

CIHR Canadian HIV Trials Network Co-Infection and Concurrent Diseases Core: Updated Canadian guidelines for the treatment of hepatitis C infection in HIV-hepatitis C coinfecting adults

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M Hull, S Shafran, A Tseng, et al. CIHR Canadian HIV Trials Network Coinfection and Concurrent Diseases Core: Updated Canadian adult guidelines for the treatment of hepatitis C infection in HIV-hepatitis C coinfecting patients. *Can J Infect Dis Med Microbiol* 2014;25(6):311-320.

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. Management of HIV-HCV coinfection 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 update national standards for the management of HCV-HIV coinfecting adults in the Canadian context.

METHODS: A standing working group with specific clinical expertise in HIV-HCV coinfection was convened by The Canadian Institute of Health Research HIV Trials Network to review recently published data regarding HCV antiviral treatments and to update the Canadian HIV-HCV coinfection guidelines.

RESULTS: Recent data suggest that the gap in sustained virological response rates between HCV mono-infection and HIV-HCV coinfection has been eliminated with newer HCV antiviral regimens. All HIV-HCV coinfecting individuals should be assessed for HCV therapy. First-line treatment for genotypes 1 through 6 includes pegylated interferon and weight-based ribavirin dosing plus the nucleotide sofosbuvir for 12 weeks. Sofosbuvir in combination with the protease inhibitor simeprevir is another first-line consideration for genotype 1 infection. Sofosbuvir with ribavirin for 12 weeks (genotype 2) and 24 weeks (genotype 3) is also recommended as first-line treatment.

DISCUSSION: Recommendations may not supersede individual clinical judgement.

Key Words: Antivirals; Coinfection; HCV; HIV; Treatment; Updated guidelines

Le domaine des co-infections et des maladies concomitantes du Réseau canadien pour les essais VIH des IRSC : mise à jour des lignes directrices canadiennes pour le traitement de l'infection par l'hépatite C chez des adultes co-infectés par le VIH

HISTORIQUE : De 20 % à 30 % des Canadiens qui vivent avec le VIH sont co-infectés par le virus de l'hépatite C (VHC), lequel est responsable d'une morbidité et d'une mortalité importantes. La prise en charge du VIH et du VHC est plus complexe en raison de l'évolution accélérée de la maladie hépatique, du choix et des critères d'initiation de la thérapie antirétrovirale et du traitement anti-VHC, de la prise en charge de la santé mentale et des toxicomanies, des obstacles socioéconomiques et des interactions entre les nouvelles thérapies antivirales à action directe du VHC et les antirétroviraux.

OBJECTIF : Mettre à jour les normes nationales pour la prise en charge des adultes co-infectés par le VHC et le VIH dans le contexte canadien.

MÉTHODOLOGIE : Le Réseau canadien pour les essais VIH des Instituts de recherche en santé du Canada a réuni un groupe d'experts possédant des compétences cliniques en co-infection par le VIH et le VHC pour réviser les publications récentes sur les traitements antiviraux contre le VHC et mettre à jour les lignes directrices canadiennes sur la co-infection du VIH et du VHC.

RÉSULTATS : Selon de récentes données, les nouvelles posologies antivirales ont éliminé la disparité entre le taux de réponse virologique soutenue de la mono-infection par le VIH et celui de la co-infection par le VIH et le VHC. Toutes les personnes co-infectées par le VIH et le VHC devraient subir une évaluation en vue de recevoir un traitement du VHC. Le traitement de première ligne du VHC des génotypes 1 à 6 inclut un régime composé d'interféron pégylé et de ribavirine dosée en fonction du poids, associé au sofosbuvir, un analogue des nucléotides, pendant 12 semaines. Le sofosbuvir combiné au siméprévir, un inhibiteur de la protéase, peut également constituer un traitement de première ligne pour l'infection par le génotype 1. Le sofosbuvir associé à de la ribavirine pendant 12 semaines (génotype 2) et 24 semaines (génotype 3) est également recommandé en première ligne.

EXPOSÉ : Les recommandations ne se substituent pas nécessairement au jugement clinique personnel.

Since the publication of the Canadian guidelines for the management and treatment of HIV-hepatitis C virus (HCV) coinfection in December 2013 (1), there have been substantial developments in the field of HCV therapeutic management. In addition to the

publication of new information regarding dosing and duration of currently available agents for HCV therapy, two new HCV direct-acting antiviral agents (DAAs) have been licensed for use in Canada and the United States. The availability of these agents (sofosbuvir and

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TABLE 1
Virological response definitions while on hepatitis C virus (HCV) therapy

Definition	Time point	HCV RNA level	Comment
RVR	Week 4	Undetectable	High positive predictive value 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 has very high (>98%) negative predictive value for SVR
eRVR	Week 4, 12	Undetectable	High positive predictive value for SVR with telaprevir- and simeprevir-based triple therapy
Partial response	Week 12+	Partial EVR at week 12 with no subsequent negative HCV RNA test	Treatment failure (pEVR + week 24 HCV RNA detectable, has 100% NPV for SVR)
EOT response	Treatment completion (number of weeks, varies by regimen)	Undetectable	
Relapser	Any time after EOT (usually checked 12 or 24 weeks after EOT)	Undetectable at EOT, detectable after EOT	Treatment failure (relapse >12 weeks after EOT suggests possibility of reinfection; viral sequencing should be considered)
SVR12	Week 60	Undetectable	Predicts SVR24 in monoinfected patients
SVR24	Week 72	Undetectable	Treatment success

EOT End of treatment; *eRVR* Extended rapid virological response; *EVR* Early virological response; *NPV* Negative predictive value; *pEVR* Partial EVR; *RVR* Rapid virological response; *SVR* Sustained virological response; *SVR12* SVR after 12 weeks of follow-up; *SVR24* SVR after 24 weeks of follow-up

simeprevir) has required revised recommendations for therapy in HCV monoinfected individuals (2). Furthermore, it is anticipated that several interferon-free, oral combination DAA regimens will be approved by Health Canada within a year (3-5). In the present article, we review current protocols for the treatment of HCV in the setting of HIV coinfection and make recommendations for the use of the newer, currently available HCV DAAs. These guidelines will continue to be updated on a regular basis as new agents become available for use.

