Clinical Profile of HIV Negative and HIV Positive Women Presenting with Cervical Cancer in Durban

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DECLARATION

I, Ayesha Ghani, hereby submit my dissertation to the university of KwaZulu-Natal for MMed degree in Obstetrics and Gynaecology. I declare that the work based in this dissertation, is original and it's my own unaided work carried out by me under the supervision of Professor J.S.Bagratee.

This work has not been submitted previously to this institution or any other university.

SIGNATURE: ……..

DATE: …….……

I, Professor J.S.Bagratee hereby declare that I have supervised the research carried out by Dr Ayesha Ghani and am satisfied with its presentation.

SUPERVISOR: ……..

DATE: ……..

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GLOSSARY

AIDS	Acquired Immune Deficiency Syndrome
ARV	Anti-Retroviral
ASIR	Age Standardized Incidence Rate
BMI	Body mass index
CCRT	Concurrent chemo-radiation therapy
CGC	Combined Gynecology –oncology clinic
DOH	Department of Health
FIGO	International Federation of Gynecology and Obstetrics
HAART	Highly Active Anti-Retroviral Therapy
HIV	Human Immunodeficiency Virus
HPV	Human Papilloma virus
IALCH	Inkosi Albert Luthuli Central Hospital
PET-FDG	Positron Emission Tomography-Flourodeoxy-glucose
PRXT	Palliative Radiotherapy
RH	Radical Hysterectomy
RRXT	Radical Radiotherapy
SA	South Africa
SC	Supportive Care
SD	Standard Deviation
SEER	Surveillance Epidemiology and End Results
UNAIDS	United Nations AIDS
WH	Wertheim's Hysterectomy
WHO	World Health Organization

ABSTRACT

BACKGROUND: KwaZulu-Natal has a high HIV prevalence and this may play a role in the presentation, progression and in the treatment of women with cervical cancer. The aim of the study was therefore to determine whether the clinical profile of HIV positive women with cervical cancer was different from that of HIV negative women. The study took place at the Gynecology –Oncology clinics at Inkosi Albert Luthuli Central Hospital (IALCH) and Addington Hospital.

METHODS: A retrospective chart review of the characteristics of women with cervical cancer were captured on an Excel data sheet from the Medicom database at IALCH and from the patient's files at Addington hospital for the period of 1st January 2009 to 31st December 2011.

RESULTS: Of the 1087 women, 425 (39%) were HIV positive, 561(51.6%) were HIV negative and 101 (9.2%) had an unknown HIV status. HIV positive women presented with cervical cancer an average of 14 years earlier than HIV negative women (41 years versus 55 years, $p<0.001$). Pap smear uptake was low in both groups (11.6% HIV negative and 17.3% HIV positive), and HIV positive women were significantly more anaemic (46.8% versus 32.7%, $p<0.001$). Ninety two percent of women were planned for radical radiotherapy and 8 % were scheduled for radical surgery. The average waiting period for radical surgery was longer for HIV positive women (84 days versus 58 days, $p <0.05$). For radical and palliative radiotherapy, the average waiting period was 85 days and 27 days, respectively. HIV status did not influence the waiting time period for radiotherapy. In women having radical hysterectomy, significantly more HIV positive compared to HIV negative women

required adjuvant radiotherapy due to positive lymph nodes, 9/15 (60%) versus 5/26 (19.2%), respectively.

CONCLUSION: HIV prevalence was 39% among women presenting with cervical cancer in Durban. HIV positive women presented at an earlier age compared to HIV negative women, and anemia was more prevalent in HIV positive women. The long waiting period for treatment adversely affected the management of HIV positive women with cervical cancer.

CHAPTER 1

LITERATURE REVIEW OF CERVICAL CANCER

1.1 INCIDENCE

Cervical cancer is the third commonest malignancy worldwide in females (GLOBOCAN, 2008), and accounts for 13% of all their cancers. In South Africa, it is the second most frequent cancer after the breast cancer among women (http://www.who.int/hpvcentre). Globally, cervical cancer is more common in low-resource than in high-resource settings. Parkin et al., (2005) reported that in 2002, 493 000 women were diagnosed with cervical cancer, and that mortality occurred in 233 000. Recently, the GLOBOCAN 2008 report revealed that more than half a million new cases of cervical cancer were diagnosed in 2008, and that 275 000 died of the disease, indicating an increase in the burden of disease worldwide, with 85%of these occurring in developing countries (GLOBOCAN, 2008). In developed countries, the incidence and mortality of cervical cancer has fallen due to strong cervical screening programs and improved socioeconomic conditions (Oaknin et al, 2012; Walker et al, 1998).

Cervical cancer is a significant public health problem among women in developing countries, particularly affecting those who are economically disadvantaged. It is the number one cancer in Bangladesh, India, Tanzania, Swaziland, Zimbabwe, and Zambia. Worldwide, after the sub-Saharan African the highest incidence rates are mostly in South-Central Asia, South and Central America and The Caribbean. Age-Standardized Incidence Rate (ASIR) was highest in Eastern and Western Africa, with

34-35 per 100 000, women followed by South Africa with 26 per100 000 (GLOBOCAN, 2008).

In the developed world, the ASIR is relatively low, with the Australia/New Zealand region being 5 per 100 000 and Europe being 8 per 100 000 (GLOBOCAN, 2008). Incidence rate has fallen in the United States from 8.3 per 100 000 in 2000 (Ries et al, 2003) to 5.7 per 100 000 women (GLOBOCAN, 2008). In United Kingdom, the ASIR was 8.3 per 100 000 in 2008 (Patnick J, 2011), as the National Health Services (NHS) implemented a screening program in 1998 in the highest risk age group (25-49 years) every 3 years, and for those aged 50-64 years, every 5 years. A recent report showed that since the cervical cancer screening programs were implemented, the incidence rate has reduced by half over 20 years from 15.9 per 100 000 in 1988 to 8.3 per100 000 in 2008 (Patnick J, 2011). In Switzerland, cervical cancer incidence has declined due to well-functioning primary and secondary prevention programs (Imesch & Fink, 2011).

1.2 MORTALITY

The mortality rate of cervical cancer has followed a similar trend as incidence rate in developed countries, as it tends to be diagnosed in the late stages and treatment requires infrastructure and resources that are often limited in resource poor settings. The mortality rate was lower in the developed world in 2008 (33 000) compared to 241 000 in developing countries such as 53 000 in Africa, 31 700 in Latin America and the Caribbean, and 159 800 in Asia and India (72,825) (GLOBOCAN Report, 2008). The age mortality rate was reported the highest in Zambia in 2008

38.6 per 100 000 followed by Tanzania, Zimbabwe and Swaziland, while in South Africa, it was 14.5 per100 000. In developed countries, the age-standardized mortality rate is lower such as in England at 2.2 per 100 000 in 2008 (Patnick J, 2011).

The racial/ethnic and socio-economic disproportion also influences the incidence and mortality of cervical cancer, a disparity which also persists in developed countries. However, the main determinant of this disparity is not well understood. McCarthy et al., (2010) reported that black and Hispanic women had a higher incidence and mortality rate than white women in developed countries. The survival rate of cervical cancer also varied in different races as reported by Adams et al., (2009), with 49% in African American (AA) women compared to 66% in European Americans (EA) (Adams et al, 2009). Similarly, low socioeconomic status of women with cervical cancer in developed countries also reported the highest mortality in comparison to affluent women (McCarthy et al, 2010; Patrick J, 2011). This study also concluded that race/ethnicity was a predictor of late stage presentation, while both race/ethnicity and low socioeconomic status were predictors of survival among women with cervical cancer. The positive relationship of good survival rate of women with cervical cancer and enhanced health care systems is well established in high income countries, whereas the health care infrastructure is limited in developing countries resulting in poor survival rates (Movva et al, 2008; Redaniel et al, 2009).

1.3 ETIOLOGY

Human Papilloma Virus (HPV) infection, a sexually transmitted infection, is etiologically linked to the development of cervical cancer. ZurHausen first demonstrated a link between HPV and cervical cancer in 1977, and subsequent

epidemiological studies supported the evidence (ZurHausen, 2000). HPV infection is easily and silently transmitted, as it does not cause any symptoms. Approximately 90% of HPV infections resolve within several months of initial infection (Stanely M, 2010), while persistent high-risk HPV infections are carcinogenic, causing high-grade cervical intraepithelial lesions, which eventually progress to cervical cancer if untreated. Persistent HPV infections are associated with integration of the viral genome into the host genome and subsequent transformation. After viral integration, two viral gene products, E6 and E7, are expressed, both of which are necessary but not sufficient for disease initiation and persistence. Their gene products are known to inactivate the major tumor suppressors, p53 and retinoblastoma protein (pRB), respectively (Yugawa and Kiyono, 2009). Disruption of these genes causes blocked apoptosis and cell–cycle arrest, leading to dysplasia.

Other causative factors include early age of sexual debut, multiple sexual partners, Human Immunodeficiency Virus (HIV) infection, smoking, oral contraceptive use, alcohol use, high parity, and chronic immunosuppression. A local study reported that lower socio-economic status, alcohol intake, being single or black race appears to be the determinant of increased sexual activity and young sexual debut, which often results in multiple sexual partners in life (Cooper et al, 2007). Therefore, these multiple factors eventually increase the risk of HPV infection, its persistence and progression to cervical cancer and other sexually transmitted diseases. In young women, HPV infection usually occurs after sexual debut and it clears after a period of one to two years in the background of a competent immune system. In contrast, HPV infection in older women takes long to clear and persistence of HPV infection even in immune competent females put them at high risk of developing cervical cancer.

HPV prevalence varies with demographic region and HIV status of women, and has been reported as 30% in all age groups in a high resource setting (Guido et al, 2013). HPV prevalence is doubled (56%) in African countries in HIV infected women (Dols et al, 2012).

