

# Interventions to improve adherence to antiretroviral therapy: a rapid systematic review

Krisda H. Chaiyachati<sup>a</sup>, Osondu Ogbuoji<sup>b</sup>, Matthew Price<sup>b</sup>,  
Amitabh B. Suthar<sup>c</sup>, Eyerusalem K. Negussie<sup>c</sup> and Till Bärnighausen<sup>b,d</sup>

**Introduction:** Access to antiretroviral treatment (ART) has substantially improved over the past decade. In this new era of HIV as a chronic disease, the continued success of ART will depend critically on sustained high ART adherence. The objective of this review was to systematically review interventions that can improve adherence to ART, including individual-level interventions and changes to the structure of ART delivery, to inform the evidence base for the 2013 WHO consolidated antiretroviral guidelines.

**Design:** A rapid systematic review.

**Methods:** We conducted a rapid systematic review of the global evidence on interventions to improve adherence to ART, utilizing pre-existing systematic reviews to identify relevant research evidence complemented by screening of databases for articles published over the past 2 years on evidence from randomized controlled trials (RCTs). We searched five databases for both systematic reviews and primary RCT studies (Cochrane Library, EMBASE, MEDLINE, Web of Science, and WHO Global Health Library); we additionally searched ClinicalTrials.gov for RCT studies. We examined intervention effectiveness by different study characteristics, in particular, the specific populations who received the intervention.

**Results:** A total of 124 studies met our selection criteria. Eighty-six studies were RCTs. More than 20 studies have tested the effectiveness of each of the following interventions, either singly or in combination with other interventions: cognitive-behavioural interventions, education, treatment supporters, directly observed therapy, and active adherence reminder devices (such as mobile phone text messages). Although there is strong evidence that all five of these interventions can significantly increase ART adherence in some settings, each intervention has also been found not to produce significant effects in several studies. Almost half (55) of the 124 studies investigated the effectiveness of combination interventions. Combination interventions tended to have effects that were similar to those of single interventions. The evidence base on interventions in key populations was weak, with the exception of interventions for people who inject drugs.

**Conclusion:** Tested and effective adherence-enhancing interventions should be increasingly moved into implementation in routine programme and care settings, accompanied by rigorous evaluation of implementation impact and performance. Major evidence gaps on adherence-enhancing interventions remain, in particular, on the cost-effectiveness of interventions in different settings, long-term effectiveness, and effectiveness of interventions in specific populations, such as pregnant and breastfeeding women.

© 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins

*AIDS* 2014, **28** (Suppl 2):S187–S204

**Keywords:** antiretroviral adherence, interventions, randomized controlled trials, systematic review

---

<sup>a</sup>Yale School of Medicine, New Haven, <sup>b</sup>Department of Global Health and Population, Harvard School of Public Health, Boston, USA, <sup>c</sup>HIV Department, World Health Organization, Geneva, Switzerland, and <sup>d</sup>Wellcome Trust Africa Centre for Health and Population Science, University of KwaZulu-Natal, Mtubatuba, South Africa.

Correspondence to Till Bärnighausen, 665 Huntington Avenue, Boston 02115, Boston, MA.

Tel: +1 617 379 0372; fax: +1 617 432 6733; e-mail: tbaernig@hsph.harvard.edu

DOI:10.1097/QAD.0000000000000252

## Background

Antiretroviral treatment (ART) has converted a highly fatal HIV infection into a chronic condition that requires lifelong care [1]. Within the past decade, worldwide access to ART has improved significantly, with almost 10 million people receiving ART by the end of 2012 [2]. In addition to its life-prolonging effects, ART can also reduce HIV transmission to uninfected people [3,4]. In this new era of HIV treatment, the continued success of ART will depend on improving our understanding of when to initiate therapy, creating continuity of care, and ensuring high treatment adherence. Adherence is the extent to which a person uses a medication according to medical recommendations, inclusive of timing, dosing, and consistency. Arguably, adherence is the most critical factor in ensuring ART success, because without good adherence, treatment failure is likely, leading to avoidable HIV-related morbidity and mortality. Additionally, imperfect adherence increases the risk of developing resistant HIV strains and transmitting the virus to others [5–7]. Because adherence behaviours and patterns can profoundly affect an individual's treatment response and potentially narrow future therapeutic options, improving and sustaining ART adherence is a critical component and priority of public health efforts.

People living with HIV and their care providers often face challenges in ensuring good adherence. A 2011 meta-analysis, which pooled ART adherence of 33 199 adults in 84 observational studies, reports that only 62% of individuals took at least 90% of their prescribed ART doses [8]. Given these adherence difficulties, effective, feasible and acceptable interventions to enhance ART adherence are urgently needed to ensure the continued success and clinical and financial sustainability of the global ART scale-up [9–11]. Multiple systematic reviews and meta-analysis of ART adherence-enhancing interventions have been conducted over the past few years, but these studies have often been limited to particular interventions, populations, or settings [12–16].

To inform the evidence base for the 2013 WHO consolidated guidelines on the Use Antiretroviral Drugs for Treating and Preventing HIV Infection [17], we conducted a rapid systematic review synthesizing the research results on ART adherence-enhancing interventions across intervention types, populations, and settings. Our review advances the existing literature in three ways: first, it is the most comprehensive compilation of the evidence on adherence-enhancing interventions to date; second, it allows evaluation of robustness of interventions across settings; and third, we indicate studies that focus on specific populations of particular interest because of comorbidities and other vulnerabilities that may interfere with their ability to

adhere to ART. In addition to the contribution to the WHO 2013 consolidated guidelines, our review aims to provide a guide for ART programme managers, policy makers, and researchers to the portfolio of ART adherence-enhancing interventions for practice, policy and further study.

## Methods

### General methodology of rapid systematic reviews

We conducted a rapid systematic review of the global evidence on interventions to improve ART medication adherence. Rapid systematic reviews differ from traditional systematic reviews in that they utilize pre-existing systematic reviews to identify relevant research evidence in addition to screening databases for recent primary studies [18–21]. This practice is useful for making health policy decisions, because it allows examination of the evidence while ensuring that information is assimilated as fast as possible given prior work [18–24].

Using pre-existing systematic reviews to identify relevant primary articles reduces the time needed to identify the relevant body of evidence on a particular topic. However, given that the time required to conduct, complete, and publish a systematic review typically ranges from 1 to 2 years [20,22], synthesis solely based on pre-existing systematic reviews runs the danger of failing to incorporate evidence that has accrued over the most recent few years. We thus supplement our systematic review of systematic reviews, with a complete screening of databases of primary evidence, but – in order to maintain rapidity in the identification of primary studies – we constrained these searches to the past 2 years (2010–2012) and to randomized controlled trials (RCTs).

### Search strategies

To identify systematic reviews, we conducted searches in the Cochrane Library, EMBASE, MEDLINE, Web of Science, and WHO Global Health Library (which includes both regional and global indices). The search algorithms are shown in Boxes A1 and A2 in the appendix (<http://links.lww.com/QAD/A499>). Abstracts from conferences and meetings were excluded because they do not undergo the same level of peer review as published full-text articles and they do not provide the necessary references for extracting study-level data. Publications on adherence interventions were excluded if they were letters to the editor, editorials, commentaries, or opinion articles. We further excluded systematic reviews of interventions studying programme retention, efficacy of combination antiretrovirals (fixed or multiple medications), dosing strategies, or use of antiretrovirals for pre-existing or post-exposure prophylaxis. We did not

limit our search to particular times, locations, or languages. Additionally, we searched ClinicalTrials.gov, Cochrane Central Register of Controlled Trials, EMBASE, MEDLINE, Web of Science, and WHO Global Health Library for RCTs published between 1 September 2010 and 31 August 2012 that investigated interventions targeted towards improving ART adherence. To be included in this review, RCTs could report an adherence intervention as the primary or secondary aim or simply report adherence measurements in the presence of an intervention. Studies comparing or validating adherence measurement approaches without reporting on an adherence-enhancing intervention were excluded. We followed the reporting standards described in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [25].

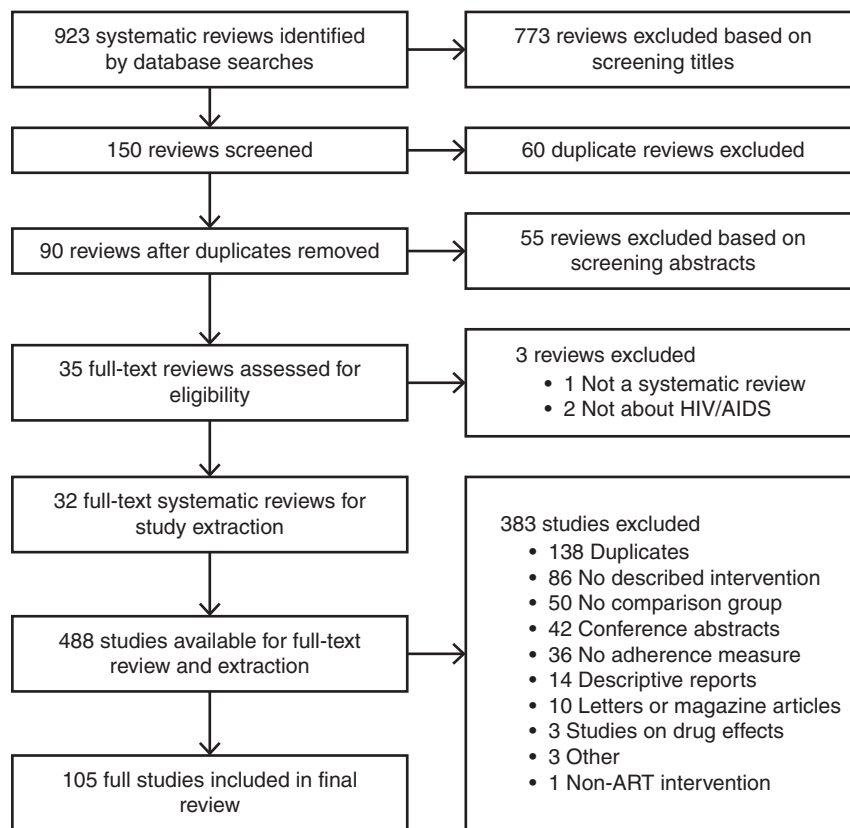
**Study selection**

Three investigators (K.C., M.P., and O.O.) worked independently, completing separate screenings of the literature. We screened titles and abstracts of studies that were identified in previous systematic reviews on the effectiveness of interventions aimed at increasing antiretroviral adherence; as well as titles and abstracts of records identified in the search of databases for RCTs investigating adherence interventions. All records were screened by two of the three reviewers; two reviewers

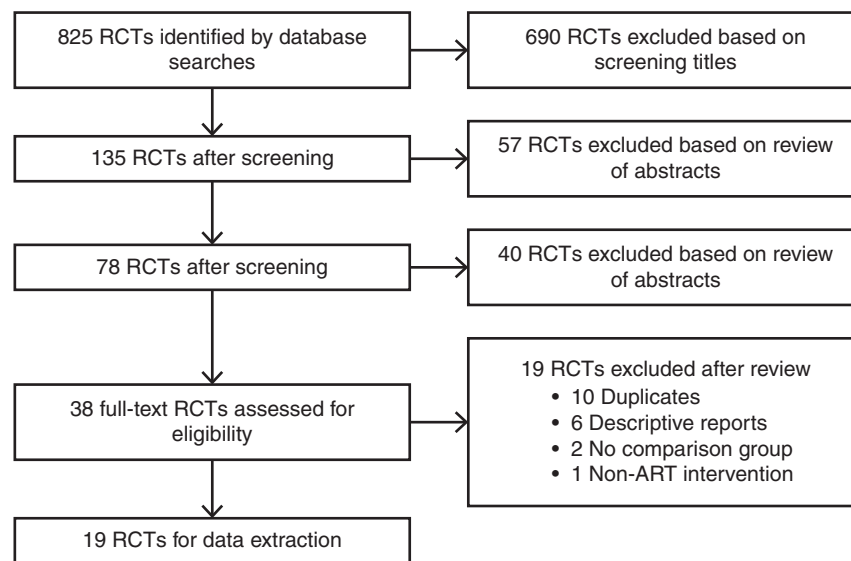
have been found to be sufficient to carry out a high-quality systematic review [26]. The same reviewers used the inclusion and exclusion criteria to independently assess the full eligibility of studies identified in the databases. Reviewers were not blinded to study authors, conclusions, or outcomes, because blinding is complicated to implement and has been shown to have little effect on the quality of systematic reviews [27]. Once all potentially relevant full-text articles and abstracts were identified, the three reviewers achieved consensus regarding eligibility and extracted data onto a standardized extraction form. Where consensus was not possible, a fourth reviewer (T.B.) served as arbiter. After relevant systematic reviews were identified, we searched for the primary studies featured in these reviews and extracted the data from the studies. Data entry was compared, and discordant information was resolved by consensus through data checks and discussion between the data extractors. When necessary, the further reviewer (T.B.), who guided but was not directly involved in the primary data extraction process, was asked to mediate. Figures 1 and 2 show flowcharts of the study selection processes.

