THE CORRELATION BETWEEN CD4 CELL COUNTS AND PHARMACY REFILL RECORDS IN NAMIBIA: A RETROSPECTIVE STUDY

Ehlers, V.J. (D Litt et Phil)  
University of South Africa  
Department of Health Studies

Tjipura, D.J. MPH (Master’s in Public Health) Graduate  
University of South Africa  
Department of Health Studies

Roos, J.H. (D Litt et Phil)  
University of South Africa  
Department of Health Studies  
Email: roosjh@unisa.ac.za.  
Corresponding author

ABSTRACT

Adherence rates of at least 95% are required for optimum viral suppression and the prevention of viral mutation of drug resistant HIV strains, measured by CD4 cell and viral load counts, especially at the beginning of highly active anti retroviral treatment (HAART). A quantitative, retrospective and descriptive research design was used to determine whether pharmacy refill records correlated with patients’ CD4 cell counts. The medical records of 176 adult patients were examined at a government hospital in Windhoek, Namibia. There was a weak positive relationship between CD4 cell counts and pharmacy refill records. The pharmacy refill records predicted CD4 cell counts to a limited extent, but should be used in combination with other adherence measurement tools, such as patients’ adherence reports, and where financially feasible, viral load counts.

KEYWORDS: adherence to HAART, anti-retroviral therapy (ART), CD4 cell counts, HIV/AIDS in Namibia, pharmacy refill records

INTRODUCTION AND LITERATURE REVIEW

During 1986 the first four cases of HIV/AIDS were reported in Namibia and by December 2003, the number of HIV/AIDS patients numbered 136 068. In 2004 Namibia’s HIV/AIDS prevalence was reported to be 19.7% and the prevalence rate at a government hospital in Windhoek, Namibia, where this study was conducted, was 22.0% (MoHSS, 2004:10). During 2005, HAART was introduced at this government hospital. HAART proved highly effective in clinical trials in decreasing HIV viral loads, even to undetect-
able levels, increasing the CD4 cell counts, and substantially reducing HIV-related morbidity and mortality rates (Fogarty, Roter, Larson, Burke, Gillespie & Levy, 2002:95). Adherence to HAART is crucial for the successful treatment of HIV infections and sustained viral control. Adherence rates of 95% or higher are required for optimum viral suppression in order to prevent viral mutation and thus drug resistance (Fairly, Pernama & Read, 2005:368; Jani, 2004:9; Saple, 2005). Plasma viral load is the test of choice used for monitoring the effectiveness of HAART in a specific patient in high income countries. However, as it is expensive, viral load tests are not routinely used in developing countries (Nachega, Hislop, Dowdy, Lo, Omer, Regensberg, Chaisson & Maartens, 2006:84).

In Namibia patients start taking HAART when their CD4 cell counts fall below 200 cells/mm³ or if they are clinically ill, deemed to be in the WHO HIV/AIDS stage 4. In Namibia CD4 cell counts are taken at baseline (prior to commencing HAART) and at six monthly intervals to test the effectiveness of HAART and/or detect adherence problems (MoHSS, 2003:7). Treatment effectiveness is associated with immunological recovery, evidenced by increases in CD4 counts. This study attempted to determine whether there was a relationship between adherence as determined by pharmacy refills and immunological recovery as reflected in the increased CD4 cell counts of patients on HAART at the participating government hospital in Windhoek, Namibia.

**Adherence**

In this study pharmacy adherence percentage was calculated by counting the number of refills during the preceding 12 months, dividing this number by 12 and then multiplying by 100. However, there is no universal definition of medication adherence. Adherence represents complex relationships among patient, provider and medication and is not necessarily a simple choice (Ostenberg & Blaschke, 2005). The main problem in studying adherence is that there is no universally acceptable measurement tool. In this study, adherence to HAART is defined as the regular monthly collection of prescribed HAART from the pharmacy. Fairly et al. (2005) compared long-term adherence to HAART as measured by self reports and pharmacy refill records in Melbourne, Australia. Pharmacy refill records identified about twice as many individuals to be non-adherent as had been identified with self reports (27% versus 14%). Pires, Ventura and Magdalena (2005) studied the correlation between patients’ pharmacy refill data and their viral responses. Over 90% adherence rates to pharmacy refills were associated with lower viral loads. Pharmacy refill records were used at the participating hospital to trace HAART defaulters and alert the other health care workers’ about potential defaulters. Pharmacy refill records might be valid indicators of HAART adherence in settings where other more labour intensive or expensive methods are impractical (Nachega et al., 2006:84).

