

Outcome and management of HCV/HIV coinfection pre- and post-liver transplantation. A 2015 update

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Summary

Liver transplantation is increasingly performed in selected HIV-infected patients in most developed countries, with excellent results reported in patients with liver diseases unrelated to HCV. In contrast, survival in HCV/HIV-coinfected liver recipients is poorer than in HCV-monoinfected patients, due to more aggressive recurrence of HCV and consequent graft loss and death. Results from American, French, and Spanish cohort studies showed a 5-year survival rate of only 50–55%. Therefore, it is debated whether liver transplantation should be offered to HCV/HIV-coinfected patients. Studies have shown that the variables more consistently associated with poor outcome are: (1) the use of old or HCV-positive donors, (2) dual liver-kidney transplantation, (3) recipients with very low body mass index and (4) less site experience. However, the most effective factor influencing transplantation outcome is the successful treatment of HCV recurrence with anti-HCV. Survival is 80% in patients whose HCV infection resolves. Unfortunately, the rates of sustained virological response with pegylated-interferon plus ribavirin in coinfecting recipients are low, particularly for genotype 1 (only 10%). Here we present a non-systematic review of the literature based on our own experience in different liver transplant scenarios. This review covers selection criteria in HIV-infected patients, pre- and post-LT management, donor selection, anti-HCV treatment, drug interactions with antiretrovirals and anti-HCV direct antiviral agents, hepatocellular carcinoma, and liver retransplantation. Recommendations are rated. Finally, we explain how the

introduction of new effective and more tolerable direct antiviral agents may improve significantly the outcome of HCV/HIV-coinfected liver recipients.

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Introduction (J.M. Miro, A. Rimola)

Since the introduction of combined anti-retroviral therapy (ART) in the mid-1990s and the subsequent drastic reduction in mortality by HIV infection [1], liver diseases, particularly those related to hepatitis C virus (HCV) infection, have become a leading cause of death in HIV-infected individuals [2]. Consequently, liver transplantation (LT) has been increasingly necessary in this population and has been performed in selected HIV-infected patients in many developed countries [3,4], mainly the United States of America (USA), France and Spain. Excellent results have been reported for LT in HIV-infected patients with liver diseases unrelated to HCV [5,6]. In contrast, survival in HCV/HIV-coinfected patients has been poorer than in HCV-monoinfected patients [7–10]. The main reason for this difference is that recurrent HCV is more aggressive in coinfecting recipients and is the major cause of graft loss and death in this group [7–10]. Therefore, it is still debated whether LT should be offered to HCV/HIV-coinfected patients.

The objective of this non-systematic review of the literature is to bring together experience on LT in HCV/HIV-coinfected liver recipients gained by American [10], French [8], and Spanish [9] investigators during the last decade. We discuss what we have learnt about different aspects of this issue, provide recommendations and present future challenges considering the introduction of new anti-HCV direct antiviral agents (DAAs). Recommendations are rated based on the Infectious Diseases Society of America – United States Public Health Service evidence grading system (Table 1) [11].

Keywords: Liver transplantation; HCV; HIV; Coinfection; Direct antiviral agents; DAA; Pegylated-interferon; Ribavirin; Simeprevir; Sofosbuvir; Liver retransplantation; Hepatocellular carcinoma.

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Key Points

- Liver transplantation is increasingly performed in developed countries in selected HCV/HIV co-infected patients with decompensated cirrhosis or hepatocellular carcinoma
- Survival in HCV/HIV co-infected liver recipients is poorer than in HCV mono-infected patients, due to a more aggressive HCV recurrence that leads to graft loss and death. Five-year survival is 50-55%
- The rates of sustained virological response with pegylated-interferon plus ribavirin in HCV/HIV co-infected recipients are low, particularly for genotype 1 (only 10%). However, the 5-year survival is almost 80% in co-infected patients whose HCV infection was cleared
- The recent introduction of the new potent and more tolerable direct-acting antiviral agents (DAAs) offers hope for significant improvements in the outcome of HCV/HIV co-infected liver transplant recipients
- This review covers selection criteria in HIV-infected patients, pre- and post-liver transplantation management, donor selection, anti-HCV treatment, drug interactions with antiretrovirals and anti-HCV DAAs, hepatocellular carcinoma, and liver retransplantation

Table 1. Infectious Diseases Society of America–United States Public Health Service Grading System for ranking recommendations in clinical guidelines.

Category, grade	Definition
Strength of recommendation	
A	Good evidence to support a recommendation for use
B	Moderate evidence to support a recommendation for use
C	Poor evidence to support a recommendation
D	Moderate evidence to support a recommendation against use
E	Good evidence to support a recommendation against use
Quality of evidence	
I	Evidence from >1 properly randomized, controlled trial
II	Evidence from >1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time-series; or from dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

Pre-transplant issues (J.M. Miro, A. Rimola)

Patient referral for LT

The risk of death after the first episode of clinical liver decompensation is higher in HIV/HCV-coinfected than in HCV-monoinfected patients with cirrhosis, with a median survival time of 16 and 48 months, respectively [12]. Thus, it seems judicious to refer these patients for LT early after the first episode of clinical decompensation.

