Awareness, Perceived Risk and Practices Related to Cervical Cancer and Pap Smear Screening Among HIV-Positive Women in an Urban HIV Clinic in Johannesburg, South Africa.

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Declaration

I, **Idah Mokhele (student number 472445)** declare that this research report is my own work. It is being submitted for the degree of Master of Science in Epidemiology in the field of Biostatistics and Epidemiology at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

Signed:

Date:  *28/05/2015*

Dedication

To my family who have sacrificed so much to afford me the incredible opportunities that I have had which have led me to this point in my life. Thank you! I appreciate your sacrifices, support and contribution, and I will endeavour to always make you proud.

Abstract

Background and objectives: Cervical cancer is a major cause of cancer-related deaths in many developing countries yet it is a preventable and treatable in early disease. Recent research has seen increasing morbidity and mortality due to cancer of the cervix attributed to the advent of the human immunodeficiency virus (HIV) epidemic worldwide. Papanicolaou smears (Pap smears) to detect cervical abnormalities are currently the best known form of early detection and prevention of invasive cervical cancer (ICC).

Knowledge and awareness about cervical cancer and associated risk factors, and cervical screening is very important in determining appropriate health seeking behaviours with the aim to reduce morbidity and mortality. This study examines awareness, perceived risk and practices related to cervical cancer screening among HIV-positive women in an urban HIV clinic in Johannesburg, South Africa. This will be useful in making recommendations with regards to designing and planning of screening programmes, and addressing cervical cancer education and awareness.

Materials and methods: This study analysed secondary data collected from an ongoing cervical cancer study undertaken by Right to Care in partnership with the Clinical HIV Research Unit (CHRU) among HIV-positive adult (18 years and older), female patients enrolled in the Themba Lethu Clinic HIV care and treatment programme in Johannesburg, South Africa from November 2009 to December 2012. Clinical data for all respondents was extracted from TherapyEdge-HIV^{TM}, the electronic medical database system used for patient management at the facility.

Descriptive statistics were used to summarise baseline characteristics. Models using logistic regression were developed to estimate odds ratios (OR) to further identify baseline socio-demographic factors and clinical characteristics associated with behaviours studied (awareness,

perceived risk and practice related to cervical cancer and Pap smear testing) and to identify the association between these factors and the prevalence and severity of cervical disease. Awareness of the Pap smear test and the human papillomavirus (HPV) was assessed based on whether the women report knowing what a Pap smear test is, and whether they have ever heard about HPV. Perceived risk about getting cervical cancer was assessed based on how worried the study participants were about getting cervical cancer. Previous Pap screening practice was assessed using reported screening history of the study participants. In addition to this, a sub-analysis was conducted to see how these responses compare to 1) the recommended practice according to the South African national cervical cancer screening guidelines based on the age of participants, and 2) the latest HIV treatment guidelines based on year of HIV diagnosis.

Analysis of attrition of study participants at 12 months of study participation was conducted using different time to event analysis techniques including Kaplan Meier, Log-rank test and Cox proportional hazards model. Cox proportional hazards models were fitted to investigate associations between baseline covariate and attrition.

A sub-analysis was also carried out using descriptive statistics and chi-square tests to compare the cohort of patients that were included in the study (the VICAR1 cohort) and the rest of the larger Themba Lethu Clinic (TLC) population that was not included in the study to see if there were any significant differences noted between the two groups. In addition, a sensitivity analysis of the of 12 month follow up study visit was conducted using descriptive statistics and chi-square tests to determine if there were any significant differences between study participants that came for their 12 month study visit and those that did not come for their 12 month study visit.

Results: Eight hundred and fifty seven (71.30%) participants reported to be aware of Pap smear screening, with only 18.15% reporting to be aware of HPV. Of the 1192 participant who had

data to ascertain perceived risk regarding cervical cancer disease, 662 (55.54%) of the women were very worried, 250 (20.97%) were somewhat worried, 280 (23.49%) were not worried about getting cervical cancer. A total of 381 (36.46%) women had adequate practice according to the national cervical cancer screening guidelines. While 304 (28.57%) had adequate practice according to the national HIV treatment guidelines.

Factors associated with Pap smear screening awareness were being in the 50+ age group (aOR=4.70, 95% CI 1.63-13.55) as compared to the 18-29 age group, being of non-South African nationality (aOR=0.41, 95% CI 0.20-0.83), having a grade 10 to matric level education (aOR=2.12, 95%CI 1.28-3.52), and a tertiary level education (aOR=2.62, 95%CI 1.07-6.41) as compared to having a less than a grade 10 level education. None of the factors assessed were found to be significantly associated with awareness regarding HPV.

Factors associated with perceived risk regarding cervical cancer disease were having a tertiary education (aOR=3.74, 95%CI 1.13-12.38) as compared to having less than a grade 10 level, taking snuff (aOR=0.55, 95%CI 0.33-0.92) and drinking alcohol (aOR=2.53, 95% CI 1.24-5.17). Being in the 30-39 age group (aOR=12.23, 95%CI 4.00-37.35) as compared to being in 18-29 age group, cohabiting with a partner (aOR=0.36, 95%CI 0.17-0.75) as compared to being single, being self-employed (aOR=2.95, 95%CI 0.82-10.66) as compared to those in full time employment, and being initiated on highly active antiretroviral therapy (aOR=0.17, 95%CI 0.06-0.55) were associated with Pap smear screening practices according to the national cervical cancer guidelines. None of the factors proved to be significantly associated with the practice according to the national HIV treatment guidelines, this is mainly because the HIV treatment guidelines have stricter screening requirements for HIV positive women.

Those that had a moderate to severe baseline study Pap smear at enrolment into the study were 92% less likely to have disease progression at their 12 month Pap smear screening (aOR=0.08,

95%CI 0.05-0.13) compared to those that had a negative baseline Pap smear at study enrolment. This is mostly because they would have had a treatment intervention based on their baseline study Pap screening result therefore they would mostly likely not have disease progression at a follow up screening.

Only seven women enrolled in the study died of non-cervical cancer related causes during the study period. In the analysis on all-cause attrition (deceased or lost to follow up) those that are initiated on highly active antiretroviral therapy were 92% less likely to be deceased or lost to follow up than those that were not initiated on highly active antiretroviral therapy (aOR=0.08, 95% CI 0.05-0.13). The global test for the overall model showed that the proportional hazard assumption had not been violated, p=0.684.

Conclusions: Results for our study showed high levels of Pap smear screening awareness amongst the study participants. However, low levels of Pap screening uptake was observed for study participants. These results and results shown in previous studies show that awareness is only the first hurdle in the challenges related to cervical cancer prevention and treatment. Adequate practice is the factor that will have the most positive influence on the disease morbidity and mortality. Rates of screening practices have been found to be worse in populations with less than 70% Pap smear screening awareness.

Findings from this study and similar findings from other studies highlight that more research needs to be done into effective health education programmes to address the gaps in adequate screening practice. These efforts should not only target the clients but also the health providers as they also have an important role to play in improving awareness, knowledge and practices related to cervical cancer and Pap smear screening amongst their clients.

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Abbreviations and acronyms

3TC - Lamuvidine

AIDS ï Acquired Immunodeficiency Syndrome

AGUS ï Atypical Glandular Cells of Undetermined Significance

ALT – Alanine aminotransferase

aOR ï Adjusted odds ratio

ASC ï Atypical Squamous cells

ASC-H ï Atypical Squamous cells where a high-grade squamous intraepithelial lesion canôt be excluded

ASCUS ï Atypical Squamous Cells of Undetermined Significance

AST – Aspartate transaminase

BMI – Body mass index

CCMT ï Comprehensive Care, Treatment and Management

CD4 ï Cluster of Differentiation 4

CEO – Chief executive officer

CHRU ï Clinical HIV Research Unit

CI ï Confidence interval

CIN ï Cervical intraepithelial neoplasia

CIS ï Carcinoma in situ

d4T ï Stavudine

EFV - Efavirenz

HAART ï Highly active antiretroviral therapy

HERS ï Health epidemiology research study

HIV ï Human immunodeficiency virus

HPV ï Human papillomavirus

HR ï Hazard ration

HREC ï Health research ethics committee

HSIL ï High grade intraepithelial lesion

ICC ï Invasive cervical cancer

IQR ï Interquartile range

LEEP ï Loop electrosurgical excision procedure

LTFU – Lost to follow up

LSIL ï Low grade squamous Iintraepithelial lesion

NGO – Non-governmental organization

NVP ï Nevirapine

OR ï Odds ratios

Pap smears ï Papanicolaou smears

SA ï South Africa

SCC ï Squamous Cell Carcinoma

SD ï Standard deviation

SIL ï Squamous Intraepithelial Lesion

SOP - Standard operating procedure

TB ï Tuberculosis

TLC ï Themba Lethu Clinic

UNAIDS ï United Nations Programme on HIV/AIDS

VICAR - Validation of implementation of cervical cancer screening applications in HIV-seropositive women

VL ï Viral Load

WHO ï World Health Organisation

CHAPTER 1: Introduction

1.1. Background

Cervical cancer is considered to be a major public health concern in Southern Africa and all over the world. It is said to be the second most common cancer to affect women globally, with close to 530 000 new cases and 270 000 deaths from the disease in 2012 (1). Over 85% of the cervical cancer related deaths are from less developed regions (1). It is a major cause of cancer-related deaths in women in many developing countries yet it is a preventable and treatable disease.

Recent studies have shown that the human papillomavirus (HPV) plays an important role in the development of pre-cancerous lesions and their progression into cancer (2, 3, 4). In addition the development of the disease has been found to also be associated with many other factors, including an early sexual debut, multiple sexual partners, smoking and extended use of oral contraceptives (5).

Human immunodeficiency virus (HIV) infection also represents a tremendous health burden worldwide. The Joint United Nations Programme on HIV/ acquired immunodeficiency syndrome (AIDS), (UNAIDS), estimated that in 2012, an estimated 35.3 million people were HIV infected; 25 million of these live in sub-Saharan Africa with over 60% of these being women (6). Recent research has seen increasing morbidity and mortality due to cancer of the cervix attributed to the advent of the HIV epidemic worldwide. The World Health Organisation (WHO) now regards invasive cervical cancer (ICC) as an AIDS-defining illness (1, 7, 8, 9).

The association between HIV and ICC is complex, with several studies now demonstrating an increased risk of pre-invasive cervical lesions among HIV-infected women (3, 4, 10). HIV-infected women with more advanced immune-suppression (CD4 count < 200 cells/μL) seem to be particularly vulnerable to infection with persistence of the high-risk HPV types that can

lead to cancer (10). The introduction of highly active antiretroviral therapy (HAART) in the fight against HIV has added new complexities in the fight against both diseases. Previous studies have shown that there is a greater lifetime risk of cervical dysplasia among HIV positive women on HAART because of the increased life expectancy as a result of HAART (7). However, some studies have shown initiation of HIV positive women on HAART may reduce the prevalence and progression of cervical pre-cancerous lesions (7, 10).

Papanicolaou smears (Pap smears) to detect cervical abnormalities are currently the best known form of early detection and prevention of ICC (11, 13, 14). It remains the most effective means of prevention of both the incidence of and mortality from ICC (11). ICC progresses slowly, often taking many years to develop therefore early detection of abnormal cells means better treatment options and a better prognosis (11).

Knowledge and awareness about cervical cancer and associated risk factors, and cervical screening is very important in determining appropriate health seeking behaviours with the aim to reduce morbidity and mortality (10). This study examines awareness, perceived risk and practices related to cervical cancer screening among HIV-positive women in an urban HIV clinic in Johannesburg, South Africa. This will be useful in making recommendations with regards to designing and planning screening programmes, and addressing cervical cancer education and awareness.

1.2. Problem statement

Cervical cancer is a disease that affects the tissues of the cervix (the organ connecting the uterus and vagina) in the female reproductive system (12). It is a typically slow-growing cancer that may not present symptoms until the very late stages when it has advanced and spread, and may be difficult to treat; resulting in low cure rates and high fatality rates (12).

Pap smear screening is a microscopic examination of cells taken from the cervix. A Pap smear can detect changes of cells caused by infections such as HPV which is the underlying cause of cervical cancer (12). The natural history of ICC shows good potential for prevention and cure as it slowly progresses through stages of pre-cancerous intraepithelial lesions before developing into an invasive form (2, 11). This allows for early detection which is pivotal as a prevention mechanism to improve the prognosis and increase the possibility of complete eradication using available treatment interventions (11).

Cervical cancer begins with the development of pre-cancerous, benign lesions in the cervix. According to WHO classification, the first stage of development is mild dysplasia, which can then progress to becoming moderate dysplasia, severe dysplasia, and then carcinoma in situ (CIS) or ICC (2, 12).

There are two systems of classification in reporting cervical screening results, one is based on a biopsy (histology section) of the cervix and the other is based on a Pap smear (also termed cytology-based Pap smear). Cell abnormalities that are seen on a biopsy of the cervix use the term cervical intraepithelial neoplasia (CIN), and according to this system mild to moderate dysplasia are classified as CIN1, intermediate dysplasia as CIN2, and severe dysplasia and carcinoma in situ are together classified as CIN3 (2, 12).

Cell abnormalities that are seen on a Pap smear are described using the Bethesda system that uses the terms squamous intraepithelial lesion (SIL) or atypical squamous cells (ASC). The Bethesda system simplifies CIN system further by classifying CIN1 as Low Grade Squamous Intraepithelial Lesion (LSIL) or atypical squamous cells of undetermined significance (ASCUS), and both CIN2 and CIN3 as High Grade Squamous Intraepithelial Lesion (HSIL) or atypical squamous cells where a high-grade squamous intraepithelial lesion cannot be excluded (ASC-H) (2, 12).

High income countries have seen a reduction of 70% in the burden of cervical cancer screening as a result of the introduction of routine Pap smear testing in organised screening programmes (15, 16). In 2000, the South African government put in place a national cervical screening guideline which used the early detection and treatment approach for prevention of the disease. The guidelines recommend three Pap smears in a lifetime at 10 year intervals, at 30, 40 and 50 years of age in public sector health facilities (17). However, cervical cancer has been found to progress earlier to ICC in women whose immune system has been compromised by HIV (18). Therefore it is very important to integrate cervical cancer screening with HIV/AIDS prevention, care and treatment services to ensure that Pap smear testing services are available in this setting and are administered according to the latest guidelines (19).

The guidelines for the management of HIV/AIDS released by the South African Department of Health in 2010, with the latest edition released in 2013, stated that all HIV-positive women need cervical cancer screening on diagnosis of HIV, and if this test is negative then subsequent screening every three years, irrespective of HAART status (18). If the results of a Pap smear is abnormal the guidelines recommend a repeat Pap smear according to the results of the first Pap smear as follows (18):

- ASCUS - repeat in one year and if still ASCUS, refer for baseline colposcopy.
- LSIL - repeat in one year and if still LSIL, refer for baseline colposcopy
- HSIL/ASC-H - refer for colposcopy
- Carcinoma in situ - refer immediately

Even so, introducing a national prevention strategy for cervical cancer not only requires the provision of the most appropriate, and cost effective screening service, but should also ensure that women who need the service, utilize and benefit from the service (20). Previous studies have shown that health promotion and advocacy around cervical cancer and Pap screening are very important in improving coverage of screening services. A comparative study among

women from Japan and Brazil showed that knowing the goal of the Pap smear test influenced women to take the test, which in turn resulted in a greater, more proactive, demand for the test (21).

Lack of knowledge and awareness of cervical cancer and cervical screening and treatment of abnormal Pap smears is seen as a major barrier to preventing cervical cancer. This is in addition to a number of other factors that include low education levels, poverty, religious/cultural beliefs and limited health resources (22). Innovative strategies to increase awareness of cervical cancer and the importance of screening as a preventive measure are needed, especially in high risk population groups such as HIV-positive women (14, 23).

According to a WHO report on comprehensive cervical cancer control, health education and promotion should be an integral part of any national cervical cancer control programme (12). It should incorporate an awareness component, behaviour change communication, and counselling (12). The challenge is that currently little is known about knowledge and awareness and screening practices among HIV positive women in Southern Africa. In addition to this, cervical cancer disease and itôs prevention does not get the same amount of recognition and media attention as the other more recognized diseases in the region; Malaria, HIV, and TB and therefore often loses out in the competition for priority in resources in the already overburdened resource-poor health systems in developing countries including those in Southern Africa.

1.3. Justification for the study

There is limited data on health-seeking behaviour of HIV positive women for conditions other than their HIV infection. Getting a better understanding of this behaviour will assist in formulating better strategies to improve uptake of services including critical prevention services crucial to this group such as cervical cancer screening.

In order for a national approach to cervical cancer screening to work, women need to be aware of cervical cancer and associated risk factors, as well as the screening and treatment services

available to them. If patients are not aware of the disease and associated risks, they will not seek timely screening or treatment services and therefore are at higher risk of disease progression and poor prognosis (22).

ICC progresses slowly, often taking many years to develop. Therefore cervical cancer screening can help find cancer or precancerous changes at an early stage, and when abnormal tissue/ pre-cancerous lesions are caught in the early stages, before they become invasive they are easier to treat (12, 24). There are a number of treatment options for pre-cancerous lesions (12, 24):

- Laser surgery uses a laser beam to destroy abnormal cells.
- Cryosurgery destroys cancerous and pre-cancerous lesions by freezing them.
- Loop electrosurgical excision procedure (LEEP) uses a thin wire loop (through which an electrical current is passed) to cut away an area of abnormal cells from the cervix.
- Conization surgically removes a cone-shaped piece of tissue from the cervix.

These procedures are not as complicated, invasive and as costly as the interventions employed when the pre-cancerous lesions have progressed to a more invasive form (12, 24).

There is a variety of treatment options for patients with ICC, of which the most common include surgery, chemotherapy and radiation. Surgery is in the form of a hysterectomy and it involves the removal of the uterus; and chemotherapy uses drugs to stop growth of the cancerous cells (24). Radiation therapy uses high energy- X-rays or other types of radiation to kill cells or keep them from growing. These procedures are not only complicated and invasive with a variety of side-effects, but they are costly and require significant resources, highly skilled health staff, and infrastructure (24). The World Bank study on cervical cancer prevention showed that screening for the early detection and treatment of abnormal cervical tissue was far cheaper than hospital-based treatment of advanced cancer (25). Therefore early detection of abnormal cells means better treatment options and a better prognosis.

This study examines awareness, perceived risk and practices related to cervical cancer screening among HIV-positive women in an urban HIV clinic in Johannesburg, South Africa. The study further assessed the association between socio-demographic characteristics and awareness, perceived risk and practices related to cervical cancer screening. The study also assessed the relationship between awareness, perceived risk and practices related to cervical cancer and the outcome of the most recent Pap smear screening. This will be useful in making recommendations with regards to addressing cervical cancer education and awareness when designing, planning and implementing screening programmes.

1.4. Literature review

Cervical cancer is largely a preventable and curable disease but despite this it is still a major burden on womenôs public health worldwide (26). Data obtained from the IARC (International Agency for research on Cancer) - GLOBOCAN 2012 database, shows that cervical cancer was responsible for close to 270 000 deaths in 2012, over 85% of which occurred in developing countries with 57 000 occurring in Africa (26, 27).

The HIV/AIDS epidemic continues to have widespread detrimental effects on people all over the world. UNAIDS reported an increase in people living with HIV worldwide in its annual AIDS epidemic update (6). They reported an estimated increase from 8 million in 1990 to 33 million by end of 2008 of which 67% live in sub-Saharan Africa, with South Africa reported to be one of the countryôs worst affected by the epidemic (6).

Research has shown that there is a link between cervical cancer and HIV/AIDS infection. Generally HIV-infected women are reported to have a greater persistence of HPV infection with higher prevalence rates of LSIL and HSIL, more rapid progression rates and higher recurrence rates following treatment interventions (7, 8, 10, 16, 28, 29, 30). Gaym et al. reported an association between HIV sero-positivity and abnormal Pap smear results in their study

among young HIV-positive women in rural KwaZulu Natal, South Africa (16). Earlier studies in Rwanda and Kenya reported a prevalence of squamous intra-epithelial lesions (SIL) among HIV-positive women ranging from 31-63% (31, 32). A study by Theiler et al. using HIV Epidemiology Research Study (HERS) data found higher rates of re-activation of latent HPV infections among HIV-infected women than in un-infected women. Low CD4 count and age younger than 35 years were found to be significant factors of re-infection amongst the HIV-infected women in the HERS study (33).

In the midst of an ever increasing burden of HIV especially among young women, researchers have also observed that HIV-positive women presenting with cervical cancer are significantly younger than their HIV-negative counterparts presenting with the same disease (16, 28). Some researchers suggests expansion of the overall resources allocated for the cervical cancer screening programme to be able to detect cervical cancer among this subgroup of women (16). The current national screening programmes in South Africa and other developing countries may overlook this subgroup of women until they are older, but by then whatever abnormalities they might have had when they were younger would have progressed further into higher grade abnormalities (16). This emphasizes the importance of integrating Pap screening services and HIV services so that this subgroup of women can be identified earlier and receive the necessary treatment (34).

Cervical cancer incidence and mortality rates have declined substantially in the developed world following the introduction of screening programmes. Screening programmes in Africa, are however, often emergent or non-existent (15). Memiah et al. found that only a mere 5% of women undergo cervical cancer screening in developing countries compared to a notably contrasting 40-50% in the developed world (10, 35). Previous studies have identified the lack of regular Pap smears as the single greatest risk factor for a poor outcome in women who develop cervical cancer (36). A study in Brazil showed an increased risk of ICC among women

who have never had a Pap test. In those women who had the test before, the risk increased proportionally to the amount of time elapsed since the last test (37).

Lack of knowledge and awareness of cervical cancer and cervical screening has been shown to be one of the significant factors hampering the uptake of cervical screening services in the developing world (23). Findings from previous studies highlighted the importance of providing accurate information about cervical cancer and the purpose of Pap smear screening in order for screening programmes to be effective (8, 13). The prevalence of ever having a Pap smear among college students in a Ghana university was 12%, with only 7.9% of the respondents knowing about the link between HPV and cervical cancer (22). A patientôs medical practitioner was identified as the main source of information about the disease and the test, and influenced whether the patient took the test or not (13, 20, 37).

Akinyemiju et al. also found low levels of screening history in a study reviewing health care access and cervical cancer screening by analysing data from the South African World Health Survey (WHS) (38). This study also found that availability of physicians was an important predictor of screening uptake (38). A concerning finding for low resource settings where increasing number of physicians is not a feasible option (38). Instead in these settings recommended strategies to increasing availability of the service include training nurses and other lower cadres of staff, and where possible to use screening methodologies not requiring complex pathology and laboratory infrastructure (39).

The Health Belief Model postulate that people will engage in health seeking behaviour if they perceive benefits to themselves accruing from that behaviour (40).Various health behaviour theories suggest that screening utilisation and information seeking behaviour are mediated by perception of risk, attitude and knowledge, social influence and self-efficacy (40). Several studies have highlighted the significance of perceived risk for cervical cancer as an important factor that influences screening behaviour (41). A study in Kenya on the perceptions of risk

and barriers to cervical cancer screening found that 35% of participants did not think they were at risk of cervical cancer and felt no need to screen for the condition (41). In the same study the fear of abnormal results was highlighted as one of the barriers to women going for cervical screening; some of the women had a fatalistic view of cervical cancer screening where diagnosis of any abnormalities was equated with certain death (41, 42). This was due mostly to lack of knowledge and awareness about the disease.

Stark et al. conducted a retrospective case-series study of cancer patients and cancer survivors and results showed little HPV knowledge, with only 19% of the participants accurately identifying HPV as the primary risk factor for cervical cancer (43). A disturbing result as one would expect that diagnosed patients who have undergone treatment would have had several opportunities to interact with the health practitioner and request/receive information or education about the disease.

A cross-sectional study relating to cervical cancer and Pap screening among HIV patients was done in Italy where intravenous drug use was cited as the main mode of HIV transmission in the population. Again, as with other studies among non-HIV patients, the level of schooling was identified as a significant risk factor to having knowledge about the disease and the test. In addition, the study also showed that the area of birth was found to significantly impact on knowledge about the disease and the test (44).

There have been limited studies assessing awareness, perceived risk and practices among HIV-positive patients conducted in the South African context. Many of the studies conducted to assess knowledge, awareness, attitude, beliefs, perceived risk or screening practices relating to cervical cancer and screening were not done amongst HIV positive women or data on study participantôs HIV status was not collected. In addition, many of the studies involving cervical cancer and HIV positive women in Southern Africa mostly focus mostly on clinical aspects related to the both disease as opposed to behavioural aspects such as the womenôs cervical

cancer screening practice (8, 9, 10, 16, 29). Screening behaviour and general health seeking behaviour related to prevention services is not widely studied amongst HIV positive women in South Africa (10, 38). Especially in the context of the comorbidities that present themselves to this subgroup of women as a result of their previous immunosuppression and their increased life expectancy as a result of being initiated on HAART. Therefore this study aims to examine the awareness, perceived risk and practices related to cervical cancer and Pap smear screening among HIV-positive women in an urban HIV clinic in Johannesburg, South Africa and identify factors associated with these and the impact on the prevalence and severity of the disease.

1.5. Study objectives:

1.5.1. Main objective

To assess the awareness, perceived risk and practices related to cervical cancer and Pap screening among HIV-positive women in an urban HIV clinic in Johannesburg, South Africa.

1.5.2. Specific objectives

1. To assess awareness, perceived risk and practices related to Pap smear testing among women enrolled in an HIV care and treatment programme in a Johannesburg public sector clinic between November 2009 and December 2012.
2. To assess the socio-demographic characteristics and clinical characteristics at HAART treatment initiation that may be associated with awareness, perceived risk and practices related to cervical cancer and Pap smear testing.
3. To assess the association of awareness, perceived risk and practices related to Pap smear testing and the prevalence and severity of cervical disease using the outcome of the most recent Pap smear test.

4. To assess mortality and outcomes related to morbidity at 12 months follow-up of patients enrolled in the cervical cancer study in relation to their awareness, perceived risk and practices related to cervical cancer and Pap smear testing.

CHAPTER 2: Materials and methods

2.1. Study design

In April 2005, the non-governmental organization (NGO) Right to Care in partnership with the South African (SA) government established a cervical cancer screening and treatment centre alongside the HIV care, management and treatment facility in the Themba Lethu Clinic, Johannesburg, South Africa. The clinic has taken the lead in offering cervical screening for HIV-positive patients presenting with cervical disease (1).

This study made use of secondary data collected from an ongoing Cervical Cancer study undertaken by Right to Care in partnership with the Clinical HIV Research Unit (CHRU) among HIV-positive adult females enrolled in the Themba Lethu Clinic HIV care and treatment programme in Johannesburg, South Africa. This primary study is a longitudinal study that aims to describe the patient population that is currently receiving cervical cancer screening at the Themba Lethu Clinic through the Validation of Implementation of Cervical Cancer Screening Applications in HIV-seropositive Women (VICAR 1) protocol, and their treatment outcomes through Validation of Implementation of Cervical Dysplasia Treatment Modalities in HIV-Seropositive Women (VICAR 2) protocol. Enrolment for VICAR 1 and VICAR 2 began in November 2009 and February 2010 respectively and is ongoing.

2.2. Study population

The study population comprised of a total of 1202 adult (Ó18 years of age), HIV-positive female patients enrolled in the HIV Care and Treatment programme at Themba Lethu Clinic in

Johannesburg, South Africa, participating in cervical cancer study (VICAR 1 and VICAR 2) from November 2009 to December 2012.

