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Association between Depression and Antiretroviral Therapy Use among People Living with HIV: A Meta-Analysis

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Abstract

Background: Depression is common among people living with HIV (PLHIV). Studies on the relationship between depression and use of antiretroviral therapy (ART) are inconclusive.

Methods: A meta-analysis was conducted to summarize the relationship between depression and ART use among PLHIV. Ten electronic databases, conference abstracts, and dissertations were searched. A random effects meta-analysis was performed to pool the odds ratio estimates from eligible studies. Subgroup analyses and meta-regression were conducted for moderator analysis. Sensitivity analysis was performed to find influential studies. A funnel plot, the Egger test, and the trim and fill analysis were used to detect publication bias.

Results: The pooled sample size was 7,375 PLHIV from nine eligible studies. The pooled prevalence of depression was 41% (95% confidence interval [CI] 29%-53%). The pooled ART use rate was 52% (95% CI 37%-67%). PLHIV with depression were 14% less likely (pooled odds ratio [OR]=0.86; 95% CI 0.71-1.05) to use ART than those without depression. Subgroup analyses showed that depression was significantly associated with no ART use (pooled OR=0.84; 95% CI 0.71-0.99) among studies with a prospective study design (11 estimates from nine studies). Moderator analyses did not show any statistically significant effects. The publication bias analyses showed small study effects may not exist.

Conclusions: Depression was associated with non-use of ART among PLHIV. Studies are needed to explore this association in other countries with varied populations, as most published studies have been conducted in the United States.

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Authors' contributions:

HQ, JT, and SV initiated this study. JT searched for related literature, information extraction, and analysis. HQ and SV provided valuable suggestions and comments for this manuscript.

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Ethical approval: This study was non-human subject study focusing on review of published literature. It did not involve animals.

Informed consent: Our study did not involve human beings.

Keywords

Depression; antiretroviral therapy; people living with HIV (PLHIV); meta-analysis; systematic review

Introduction

Depression is common among people living with HIV (PLHIV). A meta-analysis in 2014 reported that the prevalence of depression among PLHIV was 39% (95% confidence interval [CI]: 33%-45%) (1). Depression is a persistent mood disorder, characterized by feelings of sadness, loss, anger, and frustration that interfere with daily living. Depression can impair individuals' social and cognitive functioning, and lead to disability and suicide at its' worst cases. Although cost-effective treatments are available for depression, a substantial proportion of depressed individuals are never been diagnosed and treated (2). Research has shown that depression has a negative impact on the uptake of HIV testing and care (3-6). Individuals with depression can experience self-abasement, cognitive impairment, and self-isolation (7), which might explain why some depressed PLHIV are less likely to engage in HIV care.

Antiretroviral therapy (ART) is beneficial for both HIV-infected individuals and public health. For individuals, ART can boost their immune system, reduce the likelihood of opportunistic infections, slow progression to AIDS, and improve AIDS survival (8,9). Research has also shown that ART can reduce chances of both AIDS and Non-AIDS-related death (10). From a public health perspective, ART can reduce HIV secondary transmission by lowering viral load among PLHIV. HIV testing and care are the key components of the strategy of "Treatment as Prevention" for preventing new infections (11). HIV testing is the gateway to HIV care, and only those who are linked to and retained in care have the opportunity of starting ART. However, coverage of ART is less than 50% in most countries (12-14).

Depression could be one of barriers for ART use. Depressed individuals may feel desperate and have social functioning impairment, including weakening HIV care seeking behavior. However, the effect of depression on ART use is inconclusive in the literature. Some studies have shown that individuals with depression were less likely to initiate ART (15-21), while other studies have indicated that depression could increase the likelihood of ART use (22-24). An argument is that depression might be a reflection of health concern, and can motivate PLHIV to seek HIV care and use ART. Turner and Fleishman reported that the effect of depression on ART use differed by ethnic groups (25). The prevalence of depression and access to HIV care can vary among different ethnic groups. In addition, study design, measurement of depression and ART use, criteria for ART initiation, and settings where studies were conducted may have impacts on the association between depression and ART use. Given these disparate reports, we conducted a meta-analysis to summarize the evidence on the association between depression and ART use among PLHIV.

