

WJG 20<sup>th</sup> Anniversary Special Issues (9): Hepatitis B virus**Outcomes and management of viral hepatitis and human immunodeficiency virus co-infection in liver transplantation**

Stephen E Congly, Karen E Doucette, Carla S Coffin

Stephen E Congly, Carla S Coffin, Liver Unit, Division of Gastroenterology and Hepatology, University of Calgary, Calgary, AB T2N 4Z6, Canada

Karen E Doucette, Division of Infectious Diseases, University of Alberta, Edmonton, AB T6G 2R3, Canada

Author contributions: Congly SE, Doucette KE and Coffin CS contributed to this paper equally.

Correspondence to: Carla S Coffin, MD, MSc, FRCPC, Liver Unit, Division of Gastroenterology and Hepatology, University of Calgary, 6D21, Teaching, Research and Wellness Building 3280, Hospital Drive, Calgary, AB T2N 4Z6, Canada. [cscoffin@ucalgary.ca](mailto:cscoffin@ucalgary.ca)

Telephone: +1-403-5925049 Fax: +1-403-5925090

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**Core tip:** Liver transplantation is not contraindicated in viral hepatitis patients co-infected with human immunodeficiency virus. Patients should meet standard listing criteria for liver transplantation. Management of these patients should be done through a multidisciplinary management approach including pharmacists and infectious diseases physicians.

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**Abstract**

Liver transplantation for human immunodeficiency virus (HIV) positive patients with viral hepatitis co-infection is increasingly offered in many North American and European liver transplant centers. Prior studies have demonstrated acceptable post-transplant outcomes and no increased risk of HIV complications in patients co-infected with hepatitis B virus (HBV). However, liver transplantation in HIV positive patients with hepatitis C virus (HCV) has poorer outcomes overall, requiring careful selection of candidates. This review aims to summarize the published literature on outcomes after transplant in HIV patients with HBV or HCV related end-stage liver disease and recommendations for management. In particular the pre-transplant factors impacting outcomes in HCV/HIV co-infected candidates and importance of multidisciplinary management will be discussed.

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**INTRODUCTION**

Liver transplantation offers the promise of improved quantity and quality of life for patients with end stage liver disease with 1-year survival approaching 90%<sup>[1]</sup>. Historically, HIV infection was considered to be a contraindication to transplantation<sup>[2]</sup> with early outcomes in the pre-highly active anti-retroviral (HAART) era being abysmal<sup>[3]</sup>. With the improvement of HAART, patients with HIV have comparable life expectancy to the general population<sup>[4,5]</sup>; similar to those with other chronic medical conditions, such as diabetes. As such, liver transplant is now considered a potential treatment option to the over 1.1 million infected with HIV in the United States<sup>[6]</sup> and 34 million worldwide<sup>[7]</sup>.

Patients living with HIV have a significant burden of liver disease; one large series suggests that liver disease is related to over 14% of all cause mortality<sup>[8]</sup> with

three-quarters of this being attributable to hepatitis B virus (HBV) or hepatitis C virus (HCV) infection. The increased burden of co-infection with HBV or HCV in HIV patients relates to similar mechanisms of transmission of the viruses such as sexual or vertical transmission, blood transfusion or intravenous (*iv*) drug use. In areas of low HBV endemicity, such as North America and Western Europe, HIV and HBV co-infections occur primarily in immigrant populations and in adult populations due to shared sexual and percutaneous modes of transmission<sup>[9]</sup>. The prevalence of HBV co-infection in Western countries has been reported as between 6%-14%<sup>[10]</sup> with rates of co-infection in endemic areas such as Africa and southeast Asia nearing 30%<sup>[11]</sup>. For HCV, the rates of co-infection also reflect the shared risk factors for transmission with approximately 10% acquired through high risk sexual exposures and the vast majority via blood-borne contact<sup>[12]</sup>. The global burden of HIV co-infection is significant with approximately 7 million persons co-infected with HCV and 4 million with HBV worldwide<sup>[13,14]</sup>.

