

ORIGINAL ARTICLE

Perception of HIV physicians in Spain towards diagnosis and management of neuropsychiatric comorbidities in people with HIV

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Abstract

Objectives: Despite the importance of neuropsychiatric comorbidities (NPCs) in people with HIV, the degree of physician compliance with recommendations for diagnosis and management is unknown. This study assessed the perceptions, knowledge, skills, and attitudes of physicians regarding the diagnosis and management of NPCs in people with HIV in hospital settings in Spain.

Methods: This was a cross-sectional study including non-psychiatrist HIV specialist physicians responsible for antiretroviral therapy (ART) prescription and clinical care of ≥ 50 people with HIV/month, who completed an online survey of 34 questions.

Results: The 115 physicians who completed the survey (totally) agreed that assessing mental health was relevant (97.4%) and that NPCs were underdiagnosed (76.6%) and were very/fairly sensitized (67.8%). However, they reported receiving little/no training on the detection of NPCs (64.3%). Physicians considered that patients underreported NPCs (53.9%) and that alcohol (94.8%), recreational substances (97.4%), and tobacco consumption (95.6%) were (very) relevant. Physicians agreed that NPCs were difficult to identify (52.2%) and that few tools were available (53.0%) and failed to use questionnaires (79.1%) and follow guidelines (77.4%) for the detection of NPCs. The main reasons precluding appropriate diagnosis and evaluation were lack of proactive attitudes and specific training and limited visit time. Upon detection of NPCs, physicians referred patients to the in-house psychiatry/psychology centre (61.7%), adjusted ART to minimize interactions (96.5%), and managed NPCs in conjunction with mental health professionals (71.3%).

Conclusions: Physicians in hospital settings in Spain were aware of the relevance of NPC diagnosis and their underdiagnosis. However, they still failed to routinely evaluate NPCs, follow guideline recommendations, and use questionnaires, highlighting opportunities for improved NPC detection and management in people with HIV.

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KEYWORDS

diagnosis, mental health, neuropsychiatric comorbidities, people with HIV, physician's perceptions

INTRODUCTION

HIV-associated neuropsychiatric comorbidities (NPCs), including neurocognitive impairment and neuropsychiatric disorders, are a significant source of concern in the care of people with HIV because of their high impact on quality of life [1,2]. Mental health disorders contribute to poor HIV health outcomes by reducing adherence to medication and promoting unhealthy behaviors [1]. In particular, depression has been shown to reduce medication adherence, quality of life, and treatment outcomes and is considered a predictor of adverse clinical outcomes [3,4].

Despite the contribution of antiretroviral therapy (ART) to reducing HIV-associated central nervous system (CNS) disease, several studies have reported neurotoxic effects in association with some ART regimens [5,6]. ART-induced neurotoxicity contributes to increasing rates of NPCs among people with HIV, including depression, anxiety, and HIV-associated neurocognitive disorders [1,7], and people with HIV and NPCs seem to be more likely to develop ART-induced neurotoxicity [6]. Furthermore, certain CNS effects caused by ART are difficult to distinguish from the direct and indirect effects of the virus itself, and the neurotoxic effects of some ART remain controversial [5].

Given the high prevalence and negative impact of NPCs and ART-induced neurotoxicity on HIV health outcomes, healthcare practitioners acknowledge the need for mental health screening and care provision among people with HIV [1,8]. As such, guidelines recommend screening all people with HIV for depression and cognitive impairment every 1–2 years and for ART-induced neurotoxicity at least after starting a new regimen. Guidelines emphasize the importance of early detection of NPCs and referring people with HIV with a suspected diagnosis to receive specialized care [9–11].

Despite its theoretical importance, the degree of practical compliance with recommendations for the diagnosis and management of NPCs in people with HIV in the Spanish real-world setting is unknown. Previous studies suggested that mental health disorders in people with HIV may be underdiagnosed [1]. In this cross-sectional study, we assessed the perceptions, knowledge, skills, and attitudes of non-psychiatrist physicians providing care to people with HIV in hospital settings in Spain in terms of the management of NPCs and ART-induced neurotoxicity. Additionally, we assessed differences in the management

of NPCs according to physicians' demographic and professional characteristics and their hospital characteristics.

