

# Adherence to HIV antiretroviral therapy Part II: which interventions are effective in improving adherence?

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## Abstract

Interventions to support adherence to antiretroviral therapy (ART) can be classified into four categories: cognitive, behavioural and affective interventions and (modified) directly observed therapy (DOT.)

Cognitive interventions improve HIV- and ART-related knowledge, but this is not consistently associated with better adherence. Cognitive interventions that are combined with behavioural or psychological strategies are more effective in improving adherence, especially in patients who previously were less adherent. These include interventions that improve self-efficacy, provide stress management/expressive support therapy or motivational interviewing. As yet there is no evidence for the role of affective interventions and modified DOT to improve adherence to ART.

When designing interventions to address adherence, it should be borne in mind that multi-component interventions are more effective than single-focus interventions. A combination of educational, behavioural and affective components is suggested to ensure optimum adherence.

In countries with a high prevalence of HIV, such as South Africa, careful patient preparation, rather than selecting patients based on non-clinical predictors of adherence, seems an appropriate method for scaling up ART. South African guidelines focus on comprehensive adherence support to all patients, with additional support to patients with less than 80% adherence. More research on the effectiveness of interventions aimed at improving adherence is urgently needed, especially in developing countries.

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### Introduction

Adherence to medication is probably the single biggest factor that needs to be addressed when planning an ART service. Patients need to take medication several times a day, every day, for the rest of their lives. The South African National ART Guidelines state that ideal adherence means a patient must take more than 95% of his or her doses (i.e. missing less than three doses in a month).<sup>1</sup>

The National ART Guidelines recommend the following strategies to promote adherence:

- Spend time with the patient. Explain the goals of therapy and the need for adherence as many times as is necessary.
- Consider the monitoring of medications such as co-trimoxazole, or by an alternative method prior to ART initiation.
- Negotiate a treatment plan that the patient can understand and to which he/she commits.
- Encourage disclosure to family or friends who can support the treatment plan.
- Inform the patient of potential side effects – severity, duration and coping mechanisms.
- Establish 'readiness' to take medications before ART initiation.
- Provide adherence tools where available: written calendar of medications, pill boxes.
- Encourage use of alarms, pagers or other available mechanical reminder aids for adherence.
- Avoid adverse drug interactions.
- Anticipate, monitor and treat side effects.
- Include adherence discussions in support groups.
- Develop links with community-based organisations.
- Encourage links with support groups.
- Create links with patient advocates.<sup>1</sup>

Patients with adherence below 80% require increased adherence support. Suggested interventions include: tablet counts to evaluate adherence and routine open-ended adherence discussions with the counsellor, allowing enough time for questions and the repetition of information; evaluating the support structures, including the home and

family environment; considering psychosocial profiling and participation in a support group or insisting on linking with a patient advocate; increasing home visits and considering directly-observed therapy for an agreed period; reassessing the patient for alcohol or drug use; using pillboxes, pill diaries and other adherence tools where possible; promoting self-efficacy training.<sup>1</sup>

Coetzee *et al.* state that careful patient preparation, rather than selecting certain patients based on non-clinical predictors of adherence, is a better-suited approach for scaling up ART in countries with large epidemics.<sup>2</sup> In South Africa, the Khayelitsha/MSF programme developed a standard approach to patient preparation to enhance adherence. Patients attend three structured individual counselling sessions, identify a treatment assistant and attend peer support groups specifically for patients on ART. Material support, such as pillboxes, drug identification charts, diaries and educational materials, are made available. A standard 12-week approach has been developed and applied with good results for patients who experience viral rebound.<sup>2</sup>

This review, the second in a two-part series, will evaluate interventions that have been designed to improve adherence to ART. These interventions can be divided into four categories:

- 3,4
- Cognitive (designed to teach, clarify or instruct)
- Behavioural (designed to shape, reinforce or influence behaviour)
- Affective (designed to optimise social and emotional support)
- (Modified) Directly observed therapy (DOT)

