Patient Preference and Adherence

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REVIEW

Psychosocial predictors of non-adherence to chronic medication: systematic review of longitudinal studies

This article was published in the following Dove Press journal:
Patient Preference and Adherence
25 April 2014
Number of times this article has been viewed

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Objectives: Several cross-sectional studies suggest that psychosocial factors are associated with non-adherence to chronic preventive maintenance medication (CPMM); however, results from longitudinal associations have not yet been systematically summarized. Therefore, the objective of this study was to systematically synthesize evidence of longitudinal associations between psychosocial predictors and CPMM non-adherence.

Materials and methods: PUBMED, EMBASE, CINAHL, and PsychINFO databases were searched for studies meeting our inclusion criteria. The reference lists and the ISI Web of Knowledge of the included studies were checked. Studies were included if they had an English abstract, involved adult populations using CPMM living in Western countries, and if they investigated associations between psychosocial predictors and medication non-adherence using longitudinal designs. Data were extracted according to a literature-based extraction form. Study quality was independently judged by two researchers using a framework comprising six bias domains. Studies were considered to be of high quality if ≥four domains were free of bias. Psychosocial predictors for non-adherence were categorized into five pre-defined categories: beliefs/cognitions; coping styles; social influences and social support; personality traits; and psychosocial well-being. A qualitative best evidence synthesis was performed to synthesize evidence of longitudinal associations between psychosocial predictors and CPMM non-adherence.

Results: Of 4,732 initially-identified studies, 30 (low-quality) studies were included in the systematic review. The qualitative best evidence synthesis demonstrated limited evidence for absence of a longitudinal association between CPMM non-adherence and the psychosocial categories. The strength of evidence for the review's findings is limited by the low quality of included studies.

Conclusion: The results do not provide psychosocial targets for the development of new interventions in clinical practice. This review clearly demonstrates the need for high-quality, longitudinal research to identify psychosocial predictors of medication non-adherence.

Keywords: medication adherence, psychosocial factors, systematic review, longitudinal studies, somatic and chronic diseases

Introduction

In conditions such as rheumatoid arthritis, diabetes, and hypertension, long-term therapy with chronic preventive maintenance medication (CPMM) is essential for reducing risks of disease progression, comorbidity, and mortality. However, sufficient medication adherence to CPMM is a prerequisite for reducing these risks.[1]

Medication non-adherence, or the extent to which patients do not take their medications as agreed with their health care provider, averages 50% among patients suffering from chronic diseases in developed countries.[2] Non-adherence can result in poorer

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Dovepress
http://dx.doi.org/10.2147/PPA.S47290

health outcomes and a lower quality of life in patients.[3] For example, patients who did not adhere to beta-blocker therapy were four and a half times more likely to have complications from coronary heart disease than those who adhered to therapy.[4] Non-adherence also affects health care utilization. For instance, poorer adherence among elderly patients with moderate-to-severe asthma was associated with a 5% increase in annual physician visits, whereas better adherence was associated with a 20% decrease in annual hospitalization.[5]

Considering the undesired consequences of non-adherence to CPMM, interventions are needed to improve medication non-adherence. According to the World Health Organization (WHO), possible targets for these interventions can be divided into five domains:[2] socio-economic factors, health care system factors, condition-related factors, therapy-related factors, and patient-related factors. Although none of the factors within these domains are consistently associated with non-adherence across conditions, some tend to be better predictors of non-adherence than others (like poverty, the nature of the disease, and side-effects).[1,2] Also, psychosocial factors like beliefs about medication, self-efficacy, and social support can be promising intervention targets. These are mostly modifiable (in contrast to factors like poverty or side-effects), and according to reviews of cross-sectional studies, they appear to be associated with non-adherence in various somatic, chronic conditions.[6–13] Beliefs about medication were the most powerful predictors of adherence (among demographic and medical factors) in one cross-sectional study,[9] while another cross-sectional study identified low-self-efficacy as a significant predictor of non-adherence across different countries, for example.[11] However, there is no insight into psychosocial factors predicting non-adherence in longitudinal studies with a longer follow-up period (≥3 months). Such knowledge would be helpful in designing effective adherence interventions in clinical practice.

This is the first review which aims to systematically synthesize evidence of longitudinal associations between psychosocial predictors and CPMM non-adherence across adult patients living in Western countries. Since non-adherence literature is scattered across diseases,[14] we combined studies from various somatic, chronic conditions to increase the robustness of our findings.

Methods

PRISMA-guidelines were followed in performing this systematic review.[15] The steps taken regarding data searches, study selection, data extraction, study quality assessment, data synthesis, and data analyses are elaborated below.

Data sources and searches

In March 2011, according to a pre-defined search strategy, four electronic databases (PUBMED, EMBASE, CINAHL, and PsychINFO) were searched for studies up to February 2011. With this search, a first set of studies was included, the reference lists of these studies were hand searched to find additional studies. The studies were also entered into the ISI Web of Knowledge citation index (August 2011). The resulting list of studies, citing one of the initial included studies in our review, was also searched.

The search strategy (see Supplementary Materials) contains key words on medication adherence, chronic, somatic diseases, adults, longitudinal designs, and Western countries. Countries in Africa, Latin-America, South-America, Asia (excluding Indonesia and Japan), and Turkey were considered as non-Western according to Statistics Netherlands.[16] Non-Western countries were excluded because underlying mechanisms of medication non-adherence could differ from those in Western countries due to socio-economic and cultural differences.[17]

In this review, we focused on two of the three components of adherence (ie, on initiation and implementation adherence, thus the extent to which a patient's actual medication dosing regimen corresponds with the prescribed dosing regimen from initiation to last dose). We did not include discontinuation of medication.[1]

As using CPMM terms in the search strategy was unfeasible, we used the corresponding diseases for which the CPMMs were prescribed as search terms instead. The disease terms were selected as follows:

1. Chronic preventive maintenance medications were defined. CPMMs were regarded as drugs that 1) are intended to be used chronically to prevent the occurrence or worsening of a disease or its complications; and 2) may have an immediate effect, but must also have a long-term effect (>3 months).
2. From the full November 2010 Anatomical Therapeutic Chemical Classification System (ATC)-7 medication list of drugs available in the Netherlands, 246 CPMMs (Supplementary Materials) were independently selected by two pharmacists (BvdB and VH). There was an initial agreement of 96% on medications being CPMM. Disagreements were resolved by discussion between the pharmacists.
3. Disease indications for the 246 CPMMs were subsequently clustered by BvdB according to the International Classification of Diseases (WHO). Finally, 20 disease terms were used in the search strategy.

Table 1 Inclusion and exclusion criteria

Domain	Inclusion criteria	Exclusion criteria
Study population	Study population ≥18 years, living in a Western country and using chronic preventive maintenance medication for one or more somatic, chronic condition as specified in the search strategy	Studies exclusively recruiting subpopulations in special conditions, like alcohol addicts, prisoners, pregnant women*
Study types	Longitudinal retrospective or prospective study design, at least examining associations between predictor 'X' measured at baseline and outcome 'Y' measured ≥3 months after baseline†	Study is cross-sectional, controlled trial, case report, (systematic) review, meta-analysis, editorial, letter, comment, interview, newspaper article, case-control study, intervention study, thesis* or validation study*
Outcome measure	Medication non-adherence is (one of) the primary outcomes of the study. All adherence instruments (eg, different questionnaires, refill data, MEMS) are eligible for inclusion	Outcome is discontinuation of medication
Psychosocial predictors	Psychosocial predictors are defined as predictors, pertaining to the influence of social factors on an individual's mind or behavior, and to the interrelation of behavioral and social factors[18] The term psychosocial also covers internal, psychological predictors (eg, anxiety) in this systematic review. All predictor instruments (eg, different questionnaires/scales) are eligible for inclusion	Predictors measuring addiction to stimulating agents, psychosocial co-morbidity (eg, diagnosed depression according to DSM-IV criteria, and cognitive impairment. Illness symptoms, however, like depressive mood states and anxiety, are included in the review), socio-demographics, knowledge, cognitive status, behavior, satisfaction about treatment and health care, overall outcome measures (eg, social functioning of patient, general health status, perceived quality of life, behavioral intentions), predictors outside perception of individual patient (eg, beliefs of physicians)* In addition, predictors for which it was unclear what they measured (eg, 'HIV-mastery'[19] or 'coping' without specifying the type of coping), predictors for which results had not been reported in studies*
Other	English abstract available‡	No English abstract available, unpublished studies which could not be retrieved after substantial efforts

Notes: *These criteria were formulated during the selection process. We did not exclude subpopulations based on socio-demographic features. Veterans or government employees, for example, are not in a special condition per se; †when the outcome is measured multiple times after baseline, and one summary measure over the total, observational time after baseline is calculated, than the observational time should be at least 6 months. For example, studies measuring daily adherence for 3 months after baseline and calculating one summary adherence measure for a patient over these 3 months are excluded, because the mean time point of the summary adherence measure is 1.5 months after baseline; ‡please note that studies of all languages are eligible, but at least an English abstract should be available.

Abbreviations: DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision; HIV, human immunodeficiency virus; MEMS, medication event monitoring System.

Table 2 Study characteristics and results*

First author	Setting	Sample characteristics		
		Sample size, % loss to follow-up	Age†, % female	Disease duration†
Asthma (inhaled corticosteroids)				
Ponieman[33]	USA; patients from general internal medicine clinic	261, 23%	48 (13), 82%	Age of onset ≤20 years: 50% of sample
Diabetes (oral and/or parenteral antidiabetics)				
Venturini[34,††]	USA; patients from HMO-providing health services	786, 0%	59 (mean), 24–92 (range), 49%	NR
Heart disease and hypertension (cardiovascular medication)				
Gazmararian[35]	USA; community-dwelling patients‡‡	1,549, UD	Age: 65–69: 35%, 70–74: 28%, 75–79: 20%, 80–84: 12%, >84: 6%, (female): 58%	UD
Nabi[26]	Finland; local government employees	1,021, UD	26–63 (range), 32%	0–2 years: n=311 2–5 years: n=222 5–10 years: n=292 >10 years: n=196
Grégoire[36]	Canada; hypertensive adults with prescriptions from network of pharmacies	692, 26%	59 (13), 56%	47 months (adherent group), 44 months (non-adherent group)
Miller[37]	Site not reported: patients from institutions providing cardiac rehabilitation programs¶¶	141, 21%	56 (mean), 32–70 (range), 22%	NR
Molloy[38]	UK; patients admitted to hospitals with acute coronary syndrome¶¶	295, 11%	61 (mean), 32–87 (range), 23%	0 years (acute)
HIV (antiretroviral medication)				
Deschamps[25]	Belgium; outpatients at university hospital	60, 28%	43 (9) adherent group, 41 (8) non-adherent group, 16%	NR
Holmes[19]	USA; HIV-clinic patients	116, 0%§§	44 (median), 25–69 (range), 19%	5 years (median)
Delgado[39]	Canada; patients enrolled in community drug treatment program	316, 0%	NR, NR	NR
Singh[40]	USA; new, veteran patients seen at medical center	52, 12%	40 (median), 23–68 (range), 0%	NR
Singh[41]	Site not reported: patients in HIV-medical centers	138, 11%	41 (median), 24–71 (range), 7%	NR (but 7% therapy-naive)
Bottonari[42]	USA; patients treated in immunodeficiency clinic	78, 69%	36 (7), 4%	NR
Godin[43]	Canada; patients from medical HIV-clinics	400, 6%	43 (8), 4%	>5 years HIV-infected: 73%

Measures and results			
Adherence‡, follow-up period§	**Psychosocial category, number of predictors‖**	**Association present between category and adherence/non-adherence?¶**	**Number domains bias free****
Self-report (MARS), 3 months	AI, n=5 AIII, n=3	No (U: yes, M: no) No (U: no, M: no)	0 of 6
Record review, last time point flexible, but within 24 months	EI, n=1	No (U: NR, M: no)	2 of 6
Record review, 12 months	CIII, n=1	No (U: no, M: NT)	3 of 6
Record review, 12 months	D, n=4 EI, n=2	Yes (U: no, M: yes) No (U: no, M: NT)	1 of 6
Self-report (Morisky scale), 3 months	AI, n=1 AII, n=5 CIII, n=1	No (U: no, M: no) No (U: no, M: no) No (U: no, M: no)	0 of 6
Self-report (HBS), 6–9 months	AI, n=1 CII, n=1	No (U: NR, M: no) No (U: NR, M: no)	0 of 6
Self-report, 12 months	CIII, n=2	No (U: no, M: no)	1 of 6
MEMS, 5–6 months after measuring psychosocial constructs	AI, n=3 AIII, n=1 BI, n=3 BII, n=4 CIII, n=2 D, n=1 EI, n=2	No (U: no, M: NR) No (U: no, M: NR) No (U: no, M: NR) No (U: no, M: NR) No (U: no, M: NR) No (U: no, M: NR) No (U: no, M: NR)	1 of 6
MEMS, 12 months (or when viral load of ≥1,000 copies/mL was reached)	AI, n=1 AII, n=2 CI, n=1 CIII, n=1 EI, n=1 EII, n=1	No (U: no, M: no) No (U: no, M: no) No (U: no, M: NT) No (U: no, M: NT) No (U: no, M: no) No (U: no, M: no)	2 of 6
Record review, 12 months	EI, n=1	No (U: yes, M: no)	1 of 6
Record review, 6 months	BII, n=1 CIII, n=2 EI, n=4	No (U: no, M: no) No (U: no, M: no) No (U: no, M: no)	1 of 6
Record review, 6 months	BI, n=3 BII, n=6 CIII, n=4 EI, n=1	No (U: no, M: NR) No (U: no, M: NR) No (U: no, M: NR) No (U: no, M: NR)	1 of 6
Self-report (straightforward), 6–9 months	D, n=2 EI, n=1 EII, n=3	No (U: no, M: NR) No: (U: no, M: NR) No: (U: no, M: NR)	0 of 6
Self-report (straightforward), 12 months	AI, n=1 AIII, n=2 CI, n=1 CIII, n=1 D, n=1	Yes (U: NR, M: yes) No (U: NR, M: no) No (U: NR, M: no) No (U: NR, M: no) No (U: NR, M: no)	1 of 6