MATERIALS AND METHODS**Study design and population**

This was a cross-sectional study including HIV specialists with >4 years of experience from Spanish hospitals who accepted the invitation to complete an online survey regarding the management of NPCs in people with HIV between 10 February and 27 March 2020. Participant physicians were required to be directly responsible for ART prescription and the clinical care of ≥ 50 people with HIV/month; psychiatrists were excluded. Recruitment was geographically stratified to ensure a homogeneous representation of the overall Spanish territory. All study participants voluntarily took part in the study and received a compensatory fee for their time. Data were collected in an irreversibly anonymized fashion; the study was conducted in accordance with the local Personal Data Protection Law (LOPD 15/1999).

The sponsor of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report, with the exception of providing funding for medical writing assistance, provided by i2e3 biomedical research institute. Amber business and customer solutions recruited the participants, administered the online survey, and conducted the statistical analyses. The authors had full access to all the datasets and the analyses performed.

Variables and assessments

The primary objective of this study was to evaluate the perceptions, knowledge, skills, and attitudes of non-psychiatric physicians caring for people with HIV regarding the management of NPCs and to analyse differences according to physicians' demographic and professional characteristics and centre characteristics. Physicians answered an online survey consisting of 34 questions with multiple closed answers that was designed ad hoc by an expert team of infectious disease physicians, psychiatrists, and psychologists. The survey was organized in five blocks: opinion regarding management of NPCs in people with HIV (eight questions), knowledge of CNS manifestations

(eight questions), attitude towards identification of CNS manifestations (three questions), actions towards identification and management of CNS manifestations (seven questions), and knowledge regarding management of NPCs in people with HIV (eight questions) (Table S1-S4). Physicians provided information on their demographic and professional characteristics, including sex, age, specialization, treatment of only/mostly people with HIV (yes/no), years of experience (in both clinical practice and HIV), and the number of people with HIV treated per month, which was recorded in the questionnaire platform before they completed the questionnaire. Additional centre-related characteristics were hospital size (number of beds) and availability of a psychiatrist and/or psychologist for people with HIV in the same centre (yes/no).

Statistical analysis

Considering a maximum uncertainty level of $p = q = 0.5$, a sample size of 120 physicians treating people with HIV from the northeast ($n = 30$ each region), south ($n = 24$), east/south east ($n = 21$), and north ($n = 15$) of Spain was deemed necessary to represent the Spanish population with a $\pm 8.4\%$ precision and a 95.5% confidence interval.

Categorical variables were described as frequencies and percentages, and quantitative variables were described as the mean and standard deviation (SD). To identify factors potentially influencing the professionals' perceptions, physicians were categorized according to age (≤ 50 and > 50 years), the number of patients treated (≤ 110 and > 110 patients/month), experience treating patients with HIV (≤ 20 and > 20 years), and size of the hospital (≤ 500 and > 500 beds). Differences between groups according to these categories and according to categorical variables, including sex, treatment of only/mostly people with HIV (yes/no), and availability of a psychiatrist and/or psychologist for managing people with HIV at the treatment centre (yes/no), were analysed using the *T*-test over two columns. The significance threshold for all bivariate analyses was set at a two-sided $\alpha = 0.05$.

RESULTS

Characteristics of study participants

A total of 115 physicians, with mean (SD) ages of 54.8 (8.8) and 50.4 (6.9) years for men and women, respectively, participated in the study and completed the survey. Physicians treated a mean (SD) of 124.8 (49.8) patients/month and had a mean (SD) of 22.0 (8.3) and 20.2 (7.5) years of clinical experience overall and in treating people

