

This is the peer reviewed version of the following article:

Psychological distress in women and men living with HIV in Spain: a cross-sectional telephone survey

Cesar Garriga, Lourdes Gutiérrez Trujillo, Jorge Del Romero, Marta Montero, María Jesús Pérez-Elías, Dante Culqui Lévano , Félix Gutierrez, Juan Luis Gómez-Sirvent , Alejandro Peña-Monje, José Ramón Blanco, María Angeles Rodríguez-Arenas.

Evid Based Ment Health. 2020 Aug;23(3):91-99.

which has been published in final form at

<http://dx.doi.org/10.1136/ebmental-2019-300138>

Title page

Title: Psychological distress in women and men living with HIV in Spain: a cross-sectional telephone survey.

Corresponding author: César Garriga. Nuffield Department of Primary Care Health Sciences, University of Oxford, Radcliffe Observatory Quarter, Woodstock Road, Oxford, OX2 6GG, UK; email: cesar.garriga@phc.ox.ac.uk; Tel. +441865 287 846.

Author names: Cesar Garriga^{1,2,10}, Lourdes Gutiérrez Trujillo², Jorge del Romero³, Marta Montero⁴, María Jesús Pérez-Elias⁵, Dante Culqui Levano¹, Félix Gutiérrez⁶, Juan Luis Gómez-Sirvent⁷, Alejandro Peña-Monje⁸, José Ramón Blanco⁹, M. Ángeles Rodríguez-Arenas² on behalf of CoRIS.

Affiliation and address of the authors:

- 1.- Spanish Field Epidemiology Training Programme, National Centre for Epidemiology, Instituto de Salud Carlos III, Avda. Monforte de Lemos, 5 - 28029 Madrid, Spain.
2. - National School of Public Health, Instituto de Salud Carlos III, Avda. Monforte de Lemos, 5 - 28029 Madrid, Spain.
3. - Centro Sanitario Sandoval, Madrid, Spain.
- 4 - Hospital Universitario La Fe, Valencia, Spain.
5. - Hospital Universitario Ramón y Cajal, Madrid, Spain.
6. - Hospital General de Elche & Universidad Miguel Hernández, Alicante, Spain.
7. - Hospital Universitario de Canarias, Tenerife, Spain.
8. - Hospital Universitario San Cecilio, Granada, Spain.
9. - Hospital Universitario San Pedro-CIBIR, Logroño, Spain.
- 10.- Centre for Statistics in Medicine, University of Oxford. United Kingdom.

Word count: 3348; **Tables:** 3; **Supplementary Tables:** 3; **Appendix:** 1.

Keywords: Psychological distress, Anxiety, Depression, Physical health, Psychopharmacology, mood disorders

Abstract

Background

Psychological distress includes a broader range of experiences, varying from less severe symptoms of depression and anxiety to severe psychiatric disease. Global estimates for depression and anxiety in 2017 were 3.4, and 3.8%, respectively. While for people living with HIV were 16% and 33%, respectively.

Objective

We aimed to determine the prevalence of psychological distress by gender and associated characteristics in patients living with HIV.

Methods

Cross-sectional study conducted within the Spanish HIV Research Network CoRIS. Participants were interviewed by telephone between 2010 and 2014 about their psychological distress, socio-demographics, drug consumption, self-perceived health, and combined antiretroviral therapy (cART) adherence. Laboratory tests and medical history details were collected from CoRIS. Logistic regression was used to identify characteristics associated with psychological distress.

Findings

We interviewed 99 women and 464 men, both living with HIV. A greater proportion of women (51, 51.5%) reported psychological distress than men (179, 38.6%; $P < 0.01$). Non-adherence to cART (OR 4.6 and 2.3, 95% CI 1.4–15.1 and 1.3–4.2) and non-use of cART (8.4 and 1.8, 2.2–32.4 and 1.1–2.8) were related to psychological distress in women and men, respectively. Spending little time in leisure-based physical activity was related to psychological distress in women (3.1, 1.1–9.0). Living alone (2.0, 1.3–3.0) and being unemployed (2.3, 1.4–3.6) were related to psychological distress in men.

Conclusions and Clinical implications

As people living with HIV have a high prevalence of psychological distress, their regular screening appointments should include psychological assessment. A gendered approach is needed to detect and manage psychological distress.

Summary box

What is already known about this subject?

- Psychological distress is highly prevalent in people living with HIV (12-16% screen for symptoms of depression and 33% for symptoms of anxiety).
- Psychological distress relates to poor adherence to combined antiretroviral therapy (cART).
- Women have higher rates of most affective disorders than men, and men have higher rates of substance use disorders and antisocial personality disorder than women.
- When clinicians are aware of a history of mental illness they avoid prescribing efavirenz because it can aggravate these symptoms, and instead use a protease inhibitor or other drug.

What are the new findings?

- Less time spent on leisure-based physical activity was a factor for psychological distress in women.
- Living without a partner and being unemployed were associated with psychological distress in men.
- Non-adherence or non-use of cART, and poor self-perceived health were related to psychological distress in women and men.
- We did not find association between psychological distress and antiretrovirals. However, we did find a non-significant association between atazanavir and psychological distress.

How might it impact on clinical practice in the foreseeable future?

- Women and men living with HIV who report poor self-perceived health or non-adherence to cART should be tested to rule out psychological distress. Based on the findings, including psychological assessment of distress in the regular screening appointments for those living with HIV could help ensure timely interventions for 5 out of 10 women and 4 out of 10 men.
- As patients not prescribed or not adhering to cART had higher risk for psychological distress, and no antiretroviral was associated with psychological distress, interventions to improve cART adherence may also help to manage psychological distress. We consider the provision of

psychological, social work, and biomedical follow-up for people living with HIV to be fundamental in ensuring comprehensive treatment

TEXT

Background

Psychological distress describes unpleasant feelings and emotions that interfere with daily living activities. Sadness, anxiety, depression, distraction, and symptoms of mental illness are manifestations of psychological distress. Psychological distress is highly prevalent in people living with HIV (e.g., a cross-sectional study of 2863 patients from 15 countries in Western Europe and Canada found 16% screening for depression and 33% for anxiety, using the Hospital Anxiety and Depression Scale (HADS) questionnaire, 2010-2011)¹ and is related to stigma,² discrimination, fear of the disease, fear of death, poor quality of life, HIV disease progression (including death),^{3 4} and poor adherence to combined antiretroviral therapy (cART).⁵⁻⁷ Identifying which characteristics are associated with psychological distress will allow healthcare managers and policymakers to create targeted interventions. Although psychoactive treatment is effective, mental illness is underdiagnosed and undertreated in people living with HIV.⁸

Psychological distress prevalence and presentation differs between women and men in the general population.⁹ Women receive more services for psychological distress in primary care settings than do men. Married women have higher mental-health-related admission rates to hospitals than married men. Women have higher rates of most affective disorders than men, and men have higher rates of substance use disorders and antisocial personality disorder than women.⁹

Objective: In this study, we aimed to 1) determine the prevalence of psychological distress among women and men interviewed from a cohort of people living with HIV and 2) identify the characteristics associated with this distress.

