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Depression and adherence to antiretroviral therapy in low-, middle- and high-income countries: a systematic review and meta-analysis

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Abstract

We investigated the associations between depressive symptoms and adherence to antiretroviral therapy (ART) among people living with HIV (PLHIV). We searched the PubMed, EMBASE and Cochrane CENTRAL databases for studies that studies that reported an association between depression and adherence to ART as a primary or secondary outcome. We used a random-effect model to pool the risk estimates from the individual studies. The odds ratio (OR) with their 95%

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CIs were used as summary estimates. Of 2,861 citations, 111 studies that recruited 42,366 PLHIV met our inclusion criteria. When reported, the rate of PLHIV with depressive symptoms ranged from 12.8% to 78% and the proportion of PLHIV who achieved good adherence (≥ 80%) ranged from 20% to 98%. There were no significant differences in rate of depressive symptoms in PLHIV by country income group; however, the proportion of PLHIV who achieved good adherence was significantly higher in lower-income countries (as defined in the 2012 World Bank Country Income Groups) (pooled rate = 86%) compared to higher-income countries (pooled rate = 67.5%; $p<.05$). We found that the likelihood of achieving good ART adherence was 42% lower among those with depressive symptoms compared to those without (pooled OR = 0.58, 95% CI 0.55 to 0.62). The relationship between depressive symptoms and adherence to ART was consistent across the country's income group, study design, and adherence rates. We found that the magnitude of the association significantly decreases with more recent publications and increasing study sample size. The higher the prevalence of depressive symptoms of PLHIV recruited in the studies, the lower the likelihood of achieving good adherence to ART. In conclusion, the likelihood of achieving good adherence was lower among those with depressive symptoms compared to those without.

Keywords

HIV; ART; Depression; Adherence

INTRODUCTION

There is a significant global burden of psychiatric disorders among people living with HIV (PLHIV) across low-, middle-, and high-resource settings, and the presence of such disorders interferes with optimal adherence to antiretroviral therapy (ART), most notably with major depressive disorder [1, 2]. Depression is the most common psychiatric disorder among PLHIV [1], with HIV-positive individuals being twice as likely to be diagnosed with depression compared to HIV-negative individuals [3]. Even at subclinical levels, depressive symptoms have been shown to disrupt adherence to antiretroviral therapy (ART) [4, 2], which increases the likelihood of ART treatment failure, development of ART resistance, and continued HIV transmission [5–7]. Particularly in resource-limited settings, poor ART adherence may lead to failure of the only available first- and second-line ART regimens [8]. Further, depression also is associated with accelerated HIV disease progression and mortality among PLHIV [9, 10].

Although extensive research has documented the relationship between depression and nonadherence across diverse global settings, there have been few efforts to aggregate existing research using meta-analytic techniques. DiMatteo et al.[11] conducted a meta-analysis of the relationship between depression and adherence across numerous chronic conditions, although this meta-analysis did not include HIV/AIDS. More recently, there have been two other meta-analytic studies that examined ART adherence and depression with individuals with HIV. Gonzalez et al. (2011) [4] conducted a meta-analysis of the relationship between depression and ART adherence among PLHIV specifically, examining whether this relationship differed based upon key study characteristics, including types of

assessments, study design, and setting. Nakimuli-Mpungu et al. (2012) [12] pooled studies conducted in sub-Saharan Africa that examined the prevalence of clinical depression and depressive symptoms, and examined associations with ART adherence when adherence was assessed. Each of these reviews pointed to a lower likelihood of adherence among individuals with depression compared to individuals without depression, and that this relationship is consistent across diverse settings, samples, and clinical thresholds.

Further efforts are needed to ensure up-to-date analysis of existing data on the relationship between depression and ART adherence and to expand upon prior meta-analyses to understand the extent to which depression influences ART adherence and the specific circumstances in which depression is most likely to affect ART adherence. This will ultimately improve our efforts in developing treatment approaches to simultaneously address depression and adherence and will inform how and when to implement depression and adherence interventions for PLHIV. This is crucial for planning of mental health programming in the context of HIV care worldwide, mobilizing resources in resource-limited global settings to address the behavioural health needs of PLHIV, and for promoting advocacy efforts to address mental health and adherence concerns among PLHIV worldwide.

This systematic review and meta-analysis builds upon prior reviews and meta-analyses in this area [11, 4, 12] by incorporating studies on depression and ART adherence published through April 2014 using additional databases, as well as examining novel subgroup analyses to test whether the association between depression and adherence differs based upon: 1) rates of depressive symptoms and ART adherence in study samples; 2) publication date; 3) country income group (low, middle, high); and 4) study characteristics (sample size, design). Further, we sought to identify whether there was a difference in prevalence rate of depressive symptoms and ART adherence by country income group.

MATERIAL AND METHODS

Information sources and Search strategy

We conducted searches on the PUBMED, EMBASE and Cochrane CENTRAL databases from inception in April 2014. We used key words related to: with the terms “depressive disorder” OR “depressive” AND “disorder”, “Depression” AND “HIV” OR “HIV” AND adherence AND antiretroviral AND “therapy” OR “therapy” OR “therapeutics” OR “therapeutics”. In addition, we manually checked the reference list of the identified studies.

Selection criteria

We evaluated each identified study against the following predetermined selection criteria:

- *Study population*: people living with HIV on any ART, regardless of location.
- *Study design*: all studies [cross-sectional studies, cohort studies, randomized controlled trials (RCTs)].
- *Outcomes*: studies that reported an association between depression and adherence to ART as a primary or secondary outcome.

Data abstraction

For each study identified that met the selection criteria, we extracted the following data from each publication: the first author's last name, the year of publication, the country where the study was performed, study design, years of data collection, sample size, measure of exposure (indicators of adherence and depression), mean age, percentage female, depression rate and adherence to ART rate and the risk estimate with corresponding 95% CIs. The information on the country where the study was performed was then classified both according to geographical area and country's income level (high- and middle-income countries).

Study selection

Two of the authors (OU and JM) evaluated the eligibility of studies obtained from the literature search. In cases of discrepancy the third author (JBN) reviewed the studies until agreement was reached by consensus. One reviewer (OU) extracted data and others checked the extracted data.

