

## Addiction specialist's role in liver transplantation procedures for alcoholic liver disease

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### Abstract

Although liver transplantation (LT) is performed increasingly for patients with end-stage alcoholic liver disease (ALD), the topic remains controversial. Traditionally, the role of an addiction specialist focused on the screening and identification of patients with a high risk on relapse

in heavy alcohol use. These patients were in many cases subsequently excluded from a further LT procedure. Recently, awareness is growing that not only screening of patients but also offering treatment, helping patients regain and maintain abstinence is essential, opening up a broader role for the addiction specialist (team) within the whole of the transplant procedure. Within this context, high-risk assessment is proposed to be an indication of increasing addiction treatment intensity, instead of being an exclusion criterion. In this review we present an overview regarding the state of the art on alcohol relapse assessment and treatment in patients with alcohol use disorders, both with and without ALD. Screening, treatment and monitoring is suggested as central roles for the addiction specialist (team) integrated within transplant centers.

**Key words:** Liver transplantation; Alcohol use disorder; Alcoholic liver disease; Relapse; Addiction specialist

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**Core tip:** Liver transplantation is performed increasingly for patients with end-stage alcoholic liver disease. Assessment of a patients risk on relapse in alcohol use after transplantation and helping patients to achieve and maintain abstinence are crucial within this process. The addiction specialist's input is essential and needs to be integrated within the transplantation team. Ideally a multidisciplinary approach is offered to the patients, including addiction psychiatrist, behavioral therapist and social worker following up the patient before and after transplantation.

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## INTRODUCTION

Alcohol use disorders (AUDs) are highly prevalent and devastating disorders. Within the general population about one in five people meet the criteria for an AUD in their lifetime<sup>[1]</sup>. The net effect of alcohol consumption on health is detrimental, with an estimated 3.8% of all global deaths and 4.6% of global disability-adjusted life-years attributable to alcohol<sup>[2]</sup>. A large portion of these effects is due to negative consequences of (excessive) alcohol use on the liver. Indeed, there exist a direct, exponential, relationship between the amount of alcohol consumed on a population level and the prevalence of chronic, end-stage liver disease (e.g., cirrhosis)<sup>[3,4]</sup>.

Liver transplantation (LT) is increasingly used as a life-saving intervention for patients with end stage alcoholic liver disease (ALD). Currently between 30% to 50% of all LTs in Europe and about 17% in the United States, are performed in the context of ALD<sup>[5-7]</sup>. Importantly, post-operatively between 30% and 50% of the patients relapse in any alcohol use and 20% to 25% of them relapse in heavy alcohol use<sup>[8]</sup>. Relapse in long during and excessive alcohol use after LT increases the risk on allograft damage and mortality<sup>[9,10]</sup>. Thus both from the point of view of patient safety and within the context of chronic low allograft availability, efforts are justified towards using valid screening procedures to identify the most suitable candidates and offering treatment to help patients to (re) gain and maintain sobriety<sup>[7]</sup>. Ideally, both therapeutic aspects, *i.e.*, screening for relapse risk and offering personalized addiction treatment, should be integrated in a patient's treatment plan. However, within many current (pre) transplantation procedures, the focus of attention remains on screening procedures, while much less effort is invested to engage patients in continuous addiction treatment<sup>[11]</sup>.

In this review we provide first an overview of the current state of the art on AUDs as a whole and compare it to the specific situation of patients with ALD as candidates for LT. Pertinent questions are whether ALD-LT patients are different from general AUD patients and whether there are differences in alcohol use outcome and treatment modalities between both groups? Finally, we focus on the role of addiction specialist in screening and treatment of patients with ALD within the context of LT procedures.

## TWO TYPES OF AUD PATIENTS

The natural course of AUD varies vastly; from very positive outcomes reported in general population samples meeting alcohol abuse or dependence criteria to very negative outcomes in treatment seeking patients in criminal justice settings<sup>[12]</sup>. Overall, most affected individuals recover naturally without any formal type of treatment, and approximately 70% of individuals go into remission within three years<sup>[13,14]</sup>. In accordance,

longitudinal studies in general population samples show low AUD relapse rates, *i.e.*, 5.6%, 9.1% and 12.0% at respectively five, ten and twenty years of follow-up<sup>[15]</sup>. In contrast, people seeking treatment for AUD's represent a much smaller, but more vulnerable group characterized by a lower resilience, higher risk for relapse, more problems in different life domains, and overall a more negative course of the disorder. In this group AUDs develop into a chronic relapsing disorder and relapse in heavy or dependent drinking occurs in over 50% of patients. This latter group of patients, *i.e.*, high psychosocial co-morbidity, typically presents in addiction treatment programs, while the former group, *i.e.*, low psychosocial co-morbidity, is more prevalent in gastroenterology departments due to the somatic alcohol related consequences<sup>[16,17]</sup>.

