

## Improving adherence to antiretroviral therapy

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### ABSTRACT

Antiretroviral therapy (ART) has transformed HIV infection into a treatable, chronic condition. However, the need to continue treatment for decades rather than years, calls for a long-term perspective of ART. Adherence to the regimen is essential for successful treatment and sustained viral control. Studies have indicated that at least 95% adherence to ART regimens is optimal. It has been demonstrated that a 10% higher level of adherence results in a 21% reduction in disease progression. The various factors affecting success of ART are social aspects like motivation to begin therapy, ability to adhere to therapy, lifestyle pattern, financial support, family support, pros and cons of starting therapy and pharmacological aspects like tolerability of the regimen, availability of the drugs. Also, the regimen's pill burden, dosing frequency, food requirements, convenience, toxicity and drug interaction profile compared with other regimens are to be considered before starting ART. The lack of trust between clinician and patient, active drug and alcohol use, active mental illness (e.g. depression), lack of patient education and inability of patients to identify their medications, lack of reliable access to primary medical care or medication are considered to be predictors of inadequate adherence. Interventions at various levels, viz. patient level, medication level, healthcare level and community level, boost adherence and overall outcome of ART.

**Key-words:** Antiretroviral therapy, HAART, Compliance, Adherence

### INTRODUCTION

Antiretroviral drugs delay progression of HIV disease and improve the quality of life in the HIV infected. The "3 by 5" motto of WHO (treating 3 million by 2005) has provided impetus for greater use of antiretroviral therapy (ART) in developing and resource limited countries.<sup>[1]</sup> The advent of combination ART has transformed this disease into a chronic treatable condition for a significant proportion of people living with HIV and AIDS (PLWHA) with access to this treatment. However, the need to maintain patients on treatment for decades rather than years, calls for a long-term perspective of antiretroviral therapy.

A very high replication rate of HIV with increased susceptibility to mutations in the process has led to the emergence of strains less sensitive to antiretroviral agents.<sup>[2]</sup> The long lasting efficiency of ART starts with the initial decision to start ART. The initial regimen plays an important role in achieving prolonged viral suppression.<sup>[3]</sup> Therefore, it must be chosen with the intent of achieving several goals [Table 1]. However, in cases with extensive prior drug exposure, the desired goals are preservation of the immune system and prevention of clinical progression rather than maximal viral suppression.<sup>[4]</sup>

With the availability of generic ART agents at a much

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**Table 1: Goals of ART<sup>[4]</sup>**

Sr no	Goals	Indicators of goal
1	Clinical	Prolongation and improved quality of life
2	Virological	Suppress viral load to undetectable levels (< 50 copies/ ml)
3	Immunological	Quantitative (CD4 cell count in normal range) Qualitative (pathogen specific immune reconstitution)
4	Epidemiological	Reduce HIV transmission
5	Therapeutic	Rational sequencing of drugs which: a) maintains future therapeutic options b) is relatively free of side effects c) has a high probability of adherence

lower cost, there has been an increased use of ART in developing countries. Moreover, the initial encouraging response seen with these drugs has prompted their wide use across the medical fraternity, at times without considering the serious consequences of mismanaged therapy. Hence it is prudent to consider lack of adherence to ART, which adversely affects the overall outcome.

### ADHERENCE TO THERAPY

Adherence to the regimen is essential for successful treatment and hence has been rightly phrased as the 'Achilles heel of antiretroviral therapy'.<sup>[5]</sup> A major concern with ART is the emergence of viral resistance, which is mainly due to insufficient compliance.<sup>[4],[6]</sup>

Other deterrents that hamper the outcome in ART are its lifelong duration, serious side effects, the complexity of newer regimens, which may have to be used due to the emergence of resistance, and the fact that therapy is not curative. The adherence rate varies not just between individuals, but also in the same individual over time,<sup>[7]</sup> thus making adherence a variable rather than a stable characteristic of an individual. Most people will exhibit low adherence at some time during this extended therapy.<sup>[8]</sup> This also makes the physician's prediction of probable adherence achievable by a patient highly unreliable.<sup>[9]</sup>

This makes it essential to define:

1. What is the optimal adherence required?
2. What are the implications of suboptimal adherence?
3. What are the factors to be considered to achieve optimal adherence?
4. What are the predictors of inadequate adherence?

