



**UNIVERSIDADE FEDERAL DA BAHIA  
FACULDADE DE MEDICINA DA BAHIA  
PROGRAMA DE PÓS-GRADUAÇÃO  
EM MEDICINA E SAÚDE**



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JESUS-NUNES, ANA PAULA

**VALIDAÇÃO DA ESCALA DE ADESÃO À TERAPIA IMUNOSSUPRESSORA  
(ITAS), EM PORTUGUÊS BRASILEIRO PARA RECEPTORES DE TRANSPLANTE  
HEPÁTICO**

**DISSERTAÇÃO DE MESTRADO**

Salvador  
2017



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Dissertação apresentada ao Programa de Pós-graduação em Medicina e Saúde, da Faculdade de Medicina da Bahia, Universidade Federal da Bahia, como requisito parcial para a obtenção do grau de Mestre em Medicina e Saúde.

Orientador: Prof<sup>o</sup>. Dr<sup>o</sup> Lucas de Castro Quarantini

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PARA RECEPTORES DE TRANSPLANTE HEPÁTICO**

Dissertação de autoria de Ana Paula de Jesus Nunes intitulada Validação da Escala de Adesão à Terapia Imunossupressora (ITAS), em português brasileiro para receptores de transplante hepático, apresentada a Universidade Federal da Bahia, como requisito parcial para a obtenção do título de Mestre em Medicina e Saúde.

Salvador, 09 de fevereiro de 2017

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“Que os vossos esforços desafiem as impossibilidades, lembrai-vos de que as grandes coisas do homem foram conquistadas do que parecia impossível. ”

(Charles Chaplin)

## LISTA DE FIGURAS E TABELAS

### Artigo de Revisão

Figure 1 - Flow chart: selection of studies.....	16
Table 1 - Identification of articles relating to the adherence and immunosuppressant levels.....	16

### Artigo Original

Table 1 - The final version of the ITAS scale in Brazilian Portuguese.....	38
Table 2 - Socio-demographic characteristics of liver transplant recipients who were assessed by using the Portuguese version of ITAS.....	39
Table 3 - Factor analysis of the ITAS, load values (Loading) for the first factor and sum of the squared factor loadings (Communalities).....	39
Table 4 - Polychoric correlation matrix of the ITAS.....	40
Figure 1 - Correlation plot. Opacity indicates frequency of overlaid points of the ITAS and BAASIS.....	40
Figure 2 - Area Under ROC curve. Red point indicates optimal cut-point value.....	41
Figure 3 - Scree plot of the ITAS.....	41

## SUMÁRIO

<b>RESUMO</b> .....	8
<b>ABSTRACT</b> .....	9
<b>1 INTRODUÇÃO</b> .....	10
<b>2 OBJETIVOS</b> .....	12
<b>3 RESULTADOS</b> .....	13
3.1 Artigo de revisão.....	13
3.2 Artigo Original.....	22
<b>4 CONCLUSÕES</b> .....	42
<b>5 CONSIDERAÇÕES FINAIS</b> .....	42
<b>6 PERSPECTIVAS DE ESTUDO</b> .....	42
<b>REFERÊNCIAS</b> .....	44
<b>ANEXOS</b> .....	45
A – Parecer do editor da revista <i>Annals of Hepatology</i> .....	45
B – Parecer de Aprovação do Comitê de Ética e Pesquisa.....	46
C – Termo de Consentimento Livre e Esclarecido.....	48
D - Questionário sócio-demográfico.....	49
E - <i>Immunosuppressant therapy adherence scale</i> (ITAS) original .....	51
F – Escala de Adesão a Terapia Imunossupressora (ITAS) em português....	52
G – Escala Basel para a Avaliação de Aderência a Medicamentos Imunossupressores (BAASIS) .....	53
H – Artigo publicado: <i>Brazilian manicure: a potential dangerous behavior</i> .....	54
I - Artigo publicado: <i>Risk-taking behavior and impulsivity among HCV-infected patients</i> .....	56



## LISTAS DE ABREVIATURAS E SIGLAS

ITAS	Immunosuppressant Therapy Adherence Scale
BAASIS	Basel Assessment of Adherence with Immunosuppressive Medications Scale
CAPES	Coordenação de Aperfeiçoamento de Pessoal de Nível Superior
HUPES	Complexo Hospitalar Universitário Professor Edgard Santos
MEDILINE	Medical Outcome Social Support Scale
PPgMS	Programa de Pós-Graduação em Medicina e Saúde
SD	Standard Deviation
UFBA	Universidade Federal da Bahia

## RESUMO

**Contexto:** Adesão aos medicamentos imunossupressores após o transplante de fígado é essencial para a manutenção do enxerto e evitar desfechos negativos, portanto, são necessárias medidas que avaliem de forma precisa a não-adesão.

**Objetivos:** Traduzir e validar a Escala de Adesão a Terapia Imunossupressora (ITAS) em português brasileiro para receptores de transplante hepático e verificar, através de revisão de literatura, a mensuração da adesão a partir dos níveis sanguíneos de imunossupressores.

**Métodos:** A revisão dos artigos em língua inglesa foi realizada através da base de dados Medline, entre 2006 e 2016 por dois autores independentes.

No estudo original, 139 participantes foram avaliados usando a versão em português da ITAS e da Baasis com objetivo de avaliar as propriedades psicométricas.

**Resultados:** Quatro estudos foram incluídos na revisão e todos foram heterogêneos quanto a análise da adesão. O coeficiente  $\alpha$  de Cronbach foi de 0,830. ITAS e BAASIS apresentaram correlação significativa, com o coeficiente  $\rho$  de Spearman = 0,300 ( $S = 309,580$ ;  $p < 0,001$ ). A área sob a curva de *Receiver Operating Characteristics* (ROC) foi de 0,638 (IC 95%: 0,557 - 0,715). Os resultados da análise fatorial indicaram que o fator "descuido" obteve carga mais alta, e o fator "sentir-se pior" foi o mais baixo, de acordo com a classificação. **Conclusões:** Mensurar adesão em transplantados de fígado através dos níveis sanguíneos é uma estratégia possível, porém há uma escassez de artigos na literatura. A versão em Português da ITAS possui propriedades psicométricas adequada para mensurar adesão medicamentosa imunossupressora, em transplante hepático.

**Palavras-chave:** Adesão. Terapia imunossupressora. Psicometria. Transplante hepático.

## ABSTRACT

**Background:** Adherence to immunosuppressive drugs after liver transplantation is essential for maintaining the graft and avoiding negative outcomes, therefore, measures that accurately assess non-compliance are necessary. **Objectives:** To translate and validate the Immunosuppressive Therapy Adhesion Scale (ITAS) in Brazilian Portuguese for hepatic transplant recipients and to verify, through a literature review, the measurement of adhesion from the immunosuppressive blood levels. **Methods:** The review of articles in English was conducted through the Medline database between 2006 and 2016 by two independent authors. In the original study, 139 participants were evaluated using the Portuguese version of ITAS and Baasis to evaluate the psychometric properties. **Results:** Four studies were included in the review and all were heterogeneous regarding the adhesion analysis. The Cronbach's  $\alpha$  coefficient was 0.830. ITAS and BAASIS showed a significant correlation with Spearman's  $\rho$  coefficient = 0.300 ( $S = 309,580$ ;  $p < 0.001$ ). The area under the Receiver Operating Characteristics (ROC) curve was 0.638 (95% CI: 0.557 - 0.715). The results of the factorial analysis indicated that the "neglect" factor had a higher load, and the "feel worse" factor was the lowest, according to the classification. **Conclusions:** Measuring adhesion in liver transplants through blood levels is a possible strategy, but there is a shortage of articles in the literature. The ITAS Portuguese version has adequate psychometric properties to measure immunosuppressive drug adherence in hepatic transplantation.

**Keywords:** Adherence. Immunosuppressive therapy. Psychometry. Liver transplantation.

## 1 INTRODUÇÃO

As hepatopatias representam um grave problema de saúde pública e são a oitava causa de morte no Brasil. O transplante de fígado é uma opção de tratamento para pacientes com insuficiência hepática, na maioria dos casos trata-se da única alternativa para sobrevivência. Quando submetido ao transplante, o uso contínuo da medicação imunossupressora é extremamente necessário para evitar a perda do enxerto e morte. No entanto, apesar dos pacientes serem instruídos pela equipe de saúde sobre as consequências indesejáveis, a não adesão ocorre em proporção significativa. Além disso, gera impactos financeiros para o sistema público de saúde.

No Brasil, já foram realizados 15.734 transplantes hepáticos, nos últimos dez anos <sup>(1)</sup>, colocando o país em segundo lugar em relação ao número de procedimentos realizados no mundo. As doenças hepáticas e mortes relacionadas sobrecarregam o sistema público e não há perspectivas de diminuição de casos por diversas etiologias.

Adesão ainda continua sendo um desafio por envolver variáveis complexas do comportamento humano; é definida pela Conferencia Consenso <sup>(2)</sup> como qualquer desvio ao tratamento medicamentoso capaz de influenciar no efeito pretendido pela droga. Para mensurar a adesão, existem métodos diretos (níveis sanguíneos e observação da adesão) e indiretos (contagem de comprimidos, monitoramento eletrônico, auto-relato, dentro outros). Os instrumentos de auto-relato podem facilitar a identificação dos pacientes que seguem corretamente ou não o regime medicamentoso, pela característica da fácil acessibilidade e baixo custo, favorecendo possibilidades de intervenção para evitar consequências negativas e risco a vida do transplantado.

No Brasil, existem algumas escalas que avaliam adesão medicamentosa de forma geral, no entanto, poucos são os instrumentos para a população transplantada. Adicionalmente, não se conhece uma escala específica em português brasileiro para pacientes transplantados de fígado. Portanto, faz-se necessário a adaptação de um instrumento para esta população.

A *Immunosuppressant Therapy Adherence Scale* (ITAS) foi desenvolvida por Chisholm e colaboradores em 2005. As respostas foram projetadas em percentagem, ao invés de sim ou não. Os níveis de opção de resposta são: 0% do tempo, 1-20% ',

21-50% e mais de 50%. Posteriormente, uma reavaliação psicométrica foi realizada e verificou-se que a ITAS é um instrumento válido para avaliar adesão. A escala possui características como baixo custo e pode ser respondida em poucos minutos, em relação a outras medidas de adesão.

