A C U T E T O X I C I T Y I N C E R V I C A L C A N C E R H I V 
P O S I T I V E VS H I V N E G A T I V E P A T I E N T S T R E A T E D 
B Y R A D I C A L C H E M O R A D I A T I O N I N Z A M B I A 

A dissertation submitted to the Faculty of Health Sciences, University of 
Johannesburg, Johannesburg, in fulfillment of the requirements for the degree 
of Master of Technology: Radiography by 

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Johannesburg, 2012
DECLARATION

I declare that this dissertation is my own, unaided work. It is being submitted for the Degree of Master of Technology at the University of Johannesburg, Johannesburg. All the sources used or quoted have been indicated and acknowledged by means of complete references. It has not been submitted before for any degree or examination in any other Technikon or University.

__________________________________________
(Signature of Candidate)

October 2012
This was a prospective, quantitative comparative study. The aim of the study was to evaluate acute toxicity of radical combination therapy, in the form of radiotherapy and chemotherapy, in HIV +ve patients on HAART and HIV -ve patients for cervical cancer at CDH, Lusaka, Zambia. The specific objectives were to compare acute toxicity in HIV +ve on HAART and HIV -ve patients and to assess the level of severity in the levels of toxicity.

The study was conducted from January 2010 to December 2010. A hundred and twenty stage IB₂-IIIB cervical cancer patients were serially recruited and assigned study numbers for identification and confidentiality. Participants received Cisplatin based radical chemoradiation for five to six weeks during which time they were assessed for acute reactions and data was prospectively collected. Four systems namely Genitourinary, Haematopoietic, Skin, and Gastrointestinal were used for the assessment of toxicity in the study. Toxicity was scored using the NCI CTC v2.0.

The results of this study showed that, major acute reactions in the CDH study participants were grade 3 leucopenia (five in each study arm) and one grade 3 acute skin toxicity in the HIV +ve arm. Results also revealed that there were three HIV +ve study participants with grade 3 vomiting and one HIV –ve. There was one grade 3 anaemia in the HIV +ve arm, one grade 3 anaemia in the HIV –ve arm and one grade 4 anaemia in the HIV +ve arm. However, only the incidence of grade 3 leucopenia in both study arms and vomiting in the HIV +ve study participants was significantly higher.

This study demonstrated that radical chemoradiation is well tolerated by HIV +ve patients with intact immunity. Toxicity was usually mild and reversible and no exaggerated toxicities beyond those generally associated with single-agent Cisplatin were observed in the HIV +ve study participants. Therefore, radical chemoradiation in conventional doses can safely be given to cervical cancer HIV +ve patients who are on HAART.
DEDICATION

This dissertation is dedicated to my father (Mr Munkupa M.S.) who inspires me to strive for great heights and my mother for her resilience, motherly support and encouragement.

I further extend this dedication to my wife Ingrid, and my four children: Harry, Mapesho, Rabecca and Lukumo.
ACKNOWLEDGEMENTS

I would like to offer my thanks, praise and worship to the Almighty God, for the opportunity, wisdom, the strength and courage He accorded me to complete this study.

I would also like to express my sincere appreciation to the following people for their invaluable support and unending encouragement:

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<tr>
<td>5FU</td>
<td>5 Fluorouracil</td>
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<tr>
<td>AIDS</td>
<td>Acquired Immunodeficiency Syndrome</td>
</tr>
<tr>
<td>AP/PA</td>
<td>Antero-posterior/postero-anterior</td>
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<tr>
<td>ART</td>
<td>Anti-retroviral Therapy</td>
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<tr>
<td>CaCx</td>
<td>Cancer of the cervix</td>
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<td>CDDP</td>
<td>Cisplatin</td>
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<tr>
<td>Co-60</td>
<td>Cobalt-60</td>
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<tr>
<td>CTC</td>
<td>Common Toxicity Criteria</td>
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<tr>
<td>FIGO</td>
<td>International Federation of Gynaecology and Obstetrics</td>
</tr>
<tr>
<td>GFR</td>
<td>Glomerular Filtration Rate</td>
</tr>
<tr>
<td>GOG</td>
<td>Gynaecological Oncology Group</td>
</tr>
<tr>
<td>Gy</td>
<td>Gray</td>
</tr>
<tr>
<td>HAART</td>
<td>Highly active antiretroviral therapy</td>
</tr>
<tr>
<td>HDR</td>
<td>High Dose Rate</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency virus</td>
</tr>
<tr>
<td>HPV</td>
<td>Human Papilloma Virus</td>
</tr>
<tr>
<td>IARC</td>
<td>International Agency for Research on Cancer</td>
</tr>
<tr>
<td>Linac</td>
<td>Linear accelerator</td>
</tr>
<tr>
<td>NCI</td>
<td>National Cancer Institute</td>
</tr>
<tr>
<td>NCIC</td>
<td>National Cancer Institute of Canada</td>
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<td>NCICTC</td>
<td>National Cancer Institute Common Toxicity Criteria</td>
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CHAPTER 1

INTRODUCTION

1.1 BACKGROUND

Combination therapy in the form of radiotherapy with chemotherapy is the current standard of treatment for patients with stage IB₂-IIIB cervical cancer (NCI, 1999). However, Human Immunodeficiency Virus (HIV) positive (+ve) patients with invasive cervical cancer have not been evaluated in detail regarding radiation response, its toxicities and compliance with this treatment. Moreover, standards of treatment for this set of patients have not been defined (Shrivastava, Engineer, Rajadhyaksha & Dinshaw, 2005:34). Therefore, there would probably be a need to modify radiotherapy protocols, as new literature becomes available. This will ensure standardised treatment protocols and improved patient management.

Cancer Diseases Hospital (CDH) is a newly opened institution in Lusaka, Zambia, which relies on internationally standardised treatment protocols, as it has not developed a locally based protocol. This situation therefore indicates the need to evaluate the current treatment protocol of the institution. Currently, cervical cancer stage IB₂-IIIB HIV +ve patients are treated with radical chemoradiation. The external beam radiotherapy dose prescription used is 46Gy to 50Gy to the whole pelvis in 23–25 fractions using standard fields (two or four fields in 2 dimensional planning). Brachytherapy is given during the final weeks of external beam radiotherapy and the dose is prescribed as 8Gy x 3 fractions or 6.5Gy x 4 fractions to point A, as per disease stage. The patients also receive concurrent Cisplatin 80mg/m² 3X weekly (on day 1, 22 and 43). However, this is in contrast to some available literature or protocols practised by some oncology departments who omit the Cisplatin from the protocol for this group of patients (Tangsirwatthana, Chumworathayi, Yuenyao, Luanratanakorn & Pattamadilok, 2007:503; Mc Ardle & Kigula-Mugambe, 2007:95; Serkies & Jassen, 2004:815).
According to Rose, Bundy, Watkins, Thigpen, Deppe & Maiman (1999), cervical cancer treatment generally requires very high doses of radiation, and in most cases these doses exceed the normal tissue tolerance. Radiotherapy alone fails to arrest the progression of locally advanced cervical cancer. However, cervical cancer management is greatly assisted by combining radiation with chemotherapy. The essence of chemoradiation is to combat systemic micro-metastases, which are not eradicated by local radiation. In addition, current internationally published literature has documented that chemotherapy and radiation therapies are synergistic – together they have a greater effect than would be expected based on their effects when given alone. The reason for this is that chemotherapy is used as an apparent radiosensitiser because it has its own anti-tumour effects while it makes cells more sensitive to radiation resulting in improved therapeutic ratio. It is also possible that chemotherapy stops cancer cells from repairing the damage caused by radiation (Rose et al., 1999).

This improved therapeutic approach has increased the number of women surviving cervical cancer. However, the side effects associated with the treatment can have a major impact on the management of patients, since each modality has its own tumoricidal effects with significant toxicity.

With regard to the results of the five clinical trials on which the current chemoradiation regimen is based, there are a number of acute side effects that were noted (NCI, 1999). These were mainly leucopoenia (low number of white blood cells), nausea and vomiting. These were more frequent and more severe in the women who had the combined therapy than in those who had radiation alone. Therefore, it becomes vital in this era of HIV and Acquired Immunodeficiency Syndrome (AIDS) to also look at studies that can provide or yield results with regard to the toxicities experienced by the HIV +ve patients receiving radical chemoradiation.

Moreover, malignancies in HIV infection are still a problem despite highly active anti-retroviral therapy (HAART) changing the management of HIV +ve patients. Nevertheless, HAART has greatly improved the survival of HIV +ve patients with malignancies. Co-
administration of antineoplastic agents with HAART in HIV +ve patients has demonstrated an increased frequency of chemotherapy-related toxicities. This is most likely due to both therapies using similar metabolic pathways. The survival benefits to patients, however, far exceed the adverse effects as long as the efficacy and related toxicities of antineoplastic therapy are closely monitored in these patients (Klibanov & Clark-Vetri, 2007:122).

1.2 STATEMENT OF THE PROBLEM

As stated above, CDH is a newly opened institution which has been mandated to treat cancer patients, and the reality in Zambia at the moment is that 38% of cancer patients have cervical carcinoma, and 50% of these patients are co-infected with HIV. As at December 2009, the hospital had treated 1,378 new patients, of whom 429 (33.3%) had cancer of the cervix (CDH, 2009). In 2010 CDH treated 485 (38%) cervical carcinoma patients. Initially, all HIV +ve cervical cancer patients were treated without chemotherapy, regardless of their CD4 count. CDH now treats some of the HIV +ve patients whose CD4 counts are > 200/mm$^3$ with chemoradiation because the latest literature suggests that this population of patients can actually benefit from the practice (Lukawska, Cottrill & Bower, 2003:3-4), especially those on HAART, and because the protocol continues to be advocated as standard (Kirwan, Symonds, Green, Tierney, Collingwood & Williams, 2003:217; Rose, 2002: 271; Kesic, 2006:4).

In the literature, it is suggested that HIV +ve patients with a low CD4 count and not on HAART have increased acute toxicity (acute side effects) during radical chemoradiation (Hoffman, Welton, Klenke, Weinberg & Krieg, 1999:127; Kim, Sarani & Orkin, 2001:97-98). It has further been suggested in the literature that acute side effects in HIV +ve cervical carcinoma patients may not only be as a result of the effects of chemoradiation but also due to impaired cellular immunity (IAEA, 2001:9). In Zambia and most Sub-Saharan African countries, acute side effects have not been studied on a large scale in cervical carcinoma patients who are HIV +ve and are on radical chemoradiation. This situation prompted the research question addressed here: Does HIV infection enhance acute toxicity
in invasive cervical cancer stage IB₂-IIIB, HIV +ve patients when compared to the HIV –ve patients during radical chemoradiation? It was for this reason that this study was conducted in Zambia (CDH) in order to determine the acute side effects (acute toxicity) in this cluster of patients. The study also attempted to establish which are the most common acute side effects (acute toxicities) in HIV +ve patients on radical chemoradiation at CDH, Lusaka, Zambia.

1.3 RESEARCH AIM AND OBJECTIVES

1.3.1 Aim of the study

To evaluate acute toxicity in radical combination therapy, in the form of radiotherapy and chemotherapy, in HIV +ve (on HAART) and HIV –ve patients for cervical cancer at CDH, Lusaka, Zambia.

1.3.2 Objectives

1.3.2.1 The first objective

To compare acute toxicity in HIV +ve (on HAART) and HIV –ve patients receiving radical radiotherapy with chemotherapy for cervical cancer at CDH, Lusaka, Zambia.

1.3.2.2 The second objective

To assess the level of acute toxicity in HIV +ve (on HAART) versus HIV–ve cervical cancer patients receiving radical radiotherapy with chemotherapy at CDH, Lusaka, Zambia.

1.3.2.3 The third objective

To make suitable recommendations based on the above findings with regard to the future management of HIV +ve patients (on HAART).
1.4 STUDY DESIGN

A prospective quantitative comparative study was used. It comprised two arms – namely, the control (60 HIV –ve patients) and study arm (60 HIV +ve patients). These patients received a radical course of chemoradiation. The study was conducted at the CDH in Zambia. This is the only facility in Zambia which offers chemoradiation to cervical cancer patients.

The study population comprised stage IB$_2$ to IIIB cervical cancer patients who fit the inclusion criteria. Acute treatment-related toxicity was graded prospectively by an oncologist with active participation of the researcher at weekly intervals during chemoradiation using the modified National Cancer Institute Common Toxicity Criteria (appendix 1). The four systems – namely, Skin, Gastro-intestinal (GIT), Genito-urinary (GUT) and Haematopoietic – were evaluated. Toxicities were scored using a scale of 0 to 4, with 0 being no reaction and 4 being life-threatening. The assessment of GUT, Skin and GIT was clinical, while the haematopoietic system/renal function were laboratory-based.

Study participants were reviewed once a week and the toxicity scored on an individual collection form (appendix 2). After completion of treatment the participants were again assessed for toxicity during follow-up clinics one month after treatment.

The data collected was entered by the researcher into a Microsoft Access database and was then analysed by the statistician. The latest version of Statistical Package for Social Sciences (SPSS) was used to analyze the data collected during the study. Descriptive and inferential statistics were used to analyze the data. Chi-square analysis was used to test for differences in levels of toxicity between groups. Statistical significance was defined as a Pearson’s chi-square p-value < 0.05. Repeated measures of ANOVA were also used, since the data was collected repeatedly at different intervals.
1.5 SIGNIFICANCE OF THE STUDY

Significance of research in health sciences refers to the rationale for the study and its relationship to theory, knowledge or practice. The study should have the potential to contribute to health sciences knowledge in a meaningful way. Therefore, in order to ascertain and assess the relationship between acute toxicity and HIV infection in cervical cancer patients on radical chemoradiation at CDH, a comparison between the acute toxicity of radical combination therapy in the form of chemotherapy and radiotherapy, in HIV +ve patients and HIV -ve patients, must be made.

The outcome or yielded results may benefit CDH by providing guidance on the future management of cervical cancer patients, thus improving healthcare practice or policies. This will ultimately enable CDH to provide effective treatment, better quality of life and better life expectancy to its cervical cancer patients.

1.6 OUTLINE OF CHAPTERS

This dissertation is divided into the following chapters:

**Chapter 2** – consists of a literature review that underpins the theoretical framework that informed this study. This chapter reviews relevant research done internationally. It also reviews the Zambian situation under the period of study.

**Chapter 3** – outlines the research design and methodology that was used. It highlights the type of data collected, the selection of participants, statistical methods used, ethical considerations.

**Chapter 4** – presents the results of the study.

**Chapter 5** – discusses the principal findings of the results presented in chapter 4.
Chapter 6 - presents the conclusions based on the results discussed in chapter 4 and the discussion presented in chapter 5. It also highlights the study limitations and recommendations for both future research and departmental practice. This chapter is then followed by a list of references and the appendices.

1.7 SUMMARY

Chapter one highlighted the background information that prompted this research. This was supported by relevant literature. It introduced the research problem and the research question. The aim and objectives of this research, including a brief discussion on the study design, was outlined. The outline of chapters was also presented.
CHAPTER 2
REVIEW OF THE RELATED LITERATURE

2.1 INTRODUCTION

The aim of this study was to examine acute toxicity of radical combination therapy, in the form of radiotherapy and chemotherapy, in HIV +ve (on HAART) and HIV –ve patients for cervical cancer stage IB$_2$ – IIIB at CDH, Lusaka, Zambia. This chapter intends to introduce the key concepts and theories relating to this study and provide an extensive review of past studies focusing on this research area.

Therefore, this chapter contains a cohesive account of literature reviewed vital to the study. It begins with a brief overview of the global epidemiological aspects to cervical cancer, its background, and the disease burden it brings in Zambia in comparison to other cancers and with specific reference to CDH as a treatment centre. Cervical cancer staging and prognosis are presented.

In addition, the link in terms of the treatment of locally advanced cervical cancer, a statement on the randomised clinical trials of 1999–2000, Cisplatin pharmacology and its toxicity are also presented. This discussion is then narrowed to specifically look at first-, second- and third-generation chemoradiation clinical trials as well as the acute toxicity effects of chemoradiation in HIV-infected cervical cancer patients. The chapter will then conclude by highlighting the importance of this study in relation to the reviewed literature.

2.2 BACKGROUND

Cervical cancer remains one of the biggest killers of women worldwide (Berek & Lee, 2008:15). The epidemiology of cervical cancer is strongly related with a population’s standard of living: thus, underdeveloped countries present elevated mortality rates that can be as high as >70 per 100,000 inhabitants (Cetina, Rivera, Hinojosa, Poitevin, Uribe, Lopez-Graniel, Cantu, Candelaria, de la Garza & Duenas-Gonzalez, 2006:np). In Zambia,
as in many other countries with limited health resources, cervical cancer has the highest annual crude mortality rate which stands at 20.2 per 100,000 inhabitants (IARC, Globocan 2008), and the majority of cases are diagnosed in locally advanced disease stages IB$_2$ – IVA. Cervical cancer in Zambia has also been shown to have the highest annual crude incidence (29.1 per 100,000 population) among all the cancers in women (IARC, Globocan 2008).

On the other hand, even though chemoradiation has been used in the treatment of locally advanced cervical cancer for approximately 20 years, it was not until 1999 that five randomised studies, which included nearly 2,000 patients, were published, demonstrating that survival rate with radiotherapy alone was lower than with chemoradiation utilising Cisplatin (NCI, 1999). Later, a meta-analysis corroborated these findings (Green, Kirwan, Tierney, Symonds, Fresco, Collingwood & Williams (2001:781,785-6). Thus, Cisplatin-based chemoradiation has become widely accepted as the standard care for cervical cancer patients.

The realisation that cervical cancer primarily affects socio-economically disadvantaged women would suggest that the results obtained from clinical trials, usually performed at carefully prepared academic centres, cannot be easily reproduced in a community setting. Aside from the combined treatment’s complexity, socially disadvantaged women may be more susceptible to the combined treatment’s toxic effects due to poor nutritional status, presence of co-morbid chronic conditions, and/or difficulties in accessing medical care during treatment (Black, Allen, Pelto, de Mata & Chavez, 1994:1179; Kiefe, Funkhouse, Fouad & May, 1998:357).

Cervical cancer patients treated at CDH are generally socially disadvantaged. With regard to the social, economic, and political aspects of the status of the Zambian women, a range of indicators show that women are at a distinct social and economic disadvantage in Zambia. Statistics on literacy show that only 59.7% of women are literate compared to 76.15% of men (HRW, 2007:17). Poverty affects women disproportionately (HRW, 2007:17). Many women are in low-paid and low-skilled jobs with little job security. 76% of
women in Zambia are engaged in agriculture, fisheries and forestry. 63% of women engaged in agriculture work receive no payment for their work, compared to 56% of males working in the same sector who do not get paid for their work (HRW, 2007:18).

Additionally, female education has affected family health and nutrition. Lack of resources and pressures on time and energies put enormous constraints on the ability of women to maintain their own health and nutrition. This low social and economic status of Zambian women thwarts their ability to seek and adhere to treatment. This may also delay their pursuit of treatment as many struggle to find money for food and transport to treatment centres, and some miss treatment as a result (HRW, 2007:33).

Prompted by these additional concerns, the researcher further decided to analyse the effects of acute toxicity as a result of radical treatment of HIV +ve cervical cancer patients at CDH with the Cisplatin-based chemoradiation regimen, which was adopted in 1999 as routine management.

CDH treats some of the HIV +ve patients whose CD4 counts are > 200/mm³ with chemoradiation because the latest literature suggests that this population of patients can actually benefit from the practice (Lukawska et al., 2003:4), especially those on HAART, and because the protocol continues to be advocated as standard (Kirwan et al., 2003: 225; Rose, 2002: 271; Kesic, 2006: 4). Also, studies on anal cancer and Human Papilloma Virus (HPV) related malignancy with increased frequency in HIV-infected patients show that patients with a pre-treatment CD4 count >200/mm³ tolerate therapy without any undue or unexpected increased toxicity (Hoffman et al., 1999:130; Uronis & Bendell, 2007:530-531).

This observation further poses a challenge to the CDH as there is now a need to examine the different protocols in order to come up with its own protocol. This study as a result, was used to generate information needed to assist in the formulation of patient management decisions.
2.3 CERVICAL CANCER AND HPV TRANSMISSION

The HPV has been detected in virtually all invasive cervical cancers and has been cited as the major cause of this cancer (Simon, 2003:2). HPV is spread primarily by having sex with an infected partner. It should be noted, however, that most sexually active young women become infected with this virus, but only 10% remain infected for more than five years. Researchers believe that most cervical cancers develop when various aggressive genetic HPV strains activate certain oncogenes. Oncogenes called E6 and E7 are particularly important because they interfere with certain protective proteins, such as p53 and p54, respectively. Under normal conditions, these proteins limit cell growth. Once they are blocked, cell growth can be uncontrolled, leading to tumour development and cancer (Ahn, Base, Lee, Namkoong & Chun, 2004; Lai, Chu, Lin, Chang, Nieh & Yu, 2005).

2.3.1 Cervical cancer staging

This is a determination of the extent of the cancer. For cervical cancer, clinical staging is determined by physical examination, colposcopic-guided biopsies, cervical conisation, examination under anaesthesia, chest x-rays, kidney x-rays, cystoscopy and sigmoidoscopy. Surgical exploration is not used to assign a clinical stage. Staging ensures that the correct and optimal treatment option is determined for each patient (Berek & Lee, 2008:15-16).