(*Continued*)

Table 2 (*Continued*)

First author	Setting	Sample characteristics		
		Sample size, % loss to follow-up	Age†, % female	Disease duration†
Kacanek[44]	USA; patients recruited by media and physician networks	225, 0%	45 (7), 23%	NR
Martini[45]	Italy; outpatients using combination therapy¶¶	214, 71%	<30: 13%, 30–39: 56%, >39: 31%, (female): 36%	NR
Mellins[46]	USA; HIV-infected mothers recruited in waiting room of adult clinic	128, 25%	38 (mean), 22–66 (range), 100%	5 years
Nilsson Schönnesson[47]	Sweden; patients recruited by clinic nurses	203, 29%	45 (9), 22%	Mean year of diagnosis =1990
Thrasher[48]	USA; patients in public use of HCSUS data set	1,911, 33%§§	Minority versus non-minority: <35: 35% minority group, 30% non-minority group. % female: 33% versus 12%, respectively	Mean year first diagnosed with HIV: 1992, minority group; 1990, non-minority group
Horne[49]	UK; outpatients, eligible to receive HAART	136, 14%	38 (9), NR	5 years
Mugavero[50]	USA; patients receiving care at infectious disease clinics	474, 39%	40 (median), 35–46 (IQR), 29%	NR
Carrieri[51]	France; patients starting HAART-regimen	1,110, 13%	37 (median), 22%	First time since first positive HIV-test in years: 3.8 (median), 0.5–8.2 (IQR)
Transplant-related (immunosuppressant medication)				
Stilley[52]	USA; transplant patients, recruited before hospital discharge or at early clinic visit	152, 29%	55 (10), 33%	NR
De Geest[53]	Belgium; convenience sample of outpatients	101, 0%	56 (median), 20–69 (range), 13%	3 (median), 1–6 (range) years since transplantation
Russell[54]	USA; convenience sample of renal transplant patients	50, 26%	60 (5), 38%	NR
Weng[55]	USA; patients recruited at time of renal transplantation	829, 66%	48 (median), 39–57 (IQR), 39%	NR
Dew[56]	USA; heart transplant patients from academic hospital‖‖	108, 22%	<50 years: 49%, (female): 16%	NR
Dew[57]	USA; patients receiving first lung transplantation in academic hospital	178, 29%	37% <50 years, (female): 48%	NR

Measures and results			
Adherence‡, follow-up period§	**Psychosocial category, number of predictors‖**	**Association present between category and adherence/non-adherence?¶**	**Number domains bias free****
Self-report (straightforward); maximum 30 months	EI, n=1	Yes (U: yes, M: NT)	2 of 6
Self-report (straightforward); 12 months	AI, n=2	No (U: no, M: NR)	0 of 6
	CI, n=1	Yes (U: yes, M: NR)	
Self-report (AACTG, straightforward), T1 after 4–5 months, T2 8–18 months after T1	AIII, n=1	No (U: no, M: NR)	0 of 6
	EI, n=1	No (U: no, M: NR)	
	EII, n=2	Yes (U: yes, M: NR)	
Self-report (straightforward), 24 months	AI, n=3	No (U: NR, M: no)	1 of 6
	AII, n=1	No (U: NR, M: no)	
	AIII, n=2	No (U: NR, M: no)	
	BII, n=2	No (U: NR, M: no)	
	CI, n=1	No (U: NR, M: no)	
	CIII, n=2	No (U: NR, M: no)	
	D, n=1	No (U: NR, M: no)	
	EI, n=3	No (U: NR, M: no)	
	EII, n=1	No (U: NR, M: no)	
Self-report (straightforward), 12 months	CIII, n=1	No (U: no, M: NR)	1 of 6
	EI, n=2	Yes (U: yes, M: NR)	
Self-report (straightforward), 12 months	AI, n=2	Yes (U: yes, M: yes)	3 of 6
	EI, n=1	No (U: no, M: NT)	
Self-report (AACTG, straightforward), 27 months	EII, n=4	No (U: yes, M: no)	3 of 6
Self-report (AACTG, straightforward), 60 months	CII, n=1	Yes (U: yes, M: yes)	2 of 6
	EI, n=1	Yes (U: yes, M: yes)	
MEMS, 6 months	BI, n=1	No (U: no, M: NR)	1 of 6
	CII, n=1	No (U: no, M: NR)	
	D, n=2	No (U: no, M: NR)	
	EI, n=1	No (U: no, M: NR)	
MEMS, 6 months	AIII, n=1	Yes (U: NR, M: yes)	2 of 6
	CIII, n=1	No (U: NR, M: no)	
	EI, n=1	No (U: NR, M: no)	
	EII, n=1	No (U: NR, M: no)	
MEMS, 12 months	AIII, n=1	No (U: no, M: NR)	0 of 6
	CIII, n=1	No (U: no, M: NR)	
	EI, n=2	No (U: no, M: NR)	
MEMS, 12 months post-transplantation	AIII, n=1	No (U: yes, M: no)	2 of 6
	CII, n=1	No (U: no, M: NT)	
	EI, n=1	No (U: no, M: NT)	
	EII, n=1	No (U: no, M: NT)	
Self-report (straightforward), 12 months post-transplantation	AIII, n=1	No (U: no, M: NT)	2 of 6
	BI, n=2	No (U: no, M: NT)	
	BII, n=1	Yes (U: yes, M: yes)	
	CII, n=2	No (U: no, M: no)	
	EI, n=3	No (U: no, M: no)	
Self-report (straightforward), 24 months	AIII, n=3	No (U: yes***, M: no)	1 of 6
	CII, n=2	No (U: yes, M: no)	
	D, n=1	No (U: yes, M: no)	
	EI, n=3	No (U: yes, M: no)	

(*Continued*)

Table 2 (*Continued*)

First author	Setting	Sample characteristics		
		Sample size, % loss to follow-up	Age†, % female	Disease duration†
Dobbels[58]	Belgium; heart, liver and lung transplant patients listed at university hospitals	186, 24%	52 (12), 33%	NR
Other (diabetes and/or hypertension and/or heart disease)				
DiMatteo[59]	USA; patients from five medical specialties in HMOs, large multispecialty groups or solo practices‡‡,¶¶	Max 1,828, UD	60 (8), 54%	NR

Notes: *NS (non significant): as reported in the concerning study. UD (undetermined): because of inadequate description in the concerning study; †mean (and for age: standard deviation) in years reported unless indicated otherwise; ‡with straightforward, we mean that participants were directly asked to indicate how many medication doses they missed. For example: "How many pills did you take this week?"; §follow-up period = number of months between baseline (unless indicated otherwise) and last adherence measurement; ||this column shows the number of psychosocial predictors measured in the concerning study, and the assigned psychosocial category. Details about the single predictors are presented in Table S2. A = Beliefs and cognitions about I) medication and treatment; II) illness; III) self-efficacy and locus of control. B = coping styles I) task oriented, II) emotion oriented. C = Social influences and social support I) regarding medical caregiver; II) regarding friends and family; III) in general. D = personality traits. E = psychological well-being: I) mood state; II) perceived stress/stressors; ¶no = no significant association between psychosocial category and medication adherence/non-adherence within study when $P \leq 0.05$; Yes = significant association when $P \leq 0.05$; U: univariate; M: multivariate; **to determine methodological quality, six bias domains per study were judged. Here, the total amount of bias free domains is reported (for further details, see Table S3); ††retrospective design; ‡‡diagnosis for coronary heart disease, hypertension, diabetes mellitus, and/or hyperlipidemia; §§% loss to follow-up assumed by HZ/BvdB; ||||type of medication is immunosuppressants, antihypertensives, and/or antivirals; ¶¶use of chronic preventive medication assumed; ***significance of $P \leq 0.05$ assumed by HZ/BvdB.

Abbreviations: AACTG, adult AIDS clinical trials group; HAART, highly active antiretroviral therapy; HBS, health behavior scale; HCSUS, HIV cost and services utilization study; HIV, human immunodeficiency virus; HMO, health maintenance organization; IQR, interquartile range; MARS, medication adherence report scale; MEMS, medication event monitoring system; NR, not reported; NS, non significant; NT, not tested; UD, undetermined.

Study selection

Studies were selected based on the criteria in Table 1.

Studies exclusively recruiting subpopulations in special conditions (like prisoners, pregnant women) were excluded. Their results only pertain to a specific group of patients, therefore, including them might have introduced bias into this systematic review.

Two reviewers (BvdB and HZ) independently assessed studies for eligibility in two phases: 1) screening based on title and abstract; and 2) screening based on full text. Disagreements between BvdB and HZ were resolved by discussion; a third reviewer (CvdE) made decisions in case disagreements could not be resolved. Studies in Spanish or Portuguese were judged by LvdA. During the study selection process, three authors were contacted about statistics, outcome measure, or study design to determine eligibility for this review.[20–22]

Data extraction and quality assessment

For data extraction, a literature-based, standard form was developed.[23,24] Information regarding study setting, design, descriptive statistics, measures, and analysis were extracted by HZ; BvdB arbitrarily selected 15% of the included studies to check appropriateness of all extracted data of these studies, and also checked all doubts indicated on the form by HZ.

If multiple adherence measures were presented in one study (eg, about dosing, timing, or taking medication)[25], we only extracted data about taking medication. Two authors were contacted during the extraction process to check the duration of a follow-up period of ≥3 months[26] or to explain ambiguities.[19]

We adapted the framework developed by Hayden et al[27] to judge methodologic study quality. Our framework contained 23 items divided into six bias domains: study participation, study attrition, prognostic, outcome and confounding measurement, and analyses. Each item was scored as 'yes' (no unacceptable amount of bias introduced), 'partly' (/unsure), and 'no' (unacceptable amount of bias introduced). For every bias domain, a transparent method was used to reach overall judgment about the presence or absence of bias (see Table S1). Studies with ≥four domains judged as 'yes' were considered high-quality studies; studies with <four domains were considered low-quality studies.

Using three randomly selected studies not included in the review, the framework was piloted by BvdB and HZ, who also performed the actual quality assessment. Disagreements were resolved by discussion and, when necessary, a third reviewer (CvdE) made final decisions. On the domain level, a weighted extent of agreement between BvdB and HZ (quadratic weighting scheme) was calculated due to the ordinal nature of the scores.[28,29]

Data synthesis and analysis

Because over 70 non-identical psychosocial predictors (non-identical by name and/or measurement instrument) were studied in this review, and because of the variety of instruments used to measure non-adherence, a qualitative instead

Measures and results			
Adherence‡, follow-up period§	**Psychosocial category, number of predictors‖**	**Association present between category and adherence/non-adherence?¶**	**Number domains bias free****
Self-report (straightforward), 12 months post-transplantation	CIII, n=2	No (U: NR, M: no)	1 of 6
	D, n=5	No (U: NR, M: no)	
	EI, n=2	No (U: NR, M: no)	
Self-report (straightforward), 24 months	BII, n=1	No (U: NR, M: no)	0 of 6
	CI, n=2	No (U: NR, M: no)	
	CIII, n=1	No (U: NR, M: no)	
	EII, n=1	Yes (U: NR, M: yes)	

of a quantitative analysis was considered to be appropriate.[30] Therefore, the results regarding associations between psychosocial predictors and medication non-adherence were qualitatively synthesized in four steps.

In step 1, psychosocial categories were formulated. Initially, all psychosocial elements as mentioned in general health behavior models and theories[31,32] were listed (HZ). Subsequently, based on consensus, the elements were clustered by HZ and three psychologists (SvD, JV, and LK) resulting in the categories of Figure 1.

Next, the psychosocial predictors within the studies of the review were assigned to one of the categories in Figure 1 (HZ and the psychologists). In this way, the considerable number of single, non-identical predictors was dealt with.

In step 2, for each psychosocial predictor within a category and within a study, the presence of a significant univariate and multivariate association with medication non-adherence was determined (see Table S2). Statistical significance was set at $P<0.05$.

In step 3, results within studies were synthesized per psychosocial category. When ≥75% of variables within a single psychosocial category were significantly and consistently (ie, same predictors in same direction) associated with non-adherence, a 'yes' was assigned (ie, association present). When ≥75% of variables were significantly, but inconsistently, associated (eg, four of five predictors in category about depressive symptoms, of which two are positively related to non-adherence and two are negatively related), the term 'conflicting' was assigned. When <75% of variables were significantly and consistently associated, a 'no' was assigned. Multivariate results were preferably used to synthesize results in this step. When multivariate results were not reported, univariate results were used.

