Abstract

This study compared the quality of life (QoL) of HIV-infected patients with and without hepatitis C and examined the sociodemographic, HIV-related and psychological symptoms associated with the QoL domains in patients with HIV/HCV co-infection. The sample consisted of 248 HIV/HCV co-infected patients (18-74 years, 81.5% male) and 482 patients only with HIV (24-78 years, 62.7% male). Participants completed the WHOQOL-HIV-Bref questionnaire and the Brief Symptom Inventory (BSI). The HIV/HCV co-infected patients reported significantly lower QoL in all domains, as well as significantly lower scores in 10 of the 17 specific facets. Overall, among the co-infected patients, male gender, employment, combination antiretroviral therapy use and fewer depressive and anxiety symptoms were significantly associated with higher QoL. Symptoms of psychological distress accounted for significant variability in the QoL scores of co-infected patients. These data reinforce the need for tailored interventions to improve the overall well-being of HIV/HCV co-infected patients.

Keywords: co-infection; HIV; HCV; psychological symptoms; quality of life

Introduction

Both human immunodeficiency virus (HIV) and hepatitis C virus (HCV) infections represent major health problems worldwide. HCV in HIV-infected patients (herein HIV/HCV or co-infection) has become one of the leading causes of hospitalisation and death (Weber et al., 2006) and is one of the most challenging clinical conditions to manage in the context of HIV disease (Rockstroh et al., 2005). The prevalence of both viruses varies according to HIV risk group and geographical region (Averhoff et al., 2012), and about one third of patients infected with HIV in the United States and Europe are also co-infected with HCV (Cacoub et al., 2015). These rates are considerably higher among those who use injected drugs (Sulkowski, 2008), but are also increasing in other groups, such as men who have sex with men (MSM; van de Laar et al., 2010).

Portugal has one of the highest rates of HIV infection in Europe. In 2013, Portugal was the country with the third highest rate (10.4) of HIV diagnosis in the European Union and European Economic Area, and the highest rate among the countries of Western Europe (European Centre for Disease Prevention and Control/World Health Organization Regional Office for Europe [ECDC/WHO-Europe], 2013). In relation to hepatitis C, the prevalence of HCV was recently estimated at 1.8% (0.5%-2.9%), which is about the double of the regional prevalence reported in the countries of Western Europe (0.9%; 0.7%-1.5%) (Gower et al., 2014). The rate of HIV/HCV co-infection remains however less well defined. Heterosexual contact is the most commonly reported mode of HIV transmission, accounting for 45.4% of diagnoses, followed by intravenous drug use (IDU) (34.5%) and MSM (15.7%) (Martins & Shivaji, 2015). Regarding hepatitis C, it were estimated high percentages of HCV among IDU (50%), particularly in long-term users (80%) (Anjo et al., 2014). Recently, one study based on the Lisbon Cohort of MSM ($N = 2,183$) indicated that only 0.5% of participants reported a lifetime history of hepatitis C diagnosis, none of whom reporting IDU (Meireles et al., 2015). Although exact information about the prevailing mode of transmission in HIV/HCV is not currently available, recent reports indicated that IDU was the most common mode of transmission of both viruses in co-infected patients (up to 80%) (Calado et al., 2011; Viral Hepatitis Prevention Board [VHPB], 2011).

The presence of HIV, alone or in combination with other infections, can seriously affect the patient's quality of life (QoL) (Bryce & Tsevat, 2012). Therefore, describing the association between the presence of chronic health conditions (such as HCV and HIV) and QoL is particularly important, because understanding the areas of a patient's life that are affected by an infectious disease will enable health professionals to "make adjustments in treatment or develop new interventions that can limit the negative impact and/or enhance the positive impact of treatment" (Groessl et al., 2007, p. 169). Although HCV and HIV often co-exist, most research to date has focused almost exclusively on samples of HIV or HCV mono-infected patients; thus, we know little about the QoL of co-infected individuals. Moreover, because research examining the QoL of patients living with HIV/HCV co-infection and their correlates is lacking, the aim of this study was to assess the QoL of HIV/HCV patients, as well as the factors associated with the QoL of patients living with this co-infection. If one of the main goals of health care is also to improve patients' QoL and mental health, enhanced understanding of the differences in QoL of HIV mono-infected and HIV/HCV co-infected patients and of the factors associated with QoL may contribute to identify, within the larger HIV population, the subgroups that may be at increased risk of poorer QoL, and may also contribute to the development of effective interventions that could improve these patients' well-being. Given the complexity of the clinical management of dual infections (Kottilil, Pollis, & Kovacs, 2004) and the fact that dual-diagnosed patients pose unique challenges for mental health providers (Silberbogen, Ulloa, Janke, & Mori, 2009), these findings should also benefit mental health care by identifying potential targets of intervention, based on each group's specific needs, to be addressed in clinical practice.

It is well known that reduced QoL scores are common among chronic HCV (Groessl et al., 2007; Spiegel et al., 2005) and HIV-infected patients (Bing et al., 2000; Hays et al., 2000) particularly when compared to healthy controls. Because both mono-infections have been associated with significant declines in QoL, the existence of a dual infection might be expected to lead to further decreases in QoL. Despite this expectation, the literature contains inconsistent findings regarding the QoL of HIV/HCV patients. These mixed findings include studies that have reported that QoL is decreased in co-infected patients compared to HIV mono-infected patients (Baum et al., 2008), that only physical aspects of QoL are decreased in co-infected patients compared to mono-infected patients

(Tsui et al., 2007), and that QoL in co-infected patients is decreased compared only to controls and not compared to HIV-negative or HCV-negative mono-infected patients (Fleming et al., 2004). Other studies did not find significant differences in QoL between HIV/HCV patients and HIV or HCV mono-infected patients (Kanwal et al., 2005; Pantalone et al., 2012). For instance, Braitstein et al. (2005) reported lower QoL and increased fatigue among co-infected patients compared to HIV mono-infected patients; however, those authors attributed these differences to lower socioeconomic status and increased injection drug use among the co-infected group rather than to HCV co-infection. This finding suggests that, among these patients, other factors might account for poorer QoL.

