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## Patient support and education for promoting adherence to highly active antiretroviral therapy for HIV/AIDS (Review)

Rueda S, Park-Wyllie LY, Bayoumi A, Tynan AM, Antoniou T, Rourke S, Glazier R

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(Review)

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[Intervention Review]

# Patient support and education for promoting adherence to highly active antiretroviral therapy for HIV/AIDS

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## ABSTRACT

### Background

Adherence to prescribed regimens is required to derive maximal benefit from many highly active antiretroviral therapy (HAART) regimens in people living with HIV/AIDS.

### Objectives

To conduct a systematic review of the research literature on the effectiveness of patient support and education to improve adherence to HAART.

### Search methods

A systematic search of electronic databases was performed from January 1996 to May 2005.

### Selection criteria

Randomized controlled trials examining the effectiveness of patient support and education to improve adherence to HAART were considered for inclusion. Only those studies that measured adherence at a minimum of six weeks were included.

### Data collection and analysis

Study selection, quality assessments and data abstraction were performed independently by two reviewers.

### Main results

Nineteen studies involving a total of 2,159 participants met criteria for inclusion. It was not possible to conduct a meta-analysis due to study heterogeneity with respect to populations, interventions, comparison groups, outcomes, and length of follow-up. Sample sizes ranged from 22 to 367. The populations studied ranged from general HIV-positive populations to studies focusing exclusively on children, women, Latinos, or adults with a history of alcohol dependence, to studies focusing almost exclusively on men. Study interventions included cognitive behavioral therapy, motivational interviewing, medication management strategies, and interventions indirectly targeting adherence, such as programs directed to reduce risky sexual behaviours. Ten studies demonstrated a beneficial effect of the intervention on adherence. We found that interventions targeting practical medication management skills, those administered to individuals vs groups, and those interventions delivered over 12 weeks or more were associated with improved adherence outcomes. We

also found that interventions targeting marginalized populations such as women, Latinos, or patients with a past history of alcoholism were not successful at improving adherence. We were unable to determine whether effective adherence interventions were associated with improved virological or immunological outcomes. Most studies had several methodological shortcomings leaving them vulnerable to potential biases.

### **Authors' conclusions**

We found evidence to support the effectiveness of patient support and education interventions intended to improve adherence to antiretroviral therapy. Interventions targeting practical medication management skills, those interventions administered to individuals vs groups, and those interventions delivered over 12 weeks or more were associated with improved adherence outcomes. There is a need for standardization and increased methodological rigour in the conduct of adherence trials.

## **PLAIN LANGUAGE SUMMARY**

### **Patient support and education for promoting adherence to highly active antiretroviral therapy for HIV/AIDS**

People living with HIV/AIDS are required to achieve high levels of adherence to benefit from many antiretroviral regimens. This review identified 19 studies involving a total of 2,159 participants that evaluated an intervention intended to improve adherence. Ten of these studies demonstrated a beneficial effect of the intervention. We found that interventions targeting practical medication management skills, those administered to individuals vs groups, and those interventions delivered over 12 weeks or more were associated with improved adherence to antiretroviral therapy. We also found that interventions targeting marginalized populations such as women, Latinos, or patients with a past history of alcoholism were not successful at improving adherence. We did not find studies that evaluated the quality of the patient-provider relationship or the clinical setting. Most studies had several methodological shortcomings.

## BACKGROUND

High adherence to antiretroviral therapy is a key determinant of the degree and durability of viral suppression (Paterson 2000, Yeni 2002, Yeni 2004, Gross 2001, Wood 2003) and has been associated with lower rates of disease progression, hospitalization, and mortality (Press 2002). In contrast, poor adherence correlates with treatment failure (Yeni 2002, Nieuwkerk 2001, Haubrich 1999, Knobel 2001) and can limit options for future antiretroviral therapies due to cross-resistance between HIV drugs. Thus, even brief periods of non-adherence to certain antiretrovirals can have lifelong implications (Perno 2002, Wainberg 1998). Complicated HIV regimens, medication side effects and toxicities, high pill burdens, and psychosocial factors all contribute to non-adherence for persons on HAART (Singh 1999, Ferguson 2002, Carpenter 2000, Ickovics 2002, Catz 2000, Ammassari 2002, Golin 2002). Patient characteristics and the nature of health-care delivery are additional contributors (Ickovics 2002a, Ickovics 1997).

Previous studies have demonstrated that the rates of non-adherence for medications within the general population can range from 15% to 93%, with the average rate being 50% non-adherence for chronic health conditions (Haynes 1979, McDonald 2002). In a study of HIV treatment naïve patients, 95% adherence was associated with maximal therapeutic effects of antiretroviral therapy; however, only 30% of patients in the study were able to attain this level (Paterson 2000). While the optimal level of adherence may vary across regimens, strategies to improve adherence remain particularly important for persons taking antiretroviral medications.

Few systematic reviews of interventions to improve adherence to antiretroviral therapy have been published. Early reviews yielded a limited number of underpowered or poor quality studies (Haddad 2000, Fogarty 2002) and were inconclusive (Ickovics 2002a). More recent reviews have reported preliminary success of several interventions while reiterating the need for more rigour in the conduct of intervention trials (Cote 2005, Simoni 2003, Simoni 2006). The most recent systematic review, which described the literature to December 2004 and performed a meta-analysis of studies using between- and within-group designs, found that the average intervention had a small and variable effect on adherence and that stronger effects were demonstrated in populations with poor baseline adherence (Amico 2006). However, this review included uncontrolled studies and excluded controlled studies that did not provide enough information to calculate an effect size.

## OBJECTIVES

To conduct a systematic review of the research literature on the effectiveness of patient support strategies and education for improving adherence to highly active antiretroviral therapy (HAART) in people living with HIV/AIDS.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

We only considered randomized controlled trials (RCTs) for inclusion in this review because they are considered the gold standard to assess the effects of interventions. Carefully planned and properly conducted RCTs are thought to provide the highest

strength of evidence to establish causality, considering their ability to minimize potential biases by controlling for both known and unknown confounding factors.

#### Types of participants

Studies of people infected with HIV and receiving highly active antiretroviral therapy (HAART) were included. HAART was defined as at least three antiretroviral drugs consisting of: at least one protease inhibitor; at least one non-nucleoside reverse transcriptase inhibitor; or three or more nucleoside reverse transcriptase inhibitors, of which one was abacavir. We included studies of adults and children in which at least 80% of the study population had been prescribed HAART.

#### Types of interventions

We considered support- and education-based interventions intended to improve adherence to HAART. The interventions, which could be directed to individuals or groups, included all types of patient education, counseling, support, health promotion, reminders, provision of resources, supervision, consultation, and telephone hotlines. We imposed no criteria concerning the "dose" or intensity of the intervention, but the control arm had to receive usual or standard adherence support or an alternate intervention of any type.

#### Types of outcome measures

We included studies that measured and reported at least one measure of adherence to HAART for both the intervention and control arms at least 6 weeks after study initiation. Possible measures included electronic monitoring, pill counts, medication diaries, patient self-report, provider report, clinic and pharmacy records. Dropouts or withdrawals from drug trials were not considered measures of adherence. We recorded immunologic and virologic outcomes as secondary endpoints when available, but these were not a requirement for study selection.

### Search methods for identification of studies

#### Electronic Databases

The search strategy covered the literature from January 1996 (following the introduction of the first protease inhibitor) to May 2005. We made minor modifications to the search strategy over time to update the list of antiretroviral medications. We searched the following databases: Medline, CINAHL, HEALTHSTAR, Cochrane CENTRAL, PsycInfo, EMBASE, International Pharmaceutical Abstracts, Sociological Abstracts and Science Citation Index.

#### Conference Proceedings

We also searched the following conference databases in the same time frame: Conference on Retroviruses and Opportunistic Infections (CROI), International AIDS Conference, International AIDS Society (IAS), Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), and the Canadian Association of HIV/AIDS Research (CAHR).

We employed the following librarian-developed search strategy to identify studies relevant to the review. The strategy was modified as required for various databases.