**Data extraction**

We organized the synthesis of results by adherence intervention type, that is, the actual intervention activity, such as directly observed therapy (DOT) or depression



**Fig. 1. Flowchart of study selection process based on systematic reviews of ART adherence-enhancing interventions.** ART, antiretroviral therapy.



**Fig. 2. Flowchart of study selection process of randomized controlled trials of ART adherence-enhancing interventions.** RCTs, randomized controlled trials. ART, antiretroviral therapy.

treatment. In addition to the intervention types, we extracted from the studies the following data: author and year of publication, study period, study design, country of study, population, source of information, and healthcare setting, in which the study took place; study duration, sample size, loss to follow-up, intervention, control group, adherence measure, and study results. Web Appendix, <http://links.lww.com/QAD/A506> shows the study characteristics; Table 1 provides an overview of the different adherence-enhancing interventions that were tested in the studies and reports the results by outcome measure. We report on results for subjective adherence measures (self-report by patients), objective adherence measures (pill count, pharmacy refill, and electronic monitoring), and the biological correlates of adherence (viral load, CD4<sup>+</sup> cell count, and change in body weight). A few studies report composite adherence indices incorporating information from several outcome measures. We do not include the results in terms of these outcome measures in our review, because the use of these indices is usually particular to one study, and all studies using indices also report results in terms of outcome based on individual measures.

## Results

A total of 124 studies met our selection criteria (Figures 1 and 2). These studies included 86 RCTs, 6 non-randomized controlled trials (NRCT), 19 before-after studies, 8 cohort studies, 4 case-control studies, and 1 cross-sectional study. Seventy-five studies were carried out in North America, 30 in Africa, 11 in Europe, 4 in Asia, 3 in Central and South America, and 2 in Australia. Publication intensity in studies testing ART

adherence-enhancing interventions increased over time; each year before 2003 three or fewer articles were published, whereas in 2003 and thereafter, at least six articles were published each year and in many years more than 10 articles (Web Appendix, <http://links.lww.com/QAD/A506>).

Almost half (55) of the 124 studies investigated the effectiveness of combination interventions, that is, interventions that were composed of several clearly identifiable components. The most commonly tested interventions were cognitive-behavioural therapy (CBT) (60), followed by education (28), treatment supporters (26), DOT (20) and active reminder devices (20). The less commonly tested intervention types included structural interventions (such as changes in the person delivering ART, or in the location where ART were provided) (10), counselling (8), nutritional support (7), financial incentives (5), passive reminder devices (5), and drug use treatment (4). Active reminder devices included both telephone reminders and other technologies, such as pagers and pillboxes with in-built timers and alarms. Passive reminder devices included pillboxes and diary cards. Detailed information on intervention types and the interventions are shown in Table 1. Commonly (in 29 studies), CBT, education or counselling were combined with other interventions. DOT, passive reminder devices, treatment supporters, nutritional support, and financial incentives were combined with other interventions in more than two-fifths of the studies, whereas the other interventions were less likely to be investigated in combination.

The synthetic picture that emerges becomes even more complex when the success of particular interventions is considered across different outcomes. Table 2 shows the

**Table 1. Adherence-enhancing interventions and results.**

Authors and year (review authors)	Intervention type	Intervention	Results						
			SR	PC	PR	EM	VL	CD4 <sup>+</sup>	WC
Blank <i>et al.</i> , 2011 [28]	Structural intervention	Advanced practice nurse for monitoring and managing ART	-	-	-	-	Y	N	-
Berg <i>et al.</i> , 2011 [29]	DOT, other	ART DOT and methadone maintenance therapy	-	Y	-	Y	-	-	-
Chung <i>et al.</i> , 2011 [30]	Counselling, ARD	Intensive adherence counselling, pocket alarm device, or both	-	Y	Y	-	Y	N	-
da Costa <i>et al.</i> , 2012 [31]	ARD	SMS messages before last scheduled medication for the day	(Y)	(Y)	-	(Y)	-	-	-
de Bruin <i>et al.</i> , 2010 [32]	Counselling, CBT	Adherence counselling, brief motivational interviewing utilizing EM results	-	-	-	Y	Y	-	-
Duncan <i>et al.</i> , 2012 [33]	CBT	Mindfulness-based stress reduction strategies for reducing ART symptoms and stress related to ART side effects	N	-	-	-	-	-	-
Fisher <i>et al.</i> , 2011 [34]	CBT, education	Interactive computer-based antiretroviral adherence promotion programme consisting of educational materials, goal selection, and targeted interventions focused on motivational and behavioral strategies for improving adherence	Y	-	-	-	N	-	-
Hardy <i>et al.</i> , 2011 [35]	ARD	Personalized mobile phone reminder system for adherence	Y	Y	-	N	-	-	-
Holstad <i>et al.</i> , 2011 [36]	CBT	Motivational interviewing group sessions involving exploring day-to-day experiences, identifying barriers to adherence, exploring motivations and adherence strategies	-	-	-	Y	Y	N	-
Kalichman <i>et al.</i> , 2011a [37]	CBT, education	Counselling about effective decision-making, providing education, and developing skills to avoid drug use, unsafe sexual practices, and improve adherence	-	Y	-	-	-	N	-
Kalichman <i>et al.</i> , 2011 [38]	Counselling	Counselling sessions via mobile phones	Y	Y	-	-	-	-	-
Leon <i>et al.</i> , 2011 [39]	Counselling, structural intervention	Home care monitoring through an internet-based clinical system that provides consultation, telepharmacy, access to a library of resources, and a community of other individuals with HIV	N	-	N	-	N	N	-
Pyne <i>et al.</i> , 2011 [40]	Depression treatment	Depression treatment through a clinical team consisting of a psychiatrist, a case manager, and pharmacist	N	-	-	-	-	-	-
Ramirez-Garcia and Cote 2012 [41]	CBT	Nurse-led counselling sessions seeking to stimulate development and use of skills needed for proper treatment-taking behaviour, enhancing self-efficacy, and reinforcing positive attitudes toward treatment-taking in the participant	Y	-	-	-	Y	N	-
Ruiz <i>et al.</i> , 2010 [42]	Treatment supporters, education	Peer-led treatment with baseline psycho-educational component	N	-	-	-	-	-	-
Sabin <i>et al.</i> , 2010 [43]	ARD	EM feedback	-	-	-	Y	N	Y	-
Safren <i>et al.</i> , 2012 [44]	CBT	Cognitive-behavioural therapy for adherence and depression	-	-	-	Y	N	N	-
Uzma <i>et al.</i> , 2011 [45]	ARD	Phone call reminders as memory aids	Y	-	-	-	Y	-	Y
Zubaran <i>et al.</i> , 2012 [46]	CBT	Motivational interviews with information to promote motivation for adherence	-	-	-	-	-	-	N
Dilorio <i>et al.</i> , 2003 [47] (Amico <i>et al.</i> , [48])	CBT, education, other	Nurse counsellor-led motivational interview sessions, alcoholics anonymous videotape, education materials	N	-	-	-	-	-	-
Fairly <i>et al.</i> , 2003 [49] (Amico <i>et al.</i> , [48])	ARD, PRD, CBT, education	Nurse-led education about HIV and adherence, telephone-based support; medication planners, SMS text messages, medication box, and medication alarms	Y	-	-	-	N	N	-
Goujard <i>et al.</i> , 2003 [50] (Amico <i>et al.</i> , [48])	CBT, PRD, education	Personalized educational diagnoses made for each patient, planning cards, pill boxes	(Y)	-	-	-	N	N	N
Lyon 2003 [51] (Amico <i>et al.</i> , [48])	CBT, education, nutritional support	Education on medication choices, side effects, and nutrition treatments	Y	-	-	-	(Y)	(Y)	-
Mann, 2001 [52] (Amico <i>et al.</i> , [48])	Other	Future writing	N	-	-	-	-	-	-
Margolin <i>et al.</i> , 2003 [53] (Amico <i>et al.</i> , [48])	CBT	Manual-guided group therapy sessions with harm reduction skills training, adherence training, and exploration of barriers to adherence	Y	-	-	-	Y	-	-

(continued)

Table 1 (continued)

Authors and year (review authors)	Intervention type	Intervention	Results									
			SR	PC	PR	EM	VL	CD4 <sup>+</sup>	WC	O		
McPherson-Baker <i>et al.</i> , 2000 [54] (Amico <i>et al.</i> [48])	CBT, PRD, counselling, education	Medication counselling, pill boxes, education on problem solving strategies	-	-	Y	-	N	N	-	-	Y	
Molassiotis <i>et al.</i> , 2003 [55] (Amico <i>et al.</i> [48])	CBT, ARD, education	Individual education sessions about antiretroviral medication and side effects, weekly counselling, and follow-up phone calls	Y	-	-	-	N	Y	-	-	Y	
Murphy <i>et al.</i> , 2002 [56] (Amico <i>et al.</i> [48])	CBT	Intervention sessions by cognitive-behavioural therapist and psychiatric nurse	N	-	-	-	-	-	-	-	-	
Powell-Cope <i>et al.</i> , 2003 [57] (Amico <i>et al.</i> [48])	ARD	Timer, pager, or pillbox with timer integrated into box	N	-	-	-	-	-	-	-	-	
Pradier <i>et al.</i> , 2003 [58] (Amico <i>et al.</i> [48])	Counselling, education	Individual educational and counselling sessions with a trained nurse	Y	-	-	-	Y	-	-	-	-	
Rawlings <i>et al.</i> , 2003 [59] (Amico <i>et al.</i> [48])	CBT, education	Education modules, focused on patient empowerment, HIV pathogenesis and treatment, and medication management or adherence; and education modules focused on names and physical description of medications, dosage instructions, use of MEMS, importance of adherence, and side-effects	-	-	-	N	N	N	-	-	-	
Rigsby <i>et al.</i> , 2000 [60] (Amico <i>et al.</i> [48])	Financial incentives, ARD	Customized medication schedules, daily reminders, with or without cash incentives	-	-	-	Y	N	-	-	-	-	
Safren <i>et al.</i> , 2001 [61] (Amico <i>et al.</i> [48])	CBT	Life-Steps protocol, a single-session intervention utilizing cognitive-behavioural, problem-solving, and motivational interviewing techniques to enhance motivation, rehearse adherence-related behaviours, and solve problems that interfere with adherence to HIV medications, with one follow-up telephone review	Y	-	-	-	-	-	-	-	-	
Safren <i>et al.</i> , 2003 [62] (Amico <i>et al.</i> [48])	ARD	Daily pill diary, paged electronic reminders through www.medimom.com	-	-	-	Y	-	-	-	-	-	
Smith <i>et al.</i> , 2003 [63] (Amico <i>et al.</i> [48])	CBT, education	Feedback on adherence, rooted in social cognitive theory, education and assistance with medication self-management skills	-	-	-	Y	N	-	-	-	-	
Stenzel <i>et al.</i> , 2001 [64] (Amico <i>et al.</i> [48])	DOT, counselling, other	Nurse-led DOT and adherence support, side effects information relayed to physician for follow-up	(Y)	-	-	-	(Y)	(Y)	-	-	-	
Tuldra <i>et al.</i> , 2000 [65] (Amico <i>et al.</i> [48])	CBT, education, counselling	Psycho-education, education material, counselling support	N	-	-	-	Y	-	-	-	-	
Berrien <i>et al.</i> , 2004 [66] (Bain-Brickley <i>et al.</i> [67])	Treatment supporters, education	Structured home-based support for education and identifying barriers for intervention group	N	-	Y	-	Y	N	-	-	-	
Funck-Brentano <i>et al.</i> , 2005 [68] (Bain-Brickley <i>et al.</i> [67])	Treatment supporters, CBT	Peer support sessions, in which ART patients discuss their feelings, fears and attitudes about ART	N	-	-	-	N	N	-	-	-	
Wamalwa <i>et al.</i> , 2009 [69] (Bain-Brickley <i>et al.</i> [67])	Treatment supporters, CBT	Medication diaries and counselling	N	-	-	-	N	N	-	-	-	
Cantrell <i>et al.</i> , 2008 [70] (Barnighausen <i>et al.</i> [71])	Nutritional support	Food rations (individual rations if patient is not the primary income earner in his/her family; rations for a total of seven household members if patient is primary income earner)	-	-	Y	-	-	N	-	-	-	
Chang <i>et al.</i> , 2010 [72] (Barnighausen <i>et al.</i> [71])	Treatment supporters	Home visits by treatment supporters to promote adherence through questions and pill count, and to discuss treatment benefits and side effects	N	N	-	-	Y	N	-	-	-	
Idoko <i>et al.</i> , 2007 [73] (Barnighausen <i>et al.</i> [71])	DOT	DAOT, TWOT, or WOT; provided by patient-selected treatment supporters (from the community or the patient's family)	-	-	-	-	N	N	-	-	-	
Kabore <i>et al.</i> , 2010 [74] (Barnighausen <i>et al.</i> [71])	Treatment supporters, nutritional support	Treatment supporter and/or nutritional support within a community-based model of ART care	Y	Y	-	-	-	N	-	-	-	
Lester <i>et al.</i> , 2010 [75] (Barnighausen <i>et al.</i> [71])	ARD	SMS from study clinicians asking 'How are you?' requiring a response within 48 h	Y	-	-	-	Y	-	-	-	-	
Mugusi <i>et al.</i> , 2009 [76] (Barnighausen <i>et al.</i> [71])	Treatment supporters, other	Calendar for record-keeping of dose intake, or treatment supporters	N	-	-	-	-	N	-	N	N	