### 5. What are the strategies to improve adherence?

#### What is the optimal adherence required?

Optimal adherence is the compliance to ART that achieves a sustained plasma drug concentration that will inhibit viral replication. Studies have indicated that at least 95% adherence to ART regimens is optimal.<sup>[6],[10]</sup> With 95% adherence, viral suppression to below detectable levels occurs in 80%. However, a fall in adherence to 70% (i.e. 25% less than optimal) drastically decreases viral suppression to 33% (i.e. less than 50% achieved with optimal adherence).<sup>[10]</sup> Also, it has been demonstrated that a 10% higher level of adherence results in a 21% reduction in disease progression.<sup>[11]</sup>

#### What are the implications of suboptimal adherence?

- A. Failure of the regimen
- B. Increase in morbidity and mortality
- C. Emergence of resistant strains of virus: If adherence is particularly poor, virologic failure is associated with a wild type of virus, but intermediate levels of adherence are likely to lead to the development of virus with resistant mutations in the genome.<sup>[12]</sup>

#### What are the factors to be considered to achieve optimal adherence?

Factors to be considered before starting ART are:

##### A. Social aspects

- i. *Motivation to begin therapy*: Because of the long course of therapy, the patient should be sufficiently motivated to begin treatment.
- ii. *Ability to adhere to therapy*: A busy work schedule may hinder a patient from taking medications 6-hourly or 4-hourly, leading to poor compliance.
- iii. *Lifestyle pattern*: Extensive travelling,<sup>[13]</sup> substance abuse and alcoholism<sup>[14]</sup> are associated with poor adherence. The practice of meditation decreases anxiety and strengthens mental resolve.<sup>[15]</sup> Spirituality is an important dimension in the assessment of psychosocial factors affecting HIV.<sup>[16],[17]</sup>
- iv. *Financial support*: This is essential for this expensive and prolonged treatment.
- v. *Family support*: Expensive regimens and social stigma make psychological and financial support by the family crucial.

vi. *Pros and cons of starting therapy*:<sup>[4]</sup> The various pros and cons of starting therapy either early or late in the course of disease must be considered and preferably discussed with the patient.

### **B. Pharmacological aspects**

- i. *Tolerability of the regimen*: The drugs used in the regimen have overlapping toxicities, which hamper adherence and cause organ dysfunction.
- ii. *Availability of drugs*: Most of the newer and secondary regimen drugs are not widely available.

Considerations should also be given to the regimen's pill burden, dosing frequency, food requirements, convenience, toxicity and drug interaction profile compared with other regimens.

### **What are the predictors of inadequate adherence?**

Apart from the social and pharmacological aspects mentioned, there are some more factors that predict poor adherence:<sup>[4]</sup>

- A. Poor interpersonal relation between the patient and the treating physician.
- B. Active psychiatric illness (e.g. depression).
- C. Inability of illiterate patients to identify medications.
- D. Restricted access to primary medical care or medications.

### **What are the possible interventions to improve adherence?**

Possible interventions that could be done at various levels to improve adherence are:

#### **A. Interventions at the patient level**

- Achieve a good rapport with the patient.
- Educate the patient about the disease and its course.
- Assess and establish the patient's readiness to take medication.
- Discuss the goals of therapy, need for adherence, and the outcome with the patient.
- Make him understand that the initial regimen has the best chance for long-term success.
- Implement a treatment plan that the patient understands and to which he/she commits.
- It is essential to discuss the importance of the

impact of resistance on future options and what to do if doses are missed, delayed, or vomited.<sup>[4],[18]</sup>

- Daily or weekly pillboxes, timers with alarm, pagers or other devices can be used to remind patients of doses.
- Use visual aids and audio/video information sources for patients with low literacy levels.
- Factors like sex, race, low socioeconomic status or education level and past drug use are not reliable predictors of suboptimal adherence.<sup>[8]</sup>
- Assessment of behavioral skills (goal-setting, time-tabling, assertiveness/communication, problem-solving, etc.) and behavioral determinants of adherence (daily routine, e.g. eating, sleeping and working patterns; recreational activities; familial/social relationships and responsibilities; travel plans, etc.) are necessary for ensuring adequate adherence.<sup>[4],[18]</sup>