Data synthesis

We used odds ratio (OR) to quantify the association between depression and adherence to ART. We used 80% or more as the threshold for good adherence as used by studies included in this meta-analysis as well as in our previous published work [13, 14]. If risk estimates were not reported, we calculated them from the raw data presented in the article, we followed Lipsey and Wilson [15] and Borenstein et al [16] procedures for computing odds ratios from effect sizes, mean, standard deviations, t tests, contingency table data, or exact p-values. Study specific natural logarithm of odds ratio were weighted by the inverse of the variance (presented or calculated from the confidence limits) to compute summary natural logarithm of odds ratio with 95% CIs. The meta-analyses were performed using a random-effects model of DerSimonian and Laird [17], which incorporates both within- and between-study variability, since we anticipated between-study heterogeneity. The pooled estimates were then converted back to odds ratios and 95% CIs for presentation.

Following the overall analyses, a number of subgroup analyses were performed with respect to publication year, study design, country's income group, sample size, adherence measure methods, rate of depression and adherence rate. To evaluate the stability of the results and to test whether one study had an excessive influence on the meta-analysis, leave-one-study-out sensitivity analysis was performed [18]. The scope of this analysis was to evaluate the influence of individual studies, by estimating pooled estimate in the absence of each study. We assessed heterogeneity amongst trials by inspecting the forest plots and using the chi-squared test for heterogeneity with a 10% level of statistical significance, and using the I^2 statistic with a value of 50% representing moderate heterogeneity [19, 20]. Random-effect meta-regression was performed to investigate the source of heterogeneity. The independent variable was natural logarithm of odds ratio and explanatory factors were study-level variables listed above. All tests were two tailed. For all tests, a probability level less than 0.05 was considered significant. This review was reported according to the PRISMA recommendations for meta-analyses [21]. Stata 12.1 (Stata Corporation, College Station, TX) software was used for statistical analyses.

RESULTS

Study characteristics

Figure 1 shows the process of study identification and selection. The literature search yielded 2861citations. After review of the title and abstract 134 full text articles were selected for critical reading. A total of 111 studies [22–77, 10, 78–98, 6, 99–130] that recruited 42,366 PLHIV met the inclusion criteria. Table 1 shows the characteristics of the included studies. These studies were published between 1993 and 2013. Most of the studies were conducted in the USA (n=74, 67.0%), followed by France (n=4, 4.5%), Ethiopia (n=4, 3.6%) and South Africa (n=4, 3.6%). Most of the studies were cross-sectional (n=86, 77.5%). Twenty-four studies had a cohort design (21.4%). Only one was a case-control study. Most of the studies used self-reported questionnaires to measure adherence (n=92, 82.8%), followed by pharmacy refills (n=8, 7.1%), MEMS caps (n=7, 6.2%) and pill count (n=4, 3.6%).

Overall summary of the meta-analyses

When reported, the rate of people living with HIV (PLHIV) with depressive symptoms ranged from 12.8% to as much as 78% (Figure 2); and proportion of PLHIV who achieved good (≥ 80%) adherence ranged from as low as 20% to as much as 98% (Figure 3). There was no significant difference in the rate of depressive symptoms in PLHIV across low-income (pooled rate = 31.8%, 95% CI 17.0% to 51.5%), middle-income (pooled rate = 47.4%, 95% CI 31.3 to 64.1%) and high-income countries (pooled rate = 37.1%, 95% CI 30.6 to 44.2%)(p-value for interaction = 0.313). The overall pooled rate was 39.1% (95%CI: 33.2% to 45.2% (Figure 2). However, the proportion of PLHIV who achieved good adherence was significantly higher in lower income countries (pooled rate = 86%, 95% CI 62.2% to 95.8%) than high-income countries (pooled rate = 67.5%, 95% CI 61.6% to 72.9%) (p-value for interaction = 0.017) (Figure 3). The proportion of PLHIV who achieved good adherence tended to be higher in lower income countries (pooled rate = 86%, 95% CI 62.2% to 95.8%) than middle income countries (pooled rate = 74.4%, 95% CI 62.7% to 83.4%), but this difference did not reach statistical significant level (p-value for interaction = 0.145). The random-effect meta-analysis yielded a pooled OR of 0.58 (95% CI 0.55 to 0.62, n=112), such that the likelihood of achieving good adherence was 42% lower among those with depressive symptoms compared to those without (Figure 4). There was evidence of substantial statistical heterogeneity between the study results (χ^2 = 849; df = 111; p=0.000) with the degree of heterogeneity quantified by the I^2 as 86.6%.

Association by different subgroups

The results of subgroup analyses are shown in Table 2. There was not a significant difference in the likelihood of achieving good adherence among PLHIV with depression symptoms in studies conducted in middle-income countries (pooled OR = 0.39, 95% CI 0.25 to 0.63) compared with those from both low- (pooled OR = 0.52, 95% CI 0.40 to 0.68) and high-income countries (pooled OR = 0.59, 95% CI 0.56 to 0.63)(p-value for interaction = 0.338). Similarly, we found no evidence of statistically significant differentials in the association between depression and adherence to ART across study design, adherence rate and adherence measures.

However, we found evidence that the magnitude of the association between depression and adherence to ART decreases with increasing year of publication, such that the likelihood of achieving good adherence among PLHIV with depressive symptoms were higher in the most recent studies (2011 to 2013) compared with those reported between 1993 and 2000 (pooled OR = 0.63 versus 0.33, p-value for interaction = 0.007) (Figure 5A). Similarly, we found evidence of small study bias, i.e. the association was more pronounced among studies with small sample sizes (Figure 5B). The result of subgroup analysis also showed statistically significant differentials in the reported association across depression rates, such that the likelihood of achieving good adherence among PLHIV with depression was lower in studies with the highest depression rates (50% or more) compared with studies with moderate (20 to 50%) and low (<20%) depression rates (pooled OR = 0.48 vs. 0.66 vs 0.63, p-value for interaction = 0.038).

Factors modifying the association between depression and adherence to ART as identified by meta-regression analyses

Factors modifying the association between depression and adherence and proportion of explained between-study variability as identified by meta-regression analyses are shown in Table 3. In the multivariable model, only publication year, sample size and depression rate were statistically significantly associated with pooled estimates. Differences in depression rates, sample sizes and publication year explained 30.1%, 23.3%, and 17.4% in between study variability in measure of association between depression and adherence respectively.