In the fourth and final step, a best evidence synthesis (BES) per psychosocial category between studies was performed to summarize evidence of longitudinal associations between the predictors in the psychosocial

A. Beliefs and cognitions
- I About medication and treatment
- II About illness
- III Regarding self-efficacy and locus of control

B. Coping styles
- I Task-oriented
- II Emotion-oriented

C. Social influences and social support
- I Regarding medical caregiver
- II Regarding friends and family
- III In general

D. Personality traits

E. Psychosocial well-being
- I Mood state
- II Perceived stress(ors)

Figure 1 Psychosocial categories.

categories and medication non-adherence. We defined four levels of evidence as used in previous reviews of longitudinal studies:[60–62]

1. Strong evidence: consistent findings (≥75% of studies within psychosocial category report same conclusion about association; ie, 'yes, present' or 'no, not present') in at least two high-quality studies.
2. Moderate evidence: consistent findings in one high-quality study AND at least two low-quality studies.
3. Limited evidence: findings in one high-quality study OR consistent findings in at least two low-quality studies.
4. Conflicting evidence: inconsistent findings in at least two studies irrespective of study quality (ie, <75% of studies report same conclusion about association). Note that this level of evidence was checked first before assigning strong, moderate or limited evidence level to a category.

The level of evidence was undeterminable when ≤one study of low quality was available for a psychosocial category.

Sensitivity analyses were performed to examine the robustness of findings, regarding the cut-off point for methodological quality, diseases, adherence measurement, and statistical analyses (ie, focusing on univariate analyses only). Also, an additional analysis on single predictors was carried out, since associations between single predictors like 'avoidance coping' and non-adherence could be overshadowed by combining them into a single category with generally non-significant psychosocial predictors, such as hopelessness and confusion. Three steps were taken: 1) all significant predictors ($P \leq 0.05$) were listed; 2) each of these predictors was grouped with identically named, significant and non-significant predictors; and 3) when at least two studies were available for those predictors, the BES rules were applied.

Results

Study inclusion

Of 4,732 non-duplicate references, 30 met our inclusion criteria (Figure 2).[19,25,26,33–59] In all, 1,255 records were identified by screening the reference lists and the ISI Web of Knowledge citation index of the initial included studies.

Initially, the percentage of agreement regarding the eligibility of studies was 86% (of the 272 studies selected on title and abstract, agreement was obtained in about 235 studies after reading the full-text). Disagreements were mainly due to misconceptions about psychosocial predictors (eg, clinically diagnosed depression versus symptoms of depression), study design, and adherence measure (ie, discontinuation or execution adherence). For one study,[52] disagreement could not be resolved by discussion and thus a final decision was made by CvdE.

Study characteristics and quality assessment

Table 2 displays study characteristics, measures, and results. A comprehensive table of measures and results is presented in Table S2.

The included studies (all based on different data sets) covered CPMMs for asthma, diabetes, heart diseases/hypertension, human immunodeficiency virus (HIV), and organ transplants. Medication type was not explicitly mentioned in four studies,[37,38,45,59] but we assumed CPMM was used since CPMM is the standard medical treatment for the 20 selected diseases in this review. In most studies, patients were recruited from medical clinics or hospitals and the sample size ranged from 50–1,911. Attrition rates varied from 0%–71%. Participants were predominantly men and often ≥37 years of age and a disease duration of >2 years. The observation period between baseline and last adherence measurement was ≥3 and <12 months in ten studies and ≥12 months in 20 studies, with a maximum of 60 months. Medication adherence was mostly measured by self-report (18 studies, predominantly questionnaires); seven studies used a validated adherence questionnaire.[33,36,43,46,49–51] Other adherence measurements were carried out by reviewing medical records or the medication event monitoring system (MEMS). In 15 studies, both univariate and multivariate analyses were reported.

All 30 included studies were judged to be 'low-quality' (Table S3). This was mainly due to poor descriptions and/or bias regarding the study sample, the use of non-validated questionnaires, the lack of accounting for confounding variables, and a poor description of the data analyses. Most studies, moreover, did not appropriately describe actions taken in case of missing data.

A total of 180 bias domains were judged (30 studies by six domains). Initially, BvdB and HZ fully agreed on 78 domains, partially agreed (ie, 'partly' versus 'no' or 'partly' versus 'yes') on 79 domains and fully disagreed (eg, 'yes' versus 'no') on 23 domains, resulting in a weighted agreement of 76%. Disagreements were caused by poor description of methods, different interpretations of missing data, differences in calculating study attrition rates, and different interpretations regarding the appropriateness of study sample descriptions. On this latter point, disagreements about three studies[35,48,52] could not be resolved by discussion between BvdB and HZ and, thus, CvdE made the final decision.

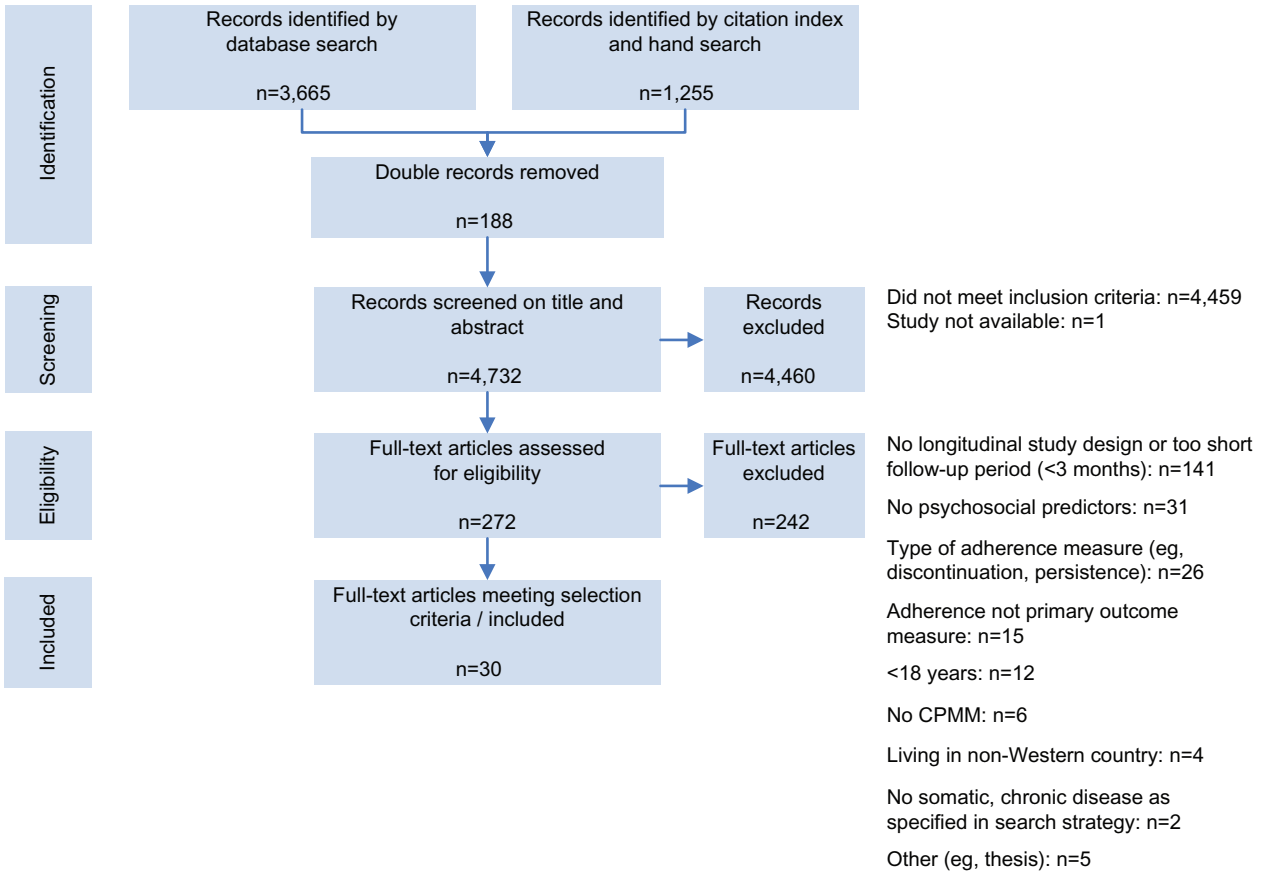

Figure 2 Flowchart of study inclusion process.
Abbreviation: CPMM, chronic preventive maintenance medication.

Best evidence synthesis

Table 3 shows there is limited evidence for the absence of a longitudinal association with medication non-adherence in all of the eleven psychosocial subcategories.

Beliefs and cognitions

Regarding category AI (beliefs and cognitions about medication and treatment), two of nine studies found a longitudinal, multivariate association between having a positive attitude towards taking medication and adherence (odds ratio [OR] =1.56, 95% confidence interval [CI] 1.18, 2.06),[43] and between necessity beliefs and concern beliefs about medication and adherence (OR =2.19, 95% CI 1.02, 4.71 and OR =0.45, 95% CI 0.22, 0.96, respectively).[49] One other study[33] found univariate associations between necessity and concern beliefs about medication and adherence, but these associations did not hold in the multivariate analysis.

One study demonstrated a longitudinal, multivariate association between low self-efficacy and medication non-adherence;[53] however, the effect size was small. Univariate, but not multivariate associations between self-efficacy and adherence were demonstrated in two studies.[55,57]

Coping styles

No univariate and multivariate associations were found between the task-oriented coping style category and medication adherence.

Regarding emotion-oriented coping styles, one of six studies revealed a multivariate association with non-adherence (eg, OR of 9.71 for avoidance coping).[56] Furthermore, avoidance coping as a single predictor was associated with non-adherence in three of four studies measuring this construct.[25,40,56]

Social influences and social support

Two of the 25 studies demonstrated significant associations between predictors within the category social influences and social support and (non-)adherence, but only one of these studies reported on a multivariate association between having support from a partner and non-adherence (regression coefficient =–0.15, 95% CI –0.25, –0.05).[51] Receiving practical social support was associated with better adherence as a single predictor.[38,41]

Table 3 Level of evidence for longitudinal associations between psychosocial categories and medication non-adherence

Psychosocial category	N of studies	Quality	Longitudinal association	Level of evidence
A. Beliefs and cognitions				
I. About medication and treatment	9	All low	2 × yes[43,49] 7 × no[19,25,33,36,37,45,47]	No association (limited evidence)
II. About illness	3	All low	3 × no[19,36,47]	No association (limited evidence)
III. Self-efficacy and locus of control	10	All low	1 × yes[53] 9 × no[25,33,43,46,47,54–56,57]	No association (limited evidence)
B. Coping styles				
I. Task-oriented	4	All low	4 × no[25,41,52,56]	No association (limited evidence)
II. Emotion-oriented	6	All low	1 × yes[56] 5 × no[25,40,41,47,59]	No association (limited evidence)
C. Social influences and social support				
I. Regarding medical caregiver	5	All low	1 × yes[45] 4 × no[19,43,47,59]	No association (limited evidence)
II. Regarding friends and family	6	All low	1 × yes[51] 5 × no[37,52,55–57]	No association (limited evidence)
III. In general	14	All low	14 × no[19,25,35,36,38,40,41,43,47,48,53,54,58,59]	No association (limited evidence)
D. Personality traits	8	All low	1 × yes[26] 7 × no[25,42,43,47,52,57,58]	No association (limited evidence)
E. Psychosocial well-being				
I. Mood state	21	All low	3 × yes[44,48,51] 18 × no[19,25,26,34,39–42,46,47,49,52–58]	No association (limited evidence)
II. Perceived stress/stressors	8	All low	2 × yes[46,59] 6 × no[19,42,47,50,53,55]	No association (limited evidence)

Personality traits

One of eight studies showed a multivariate, longitudinal association between the category of personality traits and medication non-adherence:[26] a lower sense of coherence (a global life orientation in which life is perceived as comprehensible, manageable and meaningful)[63] was associated with greater non-adherence (OR=0.55, CI 0.31–0.96). Associations between other predictors within the personality traits category and non-adherence were lacking.

Psychological well-being

Regarding categories EI (mood state) and EII (perceived stress/stressors), no associations between predictors in those categories and medication non-adherence could be established for the vast majority of studies (24 out of 29). Two of the five studies which did show significant associations reported on multivariate analyses: the regression coefficient for depressive symptoms was 0.18 (95% CI 0.07, 0.29) in predicting non-adherence;[51] the standardized beta for health distress was −0.22 (CI not reported) for predicting adherence.[59]

Table S2 can be consulted for detailed information about associations between single psychosocial predictors and medication adherence/non-adherence.

Sensitivity analyses

The sensitivity analyses confirmed that, generally, no association was found between the psychosocial categories and medication non-adherence (Table S4).

The additional analysis on single predictors showed no association between most single, psychosocial predictors and medication non-adherence. However, conflicting evidence was found for having a positive attitude towards taking medication,[37,43] necessity beliefs and concern beliefs about medication,[33,49] self-efficacy in medication-taking,[25,33,43,47,53,54] the coping style "planful problem solving",[25,41] and (the number of) stressful (life) events.[38,42,46] Limited evidence was found for an association between escape-avoidance coping and medication non-adherence,[25,41,56,59] and for an association between receiving practical, social support and medication adherence.[38,41]

Discussion

To the best of our knowledge, this is the first systematic review summarizing evidence of longitudinal associations between psychosocial factors and non-adherence to CPMM, irrespective of somatic disease. Due to the low quality of the included studies, limited evidence was found for absence of longitudinal associations between categories of psychoso-

cial predictors and medication non-adherence. In general, findings were robust according to sensitivity analyses.