Identificar pacientes não aderentes pode contribuir, primeiramente para uma melhor compreensão do fenômeno da baixa adesão terapêutica, além de favorecer a promoção de intervenções que possam contribuir para aperfeiçoar os cuidados em saúde, reduzindo taxas de mortalidade por rejeição de enxertos.

## **2 OBJETIVOS**

### **2.1 Geral**

Traduzir e validar a Escala de Adesão a Terapia Imunossupressora (ITAS) em português brasileiro para receptores de transplante hepático e verificar, através de revisão de literatura, a mensuração da adesão a partir dos níveis sanguíneos de imunossupressores.

### **2.2 Específico**

Revisar a literatura acerca da adesão medicamentosa e correlatos de níveis sanguíneos medicamentosos.

Testar as propriedades psicométricas do instrumento ITAS em transplantados de fígado;

Avaliar a confiabilidade da escala ITAS, verificando a consistência interna dos seus itens.

Avaliar a validade de critério e de constructo da versão em Português em uma amostra de pacientes transplantados de fígado.

## 5 RESULTADOS

### 5.1 Artigo de Revisão

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University Hospital, Universidade Federal da Bahia, UFBA, Salvador, BA, Brazil.

#### **Blood immunosuppressant levels and measure adherence in liver transplantation: literature review**

**Background and aim.** Nonadherence is deeply related with graft loss and patient survival. This study aimed conduct a review of the literature on the adherence in liver transplant using blood immunosuppressant levels. **Methods** We performed a retrospective review of the last ten years with PubMed and MEDLINE searches using the following search terms: *medication adherence or medication compliance or medication noncompliance or medication nonadherence or medication persistence and liver transplantation or hepatic transplantation*. **Results** Four studies were included in the review. There is no homogeneity in the categorization of accession-related data. **Conclusions.** The findings suggest that immunosuppressant serum levels are useful for measurement of adherence, without be, however, a gold standard for analysis.

**Keywords:** medication adherence, liver transplantation, immunosuppressant levels

## Introduction

Liver transplantation is the main treatment for patients with liver failure and adherence to medications is essential for graft survival [1]. Despite this, the study of adherence remains a challenge [2]. The Consensus Conference defined nonadherence (NA) as: "Deviation from the prescribed medication regimen sufficient to influence adversely the regimen's intended effect" [3]. NA to immunosuppressants affects about one-third of patients [4] and increases the likelihood of graft loss and death, resulting in higher financial costs for the health systems. [5]; [6].

There are many methods for measuring adherence to medications immunosuppressant, without, however, a consensus on the gold standard [7], [8, 9]. Examples of indirect methods are patient's clinical evaluation, self-reports, pill counts, and electronic medication monitors. The direct methods are based on the observation of the administration of therapy and measurement of blood levels of immunosuppressive [7].

NA has a significant relationship with graft loss and death [5], and influence immunosuppressive drug level variability [10]. Therefore, the main purpose of this study was to conduct a review of the literature on the adherence in liver transplant using blood immunosuppressant levels. Measurement of adherence through this direct method might help health professionals in intervention to prevent graft loss and other negative consequences.

## Methods

### 2.1. Search strategy and study selection

The electronic database PubMed and MEDLINE on November 2016 were searched of the literature between 2006-2016. The following string terms were used: medication compliance OR medication adherence OR medication persistence OR medication noncompliance OR medication nonadherence AND hepatic transplantation OR liver



transplantation. The language of the literature was restricted to English. Studies were identified and selected independently by two reviewers according to inclusion and exclusion criteria. Any disagreement of the study selection was resolved by discussion and a third author was requested for adjudication.

## 2.2 Eligibility criteria

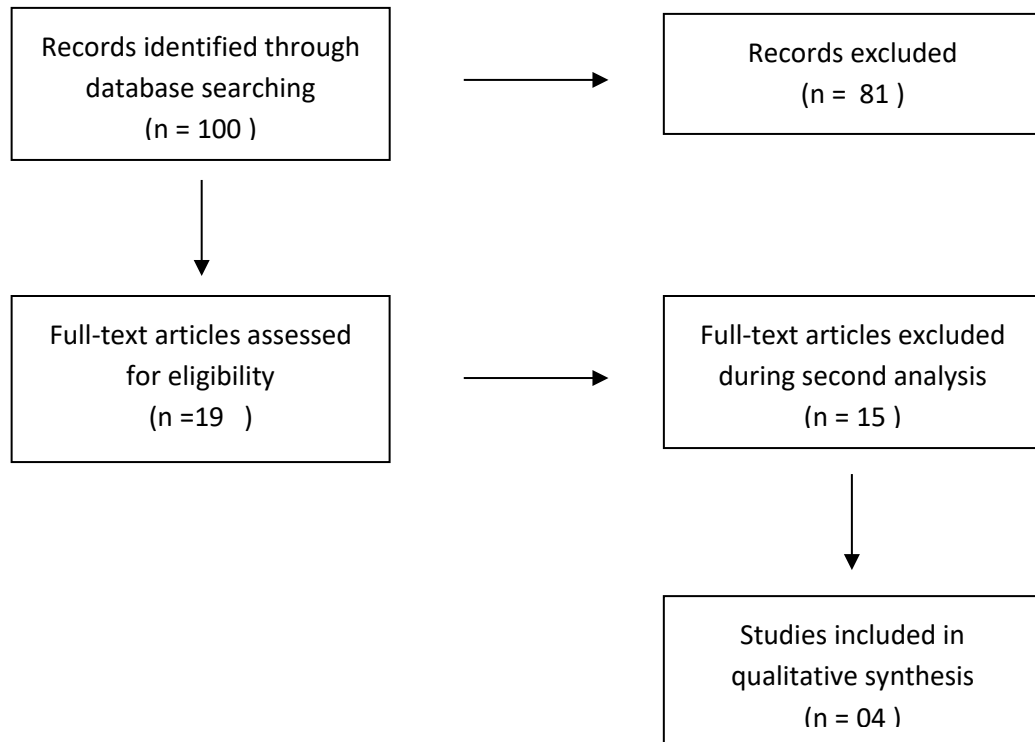
The studies were considered eligible if they completed the following inclusion criteria: originals studies, published in the last ten years, which measured adherence in adult liver transplantation using immunosuppressant serum levels. The exclusion criteria were as follows: pediatric liver transplantation and transplantation of other organs.

## 2.3 Data extraction

Relevant data was extracted using a form by two authors independently, containing: journal, study design, sample characteristics and outcome assessed.

## **Results**

A total of 100 articles were found in the database searches. After filtering the results, 19 studies were screened for primary analysis and four met the inclusion criteria for the review (Figure 1).



**Figure 1.** Flow chart detailing inclusion and exclusion selection criteria

The four studies are retrospective. Table 1 provides a summary of recent (published in 2006 or later) studies examining adherence and immunosuppressant levels in liver transplant recipients [11-14].

**Table 1.** Identification of articles relating to the adherence and immunosuppressant levels

Autor/ano	Journal	Design	Participants	Resultados
Serper, Patzer at al. 2015	Liver transplantation	Retrospective	105	Roughly one-third (32%) of patients were nonadherent according to tacrolimus levels ( $SD \geq 2.5 \mu\text{g/dL}$ ).
Christina Annunziato et al. 2014	Liver transplantation	Retrospective cohort	150	The Medication Level Variability Index (MLVI) was higher in patients who had rejection, with a cutoff point of 2.5.
Lieber and Volk (2013)	Digestive Diseases and Sciences	retrospective cohort	Sample A: 318/ Sample B: 359	Standard Deviation (SD) tacrolimus levels were measured between 6 and 18 months post-transplant. Non-adherence was found in 22% and 62% of subjects.

O'Carroll, McGregor et al. (2006)	Liver transplantation	Retrospective	302 living patients and 51 patients who had died.	The percentage of immunosuppressant levels found to be below the minimum level (5 µg/L and 60 µg/L for tacrolimus and ciclosporin, respectively)
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In the first study, Serper and colleagues [11] contacted 105 participants, recruited from two transplant centers. The measure of non-adherence was Standard Deviation (SD)  $SD \geq 2,5 \mu\text{g}/\text{dl}$ , calculated from at least 6 outpatient values. According to these results, one-third (32%) of patients using tacrolimus were nonadherent.

Christina et al. [12] carried out a retrospective cohort in 150 participants to evaluate the variability between individual measures of blood levels of tacrolimus, resulting the Medication Level Variability Index (MLVI). A threshold of 2.5 was used. The patients with biopsy-confirmed rejection had MLVI higher, concluding the MLVI is associated rejection likely related to nonadherence in adult liver transplant recipients.

A retrospective cohort study [13], was studied a immunosuppressant variability, considering SD tacrolimus levels were measured between 6 and 18 months post-transplant. The sample A (n= 318), the median SD of tacrolimus level was 2.1 (range 0.3–11.2) and 0.56 higher standard deviation associated with non-adherence. In sample B (n = 359) demonstrated that a increased drug variability was associated with a higher risk of graft failure. The results demonstrate that SD tacrolimus can be used to measure non-adherent behavior.

In a retrospective study [14], the minimum required was 5 µg/L for tacrolimus and 60 µg/L for cyclosporine. The data were collected in 302 living patients and 51 patients who had died and the result demonstrate that 15% showed low blood Immunosuppressant levels on more than a quarter of occasions. However, other methods were utilized for measure adherence: behavioral and self-report.

## Discussion

To our knowledge, this is the first review to analyze the blood immunosuppressant levels as a measure of adherence in liver transplant recipient patients. The variability in blood levels occasion negative consequences [15], therefore, it is important to identify patients at risk of poor medication adherence and it is necessary to adopt measures to assess adherence with the prescribed treatment. Based on the evidence reviewed in this article, there is no homogeneity in the categorization of accession-related data. The authors use different criteria, demonstrating that there is no consensus in the evaluation of immunosuppressive levels.

The below the minimum level can be explained by poor adherence to the immunosuppressant medication [14], characterizing an advantage of direct methods, because, often, patients tend to omit about adherence through self-reporting. A study indicated a lower prevalence nonadherence measured by self-report than that obtained with immunosuppressant levels and evidences the importance of strictly capturing nonadherence [11]. To date, there is no gold standard for detecting adherence to immunosuppressant [7-9].

This method has limitations, because it measures only medication intake during the last days of blood collection [16] and it is possible that the best results are reflected when they were taking their medications correctly [11].

