The Double Burdens of Mental Health Among AIDS Patients With Fully Successful Immune Restoration: A Cross-Sectional Study of Anxiety and Depression in China

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Background: Anxiety and depression continue to be significant comorbidities for people with HIV infection. We investigated the prevalence of and factors associated with anxiety and depression among adult HIV-infected patients across China.

Methods: In this cross-sectional study, we described clinical and psychosocial variables related to depression and anxiety in 4103 HIV-infected persons. Doctors assessed anxiety and depression by asking patients whether they had experienced anxiety or depression in the prior month. Patients also self-administered the Hospital Anxiety and Depression (HAD) scale; those with score ≥8 on HAD-A/D were considered to be at high risk of anxiety or depression.

Results: Associations between socio-demographic, psychosocial, and ART-related clinical factors and risk of depression or anxiety were investigated using multivariable logistic regression. Among patients assessed between 9/2014 and 11/2015, 27.4% had symptoms of anxiety, 32.9% had symptoms of depression, and 19.0% had both. Recentness of HIV diagnoses (P = 0.046) was associated with elevated odds of anxiety. Older age (P = 0.004), higher educational attainment (P < 0.001), employment (P = 0.001), support from family / friends (P < 0.001), and sleep disturbance (P < 0.001), and number of ART regimen switches (P = 0.046) were associated with risk of...
INTRODUCTION

Over half of all HIV-1-infected individuals suffer from mental health disorders (1–3) and anxiety and depression are common comorbidities in HIV-infected populations (4–6). The impact of mental health issues on HIV patients in resource-limited settings is often underestimated due to a lack of education and awareness both among physicians and patients, resulting in insufficient and ad-hoc screening and diagnosis of mental health conditions in this population (4, 7). The pathophysiology of anxiety/depression among HIV-infected patients is unclear, but may be related to clinical factors (e.g., the ability of HIV to infect the central nervous system (CNS) or impact of antiretroviral medications) or psychosocial in nature (e.g., availability of social support, issues related to substance abuse) (8–10). Recent studies have largely focused on the impact of specific antiretroviral agents (e.g., efavirenz) on mental health (11, 12). Regardless of its etiology, anxiety and depression is clinically important in this population and has the potential to impact quality of life, adherence to anti-retroviral medications, cognition, cause sleep disturbance and may weaken patients’ immune system (13–16).

There are currently no guidelines to manage psychiatric disorders in the HIV clinic setting in China, despite the reality that these disorders adversely affect the course of HIV infection (17). Major anxiety and depression frequently go unrecognized and untreated and may foster severe consequences, such as rapid disease progression, suicide, high-risk behaviors and immune system impairment (18–20). In this study, we characterized the prevalence of symptoms of anxiety and depression in Chinese HIV-infected patients, identified risk factors, and sought to assess clinical impacts of anxiety and/or depression on treatment outcomes. We also investigated the utility of the Hospital Anxiety and Depression (HAD) instrument to identify missed-diagnoses when compared to a clinician-initiated one-item question asking patients to self-report anxiety and depression in the previous month.

METHODS

We conducted a cross-sectional study among 4724 HIV-infected adults on treatment, collecting data from patients at 20 HIV treatment clinics across China. All participants provided written informed consent to complete a survey and have their medical data abstracted from their medical records. The study was approved by the Beijing You’an Hospital institutional review board.

Each participant completed the Hospital Anxiety and Depression (HAD) scale questionnaire, which consists of seven items each relating to depression (HAD-D) and anxiety (HAD-A) respectively. High risk of anxiety and depression was defined as a HAD score ≥8 on each subscale (21). Before self-administration of the HAD, clinicians asked patients if they had experienced any depressed mood or anxiety in the previous month and results were coded yes vs. no.

