

CHAPTER 2 - LITERATURE REVIEW

2.1 Measurement of Adherence

Several methods including Medication Event Monitoring System (MEMS), patient self-report (SR), antiretroviral plasma drug levels, physician report, pill counts, and pharmacy logs have been used to measure adherence to medications including ART. None of these methods have been accepted as the ‘gold standard’ test.^[15]

MEMS is an electronic device (a microchip housed in the cap of a standard medication container of patient), which records the number of times the container is opened to coincide with the time patient removes medication for administration. This method underestimates the adherence of patients who remove multiple doses from the MEMS container. However, if properly used, MEMS is an excellent day-to-day monitor of medication dosing patterns. But the use of MEMS is more common in developed countries.^[15]

The pill count method of determining adherence relies on the number of leftover pills of patient to determine adherence. It is said to be most successful in measuring adherence if carried out during unannounced home visits, because the predictability of pill count by patient usually results in “dumping” of pills, thereby overestimating adherence.^[16] As a result, pill count is often used as an adjunct to other methods such as MEMS and self-report.^[17] A strong association has been found between pill count and MEMS and self-reported measurement of adherence.^[14]

In pharmacy log method, the number of refill missed is used to measure adherence. Therefore, it underestimates the adherence of patients who refill their prescriptions outside the hospital pharmacy.^[15]

In self-reported measures, adherence is based on patient's responses to questionnaire and/or interview. The accuracy of this tool depends on how well questions are structured in a manner that is both specific and non-judgemental as well as the length of the recall period used to determine adherence.^[12, 14] Other inaccuracies have been attributed to patient forgetfulness of missed doses and also patients' desire to appease the health worker whose aim is to enforce adherence.^[18] Different recall periods such as "yesterday", "last 2 days", "past four weeks", and up to several weeks) have been used in self-reported adherence measurement.^[19, 20] This makes it difficult to compare different studies. Some authors have argued that non-adherence rates are higher in studies where a longer recall time is used and that with a longer recall period the chance of inaccuracy increases.^[18] However, some other studies find that the longer the recall period the higher the chances of overestimating adherence by patients.^[21] The SMAQ (Simplified Medication Adherence Questionnaire) study measured adherence by self-report from the 'last week' up to 'over the past 3 months', covering a wide range of time. In another study that used two different recall periods, the day before the interview and the two days prior, the less adherent patients reported lower adherence self-efficacy ($p=0.006$), and were less sure of the link between non-adherence and the development of drug resistance.^[20] Adherence assessments now commonly ask about adherence over more recent periods of time (e.g. past 3 days and/or past 7 days) and over longer periods (e.g. past 1 month).^[14] Walsh et al compared questionnaire responses with MEMS Track Cap

(MC, a medication event monitoring system), pill count (PC) and plasma HIV vitamin in order to test the validity of self-reported adherence. Agreement between MC and responses to items about doses missed 1, 2 or 3 days ago was low ($\kappa = 0.23$ ($P < 0.03$), 0.44 ($P < 0.001$) and 0.28 ($P < 0.01$) respectively). But this improved when these responses were summated ($\kappa = 0.46$; $p < 0.001$) and was similar to that for recall of non-adherence over the preceding 2 weeks ($\kappa = 0.54$; $P < 0.001$).^[14] Irrespective of the study design, several studies in which self-report was one of the methods used to determine adherence, has found a significant association between adherence to medication and virologic suppression,^[19, 22, 23, 24] which suggests that self-reports may be a valid indicator of adherence. However, Patterson et al suggest four reasons why adherence might not necessarily directly correlate with virological success or failure.^[25]

- The early stages of treatment had the greatest risk of high viral load; because virological rebound decreases over time.
- Patients on their second treatment regimens were at higher risk of higher levels of viral rebound.
- New nucleosides reduced the risk of viral rebound.
- Patients that started treatment with low viral loads (below 50 copies/mL) also had lower risk of viral rebound.^[25]