Criteria for LT indication

The criteria for LT in HIV-infected patients are the same as for non-HIV-infected persons in all centers. Additionally, HIV-infected patients must have a favorable psychosocial evaluation and have abstained from drug and/or alcohol consumption [13].

Initially, the HIV-related criteria for LT were the absence of previous AIDS-defining events (ADE), CD4+ T-cell count >200 cells/mm³, and full suppression of HIV replication by ART [13]. However, these criteria have been modified over time.

Although LT candidates should ideally not have a history of ADE, most groups currently include patients with previous opportunistic infections that can be treated and prevented effectively, such as tuberculosis, esophageal candidiasis, and *Pneumocystis jiroveci* pneumonia. In fact, the US multicenter cohort study recently expanded the criteria for LT, and only untreatable diseases continue to be exclusion criteria for LT (e.g., progressive multifocal leukoencephalopathy, chronic cryptosporidiosis, multidrug-resistant systemic fungal infections and primary CNS lymphoma). In light of the efficacy of the immunosuppressive agent sirolimus in the treatment of Kaposi's sarcoma, potential recipients with resolved systemic Kaposi's sarcoma may be considered for transplantation provided that they meet the other criteria [3].

At present, a minimum CD4+ T-cell count of 100 cells/mm³ is required in almost all centers [3,8,13–15], although in most countries this limit is increased to 200 cells/mm³ in specific circumstances, such as previous history of opportunistic infections (USA and Spain), clinically compensated cirrhosis (Italy), and absence of portal hypertension (UK).

HIV should be suppressed in all patients on ART [3,8,13–15]. In patients with transiently detectable viral load, effective, safe, and long-lasting ART must be ensured after LT.

The current HIV-related criteria for LT are summarized in Table 2. Nevertheless, it should be noted that these criteria were established on the basis of common sense, but have not been validated with appropriate studies yet.

Waiting list management

The risk of death in HIV-infected patients on the waiting list increases sharply with the MELD score (MELD <15), as follows: HR = 5.7 for MELD 15–19, HR = 21.4 for MELD 20–24, and HR = 101 for MELD ≥25. After adjustment for baseline CD4 count and detectability of HIV RNA, the risk of waiting list mortality increased by 20% for each unit increase in MELD from baseline [16]. Once a patient is included on the waiting list, MELD has been shown to accurately reflect the short-term risk of mortality and priority for LT [16]. Therefore, there are no MELD exceptions

regarding HIV infection per se. It should be noted that waiting list mortality has been associated with lower CD4 count [16].

Recommendations

1. Coinfected patients should be referred for liver transplantation early after the first episode of hepatic decompensation (AII).
2. HIV-specific criteria for LT include (a) HIV RNA suppressible by ART, (b) a CD4+ T-cell count >100/μl, and (c) no previous ADEs, although some preventable opportunistic infections can be included (AIII).

Challenges

1. To define the specific timing for referring patients to a liver transplant unit.
2. To validate current HIV-specific criteria for LT with the aim of determining which of these criteria – if any – need to be modified to improve long-term post-transplant outcomes.

Donor selection (P. Stock, N. Terrault)

The poorer results observed in coinfecting liver transplant recipients than in HCV-monoinfected patients may be related to the quality of the donor organs [9,10]. The donor risk index, which estimates the relative risk of graft failure based on donor characteristics, is associated with graft loss in both coinfecting and monoinfected groups in the USA and Spanish multicenter cohort studies [9,10]. However, within the HCV/HIV-coinfecting cohort, the use of anti-HCV-positive and older donors were both independent predictors of poor outcome in a multivariate analysis [10].

Poorer outcomes with older donors have also been observed in HCV-monoinfected recipients, prompting many centers to exclude donors over the age of 50 in the case of HCV-infected recipients. The use of HCV-infected donors in HCV-monoinfected recipients had no impact on graft or patient survival compared with HCV-negative donors, provided that the donor biopsy

revealed no evidence of fibrosis. However, the practice of using HCV-infected donors in genotype 1 HCV/HIV-coinfecting patients resulted in significantly poorer outcome in the coinfecting recipients [10]. The American cohort study [5] does not recommend the use of older donors (>50 years) or HCV-infected donors (even when histology results are normal). Of note, these restrictions on donors will likely be less relevant with the increasingly frequent use of DAAs.

Recommendations

1. Avoid the use of deceased donors aged >50 years (EII).
2. Avoid the use of HCV-positive donors (EII)

Challenges

1. Coinfecting patients deteriorate quickly while on the waiting list, thus prompting many centers to use “extended” donors to facilitate transplantation at a lower MELD score in coinfecting patients. Larger cohort studies are needed to determine an optimal HIV-specific donor risk index.