Cervical cancer is staged using the International Federation of Gynaecology and Obstetrics (FIGO) system (Berek & Lee, 2008:16). This system has five classifications; 0 – 4:

- Stage 0 – (carcinoma in situ) – abnormal cells confined to the lining of the cervix
- Stage I – invaded deeper structures of the cervix, but still confined to cervix
- Stage II – has gone beyond the cervix but not to pelvic side wall or lower-third of the vagina
• Stage III – cancer has spread to the lower-third of the vagina or the pelvic wall or caused ureters to block

• Stage IV – cancer has spread to pelvic organs, inguinal or femoral nodes or distant spread.

2.3.2 HIV and cervical cancer

Since 01 January 1993, the Centre for Disease Control (CDC) revised the AIDS case definition to include those patients with cervical carcinoma in the setting of HIV infection for several reasons. Studies have shown that patients infected with HIV are at an increased risk of having cervical cancer or anal intraepithelial lesions in conjunction with detectable HPV infections compared with HIV –ve patients from similar risk groups (Libell & Phillips, 2004:1515).

In Zambia, for example, a ‘see’ and ‘treat’ cervical cancer prevention programme was established in Lusaka (Parham, Sahasrabuddhe, Mwanahamuntu, Pfaendler, Mkumba, Sahasrabuddhe, Hicks, Welty & Stringer, 2004: np). In the see and treat programme, nurses apply acetic acid to the cervix for 3 minutes and visually inspect for signs of neoplasia. Patients with cervical lesions that are complex or suspicious for cervical cancer (invasive cervical cancer– ICC) underwent histological evaluation. 21,010 women were screened between January 2006 and August 2008. 16,442 were under 40 years and 157 had invasive cervical cancer (below 40 years). A multivariate and univariate analysis of the programme revealed that 5,258 (32%) were HIV-infected, 6,120 (37%) were HIV -ve and 5,455 (33%) had an unknown HIV status. The odds of invasive cancer of the cervix among women under 40 appear elevated in HIV-infected women (Parham et al., 2004: np).

Neoplastic changes are also more frequently encountered in patients with low CD4 counts than in HIV-infected patients with higher CD4 counts (Delmas, Larsen & van Benthem, 2000:1775). Cervical cancer is preventable if detected early in its pre-invasive stage, so its
inclusion in the CDC criteria was meant to emphasise the importance of gynaecological care and surveillance in HIV-infected women (Maiman, Fruchter, Clark, Arrastia, Mathews & Gates, 1997:77) Maiman, 1998:45). The introduction of HAART has resulted in decreased morbidity and mortality (Hoggs, Heath, Yip & Craib, 1998:450) and the majority of people infected with HIV are living with only mild to moderate immunosuppression because of wide access to antiretroviral therapy (Grulich, McDonald, Correll, Law & Kaldor, 2002:1155). Moreover, the use of HAART has been shown to reduce the rate of persistence of cervical intraepithelial neoplasia and to prevent its progression to more aggressive clinical manifestations (Heard, Tassie, Kazatchkine & Orth, 2002:1802; Moore, Sabin & Madge, 2002:927).

2.4 MANAGEMENT OF HIV-INFECTED PATIENTS

Treatment plans should take into account the patient’s overall immune status. That is, those with relatively intact immune systems (CD4>200/mm$^3$, no major opportunistic disease), who have a reasonable chance of surviving several years with appropriate medical care and prophylaxis, should be managed much as they would be in the absence of HIV disease. The use of prophylactic para-aortic irradiation or the addition of chemotherapy should be used prudently in these patients, as these treatments might excessively stress the marrow and the small intestines. The maintenance of HAART is important during this process. Patients with stage IB/IIA – III/IVA disease should be treated aggressively with standard radiotherapeutic approaches, since death due to progressive cervical disease is a more immediate risk than the progression of AIDS. In addition, the use of antiretroviral agents and continuation of appropriate prophylaxis against opportunistic infections is recommended during this period of potentially iatrogenic immunosuppression (Libell & Phillips, 2004:1516).
2.4.1 Treatment of locally advanced cervical cancer

As a general rule, very high doses of radiation, which go above the normal tissue tolerances, are needed to cure locally advanced cancer of the cervix (FIGO stage IIB–IVA). Radiotherapy, when it is the one and only treatment, fails to control the progression of locally advanced cervical cancer in 35% to 90% of women (Rose et al., 1999:1144).

Fundamentally based on the publication of large randomised clinical trials in 1999 and 2000, concomitant chemoradiation using Cisplatin-based regimens is currently the standard treatment for locally advanced cervical cancer (NCI, 1999). However, the treatment of locally advanced cervical cancer is still challenging. The five-year survival rates are 80%, 65%, 40%, and <20% for stages IB bulky, IIB, III, and IV, respectively, after treatment with synchronous Chemoradiotherapy (Cannistra & Niloff, 1996:1030).

The underlying principle for combining chemotherapy with radiation is to eradicate systemic micro-metastases, which are not treated by local radiation. In addition, Cisplatin-based chemotherapy, used in conjunction with radiation, may inhibit the repair of radiation induced sub-lethal damage and by sensitizing hypoxic cells to radiation damage. It may also have an intrinsic cytotoxic effect (Rose et al., 1999:1144).

2.4.2 Concurrent chemotherapy and radiation therapy

2.4.2.1 Justification for combining chemotherapy with radiation therapy

Quite a few phase II studies (to determine therapeutic efficacy) showed promising results of radiotherapy and concurrent chemotherapy with three-year survival rates of 40% to 60% in stage III and IV tumours (Pearcy, Stuart, & Maclean, 1995:34; Lin, Ho, Jan, Yang & Liu, 1996:101), to mention but a few. Cisplatin is believed to augment the effects of radiotherapy by inhibiting the repair of radiation-induced sublethal damage and by sensitising hypoxic cells to radiation. Because of its cytotoxic effect, the drug reduces the
bulk of tumours, which leads to reoxygenation of the tumour and entry into a radiosensitive phase of the cell cycle (Fu, 1985:2123).

### 2.4.2.2 Scientific authentication

From 1999, five randomised studies, as illustrated in Table 2.1, have studied the addition of chemotherapy to radiotherapy and shown that concomitant chemotherapy with radiotherapy improves overall survival and progression-free survival, and reduces local and distant recurrence (NCI, 1999).

**Table 2.1: Prospective randomized clinical trials of concurrent chemotherapy with radiation in cancer of the cervix.**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Stage</th>
<th>N</th>
<th>Treatment</th>
<th>Overall survival (3-year) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whitney et al., 1999:1339 GOG 85</td>
<td>IIB-IVA</td>
<td>368</td>
<td>CDDP + 5FU HU</td>
<td>67</td>
</tr>
<tr>
<td>Rose et al., 1999:1144 GOG 120</td>
<td>IIB-IVA</td>
<td>526</td>
<td>CDDP + 5FU + HU HU</td>
<td>65</td>
</tr>
<tr>
<td>Keys et al., 1999:1154 GOG 123</td>
<td>IB Bulky</td>
<td>369</td>
<td>CDDP -</td>
<td>83</td>
</tr>
<tr>
<td>Morris et al., 1999:1137 RTOG 9001</td>
<td>IIB-IVA</td>
<td>403</td>
<td>CDDP + 5FU -</td>
<td>75</td>
</tr>
<tr>
<td>Peters et al., 2002:1606 SWOG 8797</td>
<td>IA2-IIA</td>
<td>268</td>
<td>CDDP + 5FU -</td>
<td>87</td>
</tr>
</tbody>
</table>

HU-Hydroxyurea, 5-FU-5 Fluorouracil, CDDP-Cisplatin
2.4.3 Acute toxicity

The early side effects of radiotherapy to the pelvis, such as fatigue, bowel and bladder irritation, and of chemotherapy, such as bone marrow suppression and bowel toxicity, are well known and usually reversible (Green, Kirwan, Tierney, Vale, Symonds, Fresco, Williams & Collingwood, 2009:3). Chemoradiation seems to offer substantial benefit for women with cervical cancer. However, acute toxicity, predominantly haematological and gastro-intestinal, increases. Toxicity may be harmful if it leads to prolongation of radiotherapy, as control of local disease has been shown to fall by up to 1% per day if treatment is prolonged (Green et al., 2009:11). Acute side effects are generally of short duration and can be resolved with medical management.

2.4.4 HIV infection, radiotherapy and acute toxicity

Enhanced mucosal reactions in HIV/AIDS patients receiving radiotherapy have been reported (Tomadoni & Wainstein, 1998:44; Shrivastava et al., 2005:31). This increased radiosensitivity has been attributed to inherent cellular radiosensitivity (Formenti, Chak, Gill, Buess & Hill, 1995:411-2), and glutathione deficiency—found to be low in HIV +ve patients (Simonds, 2008).

2.5 CISPLATIN PHARMACOLOGY

Platinum compounds are widely used in the treatment of solid tumours. The compound cis-PtCl$_2$ (NH$_3$)$_2$ were first described by M.Peyrone in 1845 (known as Peyrones salts). Barnett Rosenberg discovered Cisplatin serendipitously, while investigating the effects of electric currents on bacteria in 1965 (Matysiak & Gustaw-Rothenberg, 2009:20). Wiltshaw did the first clinical studies on Cisplatin in the early 1970s (Wiltshaw & Carr, 1974:178-82; Wiltshaw & Kroner, 1976:1976). Following approval for clinical use by the United States
Food and Drug Administration (FDA) in 1978, Cisplatin revolutionised the treatment of certain cancers (Matysiak & Gustaw-Rothenberg, 2009:20)

Chemically, Cisplatin is Cis-diamminedichloroplatinum II (CDDP) (Figure 2.1) (Matsusaka, Nagareda & Yamasaki, 2005:387; McEvoy, 2004:929; Pizzo & Poplack, 2002:256). It is a heavy metal platinum complex similar to the bifunctional alkylating agents. It covalently binds to DNA and disrupts DNA function (Chabner & Longo, 2001:453).

The drug becomes aquated in the tissues and can then interact with macromolecules, such as DNA, to form intrastrand adducts and interstrand cross-links (Murry, 1997:140-45). The aquated platinum species binds preferentially with highly nucleophilic N-7 positions of the purine bases guanine and adenine (Reed, 2001). The intrastrand adducts account for well over 90% of total platinum binding to DNA (Zwelling, Michaels, Schwartz, Dobson & Kohn, 1981:640; Plooy, van Dijk & Lohman, 1984). Cisplatin can also bind to RNA and cellular proteins (Mosby, 2007:51). The major effect of Cisplatin is to inhibit cell replication and DNA synthesis (Mosby, 2007:51).

Following intravenous (IV) administration, Cisplatin is bound to plasma proteins. Approximately a quarter of the intravenous dose is excreted through the kidneys during the
first 24 hours. The total Cisplatin (free and bound) has a prolonged half-life of two to three days. Cisplatin can remain bound to protein tissues for a long period of time (Reed, 2001).

Cisplatin potentiates the sub-lethal damage induced by radiation (Carde & Laval, 1981:927) and inhibits repair of potentially lethal damage (Wallner & Li, 1987). Cisplatin radiosensitisation is a free radical mediated by its ability to scavenge for free electrons formed by the interaction between radiation and DNA. The reduction of the platinum moiety may serve to stabilize DNA damage that would otherwise be irreparable. The additive effects of Cisplatin are improved when the drug is administered with fractionated radiotherapy. This is explained by its inhibition of sub-lethal damage repair.

2.5.1 TOXICITY OF CISPLATIN

The most common and most feared side effect of Cisplatin in patients who do not receive adequate premedication is emesis. Nausea and vomiting can be acute or delayed (≤ 24 or > 24 hours post-chemotherapy, respectively). This side effect has been alleviated by the introduction into routine clinical practice of 5-hydroxytryptamine-3 (5HT3) receptor antagonists, for example, Granisetron or Ondansetron, which have significantly reduced the incidence of acute Cisplatin-induced emesis (Mosby, 2007:54). Prophylaxis against delayed emesis is recommended. In addition to 5-HT3 receptor antagonists, corticosteroids are required to help control nausea and vomiting (Mosby, 2007:54).

Cisplatin-induced nephrotoxicity was dose-limiting in early clinical trials (Go & Adjey, 1999:409). Nephrotoxicity can be minimised by hydration with normal or hypertonic saline and by maintaining good diuresis with mannitol or frusemide, if necessary (Chu & DeVita, 2003:89; Mosby, 2007:54). Dose adjustments must be made based on the glomerular filtration rate (GFR). If this is more than 50 ml/min, full doses may be given, but if it is less than 30 ml/min, Cisplatin should not be administered. For a GFR between 30 ml/min and 50 ml/min, the Cisplatin dose must be reduced in proportion to the GFR (Go & Adjey, 1999). In addition, Reed (2001) recommended that alternative chemo-therapeutic agents should be considered, if the 24-hour creatinine clearance is < 60 ml/min.
A loss of cations in the urine is common after treatment with Cisplatin (Reed, 2001). In particular, hypomagnesaemia occurs, despite adding magnesium to the hydration fluid. Hypocalcaemia and hypokalaemia are common.

Cisplatin-induced Myelosuppression is mild, but reversible. Dose-related anaemia, leucopenia, and thrombocytopenia are found. Severe thrombocytopenia or leucopenia occurs in 5% of cases (McEvoy, 2004:929; Cisplatin USP DI, 2002). Hypersensitivity reactions are rare.

2.6 CLINICAL PHARMACOLOGY: DRUG-DRUG INTERACTIONS IN ONCOLOGY AND IMPLICATIONS FOR GENERAL USE

Drug interactions in oncology are of particular importance owing to the narrow therapeutic index and the inherent toxicity of anticancer agents (Scripture & Figg, 2006:546). With regard to ART, malignancy remains an important cause of death despite the reduction of HIV-related morbidity and mortality associated with highly active antiretroviral therapy (Van Der Walt & Maartens, 2007:82-3). Highly active antiretroviral therapy (HAART) is known to be fraught with clinically relevant pharmacokinetic and pharmacodynamic interactions and the addition of anticancer therapies to HAART increases the risk even further (Van Der Walt & Maartens, 2007:82).

Combination of drugs may lead to an increased toxicity. Therefore, it is cardinal to understand and address the drug interactions that can be encountered in the treatment of HIV-infected cervical cancer patients with chemotherapy. Awareness of the mechanisms of drug interactions and clinical consequences, as well as interventions to minimise these interactions, are pivotal in the optimisation of treatment of HIV-infected cervical cancer patients (de Maat, Ekhart, Huitema, Koks, Mulder & Beijnen, 2003:274-6).

In addition, for some drug combinations, well-designed drug interaction studies have been performed, but not all involve HIV-infected patients. Pharmacokinetic studies are often performed in volunteers who are exposed to two-drug combinations, whereas in the
treatment of HIV infection more complex multidrug regimens are used (de Maat et al. 2003:275). The CYP enzymes most often implicated in drug-drug resistance (CYP3A4) activity appear to be more variable in HIV +ve patients than in non-infected subjects (Slain, Pakys & Israel, 2000:898). Moreover, Lee, Wong and Benowitz (1993:529) also demonstrated that AIDS patients with acute illnesses had altered patterns of drug metabolism. Data collected from studies performed in healthy volunteers should thus be extrapolated carefully to HIV-infected patients (de Maat et al., 2003:275).

2.7 TOXICITY OF HAART

Patients on HAART commonly suffer from side effects. As a result, treatment of HIV infection has become a complicated balancing act between the benefits of durable HIV suppression and the risk of drug toxicity. About 25% of patients stop therapy within the first year on HAART because of side effects (d'Arminio Monforte, Lepri & Rezza, 2000:499). About the same number of patients does not take recommended dosages of their medication due to concerns about the side effects (Chesney, Ickovics, Chambers, Gifford, Neidig, Zwickl & Wu, 2000: 255). Patients who report significant side effects are more often non-adherent to therapy (Ammassari, Murri, Pezzotti, Trotta, Ravasio, de Longis, Caputo, Narciso, Pauluzzi, Carosi, Nappa, Piano, Izzo, Lichtner, Rezza, d'Arminio, Ippolito, Moroni, Wu & Antinori, 2001: 445).

While side effects of HAART treatment may vary considerably between individuals and the particular medicines making up their therapy, the most common side effects include diarrhoea, nausea, and vomiting. Lipodystrophy is another common side effect in which fat is redistributed to other parts of the body (Ammassari et al., 2001:445). Hyperglycaemia and diabetes have also occurred in a significant number of HAART patients. Liver toxicity, including liver failure, pancreatitis and neuropathy, are other unpleasant and potentially life-threatening side effects experienced by some patients. These side effects can amount to such a physical and psychological burden that patients skip doses or stop taking their medications all together, which increases the likelihood of drug resistance developing. As
regards these HAART toxicities, suffice it to say that the combined toxicity of HAART and chemoradiation can potentially lead to increased overall toxicity. Pharmacodynamic interactions have been described with several antiretroviral drugs and anticancer therapy. Zidovudine, for instance, increases the risk of haematological toxicity associated with anticancer drugs. The concomitant use of stavudine or didanosine with vinca alkaloids, taxanes and ifosfamide may increase the risk of peripheral neuropathy. Shared gastrointestinal tract adverse effects are also common, notably diarrhoea (Van Der Walt & Maartens, 2007:84).

However, some publications have credited HAART for saving many lives (Walensky, Paltiel, Losiana, Mercincavage, Schackman, Sax, Weinstein and Freedberg, 2006: 11). HAART is the standard treatment for HIV (Walensky et al., 2006:11). It is composed of a combination of three or four drugs that fit into as many as three categories: reverse transcriptase inhibitors, protease inhibitors, and fusion inhibitors. Each of these categories of drugs attempt to interrupt the viral life cycle at a different point. Reverse transcriptase inhibitors block the activity of reverse transcriptase, an enzyme the virus uses to build new DNA from its RNA. Protease inhibitors inhibit the activity of viral enzymes used by HIV to cleave new proteins for final assembly into new HIV virions. Fusion inhibitors block entry of HIV into the cell membrane, preventing infection of uninfected cells (Walensky et al., 2006:11). HAART (protease inhibitors) has been reported to block Kaposi’s sarcoma and tumour growth (Sgadari, Monini, Barillari & Ensoli, 2003:537). HAART has also been reported to be a radiosensitiser (Gupta, Cerniglia, Mick, Ahmed, Bakanauskas, Muschel & McKenna, 2003:850) as well as a chemosensitiser (Gupta, Cerniglia, Mick, McKenna & Muschel, 2005:8256, 8262-3; Brunner, Geiger, Grabenbauer, Lang-Welzenbach, Mantoni, Cavallaro, Sauer, Hohenberger & McKenna, 2008:2699, 2701-2).
2.8 CLINICAL TRIALS OF CONCURRENT CHEMOTHERAPY WITH RADIATION IN CANCER OF THE CERVIX

Despite the fact that radiation had long been used for the treatment of locally advanced cervical cancer, several randomised trials published in the 1990s established the benefit of concurrent chemotherapy and radiation therapy (Berek & Lee, 2008:18). Also, good numbers of clinical trials of concurrent chemotherapy and radiation therapy strategies for the treatment of cervical cancer have been conducted on patients with locally advanced disease.

2.8.1 First-generation trials

In a randomised controlled trial of 40 patients with stage IIB cervical carcinoma treated at Roswell Park Memorial Institute with radiation therapy and hydroxyurea versus placebo, Piver, Barlow, Vongtama and Blumenson (1983:803) reported a significant survival advantage in the hydroxyurea arm. All the patients underwent pre-treatment surgical staging, which documented the absence of para-aortic lymph node metastasis. The five-year survival rate was 94% in the hydroxyurea group, versus 53% in the placebo group.

Also, Hreshchyshyn, Aron, Boronow, Franklin, Shingleton & Blessing (1979:317), conducted a trial of hydroxyurea, versus placebo with concomitant radiation therapy in patients with stage IIIB – IV cervical cancer. Several problems were identified in the conduct of this study, including the lack of either radiological imaging or retroperitoneal surgical staging of the aortic lymph nodes. Among the 190 women treated in this trial, only 104 were evaluable for toxicity and only 97 were evaluable for survival. Consistent with Piver’s experience, the frequency of leucopaenia in the hydroxyurea treated group was substantial. Complete tumour regression was reported for 68% in the hydroxyurea group, versus 49% in the placebo group. The expected median survival was also improved with the administration of hydroxyurea (19.5 months versus 10.7 months).
2.8.2 Second-generation chemoradiation trials

This generation of clinical trials of chemoradiation for locally advanced cervical carcinoma tested compounds with high electron affinity, which mimic the effects of oxygen as closely as possible, namely, “hypoxic cell sensitisers”. The nitroimidazoles were the most widely researched of these compounds and misonidazole was the first of the nitroimidazoles to be combined with radiation therapy for the treatment of cervical cancer.