CURRENT HCV THERAPY IN GENOTYPE 1 COINFECTED PATIENTS

The standard of care for genotype 1 HCV-infected individuals since the latter part of 2011 comprises triple therapy with pegylated interferon, ribavirin and a HCV protease inhibitor (boceprevir or telaprevir). Published phase III studies investigating both boceprevir and telaprevir in HCV-monoinfected populations demonstrate markedly improved sustained virological response (SVR) rates compared with dual peginterferon plus ribavirin therapy in treatment-naive, previous relapser, previous partial responder and previous null responder populations (6-9).

Results from two phase II randomized comparative studies indicate markedly improved SVR outcomes with these triple-therapy regimens for HCV genotype 1 treatment-naive patients coinfecting with HIV (10,11). SVR rates achieved in these studies now approximate those observed in monoinfected patients (63% to 74%), a significant improvement over the rates observed in pegylated interferon/ribavirin trials (12).

Telaprevir-based therapy in coinfection

A randomized, double-blinded clinical trial compared pegylated interferon α -2a and ribavirin with or without telaprevir in HIV-seropositive, HCV genotype 1-infected patients not receiving antiretroviral therapy (ART) with CD4 counts >500 cells/ μ L (n=13, Part A) and in patients receiving suppressive ART (n=24, Part B) (10). Overall, 74% of patients receiving telaprevir achieved an SVR, compared with 45% of those receiving pegylated interferon and ribavirin. Relapse rates were 3% for patients receiving telaprevir versus 15% in patients receiving pegylated interferon and ribavirin. SVR rates were similar between patients taking ART and those not taking ART. Serious adverse events were observed in 5% of patients receiving 48 weeks of fixed-duration pegylated interferon α -2a and ribavirin (the majority received fixed 800 mg ribavirin dosing with a few subjects receiving weight-based dosing). Patients were dosed with either 12 weeks of telaprevir 750 mg every 8 h, or 1125 mg every 8 h for patients on efavirenz due to anticipated drug-drug interactions.

Interim analyses from three additional studies now support the use of telaprevir in treatment-experienced coinfecting patients. These

trials demonstrate comparable outcomes with a twice-daily dose of 1125 mg telaprevir in coinfecting patients, which has previously been shown to be noninferior to standard dosing (every 8 h) in mono-infected individuals (13). In addition, they provide supportive evidence for the use of response-guided therapy in HCV treatment-naive patients and those with previous relapse. Finally, these new data provide evidence for the use of telaprevir in treatment-experienced patients, a population not included in the original coinfection trial.

In the UNITE phase III open-label study, 182 participants received telaprevir-based therapy (dosed twice daily); treatment-naive and previous relapsers received response-guided therapy if rapid virological response (RVR; refer to Table 1 for definitions) on treatment was demonstrated, while patients without RVR as well as previous partial and null responding patients were offered a fixed 48-week course of therapy (14). The SVR at 12 weeks of follow-up (SVR12) rates obtained were similar to those observed previously, with 67% of naive individuals, 68% of previous relapsers and 60% of partial responders achieving SVR. SVR rates were lower in previous null responders, with only 39% achieving SVR12. Overall, 97% experienced an adverse event during therapy, 13% of which were serious adverse events. In the INSIGHT open-label trial, 164 participants (98 of whom were treatment-experienced, including 51 previous null-responders) received standard telaprevir-based therapy dosed three times daily (every 8 h) in a similar response-guided algorithm (15). Complete early virological response rates were high, with 80% of naive individuals, 83% of those with previous partial response and 57% of null responders achieving undetectable HCV RNA levels at week 12 of treatment (15).

In ANRS HC-26 (n=69, 39% relapsers, 31% previous partial responders/breakthrough and 30% noncirrhotic null responders) participants received a four-week lead-in of pegylated interferon and weight-based ribavirin, 12 weeks of triple therapy with the addition of telaprevir, with an additional course of pegylated interferon and ribavirin for a total of 48 or 72 weeks in a response-guided manner dependent on results of the week 8 (week 4 triple-therapy outcome) (16). Patients were included if they had stable CD4 cell counts >200 cells/ μ L (CD4% >15%) with suppressed HIV viral load on efavirenz, atazanavir/ritonavir or raltegravir-based regimens. The METAVIR score was F3 in 16%, and 23% were cirrhotic (F4). SVR at 24 weeks of follow-up (SVR24 response; Table 1) was achieved in 80% of individuals and did not appear to be influenced by the fibrosis stage (F1 to F2 83%, F3 to F4 78%), or previous response type (with EOT achieved by those with previous relapse 74%, previous breakthrough 83%, partial response 100% and previous null response 71%), although sample size for these subgroups was small. Grade 4 adverse events occurred in 22% of cases, including anemia (10%) and

infections (3%). Dose reduction of pegylated interferon or ribavirin was required in 22% and 43%, respectively. Sixty-five percent of study participants were administered erythropoietin and 23% required blood transfusion during the extended course of therapy (17).

