The HIV profile of patients with Invasive Cervical Cancer at Harare's Central Hospitals by:

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Abstract

A cross sectional, descriptive study of Invasive Cervical Cancer(ICC) patients managed at Harare's 2 central hospitals. The association of HIV with ICC has been investigated by several studies, however there is no published local data on patients with both disease entities. This study aimed to produce data that would provide a better understanding of the magnitude of the problem of ICC and HIV currently, in order to inform policy and identify further research potential. One hundred and ten women were recruited between February and December of 2013 and data was obtained using a standard questionnaire by participant interview and extracted from treatment records. The main findings were that 41.8% of the participants were HIV seropositive. The HIV positive patients were significantly younger than the HIV negative patients, with a mean age of 42.7, s.d= 8.0 years versus mean age of 53.0 years, s.d=12.7 years($p<0.001$). Of the HIV positive participants 35(76.1%) were on HAART. The majority(63%) of HIV positive participants had CD4 cell counts greater than 350 cells/ul. HIV positive patients were more likely to have advanced disease, that is FIGO stage 2b or greater O.R 1.23(C.I 0.41-3.68). This study found a large proportion of ICC patients to be HIV positive. The majority of HIV positive participants with ICC were also accessing HAART implying a possible missed opportunity for screening. Therefore provision for screening may be considered within the setting of opportunistic infections clinics.

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Last and by no means least, I thank God who makes all things possible.

I dedicate this thesis to my son Sean, who daily gives me a reason to smile even when academia is weighing heavily on my shoulders.

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Abbreviations,

HIV	Human Immunodeficiency syndrome
ICC	Invasive cervical cancer
PMTCT	Prevention of mother to child transmission
HAART	Highly active antiretroviral therapy
HPV	Human papilloma virus
FIGO	International Federation of Obstetrics and Gynaecology
CDC	Centre for disease control
CIN	Cervical intraepithelial neoplasia
OR	Odds ratio
CI	Confidence infections
ZDHS	Zimbabwe Demographic Health Surve

Chapter 1

1.1: Introduction

Invasive cervical cancer(ICC) is a major cause of cancer death in women worldwide with approximately 300 000 women dying of ICC annually(World Health Organisation 2006).This would be equivalent to the death of the entire population of San Salvadore, the capital of El Savador(United Nations 2014).

The incidence varies from 4-6/100 000 in the developed world to 20-60/100 000 in developing countries. This large difference is attributable mainly to effective, large scale screening programs as well as availability of effective treatment of pre-invasive lesions detected, which have resulted in the significant reduction in incidence, compared to that still found in developing countries where screening is not available on a large scale(World Health Organisation 2006). With 528 000 new cases every year it is the fourth most common cause of cancer death (266 000 deaths in 2012) in women worldwide. ICC however still remains the most common cancer among women in low resource settings, mainly due to unavailability of screening and treatment for pre-invasive disease. Almost 70% of the global burden falls in developing countries such as Zimbabwe(World Health Organisation 2013)

According to The Zimbabwe Cancer Registry data for 2011, 34.8%(1 in every 3) of cancers diagnosed in women were ICC. It was overall the most commonly diagnosed cancer among all women(Zimbabwe Cancer Registry 2009; E. Chokunonga and Makunike-Mutasa 2014). Among Zimbabwean women, the majority (80%) of women present with advanced disease implying a poor prognosis even with optimal treatment(Chirenje, Rusakaniko et al. 2000)

The burden of Human immunodeficiency virus(HIV) in Zimbabwe remains high in spite of reported decrease in prevalence from an estimate of 24% in 1997 to 13.1% in 2011(ZIMSAT and ICF International 2012). This decline is a result of behavioral change, largely due to the good level of education which improves the effectiveness of prevention programmes(Bateman 2011; Halperin, Mugurungi et al. 2011). Good coverage of Prevention of mother to child transmission(PMTCT) may have also contributed to this decline.Women aged 15-49 years account for a consistent 57-58% (512 852-703 845) of people living with HIV(UNAIDS 2012). Highly active antiretroviral therapy (HAART) availability since 2004 has since given rise to a population of chronically infected HIV individuals with improved life expectancy, a subgroup of patients who may have unique health needs(Palefsky 2009). Human papilloma virus(HPV) is the main aetiological agent in ICC(Bosch, Lorincz et al. 2002; Munoz, Castellsague et al. 2006) and there are known similarities between HPV and HIV infection which will be elaborated in the literature review.