Stehman, Brundy, Keys, Thomas, d’Ablain III & Fawler, (1993:1523) in a Gynae-Oncology Group (GOG) study reported on a Phase III trial of misonidazole versus hydroxyurea in combination with radiation therapy in patients with stage IIB – IVA cervical cancer. The initial publication of the clinical trial results did not report a survival difference between the two arms. The pelvic failure rate was higher in the misonidazole group (23.6%), than in the hydroxyurea group (18.0%), and the overall recurrence rate was also higher in the misonidazole group, (44%) versus the hydroxyurea group (37%). After extended follow-up, a subsequent analysis confirmed both progression-free and overall survival advantages for the hydroxyurea group. Similar findings were also reported earlier (Stehman et al., 1988:87).

2.8.3 Third-generation chemoradiation trials in the United States

These trials used Cisplatin-based chemotherapy, as earlier illustrated in 2.4.2.2 (Table 2.1). They were performed by the NCIs Clinical Trials Cooperative Groups. These were large phase III randomized clinical trials which showed that women in the studies benefited from the use of radiotherapy and chemotherapy given together (NCI, 1999).

Whitney et al., (1999:1339) published results from an inter-group study conducted by the GOG and the South West Oncology Group (SWOG). This study compared concurrent Cisplatin plus 5-FU chemotherapy and pelvic radiation therapy with Hydroxyurea plus pelvic radiation therapy. All the patients treated had stage IIB – IVA disease and negative common iliac and aortic lymph nodes, as was confirmed by pre-treatment surgical staging.
There were 386 eligible patients and the median follow-up time among surviving patients was 8.7 years. Disease progression occurred in 43% of the patients who received Cisplatin plus 5-FU, versus 53% of patients who received Hydroxyurea. The progression-free survival was significantly better among patients treated with Cisplatin plus 5-FU ($p = 0.033$). The three-year survival rate for women who received Cisplatin plus 5-FU was 67%, versus 57% for women who received Hydroxyurea.

Ninety-one percent of patients, who were randomised to Cisplatin plus 5-FU, received both drugs and 10% received fewer than four courses. The side effects were predominantly gastro-intestinal and haematologic in both treatment arms. More grades III-IV leucocytopenia were found in the Hydroxyurea arm than in the Cisplatin plus 5-FU arm, 24% and 4%, respectively. Gastro-intestinal side effects were more pronounced in the Cisplatin + 5-FU group (8%) than in the Hydroxyurea arm.

On the other hand, Morris et al. (1999:1137) treated 403 patients with concurrent Cisplatin plus 5-FU chemotherapy plus pelvic radiation therapy versus extended field radiation therapy. The eligibility requirements for this trial differed from the previous GOG studies in that it included patients with stage IB2 – IIA cervical cancer. With a median follow-up of 43 months, the estimated cumulative five-year survival rates were 73%, versus 58%, respectively, for patients treated with chemoradiation therapy versus radiation therapy alone ($p = 0.004$). A significant difference in disease-free survival was noted in the chemotherapy group. The addition of chemotherapy to radiation therapy was effective in reducing the frequency of both local recurrences and distant metastasis ($p < 0.001$). More grades 3-4 acute side effects were found in the chemoradiotherapy group. There were no significant differences in late complications in the two treatment groups.

In addition, Eifel, Winter, Morris, Levenback, Grigsby, Cooper, Rotman, Gershenson & Mutch (2004:872), reported on the mature results of the Morris et al. (1999) trial, as described above, which compared pelvic plus para-aortic radiation (extended field radiotherapy), versus pelvic radiotherapy with concurrent Cisplatin and 5-FU. The median follow-up time was 6.6 years for the 228 surviving patients. The addition of Cisplatin and 5-
FU to radiotherapy led to a significant improvement in the survival rate of patients with locally advanced cancer of the cervix, without increasing the rate of treatment-related toxicity. The overall survival rates at 8 years (67% versus 41%, p<0.0001) were much improved in the combined modality arm. This approach of concurrent chemoradiotherapy is preferred over the use of para-aortic radiation alone in a prophylactic setting.

Rose et al. (1999:1144) enrolled 526 patients in a 3-arm trial of pelvic radiation therapy plus concurrent, single-agent Cisplatin, versus Cisplatin plus 5-FU plus Hydroxyurea, versus Hydroxyurea alone. All patients had stage IIB – IVA cervical cancer with surgically confirmed negative common iliac and aortic lymph nodes. The median duration of follow-up was 35 months. Both groups of patients who had received Cisplatin, had longer progression-free survivals than the patients who had received Hydroxyurea alone (p<0.001). The addition of 5-FU did not increase the response rate, or the survival, but did increase the toxicity. The authors recommended weekly doses of Cisplatin as the standard drug for chemoradiation therapy of cervical cancer.

The median time of treatment duration was nine weeks for the group receiving weekly Cisplatin with radiotherapy, with a median delay of eight days in administering radiotherapy.

The eligibility criteria for the clinical trial mandated a serum creatinine level of not more than 2.0mg/dL (177µmol/L). Cisplatin was discontinued if the serum creatinine rose to more than 2.0 mg/dL. The Cisplatin dose was reduced to 30mg/m²/week for grade 2 neurotoxicity and grade 4 emesis and it was discontinued for grade 3 or higher neurotoxicity. The group receiving three drugs had more grade 3 - 4 haematologic toxicity than the other two arms (Rose et al. 1999:1144).

In addition, Peters et al. (2000:1608-10) also reported results from an inter-group trial conducted by SWOG and GOG. 268 patients with cervical cancer stage IA2 – IIA were randomised, and 243 of these patients were assessable. All the patients participating in the trial had undergone a radical hysterectomy and lymph node dissection, and had +ve pelvic lymph nodes, +ve surgical margins, or tumour extension to the parametria. Eligible patients
were randomised to receive either chemoradiation with Cisplatin plus 5-FU, or radiation therapy alone. The addition of Cisplatin plus 5-FU chemotherapy to radiation therapy improved both the progression-free and overall survivals. The median follow-up was 43 months. The projected 4-year survival rate for women on the concurrent Cisplatin and 5-FU and irradiation arm was 81%, versus 71% for women in the pelvic radiation arm. The difference was statistically significant. Only 71% of the patients in the chemoradiotherapy arm received at least three cycles of chemotherapy. The GIT and haematologic toxicity was greater in the women who were in the chemoradiotherapy group.

In another development, Keys et al. (1999:1154) treated 369 patients with bulky stage IB2 cervical cancer, with weekly Cisplatin plus radiation therapy versus radiation therapy alone. All patients had a CT scan, lymphangiography, or negative aortic lymph nodes, as was confirmed by pre-treatment surgical staging. An extrafascial hysterectomy was performed 3 to 6 weeks after the conclusion of the radiation-based treatment. The progression-free and overall survivals were significantly higher among the patients who had received concurrent Cisplatin. The three-year survival rates were 83% for the chemotherapy group, versus 74% in the arm, who had received radiation alone (p = 0.008).

Ninety percent of the patients in the chemoradiotherapy arm received at least 4 cycles of chemotherapy. There were no treatment delays due to chemotherapy, as the median duration of the radiotherapy was 50 days in both arms. There were more grade 3 or 4 adverse events in the combined arm compared to radiotherapy alone, namely, 35% versus 13%, respectively. The majority of these toxic effects were haematologic and gastro-intestinal.

The results from the five American clinical trials referred to above, (NCI, 1999), demonstrate that Cisplatin-based chemotherapy, when given concurrently with radiation therapy, prolong survival in women with stage I – IIA disease, who have:

- metastatic disease in the pelvic lymph nodes;
- parametrial disease;
- or +ve surgical margins at the time of primary surgery; and
- locally advanced cervical cancers.

Based on these trials, Cisplatin-based concurrent chemoradiation is the recommended standard of care for patients with bulky FIGO stage IB through to stage IVA cervical cancer. These trials were distinguishable in that different stages of disease were treated, different doses of radiation were used, and the scheduling of Cisplatin and 5-Fluorouracil (5-FU) varied. Only two of the five trials used weekly doses of Cisplatin, namely, GOG 120 and GOG 123. The dose of Cisplatin used in these two trials was 40 mg/m² intravenously weekly, with a maximum weekly dose of 70 mg/m² (Rose et al., 1999:1144; Keys et al., 1999:1154).

*The GOG 120 study was a landmark trial in that it established Cisplatin as the single agent of choice for chemoradiation of locally advanced cervical cancer.*

These results had a significant impact on the standard of care for treatment of cervical cancer. As a result of the GOG 120 trial, the NCI, in 1999, issued a clinical announcement to the effect that “Strong consideration should be given to the incorporation of concurrent Cisplatin based chemotherapy with radiation therapy in women who require radiation therapy for treatment of cervical cancer” (NCI, 1999). Two common difficulties with this treatment protocol are acute toxicities and completion of the prescribed chemotherapy régime.

### 2.8.4 The Cochrane meta-analyses – 2010 publication

The five trials discussed by the NCI differed in terms of the local and experimental treatments and the selected patient populations. In addition, they found only a subset of all trials of concomitant chemotherapy and radiotherapy for cervical cancer. However, this systematic review and meta-analysis includes all available studies and examines the effects of chemoradiation in terms of survival, progression-free survival, local and distant, and acute toxicity. Currently, this is the only known systematic review of all concomitant
chemoradiation trials and it updates the original Cochrane review by the same authors, first published in 2001. This analysis has stated that combined chemoradiation seems to offer substantial benefit for women with cervical cancer. However, acute toxicity, predominantly haematological and gastro-intestinal, was increased with chemoradiation. Chemoradiation toxicity may be harmful if this leads to prolongation of radiotherapy, as control of local disease is compromised. Acute side effects are generally of short duration and resolve with medical management (Green et al., 2010:2, 5-12).

2.8.5 Third-generation randomised chemoradiation trials in other countries
Wong, Ngan, Cheung, Cheng, Ng & Choi (1999:2055) in a Chinese study treated 220 patients with clinically staged bulky stage II - III cervical cancer with either standard pelvic irradiation alone, or combined with Epirubicin (Epirubicin 60 mg/m$^2$ at start + Epirubicin 90 mg/m$^2$ every week for 5 courses). The median follow-up was 77 months. Patients who received irradiation and Epirubicin had a significantly longer disease-free and cumulative survival rate than those who were treated with radiation therapy alone. The 9-year cumulative survival rate was 78% in the chemoradiation arm, versus 66% in the radiation arm.

Roberts, Urdaneta and Vera (2000:206), in Venezuela / Yale University reported on 160 patients with stage IB – IVA disease randomised to receive either irradiation alone, or chemoradiation. Concurrent chemotherapy consisted of Mitomycin C 15 mg/m$^2$ in weeks 1 and 6. There was a significant improvement in the disease-free survival of all patients in the chemotherapy arm. The disease-free survival rate at 4 years was 82% (p = 0.03) in the chemoradiation arm, versus 75% in the radiation arm.

2.8.6 Negative trial
Pearcey, Brundage, Drouin, Jeffrey, Lukka & Maclean (2002:966) recruited about 259 patients to participate in this National Cancer Institute (NCI) of Canada study. Patients with FIGO Stage IB – IVA cervical cancer having central disease of more than 5 cm, with +ve
histologically confirmed pelvic lymph node involvement were randomised. 127 patients received radiotherapy with concurrent Cisplatin chemotherapy 40 mg/m² weekly X 6 (arm 1), and 126 patients received radiotherapy only (arm 2). At a median follow-up of 82 months there were no significant differences between the two arms in the three- and five-year survival rates (3-year – 69% arm 1 versus 66% arm 2 and 5-year – 62% arm 1 versus 58% arm 2: p = 0.42). This study did not show a benefit for either pelvic control or survival by adding concurrent weekly Cisplatin chemotherapy in a dose of 40 mg/m² to radical radiotherapy.

These results, which conflict with the results of previous clinical trials, could have been caused by a higher incidence of anaemia in the Cisplatin receiving arm, which may have had a negative influence on the efficacy of radiotherapy in this arm. It was postulated that the Cisplatin chemotherapy is effective if the radiotherapy is protracted, as in the GOG 120 and GOG 85 trials (Rose et al., 1999:1144; Whitney et al., 1999:1339). In these trials, there was a delay in delivery of radiation, with the median treatment duration being 62 and 64 days respectively, compared to the duration of 51 days in the Canadian trial. It is generally accepted that there is a 1.2% loss of local control for each day the treatment is protracted and this may have exaggerated the benefit of adjuvant chemotherapy in the GOG trials.

2.8.7 Trials reporting on toxicity of concomitant chemoradiotherapy
In their study, Kantaradzic, Beslija & Kalamujic (2004:214) randomised 80 patients into two arms. The first arm of 40 patients received chemoradiotherapy and the second arm of 40 patients received radiotherapy alone. All the toxicities were reported using the CTC criteria. After three months of follow-up, there was no difference in acute toxicity between the two arms. In another development, Tan, Russel & Burgess (2004:255) conducted a study of 74 patients who received radical radiotherapy given concurrently with chemotherapy. The toxicity was recorded using the CTC criteria. The most common side effects were diarrhoea (80.6%), malaise (66.7%) and nausea (62.5%). Only three patients had grade 3–4 toxicity (one patient grade 3 thrombocytopaenia, one patient grade 4 neutropaenia and
the third patient had grade 3 diarrhoea). Haematological toxicity was mainly anaemia, with 41.7% of the patients developing grades 1–2 toxicity. Only 70.2% of the patients completed the planned number of chemotherapy cycles, with a further 20.3% receiving at least three cycles. Most patients failed to complete the planned chemotherapy due to gastro-intestinal toxicity.

In addition, Serkies & Jassem (2004:814) recruited 112 patients with a median age of 48 years. These were treated with radiotherapy plus weekly Cisplatin at 40 mg/m$^2$. Overall, 74% of the patients received at least four Cisplatin cycles. The planned five Cisplatin cycles were given to only 45% of the patients. A full and timely Cisplatin dose was administered to 26% of the patients. The most common toxicities reported were gastro-intestinal and renal in nature.

### 2.8.8 Cisplatin dose studies

Twiggs, Potish, McIntyre, Adcock, Savage & Prem (1986:143) reported on a dose-escalating toxicity study using concurrent weekly Cisplatin and radiotherapy in patients with advanced cervical cancer. A total of 16 patients with cancer of the cervix FIGO stage IB – IVB participated. Patients were treated with two dose levels, namely, Cisplatin 10 mg/m$^2$/week and 20 mg/m$^2$/week. There was no escalation beyond Cisplatin 20 mg/m$^2$/week, as previous experience indicated that higher doses resulted in unacceptable toxicity in head and neck cancer patients. A total of four patients were treated with Cisplatin 10 mg/m$^2$/week and 12 patients were treated with Cisplatin 20 mg/m$^2$/week. The percentage of prescribed Cisplatin cycles administered were 87% and 79%, respectively, at these dose levels. Doses of Cisplatin 20 mg/m$^2$/week were well tolerated, with no life-threatening toxicity, and patient compliance was good.

Similarly, Souhami, Seymour, Roman, Stanimir, Trudeau & Clark (1993:871), undertook a prospective single arm phase I/II trial. 50 patients were treated with Cisplatin 30 mg/m$^2$/week starting on the first day of radiotherapy. This dose was chosen based on a dose-finding study performed by Schaaek-Koning (Schaaek-Koning, Van Den Bogaert,
Dalesio, Featen, Hoogenhout & Van Houte, 1992:524-30) in lung cancer patients. The Cisplatin was administered over a period of one hour in 250 ml of NS, or 3% NaCl following prehydration with at least a ½ litre of fluid over a period of 1 to 1½ hours. The median number of cycles administered was five, and a total of 82% of the patients received four or more cycles. No renal abnormalities were reported. A high response rate was noted with this regimen, but the regimen was also associated with a relatively high frequency of late GIT complications.

Also, Malfetano, Keys, Kredentser, Cunningham, Kotlove & Weiss (1993:3703) conducted a phase I – II trial of weekly Cisplatin with radical radiotherapy in patients with FIGO stage IIB – IVB, recurrent and poor prognostic cervical carcinoma. The weekly Cisplatin dose was 1 mg/kg (not to exceed 60 mg/week). This regimen was well tolerated, with no interruption in the administration of radiotherapy. Cisplatin was not administered if the serum creatinine was more than 2.0 mg/dL. Only 64% of the patients completed at least five cycles of chemotherapy without interruption. There was little or no nausea and the nausea was confined to the day of the Cisplatin administration. There was no nephrotoxicity and other side effects were minimal.

2.8.9 The role of chemoradiation in the management of cancer patients infected by HIV in current times

HIV-infected patients have impaired immunity and marrow function and will therefore be more susceptible to the myelosuppresive and immunosuppressive effects of anti-cancer treatment (IAEA, 2001:9). The same article also states that minimal information on treatment of HIV-infected women in pelvic irradiation currently exists and that HIV +ve patients not on ARVs are likely to fare less well; hence, it may be more reasonable to treat palliatively and to use radiation with caution. However, Maiman (1998:46-47) reported that the best way to manage cervical cancer in HIV +ve patients is unclear and that these patients should be treated like immuno-competent patients, but with increased monitoring for efficacy and toxicity. Standard treatment for this population has not been defined.
Current treatments in the non-HIV-infected cancer of the cervix patients include concurrent Cisplatin-based chemotherapy with radiation therapy (Thomas, 1999:1198-1200; Cetina et al., 2006:3; Ozsaran, Yalman, Yurut, Aras, Ozsaran & Hanhan, 2003:191-194; Pearcy et al., 2002:966).

Shrivastava et al. (2005:31, 35) conducted a retrospective study to review 42 HIV +ve cervical cancer patients with the purpose of determining the effect of radiotherapy with regard to toxicity and compliance with treatment. The study reported poor compliance with radiotherapy with Grade III-IV acute GIT toxicity in 14% of patients and Grade III skin toxicity in 27% of patients, leading to treatment delays. The incidence of genito-urinary toxicity was also high. The increased reactions may be due in part to the compromised immune system, thus making radiation-induced mucosal injury more aggravated by common infections. The increased mucosal reactions in AIDS patients receiving radiotherapy may necessitate a reduction in their prescribed doses, and this may compromise treatment outcome, or indeed a break in their treatment causing an increase in the overall treatment time which may also have a negative effect on tumour control. A study undertaken by Gichangi, Bwayo, Estambale, Rogo, Njuguna, Ojwang & Temmerman (2006:405, 407-8) also reported similar findings.

Concurrent Cisplatin-based chemoradiation significantly improves treatment outcomes compared with radiotherapy alone for patients with locally advanced cervical cancer (Uno, Mitsuhashi, Isobe, Yamamoto, Kawakami, Ueno, Usui, Tate, Kawata & Ito, 2008:80; Chao, Perez & Brady, 2002:5; Morris et al., 1999:1137; Rose, 2002:270; Whitney et al., 1999:1339; Peters et al. 2000:1606; Keys et al. 1999:1154). However, the benefit of adding concurrent chemotherapy to radiation should always be weighed against the risk of serious acute side effects, particularly in patients who have serious coexisting medical conditions. The addition of concurrent chemotherapy considerably complicates the therapeutic management of patients with cervical cancer. In particular with chemoradiotherapy, the incidence and severity of haematological and gastro-intestinal complications are markedly increased (Eiffel, 2006:182; Berclas, Gerber, Beer, Aebi, Greiner, Dreher & Buser, 2002:1313).
Developing a strategy for the optimal therapeutic management of cervical cancer in the setting of HIV requires the oncologist to become aware of a number of factors such as the patient’s immune status at the time of diagnosis; history of prior opportunistic infections; current viral burden; antiretroviral interventions previously attempted or currently in use; presence of a polyresistant strain or strains of HIV; potential interaction between antiretroviral drugs and oncological interventions; and the patient’s willingness to risk significant morbidity and further stress of immune system associated with systemic chemotherapy or large-field irradiation in the setting of an already reduced life expectancy (Libell & Phillips, 2004:1504).

Additionally, malignancies in HIV infection are still a problem despite HAART changing management of HIV +ve patients. Nonetheless, HAART has greatly improved the survival of HIV patients with malignancies. Co-administration of antineoplastic agents with HAART in HIV +ve patients with malignancies has demonstrated an increased frequency of chemotherapy-related toxicities. This is most likely due to both therapies using similar metabolic pathways. The survival benefits to patients, however, far exceed the adverse effects as long as the efficacy and related toxicities of antineoplastic therapy are closely monitored in these patients (Klibanov & Clark-Vetri, 2007:122).

Other centres are also incorporating intensity-modulating radiotherapy (IMRT) into cervical cancer treatment in order to minimise toxicity to bowel, bladder, bone marrow, and skin (Berek & Lee, 2008:19). Instead of the fixed doses delivered to set fields in standard external beam radiation, IMRT uses complex three-dimensional imaging to establish a set tumour target volume and uses varying intensities of beams to spare specific tissues (Berek & Lee, 2008:19). Several studies have investigated the role of IMRT in cervical cancer and its ability to lessen gastro-intestinal and urinary complications associated with pelvic irradiation (Ahmad, D’ Souza & Salehpour, 2005:1117; Gerszten, Colonello, Heron, Lalonde, Fitian, Comerci, Selvaraj & Varlotto, 2006:182; Chen, Tseng, Tseng, Kuo, Yu & Chen, 2007:1438).
2.9 MANAGEMENT OF ANAL SQUAMOUS CELL CARCINOMA IN THE HIV +VE PATIENT

The Negro protocol of radiation therapy to the pelvis and tumour combined with systemic chemotherapy results in a cure rate of 80% to 90%, and has replaced the abdominoperitoneal rectal resection (APR) as the standard of care (Nigro, Vaitkevicius & Considine, 1974:354-6). Surgical treatment has been relegated to cases of persistent or recurrent disease, or when a patient has a contraindication to chemotherapy or radiotherapy.