Boceprevir-based therapy in coinfection

Boceprevir was evaluated in 98 coinfecting patients in a placebo-controlled randomized trial (11). All patients were on ART with stable HIV suppression. Antiretroviral regimens allowed in this study consisted of a ritonavir-boosted protease inhibitor, raltegravir or maraviroc in conjunction with two nucleoside inhibitors other than zidovudine, stavudine or didanosine. Most participants were receiving atazanavir, lopinavir or darunavir-based regimens. Non-nucleoside reverse transcriptase inhibitor-based regimens were not allowed in this protocol. Only five of 98 participants were cirrhotic. All participants received 48 weeks of therapy consisting of a standard four week lead-in phase with pegylated interferon α -2b and weight-based ribavirin, followed by a fixed duration of 44 weeks of boceprevir 800 mg every 8 h or placebo. Overall, an SVR24 was achieved in 63% of triple-therapy recipients ($n=64$) versus 29% of pegylated interferon α -2b and ribavirin treated study participants ($n=34$) (11). Adverse events were common in those receiving boceprevir (41% versus 26%). Despite the successful use of HIV protease inhibitors in this trial, subsequent pharmacokinetic studies have suggested potential for significant interactions (drug interactions with HCV DAAs are summarized in Table 2).

In ANRS HC-27, treatment-experienced patients ($n=64$) received a standard lead-in phase followed by 44 weeks of triple therapy with boceprevir (18). Individuals with cirrhosis and previous null response to pegylated interferon and ribavirin were excluded. Those without a week 8 RVR completed an additional 24 weeks (total 72 weeks) of pegylated interferon with ribavirin. The overall SVR12 rate was 53%, with SVR rates of 90% in previous relapsers, 61% in those with partial response and 24% in null responders. In this trial, there was an apparent difference in outcome based on underlying ART regimen, with a 41% SVR rate in patients receiving atazanavir/ritonavir compared with 70% in those receiving raltegravir (19).

Conclusion

These results demonstrate that response rates for treatment-naive patients are improved with pegylated interferon, ribavirin and an HCV protease inhibitor compared with SVR rates achieved with pegylated interferon/ribavirin alone. SVR rates approximate those observed in mono-infection, with reduced SVR rates observed in those with more advanced disease. In addition, the encouraging interim findings suggest that treatment-experienced coinfecting patients will achieve SVR outcomes similar to those observed in mono-infecting patients, with the highest SVR rates in previous relapsers (higher than treatment-naive patients), intermediate SVR rates in previous partial responders and the lowest SVR rates in previous null responders. Adverse events, particularly anemia, were common but similar in characteristic and rate to that of HCV mono-infecting treatment recipients. These results highlight the need for improved therapeutic options for all HCV-infected individuals with advanced disease or previous treatment failure.

NEXT-GENERATION DAAs: SIMEPREVIR AND SOFOSBUVIR

Two new DAAs have recently been approved in Canada and the United States for the treatment of HCV; the NS3/4A protease inhibitor simeprevir, and the novel uridine nucleotide NS5B RNA-dependent RNA polymerase inhibitor sofosbuvir. These agents offer marked improvement over current therapies because they exhibit much-improved side effect profiles, fewer drug-drug interactions, reduced pill burden and, in the case of sofosbuvir, offer pan-genotypic coverage with the potential for interferon-free based therapy for all genotypes. As such, they have superseded the use of both telaprevir and boceprevir in current treatment recommendations in the United States (20).

Simeprevir

Simeprevir is a second-wave NS3/4A protease inhibitor that offers a number of advantages over boceprevir and telaprevir. The recommended dose in adults with genotype 1 infection is 150 mg once daily with food. Food delays the absorption of simeprevir, increasing the time to reach maximum plasma concentration by 1 h to 1.5 h, and increases the exposure of simeprevir by approximately 60%. Simeprevir is available as a 150 mg capsule, allowing for a significant reduction in pill burden compared with its predecessors in this class. Simeprevir is a substrate of cytochrome P450 (CYP) 3A4, and a mild inhibitor of intestinal (but not hepatic) CYP3A4, 1A2, P-glycoprotein (P-gp) and organic anion transporting polypeptides 1B1 (20). Simeprevir has no clinically relevant effects on CYP2C9, 2C19 and 2D6 (20). Due to these characteristics, simeprevir is primarily the subject (rather than a perpetrator) of pharmacokinetic drug-drug interactions. Co-administration of simeprevir with moderate to strong inducers or inhibitors of CYP3A4 is not recommended due to the potential for significant alterations in simeprevir plasma concentrations. Clinically, this restricts antiretroviral choices for HIV-HCV coinfecting patients because regimens including ritonavir or cobicistat as a booster, or the non-nucleoside reverse transcriptase inhibitors efavirenz, etravirine and nevirapine, should not be used (Tables 2 and 3). Similarly, other inducing/inhibiting agents, such as anticonvulsants, rifamycins, dexamethasone, azole antifungals and macrolides, should be avoided with simeprevir. In the transplant population, simeprevir may be preferred over telaprevir or boceprevir due to the absence of drug interactions with tacrolimus and cyclosporine (21).

Use of simeprevir in conjunction with pegylated interferon and ribavirin has been shown to achieve similar improvement in SVR rates in phase II studies, in both naive and experienced HCV mono-infecting patients (22,23). Simeprevir used in a response-guided protocol has been assessed in three large phase III clinical trials in HCV mono-infecting treatment-naive individuals (QUEST-1, QUEST-2) and previous relapsers (PROMISE) (24-26). In these trials, simeprevir 150 mg daily for the initial 12 weeks of triple therapy with response-guided pegylated interferon/ribavirin for 24 or 48 weeks resulted in SVR12 rates of 80% to 81% in naive individuals compared with 50% for those receiving pegylated interferon/ribavirin alone. Overall, among naive individuals, the majority (80% in QUEST-1 and 91% in QUEST-2) met criteria for response-guided therapy (ie, 24 weeks total), based on a HCV polymerase chain reaction test <25 IU/mL at week 4 with undetectable HCV RNA at week 12. Response rates among those who met these criteria were high at 86% to 91%. Previous relapsers showed similar benefit, with 79% of those treated with simeprevir achieving SVR12 compared with 37% in the control arm (26). The majority of individuals (92.7%) were eligible for response-guided therapy and, of these, 83% achieved SVR12.