Methods

Literature search and study selection

A systematic literature search was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). We aimed to identify studies that evaluated the relationship between depression and ART use, published between 1996 advent of combination ART and December 15th, 2015. Ten electronic databases were searched: BIOSIS Previews (*Biological Abstracts & Biological Abstracts/RRM, Thomson Scientific Technical Support, New York), Embase (Elsevier, Amsterdam, The Netherlands), Ovid Medline (Ovid Technologies, Inc., New York), Pubmed (National Center for Biotechnology Information, Bethesda MD), PsycINFO (American Psychological Association, Washington), Scopus (Elsevier, Amsterdam, The Netherlands), Web of Science (Thomson Scientific Technical Support, New York), CNKI (Tongfang Knowledge Network Technology Co. Ltd., Beijing, China), CQVIP (Chongqing VIP Information Co. Ltd., Chongqing, China), and Wanfang Data (Chinese Ministry of Science & Technology, Beijing, China*). CNKI, CQVIP and Wanfang Data were Chinese Databases. We also searched conference abstracts from 2001 to 2015 of *the International AIDS Society (IAS) Conference* (http://www.abstract-archive.org/) and *Conference on Retroviruses and Opportunistic Infections (CROI)*, and searched dissertations and theses through ProQuest (1996-2015).

We used four main search terms based on the search strings developed by the Cochrane Collaboration. The search strategy for PubMed is attached in the appendix.

Study criteria and selection

The criteria for eligible studies are as follows: (1) used any study design; (2) targeted PLHIV; (3) measured depression as an exposure variable; (4) measured ART use as an outcome variable; and (5) provided sufficient information to calculate effect size (ES) estimates. We originally intended a separate assessment of anxiety, but found only one eligible paper.

Studies searched from multiple electronic databases were imported into EndNote 6.0 (*Thomson Reuters Corporation, New York*). Title screening was conducted after removing duplicates. Most irrelevant studies were excluded in this phase. The remaining studies were further screened by reading abstracts. Only studies that mentioned the association between depression and ART use were chosen for full text screening.

Data extraction

For eligible studies, the following information was extracted in a standardized manner: first author's name, year of publication, study period, study country, study design, sample size, study population (transmission route), percentage of Caucasians in study population, percentage of male participants, prevalence of depression, method of measuring depression, and method of measuring ART use.

ART use was a self-reported binary outcome in most of the eligible studies. Hence, odds ratios [OR] were used to quantify the association between depression and ART use among

PLHIV. People without depression were used as the reference group for the calculation of OR. Several studies also reported the association using risk ratio or hazard ratio; we calculated OR and 95% confidence interval [CI] based on available data for synthesis. If data were not available in the paper, we contacted corresponding authors for related information that could be used for adjusted OR, or raw data that we could use to calculate crude OR.

Statistical methods

A random effects meta-analysis using inverse variance weights was used to pool effect sizes across eligible studies. The natural logarithm of OR and 95% CI were used in the synthesis. We then transformed the overall effect size back into OR and 95% CI for ease of interpretation. The meta-analysis results were displayed with a forest plot.

To assess heterogeneity among eligible studies, the Q statistic, I^2 statistic, and τ^2 were used (26,27). The Q statistic is underpowered to detect true heterogeneity, given that a small number of studies are included. Hence, we used a 10% significance level to increase our power to detect heterogeneity using the Q statistic.

To control for the effects of potential moderators and to explore the source of heterogeneity between studies, subgroup analyses and a random effects meta-regression model were conducted. Sensitivity analyses were performed to find influential studies, and we removed one study analysis at a time (total 11 populations in nine studies). We used a funnel plot, the Egger test, and the trim and fill analysis to assess publication bias. All statistical analyses were conducted in Stata 12.0 (Stata Corporation, College Station, TX).

Results

Results of literature search

Figure 1 shows the process of our study selection. The initial searches in 10 individual electronic databases yielded 3,116 records, and in conference websites, we found 1,042 conference abstracts, of which 1,324 were duplicates and were excluded, leaving 2,834 records for title and abstract screening. Thirty-two publications were identified for full text screening of which 13 reported associations between depression and ART use, and were eligible for our meta-analysis. Two studies did not report enough information to calculate effect sizes (28,29), and two studies had overlapping samples (30,31). Hence, nine unique studies were included in our analyses. Two of these studies contributed two estimates of OR, as heterogeneous effects were observed across different study populations (e.g., drug users vs. non-users, and Caucasian vs. Black/Hispanic). Hence, we had 11 effect size estimates in the quantitative synthesis.