Regarding LT, current enrollment procedures appear to make for a consistently more favorable outcome in LT patients in comparison to alcohol treatment seeking populations, with five and ten year follow up show relapse rates (any alcohol use) of respectively 20% and 30% in LT patients, and more recent studies even lower<sup>[18]</sup>. In addition, Weinrieb *et al.*<sup>[19]</sup> suggest that ALD-LT candidates differ substantially from AUD patients within standard addiction programs. ALD-LT patients hold their medical health and transplant management to be a priority over addiction treatment, perceiving less of a need for addiction counseling. Indeed, many do not look upon themselves as being addicted and do not identify with the prototypical "chronic relapsing alcoholic" image. As a consequence, demands for addiction counseling and regular alcohol monitoring are frequently experienced as offensive by these patients, often leading to defensive reactions. However, differences between these two types of patients may be the result of a selection bias, as patients with more complicated, behavioral and psychiatric symptom cluster are often screened as "high at risk" for relapse and in current procedures not included in a subsequent LT trajectory.

## PREDICTING RELAPSE IN AUDS

Relapse prediction provides the opportunity not only to identify specific patients groups with poorer outcomes, but also - and relevant to any clinician, helps identify areas to target in treatment<sup>[20]</sup>. Research on this topic is currently highly topical within the whole of the addiction field.

### *Predictors of relapse alcohol in non-ALD alcohol patients*

Most studies looked into demographic and clinical variables. Overall, dependence severity, psychopathology ratings, alcohol-related self-efficacy, motivation, cognitive impairments, and treatment goal, are all associated with relapse risk<sup>[15,20-22]</sup>. In addition, the duration of abstinence in itself is a predictor of future relapse. Indeed, for many afflicted individuals stable

**Table 1** Assessment alcoholic liver disease patients for liver transplantation

Dimension	Variable
Severity alcohol use (disorder)	Amount of alcohol use and baseline alcohol use (TLFB) AUD diagnosis severe (DSM5) Family-history AUD Age-at-onset AUD Duration
Abstinence	Duration pre-LT abstinence
Treatment indicators	Earlier treatments for AUD (Longstanding) periods of abstinence Compliance medical treatment
Co-morbidity	Psychiatric Other substance (mis) use (Illicit drugs, tobacco)
Cognitive	Memory Executive
Social	Partner and family Living in supportive, clean, circumstances
Personal	Employment Motivation Self-efficacy

TLFB: Timeline follow-back; DSM5: Diagnostic and Statistical Manual, 5<sup>th</sup> ed (APA, 2013); AUD: Alcohol use disorders.

remission of AUD is to be expected only after about five years of abstinence<sup>[23]</sup>. Taken together, although many clinical variables have been identified, not one single one stands out as decisive. Results show for each of them a low to moderate predictive power and are not always consistent. This might reflect the fact that almost none of these studies take the heterogeneity of AUD patients into consideration. Furthermore, clinical variables may not be specific enough and might not relate directly with the underlying pathogenic processes. Recently, focus of research is shifting and consensus is growing that neurocognitive measures might help identifying patients with a high risk for relapse<sup>[24,25]</sup>. In addition, functional brain imaging markers, cue or stress-reactivity paradigms, are starting to reveal not only the underlying vulnerability mechanisms, but allow predicting relapse in alcohol addiction<sup>[26-28]</sup>. It can be argued that imaging biomarkers, for practical and financial reasons, are not of use in a standard treatment program. In contrast, a small but increasing number of treatment centers start to adopt the use of neurocognitive measures for better profiling their patients with respect to outcome prediction<sup>[29,30]</sup>.

Taken together, research into relapse prediction is still ongoing, and up to now has not delivered a set of easily measured variables that can, reliably, predict relapse on an individual's basis. Overall, clinician's judgment, helped by some clinical and neurocognitive measures, remains the core of the assessment process.