Data regarding treatment-experienced HCV mono-infecting patients are derived from the phase II ASPIRE trial (23), in which individuals who received 48 weeks of pegylated interferon and ribavirin had SVR24 rates of 88% in previous relapsers, 86% in previous nonresponders and 58% in previous null responders. Recently, the results of the phase III ATTAIN trial, the only head-to-head randomized trial of two HCV protease inhibitors, showed comparable SVR rates with 12 weeks of simeprevir versus 12 weeks of telaprevir, each given with 48 weeks of pegylated interferon α -2a for 48 weeks in patients with HCV genotype 1 infection who were partial or null responders to previous dual therapy with peginterferon plus ribavirin (27). Specifically, SVR12 rates were 70% and 44% in partial and null responders, respectively, treated with simeprevir versus 69% and 46%, respectively, in those treated with telaprevir. There was a lower incidence of anemia and fewer discontinuations for adverse events in simeprevir recipients.

The side effect profile for individuals receiving simeprevir was similar to those on pegylated interferon and ribavirin, with no significant additional toxicities identified. A naturally occurring HCV NS3 polymorphism – the Q80K mutation – was associated with reduced

TABLE 2
Drug-drug interactions between antiretroviral agents and direct-acting antivirals for hepatitis C

	Boceprevir	Telaprevir	Simeprevir	Sofosbuvir
Dose	800 mg every 8 h with food	1125 mg every 12 h with food (not low fat)	150 mg daily with food	400 mg daily
Integrase inhibitors				
Dolutegravir	No clinically significant changes in either drug. No dose adjustment required (59,60)	No clinically significant changes in either drug. No dose adjustment required (59,60)	Coadministration has not been studied but no expected clinically significant drug interaction	Coadministration has not been studied but no expected clinically significant drug interaction
Elvitegravir/cobicistat	Coadministration has not been studied but could lead to reduced drug concentrations of both boceprevir and elvitegravir/cobicistat	No clinically significant changes in either drug. No dose adjustment required (61)	Not recommended with cobicistat-boosted regimens due to risk of significantly increased simeprevir concentrations (20,62)	Coadministration has not been studied but no expected clinically significant drug interaction
Raltegravir	No clinically significant changes in either drug. No dose adjustment required (63)	No clinically significant changes in either drug. No dose adjustment required (64)	No clinically significant changes in either drug. No dose adjustment required (65)	No clinically significant changes in either drug. No dose adjustment required (20,66)
Non-nucleoside reverse transcriptase inhibitors				
Efavirenz	44% ↓ Cmin, 19% ↓ AUC of boceprevir. Avoid combination. (67,68)	47% ↓ Cmin of telaprevir; ↑ telaprevir dose to 1125 mg every 8 h with efavirenz (69,70)	91% ↓ Cmin, 71% ↓ AUC of simeprevir. Avoid combination. (20,62)	6% ↓ AUC, 19% ↓ Cmax of sofosbuvir, not considered clinically significant. No dose adjustment required (20,66)
Etravirine	29% ↓ Cmin, 23% ↓ AUC of etravirine. Use combination with caution, particularly if coadministering with other medications that may further decrease etravirine concentrations (71)	No clinically significant changes in either drug. No dose adjustment required (72)	Not recommended with etravirine due to risk of decreased simeprevir concentrations (20)	Coadministration has not been studied but no expected clinically significant drug interaction
Rilpivirine	↑ 39% AUC, ↑ 15% Cmax, ↑ 10% Cmin of rilpivirine, not considered to be clinically significant. No dose adjustment required (73)	↑ 78% AUC, ↑ 49% Cmax, ↑ 93% Cmin of rilpivirine, not considered clinically significant. No dose adjustment required (72)	6% ↑ AUC, 4% ↓ Cmin of simeprevir and 12% ↑ AUC 25% ↑ Cmin of rilpivirine, not considered clinically significant. No dose adjustment required (65)	6% ↑ AUC, 5% ↑ Cmax of rilpivirine, not considered clinically significant. No dose adjustment required (20,66)
Protease inhibitors				
Atazanavir/ritonavir	49% ↓ Ctrough, 35% ↓ AUC of atazanavir. Avoid combination (68,74)	85% ↑ Cmin of atazanavir. Combination may be used (70)	Not recommended with ritonavir, boosted or unboosted HIV protease inhibitors due to risk of significantly increased simeprevir concentrations (20)	No expected clinically significant drug interaction
Darunavir/ritonavir	59% ↓ Ctrough, 44% ↓ AUC of darunavir and 32% ↓ boceprevir. Avoid combination (68,74)	40% ↓ AUC and 42% ↓ Cmin of darunavir, 35% ↓ AUC and 32% ↓ Cmin of telaprevir. Avoid combination (70,75)	2.6-fold ↑ AUC, 1.79-fold ↑ Cmax, 4.58-fold ↑ Cmin of simeprevir and 18% ↑ AUC, 31% ↑ Cmin of darunavir. Coadministration not recommended (20)	37% ↑ AUC, 45% ↑ Cmax of sofosbuvir, not considered clinically significant. No dose adjustment required (20,66)
Fosamprenavir/ritonavir	Not recommended with ritonavir-boosted protease inhibitors (68)	47% ↓ AUC and 56% ↓ Cmin of amprenavir, 32% ↓ AUC and 30% ↓ Cmin of telaprevir. Avoid combination (70,75)	Not recommended with ritonavir, boosted or unboosted HIV protease inhibitors due to risk of significantly increased simeprevir concentrations (20,62)	Coadministration has not been studied but no expected clinically significant drug interaction
Lopinavir/ritonavir	43% ↓ Ctrough, 34% ↓ AUC of lopinavir and 45% ↓ boceprevir. Avoid combination (68,74,76)	6% ↑ AUC and 14% ↑ Cmin of lopinavir, 54% ↓ AUC and 52% ↓ Cmin of telaprevir. Avoid combination (70,75,76)	Not recommended with ritonavir, boosted or unboosted HIV protease inhibitors due to risk of significantly increased simeprevir concentrations (20)	Coadministration has not been studied but no expected clinically significant drug interaction
CCR5 Antagonist				
Maraviroc	Maraviroc AUC ↑ 202%, Cmax ↑ 233% and Ctrough ↑ 178% vs maraviroc 150 mg BID alone. Reduce maraviroc dose to 150 mg BID when coadministering with boceprevir (77,78)	Maraviroc AUC ↑ 849%, Cmax ↑ 681% and Ctrough ↑ 917% vs maraviroc 150 mg BID alone. Reduce maraviroc dose to 150 mg BID when coadministering with telaprevir (77)	No expected clinically significant drug interaction	Coadministration has not been studied but no expected clinically significant drug interaction