1.4 LINK BETWEEN HIV, HPV AND CERVICAL CANCER

The positive link between HPV infection, cervical dysplasia and HIV infection is well supported in the literature (Bitz et al, 2013; Langley et al, 1996; Moscicki et al, 2000; Seck et al,1994). The direct association between HIV and cervical cancer is inconsistent compared to HIV and cervical dysplasia (Sasco et al, 2010). The prevalence of HPV infection is high in HIV positive women (53.9%) versus 33% in HIV negative women (Jaquet et al, 2012), with Zhonghua et al., (2012) reporting almost similar findings of HPV prevalence (44% in HIV positive and 20% in HIV negative women). HIV positive women with a CD4 count of less than 200 mm^3, regardless of HIV viral load, are at greater risk of acquiring high risk HPV infection (Palefsky et al, 1999). HPV clearance depends on CD4 count, as women with a CD4 of less than 200 mm^3 and 200-500 mm^3 (71% and 32%, respectively) are less likely to clear HPV infection compared to HIV negative women (Rowhani-Rahbar et al, 2007).

There is a significant relationship between the persistence of HPV infection and the degree of immune-suppression. HIV positive women are more at risk of developing high grade cervical dysplasia and multiple HPV genotypes infection compared to HIV negative women (Peedicayil et al, 2009). HPV infection persists in immune-compromised patients, resulting in cervical dysplasia with a shorter latency period,

which leads to the development of cervical cancer in younger females (van Bogaert, 2011). High grade cervical dysplasia in HIV positive women varies with the demographics, the degree of immune suppression, such as 6 % in Brazil (Teixeira et al, 2012), 30.9 % in South Africa (Swanepoel et al, 2012) and 31 % in Cameroon (Mogtomo et al, 2009). Keller et al., (2012) reported that HIV positive women with negative HPV infection and no cervical dysplasia follow the same course as HIV negative women.

In South Africa, cancer of the cervix and HIV/AIDS are both endemic, with studies reporting an HIV prevalence of 19% in women with cervical cancer (Maiman, Fruchter et al. 1993). This led to the inclusion of cervical cancer as an AIDS defining disease by the Centre for Disease Control. HIV prevalence varies in developing and developed countries, would also impact on the prevalence of HIV in women with cervical cancer. In Tanzania, the prevalence of HIV was 21% in women with cervical cancer (Kahesa et al, 2008), while in South Africa, a similar finding was reported over two periods, 21% in 1999 (Moodley 2006) and 21.8% in 2003 (Moodley &Mould, 2005). Recent literature showed an increase of HIV prevalence in cervical cancer patients of 30% in Tanzania (Matovelo et al, 2012). In developed settings such as USA, the prevalence of HIV in women with cervical cancer was 1% (Calkins et al, 2006). Thus the dynamics of cervical dysplasia, HIV infection and cervical cancer is significantly different in developing and developed countries.

1.5 HIV INCIDENCE

The identification of HIV infection (Barre-Sinoussi et al, 1983) partly explained the increased incidence of unusual infections and malignancies reported in1981.

According to estimates (UNAIDS /WHO, 2009), approximately 33.4 million people are infected with HIV every year worldwide, and 80% are those from developing countries in Sub-Saharan Africa. The disease has been known for three decades, but is still a significant public health issue in developing countries, requiring more effective strategies and good health infrastructure to control the spread of the disease.

HIV and AIDS are substantial challenges for South Africa, as is indicated by 2008 data, which shows that approximately 5.2 million people of the total South African population were infected with HIV (http://www.hst.org.za). Population based HIV prevalence surveys have been undertaken to monitor the disease epidemic, with three having been conducted to date in 2002, 2005, and 2008. National HIV prevalence estimation of all age groups was 10.6% in 2008, 10.8% in 2005, and 11.4% in 2002. In 2008, a higher prevalence was found in females than in males, the former being 32.9% in the 25-29 year age group and the latter being 29.1 % in the 30-34 year age group (http://www.mrc.ac.za/pressreleases/2009). The highest HIV prevalence was in KwaZulu-Natal Province, with 15.8% in 2008.

In South Africa, an antenatal survey also highlighted that HIV infection is increasing (0.7% in 1990, 17% in 1997, and 29.5% in 2004) (National HIV and SYPHILIS Prevalence Survey Report, 2005). A 2010 Antenatal Survey Report, suggests that the prevalence has stabilized over the last few years at 30.2%. The highest HIV prevalence was in KwaZulu-Natal, which increased from 38.7% in 2008 to 39.5% in 2009 and then decreased to 37.4% in 2011 (Antenatal HIV and Syphilis Survey 2011 Report). This decline of 2.1% could be due to multiple factors e.g. improved

counseling or education of the patients by the medical personnel and media/school education or people are now more conscious and therefore careful.

In Europe, the number of HIV infections is also rapidly increasing, which could be due to immigrants and change in lifestyle. In 2008, 1.5 million people were living with HIV, compared to 900 000 in 2001. In Latin America, at the end of 2008, approximately 2 million people were living with HIV. During that year, an estimated 77 000 people died of AIDS, and approximately 170 000 were newly infected (UNAIDS/HIV, 2008).

1.6 PRESENTATION

Cervical cancer is traditionally a disease of women in the fifth decade of their life, with the peak age between 45 and 55 and a mean age of 51 years, but because of HIV infections, this mean age will differ. Cervical cancer in HIV positive women presents 10 years earlier than in HIV negative women, with the mean age of 44 years versus 53 years respectively (Lomalisa et al, 2000), this being similar to finding reported by another local study (41 years versus 54 years) (Moodley & Mould, 2005). HIV infection did not change the magnitude of the disease at presentation, but an HIV positive women with a CD4 count of less than 200mm^3 had a more advanced cancer at presentation compared to an HIV negative women (77% and 55.8%, respectively) (Lomalisa et al, 2000). Trends in cervical cancer have changed worldwide, with the prevalence of cervical cancer increasing in younger women < 35 years for the past 30 years (2.8% to 15.7%) (Cai et al, 2010). This could be due to earlier sexual debut, multiple partners, and acquiring sexually transmitted disease resulting in earlier premalignant and malignant changes in the cervix.

1.7 CLINICAL DIAGNOSES AND INVESTIGATIONS

The diagnosis of cervical cancer is made by histology of cervical lesions, and more than 90% of patients will present with these symptoms. The most common presenting complaints are abnormal vaginal bleeding, history of post coital bleeding, profuse purulent or sanguineous offensive discharge. It can manifest in both premenopausal and postmenopausal age groups. Approximately 10% of women with cervical cancer are diagnosed by cervical cancer screening, this group usually being asymptomatic. Less common complaints include pelvic pain, pelvic pressure, inguinal or sciatic pain, urinary frequency, hematuria, and oliguria, suggesting advanced disease. In case of advanced disease, the patient may have urinary and fecal incontinence secondary to vesico-vaginal and recto-vaginal fistula (Biewenga et al, 2010).

Other constitutional symptoms such as pallor, weight loss, and weakness may occur, while anaemia may occur in early stages due to abnormal heavy vaginal bleeding. A physical examination may reveal grossly normal appearing cervix with micro invasive disease. As the disease progresses, physical signs appear which include a large, irregular and firm cervix, with the involvement of parametrium, thickening of utero-sacral and cardinal ligaments. Growth pattern can be endophytic, a barrel shaped cervix or exophytic, where the lesions are friable, cauliflower-like, and bleeds to touch. Any gross obvious lesion should have a directed punch biopsy or small excisional biopsy. Colposcopy is offered to the asymptomatic women who have been found to have premalignant lesions on Pap smear. In the absence of an obvious lesion on colposcopy, endo-cervical curettage, endometrial biopsy and cervical cone biopsy may need to be done to reach a diagnosis.

Women with histologically confirmed cervical cancer need further investigation to stage the disease and to assist in optimizing the clinical condition of the patient where indicated before embarking on treatment. This includes biochemical (full blood count, renal and liver function test and glomerular filtration rate) and radiological (chest x-ray and ultrasound of abdomen) investigation to stage the disease. In addition, syphilis serology, HIV testing and CD4 count if indicated, are also essential. Proper staging of cervical cancer is crucial, as it influences the management of the patient and survival outcome (Allen and Narayan, 2005).

1.8 PREVENTION

Cervical cancer is a preventable disease by initiating primary and secondary prevention programs, with the primary prevention program being HPV vaccination, which has been implemented in some developed countries. Cervical cancer screening programs (secondary prevention) have contributed to the considerable decline in the prevalence of the disease in developed countries (Patnick J, 2011; Denny L, 2012). In South Africa, there is a national cervical cancer screening policy that offers all asymptomatic women three free pap smears in a lifetime beginning at the age of 30 years, 10 years apart. However, this has not been successfully implemented. The ultimate goal is to screen at least 70% of women, nationally, within the target age group within 10 years of initiating the program (http://www.kznhealth.gov.za/cervicalcancer.pdf).

It has been shown that developing countries have poor Pap smear uptake (19%) compared to developed countries (63%) (Gakidou et al, 2008). Cervical cancer screening uptake is approximately 80% in developed countries, such as Austria,

compared to 13% to 18% in South Africa (Batra et al, 2010; Hoque et al, 2008). There was a poor utilization of cervical cancer screening program in high socio-economic and high educational background women (87%) in the urban area of Durban. This reflects a poor knowledge or lack of importance of screening information provided by the health care system (Wellensiek et al, 2002). Lourenço et al., (2012) reported poor knowledge of Pap smear among the women. South Africa currently recommends annual Pap smear for the HIV positive women at the wellness clinic since the ARV roll out program, but unfortunately, coverage is still poor, even in these targeted groups. Cervical cancer screening coverage is poor in HIV positive women in Eastern Europe (30%) (Bailey et al, 2012). Similarly, local studies also reported low Pap smear coverage (13%) in HIV positive women (Batra et al, 2010).