2.3. Inclusion and exclusion criteria

Eligibility

i. HIV-positive females
ii. Between and including women of 18-65 years of age
iii. Eligible to participate in the cervical cancer study (VICAR 1 and VICAR 2) and signed written informed consent

Exclusion criteria

i. <18 years of age
ii. Pregnant
iii. Did not meet the eligibility criteria for VICAR 1 study
iv. Did not sign consent

2.4. Sample size

The study made use of use of secondary data collected from the cervical cancer study (VICAR 1 and VICAR 2). The sample size for the primary study was estimated at 1200. Our study made use of all data collected as at the end of December 2012 which consisted of all 1202 study participants.

2.5. Measurement and data sources

In the primary study participants answered an interviewer-administered structured questionnaire containing coded questions about medical, social and sexual history. Questions about parity, history of contraception methods used, details of their cervical examination plan and Pap smear results were also recorded. The questionnaire also included a section that examined awareness, perceived risk and practices concerning cervical cancer and cervical

cancer screening among the participants, these questions were the focus of this study (Appendix 7). The interviews are ongoing from November 2009, and were administered by trained female interviewers.

2.6. Study variables

Table 1. Summary of study variables

	Variables	Type	Categories
Exposure Variables			
Socio-Demographic Data	Age	Categorical	1=18- 29 2=30-39, 3=40-49, 4= >50
	Ethnicity	Categorical	0=Black, 1=Other
	Marital Status	Categorical	1= Single, 2=Married, 3= Cohabiting, 4=Divorced/separated, 4=Widowed
	Education Level	Categorical	1=< Standard 8, 2= Standard 8 ï 10 , 3=Tertiary, 4=None
	Currently Employed	Categorical	0=No, 1=Yes
	Type of Employment	Categorical	1==Full-time, 2=Part-time, 3=Self-employed, 4= Unknown Occupation, 5=Student, 6= State Grant
	Currently Smoking:	Categorical	0=No, 1=Yes
	Current smoking-How much?	Categorical	0=<5 per day, 1=>5 per day
	Currently Drinking Alcohol	Categorical	0=No, 1=Yes
Clinical Data	Baseline WHO staging:	Categorical	1= I-II, 2= III-IV
	Baseline Body mass index (BMI) *(kg/m²)*	Categorical	1= under-weight, 2= normal, 3= over-weight
	Baseline CD4 *(cells/mm³)*	Categorical	1= 0-50, 2= 51-100, 3= 101-250, 4= 251-350, 5= >350
	Baseline HIV viral load (VL) *(copies per ml)*	Categorical	1= < 100000, 2= >= 100000
	Baseline Haemoglobin (Hb) *(g/dL)*	Categorical	1= <8, 2= >=8
	Baseline Aspartate transaminase (AST) *(IU/L)*	Categorical	1= < 40, 2= >= 40
	Baseline Alanine aminotransferase (ALT) *(IU/L)*	Categorical	1= < 40, 2= >= 40
	Baseline Lactate levels *(mmol/L)*	Categorical	1=0 - 2.4, 2= 2.5 ï 4, 3=>=4
	HAART regimen at HAART initiation	Categorical	1=1a, 2=1a, 3=other
	Previous Pap smear results	Categorical	1=Negative, 2=Moderate, 3=Severe/ICC, 4=No results
	Baseline study Pap smear results	Categorical	0=Negative, 1=Moderate, 2=Severe/ICC, 3=No results
Awareness, Perceived Risk & Practice related variables			
Awareness, Perceived Risk & Practices related v ariables	Do you know about Pap smear	Categorical	0=No, 1=Yes
	Have you ever had Pap smear	Categorical	0=No, 1=Yes
	If you havenôt had a Pap smear, how come?	Categorical	1=Donôt know, 2=Afraid it would hurt, 3=No access, 4=No time to wait in another queue, 5=Work, 6=Nobody to look after children, 7= No transport, 8=Didnôt want anyone to examine me there, 9=Other, Specify_____
	Approximately how many Pap smears have you had in your life time?	Continuous	N/A
	Since your first smear, can you guess how often you have been getting your Pap smears?	Categorical	1=Never, 2=Yearly, 3=Once every 2-3 years, 4=Once every 4-5 years, 5=Once every 6-10 years, 6=Less than every 10 years
	Results of previous Pap smear	Categorical	1=Normal, 2=ASCUS, 3=Patient didnôt collect results, 4=AGUS, 5=ASC-H, 6=Patient canôt remember, 7=LSIL (CIN1), 8=CIN2, 9=CIN3, 10=SCC
	Results of current Pap smear	Categorical	1=Normal, 2=LSIL (CIN1), 3= HSIL, 4=ASCUS, 6=Glandular, 9=Pending, 10=Not done, 11=SCC, ASC-H, 99= Insufficient/inadequate sample
	Do you believe Pap smears are good for health?	Categorical	0=No, 1=Yes, 98=Donôt know, 101=Refuse to answer
	Have you ever been offered Pap smear at your healthcare clinic?	Categorical	0=No, 1=Yes, 98=Donôt know, 101=Refuse to answer
	Has health worker ever told you that you should have a Pap smear in the last two years?	Categorical	0=No, 1=Yes, 98=Donôt know, 101=Refuse to answer
	If you decide to get a Pap smear, where would you go?	Categorical	1=Casualty, 2=HIV clinic, 3=Local primary health care clinic, 4=Government Obstetrics and gynaecology department, 5=TB area, 6=Other, Specify_____
	In last three years, did you try to get a Pap smear but were unable to get one?	Categorical	0=No, 1=Yes, 98=Donôt know, 101=Refuse to answer
	Have you ever heard about HPV or Human Papillomavirus?	Categorical	0=No, 1=Yes, 98=Donôt know, 101=Refuse to answer

	How worried are you about getting cervical cancer?	Categorical	1=Very worried, 2=Somewhat worried, 3=Not worried at all, 4=Never heard of cervical cancer

2.7. Study definitions outcomes

Awareness about Pap smear, cervical cancer and HPV: Awareness regarding the Pap smear test and HPV was assessed based on whether the women report knowing what a Pap smear test is, and whether they have ever heard about HPV respectively.

To ascertain Pap smear awareness study participants were asked whether they knew what a Pap smear is and whether they have ever heard of HPV.

Table 2: Questions to ascertain awareness regarding Pap smear screening, cervical cancer and HPV

Question	Categories
Do you know what a Pap smear is?	0=No, 1=Yes, 98=Donôt know, 101=Refuse to answer
Have you ever heard about HPV or Human Papillomavirus?	0=No, 1=Yes, 98=Donôt know, 101=Refuse to answer

Perceived Risk regarding cervical cancer: Perceived risk was assessed based on whether the women are aware of the serious implications related to developing cervical cancer based on how worried they were about getting cervical cancer.

Table 3: Questions to ascertain perceived risk regarding getting cervical cancer disease

Question	Categories
How worried are you about getting cervical cancer?	1=Very worried, 2=Somewhat worried, 3=Not worried at all, 4=Never heard of cervical cancer

Practice regarding Pap smear screening: Practice regarding Pap smear testing was assessed using reported screening history of the women. In addition to this, a sub-analysis was conducted to see how these responses compare to 1) the recommended practice according to South African national cervical screening guideline based on the age of participants, and 2) the latest HIV/AIDS guidelines based on year of HIV diagnosis.

The South African national cervical screening guidelines recommend three Pap smears in a lifetime at 10 year intervals, at 30, 40 and 50 years of age in public sector health facilities (18). Therefore, for women that were between the ages of 30 and 40 during the study, practice was

considered adequate if they have had at least one Pap smear in their life time. For women who were between the ages of 40 and 50 practice was considered adequate if they had more than one Pap smear in their life time and they last had a Pap smear no more than 10 years ago.

The second sub-analysis assessed practice based on year of HIV diagnosis since the HIV/AIDS guidelines recommend cervical cancer screening on diagnosis of HIV (18). In this analysis practice was considered adequate if the women have had one Pap smear for every 3 year interval since HIV diagnosis. For example practice was considered as adequate if the women have had one Pap smear in their life time if they were diagnosed with HIV within a year to less than three years ago from the interview date. If they have been diagnosed with HIV more than three years ago from the interview date, practice was considered adequate if they had more than one Pap smear in their life time.

Table 4: Questions to ascertain practices related to Pap smear screening

Question	Categories
Approximately how many Pap smears have you had in your life time?	Continuous
Since your first smear, can you guess how often you have been getting your Pap smears?	1=Never, 2=Yearly, 3=Once every 2-3 years, 4=Once every 4-5 years, 5=Once every 6-10 years, 6=Less than every 10 years

The **prevalence and severity of cervical cancer disease** was defined using the most recent Pap smear results. Pap smear results were categorised into negative, moderate, or severe based on Pap smear results definitions.

Table 5: Definitions of Pap smear results

Pap Smear Results Severity	Pap smear (cytology) Results	Biopsy (histology) Results
Negative:	Negative	Negative
Moderate	LSIL/ASC-US/AGUS	CIN I
Severe:	HSIL/ASC-H	CIN II CIN III
ICC:	SCC/Adenocarcinoma	SCC/Adenocarcinoma
Unknown:	Results unknown	Results unknown

Pap smear results were considered as negative if the participantsô Pap smear test or biopsy samples have no cell abnormalities or are reported as negative for intraepithelial lesion or malignancy. Results were considered as moderate if participantsô Pap test samples are ASC-US, atypical glandular cells of undetermined significance (AGUS), LSIL or CIN I. Results were considered as severe if the participantsô Pap test sample results are HSIL, ASC-H, CIN II or CIN III; while squamous cell carcinoma (SCC) was considered as ICC. If participants did not recall what the results from their previous test were or they did not collect them, then the results were considered unknown.

The **12 month follow-up outcome** was analysed in relation to the participantsô awareness, perceived risk and practice related to Pap smear testing according to the following categories (dichotomous):

i) Development of dysplasia at the 12 month study follow-up visit Pap smear screening where there was none present before

ii) Worsening of dysplasia at the 12 month study follow-up visit Pap smear screening from a lower grade to a higher grade (e.g. from CIN I to CIN III)

iii) Development of ICC at the 12 month study follow-up visit Pap smear screening where there was none present before

iv) All-cause mortality for individuals enrolled in the study

Attrition of study participants at 12 months of the study was determined using study data and data extracted from TherapyEdge-HIV^{TM} the electronic medical database system used for patient management at the facility. These data was used to ascertain if at 12 months of study enrolment study participants were still alive and in HIV care or if they were deceased or lost to follow up (LTFU). Study participants were determined to be LTFU when more than three separate attempts to contact them using the contact details provided are unsuccessful and the missed visit is outside of the allowable window for the visit (3 months from appointment date).

This information was captured in the study database where a data element was included to the dataset to indicate what participantôs status was at 12 months of the study after the status was determined through study protocols and processes.

2.8. Data processing methods and data analysis

2.8.1. Data processing methods

The data from the primary study was captured using Microsoft Access. Data for this study was transferred from the Microsoft Access database to STATA (Version 11) for analysis. Clinical data for all respondents was extracted from TherapyEdge-HIV^{TM}, the electronic medical database system used for patient management at the facility. This data was exported to STATA (Version 11) for analysis. To maintain confidentiality all personal identifiers were removed from all data sources used in this study (original study database and TherapyEdge-HIV^{TM}).

A summary of socio demographic and clinical characteristics of women who participated in the study are described in Table 6 which also describes the proportion of missing data for each variable.

2.8.2. Data analysis

2.8.2.1. Descriptive statistics

Descriptive statistics was used to summarise baseline characteristics. Continuous variables were described using mean and standard deviation if their distribution was normally distributed, or median and interquartile range if their distribution was not normally distributed. Categorical variables were described using frequencies and percentages using tabulations in STATA.

2.8.2.2. Inferential statistics

Univariate analyses was used to explore the link between participantôs awareness, perceived risk and practices related to cervical cancer and Pap smear testing, socio-demographic and

clinical characteristics and most recent Pap smear results respectively. The crude odds ratio (OR) was reported as the outcomes were dichotomous.

For continuous variables we first tested for normality and for non-normally distributed variables. The T-test was used for normally distributed variables, and non-parametric tests (Mann-Whitney test or Kruskal-Wallis) for non-normally distributed variables to test for association between the exposure and outcomes. For categorical variables the Chi-squared test was used provided the conditions for using this test are met (e.g. number of observations per cell is more than 10), if not the Fischerôs exact test or other non-parametric test were used.

Models were developed using logistic regression incorporating factors identified as significant in the univariate analysis (using $p < 0.2$) and priori variables of importance, to further determine socio-demographic and clinical factors associated with behaviours studied (awareness, perceived risk and practice related to cervical cancer and Pap smear testing). The multivariate model was derived by using manual forward selection. Factors were added to the model one at a time starting with the one with the smallest p-value checking for changes in the model estimates and significance levels, compared to the preceding models. The importance of each factor included in the model was verified by using the log likelihood test and comparing each modelôs estimates with the point estimate from the univariate analysis model containing that factor. Factors that do not contribute to the model based on these criteriaôs were eliminated and a new model fitted. A log-likelihood p-value of <0.05 was used for inclusion of a factor in the final model. .

All statistical tests performed in the analysis excluded missing data. Post-estimation diagnostics test such the Hosmer-Lemeshow goodness of fit test; and the test to assess the model specification were used to examine whether the models were sound. Interaction terms were created fitted into the multivariate model to assess statistical significance.

A sub-analysis was carried out to compare the cohort of patients that were included in the study (the VICAR1 cohort) and the rest of the larger Themba Lethu Clinic (TLC) population that was not included in the study. The following socio-demographic factors were compared between the study cohort (VICAR1) and the TLC cohort; race, nationality, currently smoking, currently drinking alcohol, education level, and employment status. In addition, the following clinical factors were also compared between the two cohorts; HAART status, age at HAART initiation, HAART regimen at HAART initiation WHO staging, body mass index (BMI), haemoglobin, CD4, and viral load (VL).

Analysis of attrition of study participants was conduct using time to event analysis as the method of analysis. The overall incidence rate attrition (death or LTFU), and incidence rates at specific time periods were calculated. Person time was calculated from enrolment into the study until earliest death, transfer out, LTFU or administrative censoring (close of dataset 31 December 2012).

Time to event analysis was performed using different survival techniques including Kaplan Meier, Log-rank test and Cox proportional hazards model. Cox proportional hazards models were fitted to investigate associations between baseline covariate and attrition. Global tests to test for validity of the proportional hazards assumptions were performed using the Schoenfeld residuals. Variables with p value <0.2 in univariate analysis were considered for the multivariate Cox models, these were added to the models to further determine factors associated with attrition, these added to the model one at a time starting with the one with the smallest p-value and the adjusted (multivariate) estimates were reported. Variables which violated the proportional hazards assumption were excluded from the model.

A sensitivity analysis of the of 12 month follow up study visit was conducted to determine if there were any significant differences between study participants that came for their 12 month study visit and those that did not come for their 12 month study visit.

2.9. Ethical consideration

Ethical clearance for the proposed study was obtained from The University of the Witwatersrand Research Ethics Committee (Medicine) (HREC clearance certificate number M120310, 30/03/2012), and approval to use the data set from the head of Themba Lethu Clinic and the CEO of Helen Joseph Hospital, where Themba Lethu Clinic is situated. To maintain confidentiality all personal identifiers were removed from the data before secondary analysis.

The primary study received ethical approval in October 2009 from the University of The Witwatersrandôs Research Ethics Committee (Medicine) (HREC clearance certificate number M090516, 01/09/2009). Informed consent was obtained from each participant before data collection. Interviewers were trained and briefed regarding handling of human subjects and confidentiality. In addition, the primary study procedures were conducted in accordance with good clinical practice and ethical consideration and handling of human subjects. This is documented in the protocol and standard operating procedures (SOPs) for the primary study.

CHAPTER 3: Results

3.1. Descriptive analysis

3.1.1. Study flow chart

A total of 1202 women were screened and then enrolled in the study. Of these 4 did not have screening results reported as their sample was inadequate for analysis. Results were categorised into Negative, Moderate, Severe and ICC based on the grade of lesions found from the screening at enrolment, as outlined in Table 5. Figure 1 shows a summary of screening and enrolment outcomes of the study participants.

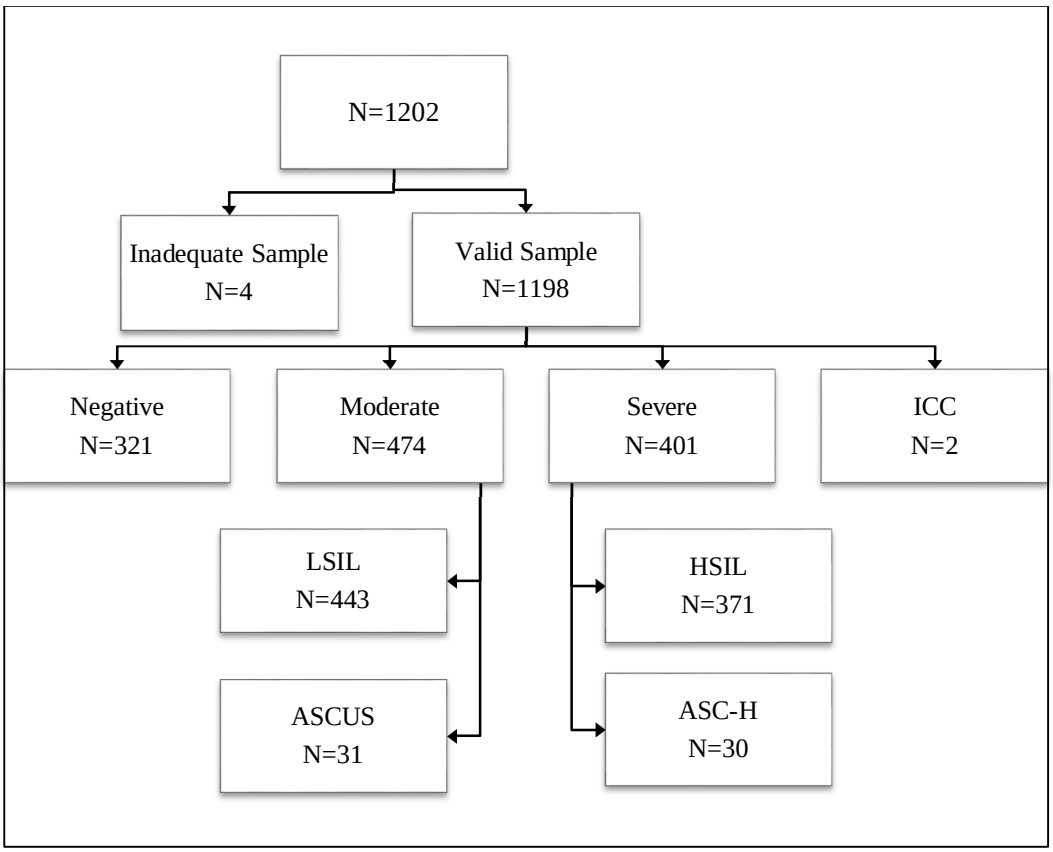

Figure 1. Study flow chart showing enrolment and Pap screening outcomes of the study participants attending Themba Lethu clinic during the November 2009 to December 2012 period (n=1202).

3.1.2. Participant baseline socio demographic characteristics

Table 6 provides a summary of socio demographic and clinical characteristics of women who participated in the study. Tables 6 also shows the proportion of missing data for each variables. A total of 1202 HIV-infected women participated in the study. A majority of the women were black (98.09%) and of South African nationality (89.27%). The women had a mean age of 38.14 years of age (SD ±7.67) at enrolment.

A total of 72 (5.99%) and 88 (7.32%) women were divorced/separated, and widowed respectively. More than half (54.74%) of the women reported to be single, while 17.80% of the women reported that they were married and 14.14% reported that they were cohabiting with a partner.

The majority of the women (69.38%) had between grade 10 and matric level education, with only 9.4% having some post-matric education. A total of 26 of the women (2.16%) reported to have had no education at all.

A total of 667 (55.49%) of the women reported that they were employed. Of these 67.17% of these had full time employment, 27.29% had part-time employment, and 3.90% were self-employed, while 11 (1.65%) had their occupation missing in the study database.

A total of 125 (10.40%) of the women reported to currently drinking alcohol, the same number report to also taking snuff. Of these, 78.40% reported to be taking snuff less than 5 times a day and 16.80% reporting to be taking snuff more than 5 times a day.

A small number reported to be smoking currently (3.49%); with 66.67% of these smoking less than 5 cigarettes a day, and 21.43% smoking more than 5 cigarettes a day. Appendix 1a provides a table of the study participantsô socio-demographic characteristics further stratified by the study outcomes.

Only the socio-demographic factors nationality, occupation, smoking frequency and snuff frequency had data missing; 1.75%, 1.65%, 11.90% and 4.80% data missing respectively which are minor rates of missing data

3.1.3. Participant baseline clinical characteristics

Participantsô baseline clinical data was sourced from TherapyEdge-HIV^{TM}, the electronic clinical decision, support and patient management system used to manage patient data at Themba Lethu clinic. Participantsô baseline indicators were collected 30-90 days before, to 7 days after HAART treatment initiation.

The majority (51.66%) of the study participants were initiated on HAART Regimen 1a ï stavudine/ lamivudine/ efavirenz, (d4T / 3TC / EFV) the regimen recommended by the South African national HIV guidelines for initiating HAART treatment at the time (prior to 2012) (18). Only 107 (8.90%) of the women were initiated on Regimen 1b - stavudine/ lamivudine/ nevirapine (d4T / 3TC / NVP), none were initiated on second line therapy. Women who were on the NVP based regimen would mostly have reported their intentions to fall pregnant. Under the previous South Africa national HIV guidelines EFV was contraindicated for women at risk of pregnancy due to concerns related to it possibly disturbing the development of the pregnancy (45).

The overall median CD4 count at HAART initiation for the group was 138 cells/mm^3 (IQR 63-205) which is significantly lower than the national HIV guideline recommended initiation CD4 count at the time which was 200 cells/mm^3 (18). The median baseline haemoglobin levels amongst all study participants was 11.6 g/dL (IQR 10.2-12.8), with less than 4% presenting with severe anaemia (<8 g/dL) at HAART initiation. A majority of the participantôs baseline viral load (VL) was missing (77.79%), this was because VL was not routine at HAART initiation as it was not the required standard of care according to the national HIV treatment guidelines (18).

Overall 285 (23.71%) of the study participants were initiated with a WHO staging of between III-IV. Their median body mass index (BMI) was 21.84 (IQR 19.26-25.29), and 7.15% of the study participantôs had a baseline BMI of less than 18.5 kg/m^2 at HAART initiation. The median baseline Alanine aminotransferase (ALT), Aspartate transaminase (AST) and lactate levels were reported as 21 IU/L (IQR 15-31), 30 IU/L (IQR 24-40) and 2.26 mmol/L (IQR 1.5-4.3) respectively.

Participants' clinical characteristics had highest proportion of data missing, with baseline WHO staging, baseline BMI, baseline VL, baseline AST, and baseline lactate levels having over 25% rates of data missing. Clinical data for all respondents in the study was extracted from TherapyEdge-HIV™, the electronic medical database system used for patient management at the facility.

Table 6: Baseline socio-demographic and clinical characteristics of study participants attending Themba Lethu clinic during the November 2009 to December 2012 period (n=1202).

SOCIO-DEMOGRAPHIC CHARACTERISTICS	n (%)	CLINICAL CHARACTERISTICS	n (%)
Age (Mean ±SD):	38.14 (±7.67)	**Baseline WHO staging:**	
Age groups:		I-II	558 (46.42)
18-29	161 (13.39)	III ï IV	285 (23.71)
30-39	546 (45.42)	Missing	359 (29.87)
40-49	397 (33.03)	**Baseline Body mass index (kg/m2): Median (IQR)**	21.84 (19.26-25.29)
50+	98 (8.15)	Underweight (<18.5)	86 (7.15)
Race:		Normal (18.5-24.9)	478 (39.77)
Black	1179 (98.09)	Overweight (Ó25)	328 (27.29)
Other	23 (1.91)	Missing	310 (25.79)
Nationality:		**Baseline CD4 (cells/mm3): Med (IQR)**	138 (63-205)
South African	1073 (89.27)	0-50	193 (16.06)
Non-South African	108 (8.99)	51-100	174 (14.48)
Missing	21 (1.75)	101-250	472 (39.27)
Marital status:		251-350	54 (4.49)
Single	658 (54.74)	>350	58 (4.83)
Married	214 (17.80)	Missing	251 (20.88)
Cohabiting	170 (14.14)	**Baseline HIV viral load (copies/ml): Median (IQR)**	14000 (107-94000)
Divorced/Separated	72 (5.99)	<100 000	209 (17.39)
Widow	88 (7.32)	Ó100 000	65 (5.41)
Education Level:		Missing	928 (77.20)
< Grade 10	229 (19.05)	**Baseline Haemoglobin (g/dL): Median (IQR)**	11.6 (10.2-12.8)
Grade10 - Matric	834 (69.38)	<8g/dL	46 (3.83)
Tertiary	113 (9.40)	Ó8g/dL	883 (73.46)
No Education	26 (2.16)	Missing	273 (22.71)
Currently Employed:		**Baseline Aspartate transaminase (IU/L): Median (IQR)**	30 (24-40)
Yes	667 (55.49)	<40	568 (47.25)
Full-time	448 (67.17)	Ó40	206 (17.14)
Part-time	182 (27.29)	Missing	428 (35.61)
Self-employed	26 (3.90)	**Baseline Alanine aminotransferase (IU/L): Median (IQR)**	21 (15-31)
Missing	11 (1.65)	<40	829 (68.97)
No	535 (44.51)	Ó40	125 (10.40)
Currently drinking alcohol		Missing	248 (20.63)
Yes	125 (10.40)	**Baseline Lactate levels (mmol/L): Median (IQR)**	2.26 (1.5-4.3)
No	1077 (89.60)	0-2.4 ï Normal	271 (22.55)
Currently Smoking:		2.5-4 ï Moderately elevated	99 (8.24)
Yes	42 (3.49)	>4 ï Severely elevated	133 (11.06)
<5 per day	28 (66.67)	Missing	699 (58.15)

	Ó5 per day	9 (21.43)	**On HAART:**
	Missing	5 (11.90)	No 37 (3.12)
No		1160 (96.51)	Yes 1150 (96.88)
Currently taking snuff:			**HAART regimen at HAART initiation*:**
Yes		125 (10.40)	1a 621 (51.66)
	<5 per day	98 (78.40)	1b 107 (8.90)
	Ó5 per day	21 (16.80)	Other 420 (34.94)
	Missing	6 (4.80)	Missing 54 (4.49)
No		1077 (89.60)	**Previous Pap smear results:**
			Negative 523 (76.02)
			Moderate/Severe/ICC 30 (4.36)
			Missing 135 (19.62)
			Baseline study Pap smear results:
			Negative 321 (26.71)
			Moderate/Severe/ICC 877 (72.96)
			Missing 4 (0.33)

* HAART regimens 1a ï stavudine/ lamivudine/ efavirenz, (d4T / 3TC / EFV), 1b - stavudine/ lamivudine/ nevirapine (d4T / 3TC / NVP)

3.1.4. Participant's baseline study Pap smear results

Figure 2a depicts the prevalence and severity of cervical cancer disease in study participantôs using their previous and baseline (at enrolment) study Pap smear results. The Y axis illustrates the number of participants while the X axis denotes the study outcome being assessed.

A total of 688 (57.24%) of women reported having had a Pap smear screening before the study. Results were self-reported in most cases, and close to 20% of the participants did not have results reported from their previous screening. They either could not remember what the results were, or they never collected their results. A majority, 523 (94.58%), reported that their previous Pap smear test before participating in the study were negative. Only 1 (0.18%) of the women reported that they had severe Pap smear results in their previous Pap smear test before the study, and 5.24% had Pap smear results classified as moderate.