TABLE 1 Sociodemographic and professional characteristics of study participants and center-related characteristics, n (%) $N = 115$

| | |
|---|-----------|
| Sociodemographic characteristics | |
| Sex | |
| Male | 69 (60.0) |
| Female | 46 (40.0) |
| Age, years | |
| ≤ 50 | 47 (40.9) |
| > 50 | 68 (59.1) |
| Geographical origin | |
| Centre | 29 (25.2) |
| North-east | 25 (21.7) |
| South | 22 (19.1) |
| East and south-east | 21 (18.3) |
| North | 18 (15.7) |
| Professional characteristics | |
| Specialization | |
| Infectious disease | 60 (52.2) |
| Internal medicine | 55 (47.8) |
| Treats only/mostly patients with HIV | |
| Yes | 87 (75.7) |
| No | 28 (24.3) |
| Centre-related characteristics | |
| HIV ⁺ psychiatry or psychology service | |
| Yes | 70 (60.9) |
| No | 45 (39.1) |
| Number of beds | |
| ≤ 500 | 63 (54.8) |
| > 500 | 52 (45.2) |

with HIV, respectively. Their baseline characteristics are summarized in Table 1.

Physicians' perception of management of HIV-1-associated NPCs

Figure 1a shows data regarding physicians' opinions about the relevance of assessing mental health in people with HIV and the rate of diagnosis of NPCs. Most clinicians agreed on the relevance of assessing mental health in people with HIV because of its impact on treatment adherence and ART selection and the high prevalence of NPCs and pointed out that NPCs were underdiagnosed in people with HIV, mainly because of a lack of proactive attitudes, time during visits, and specific training. The perception that NPCs were underdiagnosed was higher among participants from centres with a psychiatry or psychology service specifically aimed at people with HIV (Table S1).

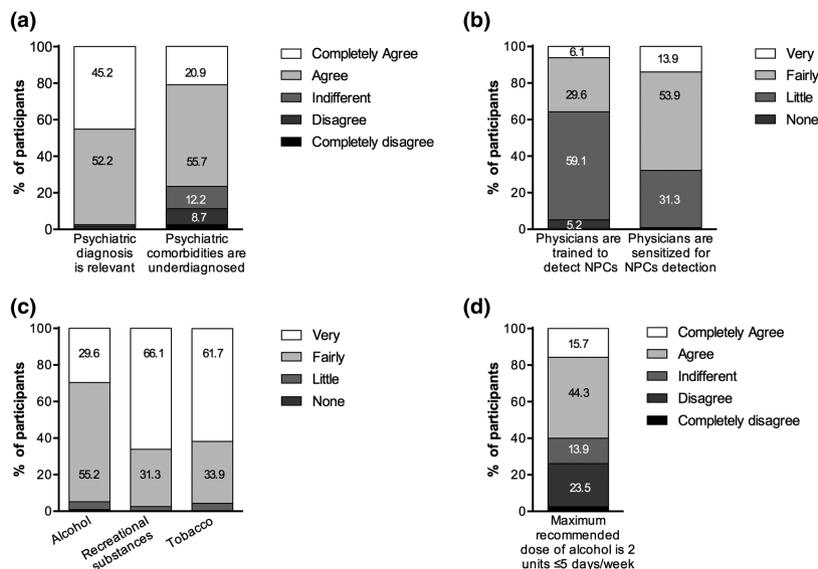


FIGURE 1 Distribution of responses to questions regarding (a) physicians' perceptions of the diagnosis of HIV-associated comorbidities, (b) physicians' training to detect NPCs and their awareness of NPCs, (c) physicians' understanding of the relevance of substance use, and (d) physicians' understanding of recommended alcohol consumption levels. The percentage of participants responding to each option is shown on the Y-axis. NPCs, neuropsychiatric comorbidities

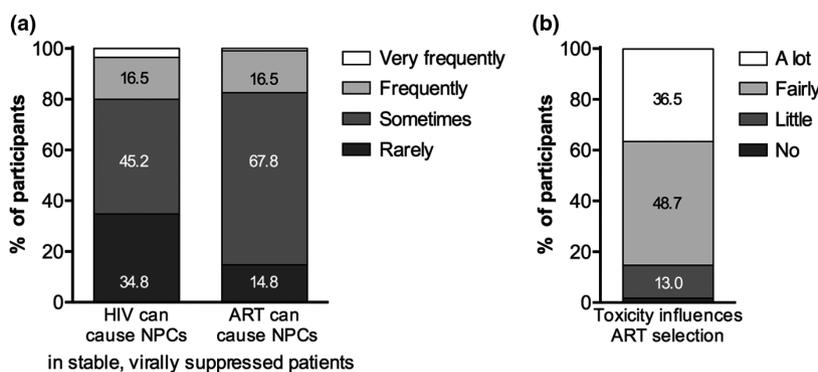


FIGURE 2 Distribution of responses to questions regarding physicians' perceptions of (a) HIV and antiretroviral therapy as causes of neuropsychiatric comorbidities and (b) the influence of toxicity on antiretroviral therapy selection. The percentage of participants responding to each option is shown on the Y-axis. ART, antiretroviral therapy; NPCs, neuropsychiatric comorbidities