## IMPACT OF VIRAL HEPATITIS/HIV CO-INFECTION

Patients co-infected with either HBV or HCV have more aggressive liver disease than those with mono-infection. In a large epidemiological study of 23441 patients infected with HIV, HIV-HBV co-infected patients were reported to have a 3-fold higher risk of liver related mortality compared to HBV mono-infection<sup>[8]</sup>. Differences in survival were demonstrated in the early HAART era; a Taiwan study showed a 5-year survival of 75% in patients with HIV and chronic hepatitis B [positive serum hepatitis B surface antigen (HBsAg)] versus approximately 90% survival in HBsAg-negative, HIV infected patients<sup>[15]</sup>. A subsequent meta-analysis of the co-infected population was concordant with this finding, although HAART did reduce the risk of death from 1.6 (95%CI: 1.07-2.39) to 1.28 (95%CI: 1.03-1.60)<sup>[16]</sup>. Accordingly, HIV co-infected patients without HAART seem to have more aggressive HBV-related liver disease and progression to cirrhosis<sup>[17]</sup>. As well, HBV co-infection has also been demonstrated to adversely impact HIV patient outcomes either with or without HAART<sup>[18,19]</sup>.

In HCV/HIV co-infection, the HCV disease course is negatively impacted with an increased HCV viral load as compared to HCV mono-infected patients<sup>[20]</sup> as well as accelerated fibrosis progression<sup>[21-24]</sup>. Insulin resistance in HCV mono-infected patients has been associated with increased fibrosis and impaired response to treatment<sup>[25,26]</sup> although in the co-infected population the impact of insulin resistance is less clear<sup>[27-30]</sup>. HCV co-infected patients have increased healthcare resource utilization<sup>[31]</sup> and increased mortality<sup>[32]</sup> versus those living with HCV alone. Treatment of HCV is often more complex, due to the interaction between HCV and HIV medications<sup>[33]</sup>. Further complicating matters is that co-infected patients have inferior responses to interferon and ribavirin based

therapy; pooled analysis showed sustained virological response rates of 38% overall with genotypes 1 and 4 being 25% and genotype 2 and 3 being 60%<sup>[34]</sup> although the addition of protease inhibitors may lead to similar responses in genotype 1 infections<sup>[35]</sup>. The evidence that HIV disease activity is aggravated by HCV co-infection is controversial<sup>[36]</sup>. Nonetheless, achieving adequate control of the HIV with the use of HAART is important as it may reduce mortality as compared to no treatment<sup>[37]</sup> and reduce the rate of fibrosis to that of a HCV mono-infected patient<sup>[38]</sup> albeit may not completely achieve fibrosis regression<sup>[39]</sup>.

## OUTCOMES AFTER LIVER TRANSPLANTATION IN HCV/HIV CO-INFECTION

The published outcomes of HCV/HIV co-infected patients with regards to survival and HCV recurrence were analyzed in a recent meta-analysis<sup>[40]</sup>. This analysis compared HIV/HCV co-infected patients to those infected with HCV alone. There was no difference between groups with regards to the rate of acute cellular rejection (OR = 0.88; 95%CI: 0.44-1.76) or with regards to HCV recurrence rates (OR = 0.66; 95%CI: 0.27-1.59) although the evidence quality is described as being low. A significant reduction in survival was seen in co-infected patients compared to the HCV mono-infected population (HR = 2.81; 95%CI: 1.47-5.37) although this again was based on weaker evidence overall. More recently, there have been two large prospective multicenter cohort studies examining outcomes of HCV-HIV co-infection published. In Spain, a series of 86 consecutive HCV-HIV co-infected patients were compared to a matched series of 252 HCV mono-infected patients<sup>[41]</sup>. Patients with HIV were eligible if they met Spanish consensus guidelines<sup>[42]</sup> including CD4<sup>+</sup> T cell counts > 100 cells/L (> 200 cells/L with history of opportunistic infection), suppressed HIV viral load and no AIDS defining events other than *Pneumocystis pneumonia*, esophageal candidiasis or tuberculosis.

In this cohort, 55% of the population had genotype 1 HCV infection and 15% were co-infected with HBV; the median model for end-stage liver disease (MELD) score at the time of transplant was 16 and the waitlist time was 4 mo. Notable differences between the HCV comparison group and the HCV/HIV co-infected group were lower rates of genotype 1 in the HCV mono-infected group, lower rates of acute rejection and lower rates of significant fibrosis (> Stage 2) with post-transplant recurrence of the HCV. Survival in the HCV/HIV co-infected group was similar in the first year (88% *vs* 90%) but diverged at 3 years (62% *vs* 76%) and 5 years post transplant (54% *vs* 71%). Similar rates and trends were seen for graft survival. Factors predicting poor survival on multivariate analysis included HCV genotype 1 and an increased donor risk index; having a low HCV RNA level had a significant protective effect. Low center experience

