

ADHERENCE TO ANTIRETROVIRAL REGIMENS

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'Any person who takes all his pills 100% of the time, on time, for the rest of his life ... is a very weird person ...'
(Dr Bill O'Brien)

'What separates man from the animals is the urge to take medicines ...' (Sir William Osler)

The advent of highly active antiretroviral therapies (HAART) in 1995/1996 ushered in a new era in the management of the HIV pandemic, with new drugs, new strategies, new vigour from treating clinicians, and enthusiasm on the part of their patients.¹ Mortality and morbidity figures dropped radically,² with associated gains in cost benefits with regard to macro- and microeconomic costs.³ What soon became evident, however, was the vital importance of patient adherence with prescribed medication in order to garner the benefits that were so rapidly becoming available. As a result, much attention has recently been paid to this aspect of management. Both clinicians and patients are recognising the importance of long-term drug acceptability, availability, and the all-important ability of patients to sustain such challenging regimens.

WHAT IS REQUIRED?

The vital role of adherence in the success of ongoing therapeutic control is well known and well studied. Studies of other chronic illnesses (for example diabetes, renal failure, and hypertension) have demonstrated a direct and causal link between patient adherence to medication and clinical outcome. In these conditions, average adherence rates range between 40% and 60%.⁴⁻⁶ A study by Patterson *et al.*⁷ (Fig. 1) demonstrated the degree of viral resistance formation measured by genotypic analysis over 48 weeks of antiretroviral therapy in a clinical trial environment.

What is evident from this study is twofold:

1. Genotypic resistance formation (accurately or less accurately associated with phenotypic resistance) to any given antiretroviral regimen seems an inevitability with time. However, it may be slowed by the degree of adherence to antiretrovirals maintained by the patient.
2. Resistance to antiretroviral regimens develops at slower rates with higher compliance with regimens. In this study a

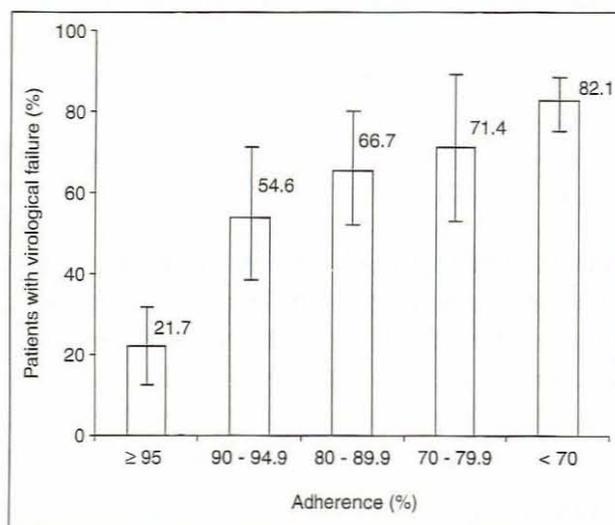


Fig. 1. Viral resistance formation measured over 48 weeks of antiretroviral therapy.

95% compliance rate (i.e. missing less than 1 dose in 20) was associated with approximately 20% genotypic resistance. Missing less than 1 dose in 10 conveyed a risk of genotypic resistance of approximately 55%.

In other words, requirements of patients in terms of adherence to antiretrovirals are very high. They are much more stringent than the best adherence levels achievable in other chronic illnesses, and are absolute in terms of virological failure being causally linked to clinical decline. This leads to a vital dictum in HIV medicine:

Patients should never be commenced on these agents until they are aware of and committed to this reality.

The relationship between the clinician and the patient must accommodate the needs for ongoing education, respect, and support required in such demanding regimens. It is never necessary to start antiretroviral regimens urgently in the treatment setting (with the obvious exception of the post-exposure prophylaxis scenarios of mother-to-child

transmission prevention, occupational exposure and sexual exposure such as rape). The treating doctor should restrain his or her enthusiasm to commence therapy and allay the patient's anxiety regarding its commencement until both are prepared to meet the adherence needs of the subsequent regimens.

WHAT MAKES REGIMENS FAIL?

Patient adherence (> 90%)

- Counselling and education
- Side-effects
- Social and family issues
- Financial

Drug resistance

- Genetic substitutions
- Genetic deletions (rare)
- Genetic insertions (rare)

Drug absorption

- Malabsorption syndromes
- Chronic diarrhoea

Drug interactions

- Cytochrome P450 interactions
- Prevention of drug absorption

Doctor-related

- Support/education
- Regimen planning

Proactive attention to all the above is necessary when selecting and maintaining antiretroviral regimens. It is also necessary to revisit this list of reasons for drug failure at each stage of the process. Acting to prevent certain of the problems and side-effects that may hamper adherence, and to explain to and inform patients in this regard, generally makes dealing with adherence to these protocols a lot easier for both doctor and patient. For example, regimens containing agents that may cause nausea (such as AZT or ritonavir) may be made easier to tolerate by the use of prophylactic anti-nauseants. (preferably utilising centrally acting agents such as cyclizine or buclizine). Likewise, the risk of diarrhoea with agents such as nelfinavir should be highlighted before the patient begins to take the drug. Treatment of this side-effect can then be effected rapidly, diminishing patient discomfort, and encouraging high adherence levels.

FACILITATING EASE OF ADMINISTRATION OF ARV REGIMENS

Various factors are associated with decreased adherence to medication regimens. (The list below is not considered exhaustive.)

Adverse drug reactions

- 'Minor' (nausea, rash, etc.)
- 'Major' (hepatitis, peripheral neuropathy, etc.)