There are many studies holding a contrary view to Patterson and colleagues by demonstrating the inverse correlation between virologic response and patient report of adherence.^[12, 22, 26, 27, 28, 29, 30] In one of these studies, 34 HIV-positive individuals taking ART over 3 months were analysed using a cross-sectional method; adherence was measured using patient report, unannounced pill counts, and MEMS caps. Each 10%

decrease in adherence was found to result in a doubling of the viral load and adherence alone explained between 40-60% of the variation in viral load. The study concluded that small differences in adherence can result in major differences in virologic control and that adherence may be the predominant factor determining virologic outcomes.^[22]

The other methods of measuring adherence also have their weaknesses in assessing patients' adherence to medication. Reports have confirmed that clinicians tend to overestimated medication adherence, inadequately detect poor adherence, and may therefore miss important opportunities to intervene to improve antiretroviral adherence.^[15, 31] The use of antiretroviral drug level in plasma to measure adherence suffers from variations in pharmacokinetic and pharmacodynamic properties of drugs. Poor absorption of drug (especially in undetected cases of drug-drug or drug-food interactions) resulting in low plasma drug levels may mislead the judgement to that of poor adherence.^[15]

Viral load is one of the surrogate markers used to gauge the ability of tools to measure adherence^[15]. The quantification of the viral load in plasma is a predictor of the progression of HIV disease^[32] and plasma levels of viral RNA (viral load) have been shown to correlate closely with clinical outcome.^[33] Hence, the ultimate goal of ART is to maintain an undetectable viral load, through strict adherence to medication. In the guidelines for the national roll out of HIV treatment in South Africa, viral load over 400 copies/ml is an indicator of treatment failure.^[8]

2.2 Factors Affecting Patient's Adherence to Antiretroviral Therapy

2.2.1 Socio-demographic factors

Some studies on adherence to HAART have focussed on comparing adherence rates among demographic sub-groups of patients in attempt to finding demographic variables predictive of adherence to HAART. However, recent studies suggest that demographic variables such as age, race and gender are inconsistent predictors of adherence.^[34] In their study, Penedo et al showed that only age was significantly associated with adherence such that older age was significantly associated with greater adherence to HAART.^[35] Among the 289 participants recruited from the Cape Town AIDS Cohort (CTAC), those who discontinued treatment were significantly younger, and age and speaking English at home were independently associated with incomplete adherence to HAART.^[36] Low social status (based on the Cape Metropolitan Council composite index which included household income, education level and unemployment status) was not significantly associated with adherence.^[36] Ferguson et al in their study of patient-perceived barriers to antiretroviral adherence, suggest “Rather than relying on demographic predictors, which may be only an indirect marker of adherence, evaluations of adherence should examine the psychological and social barriers to positive adherence outcomes in individual patients”.^[19]

2.2.2 Patient-provider relationship

Studies of other diseases (such as TB and asthma) have shown that language barriers can cause significant problems for patients in terms of communication with their

physician/provider, appreciating, understanding and retaining medical information, and consequently adherence^[37]. In one study, the quality of the health care professional-patient relationship was found to depend on factors including patient's comfort and willingness to discuss issues of medication adherence with their providers as well as provider's attitude and reaction when patient willingly admit their non-adherence^[37]. According to the authors some patients go as far as lying to their provider to avoid embarrassment. The following excerpts^[38] are noted of patients in defence of their non-adherent behaviours.

When patients do not feel comfortable discussing adherence with their health care provider, they lie.

e.g. "When I first started taking Norvir, the liquid would come out and every time I would take them I would feel nauseous; therefore, I stopped taking them. However, I would tell my doctor that I was taking them but in reality I was becoming resistant to the medicines." [Murphy et al (2003), p.225]

Some patients lie because their physician scolds them.

e.g. "I told him I wasn't taking it because I wasn't feeling good and he scolded me. 'You are sick because you are not taking the medication.' So instead I tell him I do, although I don't. So he does not scold me." [Murphy et al (2003), p.225]

Negative attitudes of some health care providers cause them to dismiss important complaints by patients, especially of drug side effects, and this has negative impacts on adherence.

e.g. “I noticed that with that medication I was warmer, my heart rate was faster and my nose would bleed a lot. I thought that it was due to the medication and I mentioned it to the doctor and he said, ‘No, it isn’t because of that.’ I continued with the medication and I was having the same effects so I stopped taking the medication for three months.” [Murphy et al (2003), p.225]