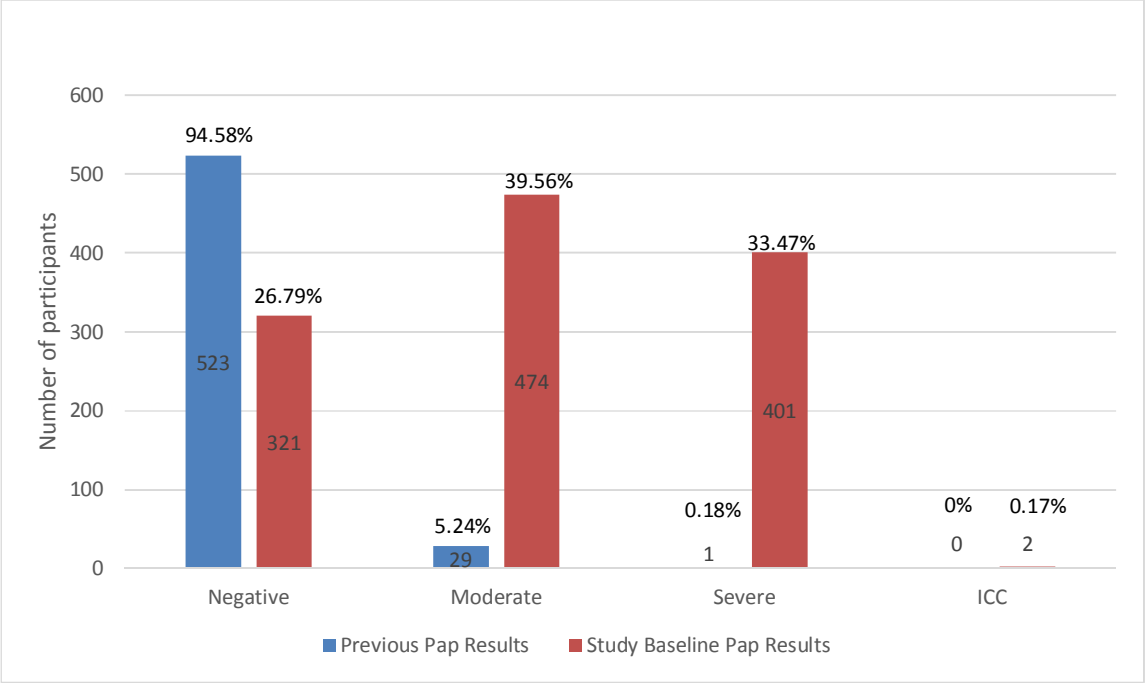

Figure 2a: Previous and current study baseline Pap smear screening results of study participants attending Themba Lethu clinic during the November 2009 to December 2012 period (Previous Pap smear results: n=553, Baseline study Pap smear results n=1198).

A majority of the results from the baseline Pap smear screening (73.04%) were in the moderate or severe category, of these 33.47% of the participantôs results were classified as severe meaning that their Pap smear results were HSIL, ASC-H, CIN II or CIN III. This is a huge contrast to the results reported from previous Pap smear test before the study. In addition, two cases of ICC disease were reported in the baseline Pap smears.

3.1.5. Description of participants' awareness, perceived risk and practices related to cervical cancer and Pap smear testing

Figure 2b illustrates the awareness related to Pap smear and cervical cancer screening amongst study participants. A total of 1202 participants were included in the analysis of awareness related to Pap smear and cervical cancer. The Y axis represents the number of participants while the X axis denotes the study outcome being assessed.

A total of 857 (71.30%) participants reported to be aware of Pap smear screening, with only a 218 (18.15%) reporting to be aware of HPV. One participant (0.08%) didnôt have data to determine whether they were aware of HPV or not as they responded that they didnôt know whether they have heard of HPV or not. Awareness regarding both Pap smear screening and HPV was significantly less amongst participants with only 186 (15.49%) of participants being aware of both the Pap smear screening test and HPV.

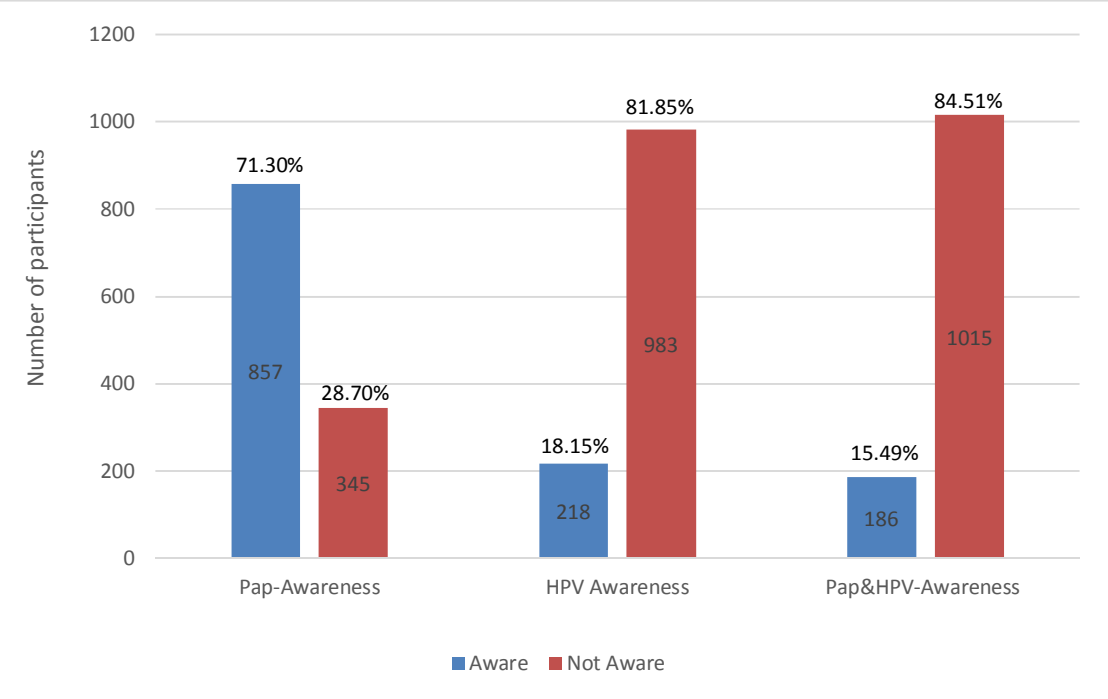

Figure 2b: Awareness of Pap smear screening and HPV amongst study participants attending Themba Lethu clinic during the November 2009 to December 2012 period (Pap awareness n=1202, HPV awareness n=1201, Pap screening and HPV awareness n=1201).

Figure 2c illustrates participantsô responses regarding perceived risk related to cervical cancer. The Y axis represents the number of participants while the X axis denotes the study outcome being assessed. Of the 1202 participants, 1192 participants had data available for perceived risk related to cervical cancer while 10 (0.83%) participants didnôt have data to determine perceived risk related to cervical cancer screening as they either never heard of cervical cancer (0.75%) or responded that they didnôt know (0.08%) how worried they were about getting cervical cancer disease. Of the 1192, 662 (55.54%) women were very worried, and a further 250

(20.97%) were somewhat worried and 280 (23.49%) were not worried about getting cervical cancer.

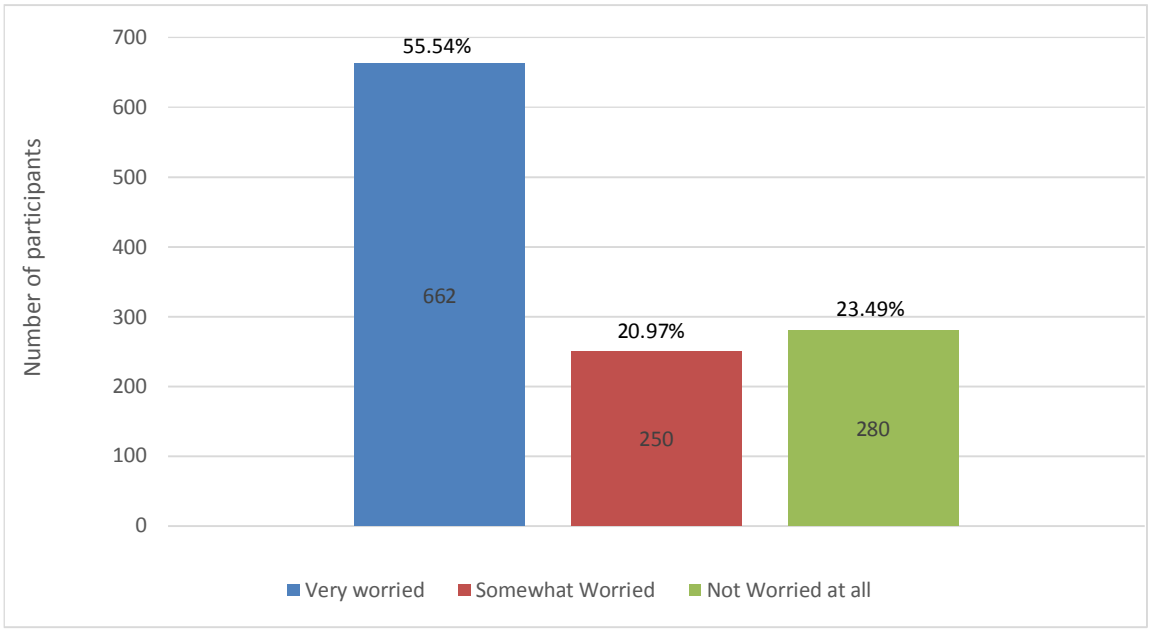

Figure 2c: Perceived risk regarding cervical cancer disease amongst study participants attending Themba Lethu clinic during the November 2009 to December 2012 period (n=1192).

Figure 2d illustrates participantsô practice related to cervical cancer screening; practice according to national cervical cancer guidelines and HIV treatment guidelines respectively. The Y axis illustrates the number of participants while the X axis denotes the study outcome being assessed. A total of 381 (36.46%) women had adequate practice according to the national cervical cancer guidelines. While 304 (28.57%) had adequate practice according to the national HIV treatment guidelines.

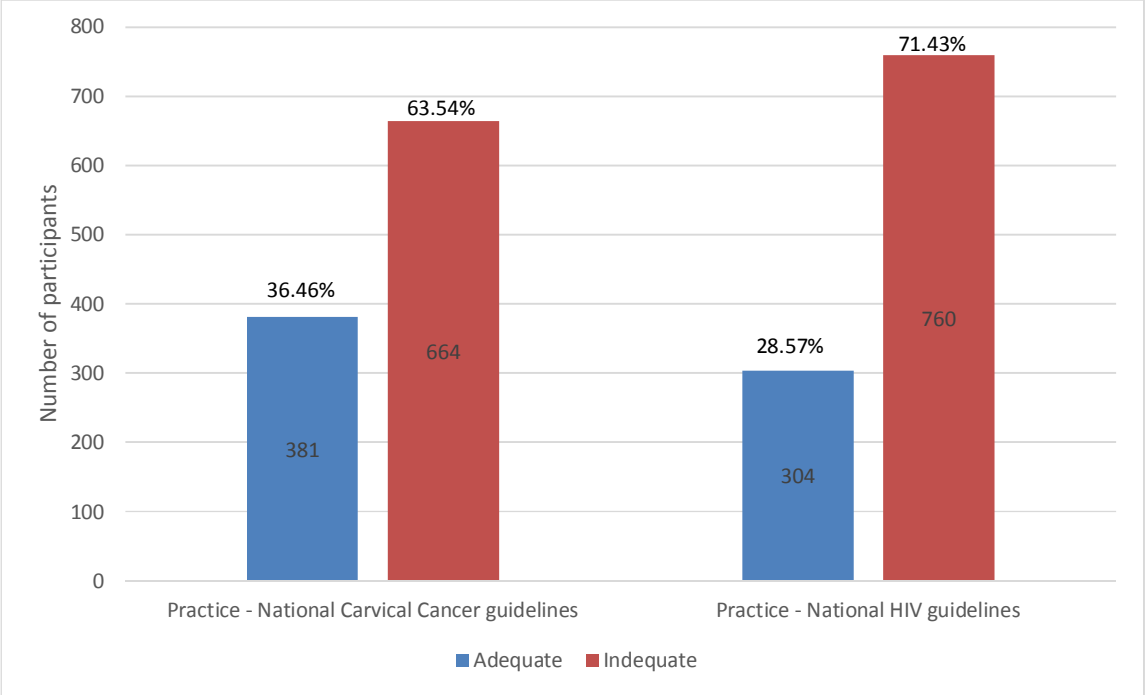

Figure 2d: Practice related to Pap smear screening amongst study participants attending Themba Lethu clinic during the November 2009 to December 2012 period (Pap smear screening practice according to cervical cancer guidelines n=1045, Pap smear screening practice according to HIV treatment guidelines n=1064).

3.1.6. Comparison between study participants and TLC cohort

A sub-analysis to compare the group of patients that were included in the study (the VICAR1 cohort) and the rest of the larger TLC cohort population that was not included in the study was carried out. Table 7 provides a summary of the results. Results indicated that there were no major difference between the two populations, only small differences were noted in most cases.

When comparing socio-demographic characteristics the two populations had similar proportions of black individuals. The TLC cohort had a slightly higher proportion (99.43%) compared to the VICAR1 cohort (98.09%). The VICAR1 cohort and TLC cohort were also similar in nationality with 90.86% and 91.09% South Africans in each cohort respectively. A slightly higher proportion of the TLC cohort were smokers (4.95%) compared to the VICAR1 cohort which had 3.49% smokers. In terms of alcohol usage the VICAR1 cohort had higher proportion of alcohol drinkers (10.40%) than the TLC cohort (6.66%). A higher proportion (55.49%) of the VICAR1 cohort were employed compared to 44.31% of the TLC cohort.

When the two population were compared according to their clinical characteristics at HAART initiation, the TLC cohort median CD4 count at initiation was lower compared to the VICAR1 cohort; 122 cells/mm^3 (IQR 48-197) compared to 138 cells/mm^3 (IQR 63-205). The TLC cohort had a lower proportions of individuals initiated on HAART at a CD4 count of Ò100 (38.59%) compared to the VICAR1 cohort which had over 40% individuals initiated on HAART at a CD4 count of Ò100. Close to 50% of the VICAR1 cohort initiated HAART at a CD4 count of between 100-250 compared to 43.17% in the TLC cohort, with 5.68% and 8.41% respectively starting at between 250-350 CD4 count. A larger portion (6.10%) of the VICAR1 cohort were initiated at a CD4 count of more than 350 compared to the TLC cohort (5.38%). As with the VICAR1 cohort a major proportion of the TLC cohort (84.7%) also had baseline VL data missing, for similar reasons. A higher proportion of TLC cohort (31.30%) compared to the VICAR1 cohort (23.72%), were initiated on HAART at a VL on >100 000.

Compared to the VICAR1 cohort the TLC cohort had a slightly higher proportion of individuals, 38.83%, were initiated at WHO stage III-IV. The median BMI at HAART initiation amongst the TLC cohort was 21.78 (IQR 19.21-25.19) which was slightly less than the VICAR1 cohort 22.92 (IQR 19.88-26.67). Close to double the proportion of individuals in the TLC cohort (15.25%) were initiated at a baseline BMI of less than 18.5 kg/m^2 compared to in those in VICAR1 cohort (9.62%).

The two cohorts had the same haemoglobin levels if 11.6 d/dL (IQR 10.2-12.8) at HAART initiation. A higher proportion of the TLC cohort (6.61%) had haemoglobin levels less than 8b/dL compared to the VICAR1 cohort (4.95%) at HAART initiation.

A larger proportion of the VICAR1 cohort (96.88%) were on HAART compared to the TLC cohort (74.31%). Of the patients in the TLC cohort who were not in the study 49.34% were initiated on HAART regimen 1a compared to 54.09% of those in the VICAR1 cohort, while 7.09% were initiated on Regimen 1b compared to 9.32% in the VICAR1 cohort. Similar to the

VICAR1 cohort none of the patients in the TLC cohort were initiated on second line therapy. When comparing the two cohortsô age at HAART initiation both cohort had a similar mean ages. The TLC cohort had a mean age of 36.26 years (SD ±9.34) at HAART initiation compared to the VICAR1 cohortôs mean age of 36.16 (SD ±7.69). The VICAR1 cohort had a higher proportion (47.22%) initiate HAART at the 30-39 age category compared to the TLC cohort (42.44%); 25.65% of the VICAR1 cohort compared to 21.53% of the TLC cohort were initiated at the 40-49 age category, while 22.61% of the VICAR1 cohort compared to 26.18% of the TLC cohort were initiated at the 18-29 age category. In addition, more than double of the TLC cohort (9.13%) were initiated at the 50+ age category compared to the VICAR1 cohort (4.5%), and 0.72% of the TLC cohort were initiated on HAART at the 0-17 age category while none of the study cohort was initiated in this age category as it was below the cut off age for inclusion in the study.

Table 7: Comparison of the study participants attending Themba Lethu clinic during the November 2009 to December 2012 period with the Themba Lethu cohort of females not included in the study (VICAR cohort n=1202, Themba Lethu cohort n=36134).

Factor	**VICAR1 (n=1202)** n (%)	**TLC (n=21544)** n (%)
Race: Black	1179 (98.09)	20094 (99.43)
Other	23 (1.91)	116 (0.57)
Nationality: South African	1073 (90.86)	19388 (91.09)
Non-South Africa	108 (9.14)	1896 (8.91)
Currently Smoking: Yes	42 (3.49)	818 (4.95)
No	1160 (96.51)	16509 (95.05)
Currently drinking Alcohol: Yes	125 (10.40)	1101 (6.66)
No	1077 (89.60)	15422 (93.34)
Employed: Yes	667 (55.49)	9545 (44.31)
No	535 (44.51)	11998 (55.69)
Baseline WHO staging: I-II	558 (66.19)	6430 (61.17)
III - IV	285 (33.81)	4081 (38.83)
Baseline Body mass index (kg/m2): (Med IQR)	21.84 (19.26-25.29)	22.92 (19.88-26.67)
Underweight (<18.5)	86 (9.62)	1817 (15.25)
Normal (18.5-24.9)	479 (53.58)	5934 (49.82)
Overweight (Ó25)	329 (36.80)	4161 (34.93)
Hemoglobin (Hb; g/dL): (Med IQR)	11.6 (10.2-12.8)	11.6 (10.2-12.8)
<8g/dL	46 (4.95)	850 (6.61)
Ó8g/dL	883 (95.05)	12011 (93.39)
Baseline CD4: (Med IQR)	138 (63-205)	122 (48-197)
0-50	193 (20.29)	3371 (25.93)
51-100	174 (18.30)	2226 (17.12)
101-250	472 (49.63)	5612 (43.17)
251-350	54 (5.68)	1093 (8.41)
>350	58 (6.10)	699 (5.38)
Baseline VL: (Med IQR)	14000 (107-94000)	22022 (163-153000)
<100000	209 (76.28)	2259 (68.70)

>100000	65 (23.72)	1029 (31.30)
On HAART: No	37 (3.12)	5535 (25.69)
Yes	1150 (96.88)	16009 (74.31)
Age at HAART initiation (Mean SD):	36.16 (±7.69)	36.26 (±9.34)
Age group at HAART initiation: 0-17	0 (0)	115 (0.72)
18-29	260 (22.61)	4191 (26.18)
30-39	543 (47.22)	6794 (42.44)
40-49	295 (25.65)	3446 (21.53)
50+	52 (4.52)	1462 (9.13)
HAART regimen at initiation*: 1a	621 (54.09)	7808 (49.34)
1b	107 (9.32)	1122 (7.09)
Other	420 (36.59)	6896 (43.57)

*HAART regimens 1a ï stavudine/ lamivudine/ efavirenz, (d4T / 3TC / EFV), 1b - stavudine/ lamivudine/ nevirapine (d4T / 3TC / NVP)

3.2. Factors associated with the study outcomes

3.2.1. Univariate analysis

Univariate analysis was used to investigate the relationship between participantôs awareness, perceived risk and practices related to cervical cancer and Pap smear testing, and participant socio-demographic and clinical characteristics. The crude odds ratio (OR) was reported.

Tables 8a, presents results of the analysis examining association between socio-demographic and clinical characteristic factors with the outcome awareness related to Pap smear testing and HPV. The significant factors associated with awareness regarding Pap smear screening were older age, non-black race, non-South African nationality, marital status, higher education levels, taking snuff, drinking alcohol, elevated baseline lactate levels at HAART initiation, and being initiated on HAART. In addition, the significant factors associated with HPV awareness were older age, higher education levels, self-employment occupation, higher smoking frequency, drinking alcohol, normal baseline BMI at HAART initiation, higher baseline VL at HAART initiation, elevated baseline ALT at HAART initiation, being initiated on HAART, and a non-negative baseline study Pap screening result.

Table 8a: Factors associated with awareness of Pap smear screening and awareness of HPV amongst of study participants attending Themba Lethu clinic during the November 2009 to December 2012 period.

Factor	Awareness about Pap Smears				Awareness about HPV			
	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Age groups: 18-29	ref		ref		ref		ref	
30-39	1.29 (0.88-1.87)	0.189	1.47 (0.74-2.92)	0.274	1.37 (0.86-2.21)	0.188	1.19 (0.48-2.95)	0.703
40-49	1.30 (0.88-1.93)	0.184	1.59 (0.77-3.26)	0.209	1.23 (0.74-2.01)	0.422	1.13 (0.44-2.91)	0.800
50+	2.02 (1.12-3.35)	0.019	4.70 (1.63-13.55)	0.004	0.62 (0.28-1.35)	0.227	0.85 (0.22-3.29)	0.816
Race: Black	ref		ref		ref			
Other	4.31 (1.00-18.47)	0.049	3.08 (0.38-24.86)	0.290	1.61 (0.63-4.13)	0.323		
Nationality: South African	ref		ref		ref			
Non-South African	0.57 (0.38-0.86)	0.007	0.41 (0.20-0.83)	0.013	1.02 (0.61-1.70)	0.933		
Marital Status: Single	ref		ref		ref			
Married	1.06 (0.76-1.50)	0.713	1.23 (0.70-3.11)	0.467	1.21 (0.82-1.78)	0.341		
Cohabiting	0.78 (0.55-1.12)	0.184	1.57 (0.79-3.11)	0.202	0.88 (0.56-1.39)	0.586		
Divorced/ Separated	1.54 (0.85-2.79)	0.152	1.75 (0.61-4.98)	0.295	1.33 (0.74-2.41)	0.341		
Widow	1.14 (0.69-1.90)	0.593	0.81 (0.39-1.69)	0.579	0.96 (0.53-1.73)	0.888		
Education Level: < Grade 10	ref		ref		ref		ref	
Grade 10ï Matric	1.85 (1.36-2.52)	0.000	2.12 (1.28-3.52)	0.004	3.24 (1.93-5.47)	0.000	1.06 (1.12-9.14)	0.958
Tertiary	2.45 (1.45-4.12)	0.001	2.62 (1.07-6.41)	0.035	4.11 (2.14-7.89)	0.000	3.00 (0.38-23.84)	0.299
None	0.90 (0.40-2.05)	0.800	0.53 (0.13-2.26)	0.392	0.50 (0.06-3.91)	0.508	3.25 (0.38-27.81)	0.281
Currently Employed: No	ref				ref			
Yes	0.96 (0.75-1.23)	0.743			0.87 (0.65-1.17)	0.353		
Occupation: Full-time	ref				ref		ref	
Part-time	1.06 (0.73-1.57)	0.763			1.16 (0.73-1.82)	0.530	0.89 (0.49-1.61)	0.699
Self-Employed	1.83 (0.68-4.95)	0.235			2.32 (0.97-5.54)	0.058	2.12 (0.61-7.40)	0.237
Currently Smoking: No	ref				ref			
Yes	1.30 (0.63-2.67)	0.477			1.43 (0.69-2.95)	0.335		
Smoking Frequency: <5 per day	ref				ref		ref	
> 5 per day	1.17 (0.19-6.98)	0.866			4.8 (0.89-25.96)	0.069	5.25 (0.59-46.50)	0.195
Currently taking snuff: No	ref				ref			
Yes	0.59 (0.40-0.86)	0.007			0.79 (0.47-1.32)	0.367		
Snuff Frequency: <5 per day	ref				ref			
> 5 per day	0.99 (0.37-2.60)	.997	ref		0.58 (0.12-2.76)	0.496		
Currently Drinking Alcohol: No	ref		0.67 (0.35-1.26)	0.211	ref		ref	
Yes	2.01 (1.24-3.24)	.004			1.73 (1.13-2.65)	0.012	1.52 (0.80-2.91)	0.204
Baseline WHO staging: I-II	ref				ref			
III -IV	0.82 (0.60-1.13)	.226	ref		0.85 (0.58-1.25)	0.417		
Baseline BMI (kg/m2): Underweight (<18.5)	ref		1.31 (0.61-2.82)	0.490	ref		ref	
Normal (18.5-24.9)	1.19 (0.73-1.95)	.483	ref		0.69 (0.39-1.21)	0.190	0.77 (0.31-1.92)	0.577
Overweight (Ó25)	1.12 (0.67-1.86)	0.659	0.85 (0.59-1.23)	0.392	0.85 (0.48-1.52)	0.595	1.13 (0.44-2.90)	0.793
Baseline CD4 (cells/mm3): 0-50	ref				ref			
51-100	0.99 (0.63-1.55)	0.960			0.86 (0.50-1.49)	0.591		
101-250	1.07 (0.74-1.55)	0.706						
					0.94 (0.60-1.46)	0.782		
251-350	1.30 (0.63-2.69)	0.473			1.36 (0.63-2.94)	0.431		
>350	1.44 (0.72-2.89)	0.299			0.65 (0.27-1.56)	0.334		
Baseline HIV viral load (copies/ml): <100 000	ref				ref		ref	
Ó100 000	1.09 (0.57-2.12)	0.788			1.68 (0.84-3.35)	0.142	2.52 (0.49-12.84)	0.266
Hemoglobin (g/dL): <8g/dL	ref				ref			
Ó8g/dL	0.94 (0.49-1.82)	0.864			1.79 (0.70-4.60)	0.227		
AST (IU/L): <40	ref				ref			
>=40	1.19 (0.83-1.72)	0.344			0.92 (0.60-1.41)	0.692		
ALT (IU/L): <40	ref				ref		ref	
>=40	1.00 (0.66-1.52)	0.987			1.36 (0.86-2.16)	0.194	1.29 (0.58-2.85)	0.529
Lactate levels (mmol/L): 0-2.4 - Normal	ref		ref		ref			
2.5-4 ï Moderately elevated	1.07 (0.63-1.82)	0.811	1.02 (0.58-1.77)	0.956	0.69 (0.37-1.29)	0.251		
>4 ï Severely elevated	0.74 (0.47-1.17)	0.196	0.59 (0.36-0.96)	0.032	0.89 (0.53-1.50)	0.660		
On HAART: No	ref		ref		ref		ref	
Yes	038 (0.16-915)	<0.001	0.39 (016-0.94)	0.036	1.00 (0.46-2.19)	<0.001	1.15 (0.37-3.58)	0.803
HAART regimen*: 1a	ref				ref			
1b	0.85 (0.55-1.33)	0.482			1.09 (0.65-1.83)	0.741		
Other	0.94 (0.72-1.24)	0.683			0.96 (0.70-1.33)	0.817		
Baseline study Pap smear results: Negative	ref				ref		ref	
Moderate/Severe/ICC	0.86 (0.64-1.14)	0.304			0.71 (0.52-0.98)	0.035	0.90 (0.49-1.64)	0.729
Previous Pap smear results: Negative	ref				ref			
Moderate/Severe/ICC	0.89 (0.67-1.18)	0.408			1.30 (0.57-3.01)	0.533		

*HAART regimens 1a ï stavudine/ lamivudine/ efavirenz, (d4T / 3TC / EFV), 1b - stavudine/ lamivudine/ nevirapine (d4T / 3TC / NVP)

Tables 8b, shows results of the analysis examining association between socio-demographic and clinical characteristics with the outcome perceived risk related to cervical cancer and Pap smear testing. The significant factors for this outcome were older age, marital status, higher education

levels, being employed, self-employed occupation, taking snuff, higher snuff frequency, drinking alcohol and elevated baseline ALT at HAART initiation.