Figure 1b shows data regarding physicians' level of training for the detection of NPCs and their degree of awareness about NPCs. Most participants reported that physicians lacked enough training on the detection of NPCs even though older physicians more often reported that physicians were 'fairly' trained (Table S1). Likewise, physicians working in larger hospitals (>500 beds) and those treating only/mostly people with HIV reported being more trained than those working in smaller hospitals and not treating only/mostly people with HIV (Table S1). Most participants considered that physicians were aware of the need to detect NPCs. Far more participants treating >110 patients/month than those treating ≤110 patients/month considered that physicians were very sensitized (Table S1).

Regarding the use of substances (Figure 1c,d), almost all physicians considered alcohol, recreational substances,

and tobacco consumption to be relevant or very relevant, and most agreed or totally agreed that the maximum recommended units of alcohol was 2, up to 5 days a week. Subgroup analyses revealed significant differences regarding the perception of recreational substance use and the maximum recommended alcohol units between the two categories according to the number of patients treated and centre size (Table S1).

Knowledge of neuropsychiatric manifestations

Regarding the frequency of NPCs, most physicians ($n = 102$ [88.7%]) estimated that the rate of NPCs among their patients was between 10% and 50%, whereas few

estimated having <10% (3.5%) or >50% (7.8%). Physicians believed that most patients failed to report NPCs actively, and $n = 3$ (2.6%), $n = 50$ (43.5%), $n = 60$ (52.2%), and $n = 2$ (1.7%) physicians stated that their patients reported neuropsychiatric symptoms very frequently, frequently, sometimes, and rarely, respectively. The numbers of responses were similar across categories (Table S2).

Figure 2a summarizes data regarding perceptions of the impact of HIV and ART on NPCs. Most physicians considered that, in patients with stable viral suppression, HIV and ART sometimes caused NPCs. Subgroup analysis showed differences according to sex, age, years of experience treating people with HIV, and hospital characteristics (Table S2). Dolutegravir ($n = 102$ [88.7%]) and efavirenz ($n = 98$ [85.3%]) were the antiretrovirals most frequently reported as being associated with NPCs, followed by atazanavir ($n = 8$ [7.0%]), darunavir ($n = 6$ [5.2%]), and raltegravir ($n = 6$ [5.2%]). Most physicians ($n = 98$ [85.2%]) considered that ART-related potential neurotoxicity influenced ART selection (Figure 2b). Physicians who attended >110 patients/month and who were women considered that the neurotoxicity profile influenced ART selection ‘a little’ and ‘much’, respectively, more often than those treating ≤ 110 patients/month and who were men ($p < 0.05$ for both).

The most frequent NPCs were emotional ($n = 54$ [47.0%]), sleep ($n = 40$ [34.8%]), substance use ($n = 10$

[8.7%]), personality ($n = 7$ [6.1%]), and cognitive ($n = 4$ [3.5%]) disorders, which were considered to be unresolved by 77 (67.0%) physicians, whereas 32 (27.8%) considered them resolved, and six (5.2%) did not know. The number of participants who reported substance use disorders as being most frequent differed according to the presence of an in-house HIV-1 psychiatry/psychology service and centre size (Table S2). The perception of NPCs as resolved and unresolved issues differed according to respondent sex (Table S2).

Management of neuropsychiatric manifestations

Regarding the management of NPCs (Figure 3a), most physicians considered brain magnetic resonance imaging to be unnecessary in patients with depression and anxiety symptoms and reporting cognition problems. In contrast, almost all physicians believed that a neurocognitive study was necessary in patients reporting cognitive issues. The frequencies of responses were similar between subgroups (Table S3).

