# ADHERENCE: THE ACHILLES HEEL OF ANTI-RETROVIRAL THERAPY - A Paradigm for Integration of Biology and Behaviour

(Invited Presentation / "Brown Bag Lunch Meeting", hosted by HIVAN on 17 October 2001 in the Athlone Skinner Conference Room, University of Natal, Durban)

Introducing the speaker for HIVAN's first Invited Presentation, the Centre's Director of Social and Behavioural Sciences, Professor Eleanor Preston-Whyte, welcomed Professor Gerald Friedland of Yale University's School of Medicine. She said that it was fortuitous for HIVAN to have a researcher of Prof Friedland's eminence to address staff from various schools, departments and service organisations on all campuses on this important topic. She invited all present to participate in the brainstorming session scheduled to follow Prof Friedland's scan of the relevant literature, with the aim of planning a pilot research project tailored to focus on probable needs in KwaZulu-Natal.

Friedland proceeded to describe his involvement at the clinical interface between the bio-behavioural aspects of the HIV/AIDS epidemic, explaining that the issue of adherence to Anti-Retroviral Therapy (ART) highlights, as a paradigm, the significance of this interface.

His presentation covered the definition, importance, measurement, components and determinants of adherence to ART, as well as a review of previous and proposed interventions and strategies, and a perspective on the topic within a South African context.

## Definition:

"Adherence" used to be called "compliance", but the latter term tended to imply that the patient was required to bend to the will of the healthcare provider. The contemporary view is that the dynamic should be one involving a shared decision, although it is felt that the concept would be better described as a "therapeutic alliance". "Adherence", then, means the extent to which a person's behaviour corresponds with medical advice, i.e. the ability to take medication as prescribed (as opposed to not at all, too little, too much or intermittently).

## Importance:

Adherence can be regarded as a highly significant determinant of the biologic, clinical and public health outcomes of ART, as poor adherence is a major cause of ART failure, of ART resistance, and of continued risky behaviour and transmission of resistant organisms. These pitfalls and concomitant negative outcomes are well-known in studies of other diseases such as tuberculosis.

HIV/AIDS is the only modern disease that requires such protracted therapy, and without the expertise and resources to evaluate and support adherence, ART can be ineffective, wasteful and dangerous. Adherence is, therefore, a process that needs careful study, and in the developing world context, this is a crucial and immediate area for research.

Studies in the US show that from 1982 to 1994, AIDS became the leading cause of death among the 25-44 years age group. With the introduction of ART, the trend flattened for approximately two years, and then showed a decrease by 1998 (although this decline occurred with ART being used in conjunction with other supportive interventions). At least three potent drug combinations have to be taken, some with toxicity and side-effects, making the regimen unpleasant to follow, but with the goal being to inhibit viral replication.

Failure to follow the ART regimen precisely can result in hospitalisation, new opportunistic infections, death, and transmission across the population. The durability of adherence is marred by pill-fatigue, change in life circumstances and long-term toxicities (although study in this area is insufficient).

**Measurement:**

Indirect measurement relies on:
* the clinician's estimate;
* the pill count (announced or unannounced);
* MEMS caps (a computer chip fitted inside the cap of the pill bottle that records the time and frequency of opening, a very expensive and non-foolproof mechanism);
* pharmacy refills;
* self-report (which Friedland believes is best as it strikes at the heart of the clinician-patient alliance, ensuring honesty, requiring the correct posing of questions, and being more valuable as to the assimilation of behavioural information);
* the biologic and clinical outcome (e.g. seeing a decline in the viral load, a decrease in hospitalisation)

Direct measurement relies on:
* Testing drug levels (although this provides incomplete information as it only indicates the intake of the day before the test, is an expensive route and inaccurate, because the half-lives of the dfiferent drugs vary). Testing of drug levels can be undertaken using hair and nail samples, displaying the cumulative effects of the medication, but Friedland felt that this was an "esoteric" method.

*Question: How reliable is self-report in terms of efficacy?*
Friedland's response: self-report should be balanced with a test of the viral load. A current method of testing the validity of self-report involves the patient's anonymous completion of a questionnaire covering a seven-day

"total recall" period; in an experimental stage is a three-day version of this record, which also asks "How many pills did you MISS?", thereby giving permission to the patient to disclose any lack of adherence and offering a list of options for explaining such non-adherence.

**Components and Determinants:**

These factors are only really known in the context of the developed world:

* patient characteristics: demography of age, sex, race/tribe/language, socio-economic status;
* Information, knowledge and cognition;
* Motivation: beliefs, depression, drug use;
* Behaviour skills: pill-taking, scheduling;
* provider-expertise, trust;
* regimen: simplicity, toxicity, disruption
* disease stage
* clinical setting

Friedland noted that by and large, the older the patient, the more successful the level of adherence. Recently published research (in the JAIDS, by Altice, Mostashari, Thompson and Friedland) on the Acceptance of and Adherence to ART, studied the topic in a subject community of prisoners and revealed that the issues of trust in the physician and mistrust of the medication are very important, as are the factors of side-effects, social isolation and the complexity of the regimen.

Some figures extracted from a study on self-report by Chesney et al (AIDS Care 2000), showed :

| | | |
|---|---|---|
| simply forgot | = | 66 |
| away from home | = | 57 |
| change in routine | = | 51 |
| busy | = | 40 |
| slept through | = | 28 |
| too depressed | = | 18 |

revealing the importance of how a regimen correlates with a patient's daily life. This kind of work has helped in the design of interventions to simplify regimens, (e.g. reducing the dosing frequency to a once-a-day regimen, fewer pills, fewer side effects, food-neutral pills).