**Table 1 Summary of outcomes post orthotopic liver transplant in hepatitis C virus/human immunodeficiency virus co-infection**

Ref. <sup>1</sup>	Study period	Country	Patients	Median follow-up (mo)	Survival	Graft survival
Terrault <i>et al</i> <sup>[2]</sup>	2003-2010	United States	89	32	76% 1 yr 60% 3 yr	72% 1 yr 53% 3 yr
Miro <i>et al</i> <sup>[41]</sup>	2002-2006	Spain	84	44	88% 1 yr 62% 3 yr 54% 5 yr	NR
Duclos-Vallée <i>et al</i> <sup>[45]</sup>	1999-2005	France	35	44	82% 1 yr 73% 2 yr 51% 5 yr	NR
De Vera <i>et al</i> <sup>[44]</sup>	1997-2005	United States	27	27	67% 1 yr 56% 3 yr 33% 5 yr	63% 1 yr 52% 3 yr 31% 5 yr
Ragni <i>et al</i> <sup>[94]</sup>	1997-2001	United States	15	17	80% 1 yr 57% 3 yr 36% 5 yr	NR
Vennarecci <i>et al</i> <sup>[95]</sup>	2002-2006	Italy	11	26	83% 1 yr 58% 3 yr <sup>2</sup>	NR
Anadol <i>et al</i> <sup>[96]</sup>	1997-2011	Germany	19	61 <sup>3</sup>	58% 5 yr	NR

<sup>1</sup>Studies with  $\geq 10$  patients; <sup>2</sup>Survival reported for cohort of 12, including one hepatitis B virus/human immunodeficiency virus co-infected patient; <sup>3</sup>For all patients. NR: Not reported.

was also independently associated with an increased risk of death.

The main North American experience published to date is based on data from the National Institutes of Health-sponsored Solid Organ Transplantation in HIV study. This multicenter United States trial compared a group of 86 HIV/HCV co-infected patients to HCV mono-infected patients and to all transplants in patients over the age of 65 years using the United Network for Organ Sharing (UNOS) database<sup>[2]</sup>. Eligible patients had similar entry criteria to the Spanish study including a CD4<sup>+</sup> T cell count > 100 cells/L for 6 mo and being on a stable HAART regimen for at least 3 mo with undetectable viral loads; patients intolerant to HAART were allowed entry if they were predicted to have suppression of HIV post transplant based on past medication exposure and anti-HIV drug resistance testing. There was a more liberal policy regarding opportunistic infections in that after April 2002, patients with treated opportunistic infections (excluding lymphoma, visceral Kaposi's sarcoma, chronic cryptosporidiosis and progressive multifocal leukoencephalopathy) were eligible for enrolment in the trial.

In this study, the HCV/HIV group was younger, had a lower body mass index (BMI), longer warm graft ischemic time and were more likely to have a deceased donor transplant than the HCV mono-infected group. More patients in the co-infected group received anti-HCV treatment. The co-infected group had significantly poorer survival compared to the HCV mono-infected population with 1-year survivals of 76% *vs* 92% and 3 year survivals of 60% *vs* 79%. The graft survival was also worse in HCV/HIV coinfecting patients with 1-year graft survival rates of 72% *vs* 88% and 3 year graft survival of 53% *vs* 74%. The only factor identified as a risk factor for patient survival in this group was HIV infection. Risk factors for losing graft function included having a combined liver-kidney transplant (HR = 3.8), BMI < 21 kg/m<sup>2</sup> (HR

= 3.2), HCV+ donor (HR = 2.5) and an older donor (HR = 1.3/decade). Table 1 summarizes the data from the larger HCV trials published to date.

Based on the literature, several major risk factors for poor transplant survival in the HCV/HIV co-infected population have been reported. These include high MELD scores<sup>[43,44]</sup>, HCV genotype 1<sup>[41]</sup>, African descent<sup>[44]</sup>, as well as viral load<sup>[41,44]</sup>. Few studies have looked at factors impacting graft survival; Terrault *et al*<sup>[2]</sup> identified that receiving either a HCV+ graft or an older organ, undergoing a simultaneous liver-kidney transplant or being underweight decreased graft survival. Fibrosing cholestatic hepatitis (FCH), an often fatal complication of hepatitis C post transplant is relatively uncommon in the mono-infected population with an incidence of about 5%-8%<sup>[41,45,46]</sup>. The incidence is increased in the co-infected population by two to three fold with the largest series suggesting a prevalence of 19%<sup>[41,44,47]</sup>. Commonly associated factors for FCH in the mono-infected population including acute rejection and older donor age<sup>[48]</sup> were not identified as predictors in the co-infected population<sup>[47]</sup>.

