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O Impacto dos Vírus Hepatotrópicos no Paciente Infectado pelo HIV e o papel da elastometria transitória.

Tese apresentada á Universidade Federal de São Paulo – Escola Paulista de Medicina para obtenção do título de Doutor em Ciências.

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Orientador: Prof. Dr. Ricardo Sobhie Diaz

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Resumo

A doença hepática foi um evento negligenciado no paciente infectado pelo HIV por muitos anos, principalmente em virtude da alta mortalidade por doenças oportunistas relacionadas á síndrome da imunodeficiência adquirida (aids). Com o advento da terapia antirretroviral de grande atividade (HAART), a mortalidade relacionada às doenças oportunistas caiu substancialmente e a mortalidade por doenças hepáticas emergiu como uma das principais causas de morte não relacionadas à aids.

Desde o reconhecimento de seu impacto na morbidade, muitas modificações vêm ocorrendo. Atualmente, os antirretrovirais disponíveis são menos hepatotóxicos, há um melhor entendimento e busca de aperfeiçoamento no tratamento das hepatites virais, novas tecnologias estão disponíveis para seguimento e diagnóstico da doença hepática, bem como novas formas de avaliar a gravidade desses pacientes. Portanto, avaliar o paciente infectado pelo HIV nesse novo “ambiente” se faz necessário.

A presente série de estudos revisa tópicos relacionados á doença hepática em pacientes infectados pelo HIV na atualidade. Primeiramente, comparam-se duas novas técnicas diagnósticas para determinação do grau da fibrose hepática: o Impulso Potente por Radiação Acústica comparado a Elastometria Transitória. Demonstra-se boa correlação diagnóstica entre as duas técnicas e utilizando a elastometria transitória, acessamos a incidência de cirrose em pacientes HIV positivos independente da etiologia. Não surpreendentemente, demonstra-se que atualmente os pacientes que atingem o estádio de cirrose hepática são portadores de hepatite C que não receberam tratamento para essa última ou não atingiram a cura quando tratados.

Por último, avaliamos a mortalidade entre pacientes cirróticos infectados pelo HIV. Observa-se uma taxa de mortalidade relativamente elevada quando se compara com dados recentes de literatura que avaliam a mortalidade geral em pacientes HIV positivos. Interessantemente, os fatores associados a uma maior mortalidade foram CD4<200, HIV-RNA>50 cópias/mL, grau de fibrose hepática avaliado por elastometria transitória e o MELD.

Sendo assim, nota-se que as inovações apresentadas no campo da co-infecção vêm beneficiando de forma importante os pacientes infectados pelo HIV. Contudo, a mortalidade entre pacientes que possuem cirrose estabelecida segue alta e novos caminhos para acessar a gravidade na cirrose hepática devem ser mais explorados no paciente infectado pelo HIV.

Introdução

A enfermidade hepática crônica é responsável por 27.555 mortes anuais nos Estados Unidos, representando 1,1% do total de mortes registrado [1]. A evolução final da enfermidade hepática crônica é a cirrose hepática. O termo cirrose provém do termo grego *Kirrhos*, que significa cor amarelo-alaranjado, referência clara à icterícia muitas vezes encontrada nesses pacientes.

No paciente infectado pelo HIV, a doença hepática foi um evento negligenciado por muitos anos, principalmente em virtude da alta mortalidade por doenças oportunistas relacionadas à síndrome da imunodeficiência adquirida (aids). Com o advento da terapia antiretroviral de grande atividade (HAART), a mortalidade relacionada às doenças oportunistas caiu substancialmente e a decorrente de doenças hepáticas emergiu como umas das principais causas de morte não relacionadas à aids [2]. A principal causa de doença hepática entre pacientes HIV positivo são as hepatites virais seguido do abuso de álcool [3, 4]. O reconhecimento deste dado intensificou pesquisas que visaram ao entendimento da doença hepática no paciente infectado pelo HIV, bem como a proposição de tratamento para pacientes co-infectados com HIV e hepatites virais.

Estudos demonstraram que pacientes co-infectados com HIV e o vírus da hepatite C (HCV) evoluíam mais rápido para a cirrose [5, 6]. Enquanto os pacientes monoinfectados evoluíam em um grau de fibrose a cada 5 anos, os pacientes co-infectados HIV-HCV evoluíam um grau a cada 3 anos [7]. É importante ressaltar que o uso da HAART traz comprovadamente benefícios diminuindo a velocidade de progressão da fibrose hepática [8-10]. Entretanto, seu uso não é capaz de frear totalmente essa evolução e tampouco reverte

totalmente o aumento da velocidade da progressão causada pela infecção [8]. Sendo assim, o tratamento das hepatites virais tornou-se crucial na tentativa de reverter esse quadro.

Inúmeros obstáculos acompanham o tratamento das hepatites virais no paciente HIV, destacando-se primeiramente o fato de que a efetividade do tratamento para a hepatite C no paciente HIV é substancialmente menor quando comparado ao paciente monoinfectado HCV [11, 12]. As taxas de resistência a análogos núcleos(t)ideos para hepatite B é mais alta [13] e se configura como segundo obstáculo. Um terceiro fator está relacionado aos efeitos colaterais de medicamentos como o interferon e a ribavirina que podem ser mais pronunciados nesse grupo de pacientes [12]. Por fim, existem inúmeras interações medicamentosas entre a terapia antiretroviral e o tratamento das hepatites virais [14, 15]. Nesse contexto são propostas formas para a melhoria da efetividade e diminuição dos riscos do tratamento principalmente da hepatite C. Fármacos antiretrovirais mais modernos e menos hepatotóxicos facilitaram essa tarefa.

Assim, algumas condutas tornaram-se primordiais no tratamento da hepatite C no HIV, como por exemplo: 1. não associar o tratamento a antiretrovirais como zidovudina[16, 17], estavudina [18] e mais recentemente, foi lançada a dúvida sobre a interação da ribavirina ao abacavir [14, 19, 20]; 2. usar ribavirina com dose ajustada para o peso [21] 3. avaliar a resposta à terapia na semana 4 e 12 para identificar bons e maus respondedores, respectivamente [22-24]; 4. tratar a hepatite C de pacientes infectados pelo HIV com CD4 alto [12, 25]. Em relação à hepatite crônica B, o uso de fármacos como a lamivudina e especialmente, o tenofovir vem modificando a história natural da enfermidade

[26, 27]. O tenofovir é de amplo acesso para o paciente infectado pelo HIV, visto que também é um antiretroviral. Este fármaco é extremamente potente e possui alta barreira genética, o que gera a expectativa de que com seu uso se aperfeiçoe o tratamento da hepatite diminuindo a incidência de pacientes que progridem para cirrose.

A cirrose hepática é definida como processo difuso caracterizado por fibrose e alteração arquitetural do tecido hepático onde o colágeno é substituído por tecido fibroso, caracterizando nódulos estruturalmente anormais [28]. Portanto, para seu diagnóstico é necessária a análise anatomopatológica de um fragmento de tecido hepático. Dessa forma, a biópsia hepática é considerada o padrão-ouro para seu diagnóstico. Entretanto, estudos demonstram inúmeras desvantagens dessa técnica, tais como: alto custo; variabilidade inter-observador; diferenças no grau de fibrose dependendo do local de punção ao que podemos acrescentar o fato de que é um procedimento invasivo com riscos de complicações graves ao redor de 0,5% [29-31]. Inúmeros escores baseados em marcadores séricos foram propostos na tentativa de evitar a biópsia hepática [32, 33], apresentando alguns deles alta validez para inferência do diagnóstico de cirrose [34, 35], dentre eles, a elastometria transitória tem se mostrado como o meio mais válido para avaliação não invasiva da fibrose hepática [35, 36].

A elastometria transitória (FibroScan®) é um aparato que por meio de uma sonda com transdutor de ultra-som é montado no eixo de um vibrador. Emitindo vibrações de leve amplitude e baixa freqüência transmitidas do vibrador para o tecido, induz uma onda de cisalhamento elástico que se propaga através do tecido. A velocidade com que essa onda penetra no tecido hepático é

diretamente correlacionada com a rigidez hepática [37]. A elastometria transitória vem cada vez mais sendo usada em centros internacionais por apresentar vantagens como baixo custo, ser uma prova não invasiva e de fácil manejo que permite avaliações seriadas da fibrose hepática. Avaliações seriadas da fibrose hepática são particularmente importantes para o paciente infectado pelo HIV pois estes apresentam a evolução da cirrose de forma acelerada [5]. A elastometria transitória parece ter também algum valor prognóstico, visto que seu resultado foi correlacionado com a presença de varizes esofágicas e ascites [35] [38]. Uma das desvantagens da elastometria transitória é que a mesma não permite a visualização do local onde a fibrose hepática está sendo mensurada e isso pode gerar incertezas em algumas medições. Neste contexto, um novo aparato que une a medição da rigidez hepática a um aparelho de ultra-som de alta qualidade foi recentemente lançado, sendo os dados de literatura sobre esta inovação ainda escassos [39, 40].

As inovações no cenário da saúde desenvolvidas nos últimos anos, tais como terapias antiretrovirais mais potentes, menos tóxicas, o aperfeiçoamento do tratamento das hepatites virais no paciente HIV e a novas formas de diagnosticar a cirrose hepática trouxeram a necessidade de avaliação das modificações da incidência da cirrose hepática no paciente HIV. Espera-se que todas as inovações no cenário da infecção do HIV se reflitam em uma maior sobrevida do paciente infectado pelo HIV com cirrose. Nesse contexto, o transplante de órgãos tornou-se uma realidade para esses pacientes. Contudo, apesar do otimismo inicial, estudos de sobrevida ao longo de 5 anos demonstraram uma maior mortalidade em pacientes co-infectados HIV-HCV

quando comparados a mono-infectados HCV [41]. Enquanto alguns estudos sugerem que tais eventos ocorrem principalmente em decorrência da recidiva da doença pelo HCV e descompensação hepática [41-43], outros estudos foram incapazes de elucidar a razão do aumento desta mortalidade[44]. Portanto, passa a ser de extrema importância a análise de fatores da mortalidade nos pacientes infectados pelo HIV com cirrose hepática relacionados à validade da utilização de instrumentos, tais como o escore de modelo para doença hepática em estágio final (MELD) e a escala de Child-Pugh, que são amplamente utilizados na avaliação da gravidade da doença hepática e/ou alocação de órgãos para transplante no paciente infectado pelo HIV.

Nesta série de estudos pretende-se revisar os principais tópicos relacionados com a cirrose hepática em pacientes infectados pelo HIV, abrangendo desde a determinação do grau da fibrose hepática e diagnóstico não-invasivo de cirrose hepática até a identificação do paciente infectado pelo HIV de maior risco de evolução à cirrose. Por fim, serão avaliados os fatores e instrumentos relacionados à mortalidade de pacientes com cirrose hepática e infectados pelo HIV.

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Madrid, November 10th 2009

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Sincerely yours,

Pablo Barreiro, MD, PhD

Validity of Acoustic Radiation Force Impulse (ARFI) Ultrasound for the Estimation of Liver Fibrosis

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Running title: ARFI-US for estimation of liver fibrosis

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Abstract

Background: Non-invasive assessment of liver fibrosis (LF) is rapidly being introduced in the routine management of chronic viral hepatitis. Imaging techniques are for the moment more reliable than fibrosis scores; transient elastography (TE) has shown high accuracy in the diagnosis of advanced LF and cirrhosis in comparison with liver biopsy. Acoustic radiation force impulse ultrasound (ARFI-US) is a new technology, that measures LS in the context of high-quality abdominal ultrasound examination.

Methods: All consecutive patients with chronic viral hepatitis attending our reference clinic for routine follow-up during the first 2 weeks of February 2009 prospectively underwent parallel TE and ARFI-US examinations. Agreement between TE and ARFI-US results was determined using the Intraclass Correlation Coefficient (ICC) and the Bland-Altman method. Validity of ARFI-US for the diagnosis of cirrhosis was analyzed by area under the receiver operating characteristic (AUROC) curve.