The language of communication between provider and patient has been found to be one of the most silent barriers to treatment.^[37] It has been reported that patients make mistakes taking their medications because they did not understand their physicians’ instructions. Patients having language difficulties with pharmacy personnel have problems understanding the written instructions for their medications because such instructions were in a different language from his. In a study of the Latino population, Flores G. notes that certain cultural values are better expressed by patients in their preferred language understood by their providers as well.^[39] Murphy et al found that the use of an interpreter impedes adherence in that patients may not tell the doctor what other people don’t have to know.^[38]

2.2.3 Treatment regimens

Antiretroviral therapy has been viewed as complex.^[40, 41] More often than not antiretroviral medications with different mechanisms of suppressing HIV are used in a combination therapy to reduce the chances of drug resistant mutants from developing.^[42] Resistant strains of HIV interfere with future therapeutic options for the individual being treated and for those who subsequently become infected with the resistant strains.^[43] Despite the fact that combination therapy has been proven to be effective against HIV it

creates complicated regimens that often hampers adherence.^[42] Studies have shown an association between non-adherence and the number of daily doses, frequency of drug administration, and untoward effects/toxicities of treatment.^[32, 36, 41] Also, it was reported that the "fit" of the regimen into an individual's daily routine, inconvenient dosing frequency, dietary restrictions, pill burden, and side effects; are important determinants of adherence.^[28, 43] The specific type of pills prescribed was not significantly associated with adherence behaviour to antiretroviral medications.^[44]

2.2.4 Patient knowledge of HIV treatment

Despite the complexities associated with HIV treatment regimen, it has been suggested that knowledge of HIV and its treatment may promote the motivation and development of adherence skills (such as scheduling medication, coping with side effects of ARVs).^[9] It has been relatively difficult finding research that examined directly the connection between HIV treatment knowledge and adherence. Kalichman et al showed that high literacy is associated with adherence and high literacy correlates with better knowledge of HIV and its treatment.^[45] One study also found that greater knowledge of HIV-related treatment issues was associated with higher education, and that time on antiretrovirals was significantly associated with the ability to understand prescription bottle instructions, which indirectly impact on adherence to antiretroviral therapy.^[46] For patient to improve in their knowledge of health and HIV treatment they need be provided with all necessary adherence-related information. Amico et al cite Fisher et al who stated that a prerequisite of adequate adherence encompasses accurate information concerning one's specific regimen, about how to utilize antiretroviral medications, about requirements for adequate adherence, about specific side effects associated with one's regimen. The information

construct also include ways of counteracting some of the heuristic theories concerning adherence (for example, the notion that ‘If I’m feeling well, then missing a few doses doesn’t really matter’) which negatively affect adherence.^[47]

2.2.5 Support for patient

During HIV/AIDS treatment, support for patients includes any measures aimed at continuing the treatment. Patient education, which is the hallmark of treatment literacy, involves training people to understand HIV as a disease; to promote understanding of self-management of health; to recognise and understand all aspects of antiretroviral treatment, including the names of medicines (or appropriate identification technique for people with no formal education), its side-effects and benefits. Counselling provides psychological support and improves the mental status of those infected and affected by HIV/AIDS and gears the patient’s mind towards adherence to treatment.

Laboratory facilities are essential for monitoring progress during treatment through the provision of data on drug efficacy, virologic and biological outcomes, and improves adherence especially among enlightened patients who could understand the meaning of the test results.^[33]

It’s often said that the basic needs of people living with HIV/AIDS (PLWHA) remain unmet, especially in the area of nutrition and finances for the very poor patients. In such instances, patients miss clinic visits and fail to secure medication refill due to lack of transportation to health facility and inability to pay for treatment, thus resulting in non-adherence to HAART.^[15] Where there is no social support from family or work places, patients often find it difficult to take treatments and tablets openly and integrating treatments into a very tight schedule is often a difficult task.^[48] In a study of patients with

excellent adherence, family members often reminded patients to take their medications. Patients with sub-optimal adherence were much more secretive about their HIV status, and preferred dealing with the problem all by themselves.^[34]