Our findings of longitudinal associations between psychosocial factors and medication non-adherence are in line with the few conducted cross-sectional studies about associations between medication adherence, coping styles, personality traits, and psychosocial well-being (except depressive symptoms) in somatic conditions. The findings in these cross-sectional studies are ambiguous at best.[8,64–68] For example, an active coping style was associated with medication adherence in some studies[8,68] but not in others,[64,66] and stress was associated with lesser adherence in a study of Holt et al,[67] but was unrelated to non-adherence in a study of Ediger et al.[65]

In contrast to coping styles and personality traits, depression is often studied as possible predictor of medication non-adherence. Here, our results are not in line with results from other reviews, reporting depression to be a predictor of medication non-adherence.[6,69–74] Initially, this discrepancy might be explained by the fact that clinical depression is within the scope of most other studies, but beyond the scope of our systematic review since we did not study morbidity as a predictor of non-adherence; instead, we studied depressive symptoms. Second, an explanation might be that those other reviews included studies with mainly cross-sectional designs. Feelings of depression might increase and decrease over the course of a disease. A high degree of depressive feelings might correlate well with non-adherent behavior at that same time, but just might not be predictive of non-adherent behavior in the future due to this changeability. Thus, longitudinal associations between depressive feelings and non-adherence might not be applicable.

This thought might also apply to discrepancies in findings between our review and other reviews on associations between beliefs about medication/treatment, poor social support, and non-adherence. These other reviews underline the importance of beliefs about medication/treatment and poor social support in predicting medication non-adherence[6,10,69–76] in contrast to our review findings, but again, those other reviews are mainly based on studies with cross-sectional designs.

In terms of internal validity, a strength of this review is that we, in contrast to others, systematically defined and categorized psychosocial factors. By doing so, we were able to 1) draw a concise number of conclusions about associations between psychosocial predictors and medication non-adherence in a reproducible manner; 2) address the heterogeneity between single, psychosocial predictors; and 3) address an important goal of a systematic review: converging information. The pitfall of categorization (eg, the possibility of overlooking significant associations between certain, single predictors and non-adherence, by pooling them with other types of [non-significant] predictors), was avoided by performing an extended sensitivity analysis on single predictors. This analysis revealed our conclusions to be robust for almost all single, psychosocial predictors included in this review.

Another strength of this review is that we systematically synthesized results using a best evidence synthesis in contrast to most other reviews, which tend to be characterized by narrative designs.[6,10,69,70,73,74,76] Narrative designs often do not rely on systematic methods to assign weight of evidence; eg, by incorporating methodological quality of included studies.[77] Although no review procedure eliminates the chance that reviewers' biases will affect the conclusions drawn,[77] the application of a best evidence synthesis makes a review procedure transparent and reproducible.

A limitation of this systematic review is that we used chronic disease terms instead of medication terms in the search strategy and, consequently, we may have missed relevant studies about chronic preventive maintenance medication. However, we assume that the number of missed studies is minimal, since diseases are usually mentioned in medication adherence studies.

Another limitation could be the use of results of univariate analyses to draw conclusions about associations in the absence of multivariate analysis data, as univariate analyses could lead to an overestimating of the strength of associations. However, our sensitivity analyses on data from univariate analyses confirmed the robustness of our findings.

Concerning external validity, a strong feature of this review is that it focused exclusively on longitudinal associations between psychosocial predictors and medication non-adherence, thereby providing insight into the temporality and robustness of associations. However, only 5 of the 30 studies included in our review corrected for baseline non-adherence.[34,50,53,58,59] Failure to account for baseline non-adherence when suggesting predictive longitudinal associations is considered a liberal approach,[78] since baseline non-adherence is likely to explain a substantial part of the variance in non-adherence over time. Because we did not find any associations using a liberal approach, however, we believe it is unlikely that handling a strict longitudinal approach in this review would have altered our findings.

Another limitation concerning external validity is that the poor quality of the included studies prevented us from drawing firm conclusions about the lack of associations between psychosocial predictors and medication adherence

The lack of a gold standard for adherence measurement[73] also restricts the validity of our findings. The adherence measures used in the included studies of this review (self-report, refill data, and electronic monitoring) do not measure actual ingestion, and the use of self-report and electronic monitoring might have introduced response bias because of participants' awareness of the measurements. However, all medication adherence related research has to deal with the limitations of adherence measurements. For now, our review provides the best evidence currently available, and clearly demonstrates the need for more high-quality, longitudinal research into associations between psychosocial predictors and medication non-adherence.

Two recommendations for future research can be made. First, future longitudinal research into psychosocial predictors of medication non-adherence should be of high quality. Researchers should, for example, use valid measures of psychosocial predictors and medication non-adherence and should thoroughly describe which steps were performed in the study, especially those relating to handling missing data and avoiding bias.

Second, the research gap in longitudinal studies into associations between psychosocial predictors and medication non-adherence in patients with conditions such as rheumatic diseases, migraine disorders, gout, glaucoma, and stomach ulcers (see Supplementary Materials) should be complemented. Although we assume that review findings will also apply to these diseases, this assumption needs to be confirmed.

The conclusion of this systematic review is that there is limited evidence for absence of longitudinal associations between psychosocial predictors and medication non-adherence. Consequently, our results do not provide psychosocial targets for the development of new interventions in clinical practice. However, the usefulness of psychosocial predictors in improving medication adherence should not be ruled out, as more high-quality research is needed to confirm or refute the conclusion of this review. Such future research could also further explore the associations found in this review between escape-avoidance coping and medication non-adherence, and between receiving practical, social support and medication adherence.

Acknowledgments

We would like to thank Linda Kwakkenbos for her contribution in defining the psychosocial categories, Lieke van der Aa for translating studies of the Spanish/Portuguese language and Victor Huiskes for selecting chronic preventive maintenance medication.

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials
Pubmed search strategy

(((adult[MeSH Terms] OR mature[tw] OR adult[tw])

AND

((Ischaemic heart diseases[TW] OR angina pectoris[TW] OR Myocardial Ischemia[TW] OR asthma[TW] OR Diabetes mellitus[TW] OR diabetes mellitus[TW] OR hypercholesterolaemia[TW] OR hyperlipidaemia[TW] OR Dyslipidemias[TW] OR Gastric ulcer[TW] OR Duodenal ulcer[TW] OR Stomach Ulcer[TW] OR glaucoma[TW] OR glaucoma[TW] OR heart failure[TW] OR Heart failure[TW] OR arrhythmias[TW] OR Arrhythmias, Cardiac[TW] OR "Human immunodeficiency virus" OR HIV disease[TW] OR HIV-disease[TW] OR HIV infections[TW] OR HIV-infections[TW] OR Hypertensive diseases[TW] OR Hypertension[TW] OR Ulcerative colitis[TW] OR Crohn's disease[TW] OR Inflammatory Bowel Diseases[TW] OR Arthropathies[TW] OR gout[TW] OR Malignant neoplasm of breast[TW] OR Breast Neoplasms[TW] OR Hereditary angioedema[TW] OR Angioedemas, Hereditary[TW] OR transplantation[TW] OR Organ Transplantation[TW] OR migraine[TW] OR Migraine Disorders[TW] OR osteoporosis[TW] OR arthropathy[TW] OR Systemic connective tissue disorders[TW] OR psoriatic arthropathy[TW] OR rheumatoid arthritis[TW] OR Systemic lupus erythematosus[TW] OR Systemic sclerosis[TW] OR Arthritis, Psoriatic[TW] OR Arthritis, Rheumatoid[TW] OR Lupus Erythematosus, Systemic[TW] OR Scleroderma, Systemic[TW] OR Arterial embolism[TW] OR thrombosis[TW] OR venous embolism[TW] OR Embolism and Thrombosis[TW] OR Paget Disease[TW] OR Osteitis Deformans[TW]) OR (Myocardial Ischemia[MH] OR asthma[MH] OR diabetes mellitus[MH] OR Dyslipidemias[MH] OR Stomach Ulcer[MH] OR glaucoma[MH] OR Heart failure[MH] OR Arrhythmias, Cardiac[MH] OR HIV infections[MH] OR Hypertension[MH] OR Inflammatory Bowel Diseases[MH] OR gout[MH] OR Breast Neoplasms[MH] OR Angioedemas, Hereditary[MH] OR Organ Transplantation[MH] OR Migraine Disorders[MH] OR osteoporosis[MH] OR Arthritis, Psoriatic[MH] OR Arthritis, Rheumatoid[MH] OR Lupus Erythematosus, Systemic[MH] OR Scleroderma, Systemic[MH] OR Embolism and Thrombosis[MH] OR Osteitis Deformans[MH]))

AND

((medication adherence[MH] OR patient compliance[MH]) OR (medication compliance[TW] OR medication non-compliance[TW] OR medication non compliance[TW] OR medication noncompliance[TW] OR medication adherence[TW] OR medication non-adherence[TW] OR medication non adherence[TW] OR medication nonadherence[TW] OR medication adherance[TW] OR medication non-adherance[TW] OR medication non adherance[TW] OR medication nonadherance[TW] OR medication persistence[TW] OR medication non-persistence[TW] OR medication non persistence[TW] OR medication nonpersistence[TW] OR medication persistance[TW] OR medication non-persistance[TW] OR medication non persistance[TW] OR medication nonpersistance[TW] OR medicine compliance[TW] OR medicine non-compliance[TW] OR medicine non compliance[TW] OR medicine noncompliance[TW] OR medicine adherence[TW] OR medicine non-adherence[TW] OR medicine non adherence[TW] OR medicine nonadherence[TW] OR medicine adherance[TW] OR medicine non-adherance[TW] OR medicine non adherance[TW] OR medicine nonadherance[TW] OR medicine persistence[TW] OR medicine non-persistence[TW] OR medicine non persistence[TW] OR medicine nonpersistence[TW] OR medicine persistance[TW] OR medicine non-persistance[TW] OR medicine non persistance[TW] OR medicine nonpersistance[TW] OR medical compliance[TW] OR medical non-compliance[TW] OR medical non compliance[TW] OR medical noncompliance[TW] OR medical adherence[TW] OR medical non-adherence[TW] OR medical non adherence[TW] OR medical nonadherence[TW] OR medical adherance[TW] OR medical non-adherance[TW] OR medical non adherance[TW] OR medical nonadherance[TW] OR medical persistence[TW] OR medical non-persistence[TW] OR medical non persistence[TW] OR medical nonpersistence[TW] OR medical persistance[TW] OR medical non-persistance[TW] OR medical non persistance[TW] OR medical nonpersistance[TW] OR drug compliance[TW] OR drug non-compliance[TW] OR drug non compliance[TW] OR drug noncompliance[TW] OR drug adherence[TW] OR drug non-adherence[TW] OR drug non adherence[TW] OR drug nonadherence[TW] OR drug adherance[TW] OR drug non-adherance[TW] OR drug non adherance[TW] OR drug nonadherance[TW] OR drug persistence[TW] OR drug non-persistence[TW] OR drug non persistence[TW] OR drug

nonpersistence[TW] OR drug persistance[TW] OR drug non-persistance[TW] OR drug non persistance[TW] OR drug nonpersistance[TW] OR drugs compliance[TW] OR drugs non-compliance[TW] OR drugs non compliance[TW] OR drugs noncompliance[TW] OR drugs adherence[TW] OR drugs non-adherence[TW] OR drugs non adherence[TW] OR drugs nonadherence[TW] OR drugs adherance[TW] OR drugs non-adherance[TW] OR drugs non adherance[TW] OR drugs nonadherance[TW] OR drugs persistence[TW] OR drugs non-persistence[TW] OR drugs non persistence[TW] OR drugs nonpersistence[TW] OR drugs persistance[TW] OR drugs non-persistance[TW] OR drugs non persistance[TW] OR drugs nonpersistance[TW]))

AND

(Prospective Studies[MH] OR Longitudinal Studies[MH] OR Cohort Studies[MH] OR Follow-up Studies[MH] OR Retrospective Studies[MH] OR Prospective Studies[TIAB] OR Longitudinal Studies[TIAB] OR Cohort Studies[TIAB] OR Follow-up Studies[TIAB] OR Retrospective Studies[TIAB] OR observational stud*[TIAB] OR predict*[TW] OR prognos*[TW] OR prognostic factor*[TW] OR course[TW] OR determinant*[TW]))

NOT

"Africa"[Mesh] OR "Latin America"[Mesh] OR "Asia, Central"[Mesh] OR "Borneo"[Mesh] OR "Brunei"[Mesh] OR "Cambodia"[Mesh] OR "East Timor"[Mesh] OR "Laos"[Mesh] OR "Malaysia"[Mesh] OR "Mekong Valley"[Mesh] OR "Myanmar"[Mesh] OR "Philippines"[Mesh] OR "Singapore"[Mesh] OR "Thailand"[Mesh] OR "Vietnam"[Mesh] OR "Bangladesh"[Mesh] OR "Bhutan"[Mesh] OR "India"[Mesh] OR "Afghanistan"[Mesh] OR "Bahrain"[Mesh] OR "Iran"[Mesh] OR "Egypt"[Mesh] OR "Iraq"[Mesh] OR "Israel"[Mesh] OR "Jordan"[Mesh] OR "Kuwait"[Mesh] OR "Lebanon"[Mesh] OR "Oman"[Mesh] OR "Qatar"[Mesh] OR "Saudi Arabia"[Mesh] OR "Syria"[Mesh] OR "United Arab Emirates"[Mesh] OR "Yemen"[Mesh] OR "Nepal"[Mesh] OR "Pakistan"[Mesh] OR "Sri Lanka"[Mesh] OR "China"[Mesh] OR "Korea"[Mesh] OR "Mongolia"[Mesh] OR "Taiwan"[Mesh]

NOT

(youth[TIAB] OR child*[TIAB])

NOT

(Clinical Trial[MH] OR case reports[PT] OR review[PT] OR meta-analysis[MH] OR Cross-sectional Studies[MH] OR Case-control Studies[MesH:NoExp] OR Clinical Trial*[PT] OR case report*[PT] OR review*[PT] OR meta-analys*[PT] OR case report*[TIAB] OR case-report*[TIAB] OR review*[TIAB] OR systematic review*[TIAB] OR meta-analys*[TIAB] OR randomized controlled trial*[TIAB] OR randomised controlled trial*[TIAB] OR clinical trial*[TIAB] OR controlled clinical trial*[TIAB] OR cross-sectional*[TIAB] OR cross sectional*[TIAB] OR Case-control Studies[TIAB] OR case-control[TIAB] OR case control[TIAB] OR Editorial[ptyp] OR Letter[ptyp] OR Comment[ptyp] OR Interview[ptyp] OR Newspaper Article[ptyp])

