WHO STAGING, ADHERENCE TO HAART AND ABNORMAL CERVICAL SMEARS AMONGST HIV-INFECTED WOMEN ATTENDING DR YUSUF DADOO HOSPITAL.

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in partial fulfilment of the requirements for the degree of Master of Medicine in Family Medicine.
DECLARATION

I, Appolinaire Ciamalenga Katumba, declare that this research report is my own work. It is submitted for the degree of Master in Family Medicine to the University of the Witwatersrand, Johannesburg. It has not been submitted for any degree or examination at this or any other university.

........................................

15th April 2014

Student No: 521774
DEDICATION

In Memory of my beloved father

Vincent de Paul Mubenga Katumba wa Lukusa

1934-2007

May the Roses bloom upon your cross
ABSTRACT

Introduction

South Africa has more people living with HIV than any other country in the world.\textsuperscript{1} Women infected with HIV have a high risk in the development of cervical dysplasia and cancer of the cervix more so than women who are not infected.\textsuperscript{2,3}

Methods

A cross-sectional descriptive study was carried out by reviewing cervical smears of HIV positive women in a district hospital. Three hundred and ninety cervical Pap smears were classified according to the Bethesda system. Adherence was measured by the patient’s report and viral load. Data was collected through the use of self administered questionnaire and data capture sheet.

Results

The prevalence of abnormal Pap smears was 57 per cent and LSIL was the commonest abnormality seen (142/390, 36%). Eighty-four per cent (328/390) had stage 1 WHO-HIV classification. WHO stage 3 participants seemed to be three times more likely to have abnormal Pap smears than those with WHO stage 1 (OD 3.3, STD. error 1.70, p=0.018, 95% CI 1.23-9.04). Abnormal pap smears were seen more in participants with CD4 cell count $\leq$ 350 cells/$\mu$L as compared to participants with CD4 cell count $\geq$ 500 cells/$\mu$L { 122/172, (71.00 %) vs 48/117, (41.03%), p=0.000, 95% CI : 0.09-0.37}. Similarly, participants who did not use HAART had more abnormal results as compared to those who used HAART {42/60(70.00%) vs 180/330 (55.00%), p=0.028, 95% CI 0.28-0.93}. Adherence to HAART did not show any link with abnormal smears.

Conclusion

The more immune-suppressed a woman is, the higher the risk of developing cervical cancer precursors. The high risk group in this study was found to be the participants with the CD4
cell count of ≤ 350 cells/µL and the viral load ≥1000 copies/mm³. The self-reported adherence level did not show any impact.
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ABBREVIATIONS

AGUS: Atypical glandular cell of undetermined significance
ART: Antiretroviral treatment
ASCUS: Atypical squamous cells of undetermined significance
CDC: Center for disease control
CI: Confidence interval
CIN: Cervical intraepithelial neoplasia
ELISA: Enzyme-linked immunosorbent assay
HAART: Highly active antiretroviral therapy
HIV: Human immunodeficiency virus
HPV: Human papilloma virus
HSIL: High-grade squamous intraepithelial lesions
HSV: Herpes simplex virus
ICC: Invasive cervical carcinoma
LSIL: Low-grade squamous intraepithelial lesions
NHLS: National health laboratory services
NNT: Number needed to treat
OR: Odds ratio
SCC: Squamous cell carcinoma
SIL: Squamous intraepithelial lesions
STDs: Sexually transmitted diseases
WHO: World health organization

WIHS: Women’s interagency HIV study
CHAPTER 1

INTRODUCTION

1.1 Background and rationale:

Sixty-eight percent of all people living with HIV resided in the Sub-Saharan Africa, a region with only 12.00% of the global population, and where women are more than 50.00% of the epidemic.¹ The epidemic continues to be most severe in Southern Africa, with South Africa having more people living with HIV (an estimated 5.6 million) than any other country in the world.¹

Women infected with HIV have a high risk of developing cervical dysplasia and cancer of the cervix higher than women who are not infected.²,³

Cervical cancer is the second most common cause of cancer mortality in women worldwide, and the leading cause of cancer mortality in Africa, where access to screening programmes is limited.¹,² Multivariable factors have been identified as factors in the development of cervical cancer.⁴ Among these multivariable factors, HIV-positive status was established as a risk factor in the pathogenicity of cervical cancer,⁴ and the CDC in 1993 declared it an acquired immunodeficiency syndrome (AIDS) defining illness.⁵ In addition, Moodley et al in South Africa described cervical cancer and infection with HIV as important public health problems.⁶

Cervical cancer is a preventable condition. Some authors advocated Papanicolaou screening as an early screening tool for cervical cancer.⁶,⁷ The late Dr George Papanicolaou invented the Pap smear in 1940. The Pap smear has been found to be the only screening method that shown to reduce mortality from cervical cancer.⁸
According to the South African clinical guidelines of 2010 on the management of HIV patients all HIV-positive women need cervical cancer screening on diagnosis, and if normal, every three years irrespective of HAART treatment.\textsuperscript{9} Hence, the justification of a cervical smear as a prerequisite to a pre-HAART work-up by some institutions was found justified.\textsuperscript{10,11}

There are several publications that have reviewed different risk factors associated with the abnormal Pap smears in HIV-positive women, such as the CD4 cell count and antiretroviral therapy, but not much is known about other factors like WHO staging and adherence to effective antiretroviral therapy use on abnormal cervical smears in HIV-infected women.

1.2 Motivation for the study

This observation led the researcher to undertake a study looking at factors other than the known ones associated with the development of abnormal cervical smears in HIV-infected women in this hospital, such as WHO staging and HAART use, and adherence to them. It is hoped that this study will help clinical services to focus on Pap smears amongst HIV-infected women most at risk of developing cervical cancer.
CHAPTER 2

LITERATURE REVIEW

2.1 Introduction

The prevalence of HIV infection is reported to be 11.50% in South Africa.\(^1\) It is estimated that approximately 1,500 people are daily infected with the disease in South Africa.\(^1\) South Africa has the largest burden of HIV/AIDS and is currently implementing the largest antiretroviral treatment (ART) programme in the world.\(^12\)

Studies have shown that HIV-positive women are at an increased risk of developing cervical squamous intraepithelial lesions (SIL) and cervical cancer.\(^4,6,13\) In developed countries, where screening is high and of good quality, the Pap smear screening efforts have reduced invasive cervical cancer incidence by about 70.00% to 90.00%.\(^14,15\)

2.2 Prevalence of cervical cancer or cervical dysplasia in HIV-seropositive women.

Cervical cancer is the second most common type of cancer among women in South Africa, i.e. one in every 31 women will, within their lifetime, develop this form of cancer.\(^16\) The prevalence of abnormal Pap smears varies from study to study: so far, it ranges between 36.00%\(^14\) to 55.50%\(^17\) in HIV-infected women. It was found to be higher (66.30%) among HIV-infected females before initiation to HAART.\(^6\) The prevalence of abnormal Pap smears in HIV-negative women in Soweto, Southern Africa was 6.70%.\(^18\) This demonstrates that immunosuppression from HIV infection is a potential risk factor in the development of cervical dysplasia.

2.3 Classification of cervical cancer/dysplasia

A classification from a workshop initiated by the US National Council Institute developed the 2001 Bethesda System\(^19\) whereby the cytology results are named squamous intra-epithelial lesions (SIL), which are also divided into atypical squamous cells of undetermined
significance (ASCUS), low-grade SIL (LGSIL-similar to histology result of CIN 1) and high-grade SIL (HGSIL-similar to the histology result of CIN 2 and CIN 3), and squamous cell carcinoma (SCC).

2.4 Ways of detecting cervical abnormality

There are different ways of detecting abnormal cervical lesions. In most areas in South Africa, a conventional Pap smear is used.

- Pap smear

The Papanicolaou (Pap) smear is a primary screening tool which is simple, safe, non-invasive, and an effective method for the detection of pre-cancerous, cancerous and non-cancerous changes in the cervix and vagina. The use of the Pap smear has reduced morbidity and mortality from invasive cancer in various population groups. There are two types of cytology screening: the conventional cytology screening using the dry slide test using a wooden spatula, and the liquid-based cytology screening. The liquid-based and conventional cytology methods were found to be equivalent in the detection of cervical epithelial abnormalities.

The public health sector in South Africa uses the conventional Pap smear, since it is cost effective.

2.5 Causes / Association of cervical cancer

2.5.1 Epidemiological association

Young age at first coitus (before 20 years), multiple sexual partners, a sexual partner with multiple sexual partners, young age at first pregnancy, high parity and low socio-economic status are factors found to be associated with cervical cancer and its precursors.

Among sexually transmitted diseases (STDs) other than Human papillomavirus (HPV), Chlamydia trachomatis may be an important HPV cofactor for cervical carcinogenesis. HPV is the main cause of cervical neoplasia. Recent studies of the aetiology of cervical neoplasia aimed to identify factors that may influence susceptibility or progression of HPV
infection to cervical neoplasia. Identification of the above cofactors is important because these factors can be amenable to prevention. Some studies have demonstrated that HIV-positive women are at an increased risk of developing cervical SIL, and another study has linked HIV-positive women with cervical cancer. HIV-negative women (6.70%) have a lower prevalence of cervical cancer than HIV-positive women (36.00%). Therefore, being HIV-positive may be a risk factor for the developing of cervical SIL and cervical cancer.