Similarly, some studies have indicated that QoL might be reduced in co-infected patients and that several factors that range from demographic and clinical to psychological are related to lower QoL ratings. Among these factors, the association between psychological symptoms and QoL represents a topic of growing interest in the HIV and HCV literatures. Understanding this association among co-infected patients is critical primarily due to the association between psychological status and QoL and its potentially negative association with adherence to anti-retroviral treatments (Blashill et al., 2011; Roux et al., 2014; Sherr et al., 2008). There is evidence suggesting that co-infected patients report significantly more psychological symptoms than HIV mono-infected patients particularly somatic (Baum et al., 2008; Hilsabeck et al., 2003) and depressive symptoms (Baum et al., 2008; Braitstein et al., 2005; Gillis et al., 2013; Pantalone et al., 2012; Yoon et al., 2011). Also, it has been shown that patients with higher levels of psychological distress exhibit reduced QoL, and strong negative associations between symptoms of psychological distress and QoL have been reported in HIV (Pereira & Canavarro, 2011; Préau et al., 2007a), HCV (Fontana et al., 2002; Hauser et al., 2004) and HIV/HCV (Marcellin et al., 2007; Pereira et al., 2014).

Besides psychological symptoms, across multiple samples of HIV-infected patients, QoL has been associated with several sociodemographic and clinical variables. Although many studies have reported mixed findings, there is some consistency regarding the associations between poorer QoL and female gender (Chandra et al., 2009; Degroote et al., 2013; Pereira & Canavarro, 2011), older age (Hays et al., 2000; Préau et al., 2007b; Skevington, 2012), living alone or not having a stable partner (Degroote et al., 2013; Préau et al., 2007b), lower education (da Silva et al., 2013; Liu et al., 2006),

unemployment or lack of work activity (Fleming et al., 2004; Liu et al., 2006; Rueda et al., 2011), and IDU (Degroote et al., 2013; Préau et al., 2007b). Regarding clinical variables, lower CD4+ T-cell (CD4 for short) count (Canavarro & Pereira, 2012; Hays et al., 2000; Safren et al., 2012), and advanced HIV stages (Hays et al., 2000; Ruiz Perez et al., 2005; Zimpel & Fleck, 2014) have also been associated with lower QoL. Similarly, among HCV patients, QoL has also been associated with demographic variables (Strauss & Teixeira, 2006), although the results of the studies that have examined these associations are mixed. In HCV studies, factors that were found to be associated with decreased QoL include female gender (Bonkovsky et al., 2007; Kallman et al., 2007; Teuber et al., 2008), older age (Bonkovsky et al., 2007; Fleming et al., 2004; Helbling et al., 2008; Teuber et al., 2008), not being married or living as married (Bonkovsky et al., 2007; Fábregas et al., 2013), unemployment or lack or work activity (Miller et al., 2001), lower education (Alves et al., 2012) and IDU (Braitstein et al., 2005; Helbling et al., 2008).

Among HIV/HCV patients, the number of assessments of the sociodemographic and clinical factors associated with QoL is much more limited. To the best of our knowledge, only two studies (Mandorfer et al., 2014; Marcellin et al., 2007) have performed such analyses. Marcellin et al. (2007) found that sociodemographic variables accounted only for a small amount of the variances in QoL dimensions and that the variables that were more consistently associated with QoL domains were employment status and being in a stable relationship. No significant correlations were found between clinical variables and any of the QoL domains. In the study by Mandorfer et al. (2014), female gender and history of IDU was associated with lower mental QoL, but no significant associations were found regarding physical QoL.

Thus, given the existing inconsistencies and particularly the limited evidence, the aims of this study were to assess the QoL of patients with HIV/HCV, to compare the QoL to those from patients with HIV only and to examine how sociodemographic, HIV-related variables and psychological symptoms are related to QoL domains separately for co-infected and mono-infected patients. On the basis of existing literature, we hypothesized that co-infected patients would report poorer QoL, as well as increased psychological symptoms, particularly somatic and depressive symptoms. Based on the research examining the sociodemographic and HIV-related factors associated with QoL, for both study

groups, we expected that poorer QoL would be associated with female gender, older age, being single or not having a partner, lower education and unemployment or lack of work activity, IDU and advanced HIV stage. In addition, we hypothesized that lower QoL would be associated with increased symptoms of psychological distress, particularly depressive symptoms.

Methods

Participants and procedure

This cross-sectional study was part of a larger research project about the quality of life and mental health of Portuguese people living with HIV/AIDS (PLWHA). The study protocol was reviewed and approved by the ethics committee at each participating institution. The study sample consisted of 730 HIV-infected patients who had been in contact with the main departments of infectious diseases of 10 hospitals across the country. The sample was recruited by convenience between September 2007 and July 2008. The general inclusion criteria were an age above 18 years, diagnosis of HIV, and enough knowledge of Portuguese to complete the set of questionnaires. All participants were informed of the aim of the study, and those who agreed to participate provided us with written informed consent. Trained researchers (mainly psychologists) were available to provide assistance when needed.

The patients were invited to participate in the study while attending consultations with their infectious disease specialist. A total of 1251 patients were contacted. The participants who reported more than 20% of systematic missing data in a particular questionnaire (e.g., participants who did not provide data for more than six items on the WHOQOL-HIV-Bref) or did not complete the entire set of questionnaires ($n = 54$) were not considered eligible for the analysis. In order to avoid bias due to the presence of other co-morbidities, only patients with these two medical conditions were selected for this study. Therefore, a total of 467 patients were also excluded because they mentioned other co-infections (e.g., hepatitis B and syphilis) or other co-morbid illnesses (e.g., pulmonary tuberculosis, diabetes, depression, and asthma). In total, 248 (20.7%) co-infected patients and 482 (40.3%) HIV mono-infected patients were included in the study.

Measures

Sociodemographic and HIV-related variables

Sociodemographic and HIV-related variables were collected by self-report. These included age, gender, marital status, education, employment status, mode of HIV acquisition, HIV stage, CD4 count, year of HIV diagnosis and combination antiretroviral therapy (cART).

