Effects of Depression and Anxiety on Antiretroviral Therapy Adherence among Newly Diagnosed HIV-infected Chinese Men Who Have Sex with Men

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Abstract

Objective—To explore the effect of depression and anxiety on adherence to antiretroviral therapy (ART) among men who have sex with men (MSM) with newly diagnosed HIV infections.

Design—We conducted a prospective study of Chinese MSM with newly diagnosed HIV infections.

Methods—The Hospital Anxiety and Depression Scale (HADS) was used to measure depression and anxiety at baseline, 6 and 12 months, separately. ART adherence was self-reported once every three months ("perfect" or no missing dose in the past three months vs. "imperfect" adherence or at least one missing dose in the past three months). We utilized a priori substantial knowledge guided by causal models to identify confounding covariates, and performed mixed-effect logistic regression to assess the effects of depression and anxiety on ART adherence.

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Results—We included 228 participants who initiated ART after HIV diagnosis and before the end of study. A one-unit increase in the depression and anxiety score was associated with a 16% increase (adjusted odds ratio [aOR], 1.16; 95% confidence interval [CI], 1.02–1.32) and a 17% increase (aOR, 1.17; 95% CI, 1.03–1.33) in the odds of reporting imperfect ART adherence, respectively. When depression and anxiety were categorized (normal, borderline, and likely), only likely anxiety had a significant association with ART adherence (aOR, 4.79; 95% CI, 1.12–20.50).

Conclusions—Depression and anxiety are risk factors for imperfect ART adherence among Chinese MSM with newly diagnosed HIV infections. Intensive intervention on depression and/or anxiety beyond regular post HIV-testing counseling may increase adherence to ART, and improve HIV treatment outcomes.

Introduction

"Treatment as Prevention (TasP)" is a promising strategy for HIV prevention and intervention, as it can reduce the risk of HIV secondary transmission by suppressing viral replication [1, 2]. The TasP strategy was first utilized to control the HIV epidemic among serodiscordant heterosexual couples in China. It has been expanded to Chinese men who have sex with men (MSM), as Chinese MSM have accounted for more than 20% of new cases in each year since 2013 [3]. However, there are several barriers to achieving the expected prevention effect. Maintaining good adherence to antiretroviral therapy (ART) is one of these major challenges [1]. A meta-analysis of 111 studies from both developed and developing countries reported an average of 71% of patients had "good" (80% or more doses taken) adherence (95% confidence interval [CI]: 66.0%–75.3%) [4]. In China, recent reports suggest that about 77.6% (95% CI, 71.6%–83.1%) of people living with HIV (PLHIV) on ART report adequate adherence (90%) [5]. Although the evidence is somewhat mixed with some reports of 80–90% of MSM reporting adequate adherence [6, 7]. Suboptimal adherence can compromise the prevention effect of TasP strategy at the community level, and can lead to drug resistance and viral rebound at the individual level [8, 9].

Mental health disorders may interrupt a patient's ability to adhere to treatment. Depression and anxiety are of particular concerns among PLHIV who are on ART. The prevalence of depression among PLHIV has been estimated 40% [4, 10, 11]. Anxiety is also common, 28% as reported in another meta-analysis [11]. In MSM with unknown HIV serostatus in China, the self-reported lifetime prevalence of depression and anxiety were 11.7% and 18.6% [12]. Studies have shown that PLHIV are twice likely to be depressed and/or anxious than comparable HIV-negative persons [13]. Hence, depression and anxiety would be expected to be more common among HIV-infected Chinese MSM.

Studies have showed that depression and anxiety are associated with poor adherence among PLHIV [4, 14–17]. Little is known about their prevalence rates and effects on ART adherence among newly diagnosed PLHIV. We conducted this study to fill in these

knowledge gaps, and test our hypothesis that depression and anxiety are associated with "imperfect" adherence (at least one missing dose in the past three months) to ART among Chinese MSM with newly diagnosed HIV infections. Scaling-up treatment of depression and anxiety is a cost-effective global strategy with multiple health benefits [18], and our research addresses the extent to which benefits on ART adherence might accrue among newly diagnosed HIV-infected Chinese MSM.

