Adherence to HIV antiretroviral therapy

Part I: A review of factors that influence adherence

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Abstract

Near perfect adherence to ART is required to prevent treatment failure in the individual and to prevent the spread of drug-resistant viruses. Factors that influence adherence to ART can be divided into factors related to the treatment regimen; social and psychological factors; institutional resources; and personal attributes.

The treatment regimen should be kept as simple as possible and be tailored to the patient's lifestyle. Untreated side effects are one of the strongest predictors of non-adherence. Mental disorders and drug/alcohol abuse should be addressed before initiating treatment. The patient's attitude towards medication and health beliefs could adversely influence adherence. The development of healthcare infrastructure should be a high priority and services should be patient orientated. Few personal attributes are consistently associated with adherence. Healthcare workers are poor at predicting adherence. The South African guidelines therefore focus on providing comprehensive adherence support to all patients.

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Introduction

The arrival of Highly Active Antiretroviral Therapy (HAART) has given hope to millions of people living with HIV/AIDS. HAART has turned what was once a fatal disease into a chronic manageable disease, with the potential of prolonging patients' lives by decades. In April 2004, South Africa started the national rollout of antiretroviral therapy, giving hope to the estimated 5.3 million people living with HIV/AIDS (PLWHA).

Close to perfect adherence is required to suppress a patient's viral load to undetectable levels and prevent the development of drug-resistant viruses. Failure to do this will not only lead to treatment failure for the individual, but would also have led to the spread of drug-resistant viruses to other individuals. In developed countries, the estimated prevalence of drug-resistant HIV-1 in recently infected individuals ranges from 5 to 16%.[1] It would be unethical to slow down access to treatment in developing countries on the basis of resistance patterns in developed countries. Efforts should rather be directed towards developing healthcare infrastructure that will maximise the effectiveness of treatment and minimise drug resistance.[2]

In South Africa, the Khayelitsha/MSF ART programme has proven that patients on ART can be retained in resource-limited settings in developing countries. The focus in this programme is on careful preparation of the patients before ART initiation, rather than selecting certain patients based on non-clinical criteria.[3] In Soweto, 88% of patients reported adherence levels of higher than 95%.[4] In Cape Town, the median (mean) adherence was 93.5% (87.2%).[5]

South African National ART guidelines recommend that the following psychosocial considerations (although not exclusion criteria) be taken into account before ART is initiated:[6]

- Demonstrated reliability, i.e. attended three or more scheduled visits to an HIV clinic
- No active alcohol or other substance abuse
- No untreated active depression
- Disclosure to friend or family member OR member of a support group
- Acceptance of HIV status and insight into consequences of HIV infection and the role of ART
- Ability to attend the antiretroviral centre on a regular basis
- An expression of willingness and readiness to take ART adherently

A treatment readiness assessment is done over three clinic visits. Comprehensive adherence support is offered to all patients, with additional support to patients who do not fulfil all the criteria or who have demonstrated lower adherence. The SA guidelines stress that it is not possible for healthcare providers to reliably predict which individuals will be adherent to their treatment plan based on gender, cultural background, socio-economic level or education level.[6]

This review is the first in a two-part series and will look at the various factors that influence a patient's ability to adhere optimally to an antiretroviral

treatment regimen. The second part will look at interventions to improve adherence to ART.

Factors that influence adherence to ART can be divided into: (1) factors related to the treatment regimen; (2) social and psychological factors; (3) institutional resources; and (4) personal attributes.[7]

Factors related to treatment regimen

Regimen complexity

Pill burden and regimen complexity are important contributors to poor adherence.[8,9,10] Optimum treatment regimens selected by patients include two or less pills per day, no dietary restrictions, small pills, all drugs combined into one pill and once-a-day dosing.[9]

In a meta-analysis by Bartlett *et al.*, increased pill burden was negatively associated with the maintenance of viral suppression at 48 weeks and seemed to be the most significant predictor of response to therapy.[11] A pill burden of up to six tablets was suitable for administration once daily, whereas twice daily therapy was preferred for a higher pill burden.[9] Good adherence is associated with dosing twice a day or less.[5,12,13,14] Several small, uncontrolled studies explored the use of once-a-day therapy.[9] Only one prospective randomised controlled study has been published, comparing a once-a-day regimen to two standard treatment regimens. Didanosine, lamivudine and efavirenz taken once daily was compared with zidovudine, lamivudine (Combivir) and efavirenz (low pill burden) taken twice daily, as well as with zidovudine, lamivudine (Combivir) and Nelfinavir (high pill burden.) The protease inhibitor (PI)-containing regimen (high pill burden) had a statistically significantly lower rate of successful outcome ($p<0.05$) than the other two treatments. The proportion of patients who achieved HIV-1 RNA levels of less than 50 copies/ml at 52 weeks (ITT analysis) was 77% in the once-daily and low pill burden groups, versus 50% in the high pill burden PI-containing regimen.[9,15]

The following medications are suitable for once-daily dosing:[9]

NRTI:

- Didanosine and lamivudine are licensed for once-daily administration. Although the plasma half-life is short, the intracellular half-life is 25 and 15 hours respectively. A new extended release formulation of stavudine is currently being tested (100 mg once a day.)
- Tenofovir (a nucleotide reverse transcriptase inhibitor) is administered as a single daily 300 mg tablet.
- Emtricitabine (cytosine analogue similar to lamivudine) may be dosed daily as a single 200 mg tablet.