1.9 STAGING

Cervical cancer survival outcome depends on the stage of the disease, histology type, tumor grading, age of women and their immune status. Staging of cervical cancer according to the extent of the growth was first published in 1929 by the Cancer Commission of Health Organization (http://www.figo.org/publications/annual). FIGO (International Federation of Gynecology and Obstetrics) was founded in 1957 and adopted the staging system in 1958, which is largely based upon physical examination. A good pelvic examination is essential, and should be performed by an experienced gynecologist or Gynae-Oncologist and, under certain circumstances, may be performed under anesthesia.

Cervical cancer spreads locally by extension to the corpus, parametrium and vagina, and the cervix and entire vagina should therefore both be inspected and palpated to

identify overt tumors and sub-epithelial vaginal extension. Tumor size and parametrial involvement are best assessed by recto-vaginal examination. Cystoscopy, intravenous pyelography and sigmoidoscopy may be used to assess adjacent areas in case of uncertainty and suspicious lesions should confirmed by biopsy (Allen and Narayan, 2005).

Proper staging of cervical cancer is essential, as it influences the management of the patient and their survival. Unfortunately, clinical staging is subjective and only gives an approximate estimate of extent. This can result in over-staging and/or under-staging of the disease, which are common when compared to the surgical staging (Lagasse et al, 1980). Non-surgical staging is still a gold standard for advanced cervical cancer treatment planning.

Imaging evaluation may be of additional benefit to clinical examination in certain cases where resources allow. Compared to CT scan/MRI, PET-fdg imaging technique is more accurate in detecting metastatic lymphadenopathy, having the potential to significantly change the management and survival. Sensitivities remain suboptimal and possibly secondary to technique dependent (www.sign.ac.uk/cervical cancer guidelines). Surgery may be avoided in patients with PET-FDG –avid primary tumors. However, there is insufficient evidence of its routine use in operable stage of cervical cancer. The long-term survival of patients who had surgical staging-guided radiation therapy is no different to imaging guided radiotherapy in advanced cervical cancer, (overall survival 68% versus 62%, respectively), and disease free survival is similar (52% versus 55%, respectively) (Hong et al, 2010).

Cervical cancer stage presentation showed geographical variation, depends upon the healthcare system, early diagnosis (Kinney et al, 2003) good socioeconomic conditions and immune status of women (Akinyemiju TF, 2012; Lomalisa et al, 2000). Women with advanced stage disease at presentation in South Africa are usually of rural background, African ethnicity, old age and lack of health insurance coverage (Ibrahim et al, 2011). HIV infected women with high CD4 count presented at an early stage compared to low CD4 count (Lomalisa et al, 2000).

1.10 HISTOLOGY

Different pathological types of cervical cancer occurs, but data based on SEER (data of 2000-2004 assessed in 2007) showed that squamous cell carcinomas account for approximately 70% of cervical cancers, adeno-carcinomas 25 %, and adeno-squamous carcinomas 3-5 %. Adeno-squamous tumors exhibit both glandular and squamous differentiation, and are associated with a poorer outcome than squamous cell carcinomas or adenocarcinomas. Other tumors, such as neuro-endocrine or small cell carcinomas, can originate in the cervix but are infrequent. Rhabdo-myosarcoma of the cervix is rare, usually occurring in adolescents and young women, while primary cervical cancer lymphoma (Binesh et al, 2012) and cervical sarcoma are also rare (http://screening.iarc.fr/atlasclassifwho.php).

The histological pattern of cervical cancer has also changed over the last three decades and exhibit geographic variations. Squamous cell carcinoma is declining compared to adenocarcinoma, and the etiology remains elusive (Smith et al 2000; Wang et al, 2004). Wang et al., (2004) reported the linear increase in adenocarcinoma in black women, while recent literature reported a higher incidence of adenocarcinoma in white women compared to black women based on 35 year population analysis (USA)

(Adegoke et al, 2012). This implies the need of better cervical screening program including HPV typing. In sub-Saharan Africa, squamous cell carcinoma is more common and presents in an advanced stage (Adewuyi et al, 2008; Chirenje et al, 2000; Ndlovu N, &Kambarami R, 2003). HIV infection found to be six times more likely to have poor tumor differentiation (Matovelo et al, 2012).

1.11 TREATMENT

Cervical cancer treatment modality depends on the stage of the disease, the clinical condition and the desire for fertility, with accurate clinical staging being crucial before deciding on the choice of treatment to be offered. Radical hysterectomy with or without neo-adjuvant therapy is the preferred treatment of choice for early stage disease (stage Ia1-IIa1). Stage I B2 and above are the bulky tumors and usually require neo-adjuvant therapy. The outcome following surgery depends on various prognostic factors including tumor size, depth of stromal invasion, nodal involvement and presence or absence of lymph-vascular involvement. The presence of these factors determines the need for adjuvant chemo-radiation therapy, which may reduce the risk of recurrence and improves the survival of women (Memarzadeh et al, 2003; Mouková et al, 2013).

Concurrent chemo-radiation (CCRT) or radical radiotherapy are option of treatment for women with locally advanced stage cervical cancer (stage IIa and above). CCRT is a platinum based therapy and is better than radiation alone, and significantly improve the survival benefit (Green et al, 2005). Distant metastatic disease may also be treated by systemic chemotherapy, while advanced stage disease requires palliative care and /or palliative radiotherapy.

In developed countries, the well-established health care system offers earlier diagnosis of cervical cancer and earlier treatment, which influences the survival outcome. Generally, 4-5 weeks are an accepted waiting time for initiating radiotherapy or chemo radiation after the treatment plan (http://www.cancerresearchuk.org). The recommended initiation of treatment within 6-8 weeks is acceptable by most authorities (González San Segundo et al, 2005).

Wyatt et al., (2003) reported that a delay of 1-2 months would influence the tumor progression and survival outcome in the case of fast growing tumors. A continuum increase in waiting time has been observed in the initiation of radical radiotherapy treatment as compared to palliative treatment, even in developed countries (Coles et al, 2003). Similarly, waiting time for surgery of cancer has also increased over the years (Bardell et al, 2006). Various factors contribute to this delay, including patient related and health care system factors, which result in delayed diagnosis and referral, long waiting lists for treatment, shortage of resources and missed appointments due to poor socio-economic status. Patient related factors are usually old age and delay in seeking help for cervical cancer, and are more prevalent in developing than developed countries (Kaku et al, 2008; Ma et al, 2012).

1.12 OUTCOME

Survival outcome of women with cervical cancer depends on several prognostic factors, these being the stage of the disease, nodal status, tumor volume, depth of cervical stromal invasion, lympho-vascular space invasion (LVSI), and histology type and grade. Furthermore, HIV status of the women, CD4 count, tolerance and completion of radiotherapy also influence the outcome (Simonds et al, 2012).

In HIV positive women with cervical cancer, radiotherapy toxicity contributes to delayed or incomplete treatment. Shrivastava et al., (2005) reported that more than 50% of women who presented with advanced stage cancer showed poor compliance (24%) to radiotherapy. In a local study, Simonds et al., (2012) also showed that 53% of HIV positive women with advanced stage disease were less compliant with radiotherapy treatment, resulting in poor survival.

The 5-year survival of cervical cancer after radical hysterectomy and lymph-node dissection in early staged disease (FIGO Stage IB or IIA) was 88% to 96% in those who had negative pelvic lymph nodes, compared to 64% to 74% in those with similar stage disease and pelvic nodal metastasis. For the advanced stage disease (Stage II B to Stage IV), the 5-year survival rate is 65% to 9.3%, respectively (Quinn et al, 2006). However, overall survival of the women with cervical cancer depends on the other co-morbidities such as HIV infection with low CD4 count, tolerance to antiretroviral therapy, response to chemo-radiation and occurrence of side effects, and patient's performance status (Simonds et al, 2012; Spoozak et al, 2013).

1.3 PURPOSE OF STUDY

The purpose of the study was to determine whether the clinical profile of HIV positive women with cervical cancer was different from that of HIV negative women. New information gathered from this study may assist in modifying existing practices of care in HIV positive women with carcinoma of the cervix.

CHAPTER 2

AIM AND METHODOLOGY

2.1 Aim of the study

To determine the clinical profile of HIV negative and HIV positive women presenting with cervical cancer.

2.2 Methods:

This is a retrospective descriptive study. Inkosi Albert Luthuli Central Hospital (IALCH) and Addington Hospital are the main sites of the study which serves tertiary level oncology services in KwaZulu-Natal (KZN). Women who presented with histologically confirmed cervical cancer to the Gynecology Oncology clinics and who were admitted to the oncology ward at IALCH and Addignton hospitals were included in the study.

The study period was from 1st January 2009 to 31st December 2011. Information regarding demographic and clinical characteristics, HIV infection and HAART, staging and treatment of women with cervical cancer was captured on an Excel data sheet from the Medicom database at IALCH and from the patient's files at Addington hospital and imported to SPSS version 21 for the statistical analysis..

The analysis of patients' demographics and outcome variables were summarized using descriptive summary measures: expressed as mean (standard deviation) or median (minimum-maximum) for continuous variables and as percentages for categorical variables. All statistical tests were performed using paired student t-test at

the 0.05 level of significance. Anova test was performed for the comparative analysis of treatment in HIV negative and HIV positive women with cervical cancer.