- 1 exp human immunodeficiency virus/ (25780)
- 2 exp Human Immunodeficiency Virus Infection/ (55232)

- 3 exp Anti Human Immunodeficiency Virus Agent/ (1163)  
 4 exp Proteinase Inhibitor/ (44472)  
 5 exp Rna Directed DNA Polymerase Inhibitor/ (16016)  
 6 Protease inhibitors/ (8939)  
 7 NEVIRAPINE/ (3068)  
 8 DELAVIRDINE/ (1197)  
 9 INDINAVIR/ (4956)  
 10 NELFINAVIR/ (3157)  
 11 SAQUINAVIR/ (3651)  
 12 RITONAVIR/ (4212)  
 13 hiv.tw. (51525)  
 14 human immunodeficiency.tw. (19547)  
 15 acquired immunodeficiency syndrome.tw. (2837)  
 16 acquired immune deficiency syndrome.tw. (756)  
 17 aids.tw. (22140)  
 18 (Fosamprenavir or Atazanavir or Indinavir or Nelfinavir or Saquinavir or Ritonavir or Amprenavir or Lopinavir or ritonavir or kaletra or Tripanavir or tipranavir).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name] (7561)  
 19 (Nevirapine or Delavirdine or Efavirenz).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name] (4061)  
 20 Tenofovir.mp. (436)  
 21 (Abacavir or Stavudine or Didanosine or Lamivudine or Zidovudine or Zalcitabine or Combivir or "AZT + 3TC" or Trizivir or "AZT + 3TC + abacavir").mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name] (13735)  
 22 or/1-21 (116766)  
 23 Patient Compliance/ (16643)  
 24 exp Patient Education/ (11307)  
 25 complian:.tw. (18802)  
 26 comply.tw. (1480)  
 27 complied.tw. (555)  
 28 noncomplian:.tw. (1510)  
 29 non-complian:.tw. (1023)  
 30 adher:.tw. (19834)  
 31 non-adher:.tw. (522)  
 32 nonadher:.tw. (836)  
 33 or/23-32 (57959)  
 34 randomization/ (6224)  
 35 random:.tw. (136023)  
 36 Double Blind Procedure/ (30795)  
 37 Single Blind Procedure/ (3517)  
 38 Clinical Trial/ (210296)  
 39 Placebo/ (27809)  
 40 Methodology/ (26448)  
 41 exp comparative study/ (73529)  
 42 exp Evaluation/ (19562)  
 43 exp Follow Up/ (88126)  
 44 exp Prospective Study/ (25781)  
 45 Crossover Procedure/ (10286)  
 46 exp types of study/ or exp controlled study/ (2917667)  
 47 Meta Analysis/ (13759)  
 48 meta-analy:.tw. (6674)  
 49 exp POSTMARKETING SURVEILLANCE/ (3124)  
 50 exp Case Control Study/ (6621)  
 51 exp Cohort Analysis/ (14622)  
 52 clinic: trial:.tw. (41235)  
 53 ((singl: or doubl: or tripl: or trebl:) adj (mask: or blind:)).tw. (29579)  
 54 placebo:.tw. (36863)  
 55 latin square:.tw. (343)  
 56 control:.tw. (492259)  
 57 prospectiv:.tw. (93042)  
 58 volunteer:.tw. (32818)  
 59 metaanaly:.tw. (465)  
 60 ((systematic: or quantitativ:) adj (review: or overview)).tw. (4319)  
 61 (medline or embase or cinahl or psycinfo or psychinfo or psyclit or psychlit or scisearch).tw. and review.pt. (3763)  
 62 data synthes:.tw. (1734)  
 63 usual care.tw. (820)  
 64 intervention.tw. (58279)  
 65 strateg\$.tw. (97031)  
 66 enhance.tw. (34962)  
 67 improve.tw. (72635)  
 68 Major Clinical Study/ (398303)  
 69 treatment outcome/ (159281)  
 70 controlled study/ (1090196)  
 71 or/34-70 (2983259)  
 72 22 and 33 and 71 (3199)  
 73 limit 72 to human (3004)  
 74 ((2002: or 2003:) not (200201: or 200202: or 200203: or 200204:)).em. (916265)  
 75 73 and 74 (1082)  
 76 from 75 keep 1-500 (500)  
 77 from 75 keep 501-1000 (500)  
 78 from 75 keep 1001-1082 (82)  
 79 from 75 keep 1 (1)

## Data collection and analysis

### Study Selection

Two reviewers independently assessed the studies for potential relevance by reading the abstract and title to eliminate obvious exclusions. If the abstract was unavailable, the full text paper was retrieved. We used a customized form reflecting the selection criteria to facilitate the selection process. Studies published in all languages were considered for inclusion.

Full-text versions of the papers identified from the abstract screening process were subsequently retrieved and assessed independently by two reviewers for inclusion in the review. Full-text papers were not examined in cases where both reviewers agreed that the study did not meet inclusion criteria. In the case of uncertainty regarding the relevance of a study, the authors of the study were contacted to clarify the necessary aspects of the study design. When disagreements about the relevance of a study emerged, the reviewers met to discuss their disagreement until consensus was reached. If consensus could not be reached, a third reviewer was available to arbitrate the decision. References from retrieved studies were also reviewed in an attempt to locate additional relevant studies.

### Data Abstraction

Data abstraction was performed independently by two reviewers. We attempted to contact study authors to obtain data identified

as missing during data abstraction. Disagreements were discussed between the reviewers until consensus was reached. If consensus could not be reached, a third reviewer was invited to settle the disagreement.

#### Quality Assessment

The methodological quality was appraised for the included studies. The purpose of this appraisal was not to exclude studies based on a pre-determined cut-off, but to discuss the overall quality of the studies available for inclusion. We created a list of quality criteria, based on Sackett (Sackett 1979) and the Consort Statement (Moher 2001, Altman 2001), outlining the following important design issues specific to adherence enhancing intervention studies:

**Randomization Method:** The method used to generate the random allocation sequence was described and appropriate. We were unable to judge whether or not the randomization method was appropriate when the authors used the following terms without elaboration: random, randomization, or random allocation. Following the Consort Statement (item 8a) (Moher 2001, Altman 2001), several sequence generation methods were considered appropriate, including the use of a random-number table or a computerized random-number generator.

**Allocation Concealment:** The method used to implement the random allocation sequence needed to be described and appropriate. This criterion refers to the requirement that the investigators or clinicians should not have prior information of the treatment group to which the patient would be randomized. Following the Consort Statement (Moher 2001, Altman 2001) (item 9), the authors needed to clarify whether or not the allocation sequence was concealed until the groups were assigned. The best methods to allocation concealment include the involvement of external sources, such as a central telephone randomization system. We also considered the use of opaque, sealed envelopes to be an appropriate concealment mechanism.

**Objective Measure of Adherence:** Subjective measures of adherence, such as patient self-report, are commonly used but tend to yield overestimates (Sackett 1979). Objective measures of adherence include electronic monitoring, pill counts, pharmacy or clinic medication data, and direct observation.

**Attention Control:** Control patients should receive similar contact time with the adherence support provider as patients receiving the intervention (Sackett 1979). Otherwise, the observed effects may be due to either the intervention or the non-specific effects of the increased attention paid to the intervention group (McDonald 2002).

**Participants Lost to Follow-up:** Details regarding participants lost to follow-up should be provided for both the intervention and control arms. We considered follow-up to be successful if 80% or more of both the intervention and the control groups were available at the end of the study. Following the Consort Statement (Moher 2001, Altman 2001) (item 13a), attrition as a result of loss to follow up should be distinguished from exclusion, withdrawal from the study, and poor adherence to the protocol.

**Length of Follow-up:** We considered at least 6 months from study initiation to be an adequate length of follow-up because HAART regimens are life-long and adherence interventions need to show persistent effects to be beneficial. In addition, we considered

(as a separate criterion) whether follow-up measurements were available for 80% or more of the participants in both the intervention and control groups at six months since study initiation.

**Analysis of All Randomized Participants:** This criterion refers to whether or not the investigators included in the analysis all the participants who underwent randomization and were analyzed in the groups to which they were randomized.

## RESULTS

### Description of studies

We identified 7,512 citations from the searches conducted of the electronic databases from January 1996 to May 2005. Nineteen studies involving a total of 2,159 participants met criteria for inclusion (Berrien 2004, Dilorio 2003, Fairley 2003, Goujard 2003, Jones 2003, Knobel 1999, Levy 2004, Murphy 2002, Pradier 2003, Rathbun 2005, Rawlings 2003, Safren 2001, Safren 2003, Samet 2005, Smith 2003, Tuldra 2000, van Servellen 2003, Weber 2004, Wyatt 2004). The most common reasons for exclusion were the absence of a comparison group and the failure to report a measure of adherence for both the intervention and control groups at 6 weeks from study initiation. Studies were heterogeneous with respect to populations, interventions, comparison groups, outcomes, and lengths of follow-up. Accordingly, we did not attempt to pool results using meta-analysis.