NNRTI:

- Both efavirenz and nevirapine appear suitable for once-daily dosing, although only efavirenz has been approved for that dosing schedule.

PI:

- Low-dose Ritonavir has been used to boost the pharmacokinetics of several other PIs. Ritonavir-boosted PIs that are suitable for daily administration include Amprenavir (boosted Amprenavir is licensed for once-daily use), Indinavir, Saquinavir, Nelfinavir, Lopinavir-ritonavir and Fos-Amprenavir.
- Once-daily administration of the above PIs compared favourably in clinical trials to twice-daily administration. Atazanavir is a once-daily PI that does not require Ritonavir boosting.[9]

Scheduling demand/accommodation

Scheduling demands, i.e. work, difficulty fitting medication into daily routine, mealtime and food restrictions and difficult dosing schedules, are consistently associated with decreased adherence.[7,8,12] The use of interventions, such as pill boxes labelled with the dosing regimen and instructions, using a timer, and medication fitted into the daily schedule, can overcome some of the scheduling demands and is associated with increased adherence.[7,16] Longer periods on ART are associated with poorer adherence.[10,17]

Cognitive demands/accommodation

Patients who experience difficulty with concentrating or are forgetful, who have received inadequate information about ART or who have difficulty understanding medication schedules and the relationship between adherence, viral load and disease progression, adhere significantly poorer[7,12,18] than patients who have an accurate understanding of the purpose of ART.[19] Clear, written instructions, pill boxes, asking questions about how the treatment can fit into daily activities and medication event monitoring feedback (MEMF) have been associated with improved adherence.[7,16]

Regimen side effects

Adverse drug events influence willingness to take medication and are consistently associated with poorer adherence.[7,8,12,20] In one study, patients with adverse events, e.g. dermatological and gastrointestinal symptoms, were 12.8 times less likely to be 95-100% adherent.[21] HAART is often discontinued when side effects occur, whether the side effects are actual or perceived. The patients' subjective side-effect experiences in the first four months predict long-term adherence more strongly than do other variables.[12]

Distressing side effects that can be treated successfully include fatigue, diarrhoea, nausea and stomach pain.[12] Lipodystrophy cannot be treated successfully and a change in the regimen to medication that causes less lipodystrophy should be considered.[12] Collaboration between the patient and the provider can result in the selection of a lifestyle-tailored regimen characterised by convenient dosing, a low pill burden and tolerable side effects. Side effects should be dealt with actively to prevent discontinuation of treatment.

Social and psychological factors

Mental health

Depression and stress are some of the strongest predictors of non-adherence.[7,12] A feeling of hopelessness and negative feelings reduce the motivation for self-care. Other psychological factors that have been associated with poor adherence include coping by denial and behavioural disengagement.[19] The presence of social support systems, such as supportive family members and friends

or treatment buddies, peer counselling,[12] participation in cognitive-behavioural support therapy,[19] a positive attitude to the future, long-term plans and goals and stable mental health are consistently associated with better adherence.[7]

Self-efficacy

Self-efficacy can be defined as the patient's belief in his/her ability to take the medication. Self-efficacy is associated with better adherence,[7,14,22,23] whereas an increased effort to take the medication is associated with poorer adherence.[22]

Treatment/medication attitudes

The patient's belief systems significantly influence adherence to HAART. Greater adherence is observed in patients who believe HAART is effective, while negative beliefs reduce adherence.[7,12,19] Godin *et al.* showed that a positive attitude towards taking medication was associated with higher adherence, a high level of patient satisfaction with the physician, high perceived social support, being optimistic, living with HIV for five years or less and experiencing no side effects.[23] Fear, scepticism, mistrust and myths regarding the drug regimens are all negatively related to adherence.[7]

HIV disease attitudes

Negative evaluations, such as pessimism about HIV, have negative associations with adherence.[7] News of the worsening of others or the death of others can influence adherence negatively or positively.[7]

Social climate

The lack of social or family support and a fear of stigmatisation are generally associated with non-adherence.[4,7,8,23] In the study by Wagner, living alone was associated with better adherence than living in a large household ($p<0.05$).[18]