Chronic preventive maintenance medication

A02BA01	Cimetidine
A02BA02	Ranitidine
A02BA03	Famotidine
A02BA04	Nizatidine
A02BA07	Ranitidinebismutcitrate
A02BB01	Misoprostol
A02BC01	Omeprazole
A02BC02	Pantoprazole
A02BC03	Lansoprazole
A02BC04	Rabeprazole
A02BC05	Esomeprazole
A07EA04	Betamethasone
A07EA06	Budesonide
A07EA07	Beclomethasone
A07EC01	Sulphasalazine
A07EC02	Mesalazine
A07EC03	Olsalazine
A10A	Insulin
A10BA02	Metformin
A10BB01	Glibenclamide
A10BB03	Tolbutamide
A10BB07	Glipizide
A10BB09	Gliclazide
A10BB12	Glimepiride
A10BF01	Acarbose
A10BG02	Rosiglitazone
A10BG03	Pioglitazone
A10BH01	Sitagliptine
A10BX02	Repaglinide
A11CC03	Alfacalcidol

A11CC04	Calcitriol	C03DA01	Spironolactone
A11CC05	Colecalciferol	C03DA04	Eplerenone
A12AA01	Calciumphosphate	C03DB01	Amiloride
A12AA02	Calciumglubionate	C03DB02	Triamterene
A12AA03	Calciumgluconate	C04AC01	Nicotinic acid
A12AA04	Calciumcarbonate	C04AD02	Xantinolnicotinate
A12AA05	Calciumlactate	C07AA02	Oxprenolol
A12AA07	Calciumchloride	C07AA03	Pindolol
A12AA12	Calciumacetate	C07AA05	Propranolol
A12AA30	Calciumlevulinate	C07AA07	Sotalol
B01AA03	Warfarin	C07AB02	Metoprolol
B01AA04	Fenprocoumon	C07AB03	Atenolol
B01AA07	Acenocoumarol	C07AB04	Acebutolol
B01AC04	Clopidogrel	C07AB05	Betaxolol
B01AC06	Acetylsalicylic acid	C07AB07	Bisoprolol
B01AC07	Dipyridamole	C07AB08	Celiprolol
B01AC08	Carbasalate calcium	C07AB12	Nebivolol
B01AC09	Epoprostenol	C07AG01	Labetalol
B01AC21	Treprostinil	C07AG02	Carvedilol
B03BB01	Folic acid	C08CA01	Amlodipine
C01AA05	Digoxin	C08CA02	Felodipine
C01BA01	Quinine	C08CA03	Isradipine
C01BA02	Procainamide	C08CA04	Nicardipine
C01BA03	Disopyramide	C08CA05	Nifedipine
C01BB01	Lidocaine	C08CA06	Nimodipine
C01BB04	Aprindine	C08CA07	Nisoldipine
C01BC03	Propafenone	C08CA08	Nitrendipine
C01BC04	Flecainide	C08CA09	Lacidipine
C01BD01	Amiodarone	C08CA12	Barnidipine
C01DA08	Isosorbidedinitrate	C08CA13	Lercanidipine
C01DA14	Isosorbidemononitrate	C08DA01	Verapamil
C01DX16	Nicorandil	C08DB01	Diltiazem
C01EB17	Ivabradine	C09AA01	Captopril
C02AB01	Methyldopa	C09AA03	Lisinopril
C02CA01	Prazosin	C09AA04	Perindopril
C02CA04	Doxazosin	C09AA05	Ramipril
C02CA06	Urapidil	C09AA06	Quinapril
C02DB02	Hydralazine	C09AA07	Benazepril
C02DC01	Minoxidil	C09AA08	Cilazapril
C02KD01	Ketanserin	C09AA09	Fosinopril
C02KX01	Bosentan	C09AA10	Trandolapril
C02KX03	Sitaxentan	C09AA15	Zofenopril
C03AA03	Hydrochloorthiazide	C09CA01	Losartan
C03AA04	Chlorthiazide	C09CA02	Eprosartan
C03BA04	Chlortalidone	C09CA03	Valsartan
C03BA11	Indapamide	C09CA04	Irbesartan
C03CA01	Furosemide	C09CA06	Candesartan
C03CA02	Bumetanide	C09CA07	Telmisartan

C09CA08	Olmesartan	J05AF02	Didanosine
C10AA01	Simvastatin	J05AF03	Zalcitabine
C10AA03	Pravastatin	J05AF04	Stavudine
C10AA04	Fluvastatin	J05AF05	Lamivudin
C10AA05	Atorvastatin	J05AF06	Abacavir
C10AA07	Rosuvastatin	J05AF07	Tenofovir
C10AB01	Clofibrate	J05AF08	Adefovir
C10AB02	Bezafibrate	J05AF09	Emtricitabine
C10AB04	Gemfibrozil	J05AF10	Entecavir
C10AB08	Ciprofibrate	J05AF11	Telbivudine
C10AC01	Colestyramine	J05AG01	Nevirapine
C10AC02	Colestipol	J05AG03	Efavirenz
C10AC04	Colesevelam	J05AX07	Enfuvirtide
C10AD02	Nicotinic acid	L01AA01	Cyclophosphamide
C10AD06	Acipimox	L01BA01	Methotrexate
C10AX09	Ezetimib	L02BG01	Aminoglutethimide
G03XA01	Danazol	L02BG03	Anastrozole
G03XC01	Raloxifene	L02BG04	Letrozole
G04BD02	Flavoxate	L04AA06	Mycophenol acid
G04BD04	Oxybutynin	L04AA10	Sirolimus
G04BD07	Tolterodine	L04AA13	Leflunomide
G04BD08	Solifenacin	L04AA18	Everolimus
G04BD10	Darifenacin	L04AB01	Etanercept
G04CA01	Alfuzosin	L04AB02	Infliximab
G04CA02	Tamsulosin	L04AB04	Adalimumab
G04CA03	Terazosin	L04AC03	Anakinra
G04CB01	Finasterid	L04AD01	Ciclosporine
G04CB02	Dutasterid	L04AD02	Tacrolimus
H02AA02	Fludrocortisone	L04AX01	Azathioprine
H02AB01	Betamethasone	L04AX03	Methotrexate
H02AB02	Dexamethasone	M01CB01	Aurothiomalate
H02AB04	Methylprednisolone	M01CB03	Auranofin
H02AB06	Prednisolone	M01CC01	Penicillamine
H02AB07	Prednisone	M04AA01	Allopurinol
H02AB08	Triamcinolone	M04AB01	Probenecid
H02AB09	Hydrocortisone	M04AB03	Benzbromarone
H02AB10	Cortisone	M05BA01	Etidronate
J05AE01	Saquinavir	M05BA02	Clodronate
J05AE02	Indinavir	M05BA03	Pamidronate
J05AE03	Ritonavir	M05BA04	Alendronate
J05AE04	Nelfinavir	M05BA05	Tiludronate
J05AE05	Amprenavir	M05BA06	Ibandronate
J05AE06	Lopinavir	M05BA07	Risedronate
J05AE07	Fosamprenavir	M05BA08	Zoledronate
J05AE08	Atazanavir	M05BX03	Strontiumranelate
J05AE09	Tipranavir	N02CX01	Pizotifen
J05AE10	Darunavir	N02CX02	Clonidine
J05AF01	Zidovudine	R03BA01	Beclomethasone

R03BA02	Budesonide	S01EC01	Acetazolamide
R03BA05	Fluticasone	S01EC03	Dorzolamide
R03BA08	Ciclesonid	S01EC04	Brinzolamide
R03BC01	Cromolyn sodium	S01ED01	Timolol
R03BC03	Nedocromil	S01ED02	Betaxolol
R03DC03	Montelukast	S01ED03	Levobunolol
S01EA02	Dipivefrine	S01ED04	Metipranolol
S01EA03	Apraclonidine	S01ED05	Carteolol
S01EA05	Brimonidine	S01ED06	Befunolol
S01EA51	Epinephrine	S01EE01	Latanoprost
S01EB01	Pilocarpine	S01EE03	Bimatoprost
S01EB08	Aceclidine	S01EE04	Travoprost

Table S1 Framework for judging methodological quality

Bias domain	Criterion
1. Study participation	1.1. The setting of the source population is adequately described by key characteristics (setting/geographical location)
	1.2. The (baseline) study sample is adequately described by key characteristics (descriptive data about age, sex, diagnosis, disease duration and medication type/group), and no unacceptable level of bias is present
	1.3. The method of recruitment or sampling is adequately described. If method of recruitment is not 'consecutive', then, for example, descriptions are given about the sampling frame, numbers, methods to identify the sample (such as a description of referral patterns in health care) and period of recruitment, and no unacceptable level of bias is present
	1.4. Inclusion and exclusion criteria are adequately described, and no unacceptable level of bias is present
	1.5. There is adequate participation in the study by eligible individuals (power analysis is described or the sample size (n) is adequate in relation to the number of prognostic variables (K) in the statistical analyses (ratio n:K exceeds 10:1)
2. Study attrition	2.1. Response rate (ie, proportion of study sample completing the study and providing outcome data) is adequate If study sample size ≤50 participants: 'yes' when total number of participants lost to follow-up was <10% at follow-up ≥three months. 'Partly': if this percentage was between 10% and 20%. 'No': if this percentage was ≥20% If study sample size >50 participants: 'yes', when total number of participants lost to follow-up was <20% at follow-up $three months. 'Partly': if this percentage was between 20% and 33%. 'No': if this percentage was ≥33%
	2.2. Attempts to collect information about participants who dropped out of the study are described: 1) reasons for loss to follow-up are provided OR 2) participants lost to follow-up are adequately described by key characteristics and outcomes. No unacceptable level of bias is present
3. Prognostic factor measurement	3.1. A clear description of the main prognostic factors is provided (not covariates) AND/OR measures/methods regarding the main prognostic factors, at baseline and follow-up are adequately described to allow assessment of their validity and reliability. No unacceptable level of bias is present ○ Objective measures (such as number of life-changing events) and clear description is 'yes'. Poor/no description = 'partly' ○ Validated, subjective measures (eg, opinions) and clear description = 'yes'. Poor/no description = 'partly' ○ Non-validated, subjective measures and clear description = 'partly'. Poor/no description = 'no'
	3.2. The method and setting of measurement are the same for all study participants at baseline and follow-up
	3.3. Continuous variables are reported or appropriate cut-off points are used
	3.4. Authors appropriately described and dealt with missing data on prognostic factors
4. Outcome measurement	4.1. A clear description of medication adherence is provided AND/OR measures/methods of medication adherence (at baseline and follow-up) are adequately described, to allow assessment of their validity and reliability. No unacceptable level of bias is present ○ Objective measures (such as pill count, refill rates, MEMS) and clear description = 'yes'. Poor/no description is 'partly' ○ Validated, subjective measures (eg, questionnaires) and clear description = 'yes'. Poor/no description = 'partly' ○ Non-validated, subjective measures and clear description = 'partly'. Poor/no description = 'no'
	4.2. The method and setting of measurement are the same for all study participants at baseline (if measured) and follow-up
	4.3. Authors appropriately described and dealt with missing outcome data
5. Confounding measurement and account	5.1. The most important confounders are measured Examples of possible confounders: age; socioeconomic status/educational level/financial situation/illiteracy; social support/networks; depression/anxiety/emotional distress/lack of acceptance of disease; fatigue/pain/physical disability; self-efficacy/coping; regimen complexity/route of administration/number of medications; satisfaction with patient-provider relationship/autonomy

Score	Judgment	Final score
○ Yes ○ Partly ○ No	5 × yes = yes 1 × no = no Else = partly	○ Yes ○ Partly ○ No
○ Yes ○ Partly ○ No		
○ Yes ○ Partly ○ No		
○ Yes ○ Partly ○ No		
○ Yes ○ Partly ○ No		
○ Yes ○ Partly ○ No	2.1 yes = yes (you can leave 2.2 open) 2.1 no = no OR 2.1 partly, 2.2 no = no Else = partly	○ Yes ○ Partly ○ No
○ Yes ○ Partly ○ No		
○ Yes ○ Partly ○ No	4 × yes = yes 3.1 or 3.2 no = no OR 3.1 or 3.2 partly (no no's), 3.3 or 3.4 no = no Else = partly	○ Yes ○ Partly ○ No
○ Yes ○ Partly ○ No		
○ Yes ○ Partly ○ No		
○ Yes ○ Partly ○ No		
○ Yes ○ Partly ○ No	3 × yes = yes 4.1 or 4.2 no = no OR 4.1 or 4.2 partly (no no's), 4.3 no = no Else = partly	○ Yes ○ Partly ○ No
○ Yes ○ Partly ○ No		
○ Yes ○ Partly ○ No		
○ Yes ○ Partly ○ No		

(*Continued*)

Table S1 (*Continued*)

Bias domain	Criterion
	5.2. A clear description of the most important confounders measured is provided AND/OR measures/ methods of the most important confounders (at baseline) are adequately described to allow assessment of their validity and reliability. No unacceptable level of bias is present ○ Objective measures (such as age, sex) and clear description = 'yes'. Poor/no description is 'partly' ○ Validated, subjective measures (eg, opinions) and clear description = 'yes'. Poor/no description = 'partly' ○ Non-validated, subjective measures and clear description = 'partly'. Poor/no description = 'no'
	5.3. The method and setting of confounding measurement are the same for all study participants at baseline
	5.4. Important potential confounders are accounted for in the study design (eg, matching for key variables/ restriction) OR in analysis (stratification/multivariate techniques)
	5.5. Authors appropriately described and dealt with missing confounding data
6. Analysis	6.1. There is sufficient presentation of data to assess the adequacy of the analysis 'Yes', if main findings of the study and statistical methods used are clearly described: simple outcome data, crude data and estimates of random variability should be reported, so that the reader can check the major analyses and conclusions
	6.2. The statistical tests used to assess the main outcome are appropriate For example, non-parametric methods should be used for small sample sizes
	6.3. The strategy for model building (ie, inclusion of variables) is appropriate, and is based on conceptual thoughts, a framework or a model For example: variables that do not correlate with the main outcome of interest are not used in multivariate analysis. Proper variables are entered in logical steps into the multivariate model
	6.4. The selected model is adequate for the design of the study For example: in repeated measures, a repeated-measure model should be used. If outcome is binominal, logistic regression should be used, etcetera. If delta outcome is being investigated, models should to be adjusted for baseline outcome values

Abbreviation: MEMS, medication event monitoring system.

