIONS

- ALT criteria alone should not be used to determine the need for treatment initiation in coinfecting patients (Class 2a, Level C).
- Baseline abdominal ultrasound should be considered in all patients (Class 2a, Level B).
- Baseline evaluation of liver fibrosis (eg, Fibroscan, Fibrotest, APRI) to determine the degree of hepatic fibrosis and urgency for HCV therapy is advised (Class 2a, Level B).
- Evaluation of liver fibrosis with liver biopsy can be considered if noninvasive methods of determining fibrosis are not available or if alternative diagnoses are being considered.
- Patients with evidence of underlying cirrhosis should be screened every six months for HCC using ultrasound (Class 1, Level B).
- Patients with underlying cirrhosis should be considered for gastroscopy to screen for esophageal varices (Class 1, Level B).

IV. HCV THERAPY IN COINFECTED PATIENTS

There is clear evidence that successful HCV treatment leads to reduced disease burden from HCV infection. Successful HCV treatment has, to date, been the most effective means of preventing liver-related complications in the setting of HIV-HCV coinfection (114). Despite this, a minority of individuals have initiated treatment; only 1.1% (15 of 1360) initiated treatment for HCV from January 2000 to December 2004 in an inner-city cohort in British Columbia (115). In the CCC, 16% had been previously treated at the time of cohort enrollment baseline and 13% initiated treatment follow-up (total 29%). While low, this is consistent with treatment rates reported in the literature elsewhere in the world (116).

All coinfecting patients should be assessed for HCV therapy. At present, therapy for HCV is determined by HCV genotype. Genotype 1 infections are treated with combination therapy including pegylated interferon, ribavirin and an orally administered NS3/4A PI (a class of HCV-specific DAAs). Presently, two formulations of pegylated interferon are available in Canada: pegylated

interferon alfa-2a (Pegasys [Hoffmann-La Roche Ltd, Canada], dosed as 180 µg subcutaneously once weekly) or pegylated interferon alfa-2b (Pegetron [Merck Canada Inc, Canada], dosed as 1.5 µg/kg subcutaneously once weekly). Other genotypes, including genotypes 2, 3 and 4, continue to receive pegylated interferon and ribavirin, with length of therapy for genotypes 2/3 determined, in part, by virological response while on therapy and underlying fibrosis (see below). Classification of virological responses to therapy are presented in Table 5.

Preparation for HCV therapy

Baseline laboratory determination of HCV status as outlined is necessary to evaluate HCV genotype and degree of hepatic fibrosis/disease.

Given the burden of comorbid conditions in the setting of coinfection, evaluation of factors, such as substance use/addictions, mental health, and housing and food security, is vital when preparing for HCV therapy. Substance use, lack of housing or lack of adequate food supply may limit the adherence to HCV therapy, with deleterious effects on treatment outcome. Underlying mental health conditions may be exacerbated by interferon-based therapy, and multidisciplinary follow-up is recommended.

Individuals considering HCV therapy should be assessed for potential contraindications to receipt of interferon and ribavirin, which remain a core component of current HCV therapy. Contraindications include:

- pregnancy;
- decompensated liver disease;
- autoimmune hepatitis;
- unstable depression/psychosis; and
- unstable coronary artery disease.

Individuals >50 years of age with history of hypertension, diabetes or previous retinopathy should undergo a baseline ophthalmology assessment because interferon therapy has been associated with exacerbation/new onset of retinopathy (117,118).

When considering HCV therapy in injection drug user populations, concomitant use of harm-reduction strategies is necessary given the risk of potential reinfection if IDU resumes after successful therapy (119). Mathematical models suggest that HCV therapy in this population has the potential to reduce transmission within networks of injection drug user populations (120). Individuals who have previously undergone successful HCV therapy should be reevaluated if ALT elevation recurs to rule out reinfection.

In some regions, HIV-HCV coinfecting individuals face obstacles to engaging HCV care and initiating HCV antiviral therapy due to inadequate funding of HCV treatment programs and limitations placed on access to HCV antiviral therapy.

Adherence to HCV antiviral therapy is critical to achieving treatment success. The importance of this should be discussed with potential treatment candidates; potential obstacles to adherence should be

TABLE 6
Sustained virological response outcomes of hepatitis C genotype 1 therapy in monoinfected individuals treated with hepatitis C protease inhibitors telaprevir and boceprevir

	Telaprevir	Boceprevir
Naive patients	75% versus 44%*	63% versus 38%*
Naive with RVR	92% (eRVR)	88% (at week 4 of triple therapy)
Naive/cirrhosis	62% versus 33%	52% versus 38%
Previous relapser	83% versus 24%	75% versus 29%
Partial responder	59% versus 15%	52% versus 7%
Null responder	29% versus 5%	38% in a single-arm study

*When compared with standard pegylated interferon and ribavirin. eRVR Early rapid virological response (RVR). Data from references 121-124 and 213

identified and strategies to maximize adherence should be developed. Adherence should be monitored and reinforced throughout the entire course of treatment. If nonadherence is encountered and cannot be rapidly corrected while on therapy, therapy should be interrupted.

RECOMMENDATIONS

- All coinfecting patients should undergo evaluation for HCV therapy (Class 1, Level A).
- Evaluation of factors such as substance use/addictions, mental health, and housing and food security is vital when preparing for HCV therapy (Class 1, Level B).
- Addiction should not be considered to be an absolute exclusion criteria for HCV therapy.
- Multidisciplinary care is recommended to optimally support patients as they progress through HCV work-up and treatment (Class 1, Level B).
- A detailed assessment for interferon-based treatment contraindications is essential (Class 1, Level C).
- Appropriate levels of funding for HCV treatment programs and removal of barriers to HCV antiviral therapy are necessary to optimize engagement in care and treatment outcomes (Class 1, Level C)

Timing of therapy initiation in individuals naive to both HIV and HCV therapy

Individuals presenting with evidence of advancing HIV infection (CD4 count <500 cells/ μ L) should be considered for initiation of ART as per current HIV guidelines (66-69). In individuals with CD4 count \geq 500 cells/ μ L, consideration should be given to early initiation of HCV therapy. Benefits of early HCV therapy include effects on HCV-related liver disease progression, avoidance of drug-drug interactions and pill burden issues arising from concomitant ART and HCV therapy, and potential improvement in tolerability of future ART due to decrease in risk for ART-related hepatotoxicity (70). Individuals who cannot initiate early HCV therapy may be considered for early ART as described above (Section II Recommendation).

An additional consideration in individuals with relatively mild liver disease is the anticipated availability of either simpler once-daily DAAs or use of combination DAAs without the use of pegylated interferon, with potential for simpler, less toxic and more effective therapy. Individuals with early fibrosis and no HCV-related symptoms could, therefore, be counselled to defer therapy and undergo conservative monitoring with serial noninvasive methods of fibrosis assessment while awaiting studies of these agents in coinfecting patients and eventual regulatory approval. Individuals with METAVIR stage 2 to 4 fibrosis should be considered for therapy with currently available agents.