Quality of life

Quality of life was assessed by the European Portuguese validated version of the WHOQOL-HIV-Bref (Canavarro & Pereira, 2012). The WHOQOL-HIV-Bref is a 31-item self-reported questionnaire that yields a multidimensional profile across six domains (factors): Physical, Psychological, Level of Independence, Social Relationships, Environment, and Spirituality (O'Connell & Skevington, 2012). The WHOQOL-HIV-Bref contains 29 items, each one representing specific facets or aspects of QoL (e.g., pain and discomfort, self-esteem, social support). One additional facet (2 items) pertains to global QoL and general health. In this study, only the physical and psychosocial domains of QoL were used (the first four domains listed above, which cover 17 specific facets – a description of the specific facets is presented in Table 3), because of the literature consensus suggesting that these domains are assumed to reflect QoL rather well (Arnold et al., 2004). The individual items were rated on a 5-point scale in which 1 indicated a low, negative perception and 5 indicated a high, positive perception of QoL. All domain scores were transformed to create a 0 to 100 scale on which a higher score corresponded to a better QoL. There is no total score for the WHOQOL-HIV-Bref. In this sample, all Cronbach's α were above .70.

Psychological symptoms

The Brief Symptom Inventory (BSI; Derogatis, 1993) is a 53-item self-reported inventory of psychological distress. In the BSI, respondents are asked to rate the extent to which each identified psychological symptom has caused them discomfort in the past week on a 5-point scale ranging from "Never" (0) to "Very often" (4). The BSI measures nine symptom dimensions and three global indices. The Global Severity Index (GSI) and the combined somatisation, anxiety and depression ratings are the most widely used measures of psychological distress. Since somatisation, anxiety and depression are the most common types of psychological symptoms occurring in medical populations

(Kroenke et al., 2010), we used this combination as measure of psychological distress. In this study, the Portuguese validated version of the BSI was used (Canavarro, 2007). The Cronbach's αs in this sample ranged from .82 (Somatisation for HIV/HCV patients) to .88 (Depression for HIV/HCV patients).

Data analysis

The data were analysed using the Statistical Package for Social Sciences (IBM SPSS, v. 20.0; Armonk, NY, USA). Descriptive statistics were calculated to explore the sample's characteristics. A χ^2 analysis and a Student's t test were conducted to compare the two groups in terms of categorical and continuous variables, respectively. Multivariate analyses of covariance (MANCOVAs) were used to test for group differences (as between-subjects factors) in the QoL domains and psychological symptoms. Because the two groups exhibited differences in the sociodemographic and HIV-related variables, analyses were performed to control for these variables using the group as the factor and age, gender, living with a partner, employment status, mode of transmission, and cART use as the covariates. Subsequent univariate analyses of variance (ANOVAs) were conducted to identify the sources of the significant multivariate effects. Bonferroni adjustments were applied to correct for multiple comparisons ($p < .01$). The association between sociodemographic, HIV-related variables and psychological symptoms and the QoL domains were separately evaluated for the patients infected with HIV alone and those co-infected with HCV using hierarchical multiple regression (HMR) analyses. All variables were checked for multicollinearity. The regression models of the study groups were compared using Fisher's Z-transformation; that is, changing correlation (R) values to Z-scores, and then using Fisher's Z test for the statistical comparison.

Post hoc power calculations that were performed for all statistical analyses with a $p < .05$ and a power ≥ 0.90 indicated that small to medium effects could be detected (Faul, Erdfelder, Lang, & Buchner, 2007). The effect sizes are presented for all analyses (small effects: Cohen's $d \geq 0.20$, Cramer's $V \geq 0.10$, and Cohen's $f^2 \geq 0.02$; medium effects: Cohen's $d \geq 0.50$, Cramer's $V \geq 0.30$, and Cohen's $f^2 \geq 0.15$; large effects: Cohen's $d \geq 0.80$, Cramer's $V \geq 0.50$, and Cohen's $f^2 \geq 0.35$) (Cohen, 1992).

Results

Participant characteristics

The mean age of all participants was 40.4 years ($SD = 9.1$). Most of co-infected patients were male and single and nearly half were employed. Regarding self-reported HIV transmission, most of co-infected patients acquired their infections through IDU (68.8%), and most of the HIV patients were infected through sexual transmission (96.3%). Approximately 80% of the patients were on a cART at enrolment. Compared to the patients with HIV only, the co-infected patients were more likely to be younger, male, single, unemployed or not currently working, diagnosed with HIV for a longer time, and to be on cART (see Table 1).

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Quality of life and psychological symptoms

The results of a MANCOVA with co-infection as the between-subject factor and the QoL domains as dependent variables revealed a significant multivariate effect of group (Wilks' $\lambda= .95$, $F(5, 707) = 7.14$, $p < .001$, $\eta_p^2 = .048$). Subsequent univariate tests revealed that co-infected patients reported significantly lower QoL in all domains, as well as in the general facet on QoL and health. Table 2 displays the means and standard errors (SE) for the QoL indicators and psychological symptoms.

Regarding the specific facets of the WHOQOL-HIV-Bref, the co-infected patients reported significantly lower scores in 12 out of 17 facets. The differences remained statistically significant in 10 facets after Bonferroni correction (see Table 3).

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Regarding the psychological symptoms, the results revealed a significant multivariate effect of group (Wilks' $\lambda= .98$, $F(3, 704) = 2.798$, $p = .006$, $\eta_p^2 = .017$). Follow-up tests indicated that patients with HIV/HCV reported significantly higher scores on all symptom dimensions (Table 2).

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Factors associated with the quality of life domains

To assess the association between sociodemographic, HIV-related variables and psychological symptoms and the QoL domains, HMR analyses were conducted separately for the HIV mono-

infected and HIV/HCV co-infected patients. Each model consisted of two blocks: block 1 included the sociodemographic and HIV-related variables, and block 2 included the psychological symptoms. The collinearity statistics in the regression models (Variance Inflation Factor [VIF] < 10; tolerance > 0.2; Condition Index < 30) suggested that there were no multicollinearity problems.