Nacheaga <i>et al.</i> , 2010 [77] (Bärnighausen <i>et al.</i> [71])	DOT, education, treatment supporters	DAOT by a treatment supporter chosen using a personal network inventory instrument, one baseline education session for treatment supporter, four additional baseline education sessions and refresher course every three months for patients and treatment supporter	-	N	-	-	Y	-
Ndekha <i>et al.</i> , 2009 [78] (Bärnighausen <i>et al.</i> [71])	Nutritional support	Supplementary feeding with ready-to-use fortified, energy-dense, lipid paste	N	-	-	-	N	-
Ndekha <i>et al.</i> , 2009 [79] (Bärnighausen <i>et al.</i> [71])	Nutritional support	Supplementary feeding with ready-to-use fortified, energy-dense, lipid paste	N	-	-	-	N	-
Pearson <i>et al.</i> , 2007 [80] (Bärnighausen <i>et al.</i> [71])	DOT, treatment supporters, education	Treatment supporter-delivered DAOT, patient education about treatment, identification and mitigation of adherence barriers	Y	-	-	-	N	-
Pienaar <i>et al.</i> , 2006 [81] (Bärnighausen <i>et al.</i> [71])	Structural intervention	Five different models of ART delivery; three community-based models (doctor-led primary care clinic, nurse-led primary care clinic, integrated primary care clinic) and two hospital-based models (rural district hospital, hospital-based specialist service)	N	-	-	-	Y	-
Pop-Eleches <i>et al.</i> , 2011 [82] (Bärnighausen <i>et al.</i> [71])	ARD	Different types of SMS (short daily reminders, long daily messages, short weekly reminders, or long weekly reminders)	-	-	Y	-	-	-
Roux <i>et al.</i> , 2004 [83] (Bärnighausen <i>et al.</i> [71])	PRD	Diary cards with calendars showing medication dosing schemes	N	-	-	-	-	-
Sarna <i>et al.</i> , 2008 [84] (Bärnighausen <i>et al.</i> [71])	DOT	TWOT at nearby clinics, pill counting, and treatment support	Y	N	-	-	N	Y
Sherr <i>et al.</i> , 2010 [85] (Bärnighausen <i>et al.</i> [71])	Structural intervention	Assignment to non-physician clinicians	-	-	Y	-	Y	-
Stubbs <i>et al.</i> , 2009 [86] (Bärnighausen <i>et al.</i> [71])	Treatment supporters	Treatment supporters (from the community or the patient's family) provided psycho-social support	-	-	Y	-	-	-
Taiwo <i>et al.</i> , 2010 [87] (Bärnighausen <i>et al.</i> [71])	Treatment supporters, DOT	Treatment supporters provided DOT, assisted in reporting and managing adverse effects, and reminded patients of drug pick-up	-	-	Y	-	N	-
Thuman <i>et al.</i> , 2010 [88] (Bärnighausen <i>et al.</i> [71])	Structural intervention	Case managers (nurses or social workers) identified patients' needs, linked patients to community service providers, and coordinated care with medical staff and community health workers	(Y)	-	-	-	-	-
Torpey <i>et al.</i> , 2008 [89] (Bärnighausen <i>et al.</i> [71])	Treatment supporters	Treatment supporters followed up with patients in the community and provided support to improve adherence	N	-	-	-	-	-
Antoni <i>et al.</i> , 2006 [90] (Brown <i>et al.</i> [91])	CBT	Cognitive medication adherence and management training	N	-	-	-	N	-
Creswell <i>et al.</i> , 2009 [92] (Brown <i>et al.</i> [91])	CBT	A mindfulness-based stress reduction meditation programme	-	-	-	-	N	-
Johnson <i>et al.</i> , 2011 [93] (Brown <i>et al.</i> [91])	CBT	Individually tailored CBT sessions designed to improve HIV treatment coping skills and medication adherence	Y	-	-	-	-	-
Weiss <i>et al.</i> , 2011 [94] (Brown <i>et al.</i> [91])	Drug use treatment, CBT, education	Cognitive stress management with expressive-supportive therapy and educational material	Y	-	-	-	Y	-
Jaffar <i>et al.</i> , 2009 [95] (Brown <i>et al.</i> [91])	Structural intervention	Home-based ART delivery	N	-	-	-	N	-
Wall <i>et al.</i> , 1995 [96] (Fogarty <i>et al.</i> [97])	DOT	Nurse-supervised DAOT	N	N	-	-	-	Y
Knobel <i>et al.</i> , 1999 [98] (Haddad <i>et al.</i> [16])	CBT, education	Individual advise and education on ART adherence, addressing lifestyle issues, by pharmacist at first ART dispensing interaction	Y	Y	-	-	-	-
Alice <i>et al.</i> , 2007 [99], Maru <i>et al.</i> , 2009 [100] (Hart <i>et al.</i> [101])	DOT, treatment supporters, CBT	Enhanced community-based DOT, beeper reminders, mobile vans with on-site clinician, drug treatment coordinator, case manager, outreach workers, methadone co-management	N	-	-	-	Y	-
Gross <i>et al.</i> , 2009 [102] (Hart <i>et al.</i> [101])	DOT	DOT by a healthcare professional	-	-	-	-	N	-
Lucas <i>et al.</i> , 2006 [103] (Hart <i>et al.</i> [101])	DOT, drug use treatment	DOT by nurse or medical assistant and prepackaged doses on non-DOT days	-	-	-	-	Y	-
Macalino <i>et al.</i> , 2007 [104] (Hart <i>et al.</i> [101])	DOT	DOT by trained outreach worker, prepackaged pills	Y	-	-	-	Y	-

(continued)

Table 1 (continued)

Authors and year (review authors)	Intervention type	Intervention	Results									
			SR	PC	PR	EM	VL	CD4 <sup>+</sup>	WC	O		
Munoz <i>et al.</i> , 2010 [105] (Hart <i>et al.</i> [101])	DOT, treatment supporters, nutritional support	DOT by lay healthcare worker who also monitored side effects and provided social support; financial aid for tests, medication, transportation; nutritional support	Y	-	-	-	Y	N	-	-	-	
Tinoco <i>et al.</i> , 2004 [106] (Hart <i>et al.</i> [101])	DOT	DOT by lay healthcare worker who also monitored side effects and provided social support; financial aid for tests, medication, transportation; nutritional support	-	-	-	-	Y	Y	-	-	-	
Wohl <i>et al.</i> , 2006 [107] (Hart <i>et al.</i> [101])	DOT, treatment supporters, financial incentive	DOT by community health worker who also discussed adherence problems with the patient, financial incentives, or intensive adherence case management	N	-	-	-	N	N	-	-	-	
Andrade <i>et al.</i> , 2005 [108] (Haynes <i>et al.</i> [109])	ARD	Disease Management Assistance system (DMAS), an electronic reminder message system to remind patients to take medications	N	-	-	N	Y	N	-	-	-	
Collier <i>et al.</i> , 2005 [110] (Haynes <i>et al.</i> [109])	ARD	Serial, supportive phone calls using a standardized script, side effect management	N	-	-	-	N	-	-	-	-	
Remien <i>et al.</i> , 2005 [111] (Haynes <i>et al.</i> [109])	Treatment supporters, CBT, education	A couple-focused adherence programme to provide support and education about coping strategies and the medical impact of adherence	-	-	-	Y	N	N	-	-	-	
Samet <i>et al.</i> , 2005 [112] (Haynes <i>et al.</i> [109])	CBT	Assessment of alcohol use and readiness for behaviour change, enhancement of perceived medication efficacy, individualized HIV counselling and exploration	N	-	-	N	N	N	-	-	-	
Van Servellen <i>et al.</i> , 2005 [113] (Haynes <i>et al.</i> [109])	Treatment supporters, CBT, education	Educational sessions with nurse practitioners, motivational interviewing, problem-solving skills strategy, and support groups	N	-	-	-	Y	(N)	-	-	-	
Weber <i>et al.</i> , 2004 [114] (Haynes <i>et al.</i> [109])	CBT	Psychotherapy sessions based on concepts of cognitive-behavioural therapy	Y	-	-	Y	N	-	-	-	-	
Dilorio <i>et al.</i> , 2008 [115] (Hill and Kavookjian [116])	CBT	Motivational interviewing	-	-	-	N	N	N	-	-	-	
Parsons <i>et al.</i> , 2007 [117] (Hill and Kavookjian [116])	CBT	Motivational interviewing and cognitive-behavioural skills training	Y	-	-	-	Y	Y	-	-	-	
Mitty <i>et al.</i> , 2005 [118] (Kenya <i>et al.</i> [119])	DOT	DAOT by peer outreach workers	-	-	-	-	(Y)	(Y)	-	-	-	
Purcell <i>et al.</i> , 2007 [120] (Kenya <i>et al.</i> [119])	Treatment supporters, CBT	Peer-led sessions on HIV care, adherence, and risk behaviours	N	-	-	-	-	-	-	-	-	
Simoni <i>et al.</i> , 2007 [121] (Kenya <i>et al.</i> [119])	Treatment supporters	Peer-led sessions to identify barriers, create coping strategies, and peer-directed phone calls	N	-	-	N	N	-	-	-	-	
Visnegarwala <i>et al.</i> , 2006 [122] (Kenya <i>et al.</i> [119])	DOT, treatment supporters, CBT	Care management team consisting of social worker, peer caseworker, and pharmacist, or peer DAOT and social support	-	-	-	-	Y	N	-	-	-	
Williams <i>et al.</i> , 2006 [123] (Kenya <i>et al.</i> [119])	Treatment supporters, CBT	Home visits by nurses and community support workers to discuss barriers to adherence and propose solutions	-	-	-	Y	N	N	-	-	-	
Golin <i>et al.</i> , 2006 [124] (Leeman <i>et al.</i> [125])	CBT	Motivational interviewing focused on adherence, including audiotape and booklet, one-on-one sessions with a health educator, mail follow-up after each session	N	N	-	N	N	-	-	-	-	
Harwell <i>et al.</i> , 2003 [126] (Leeman <i>et al.</i> [125])	DOT	DAOT by outreach worker	-	-	-	-	(Y)	(Y)	-	-	-	



Holzemer <i>et al.</i> , 2006 [127] (Leeman <i>et al.</i> [125])	CBT	Individually tailored, nurse-delivered adherence intervention programme with a range of interventions, including teaching and discussions about adherence, self-care management of perceived side-effects, role performance, and improvement in the client-provider relationship	N	N	N	N	N	N	N
Javanbakht <i>et al.</i> , 2006 [128] (Leeman <i>et al.</i> [125])	Financial incentives, drug use treatment, treatment supporters	Individualized case management with treatment supporters and monetary reinforcement	-	-	-	-	-	Y	-
Johnson <i>et al.</i> , 2007 [129] (Leeman <i>et al.</i> [125])	CBT	Individually cognitive-behavioural interventions	Y	-	-	-	-	-	-
Jones <i>et al.</i> , 2007 [130] (Leeman <i>et al.</i> [125])	CBT, education	Group cognitive-behavioural stress management sessions and expressive supportive therapy intervention with education on a healthier lifestyle	N	-	-	-	-	-	-
Koenig <i>et al.</i> , 2008 [131] (Leeman <i>et al.</i> [125])	Treatment supporters, CBT	Structured interviews to help patients identify adherence barriers, generate possible solutions, select strategies to overcome the barriers, and evaluate how strategies are working) treatment supporter, MEMS providing electronic adherence cues	-	-	-	-	Y	Y	N
Levin <i>et al.</i> , 2006 [132] (Leeman <i>et al.</i> [125])	ARD, PRD	Printed cards with information about each drug, pill boxes, and bimonthly postal reminders	N	-	-	-	-	N	N
Ma <i>et al.</i> , 2008 [133] (Leeman <i>et al.</i> [125])	DOT	DOT	(Y)	-	-	-	-	(Y)	-
Milam <i>et al.</i> , 2005 [134] (Leeman <i>et al.</i> [125])	CBT	Printed and verbal adherence information, self-efficacy and skill building, behavioural cues	Y	-	-	-	-	N	N
Parsons <i>et al.</i> , 2005 [135] (Leeman <i>et al.</i> [125])	CBT	Motivational interviewing and cognitive-behavioural therapy	(Y)	-	-	-	-	-	-
Reynolds <i>et al.</i> , 2008 [136] (Leeman <i>et al.</i> [125])	ARD	Structured telephone calls by specifically trained nurse	Y	-	-	-	-	N	-
Rosen <i>et al.</i> , 2007 [137] (Leeman <i>et al.</i> [125])	Financial incentives, drug use treatment, CBT	Reinforcement of medication taking with prizes or monetary rewards	N	-	-	-	N	N	-
Sorenson <i>et al.</i> , 2007 [138] (Leeman <i>et al.</i> [125])	Financial incentives	Medication coaching and voucher reinforcement for opening MEMS devices on time	Y	(Y)	-	-	(Y)	-	-
Wagner <i>et al.</i> , 2006 [139] (Leeman <i>et al.</i> [125])	CBT	Cognitive-behavioural adherence intervention with or without practice ART	Y	-	-	-	N	N	N
Jones <i>et al.</i> , 2003 [140] (Manias and Williams [141])	CBT	Cognitive-behavioural stress management and expressive supportive therapy	N	-	-	-	-	-	-
Rathbun <i>et al.</i> , 2005 [142] (Manias and Williams [141])	CBT, education	Visit and phone follow-up to provide education about ART, food restrictions, adverse-event management strategies, and monitoring of patient progress after therapy initiation	N	-	-	-	N	Y	N
von Servellen <i>et al.</i> , 2003 [143] (Manias and Williams [141])	CBT	Instructional support programme to enhance health literacy with follow-up with case management	N	-	-	-	-	-	-
Wyatt <i>et al.</i> , 2004 [144] (Manias and Williams [141])	CBT, education	Sessions guided by cognitive-behavioural principles, psycho-education	N	-	-	-	-	-	-
Levy <i>et al.</i> , 2004 [145] (Rueda <i>et al.</i> [15])	CBT, education	Adherence education programme, individualized counselling, adherence tools (dosette boxes for antiretroviral pills and electronic alarms)	Y	-	-	-	-	N	N
Mannheimer <i>et al.</i> , 2006 [146] (Saberi and Johnson, 2011 [147])	CBT	Medication manager involving research staff member providing tailored adherence support in a protocol-guided manner, or electronic medication reminder system using a small portable alarm for all antiretroviral doses, or both	Y	-	-	-	-	N <sup>a</sup>	Y

