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## **Living positive: eHealth for people with HIV and depressive symptoms**

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## Chapter 3

# Psychosocial interventions enhance HIV medication adherence: A systematic review and meta-analysis

Article in press:

Spaan, P., van Luenen, S., Garnefski, N. & Kraaij V. (2018). Psychosocial interventions enhance HIV medication adherence: A systematic review and meta-analysis. *Journal of Health Psychology*. DOI 10.1177/1359105318755545.

### **Abstract**

About 40% of people living with HIV do not sufficiently adhere to their medication regimen, which adversely affects their health. The current meta-analysis investigated the effect of psychosocial interventions on medication adherence in people living with HIV. Databases were systematically searched, resulting in 43 included randomized controlled trials. Study and intervention characteristics were investigated as moderators. The overall effect size indicates a small to moderate positive effect (Hedges'  $g = 0.37$ ) of psychosocial interventions on medication adherence in people living with HIV. No evidence for publication bias was found. This meta-analysis study concludes that various psychosocial interventions can improve medication adherence and thereby the health of people living with HIV.

**Keywords:** HIV, medication adherence, psychotherapy, meta-analysis.

## Introduction

The WHO (2016) estimated that by the end of 2014, 37 million people worldwide were living with HIV, and two million became infected that year. If the virus is not treated with medication, it attacks the immune system, which may result in various health problems, AIDS, and eventually death (1). Medication adherence is important in tackling this pandemic and promoting health in people living with HIV (PLWH). Effective drug treatment has made HIV a chronic rather than a lethal condition. However, it also introduced new challenges. HIV drug treatment involves taking pills daily and adhering to treatment is difficult for many PLWH.

Antiretroviral therapy (ART) is a combination of at least two, but usually three, antiretroviral drug classes that suppresses viral replication (2). In addition, ART lowers the chances of transmission through sexual risk behaviour (3), birth and breastfeeding (4), and prevents spreading of the HIV pandemic. Its introduction in 1996 provided PLWH with the chance to stop disease progression and lethality (5). Initially, treatment involved taking several pills daily and had many adverse effects. Nowadays, ART has less side effects and simpler pill regimens. These developments have increased treatment adherence (6). Major remaining challenges are the daily dosing, lifelong treatment, and side effects. A meta-analysis that included 84 studies conducted worldwide from 1999 to 2009 found that only 62% of people on ART took their prescribed doses > 90% of the time (7). Increasing medication adherence should be a focus in the HIV care.

Non-adherence to ART is associated with mental health problems and psychological stressors such as depression (8), life events (9), substance abuse (10), and anxiety (11). A meta-analysis found that psychological factors are among the strongest correlates of non-adherence, stronger than other factors, for example, pill burden (12). Furthermore, mental health problems are highly prevalent in PLWH; the prevalence of depression is about 34%, and of anxiety 28% (13). The way in which mental health problems and non-adherence are related is complex. Some antiretroviral drugs can have side effects such as mood changes, depression, and anxiety. In turn, PLWH with mental health problems may have more difficulty adhering, because of cognitive or behavioural problems, for example, fatigue, hopelessness, lowered motivation and concentration (14).

Like physical and mental health, sexual health is related to ART. ART non-adherence has been linked to more sexual risk taking, for example, having unprotected sex, and greater risk of transmission. Depression, sexual risk behaviour, and adherence may be related: it was found that depression leads to less ART adherence and condom use (15). Non-adherence may also be related to lower socioeconomic status, such as lower income and education, and more unemployment. However, not all studies support this relationship (16). Psychosocial interventions may influence vulnerabilities in socioeconomic status physical, mental and sexual health.

It is important to treat medication non-adherence in PLWH, because optimal adherence should improve PLWH's health and well-being, and lower transmission risks. Treatments that do not address mental health problems as possible causes of non-adherence may be less effective than those that do. For instance, medication reminder devices focus on forgetfulness rather than mental health and have shown inconsistent effectiveness (17). In contrast, antidepressant treatments for PLWH consistently increase ART adherence (18). However, psychopharmacological treatment may cause side effects (e.g. reduced libido and inorgasmia), drug interaction, and increased pill burden, which predict lower adherence and worse virologic suppression (6). Therefore, psychosocial treatments may be preferred to treat non-adherence in PLWH.

Psychosocial interventions are primarily focussed on psychological or social factors, instead of purely focussing on medical factors such as pharmacological treatment or exercise (19). Systematic reviews and meta-analyses that investigated the effectiveness of psychosocial interventions on ART adherence, such as motivational interviewing, cognitive behavioural therapy (CBT), peer support, or counselling, have found promising but inconsistent results. Most reviews (20) and meta-analyses (21-23) found that psychosocial interventions may increase ART adherence. However, some reviews showed negative or mixed results (24-26). A limitation of these findings is that they are partly based on low quality studies. Furthermore, some results come from systematic reviews that do not recombine the raw data.

In addition to investigating the effectiveness of psychosocial interventions, it is important to examine factors (moderators) that may influence it. First, treatment characteristics are factors of the therapy, such as duration. Knowledge about which treatment characteristics influence effectiveness positively may be used when designing interventions. Furthermore, study characteristics, such as the geographical and temporal context of data collection, may partially explain differences between studies. Previous reviews and meta-analyses found larger effects on ART adherence when interventions involved CBT components (24), more therapist training (20), targeted adherence risk or difficulty groups (21) or people with more severe depression (23), longer duration (23, 26), individual setting (26), and adherence measures with recall periods > 7 days (22).

The current meta-analysis investigated the effectiveness of various types of psychosocial interventions on medication adherence in PLWH. To promote the methodological quality of the meta-analysis and strength of the conclusions, only randomized controlled trials (RCTs) were included. Furthermore, the effects of study characteristics and treatment characteristics were investigated.

## Methods

### Literature search and study selection

Published literature was searched on November 5, 2014 through the databases PsycInfo (EBSCOhost), Embase (Ovid), and Medline (PubMed). Search words were related to three categories; that is, words related to HIV, psychosocial interventions, and ART adherence. An overview of the used search terms is provided in Supplement A. Trials were also identified in published review articles and meta-analyses. Unpublished studies were not included.

Database searches yielded 687 unique articles; Figure 1 shows the search and selection process. Titles and abstracts were reviewed, and if the article appeared to meet inclusion criteria (described below), its full text was retrieved. Then, a final selection was made based on their accordance with the inclusion criteria. This process resulted in 51 unique articles. Consulting previous review articles and meta-analyses resulted in another three articles. Data from 19 articles were not sufficient to calculate an effect size. The study authors were requested by e-mail to provide such data; eight authors provided the data (42%), nine replied but could not provide data (47%), and two could not be reached (11%). The final analysis included 43 studies.