Methods

Study patients and ethical information

Participants were recruited from a cohort of people living with HIV enrolled by the AIDS Research Network (CoRIS). CoRIS is a prospective, open, multicentre cohort of patients newly diagnosed with HIV who are over 13 years of age and naïve to antiretroviral treatment at cohort entry (eAppendix A). Each participant signs an informed consent form. CoRIS started to recruit patients in 2004. The cohort has been described in detail elsewhere.¹⁰

Our cross-sectional study started in 2009. At the time, twenty-seven public hospitals and one sexually transmitted infections (STI) clinic were connected to CoRIS.¹¹ Six of the hospitals and the one STI clinic, covering five Spanish regions between them, had available staff and agreed to participate in this study. Physicians from these centres offered the opportunity to participate in this study to their patients who were already included in CoRIS and were 18 years of age or over.

The study was approved by the Institute of Health Carlos III Ethics Committee. Patients signed consent to participate (reference number: PI 45_2009) after they were informed of the nature of the study by clinicians and before the telephone interview.

Data collection

The outcome (psychological distress), socio-demographics, substance and drug consumption, self-perceived health, and cART adherence data were collected in a single telephone interview administered by one trained researcher (LGT) between September 2010 and August 2014. LGT asked the participants questions from a structured questionnaire created for this study. LGT fulfilled the question set during the interview and produced a database with that information.

Outcome

We assessed psychological distress using the 12-item General Health Questionnaire (GHQ-12): 1. Able to concentrate, 2. Lost much sleep, 3. Playing useful part, 4. Capable of making decisions, 5. Under stress, 6. Could not overcome difficulties, 7. Enjoy normal activities, 8. Face up to problems, 9. Feeling unhappy and depressed, 10. Losing confidence, 11. Thinking of self as worthless, and 12. Feeling reasonably happy. The GHQ-12 score has been validated for use in the general population in Spain and has been used

to estimate psychological distress in patients living with HIV.¹² This tool has been used in the Spanish National Health Survey since 2006.

During the telephone interview, participants were asked 12 questions about their symptoms and behaviours during the last month. Each item was rated on a 4-point scale (less than usual, no more than usual, rather more than usual, or much more than usual). A total score was obtained using a bimodal (0-0-1-1) scoring method. Individuals scoring 3 or more (maximum 12) were classified as being in psychological distress.

Potential risk factors collected during the telephone interview

Information on socio-demographics, substance and drug consumption, self-perceived health, and cART adherence were collected during the telephone interview.

Participants were asked their sex, age, origin, completed education level (education answers were then grouped into low and high), marital status, cohabitation, work status.

Interviewees were asked about their monthly income, we included two categories ($\leq 633\text{€}$ or $>633\text{€}$ per month). We binned the eight categories for monthly household income collected in the Spanish into two categories, $\leq 900\text{€}$ and $>900\text{€}$ (eTable 1)

Participants were asked about their drug and substance consumption. They were asked about any psychoactive drug consumption at the time of interview (eTable 2) and their consumption of stimulant drugs in the last month. We grouped illegal and legal drugs for recreational consumption. Participants were asked how many standard units of alcohol they had consumed in the last week.

Participants were asked to self-assess their health. Fair health status was grouped with poor self-assessed health following Spanish norms. Participants self-reported their leisure-based physical activity, and their cART adherence. The Simplified Medication Adherence Questionnaire (SMAQ) was used to assess adherence, as it has been validated for people living with HIV in Spain.¹³

Cohort risk factors

The managers of CoRIS merged the most up-to-date version of their dataset with our interview variables in September 2014. We used follow-up data collected at the latest date before each individual's interview. All clinical, laboratory test, and therapeutic variables associated with HIV infection were collected from

the CORIS database. We obtained a) years since HIV diagnosis, b) HIV transmission route; c) HIV infection stage; d) CD4 cell count/ μl ; e) HIV RNA viral load copies/mL; and f) days on cART.

Current use of cART was stratified into three levels for analysis: inhibitor, inhibitor family, and type of antiretroviral treatment. The five inhibitor families (and specific inhibitors) were nucleos(t)ide analogue reverse transcriptase inhibitors (NRTI), non-nucleoside analogue reverse transcriptase inhibitors (NNRTI), boosted protease inhibitors (PI/r), integrase inhibitors (INSTI), and CCR5 antagonists. We grouped antiretroviral treatment into two categories, the most prescribed triple therapy combining two NRTIs and one NNRTI against other less frequent inhibitor combinations.

Statistical information

Descriptive analysis

Characteristics influencing psychological distress were modelled separately for women and men. Categorical variables were tested using the χ^2 test or Fisher's exact test. Student's t-tests were used for continuous variables with a normal distribution, and the Mann–Whitney U test was used for other distributions. Continuous variables are summarised with the mean and standard deviation. Categorical variables are showed as absolute values and percentages.

Missing data

The CoRIS database was missing information due to the database update process. These data were thus missing completely at random, which allowed us to use the multiple imputation technique to avoid the effects of the missing data.¹⁴ Fifty imputed datasets were created using chained equations and the outcome, HIV transmission category, and selected characteristics. We imputed the following variables: cohabitation, household income, years after HIV diagnosis, HIV transmission category, HIV infection status, CD4 counts, viral load, emtricitabine, nevirapine, efavirenz, atazanavir, and foscarnet. Zidovudine, lamivudine, abacavir, tenofovir, darunavir, lopinavir, saquinavir, raltegravir, dolutegravir, and maraviroc were not included because multicollinearity prevented a stable imputed model from being reached. The estimated parameters were combined using Rubin's rules.