(continued)

Table 1 (continued)

Authors and year (review authors)	Intervention type	Intervention	Results								
			SR	PC	PR	EM	VL	CD4 <sup>+</sup>	WC	O	
Murphy <i>et al.</i> , 2007 [148] (Saberi and Johnson, 2011 [147])	CBT	Sessions focused on role-playing, problem-solving, coaching, reinforcement strategies	-	Y	-	Y	-	-	-	-	-
Simoni <i>et al.</i> , 2009 [149] (Saberi and Johnson, 2011 [147])	ARD, treatment supporters	Pager messaging with a reminder device or phone, or peer support with group meetings, or both	N <sup>a</sup>	-	-	N	-	N	N	-	-
Simoni <i>et al.</i> , 2011 [150] (Saberi and Johnson, 2011 [147])	ARD, CBT	Electronic reminder device, or counselling on cognitive-behavioural and problem-solving approaches, or both	Y	-	-	N	-	N	N	-	-
Wu <i>et al.</i> , 2006 [151] (Saberi and Johnson, 2011 [147])	ARD, CBT, education	Prompting device that verbally reminds patients at medication times and electronically records doses, adherence education session	-	-	-	(Y)	-	-	-	-	-
Frick <i>et al.</i> , 2006 [152] (Saberi <i>et al.</i> , 2012 [153])	CBT, education	One-on-one sessions with a pharmacist, dietician, and social worker focused on ART education, ART readiness, and identification and mitigation of adherence barriers	-	-	-	N	-	Y	N	-	-
Hirsch <i>et al.</i> , 2011 [154] (Saberi <i>et al.</i> , 2012 [153])	Structural intervention	Pharmacist-provided ART medication management	-	Y	-	-	-	-	-	-	-
Horberg <i>et al.</i> , 2007 [155] (Saberi <i>et al.</i> , 2012 [153])	CBT	Care at clinics employing an HIV clinical pharmacist	-	-	-	Y	-	Y	N	-	-
March <i>et al.</i> , 2007 [156] (Saberi <i>et al.</i> , 2012 [153])	Structural intervention	Pharmacist-provided ART medication management	-	-	-	-	-	Y	Y	-	-
Pirkle <i>et al.</i> , 2009 [157] (Saberi <i>et al.</i> , 2012 [153])	DOT	DOT with weekly follow-up visits from pharmacists or adherence counsellors	-	-	-	-	-	-	(Y)	-	-
Rotheram-Borus <i>et al.</i> , 2004 [158] (Simoni <i>et al.</i> , [159])	ARD, CBT	Phone or in-person sessions focused on improving physical health, reducing sexual and drug use acts, and improving mental health	N	-	-	-	-	-	-	-	-
Byron <i>et al.</i> , 2008 [160] (Tirivayi and Groot [161])	Nutritional support	Food support programme	(Y)	-	-	-	-	-	(Y)	-	-
Feaster <i>et al.</i> , 2010 [162] (Wechsberg <i>et al.</i> , [163])	CBT, other	Family-based interventions therapy, emphasizing the female patient's interaction with her family and other social groups	N	-	-	-	-	-	-	-	-
Ingersoll <i>et al.</i> , 2011 [164] (Wechsberg <i>et al.</i> , [163])	CBT, education	Motivational interviewing and counselling sessions, educational hand-outs	Y	-	-	-	-	N	-	-	-
Page <i>et al.</i> , 2003 [165] (Wong <i>et al.</i> , [166])	Structural intervention	HIV services provided by general practitioners	N	-	-	-	-	N	N	-	-
Igumbor <i>et al.</i> , 2011 [167] (Wouters <i>et al.</i> , [168])	Treatment supporters	Patient advocates, a community-based adherence support programme provided by adherence supporters	-	-	-	Y	-	Y	-	-	-
Kunutsor <i>et al.</i> , 2011 [169] (Wouters <i>et al.</i> , [168])	Treatment supporters, education	Treatment supporter initiative designed to improve access, adherence diaries, and education	-	N	-	-	-	-	-	-	-
Rich <i>et al.</i> , 2012 [170] (Wouters <i>et al.</i> , [168])	Structural intervention	Community-based treatment programme providing nutritional support, financial assistance, patient support groups, and transportation	-	-	-	-	-	(Y)	(Y)	(Y)	(Y)

ART, antiretroviral therapy; CBT, cognitive and/or behavioural therapy; CD4<sup>+</sup>, CD4<sup>+</sup> cell count; DAOT, daily DOT; DOT, directly observed therapy; EM, electronic monitoring; MEMS, medication event monitoring system; O, other; PC, pill count; PR, pharmacy refill; PRD, passive reminder devices; RD, active reminder devices; SR, self-report; TWOT, twice weekly DOT; VL, viral load; WC, weight change; WOT, weekly DOT.

Y means significantly better outcome in the intervention group (at least at one time point); N means not significantly better outcome in the intervention group; results (Y, N) are shown in parentheses if an effect size is reported and the authors draw a conclusion as to whether the intervention has improved adherence or not but without reporting significance levels.

<sup>a</sup>The study showed that the intervention decreased adherence as assessed by this outcome measure.

distribution of outcome measures used across the 124 studies. Two-fifths of studies followed the general recommendation to use both outcomes that capture adherence (subjective measures—self-reported adherence levels, or objective measures – pill count, pharmacy refill, etc.), as well as those that capture the biological outcomes determined by adherence behaviour (viral load, CD4<sup>+</sup> cell count, body weight). However, 16% of the studies measured adherence using only subjective outcomes. Overall, 72 of the 124 studies were found to generate significant positive effects as assessed by at least one outcome measure. But only 24 studies (or one-fifth) found significant positive effects in at least one biological and one (objective or subjective) ART-adherence measure. Combination interventions were not more or less likely to succeed in significantly improving outcomes than single interventions ( $P=0.80$  for having at least one positive effect across all outcomes;  $P=0.55$  for having at least one positive effect each for a biological and a subjective or objective adherence outcome).

Table 3 shows a synthesis of the study results by intervention type. In the case of combination interventions, each component intervention is counted separately. The table shows that for most interventions, at least three-fifths of the studies found a positive result for at least one outcome, but the proportion of studies finding positive results for both at least one biological and one subjective or objective adherence outcome is less than 50%.

Most studies (87) investigated adherence-enhancing interventions in the general population; the remainder focused on particular sub-populations. The most commonly researched sub-populations were persons who use drugs (PWUD), with 22 studies, followed by women (8 studies), children (4 studies), and persons with mental health disorders (2 studies). It is an important finding that despite overall small sample sizes, there were significant effects in 12 out of the 22 studies in PWUD. Syntheses of results by outcome measure are presented in Table 1.

## Discussion

A large global evidence base on ART adherence-enhancing interventions – a total of 124 studies including 86 RCTs – provides important information for ART programming and planning. The field of ART adherence intervention research is developing rapidly and relatively more rapidly than research into ART access, linkage to care, and retention. The reason for this differential in research intensity within the overall field of HIV operations and health services research plausibly reflects the importance of ART adherence – we would prefer

only to initiate patients on ART once we are able to ensure good ART adherence. It could also reflect the fact that ART adherence is more easily conducted than research into other aspects of ART services, because unlike studies of access, linkage, and retention, it only requires data collection in clinical cohorts and not in HIV-infected populations in communities. Whatever the reason for the intensity of the research on ART adherence-enhancing interventions, the speed of study implementation, analysis, and publication means that evidence syntheses will rapidly grow out of date. Our review provides an updated synthesis on the body of knowledge on the effectiveness of ART adherence-enhancing interventions.

Each of the following interventions has been tested in more than 20, mostly rigorous studies, either singly or in combination with other interventions: CBT, education, treatment supporters, DOT, and active adherence reminder devices (such as mobile phone text messages). Whereas there is strong evidence that all five of these interventions can significantly increase ART adherence in some settings, each intervention has also been found not to produce significant effects in several studies.

The 2013 WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection describe the portfolio of adherence-enhancing interventions and recommends that '[M]obile phone text messages could be considered as a reminder tool for promoting adherence to ART as part of a package of adherence interventions'. This recommendation, as well as the descriptions of the evidence on other adherence-enhancing interventions in the guidelines, have been informed and are broadly supported by this systematic review. In addition – and with the caveats regarding context-specificity of findings discussed below – our review suggests that the other four interventions which have been widely tested in rigorous studies – CBT, education, treatment supporters, and DOT – warrant consideration by ART programme managers. Given the critical importance of adherence for the long-term individual and population-level success of ART, routine implementation of adherence-enhancing interventions should be considered.

Whereas the current evidence base provides a portfolio of interventions that have been shown to be effective in high-quality studies at least in some settings, adherence is a behaviour and as such is affected by culture and circumstance. The standard approaches to synthesizing evidence on effectiveness take on a different meaning when considering behavioural interventions as opposed to biological interventions. For behavioural interventions, consistency of causal effects across studies is an indicator of the degree of generalizability of an intervention effect to other settings rather than a measure

**Table 2. Distribution of outcome measures.**

Type of outcome measure	% of studies (N = 124)
Subjective adherence measure only	16
Objective adherence measure only	6
Subjective and objective adherence measure	4
Biological measure only	10
Biological measure and subjective and/or objective adherence measure	63
Other	1

of the degree to which an effect is 'true' as in the case of biological interventions.

We would expect that behavioural interventions that have been truly successful in one setting may not be effective in another one with different economic, social and behavioural barriers to adherence. Thus, health policy makers and programme planners need to carefully consider which adherence intervention to choose for routine implementation in a particular setting based on socio-cultural context, feasibility, acceptability, and health systems organization. The adherence-enhancing interventions identified in this review are likely to differ widely in implementation-relevant aspects, such as costs, human resources requirements, and scalability. Thus, other factors than the effectiveness evidence covered in this review will likely guide implementation decisions. For instance, DOT is labour-intensive and expensive, but it may be a good strategy for particular settings, for example, where patients can be easily reached, such as in hospitals or prisons. In contrast, some types of mobile phone text messaging interventions are comparatively inexpensive and do not require substantial human resources investment. As such, they may be a good option for general populations with high individual mobile phone coverage. Future meta-analyses of the contextual predictors of success of particular types of ART adherence interventions can further inform these choices. Additionally, it will be critical to monitor the performance of an adherence-enhancing intervention

as it is introduced into routine ART services. Quasi-experimental designs, such as stepped wedge scale-up of adherence interventions across HIV clinics, might offer 'natural' opportunities for rigorous confirmation of effectiveness of the five interventions that the currently available body of evidence can increase adherence.

Whereas the global evidence on effectiveness of adherence-enhancing interventions is rich, our review has identified several important knowledge gaps that will be relevant for implementation decisions and should increasingly be filled with evidence from implementation science research. First, more evidence is needed to examine interventions that have shown promise in a few studies, but have only been tested in a limited range of settings. Our review finds that these interventions include the following: alternative health system structures for ART delivery, nutrition support, financial incentives, passive reminder devices (such as diary cards and compartmentalized pill boxes), drug use treatment, and anti-depressive treatment.