### Predictors of relapse after LT

Although both the number of studies and the sample sizes are (much) smaller than in AUD studies, research into relapse prediction in LT patients identified the same set of clinical variables that are associated with relapse

in AUD patients<sup>[31]</sup> (Table 1). Typical for the LT context is the importance that has been given in most screening-procedures to pre LT abstinence period as a predictor for relapse. This, so called 6-mo abstinence rule has recently come under discussion. Indeed, although abstinence duration is one of the clinical predicting, albeit moderately powerful, relapse-predicting factors, the specific six-month minimum period is not supported by the data. In addition, many patients with end stage ALD simply do not have that time and many will die in the process of bridging these 6-mo. Unquestionably, a substantial period of abstinence is warranted allowing for a stable abstinence and recuperation of the liver functionality (EASL Guideline, 2012). Given that recuperation of liver functioning is not expected after more than 3 mo of abstinence, prolonging this period likely results in a higher patient mortality risk, which is not compensated by a gain in power when assessing relapse risk after ALD. Taken together, accepting abstinence periods of less than 6 mo within LT screening procedures may include a small increase of risk on post-LT relapse in alcohol use. However, this must be balanced with the other clinical risk factors. Shorter abstinence periods cannot be used as a single criterion for non-inclusion. Instead this should be considered an indication to intensify addiction treatment, in order to reduce relapse risk.

Concluding, when evaluating an ALD patient in view of LT, it is important to acknowledge that currently no single clinical variable can be used when assessing the relapse risk. This implies that within the context of the LT screening procedure the addiction specialists (or team), needs to rely on a comprehensive assessment, evaluating a set of different, *i.e.*, clinical, demographic, and social, variables. Recently, some groups have suggested scoring systems<sup>[31-33]</sup>, incorporating a fixed set of variables and related scoring. Although of interest, a systematic, multi center evaluation into the validity with respect to relapse prediction of these scoring systems is currently missing.

## TREATMENT OPTIONS

### AUDs

One of the most important problems regarding AUDs is the extreme treatment gap. Indeed, within Western countries only about 10% of the potential patients receive any form of alcohol treatment<sup>[34]</sup>. Decreasing this gap would be the sole most important intervention from the point of view of population health. Indeed, when a patient can be reached, a variety of (moderate) effective treatments can be offered.

**Psychosocial interventions:** Many types of, mostly behavioral, therapies have been developed and tested with well-performed studies<sup>[35]</sup>. Overall these studies show that these treatments are effective in reducing alcohol use, although, comparable with pharmacological treatments the effect sizes are moderate. Of importance, short interventions are very effective for the

large majority of individuals with a heavy or hazardous, but not dependent drinking-pattern. Next, in addition to (cognitive) behavioral therapies, more complex, multi-target interventions (e.g., Community Reinforcement Approach) have been developed for patients with a high problem severity and earlier treatment failure.

Of interest, treatments for AUD are increasingly offered in online formats<sup>[36]</sup>. Specifically, complex attentional- and approach bias modification strategies have proven significant results both as stand alone and on top of treatment as usual procedures. Remarkable, these interventions not only improve alcohol outcome, but have recently also shown to change underlying neurobiological cue-reactivity pathways<sup>[37,38]</sup>. The advantages of online treatment modalities are multiple; low barrier for patients with limited mobility or time availability, anonymity, and lower cost especially when (quasi) fully automated.

**Pharmacological interventions:** A small number of medications are registered for the treatment of AUDs (disulfiram, naltrexone, acamprosate, nalmefene) while some other medications have shown promise mainly in short-term studies (e.g., topiramate, GHB, baclofen, and gabapentin)<sup>[12]</sup>. While most of these treatments take abstinence as main treatment goal, recently interest is growing for a reduction of alcohol use as a valid treatment goal<sup>[39,40]</sup>. Overall, effect sizes of pharmacological treatments are moderate, *i.e.*, on the same level as antidepressants for depression, and there is no treatment that seems to fit all patients. In search for a more personalized approach in patient-treatment matching, pharmacogenetics seems promising<sup>[12,41]</sup>.

### Liver transplant patients

Compared to the number of studies on screening and relapse prediction, a remarkable limited number explore the effect of addiction treatment interventions in this population.