Previous research in the African context of high HIV prevalence has varied in terms of the seroprevalence of HIV in ICC patients. Reporting figures as low as 2% to as high as 42% (Nel CPG 2006; Lomalisa P 2007; Abdus-Salam, Ogunnorin et al. 2008; Adjorlolo-Johnson, Unger et al. 2010). The varying data and lack of local data limit the strength of prevention and treatment programmes which may strategically address both disease entities.

This study sought to address this problem by determining the proportion of ICC patients who are also HIV positive, and gives a description of their CD4 cell counts and HAART status, in addition to demographic data, risk factor profiles, clinical staging and histological findings

1.2: **Background**

ICC has several known risk factors including early sexual debut, multiparity, multiple sexual partners all of which are linked to HPV infection(Bosch, Lorincz et al. 2002). Oncogenic serotypes of HPV have been identified which include 16 and 18(found in 70% of cervical cancer specimens) but also 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 and 79 on the basis of pooled data(Munoz, Bosch et al. 2003). Locally multiple serotypes have been identified in HIV positive women, with cellular changes typical of HPV(koilocytosis) being found in 6.4% of HIV positive subjects compared to 1.7% in HIV negative patients(Chirenje, Loeb et al. 2002).

This study is set against a background of high cervical cancer prevalence as compared to that in Eastern Africa or the overall prevalence rate world wide as shown in Table 1. Table 2 shows the estimated age standardized rates of ICC per year.

Table 1.Cervical cancer statistical comparison (adapted from WHO/ICO Information Centre on HPV and Cervical cancer (HPV Information Centre) Human Papillomavirus and Related Cancers in Zimbabwe. Summary Report 2010.)

Indicator	Zimbabwe	Eastern Africa	World
Crude incidence rate	28.8	20.1	15.8
Age standardized incidence rate	47.4	34.5	15.3
Cumulative risk(%) 0-74yrs	5.3	3.8	1.6
New Cancer Cases	1 855	31 516	529 828

Standardized rates have been estimated using the direct method and the World population as the reference.

Table 2: Estimated age standardised rate of ICC

Cancer Registry	Period	N cases	Crude Rate	ASR

Harare	1998- 2002	818	18.8	47.3

ASR: Age-standardized rate. Standardized rates have been estimated using the direct method and the World population as the reference.

1. Accumulated number of cases during the period
2. Rates per 100,000 women per year.

Cervical cancer is undeniably a cause for concern internationally, it being the second most common malignancy diagnosed in women after cancer of the breast(World Health Organisation 2013). It is even more of a concern in Zimbabwe where it is the most diagnosed cancer among women at an incidence of 28.8/100 000 women followed by Kaposi Sarcoma(17.6/100 000) and breast carcinoma(9.9/100 000)(S. de Sanjosé 2012)

ICC appears to be increasing in significance in Zimbabwe. In 2005 28.9% of women diagnosed of cancer had ICC. Then in 2011, 6 years later, 34.8% of cancers diagnosed in women were ICC. It is diagnosed more frequently than breast cancer and Kaposi's sarcoma in this population. This data is illustrated in the Figure 1 and 2 below.