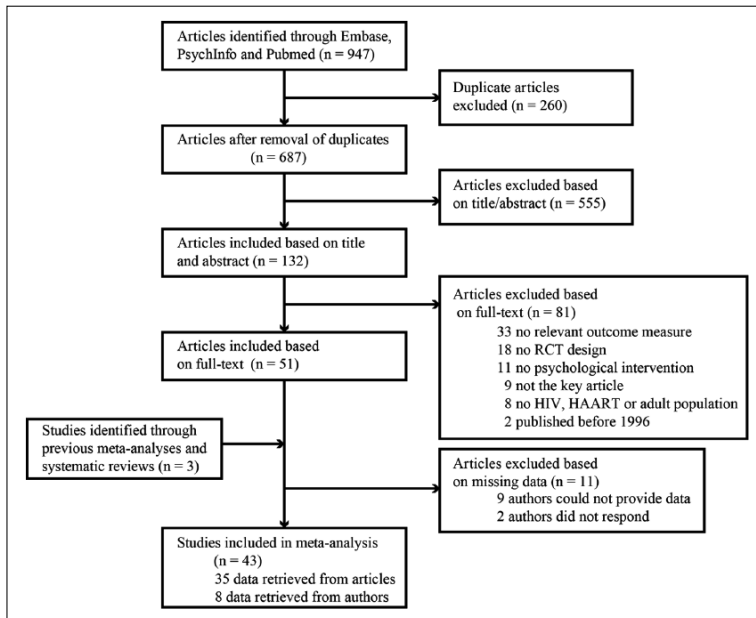
The selection of the first 50 titles and abstracts was executed independently by two researchers (first and second authors). The interrater reliability for this selection indicated substantial agreement (27),  $\kappa = 0.63$ ,  $p < 0.001$ . The rest of the studies were selected by the first author. In cases of uncertainty, the co-authors were consulted and eligibility was discussed until consensus was reached.

### Inclusion criteria

Studies were included in the meta-analysis if they (a) used a randomized controlled design, (b) provided a psychosocial intervention, (c) provided the intervention post 1996, after development of ART, (d) included PLWH age  $\geq 18$  years, (e) reported ART adherence as outcome, and (f) were published in English. For criterion (b), psychosocial interventions are defined as interventions primarily focussed on psychological or social factors, in contrast to treatments that focus purely on medical factors such as pharmacological treatment or exercise (19). Full-text articles' eligibility was inspected in the order: (f), (d), (a), (c), (b), and (e).

Using these criteria, selected studies could overlap in terms of sample or data. Rules for addressing multiplicity were set a priori. First, if multiple articles reported on the same trial, the article with the most relevant outcome data (e.g. on the complete sample) was used to determine the effect size. Second, if a study researched multiple interventions and a control group, the most intensive intervention was used in the analysis. Third, when studies had multiple control groups, the control group most similar to standard care was used in the analysis. Studies including only active interventions,

but no control group, were not included. If multiple outcome measures were used, the most precise or objective measure of adherence was selected (e.g. monitoring device).



**Figure 1.** Flowchart illustrating study identification, inclusion and exclusion.

### Data coding

Data coding was conducted with an a priori developed protocol. Coding included effect size data and sample, study and intervention characteristics data. Ten studies were coded by two independent researchers (first and second authors). The percentage of agreement over 37 variables was 86%, indicating acceptable agreement in most situations (28). In case of disagreement the article was consulted again. The first author coded the remaining studies.

Medication adherence was coded for the treatment and control group based on the average percentage of post-treatment ART adherence. When articles did not provide the statistics necessary to calculate the effect size (sample size, mean and standard deviation (*SD*) or mean difference, *t*-value or *p*-value), the authors were contacted by e-mail. When the data could be not obtained, studies were excluded.

Coding of study characteristics included study aim (increasing adherence or improving overall mental or physical health), location, type of control group (waiting list, standard care or active control group), measurement type (self-report, monitoring device or pill count), recall period of the measure



( $\leq 14$  days,  $> 14$  days or no recall: monitoring devices or pill count), percentage retention (participants that were available at the post-treatment assessment), mean age of the sample, percentage of females, sexual orientation or identity (homosexual/gay, heterosexual/straight or bisexual), ethnicity (African American or Black, Caucasian or White and Hispanic or Latino), percentage of participants with AIDS, years since HIV diagnosis and type of risk group (general, risk group or difficulty group). The sample was considered an a priori risk group if known risk factors, for example, experiencing distress from side effects, were an inclusion criterion. The sample was considered an a priori difficulty group if problematic adherence was an inclusion criterion. Other samples were considered general PLWH groups. Standard care control groups usually consisted of consultations with a physician or nurse and short education on medication use and adherence (e.g. (29)). An active control group was an intensive control condition, for example, of similar duration (time-matched) or intensity (dose-matched) as the intervention.

The intervention characteristics included treatment type (CBT, peer/social support or counselling), provider (psychologist/psychiatrist, counsellor, nurse, peer, healthcare professional or other), setting (individual, group or both), treatment duration (1-5, 5-12, 12-30 hours), and use of cognitive and/or behavioural techniques, motivational interviewing and relaxation. An intervention was categorised as CBT if it involved treatment techniques aimed at behavioural and cognitive change. Peer or social support interventions included support through peers or others. Counselling interventions were non-directive or aimed at problem-solving or changing adherence motivation or behaviour. Treatment duration would originally be used in meta-regression to test a dose-response effect. However, meta-regression assumptions (normality and linearity) were not met. Therefore, it was transformed to a categorical variable.

### Statistical analysis

The meta-analysis was conducted using Comprehensive Meta-Analysis Version 2 (CMA; (30)). Effect sizes were expressed as Hedges'  $g$ , computed with the standardized mean difference between the intervention and control group in average percentage of post-treatment medication adherence. Effect sizes of 0.2 were considered small, 0.5 medium and 0.8 large (31). Reported  $p$ -values are two-tailed. The effect sizes were checked for outliers with standardized residuals  $> 3$ . Outliers were transformed toward the mean (winsorized), so that they had a less disproportionate effect on the analyses. The effect sizes were winsorized to 3 SDs from the mean in the original direction (32). Two positive outliers were found and transformed (33, 34).

Effect sizes were analysed using the random effects model. This model assumes heterogeneity across studies (32). For moderator analyses, a mixed model was used. The random effects model combined the studies per subgroup. Because subgroups were assumed to be exhaustive, a fixed effects

model combined the subgroup effects. Between-study variance was assumed to be similar across subgroups and was pooled. To examine heterogeneity between studies, the  $Q$  and  $I^2$  statistics were used. When  $Q$  is significant, this indicates important outcome differences across studies.  $I^2$  represents the amount of heterogeneity, where values of 25%, 50% and 75% indicate low, moderate and high heterogeneity respectively (35). Unfortunately, CMA version 2 does not allow post hoc multiple comparisons. If a significant moderator analysis compares more than two subgroups, it is unclear which subgroups differ from each other. In these cases, confidence intervals (CIs) were inspected to interpret differences.