## OUTCOMES AFTER LIVER TRANSPLANTATION IN HBV AND HIV CO-INFECTION

In general, the results for HBV/HIV co-infected patients are very good and are similar to that of HBV mono-infected patients. One of the largest published series of HBV/HIV co-infected patients undergoing transplant consists of 22 patients predominantly from the Solid Organ Transplantation in HIV Multi-Site Study<sup>[49]</sup>. Patients were required to have either undetectable HIV viral loads or be predictably suppressible, CD4<sup>+</sup> T cell count > 100 cells/L, absence of prior opportunistic infections and no history of visceral Kaposi's sarcoma. Post transplantation, patients received a combination of hepatitis

**Table 2 Summary of outcomes post orthotopic liver transplant in hepatitis B virus/human immunodeficiency virus co-infection**

Ref.	Study period	Country	n	Median follow-up (mo)	Survival	Graft survival	Comments
Coffin <i>et al</i> <sup>[49]</sup>	2001-2007	United States	22	42	85% 1 yr 85% 3 yr	85% 1 yr 85% 3 yr	About 50% had detectable HBV pre transplant
Tateo <i>et al</i> <sup>[97]</sup>	1999-2007	France	13	32	100%	100%	1 co-infected with HDV, 2 with HCV, 4 with HCV and HDV
Anadol <i>et al</i> <sup>[96]</sup>	1997-2011	Germany	10	61 <sup>1</sup>	90% 1 yr 80% 5 yr	NR	
Schreibman <i>et al</i> <sup>[98]</sup>	1999-2006	United States	8	NR	75% 1 yr 75% 3 yr	NR	2 co-infected with HCV, 1 fulminant hepatic failure
Norris <i>et al</i> <sup>[99]</sup>	1995-2003	United Kingdom	4	22	100% 1 yr	NR	

<sup>1</sup>For entire series. HBV: Hepatitis B virus; HCV: Hepatitis C virus; NR: Not reported; HDV: Hepatitis D virus.

B immune globulin (HBIG) and antiviral therapy with indefinite use of HBIG targeting anti-HBs titers of > 100 IU/L; HBV antiviral treatment was based on their treatment prior to transplant. Co-infected patients were compared to patients with HBV undergoing transplantation at the University of California, San Francisco. Overall, the co-infected group was younger (median age 47 years *vs* 58 years), included more males (100% *vs* 65%) and fewer were transplanted for HCC as a primary indication (9% *vs* 25%). Both groups had similar donor characteristics other than the co-infected group receiving younger donors (39 years *vs* 51 years); immunosuppression regimens in the co-infected population were more likely to use cyclosporine and less likely to be receiving mycophenolate mofetil. The three-year survival of 85% was not significantly different to the HBV mono-infected population; there was no evidence of HBV disease activity in either group. Similar positive outcomes have been seen in other small trials (Table 2).

## ECONOMIC STUDIES OF CO-INFECTED LIVER TRANSPLANTATION

Liver transplant has significant cost to payers with estimated costs of transplant in the HCV mono-infected population of \$169000 USD initially and subsequent annual costs of \$38000<sup>[50]</sup>. Very limited study has been done on the economic impact of HIV on the cost of transplantation. One study estimated that the presence of HIV adds an additional cost of approximately \$38000 to the cost of liver transplantation<sup>[40]</sup>. Further economic analyses to assess cost-effectiveness are needed.

## SELECTION OF HIV POSITIVE PATIENTS FOR LIVER TRANSPLANTATION

Patients with HIV should meet the generally accepted indications for liver transplant as patients without HIV including advanced liver disease with a MELD of at least 15 or having an indication for an appealed MELD score (*i.e.*, MELD exception points) such as hepatocellular carcinoma, hepatopulmonary syndrome or portopulmonary syndrome<sup>[51]</sup>. They must be able to tolerate the surgery from a cardiovascular and respiratory standpoint and

have a satisfactory psychosocial assessment. Patients with a history of substance abuse, including alcohol, must be abstinent and have completed a treatment program. Most programs, including ours, require a minimum of 6 mo of abstinence even though this interval is arbitrary<sup>[52]</sup>.