Demographic, behavioral, and psychosocial data were collected through self-administered survey. Clinical data was abstracted from medical records. This included HIV-specific data, including date of HIV diagnosis, history of medical conditions, current CD4+ cell counts and HIV RNA levels, and antiretroviral therapy (ART) regimen. The Pittsburgh Sleep Quality Index (PSQI) questionnaire, a 19-item questionnaire that assesses seven sleep components, was completed by each participant to evaluate sleep disturbance during the prior month. We used the PSQI cut off of a global score ≥5 on the PSQI instrument (15) (sensitivity of 90% and specificity of 87%) to define sleep disturbance in this cohort (22).

STATISTICAL ANALYSIS

Descriptive statistics are presented as means with standard deviations (SDs), or counts with proportions, as appropriate. Two sample t-tests were used to compare means, and χ²-tests were used to compare proportions. Logistic regression analysis was used to investigate associations between demographic, behavioral, psychosocial, and clinical factors and anxiety or depression. Odds ratios (ORs) for depression or anxiety were estimated with 95% confidence intervals (CIs). Factors with a P-value < 0.10 in univariate Logistic models were initially included in the multivariable Logistic model and were then eliminated using backward selection. Crude ORs are reported from univariate analysis; adjusted ORs are reported from multivariable logistic regression. All P-values were 2-sided, and...
P-values < 0.05 were considered significant. Analyses were conducted using SPSS 21.0.

RESULTS

Characteristics of Study Population

4103 HIV-infected persons were eligible for data analysis with the mean age being 37.6 ± 11.7 years (Table 1). Over three-quarters of the cohort were male patients. The cohort represented a diverse sample of educational achievement and employment status. Over 40% were infected through anal sex. The median time from HIV diagnosis to study enrollment was 27 months (interquartile range [IQR], 11–58 months); median duration of ART was 18 months (IQR, 6–43 months); 15.5% had a current CD4+ T cell count below 200 cells/mm³, and 40.8% were virally-suppressed. Three-quarters of patients were on first-line ART regimen (Table 1). Over 60% had disclosed their HIV status to their family members and close to 70% expressed feeling supported by their family members. In contrast, just over one-quarter had disclosed their status to a friend.

Prevalence of Depression and Anxiety

1,349 (32.9%) and 1,125 (27.4%) HIV-infected persons had symptoms of depression and anxiety based on the HAD-D and HAD-A, respectively, among whom 779 persons (19.0%) had symptoms consistent with both depression and anxiety. Out of 1,344 patients whose HAD-D score indicated likely depression, 715 (53.2%) did not report feeling depressed in the previous month in response to the clinician-initiated question (Table 2). Meanwhile, 578 (21.0%) of those whose HAD-D score suggested that they were not depressed responded that they had in fact experienced depressed mood in the last month.

Factors Associated With Depression and Anxiety

In univariate analyses, factors associated with likely depression (HAD-D ≥ 8) or anxiety (HAD-A ≥ 8) included age, sex, education, transmission route, employment, support from family/friends, time of diagnosed with HIV infection, drug adherence, duration of EFV exposure, duration of ART,

| TABLE 1 | Demographic, clinical, and psychosocial characteristics of 4103 HIV patients. |
|-----------------|-----------------|-----------------|
| **Demographic factors** | **Clinical factors** | **Psychosocial factors** |
| **Age, years** | **Current CD4 cell count, cells/mm³** | **Family history of mental illness** |
| <30 | 1,175 (28.5) | 128 (3.1) | Yes |
| 30–60 | 2,306 (56.2) | 506 (12.3) | No |
| >60 | 569 (13.9) | 2,160 (52.6) | Missing |
| Missing | 53 (1.3) | 1,272 (31.0) | |
| **Gender** | | | |
| Male | 3,204 (78.1) | Current viral load | |
| Female | 831 (20.3) | Undetectable | |
| Missing | 68 (1.7) | Missing | |
| **Education** | | | |
| <High school | 1,528 (37.2) | Time since HIV diagnosis | |
| High school | 988 (24.1) | <3 months | |
| >High school | 1,527 (37.2) | ≥3 months | |
| Missing | 60 (1.5) | Missing | |
| **Transmission route** | | | |
| Heterosexual | 1,589 (38.9) | Adherence to ART | |
| Homosexual/bisexual | 1,730 (42.2) | ≥95 | Yes |
| Blood transfusion | 39 (1.0) | <95 | No |
| **PIMD** | | | |
| **Unknown** | 520 (12.7) | Current EFV-based regimen | |
| **Marital status** | | | |
| Married | 1,698 (41.4) | Yes | |
| Divorced | 456 (11.1) | No | |
| Widowed | 132 (3.2) | Duration of EFV exposure | |
| Single | 1,718 (41.9) | 0 month | |
| Missing | 99 (2.4) | <3 months | |
| **Employment** | | | |
| White collar | 1,158 (28.2) | 1,159 (28.2) | |
| Blue collar | 1,835 (44.7) | 2,217 (54.0) | |
| Unemployed | 280 (6.8) | 46 (1.1) | |
| Student | 830 (20.2) | |