In studies by Tansupswatdikul in Thailand and Denny et al in South Africa, it was found that low a CD4 cell count was significantly associated with the presence of abnormal cytological lesions. Another study revealed that there was a significant association between HPV infection and the number of sexual partners in the last six months (p ≤ 0.001) in a study conducted in United States of America. This study also suggested that the use of condoms might protect against the incidence of HPV in HIV-infected women with multiple recent sexual partners. A case-control study done in Johanessburg reported a low prevalence of abnormal Pap smear in women who reported current condom use as compared to women who did not use condom.

2.5.2 Association of SILs and cervical cancer with HPV

During the 1990s, epidemiological studies supported by molecular technology, provided evidence on the causal role of some HPV infections in the development of cervical cancer. This association was evaluated under all proposed sets of causality criteria and endorsed by the scientific community and major review institutes. The finding was universally consistent, and to date there are no documented alternative hypotheses for the aetiology of cervical cancer. The HPV types considered by this study as human carcinogens were 16, 18, 31, 33, 35, 45, 51, 52, 58 and 59.
As a result of HIV-induced immune impairment, there is an increased probability that HPV infection will become persistent in HIV-infected women, and evolve into precancerous and cancerous lesions of the cervix.\textsuperscript{32,33} Other studies found an association between the development of SILs and other HPV types 53 and 56 for LSIL, and 35, 51, 52, 58, 66, 69 and 73 for HSIL in HIV-positive women.\textsuperscript{34,35} HPV typing and screening is available in private practice in South Africa. However, it is too expensive for the public sector at this point. HIV-infected women also have high rates of HPV infection (up to 90.00% in some studies)\textsuperscript{35,36} which would make HPV testing an ineffectual screening test in South Africa HIV-infected women.

2.5.3 Effect of CD4 cell count levels on abnormal Pap smears

Women with HIV infection are at increased risk for cervical disease and this risk increases with severe immuno-suppression.\textsuperscript{4} Another study reported that lower CD4 cell count levels (less than 200 cells/$\mu$L vs more than 500 cell/$\mu$L) were consistently associated with all grades of cervical neoplasia.\textsuperscript{28} In a prospective study of untreated HIV-1-infected women in Cape Town,\textsuperscript{2} Denny et al found that abnormal cytology was strongly correlated with low CD4 cell counts. Thus, the more immunocompromised the patient, the higher the chance of developing cervical dysplasia.

2.5.4 Effect of HAART on abnormal Pap smears

Highly active antiretroviral therapy (HAART) was shown to decrease the HIV viral load, increase the CD4 cell count, and decrease most opportunistic infections in HIV-infected patients. Since the introduction of HAART there has been a reduction in the incidence of certain malignancies in HIV-infected individuals.\textsuperscript{37,38} However, studies on the impact of HAART on the natural history of SILs have produced inconsistent results.\textsuperscript{39,40} As HAART
has become increasingly available in the public health sector in South Africa, the life span of HIV-infected women has increased.\textsuperscript{41} According to Heard et al\textsuperscript{42} the regression of SIL was defined as a regression to normality or to a lower grade. This regression was noticed from high-grade SIL to low-grade SIL (31/80, 38.80\%.) and to normal (6/80, 7.50\%).\textsuperscript{42} Similarly, it was also reported that women on HAART were more than twice as likely than non-HAART users to demonstrate regression in consecutive cervical smears compared.\textsuperscript{43} These two studies suggested that HAART had a positive effect on the regression of cervical lesions. In view of the above, it was also found that HAART use was associated with the reduction of the cervical lesions incidence among HIV-positive women.\textsuperscript{44} Contrary to the above, some findings reported no association between current HAART use and the progression of cervical neoplasia.\textsuperscript{28} However, it was found that HIV-infected women not on HAART were at a higher risk of developing HSIL than those on HAART.\textsuperscript{17} From the above studies, it can be seen that there was controversial evidence supporting the effects of HAART on cervical lesions.

2.5.5 Effect of use of and adherence to HAART on abnormal Pap smears.

Effective use HAART was defined as a reduction in the viral load by > 90.00\% or to undetectable levels for at least two sequential visits starting within 12 months of HAART initiation.\textsuperscript{46} Regular monitoring of the viral load is critically important to identify poor adherence to therapy, or treatment failure. HAART, the viral load should be undetectable (<50 copies/ml) after 16 to 24 weeks of therapy.\textsuperscript{45} Viral failure is defined as a sustained increase to >1000 copies/ml despite a good adherence.\textsuperscript{45} Adherence to the treatment is defined as self-reported use of HAART as prescribed \( \geq 95.00\% \) of the time for at least two sequential visits, starting within 12 months of HAART initiation.\textsuperscript{46} Although self-reporting of
adherence is a good measure of treatment effectiveness,\textsuperscript{45} it has interview bias. The viral load is a far better guide to true adherence to HAART.\textsuperscript{45}

The WHIS (Women’s Interagency HIV Study) cohort study proved that the use and adherence to HAART was associated with a significant reduction of HPV infection and SILs among HIV-infected women who took HAART; this may be a reason why HIV-positive women live longer without an increased rate of cervical cancer.\textsuperscript{46} Abnormal cytology was found to be strongly correlated with high HIV viral loads in a Cape Town study by Denny et al.\textsuperscript{2}

Thus, HAART (viral load suppression) use may reduce the progression rates and/or increase the regression of cervical lesions. Adherence to HAART needs to be evaluated if HAART affects the rates of cervical dysplasia progression and/or regression in HIV-positive women. The findings may stand as a call to the opportunity of offering HAART to all HIV-infected women particularly in developing countries where cervical cancer screening is limited.

2.5.6 WHO staging and abnormal Pap smears

Many countries do not have CD4 cell count tests, and rely on WHO staging. There is a paucity of studies looking at the association between WHO staging and cervical dysplasia. This study hoped to help these countries to stratify the risk of developing cervical abnormality or cervical cancer in HIV-positive women, based on WHO staging (See annexure 7). This study aimed to improve on the available knowledge on the abnormal Pap smear in HIV-infected women.
CHAPTER 3

MATERIAL AND METHODS

3.1 Definition of variables

**WHO staging:** Clinical staging or classification of HIV/AIDS for adults and adolescents with confirmed HIV infection. (see annexure 8)

**Adherence to HAART:** Self-reported use of HAART as prescribed $\geq 95.00\%$ of the time and a reduction in the viral load by $> 90.00\%$ or to an undetectable levels for at least two sequential visits starting within 12 months of HAART initiation.

**Abnormal cervical smears:** Presence of pre-cancerous or squamous intraepithelial lesions on cervical smears.

**HIV-infected women:** Women who have tested positive for the human immunodeficiency virus.

**DR YUSUF DADOO HOSPITAL:** Is a level one district hospital with 245 approved beds, situated in Mogale City in Krugersdorp. Mogale City is situated in the Western part of Gauteng province. Phedisong clinic is a HIV clinic in the Dr Yusuf Dadoo Hospital.

**MULTIPLE SEXUAL PARTNERS:** Is defined in this study as more than one lifetime sexual partner.

3.2 Aim:

To assess the association of WHO staging, adherence to HAART with abnormal cervical smears among HIV-infected women attending Dr Yusuf Dadoo Hospital.
3.3 Objectives:

1. To determine the prevalence of abnormal cervical smears in HIV-infected women at Dr Yusuf Dadoo Hospital.
2. To describe the basic characteristics (sociodemographic, sexual activities and reproductive health) of the participants in the study sample.
3. To describe the clinical characteristics of the participants including WHO staging, CD4 cell count levels, viral load, treatment on HAART and not on HAART, the period on HAART, adherence to treatment or not.
4. To ascertain whether the WHO staging and use of and adherence to HAART have any correlation with abnormal cervical smears.

3.4 Study area and setting:

This study was conducted in an HIV clinic (Phedisong Clinic) of the Dr Yusuf Dadoo Hospital. Phedisong Clinic dealt with an estimated monthly average of 250 patients this year, who were cared for by three nurses and two doctors. The total number of patients seen in 2011 was 1260. About 70.00% of these patients were female, of which 56.00% were on HAART and 44.00% were not on HAART. All women were offered a Pap smear when they came to the clinic.

3.5 Study design

The study design was a quantitative, cross-sectional, descriptive survey.

3.6 Study period

The pilot study and its analysis were conducted from 15 March to 28 March 2013. The actual research was conducted from the 1 April to 30 June 2013.
3.7 Study population

All HIV-infected women who attended Phedisong Clinic at the time of the research and who gave consent to participate in the study formed the study population. The total number of HIV-infected women who attended this clinic during the study period was 500.

3.8 Study sample, sample size and sampling

With the help of the statistician the minimum sample size was calculated using the formula:

\[ \text{Sample size} = \frac{Z^2 \times P \times (1-P)}{C^2} \]

where \( Z = 95\% \text{ Confidence interval (1.96 SD), } P = \text{Prevalence of HIV patients with abnormal Pap smears.} \) Since there was no study on the prevalence of abnormal cervical smears in this district, the prevalence of abnormal cervical smears was considered to be 50.00\%. \( C = \text{Significance level (0.05).} \) The calculated sample size was \((1.96)^2 \times 50 \times (1-50)/ (0.05)^2 = 384\). An attempt was made to see all HIV-positive women. The study sample was 390.

