RESPONSE AND ADHERENCE OF HIV POSITIVE WOMEN TO CERVICAL CANCER TREATMENT

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by

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ABBREVIATIONS

3TC	Lamivudine
AIDS	Acquired Immunodeficiency Syndrome
ARVs	Antiretrovirals
ASCUS	Atypical Squamous Cells of Undetermined Significance
AZT	Zidovudine
CCCMAC	Chemoradiotherapy for Cervical Cancer Meta-analysis Collaboration
CCRT	Concurrent Chemoradiation
CDC	Centers for Disease Control
CIN	Cervical Intraepithelial Neoplasia
CIPN	Chemotherapy Induced Peripheral Neuropathy
CT	Chemotherapy
d4T	Stavudine
DDI/ddI	Didanosine
df	Degrees of Freedom
DNA	Deoxyribonucleic Acid
DVT	Deep Vein Thrombosis
EBRT	External Beam Radiation Therapy
EFV	Efavirenz
FIGO	International Federation of Obstetrics and Gynaecology
Gy	Gray
HAART	Highly Active Antiretroviral Therapy

Hb	Haemoglobin
HIV	Human Immunodeficiency Virus
HSD	Honestly Significant Difference
HSIL	High grade Squamous Intraepithelial Lesions
HPV	Human Papillomavirus
IARC	International Agency for Research on Cancer
ICC	Invasive Cervical Cancer
ICO	Institut Catala d'Oncologia
ICT	Intracavitary
IPD	Individual Patient Data
LEEP/LLETZ	Loop Excision of the Transformation Zone
LMWH	Low Molecular Weight Heparin
LPV	Lopinavir
LSIL	Low grade Squamous Intraepithelial Lesions
NNRTI	Non Nucleoside Reverse TranscriptaseInhibitor
NRTI	Nucleoside Reverse TranscriptaseInhibitor
NVP	Nevirapine
PRT	Palliative Radiotherapy
rhEPO	recombinant human Erythropoietin
RT	Radiotherapy
RTV	Ritonavir
RVF	Rectovaginal Fistula

SA	South Africa
SIL	Squamous Intraepithelial Lesions
STI	Sexually Transmitted Infection
UK	United Kingdom
USA	United States of America
VIA	Visual Inspection using Acetic acid
VTE	Venous Thromboembolism
WHO	World Health Organisation

SUMMARY

It is estimated that 6742 South African women are diagnosed with cervical cancer and 3681 women die from the disease every year. In 1993, The Centers for Disease Control declared cervical cancer an Acquired Immunodeficiency Syndrome defining illness. Apart from persistent human papillomavirus infection, HIV infection is the most common co-factor contributing to cervical cancer in South Africa. Studies have noted that in HIV positive women, there has been an occurrence of faster progression to more advanced stages of cervical cancer with high cases of treatment failure and recurrence. There is limited literature available regarding the prognosis of HIV positive women who suffer from cervical cancer. Women who are HIV positive and have cervical cancer have not been evaluated in detail regarding their response and adherence to cervical cancer treatment. Standard treatment protocols for this set of patients have not been defined.

The aim of this study was to assess how HIV positive women who have been diagnosed with cervical cancer responded and adhered to cervical cancer therapy which includes: curative radiotherapy; curative chemotherapy; concurrent chemoradiation or palliative radiotherapy. The study also evaluated the effects of the concurrent use of antiretrovirals and cervical cancer treatment. This was done to determine whether invasive cervical cancer in women who were HIV positive could be managed using the same treatment protocols as patients who were HIV negative.

A historical cohort design was employed for the study. The study was conducted at the Oncology Department of a tertiary level hospital located in the Eastern Cape Province, South Africa. The total sample consisted of 196 medical records of women diagnosed with cervical cancer between 2005 and 2008. One hundred women were HIV negative, 83 were HIV positive and the HIV status of 13 women could not be determined. The records were audited over a period of two years from the date of diagnosis.

The term ‘complete response’ referred to patients who had no recurrence of cervical cancer and no evidence of metastases after undergoing treatment. At one month following treatment there was a significant difference in the incidence of complete response between the HIV positive patients and the HIV negative patients (Chi^2 =

16.4, d.f. = 1, p = 0.00005, Cramer's V = 0.31). The significant difference in response to treatment between the HIV positive patients and the HIV negative patients was maintained at six months after treatment (Chi^2 = 15, d.f. = 1, p = 0.00011, Cramer's V = 0.34), 12 months after treatment (Chi^2 = 20.5, d.f. = 1, p = 0.00001, Cramer's V = 0.37), 18 months after treatment (Chi^2 = 9.8, d.f. = 1, p = 0.00173, Cramer's V = 0.28) and 24 months after treatment (Chi^2 = 5.0, d.f. = 1, p = 0.02571, Cramer's V = 0.26). At each of these intervals, cases of treatment failure and metastases were significantly higher in the HIV positive women than in the HIV negative women. Although there was no significant difference in the incidence of adherence between the HIV negative women, the HIV positive women who were on HAART and the HIV positive women who were not on HAART, there was a significant difference in the incidence of the various reasons for non adherence between the various groups. These reasons included: missed scheduled appointments (Chi^2 = 2.9, d.f. = 2, p = 0.02385, Cramer's V = 0.31); low blood count (Chi^2 = 4.0, d.f. = 2, p = 0.01327, Cramer's V = 0.15); radiotherapy induced skin breakdown (Chi^2 = 0.6, d.f. = 2, p = 0.04581, Cramer's V = 0.16) and radiotherapy induced diarrhoea (Chi^2 = 6.9, d.f. = 2, p = 0.03118, Cramer's V = 0.19). According to the 2004 National Antiretroviral Treatment Guidelines, cervical cancer patients would fall into the WHO stage IV category of HIV disease thus all patients with confirmed diagnosis of invasive cervical cancer should be commenced on antiretrovirals as soon as the cancer diagnosis is made regardless of their CD4 count. However, in the current study, 13% (n= 83) of the HIV positive women were not on antiretrovirals.

The study concluded that HIV positive women had a higher incidence of both treatment failure and metastases to cervical cancer treatment. Standard radiotherapy and concurrent chemoradiation cervical cancer treatment protocols should be still be used in both HIV negative patients and HIV positive patients so as not to compromise tumour control. Furthermore, in accordance with the antiretroviral treatment guidelines, all HIV positive patients with cervical cancer should receive antiretrovirals irrespective of their CD4 count.

Keywords: adherence; chemotherapy; concurrent chemoradiation; HIV positive; invasive cervical cancer; radiation therapy; response; toxicity.

Chapter 1

INTRODUCTION

1.1 INTRODUCTION

Cervical cancer is the third most commonly diagnosed cancer and the fourth most common cause of cancer deaths in women worldwide, accounting for 9% (529 800) of the total new cancer cases and 8% (275 100) of the total cancer deaths among females in 2008. More than 85% of these cases and deaths occur in developing countries. In developing countries, the incidence rate of cervical cancer is five times higher and the mortality rate is 10 times higher than in developed countries. In South Africa, it is estimated that every year 6742 women are diagnosed with cervical cancer and 3681 women die from the disease. (WHO Organisation Databank, 2010)

In 1993, the Centers for Disease Control (CDC) declared cervical cancer an Acquired Immunodeficiency Syndrome (AIDS) defining illness (Centers for Disease Control and Prevention, 1993:730). In the general population, invasive cervical cancer (ICC) appears at a mean age of between 44 and 52 years. Among Human Immunodeficiency Virus (HIV) positive women, ICC occurs at a mean age of between 30 and 40 years. (Chirenje, 2005:273)

1.2 BACKGROUND

Most cases of ICC can be prevented by screening. Developed countries provide effective screening services which have reduced the incidence of ICC by about 70% to 90%. About 40% to 90% of women in developed countries are screened for cervical cancer; however, less than five percent of women in developing countries undergo cervical cancer screening. (WHO Organisation Databank, 2010) Although a national cervical cancer screening policy was developed and implemented in South Africa in 2000, statistics have shown that less than 20% of South African women have used this service (Department of Health, South Africa, 2000:2). Consequently, cervical cancer cannot be detected in its earlier stages and most women present with locally advanced disease.

There are three methods of treatment for patients with cervical cancer: surgery; radiation therapy (RT) and chemotherapy (CT). Currently, concurrent chemoradiation (CCRT), which is the concurrent use of radiotherapy and chemotherapy, is considered the standard treatment for locally advanced cervical cancer. However, around 30% of patients with ICC will die due to local tumour relapse or the development of distant metastases. (National Cancer Institute, 1999)

Advances in Antiretrovirals (ARVs) continue to improve the prognosis of HIV positive individuals. Thirty six percent (971 556) of the 5.6 million HIV positive South Africans were receiving ARVs in December 2009 (UNAIDS, 2010:113). At present, women on ARVs have a higher life expectancy thus there should be a focus on long term management. Women who are HIV positive have a higher risk of developing AIDS defining illnesses such as cervical cancer. There is limited literature available regarding the prognosis of HIV positive women who suffer from cervical cancer. Women who are HIV positive and have ICC have not been evaluated in detail regarding their response and adherence to cervical cancer treatment. Standard treatment protocols for this set of patients have not been defined.

1.3 RESEARCH AIM AND OBJECTIVES

The aim of this study was to assess how HIV positive women who have been diagnosed with cervical cancer responded and adhered to cervical cancer therapy which includes: curative RT; CCRT or palliative radiotherapy (PRT). The study also evaluated the effects of the concurrent use of ARVs and cervical cancer treatment. This was done to determine whether ICC in HIV positive women could be managed using the same treatment protocols as ICC in HIV negative women.

In order to achieve the aim the following objectives were required to be fulfilled:

- The assessment of the patients' response to cervical cancer treatment. This involved the analysis of test results such as: laboratory tests; ultrasound; audiogram and cystogram. The clinician's rectal and vaginal physical examination results were included in the assessment.
- The effects of the use of ARVs on the patients' response to cervical cancer treatment was also determined. This was achieved by assessing the response to

cervical cancer treatment in: HIV positive patients who were on ARVs; HIV positive patients who were not on ARVs and HIV negative women.

- The patients' adherence to cervical cancer treatment was also determined in order to identify the extent to which tumour recurrence or metastases occurred due to failure to complete treatment. This was determined by looking at the patients' total number of prescribed doses, the number of missed doses and the reasons for missing the dose.
- The relationship between patient response and several prognostic factors such as the patients' age, tumour size and the duration of cervical cancer treatment was also assessed.

1.4 RESEARCH DESIGN

A historical cohort study design was employed for the study. The study was historical because the events that were evaluated took place before the onset of the study. The cohort consisted of all women diagnosed with cervical cancer between 2005 and 2008. Cohort studies are the most suitable for studying the course of a disease, for instance the course of cervical cancer. They possess the correct time sequence to provide the strong evidence for possible causes and effects, as in the effect of CCRT/RT in cervical cancer patients. (Dawson & Trapp, 2001:10-19)

1.5 SAMPLE AND SETTING

The study was conducted at the Oncology Department of a tertiary level hospital located in the Eastern Cape Province, South Africa. The Oncology Department at the study site treats about 200 cervical cancer patients annually (newly diagnosed and follow up cases) and provides RT and CT for curative or palliative purposes.

The sample was a total sample in that it consisted of the medical records of all HIV positive and HIV negative women diagnosed with cervical cancer between 2005 and 2008 who were older than 18 years of age at the time of diagnosis and received CT, RT, CCRT or PRT. The medical files of patients who only received surgical treatment and patients who were younger than 18 years of age at the time of diagnosis were excluded from the study.

1.6 DATA COLLECTION

A researcher completed questionnaire, which was referred to as an audit form, was employed as the data collection tool. Data was collected by reviewing the patients' medical records and noting the information on the audit form. A pilot study was conducted on the 5th and 6th of August 2010. Ten medical records of women diagnosed with cervical cancer in 2004 were reviewed in order to test the reliability and reproducibility of the audit form. Data collection for the main study occurred over a three month period, from September to November 2010. A retrospective review of case records of women diagnosed with cervical cancer between 2005 and 2008 was performed. The record of each patient was audited for a two year period from the date of diagnosis.

1.7 ETHICAL CONSIDERATIONS

The research proposal was submitted to the Faculty of Health Science Research Technology and Innovative Committee and to the Research Ethics Committee-Human at NMMU in order to obtain ethical approval. Permission was also requested from the Head of the Oncology Department at the study site. The letter of approval from the Research Ethics Committee Human is included as Appendix 1 (ethics clearance number: H10-HEA-PHA-001) and the letter of approval from the Head of Oncology Department at the study site is included as Appendix 2. Confidentiality was maintained at all times during the study. No patient identifiers were linked to the data. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki (World Medical Association, 2008).

1.8 RELEVANCE OF THE STUDY

With an estimated 5.6 million people living with HIV, of which 3 million were women above 15 years of age, South Africa's epidemic remains the largest in the world. Apart from persistent human papillomavirus (HPV) infection, HIV is the most common co-factor contributing to cervical cancer in South Africa. The adult (15 to 49 years) prevalence rate of HIV is 18.1%, thus there is a large proportion of South African HIV positive women who are susceptible to cervical cancer. (UNAIDS, 2010:30) Additionally, cervical cancer is the most common cancer in black South African females, with a risk of 1 in 26, compared with 1 in 83 in white females (WHO Organisation Databank, 2010).

Studies have noted that in HIV positive women, there has been an occurrence of faster progression to more advanced stages of cervical cancer with high cases of treatment failure and recurrence. (Silverberg *et al*., 2006:511-513) Therefore, there is a need to determine whether HIV positive women with cervical cancer should be managed in the same way as their HIV negative counterparts, as is the current practice or whether different protocols should be developed.

1.9 OUTLINE OF THE STUDY

The first chapter provides an outline of the background to the study, the rationale for the study and a list of the aim and objectives. The literature review of the study is outlined in chapters two and three. Chapter two entails a detailed discussion on cervical cancer and the link between HIV/AIDS and cervical cancer. The main focus of chapter three is the use of CCRT as the standard treatment for advanced cervical cancer in both HIV positive and HIV negative women.

Chapter four contains a detailed outline of the study methodology. The limitations of the study are also outlined in chapter four. The results of this study are presented and discussed in chapter five. Chapter six summarises the chief findings of the study and provides recommendations, which are based on the most significant observations of this study.

Chapter 2

HUMAN PAPILLOMAVIRUS AND CERVICAL CANCER

2.1 INTRODUCTION

The human papillomavirus is the causative agent of many sexually transmitted diseases. About 75% of sexually active women and men in the world will probably be infected with at least one or several types of HPV during their sexual life. (Baseman & Koutsky, 2005:S16) Most HPV infections can be cleared within 14 months in immunocompetent women. However, persistent HPV infection occurs in immunocompromised women, resulting in cervical dysplasia and cancer. The HPV types are classified as either high risk or low risk depending on their propensity to disrupt the normal cell cycles and lead to the development of malignancy. There are more than 150 types of HPV. (Knodel, 2008:1929 and Firnhaber & Michelow, 2009:23) Of these, 12 are classified as low risk (6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81 and CP6108), three as probable high risk (26, 53 and 66) and 15 as high risk (16, 18, 31, 33, 35, 39, 45, 51 52, 56, 58, 59, 68, 73 and 82). Infection with HPV-16 and HPV-18 causes approximately 70% of cervical cancer and 50 to 60% of cervical precancerous lesions (Table 2.1). Table 2.1 illustrates the proportion of cervical cancer caused by the different HPV types. (Smith *et al*., 2007:622)

Table 2.1: The proportion of cervical cancer caused by the different HPV types

HPV type	Proportion of cervical cancer caused (%)	HPV type	Proportion of cervical cancer caused (%)
16	54.6	59	1.1
18	15.8	56	0.8
33	4.4	51	0.7
45	3.7	39	0.7
31	3.5	73	0.5
58	3.4	68	0.5
52	2.5	82	0.2
35	1.8	Not identified	5.2

Source: Smith *et al*., 2007:622.

2.2 CERVICAL CANCER

Cervical cancer is the third most commonly diagnosed cancer and the fourth most common cause of cancer deaths in women worldwide, accounting for 9% (529 800) of the total new cancer cases and 8% (275 100) of the total cancer deaths among females in 2008. (WHO Organisation Databank, 2010)Overall, cervical cancer is the second leading cancer in South African women and the leading cancer in black South African women. Up to 30% of these patients are HIV positive. (Mqoqi *et al*., 2004:21-22)

Table 2.2 outlines the HIV/AIDS and cervical cancer statistics from the United States of America (U.S.A.), the United Kingdom (U.K.), South Africa (S.A.) and Kenya. Cervical cancer ranks as the most frequent cancer in the developing countries, Kenya and South Africa and has a lower incidence ranking in the developed countries, U.S.A and U.K. (13^{th} and 11^{th} respectively) (Table 2.2).

Table 2.2: HIV/AIDS and cervical cancer statistics, 2009

	U.S.A.	**U.K.**	**S.A.**	**KENYA**
Population of women (millions)	122.84	25.51	16.84	10.32
HIV prevalence (%) in adults aged 15-49 years	0.4	0.4	16.9	7.8
Age standardised incidence rate	7.7	8.3	37.5	28.7
Age standardised mortality rate	2.3	3.1	21	23.4
Annual number of new cases	13162	3181	6742	2635
Annual number of deaths	5214	1529	3681	2111
Incidence ranking of cervical cancer (all ages)*	13^{th}	11^{th}	1^{st}	1^{st}
Mortality ranking of cervical cancer (all ages)*	12^{th}	11^{th}	1^{st}	1^{st}
Incidence ranking of cervical cancer (15-44 years)*	4^{th}	2^{nd}	1^{st}	2^{nd}
Mortality ranking of cervical cancer (15-44 years)*	8^{th}	2^{nd}	1^{st}	1^{st}
Most frequent HPV type among women with cervical cancer	16	16	16	16

Rates are per 100,000 women per year.
*Ranking among all cancers
Sources: UNAIDS, 2009.

WHO/ICO Information centre on HPV and cervical cancer, 2010.

2.2.1 Development of cervical cancer

Cervical cancer develops in four steps: HPV transmission, viral persistence, progression of persistently infected cells to precancer and invasion. The reverse process can also occur, for instance, clearance of HPV infection and regression of precancer to normality. (Schiffman *et al*., 2007:892)

2.2.2 Classification

There are two classification systems used to describe cervical carcinoma precursor lesions: the World Health Organisation (WHO) system and the Bethseda system. The WHO system uses the term, Cervical Intraepithelial Neoplasia (CIN) to describe the abnormal cervical lesions. Mild dysplasia is classified as CIN1, moderate dysplasia as CIN2 and severe dysplasia as CIN3. The Bethseda System is the most recent and widely used classification system. It divides all cervical epithelial precursor lesions into two groups: Low grade squamous intraepithelial lesions (LSIL) which corresponds to CIN1 and High grade squamous intraepithelial lesions (HSIL) which corresponds to CIN2 and CIN3. (Cancer Research UK, 2009) Precancer includes the diagnoses of CIN3, severe dysplasia or carcinoma in situ (Von Knebel, 2002:2231).

Non-carcinogenic types of HPV can sometimes produce CIN2, thus the diagnoses of CIN1 and CIN2 is not precancer. In addition, errors that might have occurred during the processing and interpretation of the cervical tissue biopsy might lead to CIN1 diagnosis. Diagnosing CIN1 does not necessarily predict a higher risk of CIN3 than a negative biopsy. (Cox *et al*., 2003:1410)

The time between infection and microscopic evidence of precancer is often within 5 years. The average age of diagnosis of precancer is between 25 and 35 years and depends on the age at first sexual intercourse. (Herrero *et al*., 2005:1797) In some cases, precancer has been diagnosed within 2 years of sexual debut (Woodman *et al*., 2001:1831). The strongest risk factor for precancer diagnosis is the HPV type. For instance, persistent HPV-16 infection has a 40% risk of a precancer diagnosis, after 3 to 5 years of persistent infection. (Khan *et al*., 2005:1075) A woman with several HPV types has a higher risk of precancer than a woman with any one of the

HPV types. However, it is unknown whether the total risk of precancer for the woman with several HPV types is greater than the sum of the risks of individual HPV types. (Herrero *et al*., 2005:1796-1802)

Invasive cancer involves the integration of the HPV genome into the host genome. In the general population, ICC is observed in women between 44 and 52 years. The average time between HPV infection and development of precancer appears to be shorter than the time it takes for precancer to develop to ICC. (Peitsaro *et al*., 2002:886-887)

2.2.3 Signs and symptoms

Symptoms usually do not appear until abnormal cervical cells become cancerous. The most common symptom in the early stages is abnormal vaginal bleeding which may start and stop between regular menstrual periods, or after sexual intercourse, douching, or a pelvic exam. Menstrual bleeding may last longer and be heavier than usual. In addition, bleeding after menopause or increased vaginal discharge may also be symptoms of cervical cancer. Symptoms of advanced disease include voiding problems, lower back pain, leg pain, lymphoedema, weight loss and uraemia. (American Cancer Society, 2009:22)

On physical examination, an ulcerating tumour originating from the cervix can be seen. The tumour may be confined to the cervix but it usually grows into the vagina. Histological examination of the tissue biopsy confirms the diagnosis. (Ansink, 2007:69)

2.2.4 Risk factors

Apart from persistent HPV infection, there are socio-cultural, socio-economic and biological risk co-factors for HPV infection (Table 2.3). The socio-cultural co-factors include: early marriage; polygamy and high parity. In addition, low socioeconomic status among HPV infected women might be a risk co-factor because poverty is one of the barriers that hinder effective prevention and treatment of cervical cancer. The biological co-factors include: family history of cervical cancer; HIV infection; Sexually Transmitted Infections (STI) (chlamydia, gonorrhoea, herpes type 2); and poor nutritional status. (Anorlu, 2008:42-43) Other risk co-factors for cervical cancer are

smoking and long term use of hormonal contraception (Firnhaber & Michelow, 2009:23).

Table 2.3: Co-factors contributing to cervical cancer

Co-factor	
Socio-cultural factors	Early marriage, polygamy, high parity
Socio-economic factors	Poverty
Biological factors	Family history, HIV infection, STI infection, poor nutritional status
Other factors	Smoking, long term use of hormonal contraception

Sources: Anorlu, 2008:42-43 and Firnhaber & Michelow, 2009:23.

2.2.5 Stages of cervical cancer

The International Federation of Obstetrics and Gynaecology (FIGO) staging system is used for cervical cancer (Table 2.4). Cervical cancer can spread through three ways. Firstly, by spreading directly into the cervical stroma, parametria and then into the vagina, uterus, bladder and the rectum. Secondly, cervical cancer can spread through the lymph nodes, first to the parametrial nodes then to the pelvic nodes and the para-aortic nodes. This is the main way that cervical cancer spreads. Finally, cervical cancer can spread through the blood, although this is unusual. (Ansink, 2007:69)

Table 2.4: FIGO staging for cervical cancer

Stage 0	Carcinoma in situ, cervical intraepithelial neoplasia Grade III.
Stage I	The carcinoma is strictly confined to the cervix. (extension to the corpus would be disregarded)
IA	Invasive carcinoma which can only be diagnosed only by microscopy. All macroscopically visible lesions –even with superficial invasion-are allotted to Stage IB carcinomas. Invasion is limited to a measured stromal invasion with a maximal depth of 5.0 mm and a horizontal extension of not more than 7.0 mm. Depth of invasion should not be greater than 5.0 mm taken from the base of the epithelium of the original tissue-superficial or glandular. The involvement of vascular spaces, venous or lymphatic, should not change the stage allotment.
Stage IA1	Tumour limited to the cervix, invasion of not greater than 3 mm in depth and extension of not greater than 7 mm
Stage IA2	Tumour limited to cervix, invasion between 3 and 5 mm and extension of not greater than 7 mm
Stage IB	All larger tumours that are limited to the cervix or preclinical cancers greater than Stage IA.
Stage IB1	Clinically visible lesions not greater than 4.0 cm
Stage IB2	Clinically visible lesions greater than 4.0 cm
Stage II	Cervical carcinoma invades beyond the uterus, but not to the pelvic wall or to the lower third of the vagina.
Stage IIA	Tumour with extension to upper two thirds of vagina. No obvious parametrial involvement.
Stage IIB	Tumour with extension to parametria, pelvic side wall is not involved

Stage III	The carcinoma has extended to the pelvic wall. On rectal examination, there is no cancer free space between the tumour and the pelvic wall. The tumour involves the lower third of the vagina. All cases with hydronephrosis or non functioning kidney are included, unless they are known to be due to other causes.
Stage IIIA	Tumour with extension into lower one third of vagina, with no extension to the pelvic wall.
Stage IIIB	Tumour extended to pelvic side wall and/or hydronephrosis
Stage IV	The carcinoma has extended beyond the true pelvis, or has involved the mucosa of the bladder or rectum (biopsy-proven).
Stage IVA	Invasion into bladder and/or rectum
Stage IVB	Distant metastases

Source: Ansink, 2007:68-69.

2.2.6 Treatment

2.2.6.1 Treatment of pre-invasive lesions

The majority of pre-invasive lesions can be effectively treated by cryotherapy, large loop excision of the transformation zone (LEEP/LLETZ) or conisation. In cryotherapy, the abnormal cells are frozen and killed using a metal probe cooled with nitrous oxide. Carbon dioxide can be used as an alternative gas in remote areas because it is cheaper and is readily available; however, it often blocks equipment. Cryotherapy is suitable in low resource settings because it can be provided without local anaesthesia or electricity. This method's main disadvantage is that the patients require a few weeks to recover and might experience discharge with some possibility of infection. (Seamans *et al*., 2006:2)

The LEEP or LLETZ procedure involves the use of a thin wire heated with electricity to remove tissue from the cervix. This method is often preferred as it can be done as an outpatient procedure with local anaesthesia and it removes a small amount of cervical tissue. Cold knife conisation is used when extensive tissue removal is needed. Hysterectomy would also be another appropriate treatment option if LEEP or cold knife conisation are not feasible and if fertility is not desired. (Kyrgiou *et al*., 2006:493)

Cytology and HPV testing are used to assess the efficacy of the LEEP procedure. Patients who have been successfully treated test HPV negative. The women testing HPV negative four to six months after the LEEP procedure have no significant risk of recurrent CIN2 within the subsequent two or more years. The women who test HPV positive must be closely monitored in order to prevent the development of ICC. (Arbyn *et al*., 2005:S7-10)

2.2.6.2 Treatment of invasive cancer

In general, both immunocompetent and HIV positive women are managed in the same way. However, HIV positive women must be closely monitored for both therapeutic efficacy and unusual toxicity. (Msadabwe, 2009:34) Developing countries

lack adequate resources and skills thus standard treatment for cervical cancer as described in textbooks is not often feasible.

2.2.6.3 Guideline recommendations for the management of cervical cancer

The possible options recommended for the treatment of cervical cancer are summarised in Table 2.5. These recommendations were obtained from the 2008 British Associated Guidelines for HIV associated malignancies and from the United States National Cancer Institute website. The British and the American guidelines are identical and are used to manage the various stages of cervical cancer (Bower *et al*., 2008:359-360 and United States National Cancer Institute, 2010). The South African Department of Health has not published guidelines for the management of cervical cancer, thus the study site used the recommendations from the British and American guidelines to manage the cervical cancer patients at the study site.

Table 2.5: U.K. and U.S.A. guideline recommendations for the management of cervical cancer

Stage	Treatment options
IA	1. Total hysterectomy: if the depth of invasion is less than 3 mm and no vascular or lymphatic channel invasion is noted, Oophorectomy is optional and should be deferred for younger women. 2. Conization: In women wishing to preserve fertility, if the depth of invasion is less than 3 mm, no vascular or lymphatic channel invasion is noted, and the margins of the cone are negative. 3. Modified radical hysterectomy: For patients with tumour invasion between 3 mm and 5 mm and for patients where the depth of tumour invasion was uncertain because of invasive tumour at the cone margins. 4. Intracavitary radiation therapy alone: For women who are not surgical candidates, if the depth of invasion is less than 3 mm and no lymphatic invasion is noted. The recommended dose is 100 Gy to 125 Gy.
IB/IIA	1. Radiation therapy: External beam pelvic radiation therapy combined with two or more intracavitary brachytherapy applications. Radical hysterectomy and bilateral pelvic lymphadenectomy. 2. Postoperative total pelvic radiation therapy plus chemotherapy following radical hysterectomy and bilateral pelvic lymphadenectomy: The recommended radiation dose is 50 Gy that should be administered for five weeks plus chemotherapy with cisplatin with or without fluorouracil (5-FU) for patients at high risk of recurrence including those with positive pelvic nodes, positive surgical margins, and residual parametrial disease. 3. Radiation therapy plus chemotherapy with cisplatin or cisplatin/5-FU for patients with bulky tumours.
IIB/III/IVA	1. Radiation therapy plus chemotherapy: Intracavitary radiation therapy and external beam pelvic radiation therapy to the pelvis combined with cisplatin or cisplatin/fluorouracil.

Stage	Treatment options
IVB	No standard chemotherapy treatment that provides substantial palliation is available. Therefore, these patients are suitable candidates for clinical trials testing single agents or combination chemotherapy agents listed below or new anticancer treatments in phase I and II clinical trials. 1. Radiation therapy may be used to palliate central disease or distant metastases. 2. Chemotherapy. • Cisplatin (15%–25% response rate). • Ifosfamide (31% response rate). • Paclitaxel (17% response rate). • Ifosfamide/cisplatin. • Irinotecan (21% response rate in patients previously treated with chemotherapy). • Paclitaxel/cisplatin (46% response rate). • Cisplatin/gemcitabine (41% response rate). • Cisplatin/topotecan (27% response rate).

Stage	Treatment options
Recurrent disease	No standard chemotherapy treatment that provides substantial palliation is available. Therefore, these patients are suitable candidates for clinical trials testing single agents or combination chemotherapy agents listed below or new anticancer treatments in phase I and II clinical trials. 1. For recurrence in the pelvis following radical surgery, radiation therapy in combination with chemotherapy (fluorouracil with or without mitomycin) may cure 40% to 50% of patients. 2. Chemotherapy can be used for palliation. • Cisplatin (15%–25% response rate). • Ifosfamide (15%–30% response rate). • Paclitaxel (17% response rate). • Irinotecan (21% response rate in patients previously treated with chemotherapy). • Bevacizumab (11% response rate). • Ifosfamide/cisplatin. • Paclitaxel/cisplatin (46% response rate). • Cisplatin/gemcitabine (41% response rate). • Cisplatin/topotecan (27% response rate). • Cisplatin/vinorelbine (30% response rate).

Sources: Bower *et al*., 2008:359-360 and United States National Cancer Institute, 2010.

2.2.7 Prognosis

There are several prognostic factors that influence the survival of cervical cancer patients. These factors include: patient characteristics (age, blood haemoglobin level); tumour characteristics (stage, lymph node involvement, size of tumour); and treatment characteristics (doses, duration of treatment). (Borowsky *et al*., 2005:E19)

2.2.7.1 Patient characteristics: age and blood haemoglobin (Hb) level

It is believed that cervical cancer in younger patients is more aggressive than in older ones (Brewster *et al*., 1999:1466). However, age is not an independent prognostic factor for the survival of cervical cancer patients due to the selection of different treatment options. Younger women with small tumours undergo surgical treatment, while women of the same age with bigger tumours usually receive radiotherapy. Therefore, poor prognosis cannot be related to age alone. (Ho *et al*., 2004:461)

Blood Hb level is an independent prognostic factor for the overall survival, disease free survival and the local control of the tumours. However, it has no prognostic value for distant metastases free survival. The link between anaemia, a condition associated with low Hb levels and poor prognosis in cervical cancer patients remains unclear. One theory suggests that anaemia is usually present at the moment of diagnosis in patients with poor prognosis. Therefore tumour related anaemia is a sign of tumour aggressiveness. In these cases, correction of the Hb level during treatment will have no impact on the effect of the treatment. (Grogan *et al*., 1999:1528)

Another theory suggests that the relationship between anaemia and poor prognosis of cervical cancer could be linked to poor tumour sensitivity to RT due to decreased oxygen supply. In these cases, correction of the Hb level during treatment could have a positive impact on the effect of the treatment. (Grogan *et al*., 1999:1528)

More severe anaemia develops in patients treated with CCRT than with RT alone, because of the additive myelosuppressive effect of chemotherapeutic drugs. Therefore, effective prevention and management of anaemia is essential in order to improve the prognosis of cervical cancer patients. (Kim *et al*., 2007:199)

2.2.7.2 Tumour characteristics: clinical stage and lymph node involvement

Although clinical stage is one of the main prognostic factors in cervical cancer patients, it depends on other factors such as lymph node involvement and the selected treatment option (Waggoner, 2003:2217). It has been found out that rapid disease progression and a shorter survival occurs in patients whose lymph nodes are more than 10 mm before treatment (Ho *et al*., 2004:463).

2.2.7.3 Treatment characteristics

The prognosis of cervical cancer depends on when treatment is initiated. Detection and treatment of cervical cancer in its earliest stages significantly improves prognosis. This is due to the fact that treatment of local lesions is more effective than systemic treatments such as CT. (Committee on Practice Bulletins-Gynaecology, 2002:857) With treatment, the five year relative survival rate for the earliest stage of invasive cervical cancer is 92% and the rate for all the stages combined is 72% (American Cancer Society, 2009:22). Approximately, 80% to 90% of women with stage I cancer and 50% to 65% of women with Stage II cancer who receive treatment are still alive five years after diagnosis. Only 25% to 35% of women with Stage III cancer and 15% or less of women with Stage IV cancer are alive five years after diagnosis. (Gershenson & Ramirez, 2008)

According to literature, the longer the duration of chemoradiotherapy, the shorter the overall survival, disease free survival and local control of the tumour (Waggoner, 2003:2223 and Taylor *et al.*, 1990:97). The American Brachytherapy Society recommends that the total treatment duration for cervical cancer should be less than eight weeks (Nag *et al*., 2000:202). Prolonging the duration of treatment could interfere with the therapeutic effect of CCRT (Green *et al*., 2001:785 and Lukka *et al*., 2002:209).

2.2.8 Prevention of cervical cancer

There are primary and secondary prevention strategies. The primary prevention strategies include creating awareness, implementing safe sexual practices, smoking avoidance, good nutrition and HPV vaccination. Secondary prevention strategies

include cytology, visually inspecting the cervix and HPV deoxyribonucleic acid (DNA) testing. (Firnhaber & Michelow, 2009:24)

2.2.8.1 Primary prevention strategies

2.2.8.1.1 Creating awareness

This involves educating women about the causes, risk factors, symptoms and prevention strategies of cervical cancer. (Firnhaber & Michelow, 2009:24)

2.2.8.1.2 Implementing safe sexual practices and family planning methods

It is important to adopt safe sexual practices such as the use of condoms. A study showed that regular use of condoms may increase HPV clearance and increase the rate of regression in HIV negative women. However, the impact of condom use on HPV transmission in HIV positive women remains unknown. (Holmes *et al*., 2004:456) In addition, the rate of HPV transmission may be lower in circumcised males (Castellsague *et al*., 2002:1107). The tough keratinised epithelium of the circumcised penis might decrease male HPV infection and carriage. Supposedly, the mucosal epithelium of the uncircumcised penis is more susceptible to HPV infection and replication. The keratinised stratified squamous epithelium provides better protection from HPV infection than the mucosal epithelium. (Thompson *et al*., 2004:1567-1571)

Family planning is also important because it helps an individual to attain the desired number of children thus avoiding multiparity. A study conducted in Mali to determine the association between parity and invasive cervical cancer found that women with higher parity were more likely to have cervical cancer than women of lower parity, with the risk of cervical cancer increasing by 1.1 times for each additional birth. (Bayo *et al*., 2002:204) Other case control studies conducted by the International Agency for Research on Cancer (IARC) reported that women with HPV infection who had seven or more full term pregnancies were four times more likely to develop cervical cancer as compared to nulliparous women with HPV infection. Furthermore, a two-fold increased risk of cervical cancer was noted in women who had HPV infection and had one or two full term pregnancies. (Munoz *et al.*, 2002:1096) Similar

results were also obtained in cohort studies conducted in Costa Rica, Thailand and United States (Castellasague & Munoz, 2003:20-28).

It has been suggested that parity is a marker of the oestrogen-hormonal environment throughout the fertile years of women as well as a marker of repeated cervical trauma among women who are highly parous. Oestradiol has been noted to induce immortalization of HPV infected cells. (Bayo *et al*., 2002: 204)

2.2.8.1.3 Smoke avoidance

Cohort studies in Costa Rica, Portland, Copenhagen and Manchester were conducted to explore a link between cigarette smoking and cervical cancer. The participants were divided into 'currently smoking vs. never smoked' women who had HPV infection. The studies indicated that women who reported that they had ever smoked were two times more likely to have cervical cancer than women who had no history of smoking. These studies provided evidence that cigarette smoking can increase the risk of cervical cancer in women with persistent HPV infection. (Castellasague & Munoz, 2003:20-28) This evidence was reviewed in 2002 by the monograph programme at IARC and cigarette smoking was found to be an independent risk factor for cervical cancer (IARC, 2002).

Studies have suggested that chemicals such as benzopyrene from cigarette smoke damage the cervix and make it vulnerable to HPV infection (Plummer *et al*., 2003: 810). There is some evidence that smoking cessation can resolve HPV induced cervical abnormalities (Prokopczyk *et al*., 1997:871). Health workers should advise women with cervical abnormalities to stop smoking in order to prevent the progression of precancer to ICC.

2.2.8.1.4 HPV vaccination

Two vaccines, Cervarix® and Gardasil® provide protection against some HPV types. Cervarix® provides protection against HPV types 16 and 18, while Gardasil® protects against HPV types 6, 11, 16 and 18. Approximately 70% of cervical cancer is caused by HPV types 16 and 18. These vaccines target females between the ages of 9 and 26 years because the vaccine only works if given before HPV infection occurs. Therefore, the timing of HPV vaccination requires knowledge of the median

age of sexual debut in the population. Health workers are thus targeting females before they start having sex and become exposed to HPV or HIV. The vaccines are administered as three 0.5 ml intramuscular injections over a six month period. The duration of protection is not yet known, but there is evidence of protection for at least five years after vaccination. (Sankaranarayanan, 2007:5-9) Larger studies are currently being conducted in Nordic countries to evaluate longer term duration. (Firnhaber & Michelow, 2009:25)

Multivalent vaccines which target a wide range of HPV types are being tested (Schiller & Nardelli-Haefliger, 2006:S148). There is also a therapeutic HPV vaccine that is in the early phases of testing. This vaccine will be given to women who are already infected with HPV to prevent the progression of the virus. (De Jong *et al*., 2002:3456)

Unfortunately, the vaccines are very expensive and very few countries have programmes to fund HPV vaccination (Table 2.6). Currently there are two vaccines that are available in South Africa, Cervarix® and Gardasil®. These vaccines were introduced in 2008 but are not yet available in the public health sector. (Harries *et al.,* 2009:39) Furthermore, cervical screening may still be required as 30% of cervical cancer is caused by HPV types other than 16 and 18. The use of the HPV vaccines in men and the duration of immunity is unknown. (Knodel, 2008:1929 and Firnhaber & Michelow, 2009:25) Vaccination could also increase the risk of irresponsible sexual behaviour because people might think that once they are vaccinated they are completely immune to developing cervical cancer (Rydstorm & Tornberg, 2006:301). The safety and efficacy of HPV vaccines in HIV positive women is still unclear because it is not known whether a sufficient antibody response to the vaccine will be obtained. (Firnhaber & Michelow, 2009:25)

Table 2.6: HPV vaccine programmes in U.S.A., U.K., S.A. and Kenya

	U.S.A.	U.K.	S.A.	KENYA
Bivalent vaccine (Cervarix)	No	Yes	Yes	Yes
Quadrivalent vaccine (Gardasil/Silgard)	Yes	Yes	Yes	Yes
HPV vaccine schedule	11-12 years	12-13 years x 3	No	No
Introduction in entire or part of the country	Entire	Entire	Part	Part

Source: WHO/Institut Catala d'Oncologia (ICO) Information centre on HPV and cervical cancer, 2010.

2.2.8.2 Secondary prevention strategies

Cervical cancer, unlike other cancers, can be prevented but is fatal if left untreated. Screening programmes detect the disease at an early stage thus reduce the cases of cervical cancer. These programmes are based on cervical smears. There are three methods used to detect cervical abnormalities: cervical cytology; visual inspection using acetic acid (VIA) and HPV DNA testing. (Firnhaber & Michelow, 2009:24) Although most cervical abnormalities clear without treatment, close monitoring is still needed as most precancers and cancers are diagnosed in women with abnormal cytological findings (Kinney *et al*., 2006:973).

Usually women are screened and if any abnormalities are detected, the women are referred to a colposcopy centre for a colposcopic biopsy. The biopsy is used to diagnose precancer or to make distinctions such as CIN1, 2, or 3. The biopsy also provides information about the location and extent of disease which is important for choosing the most appropriate treatment option. (Ferris & Litaker, 2006:706-708) Once the diagnosis is confirmed, women are referred for treatment (Firnhaber & Michelow, 2009:24).

Cervical cytology involves the use of the Papanicolaou test, or Pap smear for cervical cancer screening. Cells from the cervix are collected using a brush, put on a microscope slide and screened by a cytologist for abnormalities. It is the only proven method for reducing the incidence and mortality of cervical cancer in large-scale population screening.The range of sensitivities and specificities of conventional cytology for the detection of HSIL in screening studies are 40% to 86% and 88% to 99%, respectively. However, in routine screening settings the estimated sensitivity

for HSIL is only 50% to 60%. Cytology is also associated with a significant false negative rate. (Firnhaber & Michelow, 2009:25) Pap smear screening involves people who are skilled in collecting the smears, cytologists, pathologists, laboratory services and an effective follow up system. These professionals are often lacking in developing countries. (Ansink, 2007:68)

Precancerous lesions can be highlighted by VIA so that the lesions can be viewed with the naked eye. The cervix is inspected with the naked eye before and after application of acetic acid. The sensitivity for detecting HSIL ranges from 66% to 96% and the specificity from 64% to 98%. (Firnhaber & Michelow, 2009:25)

The VIA method has several advantages: the results are available immediately thus avoiding the need for multiple visits in most cases, and reducing loss to follow-up; it can be taught to nurses, midwives and other health workers in a short space of time and it costs less than other approaches such as cervical cytology in routine use because no specimen transport, expensive laboratory equipment or highly trained professions are needed. (Firnhaber & Michelow, 2009:26)

The disadvantages of VIA include: low specificity – a considerable number of women who test positive do not have disease, resulting in unnecessary anxiety and treatment; lack of standardised methods of quality control because there is no permanent record of the test and the results highly depend on the accuracy of the screener's interpretation. Moreover, the efficacy and cost-effectiveness of large scale VIA based population screening programmes in reducing the incidence of, and mortality from, cervical cancer are not known. Most of the time, VIA has been evaluated as a once in a lifetime screening test, and its performance in periodic screening has not been assessed. (Firnhaber & Michelow, 2009:26)

One advantage of the HPV DNA testing method is that this method does not require subjective interpretation of the results like the Pap smear and VIA (Knodel, 2008:1929). Unfortunately, HPV DNA testing is expensive, it depends on reagents that are currently produced by very few commercial manufacturers, and has low specificity in younger women. In addition, the tests need to be transported to the laboratory and highly trained personnel are required to carry out the tests. The patients need to return to the clinic for results, so there is potential loss to follow-up.