All studies were randomized controlled trials and were published in English with the exception of one paper that was published in Spanish (Knobel 1999). Twelve studies were conducted in the US, two in Spain, two in France, two in Australia, and one in Switzerland. Sample sizes ranged from 22 to 367. Length of follow-up ranged from 6 weeks to 15 months. While some studies focused exclusively on children (Berrien 2004), women (Jones 2003, Wyatt 2004), Latinos (van Servellen 2003), or adults with a history of alcohol dependence (Samet 2005), others included all patients with HIV, some of which had a large proportion of men in the study population (>80%). Six studies specifically targeted patients who reported difficulties with adherence or who presented with poor adherence at study baseline (Safren 2001, Murphy 2002, Jones 2003, van Servellen 2003, Safren 2003; Weber 2004). The duration of the interventions ranged from a single session to multiple sessions delivered over one year. Five studies included participants who were either antiretroviral naïve or switching to a new antiretroviral regimen (Knobel 1999, Tuldra 2000, Smith 2003, Rawlings 2003, Rathbun 2005); the remainder included treatment-experienced participants who were taking antiretroviral medications at baseline.

The types of interventions varied from cognitive behavioral therapy, motivational interviewing, or medication management strategies, to interventions indirectly targeting adherence such as programs directed to reduce risky sexual behaviours. All interventions were directed at patients, individually or in groups, rather than at providers or health care systems. The interventions were delivered by lay individuals, health advocates, social workers, psychologists, nurses, pharmacists, and physicians.

Adherence outcomes were calculated as dichotomous and/or continuous variables, ranging from the proportion of participants reaching a pre-determined threshold of adherence (e.g., <sup>3</sup>95% adherence) to the mean difference in adherence levels from the end



of the study to baseline. In general, the overall level of adherence at baseline in most studies ranged between 55% and 95%, which is consistent with reported estimates from other studies (Paterson 2000, Bangsberg 2002, Bangsberg 2000, Bangsberg 2001). Between 68% and 82% of study populations reported 95% or greater adherence at baseline, which is also consistent with the wide range seen in past studies (Paterson 2000, Hugen 2002, Howard 2002). Virological or immunological outcomes were reported in 12 studies and ranged from the number of participants with a viral load above a pre-determined level to a mean difference in viral load from the end of the study to baseline. Some statistical analyses controlled

for baseline values, others used the differences between follow-up and baseline values, and others used only follow-up and neglected baseline values.

**Risk of bias in included studies**

The quality assessment showed that the examined studies had several methodological shortcomings (Figure 1). In general, the quality of the studies was weak leaving most of the studies vulnerable to several potential biases. Because there were so few studies of good quality, we were unable to assess the effect of quality on study outcomes.

**Figure 1. Quality assessment.**

	Randomization method described & appropriate	Allocation concealment method described & appropriate	Objective measure of adherence	Attention control	Follow-up ≥ 80% of participants in both groups at the end of the intervention	Follow-up ≥ 6 months since study initiation	Follow-up ≥ 80% of participants in both groups at 6 months (if available)	All randomized participants analyzed
Knobel 1999			Unsure		Yes	Yes	Yes	
Tuldra 2000						Yes		Yes
Safren 2001					Unsure			
Murphy 2002	Yes							
Dilorio 2003								
Pradier 2003					Yes	Yes	Yes	Yes
Smith 2003			Yes					
Jones 2003				Yes	Unsure	Yes		
Goujard 2003						Yes		
Rawlings 2003			Yes		Yes	Yes	Yes	Unsure
van Servellen 2003	Yes				Yes			
Fairley 2003								
Safren 2003			Yes					
Weber 2004	Yes	Yes	Yes		Yes	Yes		
Berrien 2004	Yes	Yes	Yes	Yes	Yes	Yes		
Levy 2004								
Wyatt 2004				Yes	Yes			
Samet 2005					Yes	Yes		
Rathbun 2005	Yes	Yes	Yes			Yes		Yes

The randomization method was described and was considered appropriate in only 5 studies (Murphy 2002, van Servellen 2003, Weber 2004, Berrien 2004, Rathbun 2005). All the included studies implemented the traditional two-group, parallel, randomized controlled trial design with the exception of three studies. Two studies from the same research group (Fairley 2003, Levy 2004) used an unconventional randomized design (a "Stepped-Wedge" design) while another study (Wyatt 2004) used a time-lagged wait-list control.

We identified four design features that may have resulted in an overestimation of the treatment effects:

(1) Allocation concealment: Only 3 studies described the method of allocation concealment (Weber 2004, Berrien 2004, Rathbun 2005). It has been shown that studies that failed to report allocation concealment may overestimate the intervention effect by 41% and studies that incompletely report allocation concealment may overestimate the intervention effect by 30% (Schulz 1995).

(2) Objective measure of adherence: Only 6 studies used an objective measure of adherence (Smith 2003, Rawlings 2003, Safren 2003, Weber 2004, Berrien 2004, Rathbun 2005) (an additional study used an objective measure of adherence to corroborate the validity of the self-reports (Knobel 1999)). A major limitation of using subjective reports is low sensitivity (i.e., many patients with low adherence would not be identified by self-report). In several studies where self-reported adherence methods were compared to Medication Event Monitoring System (MEMS) methods, self-reported methods have consistently overestimated adherence by 5-20% (Liu 2001, Miller 2000, Gallant 1998).

(3) Analysis of all randomized participants: Only 3 studies analyzed all randomized participants (Tuldra 2000, Pradier 2003, Rathbun 2005). The conclusions derived from studies that fail to analyze all randomized participants can be misleading, particularly when there are imbalances between the intervention and control groups. Only two studies reported a method to handle missing data. One study imputed adherence rates by regression and the other study imputed missing data as last observation carried forward.



(4) Attention control: Only 3 studies reported that participants in both the intervention and control groups received a similar amount of contact time (Jones 2003, Berrien 2004, Wyatt 2004). This factor is particularly important when the intervention involves a considerable amount of contact time with the participants. If the contact time variable is not accounted for, the treatment effects may be the result of the non-specific effects of the increased attention paid to the intervention group as opposed to the intervention itself (McDonald 2002).

Regarding loss of participants to follow-up, less than half the studies (8 studies) reported following up successfully 80% or more of the participants in both the intervention and control groups at the end of the intervention (Knobel 1999, Pradier 2003, Rawlings 2003, van Servellen 2003, Weber 2004, Berrien 2004, Wyatt 2004, Samet 2005) (this was unclear for two additional studies (Safren 2001, Jones 2003)). A high level of attrition is a particular concern for adherence trials given the observation that adherence trials may already be intrinsically biased since they focus on participants who are already willing to take part on studies (McDonald 2002).

In addition, regarding the length of the follow-up, just over half the studies (10 studies) reported follow-up times of 6 months or more since study initiation (Knobel 1999, Tuldra 2000, Pradier 2003, Jones 2003, Goujard 2003, Rawlings 2003, Weber 2004, Berrien 2004, Samet 2005, Rathbun 2005). This is particularly important for interventions designed to improve adherence to long-term treatments, such as HAART. Of these, however, only 3 studies reported 80% or more participants in both the intervention and control groups at six months (Knobel 1999, Pradier 2003, Rawlings 2003).

## Effects of interventions

### Effects on Adherence Outcomes

Ten studies demonstrated a beneficial effect of the intervention on antiretroviral adherence (Knobel 1999, Tuldra 2000, Pradier 2003, Smith 2003, Goujard 2003, Fairley 2003, Safren 2003, Weber 2004, Berrien 2004, Levy 2004), eight studies failed to demonstrate an improved level of adherence resulting from the intervention (Safren 2001, Murphy 2002, Dilorio 2003, Rawlings 2003, van Servellen 2003, Wyatt 2004, Samet 2005, Rathbun 2005), and we were unable to determine a clear presence or absence of a benefit for one study because it failed to report a between-group comparison (Jones 2003).

We examined a number of intervention features to identify any recurring characteristics that may be linked to successful adherence outcomes. This semi-qualitative approach has been used by others to help identify the relationship between intervention characteristics and study outcomes (Kawamoto 2005). Features that tended to be associated with success included those interventions provided to individuals vs groups, those provided over longer periods of time (<sup>3</sup> 12 weeks), and those interventions targeting practical medication management skills vs cognitive behavioral or motivational approaches.