Logistic regression analysis

We generated univariate logistic regression models unadjusted and adjusted by age, years after HIV diagnosis, and education level to identify the characteristics associated with psychological distress separately in women and men. The odds ratio (OR) and 95% confidence interval (CI) were used to measure association. Bootstrap logistic regression model method was used to get final adjusted models. We drew 100 bootstrap samples with replacement from the combined 50 imputed datasets. Collinearity between variables was assessed by the variance inflation factor (VIF). A backward procedure based on the Wald test was used to select significant variables. We omitted antiretrovirals from adjusted model to avoid collinearity with cART adherence.

Sensitivity analysis

Patients on psychoactive drugs were excluded in a sensitivity logistic regression analysis, as these drugs may indicate existing mental health problems.

A trained medical statistician and epidemiologist (CG) conducted all analyses using SPSS v.22.0 and Stata v.13.1. We followed the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement to report this study.

Findings

Study population

We recruited and interviewed 563 individuals living with HIV from the CoRIS cohort. Clinical, laboratory test, and therapeutic variables associated with HIV infection were not available in the CoRIS database for 82 participants (14.6%).

Almost one in five participants were women (99, 17.6%). Women (mean 40 years, SD 10) were older than men (mean 38 years, SD 10).

Psychological distress

More than half of the women (51, 51.5%, 95% CI: 41.2%-61.7%) were in psychological distress, whereas a third of the men were in psychological distress (179, 38.6%, 95% CI: 34.1%-43.2%). Table 1 shows summary statistics of the investigated characteristics of women and men living with HIV.

Characteristics associated with psychological distress

The univariable analysis indicated that lower monthly income, on psychoactive drugs, poorer self-perceived health, and non-adherence to cART or non-cART use were associated with psychological distress in both women and men. Lower physical activity was also associated with psychological distress in women, but not men. Living alone, being unemployed, lower monthly income, lower household income (Table 1), consumption of stimulants and alcohol, primary infection or no symptoms, and shorter time on cART were related to psychological distress in men, but not women (Table 1).

Antiretroviral therapies and inhibitors were not associated with psychological distress in women or men on cART, except for nevirapine and efavirenz in men (Table 2). Atazanavir was used more often by men with psychological distress than men without distress ($P=0.06$).

Eight characteristics were included in the initial multivariable model of psychological distress in women living with HIV before adjustment, falling to four characteristics after adjustment: taking psychoactive drugs, reporting fair or bad health, reporting poor physical activity, and either not adhering to prescribed cART or not prescribed cART (Table 3).

Ten characteristics were included in the initial multivariable model of psychological distress in men living with HIV before adjustment, falling to seven characteristics after adjustment (Table 3). We found a

higher likelihood of psychological distress among men living without a partner, who were unemployed, and who were taking psychoactive drugs (Table 3). As with women, psychological distress in men living with HIV was related to fair or bad health, and either not adhering to prescribed cART or not prescribed cART. Men with symptomatic illness but not AIDS (B stage) were less likely to experience psychological distress than men with a primary infection or no symptoms (A stage) (Table 3).

A sensitivity analysis that excluded women on psychoactive drugs selected the same characteristics as the model of psychological distress in women living with HIV, although it excluded physical activity (OR: 3.2; 1.0 to 10.1; $P=0.052$) (eTable 3). Similarly, the sensitivity analysis excluding male psychoactive drug users selected the same characteristics as the model of psychological distress in men living with HIV, although it excluded symptomatic vs. non-symptomatic HIV status.

Discussion

This study investigated the prevalence of psychological distress among people living with HIV in Spain and identified characteristics that correlated with that distress, by gender. Sex ratio of ~5 men/1 woman found in our study reflects concentrated HIV sub-epidemics characterising European countries, confined mainly to individuals who engage in high risk behaviours, such as men who have sex with men and people who inject drugs. We found a higher prevalence of psychological distress among women living with HIV in Spain than men. Fewer characteristics were associated with psychological distress in women living with HIV (four characteristics) than in men (seven characteristics). Less time spent on leisure-based physical activity was a factor for psychological distress in women, whereas living without a partner and being unemployed were associated with psychological distress in men. Both men and women correctly adhering to cART were less likely to experience psychological distress than those either not prescribed cART or prescribed but being inconsistent in taking cART.

Our population of people living with HIV in Spain had twice the prevalence of psychological distress (51.5% women, 38.6% men) than the general Spanish population (24% women, 17% men in 2011/12) , with a higher prevalence in women than in men in both populations. A cohort of people living with HIV in Stockholm also showed a higher prevalence of psychological distress than the general population of Stockholm County.¹⁵

We found that psychoactive drug consumption was associated with psychological distress in Spanish people living with HIV. The GHQ-12 questionnaire scores that indicated distress correlated with the participants who were undergoing treatment for a psychological condition, as was expected. Treatments for depression and psychological distress in people living with HIV help to reduce depressive symptoms and alleviate psychological distress, and are related to improve adherence to cART.¹⁶

The consumption of psychoactive drugs is high in Spain. The biannual Spanish Household Survey on Alcohol and Drugs for 2013 reported that 27.6% of women and 16.8% of men aged 15–64 had used these drugs at least once in their lives, typically under medical prescription.¹⁷ Only 1.2% of users aged 15–64 who reported consumption of psychoactive drugs in the last 12 months did not have a medical prescription for these drugs, and this subgroup reported worse self-perceived health than those taking the drugs following a medical prescription.

We expected worse self-perceived health and greater HIV disease progression to be associated with psychological distress. This was true for poor self-perceived health in both women and men living with HIV. However, men with symptomatic non-AIDS disease were less likely to report experiencing psychological distress. In contrast, a meta-analysis of 37 prospective cohort studies found that psychological distress was an important risk factor for HIV infection status.¹⁸ Our result may have been affected by the low number of men with symptomatic non-AIDS disease in our cohort.

