Living positive: eHealth for people with HIV and depressive symptoms

Luenen, S. van

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 ≥ 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).

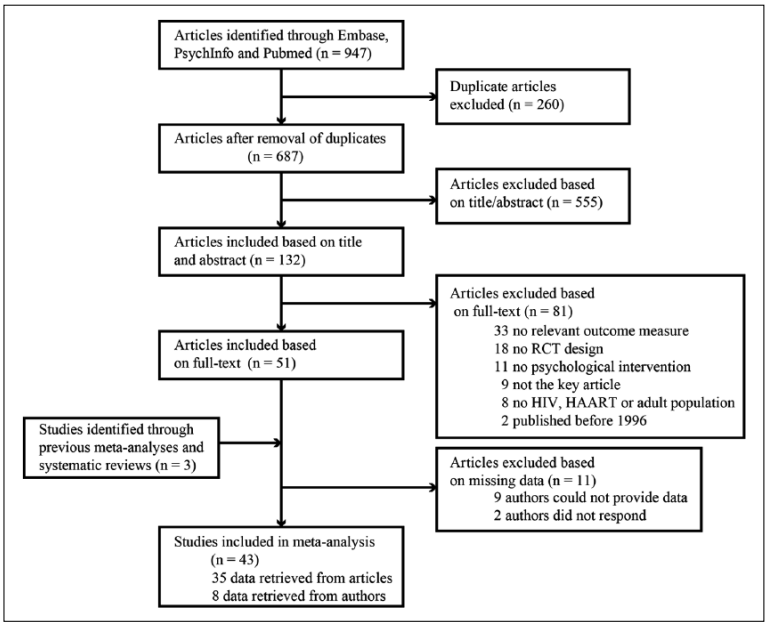

Figure 1. Flowchart illustrating study identification, inclusion and exclusion.

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

(≤ 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 ≤ 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.

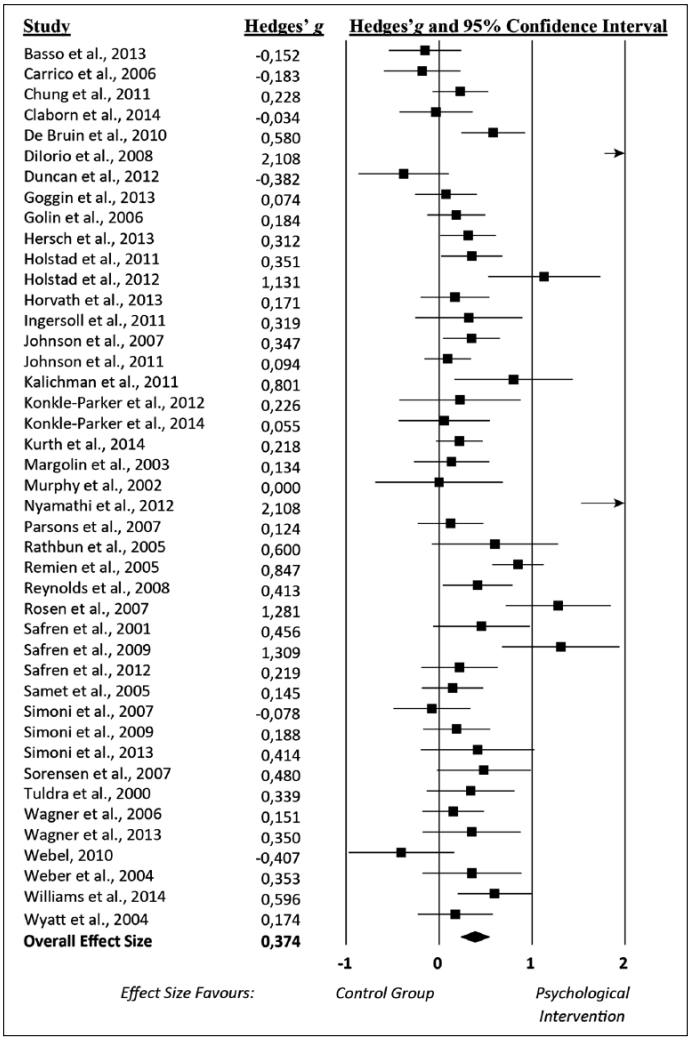

Figure 2. Forest plot showing the effect of psychosocial interventions on medication adherence.