Second, comparative information on costs and cost-effectiveness of different effective adherence interventions is largely lacking, and when it is available, it is unclear in how far the costs assessed in a research setting are transferable to routine implementation situations. More cost-benefit studies as part of routine care are needed to provide this critical component for deciding between alternative effective adherence-enhancing interventions. Whereas several studies investigated combination interventions (see Table 1), differential effectiveness of alternative combination portfolios and interaction effects between different intervention components were rarely examined. It would seem plausible that combination adherence interventions will be particularly successful in increasing ART adherence because they commonly work through different pathways. However, our synthesis shows that combination interventions tend to be similarly likely to succeed in increasing ART adherence as single interventions. One reason for this finding could be that

**Table 3. Summary of effects of adherence-enhancing interventions.**

Intervention component	Number of studies	% with positive results for at least one outcome measure	% with positive results for at least one positive effect each for a biological and a subjective or objective adherence outcome
CBT	60	67	20
Education	28	79	21
Treatment supporter	26	62	19
DOT	20	85	30
ARD	20	75	25
Structural	10	70	10
Counselling	8	88	63
Nutrition support	7	71	43
PRD	5	60	0
Financial incentives	5	60	0
Drug use treatment	5	80	40
Depression treatment	1	0	0

ARD, active reminder device; CBT, cognitive-behavioural therapy; DOT, directly observe therapy; PRD, passive reminder device.

there is usually one dominant intervention within the combination, and the other interventions merely moderately enhance the effectiveness of the dominant intervention. Another reason could be that combination interventions are more difficult to implement than single interventions, and the achieved effects reflect these implementation difficulties. Future experimental research should increasingly use factorial designs that allow precise determinations of component intervention and interaction effects.

Third, the majority of studies establishing the effectiveness of adherence-enhancing interventions have lasted 2 years or less. Antiretroviral therapy, however, requires life-long adherence, spanning several decades for many patients. Long-term studies of ART adherence are urgently needed, and several teams are currently conducting follow-up studies, which will generate these important results [171–174]. Fourth, many studies are internally inconsistent in their findings, establishing significant effects on some outcomes (e.g. self-reported adherence), but not on other, related outcomes (e.g. immunological recovery). Technological improvements in capturing ART adherence could substantially improve the strength of the evidence regarding adherence behaviours, which tend to be unreliably reported [175] and may also not be accurately measureable with objective approaches, such medication event monitoring systems (MEMS), pill counts, or observation of pharmacy refill. Finally, as ART initiation is moving into earlier disease stages, average effects of ART adherence-enhancing interventions may change, because the population composition of people on ART changes. For instance, people initiating in earlier stages of HIV infection are less likely to have experienced recovery from advanced HIV-related disease and may thus require different cognitive and behavioural strategies and different technological support to ensure good adherence than people who initiated in late stages of the infection [176].

Our study has several limitations. Although it was a systematic review, it was ‘rapid’ in the methodological sense that it utilized existing systematic reviews to identify studies on adherence-enhancing interventions. Some of these systematic reviews may have missed relevant studies related to their objective and timeframe, and these studies could have also been missed in our review. In particular, the reliance on previous systematic reviews and our focused search of recent published results from RCTs imply that our synthesis is largely based on experimental studies, and that an additional review of quasi-experimental and non-experimental evidence may provide important additional insights. Additionally, our selection of reviews to identify primary studies under the rapid review methodology we employed excluded reviews that were not systematic, for example, narrative reviews; and our identification of records reporting primary RCT-based results was limited to studies

whose primary aim was to enhance ART adherence. These selection criteria may have led to the exclusion of some interventions that can be of use in enhancing ART adherence, in particular, approaches to optimize ART regimens [177]. One example of such an intervention is single-tablet ART regimens, which have not been included in our review. Recently published reviews concluded that single-tablet regimens improve adherence and quality of life among ART patients in comparison to multi-tablet regimens [178,179].

Another unavoidable limitation of a systematic review based on formally published studies in a fast moving research field is that evidence that is emerging informally but has not yet been formally published will likely have been ignored, because academic writing, review and publication times in global health can last several years. These delays would have been particularly limiting if they led to the exclusion of completely novel interventions, for example, based on new technologies.

Although some studies were identified related to PWUD, data on other key populations were scarce. Given that these populations are disproportionately affected by the HIV epidemic and commonly face multiple challenges in ART adherence, future research focused on ART adherence-enhancing interventions tailored to key populations will be important, in particular, in sub-Saharan Africa, where such focused studies have been especially scarce.

In conclusion, we find a large and overall strong evidence base to support the claim that five interventions – CBT, education, treatment supporters, DOT, and active reminder devices – can improve ART adherence at least in some settings. These tested and effective adherence-enhancing interventions should increasingly be considered for routine implementation in ART programmes and health systems. However, rigorous on-going evaluation of the impact and performance of these interventions will be critical, because all interventions that proved effective in at least one setting were also found not to significantly increase adherence in at least one other setting. Significant evidence gaps on adherence-enhancing interventions need to be closed, including on cost-effectiveness, long-term effectiveness, and effectiveness in specific key populations.

## Acknowledgements

### Conflicts of interest

There are no conflicts of interest.

TB and KC were the lead authors, designing the study in close collaboration with EN and AS. KC, OO and MP

scrutinized identified studies for eligibility and extracted data. TB and KC wrote the first draft of the manuscript; all authors contributed to the interpretation of the extracted data and critically reviewed the manuscript before submission.

## References

- Swendeman D, Ingram BL, Rotheram-Borus MJ. **Common elements in self-management of HIV and other chronic illnesses: an integrative framework.** *AIDS Care* 2009; **21**:1321–1334.
- WHO, UNICEF, UNAIDS. Global update on HIV treatment 2013: results, impact and opportunities. [www.who.int/hiv/pub/progressreports/update2013/en](http://www.who.int/hiv/pub/progressreports/update2013/en). [Accessed 26 January 2014]
- Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. **Prevention of HIV-1 infection with early antiretroviral therapy.** *N Engl J Med* 2011; **365**:493–505.
- Tanser F, Bärnighausen T, Grapsa E, Zaidi J, Newell ML. **High coverage of ART associated with decline in risk of HIV acquisition in rural KwaZulu-Natal, South Africa.** *Science* 2013; **339**:966–971.
- Press N, Tyndall MW, Wood E, Hogg RS, Montaner JS. **Virologic and immunologic response, clinical progression, and highly active antiretroviral therapy adherence.** *J Acquir Immune Defic Syndr* 2002; **31** (Suppl 3):S112–117.
- Wood E, Hogg RS, Yip B, Harrigan PR, O'Shaughnessy MV, Montaner JS. **Effect of medication adherence on survival of HIV-infected adults who start highly active antiretroviral therapy when the CD4+ cell count is 0.200 to 0.350 x 10(9) cells/L.** *Ann Intern Med* 2003; **139**:810–816.
- Bangsberg DR, Perry S, Charlebois ED, Clark RA, Roberston M, Zolopa AR, et al. **Nonadherence to highly active antiretroviral therapy predicts progression to AIDS.** *AIDS* 2001; **15**:1181–1183.
- Ortego C, Huedo-Medina TB, Llorca J, Sevilla L, Santos P, Rodriguez E, et al. **Adherence to highly active antiretroviral therapy (HAART): a meta-analysis.** *AIDS Behav* 2011; **15**:1381–1396.
- Altice FL, Kamarulzaman A, Soriano VV, Schechter M, Friedland GH. **Treatment of medical, psychiatric, and substance-use comorbidities in people infected with HIV who use drugs.** *Lancet* 2010; **376**:367–387.
- Atkinson MJ, Petrozzino JJ. **An evidence-based review of treatment-related determinants of patients' nonadherence to HIV medications.** *AIDS Patient Care STDS* 2009; **23**:903–914.
- Gordon CM. **Commentary on meta-analysis of randomized controlled trials for HIV treatment adherence interventions. Research directions and implications for practice.** *J Acquir Immune Defic Syndr* 2006; **43** (Suppl 1):S36–40.
- Simoni JM, Pearson CR, Pantalone DW, Marks G, Crepaz N. **Efficacy of interventions in improving highly active antiretroviral therapy adherence and HIV-1 RNA viral load. A meta-analytic review of randomized controlled trials.** *J Acquir Immune Defic Syndr* 2006; **43** (Suppl 1):S23–35.
- Ford N, Nachega JB, Engel ME, Mills EJ. **Directly observed antiretroviral therapy: a systematic review and meta-analysis of randomised clinical trials.** *Lancet* 2009; **374**:2064–2071.
- Hart JE, Jeon CY, Ivers LC, Behforouz HL, Caldas A, Drobac PC, et al. **Effect of directly observed therapy for highly active antiretroviral therapy on virologic, immunologic, and adherence outcomes: a meta-analysis and systematic review.** *J Acquir Immune Defic Syndr* 2010; **54**:167–179.
- Rueda S, Park-Wyllie Laura Y, Bayoumi A, Tynan A-M, Antoniou T, Rourke S, et al. **Patient support and education for promoting adherence to highly active antiretroviral therapy for HIV/AIDS.** *Cochrane Database of Systematic Reviews*: John Wiley & Sons, Ltd; 2006.
- Haddad M, Inch C, Glazier RH, Wilkins AL, Urbshott G, Bayoumi A, et al. **Patient support and education for promoting adherence to highly active antiretroviral therapy for HIV/AIDS.** *Cochrane Database Syst Rev* 2000; **3**:CD001442.
- World Health Organization. *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection.* Geneva: World Health Organization; 2013, [www.who.int/hiv/pub/guidelines/arv2013](http://www.who.int/hiv/pub/guidelines/arv2013). [Accessed 26 January 2014]
- Smith V, Devane D, Begley CM, Clarke M. **Methodology in conducting a systematic review of systematic reviews of health-care interventions.** *BMC Med Res Methodol* 2011; **11**:15.
- Whitlock EP, Lin JS, Chou R, Shekelle P, Robinson KA. **Using existing systematic reviews in complex systematic reviews.** *Ann Intern Med* 2008; **148**:776–782.
- Ganann R, Ciliska D, Thomas H. **Expediting systematic reviews: methods and implications of rapid reviews.** *Implementation Sci* 2010; **5**:56.
- Bärnighausen T, Tanser F, Dabis F, Newell ML. **Interventions to improve the performance of HIV health systems for treatment-as-prevention in sub-Saharan Africa: the experimental evidence.** *Curr Opin HIV AIDS* 2012; **7**:140–150.
- Khangura S, Konnyu K, Cushman R, Grimshaw J, Moher D. **Evidence summaries: the evolution of a rapid review approach.** *Syst Rev* 2012; **1**:10.
- Bambra C, Joyce KE, Bellis MA, Greatley A, Greengross S, Hughes S, et al. **Reducing health inequalities in priority public health conditions: using rapid review to develop proposals for evidence-based policy.** *J Public Health (Oxf)* 2010; **32**:496–505.
- Greenhalgh T, Peacock R. **Effectiveness and efficiency of search methods in systematic reviews of complex evidence: audit of primary sources.** *Br Med J* 2005; **331**:1064–1065.
- Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. **The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration.** *J Clin Epidemiol* 2009; **62**:e1–e34.
- Buscemi N, Hartling L, Vandermeer B, Tjosvold L, Klassen TP. **Single data extraction generated more errors than double data extraction in systematic reviews.** *J Clin Epidemiol* 2006; **59**:697–703.
- Berlin JA. **Does blinding of readers affect the results of meta-analyses? University of Pennsylvania Meta-analysis Blinding Study Group.** *Lancet* 1997; **350**:185–186.
- Blank MB, Hanrahan NP, Fishbein M, Wu ES, Tennille JA, Ten Have TR, et al. **A randomized trial of a nursing intervention for HIV disease management among persons with serious mental illness.** *Psychiatr Serv* 2011; **62**:1318–1324.
- Berg KM, Litwin A, Li X, Heo M, Arnsten JH. **Directly observed antiretroviral therapy improves adherence and viral load in drug users attending methadone maintenance clinics: a randomized controlled trial.** *Drug Alcohol Depend* 2011; **113**:192–199.
- Chung MH, Richardson BA, Tapia K, Benki-Nugent S, Kiarie JN, Simoni JM, et al. **A randomized controlled trial comparing the effects of counseling and alarm device on HAART adherence and virologic outcomes.** *PLoS Med* 2011; **8**:e1000422.
- da Costa TM, Barbosa BJ, Gomes e Costa DA, Sigulem D, de Fatima Marin H, Filho AC, et al. **Results of a randomized controlled trial to assess the effects of a mobile SMS-based intervention on treatment adherence in HIV/AIDS-infected Brazilian women and impressions and satisfaction with respect to incoming messages.** *Int J Med Inform* 2012; **81**:257–269.
- de Bruin M, Hospers HJ, van Breukelen GJP, Kok G, Koevoets WM, Prins JM. *Electronic monitoring-based counseling to enhance adherence among HIV-infected patients: a randomized controlled trial.* 4th ed. United States: American Psychological Association Inc; 2010. pp. 421–428.
- Duncan LG, Moskowitz JT, Neilands TB, Dilworth SE, Hecht FM, Johnson MO. **Mindfulness-based stress reduction for HIV treatment side effects: a randomized, wait-list controlled trial.** *J Pain Symptom Manage* 2012; **43**:161–171.
- Fisher JD, Amico KR, Fisher WA, Cornman DH, Shuper PA, Traylor C, et al. **Computer-based intervention in HIV clinical care setting improves antiretroviral adherence: the LifeWindows Project.** *AIDS Behav* 2011; **15**:1635–1646.
- Hardy H, Kumar V, Doros G, Farmer E, Drainoni ML, Rybin D, et al. **Randomized controlled trial of a personalized cellular phone reminder system to enhance adherence to antiretroviral therapy.** *AIDS Patient Care STDS* 2011; **25**:153–161.
- Holstad MM, Dilorio C, Kelley ME, Resnicow K, Sharma S. **Group motivational interviewing to promote adherence to antiretroviral medications and risk reduction behaviors in HIV infected women.** *AIDS Behav* 2011; **15**:885–896.