We found that people living with HIV who reported exercising at least once a week were less likely to report psychological distress. As in the general population, people living with HIV who take part in moderate or vigorous physical activity have less distress. For instance, one study showed that among ageing people with well-controlled HIV, higher levels of physical activity were associated with better physical and mental quality of life.¹⁹

An important concern is how little leisure time that women living with HIV reported spending on physical activity, which was related to psychological distress. The association between physical activity and a lack of psychological distress in women living with HIV mirrors the association seen in women in the general population.^{20 21} There is growing evidence that the social aspects of physical activity may be particularly beneficial for alleviating psychological distress in women, due to the enjoyment associated with spending leisure time in this way.²² This evidence begins to explain why leisure-based physical activity is more consistently associated with a lack of psychological distress than domestic or work-related physical activity.²²

In Spanish culture, as in many others around the world,^{23 24} some gender norms that attribute to women the traditional roles of day-to-day care of the home and family are still maintained,²⁵ resulting in more unpaid work time than men.²⁶ E.g. women spent two hours and a quarter more doing household chores than men every day between 2009 and 2010.²⁶

We found that 41.8% of women living with HIV and 68.1% of men living with HIV who were younger than 65 years were employed. Women living with HIV therefore had lower rates of employment than women in the general population (53.8%). Stigma, self-stigma, and difficulties reconciling working hours and consultations might affect the ability of people living with HIV to work. However, men living with HIV had a similar employment rate to men in the general population (65.5%).

Although women were more likely to be unemployed, unemployment was only a risk factor for psychological distress in men living with HIV. This result suggests that men's function as primary provider of the household income is important for their psychological state.²⁷ In contrast, women may receive the same rewards beyond the workplace, such as caring for children.^{28 29}

In men, living alone was associated with psychological distress in comparison with living with a partner. Women's psychological distress was not affected by whether they lived alone or with a partner, probably because regardless of who they live with, they have to take care of others, whether that be a husband, children, or parents. In contrast, in the traditional family model, a man living with a partner is taken care of. However, more than half of the participants in our study were men in same-sex relationships. As a consequence, traditional gender norms (provider-caregiver) may not apply. Therefore, other explanatory factors may determine who in the couple assumes the function of provider or caregiver.³⁰ Some studies have shown disadvantages in health, especially in mental health, in homosexual people, due to their exposure to discrimination. However, these health disadvantages may also be an effect of their family structure, which may not afford these men the advantages of the traditional partnership.³¹

cART has been associated with side effects such as fatigue, insomnia, dizziness, and neuropathy, which can all cause poorer self-perceived health.³² However, we found that participants with poor adherence to, or no prescription for, cART were more likely to report psychological distress. Our findings agree with other studies showing significant improvements in emotional outlook and less distress in patients on cART.^{33 34}

Atazanavir was the only protease inhibitor related to psychological distress in the multivariable model for men. Uncommon psychological disorders (between 1 in 100 and 1 in 1000 cases) have reportedly been caused by atazanavir, including depression, disorientation, anxiety, insomnia, sleep disorder, and abnormal dreams³⁵. The lack of association between psychological distress and antiretrovirals found here may be because the physicians in our study prescribed the antiretrovirals that had the smallest chance of producing psychological distress in their patients.

Limitations

The main limitation of our study was the low number of women in comparison with men, which resulted in wider confidence intervals in the women's model than in the men's model. Samples of 99 women and

464 men allow to find odds ratios associated with psychological distress equals or higher than 3.7 and 1.8 respectively. A further study including higher number of women might help to find less strong associations with psychological distress in women. A telephone interview would be able to introduce bias reporting responses by participants.³⁶ Underreporting bias could occur for socially undesirable behaviours, such as alcohol consumption and illicit drug consumption that a self-completed questionnaire could have had less influence on the response.³⁷ These biases were minimised using a structured questionnaire administered by a trained interviewer.

Clinical information was missing from the CoRIS database for 3% of women and 11% of men. However, the data were missing completely at random, allowing us to use multiple imputation methods to negate the effects of the missing data.

Screening positive on the GHQ-12 for psychological distress has been related to anxiety and depression.³⁸ This tool is less sensitive to other disorders that are more common in men, such as alcoholism and drug addiction.³⁹ The tool is therefore likely to overestimate psychological distress in women (who have a higher prevalence of anxiety and depression than men) and underestimate it in men.⁹³⁹ Finally, as this is a cross-sectional study, we cannot establish risk factors that preceded the reported psychological distress.

Clinical implications

Clinicians could advise women living with HIV who report psychological distress to increase their leisure-based physical activity, in addition to psychoactive drugs, as little time in this activity is a risk factor for psychological distress in this group. Interventions to cope with unemployment and living alone could help men living with HIV to manage their emotional status.

Women and men living with HIV who report poor self-perceived health or non-adherence to cART should would be tested to rule out psychological distress. Based on the findings, including psychological assessment of distress in the regular screening appointments for those living with HIV could help ensure timely interventions for 5 out of 10 women and 4 out of 10 men.

Acknowledgements

This study would not have been possible without the collaboration of the participating patients, medical and nursery staff, and data managers. The authors thank to the pharmacist Marta Rodríguez-Alarcón Martín for classifying psychoactive drugs. The authors also thank Ed Burn for revising the manuscript. We acknowledge English language editing by Dr Jennifer A de Beyer of the Centre for Statistics in Medicine, University of Oxford. Centres and investigators involved in CoRIS are listed in Appendix A.

Competing Interests

Dr Garriga, Ms Gutiérrez-Trujillo, Dr Culqui Levano, Dr del Romero, Dr Gómez-Sirvent, Dr Peña-Monje, and Dr Rodríguez-Arenas declare that they have no conflicts of interest. Mrs Montero reports personal fees outside the submitted work from Bristol-Myers Squibb, ViiV Healthcare, Merck, Abbvie, Gilead Sciences, Janssen, Abbott Laboratories, and Pfizer. Dr Pérez-Elías reports personal fees from Bristol-Myers Squibb and grants and personal fees from ViiV Healthcare, Janssen, and Gilead Sciences, outside the submitted work. Dr Gutiérrez reports personal fees from Gilead Sciences, Janssen Cilag, and ViiV Healthcare, outside the submitted work. Dr Blanco has carried out consulting work for Abbvie, Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck, and ViiV Healthcare; received compensation for lectures from Abbvie, Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck, and ViiV Healthcare; and received grants and payments for the development of educational presentations from Gilead Sciences, Bristol-Myers Squibb, and ViiV Healthcare, outside the submitted work.