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 ≤ 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[b]	*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[d]
	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[d]
	>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		

[a] *k* = number of studies, [b] *CI* = confidence interval, [c] *Q* = between-group *Q*, [d] $p < .05$.

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

Moderator	Subgroup	*k*[a]	Hedges' *g*	95% CI[b]	*Q*[c]	*p*
Intervention	CBT[d]	15	0.29	0.03, 0.55	0.67	0.72
type	Peer or social support	6	0.45	0.05, 0.85		
	Counselling	22	0.41	0.20, 0.62		
CB[e]	No	18	0.49	0.27, 0.72	1.83	0.18
	Yes	25	0.29	0.09, 0.48		
MI[f]	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	Psychologist/psychiatrist	10	0.39	0.07, 0.71	3.37	0.64
provider	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	Short	16	0.40	0.15, 0.64	1.13	0.57
duration	Medium	8	0.29	−0.06, 0.65		
	Long	8	0.17	−0.19, 0.52		
	Missing	10				

[a] *k* = number of studies, [b] *CI* = confidence interval, [c] *Q* = between-group *Q,* [d] *CBT* = cognitive behavioural therapy, [e] *CB* = cognitive and/or behavioural techniques, [f] *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 disproportionally 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.

Acknowledgements

The authors would like to thank all authors who shared their data for use in this study.

Funding

The author(s) received no financial support for the research, authorship and/or publication of this article.

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

Study	Population[a]	Intervention[b]	Study Design[c]	Outcome[d]
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		
		Length: 1 hour; Setting: individual		
Dilorio, 2008 (33)	*N* = 247 PLWH	*Motivational Interviewing*	Aim: increasing adherence.	MEMS
USA	Mean age: 42 years; 28% female	Provider: HIV-nurse	CG: SC	
	Screened on initiating or changing ART (RG)	Categorized as: counselling (MI)		
		Length: 2.8 hrs; Setting: individual		
Duncan, 2012 (48)	*N* = 76 PLWH	*"FOCUS" MBSR*	Aim: improving health	VAS, self-report, 30 days recall
USA	Mean age: 48 years; 16% female	Provider: MBSR (healthcare) professional	CG: SC	
	Screened on experiencing distress from side effects (RG)	Categorized as: CBT (CB, REL)		
		Length: 30 hrs; Setting: group		
Goggin, 2013 (49)	*N* = 135 PLWH	*Motivational Interviewing - CBT*	Aim: increasing adherence	MEMS
USA	Mean age: 40.6 years; 26% female	Provider: psychologist	CG: SC	
	Screened on adherence problems, initiating or changing ART (DG)	Categorized as: counselling (CB, MI)		
		Length: 4.2 hrs; Setting: individual		
Golin, 2006 (50)	*N* = 155 PLWH	*Motivational Interviewing*	Aim: increasing adherence	MEMS
USA	Mean age: 40 years; 34% female	Provider: healthcare professional	CG: Active control group: PE	
	Screened on detectable or increased viral load or initiating ART (DG)	Categorized as: counselling (MI)		
		Length: 2.3 hrs; Setting: individual		
Hersch, 2013 (51)	*N* = 168 PLWH	*eLifeSteps*	Aim: increasing adherence	MEMS
USA	Mean age:46 years; 24% female	Provider: computer	CG: WLC[p]	
	Screened on detectable viral load(DG)	Categorized as: CBT (CB, REL)		
		Length: 1 hour; Setting: individual		