Score	Judgment	Final score
○ Yes ○ Partly ○ No	One of 5.1 to 5.4 = no (if 5.1 no, you can leave 5.2 to 5.5 open) OR 5.1 to 5.4 partly, 5.5 no = no All partly = partly OR 5.1 to 5.4 partly, 5.5 yes = partly OR none of 5.1 to 5.4 no, 5.5 no = partly OR 5.1 to 5.4 yes, 5.5 not yes = partly Else = yes	○ Yes ○ Partly ○ No
○ Yes ○ Partly ○ No		
○ Yes ○ Partly ○ No		
○ Yes ○ Partly ○ No		
○ Yes ○ Partly ○ No	4 × yes = yes At least 1 × no = no Else = partly	○ Yes ○ Partly ○ No
○ Yes ○ Partly ○ No		
○ Yes ○ Partly ○ No		
○ Yes ○ Partly ○ No		

Table S2 Explanation of measures and results*

First author	Setting, n patients	Measures	
		Adherence†, follow-up period‡	**Psychosocial predictors§**
Asthma (inhaled corticosteroids)			
Ponieman[1]	USA; patients from general internal medicine clinic, n=261	Adherence by self-report (MARS), 3 months	(Items derived from BMQ and Self-Regulation Theory): concerns beliefs: worried about side effects of ICS? Concerns beliefs: worried about getting addicted to ICS? Concerns beliefs: if I use ICS all the time they will stop working Necessity beliefs: important to use ICS when symptomatic? Necessity beliefs: important to use ICS when asymptomatic? Self-efficacy: confident in ability to use ICS as prescribed Self-efficacy: confident in ability to control asthma Self-efficacy: confident in controlling future health
Diabetes (oral and/or parenteral anti-diabetics)			
Venturini[2,§§]	USA; patients from HMO-providing health services, n=786	Adherence by record review (continuous measure corrected for self-reported baseline adherence), last time point flexible, but within 24 months	Perception of mental health (mood state, SF-36)
Heart disease and hypertension (cardiovascular medication)			
Gazmararian[3,‖‖]	USA; community-dwelling patients, n=1,549	Non-adherence by record review, 12 months	Social support (instrument NR)
Nabi[4]	Finland: local government employees, n=1,021	Non-adherence by record review (ordinal measure), 12 months	Anxiety (ATS) Hostility (FTSSH) Optimism (LOT-R) Pessimism (LOT-R) Psychological distress (GHQ) Sense of coherence (SOC)
Grégoire[5]	Canada: hypertensive adults with prescription from network of pharmacies, n=692	Non-adherence by self-report (Morisky Scale), 3 months	(Interview, self-developed items): beliefs concerning efficacy of antihypertensive medication Beliefs concerning hypertension as risk factor for other diseases How much are you at risk of a heart attack because of your hypertension if you follow your doctor's advice? How much are you at risk of a stroke because of your hypertension if you follow your doctor's advice?

Psychcat‖	Results¶		Direction of association (regarding adherence)**	N domains bias free††
	Univariate	Multivariate		
AI	OR =0.3 (0.2, 0.7), $P<0.05$	OR =0.52 (0.36, 0.74), $P<0.001$	U: – M: –	0 of 6
AI	OR =0.4 (0.2, 0.8), $P<0.05$	NS‡‡	U: – M: 0	
AI	OR =0.4 (0.2, 0.9), $P<0.05$	NS‡‡	U: – M: 0	
AI	NS	NS‡‡	U: 0 M: 0	
AI	OR =5.8 (2.3, 14.6), $P<0.05$	OR =4.15 (2.54, 6.77), $P<0.001$	U: + M: +	
AIII	OR =3.5 (1.6, 7.6), $P<0.05$	OR =2.23 (1.42, 3.52), $P<0.001$	U: + M: +	
AIII	NS	NS‡‡	U: 0 M: 0	
AIII	NS	NS‡‡	U: 0 M: 0	
EI	NR	NS	U: NR M: 0	2 of 6
CIII	NS	NT	U: 0 M: NT	3 of 6
EI	NS	NT	U: 0 M: NT	1 of 6
D	NS	NT	U: 0 M: NT	
D	NS	NT	U: 0 M: NT	
D	NS	NT	U: 0 M: NT	
EI	NS	NT	U: 0 M: NT	
D	OR =0.62 (0.36, 1.05), $P<0.10$	OR =0.55 (0.31, 0.96), $P<0.05$	U: 0 M: +	
AI	NS	NS	U: 0 M: 0	0 of 6
AII	"No effect" versus "a lot of effect" (ref cat): OR =1.74 (1.08, 2.81), $P=0.02$	"No effect" versus "a lot of effect": OR =2.00 (1.21, 3.33), $P\leq0.05$	U: – M: –	
AII	NS	NS	U: 0 M: 0	
AII	NS	NS	U: 0 M: 0	

(*Continued*)

Table S2 (*Continued*)

First author	Setting, n patients	Measures	
		Adherence†, follow-up period‡	**Psychosocial predictors§**
			How much are you at risk of heart attack because of your hypertension if you do not do anything about it?
			How much are you at risk of stroke because of your hypertension if you do not do anything about it?
			Social support (Pearlin et al[31])
Miller[6,§§§]	Site not reported: patients from institutions providing cardiac rehabilitation programs, n=141	Adherence by self-report (continuous measure, HBS), 6–9 months	Attitude towards medication taking (MAS)
			Beliefs about which steps of the medical regimen people most important to them think they should perform (HIS)
Molloy[7,§§§]	UK; patients admitted to one of four London hospitals with Acute Coronary Syndrome, n=295	Adherence by self-report, 12 months	Emotional support (derived from Berkman et al[32] and Seeman et al[33])
			Practical support
HIV (antiretroviral medication)			
Deschamps[8]	Belgium; outpatients of university hospital, n=60	Non-adherence by MEMS, 5–6 months after measuring psychosocial constructs	Anxiety (AMHI)
			Coping style: confrontational (AWC)
			Coping style: distancing
			Coping style: self-controlling
			Coping style: seek social support
			Coping style: accept responsibility
			Coping style: escape-avoidance (higher score = more escape-avoidance)
			Coping style: planful problem solving (higher score = more planful problem solving)‖ ‖ ‖
			Coping style: positive reappraisal
			Depression (AMHI)
			Perceived benefits of treatment (APIAQ)
			Perceived severity of seriousness of implications when not taking medications adequately
			Perceived susceptibility of developing AIDS when not taking medications as prescribed
			Positive affect (eg, happiness person)
			Received social support (AGSRP)
			Self-efficacy in taking HAART medication (ALTMBSES)

Psychcat‖	Results¶		Direction of association (regarding adherence)**	N domains bias free††
	Univariate	Multivariate		
AII	"Do not know" versus "no to moderate risk" (ref cat): OR =0.46 (0.19, 1.12), *P*=0.09	NS	U: 0 M: 0	
AII	"Do not know" versus "no to moderate risk" (ref cat): OR =0.44 (0.17, 1.16), *P*=0.10	"Do not know" versus "no to moderate risk": OR =0.40 (0.15, 1.09), *P*=0.07	U: 0 M: 0	
CIII	NS	NS	U: 0 M: 0	
AI	NR	NS	U: NR M: 0	0 of 6
CII		NS	U: NR M: 0	
CIII	NS	NS	U: 0 M: 0	1 of 6
CIII	Number of patients providing practical support: 0: 39.7% adherent. 1: 40.5% adherent. Two or more: 59.2% adherent, *P*=0.004	OR =2.12 (1.06, 4.26), *P*=0.03	U: + M: +	
EI	NS	NR	U: 0 M: NR	1 of 6
BI	NS		U: 0 M: NR	
BII	NS		U: 0 M: NR	
BII	NS		U: 0 M: NR	
CIII	NS		U: 0 M: NR	
BII	NS		U: 0 M: NR	
BII	Adherent patients 7.2, (2.2) versus non-adherent patients 10.1 (2.8), *P*=0.003		U: – M: NR	
BI	Adherent patients 7.5 (median), 3 (IQR) versus non-adherent patients 9 (median), 2 (IQR), *P*=0.049		U: – M: NR	
BI	NS		U: 0 M: NR	
EI	NS		U: 0 M: NR	
AI	Adherent patients 21 (3.5) versus non-adherent patients 18.7 (3.9), *P*=0.07		U: 0 M: NR	
AI	NS		U: 0 M: NR	
AI	NS		U: 0 M: NR	
D	NS		U: 0 M: NR	
CIII	NS		U: 0 M: NR	
AIII	NS		U: 0 M: NR	

(*Continued*)

Table S2 (*Continued*)

First author	Setting, n patients	Measures	
		Adherence[†], follow-up period[‡]	**Psychosocial predictors[§]**
Holmes[9]	USA; HIV-clinic patients, n=116	Adherence by MEMS, 12 months (or when viral load of ≥1,000 copies/mL was reached)	Depressive symptoms (CES-D)
			HIV-disclosure worries (HAT-QOL)
			Health worries (higher score = fewer worries)
			Medication worries (higher score = fewer worries)
			Provider trust
			Social support (ISEL)
			Stress (PSS)
Delgado[10]	Canada; patients enrolled in community drug treatment program, n=316	Adherence by record review, 12 months	Depressive symptoms (CES-D)
Singh[11]	USA; new veteran patients seen at medical center, n=52	Non-adherence by record review, 6 months	Confusion and bewilderment (POMS)
			Depression and dejection
			Mood disturbance
			Religious support (instrument NR)
			Social support (instrument NR)
			Symptoms of depression (BDI)
			Tension and anxiety (POMS)
Singh[12]	Site not reported: patients in HIV-medical centers, n=138	Non-adherence by record review, 6 months	Coping style: active-behavioral focused (higher score = greater applicability of coping style to patient, BMICIS)
			Coping style: active-cognitive focused
			Coping style: avoidant coping
			Coping style: emotion-focused
			Coping style: problem-focused
			Hopelessness: future expectations
			Hopelessness: loss of motivation (higher score = more hopelessness, BHS)
			Hopelessness: negative feelings about future
			Hopelessness: total score
			Quality of life: psychological functioning (MOS SF-36)
			Satisfaction with social support: emotional (SSQ)

Psychcat‖	Results¶		Direction of association (regarding adherence)**	N domains bias free††
	Univariate	Multivariate		
EI	High adherence 12.6 (11.3), low adherence 16.5 (11.7), *P*=0.06	NS	U: 0 M: 0	2 of 6
AII	NS	NT	U: 0 M: NT	
AII	High adherence 79.2 (23.9), low adherence 70.4 (28.9), *P*=0.06	NS	U: 0 M: 0	
AI	High adherence 86.1 (20.4), low adherence 83.3 (18.3), *P*=0.06	NS	U: 0 M: 0	
CI	NS	NT	U: 0 M: NT	
CIII	NS	NT	U: 0 M: NT	
EII	High adherence 12.4 (7.8), low adherence 15.3 (8.2), *P*=0.07	NS	U: 0 M: 0	
EI	Not reporting depression: 79.8% adherent, reporting depression: 68.1% adherent, *P*=0.02	NS	U: – M: 0	1 of 6
BII	NS	NT	U: 0 M: NT	1 of 6
EI	Adherent 14.2 (SEM 1.9), non-adherent 22.1 (SEM 3.4), *P*=0.04	NS	U: – M: 0	
EI	39% in adherent patients, 76% in non-adherent patients, *P*=0.03	OR =1.4 (1.1, 1.8), *P*=0.01	U: – M: –	
CIII	NS	NT	U: 0 M: NT	
CIII	NS	NT	U: 0 M: NT	
EI	NS	NT	U: 0 M: NT	
EI	NS	NT	U: 0 M: NT	
BI	(Mean score, SEM): non-adherent 5.2 (0.5) versus adherent 6.6 (0.2), *P*=0.01	NR	U: + M: NR	1 of 6
BI	NS		U: 0 M: NR	
BII	Non-adherent 3.3 (0.3) versus adherent 2.6 (0.2), *P*=0.02		U: – M: NR	
BII	NS		U: 0 M: NR	
BI	Non-adherent 6.0 (0.5) versus adherent 7.1 (0.2), *P*=0.02		U: + M: NR	
BII	NS		U: 0 M: NR	
BII	Non-adherent 1.75 (0.5), adherent 0.6 (0.1), *P*=0.006		U: – M: NR	
BII	NS		U: 0 M: NR	
BII	NS		U: 0 M: NR	
EI	NS		U: 0 M: NR	
CIII	NS		U: 0 M: NR	