Table 8b: Factors associated with perceived risk related to cervical cancer disease amongst of study participants attending Themba Lethu clinic during the November 2009 to December 2012 period.

Factor	Perceived Risk regarding cervical cancer			
	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Age groups: 18-29	ref		ref	
30-39	0.88 (0.62-1.26)	0.489	1.48 (0.84-2.61)	0.174
40-49	0.61 (0.42-0.88)	0.008	0.91 (0.51-1.62)	0.739
50+	0.65 (0.40-1.07)	0.089	1.13 (0.51-2.47)	0.768
Race: Black	ref		ref	
Other	1.21 (0.53-2.76)	0.647		
Nationality: South African	Ref			
Non-South African	0.96 (0.65-1.41)	0.830		
Marital Status: Single	Ref		ref	
Married	0.83 (0.62-1.12)	0.229	0.61 (0.38-0.99)	0.062
Cohabiting	1.29 (0.93-1.80)	0.132	1.40 (0.82-2.40)	0.220
Divorced/ Separated	1.19 (0.73-1.93)	0.483	1.53 (0.67-3.48)	0.313
Widow	0.70 (0.46-1.05)	0.086	0.65 (0.34-1.22)	0.180
Education Level: < Grade 10	ref		ref	
Grade 10ï Matric	1.48 (1.13-1.96)	0.005	2.60 (0.77-8.86)	0.126
Tertiary	2.29 (1.44-3.63)	0.000	3.74 (1.13-12.38)	0.031
None	0.76 (0.35-1.62)	0.472	6.35 (1.60-25.19)	0.125
Currently Employed: No	Ref		ref	
Yes	0.80 (0.64-0.99)	0.042	0.92 (0.71-1.19)	0.523
Occupation: Full-time	ref		ref	
Part-time	1.00 (0.72-1.38)	0.984	1.00 (0.69-1.45)	0.995
Self-Employed	2.10 (0.91-4.84)	0.081	2.45 (0.85-7.08)	0.098
Currently Smoking: No	ref			
Yes	1.26 (069-2.30)	0.447		
Smoking Frequency: <5 per day	ref			
>5 per day	2.33 (0.41-13.29)	0.340		
Currently taking snuff: No	ref		ref	
Yes	0.66 (0.47-0.94)	0.022	0.55 (0.33-0.92)	0.024
Snuff Frequency: <5 per day	ref		ref	
>5 per day	0.53 (0.21-1.31)	0.167	0.62 (0.23-1.69)	0.348
Currently Drinking Alcohol: No	ref		ref	
Yes	1.41 (0.98-2.04)	0.063	2.53 (1.24-5.17)	0.011
Baseline WHO staging: I-II	ref			
III -IV	1.17 (0.89-1.54)	0.266		
Baseline BMI(kg/m2): Underweight (<18.5)	ref			
Normal (18.5-24.9)	0.92 (0.59-1.44)	0.725		
Overweight (Ó25)	0.83 (0.52-1.30)	0.411		
Baseline CD4 (cells/mm3): 0-50	ref			
51-100	1.00 (0.67-1.50)	0.994		
101-250	0.95 (0.69-1.32)	0.769		
251-350	0.72 (0.39-1.31)	0.278		
>350	0.87 (0.48-1.58)	0.658		
Baseline HIV viral load (copies/ml): <100 000	ref			
Ó100 000	0.93 (0.55-1.58)	0.795		
Hemoglobin (g/dL): <8g/dL	ref			
Ó8g/dL	0.72 (0.39-1.30)	0.274		
AST (IU/L): <40	ref			
>=40	0.94 (0.69-1.27)	0.669		
ALT (IU/L): <40	ref		ref	
>=40	0.76 (0.53-1.09)	0.141	0.65 (0.38-1.09)	0.104
Lactate levels (mmol/L): 0-2.4 - Normal	ref			
2.5-4 ï Moderately elevated	1.03 (0.66-1.61)	0.882		
>4 ï Severely elevated	1.20 (0.80-1.81)	0.372		
On HAART: No	ref		ref	
Yes	072 (0.40-1.28)	0.259	0.83 (0.46-1.50)	0.534
HAART regimen*: 1a	ref			
1b	1.09 (0.74-1.62)	0.666		
Other	1.01 (0.79-1.28)	0.961		
Baseline study Pap smear results: Negative	ref			
Moderate/Severe/ICC	0.90 (0.70-1.16)	0.429		
Previous Pap smear results: Negative	ref			
Moderate/Severe/ICC	0.79 (0.40-1.56)	0.500		

*HAART regimens 1a ï stavudine/ lamivudine/ efavirenz, (d4T / 3TC / EFV), 1b - stavudine/ lamivudine/ nevirapine (d4T / 3TC / NVP)

Tables 8c, shows results of the analysis examining association between socio-demographic and clinical characteristics with the outcome practice related to cervical cancer and Pap smear

testing. The significant factors associated with practice according to the national cervical cancer guidelines were older age, non-black race, marital status, higher education levels, a self-employment occupation, drinking alcohol, higher baseline CD4 at HAART initiation, higher baseline VL at HAART initiation, elevated baseline ALT at HAART initiation, elevated baseline lactate levels at HAART initiation, being initiated on HAART and being initiation on a baseline HAART regimen of 1b. The significant factors associated with practice according to the HIV treatment guidelines were older age, marital status, higher education levels, part-time employment, taking snuff, higher snuff taking frequency, drinking alcohol, baseline WHO staging, higher baseline BMI at HAART initiation, higher baseline VL at HAART initiation, elevated baseline ALT at HAART initiation, being initiated on HAART, baseline HAART regimen, and having a non-negative previous Pap screening result.

Table 8c: Factors associated with practice related to Pap smear screening amongst of study participants attending Themba Lethu clinic during the November 2009 to December 2012 period.

Factor	Practice according to national cervical cancer guidelines				Practice according to HIV treatment guidelines			
	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Age groups: 18-29	ref		ref		ref		ref	
30-39	10.81 (5.50-21.24)	<0.001	12.23 (4.00-37.35)	<0.001	1.35 (0.85-2.15)	0.201	1.40 (0.37-5.32)	0.619
40+	1.88 (0.93-3.81)	0.078	1.32 (0.42-4.11)	0.637	1.74 (1.09-2.79)	0.021	1.37 (0.35-5.40)	0.655
50+	6.38 (4.76-8.54)	0.098	5.74 (2.35-7.15)	0.425	2.83 (1.56-5.13)	0.001	2.32 (0.44-12.34)	0.320
Race: Black	ref		ref		ref			
Other	2.11 (0.90-4.94)	0.084	1.05 (0.26-4.24)	0.942	1.75 (0.74-4.14)	0.201		
Nationality: South African	ref				ref			
Non-South African	1.05 (0.66-1.67)	0.837			0.93 (0.57-1.50)	0.752		
Marital Status: Single	ref		ref		ref		ref	
Married	1.21 (0.87-1.68)	0.252	1.27 (0.68-2.37)	0.449	1.10 (0.77-1.58)	0.600	1.18 (0.46-3.02)	0.728
Cohabiting	0.72 (0.48-1.07)	0.104	0.36 (0.17-0.75)	0.006	0.75 (0.49-1.14)	0.178	0.83 (0.22-3.15)	0.788
Divorced/ Separated	0.83 (0.49-1.39)	0.476	1.50 (0.53-4.25)	0.451	1.49 (0.86-2.57)	0.151	3.42 (0.90-12.93)	0.070
Widow	0.52 (0.31-0.87)	0.013	0.53 (0.21-1.35)	0.186	1.10 (0.65-1.85)	0.726	0.68 (0.16-2.94)	0.606
Education Level: < Grade 10	ref		ref		ref		ref	
Grade 10 ï Matric	1.77 (1.26-2.51)	0.001	1.18 (0.11-12.26)	0.892	0.68 (0.49-0.96)	0.027	0.48 (0.20-1.12)	0.089
Tertiary	5.15 (3.03-8.73)	<0.001	1.26 (0.12-12.75)	0.844	1.38 (0.84-2.28)	0.206	2.52 (0.70-9.06)	0.158
None	0.50 (0.14-1.75)	0.277	3.08 (0.27-35.34)	0.366	0.77 (0.31-1.94)	0.582	6.30 (0.47-83.84)	0.163
Currently Employed: No	ref				ref			
Yes	0.88 (0.68-1.13)	0.316			1.09 (0.84-1.43)	0.520		
Occupation: Full-time	ref		ref		ref		ref	
Part-time	1.06 (0.72-1.56)	0.758	0.85 (0.52-1.41)	0.538	0.69 (0.45-1.04)	0.079	0.64 (0.39-1.08)	0.094
Self-Employed	2.27 (0.96-5.40)	0.062	2.95 (0.82-10.66)	0.040	1.49 (0.60-3.75)	0.393	1.71 (0.52-5.65)	0.376
Currently Smoking: No	ref				ref			
Yes	1.04 (0.50-2.15)	0.914			1.42 (0.73-2.77)	0.304		
Smoking Frequency: <5 per day	ref				ref			
> 5 per day	2.67 (0.46-15.35)	0.272			0.36 (0.06-2.05)	0.248		
Currently taking snuff: No	ref				ref		ref	
Yes	0.90 (0.60-1.35)	0.616			0.64 (0.40-1.02)	0.061	0.63 (0.20-2.00)	0.432
Snuff Frequency: <5 per day	ref				ref		ref	
> 5 per day	1.86 (0.68-5.06)	0.224			0.36 (0.08-1.67)	0.191	0.41 (0.15-2.45)	0.652
Currently Drinking Alcohol: No	ref		ref		ref		ref	
Yes	2.01 (1.34-3.04)	0.001	1.27 (0.52-3.07)	0.599	1.52 (1.00-2.32)	0.050	1.31 (0.39-4.37)	0.657
Baseline WHO staging: I-II	ref				ref		ref	
III -IV	0.91 (0.66-1.25)	0.552			0.78 (0.56-1.08)	0.139	1.00 (0.46-2.16)	0.991
Baseline BMI(kg/m2): Underweight (<18.5)	ref				ref		ref	
Normal (18.5-24.9)	1.40 (0.80-2.46)	0.235			1.35 (0.77-2.38)	0.291	0.43 (0.11-1.62)	0.214
Overweight (Ó25)	1.23 (0.69-2.18)	0.483			1.72 (0.97-3.05)	0.066	0.53 (0.13-2.13)	0.369
Baseline CD4 (cells/mm3): 0-50	ref		ref		ref			

	51-100	1.23 (0.78-1.93)	0.381	0.55 (0.55-55.50)	0.358	1.04 (0.64-1.68)	0.871		
	101-250	0.93 (0.63-1.36)	0.705	0.49 (0.16-1.48)	0.204	1.24 (0.84-1.83)	0.274		
	251-350	0.94 (0.46-1.92)	0.865	8.60 (0.96-77.31)	0.555	1.19 (0.57-2.46)	0.648		
	>350	1.53 (0.80-2.92)	0.197	0.33 (0.38-2.86)	0.315	0.99 (0.48-2.02)	0.973		
Baseline HIV viral load (copies/ml):									
	<100 000	ref		ref		ref		ref	
	Ó100 000	0.61 (0.32-1.17)	0.138	4.67 (0.39-55.50)	0.223	0.53 (0.26-1.10)	0.087	0.75 (0.31-1.81)	0.527
Hemoglobin (g/dL): <8g/dL		ref				ref			
	Ó8g/dL	0.70 (0.35-1.39)	0.304			0.88 (0.46-1.69)	0.706		
AST (IU/L): <40		ref				ref			
	>=40	1.25 (0.88-1.77)	0.222			1.03 (0.71-1.48)	0.895		
ALT (IU/L): <40		ref		ref		ref		ref	
	>=40	1.66 (1.10 -2.51)	0.015	1.74 (0.61-5.00)	0.304	1.33 (0.88-2.02)	0.179	1.73 (0.63-4.7)	0.287
Lactate levels (mmol/L): 0-2.4 - Normal		ref		ref		ref			
	2.5-4 ï Moderately elevated	1.05 (0.64-1.74)	0.838	1.08 (0.61-1.91)	0.789	0.92 (0.54-1.57)	0.755		
	>4 ï Severely elevated	0.69 (0.43-1.01)	0.120	0.75 (0.43-1.28)	0.290	0.73 (0.43-1.21)	0.221		
ON HAART: No		ref		ref		ref		ref	
	Yes	0.39 (0.20-0.79)	0.009	0.17 (0.06-0.55)	0.003	0.53 (0.22-1.26)	0.150	0.79 (0.29-2.12)	0.638
HAART regimen*: 1a		ref		ref		ref		ref	
	1b	1.53 (0.97-2.41)	0.065	1.05 (0.63-1.73)	0.863	0.77 (0.46-1.28)	0.310	1.01 (0.19-5.27)	0.993
	Other	1.19 (0.90-1.57)	0.227	0.98 (0.71-1.34)	0.900	1.26 (0.94-1.68)	0.118	1.02 (0.39-2.66)	0.972
Baseline study Pap smear results: Negative		ref				ref			
	Moderate/Severe/ICC	1.05 (0.79-1.39)	0.727			1.13 (0.84-1.53)	0.424		
Previous Pap smear results: Negative		ref				ref		ref	
	Moderate/Severe/ICC	0.81 (0.37-1.81)	0.611			1.66 (0.77-3.60)	0.196	5.42 (0.65-45.41)	0.119

*HAART regimens 1a ï stavudine/ lamivudine/ efavirenz, (d4T / 3TC / EFV), 1b - stavudine/ lamivudine/ nevirapine (d4T / 3TC / NVP)

3.2.2. Multivariate analysis

Factors associated with awareness, perceived risk and practice related to cervical cancer and Pap screening amongst our study participants are listed in Tables 8a ï 8c.

In the analysis of awareness related to Pap smear screening the significant factors were older age, non-South African nationality, an education level higher than grade 10, and severely elevated lactate levels at HAART initiation and being initiated on HAART. Compared to the 18-29 age group women in the 50+ age group had over four and a half times more likely to be aware of Pap smear screening (aOR=4.70, 95% CI 1.63-13.55). Compared to South Africans in the study, non-South Africans were 59% less likely to be aware of Pap smear screening (aOR=0.41, 95% CI 0.20-0.83). Having a grade 10 to matric level education increased the likeliness of awareness regarding Pap smear screening to just over two times compared to those with less than a grade 10 education (aOR=2.12, 95%CI 1.28-3.52); the likeliness of Pap smear awareness was also over two times more amongst the participants that had a tertiary level education as compared to those with less than a grade 10 education (aOR=2.62, 95%CI 1.07-6.41). Compared to those that had normal baseline lactate levels, those with severely elevated baseline lactate levels were 41% less likely to be aware of Pap smear screening (aOR=0.59,

95% CI 0.36-0.96). Those that are initiated on HAART were 61% less likely to be aware of Pap smear screening than those that were not initiated on HAART (aOR=0.39, 95% CI 0.16-0.94).

In the analysis of perceived risk related to cervical cancer disease the significant factors identified were higher education levels, taking snuff and drinking alcohol. Compared to having less than a grade 10 education, having a tertiary education increased perception of risk related to cervical cancer disease by close to four times (aOR=3.74, 95%CI 1.13-12.38). Compared to those that did not take snuff those that took snuff were 45% less perceived risk related to getting cervical cancer disease (aOR=0.55, 95%CI 0.33-0.92). While those who reported that they currently drink alcohol had over two and a half times increased perceived risk related to getting cervical cancer disease compared to those that did not drink alcohol (aOR=2.53, 95% CI 1.24-5.17).

In the analysis of practice related to cervical cancer and Pap smear testing according to the national cervical cancer guidelines significant factors identified were older age, marital status, self-employment occupation and being initiated on HAART. Those in the 30-39 age group were over fourteen times more likely to have adequate practice according to the national cervical cancer guidelines compared to those in the 18-29 age group (aOR=12.23, 95%CI 4.00-37.35), however this association was imprecise. Compared to those that were single at enrolment in the study, those that reported to be cohabiting with a partner were over 60% times less likely to have adequate practice according to the national cervical cancer guidelines (aOR=0.36, 95%CI 0.17-0.75). Participants that were self-employed were almost three times more likely to have adequate practice according to the national cervical cancer guidelines than those who had full time employment (aOR=2.95, 95%CI 0.82-10.66). Those that are initiated on HAART were 83% less likely to have adequate Pap smear screening practice according to the national cervical cancer guidelines than those that were not initiated on HAART (aOR=0.17, 95% CI 0.06-0.55).

In the analysis of awareness related to HPV, and the analysis of practice according to the national HIV treatment guidelines none of the factors proved to be significantly associated with both outcomes. Results from these analyses are summarised in Table 8a and 8c respectively.

3.3. Disease progression at 12 Month

The **12 month follow-up outcome,** disease progression, was analysed in relation to the participantsô awareness, perceived risk and practice related to Pap smear testing, specifically:

i) Development of dysplasia where there was none present before

ii) Worsening of dysplasia from a lower grade to a higher grade

iii) Development of ICC where there was none present before

A total of 688 participants had a 12 month follow study up visit. This represents 57.24% of the total participants enrolled in the study at baseline. Earliest enrolment of participants into the study was November 2009, and the latest enrolment was in December 2012 therefore as of the 31st October 2013 (the date of which the 12 month follow up data was collected up until) all participants were eligible for a 12 month follow up study visit. Figure 3 represents a summary of participantôs 12 months of follow up visit and screening outcomes.

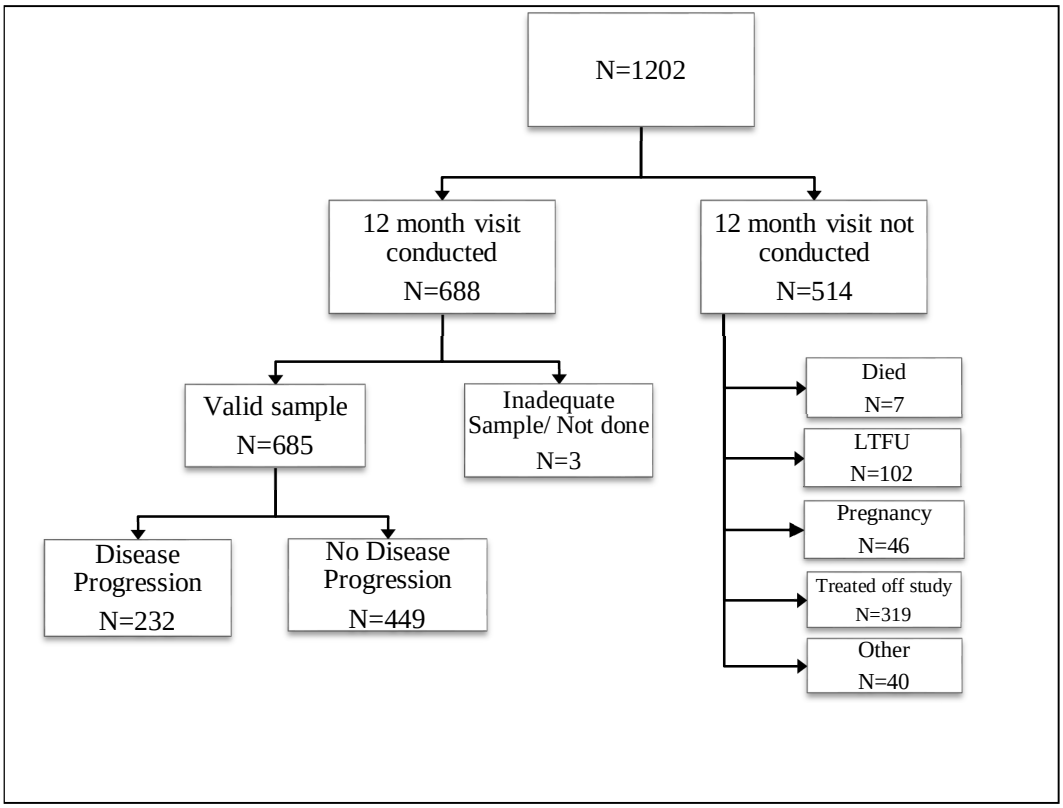

Figure 3: Study flow chart showing 12 month follow-up enrolment and Pap smear screening outcomes of study participants attending Themba Lethu clinic during the November 2009 to December 2012 period.

Out of the 1202 study participants 688 (57.24%) participants had a 12 month follow up visit for the study. Of these 685 (99.56%) had a valid sample collected during Pap smear screening and had Pap screening results recorded in the study database. A total of three participants did not have a valid sample, of these two did not undergo Pap screening during their 12 month follow up visit and one had an inadequate sample collected during the screening procedure. Out of the 685 study participants who had a result reported from their 12 month follow up study Pap smear 107 (15.62%) participants had negative Pap smear results. The majority of the participants, 483 (70.51%), had moderate results and 95 (13.89%) had severe results.

Out of the 685 participants with a valid sample collected during the 12 month follow up Pap smear screening a total of 681 (99.42%) of the study participants that had a valid sample were included in the analysis. The four participants who were not included in the analysis for disease progression did not have baseline Pap results as they had inadequate samples collected,

therefore it could not be determine whether they had worsening of their Pap smear screening results from their baseline Pap smear screening results. A total of 232 (34.07%) participants had worsening of their Pap smear results compared to their baseline study Pap smear results (disease progression). Of the rest of the study participants included in the analysis, 449 (65.93%) did not have any disease progression noted (Figure 3). Of these 449 participants who did not have any disease progression noted a majority, 366 (53.74%), had their results stay the same as their baseline results from their Pap smear screening from the preceding 12 months while 83 (12.19%) had their results improve from their Pap smear screening from the preceding 12 months.

A total of 514 (42.76%) study participants did not have a 12 month follow up visit conducted. Out of these 102 (19.84%) LTFU, 46 (8.95%) became pregnant thereby making them no longer eligible to be in the study. Study participants were determined to be LTFU when more than three separate attempts to contact them using the contact details provided are unsuccessful and the missed visit is outside of the allowable window for the visit (3 months from appointment date). The rest of the study participants who did not have a 12 month follow up study visit conducted were removed from the study because they had relocated (2.53%), transferred out of the study site (0.97%) or were treated off study (62.06%) because they had severe screening results from their baseline Pap smear screening results and needed to be treated. They were where either referred to VICAR 2 or treated elsewhere; treated at other health facilities outside both VICAR 1 and VICAR 2 studies. A total of seven (1.36%) participants withdrew their consent to be part of the study as they were no longer interested in participating in the study. A further 15 (2.92%) participants were unable to be treated because of the severity of the cervical cancer disease detected during their baseline Pap screening, and therefore did make up part of the 12 month follow study visit data set. These are the patients who had severe screening results from their baseline Pap smear screening results and needed to be treated, however the

doctor had difficulty performing treatment procedures and were referred elsewhere for further management.

3.3.1. Descriptive analysis: disease progression at 12 month

Of the 232 participants who experienced disease progression at 12 months, the majority 173 (74.57%) knew what a Pap smear was at study enrolment while 25.43% were not aware. Less participants, 50 (21.55%), that had disease progression noted were aware of HPV at study enrolment. Out of those that did not have disease progression noted at 12 months a majority, 76.17%, were aware what a Pap smear was at study enrolment while only 17.37% were aware of HPV at study enrolment.

A majority 128 (55.90%) of the study participants that had disease progression noted on their 12 month Pap screening were very worried about getting cervical cancer disease at study enrolment while 19.65% were somewhat worried about getting cervical cancer disease at study enrolment, and 24.45% were not worried at all about getting cervical cancer disease at study enrolment. As with those that had disease progression, the majority (53.93%) of those that did not have disease progression in their 12 month Pap screening were very worried about getting cervical cancer disease at study enrolment, while 23.82% of these were not worried at all about getting cervical cancer disease at study enrolment.

The majority of both study participants who had disease progression noted (63.68%) and those that did not have disease progression (61.90%) had inadequate practice according to the national cervical cancer guidelines at study enrolment. While higher proportions of just over 70% of those that had disease progression and those that didnôt, had inadequate practice according to the national HIV treatment guidelines at study enrolment. Results from these analyses are summarised below in Tables 9a-9e. Included in Tables 9a-9e are also estimates for the univariate and multivariate analysis to assess if there is significant association with the main study outcomes as assessed at the beginning of the study (awareness, perceived risk and

practices related to cervical cancer and Pap screening) and disease progression at 12 months of the study the crude and adjusted odds ratio (OR) were reported. No association was noted between the main study outcomes and disease progression at 12 months of the study.

Table 9a: Association between study participantsô disease development and Pap smear awareness at 12 month for study participants attending Themba Lethu clinic during the November 2009 to December 2012 period (n=681).

Factor	Disease Development at 12month Follow up		Univariate and Multivariate Analysis – Disease Development at 12 month follow up			
	Progressed 232 (34.07)	Not Progressed 449 (65.93)	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Pap Awareness:						
Aware	173 (74.57)	342 (76.17)	ref		ref	
Not Aware	59 (25.43)	107 (23.83)	0.92 (0.64-1.32)	0.645	0.91 (0.47-2.01)	0.824

Table 9b: Association between study participantsôdisease development and HPV awareness at 12 month for study participants attending Themba Lethu clinic during the November 2009 to December 2012 period (n=681).

Factor	Disease Development at 12month Follow up		Univariate and Multivariate Analysis – Disease Development at 12 month follow up			
	Progressed 232 (34.07)	Not Progressed 449 (65.93)	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
HPV Awareness						
Aware	50 (21.55)	78 (17.37)	ref		ref	
Not Aware	182 (78.45)	371 (82.63)	1.31 (0.88-1.94)	0.187	1.39 (0.55-3.51)	0.487

Table 9c: Association between study participantsô disease development and perceived risk related to cervical cancer diseaseat 12 month for study participants attending Themba Lethu clinic during the November 2009 to December 2012 period (n=674).

Factor	Disease Development at 12month Follow up		Univariate and Multivariate Analysis – Disease Development at 12 month follow up			
	Progressed 229 (33.98)	Not Progressed 445 (66.02)	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Perceived Risk						
Not Worried at All	56 (24.45)	106 (23.82)	ref		ref	
Somewhat Worried	45 (19.65)	99 (22.25)	0.86 (0.53-1.39)	0.538	1.96 (0.75-5.15)	0.171
Very Worried	128 (55.90)	240 (53.93)	1.01 (0.68-1.49)	0.962	0.70 (0.31-1.57)	0.383

Table 9d: Association between study participantsô disease development and Pap smear screening practice according to national cervical cancer guidelines at 12 month for study participants attending Themba Lethu clinic during the November 2009 to December 2012 period (n=600).

Factor	Disease Development at 12month Follow up	Univariate and Multivariate Analysis – Disease Development at 12 month follow up

	Progressed 201 (33.50)	Not Progressed 399 (66.50)	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Practice according to the national cervical cancer guidelines						
Adequate	73 (36.32)	152 (38.10)	ref		ref	
Not Adequate	128 (63.68)	247 (61.90)	0.93 (0.65-1.32)	0.671	1.32 (0.53-3.29)	0.558

Table 9e: Association between study participantsô disease development and Pap smear screening practice according to national HIV treatment guidelines at 12 month for study participants attending Themba Lethu clinic during the November 2009 to December 2012 period (n=611).