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

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

Study	Population[a]	Intervention[b]	Study Design[c]	Outcome[d]
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		
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 ≥ 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 ≥ 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	*SMART Couples Support Study*	Aim: increasing adherence	MEMS
USA	seronegative partner (≥ 6 months)	Provider: nurse	CG: SC	
	Mean age: 42 years; 46% female	Categorized as: social support (CB)		
	Screened on ≤ 80% adherence (DG)	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[a]	Intervention[b]	Study Design[c]	Outcome[d]
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)**	
	Screened on initiating ART (RG)	Categorized as: counselling		
		Length: 1.5 hrs; Setting: individual		
Rosen, 2007 (67)	*N* = 56 PLWH	*Contingency Management and counselling*	Aim: increasing adherence	MEMS
USA	Mean age: 44 years; 41% female	Provider: psychologist	CG: Active control group:	
	Screened on ≤ 80% adherence (DG)	Categorized as: CBT (CB)	counselling	
		Length: NR; Setting: individual		
Safren, 2001 (68)	*N* = 56 PLWH	*Life-Steps: CBT for Adherence*	Aim: increasing adherence	ACTG, self-report, 14 days recall
USA	Mean age: 41 years; 13% female	Provider: healthcare professional	CG: SC	
	Screened on adherence problems (DG)	Categorized as: counselling (CB, MI)		
		Length: NR; Setting: individual		
Safren, 2009 (69)	*N* = 45 PLWH	*Life-Steps: CBT for Adherence*	Aim: improving health.	MEMS
USA	Mean age: NR; 16% female	Provider: psychologist	CG: Enhanced SC	
	Screened on mood disorder (RG)	Categorized as: CBT (CB, MI, REL)		
		Length: 9.2 hrs; Setting: individual		
Safren, 2012 (70)	*N* = 89 PLWH	*Life-Steps: CBT for Adherence*	Aim: improving health	MEMS
USA	Mean age: 47 years; 39% female	Provider: psychologist	CG: Enhanced SC	
	Screened on opioid dependence & mood disorder (RG)	Categorized as: CBT (CB, MI, REL)		
		Length: 7.5 hrs; Setting: individual		
Samet, 2005 (71)	*N* = 151 PLWH	*ADHERE – Motivational Interviewing*	Aim: increasing adherence	ACTG, self-report, 30 days recall
USA	Mean age: 43 years; 46% female	Provider: nurse	CG: SC	
	Screened on alcohol problems (RG)	Categorized as: counselling (MI)		
		Length: 2.4 hrs; Setting: individual		

Study	Population[a]	Intervention[b]	Study Design[c]	Outcome[d]
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	*Peer Support*	Aim: increasing adherence	MEMS
USA	Mean age: 43 years; 45% female	Provider: peer	CG: SC	
		Categorized as: peer support		
		Length: 6 hrs; Setting: group & individual		
Simoni, 2009 (73)	*N* = 114 PLWH	*Peer Support*	Aim: improving health	MEMS
USA	Mean age: 40 years; 24% female	Provider: peer	CG: SC	
	Screened on initiating or changing ART (RG)	Categorized as: peer support		
		Length: 6 hrs; Setting: group & individual		
Simoni, 2013 (74)	*N* = 40 PLWH of Mexican descent	*CBT for Depression & Life-Steps*	Aim: improving health	MEMS
USA	Mean age: 46 years; 28% female	Provider: psychologist	CG: SC	
	Screened on depressive complaints & non-adherence or detectable viral load (DG)	Categorized as: CBT (CB, MI, REL)		
		Length: 9.17 hrs; Setting: individual		
Sorensen, 2007 (75)	*N* = 66 PLWH	*Contingency Management and Counselling*	Aim: increasing adherence	MEMS
USA	Mean age: 43 years; 41% female	Provider: other (not specified)	CG: Active control group: counselling and reward	
	Screened on receiving methadone treatment and ≤ 80% adherence (DG)	Categorized as: CBT (CB)		
		Length: NR; Setting: individual		
Tuldra, 2000 (76)	*N* = 116 PLWH	*Psycho-educative Counselling*	Aim: increasing adherence	Self-report item, 30 days recall
Spain	Mean age: 39 years; 24% female	Provider: psychologist	CG: SC	
	Screened on initiating ART (RG)	Categorized as: counselling		
		Length: NR; Setting: individual		