When interventions were provided at the individual level, 67% (10/15) were successful (Knobel 1999, Tuldra 2000, Pradier 2003, Smith 2003, Goujard 2003, Fairley 2003, Safren 2003, Weber 2004, Berrien 2004, Levy 2004) compared to a 0% (0/4) success rate observed with interventions provided in a group setting. In addition, 86% (6/7) of the interventions provided over 12 weeks or

more successfully improved adherence (Knobel 1999, Pradier 2003, Smith 2003, Goujard 2003, Safren 2003, Berrien 2004) compared to those interventions delivered under 12 weeks (0/8 or 0% success rate).

Interventions that targeted the improvement of patient's medication management skills were fairly successful (6/8 or 75% success rate) (Tuldra 2000, Smith 2003, Goujard 2003, Fairley 2003, Safren 2003, Levy 2004) when compared to interventions designed around cognitive behavioral therapy and motivational interviewing approaches (1/7 or 14% success rate) (Weber 2004). The interventions that focused on medication management skills consistently used reminders or memory aids, such as beepers, alarms, medication boxes, planning cards, paging systems, text messaging, or visual aids (i.e., a study had to provide these reminders exclusively to the intervention group for that study to be labeled as having this feature; we excluded from this category those studies that also provided these reminders to the control group). In general, these interventions were designed to improve the levels of adherence by improving the participant's medication management skills (e.g., medication information, tailored drug schedules, medication dosettes, side-effect management, and reminder devices) and by helping patients identify and address barriers to adherence (e.g., problems patients might face in real-life situations or strategies to manage side-effects).

Several of the studies that looked at marginalized populations such as women (Wyatt 2004), Latinos (van Servellen 2003), or patients with a past history of alcoholism (Samet 2005) were not successful at improving adherence. This may suggest that a different approach needs to be developed in order to design effective interventions for these populations.

The presence of inconsistent outcomes or intervention features that appeared in only a small number of studies limited our ability to reach conclusions about the relationship between other types of interventions and outcomes. We were unable to ascertain whether success was associated with the type of provider administering the intervention, the number of visits over which the intervention was provided, the antiretroviral experiences of patients, delivery at tertiary or academic centers, or the targeting of patients reporting poor adherence at baseline.

We were unable to determine the effect of the type of provider because many interventions were delivered by different combinations of providers (e.g., pharmacists/ nurses, physicians/ nurses) and it was not feasible to disentangle the effects of a single provider or a particular combination of providers. The effect of providing the intervention over multiple visits was also difficult to interpret as six out of twelve interventions (50%) that included 3 visits or more were successful, but 3 out of 4 (75%) that included less than 3 visits were also successful. Whether the intervention was provided to patients already on established regimens or those initiating/switching to a new regimen affected the success of the interventions was also difficult to interpret. Three of the five studies (60%) that offered the intervention to patients initiating or switching to new antiretroviral regimens were positive studies, compared to 7 of 14 studies targeting patients who were already on existing regimens (50% success rate). Even though the interventions that were implemented in tertiary or academic centers had a 62% success rate (8/13), those interventions that were delivered in non-tertiary centers had a 33% success rate (1/3).

Lastly, two out of six interventions (33%) that targeted patients presenting with poor adherence or who reported difficulties with adherence at baseline were successful while 8 out of 13 studies (62%) that did not mention whether or not they targeted patients reporting poor adherence were also successful.

#### Effects on Virological and/or Immunological Outcomes

We were unable to determine whether improved adherence extended to improved viral or immunologic outcomes. Six studies included virological outcomes only (Tuldra 2000, Pradier 2003, Smith 2003, Weber 2004, Berrien 2004, Rathbun 2005) and six studies included both virological and immunological outcomes (Knobel 1999, Goujard 2003, Rawlings 2003, Fairley 2003, Levy 2004, Samet 2005). Only 5 out of 12 studies that reported virological and/or immunological results found at least one significant effect associated with the intervention (Knobel 1999, Tuldra 2000, Pradier 2003, Samet 2005, Rathbun 2005). These studies reported conflicting statistical findings. For example, three studies reported a statistical significant result for one outcome (e.g., reduction in viral load) but not another (e.g., proportion of patients with a viral load below a pre-determined level) (Knobel 1999, Pradier 2003, Samet 2005). Another study reported a significant finding when the analysis included only those participants who completed the study but not when the analysis included all those participants that were randomized at study entry (Tuldra 2000). Another study reported statistically significant findings for some points in time (e.g., week 4 and 28), but not for others (e.g., week 16) (Rathbun 2005).

## DISCUSSION

We found evidence to support the effectiveness of some types of patient support and education interventions in improving adherence to antiretroviral therapy. Overall, several key intervention features such as interventions delivered to individuals vs groups, those delivered over 12 weeks or more, and those interventions targeting practical medication management skills vs cognitive behavioural or motivational approaches, were present in many of the successful intervention studies. To our knowledge, our systematic review is the first to suggest that interventions directly targeting practical medication management skills tended to be effective at improving adherence, and that interventions targeting psychological constructs (e.g., self-efficacy, attitudes, motivation, emotions, stress management, cognitive distortions and automatic thoughts) may be ineffective or may take longer to have an impact.

We also found that interventions targeting marginalized groups such as women, Latinos, or patients with a past history of alcohol dependence were not associated with improved adherence.

We were unable to determine whether the advantage associated with adherence outcomes translated to improved virological or immunological outcomes. This finding may be attributable to participant selection, since laboratory responses may be more difficult to demonstrate in patients using antiretroviral drugs at study baseline, or due to time factors, since virological and immunological responses may lag behind improved adherence. Alternatively, our results may indicate that average incremental improvements in adherence are nevertheless too small to improve clinical outcomes. Studies of adequate power and duration are required to resolve this question.

Our findings are in contrast to a recent systematic review (Amico 2006), which found that patients reporting low levels of adherence

at baseline benefited the most from adherence interventions. This difference may be the result of differing inclusion criteria. For example, while we included only randomized controlled trials, Amico et al included both between- and within-group designs (Amico 2006). Furthermore, we included 9 more randomized controlled trials because our search window extended until May 2005 and we included all eligible studies, even if we could not calculate effect sizes.

Inconsistencies and small number of studies limited our ability to reach conclusions about the effectiveness of the type of providers, the type of settings (e.g., tertiary vs community settings), the status of antiretroviral regimen at the time of consultation (whether patients are initiating a new regimen, switching to a new regimen, or already on an existing regimen), or the "dose" or intensity of the interventions.

There were several limitations to our systematic review. We were unable to pool the data for meta-analysis because of significant heterogeneity in many study features. As well, we were unable to assess the clinical significance of the reported adherence outcomes. Such concerns may be particularly important for future studies as the understanding of optimal adherence evolves. In addition, some studies included unvalidated adherence measures (e.g., an ordinal score ranging from one to four (Goujard 2003) or the proportion of patients reporting being adherent on 14 consecutive days (Wyatt 2004)).

Lastly, some of the included studies were conceived as pilot studies, a development that is consistent with the increasing level of maturity of any new technology. These studies, either by definition or as a result of feasibility issues, may have lacked the power to detect meaningful differences between the intervention and control groups. McDonald et al suggested as a rule of thumb that adherence studies require the inclusion of at least 60 participants per group in order to have 80% power to detect an absolute difference of 25% in the proportion of participants judged to have adequate adherence (McDonald 2002). Only 7 studies met this rule of thumb (Knobel 1999, Pradier 2003, Jones 2003, Goujard 2003, Rawlings 2003, Wyatt 2004, Samet 2005). Of these, three reported a statistical advantage favouring the intervention (Knobel 1999, Pradier 2003, Goujard 2003) and an additional one reported an improvement in mean CD4 cell counts (Samet 2005) (this study did not report significant findings for the adherence outcome).

## AUTHORS' CONCLUSIONS

### Implications for practice

This systematic review found evidence to support the effectiveness of some patient support and education interventions to improve adherence to antiretroviral therapy. We found that those interventions targeting practical medication management skills, those administered to individuals vs groups, and those delivered over 12 weeks or more could improve adherence to antiretroviral therapy. We did not find evidence to suggest that interventions targeting more complex psychological constructs were effective at improving adherence outcomes. We also failed to find evidence that interventions targeting marginalized populations such as women, Latinos, or patients with a past history of alcoholism were successful at improving adherence. Further studies should focus on medication management skills interventions to confirm the

effectiveness of these approaches and the generalizability of these results to a wider range of populations.