HIV +ve patients with anal cancer are likewise treated with chemoradiation. Initial reports of HIV +ve patients who were not on HAART, albeit small patient studies, were discouraging, with inability to complete treatment and absent disease control (Stadler, Gregorcyk, Euhus, Place, Huber & Simmang, 2004:1305). Other studies compared HIV +ve with HIV –ve patients and found a significant worsening of acute treatment toxicity for HIV +ve patients and decreased tumour response to treatment (Kim et al., 2001:1496).

However, after the development of HAART, HIV +ve patients fared better with combined chemoradiation. Recent studies show reasonable tolerance of therapy in these patients, but with a consistent trend to greater dermatologic, gastro-intestinal, and haematologic acute toxicity (Edelman & Johnson, 2006:206; Oehler-Janne, Huguet & Provencher, 2008:2550; Wexler, Berson & Goldstone, 2008:73).

Conversely, results of chemoradiation for anal HIV +ve patients appear to have improved and in some cases are equivalent to HIV +ve patients (Seo, Kinsela, Reynolds, Chipman, Remick & Kinsela, 2009: np). These results may reflect better immune reconstitution and better supportive management of expected toxicities during treatment. In their study, Chiao, Giordani, Richardson & Ei-Serag (2008:474) further reported that survival was equivalent between HIV +ve and HIV –ve patients in the era of HAART and concluded that no patient should be denied treatment based on HIV status.
2.10 SUMMARY

This chapter has highlighted the literature showing that chemoradiation should be the standard of care for all stage 1B<sub>2</sub>-IIIB cervical cancer patients, regardless of HIV status. The chapter has also provided data indicating why treatment of cervical cancer in comparison to anal squamous cell carcinoma of similar histology and etiology should not be modified based on HIV status, although additional treatment supports may be necessary. The chapter also pointed out that HIV +ve patients who are on HAART clearly fare better during radical chemoradiation, that acute toxicity and local control of the disease in some centres remain a challenge, and that HAART can as well be used as a radiosensitiser and chemosensitiser.
CHAPTER 3
METHODOLOGY

3.1 INTRODUCTION

This chapter outlines the detailed aspects of the study design, research setting, description of the data collection tool and internal consistency, sampling, data collection, data analysis, ethical considerations and validity as well as reliability.

3.2 RESEARCH DESIGN

This is a plan of how the research will take place. It forms the blueprint or master plan of the study and determines the methodology used by the researcher. Designing a study enables the researcher to plan and execute the study in a way that will assist in getting the intended results (Brink, 2007:92).

This study used a quantitative, two-arm comparative descriptive approach to evaluate acute toxicity of radical combination therapy, in the form of radiotherapy and chemotherapy, in HIV +ve (on HAART) and HIV -ve patients for cervical cancer at CDH, Lusaka, Zambia. This is a quantitative study since it is concerned with the numbers and severity of acute toxicity in cervical cancer stage IB$_2$-IIIB patients receiving radical chemoradiation. This study was a comparative descriptive study because it complies with the characteristics of descriptive research as outlined by Brink (2007:104).

According to Brink (2007:104), a descriptive study is merely intended to describe a phenomenon. The researcher does not manipulate any variables, and makes no effort to determine the relationship between variables. The researcher merely searches for accurate information about the characteristics or the frequency of a phenomenon’s occurrence. This approach, therefore, allowed searching for accurate information about acute toxicity experienced by participants in the control and study arms.
3.3 RESEARCH SETTING

The study was conducted at CDH in Lusaka, Zambia. This is the only hospital in the country which offers chemoradiation. It is a day care centre and therefore has no admission facilities. It is situated within the premises of the University Teaching Hospital (UTH), which is the largest referral hospital in the country.

CDH attends only to biopsy-proven malignancy cases. The most common cases attended to at this hospital are cancers of the cervix, head and neck, breast, prostate, lymphomas and Kaposi’s sarcoma. Since 2006, the hospital has seen and treated 4,200 new cancer patients (CDH, 2010).

The hospital has a staff complement of ten radiation therapists who work eight-hour shifts and are rotated through all the treatment units every one to two months. The hospital has two megavoltage teletherapy units (a linear accelerator and a cobalt 60), one remote loading high dose rate Brachytherapy unit, treatment planning simulator and mould room, a mammography unit, CT and MRI. It furthermore has five consulting clinical oncologists, one consulting radiologist, and one pathologist. The nursing staff comprises 14 people. These are divided to work in the outpatients’ clinic, chemotherapy section, Brachytherapy section and CT/MRI area or sections. In this study, participants were evaluated and assessed in the consultation or clinical review area at CDH, Lusaka, Zambia. Acute treatment-related toxicity was graded prospectively by an oncologist with active participation of the researcher at weekly intervals.

3.4 DATA COLLECTION METHOD

Data was collected using the modified NCI CTC, v2.0 (appendix 1). The four systems, namely: Skin, Gastro-intestinal (GIT), Genito-urinary (GUT) and Haematopoietic were evaluated. The toxicities were scored using a scale of 0 to 4, with 0 being no reaction and 4 being life-threatening. The assessment of GUT, Skin and GIT was clinical, while the
haematopoietic system/renal function were laboratory-based. The participants were reviewed once a week and the toxicity scored on an individual collection form (appendix 2). After completion of treatment the participants were again assessed for toxicity when they came for their regular follow-up one month after treatment.

3.5 DATA COLLECTION TOOL AND INTERNAL CONSISTENCY

According to Summers (2006:397), data is defined as information or facts acquired in the course of a study. According to Creswell (2007: 118), data collection is a series of activities that are interrelated and are focused on gathering good information to answer research questions. Creswell (2007:118) further advises that the collection of data must be done using a method that will generate the most data. In this study, data was collected by using the NCI CTC v2.0.

3.5.1 Common toxicity criteria (CTC)

The NCI CTC were developed in 1982 for use in adverse drug experience reporting, study of adverse event summaries, Investigational New Drug (IND) reports to the Food and Drug Administration (FDA), and in publications. The CTC have been used widely for collecting treatment-related complications or reactions data to facilitate the evaluation of new cancer therapies, treatment modalities, and supportive measures.

The NCI CTC, v2.0 provides a descriptive terminology for toxicity (acute reactions) or adverse event reporting. A grading (severity) scale is provided for each toxicity (NCI, 1999). There are 24 categories in the CTC v2.0 and these are organised by pathophysiology and anatomy. Alphabetical listing of toxicity is placed within categories (NCI, 1999). NCI CTC, v2.0 uses a numeric scale to grade or score the severity of toxicity, as shown in Table 3.1.
Table 3.1: Grade of Severity of the NCI CTC (NCI, 1999)

<table>
<thead>
<tr>
<th>Grade</th>
<th>General Definitions</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Absent or none</td>
</tr>
<tr>
<td>1</td>
<td>Mild</td>
</tr>
<tr>
<td>2</td>
<td>Moderate</td>
</tr>
<tr>
<td>3</td>
<td>Severe and undesirable</td>
</tr>
<tr>
<td>4</td>
<td>Life-threatening or disabling</td>
</tr>
</tbody>
</table>

3.5.1.1 Grading of toxicity

The following principles were observed in grading of toxicity experienced by the participants:

- Any treatment-related toxicity experienced by participants was graded using the specific toxicity terms listed in the NCI CTC, v2.0.
- Grading is not modified based on a patient’s condition at baseline. Baseline data, including laboratory data and signs and symptoms noted at study entry, should be collected within the institution as course 0.
- If a given acute reaction is experienced more than once, only the grade associated with the most severe toxicity is reported.
- Syndromes are graded only when diagnosed by a physician; notes within the NCI CTC, v2.0 provide guidelines to determine when to grade components of each syndrome.
- Toxicity not included in the NCI CTC, v2.0 should be reported and graded under the “Other” acute reactions or toxicity within the appropriate category and graded 0 to 4 according to the general grade definitions provided above (NCI, 1999).
3.5.1.2 What not to Grade

Disease progression or signs and symptoms related to disease related to disease should not be graded (NCI, 1999). In this study, only that toxicity most consistent with the patient population or treatment modality was reported.

3.5.1.3 Organisation of the NCI CTC

The CTC, v2.0 includes 24 categories of adverse events with more than 200 individual adverse events. The primary organisation of the CTC, v2.0 is based on pathophysiological (e.g., allergy/immunology) and anatomical (e.g., dermatology/skin) categories as illustrated in Table 3.2 to facilitate location of related adverse events.

Table 3.2: Categories in the NCI CTC v2.0 (NCI, 1999)

<table>
<thead>
<tr>
<th>1. Allergy / Immunology</th>
<th>2. Ocular / Visual</th>
<th>3. Auditory / Hearing</th>
</tr>
</thead>
<tbody>
<tr>
<td>16. Vascular</td>
<td>17. Endocrine</td>
<td>18. Infection or febrile neutropenia</td>
</tr>
</tbody>
</table>
Within each of these categories, specific adverse events or toxicity are listed alphabetically and accordingly graded (NCI, 1999).

3.5.2 Internal consistency

3.5.2.1 Making the entire NCI CTC available to those responsible for grading toxicity

To ensure accuracy, the entire NCI CTC, v2.0 should be readily available. NCI requires the grading of only those toxicities that occur (unless protocol mandates grading of specific terms, even when they do not occur) (NCI, 1999). In this study, a NCI CTC manual was part of the day to day reference material during weekly participant review, as it was readily available.

3.5.2.2 Specificity of the NCI CTC

The NCI CTC, v2.0 and its associated grading criteria are very specific. Each adverse event or toxicity represents a clearly definable clinical entity. In most instances, the NCI CTC, v2.0 will provide an adverse event term and grade that more precisely describes the toxicity. The compilation of toxicity used to describe an incident will provide more complete characterisation of the events that occur; they do not necessarily indicate more toxic agents. The goal of the NCI CTC, v2.0 is to facilitate a description of the adverse event or toxicity that does occur. The NCI CTC, v2.0 includes notes associated with adverse events or toxicity to direct the user toward other adverse events that require grading if they also occurred (NCI, 1999).
3.6 RESEARCH POPULATION AND SAMPLING

3.6.1 Population

A population is a group of elements with the same characteristics as those that a researcher wants to investigate (Brink, 2007:123). In this study, the population was stage IB2 - IIIB cervical cancer patients who fit the inclusion criteria. According to the CDH 2008 Annual Report, 304, (25.23%) cervical cancer patients were seen between January and December in 2008. In the 2009 Annual Report, 429 (33.3%) cervical cancer patients were seen between January and December. In the 2010 Annual Report, 485 (38%) were seen. This translates into an average of 25 to 30 patients per month.

3.6.2 Study Sample

A sample is a subset of the population which permits a researcher to study the population by investigating only a small proportion of it (Brink, 2007:124). A modified systematic random sampling method as discussed by Trochim (2006:3) to recruit every second patient on the simulation list fitting the inclusion criteria was used in this study. Simulations of cervical carcinoma patients were done on Tuesdays and Fridays of every week in the time period in order to allow the study to reach the projected sample size of the would-be participants.

To achieve this modified systematic random sample for CDH, the needed sample size was first identified, and then divided by the total number of the sample population to obtain the sampling fraction. The sampling fraction was then used as the constant difference between study participants (Castillo, 2009:1). The sample size was designed using a guide advocated by Welman and Kruger (1994: 63), and in consultation with a statistician. The authors suggest that the following should be well thought out when the sample size is determined:

- the size of the population (N),
• the fact that the number of units of analysis from which usable data is obtained may be much smaller than the number that was drawn originally, and;
• the variation (heterogeneity) of the variables (Welman & Kruger, 1994 : 64).

The required sample size was therefore calculated as follows:

**A. Sample size**

\[ SS = Z^2 (P) (1-P ) / C^2 \]

Where:

- \( Z \) = Z value (1.96 for 95% confidence level)
- \( P \) = percentage picking a choice, expressed as decimal (0.5 used for sample size needed)
- \( C \) = confidence interval, expressed as a decimal

*Using the above, \( SS = 1.96^2 (0.5) (1-0.5) / 0.05^2 = 384 \)

**B. Correction for CDH finite population**

Cancer of the cervix patient population according to CDH 2008 report was 304. Approximately 70 patients were HIV –ve. Since two arms were required, 70 were used as a number for the finite population using the following formula:

\[ \text{New ss} = \frac{SS}{((SS-1)/\text{pop}+1)} \]

Where:

- \( \text{New ss} \) - actual sample size
- SS- infinite sample size
- Pop- finite population

*Therefore, New ss = 384/ ((384-1) / 70 +1) = 59.34 \approx 60 \)
Hence 60 were obtained as sample size for the HIV -ve sample. For comparison a similar number of HIV +ve was taken (60) making the total sample size of 120. These patients were serially stratified into two arms (HIV +ve and HIV -ve) with each arm having 60 participants.

The inclusion criteria for the HIV +ve study participants were:

- HIV +ve on HAART and performance status ECOG I & II.
- Histological confirmed cervical cancer FIGO stages IB₂ to IIIB without hydronephrosis.
- Haemoglobin >10g/dl without or with transfusion.
- Adequate renal function with creatinine clearance of > 60ml/min.
- CD4 count equal or greater than 200/mm³.
- Histology: either squamous cell carcinoma or adenocarcinoma.

The inclusion criteria for the HIV –ve study participants were:

- HIV -ve patients with performance status ECOG I & II.
- Histologically confirmed cervical cancer FIGO stages IB₂ to IIIB without hydronephrosis.
- Haemoglobin >10g/dl without or with transfusion.
- Adequate renal function with creatinine clearance of > 60ml/min.
- Histology: either squamous cell carcinoma or adenocarcinoma.

Exclusion criteria for both arms were:

- Previous radiotherapy to the pelvic region.
- Any other active AIDS-defining illness.
- Hydronephrosis.
- Uncontrolled previous malignancy.
- Any severe medical ailment that may interfere with the proposed treatment.
- Previous chemotherapy in the last one year.
- Severe psychiatric disorder, pregnancy or breast feeding.

The rationale for the above exclusion and inclusion criteria was to control situations that would limit compliance with study requirements and conditions.

Control of Confounders:

As indicated in the exclusion criteria, these measures ensured that:

1. Patients who required chronic treatment with steroids (e.g. > prednisolone 5mg/day) or other immunosuppressive agents are excluded. Both Cisplatin and radiation are immunosuppressive, and chronic steroid use (>prednisolone 5mg/day) or use of other immunosuppressive agents might increase the risk of lethal infection in this setting.
2. Impairment of gastro-intestinal function or gastro-intestinal disease e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhoea, malabsorption syndrome, rendered the patient excluded.
3. Active infection or serious underlying medical condition that would impair the patient’s ability to receive protocol treatment is an exclusion criterion. Other concurrent severe and/or uncontrolled medical disease which would compromise participation in the study in the opinion of the investigator (e.g. uncontrolled diabetes, collagen diseases like systemic lupus erythematosus and sjogrens, etc) are also part of the exclusion criteria because they cause patients to have unusual sensitivity to chemoradiation and result in increased treatment toxicity.

These measures ensured the elimination of any confounders in the two groups of the study participants and this made these two groups, that were both on chemoradiation,
comparable or similar to the only distinguishing feature between the two groups, that being their HIV status and HAART.

Staging workup done on the study participants was:

1. Complete history and physical examination.
2. Blood tests which included the following:
   a. Full blood count.
   b. Renal function tests.
   c. Liver function tests.
   d. Serum electrolytes.
4. Ultrasound abdomen and pelvis examination (to assess status of the kidneys).
5. Histopathology of the tumour.

Every second patient fitting the inclusion criteria was then recruited after the initial radiotherapy treatment simulation. This was so because it was only after simulation that a prescription of the treatment was done.

3.7 RESEARCH PROCEDURE

3.7.1 Ethical considerations

“Ethics are a set of prescribed moral rules and behavioural codes relating to what is right or wrong, or appropriate and inappropriate” (Lugosi, 2006).

Research ethics that were observed and adapted to this study are in accordance with those stated by Brink (2007:31-33), namely, the principle of respect for persons, of beneficence and of justice.
The principle of respect for persons

This principle includes the right to self-determination and the right to full disclosure (Brink, 2007:32). The right to self-determination was followed by providing the participants with the right to refuse to participate in the study, the right to discontinue the study if they felt uncomfortable, the right not to answer specific questions if they did not want to disclose that information and the right to ask for clarification if they were not sure of any aspect of the research project or motive, any specific question, or the HIV status in general.

Addressing the participants’ right to full disclosure, the researcher described the nature of the study. It was made certain that the HIV status of the participants was already known, hence this was not unique to the study and besides, most of the immunocompromised patients due to HIV/AIDS in Zambia, and CDH in particular, are put on ART. However, the participants retained the right to refuse participation. The researcher also described the responsibilities and the risks involved as well as the benefits to the participants before the actual evaluation and assessment or final recruitment of participants started.

The principle of beneficence

The principle of beneficence includes freedom from harm, from exploitation and the risk/benefit ratio (Brink, 2007:32, 39). In handling the issue of freedom from harm, there was no physical harm produced by participating in the study. Psychological discomfort might have been experienced as a result of the nature of the questions asked. Each participant was accorded an opportunity to ask questions and to seek any clarity with regard to her feelings or fears. Each participant was given information about toxicity to help make informed decisions.

Freedom from exploitation was observed by not exploiting the participant’s vulnerability. The participants were regarded as vulnerable because of the stigma that is attached to the HIV/AIDS status. Careful explanations were given to the women about their right to refuse
to participate in the study, and that their participation or refusal would not influence the care provided to them in any way.

With regard to the risk/benefit ratio, the risk meant the expected psychological discomfort resulting from the questions asked and the sero status. The benefit was the care accorded and the body of knowledge that allayed fears and probably removed the stigma that surrounds this population of patients by making them realise and know that they enjoy the same rights as the seronegative or immunocompetent population. This information could be used to encourage other women to make better informed decisions in future.

The principle of justice

The principle of justice refers to the right to fair treatment and the right to privacy (Brink, 2007:33). In the right to fair treatment, the participants were professionally treated by respecting their beliefs, habits, culture and lifestyle as well as their status. An opportunity was accorded to each participant to express their opinion at any given stage or time of the study.

The right to privacy was upheld because participants were assessed individually in a private consultation room/clinical area and by treating data collected with confidence. Confidentiality was observed and upheld by not indicating the name of the patient on the data collecting tool and in the subsequent report. The collected data was only accessible to the researcher, the evaluating clinical oncologist and the statistician, and was kept under lock and key by the researcher. Data collected was used only for the purpose of this study. The research report would provide facts, figures, graphs and tables but no names of participants will appear in this report. Participants were represented by research numbers.
3.7.2 Recruitment of participants

Every second patient fitting the inclusion criteria was recruited after the initial radiotherapy treatment simulation. This was so because it was only after simulation that a prescription of the treatment was done. Prior to recruitment, all patients were given a clear explanation of the purpose and method of the study using the participant information sheet (appendix 3). The participants were then asked to sign the informed consent form as a prerequisite to enrol in the study. The consent form indicated acknowledgement by the participants that the nature of the study was understood and that they were at liberty to withdraw from the study at any given time (appendix 4).

Participants were prescribed the normal course of treatment and their management was not changed in any way by their inclusion into the study. Participants were recruited once the radiotherapy treatment had been prescribed by the oncologist. Generally, the HIV status of the possible candidates to be recruited as study participants and CD4 count values were known prior to the radiotherapy treatment prescription. HIV screening or testing is a routine requirement. Recruited participants were then placed into either the control arm or study arm, depending on their HIV status.

3.7.3 Treatment

3.7.3.1 Radiotherapy

External beam mega-voltage RT was administered to a clinical target volume that included the primary cancer, uterus, internal iliac, presacral, upper external iliac and lower common iliac lymph nodes. Patients with stages IB2, IIA and IIB lesions received 46 Gy external beam therapy delivered homogeneously to the pelvis 5 days/week in 23 fractions at 2 Gy per fraction. This was supplemented with high dose rate brachytherapy 6.5 Gy x 4 fractions with a minimum of 1 day spacing in between fractions.

Patients with stage IIB distal (outer half of parametria involved), IIIA and IIIB early (fixed to one pelvic sidewall only) received 50 Gy in 25 fractions at 2 Gy per fraction 5 days per
week + HDR brachytherapy 8 Gy x 3 fractions. An AP – PA or “four field box technique” was used depending on the AP separation and weight of the patient. These field arrangements and energy were chosen as follows:

- AP separation less than 18 cm: AP-PA parallel opposed fields on cobalt
- AP separation more than 18 cm but below 24 cm, and lateral separation below 36 cm: a four field box technique on cobalt.
- AP separation between 18 cm and 24 cm, and lateral separation >36 cm: AP-PA on linac
- AP separation greater than 24 cm: four fields on linac

The weight limit for our cobalt couch is 105 Kg and 135 Kg for the linac

**Field borders were as follows:**

a) Lower border for anterior and posterior fields.
   - Bottom of obturator foramen.
   - If the lower-half vagina was involved, this was marked and the lower border of the field was placed 2 cm below the mark for Cobalt-60 (Co-60) machine and 1 – 2 cm below the mark for linear accelerators.

b) Upper border for anterior and posterior fields – Middle of the fifth lumbar vertebra body (mid-L5).

c) Lateral borders 1.5 – 2 cm beyond pelvic brim, unless the lower ⅕ of the vagina was involved. Inguinal nodes treated to beyond acetabulum margin.

d) Posterior margin for lateral fields.
   - IB2 – IIB proximal – bottom S3.
   - IIB distal (outer half of parametria involved) – IIIB: entire anterior sacrum.

e) Anterior margin lateral fields.
   - Top of pubic symphysis.