Survival of HCV/HIV-coinfecting recipients. Prognostic factors

(J.C. Duclos-Vallée, E. Teicher)

Several cohort studies, systematic reviews, and meta-analyses have demonstrated that patient and graft survival rates are poorer in HCV/HIV-coinfecting transplant recipients than in HCV-monoinfected recipients [17–19]. Table 3 shows the survival rate reported in 3 published national HCV/HIV-coinfecting liver transplant cohort studies, and compares outcomes with their respective HCV-monoinfected counterparts [8–10]. In the French and Spanish studies, 5-year survival in HCV/HIV-coinfecting patients vs. HCV-monoinfected patients was 51% vs. 81%, and 54% vs. 71%, respectively. In the American study, 3-year survival was 60% vs. 79%. As shown in Table 4, HIV coinfection was identified as an independent predictor for mortality in the

Table 2. HIV criteria for liver transplantation (LT) in HIV-infected patients in Europe and the USA.

	Spain [13]	France [8]	Italy [14]	UK [15]	US [3]
Previous AIDS-defining events					
Opportunistic infections (OIs)	Some*	Some*	None in the previous year	None after HAART-induced immune reconstitution	Most**
Neoplasms	No	Not defined	No		No**
CD4 cell count/mm³					
No previous OIs	>100	>100***	>200 or >100 if decompensated cirrhosis	>200 or >100 if portal hypertension	>100
Previous OIs	>200	>100***			>200
Plasma HIV-1 RNA viral load <50 copies/ml on HAART****	Yes		Yes	Yes	Yes

*In Spain and France, patients with previous tuberculosis, *Pneumocystis jiroveci* pneumonia, or esophageal candidiasis can be evaluated for LT.

**In the USA, only progressive multifocal leukoencephalopathy, cryptosporidiosis, multidrug systemic fungal infections, lymphoma, and visceral Kaposi’s sarcoma are exclusion criteria.

***Patients under 100 CD4 cells/mm³ were not excluded in France (case by case evaluation).

****If HIV plasma viral load was detectable, post-LT suppression with HAART should be predicted in all patients.

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Table 3. Patient survival after transplantation in HCV/HIV-coinfected and HCV-monoinfected liver recipients in France [8], Spain [9], and the USA [10].

Country	1 year	2 years	3 years	4 years	5 years	p value
France						
HCV/HIV coinfection (N = 44)	-	73%	-	-	51%	0.004
HCV monoinfection (N = 35)	-	91%	-	-	81%	
Spain						
HCV/HIV coinfection (N = 84)	88%	71%	62%	60%	54%	0.008
HCV monoinfection (N = 252)	90%	81%	76%	73%	71%	
United States						
HCV/HIV coinfection (N = 89)	76%	-	60%	-	-	<0.001
HCV monoinfection (N = 235)	92%	-	79%	-	-	

American and Spanish studies. Importantly, recurrence of HCV was the most frequent cause of death in coinfecting patients from the French and Spanish cohorts and the second cause of death in coinfecting patients from the American study [8–10].

Table 4 summarizes the variables identified as prognostic factors in HCV/HIV-coinfected LT recipients in the American and Spanish cohort studies [9,10], as well as in the whole series of HCV/HIV-coinfected and HCV-monoinfected patients taken together in the French study [8]. Donor age or donor risk index (of which donor age is a major component) were predictive of mortality in the three series. Other factors adversely influencing survival in the American study were a low pre-transplant body mass index (BMI <21 kg/m²), combined liver-kidney transplantation, and, the use of HCV-infected grafts (see above). Since in the other two studies no combined liver-kidney transplantation was performed and no HCV-infected donors were used, the prognostic value of these variables could not be assessed in the French and Spanish cohorts. BMI did not have prognostic significance in the Spanish study, although very few patients had a BMI lower than 21 kg/m²; therefore, this threshold could not be properly assessed. BMI was not investigated in the French cohort. Only in the Spanish study, HCV genotype 1 was associated with increased mortality; however, because of the availability of new antiviral therapies, soon this genotype may no longer be considered a poor prognostic factor. Negative serum HCV RNA remarkably improved the probability of survival in the Spanish cohort; no information on this variable was given in the other studies. Interestingly, in the French and the Spanish studies, but not in the American study, a high MELD score was found to have poor prognostic significance. However, in the Spanish study a high MELD score was associated with mortality when the analysis only included pre-LT variables (not shown in Table 4); therefore, this discrepancy makes the prognostic value of the MELD score in HCV/HIV-coinfected patients uncertain. Finally, site experience was identified as a prognostic factor in the Spanish cohort. Patients transplanted at centers with less than 1 LT per year in HIV-infected patients had a 3-fold higher risk of death. This variable was not investigated in the American study, and the French study only included patients who received LT at 1 center. The prognostic significance of these factors must be re-assessed in the context of new anti-HCV DAA.

Concerning the potential effect of ART on post-transplant outcomes, some groups have suggested that survival was significantly poorer among HIV-infected transplant recipients with post-LT antiretroviral intolerance [7,20]. A French study demonstrated that mitochondrial toxicity potentially induced by old

Table 4. Predictive factors of mortality in HCV/HIV-coinfected liver recipients in the French, Spanish, and US cohorts [8–10].