The number of original studies about adherence and blood immunosuppressant levels conducted with liver transplant patients adult is still very limited. This study demonstrates that the literature on the subject is still scarce, although it is an extremely relevant phenomenon.

## **Conclusion**

Measure adherence to medications immunosuppressant through serum levels is a practical method, but with limitations, mostly because there is no consensus about the critical levels that suggest non-adherence. More studies on adherence and immunosuppressant serum levels are required to better understand the topic and intervene in nonadherence patient.

**Conflicts of interest**

The authors declare no conflicts of interest.

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## 5.2 Artigo Original

### **Artigo nº1**

#### **The portuguese version of the Immunosuppressant Therapy Adherence Scale (ITAS) among liver transplant recipient patients: translation and psychometric properties**

Annals of Hepatology (Manuscript number: ANNHEPATOL-D-16-00198).

Submetido à publicação com parecer do editor



## Annals of Hepatology

### The Portuguese Version of the Immunosuppressant Therapy Adherence Scale (ITAS) among Liver Transplant Recipient Patients: translation and psychometric properties.

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<b>Abstract:</b>	<p><b>ABSTRACT</b></p> <p>Introduction and aim Transplant recipients are chronically ill patients who rely on medical treatment throughout life to achieve positive results. Despite that, medication nonadherence after liver transplantation is extremely common. The self-report, one of several methods for measuring adherence, is easy to apply and low cost. Thus, this study aims to translate and validate the Immunosuppressant Therapy Adherence Instrument (ITAS) in Brazilian Portuguese for liver transplant recipients. Materials and methods A total of 139 liver transplant recipients were selected from a general hospital, who were assessed by using the Portuguese version of ITAS. The scale was translated based on the model proposed by Wild et al. and its psychometric properties were assessed. Results. The average Cronbach's <math>\alpha</math> coefficient was 0.830. ITAS and Basel Assessment of Adherence with Immunosuppressive Medications Scale (BAASIS) presented significant correlation, with a Spearman's <math>\rho</math> coefficient = 0.300 (<math>S = 309,580</math>; <math>p &lt; 0.001</math>). The area under the receiver operating characteristics (ROC) curve was 0.638 (95% CI: 0.557 - 0.715). Factor analysis results indicated that the carelessness factor model was the optimal model, and the factor "feeling worse" was the lowest. Conclusion. The Portuguese version of ITAS has adequate psychometric properties to measure adherence to immunosuppressant therapy.</p>
<b>Manuscript Classifications:</b>	17: LIVER TRANSPLANTATION

**The Portuguese Version of the Immunosuppressant Therapy Adherence Scale (ITAS) among Liver Transplant Recipient Patients: translation and psychometric properties.**

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## FOOTNOTE PAGE

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## ABBREVIATIONS

**ITAS** Immunosuppressant Therapy Adherence Instrument

**BAASIS** Basel Assessment of Adherence with Immunosuppressive Medications Scale

**AUROC** Area Under the Receiver Operating Characteristic

## SUPPORT

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## ABSTRACT

**Introduction and aim** Transplant recipients are chronically ill patients who rely on medical treatment throughout life to achieve positive results. Despite that, medication nonadherence after liver transplantation is extremely common. The self-report, one of several methods for measuring adherence, is easy to apply and low cost. Thus, this study aims to translate and validate the Immunosuppressant Therapy Adherence Instrument (ITAS) in Brazilian Portuguese for liver transplant recipients. **Materials and methods** A total of 139 liver transplant recipients were selected from a general hospital, who were assessed by using the Portuguese version of ITAS. The scale was translated based on the model proposed by Wild et al. and its psychometric properties were assessed. **Results.** The average Cronbach's  $\alpha$  coefficient was 0.830. ITAS and Basel Assessment of Adherence with Immunosuppressive Medications Scale (BAASIS) presented significant correlation, with a Spearman's  $\rho$  coefficient = 0.300 ( $S = 309,580$ ;  $p < 0.001$ ). The area under the receiver operating characteristics (ROC) curve was 0.638 (95% CI: 0.557 – 0.715). Factor analysis results indicated that the carelessness factor model was the optimal model, and the factor "feeling worse" was the lowest. **Conclusion.** The Portuguese version of ITAS has adequate psychometric properties to measure adherence to immunosuppressant therapy.

**Key words:** Adherence, Liver Transplantation, Immunosuppression, Psychometrics.

## INTRODUCTION

Adherence to a medical regimen is defined as the extent to which the patient's behavior coincides with the clinical prescriptions (1). Among the greatest challenges to the success of transplants is to ensure regular adherence of immunosuppressive drugs; it is essential for the proper functioning of the graft, and to avoid medical complications and negative outcomes (2, 3).

Immunosuppressant therapy nonadherence after liver transplantation is reported in 72.9% subjects who took less than 100% of the prescribed doses, tracked with electronic monitoring (4). The average rate for immunosuppressant nonadherence reached nearly 23 out of 100 patients (5). Although patients are usually informed about the importance of immunosuppression to the maintenance of the graft, to avoid graft rejection and graft loss, almost half of transplant recipients have some non-adherent behavior, such as not using the medication regularly, nor taking the correct dose, nor the required timescales (6, 7).

There are several methods for measuring adherence. One of them, the self-report can measure adherence easily and with very low cost, that being the most employed method in the clinical setting and research of medication nonadherence. (5, 8). However, there is plenty of evidence suggesting disagreement between self-reported and objective measures, such as serum levels (9).

Brazil is the second country in the world in terms of numbers of liver transplantations (10). Despite this fact there is no validated specific instrument to measure immunosuppressant therapy adherence for liver transplantations in Brazil. The aim of this study was to translate and assess the validation of the *Immunosuppressant Therapy Adherence Instrument* (ITAS) to Brazilian Portuguese for patients submitted to liver transplantations.

## MATERIALS AND METHODS

### Design, sample and setting

This psychometric study was conducted in a general hospital (*Hospital Português da Bahia*) and in a Teaching Hospital (*Universidade Federal da Bahia*). Patients were recruited between September 01, 2014 and June, 20, 2015. The assessments were applied to the participants who agreed to sign an informed consent form. The general sociodemographic survey was administered to all participants (n=139). Patients were included in the study if they met the following criteria: received a liver transplant, able to understand the Portuguese language, and 18 years or older at the time of the study. Patients unable to read (illiteracy) and those who were submitted to retransplantation were excluded from the sample.

### **Demographic Characteristics**

Age, gender, marital status, and time post-transplant were assessed.

### **Variables and measurement**

The ITAS is a self-report measure of immunosuppressant therapy adherence targeted to solid-organ transplant recipients, developed to be a reliable measure of adherence to immunosuppressant therapy in the three months prior to when research is conducted (11). The four items assess the behaviors of forgetfulness, carelessness, neglect and cessation due to feeling worse. Responses are designed for the patient to choose each behavior's frequency, in order to minimize patients' providing a positive adherence response of "yes". Response option levels are: 0 % of the time, 1-20 %, 21-50 % and greater than 50%. Raw scores can range from 0 (greater than 50% for all items), indicating very poor adherence, to 12 (0% for all items), indicating perfect adherence. Scores below 80% indicate poor adhesion. (11).

A psychometric re-evaluation of the ITAS was performed and two theoretically linked psychosocial constructs were selected to design the construct validity analysis:

social support and resilience. The results demonstrated the ITAS statistical relationships with these constructs and confirmation that the ITAS is a valid and reliable measure of IST adherence (12).

The Brazilian Portuguese version of the *Basel Assessment of Adherence with Immunosuppressive Medications Scale* (BAASIS), validated in kidney transplant patients was used as a standard for comparison. The BAASIS is a self-report instrument for measuring nonadherence (NA) in transplantations, that measures: taking adherence, drug holidays, timing adherence, and dose reduction in a four week period. Responses are given a six-point scale: never (0), once per month (1), every second week (2), every week (3), more than once per week (4), and every day (5) (13).

## **Translation**

The ITAS was translated as according to the method proposed by Wild et al (14). The original questionnaire was translated independently by two fluent English speakers. This process resulted in two preliminary versions. A consensus among both translators resulted in a reconciled version. Next, a reverse translation from Portuguese to English was conducted.

The final version (table 1) was applied to 30 liver transplant patients, who were asked about their understanding of the instrument.

## **Statistical analysis**

Items were coded as 0, 1, 2, and 3 according to the Likert scale responses of “greater than 50%”, “21–50%”, “1–20%”, and “0%”, respectively (11). Since ITAS and BAASIS present opposite punctuation directions, BAASIS raw score was inverted before analysis.

Cronbrach's  $\alpha$  based on a polychoric correlation matrix was calculated to assess internal validity. Polychoric based  $\alpha$  is considered to be more reliable in ordinal structured data(15).

Convergent validity was assessed with Spearman's  $\rho$  correlation coefficient between ITAS and BAASIS (previously validated). ITAS accuracy considering BAASIS classification as a gold standard was evaluated by logistic regression. Individuals were labeled non-adherent if BAASIS items presented any answer different from "never". (16) (17).

The Area Under the Receiver Operating Characteristic (AUROC) curve was calculated with respective confidence intervals estimated using bootstrap resampling. An optimal cut-point was determined using Youden criterion and used to determine accuracy, sensitivity, specificity, positive and negative predictive values.

Maximum-likelihood factor analysis with Varimax rotation was performed to analyze the optimal number of latent factors and to investigate factor loadings related to each item.

Analysis was performed using R programming language and environment. (18)

## **Ethic**

This study was approved by the local Institutional Review Board (MCO-UFBA - process number 14/2002) and was carried out in accordance to Declaration of Helsinki, (version dated 2013). The researchers ensured that the documents would be kept confidential.

## **RESULTS**

### **Sample characteristics**



Descriptive analysis on the overall sample ( $n = 139$ ) revealed that the majority of the participants were male (77%). The mean age of respondents was 54 years [standard deviation (SD) = 12.82]. The participants were predominantly married (67.4%). The average time between transplant and collection was approximately 56,7 months [interquartile range (IQR) 30,00-79,00] (Table 2).

## **Psychometric properties**

### **Internal Consistency**

Internal consistency measured by polychoric Cronbach's alpha coefficient value was high ( $\alpha = 0.830$ ; Standardized  $\alpha = 0.800$ ).

### **Convergent validity**

ITAS and BAASIS (inverted) presented significant correlation, with a Spearman's  $\rho$  coefficient = 0.302 ( $S = 312.500$ ;  $p < 0.001$ ) (Figure 1).