Genotype 1 treatment

Current standard of care for genotype 1 HCV monoinfected individuals consists of triple therapy with pegylated interferon, ribavirin and a PI

TABLE 7
Differences in administration and duration of therapy for telaprevir and boceprevir in hepatitis C monoinfected individuals

	Telaprevir	Boceprevir
Dose	750 mg every 8 h/ 1125 mg twice daily	800 mg three times daily
Food requirement	Yes: meals should contain at least 9 g of fat	Yes
Lead-in phase	No	Yes: 4 weeks of PegIFN/ RBV first
Duration of protease inhibitor	First 12 weeks of therapy only	Response-dependent: 24 week minimum
Response-guided therapy possible?	Yes: 58%–65% naive/ relapsers stop all treatment at week 24	Yes: 44%–47% of naive/ experienced patients stop at week 28/36, respectively

PegIFN/RBV Pegylated interferon/ribavirin

(boceprevir or telaprevir are the only PIs currently approved). Published phase III studies with both boceprevir and telaprevir in HCV mono-infected populations demonstrate markedly improved SVR rates compared with dual pegylated interferon plus ribavirin therapy in treatment-naive, previous relapser, previous partial responder and previous null responder populations (121-124). Boceprevir has a short half-life and, thus, requires dosing every 8 h. Telaprevir is also approved for dosing every 8 h. However, data from a large randomized clinical trial involving treatment-naive monoinfected individuals indicate that telaprevir can be dosed twice daily with similar SVR rates and side effect profile (125). Absorption of both drugs is highly dependent on food; boceprevir bioavailability increases 60% when taken with food, regardless of meal type (126). Telaprevir should be taken with a meal or snack comprising at least 9 g and up to 20 g of fat (127). Tables 6 and 7 outline major differences between telaprevir and boceprevir.

Interim results from two phase II randomized comparative studies describing markedly improved SVR outcomes with triple therapy (containing pegylated interferon, ribavirin and a HCV PI) versus dual therapy with peginterferon plus ribavirin can guide antiviral therapy for HCV genotype 1 treatment-naive patients coinfecting with HIV (Table 8) (128-131). There are no published studies at this time. The interim nature of these results and the relatively small sample sizes ($n < 100$ for each) should be considered when evaluating virological response, relapse and adverse event results.

Boceprevir: In a randomized, double-blinded trial of pegylated interferon alfa-2b and ribavirin with or without boceprevir, SVR 12 weeks post-therapy (SVR12) was achieved in 62.5% of triple therapy recipients ($n=64$) versus 26.5% of pegylated interferon alfa-2b and ribavirin-treated study participants ($n=34$) (128,130) (Figure 1). All patients were on ART with stable HIV suppression. Antiretroviral regimens allowed in this study consisted of a PI boosted by ritonavir, raltegravir or maraviroc, in conjunction with two nucleoside inhibitors other than zidovudine, stavudine or didanosine. Most participants were on atazanavir-, lopinavir- or darunavir-based regimens. NNRTI-based regimens were not allowed in this protocol. Only five of 98 participants were cirrhotic. Approximately two-thirds were infected with genotype 1a, which is a negative predictor of HCV PI efficacy. All participants received 48 weeks of therapy. A four-week lead-in phase with pegylated interferon alfa-2b and ribavirin was used in this study followed by a fixed duration of 44 weeks of boceprevir 800 mg every 8 h or placebo. A weight-based approach to ribavirin dosing was used (600 mg to 1400 mg per day divided twice daily). Stopping rules for virological futility were similar to those previously used for pegylated interferon alfa-2b and ribavirin therapy ($< 2 \log_{10}$ reduction in HCV RNA from baseline at week 12 of therapy or detectable HCV RNA at week 24) (Table 9), which differ from the current criteria for futility for boceprevir-containing HCV antiviral treatment in HCV mono-infected individuals.

TABLE 8
Treatment protocols for hepatitis C (HCV) genotype 1 in HIV-HCV coinfection

	Treatment-naive	Relapser	Partial responder	Null responder
Boceprevir				
HIV-HCV coinfectd				
SVR rate (versus PegIFN α2b + RBV)	63% versus 27%	–	–	–
Relapse rate	3%	–	–	–
Duration of PegIFN α2b + RBV	Fixed 48-week duration	–	–	–
Duration of HCV PI	44 weeks	–	–	–
PegIFN α2b + RBV lead-in	Yes: 4 weeks	–	–	–
HCV monoinfected				
SVR rate (versus PegIFN α2b + RBV)	63% (n=368) versus 38% (n=363)	69% (n=72/105) versus 29% (n=15/51)	40% (n=23/57) versus 7% (n=2/29)	40% (n=47) (no control)†
Relapse rate (versus PegIFN α2b + RBV)	9% versus 22%	14% (n=12/83) versus 32% (n=7/22)	18% (n=5/28) versus 33% (n=1/3)	14% (no control)
Duration of PegIFN α2b + RBV	Response guided (28 versus 48 weeks)	Response-guided (36 versus 48 weeks)*	Response-guided (36 versus 48 weeks)*	Fixed 48-week duration
PegIFN α2b + RBV lead-in	Yes: 4 weeks	Yes: 4 weeks	Yes: 4 weeks	Yes: 4 weeks
Telaprevir				
HIV-HCV coinfectd				
SVR rate (versus PegIFN α2a + RBV)	74% versus 45%	–	–	–
Relapse rate	–	–	–	–
Duration of PegIFN α2a + RBV	Fixed 48-week duration	–	–	–
Duration of HCV PI	12 weeks	–	–	–
PegIFN α2a + RBV lead-in	No	–	–	–
HCV monoinfected				
SVR rate (versus PegIFN α2a + RBV)	75% (n=271/363) versus 44% (n=158/361)	86% (n=245/286) versus 24% (n=16/68)	57% (n=55/97) versus 15% (n=4/27)	31% (n=46/147) versus 5% (n=2/37)
Relapse rate (versus PegIFN α2a + RBV)	9% (n=27/314) versus 28% (n=64/229)	3% (n=19/278) versus 63% (n=27/43)	20% (n=14/71) versus 0% (n=0/4)	24% (n=15/62) versus 50% (n=2/4)
Duration of PegIFN α2a + RBV	Response-guided (24 or 48 weeks)	Response-guided (24 versus 48 weeks)	Fixed 48-week duration	Fixed 48-week duration
Duration of HCV PI	12 weeks	12 weeks	12 weeks	12 weeks
PegIFN α2a + RBV lead-in	No	No	No	No

*If cirrhotic, then 48 weeks fixed duration, †Interim results from rollover study (132). PegIFN α2a Pegylated interferon alfa-2a; PI Protease inhibitor; RBV Ribavirin; SVR Sustained virological response

Telaprevir: In a randomized, double-blinded clinical trial, pegylated interferon alfa-2a and ribavirin with or without telaprevir was assessed in HIV-infected patients not on ART with CD4 lymphocyte counts >500 cells/μL (n=22, part A) and in patients receiving suppressive ART (n=38, part B) (Figure 1) (129). Antiretroviral regimens allowed in the study consisted of either efavirenz or atazanavir boosted with ritonavir, in combination with a tenofovir/emtricitabine or tenofovir/lamivudine backbone. Only two patients were cirrhotic and 43% to 80% of participants in the randomization groups were infected with genotype 1a. Most participants received a ribavirin dose of 800 mg per day based on the United States product monograph for pegylated interferon alfa-2a in HIV-HCV coinfectd individuals. A small number of participants from Germany and France received higher ribavirin doses as per the product monographs in these countries. Recipients received 48 weeks of fixed-duration pegylated interferon alfa-2a and ribavirin. Patients were dosed with either 12 weeks of telaprevir 750 mg every 8 h (1125 mg every 8 h for patients receiving efavirenz due to anticipated drug-drug interactions) or placebo. No lead-in was used. An overall SVR12 of 74% (n=38) was reported in triple therapy recipients compared with 45% in pegylated interferon alfa-2a and ribavirin recipients (n=22) (129). These data have subsequently been updated with release of SVR results at 24 weeks post-therapy (131). Overall, 74% of patients receiving telaprevir achieved an SVR compared with 45% of those receiving pegylated interferon and ribavirin. Overall relapse rates were 3% for those receiving telaprevir versus 15% for those receiving pegylated interferon and ribavirin. These SVR rates were similar