The required resources are often not available in developing countries. A rapid HPV test, the HPV Digene Fast Test, has been developed for use in countries with low resources. The test eliminates the need for laboratories. (Firnhaber & Michelow, 2009:26)

The best method of screening in both HIV positive and HIV negative women has yet to be determined. Even though there is no evidence that VIA is more accurate than Pap smears, VIA might decrease the proportion of inadequate smears. Inadequate smears are not abnormal smears. They are observed in settings like the tropics where conventional smears are susceptible to air drying or where there is widespread cervical inflammation. Thus VIA may decrease the risk of interpreting inadequate smears as abnormal smears and avoid patient anxiety and unnecessary treatment. (Ronco *et al*., 2007:28)

2.2.9 Barriers that prevent the early diagnosis, prevention or treatment of cervical cancer.

Women in many developing countries experience barriers that hinder the early detection and treatment of cervical cancer. Approximately, 80% of cervical cancer cases occur in developing countries where screening only covers 5% of the female population. (Munoz *et al.*, 2002:1093) About 60% to 75% of women who develop cervical cancer in sub-Saharan Africa live in rural areas. Many women with cervical cancer lack access to health care due to financial or geographical reasons. (Anorlu, 2008:43) In a situational analysis for cervical cancer diagnosis and treatment in the East, Central and Southern African countries, it was found that, although 95% of health care facilities had the infrastructure for cervical screening, very few women were screened due to lack of policy guidelines, infrequent supply of basic materials, and lack of suitably qualified staff. (Chirenje *et al*., 2001: 129-131)

2.2.9.1 Lack of education

The lack of knowledge about cervical cancer and screening practices has been found to impede screening programmes in South Africa. Only 2% of women in rural South Africa, who were found to have a STI had sought medical attention. (Denny *et al*., 2006:73) This finding is consistent with other studies that revealed lack of public

awareness of HPV infection (Anhang *et al*., 2004:318-319; Kaiser Family Foundation, 2000; Katz *et al*., 2007:131; Mays *et al*., 2000:372-374 and Van Til *et al*., 2003:1116). In addition, various studies have shown that most health care workers lack the necessary skills required to screen for abnormal cervical abnormalities and to effectively educate patients about HPV infection. (Jain *et al*., 2006:484 and Sussman *et al*., 2007:302)

2.2.9.2 Inadequate human resources

The management of cervical cancer involves a multidisciplinary team of cytologists, gynaecologists, oncologists, nurses and counsellors. These medical professionals are lacking in many developing countries and where the professionals exist they tend to work in isolation rather than in teams. (Anorlu, 2008:45)

2.2.9.3 Lack of policy guidelines or lack of implementation of policy guidelines

In South Africa, it is estimated that 1 in every 41 women will develop cervical cancer at some point in their lives, however, the national screening policy is yet to be fully implemented. There are few screening programmes throughout the rest of sub-Saharan Africa. This is in contrast to developed countries, where the implementation of screening programmes has resulted in a decline in the incidence of cervical cancer over the last 40 to 50 years. (Wake *et al*., 2009:44-45)

2.2.9.4 Lack of integration of cervical cancer and HIV management programmes

There are very few facilities that offer both cervical screening services and HIV/AIDS management services. This means that the women have to sacrifice a lot of time and incur additional transport costs to visit different clinics for these services. Therefore, most HIV positive women do not adhere to the cervical screening recommendations. Women with HIV at highest risk for invasive cervical cancer are those receiving both inadequate screening and treatment for precancer and suboptimal antiretroviral therapy. (Wake *et al*., 2009:46)

A study conducted in South Africa to determine HIV positive women's perceptions to cervical screening services found that cervical screening practices were not adherent to the screening recommendations. Only around 50 of the 100 surveyed women had

been screened during the last 10 years and less than a quarter had received a test within the previous year. Screening usually occurred at other health facilities and therefore, was not integrated with HIV management. (Wake *et al*., 2009:46-47)

In summary, an integrated and coordinated approach in the management of both cervical cancer and HIV/AIDS would reduce cancer incidence, morbidity and mortality through prevention, early detection, treatment and palliation.

2.2.9.5 Lack of follow up

In sub-Saharan Africa, most centres for the management of cervical cancer are located in urban areas even though the majority of cervical cancer patients are located in rural areas. Consequently, follow up is poor because many of the women who live in rural areas may lack time, money or the means of transport to travel to urban centres for follow up after treatment. (Anorlu, 2008:45)

2.2.9.6 Lack of support from male counterparts

Findings from a study whose aim was to determine the knowledge, beliefs and attitudes of HPV and cervical cancer testing among Hispanic women in the United States showed that some participants preferred using condoms to prevent HPV infection. However, the participants reported some negative aspects of condom use such as: inconvenience; unreliability; stigma; and resistance by many Hispanic men. Many women said that they would be subjected to stigma or even physical abuse if they suggested using a condom with their husbands. These findings are consistent with other studies conducted in some African countries where women find it difficult to suggest the use of condoms to their partners. (Vanslyke *et al*., 2008:594) Moreover, the knowledge and attitude of men toward gynaecological diseases such as cervical cancer is important. In developing countries, men often influence the women's willingness to seek treatment for such diseases. Therefore, women are more likely to seek medical advice if they receive support from their male counterparts. (Singh *et al.*, 1998:393)

In summary, several factors hinder the prevention, early diagnosis and treatment of cervical cancer. These factors include: lack of education about HPV infection; lack of policy guidelines or lack of implementation of the policy guidelines; inadequate

integration of cervical cancer and HIV/AIDS management programmes; lack of follow up and insufficient support from male partners.

2.3 THE LINK BETWEEN HIV/AIDS AND CERVICAL CANCER

2.3.1 Introduction

In 1993, the CDC declared cervical cancer an AIDS defining illness (Centers for Disease Control and Prevention, 1993:730). Apart from persistent HPV infection, HIV is the most common co-factor contributing to cervical cancer in South Africa. Though ARVs reduce AIDS mortality, HIV positive women could still die due to cervical cancer unless they acquire access to appropriate screening and treatment services (Castellsague *et al*., 2002:1110).

Highly Active Antiretroviral Therapy (HAART) may increase the life expectancy of HIV positive women thus increasing their exposure to oncogenic HPV and significantly increase the risk for cervical cancer (Mbulaiteye *et al*., 2006:985). Furthermore, a significant number of HIV positive women are in the age group which has the highest cervical cancer rates (Ries *et al*., 2007). In the general population, ICC appears at a mean age of between 44 and 52 years. Among HIV positive women, ICC occurs at a mean age of between 30 and 40 years. In South Africa, the adult (15 to 49 years) prevalence rate of HIV is 18.1% (UNAIDS, 2010:30). Thus there is a large proportion of HIV positive women who are susceptible to cervical cancer. Compared to HIV negative women, HIV positive women tend to have a higher prevalence of HPV, more HPV types, more HPV persistence and a higher prevalence of cytological abnormalities. Therefore, immune suppression caused by HIV infection results in poor prognosis of HPV infection. (Chirenje, 2005:273)

2.3.2 The relationship between HIV and HPV viruses

Cervical cancer and AIDS are both sexually transmitted diseases. Local cervical immunity has an influence on the degree of cervical neoplasia. Consequently, the immune response affects whether HPV infection is cleared or persists to create a risk of cervical cancer. It has been noted that the changes that occur in the HPV cell are related to the functioning of the immune system. Thus, when an individual's immunity deteriorates or CD4 count lowers the HPV cell changes increase. In HIV

positive women, a high HPV load may indicate the reactivation of latent HPV infection and high HPV replication due to HIV induced immunosuppression. (Silverberg *et al*., 2006:511-513) However, studies have produced differing data regarding the influence of a patient's CD4 cell count and antiretroviral therapy on the course of HPV infection. This could be due to differences in the study design, study population and HAART use. (Committee on Practice Bulletins-Gynaecology, 2002:858)

2.3.3 The frequency of LSIL and HSIL in HIV positive women

Various studies have reported that women who are HIV positive are at a higher risk of LSIL and HSIL (Schuman *et al*., 2003:129 and Hawes *et al*., 2003:555). A study of 400 untreated HIV positive women who underwent HPV DNA testing, cytology, colposcopy, histology and a CD4 count every 6 months for 36 months showed that 68% of women were positive for high risk HPV DNA, 35% had LSIL on Pap smear, and 13% had HSIL on Pap smear (Denny *et al*., 2008:1385-1387). Low CD4 counts and high viral loads are linked to abnormal cytology and high-risk HPV DNA. Another study in Kenyademonstrated HPV infection in 17% of HIV negative women and 49% of HIV positive women. The study also reported that LSIL was found in 6.9% HIV-negative and 21% of HIV positive women, and HSIL in 0.6% of negative and 5.8% of positive women. High risk HPV types and low CD4 counts were linked to HSIL. (Yamada *et al.*, 2008:847)

The patients' CD4 count could also influence the rate at which HPV induces abnormal lesions in the cervix. In one study of 647 HIV positive women in Rwanda, abnormal cytological findings caused by HPV were observed in 91% of the women with a CD4 count below 200 cells/mm^3, compared to 51% of women with a CD4 count above 350 cells/mm^3. (Singh *et al*., 2009:1856)

However, other studies have produced contrasting results. In a study conducted in Finland, 153 HIV positive participants were followed up for a mean of 5.6 years. Thirty three percent of the women were shown to have cervical neoplasia. The risk of cervical neoplasia was not associated with decreased CD4 counts, duration of HIV infection or use of antiretrovirals. (Lehtovirta *et al*., 2008:40-41)

The LSIL found in HIV negative women regress spontaneously. However, HIV positive women with LSIL have a lower rate of regression and a greater tendency to progression. Progression of cervical dysplasia was observed in 14% of HIV positive women compared with 7% of HIV negative women. Regression to normal was noted in 43% of HIV positive women and 66% of HIV-negative women. Cervical dysplasia regressed in only 45% of HIV positive women after two years, which was significantly lower than the regression rate in HIV negative women. (Ahdieh-Grant *et al.*, 2004:1076)

In conclusion, HIV positive women are at higher risk of developing cervical abnormalities due to HIV induced immunosuppression. When compared to their HIV negative counterparts, LSIL or HSIL found in HIV positive women do not regress spontaneously and in fact tend to progress to invasive cervical cancer.

2.3.4 The HPV oncogenic types found in HIV positive women from various countries

It has been suggested that HPV types 16 and 18 account for 70% of high grade intraepithelial precursor lesions in HIV negative women (Smith *et al*., 2007:630).However, data from various studies have shown that simultaneous infection with multiple HPV types occurs more frequently in HIV positive women. This observation has been linked to the mode of transmission of HIV and HPV, the inability to clear HPV infections and reactivation of latent HPV infections due to immune suppression. (Levi *et al*., 2004:228 and Strickler *et al*., 2003:1064-1065)

A study conducted in South Africa, with 148 HIV positive women as participants, indicated that 95% of the women had HPV. There was a median of three HPV types per participant, and 85% of women had one or more oncogenic HPV types (HPV 16 accounted for 30%, followed by HPV type 35 and 53). (Firnhaber *et al*., 2009:10-12)

Results from a study in Kenya indicated that the prevalence of HPV 16 was similar in HIV positive and HIV negative women with invasive cervical cancer (De Vuyst, 2008:246). In Zambia, a 150 women study found that 98% of HIV positive women had at least one type of HPV (85% had a high risk HPV type), with a median of four types per participant. The most common oncogenic type was HPV 52. (Parham *et*

al., 2006:1020-1022)Data from South America and Asia also show a variety of oncogenic HPV types such as 16, 18, 33, 35, 52 and 81 (Bollen *et al*., 2006:263 and Cerquiera *et al*., 2007:80).

Some low risk HPV types such as types 11, 53 and 61 have been detected more frequently in HIV positive women with HSIL than in HIV negative women with HSIL. This suggests that low risk HPV types that have little potential to cause oncogenic changes in HIV negative women may induce malignancy in HIV positive women. (Schiffman *et al*., 2005:79-81) This finding is consistent with a study that was conducted in South Africa to examine prevalence of HPV infection in HIV positive and HIV negative couples. The study revealed that oncogenic HPV types were dominant in 60% of the HIV negative female participants and in 73% of the HIV positive female participants. In addition, HIV positive women had non oncogenic HPV types (HPV types 11, 40, 67, 71, 72, 83 and 84) that were not detected in HIV negative women. (Mbulawa *et al*., 2009:1516)

Data concerning the association between HIV induced immunosuppression and HPV type is important because currently available prophylactic vaccines target HPV type 16 and 18 yet low risk HPV types have potential to cause neoplastic changes in the cervix of HIV positive women (Firnhaber *et al*., 2010:438). In North America and Europe, the prevalence of HPV 16 was more weakly associated with immune suppression (as determined by CD4 counts) than other types of HPV (Koshiol *et al*., 2006:1628-1629). A similar study by Firnhaber *et al*. (2010:433-443) was conducted among 1,010 HIV positive women in South Africa. Lower CD4 count was linked to increased cervical abnormalities. HPV type 16 was more prevalent in advanced cervical dysplasia. Women who were HIV positive with CD4 counts less than 200 cells/mm^3 had higher prevalence of overall HPV types. (Firnhaber *et al*., 2010:443)

The study by Firnhaber *et al*. (2010:433-443) revealed that HPV 16 prevalence may be affected by the CD4 count. This was in contrast to the results obtained from the study conducted by Koshiol *et al*. (2006:1623-1629). Therefore, further studies need to be performed in both the developed and the developing countries. In summary, HIV positive women are often infected with more HPV types than HIV negative women and low risk HPV types have the potential to cause malignancy in the cervix. (Firnhaber *et al*., 2010:441)

2.3.5 Influence of Antiretroviral Therapy on HPV infection

Antiretroviral drugs are linked to immune restoration and a reduction in the incidence and mortality from opportunistic infections. The use of HAART increases CD4 counts and decreases viral load thus partially restores immunocompetence. Research has produced conflicting data regarding the impact of antiretroviral therapy on the course of HPV infection. This could be due to differences in the study design, study population, the HAART regimen and variations in patient adherence. (Heard *et al*., 2004:15-19) Some of the data suggests that the use of HAART positively impacts the course of CIN, by reducing the incidence of HSIL and increasing the regression rate from HSIL to LSIL. However, there has not been a HAART associated reduction in the incidence of cervical cancer. (Minkoff *et al.*, 2001:2164)

A systematic literature review by Bratcher & Sahasrabuddhe (2010:1-13) using the database PubMed®, investigated the impact of HAART on the development of CIN in HIV positive women. Twenty two articles were analysed based on the impact of HAART on: HPV incidence, persistence and clearance; progression and regression of cervical disease and the rates of invasive cervical cancer (Table 2.7). (Bratcher & Sahasrabuddhe, 2010:2)

Table 2.7: Review of trials used to investigate the impact of HAART on HPV infection

	Impact of HAART					
Study	**Incidence**	**Persistence**	**Clearance**	**Progression**	**Regression**	**ICC rate**
Heard *et al.,*1998	N/A	N/A	N/A	N/A	Yes	N/A
Heard *et al.,* 2002	N/A	N/A	N/A	N/A	Yes	N/A
Heard *et al.,* 2006	No	N/A	N/A	N/A	N/A	N/A
Orlando *et al.,* 1999	N/A	N/A	N/A	No	N/A	N/A
Ellerbrock *et al.,* 2000	No	N/A	N/A	N/A	N/A	N/A
Intl Collaboration on HIV and Cancer, 2000	N/A	N/A	N/A	N/A	N/A	Higher incidence post HAART, but stats not significant
Dorucci *et al.,* 2001	N/A	N/A	N/A	N/A	N/A	Higher incidence post HAART, but stats not significant
Minkoff *et al.,* 2001	N/A	N/A	N/A	No	No	N/A
Lillo *et al.,* 2001	No	No	N/A	No	N/A	N/A
Moore *et al.,* 2002	N/A	N/A	N/A	N/A	No	N/A
Schuman *et al.,* 2003	No	N/A	N/A	No	No	N/A

Ahdieh-Grant *et al.*, 2004	N/A	N/A	N/A	N/A	No	N/A
Del Mistro *et al.,* 2004	No	No	N/A	No	N/A	N/A
Clifford *et al.,* 2005	N/A	N/A	N/A	N/A	N/A	No
Engels *et al.,* 2006	N/A	N/A	N/A	N/A	N/A	Higher incidence post HAART, but stats not significant
Engels *et al.,* 2008	N/A	N/A	N/A	N/A	N/A	Lower incidence post HAART, but stats not significant
Biggar *et al.,* 2007	N/A	N/A	N/A	N/A	N/A	Higher incidence post HAART, but stats not significant
Soncini *et al.,* 2007	Yes	N/A	N/A	N/A	N/A	N/A
Sirera *et al.,* 2007	No	N/A	N/A	N/A	N/A	N/A
Sirera *et al.,* 2008	No	N/A	N/A	N/A	N/A	N/A
Dal Maso *et al.*, 2009	N/A	N/A	N/A	N/A	N/A	Lower incidence post HAART, but stats not significant
Paramsothy *et al.,* 2009	N/A	N/A	Yes	No	No	N/A

Source: Bratcher & Sahasrabuddhe, 2010:4

The data on the impact of HAART on the incidence, progression and clearance of HPV infection obtained from the review was inconclusive. Comparison across studies was difficult due to differences in sample size, treatment regimens and limited availability of high quality methods used to assess the cervical samples. Most studies indicate that HAART did not reduce the incidence of cervical precancerous lesions or the progression from low to higher grade SIL/CIN. One theory proposed to explain this finding suggested that SIL/CIN represent oncogenic changes in the cervical cells caused by persistent HPV infection that may not be changed by the modification of the immune status induced in the short term by HAART. New studies need to be conducted that will follow up HIV positive women without cervical abnormalities while comparing differences in duration needed for development of these precancerous lesions. (Bratcher & Sahasrabuddhe, 2010:7-10)

Data on the impact of HAART on the regression of cervical lesions also produced conflicting results. The definitions of the clinical endpoints of SIL/CIN differed in the studies thus there could have been misclassification of results. In the context of regression, the relationship between HIV, HPV and HAART was unclear. Enhancement of the HPV gene expression, which is important in SIL/CIN development, has been shown to occur in the presence of the HIV gene. (Olaitan *et al*., 1996:759-760) Moreover, HIV positive women seem to have decreased vaginal Langerhans cells which promote local cervical immunity (Bratcher & Sahasrabuddhe, 2010:10). There is some data that indicates that some HAART drugs such as protease inhibitors may have an anti-tumour effect that is independent of increased immunocompetence, however, this has not been proven in clinical studies. (Monini *et al*., 2004:868)

There is also mixed evidence of the impact of HAART on the rates of ICC. All of the studies were conducted in industrialised countries where early detection and high quality treatment options may have prevented ICC among the HIV positive women. In addition, it was difficult to interpret the significance of the studies in the pre and post HAART eras. (Bratcher & Sahasrabuddhe, 2010:11)

Therefore, studies which assess the impact of HAART on the incidence, progression, regression of SIL/CIN and development of ICC should be conducted in developing countries. This is vital not only for scientific purposes but also for appropriate resource allocation and programme implementation. (Bratcher & Sahasrabuddhe, 2010:13)

In 2009, a prospective cohort study was conducted to assess the influence of adherence and effective ARV use on CIN and cervical cancer in HIV positive women. The participants were assessed prior to and after HAART initiation. The oncogenic HPV prevalence rates were compared before and after HAART initiation. The average prevalence of oncogenic HPV infection decreased 36% in adherent women and 12% in non-adherent women. (Minkoff *et al*., 2010:684)

Adherence to HAART was also associated with a reduction in the incident detection rate of oncogenic HPV infection. In adherent women, the rate of incident detection decreased 33% from a mean of 5.4/100 person visits to 3.4/100 person visits, whereas in non adherent women it decreased 9% from 6.1/100 person visits to 5.6/100 person visits. In terms of HPV clearance, adherent HAART users had marginally greater clearance of HPV after HAART compared with before HAART, whereas there was no relationship with non adherent users. (Minkoff *et al*., 2010:685)

Women who were adherent to HAART had a reduction in SIL prevalence after HAART initiation. However, the incidence of SIL was not lower among adherent women compared to non adherent women. (Minkoff *et al*., 2010:688)

In conclusion, adherent and effective use of HAART was significantly linked to reduced HPV infection and SILs among HIV positive women. Therefore, HAART adherence and effectiveness should be considered when determining the impact of HAART on HPV infection and cervical neoplasia.

2.3.6 Social factors that impact on cervical cancer and HIV

There are social factors that increase the risk of women contracting both HIV and cervical cancer. For instance, cervical cancer and HIV are diseases of poverty and inequity. These conditions are more prevalent in developing countries than the

industrialised countries. The developing countries have insufficient resources that would be used to manage these conditions. (Jewkes *et al*., 2001:742) Furthermore, the high rate of violence against women has increased the risk of women contracting sexually transmitted infections such as HIV and HPV. Sexual abuse has been linked to high risk HPV infection and cervical squamous intraepithelial lesions in women. (Kahn *et al*., 2005:363)

2.3.7 Methods to improve the integration of cervical cancer and HIV/AIDS management

Cervical cancer is an AIDS defining illness, thus a link exists between these two conditions. There is a need to integrate cervical cancer services within HIV/AIDS management services. This would require: the adequate allocation of financial and human resources to HIV/AIDS and cervical cancer management services; appropriate cervical cancer education programmes for both health care workers and women; policy development; providing HPV vaccinations for both teenage girls and boys; and developing effective follow up systems for cervical cancer patients.

2.3.7.1 Increase funding

Governments must recognise that cervical cancer and HIV are serious public health problems and adequate resources need to be allocated to prevention and treatment services (Anorlu, 2008:46). Sexual and reproductive health services should be considered during the allocation of funds for HIV/AIDS management. Resources should be invested in providing essential equipment and supplies. Increased funding would allow for scale up of laboratory and radiation services and procurement of expensive chemotherapeutic drugs. The HPV vaccine, which has proven to be effective, could also be made available in the public sector health services. Most South African women are not able to access this vaccine due to its cost as it is available only in the private sector. (Bourke, 2007)

2.3.7.2 Increased human resources

World Health Organisation statistics for 2006 put South Africa's doctor to patient ratio at 77 doctors for every 100,000 people (WHO, 2006). Africa bears 24% of the global burden of disease but has only 3% of the global health workers. In addition, most of the health workers are situated in urban areas, leaving people living in the rural areas with limited access to health care. Therefore, health ministries in Africa should increase the number of health workers, particularly those trained in the management of cervical cancer such as oncologists and gynaecologists. (Jewkes *et al*., 2001:736-737)

2.3.7.3 Communication and education

Previous findings have shown that South African women lack awareness of cervical cancer as a disease. Women and health care workers need to be educated on the link between HIV/AIDS and cervical cancer. Women should be made aware of the current cervical cancer screening policy. Women should be educated about the causes, risk factors, symptoms and prevention strategies of cervical cancer. Women should also be aware of their rights with regards to the cervical cancer screening policy. (Maree & Wright, 2007:55-58 and Lartey *et al*., 2003:315-316)

The low levels literacy levels in South Africa could have a negative influence on the cervical cancer awareness programmes. The Department of Health found that eight million of the South African population would not benefit from written health promotion material due to low levels of literacy. (Department of Health, South Africa, 2007) Therefore, cervical cancer and HIV management programmes need to be tailored to the literacy levels of women (Paul *et al*., 2003:2932).

Cultural beliefs may influence women's perceptions of cervical cancer. Abnormal vaginal bleeding, one of the signs of cervical cancer, is believed to be caused by witchcraft. Therefore, to avoid stigma, women who experience abnormal vaginal bleeding might not disclose their condition. Influential people such as community leaders and traditional healers should be educated about cervical cancer so that they

can relay accurate information to the other members of the community. The women would then be willing to seek treatment. (Vorobiof *et al*., 2001:S125-127)

In addition, health workers also need training on how to provide services safely and effectively for instance, how to conduct smears properly. The quality of observations and interpretations made by cytotechnologists depends on their training and experience. Due to the shortage of health care professionals in the public sector, task shifting must be considered. For instance, the Department of Health could be responsible for HPV vaccination in schools and community health workers could perform services like cervical cancer screening follow up. (Bourke, 2007) Women's health days can be created, where health facilities are dedicated to screening for cervical cancer and performing HPV vaccinations (Reeler *et al*., 2009:524). Mobile clinics should also be established to target women in remote areas as most women who suffer from cervical cancer live in the rural areas (Bourke, 2007).

2.3.7.4 Policy development

The extent to which women participate in organised screening is linked to the structure of the population and how the screening programme is organised (Fylan, 1998:1509). In 2000, a national cervical cancer screening policy was developed and implemented in South Africa. If the programme achieves over 75% coverage, it is expected to reduce the incidence of cervical cancer by half. Screening occurs by performing three free Pap smears for women at the ages of 30, 40 and 50. Statistics have shown that less than 20% of women have used this service in South Africa. (Department of Health, South Africa, 2000:2)

In 2010, the South African Department of Health revised the clinical guidelines for the management of HIV and AIDS in adults. The guidelines stipulate that women who are HIV positive should be offered cervical cancer screening on diagnosis and if the test is normal, it should be repeated every three years, irrespective of ART status. Abnormal Pap smears will be managed according to the result (Table 2.8). (Department of Health, South Africa, 2010:31)

Table 2.8: 2010 South African guidelines for the management of abnormal Pap smears in HIV positive women

Abnormal pap smear result	Management
ASCUS	Repeat in one year and if still ASCUS, refer baseline colposcopy.
LSIL	Repeat in one year and if still LSIL, refer baseline colposcopy.
HSIL	Refer colposcopy
Carcinoma in situ	Refer immediately

ASCUS, atypical squamous cells of undetermined significance; LSIL, low grade squamous intraepithelial lesions; HSIL, high grade squamous intraepithelial lesions.
Source: Department of Health, South Africa, 2010:31.

An organised nationally coordinated programme that integrates the management of HIV and cervical cancer should monitor quality controls and ensure the implementation of the most cost effective therapies and routines (Bourke, 2007). Single or twice in a life time cervical cancer screening models have been proposed to improve cost effectiveness and efficiency in some developing countries such as India, Peru, Kenya, South Africa and Thailand. These computer based cervical cancer screening models target women between the age of 40 and 59 years. The model uses HPV DNA testing as the primary screening test followed by cytology. In low resource areas, HPV DNA testing is followed by VIA. The women who have cervical abnormalities but do not present with invasive cervical cancer are then treated using cryotherapy or loop electrosurgical excision procedure in the same screening session. This model estimates a 25% to 36% reduction in the lifetime risk of cancer. (Goldie *et al*., 2005:2165-2168)

2.3.7.5 HPV vaccination for boys

Vaccinating girls can only reduce the efficacy of the HPV vaccine if unprotected sex occurs between a vaccinated girl and unvaccinated boy. Hence, HPV vaccination for boys should also be considered. (Bourke, 2007)

2.3.7.6 Research

In 2000, it was reported that less than 20% of the world population were covered by cancer registries. Therefore, the majority of the world's health ministries lack the basic data that is required to allocate resources to HIV/AIDS and cervical cancer management programmes. The health ministries should establish cancer registries to determine the extent of cervical cancer cases in their countries. This will ensure effective planning. South Africa has a National Cancer Registry, however, the cervical cancer statistics were last recorded in 2001 and are outdated. (Bourke, 2007)

Research should be undertaken in order to understand the local perceptions of cervical cancer as well as to establish the experiences faced by women diagnosed with cervical cancer. This might promote community engagement and support, thus ensuring effective service delivery through collaboration between the health care system and the community. (Reeler *et al*., 2009:524)

2.3.7.7 Effective follow up systems

In the developing world, most of the cervical cancer patients are found in the rural areas thus have limited access to health care centres due to geographical or financial reasons. Consequently, good monitoring and evaluation systems need to be instituted in order to determine the efficacy of the integrated HIV and cervical cancer management programmes. (Reeler *et al*., 2009:523)

Chapter 3

CONCURRENT CHEMORADIATION

3.1 INTRODUCTION

Concurrent chemoradiation refers to the simultaneous use of two forms of therapy of cervical cancer, namely radiation therapy and chemotherapy. Previously, the therapies have been administered sequentially. Radiation therapy uses high energy photons to kill the cancerous cells. There are two forms of radiation therapy: external beam radiation therapy (EBRT) and intracavitary (ICT) brachytherapy. Radiation produces secondary charged particles and free radicals that interact with nucleic acids and kill cells. In EBRT, the photons are given externally in a procedure that is similar to a diagnostic x-ray. The dose can be increased according to the volume of the tumour while sparing normal tissues. This treatment usually takes six to seven weeks to complete. In brachytherapy or internal radiation therapy, a capsule of radioactive material is placed in the vagina near the tumour, or the radioactive material may be placed in thin needles that are inserted directly in the tumour. This treatment takes a few days to complete. Brachytherapy permits the delivery of high doses of radiation to the tumour with minimal radiation of the surrounding tissue thus reduces toxicity. (Harries & Botha, 2007:66-67) Chemotherapy involves the use of cytotoxic agents that are administered orally or intravenously. The cytotoxic agents used in combination with radiotherapy include: cisplatin; carboplatin; 5-fluorouracil; hydroxyurea; misonidazole; mitomycin; bleomycin; etoposide; ifosfamide; epirubicin and the taxanes. (Serkies & Jassem, 2004:204)

3.2 MECHANISM OF ACTION OF CONCURRENT CHEMORADIATION

The objectives of combining chemotherapy and radiotherapy are to increase local tumour control, decrease distant metastases and improve survival with minimal impact to normal tissue (Fu, 1985:2123). Several mechanisms of interaction between chemotherapy and radiotherapy have been proposed (Table 3.1).

Table 3.1: Possible mechanisms of interaction between chemotherapy and radiotherapy

Proposed mechanism
Modification of the slope of the dose response curve.
Decreased accumulation of or inhibition of repair of sublethal damage.
Inhibition of recovery from potentially lethal damage.
Perturbation in cell kinetics with an increase of the proportion of cells in sensitive cell cycle phase and proliferative state.
Decrease in tumour bulk, improved blood supply, reoxygenation and recruitment and increased radiosensitivity and chemosensitivity.
Increased drug delivery and uptake.

Source: Fu, 1985:2125

The slope of the dose response curve is altered when CCRT is employed. Chemotherapeutic agents that intercalate the DNA such as cisplatin increase the slope of radiation dose response curves thus enhancing the effects of radiation on both the tumour and normal tissues. (Fu, 1985:2123) Concurrent chemoradiation results in decreased accumulation or inhibition of repair of sublethal damage. Chemotherapeutic agents such as cisplatin inhibit the repair of sublethal radiation damage. (Fu, 1985:2125)

The use of CCRT may cause perturbation in cell kinetics which is beneficial as the effect of chemotherapeutic agents and RT may be dependent on the phase of the cell cycle. Chemoradiotherapy can induce synchrony in tumours and in normal tissues. For instance, hydroxyurea, a chemotherapeutic agent that kills cells in the S phase, partially synchronises and blocks cells at G1/S phase of the cell cycle. If radiation therapy is administered after treatment with hydroxyurea during the sensitive phase as the cells emerge from the block, an enhanced effect may be expected. (Fu, 1985:2126)

A decrease in tumour bulk, improved blood supply, reoxygenation and recruitment and increased radiosensitivity and chemosensitivity are consequences of CCRT. This is beneficial as the response to CCRT is tumour size dependent and the cytotoxic effect of agents such as cisplatin reduces the bulk of tumours which improves blood supply to the tumour. Reoxygenation of the tumour then occurs and the tumour shifts into a radiosensitive phase of the cell cycle. Increased drug delivery and uptake has been reported following CCRT. Increased drug delivery and uptake may be as a result of tumour shrinkage and improved blood supply after radiation. (Fu, 1985:2126) The chemotherapeutic agents used in the treatment of cervical cancer have been shown to display one or more of the mechanisms of interaction (Table 3.2).

Table 3.2: Mechanism of cytotoxicity and enhancement of radiation effects of some chemotherapeutic drugs used in the treatment of cervical cancer

Drug	Mechanism of cytotoxicity	Possible mechanism of enhancement of radiation effects
Bleomycin	Causes single and double strand breaks in DNA, inhibits DNA synthesis, and preferentially kills cells in G_2 and M phases	Inhibition of recovery from potentially lethal damage and perturbation in cell kinetics
Cisplatin	Causes DNA intrastrand crosslinks and changes in DNA conformation and inhibits DNA synthesis, causes delay in S phase	Reduces the repair of sublethal and potentially lethal damage induced by radiation therapy Increases the slope of hypoxic cell radiation dose response curves
5-Fluorouracil	Binds and inhibits thymidylate synthetase and inhibits ribonucleic acid (RNA) processing and function	Perturbation in cell kinetics Increases the slope of hypoxic cell radiation dose response curves
Hydroxyurea	Inhibits ribonucleoside diphosphate reductase and DNA synthesis, selectively kills cells in S phase	Perturbation in cell kinetics
Mitomycin C	Causes intrastrand and interstrand crosslinks in DNA by alkylation and inhibits DNA synthesis	Additive cytotoxicity

Source: Fu, 1985:2127.

3.3 CONCURRENT CHEMOTHERAPY AND RADIOTHERAPY

In 1999, the United States National Cancer Institute recommended that CCRT should be considered for all patients with advanced cervical cancer (National Cancer Institute, 1999). This recommendation was based on five randomised controlled trials (Keys *et al*., 1999; Morris *et al.,* 1999; Rose *et al*., 1999; Whitney *et al*., 1999 and Peters *et al*., 2000) (Table 3.3). Each of these trials showed a significant improvement in survival rates and progression free survival among women with locally advanced cervical cancer treated with concomitant cisplatin based chemotherapy and radiotherapy (Table 3.4). These guidelines have been adopted worldwide and CCRT is now considered the standard treatment of advanced cervical cancer. (Cairns *et al*., 2008: 565)

Table 3.3: Randomised controlled trials that provided evidence for the decision that concurrent chemoradiation should be considered for patients with locally advanced cancer

Trial	Eligibility	No. of participants	Investigational group	Control group
Keys *et al.,* 1999	IB (tumours ≥4cm)	369	CDDP 40mg/m^2/wk (6 cycles) EBRT and intracavitary radiation 75Gy and 55 Gy Hysterectomy	EBRT and intracavitary radiation 75Gy and 55 Gy Hysterectomy
Morris *et al.,* 1999	IB-IIA >5cm IIB-IVA	403	CDDP 75mg/m^2 5FU 4mg/m^2/96h (3 cycles) Pelvis and para-aortic nodes RT 45Gy	Pelvis and para-aortic nodes RT 45Gy
Peters *et al.,* 2000	I-IIA after radical hysterectomy with nodes, margins or parametrium positive	268	CDDP 70mg/m^2 5-FU 4g/m^2/96h (2 concurrent & 2 adjuvant cycles) RT 49.3Gy	RT 49.3Gy
Whitney *et al.,* 1999	IIB-IVA	368	CDDP 50mg/m^2 5-FU 4mg/m^2/96h Standard whole pelvic RT	Standard whole pelvic RT HU 3g/m^2 (2xweekly)

Rose *et al.,* 1999	IIB-IVA	526	CDDP 40mg/m^2/wk (6 cycles) RT OR CDDP 50mg 5-FU 4g/m^2/96hrs (3 cycles) HU 2g/m^2 (2x weekly) 2 cycles RT	RT HU 3g/m^2 (2x weekly)

CDDP, cisplatin; EBRT, external beam radiation therapy; 5-FU, 5-Fluorouracil, HU, hydroxyurea; Gy, Gray; RT, radiation therapy
Source: Green *et al*., 2001:782

3.4 SURVIVAL OUTCOME MEASURES

Various survival outcome measures were used in the randomised controlled trials. Overall survival refers to the time from randomisation until death by any cause. Locoregional disease free survival is defined as the time from randomisation until locoregional recurrence or progression or death by any cause. Metastases free survival refers to the time from randomisation until first metastasis or death by any cause. Overall disease free survival is the time from randomisation until locoregional recurrence, metastasis or death by any cause. Time to metastases is defined as the time from randomisation until first metastases. (Chemoradiotherapy for Cervical Cancer Meta-analysis Collaboration (CCCMAC), 2010:3)

Table 3.4: Survival outcomes of the five randomised controlled trials used by the National Cancer Institute as a basis for using concurrent chemoradiation as treatment for locally advanced cervical cancer

Trial	Conclusion
Keys *et al.,* 1999	Overall survival was significantly higher in the CCRT group at 3 years.
Morris *et al.,* 1999	The 5 year survival rate was 73% in the CCRT group and 58% in the radiation group. The disease free survival rates at 5 years was 67% in the CCRT group and 40% in the radiation group. The rate of distant metastasis and locoregional recurrence were significantly higher in the radiation group.
Peters *et al.,* 2000	Overall survival was significantly higher in the CCRT group. The 4 year survival rate was 81% in the CCRT group and 71% in the radiation group.
Whitney *et al.,* 1999	Overall survival was significantly higher in the CCRT group.
Rose *et al.,* 1999	Both groups that received cisplatin had a higher progression free survival than the group that received hydroxyurea alone.

Source: Cairns *et al*., 2008: 566-568.

Although these five randomised controlled trials, (Keys *et al*., 1999; Morris *et al.,* 1999; Rose *et al*., 1999; Whitney *et al*., 1999 and Peters *et al*., 2000) favoured the use of CCRT, a negative trial was also conducted by Pearcey *et al*., (2002:966-972). This negative trial randomised 259 patients with stage IB to IVA cervical cancer. The investigational group received radiotherapy (EBRT and brachytherapy) plus weekly cisplatin chemotherapy 40 mg/m^2/wk (6 cycles) and the control group received radiotherapy alone (external beam radiotherapy and brachytherapy). No significant difference in progression free survival or 3 and 5 year survival rates were noted. (Pearcey *et al*., 2002:966-972)

The five randomised controlled trials and the negative trial had various limitations because they differed in terms of the local and experimental treatments used and the stages of disease included. Moreover, the negative trial questioned the value of adding cisplatin to radiation therapy. Therefore, a systematic review of 19 trials done between 1980 and 2000 was performed in order to summarise the effects of CCRT based on all the trials (Table 3.5). (Green *et al*., 2001:781-786)

Of the 19 trials, 16 compared CCRT with the same radiotherapy, one trial compared CCRT with extended field radiotherapy and two trials compared cisplatin based CCRT with hydroxyurea based CCRT. Cisplatin was used in 10 of the trials, either weekly as a single agent or every two to six weeks in combination with 5-fluorouracil, vincristine or bleomycin. The other seven trials used 5-fluorouracil either as a single agent or in combination with mitomycin C, or mitomycin C either as a single agent or in combination with bleomycin or epirubicin. These trials included 4580 women who mostly had stage IIB to IVA cancer, but some trials included or were confined to women with stage IA to IIA. (Green *et al*., 2001:781-786)

Table 3.5 : Characteristics of trials reviewed by Green *et al*., (2001)

Trial	Eligibility	Number of participants	Investigational group	Control group
Platinum based trials:				
Wong *et al.,* 1989	IIB-IIIB	64	CDDP 25mg/m2/wk for 4 weeks + RT OR CDDP 50mg/m2/wk for 4 weeks + RT	RT
Lira-Puerto *et al.,* 1990	IIB-IV	24	CDDP 20mg/m2 /wk (9 cycles) + RT	RT
Whitney *et al.,* 1999	IIB-IVA	368	CDDP 50mg/m2 5-FU 4mg/m2/96h + RT	HU 3g/m2 (2xweekly) + RT
Tseng *et al.,* 1997	IIB-IIIB	122	CDDP 50mg/m2 VCR 1mg/m2 BLM 75mg/m2 every 21 days (4 cycles) + RT	RT
Morris *et al.,* 1999	IB-IIA >5cm IIB-IVA	403	CDDP 75mg/m2 5FU 4mg/m2/96h (3 cycles) + RT	RT
Peters *et al.,* 2000	I-IIA	268	CDDP 70mg/m2 5-FU 4g/m2/96h (2 concurrent & 2 adjuvant cycles) + RT + S	RT + S
Keys *et al.,* 1999	IB(tumours >4cm)	369	CDDP 40mg/m2/wk (6 cycles) + RT +S	RT +S

Rose *et al.,* 1999	IIB-IVA	526	CDDP 40mg/m2/wk (6 cycles) + RT OR CDDP 50mg/m2 5-FU 4g/m2/96hrs (3 cycles) HU 2g/m2 (2x weekly) 2 cycles + RT	HU 3g/m2 (2x weekly) + RT
Hong Wei *et al.,* 1997	IIB-IIIB	120	CDDP 60mg/m2 5-FU 1500mg/m2 VCR 2mg/m2 every 21 days (2 cycles) + RT + hyperthermia	RT + hyperthermia
Pearcey *et al.,* 2000	IB2-IIA>4cm, IIB-IVA	259	CDDP 40mg/m2/wk (5 cycles) + RT	RT
Pras *et al.,* 1985 cited in Green *et al.,* 2001	IB-IIA> 4cm, IIB-IVA	52	CDBCA 300mg/m2 5-FU 2400mg/m2 every 28 days (2 cycles) + RT	RT
Leborgne, 1995 cited in Green *et al.,* 2001	IB2-IVA	153	CDDP 80mg/m2 5-FU 2400mg/m2 every 28 days (2 cycles) + RT	RT
Non-platinum based trials:				
Singh *et al.,* 1985	IIB-IVA	560	MMC 4mg/m2 and BLM 15mg/m2	RT
Hernandez *et al.,* 1999	III	27	MMC 30mg/m2/wk (5 cycles) before RT OR MMC 30mg/m2/wk (5cycles) after RT	RT
Thomas G.M., 1999	IB-IVA>5cm	234	5-FU 1000 mg/m2/day for first and	RT

			last 4 days of RT	
Lorvidhaya *et al.,* 2003	IIB-IVA	673	MMC 10 mg/m2, 5-FU (oral) 4200mg every 28 days (2 cycles) + RT OR MMC 10 mg/m2, 5-FU (oral) 4200mg every 28 days (2 cycles) + RT+ Adjuvant CT: 5-FU (oral) 5600mg every 28 days (3 cycles) 2 weeks rest every 6 weeks.	RT OR RT + Adjuvant CT: 5-FU (oral) 5600mg every 28 days (3 cycles) 2 weeks rest every 6 weeks
Wong *et al.,* 1999	IA, IIA>4cm, IIB-IIIB	220	EPI 60 mg/m2 on day one of RT + Adjuvant CT: EPI 90mg/m2 every 28 days (5 cycles)	RT
Fernandez *et al*., 1995	IIB, IIIB bulky	82	5-FU, MMC	RT
Roberts *et al.,* 2000	IB2, II-IVA	212	MMC 30 mg/m2 every 42 days (2 cycles) + RT	RT

BLM, bleomycin; CBDCA, carboplatin; CDDP, cisplatin; CT, chemotherapy; EPI, epirubicin; HU, hydroxyurea; MMC, mitomycin C; RT, radiation therapy; S, hysterectomy and pelvic lymphadenectomy; VCR, vincristine; 5-FU, 5-fluorouracil; Source: Green *et al*., 2001:782.