Ethical approval was obtained from the University of KwaZulu-Natal before the study was commenced (Reference no: BE 074/12)

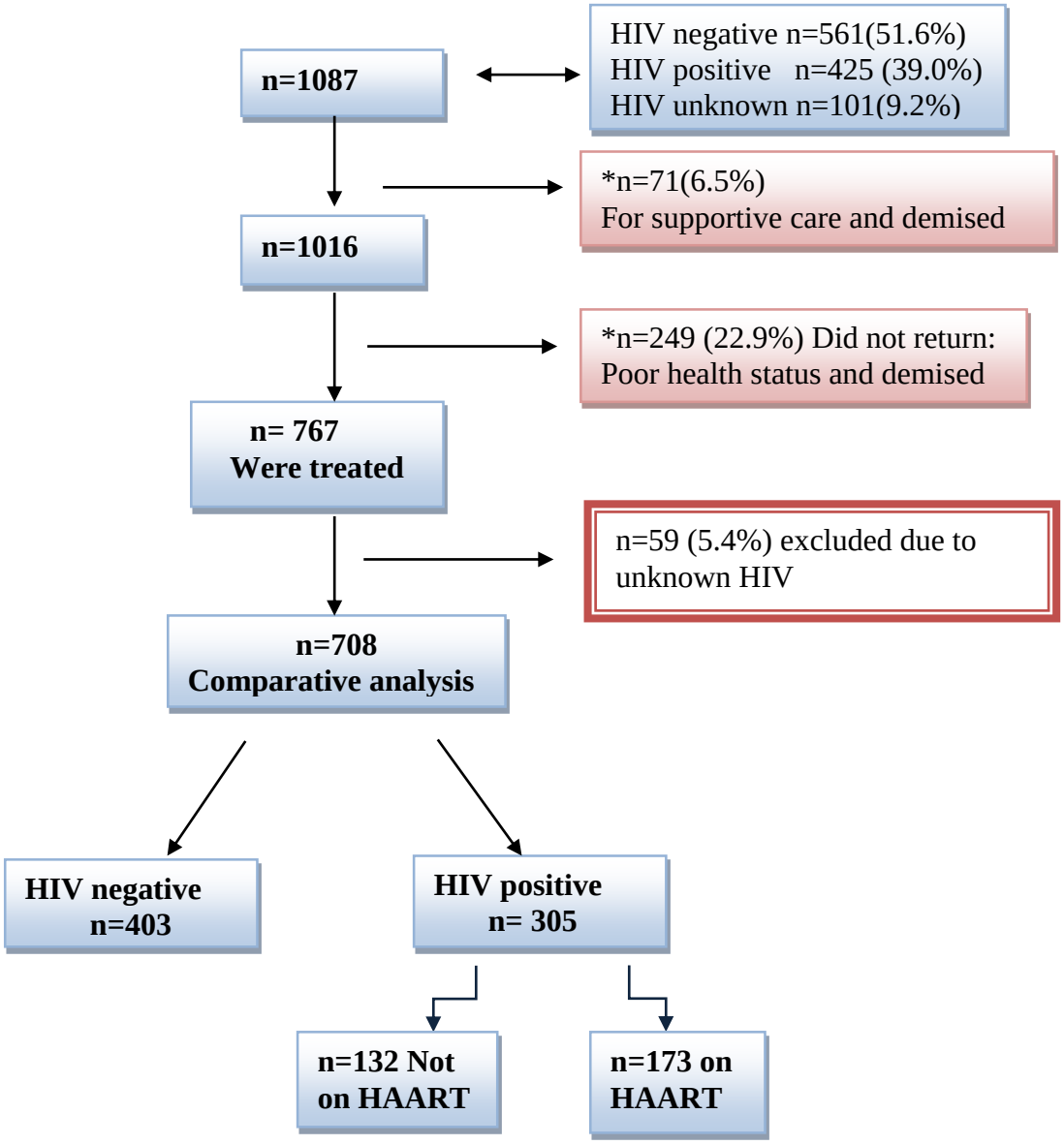
CHAPTER 3

RESULTS

3.1 Introduction

This chapter presents the study findings with respect to the number of women who were recruited to study both HIV negative and positive women with cervical cancer (figure 1).

Figure 1: Flow diagram of women with cervical cancer recruited to study



3.2 Demographics characteristics

The demographic analysis of 708 women with cervical cancer who received treatment and followed up is displayed in table 1 and age presentation in figure 2.

Table 1: Demographic characteristics of 708 women with cervical cancer

	HIV negative n=403	HIV Positive n=305	p Value
Age (years) (mean ± SD)	55.94±11.68	41.75±9.32	<0.001
Age (<35 years) n (%)	13 (3.2)	80 (26.2)	<0.001
Parity median(range)	5 (0-14)	3 (0-11)	<0.001
Weight (kg) (mean ± SD)	74.66±17.43	72.14±18.49	0.63
BMI* (kg/m^2) (mean ± SD)	29.91±7.11	28.45±6.90	0.38
Race n (%)			<0.001
African	342 (84.8)	300 (98.3)	
Indian	50 (12.4)	2 (0.65)	
White	7 (1.7)	1 (0.32)	
Colored	4 (0.99)	2 (0.65)	
Previous Pap Smear n (%)	47 (11.6)	53 (17.3)	<0.001
Co-morbidities n (%)			
Hypertension	165 (40.9)	42 (13.7)	<0.001
Diabetes	49 (12.1)	9 (2.9)	<0.001
Tuberculosis	13 (3.2)	36 (11.8)	<0.001

*BMI: Body mass index; SD: Standard Deviation

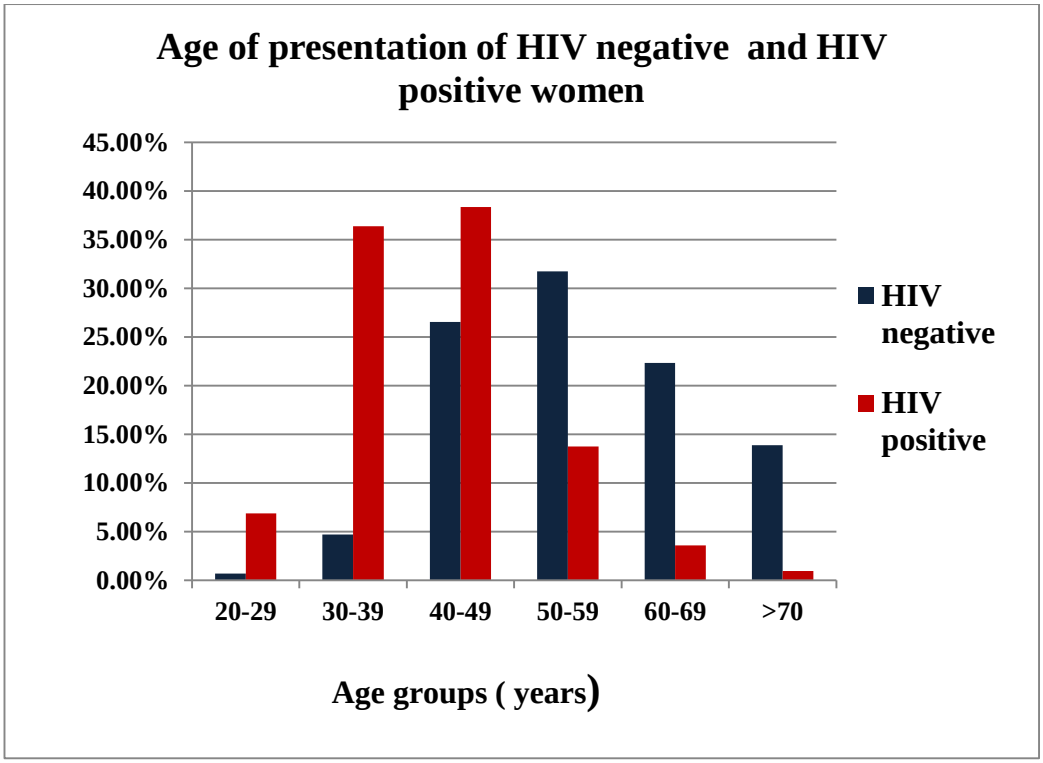


Figure 2: Age of presentation of HIV negative and HIV positive women

3.3 Clinical characteristics

The clinical characteristics of women with cervical cancer regarding stage presentation, histology and investigations among the two groups are displayed in Table 2 and Table 3.

Table 2: Staging and Histology of cervical cancer

	HIV negative n=403	HIV positive n=305	p value
Stage I n (%)	**27 (6.6)**	**16 (5.2)**	**0.61**
Ia1	3	4	
Ia2	6	0	
Ib1	15	10	
Ib2	3	2	
Stage II n (%)	**130 (32.2)**	**98 (32.1)**	**0.61**
IIa1	7	9	
IIa2	7	7	
IIb	116	82	
Stage III n (%)	**217 (53.8)**	**168 (55)**	**0.61**
IIIa	13	10	
IIIb	204	158	
Stage IV n (%)	**29 (7.1)**	**23 (7.5)**	**0.61**
IVa	16	14	
IVb	13	9	
Histology n (%)			**NS**
Squamous cell carcinoma	332 (82.3)	262 (85.9)	
Adeno squamous carcinoma	18 (4.4)	14 (4.5)	
Adenocarcinoma carcinoma	24 (5.9)	13 (4.2)	
Undifferentiated carcinoma	11 (2.7)	8 (2.6)	
Small cell carcinoma	7 (1.7)	5 (1.6)	
Others	10 (2.4)	1 (0.3)	

See Staging in Appendix B

Table 3: Investigations and performance score of HIV negative and HIV positive

	HIV negative n=403	HIV positive n=305	p value
Hemoglobin n (%)			
> 10gm/dl	271 (67.2)	162 (53.1)	<0.001
8-10 gm/dl	92 (22.8)	90 (29.5)	<0.001
<8gm/dl	40 (9.9)	53 (17.3)	<0.001
Anemia < 10 gm/dl n(%)	132 (32.7)	143 (46.8)	<0.001
Renal failuren (%)			NS
GFR < 60	87 (21.5)	63 (20.6)	
Requiring dialysis	16 (3.9)	12 (3.9)	
Metastases n (%)	29 (7.1)	24 (7.8)	NS
Chest	11 (2.7)	8 (2.6)	
Liver	10 (2.4)	4 (1.31)	
Bladder	7 (1.7)	12 (3.93)	
Rectum	1 (0.24)	0	
Performance score (Zubrod) n (%)			NS
Asymptomatic(score0)			
Symptomatic but completely ambulatory (Score1)	314 (77.9)	233 (76.39)	
Symptomatic, <50% in bed during the day (score 2)	64 (15.8)	45 (14.7)	
Symptomatic, >50% in bed, but not bedbound (score3)	24 (5.9)	26 (8.5)	
Bedbound (score 4)	1 (0.24)	1 (0.32)	

3.4 Treatment Planned and Received

Table 4 presents the cervical cancer treatment was scheduled at the first visit to gynecology oncology clinic. Ninety two percent of the women were scheduled for non-surgical treatment and 8% for surgical treatment. Between 17 to 20 % of women in both groups were planned for palliative radiotherapy.