Methods

Study design and population

The parent study ("Multi-component HIV Intervention Packages for Chinese MSM" or China-MP3 project, ClinicalTrials.gov Identifier: NCT01904877) was a two-phase randomized clinical trial (RCT) of using peer counseling and short messaging services to increase HIV testing and linkage to care among HIV-infected MSM in comparison to the standard of care (SOC). SOC included linkage to care, HIV risk reduction counseling, ART referral, and other relevant medical services provided by local Centers for Disease Control and Prevention (CDCs) or hospitals in Beijing City. In addition to SOC, participants in the intervention arm received additional five sessions of face-to-face peer counseling and 32 text messages during the study period. A total of 455 HIV infections were newly identified among 3,588 eligible MSM in Beijing, China in the Phase I study, and 81% (367/455) of HIV-infected participants were successfully enrolled into the Phase II of the study. We assessed the effects of depression and anxiety on ART adherence among a subgroup of MSM participants who initiated ART after HIV diagnosis.

Data collection

In the Phase I study, we collected information on demographics, drug and alcohol use, and sexual behaviors, as well as laboratory data on HIV and syphilis sero-status. In the RCT, we measured entry to care, initiation of ART, adherence, and drug and alcohol use every three months. We also measured depression and anxiety [19], quality of life, self-efficacy [20], and stigma related to homosexuality [21] and HIV/AIDS [22] every six months.

Measurement of depression and anxiety

Depression and anxiety were measured by the Hospital Anxiety and Depression Scale (HADS) - a scale validated for identifying depression and anxiety in multiple populations across countries [23]. The HADS has 7 items to measure depression, and another 7 items for anxiety. The score of each item ranges from 0 to 3. Hence, the total scores for depression or anxiety range from 0 to 21 each. The thresholds for categorizing depression and anxiety are 7 and 11: a score of 0–7 is considered "normal", 8–10 "borderline depression or anxiety"; and 11–21 "likely depression or anxiety". Depression and anxiety are commonly used as categorical variables in clinical practice. To avoid categorization leading to low statistical power to detect the true difference by categorizing individuals with heterogeneous effects into the same group, we analyzed the data using both continuous and categorical variables.

Measurement of ART adherence

Participants self-reported missing any ART doses in the past three months in the follow-up surveys. We categorized adherence as a binary outcome: "perfect" adherence indicating not missing any dose, or "imperfect" adherence meaning missing at least one dose. As participants initiated ART at varying time points, the number of measurements of ART adherence varied from 1 to 4 (median 4; interquartile range [IQR] 2–4) among participants.

Statistical analysis

We included 228 Chinese MSM who initiated ART after HIV diagnosis, and had at least one measurement of adherence during 12 months of follow-up. Depression and anxiety were also repeated measurements. Mixed-effect models were used to analyze the association between depression and anxiety and ART adherence. Measurements of depression and anxiety at RCT enrollment were adjusted in the model, and the next two measurements at 6 and 12 months were treated as time-varying covariates. As we did not measure depression and anxiety at 3 and 9 months, the measurement of ART adherence at RCT enrollment, 6 and 12 months was used in the mixed effects models. For the continuous depression and anxiety scores, restricted cubic splines were used, when the linearity assumption did not hold. A priori substantial knowledge guiding by causal graphs were utilized to determine potential confounding variables [24]. Drug and/or alcohol use can have an impact on depression and/or anxiety, and vice versa [25]. Hence, we had two sets of confounding variables. The first set included age, study intervention assignment, study site, education, social support, HIV-related stigma, and drug and alcohol use (Model-1). The second set included all listed variables except drug and alcohol use (Model-2). We used likelihood ratio test to test whether the study intervention arm (control vs. intervention) and/or HIV-related stigma were potential effect modifiers. All analyses were run using Stata 12.0 (*StataCorp LP, College Station, Texas*).

Results

Demographics of study population

The median age of 228 eligible Chinese MSM was 28 years (IQR: 25–32). Most of them were of Han ethnicity (94%), single (86%), had received at least a college education (82%), and were employed (87%). Around half of our study population (49%) came from small cities or township/countryside. Eighty percent of participants did not have Beijing "*hukou*" (registered household residence). The majority reported having health care insurance (58%), and being satisfied about the support received from family members and/or friends (74%). In the past three months, 37% of participants reported drug use, and 56% reported alcohol use. At baseline, the prevalence of likely or borderline depression was 43%, and likely or borderline anxiety was 49% (Table 1). The median score for baseline depression was 7 (IQR 4–10), and for anxiety was 7 (IQR 4–11) at baseline. Continuous depression and anxiety scores were highly correlated at baseline (correlation coefficient (r) =0.85).