We did not find any studies that examined the effectiveness of provider-level interventions (e.g., those interventions that provide feedback to practitioners) and system-level interventions (e.g., those interventions that address access and affordability to services). Future efforts may need to look at the effectiveness of these interventions as evidence suggests that the quality of the patient-provider relationship and clinical setting are also important influences on adherence ([Ickovics 2002a](#)).

### Implications for research

There is a need for standardization and improved methodological rigour in the conduct of adherence trials. Adherence studies should follow a randomized design that implements and reports appropriate randomization and allocation concealment methods, uses an objective measure of adherence, follows up participants over at least 6 months since study initiation, and analyzes patients to the groups to which they were randomized.

The statistical analyses should also control for baseline values or use the differences between follow-up and baseline values as the

main outcome to make sure that the intervention and control groups are equivalent at study entry. In addition, adherence trials need to be powered to detect clinically significant differences using appropriate adherence outcomes that are clearly specified a priori.

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\* Indicates the major publication for the study

**CHARACTERISTICS OF STUDIES**
**Characteristics of included studies [ordered by study ID]**
**Berrien 2004**

Methods	RCT  Setting: Tertiary outpatient clinic (Connecticut, US)  Adherence measure(s): Pharmacy refill history (scored from 0-3) (3 points: monthly; 2 points: less than monthly; 1 point: much less than monthly; 0 points: never)  Self-report (10 questions for a maximum score of 37, 37-perfect adherence)
Participants	Children/Youth Mean age:10 (range 1.5-20) 45-55% Male

**Berrien 2004** (Continued)

 50-64% Hispanic  
 29-35% African- American

Interventions	<p>Intervention: Individual education program designed to improve knowledge of HIV &amp; resolve barriers to adherence, delivered by a nurse in 8 home visits over 3 months (including aids). The interventions was also offered in Spanish</p> <p>Control: Standard medication adherence education, including visual aids, medication boxes, beepers &amp; emotional support + 1 home visit</p>
Outcomes	<p>Adherence outcome(s): Mean pharmacy refill score at 3 or 8 months</p> <p>Follow-up:            I: 2.7            C: 1.7</p> <p>p-value between groups: .002</p> <p>Difference in mean adherence scores at 3 or 8 months</p> <p>Baseline:            I:32.2 (1.1)            C:31.7(.61)</p> <p>Follow-up:            I:34.8 (.41)            C:31.9(1.0)</p> <p>Change:            I: 2.7 (.88)            C: .2 (.96)</p> <p>p-value between groups: .07</p>
Notes	<p>Severity: CDC-C: 10%-24%, Mean CD4: 839-861, Mean VL: 3.67-3.92</p> <p>Regimen at study baseline: Already existing regimen</p> <p>Duration of intervention: 3 months</p> <p>Length of follow-up: Average of 8 months?</p>

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

**Dilorio 2003**

Methods	<p>RCT</p> <p>Setting: Clinic in large city (US)</p> <p>Adherence measure(s): Self-report            5-item scale recording ease and ability to be adherent in previous 30 days</p>
Participants	<p>Mean age: 42(SD 8)</p> <p>53% Male</p> <p>82% Single</p>

**Dilorio 2003** (Continued)

88% African American

Interventions Intervention: 3 motivational interviewing sessions delivered 2 weeks apart by trained and supervised nurses + motivational materials (e.g., videotape, journal, calendar)

Control: Usual adherence education

Outcomes Adherence outcome(s): Mean adherence from a scale with a total score ranging from 5 to 30

Follow-up:  
 I: 26.5(4.8)  
 C: 23.4 (5.1)

p-value between groups:  
 .22

Notes Severity: Mean Yrs since HIV Dx: 11(4), CD4<200 at clinic entry

Regimen at study baseline: Already existing regimen

Duration of intervention: 6 weeks

Length of follow-up: 8 weeks

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

**Fairley 2003**

Methods RCT

Setting: Sexual health centre (Melbourne, Australia)

Adherence measure(s): Self-report (number of missed doses in previous 4, 7 & 28 days)

Participants Mean age: 38  
 95-100% Male  
 90-91% MSM  
 5-14% IDU  
 Difficulty with adherence

Interventions Intervention: Individual education program delivered by a nurse in a single session (2-3 hours) including regimen analysis, computer-generated medication planner, and a choice of a variety of aids (e.g., short message service and medication alarm). Nurse or pharmacist available for advice after clinic hours

Control: Usual care. Delay in receiving the education program

Outcomes Adherence outcome(s):  
 Mean number of missed doses

Baseline:  
 4 days:  
 .76  
 (SD 1.5)

**Fairley 2003** (Continued)

7 days:  
 1.5  
 (SD 2.5)

28 days  
 2.5  
 (SD 4.1)

Follow-up:  
 4 days  
 .38  
 (SD .9)

7 days  
 .74  
 (SD 1.5)

28 days:  
 2.5  
 (SD 6.3)

p-value between groups:  
 4 days  
 .03

7 days  
 .008

28 days  
 .96

Notes

Severity: Mean VL: 3.71, Mean CD4: 513, Undetectable VL: 73%

Regimen at study baseline: Already existing regimen

Duration of intervention: Variable (1 visit + electronic reminder for up to 20 weeks)

Length of follow-up: Up to 20 weeks

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

**Goujard 2003**

Methods

RCT

Setting: Tertiary outpatient clinic (France)

Adherence measure(s): Self-report (global adherence score based on non-specified qualitative criteria)

Participants

Mean age: 41  
 80% Male

Interventions

Intervention: Educational program of 4 individual 1-hour sessions, delivered over 12 months by trained professionals, including provision of pill boxes and therapeutic planning cards

Control: Provision of a therapeutic planning card at enrolment

**Goujard 2003** (Continued)

Outcomes	<p>Adherence outcome(s): Adherence ordinal score ranging from 1 (poor) to 4 (good)</p> <p>Change:</p> <p>6 months: I:+.25 C:-.19</p> <p>12 months: I:+.22 C:-.05</p> <p>p-value between groups:</p> <p>6 months: .025</p> <p>12 months: .22</p>
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Notes	<p>Severity: AIDS: 33%, CD4 &lt;200 : 17%, CD4 200-500: 49%, CD4&gt;500: 34%, VL&lt;200: 55%, VL&lt;5k: 23%, VL&gt;5k: 23%</p> <p>Regimen at study baseline: Already existing regimen</p> <p>Duration of intervention: Minimum of 3 sessions during first 12 months</p> <p>Length of follow-up: 6 months + 12 months</p>
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**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

**Jones 2003**

Methods	<p>RCT</p> <p>Setting: Tertiary outpatient clinics &amp; Community health centres (Miami, NY, NJ; US)</p> <p>Adherence measure(s): Self-report (rate of adherence over the previous 7 days)</p>
Participants	<p>100% Women Mean age: 37(+/-10) 76% unemployed 54% African- American 18% Hispanic 55% History of drug dependence</p>
Interventions	<p>Intervention: 10 weekly 2-hr group cognitive-behavioural stress management/expressive supportive therapy sessions delivered by trained and supervised therapists</p> <p>Control: 10 weekly 2-hr individual informational and educational sessions (including entertainment tapes)</p>
Outcomes	<p>Adherence outcome(s): Mean adherence at week 10-baseline</p> <p>Change: I: +30.4% C:+19.6%</p>



**Jones 2003** (Continued)

p-value within groups:

I: &lt;.01

C: &gt;.05

Notes	Severity: AIDS: 100%
	Regimen at study baseline: Already existing regimen
	Duration of intervention: 10 weeks
	Length of follow-up: 15 months

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

**Knobel 1999**

Methods	RCT  Setting: Tertiary outpatient clinic (Barcelona, Spain)  Adherence measure(s): Self-report questions + Pill counts every 2 months
Participants	Age: 36(+/- 8) 73% Male 48-50% current or past IDU
Interventions	Intervention: Individual intervention consisting of educational and supportive counseling delivered by a pharmacist at first medication fill + telephone support + monthly visits to outpatient unit  Control: Conventional dispensing of pills every two months
Outcomes	Adherence outcome(s): Proportion of patients reaching >=90% adherence at week 24  Follow-up:  I: 77% (46/60) C:53% (58/110)  RR=1.45 (1.16-1.82)  p-value between groups: .002
Notes	Severity: CD4: 232-245*, VL: 5.02-5.15†, CDC-C: 32%  Regimen at study baseline: Initial regimen  Duration of intervention: 24 weeks