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TABLE 2 | Agreement of depression diagnosis based on HAD-D and self-report [n (%)].

| Patient report of depression | Depression diagnosis based on HAD-D ≥ 8 | Total |
|-----------------------------|----------------------------------------|-------|
|                             | Presence | Absence | Presence | Absence | Presence | Absence | Total |
| Presence                    | 629 (46.8) | 578 (21.0) | 1,207 |
| Absence                     | 715 (53.2) | 2,169 (79.0) | 2,884 |
| Total                       | 1,344 | 2,747 | 4,091 |

number of ART regimens, and sleep disturbance. There were no significant associations with HIV-specific clinical factors including current CD4+ T cell count and current viral load.

In the final multivariate model, factors associated with depression based on the HAD included age (P = 0.004), education (P < 0.001), and employment (P = 0.001), while factors associated with anxiety included time since HIV diagnosis (P = 0.046), number of ART regimen (P = 0.046), employment (P < 0.001), support from family/friends (P < 0.001), and sleep disturbance (P < 0.001) (Table 3).

DISCUSSION

This study represents one of the largest epidemiologic studies of the prevalence of symptoms of anxiety and depression among HIV-infected persons in the ART era as measured by the validated and frequently-used HAD scale (22–25). Our estimates of 32.9% prevalence of depressive symptoms and 27.4% prevalence of anxiety symptoms are lower than those reported in a systematic review of studies measuring mental health burden among people living with HIV in China that reported median prevalence of depression and anxiety of 60.4 and 43.1% respectively (2). However, the authors of the review caution that their data may not be generalizable due to low quality of studies and high risk of bias in the samples (2) as many of these studies were conducted among former plasma donors and injecting drug users who were infected in the first waves of the HIV epidemic in China and may not be representative of more recently diagnosed individuals who tend to be infected through sexual contact (2). In addition, our study was conducted among patients currently accessing ART whereas earlier studies included both treated and untreated patients. A recent study of current depression among recently-diagnosed men who have sex with men (MSM) found 36% prevalence of depression, (26) in line with our finding of 34% depression prevalence among recently-diagnosed patients. People who inject drugs had the highest prevalence of depression and anxiety, in line with a rich literature documenting the comorbidities of mental health and substance use (4, 27, 28).

Students had higher rates of both anxiety and depression, an effect that remained even after controlling for age. As infections among young people and students continue to rise in China (29), it will become increasingly important to develop mental health interventions that have been shown to be effective for young people in other contexts, including ones that could be group-based, web-based, dyadic or individual (30, 31). Age older than 30 and less education were also associated with increased odds of depression in this cohort, a trend that has been seen in other studies as well (32).

In our study the length of time since HIV diagnosis was found to be associated with high anxiety symptoms, with a significant association between shorter duration since diagnosis and anxiety. Anxiety can be considered a normal emotional response to the reality of living with HIV and this may explain the higher rate of anxiety in the first several months after diagnosis (20). This finding is in line with that of another study that found high rates of depression in relation to duration of infection (6), suggesting that the provision of mental health services at the time of diagnosis could be critical to manage the risk of depression and anxiety among recently-diagnosed individuals. Positive-affect skills interventions to support newly-diagnosed individuals have been shown to improve psychological health, decrease the use of anti-depressants, and support adjustment to HIV-positive status (33) and could be piloted in Chinese patient populations.