Approximately, 11 to 13 of the trials were available for meta-analysis. The results showed a 29% reduction in the risk of death and an absolute improvement in survival of 12% with CCRT compared to radiotherapy alone. Furthermore, CCRT significantly improved disease free survival. An absolute improvement of progression free survival of 13% and a reduction of local and distant recurrence rates was also noted with the use of both platinum and non platinum CCRT groups. The most prominent finding in the meta-analysis was the significant reduction of distant metastases in the CCRT group. This suggested that, at the doses and the schedules used, the chemotherapeutic agents exerted a systemic effect. Therefore, the increase in local control may have been due to independent cell death by radiation and cytotoxic agents. Agents such as cisplatin and mitomycin might also have had a synergistic effect with radiation thus help to improve local control and survival. (Green *et al*., 2001:786)

The trials reviewed by Green *et al*. (2001:781-786) also provided information about toxicity caused by the use of CCRT. Toxicity can be classified as acute or late. Acute toxicity is defined as adverse events which occur during treatment and up to 90 days after completion of chemotherapy or radiotherapy. Acute adverse events are of a short duration and normally diminish with medical management, while late adverse events are difficult to reverse and may permanently impair the patient's quality of life. Late toxicity appears nine months to five years after treatment. Chemotherapy toxicity might be detrimental if radiotherapy is prolonged. This is because local control falls by up to 1% per day if treatment continues for more than 7 weeks (Perez *et al*., 1995:1277). Therefore, toxicity caused by CCRT complicates treatment. (Green *et al*., 2001:785)

Only a few trials reported acute toxicity in detail and different scales of measurement were employed. Thus, the toxicity data from the trials was classified as haematological, gastrointestinal, genitourinary, dermatological or neurological. Acute toxicity was reported in detail in eight published trials (Wong *et al*., 1989; Tseng *et al*., 1997; Keys *et al*., 1999; Morris *et al.,* 1999; Rose *et al*., 1999; Whitney *et al*., 1999; Wong *et al*., 1999 and Peters *et al*., 2000) and one unpublished trial (Leborgne, 1995 cited in Green *et al*., 2001). (Green *et al*., 2001:785)

Severe or life threatening haematological toxicity, particularly leucopenia, was noted more frequently in patients in the CCRT group than in the control group. Pelvic irradiation and chemotherapy can have a significant effect on the bone marrow thus cause haematological toxicity. In contrast, genitourinary toxicity was lower in the CCRT group than in the control group. Neurological and dermatological toxicity was not significantly different between the groups. (Green *et al*., 2001:785)

Usually haematological toxicity is self limiting or resolved with medical management. On the contrary, gastrointestinal side effects like diarrhoea and faecal incontinence may become chronic (Kirwan *et al*., 2003:220). The bladder and the gastrointestinal tract were the main systems affected by late toxicity. Toxicity was not significantly different between the groups. However, long term follow up was not available. Seven deaths due to toxicity were reported, one in the control group (fistula), five in the investigational group (chemotherapy related death) and one due to complications. (Green *et al*., 2001:785)

This systematic review and meta-analysis had several limitations. Heterogeneity was evident in the results for overall survival, progression free survival and local recurrence. Differences in the platinum based trials were also observed, particularly in the type and timing of local and systemic treatments. In addition, the length of follow-up and analyses of the various outcomes varied between trials. Another limitation was the fact that only a small proportion of the participants had advanced stages of cervical cancer, stage III and IV. Therefore, extrapolation of the results to patients with advanced stages of cervical cancer may lead to invalid conclusions. (Green *et al*., 2001:785)

A subsequent systematic review and meta-analysis by Lukka *et al*. (2002:203-212) investigated the effects of the use of cisplatin based CCRT to treat cervical cancer. Eight randomised controlled trials were evaluated (Wong *et al*., 1989; Tseng *et al*., 1997; Keys *et al*., 1999; Morris *et al*., 1999; Rose *et al.,* 1999; Whitney *et al*., 1999; Pearcey *et al*., 2000 and Peters *et al*., 2000). The meta-analysis was conducted using four-year mortality rates from survival curves from six of the trials. These were combined with the three-year mortality rates reported by Pearcey *et al*. (2000:378) and the number of deaths by the end of the trial that was conducted by Wong *et al*. (1989). (Lukka *et al.,* 2002:208-209)

The meta-analysis by Lukka *et al*. (2002:203-212) demonstrated that the use of cisplatin based CCRT resulted in the absolute reduction of the risk of death by 11%. The relative risk of death was similar in the studies that used different treatment interventions (cisplatin alone or cisplatin plus 5-FU) and different control interventions (RT alone or RT plus hydroxyurea). Six of the trials also showed a reduction in both local and distant metastatic rates. (Lukka *et al.,* 2002:210)

The systematic review and meta-analysis conducted by Lukka *et al.* (2002:203-212) showed increased acute toxicity, particularly haematological and gastrointestinal in the CCRT groups. This finding is consistent with the systematic review and meta-analysis conducted by Green *et al.* (2001:781-786). Late toxicity rates were not significantly different between the experimental groups and the control groups. (Lukka *et al.,* 2002:211)

Although the systematic review and meta-analysis by Lukka *et al.* (2002:203-212) confirmed the benefit of the use of cisplatin based CCRT, several issues were raised. The use of protracted radiotherapy or suboptimal doses of RT may lead to poor local control (Fyles *et al*., 1992). Several authors (Thomas, 1998:137-145 and Pearcey *et al*. 2000:378) have observed the relatively low doses of RT used in the trial by Keys *et al.* (1999:1154-1161) and the low total dose of RT and protracted treatment time in the trial by Rose *et al*., (1999:1144-1153). Therefore, the potential benefit of the concurrent use of cisplatin and an optimum RT regimen remains unclear. (Lukka *et al.,* 2002:211)

The randomised controlled trials used in the systematic review and meta-analysis by Lukka *et al.* (2002:203-212), used different chemotherapeutic agents and regimens as well as different control treatments. Consequently, there were difficulties that were encountered during the interpretation of the effects of cisplatin based CCRT. Nevertheless, the reduction of the relative risk of death for cisplatin based CCRT appeared to be comparable to that for concurrent cisplatin plus 5-FU with radiotherapy. (Lukka *et al.,* 2002:211)

Although the systematic reviews and the meta-analysis by Lukka *et al.* (2002:203-212) and Green *et al*. (2001:781-786) showed a benefit of CCRT for all stages of disease, only a small proportion of the participants had advanced stages of cervical

cancer, stage III and IV. Therefore, the data did not sufficiently represent the cervical cancer population in developing countries, where many women present with advanced disease at diagnosis. Arandomised controlled trial was initiated in India which compared cisplatin based CCRT with RT alone in 160 women with stage IIB to IVA cervical cancer. All the patients received EBRT (5000 cGy) and brachytherapy. Patients in the CCRT arm received 30mg/m^2 of cisplatin. Cisplatin, which is readily available and affordable, was administered weekly for five weeks during the course of external radiotherapy. The complete response rate was 83% in the CCRT arm and 73% in the RT arm. The adherence rate was similar in both arms. At 54 months, the overall survival rate had increased from 47% to 56% and the disease free survival had increased from 37% to 51% in the CCRT arm. Neutropenia was the major dose limiting toxicity and was observed more in the CCRT arm. Radiation proctitis was the most common late toxicity that was reported. (Mitra *et al*., 2006:432-436)

Both reviews (Lukka *et al*., 2002:203-212 and Green *et al*., 2001:781-786) noted that it was difficult to interpret the benefits of CCRT due to the different treatments employed in the included studies. The authors concluded that a meta-analysis of individual patient data (IPD) was required to fully review all the existing evidence. The IPD meta-analysis would: explain the heterogeneity observed in the evaluated trials and give more consistent analysis with respect to progression free survival, local and distant recurrence and CCRT induced toxicity. (Lukka *et al*., 2002:203-212 and Green *et al*., 2001:781-786)

A further meta-analysis was initiated and coordinated by the U.K. Medical Research Council Clinical Trials Unit and was carried out by the Concomitant chemoradiotherapy in Cervical Cancer Meta-Analysis Collaboration (CCCMAC). Although 18 trials were identified, only 15 were eligible for the meta-analysis. Of the 15 trials, 13 trials compared CCRT versus the same radiotherapy. In the other two trials, chemotherapy was administered after CCRT. (Chemoradiotherapy for Cervical Cancer Meta-analysis Collaboration (CCCMAC), 2010:3)

The meta-analysis was limited to include trials that compared CCRT and radical RT (with or without surgery) with the same radical RT (with or without surgery). The 15 trials were conducted between May 1987 and June 2006. Table 3.6 shows the regimens that were used in the experimental arms of the trials. The prescribed EBRT

dose used in the trials was between 40 and 61.2 Gy. (Chemoradiotherapy for Cervical Cancer Meta-analysis Collaboration (CCCMAC), 2010:3)

Table 3.6: Regimen used in the experimental arms of the trials included in the meta-analysis conducted by The Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration (CCCMAC)

Regimens used in the experimental arm	Number of trials	Trials
Platinum based chemoradiotherapy	11	Leborgne, 1995; Pras, 1995; Chen *et al*., 1997; Keys *et al*., 1999; Onishi *et al*., 2000; Peters *et al*., 2000; Pearcey *et al*., 2002; Cikaric *et al*., 2005; GaripaAYaoAYlu *et al*., 2004; Kantardzic *et al*., 2004 and Lal *et al.,* 2004
Non- platinum based chemoradiotherapy: 5-FU OR mitomycin-C OR 5-FU plus mitomycin-C	3	Thomas *et al*., 1998; Roberts *et al*., 2000 and Lorvidhaya *et al.,* 2003.
Cisplatin based or 5-FU based chemoradiotherapy	1	Lanciano *et al*., 2005

Source: Chemoradiotherapy for Cervical Cancer Meta-analysis Collaboration (CCCMAC), 2010:6.

The CCCMAC meta-analysis found that the type of CT (platinum based or non platinum based), the planned RT dose and the total planned duration of radiation did not affect the effect of CCRT. Similarly, for the ten cisplatin based trials, the effect of CCRT was not affected by the dose of cisplatin or the cycle length. (Chemoradiotherapy for Cervical Cancer Meta-analysis Collaboration (CCCMAC), 2010:8)

In terms of survival, there was a significant difference between the 13 trials that used CCRT and the two trials that used additional CT after CCRT was administered. A 54% reduction in the risk of death and an absolute survival benefit of 19% at 5 years was observed in the two trials that used adjuvant CT after CCRT. In the other 13 trials that used CCRT only, a 19% reduction in the risk of death and an absolute

survival benefit of 6% at 5 years was observed. Data on disease free survival and metastases free survival was also obtained from the 13 trials (Table 3.7). (Chemoradiotherapy for Cervical Cancer Meta-analysis Collaboration (CCCMAC), 2010:8) Thus from the 13 trials it can be summarised that there is an improvement in the 5 year survival rate when CCRT is used instead of RT and that the two trials where CT was administered after CCRT had a larger survival benefit.

Table 3.7: Absolute survival benefit at 5 years (%) after administration of CCRT

Outcome	Absolute survival benefit at 5 years (%)
Overall disease free survival	8%
Locoregional disease free survival	9%
Metastases free survival	7%

Source: Chemoradiotherapy for Cervical Cancer Meta-analysis Collaboration (CCCMAC), 2010:8.

Data on toxicity was obtained from all the trials. Serious gastrointestinal toxicity was noted in the trials that used platinum based CCRT and the trials where additional CT was administered after CCRT. Increased cases of acute haematological toxicity were observed in the groups that received CCRT as opposed to RT. (Chemoradiotherapy for Cervical Cancer Meta-analysis Collaboration (CCCMAC), 2010:14)

Most of the trials analysed by CCCMAC did not record late toxicity thus it was difficult to assess the effect of the type of treatment on late toxicity. Late rectal toxicity was recorded in seven trials, late bladder toxicity was recorded in five trials and late intestinal and vaginal toxicity was recorded in four trials. Nine deaths were recorded. (Chemoradiotherapy for Cervical Cancer Meta-analysis Collaboration (CCCMAC), 2010:14)

The CCCMAC meta-analysis confirmed the benefit of CCRT on metastases as suggested in the previous reviews (Lukka *et al*., 2002:203-212 and Green *et al*., 2001:781-786). Thus, CCRT may have a systemic effect. Furthermore, the meta-analysis showed that the benefit of CCRT may not depend on the use of a platinum-based chemotherapeutic agent. The National Cancer Institute (National Cancer

Institute, 1999) recommendations were limited to platinum based CCRT regimen. Significant benefits have been noted with non-platinum based CCRT, particularly with the use of 5-Fluorouracil and mitomycin C. Although a larger benefit was observed in the trials that used additional CT after CCRT, the trials differed in design thus the results may not be conclusive. (Chemoradiotherapy for Cervical Cancer Meta-analysis Collaboration (CCCMAC), 2010:15)

In conclusion, the systematic reviews and IPD meta-analysis indicated a significant benefit for CCRT in cervical cancer.

3.5 HIV INFECTION AND CHEMORADIATION

Currently, HIV positive and HIV negative women with cervical cancer are managed in the same way. It is unknown whether the therapeutic ratio for CCRT in HIV negative women is maintained or altered in HIV positive women. There is inadequate literature available on HIV positive women with invasive cervical cancer regarding the response to chemoradiation, side effects, patient adherence and rate of survival. Thus, standard treatments for these patients have not been defined. (Formenti *et al*., 1995:411-412) Some studies suggest that HIV positive cervical cancer patients are known to have poor response to RT and early recurrence, resulting in poorer overall survival (Maiman *et al*., 1990:377).

A few studies have been conducted to assess the impact of RT on HIV positive women with cervical cancer. A retrospective study by Shrivastava *et al.* (2005:31-35) looked at 42 HIV positive women with cervical cancer. Radical RT was prescribed for 32 participants, however, only 22 patients completed the prescribed RT and only 50% of these patients achieved complete response. Treatment delays occurred due to gastrointestinal toxicity in 14% of the patients and skin toxicity in 27% of the patients. (Shrivastava *et al*., 2005:34-35)

Another prospective study by Gichangi *et al.* (2006:405-411) looked at 218 cervical cancer patients who underwent RT. Twenty percent of these participants were HIV positive. It was noted that HIV infection was an independent factor that led to treatment interruptions. In addition, HIV positive women were six times more likely to have residual tumours after RT. A seven fold higher risk of gastrointestinal, skin and

genitourinary toxicity was also noted in HIV positive women. (Gichangi *et al.*, 2006:405-411)

The immune status influences the response to cervical cancer treatment. Patients with CD4 counts greater than 500 cells/mm^3 have a more favourable prognosis. If HAART is not administered during ICC treatment, the viral load may increase. (Little *et al*., 2000:A11) With the concomitant use of HAART and CCRT, there is no increase in viral load during CT. The CD4 count falls by 50% but recovers rapidly within a month after treatment. Therefore, improving the immune function of HIV positive women through the administration of ARVs should be considered when making management decisions in HIV infected women with cervical cancer. (Maiman, 1998:49) However, it has been stated that drug interactions and toxicities of antiretroviral agents may affect the patient response and adherence to CCRT (Powles *et al*., 2002:535).

Chemotherapeutic agents have a narrow therapeutic index and inherent toxicity thus it is important to be aware of other drugs that may interact with these cytotoxic agents. Antiretroviral agents such as didanosine and stavudine may cause peripheral neuropathy. The risk of peripheral neuropathy is increased if cisplatin is concomitantly administered with these ARVs. Other interactions include myelosuppression which is caused by zidovudine and chemotherapeutic agents such as cisplatin. Protease inhibitors such as indinavir may induce or inhibit enzymes that are responsible for the metabolism of the chemotherapeutic agents resulting in pharmacokinetic interactions. Protease inhibitors also cause lactic acidosis which may mimic tumour progression. The route of elimination of HAART and the effect on the cytochrome P450 (CYP450) system is summarised in Table 3.8. Potential pharmacokinetic interactions may occur between HAART and chemotherapeutic agents (Table 3.9). Interpatient variability can also influence drug interactions. Variables such as gender, age, genetics and/or comorbid conditions can affect the patients' response to treatment and the toxic effects that they might experience. (Mounier *et al*., 2009:10-13) Therefore, close monitoring of HIV positive women who are receiving CCRT and ARVs must be instituted (Powles *et al*., 2002:531).

Table 3.8: Route of elimination of HAART and the effect on the CYP 450 system

Drug	Elimination	Effect on CYP450 system
Nucleoside and nucleotide reverse transcriptase inhibitors:		
Zidovudine (ZDV)	Hepatic metabolism with renal excretion	None
Didanosine (ddI)	Renal excretion 50%	None
Stavudine (d4T)	Renal excretion 50%	None
Lamivudine (3TC)	Renal excretion 70%	None
Abacavir (ABC)	Hepatic	Minimal
Emtricitabine (FTC)	Renal excretion 86%	None
Tenofovir (TDF)	Renal excretion 70–80%	None
Non-nucleoside reverse transcriptase inhibitors:		
Nevirapine (NVP)	Hepatic	CYP3A4 inducer
Efavirenz (EFV)	Hepatic	CYP3A4 inducer
Protease inhibitors:		
Saquinavir (SQV)	Hepatic	CYP3A4 inhibitor
Ritonavir (RTV)	Hepatic	CYP3A4 and CYP2D6 inhibitor; CYP3A4 and CYP1A2 inducer
Indinavir (IDV)	Hepatic	CYP3A4 inhibitor
Fosamprenavir (f-APV)	Hepatic	CYP3A4 inhibitor
Lopinavir/ritonavir (LPV/r)	Hepatic	CYP3A4 and CYP2D6 inhibitor; CYP3A4 and CYP1A2 inducer
Atazanavir (ATZ)	Hepatic	CYP3A4 inhibitor, CYP1A2, CYP2C9 inhibitor
Darunavir (DRV)	Hepatic	CYP3A4 inhibitor

Tipranavir (TPV)	Hepatic	CYP3A4 inducer
Integrase inhibitors:		
Raltegravir (RTV)	Hepatic	None
Fusion inhibitors:		
Enfuvirtide (INN)	Hepatic	None

Source: Mounier *et al*., 2009:13

Table 3.9: Potential pharmacokinetic interactions that may occur between HAART and chemotherapeutic agents

Chemotherapy	Enzymes that mediate bio-transformation	Interaction with NNRTI drugs (CYP inducers)	Interaction with PI drugs (CYP inhibitors)
Alkylating agents:			
Cyclophosphamide	3A4, 2B6, 2D6	↑	_
Ifosfamide	3A4	↑	↓
Lomustine	3A4	↑	↓
Anthracyclines:			
Doxorubicin	3A4	_	↓
Mitoxantrone	3A4	_	↓
Camptothecins:			
Irinotecan	3A4	↓	↑
Topotecan	3A4	↑	_
Epipophyllotoxins:			
Etoposide	3A4	↓	↑
Taxanes:			
Docetaxel	3A4	↓	↑↑

Paclitaxel	3A4, 2C8	↓	↑
Vinca alkaloids:			
Vincristine	3A4	↓	↑
Kinase inhibitor:			
Imatinib	3A4	↓	↑
Erlotinib	3A4, 1A2	↓	↑
Proteasome inhibitor:			
Bortezomib	3A4	↓	↑

NNRTI, Non nucleoside reverse transcriptase inhibitor; PI, Protease inhibitor.
Source: Mounier *et al*., 2009:14

A randomised study by Msadabwe (2009) compared CCRT against RT as treatment of cervical cancer in HIV positive patients. Sixty four patients with stages IB to IIIB were recruited to the study, 31 patients in the CCRT arm and 33 in the RT arm (Table 3.10). Six patients were on ARVs at the start of treatment, three in each arm. (Msadabwe, 2009:37)

Table 3.10: Characteristics of participants in the trial by Msadabwe (2009)

Therapy	Patients randomised	Patients who received treatment	Regimen
CCRT	31	25	Cisplatin 30mg/m^3 weekly EBRT 46 Gy in 23 fractions Brachytherapy 8 Gy x 3 fractions
RT	33	28	EBRT 46 Gy in 23 fractions Brachytherapy 8 Gy x 3 fractions

Source: Msadabwe, 2009:30-42

Response to treatment was classified as complete or incomplete. Complete response was defined as the total disappearance of disease at three months and incomplete response was defined as the presence of disease based on physical examinations. At three months, 25 patients in the CCRT arm and 26 patients in the RT arm were evaluated for response. Twenty patients in the CCRT arm and 21

patients in the RT arm had complete response. At three, months the response rates were similar in both arms and residual disease was noted in 20% of the patients. (Msadabwe, 2009:49)

Twenty five patients completed CCRT treatment and 26 patients completed radiation therapy. Three patients had treatment interruptions, two of these patients had residual tumour at three months after treatment. Five patients in the CCRT arm and four patients in the RT arm died before treatment. None of the patients in the CCRT arm died and only one patient in the RT arm died during treatment. At three months, one patient in the CCRT arm died of progressive disease and one patient in the RT arm died from lung metastasis. (Msadabwe, 2009:50-55)

The number of chemotherapy cycles received by patients in the CCRT arm varied between 0 and 5 cycles. Only 40% of patients received the planned five cycles, 76% received four cycles of chemotherapy and 92% received three cycles of chemotherapy. This was due to logistical reasons (3 observations), non adherence (3 observations), renal toxicity (11 observations) and leucopenia (2 observations). (Msadabwe, 2009:57) It has been observed that HIV positive women were more likely to have multiple factors that would prevent the safe administration of cisplatin based chemotherapy (McArdle & Kigula-Mugambe, 2007:95).

Most of the toxicity was mild and reversible. Haematological toxicity was the most common toxicity followed by skin toxicity, gastrointestinal toxicity and bladder toxicity (Table 3.11). (Msadabwe, 2009:42)

Table 3.11: Toxicity observed in the Msadabwe trial (2009)

Toxicity	Total no. of patients	Incidence of toxicity in the CCRT arm (31)	Incidence of toxicity in the RT arm (33)
Leucopoenia	54	29	25
Skin	44	17	27
Gastrointestinal (Lower)	28	12	16
Gastrointestinal (Upper)	15	10	5
Bladder	15	9	6

Source: Msadabwe, 2009:44-46.

The toxicity rates of the HIV positive women in this study were compared to those of HIV negative women in other published studies (Rose *et al*., 1999; Keys *et al.,* 1999 and Pearcey *et al*., 2002). The HIV positive patients did not experience greater haematological toxicity than that reported in the other three studies. However, cutaneous toxicity was higher in HIV positive women who underwent CCRT than HIV negative women who underwent CCRT in the other three studies. (Msadabwe, 2009:51) One theory suggests that HIV positive women have increased sensitivity of the normal tissues to RT leading to excessive acute adverse effects of the normal tissues (Formenti *et al*., 1995:411-412 and Gichangi *et al*., 2006:409).

In summary, the literature suggests that HIV positive and HIV negative women with cervical cancer should be managed using the same principles. However, health professionals that are managing HIV positive patients need to be aware of the important drug interactions and toxicities of antiretroviral agents when used in combination with CCRT.

Chapter 4

METHODOLOGY

4.1 INTRODUCTION

The primary aim of the study was to assess how HIV positive women who have been diagnosed with cervical cancer responded and adhered to cervical cancer therapy. The study also evaluated the effects of the concurrent use of ARVs and CCRT/RT. The methodology employed in the research project is discussed in this chapter.

4.2 LITERATURE REVIEW

Prior to data collection, a comprehensive literature review was conducted on: the course of HPV infection; the relationship between HIV and HPV; HIV and cervical cancer statistics of selected developing and developed countries; CCRT and RT as treatment options and the evaluation of previous studies and randomised trials which investigated the response and adherence to CCRT/RT in HIV positive and HIV negative women. Several electronic online databases such as: PubMed®; Science Direct®; Medline®; EBSCOHOST® and Nexus® were used to obtain journal articles. The literature search extended from 1999 to 2010, however, where applicable, references outside this time frame were consulted.

4.3 ETHICAL APPROVAL

The research proposal was submitted to the Faculty of Health Science Research Technology and Innovative Committee and to the Research Ethics Committee Human at NMMU in order to obtain ethical approval. Permission was also requested from the Head of the Oncology department at the study site (Figure 4.1, step 1). Confidentiality was maintained at all times during the study. No patient identifiers were linked to the data. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki (World Medical Association, 2008).

4.4 STUDY DESIGN

A historical cohort study design was employed for the study. The study was historical or retrospective because the events that were evaluated took place before the onset of the study. The main advantage of retrospective studies is that they make use of data that have already been collected and can, therefore, be performed quickly and

at a low cost. Dawson and Trapp (2001:10) define a cohort as ‘a group of people who have something in common and who remain part of a group over an extended period of time’. Therefore, the cohort consisted of women diagnosed with cervical cancer between 2005 and 2008. Cohort studies are the most suitable for studying the course of a disease, for instance the course of cervical cancer. They possess the correct time sequence to provide the strong evidence for possible causes and effects, as in the effect of CCRT/RT in cervical cancer patients. (Dawson & Trapp, 2001:10-19)

4.5 STUDY SITE AND SAMPLE

The study was conducted at the Oncology Department of a tertiary level hospital located in the Eastern Cape Province, South Africa. The Oncology Department at the study site treats about 200 cervical cancer patients annually (newly diagnosed and follow up cases) and provides radiotherapy and chemotherapy for curative or palliative purposes. The Eastern Cape has a population of about 6.8 million and over 95% of the population depends on the state for health care. The Oncology Department at the study site is not part of a teaching hospital set up, hence it is not funded like other teaching hospitals and cannot provide oncological services to a large number of cervical cancer patients. (Reddi, 2003)

The sample was a total sample in that it consisted of the medical records of all HIV positive and HIV negative women diagnosed with cervical cancer between 2005 and 2008 who were older than 18 years of age at the time of diagnosis and received CCRT, CT, curative RT or PRT.

4.6 DATA COLLECTION

The data was acquired from the patient records kept at the Oncology Department at the study site. The researcher had an introductory meeting with the Head of the Oncology Department at the study site (Figure 4.1, step 2). During the meeting, the oncologist confirmed that both the electronic and hard copies of the patients’ medical files would be made available to the researcher.

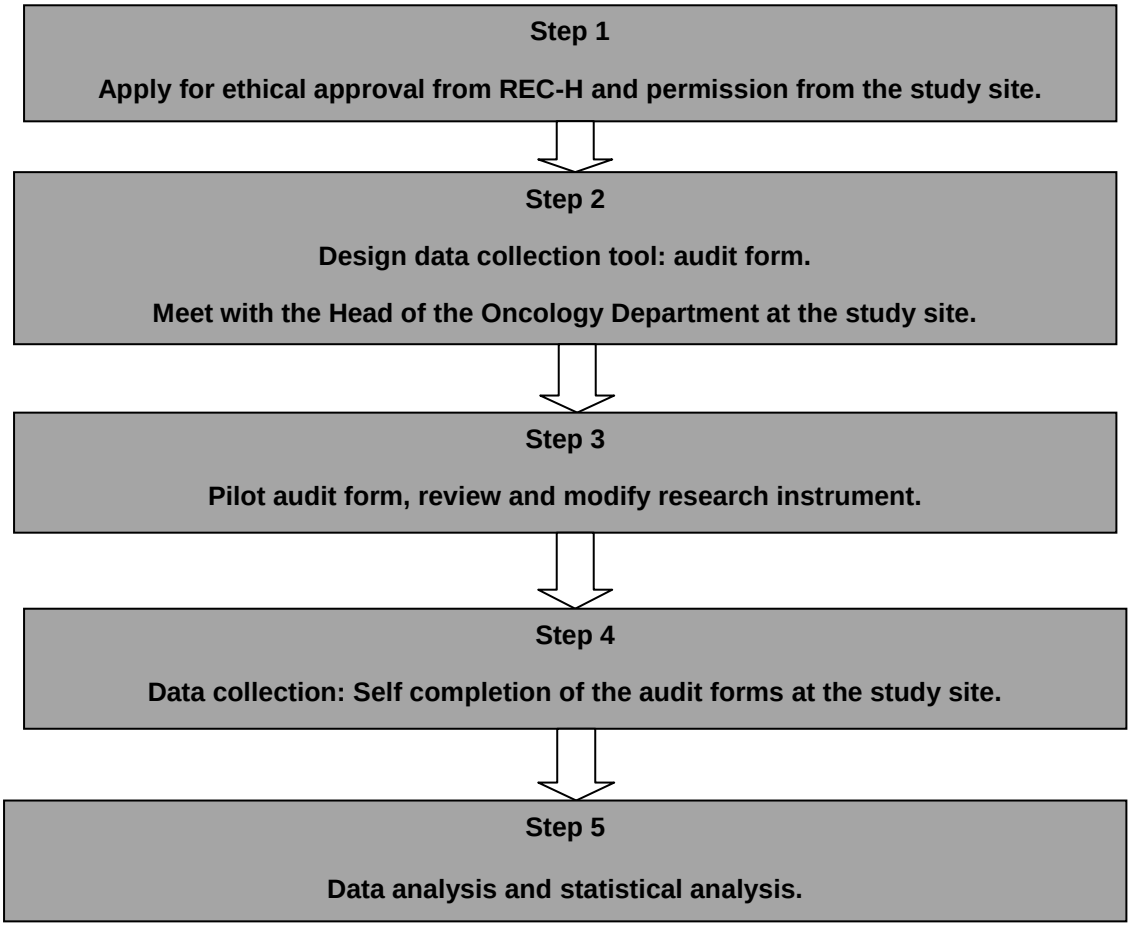

Figure 4.1: Flow diagram outlining the methodology of the research study

A purpose designed researcher completed questionnaire, which was referred to as an audit form, was employed as the data collection tool. Data was collected by reviewing the patients' medical records and capturing the information on an audit form (Appendix 4). A retrospective review of case records over a period of two years was performed. The records were audited for a two year period from the date of diagnosis. Therefore, medical records of the women diagnosed in 2005, were audited from 2005 to 2007, the medical records of the women diagnosed in 2006 were audited from 2006 to 2008, the medical records of the women diagnosed in 2007 were audited from 2007 to 2009 while the medical records of the women diagnosed in 2008 were audited from 2008 to 2010.

The data that was obtained from the medical records was based on results from physical and pelvic examinations, blood counts, chest x-rays, computed tomography (CT) scans and ultrasounds as well as clinical notes. Data collection occurred over a three month period, from September to November 2010. The study population's

laboratory test results and the HIV positive women's ARV regimen were obtained from the National Health Laboratory Service (NHLS) database. The database was accessed from the study site.

4.6.1 Design of the data collection tool

The audit form (Appendix 3)that was used to analyse the patient records was designed using Microsoft® Word. Closed ended questions were used as these types of questions are specific and are preferred in self completion questionnaires. Closed ended questions are also easier for the researcher to code and incorporate into quantitative analyses. (Figure 4.1, step 2) (Smith, 2005: 64)

The audit form (Appendix 3), was eight pages in total and consisted of seven main sections:

- Patient demographics;
- HIV status;
- Cervical cancer status;
- Response to cervical cancer treatment;
- Adherence to cervical cancer treatment;
- Adverse effects; and
- Mortality.

4.6.2 Piloting of the data collection tool

A pilot study was conducted to test the research instrument i.e. the audit form (Figure 4.1, step 3). The questionnaire was piloted to test for validity and reproducibility. Reliability refers to 'the extent to which procedures, measures and data are reproducible or internally consistent' (Smith, 2005:60). Validity refers to 'the extent to which the measures (e.g. records maintained by a researcher) actually measure what they are designed to measure' (Smith, 2005:60). The pilot study sample consisted of a convenience sample of ten medical records from the Oncology Department. The pilot study involved the review, using the audit form (Appendix 3), of ten files that belonged to women who were diagnosed with cervical cancer in 2004. The pilot study was conducted in order to identify any potential problems that would occur while collecting data for the main study.

The audit form was piloted on the 5th and 6th of August 2010. The pilot study revealed that the researcher required 28 ± 2 minutes to evaluate each patient file. After the pilot study, the researcher reviewed and modified the research instrument to ensure that the data acquired in the main study met the study objectives (Appendix 4). The following changes were made to the audit form:

- The audit form used in the main study consisted of six main sections. The mortality section was removed from the audit form. The mortality rate of the participants could not be determined because most of the patients did not attend their follow up visits after treatment.

- Other sections were also modified, for instance Section E2 which consisted of the reasons that led to the non adherence of the patients to cervical cancer treatment. The patients' risk factors were also included in the modified audit form (section C2) (Appendix 4).

- Originally, the researcher's aim was to retrospectively investigate the management of women diagnosed with cervical cancer during 2004 and 2005. The medical records of the women diagnosed in 2004, were to be audited from 2004 to 2008 and the medical records of the women diagnosed in 2005 were to be audited from 2005 to 2009. However, during the pilot study, the researcher realised that this sample would be too small for the main study. "When the sample size is too small, errors may occur and this may give rise to a negative study. A negative study means that the results of the study were not statistically significant but the results would possibly have been significant if the sample size had been larger" (Dawson & Trapp, 2001:124-125). Consequently, the researcher decided to increase the sample size. In the main study, the sample consisted of the medical records of women diagnosed with cervical cancer between 2005 and 2008. The records were audited for a two year period from the date of diagnosis as opposed to a five year period as was earlier proposed.

4.6.3 Administration of the data collection tool

The researcher completed the audit forms at the Oncology Department located at the study site (Figure 4.1, step 4).

4.7 DATA ANALYSIS

Data from the audit form (Appendix 4) was captured on a purpose designed Microsoft Excel ® spreadsheet, collated and analysed (Figure 4.1, step 5). The data was coded by assigning a number for each response choice, for instance, 'Yes' =1 and 'No' =2.

4.8 STATISTICAL ANALYSIS

Microsoft Excel® and StatSoft Statistica® were used for the statistical analysis of the data. Descriptive statistics were used in the summarisation of data and where appropriate, results were presented as mean ± standard deviation. Minimum and maximum values were also reported. The following inferential tests were employed in the study:

4.8.1 The t-test and Cohen's d Statistic

The *t-test* (at a 95% confidence interval) was used to evaluate the differences in means between two groups. The practical significance of the differences in the study sample was represented by the Cohen's d statistic. (Dawson & Trapp, 2001:132) If the calculated d-value was found to be ≤ 0.35, the difference was of small practical significance, if the d-value was between 0.36 and 0.65, the difference was of medium practical significance and a calculated d-value > 0.65, signified a difference that was of high practical significance.

4.8.2 Chi-Square Test of Independence and Cramer's V statistic

The Chi-square test was used to evaluate the differences between the three main groups in the study sample: the HIV negative patients; the HIV positive patients who were on HAART and the HIV positive patients who were not on HAART. The Cramer's V statistic is a post test used with the Chi-square test and was calculated in order to determine the practical significance of a particular result. The degrees of freedom (d.f.) are the number of values in the final calculation of a statistic that are free to vary. The d.f. for an estimate equals the number of observations (values) minus the number of additional parameters estimated for that calculation. For a finding to be practically significant, Cramer's V needs to be equal to or greater than a predetermined value associated with a particular number of degrees of freedom.

(Dawson & Trapp, 2001:152) Table 4.1 depicts the minimum values for Cramer's V (required to denote practical significance) that are associated with a specified number of degrees of freedom.

Table 4.1: Cramer's V values relative to degrees of freedom

Degrees of freedom	Cramer's V		
	Small	**Medium**	**Large**
1*	0.10**	0.30**	0.50**
2	0.07	0.21	0.35
3	0.06	0.17	0.29

* When the degrees of freedom equals one, Cramér's V must be ≥ 0.10 in order to depict practical significance.

** The following ranges for Cramér's V (when d.f. = 1) are indicative of varying degrees of significance: ≤ 0.2 (small); 0.21 - 0.40 (medium); and > 0.40 (large).

4.8.3 Tukey's HSD Procedure

The Tukey's HSD (honestly significant difference) was used to compare mean differences among HIV negative patients; the HIV positive patients who were on HAART and the HIV positive patients who were not on HAART.

For tests pertaining to statistical significance, a calculated p-value of less than 0.05, presented a finding that was significant at the 95% confidence interval. In the current study, a result that was found to be 'significant' was interpreted as being both statistically and practically significant. Furthermore, in instances where statistical analyses involved 'large' Cramér's V yield values (Table 4.1), findings were reported as being 'highly' significant.

4.9 EXCLUSION CRITERIA

The medical files of patients who: only underwent surgical treatment to manage cervical cancer and patients who were younger than 18 years of age at the time of diagnosis were excluded from the study.

4.10 LIMITATIONS OF THE STUDY

The study was retrospective in nature thus some difficulties arose:

- The researcher had no control over how the original data was collected. A few of the doctors who collected some of the data had been transferred to other hospitals thus there was often no way of verifying whether the data was biased or incomplete.

- Due to the transfer of doctors, the data may be inconsistent. Different doctors have different ways of recording data or they may differ in the diagnosis of conditions that occur after cervical cancer treatment. This may lead to the recording of inconsistent data.

- The data did not include all the variables pertaining to the objectives of the study thus the value of the findings was limited. For instance, the mortality rate of the participants could not be determined because some patients did not attend their follow up visits after treatment.

- The patients' HPV types could not be established thus it was not possible to determine the HPV oncogenic types in HIV positive women and in HIV negative women.
- It could not be determined if the patients had access to the primary and secondary prevention strategies. The primary prevention strategies included creating awareness, implementing safe sexual practices, smoking avoidance, good nutrition and HPV vaccination. Secondary prevention strategies included cytology, VIA and HPV DNA testing. (Firnhaber & Michelow, 2009:24)

Chapter 5

RESULTS AND DISCUSSION

5.1 INTRODUCTION

In this chapter the results of the study will be presented. Results are reported, where applicable, as mean ± standard deviation. The results and discussion will be presented in the following main sections:

- Patient demographics;
- HIV status;
- Risk co-factors for cervical cancer treatment;
- Treatment options used at the study site;
- Prognostic factors in cervical cancer;
- Response to cervical cancer treatment;
- Toxicity due to cervical cancer treatment; and
- Adherence to cervical cancer treatment.

5.2 ETHICAL CONSIDERATIONS

Ethical approval to conduct the study was obtained from the Research Ethics Committee Human at NMMU on the 5th July 2010 (REF NO H10-HEA-PHA-001) (Appendix 1). Permission was also granted by the Head of the Oncology Department at the study site (Appendix 2). Confidentiality was maintained at all times during the study. No patient identifiers were linked to the data. The study was conducted in accordance to the ethical principles of the Declaration of Helsinki (World Medical Association, 2008).

5.3 PATIENT DEMOGRAPHICS

The study was conducted at the Oncology Department of a tertiary level hospital located in the Eastern Cape Province, South Africa. The sample consisted of the medical records of 196 HIV positive and HIV negative women diagnosed with cervical cancer between 2005 and 2008 who received CCRT, RT or CT and were older than 18 years of age at the time of diagnosis. Patients who only received surgical treatment and patients who were younger than 18 years of age at the time of diagnosis were excluded from the study.

Age: The average age of all the patients was 57 ± 11.7 years (min = 25 years; max = 96 years). The average age of the HIV negative women was 58 ± 12.0 years (min = 33 years; max = 96 years) and that of the HIV positive women was 54 ± 11.3 years (min = 25 years; max = 91 years).

The results indicated that only one (0.5%; n=196) participant was less than 30 years. Nine (4.5%; n=196) participants were between 31 and 40 years, 49 (25%; n=196) participants were between 41 and 50 years and 69 (35%; n=196) participants were between 51 and 60 years (Figure 6.1). Forty one (21%; n=196) participants were between 61 and 70 years, 21 (11%; n=196) participants were between 71 and 80 years and 2 (1%; n=196) participants were between 81 and 90 years. Three (1.5%; n=196) participants were between 91 and 100 years and one participant's (0.5%; n=196) age was not indicated in the medical file. Therefore, the 51 to 60 years age category had the highest (69; 35%; n=196) number of participants.

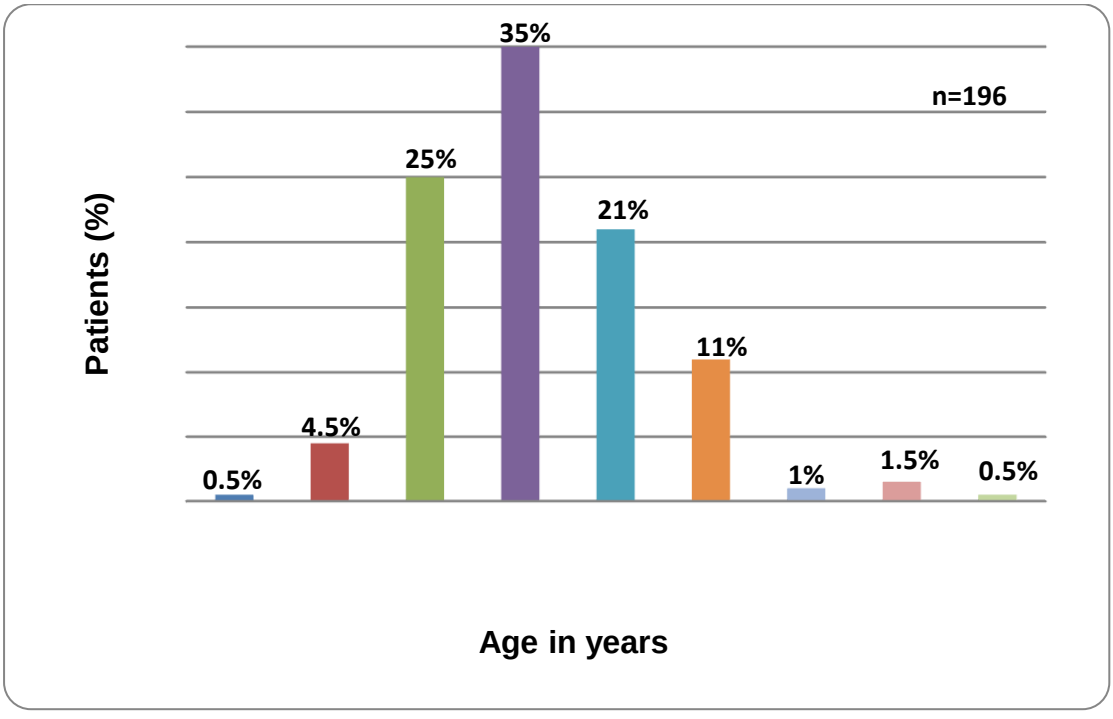

Figure 5.1: Age distribution of the study population

The age distribution in this study is in line with data from other developing countries where 80% to 90% of cervical cancer cases occurred in women who were 40 years and older. The incidence of cervical cancer in most countries was very low in women under 35 to 40 years and was highest in women who were aged between 50 and 65

years. This is because cervical cancer progresses slowly from precancer to ICC. Thus, the high number of patients in the 51 to 60 years age category is expected. (Freedman *et al*., 2006)

The mean age of the HIV positive women with cervical cancer (54 ± 11.3 years) was four years lower than the mean age of HIV negative women (58 ± 12.0 years). Although this result was not significant (t-test = 1.8409; d.f. = 180; p = 0.06728; Cohen's d = 0.27), three other studies that were also conducted in South Africa reported that the mean age of HIV positive women was lower than that of the HIV negative women (Lomalisa *et al*., 2000; Moodley *et al*., 2001 and Moodley *et al*., 2006). These three studies compared the prevalence of cervical cancer in HIV positive and HIV negative women (Table 5.1). Lomalisa *et al*., (2000:460-463) reported that the mean age of HIV positive patients was nine years younger than the HIV negative patients, Moodley *et al*. (2001:194-197) noted that the mean age of the HIV positive women was 15 years younger than the HIV negative women and Moodley *et al.* (2006:1-6) observed that the HIV positive patients presented with ICC six years earlier than the HIV negative patients. This trend was mainly associated with immunosuppression caused by HIV infection that lead to the rapid progression from precancer to ICC (Strickler *et al.,* 2003:1069).