Results: A total of 80 patients were examined (median age 46 years-old, 42% HCV-monoinfected, 26% HIV/HCV-coinfected, 4% HBV monoinfected patients, 5% HIV/HBV coinfected). A 0.68 ICC was found between TE and ARFI-US, and linear correlation was observed between both techniques (R^2: 0.46). Correlation for TE and ARFI-US in patients with cirrhosis was high (AUROC curve of 0.92). Best ARFI-US cut-off for cirrhosis was 2.2 m/s (positive and negative predictive value of 93.3% and 89.6%, respectively).

Conclusion: ARFI-US has good concordance with TE. Both techniques may accurately detect patients with advanced LF or cirrhosis.

Introduction

The extent of liver fibrosis is the most reliable information to establish prognosis and best treatment in patients with chronic viral hepatitis. Given limitations and complications of liver biopsy (1-3), several non-invasive methods have recently developed to stage liver fibrosis (LF). Biological fibrosis scores, constructed from demographic and blood parameters, show in general modest correlation with histological stages of LF (4-7).

Ultrasound-based determination of liver stiffness (LS) by transient elastometry (TE) has proven high accuracy to diagnose advanced LF and cirrhosis, Metavir scores F3 and F4 at liver biopsy, respectively (8-14). In order to measure LS, TE accesses the liver through intercostal spaces. This technical requirement limits liver examination to a restricted area, the most lateral aspect of the right lobe of this organ. Also, the small size of the ultrasound probe used in TE renders low quality bidimensional images of the liver, what does not allow selecting for the most appropriate area to determine LS (i.e. free of vessels, granulomata or calcifications). Finally, the low-energy shear-wave used to determine LS makes TE of little utility in obese patients; in these individuals the impulse produced in the chest-wall is frequently unable to progress through thick adipose tissue into the liver. Acoustic radiation force impulse ultrasound (ARFI-US) is new method to measure LS (15), which may in part overcome these technical limitations of TE.

This technique uses high-energy and short-duration acoustic pulses, to generate localized and micron-scale displacements of tissue in a selected region of interest. This displacement is tracked using ultrasound methods to finally calculate shear wave velocity, which directly correlates with the elasticity

of the liver. The high energy of the impulse used, together with the high quality of US imaging, allows better selection of the optimal region of interest where LS will be measured. Also, ability for abdominal approach facilitates examination of obese patients.

There is for the moment little information on the validity of ARFI-US to stage LF, mostly restricted to patients with chronic hepatitis C (16-18). The decrease in the practice of liver biopsies, in part caused by the development of non-invasive methods, may hinder comparison of ARFI-US with histology. Herein we present a concordance study of TE, already validated against liver biopsy, with ARFI-US in patients with chronic viral hepatitis.

Materials and Methods

*Patients. A*ll consecutive patients with chronic viral hepatitis regularly attending an Outpatient Clinic in Madrid, Spain, were proposed to undergo parallel TE and ARFI-US examinations during the first 2 weeks of February 2009. Only two operators were involved in the examination, one set at TE and the other at ARFI-US. Both operators were blinded for the results of the technique of comparison, and for any clinical or laboratory patient´s information.

Subjects with less than 12 months of follow-up at the clinic, current pegylated interferon therapy, initiation of any new antiviral therapy within the previous 6 months, active alcohol or illicit drugs consumption, or more than 0.5-fold increase in AST or ALT with respect to previous values, were excluded from the study. Clinical and laboratory data of studied patients were obtained from medical records.

Transient elastometry (FibroScan®, Echosens, France). Following manufacturer's instructions, a minimum of ten valid measurements were obtained on the right lobe of the liver through an intercostal space. Patients were placed in supine decubitus position with the right arm in abduction, and the probe of the system was applied between the ribs. Valid TE examinations were those with success rates (number of valid against number of total measurements) of at least 70% and interquartile range (IQR) less than one-third of the median of all measurements. Unreliable TE examinations were excluded for the analysis. Median value of all measures, expressed in kilopascals (KPa), was chosen as representative of overall LS. According to prior publications (9), TE values were grouped in four to establish LF by Metavir score (F): less than 7.1 KPa (F1); 7.1 - 9.4 KPa (F2); 9.4 - 14.5 KPa (F3); and more than 14.5 KPa (F4).

ARFI-ultrasound (Siemens, Germany). Patients were placed in supine decubitus position with the right arm in abduction. The probe of the system was applied to obtain 3 abdominal and 2 intercostal exams. Median value of all LS records in meters per second (m/s) was calculated in each patient.

Statistical analysis. Descriptive statistics are presented as percentages for categorical variables and median (IQR) for continuous variables. Agreement between TE and ARFI-US was determined using: i) intraclass correlation coefficient (ICC) for agreement and for concordance, and was interpreted according to the classification proposed by Fermanian (19) and, ii) Bland-Altman method, which shows the differences against the average of both techniques (20). Standardization of TE and ARFI-US measurements, by

transformation to corresponding Z-scores (X – Ẋ / SD) was done before comparison of both techniques.

Scatter plots were displayed for global values of TE and ARFI-US, and for each Metavir stage. Analyses of LS data, as evaluated by histograms of frequencies, and Kruskal-Wallis, Kolmogorov-Smirnov or Shapiro-Wilk tests, showed not normal distribution, so that non-parametric tests were used. Post-hoc multiple comparisons for independent samples, between ARFI-US values and Metavir stages, were analyzed using Mann-Whitney U-test with the Bonferroni correction. The non-parametric Wilcoxon T-test for paired samples was used to compare median values of TE and ARFI-US, and for comparing both techniques in each of the four Metavir stages. These comparisons were also shown using box plots for each Metavir stage.

Power of ARFI-US for the diagnosis of cirrhosis (median TE of >14.5 KPa) was established by calculation of the area under the receiver operating characteristic (AUROC) curve. Best ARFI-US cut off for cirrhosis was selected as the value of LS with sensitivity closer to AUROC curve. Positive and negative predictive value of this cut-off was determined by Chi-square analysis.

All tests were two-tailed with a p-value ≤0.05 considered to be significant. For Bonferroni correction, α-value for each comparison should be equal to 0.05 per number of comparisons. Statistical analysis was made using SPSS 17.0 statistical software package (SPSS Inc, Chicago, Illinois, USA).

Results

A total of 86 patients were examined, 5 were excluded in the absence of clinical data and one obese patient due to inability to obtain at least 10 valid TE

measurements. Among a total of 80 patients with valid TE and ARFI-US exams, 76 had clinical plus laboratory data. Baseline characteristics of these patients are shown in **Table 1**.

According to non invasive assessment of LF, overall median LS was 8.2 KPa (6.3-11.9) and 1.6 m/s (1.3-2.2) by TE and ARFI-US, respectively. Based on TE examination, the distribution of patients by stage of fibrosis was: 28 (35%) at F1; 25 (31%) at F2; 12 (15%) at F3 and 15 (19%) at F4. Median and range of liver stiffness by ARFI-US across Metavir stages of LF are depicted in **Figure 1**. Comparisons among mean ARFI-US values by Metavir score were statiscally significant for cirrhosis (F4) against any other level of fibrosis, and for advanced fibrosis (F3) against non-significant fibrosis (F0-F1). All other comparisons were not statistically significant.

Intra class correlation (ICC) between TE and ARFI-US was 0.68 (95% CI, 0.54 - 0.78). Scatter and Bland-Altman plots for values of LS as determined by TE and ARFI-US are shown in **Figure 2**. Linear correlation was observed between both techniques R^2: 0.46 (**Figure 2a**). The non-random distribution of the dots on both sides of the horizontal line at Bland-Altman graphic (**Figure 2b**) indicates a systematic bias in the ARFI-US measurements with respect to TE. It seems that at growing levels of fibrosis ARFI-US tends to measure greater liver stiffness than TE. Also, mean Z-scores for TE and ARFI-US values (data not shown), grouped by Metavir score, were non-significantly different in all stages of LF (Wilcoxon test, $p > 0.05$).

Figure 3 shows the ROC curve for the diagnosis of liver cirrhosis by ARFI-US. Correlation of ARFI-US and TE in patients with cirrhosis was high, with a AUROC curve value of 0.92 (95% CI, 0.83-0.99). Best ARFI-US cut-off for the detection of cirrhosis was 2.2 m/s, which has a positive and negative predictive value of 93.3% and 89.6%, respectively.

Discussion

The present study offers data on the performance of a novel imaging technique (ARFI-US) for the staging of liver stiffness in patients with chronic hepatitis B or C, and/or HIV infection. For this purpose we determined a good concordance between ARFI-US measures and TE exams, another US-based imaging technique, already validated against liver histology for the staging of LF (9-14). As an advantage of our study as compared with recent publications that have tested ARFI-US only in HCV-infected population, we have included for the first time subjects with hepatitis B and HIV coinfection.

The high ICC index (0.68) and the good linear correlation (R^2: 0.46) obtained between TE and ARFI-US may indicate that both techniques share indications and limitations for the diagnosis of different stages of LF. Almost all published studies indicate that the strength of concordance of TE and liver biopsy is only high for patients with advanced LF (Metavir ≥F3) or overt cirrhosis (Metavir F4) (9-14). Thus, it is very likely that ARFI-US neither will be able to discriminate between milder levels of fibrosis when compared with liver biopsy. Not surprisingly ARFI-US values were only different for patients, according to TE,

with vs without cirrhosis (Metavir F4) and with advanced (Metavir ≥F3) vs non-significant (Metavir F0-F1) LF.

The Bland-Altman graphic confirmed a good concordance between the two techniques studied, given that most dots appeared within the ±1 SD area. A possible systematic bias may be inferred from a trend of ARFI-US vs TE to determine greater LS, as mean LS increases. In this respect it may be that with greater fibrosis ARFI-US is able to detect small areas with increased liver density, while TE offers a broader examination of liver tissue. Given that LF is a heterogeneous and disperse histological damage, the ability of TE over ARFI-US to offer a more ample measure of liver stiffness should be viewed as an advantage. In this regard, two recent studies have found better accuracy for the diagnosis of liver fibrosis for TE as compared with ARFI-US (16,17), particularly in non-cirrhotic patients. On the other hand, ARFI technology mounts over a last generation US device, so that ARFI-US offers assessment of liver stiffness plus, in expert hands, high quality imaging of the liver and the rest of the abdominal cavity.

The lack of liver histology is a major limitation in our study. Paired biopsies are golden reference to finally validate ARFI-US as a tool to determine the extent of LF. Interestingly, one study that used ARFI-US in patients with liver biopsy found a median of 1.1 m/s in healthy volunteers (17). This value is very close to the median of 1.3 m/s that we observed in subjects with TE value of <7.1 KPa (Metavir F0-F1). The accuracy of TE to detect liver cirrhosis by histology has been shown to be very high, with AUROC curves of 0.89 to 0.98 (13-14). For this reason we opted for testing the validity of ARFI-US to detect TE values corresponding to cirrhosis (>14.5 KPa). The high AUROC curve found allowed

us to determine that the best ARFI-US cut-off point for the diagnosis of cirrhosis is 2.2 m/s. Two recent studies have determined liver elasticity of 1.8 to 2.0 m/s as the best cut-offs for cirrhosis as diagnosed by liver biopsy (17,18).

In conclusion, ARFI-US shares the physical principle of TE for the estimation of LF, what renders high concordance between both techniques. It is very likely that ARFI-US as TE will not be valid to determine low-moderate levels of LF. Conversely, ARFI-US is expected to be very useful for the diagnosis of advanced LF and cirrhosis, which is very relevant clinical information in patients with chronic liver diseases.