3.9 Inclusion criteria

- HIV-positive (by two different rapid tests), Western blot, ELISA or HIV viral load > 5000 copies/ml
- Willing to do one Pap smear test at the time of consultation
- Women aged 18-65 years
- Not menstruating but screened after menstruation was over
- Was able to give consent
- Was able to follow the study protocol
3.10 Exclusion criteria

- Was pregnant at the time of the study
- Was clinically active with sexually transmitted disease as determined by the clinical history and/or physical examination and was advised to participate after adequate treatment by syndromic management
- Known and previous hysterectomy with removal of the cervix
- Significant medical illness/mental illness that investigator felt that it would prevent the participant from complying with the protocols or would place the participant at medical risk
- Pilot study participants

3.11 Data collection

The researcher worked in this clinic for three months. Every day, the researcher briefly introduced himself to the potential participants and explained the purpose of the study, the questionnaire to them and gave the consent form to all the female patients. Those who signed the consent form met the professional nurse at the front desk who directed them to the researcher’s room. The questionnaire was filled in by the researcher. The researcher looked into their files and collected data such as CD4 cell count levels, viral load, HAART or not, period on HAART, and whether the patient was adherent or not, using a different data capture sheet which was linked to the questionnaire. They then did a clinical examination and WHO staging. A Pap smear test using a standard slide preparation was performed in the presence of a female nursing assistant (chaperone), using a wooden spatula. After the collection of the Pap smear, the sample and completed laboratory forms were sent to the National Health Laboratory Services (NHLS) for cytology evaluation. The relevant treatment was prescribed for the patients by the researcher. The patient was given a monthly
appointment to follow up on the results. The relevant education and/or referral for treatment for HIV or high grade dysplasia was given to the patients at this visit, as per the South African standard of care. At the end of each day, the researcher collected all the questionnaires and kept them safely in a locked cupboard. Each questionnaire had a unique number identifier to maintain confidentiality. The results were collected after a month by the researcher, and entered onto the data capture sheet (The Bethesda classification system was used since that is the system used by the NHLS).\textsuperscript{18} The questionnaire was anonymized by having the same code as the respondents’ Pap smear, for statistical analysis. The identity of the patient and the patient’s unique number identifier were transferred to a separate MS-Excel spreadsheet which was password-protected; only the researcher was able to access it to identify the Pap smear results.

3.12 Questionnaire and data capture sheet (See annexure 1 and 2)

The first tool was a directed questionnaire and was written in English, as the researcher conducted the data collection. The researcher sought the help of a professional nurse for the participants who did not speak English. It was a simple, structured and closed-ended questionnaire, created from many articles looking at the factors associated with abnormal Pap smears in HIV-positive women.

The questionnaire was divided into two sections.

- Sociodemographic characteristics like the unique number identifier, age, race, marital status, employment status and educational level were discussed under questions 1-8.

- Sexual activity included age of first sexual intercourse, age of first pregnancy, number of sexual partners, gravidity and parity, type of contraceptive and history of STDs. These were discussed under questions 9-17.

The data capture sheet was linked to the questionnaire in order to collect the clinical factors at the time of the Pap smear test. These clinical factors included WHO staging, CD4 cell

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count, viral load, on HAART or not, period on treatment, adherent or not and current Pap smear results.

3.13 Pilot Study

The researcher conducted a pilot study in this clinic with a sample of 10 participants. The pilot study was conducted in March 2013 and then analysed. The data were coded and not used for the final analysis. These participants were excluded from the research sample and were given treatment for HIV or high grade dysplasia as per the South African guidelines. The researcher used this clinic because of convenience in terms of costs of travel and time, as the researcher was working in the same hospital. The aim of this pilot study was to:

- Estimate the time to complete the questionnaire.
- Identify questions that needed to be modified, added or removed.

From the findings of the pilot study, the time to complete the questionnaire was found to be 15 minutes. There were no sensitive questions that needed to be modified or removed as it seemed that the participants understood the questionnaire, the procedures and were willing to participate (they answered the questions without complaint or hesitation). Hence, the final questionnaire was prepared to be used in the main study.

3.14 Data analysis

- Data entry: Data was entered onto an MS-Excel spreadsheet and the data was cleaned to exclude missing values, inconsistencies and extreme values. The extreme values were rechecked with the files and corrected as needed.
- Data analysis: Data was imported from the MS-Excel spreadsheet to the statistical software (STATA vs 10). Two statisticians helped with the analysis of the data. Descriptive analysis of the categorical variables was done and the results were presented using frequencies and percentages, whereas for continuous variables means, median and
standard deviation were used. The Chi-square test was used to determine the association between WHO staging and adherence to HAART with abnormal Pap smears. Statistical parameters like the 95.00% confidence interval were used to confirm the strength of associations. The p < 0.05 was considered as statistically significant.

3.15 Ethical considerations

- The questionnaire was anonymized; hence confidentiality was maintained. The identity of the patient and the patient’s unique number identifier were transferred onto a separate MS-Excel spreadsheet which was password-protected, and only the researcher was able to access it to identify the Pap smear results.
- Patient participant letters and informed consent forms were copied. One copy was given to all the women in the HIV clinic and the original copy was saved by the researcher. Only those who signed the consent form were considered for the study. The participants who did not speak/read English were offered a translation of the above-mentioned letters by the professional nurse. They had the right to refuse to participate in the study, and this right was respected (See annexure 3). The participants found with an abnormal Pap smears or detectable viral load results were managed as per South African’s guidelines and those found with an undetectable viral load were encouraged to be adherent to the treatment.
- Written permission was obtained from the CEO of Dr Yusuf Dadoo Hospital in order to conduct this study in this clinic. (See annexure 4).
- Written permission from the Director of the West Rand Health District was obtained. (See annexure 5).
- An ethics clearance was sought from the Human Research Ethics Committee of the University of Witswatersrand. (See annexure 7)
3.16 Bias

Information bias could not be excluded, as it was self-reported by the participants.

3.17 Funding of the research

The research was funded by the researcher’s personal funds.
CHAPTER 4

RESULTS

This chapter represents the results of the study conducted to assess the association of WHO staging and adherence to HAART with abnormal cervical smears among HIV-infected women attending Dr Yusuf Dadoo Hospital.

4.1 Number of participants

A total number of 500 hundred HIV-infected women were targeted to participate in the research; three hundred and ninety-eight participants gave consent to participate in the study and had Pap smear tests done. One hundred and two HIV-infected women did not participate in the study because of the following reasons:

- Not willing to participate in the study or to give consent (N=77) 15.40%
- Below 18 years of age (N=10) 2.00%
- Above 65 years of age (N=5) 1.00%
- Participants who participated in the pilot study (N=10) 2.00%

From the participants who took part in the study, only 390 Pap smears results were retrieved. Eight Pap smear results were missing (all results were retrieved from the laboratory (NHLS) and those missing could not be traced). Hence, the total number of participants was 390. The total response rate was 78.00 percents.
4.2. Sociodemographic characteristics of the participants

Table 4.1 Sociodemographic characteristics of the participants

<table>
<thead>
<tr>
<th>Variables</th>
<th>Number of participants</th>
<th>Percentages</th>
<th>Mean +/-SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group (Years)</td>
<td>N=390</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Less than 30</td>
<td>63</td>
<td>16.15</td>
</tr>
<tr>
<td></td>
<td>30-34</td>
<td>68</td>
<td>17.44</td>
</tr>
<tr>
<td></td>
<td>35-39</td>
<td>93</td>
<td>23.85</td>
</tr>
<tr>
<td></td>
<td>40-44</td>
<td>80</td>
<td>20.51</td>
</tr>
<tr>
<td></td>
<td>More than 45</td>
<td>86</td>
<td>22.05</td>
</tr>
<tr>
<td>Ethnic group</td>
<td>N=390</td>
<td></td>
<td></td>
</tr>
<tr>
<td>African</td>
<td>381</td>
<td>97.69</td>
<td></td>
</tr>
<tr>
<td>Coloured</td>
<td>9</td>
<td>2.31</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>0</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>Indian</td>
<td>0</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>Marital status</td>
<td>N=321</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not married</td>
<td>321</td>
<td>82.31</td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>69</td>
<td>17.69</td>
<td></td>
</tr>
<tr>
<td>If not married, what is your status</td>
<td>N=321</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>184</td>
<td>47.18</td>
<td></td>
</tr>
<tr>
<td>Cohabitng</td>
<td>108</td>
<td>27.69</td>
<td></td>
</tr>
<tr>
<td>Widowed</td>
<td>21</td>
<td>5.38</td>
<td></td>
</tr>
<tr>
<td>Divorced</td>
<td>8</td>
<td>2.05</td>
<td></td>
</tr>
<tr>
<td>Employment status</td>
<td>N=390</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not employed</td>
<td>132</td>
<td>33.85</td>
<td></td>
</tr>
<tr>
<td>Employed</td>
<td>258</td>
<td>66.15</td>
<td></td>
</tr>
<tr>
<td>If you are not working, what is your professional status</td>
<td>N=132</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>126</td>
<td>95.45</td>
<td></td>
</tr>
<tr>
<td>Student</td>
<td>4</td>
<td>3.04</td>
<td></td>
</tr>
<tr>
<td>Pensioner</td>
<td>2</td>
<td>1.51</td>
<td></td>
</tr>
<tr>
<td>Educational status</td>
<td>N=390</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No education</td>
<td>11</td>
<td>2.82</td>
<td></td>
</tr>
<tr>
<td>Pre-matric</td>
<td>291</td>
<td>74.62</td>
<td></td>
</tr>
<tr>
<td>Matric</td>
<td>59</td>
<td>15.13</td>
<td></td>
</tr>
<tr>
<td>Post-matric</td>
<td>29</td>
<td>7.44</td>
<td></td>
</tr>
</tbody>
</table>