37. Kalichman SC, Cherry C, Kalichman MO, Amaral CM, White D, Pope H, et al. **Integrated behavioral intervention to improve HIV/AIDS treatment adherence and reduce HIV transmission.** *Am J Public Health* 2011; **101**:531–538.
38. Kalichman SC, Kalichman MO, Cherry C, Swetzes C, Amaral CM, White D, et al. **Brief behavioral self-regulation counseling for HIV treatment adherence delivered by cell phone: an initial test of concept trial.** *AIDS Patient Care STDS* 2011; **25**:303–310.
39. Leon A, Caceres C, Fernandez E, Chausa P, Martin M, Codina C, et al. **A new multidisciplinary home care telemedicine system to monitor stable chronic human immunodeficiency virus-infected patients: a randomized study.** *PLoS One* 2011; **6**.
40. Pyne JM, Fortney JC, Curran GM, Tripathi S, Atkinson JH, Killbourne AM, et al. **Effectiveness of collaborative care for depression in human immunodeficiency virus clinics.** *Arch Intern Med* 2011; **171**:23–31.
41. Ramirez-Garcia P, Cote J. **An individualized intervention to foster optimal antiretroviral treatment-taking behavior among persons living with HIV: a pilot randomized controlled trial.** *J Assoc Nurses AIDS Care* 2012; **23**:220–232.
42. Ruiz I, Olry A, Lopez MA, Prada JL, Causse M. *Prospective, randomized, two-arm controlled study to evaluate two interventions to improve adherence to antiretroviral therapy in Spain.* 7th ed. Spain: Ediciones Doyma, S.L., Spain; 2010. pp. 409–415.
43. Sabin LL, DeSilva MB, Hamer DH, Xu K, Zhang J, Li T, et al. **Using electronic drug monitor feedback to improve adherence to antiretroviral therapy among HIV-positive patients in China.** *AIDS Behav* 2010; **14**:580–589.
44. Safren SA, O'Leirigh CM, Bullis JR, Otto MW, Stein MD, Pollack MH. **Cognitive behavioral therapy for adherence and depression (CBT-AD) in HIV-infected injection drug users: a randomized controlled trial.** *J Consult Clin Psychol* 2012; **80**:404–415.
45. Uzma Q, Emmanuel F, Ather U, Zaman S. *Efficacy of interventions for improving antiretroviral therapy adherence in HIV/AIDS cases at PIMS, Islamabad.* 6th ed. United States: SAGE Publications Inc; 2011. pp. 373–383.
46. Zubarán C, Michelim L, Medeiros G, May W, Foresti K, Madi JM. *A randomized controlled trial of a protocol of interviews designed to improve adherence to antiretroviral medications in Southern Brazil.* 6th ed. United Kingdom: Royal Society of Medicine Press Ltd, UK; 2012. pp. 429–434.
47. Dilorio C, Resnicow K, McDonnell M, Soet J, McCarty F, Yeager K. **Using motivational interviewing to promote adherence to antiretroviral medications: a pilot study.** *J Assoc Nurses AIDS Care* 2003; **14**:52–62.
48. Amico KR, Harman JJ, Johnson BT. **Efficacy of antiretroviral therapy adherence interventions: a research synthesis of trials, 1996 to 2004.** *J Acquir Immune Defic Syndr* 2006; **41**:285–297.
49. Fairley CK, Levy R, Rayner CR, Allardice K, Costello K, Thomas C, et al. **Randomized trial of an adherence programme for clients with HIV.** *Int J STD AIDS* 2003; **14**:805–809.
50. Goujard C, Bernard N, Sohler N, Peyramond D, Lancon F, Chwalow J, et al. **Impact of a patient education program on adherence to HIV medication: a randomized clinical trial.** *J Acquir Immune Defic Syndr* 2003; **34**:191–194.
51. Lyon ME, Trexler C, Akpan-Townsend C, Pao M, Selden K, Fletcher J, et al. **A family group approach to increasing adherence to therapy in HIV-infected youths: results of a pilot project.** *AIDS Patient Care STDS* 2003; **17**:299–308.
52. Mann T. **Effects of future writing and optimism on health behaviors in HIV-infected women.** *Ann Behav Med* 2001; **23**:26–33.
53. Margolin A, Avants SK, Warburton LA, Hawkins KA, Shi J. **A randomized clinical trial of a manual-guided risk reduction intervention for HIV-positive injection drug users.** *Health Psychol* 2003; **22**:223–228.
54. McPherson-Baker S, Malow RM, Penedo F, Jones DL, Schneiderman N, Klimas NG. **Enhancing adherence to combination antiretroviral therapy in nonadherent HIV-positive men.** *AIDS Care* 2000; **12**:399–404.
55. Molassiotis A, Lopez-Nahas V, Chung WY, Lam SW. **A pilot study of the effects of a behavioural intervention on treatment adherence in HIV-infected patients.** *AIDS Care* 2003; **15**:125–135.
56. Murphy DA, Lu MC, Martin D, Hoffman D, Marelich WD. **Results of a pilot intervention trial to improve antiretroviral adherence among HIV-positive patients.** *J Assoc Nurses AIDS Care* 2002; **13**:57–69.
57. Powell-Cope GM, White J, Henkelman EJ, Turner BJ. **Qualitative and quantitative assessments of HAART adherence of substance-abusing women.** *AIDS Care* 2003; **15**:239–249.
58. Pradier C, Bentz L, Spire B, Tourette-Turgis C, Morin M, Souville M, et al. **Efficacy of an educational and counseling intervention on adherence to highly active antiretroviral therapy: French prospective controlled study.** *HIV Clin Trials* 2003; **4**:121–131.
59. Rawlings MK, Thompson MA, Farthing CF, Brown LS, Racine J, Scott RC, et al. **Impact of an educational program on efficacy and adherence with a twice-daily lamivudine/zidovudine/abacavir regimen in underrepresented HIV-infected patients.** *J Acquir Immune Defic Syndr* 2003; **34**:174–183.
60. Rigsby MO, Rosen MI, Beauvais JE, Cramer JA, Rainey PM, O'Malley SS, et al. **Cue-dose training with monetary reinforcement: pilot study of an antiretroviral adherence intervention.** *J Gen Intern Med* 2000; **15**:841–847.
61. Safren SA, Otto MW, Worth JL, Salomon E, Johnson W, Mayer K, et al. **Two strategies to increase adherence to HIV antiretroviral medication: life-steps and medication monitoring.** *Behav Res Ther* 2001; **39**:1151–1162.
62. Safren SA, Hendriksen ES, Desousa N, Boswell SL, Mayer KH. **Use of an on-line pager system to increase adherence to antiretroviral medications.** *AIDS Care* 2003; **15**:787–793.
63. Smith SR, Rublein JC, Marcus C, Brock TP, Chesney MA. **A medication self-management program to improve adherence to HIV therapy regimens.** *Patient Educ Couns* 2003; **50**:187–199.
64. Stenzel MS, McKenzie M, Mitty JA, Flanigan TP. **Enhancing adherence to HAART: a pilot program of modified directly observed therapy.** *AIDS Reader* 2001; **11**:317–319.
65. Tuldra A, Fumaz CR, Ferrer MJ, Bayes R, Arno A, Balague M, et al. **Prospective randomized two-arm controlled study to determine the efficacy of a specific intervention to improve long-term adherence to highly active antiretroviral therapy.** *J Acquir Immune Defic Syndr* 2000; **25**:221–228.
66. Berrien VM, Salazar JC, Reynolds E, McKay K, Group HIVMAI. **Adherence to antiretroviral therapy in HIV-infected pediatric patients improves with home-based intensive nursing intervention.** *AIDS Patient Care STDS* 2004; **18**:355–363.
67. Bain-Brickley D, Butler LM, Kennedy GE, Rutherford GW. **Interventions to improve adherence to antiretroviral therapy in children with HIV infection.** *Cochrane Database Syst Rev* 2011; **12**:CD009513.
68. Funck-Brentano I, Dalban C, Veber F, Quartier P, Hefez S, Costagliola D, et al. **Evaluation of a peer support group therapy for HIV-infected adolescents.** *AIDS* 2005; **19**:1501–1508.
69. Wamalwa DC, Farquhar C, Obimbo EM, Selig S, Mbori-Ngacha DA, Richardson BA, et al. **Medication diaries do not improve outcomes with highly active antiretroviral therapy in Kenyan children: a randomized clinical trial.** *J Int AIDS Soc* 2009; **12**:8.
70. Cantrell RA, Sinkala M, Megazinni K, Lawson-Marriott S, Washington S, Chi BH, et al. **A pilot study of food supplementation to improve adherence to antiretroviral therapy among food-insecure adults in Lusaka, Zambia.** *J Acquir Immune Defic Syndr* 2008; **49**:190–195.
71. Barnighausen T, Chaiyachati K, Chimbindi N, Peoples A, Haber J, Newell ML. **Interventions to increase antiretroviral adherence in sub-Saharan Africa: a systematic review of evaluation studies.** *Lancet Infect Dis* 2011; **11**:942–951.
72. Chang LW, Kagaayi J, Nakigozi G, Ssemplija V, Packer AH, Serwadda D, et al. **Effect of peer health workers on AIDS care in Rakai, Uganda: a cluster-randomized trial.** *PLoS One* 2010; **5**:e10923.
73. Idoko JA, Agbaji O, Agaba P, Akolo C, Inuwa B, Hassan Z, et al. **Direct observation therapy-highly active antiretroviral therapy in a resource-limited setting: the use of community treatment support can be effective.** *Int J STD AIDS* 2007; **18**:760–763.