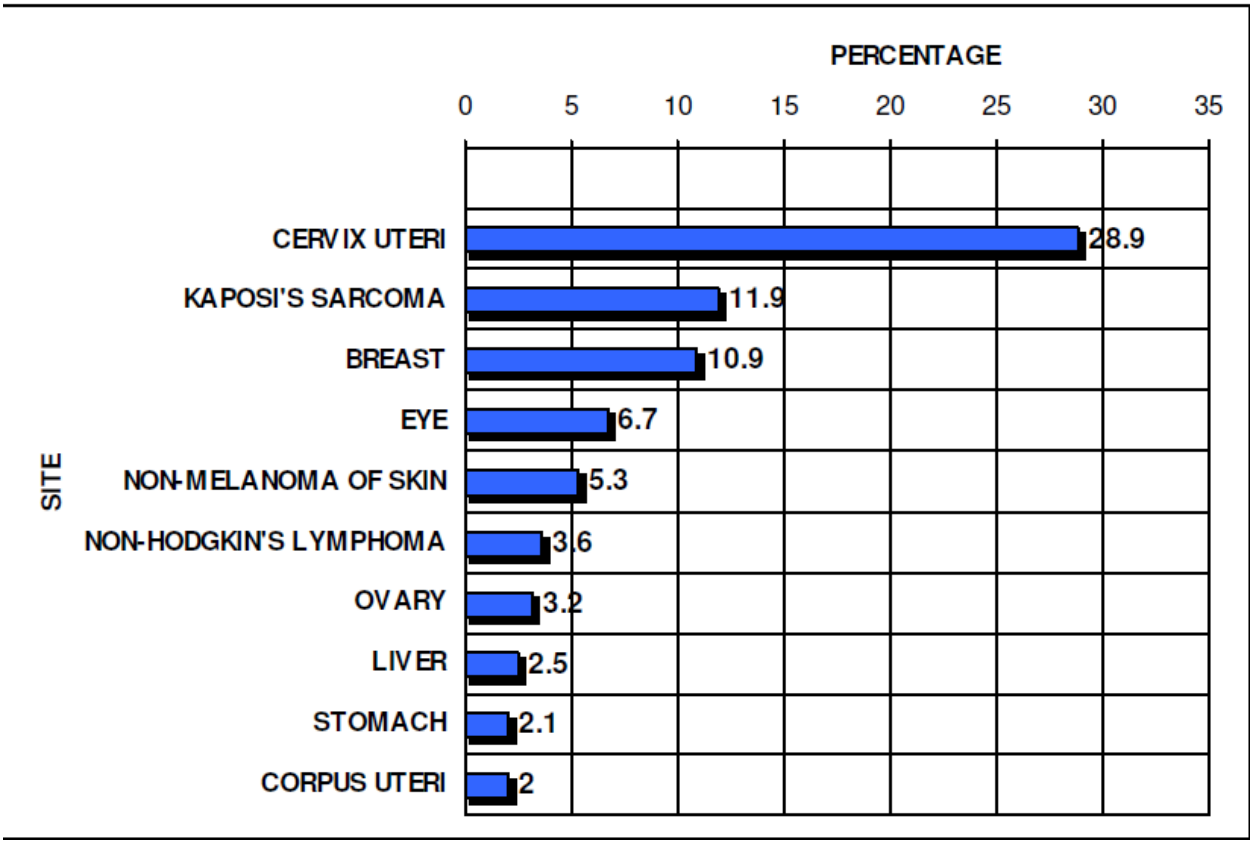

Figure 1: Zimbabwe Cancer Registry 2005 data on cancers diagnosed in all women

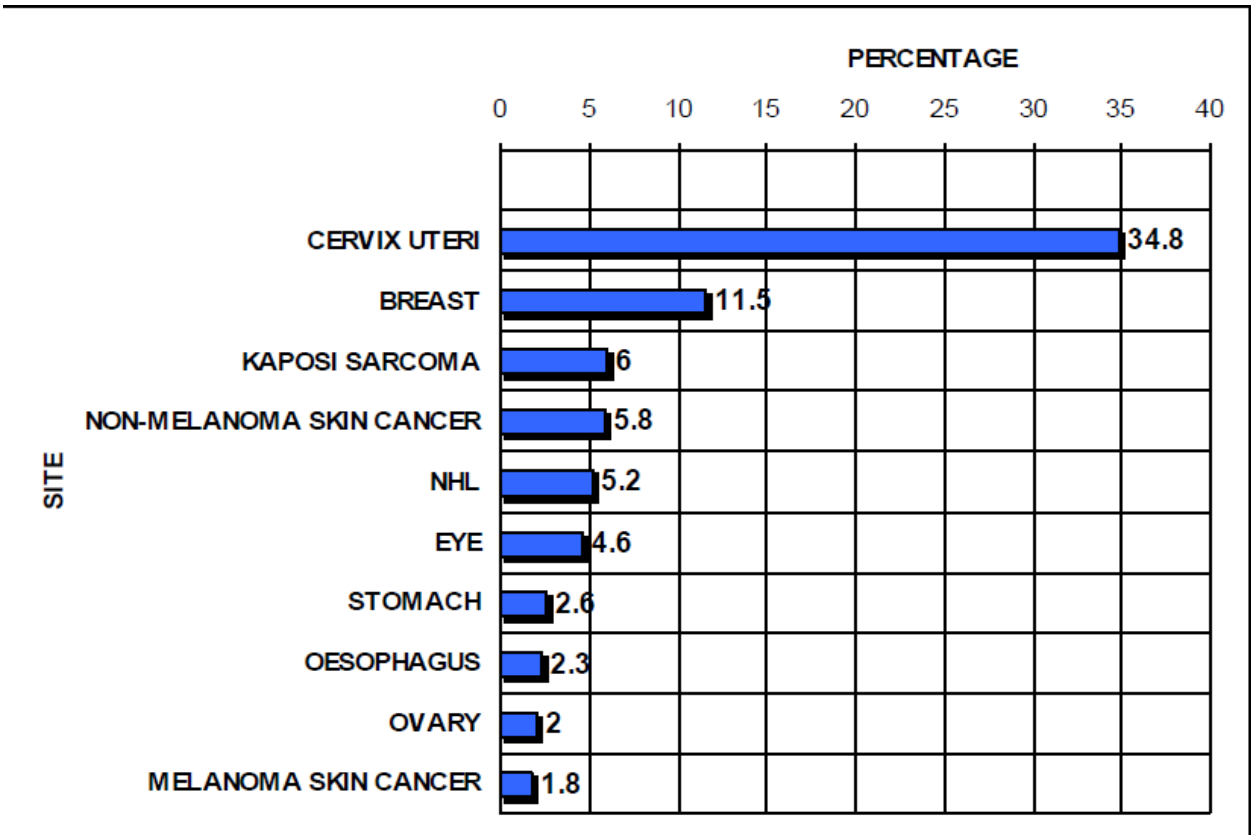

Figure 2: Zimbabwe Cancer Registry 2011 data on cancers diagnosed in all women

HIV in Zimbabwe is a major public health problem with 83 000 HIV related deaths estimated for the country by UNAIDS who also reported a prevalence of 14.3%. An estimated 620 000 women (15yrs and up) are living with HIV out of an estimated 6 million total female population. This accounts for 57% of people living with HIV in the country(UNAIDS 2012)

The prevalence of HIV in Zimbabwe as reported by the Demographic health survey 2010- 2011 was 18% in women between the ages of 15- 49 years of age. This was significantly higher than men in the same age group who had a prevalence of 12%(ZIMSAT and ICF International 2012).

In 1993, the Centre for disease control(CDC) classified moderate and severe cervical intraepithelial neoplasia characterising early HIV infection. ICC was classified as AIDS –

defining disease along with Kaposi sarcoma and non-Hodgkin lymphoma(1993). The expected increase in women diagnosed with ICC during the HIV pandemic has not been consistently observed, most likely due to at risk women dying from opportunistic infections prior to development of ICC or CIN disease. With the advent of HAART women with HIV are living longer and chances of persistent HPV developing into CIN and ICC are now higher(Adler)

The setting of high prevalence of both HIV and ICC necessitate a better understanding of local trends in order to anticipate the health needs of patients with both conditions.