Factor	Disease Development at 12month Follow up		Univariate and Multivariate Analysis – Disease Development at 12 month follow up			
	Progressed 208 (34.04)	Not Progressed 403 (65.96)	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Practice according to national HIV treatment guidelines						
Adequate	61 (29.33)	119 (29.53)	ref		ref	
Not Adequate	147 (70.67)	284 (70.47)	0.99 (0.69-1.43)	0.959	1.17 (0.55-2.50)	0.688

3.3.2. Univariate: disease progression at 12 month

Univariate analysis was conducted to assess association between disease progression at 12 months of study and the baseline covariates assessed in the main analysis (participantsôbaseline socio demographic and baseline clinical characteristics). The crude odds ratio (OR) was reported.

Non-South African nationality, being employed, part-time occupation, higher snuff taking frequency, elevated haemoglobin at HAART initiation, a non-negative Pap screening result at study baseline Pap screening, and not being aware of HPV at study enrolment were found to have significant association with disease progression at 12 months of the study. Results from these analyses are summarised above in Table 9f.

3.3.3. Multivariate analysis: disease progression at 12 month

There was only one significant factor that was found to be significantly associated with disease progression in the multivariate analysis, this was having a non-negative baseline study Pap smear screening at study enrolment.

Compared to those that had a negative baseline study Pap smear at study enrolment those that had a moderate to severe baseline study Pap smear at enrolment into the study were 92% less likely to have disease progression at their 12 month Pap smear screening (aOR=0.08, 95%CI 0.05-0.13). Results from this analysis are provided in Table 9f.

Table 9f: Factors association with study participantsô disease development at 12 month for study participants attending Themba Lethu clinic during the November 2009 to December 2012 period (n=681).

Factor	Disease progression at 12 months of the study			
	Crude OR (95% CI)	**p-value**	**Adjusted OR (95% CI)**	**p-value**
Age groups: 18-29	ref			
30-39	0.82 (0.49-1.37)	0.457		
40-49	0.83 (0.49-1.39)	0.468		
50+	0.71 (0.35-1.44)	0.344		
Race: Black	ref			
Other	0.52 (0.14-1.89)	0.321		
Nationality: South African	ref		ref	
Non-South African	1.58 (0.88-2.83)	0.124	1.79 (0.73-4.38)	0.206
Marital Status: Single	ref			
Married	1.19 (0.79-1.80)	0.397		
Cohabiting	0.85 (0.52-1.39)	0.526		
Divorced/ Separated	1.17 (0.59-2.29)	0.656		
Widow	0.74 (0.38-1.46)	0.389		
Education Level: < Grade 10	ref			
Grade 10ï Matric	1.07 (0.72-1.60)	0.725		
Tertiary	0.83 (0.43-1.58)	0.567		
None	1.73 (0.55-5.44)	0.347		
Currently Employed: No	ref		ref	
Yes	0.67 (0.49-0.92)	0.014	1.24 (0.77-2.02)	0.378
Occupation: Full-time	ref		ref	
Part-time	0.67 (0.40-1.12)	0.125	0.90 (0.42-1.93)	0.778
Self-Employed	0.74 (0.23-2.39)	0.615	1.51 (0.34-6.81)	0.590
Currently Smoking: No	ref			
Yes	0.91 (0.39-2.14)	0.824		
Smoking Frequency: <5 per day	ref			
> 5 per day	1.22 (0.16-9.47)	0.848		
Currently taking snuff: No	ref			
Yes	0.92 (0.54-1.55)	0.753		
Snuff Frequency: <5 per day	ref		ref	
> 5 per day	2.5 (0.70-8.92)	0.158	2.59 (0.30-22.29)	0.387
Currently Drinking Alcohol: No	ref			
Yes	1.14 (0.68-1.92)	0.621		
Baseline WHO staging: I-II	ref			
III -IV	0.82 (0.61-1.39)	0.697		
Baseline BMI *(kg/m2):* Underweight (<18.5)	ref			
Normal (18.5-24.9)	0.85 (0.44-1.64)	0.631		
Overweight (Ó25)	0.67 (0.34-1.32)	0.244		
Baseline CD4 *(cells/mm3):* 0-50	ref			
51-100	0.80 (0.43-1.46)	0.462		
101-250	0.83 (0.51-1.33)	0.432		
251-350	0.65 (0.26-1.61)	0.355		
>350	0.82 (0.36-1.86)	0.632		

Baseline HIV viral load *(copies/ml):* <100 000	ref			
Ó100 000	0.85 (0.39-1.83)	0.674		
Hemoglobin *(g/dL):* <8g/dL	ref		ref	
Ó8g/dL	0.55 (0.25-1.22)	0.141	0.49 (0.77-2.02)	0.151
AST (IU/L): <40	ref			
>=40	1.36 (0.88-2.09)	0.164		
ALT (IU/L): <40	ref			
>=40	1.30 (0.74-2.27)	0.359		
Lactate levels (mmol/L): 0-2.4 - Normal	ref			
2.5-4 ï Moderately elevated	1.05 (0.58-1.88)	0.872		
>4 ï Severely elevated	0.73 (0.42-1.28)	0.273		
On HAART: No	ref			
Yes	0.97 (0.40-2.31)	0.938		
HAART regimen*: 1a	ref			
1b	0.80 (0.45-1.44)	0.461		
Other	0.87 (0.61-1.25)	0.451		
Baseline study Pap smear results: Negative	ref		ref	
Moderate/Severe/ICC	0.07 (0.05-0.10)	<0.001	0.08 (0.05-0.13)	<0.001
Previous Pap smear results: Negative	ref			
Moderate/Severe/ICC	0.711 (0.27-1.87)	0.489		
	r			
Pap Awareness: Aware	ref			
Not Aware	0.92 (0.64-132)	0.645		
HPV awareness: Aware	ref		ref	
Not aware	1.31 (0.88-1.94)	0.187	1.51 (0.84-2.73)	0.171
Perceived Risk : Not Worried at All	ref		ref	
Somewhat Worries	0.86 (0.53-1.39)	0.538		
Very Worried	1.01 (0.68-1.49)	0.962		
Practice according to the national cervical cancer guidelines:				
Adequate	ref		ref	
Not Adequate	0.93 (0.65-1.32)	0.671		
Practice according to national HIV treatment guidelines:				
Adequate	ref		ref	
Not Adequate	0.99 (0.69-1.43)	0.959		

*HAART regimens 1a ï stavudine/ lamivudine/ efavirenz, (d4T / 3TC / EFV), 1b - stavudine/ lamivudine/ nevirapine (d4T / 3TC / NVP)

A sensitivity analysis was conducted among patients that did not have a 12 month visit (n=514) and thus did not have their disease progression assessed, to evaluate whether excluding them had any impact on the estimates in the main analysis of disease progression. Although there are some minor deviations in estimates from main analysis, the confidence intervals for the sensitivity analysis look similar to the main analysis therefore it is unlikely that excluding those that did not have a 12 month follow up visit biased the main analysis, the results from this analysis are listed in Appendix 2b.

3.4. Analysis of attrition

During the study period a total of 7 women enrolled in the study died out of the 1202 enrolled in the study, this equates to 0.58% of study participants who became deceased by the end of the study. This was all-cause mortality and the deceased participants didnôt necessarily die of cervical cancer disease related causes, in most cases data on the cause of death could not be acquired.

All study participantsô deaths occurred in the 30-39 years age group. The mean time to death from enrolment in the study was 156 days (SD ±126.28 days). The earliest a participant died was 1 month after enrolment into the study, and the latest that a participant died was 13.5 months after enrolment into the study. Although this was outside the 12 month study follow up, in general study participants were given some leeway (a maximum of 3 months) to be able to return for their 12 month study follow up visit and still be included in the 12 month follow up analysis. The mortality observed corresponds to an overall incidence rate of 0.048 (95% CI: 0.023-0.101) cases per 100 person months of follow-up.

Figure 4 provides survival estimates for the study population.

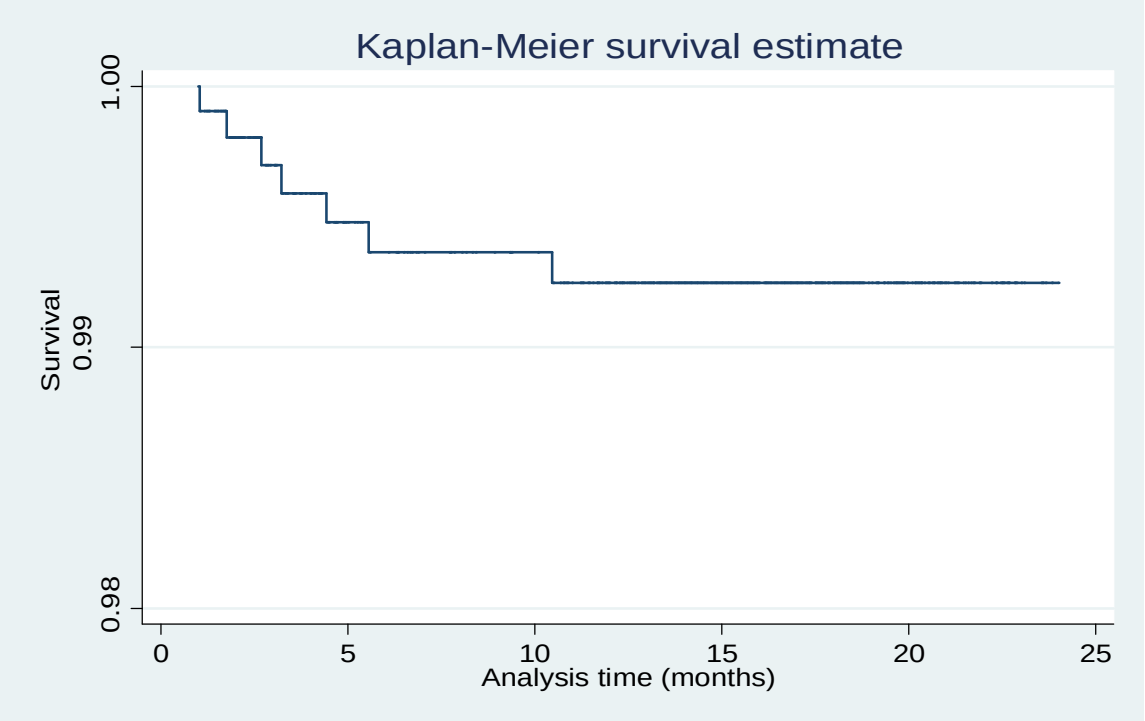

Figure 4. Kaplan Meier estimates of mortality by 12 month study follow up for study participants attending Themba Lethu clinic during the November 2009 to December 2012 period (n=7).

Survival analysis to assess estimates for the outcome death did not yield meaningful results as the sample size was so small and therefore did not have sufficient power for meaningful analysis. The study was an analysis of secondary data we therefore did not have control over the sample size determination.

Further analysis was conducted to examine all-cause attrition. The number of study participants that were alive and in HIV care were compared to those that were no longer alive and in HIV care (those that died, or were lost to follow up). Table 10 below summarises period incidence for attrition for the study population.

Out of 1202 study participants followed up for a total of 1835 person-months, a total of 109 cases of attrition were observed, corresponding to an overall incidence rate of 5.95 (95% CI: 4.93-7.18) cases per 100 person months of follow-up. Study participants were determined to be LTFU when more than three separate attempts to contact them using the contact details provided are unsuccessful and the missed visit is outside of the allowable window for the visit (3 months from appointment date).

Table 10. Period incidence rates of attrition at specified time points per 100 person months for study participants attending Themba Lethu clinic during the November 2009 to December 2012 period (n=109)

Period (months)	Person time (months)	Failures	Surviving	Period incidence rate (per 100 person months)	95% CI
0-3 months	324.54	4	106	1.23	0.46-3.28
3-6 months	309.95	3	103	0.97	0.31-3.00
6-9 months	300.15	3	100	1.00	0.32-3.10
9-12 months	289.23	6	94	2.07	0.93-4.62
12-15 months	258.20	11	83	4.26	2.36-7.69
>15 months	349.54	82	0	23.46	18.89-29.13
Total	**1831.61**	**109**	**0**	**5.95**	**4.93-7.18**

The incidence rate was the highest during the period >15 months at 23.46 per 100 person months (95% CI 18.89-29.13). The incidence rate was at its lowest during the 3-6 months period at 0.97 per 100 person months (95% CI 0.31-3.00). The majority of study participants (46.79%) became decease or LTFU after 12 months in the study..

The Kaplan Meier curve was used to determine the overall survival for the study population. Figure 5 shows the overall survival of patients during the study period.

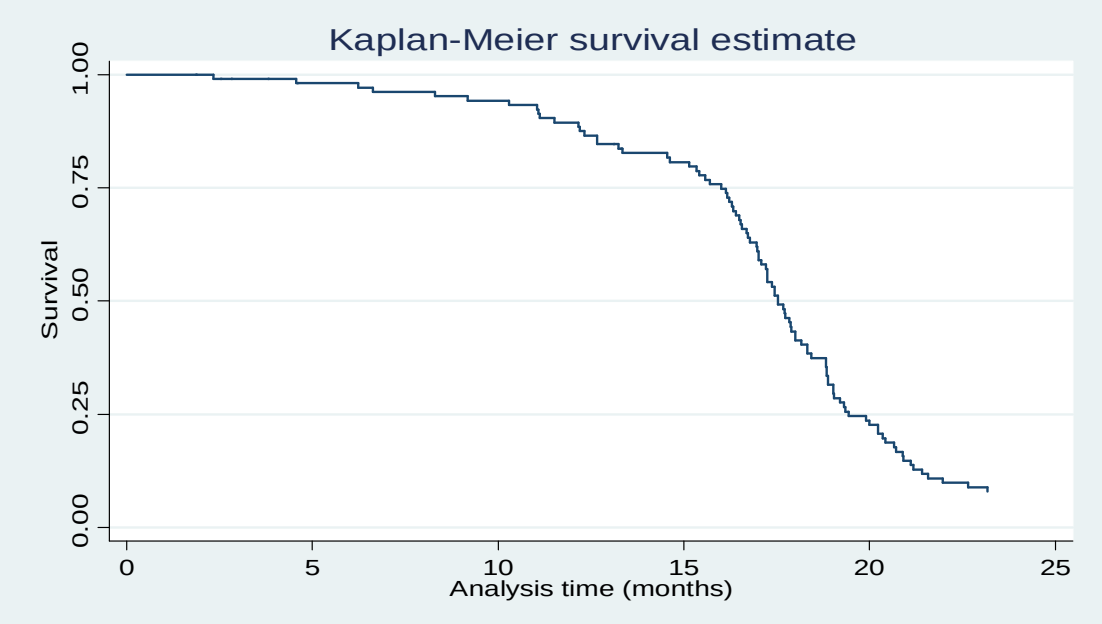

Figure 5. Kaplan Meier estimates for all-cause attrition (death and LTFU) by 12 month study follow up for study participants attending Themba Lethu clinic during the November 2009 to December 2012 period (n=109).

3.4.1. Predictors of all-cause attrition

Attrition was also further assessed according to the main study outcomes; awareness, perceived risk and practice related to Pap smear testing as assessed as at the beginning of the study, and baseline covariates, namely study participantsô baseline socio-demographic and clinical characteristic at HAART initiation.

When attrition was assessed according to the main study outcomes a slightly higher proportion (55.96%) of the study participant became deceased or LTFU by the end of the study were aware what a Pap smear was at study enrolment, while a majority (83.49%) were not aware of HPV at study enrolment. A total of 59 (54.63%) of study participants that became deceased or LTFU by the end of the study were very worried about getting cervical cancer disease at study enrolment, while 12.96% were somewhat worried about getting the disease at study enrolment. A total of 35 (32.41%) were not worried at all about getting the disease at study enrolment. In addition, a majority (73.20%) of them had inadequate Pap screening practice according to both

the national cervical cancer guidelines and the national HIV treatment guidelines at study enrolment (80%). The above results and results from the descriptive analysis of attrition according to baseline covariates are summarised below in Tables 11.

The equality of survival curves were tested using log rank tests. Results are summarised in appendix 2c. From the results, a p-value <0.05 was considered significant. Significant difference in Kaplan Meier survival curves between different groups were only noted for the covariate baseline study Pap screening results, this Kaplan Meier curve is listed below.

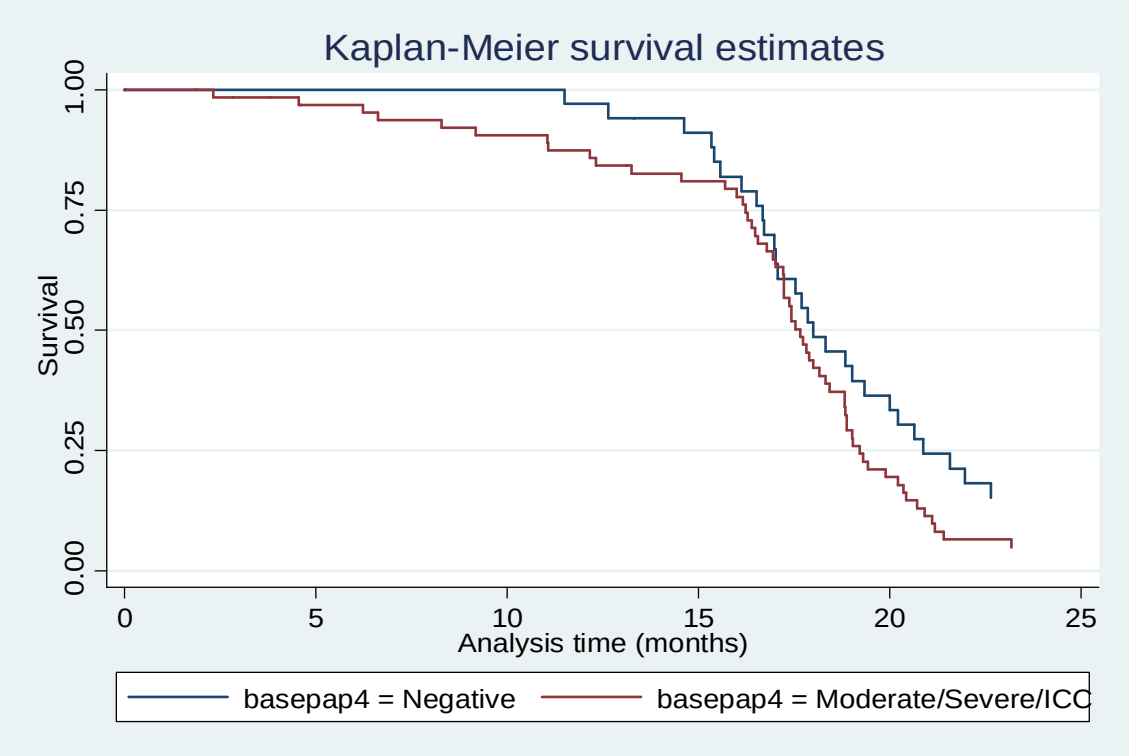

Figure 6a. Kaplan Meier estimates for all-cause attrition (death and LTFU) according to study participants baseline study Pap screening results at study enrolment for study participants attending Themba Lethu clinic during the November 2009 to December 2012 period (n=109).

Study participants with a negative baseline study Pap smear at study enrolment were less likely to become deceased or LTFU than those with a moderate and severe results. The log rank test of equality of survival functions was significant (p=0.043).

Kaplan Meier curves were used to determine survival for the study population according to main study outcomes; Pap smear and HPV awareness, perceived risk of getting cervical cancer

disease, and practice according to nation HIV treatment and cervical cancer guidelines. Figure 6b-6d shows the survival of study participants during the study period according to the main study outcomes.

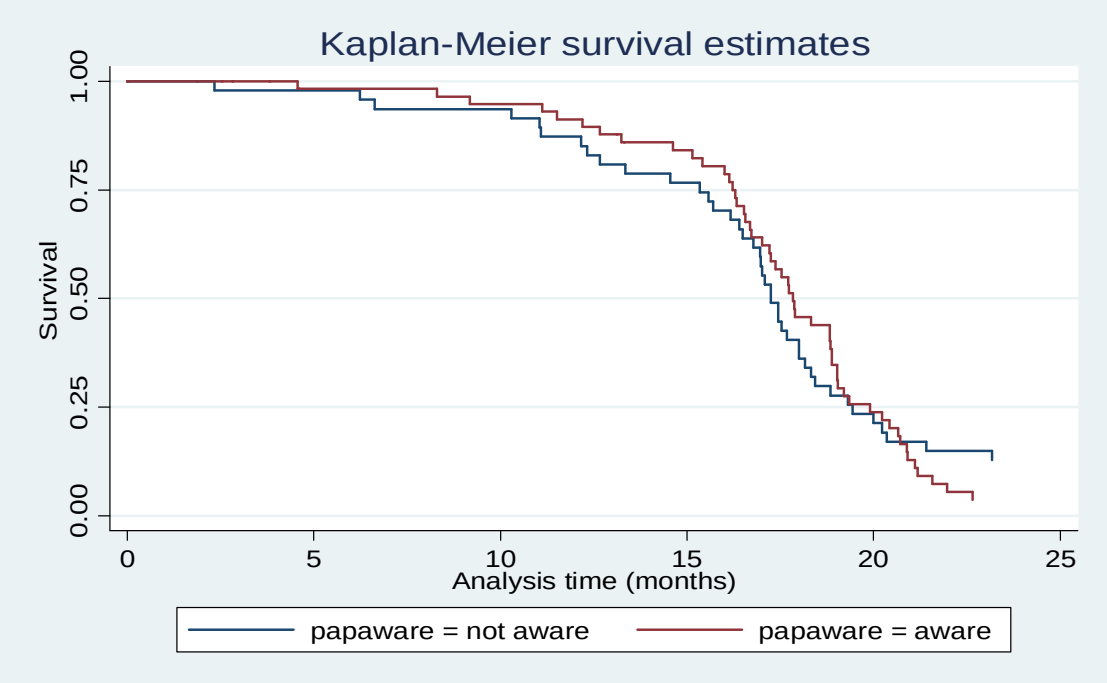

Figure 6b. Kaplan Meier estimates for all-cause attrition (death and LTFU) according to study participants awareness of Pap smear screening at study enrolment for study participants attending Themba Lethu clinic during the November 2009 to December 2012 period (n=109).

Study participants that were aware of the Pap smear screening test at study enrolment had similar risk to become deceased or LTFU to study participants that were not aware of Pap smear screening (p=0.633).

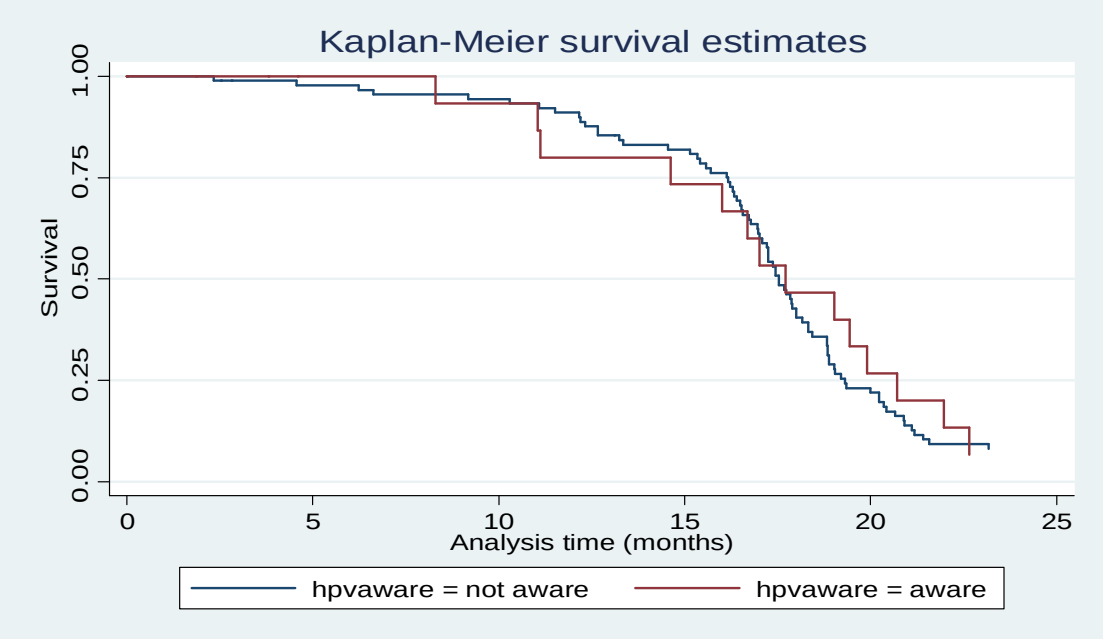

Figure 6c. Kaplan Meier estimates for all-cause attrition (death and LTFU) according to study participants awareness of HPV at study enrolment for study participants attending Themba Lethu clinic during the November 2009 to December 2012 period (n=109).

Study participants that were aware of HPV at study enrolment had similar risk to become deceased or LTFU to study participants that were not aware of Pap smear screening (p=0.988).

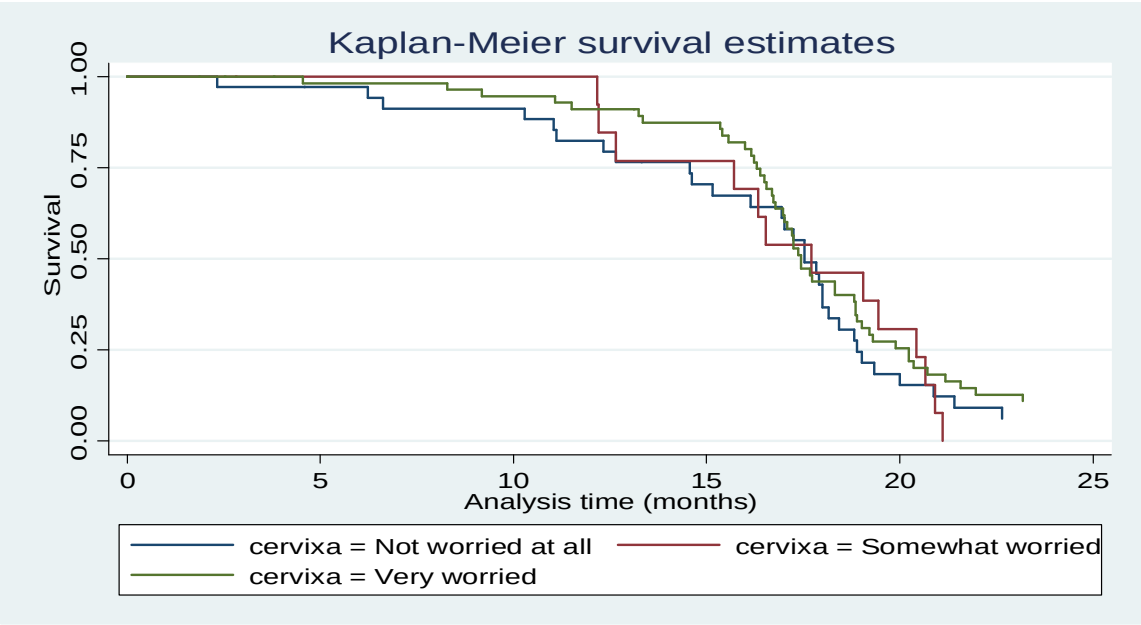

Figure 6d. Kaplan Meier estimates for all-cause attrition (death and LTFU) according to study participants perceived risk of getting cervical cancer at study enrolment for study participants attending Themba Lethu clinic during the November 2009 to December 2012 period (n=109).

Study participants that were very worried about getting cervical cancer disease at study enrolment were more likely to become deceased or LTFU than those that were somewhat worried and those that were not worried at all, however this difference between risk was not significantly different (p=0.678).