	HCV/HIV and HCV liver recipients	Including only the HCV/HIV cohort
French cohort		
HIV-1 infection	1.91 (0.7-5.18)*	n.p.
MELD score (1-unit increase)	1.08 (1.01-1.15)	
Donor age	1.04 (1.00-1.07)	
Spanish cohort		
HIV-1 infection	2.20 (1.42-3.41)	n.a.
HCV genotype 1	2.14 (1.24-3.41)	2.98 (1.32-6.76)
Donor risk index	3.03 (1.57-5.83)	9.48 (2.75-32.73)
Negative plasma HCV RNA viral load**	0.23 (0.10-0.49)	0.14 (0.03-0.62)
US cohort		
HIV-1 infection	2.3 (1.3-3.8)	n.a.
BMI at listing <21		3.2 (1.3-7.7)
Combined kidney-liver transplant		3.8 (1.6-9.1)
Anti-HCV positive donor		2.5 (1.1-5.6)
Donor age (by decade)		1.3 (1.0-1.6)

n.p., analysis not performed; n.a., not applicable; BMI, body mass index.

*Hazard ratio (95% confidence interval).

**RNA HCV clearance with/out anti-HCV therapy before or after liver transplantation.

nucleoside analogs (didanosine, stavudine) and/or ribavirin (RBV) may worsen the recurrence of HCV infection on the liver graft [20]. However, these antiretroviral drugs are no longer used. With current ART regimens, most HCV/HIV-coinfected liver transplant recipients are virologically suppressed, with a CD4 cell count remaining above 200 cell/mm³ over time [21]. The CD4 cell count at inclusion on the waiting list was not identified as a poor prognostic factor [8,9].

Recommendations

1. Avoid combined liver and kidney transplantation (EII).
2. Avoid LT in patients with very low pre-transplant body mass index (<21 kg/m²) (EII).
3. Avoid LT in centers with a low volume of LT in HIV-infected patients and no well-organized multidisciplinary team (EII).

Challenges

1. To re-assess all prognostic factors after the full introduction of effective and well-tolerated anti-HCV DAAs.

Management of HCV recurrence before the DAA era.

(J.C. Duclos-Vallée, E. Teicher)

Recurrence of HCV infection is the main problem during the post-LT period, since it has a strongly negative impact on patient and graft survival. Similarly, studies comparing HCV/HIV-coinfected and HCV-monoinfected LT recipients showed that progression of fibrosis was significantly higher in the coinfecting population. In a French study, histology findings assessed 12 months after transplant showed a mean fibrosis score of 1.7 in coinfecting patients compared with 1.1 in monoinfected patients ($p = 0.06$); at 24 months, these scores had reached 2.4 vs. 1.4, respectively ($p = 0.01$) [8]. Similar results were obtained in the Spanish study [9]. In the American study, graft fibrosis was not found to be more severe in the coinfecting group, although this result could be due to a bias in the analysis of progression of fibrosis between the coinfecting group and the control group [10,22]. One of the main objectives in managing HCV/HIV-coinfected patients is to avoid severe recurrence of HCV infection in the liver graft and, more specifically, the occurrence of fibrosing cholestatic hepatitis (FCH), which is associated with a particularly poor prognosis in this population. The French group recently reported a 21-month mortality rate of 82% in 11 coinfecting patients with FCH [23]. Interestingly, FCH seems to be related to very severe necroinflammatory activity and high viral load at the time of recurrence of acute HCV infection, thus suggesting the need for very early anti-HCV therapy in coinfecting patients with high HCV viral load shortly after LT and/or moderate to severe acute HCV infection [23].

Since early detection of severe and/or rapidly progressive recurrence of HCV infection seems to be crucial, protocol-based liver biopsies are highly recommended as soon as the recurrence is suspected, and must be repeated at least yearly. As in non-HIV-infected LT recipients, periodical transient elastography could be very helpful when assessing progression of fibrosis.

Pegylated interferon (PegIFN) and RBV may benefit non-HIV-infected recipients with HCV re-infection. A sustained virological response (SVR) in the range of 20-30% for patients with HCV genotype 1 and 40-50% for patients with HCV genotype 3 has been recorded [24]. In the first French study analyzing the efficacy of either standard IFN alpha 2b or PegIFN with different doses of RBV (400-800 mg/day) in HCV/HIV-coinfected patients, a virological response was observed in 4 of 19 (21%) treated coinfecting patients. The response was sustained in 3 (16%) [8]. In the most recent French study, in which anti-HCV therapy (mean duration 7.5 months) was administered in 40 coinfecting patients after a mean of 11 months after LT, an SVR was obtained in 6 (15%) patients and a null response in 27 (67.5%) [18]. These results were recently confirmed by the American and Spanish cohort studies, with an SVR of only 10% in patients with genotype 1 [25,26]. In the Spanish study, a 59% rate of SVR was obtained in patients with genotypes 2-3 and only 7% in patients with genotype 4.

Possible explanations for the poor results of anti-HCV therapy include (1) higher rates of premature discontinuation due to

intolerability, (2) higher severity of liver disease at initiation of treatment, and (3) host factors related to HIV coinfection. The only factor associated with SVR in these patients was a non-1 genotype [25]. Experience with protease inhibitor (PI)-based triple therapy is limited to case reports, and although a higher SVR can be predicted with PI-based triple therapy, poor tolerability of PegIFN and RBV continues to hamper treatment. Earlier treatment (prior to the development of advanced fibrosis or FCH) and use of growth factors to minimize treatment discontinuations due to cytopenia have the potential to improve SVR rates with PegIFN-based therapy [25].