### Cognitive behavioural interventions

Cognitive interventions that commonly are used to improve adherence to ART include counselling sessions by healthcare workers and education sessions (providing information on ART, dosing instructions, drug interactions, etc.). Several studies have described the use of an educational component in an attempt to improve

adherence to ART.<sup>4,5,6,7,8</sup> The results are variable, as most studies have shown an increase in knowledge of HIV and ART, but this was not consistently associated with better adherence. Cognitive interventions combined with behavioural or psychological strategies were more effective in improving adherence.<sup>9,10,11,12</sup>

Van Servellen *et al.* evaluated the acceptability and effectiveness of a programme to enhance health literacy in low-income HIV-infected Latino men and women on ART. A significant improvement in the participants' knowledge regarding HIV/AIDS and their treatment-related knowledge was demonstrated in the intervention group, but there were no significant changes in adherence mastery and behaviour at the six-week follow-up visit. The participants rated the programme highly on measures of satisfaction, proving its acceptability.<sup>5</sup>

The impact of an educational intervention on adherence was evaluated at six, twelve and eighteen months by Goujard *et al.*<sup>6</sup> The intervention had an impact on adherence and knowledge in the experimental group at six months, and this was maintained at 12 and 18 months. A delayed increase in adherence was observed in the control group at 12 months. The intervention did not have a significant impact on quality of life and there was no significant difference in viral load and CD4 count.<sup>6</sup>

Pradier *et al.* evaluated the impact of an educational and counselling intervention on ART adherence compared to standard of care (SOC). The viral load decreased significantly more in the intervention group (mean difference -0.22 log,  $p=0.013$ ) than in the control group (+0.12 log,  $p=0.14$ ). The proportion of patients that was adherent at six months was significantly better in the intervention group (75% vs. 61%,  $p=0.04$ ).<sup>13</sup> In an open label clinical trial, Rawlings *et al.* evaluated the impact of an educational intervention plus routine counselling compared to routine counselling only.<sup>7</sup> There was no significant difference between the groups with respect to the proportion of patients achieving viral load (VL) < 40 copies/ml (60 vs. 55%) or less

than 400 copies/ml (80 vs. 80%) at 24 weeks, the increase in median CD4 count (78.3 vs. 104.8) or the adherence rates as measured with MEMS (70 vs. 74%).<sup>7</sup>

Fairley *et al.* offered a comprehensive adherence package, including an education programme, individualised planning of regimens and the opportunity for patients to choose from a number of adherence aids and reminder devices. The intervention group self-reported a significant improvement in adherence during the previous four days ( $p=0.03$ ) and seven days ( $p=0.005$ ), but not for the previous 28 days ( $p=0.63$ ).<sup>9</sup>

Jones *et al.* examined the effects of a ten-session cognitive-behavioural stress management/expressive support therapy intervention on adherence. The intervention did not improve adherence for the entire population, but **women with low adherence** showed a significant increase post-intervention (30.4% increase in adherence) when compared to the control group (19.6% increase,  $p<0.01$ ).<sup>10</sup> Accurate knowledge of HIV-related medication and a belief in the efficacy of the medication were consistently associated with higher levels of adherence, highlighting the importance of **assessing beliefs** regarding medications. Women participating in the intervention decreased their levels of denial-based coping.<sup>10</sup>

In a small pilot study (data for 33 participants), Murphy *et al.* evaluated the impact of a multi-component (cognitive-behavioural intervention and social support), multidisciplinary intervention on medication adherence. Patients in the intervention group had significantly higher self-efficacy to communicate with clinic staff ( $p=0.04$ ), to continue treatment ( $p=0.04$ ), and to use behavioural and cognitive strategies ( $p=0.01$  and  $0.04$ ). They reported higher life satisfaction ( $p=0.03$ ) and increased feelings of social support ( $p=0.04$ ). Although they did not significantly improve their adherence, the patients showed a trend towards taking their medication on time ( $p=0.06$ ).<sup>11</sup>

The effect of a psycho-educative intervention on self-reported adherence and HIV-1 RNA levels was evaluated by Tuldra *et al.*<sup>12</sup> At week