Table 5.1: Mean age difference between HIV positive and HIV negative women with cervical cancer

Author	Mean age of HIV positive women (years)	Mean age of HIV negative women (years)	Age difference
Lomalisa *et al*., 2000	44	53	9
Moodley *et al*., 2001	40	55	15
Moodley *et al*., 2006	40	46	6
Current study	54	58	4

Sources: Lomalisa *et al*., 2000; Moodley *et al*., 2001 and Moodley *et al*., 2006.

5.4 HIV STATUS

One hundred participants (51%; n=196) were HIV negative, 83 participants (42%; n=196) were HIV positive and 13 women's HIV status was unknown (7%; n=196) (Figure 5.2). Therefore, most (100; 51%; n=196) of the participants were HIV negative.

In the literature, a strong association between HIV infection and HPV infection has been shown. It has been noted that the changes that occur in the HPV cell are related to the functioning of the immune system. Thus, when an individual's immunity deteriorates or CD4 count lowers the HPV cell changes increase. A rapid progression from precancer to ICC in HIV positive women has also been reported. (Chirenje, 2005:270 and Holcomb *et al*., 1998:849).

It has been reported that in South Africa, up to 30% of cervical cancer patients are HIV positive (Mqoqi *et al*., 2004:22). In the current study, 42% of the patients were HIV positive. It is difficult to determine the actual incidence of cervical cancer in HIV positive women in countries like South Africa, where the burden of both HIV/AIDS and cervical cancer is high because cancer registries are very inadequate. South Africa has a National Cancer Registry; however, the cervical cancer statistics were last recorded in 2001 and may be outdated. (Bourke, 2007) Therefore, it is quite a challenge, in South Africa, to establish the incidence of ICC in HIV positive and HIV negative women in order to determine the extent to which HIV infection is associated with HPV infection.

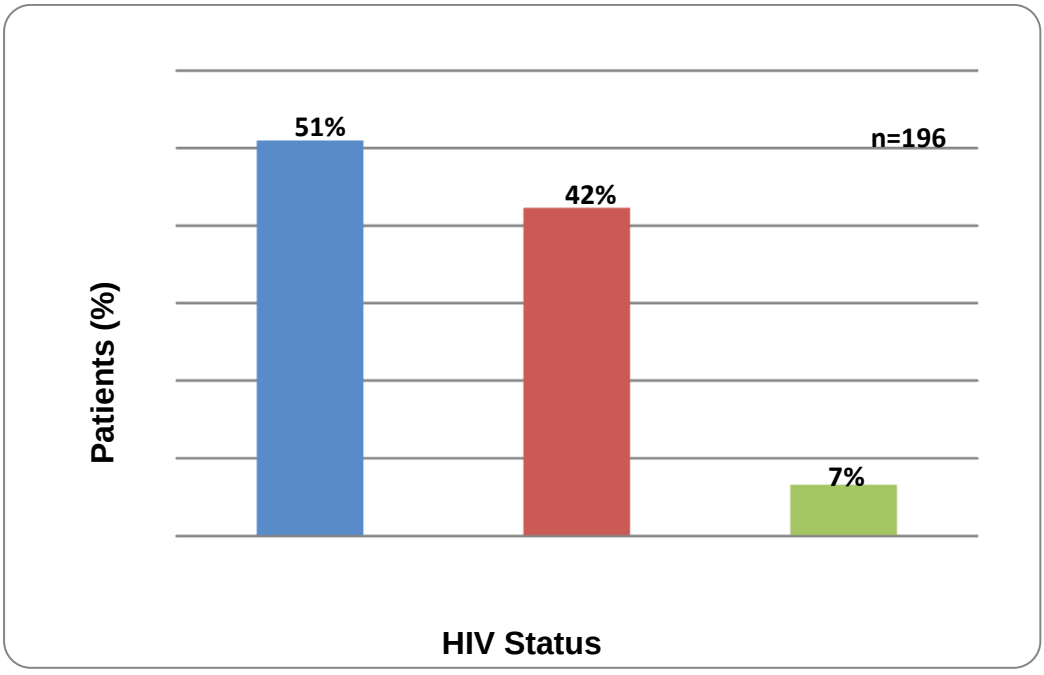

Figure 5.2: HIV status of the participants

5.5 RISK CO-FACTORS FOR CERVICAL CANCER

Apart from persistent HPV infection, there are several soci+o-cultural, socio-economic and biological risk co-factors for HPV infection (Table 2.3). This study looked at some of the risk co-factors that were present in the study population. These included: socio-cultural co-factors such as high parity; biological co-factors such as HIV infection; STIs (chlamydia, gonorrhoea, herpes type 2) and other risk co-factors for cervical cancer such as cigarette smoking and long term use of hormonal contraception (Firnhaber & Michelow, 2009:23).

In the current study, 37% (72; n=196) of the participants had no risk co-factors, 41% (80; n=196) had one risk co-factor, 20% (39; n=196) had two risk co-factors and 2% (5; n=196) of the participants had three risk co-factors for cervical cancer (Figure 5.3).

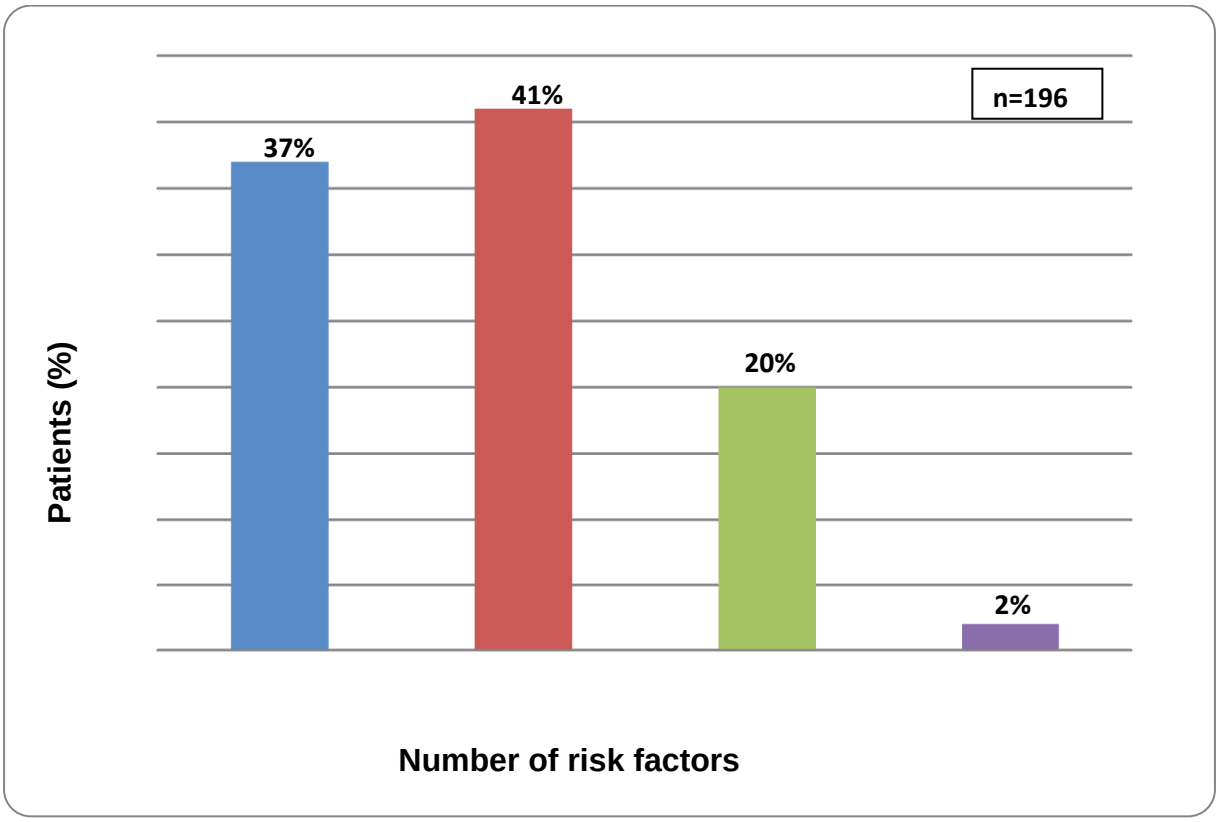

Figure 5.3: Number of risk factors presenting in the study population

5.5.1 Cigarette smoking

Studies have provided data that cigarette smoking can increase the risk of cervical cancer in women with persistent HPV infection. Evidence of nicotine metabolites in

the cervical mucus of smokers suggests that cigarette smoking may have a direct carcinogenic effect on the cervix. Another theory is that cigarette smoking may suppress the local immune response to HPV infection. (Castellasague & Munoz, 2003:1109-1110) In the current study, 28% (55; n=196) of the participants were smokers while 67% (131; n=196) had never smoked a cigarette (Table 5.2). Five percent (10; n=196) of the participants were classified as ex-smokers; these were patients who had a history of cigarette smoking but did not smoke anymore. Therefore, most of the participants were non smokers.

5.5.2 Sexually Transmitted Infections

Thirteen percent (25; n=196) of the participants had contracted at least one STI prior to their cervical cancer diagnosis (Table 5.2). These infections included chlamydia, gonorrhoea and herpes type 2. Eighty seven percent (171; n=196) of the participants had never contracted an STI.

5.5.3 Concurrent HIV infection

Another important risk co-factor is HIV/AIDS, a sexually transmitted disease. As previously reported, 51% (100; n=196) of the participants were HIV negative, 42% (83; n=196) were HIV positive and 7% (13; n=196) of the women's HIV status was unknown (Figure 5.2). Thus, most of the participants had never contracted an STI and were HIV negative.

5.5.4 Long term use of hormonal contraception

Long term use of oral hormonal contraception can increase the risk of cervical cancer among women infected with carcinogenic types of HPV (Schiffman *et al*., 2007:893). Hormones may trigger events that could result in the integration of the HPV virus into the host's genome. Women who use oral hormonal contraception are also less likely to use barrier methods of contraception, which have been shown to have a protective effect against cervical cancer. However, the long term use of oral hormonal contraception being regarded as a risk co-factor for cervical cancer may be due to detection bias because users undergo more frequent gynaecological examinations than non users, thus it is easier to detect cervical cancer in its early stages in women who use oral hormonal contraception. (Duarte-Franco & Franco,

2004:6) Long term use of oral hormonal contraception was reported in 27% (53; n=196) of the participants while 72% (141; n=196) of the participants did not use hormonal contraception (Table 5.2). The use of oral hormonal contraception could not be established for one percent (2; n=196) of the participants because this information was not indicated in their medical records. Therefore, the majority of the participants had not used oral hormonal contraception.

5.5.5 Parity

Parity is the number of times a woman has given birth. It has been suggested that women with higher parity are more likely to have cervical cancer than women of lower parity (WHO/ICO Information centre on HPV and cervical cancer, 2010:20). Multiple pregnancies have a cumulative traumatic or immunosuppressive effect on the cervix and this may facilitate the contraction of HPV infection. Pregnancy induced hormonal effects on the cervix may also stimulate the immortalization of HPV infected cells. (Bayo *et al*., 2002: 204) Data from case control studies conducted by the IARC in four continents, reported that women with HPV infection who had seven or more full term pregnancies were four times more likely to develop cervical cancer as compared to nulliparous women with HPV infection (Munoz *et al.*, 2002:1096). Therefore, using the IARC findings as a guideline, in the current study, women with seven or more full term pregnancies were classified under the 'high parity' category and women who had less than seven full term pregnancies or had never given birth were classified under the 'low parity' category. Fifteen percent (30; n=196) of participants were in the 'high parity' category and 85% (166; n=196) were in the 'low parity' category (Table 5.2). Therefore, most of the participants had low parity.

Table 5.2: Risk co-factors in the study population

Co-factors	Risk co-factors present				Risk co-factors absent	
N=196	Number		Percentage		Number	Percentage
Smoking	Smoker	Ex smoker	Smoker	Ex smoker		
	55	10	28	5	131	67
STI	25		13		171	87
HIV infection	83		42		100	51
Hormonal Contraception	53		27		141	72
High parity	30		15		166	85

5.5.6 Summary

In 2010, the WHO/ICO Information Centre on HPV and cervical cancer published a report that listed the risk co-factors for cervical cancer. The prevalence of these risk co-factors in four countries has been summarised in Table 5.3.

Table 5.3: Risk co-factors for cervical cancer in U.S.A., U.K., S.A. and in the current study

Co-factor	U.S.A.	U.K.	S.A.	Current study (%) n=196
Smoking prevalence (%) women	20.3	31.1	8.9	33
Total fertility rate (live births per women)	2.0	1.6	2.9	N/A
Oral contraceptive use (%)	18.3	26.0	11.1	27
HIV prevalence (%) adults (15-49 years)	0.6	0.2	18.1	42

Source: WHO/ICO Information centre on HPV and cervical cancer, 2010.

The prevalence of the risk co-factors that were identified in the WHO/ICO South African report was compared to that in the current study. The risk co-factor with the highest incidence in both the current study (42%) and the WHO/ICO South African report (18.1%) was HIV infection (Table 5.3). The high percentage of HIV in the

current study (42%) could be due to the fact that the current study was based on a sample from the western region of the Eastern Cape Province as opposed to the WHO/ICO South African report whose percentage (18.1%) pertained to the incidence of HIV in South Africa. Cigarette smoking ranked as the second highest risk co-factor in the current study (33%) as opposed to the WHO/ICO South African report which ranked oral contraceptive use (11.1%) as the second highest risk co-factor for cervical cancer among South African women. The third highest risk co-factor in the current study was found to be oral contraceptive use (27%) while that of the WHO/ICO South African report was cigarette smoking (8.9%). Parity was found to be the lowest risk co-factor for cervical cancer in both the current study and in the WHO/ICO South African report. (WHO/ICO Information centre on HPV and cervical cancer, 2010)

The majority (63%; n=196) of the participants had at least one risk co-factor for cervical cancer and the most prevalent risk co-factor was found to be HIV infection (42%). Therefore, HIV positive women were at a high risk of developing cervical cancer.

5.6 THE TREATMENT PROTOCOLS USED AT THE STUDY SITE

The prescribed treatment options used to treat the different stages of cervical cancer at the study site were examined in the current study (Table 5.4). The study population consisted of six (3%; n=96) stage I patients, 27 (14%; n=196) stage II patients, 106 (54%; n=196) stage III patients and 57 (29%; n=196) stage IV cervical cancer patients. Thus, the majority (106; 54%; n=196) of the patients were diagnosed with Stage III cervical cancer (Table 5.4). The stage I, II and III patients received either curative RT or CCRT and the stage IV patients received palliative RT. The patients who only received surgical treatment to treat stage I cervical cancer were excluded from this study.

Curative RT was prescribed for all six of the stage I cervical cancer patients and this was also the option that was prescribed to treat majority of the stage II cervical cancer patients (14; 52%; n=27) (Table 5.4). Concurrent chemoradiation was the recommended treatment of choice for most of the stage III cervical cancer patients (55; 52%; n=106). In the majority of the stage IV cervical cancer patients (49; 86%;

n=57), RT was prescribed to palliate central disease or distant metastases. The adherence patterns of the study population to their prescribed treatment will be discussed in Section 5.10.

Table 5.4: The treatment options used to treat the different stages of cervical cancer

Stage at diagnosis	Radiation therapy		Chemotherapy		Concurrent Chemoradiation		Palliative Radiotherapy		Totals
	No.	%	No.	%	No.	%	No.	%	
I (n=6)	6	100%	0	0%	0	0%	0	0%	6
II (n=27)	14	52%	0	0	12	44%	1	4%	27
III (n=106)	44	41%	1	1%	55	52%	6	6%	106
IV (n=57)	2	3.5%	2	3.5%	4	7%	49	86%	57
									196

The treatment protocols used to treat the different stages of cervical cancer at the study site (Table 5.4) were compared to, and were found to be in line with the recommendations presented in the 2008 U.K. HIV Association Guidelines for HIV Associated Malignancies and the guideline from the U.S.A. National Cancer Institute (Bower *et. al*., 2008:359 and United States National Cancer Institute, 2010) (Table 2.5). For instance, according to the British and American guidelines, surgical treatment such as hysterectomy or conisation is the recommended treatment option for stage I cervical cancer patients and radiation therapy should only be considered in women who are not surgical candidates. Similarly, in the current study, RT was prescribed for only six of the stage I patients who were not surgical candidates. Most of the stage I patients at the study site had been managed surgically and these patients were excluded from the current study.

According to the British and American guidelines radiation therapy is the recommended treatment option for stage II patients. In the current study, curative RT was prescribed for majority (14; 52%; n=27) of the stage II cervical cancer patients. Concurrent chemoradiation which was recommended for most (55; 52%; n=106) of the stage III cervical cancer patients in the current study, is the treatment option that is recommended to treat stage III cervical cancer according to the British and

American guidelines. Majority of the stage IV cervical cancer (49; 86%; n=57) patients, were prescribed radiation therapy to palliate central disease or distant metastases and this is the recommended option used to manage stage IV cervical cancer based on the British and American guidelines. (Bower *et. al*., 2008:359-360 and United States National Cancer Institute, 2010)

In summary, most of the patients in the current study were managed according to the treatment of choice for the different stages of cervical cancer based on the recommendations presented in the 2008 U.K. HIV Association Guidelines for HIV Associated malignancies and from the U.S.A. National Cancer Institute guideline. (Bower *et. al*., 2008:359-360 and United States National Cancer Institute, 2010)

The majority (83%; 163; n=196) of the patients in the current study were diagnosed with advanced stage cervical cancer (Stage III and IV). This is in line with a comment by Stewart & Kleihues (2003:152), that 'It is estimated that over 80% of women with cervical cancer in developing countries are diagnosed at advanced stages'.Other studies conducted in developing countries have also reported that a large number of women were diagnosed with cervical cancer at its advanced stages due to lack of effective screening programmes used to detect and treat the disease in its early stages (Wabinga *et al*., 2003:68 and Sbilinarayanan *et al*., 2001:10). Most cases of ICC can be prevented through regular screening. In 2000, a national cervical cancer screening policy was developed and implemented in South Africa. Screening occurs by performing three free Pap smears for women at the ages of 30, 40 and 50. Statistics have shown that less that 20% of women have used this service. (Department of Health, South Africa, 2000:2) Consequently, most women seek medical advice only when they have developed symptoms and advanced stages of cervical cancer which is difficult to treat. Thus, in this study, the observation that a high number (163; 83%; n=196) of patients were diagnosed with advanced cervical cancer (stage III and IV) was not surprising.

5.7 PROGNOSTIC FACTORS IN CERVICAL CANCER

The prognostic factors that influence the survival of cervical cancer patients include: patient characteristics (age and blood Hb level); tumour characteristics (stage); and

treatment characteristics (doses and duration of treatment) (Borowsky *et al*., 2005:E19).

In this study, the term 'complete response' to treatment referred to patients who had no recurrence of cervical cancer and no evidence of metastases following RT or CCRT and 'incomplete response' to treatment referred to patients who either had a recurrence of cervical cancer or displayed evidence of metastases after receiving RT or CCRT. This only applied to patients who had stage I, II or III cervical cancer.

In patients who received palliative radiotherapy, the term 'complete response' referred to patients who had experienced relief from pain and other symptoms such as bleeding or vaginal discharge after receiving PRT and 'incomplete response' referred to patients who did not experience relief from pain or the other symptoms following PRT. This only applied to patients who had stage IV cervical cancer.

5.7.1 Patient characteristics

5.7.1.1 Age

The mean age of all the patients (stage I to IV) who displayed complete response to cervical cancer treatment was 56.7 $\pm$ 12.3 years and the mean age of all the patients who displayed incomplete response to treatment was 57.4 $\pm$ 11.0 years. There was no significant difference in the mean age between the women who displayed complete response to treatment and those who displayed an incomplete response to treatment (t-test = 0.3766; p = 0.7069; Cohen's d = 0.05).

It is believed that cervical cancer in younger patients is more aggressive than in older patients (Brewster *et al*., 1999:1466). However, age is not an independent prognostic factor for the survival of cervical cancer patients due to the selection of different treatment options for patients of the same age. For instance, women of the same age who have small tumours may receive surgical treatment and those who have bigger tumours may receive RT or CCRT. Therefore, poor prognosis cannot be related to age alone. (Ho *et al*., 2004:461 and Moore *et al*., 2010:45) This may explain why, in the current study, there was no significant difference in the mean age between the women who displayed complete response to treatment and those who

displayed an incomplete response to treatment (t-test = 0.3766; p = 0.7069; Cohen's d = 0.05).

5.7.1.2 Blood Hb levels

Anaemia is a disease characterised by low Hb levels. About 30% to 90% of patients with cancer experience anaemia. Anaemia may occur as a result of the cancer interfering with haematopoiesis or from myelosuppression caused by chemotherapeutic agents. Radiotherapy can also have a significant effect on the bone marrow, thus worsening haematological toxicity caused by chemotherapy. Various studies have suggested that anaemia at diagnosis and/or during treatment may affect the prognosis of cervical cancer patients. (Grogan *et al*., 1999:1532 and Dunst *et al*., 2003:782) An anaemic cervical cancer patient may not be able to undergo her scheduled radiotherapy or chemotherapy regimen and this may lead to suboptimal outcomes of treatment (Hinkel *et al*., 2010: S39). Thus, anaemia may present a challenge in the management of cervical cancer. In the current study, patients with a blood Hb level less than 12g/dl were classified as anaemic. The patients' Hb levels during and after treatment were investigated rather than the Hb levels at presentation as studies have shown that the former is the stronger prognostic factor (Grogan *et al*., 1999:1531 and Obermair *et al*., 2001:904).

Eighty four percent (164; n=196) of the patients had anaemia during ICC treatment while 16% (32; n=196) of the patients did not have anaemia during ICC treatment (Table 5.5). Of the 164 patients who had anaemia, 47% (77; n=164) responded favourably to ICC treatment and 53% (87; n=164) did not respond well to ICC treatment. Of the 32 patients who did not have anaemia during ICC treatment, 65% (20; n=32) responded well to ICC treatment and 35% (12; n=32) did not respond well to ICC treatment. Thus the majority (164; 84%; n=196) of patients experienced anaemia during treatment and a large number of these anaemic patients (87; 53%; n=164) had a poor response to treatment.

Table 5.5: Presentation of anaemia in the study participants who experienced a 'complete' or 'incomplete' response to treatment

	Complete response		Incomplete response		Totals
Anaemic	77	47%	87	53%	164
Not anaemic	20	65%	12	35%	32
					196

In the current study, there was no significant difference between the prognosis of the anaemic patients and that of the non anaemic patients (Chi^2 = 1.46, d.f. = 1, p = 0.22644, Cramer's V = 0.09). However, other studies have reported that anaemia was significantly associated with poor prognosis of cervical cancer patients (Grogan *et al*., 1999:1534; Dunst *et al*., 2003:783 and Obermair *et al.*, 2001:906). These studies postulated that anaemia could be linked to poor tumour sensitivity to radiotherapy due to decreased oxygen supply. Radiation induced killing of tumours increased three-fold in the presence of oxygen. The cytotoxic activity of the alkylating agents also appeared to be linked to the oxygen dependent production of free radicals. In addition, anaemia might have promoted the transcription of genes that were vital for tumour cell adaptation and survival. This resulted in tumour aggressiveness, resistance to chemotherapy or radiotherapy and poor prognosis. Therefore, low blood Hb levels could be regarded as an independent factor that affects the clinical outcome of cervical cancer patients. (Grogan *et al*., 1999:1534; Dunst *et al*., 2003:783 and Obermair *et al.*, 2001:906)

Of the 164 patients who had anaemia, 31% (52; n=164) received curative RT, 2% (3; n=164) received CT, 39% (64; n=164) received CCRT and 28% (45; n=164) received PRT (Figure 5.4). Hence, the highest cases of anaemia were reported in patients who received CCRT.

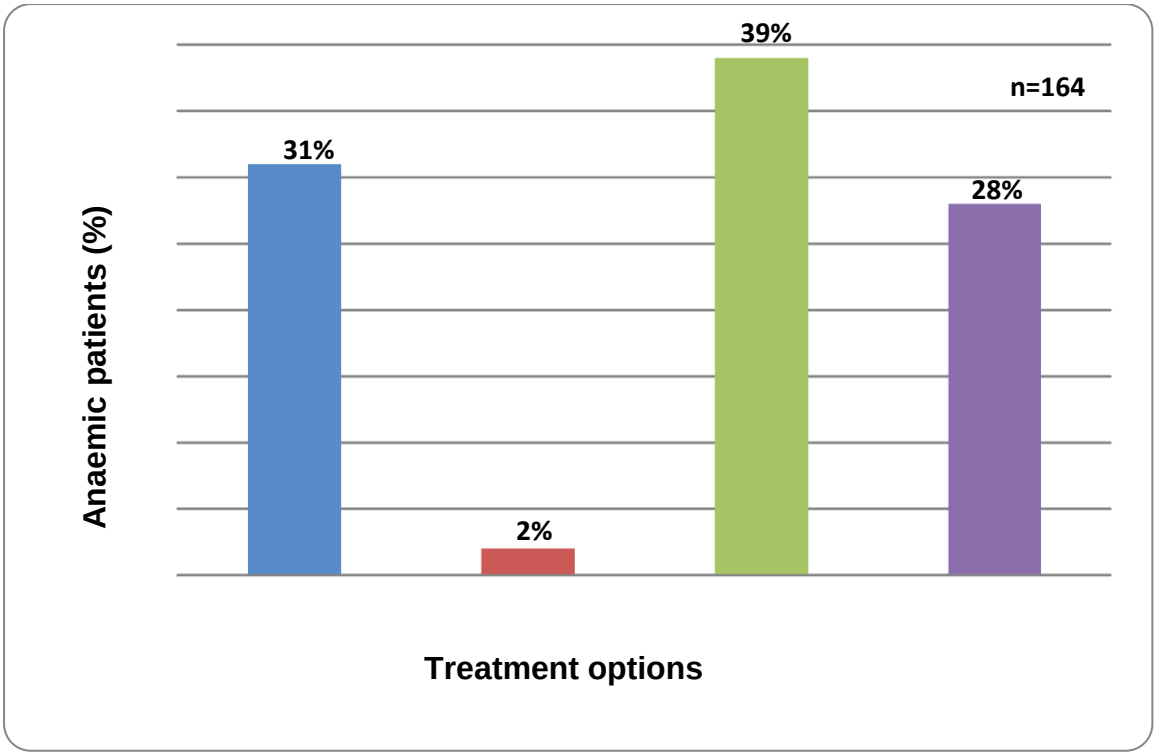

Figure 5.4: Relationship between anaemia and treatment options
(RT= radiotherapy; CT=chemotherapy; CCRT=concurrent chemoradiation; PRT=palliative radiotherapy)

In 1999, the United States National Cancer Institute recommended that CCRT should be considered as the standard treatment for advanced cervical cancer. This recommendation was based on the results of five randomised controlled trials: Keys *et al*., 1999:1154-1161; Morris *et al.,* 1999:1137-1143; Rose *et al*., 1999:1144-1153; Whitney *et al*., 1999:1606-1613 and Peters *et al*., 2000:1606-1613 (Table 3.3). Since this recommendation, systematic reviews and meta-analysis conducted by Lukka *et al*. (2002:203-212) and Green *et al*. (2001:781-786) reported on the effects of CCRT. Kirwan *et al*. (2003:216-226) later evaluated the trials that met the inclusion criteria of the Green *et al*., (2001:781-786) systematic review and meta-analysis in order to examine the toxicity of CCRT for cervical cancer. This involved the identification of 19 trials that were carried out between 1980 and 2000 and included 4580 randomised patients. Kirwan *et al.,* (2003:216-226) found that there was no significant difference in the Hb levels among the CCRT groups and RT groups but showed a trend towards more cases of anaemia being reported in the CCRT groups. This observation was in line with the current study in that there was no significant difference in the Hb levels between the CCRT group and the RT group (Chi^2 = 4.83,

d.f. = 3, p = 0.18497, Cramer's V = 0.16) but more cases of anaemia were reported in the CCRT group (64; 39%; n=164) than in the RT group (51; 31%; n=164).

More severe anaemia develops in patients treated with CCRT than with RT alone, because of the additive myelosuppressive effect of chemotherapeutic drugs (Kim *et al*., 2007:199). Therefore, it is important to effectively manage this condition as it not only prevents the administration of chemotherapy but is in itself associated with poor treatment outcomes.

In summary, the current study could not determine whether the presence of anaemia could significantly affect the prognosis of the cervical cancer patients despite the fact that a large number (87; 53%; n=164) of the anaemic patients had a poor response to treatment. There was also no significant difference in the Hb levels between the CCRT group and the RT group (Chi^2 = 4.83, d.f. = 3, p = 0.18497, Cramer's V = 0.16). However, more cases of anaemia were reported in the CCRT group (64; 39%; n=164) than in the RT group (51; 31%; n=164).

5.7.2 Tumour characteristics

5.7.2.1 Stage at initiation of treatment

According to literature, the stage of cervical cancer is not an independent prognostic factor but relies on when treatment was initiated. Detection and treatment of cervical cancer in its earliest stages significantly improves prognosis. (Committee on Practice Bulletins-Gynaecology, 2002:857)

In the current study, the stage of cervical cancer at initiation of treatment was compared to response to treatment. This was done at one month, six months, 12 months, 18 months and 24 months after treatment. Not all patients returned for follow up after each time period so sample size varies at the different periods.

All of the 196 patients returned to the study site one month after treatment. Complete response was noted in 83% (5; n=6) of the stage I patients, 93% (25; n=27) of the stage II patients, 61% (65; n=106) of the stage III patients and 4% (2; n=57) of the stage IV patients (Figure 5.5). Thus at one month following treatment there was a highly significant difference in the incidence of complete response in patients at different stages of cervical cancer (Chi^2 = 88.9, d.f. = 3, p = 0.0000, Cramer's V

=0.67). The highly significant difference in response to treatment by patients at different stages of cervical cancer was maintained at six months after treatment (Chi^2 = 70.94, d.f. = 3, p = 0.0000, Cramer's V = 0.62), 12 months after treatment (Chi^2 = 48.53, d.f. = 3, p = 0.0000, Cramer's V = 0.54), 18 months after treatment (Chi^2 = 32.02, d.f. = 3, p = 0.0000, Cramer's V = 0.5) and 24 months after treatment (Chi^2 = 18.69, d.f. = 3, p = 0.0032, Cramer's V = 0.45).

At six months after treatment (n=184), complete response was noted in 83% (5; n=6) of the stage I patients, 93% (25; n=27) of the stage II patients, 66% (70; n=106) of the stage III patients and 1% (2; n=57) of the stage IV patients (Figure 5.5).

Twelve months after completion of treatment (n=168), complete response was noted in 67% (4; n=6) of the stage I patients, 70% (19; n=27) of the stage II patients, 53% (56; n=106) of the stage III patients and 5% (3; n=57) of the stage IV patients (Figure 5.5).

At 18 months after treatment (n=146), complete response was noted in 50% (3; n=6) of the stage I patients, 67% (18; n=27) of the stage II patients, 49% (52; n=106) of the stage III patients and 4% (2; n=57) of the stage IV patients (Figure 5.5).

Twenty four months after treatment (n=139), complete response was observed in 67% (4; n=6) of the stage I patients, 37% (10; n=27) of the stage II patients, 39% (41; n=106) of the stage III patients and 2% (1; n=57) of the stage IV patients (Figure 5.5).

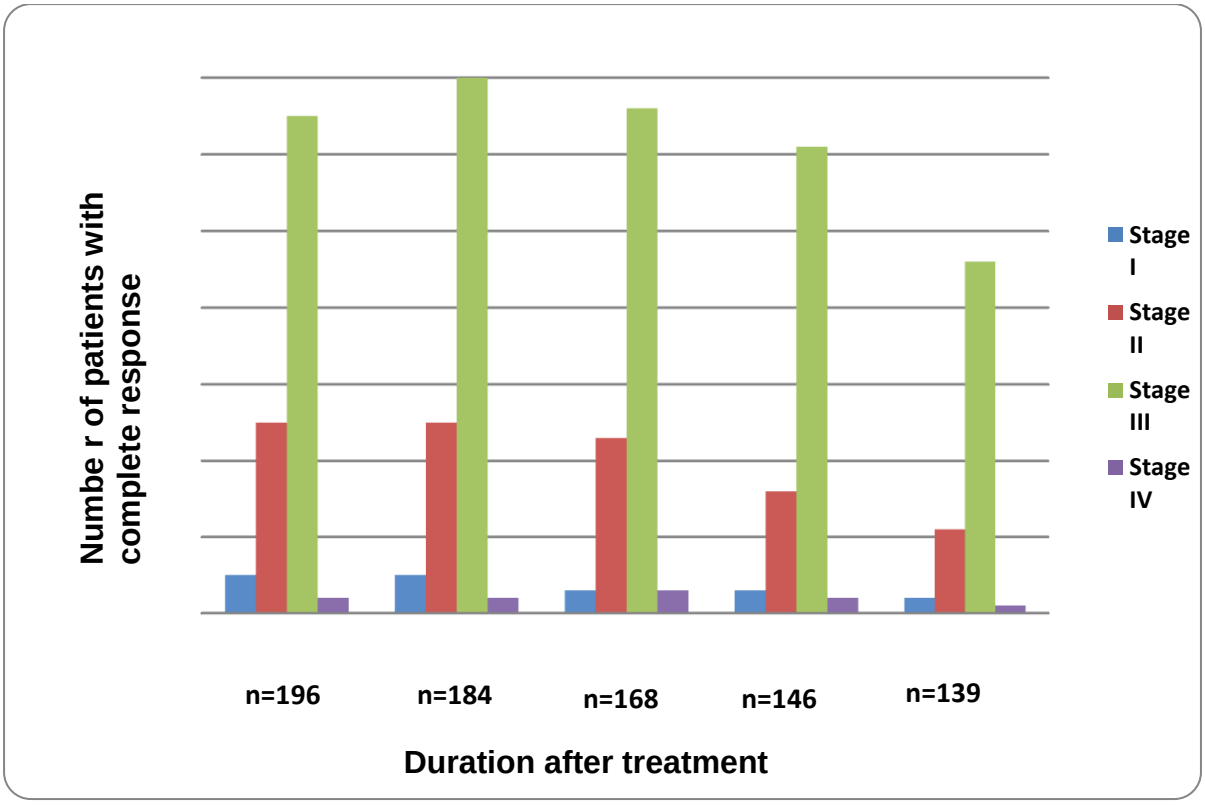

Figure 5.5: Patients diagnosed at various stages of ICC who experienced complete response to treatment

In summary, the study revealed that there was a highly significant difference in the response to cervical cancer treatment between the patients with early stage cervical cancer (stage I and II) and the patients with advanced stage cervical cancer (stage III and IV). These significant differences were observed at each interval: one month after treatment (Chi^2 = 88.9, d.f. = 3, p = 0.0000, Cramer's V =0.67); six months after treatment (Chi^2 = 70.94, d.f. = 3, p = 0.0000, Cramer's V = 0.62); 12 months after treatment (Chi^2 = 48.53, d.f. = 3, p = 0.0000, Cramer's V = 0.54); 18 months after treatment (Chi^2 = 32.02, d.f. = 3, p = 0.0000, Cramer's V = 0.5) and 24 months after treatment (Chi^2 = 18.69, d.f. = 3, p = 0.0032, Cramer's V = 0.45). At each of these intervals, the response to cervical cancer treatment was poorer among women with advanced stage cervical cancer.

Cervical cancer is one of the few cancers that can be easily managed if it is detected in its earliest stages. The current study showed a trend that patients with stage I and stage II disease responded to treatment more favourably than the patients with stage III and stage IV. This is due to the fact that the local treatment of cervical cancer in

its earliest stages using surgery or radiotherapy is more effective than systemic treatments such as concurrent chemoradiation that is used to manage the advanced stages of the disease (Committee on Practice Bulletins-Gynaecology, 2002:857).

The American Cancer Society has found that, with treatment, the five year relative survival rate for the earliest stage of invasive cervical cancer is 92% and the rate for all the stages combined is 72%. Approximately, 80% to 90% of women with stage I cancer and 50% to 65% of women with Stage II cancer who receive treatment are still alive five years after diagnosis. Only 25% to 35% of women with Stage III cancer and 15% or less of women with Stage IV cancer are alive five years after diagnosis. (American Cancer Society, 2009:22) Although the study carried out by the American Cancer Society looked at the relationship between the clinical stage and the five year survival rate and this current study looked at the relationship between the clinical stage and the response to treatment, it is clear that with treatment, patients who had cervical cancer detected at its earliest stages had a more favourable prognosis than those patients that were diagnosed with advanced stage cervical cancer.

In conclusion, most of the participants in the current study (163; 83%; n=196) were diagnosed with cervical cancer in its advanced stages (stage III and stage IV). The patients with early stage cervical cancer (stage I and II) responded more favourably to treatment than the patients with advanced stage cervical cancer. It has been shown that the treatment of cervical cancer in its earliest stages using surgery or RT is more effective than using systemic treatments such as CCRT that is used to manage the advanced stages of the disease (Committee on Practice Bulletins-Gynaecology, 2002:857). Therefore, it is imperative to detect and treat cervical cancer in its earliest stages in order to prevent the disease from progressing into an advanced stage.

5.7.3 Treatment characteristics

5.7.3.1 Introduction

At the study site, the prescribed radiotherapy treatment for Stage Ib to III disease included EBRT 50 Gray (Gy) in 25 fractions, 2 Gy daily over five weeks and ICT brachytherapy 24.8 Gy in four fractions (6.2 Gy/fraction). Carboplatin and cisplatin

were the two chemotherapeutic agents that were used at the study site to treat cervical cancer. The prescribed dose of carboplatin was between 450 and 600 mg/m^2 weekly and the dose of cisplatin ranged between 50 and 60 mg/m^2 weekly. The number of cycles received by patients who were in the chemotherapy or chemoradiation group ranged between 4 and 7 cycles. In order to minimise cisplatin or carboplatin induced nephrotoxicity, one litre of normal saline infusion was used to hydrate the patients before they received chemotherapy. The prophylactic antiemetics that were administered comprised dexamethasone 8 mg intravenous (IV) and granisetron 1 mg (IV). After prehydration and the administration of the antiemetics, carboplatin or cisplatin was then added to one litre of normal saline and administered to the patients. Cisplatin was withheld in patients with severe nephrotoxicity and ototoxicity.

Radiotherapy was administered to patients with stage IV disease for palliation of central or metastatic disease. These patients received 30 Gy in 10 fractions over two weeks. These patients also received analgesics and antibiotics as symptomatic treatment of advanced disease.

Since the 1999 National Cancer Institute publication that recommended the use of CCRT to treat cervical cancer patients with inoperable disease, oncology departments worldwide have adopted this practice in their treatment protocols. The widely accepted standard includes EBRT 45 to 50 Gy in 25 fractions, ICT brachytherapy 15 to 28 Gy in two to four fractions and weekly concomitant cisplatin chemotherapy 40mg/m^2 for six cycles (Eifel *et al*., 2004:1150). The prescribed radiotherapy protocols used at the study site were in line with this universally acceptable standard, however, the study site prescribed weekly concomitant cisplatin chemotherapy 50mg/m^2 as opposed to 40 mg/m^2 which is more frequently prescribed. In the case of palliative treatment, three fractions of 10 Gy is the most frequently prescribed dose and this was the dose that was used at the study site (Lonkhuijzen & Thomas, 2011:288).

5.7.3.2 Duration of therapy

In the current study, in patients who only received curative RT (stage I, II and III), the average duration of treatment in patients who had a complete response was 41.9 $\pm$ 8

days (6 weeks) and that of patients who had an incomplete response to RT was 33.2 ± 16 days (5 weeks). In stage I, II and III patients who received CCRT, the average duration of treatment in patients who had a complete response was 64.9 ± 12 days (9 weeks) and that of patients who had an incomplete response to treatment was 58.2 ± 30.5 days (8 weeks).

According to literature, the longer the time period over which the prescribed treatment is administered (for example, longer periods between doses), the shorter the overall survival, disease free survival and local control of the tumour (Waggoner, 2003:2223 and Taylor *et al.*, 1990:97). The American Brachytherapy Society recommends that the total treatment duration for cervical cancer should be less than eight weeks. After approximately eight weeks of therapy, the increase in local failure is 0.7% to 1.0% per day for everyday of treatment missed. (Nag *et al*., 2000:202)

There was no significant difference in the average duration of treatment between the patients who had a complete response to CCRT and the patients who had an incomplete response to CCRT (t-test = 0.93828 p = 0.35137, Cohen's d = 0.3). However, a highly significant difference in the average duration of treatment between the patients who had a complete response to RT and the patients who had an incomplete response to RT was reported whereby the patients who had a complete response to RT received treatment over a longer period of time (t-test = 2.91678 p = 0.00487, Cohen's d = 0.79).

In the current study, the average duration of treatment of the patients who had a complete response to RT was less than eight weeks (6 weeks) while the average duration of treatment of the patients who had a complete response to CCRT was more than eight weeks (9 weeks). The average duration of treatment of the patients who had an incomplete response to RT (5 weeks) and CCRT (8 weeks) was lower than that of the patients who displayed complete response to RT (6 weeks) or CCRT (9 weeks). The results of the current study, in terms of duration of treatment, are in contrast to the recommendation made by the American Brachytherapy Society in that the patients who experienced complete response to RT or CCRT received treatment over a longer period of time than the patients who experienced an incomplete response to RT or CCRT. This was due to the fact that in the current study some of the patients who exhibited an incomplete response to RT or CCRT did

not complete the prescribed treatment either due to non adherence to the prescribed treatment or early termination of treatment by the oncologist. Therefore, in the current study a link could not be established between the duration of cervical cancer treatment and patient outcome.