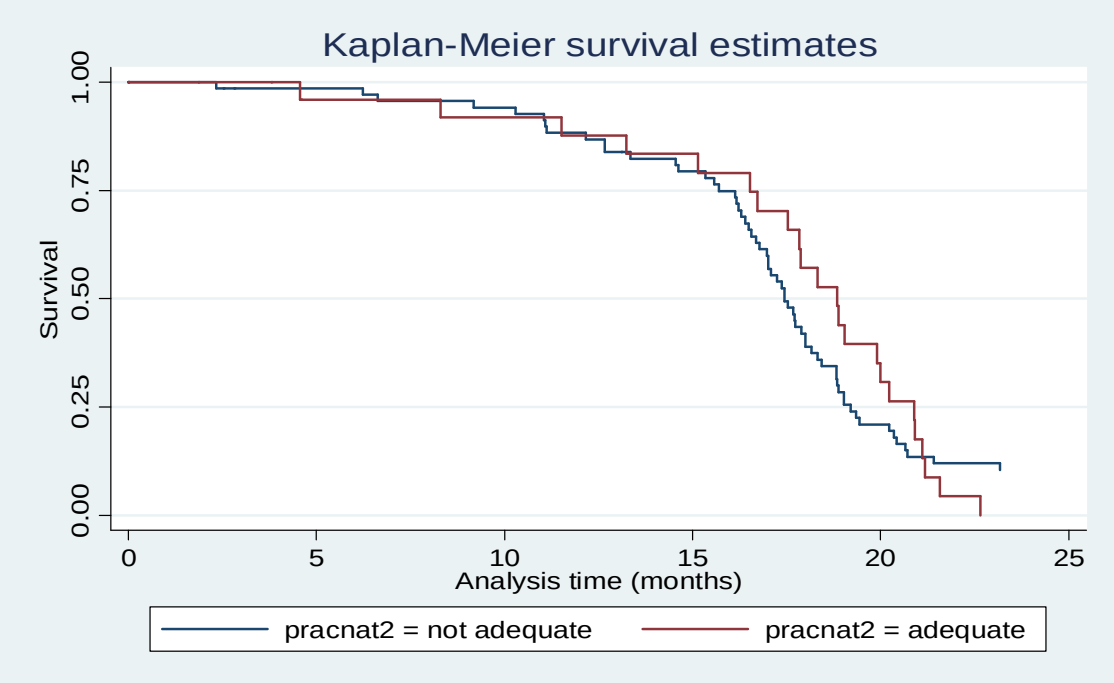

Figure 6e. Kaplan Meier estimates for all-cause attrition (death and LTFU) according to study participants practice according to the national cervical cancer guideline for study participants attending Themba Lethu clinic during the November 2009 to December 2012 period (n=97).

Study participants that had adequate Pap screening practice according to the national cervical cancer guidelines at study enrolment had similar risk to become deceased or LTFU to study participants that did not have adequate Pap screening practice according to the national cervical cancer guidelines at study enrolment (p=0.897).

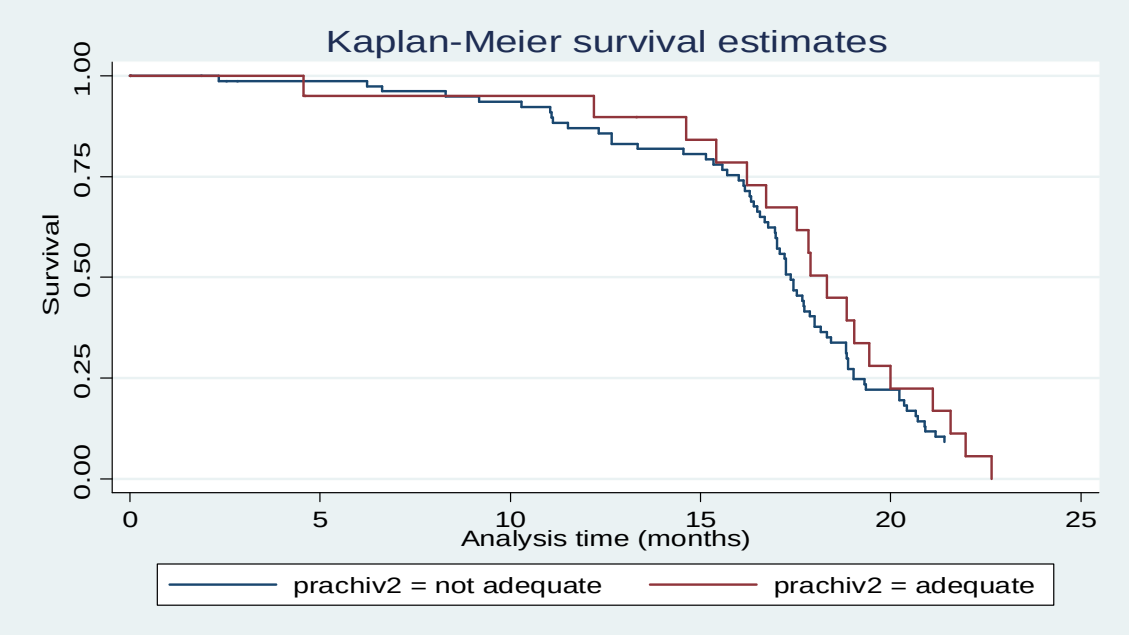

Figure 6f. Kaplan Meier estimates for all-cause attrition (death and LTFU) according to study participants practice according to the national HIV treatment guideline for study participants attending Themba Lethu clinic during the November 2009 to December 2012 period (n=100).

Study participants that had adequate Pap screening practice according to the national HIV treatment guidelines at study enrolment had similar risk to become deceased or LTFU to study participants that did not have adequate Pap screening practice according to the national HIV treatment guidelines at study enrolment (p=0.890).

3.4.2. Univariate analysis: analysis of attrition

Cox proportional hazards models were fitted to identify predictors of attrition. The crude hazards ratio (HR) was reported.

Results from the univariate analysis indicated that having no education, part-time occupation, taking snuff, higher snuff taking frequency, lower baseline CD4 at HAART initiation, higher baseline ALT at HAART initiation, moderately high baseline Lactate levels at HAART , being initiated of HAART and non-negative baseline study Pap smear results at study enrolment were significantly associated with a greater risk of attrition. Table 11 shows hazard ratios for each covariate in the univariate analysis.

Global tests for proportional hazards assumptions based on Schoenfeld residuals were conducted after fitting univariate Cox models on all covariates. With the exception of nationality, all co-variates had p>0.05 indicating that the proportional hazards assumption was not violated.

3.4.3. Multivariate analysis: analysis of attrition

There was only one significant factor associated with attrition which was being initiated on HAART. Results from this analysis are provided in Table 11.

Those that are initiated on HAART were 90% less likely to be deceased of LTFU than those that were not initiated on HAART (aOR=0.10, 95% CI 0.01-0.81). The global test for the overall model showed that the proportional hazard assumption had not been violated, p=0.684.

Table 11: Analysis of all-cause attrition for study participants attending Themba Lethu clinic during the November 2009 to December 2012 period (n=1202).

Factor	All-cause Attrition (Deceased or LTFU) n (%)					
	Alive and in Care 1093 (90.93)	Attrition (Deceased or LTFU) 109 (9.07)	Crude HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
Age groups: 18-29	149 (13.63)	12 (11.01)	ref			
30-39	485 (44.37)	61 (55.96)	0.88 (0.47-1.64)	0.687		
40-49	368 (33.67)	29 (26.61)	1.00 (0.51-1.97)	0.996		
50+	91 (8.33)	7 (6.42)	0.86 (0.34-2.20)	0.757		
Race: Black	1055 (96.52)	107 (98.17)	ref			
Other	38 (3.48)	2 (1.83)	1.63 (0.40-6.67)	0.499		
Nationality: South African	978 (90.64)	97 (89.81)	ref			
Non-South African	101 (9.36)	11 (10.19)	0.63 (0.31-1.28)	0.200		
Marital Status: Single	592 (54.16)	66 (60.55)	ref			
Married	202 (18.48)	12 (11.01)	0.76 (0.40-1.45)	0.411		
Cohabiting	152 (13.91)	18 (16.51)	0.95 (0.56-1.60)	0.842		
Divorced/ Separated	67 (6.13)	5 (4.59)	1.22 (0.49-3.04)	0.676		
Widow	80 (7.32)	8 (7.34)	0.93 (0.45-1.95)	0.854		
Education Level: < Grade 10	214 (19.58)	15 (13.76)	ref		ref	
Grade 10ï Matric	756 (69.17)	78 (71.56)	1.25 (0.70-2.21)	0.452	2.16 (0.70-6.64)	0.181
Tertiary	99 (9.06)	14 (12.84)	0.97 (0.46-2.06)	0.945	1.51 (0.53-2.51)	0.724
None	24 (2.20)	2 (1.83)	4.22 (0.93-19.18)	0.063	2.51 (0.84-7.50)	0.600
Currently Employed: No	493 (45.11)	42 (38.53)	ref			
Yes	600 (54.89)	67 (61.47)	0.93 (0.56-1.23)	0.348		
Occupation: Full-time	400 (67.91)	48 (71.64)	ref		ref	
Part-time	165 (28.01)	17 (25.37)	1.54 (0.87-2.73)	0.138	4.90 (0.69-34.80)	0.112
Self-Employed	24 (4.07)	2 (2.99)	0.71 (0.17-2.98)	0.643		
Currently Smoking: No	1055 (96.52)	105 (96.33)	ref			
Yes	38 (3.48)	4 (3.67)	1.82 (0.66-4.98)	0.244		
Smoking Frequency: <5 per day	24 (72.73)	4 (100)	ref			
> 5 per day	9 (27.27)	0 (0)	3.82 (1.66-25.98)	0.999		
Currently taking snuff: No	986 (90.21)	91 (83.49)	ref		ref	
Yes	107 (9.79)	18 (16.51)	0.67 (0.40-1.13)	0.132	0.25 (0.02-3.14)	0.283
Snuff Frequency: <5 per day	85 (81.73)	13 (86.67)	ref		ref	
> 5 per day	19 (18.27)	2 (13.33)	3.84 (0.74-19.94)	0.110	0.63 (0.03-14.63)	0.773
Currently Drinking Alcohol: No	975 (89.20)	102 (93.58)	ref			
Yes	118 (10.80)	7 (6.42)	0.96 (0.44-2.08)	0.920		
Baseline WHO staging: I-II	512 (66.67)	46 (61.33)	ref			
III -IV	256 (33.33)	29 (38.67)	1.02 (0.64-1.63)	0.934		
Baseline BMI *(kg/m2):* Underweight (<18.5)	76 (9.34)	10 (12.50)	ref			
Normal (18.5-24.9)	434 (53.32)	45 (56.25)	0.99 (0.49-1.97)	0.968		

Overweight (Ó25)	304)37.35)	25 (31.25)	1.22 (0.58-2.56)	0.604		
Baseline CD4 *(cells/mm3):* 0-50	171 (19.77)	22 (25.58)	ref		ref	
51-100	163 (18.84)	11 (12.79)	0.50 (0.23-1.12)	0.092	0.32 (0.02-4.23)	0.387
101-250	425 (49.13)	47 (54.65)	0.85 (0.51-1.41)	0.521	0.43 (0.03-6.70)	0.549
251-350	51 (5.90)	3 (3.49)	1.80 (0.53-6.10)	0.346	0.69 (0.01-33.81)	0.854
>350	55 (6.36)	3 (3.49)	2.12 (0.62-7.29)	0.233		
Baseline HIV viral load *(copies/ml):* <100 000	191 (76.40)	18 (75.00)	ref			
Ó100 000	59 (23.60)	6 (25.00)	0.61 (0.24-1.58)	0.311		
Hemoglobin *(g/dL):* <8g/dL	42 (4.94)	4 (5.13)	ref			
Ó8g/dL	809 (95.06)	74 (94.87)	1.28 (0.46-3.52)	0.633		
AST (IU/L): <40	520 (73.76)	48 (69.57)	ref			
>=40	185 (26.24)	21 (30.43)	1.21 (0.72-2.05)	0.476		
ALT (IU/L): <40	761 (87.27)	68 (82.93)	ref		ref	
>=40	111 (12.73)	14 (17.07)	1.60 (0.89-2.88)	0.118	1.23 (0.46-3.29)	0.682
Lactate levels (mmol/L): 0-2.4 - Normal	246 (53.60)	26 (56.52)	ref		ref	
2.5-4 ï Moderately elevated	93 (20.26)	7 (15.22)	2.42 (0.96-6.05)	0.060	24.24 (0.71-122.84)	0.076
>4 ï Severely elevated	120 (26.14)	13 (28.26)	0.98 (0.50-1.95)	0.962	0.50 (0.08-3.19)	0.467
On HAART: No	43 (4.00)	1 (0.93)	ref		ref	
Yes	1031 (96.00)	107 (99.07)	0.15 (0.02-1.14)	0.067	0.10 (0.01-0.81)	0.031
HAART regimen*: 1a	569 (54.66)	52 (48.60)	ref			
1b	96 (9.22)	11 (10.28)	1.54 (0.79-3.02)	0.206		
Other	376 (36.12)	44 (41.12)	1.37 (0.91-2.08)	0.136		
Baseline study Pap smear results: Negative	286 (26.31)	34 (33.66)	ref		ref	
Moderate/Severe/ICC	801 (73.69)	67 (66.34)	1.44 (0.94-2.19	0.092	11.67 (1.30-104.64)	0.068
Previous Pap smear results: Negative	493 (94.44)	30 (96.77)	ref			
Moderate/Severe/ICC	29 (5.56)	1 (3.23)	0.62 (0.08-4.60)	6.37		
Disease Development: Not Progressed	445 (65.93)	4 (66.67)	ref			
Progressed	230 (34.07)	2 (33.33)	2.44 (0.01-0.52)	0.990		
Pap Awareness: Aware	789 (72.45)	60 (55.05)	ref			
Not aware	300 (27.55)	49 (44.95)	1.07 (0.73-1.58)	0.722		
HPV Awareness: Aware	200 (18.33)	18 (16.51)	ref			
Not aware	891 (81.67)	91 (83.49)	1.02 (0.62-1.70)	0.940		
Perceived Risk: Not Worried at All	245 (22.60)	35 (32.41)	ref			
Somewhat Worried	236 (21.77)	14 (12.96)	0.98 (0.52-1.83)	0.951		
Very Worried	603 (55.63)	59 (54.63)	0.85 (0.56-1.29)	0.449		
Practice According to Cervical Cancer guidelines:						
Adequate	355 (37.61)	26 (26.80)	ref			
Not adequate	589 (62.39)	71 (73.20)	0.96 (0.61-1.52)	0.869		
Practice According to HIV treatment guidelines:						
Adequate	284 (29.46)	20 (20.00)	ref			
Not adequate	680 (70.54)	80 (8000)	0.96 (0.59-1.58)	0.879		

*HAART regimens 1a ï stavudine/ lamivudine/ efavirenz, (d4T / 3TC / EFV), 1b - stavudine/ lamivudine/ nevirapine (d4T / 3TC / NVP)

In a sub-analysis, participants with a 12 month follow up visitôs characteristics and demographics were compared (by age, CD4 count, HAART status etc.) with study participants who did not have a 12 month follow up visit to determine if they are significantly different. This analysis showed that the two population groups were similar based on most of the characteristics assessed. However, the most notable difference noted was that the results of their baseline Pap screening results. Those that did not have a 12 month follow up visit conducted had the highest proportion of women with a severe baseline study Pap results (61.23%) compared to those that had a 12 month follow up study visit where most of the women had a moderate Pap screening results (50.07%).

CHAPTER 4: Discussion

4.1. Introduction

The studyôs main objectives were to assess the awareness, perceived risk and practices related to cervical cancer and Pap screening among HIV-positive women in an urban HIV clinic in Johannesburg, South Africa. The findings of the study are discussed below according to each specific objective.

4.2. Study participants' baseline characteristics

A majority of the women were Black (98.09%) and of South African nationality (90.86%). The majority (45.42%) of the women were in the 30-39 age group with a mean age of 38.14 years (SD ±7.67) which is similar to a studies conducted in Kenya to assess awareness related to cervical cancer and Pap smear screening (46) and in Cameroon assessing HPV and cervical cancer prevention amongst health workers (47). Over 50% of the women were single with just over a third reporting to be in some sort of relationship with a partners; with 17.80% reporting that they were married and 14.14% reporting to be cohabiting with a partner.

The study population were generally better educated than the overall South Africa female population. The overall South Africa population had on average 55.8% of the female population completing high school to Matric level education, while a higher proportion (11.9%) had no schooling at all compared to the study population (2.16%) (48). However, the overall South Africa female population had higher proportions (12.3%) of individuals that had tertiary level education (48). A majority of the participants in previous studies that did not target participants with technical jobs such as teachers or nurses had secondary school education (14, 49).

The majority (96.88%) of the study participants were initiated on HAART which is a higher proportion than the larger TLC population which only had 74.31%. The study participantsô overall median CD4 count at HAART initiation was 138 cells/mm3 (IQR 63-205) which is lower than the recommended initiation CD4 count at the time which was less than 200

cells/mm^3 (17). The current national HAART guideline recommendation has recently been changed to 500 cells/mm^3 (50). The majority of the participantôs baseline viral load (VL) were missing (77.20%). VL was not required at baseline at HAART initiation as it was not the required standard of care according to the national HIV treatment guidelines (17, 18, 29). The majority (51.66%) of the study participants were initiated on HAART Regimen 1a ï stavudine/ lamivudine/ efavirenz, (d4T / 3TC / EFV), with 107 (8.90%) initiated on Regimen 1b - stavudine/ lamivudine/ nevirapine (d4T / 3TC / NVP). Women who were on the NVP based regimen would mostly have reported their fertility intentions. Under the previous South Africa national HIV guidelines EFV was contraindicated for women who have reported their intentions to fall pregnant due to concerns related to the drug possibly negatively affecting the development of the pregnancy (45).

Results when comparing the study population and the larger TLC cohort population indicated that there were no major difference between the two populations, only small differences were noted in most cases. However, it was noted that the study population was healthier at HAART initiation than the TLC cohort population. A higher proportion of the TLC cohort were initiated on HAART at a lower CD4 count, higher VL, and lower BMI compared to the study population. This could indicate there might be better health seeking behaviour from the study participant to be more likely to have been initiated on HAART, and to also be initiated on HAART when theyôre healthier than their counterparts attending the same clinic.

4.3. Awareness related to cervical cancer and Pap smear screening

Several studies have consistently shown that lack of awareness and in particular lack of detailed knowledge about the disease and its prevention methods has led to an increase in incidence and prevalence of the disease (46, 51).

Results from our study showed that a total of 857 (71.30%) participants reported to be aware of Pap smear screening. A study conducted amongst much younger (mean age 22 years SD 2.3

years) tertiary students in the Eastern Cape in South Africa showed similar results; 70% awareness of Pap smear screening amongst the study participants (52). We identified older age (>= 50 years), South African nationality and higher than grade 10 education level as significant factors associated with being aware of Pap smear screening in our study.

In a number of previous studies low literacy or low education has been consistently shown to be correlated to negative health behaviours and a cause for higher risk of morbidity and mortality (46, 53). Other studies have demonstrated that better education means better awareness and better knowledge regarding cervical cancer disease and screening (51, 54, 55). However, awareness did not necessarily translate to practice as screening history collected in our study indicated. This is a finding that has found in previous studies which indicates that practice is probably influenced by an array of factors differing in complexity, priority, and different contexts (47, 49, 51). All of the assortment of factors need to be better understood in order to implement adequate interventions to address this deficiency in HIV positive women seeking cervical cancer prevention services (47, 49, 51).

Some of these studies theorised that older women were generally more concerned about getting cervical cancer disease more than younger women because cervical cancer was traditionally a disease that mostly affected older women (14, 56).

Non-South Africans were shown to be less likely to be aware of Pap smear screening than South Africans. This could be accounted for by the fact that South Africa has one of the most progressive cervical cancer screening policies and programmes when compared to many countries in the Southern African region where over 90% of the non-South African participants originate from. This could also indicate the impact of the language barrier. Messaging related to cervical cancer disease prevention and treatment may be discussed by the health care workers and patients during the patientôs clinic visits during their care at the clinic, non-South African patients may not be getting the same quality of messaging as a result of a language barrier as

most likely health care workers at the clinic could not speak their language. Or it could be that because of the language barrier these non-South African study participants may not have understood the question clearly during the study interview.

Remarkably, those that were initiated on HAART were found to be less likely to be aware of Pap smear screening than those that were not initiated on HAART. One would expect study participants that are initiated on HAART to have had more exposure to health messaging related to cervical cancer screening and have also had cervical screening conducted. The national HIV treatment guidelines recommend cervical cancer screening on diagnosis of HIV and if this screening test is negative then subsequent screening every three years, irrespective of HAART status (18). More needs to be done to provide adequate and appropriate patient education to patients in order to empower them with the knowledge to be able to seek these services (14, 47, 51). Moreover, it is also very important for health facilities to be adequately resourced to be able to offer these services (14, 47).

None of the factors being assessed in the study proved to be significantly associated with the outcome in the analysis of awareness related to HPV. Nevertheless, lack of awareness and knowledge regarding HPV and its role in cervical cancer disease and its prevention is an important issue that has been identified in many studies. This further highlights the urgent need to address this through effective health education programmes (14, 29, 47).

4.4. Perceived risk related to cervical cancer and Pap screening

Previous studies found that womenôs perceived risk may negatively influence screening behaviours and lead to higher risk of morbidity and mortality (41, 42). In the analysis of perceived risk related to cervical cancer disease the significant factors identified were a tertiary education level, taking snuff and drinking alcohol.

The results showed that compared to those with less than a grade 10 level education, having a tertiary level education increased the likelihood of study participants being more worried about

getting cervical cancer disease. In addition, study participants that took snuff and those that drank alcohol also were more worried about getting cervical cancer disease. Taking snuff is factor that has not been explored in previous studies that have evaluated the perceived risk related to cervical cancer especially amongst women from more rural areas where snuff use is more common than in urban areas. Long term use of tobacco has long been established as a risk factor to many cancers including cervical cancer (5). Perhaps the study participantôs perception of risk may have been influenced by knowledge that the taking snuff, which is a type of tobacco, is unhealthy and may contribute to poor health. The knowledge of their unhealthy habit may lead to having despondent views related to getting cervical cancer. In contrast, smoking cigarettes was not associated to perceived risk of related to cervical cancer. However, snuff use was more prevalent in our study population than smoking which might be because snuff is much cheaper than cigarettes.

In our study a majority (55.54%) of the participants reported to be very worried about getting cervical cancer. Women may have a fatalistic view of the disease outcomes and not seek screening services as they may see no hope of any positive outcomes should they have the disease (14, 46, 57). This state of mind can be further exacerbated by use of alcohol, one of the factors found to be associated with perceived risk related getting cervical cancer disease. On the other hand, the belief that they are not susceptible to the disease may lead women to forgo screening thereby missing on the chance to detect and treat the disease appropriately (39). In both cases lack of awareness and knowledge regarding the disease and its prevention was seen as important factors influencing the womenôs perception regarding their risk related to the disease (39, 57).

More needs to be done towards ensuring that women have detailed and correct knowledge regarding cervical cancer, its related risk factors and its methods of prevention. This will ensure that their perception of risk related to the disease is more accurate, and will hopefully positively influence their screening practices (14, 46).

4.5. Practice related to Pap smear screening

Although our study population may have high rates of awareness related to Pap smear screening, many studies have shown that awareness doesnôt necessarily translate to adequate practice related to seeking prevention services (39, 49, 58). A majority of the women in the study had inadequate screening practices. Only 36.46% women had adequate practice according to the national cervical cancer guidelines, and even fewer (28.57%) had adequate practice according to the national HIV treatment guidelines.

The factors age, marital status, being initiated on HAART and occupation were found to have significant association with Pap screening practice according to the national cervical cancer guideline. Our results showed that women in the 30-39 age category at enrolment in the study had increased odds of adequate practice related to cervical cancer screening when compared to younger women. This could be because cervical cancer was traditionally a disease that mostly affected older women, and according to the national cervical cancer guidelines this age group would have been targeted for screening as part of the national screening programme (14, 17, 56).

Those that were self-employed were more likely to have adequate practice according to the national cervical cancer guidelines than those with full time employment. These results were similar to those in a study in Zimbabwe assessing knowledge, attitudes, and demographic factors influencing cervical cancer screening behaviour (59). This study showed that women who were financially independent were more likely to access cervical cancer screening than those that were financially dependent on their husbands (59). Previous studies have shown that women from higher resource settings demonstrated better health seeking behaviour, and self-employed women may be seen to be of a better economic status than their unemployed counterparts as they may be more economically active and economically independent (55, 57, 59). Results also showed that women who reported to be cohabiting with a partner were less

likely to have adequate practice according to the national cervical cancer guidelines compared to their single counterparts. They may be facing the challenge of being economically depended of their partners and thus they would be less likely to access screening services, and this also reduces their opportunity to be exposed to health messaging related to cervical cancer screening.

Those that were initiated on HAART were found to be less likely to have adequate Pap screening practices according to the national cervical cancer guidelines than those that were not initiated on HAART. This finding is concerning since patients that were initiated on HAART shouldôve had more exposure to health messaging including the importance of cervical cancer screening, and they should have had screening conducted on treatment initiations as recommended in the national HIV treatment guidelines. In addition, all the women included in the analysis were over the age of 30 years and according to the national cervical cancer guidelines they would have been targeted for screening according to the cervical cancer guideline as part of the national screening programme. More needs to be done to ensure services are adequately available to patients; ensuring that health practitioners have adequate skills, knowledge, and resources to be able to implement screening programmes as per guidelines. However, patients also need to be provided with appropriate information, education and communication to gain the knowledge and empowerment to be able to seek these services (14, 47, 51).

In the analysis of practice related to Pap smear testing none of the factors proved to be significantly associated with the practice according to the national HIV treatment guidelines.

In a cross sectional study assessing awareness of HPV and cervical cancer prevention amongst Cameroonian health workers it was found that although a high proportion of the study participants were aware of cervical cancer and Pap smear screening only 40% had adequate screening practice (47). Similar results were found by Mutyaba et al in their assessment of

knowledge, attitude and screening practices on cervical cancer screening among medical workers in Mulago Hospital in Uganda 39). These are concerning results especially considering that these were educated healthcare workers with adequate knowledge regarding the disease and its prevention, and had access to free screening at their place of work (14, 39, 47). They should be at the forefront of opportunistic screening of women they care for, and if they are not getting screened themselves then chances are this will have a negative effect on them screening their patients or referring them appropriately for screening (14, 39, 47). Wellensiek et al found that most patients who participated in their study to evaluate knowledge of cervical cancer screening and use of cervical screening facilities among women from various socioeconomic backgrounds in Durban, resided within a 12-kilometer radius of a facility that either provided or could potentially provide screening (55). Despite this the study found very poor Pap smear screening practice among these patients, only 27.3% of the patients reported having had a Pap smear test. One of the factors that was reported to be affecting this was the role of health providers. They did not provide adequate information to patients regarding the need for cervical screening, and its benefit (55).

Results from this study and previous studies highlight the fact that practice related to cervical cancer screening is more complex and there is an urgent need to better understand all the factors affecting womenôs cervical screening practices (39, 47, 55,). Current data for South Africa indicate that a large number of women remain unscreened (58). This and data from other countries shows that good screening policies and availability of screening facilities does not lead to the reduction in morbidity and mortality related to cervical cancer disease if uptake of screening services is not adequate. (39, 57, 58). This calls for more innovative health education strategies which may include nationwide campaigns that use local languages, leveraging local community groups that women have regular contact with and that have influence over them such as churches and burial societies or groups (51). Concerted effort is also needed in targeting

husbands and partners of these women as they also have influence in the womenôs health seeking practices including seeking Pap screening services (59, 60).