### **Classificatory performance and accuracy measures**

ITAS discriminatory performance can be seen in Figure 2 (AUROC = 0.638; 95% CI: 0.557 – 0.715). Reporting at least one negative response was the optimal cut-point (Accuracy = 0.647; Sensitivity = 0.492; Specificity = 0.792; Positive Predictive Value = 0.688; Negative Predictive Value = 0.626).

### **Factor analysis**

A single factor model was adequate to ITAS test data ( $X^2 = 2.77$ ;  $df=2$ ;  $p = 0.250$ ). Carelessness presented higher loading (0.997), followed by Forgetfulness (0.362) and Neglect (0.358), in table 3. Factor analysis data is shown in Table 4 and the scree plot with eigenvalues for different number of factors is displayed in Figure 3.

## DISCUSSION

The ITAS contributes as a valid instrument for immunosuppressant medication adherence in solid organ transplants (11) and several studies use the ITAS as an adherence measure (19) (20), (21) (22). The aim of this study was to translate the ITAS to Brazilian Portuguese and to evaluate its psychometric properties in adult liver transplant recipients. The version of the ITAS - scale Brazilian Portuguese facilitates the measurement of immunosuppressant adherence in transplant patients, and reduces negative outcomes for example graft loss and death.

The ITAS is an instrument easy to apply that takes no longer than 05–10 minutes to complete. It is relatively inexpensive, simple, and can be conducted rapidly when compared with other methods of adherence assessment. In this study, we included patients from various parts of Brazil who had their transplants in the state of Bahia, therefore our study sample reflects a wider scale in Brazil. The answers (in percentage ranges) of this version were maintained to preserve continuity, but may present difficulties to patients presenting cognitive deficits, poor educational levels and low social support (11).

Internal consistency provides an estimate of the equivalence of items from the same scale, and values between 0,70 and 0,95 are considered to be acceptable (23) (24). Our Brazilian Portuguese version of the scale presented good internal consistency and was similar to previously published studies - Cronbach's alpha = 0.81. (12). Items within the scale were correlated as expected.

Factor analysis solution with a single factor was adequate, indicating higher loading values for Carelessness (0.997), Forgetfulness (0.362), and Neglect (0.358).

Feeling Worse (item 3) factor loading was close to zero (-0.050), since almost all patients included in the sample (98.6%) answered this item with option A: 0% (none). This behavior was not observed in the original ITAS validating studies (11) and might be due to regional differences. This hypothesis can be verified in further studies replicating the experiments in other regions.

Concerning convergent validity, our findings indicate that the translated ITAS correlates well with the translation of the BAASIS<sup>a</sup> scale, an instrument validated in Brazil (13). AUROC value of 0,5 should be considered a minimum (25). Therefore, our results (AUROC = 0.638) indicate satisfactory discrimination for adherence.

The result of the psychometric properties analysis suggest that the Portuguese translated version of ITAS in Brazil is a psychometric scale internally consistent, with good convergent validity with BAASIS<sup>a</sup>. These findings need to be replicated in further studies. Altogether, these results require confirmation in larger samples with regional variance.

This study has some limitations. The sample may be subject to a bias recruitment due to convenience sampling, because the participants included in the study were those who attended routine consultations. Non adherent patients may be more prone to miss consultations and, therefore, to not be included in the survey. Our sample covers only liver transplant patients and the results cannot be generalized to other types of transplants.

In conclusion, the ITAS instrument was successfully translated and an analysis of the data confirmed its consistency and convergent validity with a validated tool. The translation and validation of the ITAS instrument contributes to the applicability and relevance of the instrument for the Brazilian population.

## **CONFLICTS OF INTEREST**

The authors declare no conflicts of interest.

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**Anexos: *Annals of Hepatology***

Table 1 The final version of the ITAS scale in Brazilian Portuguese.

**Escala de Adesão a Terapia Imunossupressora (ITAS)**

Circule a letra da resposta que melhor estima a porcentagem de tempo descrita em cada uma das 4 questões.

	0% nenhuma	1% - 20%	21% - 50%	Mais de 50% (muito freqüentem ente)
1.Nos últimos 3 meses, com que frequência você esqueceu de tomar seu(s) medicamento(s) imunossupressor(es)?	<b>A</b>	<b>B</b>	<b>C</b>	<b>D</b>
2.Nos últimos 3 meses, com que frequência você foi descuidado ao tomar seu(s) medicamento(s) imunossupressor(es)?	<b>A</b>	<b>B</b>	<b>C</b>	<b>D</b>
3.Nos últimos 3 meses, com que frequência você parou de tomar seu(s) medicamento(s) imunossupressor(es) porque se sentiu pior?	<b>A</b>	<b>B</b>	<b>C</b>	<b>D</b>
4.Nos últimos 3 meses, com que frequência você deixou de tomar seu(s) medicamento(s) imunossupressor(es) por qualquer razão?	<b>A</b>	<b>B</b>	<b>C</b>	<b>D</b>

Legenda: **3** para “0% (nenhuma frequência) do tempo”; **2** para “1%-20% do tempo”; **1** para “21-50% do tempo”; **0** para “mais de 50% do tempo”.

Pontuação: alta – baixa; sendo 0 baixa e 12 alta.



Table 2. Socio-demographic characteristics of liver transplant recipients who were assessed by using the Portuguese version of ITAS.

Variable	Patients (n = 139)
Male gender (%)	108 (77.7)
Age (Mean $\pm$ SD, years)	54.00 $\pm$ 12.82
Marital Status (%)	
Married	93 (67.4)
Single	24 (17.4)
Divorced	15 (10.9)
Widower	6 (4.3)
Post-transplant (mean, months)	56.7

ITAS- Immunosuppressant Therapy Adherence Instrument; SD- Standard Deviation

Table 3 Factor analysis of the ITAS, load values (Loading) for the first factor and sum of the squared factor loadings (Communalities).

Questions	Loading (F1)	Communalities
Forgetfulness	0.362	0.131
Carelessness	0.997	0.995
Feeling worse	-0.050	0.002
Neglect	0.358	0.128

Table 4 Polychoric correlation matrix of the ITAS.

	Forgetfulness	Carelessness	Feeling worse	Neglect
Forgetfulness	1,000	*	*	*
Carelessness	0,554	1,000	*	*
Feeling worse	0,449	0,512	1,000	*
Neglect	0,451	0,634	0,655	1,000

\*  $X_{ij} = X_{ji}$

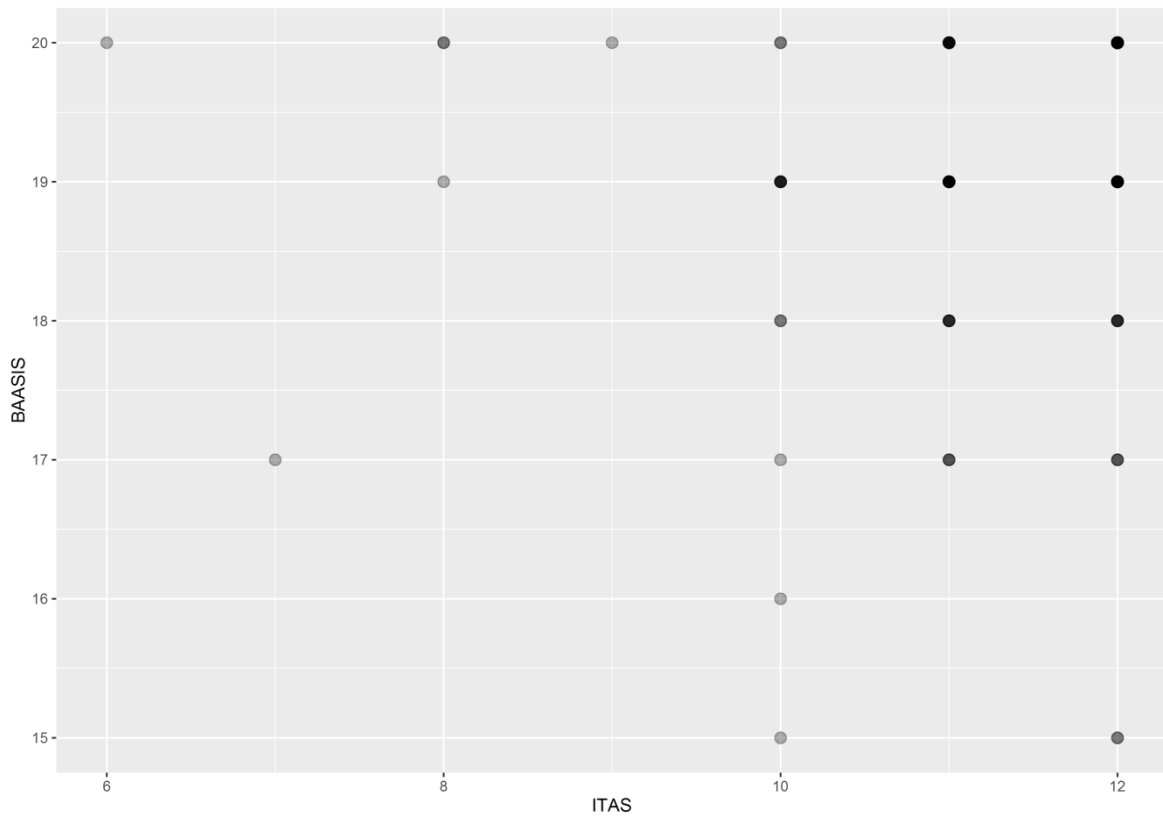


Figure 4 – Correlation plot. Opacity indicates frequency of overlaid points of the ITAS and BAASIS.