Consistent with other studies, we found the patients who reported high levels of support from family or friends had lower rates of symptoms of anxiety and depression (10, 34). This suggests that interventions designed to build the capacity of family and friends to support newly-diagnosed patients in the acceptance of their disease and in developing positive coping strategies could have mental health benefits.

Despite a high prevalence of anxiety and depression among HIV-infected persons, less than 5% of patients with borderline or likely depression were regularly using anti-depressants. Prior studies have also noted that most patients in China with anxiety or depression remain untreated and often have a poor understanding of available treatment options (20, 35). This is perhaps not surprising given the chronic and severe undersupply of mental health services in China (36, 37).

We did not find a relationship between high likelihood of depression and anxiety and clinical factors like immune function. However frequent switching of ART regimens was associated with higher proportion of depression, which makes sense: someone who has had trouble achieving or maintaining viral suppression is likely to experience anxiety and depression related to anticipated downward progression of their disease. Unlike in other studies (11, 19), patients on EFV-based regimens did not have elevated odds of anxiety or depression. However, this is likely due to a bias in the sample in that patients who had suffered CNS side effects like anxiety/depression from EFV may have switched regimens prior to this cross-sectional study, leaving only patients who did not suffer EFV-related side effects in the sample.

Asking patients to report experience of anxiety or depression in the previous month resulted in significant under-reporting of depression when compared to the HAD scales. Low recognition of mental health needs have been well studied in the US and Western Europe (8) and leads to under-utilization of mental health services. Fewer studies have been conducted in China, though two recent studies among rural residents...
TABLE 3 | Demographic and clinical factors associated with depression and anxiety.