Trim-and-fill analysis and Egger's regression were conducted to test for publication bias. Duval and Tweedie's trim-and-fill analysis (36) estimates the amount of missing studies due to publication bias and the effect size when correcting for it. Egger's regression tests whether the intercept statistically differs from zero, indicating publication bias (37).

## Results

### Study characteristics

The 43 studies included 5095 participants recruited from 1997 to 2013. Key characteristics per study are presented in Supplement B. Almost two-thirds of the participants were male (65%). Study samples ranged from 33 to 249 participants. Most studies were conducted in the United States (35/43) and the rest in Brazil, China, India, Kenya, the Netherlands, Nigeria, Spain and Switzerland. Participant's average age was 42 years ( $k = 42$ , pooled  $SD = 8.9$ ,  $k = 37$ ; the discrepancy in the amount of studies is due to reporting differences). In studies that reported on the sexual orientation or identity of their sample, most participants described themselves as heterosexual or straight (38%,  $k = 17$ ), homosexual or gay (35%,  $k = 13$ ) and some as bisexual (8%,  $k = 13$ ). Regarding ethnicity, the authors reported that 45% of participants self-identified as Black or African American ( $k = 35$ ), 35% as White or Caucasian ( $k = 34$ ) and 21% as Latino or Hispanic ( $k = 25$ ). The average time of HIV infection at baseline was 10 years in the 18 studies that reported on it (pooled  $SD = 6.8$ ,  $k = 14$ ) and 41% of participants had AIDS ( $k = 11$ ). Forty percent of studies focussed on at-risk populations (17/43), 42% on adherence difficulties' populations (18/43) and 19% screened neither on risk factors nor difficulties (8/43).

Study aim was mostly increasing adherence (28/43) and sometimes improving (mental) health (15/43). Adherence was mostly measured with self-report (21/43) or a monitoring device (19/43), and rarely by pill count (3/43). Eleven self-report studies had recall periods  $\leq 2$  weeks; 10 had longer periods. Control groups frequently received standard care (28/43) and sometimes more active interventions (9/43). Alternatively, participants were put on a waiting list (6/43). The average percentage of retention was 83% in treatment groups and 84% in control groups ( $k = 41$ ).

### Intervention characteristics

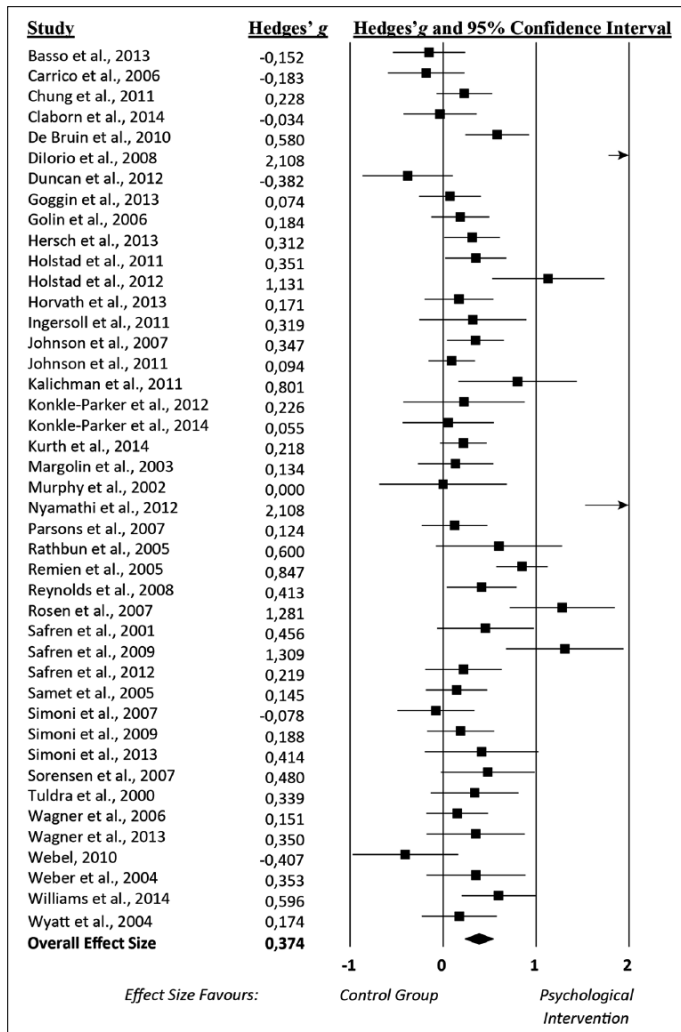
In all, 22 studies investigated the effectiveness of counselling, 15 investigated CBT and 6 peer support. Cognitive and/or behavioural techniques were used in 58% of interventions (25/43), motivational interviewing in 40% (17/43) and relaxation in 19% (8/43). Most interventions were provided individually (32/43), some in group format (7/43) or a combination (4/43). All interventions except one were provided in an outpatient setting. Interventions were provided by psychiatrists or psychologists (10/43), counsellors (4/43), nurses (8/43), peers (7/43), healthcare professionals (case or social workers, 9/43) or other (including online interventions; 5/43).

Treatment duration could be estimated for 33 studies (77%). An outlier was removed from this analysis because the study was unique in terms of setting and an extreme, influential outlier (38). Its treatment duration was 104 hours and it was the only study with an inpatient setting. The average treatment duration in the rest of the studies was 8.15 hours ( $SD = 8.08$ , range: 1–30).

### Main analysis

The random effects model meta-analysis of the overall sample ( $k = 43$ ) resulted in a Hedges'  $g$  effect size of 0.37 (95% CI [0.23, 0.52],  $p < 0.001$ ). This indicates that average post-treatment medication adherence was higher in treatment than control groups, and the overall effect size was statistically different from zero. It shows a small to moderate positive effect of psychosocial interventions on medication adherence in PLWH. Figure 2 shows the effect size and 95% CI per study in a forest plot.

The test of heterogeneity indicated significant between-study variance,  $Q(42) = 240.05$ ,  $p < 0.001$ . The variance caused by effect differences between studies, rather than chance ( $I^2 = 83\%$ ), was considerable (35). This result supports the a priori choice of the random effects model and allows moderator analyses to explain heterogeneity.



**Figure 2.** Forest plot showing the effect of psychosocial interventions on medication adherence.

### Moderator analyses

Study characteristics explain some heterogeneity between studies, specifically the measurement type and recall period; see Table 1. Effect sizes were largest for studies measuring adherence by pill count; next were studies that used a monitoring device and the smallest effects were found for studies that used self-report measures. Unfortunately, the measurement type moderator analysis was unfit for further inferential interpretation; it included a subgroup based on three samples (pill count) and had incomparable CIs. Because the pill-count group was small, the results were influenced largely by a winsorized outlier, regardless of its transformation toward the mean (34). Therefore, the results in Table 2 regarding measure type should be interpreted with caution. The moderator analysis with recall

periods showed that studies with recall periods  $\leq 14$  days had smaller effect sizes than studies with no recall period. The studies with a recall period  $> 14$  days did not differ significantly from those with shorter or no recall periods. Study aim, population, type of control group, and location did not moderate effect size, nor did intervention characteristics; see Table 2.