Recommendations

1. Monitor disease progression with liver biopsy or hepatic elastography at least annually to assess for progression of fibrosis (AIII).
2. Early anti-HCV therapy is indicated in patients with moderate or severe acute hepatitis, FCH, or rapid progression of fibrosis (AII).

Challenges

1. Given the poor virological response to IFN and RBV, other combinations must be evaluated. Since the efficacy of IFN and RBV for genotype 1 has been very low (10%), control groups with this combination should not be included in future trials.

Treatment of HCV with DAAs (P. Stock, N. Terrault)

The availability of IFN-free therapy for treatment of HCV-infected patients on the waiting list and during the post-LT period has resulted in enhanced tolerability and greater success in managing HCV infection in transplant candidates and recipients. While studies on IFN-free therapy in waiting list and post-LT HCV/HIV-coinfected patients are not available, studies in non-transplant patients suggest that HIV infection per se does not negatively affect SVR rates; therefore, the rates of SVR seen in HCV-monoinfected LT candidates and recipients are likely to be similar in coinfecting patients. In a study using sofosbuvir and RBV for 12-24 weeks (depending on the HCV genotype) in HCV/HIV-coinfected patients, the SVR rates were 76% for genotype 1, 88% for genotype 2, and 67% for genotype 3. All patients were treated with tenofovir-emtricitabine combined with efavirenz and boosted with atazanavir, darunavir, raltegravir, or rilpivirine [27]. Tolerability was excellent. The combination of sofosbuvir and RBV achieved an SVR rate of 70% and was very well tolerated in a recent prospective – a multicenter study of 40 non-HIV-infected HCV-infected LT patients with recurrent HCV, most of whom with advanced fibrosis and experienced failure of treatment with PegIFN and ribavirin [28]. The SVR rate was 62% in a compassionate access study of sofosbuvir and RBV used to treat FCH and decompensated cirrhosis in patients with recurrent HCV, [29]. Thus, for the HCV/HIV-coinfected transplant recipients, treatment with sofosbuvir and RBV would be a good option. More recently, the combination of daclatasvir and sofosbuvir with/without RBV was used to treat post-LT patients with advanced recurrent disease and was shown to achieve on-treatment

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responses in 9 of 9 patients and SVR4 in 5 of 5 patients [30]. Although these numbers are small, these data would suggest that sofosbuvir and daclatasvir with/without RBV is another option for treatment of recurrent HCV infection. Importantly, sofosbuvir and daclatasvir do not interact with calcineurin inhibitors or with many HAART regimens [31]. Consequently, these drugs are ideally suited for HCV/HIV-coinfected patients. In contrast, the combination of simeprevir and sofosbuvir is recommended for HCV-monoinfected transplant patients in the USA, and data from non-transplant studies showed SVR rates of $\geq 90\%$ [32]. However, given that simeprevir interacts with PIs, efavirenz, and ciclosporin, it is less-frequently preferred for coinfecting transplant patients. The main advantage of IFN-free therapy is the marked improvement in tolerability. Moreover, RBV-sparing therapy is also expected to further enhance tolerability (RBV-associated anemia is an issue in post-LT patients).

IFN-free antiviral regimens may also be used to prevent HCV infection after transplant. In a study of HCV-monoinfected waiting list patients with HCC, pre-LT therapy with sofosbuvir and RBV achieved on-treatment responses in 93%; of those with an undetectable HCV viral load for at least 4 weeks before transplant, 95% were HCV-free after transplant [33]. This strategy is likely to be expanded as drugs with demonstrated safety in decompensated cirrhosis are approved. However, it may be limited by lack of drugs with established safety in patients with advanced decompensated cirrhosis (Child-Pugh B or C) and/or renal insufficiency. The latter is a frequent complication in patients with high MELD scores, and some drugs, such as sofosbuvir, are not recommended in patients with CrCl ≤ 30 ml/min. Thus, in the near future, options for treating HCV after transplant rather than before may be more limited in coinfecting patients.

Recommendations

1. IFN-free regimens, such as sofosbuvir plus RBV and daclatasvir plus sofosbuvir \pm RBV are the current regimens of choice for treatment of post-LT recurrence of HCV (**BIII**).
2. Given the rapidly evolving treatment landscape, patients with mild recurrence ($\leq F2$) can defer treatment in the short term and await newer drug combinations. Patients with fibrosis (F3/F4) or FCH should be offered treatment with current all-oral combinations (**BIII**).
3. In patients with a predictable time to LT, such as those with HCC or living donors, pre-transplant antiviral therapy with sofosbuvir and ribavirin or sofosbuvir plus daclatasvir is an option for prevention of post-LT HCV recurrence (**BIII**).