Study	Population[a]	Intervention[b]	Study Design[c]	Outcome[d]
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)**	
Wagner, 2006 (77)	*N* = 230 PLWH	*CBT or CBT plus Adherence Practice Trial*	Aim: improving health	MEMS
USA	Mean age: 39 years; 20% female	Provider: nurse	CG: SC	
	Screened on adherence problems & initiating or changing ART (DG)	Categorized as: CBT (CB)		
		Length: 3.1 hrs; Setting: individual		
Wagner, 2013 (78)	*N* = 60 PLWH	*Adherence Readiness Program*	Aim: increasing adherence	MEMS
USA	Mean age: 39 years; 6% female	Provider: counsellor	CG: SC	
	Screened on initiating or changing ART (RG)	Categorized as: counselling (CB, MI)		
		Length: 3.5 hrs; Setting: individual		
Webel, 2010 (79)	*N* = 89, female and transgender (identifying female), PLWH	*Peer-Supported Self-management*	Aim: improving health	ACTG, self-report, 7 days recall
USA	Mean age: 47 years; 100% female	Provider: peer	CG: WLC	
		Categorized as: peer support (CB, REL)		
		Length: 14 hrs; Setting: group		
Weber, 2004 (80)	*N* = 60 PLWH	*CBT*	Aim: improving health	MEMS
Switzerland	Mean age: 41 years; 17% female	Provider: psychologist	CG: SC	
	Screened on detectable viral load (RG)	Categorized as: CBT (CB)		
		Length: 18.8 hrs; Setting: individual		
Williams, 2014 (81)	*N* = 110 PLWH	*Ai Sheng Nuo (Love, Life, Hope)*	Aim: increasing adherence	VAS, self-report, 30 days recall
China	Mean age: 38 years; 29% female	Provider: peer	CG: SC	
	Screened on ≤ 90% adherence and detectable viral load (DG)	Categorized as: counselling		
		Length: NR; Setting: individual		
Wyatt, 2004 (82)	*N* = 147, female, PLWH	*ESHI: Enhanced Sexual Health Intervention*	Aim: increasing adherence	Self-report item, 14 days recall
USA	Mean age: 41 years; 100% female	Provider: peer	CG: WLC	

Study	Population[a]	Intervention[b]	Study Design[c]	Outcome[d]
First author, year	**Randomized sample**	**Name**	**Study Aim**	**Measure type**
Country	**Mean age and % female**	**Provider**	**Control Group**	
	Screening and risk type (when	**Type and techniques used**	**Analysed sample (when**	
	applicable)	**Duration and setting**	**applicable)**	
	Screened on childhood sexual abuse	Categorized as: counselling (CB, REL)		
	history (RG)	Length: 27.5 hrs; Setting: group		

[a] Population. With *ART* = antiretroviral therapy, *CD4* = cluster of differentiation 4 (immune parameter), *DG* = difficulties group, *PLWH* = people living with HIV, *RG* = risk group.

[b] 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.

[c] Study design. With *CG* = control group, *SC* = standard care, *WLC* = waiting-list condition.

[d] 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.

[e] *NR* = not reported.