Description of studies

Table 1 summarizes the characteristics of the studies. Of 7,375 pooled study participants, 68% were women, Caucasians represented 30%, and 15% had a CD4+ T-lymphocyte (CD4) count less than 350 cells/μL. Seven of nine studies used a scale for measuring depression, one study was based on physician's diagnosis (16), and one study used self-report of

depressive symptoms (22). For ART use, six studies used self-report, and the other three studies were based on medical records. Seven studies used a prospective cohort design, and two were cross-sectional. Six of nine studies were conducted in the continental United States, with the other three from Puerto Rico, Uganda, and Russia. All of them were published between 2004 and 2014.

Effect of depression on ART use

The prevalence of depression ranged from 19% to 77% in the included studies, and the pooled depression prevalence was 41% (95% CI 29%-53%). ART use rate varied from 11% to 71%, and the pooled estimation was 52% (95% CI 37%-67%). The pooled synthesis showed that depressed PLHIV were 14% less likely to use ART than those without depression (OR=0.86; 95% CI 0.71-1.05; Figure 2). The Q statistic rejected the null hypothesis that the true heterogeneity was due to chance (chis-square: 32.20, degree of freedom=10, $P<0.001$) at a 10% significance level. The I^2 statistic indicated that 68.9% of variance could be explained by true heterogeneity. The variability of effect sizes (τ^2) across studies was 0.061.

Moderator analyses

Table 2 presents results of pooled OR from the subgroup analyses. The synthesized point estimates from studies with a prospective design, studies conducted in the continental United States, and studies using scale screening for depression showed that depression was associated with a lower likelihood of ART use. The pooled estimate from studies with a prospective study design showed a statistically significant association between depression and ART use (pooled OR=0.84; 95% CI 0.71-0.99). The pooled results from studies conducted in the continental United States showed a marginally significant effect on ART use (pooled OR=0.85; 95% CI 0.71-1.01). In the subgroup analyses by the measurement methods of ART use, the pooled point estimates were different (0.91 for scale screening vs. 0.62 for medical records), and their 95% confidence intervals did not substantially overlap. The pooled point estimate in studies without limitation on CD4 count was 0.91 (95% CI 0.71-1.17), and the synthesized estimate from studies targeting patients with a CD4 count less than 350 cells/μL was 0.75 (95% CI 0.55-1.03). However, none of these differences was statistically significant in the random effects meta-regression model. Publication year and percentage of Caucasian participants were not significant factors, either.

Sensitivity analyses and publication bias

Sensitivity analyses were conducted to detect influential studies in our meta-analysis. Table 3 lists the pooled OR, with one study at a time removed from the meta-analysis. We found that two studies caused a relative large change on point estimation, and both confidence intervals excluded 1.00, when either was removed (22,25). This indicated that the two studies were influential studies compared to the rest of the studies included in this synthesis. The study by Turner and colleagues showed depressed PLHIV were more likely to be on ART, and this conclusion was contrary to most other studies in our analysis. This study was conducted among Caucasian whites who might have more access to care for both depression and ART, and the association between depression and ART use among them might differ from other populations (22,25). The study by Feliciano and colleagues also had the similar

finding. Depression was measured by self-report in response to a study question “are you depressed?” This measurement might introduce information bias (22,25). These two studies were influential in our meta-analysis.

For publication bias, the funnel plot was asymmetric (Figure 3). However, the Egger test failed to reject the null hypothesis that no small study effects exist at a 5% significance level. The trim and fill analysis did not yield any trimmed or filled studies. There is no significant publication bias.

Discussion

Our meta-analysis of 11 populations in nine studies including 7,375 PLHIV suggested that depression was associated with a lower likelihood of ART use. Though the overall finding was not significant at a 5% significance level, subgroup analyses showed a statistically significant reduction in ART use among depressed patients in the subset of studies with a prospective study design, or using a scale for depression measurement, or utilizing medical records to assure ART use. Prospective studies could provide more convincing evidence due to the ascertained temporal relationship. Studies with more rigorous measurements of depression and ART use could reduce reporting bias. Hence, pooled results from these subgroup analyses should be more reliable. Of nine included studies, six were conducted in the continental United States, and three studies (four populations) were from the Women's Interagency HIV Study (WIHS) that contributed significantly to the overall effect (18,19,21). WIHS is a multi-site prospective cohort study to understand how HIV impacts women’s lives, in which depression and anxiety were evaluated. More studies in different regions and populations are needed to provide more evidence for the effect of depression on ART use among PLHIV.