Pill burden⁹ (Fig. 2)

Food restrictions⁹

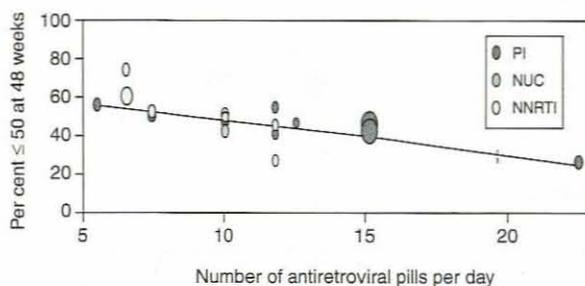
Frequency of dosing (b.i.d. better than t.i.d.)¹⁰

Depression

Financial problems

Relationship problems

Confidentiality and disclosure issues¹¹



Note: Size of symbol is directly proportional to weight of the data point in the analysis.

Fig. 2. Plot of virological response by pill burden ($r = -0.61$, $P = 0.0056$) (from Bartlett et al.⁹).

PATIENT PREPAREDNESS

As has already been alluded to, patient preparedness (initially and ongoing) is the most important factor in beginning therapy, and vital to ongoing adherence to antiretroviral agents. Education regarding the illness itself, the benefits and drawbacks of antiretroviral and other therapies, and the longstanding nature of such therapy needs to be exhaustive and ongoing. Patients should be given sufficient time to consider the personal ramifications of taking medication lifelong, as well as the associated issues of confidentiality, disclosure and social stigma that may or may not impact on their decision. Follow-up consultations, with family and caregivers if possible, can assist in this process. This is generally true in all settings, but particularly if medication is commenced in the presence of index patient dementia or other illnesses (e.g. cryptococcal meningitis) that may impair memory and mentation. Here carers may assist with medication administration until such time as the patient is able to take it independently, in addition to providing ongoing practical and emotional support.

PILL BURDENS

It makes empiric sense that, given the choice of taking 16 large capsules or 2 small pills to generate equivalent clinical, virological and immunological success, most people will opt for the smaller pill burden. It would also seem logical that, presented with large numbers of pills and

capsules to take on a continuous basis, as opposed to having to take only small numbers, patients are more likely to remain adherent to the latter regimen. Bartlett⁸ has demonstrated this with virological data from clinical trials, showing that increasing pill burden is negatively correlated with sustained undetectable (< 50 copies HIV-1 RNA/ml) virological response.

FOOD RESTRICTIONS

When an antiretroviral regimen is further complicated by food restrictions, for example the requirement of dosing on an empty stomach for buffered didanosine preparations, and the separation of buffered didanosine from indinavir preparations in the same regimen (both requiring empty-stomach dosing), the potential for missing doses increases, as does the risk of long-term intolerance of the regimen as a whole.

The advent of enteric-coated didanosine (not yet available in southern Africa) has removed the need for food restrictions with this agent, allowing it to be taken with other antiretrovirals and other medications.

The use of 'boosted' protease regimens (inhibiting cytochrome 3A4 by the use of low-dose ritonavir in order to increase serum levels or serum half-lives of other protease inhibitors) has similarly altered food restrictions with many of this class of agents, and has also changed dosing frequencies.

DOSING FREQUENCY

Taking medication on a rigid schedule is made easier by limiting the frequency of dosing. In trials of antihypertensives adherence was improved from 59% on 3 times a day dosing to 84% on once-daily regimens.¹² Data from the Somerset Hospital HIV Clinical Trial Unit¹³ have shown that tablet dosing complexity (as measured by pill counts) correlates with decreased adherence to antiretroviral regimens. Three times a day regimens are shown by the same group to be statistically correlated with poorer adherence outcomes than twice a day regimens. The same adherence benefit has been seen in 'switch regimens', where 3 times a day protease inhibitor containing regimens are converted to twice a day regimens by the addition of ritonavir.¹³

SIDE-EFFECT PROFILES AND ADVERSE DRUG INTERACTIONS

As has been mentioned above, paying attention to minimising side-effect profiles of individual agents and combinations of drugs is vital to the success of antiretroviral regimens. Some side-effects cannot be

avoided, but may be successfully treated with simple remedies. Medium- to long-term side-effect profiles are becoming increasingly predictable, allowing for regimen planning that minimises or prevents overlapping toxicities and side-effects. Ongoing support and education in this regard empowers the patient to take control of such events, demystifying them and allowing for earlier reporting of adverse events.

Similarly, as knowledge increases regarding adverse drug reactions (particularly when interactions with antiretrovirals generate or worsen side-effect profiles), the clinician is enabled to select concomitant medications wisely and appropriately. The patient's knowledge of the fact that interactions may occur, in conjunction with easy access to the clinician to discuss proposed additions to the medication regimen (for example OTC agents, traditional and herbal medications or drugs prescribed by another practitioner), can diminish the chance of such events occurring.

Minimising adverse events in these ways improves the tolerability of antiretroviral regimens, in turn leading to increased adherence and improved sustained virological control.

ASSISTING WITH ADHERENCE TO ANTIRETROVIRALS

Improving adherence is an ongoing exercise, founded equally in the empowerment of the patient and the expertise and attention of the clinician. Regimens should only be commenced when the patient is fully prepared to commit to them, and the physician to the ongoing management of the patient.

Attention should be paid, on an ongoing basis, to:

- Patient-related issues
- Drug regimen complexity
- Dosing regimens requiring food restrictions
- Side-effect profiles and concomitant medication interactions.

Finally, it is vital never to underestimate the role of the doctor-patient relationship and the importance of family and friends in maintaining and improving adherence. Taking medications on a strict regimen for the rest of one's life is greatly eased by having a network of supportive persons to assist one.

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