Literature Review

Several studies have aimed at assessing the relationship between ICC and HIV infection. The suspicion of an association was made in the late 1980's when a case series was published describing HIV positive ICC patients. The group of patients included a 16 year old girl with stage 111b disease. The other patients described were younger than expected and also had advanced disease(Maiman, Fruchter et al. 1990).

It is thought that impairment of cell mediated immunity in particular CD4 T- cells caused by HIV infection would result in persistence of oncogenic HPV infection as well as disease recurrence, resulting in higher probability of progression to ICC. This inference is based on the host immunological response to HPV infection(Stanley and Sterling) However, in a cohort study of high risk women who were tested for HPV strains initially then subsequently tested for HIV. The patients who acquired HIV were 4.9 times [95% confidence interval = 1.2-19.7] more likely to have high risk HPV serotypes at the initial visit. Implying that high risk HPV increases the risk of HIV infection.(Veldhuijzen, Vyankandondera et al. 2010) A case control study also evaluating whether HPV infection is independently associated with heterosexual acquisition of

HIV in a cohort of high risk Zimbabwean women found that women with HPV were 2.4 times more likely to acquire HIV than HPV negative controls. This study did not report a difference between high or low risk HPV serotypes in the cases(Averbach, Gravitt et al.). This implies that the relationship is more complex and may be in either direction.