HIV/HCV co-infected group

The models for the co-infected patients are presented in Table 4. Overall, the most variance in the QoL domains was explained by depressive and anxiety symptoms. The explained variances ranged from 29.5% (Physical) to 45.3% (Psychological). The effect sizes attributable to the addition of the psychological symptoms [Cohen's f^2] ranged from 0.32 (Physical) to 0.67 (Psychological).

For the *Physical* domain, the results revealed significant associations for employment status and being on a cART. In addition, having fewer somatic and depressive symptoms was significantly associated with higher physical QoL. Higher *Psychological* QoL was significantly associated with the male gender, being on a cART, and having fewer depressive and anxiety symptoms. Being employed, being male, and having fewer somatic, depressive, and anxiety symptoms were related to higher scores for the *Independence* QoL. Regarding the *Social Relationships* domain, significant associations were found for CD4 count, cART use and anxiety and depressive symptoms. Specifically, having a higher CD4 count, being on a cART, and having fewer depressive and anxiety symptoms were significantly related to better social QoL.

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HIV mono-infected group

The final models for the HIV mono-infected patients are displayed in Table 5. Similar to the co-infected patients, the psychological symptoms were the main variables that were associated with the QoL domains. The explained variances ranged from 27.3% (Social relationships) to 50.1% (Psychological). The Cohen's f^2 ranged from 0.27 (Independence) to 0.91 (Psychological).

Regarding the *Physical* domain, the highest regression coefficients were observed for age and education. Being younger, having more education and having fewer somatic and depressive symptoms were associated with higher physical QoL. Having more education and having fewer depressive and anxiety symptoms were associated with higher *Psychological* QoL scores. Regarding the

Independence domain, the results revealed significant associations with education, employment and CD4 count. Having more education, being employed, having a higher CD4 count, and reporting fewer somatic, depressive, and anxiety symptoms were related to greater independence. Regarding the *Social Relationships* domain, the results revealed that living with a partner, being infected through IDU, and fewer depressive and anxiety symptoms were associated with better social QoL.

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The comparison of the models of both groups indicated that there were no significant differences between the respective R^2 values in relation to *Physical*, *Psychological* and *Social Relationships* domains (Z-scores ranged from 0.390 to 0.913, $p > .05$). A significant difference in the R^2 values was found in relation to the *Independence* domain (Z = 1.99, $p < .05$). However, further analyses revealed that the β weights were not significantly different between the two groups (Z-scores ranged from 0.372 to 1.545, $p > .05$).

Discussion

The main findings of this study revealed that the patients with HIV/HCV exhibited consistently decreased QoL compared to the patients with HIV only and that the difference on QoL was most noticeable in terms the Physical and Social Relationships domains, and the general facet on QoL and health, therefore suggesting reduced QoL in HIV/HCV co-infection across a wide spectrum of domains. In addition, the presence of psychological symptoms was significantly increased among co-infected patients. A number of sociodemographic and HIV-related variables were independently associated with QoL domains; however, psychological symptoms accounted for the greatest amount of variability in QoL scores in both the HIV mono-infected and co-infected patients. These findings represent a significant contribution to the literature, indicate that the QoL assessment is a key issue for co-infected patients (Braitstein et al., 2005) and suggest that early identification and effective management of psychological symptoms might improve the overall functioning and QoL of HIV and co-infected patients.

Consistent with our prediction, and supporting previous literature (Baum et al., 2008; Braitstein et al., 2005), our findings indicated that co-infected patients exhibited lower QoL in the four

QoL domains, compared to patients with HIV only. Our findings also partially agree with prior studies that found reduced physical QoL among co-infected patients compared to patients with HIV only (Tsui et al., 2007) and that co-infection with HCV is related to lower mental health scores (Briongos Figuero et al., 2011). Some explanations may account for these results. The burden of living with HIV is likely to be greater in an individual with a coexisting chronic medical condition, such as HCV. Such results might also be explained by the specificities of HIV/HCV populations, which, as observed in this study, are often characterised by the presence of psychosocial vulnerabilities, such as a high prevalence of IDU (in this study, 66.5% of co-infected patients reported IDU as mode of transmission) and psychological symptoms/disorders (Braitstein et al., 2005; Pantalone et al., 2012; Pereira et al., 2014; Silva et al., 2012). However, our findings differ from those of other studies that did not find significantly lower QoL among HIV/HCV patients compared to patients with HIV only (Fleming et al., 2004; Kanwal et al., 2005; Pantalone et al., 2012). A possible reason for this divergence may be the differences in the samples' characteristics of the existing studies with this population, whether in terms of the sample size or the sample composition (e.g., some of the studies examined only MSM). Further studies are needed to confirm our findings.

The analyses of the specific facets revealed that the co-infected patients reported lower QoL in 10 of the 17 facets. The strongest differences were found on items such as the energy and fatigue and symptoms of PLWHA (Physical domain), negative feelings (Psychological), activities of daily living and work capacity (Independence), personal relationships, social support and sexual activity (Social Relationships). The lower scores on energy and fatigue corroborate prior evidence indicating that fatigue is a symptom that is often reported by people living with hepatitis C (Kallman et al., 2007; Marcellin et al., 2007), even in untreated patients (Mandorfer et al., 2014; Schaefer et al., 2012). Because symptoms of PLWHA and fatigue are likely to contribute to further impairments in individuals' life, it is plausible that lower scores on the items of the Independence domain may reflect the presence of these potential disabling symptoms. The lower scores on the Social Relationships facets among the co-infected patients may be related to experiences of stigmatisation and decreased perceived social support, which have been previously reported to be a common theme among co-infected patients (Farrell & Comiskey, 2014). It is possible that the stigma that is often associated with

these conditions (Lekas, Siegel, & Leider, 2011) may be a significant driver of social isolation and reduced closeness in relationships. As well, because both HIV and HCV-related stigmas are often shaped by their association with "devalued social groups" (Butt, 2008, p. 721), it is also plausible that they may reinforce existing stigmas against marginalized groups, such as intravenous drug users (Pulerwitz, Michaelis, Weiss, Brown, & Mahendra, 2010), therefore contributing to poorer QoL. Moreover, living together as a couple might be an influential factor in QoL, as has been suggested (Ruiz Perez et al., 2005). In this study, co-infected patients were more likely to be single (and nearly 70% were not living with a partner); thus, it is possible that these findings may also reflect this specific characteristic.