While it is acknowledged that collecting HAART does not guarantee the actual swallow-
ing of these medicines, the regular collection of HAART indicates patients’ sustained responsibilities in maintaining access to their prescribed medicines. According to the WHO (2006:23), a review of 500 studies done over 50 years showed that adherence ranged from as low as 4.6% to 100% while only eight articles focused on HAART and the mean adherence in these studies was 88%. This was below the required adherence level of >95% to derive the maximum benefit from HAART (Paterson, Swindells, Mohr, Brester, Vergis, Squier, Wagener & Singh, 2000:27). According to the WHO (2006:29), the experience from Senegal was that 95% of patients had adherence levels exceeding 80% after one month of therapy but after 18 months, only 80% remained above that level. The 80% level of adherence would not be sufficient to prevent treatment failure nor the development of drug resistance, because the percentage of patients with undetectable viral loads fell from 80% to 59% over that period of time. Non-adherence is common among approximately half of the individuals treated with HAART (Ickovics & Meade, 2002:S98). According to Goudge, Ngoma and Schneider (2004:6), patients taking less than 85.0% of their HAART doses, have an 83.0% chance of viral failure. However, Paterson et al. (2000:27) maintain that missing 5.0% of the HAART doses impacts negatively on viral suppression. Premises have been put forward that more modern HAART drugs, such as PI-based regimens with ritonavir boosting or NNRTI-based regimens, could be effective with adherence rates below 95% (Bangsberg, Moss & Deeks, 2004:696; Gulick, 2006). No studies to this effect have been conducted in Namibia, where PI-based drugs are only prescribed in cases where the 1st line HAART regimens have failed.

No published studies could be identified that have estimated the magnitude of the problem of HAART non-adherence in Namibia, probably because HAART had been provided free of charge at Namibian government hospitals and clinics since 2005 and this study was conducted during 2006.

The role of adherence to HAART in HIV/AIDS

Without adequate adherence levels of at least 95%, HAART drug levels might not be maintained at sufficient concentrations to suppress HIV replications in infected cells nor to reduce the viral load (Chesney, 2000:S172). The transmission of HAART-resistant strains of HIV poses threats for individuals, communities and countries (Jani, 2004:17; Wu, Ammassari & Antinori, 2002:S96).

Friedland, Abdool-Karim, Abdool-Karim, Laloo, Jack, Gandhi and El Sadr (2004:S423) studied 20 patients using HAART through directly observed treatment in South Africa. The outcome indicated enhanced immunological and viral responses among the 17 patients who completed the study. They achieved a viral load of <50 copies/ml and a mean increase in CD4 cell counts of 148 cells/mm³. This supported other studies’ findings that adherence correlated with immunological (increased CD4 counts) and viral
(reduced viral load) responses (Ickovics & Meade, 2002; Palela, Delaney, Moorman, Loveless, Fuhrer, Satten, Aschman & Holmberg, 1998:853). A study done on 99 HIV patients using protease inhibitors (PI) in the USA (Paterson et al., 2000), reported that only 22% of patients with adherence of 95% or greater had virological failure, while 61% of patients with adherence between levels between 80% and 94% had viral failure, where viral failure was defined as the detection of a viral load of more than 400 copies/ml. Clinical outcomes, excluding increased CD4 cell counts and reduced viral loads, include weight gain, decreased numbers of opportunistic infections, and enhanced general well-being. Fairley et al. (2005) in Australia, and Pires et al. (2005) in Portugal, reported that pharmacy refill records provided simple and useful assessments of HAART adherence where more than 90.0% pharmacy refill adherence rates were associated with decreased viral loads and increased CD4 cell counts.

**Definitions of key concepts**

**Adherence:** It refers to the ability of the person living with HIV/AIDS to be involved in choosing, starting, managing and maintaining a given therapeutic combination medication regimen to control viral (HIV) replication and improve immune function (Jani, 2004:3). Effective use of ARVs requires an adherence of at least 95%. In this study adherence is measured as the regular and consistent collection of ARVs from the pharmacy.

**Adult patient:** Any patient 18 years and older who is HIV positive and on HAART at the participating hospital.

**Anti-retroviral drugs:** These are medications that are used in the treatment of infections caused by HIV. There are different classes of anti-retroviral drugs and they act at different stages of the HIV life cycle (WHO, 2006:24).

**CD4 cell:** These are immune system cells which fight infections.

**CD4 cell counts:** This is one of the useful and reliable methods to assess if an HIV positive patient should start ART as well as assessing the effectiveness of ART. An increase of more than 100 CD4 cells/mm$^3$ during the first six to twelve months of treatment is typically seen in adherent ARV treatment-naïve patients, implying that they were using ART for the first time (MoHSS, 2003:13).