Key: Avoid combination; Caution/dose adjustment; Combination OK. ↑ Increase; ↓ Decrease; AUC Area under the curve; BID Twice per day; CCR5 C-C chemokine receptor-5; Cmax Concentration maximum; Cmin Concentration minimum; Ctrough Concentration trough; vs Versus

TABLE 3
Summary of antiretroviral regimen recommendations for patients who require concomitant HIV and hepatitis C treatment

	Recommended	Alternative	NOT recommended
Sofosbuvir 400 mg daily	No restrictions on antiretroviral choices	No restrictions on antiretroviral choices	
Simeprevir 150 mg daily with food	Dolutegravir-, raltegravir- or rilpivirine-based regimens		Ritonavir- or cobicistat-boosted regimens; efavirenz, etravirine, nevirapine
Telaprevir 1125 mg BID with food (not low fat)	Atazanavir/ritonavir-, dolutegravir-, elvitegravir-, raltegravir- or rilpivirine-based regimens	Efavirenz (with increase in telaprevir dose to 1125 mg every 8 h), etravirine	Other protease inhibitor-based regimens including darunavir/ritonavir, fosamprenavir/ritonavir, lopinavir/ritonavir
Boceprevir 800 mg every 8 h with food	Dolutegravir-, raltegravir- or rilpivirine-based regimens		Protease inhibitor-based regimens including atazanavir/ritonavir, darunavir/ritonavir, lopinavir/ritonavir; other NNRTI-based regimens including efavirenz, etravirine, nevirapine

BID Twice daily; NNRTI Non-nucleoside reverse transcriptase inhibitors

SVR rates in genotype 1a patients. This polymorphism occurs in approximately 45% of North Americans with genotype 1a (28) but only approximately 18% of Europeans (29). In the QUEST-1 study, those with this mutation had no better response rate with the addition of simeprevir compared with those in the pegylated interferon/ribavirin arm (24). Screening at baseline for this mutation in genotype 1a is recommended.

Data in coinfecting patients

Simeprevir has been evaluated in treatment-naive and -experienced HIV coinfecting patients (30). In the C212 open-label phase III study, 106 individuals received either response-guided therapy for naive/relapsers (n=64) or standard 12 weeks of triple therapy followed by 36 weeks of pegylated interferon/ribavirin in treatment-experienced patients or those with underlying cirrhosis. Due to potential drug interactions, ART regimens were limited to raltegravir, maraviroc or rilpivirine, with either tenofovir/emtricitabine or abacavir/lamivudine. Overall SVR12 rates were achieved in 79% of naive individuals, 87% of previous relapsers, 70% of previous partial responders and 57% of null responders. Response rates were reduced in those with cirrhosis (64%) versus noncirrhotics (80%) and side effect profile was similar to what is expected with peginterferon plus ribavirin alone.

Sofosbuvir

Sofosbuvir is a nucleotide prodrug that undergoes intracellular metabolism to form the pharmacologically active uridine analogue triphosphate GS-461203, which is incorporated into HCV RNA by the NS5B polymerase and acts as a chain terminator. Sofosbuvir is available as a 400 mg tablet. The approved dose in adults is 400 mg once daily taken without regard to food. After oral administration, sofosbuvir is rapidly converted to the predominant circulating metabolite GS-331007. Sofosbuvir and GS-331007 do not inhibit any CYP450 isoenzymes or UGT1A1. Sofosbuvir is a P-gp substrate and breast cancer resistance protein substrate whereas GS-331007 is not. Sofosbuvir should not be coadministered with potent P-gp inducers such as rifampin or St John's wort (31). Significant interactions have not been demonstrated or are not expected between sofosbuvir and antiretrovirals.

Sofosbuvir has been widely evaluated in HCV mono-infected individuals. In the phase III NEUTRINO study, 291 genotype 1-infected treatment-naive individuals received 12 weeks of triple therapy with sofosbuvir 400 mg daily in conjunction with pegylated interferon and ribavirin (32). Overall SVR12 rates were achieved in 89% of individuals, with lower rates observed in those with cirrhosis than in those without (80% versus 92%). Side effects appear to be driven predominantly by the receipt of pegylated interferon/ribavirin, although a control group for definitive comparison was not built into the study design. In addition, use of sofosbuvir with ribavirin alone has been evaluated for interferon-ineligible patients with genotype 1 infection. In a small (n=60) phase II study, sofosbuvir with weight-based ribavirin

for 24 weeks achieved an SVR24 rate of 68% in individuals deemed to be interferon-ineligible (33). A relatively high rate of relapse (54%) was observed in those with more advanced disease. Other small trials (ELECTRON, QUANTUM trials) of this interferon-sparing strategy have found SVR rates ranging from 50% to 84% (34,35).

Limited data exist for treatment-experienced patients. However, given the response observed in individuals with characteristics that would normally be considered to be unfavourable for response to pegylated interferon and ribavirin, modelling conducted during the approval of sofosbuvir by the United States Food and Drug Administration (FDA) predicts an approximate 78% response in treatment-experienced patients (36).