#### **B. Interventions at the medication/ treatment level**

- Implement a tailor made regimen for each patient after thoughtful consideration of the simplicity or complexity of the regimen.
- Use the best of medications locally available.
- Consider the cost factor whenever and wherever applicable.
- Be aware of the job constraints, especially for a regimen requiring doses to be taken 4- or 6-hourly. Keep the dose frequency and number of pills to the minimum.
- Convey the common and probable side effects of ART to the patient before starting therapy. This awareness improves the patient's confidence in the physician and hence the adherence. Anticipate side effects and treat them as soon as possible.
- Modify the dietary pattern to suit the antiretroviral agents.
- Avoid adverse drug interactions amongst ART drugs and drugs used for controlling other symptoms as well as opportunistic infections.
- Detect and treat any intervening illness and opportunistic infections at the earliest.
- Direct observed therapy (DOTS) and modified DOTS are being explored to enhance adherence.<sup>[19],[20]</sup> Their relevance in resource limited countries is speculative at present.

### C. Interventions at the healthcare delivery level

It is essential to establish a health care team comprising of clinicians, psychologists and volunteers to cater to the various needs of HIV patients. It is but natural to expect a reduction in adherence as time progresses, even among patients whose adherence has been optimal. This phenomenon is termed as 'pill fatigue or treatment fatigue',<sup>[21],[22]</sup> Regular and intensive monitoring is the only solution to this. Though there are many methods to measure adherence to ART like electronic, pill count, drug assay, MEMS cap (medication event monitoring system), provider estimates and visual analogue scale,<sup>[23]</sup> in clinical practice, the most efficient method is to simply ask the patient in supportive and non-judgmental ways. Most patients are truthful about their medication taking when asked.<sup>[24]</sup>

To get the most reliable information, the patient should be given the chance to err with dosages and should be asked in a non-judgmental way and given a specific period. For example, "Everyone misses doses some of the time. In the last two weeks, how many doses have you missed?"<sup>[25]</sup> This self-reporting technique of adherence measurement makes patients aware of the importance of their role in the achievement of optimal adherence.

#### Other measures to improve adherence include:

- Serve as an educator and an information source with ongoing support and monitoring. Adherence to antiretroviral therapy is improved where patients view their relationship with their doctor positively.<sup>[26]</sup>
- Supportive and non-judgmental attitudes and behaviours encourage the patient's honesty regarding adherence and associated problems.
- Provide access between visits for any problems or queries, including during vacations (e.g. by providing pager number etc.).
- Intercurrent medical, surgical or psychological illness (e.g. liver disease, wasting, recurrent chemical dependency) can adversely affect adherence and necessary modification in management is essential
- Offer specific training to all health care team members and periodically update them.

Alternative medicines are in common use by patients with chronic ailments and this is true with HIV infected patients too. Traditional healers still play a major role in providing initial health care in many developing countries and the possibility of involving them in the HIV health care system for better patient care is being explored.<sup>[27],[28]</sup>

### D. Interventions at the community level

The apprehension of social ostracization is a major hindrance to adherence as it limits a patient from taking medications in front of others, especially with complex regimens. Thus, the psychological support by the family and friends is a major factor in antiretroviral therapy.

- Recruit family and friends to support the treatment plan.
- Develop a link with local community based organizations regarding adherence combined with educational sessions and practical strategies.
- Use peer education for adolescents and injection drug users.
- Encourage HIV affected patients to form support groups, which guide and help others in coping up with the situation.
- Mobilize sufficient funds for expensive medications through charitable trusts and NGOs.
- Vocational and occupational rehabilitation.

In India, there is complete lack of awareness among the masses regarding ART. Health care providers need vigorous training in delivering all aspects of ART. Busy medical practitioners find it difficult to spare enough time for the extended counseling that is needed for the success of any therapy, especially ART. Moreover, adequate supply of medicines for ART as well as for treating opportunistic infections is essential for achieving the expected adherence to ART.

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