**Knobel 1999** (Continued)

Length of follow-up: 24 weeks

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

**Levy 2004**

Methods	RCT  Setting: Tertiary outpatient clinic (Melbourne, Australia)  Adherence measure(s): Self-report
Participants	Mean age: 41-42 81-88% Male 38-58% MSM 21-25% IDU 0-22% Higher education
Interventions	Intervention: Individual education program delivered by a pharmacist and/or nurse in a single session (2 hours) including counseling, a computerized medication planner and adherence aids (i.e., dosette boxes and electronic alarms). Pharmacist available for advice after clinic hours  Control: Usual care. Delay in receiving the education program
Outcomes	Adherence outcome(s): Mean number of missed doses in previous 4, 7 & 28 days, measured on monthly basis  Baseline: 4 days: 1.9 (SD 3.0)  7 days: 3.0 (SD 4.1)  28 days: 7.4 (SD 11.5)  Follow-up: 4 days: 1.0 (SD 2.6)  7 days: 1.8 (SD 3.7)  28 days: 4.2 (SD 8.3)  p-value between groups: 4 days: <.001

**Levy 2004** (Continued)

 7 days:  
 <.001

 28 days:  
 <.001

Notes

Severity: Mean CD4: 382, Mean VL: 4.34

Regimen at study baseline: Already existing regimen

Duration of intervention: Variable (1 visit + electronic reminder for up to 20 weeks)

Length of follow-up: Up to 20 weeks

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment?	High risk	C - Inadequate

**Murphy 2002**

Methods

RCT

Setting: Tertiary outpatient clinic (California, US)

Adherence measure(s): Self-report (percent of medications taken in previous 3 days)

Participants

Mean age: 39(SD 7)  
 88% Male  
 46% African American  
 18% Hispanic  
 73% Unemployed  
 Poor adherence at study baseline

Interventions

Intervention: 3 group and 2 individual cognitive behavioural sessions (including role-playing and homework assignments) delivered by a psychologist and a nurse, over 7 weeks, using a manual

Control: Regular care provided at the clinic. One 30 minute consultation and medication schedule

Outcomes

Adherence outcome(s):  
 Mean adherence (SD) at week 7-8 & 20

Baseline:  
 I: 69% (41%)  
 C: 62% (46%)

Follow-up:  
 7-8 wks:  
 I: 87%  
 (SD 30%)  
 C: 87%  
 (SD 28%)

20 wks:  
 I: 86%  
 (SD 33%)  
 C: 83%  
 (SD 36%)

**Murphy 2002** (Continued)

Change:

7-8 wks:  
+18%  
(SD 35%)  
+25%  
(SD 45%)

20 wks:  
+18%  
(SD 48%)  
+21%  
(SD 41%)

p-value between groups:

7-8 wks:  
.62

20 wks:  
.82

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Notes                      Severity: Mean CD4: 340(291), VL<400: 33%, VL<10k: 30%, VL<50k: 15%, VL>50k: 9%

                                  Regimen at study baseline: Already existing regimen

                                  Duration of intervention: 7-8 weeks

                                  Length of follow-up: 20 weeks

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**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

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**Pradier 2003**

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Methods                      RCT

                                  Setting: Tertiary outpatient clinic (Nice, France)

                                  Adherence measure(s): Self-report (doses taken/ prescribed in previous 4 days)

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Participants                      Median age: 38-40  
87-91% Male  
64-70% Single  
30-33% IDU transmission  
24-25% Unemployed

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Interventions                      Intervention: 3 individual counseling and educational sessions (addressing cognitive, emotional, behavioral and social components) delivered by trained, supervised nurses using a manual (at baseline, 2 and 4 months)

                                  Control: Standard of care (usual clinical follow-up; medical consultations every 2-3 months)

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Outcomes                      Adherence outcome(s):  
Proportion of patients reaching 100% adherence at month 6

                                  Baseline:

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**Pradier 2003** (Continued)

I: 58%  
 C: 63%

Follow-up:  
 I: 75%  
 C: 61%

Change:  
 OR=2.5±1.5  
 (1.4-4.2)

p-value within groups:  
 I: .004  
 C: >.05

p-value between groups:  
 .001

Notes Severity: CDC-C: 30-32%, Median CD4: 340-361, Mean VL: 2.6-2.7, Undetectable VL: 40-41%

Regimen at study baseline: Already existing regimen

Duration of intervention: 4 months

Length of follow-up: 6 months

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

**Rathbun 2005**

Methods	RCT  Setting: Tertiary clinic (Oklahoma, US)  Adherence measure(s): Electronic monitoring (doses consumed/ prescribed)
Participants	Adult Indigents Median age: 38 85% Male 65-75% Caucasian 63-76% MSM 6-19% IDU transmission
Interventions	Intervention: Education on adherence strategies and monitoring of patient progress, including visual aids and reminder devices, delivered by pharmacists in clinic visits and phone follow-up for up to 12 weeks  Control: Standard of care, delivered by patient's primary care providers (physician or nurse)
Outcomes	Adherence outcome(s): Mean adherence rate at 4, 16 & 28 weeks (number of consumed/ prescribed doses)  Follow-up: Week 4: I: 86%

**Rathbun 2005** (Continued)

(SD 27%)  
 C: 73%  
 (SD 32%)

Week 16:  
 I: 77%  
 (SD 28%)  
 C: 56%  
 (SD 39%)

Week 28:  
 I: 74%  
 (SD 31%)  
 C: 51%  
 (SD 41%)

p-value between groups:

Week 4:  
 .23

Week 16:  
 .08

Week 28:  
 .08

**Notes**

Severity: Median CD4: 103-296, Median VL: 4.34- 5.25, AIDS: 79%, CDC C: 56-59%

Regimen at study baseline: Initial or switching to new regimen

Duration of intervention: 2 weeks (additional visits allowed up to 12 weeks for participants needing more assistance)

Length of follow-up: 28 weeks

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

**Rawlings 2003**

Methods RCT  
 Setting: Tertiary outpatient clinic (25 sites, US)  
 Adherence measure(s): Electronic monitoring (doses observed/ expected in 24 weeks)

Participants Mean age: 37(SD 9)  
 65% Male  
 71% African American  
 21% Hispanic  
 20% current IDU  
 43% MSM transmission  
 91% Treatment naïve

Interventions Intervention: Group educational program delivered in 4 sessions (one per week) to patients and care-givers and facilitated by a health care professional with skills-building exercises, including videotapes, charts and patient logbooks + Routine counselling

**Rawlings 2003** (Continued)

Control: Routine counseling alone

Outcomes	Adherence outcome(s): Mean overall adherence in 24 weeks  Follow-up: I: 70% C: 74%  p-value between groups: >.05
Notes	Severity: Median CD4: 379, Median log VL: 4.18, CDC Asympt: 80%, CDC AIDS: 2%  Regimen at study baseline: Initial regimen  Duration of intervention: 4 weeks  Length of follow-up: 24 weeks

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

**Safren 2001**

Methods	RCT  Setting: Community health centre (Boston, US)  Adherence measure(s): Self-report (pills taken/ prescribed in previous 2 weeks)
Participants	Mean age: 41(SD 8) 88% Male 29% African American 20% Hispanic 67% MSM Poor adherence at study baseline
Interventions	Intervention: Single-session individual intervention utilizing cognitive-behavioral, problem-solving, and motivational interviewing techniques, including a videotape presentation + one follow-up telephone review (10 min) one week later  Control: Self-monitoring medication diary. One follow-up interview
Outcomes	Adherence outcome(s): Mean adherence at week 12  Baseline: I: 74% C: 84%  Follow-up: I: 94% C: 93%



**Safren 2001** (Continued)

p-value between groups:  
>.05‡

**Notes**

Severity: None provided

Regimen at study baseline: Already existing regimen

Duration of intervention: One session

Length of follow-up: 12 weeks

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

**Safren 2003**
**Methods**

RCT

Setting: Community health centre (Boston, US)

Adherence measure(s): Electronic monitoring (doses taken/ prescribed in previous 2 weeks)

**Participants**

74% Unemployed or on disability

30% African-American

17% Hispanic

Adherence <90%

**Interventions**

Intervention: An on-line pager reminder system, which used a website (Medi-Mom) to deliver alerts in the form of text messages at the designated times

Control: Medication monitoring only

**Outcomes**

Adherence outcome(s):

Mean adherence at week 2 & 12

Baseline:

I: 55% (n=30)

C: 57% (n=30)

Follow-up:

Week 2:

I: 70% (n=30)

C: 56% (n=30)

Week 12:

I: 64% (n=19)

C: 52% (n=25)

p-value between groups:

Week 2:

<.004

Week 12:

<.03

**Notes**

Severity: CD4<200: 19%, CD4 200-350: 23%, CD4>350: 58%, VL<400: 51%, VL<5k: 29%, VL>5k: 20%

### Safren 2003 (Continued)

Regimen at study baseline: Already existing regimen

Duration of intervention: 12 weeks

Length of follow-up: 12 weeks

#### Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

### Samet 2005

Methods	<p>RCT</p> <p>Setting: Tertiary outpatient clinic (Boston, US)</p> <p>Adherence measure(s): Self-report (pills taken/ prescribed in previous 3 days and 30 days)</p>
Participants	<p>Adults with history of alcohol dependence</p> <p>Mean age: 43</p> <p>78-84% Male</p> <p>42-52% African American</p> <p>20-25% Homeless</p> <p>57-60% IDU Transmission</p> <p>22-25% MSM transmission</p> <p>6-7% IDU in past 6 months</p>
Interventions	<p>Intervention: 4 (15-60min) educational sessions over 3 months (including 1 home visit). Nurse trained in motivational interviewing provided individualized counseling, discussed alcohol use, and provided a timer. The intervention was also offered in Spanish</p> <p>Control: Standard of care (verbal or written instructions)</p>
Outcomes	<p>Adherence outcome(s): Proportion of patients with 100% adherence in previous 3 days at 6 and 12-13 months</p> <p>Baseline: I: 58% C: 65%</p> <p>Follow-up: 1-6 month: I: 65% C: 63%</p> <p>12-13 month: I: 71% C: 62%</p> <p>p-value between groups: 1-6 month: &gt;.05</p> <p>12-13 month: &gt;.05</p>

**Samet 2005** (Continued)

Proportion of patients with  
>=95% adherence in previous 30 days at 6 months and 12-13 months

Baseline:

I: 68%

C: 69%

Follow-up:

1-6 month:

I: 63%

C: 62%

12-13 month:

I: 67%

C: 64%

p-value between groups:

1-6 month:

>.05

12-13 month:

>.05

Notes

Severity: Mean CD4: 364-480, Mean VL: 1.9-2.2, Undetectable VL: 28-30%, AIDS: 24-31%

Regimen at study baseline: Already existing regimen

Duration of intervention: 3 months

Length of follow-up: 12-13 months

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

**Smith 2003**

Methods

RCT

Setting: Tertiary outpatient clinic (North Carolina, US)

Adherence measure(s): Electronic monitoring (doses taken/ prescribed in previous week)

Participants

Mean age: 37

91% Male

74% Non-White

53% Unemployed

2-5% IDU transmission

21-33% MSM transmission

Interventions

Intervention: Individual medication self-management program including 3 monthly follow-up education sessions, assistance with scheduling of doses and skills training, delivered by a pharmacist or a nurse

Control: Education session + assistance with scheduling of doses + electronic monitoring

Outcomes

Adherence outcome(s):

Mean adherence at week 12

**Smith 2003** (Continued)

Follow-up:  
 I: 96% (n=8)  
 C: 37% (n=9)

p-value between groups:  
 <.001

Notes

Severity: None provided

Regimen at study baseline: Initial or switching to new regimen

Duration of intervention: 12 weeks

Length of follow-up: 12 weeks

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

**Tuldra 2000**

Methods

RCT

Setting: Tertiary outpatient clinic (Baladona, Spain)

Adherence measure(s): Self-report (pills taken/ prescribed in previous month)

Participants

Mean age: 39(+/- 8)  
 75% Male  
 38% IDU transmission  
 38% MSM transmission

Interventions

Intervention: Education program including patient tailored medication schedule, medication management skills, problem solving skills and telephone support + follow-up visits

Control: Standard assessment with a psychologist following a regular medical visit

Outcomes

Adherence outcome(s):  
 Proportion of patients reaching  $\geq 95\%$  adherence at week 48§

Follow-up:  
 48 wks:  
 I: 94%  
 (32/34)  
 C: 69%  
 (25/36)

I: 58%  
 (32/55)  
 C: 41%  
 (25/61)

p-value between groups:  
 .008

.064±

**Tuldra 2000** (Continued)

Notes

Severity: Mean CD4: 355, Median VL: 4.02, Yrs since HIV Dx: 6(4)

Regimen at study baseline: Initial or switching to new regimen

Duration of intervention: Unclear

Length of follow-up: 48 weeks

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

**van Servellen 2003**

Methods	<p>RCT</p> <p>Setting: Community-based not-for profit clinics (Los Angeles, US)</p> <p>Adherence measure(s): Self-report (number of missed doses in previous 4 days &amp; 24 hours)</p>
Participants	<p>Spanish-Speaking low income/ homeless adults</p> <p>Mean age: 40-42</p> <p>88-93% Male</p> <p>93-98% Born outside US</p> <p>Poor adherence at study baseline</p>
Interventions	<p>Intervention: 5-week instructional support modular program conducted in Spanish by treatment advocates and a nurse practitioner in small groups of 3-7 participants</p> <p>Control: Standard care only</p>
Outcomes	<p>Adherence outcome(s): 4 day and 24 hour total number of doses missed at 6 weeks</p> <p>Baseline:</p> <p>4 days: I: 2.38 (SD 4.55) C: 1.82 (SD 4.86)</p> <p>24 hours: I: .56 (SD 1.45) C: .29 (SD 1.21)</p> <p>Follow-up:</p> <p>4 days: I: 1.26 (SD 3.02) C: 2.16 (SD 3.23)</p> <p>24 hours: I: .29</p>

**van Servellen 2003** (Continued)

(SD 0.96)  
 C: .32  
 (SD 0.96)

p-value between groups:  
 4 days:  
 >.05

24 hours:  
 >.05

Notes

Severity: Mean CD4: 214-353, Mean VL: 4.84-4.52, Mean Yrs since HIV Dx: 5-8

Regimen at study baseline: Already existing regimen

Duration of intervention: 5 weeks

Length of follow-up: 6 weeks

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

**Weber 2004**

Methods

RCT

Setting: Tertiary outpatient clinic + Private practice psychotherapists (Zurich, Switzerland)

Adherence measure(s): Electronic monitoring (doses observed/ expected)

Electronic monitoring (doses observed/ prescribed in previous month)

Self-report (VAS on whether antiretrovirals taken as prescribed ranging from 0-never- to 10-always)

Participants

Median age: 40-42  
 50-60% MSM  
 13-25% Past IDU  
 No current IDU/methadone

Interventions

Intervention: Median of 11 45-min cognitive behavioral therapy sessions (range 2-25) in 1 year, delivered by licensed and supervised psychotherapists + standard of care

Control: Standard of care

Outcomes

Adherence outcome(s):  
 Mean adherence at month 12

Baseline:  
 I: 94.3%  
 C: 94.9%

Follow-up:  
 I: 92.8%  
 C: 88.9%

p-value within groups:  
 I: .14

**Weber 2004** (Continued)

C: .006

p-value between groups:  
 .15‡

Proportion of patients reaching >= 95% adherence at month 12

Baseline:  
 I: 82.1%  
 C:69.6%

Follow-up:  
 I: 70.8%  
 C: 50%

p-value between groups:  
 .29 at BL  
 .014 at F/U

Mean adherence at month 10-12

Baseline:  
 I: 9.97  
 C: 9.92

Follow-up:  
 I: 9.93  
 C:9.80

p-value between groups:  
 .4 at BL  
 .012 at F/U

Notes

Severity: Median CD4 nadir: 120-173, Median CD4: 380-499, VL<50: 100%, AIDS: 33%

Regimen at study baseline: Already existing regimen

Duration of intervention: Variable (Range 2-25 visits within 12 months, median of 11 visits)

Length of follow-up: 12 months

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

**Wyatt 2004**

Methods

RCT

Setting: County hospitals, community- based clinics, AIDS service organizations, drug rehab centers (Los Angeles, US)

Adherence measure(s):  
 Self-report (number of days participants took their medication "exactly as prescribed" in the past 2 weeks)

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Participants

100% Women with history of child sexual abuse  
 Mean age: 41 (SD 8.2)  
 51% African American



**Wyatt 2004** (Continued)

49% Latina  
 56% High school  
 93% Unemployed

**Interventions**

Intervention: Psychoeducational group program to reduce sexual risks and increase adherence in women with a history of child sexual abuse, delivered in 11 weekly sessions (2.5 hours each) by a facilitator with a peer mentor in English or Spanish.