Depression measured among PLHIV is less likely to be a reflection of the immediate emotional reaction to HIV positive status and health concerns (32), as these studies included participants who had typically known their positive status for years or months. Depressed individuals can experience impairment of cognitive and social functioning (33). In such cases, they might be less likely to seek HIV care and initiate ART use. Intervention for depression among PLHIV is important to improve their mental health in the long-run, and may have an indirect effect on increasing ART use.

Both depression and ART use rates may vary in different ethnic groups. Some studies found that HIV-infected Caucasians had a higher prevalence of both depression and ART use compared to those of Hispanics and African Americans (25). However, few studies have treated ethnicity as a potential effect modifier. Ethnicity was only considered as a confounding variable for adjustment in most of included studies. Given the potential effect modification of ethnic group, failure to consider this may lead to a misleading combined result, given that heterogeneous effects exist. Illicit drug use might be an effect modifier for the association between depression and ART use (18). Most studies in our meta-analysis did not report on this potential interaction. Hence, the pooled effect size on depression and ART use can be biased, due to ignoring the potential heterogeneous effects across different groups.

Research has shown that the prevalence of depression among PLHIV can vary among countries with varied income levels (1). Some studies suggested that PLHIV from high- and middle-income countries had higher prevalence of depression than those from low-income countries (1). The coverage of ART also varied in countries with different income levels (34). Six of nine studies included in this analysis were conducted in a high-income country-the United States, so we could not perform a subgroup analysis by country income level. Thus, our study findings may not be generalized to the entire HIV-infected global population, as we did not have a representative sample from countries with varied income levels. We excluded two eligible studies due to incomplete data to calculate effect sizes, and we failed to elicit responses from the authors (28,29). One study was conducted in Nepal, and the other was in the continental United States. If we could add these two studies to our meta-analysis, our results might change.

Heterogeneity assessment suggested that the majority of variance was due to the true heterogeneity. We did not find a significant moderator effect in either the subgroup analyses or Meta regression between different groups (Table 2). A small number of studies in our meta-analysis might limit our power to detect the true difference. In addition, we cannot evaluate the variance within groups, as studies within groups used different methods to measure a certain variables. Take the measurement of depression as an example. Within the group of studies using scales for screening depression, some studies used the Center for Epidemiologic Studies Depression Scale (CES-D), and other used the Composite International Diagnostic Interview short-form (CIDI-SF) (Table 1). Even though studies used the same scale for depression, they might choose different thresholds for depression (CES-D: 16 vs. 23 as the cutoff value). Self-reported depression is a potentially biased measure. Hence, further studies on depression and ART use with a common measurement method are necessary to provide a more convincing pool estimate.

Publication bias was not noted in this meta-analysis. The Egger test failed to reject small study effects, and the trim and fill analysis did not trim or add a single study. As studies included in our meta-analysis were mostly from the continental United States, studies conducted in other regions might have different results. In conclusion, our study was the first meta-analysis to evaluate the association between depression and ART use among PLHIV. The evidence suggests that depression is associated with lower uptake of ART, particularly noted in the higher quality studies, and integrating mental health service into HIV care may improve ART use among PLHIV. As most of studies related to depression and ART use were implemented in the continental United States, more research is needed to provide evidences from other countries with varied ethnicities and income levels, especially low- and middle-income countries.

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Appendix

The search strategy for PubMed is listed below:

1. HIV/AIDS strings: (HIV Infections[MeSH] OR HIV[MeSH] OR hiv[tiab] OR hiv1[tiab] OR hiv-2*[tiab] OR hiv1[tiab] OR hiv2[tiab] OR hiv infect*[tiab] OR human immunodeficiency virus[tiab]OR human immune deficiency virus[tiab] OR human immuno-deficiency virus[tiab] OR human immune-deficiency virus[tiab] OR ((human immun*) AND(deficiency virus[tiab])) OR acquired immunodeficiency syndromes[tiab] OR acquired immune deficiency syndrome[tiab] OR acquired immuno-deficiency syndrome[tiab] OR acquired immune-deficiency syndrome[tiab] OR ((acquired immun*) AND (deficiency syndrome[tiab])) or “sexually transmitted diseases, viral”[mh] OR HIV[tiab] OR HIV/AIDS[tiab] OR HIV-infected[tiab] OR HIV[title] OR HIV/AIDS [title] OR HIV-infected[title])
2. ART strings: (“antiretroviral therapy, highly active” [MeSH] OR “anti-retroviral agents”[MeSH] OR “antiviral agents”[MeSH:NoExp] OR ((anti[tiab]) AND (hiv[tiab])) OR antiretroviral*[tiab] OR ((anti[tiab]) AND (retroviral*[tiab])) OR HAART[tiab] OR ((anti[tiab]) AND (acquired immun*[tiab]) AND (deficiency[tiab]))
3. Use strings: (initiate[tiab] OR initiating[tiab] OR initiation[tiab] OR “when to start”[tiab] OR early treatment[tiab] OR deferred treatment[tiab] OR earlier treatment[tiab] OR use[tiab] OR acceptance[tiab] OR (start*[tiab] AND therapy[tiab]))
4. Depression strings: (depress* OR dysthymi* OR anxiety [MeSH] OR anxious[MeSH] OR GAD)
5. Published year: "1996"[PDAT]: "2015"[PDAT]
6. The strategy was 1&2&3&4&5.

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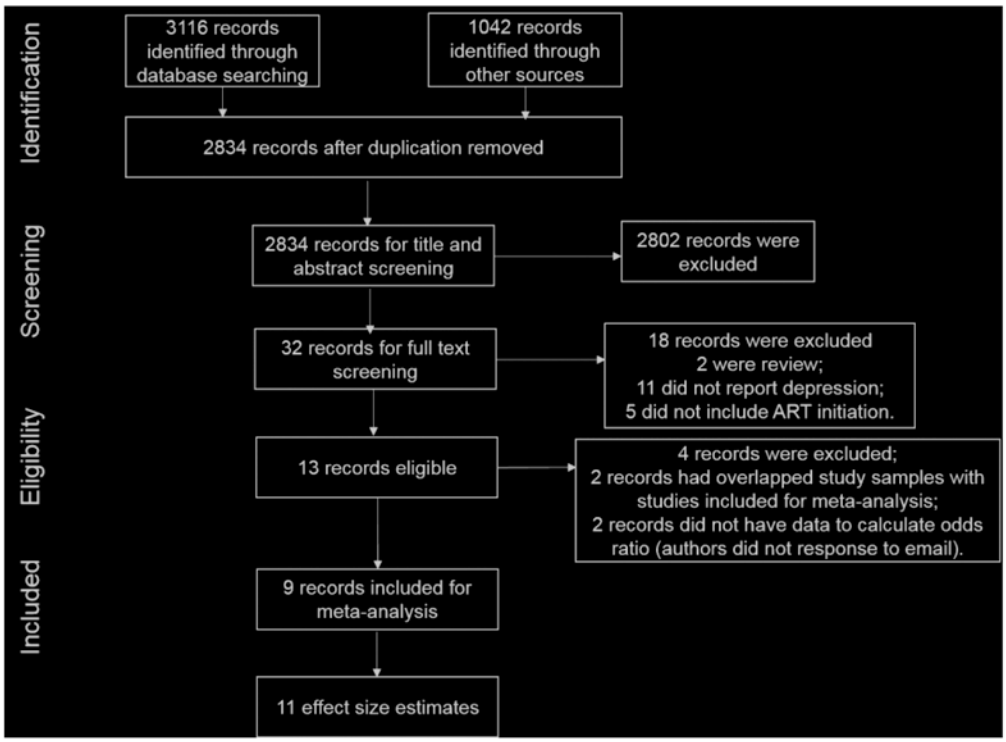