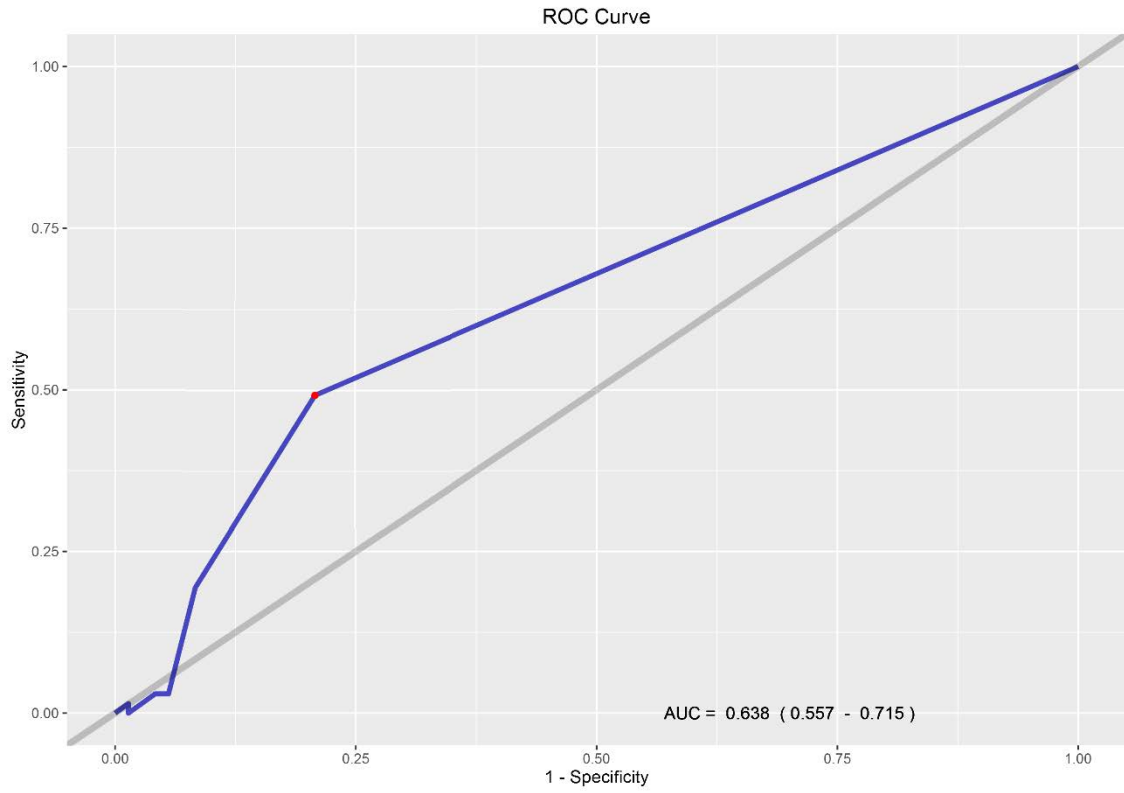


Figure 5 – Area Under ROC curve. Red point indicates optimal cut-point value.

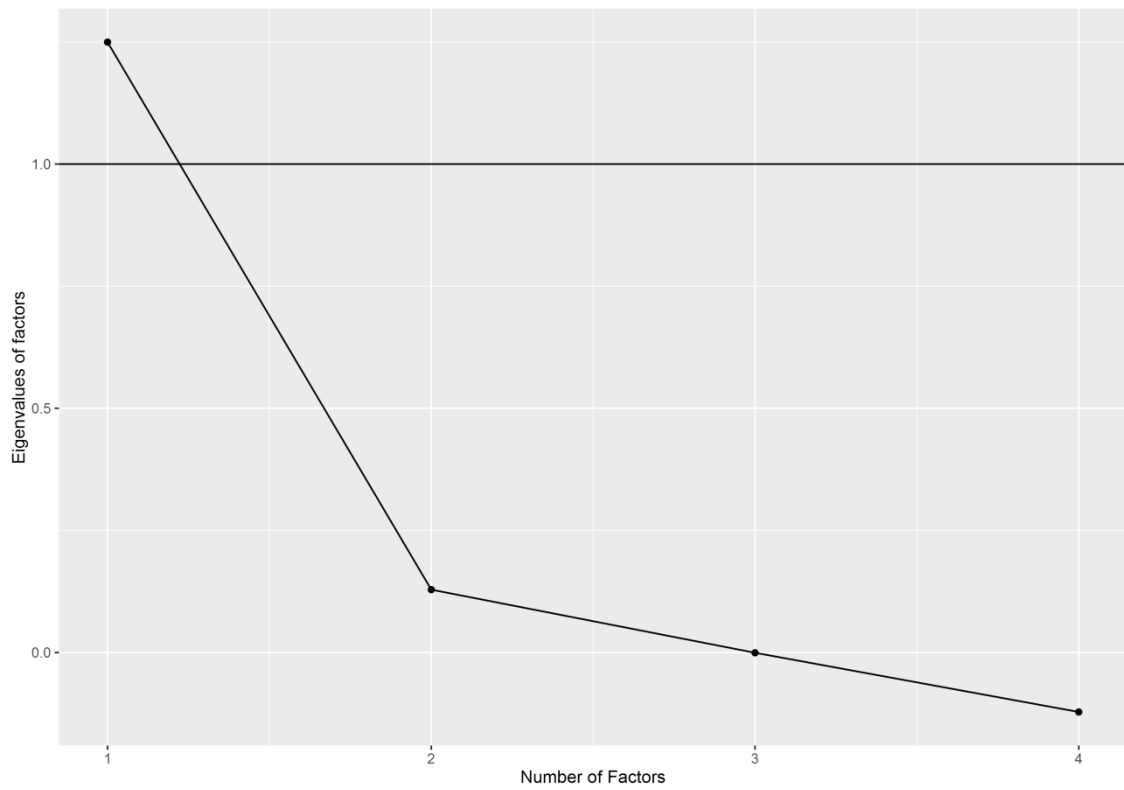


Figure 6 – Scree plot of the ITAS

## **6 CONCLUSÕES**

- A escala ITAS possui propriedades psicométricas adequadas para o uso em contexto brasileiro;
- A ITAS apresenta uma adequada consistência interna, com alpha de Cronbach de 0,8.
- A ITAS revela um alto coeficiente de correlação de Pearson em relação a BAASIS;
- A análise fatorial do ITAS indicou o item esquecimento com as cargas mais altas.

## **7 CONSIDERAÇÕES FINAIS**

A adesão ainda constitui um desafio, predominando na literatura muitas lacunas. Esta Dissertação de Mestrado apresentou um primeiro trabalho de revisão de literatura, limitado, porém, pela escassez de artigos, o que impossibilitou a inclusão de mais estudos ou uma síntese meta-analítica conclusiva. Como segundo trabalho resultante desta Dissertação, encontra-se a validação da escala de adesão à medicamentos imunossupressores após o transplante de fígado, que foi adaptada ao contexto brasileiro que pode auxiliar equipes de saúde na identificação dos pacientes que apresentam dificuldade em seguir a terapêutica prescrita. A disponibilização desta ferramenta de identificação de comportamento de baixa adesão visa apoiar intervenções que favoreçam a redução de desfechos negativos, como a rejeição de enxerto e até o óbito.

## **8 PERSPECTIVAS DE ESTUDOS**

Futuramente, novos estudos são necessários para a reavaliação psicométrica de escalas existentes e validações de escalas mais abrangentes. Mais estudos que avaliem adesão através dos níveis sanguíneos de imunossupressores são


imprescindíveis, por se tratar de uma medida objetiva acessível em centros de transplante, correlacionando com outras medidas comportamentais. Igualmente importante é conhecer essas medidas assim como desenvolver estratégias que otimizem a adesão, levando em consideração sua etiologia multifatorial e complexa. Portanto, pesquisas que investiguem as variáveis que possam predizer uma melhor ou pior adesão podem proporcionar uma intervenção precoce em pacientes que serão submetidos ao transplante de fígado. Pretende-se continuar a linha de pesquisa com tese de doutorado (em fase de coleta de dados) sobre adesão abrangendo hepatopatias na tentativa de contribuir com as lacunas mencionadas.



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## ANEXOS

### Anexo A – Parecer do editor da revista Annals of Hepatology

**Nahum Méndez-Sánchez** <em@editorialmanager.com> 8 de mar (Há 6 dias) ☆ 

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Dear Dr. C. Quarantini,

Your manuscript has been considered by outside reviewers and by the Board of Editors. We are interested in your manuscript. However, there are some concerns with its present form. Please see the reviewers' comments and resubmit the revised version of your manuscript with all changes highlighted and a cover letter with a point-by-point response to each comment done by all reviewers. This letter must indicate which lines and paragraphs has been changed in response to the reviewers' comments. You have three months to resubmit otherwise your manuscript will be considered as a new article. We look forward to hearing from you at your earliest convenience.

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## Anexo B – Parecer de aprovação no Comitê de Ética e Pesquisa



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## PARECER/RESOLUÇÃO ADITIVA N.º 003/2014

Para análise e deliberação deste Institucional o Doutor **Lucas de Castro Quarantini**, Pesquisador Responsável pelo Projeto de Pesquisa “**Incidência de Sintomas Psiquiátricos em Portadores de Hepatite C Crônica tratados com Interferon Peguilado Alfa e Ribavirina**”, aprovado em 28 de Agosto de 2002 por este Colegiado através do Parecer/Resolução nº 14/2002, encaminhou, em 30 de janeiro de 2014, a “**Emenda nº 03/2014**”, adequação do título do projeto supracitado para “**Aspectos Comportamentais de hepatopatias**”, “**Inclusão das variáveis a serem coletadas de prontuário**”, “**Inclusão dos sub-investigadores: Adriana Dantas Duarte Dias e Ana Paula Nunes (Psicólogas, currículos anexos)**”, “**Relatório Anual de 2010 a 2013**”.

Inexistindo nas referidas proposições conflitos administrativo, processual e ético que contra-indiquem as incorporações pretendidas e a consequente continuidade da pesquisa, fica a mesma **aprovada** por esta Instância.

Salvador, 06 de Fevereiro de 2014.

Professor, Doutor, Eduardo Martins Netto  
 Coordenador – CEP/MCO/UFBA

**Observações importantes.** Toda a documentação anexa ao Protocolo proposto e rubricada pelo (a) Pesquisador (a), arquivada neste CEP, e também a outra devolvida com a rubrica da Secretária deste ao (à) mesmo (a), faz parte intrínseca deste Parecer/Resolução Aditiva e nas “Recomendações Adicionais” apenas, **bem como a impostergável entrega de relatórios parciais e final como consta nesta liberação** (Modelo de Redação para Relatório de Pesquisa, anexo).