Table 4: Treatment modality planned at the first visit in gynecology oncology clinic

	HIV negative n=403	HIV positive n=305	p value
Surgical treatment n (%)	**34 (8.4)**	**25 (8.1)**	0.46
Cone biopsy	0	1 (0.32)	
Total abdominal hysterectomy	2 (0.49)	3 (0.98)	
Radical hysterectomy	32 (7.9)	21(6.8)	
Non-surgical treatment n (%)	**369 (91.5)**	**280 (91.8)**	0.46
Concurrent chemo-radiation therapy	238 (59.0)	175(57.3)	
Radical radiotherapy	60 (14.8)	43 (14.0)	
Palliative radiotherapy	71 (17.6)	62 (20.3)	
***Additional surgical procedures n(%)**	**31 (7.6)**	**17 (5.5)**	
Ileal conduit	6	3	
Colostomy	1	0	
Nephrostomy	14	6	
Uterine artery embolization	8	5	
Stenting and dialysis	2	3	

*In patients planned for radical or palliative radiotherapy

Table 5 displays the treatment received by the women. The planned surgical treatment was accomplished for approximately 80% of the women with cervical cancer.

Table 5: Treatment received by the cervical cancer patients

	HIV negative n=403	HIV positive n=305	p value
Surgery cancelled n (%)	**6 (17.6)**	**6 (24.0)**	
Surgery received n(%)	**28 (6.9)**	**19 (6.2)**	0.64
Cone biopsy	0	1 (0.32)	
Total abdominal hysterectomy	2 (0.49)	3 (0.98)	
Radical hysterectomy (RH)	26 (6.4)*	15 (4.9)**	0.08
Negative Lymph nodes	21 (80.7)	6 (40.0)	
Positive Lymph nodes	5 (19.2)	9 (60.0)	0.002
Non-surgical treatment n (%)	**341 (84.6)**	**251 (82.2)**	0.64
Concurrent chemo-radiation therapy	179 (44.4)	118 (38.6)	0.002
Radical radiotherapy	114 (28.2)	32 (10.4)	<0.001
Palliative radiotherapy	48 (11.9)	101 (33.1)	<0.001
Supportive care n(%)	**34 (8.4)**	**35 (11.4)**	0.007
***Additional surgical procedures n(%)**	**21 (5.2)**	**11 (3.6)**	
Ileal conduit	2	3	
Colostomy	1	0	
Nephrostomy	10	2	
Uterine artery embolization	8	5	
Stenting and dialysis	0	1	

*HIV negative RH (Stage I=19, Stage IIa1=7) ** HIV positive RH (Stage 1=7, Stage IIa1=8)
***Received either Radical or Palliative radiotherapy after the additional surgery.

The difference in women requiring adjuvant radiotherapy was higher in HIV positive group, even when the stage of treatment was breakdown as shown in table 6 below.

Table 6: Lymph Node Stage and Radical Hysterectomy

	HIV negative n=26		HIV positive n= 15	
Stages	Positive lymph nodes n=5 (%)	Negative lymph nodes n=21	Positive lymph nodes n=9 (%)	Negative lymph nodes n=6
I A1	0	0	0	0
I A2	0	5	0	0
I B1 n (%)	3 (25)	9	3 (43)	4
I B2	0	2	0	0
II A1 n (%)	2 (28.5)	5	6 (75)	2
Adjuvant treatment n (%)	5 (19.2)	0	9 (60)	0

Table 7 displays the treatment planned and received by both groups. Significantly more women were changed to supportive care when none was planned (8.4% HIV negative versus 11.4 % HIV positive women).

Table 7: Treatment Planned and Treatment Received by the women with cervical cancer

	HIV negative n=403 Planned	Received	HIV positive n=305 Planned	Received	**p value
Surgery n(%)	**34 (8.4)**	**28 (6.9)**	**25 (8.1)**	**19(6.2)**	**0.55**
Cone biopsy	0 (0)	0 (0)	1 (0.32)	1(0.32)	
Total abdominal hysterectomy	2 (0.49)	2 (0.49)	3 (0.98)	3 (0.98)	
Radical hysterectomy	32 (7.9)	26(6.4)	21 (6.8)	15(4.9)	0.41
Negative Lymph nodes		21		6	
Positive Lymph nodes		5(19.2)		9 (60)	0.002
Non-surgical treatment n(%)	**369 (91.5)**	**341(84.6)**	**280 (91.8)**	**251(82.2)**	**0.21**
Concurrent chemo-radiation therapy	238 (59.0)	179(44.4)	175 (57.3)	118(38.6)	0.10
Radical radiotherapy	60 (14.8)	114(28.2)	43 (14.0)	32 (10.4)	0.001
Palliative radiotherapy	71 (17.6)	48 (11.9)	62 (20.3)	101(33.1)	<0.001
Supportive care n(%)	**0 (0)**	**34(8.4)**	**0 (0)**	**35(11.4)**	**0.007**
*Additional surgical procedures n(%)	**31 (7.6)**	**21(6.7)**	**17 (5.5)**	**11(6.4)**	
Ileal conduit	6	2	3	3	
Colostomy	1	1	0	0	
Nephrostomy	14	10	6	2	
Uterine artery embolization	8	8	5	5	
Stenting and dialysis	2	0	3	1	

*Received either Radical or Palliative radiotherapy after the additional surgery

** Anova test used

3.5 Waiting time Period

Table 8 displays an average waiting period from decision to radical hysterectomy (RH), RH performed and RH not performed in HIV negative and HIV positive women. The waiting period (range) given to patients was similar between both groups; however, average waiting period given to patient from decision to planned RH was significantly longer in HIV positive women (84 versus 58 days, $p<0.05$).

Table 8: Decision – treatment time interval in women scheduled for radical hysterectomy (RH)

Waiting Time	HIV Negative n=32	HIV positive n=21	p value
Average waiting time given from decision to surgery	58.38 days	84.92 days	<0.05
Time range	0-231 days	7- 238 days	
	n=26	n=15	
RH performed	50 days	72.57 days	0.08
	n=6	n=6	
RH not performed	93.31 days	127.52 days	0.8

The waiting time to RH performed was the time coincided with the planned date given at the time of 1st appointment. In 12 women, six women in either group returned on the planned date of surgery which was an average of 93 days and 127 days, respectively, but were found to be unsuitable for RH d as the stage had advanced from the initial stage and the treatment plan was changed to CCRT or RRXT.

Figure 5 shows the waiting period for RH not performed. It shows the longer waiting period in HIV positive women with one outliner in each group.

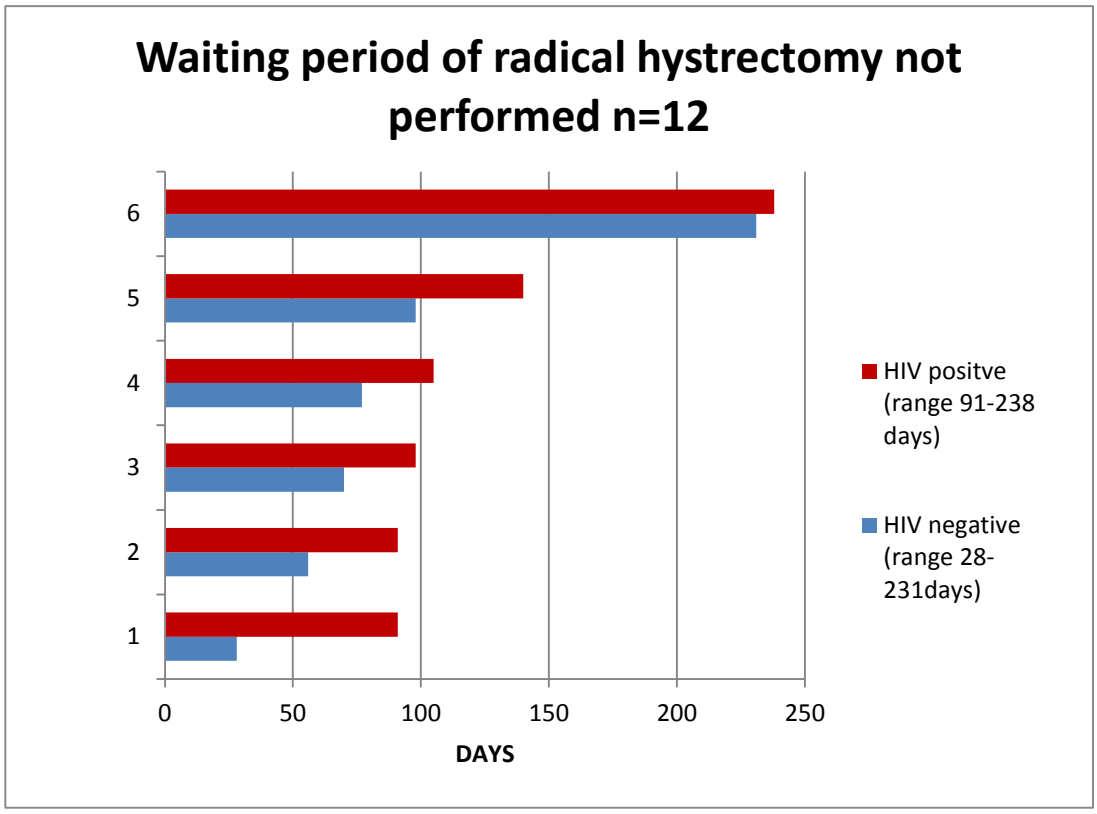


Figure 5: Waiting period of RH not performed group

Table 9: Average waiting period for radical and palliative radiotherapy in HIV negative and positive women

	HIV negative n=403	HIV positive N=305	P value
Radical radiotherapy Mean (range)	88.1 days (0-217days)	83.22days (7-210 days)	0.1
Palliative radiotherapy Mean (range)	31.07days (7- 119 days)	23.93 days (0-77days)	0.07

3.6 Outcome and complication

Table 10 demonstrates the number of women required change in treatment and its causes. The long waiting period resulted in the change of treatment in different stages of cervical cancer.