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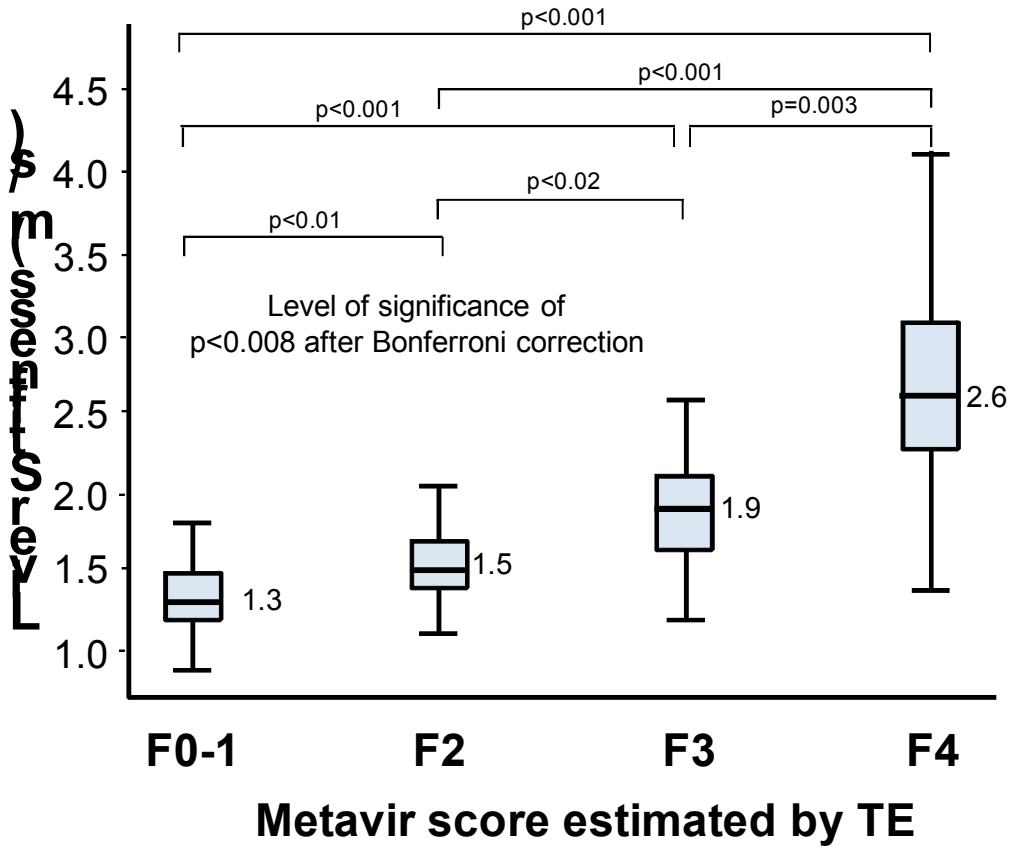
Table 1. Baseline characteristics of patients

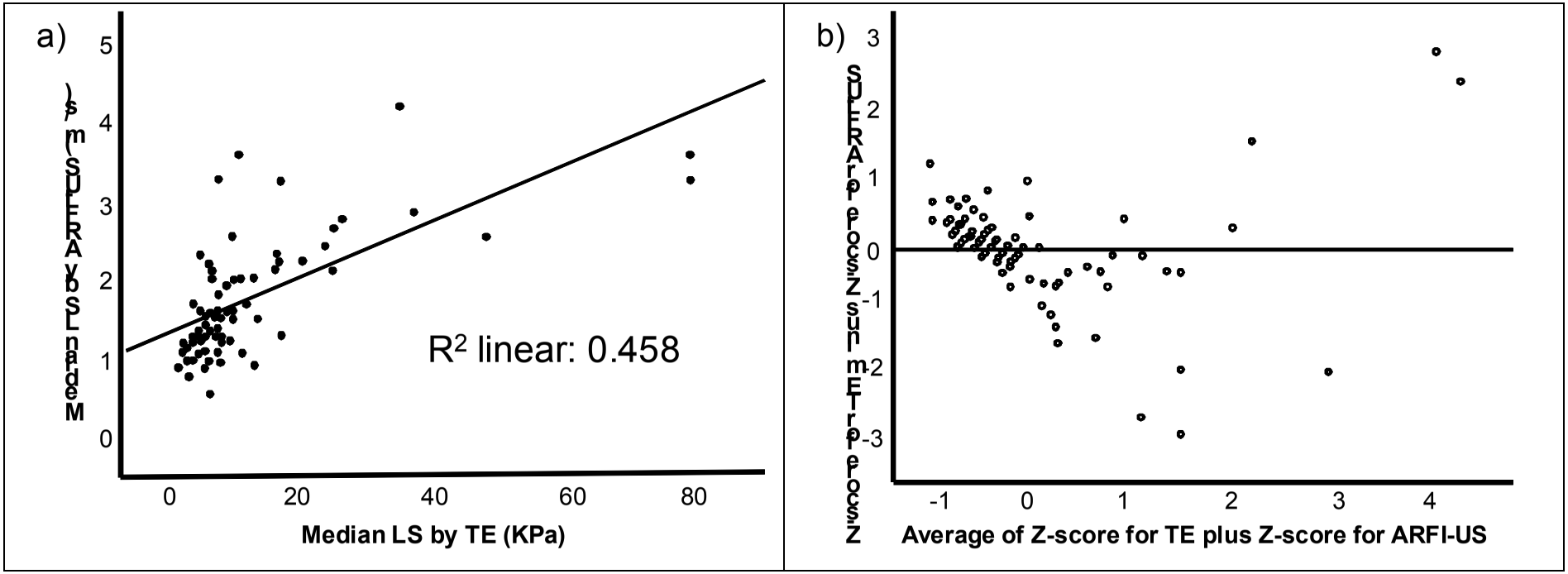
No. of Patients	80
Median age (IQR) years-old	46 (42-55)
Male sex (%)	64 (78)
Median AST (IQR) IU/L	31 (25-53)
Median ALT (IQR) IU/L	34 (26-57)
Median CD4 count (IQR) cells/mm^3	473 (367-862)
HCV monoinfection (%)	32 (42)
HCV-HIV coinfection (%)	20 (27)
HBV monoinfection (%)	3 (4)
HBV-HIV coinfection (%)	4 (5)
HIV-HCV-HBV triple infection (%)	3 (4)
HIV monoinfection (%)	14 (18)

Figure 1. Box-Plot for liver stiffness as measured by ARFI-US, across Metavir scores established by TE.



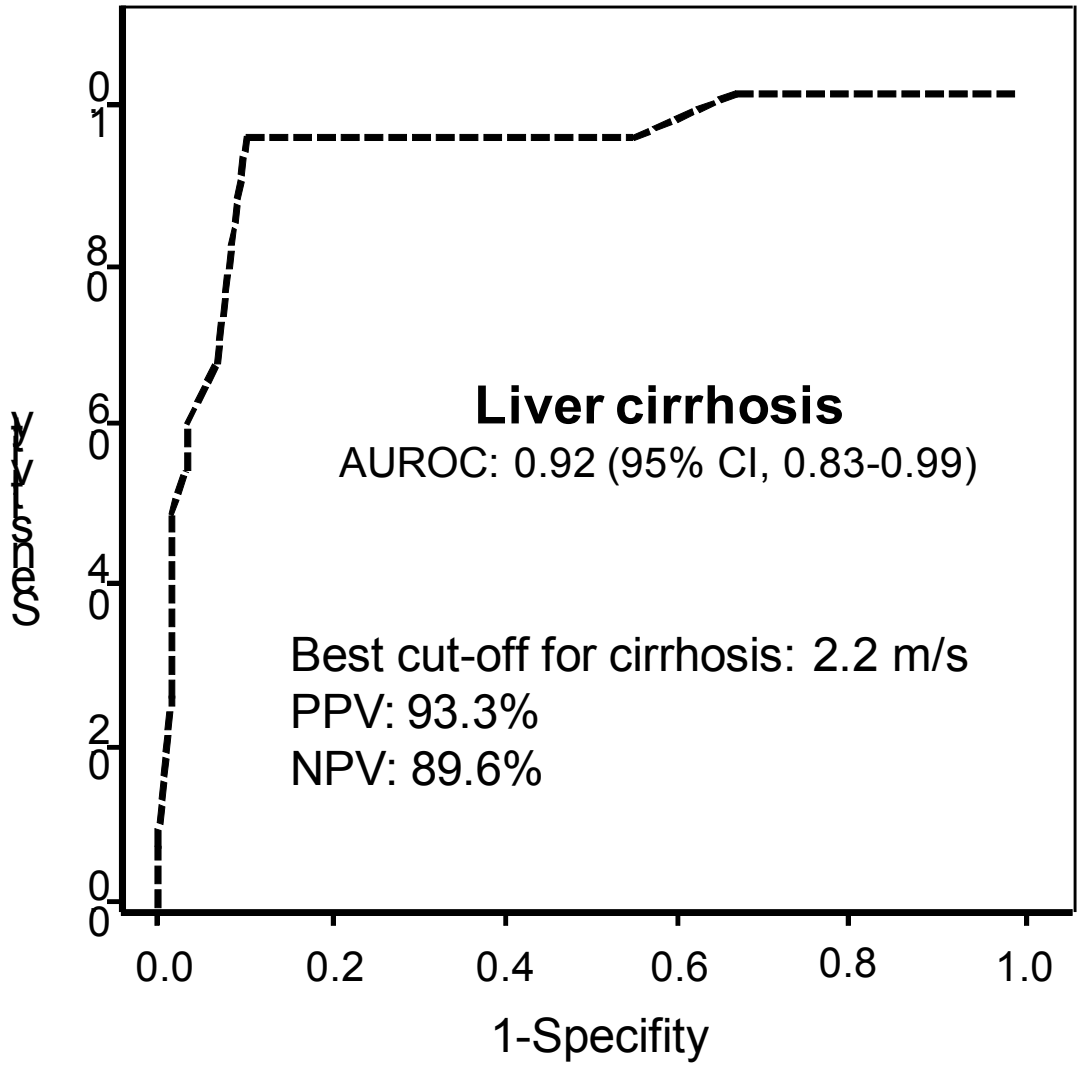
Line, median; rectangle, inter quartile range; whiskers, extreme values.

Figure 2. Scatter Plot (a) and Bland-Altman (b) representation for TE and ARFI-US



LS, liver stiffness; TE, transient elastometry; ARFI-US, acoustic radiation force impulse ultrasound.

Figure 3. ROC curve for the estimation by ARFI-US of liver cirrhosis, according to TE.



PPV, positive predictive value; NPV, negative predictive value

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Original article

Incidence of liver cirrhosis in HIV-infected patients with chronic hepatitis B or C in the era of highly active antiretroviral therapy

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Background: Longitudinal assessment of liver fibrosis with transient elastometry (TE) in patients with chronic viral hepatitis is becoming routine clinical practice in many clinics, as this procedure is non-invasive, easy to perform and relatively inexpensive, allowing early detection of cirrhosis. Herein, we examine the incidence of cirrhosis, using TE assessment, in HIV-infected individuals with chronic hepatitis B or C receiving highly active antiretroviral therapy (HAART).
Methods: A longitudinal study was performed on a cohort of HIV-infected patients with chronic hepatitis B or C who were followed since 2004 at Hospital Carlos III (Madrid, Spain) with periodic TE assessments. The primary outcome was the development of cirrhosis, defined as liver stiffness >12.5 KPa.
Results: A total of 508 HIV-infected patients were examined, of whom 54 developed liver cirrhosis during a mean ±SD follow-up of 2.6 ±1.0 years (overall incidence was 41.13 cases per 1,000 person-years). The risk of developing cirrhosis was significantly higher in 297 HCV-RNA-positive patients (either untreated or non-responders to hepatitis C therapy) compared with 55 patients who had cleared HCV with therapy (odds ratio 3.73, 95% confidence interval 1.06–13.17; P=0.04). By contrast, the risk of developing cirrhosis was low and similar in 24 HIV–HBV-coinfected patients under long-term suppressive HBV therapy (mainly tenofovir disoproxil fumarate), 132 HIV-infected patients without chronic liver disease and those who had cleared HCV with therapy.
Conclusions: Development of liver cirrhosis in HIV-infected individuals in the HAART era is mainly associated with active HCV coinfection. The risk of developing cirrhosis is negligible in patients who cleared HCV with therapy, as well as in HIV–HBV-coinfected patients on long-term suppressive tenofovir disoproxil fumarate therapy.