Challenges

1. Performing broader drug interaction studies to insure that direct antiviral drugs for treatment of HCV can be used with HCV/HIV-coinfected patients taking any ART regimen.
2. Defining the risk-benefit ratio of pre- vs. post-LT HCV treatment in order to inform future treatment algorithms.

Other post-LT complications (P. Stock, N. Terrault)

A multivariable analysis of the American cohort revealed a higher frequency of multisystem organ failure/sepsis in the coinfecting

group, likely the result of liver dysfunction related to severe HCV recurrence. The Spanish group reported that severe infections (defined as sepsis, bloodstream infections, invasive fungal infections, CMV disease, invasive viral infection, and mycobacterial disease) increased the mortality rate almost 3-fold [34]. In the American series, there were no graft losses related to HIV-associated infections or malignancies in the coinfecting group. A pre-transplant history of AIDS-related opportunistic infections or neoplasms did not significantly affect post-transplant survival. Furthermore, the incidence of surgical complications (hepatic artery thrombosis, biliary complications requiring further technical intervention, wound infections, and reoperations) was similar in both coinfecting and monoinfected recipients [35], although some authors have reported a higher incidence of arterial complications [36]. A preliminary report from Spain suggests that the incidence of *de novo* tumors in HCV/HIV-coinfected patients is similar to that recorded in non-HIV-infected LT recipients: 4% vs. 5%, respectively [37]. Follow-up and screening for *de novo* tumors in HCV/HIV-coinfected patients should be similar to those in non-HIV-infected LT patients.

The incidence of acute rejection was unexpectedly high in the coinfecting group, and management of this complication had a very significant impact on the outcome. In the American multicenter study, the cumulative incidence of acute rejection at 3 years was 39% in the coinfecting group compared with 24% in the monoinfected group ($p = 0.01$) [10]. A similar incidence was seen in the Spanish study [9]. More than 50% of the rejection episodes occurred within 21 days after the transplant, and most were graded as moderate to severe by a central pathologist [10]. Furthermore, treatment of acute rejection was significantly correlated with progression to severe fibrosis associated with recurrence of HCV infection, as were poorer graft and patient survival. Interactions between calcineurin inhibitors and PIs may have contributed to the higher incidence of rejection observed in HIV-infected recipients. The results from series in France and Spain suggest that raltegravir-based regimens and avoidance of PIs may reduce the high rejection rates following LT [38,39]. Minimizing the impact of drug interactions to reduce immunosuppression may help reduce rejection rates, but the higher incidence of rejection could also be related to immune activation and dysregulation associated with HIV infection. Current studies are attempting to dissect the mechanisms responsible for the high incidence of rejection, and strategies to minimize this complication will be an important step forward in improving the results in the HCV/HIV-infected cohort.

PI-sparing antiretroviral regimens based on the integrase inhibitor raltegravir will facilitate adequate immunosuppressive coverage and hopefully lead to a decrease in the high rates of rejection observed in the initial trials. Finally, access to better tolerated and more efficacious HCV treatment regimens, before and after transplantation, is necessary to facilitate prevention and management of rejection in case of recurrent HCV disease.

Recommendations

1. In order to minimize drug interactions that could potentially result in insufficient exposure to immunosuppressive agents (calcineurin inhibitors), PI-sparing ART should be prescribed, if feasible (**BII**).

Table 5. Metabolism and PK interactions between anti-HCV direct-acting antivirals (DAA) and antiretroviral drugs, immunosuppressors and PegIFN and ribavirin.

	Ribavirin	HCV NS3/4 PIs			HCV NS5A inhibitors		HCV NS5B polymerase inhibitor
		Boceprevir 800 mg tid	Telaprevir 750 mg tid	Simeprevir 150 mg qd	Daclatasvir 60 mg qd	Ledipasvir 90 mg qd	Sofosbuvir 400 mg qd
Route of metabolism or excretion	Hepatic (deribosylation and hydrolysis) Renal excretion	CYP3A4, CYP3A5 AKR	CYP3A4	CYP3A4	CYP3A4	Not a substrate, of CYP 450/UGT Excreted in faeces (>98%)	Not substrate of CYP 450/UGT Renal excretion
HIV PIs							
Lopinavir/r	Recommended	Not recommended	Not recommended	Not recommended	No data	No data	Recommended
Darunavir/r	Recommended	Not recommended	Not recommended	Not recommended	No data	No data	Recommended
Atazanavir/r	Close monitoring	Consider on an individual basis	Recommended	Not recommended	Recommended at 30 mg qd	No data	Recommended
HIV NNRTIs							
Efavirenz	Recommended	Not recommended	Recommended at 1125 mg tid	Not recommended	Recommended at 90 mg qd	Recommended	Recommended
Rilpivirine	Recommended	Recommended	Caution for QT prolongation	Recommended	No data	Recommended	Recommended
Etravirine	Recommended	Recommended	Recommended	No data	No data	No data	No data
HIV InSTIs							
Dolutegravir	Recommended	Recommended	Recommended	No data	No data	No data	No data
Raltegravir	Recommended	Recommended	Recommended	Recommended	No data	Recommended	Recommended
Elvitegravir/cobicistat	Recommended	No data	Recommended	Not recommended	No data	No data	No data
HIV NtRTI							
Tenofovir	Recommended	Recommended	Recommended	Recommended	Recommended	Recommended	Recommended
CCR5 inhibitor							
Maraviroc	Recommended	Reduce maraviroc to 150 mg bid	Reduce maraviroc to 150 mg bid	No data	No data	No data	No data
IS drugs							
Calcineurin inhibitors							
Cyclosporin	No data	↓Cyclosporin dose	↓↓Cyclosporin dose	Not recommended	No data	No data	No dose adjustment
Tacrolimus (FK)	Recommended	↓FK dose	↓↓FK dose	No dose adjustmet Close monitoring	No data	No data	No dose adjustment
mTOR inhibitors							
Sirolimus	Close monitoring	↓↓Sirolimus dose	↓↓Sirolimus dose	↓↓Sirolimus dose	No data	No data	Recommended
Prednisone	No data	No dose adjustmet Close monitoring	No data	No data	No data	No data	Recommended
Anti-HCV therapies							
Pegylated interferon	Recommended	Recommended	Recommended	Recommended	Recommended	No data	Recommended
Ribavirin		Recommended	Increasing ribavirin concentration. Close monitoring	Recommended	Recommended	No data	Recommended