The age range of the participants in the study was from 21 to 65 years; twenty-four per cent (93/390) were in the 35-39 years age group, and ninety-eight per cent (381/390) were Africans. Eighty-two per cent (321/390) of the participants were either single, cohabiting, widowed or divorced. Sixty-six per cent (258/390) of the participants were employed and seventy-five per cent (291/390) had pre-matric qualification. Thirty-four per cent (132/390) of the participants not employed were either unemployed, students or pensioners.
### 4.3. Reproductive health and sexual activities of the participants

#### Table 4.2 Reproductive health and sexual activities of the participants

<table>
<thead>
<tr>
<th>Variables</th>
<th>Number of participants</th>
<th>Percentages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group at the first sexual encounter</td>
<td>N=390</td>
<td></td>
</tr>
<tr>
<td>Less than 10 years</td>
<td>1</td>
<td>0.26</td>
</tr>
<tr>
<td>10-14 years</td>
<td>10</td>
<td>2.56</td>
</tr>
<tr>
<td>15-19 years</td>
<td>296</td>
<td>75.90</td>
</tr>
<tr>
<td>20-24 years</td>
<td>78</td>
<td>20.00</td>
</tr>
<tr>
<td>More than 25 years</td>
<td>5</td>
<td>1.28</td>
</tr>
<tr>
<td>Age group at the first pregnancy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never fell pregnant</td>
<td>16</td>
<td>4.10</td>
</tr>
<tr>
<td>Less than and equal to 24 years</td>
<td>302</td>
<td>77.43</td>
</tr>
<tr>
<td>25-30 years</td>
<td>56</td>
<td>14.36</td>
</tr>
<tr>
<td>Greater than 30 years</td>
<td>16</td>
<td>4.10</td>
</tr>
<tr>
<td>Number of lifetime pregnancies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never fell pregnant</td>
<td>16</td>
<td>4.10</td>
</tr>
<tr>
<td>1-4 pregnancies</td>
<td>338</td>
<td>86.67</td>
</tr>
<tr>
<td>Greater than and equal to 5 pregnancies</td>
<td>36</td>
<td>9.23</td>
</tr>
<tr>
<td>Number of children born after completing 7 months of pregnancy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>26</td>
<td>6.67</td>
</tr>
<tr>
<td>1-4</td>
<td>344</td>
<td>88.21</td>
</tr>
<tr>
<td>Greater than and equal to 5</td>
<td>20</td>
<td>5.13</td>
</tr>
<tr>
<td>Number of sexual partners in a lifetime</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>31</td>
<td>7.95</td>
</tr>
<tr>
<td>Greater than and equal to 2</td>
<td>359</td>
<td>92.05</td>
</tr>
<tr>
<td>History of Sexually Transmitted Diseases (STDs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No history of STDs</td>
<td>236</td>
<td>60.51</td>
</tr>
<tr>
<td>Had history of STDs</td>
<td>154</td>
<td>39.49</td>
</tr>
<tr>
<td>Types of STDs reported</td>
<td>N=154</td>
<td></td>
</tr>
<tr>
<td>Vaginal discharge</td>
<td>120</td>
<td>77.92</td>
</tr>
<tr>
<td>Genital ulcer</td>
<td>8</td>
<td>5.11</td>
</tr>
<tr>
<td>Genital warts</td>
<td>4</td>
<td>2.59</td>
</tr>
<tr>
<td>Herpes simplex</td>
<td>4</td>
<td>2.59</td>
</tr>
<tr>
<td>Herpes simplex &amp; Vaginal discharge</td>
<td>4</td>
<td>2.59</td>
</tr>
<tr>
<td>Genital ulcer &amp; Herpes simplex</td>
<td>4</td>
<td>2.59</td>
</tr>
<tr>
<td>Genital ulcer &amp; Vaginal discharge</td>
<td>4</td>
<td>2.59</td>
</tr>
<tr>
<td>Genital warts &amp; Vaginal discharge</td>
<td>2</td>
<td>1.29</td>
</tr>
<tr>
<td>Genital ulcers &amp; genital warts</td>
<td>2</td>
<td>1.29</td>
</tr>
<tr>
<td>Not sure of the type of STDs</td>
<td>2</td>
<td>1.29</td>
</tr>
<tr>
<td>Use of contraception (prevention)</td>
<td>N=390</td>
<td></td>
</tr>
<tr>
<td>Did not use contraception</td>
<td>88</td>
<td>22.56</td>
</tr>
<tr>
<td>Did use contraception</td>
<td>302</td>
<td>77.44</td>
</tr>
<tr>
<td>If using contraception, what types of contraception did they use?</td>
<td>N=302</td>
<td></td>
</tr>
<tr>
<td>Condom</td>
<td>182</td>
<td>60.26</td>
</tr>
<tr>
<td>Other methods (Bilateral tubal ligation, Intra uterine device &amp;abstinence)</td>
<td>58</td>
<td>19.20</td>
</tr>
<tr>
<td>Injection</td>
<td>23</td>
<td>7.61</td>
</tr>
<tr>
<td>Oral Contraceptive Pills</td>
<td>6</td>
<td>1.98</td>
</tr>
<tr>
<td>Condom &amp; Intra uterine device &amp;abstinence</td>
<td>19</td>
<td>6.29</td>
</tr>
<tr>
<td>Condom &amp; other methods(Bilateral tubal ligation, Intra uterine device &amp;abstinence)</td>
<td>7</td>
<td>2.31</td>
</tr>
<tr>
<td>Condom &amp; Oral Contraceptive Pills</td>
<td>3</td>
<td>0.99</td>
</tr>
<tr>
<td>Injection &amp; other methods(Bilateral tubal ligation, Intra uterine device &amp;abstinence)</td>
<td>2</td>
<td>0.66</td>
</tr>
<tr>
<td>Oral Contraceptive &amp; Other methods(Bilateral tubal ligation, Intra uterine device &amp;abstinence)</td>
<td>2</td>
<td>0.66</td>
</tr>
</tbody>
</table>
Seventy-six per cent (296/390) of the participants had their first sexual encounter between the age of 15 and 19 years, and seventy-seven per cent (302/390) had their first pregnancy at the age below or equal to 24 years. Eighty-seven per cent (338/390) of the participants had one to four pregnancies in their lifetime and eighty-eight per cent (344/390) had one to four children born after completing seven months of pregnancy. Ninety-two per cent (359/390) of the participants had multiple lifetime sexual partners. Sixty-one per cent (236/390) of the participants reported that they had had no STDs in their lifetime. Seventy-eight percent (120/154) of the participants who reported as having had STDs were having vaginal discharge. Seventy-seven per cent (302/390) of the participants had used contraception and sixty per cent (182/302) used condoms as a preventive method.