Directly Observed Therapy (DOT) has been used to promote adherence especially in patients with unstable lifestyles including injection drug users and the homeless. While it has proved successful to a reasonable extent in TB treatment, the success of DOT in antiretroviral therapy is best conjectural.^[49] This is partly due to problems arising from stigmatisation of HIV infected individuals and the need to protect confidentiality. The dominant stereotype of people living with HIV is one that stigmatizes them as immoral,^[50] leading to situations where they are labelled with 'spoilt identity' as described by Goffman.^[51] Antiretroviral drugs may also be stigmatising as found by Desclaux A. that patients taking antiretroviral drugs in Senegal often hide their medicines. Although most of their families are supportive, some relatives still reject them. Neighbourhood or professional relationships still convey a danger of rejection, especially in contexts of conflict or competition.^[52] Recent research suggests that in some part of Africa like Ethiopia, Tanzania and Zambia the use of HIV testing services, treatment programmes and disclosure of HIV status is constrained because of "anticipated and actual stigma experienced by people living with HIV."^[53]

In response to non-adherence to medication, several interventions have been employed with the aim of improving adherence. Hospital/clinic pharmacy intervention is one in which patients are counselled individually with regard to the patient's lifestyle (scheduling medication and setting up pillbox and other reminder devices), explaining the clinical benefits of optimal adherence and identifying any risk factor for non-compliance,

and providing telecommunication support (phone call and text message). In a study that compared clinic pharmacy intervention with conventional care intervention (attending physician prescribed treatment), a more significant adherence coinciding with a decrease in viral load was observed among the former group.^[41] Other interventions such as the use of alarm devices, modified directly observed therapy, keeping of diary and scheduling doses around events (e.g. television programme and meal time) have been shown to enhance adherence.^[54, 55] An advanced alarm device called Disease Management Assistance System (DMAS) verbally calls the patient by name and reminds him to take his medicines; the correct dosage and what medication to take at the correct time. In a study that tested this device, participants that used the device in conjunction with adherence counselling took 80% of their medication compared with another group on only counselling who took 65% of prescribed medications.^[56]

2.3 Study aims and objectives

The overall aims of the study were to measure the level of adherence to antiretroviral medications among HIV-infected patients in Helen Joseph Hospital, and determine the factors influencing adherence.

The specific objectives of the study were

To measure adherence to ART using two different measures:

- Self-report (using different recall periods)
- Pill count; and compare the results with viral load of the patients.

II. To assess the effect of the following factors on adherence:

- Patient understanding of HIV treatment

- Patient-provider relationship
- Barriers to adherence including complexity of treatment regimens, socio-economic and psychological barriers as well as social support for patient

III. To recommend ways of improving medication adherence among the studied population.

2.4 The study site

The study was conducted in the HIV clinic of Helen Joseph Hospital located in the Auckland suburb of Johannesburg. At the time of the study, the clinic had enrolled 312 patients into the HIV treatment roll-out of the government. Different sections of the clinic, each dealt with a specific aspect of service delivery ranging from booking of appointments and administrative tasks to those of patient care. There was a pharmacy section adjacent to a consulting room where patients were scheduled to consult with physicians during clinic visits. The pharmacy had the services of a pharmacist and one pharmacy technician, who had been trained in relevant HIV care. Also prominent in the clinic was the voluntary counselling and testing unit, under the direct management of a registered nurse who supervised a number of volunteer counsellors. All activities in the clinic were coordinated by a HIV specialist nurse. Laboratory tests were carried out to determine viral load 3 monthly and cd4 cell counts more frequently including other tests of clinical importance.