Almost half of the physicians would recommend benzodiazepine treatment for generalized anxiety disorders, and most considered lorazepam as the benzodiazepine at lowest risk of pharmacokinetic interactions with

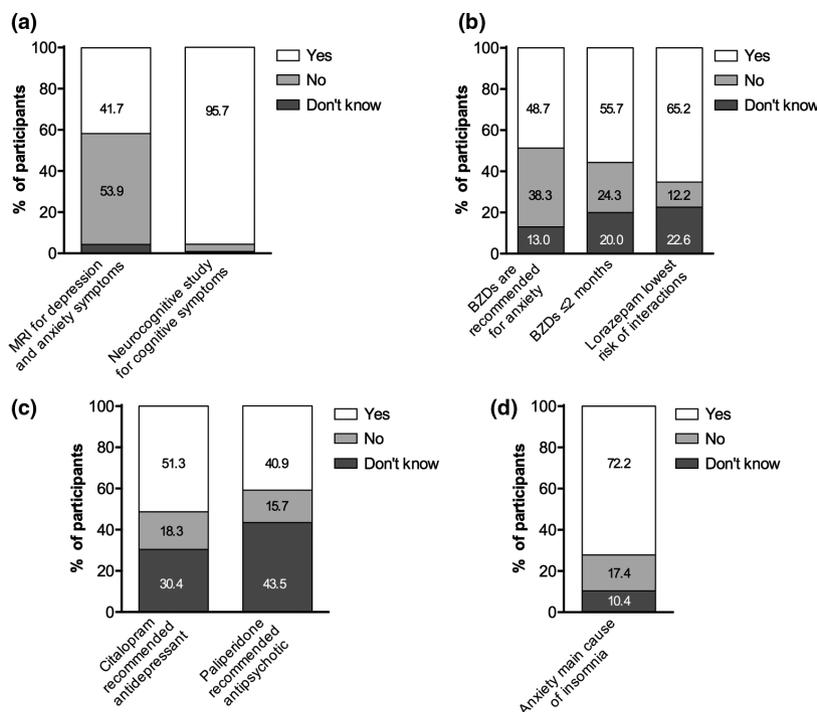


FIGURE 3 Distribution of responses to questions regarding physicians' practice (a) when dealing with neuropsychiatric symptoms, (b) in the prescription of benzodiazepines, (c) in the prescription of antidepressants and antipsychotics, and (d) regarding their perception of anxiety as a primary cause of insomnia. The percentage of participants responding to each option is shown on the Y-axis. BZDs, benzodiazepines; MRI, magnetic resonance imaging

antiretrovirals. Most physicians would recommend benzodiazepines for a maximum of 2 months (Figure 3b). The frequencies of answers regarding benzodiazepine treatment duration and lorazepam differed according to age, years of experience, and treating mostly/only people with HIV (Table S3). Regarding antidepressants and antipsychotics, half and almost half of the physicians agreed that citalopram and paliperidone were the most recommendable antidepressants and antipsychotics, respectively (Figure 3c). Most physicians agreed that anxiety was one of the main causes of sleep disorders (Figure 3d). Subgroup analyses revealed differences according to sex, treating only/mostly people with HIV, and centre size (Table S3).

NPC identification and management skills

Regarding attitudes towards the identification of NPCs, most physicians considered that NPCs were difficult to identify in people with HIV and reported that tools to identify NPCs were unavailable (Figure 4a). Older physicians (>50 years) considered that NPCs were easy to identify more frequently than did younger physicians (Table S4). Almost all physicians considered that the detection of NPCs in people with HIV should be improved, and more physicians treating only/mostly people with HIV considered that improved detection was not necessary than those not treating only/mostly people with HIV (Figure 4a, Table S4). Overall, when asked to elaborate on the above responses, physicians reported that the limited time for each visit prevented the appropriate evaluation of NPCs.