Consistent with the finding of significantly lower scores on the specific facet of negative feelings, the psychological symptoms were also significantly increased among patients with HIV/HCV even after adjusting for the covariates. These results are in line with previous reports that found higher somatisation or somatic concerns (Grassi et al., 2002; Hilsabeck et al., 2003), depressive symptoms (Baum et al., 2008; Braitstein et al., 2005; Yoon et al., 2011), and general psychological distress (Pereira et al., 2014) among co-infected patients. These increased psychological symptoms are not surprising, and may be associated with HIV or HCV (as well as the psychological strain of living with two stigmatising medical conditions), the well-known psychosocial vulnerabilities of co-infected patients, such as the higher likelihood of having past or current drug use and psychiatric comorbidity, antiviral treatments and its side-effects, or a combination of these factors. It is known that depressive symptoms are prevalent in HCV-infected patients, whether receiving treatment for HCV or not (Schaefer et al., 2012). Although this study did not provide data regarding current or past treatment for hepatitis C, it is also likely that these increased symptoms among co-infected patients may reflect the evidence suggesting that these symptoms are recognised adverse consequences of interferon-based HCV therapy (the most commonly used treatment for HCV infection at the time of data collection) (Huckans et al., 2015; Whale et al., 2015), which often persist after the cessation of treatment (Fransen Van De Putle et al., 2011). The lower symptoms of psychological distress among patients with HIV only may also be explained by specific characteristics of this group, which is mostly composed of individuals reporting heterosexual transmission of HIV and MSM. Specifically in relation to MSM,

although individuals endorsing sexual minority status are more likely to report symptoms of psychological distress, as posited by the model of minority stress (Meyer, 2003), the cultural context of same-sex sexuality in Portugal may provide an important input for these results. In Portugal, there is a growing acceptance of same-sex sexuality, mostly related to the recent political and legislative changes, such as the introduction in the Portuguese Constitution, in 2004, of a clause of nondiscrimination on the basis of sexual orientation, the legal recognition of same-sex couples in civil partnerships in 2001, as well as the 2010 law allowing same-sex couples marriage (Costa, Pereira, & Leal, 2013). Thus, in this specific group, it is possible that this growing acceptance may be associated with reduced experiences of discrimination, and consequently with reduced psychological burden imposed by sexual minority status.

For both co-infected and mono-infected patients, the amounts of variance in the QoL domains explained by demographic and HIV-related variables were relatively small. Among co-infected patients, the variance in the QoL domains explained by these variables ranged from 6.8% to 11.4%, and among HIV mono-infected patients, the explained variances ranged from 4.9% to 9.4%. For both groups, the psychological symptoms accounted for the most variance in the QoL domains. As expected, the strongest and most consistent factor associated with reduced QoL was depressive symptoms. These findings highlight the important link between more symptoms of psychological distress and lower QoL among patients with these infectious diseases (Ballester-Arnal et al., 2015; Fontana et al., 2002; Liu et al., 2006; Marcellin et al., 2007; Zimpel & Fleck, 2014). Psychological symptoms have been recognised as interfering with activities of daily life, physical functioning, emotional regulation and interpersonal relationships. Although the presence of these symptoms may be directly associated with reduced QoL, other explanations cannot be ruled out. For example, symptoms of anxiety and depression are known correlates of impaired self-care behaviours (Tucker et al., 2003). It is likely that these symptoms may interfere with patients' medication taking, enhance the difficulties in integrating medications into their daily life and, consequently, to compromise compliance with treatment. The association between depression and non-adherence to cART is well-known (Gonzalez et al., 2011); thus, non-adherence may be one potential pathway to understand the associations between more psychological symptoms and poorer QoL. This may be especially relevant

for co-infected patients, as treatment for hepatitis C in these patients is notoriously more complex and challenging. Although causal inferences cannot be made, our results suggest that an effective clinical management of psychological symptoms, particularly of depression and anxiety, may improve the functioning and well-being of both co-infected and mono-infected patients. The recognition and effective management of these symptoms are relevant concerns largely because of the negative effects of such symptoms on cART adherence and persistence (Gonzalez et al., 2011; Schönnesson et al., 2007; Springer et al., 2012) and the possible worsening of disease progression (Nanni et al., 2015).

Regarding the sociodemographic and HIV-related variables, our findings relate reasonably well with those of prior work that has addressed the correlates or predictors of QoL among patients with HIV and HCV. Among HIV mono-infected patients, younger age was associated with increased Physical QoL. This finding is consistent with the literature indicating that QoL is decreased in higher-age groups (e.g., Hays et al., 2000; Skevington, 2012) and that the decrease is mostly related to physical functioning (Nokes et al., 2000). Also consistent with our hypothesis, having more education and being employed were more consistently related to higher QoL on the majority of the domains. Our findings are in line with these associations, which have been previously recognised (e.g., da Silva et al., 2013; Degroote et al., 2013; Hays et al., 2000; Liu et al., 2006; Rueda et al., 2011). Because higher education and employment have been considered a proxy of a higher socioeconomic status in general, these findings are comprehensible and support the notion that socioeconomic circumstances are an important part of one's life and QoL and may provide more than simple financial benefits for PLWHA (Swindells et al., 1999). It is also likely that higher education may denote an improved ability to comprehend the treatment recommendations and, accordingly, to a better engagement in medical care, which therefore may reflect better QoL. Surprisingly, among patients with HIV only, we found that being infected through IDU was associated with higher scores in Social Relationships. When examining the specific facets of this domain, the results indicated that intravenous drug users reported higher scores in all facets, particularly in social inclusion, personal relationships and sexual activity. Because the IDU group was also significantly more likely to be diagnosed with HIV for longer time (on average about 9.3 years) and to be on cART (90.3% vs. 71.3%), these results may reflect the various changes associated with HIV-related treatments and eventually of drug injection cessation

following the HIV diagnosis. In fact, it has been shown that the process that leads to drug cessation among HIV-infected individuals may be accompanied by a reduction in addiction practices and of unsafe sexual behaviours, as well as by positive psychosocial factors, such as reduced contact with drug networks and increased access to different sources of support (Bouhnik et al., 2004). The Portuguese decriminalization law of drug use of 2001 (Hughes & Stevens, 2010) may also account for this result, particularly because of its consolidated focus in the areas of harm reduction, treatment and social reintegration/inclusion of drug users. However, future studies confirming this specific finding would be of value. Across multiple studies, findings regarding the link between immunological status and QoL have been mixed (for a review, see Degroote, Vogelaers, & Vandijck, 2014). In our study, biological markers were associated with QoL, but these associations were limited to the functional aspects of QoL, as previously reported (Zimpel & Fleck, 2014).

