Antiretroviral adherence and virological outcomes in HIV-positive patients in Ugu district, KwaZulu-Natal province

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Adherence to antiretroviral therapy is crucial to ensure viral suppression. In the scientific community it is widely accepted that an adherence level of at least 90% is necessary to achieve viral suppression. This study uses pharmacy refill records to describe antiretroviral adherence in HIV-positive patients in Ugu District, KwaZulu-Natal, South Africa and to describe pharmacy refill records as reliable monitoring method of antiretroviral therapy. In total, 61 patients’ records were reviewed. Overall, 50 (82%) of the patients achieved an optimum adherence level of at least 90%, whereas 19 (38%) of these patients did not show any related viral suppression. A statistically significant relationship between adherence and viral suppression was not demonstrated. Therefore, pharmacy refill records cannot be recommended as an alternative method of monitoring response to antiretroviral therapy, but laboratory tests including CD4 cell count and or viral load must be combined with the pharmacy refill method for monitoring of antiretroviral therapy in HIV-positive patients.

Keywords: adherence, antiretroviral therapy; pharmacy refill records; viral suppression; HIV-positive patients.

Introduction

Worldwide, the number of people newly infected with human immunodeficiency virus (HIV) continues to decline (United Nations Programme on HIV/AIDS (UNAIDS) 2012). There were 2.3 (1.9–2.7) million new HIV infections globally in 2012, showing a 33% decline in the number of new infections from 3.4 (3.1–3.7) million in 2001 (UNAIDS, 2013). Also, the annual number of people dying from AIDS-related causes declined by at least 50% from 2005 to 2011 because of scaled-up antiretroviral therapy and the steady decline in HIV incidence since the peak in 1997. As programmatic scale-up has continued, health gains have accelerated and the number of life-years saved by antiretroviral therapy in sub-Saharan Africa quadrupled in the last four years (UNAIDS, 2012). In addition to the effects on acquired immune deficiency syndrome (AIDS) mortality and overall HIV prevalence, it is believed that improved treatment access could help to lower HIV incidence by reducing the viral load at the individual and community level (Centres for Disease Control and Prevention (CDC), 2013).

Antiretroviral therapy (ART) aims to reduce and sustain plasma viral load levels to below the level of detectable limit of the assay. The sustained inhibition of viral replication results in partial reconstitution of the immune system in most patients, substantially reducing the risk of clinical disease progression and death (Adler, Edwards, Miller, Sethi, & Williamset, 2012). Adherence to antiretroviral therapy is crucial to ensure viral suppression, and decrease. The best biological marker of adherence is an undetectable viral load in patients on ART (Meintjes et al., 2012). In the scientific community, it is widely accepted that an adherence level of at least 90% is necessary to suppress the virus sufficiently to avoid the risk of mutation and to prevent the development of drug resistant strains and drug failure (Van Dyk, 2013). Improving the ability of providers to access adherence is essential for routine care of HIV-infected patients, especially in settings where viral load monitoring is limited.

Statement of the research problem

The South African antiretroviral treatment guidelines recommend monitoring viral load at six months after starting ART, one year and then annually, to identify treatment failures and problems with adherence (Statistics South Africa, 2013). The researchers identified that despite standardised and supportive policy, plasma viral load measurements are not promptly done for HIV-positive patients on ART, which could lead to the emergence of drug resistance and result in therapeutic failure. Thus the need for an alternative strategy method for monitoring the response to antiretroviral therapy in HIV-positive patients is imperative. Based on the above statement, the Provincial Department of Health in KwaZulu-Natal came up with the pharmacy refill system as a way to monitor ART adherence. This study looked and evaluated the efficacy of this new system of monitoring adherence to ART (Statistics South Africa, 2013).

Research purpose

The purpose of this study was to describe antiretroviral adherence in HIV-positive patients using pharmacy refill records and to describe pharmacy refill records as an alternative method of monitoring response to antiretroviral therapy.
Research objectives
The objectives for this study are to
• describe adherence to antiretroviral therapy by HIV-positive patients in Ugu district
• establish if pharmacy refill records are a reliable monitoring method of HIV-positive patients on antiretroviral therapy.