ART initiation and adherence

Among 367 enrolled Chinese MSM, 228 individuals (62%) started ART by the end of the RCT. Three of 228 participants initiated treatment after HIV diagnosis, but before enrollment in the RCT. The percentage of self-reported "perfect" ART adherence was 92% (140/153) at 3 months follow-up, 89% (148/167) at 6 months, 88% (170/194) at 9 months, and 88% (167/189) at 12 months (Table 2). The number of ART initiators at each follow-up visit varied as per their initiation time points and missing visits. By the end of the study, 21% of our study participants missed at least one visit.

Depression and ART adherence

There was insufficient evidence to conclude that the association between depression and the log-odds of depression was non-linear (p>0.05). We used the linear depression score in our models rather than restricted cubic splines. Since intervention and HIV-related stigma were not effect modifiers in our analysis, they were treated as potentially confounding variables. Table 3 presents results of associations between depression and ART adherence. In the Model-l, we observed that a one-unit increase in depression score was associated with a 16% increase in the odds of reporting "imperfect" ART adherence (adjusted odds ratio [aOR] 1.16; 95% confidence interval [CI] 1.02–1.32). The association was similar in the Model-2 (aOR 1.13; 95% CI 0.99–1.29).

When depression scores were collapsed into categories, all point estimates indicated that depression was likely to be a risk factor of self-reported "imperfect" ART adherence in all models (Table 2). However, none of these associations was statistically significant. In the Model-1 and Model-2, likely depression had a relatively large effect on ART adherence in its magnitude of association, when compared to borderline depression.

Anxiety and ART adherence

We used linear anxiety score in our analyses, as the linearity assumption held (Table 3). The likelihood ratio tests failed to identify intervention and HIV-related stigma as effect modifiers in our study. Hence, we treated them as potentially confounding variables. We found that a one-score increase in anxiety score was associated with a 17% increase (aOR: 1.17, 95% CI: 1.03, 1.33) in the odds of reporting "imperfect" ART adherence in the Model-1. The result from Model-2 was similar to that from Model-1 (Table 2).

Results from models using the categorical designation of anxiety also suggested that anxiety was likely associated with "imperfect" ART adherence. For likely anxiety, we observed a strong and significant association with the point estimates ranging from 4.79 to 4.83 in the Model-1 and Model-2. Individuals with borderline anxiety were 85% more likely to report "imperfect" ART adherence than ones without anxiety, but this association was not significant in any model.

Discussion

Our study found that both depression and anxiety were risk factors for "imperfect" ART adherence among Chinese MSM with newly diagnosed HIV infections. This is consistent

with prior findings in PLHIV from a variety of venues and backgrounds [4, 14, 15]. A one-unit increase in the depression score was significantly associated with "imperfect" ART adherence, and the association (aOR 1.16; 95% CI 1.02–1.31) was stronger than that reported previously from Brazil (aOR 1.04; 95% CI 1.01–1.06) [26]. We used HADS to measure depression among newly diagnosed Chinese MSM in our cohort study, while the Brazilian study used the Hamilton Rating Scale for Depression (HRSD) to assess depression in PLHIV in a cross-sectional study [26]. This may lead to the difference in the magnitude of the effect size. Even though we did not find significant associations between categorical depression and ART adherence, the point estimates (aOR varying from 1.74 to 1.80) suggested that depression (borderline or likely) was likely associated with "imperfect" ART adherence.

For anxiety, a one-score increase was associated with a 17% increase in the odds of reporting "imperfect" ART adherence (aOR 1.17; 95% CI 1.03–1.33). For the categorical anxiety analysis, we only found a significant association between "likely" anxiety and "imperfect" adherence to ART (aOR 4.79; 95% CI 1.12–20.50). The literature has also reported similar effects of depression and anxiety (categorical) on "imperfect" adherence to ART [4, 17]. Loss of statistical power in the categorical analysis could be a potential explanation for nonsignificant results with wide confidence intervals. The weight of evidence from both continuous and categorical analyses supports the hypothesis that depression and anxiety are associated with lower ART adherence among newly diagnosed Chinese MSM, consistent with findings in other PLHIV.