The entire treatment was to be completed in 6 weeks. High dose rate brachytherapy (HDR) was given concurrently during the final weeks of external beam, and not on the same day as chemotherapy.
3.7.3.2 Brachytherapy

Three or four intracavitary applications with High Dose Brachytherapy with either 8Gy x 3 fractions or 6.5Gy x 4 fractions to a point 2cm superior to the external cervical os (or cervical end of the tandem), and 2cm lateral to the cervical canal (point A), were used to treat the uterus, upper vagina, cervix and part of the parametria on both sides. A rigid intrauterine tandem of 6cm, 4cm or 2cm in length and a ring applicator (Nucleotron 3.4cm, 3cm or 2.6cm in diameter) were used with a rectal shield. High Dose Rate Brachytherapy (HDR) was not started earlier than the third week of external beam radiotherapy. A Foley’s catheter was inserted into the urinary bladder and a balloon inflated with 7cc of diluted urografin to identify the bladder. The vagina was packed with gauze to displace the bladder anteriorly and the rectum posteriorly to minimize dose to these organs. AP and lateral orthogonal films were taken with the help of a C-arm x-ray machine at the same plane for all insertions. Dose prescription was to point “A” with bladder and rectum dose being optimised to less or equal to 80% of the prescribed point “A” dose.

In a few cases (three study participants), a Sorbo (vaginal applicator) technique was used to administer Brachytherapy of 5Gy x 3 fractions mainly to treat vaginal vault post-hysterectomy and upper part of the vagina as well as small part of parametria. Bladder and rectal doses with Sorbo (vaginal applicator) are usually very high.

3.7.3.3 Chemotherapy

The chemotherapy protocol used at CDH is adapted from the five randomised trials (NCI, 1999) as well as the CMJAH way of treating locally advanced cervical cancer with Cisplatin-based chemoradiation. In this study, patients were given 80mg/m\(^2\) IV three-weekly (day 1, day 22 and day 43) as from day one through the course of radiotherapy. The creatinine clearance was calculated and only patients with values of 60ml/min and above, white cell count 3,000, platelets 100,000 and HB of 10g/dl received the chemotherapy with 1 litre normal saline for prehydration, supplemented by 1 vial of calcium gluconate, 1 vial of magnesium sulphate and 1 vial of potassium chloride. Then 16mg of
dexamethasone IV and 100mg dalasentrone IV bolus injection were given to prevent emesis.

The Cisplatin was infused over 3 to 4 hours. Another litre of normal saline was given with oral antiemetic for the patient to take home. The patients were then sent for radiotherapy after the chemotherapy was complete.

### 3.8 CALCULATION OF CREATININE CLEARANCE

A reduction in creatinine clearance to less than 60 ml/min should be viewed as a dose-limiting toxicity, although it does not form part of the NCI CTC (Nyongesa, Ruff, Donde & Kotzen, 2006:1616). This is based on the fact that creatinine clearance has to be calculated before administration of Cisplatin. Entry criteria mandated serum creatinine within normal limits for the NCI of Canada, or not greater than 2.0 mg/dl in the GOG 123, and treatment with Cisplatin was withheld where the creatinine clearance fell to less than 60 ml/min.

#### 3.8.1 Cockcroft-Gault Formula

Creatinine clearance is a more effective way of assessing renal function than serum creatinine. The use of endogenous serum creatinine to assess renal function is simple and is widely accepted. A limiting factor, however, is that creatinine is not filtered by the glomerulus alone, but is also secreted by the renal tubular cells. The rate of secretion by the renal tubular cells is highly variable and is individual-specific and time-specific. This may lead to inaccurate prediction of GFR. The serum creatinine concentration also depends on lean body mass (muscle), which varies according to age and body size (as assessed by body weight) and sex.

The Cockcroft-Gault formula is widely used by clinicians to estimate the GFR by calculating the creatinine clearance from the serum creatinine (Cockcroft & Gault, 1976; Gault,
Longerich, Harnett & Wesolowski, 1992). The factors required for these calculations are readily accessible, namely, serum creatinine, age, weight and gender of the individual. The formula takes into account the effects of progressive decline in muscle mass in ageing adults as well as variations in muscle mass between males and females, on creatinine production. For this reason, there is a different formula for males and females.

### 3.8.1.1 Cockcroft-Gault Formula for females

Creatinine measured in µmol/l

\[
\text{Creatinine Clearance} = \frac{[140 - \text{Age}] \times \text{Weight} \times 1.02}{\text{Serum Creatinine}}
\]

The weight is measured in kilograms (Kg), age in years and creatinine clearance in mls/min.

The determination of biochemical creatinine by 24-hour urine creatinine collection provides a more accurate estimation of GFR than serum creatinine concentration alone, but it is often inconvenient for patients and the results cannot always be relied upon. 24-hour urine collection is problematic: for example, inaccurate urine collections, uncooperative patients and the need for indwelling catheters cause delays in diagnosis and the dose modification of nephrotoxicity drugs. Practically, creatinine results are only available, at best, after 12 hours, and more often between 24 to 36 hours after completion of urine collection. Other more practical methods are accordingly preferred. In order to quickly assess the GFR, the Cockcroft-Gault formula is preferred.

In this study, a calculated creatinine clearance was used, rather than GFR. It is strongly considered that creatinine clearance should be deemed to be dose-limiting toxicity. The cut-off for creatinine clearance at which Cisplatin is to be given was chosen to be 60 ml/min, because most studies use this cut-off. Reed (2001) recommends that caution
should be exercised if the 24-hour creatinine clearance is less than 60 mL/min, and that alternative chemotherapeutic agents should be used in these circumstances.

3.8.2 Treatment modifications

Cisplatin was discontinued if a participant developed significant renal abnormalities ≥ grade 3 or any other non-haematological grade III/IV toxicity, other than nausea and vomiting. In addition, Cisplatin was discontinued if the creatinine clearance dropped to < 60 ml/min.

3.9 EVALUATION OF TOXICITY

Acute treatment-related toxicity was graded prospectively by an oncologist with active participation of the researcher at weekly intervals during chemoradiation using the modified NCI CTC (appendix 1). The four systems, namely, Skin, Gastro-intestinal (GIT), Genito-urinary (GUT) and Haematopoietic were evaluated. The toxicities were scored using a scale of 0 to 4, with 0 being no reaction and 4 being life-threatening. The assessment of GUT, Skin and GIT was clinical, while the haematopoietic system/renal function were laboratory-based.

The participants were reviewed once a week and the toxicity scored on an individual collection form (appendix 2). After completion of treatment the participants were again assessed for toxicity when they came for their regular follow-up one month after treatment.

3.10 RELIABILITY AND VALIDITY OF THE RESEARCH PROCESS

Reliability is the degree of consistency with which the instrument measures an attribute. It further refers to the extent to which independent administration of the same instrument yields the same results under comparable conditions. The less variation the instrument produces in repeated measurements of an attribute, the higher the reliability. There is also
a relationship between reliability and validity. An instrument which is not valid cannot possibly be reliable (Brink, 2007:163-164).

Validity is defined as a measure of truth or falsity of the data obtained through using the research data collection instrument. In science and statistics, validity has no single agreed definition but generally refers to the extent to which a concept, conclusion or measurement is well-founded and corresponds accurately to the real world (Brink, 2007:159).

In this study, NCI CTC version 2.0 was used as a tool for data collection. The validity and reliability of this tool has been assessed, tried and tested in several clinical trials (Trotti, Byhardt, Stetz, Gweda, Corn, Fu, Grunderson, McCormick, Morris, Shipley, Curran, 2000:18; Kirwan et al., 2003:225) and this is the strength of using an existing tool.

The NCI CTC were developed in 1982 for use in adverse drug experience reporting, to study adverse event summaries, and for use in Investigational New Drug (IND) reports to the Food and Drug Administration (FDA), and in publications. The NCI CTC have been used widely for collecting treatment-related complications or reactions data to facilitate the evaluation of new cancer therapies, treatment modalities, and supportive measures. The original version of the NCI CTC had 49 adverse event terms grouped in 18 categories, each with criteria for grading the severity of the adverse event. In the intervening years, in an effort to report additional adverse events seen in their studies, many groups independently added supplemental adverse event criteria to describe toxicities that were not originally included. Consequently, criteria adopted by various groups differed. To improve completeness, accuracy and precision of the NCI CTC, and to standardise reporting across groups and therapeutic modalities, a CTC review committee was assembled to revise and expand the NCI CTC to meet current needs (NCI, 1999).

In addition, it is well documented that acute and chronic radiation adverse events may be exacerbated by the simultaneous administration of some chemotherapy agents with radiation. Some protocols are developed to take advantage of the radiosensitising nature of some chemotherapy agents. When an adverse event occurs in a multimodality therapy, it should be graded using the most relevant description of toxicity, whether it is from the
standard list or one that is specifically for radiation therapy. Toxicity should be graded using the grading criterion that most closely matches the clinical situation. It should not be modified to account for the anticipated increased effect. Most often, it is not possible to separate the contribution of the individual modalities, and it is not the purpose of the NCI CTC, v2.0 to do so. The purpose of the NCI CTC, v2.0 is to describe the toxicity (NCI, 1999).

In this study, NCI CTC, v2.0 was used as a tool because it has been proven to be a well-defined instrument for reproducible grading and recording of toxicity more accurately. It also allows comparison with other studies using this tool.

3.11 STATISTICAL ANALYSIS

This study was designed to evaluate the acute toxicities of radical chemoradiation. Descriptive data analyses were used as the primary statistical analysis tool, to report demographics and adverse events or acute reactions. Collected data was entered by the researcher into a Microsoft Access data base and was then analysed by the statistician. The latest version of Statistical Package for Social Sciences (SPSS) was used to analyse data collected during the study. Data was analyzed using descriptive and inferential statistics. Chi-square tests were used to indicate the strength and direction of the relationship between variables and the level of significance. A p-value of 0.05 was used to define the chosen level of statistical significance. Statistical significance was defined as a Pearson’s chi-square p-value < 0.05. A p-value > 0.05 indicated that there is no difference between the variables. Repeated measures of ANOVA were also used since the data was collected repeatedly at different intervals. Where indicated, tables and graphs were used to display data.
3.12 SUMMARY
This chapter outlined the research design that was used in this study, the population and sampling procedure, data collection method and data collection tool as well as internal consistency; the research process is also presented. Measures were upheld that allowed enhancing the validity and reliability of the research results. Ethical concerns which could impact on the research process and study participants were addressed.
CHAPTER 4

RESULTS AND DATA ANALYSIS

4.1 INTRODUCTION

This chapter presents the results and data analysis of this research. Tables, graphs and charts will be used where necessary to display results. The latest version of statistical package for social sciences (SPSS) was used to analyze data collected during the study. Chi-square tests were used to indicate the strength and direction of the relationship between variables and the level of significance. A p-value of 0.05 was used to define the chosen level of statistical significance and indicate the differences in levels of toxicity between the two study groups. Statistical significance was defined as a Pearson’s chi-square p-value < 0.05. The results are classified starting with the general characteristics of the patients and then according to the evaluated systems.

Furthermore, the results will be presented in the light of the aim and objectives of this research as presented in the first chapter. These objectives were:

- To compare acute toxicity in HIV +ve (on HAART) and HIV –ve patients receiving radical radiotherapy with chemotherapy for cervical cancer at CDH, Lusaka, Zambia.

- To assess the degree of acute toxicity in HIV +ve (on HAART) versus HIV–ve cervical cancer patients receiving radical radiotherapy with chemotherapy at CDH, Lusaka, Zambia.

- To make suitable recommendations based on the above findings with regard to the future management of HIV +ve patients (on HAART).

This outline will be used to answer and address objectives one and two. Demographic data will also be presented in order to give an understanding of the sample, its characteristics and the nature of the findings.
4.2 PATIENT DATA

4.2.1 Breakdown of the study population (n = 120)

120 patients met the inclusion criteria. 60 patients were allocated to the HIV +ve arm and 60 to the HIV –ve arm according to the predetermined approach. However, 10 participants (5 HIV +ve and 5 HIV –ve) were not eligible for inclusion in the analysis as they did not satisfy entry criteria at time of starting chemoradiation i.e. their creatinine clearances were low. Therefore, only 110 patients were eligible for data analysis (hereafter referred to as study participants) with each arm having 55 participants (Fig 4.1).

![Sample size (n=120)](image)

**Fig 4.1: Sample size (n=120)**

4.2.2 Performance status (n = 110)

All the participants had a functional status equivalent to ECOG I at the beginning of the study. This is a performance status, which meant that the participants had symptoms of cervical cancer, but were still ambulatory (Rubin, 2001:153). This was important for the
study because a poor functional status often predicts an unsatisfactory tumour response and poor tolerance of side effects of chemoradiation.

4.2.3 Histological classification (n = 110)

The analysis showed that 108 participants (98.2%) were classified as squamous cell carcinoma and two (1.8%) were adenocarcinoma. This is in conformity with available literature which documents that most carcinoma of the cervix cases arise from flat and scaly squamous cells of the epithelium (Simon, 2003: 1).

4.2.4 Stage of cervical cancer in study participants

The analysis of the study results showed that there was not much difference in the disease stage in both arms, as illustrated in Table 4.1. The analysis further showed that a majority of the participants in both arms had locally advanced disease (IIB).

Tumour grading and staging is useful in determining the prognosis of the tumour. The higher the grade and stage the poorer the prognosis and the patient’s ability to tolerate treatment (Rubin, 2001:153). Therefore, adherence to clinical staging allows appropriate comparison of treatment, survival, and patient outcomes from diverse resource settings.
Table 4.1: FIGO cervical cancer stage of study participants (n = 110)

<table>
<thead>
<tr>
<th>STAGE</th>
<th>HIV –ve arm</th>
<th>HIV +ve arm</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>IB2 – SCC</td>
<td>5</td>
<td>4.5</td>
<td>7</td>
</tr>
<tr>
<td>IIA – SCC</td>
<td>4</td>
<td>3.6</td>
<td>4</td>
</tr>
<tr>
<td>IIB – Adenocarcinoma</td>
<td>2</td>
<td>1.8</td>
<td>0</td>
</tr>
<tr>
<td>IIB – SCC</td>
<td>34</td>
<td>30.9</td>
<td>33</td>
</tr>
<tr>
<td>IIIA – SCC</td>
<td>2</td>
<td>1.8</td>
<td>1</td>
</tr>
<tr>
<td>IIIB – SCC</td>
<td>8</td>
<td>7.3</td>
<td>10</td>
</tr>
<tr>
<td>TOTAL</td>
<td>55</td>
<td>50</td>
<td>55</td>
</tr>
</tbody>
</table>

4.3 BIOGRAPHICAL DATA

4.3.1 Participants’ age (n=110)

The median age for patients in the HIV –ve group was 55 years and that in the +ve group was 40 years. Table 4.2 depicts the distribution of age ranges. The analysis indicated an older population for the HIV –ve arm with more than 50% of the participants falling into the over-50 years category. The HIV +ve arm had a youthful population with more than 50% of the participants falling into the 20-49 year range category. The chi-square test indicated that the differences in age between the two groups were significant with a p-value of 0.0009.
Table 4.2: Participants’ ages (n=110)

<table>
<thead>
<tr>
<th>AGE</th>
<th>HIV –ve arm</th>
<th>HIV +ve arm</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>20 – 29</td>
<td>1</td>
<td>0.9</td>
<td>1</td>
</tr>
<tr>
<td>30 – 39</td>
<td>8</td>
<td>7</td>
<td>24</td>
</tr>
<tr>
<td>40 – 49</td>
<td>14</td>
<td>13</td>
<td>19</td>
</tr>
<tr>
<td>50 – 59</td>
<td>19</td>
<td>17</td>
<td>9</td>
</tr>
<tr>
<td>60 – 69</td>
<td>10</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>70 – 79</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>TOTAL</td>
<td>55</td>
<td>50</td>
<td>55</td>
</tr>
</tbody>
</table>

4.3.2 Employment status of the study participants (N=110)

The analysis illustrates the distribution of study participants in this research with regard to employment status. Participants fell into three categories: employed (six HIV –ve versus 13 HIV +ve), unemployed (35 HIV –ve versus 20 HIV +ve) and self-employed (14 HIV –ve versus 22 HIV +ve), as indicated in Table 4.3.

The HIV +ve arm therefore had a higher number of the employed and self-employed study participants. The chi-square test of this analysis showed a statistically significant difference between the two arms with respect to employment and HIV status (p-value = 0.014). This correlates with the significant age difference between the HIV +ve and -ve arms, as was shown in 4.3.1. However, this variable was not looked at prospectively.
Table 4.3: Participants’ employment status (n=110)

<table>
<thead>
<tr>
<th>EMPLOYMENT STATUS</th>
<th>HIV –ve arm</th>
<th>HIV +ve arm</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Employed</td>
<td>6</td>
<td>5.5</td>
<td>13</td>
</tr>
<tr>
<td>Unemployed</td>
<td>35</td>
<td>31.8</td>
<td>20</td>
</tr>
<tr>
<td>Self-employed</td>
<td>14</td>
<td>12.7</td>
<td>22</td>
</tr>
<tr>
<td>TOTAL</td>
<td>55</td>
<td>50</td>
<td>55</td>
</tr>
</tbody>
</table>

4.3.3 Marital status of study participants (n=110)

This variable was also not looked at prospectively by the researcher. The chi-square test indicated that there was no significant difference between the two groups with p-value being 0.262. However, the only variations to note were that there were more widowed respondents, 22 (20%) in the HIV +ve arm as compared to the HIV –ve arm, which had 13 (11.8%). Also, there were more married respondents in the HIV –ve arm, 34 (30.9%) than the HIV +ve arm which had 27 (24.5%), as illustrated in Table 4.4.

Table 4.4: Participants’ marital status (n=110)

<table>
<thead>
<tr>
<th>MARITAL STATUS</th>
<th>HIV –ve arm</th>
<th>HIV +ve arm</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Married</td>
<td>34</td>
<td>30.9</td>
<td>27</td>
</tr>
<tr>
<td>Single</td>
<td>2</td>
<td>1.8</td>
<td>2</td>
</tr>
<tr>
<td>Divorced</td>
<td>3</td>
<td>2.7</td>
<td>4</td>
</tr>
<tr>
<td>Widowed</td>
<td>13</td>
<td>11.8</td>
<td>22</td>
</tr>
<tr>
<td>Unknown</td>
<td>3</td>
<td>2.7</td>
<td>0</td>
</tr>
<tr>
<td>TOTAL</td>
<td>55</td>
<td>50.0</td>
<td>55</td>
</tr>
</tbody>
</table>
4.4 TREATMENT DELIVERY

4.4.1 Radiotherapy Delivery

110 study participants received and completed the external beam radiotherapy (EBRT) as prescribed. Figure 4.2 illustrates that in this study there were 37 HIV –ve study participants and 27 HIV +ve study participants who were treated on the linear accelerator. The Co-60 megavoltage unit had 18 HIV –ve and 28 HIV +ve study participants treated on it. HIV +ve patients had lower weights and smaller separations making Co-60 an attractive option for treatment.

![Figure 4.2: Distribution of participants to the treatment units (HIV +ve and HIV –ve)](chart.png)

4.4.1.1 Treatment Fields

The majority of the participants in this study were treated with AP-PA fields and only 10 were treated with four fields, three in the HIV +ve arm and seven in the HIV –ve arm. Patients were allocated to these treatment units according to standard operating procedures for AP separation (as described in section 3.7.3.1). The median number of
days it took to complete treatment was 38 days and 37 days in the HIV –ve group and HIV +ve group, respectively.

4.4.1.2 Brachytherapy

The analysis of the results and distribution of participants regarding Brachytherapy fractionation showed that the HIV +ve arm had more participants treated with 6.5Gy x 4 fractions (58%). The results also showed that there were more HIV –ve participants treated with 8Gy x 3 fractions (58%) (Table 4.5). The study analysed acute toxicities for Chemoradiation though it is recognized that brachytherapy is an important component for control of cervical cancer. Future studies may look at this effect separately.

<table>
<thead>
<tr>
<th>HDR- fractionation</th>
<th>HIV +ve arm</th>
<th>HIV –ve arm</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>8Gy x 3 fractions (Ring &amp; tandem)</td>
<td>22</td>
<td>40</td>
<td>32</td>
</tr>
<tr>
<td>6.5Gy x 4 fractions (Ring &amp; tandem)</td>
<td>32</td>
<td>58</td>
<td>21</td>
</tr>
<tr>
<td>5Gy x 3 fractions (Vaginal applicator)</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>55</td>
<td>100</td>
<td>55</td>
</tr>
</tbody>
</table>

4.4.2 Chemotherapy

The number of chemotherapy cycles received by patients in both arms ranged between one and two (Table 4.6). A total of 190 chemotherapy cycles were administered, with a median of two cycles per patient. 80 (73%) participants received at least two cycles of
chemotherapy. The full two intended courses of Cisplatin per patient (day one & day 22), were not administered in 30 (27%) participants. Day 43 chemotherapy was not included in the analysis since it fell outside the radiotherapy delivery period.