Patients should be on a stable treatment regimen for their HIV with documented adherence and viral loads being undetectable for at least a 6-mo interval. Preferred antiretroviral agents as part of the HAART regimen include raltegravir, efavirenz, maraviroc and rilpivirine. Zidovudine and protease inhibitors are avoided when possible due to significant anemia and drug interactions respectively. Most nucleoside reverse transcriptase inhibitors can be used. Didanosine and stavudine are the only agents truly contraindicated given the risk of potentially fatal lactic acidosis. Antiretroviral therapy is now recommended in all HIV-infected patients, regardless of CD4 count, assuming they understand the risks and benefits of therapy and are committed to adherence<sup>[53]</sup>. In the context of potential transplantation and subsequent immunosuppression as well as the numerous options for therapy currently, we would recommend all patients be on HAART prior to transplant.

Current guidelines from the American Society of Transplantation (AST), based on the National Institutes of Health studies, suggest that patients with no AIDS defining conditions should have a CD4<sup>+</sup> T cell count > 100 cells/L and for patients with AIDS defining disease, a CD4<sup>+</sup> T cell count > 200 cells/L for at least 3 mo before transplant<sup>[54]</sup>. In practice, there may be significant variation between centers. In our center, we require a CD4 count  $\geq$  150 cells/L for at least 6 mo or, if the CD4 count is between 100-150, as is not uncommon in those with portal hypertension and hypersplenism, the CD4% should be  $\geq$  20% for at least 6 mo. Patients treated with interferon based anti-HCV treatment experience a drop in their absolute CD4 counts<sup>[55]</sup>. Therefore, to accurately reflect their immune status in the context of transplantation, they should have their CD4 count performed prior to beginning interferon treatment; a reasonable interval would be 4-6 mo. We consider a history of multi-drug resistant HIV a relative contraindication to transplantation given the potential challenges of controlling HIV post transplant; however as newer options for therapy continue to be developed, this needs to be reviewed on a

**Table 3** Contraindications to liver transplantation in human immunodeficiency virus positive patient

Condition	Comment
Progressive multifocal leukoencephalopathy	Chronic intestinal > 1 mo duration Primary CNS
Cryptosporidiosis	
Lymphoma	
Visceral Kaposi's sarcoma	Cutaneous KS considered if remission with immune reconstitution and no active/vascular residual cutaneous lesions on physical exam and chest CT scan
Encephalopathy, HIV-related	Unless diagnosed prior to HAART and resolved on HAART with marked improvement in mental status and increased CD4 <sup>+</sup> T-cell count and no evidence of progression of CNS disease and are otherwise considered eligible from a functional standpoint

HIV: Human immunodeficiency virus; CNS: Central nervous system; CT: Computerized tomography; KS: Kaposi's sarcoma; HAART: Highly active anti retroviral therapy.

case by case basis by the infectious diseases consultant to assess the likelihood of HIV viral breakthrough and the potential for future options.

In general, most opportunistic infections (OI) are not absolute contraindications to transplantation; absolute contraindications are listed in Table 3, which are congruent with the AST guidelines<sup>[54]</sup>. Patients should have been successfully treated for the OI with a reasonable interval of time elapsing following the completion of therapy to allow for immune reconstitution with HAART; we suggest at least 12 mo since the infection. Consultation with an infectious diseases specialist with regards to the risk of recurrence post transplant as well as the need for any additional prophylactic therapies post transplant is also recommended.

For the HIV/HCV co-infected patient, simultaneous liver-kidney transplantation is not recommended given poor outcomes<sup>[2]</sup> as compared to the mono-infected HCV patient<sup>[56]</sup>. Similarly, HCV positive grafts should be avoided in HIV co-infected patients given inferior survival<sup>[2]</sup>. Patients should ideally have a BMI > 21 kg/m<sup>2</sup>; in otherwise acceptable candidates with BMIs < 21 kg/m<sup>2</sup>, nutritional supplementation and reassessment once the BMI exceeds 21 is reasonable; this is in keeping with the 2013 AST guidelines<sup>[54]</sup>. We would suggest that patients with natural MELD scores > 25 be reviewed on a case by case given the worse outcomes seen in this population. Additionally, it is recognized that co-infected patients have more rapid deterioration of liver disease and a higher risk of death on the list than mono-infected patients<sup>[1,57]</sup>, thus a detailed discussion of potential benefit of live donor liver transplantation should occur. At this time, we do not recommend re-transplantation of patients with HIV/HCV co-infection outside of study protocols given the poor 42% 3 year survival seen in a small series of 14 patients<sup>[58]</sup>.