4.4 Clinical characteristics

Table 4.3.1 Clinical characteristics of the participants

<table>
<thead>
<tr>
<th>Variables</th>
<th>Number of participants (N=390)</th>
<th>Percentages %</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WHO staging</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 1</td>
<td>328</td>
<td>84.10</td>
<td></td>
</tr>
<tr>
<td>Stage 2</td>
<td>36</td>
<td>9.23</td>
<td></td>
</tr>
<tr>
<td>Stage 3</td>
<td>26</td>
<td>6.67</td>
<td></td>
</tr>
<tr>
<td>Stage 4</td>
<td>0</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td><strong>Most recent CD4 cell count levels at the time of the pap smear (in cell/µL)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than 200</td>
<td>59</td>
<td>15.13</td>
<td></td>
</tr>
<tr>
<td>200-349</td>
<td>113</td>
<td>28.97</td>
<td>381</td>
</tr>
<tr>
<td>350-499</td>
<td>101</td>
<td>25.90</td>
<td></td>
</tr>
<tr>
<td>Greater than and equal to 500</td>
<td>117</td>
<td>30.00</td>
<td></td>
</tr>
<tr>
<td><strong>Viral load (in copies/ml)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral load not done (Participants not on HAART and participants on HAART for a period of less than 6 months)</td>
<td>66</td>
<td>16.92</td>
<td></td>
</tr>
<tr>
<td>Less than 50</td>
<td>198</td>
<td>50.77</td>
<td></td>
</tr>
<tr>
<td>50-399</td>
<td>69</td>
<td>17.69</td>
<td></td>
</tr>
<tr>
<td>400-999</td>
<td>16</td>
<td>4.10</td>
<td></td>
</tr>
<tr>
<td>Greater than and equal to 1000</td>
<td>41</td>
<td>10.51</td>
<td></td>
</tr>
<tr>
<td><strong>Use of HAART</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did not use HAART</td>
<td>60</td>
<td>15.38</td>
<td></td>
</tr>
<tr>
<td>Did use HAART</td>
<td>330</td>
<td>84.62</td>
<td></td>
</tr>
<tr>
<td><strong>Duration of current HAART treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Eighty-four per cent (328/390) of participants were in stage 1 of WHO-HIV classification, and fifteen per cent (59/390) had a CD4 cell count level below 200 cells/µL. The median CD4 count level for the study was 381 cells/µL. Fifty-one per cent (198/390) of the participants had a viral load below 50 copies/ml. Eighty-five per cent (330/390) of participants were using HAART. Seventy-three per cent (283/390) of the participants were on the HAART treatment for more than one year at the time of Pap smear testing. Seventy-two per cent (281/390) of participants had not changed their HAART treatment since the treatment was initiated. Eighty-four per cent (41/49) of participants who changed their HAART treatment were on the previous HAART treatment for more than one year. Fifty-six per cent (219/390) of the participants reported HAART adherence for two sequential visits within a year of treatment.

Table 4.3.2 Current Pap smear results of the participants

<table>
<thead>
<tr>
<th>Pap smear results</th>
<th>Number of participants</th>
<th>Percentages</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=390</td>
<td>%</td>
</tr>
<tr>
<td>Normal</td>
<td>168</td>
<td>43.08</td>
</tr>
<tr>
<td>Abnormal</td>
<td>222</td>
<td>56.92</td>
</tr>
<tr>
<td>• ASCUS</td>
<td>16</td>
<td>4.10</td>
</tr>
<tr>
<td>• AGUS</td>
<td>0</td>
<td>0.00</td>
</tr>
<tr>
<td>• LSIL</td>
<td>142</td>
<td>36.41</td>
</tr>
<tr>
<td>• HSIL</td>
<td>64</td>
<td>16.41</td>
</tr>
</tbody>
</table>
Fifty-seven per cent (222/390) of the participants had abnormal Pap smears, of which thirty-six per cent (142/390) had low squamous intraepithelial lesions and sixteen per cent (64/390) had high squamous intraepithelial lesions.

4.5 Association between WHO staging, and use of and adherence to HAART with abnormal Pap smears

Table 4.4.1 WHO staging with abnormal Pap smears

<table>
<thead>
<tr>
<th>Variables</th>
<th>Normal Pap smears N=168</th>
<th>Abnormal Pap smears N=222</th>
<th>P value</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO staging</td>
<td>Total number N=390</td>
<td>Number</td>
<td>Percentages</td>
<td>Number</td>
</tr>
<tr>
<td>Stage 1</td>
<td>328</td>
<td>145</td>
<td>44.20</td>
<td>183</td>
</tr>
<tr>
<td>Stage 2</td>
<td>36</td>
<td>18</td>
<td>50.00</td>
<td>18</td>
</tr>
<tr>
<td>Stage 3</td>
<td>26</td>
<td>5</td>
<td>19.20</td>
<td>21</td>
</tr>
<tr>
<td>Stage 4</td>
<td>0</td>
<td>0</td>
<td>0.00</td>
<td>0</td>
</tr>
</tbody>
</table>

Figure 1 WHO staging with abnormal Pap smears

Pearson Chi2(2) = 7.50 p-value= 0.023

This result indicates that there was a statistical significant relationship between WHO staging at the time of Pap smear and abnormal Pap smears (Chi square with two degrees of freedom= 7.50, p=0.023). WHO stage 3 participants were three time more likely to have abnormal Pap
smears as compared to those with WHO stage 1 (OD 3.3, STD. error 1.7, p=0.018, 95% CI 1.23-9.04).

Table 4.4.2 Use of HAART with abnormal Pap smears

<table>
<thead>
<tr>
<th>Variables</th>
<th>Normal Pap smears N=168</th>
<th>Abnormal Pap smears N=222</th>
<th>Median CD4 cell count level (in cell/µL)</th>
<th>P value</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total number N=390</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of HAART</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did not use HAART</td>
<td>60</td>
<td>18</td>
<td>30.00</td>
<td>42</td>
<td>70.00</td>
</tr>
<tr>
<td>Did use HAART</td>
<td>330</td>
<td>150</td>
<td>45.40</td>
<td>180</td>
<td>54.60</td>
</tr>
</tbody>
</table>

![Figure 2](Use of HAART with abnormal Pap smears)

This result indicates that there was a statistical significant relationship between the use of HAART and abnormal Pap smears (Chi square with one degree of freedom= 4.9452, p=0.024). Abnormal Pap smears results were seen more in participants who did not use HAART as compared to those who used HAART [ 42/60, (70.00%) vs. 180/330, (54.60%) p-
0.028, 95% CI: 0.28-0.93], and the median CD4 cell count level was (227.50 cell/µL) is lower than the median CD4 cell count of the participants who did use HAART (426 cell/µL).

**Figure 3  Adherence to HAART with abnormal Pap smears**

Pearson Chi2( 1) =0.0212  p-value=0.884

This result indicates that there was no relationship between adherents to HAART and abnormal Pap smears.

**Figure 4  Viral load with abnormal Pap smears**

Pearson Chi2( 2) =2.8128  p-value=0.245

This result indicates that there was no relationship between viral load and abnormal Pap smears.
Table 4.4.3  CD4 cell count with abnormal Pap smears

<table>
<thead>
<tr>
<th>CD4 cell count (in cell/µL)</th>
<th>Total number N=390</th>
<th>Normal Pap smears N=168</th>
<th>Abnormal Pap smears N=222</th>
<th>P-value</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 200</td>
<td>59</td>
<td>12</td>
<td>20.33</td>
<td>47</td>
<td>79.67</td>
</tr>
<tr>
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<td>33.63</td>
<td>75</td>
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<td>48.51</td>
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<td>69</td>
<td>58.97</td>
<td>48</td>
<td>41.03</td>
</tr>
</tbody>
</table>

Figure 5  CD4 cell count with abnormal Pap smears

Pearson Chi2( 3) =29.8311  p-value=0.001

This result indicates that there was a statistical significant relationship between the CD4 cell count and abnormal Pap smears (Chi square with three degrees of freedom= 29.8311, p=0.001) with CD4 cell count levels greater than 500 cells/µL presenting less abnormal Pap smears (41.00 %, 48/117) as compared to those with the CD4 cell count less than 350 cells/µL (70.93%, 122/172).
CHAPTER 5

5.0 DISCUSSION

This study was conducted to assess the association of WHO staging and adherence to HAART among HIV-infected with abnormal cervical smears, attending Dr Yusuf Dadoo Hospital. The researcher was satisfied with a 78.00 % response rate. This suggests that the study findings are reliable and valid.

5.1 COMPARISON OF THE RESULTS WITH OTHER STUDIES

5.1.1 Basic characteristics

5.1.1.1 Sociodemographic characteristics

A total of 390 HIV-infected women were screened for abnormal cervical smears. They were aged between 21 and 65 years with a mean age of 38 ± 8.67 years. The majority of the study participants (97.69%, 381/390) were Africans reflecting the demographic composition of the population from which the sample was drawn. This ethnic trend was not seen in Cape Town, where the majority of the study participants (75.50%, 367/486) were of coloured origin. The majority of the study participants (47.18%, 184/390) were not married and were singles. This observation was also made by Gayman et al in Kwazulu Natal. The majority of the study participants (74.62%, 291/390) had pre-matric qualification, contrasts with the findings of Swende et al in Nigeria, where the majority of their study participants (27.30%, 69/253) had no educational background.

5.1.1.2 Reproductive health and sexual activities of the participants

Most of the study participants (75.90%, 296/390) had their first sexual encounter between 15 and 19 years of age. This observation concurs with the findings made by Firnhaber et al. In some studies done in America and Africa, three per cent of their samples had their
first sexual encounter before age 15 years, and revealed a decrease in the rate of the first sexual intercourse before 15 years of age. Seventy-seven per cent of participants (302/390) in this study had their first pregnancy before 25 years of age. This suggests that a study should be done to link early sexual engagement with the age of first pregnancy.

Ninety-six per cent (374/390) of the participants reported to have had at least one lifetime pregnancy and ninety-three per cent (366/390) had at least one child. These observations were also found in some studies cited in the literature review, and the lowest percentage (36.00%, 110/280) was found by Tansupswatdikul. This implies the vulnerability of the study participants to develop abnormal cervical smears regardless of their HIV status.

Ninety two per cent (359/390) of the participants reported to have multiple sexual partners. The same observation was seen in studies conducted in Johannesburg and in Israel. This seems to be higher as reported by Tansupswatdikul et al. (69.00%, 192/280) in the literature. Vaginal discharge seemed to be the most common presentation in those who reported to have had a sexually transmitted disease. Genital warts and herpes were found to be at three per cent in this population, as compared to another study by Ellerbrock et al. with 14.00% (46/328) of their study population presenting with genital warts and herpes.