Table 4.6: Cycles of chemotherapy received

<table>
<thead>
<tr>
<th>Chemotherapy cycles</th>
<th>HIV +ve arm</th>
<th>HIV –ve arm</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>1</td>
<td>14</td>
<td>25</td>
<td>16</td>
</tr>
<tr>
<td>2</td>
<td>41</td>
<td>75</td>
<td>39</td>
</tr>
<tr>
<td>Total</td>
<td>55</td>
<td>100</td>
<td>55</td>
</tr>
</tbody>
</table>

The planned two Cisplatin cycles per patient (day one & day 22), were not administered in 30 (27%), 14 HIV +ve versus 16 HIV –ve participants (Table 4.6). This was due either to the time factor between cycles as a result of waiting for participants to recuperate, or due to treatment toxicity, as indicated in Table 4.7.

Table 4.7: Reasons for omitting or delaying chemotherapy

<table>
<thead>
<tr>
<th>Reason</th>
<th>HIV +ve arm (n=55)</th>
<th>HIV –ve arm (n=55)</th>
<th>Total (n=110)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Hb</td>
<td>2 (4%)</td>
<td>0 (0%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Low creatinine clearance</td>
<td>4 (7%)</td>
<td>6 (11%)</td>
<td>10 (9%)</td>
</tr>
<tr>
<td>Low WBC</td>
<td>10 (18%)</td>
<td>8 (15%)</td>
<td>18 (16%)</td>
</tr>
<tr>
<td>High serum creatinine</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Total</td>
<td>17 (31%)</td>
<td>15 (28%)</td>
<td>32 (29%)</td>
</tr>
</tbody>
</table>
Toxicity and biochemical profile were assessed before each chemotherapy cycle. Complete blood counts and clinical assessments were also performed weekly.

Cisplatin was also discontinued if a patient developed significant renal toxicity > grade three, grade IV neutropenia, grade IV thrombocytopenia, complicated grade III haematologic toxicity (neutropenia with fever, thrombocytopenia with bleeding requiring platelet transfusion), grade III or IV nonhaematologic toxicity other than nausea and vomiting. A reduction in calculated creatinine clearance less than 60mL/min was viewed as a dose-limiting toxicity, although it does not form part of the NCI CTC v2.0. Raised serum creatinine can also be a manifestation of severe toxicity during chemoradiation.

### 4.5 COMPARISON OF TOXICITY

The first and second objectives compared acute toxicity in the HIV +ve (on HAART) and HIV –ve patients receiving radical radiotherapy with chemotherapy for cervical cancer at CDH, Lusaka, Zambia. Acute toxicity in four systems: skin (cutaneous), gastro-intestinal, genito-urinary and haemopoietic was evaluated. Results of this study are presented system by system.

#### 4.5.1 Skin

Toxicity was scored as Grade 0, grade 1, grade 2, grade 3 and grade 4. According to the NCI CTC v2, these scores represent:

- **Grade 0 = none**
- **Grade 1 = faint erythema/dry desquamation**
- **Grade 2 = moderate to brisk erythema or patchy moist desquamation, mostly confined to the skin folds: moderate oedema**
• Grade 3 = confluent moist desquamation > 1.5 cm diameter and not confined to skin folds: pitting oedema

• Grade 4 = skin necrosis/ulceration

A cross tabulation of acute skin toxicity versus HIV status for week two, three, four and five revealed no statistically significant difference between the two arms in the levels of acute skin reactions with respect to HIV status (Table 4.8). However, of note where the following:

• One participant in the HIV +ve arm had grade 2 toxicity in week two. This manifestation was rather too early. The reason for this could be that, HIV +ve patients have altered ability of their cellular system to maintain protective mechanisms both acutely and chronically (Watkins-Bruner, More-Higgs and Hass 2001:495).

<table>
<thead>
<tr>
<th>Week number</th>
<th>Grade</th>
<th>HIV –ve arm</th>
<th>HIV +ve arm</th>
<th>P -value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 2</td>
<td>Grade 1</td>
<td>16</td>
<td>13</td>
<td>0.506</td>
</tr>
<tr>
<td></td>
<td>Grade 2</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Week 3</td>
<td>Grade 1</td>
<td>34</td>
<td>27</td>
<td>0.3711</td>
</tr>
<tr>
<td></td>
<td>Grade 2</td>
<td>7</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Week 4</td>
<td>Grade 1</td>
<td>31</td>
<td>30</td>
<td>0.361</td>
</tr>
<tr>
<td></td>
<td>Grade 2</td>
<td>24</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Week 5</td>
<td>Grade 1</td>
<td>31</td>
<td>27</td>
<td>0.5019</td>
</tr>
<tr>
<td></td>
<td>Grade 2</td>
<td>24</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grade 3</td>
<td>0</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>
4.5.1.1 Comparison of skin toxicity: Linac and CO-60 machines

When a comparison of acute skin toxicity results for study participants treated on the linear accelerator and those treated on the Co-60 machine was made, a chi-square test for week two and three in the HIV –ve study participants revealed statistically significant differences (p-values 0.0009 and 0.0148, respectively). There was also a statistically significant difference (p-value 0.0004) in the HIV +ve study participants in week three. Furthermore, of note were the following:

- Higher percentages of acute skin toxicity among the HIV –ve study participants treated on the Co-60 machine in the first three weeks as compared to those treated on the Linac (figure 4.3). However, at week four, the thresholds of acute skin toxicity were observed to have levelled at both treatment units.

![Figure 4.3](image)

**Figure 4.3 A comparison of acute skin toxicity in HIV –ve study participants treated at the Co-60 & linear accelerator**

- Consistently higher percentages of acute skin toxicity in the HIV +ve study participants who were treated on the Co-60 machine as compared to those treated on the Linac (Figure 4.4).
Figure 4.4 A comparison of acute skin toxicity in HIV +ve study participants treated at the Co-60 & linear accelerator

- Analysis of the results for the Co-60 study participants showed higher percentages of acute skin toxicity in the HIV –ve study participants in the first two weeks (Figure 4.5).

Figure 4.5 A comparison of acute skin toxicity between the HIV –ve & HIV +ve study participants at the Co-60
• Analysis of the results for the linear accelerator indicated similar observations of acute skin toxicity in the HIV –ve study participants (Figure 4.6).

![Graph showing skin reaction in HIV –ve & HIV +ve study participants at the linear accelerator](image)

**Figure 4.6 A comparison between the HIV –ve & HIV +ve study participants at the linear accelerator**

### 4.5.2 Gastro-intestinal tract system

#### 4.5.2.1 Diarrhoea

Toxicity was scored as Grade 0, grade 1, grade 2, grade 3 and grade 4. According to the NCI CTC v2, these scores represent:

- Grade 0 = none
- Grade 1 = Increase of < 4 stools/day over pre-treatment
- Grade 2 = Increase of 4-6 stools/day or nocturnal stools
- Grade 3 = Increase of > 6 stools/day or incontinence; or need for parenteral support for dehydration
Grade 4 = Physiologic consequences requiring intensive care or haemodynamic collapse

Cross tabulation of diarrhoea versus HIV status for the first four weeks revealed no statistically significant differences between the two arms in the levels of diarrhoea with respect to HIV status. This evaluation is indicated in table 4.9 showing a summary of the P values of the cross tabulations. However, there was a statistically significant difference in toxicity for week five with p-value being 0.0395. 29.2% (7) HIV -ve versus 70.8% (17) HIV +ve had grade 1 levels of diarrhoea. 40% (4) HIV -ve versus 60% (6) HIV +ve had grade two levels of diarrhoea in week five. Therefore, HIV +ve status could be said to have influenced the degree of level one and two diarrhoea in the HIV +ve study participants on chemoradiation when compared to the HIV -ve arm in that week.

Table 4.9  Cross-tabulation results of acute diarrhoea vs HIV status

<table>
<thead>
<tr>
<th>Week number</th>
<th>Grade</th>
<th>HIV -ve</th>
<th>HIV +ve</th>
<th>P -value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1</td>
<td>Grade 1</td>
<td>26</td>
<td>31</td>
<td>0.6018</td>
</tr>
<tr>
<td></td>
<td>Grade 2</td>
<td>17</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Week 2</td>
<td>Grade 1</td>
<td>11</td>
<td>16</td>
<td>0.3281</td>
</tr>
<tr>
<td></td>
<td>Grade 2</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Week 3</td>
<td>Grade 1</td>
<td>8</td>
<td>13</td>
<td>0.4657</td>
</tr>
<tr>
<td></td>
<td>Grade 2</td>
<td>4</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Week 4</td>
<td>Grade 1</td>
<td>14</td>
<td>19</td>
<td>0.2759</td>
</tr>
<tr>
<td></td>
<td>Grade 2</td>
<td>13</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Week 5</td>
<td>Grade 1</td>
<td>7</td>
<td>17</td>
<td>0.0395</td>
</tr>
<tr>
<td></td>
<td>Grade 2</td>
<td>4</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>
4.5.2.2 Nausea

Toxicity for nausea was also scored as Grade 0, grade 1, grade 2, grade 3 and grade 4. According to the NCI CTC v2, these scores represent:

- Grade 0 = none
- Grade 1 = Able to eat
- Grade 2 = Oral intake significantly reduced
- Grade 3 = No significant intake requiring IV fluids: >5 episodes in 24 hrs over pre-treatment/requiring IV fluids
- Grade 4 = Physiologic consequences requiring intensive care or haemodynamic collapse

Cross tabulations of nausea versus HIV status for week two up to week five did not show statistically significant differences between the two arms (p-values are indicated in table 4.10). Therefore, the HIV +ve status did not confer additive adverse reactions in the form of nausea in the HIV +ve arm during chemoradiation. However, Crosstabulation of nausea versus HIV status for week one showed a significant difference between the two groups (p-value 0.010). There were 79 study participants who developed grade 1 nausea and seven participants with grade 2 nausea. Of the 79 participants, 45 (57%) were HIV -ve and 34 (43%) were HIV +ve. There were no grade 3 and four levels of nausea.
Table 4.10 Cross-tabulation results of acute nausea vs HIV status

<table>
<thead>
<tr>
<th>Week number</th>
<th>Grade</th>
<th>HIV -ve</th>
<th>HIV +ve</th>
<th>P -value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1</td>
<td>Grade 1</td>
<td>45</td>
<td>34</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>Grade 2</td>
<td>0</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Week 2</td>
<td>Grade 1</td>
<td>21</td>
<td>26</td>
<td>0.189</td>
</tr>
<tr>
<td></td>
<td>Grade 2</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Week 3</td>
<td>Grade 1</td>
<td>18</td>
<td>24</td>
<td>0.2741</td>
</tr>
<tr>
<td></td>
<td>Grade 2</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Week 4</td>
<td>Grade 1</td>
<td>30</td>
<td>28</td>
<td>0.8485</td>
</tr>
<tr>
<td>Week 5</td>
<td>Grade 1</td>
<td>23</td>
<td>30</td>
<td>0.215</td>
</tr>
<tr>
<td></td>
<td>Grade 2</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

4.5.2.3 Vomiting

Toxicity was scored as Grade 0, grade 1, grade 2, grade 3 and grade 4. According to the NCI CTC v2, these scores represent:

- Grade 0 = none
- Grade 1 = 1 episode in 24 hours
- Grade 2 = 2-5 episodes in 24 hours over pre-treatment
- Grade 3 = >5 episodes in 24 hrs over pre-treatment/requiring IV fluids
- Grade 4 = requiring parenteral nutrition/physiological consequences requiring intensive: haemodynamic collapse

Cross tabulations of vomiting versus HIV status for weeks one, two, four and five did not show statistically significant differences between the two arms in the levels of vomiting. This evaluation is indicated in table 4.11 showing a summary of the P values of the cross tabulations. However, particularly noticeable were the following:

- Two cases of grade 3 vomiting were recorded in the HIV +ve arm in week one.
• Week two results showed one grade 3 observation of vomiting in the HIV +ve arm.
• Week three recorded two (66.7%) HIV -ve versus one (33.3%) HIV +ve study participants with grade 1 levels of vomiting. Grade 2 levels of vomiting were as follows: 10 (83.3%) HIV -ve versus two (16.7%) HIV +ve study participants. This analysis showed that there were statistically significant differences in the levels of vomiting between the two arms with the p-value being 0.0384.
• There was one study participant with grade 3 level of vomiting in the HIV +ve arm in week four.
• HIV -ve patients had a high incidence of chemoradiation induced vomiting as compared to HIV +ve patients on HAART receiving chemoradiation.

Table 4.11 Cross-tabulation results of vomiting vs HIV status

<table>
<thead>
<tr>
<th>Week number</th>
<th>Grade</th>
<th>HIV -ve</th>
<th>HIV +ve</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1</td>
<td>Grade 1</td>
<td>13</td>
<td>13</td>
<td>0.2185</td>
</tr>
<tr>
<td></td>
<td>Grade 2</td>
<td>30</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grade 3</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Week 2</td>
<td>Grade 1</td>
<td>2</td>
<td>4</td>
<td>0.1978</td>
</tr>
<tr>
<td></td>
<td>Grade 2</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grade 3</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Week 3</td>
<td>Grade 1</td>
<td>2</td>
<td>1</td>
<td>0.0384</td>
</tr>
<tr>
<td></td>
<td>Grade 2</td>
<td>10</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Week 4</td>
<td>Grade 1</td>
<td>4</td>
<td>8</td>
<td>0.094</td>
</tr>
<tr>
<td></td>
<td>Grade 2</td>
<td>15</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grade 3</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Week 5</td>
<td>Grade 1</td>
<td>3</td>
<td>7</td>
<td>0.408</td>
</tr>
<tr>
<td></td>
<td>Grade 2</td>
<td>8</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>
4.5.2.4 Proctitis

In this study, the experiences of respondents with regard to proctitis will be presented starting from week one up to week five of radical chemoradiation. Toxicity was scored as Grade 0, grade 1, grade 2, grade 3 and grade 4. According to the NCI CTC v2, these scores represent:

- Grade 0 = none
- Grade 1 = Increased stool frequency, occasional blood-streaked stools or rectal discomfort not requiring medication
- Grade 2 = increased stool frequency, bleeding, mucus, discharge or rectal discomfort requiring medication: anal fissure
- Grade 3 = increased stool frequency/diarrhoea requiring parenteral support; rectal bleeding requiring transfusion; or persistent mucus discharge necessitating pads
- Grade 4 = Perforation, bleeding or other life-threatening complications requiring surgical intervention (e.g. colostomy)

Cross tabulation results of acute proctitis versus HIV status for weeks one, three and four did not show statistically significant differences between the two arms in the levels of proctitis with respect to HIV status. This evaluation is indicated in table 4.12 showing p-values of the cross tabulations. Most salient in the analysis of proctitis versus HIV status were the following:

- Results for week two showed that there were 15 (36.6%) HIV -ve versus 26 (63.4%) HIV +ve study participants with grade 1 proctitis. Single table analysis was done and it showed that there was a statistically significant variation between the two arms with respect to their HIV status and proctitis. This indicates that there were more respondents with grade 1 proctitis in the HIV +ve arm.
- The Chi-squared test for week five data showed that the differences between the two arms with respect to acute toxicity were statistically significant, with p-value being 0.00271. There were more HIV +ve study participants with grade 2 proctitis indicating that the sero status had influenced the severity of proctitis.
There were no grade 3 and 4 levels of proctitis.

**Table 4.12 Cross-tabulation results of acute proctitis vs HIV status**

<table>
<thead>
<tr>
<th>Week</th>
<th>Grade</th>
<th>HIV -ve</th>
<th>HIV +ve</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1</td>
<td>Grade 1</td>
<td>1</td>
<td>1</td>
<td>0.752</td>
</tr>
<tr>
<td>Week 2</td>
<td>Grade 1</td>
<td>15</td>
<td>26</td>
<td>0.0486</td>
</tr>
<tr>
<td></td>
<td>Grade 2</td>
<td>28</td>
<td>34</td>
<td>0.1186</td>
</tr>
<tr>
<td>Week 3</td>
<td>Grade 1</td>
<td>1</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grade 2</td>
<td>46</td>
<td>38</td>
<td>0.089</td>
</tr>
<tr>
<td>Week 4</td>
<td>Grade 1</td>
<td>6</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grade 2</td>
<td>47</td>
<td>31</td>
<td>0.00271</td>
</tr>
<tr>
<td>Week 5</td>
<td>Grade 2</td>
<td>7</td>
<td>23</td>
<td></td>
</tr>
</tbody>
</table>

**4.5.3 Genito-urinary system**

**4.5.3.1 Cystitis**

Cystitis became symptomatic after 10 to 14 days of treatment. Symptoms included dysuria, urinary frequency and urgency. Results are presented from week two up to week five. Toxicity was scored as Grade 0, grade 1, grade 2, grade 3 and grade 4. According to the NCI CTC v2, these scores represent:

- Grade 0 = None
- Grade 1 = Mild symptoms
- Grade 2 = Symptoms relieved with therapy
- Grade 3 = Unrelieved symptoms
Cross tabulation results of acute cystitis versus HIV status for weeks two, three, four and five did not show statistically significant differences between the two arms in the levels of cystitis with respect to HIV status. This evaluation is indicated in table 4.13 showing a summary of the p-values of the cross tabulations. Most prominent, about the analysis of cystitis versus HIV status were the following:

- No significant statistical difference in the toxicity levels was noted for cystitis for the two arms represented in the study population. Therefore, the HIV +ve status did not contribute to increased levels of acute toxicity in the HIV +ve study participants for as long as they were on HAART when compared to their HIV -ve counterparts.
- These results showed that chemoradiation does not confer additive toxicity upon the HIV +ve population who have an intact immune status (on HAART).

Table 4.13 Cross-tabulation results of acute cystitis vs HIV status

<table>
<thead>
<tr>
<th>Week number</th>
<th>Grade</th>
<th>HIV -ve</th>
<th>HIV +ve</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 2</td>
<td>Grade 1</td>
<td>15</td>
<td>7</td>
<td>0.0952</td>
</tr>
<tr>
<td></td>
<td>Grade 1</td>
<td>23</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grade 2</td>
<td>3</td>
<td>1</td>
<td>0.0844</td>
</tr>
<tr>
<td>Week 3</td>
<td>Grade 1</td>
<td>37</td>
<td>32</td>
<td>0.567</td>
</tr>
<tr>
<td></td>
<td>Grade 2</td>
<td>15</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Week 4</td>
<td>Grade 1</td>
<td>37</td>
<td>33</td>
<td>0.709</td>
</tr>
<tr>
<td></td>
<td>Grade 2</td>
<td>16</td>
<td>19</td>
<td></td>
</tr>
</tbody>
</table>

4.5.4 Haematopoietic system

Haematological toxicity following chemoradiation has commonly included leucopenia, thrombocytopenia and anaemia.
4.5.4.1 Haemoglobin (HB)

Toxicity grades of haemoglobin to indicate levels of anaemia in this study are presented starting with week two up to week five of radical chemoradiation, as there were no reactions in week one. Toxicity was scored as grade 0, grade 1, grade 2, grade 3 and grade 4. According to the NCI CTC v2, these scores represent:

- Grade 0 = 12.1 - 16.3g/dL
- Grade 1 = 10 - <12.1g/dL
- Grade 2 = 8 - <10g/dL
- Grade 3 = 6.5 - <8g/dL
- Grade 4 = <6.5g/dL

Cross tabulation results of acute haemoglobin toxicity versus HIV status for weeks two, three, four and five did not show statistically significant differences between the two arms in the levels of haemoglobin with respect to HIV status. This evaluation is indicated in table 4.14 showing a summary of the p-values of the cross tabulations. Most outstanding about the analysis of haemoglobin versus HIV status were the following:

- One HIV -ve participant developed grade 3 level of anaemia in week three.
- There was one HIV +ve participant with grade 3 level of anaemia in week four.
- One HIV +ve participant had grade 4 level of anaemia in week five.
- Chemoradiation did not confer exaggerated toxicity in the HIV +ve arm for as long as they were on HAART when compared to their HIV -ve counterparts.
Table 4.14 Cross-tabulation results of acute anaemia vs HIV status

<table>
<thead>
<tr>
<th>Week number</th>
<th>Grade</th>
<th>HIV -ve</th>
<th>HIV +ve</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 2</td>
<td>Grade 1</td>
<td>4</td>
<td>8</td>
<td>0.359</td>
</tr>
<tr>
<td>Week 3</td>
<td>Grade 1</td>
<td>13</td>
<td>10</td>
<td>0.221</td>
</tr>
<tr>
<td></td>
<td>Grade 2</td>
<td>0</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grade 3</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Week 4</td>
<td>Grade 1</td>
<td>15</td>
<td>7</td>
<td>0.206</td>
</tr>
<tr>
<td></td>
<td>Grade 2</td>
<td>5</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grade 3</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Week 5</td>
<td>Grade 1</td>
<td>12</td>
<td>5</td>
<td>0.230</td>
</tr>
<tr>
<td></td>
<td>Grade 2</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

4.5.4.2 White blood cell count (WBC)

The results of leucopenia for this study are presented from week two up to week five of chemoradiation because there were no observations of reduced white blood cells in week one. Toxicity was scored as grade 0, grade 1, grade 2, grade 3 and grade 4. According to the NCI CTC v2, these scores represent:

- Grade 0 = 3.92 – 9.88 x 10⁹/L
- Grade 1 = <3.92 – 3 x 10⁹/L
- Grade 2 = <3 - >2 x 10⁹/L
- Grade 3 = <2 - >1 x 10⁹/L
- Grade 4 = <1 x 10⁹/L

Cross tabulation results of acute leucopenia versus HIV status for weeks three, four and five did not show statistically significant differences between the two arms in the levels of leucopenia with respect to HIV status. This evaluation is indicated in table 4.15 showing a
summary of the p-values of the cross tabulations. Most exceptional about the analysis of leucopenia versus HIV status were the following:

- There were 24 study participants with grade 1 leucopenia out of which six (25%) were HIV -ve compared to 18 (75%) HIV +ve in week two. The results also showed that there was one observation of grade 2 level of leucopenia in the HIV -ve arm. This result indicated a statistically significant difference between the two arms with respect to leucopenia and HIV status. The p-value was 0.015. Therefore, there was enhanced grade 1 leucopenia in the HIV +ve arm.