**Psychosocial interventions:** Some studies showed that offering treatment in the pre-LT (waiting list) period was associated with reduce the number of patients relapsing in (any) alcohol use during the waiting period and after LT<sup>[7,19,42,43]</sup>. Of importance, successful treatment effect was reported in an other study, only in the subsample that engaged in treatment both before and after LT, underscoring the importance of post-LT treatment<sup>[44]</sup>.

Finally, Addolorato *et al.*<sup>[11]</sup> found that AUD treatment offered by addiction specialists integrated within the transplant team had superior results, *i.e.*, less alcohol recidivism and lower mortality rates, than treatment offered by an addiction specialist outside the transplant team.

**Pharmacological interventions:** When considering pharmacological interventions for AUD treatment in ALD patients, one needs to take the severe liver

dysfunction into consideration. Currently, only a very limited number of studies explored the feasibility, safety and effectiveness relapse-prevention medication in these patients<sup>[7]</sup>. As of consequence, the use of alcohol medication pre LT or in patients with liver cirrhosis is extremely limited. Recently baclofen, which is not metabolized in the liver, showed both safety in use and positive effect (continuous days abstinence, craving) in patients with end-stage ALD<sup>[45]</sup>. Currently, no studies have been done using pharmacotherapy for alcohol relapse in post-LT patients. Based upon their pharmacological profile, specifically those medications that are not metabolized in the liver can be considered as potential candidates (e.g., acamprosate, baclofen, topiramate).

## MONITORING

During both the pre- and the post LT period, a close monitoring of alcohol use is needed, as an integrated part of the psychosocial follow-up. In addition to self-report and collateral information, the importance of biomarkers is increasingly recognized (see for review Vonghia *et al.*<sup>[46]</sup>). Traditional alcohol biomarkers such as gamma-glutamyltransferase are not recommended in ALD patients because they will be elevated as a result of the liver damage itself. They could provide some information in post-transplant patients, however, as also within non-ALD alcohol patients, they have low sensitivity (30%-60%) and specificity (60%-95%). Other often-used biomarkers in blood (MCV, ALT, and AST) also have low sensitivity (< 50%) and specificity (60% to 95%), and are also confounded by liver damage itself<sup>[47,48]</sup>.

Carbohydrate-deficient transferrin (CDT) is more specific for heavy (from 5 to 6 standard drinks per day for several days) alcohol use and will be elevated for about two weeks after the drinking bout. However, in pre-transplant ALD patients, CDT lacks specificity. However, as a post-transplant measure it has value as an indicator of heavy alcohol use. In comparison with other biomarkers, CDT would be a biomarker that is less affected by false positive results due to liver disease<sup>[49,50]</sup>.

Recently, several recent studies suggest a promising role for using ethylglucuronide in hair samples (hEtG) as a biomarker for alcohol use detection. Indeed, traditional biomarkers for alcohol use in blood and urine allow only limited detection windows (hours to days). In contrast, hair serves as a long-term storage of EtG, covering much larger time periods (months). In addition, collecting hair samples is non-invasive and samples can be saved easily and for longer periods. Increasingly, validated cut-off scores are available, that allow distinguishing between chronic, excessive, moderate alcohol use and abstinence (Society of Hair Testing; [www.soht.org](http://www.soht.org))<sup>[51-53]</sup>. Specifically within the context of monitoring LT patients, the use of hEtG has proved to be a highly specific and practically implementable biomarker that is superior to traditional



markers<sup>[50,54-56]</sup>.