Figure 1.
Flow chart of study selection

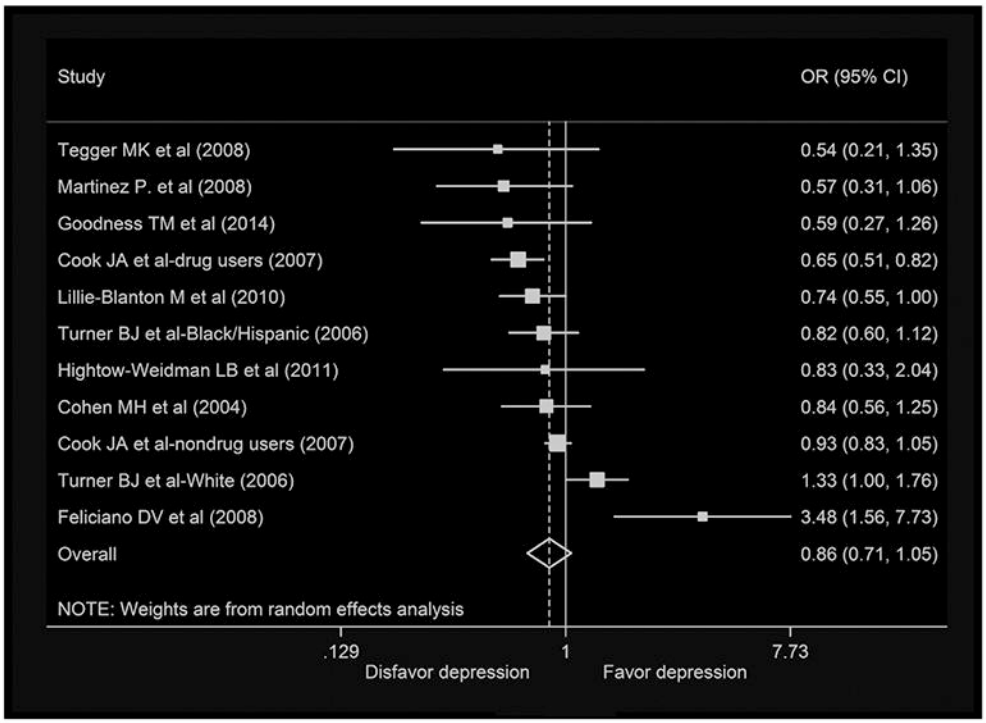

Figure 2.

Forest plot of the effect of depression on antiretroviral therapy use among people living with HIV

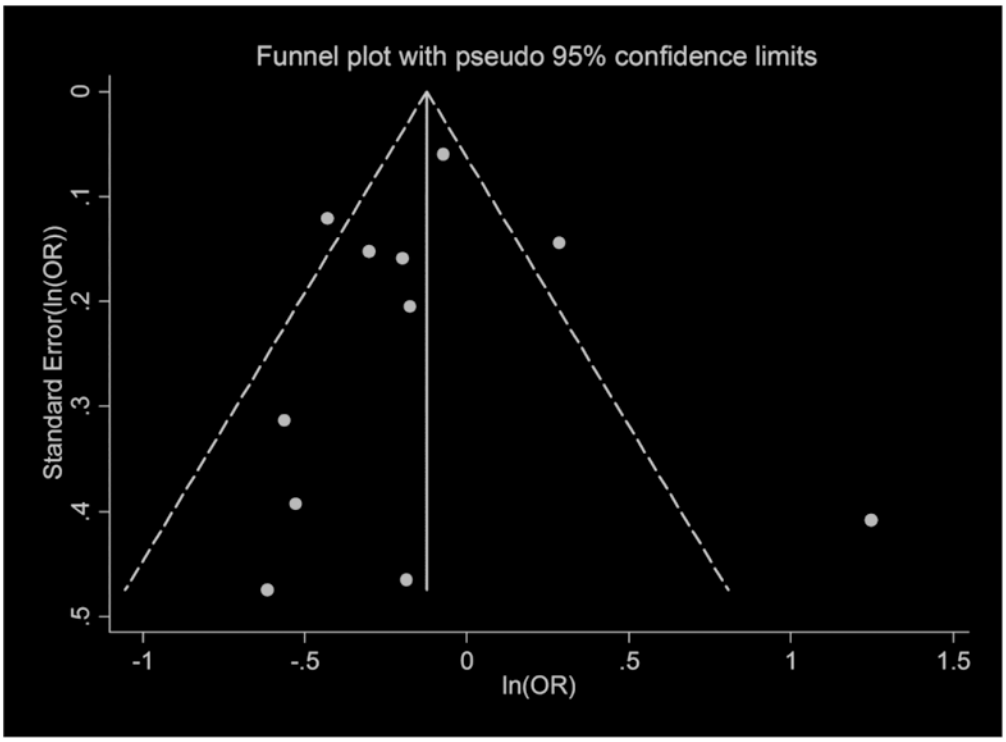

Figure3.
Funnel plot for assessing publication bias

Table 1.