48, 94% of the participants in the intervention group versus 69% of the participants in the control group achieved an adherence of  $\geq 95\%$  ( $p=0.008$ ). The proportion of participants with HIV-1 RNA level  $<400$  copies/ml was significantly higher in the intervention group (89% vs. 66%,  $p=0.026$ ).<sup>12</sup>

A Cochrane Review of the literature identified one study that addressed interventions to improve adherence to ART. The study compared a pharmacist-led intervention, consisting of educational counselling and the availability of follow-up telephone support, with the conventional dispensing of HAART pills. This intervention significantly improved adherence to highly active antiretroviral therapy (HAART), and adherence to HAART significantly predicted undetectable viral load at 24 weeks. However, participating in the intervention did not significantly predict a subsequently undetectable viral load at 24 weeks.<sup>8</sup>

### Behavioural interventions

Behavioural interventions are designed to shape, reinforce or influence behaviour. Some suggested strategies that can be used to support adherence include giving the patient forms with pictures of the relevant pills and daily activities in order to communicate to the patient how many and when pills are to be taken, providing clearly written instructions, and questioning patients about their daily activities to identify regularly occurring events as triggers for taking medication. Devices such as pill boxes and alarms may also be used.<sup>14</sup>

Other behavioural strategies that are employed to assist adherence include cue-dose training with monetary reinforcement<sup>15</sup> and the use of alarmed vials to remind patients to take their medication.<sup>16</sup> Two-way pagers have been used in uncontrolled trials.<sup>17</sup> Psychological interventions described in one of the studies used self-management interventions to improve self-efficacy,<sup>18</sup> and in another study motivational interviewing was used.<sup>19</sup>

Rigsby *et al.* assessed the feasi-

bility and efficacy of an intervention using cue-dose training with and without monetary reinforcement versus standard care in a randomised controlled pilot study with three arms.<sup>15</sup> MEMS pill bottle caps were used to measure adherence (opening the bottle within two hours of a predetermined time). Adherence to taking medication was significantly enhanced during the four-week training period for the group that received cash reinforcements, while no significant improvement in comparison to the control group was observed in the group that received cue-dose training only. Eight weeks after training and reinforcements had been discontinued, adherence in the cash-reinforcement group returned to near baseline levels.<sup>15</sup>

Frick *et al.* conducted a study on the efficacy and acceptability of an alarm device to improve adherence among women in a resource-poor country.<sup>16</sup> Women received a one-month supply of multivitamins in an electronic medication vial with or without an alarm device. Although the study had several limitations (multivitamins cannot be compared to the complexities of taking HAART,) women in the intervention arm were significantly more likely to have adherence levels of  $\geq 95\%$  (82% vs. 36%,  $p<0.001$ ). Vial acceptability was high, with 99% of the women indicating that they would use the vial again.<sup>16</sup>

One factor shown in past studies to be positively associated with antiretroviral adherence is *self-efficacy*. Self-efficacy is defined as one's belief in one's capability to organise and execute the course of action required to perform a particular activity. Bandura proposed that self-efficacy is the most important prerequisite for behavioural change, because it affects how much effort is invested in a given task and what level of performance is attained.<sup>20</sup> Individuals who regard themselves as highly self-efficacious in their ability to adhere will set higher goals, be more firmly committed to them and, therefore, exercise higher control over behaviour that fosters adherence.<sup>18</sup>

According to social cognitive theory, information about the medication regimen is necessary, although not sufficient, to maintain adherence. Patients usually need guidance on how to cultivate self-regulatory and coping skills to translate information into action. An intervention to cultivate self-efficacy was evaluated by Smith *et al.*<sup>18</sup> The three components of the intervention were self-monitoring, goal setting and the enlistment of self-incentives. Individuals in the self-management group were significantly more likely to take 80% or more of their doses each week than those in the control group ( $n=29$ ,  $OR=7.8$ ,  $95\% CI=2.2-28.1$ ).<sup>18</sup>