**COMITÊ DE ÉTICA EM PESQUISA – CEP/MCO/UFBA**  
**MATERNIDADE CLIMÉRIO DE OLIVEIRA**  
**UNIVERSIDADE FEDERAL DA BAHIA**  
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### PARECER/RESOLUÇÃO ADITIVA Nº 019/2014

Para análise e deliberação deste Institucional ao Doutor, **Lucas de Castro Quarantini** Pesquisadora Responsável pelo “**Aspectos comportamentais de hepatopatias**”, aprovado através do Parecer/Resolução Nº 14/2002, encaminhou em 04 de julho de 2014, a “**Emenda Nº 04, datada de 30 de junho de 2014 e os questionários: 1. *Immunosuppressant therapy adherence scale (ITAS)* – 2. Escala para Avaliação de Aderência a Terapia Imunossupressora (BAASIS) – 3. Escala de Experiência Sexual do Arizona (ASEX) – 4. Questionário de qualidade de vida – SF 36.**

Inexistindo nas referidas proposições conflitos administrativo, processual e ético que contraindiquem a conseqüente continuidade da pesquisa, ficam o mesmo **aprovado**.

Salvador, 21 de Julho de 2014.

  
 Professor, Doutor Eduardo Martins Netto  
 Coordenador – CEP/MCO/UFBA

**Observações importantes.** Toda a documentação anexa ao Protocolo proposto e rubricada pelo (a) Pesquisador (a), arquivada neste CEP, e também a outra devolvida com a rubrica da Secretária deste (a) ao (à) mesmo (a), faz parte intrínseca deste Parecer/Resolução e nas “Recomendações Adicionais” apenas, **bem como a impostergável entrega de relatórios parciais e final como consta nesta liberação**, (Modelo de Redação para Relatório de Pesquisa, anexo).

## Anexo C – Termo de Consentimento Livre e Esclarecido

### Termo de consentimento livre e esclarecido

**Projeto:** Aspectos comportamentais de hepatopatias

Você está sendo convidado (a) para participar voluntariamente de um estudo que investiga sintomas como fadiga, depressão e alterações de qualidade de vida, relacionados às diferentes hepatopatias. Antes de concordar em participar desta pesquisa é importante que você leia este documento.

Estas avaliações consistem somente de questionários, que têm duração aproximada de 60 minutos. Algumas exigências para participar deste estudo são:

- Você deve ter idade maior que 18 anos.
- Deve ser portador de hepatopatias.

Você estará ajudando no estudo e compreensão de **doenças do fígado, seja você transplantado ou não**, permitindo benefícios futuros para si próprio e para outras pessoas. Você poderá sair desse estudo a qualquer momento, caso decida. Os investigadores não são remunerados para a realização dessa pesquisa, assim como os pacientes voluntários não receberão benefícios financeiros para sua participação no mesmo.

Dúvidas poderão ser esclarecidas com Dr. Lucas Quarantini, no Hospital Universitário Edgard Santos, terceiro andar, Serviço de Psiquiatria Tel - 32838076. Você pode ainda contatar o Comitê de Ética em Pesquisa no endereço Rua Augusto Viana, s/nº, 1º andar – Canela, Hospital Universitário Professor Edgard Santos, Salvador- Bahia, que é membro de um grupo independente que analisou este estudo.

**Suas informações clínicas são totalmente confidenciais.**

Para participar deste estudo, você precisa assinar esta página.

---

Nome do indivíduo

---

Assinatura do indivíduo

---

Data

---

Assinatura do investigador

---

Data

## Anexo D - Questionário Sócio-demográfico

**Informações confidenciais**

Pré-Pós / Pós

Termo de consentimento assinado? Sim Não

1 – Data do Transplante: \_\_\_\_\_/\_\_\_\_\_/\_\_\_\_\_ 2 - Data: \_\_\_\_/\_\_\_\_/\_\_\_\_

3 - Instituição: \_\_\_\_\_

4 Nome: \_\_\_\_\_

5 - Data de nascimento: \_\_\_\_\_/\_\_\_\_\_/\_\_\_\_\_ 6 – Peso: \_\_\_\_\_.

7 Tels: \_\_\_\_\_ Cel: \_\_\_\_\_

8 - Doenças atuais:  
\_\_\_\_\_

9 Diagnostico antes do transplante:

0 -VHC 1- VHB 2- HIV 3- HTLV 4 Cirrose Hepática 5 Hepatite auto-imune 6  
Encefalopatia hepática 7Doença de Wilson 8 PAF

Outro \_\_\_\_\_

As perguntas 10, 11, 12, 13 são relacionadas a adesão, independe da doença que o paciente tem no momento.

10 – Descreva a seguinte pergunta para o paciente:

“Quando o médico te passa algum tratamento para determinada doença clínica, você considera que segue corretamente o tratamento? ”

0- Não 1- Sim 2- Às vezes

11- De quanto em quanto tempo você deixa de tomar algum medicamento?

Nunca Raramente Às vezes Frequentemente Sempre

12 - Qual o motivo? (Nenhum, esquecimento, Descuido, Condições Financeiras, Não fornecimento nos Serviços, Sentiu-se pior, excesso de medicamentos, outro)  
\_\_\_\_\_

13- Medidas dietéticas: 0- Não 1- Sim 2- Às vezes

14 - Realiza atividade física? \_\_\_\_\_ 15 – Tempo semanal \_\_\_\_\_

**16** Escolaridade \_\_\_\_\_

**17** – Ocupação:

---

**18** - Estado Civil:

**19** - Usa preservativo (camisinha) quando mantém relação sexual?

0- Sempre / 1 - Quase sempre / 2 – Raramente / 3 - Nunca / 4 – Não se aplica

**20** – Usa equipamentos de manicure de outros?

0- Não

1- Sim

2- Não sei

Ou já usou antes? 0 –Não / 1- Sim / 2 – Não sei

**21** – Qual(is) medicamento(s) imunossupressor(es)?(Tacrolimus, Ciclosporina, Prednizona, Micofenolato de Sódio, Micofenolato Mofetil, Sirolimo, Azatioprina, Flamacorten, Everolimo.

**22**- Níveis Séricos:

## Anexo E - Immunosuppressant therapy adherence scale (ITAS) original

Circle the letter of the response that best estimates the percentage of time described in each of the 5 questions.

	0% none	1% - 20%	21% - 50%	Greater than 50% (very frequent)
1. In the last 3 months, how often did you forget to take your immunosuppressant medication(s)?	A	B	C	D
2. In the last 3 months, how often were you careless about taking your immunosuppressant medication(s)?	A	B	C	D
3. In the last 3 months, how often did you stop taking your immunosuppressant medication(s) because you felt worse?	A	B	C	D
4. In the last 3 months, how often did you miss taking your immunosuppressant medication(s) for any reason?	A	B	C	D

Coded: 3 for "0% (none) of the time"; 1 for "21%-50% of the time", 0 for "greater than 50% of the time".

Scoring: high – low; low of 0 to a high of 12.

## Anexo F - Escala de Adesão a Terapia Imunossupressora (ITAS) em português

Circule a letra da resposta que melhor estima a porcentagem de tempo descrita em cada uma das 4 questões.

	0% nenhuma	1% - 20%	21% - 50%	Mais de 50% (muito freqüentem ente)
1.Nos últimos 3 meses, com que frequência você esqueceu de tomar seu(s) medicamento(s) imunossupressor(es)?	A	B	C	D
2.Nos últimos 3 meses, com que frequência você foi descuidado ao tomar seu(s) medicamento(s) imunossupressor(es)?	A	B	C	D
3.Nos últimos 3 meses, com que frequência você parou de tomar seu(s) medicamento(s) imunossupressor(es) porque se sentiu pior?	A	B	C	D
4.Nos últimos 3 meses, com que frequência você deixou de tomar seu(s) medicamento(s) imunossupressor(es) por qualquer razão?	A	B	C	D

Legenda: **3** para “0% (nenhuma frequência) do tempo”; **2** para “1%-20% do tempo”;

**1** para “21-50% do tempo”; **0** para “mais de 50% do tempo”.

Pontuação: alta – baixa; sendo 0 baixa e 12 alta.

Anexo G - Escala Basel para a Avaliação de Aderência a Medicamentos Imunossupressores (BAASIS)

**1)** Você se lembra de não ter tomado seus remédios imunossupressores (dê o nome dos remédios) alguma vez nas últimas 4 semanas?

**2)** Você deixou de tomar várias doses consecutivas de sua medicação imunossupressora nas 4 últimas semanas?

**3)** Você se lembra de ter tomado seus remédios imunossupressores com mais de 2 horas de diferença em relação ao horário prescrito, nas últimas 4 semanas?

**4)** Você tomou uma dose menor do que a dose prescrita pelo seu médico, nas últimas quatro semanas?

sim  não

Você pode me dizer com que frequência isto aconteceu:

Nunca

Uma vez no mês

A cada duas semanas

Toda semana

Mais de uma vez por semana

Todo dia

## Anexo H – Artigo publicado: Brazilian manicure: a potential dangerous behavior

BRAZ J INFECT DIS. 2016;20(1):109-110



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### Letter to the Editor

## Brazilian manicure: a potential dangerous behavior



Dear Editor,

Hepatitis C virus (HCV) is a public health issue that affects about 150 million people worldwide. Transmission most commonly occurs through sharing of injection equipment for injecting drug use, transfusion of unscreened blood and blood products, and reuse or inadequate sterilization of medical equipment, such as syringes and needles.<sup>1</sup> Surprisingly, under these circumstances, it is customary and a cultural phenomenon in Brazil to visit beauty salons and remove the cuticles of the nails in the hands and feet.<sup>2</sup> Manicurists have little knowledge about transmission routes and prevention of infectious agents, despite the underlying risk from an invasive procedure which involves handling of biological material.<sup>3</sup>

We conducted an observational study, at the University Hospital of the Federal University in Salvador, Bahia, from 2010 to 2014, including 95 individuals with hepatitis C on a waiting list for liver transplantation, with the objective of determin-



**Fig. 1 – Distribution of shared use of manicure equipment among patients diagnosed with HCV in the municipality of Salvador, 2010-2014.**

occurs, and 95% did not know how to prevent it.<sup>3</sup> Therefore, the low level of knowledge about transmission routes, prevention, biosafety, basic care, and risk perception elevates the risk of viral hepatitis infection.<sup>2</sup>

The hepatitis C virus infection can be minimized by



### Acknowledgements

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## Anexo I – Artigo publicado: Risk-taking behavior and impulsivity among HCV-infected patients.