Control: Wait-list group with a one-time group meeting focusing on HIV prevention and child sexual abuse information. Participants were offered the intervention at the end of the study.

**Outcomes**

Adherence outcome(s):  
 Proportion of patients reporting adherence on all 14 days

Follow-up:  
 I: 75.6%  
 C: 73.3%

Change:  
 OR: 1.13

p-value between groups:  
 .41†

**Notes**

Severity: AIDS: 13%

Regimen at study baseline: Already existing regimen

Duration of intervention: 11 weeks

Length of follow-up: Not reported

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

\* CD4 units reported as cells/mm<sup>3</sup> or cells/ml

† Viral load reported as log<sub>10</sub> copies/ml

IDU: Injection Drug Use

MSM: Men who have Sex with Men

± All randomized participants analyzed

‡ Controlling for baseline measures

§ Participants lost to follow up = failure

| Missing adherence rates imputed by regression

**Characteristics of excluded studies** [ordered by study ID]

Study	Reason for exclusion
<a href="#">Adamian 2004</a>	Not a RCT Adherence not measured at 6 weeks for both groups No control arm
<a href="#">Albert 1999</a>	Not a RCT Not an adherence intervention Adherence not measured at 6 weeks for both groups

Study	Reason for exclusion
<a href="#">Aloisi 2002</a>	Not a RCT Not an adherence intervention No control arm
<a href="#">Altice 2004</a>	Not a RCT Adherence not measured at 6 weeks for both groups No control arm
<a href="#">Ammassari 2002</a>	Not a RCT Not an adherence intervention No control arm
<a href="#">Ammassari 2002 (a)</a>	Review
<a href="#">Bamberger 2000</a>	Program Description
<a href="#">Bangsberg 2002</a>	Description of an adherence assessment technique
<a href="#">Barreiro 2002</a>	Review
<a href="#">Bouhnik 2002</a>	Not a RCT Not an adherence intervention
<a href="#">Broadhead 2002</a>	Not a RCT 80% of people not on HAART No control arm
<a href="#">Cegala 2000</a>	80% of people not on HAART Adherence not measured at 6 weeks for both groups
<a href="#">Chesney 1999</a>	Review
<a href="#">DeFino 2004</a>	Not a RCT Adherence not measured at 6 weeks for both groups No control arm
<a href="#">Dorz 2003</a>	Not a RCT Not an adherence intervention Adherence not measured at 6 weeks for both groups No control arm .
<a href="#">Dunbar 2003</a>	Not a RCT No control arm
<a href="#">Flandre 2002</a>	Not an adherence intervention No control arm
<a href="#">Fogarty 2002</a>	Review
<a href="#">Fourney 2003</a>	Not a RCT Adherence not measured at 6 weeks for both groups No control arm
<a href="#">Frick 2001</a>	80% of people not on HAART Adherence not measured at 6 weeks for both groups

Study	Reason for exclusion
Garcia 2003	Review
GarciaP 2003	Review
GarciaR 2003	Description of an adherence assessment technique
Gifford 1998	Not an adherence intervention Adherence not measured at 6 weeks for both groups No control arm
Greenberg 1999	Not a RCT Not an adherence intervention Adherence not measured at 6 weeks for both groups No control arm
Guarinieri 2002	Review
Haddad 2000	Review
Haubrich 1999	Not a RCT Not an adherence intervention Adherence not measured at 6 weeks for both groups
Holzemer 2000	Not a RCT Adherence not measured at 6 weeks for both groups No control arm
Ickovics 2002	Review
Ickovics 2002a	Review article.
Ironson 2005	Not an adherence intervention
Jane 2004	Not a RCT No control arm
Kalichman 2003	Not a RCT Not an adherence intervention Adherence not measured at 6 weeks for both groups No control arm
Khanlou 2003	Not a RCT Adherence not measured at 6 weeks for both groups No control arm
Knobel 2001	Not a RCT Not an adherence intervention Adherence not measured at 6 weeks for both groups No control arm
Knobel 2004	Review
Lanzafame 2000	Not a RCT Adherence not measured at 6 weeks for both groups
Lucas 2002	Review

Study	Reason for exclusion
Lucas 2004	Adherence not measured at 6 weeks for both groups
Lyon 2003	Not a RCT No control arm
Macalino 2004	Not a RCT No control arm
Malow 1998	Not a RCT No control arm
Mann 2001	Adherence not measured at 6 weeks for both groups
Margolin 2003	Not an adherence intervention
Martin 2001	Adherence not measured at 6 weeks for both groups No control arm
McCance-Katz 2002	Not a RCT No control arm
McDonald 2002	Review
McPherson-Baker 2000	Not a RCT 80% of people not on HAART
Molassiotis 2003	Not a RCT No control arm
Murri 2002	Review
Orrell 2003	Not a RCT Not an adherence intervention No control arm
Palepu 2004	Not a RCT 80% of people not on HAART Not an adherence intervention Adherence not measured at 6 weeks for both groups No control arm
Park-Wyllie 2003	Review
Parsons 2005	Not a RCT No control arm
Paterson 2002	Review
Perno 2002	Review
Poppa 2004	Review /Guidelines
Press 2002	Review
Reynolds 2004	Review

Study	Reason for exclusion
<a href="#">Rigsby 2000</a>	80% of people not on HAART
<a href="#">Safren 1999</a>	Description of intervention
<a href="#">Schroeder 2004</a>	Commentary
<a href="#">Selnes 2002</a>	Review
<a href="#">Simoni 2003</a>	Review
<a href="#">Sommers 2001</a>	Not a RCT No control arm
<a href="#">Sorensen 1998</a>	Not a RCT 80% of people not on HAART
<a href="#">Stenzel 2001</a>	Not a RCT No control arm
<a href="#">Stone 2004</a>	Review
<a href="#">Sullivan 2004</a>	Review
<a href="#">Tesoriero 2003</a>	Not a RCT No control arm
<a href="#">Trotta 2002</a>	Review
<a href="#">Tucker 2003</a>	Not a RCT Not an adherence intervention No control arm
<a href="#">Tuldra 2002</a>	Review
<a href="#">Wagner 2002</a>	Adherence not measured at 6 weeks for both groups
<a href="#">Wagner 2002a</a>	Not a RCT Adherence not measured at 6 weeks for both groups No control arm
<a href="#">Wagner 2003</a>	Not a RCT Not an adherence intervention Adherence not measured at 6 weeks for both groups No control arm
<a href="#">Weiss 2003</a>	Not a RCT Not an adherence intervention Adherence not measured at 6 weeks for both groups No control arm
<a href="#">Wohl 2004</a>	Adherence not measured at 6 weeks for both groups No control arm
<a href="#">Wu 2002</a>	Review
<a href="#">Yun 2005</a>	Not a RCT

Study	Reason for exclusion
	Not an adherence intervention

## WHAT'S NEW

Date	Event	Description
29 October 2008	Amended	Converted to new review format.

## HISTORY

Protocol first published: Issue 1, 1999

Review first published: Issue 3, 2000

Date	Event	Description
24 May 2006	New citation required and conclusions have changed	Substantive amendment

## CONTRIBUTIONS OF AUTHORS

S Rueda:

Designing the review, coordinating the review, screening search results, organizing retrieval of papers, screening retrieved papers against inclusion criteria, appraising quality of papers, extracting data from papers, analysis and interpretation of data, providing a methodological perspective, providing a clinical perspective, providing a policy perspective, writing the review, providing general advice on the review

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AM Bayoumi:

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AM Tynan:

Coordinating the review, screening search results, organizing retrieval of papers, screening retrieved papers against inclusion criteria, writing to authors of papers for additional information, entering data into RevMan

TA Antoniou:

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RH Glazier:

Conceiving the review, analysis and interpretation of data, providing a methodological perspective, providing a clinical perspective, writing the review, performing previous work that was the foundation of the current review, providing general advice on the review

## DECLARATIONS OF INTEREST

None known.

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## SOURCES OF SUPPORT

### Internal sources

- Centre for Research on Inner City Health, St Michael's Hospital, Toronto, Canada.
- Department of Family and Community Medicine, St Michael's Hospital, Toronto, Canada.

### External sources

- Ontario HIV Treatment Network, Canada.

## INDEX TERMS

### Medical Subject Headings (MeSH)

\*Antiretroviral Therapy, Highly Active; \*Patient Compliance; \*Patient Education as Topic; Acquired Immunodeficiency Syndrome [drug therapy]; HIV Infections [\*drug therapy]; Pharmacies; Randomized Controlled Trials as Topic

### MeSH check words

Humans