Depression and anxiety measured right after HIV diagnosis can be a reflection of immediate health concerns. Unlike initiation that just needs a one-time effort, maintaining ART adherence takes a persistent effort. It is presumably hard for patients with sustained depression or anxiety to adhere to ART over months and years. Depressed and/or anxious individuals may lose interest in HIV care, and may be less capable in keeping to daily schedules.

Depression and anxiety are common among Chinese MSM with newly diagnosed HIV infections. The prevalence of depression and anxiety in our study population were similar to those reported in other studies with PLHIV [4, 10, 11]. However, our scale-based measurements revealed prevalence of depression and anxiety to be twice those reported among Chinese MSM with a HIV negative or unknown serostatus [12]. The proportion of MSM with "perfect" ART adherence was around 90% in all four follow-up visits over 12 months, higher than that reported in HIV-infected people in several meta-analyses (77%) [4, 10, 11]. Although self-reported perfect ART adherence might be overestimated by self-report, other studies of ART adherence among Chinese MSM also reported a comparatively high proportion adhering to ART [7, 12]. Education could be possible explanations for this favorable difference. Chinese MSM are a highly educated population with 80% having at least a college education [7, 12, 27]. Among Chinese PLHIV as a whole, less than 19% had a college degree [28]. In addition, better educated HIV-infected individuals are more likely to adhere to ART [29, 30].

Our study's strengths include its longitudinal study design nested within a randomized clinical trial. Both our exposure (depression and anxiety) and outcome (ART adherence) were repeated measurements, and we had a higher power to detect the true difference. All our study participants were enrolled in a short time interval after HIV diagnosis, that enabled us to draw inferences among MSM who recently learned of their HIV positive status.

There were also several limitations in our study. We recruited MSM from a single metropolian city Beijing. We cannot generalize our finding to MSM in all of China. Futher studies with representative samples are needed to replicate our findings. By the end of the study, 21% participants missed at least one visit. Our results can be either attenuated or overestimated due to missing visits. Reporting bias may be an issue, as adherence to ART was self-reported.

Early ART initiation and "perfect" adherence to treatment in this newly diagnosed population are critical to achieve successful viral suppression and good treatment outcomes. ART adherence can also contribute to controlling the HIV epidemic among Chinese MSM through reduced infectiousness of HIV-infected persons. Depression and anxiety were associated with reporting "imperfect" ART adherence. Psychiatrists or other qualified mental health professionals are needed to assess the severity of depression and anxiety, and to provide therapeutic advice to newly diagnosed HIV-infected MSM. Other medical conditions that may cause depression or anxiety should be investigated, especially if the history suggests that the HIV diagnosis was not the precipitant of the psychological symptoms. For MSM with mild or moderate depression and/or anxiety, peer counseling and support may help to deal with their symptoms. For severe cases, antidepressant or anti-anxiety medications may be given besides peer counseling and support. Intensive early interventions targeting depression and anxiety, beyond routine counseling, may help improve ART adherence among newly diagnosed Chinese MSM.

Acknowledgments

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Table 1

Demographics, behaviors, and health status among 228 Chinese men who have sex with men (MSM) who initiated antiretroviral therapy (ART)

Variable	No. of participants (%)
Age, year (median, IQR)	28 (25–32)
Ethnicity	
Han	214 (93.9)
Other	14 (6.1)
Marital status	
Single	196 (86.0)
Currently married	23 (10.1)
Divorced or separated or widowed	9 (3.9)
Education	
College education or above	187 (82.0)
High school or less	41 (18.0)
Employment status	
Employed	198 (86.8)
Unemployed or other	30 (13.2)
Health care	
Yes	132 (57.9)
No	96 (42.1)
Place of birth	
Large city	59 (25.9)
Medium city	58 (25.4)
Small city	46 (20.2)
Township/countryside	65 (28.5)
Beijing *Hukou* (legal local residency)	
No	183 (80.3)
Yes	45 (19.7)
Alcohol use in the past three months	
No	100 (43.9)
Yes	128 (56.1)
Drug use in the past three months	
No	144 (63.4)
Yes	83 (36.6)
Social support	
Very satisfied	96 (42.1)
Somewhat satisfied	73 (32.0)
Somewhat dissatisfied	34 (14.9)
Very dissatisfied	25 (11.0)
Syphilis serostatus	
Negative	200 (87.7)