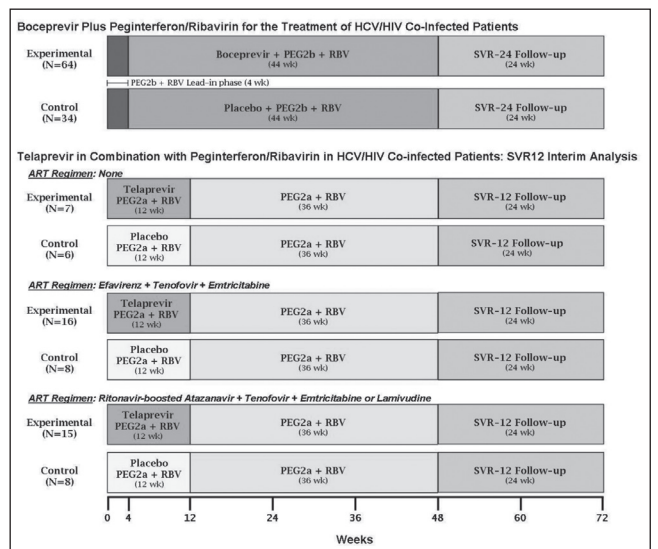


Figure 1 Study designs for hepatitis C virus (HCV) protease inhibitors in HIV-HCV coinfection. ART Antiretroviral therapy; PEG2a Pegylated interferon alfa-2a; RBV Ribavirin; SVR Sustained virological response; SVR12/24 SVR after 12 and 24 weeks' follow-up between those on ART and those who were not. SVR rates were comparable between atazanavir/ritonavir recipients and efavirenz recipients in both randomization groups.

TABLE 9
Stopping rules for protease inhibitor-containing hepatitis C (HCV) antiviral therapy in HIV-HCV coinfection

	Boceprevir		Telaprevir	
	HIV-HCV coinfection*	HCV mono-infection†	HIV-HCV coinfection*	HCV mono-infection‡
Week 4			HCV RNA >1000 IU/mL§	HCV RNA >1000 IU/mL§
Week 8			HCV RNA >1000 IU/mL§	
Week 12	Detectable HCV RNA, <2 log ₁₀ decline	HCV RNA >100 IU/mL‡	<u>Telaprevir patients:</u> HCV RNA ≤1000 IU/mL§ (at weeks 4 and 8), >1000 IU/mL§ (at week 12) <u>All other patients:</u> HCV RNA <2 log ₁₀ decline	HCV RNA >1000 IU/mL§
Week 24	HCV RNA ≥ LLOQ	Detectable HCV RNA	Detectable HCV RNA	Detectable HCV RNA

*Study criteria; †Product monograph, reference 126; ‡Product monograph, reference 169; §Discontinue telaprevir, continue pegylated interferon and ribavirin. LLOQ Lower limit of quantitation

Stopping rules were similar to those recommended for HCV mono-infected individuals: HCV RNA >1000 IU/mL or <2 log₁₀ reduction at week 12 of therapy or detectable HCV RNA at week 24 (Table 9).

There is limited research evaluating triple therapy in cirrhotic HIV-HCV coinfecting individuals because few cirrhotic patients were enrolled in the above-described treatment-naïve studies. HCV mono-infected cirrhotic patients achieved SVR rates in the range of 60% with triple therapy (Table 7) (122,124).

RECOMMENDATIONS

25. Genotype 1-infected HIV-HCV coinfecting patients should be treated with either boceprevir or telaprevir in combination with pegylated interferon and ribavirin (Class 1, Level A).
26. Telaprevir should be used for the first 12 weeks, while boceprevir should begin after a four-week lead-in of pegylated interferon and ribavirin and continue for the remainder of therapy (Class 1, Level A).
27. At this time, a full 48-week course of pegylated interferon and ribavirin is recommended because there is no current evidence regarding response-guided therapy in coinfecting patients (Class 1, Level C).
28. Standard stopping rules at weeks 4, 12 and 24 (telaprevir), or weeks 8, 12 and 24 (boceprevir) developed for mono-infection should be applied to the HIV-HCV coinfection context (Class 1, Level C).

Retreatment of coinfecting patients

There are currently no published data to guide triple therapy in previous genotype 1 HCV treatment-experienced HIV-HCV coinfecting individuals, although interim data on the use of both boceprevir and telaprevir have been presented in abstract form.

Data in HCV mono-infected patients demonstrate superior SVR rates in previous relapsers, partial responders and null responders receiving a PI plus pegylated interferon and ribavirin compared with pegylated interferon and ribavirin alone (122,124,132) (Table 6).

In two parallel, open-label, single-arm phase II studies (ANRS HC26 and HC27), HCV treatment-experienced HIV-HCV coinfecting patients received either telaprevir or boceprevir therapy (133,134). Patients were included if they had stable CD4 cell counts >200 cells/μL (CD4% >15%) with suppressed viral load on atazanavir/ritonavir- or raltegravir-based regimens (efavirenz was allowed in patients in the telaprevir trial). Both trials made use of a four-week lead-in of pegylated interferon and ribavirin. In ANRS HC26, participants (n=68) received 12 weeks of triple therapy following the lead-in, with additional pegylated interferon and ribavirin for a total of 48 or 72 weeks in a response-guided fashion dependent on results of the week 8 (week 4 of triple therapy) outcome (133). In ANRS HC27 (n=64), the lead-in phase was followed by 44 weeks of triple therapy with boceprevir (134). Those without a week 8 rapid virological response (RVR) would receive an additional 24 weeks

(total 72 weeks) of pegylated interferon. Interim results reveal high rates of early virological response (EVR) (measured in these trials at week 16 [EVR16] of therapy). In those receiving telaprevir, the overall EVR16 was 88%. There were no significant differences observed in terms of ART regimen, degree of fibrosis or previous response to therapy, with 85% response in previous relapsers, 100% in previous partial responders and 86% in null responders. For subjects receiving boceprevir, overall EVR16 was 63%. In this study, a graduated response was observed based on previous response, with 90%, 61% and 38% EVR16 observed in previous relapsers, nonresponders and null responders, respectively.

It is reasonable to assume that these encouraging interim findings will result in similar SVR outcomes to those observed in trials involving mono-infected patients, with highest SVR rates in previous relapsers (higher than treatment-naïve patients), intermediate SVR rates in previous partial responders and the lowest SVR rates in previous null responders, but it is unclear whether coinfecting patients will achieve similar outcomes. Cirrhotic patients with previous null response to pegylated interferon and ribavirin achieved very low SVR rates in HCV mono-infected studies. In the REALIZE study, only 14% (seven of 50) of cirrhotic patients with a previous null response achieved SVR when treated with telaprevir plus peginterferon and ribavirin (124). There are no data to guide treatment of HIV-HCV coinfecting patients with cirrhosis and a history of previous null response to pegylated interferon and ribavirin because these patients were excluded in the ANRS trials. However, a similarly low SVR rate would be anticipated with triple therapy.

The need to optimize additional factors such as CD4 cell count, steatohepatitis or insulin resistance in individuals undergoing retreatment is unclear in the setting of retreatment with HCV PI-containing regimens. Previous studies have suggested that insulin resistance may compromise retreatment with pegylated interferon and ribavirin alone (135). As in the case of treatment-naïve individuals, in patients being considered for retreatment, individuals with relatively stable mild hepatic disease may be followed with conservative management pending availability of combination DAA-based therapies. Individuals with more advanced liver disease may need to be retreated with currently available DAAs to prevent further disease progression. Retreatment in individuals with previous history of decompensated disease should be undertaken only in experienced centres with access to transplant services due to the risk of treatment-related decompensation.