Research questions
The study sought the answer the following questions:
• To what extent do HIV-positive patients in Ugu District adhere to ART?
• Can pharmacy refill records be used as a reliable method of monitoring patients adherence to antiretroviral therapy?

Significance of the study
The findings will help specifically in the clinical practice to achieve the following:
• To assess the response to antiretroviral therapy by using a very simple measure of adherence, namely pharmacy refill for clinics that do not have CD4 counts or viral load monitoring capabilities.
• For clinics to be able to perform viral load assessment in all patients routinely. Adherence monitoring using pharmacy refill could guide decision-making on timing of these tests.
• For clinics that are unable to perform routine viral load measurement, the findings of this study will help to recommend the use of pharmacy refill as practical monitoring tool for early identification of patients at high risk of virological failure.

Research design and method
The research design is the overall plan for obtaining answers to the questions being studied and for handling some of the difficulties encountered during the research process. A design is the blueprint for conducting a study that maximises control over factors that could interfere with the validity of the findings (Polit & Beck, 2008; Burns & Grove, 2009). The researcher used a cohort study, which was quantitative, retrospective and descriptive in nature.

Quantitative research is a formal, objective, systematic process in which numerical data are used to obtain information about the world (Burns & Grove, 2009). Descriptive research refers to research that has as its main objective the accurate portrayal of the characteristics of persons, situations, or groups, and/or the frequency with which certain phenomena occur (Polit & Beck, 2008). Most importantly, the purpose of descriptive research is to explore and describe phenomena in real-life situations. In addition, this approach is used to generate new knowledge about concepts or topics about which limited or no research has been conducted (Burns & Grove, 2009). Retrospective design involves collecting data on an outcome occurring in the present, and then linking it retrospectively to antecedents or determinants occurring in the past (Polit & Beck, 2008).

Baseline demographic data, medical records on file, HIV viral load measurements as well as pharmacy refill records of HIV-positive patients who were initiated on ART between January 2011 and December 2012 were retrieved from the hospital’ records. Therefore, the data collected were used to measure the adherence to antiretroviral therapy by HIV-positive patients.

This study systematically and objectively reviewed viral load measurements of HIV-positive patients who have been on ART and their pharmacy refill records in order to describe antiretroviral adherence in HIV-positive patients and to determine the ability of pharmacy refill adherence to detect virological outcomes.

Research setting
The researchers conducted the study at one of the district hospitals in Ugu Health District found in the lower south coast of the province of KwaZulu-Natal in South Africa. The district provides health service to the population using the primary health care approach through the district health system and this is done at all levels of care. The Ugu district has three district hospitals, one regional hospital, one specialised hospital, two community health centres, 56 fixed clinics (including three gateway clinics) and 15 mobile clinics. The hospital where the study was conducted had about 1 987 patients who were still attending the institution for routine check-up and collection of antiretroviral drugs (ARV) at the end of December 2012.

Research population and sampling
The population is all the elements (individuals, objects, or substances) that meet certain criteria for inclusion in a given universe (Burns & Grove, 2009). The population for this study were the records of HIV-positive patients who attended designated district hospital for antiretroviral therapy between January 2011 and December 2012, and that met the eligibility criteria.

Sampling is a process of selecting subjects, events, behaviours, or elements for participation in a study (Burns & Grove, 2009). A sample is a subset of the population that is selected for a particular study, and sampling defines the process for selecting a group of people, events, behaviours, or other elements with which to conduct a study (Burns & Grove, 2009). The sampling plan specifies in advance how the sample will be selected and recruited, and how many subjects there will be (Polit & Beck, 2008).

Probability sampling design using systematic sampling technique was used to select every 10th patients’ records that meet the following criteria: 18 years and older, had completed at least 12 months of treatment and had at least two viral load measurements recorded after initiation of antiretroviral therapy (Polit & Beck, 2008). The medical records on file, HIV viral load measurements as well as pharmacy refill records were utilised as data sources of information for the study.