DISCUSSION

This study builds upon prior reviews and meta-analyses of the relationship between depression and ART nonadherence in low-, middle-, and high-income countries and examined whether the association between depression and ART adherence differs based on study characteristics, rates of adherence and/or depression, publication year, and country income level. Based upon 111 eligible studies with over 42,000 PLHIV across low-, middle-, and high-income countries, rates of depressive symptoms ranged from approximately 13% to 78%, and the proportion of PLHIV who achieved optimal adherence (≥ 80%) ranged from 20% to 98%. The wide range of rates of depressive symptoms reported across studies may reflect the variability in measurement tools to assess depressive symptoms among PLHIV and variability in the clinical cut-offs used across studies [131]. The overall pooled rate of depressive symptoms in our analysis (39.5%) is in line with prior pooled rates of depressive symptoms (as opposed to clinical levels of depression) (31.2%[12]; 29.5%[131]). The higher rate found in our analysis may reflect that we did not distinguish between clinical levels of depression and depressive symptoms, which may have inflated estimates in the current analysis. Pooled estimates from the combined studies indicated that the likelihood of achieving optimal adherence was 42% lower among those with depressive symptoms compared to those without. This is in line with a prior meta-analysis that included studies conducted in sub-Saharan Africa, which found that individuals with depressive symptoms had a 55% lower likelihood of achieving optimal adherence compared to individuals without depressive symptoms [12]. Prior meta-analyses not specific to low-resource settings have found the relationship between depression and ART non-

adherence to have a small to moderate effect size (i.e., r = .19–.21) [11, 4]; with studies consistently demonstrating a lower likelihood of optimal ART adherence in the context of depression.

This study hypothesized that variations in the strength of the association between depression and ART non-adherence may be affected by a range of factors, including those related to study characteristics (study design, assessments, sample size, publication year, setting), rates of adherence and/or depression. Subgroup analyses showed that the relationship between depression and ART adherence did not significantly vary by country income group (low, middle, high), study design (cross-sectional vs. cohort), adherence measure used (MEMS, pill count, or pharmacy refills compared to self-report) or adherence rates (50–75% and >75% vs. <50%). A prior meta-analysis of the relationship between depression and ART adherence [4] found significantly greater associations between depression and ART adherence when adherence was assessed via interview vs. self-report, and via continuous vs. dichotomous measurement; however, in line with our findings, their analysis showed that the association did not differ when comparing MEMS and pharmacy refill to self-report. This further supports their conclusion that the relationship between depression and self-reported ART non-adherence cannot be explained exclusively by biased recall evident in the context of depression [4].

Our findings that the association between depression and ART adherence did not differ based upon study design or country income level was also consistent with the prior meta-analysis by Gonzalez et al [4]. Although the data available in our review was similarly skewed towards higher-income countries (n=93), there were more studies conducted in middle (n=10) and low-income counties (n=8) included in comparison to the previous meta-analysis, which compared only low (n=5) to high (n=90) resource settings. Findings demonstrate no significant differences by income group, with only a non-significant trend pointing to the lowest likelihood of depressed PLHIV achieving optimal adherence in middle-income countries compared to PLHIV in low- or high-income countries in our analysis.

When examining differences in rates of depression and ART adherence by country income group, there were no differences in rates of depression in PLHIV across low-, middle-, and high-income countries, further supporting prior evidence that depression is also a significant public health burden in developing countries. Although in this meta-analysis we did not examine whether the included studies used a culturally-validated measure of depression, a recently published meta-analysis [131] identified that assessments used to screen for depression among PLHIV in low-resource settings (i.e., Sub-Saharan Africa) largely demonstrated good internal consistency (alphas ranging from .63 to .95).. Our findings, along with those from prior meta-analyses [12, 131], suggest that PLHIV in developing countries are self-reporting symptoms that are in line with DSM-defined models of depression.

When comparing rates of ART adherence by income group, there were significant differences in rates of ART adherence across country income groups, such that PLHIV in lower-income countries were more likely to adhere than individuals in higher- and middle-

income countries. These results continue to support the notion that optimal levels of ART adherence can be achieved in lower-resource settings [132], even in the context of psychiatric symptoms such as depression.

The lack of differences in the association between depression and ART adherence based upon cross-sectional vs. longitudinal design may suggest that depression is as strongly associated to adherence over time as it is when assessed simultaneously. However, more studies that incorporate longitudinal designs are necessary to replicate this finding, as well as to better understand the directionality of the association. Additionally, given that weaker associations were detected when study sample sizes were larger, future studies should also incorporate larger sample sizes to ensure stability of estimates and replication of existing findings.

There was a significantly weaker association between depression and ART adherence in more recent studies, such that the likelihood of PLHIV with depression achieving optimal adherence was higher in the most recent studies (i.e., since 2011 when the prior meta-analyses were published) compared to earlier studies published between 1993 and 2000. Although not formally tested, this may be due to design characteristics of the eight studies published between 2011 and 2013, or may potentially reflect the increased attention to and efforts to integrate depression and mental health interventions into HIV care for PLHIV in recent years [133–135] and possibly the impact of simplified ART regimens (lower pill burden and once-daily dosing frequency) which has been shown to improve adherence [136].

Studies that recruited samples with higher depression prevalence rates (i.e., >50%) had lower likelihood of ART adherence; given the higher rates of depression in these samples, these studies may have had targeted inclusion criteria based upon depression severity and may have in turn recruited a more impaired population (i.e., with greater psychiatric or medical co-morbidity), which may have also contributed to worse ART adherence. There also may have been greater power to detect a relationship between depression and ART nonadherence in a sample with higher rates of depression. Although we did not examine depression severity and its impact on the relationship between depression and ART adherence in the current meta-analysis, prior research has pointed to subclinical levels of depression also being disruptive to ART adherence [4]. However, to inform screening and targeted intervention efforts, continued research is needed to understand the clinical threshold in which depressive symptoms are most likely to interfere with ART adherence.