### SUMMARY OF RECOMMENDATIONS FOR THE PRE-TRANSPLANT MANAGEMENT OF THE PATIENT WITH HIV AND VIRAL HEPATITIS CO-INFECTION

In co-infected HCV patients, successful treatment of

HCV will likely offer significant improvement in transplant outcomes given the adverse effects of recurrent HCV in the co-infected<sup>[44]</sup> and mono-infected HCV populations<sup>[59]</sup> as well as increased mortality on the wait-list<sup>[60]</sup>. However, treatment can be challenging due to the interaction of novel directly acting anti-HCV agents (*i.e.*, viral protease and polymerase inhibitors) with HAART<sup>[33]</sup> especially in the context of advanced liver disease and risk of decompensation. If treatment is not feasible, complications of liver disease should be managed similar to the non-HIV infected population.

For patients with HIV-HBV co-infection, the ideal antiretroviral regimen should contain tenofovir, with appropriate dose adjustment for renal function. If tenofovir is poorly tolerated, entecavir is suggested in conjunction with a fully suppressive HIV treatment regimen. If patients have any history of lamivudine exposure, given high rates of lamivudine resistant HBV in the co-infected population, it is recommended that if entecavir is used, it be at a 1 mg dose daily.

Both HBV/HIV and HCV/HIV co-infected patients with HCC seem to have a higher risk of tumor progression outside of most transplant centers' criteria including the current UNOS standard of the Milan criteria<sup>[61]</sup>, and total tumor volume<sup>[62]</sup>. Given this, we would obtain imaging every 3 mo to monitor tumor development. As well, given that an  $\alpha$ -fetoprotein (AFP) rise of > 15  $\mu$ g/L per month is associated with a poor prognosis in this population<sup>[63]</sup>, it is suggested that AFP be done monthly as a marker of tumor progression.

### SUMMARY OF RECOMMENDATIONS FOR THE POST TRANSPLANT MANAGEMENT OF THE HIV/VIRAL HEPATITIS CO-INFECTION PATIENT

#### **Immunosuppression**

Overall, immunosuppression in the HIV co-infected population is similar in principle to that of the mono-infected patient. The use of an induction agent is controversial; however, given high rejection rates seen<sup>[2]</sup>, we feel that the use of the interleukin 2 inhibitor basiliximab as a steroid sparing agent is reasonable. Thymoglobu-

**Table 4 Drug-drug interactions: Antiretrovirals and immunosuppressants**<sup>[54,102]</sup>

	<b>Steroids</b>	<b>Calcineurin inhibitors (cyclosporine/tacrolimus)</b>	<b>mTOR inhibitors (sirolimus, everolimus)</b>	<b>Antimetabolites (mycophenolate mofetil)</b>
PI	Significant increase	Significant increase in immunosuppression levels in general. Calcineurin inhibitor levels may increase or decrease with exposure to either amprenavir or fosamprenavir	Significant increase in immunosuppression levels	Generally no effect; levels may decrease with nelfinavir, lopinavir/ritonavir
NNRTI	Mild decrease in level	Mild decrease in level	Mild decrease in level	No effect on immunosuppressant levels. May decrease nevirapine levels
NRTI	No effect	No effect	No effect	May be increased with zidovudine
Integrase inhibitors	No effect	Increased with elvitegravir	Increased with elvitegravir	Increased with elvitegravir
CCR5-agonists			No effect	
Fusion inhibitors			No effect	

PI: Protease inhibitor; mTOR: Mammalian target of rapamycin; NNRTI: Non-nucleoside reverse transcriptase inhibitors; NRTI: Nucleoside reverse transcriptase inhibitors; CCR5: Chemokine receptor type.