The WHO defines palliative care as 'the active total care of patients whose disease is not responsive to curative treatment' (WHO, 1990). Therefore PRT is not aimed at curing cervical cancer but at providing relief from pain and other physical symptoms such as bleeding and vaginal discharge. In this study, patients who had a complete response to PRT experienced relief from pain and other symptoms and patients who had an incomplete response to PRT did not experience pain relief and other symptoms. Bleeding was the symptom that was often the reason for palliative treatment in women with advanced cervical cancer. The average duration of treatment in patients who had a complete response to PRT was 9 $\pm$ 1 days and that of patients who had an incomplete response to PRT was 10.6 $\pm$ 6 days. There was no significant difference in the average duration of treatment between the patients who had a complete response to PRT and the patients who had an incomplete response to PRT (t-test = 2.61688 p = 0.92613, Cohen's d = 0.79).

5.7.3.3 Doses employed

Many oncologists, including the ones at the study site, believe that prescribing PRT in multiple fraction regimens (20 Gy in five fractions, 30 Gy in 10 fractions, and 45 Gy in 20 to 25 fractions) leads to better symptom reduction than administering PRT in a large single fraction. In resource constrained countries such as South Africa, where there are insufficient trained health care staff and radiation equipment and most cervical cancer patients have limited access to treatment facilities due to financial or geographical factors, large single fractions of PRT may be preferable if similar palliative results could be achieved (Lonkhuijzen & Thomas, 2011:288). This was, however, not the practice at the study site.

Studies have been conducted in order to identify a palliative radiation schedule that would provide an optimal palliative effect with the least burden on the cervical cancer patients or on the health care system. Lonkhuijzen & Thomas (2011:287-291) performed a systematic literature review of eight studies in order to identify an

optimal palliative radiation schedule for treatment of patients with advanced cervical cancer (Table 5.6). In three of the studies, which used the 30 Gy in 10 fraction regimen (multiple fraction regimen), complete cessation of bleeding was reported in 45%, 31% and 0% of the patients (based on 86, 76 and 41 patients respectively) (Boulware *et al*., 1979:337; Onsrud *et al*., 2001:1899 and Mishra *et al*., 2005:212). Pain relief was noted in 15% of 86 patients in the Boulware *et al*. study (1979:333-338). The 30 Gy in 10 fraction regimen was also used in the current study and when the stage IV cervical cancer patients were evaluated one month after treatment, complete cessation of bleeding and pain relief was reported in 4% (2; n=57) of the patients. In contrast, a study by Patricio *et al*. (1987:133-135), which used a dose of 13 Gy in two fractions (low fraction regimen), led to a cessation of bleeding in 46% and provided pain relief in 14% of 56 patients. Another low fraction regimen dose of 10 Gy given in two fractions stopped bleeding in 93% of 15 patients in the study by Grigsby *et al.* (2002:18-21).

Two studies investigated relief from vaginal discharge as a study outcome (Onsrud *et al*., 2001:1896-1901 and Mishra *et al*., 2005:208-212). The studies which used a multiple fraction regimen of 30 Gy in 10 fractions reported that radiation improved this symptom. One study also reported relief from other symptoms such as dysuria, ulceration, constipation and tenesmus (Spanos *et al*., 1996:1479-1482). This systematic review drew inconclusive results in that it did not determine a palliative radiation regimen that would provide optimal symptom relief and have minimal burden on both patients and the health care system.

Table 5.6: Studies reviewed by Lonkhuijzen and Thomas (2011)

Study	Number of patients (total)	RT dose	Bleeding cessation	Pain relief
Boulware *et al*., 1979	86	30 Gy in 10 fractions	45%	15%
Hodson & Krepart, 1983	14	30 Gy in 10 fractions		
Halle *et al*., 1986	42	30 Gy in 10 fractions		
Onsrud *et al*., 2001	28	30 Gy in 10 fractions	31%	
Mishra *et al*., 2005	100	30 Gy in 10 fractions	0%	
Patricio *et al*., 1987	56	13 Gy in 2 fractions	46%	14%
Spanos *et al*., 1996	61	14.8 Gy in 4 fractions		
Grigsby *et al*., 2002	15	10 Gy in 5 fractions	93%	
Current study (one month after treatment)	57	30 Gy in 10 fractions	4%	4%

Source: Lonkhuijzen & Thomas, 2011:287-291

5.7.3.4 Summary

The current study could not determine whether the prolongation of curative RT or CCRT would lead to poor patient outcome. This was due to the fact that some of the patients who exhibited an incomplete response to RT or CCRT did not complete the prescribed treatment either due to non adherence to the prescribed treatment or early termination of treatment by the oncologist. In the case of PRT, although the average duration of treatment in patients who had a complete response to PRT (9 $\pm$ 1 days) was shorter than that of patients who had an incomplete response to PRT (10.6 $\pm$ 6 days), there was no significant difference in the response to treatment between these two groups (t-test = 2.61688 p = 0.92613, Cohen's d = 0.79). More studies need to be conducted in order to find out if large single fractions of PRT, rather than multiple fractions of PRT, which provide optimal patient outcome with

minimal use of resources may be preferable if similar palliative results could be achieved.

5.8 RESPONSE TO CERVICAL CANCER TREATMENT IN HIV POSITIVE VERSUS HIV NEGATIVE WOMEN

This section will look at the response to cervical cancer treatment in the HIV negative women compared to the HIV positive women. The study population consisted of 100 (51%; n=196) HIV negative participants and 83 (42%; n=196) HIV positive participants. This section will exclude 13 of the 196 participants whose HIV status could not be determined as the data was not present in the patient files.

5.8.1 Complete versus incomplete response to cervical cancer treatment

In this study, the term 'complete response' referred to patients who had no recurrence of cervical cancer and no evidence of metastases and 'incomplete response' referred to patients who either had a recurrence of cervical cancer or displayed evidence of metastases. This only applied to patients who received RT and CCRT for curative purposes (stage I, II and III patients). In patients who received PRT (stage IV patients), the term 'complete response' referred to patients who had experienced relief from pain and other symptoms such as bleeding or vaginal discharge and 'incomplete response' referred to patients who did not experience relief from pain or the other symptoms.

The response of the cervical cancer patients was evaluated one month after treatment, six months after treatment, 12 months after treatment, 18 months after treatment and 24 months after treatment.

All the 183 patients with known HIV status returned to the study site one month after treatment. Complete response was noted in 65% (65; n=100) of the HIV negative patients and in 35% (29; n=83) of the HIV positive patients (Figure 5.6). At one month following treatment there was a significant difference in the incidence of complete response between the HIV positive patients and the HIV negative patients (Chi^2 = 16.4, d.f. = 1, p = 0.00005, Cramer's V =0.31). The significant difference in response to treatment between the HIV positive patients and the HIV negative patients was maintained at six months after treatment (Chi^2 = 15, d.f. = 1, p =

0.00011, Cramer's V = 0.34), 12 months after treatment (Chi^2 = 20.5, d.f. = 1, p = 0.00001, Cramer's V = 0.37), 18 months after treatment (Chi^2 = 9.8, d.f. = 1, p = 0.00173, Cramer's V = 0.28) and 24 months after treatment (Chi^2 = 5.0, d.f. = 1, p = 0.02571, Cramer's V = 0.26).

At six months after treatment (n=171), complete response was noted in 61% (61; n=100) of the HIV negative patients and in 34% (28; n=83) of the HIV positive patients. Twelve months after completion of treatment (n=155),complete response was noted in 60% (60; n=100) of the HIV negative patients and in 27% (22; n=83) of the HIV positive patients.

At 18 months after treatment (n=133), complete response was noted in 54% (54; n=100) of the HIV negative patients and in 25% (21; n=83) of the HIV positive patients.

The response of 126 patients was evaluated 24 months after treatment. Complete response was noted in 41% (41; n=100) of the HIV negative patients and in 18% (15; n=83) of the HIV positive patients.

In summary, the study revealed that there was a significant difference in the response to cervical cancer treatment between the HIV positive patients and the HIV negative patients. These significant differences were observed at each interval: one month after treatment (Chi^2 = 16.4, d.f. = 1, p = 0.00005, Cramer's V =0.31); six months after treatment (Chi^2 = 15, d.f. = 1, p = 0.00011, Cramer's V = 0.34); 12 months after treatment (Chi^2 = 20.5, d.f. = 1, p = 0.00001, Cramer's V = 0.37); 18 months after treatment (Chi^2 = 9.8, d.f. = 1, p = 0.00173, Cramer's V = 0.28) and 24 months after treatment (Chi^2 = 5.0, d.f. = 1, p = 0.02571, Cramer's V = 0.26). At each of these intervals, the response to cervical cancer treatment was poorer among HIV positive women.

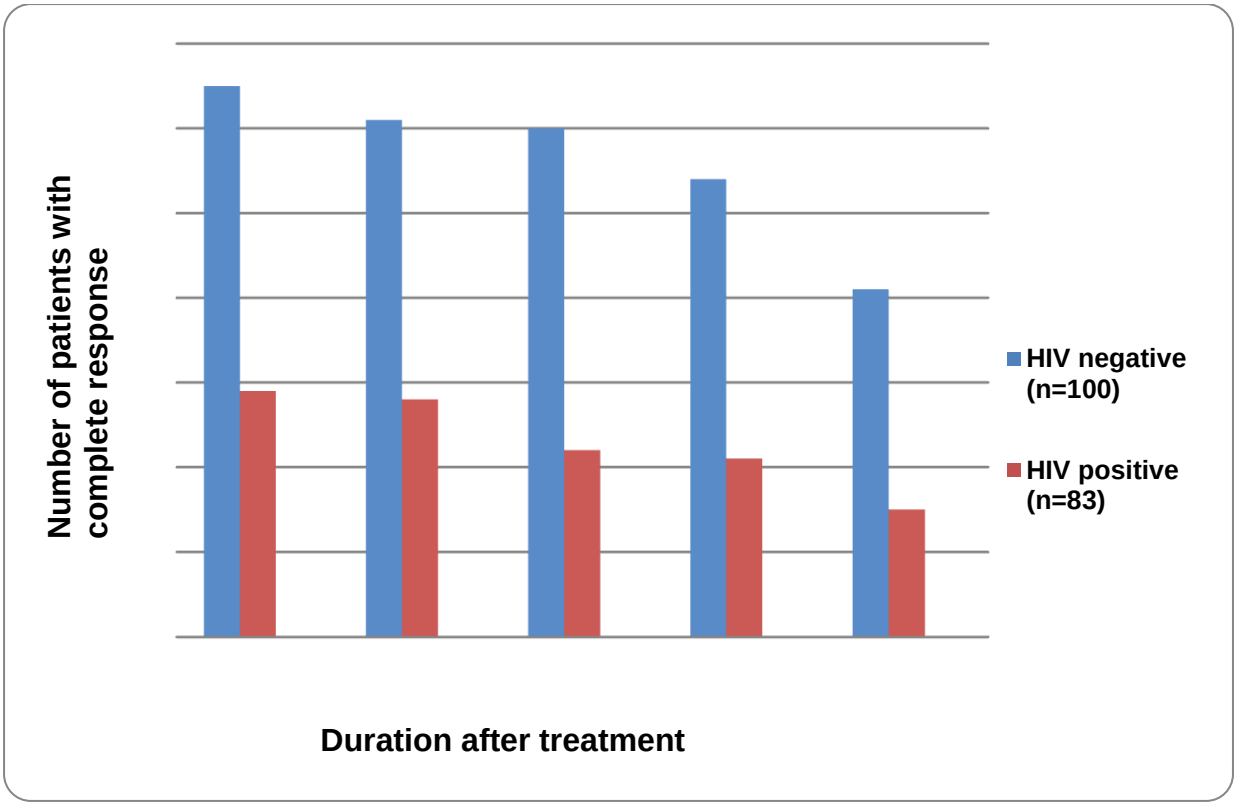

Figure 5.6: HIV negative and HIV positive patients who experienced complete response to treatment

5.8.2 Recurrence and metastases of cervical cancer

In this study, 'recurrence' referred to the detection of disease, following curative RT or CCRT, upon physical examination of the cervix by an oncologist. Forty percent (40; n=100) of the HIV negative patients and 72% (60; n=83) of the HIV positive patients displayed recurrence of cervical cancer after receiving treatment. The number of HIV positive patients with recurrence of cervical cancer was significantly higher than that of the HIV negative patients (Chi^2 = 17.8, d.f. = 2, p = 0.00013, Cramer's V = 0.31).

Metastases referred to the detection of cancerous cells in the other parts of the body such as: rectum/bladder; lungs; bone; brain; liver; kidney; ovaries and breast. The presence of metastases was determined by performing tests such as the ultrasound of the kidney and pelvis, bone scans and Magnetic Resonance Imaging (MRI) of the brain.

The study revealed that cancer had spread from the cervix to the other parts of the body in 14% (14; n=100) of the HIV negative women and in 44% (35; n=83) of the HIV positive women (Table 5.7). The number of HIV positive patients with metastases of cervical cancer was significantly higher than that of the HIV negative patients (Chi^2 = 13.6, d.f. = 2, p = 0.00109, Cramer's V = 0.28).

Table 5.7: Metastases observed in the study population

Area	HIV negative (n=100)		HIV positive (n=83)	
	Number	Percentage	Number	Percentage
Bladder/rectum	0	0	2	3
Lung	4	4	4	5
Bone	5	5	12	15
Brain	1	1	3	4
Liver	2	2	7	8
Kidney	2	2	4	5
Ovaries	0	0	1	1
Breast	0	0	2	3
Totals	14	14	35	44

In summary, the study revealed that there were significantly more cases of recurrence (Chi^2 = 17.8, d.f. = 2, p = 0.00013, Cramer's V = 0.31) and metastases (Chi^2 = 13.6, d.f. = 2, p = 0.00109, Cramer's V = 0.28) of cervical cancer among HIV positive patients.

In 1993, the CDC declared cervical cancer an AIDS defining illness after it was discovered that HIV infection was associated with an increased risk of developing CIN and rapid progression to ICC (Centers for Disease Control and Prevention, 1993:730). The main treatment options used to manage cervical cancer are RT and CCRT. Currently, HIV positive and HIV negative women with cervical cancer are managed in the same way. It is unknown whether the therapeutic ratio for CCRT in HIV negative women is maintained or changed in HIV positive women. There is

inadequate literature available on HIV positive women with invasive cervical cancer regarding the response to CCRT, side effects, patient adherence and rate of survival. Thus, standard treatments for these patients have not been defined. (Formenti *et al*., 1995:411-412)

However, some studies have reported similar findings to the current study in that HIV positive cervical cancer patients have a poor response to radiotherapy and early recurrence, resulting in poorer overall survival. Maiman *et al*. (1990:377-384) assessed 84 women with ICC in terms of disease characteristics, recurrence rates and survival rates. Sixteen of these patients were HIV positive and 68 were HIV negative. It was found that the response to therapy and prognosis was poorer among the HIV positive women, with higher recurrence and death rates compared with the HIV negative women. Another study by Maiman *et al*. (1997:76-80), that investigated women with ICC in New York City, also observed that treatment outcomes were poorer in HIV positive women than in HIV negative women and 88% of recurrence rates were reported among the HIV positive women.

Gichangi *et al*. (2006:405-411) prospectively investigated the impact of HIV infection on tumour control following radiotherapy for cervical cancer. Twenty percent of the 218 participants were HIV positive. It was observed that HIV positive women were significantly associated with a six fold higher risk of residual tumour after receiving radiotherapy than the HIV negative women.

The findings of Maiman *et al.* (1990:377-384 and 1997:76-80)and Gichangi *et al.* (2006:405-411) are similar to those of the current study in that the response to cervical cancer therapy was poorer among the HIV positive women. Additionally, higher recurrence rates were reported in the two studies by Maiman *et al.* (1990:377-384 and 1997:76-80) and in the current study. Therefore, HIV infection could significantly affect the treatment outcomes of cervical cancer patients.

5.8.3 Response to cervical cancer treatment in HIV positive women on ARVs and HIV positive women who were not on ARVs

The response to cervical cancer treatment among HIV positive women who were on ARVs and the HIV positive women who were not on ARVs was investigated. The

CD4 count which is an indicator of the level of immunity in HIV positive women was the most important factor that was considered in making the decision to initiate ARV therapy in HIV positive women. Classes of ARVs presented included: nucleoside reverse transcriptaseinhibitors (NRTIs); non nucleoside reverse transcriptaseinhibitors (NNRTIs) and protease inhibitors. The ARVs were used in combinations, known as HAART which consists of three active drugs to prevent resistance, with initial regimens including combinations of two NRTIs with an NNRTI. (Rudek *et al*., 2011:1)

Of the 83 HIV positive patients, 87% (72; n=83) were on HAART and 13% (11; n=83) were not on HAART. Furthermore, HAART was only initiated in HIV positive women whose CD4 count was less than 200 cells/mm^3.

The HAART regimens used were classified as regimen 1a, 1b and 2 according to the 2004 South African national antiretroviral treatment guidelines. Regimen 1a consisted of: stavudine (d4T), lamivudine (3TC) and efavirenz (EFV); regimen 1b consisted of d4T, 3TC and nevirapine (NVP) and regimen 2 consisted of zidovudine (AZT), didanosine (DDI) and lopinavir (LPV)-ritonavir (RTV). (Department of Health, South Africa, 2004:14) Of the 72 HIV positive women who were on HAART, 81% (58; n=72) were on regimen 1a, 5% (4; n=72) were on regimen 1b and 14% (10; n=72) were on regimen 2.

All 83 HIV positive patients returned to the study site one month after treatment. Complete response was noted in 38% (27; n=72) of the HIV positive patients who were on HAART and in 18% (2; n=11) of the HIV positive patients who were not on HAART (Figures 5.7).

At six months after treatment (n=71), complete response was noted in 39% (28; n=72) of the HIV positive patients who were on HAART and in none (0; n=11) of the HIV positive patients who were not on HAART.

Twelve months after completion of treatment (n=55), complete response was noted in 29% (21; n=72) of the HIV positive patients who were on HAART and in 9% (1; n=11) of the HIV positive patients who were not on HAART.

At 18 months after treatment (n=33), complete response was noted in 29% (21; n=72) of the HIV positive patients who were on HAART and in none (0; n=11) of the HIV positive patients who were not on HAART.

Twenty four months after treatment (n=26), complete response was noted in 21% (15; n=72) of the HIV positive patients who were on HAART and in none (0; n=11) of the HIV positive patients who were not on HAART.

At one month following treatment there was no significant difference in the incidence of complete response between the HIV positive patients who were on HAART (37.5%; 27; n=72) and the HIV positive patients who were not on HAART (18%; 2; n=11) (Chi^2 = 1.6, d.f. = 1, p = 0.21071, Cramer's V =0.14). However, at six months after treatment, a significant difference in the response to cervical cancer treatment was observed between the HIV positive patients who were on HAART (39%; 28; n=72) and the HIV positive patients who were not on HAART (0%; 0; n=11) (Chi^2 = 0.5, d.f. = 1, p = 0.02546, Cramer's V = 0.25). Complete response was significantly higher in the HIV positive women who were on HAART. There was no significant difference in the response to treatment between the HIV positive patients who were on HAART (29%; 21; n=72) and the HIV positive patients who were not on HAART (9%; 1; n=11) at 12 months after treatment (Chi^2 = 1.2, d.f. = 1, p = 0.28067, Cramer's V = 0.13). At 18 months after treatment and at 24 months after treatment, the response to cervical cancer in these two groups could not be statistically analysed because the sample size was too small.

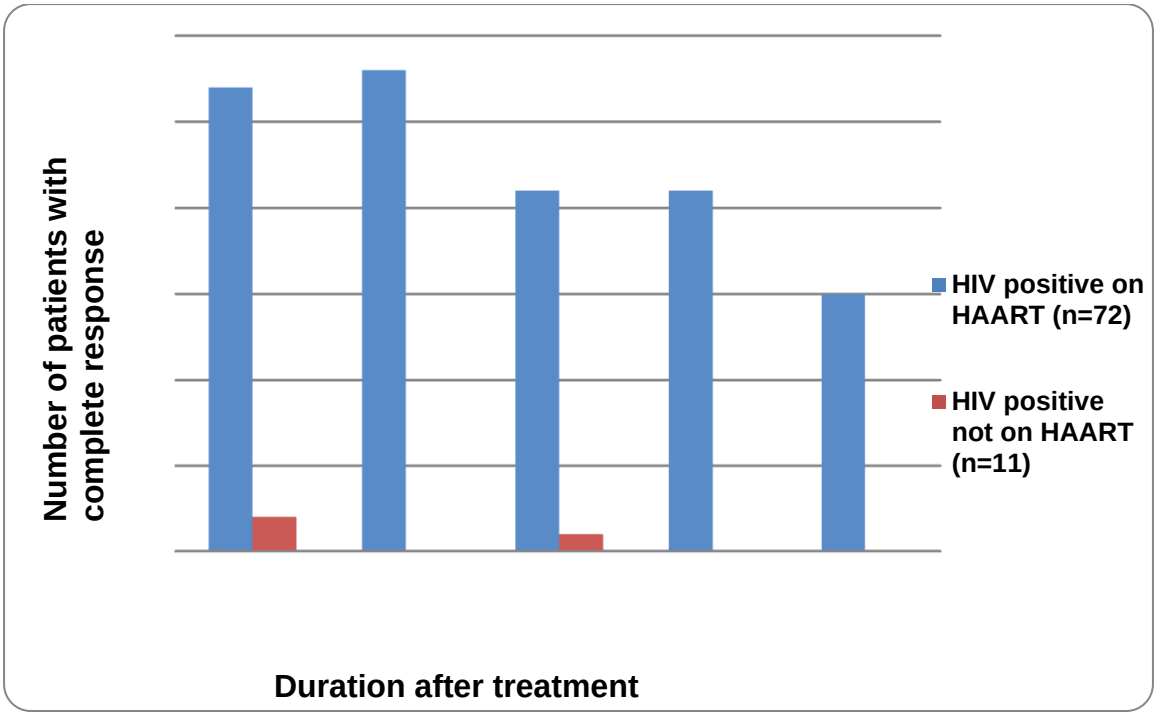

Figure 5.7: HIV positive patients who were on HAART and HIV positive patients who were not on HAART who experienced complete response to treatment

In summary, a significant difference in the incidence of complete response to cervical cancer treatment between the HIV positive patients who were on HAART and the HIV positive patients who were not HAART was only noted six months after these patients received treatment (Chi^2 = 0.5, d.f. = 1, p = 0.02546, Cramer's V = 0.25) where complete response was observed in 39% (28; n=72) of the HIV positive patients who were on HAART and in none (0; n=11) of the HIV positive patients who were not on HAART. No significant differences in the incidence of complete response between these two groups were noted at the other time intervals: one month after treatment (Chi^2 = 1.6, d.f. = 1, p = 0.21071, Cramer's V =0.14) and 12 months after treatment (Chi^2 = 1.2, d.f. = 1, p = 0.28067, Cramer's V = 0.13). The number of HIV positive patients who returned to the study site 18 months and 24 months after they had received treatment was too small to be statistically analysed. Therefore, the use of HAART by the HIV positive participants in the current study did not have a significant impact in the patient outcome.

According to the 2004 South African national antiretroviral treatment guidelines, ARVs should be commenced in HIV positive patients with a CD4 count of 200

cells/mm^3 or less. In addition, ARVs should be commenced in patients with WHO stage IV disease irrespective of their CD4 count. The WHO stage IV category includes ICC. (Department of Health, South Africa, 2004:12) This implies that patients with confirmed diagnosis of ICC should be commenced on ARVs as soon as the ICC diagnosis is made whether their CD4 count is above 200 cells/mm^3 or less. In the current study, only 72 of the 83 (87%; n=83) HIV positive participants were on HAART and 11 (13%; n=83) participants were not on HAART. Furthermore, HAART was only initiated in HIV positive women whose CD4 count was less than 200 cells/mm^3. Therefore the patients in the current study were not managed according to the 2004 South African national antiretroviral treatment guidelines because 13% of the HIV positive patients were not on HAART.

In most hospitals, including the site used for the current study, HIV positive patients are treated using the same protocols as HIV negative patients with cervical cancer. Standard treatment guidelines for HIV positive patients with cervical cancer have not been defined. The cervical cancer treatment modalities (RT and CCRT) have been shown to decrease various immunologic parameters such as CD4 counts thus the response and tolerance of HIV positive women to these treatment options is of major concern. It is also important to identify the impact of HAART on the CD4 count and subsequently on the ICC treatment outcomes. (Housri *et al.,* 2010:277)

The use of HAART has led to an increased life expectancy of HIV positive women and an increased incidence of AIDS defining malignancies such as cervical cancer. There is limited data available regarding the impact of HAART on ICC and this data has produced conflicting results. Some studies suggest that HAART induced elevation of CD4 count levels and suppression of HIV viral load has led to improved tolerance of full doses of RT or CCRT and improved response to cancer treatment (Antoniou & Tseng, 2005:143 and Ntekim & Folasire, 2010:64). In contrast, other studies suggest that the use of HAART does not seem to have a significant effect on patient outcome (Brunner *et al*., 2008:2706 and Caceres *et al.*, 2010:73) and some ARVs such as protease inhibitors may potentially increase both tumour control and toxicity.

A study conducted by Ntekim & Folasire (2010:61-66) examined the outcome of 22 HIV positive patients treated for cancer. Nine of the 22 patients had cervical cancer. Three patients had initial CD4 counts of 450, 460 and 500 cells/mm^3 respectively thus were not on HAART. They were able to complete the prescribed RT and CT. These patients were alive and well six months after treatment. Three other patients were already on HAART before they were diagnosed with cervical cancer. Their initial CD4 counts were from 350 to 370 cells/mm^3. They continued with HAART and were able to complete the prescribed cervical cancer treatment. These patients were also alive and well six months after treatment. The other three patients had initial CD4 counts between 250 and 320 cells/mm^3 and were started on HAART prior to the cervical cancer treatment. At six months after treatment, one patient was alive but had recurrent cervical cancer and the other two patients had died. Thus the study demonstrated that the use of HAART helped to maintain adequate CD4 count levels in HIV positive women with cervical cancer thus enabling them not only to be managed in the same way as their HIV negative counterparts but also to complete their prescribed treatment and achieve the desired treatment outcome indicating the possible relevance for the 13% of the HIV positive patients in the current study who were not on HAART to be initiated on HAART.

Shrivastava *et al*. (2005:31-35) looked at the outcome of 32 HIV positive patients with ICC who underwent RT. The information about the patients' ARV treatment was not available. Only 12 of the 32 patients could complete the full course of RT and 11 of these 12 patients experienced complete response. Thus, the response of ICC to treatment in HIV positive patients is almost the same as that of HIV negative patients but the challenge is to ensure that the HIV positive patients complete the prescribed treatment and that the modalities are chosen wisely.

The International Atomic Energy Association (IAEA) has developed a guideline for the treatment of cervical cancer in HIV positive women depending on their CD4 count. If the CD4 count is greater than 200 cells/mm^3, they should be managed the same way as HIV negative women. If the CD4 count is greater than 50 cells/mm^3but less than 200 cells/mm^3, the standard management protocols should still be followed but with caution as the HIV positive women may exhibit intolerance to RT/CCRT or may develop opportunistic infections. If the CD4 count is less than 50 cells/mm^3 then

only palliative RT should be used. (Mallik *et al*., 2010:433) At the University of Miami, dose modifications of CCRT were undertaken in HIV positive patients whose CD4 count was less than 200 cells/mm^3. The daily fraction size was reduced from 2 Gy, which is the widely accepted dose to 1.5 Gy and the most frequently prescribed cisplatin dose of 40 mg/m^2 weekly was reduced to 30 or 35 mg/m^2 weekly. These dose modifications resulted in tolerance similar to that of HIV negative patients. (Housri *et al.,* 2010:277)

In summary, standard RT and CCRT cervical cancer treatment protocols should be used in both HIV negative patients and HIV positive patients so as not to compromise tumour control. The use of HAART by the HIV positive participants in the current study did not have a significant impact on the patient outcome. However, the available literature seems to provide compelling evidence that HAART elevates the CD4 count levels and suppresses the HIV viral load leading to improved tolerance to full doses of RT or CCRT. Therefore, in accordance with the South African ARV treatment guidelines, all HIV positive patients with cervical cancer should receive HAART irrespective of their CD4 count.

5.9 TOXICITY DUE TO TREATMENT IN HIV POSITIVE VERSUS HIV NEGATIVE CERVICAL CANCER PATIENTS

Toxicity can be classified as acute or late. Acute toxicity is defined as adverse events which occur during treatment and up to 90 days after completion of treatment. This toxicity occurs in rapidly proliferating cells such as the skin epithelium, mucosal lining of the upper digestive tract or the surface lining of the small intestine. Acute adverse events are of a short duration and normally diminish with medical management. Late toxicity which appears from nine months up to five years after treatment is difficult to reverse and may permanently impair the patient's quality of life. The slowly proliferating tissue such as the vascular endothelium is damaged and this results in fibrosis, stricture, necrosis and fistulae. (Green *et al*., 2001:785) In this section, the acute and late toxicity observed in the HIV positive and HIV negative patients will be discussed.

In the current study, toxicity was grouped as: haematological (anaemia, leucopenia, thrombocytopenia); gastrointestinal (nausea and vomiting, diarrhoea, constipation);

genitourinary (rectovaginal fistula, radiation proctitis), dermatological (skin desquamation) and neurological (peripheral neuropathy). Other toxicities that could not be grouped included: renal toxicity; weight loss; pain and deep vein thrombosis (DVT).

All of the patients experienced toxicity/side effects during or after treatment except for one (1%; n=93) HIV negative woman. The number of side effects that were noted in the rest of the patients ranged from one to ten (Figure 5.8). The most common number of side effects per patient was four side effects (46; 27%; n=171).

On average, HIV negative patients experienced 3.8 $\pm$ 1.6 side effects per patient, HIV positive patients who were on HAART experienced 4.9 $\pm$ 2.1 side effects per patient and HIV positive patients who were not on HAART experienced 4.3 $\pm$ 1.3 side effects per patient (Figure 5.9). There was a significant difference in the incidence of the number of side effects per patient in the HIV negative patients compared to the HIV positive patients who were on HAART (Tukey's HSD procedure, $p = 0.00013$). However no significance was noted in the incidence of the number of side effects per patient in the HIV positive patients who were not on HAART (Tukey's HSD procedure, $p = 0.50984$).

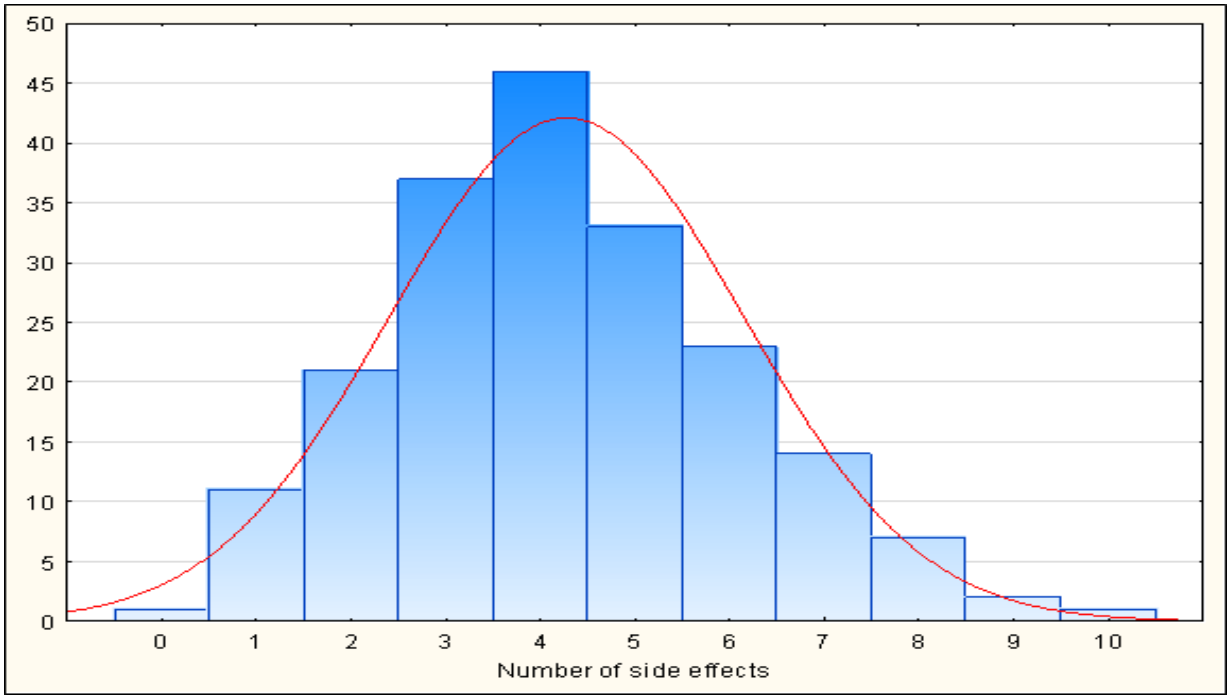

Figure 5.8: Distribution of side effects observed in the study population

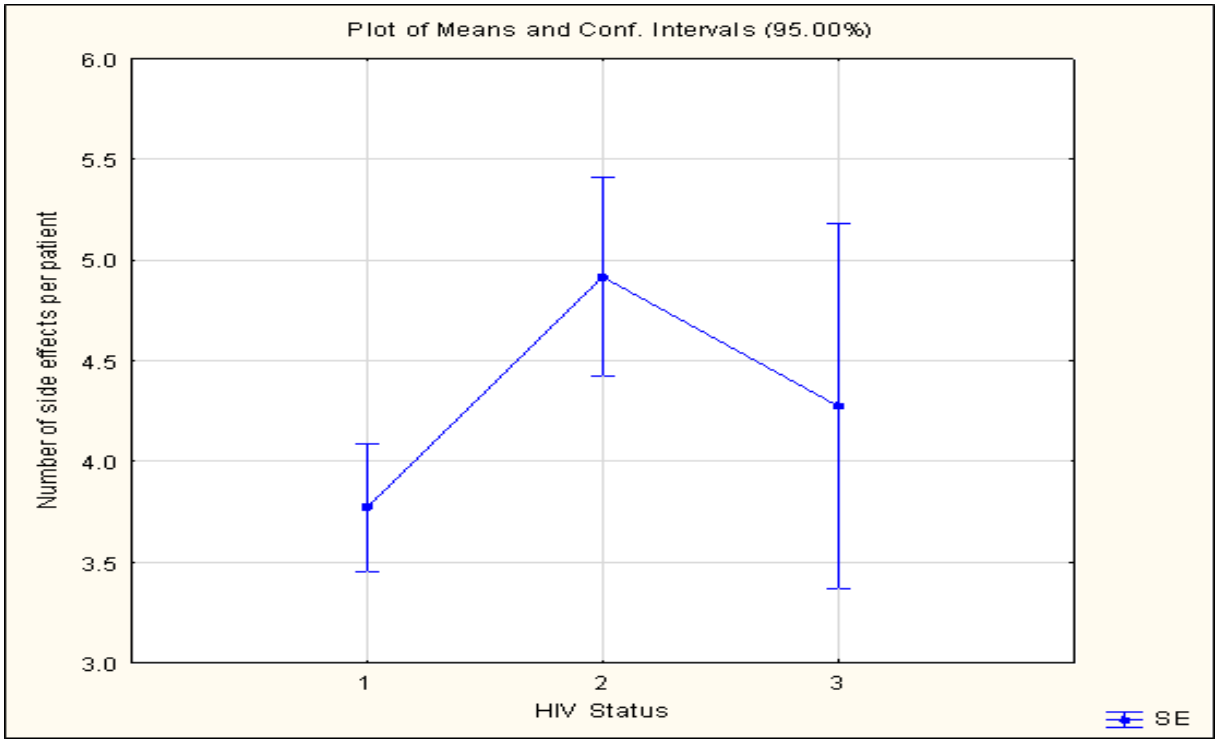

Figure 5.9: Comparison of the number of side effects in the HIV negative women, HIV positive women who were on HAART and HIV positive women who were not on HAART

1, HIV negative patients (n=100); 2, HIV positive patients who were on HAART (n=72); 3, HIV positive patients who were not on HAART (n=11)

5.9.1 Haematological toxicity

Haematological toxicity consisted of anaemia, leucopenia and thrombocytopenia. Anaemia, which was characterised by Hb levels below 12 g/dl was noted in 95% (87; n=92) of the HIV negative patients; 93% (67; n=69) of the HIV positive patients who were on HAART and in ten of the HIV positive patients who were not on HAART (100%; n=10) (Chi^2 = 2.7, d.f. = 2, p = 0.26446, Cramer's V = 0.12) (Table 5.8). Thrombocytopenia (platelet count less than $100x10^9$/l) occurred in 15% (14; n=92) of the HIV negative patients; 36% (25; n=69) of the HIV positive patients who were on HAART and in 20% (2; n=10) of the HIV positive patients who were not on HAART. Leucopenia (white cell count below $4x10^9$/l) was noted in 41% (38; n=92) of the HIV negative patients; 59% (41; n=69) of the HIV positive patients who were on HAART and in 20% (2; n=10) of the HIV positive patients who were not on HAART.

Haematological toxicity was the most common toxicity reported in the study population (164; 84%; n=196). This data was in line with the trials that were reviewed in the meta analysis conducted by Green *et al.* (2001:781-786), Lukka *et al*. (2002:203-212) and the Concomitant Chemoradiotherapy in Cervical Cancer Meta-Analysis Collaboration (CCCMAC) (2010:1-46) (Table 3.3, 3.5 and 3.6) where haematological toxicity was also the most frequently reported toxicity in cervical cancer patients who received RT or CCRT.

Although the haematological toxicity that was reported in the current study was usually self limiting or was resolved with medical management (blood transfusions or colony stimulating factors such as filgrastim), it still had an impact on the patients' adherence and response to cervical cancer treatment. Thirty three percent (64; n=196) of the study population did not complete their prescribed cervical cancer treatment or received treatment for a prolonged period due to low blood count (low Hb, white blood cell and platelet count) (Table 5.11). In addition, 47% (77; n=164) of the patients who had anaemia experienced incomplete response to cervical cancer treatment (Table 5.5).

The highest cases of haematological toxicity were reported among HIV positive patients who were on HAART. The incidence of leucopenia and thrombocytopenia was significantly highest in this specific group (Chi^2 = 9.3, d.f. = 2, p = 0.00948,

Cramer's V = 0.23 and Chi^2 = 10.5, d.f. = 2, p = 0.00535, Cramer's V = 0.24 respectively) (Table 5.8). The majority of the patients who did not adhere to their prescribed cervical cancer treatment or who received treatment over an extended duration due to haematological toxicity were also HIV positive patients who were on HAART (39; 54%; n=72) (Chi^2 = 4.0, d.f. = 2, p = 0.01327, Cramer's V = 0.15). Thus RT or CCRT induced myelosuppression appeared to have been exacerbated by the use of HAART. Of the 72 HIV positive women who were on HAART in the current study, 81% (58; n=72) were on regimen 1a (d4T; 3TC; EFV); 5% (4; n=72) were on regimen 1b (d4T; 3TC; NVP) and 14% (10; n=72) were on regimen 2 (AZT; DDI; LPV-RTV).

This result was expected as cisplatin, carboplatin and ARVs are known to have a myelosuppressive effect. In fact, many oncologists avoid the combination of NRTIs that cause marked myelosuppression such as AZT with any myelosuppressive regimen and many would interrupt HAART for continuous or high dose chemotherapy regimens. Therefore, oncologists should monitor the myelosuppression that would occur due to the concomitant use of ARVs and chemotherapeutic agents. (Rudek *et al*., 2011:5)

Table 5.8: Acute and late toxicity observed in the HIV negative patients, HIV positive patients who were on HAART and HIV positive patients who were not on HAART

Toxicity (Chi^2 test)	**HIV negative patients (n=92)**	**HIV positive patients on HAART (n=69)**	**HIV positive patients not on HAART (n=11)**
	Number (%)	**Number (%)**	**Number (%)**
Haematological Toxicity			
Anaemia p = 0.26446	87 (95)	67 (97)	10 (100)
Leucopenia* p = 0.00948	38 (41)	41 (59)	2 (20)
Thrombocytopenia* p = 0.00535	14 (15)	25 (36)	2 (20)

Gastrointestinal Toxicity			
Nausea and vomiting p = 0.34665	2 (2)	4 (6)	0 (0)
Diarrhoea* p = 0.04536	33 (36)	51 (74)	9 (90)
Constipation p = 0.28757	11 (12)	4 (6)	2 (20)
Genitourinary Toxicity			
Rectovaginal fistula p = 0.16993	2 (2)	4 (6)	1 (10)
Radiation proctitis p = 0.39907	8 (9)	3 (4)	0 (0)
Dermatological Toxicity			
Skin desquamation* p = 0.02512	39 (42)	59 (86)	8 (80)
Neurological Toxicity			
Peripheral Neuropathy* p = 0.00029	3 (3)	15 (22)	0 (0)
Other			
Renal toxicity p = 0.32294	1 (1)	2 (3)	0 (0)
Deep vein thrombosis p = 0.10446	8 (9)	1 (1)	0 (0)
Weight loss* p = 0.00074	29 (32)	41 (59)	3 (30)
Pain p = 0.13203	64 (70)	57 (83)	10 (100)

*statistically significant (Chi^2 with Cramer's V)

5.9.2 Dermatological toxicity

Radiation induced dermatological toxicity was the next most common toxicity that was observed in the study population (106; 54%; n=196) (Table 5.8). Forty two percent (39; n=92) of the HIV negative patients; 86% (59; n=69) of the HIV positive patients who were on HAART and in 80% (8; n=10) of the HIV positive patients who were not on HAART experienced this adverse effect. Dermatological toxicity also had an impact on the patients' adherence to cervical cancer treatment. Moist desquamation of the irradiated areas caused 36% (70; n=196) of the study population either to be non adherent to their prescribed treatment or to complete treatment over a period that was longer than the prescribed duration (Table 5.11).

A large number of patients in the study (83%; 163; n=196) had advanced cervical cancer (stage III and IV) and thus required larger RT treatment fields. This may have lead to the high incidence of cutaneous toxicity in the study population. Cutaneous toxicity was significantly higher in HIV positive patients (67; 85%; n=79) than in HIV negative patients (39; 42%; n=92) ($Chi^2 = 4.2$, d.f. = 2, p = 0.02512, Cramer's V = 0.15).

Studies on HIV positive patients with Kaposi's Sarcoma suggest that the HIV virus induces glutathione deficiency that makes HIV positive patients more sensitive to RT thus increasing the risk of cutaneous and mucosal toxicity. This results in moist desquamation of the skin. (Housri *et al*., 2010:273) At the study site, the patients who had cutaneous reactions in the perianal or groin area were put on bed rest and dressings were applied daily until the reactions subsided and the patients could resume RT.

5.9.3 Gastrointestinal toxicity

Nausea and vomiting, diarrhoea and constipation were classified under gastrointestinal toxicity.