RECOMMENDATION

29. No published SVR data currently exist for retreatment of genotype 1 null responders, partial responders or previous relapsers in the setting of HIV coinfection. However, retreatment following protocols developed for mono-infected patients can be considered (Class 2b, Level C).

Novel DAAs for genotype 1 coinfecting patients

Preliminary interim results of a phase III single arm study of the use of the once-daily HCV PI simeprevir in combination with pegylated

interferon and ribavirin have been presented (the TMC435-C212 study) (136). This trial enrolled treatment-naive individuals (n=50), previous relapsers (n=14), partial responders (n=10) and null responders (n=28) to receive 12 weeks of triple therapy with simeprevir, pegylated interferon and ribavirin followed by either response-guided pegylated interferon/ribavirin (24 or 48 weeks) in naive/relapsers, or 48 weeks total of pegylated interferon/ribavirin in treatment-experienced patients or those with cirrhosis. Acceptable antiretrovirals included raltegravir, rilpivirine and maraviroc in addition to standard NRTI backbones. Among treatment naive/relapsers, the combined SVR12 was 75%, and 88% of those eligible for response-guided therapy were able to stop after 24 weeks with SVR12 of 75%. No SVR data are currently available for partial and null responder patients, but in those with on-treatment virological failure, 37.5% were previous null responders.

At the present time, no recommendations can be made regarding simeprevir use in coinfecting patients in Canada. Simeprevir is not currently approved but has been submitted for regulatory review in the United States, Canada and Europe.

HCV therapy for nongenotype 1 infection

Genotype 2 and 3: The treatment of choice for HCV genotypes other than genotype 1 is dual therapy with pegylated interferon in combination with ribavirin. There are HIV-HCV coinfection data with significant numbers of patients with genotype 3, moderate numbers with genotype 4, limited numbers with genotype 2 and no data for genotypes 5 and 6 (137-139).

For HCV genotypes 2 and 3, the dose of ribavirin and the treatment duration in the HIV-coinfecting population are controversial. In HCV mono-infection, two randomized trials found no difference in SVR rates with 24 versus 48 weeks of therapy (140,141). Another randomized trial involving HCV mono-infected patients demonstrated higher SVR rates with 24 weeks than 16 weeks of therapy, even among those who achieved a RVR (142). Two randomized trials found no significant difference in SVR rates in mono-infected patients receiving an 800 mg daily dose of ribavirin compared with those receiving weight-based dosing (140,141). On the basis of the above studies, HCV mono-infected patients are treated for 24 weeks and 800 mg/day ribavirin.

In genotype 2 or 3 HIV-HCV coinfecting patients, treatment with pegylated interferon and ribavirin for 24 weeks using a ribavirin dose of 800 mg/day is associated with relapse rates of 32% to 40% (143-145). In contrast, treatment with pegylated interferon and ribavirin for 24 weeks using weight-based dosing is associated with a relapse rate of 9% to 15% (146,147). This is comparable with relapse rates of 10% to 16% observed with 24-week pegylated interferon/ribavirin therapy in the genotype 2 or 3 mono-infected populations (140,142,148). The probable explanation for the lower relapse rates observed with weight-based dosing in the HIV-coinfecting population is the substantially higher rate of RVR achieved compared with dosing at 800 mg/day. In a large randomized trial of pegylated interferon and ribavirin compared with standard interferon-based regimens (the APRICOT trial [138]), in which patients received ribavirin 800 mg daily, only 37% of genotype 2 and 3 patients achieved RVR. In contrast, in a subsequent trial conducted in Spain (the PRESCO trial [139]), in which patients received ribavirin 1000 mg daily if they weighed <75 kg and 1200 mg daily if they weighed ≥75 kg, RVR rates were 67%. Treating HIV-HCV genotype 2 and 3 coinfecting patients with pegylated interferon/ribavirin for 48 weeks is associated with low relapse rates of 3% to 13%, regardless of whether ribavirin is dosed at 800 mg or is weight-based (137-139). Overall, the data support current international guidelines, which recommend weight-based ribavirin dosing for coinfecting individuals with genotype 2 or 3 infection, a 24-week treatment duration in those who achieve RVR, and a 48-week treatment duration in those without RVR (Figure 2) (149). Additional consideration should be given to factors, such as degree of underlying fibrosis, that have been associated with decreased response, and longer duration of therapy in these individuals may be warranted.

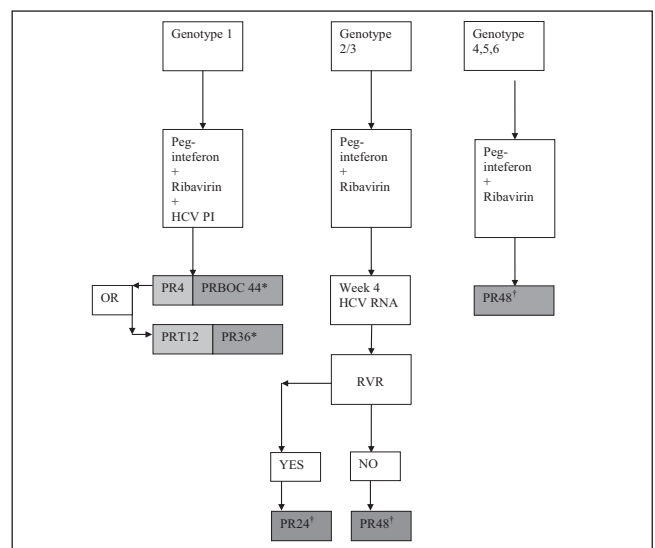


Figure 2 Treatment algorithms for coinfecting patients. *Standard stopping rules apply (telaprevir [T]: HCV RNA >100 IU/mL at week 4 and 12, detectable at week 24; boceprevir [BOC]: HCV RNA >1000 IU/mL at week 12, detectable at week 24); †Standard stopping rules apply: lack of early virological response at week 12, detectable hepatitis C virus (HCV) RNA at week 24. 4, 12, 24, 48 refer to weeks of therapy; PI Protease inhibitor; PR Pegylated interferon/ribavirin; RVR Rapid virological response (undetectable HCV RNA)

There are limited data regarding retreatment in individuals with genotypes 2 or 3. If flat-dose ribavirin and/or short treatment duration had initially been used, consideration may be given to retreatment, but no precise estimates of SVR in coinfecting patients are available.

At present, boceprevir and telaprevir are not believed to have significant activity against genotypes 2 and 3, and there are currently no data available regarding novel DAAs in genotypes 2 and 3 in HIV-HCV coinfecting patients.

Genotypes 4 to 6: For these genotypes, the traditional stopping rules for dual therapy apply, ie, failure to achieve at least a 2 log₁₀ decline in HCV RNA from baseline at week 12 of therapy or detectable HCV RNA at week 24 of therapy. For genotype 4, weight-based dosing of ribavirin is recommended, and the treatment duration is 48 weeks. There are no data regarding the use of DAAs in genotype 4 coinfecting patients currently available.

RECOMMENDATION

30. For genotypes 2 and 3, weight-based ribavirin dosing, a 24-week treatment duration in those who achieve RVR, and a 48-week treatment duration in those without RVR or in those with significant fibrosis is recommended (Class 1, Level A).