Data collection instrument
Quantitative researchers typically develop a detailed data collection plan; researchers often use formal data collection instruments (Polit & Beck, 2008). The gathering of information to address a research problem was done by using a checklist as data collection instrument. It was developed by the researchers for recording the variables related to patient demographic information, medical information, and pharmacy refill records. The instrument used was not adapted from any previously published literature.
Ethical considerations for this study
Permission to conduct this study was granted by the Higher Degrees Committee of the University of South Africa (UNISA). Further permission was granted by the Provincial Department of Health KwaZulu-Natal. The hospital where the records accessed are kept also gave permission for this study to be conducted.

Data collection
In quantitative research, data collection involves obtaining numerical data to address the research objectives, questions, or hypotheses (Burns & Grove, 2009). Data were collected by the researchers and the field workers using the checklist for recording of patient demographic data, clinical data and pharmacy drug information retrieved from patient’s records.

Data analysis
Data analysis is defined as the systematic organisation and synthesis of research data (Polit & Beck, 2008). Analysis of the data was carried out by using the Statistical Package for Social Sciences (SPSS) for Windows (Version 17), and a statistician assisted the researcher in analysing and interpreting collected data.

Descriptive statistics were used to describe key research variables and summarise sample characteristics in terms of frequency distribution, measures of central tendency and measures of variability. Once these features were known, the researchers used bivariate descriptive statistics to describe the relationship between antiretroviral adherence and virological outcomes.

Findings
A total of 61 (30.8%) records of HIV-positive patients who met the inclusion criteria were reviewed for this study. Out of 198 (100%) records of patients selected, 137 (69.2%) records were not included because they did not meet the above set criteria. Out of 61 (100%) of patients’ records reviewed, about 41 (67.2%) were initiated on antiretroviral therapy in year 2011, while 20 (32.8%) were initiated in year 2012.

Gender distribution (n = 61)
Table 1 shows that there were more females (33 or 54.1%) than males (28 or 45.9%) living with HIV. This confirms the inequalities between men and women that are created and reinforced by gender roles, typically leaving women especially vulnerable to HIV infection. According to Van Dyk (2013), women are more likely than men to become infected with HIV during unprotected vaginal intercourse. There are various biological, cultural, and social reasons which make women more susceptible to HIV infection than men. As the recipients of semen, they are exposed to semen for a longer time. They also have a larger surface area of mucosa (the thin lining of the vagina and cervix) exposed to the partner’s secretions during sexual intercourse. Apart from their biological vulnerability, women become more vulnerable in societies in which they are seen as having lower status than men, which makes them dangerously vulnerable in sexual relationships (Van Dyk, 2013).

The findings of this study are supported by the previous studies which found that in South Africa, just over 51% (27.08 million) of the population are females and the ratio of new female infections to male for those aged 15 to 49 was 1.5 by 2013 (El-Khatib et al., 2011; Statistics SA, 2013).

Age in years (patients)
Most records of patients reviewed showed that 22 (36.1%) were aged between 30 and 34 years old. The key age group of adults aged between 20 and 49 years represented the majority of patients, with about 57 (93.4%); among these 31 (54.4%) were females and 26 (45.6%) were males. This shows that there are higher HIV infection rates among young and working class women especially those aged between 20 and 49 years compared to young men.

The finding of this study correlate with the evidence from South African studies which show that some gender norms related to masculinity encourage men to have more sexual partners and older men to have sexual relations with much younger women. In addition, this contributes to higher HIV infection rates among young and working class women, especially those aged between 15 and 49 years compared to young men (Mutinta, Gow, George, Kunda & Ojteg, 2011).

Marital status (n = 61)
Table 2 shows that about 37 (60.7%) patients were single while 24 (39.9%) were married. This shows that in relation to the marital status and HIV infection, being single amplifies the risk of getting infected with HIV because these individuals are likely to be engaged in many risk-taking behaviours including casual sex, multiple and concurrent sexual partnership and failure to use condoms during sex. This finding agrees with a study done in Zimbabwe which found that being single was associated with HIV infection (Ministry of Health and Child Care, 2014). In addition, Shisana et al. (2014) found that in South Africa HIV infection varies considerably by marital status. Those that are married are less likely to be HIV positive compared to any other reported marital status.