4.6. Participant's baseline study Pap smear results

Out of the 688 (57.24%) study participants that reported to have ever had Pap smear screening before the study a majority, 523 (94.58%), reported that their previous Pap smear test before participating in the study were negative. Results were self-reported in most cases, and close to 20% of the participants did not have results reported from their previous screening. They either could not remember what the results were, or they never collected their results. Both factors have been observed in other studies that involved details of participantsô screening history and results from previous screening (46, 55). Similar findings were noted in a study by Wellensiek et al conducted amongst women from various socioeconomic backgrounds in Durban, KwaZulu Natal, South Africa (55). The study assessed knowledge of cervical cancer screening and use of screening facilities by study participants (55). Results from this study indicated that some women reported not being informed what the purpose of the screening test was in their previous Pap screening encounters (55). A very concerning finding as this does not benefit women actively participating and taking responsibility in their own health care. Taking responsibility for their own health care is something to be encouraged as it is hoped that it can positively contribute to the womenôs health seeking behaviour including their uptake of prevention screening services like cervical cancer screening.

Only one (0.18%) of the women reported that they had a severe Pap smear results in their previous Pap smear test before the study, and 29 (5.24%) had Pap smear results classified as moderate. We did not confirm the self-reported results against previous laboratory results so it was not possible to determine if women could accurately report/recall their previous Pap smear results. It has been shown that self-reports often overestimate participation in cervical cancer screening (46, 55). Ombech et al reported that after examining medical records to confirm

reported screening practices, most women overestimated the number of smears taken and how recent the screening was conducted (46).

Out of the 1198 study participants who had a result reported from their baseline study Pap smear two (0.17%) cases of ICC were reported. A total 321 (26.79%) participants had negative baseline study Pap smear results. A majority (39.57%) of the results reported were moderate while 33.47% of the participantôs results were classified as severe, meaning that their Pap smear results were HSIL, ASC-H, CIN II or CIN III. These are a huge contrast to the results reported from previous Pap smear test before the study. Most of the previous Pap results were self-reported and not sourced from participantsô medical records therefore there could be some discrepancies with what the patients reported to what the actual results were. In addition, there could have been some progression of dysplasia from their previous Pap smear. These rates of higher grade (severe) Pap smear results are much higher than previous studies, including a study conducted in the same clinic in 2010 on a different cohort of women (29). In that study the prevalence of severe results was almost half of what is reported in our study results (29). Of the women reported with severe results in our study 15% were from participants in the 18-29 age group. Interestingly, age was not associated with severity of baseline Pap results in our study. It is important to note that it has been found that age and dysplasia correlate in HIV negative populations, however HIV positive status has now been shown to be a more important risk factor to dysplasia in HIV positive women than age. This has been attributed to the HIV-related immunosuppression which may impact disease development and progression (9, 10, 29). Research has consistently shown more women are presenting with dysplasia younger which has been linked to HIV infection (16, 28). The higher proportion of severe Pap results could be linked to several factors including: i) the study cohort is HIV positive (33), ii) they have a previous history of immune suppression (7), and iii) because they have been initiated on HAART, they are getting to live longer (7, 29).

These are all reasons which previous studies have listed for HIV positive women having a higher cervical cancer rate, as well as more severe, and more persistent cervical cancer (7, 29). This further highlights the importance of strengthening cervical cancer screening practices amongst all at risk women, especially HIV positive women.

4.7. 12 month follow up outcomes

4.7.1. Disease progression

The majority of the study participants included in the analysis (65.93%) did not have any disease progression noted; their results indicate that either their results stayed the same as their baseline results from their Pap smear screening from the preceding 12 months or that they had improved. It is important to note that the group that experienced disease progression had a slightly lower CD4 count at HAART initiation, a factor that indicates a history of immune suppression which could possibly have influenced this groupôs noted disease progression. Findings from other studies, including a study conducted in a different cohort of women in the same clinic as our study found that the risk of cervical abnormalities was higher with lower CD4 count (10, 29). These findings highlights the importance of cervical screening of HIV positive women as directed by the national cervical cancer screening guidelines

A sub-analysis (Appendix 2a) comparing characteristics and demographics of participants with a 12 month follow up visitôs and those that did not have a 12 month follow up visit conducted (by age, CD4 count, HAART status etc.) showed that the two population groups were similar based on most of the characteristics assessed. However, the most notable difference noted was that the results of their baseline Pap screening results. Those that did not have a 12 month follow up visit conducted had the highest proportion of women with a severe baseline study Pap results (61.23%) compared to those that had a 12 month follow up study visit where most of the women had a moderate Pap screening results (50.07%). It was found that those that were treated off study (77.43%), died (42.86%), and those that were unable to treated (70.59%) had

the highest proportion of women with a severe baseline Pap screening results at study enrolment.

Association of disease progression and awareness, perceived risk and practices related to Pap smear testing was assessed. Disease progression had significant association with having a non-negative baseline study Pap smear at study enrolment. Compared to those that had a negative baseline study Pap smear those that had a moderate to severe baseline study Pap smear were less likely to have disease progression at their 12 month Pap smear screening. This is probably because they would have had a treatment intervention based on their baseline study Pap result and would therefore likely not have disease progression at a follow up screening. This is evidence of how screening can be an important prevention tool in the fight against the development of cervical cancer disease.

4.7.2. Analysis of all-cause attrition

Of the 42.76% attrition experienced for the 12 month follow up study visit, seven (1.36%) can be attributed to death, and 102 (19.84%) due to lost to follow up. The majority of the 319 (62.06%) participants who did not have a 12 month study visit were treated off study as a result of the severity of their baseline study Pap results. These individuals were either referred to VICAR2 for treatment or were treated off study. A total of 46 (8.95%) participants became pregnant thereby making them no longer eligible to be in the study. A further assessment was conducted to assess association between awareness, perceived risk and practices related to cervical cancer screening, disease progression, and being treated off study. The results from this assessment found significant association between disease progression and being treated off study. Where those that were treated off study were less likely to have disease progression noted in their 12 month follow up Pap screening results. This could be because there would have been an intervention based on the baseline study Pap screening conducted at enrolment in

the study, the intervention would expectantly improve patient prognosis as a result of the cervical cancer related disease.

A total of seven (1.36%) withdrew their consent to be part of the study. A further 15 (2.92%) participants were unable to be treated, and therefore did make up part of the 12 month follow up study visit data set. All in all, the study experienced over a third attrition with most resulting from lost to follow up. If this is examined even further only 9.1% of the original study population were truly lost (deceased or lost to follow up), the rest of the attrition was as a result of the study protocol requirements for 1) referral to treatment interventions where they were needed based of severe baseline Pap results, 2) women falling pregnant and study protocol requiring they no longer participate in the study as they no longer met criteria. The reason why most of the study participants could be accounted for by the end of the study could be that the study is clinic-based and the clinic is where the participants normally attend for their HIV care and treatment services and because the study was undertaken in an urban hospital. The clinic may be more accessible because of convenience of direct public transport routes. The study itself was well resourced to be better able to follow up with patients who miss appointments.

The seven deaths reported in the study equate to a proportion of 0.58% study participants becoming deceased by the end of the study. All study participantsô deaths occurred in the 30-39 years age group. Survival analysis to analyse those that were deceased by the end of the study did not yield meaningful results as the sample size was small and therefore did not have sufficient power. The study was an analysis of secondary data and we therefore did not have control over the sample size determination. Further analysis was conducted to examine all-cause attrition. The number of study participants that were alive and in HIV care were compared to those that were no longer alive and in HIV care (those that died or were lost to follow up), in relation to participantsô awareness, perceived risk and practice related to Pap smear testing and baseline covariate, namely study participantsô baseline socio-demographic and clinical characteristic at HAART initiation.

The only significant factor noted in this adjusted model which was being initiated on HAART. Those that were initiated on HAART were less likely to be deceased or LTFU than those that were not initiated on HAART. This is understandable as patients initiated on HAART wouldôve been expected to have better clinical outcomes. They would be under clinical care at the clinic meaning they would have regular contact with health care providers which may account for them being less likely to be lost to follow up or deceased.

4.8. Study limitations

4.8.1. Information bias

Some of the questions on the questionnaire are of a personal nature and some individuals may have been too embarrassed to answer them truthful. Information bias was minimised by the fact that the interviewers received standard training and had a standard operating procedure (SOP) for conducting interviews. In addition, interviewers are fluent in the local languages therefore the participants were in most cases interviewed in their own languages.

Recall bias might also be a factor regarding medical history. Respondents that were previously diagnosed with a severe form of the disease might have remembered the diagnosis more accurately. They would have had invasive procedures conducted as compared to those who had a negative Pap smear or had only minor indications of the disease. In addition, these respondents might also be reluctant to disclose previous diagnosis because of fear of stigmatization.

Another limitation was missing data for some of the study variables, and no follow up data for the study participants without 12 months follow up study visit could also have added some bias to the analysis.

In addition, there were a small number of study participants (37 or 3.12%) that were not initiated on HAART and therefore did not have baseline clinical data to be able to be assessed in the analysis that involved analysing clinical data.

There is also a possibility of selection bias as respondents selected for the study are HIV-positive and the general population (HIV-negative patients) differ in terms of general health status. As a result the study will not be able to be generalised to the general population as participants from this study differ systematically from the general population.

Selection bias may exist in this study as participants enrol in the study either because they are unwell (lower CD4 cell count) or because their health care provider is particularly worried about the exposure. Because they are seeking care and HAART treatment, these patients may be healthier than their HIV-positive counterparts who are eligible for HAART but are not on HAART and are not seeking care and treatment (54). At the same time this group of patients (those enrolled in the study) may not be as healthy as their counterpart who are not yet initiated on HAART as their CD4 count would have had to drop to a certain level or they would have had to have other AIDS defining illnesses in order to be initiated on HAART (14). To minimise this participants were compared to female patients (by age, CD4 count, HAART status etc.) enrolled in the same clinic for HIV care and treatment but are not enrolled in the study, and we assessed whether women in the study differ significantly from those that did not enrol in the study. Results indicated that there were no major difference between the two populations, only slight differences were noted in most cases.

4.8.2. Generalisability

Themba Lethu Clinic is an urban Comprehensive Care Treatment and Management (CCMT) site which is located in a tertiary hospital. Therefore generalizability of our study findings beyond the study population may be limited as Themba Lethu clinic is different from many non-tertiary, smaller, or rural facilities found throughout the country.

4.8.3. Confounding

Information of possible confounders, for instance socio-demographic data such as age education level, employment status, smoking status, and alcohol consumption was collected during the data collection stage of the study, and they were adjusted for during the statistical analysis stage of the study using multivariate analysis. This method assisted to control for the confounding effect of several factors at the same time.

However, unmeasured confounding could still be a limitation; variables which couldôve been potential confounders that were not collected as part of the study or routine patient management data could add some bias.

In addition, as part of the statistical analysis interaction terms were created between variables found to be significant in the multivariable model. These interaction terms were fitted into the multivariable model to assess statistical significance however there was no significant relationship in any of the models.

4.9. Conclusion

Results for our study showed high levels of Pap smear screening awareness amongst the study participants. However, low levels of Pap screening uptake was observed for study participants. These results and results in previous studies demonstrate that awareness is only the first hurdle in the challenges related to cervical cancer prevention and treatment. Adequate practice is the factor that will have the most positive influence on the disease morbidity and mortality.

Although South Africa has national programmes for cervical cancer screening and HIV treatment this does not necessarily translate to adequate implementation in terms of provision of services and also clients adequately seeking the services according to policy. This highlights that more research needs to be done into effective health education programmes to address the

gaps in adequate screening practice. These efforts should not only target the clients but also the health providers as they also have an important role to play in improving awareness, knowledge and practices related to cervical cancer and Pap smear screening amongst their clients. These efforts will hopefully contribute positively in positively influence screening behaviour and thus improve disease outcomes.

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6. Appendices

Appendix 1a: Study participant socio-demographic characteristics stratified by study outcomes

Total (n= 1202)	Awareness about Pap Smears n (%)		Awareness about HPV n (%)		Perceived Risk regarding cervical cancer n (%)			Practice according to National cervical cancer guidelines n (%)		Practice according to HIV guidelines n (%)	
	Aware 857 (71.30)	Not aware 345 (28.70)	Aware 218 (18.15)	Not aware 983 (81.85)	Very Worried 662 (55.54)	Somewhat Worried 250 (20.97)	Not Worried at all 280 (23.49)	Adequate 381 (36.46)	Not Adequate 664 (63.54)	Adequate 304 (28.57)	Not Adequate 760 (71.43)
Age (Mean, ± SD)	38.4 (7.80)	37.37 (7.29)	37.42 (7.14)	38.31 (7.78)	37.47 (7.61)	38.93 (7.69)	38.94 (7.65)	36.97 (5.23)	41.53 (6.92)	39.82 (8.06)	37.73 (7.37)
Age groups: 18-29	106 (12.37)	55 (15.94)	25 (11.47)	136 (13.84)	101 (15.26)	24 (9.60)	35 (12.50)	-	-	28 (9.21)	107 (14.08)
30-39	389 (45.39)	157 (45.51)	110 (50.46)	435 (44.25)	317 (47.89)	112 (44.80)	112 (40.00)	301 (79.00)	245 (37.12)	125 (41.12)	353 (46.45)
40-49	284 (33.14)	113 (32.75)	73 (33.49)	324 (32.96)	194 (29.31)	93 (37.20)	107 (38.21)	70 (18.37)	327 (49.55)	114 (37.50)	250 (32.89)
50+	78 (9.10)	21 (3.02)	10 (4.59)	88 (8.95)	50 (7.55)	21 (8.40)	26 (9.29)	10 (2.62)	88 (13.33)	37 (12.17)	50 (6.58)
Race: Black	836 (97.55)	343 (99.42)	212 (97.25)	966 (98.27)	648 (97.89)	246 (98.40)	275 (98.21)	369 (96.85)	650 (98.48)	295 (97.04)	747 (98.29)
Other	21 (2.45)	2 (0.58)	6 (2.75)	17 (1.73)	14 (2.11)	4 (1.60)	5 (1.79)	12 (3.15)	10 (1.52)	9 (2.96)	13 (1.71)
Nationality: South African	778 (92.29)	295 (87.28)	195 (90.70)	877 (90.88)	592 (91.08)	223 (91.02)	250 (90.58)	345 (91.76)	596 (92.12)	279 (91.78)	692 (91.17)
Non-South African	65 (7.71)	43 (12.72)	20 (9.30)	88 (9.12)	58 (8.92)	22 (8.98)	26 (9.42)	31 (8.24)	51 (7.88)	25 (8.22)	67 (8.83)
Marital Status: Single	468 (54.61)	190 (55.07)	116 (53.21)	541 (55.04)	366 (55.29)	132 (52.80)	154 (55.00)	208 (54.59)	337 (51.06)	168 (55.26)	425 (55.92)
Married	155 (18.09)	59 (17.10)	44 (20.18)	170 (17.29)	111 (16.77)	43 (17.20)	59 (21.07)	86 (22.57)	115 (17.42)	57 (18.75)	131 (17.24)
Cohabiting	112 (13.07)	58 (16.81)	27 (12.39)	143 (14.55)	104 (15.71)	37 (14.80)	29 (10.36)	42 (11.02)	95 (14.39)	33 (10.86)	112 (14.74)
Divorced/ Separated	57 (6.65)	15 (4.35)	16 (7.34)	56 (5.70)	41 (6.19)	15 (6.00)	13 (4.64)	24 (6.30)	47 (7.12)	23 (7.57)	39 (5.13)
Widow	65 (7.58)	23 (6.67)	15 (6.88)	73 (7.43)	40 (6.04)	23 (9.20)	25 (8.93)	21 (5.51)	66 (10.00)	23 (7.57)	53 (6.97)
Education: < Grade 10	138 (16.10)	91 (26.38)	17 (7.80)	212 (21.57)	104 (15.71)	56 (22.40)	65 (23.21)	54 (14.17)	161 (24.39)	68 (22.37)	135 (17.76)
Grade 10 ï Matric	615 (71.76)	219 (63.48)	172 (78.90)	661 (67.24)	472 (71.30)	172 (68.80)	186 (66.43)	267 (70.08)	448 (67.88)	190 (62.50)	551 (72.50)
Tertiary	89 (10.39)	24 (6.96)	28 (12.84)	85 (8.65)	76 (11.48)	16 (6.40)	20 (7.14)	57 (14.96)	33 (5.00)	39 (12.83)	56 (7.37)
None	15 (1.75)	11 (3.19)	1 (0.46)	25 (2.54)	10 (1.51)	6 (2.40)	9 (3.21)	3 (0.79)	18 (2.73)	7 (2.30)	18 (2.37)
Currently Employed : Yes	481 (56.13)	198 (57.39)	119 (54.59)	560 (56.97)	361 (54.53)	140 (56.00)	173 (61.79)	210 (55.12)	382 (57.88)	174 (57.24)	425 (55.92)
No	376 (43.87)	147 (42.61)	99 (45.41)	423 (43.03)	301 (45.47)	110 (44.00)	107 (38.21)	171 (44.88)	278 (42.12)	130 (42.76)	335 (44.08)
Occupation: Full-time	314 (65.28)	134 (67.68)	72 (60.50)	376 (67.14)	240 (66.48)	81 (57.86)	124 (71.68)	137 (65.24)	260 (68.06)	121 (69.54)	271 (63.76)
Part-time	129 (26.82)	53 (26.77)	33 (27.73)	149 (26.61)	91 (25.21)	48 (34.29)	41 (23.70)	56 (26.67)	100 (26.18)	39 (22.41)	127 (29.88)
Self-Employed	21 (4.37)	5 (2.53)	8 (6.72)	18 (3.21)	18 (4.99)	5 (3.57)	3 (1.73)	12 (5.71)	10 (2.62)	8 (4.60)	12 (2.82)
Unknown Occupation	8 (1.66)	3 (1.52)	2 (1.68)	9 (1.61)	4 (1.11)	4 (2.86)	3 (1.73)	1 (0.48)	8 (2.09)	5 (2.87)	6 (1.41)
Student	3 (0.62)	3 (1.52)	3 (2.52)	3 (0.54)	4 (1.11)	1 (0.71)	1 (0.58)	2 (0.95)	0 (0)	0 (0)	4 (0.94)
State grant	6 (1.25)	0 (0)	1 (0.84)	5 (0.89)	4 (1.11)	1 (0.71)	1 (0.58)	2 (0.95)	4 (1.05)	1 (0.57)	5 (1.18)
Currently Smoking: Yes	32 (3.73)	10 (2.90)	10 (4.59)	32 (3.26)	25 (3.78)	10 (4.00)	7 (2.50)	12 (3.15)	20 (3.03)	14 (4.61)	25 (3.29)
No	825 (96.27)	335 (97.10)	208 (95.41)	951 (96.74)	637 (96.22)	240 (96.00)	273 (97.50)	369 (96.85)	640 (96.97)	290 (95.39)	735 (96.71)
Smoking Frequency: <5 per day	21 (75.00)	7 (77.78)	4 (50.00)	24 (82.76)	15 (68.18)	8 (100.00)	5 (71.43)	7 (63.64)	14 (82.35)	12 (85.71)	15 (68.18)
> 5 per day	7 (25.00)	2 (22.22)	4 (50.00)	5 (17.24)	7 (31.82)	0 (0)	2 (28.57)	4 (36.36)	3 (17.65)	2 (14.29)	7 (31.82)
Currently taking snuff: Yes	76 (8.87)	49 (14.20)	19 (8.72)	106 (10.78)	60 (9.06)	24 (9.60)	41 (14.64)	40 (10.50)	76 (11.52)	25 (8.22)	93 (12.24)
No	781 (91.13)	296 (85.80)	199 (91.28)	877 (89.22)	602 (90.94)	226 (90.40)	239 (85.36)	341 (89.50)	584 (88.48)	279 (91.78)	667 (87.76)
Snuff Frequency: <5 per day	61 (82.43)	37 (82.22)	15 (88.24)	83 (81.37)	49 (85.96)	20 (86.96)	29 (74.36)	30 (76.92)	62 (86.11)	23 (92.00)	70 (80.46)
> 5 per day	13 (17.57)	8 (17.78)	2 (11.76)	19 (18.63)	8 (4.04)	3 (13.04)	10 (25.64)	9 (23.08)	10 (13.89)	2 (8.00)	17 (19.54)
Currently Drinking Alcohol: Yes	103 (12.02)	22 (6.38)	33 (15.14)	92 (9.36)	76 (11.48)	30 (12.00)	18 (6.43)	53 (13.91)	49 (7.42)	39 (12.83)	67 (8.82)
No	754 (87.98)	323 (93.62)	185 (84.86)	891 (90.64)	586 (88.52)	220 (88.00)	262 (93.57)	328 (86.09)	611 (92.58)	265 (87.17)	693 (91.18)

Appendix 1b: Study participants baseline clinical characteristic at HAART initiation stratified by study outcomes

Total (n= 1202)	Awareness about Pap Smears n (%)		Awareness about HPV n (%)		Perceived Risk regarding cervical cancer n (%)			Practice according to national cervical cancer guidelines n (%)		Practice according to HIV treatment guidelines n (%)	
	Aware 857 (71.30)	Not aware 345 (28.70)	Aware 218 (18.15)	Not aware 983 (81.85)	Very Worried 662 (55.54)	Somewhat Worried 250 (20.97)	Not Worried at all 280 (23.49)	Adequate 381 (36.46)	Not Adequate 664 (63.54)	Adequate 304 (28.57)	Not Adequate 760 (71.43)
Baseline WHO staging: I-II	406 (67.44)	152 (63.07)	103 (69.13)	455 (65.66)	291 (64.38)	118 (68.60)	145 (68.08)	185 (68.01)	303 (65.87)	162 (68.94)	354 (63.44)
III -IV	196 (32.56)	89 (36.93)	46 (30.87)	238 (34.34)	161 (35.62)	54 (31.40)	68 (31.92)	87 (31.99)	157 (34.13)	73 (31.06)	204 (36.56)
Baseline BMI (kg/m2) (Med, IQR)	23.32 (20.93-27.14)	23.38 (20.15-26.71	23.58 (20.12-28.39)	23.30 (20.76-26.85)	23.38 (20.42-26.98	22.90 (20.85-26.76)	23.67 (20.78-27.34)	23.59 (21.30-27.87)	23.53 (20.74-27.30)	23.82 (21.39-28.40)	23.07 (20.36-26.71)
Underweight (<18.5)	58 (9.22)	28 (10.57)	19 (11.80)	67 (9.15)	48 (10.11)	19 (10.11)	19 (8.52)	20 (7.25)	47 (9.40)	18 (7.38)	63 (10.64)
Normal (18.5-24.9)	341 (54.21)	138 (52.08)	78 (48.45)	401 (54.78)	258 (54.32)	103 (54.79)	115 (51.57)	153 (55.43)	256 (51.20)	125 (51.23)	323 (54.56)
Overweight (Ó25)	230 (36.57)	99 (37.36)	64 (39.75)	264 (36.07)	169 (35.58)	66 (35.11)	89 (39.91)	103 (37.32)	197 (39.40)	101 (41.39)	206 (34.80)
Baseline CD4 (cells/mm3) (Med, IQR)	141 (63-205)	120.5 (56.5-203.5)	136.5 (57-205)	133.5 (63-204)	132 (61-201)	131 (63-204)	151 (64-223)	132 (59.5-205)	131 (62-204)	137.5 (63-206)	132 (57.5-200)
0-50	132 (20.59)	59 (22.01)	35 (22.15)	156 (20.80)	106 (21.59)	38 (20.43)	46 (20.44)	58 (20.71)	109 (21.33)	49 (19.60)	134 (22.19)
51-100	115 (17.94)	52 (19.40)	27 (17.09)	140 (18.67)	89 (18.13)	36 (19.35)	37 (16.44)	60 (21.43)	92 (18.00)	43 (17.20)	113 (18.71)
101-250	317 (49.45)	132 (49.25)	78 (49.37)	370 (49.33)	243 (49.49)	95 (51.08)	110 (48.89)	126 (45.00)	255 (49.90)	132 (52.80)	291 (48.18)
251-350	35 (5.46)	12 (4.48)	11 (6.96)	36 (4.80)	22 (4.48)	11 (5.91)	14 (6.22)	14 (5.00)	28 (5.48)	13 (5.20)	30 (4.97)
>350	42 (6.55)	13 (4.85)	7 (4.43)	48 (6.40)	31 (6.31)	6 (3.23)	18 (8.00)	22 (7.86)	27 (5.28)	13 (5.20)	36 (5.96)
Baseline HIV VL (copies/mL) (Med,IQR)	17000 (176-94000)	6700 (49-83000)	42007 (189-170000)	12200 (68.5-78000	12700 (58-78000)	39000 (274-170000)	6700 (107-89824)	11500 (84.5-74500)	23500 (62-114739)	9550 (229.5-62000)	17000 (91-111000)
<100 000	152 (76.00)	52 (77.61)	32 (68.09)	172 (78.18)	113 (78.47)	30 (63.83)	60 (80.00)	72 (81.82)	110 (73.33)	57 (83.82)	132 (73.33)
Ó100 000	48 (24.00)	15 (22.39)	15 (31.91)	48 (21.82)	31 (21.53)	17 (36.17)	15 (20.00)	16 (18.18)	40 (26.67)	11 (16.18)	48 (26.67)
Haemoglobin (g/dL) (Med, IQR)	11.6 (10.35-12.9)	11.6 (10.1-12.6)	11.7 (10.7-12.7)	11.6 (10.2-12.8)	11.6 (10.1-12.8)	11.5 (10.3-12.9)	11.7 (10.4-12.8)	11.6 (10.6-12.9)	11.6 (10.2-12.7)	11.6 (10.5-12.9)	11.6 (10.2-12.8)
<8g/dL	33 (5.03)	13 (4.76)	5 (3.07)	41 (5.36)	29 (5.78)	7 (3.83)	10 (4.24)	15 (5.19)	19 (3.67)	14 (5.51)	30 (4.89)
Ó8g/dL	623 (94.97)	260 (95.24)	158 (96.93)	724 (94.64)	473 (94.22)	176 (96.17)	226 (95.76)	274 (94.81)	499 (96.33)	240 (94.49)	583 (95.11)
AST (IU/L) (Med, IQR)	30 (24-41)	30 (24-39)	30 (23-41)	30 (24-40)	30 (24-40)	30 (24-42)	30 (24-40)	30 (24-42)	30 (24-39)	30 (24-41)	30 (24-40)
<40	405 (72.32)	159 (75.71)	97 (74.62)	466 (72.93)	318 (74.47)	97 (69.29)	146 (74.11)	174 (70.73)	319 (75.06)	140 (72.54)	390 (73.03)
>=40	155 (27.68)	51 (24.29)	33 (25.38)	173 (27.07)	109 (25.53)	43 (30.71)	51 (25.89)	72 (29.27)	106 (24.94)	53 (27.46)	144 (26.97)
ALT (IU/L) (Med, IQR)	22 (16-32)	20 (14-29)	20 (16-32)	21 (15-31)	21 (15-31)	21 (16-30)	22 (15-31)	23 (16-33)	21 (15-30)	23 (16-33)	21 (15-31)
<40	578 (86.92)	240 (86.96)	140 (83.83)	677 (87.58)	452 (88.11)	162 (87.57)	197 (83.83)	238 (82.93)	469 (88.99)	214 (84.58)	548 (87.96)
>=40	87 (13.08)	36 (13.04)	27 (16.17)	96 (12.42)	61 (11.89)	23 (12.43)	38 (16.17)	49 (17.07)	58 (11.01)	39 (15.42)	75 (12.04)
Lactate levels (mmol/L) (Med, IQR)	2.2 (1.50-3.93)	2.45 (1.54-5.32)	2.09 (1.49-4.01)	2.3 (1.52-4.4)	2.34 (1.53-4.5)	2.28 (1.51-3.77)	2.07 (1.49-3.9)	2.21 (1.60-3.8)	2.42 (1.52-4.98)	2.12 (1.45-3.46)	2.4 (1.53-4.5)
0-2.4 - Normal	202 (54.89)	69 (51.11)	56 (58.33)	215 (52.96)	149 (53.02)	49 (53.26)	72 (57.14)	88 (55.70)	150 (51.02)	67 (57.26)	187 (51.94)
2.5-4 ï Moderately elevated	75 (20.38)	24 (17.78)	15 (15.63)	83 (20.44)	53 (18.86)	21 (22.83)	23 (18.25)	34 (21.52)	55 (18.71)	24 (20.51)	73 (20.28)
>4 ï Severely elevated	91 (24.73)	42 (31.11)	25 (26.04)	108 (26.60)	79 (28.11)	22 (23.91)	31 (24.60)	36 (22.78)	89 (30.27)	26 (22.22)	100 (27.78)
HAART regimen: 1a	443 (54.96)	176 (53.01)	113 (54.59)	505 (54.30)	339 (54.24)	120 (51.95)	152 (55.88)	186 (52.25)	366 (57.82)	158 (53.56)	425 (56.82)
1b	73 (9.06)	34 (10.24)	21 (10.14)	86 (9.25)	60 (9.60)	25 (10.82)	22 (8.09)	39 (10.96)	50 (7.90)	22 (7.46)	77 (10.29)
Other	290 (35.98)	122 (36.75)	73 (35.27)	339 (36.45)	226 (36.16)	86 (37.23)	98 (36.03)	131 (36.80)	217 (34.28)	115 (38.98)	246 (32.89)
Baseline study Pap smear results: Negative	234 (27.30)	87 (25.22)	71 (32.57)	250 (25.43)	183 (27.64)	61 (24.40)	73 (26.07)	104 (27.30)	188 (28.48)	76 (25.00)	210 (27.63)
Moderate	354 (41.31)	120 (34.78)	81 (37.16)	392 (39.88)	244 (36.86)	99 (39.60)	126 (45.00)	162 (42.52)	243 (36.82)	126 (41.45)	299 (39.34)
Severe/ICC	266 (31.04)	137 (39.71)	66 (30.28)	337 (34.28)	233 (35.20)	89 (35.60)	80 (28.57)	114 (29.92)	227 (34.39)	101 (33.22)	248 (32.63)
Unknown	3 (0.35)	1 (0.29)	0 (0)	4 (0.41)	2 (0.30)	1 (0.40)	1 (0.36)	1 (0.26)	2 (0.30)	1 (0.33)	3 (0.39)
Previous Pap smear results: Negative	514 (76.15)	9 (69.23)	114 (78.62)	409 (75.32)	289 (75.06)	109 (76.76)	122 (77.71)	297 (77.95)	177 (74.37)	234 (76.97)	238 (75.80)
Moderate	28 (4.15)	1 (7.69)	7 (4.83)	22 (4.05)	14 (3.64)	8 (5.63)	7 (4.46)	14 (3.67)	11 (4.62)	18 (5.92)	10 (3.18)
Severe/ICC	1 (0.15)	0 (0)	1 (0.69)	0 (0)	0 (0)	1 (0.70)	0 (0)	1 (0.26)	0 (0)	0 (0)	1 (0.32)
Unknown	132 (19.56)	3 (23.08)	23 (15.86)	112 (20.63)	82 (21.30)	24 (16.90)	28 (17.83)	69 (18.11)	50 (21.01)	52 (17.11)	65 (20.70)