Introduction

Since the advent of highly active antiretroviral therapy (HAART) in the late 1990s, liver-related mortality has steadily become one of leading causes of non-AIDS-related death in HIV-infected individuals [1]. With large recovered CD4+ T-cell counts [7,8]. The mechanisms underlying the accelerated liver fibrosis progression characteristically seen in HIV-infected individuals with chronic viral hepatitis are not well understood, although

Introduction

Since the advent of highly active antiretroviral therapy (HAART) in the late nineties, liver-related mortality has steadily become one of leading causes of non-AIDS related death in HIV+ individuals [1]. With large variability depending on the prevalence of risk factors for liver disease, around 8 to 18% of HIV+ persons may currently show liver cirrhosis, and chronic viral hepatitis is generally the most common cause [2-4]. Coinfection with HIV leads to faster liver fibrosis progression in patients with chronic viral hepatitis [2,5,6], especially in those with low CD4 counts, although it do not seem to normalize completely in patients on successful HAART and recovered CD4 counts [7,8]. The mechanisms underlying the accelerated liver fibrosis progression characteristically seen in HIV+ persons with chronic viral hepatitis are not well understood, although HIV itself, immunedeficiency and/or antiretroviral-related toxicity might play a role [9-12].

Although some antiretrovirals have been implicated in liver damage [13-16], it is clear that the use of HAART diminishes liver-related deaths and improves survival in HIV+ patients with chronic viral hepatitis [17,18]. Cohort studies have demonstrated a reduction in the hepatic necro-inflammatory activity and a reduction in liver disease in patients under HAART [19].

Besides the use of HAART for minimizing the deleterious impact of HIV infection on liver damage in patients with chronic viral hepatitis, treatment of either HBV or HCV infections with specific antivirals has demonstrated to significantly reduce liver fibrosis progression, development of hepatic events and mortality [20-29]. A halt or even regression of liver fibrosis may be recognized in the subset of patients who keep HBV persistently suppressed [20,21] or clear HCV following a course of pegylated interferon plus ribavirin [25-29].

Cirrhosis is the final step of liver fibrosis progression and its diagnosis is critical in patients with chronic liver disease. The recent availability of non-invasive tools to estimate liver fibrosis has allowed circumvent the limitations of liver biopsy as procedure for staging hepatic fibrosis [30]. Transient elastometry (TE) is increasingly becoming standard method to longitudinally assess liver fibrosis in patients with chronic liver disease, with good concordance with histology, especially for the diagnosis of advanced liver fibrosis stages [31]. In HIV+ patients with chronic viral hepatitis, accuracies above 90% have been reported for diagnosing cirrhosis when stiffness values are above certain thresholds [32,33]. The aim of this study was to examine the progression of liver fibrosis to cirrhosis in a relatively large group of HIV+ individuals with chronic hepatitis either B or C and the impact of HAART.

Patients and Methods

Study population. A longitudinal retrospective study was conducted on a cohort of HIV+ patients on regular follow-up at one large HIV outpatient clinic in Madrid, Spain, who had underwent at least two separate liver fibrosis examinations using TE since October 2004 until February 2009. Patients with a diagnosis of cirrhosis at entry were excluded. Demographics, clinical and laboratory information was obtained from computerized medical registers.

Patients were classified into four main groups: i) HCV-coinfected individuals who either never had been exposed to HCV therapy or had failed interferon-based treatment; ii) HCV-coinfected patients who had cleared HCV following a course of HCV treatment in the past; iii) HIV-HBV coinfected subjects, and iv) HIV+ individuals with no evidence of chronic liver disease. Records of alcohol abuse (daily intake >50 g/dL) were based on medical records.

***Liver fibrosis assessment**. Transient elastometry (FibroScan®, Echosens)* was performed following manufacturer's instructions [34]. Briefly, a minimum of ten valid measurements through an intercostal space on the right lobe of the liver were obtained. Patients were placed in supine decubitus position with the right arm in abduction; then, the probe of the system was applied between the ribs. The median value was assumed to be representative of liver stiffness and median liver stiffness values were expressed in kilopascals (KPa). A set of measurements was considered to be reliable if the success rate was ≥70% and the interquartile range was less than one-third of the median liver stiffness value. Unreliable measurements were excluded from the analysis. All measurements were obtained from three trained operators using a single device.

The primary outcome was the development of liver cirrhosis in HIV+ patients with prior liver stiffness values below 12.5 KPa. In prior studies, this threshold in liver stiffness has shown an accuracy of 92% for diagnosing cirrhosis, with a negative predictive value of 96% and a positive predictive value of 74% [31]. Liver stiffness values <7.0, between 7.1 and 9.4, and between 9.5 and 12.5 were considered as corresponding to Metavir scores F0-F1, F2 and F3, respectively [31].

***Laboratory evaluation**.* All patients had standard laboratory assessments performed by licensed clinical laboratories, including a complete blood cell count, serum chemistry panels, alanine aminotransferase (ALT) and aspartate transferase (AST), CD4 cell counts and plasma HIV-RNA levels. Serum HBsAg and HBeAg were analyzed by a commercial enzyme immunoassays (EIA), using AxSYM HBsAg (v2), AxSYM HBeAg (v2) and AxSym anti-HBe (Abbott Laboratories, North Chicago, IL, USA). Total HDV antibodies were analyzed using a commercial EIA (Radim Iberica, Barcelona, Spain). Serum HBV-DNA and HCV-RNA extraction was carried out using the Qiagen DNA kit (Qiagen, Mannheim, Germany), following manufacturer's instructions. Serum HBV-DNA and HCV-RNA were measured using real-time PCR assays (Roche Cobas Taqman, Barcelona, Spain), which have a lower detection limit of 10 IU/mL for either nucleic acid. HBV and HCV genotyping were performed using Inno-Lipa (Innogenetics, Ghent, Belgium).

***Statistical analysis**.* Descriptive statistics were expressed as mean and standard deviations. Multivariate logistic regression analyses were performed to calculate the odds ratio (OR) and 95% confidence intervals (95% CI) for developing cirrhosis. The main variables included in this analysis were hepatitis virus coinfection and HCV clearance following interferon-based therapy. The model was adjusted for the most relevant baseline characteristics, including age, gender, ALT, CD4 count, CD4 nadir, plasma HIV-RNA, alcohol abuse, intravenous drug use and baseline liver stiffness. The most influent of these variables was examined following a multivariate stepwise logistic regression, using p values for entry and exit of <0.05 and >0.10, respectively. Based on these criteria, baseline liver stiffness values and ALT were the chosen variables. The SPSS software package version 15.0 (SPSS Inc., Chicago, IL) was used in all instances. All tests were two-tailed with p values only <0.05 considered as significant.

Results

Study population. A total of 2,168 HIV+ patients were the original HIV cohort established in year 2004. From them, prospective evaluation using TE with at least two measurements was available for 672 patients. At entry, 164 of these subjects had already cirrhosis and were excluded from further analysis. Thus, the study population was performed on 508 HIV+ patients. The mean time between the first

and last TE examination was 2.6 (±1.0) years. The main baseline characteristics of the study population are depicted in **Table 1**.

Incidence of liver cirrhosis. A total of 54 out of 508 patients (10.6%) developed cirrhosis during the study period, which represents an overall incidence of cirrhosis of 41.13 cases per 1000 persons-year. Patients with active chronic hepatitis C, either because never had been treated or because had failed a prior interferon-based treatment, had a more than 2.5-fold greater incidence of cirrhosis than HCV-seropositive individuals who had cleared the virus following a course of interferon-based therapy [42/297 (14.1%) vs 3/55 (5.4%)]. On the other hand, only a minority of patients coinfected with HIV and HBV (1 out of 24; 4.2%) and of HIV+ subjects without chronic viral hepatitis (8 out of 132; 6.1%) developed cirrhosis during the study period (**Table 2**). It should be noted that progression to cirrhosis in these subjects was almost always associated to concomitant alcohol abuse.

Univariate and multivariate logistic regression analyses adjusted by baseline liver stiffness and ALT values were performed to measure the effect of HCV replication on liver cirrhosis progression (**Table 2**). The risk of developing liver cirrhosis was significantly higher in HCV viremic patients (either untreated patients or failures) than in patients who cleared the virus following HCV therapy (p=0.04). In contrast, HIV-HBV coinfected patients with suppressed viral replication mainly under tenofovir therapy displayed a low and similar risk of developing cirrhosis than HIV+ control patients without chronic viral hepatitis. Moreover, there were no significant differences in the risk of developing cirrhosis comparing these two groups with the subset of patients who cleared HCV with therapy. Finally, in this model baseline liver stiffness was independently associated with the risk of developing cirrhosis (OR: 1.55; 95% CI: 1.35 to 1.89; p<0.001) while ALT values were not (OR: 1.00; 95% CI: 0.99 to 1.08; p=0.09].

Discussion

The advent of potent antiretroviral therapy has modified the main causes of morbidity and mortality in HIV+ patients. Non-AIDS conditions are now replacing opportunistic infections and malignancies as the majority of infected subjects no longer show advanced immunodeficiency [35]. Liver disease and cardiovascular events are currently among the most frequent causes of hospitalization and death in HIV+ individuals under regular medical care [1]. Hepatic complications specially are seen in subjects with underlying chronic viral hepatitis. In our study we showed that chronic hepatitis C but not chronic hepatitis B is the main responsible for the desfavourable outcome. Moreover, control of HBV replication with potent antivirals as tenofovir and clearance of HCV with interferon-based therapies seem to largely counteract the progression of liver fibrosis to cirrhosis in the coinfected population, in such a way that HIV-HCV coinfected patients who have not been treated or failed therapy are by far the ones currently progressing to cirrhosis.

Our results are in line with recent data that highlight that serum HBV-DNA level is the main driver of the natural history of chronic hepatitis B, with a positive correlation between baseline viral load and risk for developing cirrhosis in the long-term [36]. Accordingly, prolonged complete suppression of HBV viremia with antiviral therapy results in a halt and/or regression of liver fibrosis in HBsAg+ carriers [20,21]. Similarly, clearance of HCV following a course of interferon-based therapy seems to be associated with an amelioration or even reversion of liver fibrosis and reduced incidence of liver complications in chronic hepatitis C patients [23-29]. While the widespread use of tenofovir as part of HIV therapy [37] and its success as anti-HBV agent [38,39] may have both resulted in a broad control of HBV-related disease in

HIV-HBV coinfected patients, the situation is totally different for chronic hepatitis C. Treatment with peginterferon-ribavirin is prescribed in only a small proportion of HIV-HCV coinfected patients [40,41]; furthermore HCV clearance is obtained in only 25-40% of treated patients [42-44]. Altogether, these facts explain that progression to cirrhosis in HIV+ patients will largely occur in HIV-HCV coinfected individuals. While waiting for new and more effective treatments against HCV in this population [45], efforts to identify subjects who may benefit from current therapy must be encouraged. Moreover, avoidance of potentially hepatotoxic drugs, including some antiretroviral agents (eg, didanosine and stavudine) [11,14,15], adequate management of metabolic abnormalities (eg, dislipidemias and insulin resistance) which may accelerate liver damage [11,16,46,47] and strong advise against alcohol abuse are warranted. Of note, in our study progression to cirrhosis in patients without chronic viral hepatitis was rare and mainly seen in association with alcohol abuse.

In summary, the incidence of cirrhosis in HIV+ patients in the HAART era is mainly associated to HCV coinfection. While the advent of new antivirals against HCV will fuel treatment of this population, the current data support that in the absence of contraindication for peginterferon and/or ribavirin use, treatment of chronic hepatitis C must be pursued in this population. It is very encouraging that HCV clearance following a successful course of interferon-based therapy as well as prolonged HBV suppression with potent antivirals as tenofovir are both associated with a halt or even reversion of liver fibrosis in HIV+ patients with chronic viral hepatitis.

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Table 2: Main baseline characteristics of the study population.