Employment status
Figure 1 depicts that about 72% (44) of all patients whose records were reviewed showed that they were unemployed, with about 25 (56.8%) being females and 19 (43.8%) being males. This finding suggests that the socio-demographic context in which people live highly influences the individual

| Gender | Frequency (n) | Percentage |
|--------|---------------|------------|
| Female | 33            | 54.1       |
| Male   | 28            | 45.9       |
| Total  | 61            | 100.0      |

| Marital status | Frequency (n) | Percentage |
|----------------|---------------|------------|
| Single         | 37            | 60.7       |
| Married        | 24            | 39.3       |
| Total          | 61            | 100.0      |
risk of exposure to HIV-infection. In addition, this finding agrees with a study done by Blattman (2011) which found that being HIV positive is associated with increase in the likelihood of being unemployed.

McLaren (2011) found that in South Africa, individuals with HIV tend to be unemployed, and unemployed people are more likely to be HIV positive. Furthermore, Levinsohn et al. (2011) found that being HIV-positive is associated with a 6 to 7% point increase in the likelihood of being unemployed.

 Disclosure of HIV status
Table 3 shows that about 56 (92%) of patients had disclosed their HIV status to someone and only 4 (7%) had not disclosed their HIV status. This disclosure of the status to a confidant could improve adherence as patients will be reminded by the confidants. Sendagala (2010) noted that, having disclosed their status, people living with HIV would probably adhere to the treatment as they will get both physical and psychological support. In addition, disclosure of HIV status and support by treatment partner or peer counsellor have been shown to have a great impact on adherence (Meintjes et al, 2012).

 Adherence level
Of the 61 records reviewed for this study, overall 50 (81.9%) of the patients achieved an optimum adherence level of 90% and above, while 6 (9.9%) reached an adherence level between 80 and 89%, and 5 (8.2%) achieved an adherence level of between 70 and 79%. The mean the average adherence level was 94.8%, ranging from 71% to 100% (Figure 2).

Table 3: HIV status disclosure by participants

| HIV disclosure | Frequency (n) | Percentage |
|----------------|--------------|------------|
| No answer      | 1            | 1.6        |
| Disclosed      | 56           | 91.8       |
| Not disclosed  | 4            | 6.6        |
| Total          | 61           | 100.0      |

Figure 1: Employment status of participants

Figure 2: Adherence level of participants

In this study, adherence is measured as the consistent collection of antiretroviral medications from the pharmacy at prescribed intervals. It is assumed that if patients collect their medication, then they are likely to take the medication. Adherence level is expressed as a percentage of the number of times they should have collected medication over the period of 12 months or more.

Adherence to antiretroviral therapy results in suppression in plasma viral load combined with increase in CD4 count. Therefore, the treatment adherence of antiretroviral should be monitored by checking the plasma viral load and CD4 counts measurement.

In this study, the mean CD4 T-cell count at antiretroviral therapy initiation was 250.67 cells/mm³. About half (31 or 50%) of patients had severe immune suppression with recorded CD4 T-cell counts lower than 200 cells/mm³, while 19 (31%) had CD4 T-cell counts of 200–349 cells/mm³. After 12 months of antiretroviral therapy, the mean CD4 T-cell count was 347.56 cells/mm³ with 19 (31%) of patients recording CD4 T-cell counts of lower than 200 cells/mm³ and 15 (25%) patients achieved a CD4 T-cell count of more than 500 cells/mm³. Thirty-seven (60%) achieved a sustained viral load of less than 50 copies/ml 12 months after commencing antiretroviral therapy.

The finding in this study shows that although overall 50 (82%) of patients had adherence levels of 90 or above, only 15 (25%) patients achieved immunological recovery with CD4 T-cell counts of more than 500 cells/mm³ while 19 (31%) still had severe immune suppression, with lower CD4 T-cell counts of less than 200 cells/mm³. Only 37 (60.7%) patients achieved a sustained viral load less than 50 copies/ml after 12 months of antiretroviral therapy. However, the mean CD4 T-cell count increased from 250.67 cells/mm³ to 347.56 cells/mm³.