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### Risk-taking behavior and impulsivity among HCV-infected patients



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#### ABSTRACT

The association between risk behaviors and hepatitis C virus (HCV) has been extensively studied. It is also proved that impulsivity is associated with risk behaviors. However, there is a lack of studies investigating the association between HCV and impulsivity, a characteristic that can contribute directly to these risk behaviors. This study aimed to investigate HCV-infected individuals' impulsivity and whether this feature mediates risk behavior. Adult patients with liver diseases ( $n=269$ ) were divided into two groups: viral group ( $n=157$ ) – patients with HCV and nonviral group ( $n=112$ ). Risk behaviors were evaluated by a sociodemographic questionnaire. Impulsivity was assessed through Barratt Impulsiveness Scale – BIS-11. Psychiatric comorbidities were investigated by the Mini International Neuropsychiatric Interview 5.0.0. The viral group patients had higher impulsivity than the nonviral group in all domains: attentional impulsivity, motor impulsivity, and nonplanning. Risk behaviors were also shown to be associated with impulsivity levels. Our results suggest that HCV-infected patients are more impulsive than individuals with other liver diseases, even when analyses are controlled for the presence of comorbid mental disorders. In addition, at-risk behavior was significantly mediated by impulsivity.

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(Patton et al., 1995). The current version of BIS-11 consists of 30 items designed to measure three dimensions: 1 – attentional: defined as lack of focus; 2 – motor: defined as acting without thinking, and 3 – nonplanning: defined as orientation to the present and not the future (Patton et al., 1995).

Although impulsivity can be seen as a normal dimension of personality (Eysenck and Eysenck, 1977), elevated levels can be associated with mental disorders such as attention-deficit/hyperactivity disorder (ADHD), mania, substance abuse, and personality disorders (Winstanley et al., 2006).

Only two studies have assessed impulsivity as a primary aim (Huckans et al., 2011; Fabregas et al., 2013). Huckans and collaborators found through neuropsychological testing that adults with HCV were significantly more likely to choose smaller immediate rewards than larger delayed rewards, which shows that these individuals are susceptible to impulsive behavior. However, this study assessed a small sample size of HCV-infected patients and involved exclusively armed forces veterans from the United States (Huckans et al., 2011). Fabregas et al. (2013) investigated a sample of chronic HCV patients and showed that impulsivity was associated with psychiatric comorbidity, such as ADHD and bipolar disorder, which are associated with impulsivity per se regardless of HCV infection. Thus, it does not provide clear evidence about impulsivity as an intrinsic characteristic of HCV-infected patients. In addition, it is not known how important is the apparent higher impulsivity in those individuals.

The aim of this study is to investigate whether HCV-infected patients show an association with impulsiveness and whether this characteristic mediates an association with at-risk behavior, such as drug use, unprotected sex, and alcohol abuse.

## 2. Methodology

### 2.1. Ethical aspects

This study was approved by the Institutional Review Board of MCO-UFBA (protocol 14/2002) and follows the Guidelines and Rules of Resolution 196/96 as well as the Declaration of Helsinki (1989) about human research.

### 2.2. Data collection

This is a cross-sectional study, whose participants were > 18 years of age and provided an informed consent. The sample consisted of 269 outpatients with liver disease, whether indicated or not for a liver transplant, who have been monitored in the University Hospital Professor Edgard Santos Complex (ComHUPES) – Federal University of Bahia (UFBA), Brazil. The data were collected between 2010 and 2014.

### 2.3. Instruments

Patients were assessed through a clinical interview using a sociodemographic questionnaire. The Mini International Neuropsychiatric Interview Brazilian version 5.0.0 (MINI PLUS) (Amorim, 2000) was used to assess the occurrence of psychiatric disorders. In order to evaluate impulsivity, BIS 11 was used, which is a self-administered scale consisting of 30 items that provide a total score of impulsivity in three second-order factors: attentional (lack of focus), motor (acting without thinking), and nonplanning (guidance for the present and not the future). BIS-11 is the most widely used instrument to assess impulsivity in research and clinical practice. The total score was analyzed with regard to the following cutoff points: < 52, low impulsivity; between 52 and 71, normal limit of impulsivity; and > 71, high impulsivity (Stanford

et al., 2009). However, second-order factors of BIS-11 do not have established cutoffs; for this reason, our option was to analyze them by using tertiles.

### 2.4. Data analysis

The patients were divided into two groups: “Viral,” who are suffering from HCV and “nonviral,” including all those with other hepatic diseases and without HCV. Comorbidities and impulsivity were compared between these groups. Comorbidities were analyzed as dichotomous variables, such as suicide risk, current alcohol abuse and dependence, past alcohol abuse and dependence, substance abuse and dependence, and risk behaviors. On the contrary, impulsivity was analyzed as a polytomous variable, such as attentional impulsivity, motor impulsivity, and lack of planning.

Statistical analyses were performed using SPSS version 16.0 software. The following variables were selected for the groups’ descriptive analysis: gender, age, marital status, occupation, and psychiatric comorbidities.

In order to verify the differences between the groups regarding impulsivity levels and comorbidities, bivariate analysis using Pearson’s test was performed.

A multivariate analysis using a logistic regression model was used for dichotomous outcomes (suicide risk, dependence abuse and actual alcohol, dependence past abuse and alcohol, abuse and substance dependence, risk behaviors) and multinomial for polytomous outcome (attentional impulsivity, motor impulsivity, lack of planning) as well as for the odds ratio (OR) and confidence intervals (CI) of 95% between the “viral” and “nonviral” Groups. The tests were performed with a significance level of  $p < 0.05$ .

## 3. Results

The groups analyzed predominantly involved male patients (66.24% viral and 75.89% nonviral), with the corresponding average ages 53.5 and 48.6 years. The groups had a different percentage of individuals with a stable partner (38.71% viral, 72.97% nonviral); most individuals in the viral group (57.14%) had paid employment, while in the nonviral group about 50.45% did. The presence of psychiatric comorbidity was observed in both groups. In the viral group, the highest prevalence was of current major depressive episode (MDE), with 13.38% ( $p=0.006$ ) and past major depressive episode with 17.20% ( $p=0.017$ ). In the nonviral group, the highest prevalence was of anxiety disorder 14.29% ( $p=0.342$ ), although not statistically significant, and the prevalence of adjustment disorder was 14.41% ( $p=0.064$ ).

The total score of the BIS did not reveal any statistically significant difference between the two groups when using the cutoff point presented in the literature; according to this cutoff, 15.13% and 11.43% in the viral and nonviral groups, respectively, presented higher impulsivity (> 71). On the contrary, when using the tertiles division to compare intensity domains of impulsivity areas, there was a relevant absolute difference with statistical significance. The viral group showed a higher prevalence of impulsivity, and the highest score was in attentional impulsivity (45.16%), followed by nonplanning impulsivity (42.76%). The lowest levels (26.80%) were found for motor impulsivity.

The bivariate analysis showed significance in the variable: abuse and dependence on psychoactive substances ( $p=0.005$ ) when comparing between viral and nonviral groups, the OR for abuse and dependence on psychoactive substances in viral group was 10.87 [CI 1.40; 83.90]. There was no significant difference between the groups by bivariate analysis of the variable: risk of suicide ( $p=0.385$ ). We also found no significant difference between the two groups in the bivariate analysis of the following



**Table 3**  
Bivariate and multivariate analyses of comorbidities according to the groups.

Variables	Viral (157) N [%]	Nonviral (112) N [%]	p-value	Bivariate Analysis OR [95% Conf. Interval]	Multivariate Analysis OR [95% Conf. Interval]
Suicide risk	11 (7.01)	5 (4.46)	0.443 <sup>a</sup>	1.61 [0.54; 4.77]	0.79 [0.22; 2.70] <sup>b</sup>
Dependence abuse and current alcohol	13 (8.28)	9 (8.04)	1.000 <sup>a</sup>	1.03 [0.42; 2.50]	0.88 [0.34; 2.20] <sup>b</sup>
Dependence past abuse and alcohol	47 (29.94)	42 (37.50)	0.237 <sup>a</sup>	0.71 [0.42; 1.18]	0.68 [0.40; 1.15] <sup>b</sup>
Abuse and Substance Dependence	14 (8.92)	1 (0.89)	0.005 <sup>a</sup>	10.87 [1.40; 83.90]	10.13 [1.29; 80.08] <sup>b</sup> 8.15 [0.99; 67.19] <sup>c</sup>
Risk behaviors <sup>d</sup>	150(95.54)	104(92.86)	0.422 <sup>a</sup>	1.64 [0.58; 4.69]	1.42 [0.50; 4.11] <sup>b</sup> 0.42 [0.05; 0.80] <sup>c</sup> 0.41 [0.05; 0.77] <sup>e</sup>

<sup>a</sup> Fisher Exact Test.

<sup>b</sup> Adjusted current depressive episode, past depressive episode, and adjustment disorder.

<sup>c</sup> Adjusted current depressive episode, past depressive episode, adjustment disorder, and by the areas of impulsivity: attentional, motor, and nonplanning.

<sup>d</sup> Risk behaviors: unprotected sex; promiscuity; drug use; unhygienic tattooing, body piercing, and acupuncture; sharing of razor and toothbrush; and manicure service.

<sup>e</sup> Adjusted current depressive episode, past depressive episode, adjustment disorder, and for total BIS.

disorders (past MDE, MDE current, and adjustment disorder), multivariate analysis showed that these values remained high. Previous studies suggest cognitive changes associated with HCV, especially in the following areas: attention, learning, psychomotor speed, and mental flexibility (Huckans et al., 2009). The most common complaints of HCV carriers related to cognitive impairment are characterized by impaired concentration and slow thinking. Attentional impulsivity refers to a lack of focus on activities and may be associated with mechanisms leading to cognitive dysfunction reported by HCV-positive patients. A study by Hilsabeck et al. (2002) examined the cognitive functioning of patients with HCV and other patients with chronic liver diseases, and the results showed that patients with HCV have a tendency toward lower cognitive performance than those with other chronic liver diseases. Furthermore, patients with HCV plus other medical comorbidities had an even worse performance. These cognitive difficulties may interfere with daily activities and with the ability to maintain independent functioning. Problems with attention and concentration can interfere with the ability to learn new information and may result in taking long durations to perform simple routine tasks. Because of these difficulties, such patients can become frustrated and may develop mood disorders such as depression and pathological anxiety. In addition, we should also consider the high comorbidity with other mental disorders in HCV-infected patients such as posttraumatic stress disorder (PTSD), which has, among its clinical aspects, attentional impairment (Forton et al., 2005; Morais-de-Jesus et al., 2014).