Treatment of acute HCV infection in coinfecting patients

Early studies with standard interferon alpha demonstrated high rates of virological response to therapy for acute HCV infection (150). With the advent of widespread recognition of sexual transmission of HCV in MSM populations, treatment for acute HCV is an increasingly common phenomenon (151). Although small studies have the use of non-ribavirin-containing regimens, SVR rates with this approach have been diminished, and the European NEAT consensus panel on the management of acute HCV currently recommends standard doses of pegylated interferon and weight-based ribavirin therapy for treatment of acute HCV (41). In cases in which an RVR is achieved, 24 weeks of therapy are recommended, with full 48-week therapy for those without RVR (41). Outcomes for those treated within 12 to 24 weeks of acquisition of HCV are higher than if therapy is delayed for >1 year (152, 153).

TABLE 10
Drug-drug interactions among antiretroviral agents, and telaprevir and boceprevir

Antiretroviral agent	Boceprevir	Telaprevir
Non-nucleoside reverse transcriptase inhibitors		
Efavirenz	44% ↓ C _{min} , 19% ↓ AUC of boceprevir (183). Avoid combination (126)	47% ↓ C _{min} of telaprevir (214); consider ↑ telaprevir dose to 1125 mg every 8 h with efavirenz (172)
Etravirine	29% ↓ C _{min} , 23% ↓ AUC of etravirine. Clinical relevance unclear (175)	No clinically significant changes in either drug. No dose adjustment required (173)
Rilpivirine	↑ 39% AUC, ↑ 15% C _{max} , ↑ 10% C _{min} of rilpivirine, not considered clinically significant. No dose adjustment required (176)	↑ 78% AUC, ↑ 49% C _{max} , ↑ 93% C _{min} of rilpivirine, not considered clinically significant. No dose adjustment required (173)
Protease inhibitors		
Atazanavir/ritonavir	49% ↓ C _{trough} , 35% ↓ AUC of atazanavir (170). Avoid combination	85% ↑ C _{min} of atazanavir (172). Combination may be used
Darunavir/ritonavir	59% ↓ C _{trough} , 44% ↓ AUC of darunavir and 32% ↓ boceprevir (170). Avoid combination	40% ↓ AUC and 42% ↓ C _{min} of darunavir, 35% ↓ AUC and 32% ↓ C _{min} of telaprevir (172). Avoid combination (169)
Fosamprenavir/ritonavir	No data	47% ↓ AUC and 56% ↓ C _{min} of amprenavir, 32% ↓ AUC and 30% ↓ C _{min} of telaprevir (172). Avoid combination (169)
Lopinavir/ritonavir	43% ↓ C _{trough} , 34% ↓ AUC of lopinavir and 45% ↓ boceprevir (170). Avoid combination	6% ↑ AUC and 14% ↑ C _{min} of lopinavir, 54% ↓ AUC and 52% ↓ C _{min} of telaprevir (172). Avoid combination (169)
Integrase inhibitors		
Raltegravir	No clinically significant changes in either drug. No dose adjustment required (177)	No clinically significant changes in either drug. No dose adjustment required (178)
Reverse transcriptase inhibitors		
Tenofovir	No clinically significant changes in either drug. No dose adjustment required (183)	No clinically significant changes in either drug. No dose adjustment required (184)

↑ Increase; ↓ Decrease; AUC Area under the curve; C_{max} Maximum plasma concentration; C_{min} Minimum plasma concentration occurring during the dosing interval; C_{trough} Minimum plasma concentration immediately before the next dose

Drug-drug interactions between antiretrovirals and HCV therapeutic agents

Didanosine, stavudine and zidovudine should be avoided with pegylated interferon and ribavirin because of increased risks of mitochondrial toxicity and anemia (154,155). It is important to achieve adequate ribavirin trough levels via weight-based dosing (154,156). Although some controversy exists as to whether concomitant abacavir diminishes ribavirin activity, larger cohort studies have not demonstrated diminished SVR (157-161). In addition, recent *in vitro* studies have demonstrated no such effect (162,163). There is sufficient evidence to recommend continued use of this agent during HCV therapy with weight-based ribavirin dosing (164).

Drug-drug interactions of DAAs

The potential for interactions between HCV PIs and other drug classes is high due to the pharmacological characteristics of these HCV agents, particularly in the context of earlier ART initiation, the aging HIV population and need for management of comorbidities (165-167).

Boceprevir and telaprevir are substrates and inhibitors of cytochrome P450 (CYP450) 3A4 (CYP3A4). Both agents also inhibit P-glycoprotein, and telaprevir may inhibit renal transporters. Similarly, HIV PIs and NNRTIs are substrates and inhibitors or inducers of numerous CYP450 hepatic enzymes and transporters. The CCR5 inhibitor maraviroc is a CYP3A4 substrate but does not exert inhibiting or inducing effects on the P450 system. Therefore, there is a high potential for drug interactions in the coinfecting population, particularly if simultaneous treatment of HCV and HIV is required.

Negative consequences of drug interactions include HIV and HCV viral breakthrough and development of resistance, suboptimal disease/symptom management, or drug toxicities and possible nonadherence (168).

A summary of potential and demonstrated pharmacokinetic interactions between antiretroviral agents and DAAs is presented in Table 10. Negative two-way pharmacokinetic interactions have been observed in healthy volunteers between both boceprevir and telaprevir, and ritonavir-boosted PIs, with significant reductions in exposures of HCV agents and HIV PIs. Therefore, telaprevir should not be

coadministered with ritonavir-boosted darunavir, fosamprenavir or lopinavir (169), and boceprevir is not recommended for use with ritonavir-boosted atazanavir, darunavir or lopinavir (170). It is worth noting that in the trial of boceprevir in coinfecting patients, use of these PI agents was allowed, with no obvious rebound in HIV viral load (130). Recent case reports support this finding in patients with full virological suppression, and the potential increase in HIV PI levels in advanced liver disease as well as the anti-HIV activity of interferon may overcome negative interactions (171).

Telaprevir should be used at a higher dose (1125 mg every 8 h) with efavirenz (172). Dose adjustment with etravirine or rilpivirine is not required based on healthy volunteer data (173). In contrast, boceprevir concentrations are significantly reduced in the presence of efavirenz. This combination should be avoided (174). Etravirine concentrations are reduced in the presence of boceprevir but the clinical significance is uncertain. Therefore, recommendations pertaining to coadministration cannot be made (175). Recent data in healthy volunteers did not demonstrate significant interactions between rilpivirine and boceprevir, and concomitant therapy may be possible (176). Rilpivirine was safely coadministered with simeprevir in the TMC435-C212 study (138).

Raltegravir is not a CYP450 substrate, inducer or inhibitor, and may be used with both HCV PIs without dosage adjustment (177-179). Underlying HIV resistance mutations may compromise HIV suppression if individuals are switched from a robust PI-based regimen to raltegravir to accommodate DAA use. Regimen switches of this nature must take into account previous HIV therapies (180). Of note, the integrase inhibitor elvitegravir is a CYP3A4 substrate, and is coformulated with the pharmacokinetic booster cobicistat. There is potential for interaction with boceprevir and telaprevir based on pharmacokinetic properties; therefore, coadministration should be avoided until additional data are available (181). Dolutegravir is an integrase inhibitor in late-stage development. Similar to raltegravir, it is not a P450 substrate, inducer or inhibitor, and may be used with both boceprevir and telaprevir without dosage adjustment (182).