**Table 1.** Overview of subgroup effect sizes and heterogeneity for study characteristics.

Moderator	Subgroup	$k^a$	Hedges' $g$	95% CI <sup>b</sup>	$Q^c$	$P$
Study aim	Increasing adherence	28	0.44	0.25, 0.62	1.34	0.25
	Improving health	15	0.25	-0.001, 0.51		
Sample	General	8	0.43	0.08, 0.78	0.17	0.92
	Risk group	17	0.38	0.14, 0.63		
	Difficulties' group	18	0.34	0.11, 0.58		
Control group	Waiting list	6	0.13	-0.25, 0.52	5.52	0.06
	Standard care	28	0.33	0.14, 0.51		
	Active control group	9	0.71	0.37, 1.04		
Measure type	Self-report	21	0.19	-0.02, 0.39	8.65	0.01 <sup>d</sup>
	Monitoring device	19	0.49	0.28, 0.71		
	Pill count	3	0.97	0.41, 1.53		
Recall period	<14 days	11	0.13	-0.16, 0.42	6.52	0.04 <sup>d</sup>
	>14 days	10	0.25	-0.05, 0.54		
	No recall	22	0.55	0.35, 0.75		
Location	United States	35	0.32	0.16, 0.49	2.09	0.15
	Other	8	0.61	0.26, 0.95		

<sup>a</sup>  $k$  = number of studies, <sup>b</sup> CI = confidence interval, <sup>c</sup>  $Q$  = between-group  $Q$ , <sup>d</sup>  $p < .05$ .

**Table 2.** Overview of subgroup effect sizes and heterogeneity for intervention characteristics.

Moderator	Subgroup	$k^a$	Hedges' $g$	95% CI <sup>b</sup>	$Q^c$	$p$
Intervention type	CBT <sup>d</sup>	15	0.29	0.03, 0.55	0.67	0.72
	Peer or social support	6	0.45	0.05, 0.85		
	Counselling	22	0.41	0.20, 0.62		
CB <sup>e</sup>	No	18	0.49	0.27, 0.72	1.83	0.18
	Yes	25	0.29	0.09, 0.48		
MI <sup>f</sup>	No	26	0.31	0.12, 0.50	1.19	0.28
	Yes	17	0.48	0.24, 0.71		
Relaxation	No	35	0.42	0.26, 0.58	1.69	0.19
	Yes	8	0.16	-0.18, 0.51		
Setting	Group	7	0.11	-0.26, 0.48	2.47	0.29
	Individual	32	0.41	0.24, 0.59		
	Combination	4	0.52	0.02, 1.03		
Therapy provider	Psychologist/psychiatrist	10	0.39	0.07, 0.71	3.37	0.64
	Counsellor	4	0.35	-0.15, 0.84		
	Nurse	8	0.62	0.29, 0.95		
	Peer	7	0.37	0.00, 0.73		
	Healthcare professional	9	0.24	-0.08, 0.56		
	Other	5	0.21	-0.22, 0.63		
Treatment duration	Short	16	0.40	0.15, 0.64	1.13	0.57
	Medium	8	0.29	-0.06, 0.65		
	Long	8	0.17	-0.19, 0.52		
	Missing	10				

<sup>a</sup>  $k$  = number of studies, <sup>b</sup> CI = confidence interval, <sup>c</sup>  $Q$  = between-group  $Q$ , <sup>d</sup> CBT = cognitive behavioural therapy, <sup>e</sup> CB = cognitive and/or behavioural techniques, <sup>f</sup> MI = motivational interviewing.

### Publication bias

Duval and Tweedie's trim-and-fill funnel plot showed that the studies in this meta-analysis are distributed symmetrically around the mean effect size. No studies were trimmed or filled, indicating no evidence of publication bias. Egger's test of the intercept was not significant, intercept 1.02, (95% CI [-1.74, 3.78],  $t(41) = 0.75$ ,  $p = 0.46$ ). This also indicates that there is no publication bias.

### Discussion

The results of the current meta-analysis show that psychosocial interventions have a small to moderate positive effect on medication adherence in PLWH. This finding has important implications because better ART adherence is related to disease suppression and lowers transmission risk. This effect is likely due to psychosocial interventions treating important causes of ART non-adherence. Those may include the psychological correlates found in an earlier meta-analysis, such as depressive symptoms, stigma

and lack of social support. In addition to mental health, non-adherence is related to many factors including pill burden, side effects, physical health, sexual health and socioeconomic status. Psychosocial interventions may influence how PLWH cope with challenges in these fields. The findings of this study are in line with previous meta-analyses and reviews that have shown promising results for treatments involving behavioural components (22), counselling (21), motivational interviewing (20) and treatments aimed at depression (23). Contrastingly, some reviews found negative or mixed results of psychosocial interventions aimed at improving adherence (24-26). This may be explained by the method; this study uses meta-analysis on 43 studies, while previous reviews did not combine the individual study data to determine an overall effect. In addition, two reviews had fewer studies than the current meta-analysis (24, 26). In terms of geographical and temporal context, previous reviews and meta-analyses were similar to the current meta-analysis and featured studies conducted post 1996 and mainly in the United States. In short, the results of this meta-analysis are in line with a number of previous studies and indicate that offering psychosocial interventions to PLWH may improve medication adherence.

Intervention characteristics did not explain differences in treatment effectiveness in this study. Therefore, findings that interventions were more effective when they included at-risk or adherence difficulty groups (21), involved CBT components (24), had longer treatment duration (23, 26) or provided individual therapy (26) were not replicated. The current meta-analysis results indicate that many different forms of psychosocial treatment in many different settings may be effective. The results are in accordance with the dodo bird verdict and common factors theory. These claim that various psychosocial interventions lead to similar outcomes, due to common effective factors such as therapeutic alliance (39).

Differences in methodology and included studies may explain differences in results regarding the moderating effect of intervention characteristics between this study and previous studies. It may be that moderating factors that seem effective in a systematic review, based on the number of studies with positive findings, were not found to be effective in this meta-analysis, based on pooled and weighted results. It could also be that such findings were not present in this sample because it is based on RCTs only, or because the sample consists of a various psychosocial interventions rather than, for instance, motivational interviewing alone. Another explanation might be that moderating effects of these characteristics are small and more studies are necessary to find subgroup differences.