Regarding practice in the identification of CNS manifestations and their management, almost half of the physicians reported frequent evaluation of CNS manifestations in patients newly diagnosed with HIV and followed-up patients (Figure 4b). However, most physicians (>77%) reported not using any questionnaires or following guidelines for the detection of NPCs (Figure 4c). The most frequently used guidelines were those of the “Grupo de Estudio del SIDA” (AIDS Study Group) of the “Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica” (Spanish Society of Infectious Diseases and Clinical Microbiology) (62%), followed by those from the European AIDS Clinical Society (23%), and the Minimal State Examination (12%). Upon detection of NPCs, most physicians referred patients to an in-house psychiatry/psychology service, and almost one-third prescribed drugs for their treatment. Almost all physicians adjusted ART treatment to minimize interactions, and most managed NPCs in coordination with mental health professionals (Figure 4d–f). ART changes were considered when

interactions were relevant, and the new treatment was selected based on the symptomatology and the psychiatric treatment. Furthermore, physicians stated that multiple options with fewer interactions and sustained potency are currently available and that the different options were evaluated in conjunction with psychiatrists for patients with HIV receiving rescue ART regimens. The responses of the different physician subgroups are summarized in Table S4.

DISCUSSION

In this cross-sectional study, we conducted an online survey to assess the perceptions, knowledge, skills, and attitudes of HIV specialists with >4 years of experience regarding the management of NPCs of people with HIV. Participants acknowledged that psychiatric diagnosis in this population may be relevant and that NPCs are underdiagnosed in people with HIV. While reporting having little or no training in the detection of NPCs, participants had enough awareness to detect NPCs and considered that people with HIV underreported them. Participants identified HIV infection and ART as potential causes of NPCs and selected ART according to its neurotoxicity profile. The antiretrovirals considered most frequently associated with NPCs were dolutegravir and efavirenz. Even though more than half of the physicians evaluated NPCs frequently, most considered that the identification of NPCs was difficult, identification tools were insufficient, and that NPC detection should be improved.

Results from this study indicate that, similar to other settings and despite the awareness of physicians in hospital settings in Spain regarding the high prevalence and impact of NPCs in people with HIV, NPCs remain underdiagnosed [12–14]. Detection of NPCs is the first step to providing appropriate mental health care to people with HIV [1]. However, diagnosis of neuropsychiatric and neurocognitive disorders remains challenging because of the complex factors associated with HIV infection, manifestations of NPCs, which may be similar to physical symptoms of HIV, and close associations between depressive symptoms and cognitive function [3,15,16]. Results from this study showing that the identification of NPCs was mostly perceived as not easy and that physicians were considered insufficiently trained agree with the general view of NPC diagnosis and point to suboptimal training as one of the barriers to diagnosis in this study's setting.

Participating physicians evaluated people with HIV for NPCs ‘sometimes’ and ‘rarely’, and a reduced proportion reported using instruments (i.e., questionnaires) and following guidelines. However, several validated questionnaires of variable lengths are available to screen for