Among co-infected patients, only limited associations were found. Partially consistent with the findings of a study with co-infected patients (Mandorfer et al., 2014), but consistent with extensive research in HIV and HCV mono-infected samples (e.g., Bonkovsky et al., 2007; Degroote et al., 2013; Teuber et al., 2008), male gender was associated with higher Psychological QoL. As possible explanation for this result may be the myriad of psychosocial stressors observed in women living with HIV, such as caregiving issues and household responsibilities, financial-related stress and relationship problems (Durvasula, 2014), which may not affect so prominently their male counterparts. Interestingly, and in contrast to prior findings (e.g., Briongos Figuero et al., 2011; Mandorfer et al., 2014), we found that being on cART was significantly associated with higher QoL among co-infected patients but not among patients with HIV only. A probable explanation may be related to the evidence suggesting that cART-induced immune reconstitution might reverse the unfavourable course of hepatitis C in patients with advanced HIV disease (Vogel & Rockstroh, 2009) and that patients on cART have lower liver-related mortality (Quirishi et al., 2003). Indeed, liver disease progression is especially pronounced in patients with CD4 count below 200 cells/mm^3. Hence, because CD4 count increases with cART use (Boesecke et al., 2010), cART use might have a positive effect on the course of liver disease and therefore influence patients' QoL. It is also likely that co-infected patients may perceive their health status as more fragile (because they live with two infectious diseases) and, as a

result, they may feel more motivated to adhere to treatment. This is a plausible argument since it has been recently shown higher self-reported adherence to cART in co-infected patients when compared to patients with HIV only (Pantalone et al., 2012) and that patients treated for HCV were less likely to be non-adherent to cART (Roux et al., 2014).

This study is not without limitations. First, the limitations imposed by the convenience sample and the cross-sectional study design imply that the generalisation of the results of this study to the HIV/HCV population should be performed with caution. Specifically, all of our participants were recruited from health settings; accordingly, they were actively engaged in health care. The cross-sectional design precludes any conclusions regarding the causal associations between the study variables. Further longitudinal studies should be undertaken to determine the directions of the associations reported herein. Second, it is possible that variables that were not assessed might have been able to explain additional variance in QoL. Because this study involved a subgroup analysis of a wider research project, no data were collected regarding current or recent substance use, mode of HCV transmission, lifetime IDU status, genotype, significant health consequences of HCV (such as end-stage liver disease), or the proportion of patients who had undergone or were presently undergoing HCV treatment; the non-inclusion of these factors might represent a potential omission bias. However, this study seems justified from the perspective of the aim of the initial project, which focused almost exclusively on HIV-related variables. To overcome this limitation, future studies with larger and more diverse samples of co-infected patients and specific variables related to HCV are warranted. Since the primary aim of this study was to compare the QoL of HIV mono-infected and HIV/HCV co-infected patients, in order to avoid bias due to other co-morbidities, we decided to select patients with only these two medical conditions. This may have led to selection bias and, accordingly, we may have selected the HIV mono-infected individuals who were more likely to report higher QoL. Therefore, these findings should be interpreted cautiously. Finally, it is noteworthy that this sample was collected during 2008. Since then, notable advances in antiviral treatments have been achieved and new options are available for co-infected patients (Del Bello et al., 2015). Recently, it has been reported that removing interferon and ribavirin has led to substantial improvements of QoL during HCV treatment (Younossi et al., 2015). However, although a recent study suggested positive results of HCV treatment

in co-infected patients, the authors also noted that ongoing substance use weakened the short- and long-term benefits associated with curing HCV (Yeung et al., 2015). Therefore, because HCV therapy in co-infection is not as straightforward as in HCV mono-infection due to potential drug-drug interactions (Chen & Jain, 2015), future studies exploring the benefits of these new treatments on the QoL of co-infected patients, as well as the potential role of psychosocial and behavioural factors, would still be a valuable point of investigation.

This study also has important strengths. First, it contributes significantly to the literature on QoL among co-infected patients by providing additional evidence that QoL domains and their correlates differ between co-infected and mono-infected patients and bridges a knowledge gap regarding this co-infection. Another relevant strength is that this study is based on data from a sample of considerable size that was recruited from the country's main departments of infectious diseases. In this study, heterosexual contact is the most commonly reported mode of HIV transmission, accounting for 48.9% of diagnoses, followed by IDU (35.3%). In addition, MSM represent 9.9% of the total sample, and 14.3% among HIV mono-infected patients. This percentage is similar to the official proportion of reported cases in Portugal (15.7%) and also of the Portuguese results of the European Men who have sex with Men Internet Survey (EMIS), which found a self-reported HIV prevalence of 11% (Carvalho et al., 2013). Thus, this sample seems to accurately reflect the type of people that are officially notified with HIV in Portugal (Martins & Shivaji, 2015). Also of note, in this study, MSM represent only 1.2% of co-infected patients. However, over the past decade, there were important changes in the epidemiology of HIV in Portugal. In 2012, the lifetime prevalence of drug use (population aged 18-64 years old) in Portugal was of 9.5%, which is lower than the 12% observed in 2007 (Balsa, Vital, & Urbano, 2014). Accordingly, the number of new drug users with HIV diagnosis has also declined. This is an important trend that has been attributed primarily to the expansion of harm-reduction services, resulting from the Portuguese decriminalization law (Hughes & Stevens, 2010). However, a significant increase of newly diagnosed HIV cases among MSM has also been reported. Specifically, in 2014, MSM accounted for 42.7% of all HIV cases reported among men and 31% of all cases (Martins & Shivaji, 2015). This rise of new diagnosis among MSM, along with recent evidence of a retrospective analysis of medical records of 348 co-infected patients from 2001 to 2011,

which indicated that 8.3% of infections were related to MSM (Silva et al., 2012) merits the consideration of an improved understanding of the epidemiology of HIV/HCV in Portugal.