Genotypes 2 and 3 HCV mono-infection

Sofosbuvir has also been evaluated for use in genotypes 2 and 3 in an initial large noninferiority comparison to standard pegylated interferon/ribavirin (32). In the FISSION trial, 499 treatment-naive individuals were randomly assigned to 12 weeks of therapy with sofosbuvir/ribavirin or 24 weeks of pegylated interferon/ribavirin. Individuals with genotype 2 infection had exceptional SVR rates of 97% with sofosbuvir/ribavirin versus 76% with pegylated interferon/ribavirin, while those with genotype 3 achieved similar SVR rates to pegylated interferon/ribavirin (56% versus 63%). Cirrhosis markedly reduced SVR rates for genotype 3 individuals to approximately 30% in both arms. Similar SVR rates were observed in the POSITRON trial in interferon-ineligible patients (37). In the phase III VALENCE study, improved SVR rates were observed in genotype 3 treatment-naive individuals who received 24 weeks of sofosbuvir/ribavirin with SVR rates 94%, with the subgroup of cirrhotic patients achieving SVR of 90% (38).

Sofosbuvir has also been evaluated in treatment-experienced genotype 2 and 3 patients. In the FUSION trial, individuals were randomly assigned to receive 12 or 16 weeks of therapy with sofosbuvir and ribavirin. Those with genotype 2 achieved an SVR rate of 86% after 12 weeks and 94% after 16 weeks. SVR rates were much lower for genotype 3, with an SVR rate of 30% in patients receiving 12 weeks versus 62% in those who received 16 weeks of therapy (37). In the VALENCE study, treatment-experienced genotype 2 patients experienced similar high rates of response (91%) after 12 weeks of therapy of dual therapy. Treatment-experienced patients with genotype 3 treated with 24 weeks of sofosbuvir and ribavirin achieved an SVR of 87% in those without cirrhosis, and only 60% in those with cirrhosis (39). In the LONESTAR-2 phase II trial, the addition of pegylated interferon to a 12 week course of sofosbuvir/ribavirin resulted in SVR rates of 83% for genotype 3, with or without cirrhosis (40).

Data in HIV-HCV coinfecting patients

Sofosbuvir was evaluated in HIV coinfecting patients in the phase II Study 1910 trial (41). In this open-label study, 23 coinfecting treatment-naive individuals received sofosbuvir 400 mg daily in conjunction

with pegylated interferon and weight-based ribavirin for 12 weeks. Individuals were predominantly genotype 1-infected, with two individuals with genotype 3, and one individual each with genotype 2 and 4, respectively, were also enrolled. The ART regimens included efavirenz, rilpivirine, raltegravir and the boosted protease inhibitors atazanavir and darunavir. Overall, the SVR12 was 91%. Side effects were predominantly those of pegylated interferon and ribavirin.

In the phase III PHOTON-1 study, three cohorts of coinfecting patients (genotype 1 treatment-naïve patients n=114, genotype 2 (n=28) and 3 (n=42) naïve patients, and genotypes 2/3 treatment-experienced patients (n=41) were enrolled to receive either 12 weeks or 24 weeks (genotype 1 and treatment-experienced patients) of sofosbuvir with ribavirin (42). Individuals could be on a wide range of ART regimens due to the lack of drug interactions, or naïve to ART if baseline CD4 cell count was >500 cells/mm³. The majority of those enrolled were on ART, receiving predominantly efavirenz-, atazanavir- or darunavir-based regimens. The SVR24 rate was 75% for genotype 1 participants, 88% for genotype 2 and 67% for genotype 3 patients. Among treatment-experienced patients, SVR24 was attained by 92% of genotype 2 and 88% of genotype 3 individuals. Overall, the regimen was well tolerated, with more adverse events related to sofosbuvir/ribavirin observed in patients receiving a 24-week course of therapy.

DAA COMBINATION REGIMENS OF CURRENTLY APPROVED AGENTS

Proof-of-concept studies investigating interferon-free and ribavirin-sparing combinations of potent DAA agents have rapidly advanced the potential for simple, potent and well-tolerated therapies for HCV (43-45). Further evaluation of combination DAA therapy has demonstrated potential therapy in patients with advanced disease, in previous null responders and as salvage therapy in patients previously nonresponsive to telaprevir and boceprevir-based therapy (3,46,47). In the COSMOS study, HCV mono-infected, treatment-naïve and previous null responders with HCV genotype 1 mono-infection received once-daily simeprevir and sofosbuvir, with or without ribavirin for either 12 or 24 weeks (46). In the first cohort of 80 null responders with METAVIR F0-F2 disease, SVR12 rates with dual therapy were high (92% to 93% after 12 or 24 weeks of therapy) and the addition of ribavirin was not clearly associated with improvement in SVR rates (48). For the second cohort of 87 naïve and null responders with F3-F4 disease, SVR12 rates were 93% with 12 weeks of therapy and 96% with 24 weeks of therapy (49). The addition of ribavirin did not increase SVR rates but did result in some cases of anemia (4). On the basis of the COSMOS data, two phase III studies will evaluate eight versus 12 weeks of sofosbuvir plus simeprevir in noncirrhotic patients (OPTIMIST-1) and 12 weeks in cirrhotic patients (OPTIMIST-2) in HCV genotype 1 mono-infected treatment-naïve patients (50). Ribavirin will not be included in the phase III studies. At present, no data exist for this combination in coinfecting individuals.

FUTURE DAA COMBINATIONS

Interferon-free combination DAA regimens have been or soon will be approved by regulatory agencies, including Health Canada. We anticipate that the regimens mentioned below will rapidly be identified as first-line therapies for HCV. However, as HIV-HCV coinfection-specific clinic trials evaluating these new regimens have yet to be published, they have not been included in this current iteration of the Canadian Institutes of Health Research Canadian HIV Trials Network HIV-HCV coinfection guidelines.