Studies on association between depression and use of antiretroviral therapy (ART) among people living with HIV (PLHIV)

Study	Country	Population	Study design	Depression measurement	ART use measurement	Sample size	% of Caucasians	% of males	Depression prevalence (%)	CD4 as ART criteria (cells/μL)
Martinez et al (2008) [13]	Uganda	PLHIV	cross-sectional	Hopkins Symptom Checklist	Medical records	421	0	37	19	All
Tegger et al (2008) [14]	U.S.	PLHIV	prospective	Physician	Medical records	173	53	82	31	<350
Hightow-Weidman et al (2011) [18]	U.S.	HIV-infected young MSM	prospective	CES-D	Medical records	60	0	100	30	<350
Goodness et al (2014) [15]	Russia	HIV-infected heavy drinkers	prospective	BDI-II score	self-report	133	100	53	59	<350
Cook et al among nondrug users (2007) [16]	U.S.	HIV-infected women	prospective	CES-D	self-report	1371	22	0	55	All
Cook et al among drug users (2007) [16]	U.S.	HIV-infected women	prospective	CES-D	self-report	339	22	0	55	All
Cohen et al (2004) [17]	U.S.	HIV-infected women	prospective	CES-D	self-report	750	16	0	45	<350
Turner et al among Whites (2006) [23]	U.S.	PLHIV	prospective	CIDI-SF	self-report	1062	100	84	28	All
Turner BJ et al-among Blacks and Hispanics (2006) [23]	U.S.	PLHIV	prospective	CIDI-SF	self-report	920	0	56	28	All
Lillie-Blanton et al (2010) [19]	U.S.	HIV-infected women	prospective	CES-D	self-report	1354	14	0	26	All
Feliciano et al (2008) [20]	Puerto Rico	HIV-infected PWID	cross-sectional	Self-report	self-report	792	0	84	77	All

Notes: MSM stands for men who have sex with men; CES-D: Center for Epidemiologic Studies Depression Scale; BDI-II: Beck Depression Inventory-II. CIDI-SF: Composite International Diagnostic Interview short-form; PWID: people who inject drugs.

Table 2.

Subgroup analyses of association between depression and antiretroviral therapy (ART) use

Subgroup	No. of publications	Pooled odds ratio (95% confidence interval)
Overall	11	0.86 (0.71-1.05)
Study design		
Prospective	9	0.84 (0.71-0.99)
Cross-sectional	2	Not done
Country		
Continental United States	8	0.85 (0.71-1.01)
Russia, Puerto Rico, Uganda	3	1.04 (0.34-3.17)
Measurement of Depression		
Scale screening	9	0.83 (0.70-0.98)
Physician diagnosis	1	Not applicable
Self-report	1	Not applicable
Measurement of ART use		
Self-report	8	0.91 (0.73-1.13)
Medical record	3	0.62 (0.39-0.96)
CD4 count criterion for starting ART (cells/μL)		
<350	4	0.75 (0.55-1.03)
No limitation	7	0.91 (0.71-1.17)

Table 3.

Sensitivity analyses of association between depression and antiretroviral therapy use

Removed study	Pooled odds ratio (95% confidence interval)
Martinez et al (2008)[13]	0.89 (0.72-1.09)
Tegger et al (2008)[14]	0.88 (0.72-1.08)
Hightow-Weidman et al (2011) [18]	0.86 (0.70-1.06)
Goodness et al (2014)[15]	0.88 (0.72-1.08)
Cook et al among nondrug users (2007)[16]	0.85 (0.66-1.10)
Cook et al among drug users (2007) [16]	0.90 (0.73-1.11)
Cohen et al (2004) [17]	0.87 (0.70-1.08)
Turner et al among White (2006) [23]	0.81 (0.66-0.98)
Turner et al among Black and Hispanic (2006) [23]	0.87 (0.69-1.09)
Lillie-Blanton et al (2010) [19]	0.88 (0.71-1.10)
Feliciano et al (2008) [20]	0.82 (0.69-0.97)
Overall effect, no study removed	0.86 (0.71-1.05)