While informative, the results of this meta-analysis should be interpreted with caution. The observational nature of the data limits the ability to draw causal inferences. We found statistically significant heterogeneity across the studies, thus suggesting that the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) is important. The heterogeneity may be due to differences in year of publication, study sample sizes, geographical location, population recruited, reporting of adherence measures and variability in handling confounding and mediating factors. Despite the limitations noted, the findings of this systematic review and meta-analysis have important implications for guiding future research on the association between depression and ART

nonadherence, including the need for more studies conducted in low- and middle-income countries, studies that incorporate a longitudinal design and larger sample sizes to further ascertain the strength and directionality of this relationship.

In conclusion, we found that the likelihood of achieving good adherence was lower among those with depressive symptoms compared to those without, and this association did not differ by country income level, although there were significantly higher rates of adherence in low- vs. higher income countries. The factors that were most relevant to the strength of the association between depression and ART adherence included the year of study, sample size, and depression prevalence rate in sample. Despite some remaining unanswered questions regarding the relationship between depression and ART adherence, research continues to point to the lower rates of adherence among individuals with depression, further suggesting the need to screen and treat depression in the context of HIV care [133–135] and to further develop parsimonious, cost-effective interventions to simultaneously address symptoms of depression and ART adherence among PLHIV [137, 138].

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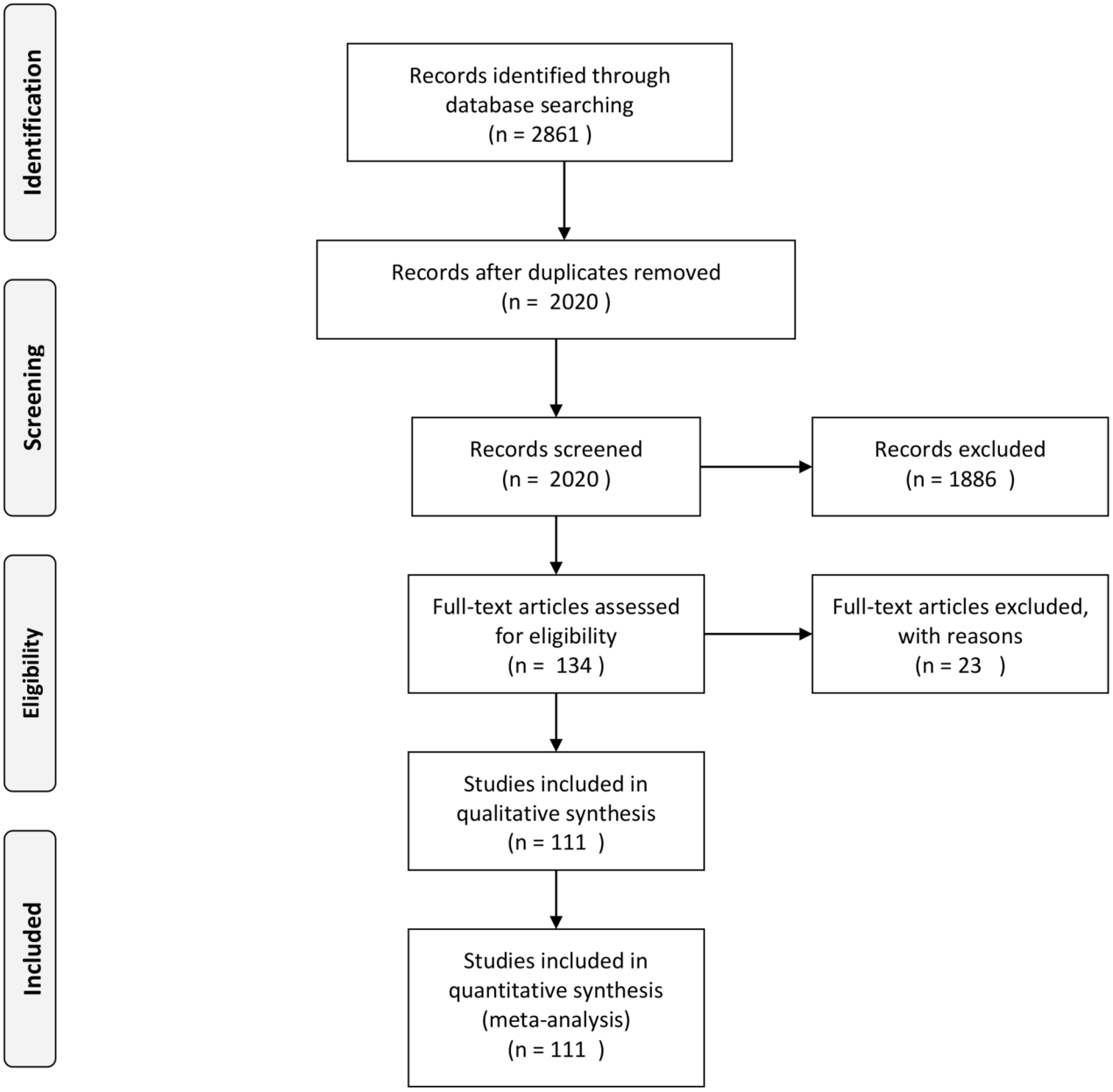