Before a patient could be enrolled into the HIV treatment programme, he must undergo a two-week pre-treatment education/training programme. During such training issues relating to understanding of HIV/AIDS as a disease, its treatment and adherence to

therapy were discussed. Patients were assigned to ART based on the clinic assessment that the patient can cope with treatment, and that all other requirements including clinical parameters such as cd4 cell counts have been certified. A cd4 count ≤ 200 cells/mm³, or WHO stage 4 AIDS-defining illness despite cd4 count and patient willingness to take ART adherently were the major criteria for admission to ARV therapy in the clinic and around the country.^[8] After the commencement of therapy, compliance to medication was monitored using compliance form that documented pattern of medication behaviour. This is in addition to a sheet of diary in which patients themselves were expected to record time of medication. They were advised to return any left over pills during subsequent clinic visit. During each clinic visit, patients were observed to be attended by experienced HIV clinicians and allied staff of the clinic including doctor, counsellor, nurse, and pharmacist, each reiterating the contents of the pre-treatment education and the need to fit treatment into daily routine. A telephone number was given to every patient as an access to the clinic if problems are experienced. Some patients were given pill boxes which should remind them of daily doses. Possible side effects of medications and ways to minimize them were explained to patients especially at the start of therapy. There are no indications of home visits or directly observed therapy taking place in the clinic.

Around the HIV clinic there were organisations such as CARE (Community Aids Response) and other organisations some of which were affiliated to Wits Health Consortium. The major objective of these organisations was to raise awareness about HIV/AIDS, make information accessible to all communities by promoting the need for communities to participate in health issues and HIV/AIDS in particular. As observed

during the study some organisations were assisting in VCT services and provision of condoms aimed at safer sex practice.

2.5 Definition of terms

Adherence

In many cases adherence to medication is calculated as the percentage or proportion of the drug consumed relative to the prescribed quantity. By this a known concentration of the drug in body circulation is expected to produce a known pharmacologic effect. This is the dose-response relationship paradigm. Presently, adherence to antiretroviral drugs takes a little different consideration in that the dose-response equilibrium is easily distorted in favour of the virus.^[22] The expected therapeutic effect of ARVs is no less than suppression of HIV virus below a detectable levels of plasma viral load. This has been postulated to occur mainly when all prescribed doses have been taken at the right time. In practice, many HIV infected individual has found it problematic to maintain a 100% medication rate throughout the chronic phase of the disease.^[47] Therefore, one may infer that the maximum dose level that suppressed the virus tends to be the basis for defining adherence, though not without other clinical considerations. Thus the cut-off and definition of adherence varies across settings and studies.

Based on the protocol for HIV treatment of the hospital (the study site) if a patient misses 1 dose of his antiretroviral drugs in a space of two weeks, he is 95% adherent, and has 1 in 5 chances of virological failure. This definition is a function of time. As the study sought to, adherence was measured over 23 days, and increased the number of missed doses to 2 for the same chance of virological failure. Thus, if a participant had missed 2

or less of the total doses of ARVs prescribed during the 23-day period assessed, he was 95% or more adherent (or had higher adherence) compared to the participant who missed more than 2 doses (had lower adherence) within the same period of time. Adherence means an optimal following of a treatment according to prescription.

Plasma viral load (PVL)

This is a measure of the quantity of HIV RNA levels in the plasma component of blood. Different studies have used various cut-offs for undetectable viral load: < 500 copies/ml,^[23] < 400 copies/ml,^[8] < 80 copies/ml^[57] and < 50 copies/ml^[27] depending on the sensitivity of the laboratory test used^[58]. In this study viral load < 50 copies/ml is termed undetectable and viral load \geq 50 copies/ml is detectable as according to the laboratory results in the study site. Periodic monitoring of PVL is important to promptly identify treatment failure, with a typical goal of achieving a 1- to 2-log reduction within four to eight weeks (e.g., from 5,000 copies per mL to 50 copies per mL).^[59]

Antiretroviral drugs - These are drugs used solely for the treatment of HIV infection.

Basically there are three classes of those commonly prescribed in the study clinic:

Nucleoside reverse transcriptase inhibitors (NRTIs)

- Didanosine (Videx®, Videx® EC) - DDI
- Lamivudine (Epivir®) - 3TC
- Stavudine (Zerit®, Zerit XR®) - D4T
- Zidovudine (Retrovir®) - AZT

Non-nucleoside reverse transcriptase (NNRTIs)

- Efavirenz (Sustiva®) - EFV,

- Nevirapine (Viramune®) - NVP
- Protease inhibitors (PIs)
- Lopinavir/ritonavir (Kaletra®) - LVP/r