74. Kabore I, Bloem J, Etheredge G, Obiero W, Wanless S, Doykos P, *et al.* **The effect of community-based support services on clinical efficacy and health-related quality of life in HIV/AIDS patients in resource-limited settings in sub-Saharan Africa.** *AIDS Patient Care STDS* 2010; **24**:581–594.
75. Lester RT, Ritvo P, Mills EJ, Kariri A, Karanja S, Chung MH, *et al.* **Effects of a mobile phone short message service on antiretroviral treatment adherence in Kenya (WeITel Kenya1): a randomised trial.** *Lancet* 2010; **376**:1838–1845.
76. Mugusi F, Mugusi S, Bakari M, Hejdemann B, Josiah R, Janabi M, *et al.* **Enhancing adherence to antiretroviral therapy at the HIV clinic in resource constrained countries; the Tanzanian experience.** *Trop Med Int Health* 2009; **14**:1226–1232.
77. Nachega JB, Chaisson RE, Goliath R, Efron A, Chaudhary MA, Ram M, *et al.* **Randomized controlled trial of trained patient-nominated treatment supporters providing partial directly observed antiretroviral therapy.** *AIDS* 2010; **24**:1273–1280.
78. Ndekha M, van Oosterhout JJ, Saloojee H, Pettifor J, Manary M. **Nutritional status of Malawian adults on antiretroviral therapy 1 year after supplementary feeding in the first 3 months of therapy.** *Trop Med Int Health* 2009; **14**:1059–1063.
79. Ndekha MJ, van Oosterhout JJ, Zijlstra EE, Manary M, Saloojee H, Manary MJ. **Supplementary feeding with either ready-to-use fortified spread or corn-soy blend in wasted adults starting antiretroviral therapy in Malawi: randomised, investigator blinded, controlled trial.** *Br Med J* 2009; **338**:b1867.
80. Pearson CR, Micek MA, Simoni JM, Hoff PD, Matediana E, Martin DP, *et al.* **Randomized control trial of peer-delivered, modified directly observed therapy for HAART in Mozambique.** *J Acquir Immune Defic Syndr* 2007; **46**:238–244.
81. Pienaar DH, Myer L, Cleary S, Coetzee D, Michaels D, Cloete K, *et al.* *Models of Care for Antiretroviral Service Delivery.* Cape Town: University of Capetown; 2006.
82. Pop-Eleches C, Thirumurthy H, Habyarimana JP, Zivin JG, Goldstein MP, de Walque D, *et al.* **Mobile phone technologies improve adherence to antiretroviral treatment in a resource-limited setting: a randomized controlled trial of text message reminders.** *AIDS* 2011; **25**:825–834.
83. Roux SM. *Diary cards: preliminary evaluation of an intervention tool for improving adherence to antiretroviral therapy and TB preventive therapy in people living with HIV/AIDS [MPH thesis].* University of the Western Cape; 2004.
84. Sarna A, Luchters S, Geibel S, Chersich MF, Munyao P, Kaai S, *et al.* **Short- and long-term efficacy of modified directly observed antiretroviral treatment in Mombasa, Kenya: a randomized trial.** *J Acquir Immune Defic Syndr* 2008; **48**:611–619.
85. Sherr KH, Micek MA, Gimbel SO, Gloyd SS, Hughes JP, John-Stewart GC, *et al.* **Quality of HIV care provided by nonphysician clinicians and physicians in Mozambique: a retrospective cohort study.** *AIDS* 2010; **24** (Suppl 1):S59–66.
86. Stubbs BA, Micek MA, Pfeiffer JT, Montoya P, Gloyd S. **Treatment partners and adherence to HAART in central Mozambique.** *AIDS Care* 2009; **21**:1412–1419.
87. Taiwo BO, Idoko JA, Welty LJ, Otoh I, Job G, Iyaji PG, *et al.* **Assessing the virologic and adherence benefits of patient-selected HIV treatment partners in a resource-limited setting.** *J Acquir Immune Defic Syndr* 2010; **54**:85–92.
88. Thurman TR, Haas LJ, Dushimimana A, Lavin B, Mock N. **Evaluation of a case management program for HIV clients in Rwanda.** *AIDS Care* 2010; **22**:759–765.
89. Torpey KE, Kabaso ME, Mutale LN, Kamanga MK, Mwangi AJ, Simpungwe J, *et al.* **Adherence support workers: a way to address human resource constraints in antiretroviral treatment programs in the public health setting in Zambia.** *PLoS One* 2008; **3**:e2204.
90. Antoni MH, Carrico AW, Duran RE, Spitzer S, Penedo F, Ironson G, *et al.* **Randomized clinical trial of cognitive behavioral stress management on human immunodeficiency virus viral load in gay men treated with highly active antiretroviral therapy.** *Psychosom Med* 2006; **68**:143–151.
91. Brown JL, Venable PA. *Stress management interventions for HIV-infected individuals: review of recent intervention approaches and directions for future research.* 1st ed. New Zealand: DOVE Medical Press Ltd., New Zealand; 2011. pp. 95–106.
92. Creswell JD, Myers HF, Cole SW, Irwin MR. **Mindfulness meditation training effects on CD4+ T lymphocytes in HIV-1 infected adults: a small randomized controlled trial.** *Brain Behav Immun* 2009; **23**:184–188.
93. Johnson MO, Dilworth SE, Taylor JM, Neilands TB. **Improving coping skills for self-management of treatment side effects can reduce antiretroviral medication nonadherence among people living with HIV.** *Ann Behav Med* 2011; **41**:83–91.
94. Weiss SM, Tobin JN, Antoni M, Ironson G, Ishii M, Vaughn A, *et al.* **Enhancing the health of women living with HIV: the SMART/EST Women's Project.** *Int J Womens Health* 2011; **3**:63–77.
95. Jaffar S, Amuron B, Foster S, Birungi J, Levin J, Namara G, *et al.* **Rates of virological failure in patients treated in a home-based versus a facility-based HIV-care model in Jinja, southeast Uganda: a cluster-randomised equivalence trial.** *Lancet* 2009; **374**:2080–2089.
96. Wall TL, Sorensen JL, Batki SL, Delucchi KL, London JA, Chesney MA. **Adherence to zidovudine (AZT) among HIV-infected methadone patients: a pilot study of supervised therapy and dispensing compared to usual care.** *Drug Alcohol Depend* 1995; **37**:261–269.
97. Fogarty L, Roter D, Larson S, Burke J, Gillespie J, Levy R. **Patient adherence to HIV medication regimens: a review of published and abstract reports.** *Patient Educ Couns* 2002; **46**:93–108.
98. Knobel H, Carmona A, Lopez JL, Gimeno JL, Saballs P, Gonzalez A, *et al.* [Adherence to very active antiretroviral treatment: impact of individualized assessment]. *Enferm Infecc Microbiol Clin* 1999; **17**:78–81.
99. Altice FL, Maru DS, Bruce RD, Springer SA, Friedland GH. **Superiority of directly administered antiretroviral therapy over self-administered therapy among HIV-infected drug users: a prospective, randomized, controlled trial.** *Clin Infect Dis* 2007; **45**:770–778.
100. Maru DS, Bruce RD, Walton M, Springer SA, Altice FL. **Persistence of virological benefits following directly administered antiretroviral therapy among drug users: results from a randomized controlled trial.** *J Acquir Immune Defic Syndr* 2009; **50**:176–181.
101. Hart JE, Jeon CY, Ivers LC, Behforouz HL, Caldas A, Drobac PC, *et al.* **Effect of directly observed therapy for highly active antiretroviral therapy on virologic, immunologic, and adherence outcomes: a meta-analysis and systematic review.** *J Acquir Immune Defic Syndr* 2010; **54**:167–179.
102. Gross R, Tierney C, Andrade A, Lalama C, Rosenkrantz S, Eshleman SH, *et al.* **Modified directly observed antiretroviral therapy compared with self-administered therapy in treatment-naive HIV-1-infected patients: a randomized trial.** *Arch Intern Med* 2009; **169**:1224–1232.
103. Lucas GM, Mullen BA, Weidle PJ, Hader S, McCaul ME, Moore RD. **Directly administered antiretroviral therapy in methadone clinics is associated with improved HIV treatment outcomes, compared with outcomes among concurrent comparison groups.** *Clin Infect Dis* 2006; **42**:1628–1635.
104. Macalino GE, Hogan JW, Mitty JA, Bazerman LB, Delong AK, Loewenthal H, *et al.* **A randomized clinical trial of community-based directly observed therapy as an adherence intervention for HAART among substance users.** *AIDS* 2007; **21**:1473–1477.
105. Munoz M, Finnegan K, Zeladita J, Caldas A, Sanchez E, Callacna M, *et al.* **Community-based DOT-HAART accompaniment in an urban resource-poor setting.** *AIDS Behav* 2010; **14**:721–730.
106. Tinoco I, Giron-Gonzalez JA, Gonzalez-Gonzalez MT, Vergara de Campos A, Rodriguez-Felix L, Serrano A, *et al.* **Efficacy of directly observed treatment of HIV infection: experience in AIDS welfare homes.** *Eur J Clin Microbiol Infect Dis* 2004; **23**:331–335.
107. Wohl AR, Garland WH, Valencia R, Squires K, Witt MD, Kovacs A, *et al.* **A randomized trial of directly administered antiretroviral therapy and adherence case management intervention.** *Clin Infect Dis* 2006; **42**:1619–1627.
108. Andrade AS, McGruder HF, Wu AW, Celano SA, Skolasky RL Jr, Selnes OA, *et al.* **A programmable prompting device improves adherence to highly active antiretroviral therapy in HIV-infected subjects with memory impairment.** *Clin Infect Dis* 2005; **41**:875–882.
109. Haynes RB, Ackloo E, Sahota N, McDonald HP, Yao X. **Interventions for enhancing medication adherence.** *Cochrane Database Syst Rev* 2008; **2**:CD000011.



110. Collier AC, Ribaudo H, Mukherjee AL, Feinberg J, Fischl MA, Chesney M. **A randomized study of serial telephone call support to increase adherence and thereby improve virologic outcome in persons initiating antiretroviral therapy.** *J Infect Dis* 2005; **192**:1398–1406.
111. Remien RH, Stirratt MJ, Dolezal C, Dognin JS, Wagner GJ, Carballo-Dieguez A, *et al.* **Couple-focused support to improve HIV medication adherence: a randomized controlled trial.** *AIDS* 2005; **19**:807–814.
112. Samet JH, Horton NJ, Meli S, Dukes K, Tripps T, Sullivan L, *et al.* **A randomized controlled trial to enhance antiretroviral therapy adherence in patients with a history of alcohol problems.** *Antivir Ther* 2005; **10**:83–93.
113. van Servellen G, Nyamathi A, Carpio F, Pearce D, Garcia-Teague L, Herrera G, *et al.* **Effects of a treatment adherence enhancement program on health literacy, patient-provider relationships, and adherence to HAART among low-income HIV-positive Spanish-speaking Latinos.** *AIDS Patient Care STDS* 2005; **19**:745–759.
114. Weber R, Christen L, Christen S, Tschopp S, Znoj H, Schneider C, *et al.* **Effect of individual cognitive behaviour intervention on adherence to antiretroviral therapy: prospective randomized trial.** *Antivir Ther* 2004; **9**:85–95.
115. Dilorio C, Mccarty F, Resnicow K, Holstad MM, Soet J, Yeager K, *et al.* **Using motivational interviewing to promote adherence to antiretroviral medications: a randomized controlled study.** *AIDS Care* 2008; **20**:273–283.
116. Hill S, Kavookjian J. **Motivational interviewing as a behavioral intervention to increase HAART adherence in patients who are HIV-positive: a systematic review of the literature.** *AIDS Care* 2012; **24**:583–592.
117. Parsons JT, Golub SA, Rosof E, Holder C. **Motivational interviewing and cognitive-behavioral intervention to improve HIV medication adherence among hazardous drinkers: a randomized controlled trial.** *J Acquir Immune Defic Syndr* 2007; **46**:443–450.
118. Mitty JA, Macalino GE, Bazerman LB, Loewenthal HG, Hogan JW, MacLeod CJ, *et al.* **The use of community-based modified directly observed therapy for the treatment of HIV-infected persons.** *J Acquir Immune Defic Syndr* 2005; **39**:545–550.
119. Kenya S, Chida N, Symes S, Shor-Posner G. **Can community health workers improve adherence to highly active antiretroviral therapy in the USA? A review of the literature.** *HIV Med* 2011; **12**:525–534.
120. Purcell DW, Latka MH, Metsch LR, Latkin CA, Gomez CA, Mizuno Y, *et al.* **Results from a randomized controlled trial of a peer-mentoring intervention to reduce HIV transmission and increase access to care and adherence to HIV medications among HIV-seropositive injection drug users.** *J Acquir Immune Defic Syndr* 2007; **46** (Suppl 2):S35–47.
121. Simoni JM, Pantalone DW, Plummer MD, Huang B. **A randomized controlled trial of a peer support intervention targeting antiretroviral medication adherence and depressive symptomatology in HIV-positive men and women.** *Health Psychol* 2007; **26**:488–495.
122. Visnegarwala F, Rodriguez-Barradass MC, Graviss EA, Caprio M, Nykyforchyn M, Laufman L. **Community outreach with weekly delivery of antiretroviral drugs compared to cognitive-behavioural healthcare team-based approach to improve adherence among indigent women newly starting HAART.** *AIDS Care* 2006; **18**:332–338.
123. Williams AB, Fennie KP, Bova CA, Burgess JD, Danvers KA, Dieckhaus KD. **Home visits to improve adherence to highly active antiretroviral therapy: a randomized controlled trial.** *J Acquir Immune Defic Syndr* 2006; **42**:314–321.
124. Golin CE, Earp J, Tien HC, Stewart P, Porter C, Howie L. **A 2-arm, randomized, controlled trial of a motivational interviewing-based intervention to improve adherence to antiretroviral therapy (ART) among patients failing or initiating ART.** *J Acquir Immune Defic Syndr* 2006; **42**:42–51.
125. Leeman J, Chang YK, Lee EJ, Voils CI, Crandell J, Sandelowski M. **Implementation of antiretroviral therapy adherence interventions: a realist synthesis of evidence.** *J Adv Nurs* 2010; **66**:1915–1930.
126. Harwell JI, Flanigan TP, Mitty JA, Macalino GE, Caliendo AM, Ingersoll J, *et al.* **Directly observed antiretroviral therapy to reduce genital tract and plasma HIV-1 RNA in women with poor adherence.** *AIDS* 2003; **17**:1990–1993.
127. Holzemer WL, Bakken S, Portillo CJ, Grimes R, Welch J, Wantland D, *et al.* **Testing a nurse-tailored HIV medication adherence intervention.** *Nurs Res* 2006; **55**:189–197.
128. Javanbakht M, Prosser P, Grimes T, Weinstein M, Farthing C. **Efficacy of an individualized adherence support program with contingent reinforcement among nonadherent HIV-positive patients: results from a randomized trial.** *J Int Assoc Phys AIDS Care (Chic)* 2006; **5**:143–150.
129. Johnson MO, Charlebois E, Morin SF, Remien RH, Chesney MA. **Effects of a behavioral intervention on antiretroviral medication adherence among people living with HIV: the healthy living project randomized controlled study.** *J Acquir Immune Defic Syndr* 2007; **46**:574–580.
130. Jones DL, McPherson-Baker S, Lydston D, Camille J, Brondolo E, Tobin JN, *et al.* **Efficacy of a group medication adherence intervention among HIV positive women: the SMART/EST Women's Project.** *AIDS Behav* 2007; **11**:79–86.
131. Koenig LJ, Pals SL, Bush T, Pratt Palmore M, Stratford D, Ellerbrock TV. **Randomized controlled trial of an intervention to prevent adherence failure among HIV-infected patients initiating antiretroviral therapy.** *Health Psychol* 2008; **27**: 159–169.
132. Levin TR, Klibanov OM, Axelrod P, Finley GL, Gray A, Holdsworth C, *et al.* **A randomized trial of educational materials, pillboxes, and mailings to improve adherence with antiretroviral therapy in an inner city HIV clinic.** *J Clin Outcomes Manag* 2006; **13**:217–221.
133. Ma M, Brown BR, Coleman M, Kibler JL, Loewenthal H, Mitty JA. **The feasibility of modified directly observed therapy for HIV-seropositive African American substance users.** *AIDS Patient Care STDS* 2008; **22**:139–146.
134. Milam J, Richardson JL, McCutchan A, Stoyanoff S, Weiss J, Kemper C, *et al.* **Effect of a brief antiretroviral adherence intervention delivered by HIV care providers.** *J Acquir Immune Defic Syndr* 2005; **40**:356–363.
135. Parsons JT, Rosof E, Punzalan JC, Di Maria L. **Integration of motivational interviewing and cognitive behavioral therapy to improve HIV medication adherence and reduce substance use among HIV-positive men and women: results of a pilot project.** *AIDS Patient Care STDS* 2005; **19**: 31–39.
136. Reynolds NR, Testa MA, Su M, Chesney MA, Neidig JL, Frank I, *et al.* **Telephone support to improve antiretroviral medication adherence: a multisite, randomized controlled trial.** *J Acquir Immune Defic Syndr* 2008; **47**:62–68.
137. Rosen MI, Dieckhaus K, McMahon TJ, Valdes B, Petry NM, Cramer J, *et al.* **Improved adherence with contingency management.** *AIDS Patient Care STDS* 2007; **21**:30–40.
138. Sorensen JL, Haug NA, Delucchi KL, Gruber V, Kletter E, Batki SL, *et al.* **Voucher reinforcement improves medication adherence in HIV-positive methadone patients: a randomized trial.** *Drug Alcohol Depend* 2007; **88**:54–63.
139. Wagner GJ, Kanouse DE, Golinelli D, Miller LG, Daar ES, Witt MD, *et al.* **Cognitive-behavioral intervention to enhance adherence to antiretroviral therapy: a randomized controlled trial (CTG 578).** *AIDS* 2006; **20**:1295–1302.
140. Jones DL, Ishii M, LaPerriere A, Stanley H, Antoni M, Ironson G, *et al.* **Influencing medication adherence among women with AIDS.** *AIDS Care* 2003; **15**:463–474.
141. Manias E, Williams A. **Medication adherence in people of culturally and linguistically diverse backgrounds: a meta-analysis.** *Ann Pharmacother* 2010; **44**:964–982.
142. Rathbun RC, Farmer KC, Stephens JR, Lockhart SM. **Impact of an adherence clinic on behavioral outcomes and virologic response in treatment of HIV infection: a prospective, randomized, controlled pilot study.** *Clin Ther* 2005; **27**: 199–209.
143. van Servellen G, Carpio F, Lopez M, Garcia-Teague L, Herrera G, Monterrosa F, *et al.* **Program to enhance health literacy and treatment adherence in low-income HIV-infected Latino men and women.** *AIDS Patient Care STDS* 2003; **17**:581–594.
144. Wyatt GE, Longshore D, Chin D, Carmona JV, Loeb TB, Myers HF, *et al.* **The efficacy of an integrated risk reduction intervention for HIV-positive women with child sexual abuse histories.** *AIDS Behav* 2004; **8**:453–462.
145. Levy RW, Rayner CR, Fairley CK, Kong DC, Mijch A, Costello K, *et al.* **Multidisciplinary HIV adherence intervention: a randomized study.** *AIDS Patient Care STDS* 2004; **18**:728–735.