Tenofovir is eliminated renally. In healthy volunteer studies, peak plasma concentration of tenofovir was increased in the presence of boceprevir (183) and tenofovir area under the curve was increased in

TABLE 11
Contraindicated medications arising from drug-drug interactions with boceprevir (BOC) and telaprevir (TVR)

Medication	Contraindicated	Potential clinical impact
Aldosterone antagonist	Eplerenone (TVR)	Hyperkalemia
Alpha-1-adrenoreceptor antagonist	Alfuzosin	Hypotension, cardiac arrhythmia
Antiarrhythmics	Amiodarone, quinidine, propafenone, flecainide (TVR)	Serious/life-threatening cardiac arrhythmia
Anticonvulsants	Carbamazepine, phenytoin, phenobarbital (BOC)	Loss of HCV virological response
Antihistamines	Astemizole, terfenadine (TVR)	Serious/life-threatening cardiac arrhythmia
Antimycobacterials	Rifampin	Loss of HCV virological response
Benzodiazepines	Oral midazolam, triazolam	Increased sedation or respiratory depression
Ergot derivatives	Dihydroergotamine, ergonovine, ergotamine, methylergonovine	Acute ergot toxicity characterized by peripheral vasospasm or ischemia
Gastrointestinal motility agent	Cisapride	Serious/life-threatening cardiac arrhythmia
Herbal products	St John's wort	Loss of HCV virological response
HMG-CoA reductase inhibitors	Lovastatin, simvastatin, atorvastatin (TVR)	Myopathy including rhabdomyolysis
Neuroleptic	Pimozide	Serious/life-threatening cardiac arrhythmia
Oral contraceptives	Drospirenone (BOC)	Hyperkalemia
Phosphodiesterase type 5 inhibitors	Sildenafil, tadalafil (BOC), vardenafil (TVR)	Visual abnormalities, hypotension, prolonged erection, syncope
Triptans	Eletriptan	Coronary artery vasospasm, myocardial infarction, ventricular tachycardia, ventricular fibrillation

HCV Hepatitis C virus; HMG-CoA 5-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins)

the presence of telaprevir (184). These changes are not considered to be clinically relevant, and tenofovir may be coadministered with both boceprevir and telaprevir.

Maraviroc is a CYP3A4 substrate, but does not exert enzyme inhibiting or inducing effects itself. Maraviroc should be dosed at 150 mg twice daily when given concomitantly with either boceprevir or telaprevir (185).

RECOMMENDATIONS

31. Careful attention to drug-drug interactions between HCV antivirals and concurrently administered HIV and non-HIV medications is critical to avoid viral breakthrough of either HIV or HCV, development of resistance, suboptimal disease/symptom management and drug toxicities (Class 1, Level C).
32. Use of zidovudine, stavudine and didanosine regimens should be avoided in coinfecting patients being considered for HCV therapy (Class 1, Level C).
33. For individuals with genotype 1 infection initiating HCV therapy, use of raltegravir-based regimens (boceprevir and telaprevir) or atazanavir/ritonavir (telaprevir) are first-line antiretroviral options (Class 2b, Level B). Rilpivirine-based therapy may be an acceptable first-line regimen (telaprevir, boceprevir).
34. For individuals with genotype 1 infection initiating HCV therapy, use of efavirenz (telaprevir with dose adjustment), or etravirine (acceptable with telaprevir but clinical implications of a potential interaction with boceprevir remain uncertain) and maraviroc (telaprevir, boceprevir) may be considered (Class 2b, Level B).
35. For individuals with genotype 1 infection initiating HCV therapy, switching from alternative regimens to an acceptable regimen as listed above can be considered if HIV treatment history and resistance profile permits such a switch.
36. For patients with HIV multidrug resistance who are well controlled on nonpreferred ART regimens, initiation of triple therapy, including DAAs, may be considered in consultation with an expert physician and pharmacist with experience in managing HIV and HCV drug interactions.

Interactions between DAAs and other drug classes

Many common drugs from multiple different classes are at risk of drug interactions with DAAs. (Table 11). The product monographs of

boceprevir and telaprevir provide a list of drugs with known or potential CYP3A4 interactions (126,169). Examples of interacting drug classes include benzodiazepines (eg, midazolam), 5-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins), macrolides, rifamycins (eg, rifampin), anticonvulsants, antiarrhythmics, psychotropics, antifungals, erectile dysfunction drugs, antipsychotics, inhaled corticosteroids, calcium channel blockers, immunosuppressants and others (126,166,169,186). The management of these complex medication combinations requires expert knowledge. Substitution or safe discontinuation of the interacting drug can be attempted after careful evaluation of the benefit-risk ratio.

Methadone has the potential to interact with DAAs because it is metabolized by CYP2C19 and 3A4. The coadministration of methadone and telaprevir was shown to result in a 21% decrease of the active enantiomer R-methadone exposure (187). However, free concentrations of the active enantiomer R-methadone were unaffected and, therefore, no dose adjustment is necessary. Buprenorphine pharmacokinetics are not affected by telaprevir and it is safe for coadministration (188). Boceprevir was studied with methadone, buprenorphine and naloxone. Similar to telaprevir, boceprevir led to a 15% decrease of R-methadone exposure. No free methadone concentrations were performed. Boceprevir was also associated with an increase of naloxone and buprenorphine exposure by 19% and 33%, respectively, which is considered to be clinically nonsignificant (189).

RECOMMENDATIONS

37. Assessment and monitoring of drug-drug interactions between boceprevir and telaprevir and commonly prescribed medications should occur at baseline and at frequent intervals during HCV therapy (Class 1, Level C).
38. Ensuring that medication records are up to date, use of a systematic approach to identify combinations of potential concern, consulting pertinent HIV and/or HCV drug interaction resources (eg, www.hiv-druginteractions.org, www.hivclinic.ca, www.hep-druginteractions.org, www.hcvdruginfo.ca) and frequent patient monitoring are recommended to mitigate drug-drug interaction risk (Class 1, Level C).
39. Nonessential medications should be discontinued for the duration of HCV treatment, particularly when HCV PIs are used (Class 1, Level C).

V. ADVERSE EVENTS AND MANAGEMENT OF TREATMENT-RELATED CYTOPENIAS

Both HIV antiretrovirals and current HCV antivirals have multiple side effects. For instance, pegylated interferon and ribavirin have side effects that overlap with those of efavirenz, potentially resulting in additive central nervous system effects including depression, mood changes and suicidality. A comprehensive review of HCV antiviral treatment side effects and management is beyond the scope of the present guideline statement but can be found elsewhere (190).

With boceprevir-containing triple therapy, the types of adverse events appear to be similar in frequency and severity to those reported in HCV monoinfected patients (128). Gastrointestinal adverse effects, including anorexia, diarrhea, vomiting and dysgeusia, were more frequent in boceprevir recipients (28% to 34%) versus 15% to 18% in those who received only pegylated interferon and ribavirin. Adverse events with HIV-HCV coinfecting recipients of telaprevir-interferon-ribavirin therapy were similar in frequency and severity to HCV monoinfected study populations receiving telaprevir-containing therapy (131). No severe rashes occurred in either group. Mild and moderate severity rashes occurred in 34% and 23% of telaprevir and placebo recipients, respectively.

Cytopenias are of particular relevance in HIV-HCV coinfection. Interferon causes a decrease in the total lymphocyte count, which can affect CD4 T cell count interpretation. CD4 percentage, rather than the absolute number, may be a more appropriate measure of immunological efficacy during HCV antiviral treatment. Prophylaxis for *Pneumocystis carinii* pneumonia and other opportunistic infections is not routinely recommended in cases in which the absolute CD4 count falls below 200 cells/ μ L or CD4 percentage declines below 20% during therapy with pegylated interferon and ribavirin, although some practitioners may choose to do so.