Table 10: Change and causes of change in treatment

	HIV negative n=403	HIV positive n=305	p value
Change in treatment n (%)	**95 (23.5)**	**86 (28.9)**	0.009
Causes of change in treatment n(%)			0.30
Worsening of performance score	27 (28.4)	37 (43.0)	<0.001
Progressive disease(upstaged)	49 (51.5)	32 (37.2)	0.01
Patient related factor	19 (20.0)	14 (16.2)	0.19
Shortage of staff	0	3 (3.4)	
Recurrent Disease n(%)	**15 (3.7)**	**7 (2.2)**	0.86
Surgical group	3 (20)	1 (14.2)	
Radiotherapy group	12 (80)	6 (85.7)	

*patient declining treatment, cannot wait for long radical RXT date requesting palliative RXT and defaulting follow-up appointment during the treatment phase.

Table 11: Complication of surgery and radiotherapy and Deaths

	HIV negative n=403	HIV positive n=305	P value
Surgical complication n (%)	**4 (1)**	**3 (.98)**	**NS**
Bleeding	2	1	
Burst Abdomen	1	1	
Massive Pulmonary embolism	1 (died)	1	
Radiotherapy complication n (%)	**15 (3.7)**	**15 (4.91)**	**NS**
Radiation cystitis	1	2	
Proctitis	2	3	
Rectovaginal/vesicovaginal fistula	12	10	
Deaths (oncology ward) n (%)	**9 (2.2)**	**10 (3.2)**	**NS**
Average age (years)	58 years	45 years	

3.7 HIV positive women based on CD4 Count

The cohort of HIV positive women were further analyzed based on CD4 count (< 200mm^3 and >200mm^3) (Table 12 and 13). Antiretroviral treatment was significantly different between the two groups (p <0.001). In the study population, the average CD4 count was 375 mm^3. Furthermore, in women with CD4 count <200mm^3, 75 % presented in advanced stage in the group not on HAART compared to those On HAART (56%) (Table13).

Table 12: Clinical characteristics of HIV positive women in CD4 count groups

	CD4<200mm^3 n=79 Group A	CD4 >200mm^3 n=226 Group B	p value
Age (years) Mean ±SD	42.43±9.33	41.22±9.39	0.72
Parity Median (range)	3 (0-11)	3 (0-10)	0.60
***BMI** (kg/mm2)	27.27±7.62	28.75± 6.40	0.24
Hemoglobin n (%)			0.89
>10 gm/dl	35 (44.3)	114 (50.4)	
8-10 gm/dl	28 (35.4)	70 (30.9)	
<8 gm /dl	16 (20.2)	42 (18.5)	
Renal failure n (%)			0.17
GFR <60	19 (24.0)	46 (20.3)	
Dialysis	4 (5.0)	8 (3.5)	
On HAART	67 (84.8)	106 (46.9)	<0.001
NO HAART	12 (15.1)	120 (53.0)	

*BMI : Body mass index

Table 13: Staging and treatment received in CD4 count sub groups

	CD4 <200mm^3 n=79 Group A		CD4 >200mm^3 n=226 Group B		p value
Stages n(%)	Not on HAART n=12	On HAART n=67	Not on HAART n=120	On HAART n=106	0.4
Stage I	0 (0)	4 (5.9)	5 (4.1)	7 (6.6)	
Stage II	3 (25.0)	25 (37.3)	41 (34.1)	29 (27.3)	
Stage III	**6 (50.0)**	**33 (49.2)**	69 (57.5)	60 (56.6)	
Stage IV	**3 (25.0)**	**5 (7.4)**	5 (4.1)	10 (9.4)	
Treatment P(R)					P (0.07)
Surgery n(n)	0 (0)	4 (2)	12 (8)	9 (9)	R(0.32)
CCRT	8 (5)	33 (21)	71 (47)	59 (45)	
RRXT	0 (0)	14 (12)	14 (11)	15 (9)	
PRXT	4 (6)	16 (26)	23 (39)	23 (30)	
SC	0 (1)	0 (6)	0 (15)	0 (13)	

P (R): Planned (Received); CCRT: concurrent chemo-radiation therapy; RRXT: radical radiotherapy**;** PRXT: palliative radiotherapy; SC: supportive care.

CHAPTER 4

DISCUSSION AND LIMITATIONS

4.1 DISCUSSION

KwaZulu-Natal is the second most densely populated province of South Africa and carries the highest burden of HIV disease (National HIV Prevalence Survey Report 2008; Antenatal Survey Report, (2010). Under these circumstances, it is valuable to ascertain the cervical cancer burden and to understand how HIV infection influences the dynamics of the disease even with HAART coverage. With this in mind, an audit of the clinical profile of HIV positive and HIV negative women with cervical cancer in a background of high HIV prevalence was conducted.

This study found a higher HIV sero-prevalence of 39% in women with cervical cancer compared to national the HIV Prevalence Survey Report 2008, maximum of 32.9% in female (http://www.mrc.ac.za/pressreleases/2009). This audit also revealed an increase in HIV prevalence in women with cervical cancer women compared to 21% in 1999 (Moodley 2006) and 21.8% in 2003 (Moodley & Mould, 2005). Elsewhere in Africa, Matovelo et al., (2012) reported an increase of HIV prevalence of 29.7% in women with cervical cancer in Tanzania compared to 21% reported by Kahesa et al., (2008). This could be due to multiple factors such as early sexual debut, multiple partners resulting in women more at risk of acquiring HIV infection as compared to men.

HIV infection was found to influence the age of presentation of women with cervical cancer in this study. Our study confirms the earlier studies reported by Lomalisa et

al., (2000) and Moodley (2006). In women under 35 years of age, there was almost eight fold increase in HIV positive women presented with cervical cancer. Abraham et al., (2012) reported that HIV positive women were three times more prone to have cervical cancer than HIV negative women, and that their risks increased with a low CD4 count. Cai et al., (2010) reported an increase in cervical cancer in younger women (< 35 years) over the past 30 years from 2.8% to 15.7%, though the study did not consider HIV status. High HIV prevalence in young women would result in early acquisition of HPV infection and its persistence, particularly in women with a low CD4 count and high viral load. HIV positive women have a shorter latency period from dysplastic lesions to cervical cancer. The need for earlier cervical cancer screening in South Africa is indicated in the high risk group of HIV positive women compared to the Department of Health recommended screening protocol of first Pap smear at the age of 30 years.

HIV positive women did not show the high uptake of Pap smear despite the CDC guidelines of annual Pap smear. The poor coverage of Pap smear falls with the health care worker/system and women related factors and are missed opportunities by the health care workers at hospitals and primary health care facilities about who to screen. Poor uptake of cervical screening is multi-factorial. These include lack of availability in deep rural areas, poor quality or shortage of health care providers, poor accessibility, and lack of awareness due to education level or poor knowledge of disease and its prevention programs. In addition, women ignore their own wellbeing and prioritize their family needs. Furthermore, capacity to track women with abnormal cytology as well as to provide quality assured colposcopy, pathology, and treatment services are limited. Public health spending on the HIV pandemic and

tuberculosis remain a major focus of health care budget such that the capacity to develop infrastructure for cytology-based cervical cancer screening program remains inadequate. The alternative screening modalities in a low resource setting such as Visual Inspection with Acetic acid (VIA) and molecular testing for high-risk types of human papillomavirus (HPV) need to be considered in our country. The data regarding VIA value is inconsistent and varies with regions. The diagnostic values of VIA has been reported to be of value in extremely low resource settings where Pap smear facility or equipment is not available (Li et al, 2013; Zhang et al 2010). However, VIA is not superior to Pap smear in specificity, positive predictive value and negative predictive value but has a comparable sensitivity (Albert et al, 2012). The disadvantage of VIA is the necessity of on-going training of the health care worker which also need infrastructure. Visual inspection with acetic acid is a poor screening test in comparison to HPV testing and cytology in the reduction of incidence of cervical cancer and deaths (Sanakaranararyanan et al, 2009). HPV testing was found to be superior among the three, viz., VIA and HPV and cytology.

HPV testing has high sensitivity in detecting high grade lesions than cytology (96.1% vs. 53.0%) but less specific (90.7% vs. 96.3%) (Cuzick et al, 2006). HPV testing was found to be of value in Denny et al, (2010) study. They reported that at the 36 month follow-up, in the screen and treat approach using HPV testing a 3.6 fold decrease in high grade dysplasia was noted as compared to the VIA and treat and no intervention group.

In our setting, HPV testing and treat, and HPV testing incorporated into a cervical screening program may help to increase the interval of Pap smears in a high risk group

if the HPV test is negative. This seems more cost-effective compared to VIA in order to decrease the burden of cervical cancer.

There was a significantly higher prevalence of hypertension and diabetes among the HIV negative women. This reflects the older mean age of 55 years in HIV negative women compared to the mean age of 41 years in HIV positive women. However, HIV positive women were almost four times at higher risk of having an opportunistic infection such as Tuberculosis compared to HIV negative women, which is an expected finding in our setting with high HIV prevalence.