## ETHICAL CONCERNS

End stage liver disease (ESLD) has a high mortality ratio and often, liver transplantation is the only, life-saving, therapy. For many years, given on the one hand the imbalance between organ availability and demand, and on the other hand the continuum "moral" attitude (*i.e.*, "not a disease but a weakness of will") towards individuals with alcohol problems, controversy existed and sometimes remains, whether ALD was an indication for LT. This controversy contrasts with the accumulating data showing that: (1) similar and even better survival rates than LT for ESLD of other etiology (*e.g.*, hepatitis C); (2) low alcohol relapse rates compared with non-ALD alcohol dependent patients; and (3) limited alcohol use after LT is not associated with severe negative consequences. One of the consequences of this controversy is that when evaluating a patient, procedures and protocols are mainly focused on "screening out" those at risk for relapse in alcohol use, instead of focusing on developing tools and methods to help patients gain and maintain sobriety<sup>[7]</sup>. In addition, alcohol outcome goals are used at their most severe, *i.e.*, complete abstinence and the 6-mo rule. These goals are more severe than in standard addiction treatment programs where the focus is increasingly put on shared decision-making concerning treatment goals, reduction of use to safe levels, and enhancing continuous motivation. However, the research data do not support the need for this degree of severity in treatment goals in LT patients. Of interest, this "selective" focus on alcohol-abstinence is all the more remarkable when one notices the much lesser attention on, potential also harmful, health-behaviors, *e.g.*, abuse or intoxication acetaminophen, intravenous drug use with hepatitis and continuing cigarette smoking. Several reasons may be at play maintaining this alcohol-controversy. First, financing bodies might keep up with these high barriers, in the hope of containing the number of these, indeed, expensive treatments. Second, concerns might rise that lowering the threshold would be poorly perceived by the general public, hence risking decrease in willingness to donate organs<sup>[57,58]</sup>. Finally, continuing moral and stigmatizing thinking about addictive behaviors might still play an important role both within the general public as within the medical profession, resulting in poor professional and patient-lobbying towards changing the procedures and financing contingencies.

Taken together, individuals with alcohol remain frequently negatively regarded upon. Even in highly specialized medical settings such as hepatology and transplant centers, the risk on stigmatizing attitudes and consequent actions is not illusionary. An important advocacy-role for the addiction specialists (team) is to constantly be alert for and act on signs of possible discriminatory behaviors and procedures, so that ALD patients receive the same quality of care and respectful

context that every patient is entitled to.

## ROLE OF THE ADDICTION SPECIALIST (TEAM)

Addictions specialists (team) have important roles during the whole process of the ALD-LT procedure (Table 2). Given the complexity and diversity of the core services to be provided, as described *infra*, ideally this work is taken on by a multidisciplinary addiction specialist team. Although economic barriers and possibilities may differ widely between countries, team composition should at least contain a psychiatrist, psychologist-psychotherapist, and social worker, all trained in addiction work. Their services need to be offered as an integrated part of the transplant program<sup>[11]</sup>.

### Screening

The addiction specialist role is a thorough screening, leading to an assessment and assignment to risk categories. This is a comprehensive assessment including interviews with patients, family and relevant others. Given that none of the known risk factors is conclusive, the final decision is by definition based upon a careful balancing of all elements. Different dimensions need to be assessed (Table 1), *i.e.*, individual (motivation, treatment compliance), co-morbidities (psychiatric and other substances), cognitive, AUD severity and treatment history, and social support systems. Categorizing patients will help to allocate them to better matched treatment and follow-up procedures. Broadly two groups can be identified. First, patients with low psychosocial co-morbidity. Individuals with this profile, tend to have a positive course of their AUD, low-relapse risks, and a good change on stable abstinence and/or reduction of drinking to save levels. They can be allocated to less intensive addiction treatment, *e.g.*, short interventions, aimed at enhancing motivation, counseling, self-help and monitoring. A second category, *i.e.*, "high risk", is those people that accumulate risk factors for a negative, chronic relapsing nature of their AUD. This group is within the current LT procedures often excluded. A much more intensive addiction treatment is needed. Whether this should be mandatory for all patients is a matter for discussion, but mandatory treatment needs to be considered with poorly compliant patients.

Both within the screening-assessment procedures as to the monitoring during waiting list periods, one of the most challenging questions remains how much information is shared between the addiction team and the transplant team. Indeed, a high level of confidentiality is needed in the relation between the addiction specialist and the patients, facilitating an open sharing, necessary for treatment and growth of motivation. On the other hand, when relapse risks are high some information needs to be communicated allowing a balanced discussion between transplant and addiction team on very difficult questions of candidacy

**Table 2** Role of the addiction specialist (team) in the screening, treatment and monitoring liver transplantation candidates