Modified from Karageorgopoulos *et al.* [47]; Kiser *et al.* [46] and Antiretroviral Treatment Options for Patients on DAAs. Summary available at <<http://www.hcvdruginfo.ca>> [accessed October 1, 2014] [46]. HIV, human immunodeficiency virus; HCV, hepatitis C virus; PIs, protease inhibitors; NNRTIs, non-nucleoside reverse-transcriptase inhibitors; InSTIs, integrase strand transfer inhibitors; ARV, antiretroviral; tid, three times a day; bid, twice daily; qd, once daily; AKR, aldoketoreductase; UGT, uridine glucuronyl transferase; r, ritonavir; IS, immunosuppressant.

Review

2. If PIs are necessary to control HIV infection, strict and frequent monitoring of immunosuppressive drug levels is required to minimize the risk of rejection and toxicity (**AII**).

Challenges

1. Based on the high incidence of rejection observed in HCV/HIV-coinfected liver transplant recipients, treatment of HCV infection with IFN-based strategies after transplant can potentially exacerbate the already high incidence of rejection. Therefore, the availability of IFN-free regimens will facilitate post-transplant outcomes.

HIV-infection after liver transplantation. Antiretroviral therapy (J.M. Miro)

HIV infection is very well controlled with ART after LT. Several cohort studies have shown that most patients remained virologically suppressed with good immunological control and with a low rate of opportunistic infections [8–10].

Antiretroviral drug regimens in LT recipients should follow general recommendations for ART, namely combining 2 nucleoside reverse transcriptase inhibitors (NRTI, tenofovir and emtricitabine or abacavir and lamivudine) plus a non-NRTI (efavirenz), or a ritonavir-boosted PI (atazanavir, darunavir), or an integrase inhibitor (raltegravir, elvitegravir/cobicistat, dolutegravir) [40,41]. Abacavir must only be given if both donor and recipient are HLA-B57 * 01–negative in order to avoid a life-threatening hypersensitivity reaction [40,41]. Tenofovir should be used with caution, and its dosage must be adjusted to the glomerular filtration rate in LT recipients with renal failure [40,41]. The combination of elvitegravir/cobicistat/tenofovir/emtricitabine is not recommended in patients with mild or moderate renal insufficiency (estimated CrCl <70 ml/min) and is rarely used in transplant settings.

Pharmacokinetic/pharmacodynamic (PK/PD) interactions between ART, immunosuppressive drugs, and anti-HCV drugs are frequent [42–45]. As ritonavir and cobicistat are strong CYP450 inhibitors that can increase many times the AUC of calcineurin inhibitors (cyclosporin and tacrolimus), Efavirenz, a modest CYP450 inducer, has been the preferred antiretroviral for many years [8–10]. However, the recent introduction of raltegravir, the first HIV integrase inhibitor, prevents these PK/PD interactions because it is not a substrate of CYP450 and does not influence the activity of this enzyme complex [38]. Therefore, the combination of 2 NRTIs plus raltegravir is currently the antiretroviral regimen of choice for HIV-infected LT recipients. Dolutegravir has a similar PK safety profile as raltegravir, although there is no experience in transplantation.

Other major PK/PD interactions have been recognized with the HCV NS3/4A PIs boceprevir and telaprevir [42,44,45]. These drugs had significant and non-predictable interactions with antiretrovirals, particularly non-NRTIs and HIV PIs, thus precluding many combinations. In addition, telaprevir and boceprevir also increased levels of calcineurin inhibitors by a magnitude similar to that seen with HIV ritonavir-boosted PIs. Therefore, if boceprevir or telaprevir are used, the ideal concomitant antiretroviral regimen is the combination of 2 NRTIs plus raltegravir. Simeprevir is the only second-generation DAA that interacts with specific antiretroviral and immunosuppressive drugs (see above); sofosbuvir interacts neither with antiretrovirals nor with

immunosuppressive drugs. Table 5 summarizes the interactions between ART, DAA, and immunosuppressive drugs [46,47]. Sofosbuvir and the combination of sofosbuvir/ledipasvir is not recommended in patients with estimated CrCl <30 ml/min.