References

1. Bangsberg DR, Perry S, Charlebois ED, Clark RA, Roberston M, Zolopa AR, et al. Non-adherence to highly active antiretroviral therapy predicts progression to AIDS. AIDS. 2001;15(9):1181-3.
2. Günthard HF, Aberg JA, Eron JJ, et al. Antiretroviral treatment of adult hiv infection: 2014 recommendations of the international antiviral society–usa panel. JAMA. 2014;312(4):410-25.
3. Castilla J, Del Romero J, Hernando V, Marincovich B, García S, Rodríguez C. Effectiveness of highly active antiretroviral therapy in reducing heterosexual transmission of HIV. JAIDS Journal of Acquired Immune Deficiency Syndromes. 2005;40(1):96-101.
4. Kouanda S, Tougri H, Cissé M, Simporé J, Pietra V, Doulougou B, et al. Impact of maternal HAART on the prevention of mother-to-child transmission of HIV: results of an 18-month follow-up study in Ouagadougou, Burkina Faso. AIDS Care. 2010;22(7):843-50.
5. Moore RD, Chaisson RE. Natural history of HIV infection in the_era of combination antiretroviral therapy. AIDS. 1999;13(14):1933-42.
6. Nachega JB, Parienti JJ, Uthman OA, Gross R, Dowdy DW, Sax PE, et al. Lower Pill Burden and Once-Daily Antiretroviral Treatment Regimens for HIV Infection: A Meta-Analysis of Randomized Controlled Trials. Clin Infect Dis. 2014;58(9):1297-307.
7. Ortego C, Huedo-Medina TB, Llorca J, Sevilla L, Santos P, Rodríguez E, et al. Adherence to Highly Active Antiretroviral Therapy (HAART): A Meta-Analysis. AIDS Behav. 2011;15(7):1381-96.
8. Gonzalez JS, Batchelder AW, C P, Safren SA. Depression and HIV/AIDS treatment nonadherence: A review and meta-analysis. J Acquir Immune Defic Syndr. 2011;58:181-7.
9. Brinkley-Rubinstein L, Chadwick C, Graci M. The connection between serious life events, anti-retroviral adherence, and mental health among HIV-positive individuals in the Western Cape, South Africa. AIDS Care. 2013;25(12):1581-5.
10. Lucas GM. Substance abuse, adherence with antiretroviral therapy, and clinical outcomes among HIV-infected individuals. Life Sci. 2011;88(21-22):948-52.
11. Safren SA, Gershuny BS, Hendriksen E. Symptoms of posttraumatic stress and death anxiety in persons with HIV and medication adherence difficulties. AIDS Patient Care STDS. 2003;17(12):657-64.
12. Langebeek N, Gisolf EH, Reiss P, Vervoort SC, Hafsteinsdóttir TB, Richter C, et al. Predictors and correlates of adherence to combination antiretroviral therapy (ART) for chronic HIV infection: a meta-analysis. BMC Med. 2014;12(1):142.
13. Lowther K, Selman L, Harding R, Higginson IJ. Experience of persistent psychological symptoms and perceived stigma among people with HIV on antiretroviral therapy (ART): A systematic review. Int J Nurs Stud. 2014;51(8):1171-89.
14. Wagner GJ, Goggin K, Remien RH, Rosen MI, Simoni J, Bangsberg DR, et al. A closer look at depression and its relationship to HIV antiretroviral adherence. Ann Behav Med. 2011;42(3):352-60.
15. Wagner GJ, Ghosh-Dastidar B, Holloway IW, Kityo C, Mugyenyi P. Depression in the pathway of HIV antiretroviral effects on sexual risk behavior among patients in Uganda. AIDS Behav. 2012;16(7):1862-9.
16. Falagas ME, Zarkadoulia EA, Pliatsika PA, Panos G. Socioeconomic status (SES) as a determinant of adherence to treatment in HIV infected patients: a systematic review of the literature. Retrovirology. 2008;5(1):13.
17. Wise J, Operario D. Use of electronic reminder devices to improve adherence to antiretroviral therapy: a systematic review. AIDS Patient Care STDS. 2008;22(6):495-504.
18. Springer SA, Dushaj A, Azar MM. The impact of DSM-IV mental disorders on adherence to combination antiretroviral therapy among adult persons living with HIV/AIDS: a systematic review. AIDS Behav. 2012;16(8):2119-43.
19. Ruddy R, House A. Psychosocial interventions for conversion disorder. Cochrane Database of Systematic Reviews. 2005(4).
20. Hill S, Kavookjian J. Motivational interviewing as a behavioral intervention to increase HAART adherence in patients who are HIV-positive: a systematic review of the literature. AIDS Care. 2012;24(5):583-92.
21. Amico KR, Harman JJ, Johnson BT. Efficacy of antiretroviral therapy adherence interventions: a research synthesis of trials, 1996 to 2004. JAIDS Journal of Acquired Immune Deficiency Syndromes. 2006;41(3):285-97.
22. Simoni JM, Pearson CR, Pantalone DW, Marks G, Crepaz N. Efficacy of interventions in improving highly active antiretroviral therapy adherence and HIV-1 RNA viral load: a meta-analytic review of randomized controlled trials. Journal of acquired immune deficiency syndromes (1999). 2006;43(0 1):S23.
23. Sin NL, DiMatteo MR. Depression treatment enhances adherence to antiretroviral therapy: a meta-analysis. Ann Behav Med. 2014;47(3):259-69.
24. Charania MR, Marshall KJ, Lyles CM, Crepaz N, Kay LS, Koenig LJ, et al. Identification of evidence-based interventions for promoting HIV medication adherence: findings from a systematic review of US-based studies, 1996–2011. AIDS Behav. 2014;18(4):646-60.
25. Mathes T, Pieper D, Antoine SL, Eikermann M. Adherence-enhancing interventions for highly active antiretroviral therapy in HIV-infected patients–a systematic review. HIV Med. 2013;14(10):583-95.