lin would not be recommended given the high rate of graft loss seen in the HIV renal transplant group due to increased HCV replication<sup>[64]</sup>. The maintenance immunosuppression regimen in HIV-positive recipients is not well defined, and even less is known in HCV/HIV in co-infected patients<sup>[54]</sup>. Most programs have used calcineurin inhibitors as the backbone of the maintenance protocol with cyclosporine potentially having some in vivo suppression of HIV<sup>[65]</sup> although cyclosporine may put patients at higher risk of rejection as compared to tacrolimus<sup>[64]</sup> and may lead to poorer outcomes in the HCV population<sup>[66]</sup>. Mycophenolate mofetil as an adjunct agent may have anti-HCV<sup>[67]</sup> and anti HIV effects<sup>[68,69]</sup>. Sirolimus may be considered as a calcineurin inhibitor-sparing agent in the context of renal insufficiency. As well, sirolimus may reduce HIV replication through blocking of the HIV entry receptor, CCR5<sup>[70]</sup>, has antitumor properties in HCC<sup>[71]</sup> and demonstrated improved outcomes in a small series of HIV/HCV coinfecting patients<sup>[72]</sup>. However, analysis of the Scientific Registry of Transplant Recipients database showed worse graft survival and overall HCV patient survival<sup>[73]</sup> as well as an increased risk of hepatic artery thrombosis<sup>[74]</sup>. Thus the risk-benefit ratio of sirolimus will need to be carefully considered.

Medication management in HIV positive transplant recipients is challenging due to bidirectional drug interactions between immunosuppressants and antiretrovirals which may lead to altered drug exposure, toxicity, rejection or poorly controlled HIV<sup>[75]</sup>. Close communication between pharmacists managing the HIV antivirals and immunosuppression will be critical. Therefore, both the HIV team and the transplant teams should be informed about any medication changes. Antiretroviral therapy should be given up to the time of transplant and then restarted as soon as possible post transplant once oral therapy is tolerated and ideally no longer than a week post operatively; generally in well suppressed patients before transplant, the HIV viral loads will not rebound within that time-frame. If there is poor oral absorption, HAART levels may be sub-therapeutic leading to in-

creased risk of resistance and viral breakthrough. The key drug-drug interactions are summarized in Table 4.

### Prophylaxis

In HBV patients post transplant, most patients initially receive HBIG as prophylaxis for recurrent infection<sup>[76]</sup>. The use of a potent HBV medication such as tenofovir or entecavir is also recommended. Likely, with suppression of HBV with a newer nucleos(t)ide analogue, HBIG may be able to be stopped in many patients<sup>[77-79]</sup> or may not even be required<sup>[80]</sup>. In the context of a HBV-HIV co-infected patient, until further data exists with regards to HBIG sparing therapy, we would use HBIG in combination with tenofovir or entecavir with consideration of indefinite HBIG use due to a high incidence of occult HBV post liver transplant as well as to account for possible anti-HBV drug interruptions.

Given the immunodeficiency from the HIV as well as the antirejection medication, infection prophylaxis is critical (Table 5). From an infection standpoint, perioperative prophylaxis to cover gastrointestinal pathogens, including *Enterococcus*, as well as *Candida* in those at high risk, in addition to cytomegalovirus prophylaxis with valganciclovir is identical to patients without HIV. All co-infected patients should remain on lifelong prophylaxis for *Pneumocystis jirovecii* pneumonia with one tablet of single strength trimethoprim/sulfamethoxazole daily. For those intolerant, alternatives include monthly inhaled pentamidine, oral dapsone or atovaquone.

### Summary of post transplant management issues in HIV/viral hepatitis co-infection

**Rejection:** Patients with HIV are at increased risks of acute cellular rejection<sup>[2,41]</sup>; careful monitoring is required. Given the increased risk, protocol biopsies are recommended peritransplant at baseline, 6 mo, 12 mo and then annually subsequently. When rejection is clinically suspected, a biopsy should be obtained. The preferred method to treat rejection is to increase calcineurin inhibitor levels or sirolimus levels depending on the agent being

Table 5 Post transplant prophylaxis

Post transplant prophylaxis	Comment
PJP prophylaxis	Trimethoprim/sulfamethoxazole SS one tablet daily life long
CMV	Alternatives: Dapsone 100 mg daily, pentamidine 300 mg inhaled or <i>iv</i> monthly or atovaquone 1500 mg daily <sup>[54]</sup> Valganciclovir 900 mg daily <sup>1</sup> ; oral (1 g <i>tid</i> ) or <i>iv</i> (5 mg/kg daily) ganciclovir for 3 mo in D+/R-; prophylaxis or pre-emptive monitoring and therapy in R+
Fungal	High risk patients <sup>2</sup> should receive Fluconazole 400 mg <i>po</i> daily × 14 d minimum <sup>[100]</sup>
HBV (in HBV co-infected patients)	Life long HBIG targeting 100 IU/L plus either tenofovir or entecavir