Anemia is a common treatment-related adverse event and is a consequence of ribavirin-related hemolysis, and boceprevir, telaprevir and interferon bone marrow suppression. Anemia developed in 37% of monoinfected treatment-naïve individuals receiving telaprevir compared with 19% in pegylated interferon/ribavirin recipients (123), with 9% developing a hemoglobin level <85 g/L compared with 2% in the control arm. In boceprevir studies involving treatment-naïve populations, anemia was observed in 49% of boceprevir subjects versus 29% of controls (121). Overall, 13% of controls and 21% of boceprevir recipients required ribavirin dose reductions because of anemia. Erythropoietin was administered in 24% of controls and 43% of boceprevir recipients (121).

Anemia rates in HIV-HCV coinfecting patients appear to be similar to those observed in monoinfected individuals. In boceprevir-treated patients, rates of anemia were 41% compared with 26% in the control arm (128). Erythropoietin was used in 38% and 21% of study patients.

Development of anemia or ribavirin dose reduction in mono-infected individuals is not associated with decreased SVR in boceprevir- or telaprevir-treated patients. Furthermore, there was no difference in SVR between those in whom ribavirin dose reduction was used to manage anemia compared with patients managed with erythropoietin (191). Similar data are not available for HIV-HCV coinfecting populations.

Neutropenia is related to interferon therapy, and increased rates of neutropenia were also observed in individuals receiving boceprevir (121). However, infection risk is not increased with HCV treatment-related neutropenia. In a retrospective analysis of 192 individuals who received HCV therapy between 2000 and 2005 (192), the infection rate was 1.17 per 100 person-weeks of therapy. In regression analysis, no association with degree of neutropenia was identified (192). Similar results have been observed in other cohorts (193,194) and a randomized trial of dose reduction versus growth factor (granulocyte colony stimulating factor or erythropoietin) for HCV-related cytopenias in HIV-HCV coinfection (195). These results suggest use of aggressive dose reduction of interferon or use of granulocyte colony-stimulating factor are not warranted.

Cirrhotic HCV monoinfected patients treated with boceprevir and telaprevir through the compassionate access program in France (CUPIC ANRS C020) experienced increased risk of severe side effects, including anemia, with need for transfusions and use of erythropoietin. Overall, side effects were more severe in this cohort, and included sepsis, liver decompensation and several reported deaths (196). In CUPIC, the combination of baseline albumin level <35 g/L and platelets <100 \times 10⁹/L identified patients at high risk for experiencing sepsis, liver decompensation or death.

RECOMMENDATIONS

40. Close monitoring for side effects during HCV therapy is required (Class 1, Level C).
41. Anemia related to HCV PIs should be primarily managed with ribavirin dose reduction. Erythropoietin use is not recommended for first-line management of anemia (Class 2b, Level B).
42. Neutropenia developing during HCV therapy is not associated with increased infection risk. Aggressive dose reduction of pegylated interferon and/or ribavirin, or granulocyte colony stimulating factor use is not recommended (Class 2b, Level C).

VI. HIV AND LIVER TRANSPLANTATION

The management of ESLD includes orthotopic liver transplantation. HIV should not be a contraindication to transplant. Guidelines for liver transplant have been developed in both Europe and the United States (197-199). In addition to meeting requirements for liver transplantation, HIV-infected patients must demonstrate virological suppression and CD4 counts >200 cells/ μ L, and must have no recent history of opportunistic infections. Although outcomes of transplant among HIV-infected individuals have been evaluated in only small cohort studies, short-term outcomes appear to be similar to general transplant populations, while long-term survival may be reduced and infectious complications increased (200-202). A recent review (203) of the transplant program in Spain (84 coinfecting patients) found a five-year survival rate of 54% compared with 71% for HCV monoinfected patients. Similarly, in a review of the German transplant experience (204), 60% (19 of 32) of patients had a median survival of 60 months.

HCV recurrence is nearly universal after transplantation in both monoinfected and coinfecting patients. Treatment of HCV post-transplant is complex. Consideration of use of current DAAs is, again, limited by drug-drug interactions. DAAs are known to interfere with CYP3A4 and P-glycoprotein, but the predicted interaction is not always as expected (205). Liver transplant patients on immunosuppressive drugs are at particular risk for serious drug interactions because cyclosporine and tacrolimus metabolism are highly dependent on CYP3A4 (206). Boceprevir and telaprevir interaction with cyclosporine in healthy volunteers led to an increase of cyclosporine exposure by 2.7- and 4.6-fold, respectively (207,208). The magnitude of the interaction was greater with tacrolimus, with an increase of 17- and 70-fold for boceprevir and telaprevir exposure, respectively. Clearly, there is a need for the development of a dosing protocol for immunosuppressive drugs. In the meantime, extreme caution is to be exercised. Until more information is available in HCV-infected individuals, the decision to coadminister current DAAs with cyclosporine or tacrolimus should be made on a case-by-case basis with the support of experts in pharmacology, hepatology and infectious diseases (209,210). Fortunately, the investigational DAAs simeprevir and sofosbuvir, both of which have been submitted for regulatory review, have no significant drug interactions with tacrolimus or sirolimus.

RECOMMENDATION

43. HIV-HCV coinfecting patients should be considered for liver transplantation, assuming all necessary criteria are met (Class 2a, Level C).

CONCLUSIONS

HIV-HCV coinfection is common in Canada and is associated predominantly with history of receipt of HCV-infected blood products before universal screening, or history of substance use; sexual transmission among HIV-infected MSM has also emerged as a risk for acquiring HCV. Coinfected individuals have a heavy burden of concurrent comorbid conditions that affect health status and outcomes. As such, harm-reduction strategies should be implemented to decrease risk of infection among high-risk populations such as injection drug users and incarcerated individuals.

Coinfection is associated with increased risk of progression of liver disease. ESLD is a chief cause of morbidity and mortality among coinfecting individuals.

All HIV-HCV coinfecting individuals should be assessed for HCV therapy. Early initiation at CD4 cell counts ≥ 500 cells/ μ L may avoid drug-drug interactions, diminish pill burden issues due to concomitant HIV and HCV medication dosing, and improve future tolerability of antiretroviral agents. In individuals who are unable to initiate HCV therapy due to unstable comorbid conditions, consideration should be given to early ART initiation as a means to slow liver disease progression.

Current standard of care for genotype 1-infected patients consists of pegylated interferon, ribavirin and a HCV PI (boceprevir or telaprevir). Careful assessment of drug-drug interactions with ART and other common medications is necessary when using these agents. At present, a fixed-duration 48-week course of total therapy with pegylated interferon and ribavirin, with 12 weeks of telaprevir or 44 weeks of boceprevir, is recommended. Currently, there are no data to guide decisions regarding shortening treatment length or retreatment in coinfecting individuals.

Current standard of care for genotype 2/3-infected patients remains dual therapy with pegylated interferon and ribavirin. Weight-based dosing of ribavirin is recommended. Response-guided therapy can be undertaken with 24 weeks of therapy if an RVR is achieved, and 48 weeks if a RVR is not attained or cirrhosis is present.

In individuals with mild liver disease, conservative monitoring with deferral of therapy pending access to novel DAA regimens with anticipated lower pill burden and fewer adverse events may be considered.

HIV should not be considered a barrier to liver transplant in coinfecting patients.