(*Continued*)

Table S2 (*Continued*)

First author	Setting, n patients	Measures	
		Adherence[†], follow-up period[‡]	**Psychosocial predictors[§]**
			Satisfaction with social support: informational (higher scores = less satisfaction) Satisfaction with social support: tangible
			Satisfaction with social support: total score
Bottonari[13]	USA; patients treated in immunodeficiency clinic, n=78	Adherence by self-report (straightforward), 6–9 months	Depressive symptoms (IDD)
			Experience of general (stressful) life events (LES)
			HIV-specific (stressful) life events (BHLES)
			Neuroticism: personality style indicative of affective instability (NSEPQSS) Perceived stress (PSS)
			Self-esteem (RSEQR)
Godin[14]	Canada; patients from medical HIV-clinics, n=400	Adherence over time by self-report (straightforward), 12 months	Change in predictors related to adherence over time: attitude towards medication-taking (more positive attitude = greater adherence, self-developed scale) Optimism (DOS)
			Outcome expectations (eg, believe that specific course of action will lead to desired outcome, self-developed scale) Patient-doctor satisfaction (Pat SS)
			Self-efficacy regarding medication taking (self-developed scale)
			Social support (SPS)
Kacanek[15]	USA; patients recruited by media and physician networks, n=225	Suboptimal adherence by self-report (straightforward): max 30 months	Development of depressive symptoms (BST)
Martini[16,§§§]	Italy; outpatients using combination therapy, n=214	Adherence by self-report (ordinal measure, straightforward questionnaire), 12 months	(Interview, instrument NR): perception of therapy: reliable?
			Perception of therapy: enslaving?
			Satisfied about doctor/patient discussion regarding clinical and therapeutic aspects of treatment?
Mellins[17]	USA; HIV-infected mothers recruited in waiting room of adult clinic, n=128	Non-adherence by self-report (AACTG, straightforward), T1 after 4–5 months, T2 8–18 months after T1	Negative stressful events (PEI)
			Parenting stress (low scores = more stress, PPCS)
			Psychological distress (aggregated demoralization score, DSPERI) Self-efficacy in carrying out health-related behaviors (Chesney et al[34])

Psychcat‖	Results¶		Direction of association (regarding adherence)**	N domains bias free††
	Univariate	Multivariate		
			U: +	
CIII	Non-adherent 7.9 (1.1), adherent 6.1 (0.3), *P*=0.04		M: NR	
			U: 0	
CIII	Non-adherent 7.7 (1.1), adherent 5.5 (0.3), *P*=0.07		M: NR	
			U: +	
CIII	Non-adherent 22.9 (3.3), adherent 16.8 (0.75), *P*=0.03		M: NR	
EI	NS	NR	U: 0	0 of 6
			M: NR	
EII	NS		U: 0	
			M: NR	
EII	NS		U: 0	
			M: NR	
D	NS		U: 0	
			M: NR	
EII	OR =0.88 (0.77, 0.98), *P*=0.04		U: –	
			M: NR	
D	NS		U: 0	
			M: NR	
AI	NR	OR =1.56 (1.18, 2.06), *P*≤0.05	U: NR	1 of 6
			M: +	
D		NS	U: NR	
			M: 0	
AIII		NS	U: NR	
			M: 0	
CI		NS	U: NR	
			M: 0	
AIII		OR =1.68 (1.27, 2.22), *P*≤0.05	U: NR	
			M: +	
CIII		NS	U: NR	
			M: 0	
EI	Suboptimal adherence in those who developed depressive symptoms =45.1% versus 25.9% in those with no depressive symptoms, *P*=0.01	NT	U: –	2 of 6
			M: NT	
AI	In "high adherence" category, therapy perceived as "reliable" by 15.6%, and "not reliable" by 84.4%. In "variable adherence" cat 4.8% versus 95.2%. In "low adherence" cat 0% versus 100%, *P*=0.02	NR	U: +	0 of 6
			M: NR	
AI	NS		U: 0	
			M: NR	
CI	In "high adherence" category: "sufficient/highly satisfied" = 73.9%, "little/not satisfied" =26.1%. In "variable adherence" cat 80% versus 20%. In "low adherence" cat 50% versus 50%, *P*=0.05		U: ?	
			M: NR	
EII	OR =1.27 (1.09, 1.49), *P*<0.01 at T1, OR =1.28 (1.05, 1.57), *P*=0.02 at T2	NR	U: –	0 of 6
			M: NR	
EII	OR =0.86 (0.76, 0.98), *P*=0.02 at T2		U: –	
			M: NR	
EI	NS		U: 0	
			M: NR	
AIII	NS		U: 0	
			M: NR	

(*Continued*)

Table S2 (*Continued*)

First author	Setting, n patients	Measures	
		Adherence[†], follow-up period[‡]	**Psychosocial predictors[§]**
Nilsson Schönnesson[18]	Sweden; patients recruited by clinic nurses, n=203	Adherence by self-report (straightforward), 24 months	Anxiety symptoms (ASBSI) Belief in adherence necessity (one item) Belief that ART prolongs one's life (one item) Belief in future HIV-related health problems (self-developed scale) Belief in influencing HIV disease (MAH) Beliefs in ART health concerns (eg, believe that medication makes sicker, one item) Coping mode: helplessness (MAH) Coping mode: resilience (MAH) Depressive symptoms (DSBSI) Global social support satisfaction (one item) Hopelessness (BHS) Life stress (LSS) Patient-provider relationship (self-developed scale) Perceived pressure to take HIV medication (self-developed scale) Posttraumatic stress disorder symptoms related to HIV diagnosis (HIE) Self-efficacy in taking medication (self-developed scale)
Thrasher[19]	USA; patients in public use of HCSUS data-set, n=1,911	Adherence by self-report (straightforward), 12 months	(Instruments NR): depressive symptoms Dysthymia symptoms Social support
Horne[20]	UK; outpatients, eligible to receive HAART, n=136	Adherence by self-report (VAS-scale from MASRI, straightforward), 12 months	Depressive symptoms (HADS) HAART concern beliefs about medication (BMQ) HAART necessity beliefs about medication
Mugavero[21]	USA; patients receiving care at one of eight infectious disease clinics, n=474	Non-adherence by self-report (AACTG, straightforward, corrected for baseline non-adherence), 27 months	Number of severe stressful events (LES, modified version) Number of stressful events (moderate + severe stressful events) Number of traumatic events Number of types of lifetime traumatic experiences (composite measure of diverse questionnaires)

Psychcat‖	Results¶		Direction of association (regarding adherence)**	N domains bias free††
	Univariate	Multivariate		
EI	NR	NS	U: NR M: 0	1 of 6
AI		NS	U: NR M: 0	
AI		NS	U: NR M: 0	
AII		NS	U: NR M: 0	
AIII		NS	U: NR M: 0	
AI		NS	U: NR M: 0	
BII		NS	U: NR M: 0	
D		NS	U: NR M: 0	
EI		NS	U: NR M: 0	
CIII		NS	U: NR M: 0	
BII		NS	U: NR M: 0	
EII		NS	U: NR M: 0	
CI		NS	U: NR M: 0	
CIII		NS	U: NR M: 0	
EI		NS	U: NR M: 0	
AIII		NS	U: NR M: 0	
EI	OR =0.98 (0.96, 0.99), *P*=0.007	NR	U: – M: NR	1 of 6
EI	OR =0.92 (0.87, 0.96), *P*=0.001		U: – M: NR	
CIII	NS		U: 0 M: NR	
EI	NS	NT	U: 0 M: NT	3 of 6
AI	High adherence 2.9 (0.6) versus low adherence 3.3 (0.6), *P*=0.005	OR =0.45 (0.22, 0.96), *P*=0.038	U: – M: –	
AI	High adherence 4.0 (0.6) versus low adherence 3.7 (0.6), *P*=0.006	OR =2.19 (1.02, 4.71), *P*=0.045	U: + M: +	
EII	OR (per event) =1.14 (1.03, 1.26)	NS	U: – M: 0	3 of 6
EII	OR (per event) =1.09 (1.04, 1.13)	OR (per event) =1.10 (1.04, 1.16)	U: – M: –	
EII	OR (per event) =1.73 (1.24, 2.39)	NS	U: – M: 0	
EII	NS	NS	U: 0 M: 0	

(*Continued*)

Table S2 (*Continued*)

First author	Setting, n patients	Measures	
		Adherence[†], follow-up period[‡]	**Psychosocial predictors[§]**
Carrieri[22]	France; patients starting HAART-regimen including at least one protease inhibitor, n=1,110	Non-adherence by self-report (AACTG, straightforward), 60 months	Depressive symptoms (CES-D) Support from partner (whether principal or not, instrument NR)
Transplant-related (immunosuppressant medication)			
Stilley[23]	USA; transplant patients, recruited before hospital discharge or at early clinic visit, n=152	Adherence by MEMS (continuous measure), 6 months	Affective dysregulation (degree of negative affectivity and irritability, DI) Behavioral dysregulation (impulsivity, sensation seeking, aggression) Cognitive dysregulation (less strategic thinking, problem solving, self-monitoring) Family environment (family support, FRI) Hostility (CMHS)
De Geest[24]	Belgium; convenience sample of outpatients, n=101	Non-adherence by MEMS (ordinal measure, correction for past adherence), 6 months	Depressive symptoms (BDI) Self-efficacy in taking medication (LTMSES) Social support (PRQ) Symptom distress (ATSFDS)
Russell[25]	USA; convenience sample of renal transplant patients, n=50	Adherence by MEMS (ordinal measure), 12 months	Depressive symptoms (BDI) Emotional burden (MS) Self-efficacy in taking medication (LTMSES) Social support (SSAI)
Weng[26]	USA; patients recruited at time of renal transplantation, n=829	Adherence by MEMS (ordinal measure), 12 months post-transplantation	Beliefs regarding who or what controls and influences one's health (MHLCS) Depressive symptoms (CES-D) Perceived stressfulness of transplant-related issues (TSQ) Perceptions that social needs are being met (friends and family sub-score, SSAS)
Dew[27]	USA; heart transplant patients at academic hospital[‡‡‡], n=108	Non-adherence by self-report (straight-forward), 12 months post-transplantation	Coping strategies: use of active-behavioral coping (Coping checklist) Coping strategies: use of active-cognitive coping Coping strategies: use of avoidance coping (% high) Emotional status: anger-hostility symptoms (SCL-90) Emotional status: anxiety symptoms Emotional status: depressive symptoms

Psychcat‖	Results¶		Direction of association (regarding adherence)**	N domains bias free††
	Univariate	Multivariate		
EI	b =0.22 (95% CI =0.12, 0.32), $P<0.001$	b =0.18 (0.07, 0.29)	U: – M: –	2 of 6
CII	b =–0.16 (–0.26, –0.07), $P=0.001$	b =–0.15 (–0.25, –0.05)	U: + M: +	
EI	Correlation coefficient: NS¶¶	NR	U: 0 M: NR	1 of 6
D	r=0.26, $P\leq0.05$***		U: –††† M: NR	
BI	NS¶¶		U: 0 M: NR	
CII	NS¶¶		U: 0 M: NR	
D	NS¶¶		U: 0 M: NR	
EI	NR	NS	U: NR M: 0	2 of 6
AIII		Median =4.85 (Q1 =4.70, Q3 =5.00) for excellent adherers, 4.81 (Q1 =4.70, Q3 =4.89) for moderate non-adherers, 4.41 (Q1 =4.30, Q3 =4.81) for minor adherers, $P=0.04$	U: NR M: +	
CIII		NS	U: NR M: 0	
EII		NS	U: NR M: 0	
EI	NS	NR	U: 0 M: NR	0 of 6
EI	NS		U: 0 M: NR	
AIII	NS		U: 0 M: NR	
CIII	NS		U: 0 M: NR	
AIII	OR =1.05 (1.00, 1.11), $P=0.05$ (powerful others subscale)	NS	U: + M: 0	2 of 6
EI	NS	NT	U: 0 M: NT	
EII	NS	NT	U: 0 M: NT	
CII	NS	NT	U: 0 M: NT	
BI	NS	NT	U: 0 M: NT	2 of 6
BI	NS	NT	U: 0 M: NT	
BII	Non-adherent 58.8%, adherent 29.9%, $P<0.05$	OR =9.71, $P<0.05$	U: – M: –	
EI	Non-adherent 47.1%, adherent 12.1%, $P<0.001$	OR =13.40, $P<0.05$	U: – M: –	
EI	Non-adherent 82.4%, adherent 53%, $P<0.05$	NS	U: – M: 0	
EI	NS	NT	U: 0 M: NT	

(*Continued*)

Table S2 (*Continued*)

First author	Setting, n patients	Measures	
		Adherence[†], follow-up period[‡]	**Psychosocial predictors[§]**
			Sense of mastery (ie, control over life, SMS)
			Social support: caregiver support (% poor) (Spanier,[35] Pearlin and Schooler)[36]
			Social support: friend support (Moos)[37]
Dew[28]	USA; patients receiving first lung transplantation in academic hospital, n=178	Non-adherence by self-report (straightforward), 24 months	Anger-hostility symptoms (SC)
			Anxiety symptoms (SC)
			Care provider locus of control (health outcomes due to professional? MHLCS)
			Chance locus of control (health outcomes occur by chance?)
			Degree to which one can rely on friends for emotional/practical support/friend support (Moos)[37]
			Depressive symptoms (SC)
			Expectations about the future/optimism (LOT)
			Internal locus of control (can I influence my health outcome? MHLCS)
			Supportiveness (both emotionally and practically) of recipient's relationship with their primary family caregiver (when low = higher odds) (DAS)
Dobbels[29]	Belgium: heart, liver and lung transplant patients listed at university hospitals, n=186	Non-adherence by self-report (straightforward, corrected for pre-transplant adherence), 12 months post-transplantation	Agreeableness (one's orientation along continuum from compassion to antagonism, NEO-FFI)
			Anxiety symptoms (HADS)
			Conscientiousness (ie, degree of organization, NEO-FFI)
			Depressive symptoms (HADS)
			Extraversion (capacity for joy, need for stimulation, NEO-FFI)
			General received practical and informational support (SSQ)
			Neuroticism (NEO-FFI)
			Openness to experience (toleration for and exploration of the unfamiliar, NEO-FFI)
			Received specific support with medication taking (SSQ)