Two study characteristics showed a relationship with treatment effectiveness: the type of adherence measure and its recall period. However, the measure type analysis included a subgroup of three studies, including one influential outlier, hence findings should be interpreted with caution. With this in mind, the results indicate that studies that used pill-count measures may have larger effect sizes than studies that used self-report measures. This suggests that pill-count measures are more sensitive

to detect differences than self-report measures, which agrees with earlier findings (40). In addition, pill count and monitoring devices are more objective than self-report measures; they do not rely on the participant's memory. Second, studies that used measures without recall period had larger effect sizes than those with recall. This may be associated with the previous result that pill-count measures, which have no recall period, have larger effect sizes than self-report measures, which have a recall period. Combining previous and current study findings, it seems that objective measures that do not rely on recall may be more sensitive to changes in adherence than subjective measures that rely on self-report. For future studies, researchers should keep in mind these possible sensitivity differences when deciding on a measurement method.

### **Strengths and limitations**

This study combined and analysed the data of 43 studies meta-analytically, which resulted in high statistical power. In addition, a wide range of psychosocial interventions were included in this meta-analysis. This study adds to previous research by analysing results from RCTs only, which are considered high-quality studies in experimental psychology. Another strength is that results indicated no influence of publication bias. However, some studies that were identified during the systematic search were excluded due to missing data.

The study also had limitations. First, the study investigated only short-term post-treatment effects. Therefore, the long-term effectiveness of psychosocial interventions remains unclear. Second, some moderators had categories with few studies, making it hard to generalize their results. Third, the mechanisms of change remain unclear, as psychosocial interventions may influence factors related to adherence, such as physical, mental and sexual health, and socioeconomic status.

The current meta-analysis was influenced by limitations of the included studies and identified some gaps in the literature. First, most studies were conducted in the United States, leaving other locations greatly influenced by HIV, such as Sub-Saharan Africa and Asia, underrepresented. The minority of women in the meta-analysis (35%) correspond with the ratio of women with HIV in the United States, (41) but not Sub-Saharan Africa (42), where HIV disproportionately impacts women. Furthermore, outcomes, study and sample characteristics, such as mean age and ethnicity, were not always reported, which hindered coding. ART pill burden and side effects were often not reported, and thus not analysed. Standardized reporting could be improved by following CONSORT guidelines (43).

### **Future research**

It would be interesting to study common factors in psychosocial treatments, such as therapeutic alliance and empathy. Second, it would be interesting to investigate long-term effects of psychosocial treatments, to assess whether positive results can be retained. Since the intervention provider was not



a significant moderator, future research could study the effectiveness of online interventions, which may be more accessible and cost-effective. Fourth, future research might focus on investigating the effectiveness of psychosocial interventions in non-USA samples. Furthermore, studying factors that are related to high or consistent adherence, rather than non-adherence, might provide new insights for psychosocial interventions. Finally, since the effect size was small to moderate, research on supplemental strategies to increase adherence is recommended. The best result may be obtained by fine-tuning and combining medical and psychosocial treatments for PLWH.

### **Conclusion**

This study adds to HIV care literature by establishing the positive effect of a wide range of psychosocial interventions on medication adherence in PLWH in the form of a meta-analysis of RCTs. Better medication adherence promotes the health of PLWH and impacts public health by lowering transmission risk. This study finds that various types of psychosocial interventions can be effective for various PLWH groups. It is important that healthcare professionals are made aware of this, so they can refer PLWH with adherence challenges. Increasing medication adherence in PLWH remains an important public health goal and can potentially help millions of people to suppress the virus and increase their well-being.

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## Appendix

### Appendix 1. Search Strategy

#### Embase Search Term

(exp "Human immunodeficiency virus"/ OR exp "Human immunodeficiency virus infection"/ OR exp "Acquired immune deficiency syndrome"/ OR hiv.tw. OR aids.tw. ) AND (exp psychotherapy/ or exp "mental health services"/ or exp "self care"/ OR exp "self help"/ OR exp teletherapy/ OR exp "computer assisted therapy"/ OR psychotherap\*.tw. OR psychological-therapy.tw. OR psychological-treatment.tw. OR psychological-intervention.tw. OR counsel\*.tw. OR cbt.tw. OR behavior-therapy.tw. OR interpersonal-therapy.tw. OR coping.tw. OR peer-support.tw. OR social-support.tw. OR problem-solving.tw. OR stress-management.tw. OR self-help.tw. OR internet-therap\*.tw. OR online-therap\*.tw. OR psychoed\*.tw. OR training.tw. OR exposure.tw. OR relaxation.tw. OR mindfulness.tw. OR reinforcement.tw. OR risk-reduction.tw. OR commitment-therap\*.tw. OR case-manage\*.tw.) AND (exp "patient compliance"/ OR adher\*.tw. OR compliance.tw. OR exp "highly active antiretroviral therapy"/ OR exp "antiviral therapy"/ OR antiretroviral-therapy.tw.)

Filters used: Human subjects, Aged ≥ 18 ('Adult' and 'Aged' categories), English Language, Article, Randomized Controlled Trial or Controlled Clinical Trial, Post 1996.

#### PsycInfo Search Term

(DE (hiv OR aids) OR TX (hiv OR aids)) AND (DE (psychotherapy OR psychotherapeutic techniques OR mental health programs OR Counseling OR Stress management OR case management OR self management OR Telemedicine OR Computer Assisted Therapy OR Psychoeducation) OR TX (psychotherap\* OR psychological-therap\* OR psychological-treatment OR psychological-intervention OR counsel\* OR cbt OR behavior-therap\* OR interpersonal-therap\* OR coping OR peer-support OR social-support OR problem-solving OR stress-manage\* OR self-help OR internet-therap\* OR online-therap\* OR psychoed\* OR training OR exposure OR relaxation OR mindfulness OR reinforcement OR risk-reduction OR commitment-therap\* OR case-manage\*)) AND (DE (treatment compliance OR antiviral drugs OR drug therapy) OR TX (adher\* OR compliance OR antiretroviral-therapy))

Filters used: Aged ≥ 18 (Adulthood), Article or Dissertation, Treatment Outcome/Clinical Trial or Follow-up study or Experimental Replication, Post 1996.

**Medline Search Term**

(hiv [mesh] OR hiv infection [mesh] OR hiv [tiab] or aids [tiab]) AND (psychotherapy [mesh] OR mental health services [mesh] OR self-care [mesh] OR self-help groups [mesh] OR telemedicine [mesh] OR therapy, computer-assisted [mesh] OR psychotherap\* [tiab] OR psychological therap\* [tiab] OR psychological treatment\* [tiab] OR psychological intervention\* [tiab] OR counsel\* [tiab] OR cbt [tiab] OR behavior therap\* [tiab] OR behaviour therap\* [tiab] OR interpersonal therap\* [tiab] OR coping [tiab] OR peer support [tiab] OR social support [tiab] OR problem solving [tiab] OR stress manage\* [tiab] OR self-help [tiab] OR internet therap\* [tiab] OR online therap\* [tiab] OR psychoed\* [tiab] OR training [tiab] OR exposure [tiab] OR relaxation [tiab] OR mindfulness [tiab] OR reinforcement [tiab] OR risk reduction [tiab] OR commitment therap\* [tiab] OR case manage\* [tiab]) AND (patient compliance [mesh] OR adher\* [tiab] OR compliance [tiab] OR HAART [mesh] OR antiretroviral therapy [tiab])

Filters used: Human Subjects, English language, Controlled Clinical Trial or Randomized Controlled Trial, Post 1996.