| Factors                        | Depression (HAD-D ≥ 8) | Anxiety (HAD-A ≥ 8) |
|--------------------------------|------------------------|---------------------|
|                                | % of subjects          | Crude OR (95% CI)   | Adjusted OR (95% CI) | % of subjects          | Crude OR (95% CI)   | Adjusted OR (95% CI) |
| **DEMOGRAPHIC AND PSYCHOSOCIAL FACTORS** |                         |                     |                     |                         |                     |                     |
| Age, years ‡&                  |                        |                     |                     |                         |                     |                     |
| <30                            | 26.3%                  | 1                   | 1                   | 26.5%                  | 1.17 (0.93–1.48)     |
| 30–50                          | 35.6%                  | 1.55 (1.33–1.81)    | **1.35 (1.13–1.62)**| 28.9%                  | 1.32 (1.07–1.64)     |
| >50                            | 34.6%                  | 1.48 (1.20–1.84)    | **1.29 (1.00–1.68)**| 23.6%                  |                     |
| Gender #                       |                        |                     |                     |                         |                     |                     |
| Female                         | 37.5%                  | 1.31 (1.12–1.54)    |                     | 29.6%                  | 1.15 (0.97–1.38)     |
| Male                           | 31.5%                  | 1                   |                     | 26.7%                  | 1                   |
| Education ‡                   |                        |                     |                     |                         |                     |                     |
| < High school                  | 39.9%                  | 1.96 (1.68–2.29)    | **1.89 (1.54–2.31)**| 27.4%                  | 1.04 (0.88–1.22)     |
| High school                    | 33.8%                  | 1.51 (1.27–1.80)    | **1.45 (1.19–1.78)**| 29.0%                  | 1.13 (0.94–1.35)     |
| > High school                  | 25.3%                  | 1                   | 1                   | 26.7%                  | 1                   |
| Transmission route #&          |                        |                     |                     |                         |                     |                     |
| Heterosexual                   | 34.7%                  | 1                   |                     | 25.7%                  | 1                   |
| Homosexual/bisexual            | 28.8%                  | 0.76 (0.66–0.88)    |                     | 27.7%                  | 1.11 (0.95–1.30)     |
| Blood transfusion              | 35.9%                  | 1.06 (0.84–1.32)    |                     | 30.8%                  | 1.29 (0.95–1.73)     |
| PWID                           | 48.8%                  | 1.78 (1.34–2.37)    |                     | 35.6%                  | 1.61 (1.19–2.17)     |
| Unknown                        | 34.0%                  | 0.97 (0.79–1.20)    |                     | 28.1%                  | 1.13 (0.91–1.41)     |
| Marital status                 |                        |                     |                     |                         |                     |                     |
| Married                        | 35.3%                  | 1                   |                     | 26.7%                  | 1                   |
| Divorced                       | 37.7%                  | 1.11 (0.90–1.38)    |                     | 31.6%                  | 1.27 (1.01–1.59)     |
| Widowed                        | 35.6%                  | 1.01 (0.70–1.47)    |                     | 31.1%                  | 1.24 (0.84–1.82)     |
| Single                         | 28.6%                  | 0.74 (0.64–0.85)    |                     | 26.8%                  | 1.01 (0.87–1.17)     |
| Employment $§                  |                        |                     |                     |                         |                     |                     |
| White collar                   | 25.9%                  | 1                   | 1                   | 24.9%                  | 1                   |
| Blue collar                    | 33.5%                  | 1.44 (1.22–1.69)    | **1.05 (0.86–1.28)**| 27.0%                  | 1.12 (0.95–1.32)     |
| Unemployed                     | 29.3%                  | 1.18 (0.89–1.58)    | **1.02 (0.72–1.44)**| 23.2%                  | 0.91 (0.67–1.24)     |
| Student                        | 42.5%                  | 2.12 (1.75–2.56)    | **1.49 (1.18–1.87)**| 33.3%                  | 1.51 (1.24–1.83)     |
| Support from family/friends $§|                        |                     |                     |                         |                     |                     |
| Yes                            | 29.1%                  | 1                   | 1                   | 24.4%                  | 1                   |
| No                             | 41.2%                  | 1.71 (1.48–1.96)    | **1.80 (1.54–2.10)**| 33.7%                  | 1.57 (1.36–1.82)     |
| CLINICAL FACTORS               |                        |                     |                     |                         |                     |                     |
| Current CD4 count, cells/mm³   |                        |                     |                     |                         |                     |                     |
| <50                            | 32.8%                  | 1                   |                     | 22.7%                  | 1                   |
| 50–199                         | 35.0%                  | 1.10 (0.73–1.66)    |                     | 29.4%                  | 1.43 (0.90–2.25)     |
| 200–499                        | 33.5%                  | 1.03 (0.71–1.51)    |                     | 28.2%                  | 1.34 (0.88–2.05)     |
| ≥500                           | 31.3%                  | 0.93 (0.63–1.37)    |                     | 25.9%                  | 1.19 (0.77–1.84)     |
| Current viral load             |                        |                     |                     |                         |                     |                     |
| Undetectable                   | 34.7%                  | 1.11 (0.97–1.28)    |                     | 27.8%                  | 1.06 (0.91–1.23)     |
| Detectable                     | 32.4%                  | 1                   |                     | 26.7%                  | 1                   |
| Time since HIV diagnosis $      |                        |                     |                     |                         |                     |                     |
| <3 months                      | 34.0%                  | 1.05 (0.82–1.35)    |                     | 34.3%                  | 1.42 (1.10–1.82)     |
| ≥3 months                      | 32.9%                  | 1                   |                     | 26.9%                  | 1                   |