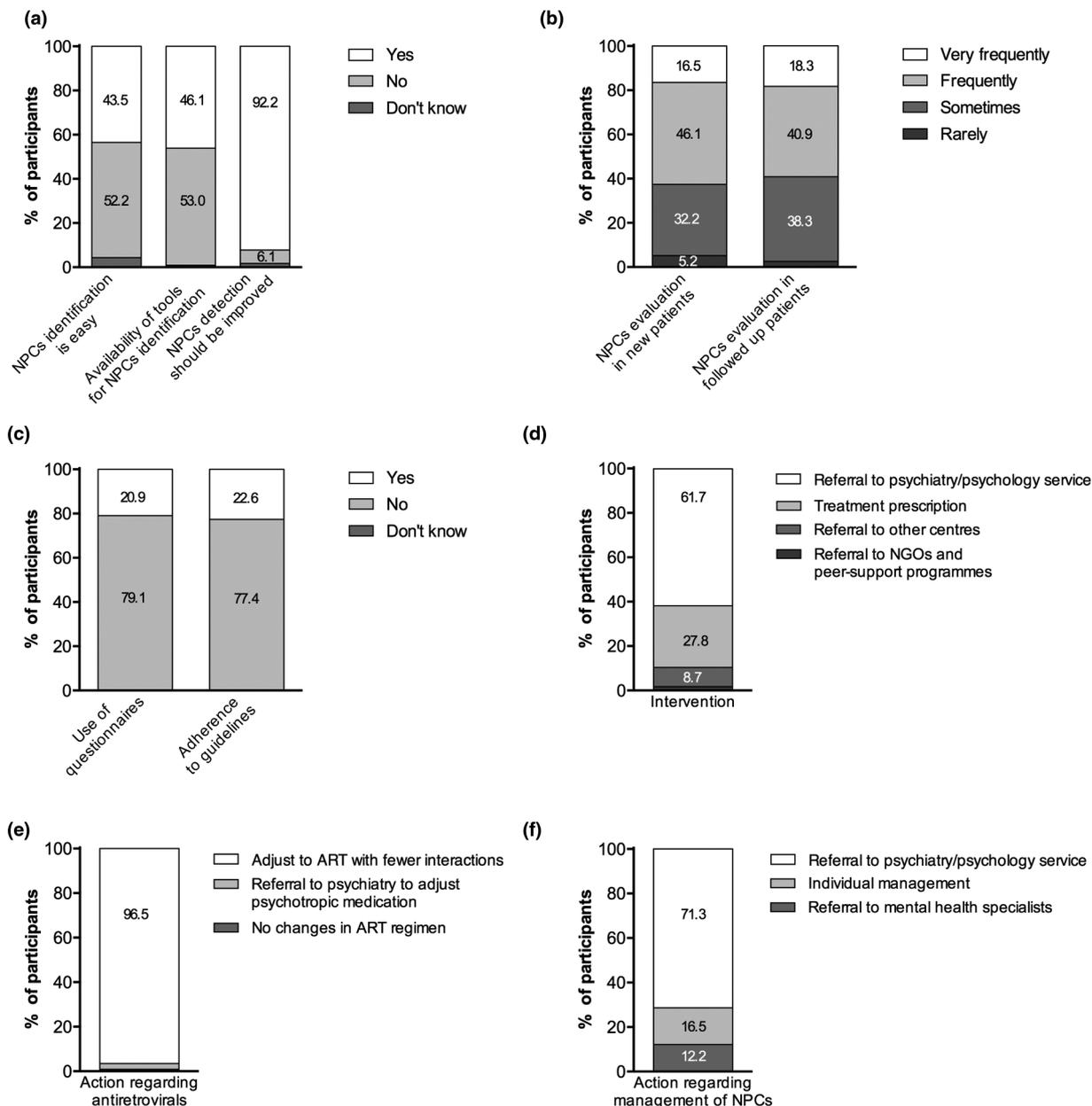


FIGURE 4 Distribution of responses to questions regarding (a) physicians' perceptions of the detection and identification of neuropsychiatric comorbidities, (b) physicians' practices when evaluating neuropsychiatric comorbidities, (c) physicians' use of questionnaires and guidelines, (d) physicians' interventions after neuropsychiatric symptoms are detected, (e) physicians' prescribing of antiretroviral therapy, and (f) physicians' perception of anxiety as a primary cause of insomnia. The percentage of participants responding to each option is shown on the Y-axis. ART, antiretroviral therapy; MRI, magnetic resonance imaging; NGOs, non-governmental organizations; NPCs, neuropsychiatric comorbidities

neuropsychiatric disorders and have been equally recommended [17]. Likewise, several other instruments are available to assess cognitive function, albeit with suboptimal sensitivity to detect the milder HIV-associated cognitive disorders, and more are being developed [18,19]. In this regard, although routine screening for neurocognitive disorders is controversial because of the limited effective treatments, routine screening for depression is encouraged to detect disorders, start treatment early, and prevent poor outcomes [12]. In this study's setting and considering

that limited time for visits was reported as one of the reasons for sporadic evaluation and underuse of diagnosis instruments, the administration of screening questionnaires by other healthcare professionals and staff might be beneficial. Given the previously reported benefits of screening strategies, results from this study suggest that routine screenings should be considered in this study's setting [20].