26. Rueda S, Park-Wyllie LY, Bayoumi A, Tynan AM, Antoniou T, Rourke S, et al. Patient support and education for promoting adherence to highly active antiretroviral therapy for HIV/AIDS. Cochrane database of systematic reviews. 2006(3).
27. Landis JR, Koch GG. Measurement of observer agreement for categorical data. Biometrics. 1977;33(1):159-74.
28. Neuendorf KA. The content analysis guidebook. Thousand Oaks, CA: Sage; 2002.
29. Basso CR, Santa Helena ET, Caraciolo JMM, Paiva V, Nemes MIB. Exploring ART intake scenes in a human rights-based intervention to improve adherence: a randomized controlled trial. AIDS Behav. 2013;17(1):181-92.
30. Borenstein M, Hedges L, Higgins J, Rothstein H. Comprehensive meta-analysis 2.0. Englewood, NJ: Biostat. 2005.
31. Cohen J. Statistical power analyses for the behavioral sciences. Hillsdale New Jersey: Lawrence Erlbaum Associates. 1988.
32. Lipsey MW, Wilson DB. Practical meta-analysis: Sage Publications, Inc; 2001.
33. DiIorio C, McCarty F, Resnicow K, McDonnell Holstad M, Soet J, Yeager K, et al. Using motivational interviewing to promote adherence to antiretroviral medications: a randomized controlled study. AIDS Care. 2008;20(3):273-83.
34. Nyamathi A, Hanson AY, Salem BE, Sinha S, Ganguly KK, Leake B, et al. Impact of a rural village women (Asha) intervention on adherence to antiretroviral therapy in southern India. Nurs Res. 2012;61(5):353.
35. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557-60.
36. Duval S, Tweedie R. Trim and fill: a simple funnel-plot–based method of testing and adjusting for publication bias in meta-analysis. Biometrics. 2000;56(2):455-63.
37. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315(7109):629-34.
38. Margolin A, Avants SK, Warburton LA, Hawkins KA, Shi J. A randomized clinical trial of a manual-guided risk reduction intervention for HIV-positive injection drug users. Health Psychol. 2003;22(2):223.
39. Laska KM, Gurman AS, Wampold BE. Expanding the lens of evidence-based practice in psychotherapy: A common factors perspective. Psychotherapy. 2014;51(4):467.
40. Sangeda RZ, Mosha F, Prosperi M, Aboud S, Vercauteren J, Camacho RJ, et al. Pharmacy refill adherence outperforms self-reported methods in predicting HIV therapy outcome in resource-limited settings. BMC Public Health. 2014;14(1):1035.
41. Prejean J, Song R, Hernandez A, Ziebell R, Green T, Walker F, et al. Estimated HIV incidence in the United States, 2006–2009. PLoS One. 2011;6(8):e17502.
42. UNAIDS. Fact sheet 2014: Global statistics. Available at: http://www.unaids.org/sites/default/files/en/media/unaids/contentassets/documents/factsheet/2014/20140716_FactSheet_en.pdf. 2014.
43. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. Ann Intern Med. 2010;152(11):726-32.
44. Carrico AW, Antoni MH, Durán RE, Ironson G, Penedo F, Fletcher MA, et al. Reductions in depressed mood and denial coping during cognitive behavioral stress management with HIV-positive gay men treated with HAART. Ann Behav Med. 2006;31:155-64.
45. Chung MH, Richardson BA, Tapia K, Benki-Nugent S, Kiarie JN, Simoni JM, et al. A randomized controlled trial comparing the effects of counseling and alarm device on HAART adherence and virologic outcomes. PLoS Med. 2011;8(3):e1000422.
46. Claborn KR, Leffingwell TR, Miller MB, Meier E, Stephens JR. Pilot study examining the efficacy of an electronic intervention to promote HIV medication adherence. AIDS Care. 2014;26(3):404-9.
47. de Bruin M, Hospers HJ, van Breukelen GJ, Kok G, Koevoets WM, Prins JM. Electronic monitoring-based counseling to enhance adherence among HIV-infected patients: a randomized controlled trial. Health Psychol. 2010;29(4):421.
48. Duncan LG, Moskowitz JT, Neilands TB, Dilworth SE, Hecht FM, Johnson MO. Mindfulness-based stress reduction for HIV treatment side effects: a randomized, wait-list controlled trial. J Pain Symptom Manage. 2012;43(2):161-71.
49. Goggin K, Gerkovich MM, Williams KB, Banderas JW, Catley D, Berkley-Patton J, et al. A randomized controlled trial examining the efficacy of motivational counseling with observed therapy for antiretroviral therapy adherence. AIDS Behav. 2013;17(6):1992-2001.
50. Golin CE, Earp J, Tien H-C, Stewart P, Porter C, Howie L. A 2-arm, randomized, controlled trial of a motivational interviewing–based intervention to improve adherence to antiretroviral therapy (ART) among patients failing or initiating ART. Journal of acquired immune deficiency syndromes (1999). 2006;42(1):42.
51. Hersch RK, Cook RF, Billings DW, Kaplan S, Murray D, Safren S, et al. Test of a web-based program to improve adherence to HIV medications. AIDS Behav. 2013;17(9):2963-76.
52. Holstad MM, DiIorio C, Kelley ME, Resnicow K, Sharma S. Group motivational interviewing to promote adherence to antiretroviral medications and risk reduction behaviors in HIV infected women. AIDS Behav. 2011;15(5):885-96.
53. Holstad MM, Essien EJ, Ekong E, Higgins M, Teplinskiy I, Adewuyi MF. Motivational groups support adherence to antiretroviral therapy and use of risk reduction behaviors in HIV positive Nigerian women: a pilot study. Afr J Reprod Health. 2012;16(3).