These findings suggest that patients may not take all collected medications or that they take them in not prescribed amounts or off the prescribed schedule, or fail to match the dose with food as directed. In addition, patients may share or sell their own medications and may hoard medications to avoid discrimination and stigma in the community/family. These findings are supported by the
study done by Zaragoza-Macias et al. (2010), which found that the relationship between refills and actual ingestion of medications is not clear and it is therefore difficult to measure adherence in the outpatient setting accurately and correctly. According to literature, antiretroviral therapy reduces the HIV viral load as much as possible, preferably to undetectable levels for as long as possible. By doing so, the CD4 T-cell lymphocyte count usually increases progressively. Typically, the CD4 count increases rapidly by approximately 50 to 100 cells/mm$^3$/year (Van Dyk, 2013; Meintjes et al., 2012). In addition, CD4 responses are highly variable and may fail to increase despite virological suppression and a small proportion of patients who start antiretroviral therapy with a very high viral load may not be fully suppressed despite being adherent to the treatment (Meintjes et al., 2012; Wilson et al., 2010).

**Discussion**

**Relationship of adherence level to virological suppression**

The findings of the study showed that about 50 (82%) of patients achieved at least 90% of treatment collection adherence. However, 19 (38%) of these patients did not show any related viral suppression. From the results, an examination of the relationship between adherence and virological suppression shows that from the 61 records of patients reviewed, there were 37 (60.7%) who achieved virological suppression and 24 (39.3%) who did not achieve virological suppression. These findings show that most patients achieved a viral load measurement of less than 50 copies/ml.

Most patients (50 or 82%) had an adherence level of at least 90%, while 11 (18%) patients did not achieve an adherence level of 90% or more. Among those who achieved adherence levels of at least 90%, only 31 (62%) patients achieved a viral load measurement of less than 50 copies/ml and 19 (38%) did not achieve viral load measurements of less than 50 copies/ml within 12 months of commencing antiretroviral therapy. However, six patients that did not have an adherence level of at least 90% also achieved a viral load of less than 50 copies/ml within 12 months of treatment.

These findings are supported by study done by Zaragoza-Macias et al. (2010) and study by Henderson, Hindman, Johnson, Valuck, & Kiser (2011, p. 221), which showed that virological suppression was associated with adherence with medication pick up of more than 90%. In addition, Nachega et al. (2007) identified a statistically significant dose-response relationship between viral load suppression and pharmacy claim adherence across all adherence strata. They found that every 10% increase in adherence beyond 50% was associated with a mean absolute increase of 0.10 in the proportion of patients with sustained virologic suppression ($p < 0.001$). Even though Sayles et al. (2012) found that despite high antiretroviral therapy (ART) coverage rates, a substantial portion of people living with HIV taking ART were not achieving HIV viral load suppression, which leads to suboptimal treatment outcomes. In contrast, several studies using pharmacy-based adherence measures with stratified adherence estimates failed to detect a threshold to achieve virological suppression (McMahon et al., 2011).

The relationship between adherence level and virological suppression was investigated using bivariate statistical analysis and Pearson’s correlation coefficient ($r$) was calculated. A statistically significant association between adherence and viral suppression was not demonstrated ($r = 0.094$, $p > 0.05$). Thus, there is no relationship between adherence and virological suppression. This finding agrees with a study done by Sayles et al. (2012), which found no association between taking antiretroviral medication and achieving HIV viral load suppression. However, there are some studies that have shown a relationship between adherence level and virological suppression.

**Pharmacy refill records adherence**

Antiretroviral medications work only if they are taken regularly every day for the rest of the life. Adherence refers to the willingness and ability of patients to follow health-related advice, take medication as prescribed, attend scheduled appointments, and complete recommended investigations (Kalichman, 2013; Moosa & Jeenah, 2012). Conversely, non-adherence to antiretroviral, evidenced as missed doses, is associated with incomplete viral suppression and the development of drug resistant virus that will eventually limit therapeutic options (Wilson et al., 2010).