Motivational interviewing (MI) was developed in the early 1980s as a therapy to promote behavioural changes in individuals who were problem drinkers. Since then it has been applied to a variety of behaviours, including cessation of cigarette smoking, diabetes self-management, fruit and vegetable intake and medication adherence. MI is a client-centred approach where counselling is tailored to the client's needs and his or her readiness to change behaviour. In a non-judgmental, supportive environment, the clients describe their own situation, the reasons for and against change and ideas for resolving barriers for initiating change.<sup>19</sup> In a small pilot study, trained nurse counsellors conducted three motivational interview sessions with the clients. The study demonstrated a trend towards the sessions having a positive impact on adherence. This was more pronounced in clients who had previous problems with adherence.<sup>19</sup>

Comprehensive interventions combining cognitive and behavioural components and involving a multidisciplinary team result in better outcomes than single approaches.<sup>21</sup>

### Affective interventions

Affective interventions are designed to optimise social and emotional support for the patient. Affective strategies formed part of multi-component interventions in two of the studies reviewed.<sup>10,11</sup> However, the effectiveness of affective interventions were not evaluated in these studies.

### Directly observed therapy (DOT) or directly administered antiretroviral therapy (DAART)

Community-based DOT interventions have shown variable success. In a pilot study by Mitty *et al.*, once-daily HAART was given to patients for five or seven days a week and gradually tapered according to patients' needs. Only 13 out of 25 patients (56%) remained in the programme for longer than six months, and 63% of these individuals had viral loads less than 50 copies/ml.<sup>22</sup> The experience in DOT programmes highlights the importance of participants understanding and having trust in the programme. The programme should be tailored according to the participants' needs, but the intrusion and structure of the programme might lead to some patients withdrawing.<sup>22</sup> A more recent study by Mitty *et al.* supports the inclusion of a modified DOT (MDOT) in the spectrum of options available to enhance adherence to HAART among patients who are unsuccessful with the self-administration of their medications.<sup>23</sup> The latter demonstrated a decrease of 2.7 log in the median baseline plasma viral load (RVL) after six months of MDOT.<sup>22</sup> In general, patients experience DOT/DAART programmes positively and many patients develop a trusting relationship with their community workers.<sup>24</sup>

The patients' preferences should be taken into consideration when deciding on a treatment regimen. Strong patient preferences for once-daily regimens seem to predominate.<sup>22</sup> The question remains whether all patients in a DOT programme should receive a once-daily observed dose or whether a twice-daily regimen, in which one dose is self-administered, is equally effective.<sup>22</sup>

### Conclusions

Various interventions combining cognitive, behavioural, affective and modified DOT approaches have been studied to assess their impact on ART adherence. Several of these studies were small pilot studies, often of short duration, and thus did not have sufficient power to demonstrate a significant impact on adherence.

Most of the cognitive interventions demonstrated a trend towards or significant impact on adherence. The study included in the Cochrane Review that evaluated a pharmacist-led intervention (educational counselling and follow-up telephone support) showed a significant improvement in adherence to HAART. However, knowledge about HIV and ART in itself is not always a sufficient force to motivate behavioural change. It is our suggestion that interventions that combine cognitive interventions with behavioural or affective strategies should be used when addressing ART adherence.

Interventions that improve self-efficacy, provide stress management/expressive support therapy or include motivational interviewing all show very promising results. The impact of these interventions is often more pronounced in participants who previously had difficulties with adherence to medication. A belief in the efficacy of the medication was consistently associated with higher levels of adherence. This highlights the importance of assessing patient beliefs regarding medications. It is of particular relevance in the South African and African contexts, where Western medical beliefs may conflict with traditional beliefs.

There is yet no evidence for the role of DOT in improving ART adherence. DOT might not be acceptable to all patients. If a DOT approach is utilised, the service should be tailored according to the patient's needs. Questions that remain to be answered relate to the duration of DOT, the efficacy of once-daily versus twice-daily regimens, and the identification of the key components of successful DOT programmes.

When designing interventions to address ART adherence, multi-component interventions are more effective than single-focus interventions. A combination of educational, behavioural and affective components is suggested to ensure optimum adherence.

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