Appendix 2a: Sensitivity analysis of 12 month follow up visit

A sensitivity analysis was conducted to determine any significant differences between study participants that came for their 12 month study visit and those that did not come for their 12 month study visit

Factor	**12mo F/U Not done** (n=514)	**12mo F/U Done** (n= 688)
On HAART		
No	19 (3.19)	25 (3.68)
Yes	484 (96.22)	654 (96.32)
Age group at HAART initiation		
18-29	114 (23.55)	142 (21.71)
30-39	247 (51.03)	292 (44.65)
40-49	106 (21.90)	185 (28.29)
50+	17 (3.51)	35 (5.35)
Baseline CD4		
0-50	88 (22.51)	103 (19.88)
51-100	81 (20.72)	86 (16.60)
101-250	183 (46.80)	266 (51.35)
251-350	18 (4.60)	29 (5.60)
>350	21 (5.37)	34 (6.56)
Baseline VL		
<100000	79 (75.24)	125 (77.16)
>100000	26 (24.76)	37 (22.84)
HAART regimen at initiation		
1a	244 (50.41)	375 (57.34)
1b	43 (8.88)	64 (9.79)
Other	197 (40.70)	215 (32.87)
Baseline study Pap smear results		
Negative	66 (13.12)	254 (37.08)
Moderate	127 (25.25)	343 (50.07)
Severe	308 (61.23)	88 (12.85)
ICC	2 (0.40)	2 (0.29)

Appendix 2b: Sensitivity analysis for disease progression at 12 month follow up visit

A sensitivity analysis was conducted among patients that did not have a 12 month visit (n=514) and thus did not have their disease progression assessed, to evaluate whether excluding them had any impact on the estimates in the main analysis of disease progression.

Factor	Disease Development at 12month Follow up - Sensitivity analysis					
	Main Analysis		No 12 month visit - No Disease Development		No 12 month visit - Disease Development	
	Adjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Nationality: South African	ref		ref		ref	
Non-South African	1.79 (0.73-4.38)	0.206	1.74 (0.69-4.40)	0.240	2.03 (0.98-5.01)	0.333
Currently Employed: No	ref		ref		ref	
Yes	1.24 (0.77-2.02)	0.378	0.82 (0.61-1.95)	0.183	0.88 (0.59-1.73)	
Occupation: Full-time	ref		ref		ref	
Part-time	0.90 (0.42-1.93)	0.778	0.94 (0.49-1.79)	0.843	0.89 (0.58-1.63)	0.562
Self-Employed	1.51 (0.34-6.81)	0.590	2.02 (0.49-7.23)	0.323	0.70 (0.36-6.80)	0.479
Snuff Frequency: <5 per day	ref		ref		ref	
> 5 per day	2.59 (0.30-22.29)	0.387	2.05 (0.49-27.00)	0.196	1.95 (0.61-24.82)	0.299
Hemoglobin *(g/dL):* <8g/dL	ref		ref		ref	
Ó8g/dL	0.49 (0.77-2.02)	0.151	0.56 (0.65-2.40)	0.752	0.81 (0.35-1.88)	0.630
Baseline study Pap smear results: Negative	ref		ref		ref	
Moderate/Severe/ICC	0.08 (0.05-0.13)	<0.001	0.08 (0.04-0.12)	<0.001	0.30 (0.08-0.18)	<0.001
HPV Awareness: Aware	ref		ref		ref	
Not Aware	1.39 (0.55-3.51)	0.487	1.22 (0.61-2.64)	0.563	1.26 (0.76-2.11)	0.372

Appendix 2c: Log rank test of equality of survival functions

The log rank tests were conducted to test for equality of survival curves.

Factor	Log rank Chi2	p-value
Pap smear screening awareness	0.23	0.633
HPV virus awareness	0.01	0.988
Perceived Risk of getting cervical cancer disease	0.78	0.678
Practice according to national cervical cancer guidelines	0.02	0.897
Practice according to national HIV treatment guidelines	0.02	0.890
Age group	0.37	0.947
Race	0.85	0.357
Nationality	1.40	0.236
Marital status	1.00	0.910
Education level	4.46	0.216
Currently employed	0.88	0.349
Occupation	2.58	0.275
Currently smoking	1.48	0.223
Smoking frequency	0.01	0.600
Currently taking snuff	2.31	0.128
Snuff frequency	2.96	0.286
Alcohol	0.01	0.976
Baseline WHO staging	0.01	0.972
Baseline Body mass index (BMI)	0.54	0.764
Baseline CD4	6.89	0.142
Baseline HIV VL	1.22	0.269
Baseline Haemoglobin (Hg)	0.24	0.622
Baseline Aspartate transaminase (AST)	0.53	0.468

Baseline Alanine aminotransferase (ALT)	2.69	0.101
Baseline Lactate levels	3.85	0.146
On HAART	2.85	0.650
HAART regimen at HAART initiation	2.49	0.288
Previous Pap screening results	0.23	0.634
Baseline study Pap screening results	3.01	0.043
Disease progression	2.45	0.263

Appendix 2d. Global tests for proportional hazards assumptions

Global tests for proportional hazards assumptions based on Schoenfeld residuals were conducted after fitting univariate Cox models on all covariates.

Factor	**P Value Global Test for PH Assumption**
Pap smear screening awareness	0.556
HPV virus awareness	0.108
Perceived Risk of getting cervical cancer disease	0.750
Practice according to national cervical cancer guidelines	0.765
Practice according to national HIV treatment guidelines	0.672
Age group	0.791
Race	0.399
Nationality	<0.001
Marital status	0.355
Education level	0.789
Currently employed	0.781
Occupation	0.970
Currently smoking	0.974
Smoking frequency	0.336
Currently taking snuff	0.834
Snuff frequency	0.532
Alcohol	0.200
Baseline WHO staging	0.261
Baseline Body mass index (BMI)	0.701
Baseline CD4	0.659
Baseline HIV VL	0.465
Baseline Haemoglobin (Hg)	0.520
Baseline Aspartate transaminase (AST)	0.367
Baseline Alanine aminotransferase (ALT)	0.341
Baseline Lactate levels	0.053
On HAART	0.402
HAART regimen at HAART initiation	0.259
Previous Pap screening results	0.150
Baseline study Pap screening results	0.574
Disease progression	0.972

Appendix 3: Ethical clearance certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Miss Idah Mokhele

CLEARANCE CERTIFICATE	**M120310**
PROJECT	Awareness, Perceived Risk and Practices Related to Cervical Cancer and Pap Smear Screening among HIV-Positive women in an Urban HIV Clinic in Johannesburg, South Africa
INVESTIGATORS	Miss Idah Mokhele.
DEPARTMENT	School of Public Health
DATE CONSIDERED	30/03/2012
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 30/03/2012 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Dr Denise Evans

DECLARATION OF INVESTIGATOR(S)
To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...

Appendix 4: Data gatekeeper letter for permission to use VICAR 1 dataset

Clinical HIV Research Unit, Department of Medicine

Helen Joseph Hospital, Themba Lethu Clinic, Perth Road, Westdene, Johannesburg 2092, South Africa
Postnet Suite 176, Private Bag X2600, Houghton 2041, South Africa • Tel: +27 11 276-6800 • Fax: +27 11 482-2130

07 March 2012

Dear Human Research Ethics Committee (HREC),

I am Avril Swarts and I work in the capacity of **Data Manager** at the Clinical HIV and Research Unit at the Clinical HIV Research Unit (CHRU). I am the **Database Administrator** for the Validation of Implementation of Cervical Cancer Screening Applications in HIV-seropositive Women (VICAR 1) protocol and the Validation of Implementation of Cervical Dysplasia Treatment Modalities in HIV- Seropositive Women (VICAR 2) protocol. These studies are by Right to Care in partnership with the Clinical HIV Research Unit (CHRU). HIV-positive adult female participants will be recruited from the Themba Lethu Clinic HIV Care and Treatment Programme at Helen Joseph Hospital in Johannesburg.

I will collaborate with **Miss Idah Mokhele** by providing data from VICAR 1 & 2, for her Master research project as part of fulfilling requirements for her Master of Science in Epidemiology in the field of Biostatistics and Epidemiology.

I understand that the core purpose of her study is to assess awareness, perceived risk and practices related to cervical cancer and Pap screening among HIV-positive women in an urban HIV clinic in Johannesburg, South Africa. I understand that this project involves accessing data on participants of the original VICAR 1 & 2 study and that all such data will be provided to her as agreed with the principal investigator.

Data will be provided with a study number and study initials. All personal identifiers will be removed, e.g., names, addresses, etc. so that the data cannot be traced to any individual. The data will be provided to her as data excerpts from the original VICAR 1 & 2 study database as per the list of data elements required for her study as listed in her ethics application.

We will look forward to receiving the results of the study, when it is completed.

Kind Regards

Avril Swarts

Data Manager

Appendix 5: Permission letter from Right to Care, the Clinical entity in which the patients are based

10th ANNIVERSARY 2011
Right to care
TREATING AIDS SERIOUSLY

7 March, 2012

Dear Human Research Ethics Committee (HREC),

I, Dr Pappie Majuba, in the capacity of Chief Medical Officer for Right to Care would like to offer cooperation from Right to Care for Miss Idah Mokhele by providing data for her Masters Research Project as part of fulfilling requirements for her Master of Science in Epidemiology in the field of Biostatistics and Epidemiology.

I understand that the purpose of this study is to assess awareness, perceived risk and practices related to cervical cancer and Pap screening among HIV-positive women in an urban HIV clinic in Johannesburg, South Africa.

I understand that this project involves accessing data on participants of the original VICAR 1 & 2 study from the study database and TherapyEdge-HIVTM - the electronic clinical decision, support and patient management system used at Themba Lethu Clinic. All data will be provided to her with all personal identifying information, e.g., names, addresses, etc. removed so that the data cannot be traced to any individual. The data will be provided to her as data excerpts from the VICAR 1 & 2 study database and excerpt TherapyEdge-HIVTM as per the respective lists of data elements required for her study as listed in the data elements/variables list documents attached to her ethics application.

We will look forward to receiving the results of the study, when it is completed.

Yours sincerely,

Dr Pappie Majuba
Chief Medical Officer
Right to Care

Helen Joseph Hospital, Themba Lethu Wing, Perth Road, Westdene, 2092
PostNet Suite 212, Private Bag X2600, Houghton, South Africa, 2041
Registration: 2001/001745/08
Telephone: +27 (0) 11 276 8850; Fax: +27 (0) 11 276 8885
Directors: Prof Ian Sanne (Managing Director), Kurt Firnhaber (US), Dr Thembisile Xulu
Non-Executive Directors: Dr Ali Bacher (Chairman), Dr Brian Brink, Dr Gustaaf Wolvaardt, Reginald Muzariri, Dr Alan Knott-Craig, Stanley Mabuza, Mthandazo Peter Moyo, Peter Goldhawk. Company Secretary: Yumna Laher

Appendix 6: VICAR 1 study inclusion and exclusion criteria

D. METHODS

i Study Participants

A total of 1,200 HIV seropositive women will be recruited in the Themba Lethu Clinic in Johannesburg, South Africa.

ii Inclusion Criteria

Women 18-65 years of age
Not menstruating (can be screened after menstruation over)
Able to sign consent
Able to follow the study protocol
HIV positive (by 2 different rapid tests, a HIV viral load >5,000, ELISA, Western blot)

iii Exclusion Criteria Pregnant
Clinically active STD (may participate after adequate treatment)
Known and previous treatment for HSIL by any method (cryotherapy, LLETZ or cone biopsy)
Previous Hysterectomy with removal of the cervix
Significant medical illness/mental illness that the investigator feels would prevent the participant from complying with the protocol or place the participant at medical risk

Appendix 7: VICAR 1 study questionnaire

VICAR1 INITIAL VISIT QUESTIONAIRE

Site: Themba Lethu Clinic

TE # _____ Date (*dd/mmm/yyyy*):_____

Hospital # _____ Time _____ Initials: _____

Interviewer name_____

Consent signed?

|__| NO (0) |__|YES (1)

Medical History

1. When were you first diagnosed with HIV?

|__|__|__|__|__|__|__|__|__|__|
D D M M M Y Y Y Y

2. How did you contract HIV?

|__| Sexual transmission
|__| Blood transfusion
|__| IV drug use
|__| Mother to child transmission
|__|Other Specify_____

3. Do you have a history of diabetes?
|__| NO (0) |__|YES (1) ⇨ 4. Start Date

⇩

go to question 6

|__|__|__|__|__|__|__|__|__|__|
D D M M M Y Y Y Y

5. What type of medication do you use?
|__| Oral (1) |__| Injection (2)

6. Do you have a history of hypertension?
|__| NO (0) |__|YES (1) ⇨ 7. Start Date

|__|__|__|__|__|__|__|__|__|__|
D D M M M Y Y Y Y

8. Have you ever had TB?
|__| NO (0) |__|YES (1) 9. Start Date 10. End Date

|__|__|__|__|__|__|__|__|__|__| |__|__|__|__|__|__|__|__|__|__|
D D M M M Y Y Y Y *D D M M M Y Y Y Y*

11. Have you ever had cancer?
|__| NO (0) |__|YES (1) |__| don't know (98) |__| refuse to answer (101)

12. Has a doctor or nurse ever told you have Kaposi's sarcoma (cancer of the skin)?
|__| NO (0) |__|YES (1) |__| don't know (98) |__| refuse to answer (101)

Designed: C.Firnhaber/D.Schulze/A. Swarts Prinsloo Page # 1
Design: 08/01/09
Update: 10/06/2010 **Data Entry** (Date/Initials): _____

VICAR1 INITIAL VISIT QUESTIONAIRE

Site: Themba Lethu Clinic

TE # _____ Date (*dd/mmm/yyyy*):_____

OBGYN History

13. How old were you when you started your periods? |__|__| years (Y Y) |__| don't know (98) |__| refuse to answer (101)

14. Last Menstrual Period:
|__| NO (0) |__|YES (1) 15. Start Date ☐☐☐☐☐☐☐☐ (D D M M M Y Y Y Y) 16. End Date ☐☐☐☐☐☐☐☐ (D D M M M Y Y Y Y)

⇩

Reason _____

17. Do you currently use Contraception?
|__| NO (0) |__|YES (1) ⇨

⇩

go to question 20

18. Type |__| Depo-Provera (1) |__| Nur-esterate (2) |__| OBC combination (3) |__| Progesterone only OBC (4) |__| IUD (5) |__| Tubal Ligation (6) |__| Other (7) Specify _____

19. For how long have you been using contraception?
|__|__| years (Y Y) |__|__| months (M M) |__| don't know (98) |__| refuse to answer (101)

20. Have you ever been pregnant in your life?
|__| NO (0) |__|YES (1) ⇨

⇩

go to question 28

21. How many times have you been pregnant in your life? |__|__|
22. How old were you when you first got Pregnant? |__|__|
23. How many of your pregnancies ended with a live birth? |__|__|
24. How many abortions have you had? |__|__|
25. How many miscarriages have you had? |__|__|
26. How many of your pregnancies ended with a still born child? |__|__|
27. How many living children do you have? |__|__|

28. Do you know what a Pap smear is?
|__| NO (0) |__|YES (1) ⇨ **go to question 29**

⇩

If no then counsellor please explain to patient.

29. Have you ever had a Pap smear?
|__| NO (0) |__|YES (1) ⇨ **go to question 31**

⇩

30. If you haven't had a Pap smear, how come?
|__| don't know (1) |__| afraid it would hurt (2) |__| no access (3)
|__| No time to wait in another queue (4) |__| work (5) |__| Nobody to look after children (6)
|__| no transport (7) |__| didn't want anyone to examine me there (8)
|__| other (9) Specify_____

⇩

go to question 34

VICAR1 INITIAL VISIT QUESTIONAIRE

Site: Themba Lethu Clinic

TE # _____ Date (*dd/mmm/yyyy*):_____

31. Approximately how many Pap smears have you had in your life? |__|__|

32. Since your first smear, can you guess how often you have been getting your pap smears?
|__| never (1) |__| yearly (2)
|__| once every 2-3 years(3) |__| once every 4-5 years(4)
|__| once every 6-10 years (5) |__| less than every 10 years (6)

33. Result of last Pap smear:
|__| normal (1) |__| ASCUS (2) |__| pat didn't collect result (3)
|__| AGUS (4) |__| ASC-H (5) |__| patient can't remember (6)
|__| LSIL (CIN1) (7) |__| CIN2 (8)
|__| CIN3 (9) |__| SCC (10)

34. Do you believe pap smears are good for your health?
|__| NO (0) |__|YES (1) |__| don't know (98) |__| refuse to answer (101)

35. Have you ever been offered a Pap smear at your healthcare clinic?
|__| NO (0) |__|YES (1) |__| don't know (98) |__| refuse to answer (101)

36. Has a health care worker ever told you that you should have a Pap smear in the last two years?
|__| NO (0) |__|YES (1) |__| don't know (98) |__| refuse to answer (101)

37. If you decided to get a Pap smear, where would you go?
|__| Casualty
|__| HIV Clinic
|__| Local primary health care clinic
|__| Government Obstetrics and gynaecology department
|__| TB Area
|__| Other Specify_____

38. In the last three years, did you try to get a Pap smear but were unable to get one?
|__| NO (0) |__|YES (1) |__| don't know (98) |__| refuse to answer (101)

39. Have you ever heard about HPV or Human Papillomavirus?
|__| NO (0) |__|YES (1) |__| don't know (98) |__| refuse to answer (101)

40. How worried are you about contracting cervical cancer?
|__| very worried
|__| somewhat worried
|__| not worried at all
|__| never heard of cervical cancer.

41. Have you ever had a sexually transmitted disease (STD)?
|__| NO (0) |__|YES (1) |__| don't know (98) |__| refuse to answer (101)

⇩ ⇨ **go to question 43**

42. What type of sexually transmitted infection did you have?
|__| Genital ulcers (1) |__| Genital warts (2)
|__| Yellow discharge(3) |__| Itchy white discharge (4)

VICAR1 INITIAL VISIT QUESTIONAIRE

Site: Themba Lethu Clinic

TE # _____ Date (*dd/mmm/yyyy*):_____

43. Do you currently have a sexually transmitted infection?
|__| NO (0) |__|YES (1) |__| don't know (98) |__| refuse to answer (101)

⇩ ⇨
go to question 45

44. What type of sexually transmitted infection do you have?
|__| Genital ulcers (1) |__| Genital warts (2)
|__| Yellow discharge(3) |__| Itchy white discharge (4)

Social History

45. Current Employment status
|__| NO (0) |__| YES (1) ⇨

⇩

46. Occupation
|__| disability (1) |__| student (2)
|__| pensioner (3) |__| part-time (piece job) (4)
|__| self employed (5) |__| full time (5)

47. Current level of Education
|__| none (0) |__| less than standard 8 (grade 10) (1)
|__| Standard 8 (grade 10) (2) |__| less than standard 10 (grade 12) (3)
|__| standard 10 (grade 12) (4) |__| tertiary education (5)

48. Marital Status
|__| single (1) |__| Married (2) |__| cohabitating(3)
|__| Divorce/separated (4) |__| Widow (5) |__| Refuse to answer (101)

49. Religion
|__| Christian (1) |__| Hindu(2) |__| Muslim(3)
|__| Jewish (4) |__| don't know (98) |__| refuse to answer (101)
|__| Other (5) Specify _____

Social History *Interviewer please advise participant that following questions are highly delicate*

50. Are you a Smoker?

|__| NO (0) |__| YES (1)
⇩ ⇨
go to question 52

51. How much?
|__| ≤ 5 per day (1)
|__| ≤ 10 per day (2)
|__| ≤ 15 per day (3)
|__| > 20 per day (4)

52. Do you use snuff?
|__| NO (0) |__| YES (1)
⇩ ⇨
go to question 54

53. How much?
|__| 1-3 times/day (1)
|__| >3-5 times/day (2)
|__| >5-7 times/day (3)
|__| > 7 times/day (4)
|__| N/A (5)

54. Have you ever used intravenous Drugs?
|__| NO (0) |__| YES (1)

VICAR1 INITIAL VISIT QUESTIONAIRE

Site: Themba Lethu Clinic

TE # _____ Date (*dd/mmm/yyyy*): _____

55. Do you drink Alcohol?
|__| NO (0) |__| YES (1)
⇩ ⇨

go to question 57

56. In the last year, can you tell me on average how many alcoholic drinks do you have a week?_____

57 Do you smoke dagga?
|__| NO (0) |__| YES (1)
⇩ ⇨

go to question 59

58. How many times a week? |__|__|

59. Have you ever had sex in your life?
|__| NO (0) |__| YES (1)
⇩ ⇨

go to question 70

60. How old were you when you first had sex? |__|__|
|__| don't know (98) |__| refuse to answer (101

61. How many people have you had sex with in your life? |__|__|
|__| don't know (98) |__| refuse to answer (101

62. Did you use a condom the last time you had sex?
|__| NO (0) |__| YES (1)
|__| don't know (98)
|__| refuse to answer (101)
|__| abstaining/no partner (102)

63. How often do you use condoms?
|__| all the time (1) |__| sometimes (2)
|__| rarely (3) |__| never (4)
|__| don't know (98) |__| refuse to answer (101)
|__| abstaining/no partner (102)

64. Do you think your partner has other sexual partners?
|__| NO (0) |__| YES (1)
|__| don't know (98) ⇩
|__| refuse to answer (101)
|__| abstaining/no partner (102)

⇩
go to question 66

65. How often?
|__| occasionally (1)
|__| frequently (2)
|__| don't know (98)
|__| refuse to answer (101)

66. Do you have other sexual partners?
|__| NO (0) |__| YES (1)
|__| refuse to answer (101) ⇩
|__| abstaining/no partner (102)

⇩
go to question 68

67. How often?
|__| Occasionally (1)
|__| frequently (2)
|__| Don't know (98)

VICAR1 INITIAL VISIT QUESTIONAIRE

Site: Themba Lethu Clinic

TE # _____ Date (*dd/mmm/yyyy*): _____
|__| refuse to answer (101)

68. Do you ever have sex for money, food or material items?
|__| NO (0) |__| YES (1)
|__| don't know (98)
|__| refuse to answer (101) ⇩

⇩
go to question 70

69. How often?
|__| occasionally (1)
|__| frequently (2)
|__| don't know (98)
|__| refuse to answer (101)

70. Rape (only if disclosed –do not ask)
|__| NO (0) |__| YES (1) |__| Not asked (2)

71. When you wash yourself, do you wash your genital areas with special attention?
|__| Yes, always wash very thoroughly (1)
|__| Yes, but only when something has happened (after sex with somebody with a discharge, I had lice or other diseases, during my period) (2)
|__| No especially, I wash it as any other part of my body (3)
|__| No, I avoid washing the genital area (4)
|__| refuse to answer (101)

72. Can you tell me how much money you received from your work/disability pension/retirement fund in the last month?
|__| R0 (refer for social grant)
|__| <R1 000
|__| R1 000 -R 3000
|__| >R3 000 but <R5 000
|__| >R5 000 but <R10 000
|__| ≥ R10 000
|__| refuse to answer (101)

Thank you for time with this questionnaire.

Do you have any questions or comments?_____
_____

Data From TE

73. WHO HIV Stage? |__| I |__| II |__| III |__| IV

74. CD4 Count known?
|__| NO (0) |__|YES (1) 7 5. Date Done

⇩ ☐☐☐☐☐☐☐☐☐☐

go to question 77 *D D M M M Y Y Y Y*

76. CD4 Count _____

VICAR1 INITIAL VISIT QUESTIONAIRE

Site: Themba Lethu Clinic

TE # _____ Date (*dd/mmm/yyyy*): _____

77. HIV viral load known?
|__| NO (0) |__|YES (1)

⇩

go to question 80

78. Date Done

D	*D*	*M*	*M*	*M*	*Y*	*Y*	*Y*	*Y*	

79. Viral load _____

80. Do you take ARVs?
|__| NO (0) |__|YES (1)

⇩

81. Start Date of medication

D	*D*	*M*	*M*	*M*	*Y*	*Y*	*Y*	*Y*	

82. What Regimen do you follow?
|__| 1a (1) |__| 1b (2) |__| 2 (3) |__| other (4)

83. Has there been a change in regiment?
|__| NO (0) |__| YES (1)

84. Date

D	*D*	*M*	*M*	*M*	*Y*	*Y*	*Y*	*Y*	

Signature _____ **Date** _____

Designed: C.Firnhaber/D.Schulze/A. Swarts Prinsloo
Design: 08/01/09
Update: 10/06/2010

Page # 7

Data Entry (Date/Initials): _____