146. Mannheimer SB, Morse E, Matts JP, Andrews L, Child C, Schmetter B, *et al.* **Sustained benefit from a long-term antiretroviral adherence intervention. Results of a large randomized clinical trial.** *J Acquir Immune Defic Syndr* 2006; **43** (Suppl 1):S41–47.
147. Saberi P, Johnson MO. **Technology-based self-care methods of improving antiretroviral adherence: a systematic review.** *PLoS One* 2011;6.
148. Murphy DA, Marelich WD, Rappaport NB, Hoffman D, Farthing C. **Results of an antiretroviral adherence intervention: STAR (Staying Healthy: Taking Antiretrovirals Regularly).** *J Int Assoc Physicians AIDS Care (Chic)* 2007; **6**:113–124.
149. Simoni JM, Huh D, Frick PA, Pearson CR, Andrasik MP, Dunbar PJ, *et al.* **Peer support and pager messaging to promote antiretroviral modifying therapy in Seattle: a randomized controlled trial.** *J Acquir Immune Defic Syndr* 2009; **52**: 465–473.
150. Simoni JM, Chen WT, Huh D, Fredriksen-Goldsen KI, Pearson C, Zhao H, *et al.* **A preliminary randomized controlled trial of a nurse-delivered medication adherence intervention among HIV-positive outpatients initiating antiretroviral therapy in Beijing, China.** *AIDS Behav* 2011; **15**:919–929.
151. Wu AW, Snyder CF, Huang IC, Skolasky R, McGruder HF, Celano SA, *et al.* **A randomized trial of the impact of a programmable medication reminder device on quality of life in patients with AIDS.** *AIDS Patient Care STDS* 2006; **20**:773–781.
152. Frick P, Tapia K, Grant P, Novotny M, Kerzee J. **The effect of a multidisciplinary program on HAART adherence.** *AIDS Patient Care STDS* 2006; **20**:511–524.
153. Saberi P, Dong BJ, Johnson MO, Greenblatt RM, Cocohoba JM. **The impact of HIV clinical pharmacists on HIV treatment outcomes: a systematic review.** *Patient Prefer Adherence* 2012; **6**:297–322.
154. Hirsch JD, Gonzales M, Rosenquist A, Miller TA, Gilmer TP, Best BM. **Antiretroviral therapy adherence, medication use, and healthcare costs during 3 years of a community pharmacy medication therapy management program for Medi-Cal beneficiaries with HIV/AIDS.** *J Manag Care Pharm* 2011; **17**:213–223.
155. Horberg MA, Hurley LB, Silverberg MJ, Kinsman CJ, Quesenberry CP. **Effect of clinical pharmacists on utilization of and clinical response to antiretroviral therapy.** *J Acquir Immune Defic Syndr* 2007; **44**:531–539.
156. March K, Mak M, Louie SG. **Effects of pharmacists' interventions on patient outcomes in an HIV primary care clinic.** *Am J Health Syst Pharm* 2007; **64**:2574–2578.
157. Pirkle CM, Boileau C, Nguyen VK, Machouf N, Ag-Aboubarine S, Niamba PA, *et al.* **Impact of a modified directly administered antiretroviral treatment intervention on virological outcome in HIV-infected patients treated in Burkina Faso and Mali.** *HIV Med* 2009; **10**:152–156.
158. Rotheram-Borus MJ, Swendeman D, Comulada WS, Weiss RE, Lee M, Lightfoot M. **Prevention for substance-using HIV-positive young people: telephone and in-person delivery.** *J Acquir Immune Defic Syndr* 2004; **37** (Suppl 2):S68–77.
159. Simoni JM, Pearson CR, Pantalone DW, Marks G, Crepaz N. **Efficacy of interventions in improving highly active antiretroviral therapy adherence and HIV-1 RNA viral load: a meta-analytic review of randomized controlled trials.** *J Acquir Immune Defic Syndr* 2006; **43**:S23–S35.
160. Byron E, Gillespie S, Nangami M. **Integrating nutrition security with treatment of people living with HIV: lessons from Kenya.** *Food Nutr Bull* 2008; **29**:87–97.
161. Tirivayi N, Groot W. **Health and welfare effects of integrating AIDS treatment with food assistance in resource constrained settings: a systematic review of theory and evidence.** *Soc Sci Med* 2011; **73**:685–692.
162. Feaster DJ, Mitrani VB, Burns MJ, McCabe BE, Brincks AM, Rodriguez AE, *et al.* **A randomized controlled trial of structural ecosystems therapy for HIV medication adherence and substance abuse relapse prevention.** *Drug Alcohol Depend* 2010; **111**:227–234.
163. Wechsberg WM, Golin C, El-Bassel N, Hopkins J, Zule W. **Current interventions to reduce sexual risk behaviors and crack cocaine use among HIV-infected individuals.** *Curr HIV/AIDS Rep* 2012.
164. Ingersoll KS, Farrell-Carnahan L, Cohen-Filipic J, Heckman CJ, Ceperich SD, Hetteima J, *et al.* **A pilot randomized clinical trial of two medication adherence and drug use interventions for HIV+ crack cocaine users.** *Drug Alcohol Depend* 2011; **116**:177–187.
165. Page J, Weber R, Somaini B, Nostlinger C, Donath K, Jaccard R. **Quality of generalist vs. specialty care for people with HIV on antiretroviral treatment: a prospective cohort study.** *HIV Med* 2003; **4**:276–286.
166. Wong WC, Luk CW, Kidd MR. **Is there a role for primary care clinicians in providing shared care in HIV treatment? A systematic literature review.** *Sex Transm Infect* 2012; **88**:125–131.
167. Igumbor JO, Scheepers E, Ebrahim R, Jason A, Grimwood A. **An evaluation of the impact of a community-based adherence support programme on ART outcomes in selected government HIV treatment sites in South Africa.** *AIDS Care* 2011; **23**:231–236.
168. Wouters E, Van Damme W, van Rensburg D, Masquillier C, Meulemans H. **Impact of community-based support services on antiretroviral treatment programme delivery and outcomes in resource-limited countries: a synthetic review.** *BMC Health Serv Res* 2012; **12**:194.
169. Kunutsor S, Walley J, Katabira E, Muchuro S, Balidawa H, Namagala E, *et al.* **Improving clinic attendance and adherence to antiretroviral therapy through a treatment supporter intervention in Uganda: a randomized controlled trial.** *AIDS Behav* 2011; **15**:1795–1802.
170. Rich ML, Miller AC, Niyigenga P, Franke MF, Niyonzima JB, Soccia A, *et al.* **Excellent clinical outcomes and high retention in care among adults in a community-based HIV treatment program in rural Rwanda.** *J Acquir Immune Defic Syndr* 2012; **59**:e35–e42.
171. Bangsberg DR, Mills EJ. **Long-term adherence to antiretroviral therapy in resource-limited settings: a bitter pill to swallow.** *Antivir Ther* 2013; **18**:25–28.
172. Mills EJ, Lester R, Ford N. **Promoting long term adherence to antiretroviral treatment.** *Br Med J* 2012; **344**:e4173.
173. Bastard M, Fall MB, Laniece I, Taverne B, Desclaux A, Ecochard R, *et al.* **Revisiting long-term adherence to highly active antiretroviral therapy in Senegal using latent class analysis.** *J Acquir Immune Defic Syndr* 2011; **57**:55–61.
174. Cambiano V, Lampe FC, Rodger AJ, Smith CJ, Geretti AM, Lodwick RK, *et al.* **Long-term trends in adherence to antiretroviral therapy from start of HAART.** *AIDS* 2010; **24**:1153–1162.
175. Chaiyachati K, Hirschhorn LR, Tanser F, Newell ML, Barnighausen T. **Validating five questions of antiretroviral nonadherence in a public-sector treatment program in rural South Africa.** *AIDS Patient Care STDS* 2011; **25**:163–170.
176. Barnighausen T, Salomon JA, Sangrujee N. **HIV treatment as prevention: issues in economic evaluation.** *PLoS Med* 2012; **9**:e1001263.
177. Flexner C, Plumley B, Brown Ripin D. **Treatment optimization: an outline for future success.** *Curr Opin HIV AIDS* 2013; **8**:523–527.
178. Aldir I, Horta A, Serrado M. **Single-tablet regimens in HIV: does it really make a difference?** *Curr Med Res Opin* 2014; **30**:89–97.
179. Nachega JB, Parienti JJ, Uthman OA, Gross R, Dowdy DW, Sax PE, *et al.* **Lower Pill Burden and Once-Daily Antiretroviral Treatment Regimens for HIV Infection: A Meta-Analysis of Randomized Controlled Trials.** *Clin Infectious Dis* 2014. [Epub].