**Appendix 2.** Summary of RCT studies on the Effect of Psychosocial Interventions on Medication Adherence in PLWH.

Study	Population <sup>a</sup>		Intervention <sup>b</sup>		Study Design <sup>c</sup>		Outcome <sup>d</sup>
	First author, year	Randomized sample	Name	Provider	Study Aim	Control Group	Measure type
Basso, 2013 (29) Brazil	N = 121 PLWH Mean age: 43 years; 37% female Screened on detectable viral load (DG).	<i>Human Right- Based Intervention</i>	Provider: healthcare professional Categorized as: counselling Length: 4 hrs; Setting: individual	Aim: increasing adherence.	CG: SC	MEMS	
Carrico, 2006 (44) USA	N = 130, male PLWH Mean age: 42 years; 0% female	<i>Cognitive Behavioural Stress Management</i>	Provider: psychologist/psychiatrist Categorized as: CBT (CB, REL) Length: 22.5 hrs; Setting: group	Aim: improving health.	CG: SC	ACTG, self-report, 4 days recall.	
Chung, 2011 (45) Kenya	N = 200 PLWH Mean age: 36 years; 66% female Screened on initiating ART (RG)	<i>Adherence Counselling</i>	Provider: counsellor Categorized as: counselling (CB) Length: 1.9 hrs; Setting: individual	Aim: increasing adherence.	CG: SC	Pill-Count	
Claborn, 2014 (46) USA	N = 97 PLWH Mean age: 44 years; 16% female Screened on adherence ≤ 95% (DG)	<i>elifeSteps</i>	Provider: computer Categorized as: CBT (CB) Length: 1 hour; Setting: individual	Aim: increasing adherence.	CG: SC	ACTG, self-report, 4 days recall.	
De Bruin, 2010 (47) The Netherlands	N = 133 PLWH Mean age: 48 years; 10% female	<i>Adherence Improving Self-Management Strategy</i>	Provider: HIV-nurse Categorized as: counselling (MI)	Aim: increasing adherence.	CG: SC	MEMS	

Study	Population <sup>a</sup>	Intervention <sup>b</sup>	Study Design <sup>c</sup>	Outcome <sup>d</sup>
First author, year Country	Randomized sample Mean age and % female Screening and risk type (when applicable)	Name Provider Type and techniques used Duration and setting Length: 1 hour; Setting: individual	Study Aim Control Group Analysed sample (when applicable)	Measure type
Dilorio, 2008 (33) USA	N = 247 PLWH Mean age: 42 years; 28% female Screened on initiating or changing ART (RG)	<i>Motivational Interviewing</i> Provider: HIV-nurse Categorized as: counselling (MI) Length: 2.8 hrs; Setting: individual	Aim: increasing adherence. CG: SC	MEMS
Duncan, 2012 (48) USA	N = 76 PLWH Mean age: 48 years; 16% female Screened on experiencing distress from side effects (RG)	"FOCUS" MBSR Provider: MBSR (healthcare) professional Categorized as: CBT (CB, REL) Length: 30 hrs; Setting: group	Aim: improving health CG: SC	VAS, self-report, 30 days recall
Goggin, 2013 (49) USA	N = 135 PLWH Mean age: 40.6 years; 26% female Screened on adherence problems, initiating or changing ART (DG)	<i>Motivational Interviewing - CBT</i> Provider: psychologist Categorized as: counselling (CB, MI) Length: 4.2 hrs; Setting: individual	Aim: increasing adherence CG: SC	MEMS
Golin, 2006 (50) USA	N = 155 PLWH Mean age: 40 years; 34% female Screened on detectable or increased viral load or initiating ART (DG)	<i>Motivational Interviewing</i> Provider: healthcare professional Categorized as: counselling (MI) Length: 2.3 hrs; Setting: individual	Aim: increasing adherence CG: Active control group: PE	MEMS
Hersch, 2013 (51) USA	N = 168 PLWH Mean age: 46 years; 24% female Screened on detectable viral load(DG)	<i>eLifeSteps</i> Provider: computer Categorized as: CBT (CB, REL) Length: 1 hour; Setting: individual	Aim: increasing adherence CG: WLC <sup>e</sup>	MEMS

Study	Population <sup>a</sup>		Intervention <sup>b</sup>		Study Design <sup>c</sup>		Outcome <sup>d</sup>
	First author, year	Country	Randomized sample	Name	Provider	Study Aim	Measure type
			Mean age and % female	Type and techniques used	Control Group	Analysed sample (when applicable)	
			Screening and risk type (when applicable)	Duration and setting			
Holstad, 2011 (52)	USA	N = 207, female PLWH Mean age: 44 years; 100% female	<i>KHARMA – Motivational Interviewing</i> Provider: nurse Categorized as: counselling (MI) Length: 14 hrs; Setting: group	Aim: improving health CG: Active control group: PE Analysed if ≥ 7 of 8 sessions were followed			MEMS
Holstad, 2012 (53)	Nigeria	N = 60, female PLWH Mean age: 31 years; 100% female	<i>KHARMA – Motivational Interviewing</i> Provider: healthcare professional Categorized as: counselling (MI) Length: 14 hrs; Setting: group	Aim: improving health CG: Active control group: PE Analysed if ≥ 7 of 8 sessions were followed			AGAS, self-report, 30 days recall
Horvath, 2013 (54)	USA	N = 145, gay or bisexual PLWH Mean age: 43 years; 0% female Screened on adherence problems (DG)	<i>Thrive With Me - online social support</i> Provider: peer Categorized as: peer support Length: NR <sup>e</sup> ; Setting: individual	Aim: increasing adherence CG: WLC			Self-report item, 30 days recall
Ingersoll, 2011 (55)	USA	N = 56, crack cocaine using PLWH Mean age: 45 years; 52% female Screened on adherence problems (DG)	<i>Motivational Interviewing</i> Provider: psychologist Categorized as: counselling (CB, MI) Length: 6 hrs; Setting: individual	Aim: improving health CG: Active control group: PE			TLB, self-report, 14 days recall
Johnson, 2007 (56)	USA	N = 204 PLWH Mean age: 40 years; 22% female (DG; see analysed sample)	<i>The Healthy Living Project</i> Provider: healthcare professional. Categorized as: counselling (CB) Length: 22.5 hrs; Setting: individual	Aim: improving health CG: WLC Analysed if ≤ 85% adherence			ACTG, self-report, 3 days recall
Johnson, 2011 (57)	USA	N = 249 PLWH Mean age: 46 years; 9% female	<i>The Balance Project</i> Provider: healthcare professional.	Aim: increasing adherence CG: WLC			VAS, self-report, 30 days recall