Variables	Values
Total of patients	508
Male gender (%)	384 (76)
Mean age (SD; years)	43 (6)
HIV transmission route (%)	
Intravenous drug use	325 (64)
Men who have sex with men	107 (21)
Heterosexual contact	37 (7)
Others / Unknown	39 (8)
Alcohol abuse	53 (10)
Chronic viral hepatitis (%)	
No (controls)	132 (26)
HBV	24 (4.7)
HCV	352 (69)
HCV not treated or non-SVR	297 (58.5)
HCV with SVR	55 (10.8)
HCV infection characteristics‡	
Mean log_{10} HCV-RNA (IU/mL; SD)	4.3 (2.2)
HCV-RNA >500,000 IU/mL (%)	134 (39)
HCV genotypes 1 or 4 (%)	244 (48)
Unknown HCV genotypes (%)	20 (6)
HBV infection characteristics*	
Mean log_{10} HBV-DNA (IU/mL; SD)	1 (0)
Undetectable HBV-DNA (%)	100
Under tenofovir (%)	87.5
HDV superinfection (%)	6 (25)
Liver parameters	
Mean AST (IU/ml, %)	48.5 (60)
Mean ALT (IU/ml, %)	57.7 (54)
Mean liver stiffness (KPa)	7.0 (2.3)
LS values <7.1 KPa (%)	295 (58)
LS between 7.0 and 9.5 KPa (%)	135 (27)
LS between 9.4 and 12.4 KPa (%)	78 (15)
HIV infection characteristics	
Mean log_{10} HIV-RNA (SD, copies/mL)	2.1 (0.9)
HIV-RNA <50 copies/mL (%)	372 (73)
Mean CD4 count nadir (SD; cells/mm^3)	271 (187)
Mean CD4 count (SD; cells/mm^3)	547 (306)
CD4 count >200 cells/mm^3 (%)	467 (92)

HCV, hepatitis C virus; HBV, hepatitis B virus; HDV, hepatitis Delta virus; SVR, sustained virologic response; LS, liver stiffness; SD, standard deviation; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

‡ *HCV-coinfected patients (n=344)*

Table 2: Incidence and odds ratio for developing cirrhosis in HIV-infected patients.

	Incidence				Crude OR		Adjusted OR	
	No. patients	Cirrhosis (%)	Person-years (py)	Incidence per 1000 py (95% CI)	OR (95% CI)	p	OR (95% CI)	p
Total	508	54 (10.6%)	1313	41.13 (30.16-52.10)	-	-	-	-
HIV	132 (26%)	8 (6.1%)	343	23.33 (7.16; 39.49)	1.18 (0.29; 4.38)	0.87	2.03 (0.48; 8.57)	0.33
HIV-HBV	24 (4.7%)	1 (4.2%)	62	16.13 (0.00; 47.74)	0.75 (0.07; 7.63)	0.81	0.69 (0.07; 7.56)	0.81
HIV-HCV not treated or without SVR	297 (58.5%)	42 (14.1%)	772	54.40 (37.95; 70.86)	2.85 (0.85; 9.56)	0.09	3.73 (1.06; 13.17)	0.04
HIV-HCV with SVR	55 (10.8%)	3 (5.5%)	143	20.98 (0.00; 44.72)	1	-	1	-

HCV, hepatitis C virus; HBV, hepatitis B virus; SVR, sustained virologic response; OR, odds ratio; 95% CI, confidence interval of 95%.

Survival of HIV-infected patients with compensated liver cirrhosis

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Introduction: Since the advent of HAART, liver-related mortality has become the leading cause of non-AIDS deaths in HIV-infected patients in western countries, complications of end-stage liver disease due to chronic hepatitis B, chronic hepatitis C or both being mainly responsible.

Methods: The incidence and predictors of mortality were examined in HIV-infected patients with compensated liver cirrhosis. The accuracy of three different methods (elastometry, Child–Pugh and Model for End-Stage Liver Disease scores) to predict mortality was further examined. Cirrhosis was defined for hepatic elastometry values above 14.5 kPa.

Results: A total of 194 (11.4%) out of 1706 HIV-positive individuals were cirrhotic and were prospectively followed since October 2004 until December 2008. Overall, 89% of cirrhotic individuals had chronic hepatitis C, 10.3% chronic hepatitis B, 4.6% hepatitis delta and 4.1% liver disease of other causes or unknown cause. The overall mortality rate was 5.8 deaths per 100 patient-years. Multivariate analyses showed that age of at least 50 years (hazard ratio 4.76, 95% confidence interval 1.66–13.59, $P = 0.004$), CD4 cell counts below 200 cells/μl (hazard ratio 3.01, 95% confidence interval 1.26–7.23, $P = 0.03$) and detectable plasma HIV-RNA (hazard ratio 3.97, 95% CI, 1.53–10.27, $P = 0.005$) were associated with mortality. A baseline Model for End-stage Liver Disease score of at least 11 ($P = 0.03$) and hepatic elastometry values above 28.75 kPa ($P = 0.001$) were independent predictors of mortality.

Conclusion: The death rate in HIV-infected patients with compensated liver cirrhosis in the HAART era is 5.8% yearly, higher than mortality previously reported for either HIV-uninfected individuals with cirrhosis or noncirrhotic HIV-positive patients. Factors associated with mortality were older age, low CD4 cell counts and detectable plasma HIV-RNA. Both Model for End-Stage Liver Disease and especially hepatic elastometry accurately predicted mortality in this population.

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Keywords: Child–Pugh score, elastometry, hepatitis C, HIV, liver cirrhosis, Model for End-Stage Liver Disease score, mortality

Introduction

Liver cirrhosis is the final stage of several conditions, which primarily cause persistent hepatic injury. Chronic infection due to hepatitis C virus (HCV), hepatitis B virus (HBV), hepatitis delta virus or all, and alcohol abuse are the most common causes of liver cirrhosis worldwide [1]. Given that, all these conditions are quite prevalent in

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Introduction

Liver cirrhosis is the final stage of several conditions which primarily cause persistent hepatic injury. Chronic infection due to hepatitis C virus (HCV), hepatitis B virus (HBV) and/or hepatitis delta virus (HDV) and alcohol abuse are the most common causes of liver cirrhosis worldwide [1]. Given that all these conditions are quite prevalent in HIV-infected individuals, it is not surprising that liver disease has become in recent years one of the leading causes of death in HIV-positive patients [2-4]. This is particularly manifest in developed countries, where the introduction of highly active antiretroviral therapy (HAART) in 1996 has been followed by a dramatic decline in the incidence of opportunistic infections and deaths associated to advanced immunodeficiency [5,6].

Liver fibrosis progression is accelerated in HIV-infected individuals with chronic viral hepatitis B and/or C, especially in patients with low CD4 counts [7-11]. In the absence of successful treatment for viral hepatitis, progression to liver cirrhosis may occur in a substantial proportion of these patients [12,13]. Once cirrhosis is established, decompensation events, including ascites, encephalopathy, variceal bleeding, jaundice, hepatorenal syndrome or even liver cancer may steadily develop, shortening survival [14,15]. Liver transplantation is often the only medical intervention which may rescue from short-term death patients with decompensated cirrhosis. However, liver transplants are particularly challenging in HIV-infected persons [16].

The recognition of early stages of liver cirrhosis may allow set up of preventive measures to reduce decompensation events. As example, the use of beta-blockers or variceal band ligations may reduce the risk of bleeding in subjects with esophageal varices [17]. Given that liver biopsies can not be made routinely and periodically in all individuals with chronic liver disease, the use of non-invasive tests for estimating liver fibrosis staging has rapidly gained support in clinical practice [18]. These tests are particularly accurate for diagnosing liver cirrhosis [19,20]. Using either serum fibrosis biomarker indexes (e.g., FIB-4, APRI, SHASTA, Fibrotest, etc) and/or transient elastometry, the prevalence of liver cirrhosis can be estimated in large populations, avoiding the bias introduced when only patients who underwent biopsies are considered.

The identification of the main predictors of mortality in cirrhotic patients with HIV infection is important, especially considering that the opportunities for liver transplantation are growing in this population [16]. In HIV-negative individuals, both Child-Pugh and MELD scores have shown to accurately predict mortality in the short and mid term, allowing prioritization and allocation of organs [21-23]. The value of these tools in HIV-infected patients has mainly been examined in decompensated cirrhosis [24-27] and information for compensated cirrhosis is scarce [27,28]. Herein, we examine the rate and predictors of survival in HIV-positive patients with compensated liver cirrhosis and assess different methods to predict mortality.

Patients and Methods

Study population. Since October 2004 to December 2008, a total of 194 HIV-infected individuals had been diagnosed of liver cirrhosis using transient elastometry (liver stiffness values above 14.5 KPa) at our institution. During this period, 2381 distinct HIV-positive individuals had been attended, of whom 1706 (71.6%) underwent at least one FibroScan evaluation. It is routine practice at our institution to perform a yearly Fibroscan examination in all HIV-infected individuals, regardless be present any underlying chronic liver disease. The overall estimated prevalence of compensated liver cirrhosis in this population was 11.4%. The threshold used to define liver cirrhosis using transient elastometry has already been shown to

accurately predict cirrhosis in paired liver biopsies, including studies conducted in HIV populations [18,19,29,30].

A prospective dynamic cohort with all HIV-infected patients with compensated liver cirrhosis was created in October 2004 and followed until December 2008. Patients with terminal end-stage liver disease and/or hepatocellular carcinoma at first assessment were excluded. Clinical and laboratory data were recorded at the time of inclusion into the dynamic cohort. The entry time was the moment of the first reliable transient elastometry measurement above 14.5 KPa. MELD [31] and Child-Pugh scores [32] were calculated for each patient at that time. Deaths were examined in all clinical records and the vital status was cross-checked in January 31st 2009 in the National Death Registry of the Ministry of Health [33], censoring for December 31st 2008 in order to allow delays in case reporting.

Statistical analysis

Descriptive analysis of patient's characteristics was carried out using frequency distributions or median and interquartile ranges (IQR) when appropriate. Person-years of follow-up were calculated from the date of entering the cohort until the date of the last visit or death. Mortality rates were calculated as the number of deaths per 100 person-years.

Kaplan-Meier estimates of the cumulative probability of survival according to baseline transient elastometry values, Child-Pugh and MELD scores were built. The severity of baseline liver cirrhosis was categorized for each of these tools as follows: tertiles for transient elastometry; A (5-6 points), B (7-9 points) or C (10-15) for the Child-Pugh score; and values <11 or ≥11 for MELD. The predictive value of mortality was then compared using the log rank test.

Cox proportional hazard models were built to assess the predictive value of transient elastometry, Child-Pugh or MELD scores for the risk of death, adjusting for potential confounders and testing for effect modification. Wald tests were used to derive p values. All statistical analyses were performed using Stata 10 (Stata Corp., College Station, TX).

Results

Study population. The 194 HIV-infected patients identified with liver cirrhosis using transient elastometry contributed with 434.69 person-years of follow-up (median 2.35, IQR: 1.4-5.5 years). **Table 1** displays the main demographic characteristics of these individuals at entry. Mean age was 44.2 years; 79.9% were male: 83.5% had a past history of intravenous drug use (IDU). Chronic hepatitis C was the most prevalent viral hepatitis, being found in 89% of the study population. Of note, infection with HCV genotypes 1 or 4 represented 59% of cases. Chronic hepatitis B was present in 10.3% and chronic delta hepatitis in 4.6% of cirrhotic patients. Finally, liver disease of other etiologies (i.e., alcohol abuse, autoimmune hepatitis, steatohepatitis, etc) or unknown cause was seen in 4.1% of cases. The median CD4 count in the study population was 325 cells/mm^3 at study entry and the median plasma HIV-RNA was 1.7 $\log_{10}$ copies/mL. Overall 93% of cirrhotic patients were on antiretroviral therapy, and accordingly 65% had plasma HIV-RNA <50 copies/mL and 77% had CD4 counts ≥200 cells/mm^3. Median AST and ALT values were 67 and 59 IU/L, respectively.