The results of this study might also have important implications for clinical practice. As QoL is increasingly recognised as an important clinical measure for assessing the burden of a chronic health condition, measurements of QoL will benefit the understanding of patients' problems and the provision of appropriate care. Such measurements also have the potential to enrich clinical data by providing information about the patients' perceptions of their health statuses and the areas most affected by the disease.

Effective provision of cART and HCV treatment will continue to be an indispensable component of medical care. However, because of the complexity of the clinical management of dual infections, the potential drug-drug interactions between treatments, and the potential complex synergy between the factors related to the QoL domains, identifying the diversity of these factors (particularly those that are potentially changeable via intervention) may provide a significant avenue toward improving patients' QoL. In situations in which these factors are present, the results reported herein could assist health providers in making more effective decisions regarding treatment or psychological/psychosocial interventions in medical settings. At the same time, because somatisation, anxiety and depression are symptoms sufficiently prevalent, disabling and costly (Kroenke et al., 2010), it is highly important to screen for and treat these symptoms (and their potential comorbidity) in both HIV mono-infected and co-infected patients. Screening measures such as the BSI-18 (Derogatis, 2001) and the Patient Health Questionnaire Somatic, Anxiety, and Depressive Symptom Scales (PHQ-SADS; Kroenke et al., 2010) may be particularly valuable. This screening may maximise the likelihood of a successful treatment course and thus improve the patients' health statuses and well-being.

Conflict of interest

None of the authors have any foreseeable financial or other conflicts of interest to disclose.

Human and Animal Rights and Informed Consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki declaration and its later revisions. Informed consent was obtained from all participants for being included in the study.

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Table 1

Sociodemographic and HIV-related characteristics of participants ($N = 730$)

	Total sample	HIV/HCV	HIV	χ^2	Cramer's V
	n (%)	n (%)	n (%)		
Sex				20.07***	.19
Male	504 (69.0)	202 (81.5)	302 (62.7)		
Female	226 (31.0)	46 (18.5)	180 (37.3)		
Marital status[a]				9.52*	.11
Single	329 (45.3)	131 (52.8)	198 (41.3)		
Married/co-habiting	244 (33.6)	71 (28.6)	173 (36.1)		
Separated/divorced	131 (18.0)	41 (16.5)	90 (18.8)		
Widowed	23 (3.2)	5 (2.0)	18 (3.8)		
Employment status				6.32*	.09
Employed	377 (51.6)	112 (45.2)	265 (55.0)		
Not currently working	353 (48.4)	136 (54.8)	217 (45.0)		
Mode of transmission				173.08***	.49
MSM	72 (9.9)	3 (1.2)	69 (14.3)		
Heterossexual	357 (48.9)	64 (25.8)	293 (60.8)		
IV Drug use	258 (35.3)	165 (66.5)	93 (19.3)		
Blood products	16 (2.2)	6 (2.4)	10 (2.1)		
Other/Unknown	27 (3.7)	10 (4.0)	17 (3.5)		
cART[a]				7.58**	.10
Yes	567 (78.0)	208 (83.9)	359 (74.9)		
No	160 (22.0)	40 (16.1)	120 (25.1)		
HIV stage				4.29	.08
Asymptomatic	521 (71.7)	175 (70.9)	346 (72.1)		
Symptomatic	75 (10.3)	30 (12.1)	45 (9.4)		
AIDS	120 (16.5)	41 (16.6)	79 (16.5)		
Unknwon	11 (1.5)	1 (0.4)	10 (2.1)		
CD4+ T-cell count[a]				5.50	.09
< 200 cells/mm^3	154 (21.3)	63 (25.6)	91 (19.1)		
201 e 499 cells/mm^3	306 (42.3)	105 (42.7)	201 (42.1)		
> 500 cells/mm^3	263 (36.4)	78 (31.7)	185 (38.8)		
	M (SD)	M (SD)	M (SD)	t	Cohen's d
Age	40.37 (9.1)	38.8 (6.5)	41.2 (10.0)	3.47**	0.29
Education	7.9 (3.9)	7.8 (3.3)	7.9 (4.2)	0.28	0.02
Time since HIV diagnosis	7.8 (5.0)	9.1 (4.8)	7.1 (5.0)	-5.08***	0.40
CD4+ T-cell count	432.5 (277.3)	399.5 (267.3)	449.6 (281.0)	2.31*	0.18

[a] The ns of these variables do not add up to 730 due to missing values.

* $p < .05$; ** $p < .01$; *** $p < .001$

Table 2

Descriptive statistics on QoL domains and psychopathological symptoms ($N = 730$)

	HIV/HCV ($n = 248$)	HIV ($n = 482$)	F	η_p^2
	Mean (SE)	*Mean (SE)*		
Quality of life				
Physical	60.45 (1.14)	69.18 (0.97)	23.23***	.032
Psychological	56.83 (1.27)	62.34 (0.87)	11.36**	.016
Level of Independence	62.54 (1.40)	68.96 (0.96)	12.79***	.018
Social Relationships	57.01 (1.35)	64.12 (0.93)	16.76***	.023
General facet on QoL and health	49.85 (1.30)	58.18 (0.89)	24.99***	.034
Psychopathological symptoms				
Somatisation	0.87 (0.05)	0.66 (0.03)	10.91**	.015
Depression	1.13 (0.06)	0.92 (0.04)	7.20**	.010
Anxiety	1.01 (0.05)	0.80 (0.04)	10.14**	.014