Nausea and vomiting: was recorded in 2% (2; n=92) of the HIV negative patients and in 6% (4; n=69) of the HIV positive patients who were on HAART (Table 5.8). This result

was not statistically significant (Chi^2 = 2.1, d.f. = 2, p = 0.34665, Cramer's V = 0.11). All of these patients were on CCRT. Nausea and vomiting is a very common acute side effect of CT. It has been estimated that approximately 70% to 80% of patients receiving CT experience nausea and vomiting. The chemotherapeutic agents that were used in the current study were cisplatin, which has an emetic risk greater than 90% without anti-emetic agents and carboplatin, which has an emetic risk of between 30% and 90% without anti-emetic agents. (Fiore & Cutsem, 2009:115) However, the low incidence of nausea and vomiting that was observed was due to the fact that all the patients who underwent CT received dexamethasone 8 mg intravenous (IV) and granisetron 1 mg (IV) before receiving the CT. This management of CT induced nausea and vomiting is based on the American Society of Clinical Oncology guidelines for antiemetics in oncology (Kris *et al*., 2006:2940). Granisetron was used to prevent acute nausea and vomiting that occurs within 24 hours of the initial administration of CT and dexamethasone was used to prevent delayed emesis that occurs from 24 hours to several days after initial treatment.

Diarrhoea: was noted in 36% (33; n=92) of the HIV negative patients; 74% (51; n=69) of the HIV positive patients who were on HAART and in 90% (9; n=10) of the HIV positive patients who were not on HAART (Table 5.8). Radiation therapy induced diarrhoea occurs as a result of damage to the jejuna crypt cells in the surface lining of the small intestine. It is estimated that 70% of patients who receive RT may experience diarrhoea during treatment. (Abayomi *et al*., 2005:354) At the study site, diarrhoea was managed by administering either loperamide or codeine phosphate to the patients. These agents form first line therapeutic options for diarrhoea in many oncology centres worldwide (Abayomi *et al*., 2005:359). In the current study the number of HIV positive patients (60; 76%; n=79) who experienced diarrhoea was significantly higher than the HIV negative patients (33; 36%; n=92) (Chi^2 = 1.2, d.f. = 2, p = 0.04536, Cramer's V = 0.23). Moreover, diarrhoea had an impact on some of the patients' adherence to cervical cancer treatment. Twenty six percent (26; n=100) of the HIV negative patients, 57% (41; n=72) of the HIV positive patients who were on HAART and 64% (7; n=11) of the HIV positive patients who were not on HAART did not adhere to their prescribed cervical

cancer treatment due to RT induced diarrhoea (Table 5.11). The incidence of non adherence was also significantly higher among the HIV positive patients (64%; 7; n=11) (Chi^2 = 6.9, d.f. = 2, p = 0.03118, Cramer's V = 0.19).

Constipation: occurred in 12% (11; n=92) of the HIV negative patients; 6% (4; n=69) of the HIV positive patients who were on HAART and in 20% (2; n=10) of the HIV positive patients who were not on HAART (Table 5.8). This result was not statistically significant (Chi^2 = 2.5, d.f. = 2, p = 0.28757, Cramer's V = 0.12). These patients had stage IV cervical cancer thus used analgesics such as paracetamol and codeine for pain relief. The constipation that these patients experienced which was caused by codeine was relieved by administering agents such as liquid paraffin or senna glycosides.

5.9.4 Neurological toxicity

Chemotherapy induced peripheral neuropathy (CIPN) which was classified under neurological toxicity was noted in 3% (3; n=92) of the HIV negative patients and in 22% (15; n=69) of the HIV positive patients who were on HAART (Table 5.8). All these patients were on CCRT. Cytotoxic agents inactivate the components required to maintain the metabolic needs of an axon and causes damage to the peripheral, motor, sensory, and autonomic neurons. This results in CIPN. Peripheral neuropathy results in pain or discomfort and compromises the quality of life of a patient. This condition is also of great concern as it can result in chemotherapy dose reductions, treatment delays, or discontinuation of treatment. (Rudek *et al*., 2011:4) Both cisplatin and carboplatin which were used to manage some of the patients in the current study have the potential to cause CIPN. The incidence of carboplatin induced CIPN is estimated at 5% to 20% and cisplatin induced CIPN is estimated at 30% to 100%. The occurrence of CIPN was significantly higher in HIV positive patients on HAART (15; 22%; n=69) (Chi^2 = 16.3, d.f. = 2, p = 0.00029, Cramer's V = 0.30). Antiretroviral agents such asDDI and d4T have been frequently associated with peripheral neuropathy, which at times may be irreversible. The onset is typically weeks to months after ARV therapy is started, however patients with pre-existing CIPN might have this toxic effect sooner. (Rudek *et al*., 2011:4)As CIPN is cumulative or dose related, the management of the patients in

the current study who developed this toxicity consisted of dose reduction of the cytotoxic agent. Amitriptyline was also administered in order to exert an analgesic effect.Rudek *et al*. (2011:1-8) suggests that if a HIV positive patient on DDI or d4T based HAART regimens develops a malignancy the options are to: select an alternative chemotherapy regimen with no overlapping toxic effects; substitute a different NRTI or other appropriate ARV or temporarily discontinue ARV therapy. As cisplatin or carboplatin are the first line chemotherapy agents in cervical cancer, substituting ARVs such as didanosine or stavudine would be the most viable option.

5.9.5 Other toxicities

Weight loss: Thirty two percent (29; n=92) of the HIV negative patients, 59% (41; n=69) of the HIV positive patients who were on HAART and 30% (3; n=10) of the HIV positive patients who were not on HAART experienced weight loss during and after cervical cancer treatment (Table 5.8). Weight loss was as a result of RT induced diarrhoea and advanced cervical disease. Weight loss was significantly higher in HIV positive patients (44; 56%; n=79) than in the HIV negative patients (29; 32%; n=92) (Chi^2 = 14.4, d.f. = 2, p = 0.00074, Cramer's V = 0.28). This finding is not surprising as HIV/AIDS and cervical cancer are individually associated with weight loss thus weight loss may be exacerbated in HIV positive cervical cancer patients.

Pain: occurred in 70% (64; n=92) of the HIV negative patients; 83% (57; n=69) of the HIV positive patients who were on HAART and in ten (100%; n=10) of the HIV positive patients who were not on HAART (Table 5.8). This result was not significant (Chi^2 = 6.9, d.f. = 2, p = 0.13203, Cramer's V = 0.19). The pain experienced by the patients in the current study was caused by: advanced disease and CIPN. Majority (96; 73%; n=131) of the patients who experienced pain had advanced cervical cancer (stage III and IV). 'Symptoms of advanced cervical cancer include back pain and pelvic pain' (Lonkhuijzen & Thomas, 2011:287). This statement is line with the current study as the participants with advanced cervical cancer complained of back pain, leg pain and pelvic pain. Oral analgesics (such as paracetamol and/or codeine) or palliative RT was used to manage pain that was not related to CIPN. Pain induced by CIPN was also reported in the

current study. According to the clinicians' notes, patients described the pain as tingling, burning or numbing sensations. Dose reduction of the cytotoxic drug and administration of amitryptiline seemed to alleviate the pain.

Renal toxicity: The chemotherapy agents, cisplatin or carboplatin were only administered in patients who had an initial creatinine clearance of 60ml/min or greater. During the course of treatment, 1% (1; n=92) of the HIV negative patients and 3% (2; n=69) of the HIV positive patients who were on HAART experienced creatinine clearances of less than 60ml/min which was indicative of mild renal toxicity (Table 5.8). All these patients were on cisplatin based CCRT. This result was not significant (Chi^2 = 7.5, d.f. = 2, p = 0.32294, Cramer's V = 0.20). The low incidence of renal toxicity in patients who received cisplatin, which is highly nephrotoxic was due to the fact that saline was administered pre and post chemotherapy in order to prevent nephrotoxicity. The renal toxicity was ameliorated by reducing the dose of cisplatin and by intensive hydration.

DVT: Nine percent (8; n=92) of the HIV negative patients and 1% (1; n=69) of the HIV positive patients who were on HAART experienced DVT. All of these patients were on CCRT (Table 5.8). This result was statistically insignificant (Chi^2 = 4.5, d.f. = 2, p = 0.10446, Cramer's V = 0.16). Some studies have reported that the incidence of venous thromboembolism (VTE) in patients with cervical cancer ranges from 0% to 34%. The use of CCRT has shown an improvement in overall survival in patients with advanced cervical cancer however the use of CT has lead to the increase of VTE. Although the underlying mechanism is unknown, cisplatin is associated with arterial and venous thrombosis, hypertension, myocardial infarction, Raynauds syndrome and stroke. (Barbera & Thomas, 2008:54)

Brachytherapy which is a vital component of curative RT may also be a risk factor for VTE. This technique which involves the insertion of a capsule of radioactive material through the vagina and directly into the tumour, requires immobilisation of the patient for hours or days to deliver treatment thus increases the risk of the patient developing DVT. Incidences of VTE reported in patients receiving brachytherapy range from 0% to 17%.

(Barbera & Thomas, 2008:57) In the current study, low-molecular-weight heparin (LMWH) was administered to patients who developed DVT. This was in line with American College of Chest Physicians guidelines which state that for the treatment of VTE in cancer the use of LMWH is recommended as it has been shown to be better than warfarin. However, no specific or different recommendations have been made for patients with cervical cancer. (Buller *et al*., 2004:425S)

5.9.6 Genitourinary toxicity

Genitourinary toxicity consisted of rectovaginal fistula (RVF) and chronic radiation proctitis. Radiation proctitis occurred in 9% (8; n=92) of the HIV negative patients and in 4% (3; n=69) of the HIV positive patients who were on HAART (Table 5.8). This result was not significant (Chi^2 = 1.8, d.f. = 2, p = 0.39907, Cramer's V = 0.10).

Radiation proctitis: is the inflammation and damage to the lower intestine. Acute radiation proctitis frequently occurs during RT and lasts up to three months, with symptoms including tenesmus, urgency, diarrhoea and occasional bleeding. Chronic radiation proctitis can continue from an acute phase or begin eight to twelve months after RT. Late radiation proctitis can lead to tenesmus, urgency, either diarrhoea or constipation, anal sphincter dysfunction, mucus discharge, bleeding, stricture, ulceration and fistula formation. (Maher & Denton, 2008:481) In the current study, metronidazole was used to manage the symptoms of patients with chronic radiation proctitis. Patients who experienced diarrhoea also received oral opioids. There is limited evidence based therapy of chronic radiation proctitis. Table 5.9 contains the interventions that are used to manage chronic radiation proctitis. A systematic review by Maher & Denton (2008:479-487) was conducted to examine the efficacy of these interventions. It was found that sucralfate enemas seemed to be the best therapy and were safe and well tolerated. Additional use of oral metronidazole 400 mg three times a day for a year may have had a synergistic effect. Mesalazine and betamethasone enemas may have had some effect, but were less well tolerated and less effective. Thus the use of metronidazole in the current study was appropriate.

In the minority of cases reviewed by Maher & Denton (2008:479-487), patients did not respond to the medical interventions thus hyperbaric oxygen therapy was considered. In South Africa, resource constraints may hinder the use of hyperbaric oxygen therapy though there are centres linked to academic institutions that can offer these services. In the Western Cape, these services are offered at a reduced rate for state patients (Simonds, 2009:67). Hyperbaric oxygen therapy services were not availableat the current study site which is located in the Eastern Cape Province in South Africa.

Table 5.9: Interventions used to manage chronic radiation proctitis

5-aminosalicylates enemas e.g. mesalazine
Corticosteroid enemas e.g. betamethasone
Sucralfate enemas
Metronidazole oral tablets
Hyperbaric oxygen therapy

Rectovaginal fistula: Two percent (2; n=69) of the HIV negative patients; 6% (4; n=69) of the HIV positive patients who were on HAART and in 10% (1; n=10) of the HIV positive patients who were not on HAART developed RT induced RVFs (Table 5.8). This result was not significant (Chi^2 = 3.5, d.f. = 2, p = 0.16993, Cramer's V = 0.14). A fistula is an abnormal communication between 2 epithelialised surfaces. A RVF is an abnormal connection between the rectum and the vagina (Simonds, 2009:68). In the current study, patients with RVFs complained of passing stools through the vagina. All the cases of RVFs were caused by RT. This complication was rectified surgically.

5.9.7 Summary

The most common toxicity that was reported in the study population was haematological toxicity (164; 84%; n=196). Fortunately, this toxicity tended to be short lived and was resolved by appropriate medical treatment. Haematological toxicity (leucopenia and thrombocytopenia) and neurological toxicity (CIPN) were predominantly reported among the HIV positive women who were on HAART (Chi^2 = 9.3, d.f. = 2, p = 0.00948, Cramer's V = 0.23; Chi^2 = 10.5, d.f. = 2, p = 0.00535, Cramer's V = 0.24 and Chi^2 =

16.3, d.f. = 2, p = 0.00029, Cramer's V = 0.30 respectively). Radiation induced dermatological toxicity (skin desquamation), gastrointestinal toxicity (diarrhoea) and weight loss were significantly higher among the HIV positive women (Chi^2 = 4.2, d.f. = 2, p = 0.02512, Cramer's V = 0.15; Chi^2 = 1.2, d.f. = 2, p = 0.04536, Cramer's V = 0.23 and Chi^2 = 14.4, d.f. = 2, p = 0.00074, Cramer's V = 0.28 respectively). Therefore, based on the current study, conclusions can be drawn that HIV positive patients have increased sensitivity of normal tissues to RT or CCRT resulting in increased adverse effects.

There is limited literature describing the acute and late toxicity experienced by HIV positive women with cervical cancer. A randomised study by Msadabwe (2009:1-87) compared CCRT against RT as treatment of cervical cancer in South African HIV positive patients. Sixty four patients with stages I to III were recruited to the study, 31 patients in the CCRT arm and 33 in the radiation arm (Table 3.10).The major adverse effects in this trial were leucopenia (four in the CCRT arm and one in the RT arm) and cutaneous reactions (two in the CCRT arm and six in the RT arm). These adverse effects were also the most frequently reported effects in the current study.

Gichangi *et al*., (2006:405-411) from Nairobi examined the outcome of cervical cancer patients who received RT. Twenty percent of the 208 participants were HIV positive. There was a high percentage of toxicity in both HIV negative and HIV positive groups. There was no difference in the received dose or duration of treatment for the HIV positive group. A seven fold higher risk of gastrointestinal, skin and genitourinary toxicity was noted in HIV positive women.

Mallik *et al*. (2010:432-441) performed a literature review that explored the issues of RT/CCRT and HIV related malignancies in order to determine the optimal management of HIV positive patients with AIDS related malignancies. One of the studies reviewed was by Oehler-Janne *et al*. (2006:29) that investigated the toxicity due to CCRT in HIV positive patients with anal cancer. In the pre HAART era, side effects were more frequent and poorer outcome was associated with CCRT. However, the authors concluded that HIV positive patients could be treated in the same way as HIV negative

patients with anal cancer as long as special precautions were put in place in order to prevent or manage toxicity especially in HIV positive patients with CD4 counts less than 200 cells/mm^3. Another study on HIV positive patients with Non Hodgkin's Lymphoma revealed that before the HAART era, oncologists often reduced the dose of chemotherapy due to poor tolerability to CT. Radiotherapy was also associated with higher toxicity rates among HIV positive patients. In the HAART era, unacceptable toxicity could be avoided even with standard dose CT however data on RT was not available. (Kaplan *et al*., 2005:1538-1543)

The data from the current study and from the available literature suggests that HIV positive patients are more sensitive to RT/CCRT thus are more likely to experience increased toxicity than the HIV negative patients. Haematological toxicity seemed to be increased in the HIV positive women who were on HAART. Additionally, radiation induced dermatological toxicity (skin desquamation), gastrointestinal toxicity (diarrhoea) and weight loss were significantly higher among the HIV positive women.

The use of HAART has allowed administration of standard doses of RT and even CT leading to improved outcomes. Therefore, RT and CCRT protocols should generally be used wherever possible, so as not to compromise disease control. All cervical cancer patients should be on HAART irrespective of their CD4 count in order to elevate the CD4 count levels and to suppress the HIV viral load leading to improved tolerance to full doses of RT or CCRT. Reducing the chances of toxicity in the HIV positive patients would lead to decreased cases of treatment interruption and thus improved patient outcomes.

The findings of the current study are based on a small patient population and a short follow up period. Therefore more extensive studies need to be conducted where patients would be followed up over a longer period of time for instance five years so as to assess the acute and especially the late toxicity to RT/CCRT in HIV positive patients with invasive cervical cancer. These studies will assist in the design of appropriate strategies for the management of RT or CCRT induced toxicities in HIV positive cervical cancer patients.

5.10 ADHERENCE TO TREATMENT IN HIV POSITIVE VERSUS HIV NEGATIVE CERVICAL CANCER PATIENTS

The World Health Organisation defines adherence as 'the extent to which a person's behaviour (medication, diet, lifestyle changes) correspond with the agreed recommendations from a health care provider (WHO, 2003). In this study, the term 'adherence' referred to the extent to which the patients followed the prescribed cervical cancer treatment plan. Therefore, the term 'adherent' referred to the patients who completed the prescribed cervical cancer treatment plan either within the prescribed duration or over a prolonged duration and 'non adherent' referred to the patients who either did not complete the prescribed cervical cancer treatment plan or who did not receive any of the prescribed treatment.

The study revealed that 61 (61%; n=100) HIV negative patients, 52 (72%; n=72) HIV positive patients who were on HAART and seven (64%; n=11) HIV positive women who were not on HAART were adherent to cervical cancer treatment (Table 5.10). There was no significant difference in the adherence patterns between these three groups (Chi^2 = 10.2, d.f. = 6, p = 0.11805, Cramer's V = 0.17).

Table 5.10: Adherence patterns in the study population

HIV status	Adherent		Non adherent		Totals
	Prescribed duration	Prolonged duration	Did not complete treatment	Did not receive treatment	n=183
HIV negative	8 (8%)	53 (53%)	32 (32%)	7 (7%)	100
HIV positive on HAART	17 (24%)	35 (48%)	17 (24%)	3 (4%)	72
HIV positive not on HAART	3 (27%)	4 (37%)	3 (27%)	1 (9%)	11

Some of the patients in the study population completed their treatment over a longer period than the prescribed duration; others did not complete their prescribed treatment while still others did not receive any of the prescribed treatment at all (Table 5.10). These observations resulted from a number of reasons that included: missed scheduled appointments due to personal reasons; radiotherapy equipment failure; low blood count; skin breakdown due to RT; diarrhoea caused by RT or CCRT; and early termination of treatment by the doctor (Table 5.11).

Table 5.11: Reasons for the prolongation of the treatment period or for non adherence in the study population

Reasons for non-adherence	**HIV negative patients (n=100)**	**HIV positive patients on HAART (n=72)**	**HIV positive patients who were not on HAART (n=11)**
Missed scheduled appointments p = 0.02385*	40 (40%)	23 (32%)	9 (82%)
Equipment failure p = 0.41311	22 (22%)	7 (10%)	0 (0%)
Low blood count p = 0.01327*	24 (24%)	39 (54%)	1 (9%)
RT induced skin breakdown p = 0.04581*	25 (25%)	37 (51%)	8 (73%)
RT/CCRT induced diarrhoea p = 0.03118*	26 (26%)	41 (57%)	7 (64%)
Early termination of treatment by doctor P = 0.09023	19 (19%)	22 (31%)	5 (64%)

*statistically significant (Chi^2 with Cramer's V)

There was a significant difference in the incidence of treatment prolongation or non adherence due to missed scheduled appointments among the HIV negative patients,

the HIV positive patients who were on HAART and the HIV positive patients who were not on HAART (Chi^2 = 2.9, d.f. = 2, p = 0.02385, Cramer's V = 0.31) (Table 5.11). The highest percentage of cases was reported in the HIV positive women who were not on HAART (82%; 9; n=11). The patients missed their scheduled appointments due to various personal reasons that were not indicated in the file.

The study site was located in an urban area in the Eastern Cape Province, South Africa. According to Somdyala *et al*. (2008), cervical cancer was the most common female cancer in the Eastern Cape with an age standardised rate of 20.2 (per 100, 000 population) and most of the cervical cancer patients were located in the rural areas. This finding was in line with data from a study by Anorlu (2008:45) which found out that in sub-Saharan Africa, most centres for the management of cervical cancer were concentrated in urban areas leaving people in the rural areas with limited access to health care. Thus in the current study, some of the patients might have missed their scheduled appointments because they lacked money or transportation means to travel to the hospital for treatment. In many developing countries, women are the primary care givers and bread winners (Anorlu, 2008:46), thus some of the patients in the current study might have lacked the time to travel to the hospital for treatment due to work or household duties. This might have led to their non adherence to the prescribed cervical cancer treatment plan or to receive treatment over an extended period of time.

Twenty two percent (22; n=100) of the HIV negative patients and 10% (7; n=72) of the HIV positive patients who were on HAART received treatment over a prolonged duration or were non adherent to the prescribed treatment due to RT equipment failure (Table 5.11). This result was not significant (Chi^2 = 1.8, d.f. = 2, p = 0.41311, Cramer's V = 0.10).

In South Africa, the increasing incidence of cervical cancer is not matched by the facilities that are available to manage the patients. There are six national academic radiation centres with a small number of additional satellite units. In total, there are 29 machines currently available in the public sector to treat cancer patients. These facilities are hardly enough to treat the large numbers of cervical cancer patients, which may be

more than 600 cases a year in some centres. Moreover, waiting lists are long as some centres do not offer chemotherapy due to insufficient resources. (Simonds, 2009:66) Thus when the already limited radiation therapy equipment is not functioning properly, many of the patients may not be able to complete the prescribed cervical cancer treatment plan. This may explain why in the current study, 22% (22; n=100) of the HIV negative patients and 10% (7; n=72) of the HIV positive patients who were on HAART were either non adherent to their treatment or their treatment was prolonged.

Low blood count (low Hb, white blood cell and platelet count) caused 24% (24; n=100) of the HIV negative patients, 54% (39; n=72) of the HIV positive patients who were on HAART and 9% (1; n=11) of the HIV positive patients who were not on HAART to complete their treatment over an extended period of time or not to complete the prescribed cervical cancer treatment at all (Table 5.11). A significantly larger number of cases was reported among the HIV positive patients who were on HAART (39; 54%; n=72) (Chi^2 = 4.0, d.f. = 2, p = 0.01327, Cramer's V = 0.15).

Twenty five percent (25; n=100) of the HIV negative patients, 51% (37; n=72) of the HIV positive patients who were on HAART and 73% (8; n=11) of the HIV positive patients who were not on HAART were either not adherent to treatment or did not complete their treatment within the prescribed period due to RT induced skin breakdown (Table 5.11). This result was significant (Chi^2 = 0.6, d.f. = 2, p = 0.04581, Cramer's V = 0.16), with the highest percentage of cases noted among the HIV positive women who were not on HAART (73%; 8; n=11).

A significant difference in the incidence of RT induced diarrhoea was observed among the HIV negative patients (26; 26%; n=100), the HIV positive patients who were on HAART (41; 57%; n=72) and the HIV positive patients who were not on HAART (7; 64%; n=11) (Table 5.11). The highest percentage of cases was reported in the HIV positive women who were not on HAART (64%; 7; n=11) (Chi^2 = 6.9, d.f. = 2, p = 0.03118, Cramer's V = 0.19).

In some of the cervical cancer patients, the doctor terminated the prescribed treatment plan if the risks of the treatment outweighed the benefits, that is if the patient

experienced unacceptable toxicity due to the treatment and had poor tumour control. This occurred in 19% (19; n=100) of the HIV negative patients, 31% (22; n=72) of the HIV positive patients who were on HAART and 64% (7; n=11) of the HIV positive patients who were not on HAART (Table 5.11). The highest percentage of cases was significantly reported among the HIV positive patients who were not on HAART (64%; 7; n=11) (Chi^2 = 4.8, d.f. = 2, p = 0.09023, Cramer's V = 0.16).

The longer the time period over which the prescribed treatment is administered (for example, longer periods between doses), the shorter the overall survival, disease free survival and local control of the tumour (Waggoner, 2003:2223 and Taylor *et al.*, 1990:97). The American Brachytherapy Society recommends that the total treatment duration for cervical cancer should be less than eight weeks. After approximately eight weeks of therapy, the increase in local failure is 0.7% to 1.0% per day for every day of treatment missed. (Nag *et al*., 2000:202) Therefore, patients need to adhere to the prescribed cervical cancer treatment plan in order to achieve complete response to treatment.

Limited studies have been conducted regarding the patterns of adherence to cervical cancer treatment among HIV positive women with cervical cancer. McArdle & Kigula-Mugambe (2007:94-97) reported that HIV positive patients were more likely to have multiple factors that would lead to interruptions of cervical cancer treatment. Another prospective study by Gichangi *et al.* (2006:405-411) noted that HIV infection was an independent factor that led to treatment interruptions. In addition, HIV positive women were six times more likely to have residual tumours after radiation therapy. The findings of the current study did not support those of McArdle & Kigula-Mugambe (2007:94-97) and Gichangi *et al.* (2006:405-411) in that there was no significant difference in the incidence of adherence between the HIV negative patients, the HIV positive patients who were on HAART and the HIV positive patients who were not on HAART. However, there was a significant difference in the incidence of the various reasons (missed scheduled appointments, low blood count, RT induced skin breakdown and RT induced diarrhoea) for non adherence between the various groups.

In summary, the current study did not find a significant difference in the incidence of adherence between the HIV negative patients, the HIV positive patients who were on HAART and the HIV positive patients who were not on HAART. However, there was a significant difference in the incidence of the various reasons for non adherence between the various groups. These reasons included: missed scheduled appointments (Chi^2 = 2.9, d.f. = 2, p = 0.02385, Cramer's V = 0.31); low blood count (Chi^2 = 4.0, d.f. = 2, p = 0.01327, Cramer's V = 0.15); RT induced skin breakdown (Chi^2 = 0.6, d.f. = 2, p = 0.04581, Cramer's V = 0.16) and RT induced diarrhoea (Chi^2 = 6.9, d.f. = 2, p = 0.03118, Cramer's V = 0.19) Larger studies assessing the adherence of HIV positive women with cervical cancer to cervical cancer treatment need to be done. It is vital to ensure that cervical cancer patients adhere to their prescribed treatment plan in order to achieve tumour control.

Chapter 6

CONCLUSIONS AND RECOMMENDATIONS

6.1 INTRODUCTION

The aim of this study was to assess how HIV positive women who have been diagnosed with cervical cancer responded and adhered to cervical cancer therapy which includes: curative RT; CCRT or PRT. The study also set out to determine the effects of the concurrent use of ARVs and cervical cancer treatment. This was done to determine whether HIV positive women with ICC could be managed using the same treatment protocols as HIV negative women with ICC.

6.2 CONCLUSIONS

In this section, an overview of the conclusions drawn from the study will first be presented (section 6.2.1) followed by detailed conclusions (section 6.2.2)

6.2.1 Overview

The study revealed that there was a significant difference in the incidence of complete response to ICC treatment between the HIV positive patients and the HIV negative patients (Section 5.8.1 and 6.2.2.5). Cases of both treatment failure and metastases were significantly higher in HIV positive women than in HIV negative women (Section 5.8.2 and 6.2.2.6). In terms of toxicity, haematological toxicity (leucopenia and thrombocytopenia) and neurological toxicity seemed to be increased in the HIV positive women who were on HAART. Dermatological (skin desquamation) and gastrointestinal toxicities (diarrhoea) as well as other toxicities such as weight loss appeared to be worse in the HIV positive patients (Section 5.9 and 6.2.2.8).

Although there was no significant difference in the incidence of adherence between the HIV negative women, the HIV positive women who were on HAART and the HIV positive women who were not on HAART, there was a significant difference in the incidence of the various reasons (missed scheduled appointments; low blood count; RT

induced skin breakdown and RT induced diarrhoea) for non adherence between the various groups (Section 5.10 and 6.2.2.9).

Finally, in terms of the 2004 South African national antiretroviral treatment guidelines, ARVs should be commenced in patients with WHO stage IV disease irrespective of their CD4 count. Patients presenting with cervical cancer would fall into the WHO stage IV category of HIV disease. (Department of Health, South Africa, 2004:12) This implies that patients with confirmed diagnosis of ICC should be commenced on ARVs as soon as the ICC diagnosis is made whether their CD4 count is above 200 cells/mm^3 or less. However, in the current study, 13% (n=83) of the HIV positiveparticipants were not on HAART.

In summary, the aims and objectives of the study were fulfilled in that:

- The patients' response to cervical cancer treatment was determined. There was a significant difference in the incidence of complete response to ICC treatment between the HIV positive patients and the HIV negative patients. The response to ICC treatment was poorer among HIV positive women. Cases of both treatment failure and metastases were significantly higher in HIV positive women than in HIV negative women.
- The effect of the concurrent use of ARVs and cervical cancer treatment was also established. Although, the use of HAART by the HIV positive participants in the current study did not have a significant impact in the patient outcome, a higher percentage of cases of both treatment failure and metastases were reported in HIV positive women who were not on HAART.
- There was no significant difference in the incidence of adherence between the HIV negative patients, the HIV positive patients who were on HAART and the HIV positive patients who were not on HAART. However, there was a significant difference in the incidence of the various reasons (missed scheduled appointments; low blood count; RT induced skin breakdown and RT induced diarrhoea) for non adherence between the various groups.

6.2.2 Detailed conclusions

6.2.2.1 Conclusions: Patient demographics

- Of the 196 participants, 100 participants (51%; n=196) were HIV negative, 83 participants (42%; n=196) were HIV positive and 13 women's HIV status was unknown (7%; n=196).
- The highest (69; 35%; n=196) number of participants were between 51 to 60 years old.
- The mean age of the HIV positive women with cervical cancer (54 $\pm$ 11.3 years) was four years lower than the mean age of HIV negative women (58 $\pm$ 12.0 years)(t-test = 1.8409; d.f. = 180; p = 0.06728; Cohen's d = 0.27).

6.2.2.2 Conclusions: Risk co-factors for cervical cancer

- Thirty seven percent (72; n=196) of the participants had no risk co-factors, 41% (80; n=196) had one risk co-factor, 20% (39; n=196) had two risk co-factors and 2% (5; n=196) of the participants had three risk co-factors for cervical cancer.
- The most prevalent risk co-factor was found to be HIV infection (42%; 83; n=196), followed by cigarette smoking (33%; 65; n=196), oral contraceptive use (27%; 53; n=196), high parity (15%; 30; n=196) and STI infection (13%; 25; n=196).

6.2.2.3 Conclusions: The treatment protocols used at the study site

- The study population consisted of six (3%; n=96) stage I patients, 27 (14%; n=196) stage II patients, 106 (54%; n=196) stage III patients and 57 (29%; n=196) stage IV cervical cancer patients. Thus, the majority (106; 54%; n=196) of the patients were diagnosed with Stage III cervical cancer.
- Curative RT was prescribed for all six of the stage I cervical cancer patients and for most of the stage II cervical cancer patients (14; 52%; n=27). Concurrent chemoradiation was the recommended treatment of choice for most of the stage III cervical cancer patients (55; 52%; n=106). In the majority of the stage IV cervical cancer patients (49; 86%; n=57), RT was prescribed to palliate central disease or distant metastases.

6.2.2.4 Conclusions: Prognostic factors for cervical cancer

Patient characteristics: age and blood Hb levels

- There was no significant difference in the mean age between the women who displayed complete response to cervical cancer treatment (56.7 $\pm$ 12.3 years) and those who displayed an incomplete response to treatment (57.4 $\pm$ 11.0 years) (t-test = 0.3766; p = 0.7069; Cohen's d = 0.05).
- Eighty four percent (164; n=196) of the patients had anaemia (blood Hb level less than 12g/dl) during treatment (Table 5.5). Of the 164 anaemic patients, 53% (87; n=164) had an incomplete response to cervical cancer treatment. There was no significant difference between the prognosis of the anaemic patients and that of the non anaemic patients (Chi^2 = 1.46, d.f. = 1, p = 0.22644, Cramer's V = 0.09).
- Of the 164 patients who had anaemia, 31% (52; n=164) received curative RT, 2% (3; n=164) received CT, 39% (64; n=164) received CCRT and 28% (45; n=164) received PRT (Figure 5.4). Hence, the highest cases of anaemia were reported in patients who received concurrent chemoradiation.

Tumour characteristics: stage at initiation of treatment

- At one month following cervical cancer treatment there was a highly significant difference in the incidence of complete response in patients at different stages of cervical cancer (Chi^2 = 88.9, d.f. = 3, p = 0.0000, Cramer's V =0.67). The high significant difference in response to treatment by patients at different stages of cervical cancer was maintained at six months after treatment (Chi^2 = 70.94, d.f. = 3, p = 0.0000, Cramer's V = 0.62), 12 months after treatment (Chi^2 = 48.53, d.f. = 3, p = 0.0000, Cramer's V = 0.54), 18 months after treatment (Chi^2 = 32.02, d.f. = 3, p = 0.0000, Cramer's V = 0.5) and 24 months after treatment (Chi^2 = 18.69, d.f. = 3, p = 0.0032, Cramer's V = 0.45). At each of these intervals, the response to cervical cancer treatment was poorer among women with advanced stage cervical cancer (stage III and IV).

Treatment characteristics: duration of treatment

- A highly significant difference in the average duration of treatment between the patients who had a complete response to RT (6 weeks) and the patients who had an incomplete response to RT (5 weeks) was reported (t-test = 2.91678 p = 0.00487, Cohen's d = 0.79).
- There was no significant difference in the average duration of treatment between the patients who had a complete response to CCRT (9 weeks) and the patients who had an incomplete response to CCRT (8 weeks) (t-test = 0.93828 p = 0.35137, Cohen's d = 0.3).
- The average duration of treatment of the patients who had an incomplete response to RT (5 weeks) or CCRT (8 weeks) was lower than that of the patients who displayed complete response to RT (6 weeks) or CCRT (9 weeks). This was due to the fact that some of the patients who exhibited an incomplete response to RT or CCRT did not complete the prescribed treatment either due to non adherence to the prescribed treatment or early termination of treatment by the oncologist. Therefore, the current study could not establish a link between the duration of cervical cancer treatment and patient outcome.
- There was no significant difference in the average duration of treatment between the patients who had a complete response to PRT (9 $\pm$ 1 days) and the patients who had an incomplete response to PRT (10.6 $\pm$ 6 days) (t-test = 2.61688 p = 0.92613, Cohen's d = 0.79).

6.2.2.5 Conclusions: Response to cervical cancer treatment in HIV positive versus HIV negative women

- There was a significant difference in the response to cervical cancer treatment between the HIV positive patients and the HIV negative patients. These significant differences were observed at each interval: one month after treatment (Chi^2 = 16.4, d.f. = 1, p = 0.00005, Cramer's V =0.31); six months after treatment (Chi^2 = 15, d.f.= 1, p = 0.00011, Cramer's V = 0.34); 12 months after treatment (Chi^2 = 20.5, d.f. = 1, p = 0.00001, Cramer's V = 0.37); 18 months after treatment (Chi^2 = 9.8, d.f. = 1, p = 0.00173, Cramer's V = 0.28) and 24 months after treatment (Chi^2 =

5.0, d.f. = 1, p = 0.02571, Cramer's V = 0.26). At each of these intervals, the response to cervical cancer treatment was poorer among HIV positive women.

6.2.2.6 Conclusions: Response to cervical cancer treatment in HIV positive women on HAART versus HIV positive women not on HAART

- Of the 83 HIV positive patients, 87% (72; n=83) were on HAART and 13% (11; n=83) were not on HAART and HAART was only initiated in HIV positive women whose CD4 count was less than 200 cells/mm^3.
- Of the 72 HIV positive women who were on HAART, 81% (58; n=72) were on regimen 1a (d4T; 3TC; EFV), 5% (4; n=72) were on regimen 1b (d4T; 3TC; NVP) and 14% (10; n=72) were on regimen 2 (AZT; DDI; LPV-RTV).
- A significant difference in the incidence of complete response to cervical cancer treatment between the HIV positive patients who were on HAART and the HIV positive patients who were not on HAART was only noted six months after these patients received treatment (Chi^2 = 0.5, d.f. = 1, p = 0.02546, Cramer's V = 0.25) where complete response was observed in 39% (28; n=72) of the HIV positive patients who were on HAART and in none (0; n=11) of the HIV positive patients who were not on HAART. No significant differences in the incidence of complete response between these two groups were noted at the other time intervals: one month after treatment (Chi^2 = 1.6, d.f. = 1, p = 0.21071, Cramer's V =0.14) and 12 months after treatment (Chi^2 = 1.2, d.f. = 1, p = 0.28067, Cramer's V = 0.13). The number of HIV positive patients who returned to the study site 18 months and 24 months after they had received treatment were too small to be statistically analysed. Therefore, the use of HAART by the HIV positive participants in the current study did not have a significant impact in the patient outcome.
- Since patients presenting with cervical cancer would fall into the WHO stage IV category of HIV disease, all patients with confirmed diagnosis of ICC should have been commenced on ARVs as soon as the ICC diagnosis was made irrespective of their CD4 count. In this study, only 72 of the 83 HIV positive patients were on HAART.

6.2.2.7 Conclusions: Recurrence and metastases of cervical cancer

- The number of HIV positive patients (72%; 60; n=83) with recurrence of cervical cancer was significantly higher than that of the HIV negative patients (40%; 40; n=100) (Chi^2 = 17.8, d.f. = 2, p = 0.00013, Cramer's V = 0.31).
- Metastases of cervical cancer was also significantly higher in HIV positive patients (44%; 35; n=83) than in HIV negative patients (14%; 14; n=100) (Chi^2 = 13.6, d.f. = 2, p = 0.00109, Cramer's V = 0.28).

6.2.2.8 Conclusions: Toxicity due to treatment in HIV positive versus HIV negative cervical cancer patients

- Only one patient did not experience toxicity/side effects during or after ICC treatment. The number of side effects that were noted in the patients ranged from one to ten. Most of the patients experienced four side effects (46; 27%; n=171).
- On average, HIV negative patients experienced 3.8 $\pm$ 1.6 side effects per patient, HIV positive patients who were on HAART experienced 4.9 $\pm$ 2.1 side effects per patient and HIV positive patients who were not on HAART experienced 4.3 $\pm$ 1.3 side effects per patient. There was a significant difference in the incidence of the number of side effects per patient in the HIV negative patients and in the HIV positive patients who were on HAART (Tukey's HSD procedure, p = 0.00013). However no significance was noted in the incidence of the number of side effects per patient in the HIV positive patients who were not on HAART (Tukey's HSD procedure, p = 0.50984).
- The most common toxicity that was reported in the study population was haematological toxicity (164; 84%; n=196) and the highest cases were reported among HIV positive patients who were on HAART. The incidence of leucopenia and thrombocytopenia was significantly highest in this specific group (Chi^2 = 9.3, d.f. = 2, p = 0.00948, Cramer's V = 0.23 and Chi^2 = 10.5, d.f. = 2, p = 0.00535, Cramer's V = 0.24 respectively).
- Radiation induced dermatological toxicity (skin desquamation), gastrointestinal toxicity (diarrhoea) and weight loss were significantly higher among the HIV

positive women (Chi^2 = 4.2, d.f. = 2, p = 0.02512, Cramer's V = 0.15; Chi^2 = 1.2, d.f. = 2, p = 0.04536, Cramer's V = 0.23 and Chi^2 = 14.4, d.f. = 2, p = 0.00074, Cramer's V = 0.28 respectively).

- The occurrence of CIPN was significantly higher in HIV positive patients who were on HAART (15; 22%; n=69) (Chi^2 = 16.3, d.f. = 2, p = 0.00029, Cramer's V = 0.30).

6.2.2.9 Adherence to treatment in HIV positive versus HIV negative cervical cancer patients

- Sixty one (61%; n=100) HIV negative patients, 52 (72%; n=83) HIV positive patients who were on HAART and seven (64%; n=11) HIV positive women who were not on HAART were adherent to cervical cancer treatment. There was no significant difference in the adherence patterns between these three groups (Chi^2 = 10.2, d.f. = 6, p = 0.11805, Cramer's V = 0.17). However, there was a significant difference in the incidence of the various reasons for non adherence between the various groups. These reasons included: missed scheduled appointments (Chi^2 = 2.9, d.f. = 2, p = 0.02385, Cramer's V = 0.31); low blood count (Chi^2 = 4.0, d.f. = 2, p = 0.01327, Cramer's V = 0.15); RT induced skin breakdown (Chi^2 = 0.6, d.f. = 2, p = 0.04581, Cramer's V = 0.16) and RT induced diarrhoea (Chi^2 = 6.9, d.f. = 2, p = 0.03118, Cramer's V = 0.19).

6.3 RECOMMENDATIONS

The following recommendations arose from the research study: creating awareness of cervical cancer prevention in order to ensure early detection and treatment of the disease; using iron supplementation to manage anaemia, a condition that affects the prognosis of ICC patients; altering the fractionation of RT which would help to reduce machine time and integrating ICC and HIV/AIDS management programmes.

6.3.1 Creating awareness of cervical cancer prevention

In the current study, there was a highly significant difference in the response to treatment by patients at different stages of cervical cancer. The response to cervical cancer treatment was poorer among women with advanced stage cervical cancer (stage

III and IV) (Section 5.7.2.1). Cervical cancer is one of the few cancers that can be easily managed if it is detected in its earliest stages. However, early detection and treatment of cervical cancer is challenging in South Africa because there is a lack of awareness of the causes, risk factors, symptoms and prevention strategies. In addition, there is a long delay, during referral of patients, between diagnosis and treatment thus the disease might progress into an advanced stage.

Although the South African Department of Health developed a national cervical cancer screening policy in 2000, statistics have shown that by 2008, less than 20% of women had used this service. This low screening rate was caused by the lack of education about cervical cancer in the community. (Maree and Wright, 2007:61) Lack of awareness about cervical cancer was associated with low literacy levels (Department of Health, South Africa, 2007). Additionally, it has been shown that presenting information about HPV infection and cervical cancer as a sexually transmitted disease could discourage women from being screened as sexual practices that increase the risk of cervical cancer are perceived to be promiscuous and this leads to stigma (Maree and Wright, 2007:62).

A low literacy level in women has been associated with lack of awareness about cervical cancer. Schalkwyk *et al*. (2008:9-17) interviewed 15 South African women with advanced cervical cancer in order to understand the routes they followed from the first signs and symptoms of disease to receiving treatment. The study showed that the women lacked awareness of cervical cancer as a disease. The participants knew that something was wrong with them, but lacked the knowledge of what was required to prevent the progression of precancer to advanced cervical cancer. Nine of the 15 participants in the study had less than eight years of education. Similar results were reported in other studies not just in developing countries such as Tanzania (Kidanto *et al.*, 2002:467-475) but also in the Netherlands which is a developed country (De Nooijer *et al*., 2002:362-369), where there was a link between the low literacy levels of women and the lack of knowledge about cervical cancer.

In 2007, the South African Department of Health found that eight million of the population would not benefit from existing written health promotional material due to low literacy levels (Department of Health, South Africa, 2007). In the case of cervical cancer, this means that women with low literacy levels would not understand the terminology used in the written material aimed at educating women about the prevention and management of cervical cancer.

