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To the Editor:

Hepatitis C virus (HCV) infection is an important cause of morbidity and mortality among individuals living with HIV (1). Before the introduction of direct-acting antivirals (DAAs), pegylated interferon (peg-IFN) and ribavirin (RBV) were standard of care for coinfected patients with dismal sustained virological response (SVR) rates of <30% (2,3). Telaprevir (TVR), an NS3/4A protease inhibitor, was a first-generation DAA approved for HCV treatment in Canada, in November 2012. In randomized trials, the rate of SVR to TVR/peg-IFN/RBV was 65% to 75% in monoinfected patients and similar in coinfected patients (4-8). Few studies have reported treatment outcomes of TVR-based therapy outside of clinical trials. Our objective was to compare clinical outcomes of HCV-monoinfected and HIV-HCV coinfected patients treated with TVR-based triple therapy at a regional referral centre in Alberta.

Patients who initiated TVR/pegIFN/RBV combination therapy from June 2011 to December 2013, were included in the study. Patients were treated according to Canadian guidelines for HCV treatment (9,10). All patients with HCV genotype 1 were eligible for therapy and were treated at the discretion of their HCV care provider. Demographic, clinical and laboratory data were collected at baseline and during therapy. Parameters of interest included HIV-coinfection, body mass index (BMI), Child-Pugh classification, previous injection drug use, haemophilia, liver transplantation, hepatitis B coinfection and previous HCV treatment. Fibrosis was determined using transient elastography by FibroScan (Echosens, France) with the following parameters: F0 to F1 ≤7.0, F2 7.1 to 9.4, F3 9.5 to 12.4, F4 (cirrhosis) ≥12.5 (11). Where applicable, HIV viral load and $CD4^+$ T cell count were collected. Severe treatment-related anemia and thrombocytopenia were defined as nadir of hemoglobin ≤80 g/L and platelet count $\leq 50\times10^9$, respectively. Treatment response was determined using established definitions according to Canadian guidelines (9). Patients lost to follow-up were considered to have virological failure.

In total, 103 patients received TVR at our clinics (Table 1). This included 13 (12.6%) HIV-HCV coinfected patients and seven (6.7%) patients who experienced recurrent HCV after liver transplantation. The median age at treatment onset was 56 years (interquartile range [IQR]: 51 to 59 years); 72% of patients were male and 86% were Caucasian. One-third (37%) of patients reported a history of injection drug use, nine (10%) had hemophilia and three (3%) were HCV-hepatitis B virus coinfected. The median BMI was 26.8 kg/m^2 (IQR 24.0 kg/m^2 to 30.5 kg/m^2). Forty-seven percent (n=45) of patients had been previously treated with pegIFN-RBV and 13% (n=12) were previous null responders. Most patients were HCV genotype 1a and IL28B non-CC genotype (71% and 70%, respectively). The majority (60%) of patients had advanced fibrosis or cirrhosis (F3 or F4). One patient had decompensated Child-Pugh B cirrhosis. HCV-HIV coinfected patients did not differ significantly with respect to previous anti-HCV therapy, HCV genotype subtype, interleukin (IL)28B genotype or degree of fibrosis. Coinfected patients were more likely to report injection drug use (P=0.05) and to have hemophilia (P=0.03). Most (92%) HIV coinfected patients had undetectable HIV RNA while receiving antiretroviral therapy, with a median baseline CD4 count of 490 cells/mm^3 (IQR 250 cells/mm^3 to 639 cells/mm^3). Most (85%) required adjustment of their antiretroviral regimen before TVR initiation. Integrase-based antiretroviral therapy was the most commonly (77%) used regimen.