Study	Population <sup>a</sup>		Intervention <sup>b</sup>		Study Design <sup>c</sup>		Outcome <sup>d</sup>
	First author, year Country	Randomized sample Mean age and % female Screening and risk type (when applicable)	Name Provider Type and techniques used Duration and setting	Study Aim Control Group Analysed sample (when applicable)	Measure type		
		Screened on side effect distress (RG)	Categorized as: counselling (CB) Length: 5 hrs; Setting: individual				
Kalichman, 2011 (58) USA	N = 41 PLWH Mean age: 51 years; 35% female Screened on ≤ 95% adherence (DG)	<i>Cell Phone Adherence Counselling</i> Provider: counsellor Categorized as: counselling (CB) Length: 3.75 hrs; Setting: individual	Aim: increasing adherence CG: Active control group: pill-count calls	Pill-count			
Konkle-Parker, 2012 (59) USA	N = 56 PLWH Mean age: 35 years; 38% female Screened on initiating or changing ART (RG)	<i>Motivational Interviewing</i> Provider: nurse Categorized as: counselling (MI) Length: 2.5 hrs; Setting: individual	Aim: increasing adherence CG: SC	VAS, self-report, 21-28 days recall			
Konkle-Parker, 2014 (60) USA	N = 100 PLWH Mean age: 37 years; 51% female Screened on adherence problems (DG)	<i>Motivational Interviewing</i> Provider: other (research coordinator) Categorized as: counselling (MI) Length: 2.5 hrs; Setting: individual	Aim: increasing adherence CG: SC	VAS, self-report, 21-28 days recall			
Kurth 2014 (61) USA	N = 240 PLWH Mean age: 45 years; 9% female	<i>CARE+; online counselling</i> Provider: computer Categorized as: counselling (MI) Length: NR; Setting: individual	Aim: increasing adherence CG: SC	VAS, self-report, 30 days recall			
Margolin, 2003 (38) USA	N = 90 PLWH in a methadone maintenance program Mean age: 41 years; 30% female Screened on injection drug use (RG)	<i>HIV+ Harm Reduction Program</i> Provider: counsellor Categorized as: CBT (CB) Length: 104 hrs; Setting: group (inpatient)	Aim: improving health CG: SC	TLB, self-report, 7 days recall			

Study	Population <sup>a</sup>	Intervention <sup>b</sup>			Study Design <sup>c</sup>		Outcome <sup>d</sup>
		Randomized sample	Name	Provider	Study Aim	Measure type	
Country	Mean age and % female	Type and techniques used	Control Group	Analysed sample (when applicable)			
	Screening and risk type (when applicable)	Duration and setting					
Murphy, 2002 (62)	N = 52 PLWH	CBT			Aim: increasing adherence		ACTG, self-report, 3 days recall
USA	Mean age: 39 years; 12% female	Provider: psychologist			CG: SC		
	Screened on missing $\geq 1$ dose per week (DG)	Categorized as: CBT (CB)					
		Length: NR; Setting: group & individual					
Nyamathi, 2012 (34)	N = 68, female PLWH, aged 18-45	ASHA-life			Aim: increasing adherence		Pill-Count
India	Mean age: 31 years; 100% female	Provider: peer			CG: Active control group: PE		
	Screened on CD4 count $\geq 100$	Categorized as: peer support					
		Length: NR; Setting: group & individual					
Parsons, 2007 (63)	N = 143 PLWH	Project PLUS – CBT and MI			Aim: improving health		Self-report item, 14 days recall
USA	Mean age: 44 years; 21% female	Provider: healthcare professional			CG: Active control group: PE		
	Screened on hazardous drinking (RG)	Categorized as: CBT (CB, MI)					
		Length: 8 hrs; Setting: individual					
Rathbun, 2005 (64)	N = 33 PLWH	Psycho-educative counselling			Aim: increasing adherence		MEMS
USA	Mean age: 38 years; 15% female	Provider: healthcare professional			CG: SC		
	Screened on initiating ART (RG)	Categorized as: counselling					
		Length: NR; Setting: individual					
Remien, 2005 (65)	N = 215 PLWH in relationship with seronegative partner ( $\geq 6$ months)	SMART Couples Support Study			Aim: increasing adherence		MEMS
USA	Mean age: 42 years; 46% female	Provider: nurse			CG: SC		
	Screened on $\leq 80\%$ adherence (DG)	Categorized as: social support (CB)					
		Length: 3.3 hrs; Setting: individual					
Reynolds, 2008 (66)	N = 109 PLWH	Telephone Adherence Counselling			Aim: increasing adherence		ACTG, self-report, 4 days recall
USA	Mean age: 37 years; 15% female	Provider: nurse			CG: SC		



Study	Population <sup>a</sup>		Intervention <sup>b</sup>		Study Design <sup>c</sup>		Outcome <sup>d</sup>
	First author, year Country	Randomized sample Mean age and % female Screening and risk type (when applicable)	Name Provider Type and techniques used Duration and setting	Study Aim Control Group Analysed sample (when applicable)	Measure type		
Rosen, 2007 (67) USA	N = 56 PLWH Mean age: 44 years; 41% female Screened on ≤ 80% adherence (DG)	<i>Contingency Management and counselling</i> Provider: psychologist Categorized as: CBT (CB) Length: NR; Setting: individual	Aim: increasing adherence CG: Active control group: counselling	MEMS			
Safren, 2001 (68) USA	N = 56 PLWH Mean age: 41 years; 13% female Screened on adherence problems (DG)	<i>Life-Steps: CBT for Adherence</i> Provider: healthcare professional Categorized as: counselling (CB, MI) Length: NR; Setting: individual	Aim: increasing adherence CG: SC	ACTG, self-report, 14 days recall			
Safren, 2009 (69) USA	N = 45 PLWH Mean age: NR; 16% female Screened on mood disorder (RG)	<i>Life-Steps: CBT for Adherence</i> Provider: psychologist Categorized as: CBT (CB, MI, REL) Length: 9.2 hrs; Setting: individual	Aim: improving health. CG: Enhanced SC	MEMS			
Safren, 2012 (70) USA	N = 89 PLWH Mean age: 47 years; 39% female Screened on opioid dependence & mood disorder (RG)	<i>Life-Steps: CBT for Adherence</i> Provider: psychologist Categorized as: CBT (CB, MI, REL) Length: 7.5 hrs; Setting: individual	Aim: improving health CG: Enhanced SC	MEMS			
Samet, 2005 (71) USA	N = 151 PLWH Mean age: 43 years; 46% female Screened on alcohol problems (RG)	<i>ADHERE – Motivational Interviewing</i> Provider: nurse Categorized as: counselling (MI) Length: 2.4 hrs; Setting: individual	Aim: increasing adherence CG: SC	ACTG, self-report, 30 days recall			