- One HIV +ve study participants had grade 3 level of leucopenia in week three.

- There were three HIV -ve study participants with grade 3 leucopenia in week four.

- Six study participants in week five had grade 3 level of leucopenia of which two (33.3%) were HIV -ve and four (66.7%) were HIV +ve.

**Table 4.15 Cross-tabulation results of acute leucopenia vs HIV status**

<table>
<thead>
<tr>
<th>Week number</th>
<th>Grade</th>
<th>HIV -ve</th>
<th>HIV +ve</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 2</td>
<td>Grade 1</td>
<td>6</td>
<td>18</td>
<td>0.015</td>
</tr>
<tr>
<td></td>
<td>Grade 2</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Week 3</td>
<td>Grade 1</td>
<td>17</td>
<td>29</td>
<td>0.078</td>
</tr>
<tr>
<td></td>
<td>Grade 2</td>
<td>9</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grade 3</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Week 4</td>
<td>Grade 1</td>
<td>21</td>
<td>23</td>
<td>0.066</td>
</tr>
<tr>
<td></td>
<td>Grade 2</td>
<td>7</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grade 3</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Week 5</td>
<td>Grade 1</td>
<td>21</td>
<td>24</td>
<td>0.731</td>
</tr>
<tr>
<td></td>
<td>Grade 2</td>
<td>6</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grade 3</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>
4.5.4.3 Platelets (PLT)

The results of the study with regard to thrombocytopenia are presented starting from week two up to week five of chemoradiation. There were no toxicity levels with respect to thrombocytopenia in week one. Toxicity was scored as grade 0, grade 1, grade 2, grade 3 and grade 4. According to the NCI CTC v2, these scores represent:

- Grade 0 = 178 – 400 x 10⁹/L
- Grade 1 = <178 - 75 x 10⁹/L
- Grade 2 = <75 - >50 x 10⁹/L
- Grade 3 = <50 - >10 x 10⁹/L
- Grade 4 = <10 x 10⁹/L

The participants only experienced grade 1 thrombocytopenia. The chi-square test indicated a significant difference between the two groups with respect to thrombocytopenia experienced for weeks three, four and five with the p-values being 0.004, 0.0185 and 0.0078, respectively. This evaluation is indicated in table 4.16 showing a summary of the p-values of the cross tabulations of haemopoietic system toxicity versus HIV status.

### Table 4.16 Cross-tabulation results of acute thrombocytopenia vs HIV status

<table>
<thead>
<tr>
<th>Week number</th>
<th>Grade</th>
<th>HIV -ve</th>
<th>HIV +ve</th>
<th>P -value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 2</td>
<td>Grade 1</td>
<td>2</td>
<td>3</td>
<td>1.000</td>
</tr>
<tr>
<td>Week 3</td>
<td>Grade 1</td>
<td>5</td>
<td>18</td>
<td>0.004</td>
</tr>
<tr>
<td>Week 4</td>
<td>Grade 1</td>
<td>9</td>
<td>21</td>
<td>0.0185</td>
</tr>
<tr>
<td>Week 5</td>
<td>Grade 1</td>
<td>7</td>
<td>20</td>
<td>0.0078</td>
</tr>
</tbody>
</table>

4.6 MAJOR ACUTE TOXICITY (GRADES 3 & 4)

The results of this study showed that the major acute reactions in CDH study participants were grade 3 leucopenia (five in each study arm) and one grade 3 acute skin toxicity in the
HIV +ve arm (Table 4.17). The results also revealed that there were three HIV +ve study participants with grade 3 level of vomiting and one HIV –ve study participant with grade 3 level of vomiting. There was one grade 3 anaemia in the HIV +ve arm versus one grade 3 anaemia in the HIV –ve arm as well as one grade 4 anaemia in the HIV +ve arm. However, only the incidence of grade 3 leucopenia in both study arms and vomiting in the HIV +ve study participants was significantly higher.

The variations in the levels of acute toxicity between the two study arms were observed to be generally minimal. Therefore, it could be said that the HIV +ve status did not present exaggerated levels or unexpected toxicity in the HIV +ve study participants.

Table 4.17 Major acute toxicity (grades 3 and 4)

<table>
<thead>
<tr>
<th>ACUTE TOXICITY</th>
<th>HIV –ve arm Incidence of toxicity</th>
<th>HIV +ve arm Incidence of toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 3</td>
<td>Grade 4</td>
</tr>
<tr>
<td>Skin</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Leucopenia</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Platelets</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cystitis</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Proctitis</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>7</td>
<td>0</td>
</tr>
</tbody>
</table>

4.7 TREATMENT FOLLOW-UP

Study participants were not followed up at six weeks due to logistical difficulties that were beyond this study but most patients were seen at three months of follow-up. Therefore, to
assess acute toxicity at six weeks post-treatment of the study proved to be a challenge for this study period.

4.8 SUMMARY
This chapter presented the results of this research project. Tables and graphs were used where necessary to simplify the understanding of the results. The demographic data was presented to highlight the sample characteristics. Cross-tabulation for toxicity versus HIV status was presented for patient data.
CHAPTER 5
DISCUSSION

5.1 INTRODUCTION

This chapter discusses the principal findings of the results presented in Chapter 4. These will be discussed in light of the research aim and objectives with reference to what is known in the literature about this subject matter.

5.2 REDEFINITION OF THE RESEARCH AIM

The aim of this study was to evaluate acute toxicity of radical combination therapy, in the form of radiotherapy and chemotherapy, in HIV +ve on HAART and HIV –ve patients for cervical cancer at CDH, Lusaka, Zambia.

5.3 DISCUSSION OF RESULTS

The results of five randomised clinical trials (NCI, 1999) and a meta-analysis of concomitant chemotherapy and radiotherapy for cervical carcinoma by Green, Kirwan, Tierney, Vale, Symonds, Fresco, Williams & Collingwood (2010:2,5-12) showing superiority of Cisplatin-based chemoradiation over radiotherapy alone have motivated the continued application of combined modality treatment in daily practice. However, these protocols of combined treatment modalities have not been evaluated in detail in HIV +ve patients with regard to radiation response, its toxicities, patient compliance and patterns of survival (Shrivastava et al., 2005:31-32). The available literature provides evidence that there has been an unwillingness to treat HIV +ve patients according to the standardised regimens of radiation combined with chemotherapy owing to concerns about the possibility of additive or unacceptable toxicity.
In the literature, it is further suggested that HIV +ve patients with low CD4 counts and not on HAART have increased acute toxicity (acute side effects) during radical chemoradiation (Hoffman et al., 1999:127; Kim et al., 2001:1496). The literature also suggests that acute side effects in HIV +ve patients may not only be as a result of the effects of chemoradiation, but also as a result of impaired cellular immunity (IAEA, 2001:9). In Zambia, and most Sub-Saharan African countries, this has not been studied. It is for this reason that this study was conducted in Zambia (CDH) in order to answer the question of acute side effects (acute toxicity) in this group of patients. The study also attempted to establish which acute side effects (acute toxicities) are the most common in HIV +ve patients undergoing radical chemoradiation.

The results of this study showed that major acute toxicities (grades 3 and 4) in the CDH study participants were leucopenia (five in the HIV +ve arm versus five in the HIV –ve arm), vomiting (one in the HIV –ve arm versus three in the HIV +ve arm) confluent desquamation (one in the HIV +ve arm) and anaemia (one in the HIV –ve arm versus two in the HIV +ve arm). As established in Chapter 4 in table 4.17, the prevalence of major toxicity was observed as being higher in the HIV +ve arm. Acute toxicity nevertheless tended to be short-lived and resolved by appropriate medical treatment.

In spite of the small number of participants in the CDH study, the results showed that toxicity scores were lower than those reported in other published studies. Table 5.1 for example, shows that study participants at CDH did not experience greater haematological toxicities than the participants in the other three studies represented in the table. The haematological toxicities observed in the CDH study participants were mainly grades1 and 2, as noted by Singh, Singh, Sharma & Singh (2003:101). There were no exaggerated severe haematological toxicities of grade 3 and 4 as reported in the study by Shibata, Kikkawa, Suzuki, Terauchi, Kajiyama, Ino & Mizutani (2004:93), and the meta-analysis of concomitant chemotherapy and radiotherapy for cervical carcinoma by Green et al., (2010:2,5-12) for as long as the study participants were on HAART.
TABLE 5.1: Grade 3 and 4 toxicity in comparison to GOG 120, GOG 123 and NCI of Canada using Cisplatin doses of 40 mg/m² weekly.

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>GOG 123 RT + CDDP n = 183(%)</th>
<th>NCIC RT + CDDP n = 127(%)</th>
<th>GOG 120 RT + CDDP n = 176(%)</th>
<th>CDH study RT + CDDP n = 110</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leucopenia</td>
<td>-</td>
<td>-</td>
<td>23</td>
<td>10</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Other haematologic</td>
<td>21</td>
<td>4.7</td>
<td>15</td>
<td>3</td>
</tr>
<tr>
<td>Gastro-intestinal</td>
<td>14</td>
<td>13</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>Genito-urinary</td>
<td>2</td>
<td>2</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Skin</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

Treatment-induced anaemia in the CDH study participants was less frequent. Anaemia during chemoradiation results into tumour hypoxia and attending to symptoms related to hypoxia is important. Improved haemoglobin has been shown to have a +ve impact on tumour control. Anoxic tumour cells are two to three times more resistant to radiation therapy than normally oxygenated cells.

Most myelosuppresive agents produce white cell (WBC) nadir 7 to fourteen days after treatment initiation. Myelosuppression from chemoradiation places cervical cancer patients at risk for significant morbidity and mortality (Langhorne, Fulton & Otto, 2007:488). Therefore, the primary outcome desired with regard to neutropenia/leucopenia is that the patient will be free of infection.

Thrombocytopenia, a decrease in the circulating platelet count below 100,000/mm³, is the most common platelet abnormality associated with cancer and Chemoradiation. The platelet count is considered to be the single most significant factor for predicting bleeding in the patient with cancer. Control of bleeding requires adequate numbers of circulating platelets, as well as their functional capacity to assist in haemostasis or clotting of the
blood. Therefore, the primary outcome desired pertaining to thrombocytopenia during Chemoradiation is that the cervical cancer patient will experience no life-threatening bleeding (Langhorne et al., 2007:493).

The gastro-intestinal toxicities in CDH study participants were mainly grades 1 and 2 for both arms. There were no treatment-related deaths as in the study by Rose et al. (1999:1144) and Keys et al. (1999:1154). Radiotherapy treatment delay because of toxicity, as noted in Bhavaraju, Reed, and Habeshaw (2001:90), and Singh et al., (2003:101), was not apparent in the CDH study. Nonetheless, there could have been radiotherapy treatment interruption for one HIV +ve study participant owing to severe toxicity (grade 4 anaemia) in this study but this was corrected through blood transfusion. A treatment gap of six or more days was to be recorded as treatment interruption. This rationale was based on the findings of the study by Wilson, McNally, Disches, Saunders, Desrochers & Lewis (1988: 423), which showed that cancer of the cervix, has a short doubling time ranging from three to five days. Prolonged treatment interruptions are said to impact negatively on the control of local disease.

Cystitis or bladder toxicity in the CDH study participants became symptomatic after 10 to 14 days of treatment. Symptoms included dysurea, urinary frequency and urgency. The results were presented as from week 2 up to week 5 as indicated in chapter 4. Cross tabulation results of acute cystitis versus HIV status did not show statistically significant differences between the two arms. Therefore, it could be postulated that the HIV +ve status did not contribute to increased levels of acute toxicity in the HIV +ve study participants for as long as they were on HAART when compared to their HIV -ve counterparts.

Skin reactions in the CDH study participants were usually confined to areas with skin folds and the perineum. Treatment to the pelvis may result in mild hyperpigmentation within the treatment fields, and moist desquamation in folds of abdominal skin, in the groin, and between the buttocks (natal cleft). Treatment to the perineum usually results in brisk
erythema ten to fourteen days after treatment was initiated, with moist desquamation shortly thereafter.

Acute skin toxicity in the CDH study participants was comparable to other studies, as illustrated later in this Chapter and in accordance with studies by Rose et al. (1999:1144), Pearce et al. (2002:966) and Keys et al. (1999:1154), as indicated in Table 5.1. Even with the high number of study participants with advanced disease requiring larger treatment fields and the use of anterior posterior fields, acute skin toxicity was not exaggerated in the CDH study participants. The theory that HIV +ve patients have increased sensitivity of the normal tissues to radiotherapy resulting in excessive acute normal tissue reactions (Formenti et al., 1995:411-12; Gichangi et al., 2006:408-9 & Kim et al., 2001:1496) was not borne out in the case of the HIV +ve study participants at CDH.

On the other hand, when comparisons of acute skin toxicity results for study participants treated on the linear accelerator and those treated on the Co-60 machine were made, chi-square tests for weeks two and three indicated a significant difference between the two groups. Furthermore, there was a higher percentage of acute toxicity among the HIV –ve study participants treated on the cobalt-60 machine in the first three weeks as compared to those treated on the Linac (figure 4.3). This was practical evidence confirming the fact that the point of maximum dose (dmax) for the Linac (6MV photons) is at 1.5cm below the skin surface while that of the Co-60 is at 0.5 cm, and the latter correlates with increased skin toxicity in patients receiving radiotherapy. However, at week four, the thresholds of acute toxicity were observed to have levelled at both treatment units (Figure 4.3).

Consistently higher percentages of toxicity in the HIV +ve study participants who were treated on the Co-60 machine as compared to those treated on the Linac (Figure 4.4). This was also further practical evidence demonstrating the superiority of Linac (6MV photons) over the Co-60 machines in terms of skin-sparing effects in patients receiving radiotherapy. The analysis of the results also showed that there were higher percentages of acute skin toxicity in the HIV –ve study participants in the first two weeks (Figure 4.5). This increased propensity to develop acute skin toxicity in the HIV –ve population earlier than the HIV +ve
study participants could probably be attributed to the old age factor (Langhorne et al., 2007:349).

The analysis of the results also indicated that the observations of acute skin toxicity were similar despite having slightly higher percentage levels in the HIV –ve study participants (Figure 4.6). This again was probably because most of the HIV –ve study participants were in the older age group category. Age is said to be one of the factors that have an impact on the severity of radio dermatitis (Langhorne et al., 2007:349).

However, it is important at this point to point out that almost all HIV +ve patients with cervical cancer at CDH are already on ART and if they are not, they are started on HAART because this is the CDH policy as well as that of the ministry of health in Zambia. Furthermore, it could be said that this might have had an effect on the side effect profile of the CDH study participants, as most of those discussed in the literature were not on HAART as compared to the CDH study participants. This also prompted the researcher to further look at the aspect of treatment tolerance and compliance of the study population compared to other published studies.

Conversely, data concerning radiotherapy of invasive cervical cancer in HIV +ve patients regarding tolerance of and compliance with chemoradiation is currently minimal. The acute toxicities of chemoradiation for cervical cancer generally have been reported in several phase II and III studies. Comparing the various studies is difficult because of the differences in the chemoradiation regimens and the total radiotherapy dose delivered as well as patients’ treatment with HAART.

Several studies have used chemotherapy schedules of 30mg/m\(^2\) to 40mg/m\(^2\) of Cisplatin weekly, which translates into a total dose of between 160mg/m\(^2\) to 240mg/m\(^2\). Most patients receive about four cycles due to toxicity. CDH uses 80mg/m\(^2\) of Cisplatin every three weeks, which adds up 240mg/m\(^2\) in total, but due to the recommended treatment duration (< 8 weeks) of cervical cancer, most patients receive a maximum of two cycles.
(160mg/m²). There is little in the literature about the dose of chemoradiation to use for the treatment of cervical cancer in the setting of HIV disease. However, the few most appropriate published studies from which a comparison could be made are discussed in the next few paragraphs.

A study by Tan et al. (2004:255), on 74 patients who received radical radiotherapy given concurrently with chemotherapy. The toxicity was recorded using the NCI CTC. The most common side effects were diarrhoea (80.6%), malaise (66.7%) and nausea (62.5%). Only three patients had grade 3 to 4 toxicity (one patient grade 3 thrombocytopenia, one patient grade 4 neutropenia and the third patient had grade 3 diarrhoea). Haematological toxicity was mainly anaemia, with 41.7% of the patients developing grades 1-2 toxicity. Only 70.2% of the patients completed the planned number of chemotherapy cycles, with a further 20.3% receiving at least three cycles. Most patients failed to complete the planned chemotherapy due to gastro-intestinal toxicity despite all the participants being HIV –ve.

A study by Serkies and Jassem (2004:814) recruited 112 HIV –ve patients with a median age of 48 years. These were treated with radiotherapy plus weekly Cisplatin at 40 mg/m². Overall, 74% of the patients received at least four Cisplatin cycles. The planned five Cisplatin cycles were given to only 45% of the patients. A full and timely Cisplatin dose was administered to 26% of the patients. The most common toxicities reported were gastro-intestinal and renal in nature.

The results of the CDH study showed that 80 study participants completed the prescribed radiotherapy treatment in less than eight weeks. The overall treatment duration was shorter than those in most trials. The number of chemotherapy cycles received by participants in both arms ranged between one and two. The planned two courses of Cisplatin were administered in 80 study participants. The remaining 30 study participants received a cycle of chemotherapy each (Table 4.6), and this was either due to the time factor between cycles as a result of participants waiting to recover, or due to treatment toxicity as indicated earlier in Table 4.7. The principal adverse effects in this study were leucopenia and
vomiting, as earlier indicated in Table 4.17. The results also showed that there was one grade 3 acute skin toxicity and one grade 4 anaemia. Grade 1 and 2 toxicity levels were mild and transient and resolved by appropriate medical treatment. These results showed that the study participants in both arms tolerated the radical chemoradiation well and their performance compares fairly well to the two study arms and to the published data.

Even though HIV +ve patients are thought to demonstrate an increased sensitivity of normal tissues to radiotherapy resulting in increased acute adverse effects, this was not observed in the CDH study. This absence of increased morbidity could be due to the relative immunocompetence of the participants, as indicated earlier in Chapter 4, as the HIV +ve study participants were on HAART and the age factor could also be contributing since most of the HIV +ve participants were younger.

5.4 ACUTE TOXICITY IN CDH STUDY PARTICIPANTS COMPARED TO OTHER PUBLISHED RESULTS OF RADICAL RADIOTHERAPY/CHEMORADIATION OF CERVICAL CANCER HIV +VE PATIENTS

There is a scarcity of data concerning radiotherapy of invasive cervical cancer in HIV +ve patients regarding tolerance, acute toxicity and compliance with chemoradiation. Preceding the onset of HIV, acute toxicity in patients on radical radiotherapy was attributed to technical factors. More recently, however, toxicity is attributed to impaired cellular immunity (Shrivastava et al., 2005:31-35) and criterion treatments for this set of patients have not been defined (Shrivastava et al., 2005:31-32). It has been documented that HIV +ve women with cervical cancer may be at increased risk of treatment complications. It is not yet clear if the therapeutic ratio for chemoradiation as in HIV –ve patients is maintained or altered in infected patients. HIV +ve cervical cancers are said to have poor response to radiotherapy and early recurrence, resulting in poorer overall survival (Maiman et al., 1993; 71:402-6, 1990; 38:377). The researcher has therefore concluded that due to lack of data,
the few most appropriate published studies from which a comparison could be made would be considered.

A study in Kenya by Gichangi et al., (2006: 405) prospectively studied the impact of HIV on acute morbidity and pelvic tumour control following radiotherapy for cervical cancer. Concurrent chemotherapy was not used in this study. Two hundred and eighteen patients, of whom 20% were HIV +ve, were evaluated. It was noted that HIV infection was associated with a seven-fold higher risk of multisystem toxicity: skin, gastro-intestinal and genito-urinary tract systems. HIV infection was independently and significantly associated with a six-fold higher risk of residual tumour post external beam radiotherapy. All study participants were not on HAART and did not receive brachytherapy, which is a very important component in the control of localised disease.