Funding

The study was supported by Fondo de Investigación Sanitaria: FIS:PI09/1889. CoRIS is supported by the Instituto de Salud Carlos III through the Red Temática de Investigación Cooperativa en Sida (RD06/006, RD12/0017/0018 and RD16/0002/0006) as part of the Plan Nacional R+D+I and cofinanced by ISCIII-Subdirección General de Evaluación y el Fondo Europeo de Desarrollo Regional (FEDER).

César Garriga was supported by the 12/PEAC-06 grant from the Spanish Field Epidemiology Training Programme (“Programa de Epidemiología Aplicada de Campo”), Institute of Health Carlos III (“Instituto de Salud Carlos III”). The funders had no role in study design, data collection and analysis, decision to publish, or manuscript preparation.

This paper presents independent results and/or research. The views expressed are those of the author(s) and not necessarily those of the Instituto de Salud Carlos III.

References

1. Robertson K, Bayon C, Molina JM, et al. Screening for neurocognitive impairment, depression, and anxiety in HIV-infected patients in Western Europe and Canada. *AIDS care* 2014;26(12):1555-61. doi: 10.1080/09540121.2014.936813 [published Online First: 2014/07/17]
2. Stangl AL, Lloyd JK, Brady LM, et al. A systematic review of interventions to reduce HIV-related stigma and discrimination from 2002 to 2013: how far have we come? *Journal of the International AIDS Society* 2013;16(3 Suppl 2):18734. doi: 10.7448/ias.16.3.18734 [published Online First: 2013/11/28]
3. Pence BW, Mills JC, Bengtson AM, et al. Association of Increased Chronicity of Depression With HIV Appointment Attendance, Treatment Failure, and Mortality Among HIV-Infected Adults in the United States. *JAMA psychiatry* 2018;75(4):379-85. doi: 10.1001/jamapsychiatry.2017.4726 [published Online First: 2018/02/22]
4. Todd JV, Cole SR, Pence BW, et al. Effects of Antiretroviral Therapy and Depressive Symptoms on All-Cause Mortality Among HIV-Infected Women. *American journal of epidemiology* 2017;185(10):869-78. doi: 10.1093/aje/kww192 [published Online First: 2017/04/22]
5. Nurutdinova D, Chrusciel T, Zeringue A, et al. Mental health disorders and the risk of AIDS-defining illness and death in HIV-infected veterans. *AIDS (London, England)* 2012;26(2):229-34. doi: 10.1097/QAD.0b013e32834e1404 [published Online First: 2011/11/18]
6. Gonzalez JS, Batchelder AW, Psaros C, et al. Depression and HIV/AIDS treatment nonadherence: a review and meta-analysis. *Journal of acquired immune deficiency syndromes (1999)* 2011;58(2):181-7. doi: 10.1097/QAI.0b013e31822d490a [published Online First: 2011/08/23]
7. Langebeek N, Gisolf EH, Reiss P, et al. Predictors and correlates of adherence to combination antiretroviral therapy (ART) for chronic HIV infection: a meta-analysis. *BMC medicine* 2014;12:142. doi: 10.1186/preaccept-1453408941291432 [published Online First: 2014/08/26]
8. Do AN, Rosenberg ES, Sullivan PS, et al. Excess burden of depression among HIV-infected persons receiving medical care in the united states: data from the medical monitoring project and the behavioral risk factor surveillance system. *PloS one* 2014;9(3):e92842. doi: 10.1371/journal.pone.0092842 [published Online First: 2014/03/26]
9. Afifi M. Gender differences in mental health. *Singapore medical journal* 2007;48(5):385-91. [published Online First: 2007/04/25]
10. Caro-Murillo AM, Castilla J, Perez-Hoyos S, et al. [Spanish cohort of naive HIV-infected patients (CoRIS): rationale, organization and initial results]. *Enfermedades infecciosas y microbiologia clinica* 2007;25(1):23-31. [published Online First: 2007/01/31]
11. Sobrino-Vegas P, Gutierrez F, Berenguer J, et al. [The Cohort of the Spanish HIV Research Network (CoRIS) and its associated biobank; organizational issues, main findings and losses to follow-up]. *Enfermedades infecciosas y microbiologia clinica* 2011;29(9):645-53. doi: 10.1016/j.eimc.2011.06.002 [published Online First: 2011/08/09]