The strong association of HIV infection with that of HPV has been demonstrated in several studies including one in Kenya where, prevalence of all 15 of the high-risk HPV types measured was higher among HIV seropositive patients, between 1.4 and 5.5 fold. Median total HPV viral load was 881 copies/cell in HIV-infected women (IQR = 33-12,110 copies/cell) and 48 copies/cell (IQR = 6-756 copies/cell; $P < 0.001$)in HIV negative patients(Luchters, Vanden Broeck et al. 2010). Another study in South Africa to assess cervical ICC with HIV infection in subjects at a Bloemfontein hospital showed that in the age range 30-34 yrs HIV prevalence was 41.9 % in ICC compared with 23.3% prevalence in the general population, implying a positive association. Higher prevalence was also demonstrated in all other age groups. However with smaller margins, in the older the age groups(Nel CPG 2006).

A 10 year follow up of women with or at risk of HIV, showed that for women between 15 and 49 years, HIV infection was associated with a staggering 13 times risk of developing ICC as compared to the general population(Serraino, Carrieri et al. 1999). Another study carried out in New York to determine if ICC is an AIDS defining illness, found that in women, ICC was the commonest malignancy in severe immunosuppressant (CD4 <200 cell/ml), found in 55% of patients. It was found to be more common than lymphoma (29%) and Kaposi sarcoma (16%). In this study, women with ICC had a mean CD4 cell count of 312 cells/ul(Maiman, Fruchter et al. 1997).

Women with HIV, diagnosed with ICC, appear to have a greater level of immunosuppression than HIV positive patient without ICC(Leitao, White et al. 2008).

In Kenya where there is high prevalence of both HIV and cervical cancer. HIV prevalence among women was 16% similar to our local 17.9% as of 2006. Women <35 years old diagnosed with ICC, were 2.6 times more likely to be HIV positive than controls. HIV positive patients were also noted to be 10 years younger than controls at presentation, having a mean age of 40, compared to 50 years ($p< 0.001$). Most patients presented with advanced disease (FIGO Stage >2b), 80% seropositive patients and 77% of seronegative patients. The odds of having a poorly differentiated tumour was three times higher for seropositive patients implying poorer prognosis(Gichangi, Bwayo et al. 2003).

On the other hand many investigators have found no relationship between HIV and ICC, noting no corresponding increase in incidence of ICC accompanying the increasing HIV incidence.

A South African study published in 2000 found no statistically significant relationship between HIV infection and ICC, They reported that with CD4 counts greater than 200cell/ul there is no difference in disease severity. However the same study reported that with CD4 cell counts of <200cell/ul patients presented with more severe disease. A significantly younger age at presentation, mean 44 years in HIV seropositive patients as opposed to 53 years in HIV negative patients was reported(Lomalisa P 2007).

No local study has been aimed at determining the proportion of ICC patients who are HIV positive that is whether requiring radiotherapy or not. However, in a 2002 study carried out, for the purpose of investigating the effect of HIV co-infection on HPV genotype distribution in a rural Zimbabwean community, HIV was associated with higher prevalence of HPV infection.

Fifty four percent in HIV seropositive women as compared to 27% in HIV seronegative women. The conclusion however was that high risk HPV serotypes as opposed to HIV infection were associated with cervical neoplasia by multiple regression analysis(Baay, Kjetland et al. 2004).

At Harare family planning clinics a study was carried out to investigate the association between cervical squamous intra epithelial lesions and HIV 1 infection. This was a cross sectional study comparing a group of HIV seropositive women with a control group of HIV seronegative women.

Cervical smears were done then examined cytologically. Abnormal cytology was found in 25.6% versus 6.7% of HIV seropositive versus HIV seronegative participants respectively. Overall HIV seropositive women had twice the risk of abnormal cytology compared to HIV negative women(Chirenje, Loeb et al. 2002).

No local study has directly set out to assess the proportion of ICC patients who are also HIV seropositive. However in a thesis which remains unpublished titled *"An evaluation of acute toxicity, quality of life and therapeutic effects of external beam therapy to cervical cancer patients with and without HIV"* an HIV seroprevalence of 29.6% was reported. HIV seropositive patients were 16.5 years younger than HIV seronegative patients. There was no statistically significant difference in histological subtypes among HIV seropositive and HIV seronegative patients(Kombe 2003).

In another thesis carried out retrospectively at the radiotherapy department at Parirenyatwa Hospital in the period, 2007-2008. The prevalence of HIV infection among the patients managed at the centre was 43.5% but of these only 45.6% had CD4 count results recorded in the notes so no analysis on CD4 counts was(Tsikai 2009).