The median baseline liver stiffness was 21.2 KPa. Following allocation of patients by tertiles, 34% of patients had values between 14.5 and 17.7, 33% between 17.8 and 28.5 and 33% between 28.6 and 75 KPa. All patients had Child-Pugh scores A or B, in a proportion of 77.3% and 16.6%, respectively. Patients with decompensated liver

cirrhosis and/or Child-Pugh score C at recruitment were excluded. The median MELD score was 9.6, with 66% of patients having MELD scores <11.

Outcome. Deaths occurred in 25 (12.5%) subjects during follow-up, yielding an all-cause mortality rate of 5.8 deaths per 100 patient-years. Mortality rates according to baseline characteristics are shown in **Table 2**. Considering tertiles of baseline liver stiffness values (14.5-17.7, 17.8-28.5, and 28.6-75), the mortality rate was 4.1, 1.9 and 12.7 deaths per 100 patient-years, respectively. Person-time was different when classifying subjects based on MELD or Child-Plough scores. Mortality rate in patients with MELD scores <11 and ≥11 was 3.9 and 11.7 deaths per 100 patient-years, respectively. Patients classified as Child-Pugh A and B had mortality rates of 5.3 and 10.4 deaths per 100 patient-years, respectively.

Hazards of death. Univariate and multivariate Cox regression analyses for risk factors associated with death in the study population are displayed in **Table 3**. In a non-adjusted analysis, patients with elastometry values ≥28.75 KPa (hazard ratio [HR]: 2.99, 95% CI: 1.17-7.65, p=0.002) had a higher risk of death. When a multivariate analysis corrected for age, gender, CD4 count, plasma HIV-RNA, mode of transmission, and liver disease etiology, a liver stiffness value >28.75 (HR: 3.46, 95% CI: 1.24-9.69, p=0.02) was predictor of mortality. **Figure 1a** displays the survival by baseline liver stiffness tertiles; again statistical differences in survival only were seen for elastometry values >28.75 KPa (log-rank test p=0.001).

The risk of death stratified by baseline Child-Pugh scores is also displayed in **Table 3.** In the unadjusted model, the relative risk of death did not differ between patients with Child-Pugh class A or B (HR: 1.85, 95% CI: 0.73-4.66, p=0.20). After adjustments for age, gender, CD4 count, plasma HIV-RNA, mode of transmission, and liver disease etiology, a Child-Pugh score class B tended to be associated with a higher risk of mortality (HR: 2.07, 95%CI: 0.75-5.71, p=0.16) but without statistical significance. In the Kaplan-Meier curve (**Figure 1b**), this not significant trend in differences between patients with Child-Pugh class A and B was reproduced.

Finally, the risk of death stratified by baseline MELD score is displayed in **Table 3**. In the multivariate analysis adjusted for age, gender, CD4 count, plasma HIV-RNA, mode of transmission, and liver disease etiology, patients with a MELD score ≥11 had a higher risk of death (HR: 3.85, 95% CI: 1.53-9.66, p=0.004) than those with lower MELD scores. Likewise, survival was significantly lower in patients with MELD ≥11 than in those with lower MELD scores (**Figure 1c**).

Discussion

This study examined the rate and predictors of survival in HIV-positive patients with compensated liver cirrhosis. Furthermore, we examined different methods to predict mortality in this population. Overall mortality rates in HIV-infected individuals have declined dramatically in the HAART era, with current estimates ranging from 1.3 to 1.6 deaths per 100 patient-years [34]. In our study, HIV-positive patients with compensated liver cirrhosis had a mortality of 5.8 deaths per 100 patient-years, which is almost 4-fold higher than in the general HIV population. The deleterious impact of liver cirrhosis on survival in HIV-infected persons has already been shown by others. In one study conducted between 1999 and 2004, the mortality rate was 7.1 deaths per 100 patient-years in HIV-positive cirrhotic patients [15]; however, in that study only 58% of subjects were under antiretroviral therapy while 93% of our study population was receiving HAART. A benefit of HAART on liver fibrosis progression and risk of liver-related complications and deaths in HIV-positive patients with chronic viral hepatitis B or C has been well proven [35-39]. In this regard, it is reassuring that

both low CD4 counts and detectable plasma HIV-RNA were independent predictors of mortality in our cirrhotic population, in whom chronic viral hepatitis represented more than 98% of all cases. Thus, our results further reinforce the current recommendation to provide antiretroviral therapy as soon as possible in all HIV-infected persons with chronic viral hepatitis [40-42].

The mortality rate we saw in HIV-infected patients with compensated cirrhosis was also higher than that previously reported in HIV-negative cirrhotics, in whom 3-4% annual rates of death have been recorded [43,44]. This occurred despite most HIV-positive cirrhotics in our study being treated with antiretroviral therapy. Thus, control of HIV replication and CD4 reconstitution with HAART might not completely overcome the deleterious impact of HIV infection on survival in HIV-positive cirrhotics.

In our study, older age was associated with increased mortality in HIV-positive patients with compensated liver cirrhosis. Other studies have found a similar strong influence of age on liver fibrosis progression and liver-related mortality in coinfected individuals [12,39,45]. In contrast with studies conducted in HIV-negative individuals with HCV-related liver cirrhosis, in which male gender was associated with accelerated liver fibrosis progression [46], in our cohort women showed nearly twice increased risk of death than men, although the difference did not reach statistical significance.

In our knowledge, our study shows for the first time that transient elastometry may predict mortality in patients with compensated liver cirrhosis. This observation is important since transient elastometry may allow diagnosis of cirrhosis in a substantial proportion of patients with chronic hepatic disease in whom liver biopsy is not performed. It is noteworthy that the prognostic value of transient elastometry has already been demonstrated for predicting clinical complications of end-stage liver disease, as esophageal varices [17,46]. In our study, liver stiffness values >28.75 in cirrhotic patients were significantly associated with shorter survival. This information may assist to prioritize persons who may be candidates for liver transplantation.

The MELD score predicts mortality in the short-term in cirrhotic patients without HIV infection [47] and recent observations have extended this value to cirrhotic HIV-infected patients [48,49]. In our study, the MELD score accurately predicted mortality, and a threshold of 11 predicted mid-term survival in HIV-positive cirrhotic patients. This information reinforces that HIV-positive cirrhotic patients should be considered for liver transplantation at lower MELD scores than HIV-negative individuals with cirrhosis in whom higher MELD scores better predict mortality.

Baseline Child-Pugh scores did not predict mortality in our HIV-positive population with liver cirrhosis. Although short-term survival tended to be shorter in patients with Child-Pugh class B than A, this difference vanished with extended follow-up. As pointed out by others [23], the heterogeneity of patients classified as Child-Pugh class B may explain this observation. The impact of this heterogeneity might be further pronounced in HIV-infected patients, as progression of liver fibrosis tends to be accelerated in this population. As in our study, in the study referred before by Murillas et al. [49], the Child-Pugh score did not predict mortality.

In summary, in a cohort of 194 cirrhotic HIV-positive patients, 89% of them with chronic hepatitis C, baseline transient elastometry values predicted mortality Further Studies are warranted to define what will be the best threshold in elastometric values to discriminate survival. A MELD score $\geq$11 was also associated with shorter survival in our series. Older age, low CD4 counts and detectable plasma HIV-RNA were predictors of increased mortality in this population.

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Table 3. Baseline characteristics of 194 HIV-infected patients with compensated liver cirrhosis.

Variable	No. (%)
Male gender	155 (79.9)
Age at entry, years, median (IQR)	44.2 (41-48)
<50	169 (87.1)
≥50	24 (12.4)
Unknown	1 (0.5)
Transmission Category	
IDU	162 (83.5)
MSM	18 (9)
Heterosexual	9 (4.6)
Unknown	5 (2.6)
Chronic Hepatitis C	172 (89)
HCV genotypes 1 or 4	115 (59)
HCV genotypes 2 or 3	37 (19)
Unknown or not typable	42 (22)
Median serum HCV-RNA, IU/mL (IQR)	489,000 (10-2,820,000)
Chronic Hepatitis B	20 (10.3)
Median serum HBV-DNA, IU/mL (IQR)	10 (10-10)
Chronic Hepatitis Delta	9 (4.6)
Other causes or unknown etiology of liver disease	8 (4.1)
Plasma HIV-RNA (log_{10} copies/mL), median (IQR)	1.7 (1.7-1.9)
≤1.7	126 (65)
>1.7	68 (35)
Patients on antiretroviral therapy	180 (93)
CD4 count (cells/mm^3), median (IQR)	325 (216-520)
<200	44 (23)
≥200	150 (77)
Median AST (IQR)	67 (44-101)
Median ALT (IQR)	59 (37-97)
Median albumin (IQR)	3.5 (3.2-3.9)
Median bilirubin (IQR)	1.2 (0.8-1.9)
Median INR (IQR)	1.2 (1.1-1.3)
Median TP (IQR)	80.1 (69.6-89)
Median platelets (IQR)	129 (87-166)
Liver stiffness (KPa), median (IQR)	21.2 (16.6-35.8)
14.5 – 17.7	66 (34)
17.8 - 28.5	64 (33)
28.6 – 75	64 (33)
Child-Pugh score	
A	150 (77.3)
B	32 (16.6)
Unknown	12 (6.1)
MELD score, median (IQR)	9.6 (8-12)
<11	128 (66.0)
≥11	59 (30.4)
Unknown	7 (3.6)
Median follow-up, years (IQR)	2.35 (1.4-5.5)

Table 2: Mortality rates (cases per 100 persons per year) in HIV-infected patients with compensated liver cirrhosis.

Variable	Person-years	Deaths	Death-rate × 100 py (95% CI)
Total	434.69	25	5.75 (3.9-8.5)
Gender			
Female	89.95	7	7.78 (3.7-16.3)
Male	344.74	18	5.22 (3.3-8.3)
Age (years)			
<50	392.60	19	4.84 (3.1-7.6)
≥50	41.53	6	14.5 (6.5-32.2)
Mode of HIV transmission			
IDU	362.14	21	5.7 (3.8-8.9)
MSM	39.45	3	7.6 (2.4-23.6)
Others	7.91	1	12.6 (1.8-89.7)
CD4 count (cells/mm^3)			
<200	89.01	9	10.1 (5.3-19.4)
≥200	345.68	16	4.6 (2.8-7.6)
Plasma HIV-RNA ($\log_{10}$ copies/mL)			
≤1.7	179.52	9	5.0 (2.6-9.6)
>1.7	78.00	10	12.8 (6.9-23.8)
Unknown	168.73	6	3.56 (1.6-7.9)
Chronic hepatitis C			
No	40.01	3	7.5 (2.4-23.3)
Yes	394.68	22	5.6 (3.7-8.5)
Chronic hepatitis B			
No	389.85	22	5.6 (3.7-8.6)
Yes	44.84	3	6.7 (2.2-20.75)
Transient elastometry (KPa)			
14.5 - 17.65	147.80	6	4.1 (1.8-9.0)
17.85 – 28.40	152.41	3	1.9 (0.6-6.1)
≥28.75	126.04	16	12.7 (7.8-20.1)

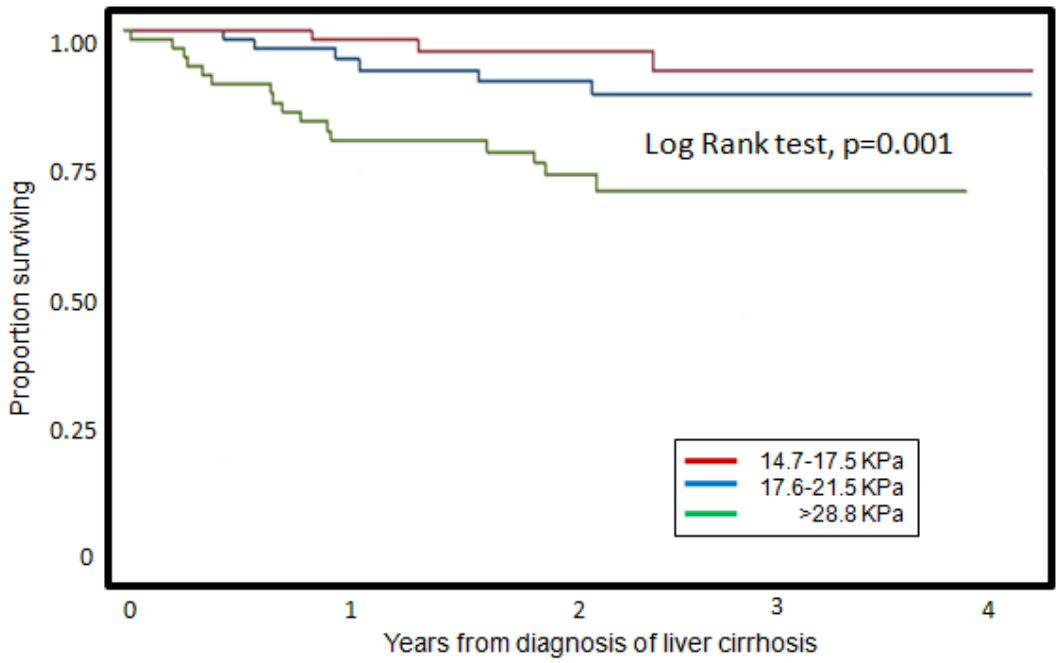
Table 3: Relative risk of death in cirrhotic HIV-infected patients according to baseline transient elastometry, Child-Pugh and MELD scores. Univariate and multivariate analyses of the effect of covariates.