12. Yi S, Chhoun P, Suong S, et al. AIDS-related stigma and mental disorders among people living with HIV: a cross-sectional study in Cambodia. *PLoS one* 2015;10(3):e0121461. doi: 10.1371/journal.pone.0121461 [published Online First: 2015/03/26]
13. Knobel H, Alonso J, Casado JL, et al. Validation of a simplified medication adherence questionnaire in a large cohort of HIV-infected patients: the GEEMA Study. *AIDS (London, England)* 2002;16(4):605-13. [published Online First: 2002/03/02]
14. Bhaskaran K, Smeeth L. What is the difference between missing completely at random and missing at random? *International journal of epidemiology* 2014;43(4):1336-9. doi: 10.1093/ije/dyu080 [published Online First: 2014/04/08]
15. Jallow A, Ljunggren G, Wandell P, et al. HIV-infection and psychiatric illnesses - A double edged sword that threatens the vision of a contained epidemic: The Greater Stockholm HIV Cohort Study. *The Journal of infection* 2017;74(1):22-28. doi: 10.1016/j.jinf.2016.09.009 [published Online First: 2016/10/09]
16. Sin NL, DiMatteo MR. Depression treatment enhances adherence to antiretroviral therapy: a meta-analysis. *Annals of behavioral medicine : a publication of the Society of Behavioral Medicine* 2014;47(3):259-69. doi: 10.1007/s12160-013-9559-6 [published Online First: 2013/11/16]
17. Survey on Alcohol and drugs in the General population in Spain. 1995-2013. Madrid: National Plan on Drugs. Health Ministry, 2015: 120 pp.
18. Chida Y, Vedhara K. Adverse psychosocial factors predict poorer prognosis in HIV disease: a meta-analytic review of prospective investigations. *Brain, behavior, and immunity* 2009;23(4):434-45. doi: 10.1016/j.bbi.2009.01.013 [published Online First: 2009/06/03]
19. Erlandson KM, Allshouse AA, Jankowski CM, et al. Relationship of physical function and quality of life among persons aging with HIV infection. *AIDS (London, England)* 2014;28(13):1939-43. doi: 10.1097/qad.0000000000000384 [published Online First: 2014/07/06]
20. Griffiths A, Kouvonen A, Pentti J, et al. Association of physical activity with future mental health in older, mid-life and younger women. *European journal of public health* 2014;24(5):813-8. doi: 10.1093/eurpub/ckt199 [published Online First: 2014/02/18]
21. Mammen G, Faulkner G. Physical activity and the prevention of depression: a systematic review of prospective studies. *American journal of preventive medicine* 2013;45(5):649-57. doi: 10.1016/j.amepre.2013.08.001 [published Online First: 2013/10/22]
22. Asztalos M, Wijndaele K, De Bourdeaudhuij I, et al. Specific associations between types of physical activity and components of mental health. *Journal of science and medicine in sport / Sports Medicine Australia* 2009;12(4):468-74. doi: 10.1016/j.jsams.2008.06.009 [published Online First: 2008/09/05]
23. Addati LC, U.; Esquivel, V.; Valarino, I. Care work and care jobs for the future of decent work. Geneva, Switzerland: International Labour Office (ILO), 2018.
24. Parent-Thirion AB, I.; Cabrita, J.; Vargas, O.; Vermeylen, G.; Wilczynska, A.; Wilkens, M. Sixth European Working Conditions Survey – Overview report (2017 update). Luxembourg: Eurofound 2017.

25. Garcia-Mochon L, Pena-Longobardo LM, Del Rio-Lozano M, et al. Determinants of Burden and Satisfaction in Informal Caregivers: Two Sides of the Same Coin? The CUIDAR-SE Study. *International journal of environmental research and public health* 2019;16(22) doi: 10.3390/ijerph16224378 [published Online First: 2019/11/14]
26. Spanish Time Use Survey 2009-2010: Spanish, Statistical Office, INE, 2011.
27. Barbaglia MG, ten Have M, Dorsselaer S, et al. Negative socioeconomic changes and mental disorders: a longitudinal study. *Journal of epidemiology and community health* 2015;69(1):55-62. doi: 10.1136/jech-2014-204184 [published Online First: 2014/09/11]
28. Artazcoz L, Benach J, Borrell C, et al. Unemployment and mental health: understanding the interactions among gender, family roles, and social class. *American journal of public health* 2004;94(1):82-8. [published Online First: 2004/01/10]
29. Garcia Calvente M, del Rio Lozano M, Marcos Marcos J. [Gender inequalities in health deterioration as a result of informal care in Spain]. *Gac Sanit* 2011;25 Suppl 2:100-7. doi: 10.1016/j.gaceta.2011.09.006 [published Online First: 2011/11/18]
30. Kurdek LA. The Allocation of Household Labor by Partners in Gay and Lesbian Couples. *Journal of Family Issues* 2007;28(1):132-48. doi: 10.1177/0192513X06292019
31. Gonzales G, Przedworski J, Henning-Smith C. Comparison of Health and Health Risk Factors Between Lesbian, Gay, and Bisexual Adults and Heterosexual Adults in the United States: Results From the National Health Interview Survey. *JAMA internal medicine* 2016;176(9):1344-51. doi: 10.1001/jamainternmed.2016.3432 [published Online First: 2016/07/02]
32. daCosta DiBonaventura M, Gupta S, Cho M, et al. The association of HIV/AIDS treatment side effects with health status, work productivity, and resource use. *AIDS care* 2012;24(6):744-55. doi: 10.1080/09540121.2011.630363 [published Online First: 2012/02/02]
33. Beard J, Feeley F, Rosen S. Economic and quality of life outcomes of antiretroviral therapy for HIV/AIDS in developing countries: a systematic literature review. *AIDS care* 2009;21(11):1343-56. doi: 10.1080/09540120902889926 [published Online First: 2009/12/22]
34. Gutiérrez F, García L, Padilla S, et al. Risk of clinically significant depression in HIV-infected patients: effect of antiretroviral drugs. *HIV medicine* 2014;15(4):213-23. doi: 10.1111/hiv.12104
35. Reyataz. Annex I - Summary of product characteristics. London: EMA, 2009.
36. Delgado-Rodríguez M, Llorca J. Bias. *Journal of epidemiology and community health* 2004;58(8):635-41. doi: 10.1136/jech.2003.008466
37. White B, Day C, Maher L. Self reported risk behaviour among injecting drug users: self versus assisted questionnaire completion. *AIDS care* 2007;19(3):441-7. doi: 10.1080/09540120701192837 [published Online First: 2007/04/25]
38. Holli MM, Marttunen M, Aalberg V. Comparison of the GHQ-36, the GHQ-12 and the SCL-90 as psychiatric screening instruments in the Finnish population. *Nordic Journal of Psychiatry* 2003;57(3):233-38. doi: 10.1080/08039480310001418
39. Bones Rocha K, Perez K, Rodriguez-Sanz M, et al. [Prevalence of mental health problems and their association with socioeconomic, work and health variables: Findings from the

Spain National Health Survey]. *Psicothema* 2010;22(3):389-95. [published Online First: 2010/07/30]

Tables

Table 1. Socio-demographic, clinical and lifestyle characteristics of women and men living with HIV at the time of interview and their association with psychological distress^a.