The results of the CDH study do, however, suggest that, as postulated in other studies, although HIV +ve patients are thought to demonstrate an increased sensitivity of normal tissues to radiotherapy resulting in increased acute toxicity, this was not observed in this study. There was less acute toxicity in the CDH study than in the study undertaken in Kenya, for example.

A study by Shrivastava et al. (2005:31) retrospectively studied 42 HIV +ve cervical cancer patients and evaluated toxicity as well as outcomes following treatment with radiotherapy. Thirty-two (76%) patients were planned for radical radiotherapy. However, the compliance was poor, with only 22 patients completing the prescribed radiotherapy, and only 50% of these achieved complete response. Grade 3 and 4 acute gastro-intestinal toxicity was seen in 14% of patients and grade 3 acute skin toxicity was seen in 27% of patients, leading to treatment delays.

The results of the study at CDH showed that participants complied with treatment, as all 110 participants completed the external beam radiotherapy. Eighty participants (41 in the HIV +ve arm and 39 HIV –ve arms) received two cycles of chemotherapy. The remaining
30 participants had one chemotherapy cycle each. The only delay in treatment was that between chemotherapy cycles due to leucopoenia and for 1 grade 3 and 1 grade 4 anaemia (table 4.17) cases that required blood transfusion and then continued with treatment.

A study by Msadabwe (2009: 39) at CMJAH prospectively studied 51 HIV +ve cervical patients and assessed the acute toxicity of combined modality treatment in these patients. This was a randomised study to compare radical concurrent chemoradiation against radiotherapy in treatment of cancer of the cervix in the HIV-infected patients. The principal grade 3 and 4 adverse effects in this trial were leucopoenia (four in the chemoradiation arm, one in the radiation-only arm) and cutaneous reactions (two in the chemoradiation arm, six in the radiation-only arm).

The CDH study produced toxicity levels comparable to those in the study by Msadabwe (2009:39), even though it had a small study population. However, the number of HIV +ve study participants in the CDH study (55) compares to that (51) in the study by Msadabwe (2009:39). The only difference between the two studies was that all the participants in the CDH study were on HAART (mean CD4 count of 437), as compared to six in the study by Msadabwe (2009:39). Moreover, there were more (eight) grade 3 and 4 skin reactions in the CMJAH study as compared to one grade 3 skin toxicity in the CDH study.

Furthermore, given the impact of chemoradiation therapy on the immune system, investigators have questioned if the superior toxicity observed in HIV +ve patients is related to the impact that HIV infection has on the immune system (Uronis & Bendell, 2007:531). Several studies have attempted to address this question by evaluating outcomes in the context of CD4 count (Hoffman et al., 1999:127; Place, Gregorcyk, & Huber, 2001:506). HIV +ve cervical cancer patients do not commonly show or produce indications for HIV infection; HIV infection is only acknowledged by routine screening. These patients usually have higher CD4 counts compared to patients with other AIDS-defining cancers (Maiman, 1998:46). In studies on anal cancer, Hoffman et al. (1999:127) and Place et al. (2001:506)
reported markedly increased morbidity if the pre-treatment CD4 count was less than 200/mm$^3$ following standard therapy. In a study by Msadabwe (2009:45, 48 & 54), it was established that during chemoradiation there was a significant drop in CD4 counts both in the chemoradiation group (from 321.06cells/mm$^3$ to 62.56cells/mm$^3$) and the radiation-only arm (from 248.09cells/mm$^3$ to 68.17cells/mm$^3$). The magnitude of the drop was similar in both arms. Thus, moderate and severe toxicities were comparable in both arms except for leucopenia, which was more frequent in the chemoradiation arm. At three months the mean CD4 counts increased in both groups, yet pre-treatment levels were not regained.

In immunocompetent patients receiving combination chemotherapy, CD8 cells, B cells and natural killer cells all decline but recover within three months of completing chemotherapy; nonetheless, the recovery of CD4 cells is protracted (Mackall, 2000:10, 13-14 ). The CD4 count is only one-third of the pre-treatment level at three months after completing treatment, and may not have recovered to pre-treatment levels after one year (Powles et al., 2002:532). Since HIV infection affects immune function primarily by infection and destruction of CD4 cells, there is concern that prolonged CD4 suppression by chemotherapy may have a major adverse influence on the course of HIV disease (Powles, Imami, Nelson, Gazzard & Bower, 2002:531-2). In the CDH study, we did not check serial CD4 counts, as our objective was to compare toxicities. However, in subsequent studies this parameter will be checked in order to attempt to correlate it with the study findings.

Studies on HIV +ve patients receiving combination chemotherapy and HAART report that the CD4 T-Lymphocyte count falls by approximately 50% but recovers rapidly within one month after treatment and reflects a global fall in T cells, as the percentage of CD4 T cells remains unchanged throughout (Powles et al., 2002:531). Studies in HIV +ve patients have shown that without HAART the viral load increases during chemotherapy (Little, Pearson, Gutierrez, Steinberg, Yarchoan, Wilson, & Dose, 2000:A11). With the concomitant use of chemotherapy and HAART, there is no increase of viral load during chemotherapy (Powles et al., 2002:531). This might explain the reduced incidence of acute toxicities in the CDH HIV +ve study participants on chemoradiation.
In the CDH study the median treatment time for the HIV +ve study participants was 37 days, while that of their HIV -ve counterparts was 38 days in the CDH study. In this study no acute toxicity in the HIV positive group was observed that required treatment interruption. This is an important observation and could be attributed to the fact that all the HIV +ve participants were on HAART. This endpoint was very important and highly relevant for this study as there were no treatment interruptions and undue delays in the HIV +ve participants as a result of exaggerated toxicity. According to the American Brachytherapy Society’s recommendations for the treatment of cervical cancer, the total treatment time should be less than eight weeks because treatment prolongation can adversely affect local control and survival (Nag, Erickson, Thomadsen, Orton, Demanes & Petereit, 2000:202). The median treatment duration in the study by Rose et al. (1999) was 63 days; in the study by Keys et al. (1999), it was 50 days and in the NCIC CTC study it was 48 days. Significant loco-regional failure due to treatment prolongation is often seen if the treatment period is beyond 50 days (Nag et al. 2000:201-2; Lanciano, Pajak, Martz & Harris, 1993:391; Petereit, Sarkaria, Chappell, Flowee, Hartmann & Kinsella, 1995:1301; Perez, Grisby & Castro-Vita, 1995:1275). Treatment prolongation contributes to loss of loco-regional control by allowing clonogenic repopulation (Petereit et al., 1995:1301-7).

Cisplatin-based concomitant chemoradiation is the standard therapy for treatment of locally advanced cervical cancer. The CDH study participants received 80mg/m² of Cisplatin every three weeks, starting with the first day of radiation therapy. In this CDH study, 73% (80) of patients received the planned two cycles of chemotherapy, with only 27% (30) of patients receiving one cycle of chemotherapy. This result was related to treatment toxicity. This, however, may be significant, as there is some evidence that the benefit from chemoradiation is apparent as long as patients receive adequate cycles of chemotherapy concomitant with radiotherapy (Peters et al., 2000:1606).

In the GOG 120 study (Rose et al., 1999:1144), 93% of patients received at least four cycles of chemotherapy, with 49% receiving the full six cycles of chemotherapy. Likewise, in the second GOG study (Keys et al., 1999:1154), 90% of patients who underwent preoperative radiation received four or more courses of Cisplatin. In the NCIC CTG study
(Pearcy et al., 2002:966), 865 of patients assigned to concurrent weekly Cisplatin received more than 90% of the recommended dose (five cycles), and toxicity accompanying radiation combined with weekly Cisplatin precluded the delivery of planned radiation in only 6% of patients.

In a prospective study that assessed the eligibility for chemoradiation in patients presenting with cervical cancer in the developing world, it was noted that the HIV +ve patients were more likely to have multiple factors such as dehydration, weight loss, other infections and malnutrition, preventing safe administration of Cisplatin-based chemotherapy (McArdle & Kigula-Mugambe, 2007:94-6).

Despite the fact that toxicity rates were similar in the HIV +ve and HIV -ve study participants at CDH, more follow-up is required to assess survival functions and local control. Also important to note is the fact that it was not easy to assess acute toxicity at six weeks post-treatment of the study participants, owing to the large time gap between last fractions of chemoradiation and first follow-up dates for study participants at CDH (about three to four months). It is also cardinal to note that HIV infection is associated with higher pelvic failure rates (Maiman et al., 1990; 1993) and one proposition is that HIV infection may modify cervical cancer cell kinetics, resulting in a more radio-resistant tumour. Another deduction is that HIV is associated with anaemia (Sullivan, Hanson, Chu, Jones & Ward, 1998:301). Therefore, chronic and transient hypoxia makes tumours radio-resistant, and this is an adverse prognostic factor for both local control and survival outcome.

5.5 SUMMARY

This chapter has discussed the principal findings of this research with reference to what is known in the literature about this subject matter. The chapter has also looked at treatment tolerance and compliance of the study population compared to other published studies. Furthermore, a few most appropriate published studies from which a comparison could be
made regarding acute toxicity of radical radiotherapy/chemoradiation of cervical cancer HIV positive patients and CDH study participants’ results, were considered.
CHAPTER 6

CONCLUSION

6.1 INTRODUCTION

This chapter presents the conclusions based on the results in Chapter 4 and the discussion presented in Chapter 5. It also highlights the study’s limitations and provides recommendations for both future research and departmental practice.

6.2 STUDY LIMITATIONS

- 120 was a small sample size. These findings need to be replicated in more far-reaching studies.

- The non-availability of serial CD4 counts affected the interpretation of some of the results of this study: e.g. the gap between last date of base-line CD4 count and the actual date of starting chemoradiation was not assessed. Assessment of CD4 count midway in chemoradiation therapy was also not done, despite knowing the fact that there is a risk of CD4 count dropping in this population of patients.

- The time gap between the last chemoradiation treatment and first review (follow-up) was long due to logistical problems. Hence, there was delay in the assessment of acute toxicity in study participants at six weeks post-treatment.

- The CDH protocol in terms of performance status and radical chemoradiation is to include patients with ECOG 1 & 2. However, during this study period, most of the patients that presented to CDH for treatment were graded as ECOG 1 by the Clinical oncologists. This meant that there were no ECOG 2 patients to include in the study.
6.3 CONCLUSIONS

This study has demonstrated that radical chemoradiation is well tolerated by HIV +ve patients with intact immunity. Toxicity was usually mild and reversible and no exaggerated toxicities beyond those generally associated with single-agent Cisplatin were observed. The major acute toxicity in this study was leucopenia, followed by vomiting. Leucopenia was the only toxicity which was significantly higher in both arms. Therefore, radical chemoradiation in conventional doses can safely be given to cervical cancer HIV +ve patients who are on HAART.

More than half of the study participants in the CDH study (73% in total) received the prescribed two cycles of Cisplatin. 27% of the study participants had one cycle of Cisplatin.

In general, the same ethics that guide the oncological management of immunocompetent patients should be applied to HIV +ve patients. These conclusions are based on a somewhat small patient population and short follow-up period. The results therefore need to be replicated in more meticulous far-reaching studies, because this will assist in putting forward appropriate treatment strategies for invasive cervical carcinoma in HIV +ve patients for as long as they are on HAART. This approach is fundamental, since HIV +ve patients are likely to swell in number at the same time as the HIV pandemic continues to grow and life expectancy increases owing to antiretroviral therapy.

6.4 RECOMMENDATIONS

6.4.1 Recommendations to the Institution:

- Since the results demonstrated no significant difference between HIV –ve and HIV +ve patients in terms of toxicity, CDH needs to undertake larger studies in order to enhance the management of HIV +ve patients.

- Better records management – the CTC form should be made part of the patient record system, as this will enable comprehensive capture and documentation of
data. This can be used for retrospective studies as well as decision-making by the hospital management.

- Treatment follow-up must be improved: the shortage of clinical oncologists is the biggest challenge. For this reason, CDH should start considering the possibility of role extension for oncology nurses, who can start assessing acute toxicity following patient treatment. Radiation Therapist Extended Scope of Practice – e.g. a Patient Review Specialist to deliver patient education, review, counseling and follow-up for the healthier patients – also needs to be seriously considered. These initiatives may reduce patient waiting times, reduce medical burden, increase patient satisfaction and improve clinical outcomes. This will ensure that those patients with acute toxicity who are in need of immediate attention are attended to in good time.

6.4.2 Recommendations for Research:

- Look at toxicity for CRT in patients with CD4 count less than 200/mm$^3$ as per protocol (patients with moderate immune impairment: CD4 count 50 to 200). HIV +ve vulva carcinoma patients are treated with CRT in spite of CD4 count and if these can tolerate treatment, the same could be thought to apply to cervical carcinoma patients.

- Retrospective study of acute toxicity in cervical carcinoma HIV +ve versus HIV –ve CDH patients once data collection is improved. This will allow an extension of data analysis to more patients in order to establish if the findings in terms of acute toxicity between the HIV +ve and HIV –ve will be consistent at CDH.

- There is a need to establish the effect of radical chemoradiation on the immune system of an HIV-infected patient with cervical carcinoma. This can be done by monitoring the levels of CD4 cell count before and after therapy and also on three-month follow-up.
Future research must ensure classification of participants into the type of megavoltage unit used (energy) and the radiotherapy field arrangement (AP/PA vs 4 fields) and document the impact of such in the toxicities experienced.

The optimal chemotherapy dose for Zambian patients has not yet been clearly established and there is need for dose escalation studies to be performed in Zambia to determine this. At CDH, concomitant Cisplatin 80mg/m$^2$ weekly (D1, D22 & D43) given with radiation is used based on the CMJAH protocol for patients undergoing radical radiotherapy for carcinoma of the cervix. This is an adopted protocol which needs to be domesticated to the Zambian environment. This is required in order to determine whether Cisplatin doses of 80mg /m$^2$ are as effective as the standard 100mg /m$^2$ doses.

6.5 SUMMARY

This chapter presented the study design limitations, conclusions and the recommendations.
REFERENCES


CDH – see Cancer Diseases Hospital.


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APPENDIX 2

DATA COLLECTION FORM FOR ACUTE TOXICITY IN CERVICAL CANCER HIV +VE (ON HAART) AND NEGATIVE PATIENTS ON RADICAL RADIOTHERAPY AT CDH, LUSAKA, ZAMBIA

CDH No:………………………………   Diagnosis: …….
Stage:…………………………………HIV status:   Negative  Positive
Age:……………………………………
Marital Status:…………………………
Occupation:…………………………..
Performance status:…………………
Treatment unit:……………………….
EBRT Radiation Dose and Fractionation:…………………………
Brachytherapy Dose and fractionation: ……………………………
Chemotherapy Given ………………………………………………….
Type of HAART and combination:……………………………………

Grades: 0  1  2  3  4 (GRADES OF TOXICITY)

1.0 SKIN

1.1 Radiation dermatitis

Week 1  week 2  week 3  week 4  week 5  week 6

(0) None   ( )   ( )   ( )   ( )   ( )   ( )

(1) Faint Erythema

(2) Patchy moist desquamation

(3) Confluent moist desquamation

(4) Skin necrosis
2.0 GASTRO-INTESTINAL (GIT)

2.1 Diarrhoea

(0) None
(1) Increase of <4 stools/ day
(2) Increase of 4-6 stools/ day
(3) Increase of >6 stools/day
(4) Haemodynamic collapse

2.2 Nausea

(0) None
(1) Able to eat
(2) Oral intake significantly reduced
(3) No IV fluids required

2.3 Vomiting

(0) None
(1) 1 episode in 24 hrs
(2) 2-5 episodes in 24 hrs
(3) More than 5 episodes in 24 hrs
(4) Intensive Haemodynamic collapse

2.4 Proctitis

(0) None
3. Mild rectal discomfort
(2) Severe rectal discomfort
(3) Rectal bleeding requiring transfusion
(4) Life-threatening complication

3.0 GENITO-URINARY (GUT)

3.1 Cystitis

(0) None
(1) Mild symptoms
(2) Symptoms relieved with therapy
(3) Unrelieved symptoms

4.0 HAEMAPOETIC

4.1 Haemoglobin

(0) 12.1-16.3g/dL
(1) <12.1-10g/dL
(2) 8-<10g/dL
(3) 6.5-<8g/dL
(4) <6.5gd/dL

4.2 White blood cell count (WBC)

(0) 3.92-9.88 x 10⁹/L
(1) <3.92-3 x 10⁹/L
(2) >2-<3 x 10⁹/L
(3) >1-<2 x 10⁹/L
(4) <1 x 10⁹/L

4.3 Platelets

(0)
(0) 178-400 x 10⁹/L
(1) <178-75 x 10⁹/L
(2) >50-<75 x 10⁹/L
(3) >10-<50 x 10⁹/L
(4) <10 x 10⁹/L
APPENDIX 3

PATIENT INFORMATION SHEET

ACUTE TOXICITY IN CERVICAL CANCER HIV +VE (ON HAART) vs. HIV -VE PATIENTS TREATED BY RADICAL CHEMORADIATION IN ZAMBIA

REQUEST FOR CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Dear Research Participant,

My name is Munkupa Harry, currently enrolled in a Master’s Degree in Technology: Radiography programme at the University of Johannesburg. As part of the degree requirements, I am expected to conduct a research project as fulfillment for the programme. The title of my research is “Acute Toxicity in Cervical Cancer HIV +ve Vs HIV -ve patients treated by Radical Chemoradiation in Zambia”.

The aim of the study is to evaluate acute toxicity of radical combination therapy in the form of radiotherapy and chemotherapy in HIV (on HAART) and HIV -ve patients for cervical cancer at Cancer Diseases Hospital, Lusaka, Zambia. The objective is to make suitable recommendations based on the findings of the study with regard to future management of HIV +ve patients (on HAART).

I am kindly requesting for your participation in the above-named study. Your confidentiality will be protected as you will be recruited and assigned study numbers for identification. You will receive Cisplatin-based radical chemoradiation for six weeks during which time you will be assessed for acute reactions. The study involves monitoring and evaluation of acute side effects of the radiation and chemotherapy treatment that you shall receive.
The information that will be obtained from this study will be used to improve on health service delivery. Please seek clarification where you do not understand. If you are not interested in participating in this study you are free to do so. Even after you have joined the study, you are free to withdraw as you wish, and that will not affect your health services at this institution. Whatever information you provide will be kept strictly confidential and will not be shown to other people.

You may choose not to provide every detail if you desire, and you may withdraw from the study at any time. Whatever you decide, your care will not be affected in any way. Any questions you have are welcome and will be answered at any point during the study.

There is no risk to you. The benefit involved in this study includes providing health care professionals with valuable information related to meeting the needs of clients. This information will be helpful by providing guidance with regard to future management of patients and will assist health care professionals in providing effective therapy to patients.

In case of any further clarification, you can contact the researcher, Munkupa Harry, telephone number 0965278555 or email to hmunkupa@yahoo.com or the Executive Director of CDH, Dr Lishimpi K, e-mail: kcmlishimpi@yahoo.co.uk or the programme coordinator, Sibusiso Mdletshe at sibusisom@uj.ac.za, or the Secretariat at unzarec@zamtel.zm

Should you have any doubts about this research, or on your rights, a summary of the results will be sent to you upon request.

Thank you for your participation.

Harry Munkupa
(Therapy- Radiography Student)
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APPENDIX 4

CONSENT FORM

ACUTE TOXICITY IN CERVICAL CANCER HIV +VE (ON HAART) vs HIV -VE PATIENTS TREATED BY RADICAL CHEMORADIATION IN ZAMBIA

I have read the request for consent to participate in the study or it has been read to and explained to me. I have asked questions about the nature of the study and what will be expected of me as well as done to me during the study period. I have also expressed my anxieties/fears and all have been answered and allayed to my satisfaction. I understand that I am at liberty to withdraw from the study at any time and that, whatever I decide, the patient care or management given to me will in no way be affected.

I consent to take part in this study.

Participant
Signature…………………………………..Date…     Thumb Print …………………………..
Cell number……..
E-mail………………

Witness
Signature…………………………………..Date….. Thumb Print …………………………
Cell number………..
E-mail………………

Researcher
Signature…………………………………..Date….. Thumb Print …………………………
Cell number………..
E-mail………………
03rd November 2009
Mrs. Heather Lawrence
University of Johannesburg
Faculty of Health Sciences
Therapy Radiography
Johannesburg

Dear Madam,

RE: PERMISSION TO CONDUCT RESEARCH AT CANCER DISEASES HOSPITAL ZAMBIA.
Permission has been granted for Mr. Harry Munkupa to undertake a research at our Hospital for the fulfillment of a Masters Degree (M.Tech Radiotherapy) with the University of Johannesburg. The title of the research being: Acute Toxicity in Cervical Cancer HIV Positive Vs HIV Negative Patients Treated by Radical Chemoradiation in Zambia.

Mr. Munkupa has been granted access to Cancer Patient's files (with Cervical Cancer stage IB2-IIIB) and clinical notes to assist him with research. These patients are counseled and tested for HIV routinely.

Yours Faithfully,

Dr. Catherine Mwaba
Head Clinical Care &
Clinical Oncologist

Dr. Kennedy Lishimpi
Executive Director &
Clinical Oncologist