Figure 1.
Study selection diagram

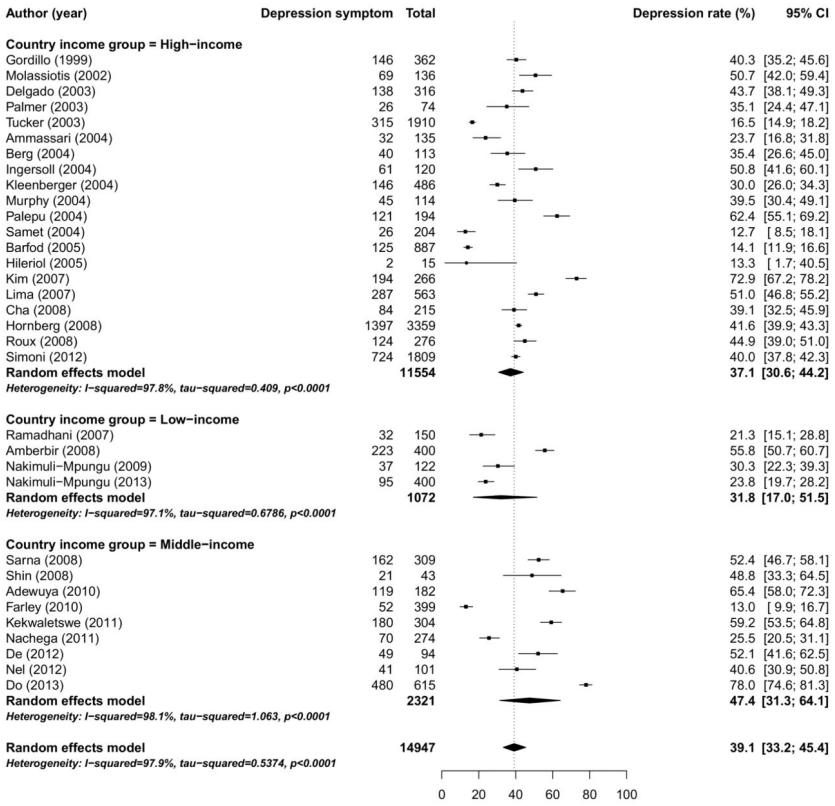

Figure 2.
Prevalence of depression among people living with HIV

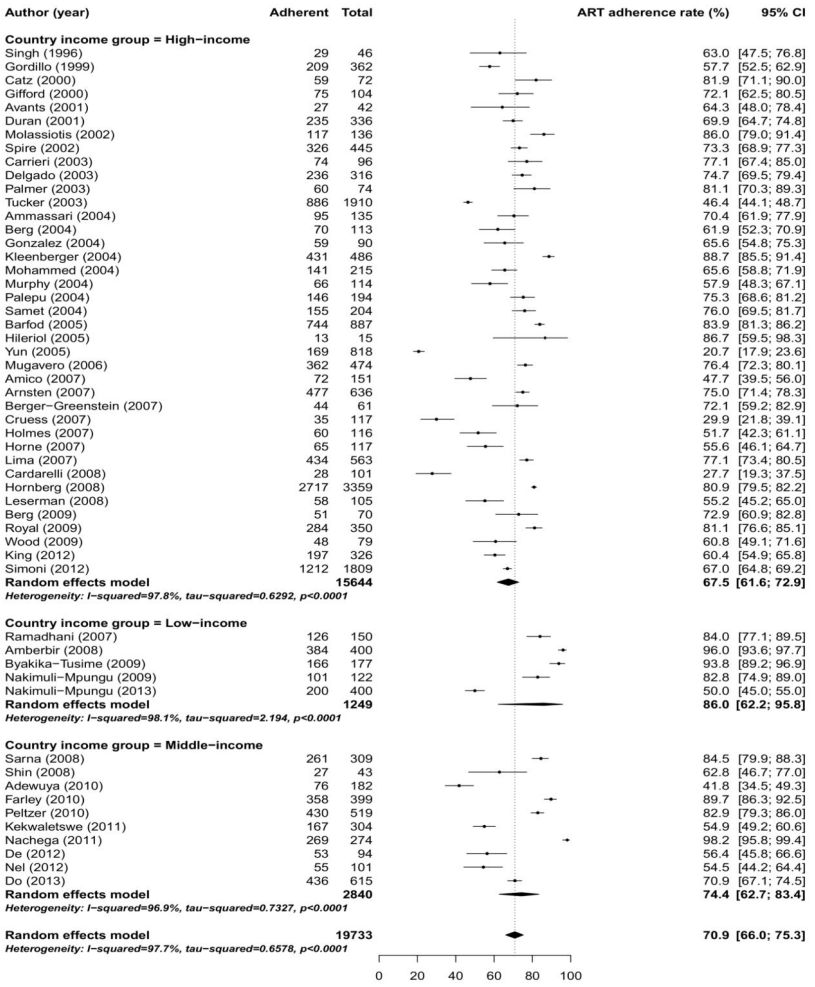

Figure 3.

Proportion of people living with HIV with optimal (≥ 75%) adherence to antiretroviral therapy

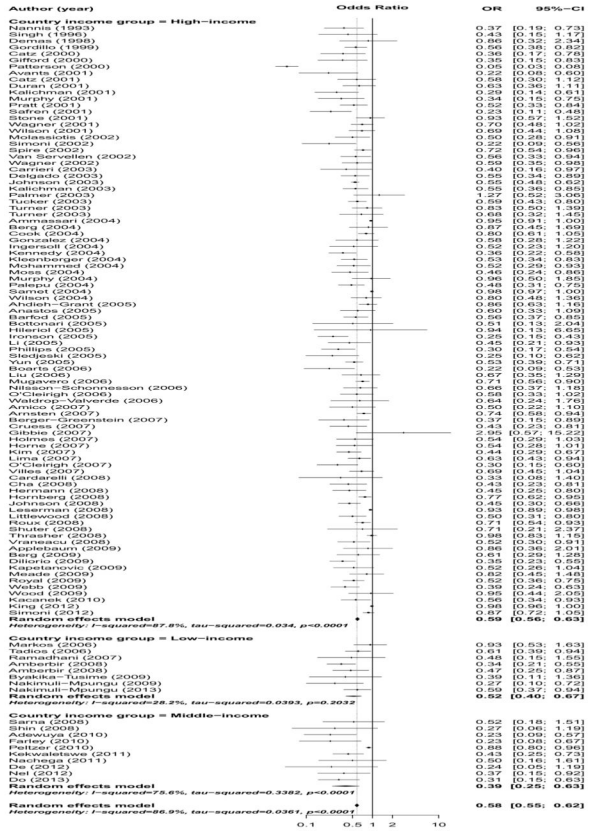

Figure 4.