The combination of sofosbuvir with a NS5A replication inhibitor is particularly promising. This was first demonstrated in a phase II study with the NS5A inhibitor daclatasvir, with SVR rates of 98% in genotype 1, 92% in genotype 2 and 89% in genotype 3 (51). Moreover, the combination of sofosbuvir plus daclatasvir resulted in SVRs in 100% of 41 patients who previously failed triple therapy with peginterferon, ribavirin and either telaprevir or boceprevir.

Very recently, three phase III trials investigating the fixed-dose combination of sofosbuvir with the NS5A inhibitor ledipasvir, with

and without ribavirin for eight or 12 weeks in patients with HCV genotype 1 mono-infection demonstrated SVR rates of 93% to 99%, including boceprevir- or telaprevir treatment experienced patients and those with cirrhosis (4,52). The addition of ribavirin did not increase SVR rates. A New Drug Application for sofosbuvir-ledipasvir was filed with the US FDA on February 10, 2014 and received approval in the United States and Canada in October 2014 (53). The combination of sofosbuvir/ledipasvir for 12 weeks is currently under study in HIV-HCV coinfecting patients in the ION-4 protocol.

The combination of three DAAs, specifically the NS3 protease inhibitor ABT-450 boosted by the CYP3A4 inhibitor ritonavir, the NS5A inhibitor ombitasvir and the NS5B non-nucleoside polymerase inhibitor dasabuvir, with ribavirin given for 12 weeks results in SVR rates of 93% to 99% in HCV genotype 1 mono-infected patients, including treatment-experienced patients and those with cirrhosis (5,54,55). It appears that ribavirin can be omitted in genotype 1b, but is needed in genotype 1a (56). A New Drug Application for this regimen was filed with the FDA on April 22, 2014 (57). This regimen is currently under evaluation in the HCV-HIV coinfecting patients (TURQUOISE I study). However, the presence of multiple CYP3A4-metabolized medications, including ritonavir, may limit antiretroviral treatment options in HIV coinfecting patients considered for this regimen.

Summary

Collectively, these clinical trial results indicate a significant paradigm shift in the management of HCV mono- and coinfection is imminent, pending regulatory approvals and eventual addition to provincial formularies. Recent data suggest that the gap in SVR rates between HCV mono-infection and HIV-HCV coinfection has been eliminated with newer HCV antiviral regimens. The 'real-world' uptake and efficacy of these agents in vulnerable populations will be important to assess their impact on the burden of HCV disease and sequelae (1).

RECOMMENDATIONS FOR THERAPY

1. Genotype 1 treatment-naïve individuals without cirrhosis

First line: Sofosbuvir 400 mg daily with pegylated interferon and weight-based ribavirin for 12 weeks of therapy. This combination offers a short duration of therapy, a high SVR rate, no concerns regarding ART drug interactions and no additional side effects beyond those of pegylated interferon and ribavirin (Class 1, Level B) (see Appendix 1 for level of evidence criteria).

Alternative: Sofosbuvir 400 mg daily with simeprevir 150 mg daily. This regimen has not been evaluated in coinfection. However, based on the SVR rates achieved in other traditionally 'hard-to-cure' populations (ie, treatment-experienced individuals with cirrhosis), this combination can be considered preferable where available (Class 1, Level C).

Alternative: Therapy for interferon-eligible patients would consist of response-guided therapy with simeprevir 150 mg daily with pegylated interferon and weight-based ribavirin (Class 1, Level B).

- Genotype 1a strains must undergo Q80K polymorphism testing before use of this regimen, and an alternative DAA should be chosen if Q80K is present.
- Response-guided therapy with treatment discontinuation at week 24 can be offered if week 4 RNA is undetectable. Response-guided therapy should not be used in individuals with underlying cirrhosis in whom a full 48-week course of pegylated interferon and ribavirin is advised.
- Drug interactions with ART must be considered with use of simeprevir.

Alternative: Interferon-ineligible individuals can be considered for 24 weeks of sofosbuvir 400 mg daily and weight-based ribavirin. Given the decreased SVR rates observed with this combination and limited information regarding patients with cirrhosis, deferral of therapy for future combination DAA regimens should be considered (Class 1, Level B).

2. Genotype 1 treatment-naive individuals with cirrhosis

First line: Sofosbuvir 400 mg daily pegylated interferon and ribavirin for 12 weeks. Patients must not have decompensated cirrhosis to receive interferon (Class 1, Level B).

Alternative: Sofosbuvir 400 mg daily with simeprevir 150 mg daily for 12 weeks. This regimen has not been evaluated in coinfection. However, based on the SVR rates achieved in other traditionally 'hard-to-cure' populations (ie, treatment-experienced individuals with cirrhosis), this combination can be considered preferable where available (Class 1, Level C).

Alternative: Simeprevir 150 mg daily for 12 weeks with pegylated interferon and ribavirin for 48 weeks (assuming genotype 1a recipient is Q80K negative) (Class 1, Level B).

3. Genotype 1 treatment-experienced patients with previous relapse (with or without cirrhosis)

See recommendations for genotype 1 treatment-naive individuals with or without cirrhosis as above. Retreatment with pegylated interferon, ribavirin and simeprevir is not recommended in previous relapsers, partial or null responders to other protease inhibitor (boceprevir, telaprevir)-based regimens (Class 1, Level B).

4. Genotype 1 treatment-experienced patients – previous nonresponders or null responders (with or without cirrhosis)

First line: Sofosbuvir 400 mg daily with simeprevir 150 mg daily for 12 weeks (note: based on HCV mono-infection studies) (Class 1, Level C).

Or

First line: Sofosbuvir 400 mg daily with pegylated interferon and weight-based ribavirin for 12 to 24 weeks (Class 1, Level C).