SUMMARY OF RECOMMENDATIONS

I. Epidemiology of HIV and hepatitis C virus coinfection

- All HIV-positive individuals should undergo screening for HCV antibodies when first evaluated. Screening should be repeated periodically – at least annually, particularly for high-risk individuals initially found to be negative (such as active injection drug users, Aboriginal peoples and individuals who are/have been incarcerated). HIV-positive MSM should undergo screening for HCV antibodies annually in combination with testing of liver enzyme levels every six months if sexually active with high-risk behaviours, and repeat HCV antibody testing (with consideration of additional HCV RNA testing) should be performed whenever unexplained elevations in liver enzyme levels are noted (Class 2a, Level C).
- Identification of HCV coinfection in HIV provides opportunities for prevention of transmission, risk reduction, counselling, and linkage to care and harm-reduction services (Class 1, Level C).
- Initiation of ART may serve to slow progression of liver disease in coinfecting patients. Early initiation of ART is recommended for all individuals with CD4 count < 500 cells/ μ L (Class 1, Level B).

II. Managing HIV in the setting of coinfection

- Initiation of ART in individuals with CD4 count ≥ 500 cell/ μ L can be considered if initiation of HCV therapy is not believed

to be an option (Class 2a, Level B) in patients who have undergone thorough assessment of barriers to ART adherence and counselling regarding the long-term nature of ART.

- Current first- and second-line ART regimens should be initiated as per current guidelines because they are effective and well-tolerated in coinfecting patients (Class 1, Level A).
- HCV therapy should be considered before ART initiation in individuals with early HIV disease as a potential means of decreasing risk of antiretroviral-related hepatotoxicity and to avoid risk of drug interactions between ART and HCV therapies (Class 2a, Level C).

III. Baseline evaluation and management of HCV in coinfecting patients

- Patients with confirmed HCV antibody should be evaluated using HCV RNA polymerase chain reaction (Class 1, Level C).
- Individuals with positive HCV RNA tests should undergo HCV genotyping (Class 1, Level C).
- Individuals with negative HCV RNA tests should undergo repeat testing at least once to confirm spontaneous clearance if liver enzyme levels are elevated (Class 1, Level C).
- All patients should undergo screening for hepatitis A and B, and should be offered vaccination if nonimmune (Class 1, Level C).
- Patients should be evaluated for other conditions that may result in or aggravate chronic liver disease (Table 4) (Class 1, Level C).
- All patients should be counselled regarding alcohol reduction/abstinence (Class 1, Level C).
- ALT criteria alone should not be used to determine the need for treatment initiation in coinfecting patients (Class 2a, Level C).
- Baseline abdominal ultrasound should be considered in all patients (Class 2a, Level B).
- Baseline evaluation of liver fibrosis (eg, Fibroscan, Fibrotest, APRI) to determine the degree of hepatic fibrosis and urgency for HCV therapy is advised (Class 2a, Level B).
- Evaluation of liver fibrosis with liver biopsy can be considered if noninvasive methods of determining fibrosis are not available or if alternative diagnoses are being considered.
- Patients with evidence of underlying cirrhosis should be screened every six months for HCC using ultrasound (Class 1, Level B).
- Patients with underlying cirrhosis should be considered for gastroscopy to screen for esophageal varices (Class 1, Level B).

IV. HCV therapy in coinfecting patients

- All coinfecting patients should undergo evaluation for HCV therapy (Class 1, Level A).
- Evaluation of factors such as substance use/addictions, mental health, and housing and food security is vital when preparing for HCV therapy (Class 1, Level B).
- Addiction should not be considered to be an absolute exclusion criteria for HCV therapy.
- Multidisciplinary care is recommended to optimally support patients as they progress through HCV work-up and treatment (Class 1, Level B).
- A detailed assessment for interferon-based treatment contraindications is essential (Class 1, Level C).
- Appropriate levels of funding for HCV treatment programs and removal of barriers to HCV antiviral therapy are necessary to optimize engagement in care and treatment outcomes (Class 1, Level C).
- Genotype 1-infected HIV-HCV coinfecting patients should be treated with either boceprevir or telaprevir in combination with pegylated interferon and ribavirin (Class 1, Level A).

26. Telaprevir should be used for the first 12 weeks, while boceprevir should begin after a four-week lead-in of pegylated interferon and ribavirin and continue for the remainder of therapy (Class 1, Level A).
27. At this time, a full 48-week course of pegylated interferon and ribavirin is recommended because there is no current evidence regarding response-guided therapy in coinfecting patients (Class 1, Level C).
28. Standard stopping rules at weeks 4, 12 and 24 (telaprevir), or 8, 12 and 24 (boceprevir) developed for mono-infection should be applied to the HIV-HCV coinfection context (Class 1, Level C).
29. No published SVR data currently exist for retreatment of genotype 1 null responders, partial responders or previous relapsers in the setting of HIV coinfection. However, retreatment following protocols developed for mono-infected patients can be considered (Class 2b, Level C).
30. For genotypes 2 and 3, weight-based ribavirin dosing, a 24-week treatment duration in those who achieve RVR, and a 48-week treatment duration in those without RVR or in those with significant fibrosis is recommended (Class 1, Level A).
31. Careful attention to drug-drug interactions between HCV antivirals and concurrently administered HIV and non-HIV medications is critical to avoid viral breakthrough of either HIV or HCV, development of resistance, suboptimal disease/symptom management and drug toxicities (Class 1, Level C).
32. Use of zidovudine, stavudine and didanosine regimens should be avoided in coinfecting patients being considered for HCV therapy (Class 1, Level C).
33. For individuals with genotype 1 infection initiating HCV therapy, use of raltegravir-based regimens (boceprevir and telaprevir) or atazanavir/ritonavir (telaprevir) are first-line antiretroviral options (Class 2b, Level B). Rilpivirine-based therapy may be an acceptable first-line regimen (telaprevir, boceprevir).
34. For individuals with genotype 1 infection initiating HCV therapy, use of efavirenz (telaprevir with dose adjustment), or etravirine (acceptable with telaprevir but clinical implications of a potential interaction with boceprevir remain uncertain) and maraviroc (telaprevir, boceprevir) may be considered (Class 2b, Level B).
35. For individuals with genotype 1 infection initiating HCV therapy, switching from alternative regimens to an acceptable regimen as listed above can be considered if HIV treatment history and resistance profile permits such a switch.
36. For patients with HIV multidrug resistance who are well controlled on non-preferred ART regimens, initiation of triple therapy, including DAAs, may be considered in consultation with an expert physician and pharmacist with experience in managing HIV and HCV drug interactions.
37. Assessment and monitoring of drug-drug interactions between boceprevir and telaprevir and commonly prescribed medications should occur at baseline and at frequent intervals during HCV therapy (Class 1, Level C).
38. Ensuring that medication records are up to date, use of a systematic approach to identify combinations of potential concern, consulting pertinent HIV and/or HCV drug interaction resources (eg, www.hiv-druginteractions.org, www.hivclinic.ca, www.hep-druginteractions.org, www.hcvdruginfo.ca) and frequent patient monitoring are recommended to mitigate drug-drug interaction risk (Class 1, Level C).
39. Nonessential medications should be discontinued for the duration of HCV treatment, particularly when HCV PIs are used (Class 1, Level C).

V. Adverse events and management of treatment-related cytopenias

40. Close monitoring for side effects during HCV therapy is required (Class 1, Level C).

41. Anemia related to HCV PIs should be primarily managed with ribavirin dose reduction. Erythropoietin use is not recommended for first-line anemia management (Class 2b, Level B).
42. Neutropenia developing during HCV therapy is not associated with increased infection risk. Aggressive dose reduction of pegylated interferon and/or ribavirin, or granulocyte colony-stimulating factor use is not recommended (Class 2b, Level C).

VI. HIV and liver transplantation

43. HIV-HCV coinfecting patients should be considered for liver transplantation assuming all necessary criteria are met (Class 2a, Level C).

APPENDIX

The CIHR Canadian HIV Trials Network HIV-HCV Coinfection Guideline Working Group includes:

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