In this study, the pharmacy refill records were used to measure adherence to antiretroviral by HIV positive patients in Ugu Health District. The method of using pharmacy refill records for estimation of adherence is related to the amount of drugs actually ingested by the patients. As discussed in this chapter, the relationship between collection of medications and actual ingestion of medications is difficult to establish. Saberi, Caswell, Amodio-Groton, and Alpert (2008) state that some advantages of utilising pharmacy refill records is that these data can easily be collected. They do not depend on patients’ self-reports and accurate recall, they are inexpensive to acquire, they allow for retrospective assessment and are readily obtainable from computerised records.

In addition, pharmacy-based adherence measures are ideally suited to monitoring adherence because they are objective and can be easily derived from data routinely collected for other purposes, such as clinical care, medication billing, fulfilment of legal requirements, or drug supply management (McMahon et al., 2011). In contrast, pharmacy refill records may overestimate actual pill taking if individuals discard or share pills. Therefore, estimated maximum possible adherence for this measurement methodology threaten the internal validity (Sattler, Lee, & Perri, 2013; McMahon et al, 2011).

In settings where frequent routine viral load monitoring is not available, pharmacy refill records can play an important role in monitoring individual and population level adherence to ART (McMahon et al., 2011). Ndubuka and Ehlers (2011) concluded that if single available measures such as pharmacy refill records could be correlated with laboratory tests, results for improved CD4 counts (indicating immunological recovery) and decreased viral load (indicating virological recovery) could be used as preliminary measures of adherence.

In this study, 50 (82%) patients achieved an adherence level of 90% or above, with a mean adherence level of
94.8%. In addition, the mean baseline CD4 counts at initiation of ART increased from 250.67 cells/mm$^3$ to 347.56 cells/mm$^3$ after 12 months of antiretroviral therapy, while only about 37 (60%) achieved undetectable viral load (below the detectable level of less than 50 copies/ml within 12 months of treatment. It can be suggested that all claimed medications were not ingested. Therefore, pharmacy refill records should be implemented with laboratory tests for monitoring of patients’ ART adherence. This is because it is difficult to predict who will not take claimed medications as directed. In addition, directly observed therapy (DOT) strategy should be also implemented for patients who have problems taking medications correctly.

**Conclusion**

In this study, the relationship between adherence to antiretroviral therapy using pharmacy refill records and virological suppression could not be determined. Multiple and varied means are more likely to identify patients with adherence problem than a single method. Therefore, pharmacy refill records cannot be recommended as an alternative method of monitoring response to antiretroviral therapy. However, pharmacy refill records as simple available measure of adherence must be combined with laboratory tests results, including CD4 cell count and or viral load measurement, to monitor response to antiretroviral therapy and for early identification of patients at high risk of virological failure.

Good adherence to ART and corresponding high rates of sustained virological suppression can be achieved in a resource-limited area with improvement in the ability of health care providers to assess adherence in routine care of HIV infected persons.

**Limitations**

There are several limitations to this study. Firstly, it is a retrospective cohort study in design and therefore reliance on record keeping was a major concern. This was due to the fact that some records were incomplete, and others did not have patients’ CD4 counts results. In some records it was also found that viral load measurements after 6 months of antiretroviral therapy initiation were not done. This led to the usage of a sample of only 61 records out of a possible cohort of 198. In addition, all participants were from only one population who lived in rural area. As a result, patients’ outcomes in this rural area may not be representative of those in urban areas. Moreover, the results of this study do not necessarily reflect practices in other settings and this may limit the generalisation of these findings.

Secondly, this study used pharmacy refill records, which do not reflect the dynamic nature of adherence. In addition, pharmacy refill records do not record the actual ingestion of medication, or the pattern of non-adherence (for example, frequency, duration). Therefore, there is an overestimation of the actual adherence because patients may not take all collected medication.

Thirdly, this study used hospital records as a source of information. Obtaining informed consent from participants for whom the records were reviewed was impracticable as most of the participants stayed far from the institution. Some of the participants did not have a proper physical address.

Forthly, the research results are only applicable to one public hospital where the data had been collected. Consequently, these results might not be generalised to other ART services in the province.

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