	Women (n=99; 51 in distress)			Men (n=464; 179 in distress)		
	N	n (%)	<i>P</i> value ^b	N	n (%)	<i>P</i> value ^b
Age^c	99	41±11	0.73	464	38±10	0.70 ^e
<30 years	15	9 (60)	0.86	110	44 (40)	0.43
30 to 39	34	16 (47.1)		183	64 (35.0)	
40 to 49	30	16 (53.3)		113	50 (44.3)	
>50	20	10 (50.0)		58	21 (36.2)	
Origin			0.84			0.73
Spaniards	65	33 (50.8)		336	128 (38.1)	
Foreigners	34	18 (52.9)		128	51 (39.8)	
Education level completed			0.14			0.32
Illiterate, primary, lower secondary	59	34 (57.6)		128	54 (42.2)	
Upper secondary, University	40	17 (42.5)		336	125 (37.2)	
Marital status			0.76			0.77
Single	53	26 (49.1)		341	134 (39.3)	
Married	20	10 (50.0)		88	31 (35.2)	
Separated, divorced, widow-er	26	15 (57.7)		35	14 (40.0)	
Cohabitation			0.94			<0.01
Living with a partner	54	28 (51.9)		176	47 (26.7)	
Living alone, others	45	23 (51.1)		288	132 (45.8)	
Work status			0.20			<0.01
Employed	41	17 (41.5)		311	103 (33.1)	
Unemployed	36	20 (55.6)		112	58 (51.8)	
Pensioner, retiree, student, housewife, others	22	14 (63.6)		41	18 (43.9)	

Monthly income			0.03		0.04	
>633€	27	9 (33.3)		338	121 (35.8)	
≈<633€	72	42 (58.3)		126	58 (46.0)	
Monthly household income			0.85		<0.01	
≤900 €	26	13 (50.0)		55	32 (58.2)	
>900 €	71	37 (52.1)		407	147 (36.1)	
On psychoactive drugs			<0.01		<0.01	
Yes	24	20 (83.3)		58	36 (62.1)	
No	75	31 (41.3)		406	143 (35.2)	
Stimulants last month			0.34 ^d		0.05	
Yes	4	3 (75.0)		107	50 (46.7)	
No	95	48 (50.5)		357	129 (36.1)	
Standard alcohol units per week^c	99	2.7±2.9	0.77 ^e	464	8.6±12.6	0.04 ^e
Drink			0.87		0.99	
Yes	40	21 (52.5)		355	137 (38.6)	
Abstainer	59	30 (50.8)		109	42 (38.5)	
Self-perceived health			<0.01		<0.01	
Very good, good	65	26 (40.0)		378	126 (33.3)	
Fair, bad, very bad	34	25 (73.5)		86	53 (61.6)	
Physical activity (/)			<0.01		0.07	
None to several a month	63	40 (63.5)		183	80 (43.7)	
Once to several a week	36	11 (30.6)		281	99 (35.2)	
Years after HIV diagnosis^c	88	5.1±4.0	0.09 ^e	337	4.2±4.1	0.80 ^e
Until 3 years	36	18 (50.0)	0.13	191	69 (36.1)	0.62
3 to 6	20	11 (55.0)		68	24 (35.3)	
6 to 29	32	13 (40.6)		78	33 (42.3)	
Unknown	11	9 (81.8)		127	53 (41.7)	
HIV transmission category			0.32		0.42	

IDU	8	5 (62.5)	28	10 (35.7)		
MSM non-IDU		0 (—)	291	112 (38.5)		
Heterosexual non-IDU	86	42 (48.8)	59	21 (35.6)		
Other ^f		0 (—)	8	1 (12.5)		
HIV infection status^g					0.21 ^d	0.03
A primary infection, non-symptomatic	72	38 (52.8)	343	136 (39.7)		
B (symptomatic)	13	7 (53.8)	25	3 (12.0)		
C (AIDS)	9	2 (22.2)	19	6 (31.6)		
Unknown	5	4 (80.0)	34	34 (44.2)		
CD4 count/μl					0.63 ^e	0.92 ^e
<200	4	2 (50.0)	13	5 (38.5)		
200 to <350	13	5 (38.5)	50	17 (34.0)		
350 to <500	25	11 (44.0)	106	38 (36.2)		
\geq 500	57	29 (55.8)	295	84 (38.9)		
Viral load (RNA copies/mL)					0.79	0.44
<50	56	26 (46.4)	171	59 (34.5)		
50 to <500	13	7 (53.9)	40	17 (42.5)		
500 to <30,000	13	8 (61.5)	110	47 (42.7)		
\geq 30,000	17	6 (50.0)	143	22 (33.9)		
cART adherence					0.02	0.04
Adherence	46	15 (32.6)	167	49 (29.3)		
Non-adherence	30	19 (63.3)	78	39 (50.0)		
Non-user	23	17 (73.9)	219	91 (41.6)		
Years since cART initiation^{c, h}	83	3.4 \pm 2.1	226	2.8 \pm 2.0	0.80 ^e	0.03 ^e
Until 2 years	24	13 (54.2)	95	40 (42.1)	0.23	0.39
2 to 4	29	12 (41.4)	69	21 (31.9)		
4 to ~8	30	14 (46.7)	59	18 (30.5)		
Unknown	2	1 (50.0)	33	12 (36.4)		

Never on cART

14 11 (78.6)

208 87 (41.8)

^aGeneral Health Questionnaire (GHQ-12) scores of 3 or higher, ^bsignificance level comparing psychological distress versus no distress, ^cmean±standard deviation; ^dFisher's exact test 2-sided, ^eMann-Whitney U test, ^ftransfusion, acupuncture, tattoo, piercing, wound, ^gcase definition for HIV infection defined by the CDC, ^honly for patients who had started cART.

IDU, injection drug users; MSM, men who have sex with men; cART, combined antiretroviral therapy.

Table 2. Antiretroviral treatments and inhibitors prescribed to women and men living with HIV and their association with psychological distress^a

Treatment variables	Women (n=74 [*] ; 34 in distress)		Men (n=217 [*] ; 78 in distress)	
	n (%)	<i>P</i> value ^b	n (%)	<i>P</i> value ^b
2 NRTI + 1 NNRTI		0.54		0.36
Yes	18 (42.9)		45 (33.6)	
Other treatments	16 (50.0)		33 (39.8)	
NRTIs		1.00 ^c		0.29 ^c
Yes	32 (45.7)		73 (35.1)	
No	2 (50.0)		5 (55.6)	
Zidovudine		1.00 ^c		0.35 ^c
Yes	2 (40.0)		3 (60.0)	
No	32 (46.4)		75 (35.4)	
Lamivudine		0.81		0.47
Yes	11 (44.0)		19 (40.4)	
No	23 (46.9)		59 (34.7)	
Emtricitabine		0.71		0.21
Yes	21 (47.7)		54 (33.5)	
No	13 (43.3)		24 (42.9)	
Abacavir		0.95		0.50
Yes	7 (46.7)		17 (40.5)	
No	27 (45.8)		61 (34.9)	
Tenofovir		0.64		0.10
Yes	23 (47.9)		54 (32.9)	
No	11 (42.3)		24 (45.3)	
NNRTI		0.29		0.34
Yes	18 (40.9)		46 (33.6)	
No	16 (53.3)		32 (40.0)	
Nevirapine		0.50 ^c		0.04