Study	Population <sup>a</sup>	Intervention <sup>b</sup>	Study Design <sup>c</sup>	Outcome <sup>d</sup>
First author, year	Randomized sample	Name	Study Aim	Measure type
Country	Mean age and % female	Provider	Control Group	
	Screening and risk type (when applicable)	Type and techniques used	Analysed sample (when applicable)	
		Duration and setting		
Simoni, 2007 (72)	N = 136 PLWH	<i>Peer Support</i>	Aim: increasing adherence	MEMS
USA	Mean age: 43 years; 45% female	Provider: peer Categorized as: peer support Length: 6 hrs; Setting: group & individual	CG: SC	
Simoni, 2009 (73)	N = 114 PLWH	<i>Peer Support</i>	Aim: improving health	MEMS
USA	Mean age: 40 years; 24% female Screened on initiating or changing ART (RG)	Provider: peer Categorized as: peer support Length: 6 hrs; Setting: group & individual	CG: SC	
Simoni, 2013 (74)	N = 40 PLWH of Mexican descent	<i>CBT for Depression &amp; Life-Steps</i>	Aim: improving health	MEMS
USA	Mean age: 46 years; 28% female Screened on depressive complaints & non-adherence or detectable viral load (DG)	Provider: psychologist Categorized as: CBT (CB, MI, REL) Length: 9.17 hrs; Setting: individual	CG: SC	
Sorensen, 2007 (75)	N = 66 PLWH	<i>Contingency Management and Counselling</i>	Aim: increasing adherence	MEMS
USA	Mean age: 43 years; 41% female Screened on receiving methadone treatment and ≤ 80% adherence (DG)	Provider: other (not specified) Categorized as: CBT (CB) Length: NR; Setting: individual	CG: Active control group: counselling and reward	
Tuidra, 2000 (76)	N = 116 PLWH	<i>Psycho-educative Counselling</i>	Aim: increasing adherence	Self-report item, 30 days recall
Spain	Mean age: 39 years; 24% female Screened on initiating ART (RG)	Provider: psychologist Categorized as: counselling Length: NR; Setting: individual	CG: SC	

Study	Population <sup>a</sup>		Intervention <sup>b</sup>		Study Design <sup>c</sup>		Outcome <sup>d</sup>
	First author, year	Randomized sample	Name	Provider	Study Aim	Measure type	
Country	Mean age and % female	Type and techniques used	Type and techniques used	Control Group	Analysed sample (when applicable)		
	Screening and risk type (when applicable)	Duration and setting	Duration and setting				
Wagner, 2006 (77)	N = 230 PLWH	<i>CBT or CBT plus Adherence Practice Trial</i>	<i>CBT or CBT plus Adherence Practice Trial</i>	Aim: improving health			MEMS
USA	Mean age: 39 years; 20% female	Provider: nurse	Provider: nurse	CG: SC			
	Screened on adherence problems & initiating or changing ART (DG)	Categorized as: CBT (CB)	Categorized as: CBT (CB)				
Wagner, 2013 (78)	N = 60 PLWH	<i>Adherence Readiness Program</i>	<i>Adherence Readiness Program</i>	Aim: increasing adherence			MEMS
USA	Mean age: 39 years; 6% female	Provider: counsellor	Provider: counsellor	CG: SC			
	Screened on initiating or changing ART (RG)	Categorized as: counselling (CB, MI)	Categorized as: counselling (CB, MI)				
		Length: 3.5 hrs; Setting: individual	Length: 3.5 hrs; Setting: individual				
Weibel, 2010 (79)	N = 89, female and transgender (identifying female), PLWH	<i>Peer-Supported Self-management</i>	<i>Peer-Supported Self-management</i>	Aim: improving health			ACTG, self-report, 7 days recall
USA	Mean age: 47 years; 100% female	Provider: peer	Provider: peer	CG: WLC			
		Categorized as: peer support (CB, REL)	Categorized as: peer support (CB, REL)				
		Length: 14 hrs; Setting: group	Length: 14 hrs; Setting: group				
Weber, 2004 (80)	N = 60 PLWH	<i>CBT</i>	<i>CBT</i>	Aim: improving health			MEMS
Switzerland	Mean age: 41 years; 17% female	Provider: psychologist	Provider: psychologist	CG: SC			
	Screened on detectable viral load (RG)	Categorized as: CBT (CB)	Categorized as: CBT (CB)				
		Length: 18.8 hrs; Setting: individual	Length: 18.8 hrs; Setting: individual				
Williams, 2014 (81)	N = 110 PLWH	<i>Ai Sheng Nuo (Love, Life, Hope)</i>	<i>Ai Sheng Nuo (Love, Life, Hope)</i>	Aim: increasing adherence			VAS, self-report, 30 days recall
China	Mean age: 38 years; 29% female	Provider: peer	Provider: peer	CG: SC			
	Screened on ≤ 90% adherence and detectable viral load (DG)	Categorized as: counselling	Categorized as: counselling				
		Length: NR; Setting: individual	Length: NR; Setting: individual				
Wyatt, 2004 (82)	N = 147, female, PLWH	<i>ESHI: Enhanced Sexual Health Intervention</i>	<i>ESHI: Enhanced Sexual Health Intervention</i>	Aim: increasing adherence			Self-report item, 14 days recall
USA	Mean age: 41 years; 100% female	Provider: peer	Provider: peer	CG: WLC			

Study	Population <sup>a</sup>	Intervention <sup>b</sup>	Study Design <sup>c</sup>	Outcome <sup>d</sup>
First author, year	Randomized sample	Name	Study Aim	Measure type
Country	Mean age and % female Screening and risk type (when applicable)	Provider Type and techniques used Duration and setting	Control Group Analysed sample (when applicable)	
	Screened on childhood sexual abuse history (RG)	Categorized as: counselling (CB, REL) Length: 27.5 hrs; Setting: group		
	<sup>a</sup> Population. With ART = antiretroviral therapy, CD4 = cluster of differentiation 4 (immune parameter), DG = difficulties group, PLWH = people living with HIV, RG = risk group.			
	<sup>b</sup> Intervention. With CB = cognitive and/or behavioural techniques, CBT = cognitive behavioural therapy, MBSR = mindfulness based stress reduction, MI = motivational interviewing techniques, PE = psychoeducation, REL = relaxation techniques.			
	<sup>c</sup> Study design. With CG = control group, SC = standard care, WLC = waiting-list condition.			
	<sup>d</sup> Outcome. With ACTG = AIDS Clinical Trials Group adherence questionnaire, AGAS = Antiretroviral General Adherence Scale, MEMS = Medication Event Monitoring System, TLB = Time-Line Back, VAS = Visual Analogue Scale.			
	<sup>e</sup> NR = not reported.			

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