It is however important to note that these studies were carried out in the radiotherapy department including only patients requiring external beam radiotherapy and therefore excluded patients

with early stage disease, curable surgically and also those diagnosed and referred to radiotherapy but who refuse radiotherapy for variable reasons including financial and personal reasons.

This literature is grounds to generate local data on HIV and ICC in order to plan interventions which are evidence based and specific to our setting.

Chapter 2

Research Methodology

2.1Justification

Cervical cancer is the most common cancer morbidity and mortality among women in Zimbabwe. The implication of HIV infection as an important variable affecting disease progression, severity as well as response to treatment in several studies necessitates the need for local data to guide policy and justify proposed interventions.

2.2: Research Question

What proportion of newly diagnosed invasive cervical cancer patients at Harare's central Hospitals are HIV positive and what is their stage at presentation, age at presentation as well as level of differentiation of their tumours?

2.3: Primary Objectives

- To determine proportion of newly diagnosed women with ICC who are HIV positive.
- To describe the demographics of patients diagnosed with ICC at Harare's Central Hospitals.

- To describe the level of differentiation and stage at presentation of ICC in severely immunosuppressed patients(CD4 < 200)

2.4: Secondary Objectives

- To determine the histological subtypes identified at biopsy, and their proportions.
- To determine the rate of HIV positive patients on HAART who are diagnosed with ICC.
- Determine risk factor profile (age sexual debut, number sexual partners, History of STI treatment) among HIV infected against HIV uninfected participants

2.5: Hypothesis

A large proportion of women diagnosed with invasive cervical cancer at Harare's Central Hospitals are HIV infected and present at an earlier age with more advanced disease and more poorly differentiated tumors than HIV negative women .

2.6: Study design

Cross sectional study, descriptive, quantitative study.

2.7: Setting

Parirenyatwa Group of Hospitals (Gynaecology Department and Radiotherapy Department), Harare Central Hospital (Gynaecology department). These are Harare's 2 central hospitals.

2.8: Study subjects

Newly diagnosed, ICC patients were eligible to participate.

2.9: Sample size

Sample size was calculated assuming an HIV prevalence rate of 41.9% in cervical cancer patients at 95% confidence level using a precision of 5%. The minimum sample size calculated was 94 patients using the following formula:

$$n = \frac{z^2 p(1-p)}{d^2}$$

$$= \frac{1.96^2(0.419 \times 0.581)}{0.05^2}$$

$$= 94$$

2.10:Inclusion Criteria

Patients within three months of diagnosis of ICC, confirmed by a histological report from a biopsy of the lesion.

Clinical staging done by Registrar or Consultant.

2.11: Exclusion Criteria

The absence of an official, histological report from a recognized pathologist.

Patients who refused to participate in the study.

2.12: Sampling method

Convenience sampling was used because of time constraints. The schedule is shown in Table 3.

Table 3: sampling schedule for data collection.

Day	Sampling Site
Tuesday	P.G.H Gynaecological Oncology Clinic
Wednesday	P.G.H Radiotherapy Outpatients Clinic
Thursday	H.C.H Gynaecology ward + Gynaecology Clinic
Friday	P.G.H Gynaecology wards

All patients meeting the selection criteria on sampling days were enrolled into the study.

2.13: Ethical Considerations

Ethical approval was given by the Harare Hospital Ethics Committee, The Joint Research Ethics Committee of Parirenyatwa and College of Health Sciences as well as the Medical Research Council of Zimbabwe.

Participants were asked for written, informed consent to participate in the study with the assurance that refusal to do so would in no way affect their management. They were also offered an opportunity at the beginning as well as at the end of the interview to ask any questions pertaining to their diagnosis and management. The investigator answered these questions or directed the patient to someone who could answer the adequately.

Minimal adverse effects were identified as a consequence of participation in the study.

There was a small risk of breach of confidentiality, but the following measures were taken to avoid this.

- Patients hospital numbers were recorded and a study number allocated on a sheet of paper seperate from the data collection sheet which was stored in a secure place in the Department of Obstetrics and Gynaecology.
- Names were recorded on a seperate sheet of paper with corresponding hospital numbers which were stored with the consent forms in a secure place under care of the chairperson of Obstetrics and Gynaecology.

2.14: Data Collection

- Data was obtained from a total of 110 patients, via face to face patient interviews, patients records, both outpatient and inpatient the above named hospitals

- The data collection was carried out by the researcher according to shown in the schedule in table 3 above.
- All patients approached consented to participation in the study.