Alternative: Simeprevir 150 mg daily for 12 weeks with 48 weeks of pegylated interferon and weight-based ribavirin (except in genotype 1a with Q80K). Response-guided therapy is recommended for noncirrhotic patients with previous relapse, whereas 48 weeks is recommended in previous partial or null responders, with or without cirrhosis (Class 1, Level B).

5. Genotype 2 treatment-naive patient

First line: Sofosbuvir 400 mg daily with weight-based ribavirin for 12 weeks (Class 1, Level B).

6. Genotype 2 treatment-experienced patient

First line: Sofosbuvir 400 mg daily with ribavirin for 24 weeks (Class 1, Level B).

Alternative: Sofosbuvir 400 mg daily with pegylated interferon and ribavirin for 12 weeks (Class 1, Level C).

Recommendations for treatment-experienced coinfections are based on expert recommendation, using data from a single trial in coinfection and data from other hard-to-cure mono-infected populations.

7. Genotype 3 treatment-naive patient

First line: Sofosbuvir 400 mg daily with pegylated interferon and ribavirin for 12 weeks, particularly if compensated cirrhosis is present and interferon is not contraindicated (Class 1, Level C).

Or

First line: Sofosbuvir 400 mg daily with ribavirin for 24 weeks if interferon is contraindicated or patient considered interferon-ineligible (Class 1, Level B).

8. Genotype 3 treatment-experienced patient

First line: Sofosbuvir 400 mg daily with pegylated interferon and ribavirin for 12 weeks (Class 1, Level C).

Alternative: Sofosbuvir 400 mg daily with ribavirin for 24 weeks if interferon ineligible or intolerant (Class 1, Level B).

9. Genotype 4 treatment-naive and experienced

First line: Sofosbuvir 400 mg daily with pegylated interferon and ribavirin for 12 weeks. (it should be noted that this is based on HCV mono-infection studies) (Class 1, Level C).

There are currently insufficient data in HIV-HCV coinfection with genotype 4 to 6 to comment on the efficacy of sofosbuvir-simeprevir. Likewise, there are currently insufficient data in HIV-HCV coinfection with genotype 5/6 to comment on the efficacy of sofosbuvir with pegylated interferon and ribavirin.

Regimens no longer recommended for first-line use

1. Telaprevir and boceprevir are no longer recommended for first-line use given the improved safety and tolerability profiles of the new DAA agents.
2. Pegylated interferon and ribavirin as dual therapy for genotype 2/3 individuals.

Circumstances may exist in which first-line regimens are not accessible to patients (eg, restricted funding). The above second-line regimens could be considered as treatment options. However, the patient must be fully aware of the diminished likelihood for cure and/or increased likelihood for adverse events compared with first-line regimens.

TIMING OF INITIATION OF HCV THERAPY IN THE ERA OF DAAs

At this time, it is unclear whether access to newer agents will be standard across the country, and/or which, if any, additional criteria may be imposed by individual provinces/payers to limit access to DAAs given the anticipated costs of these agents. Recommendations for use of newer DAA agents/combinations is based primarily on a review of the currently available data evaluating efficacy and safety in mono-infected and coinfecting patients.

Access to appropriate therapy when clinically indicated has long been recommended in Canada by experts involved in the care of patients living with HCV (58), and we would continue to advocate for such an approach for coinfecting patients. The authors recognize that due to potential restrictions to access and reimbursement of newer drugs/regimens for HCV, clinicians and patients may face difficult decisions regarding therapy. In this situation, alternate options may be considered.

Deferral of therapy

Individuals with early fibrosis may be able to defer therapy compared with those with more advanced disease because they have lower risk of medium-term progression of disease. These individuals may be able to wait for future combinations and potentially improved access to interferon-free based combinations. If deferral of therapy is considered, updated staging for fibrosis progression is recommended on an annual basis if access to transient elastography is possible, or every three years if liver biopsy is to be performed. The clinician must also consider that for dual therapy with pegylated interferon plus ribavirin and triple therapy with pegylated interferon plus one DAA, SVR rates are highest at early fibrosis stages (<F3) and decrease with advancing disease.

Additional considerations of patient readiness, and consideration of possible onward HCV transmission risk for individuals in a core transmitter group (injection drug users and certain populations of men who have sex with men) compared with those without high risk for transmission (eg, many 'baby boomers' [born between approximately 1945 and 1970]) may influence a decision to consider delaying therapy.

Utilization of nonpreferred regimens

For cost/access reasons, it may be necessary to use older therapies for HCV with a higher incidence of adverse effects and lower SVR rates in some patients. In all such cases, patients should be made aware of the existence of newer improved therapies and given the option of potentially paying for them, if they so choose.

FUNDING: Support for the development of these guidelines was provided from The Canadian Institutes for Health Research Canadian HIV Trials Network and the Canadian Association for HIV Research. Unrestricted funding from Gilead Sciences, Abbvie and Roche is gratefully acknowledged.

DISCLOSURES: MH has consulted and spoken for Bristol Myers Squibb, Gilead, Merck, Janssen and Vertex. MK has served as a consultant for GlaxoSmithKline and ViiV Healthcare, holds grants from Merck, has spoken for Bristol Myers Squibb, GlaxoSmithKline and ViiV Healthcare and has developed educational presentations from Gilead, GlaxoSmithKline and ViiV Healthcare. SS and CC have consulted and spoken for AbbVie, Bristol Myers Squibb, Gilead, Janssen, Merck, Vertex and Roche. AT has received unrestricted educational grants and/or spoken for Merck, Gilead and Vertex. PG has received educational grants from Merck and Vertex.

APPENDIX 1 Grading system for recommendations

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/treatment is not useful/effective and in some cases may be harmful
Grade of evidence	
Level A	Data derives 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 58, 79 and 80

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