Seventy-seven per cent (302/390) of the study participants used contraception. Male condoms were the most commonly used contraceptive method (60.26%, 182/302). Male condom usage was reported to be at 75.00% (756/1010) by Firnhaber et al. and at 40.00% (48/120) by Moodley et al. The study findings were similar to the above-mentioned studies. This contrasts with the finding made by Gaym et al. reporting Depo-Provera as being the most used contraceptive in their study sample, and male condom use in some of the literature, which was reported to be 25.00% and 16.00%. The remaining twenty-three per cent of the participants in this study who did not use condoms are a risk for the society, as they will
spread HIV-infection. Thus the study participants could get a secondary HIV infection and other sexually transmitted infections.

5.2 Clinical characteristics of the participants

Eighty-four per cent (328/390) of the participants in this study were in stage one WHO-HIV classification. In a retrospective study of cervical smears in HIV-infected postnatal women at Johannesburg Hospital, WHO-HIV stage one was seen in 31.00% (76/248) of the study population. Though the study sample was almost equal to this study, the difference might be due to the selection of the participants (post natal HIV-positive women).

The study findings of seven per cent (WHO-HIV stage 3) contradict the findings of Memiah et al. who found that more than one third of their study participants were in stage three, followed by stage four WHO-HIV. The difference might be due to the fact that sick patients were excluded from this study.

Forty four per cents (172/390) of the study participants had a CD4 cell count of less than 350 cells/µL and thirty per cents (117/390) had a CD4 cell count of greater than or equal to 500 cells/µL with a median CD4 cell count of 381 cells/µL. This observation contradicts other studies that have a median CD4 cell count of 174 cells/µL as seen in Nigeria (2012) where 41.10% of those participants (104/253) were on HAART treatment; 267 cells/µL as seen in South Africa (2011) where 34.00% of those participants (26/76) were on HAART treatment; 458 cells/µL as seen in Kenya (2012) where 84.30% of the participants (578/715) were on HAART treatment. The above finding in this study might explain the reason why WHO-HIV stage four participants were not seen. In this study, participants who had a CD4 cell count of less than 350 cells/µL had greater risk of developing abnormal Pap smears. This suggests that the lower the CD4 cell count the higher the chance of developing cervical cancer precursors.
The majority (82.40%, 267/324) of the participants who were on HAART had a viral load of less than 400 copies/ml and thirteen per cent (41/324) had a viral load of greater than and equal to 1000 copies/ml. As soon as the researcher got this result, advice was given to the health workers to get all patients with a viral load greater than 1000 copies/ml to get adherent counselling. In a study done by Swende et al in Nigeria, where the sample size was 253, eighty one per cents (205/253) of the study participants had a viral load of greater than 400 copies/ml and nineteen per cent (48/253) a viral load of less than 400 copies/ml.

In this study eighty-five per cent (330/390) of the participants used HAART, which implies a broader antiretroviral therapy coverage.

Fifty-six per cent (219/390) of the participants reported that they were adhering to HAART for the two sequential visits within 12 months of their treatment. Similar observations were seen in a study by Minkoff et al. These findings contradicted the study by Leibenson et al. in Israel where the adherence rate to HAART was reported to be 86.00%. This difference might be due to the small study sample in Israel (N=90). The remaining forty-four percent of the participants in the present study reported not adherent to HAART. This might lead to the occurrence of drug resistance and/or opportunistic infections including cervical cancer.

5.3 Prevalence of abnormal Pap smears and Pap smear results

The abnormal Pap smear results of the participants was fifty-seven per cent. Similar observations were reported in Africa. Contrary to the researcher’s observation, the prevalence of abnormal Pap smears was found to be below 50.00% in some studies. The difference might be due to the study sample and to the degree of illness presented by the participants (WHO-HIV stage).

Among those with abnormal Pap smear results, low-grade squamous intraepithelial lesions [36.00%, (142/390)] were the commonest pathology, followed by high-grade squamous cell lesions [16.00%, (64/390)]. Similar findings were seen in Dames et al. in United Stated of
America\textsuperscript{49} (2008), where 81.00\% of their participants (81/100) were on HAART of which 31.00\% (31/100) had low-grade squamous cell lesions, and 6.00\% (6/100) had high-grade squamous cell lesions. The above findings contradict with the findings reported by Tansupswatdikul et al.\textsuperscript{29} in Thailand (2009), where 82.10\% (230/280) of their participants were on HAART, of which 6.40\% had LGSIL (18/280) and 12.10\% had HGSIL (34/280); and by Gaym et al (2007) in South Africa\textsuperscript{14} with the limitation of no information given about how many participants were on HAART, who found 21.00\% (24/114) of LGSIL and 4.30\% (5/114) of HGSIL. The study sample size and prevalence of abnormal Pap smears might have played a role in this difference. The present study confirms that there is a high risk of cervical precursors in HIV infected women. Hence the emphasis on the importance of the cervical smear screening in all HIV-infected women.

5.4 Association of WHO staging, Adherence to HAART with abnormal Pap smears

5.4.1 Association of WHO staging with abnormal Pap smears

Though there was a statistical significant relationship between WHO staging and abnormal Pap smears (Chi square with two degrees of freedom = 7.50, $p=0.023$), WHO stage 3 participants seemed to be three times more likely to have abnormal Pap smears than those with WHO stage 1 (OD 3.3, STD. error 1.7, $p=0.018$, 95\% CI 1.23-9.04). Thus, the more advanced the WHO-HIV stage in a woman, the greater the chance of having an abnormal Pap smear.

This contradicts the findings made by Wise\textsuperscript{52} in Johannesburg who found that the WHO stage did not appear to have an impact on the final analysis of the Pap smear. The difference might lie in the fact that the raw data for the WHO classification was largely incomplete, with 45.00\% missing data in Wise’s study as it was a retrospective record review.
5.4.2 Association of the use HAART with abnormal Pap smears

There was a statistical significant relationship between the use of HAART and abnormal Pap smears (Chi square with one degree of freedom=4.9452, p=0.024). Abnormal Pap smears were seen more in participants who did not use HAART as compared to those who used HAART [42/60, 70.00% vs. 180/330, 55.00%, p=0.028, 95% CI 0.28-0.93], with a median CD4 count of 426 cells/µL. This concurs with the observations made by many authors in the literature.17,41,50,51 Thus, the immune reconstitution resulting from HAART use might not be sufficient to prevent the development of abnormal cervical smears in HIV-infected women. This observation might be due to the fact that women started HAART often with below 200 cells/µL and so would have had lower CD4 cell count nadirs and developed cervical dysplasias, and with immune-reconstitution did not have any improvement of the disease. The period on HAART was not looked at and it may be a confounder in this finding. It has a valid merit to be looked at, as another research topic.

5.4.3 Association of adherence to HAART with abnormal Pap smears

There was no association between adherence to HAART and abnormal Pap smears in HIV-infected women who participated in this study (p=0.884). The same observation was made by Leibenson et al51 in Israel where HAART compliance was not found to have an impact on HPV prevalence. (p=0.525). The above observation contradicts the findings by Minkoff et al46 in a prospective cohort study in the United State of America where adherent to HAART was associated with a significant reduction of squamous intraepithelial lesions. This difference may be attributed to the facts that it was a prospective cohort study, to HAART regimens offered to their study participants and the period on HAART. The patient’s self-report of HAART may have also contributed to this difference as an information bias can impact largely into the final result of this current study.
5.4.4 Association of viral load with abnormal Pap smears

Even though the viral load is a good surrogate for antiretroviral drug adherence no relationship between viral load and abnormal Pap smears was found (p=0.245). This finding concurs with the cross-sectional study done by Leibenson et al\textsuperscript{51} in Israel in which no statistical significant effect of viral load on HPV prevalence was found (p=0.277). In a cross-sectional study by Cardillo et al\textsuperscript{54} in United States of America, the viral load from the patients with SILs was significantly higher than that from those with normal Pap smears (109,316 copies/mL vs. 41,602 copies/ml; p=0.006). The difference with this current study may be related to the duration of the study (5 years), HAART regimen and the absence of treatment compliance data. The same observation was made by Swende et al\textsuperscript{47} in Nigeria where the viral load of their study participants on HAART was significantly higher in women with SIL as compared with that of women without SIL (102,705 vs. 64,391 copies/ml, respectively; p=0.002). The difference may be due to the fact that in their study more participants (81.00%, 205/253) had a viral load of greater than 400 copies/ml as compared to those of the current study (17.60%, 55/324).

Though there was no significant relationship between viral load and abnormal Pap smears, the graph (see fig.4 on page 25) showed that the higher the viral load count, the more abnormalities were seen in the Pap smears. This finding was similar to the graph on the association between WHO staging and abnormal Pap smears see fig.1 on page 23. Since this observation was not part of the study objectives, the researcher suggests another study looking at this link.