Psychcat‖	Results¶		Direction of association (regarding adherence)**	N domains bias free††
	Univariate	Multivariate		
			U: 0	
AIII	NS	NT	M: NT	
			U: –	
CII	Non-adherent 52.9%, adherent 27.0%, $P<0.05$	NS	M: 0	
			U: 0	
CII	NS	NT	M: NT	
EI	(Correlation coefficient, significant if r≥0.15***): r≥0.15	NS	U: ?	1 of 6
			M: 0	
EI	r≥0.15	NS	U: ?	
			M: 0	
AIII	r≥0.15	NS	U: ?	
			M: 0	
AIII	r≥0.15	NS	U: ?	
			M: 0	
CII	r≥0.15	NS	U: ?	
			M: 0	
EI	r≥0.15	NS	U: ?	
			M: 0	
D	r≥0.15	NS	U: ?	
			M: 0	
AIII	r≥0.15	NS	U: ?	
			M: 0	
CII	r≥0.15	OR =2.59 (1.20, 5.58), $P<0.05$	U: ?	
			M: –	
D	NR	NT or NS	U: NR/NS	1 of 6
			M: 0	
EI		NT or NS	U: NR/NS	
			M: 0	
D		OR =0.80 (0.67, 0.95), $P=0.01$	U: NR/NS	
			M: +	
EI		NT or NS	U: NR/NS	
			M: 0	
D		NT or NS	U: NR/NS	
			M: 0	
CIII		NT or NS	U: NR/NS	
			M: 0	
D		NT or NS	U: NR/NS	
			M: 0	
D		NT or NS	U: NR/NS	
			M: 0	
CIII		OR =0.94 (0.89, 0.99), $P=0.03$	U: NR/NS	
			M: +	

(*Continued*)

Table S2 (*Continued*)

First author	Setting, n patients	Measures	
		Adherence†, follow-up period‡	**Psychosocial predictors§**
Other (diabetes and/or hypertension and/or heart disease)			
DiMatteo[30,‖ ‖]	USA: patients from five medical specialties in HMOs, large multispecialty groups or solo practices, n=max 1,828[§§§]	Adherence by self-report (straightforward, continuous measure, correction for baseline adherence), 24 months	Health distress (instrument NR) Perceptions of physician's authoritativeness (self-developed scale) Satisfaction with interpersonal medical care (Sherbourne)[38] Social support (composite measure, Sherbourne and Stewart)[39] Tendency to use avoidance coping (instrument NR)

Notes: *NS (non significant): as reported in the concerning study. UD (undetermined): because of inadequate description in the concerning study. †Binary outcome measure, unless indicated otherwise. With a straightforward question, we mean that participants were directly asked to indicate how many medication doses they missed. For example: "How many pills did you take this week?"; ‡follow-up period = number of months between baseline (unless indicated otherwise) and last adherence measurement; §if no instrument is mentioned for predictor, then previous mentioned instrument is applicable; ‖psychosocial category, to which a predictor was assigned. A = Beliefs and cognitions about: I) medication and treatment; II) illness; III) self-efficacy and locus of control. B = coping styles: I) task oriented, II) emotion oriented. C = Social influences and social support: I) regarding medical caregiver; II) regarding friends and family; III) in general. D = personality traits. E = psychological well-being: I) mood state; II) perceived stress/stressors; ¶OR: Odds Ratio (95% confidence interval). OR <1 = lower chance of being adherent or non-adherent (for direction in relevant study, see column "Adherence, follow-up period") when predictor increases or when predictor ≠ reference category. OR >1 = greater change of being adherent or non-adherent when predictor increases (or when predictor ≠ reference category). Scores other than OR are the mean predictor scores with standard deviation, unless indicated otherwise; **+ = higher level of predictor implies higher adherence at level $P \leq 0.05$; – = higher level of predictor implies less adherence at $P \leq 0.05$; 0 = no significant association between predictor and adherence at $P \leq 0.05$; ? = association present, but direction unclear; ††to determine methodological quality, six bias domains per study were judged. Here, the total amount of bias free domains is reported (for further details, see table S3); ‡‡assumed that all variables, tested by univariate analysis, were also tested by multivariate analysis; §§retrospective design; ‖ ‖Diagnosis for coronary heart disease, hypertension, diabetes mellitus and/or hyperlipidaemia; ¶¶not reported in study is interpreted by HZ/BvdB as not significant; ***significance of $P \leq 0.05$ assumed by HZ/BvdB; †††negative association assumed; ‡‡‡type of medication is immunosuppressants, antihypertensives, and/or antivirals; §§§use of chronic preventive medication assumed; ‖ ‖ ‖unexpected direction.

Abbreviations: AACTG, adult AIDS clinical trials group; ALTMBSES, adapted long term medication behavior self efficacy scale; AGSRP, adapted gay service research project; AIDS, acquired immunodeficiency syndrome; AMHI, adapted mental health inventory; APIAQ, adapted protease inhibitor attitude questionnaire; ART, antiretroviral therapy; ASBSI, anxiety subscale of brief symptom inventory; ATS, anxiety trait scale; ATSFDS, adapted version of transplant symptom frequency and distress scale; AWC, adapted ways of coping; BDI, beck depression inventory; BHLES, buffalo HIV life events survey; BHS, beck hopelessness scale; BMICIS, Billings and Moos inventory of coping with illness styles; BMQ, beliefs about medication questionnaire; BST, Burnam interviewer-administered 8-item screening tool; CES-D, center for epidemiologic studies depression scale; CMHS, Cook-Medley hostility scale; DAS, dyadic adjustment scale; DI, dysregulation inventory; DOS, dispositional optimism scale; DSBSI, depression subscale of brief symptom inventory; DSPERI, demoralization scale of psychiatric epidemiology research interview; FRI, family relations index (from family environment scale); FTSSH, Finnish twin study scale of hostility; GHQ, general health questionnaire; HAART, highly active antiretroviral therapy; HADS, hospital anxiety and depression scale; HAT-QOL, HIV/AIDS-targeted quality of life instrument; HBS, health behaviour scale; HCSUS, HIV cost and services utilization study; HIE, Horowitz impact of events scale; HIS, health intention scale; HIV, human immunodeficiency virus; HMO, health maintenance organization; ICS, inhaled corticosteroids; IDD, inventory to diagnose depression; IQR, interquartile range; ISEL, interpersonal support evaluation list; LES, life experience survey; LOT-R, life orientation test; LSS, life stressors scale; LTMSES, long term medication self-efficacy scale; MAH, mental adjustment to HIV; MARS, medication adherence report scale; MAS, Miller attitude scale; MASRI, medication adherence self-report inventory; MEMS, medication even monitoring system; MHLCS, multidimensional health locus of control scale; MOS, medical outcome study health survey; MS, Memphis survey; NEO-FFI, NEO five factor inventory; NR, not reported; NS, non-significant; NSEPQSS, neuroticism scale of the Eysenck personality questionnaire-revised short scale; NT, not tested; OR, odds ratio; Pat SS, patient satisfaction scale; PEI, psychiatric epidemiology interview; POMS, profiles of mood states; PPCS, perceived parenting competence scale; PRQ, personal resource questionnaire; PSS, perceived stress scale; RSEQR, Rosenberg self-esteem questionnaire; SC, symptom checklist; SCL-90, Symptom Checklist-90-R; SEM, standard error of the mean; SF-36, short form-36 health survey; SMS, sense of mastery scale; SOC, sense of coherence; SPS, social provision scale; SSAI, social support appraisals index; SSAS, social support appraisal scale; SSQ, social support questionnaire; TSQ, transplant stress questionnaire; VAS, visual analog scale.

Psychcat‖	Results¶		Direction of association (regarding adherence)**	N domains bias free††
	Univariate	Multivariate		
EII	NR	β =–0.22, *P*=0.05	U: NR M: –	0 of 6
CI		NT or NS	U: NR M: 0	
CI		NT or NS	U: NR M: 0	
CIII		NT or NS	U: NR M: 0	
BII		NT or NS	U: NR M: 0	

Table S3 Results of judging methodologic quality

First author	Overall quality	Domain free of bias?					
		Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Confounding measurement and account	Analysis
Bottonari[13]	Low	No	No	Partly	Partly	No	No
De Geest[24]	Low	No	Yes	Partly	Yes	No	Partly
Delgado[10]	Low	Partly	Yes	Partly	Partly	Partly	Partly
Deschamps[8]	Low	No	Partly	No	Yes	No	No
Dew[27]	Low	No	Yes	Yes	Partly	Partly	Partly
Dew[28]	Low	Yes	Partly	Partly	Partly	Partly	Partly
DiMatteo[30]	Low	Partly	No	Partly	No	No	No
Dobbels[29]	Low	Yes	Partly	Partly	Partly	Partly	No
Gazmararian[3]	Low	Yes	Partly	Partly	Yes	Partly	Yes
Godin[14]	Low	Partly	Yes	No	Partly	Partly	Partly
Grégoire[5]	Low	Partly	No	No	Partly	No	Partly
Holmes[9]	Low	Partly	Yes	Partly	Partly	Partly	Yes
Kacanek[15]	Low	No	Yes	Partly	Partly	No	Yes
Martini[16]	Low	Partly	No	No	Partly	No	No
Mellins[17]	Low	Partly	Partly	Partly	No	No	No
Miller[6]	Low	No	Partly	Partly	No	Partly	Partly
Nabi[4]	Low	Partly	Partly	Partly	Partly	Partly	Yes
Nilsson Schönnesson[18]	Low	Partly	Yes	Partly	No	Partly	No
Ponieman[1]	Low	No	No	Partly	Partly	Partly	Partly
Russell[25]	Low	No	No	Partly	Partly	No	Partly
Singh[11]	Low	No	Yes	Partly	Partly	Partly	No
Singh[12]	Low	Partly	Yes	Partly	Partly	No	No
Stilley[23]	Low	Yes	Partly	Partly	No	No	No
Thrasher[19]	Low	Yes	Partly	Partly	Partly	Partly	Partly
Venturini[2]	Low	Yes	Partly	Partly	Yes	Partly	Partly
Weng[26]	Low	Partly	No	Yes	Partly	Partly	Yes
Molloy[7]	Low	No	Yes	Partly	No	Partly	Partly
Horne[20]	Low	Yes	Yes	Partly	Partly	No	Yes
Mugavero[21]	Low	Yes	No	Yes	Partly	Partly	Yes
Carrieri[22]	Low	No	Yes	No	Partly	Partly	Yes

Table S4 Sensitivity analyses: methodological quality, disease, adherence measures, and statistical analyses

Alteration	Relevant studies	Categories affected	Change in level of evidence
Alterations in methodological quality cut-offs			
High-quality study when all six bias domains judged at least as partly (and no no-judgment) instead of ≥four domains judged as yes	19,26,34,35,42,52,64 now high-quality, all other studies low-quality	AI, II, III and CI, II and EII CIII and EI	No association: moderate instead of limited evidence No association: strong instead of limited evidence
Low-quality study when ≥four domains judged as no instead of <four domains judged as yes	19,26,33–36,38,39,42–44,46,47,49,51–60,64,65 now high-quality, all other studies still low-quality	All categories	No association: strong instead of limited evidence
Alterations in disease			
Only focus on HIV disease	19,25,42–49,51–55 (studies in analysis)	AI CII and D	No association: conflicting instead of limited evidence Level undetermined (≤one study available)
Only focus on transplant-related diseases	56–60,64,65 (studies in analysis)	AI, II, BII and CI	Level undetermined (≤one study available)
Focus on asthma, diabetes, heart disease/hypertension	26,33–36,38,39,66 (studies in analysis)	AII, III, BI, II, CI, II, D, EII	Level undetermined (≤one study available)
Alterations in adherence measures			
Focus on objective adherence measures (MEMS, record review)	19,25,26,34,35,42–44,56–59 (studies in analysis)	D AII and CI	No association: conflicting instead of limited evidence Level undetermined (≤one study available)
Focus on subjective adherence measures (self-report)	33,36,38,39,45–49,51–55,60,64–66 (studies in analysis)	AI BI BII and EI	No association: conflicting instead of limited evidence Level of evidence undetermined (≤one study available) No association: conflicting instead of limited evidence
Alterations in statistical analysis			
Only focus on univariate analysis instead of multivariate analysis	34,38,46,51,57,65,66 (studies omitted due to lack of univariate analysis)	AI, AIII, CI, CIII, EI and EII	No association: conflicting instead of limited evidence

Notes: A = Beliefs and cognitions about: I) medication and treatment; II) illness; III) self-efficacy and locus of control. B = coping styles: I) task oriented, II) emotion oriented. C = Social influences and social support: I) regarding medical caregiver; II) regarding friends and family; III) in general. D = personality traits. E = psychological well-being: I) mood state; II) perceived stress/stressors.
Abbreviations: HIV, human immunodeficiency virus; MEMS, medication event monitoring system.

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