Screening	Category	Waiting list period	LT	Post-LT physical rehabilitation	Long term follow-up (> yr)
Following items need to be surveyed to decide upon which category patient will enter treatment trajet:	"Low risk"	Who: Addiction treatment team integrated within transplant/hepatology department What: Motivation enhancement and relapse prevention strategies		Psychosocial support patient and family	"Low intensity follow-up" (1) Who: Addiction treatment team integrated within transplant/hepatology department; or, addiction counselor in the living area of patient (2) What: Motivation enhancement Counseling Relapse prevention Anticraving medication: baclofen/acamprosate
	Monitoring alcohol, drug and use tobacco use "High risk"	Who: Addiction treatment team integrated within transplant/hepatology department What: Motivation enhancement and relapse prevention strategies		Psychosocial support patient and family	"High intensity follow-up" (1) Who: Comprehensive addiction treatment program/care provide/living area patient  (2) What: Comprehensive integrated treatment including different treatment options that can be put in function of specific patient needs: Complex behavioral interventions helping patients to control alcohol and comorbid substance (drug, nicotine) use and prevent relapse: CBT, CRA Diagnosis and psychosocial treatment interventions psychiatric co-morbidities Pharmacotherapy directed at craving control (baclofen, acamprosate, nalmefene) Availability of settings: assertive outreach, (semi) residential programs

CBT: Cognitive behavioral therapy; CRA: Community reinforcement approach.

for transplantation. As yet no clear-cut solution for this dilemma is at hand. However, it is of utmost importance that it is very transparent for the patient and family what is communicated and what the consequences can be.

### Treatment (coordination)

**Pre-LT:** Most patients during the waiting-list phase are physically very ill and often have cognitive impairments. Treatment at this phase should focus on the one hand on psychological support for patient and family, enhancing motivation for abstinence, and on the other hand permanent monitoring of alcohol use. In most settings, patients will have frequent contacts with the hepatology/transplant center, so the addiction specialists (team) of the center are best placed to engage in this follow-up.

**Post-LT:** The first phase after LT is usually a period of medical-somatic revalidation, in which for most patients alcohol use is no issue. Thus, a low-intensity addiction follow-up, with monitoring of alcohol use will be enough. Risks on relapse (and associated treatment non-compliance) will increase when physical recuperation allows the patient taking up a more active life style. At this point addiction treatment interventions need to intensify. Depending whether a patient lives close by or farther away from the transplant center, addiction

specialists (team) can or deliver treatment themselves, or function as coordinators, organizing a treatment program within the patient's region.

For patients classified as low-risk, usually a none-intensive standard alcohol treatment can be put in place; counseling aimed at motivation enhancement and coping skills relapse prevention and continued monitoring alcohol use. Self-help groups like AA can be helpful, though not many of these LT patients identify to this degree with the label "alcoholic", putting a barrier for engaging in self-help.

Patients classified as high risk will need a comprehensive and integrated treatment program allowing the (simultaneous) use of different treatment interventions, targeting the often multiple problem domains, *i.e.*, psychiatric, (other) substance use, cognitive, and social. If needed, assertive outreach and (semi) residential slots should be available. This type of comprehensive, specialized addiction treatment is often beyond the possibilities of the addiction specialists (team) within a transplant center. Thus, its role in this context is helping to organize and coordinate this program in close collaboration with an addiction-center and to ensure liaison with the transplant center.

### Monitoring

Throughout all the treatment process continued moni-

toring of alcohol use is warranted. Addiction specialists should carefully interpret data from self-report, collateral information biomarkers. Findings can be used as feedback for patients helping them to improve compliance and abstinence. It is still an open debate whether data from monitoring should be shared with members of the transplant team. Specifically during the waiting-list period, patients will be afraid that these will be used against them, so openness might be jeopardized. It might be wise to agree in the treatment plan that only addiction specialist are allowed to follow-up monitoring.

## CONCLUSION

From a broader addiction specialist point of view, ALD patients that are LT candidates do not differ much with the spectrum found in other AUD patients. Broadly two groups can be identified, *i.e.*, a group low at risk for a negative AUD course and a group with higher risk. Up to now, the latter group tends to be screened-out as candidates for LT. However, it remains an open (ethical) discussion whether a higher risk justifies exclusion of a life saving procedure or whether it indicates that higher intensity addiction treatment should be associated within the whole of the treatment trajectory.

Throughout all this process, there is an essential role for an addiction specialist's (team), both in delivering assessment and treatment interventions and as co-ordinators, liaison with specialized addiction care centers. The choice to implement a strong addiction specialists team within the hepatology/transplant center does obviously has major financial implications and in many countries funding this remains extremely challenging.

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