2.15: Data management and analysis

Data collected was captured in Epi info V3.5.3 where data cleaning was also done, and then subsequently analysed using Stata A statistician assisted with the data analysis.

Time sheet

Data collection	February 2013 – December 2013
Data processing	January 2014- April 2014
Completion of manuscript	June 2014

Chapter 3

3.1: Results

The number of participants enrolled was 110 using the above protocol. The mean age of the participants was 48.7 years (sd=12.1 years). The mean age of the HIV seronegative patients was 42.7 years (sd=8.0 years) versus a mean age of 53.0 years, (sd=12.7 years) for the HIV seropositive participants. Fifty seven point three percent of the participants were from rural areas and 43% were from urban areas. As illustrated in Figure 3.

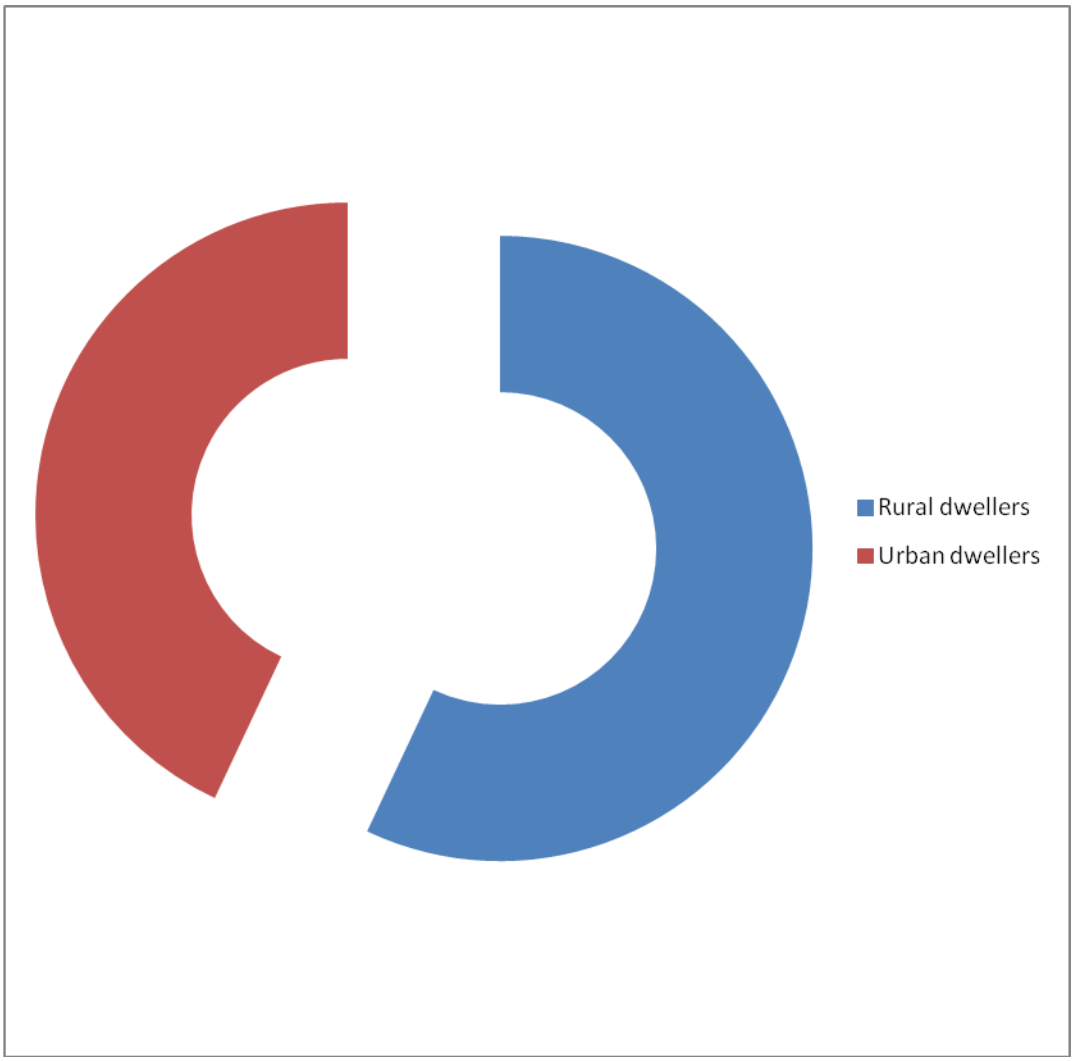

Figure 3: Composition of rural and urban dwelling of participants

The level of education of 58% of participants was primary level , 32.7% O level, 6.4% had no education and 2.7% had attained A level education or higher.This is illustrated in figure 4 below.