Forest plot showing the association between depression and adherence to ART

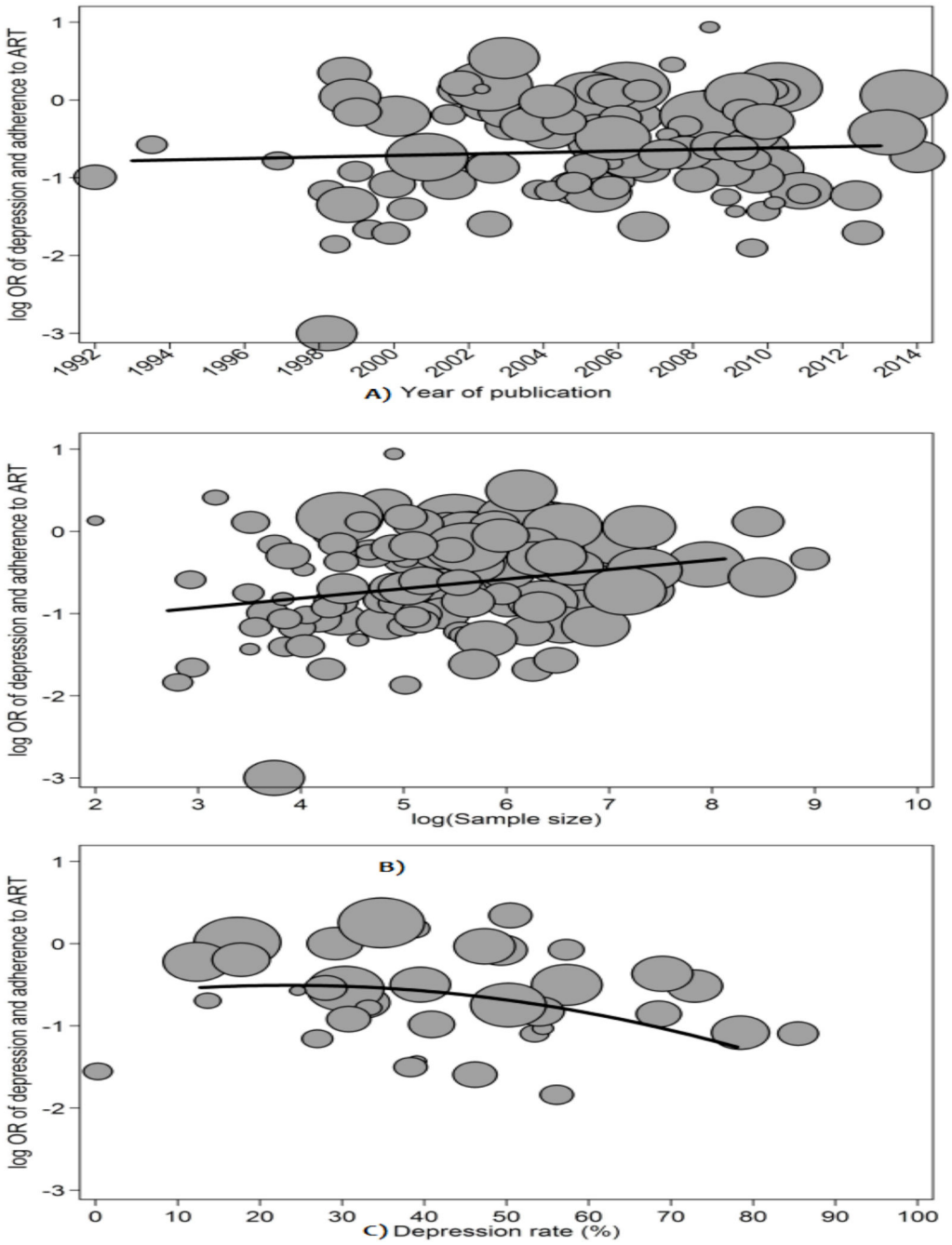

Figure 5.

Relation between natural logarithm of the odds ratio of depression and adherence to ART and publication year, sample size and depression rate.

The area of each circle is proportional to the precision of the odds ratio (inverse of its variance).

Table 1

characteristics of included studies.

First author (year)	Study design	Country	Income group	Female (%)	Adherence measure	Depression measure	Sample size
Nannis (1993)[92]	Cross-sectional	USA	High	5	self-reported	Self report	101
Singh (1996)[112]	Cohort	USA	High	0	Pharm refill	Self report	46
Demas (1998)[47]	Cross-sectional	USA	High	40	self-reported	Self report	49
Gordillo (1999)[57]	Cohort	Spain	High	24	pill count	BDI	362
Catz (2000)[41]	Cross-sectional	USA	High	13	self-reported	CES-D	72
Gifford (2000)[55]	Cross-sectional	USA	High	14	self-reported	BDI	104
Patterson (2000)[6]	Cross-sectional	USA	High		MEMS Caps	Medical Records	81
Avants (2001)[30]	Cross-sectional	USA	High	31	self-reported	BDI	42
Catz (2001)[40]	Cross-sectional	USA	High	20	self-reported	Self report	113
Duran (2001)[51]	Cross-sectional	France	High	20	self-reported	Self report	336
Kalichman (2001)[69]	Cross-sectional	USA	High	100	self-reported	Self report	72
Murphy (2001)[87]	Cross-sectional	USA	High	73	self-reported	Self report	145
Pratt (2001)[101]	Cross-sectional	England	High	13	self-reported	Interview	222
Safren (2001)[105]	Cross-sectional	USA	High	9	self-reported	Self report	84
Stone (2001)[115]	Cross-sectional	USA	High	100	self-reported	Self report	289
Wagner (2001)[124]	Cross-sectional	USA	High	1	self-reported	Self report	595
Wilson (2001)[127]	Cross-sectional	USA	High	100	self-reported	Self report as interview	247
Molassiotis (2002)[83]	Cross-sectional	Hong Kong	High	8	self-reported	Self report	136
Simoni (2002)[110]	Cross-sectional	USA	High	61	self-reported	Self report	50
Spire (2002)[114]	Cohort	France	High	22	self-reported	Self report	445
Van Servellen (2002)[120]	Cross-sectional	USA	High	30	self-reported	Self report	182
Wagner (2003)[123]	Cross-sectional	USA	High	18	self-reported	Interview	180
Carrieri (2003)[39]	Cohort	France	High	31	self-reported	Self report	96
Delgado (2003)[46]	Cohort	Canada	High	14	Pharm refill	Self report	316
Johnson (2003)[65]	Cross-sectional	USA	High	24	self-reported	Self report	2765
Kalichman (2003)[68]	Cross-sectional	USA	High	30	self-reported	Self report	255
Palmer (2003)[98]	Cross-sectional	USA	High	53	self-reported	SCID-II	74