In our study, HIV positive women had a higher prevalence of anaemia at their first visit compared to HIV negative women. Advanced stage malignancy, bleeding, poor turnover of bone marrow and poor nutritional state are the likely contributory factor to anemia (Stuklov NI, 2010). This leads to an increase in the blood transfusion burden in our limited resource setting where blood shortage is common. Anaemic patients were referred back to their base hospital for blood transfusion prior to and during the treatment period. Anaemia is probably one of the prognostic factors for advanced stage disease and furthermore affects more HIV positive women. Barkati et al., (2013) reported that patients with low hemoglobin usually presented with advanced stage disease which contributed to a poor prognosis.

Women with CD4 count of less or more than 200 mm^3 did not seem to influence the clinical characteristics in our study. However, correlation of timing of HAART initiation and cervical cancer diagnosis was not established, as this information was not recorded in patient's records. There were only a few women with CD4 count

<200mm^3 who were referred for HAART, and this group had an advanced staged disease. As cervical cancer is an AIDS-defining disease, all HIV positive women with cervical cancer should have been referred for HAART, however but no comment was found in the patient records.

HIV infection did not influence the stage presentation and histology of cervical cancer in the study. HIV positive women is more at risk of persistence of HPV infection, high grade cervical dysplasia compared to HIV negative (Peedicayil et al, 2009).
Kinney et al, (2003), reported the detection of early stage cervical cancer by cytological screening. Yamada et al, (2008) reported the higher detection of high -grade squamous intraepithelial lesions and cancer on cytology in HIV positive women compared to HIV negative women. HIV positive women should have an annual Pap smear as a part of their health care package. In a background of high HIV prevalence, a higher incidence of early stage cervical cancer presentation may be expected due to detecting premalignant or early malignant changes (micro invasive disease) earlier by Pap smear or by clinical evaluation of the symptomatic women; however, our study did not find any difference. Of concern in this study was that nearly 8% of women presented with stage IV cervical cancer. Advanced staged disease presentation highlights the poor cervical cancer screening uptake in the community, thereby increasing the burden of disease and decreasing the survival of women. A study done in Harare reported that 80% of women presented with advanced disease (stage IIb and above) (Chirenje et al, 2000). In this study, about 92 % women presented in advanced stage cervical cancer requiring radiotherapy treatment. Reasons for delayed presentation to tertiary centers are multifactorial, and include health care system and patient related factors. In the health care system, there was a long waiting period to the first visit to gynecology

oncology clinic while some patient required a second visit before deciding on definitive treatment due to incomplete workup information, and/or inappropriate referral. In some instances, the histology result was not to be found or not sent resulting in repeat biopsy. Poor socio-economic factors and low level of education contributed to delays in seeking health advice and missing their scheduled appointment, resulting in advanced stage presentation.

Advanced staged disease may result in renal failure and dialysis adds to the cost of care in women suitable for radical radiotherapy. Furthermore, due to poor social support services including hospice services, women requiring palliative care consume lot of health resources in our district hospitals. In our study, 22.9% of women did not return on their appointed date of treatment. All these women had advanced disease and poor health status and demised before their appointed date. Greater socio-political will is required to change the face of advanced cervical cancer in our country.

The long waiting period in the management of any malignancy does influence the disease progression and survival outcome. In Durban, only two centers (IALCH and ADH) provide chemotherapy and radiotherapy, with IALCH being the only center for brachytherapy. The waiting time for women requiring radical radiotherapy was about 3 month and those having palliative radiotherapy were just under 1 month. The reasons for the long waiting time included shortage of radiotherapist in the province, and few radiotherapy machines. These radiotherapy machines were old and experienced breakdowns which took long to repair and replace in 2010. In addition, there was an industrial strike action in 2009 and 2010 that also contributed to long waiting time.

The time period from diagnosis to treatment is important regarding survival outcome of women with cervical cancer. Dahrouge et al., (2005) reported that a longer waiting period of more than 6-8 weeks would affect the survival of women in radical radiotherapy treatment. Our study showed that long waiting times affected the surgical and non-surgical planned treatment in women with cervical cancer. The long waiting period allowed the health status to deteriorate and progression of disease, which resulted change of planned treatment in certain proportion of women. Furthermore, long waiting periods to treatment also created anxiety in women and families, contributing to 18% cause of changes in treatment. This information was recorded from the patient's notes. The long waiting period resulted the change in planned treatment of women with cervical cancer. The causes of change in treatment include worsening of their performance score and progressive disease such as developing renal failure or higher stage when these women presented on their date of treatment. In addition, patient related factors also contributed to the change in planned treatment. There were few (7) women with cervical cancer who were counselled about the radical radiotherapy and explained about the reasons for long waiting list for treatment due to the shortage of radiographer and oncology staff. This group of patients had an advanced stage (IIIB) and the waiting period was between 5-7 months for radical radiotherapy. These patients declined to wait that long and therefore palliative radiotherapy was offered which had a shorter waiting period of 3-4 weeks. Other patient related factors were missing their appointment during radical radiotherapy treatment and subsequently presented in poor clinical condition resulted in change of planned treatment to palliative radiotherapy or palliative care.

The reason for long waiting period for radical hysterectomy in HIV positive women was not mentioned in the patient's record. This is one of the limitations of a retrospective study, as the health care worker did not record the reason for the delays, but presumably may have been low CD4 count, time needed to respond to HAART or presence of active Tuberculosis. Other contributory factors could include physician absence in industrial action, vacation and leave from duty. These factors would result in the same waiting time for both groups. The long waiting period resulted in disease progression and also contributed to the need for adjuvant therapy due to positive lymph nodes, significantly more in HIV positive women. HIV positive women with cervical cancer need to be prioritized on the treatment list in order to decrease the progression of disease and improve the survival. As initially stated one case a month, therefore it seems there is no acceptable explanation for this delay.

In our study, women were compliant with their appointment date however the delays in treatment contributed to the change in planned treatment highlighting health system related factors. This study highlights that a prolonged waiting time adversely affected the planned treatment in especially HIV positive women with cervical cancer. The deficiency in the health care system include shortage of staff, late referral and delay in initiating the definitive treatment in women with cervical cancer further increases the advanced staged disease burden and eventually less women get radical treatment. Moreover, there is no cancer registry follow-up system to assess recurrent disease or complications in the radiotherapy group. Early referral and short waiting time to definitive treatment will help in changing the situation.

4.2 LIMITATIONS

This was a retrospective study which had limitation regarding the availability of some data such as viral load, HAART initiation in cervical cancer women, and reasons for long waiting time for surgery in HIV positive women.

A proportion of women who were diagnosed with cervical cancer may have died in their base hospital or at home before they reached tertiary level care. HIV related deaths could have occurred in these women who may have died in other wards due to other illnesses.

CHAPTER 5

CONCLUSION AND RECOMMENDATIONS

5.1 CONCLUSION

HIV prevalence was 39% among women presenting with cervical cancer, a disease that is increasing in South Africa. The HIV positive women presenting with cervical cancer did not influence the stage of presentation, but presented at an earlier age than the HIV negative women and were more at risk of developing anaemia. Ninety two percent of women presented in advanced staged disease and required radical or palliative radiotherapy. The long waiting period had significantly affected the HIV positive women with cervical cancer in the surgical group and in the radiotherapy treatment group compared to HIV negative women.

Our study highlighted the need for more radiotherapy services due to advanced stage cancer of cervical cervix at presentation. This could decrease the prolonged waiting period to treatment in these women and thereby improve their 5 year survival outcome.

5.2 RECOMMENDATIONS

The following recommendations are made following this study:

- Establishment of a Cancer registry in South Africa is needed to reflect the magnitude of the cervical cancer burden. It should have a record of the patient and periodic follow up Pap smear after treatment to indicate the survival outcome of treatment given, magnitude of recurrent disease burden, and monitor the survival of these women. In addition, it should keep a record of

complications of treatment, psychosexual morbidity and follow up management of complications and outcome. This would guide our management strategies by enabling periodic audits.

- Pap smear programs for HIV negative and HIV positive women needs to be utilized effectively at every facility to detect cervical dysplasia earlier and refer if indicated. Professional nursing sisters can deliver information about the Pap smear importance, sexually transmitted disease including HIV infection testing to women in gynecology clinics or family planning clinics in each facility similar to mother and child health education in antenatal clinics. In addition, opportunity to educate women about Pap smear who attend antenatal clinics can also be utilized.

Women empowerment is an essential component to improve their health. Health care workers both at hospital and primary health centers must utilize every opportunity to educate women about cervical cancer prevention program and HIV testing. Health facilities need to improve the uptake by adherence to the national cervical cancer screening program and the wellness clinic protocol of annual Pap smears in HIV positive women. Furthermore, community education and acceptability about the prevention programs need to be improved and can be assisted by the media, primary health care workers and by the social and religious scholars in the region.

Survey questionnaires to assess the knowledge of Pap smears and establish utilization of the service among the women attending gynecology clinics need to be conducted regularly to establish the effectiveness of strategies.

The implementation of an effective cervical cancer screening program requires sophisticated health infrastructure which is limited in developing countries. There may be probably the need to consider low cost effective strategies for cervical cancer screening such as Visual Inspection with Acetic Acid and Screen and Treat approach.

- Women with cervical cancer need to be referred and treated earlier to improve the outcome. The health services need to be improved in outreach health facilities and offer periodic in-service refresher courses or training to health care workers and nurses to update their knowledge. Feedback of the magnitude of the disease and outcome may assist them to improve the Pap smear service, prioritize these women with cervical cancer and refer them earlier.

- Continuity of care by the same medical personnel is important in terms of management and outcome which is less practiced in peripheral hospitals due to change over of junior doctors.

- Oncology services need to be increased and staff members recruited to address the long waiting period and prioritize the early stage disease for surgery to improve overall survival.

Recommendations for our department.

In our department oncology services need to be improved in the following sectors.