54. Horvath KJ, Oakes JM, Rosser BS, Danilenko G, Vezina H, Amico KR, et al. Feasibility, acceptability and preliminary efficacy of an online peer-to-peer social support ART adherence intervention. AIDS Behav. 2013;17(6):2031-44.
55. Ingersoll KS, Farrell-Carnahan L, Cohen-Filipic J, Heckman CJ, Ceperich SD, Hettema J, et al. A pilot randomized clinical trial of two medication adherence and drug use interventions for HIV+ crack cocaine users. Drug Alcohol Depend. 2011;116(1-3):177-87.
56. Johnson MO, Charlebois E, Morin SF, Remien RH, Chesney MA, Team NHLP. Effects of a behavioral intervention on antiretroviral medication adherence among people living with HIV: the healthy living project randomized controlled study. Journal of acquired immune deficiency syndromes (1999). 2007;46(5):574.
57. Johnson MO, Dilworth SE, Taylor JM, Neilands TB. Improving coping skills for self-management of treatment side effects can reduce antiretroviral medication nonadherence among people living with HIV. Ann Behav Med. 2011;41(1):83-91.
58. Kalichman SC, Cherry C, Kalichman MO, Amaral CM, White D, Pope H, et al. Integrated behavioral intervention to improve HIV/AIDS treatment adherence and reduce HIV transmission. Am J Public Health. 2011;101(3):531-8.
59. Konkle-Parker DJ, Erlen JA, Dubbert PM, May W. Pilot testing of an HIV medication adherence intervention in a public clinic in the Deep South. J Am Acad Nurse Pract. 2012;24(8):488-98.
60. Konkle-Parker DJ, Amico KR, McKinney VE. Effects of an intervention addressing information, motivation, and behavioral skills on HIV care adherence in a southern clinic cohort. AIDS Care. 2014;26(6):674-83.
61. Kurth AE, Spielberg F, Cleland CM, Lambdin B, Bangsberg DR, Frick PA, et al. Computerized counseling reduces HIV-1 viral load and sexual transmission risk: findings from a randomized controlled trial. Journal of acquired immune deficiency syndromes (1999). 2014;65(5):611.
62. Murphy DA, Lu MC, Martin D, Hoffman D, Marelich WD. Results of a pilot intervention trial to improve antiretroviral adherence among HIV-positive patients. J Assoc Nurses AIDS Care. 2002;13(6):57-69.
63. Parsons JT, Golub SA, Rosof E, Holder C. Motivational interviewing and cognitive-behavioral intervention to improve HIV medication adherence among hazardous drinkers: a randomized controlled trial. Journal of acquired immune deficiency syndromes (1999). 2007;46(4):443.
64. Rathbun RC, Farmer KC, Stephens JR, Lockhart SM. Impact of an adherence clinic on behavioral outcomes and virologic response in treatment of HIV infection: a prospective, randomized, controlled pilot study. Clin Ther. 2005;27(2):199-209.
65. Remien RH, Stirratt MJ, Dolezal C, Dognin JS, Wagner GJ, Carballo-Dieguez A, et al. Couple-focused support to improve HIV medication adherence: a randomized controlled trial. AIDS. 2005;19(8):807-14.
66. Reynolds NR, Testa MA, Su M, Chesney MA, Neidig JL, Frank I, et al. Telephone support to improve antiretroviral medication adherence: a multisite, randomized controlled trial. JAIDS Journal of Acquired Immune Deficiency Syndromes. 2008;47(1):62-8.
67. Rosen MI, Dieckhaus K, McMahon TJ, Valdes B, Petry NM, Cramer J, et al. Improved adherence with contingency management. AIDS Patient Care STDS. 2007;21(1):30-40.
68. Safren SA, Otto MW, Worth JL, Salomon E, Johnson W, Mayer K, et al. Two strategies to increase adherence to HIV antiretroviral medication: life-steps and medication monitoring. Behav Res Ther. 2001;39(10):1151-62.
69. Safren SA, O'Cleirigh C, Tan JY, Raminani SR, Reilly LC, Otto MW, et al. A Randomized Controlled Trial of Cognitive Behavioral Therapy for Adherence and Depression (CBT-AD) in HIV-Infected Individuals. Health Psychol. 2009;28(1):1-10.
70. Safren SA, O'Cleirigh CM, Bullis JR, Otto MW, Stein MD, Pollack MH. Cognitive Behavioral Therapy for Adherence and Depression (CBT-AD) in HIV-Infected Injection Drug Users: A Randomized Controlled Trial. J Consult Clin Psychol. 2012;80(3):404-15.
71. Samet JH, Horton NJ, Meli S, Dukes K, Tripps T, Sullivan L, et al. A randomized controlled trial to enhance antiretroviral therapy adherence in patients with a history of alcohol problems. Antivir Ther. 2005;10(1):83-93.
72. Simoni JM, Pantalone DW, Plummer MD, Huang B. A randomized controlled trial of a peer support intervention targeting antiretroviral medication adherence and depressive symptomatology in HIV-positive men and women. Health Psychol. 2007;26(4):488-95.
73. Simoni JM, Huh D, Frick PA, Pearson CR, Andrasik MP, Dunbar PJ, et al. Peer support and pager messaging to promote antiretroviral modifying therapy in Seattle: a randomized controlled trial. Journal of acquired immune deficiency syndromes (1999). 2009;52(4):465-73.
74. Simoni JM, Wiebe JS, Sauceda JA, Huh D, Sanchez G, Longoria V, et al. A preliminary RCT of CBT-AD for adherence and depression among HIV-positive Latinos on the U.S.-Mexico border: the Nuevo Dia study. AIDS Behav. 2013;17(8):2816-29.
75. Sorensen JL, Haug NA, Delucchi KL, Gruber V, Kletter E, Batki SL, et al. Voucher reinforcement improves medication adherence in HIV-positive methadone patients: a randomized trial. Drug Alcohol Depend. 2007;88(1):54-63.
76. Tuldrà A, Fumaz CR, Ferrer MJ, Bayés R, Arnó A, Balagué M, et al. Prospective randomized two-arm controlled study to determine the efficacy of a specific intervention to improve long-term adherence to highly active antiretroviral therapy. Journal of acquired immune deficiency syndromes (1999). 2000;25(3):221-8.