** $p < .01$; *** $p < .001$

Table 3

Descriptive statistics on specific facets of the WHOQOL-HIV-Bref ($N = 730$)

	HIV/HCV ($n = 248$)	HIV ($n = 482$)	F	η_p^2
	M (95% CI)	M (95% CI)		
Physical				
Pain and discomfort	3.90 (3.75-4.05)	4.15 (4.05-4.26)	6.23	.009
Energy and fatigue	3.19 (3.53-3.33)	3.53 (3.44-3.62)	15.38***	.021
Sleep and rest	3.00 (2.84-3.16)	3.36 (3.25-3.47)	11.51**	.016
Symptoms of PLWHAs[a,b]	3.58 (3.41-3.75)	4.03 (3.91-4.15)	16.37***	.023
Psychological				
Positive feelings	3.74 (3.60-3.87)	3.83 (3.74-3.92)	1.09	.002
Cognitions	3.19 (3.05-3.32)	3.28 (3.19-3.37)	1.15	.002
Body image and appearance	3.43 (3.28-3.57)	3.66 (3.56-3.76)	13.26***	.018
Self-esteem	3.24 (3.10-3.39)	3.59 (3.49-3.68)	6.12	.009
Negative feelings	2.77 (2.63-2.92)	3.12 (3.02-3.22)	13.18***	.018
Level of Independence				
Mobility	3.73 (3.59-3.86)	3.94 (3.84-4.03)	5.48	.008
Activities of daily living	3.32 (3.18-3.46)	3.66 (3.57-3.75)	14.77***	.020
Dependence on medication or treatment	3.78 (3.62-3.95)	3.96 (3.85-4.07)	2.72	.004
Work capacity	3.18 (3.04-3.32)	3.48 (3.38-3.57)	10.88**	.015
Social Relationships				
Personal relationships	3.37 (3.23-3.50)	3.68 (3.59-3.77)	12.76***	.018
Social support	3.36 (3.20-3.47)	3.62 (3.53-3.71)	10.10**	.014
Sexual activity	2.83 (2.68-2.98)	3.26 (3.15-3.36)	19.05***	.026
Social inclusion[a]	3.59 (3.46-3.72)	3.70 (3.61-3.79)	1.84	.003

[a] Items from the HIV module; [b] PLWHA: People living with HIV/AIDS

** $p < .01$; *** $p < .001$

Table 4

Hierarchical multiple regression analysis of the variables associated with QoL domains among HIV/HCV co-infected patients (N = 248)

	Physical		Psychological		Independence		Social relationships	
	β	p	β	p	β	p	β	p
Age (years)	-.05	.512	.10	.147	-.02	.720	.07	.295
Gender	.02	.796	.15	.033	-.05	.436	.05	.467
Marital status	-.01	.894	.08	.270	-.03	.708	.09	.180
Education (years)	-.09	.195	.05	.447	.05	.442	.09	.202
Employment	.16	.023	.10	.126	.22	.001	.06	.364
IDU	.001	.983	.03	.688	-.02	.744	.05	.479
Asymptomatic	-.14	.077	-.03	.717	-.04	.572	.05	.545
CD4+ T cell count	.001	.999	.01	.884	.14	.064	.17	.029
cART	.15	.028	.16	.017	.08	.261	.15	.031
		R^2 = .068		R^2 = .088		R^2 = .100		R^2 = .090
Somatisation	-.25	.002	.01	.900	-.20	.006	-.02	.805
Depression	-.24	.005	-.47	< .001	-.27	.001	-.32	< .001
Anxiety	-.07	.433	-.20	.014	-.19	.028	-.22	.018
		ΔR^2 = .227		ΔR^2 = .365		ΔR^2 = .308		ΔR^2 = .239
		Total R^2 = .295		Total R^2 = .453		Total R^2 = .408		Total R^2 = .329

Note: Gender [0 = Female; 1 = Male]; Marital status [0 = Living alone; 1 = Living with partner]; Employment status [0 = Unemployed or not currently working; 1 = Employed]; HIV stage [0 = Asymptomatic; 1 = Symptomatic/AIDS]; IDU [0 = No; 1 = Yes]: cART [0 = No; 1 = Yes].

Table 5

Hierarchical multiple regression analysis of the variables associated with QoL domains among HIV-infected patients ($N = 482$)

	Physical		Psychological		Independence		Social relationships	
	β	p	β	p	β	p	β	p
Age (years)	-.12	.014	-.01	.813	-.05	.259	-.06	.194
Gender	.01	.405	.08	.112	-.04	.428	.002	.968
Marital status	.02	.845	.06	.211	.09	.072	.10	.041
Education (years)	.12	.019	.12	.018	.15	.002	.04	.454
Employment	.03	.575	.07	.172	.13	.006	.08	.092
IDU	.07	.172	.10	.052	-.04	.459	.11	.031
Asymptomatic	-.05	.324	-.02	.710	-.04	.489	.02	.662
CD4+ T cell count	.06	.273	.07	.168	.13	.009	.06	.219
cART	.001	.988	.02	.752	.01	.870	.03	.575
	$R^2 = .050$		$R^2 = .049$		$R^2 = .094$		$R^2 = .039$	
Somatisation	-.32	< .001	-.01	.780	-.13	.036	-.05	.352
Depression	-.20	.001	-.56	< .001	-.15	.019	-.25	< .001
Anxiety	-.06	.335	-.14	.018	-.22	.002	-.23	.001
	$\Delta R^2 = .269$		$\Delta R^2 = .452$		$\Delta R^2 = .191$		$\Delta R^2 = .233$	
	Total $R^2 = .320$		Total $R^2 = .501$		Total $R^2 = .285$		Total $R^2 = .272$	

Note: Gender [0 = Female; 1 = Male]; Marital status [0 = Living alone; 1 = Living with partner]; Employment status [0 = Unemployed or not currently working; 1 = Employed]; HIV stage [0 = Asymptomatic; 1 = Symptomatic/AIDS]; IDU [0 = No; 1 = Yes]: cART [0 = No; 1 = Yes].