- More gynaecology-oncology clinics to increase the patient number.
- Increase the number of oncology trained nurses and radiographers to provide chemotherapy and radiotherapy.
- More and new radiotherapy machines are required in the department to serve the major bulk of the advanced stage disease.
- More gynaecology -oncology operating slates to reduce the waiting time for women for their oncology surgery.

After implications of the above changes have been made a repeat audit should be performed to see any improvement in the services and outcome of management in our department.

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APPENDIX A

DATA SHEET

Year ☐ Study No ☐

KZ no. ☐ Age ☐ Parity ☐

Height ☐ Weight ☐ BMI ☐

Race (African=1, Indian=2, white=3, coloured =4) ☐

Medical History: (Hypertension = 1, Diabetes = 2, others=3) ☐

Opportunistic infections (OI) (No=1, Yes=2) ☐

HIV Status: (Negative=1, Positive=2, unknown =3) ☐

CD4 count (<200=1, 200-350=2, >350=3, unknown =4) ☐

HAART (No=1, Yes=2, ref for ARVS=3) ☐

Histology Type: (Squamous cell ca =1, Adenosq. ca= 2, adenoca=3, undiff ca=4, small cell ca=5, others=6) ☐

Grade (Well diff=1, Moderate diff=2, poorly differ=3) ☐

Previous Pap smear (N=1, Y=2, not done =3) ☐ Pap smear not documented ☐

Prev.Colposcopy (N=1, Y=2, NA=3, Normal=4) ☐

Abnormality (CIN=1, HPV infection=2, ca=3, others = 4) ☐

Clinical staging of cervical cancer at IALCH (1-4) ☐

Extent (a=1, b=2, a1=3, a2=4, b1=5, b2=6)

Investigations:

Hb ☐ urea ☐ Creatinine ☐ CXR 2^0 (N=1, Y=2) ☐

Hydronephrosis (N=1, Y=2) ☐ Liver (N=1, Y=2) ☐ Bladder (N=1, Y=2) ☐

Rectum (N=1, Y=2) ☐ Co-incidental findings/others: No=1,yes=2,others=3)

GFR (<60=1, > 60=2) ☐

Zubrod score (1-4) ☐

RX planned at 1st visit: Rx (sx=1, CCRT=2, RRXT=3, PRXT=4, SC=5,others=6) ☐

Date of RX decision= ☐ Date of RX to be given= ☐

Time interval between = ☐

Did the patient return on specified date (N=1, Y=2,) ☐

Was the stage of the disease same (N=1, Y=2) ☐

If No, final stage at f-up visit (1-4): ☐

Initial Rx decided = ☐ Final Rx received = ☐

Any change in Rx (N=1, Y=2) ☐

If Yes, reason (Z score=1, stage=2, shortage of staff=3, patient related factors =4, others=5) ☐

SX received: (CB =1, TAH=2, RH=3, T=4, IC=5, Colos=6, neph=7, other=8) ☐

Stage I (CB =1, TAH=2, RH =3, CCRT=4) ☐

W/Sx (Neg.L.Nodes=1, Pos.L.Nodes=2, nodes not done=3) ☐

W/SX(CCRT=1,No RXT=2, RT=3, No treatment=4) ☐

StageII (SX=1, Adj.RXT=2,No RXT=3,others=4) ☐

Sx complication: (Bleeding=1, VTE=2, Anaesthetic =3, wound infection=4, Burst abdomen =5, others = 6) ☐

RXT complication: (Rad. Cystitis=1, Proctitis=2, Colitis=3, VVF and RVF =4) ☐

Recurrent disease (Y=1) ☐ Mortality (Alive=1, Died =2) ☐

Follow-up plan (Lost/Fup=1, BH/Fup=2, U/Fup=3, No record=4) ☐

(Sx=surgery, CCRT =Concurrent chemo-radiation therapy, PRXT=Palliative radiotherapy, RRXT=radical radiotherapy, PCTX=Palliative chemotherapy, SC=Supportive Care)

(CB =Cone Biopsy, TAH=Total abdominal hysterectomy, RH=Radical Hysterectomy, T=Trachelectomy, IC=Ileal Conduit, Colos=colostomy, neph=nepherostomy, other=8)

(VVF and RVF =Vesicovaginal fistula and Rectovaginal fistula)

(VTE = Venousthromoboembolic phenomena)

APPENDIX B

Revised FIGO staging of cervical cancer

Stage I - Limited to the cervix, divided into Ia & Ib

Ia- Diagnosed only by microscopy; no visible lesions

Ia1 - Stromal invasion less than 3 mm in depth and 7 mm or less in horizontal spread

Ia2 - Stromal invasion between 3 and 5 mm in depth with horizontal spread of 7 mm or less

Ib - Visible lesion or a microscopic lesion with more than 5 mm of depth or horizontal spread of more than 7 mm

Ib1 - Visible lesion 4 cm or less in greatest dimension

Ib2 - Visible lesion more than 4 cm

Stage II - invades beyond cervix (new)

IIa - Without parametrial invasion, but involve upper 2/3 of vagina

IIa1-Involvement of the upper two-thirds of the vagina, without parametrial invasion, Lesions less or equal to 4 cm in greatest dimension

IIa 2- Lesion more or equal to 4 cm in greatest dimension without parametrial involvement

IIb - With parametrial invasion

Stage III - Extends to pelvic wall or lower third of the vagina

IIIa - Involves lower third of vagina with no extension to pelvic side walls

IIIb - Extends to pelvic wall and/or causes hydro-nephrosis or non-functioning kidney

Stage IV - Involve the regional organs & distant metastasis

IVa- Invades mucosa of bladder or rectum

IVb - Distant Metastasis

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03 September 2012

Dr. A Ghani
Derpartment of Obstetrics and Gynaecology
Nelson R Mandela School of Medicine
University of KwaZulu-Natal

Dear Dr Ghani

PROTOCOL: Clinical profile of women presenting with cervical cancer to Inkosi Albert Luthuli Central Hospital. REF:BE074/12

EXPEDITED APPLICATION

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application received on 22 March 2012.

The study was provisionally approved pending appropriate responses to queries raised. Your responses dated 23 August 2012 to queries raised on 27 July 2012 have been noted by a sub-committee of the Biomedical Research Ethics Committee. The conditions have now been met and the study is given full ethics approval and may begin as from 03 September 2012.

This approval is valid for one year from 03 September 2012. To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2004), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be **RATIFIED** by a full Committee at its next meeting taking place on **09 October 2012.**

We wish you well with this study. We would appreciate receiving copies of all publications arising out of this study.

Yours sincerely

Professor D.R Wassenaar
Chair: Biomedical Research Ethics Committee

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16 November 2012

Dr. A Ghani
Derpartment of Obstetrics and Gynaecology
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Dear Dr Ghani

PROTOCOL: Clinical profile of women presenting with cervical cancer to Inkosi Albert Luthuli Central Hospital. REF:BE074/12

We wish to advise you that your correspondence dated 22 October 2012 in response to BREC letter dated 15 October 2012 for the above approved study has been noted by the sub-committee of the Biomedical Research Ethics Committee. Addington approval noted - please note that Addington approval letter also requests KZN Department of Health provincial permission.

Yours sincerely

Mrs A Marimuthu
Senior Administrator: Biomedical Research Ethics

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Durban
4000
KwaZulu-Natal, SOUTH AFRICA
Tel: 27 31 2604769 - Fax: 27 31 2604609
Email: BREC@ukzn.ac.za
Website: http://research.ukzn.ac.za/ResearchEthics/BiomedicalResearchEthics.aspx

13 September 2013

Dr. A Ghani
Derpartment of Obstetrics and Gynaecology
Nelson R Mandela School of Medicine
University of KwaZulu-Natal

Dear Dr Ghani

PROTOCOL: Clinical profile of women presenting with cervical cancer to Inkosi Albert Luthuli Central Hospital. REF: BE074/12

We wish to advise you that your correspondence dated 02 August 2013 requesting Amendment (change of Title of study) for the above approved study has been noted and approved by a sub-committee of the Biomedical Research Ethics Committee.

It is noted that the above title will change to "Clinical Profile of HIV negative and HIV positive Women Presenting with Cervical Cancer in Durban". Your letter dated 26 August 2013 in response to BREC correspondence dated 23 August 2013 informing BREC that all other aspects of the study remains the same has been noted by BREC.

The sub-committee's decision will be noted by a full Committee at its next meeting taking place on **08 October 2013.**

Yours sincerely

Mrs A Marimuthu
Senior Administrator: Biomedical Research Ethics

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

Health Research & Knowledge Management sub-component
10 – 103 Natalia Building, 330 Langalibalele Street
Private Bag x9051
Pietermaritzburg
3200
Tel.: 033 – 3953189
Fax.: 033 – 394 3782
Email.: hrkm@kznhealth.gov.za
www.kznhealth.gov.za

Reference : HRKM134 /12
Enquiries: Mrs G Khumalo
Telephone : 033 – 395 2805

17 September 2012

Dear Dr A Ghani

Subject: Approval of a Research Proposal

1. The research proposal titled **'Clinical profile of women presenting with cervical cancer to Inkosi Albert Luthuli Central Hospital (IALCH)'** was reviewed by the KwaZulu-Natal Department of Health.

The proposal is hereby **approved** for research to be undertaken at Inkosi Albert Luthuli Central Hospital.

2. You are requested to take note of the following:
   a. Make the necessary arrangement with the identified facility before commencing with your research project.
   b. Provide an interim progress report and final report (electronic and hard copies) when your research is complete.

3. Your final report must be posted to **HEALTH RESEARCH AND KNOWLEDGE MANAGEMENT, 10-102, PRIVATE BAG X9051, PIETERMARITZBURG, 3200** and e-mail an electronic copy to hrkm@kznhealth.gov.za

For any additional information please contact Mrs G Khumalo on 033-395 3189.

Yours Sincerely

Dr E Lutge
Chairperson, Health Research Committee
KwaZulu-Natal Department of Health
Date: 17/09/2012.