First author (year)	Study design	Country	Income group	Female (%)	Adherence measure	Depression measure	Sample size
Tucker (2003)[118]	Cross-sectional	USA	High	22	self-reported	Interview	1910
Turner (2003)[119]	Cross-sectional	USA	High	0	Pharm refill	Medical Records	3246
Turner (2003)[119]	Cross-sectional	USA	High	100	Pharm refill	Medical Records	1857
Ammassari (2004)[26]	Cross-sectional	Italy	High	46	self-reported	Interview	135
Berg (2004)[33]	Cohort	USA	High	43	MEMS Caps	CES-D	113
Cook (2004)[43]	Cross-sectional	USA	High	100	self-reported	Self report	684
Gonzalez (2004)[56]	Cross-sectional	USA	High	32	self-reported	Self report	90
Ingersoll (2004)[63]	Cross-sectional	USA	High	38.3	self-reported	CIDI-SF	120
Kennedy (2004)[72]	Cross-sectional	USA	High	14	self-reported	Self report	201
Kleenberger (2004)[75]	Cohort	USA	High	0	self-reported	CES-D	486
Mohammed (2004)[82]	Cross-sectional	USA	High	29.3	self-reported	Self report	215
Moss (2004)[84]	Cohort	USA	High	57	self-reported	Self report	148
Murphy (2004)[86]	Cross-sectional	USA	High	9	self-reported	CES-D	114
Palepu (2004)[97]	Cross-sectional	USA	High	21	self-reported	CES-D	194
Samet (2004)[106]	Cohort	USA	High	19	self-reported	CES-D	204
Wilson (2004)[128]	Cohort	Australia	High	10	self-reported	Self report	182
Ahdieh-Grant (2005)[23]	Cross-sectional	USA	High	100	self-reported	Self report	903
Anastos (2005)[27]	Cohort	USA	High	100	self-reported	CES-D	204
Barfod (2005)[31]	Cross-sectional	Denmark	High	21	self-reported	Self report	887
Bottonari (2005)[36]	Cross-sectional	USA	High	4	self-reported	Self report	24
Hileriol (2005)[59]	Cross-sectional	Puerto Rico	High	100	self-reported	Self report	15
Ironson (2005)[64]	Cross-sectional	USA	High	30	self-reported	Self report	160
Li (2005)[77]	Cohort	USA	High	0	self-reported	Self report	623
Phillips (2005)[100]	Cross-sectional	USA	High	100	self-reported	Self report	125
Sledjeski (2005)[113]	Cross-sectional	USA	High	16	self-reported	Self report	53
Yun (2005)[130]	Cross-sectional	USA	High	12	Pharm refill	Medical Records	818
Boarts (2006)[35]	Cohort	USA	High	18	self-reported	Self report	57
Liu (2006)[79]	Cross-sectional	USA	High	100	self-reported	Self report	114
Markos (2006)[80]	Cross-sectional	Ethiopia	Low	48	self-reported	Self report	291

First author (year)	Study design	Country	Income group	Female (%)	Adherence measure	Depression measure	Sample size
Mugavero (2006)[85]	Cross-sectional	USA	High	29	self-reported	Self report as interview	474
Nilsson-Schonnesson (2006)[94]	Cohort	Sweden	High	22	self-reported	Self report	141
O'Cleirigh (2006)[96]	Cross-sectional	USA	High	17	self-reported	Self report	152
Tadios (2006)[116]	Cross-sectional	Ethiopia	Low	49	self-reported	Self report	431
Waldrop-Valverde (2006)[125]	Cross-sectional	USA	High	23	self-reported	Self report	57
Amico (2007)[25]	Cross-sectional	USA	High	44	self-reported	CES-D	151
Arnsten (2007)[29]	Cross-sectional	USA	High	35	self-reported	BSI	636
Berger-Greenstein (2007)[34]	Cross-sectional	USA	High	35.3	self-reported	BDI-II	61
Cruess (2007)[44]	Cross-sectional	USA	High	37	self-reported	Self report	117
Gibbie (2007)[54]	Cross-sectional	Australia	High	3	self-reported	Self report	80
Holmes (2007)[60]	Cohort	USA	High	19	MEMS Caps	CES-D	116
Horne (2007)[62]	Cross-sectional	United Kingdom	High		self-reported	Self report	117
Kim (2007)[73]	Cross-sectional	USA	High	23	self-reported	CES-D	266
Lima (2007)[10]	Cohort	Canada	High	9	Pharm refill	Self report	563
O'Cleirigh (2007)[95]	Cross-sectional	USA	High	33	self-reported	Self report	91
Ramadhani (2007)[102]	Cross-sectional	Tanzania	Low	63	self-reported	Hopkins Symptom Checklist (25 items)	150
Villes (2007)[121]	Cross-sectional	France	High	22	self-reported	Self report	841
Amberbir (2008)[24]	Cross-sectional	Ethiopia	Low	60	self-reported	CES-D	400
Cardarelli (2008)[38]	Cross-sectional	USA	High	26	self-reported	Self report	101
Cha (2008)[42]	Cross-sectional	USA	High	33	self-reported	BDI-II	215
Hermann (2008)[58]	Cross-sectional	Australia	High	14	self-reported	Self report	145
Hornberg (2008)[61]	Cross-sectional	USA	High	11	Pharm refill	Medical Records	3359
Johnson (2008)[66]	Cross-sectional	USA	High	0	self-reported	Self report	328
Leserman (2008)[76]	Cross-sectional	USA	High	39	self-reported	Self report	105
Littlewood (2008)[78]	Cross-sectional	USA	High	44	self-reported	CES-D	221
Roux (2008)[103]	Cohort	France	High	28	self-reported	CES-D	276
Sarna (2008)[107]	Cross-sectional	India	Middle	13	self-reported	BDI-II	309
Shin (2008)[108]	Cross-sectional	Peru	Middle	2	self-reported	Hopkins's symptoms checklist	43
Shuter (2008)[109]	Cross-sectional	USA	High	44	MEMS Caps	Self report as interview	29