**Highly Active Anti-retroviral Therapy (HAART):** HIV/AIDS treatment containing three or more anti-HIV medicines.

**Treatment-experienced patients:** Patients who have been receiving HAART for more than six months. In this study only patients who had been using ARVs for at least twelve months were included.
**Treatment naïve patients:** Patients who have been started on HAART for the first time and have not been on HAART for at least six months.

**Viral load:** This is the term used to describe the amount of HIV in the blood. If there is an increase of the virus in the blood, then the patient loses CD4 T-cells. The result of a viral load test is described as the number of copies of HIV RNA per millilitre (copies/ml). Usually, 10,000 copies/ml or less is considered to be low, and 50,000 copies/ml or more is considered to be high (Aidsmap, 2004).

**PROBLEM STATEMENT**

Patients can get free HAART in Namibia. Adherence rates of 95% are required to derive benefits from HAART such as enhanced general well-being, increased CD4 cell counts and reduced viral load counts. Sub-optimal adherence to HAART can give rise to the development of HAART-resistant HIV strains, requiring more expensive medications with more side-effects than the first-line HAART regimens. Determining CD4 cell and viral load counts to measuring HAART adherence in resource-limited countries poses problems due to lack of finances, resources and laboratories. Therefore it is essential that affordable HAART adherence measures should be investigated.

The research question posed for this study was: Can pharmacy refill records be used to predict patients’ CD4 cell counts?

**RESEARCH METHOD**

A quantitative, retrospective and descriptive study design was used to analyse available quantifiable data to determine whether any relationship existed between adherence to HAART, as measured by pharmacy refill records and the patients’ CD4 cell counts. For the purpose of this study each patient’s pharmacy refill percentage was calculated by counting the number of times when HAART had been collected during the preceding 12 months, dividing the number of refills by 12 and multiplying this answer by 100. This method did not account for patients who might have collected their HAART early or late. The point of concern was whether the specific patient had collected HAART every month during the preceding year.

**Research population and sample**

The medical records of the population of 308 patients who had started using HAART during February and March 2005 were reviewed to select those who met the inclusion criteria: being 18 years of age or older, on HAART for at least 12 months with at least
two reported CD4 counts. A total of 176 patients’ records met these criteria and formed the study sample.

Research instrument
Data from the HAART dispensing tool and patients’ medical records were transcribed onto a checklist. Aspects recorded on the checklist included the patient’s HAART reference number, age, gender, employment status, tuberculosis (TB) treatment, baseline CD4 cell count when HAART was commenced and subsequent CD4 cell count after six months’ treatment, date of commencing HAART and the type of HAART, and a comparison of the CD4 count with the pharmacy refill adherence percentage.

The checklist was pre-tested on ten patients’ records, which were excluded from the actual study, before the data collection commenced from the population of 176 patients’ records. Problems encountered during the pre-testing phase included that patients’ places of residence were always indicated as “urban”. Consequently this question was deleted from the checklist. The results obtained during the pretest were similar to those obtained during the actual data collection phase.

Validity and reliability
The checklist’s validity was tested based on face validity, content validity and construct validity. Content validity referred to the collection of data relevant to the variable being investigated, namely the patients’ records of their collection of HAART from the pharmacy at prescribed intervals. Face validity was obtained by transcribing the data from the patient’s record onto the checklist. Construct validity is based on the reasonable relationship among variables (Babbie & Mouton, 2001). The checklist had construct validity because it only measured correlations between individual patients’ pharmacy refill records and their CD4 counts.

Each patient’s HAART number from the medical file and the HAART pharmacy number were recorded. The collected data could be verified for accuracy by comparing the transcribed data on the checklist with that from the two data sources.

The outcome measure of interest was the correlation between the patient’s consistency of pharmacy refills and his/her CD4 cell count after using HAART for at least 12 months. Measurements might have been affected by poor record keeping as routinely collected data were used; recording errors; patients with HAART-resistant HIV; patients with poor absorption due to gastrointestinal diseases; drug-drug interactions and patients with high baseline CD4 cell counts.
Data collection and analysis

The researcher transcribed data from the ARV dispensing tool and patients’ medical records onto the checklist designed specifically for the study, during April 2007. The services of a statistician from the University of Namibia were obtained to analyse the data using the Statistical Package for the Social Sciences (SPSS) version 13.

ETHICAL CONSIDERATIONS

Approval had been granted by the permanent secretary of Namibia’s Ministry of Health and Social Services, as well as by the Research and Ethics Committee of the Department of Health Studies of the University of South Africa (Unisa), before data collection commenced.