(Continued)
TABLE 3 | Continued

| Factors                        | Depression (HAD-D ≥ 8) | Anxiety (HAD-A ≥ 8) |
|-------------------------------|------------------------|---------------------|
|                               | % of subjects | Crude OR (95% CI) | Adjusted OR (95% CI) | % of subjects | Crude OR (95% CI) | Adjusted OR (95% CI) |
| Adherence to ART #              |            |                  |                      |            |                  |                      |
| ≥95%                          | 32.0%       | 1                 |                       | 26.7%       | 1                 |                       |
| <95%                          | 39.5%       | 1.38 (1.13–1.69)  | 33.4%                 | 1.38 (1.12–1.70) |
| Duration of EFV exposure #     |            |                  |                      |            |                  |                      |
| 0 month                       | 37.0%       | 1                 |                       | 27.1%       | 1                 |                       |
| <3 months                     | 31.9%       | 0.79 (0.64–0.98)  | 30.5%                 | 1.18 (0.95–1.47) |
| ≥3 months                     | 31.2%       | 0.77 (0.67–0.90)  | 26.7%                 | 0.98 (0.84–1.15) |
| Duration of ART #              |            |                  |                      |            |                  |                      |
| <1 year                       | 30.2%       | 1                 |                       | 29.0%       | 1                 |                       |
| ≥1 year                       | 34.8%       | 1.23 (1.08–1.41)  | 26.6%                 | 1.13 (0.98–1.30) |
| Number of ART Regimens $       |            |                  |                      |            |                  |                      |
| <3                            | 32.6%       | 1                 |                       | 27.2%       | 1                 |                       |
| ≥3                            | 45.5%       | 1.72 (1.09–2.71)  | 37.7%                 | 1.62 (1.01–2.57) |
| Sleep disturbance $            |            |                  |                      |            |                  |                      |
| Yes                           | 46.5%       | 3.01 (2.62–3.46)  | 3.21 (2.77–3.72)      | 43.6%       | 4.22 (3.63–4.91)  | 4.10 (3.51–4.78)      |
| No                            | 22.4%       | 1                 |                       | 15.5%       | 1                 |                       |

P < 0.05 in both univariate analysis and multivariate analysis for depression.

P < 0.05 in both univariate analysis and multivariate analysis for anxiety.

P < 0.05 in univariate analysis for anxiety.

P < 0.05 in univariate analysis for anxiety.

HAD, hospital anxiety and depression; OR, odds ratio; CI, confidence interval; ART, antiretroviral therapy.

The bold values are adjusted OR and 95% CI after controlling several confounders.

reported low recognition of depression and anxiety (38) and low awareness of where to access mental health services (39). While introducing an initial screening question could be one way to identify a proportion of people who self-identify as experiencing mental health issues and these could be referred to mental health services, the low recognition of depression and anxiety in the population suggests that relying on such a question alone would miss a large proportion of patients who are identified as at risk of depression and anxiety through the HAD screening instrument. The introduction of a standardized assessment of mental health into HIV services could be done at hospitals where patients access ART or through the Center for Disease Control system that manages follow up and could be an effective way to identify patients who could benefit from clinical evaluation given that these mental health issues are treatable.

Our study had several potential limitations. The cross-sectional study design did not allow for assessment of the temporal relationship between anxiety/depression and factors (e.g., depression improvement over time or pre- and post-ART), the direction of causality, or assessment of whether anxiety/depression were transient or chronic in nature. Among our study’s strengths is its large size and geographic diversity across 14 provinces in China and inclusion of many sub-populations. Also important was its use of validated measures to assess risk for anxiety and depression and that could easily be integrated into routine clinical practice (9, 22, 40).

In summary, the high prevalence of anxiety and depression symptoms among treatment-experienced HIV-infected individuals suggests that routinely administering a standardized mental health assessment to newly-diagnosed individuals and perhaps students would be a useful first step to identify those in need of further clinical evaluation. In order for the introduction of such an assessment to translate to better mental health outcomes, HIV clinics would need to identify optimal models for the provision of mental health interventions to their patients, whether through on-site service provision or a strong referral system to mental health professionals and other social support services.

AUTHOR CONTRIBUTIONS

XH, HC, KM, and XinL led the analysis and writing of this manuscript. XH, KM, HaW, YC, KY, HC, and JH contributed to the final version. HaW is the Principle Investigator of and designed the study. XiaL, TZ, WX, HH, CL, SH, WC, HZ, CH, SL, HuW, XuL, PM, RY, GX, TL, DD, HC, YC, AS were involved in managing the data collection. All authors reviewed and approved the final version of the manuscript.

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