Yes	6 (60.0)		9 (60.0)	
No	28 (43.8)		69 (34.2)	
Efavirenz		0.20		0.02
Yes	12 (37.5)		33 (28.9)	
No	22 (52.4)		45 (43.7)	
PI		0.77		0.25
Yes	13 (48.1)		29 (41.4)	
No	21 (44.7)		49 (33.3)	
Atazanavir		1.00 ^c		0.06
Yes	4 (50.0)		12 (54.5)	
No	30 (45.5)		66 (33.8)	
Darunavir		1.00 ^c		0.95
Yes	4 (50.0)		11 (35.5)	
No	30 (45.5)		67 (36.0)	
Lopinavir		0.75 ^c		1.00 ^c
Yes	4 (40.0)		4 (33.3)	
No	30 (46.9)		74 (36.1)	
Saquinavir		—		0.54 ^c
Yes	0 (—)		0 (—)	
No	34 (45.9)		78 (36.3)	
INI		1.00 ^c		0.93
Yes	3 (42.9)		7 (36.8)	
No	31 (46.3)		71 (35.9)	
Raltegravir		1.00 ^c		0.95
Yes	3 (42.9)		6 (35.3)	
No	31 (46.3)		72 (36.0)	
Dolutegravir		—		1.00 ^c
Yes	0 (—)		1 (50.0)	

No	34 (45.9)		77 (35.8)
Maraviroc		1.00 ^c	1.00 ^c
Yes	0 (—)		0 (—)
No	34 (46.6)		78 (36.1)

^aGeneral Health Questionnaire (GHQ-12) scores of 3 or higher, ^bsignificance level comparing psychological distress versus no distress, ^cFisher's exact test 2-sided.

^aThis table only shows participants for whom information on their antiretroviral treatment (ART) was available. It excludes the 242 non-users of ART and 30 users of ART.

NRTI, nucleos(t)ide analogue reverse transcriptase inhibitors; NNRTI, nonnucleoside analogue reverse transcriptase inhibitors; PI, protease inhibitors; INI, integrase inhibitors.

≤900 €							2.5	[1.4-4.4]*	2.5	[1.4-4.5]*		
On psychoactive drugs (no)												
Yes	7.1	[2.2-22.8]*	8.3	[2.4-29.1]*	8.0	[2.0-31.8]*	3.0	[1.7-5.3]*	3.1	[1.8-5.6]*	2.2	[1.2-4.1]*
Stimulants last month (no)												
Yes							1.6	[1.0-2.5]*	1.6	[1.0-2.5]		
Self-perceived health (very good, good)												
Fair, bad, very bad	4.2	[1.9-10.3]*	3.7	[1.4-9.7]*	4.0	[1.3-11.9]*	3.2	[2.0-5.2]*	3.2	[1.9-5.2]*	2.8	[1.6-4.7]*
Physical activity (once to several times a week)												
None to several times a month	4.0	[1.7-9.5]*	3.8	[1.5-9.5]*	3.1	[1.1-9.0]*	1.4	[1.0-2.1]	1.4	[0.9-2.1]		
Years after HIV diagnosis (until 3 years)												
3 to 6	1.2	[0.4-3.6]	1.3	[0.4-4.1]			1.0	[0.5-1.7]	1.0	[0.5-1.7]		
6 to 29	0.7	[0.3-1.8]	0.7	[0.3-1.9]			1.3	[0.7-2.2]	1.3	[0.8-2.2]		
Unknown	4.7	[0.5-45.9]	4.7	[0.5-44.4]			1.3	[0.8-2.1]	1.3	[0.8-2.0]		
HIV infection status (A primary infection, non-symptomatic)												

B symptomatic ^b	1.0	[0.3-3.4]	0.9	[0.2-3.1]			0.2	[0.1-0.8]*	0.2	[0.1-0.8]*	0.2	[0.1-0.8]*
C AIDS	0.3	[0.1-1.6]	0.2	[0.04-1.5]			0.7	[0.3-1.8]	0.6	[0.2-1.6]		
cART (adherence)												
Non-adherence	3.6	[1.4-9.4]*	4.2	[1.4-11.8]*	4.6	[1.4-15.1]*	2.4	[1.4-4.2]*	2.4	[1.4-4.2]*	2.3	[1.3-4.2]*
Non-user	5.9	[1.9-17.9]*	6.7	[2.1-21.9]*	8.4	[2.2-32.4]*	1.7	[1.1-2.6]*	1.7	[1.1-2.8]*	1.8	[1.1-2.8]*
On emtricitabine (no)												
Yes	0.7	[0.3-1.6]	0.6	[0.3-1.5]			0.8	[0.5-1.2]	0.8	[0.5-1.2]		
On nevirapine (no)												
Yes	1.2	[0.3-4.6]	1.4	[0.3-5.7]			2.4	[0.9-6.9]	2.5	[0.9-7.1]		
On efavirenz (no)												
Yes	0.4	[0.2-1.0]*	0.3	[0.1-0.8]*			0.6	[0.4-0.9]*	0.6	[0.4-0.9]*		
On atazanavir (no)												
Yes	1.0	[0.2-4.2]	1.5	[0.3-7.0]			1.9	[0.8-4.6]	2.0	[0.8-4.9]		

Reference categories are shown in brackets, * $P < 0.05$. [¥] age, years after HIV diagnosis, and education level completed.

^aGeneral Health Questionnaire (GHQ-12) scores of 3 or higher, ^bOf them, 10 (40%) lived with a partner, 15 (60%) were employed, 23 (92%) were not on psychoactive drugs, 22 (88%) reported good self-perceived health, 16 (64%) had cART adherence, and 24 (96%) were not on atazanavir. cART: combined antiretroviral therapy; CI: confidence intervals