Though the names of the patients were reflected on the patients’ medical records, the researcher only recorded the ART newly allocated unique reference numbers. From the collected data, neither the researcher nor any other person could identify a specific patient.

RESEARCH RESULTS

Demographics

The 176 patients’ ages ranged from 19 to 62, and the average age was 35.4 years. There were more females (52.8%; n=93) than males (47.2%; n=83). Out of the 176 HAART patients, 28 (15.9%) had never attended school, 56 (31.8%) had completed primary and 84 (47.7%) had completed secondary/high school. This information was absent from 6 (3.4%) patients’ files. Only 51 (29.0%) of the HAART patients were employed, 11 (6.3%) were reportedly self-employed, 78 (44.3%) were unemployed and 22 (12.5%) of the records did not contain this information.

According to the patients’ records only 4 (2.2%) used both TB drugs and HAART. This finding is in accordance with the MoHSS (2003) guidelines recommending that TB treatment should be completed prior to the commencement of HAART whenever possible, to reduce the pill burden and the potential side-effects from the combination of TB and HAART drugs.

Only 6 (3.4%) of the patients were on second line HAART, comprising 2 NRTIs and 1 PI, while 170 (96.6%) were on first line HAART, comprising 2 NRTIs and 1 NNRTI. The first line HAART is much cheaper and has fewer side-effects. So few patients might have been on second line HAART, because HAART had only been instituted during 2005 and the data collection was done during 2006.
Adherence levels

Of the 176 patients 64.2% (n=113) had a reported adherence level (as measured by pharmacy refill records) of >95% while 35.8% (n=63) had an adherence level of <95%. Of the 113 patients whose pharmacy refill adherence levels were 95% or higher, 53.1% (n=60) were females while 46.9% (n=53) were males. This finding was not statistically significant at the 5% level (p=0.04). The mean adherence level was 96.4% ranging from 75% to 100%.

Most adherent patients were in the age group 35-39 and at the 5% (p=0.05), age was found to be significant (p=0.1). No correlation was found between gender, education level, employment status and adherence level.

CD4 cell counts

The baseline CD4 counts ranged from 6 to 784, with an average count of 167.8 cells/mm³ and with a standard deviation of 105.5. Twelve months after treatment the lowest CD4 count was 80 cells/mm³ while the highest was 2000 cells/mm³.

These statistics are interpreted as a mean gain of 175.1 CD4 cells/mm³ for all 176 patients. There was a positive relationship between the pre-treatment cell count and the post-treatment cell count, implying that the higher the pre-treatment cell count, the higher the post-treatment cell count. The regression line of ‘most recent’ cell count on ‘baseline’ cell count is \( y = 0.679x + 228.993 \), where ‘y’ is ‘most recent’ cell count and ‘x’ is ‘baseline’ cell count. The gradient of the regression line is 0.679, implying that when the ‘baseline’ CD4 cell count goes up by one the ‘most recent’ cell count goes up by 0.679. The y-intercept is 228.993 implying that a patient with a ‘baseline’ CD4 cell count of zero would be expected to have ‘most recent’ cell count of 228.993. Although the relationship between the two cell counts is weak, both coefficients of the regression line are statistically significant (p=0.0 in both cases).

Correlation between adherence and CD4 counts

<table>
<thead>
<tr>
<th>Adherence</th>
<th>MeanCD4</th>
<th>No of patients</th>
<th>Standard deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adherent</td>
<td>362.1</td>
<td>113</td>
<td>274.5</td>
</tr>
<tr>
<td>Non-adherent</td>
<td>308.8</td>
<td>63</td>
<td>149.4</td>
</tr>
<tr>
<td>TOTAL</td>
<td>343.0</td>
<td>176</td>
<td>238.3</td>
</tr>
</tbody>
</table>

From the 176 patients, 113 adhered to their HAART regimens and 87 of those achieved a CD4 cell count of equal to or more than 200 cells/mm³ within one year of commenc-
ing HAART. This means that 64.2% of patients were adherent and 77.0% of them had achieved immunological recovery (CD4 Cell count of equal to or more than 200 cells/mm³). This establishes a positive relationship between adherence and increasing CD4 cell counts. The baseline mean CD4 count was 167.8 cells/mm³. Therefore there was a gain of an average of 175.3 cells/mm³.