Although there is a higher incidence of depressive symptoms among patients with HCV, other psychiatric comorbidities are also reported frequently in this population, such as anxiety disorders, psychotic symptoms, drug abuse, and alcoholism (Quarantini et al., 2006; Schaefer et al., 2012). Our data indicate a history of alcohol abuse or dependence throughout life in one-third of the viral group. This was a lower prevalence than that found in other studies conducted in North America and Europe that have high prevalence rates of up 56% (Dwight et al., 2000; Golden et al., 2005; Perry et al., 2008; Novo-Veleiro et al., 2013). Verdejo-García et al. (2008) found that there is an association between alcohol abuse and a more prominent trait of impulsivity. Our sample identified a low percentage of individuals with a history of abuse and dependence on alcohol (8.28% viral vs. 8.04% nonviral). Although there was no statistical significance ( $p=0.942$ ), these results should be treated with caution, because when dealing with patients with liver disease, alcohol use can be extremely harmful and

contribute to a worsening of symptoms and consequently a worsening liver disease (Shoreibah et al., 2014).

Regarding substance use, abuse, and dependence, there was a statistical significance ( $p=0.005$ ) in our sample and the prevalence in the viral group was higher than that in the nonviral group, confirming the literature data, which show that drug use is directly associated with HCV transmission, and a significant form of transmission by syringe sharing (Ministério da Saúde, 2011). Even after adjusting for psychiatric comorbidities and impulsivity levels using a multivariate analysis, drug use remained high: OR 8.15 [CI 0.99; 67.19]. This large CI may be explained by the fact that table cells with a value below 5 may have needed a larger sample to achieve significance. However, the expected direction is in agreement with the literature data, which associates substance abuse and dependence with contamination by the HCV. Considering previous evidence presented by Verdejo-García et al. (2008), which supports the fact that impulsive behavior is associated with vulnerability to drug use, we can hypothesize that impulsivity may be highly prevalent in HCV-infected patients.

In our study, nonplanning impulsivity levels were also higher in the viral group than the nonviral group (42.76% vs. 19.05%). This characteristic encompasses behaviors oriented to the present and not the future. These data refer to a study by Huckans et al. (2011), which found that patients with HCV were significantly more likely to choose smaller immediate rewards than larger rewards later on. One hypothesis that we raised is that patients with HCV (and perhaps other chronic diseases) are more likely to regard the future as uncertain or believe they will be seriously ill or may soon die, which could lead them to behave with a higher focus on the present and poor planning. Moreover, impulsivity may precede the acquisition of viruses and contribute to risk behavior, which would favor one's own infection by HCV. This is supported by previous evidence that impulsivity is an early-acquired trait in neurodevelopmental models (Bezdzjian et al., 2011). Furthermore, at-risk behaviors such as unprotected sex; promiscuity; drug use; unhygienic tattooing, body piercing, and acupuncture; sharing of razor and toothbrush; and manicure service were associated with impulsivity levels, as shown in bivariate and multivariate analyses.

The proportion of suicide risk was higher in the viral group, but adjusting for comorbidities in the multivariate analysis, the OR was not significant. On the contrary, a study conducted by Kristiansen et al. (2010) in Norway showed that total mortality in chronically infected HCV patients was 6.66 times higher than that in the general population. This increase was associated with liver

variables: current alcohol abuse ( $p=0.942$ ) and past alcohol abuse ( $p=0.194$ ). In both groups, > 90% of the patients reported risky behavior – comparing between the nonviral and viral groups, the OR in viral group was 1.64 [CI 0.58; 4.69].

In multivariate analysis, the OR for abuse and dependence on psychoactive substances in the viral group remained high 10.13 [CI 1.29; 80.08] even after adjusting for comorbidities (current MDE, past MDE, and adjustment disorder). However, when it was

adjusted for the impulsivity domains (attentional, motor, and nonplanning), the OR decreased to 8.15 [CI 0.99; 67.19]. After multivariate analysis of the variable, risk of suicide adjusted for psychiatric comorbidities, the OR in viral group decreased from 1.61 [0.54; 4.77] to 0.79 [CI 0.22; 2.70], which shows that higher probability of suicide risk is related to comorbidities. Multivariate analysis of the variable, risky behavior adjusted for comorbidities (current MDE, past MDE, and adjustment disorder), showed a reduction in the OR to 1.42 [0.50; 4.11]. When adjusted for impulsivity areas, the OR dropped to 0.42 [0.05; 0.80]; and after adjusting for total BIS, there was also a small reduction: the OR was 0.41 [0.05; 0.77] (Tables 1–3).

**Table 1**

Sociodemographic characteristics, clinical characteristics, and prevalence of psychiatric comorbidities according to the nonviral and viral groups.

Variables	Viral (157)		Nonviral (112)		p-value
	N (%) or M (SD)	N (%) or M (SD)	N (%) or M (SD)	N (%) or M (SD)	
<b>Gender</b>					
Male	104 (66.24)	85 (75.89)			0.105 <sup>a</sup>
Female	53 (33.76)	27(24.11)			
<b>Age (mean)</b>	53.5 (8.8)	48.6 (12.9)			
<b>Civil state</b>					
Single	7 (4.52)	19 (17.12)			< 0.001 <sup>a</sup>
With stable partner	60 (38.71)	81 (72.97)			
Divorced	33 (21.29)	11 (9.91)			
Widower	55 (35.48)	0 (0.00)			
<b>Paid occupation</b>					
Without	15 (9.74)	10 (9.01)			0.553 <sup>a</sup>
With	88 (57.14)	56 (50.45)			
Retired by age	31 (20.13)	24 (21.62)			
Retired due to illness	19 (12.34)	18 (16.22)			
Student	1 (0.65)	3 (2.70)			
<b>Psychiatry comorbidities</b>					
Current major depressive disorder	21 (13.38)	4 (3.57)			0.006 <sup>a</sup>
Last major depressive disorder	27 (17.20)	8 (7.14)			0.017 <sup>a</sup>
Anxiety disorder	16 (10.19)	16 (14.29)			0.342 <sup>a</sup>
Adjustment disorder	11 (7.01)	16 (14.41)			0.064 <sup>a</sup>

<sup>a</sup> Fisher Exact Test.

#### 4. Discussion

This study shows that there is an association between impulsivity and HCV even after controlling these results for the presence of psychiatric comorbidities. To the best of the authors' knowledge, this is the first study of its kind that shows that impulsivity may be a peculiar characteristic of patients with HCV and that it is more associated with risk behaviors. There has been a lack of studies investigating impulsivity in people infected with HCV. Although a previous study (Fabregas et al., 2013) has shown high scores of impulsivity in HCV patients, this finding has been best explained by the presence of psychiatric disorders such as ADHD, bipolar spectrum disorders, and anxiety symptoms.

In our analysis of the second-order factors of BIS-11 (attentional, motor, and nonplanning), a higher level of impulsivity was observed among patients with HCV than with other liver diseases, with a significant difference in the attentional and nonplanning domains (45.16%, viral; 15.89%, between nonviral and viral; 42.76%, nonviral 19.05%). Although the motor domain had less difference than the other two, the viral group continued to have higher scores than the nonviral group (26.80% vs. 19.63%). Even after adjusting for the covariates: substance abuse and psychiatric

**Table 2**

Prevailing levels of impulsivity in accordance with the groups.

Variables	Outcome Levels of Impulsivity	Main		p-value	Multivariate Analysis
		Viral (152)	Exhibition <sup>a</sup> Nonviral (105)		
		N (%) or M (SD)	N (%) or M (SD)		OR [95% Conf. Interval]
<b>BIS TOTAL</b>					
> 71	More impulsivity	23 (15.13)	12 (11.43)	0.619	
52–71	Normal impulsivity	102 (67.11)	71 (67.62)		
< 52	Low impulsivity <sup>b</sup>	27 (17.76)	22 (20.95)		
<b>DOMAINS</b>		<b>Viral (155)</b>	<b>Nonviral (107)</b>		
<b>Attentional Impulsivity</b>	More impulsivity	70 (45.16)	17 (15.89)	< 0.001	4.34 [2.22; 8.49] <sup>c</sup>
	Average impulsive	38 (24.52)	31 (28.97)		4.09 [2.08; 8.03] <sup>d</sup>
	Less impulsive <sup>b</sup>	47 (30.32)	59 (55.14)		
<b>Motor Impulsivity</b>	More impulsivity	60 (26.80)	21 (19.63)	< 0.001	3.34 [1.73; 6.44] <sup>c</sup>
	Average impulsive	52 (33.99)	30 (28.04)		3.21 [1.65; 6.22] <sup>d</sup>
	Less impulsive <sup>b</sup>	41 (26.80)	56 (52.34)		
<b>Lack of Planning</b>	More impulsivity	65 (42.76)	20 (19.05)	< 0.001	3.16 [1.63; 6.10] <sup>c</sup>
	Average impulsive	40 (26.32)	29 (27.62)		3.00 [1.54; 5.82] <sup>d</sup>
	Less impulsive <sup>b</sup>	47 (30.92)	56 (53.33)		

<sup>a</sup> Reference main exhibition.

<sup>b</sup> Reference outcome.

<sup>c</sup> Adjustment: current depressive episode, past depressive episode, and adjustment disorder.

<sup>d</sup> Adjustment: current depressive episode, past depressive episode, adjustment disorder, and substance abuse and dependence.



disease, alcohol dependence, drugs use, and suicide.

This study has some limitations. The cross-sectional design of this study limits the ability to determine whether impulsivity occurs before or after the interaction of the virus to the central nervous system. In our findings, we did not observe a statistically significant difference using the cutoff points for the total score of the BIS-11 available in the literature (Stanford et al., 2009). We believe that this proposed cutoff point is not suitable for this population, because we consistently found statistically significant differences in the fields of impulsivity as measured on this scale by tertiles.

## 5. Conclusion

The results of this study suggest that HCV patients are more impulsive than those with other liver diseases, even when the analyses are adjusted for the presence of comorbid psychiatric disorders. In addition, we showed that impulsivity is significantly associated with risk behaviors. Therefore, it may be considered as another extrahepatic manifestation, and it can be observed that HCV is not as mild as previously described. We stress the need for special attention to this behavioral aspect that may contribute to other lethal outcomes such as suicide and low adherence. Special attention should be paid to the approach toward drug users, because of higher vulnerability to acquiring HCV or reinfection after successful treatment (Grady et al., 2013). There is a crucial need for public policies of prevention and vigilance for the HCV population as well as a requirement for psychological/psychiatric support, not only during antiviral therapy.

## Conflict of interest

The authors declare that they have no competing interests.

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