	Transient elastometry				Child-Pugh score				MELD score			
	Unadjusted		Adjusted		Unadjusted		Adjusted		Unadjusted		Adjusted	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	P	HR (95% CI)	p	HR (95% CI)	p
Gender		0.29		0.18		0.40		0.08		0.40		0.02
Women	1.00		1.00		1.00		1.00		1.00		1.00	
Men	0.63 (0.26-1.50)		0.52 (0.21-1.34)		0.69 (0.29-1.65)		0.44 (0.18-1.09		0.69 (0.29-1.65)		0.34 (0.13-0.86)	
Age at entry, years		0.03		0.004		0.02		0.008		0.02		0.009
<50	1.00		1.00		1.00		1.00		1.00		1.00	
≥50	2.8 (1.11-7.04)		4.76 (1.66-13.60)		2.91 (1.15-7.36)		4.03 (1.43-11.33)		2.91 (1.15-7.35)		3.79 (1.41-10.66)	
Mode of transmission												
IDU	1.00		1.00		1.00		1.00		1.00		1.00	
MSM	1.35 (0.40-4.52)	0.63	1.79 (0.41-7.83)	0.44	1.22 (0.36-4.10)	0.75	1.51 (0.38-6.03)	0.56	1.22 (0.36-4.10)	0.75	1.90 (0.50-7.62)	0.35
Others	1.62 (0.22-12.10)	0.64	3.49 (0.44-27.83)	0.24	2.06 (0.28-15.40)	0.48	3.26 ((0.39-27.03)	0.27	2.06 (0.28-15.40)	0.48	2.59 (0.30-22.42)	0.39
CD4 count (cells/mm^3)		0.07		0.03		0.06		0.04		0.06		0.13
<200	1.00		1.00		1.00		1.00		1.00		1.00	
≥200	0.40 (0.17-1.06)		0.33 (0.12-0.91)		0.46 (0.20-1.05)		0.41 (0.47-0.97)		0.46 (0.20-1.05)		0.47 (0.20-1.13)	
Plasma HIV-RNA (log cop/mL)		0.04		0.005		0.01		0.003		0.18		0.04
≤1.7	1.00		1.00		1.00		1.00		1.00		1.00	
>1.7	2.53 (1.03-6.22)		3.97 (1.53-10.27)		1.72 (0.78-3.78)	0.18	2.28 (1.00-5.24)	0.05	1.72 (0.78-3.78)		2.39 (1.02-5.58)	
Chronic hepatitis C		0.86		0.60		0.71		0.96		0.71		0.92
No	1.00		1.00		1.00		1.00		1.00		1.00	
Yes	0.89 (0.27-2.99)		0.67 (0.15-3.01)		0.80 (0.24-2.67)		0.96 (0.24-3.81)		0.80 (0.24-2.67)		1.08 (0.26-4.43)	
Chronic hepatitis B		0.83		0.35		0.74		0.41		0.74		0.89
No	1.00		1.00		1.00		1.00		1.00		1.00	
Yes	1.14 (0.34-3.81)		1.96 (0.48-7.94)		1.22 (0.37-4.11)		1.76 (0.47-6.62)		1.22 (0.37-4.11)		1.11 (0.28-4.40)	
Liver fibrosis severity *		0.002		0.02		0.20		0.16		0.01		0.004
Low	1.00		1.00		1.00		1.00		1.00		1.00	
High	2.99 (1.17-7.65)		3.46 (1.24-9.69)		1.85 (0.73-4.66)		2.07 (0.75-5.71)		2.83 (1.29-6.22)		3.85 (1.53-9.66)	

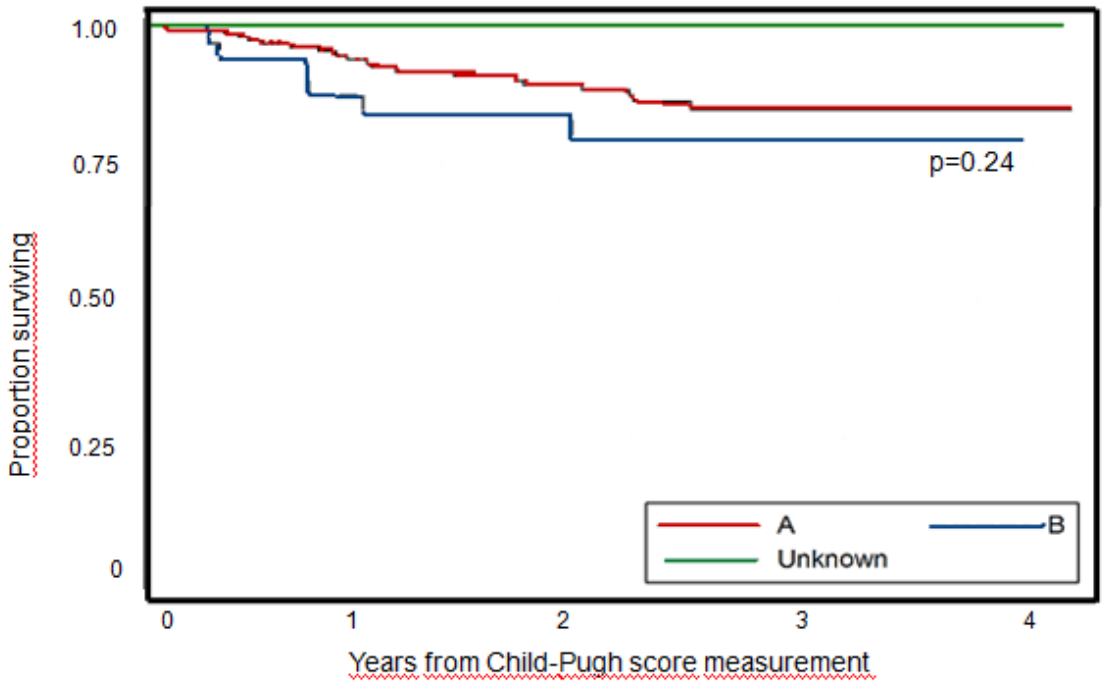
Liver fibrosis severity in this cirrhotic population was stratified according to each method. Using transient elastometry it was low (14.6-28.6 KPa) or high (>28.7 KPa). For Child-Pugh score, standard categories A and B were used. Finally, for the MELD score stratification was low (<11) or high (>11).

Figure 1. Survival of HIV-infected patients with liver cirrhosis, according to baseline transient elastometry (A), Child-Pugh (B), and MELD scores (C).

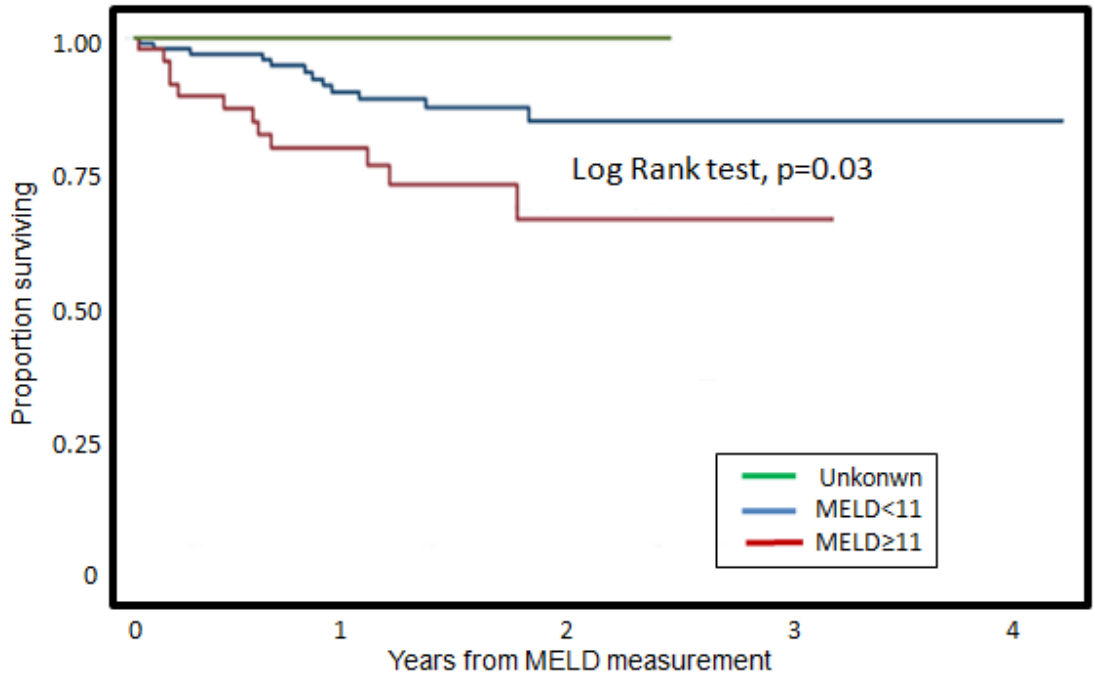
A)



B)



C)


1.00
0.75
0.50
0.25
0
Proportion surviving
Log Rank test, p=0.03
Unkonwn
MELD<11
MELD≥11
0
1
2
3
4
Years from MELD measurement

Discussão

O manuseio do paciente co-infectado com HIV e hepatites virais é um desafio na prática diária. Inúmeras peculiaridades devem ser recordadas desde o diagnóstico da co-infecção. Esta série de estudos apresentou diversos aspectos e inovações no seguimento desses pacientes.

É bem determinado que a maioria das decisões de tratamento nesses pacientes baseia-se no grau de fibrose hepática. O diagnóstico de diferentes graus de fibrose e cirrose hepática vem passando por momento único, no qual o papel definitivo da biópsia vem sendo questionado por suas inúmeras limitações como os já mencionados: erro amostral, variações intra e inter-observador, elevado custo e característica invasiva [1, 2].

O fato de ser invasivo traz o risco de complicações, além da dificuldade em realizar seguimento progressivo da fibrose hepática. Cada vez mais se reconhece que a fibrose hepática é um processo dinâmico [3], tanto na sua progressão como na sua regressão, o que faz com que o seguimento progressivo da mesma seja fundamental para o adequado manuseio dos pacientes.

A discussão sobre o diagnóstico não invasivo de diferentes graus de fibrose hepática tinha como fundamento inicial o papel de escores baseados em parâmetros sanguíneos [4]. O diagnóstico com procedimentos não-invasivos foi reforçado quando os primeiros estudos sobre a elastometria transitória foram publicados [5, 6]. Esta nova tecnologia que permite o diagnóstico e o seguimento do grau de fibrose hepática de forma não invasiva vem ganhando, paulatinamente, mais espaço, sendo que em muitos centros europeus seu uso

tornou-se rotineiro. Contudo, essa nova tecnologia não é isenta de críticas e limitações [7].