First author (year)	Study design	Country	Income group	Female (%)	Adherence measure	Depression measure	Sample size
Thrasher (2008)[117]	Cross-sectional	USA	High	22	self-reported	Self report	1886
Vraneacu (2008)[122]	Cohort	USA	High	24	MEMS Caps	Self report	156
Applebaum (2009)[28]	Cross-sectional	USA	High	33	self-reported	Interview	67
Berg (2009)[32]	Cross-sectional	USA	High	54	self-reported	Self report via ACASI	70
Byakika-Tusime (2009)[37]	Cross-sectional	Uganda	Low	70.1	pill count	Becks Depression Inventory (BDI) (21 items)	177
Diliorio (2009)[48]	Cross-sectional	USA	High	32	self-reported	Self report	236
Kapetanovic (2009)[70]	Cross-sectional	USA	High	100	self-reported	Medical Records	328
Meade (2009)[81]	Cross-sectional	USA	High	50	self-reported	Self report via ACASI	180
Nakimuli-Mpungu (2009)[91]	Cross-sectional	Uganda	Low	78	self-reported	Self-Reporting Questionnaire (20 items)	122
Royal (2009)[104]	Cross-sectional	USA	High	28	self-reported	CES-D	350
Webb (2009)[126]	Cohort	USA	High	46	self-reported	Self report	168
Wood (2009)[129]	Cohort	USA	High	15	MEMS Caps	Self report	79
Adewuya (2010)[22]	Cross-sectional	Nigeria	Middle	58	self-reported	General Health Questionnaire (12 items)	182
Etienne (2010)[52]	Cross-sectional	Kenya, Uganda, Zambia, Nigeria, and Rwand		65.4	self-reported	Center for Epidemiological studies Depression scale (20 items)	921
Farley (2010)[53]	Cross-sectional	Nigeria	Middle	70	Pharm refill		399
Kacanek (2010)[67]	Cohort	USA	High	23	self-reported	Self report as interview	225
Peltzer (2010)[99]	Cross-sectional	South Africa	Middle	73.4	self-reported	Center for Epidemiological studies Depression scale (10 items)	519
Kekwaletswe (2011)[71]	Cross-sectional	South Africa	Middle	68	self-reported	Center for Epidemiological studies Depression scale (20 items)	304
Nachega (2011)[88]	Cohort	South Africa	Middle	60	pill count	BSI	274
De (2012)[45]	Cross-sectional	India	Middle	100	self-reported	beck’s depression inventory	94
King (2012)[74]	Cohort	USA	High	27.9	self-reported	CES-D	326
Nel (2012)[93]	Cross-sectional	South Africa	Middle	82.2	self-reported	Beck Depression Inventory II	101
Simoni (2012)[111]	Cross-sectional	USA	High	33	MEMS Caps	BDI II	1809
Do (2013)[49]	Cross-sectional	Viet Nma	Middle	34	self-reported	CES-D	615
Nakimuli-Mpungu (2013)[89]		Uganda	Low	66	pill count	Mini neuropsychiatric interview (MINI)	400

Table 2

Pooled estimates for the association between depression adherence to antiretroviral therapy and series of subgroup analyses

Subgroup	n	Odds ratio (95% CI)	I^2 (%)
Overall	111	0.58 (0.54 to 0.62)	86.9
Country's income group			
High-income	92	0.59 (0.55 to 0.63)	87.8
Middle-income	10	0.39 (0.25 to 0.63)	75.6
Low-income	8	0.52 (0.40 to 0.68)	28.2
Publication year			
1993 to 2000	7	0.33 (0.13 to 0.83)	93.4
2001 to 2005	46	0.58 (0.52 to 0.64)	85.6
2006 to 2010	50	0.58 (0.52 to 0.64)	73.4
2011 to 2013	8	0.61 (0.46 to 0.82)	79.3
Study design			
Cross-sectional	86	0.53 (0.48 to 0.58)	85.5
Cohort	24	0.77 (0.71 to 0.83)	77.1
Sample size			
Less than 100	25	0.41 (0.27 to 0.62)	81.9
100 to 500	67	0.61 (0.57 to 0.65)	82.8
500 or more	19	0.70 (0.62 to 0.79)	73.4
Depression rate			
Less than 20%	5	0.63 (0.49 to 0.98)	83.4
20 to 50 %	18	0.66 (0.55 to 0.78)	70.4
50% plus	12	0.48 (0.41 to 0.57)	0.0
Adherence rate			
Less than 50%	6	0.52 (0.43 to 0.62)	0.0
50 to 75%	27	0.75 (0.69 to 0.82)	73.9
75% plus	23	0.62 (0.54 to 0.72)	80.3
Adherence measure			
Self-reported	92	0.61 (0.57 to 0.64)	83.9
MEMS cap	7	0.48 (0.18 to 1.31)	96.5
Pharmacy refills	8	0.62 (0.52 to 0.76)	29.1
Pill count	4	0.56 (0.42 to 0.74)	0.0

Table 3

Meta-regression analyses

Factor	Ratio of odds ratio (95% CI)	*P-value*	*Explained variance (%)*
Country's income group			0.0
High-income	1.10 (0.75 to 1.61)	0.632	
Middle-income	0.83 (0.49 to 1.40)	0.489	
Low-income	1 (reference)		
Publication year			17.4
1993 to 2000	1 (reference)		
2001 to 2005	1.97 (1.33 to 2.92)	0.001	
2006 to 2010	1.97 (1.33 to 2.92)	0.001	
2011 to 2013	2.07 (1.26 to 3.39)	0.004	
Study design			1.0
Cross-sectional	0.87 (0.70 to 1.08)	0.208	
Cohort	1 (reference)		
Sample size			23.3
Less than 100	1 (reference)		
100 to 500	1.48 (1.15 to 1.91)	0.002	
500 or more	1.85 (1.39 to 2.47)	0.000	
Depression rate			30.1
Less than 20%	1 (reference)		
20 to 50 %	0.96 (0.68 to 1.35)	0.815	
50% plus	0.68 (0.47 to 0.99)	0.044	
Adherence rate			5.0
Less than 50%	1 (reference)		
50 to 75%	1.34 (0.94 to 1.94)	0.102	
75% plus	1.28 (0.89 to 1.84)	0.182	
Adherence measure			0.0
Self-reported	1 (reference)		
Pharmacy refills	1.09 (0.77 to 1.54)	0.628	
Pill count	0.98 (0.57 to 1.68)	0.948	
MEMS cap	0.82 (0.56 to 1.20)	0.299	