The overall rate of SVR in our cohort was 66% (Table 2). The rate of SVR among HIV-HCV coinfected patients was 62% (eight of 13). Patients with cirrhosis and previous null responders had a lower SVR rate (54% and 42%, respectively). Fifty-seven percent (four of seven) of post-liver transplant recipients achieved SVR. Outcomes for post-liver transplant patients have been previously reported (12). Among treatment failures, discontinuation due to adverse events was the most common (20%), followed by virological relapse (15%). Five (5%) patients discontinued therapy due to hepatic decompensation. Two (2%) patients were lost to follow-up. Two (2%) patients died; one patient died due to drug and alcohol intoxication while on therapy. The other patient had Child-Pugh B cirrhosis at baseline and died from complications of decompensated cirrhosis. The most commonly reported side effects were fatigue (65%), rash (68%), mood symptoms (42%), anorectal symptoms (43%) and infections (17%). Severe anemia occurred in 15% of participants and warranted red blood cell transfusion or erythropoietin in 11% and 2%, respectively. Severe thrombocytopenia occurred in 24% of participants. Most (57%) patients required RBV dose reduction.

Comparing HCV monoinfected with HIV coinfected patients, there was no significant difference with regard to SVR (67% versus 62%, P=0.76). There was no difference between monoinfected and coinfected patients in treatment discontinuation due to adverse events (20% versus 15%; P=1.00) or virological relapse (13% versus 23%; P=0.40). One patient with HIV coinfection discontinued therapy due to hepatic decompensation, but nevertheless achieved SVR. There were no deaths among HIV-coinfected patients. Patients with HIV coinfection were more likely to have infections (12% versus 48%; P≤0.01), severe anemia (11% versus 38%; P=0.02) and to require peg-IFN dose adjustment (6% versus 46%; P≤0.01). In HIV-coinfected patients, infectious complications consisted of cellulitis (n=2), sepsis (n=1), gastroenteritis (n=1) and urinary tract infections (n=1). All HIV-coinfected patients maintained undetectable HIV RNA while receiving therapy.

In a bivariate analysis, variables associated with increased rate of SVR included lower BMI (26.0 kg/m^2 [IQR 24.0 kg/m^2 to 29.1 kg/m^2] versus 29.1 kg/m^2 [IQR 26.6 kg/m^2 to 32.0 kg/m^2]; P=0.05), IL28B genotype CC (37% versus 12%; P=0.02) and cirrhosis (37% versus 60%; P=0.03). In a multivariate analysis, only fibrosis class (F0 to F2 versus F3 to F4; adjusted OR 0.34 [95% CI 0.12 to 0.99]; P=0.05) remained significantly associated with SVR. HIV status, a history of injection drug use and previous response to peg-IFN therapy did not predict SVR.

There have been few reports of the effectiveness of TVR-based therapy in HIV-coinfected patients outside of clinical trials. In our study, the overall SVR was 67% in HCV-monoinfected patients and 62% in coinfected patients. This is comparable with clinical trials, despite a higher percentage of patients with cirrhosis (45%) in our cohort (4-6). Lower BMI, IL28B CC genotype and degree of fibrosis were associated with increased probability of SVR, although in multivariate analysis, only degree of fibrosis remained a significant predictor of SVR. Additional negative predictors of SVR with TVR-based therapy included African American race and previous treatment response (13). We also demonstrated that HIV coinfection is not a negative predictor of SVR. This was consistent with trials involving second-generation DAAs such as ledipasvir and sofosbuvir. Data from patients with HCV monoinfection treated

TABLE 1
Comparison of baseline characteristics between hepatitis C virus (HCV)-monoinfected and HIV-HCV coinfected patients