Provider support

A supportive patient-provider relationship improves adherence. Routine adherence counselling, involving the patient in treatment decisions, open communication, compassion and taking regimen inconvenience into account improve adherence.[7,12]

Institutional monetary and health service resources

A good patient-healthcare provider relationship is an important motivating factor for taking and adhering to complex combination drug therapies. Perceptions of the competence of the healthcare provider, as well as his/her communication quality and clarity, compassion and willingness to include patients in treatment decisions, the adequacy of referrals, and the convenience of visiting the doctor are associated with better adherence.[14,23] Healthcare providers should be encouraged to work with patients as "partners" in care and to involve representatives from the entire HIV community.[14] Primary care providers who exhibit judgmental behaviour, stereotyping and homophobia, and who fail to address cultural issues when administering care, are likely to cause some people with HIV infection to avoid the healthcare system.[14] A lack of financial and institutional resources, disruptions in the supply of medication and difficulty in gaining access to health services have been associated with poorer adherence.[7,20,24]

Personal attributes

Clinical status

Physiological markers of disease progression, such as the CD4 count and viral load, are generally not associated with adherence. Patients who have symptomatic disease or who feel debilitating pain and symptoms are less adherent.[7,8] The total number and severity of current symptoms are associated with lower adherence. Symptoms like insomnia, headaches and poor concentration, diarrhoea and anxiety are commonly associated with lower adherence.[18]

Socio-economic factors

Educational level, literacy, income and housing status are not consistently predictive of adherence. In 22 studies evaluated by Fogarty *et al.*, five demonstrated an association between socio-economic factors and adherence.[7] Tuldra *et al.* demonstrated that a higher income was associated with better adherence ($p=0.001$).[22] Wagner reported a positive association between college education and adherence ($p<0.05$), while employment status showed no association with adherence.[18] In Brazil, a very low educational level, which is considered the best indicator of social status, was a predictor of non-adherence.[17] Studies in India[20] and South Africa[5] have found no association between adherence and socio-economic status.

Gender

Evidence regarding the relationship between adherence and gender is weak, with most studies not finding any association.[5,7,20] In a one-year longitudinal study in Canada, being male was associated with better adherence.[23] Barriers to adherence, such as care-giving burdens, a multiplicity of roles and fear of disclosure, might disproportionately affect women and have an influence on their ability to adhere to medication.[25]

Ethnicity

Several studies reported lower adherence amongst minority groups,[7] whereas other studies showed no correlation between adherence and ethnicity.[18] Non-white races have been associated with poorer adherence.[26] These studies were all conducted in developed countries (mostly Northern America) and can thus not be used as predictive evidence for the Southern African (or developing countries) setting.

Age

Several studies have reported better adherence among older patients.[5,7,17,18,22,26,27] Special issues relating to adherence exist for HIV-infected children and adolescents.[14] Children are dependent on their caregivers for the administration of medication and adherence is thus only as good as the caregivers are able to achieve. Unpalatable liquid formulations may affect the willingness of a child to take medication. Adolescents often rebel against treatment, as they do not want to be different from their peers. A fear of disclosure of the child's HIV status

may prevent caregivers from collecting a script at local pharmacies or from sending the child to school without his/her medication. A detailed assessment of all the barriers to adherence should be implemented for all children on ART to resolve issues affecting children and their families.[14]

Substance abuse

Active substance abuse is generally associated with lower adherence.[7,12,14,19,26,28] However, in 26 studies evaluated by Fogarty *et al.*, 11 studies showed no association between lower adherence and substance abuse.[7] One study showed better adherence in patients who did not smoke (p=0.01).[27]

Conclusions

Following the studies reviewed, few personal attributes have proven strongly predictive of adherence or non-adherence, which is in support of the South African National ART guidelines. Some studies have shown that family practitioners are very poor at predicting adherence.[7,14] It is therefore important that caution be taken not to limit access to HAART on the basis of social profiling,[7,14,29] although interventions that target adherence in vulnerable populations might be useful in improving adherence.[7,14]

Other variables that are associated with decreased adherence include regimen complexity, medication scheduling, cognitive barriers such as lack of knowledge of the disease and its treatment, treatment side effects, mental health problems, adjustment to the disease, attitudes to treatment, medication efficacy, HIV associated disease and provider support. These factors are discreet, identifiable issues that can theoretically be addressed.[7] Family practitioners need to assess individual patient adherence levels and the severity of side effects, tailor regimens to fit the patients' lifestyles, assess the patients' understanding of the regimen, and refer patients for mental health consultation where needed. To overcome these barriers, the clinician and patient need to work closely towards the common goal of medication adherence. A good patient-provider relationship and a patient-centred approach are essential.[14] In addition, a multidisciplinary, patient-centred approach is essential when addressing issues that might influence adherence.

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