<sup>1</sup>Valganciclovir is not FDA approved for use in liver transplantation; many centers use this agent off label<sup>[101]</sup>; <sup>2</sup>High risk features include repeat or prolonged surgery, high transfusion requirements, renal failure, colonization with *Candida* or Cholechojejunostomy<sup>[100]</sup>. PJP: *Pneumocystis jirovecii* pneumonia; SS: Single strength; CMV: Cytomegalovirus; HBV: Hepatitis B virus; HBIG: Hepatitis B immunoglobulin; FDA: United States Food and Drug Administration.

used, as well as increasing mycophenolate mofetil levels. Use of anti-lymphocyte depleting agents, such as thymoglobulin, is to be avoided if possible due to prolonged immunosuppression of T cells with thymoglobulin<sup>[81]</sup>. High dose steroids in the context of HCV co-infection leads to more aggressive disease activity and rapid progression in fibrosis<sup>[82]</sup>.

**Occult HBV:** In patients who have occult HBV (HBsAg negative, HB core antibody positive), we would suggest annual monitoring of HBsAg levels. Given most HAART regimens includes medication that has activity for HIV and HBV, such as tenofovir, emtricitabine or lamivudine, reactivation is low risk, especially with the use of tenofovir.

**Recurrent HCV:** Treatment of the hepatitis C should be offered post-transplantation when there is histologic evidence of recurrent disease. Earlier therapy in disease may be associated with improved outcomes in the mono-infected population<sup>[83]</sup> and thus consideration could be given to starting therapy in all HIV/HCV co-infected liver transplantation recipients once stable and on low dose maintenance immunosuppression. HIV/transplant pharmacists should be consulted with regards to drug selection given the complex three-way interactions between HCV protease inhibitors, antiretroviral agents and immunosuppressants.

Treatment of hepatitis C is critical with the presentation of fibrosing cholestatic hepatitis (FCH) given its marked effect on survival. Currently, the typical treatment is the use of pegylated interferon and ribavirin with a median survival of 22 mo; this is about 20% the survival of co-infected HCV-HIV patients without fibrosing cholestatic hepatitis<sup>[47]</sup>. Recently, there has been two reports of the use of a protease inhibitor (telaprevir and boceprevir<sup>[84]</sup>) including in a co-infected patient<sup>[85]</sup> with good effect, although careful monitoring of the calcineurin inhibitors is needed with both telaprevir and boceprevir<sup>[86]</sup>. One case report exists of the combination of sofosbuvir and daclatasvir being successfully used to treat FCH<sup>[87]</sup>; these drugs are not yet commercially available. Thus, consideration may be currently given to triple therapy for managing FCH given its abysmal prognosis with likely better-tolerated and more efficacious therapy to come.

## CONCLUSION

Significant advances have been made with regards to transplanting patients with HIV including those with viral hepatitis co-infection. Transplanted HBV co-infected patients obtain similar outcomes to the HBV mono-infected patient with outcomes less successful in the HCV co-infected population. Treatment of HCV offers the best chance of improved outcomes. Many new treatment strategies for HCV are in advanced stages of development including pan-genotypic interferon free regimens and it is likely these regimens will allow for easier treatment of HCV and improved survival post transplant.

Historically, in the United States, organs could not be knowingly transplanted from donors with HIV by federal law<sup>[88]</sup> with similar policies existing in Canada<sup>[89,90]</sup>. Given the current armamentarium of antiretroviral medications and the ability to suppress HIV, there is potentially a pool of organs that could be used to benefit patients with HIV; one model suggests that over 500-600 patients with HIV could benefit from receiving organs from donors also infected with HIV<sup>[91]</sup>. A series of 14 patients with HIV receiving HIV positive kidneys has showed good 1 year outcomes suggesting that this may be a viable option<sup>[92]</sup>. Recent passage of the HIV Organ Policy and Equity Act changes previous federal policy and enables HIV positive organs to be used in HIV positive patients<sup>[93]</sup>. With this development, further research can then be conducted with regards to outcomes and determining the appropriate population these organs can be used in. In the future, further delineation of the optimal HCV/HIV co-infected candidate will be identified so as to bring outcomes closer to that of the HCV mono-infected patient.

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