	All (n=103)	HCV monoinfected (n=90)	HCV-HIV coinfected (n=13)	P*
Age at treatment onset, years, median (IQR)	56 (51–59)	56 (51–59)	53 (46–57)	0.20
Male sex	74 (72)	63 (70)	11 (85)	0.34
Race/ethnicity				
Caucasian	73 (86)	63 (88)	10 (77)	0.07
Previous injection drug use	31 (37)	23 (33)	8 (62)	0.05
Hemophilia	9 (10)	5 (7)	4 (31)	**0.03**
Post-liver transplant	7 (8)	7 (10)	0 (0)	0.59
Hepatitis B coinfection	3 (3)	3 (45)	0 (0)	1.00
Body mass index, kg/m^2, median (IQR)	26.8 (24.0–30.5)	27.1 (24.0–32.0)	25.1 (24.5–28.4)	0.22
Previous HCV treatment				
Naive	50 (53)	44 (54)	6 (46)	0.11
Relapse	28 (29)	26 (32)	2 (15)	
Null	12 (13)	9 (11)	3 (23)	
Partial	1 (1)	1 (1)	0 (0)	
Intolerant	4 (4)	2 (2)	2 (15)	
HCV genotype				
1a	48 (71)	42 (71)	6 (67)	1.00
Interleukin 28B genotype				
CC	18 (30)	16 (33)	2 (17)	0.58
CT	30 (50)	23 (48)	7 (58)	
TT	12 (20)	9 (19)	3 (25)	
FibroScan†, median (IQR)	11.3 (7.3–17.3)	10.9 (7.3–17.3)	12.0 (8.4–15.7)	0.88
Fibrosis/cirrhosis				
F0–F1	20 (20)	18 (20)	2 (15)	0.30
F2	21 (21)	20 (22)	1 (8)	
F3	15 (15)	11 (12)	4 (31)	
F4/cirrhosis	46 (45)	40 (45)	6 (46)	
Baseline labs				
Hemoglobin, g/L, median (IQR)	151 (140–162)	152 (140–162)	14.8 (142–160)	0.89
Platelets, ×10^9/L, median (IQR)	165 (126–202)	169 (130–202)	141 (123–178)	0.43
Alanine aminotransferase, U/L, median (IQR)	72 (48–115)	72 (46–114)	66 (51–132)	0.85
Total bilirubin, µmol/L, median (IQR)	9 (7–13)	9 (6–13)	10 (7–16)	0.28
Albumin, µmol/L, median (IQR)	39 (37–41)	39 (37–41)	38 (36–41)	0.55
International normalized ratio, median (IQR)	1.0 (1.0–1.1)	1.0 (1.0–1.1)	1.0 (1.0–1.1)	0.36
Glomerular filtration rate ≤60 mL/min	6 (6)	5 (6)	1 (8)	0.59
HIV-related variables				
Undetectable HIV RNA	–	–	12 (92)	–
CD4 count, median (IQR)	–	–	490 (250–639)	–
HAART regimen				
Raltegravir	–	–	10 (77)	–
Atazanavir/ritonavir	–	–	2 (15)	–
Rilpivirine	–	–	1 (8)	–
Tenofovir	–	–	9 (69)	–
Emtricitabine	–	–	7 (54)	–
Lamivudine	–	–	5 (39)	–
Abacavir	–	–	4 (31)	–
Zidovudine	–	–	1 (8)	–
HAART change before treatment	–	–	11 (85)	–

*Data presented as n (%) unless otherwise indicated. Bolded values indicate statistical siginificance (ie, P<0.05). *HCV monoinfected versus HCV-HIV coinfected. †Echosens, France. HAART Highly active antiretroviral therapy; IQR Interquartile range*

with sofosbuvir/ledipasvir have demonstrated a rate of SVR >95% for all subgroups (14-16). A phase 3 study involving HIV-HCV coinfected patients demonstrated similar rates of SVR (17). In fact, guidelines now suggest that HIV-HCV coinfected patients should be treated the same as HCV-monoinfected patients (18,19).

HIV-coinfected patients may experience a higher rate of adverse events associated with TVR-based therapy. In our cohort, coinfected patients had similar rates of fatigue, changes in mood, rash, anorectal symptoms and thrombocytopenia, but were more likely to have infections and severe anemia. However, the rate of treatment

TABLE 2
Comparison of treatment outcomes between hepatitis C virus (HCV) monoinfected and HIV-HCV coinfected patients