In addition, presenting cervical cancer as a sexually transmitted disease could discourage women from being screened as they may be perceived to be promiscuous and this might lead to stigma (Braun and Gavey, 1999:1463-1474 and Markey and Markey, 2007:55-65). In South Africa, Maree and Wright (2007:55-65) conducted a study to determine if presenting cervical cancer information in a non stigmatising way would promote cervical screening. The sample consisted of 105 women and 19% of these women had no schooling or only had primary education. The study revealed that the target group rejected the information because of the approach. By presenting HPV infection and cervical cancer as a sexually transmitted disease, the women felt that they would be perceived to be promiscuous. This could result in the avoidance of cervical screening because of the possible stigmatisation that they would experience, should cervical cancer be diagnosed.

The study by Schalkwyk *et al*. (2008:9-17) also revealed that the average number of months from the first contact with a health care professional due to the signs and symptoms of cervical cancer until diagnosis, was 17.3 months, ranging from 28.4 months for women living in rural areas to 11.8 months for women living in an urban area. The women living in Gauteng Province waited 2.8 months between diagnosis and being referred to the hospital for treatment, compared to 6.5 months for those who were referred from provincial hospitals outside Gauteng Province. The women were also not diagnosed with cervical cancer during their initial sessions with a health care professional. This was due to the nature of cervical cancer during the initial stages, the lack of insight on the part of the health professionals and some of the women did not report their main symptoms.

These problems could be addressed in various ways. Awareness programmes that are aimed at educating women about cervical cancer prevention and early detection should be tailored to the literacy level of women. The target population should be able to understand the language used and the content of the literature material. In addition, health professionals should be trained to recognise the signs and symptoms of cervical cancer. The South African Department of Health should also implement an effective referral system so as to decrease the time delay from diagnosis to treatment.

In summary, cervical cancer prevention and early detection would involve: developing appropriate cervical cancer awareness programmes aimed at promoting cervical cancer screening; training health professionals to recognise the signs and symptoms of cervical cancer and implementing an effective referral system that would support the detection and treatment of cervical cancer in its earliest stages thus improving treatment outcomes.

6.3.2 Use of iron supplementation to manage anaemia

Anaemia at diagnosis and/or during treatment may affect the prognosis of cervical cancer patients. In the current study, 164 patients experienced anaemia during treatment and of these 164 patients who had anaemia, 53% (87; n=164) had an incomplete response to treatment. Furthermore, low blood count (low Hb, white blood cell and platelet count) caused 24% (24; n=100) of the HIV negative patients, 54% (39; n=72) of the HIV positive patients who were on HAART and in 9% (1; n=11) of the HIV positive patients who were not on HAART to complete their treatment over an extended period of time or not to complete the prescribed cervical cancer treatment at all (Table 5.11).

At the study site, anaemia was corrected by administering blood transfusions to patients whose Hb level was below 12g/dl. However, the benefit of blood transfusions in cancer patients remains unclear. A randomised trial by Fyles *et al.* (2000:130-139) that investigated the benefits of blood transfusions in cervical cancer patients drew unconvincing results. In another study by Sundfor *et al*. (1997:230-236), only 50% of the cervical cancer patients showed an increase in tumour oxygenation after receiving

blood transfusions thus suggesting that blood transfusions cannot broadly reduce the number of hypoxic tumour cells that are resistant to radiotherapy. Santin *et al*. (2003:28-34) reported that the use of routine blood transfusions in anaemic cervical cancer patients did not improve the prognosis of the patients.

Blood transfusions also pose safety and financial challenges. The adverse effects of blood transfusions include transmission of infections, allergic and febrile reactions, platelet contamination, lung injury and errors relating to incorrect matching of the donor and recipient. Furthermore, the management of blood transfusion services is expensive for health care institutions, especially in developing countries such as South Africa in terms of the maintenance cost of blood banks and other operational costs such as delivering blood to patients. (Hinkel *et al*., 2010:S42)

Over the years, alternatives to blood transfusions such as recombinant human erythropoietin (rhEPO) and oral or intravenous iron supplementation have been developed to maintain Hb levels in patients with cervical cancer. Despite the existence of clinical evidence that supports the use of iron supplementation in cancer patients, this approach has not been widely accepted by oncologists. Many oncologists lack understanding regarding the use of iron supplementation to treat anaemia in cervical cancer patients. (Hinkel *et al*., 2010:S48)

Therefore, oncology pharmacists can play a vital role in this area by educating the oncologists on the benefits and risks of iron supplementation. This may dispel any misconceptions about the safety of iron supplementation. The use of iron supplementation may prove to be beneficial in the management of anaemic cervical cancer patients in South Africa where many patients have poor access to blood transfusion facilities.

As anaemia can affect the treatment outcomes, it is imperative to ensure that this condition is corrected using blood transfusions, rhEPO and oral or intravenous iron supplementation.

6.3.3 Altered fractionation of radiotherapy

At the study site, the prescribed radiotherapy treatment for Stage Ib to III disease included EBRT 50 Gy in 25 fractions, 2 Gy daily over five weeks and ICT brachytherapy 24.8 Gy in four fractions, (6.2 Gy/fraction). This is not only labour intensive but with long waiting lists for RT machine time, particularly in the public health sector, other options should be considered. Further studies need to be conducted in hypofractionation or the delivery of radiotherapy in larger fractions per dose.

Campbell *et al.* (2002:253-258) examined this concept by randomising 480 patients in Nairobi to either conventional fractionation (45 to 50 Gy over five weeks) or hypofractionation (45 to 50 Gy over three weeks). Five year survival rates of Stage III patients were 42.5% and 40.2% respectively. Early toxicity was similar in both groups but there was a higher rate of late toxicity in the hypofractionated group thus the authors recommended that caution should be applied in the use of the hypofractionated regimen. Muckaden *et al.* (2002:127-134) from Mumbai retrospectively reviewed patients with stage III cervical cancer who received 39 Gy in 13 fractions followed by a single ICT brachytherapy treatment of 25 Gy. Of the 62 patients treated, 48 completed the regimen. The three year survival rate was 50%. Six patients had severe acute toxicity and five patients had late rectal toxicity. The role that hypofractionated radiotherapy plays in treatment of cervical cancer has not been defined and thus further studies need to be conducted in order to develop a regimen that maximises tumour control and use of resources while limiting toxicities.

6.3.4 Integration of cervical cancer and HIV/AIDS management

Although South Africa has a National Cancer Registry, the cervical cancer statistics were last recorded in 2001 and may be outdated (Bourke, 2007). Therefore, it is difficult to determine the number of South African women with cervical cancer. It has been reported that in South Africa, up to 30% of cervical cancer patients are HIV positive (Mqoqi *et al*., 2004:22). In the current study, 42% (83; n=196) of the ICC patients were HIV positive. Of the 83 HIV positive patients, 87% (72; n=83) were on HAART.Since the

WHO stage IV category of HIV disease includes ICC, all patients with confirmed diagnosis of ICC should have been commenced on ARVs as soon as the ICC diagnosis was made irrespective of their CD4 count. Therefore, oncologists should ensure that HIV positive patients with ICC are started on HAART as soon as ICC diagnosis is made.

The ideal situation would be for every HIV positive woman with ICC to start HAART as soon as diagnosis is made, but the reality is that in sub Saharan African about seven out of 10 HIV positive patients who clinically need ARVs do not receive them. South Africa has the largest ARV programme in the world. In 2003, the South African Department of Health launched the national ARV roll-out with its comprehensive plan for the care, management and treatment of HIV and AIDS. The aim of the programme was to ensure that in five years time, all HIV positive women in need of ARVs had access to this medication. The ARV roll out in the Eastern Cape, where the current study site is located began in mid June 2004. By 2006, it was clear that it would take more than 5 years to fulfil this aim because less than 30% of South African HIV positive women who were in need of ARVs had access to ARVs. In 2007, the Department of Health published the National Strategic Plan which aimed to achieve access to ARVs for 80% of the people who would need them by 2011. Since the implementation of the 2007 to 2011 National Strategic Plan, the public sector ARV programme has steadily increased the numbers of monthly new enrolments on ARVs and decreased waiting times for the HIV positive patients eligible for ARVs. However, there are still delays and problems in accrediting ARV public health facility sites, providing appropriately trained health personnel and registering ARVs. (Uebel *et al*., 2010:589) Consequently, not every HIV positive patient with ICC has access to ARVs thus their CD4 count may deteriorate and they may not be able to tolerate ICC treatment and this may lead to unfavourable treatment outcomes.

In South Africa, oncology services are provided in tertiary level institutions. A feasible solution would be to test all patients diagnosed with ICC for HIV. Since patients presenting with cervical cancer would fall into the WHO stage IV category of HIV disease, oncologists should refer all the newly diagnosed HIV positive patients or HIV positive patients who were previously not eligible for HAART to the ARV clinic that is

located at the tertiary level hospital. The patients should continue to receive the ARVs from the ARV clinic located at the tertiary level hospital during their course of cervical cancer treatment (CCRT/RT). Once treatment is completed, the patients should be referred to an ARV clinic which is conveniently located within their area of residence or employment where they would continue to receive treatment for the rest of their lives.

6.4 AREAS FOR FUTURE RESEARCH

The findings of the current study identified potential areas for future research in the fields of HIV/AIDS and cervical cancer. More studies need to be conducted in order to find out if large single fractions of PRT, rather than multiple fractions of PRT, which provide optimal patient outcome with minimal use of resources may be preferable if similar palliative results could be achieved.

There is mixed evidence concerning the impact of HAART on patient outcome. Some studies suggest that the use of HAART has led to improved tolerance of full doses of RT or CCRT and improved response to cancer treatment (Antoniou & Tseng, 2005:143 and Ntekim & Folasire, 2010:64). In contrast, other studies suggest that the use of HAART does not seem to have a significant effect on patient outcome (Brunner *et al*., 2008: 2706 and Caceres *et al.*, 2010:73). In the current study, the use of HAART by the HIV positive participants did not have a significant impact on the patient outcome, though the study was based on a small population and a short follow up period. Therefore, more studies still need to be conducted so as to establish conclusive results on the impact of HAART on ICC. Larger studies assessing the adherence patterns and the acute and late toxicity experienced by HIV positive women undergoing cervical cancer treatment also need to be undertaken.

REFERENCE LIST

Abayomi, J. Kirwan, J. Hackett, A. & Bagnall G. 2005.A study to investigate women's experiences of radiation enteritis following radiotherapy for cervical cancer.*Journal of Human Nutrition Dietetics*, 18:353-363.

Ahdieh-Grant, L. Li, R. Levine, A. Massad, L.S. Strickler, H.D. & Minkoff, H. 2004. Highly active antiretroviral therapy and cervical squamous intraepithelial lesions in human immunodeficiency virus positive women.*Journal of the National Cancer Institute,* 96(14): 1070-1076.

American Cancer Society. 2009. *Cancer Facts and Figures 2009*. Atlanta: American Cancer Society.

Anhang, R. Wright, R.C.Jr. Smock, L. & Goldie, S.J. 2004.Women's desired information about human papillomavirus. *Cancer*, 100:315-320.

Anorlu, R.I. 2008. Cervical cancer: the Sub-Saharan African perspective. *Reproductive Health Matters*, 16(32):41-49.

Ansink, A.C. 2007. Cervical cancer in developing countries: how can we reduce the burden? Awareness raising, screening, treatment and palliation.*Tropical Doctor*, 37:67-70.

Antoniou, T. & Tseng, A.L. 2005.Interactions between antiretrovirals and antineoplastic drug therapy.*Clinical Pharmacokinetics*, 44:111-145.

Arbyn, M. Paraskevaidis, E. Martin-Hirsch, P. Prendiville, W. & Dillner, J. 2005. Clinical utility of HPV-DNA detection: triage of minor cervical lesions, follow up of women treated for high grade CIN: an update of pooled evidence. *Gynecologic Oncology*, 99(3 suppl 1):S7-11.

Barbera, L. & Thomas, G. 2008.Venous thromboembolism in cervical cancer.*Lancet*, 9:54-60.

Baseman, J.G. & Koutsky, L.A. 2005.The epidemiology of human papillomavirus infections.*Journal of Clinical Virology*, 32(suppl):S16-24.

Bayo, S. Bosch, F.X. de Sanjose, S. Munoz, N. Combita, A.L. Coursaget, P. Diaz, M. Dolo, A. van den Brule, A.J. & Meijer, C.J. 2002. Risk factors of invasive cervical cancer in Mali.*International Journal of Epidemiology,* 31:202-209.

Biggar, R.J. Chaturvedi, A.K. Goedert, J.J. & Engels, E.A. 2007.AIDS-related cancer and severity of immunosuppression in persons with AIDS.*Journal of the National Cancer Institute*, 99:962-972.

Bollen, L.I. Chuachoowong, R. Kilmarx, P.H. Mappstats, P.A.M. Culnane, M. Skunodom, N. Chaowanachan, T. Jetswang, B. Neeyapun, K. Asavapiriyanont, S. Roongpisuthipong, A. Wright, T.C. & Tappero, J.W. 2006. Human papillomavirus (HPV) detection among human immunodeficiency virus infected pregnant Thai women: implications for the future HPV immunization. *Sexually Transmitted Diseases,* 33(4): 259-264.

Borowsky, M.E. Elliot, K.S. Pezullo, J.C. Santoso, P. Choi, W. Choi, K. & Abulafia, O. 2005. A retrospective review of 15 years of radical radiotherapy with or without concurrent cisplatin and/or 5-fluorouracil for the treatment of locally advanced cervical cancer. *Bulletin of the World Health Organisation*, 92:E19-E24.

Boulware, R.J. Caderao, J.B. Delclos, L. Wharton, J.T. & Peters, L.J. 1979.Whole pelvis megavoltage irradiation with single doses of 1000 rad to palliate advanced gynaecologic cancers.*International Journal of Radiation Oncology *Biology *Physics*, 5:333-338.

Bourke, D. 2007. Women with AIDS face a cervical cancer threat: largest cervical cancer screening programme in developing world finds new risk for women living with AIDS. *Medical News Today*.

[Online]. Available: http://www.medicalnewstoday.com/articles/90463.php. [Date of access: 16 June 2010].

Bower, M. Collins, S. Cottrill, C. Cwynarski, K. Montoto, S. Nelson, M. Nwokolo, N. Powles, T. Stebbing, J. Wales, N. & Webb, A. 2008. British HIV association guidelines for HIV associated malignancies 2008. *HIV Medicine*, 9:359-360.

Bratcher, L.F. & Sahasrabuddhe, V.V. 2010. The impact of antiretroviral therapy on HPV and cervical intraepithelial neoplasia: current evidence and directions for future research. *Infectious Agents and Cancer*, 5(8):1-13. [Online]. Available: http://www.infectagentscancer.com/content/5/1/8. [Date of access: 28 June 2010].

Braun V. & Gavey, N. 1999. With the best of reasons: cervical cancer prevention policy and the suppression of sexual factor information. *Social Science and Medicine*, 48:1463-1474.

Brewster, W.R. DiSaia, P.J. Monk, B.J. Ziogas, A. Yamada, S.D. & Culver, H. 1999. Young age as a prognostic factor in cervical cancer: results of a population based study. *American Journal of Obstetrics and Gynecology,* 180:1464-1467.

Brunner, T.B. Geiger, M. Grabenbauer, G.G. Welzenbach, M.L. Mantoni, S. Cavallaro, A. Sauer, R. Hohenberger, W. & McKenna, G. 2008. Phase I trial of the human immunodeficiency virus protease inhibitor nelfinavir and chemoradiation for locally advanced pancreatic cancer. *Journal of Clinical Oncology,* 26:2699-2706.

Buller, H.R. Agnelli, G. Hull, R.D. Hyers, T.M. Prins, M.H. & Raskob, G.E. 2004. Antithrombotic therapy for venous thromboembolic disease.*Chest*, 126(3 suppl):401S-428S.

Caceres, W. Cruz-Amy, M. & Diaz-Melendez, V. 2010. AIDS related malignancies: revisited. *Puerto Rico Health Sciences Journal,* 29(1):70-76.

Cairns, M. Harry, V. Sarkar, T.K. & Parkin, D.E. 2008. Treatment of advanced cervical cancer: a population based study. *European Journal of Cancer Care*, 17: 565-568.

Campbell, O.B. Akinalade, I.B. Arowojolu, A. Babarinsa, I.A. Agiwimah, R.I. & Adewole, I.F. 2002. Comparative evaluation of hypofractionated radiotherapy and conventional

radiotherapy in the management of carcinoma of the cervix in Ibadan, Nigeria.*African Journal of Medicine and Medical Sciences*, 29(3):253-258.

Cancer Research UK. 2009. *Cervical cancer UK incidence statistics*. [Online]. Available: http://info.cancerresearchuk.org/cancerstats/types/cervix/incidence/. [Date of access: 9 March 2010].

Castellsague, X. Bosch, F. & Munoz, N. 2002.Male circumcision, penile human papillomavirus and cervical cancer in female partners.*New England Journal of Medicine*, 346:1105-1112.

Castellasague, X. & Munoz, N. 2003. Chapter 3: Cofactors in human papillomavirus carcinogenesis-role of parity, oral contraceptives and tobacco smoking. *Journal of The National Cancer Institute Monographs*: 20-28.

Centers for Disease Control and Prevention. 1993. 1993 revised classification system for HIV-1 infection and expanded surveillance case definition for AIDS among adolescents and adults. *Journal of the American Medical Association*, 269:729-730.

Cerqueira, D.M. Moraes, D.D. & Camara, N. 2007. High HPV genetic diversity in women infected with HIV 1 in Brazil. *Archives of Virology*, 152(1):75-83.

Chemoradiotherapy for Cervical Cancer Meta-analysis Collaboration (CCCMAC), 2010.Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: individual patient data meta-analysis.*Cochrane Database of Systematic Reviews*, 1:CD008285:1-46.

Chen, H.W. Jei, J. & Wei, L. 1997.A randomized trial of hyperthermoradiochemotherapy for uterine cancer.*Clinical Journal of Oncology*, 24:249-251.

Chirenje, Z.M. Rusakaniko, S. Kirumbi, L. Ngwalle, E.W. Makuta-Tlebere, P. Kaggwa, S. Mpanju-Shumbusho, W. & Makoae, L. 2001. Situation analysis for cervical cancer diagnosis and treatment in East, Central and Southern African countries.*Bulletin of the World Health Organisation*, 79(2):127-132.

Chirenje, Z.M. 2005.HIV and cancer of the cervix.*Best Practice & Research Clinical Obstetrics and Gynaecology*, 19(2):269-276.

Cikaric, S. Petrovic-Stupar, S. Marjanov, I. Rudan, L. Colakovic, S. & Timasevic, A. 2005. Radiotherapy versus radiotherapy and chemotherapy of advanced cervical cancer: Regression of tumour, early and late sequalaes, relapses of disease and 3 year survival (the third phase). *European Journal of Cancer*, 3(suppl):266.

Clifford, G.M. Polesel, J. Rickenbach, M. Dal Maso, L. Keiser, O. Kofler, A. Rapiti, E. Levi, F. Jundt, G. Fisch, T. Bordoni, A. De Weck, D. & Franceschi, S. 2005. Cancer risk in the Swiss HIV Cohort Study: associations with immunodeficiency, smoking, and highly active antiretroviral therapy.*Journal of National Cancer Institute*, 97:425-432.

Committee on Practice Bulletins-Gynaecology. 2002. ACOG practice bulletin. Diagnosis and treatment of cervical carcinomas, number 35, May 2002. *American Journal of Obstetrics and Gynecology,* 99(5):855-867.

Cox, J.T. Schiffman, M. & Solomon, D. 2003. Prospective follow up suggests similar risk of subsequent cervical intraepithelial neoplasia grade 2 or 3 among women with cervical intraepithelial neoplasia grade 1 or negative colposcopy and directed biopsy. *American Journal of Obstetrics and Gynecology*, 188:1406-1412.

Dal Maso, L. Polesel, J. Serraino, D. Lise, M. Piselli, P. Falcini, F. Russo, A. Intrieri, T. Vercelli, M. Zambon, P. Tagliabue, G. Zanetti, R. Federico, M. Limina, R.M. Mangone, L. De Lisi, V. Stracci, F. Ferreti, S. Piffer, S. Budroni, M. Donato, A. Giacomin, A. Bellu, F. Fusco, M. Maddedu, A. Vitarelli, S. Tessandori, R. Tumino, R. Suligoi, B. & Franceschi, S. 2009. Pattern of cancer risk in persons with AIDS in Italy in the HAART era.*British Journal of Cancer*, 100:840-847.

Dawson, B. & Trapp, R.G. 2001. *Basic and Clinical Biostatistics*. New York: McGraw-Hill.

Denny, L. Quinn, M. & Sankaranarayanan, R. 2006.Screening for cervical cancer in developing countries.*Vaccine,* 24(suppl 3):71–77.

Denny, L. Boa, R. Williamson, A.L. Allan, B. Hardie, D. Stan, R. & Myer, L. 2008. Human papillomavirus infection and cervical disease in human immunodeficiency virus 1 infected women. *American Journal of Obstetrics and Gynecology*, 111:1380-1387.

De Jong, A. O'Neill, T. Khan, A.Y. Kwappenberg, K.M.C. Chisholm, S.E. Whittle, N.R. Dobson, J.A. Jack, L.C. St Clair Roberts, J.A. Offringa, J.R. van der Burg, S.H. & Hickling, J.K. 2002. Enhancement of human papillomavirus (HPV) type 16 E6 and E7 specific T cell immunity in healthy volunteers through vaccination with TA-CIN, an HPV 16 L2E7E6 fusion protein vaccine.*Vaccine*, 20:3456-3464.

De Nooijer, J. Lechner, L. & De Vries, H. 2002. Early detection of cancer: knowledge and behaviour among Dutch adults. *Cancer Detection and Prevention*, 26(5):362-369.

De Vuyst, H. Gichangi, P. Estambale, B. Njuguna, E. Franceschi, S. & Temmerman, M. 2008. Human papillomavirus types in women with invasive cervical carcinoma by HIV status in Kenya. *International Journal of Cancer*, 122:244-246.

Del Mistro, A. Bertorelle, R. Franzetti, M. Cattelan, A. Torrisi, A. Giordani, M.T. Sposetti, R. Bonoldi, E. Sasset, L. Bonoldi, L. Minucci, D. & Chieco-Bianchi, L. 2004. Antiretroviral therapy and the clinical evolution of human papillomavirus-associated genital lesions in HIV-positive women.*Clinical Infectious Diseases*, 38:737-742.

Department of Health, South Africa. 2000. *Guidelines on cervical screening programme*. Pretoria: Government Printer.

Department of Health, South Africa. 2004. *National antiretroviral treatment guidelines.* Pretoria: Government Printer.

Department of Health, South Africa. 2007. *Strategic plan 2005/06-2007/08*. Pretoria: Government Printer.

Department of Health, South Africa. 2010. *Clinical guidelines for the management of HIV and AIDS in adults and adolescents*. Pretoria: Government Printer.

Dorucci, M. Suligoi, B. Serraino, D. Tirelli, U. & Rezza, G. 2001.Incidence of invasive cervical cancer in a cohort of HIV seropositive women before and after the introduction of highly active antiretroviral therapy.*Journal of Acquired Immune Deficiency Syndromes*, 26:377-380.

Duarte-Franco, E. & Franco, E.L. 2004.Cancer of the uterine cervix.*BMC Women's Health*, 4(suppl 1):1-6.

Dunst, J. Kuhnt, T. Strauss, H.G. Krause, U. Pelz, T. Koelbi, H. & Haensgen, G. 2003. Anaemia in cervical cancers: impact on survival, patterns of relapse and association with hypoxia and angiogenesis. *International Journal of Radiation Oncology *Biology *Physics*, 56(3):778-787.

Eifel, P.J. Moughan, J. Erickson, B. Iarocci, T. Grant, D. & Owen, J. 2004. Patterns of radiotherapy practice for patients with carcinoma of the uterine cervix: pattern of care study. *International Journal of Radiation Oncology *Biology *Physics*, 60:1144-1153.

Ellerbrock, T.V. Chiasson, M.A. Bush, T.J. Sun, X.W. Sawo, D. Brudney, K. & Wright, T.C. Jr. 2000. Incidence of cervical squamous intraepithelial lesions in HIV infected women.*Journal of the American Medical Association*, 283:1031-1037.

Engels, E.A. Pfeiffer, R.M. Goedert, J.J. Virgo, P. McNeel, T.S. Scoppa, S.M. & Biggar, R.J. 2006. Trends in cancer risk among people with AIDS in the United States 1980-2002.*AIDS,* 20:1645-1654.

Engels, E.A. Biggar, R.J. Hall, H.I. Cross, H. Crutchfield, A. Finch, J.L. Grigg, R. Hylton, T. Pawlish, K.S. McNeel, T.S. & Goedert, J.J. 2008. Cancer risk in people infected with human immunodeficiency virus in the United States. *International Journal of Cancer*, 123:187-194.

Fernandez, D.J. Vidyasagar, M.S. Rao, S. Rao, K.K. Shenoy, A. & Kasturi, D.P. 1995. Synchronous 5-fluorouracil, mitomycin-C and radiation therapy in the treatment of locally advanced carcinoma of the cervix.*Proceedings of the 16th Annual Meeting of the*

Association of Radiation Oncologists of India, Kerala, 2-4 February 1995, 97-103. Kerala: Association of Radiation Oncologists of India.

Ferris, D.G. & Litaker, M.S. 2006.Prediction of cervical histologic results using an abbreviated Reid Colposcopic Index during ALTS.*American Journal of Obstetrics and Gynecology*, 194:704-710.

Fiore, F.D. & Cutsem, E.V. 2009.Acute and long term gastrointestinal consequences of chemotherapy.*Best Practice and Research Clinical Gastroenterology*, 23:113-124.

Firnhaber, C. & Michelow, P. 2009. Cervical cancer and the human immunodeficiency virus: a review. *The Southern African Journal of HIV Medicine*, 10(2):23-27.

Firnhaber, C. Zungu, K. & Williamson, A. 2009. Diverse and high prevalence of human papillomavirus associated with a significant high rate of cervical dysplasia in HIV-infected women in Johannesburg. *ActaCytologica,* 53:10-18.

Firnhaber, C. Le, H.V. Pettifor, A. Schulze, D. Michelow, P. Sanne, I.M. Lewis, D.A. Williamson, A.L. Allan, B. Williams, S. Rinas, A. Levin, S. & Smith, J.S. 2010. Association between cervical dysplasia and human papillomavirus in HIV sero-positive women from Johannesburg, South Africa.*Cancer Causes Control*, 21:433-443.

Formenti, S.C. Chak, L. Gill, P. Buess, E.M. & Hill, C.K. 1995.Increased radiosensitivity of normal tissues fibroblasts in patients with AIDS and with Kaposis sarcoma.*International Journal of Radiation Oncology *Biology *Physics*, 68:411-412.

Freedman, L.S. Edwards, B.K. Ries, L.A.G. & Young, J.L. 2006. Cancer incidence in four member countries (MEEC) compared with US SEER. *National Cancer Institute* 06:5873.

Fu, K.K. 1985. Biologic basis for the interaction of chemotherapeutic agents and radiation therapy.*Cancer*, 55:2123-2130.

Fylan, F. 1998. Screening for cervical cancer: a review of women's attitudes, knowledge and behaviour. *British Journal of General Practice*, 48:1509-1514.

Fyles, A. Keane, T.J. Barton, M. & Simm, J. 1992.The effect of treatment duration in the local control of cervix cancer.*Radiotherapy & Oncology*, 86:1528-2536.

Fyles, A.W. Milosevic, M. Pintilie, M. Syed, A. & Hill, R.P. 2000. Anaemia, hypoxia and transfusion in patients with cervical cancer: a review. *Radiotherapy & Oncology*, 57:130-139.

GaripaAYaoAYlu, M. Kayikcioglu, F. Kose, M.F. Adli, M. GAlkesen, K.H. Kocak, Z. & Tulunay, G. 2004. Adding concurrent low dose continuous infusion of cisplatin to radiotherapy in locally advanced cervical carcinoma: A prospective randomized pilot study.*British Journal of Cancer*, 77:581-587.

Gershenson, D.M. & Ramirez, P.T. 2008. *Cervical Cancer: Cancers of the Female Reproductive System: The Merck Manual Medical Library*. [Online]. Available: http://www.merck.com/mmhe/sec22/ch252/ch252d.html. [Date of access: 11 March 2010].

Gichangi, P. Bwayo, J. Estambale, B. Rogo, K. Njuguna, E. Ojwang, S. & Temmerman, M. 2006. HIV impact on acute morbidity and pelvic tumour control following radiotherapy for cervical cancer.*Gynecologic Oncology*, 100:405-411.

Goldie, S. Gaffikin, L. Goldhaber-Fiebert, J. Gordillo-Tobar, A. Levin, C. Mahe, C. & Wright, T.C. 2005. Cost effectiveness of cervical screening in five developing countries. *New England Journal of Medicine*, 353:2158-2168.

Green, J.A. Kirwan, J.M. Tierney, J.F. Symonds, P. Fresco, L. Collingwood, M. & Williams, C.J. 2001. Systematic review of randomized trials of concomitant chemotherapy and radiation therapy for cancer of the uterine cervix: better survival and reduced distant recurrence rate. *Lancet,* 358:781-786.

Grigsby, P.W. Portelance, L. & Williamson, J.F. 2002.High dose ratio (HDR) cervical ring applicator to control bleeding from cervical carcinoma, *International Journal of Gynecological Cancer*, 12:18-21.

Grogan, M. Thomas, G.M. Melamed, I. Wong, F.L. Pearcey, R.G. Joseph, P.K. Portelance, L. Crook, J. & Jones, K.D. 1999. The importance of haemoglobin levels during radiotherapy for carcinoma of the cervix. *Cancer*, 86:1528-1536.

Halle, J.S. Roseman, J.G. Varia, M.A. Fowler, W.C. & Walton, L.A. 1986.1000 cGy single dose palliation for advanced carcinoma of the cervix or endometrium.*International Journal of Radiation Oncology *Biology *Physics*, 12:1947-1950.

Harries, J. & Botha, H. 2007.Advances in the management of cancer of the cervix.*Continuing Medical Education*, 25(2):65-68.

Harries, J. Moodley, J. Barone, M.A. Mall, S. & Sinanovic, E. 2009. Preparing for HPV vaccination in South Africa: key challenges and opinions.*Vaccine*, 27:38-44.

Hawes, S.E. Crithchlow, C.W. Niang, M.A.F. Diouf, M.B. Diop, A. Toure, P. Kasse, A. Dembele, B. Sow, P.S. Coll-Seck, A.M. Kuypers, J.M. & Kiviat, N.B. 2003. Increased risk of high grade cervical squamous intraepithelial lesions and invasive cervical cancer among African women with immunodeficiency virus type 1 and 2 infections. *Journal of Infectious Diseases*, 188:555-563.

Heard, I. Potard, V. Foulot, H. Costagolia, D. & Kazatchkine, M.D. 1998.Early regression of cervical lesions in HIV seropositive women receiving highly active antiretroviral therapy.*AIDS*, 12:1459-1464.

Heard, I. Tassie, J.M. Kazatchkine, M.D. & Orth, G. 2002. Highly active antiretroviral therapy enhances regression of cervical intraepithelial neoplasia in HIV positive women. *AIDS*, 16:1799-1802.

Heard, I. Palefsky, J.M. & Kazatchkine, M.D. 2004.The impact of HIV antiviral therapy on human papillomavirus (HPV) infections and HPV-related diseases.*Antiviral Therapy*, 9(1):13-22.

Heard, I. Potard, V. & Costagolia, D. 2006.Limited impact of immunosuppression and HAART on the incidence of cervical squamous intraepithelial lesions in HIV positive women.*Antiviral Therapy*, 11:1091-1096.

Hernandez, J.R. de la Huerta Sanchez, R. Morales Canfield, F. & Fernandez Orozco, A. 1999.Uterine cervix cancer.Clinical stage III.Combined radiotherapy and chemotherapy treatment.*Ginecologia y Obstetricia de Mexico*, 59:238-242.

Herrero, R. Castle, P.E. Schiffman, M. Concepcion, B. Hildesheim, A. Morales, J. Alfaro, M. Sherman, M.E. Wacholder, S. Chen, S. Rodriguez, A.C. & Burk, R.D. 2005. Epidemiologic profile of type specific human papillomavirus infection and cervical neoplasia in Guanacaste, Costa Rica.*Journal of Infectious Diseases,* 191:1796-1807.

Hinkel, J.M. Li, E.C. & Sherman, S.L. 2010. Insights and perspectives in the clinical and operational management of cancer related anaemia. *Journal of the National Comprehensive Cancer Network,* 8:S38-55.

Ho, C.M. Chien, T.Y. Huang, S.H. Wu, C.J. Shih, B.Y. & Chang, S.C. 2004. Multivariate analysis of the prognostic factors and outcomes in the early cervical cancer patients undergoing radical hysterectomy.*Gynecologic Oncology*, 93:458-464.

Hodson, D.I. & Krepart, G.V. 1983.Once monthly radiotherapy for the palliation of pelvic gynecological malignancy.*Gynecologic Oncology*, 16:112-116.

Holcomb, K. Maiman, M. Dimaio, T. & Gates, J. 1998. Rapid progress to invasive cervical cancer in a woman infected with human immunodeficiency virus. *Obstetrics and Gynaecology*, 91:848-850.

Holmes, K. Levine, R. & Weaver, M. 2004. Effectiveness of condoms in preventing sexually transmitted infections. *Bulletin of the World Health Organisation*, 82: 454-461.

Hong Wei, C. Junjie, F. & Mingzhong, L. 1997.The effect of a randomized trial of hyperthermo-radiochemotherapy for carcinoma of the cervix. *Journal of Clinical Oncology*, 24:249-151.

Housri, N. Yarchoan, R. & Kaushal, A. 2010. Radiotherapy for patients with the human immunodeficiency virus: are special precautions necessary. *Cancer*, 116(2):273-283.

IARC. 2002. Tobacco smoking and tobacco smoke. *IARC Monographs*, 38.

International collaboration on HIV and cancer. 2000. Highly active antiretroviral therapy and incidence of cancer in human immunodeficiency virus-infected adults. *Journal of the National Cancer Institute*, 92:1823-1830.

Jain, N. Irwin, K.L. Montano, D. Kasprzyk, D. Carlin, L. & Freeman, C. 2006. Family physicians' knowledge of genital human papillomavirus (HPV) infection and HPV related conditions, United States, 2004. *Family Medicine*, 38(7):483-489.

Jewkes, R. Vundule, C. Maforah, F. & Jordaan, E. 2001.Relationship dynamics and teenage pregnancy in South Africa.*Social Science and Medicine*, 52:733-744.

Kahn, J.A. Huang, B. Rosenthal, S.L. Tissot, A.M. & Burk, R.D. 2005.Coercive sexual experiences and subsequent human papillomavirus infection and squamous intraepithelial lesions in adolescent and young adult women.*Journal of Adolescent Health*, 36:363-371.

Kaiser Family Foundation. 2000. *National survey of public knowledge of HPV, the human papillomavirus*. [Online].

Available: http://www.kff.org/womenshealth/upload/133851.pdf. [Date of access: 26 May 2010].

Kantardzic, N. Beslija, S. & Begic, D. 2004. Comparison of parameters of myelotoxicity in patients treated with concomitant chemotherapy and radiotherapy versus radiotherapy alone. *MedicinskiArhiv*, 58:19-22.

Kaplan, L.D. Lee, J.Y. Ambinder, R.F. Sparano, J.A. Cesarman, E. Chadburn, A. Levine, A.M. & Scadden, D.T. 2005. Rituximab does not improve clinical outcome in a randomised phase 3 trial of CHOP with or without rituximab in patients with HIV associated non-Hodgkin's lymphoma: AIDS malignancies consortium trial 010. *Blood*, 106:1538-1543.

Katz, M.K. Wewers, M.E. Single, N. & Paskett, E.D. 2007. Key informants' perspectives prior to beginning a cervical cancer study in Ohio Appalachia. *Qualitative Health Research*, 17:131.

Keys, H.M. Bundy, B.N. Stehman, F.B. Muderspach, L.I. Chafe, W.E. Suggs III, C.L. Walker, J.L. & Gersell, D. 1999. Cisplatin, radiation and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. *The New England Journal of Medicine*, 340:1154-1161.

Khan, M.J. Castle, P.E. Lorincz, A.T. Wacholder, S. Sherman, M. Scott, D.R. Rush, B.B. Glass, A.G. & Schiffman, M. 2005. The elevated 10 year risk of cervical precancer and cancer in women with human papillomavirus (HPV) type 16 or 18 and the possible utility of type specific HPV testing in clinical practice. *Journal of the National Cancer Institute*, 97:1072-1079.

Kidanto, H.L. Kilewo, C.D. & Moshiro, C. 2002. Cancer of the cervix: knowledge and attitudes of female patients admitted at Muhimbili National Hospital, Dar es Salaam. *East African Medical Journal*, 79 (9):467-475.

Kim, Y.T. Kim, S.W. Yoon, B.S. Cho, H.J. Nahm, E.J. Kim, S.H. Kim, J.H. & Kim, J.W. 2007. Effect of intravenously administered iron sucrose on the prevention of anaemia in the cervical cancer patients treated with concurrent chemoradiotherapy. *Gynecologic Oncology*, 105:199-204.

Kinney, W.K. Manos, M.M. Hurley, L.B. & Ransley, J.E. 2006. Where's the high-grade cervical neoplasia? The importance of minimally abnormal Papanicolaou diagnosis.*American Journal of Obstetrics and Gynecology,* 91:973-976.

Kirwan, J.M. Symonds, P. Green, J.A. Tierney, J. Collingwood, M. & Williams, C.J. 2003.A systematic review of acute and late toxicity of concomitant chemoradiation for cervical cancer.*Radiotherapy and Oncology*, 68:216-226.

Knodel.L.C. 2008.Sexually transmitted diseases.*In* DiPiro, J.T. Talbert, R.L. Yee, G.C. Matzke, G.R. Wells, B.G. & Posey, L.M. (eds.), *Pharmacotherapy a pathophysiologic approach*. New York: McGraw-Hill. p. 1915-1931.

Koshiol, J. Schroeder, J.C. & Jamieson D.J. 2006.Time to clearance of human papillomavirus (HPV) infection by HPV type in HIV sero-positive and HIV sero-negative women.*International Journal of Cancer*, 119(7):1623-1629.

Kris, M.G. Hesketh, P.J. Somerfield, M.R. Feyer, P. Clark-Snow, R. Koeller, J.M. Morrow, G.R. Chinnery, L.W. Chesney, M.J. Gralla, R.J. & Grunberg, S.M. 2006. American Society of Clinical Oncology guideline for antiemetics in oncology: update 2006. *Journal of Clinical Oncology*, 24:2932-2947.

Kyrgiou, M. Koliopoulos, G. Martin-Hirsch, P. Arbyn, M. Prendiville, W. & Paraskevaidis, E. 2006. Obstetric outcomes after conservative treatment for intraepithelial or early invasive cervical lesions: systematic review and meta-analysis. *Lancet*, 367:489-498.

Lal, P. Saibish Kumar, E. Tiwari, A. Kumar, S. Dimri, K. Rastogi, N. & Ayyagari, S. 2004. Chemo-irradiation versus radiotherapy alone in locally advanced carcinoma of the uterine cervix: An ongoing phase III trial. *Proceedings of the 23rd Annual Meeting of the European Society for Therapeutic Radiology and Oncology*, Amsterdam, 26 October 2004, 24-28. Amsterdam: European Society for Therapeutic Radiology and Oncology.

Lanciano, R.M. Calkins, A. Bundy, B.N. Parham, G. Lucci, J.A. Moore, D.H. Monk, B.J. & O'Connor, D.M. 2005. Randomised comparison of weekly cisplatin or protracted venous infusion of fluorouracil in combination with pelvic radiation in advanced cervical cancer: A Gynecological Oncology Group Study. *Journal of Clinical Oncology*, 23:8289-8295.

Lartey, M. Joubert, G. & Cronje, H. 2003. Knowledge, attitudes and practices of rural women in South Africa regarding the Pap smear. *International Journal of Gynaecology and Obstetrics*, 83:315-316.

Leborgne, F. 1995. (Unpublished study).Cited in Green *et al*., 2001:781-786.

Lehtovirta, P. Paavonen, J. & Helkinhelmo, O. 2008. Risk factors, diagnosis and prognosis of cervical intraepithelial neoplasia among HIV infected women. *International Journal of STD and AIDS,* 19:37-41.

Levi, J.E. Fernandes, S. Tateno, A.F. Motta, E. Lima, L.P. Eluf-Neto, J. & Pannuti, C.S. 2004. Presence of multiple human papillomavirus types in cervical samples from HIV infected women. *Gynecologic Oncology*, 92(1):225-231.

Lillo, F.B. Ferrari, D. Veglia, F. Origoni, M. Grasso, M.A. Lodini, S. Mastrorilli, E. Taccagni, G. Lazzarin, A. & Uberti-Foppa, C. 2001. Human papillomavirus infection and associated cervical disease in human immunodeficiency virus infected women: effect of highly active antiretroviral therapy. *Journal of Infectious Diseases*, 184:547-551.

Lira-Puerto, V. De-la, H.R. & Cortes, H. 1990. Cisplatin (CDDP) plus radiotherapy (RT) vs. radiotherapy alone in locally advanced cervical cancer. *American Society of Clinical Oncology*, 9:633.

Little, R. Pearson, D. Guierrez, M. Steinberg, S. Yarchoan, R. & Wilson, W. 2000. Dose-adjusted chemotherapy with suspension of antiretrovirals therapy for HIV associated non-Hodgkins lymphoma. *Journal of Acquired Immune Deficiency Syndromes*, 23:A11.

Lomalisa, P. Smith, T. & Guidozzi, F. 2000.Human immunodeficiency virus infection and invasive cervical cancer in South Africa.*Gynecologic Oncology,* 77:460-463.

Lonkhuijzen, L. & Thomas G. 2011.Palliative radiotherapy for cervical carcinoma, a systematic review.*Radiotherapy and Oncology*, 98:287-291.

Lorvidhaya, V. Chitapanaraux, I. Sangruchi, S. Lertsanguansinchai, P. Kongthanarat, Y. Tangkarrat, S. & Visetsiri, E. 2003. Concurrent mitomycin, 5-fluorouracil and radiotherapy in the treatment of locally advanced carcinoma of the cervix.A randomized trial.*International Journal of Radiation Oncology *Biology *Physics*, 55:1226-1232.

Lukka, H. Hirte, H. Fyles, A. Thomas, G. Elit, L. Johnston, M. Fung, M.F. & Browman, G. 2002. Concurrent cisplatin based chemotherapy plus radiotherapy for cervical cancer-a meta-analysis. *Clinical Oncology*, 14:203-212.

Maher, E.J. & Denton, A. 2008.Survivorship, late effects and cancer of the cervix.*Clinical Oncology*, 20:479-487.

Maiman, M. Frutcher, R.G. Serur, E. Remy, J.C. Feuer, G. & Boyce, J.G. 1990.Human Immunodeficiency virus infection and cervical neoplasia.*Gynecologic Oncology*, 38:377-384.

Maiman, M. Frutcher, R.G. Clark, M. Arrastia, C.D. Matthews, R. & Gates, E.J. 1997.Cervical cancer as an AIDS defining illness.*American Journal of Obstetrics and Gynaecology*, 89(1):76-80.