Uma das maiores limitações dessa técnica é não permitir a visualização do local em que a elasticidade está sendo mensurada, aumentando a possibilidade de interpretações errôneas. Nesse contexto, surge uma nova tecnologia também baseada na medição da elasticidade hepática (ARFI), mas que apresenta como inovação o acoplamento de um ultra-som de alta qualidade[8]. Esta nova condição permite a visualização do local a ser mensurado e, inclusive, a medida de elasticidade de lesões com suspeita de malignidade, o que amplia o uso da técnica.

Considerando que as novas tecnologias sempre devem ser submetidas a estudos comparativos com outras já estabelecidas, este estudo analisa comparativamente as duas técnicas, ou seja, a elastometria transitória e a força de impulso acústico potente. Nesse estudo, foi demonstrado que ambas as técnicas se correlacionam adequadamente, porém com algumas disparidades que podem ser imputadas às diferenças trazidas pela escala utilizada e a área mensurada.

Além de ser um dos primeiros a comparar ambas as técnicas, este estudo foi o único a utilizar a técnica em uma população heterogênea composta por pacientes com hepatite B; hepatite C; co-infectados com HIV ou não. Apresenta também um grupo de pacientes infectados pelo HIV sem hepatopatias associadas, demonstrando a validade da técnica para discriminar pacientes infectados pelo HIV sem hepatopatia associada.

Por outro lado, a maior limitação desse estudo é a ausência de comparação com a biópsia hepática, ainda considerada o padrão ouro para a determinação

do grau da fibrose hepática. Essa é uma limitação principalmente para determinar a validez e valores preditivos visto que esses valores deveriam ser calculados baseados na técnica padrão.

Entretanto, outros métodos de correlação das técnicas foram utilizados para suplantar essa limitação, além do mais os dados encontrados concordam com dados de estudos recentes que comparam a biópsia hepática e o impulso potente por radiação acústica [8-10].

Outro ponto que se deve ressaltar é que a sobreposição dos intervalos entre os correspondentes graus de fibrose F2 e F3 encontrados em nosso estudo, além de hipoteticamente estarem relacionados á técnica (pequena faixa de intervalo entre os graus de fibrose) podem estar relacionados também ao reduzido número de pacientes analisados nesse estudo, principalmente quando divididos nos quatros grupos com graus de fibrose diferentes.

A determinação de fatores relacionados á progressão da fibrose hepática em pacientes infectados pelo HIV baseia-se em estudos transversais. Os estudos de coorte disponíveis são escassos, principamente os realizados com biópsias pareadas [11, 12], existindo, portanto uma necessidade de avaliação do seguimento da fibrose hepática com técnicas não invasivas.

Realizou-se, então, o seguimento da fibrose hepática com a utilização da elastometria transitória em diferentes grupos de pacientes infectados pelo HIV: co-infectados pelos HIV-HCV “curados”; co-infectados pelos HIV-HCV não tratados ou não curados; co-infectados pelos HIV-HBV e mono-infectados pelo HIV.

A avaliação dessa coorte de forma retrospectiva é uma das limitações desse estudo visto que a disponibilidade de dados pode ser escassa, pode ocorrer

seleção indireta de pacientes mais graves com necessidade de seguimento mais próximo, ou a inclusão de pacientes mais aderentes ao acompanhamento médico.

Contudo, a progressão da cirrose observada (10% em uma mediana de 3,6 anos), é semelhante a encontrada em estudos de coorte realizados de forma retrospectiva [12] e prospectiva com biópsia hepática [11] o que por um lado demonstra a utilidade da elastometria transitória para seguimento da progressão da fibrose hepática e por outro, corrobora nossos achados.

Além desse dado, demonstrou-se que na era da terapia antirretroviral de alta potência (HAART) os pacientes que evoluem para a cirrose são basicamente pacientes com hepatite C não curada. Observou-se então, a importância do sucesso do tratamento da hepatite C com interferon-peguilado e ribavirina. Estudos recentes já haviam demonstrado que o sucesso no tratamento traz a diminuição da mortalidade e de episódios de descompensação hepática [13]. Portanto, a não progressão para a cirrose nesses pacientes era um dado esperado e corroborado por outro estudo em que pacientes com resposta ao tratamento apresentaram menor risco de progressão da fibrose hepática quando comparados à pacientes sem resposta ao tratamento[12].

Por outro lado, Sulkowski *et al*, não encontrou diferença na progressão da fibrose hepática entre pacientes com sucesso ou não no tratamento da hepatite C [11]. Entretanto, somente três pacientes no correspondente estudo apresentaram resposta virológica sustentada, o que poderia justificar a diferença entre este estudo e nossos resultados.

É importante ressaltar que a progressão para a cirrose dos pacientes co-infectados pelos HIV-HBV foi semelhante á progressão observada em

pacientes mono-infectados com pelo HIV. Este resultado se fundamenta no amplo uso de tenofovir nesta coorte e demonstra sua importância não somente por suprimir a carga viral, mas também, por bloquear a progressão para a cirrose, fato este corroborado por estudos que demonstram graus de reversão da fibrose hepática em pacientes com uso prolongado de tenofovir [14, 15].

Contrário a outros estudos que demonstraram o papel do CD4 e carga viral na progressão da fibrose, nosso estudo não conseguiu demonstrar este tipo de correlação. Provavelmente, a falha em demonstrar essa associação se deve á alta porcentagem de pacientes com CD4 acima de 200 e carga viral do HIV indetectável em nossa coorte, o que levaria a falta de poder estatístico para demonstrar tais associações nessa coorte.

Com o manuseio adequado do paciente co-infectado é possível minimizar a incidência da progressão para a cirrose, entretanto, segundo nossos dados, ao redor de 3% dos pacientes anualmente evoluirão para a cirrose hepática. Entre os pacientes que atingem a cirrose hepática observa-se uma mortalidade relativamente elevada quando comparada à mortalidade entre pacientes infectados pelo HIV no geral [16]. Não foi surpresa a correlação negativa entre a mortalidade e os níveis de CD4 acima de 200 e carga viral do HIV não detectável , demonstrando que a HAART em pacientes cirróticos infectados pelo HIV não deve ser menos efetiva do que entre pacientes infectados pelo HIV em geral.

Outros fatores relacionados com a mortalidade foram o MELD e a rigidez hepática medida pela elastometria transitória. O MELD é um modelo matemático criado inicialmente para medir a gravidade de pacientes em uso de *shunt* trans-jugular intra-hepático porto-sistêmico (TIPS) [17], mas que

rapidamente foi reconhecido como importante para avaliar a gravidade e predizer a mortalidade em pacientes cirróticos em geral [18]. Sendo assim, tornou-se o instrumento utilizado para alocar fígados para transplante.

Para a determinação do momento ideal para avaliação de um paciente para transplante hepático deve-se comparar a história natural da doença com as taxas de sobrevida pós-transplante. Portanto, o momento ideal para o transplante hepático é aquele em que sua sobrevida pós-transplante é maior que a sobrevida esperada pela história natural da cirrose. Sendo assim, segundo a Diretriz Americana de Fígado esse momento seria quando o MELD do paciente fosse 15 ou o escore de Child-Pugh fosse 7 [19-21].

Em pacientes cirróticos infectados pelo HIV, até recentemente o MELD não havia sido avaliado e o valor para determinar o momento para transplante era considerado o mesmo para pacientes infectados ou não pelo HIV. Entretanto, presente estudo e outro recente estudo demonstraram que o modelo tem alta capacidade para predizer a mortalidade também entre pacientes infectados pelo HIV.

Em nosso estudo, pacientes infectados pelo HIV com um valor de MELD acima de 10 apresentaram uma mortalidade três vezes maior quando comparados aos pacientes com MELD abaixo de 10. Considerando esse resultado, pacientes cirróticos infectados pelo HIV com MELD acima de 10 deveriam ser submetidos a transplante. Hipoteticamente, esse valor poderia ter sido gerado pelo uso da elastometria transitória como forma de diagnóstico de cirrose, pois é conhecida sua capacidade para o diagnóstico precoce de cirrose hepática [22].

No entanto, em coorte recente de pacientes cirróticos infectados pelo HIV e com descompensação hepática, o ponto de corte de 10 foi encontrado e indicado como o de melhor validade para o MELD [23], o que sugere fortemente que o ponto de corte para avaliação desses pacientes deve ser mais baixo do que em pacientes HIV negativo para a indicação de transplante hepático. Estudos futuros, comparando este ponto de corte com o atual, devem ser realizados para avaliação de sua influência na mortalidade pós-transplante de pacientes infectados pelo HIV.

O escore de Child-Pugh é um dos instrumentos mais antigos utilizados para avaliar a gravidade de pacientes hepatopatas, mas não se mostrou, em nosso estudo, um instrumento válido para avaliação do risco de morte em pacientes cirróticos infectados pelo HIV. A ausência de pacientes classificados como C pelo escore de Child-Pugh é uma das limitações de nosso estudo e poderia explicar nosso achado.

Murillas *et al*, observou correlação entre a sobrevida de pacientes cirróticos infectados pelo HIV com descompensação hepática e o escore de Child-Pugh quando o mesmo foi analisado isoladamente (análise univariada) entretanto, quando analisado em conjunto com outras variáveis (analise multivariada) esse escore não se relacionou de forma independente com a mortalidade. Este dado, associado aos dados de nosso estudo, demonstra que o escore de Child-Pugh deve ser preterido em relação ao MELD na avaliação do paciente cirrótico infectado pelo HIV.

De forma inédita, nesse estudo, a elastometria transitória também apresentou alta validade para predizer a mortalidade entre pacientes cirróticos. Outros estudos já haviam demonstrado que o valor da rigidez hepática medida pela

elastometria transitória poderia ter valor de prognóstico, como por exemplo, para determinar a presença de varizes esofágicas [24, 25].

Entretanto, pela primeira vez observa-se que pacientes cirróticos com rigidez hepática acima de 28,7 KPa apresentam uma mortalidade 3,5 vezes maior que a encontrada abaixo desse valor. Este dado pode ser importante no seguimento de paciente cirrótico infectado pelo HIV, especialmente por ser a elastometria transitória um método fácil na avaliação da gravidade da rigidez hepática e também por possibilitar o estabelecimento de prioridades no encaminhamento de pacientes para transplante hepático.

Com esta série de estudos, conclui-se que o diagnóstico não invasivo é uma realidade, e que com baixo custo e de forma válida e inócua, pode melhorar o manuseio e o seguimento de pacientes infectados pelo HIV. Demonstrou-se, também, que esse instrumento diagnóstico, a elastometria transitória, possibilita predizer a mortalidade em pacientes com cirrose, sendo extremamente atraente e compensador na prática clínica diária.

A doença hepática apresenta uma incidência não desprezível de evolução á cirrose hepática, porém essa evolução parece estar confinada ao grupo de pacientes que não se beneficiou da terapia com interferon peguilado e ribavirina. Espera-se que uma parcela desses pacientes, em um futuro próximo, possa se beneficiar das novas terapias para hepatite C, pois se constata que apesar de todos os avanços da medicina atual a mortalidade entre pacientes cirróticos infectados pelo HIV continua alta. Por outro lado, o uso de terapia antirretroviral efetiva pode contribuir para a redução desta mortalidade o que é plausível com o advento de novos medicamentos antirretrovirais que sejam menos hepatotóxicos. Por fim, o MELD mostrou ser

um modelo extremamente útil na avaliação do paciente cirrótico infectado pelo HIV, devendo, contudo o valor de MELD igual a 10 ainda ser validado na prática clinica.

Estes estudos ampliam informações válidas para o entendimento e manuseio do paciente co-infectado pelos HIV e vírus das hepatites. Dados similares no Brasil devem ser explorados com a finalidade de confirmar a validade desses mesmos resultados em nossos pacientes.

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