Participating physicians reported being aware of the impact of NPCs on ART selection. Accordingly, most

physicians consulted with mental health specialists regarding treatment prescriptions to minimize interactions and, overall, prescribed the ART with fewer reported interactions. In this regard, concomitant pharmacological treatments should be considered before initiating any ART, and, conversely, the risk of interaction with ART should be considered before starting psychoactive drugs to avoid interactions and ART-induced NPCs and ensure effective treatment of NPCs. Furthermore, physicians identified ART treatments associated with neurotoxicity, with efavirenz and dolutegravir being the most frequently identified [5,21]. Efavirenz, a non-nucleoside reverse transcriptase inhibitor, has been one of the most frequently prescribed ARTs and has been associated with neurological and psychiatric adverse effects and cognitive impairment after long-term use [22]. In contrast, dolutegravir, an integrase strand inhibitor, lacks neurocognitive effects and has been associated with neuropsychiatric manifestations, including insomnia, depression, and anxiety [5]. In this regard, European guidelines recommend avoiding efavirenz in patients with a history of suicide attempts or mental illness and recommend switching efavirenz- and dolutegravir-based ART regimens in cases of documented neurotoxicity [9].

Regarding attitudes towards the management of NPCs, most physicians, upon detection of NPCs, referred patients to a psychiatry/psychology service (internal or external) and coordinated with mental health professionals to manage NPCs. Previous studies have pointed to fragmented service delivery models as one of the factors contributing to insufficient mental health screening and provision of treatment [1]. In this regard, results from this study in the Spanish setting suggest that physicians coordinated frequently with mental health specialists to manage NPCs, suggesting that basic care and mental health care for people with HIV are frequently coordinated. In this regard, the previously reported benefits of integrated care plans stress the importance of coordination among multidisciplinary teams of healthcare professionals [1,23].

The results from this study should be read in the context of the limitations associated with its design, based on a survey designed ad hoc, providing quantitative and qualitative results. Despite the mixed nature of its results (quantitative and qualitative) and the use of a non-validated instrument, the results from this study obtained from a large representative sample of physicians across Spain without strict selection criteria likely reflected the practices, attitudes, and opinions found in hospital settings in Spain. This study indicated that lack of training and time during visits were barriers to the diagnosis and identification of NPCs in people with HIV. Unfortunately, the survey did not ask about the time that clinicians allocate for visits. The lack of this information limits our ability to propose appropriate screening strategies for NPCs in this study's setting.

Considering the contribution of mental health disorders to poor outcomes in people with HIV, results from this study underscore the challenges that physicians treating people with HIV face in their daily practice regarding NPCs and provide valuable information to identify opportunities for improvement in specific areas of care for people with HIV.

CONCLUSIONS

Our results show that, despite having an awareness of the relevance of NPC diagnosis and acknowledging their inappropriate diagnosis levels, physicians treating people with HIV in Spanish hospitals fail to routinely evaluate NPCs, follow guideline recommendations, and use questionnaires. Insufficient training and lack of time during visits were identified as the main barriers to identification of NPCs. However, the results indicate that physicians understand the relationship between ART and NPCs and their management and tend to integrate and coordinate care with mental health professionals. These results provide valuable information regarding opportunities to improve the detection and management of NPCs in people with HIV, such as the implementation of self-reported questionnaires, nested to clinical records, that people with HIV could complete on their mobile devices before each clinical appointment and would help clinicians to estimate the mental health of their patients and detect NPCs.

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CONFLICT OF INTEREST

IP-V received support from Gilead Sciences for manuscript preparation during the conduct of the study and has received grants and personal fees from Gilead Sciences, ViiV, Janssen, and MSD outside the submitted work. JB has received personal fees for collaboration for conferences and meetings from Gilead Sciences, ViiV, GSK, and Ferrer International; personal fees for speaking and teaching from Menarini, Gilead Sciences, MSD, and Johnson and Johnson (Janssen); and personal fees for advisory services from Gilead Sciences. All these activities were outside the submitted work. EM has received personal fees from Gilead Sciences and Janssen and grants and personal fees from MSD and ViiV outside the submitted work.

AUTHOR CONTRIBUTIONS

All authors contributed to the conception and design of the work, the analysis and interpretation of data from the work, and the acquisition of data for the work. IPV drafted the article and all authors contributed to revising the work critically for important intellectual content. All authors reviewed and approved the final version of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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