77. Wagner GJ, Kanouse DE, Golinelli D, Miller LG, Daar ES, Witt MD, et al. Cognitive-behavioral intervention to enhance adherence to antiretroviral therapy: a randomized controlled trial (CCTG 578). AIDS. 2006;20(9):1295-302.
78. Wagner GJ, Lovely P, Schneider S. Pilot controlled trial of the adherence readiness program: an intervention to assess and sustain HIV antiretroviral adherence readiness. AIDS Behav. 2013;17(9):3059-65.
79. Webel AR. Testing a peer-based symptom management intervention for women living with HIV/AIDS. AIDS Care. 2010;22(9):1029-40.
80. Weber R, Christen L, Christen S, Tschopp S, Znoj H, Schneider C, et al. Effect of individual cognitive behaviour intervention on adherence to antiretroviral therapy: prospective randomized trial. Antivir Ther. 2004;9(1):85-96.
81. Williams AB, Wang H, Li X, Chen J, Li L, Fennie K. Efficacy of an evidence-based ARV adherence intervention in China. AIDS Patient Care STDS. 2014;28(8):411-7.
82. Wyatt GE, Longshore D, Chin D, Carmona JV, Loeb TB, Myers HF, et al. The efficacy of an integrated risk reduction intervention for HIV-positive women with child sexual abuse histories. AIDS Behav. 2004;8(4):453-62.