Therapeutic drug monitoring is indicated in all HCV/HIV-infected liver recipients. Finally, given the speed with which new antiretroviral and anti-HCV drugs are being introduced in clinical practice and the consequent report of new interactions, physicians should consult updated databases on drug interactions in HIV and HCV infection [48,49].

Recommendations

1. The best antiretroviral regimen in HCV/HIV-coinfected liver recipients is the combination of two NRTIs plus raltegravir in order to avoid PK interactions with immunosuppressive drugs and HCV PIs (**BII**).

Challenges

1. To determine the best NRTI for LT recipients: tenofovir or abacavir.
2. To ascertain whether the hypersensitivity reaction to abacavir can be transmitted by HLA-B57 * 01–positive donors.
3. To evaluate the role of new antiretroviral agents (tenofovir alafenamide fumarate, dolutegravir, rilpivirine, etravirine).

Hepatocellular carcinoma (HCC) (J.M. Miro, Dr. A. Rimola)

HCC is a growing indication for LT in HIV-infected patients [50–53]. Patients should fulfill the Milan criteria (1 HCC of ≤5 cm, or ≥3 nodules of ≤3 cm, with no vascular invasion or extrahepatic spread), which led to a 4-year survival of 75% in non-HIV-infected LT recipients, with recurrence rates of <15% [54]. It remains unclear whether these criteria can be expanded in HIV-infected patients.

In 2011, Vibert *et al.* [50] reported the results of a case-control study of patients with HCC and listed for LT (21 HIV-infected patients and 65 non-HIV-infected controls). HIV-infected patients underwent LT less frequently than non-HIV-infected controls (77% vs. 90%) and had a higher waiting list dropout rate owing to tumor progression (23% vs. 10%, despite a similar initial tumor stage in both groups), lower survival from listing (81% vs. 91% at 1 year; and 55% vs. 82% at 3 years), and higher post-LT tumor recurrence (30% vs. 15%). Conversely, Italian researchers [51] analyzed data from 30 HIV-infected patients and 125 non-HIV-infected controls who underwent LT for HCC and found no significant differences in HCC recurrence (7% vs. 14%, respectively) or survival rates (77% vs. 86% at 1 year after LT and 65% vs. 70% at 3 years). In a preliminary analysis from Spain [55], a similar incidence of HCC recurrence was observed in coinfecting and mono-infected patients: 16% vs. 14%, respectively.

Recommendations

1. HCV/HIV-coinfected patients with HCC who fulfill the Milan criteria should be considered for LT (**AII**).
2. HIV-infected patients with HCC should be considered for MELD exceptions according to local transplant policy (**CIII**).

Challenges

1. Studies with larger samples and longer follow-up are needed to determine the post-LT HCC recurrence rate and the overall prognosis of these patients.

Liver retransplantation (reLT) (*J.M. Miro, Dr. A. Rimola*)

Experience with reLT in the HIV-infected population is scarce. In 2012, Gastaka *et al.* [56] analyzed the outcome of 14 consecutive HIV-infected LT recipients who underwent reLT in Spain (2002–2011) and compared their progress with that of 157 matched non-HIV-infected reLT patients. All but 1 HIV-infected LT recipients had HCV coinfection. reLT for HCV recurrence was much less frequently indicated in coinfecting patients than in monoinfected recipients (7% vs. 37%; $p = 0.036$). Three-year survival after reLT in HIV-infected patients was lower than in non-HIV-infected patients (42% vs. 64%; $p = 0.160$). Survival was only found to be good in HIV-infected patients with undetectable HCV RNA at reLT (80% vs. 72% in non-HIV-infected recipients). Conversely, 3-year survival in HIV-infected recipients with positive HCV RNA at reLT was very poor (22% vs. 65%). Similar results were obtained in a study with HIV-infected patients undergoing reLT and included in 8 national cohorts [57]. In this multinational report, active HCV RNA replication at the time of reLT was the only variable independently associated with death. In both studies, the main cause of death was recurrence of HCV.

Recommendations

1. Given the poor outcomes recorded, HCV/HIV-coinfecting patients with active HCV infection should not undergo reLT, whether the indication for reLT is related to HCV recurrence or not (DII).

Challenges

1. The introduction of new anti-HCV DAAs can reverse this negative recommendation in the near future.

Conclusions (*P. Stock*)

LT is problematic in HCV/HIV-coinfecting recipients, and results for recurrence of HCV have been discouraging. Significant improvements in recipient and donor selection and better management of drug interactions have improved the poor patient and graft survival seen in the large European and American series. Nonetheless, interferon-free regimens with DAAs are urgently needed in HCV/HIV-coinfecting patients to improve patient and graft results to levels comparable to those of the HCV-monoinfected LT recipients. Finally, the recommendations proposed in this review will evolve with the development of more effective and safer DAAs.

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Conflict of interest

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