Maiman M. 1998. Management of cervical neoplasia in human immunodeficiency virus infected women. *Journal of the National Cancer Institute Monographs*, 23:43-49.

Mallik, S. Talapatra, K. & Goswami, J. 2010. AIDS: a radiation oncologist's perspective. *Journal of Cancer Research and Therapeutics*, 6(4):432-441.

Maree, J. & Wright S. 2007. Sexual and menstrual practices: risks for cervix cancer. *Health SA Gesondheid*, 12(3):55-65.

Markey, P. & Markey, C. 2007. Sexual and menstrual practices: risks for cervix cancer. *Health SA Gesondheid*, 12(3):55-65.

Mays, R.M. Zimet, G.D. Winston, Y. Kee, R. Dickes, J. & Su, L. 2000. Human papillomavirus, genital warts, Pap smears and cervical cancer: knowledge and beliefs of adolescent and adult women. *Health Care for Women International*, 21(5):361-374.

Mbulaiteye, S.M. Katabira, E.T. Wabinga, H. Parkin, D.M. Virgo, P. Ochai, R. Worneh, M. Coutniho, A. & Engels, E.A. 2006. Spectrum of cancers among HIV infected persons in Africa: The Uganda AIDS cancer registry match study. *International Journal of Cancer*, 118:985-990.

Mbulawa, Z.Z.A. Coetzee, D. Marais, D.J. Kamupira, M. Zwane, E. Allan, B. Constant, D. Moodley, J.R. Hoffman, M. & Williamson, A.L. 2009. Genital human papillomavirus prevalence and human papillomavirus concordance in heterosexual couples are positively associated with human immunodeficiency virus coinfection. *Journal of Infectious Diseases*, 199:1514-1524.

McArdle, O. & Kigula-Mugambe, J.B. 2007. Contraindications to cisplatin based chemoradiotherapy in the treatment of cervical cancer in Sub-Saharan Africa. *Radiotherapy and Oncology*, 83:94-97.

Minkoff, H. Ahdieh, L. Massad, L.S. Anastos, K. Watts, D.H. Melnick, S. Muderspach, L. Burk, R. & Palefsky, J. 2001. The effect of highly active antiretroviral therapy on cervical cytologic changes associated with oncogenic HPV among HIV infected women. *AIDS*, 15(16):2157-2164.

Minkoff, H. Zhong, Y. Burk, R.D. Palefsky, J.M. Xue, X. Watts, D.H. Levine, A.M. Wright, R.L. Colie, C. D'Souza, G. Massad, L.S. & Strickler, H.D. 2010. Influence of adherent and effective antiretroviral use on human papillomavirus infection and squamous intraepithelial lesions in human immunodeficiency virus positive women. *Journal of Infectious Diseases*, 201:681-690.

Mishra, S.K. Laskar, S. & Mucladen, S.A. 2005.Monthly palliative pelvic radiotherapy in advanced carcinoma of the uterine cervix.*Journal of Cancer Research and Therapeutics*, 1:208-212.

Mitra, D. Ghosh, B. Kar, A. Basu, S. Deb, A.R. & Sur, P.K. 2006. Role of chemoradiotherapy in advanced carcinoma cervix. *Journal of the Indian Medical Association*, 104(8):432-436.

Monini, P. Sgadari, C. Toschi, E. Barillari, G. & Ensoli, B. 2004. Antitumour effects of antiretroviral therapy.*Nature Reviews Cancer*, 4:861-875.

Moodley, M. Moodley, J. & Kleinschmidt, I. 2001. Invasive cervical cancer and human immunodeficiency virus (HIV) infection: a South African perspective. *International Journal of Gynecological Cancer*, 11:194-197.

Moodley, J.R. Hoffman, M. Carrara, H. Allan, B.R. Cooper, D.D. Rosenberg, L. Denny, L.E. Shapiro, S. & Williamson, A.L. 2006. HIV and pre-neoplastic and neoplastic lesions of the cervix in South Africa: a case control study. *BioMed Central Cancer*, 6:1-6.

Moore, A.L. Sabin, C.A. Madge, S. Mocroft, A. Reid, W. & Johnson, M.A. 2002.Highly active antiretroviral therapy and cervical intraepithelial neoplasia.*AIDS*, 16:927-929.

Moore, D.H. Chunqiao, T. Monk, B.J. Long, H.J. Omura, G.A. & Bloss, J.D. 2010. Prognostic factors for response to cisplatin based chemotherapy in advanced cervical carcinoma: A Gynecologic Oncology Group Study. *Gynecologic Oncology*, 116:44-49.

Morris, H.M. Eifel, P.J. Lu, J. Grigsby, P.W. Levenback, C. Stevens, R.E. Rotman, M. Gershenson, D.M. & Mutch, D.G. 1999. Pelvic radiation with concurrent chemotherapy compared with pelvic and paraaortic radiation for high risk cervical cancer. *The New England Journal of Medicine*, 340:1137-1143.

Mounier, N. Katlama, C. Costagliola, D. Chichmanian, R.M. & Spano, J.P. 2009. Drug interactions between antineoplastic and antiretroviral therapies: Implications and management for clinical practice. *Critical reviews in oncology/hematology*, 72:10-20.

Mqoqi, N. Kellet, P. Sitas, F. & Jula, M. 2004.*Incidence of histologically diagnosed cancer in South Africa, 1998-1999*. Johannesburg: National Cancer Registry of South Africa, National Health Laboratory Service.

Msadabwe, S.C. 2009. *A randomised study to compare the radical concurrent chemoradiation against radical radiotherapy, as treatment of cancer of the cervix in HIV infected patients*. Johannesburg: University of Witwatersrand. [MB BCH, MMED RAD (T)]

Muckaden, M. Budrukar, A.N. Tongaonkar, H.B. & Dinshaw, K.A. 2002.Hypofractionated radiotherapy in carcinoma cervix IIIb Tata Memorial Hospital experience.*Indian Journal of Cancer*, 39(4):127-134.

Munoz, N. Franceschi, S. Bosetti, C. Moreno, V. Herrero, R. Smith, J.S. Shah, K.V. Meijer, C.J. & Bosch, F.X. 2002. Role of parity and human papillomavirus in cervical cancer: the IARC multicentric case control study. *Lancet*, 359:1093-1101.

Nag, S. Erickson, B. Thomadsen, B. Orton, C. Demanes, J.D. & Petereit, D. 2000. The American Brachytherapy Society recommendations for the high dose rate

brachytherapy for carcinoma of the cervix. *International Journal of Radiation Oncology *Biology *Physics*, 48:201-211.

National Cancer Institute. 1999. *NCI issues clinical announcement on cervical cancer: chemotherapy plus radiation improves survival*. [Online]. Available: http://www.nih.gov/news/pr/feb99/nci22.htm. [Date of access: 31 May 2010].

Ntekim, A.I. & Folasire, A.M. 2010. CD4 count and antiretroviral therapy for HIV positive patients with cancer in Nigeria- a pilot study. *Clinical Medicine Insights*, 4:61-66.

Obermair, A. Cheuk, R. Horwoods, K. Janda, M. Schwanzelberger, B. Stoiber, A. Nicklin, J.L. Perrin, L.C. & Crandon, A.J. 2001. Impact of haemoglobin levels before and during concurrent chemoradiotherapy on the response of treatment in patients with cervical carcinoma: preliminary results. *Cancer*, 92:903-908.

Oehler-Janne, C. Siefert, B. Lutolf, U.M. & Ciernik, I.F. 2006. Local tumour control and toxicity in HIV associated anal carcinoma treated with radiotherapy in the era of antiretroviral therapy. *Radiation Oncology*, 1:29.

Olaitan, A. Johnson, M.A. MacLean, A. & Poulter, L.W. 1996.The distribution of immunocompetent cells in the genital tract of HIV positive women.*AIDS*, 10:759-764.

Onishi, H. Yagamushi, M. Kuriyama, K. Tsukamoto, T. Ishigame, K. Ichikawa, T. Aoki, S. Yoshikawa, T. Araki, T. Nambu, A. Hashi, A. Yasumizu, T. Hoshi, K. & Ito, H. 2000. Effect of concurrent intra-arterial infusion of platinum drugs for patients with stage III of IV uterine cervical cancer treated with radiotherapy. *Cancer Journal from Scientific American*, 6:40-45.

Onsrud, M. Hagen, B. & Heimsted, R. 2001.Palliative treatment in gynaecologic cancer.*TidsskrNorLaegeforen*, 121:1896-1901.

Orlando, G. Fasolo, M.M. Schiavini, M. Signori, R. & Cargnel, A. 1999.Role of highly active antiretroviral therapy in human papillomavirus-induced genital dysplasia in HIV-1-infected patients.*AIDS*, 13:424.

Paramsothy, P. Jamieson, D.J. Heilig, C.M. Schuman, P.C. Klein, R.S. Shah, K.V. Rompalo, A.M. Cu-Uvin, S. & Duerr, A. 2009. The effect of highly active antiretroviral therapy on human papillomavirus clearance and cervical cytology.*American Journal of Obstetrics and Gynecology*, 113:26-31.

Parham, G.P. Sahasrabuddhe, W. Mwanahamuntu, M.H. Shepherd, B.E. Hicks, M.L. & Stringer, E.M. 2006. Prevalence and predictors of squamous intraepithelial lesions of the cervix in HIV positive women in Lusaka, Zambia.*Gynecologic Oncology*, 103(3): 1017-1022.

Patricio, M.B. Tavares, M.A. & Guimaraes, M.F. 1987. Haemostatic and antialgic effects of the 25 MV photon beam concentrated dose in the treatment of carcinoma of the cervix. *Journal of Surgical Oncology*, 34:133-135.

Paul, C. Tzelepis, F. Walsh, R. Girgis, A. King, L. & Mckenzie, J. 2003. Has the investment in public cancer education delivered observable changes in knowledge over the past 10 years? *Cancer*, 97(12):2931-2939.

Pearcey, R. Brundage, M. Drouin, P. Jeffrey, J. Lukka, H. Maclean, G. Souhami, L. Stuart, G. & Tu, D. 2000. A clinical trial comparing concurrent cisplatin and radiation therapy versus radiation alone for locally advanced squamous cell carcinoma of the cervix carried out by the National Cancer Institute of Canada Clinical Trials Group. *American Society of Clinical Oncology*, 19:378.

Pearcey, R. Brundage, M. Drouin, P. Jeffrey, J. Lukka, H. Maclean, G. Souhami, L. Stuart, G. & Tu, D. 2002. Phase III trial comparing radical radiotherapy with and without cisplatin chemotherapy in patients with advanced squamous cell cancer of the cervix. *Journal of Clinical Oncology*, 20:966-972.

Peitsaro, P. Johansson, B. & Syranen, S. 2002. Integrated human papillomavirus type 16 is frequently found in cervical cancer precursors as demonstrated by a novel quantitative real time PCR technique. *Journal of Clinical Microbiology*, 40:886-891.

Perez, C.A. Grigsby, P.W. Castro Vita, H. & Lockett, M.A. 1995.Carcinoma of the uterine cervix.Impact of prolongation of treatment time and timing of brachytherapy on outcome of radiation therapy.*International Journal of Radiation Oncology *Biology *Physics*, 32:1275-1288.

Peters, W.A. Liu, P.Y. Barret 2nd , R.J. Stock, R.J. Monk, B.J. Berek, J.S. Souhami, L. Grigsby, P. Gordon Jr., W. & Alberts, D.S. 2000. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as an adjuvant therapy after radical surgery in high risk early stage cancer of the cervix. *Journal of Clinical Oncology*, 18:1606-1613.

Plummer, M. Herrero, R. Franceschi, S. Meijer, C.J. Snijders, P. Bosch, F.X. de Sanjosé, S. & Muñoz, N. 2003. IARC Multi-centre Cervical Cancer Study Group: Smoking and cervical cancer: pooled analysis of the IARC multi-centric case – control study. *Cancer Causes Control,* 14(9):805-814.

Powles, T. Imami, N. Nelson, M. Gazzard, B. & Bower, M. 2002. The effects of combination chemotherapy and highly active antiretroviral therapy on immune parameters in HIV associated lymphoma. *AIDS*, 16: 531-536.

Pras, E. 1995.Unpublished study.Cited in Green *et al*., 2001:781-786.

Prokopczyk, B. Cox, J.E. Hoffmann, D. & Waggoner, S.E. 1997.Identification of tobacco specific carcinogen in the cervical mucus of smokers and nonsmokers.*Journal of The National Cancer Institute*, 89:868-873.

Reddi, V.B. 2003.*Programme, discussion and feedback formats for specialty focus groups: medical and radiation oncology*. [Online]. Available:

http://www.doh.gov.za/mts/reports/oncology.html [Date of access: 29 March 2011].

Reeler, A. Qiao, Y. Dare, L. Li, J. Zhang, A.L. & Saba, J. 2009. Women's cancers in developing countries: from research to an integrated health systems approach. *Asian Pacific Journal of Cancer Prevention,* 10:519-526.

Ries, L.A.G. Melbert, D. Krapcho, M. Stinchcomb, D.G. Howlader, N. Horner, M.J. Mariotto, A. Miller, B.A. Feuer, E.J. Altekreuse, S.F. Lewis, D.R. Clegg, L. Eisner, M.P. Reichman, M. & Edwards, B.K. 2007. SEER Cancer Statistics Review, 1975-2005. National Cancer Institute. [Online]. Available: http://seer.cancer.gov/csr/1975-2005/. Based on November 2007 SEER data submission. [Date of access: 24 June 2010].

Roberts, K.B. Urdaneta, N. Vera, R. Vera, A. Guitierrez, E. Aguilar, Y. Ott, S. Medina, I. Sempere, P. Rockwell, S. Sartorelli, A.C. Fischer, D.B. & Fischer, J.J. 2000. Interim results of a randomized trial of mitomycin C as an adjunct to radical radiotherapy in the treatment of locally advanced squamous cell carcinoma of cervix.*International Journal of Cancer*, 90:206-223.

Ronco, G. Cuzick, J. Pierrotti, P. Cariaggi, M.P. Dalla, P.P. Naldoni, C. Ghiringhello, B. Giorgi-Rossi, P. Minucci, D. Parisio, F. Pojer, A. Schiboni, M.L. Sintoni, C. Zorzi, M. Segnan, N. & Confortini, M. 2007. Accuracy of liquid based versus conventional cytology: overall results of new technologies for cervical cancer screening randomized controlled trial. *British Medical Journal*, 335:28.

Rose, P.G. Bundy, B.N. Watkins, E.B. Thigpen, J.T. Deppe, G. Maiman, M.A. Clarke-Pearson, D.L. & Insalaco, S. 1999. Concurrent cisplatin based radiotherapy and chemotherapy for locally advanced cervical cancer. *The New England Journal of Medicine*, 340:1144-1153.

Rudek, M.A. Flexner, C. & Ambinder, R.F. 2011.Use of antineoplastic agents in patients with cancer who have HIV/AIDS.*Lancet*, 11:1-8.

Rydstrom, C. & Tornberg, S. 2006. Cervical cancer incidence and mortality in the best and worst of worlds.*Scandinavian Journal of Public Health*, 34:295-303.

Sankaranarayanan, R. 2007. Cervical cancer prevention strategies in the developing world.*Journal of Cytopathology*, 18(suppl 1):1-12.

Santin, A.D. Bellone, S. Parrish, R.S. Coke, C. Dunn, D. Roman, J. Theus, J.W. Cannnon, M.J. Parham, G.P. & Pecorelli, S. 2003. Influence of allogeneic blood

transfusion on clinical outcome during radiotherapy for cancer of the uterine cervix. *Gynecologic and Obstetric Investigation*, 56:28-34.

Sbilinarayanan, R. Budukh, A.M. & Rajkumar, R. 2001. Effective screening programmes for cervical cancer in low and middle income developing countries. *Bulletin of the World Health Organisation*, 79:10.

Schalkwyk, S.L. Maree, J.E. & Wright, S.C.D. 2008. Cervical cancer: the route from signs and symptoms to treatment in South Africa. *Reproductive Health Matters*, 16(32):9-17.

Schiffman, M. Herrero, R. Desalle, R. Hildesheim, A. Wacholder, S. Rodriguez, A.C. Bratti, M.C. Sherman, M.E. Morales, J. Guillen, D. Alfaro, M. Hutchinson, M. Wright, T.C. Solomon, D. Chen, Z. Schussler, J. Castle, P.E. & Burk, R.D. 2005. The carcinogenity of human papillomavirus types reflects viral evolution. *Virology*, 337:76-84.

Schiffman, M. Castle, P.E. Jeronimo, J. Rodriguez, A.C. & Wacholder, S. 2007. Human papillomavirus and cervical cancer.*Lancet*, 370:890-907.

Schiller, J.T. & Nardelli-Haefliger, D. 2006.Second generation HPV vaccines to prevent cervical cancer.*Vaccine*, 24(suppl 3):S147-153.

Schuman, P. Ohmit, S.E. Klein, R.S. Duerr, A. Cu-Uvin, S. Jamieson, D.J. Anderson, J. & Shah, K.V. 2003. Longitudinal study of cervical squamous intraepithelial lesions in human immunodeficiency virus (HIV) seropositive and at risk HIV seronegative women. *Journal of Infectious Diseases*, 188:128-136.

Seamans, Y. Sellors, J. Broekhuizen, F. & Howard, M. 2006.Preliminary report of a gas conditioner to improve operational reliability of cryotherapy in developing countries.*BioMed Central Womens Health*, 6:2.

Serkies, K. & Jassem, J. 2004.Chemotherapy in the primary treatment of cervical carcinoma.*Critical Reviews in Oncology/Hematology*, 54: 197-208.

Shrivastava, S.K. Engineer, R. Rajadhyaksha, S. & Dinshaw, K.A. 2005. HIV infection and invasive cervical cancers, treatment with radiation therapy: toxicity and outcome. *Radiotherapy and Oncology*, 74:31-35.

Silverberg, M.J. Schneider, M.F. Silver, B. Anastos, K.M. Burk, R.D. Minkoff, H. Palefsky, J. Levine, A.M. & Viscidi, R.P. 2006. Serological detection of human papillomavirus types 16 infection in human immunodeficiency virus (HIV) positive and high risk HIV negative women. *Clinical and Vaccine Immunology*, 13:511-519.

Simonds, H.M. 2009. Radiation therapy for cervix carcinoma: the benefits and constraints in sub-Saharan Africa. *Southern African Journal of Gynaecology and Oncology*, 1 (2):66-68.

Singh, P. Dharmalingam, S.K. Tan, M.K. & Tan, C.K. 1985.Chemotherapy-radiotherapy combination in the treatment of carcinoma of the cervix.*The SouthEast Asian Journal of Tropical Medicine and Public Health,* 16:665-668.

Singh, K.K. Bloom, S.S. & Tsui, A.O. 1998.Husbands' reproductive health knowledge, attitudes and behavior in Uttar Pradesh, India.*Studies in Family Planning*, 29:388-399.

Singh, D.K. Anastos, K. Hoover, D.R. Burk, R.D. Shi, Q. Ngendahayo, L. Mutimura, E. Cajigas, A. Bigirimani, V. Cai, X. Rwamwejo, J. Vuolo, M. Cohen, M. & Castle, P.E. 2009. Human papillomavirus infection and cervical cytology in HIV infected and HIV uninfected Rwandan women. *Journal of Infectious Diseases*, 199:1851-1861.

Sirera, G. Videla, S. Lopez-Blazquez, R. Llatjos, M. Tarrats, A. Castella, E. Grane, N. Tural, C. Rey-Joly, C. & Clotet, B. 2007. Evolution of cervical cytologic changes among HIV infected women with normal cytology in the HAART era. *AIDS research and human retroviruses*, 23:965-971.

Sirera, G. Videla, S. Lopez-Blazquez, R. Llatjos, M. Tarrats, A. Castella, E. Grane, N. Tural, C. Rey-Joly, C. & Clotet, B. 2008. Highly active antiretroviral therapy and incidence of cervical squamous intraepithelial lesions among HIV infected women with

normal cytology and CD4 counts above 350 cells/mm^3.*Journal of Antimicrobial Chemotherapy*, 61:191-194.

Smith, F.J. 2005. *Conducting Your Pharmacy Practice Research Project*. London: Pharmaceutical Press.

Smith, J.S. Lindsay, L. & Hoots, B. 2007. Human papillomavirus type distribution in invasive cancer and high grade cervical lesions: a meta-analysis update. *International Journal of Cancer*, 121:621-632.

Somdyala, N.I.M. Bradshaw, D. Curtis, B. & Gelderblom, W.C.A. 2008.*Cancer incidence in selected municipalities of the Eastern Cape Province, 1998 to 2002: PROMEC Cancer Registry Technical Report.* Cape Town: South African Medical Research Council.

Soncini, E. Zoncada, A. Condemi, V. Antoni, A.D. Bocchialini, E. & Soregotti, P. 2007. Reduction of the risk of cervical intraepithelial neoplasia in HIV infected women treated with highly active antiretroviral therapy.*ActaBio Medica*, 78:36-40.

Spanos, W.J. Wasserman, T. Meoz, R. Sala, J. Kong, J. & Stetz, J. 1996. Palliation of advanced pelvic malignant disease with large fraction pelvic radiation and misonidazole: final report of RTOG phase I/II study. *International Journal of Radiation Oncology *Biology *Physics*, 13:1479-1482.

Stewart, B.W & Kleihues, P. 2003. *World Cancer Report*. Lyon: International Agency for Research Cancer.

Strickler, H.D. Palefsky, J.M. Shah, K.V. Anastos, K. Klein, R.S. Minkoff, H. Duerr, A. Massad, L.S. Celentano, D.D. Hall, C.C. Fazzari, M. Cu-Uvin, S. Bacon, M. Schuman, P. Levine, A.M. Durante, A.J. Gange, S. Melnick, S. & Burk, R.D. 2003. Human papillomavirus type 16 and immune status in human immunodeficiency virus seropositive women.*Journal of the National Cancer Institute,* 95(14):1062-1071.

Sundfor, K. Lyng, H. Kongsgard, U.L. Trope, C. & Rofstad, E.K. 1997.Polargraphic measurement of pO2 in cervix carcinoma.*Gynecologic Oncology*, 64:230-236.

Sussman, A. Helitzer, D. Urquieta, B. Sanders, M.L. Salvador, M. & Ndiaye, K. 2007. HPV and cervical cancer prevention counselling: a fit or misfit for primary visits with younger adolescents? *Annals of Family Medicine*, 5:298-304.

Taylor, J.M. Withers, H.R. & Medenhall, W.M. 1990. Dose-time consideration of head and neck squamous cell carcinomas treated with irradiation. *Radiotherapy and Oncology*, 17:95-102.

Thomas, G. Dembo, A. Ackerman, I. Franssen, E. Balogh, J. Fyles, A. & Levin, W. 1998. A randomised trial of standard versus partially hyperfractionated radiation with or without concurrent 5-fluorouracil in locally advanced cervical cancer.*Gynecologic Oncology*, 69:137-145.

Thomas, G.M. 1999. Improved treatment for cervical cancer: concurrent chemotherapy and radiotherapy. *The New England Journal of Medicine*, 59:238-242.

Thompson, D.L. Douglas, J.M. Foster, M. Hagensee, M.E. Diguiseppe, C. Baron, A.E. Cameron, J.E. Spencer, T.C. Zenilman, J. Malotte, C.K. Bolan, G. Kamb, M.L. & Peterman, T.A. 2004. Seroepidemiology of infection with human papillomavirus 16, in men and women attending sexually transmitted diseases clinics in the United States.*Journal of Infectious Diseases*, 190:1563-1574.

Tseng, C.J. Chang, C.T. Lai, C.H. Soong, Y.K. Tang, S.G. & Hsueh, S. 1997. A randomized trial of concurrent chemoradiotherapy versus radiotherapy in advanced carcinoma of the uterine cervix. *Gynecologic Oncology*, 66:52-58.

Uebel, K.E. Timmerman, V. Ingle, S.M. van Rensburg, D.H. & Mollentze, W.F. 2010. Toward universal access: achievements and challenges in Free State Province, South Africa. *South African Medical Journal*, 100:589-593.

UNAIDS. 2009. *AIDS epidemic update-December 2009*. [Online]. Available: http://data.unaids.org/pub/Report/2009/JC1700_Epi_Update_2009_en.pdf. [Date of access: 6 July 2010].

UNAIDS. 2010. *Report on the Global AIDS epidemic-December 2010*. [Online]. Available: http://www.unaids.org/documents/20101123_GlobalReport_em.pdf. [Date of access: 8 July 2011].

United States National Cancer Institute. 2010. *Cervical Cancer Treatment.* [Online]. Available: http://www.cancer.gov/cancertopics/pdq/treatment/cervical/HealthProfessional/. [Date of access: 16 February 2011].

Van Til, L. MacQuarrier, C. & Herbert, R. 2003.Understanding the barriers to cervical cancer screening among older women.*Quantitative Health Research*, 13:1116.

Vanslyke, J.G. Baum, J. Plaza, V. Otero, M. Wheeler, C. & Helitzer, D.L. 2008. HPV and cervical cancer testing and prevention: knowledge, beliefs, and attitudes among Hispanic women. *Qualitative Health Research*,(5):584-597. [Online]. Available: http://qhr.sagepub.com/cgi/content/abstract/18/5/584. [Date of access: 10 March 2010].

Von Knebel, D.M. 2002.New markers for cervical dysplasia to visualize the genomic chaos created by aberrant oncogenic papillomavirus infections.*European Journal of Cancer*, 38:2229-2242.

Vorobiof, D. Sitas, F. & Vorobiof, G. 2001.Breast cancer incidence in South Africa.*Journal of Clinical Oncology*, 19(suppl 28):S125-127.

Wabinga, H. Ramanakumar, A.V. Banura, C. Luwaga, A. Nambooze, S. & Parkin, D.M. 2003. Survival of cervical cancer patients in Kampala, Uganda:1995-1997. *British Journal of Cancer*, 89:65-69.

Waggoner, S.E. 2003. Cervical cancer. *Lancet*, 361:2217-2225.

Wake, R.M. Rebe, K. & Burch, V.C. 2009.Patient perception of cervical screening among women living with human immuno-deficiency virus infection attending an antiretroviral therapy clinic in urban South Africa.*American Journal of Obstetrics and Gynaecology*, 29(1):44–48.

Whitney, C.W. Sause, W. Bundy, B.N. Malfetano, J.H. Hannigan, E.V. Fowler, W.C. Clarke-Pearson, D.L. & Liao, S.Y. 1999. Randomised comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in stage IIB-IVA carcinoma of the cervix with negative paraaortic lymph nodes: a Gynecologic Oncology Group study. *Journal of Clinical Oncology,* 18:1606-1613.

WHO. 1990. *Cancer pain relief and palliative care: report of a WHO Expert Committee.* Geneva, Switzerland.

WHO. 2003. *Adherence to long term therapies. Evidence for action*.[Online]. Available: http://www.who.int/chp/knowledge/publications/adherence_report/en/. [Date of access: 23 May 2011].

WHO. 2006. *World Health Statistics.*[Online]. Available: http://hdr.undp.org/hdr2006/statistics/indicators/58.html. [Date of access: 15 June 2011].

WHO/ICO Information centre on HPV and cervical cancer. 2010. *Human papillomavirus and related cancers South African summary report 2010*. [Online]. Available: http://www.who.int/hpvcentre. [Date of access: 6 July 2010].

WHO Organisation Databank. 2010. *WHO statistical information system*. [Online]. Available: http://www.who.int/whosis.2010. [Date of access: 28 June 2011].

Wong, L.C. Choo, Y.C. Choy, D. Sham, J.S. & Ma, H.K. 1989. Long-term follow up to potentiation of radiotherapy by cisplatinum in advanced cervical cancer. *Gynecologic Oncology*, 35:159-163.

Wong, L.C. Ngan, H.Y.S. Cheung, A.N.Y. Cheng, D.K.L. Ng, T.Y. & Choy, D.T.K. 1999. Chemoradiation and adjuvant chemotherapy in cervical cancer.*Journal of Clinical Oncology,* 17:2055-2060.

Woodman, C.B. Collins, S. Winter, H. Bailey, A. Ellis, J. Prior, P. Yates, M. Rollason, T.P. & Young, L.S. 2001. Natural history of cervical human papillomavirus infection in young women: a longitudinal cohort study. *Lancet,* 357:1831-1836.

World Medical Association. 2008. *World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects*. [Online]. Available: http://www.wma.net/en/30publications/10policies/b3/17c.pdf. [Date of access: 8 March 2010].

Yamada, R. Sasagawa, T. Kirumbi, L. Kingoro, A. Karanja, D. & Kiptoo, M. 2008.Human papillomavirus infection and cervical abnormalities in Nairobi, Kenya, an area with a high prevalence of human immunodeficiency virus infection.*Journal of Medical Virology*, 80:847-855.

APPENDIX ONE

ETHICAL APPROVAL

• PO Box 77000 • Nelson Mandela Metropolitan University
• Port Elizabeth • 6031 • South Africa • www.nmmu.ac.za

Nelson Mandela Metropolitan University

for tomorrow

Chairperson of the Research Ethics Committee (Human)
NMMU
Tel . +27 (0)41 504-2538 Fax. +27 (0)41 504-2778

Ref: [H10-HEA-PHA-001/Approval]

Contact person: Mrs U Spies

5 July 2010

Ms S-A Boschmans
NMMU
Department of Pharmacy
Faculty of Health Sciences

Dear Ms Boschmans

RESPONSE AND ADHERENCE TO CHEMO RADIOTHERAPY OF HIV POSITIVE WOMEN DIAGNOSED WITH CERVICAL CANCER

Your above-entitled application for ethics approval served at the **May 2010** ordinary meeting of the Research Ethics Committee (Human).

We take pleasure in informing you that the application was approved by the Committee.

The ethics clearance reference number is **H10-HEA-PHA-001**, and is valid for three years. Please inform the REC-H, via your faculty representative, if any changes (particularly in the methodology) occur during this time. An annual affirmation to the effect that the protocols in use are still those for which approval was granted, will be required from you. You will be reminded timeously of this responsibility, and will receive the necessary documentation well in advance of any deadline.

We wish you well with the project. Please inform your co-investigators of the outcome, and convey our best wishes.

Yours sincerely

Dr B Pretorius
Chairperson: Research Ethics Committee (Human)

cc: Department of Research Capacity Development
Faculty Officer, Faculty of Health Sciences

APPENDIX TWO

PERMISSION FROM MEDICAL SUPERINTENDENT

Province of the Eastern Cape

Iphondo Lwempuma-koloni

DEPARTMENT OF HEALTH
PROVINCIAL HOSPITAL

ISEBE EZEMPILO
PROVINCIAL ISIBHEDLELA

Private Bag / Ingxowa Eyodwa X0003, Port Elizabeth 6000

Ireferensi
Ref. No. : Dr E.R.Jansen

Ifoni
Telephone: (041) 392 3572

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Ifexi
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E. Mail : erika.jansen@impilo.ecprov.gov.za

Date 23 August 2011

Pearl Ngugi
Nelson Mandela Metropolitan University

Dear Ms Ngugi

RE: PERMISSION TO CONDUCT RESEARCH AT ONCOLOGY DEPARTMENT, PROVINCIAL HOSPITAL, PORT ELIZABETH.

Your application to conduct research at Oncology Department. Provincial Hospital. Port Elizabeth is hereby approved based on the following conditions:

1. **You must observe and respect the right of your research participants and ensure their confidentiality is maintained.**
2. **Upon completion of your study you are expected to submit a copy of your research report to this hospital and to Dr.E.R. Jansen.**

Yours sincerely

DR E.R.JANSEN
SENIOR ONCOLOGIST
H.O.D. DEPT OF RADIATION ONCOLOGY
PROVINCIAL HOSPITAL, PORT ELIZABETH

PP/ DR.L.BLAAUW
ONCOLOGIST
DEPARTMENT OF RADIATION ONCOLOGY
PROVINCIAL HOSPITAL, PORT ELIZABETH

APPENDIX THREE

AUDIT FORM USED IN THE PILOT STUDY

RESPONSE AND ADHERENCE OF HIV POSITIVE WOMEN DIAGNOSED WITH CERVICAL CANCER TO CERVICAL CANCER TREATMENT.

A. Demographics.

1. Date of birth at diagnosis:

B. HIV status

1. HIV positive:

Yes	No	Unknown

2. Year of diagnosis:

3. CD4 count (cells/mm^3):

At diagnosis	dd/mm/yy	dd/mm/yy	dd/mm/yy	dd/mm/yy	dd/mm/yy
dd/mm/yy	dd/mm/yy	dd/mm/yy	dd/mm/yy	dd/mm/yy	dd/mm/yy

4. ARV treatment:

Yes	No

5. ARV regimen:

	Diagnosis/initiation		During 5 year period	
Medication	**Date**	**Dose**	**Date**	**Dose**
Didanosine (DDI)				
Lamivudine (3TC)				
Stavudine (D4T)				
Zidovudine (ZDV)				
Efavirenz (EFV)				
Nevirapine (NVP)				
Indinavir (IDV)				
Lopinavir (LPV)				
Ritonavir (RTV)				
Other				

C. Cervical cancer status

1. Date of diagnosis:

2. Stage at diagnosis:

Stage I	IA1	IA2	IB1	IB2
Stage 2	IIA	IIB		
Stage 3	IIIA	IIIB		
Stage 4	IVA	IVB		

3. Treatment option:

Radiotherapy	Chemoradiotherapy	Surgery	Palliative

4. Treatment:

Option	Dose (Gy)			Tmnt commenced	Tmnt completed	No. of fields	Overall time (days)
Radiation	**GD**	**CD**	**SD**				
External beam							
Brachytherapy							
Option	**Dose**			**Date/yr of initiation**		**Frequency**	**Number of chemotherapy or radiation cycles**
Chemotherapy	**Mg/m^2**						
Carboplatin							
Cisplatin							
Dose/agent changes if applicable							

*GD= Given dose; CD= Central dose; SD= skin dose

5. Complications present at diagnosis (e.g. recto-vaginal fistula, vesico-vaginal fistula)

Date	Complication

D. <u>Response to cervical cancer treatment</u>

1. Laboratory tests on diagnosis:

Test	Date	Result	Normal range

FBC and platelets			
WCC			4.0-10.0 $x10^9$/l
RCC			3.80-4.80 $x10^{12}$/l
Haemoglobin			12.0-15.0 g/dl
MCV			79.1-98.9 fl
MCH			27.0-32.0 pg
MCHC			32.0-36.0
Red cell distribution width			11.6-14.0
Platelets			178-400 $x10^9$/l
Differential count			
Neutrophils			2.0-7.5 $x10^9$/l
Monocytes			0.18-0.8 $x10^9$/l
Lymphocytes			1.0-4.0 $x10^9$/l
Eosinophils			0.0-0.45 $x10^9$/l
Basophils			0.0-0.20 $x10^9$/l
Haematology			
Reticulocyte count			0.5-2.0 %
Absolute reticulocyte count			0.05-0.100 $x10^{12}$/l
Haematocrit			0.36-0.46 l/l
Liver function (LFT)			
ALP			<35-130 U/l
GGT			<70 U/l
ALT			< 60 U/l
AST			<35 U/l
Other			

2. Laboratory tests if repeated:

Test	**Date**	**Result**	**Date**	**Result**	**Date**	**Result**	**Normal range**
FBC and platelets							
WCC							4.0-10.0 $x10^9$/l
RCC							3.80-4.80 $x10^{12}$/l
Haemoglobin							12.0-15.0 g/dl
MCV							79.1-98.9 fl

MCH							27.0-32.0 pg
MCHC							32.0-36.0
Red cell distribution width							11.6-14.0
Platelets							178-400 $x10^9$/l
Differential count							
Neutrophils							2.0-7.5 $x10^9$/l
Monocytes							0.18-0.8 $x10^9$/l
Lymphocytes							1.0-4.0 $x10^9$/l
Eosinophils							0.0-0.45 $x10^9$/l
Basophils							0.0-0.20 $x10^9$/l
Haematology							
Reticulocyte count							0.5-2.0 %
Absolute reticulocyte count							0.05-0.100 $x10^{12}$/l
Haematocrit							0.36-0.46 l/l
Liver function (LFT)							
ALP							<35-130 U/l
GGT							<70 U/l
ALT							< 60 U/l
AST							<35 U/l
Other							

6. Audiogram test results:

Date	**Result**

7. Ultrasound results:

Date	Abdominal	Pelvic	Chest

8. Clinician's follow up physical examination:

Date	General	Vaginal exam	Rectal exam	Respiratory	Skin	Abdomen	Extremities	Other

9. Other tests (e.g. cystogram)

Date	Test	Result

E. Adherence to cervical cancer treatment

1. Number of missed doses:

	Total prescribed	Number of missed doses	Dates missed		
Radiation					
Chemotherapy					

2. Reason for missing dose:

Patient factors	Hospital factors	Other factors
Missed appointment	Equipment failure	
Low white blood count at time of scheduled treatment	Other	
Other		

F. Adverse effects

Adverse effect	**Present**	**Radiation and carboplatin**	**Radiation and cisplatin**	**On ARVs**
Anaemia				
Thrombocytopenia				
Leucopenia				
Nausea and vomiting				
Diarrhoea				
Constipation				
Rectovaginal fistula				
Radiation proctitis				
Skin desquamation				
Peripheral neuropathy				
Renal toxicity				
Deep vein thrombosis				
Weight loss				
Pain				

G. Mortality

1. Date of death:

	1 year	**2 years**	**3 years**	**4 years**	**5 years**
Living					
Deceased					

2. Cause of death:

Cervical cancer related	HIV related	Other

APPENDIX FOUR

AUDIT FORM USED IN THE MAIN STUDY

RESPONSE AND ADHERENCE OF HIV POSITIVE WOMEN DIAGNOSED WITH CERVICAL CANCER TO CERVICAL CANCER TREATMENT.

A. Demographics.

1. Date of birth at diagnosis:

B. HIV status

2. HIV positive:

Yes	No	Unknown

3. Year of diagnosis:

4. CD4 count (cells/mm^3):

At diagnosis	dd/mm/yy	dd/mm/yy	dd/mm/yy	dd/mm/yy	dd/mm/yy
dd/mm/yy	dd/mm/yy	dd/mm/yy	dd/mm/yy	dd/mm/yy	dd/mm/yy

5. ARV treatment:

Yes	No

6. ARV regimen:

	Diagnosis/initiation		During 2 year period	
Medication	**Date**	**Dose**	**Date**	**Dose**
Didanosine (DDI)				
Lamivudine (3TC)				
Stavudine (D4T)				
Zidovudine (ZDV)				
Efavirenz (EFV)				
Nevirapine (NVP)				
Indinavir (IDV)				
Lopinavir (LPV)				
Ritonavir (RTV)				
Other				

C. <u>Cervical cancer status</u>

1. Date of diagnosis:

2. Stage at diagnosis:

Stage I	IA1	IA2	IB1	IB2
Stage 2	IIA	IIB		
Stage 3	IIIA	IIIB		
Stage 4	IVA	IVB		

Risk factors:

Smoking	
Parity	
Hormonal contraception	
STI	

3. Treatment option:

Radiotherapy	**Chemotherapy**	**Chemoradiotherapy**	**Surgery**	**Palliative**

4. Treatment:

Option	**Dose (Gy)**			**Tmnt commenced**	**Tmnt completed**	**No. of fields**	**Overall time (days)**
Radiation	**GD**	**CD**	**SD**				
External beam							
Brachytherapy							
Option	**Dose**			**Date/yr of initiation**		**Frequency**	**Number of chemotherapy or radiation cycles**
Chemotherapy	**Mg/m^2**						
Carboplatin							
Cisplatin							
Dose/agent changes if applicable							

*GD= Given dose; CD= Central dose; SD= skin dose

5. Complications present at diagnosis (e.g. recto-vaginal fistula, vesico-vaginal fistula)

Date	Complication

D. Response to cervical cancer treatment

1. Laboratory tests on diagnosis:

Test	Date	Result	Normal range
Haematology tests			
WCC			4.0-10.0 $x10^9$/l
Haemoglobin			12.0-15.0 g/dl
Platelets			178-400 $x10^9$/l
Urea, electrolytes, creatinine			
Sodium			135-147 mmol/l
Potassium			3.3-5.3 mmol/l
Chloride			99-113 mmol/l
Urea			2.6-7.0 mmol/l
Creatinine			60-100 mmol/l
Liver function (LFT)			
Bilirubin total			0-21 µmol/l
Total protein			60-85 g/l
Albumin			35-52g/l
ALP			<40-120 U/l
GGT			<0-35 U/l
ALT			< 5-40U/l
AST			<5-40U/l
Lactate Dehydrogenase			100-190 U/l
Chemistry tests			
Calcium			2.05-2.56 mmol/l
Albumin			35-52 g/l
Calcium (corrected)			2.05-2.56 mmol/l
Magnesium			0.65-1.10 mmol/l
Other			

2. Laboratory tests if repeated:

Test	**Date**	**Date**	**Date**	**Date**	**Date**	**Date**	**Normal range**
Haematology tests							
WCC							4.0-10.0 $x10^9$/l
Haemoglobin							12.0-15.0 g/dl
Platelets							178-400 $x10^9$/l
Urea, electrolytes, creatinine							
Sodium							135-147 mmol/l
Potassium							3.3-5.3 mmol/l
Chloride							99-113 mmol/l
Urea							2.6-7.0 mmol/l
Creatinine							60-100 mmol/l
Liver function (LFT)							
Bilirubin total							0-21 µmol/l
Total protein							60-85 g/l
Albumin							35-52g/l
ALP							<40-120 U/l
GGT							<0-35 U/l
ALT							< 5-40U/l
AST							<5-40U/l
Lactate Dehydrogenase							100-190 U/l
Chemistry tests							
Calcium							2.05-2.56 mmol/l
Albumin							35-52 g/l
Calcium (corrected)							2.05-2.56 mmol/l
Magnesium							0.65-1.10 mmol/l

Other							

3. Audiogram test results:

Date	**Result**

4. Ultrasound results:

Date	**Abdominal**	**Pelvic**	**Chest**

5. Clinician's follow up physical examination:

Date	**General**	**Vaginal exam**	**Rectal exam**	**Respiratory**	**Skin**	**Abdomen**	**Extremities**	**Other**

6. Other tests (e.g. cystogram, bone scan)

Date	**Test**	**Result**

E. <u>Adherence to chemoradiotherapy</u>

1. Number of missed doses:

	Total prescribed	**Number of missed doses**	**Dates missed**		
Radiation					

Chemotherapy					

2. Reason for missing dose:

Patient factors	**Hospital factors**	**Treatment factors**
Missed appointment	Equipment failure	Low white blood count at time of scheduled treatment
		RT induced diarrhoea
		RT induced skin breakdown
		Early termination by doctor

F. Adverse effects

Adverse effect	**Present**	**Radiation and carboplatin**	**Radiation and cisplatin**	**On ARVs**
Anaemia				
Thrombocytopenia				
Leucopenia				
Nausea and vomiting				
Diarrhoea				
Constipation				
Rectovaginal fistula				
Radiation proctitis				
Skin desquamation				
Peripheral neuropathy				
Renal toxicity				
Deep vein thrombosis				
Weight loss				
Pain				