Variable	No. of participants (%)
Positive	28 (12.3)
Depression score at baseline	7 (4, 10)
Depression status at baseline	
Normal	130 (57.0)
Borderline depression	46 (20.2)
Likely depression	52 (22.8)
Anxiety score at baseline	7 (4, 11)
Anxiety status at baseline	
Normal	117 (51.3)
Borderline anxiety	46 (20.2)
Likely anxiety	65 (28.5)
HIV-related stigma at baseline (Median, IQR)	30 (12, 48)

Note: IQR, interquartile range;

ART adherence by depression and anxiety during 12-months follow up among Chinese Men who have sex with men who initiated ART

Adherence at 3-month Follow up (FU)	Depression at study entry			Anxiety at study entry		
	Normal	Borderline	Likely	Normal	Borderline	Likely
Self-report perfect adherence (N=140)	68 (91.9)	36 (94.7)	36 (87.8)	68 (91.9)	26 (89.7)	46 (92.0)
Self-report Not perfect adherence (N=13)	6 (8.1)	2 (5.3)	5 (12.2)	6 (8.1)	3 (10.3)	4 (8.0)
Adherence at 6-month FU	Normal	Borderline	Likely	Normal	Borderline	Likely
Self-report perfect adherence (N=148)	81 (92.1)	36 (90.0)	31 (79.5)	75 (91.5)	32 (91.4)	41 (82.0)
Self-report Not perfect adherence (N=19)	7 (7.9)	4 (10.0)	8 (20.5)	7 (8.5)	3 (8.6)	9 (18.0)
Adherence at 9-month FU	Normal	Borderline	Likely	Normal	Borderline	Likely
Self-report perfect adherence (N=171)	97 (88.2)	37 (86.1)	37 (88.1)	92 (89.3)	34 (89.5)	45 (83.3)
Self-report Not perfect adherence (N=24)	13 (11.8)	6 (13.9)	5 (11.9)	11 (10.7)	4 (10.5)	9 (16.7)
Adherence at 12-month FU	Normal	Borderline	Likely	Normal	Borderline	Likely
Self-report perfect adherence (N=167)	95 (88.8)	34 (87.2)	38 (88.4)	91 (89.2)	30 (93.7)	46 (83.6)
Self-report Not perfect adherence (N=22)	12 (11.2)	5 (12.8)	5 (11.6)	11 (10.8)	2 (6.3)	9 (16.4)

Table 3

Association between depression and anxiety and adherence to antiretroviral therapy (ART) among Chinese men who have sex with men (MSM) who initiated ART

Depression/anxiety	Crude odds ratio ([OR], 95% Confidence interval[CI])	Adjusted OR (95% CI)	
		Model-1*	Model-2†
Depression continuous score (0–21)	1.14 (1.01, 1.30)	1.16 (1.02, 1.32)	1.13 (0.99, 1.29)
Depression Categories			
Normal (0–7)	1.00	1.00	1.00
Borderline depression (8–10)	2.14 (0.57, 8.10)	1.74 (0.48, 6.29)	1.68 (0.47, 5.97)
Likely depression (11–21)	1.87 (0.45, 7.84)	1.77 (0.43, 7.37)	1.80 (0.43, 7.50)
Anxiety continuous score (0–21)	1.16 (1.02, 1.33)	1.17 (1.03, 1.33)	1.15 (1.01, 1.31)
Anxiety categories			
Normal (0–7)	1.00	1.00	1.00
Borderline anxiety (8–10)	2.06 (0.60, 7.13)	1.85 (0.56, 6.13)	1.85 (0.56, 6.13)
Likely anxiety (11–21)	5.87 (1.32, 26.13)	4.79 (1.12, 20.50)	4.83 (1.12, 20.71)

*
Model-1 adjusted for age, intervention, study site, education, social support, alcohol use, drug use, and HIV-related stigma;

†
adjusted for all variables listed in the Model-1, except alcohol and drug use.