5.4.5 Association of CD4 count levels with abnormal Pap smears

There was a significant statistical relationship between CD4 cell count levels and abnormal Pap smears (Chi square with three degrees of freedom=29.8311, p=0.001). The participants with the CD4 cell count levels greater than 500 cells/µL presenting less abnormal Pap smears
as compared to those with CD4 cell count of less than 350 cells/µL. If HAART treatment is being initiated at CD4 cell count level greater than 500 cells/µL, this might help reduce the prevalence of cervical dysplasias. This association with the immune status of HIV-infected women has been reported by many authors in the literature, with particularity on more Pap smear abnormalities with a CD4 cell count level <200 cells/µL. A CD4 cell count of less than 350 cells/µL could be a useful tool in the stratification of the risk in developing cervical abnormalities or cervical cancer in HIV-positive women.

Looking at the above findings in 5.1.6, 5.1.7 and 5.1.10, the researcher concludes that:

1. The more immunosuppressed a woman is, the higher her chance of developing cervical cancer precursors. The WHO staging is important in stratifying the risk of developing abnormal Pap smear in HIV-infected women.

2. HAART treatment and the CD4 count greater than 500 cells/µL were offering a protective role in the development of abnormal cervical lesions.

3. Adherence to HAART and viral load did not have any protective role in the development of abnormal Pap smears in HIV-positive women attending Dr Yusuf Dadoo hospital.

4. The high risk group to have abnormal Pap smear in this study was found to be the participants with the CD4 cell count of ≤ 350 cells/µL and the viral load ≥1000 copies/mm³. The self-reported adherence level did not show any impact.

5.5 Limitations

- As the study is a cross-sectional study, it looked only at the associations and did not look at the effectiveness of HAART on abnormal Pap smears.

- This study did not explore the CD4 cell count nadirs, the WHO staging at the start of HAART and the period on HAART. Such data might have an impact on the
establishment of an association between the CD4 cell count, and the use of HAART with abnormal Pap smears.

- This study did not explore the in depth the sexual history of the participants. Such data might have an influence on the demographic and reproductive characteristics of the participants.

- The link between the viral load levels and the WHO staging of the study participants were not explored, such a data might have had an influence on the Pap smears results.
CHAPTER 6

6.0 CONCLUSION AND RECOMMENDATIONS

Abnormalities on Pap smears in HIV-infected patients have been reported in the literature and many predicting factors for these abnormalities have been cited. Among these factors HIV-positive status was one of the independent factors found to be related to abnormal Pap smears. Others factors like WHO staging, and use of HAART and CD4 cell count levels are important factors to be considered when looking at abnormal Pap smears in HIV-infected women. These factors may be used to stratify the cervical smear risk in many under-resourced and under-developed countries, so that preventative measures can be taken and implemented.

In our research, an association was found between WHO staging, the use of HAART and current CD4 cell count levels and abnormal Pap smears among HIV-infected women attending Dr Yusuf Dadoo Hospital.

Therefore, some recommendations follow:

- Cervical cancer screening is imperative in HIV-infected women and guidelines considering the severity of immunosuppression should be provided for the health care workers. Targets should be set and monitored at the health care clinics.

- If HAART is being initiated at CD4 cell count level greater than 500 cells/µL, this might help reduce the prevalence of cervical dysplasias.

- Adherence counselling should be given generally to all HIV-infected women and specifically to those at high risk for defaulting.
REFERENCES


47. Swende TZ, Ngwan SD, Swende LT. Prevalence and risk factors for cervical squamous intraepithelial lesions among women infected with HIV-1 in Makurdy, Nigeria. IJWH. 2012:455-60.


Annexure 1     Questionnaire

WHO staging, adherence to HAART and abnormal cervical smears among HIV-infected women attending Dr Yusuf Dadoo Hospital.

Please answer the following questions.

1. Code number ..........................

2. How old are you?......................

3. What ethnic group do you belong to? African  White  
   Indian  Coloured  Others

4. Are you married? No  Yes

5. If you are not, what is your status?
   Cohabiting  Divorced  widowed  Single

6. Are you working? No  Yes

7. If you are not working, what are you doing?
   Student  Pensioner  unemployed

8. What is your educational level?
   None  Pre-matric  Matric  Post-matric

9. At what age did you have your first sexual encounter?........

10. How old were you when you first fell pregnant?........

11. How many times did you fall pregnant?........

12. How many children have been born to you after completing 7 months of pregnancy?........

13. Have you been treated for Sexually transmitted disease by a doctor/Nurse?  
   No  Yes

14. If yes, what type of Sexually transmitted disease was it?
15. How many sexual partner/s do you have in a life time ?………

16. Do you use contraception (prevention)? No  Yes

17. If yes, what type of prevention do you use? condom Injection

Oral contraceptive pills  Others

Thank you for your participation.
## Annexure 2. Data capture sheet

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<th>CD4 COUNT</th>
<th>VIRAL LOAD</th>
<th>HAART OR NOT</th>
<th>Duration on current HAART</th>
<th>Most recent switch off HAART</th>
<th>If any switch off HAART, duration on previous HAART</th>
<th>Self reporting of adherence for 2 sequential visits with in 12 months</th>
<th>Current Pap smear result</th>
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Annexure 3  Participant’s information sheet and consent form

HREC protocol approval number: M130111

Study title: WHO staging, adherence to HAART with abnormal cervical smear among HIV-infected women Dr Yusuf Dadoo Hospital.

Study doctor: Dr A.C Katumba, a Registrar in Family Medicine at the University of the Witwatersrand.

Purpose of the research: The study doctor is conducting this study as a requirement towards the completion of the MMed (Family Medicine) degree.

Institution: University of the Witwatersrand.

Introduction:

Good day, my name is Dr Appolinaire Ciamalenga Katumba, I am a Fourth-year registrar in the Department of Family Medicine at the University of the Witwatersrand. I would like to invite you to participate in a study entitled “WHO staging, adherence to HAART with abnormal cervical smear among HIV-infected women Dr Yusuf Dadoo Hospital”. I am doing this study as part of the requirements for specialization in Family Medicine.

Before agreeing to participate in this study, it is important that you read and understand the following explanation of the purpose of the study, the study procedures, benefits, risks, discomfort, and precautions as well as your right to withdraw from the study at any time.

This information leaflet is to help you to decide if you would like to participate. You should fully understand what is involved before you agree to take part in this study.

Purpose of the study:

The study is assessing the association between the WHO staging (different degrees of the HIV disease) and adherence to HAART (ability to take the HIV treatment regularly without skipping a day) and abnormal cervical smears. Many countries do not have CD4 count tests and rely on WHO clinical staging in order to assess the immunological status of the patients. This study may help those countries with limited resources to stratify the risk of developing cervical cancer in HIV-positive women.

Procedure:

As part of your treatment at this clinic you will be examined and you will be offered a Pap smear. The Pap smear is a test done to find abnormal cells on the mouth of the womb which may become a cancer if left untreated. If your Pap smear test is abnormal you will be referred
for further tests. The Pap smear result will be ready in four weeks time. The Pap smear may be uncomfortable.

I would also like to ask you some questions about yourself this will take about 15 minutes. Some of the questions may cause you some embarrassment and you do not then have to answer. I would also like to look at your medical records to see and record some factors related to your management. I would like to record the data like CD4 count levels, viral load, HAART or not, period on HAART, whether your are taking your treatment regularly or not.

**Risks and benefits:**

There are not foreseeable risks associated with your participation in the study. You will not receive any payment for participating in the study. Your treatment at this clinic will be the same whether you are in the study or not.

**Confidentiality and Data storage:**

All the information that you provide will be kept confidential. I will not be required to record your name or date of birth on the questionnaire or data capture sheet and you will not be directly identified in the research report. The questionnaire and the data capture sheet will be coded. Your name and/or your date of birth will not appear on any data collection tool used in the study.

**Are there any restrictions concerning my participation in this study?**

- If you are pregnant during the study period, you may not take part in the study.
- If you are on your period (menstruation), the Pap smear test will be done only when your period is over.

**Rights as a participant in this study:**

- Your participation in this study is entirely voluntary and you can decline to participate, or stop at any time, without stating any reason.

**Withdrawal:**

Your withdrawal will not affect your access to other medical care.

**Research results:**

If you have any questions regarding this research you can ask me now or phone me on this number 0823069325 or e-mail me.

A research report will be submitted to the University of the Witwatersrand. You may request a copy of the report or any other feedback and information that you may require. Kindly contact me on e-mail: ackatumba@gmail.com or 0823069325
Complaints:

The HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL) of the University of the Witwatersrand has approved this study. Clearance certificate No: M130111

If you have concerns or complaints about the conduct of this study please contact the Wits Research Office at 011 717 1234
INFORMED CONSENT
UNIVERSITY OF THE WITWATERSRAND

- I hereby confirm that I have been informed by the study doctor, Dr A.C Katumba, about the nature, conduct, benefits and risks of the study: WHO staging, adherence to HAART and abnormal cervical smears among HIV-infected women attending Dr Yusuf Dadoo hospital. Clearance certificate No: M130111
- I have also received, read, and understood the above information (Participant Information Leaflet and Informed Consent) regarding the study.
- I am aware that the results of the study, including personal details regarding my sex, age, date of birth, initials and diagnosis will be anonymously processed into a study report.
- In view of the requirements of research, I agree that the data collected during this study can be processed in a computerised system by the study doctor.
- I may, at any stage, without prejudice, withdraw my consent and participation in the study.
- I have had sufficient opportunity to ask questions and (of my own free will) declare myself prepared to participate in the study.