	All (n=103)	HCV monoinfected (n=90)	HCV-HIV coinfected (n=13)	P*
Treatment outcomes				
Rapid virological response	63 (61)	51 (57)	12 (92)	**0.02**
Early virological response	81 (79)	68 (76)	13 (100)	0.07
End of treatment response	73 (71)	65 (72)	8 (62)	0.52
Sustained virological response	68 (66)	60 (67)	8 (62)	0.76
Sustained virological response subcategories				
Cirrhosis	25 (54)	21 (53)	4 (67)	0.67
Previous null responder	5 (42)	4 (44)	1 (33)	1.00
Post-liver transplant	–	4 (57)	–	–
Reason for treatment discontinuation				
Partial response	3 (3)	2 (2)	1 (8)	0.34
Null response	4 (4)	4 (4)	0 (0)	1.00
Relapse	15 (15)	12 (13)	3 (23)	0.40
Hepatic decompensation	5 (5)	4 (4)	1 (8)	0.50
Adverse event	20 (19)	18 (20)	2 (15)	1.00
Death	2 (2)	2 (2)	0 (0)	1.00
Lost to follow-up	2 (2)	1 (1)	1 (8)	0.24
Side effects				
Fatigue	53 (65)	44 (65)	9 (69)	1.00
Rash	55 (68)	47 (69)	8 (62)	0.75
Mood symptoms	34 (42)	27 (40)	7 (54)	0.37
Infection	14 (17)	8 (12)	6 (46)	**<0.01**
Anorectal symptoms	35 (43)	32 (47)	3 (23)	0.14
Anemia				
Hemoglobin nadir, g/L, median (interquartile range)	105 (89–118)	105 (90–117)	105 (74–120)	0.48
Hemoglobin ≤80 g/L	15 (15)	10 (11)	5 (38)	**0.02**
Red blood cell transfusion	9 (11)	6 (9)	3 (23)	0.15
Erythropoietin use	2 (2)	1 (1)	1 (8)	0.30
Thrombocytopenia				
Platelet nadir, g/L, median (interquartile range)	83 (53–113)	86 (54–131)	67 (48–93)	0.31
Platelets ≤50×10^9/L	24 (24)	20 (22)	4 (31)	0.50
Ribavirin dose reduction	46 (57)	41 (60)	5 (38)	0.22
Pegylated interferon dose reduction	10 (12)	4 (6)	6 (46)	**<0.01**

*Data presented as n (%) unless otherwise indicated. Bolded values indicate statistical significance (ie, P<0.05). *HCV monoinfected versus HCV-HIV coinfected*

discontinuation related to adverse events did not differ from monoinfected patients. Therefore, TVR can be safely administered to coinfected patients, provided there is close monitoring. Second-generation anti-HCV DAAs have an improved side effect profile and have significantly reduced the risk for treatment-associated adverse events (20). However, HCV-HIV coinfected patients who receive anti-HCV therapy that includes RBV may require more frequent monitoring of complete blood count, given the propensity to develop severe anemia. TVR is a potent CYP 3A4 inhibitor and, therefore, another consideration among HIV-coinfected patients is drug-drug interactions with antiretroviral therapy. The majority (85%) of our patients required a change in antiretroviral medication before initiation of TVR. Many of these patients were stable on their previous HIV regimen for many years before this change. The risk for drug-drug interactions with highly active antiretroviral therapy is less of a concern with second-generation DAAs for HCV; however, due to high cost, these newer agents may not be available in resource-limited countries and, hence, TVR may still be required for anti-HCV therapy in many regions.

One limitation of the present study was the relatively small sample size. Furthermore, IL28b and HCV genotype subtype was not available for 42% (n=43) and 34% (n=35) of patients, respectively. Another possible limitation was selection bias – in that patients who were more likely to adhere to a complicated regimen and tolerate side effects were offered TVR-based therapy. Treatment may have been deferred (ie, until the second-generation DAAs were available) for more challenging-to-treat patients. However, a key strength of our study was that it was inclusive of all patients treated with TVR. Most clinical trials and observational studies specifically excluded HIV-coinfected patients, post-liver transplant recipients, patients with decompensated liver disease and hepatitis B virus-coinfected patients. Therefore, our results are generalizable to a real world clinical setting.

In summary, we present the first study to our knowledge involving HCV-HIV coinfected patients treated with TVR-based therapy in Canada. We found coinfected patients had comparable rates of SVR to monoinfected patients, albeit with an added risk for certain adverse events, namely infections and severe anemia. With the approval of second-generation DAAs, HIV-coinfected patients in Canada now have access to more potent and effective anti-HCV therapy with an improved side effect profile and shortened treatment duration. These treatment advances will ultimately reduce the burden of HCV-related morbidity and mortality in individuals living with HIV.

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