**Interventions:**

There have been few rigorous studies resulting in theoretically-based strategies to improve adherence to ART. Several existing provider-oriented interventions targeting patient involvement and rewards are effective, and it

is believed that a combined approach works best, i.e. an intervention-dose response. Durability of effect requires continuing intervention.

Behavioural models include :

* Prochaska's trans-theoretical model of change, involving pre-contemplation, contemplation, preparation, action, maintenance and possible relapse
* The IMB model (Information, Motivation, Behaviour skills, e.g. condom use)

Interventions currently under study include:

* Medication manager (using trained nurses as adherence experts)
* Peer support
* Electronic reminders (an alarm mechanism on the pillbox, SMS messages to alert the patient to take the required dosage)
* Home visiting (to balance the overuse of the clinical setting)
* Modified Daily Observation Therapy - DOT (useful in prisons, in drug treatment)

**The South African context:**

There is a need to examine the kind of resources needed to make ART widely available in this country. Friedland asked for input as to whether there are any cross-cultural studies being done in South Africa, even for other chronic diseases; he knew of only one small study conducted at Somerset Hospital in Cape Town.

A participant confirmed that there has been a study on adherence to usage of the contraceptive pill, and that there is a great deal of this kind of questionnaire material being designed and developed in South Africa.

In summarising the issues pertinent to prospective study of ART in the developing world, Friedland had compiled a set of queries entitled "Anti-Retrovirals in Resource-Constrained Settings" as follows:

- What resources are needed to make anti-retrovirals widely available?
- Can existing infrastructure be modified and strengthened to adapt to anti-retroviral provision?
- What criteria should be used for starting anti-retroviral therapy?
- Which preferred combination of first-line drugs should be offered?
- How can adherence be enhanced?
- How can therapeutic effectiveness, adverse events and the emergence of drug resistance be monitored?

Friedland had designed a protocol for a study on the integration of medication for HIV with TB Daily Observation Therapy (DOT) as a starting point, working

with the Durban Chest Clinic and King Edward VII Hospital in Durban. He invited all interested parties to assist with this project and emphasised that other proposals for study on adherence would be highly valued.

**Discussion:**

*Question: How would adherence to ART relate to condom use?*
Friedland's response: It would seem that in South Africa, prevention and treatment are still handled as separate initiatives.

*Comment*: It is unlikely that ART will be made widely available in the public health sector very soon; however, pharmaceutical companies should be brought into this kind of research so as to facilitate access to ART, and studies should be conducted within the private sector where the therapy is available, albeit expensive. Drug companies are saying that they will provide the treatment whether patients are on medical aid or not, so surely it would be possible to conduct studies amongst the workforces of large corporations?
Friedland's response: warned that this would not be as simple as offering the drugs to subjects, as it is also very difficult to secure the provision, by companies and/or the state, of the requisite infrastructure for evaluation (e.g. personnel, office space, etc)

*Question: (Cedric Mhlongo, HIVAN) How would one approach managing and evaluating these important studies in the homes of individuals in the townships and rural areas?* "Failure" takes on a new meaning in these contexts.
Friedland's response: Agreed. In studies of adherence in other chronic diseases, 80% is the benchmark for adherence vs. non-adherence; in the case of HIV, one would have to have results of nine-out-of-ten to confirm adherence.

*Question: (Helga Holst, McCord Hospital) In studies involving family units, have the patient's family members been included?*
Friedland's response: could only offer his impression of work done in the US in this regard, where parents, siblings, partners had been brought into the process, but he reiterated that there had not been much of this kind of work. He had noticed that a significant number of patients attended clinics with a companion of some description.
*Comment: (Helga Holst)* At least one other member of the patient's family would be likely to be HIV-positive and also be infected with TB.
Friedland's response: Examining one person as a starting point and then broadening the study to other family members would be the best approach.

*Question: (Jerry Coovadia, HIVAN) Is it likely that the average woman in South Africa could keep her treatment regimen a secret?*
Response: (Eleanor Preston-Whyte, HIVAN) No, not with the prevailing size of families, cramped conditions and stigma in communities against HIV/AIDS-infected people. There would be all these and much more to confront before one could ensure adherence. However, such studies and resultant

interventions could turn an issue like stigma around: if others in the household were to observe this kind of change in behaviour, it could make it safe and desirable for more people to openly take medication for the disease syndrome.
*Comment: (Sean Jones, HIVAN*) Approximately 40% of households in South Africa are woman-headed, so it would be wise to factor in these distinctions in family structure and power-relations. It's also been found that 32% of pregnant women in Umlazi (a township in KwaZulu-Natal) do not live with partners.

*Comment: (Farida Amod)* Although it would require a lot of preparatory work, it would be useful to examine adherence within the family unit, and to do so in the context of comparing support within the family vs. none. One could utilise the affordable IPAC programme for medication (R250 for a month's supply of ART). It would also be necessary to study those who attend clinics unaccompanied vs. those who attend with someone else.

**Conclusion:**

It was clear that the gathering had produced many more questions than answers, but also that these were precisely what are needed to formulate relevant proposals towards a larger research initiative. Friedland suggested that those interested in pursuing the brainstorming process form a smaller core group to examine all the issues closely. The HIVAN team undertook to arrange this via an "email blitz".