Participant: Name:.................................

Signature/ Thumbprint:

Date and Time:.........................

I, Dr A.C Katumba, herewith confirm that the above participant has been fully informed about the nature, conduct and risks of the above study.

Study doctor: Name:.................................

Signature/ Thumbprint:

Date and Time:.........................

Translator/ Other person explaining informed consent form.........(Designation):

Name..............................Signature............ Date/ Time.........
Annexure 4. HREC’s Clearance Certificate

R14/49 Dr Appolinaire C Katumba

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M130111

NAME: (Principal Investigator)  Dr Appolinaire C Katumba

DEPARTMENT:  Department of Family Medicine
Medical School

PROJECT TITLE:  WHO Staging, adherence to HAART and Abnormal Cervical Smears amongst HIV-Infected Women Attending Dr Yusuf Dadoo Hospital

DATE CONSIDERED:  25/01/2013

DECISION:  Approved unconditionally

CONDITIONS:

SUPERVISOR:  Dr Cindy Finhaber

APPROVED BY:  [Signature]

DATE OF APPROVAL:  28/02/2013

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS
To be completed in duplicate and ONE COPY returned to the Secretary in Room 10004, 10th floor, Senate House, University.
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. I agree to submit a yearly progress report.

Principal Investigator Signature  Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES
Annexure 5. Permission letter letter from the West Rand Health District’s Director

07/06/2008 06:23 0119535408 DPT OF HEALTH WRAND PAGE 01/01

GAUTENG PROVINCE
REPUBLIC OF SOUTH AFRICA

TO
Dr Appolonia C Katsha
Department of Family Medicine

FROM
Ms Puleng Muso
Director, West Rand District Council

DATE
13th March, 2013

PERMISSION TO CONDUCT RESEARCH IN WEST RAND DISTRICT

Your correspondence on the above matter refers.

Thank you for your request to conduct research in Dr Yusuf Dadoo Hospital. Permission is hereby granted to you to conduct research in Dr Yusuf Dadoo Hospital. You are requested that you conduct your research with the permission of the CEO of the institution.

I am anticipating that you will share your findings and recommendations with the district in order to improve service delivery to the people of West Rand.

Yours,

MS PULENG MUSO
Annexure 6. Permission letter from the Chief Executive Officer of Dr Yusuf Dadoo hospital.

GAUTENG PROVINCE

Dr. Yusuf Dadoo Hospital
KRUGERSDORP

Enquiries: P. M. Sofohlo
Telephone: (011) 951 - 6191
Fax: (011) 951 - 6152
E-Mail: sofohlo@usr.gov.za

Date: 2013.03.22

Attention Dr. Katumba
West Rand District Health Council
Department of Family Medicine
KRUGERSDORP
1740

RE: PERMISSION TO CONDUCT RESEARCH AT DR. YUSUF DADDO
HOSPITAL

Research Topic: WHO staging, adherence to HAART and abnormal cervical smears amongst HIV-infected women attending Dr Yusuf Dadoo Hospital

Permission is hereby granted to you, Dr. Katumba to conduct research on the above topic at Dr. Yusuf Dadoo Hospital.

You are therefore expected to adhere and comply with ethics for research as stipulated in the Ethics Policy for Research.

Regards

P. M. Sofohlo
Chief Executive Officer

Dr. Yusuf Dadoo Hospital
PRIVATE BAG 12092

KRUGERSDORP 1740

Page 1 of 1
Annexure 7. Flow chart of the research.

HIV-positive women who are willing to do a Pap smear at the time of consultation

Normal Pap smears results

Abnormal Pap smears results

- WHO staging
- Current CD4 count levels
- Not on HAART
- On HAART
- Current Viral load
- Not adherent
### WHO HIV CLINICAL STAGING (2006)

#### STAGE 1:
- ASYMPTOMATIC
- PERSISTENT GENERALIZED LYMPHADENOPATHY

#### STAGE 2:
- UNEXPLAINED MODERATE WEIGHT LOSS (<10% OF PRESUMED OR MEASURED BODY WEIGHT)
- RECURRENT RESPIRATORY TRACT INFECTIONS (SINUSITIS, TONSILLITIS, OTITIS MEDIA AND PHARYNGITIS)
- HERPES ZOSTER
- ANGULAR CHELITIS
- RECURRENT ORAL ULCERATION
- PAPULAR PRURITIC ERUPTION
- SEBORRHOEIC DERMATITIS
- FUNGAL NAIL INFECTIONS

#### STAGE 3:
- UNEXPLAINED SEVERE WEIGHT LOSS (>10% OF PRESUMED OR MEASURED BODY WEIGHT)
- UNEXPLAINED CHRONIC DIARRHOEA FOR LONGER THAN ONE MONTH
- UNEXPLAINED PERSISTENT FEVER (ABOVE 37.5 °C INTERMITTENT OR CONSTANT, FOR LONGER THAN ONE MONTH.
- PERSISTENT ORAL CANDIDIASIS
- ORAL HAIRY LEUKOPLAKIA
- PULMONARY TUBERCULOSIS
- SEVERE BACTERIAL INFECTIONS (SUCH AS PNEUMONIA, EMPYEMA, PYOMYOSITIS, BONE OR JOINT INFECTION, MENINGITIS OR BACTERAEMIA)
- ACUTE NECROTISING ULCERATIVE STOMATITIS, GINGIVITIS OR PERIODONTITIS
- UNEXPLAINED ANAEMIA (<8g/dl), NEUTROPAENIA (<0.5 X 10⁹ PER LITRE) AND/OR CHRONIC THROMBOCYTOPAENIA (<50 X 10⁹ PER LITRE)
<table>
<thead>
<tr>
<th>STAGE 4:</th>
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<tbody>
<tr>
<td>• HIV- WASTING SYNDROME (WEIGHT LOSS OF &gt; 10%, PLUS EITHER</td>
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<tr>
<td>UNEXPLAINED CHRONIC DIARRHOEA (&gt; 1MONTH) OR CHRONIC WEAKNESS AND</td>
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<tr>
<td>UNEXPLAINED PROLONGED FEVER (&gt; 1 MONTH).</td>
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<tr>
<td>• PNEUMOCYSTIS PNEUMONIA</td>
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<tr>
<td>• RECURRENT SEVERE BACTERIAL PNEUMONIA</td>
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<tr>
<td>• CHRONIC HERPES SIMPLEX INFECTION (OROLABIAL, GENITAL OR ANORECTAL</td>
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<td>OF MORE THAN ONE MONTH’S DURATION OR VISCERAL AT ANY SITE)</td>
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<tr>
<td>• OESOPHAGEAL CANDIDIASIS (OR CANDIDIASIS OF TRACHEA, BRONCHI OR</td>
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<tr>
<td>LUNGS)</td>
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<tr>
<td>• EXTRAPULMONARY TUBERCULOSIS</td>
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<td>• KAPOSI’S SARCOMA</td>
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<tr>
<td>• CMV INFECTION (RETINITIS OR INFECTION OF OTHER ORGANS)</td>
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<tr>
<td>• CNS TOXOPLASMOSIS</td>
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<tr>
<td>• HIV ENCEPHALOPATHY (DISABILITY COGNITIVE AND/ OR MOTOR</td>
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<tr>
<td>DYSFUNCTION INTERFERING WITH ACTIVITIES OF DAILY LIVING, PROGRESSING OVER WEEKS TO MONTHS,</td>
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<td>IN THE ABSENCE OF A CONCURRENT ILLNESS OR CONDITION OTHER THAN HIV INFECTION WHICH COULD</td>
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<td>EXPLAIN THE FINDINGS)</td>
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<tr>
<td>• EXTRAPULMONARY CRYPTOCOCCOSIS INCLUDING MENINGITIS</td>
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<tr>
<td>• DISSEMINATED NON-TUBERCULOUS MYCOBACTERIAL INFECTION</td>
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<tr>
<td>• PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY</td>
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<tr>
<td>• CHRONIC CRYPTOSPORIDIOSIS</td>
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<tr>
<td>• CHRONIC ISOSPORIASIS</td>
</tr>
<tr>
<td>• DISSEMINATED MYCOSIS (EXTRA-PULMONARY HISTOPLASMOSIS OR</td>
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<tr>
<td>COCCIDIOMYCOSIS</td>
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<tr>
<td>• RECURRENT SEPTICAEMIA (INCLUDING NON-TYPHOIDAL SALMONELLA)</td>
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<tr>
<td>• LYMPHOMA (CEREBRAL OR B-CELL NON-HODGKIN’S)</td>
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<tr>
<td>• INVASIVE CERVICAL CARCINOMA</td>
</tr>
<tr>
<td>• ATYPICAL DISSEMINATED LEISHMANIASIS</td>
</tr>
<tr>
<td>• SYMPTOMATIC HIV-ASSOCIATED NEPHROPATHY</td>
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<tr>
<td>• SYMPTOMATIC HIV-ASSOCIATED CARDIOMYOPATHY</td>
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