![Figure 1: Relationship of adherence to most recent CD4 cell count.](image)

**Figure 1:** Relationship of adherence to most recent CD4 cell count.

Figure 1 depicts the ability of the pharmacy refill adherence records to predict CD4 cell counts of equal to or more than 200 cells/mm³. The tool was able to predict that 87.0% of the patients, who adhered to HAART, achieved immune recovery. However, 44.0% of patients in the non-adherent group also attained CD4 cell counts of equal to or greater than 200 cells/mm³. A weak positive relationship existed between adherence and CD4 cell counts. The mean CD4 cell counts increase between baseline and most recent CD4 cell counts was 175.1 cells/mm³ (n=176). However, the mean CD4 cell counts between the adherent (362.1) and non-adherent (308.8) groups at 12 months showed no significant difference.

**DISCUSSION OF RESEARCH RESULTS**

The relationship between pharmacy refills and actual ingestion of medications is not clear and it is therefore difficult to measure adherence in the outpatient setting accurately and correctly. The sensitivity for adherence scores predicting CD4 cell counts equal to or greater than 200 cells/mm³ is 66.4%. This sensitivity value appears promising considering that pharmacy refills do not necessarily measure the actual ingestion of pills. The specificity translates to a proportion of CD4 cell count below 200 cells/mm³. The specificity value of the instrument was 39.6% for CD4 cell count. This is a low
value and therefore confirms that the adherence measurement methodology may not be able to guide clinicians to detect immunological failure during the early stages. The positive predictive value of the pharmacy refill was 77.0% for predicting the percentage of CD4 cell counts that are equal to or greater than 200 cells/mm$^3$ and that are truly equal to or truly greater than 200 cells/mm$^3$. The pharmacy refill records produced a negative predictive value of 30.0% for predicting the percentage of CD4 cell counts less than 200 cells/mm$^3$ and which were truly less than 200 cells/mm$^3$. This percentage is low and more reliable predictions could be obtained by using this method in conjunction with other more reliable adherence measurement methods.

The changes in the CD4 cell count results were used only as a measure of the validity of the adherence measurement instrument in this study because other studies such as Paterson et al. (2000:23) already found that immunological and virological failure are associated with non-adherence. Pharmacy refill records can be used to monitor adherence, but because this relationship is weak it is advisable to use this adherence measurement methodology in combination with other methods to predict immunological responses.

LIMITATIONS

The research results are only applicable to one public hospital where the data had been collected, and might not be generalisable to the other HAART services in Namibia. Incomplete records, without patients’ CD4 counts and without information about their pharmacy refills, necessitated using a sample of only 176 records out of a possible cohort of 306, amounting to 57.5%. Most of the patients who received HAART at the participating public hospital were unemployed. Working patients, belonging to medical aid schemes, obtained their HAART from private facilities. Consequently these results might not be generalised to HAART patients from the private health sector.

RECOMMENDATIONS

Commonly used adherence measurement methodologies (pill counts and patients’ self-reported adherence levels) should be used in combination with the pharmacy refill records to enhance the validity of these findings. The relationship between HAART adherence and other clinical outcomes, such as morbidity and mortality, needs to be established.

Future researchers could duplicate this study in other public health facilities; investigate the potential correlation between CD4 cell counts and adherence in the private sector using medical aid scheme records for HAART refills and laboratory results; investigate reasons for HAART patients’ non-adherence to their treatment regimens; determine why some non-adherent patients might have increased CD4 cell count results, and why
some adherent patients might have decreased CD4 cell count results. Where possible these CD4 cell counts should be correlated with viral load results.

CONCLUSIONS

Patients who had adherence levels of >95%, as measured through the pharmacy refill records, had increased CD4 cell counts from baseline to 12 months’ HAART. There is a positive but weak relationship between adherence (as measured by pharmacy refill records) and CD4 cell counts equal to or more than 200 cells/mm$^3$. The increase in the patients’ mean CD4 cell counts, after being on HAART for twelve months, to 343.1 cells/mm$^3$, indicate positive HAART outcomes. However, some non-adherent patients’ CD4 cell counts also exceeded 200 cells/mm$^3$ after being on HAART for 12 months. The pharmacy refill adherence measurement tool had a sensitivity of 66.4% and identified some patients who were not adherent and who had CD4 cell counts of equal to or greater than 200 cells/mm$^3$. As no viral load test results were available, the correlation of these patients’ viral loads with their apparently paradoxical CD4 cell counts could not be determined. Pharmacy refill records provided some indication of HAART adherence in the study setting where other more reliable and expensive adherence measurement methodologies were unavailable. Pharmacy refill records may be a simple and effective tool for monitoring adherence in a large HAART programme, in resource-limited settings, but should be augmented with periodic CD4 cell and viral load assessments.

REFERENCES


WHO – see World Health Organization


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