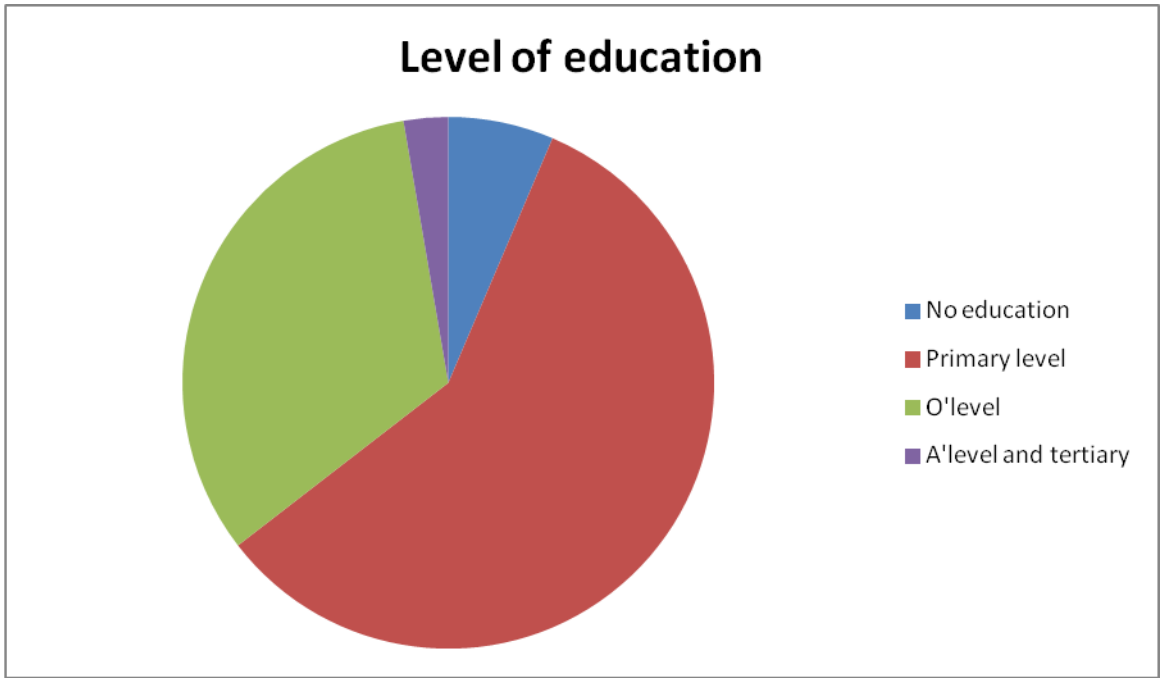

Figure 4: Level of Education of participants.

Income data could be quantified by 49% of the patients. The remaining 51% could not quantify their income as they were either peasant farmers or reliant on inconsistent support from family members. The mean income reported was US$200.00(IQR 100.00 – 280.00 US$)

Participant characteristics are shown in Table 4.

Table 4: Participant characteristics

Characteristic	**Total(%)**	**HIV positive(%)**	**HIV negative(%)**
HIV status	110 (100)	46 (41.8)	64 (58.2)
Partner circumcised			
Yes	8 (7.3)	4 (8.7)	4 (6.3)
No	102 (92.7)	42 (91.3)	60 (93.8)
History of STI treatment			
Yes	29 (26.4)	17 (40.0)	12 (18.8)
No	81 (73.6)	29 (63.0)	52 (81.3)
Sexual debut (years)			
<18	0 (0.0)	0	0
18-20	1 (0.01)	0	1 (1.6)
20+	109 (99.0)	46 (100)	63 (98.4)
Number of sexual partners			
1	58 (52.7)	21 (45.7)	37 (57.8)
2-5	51 (46.4)	24 (52.2)	27 (42.2)
6+	1 (0.9)	1 (2.2)	0
Parity			
0-2	21 (19.1)	17 (37.0)	4 (6.3)
3+	89 (80.9)	29 (63.0)	60 (93.8)
Level of differentiation			
Well	4 (3.7)	1 (2.2)	3 (4.8)
Moderate	71 (65.1)	31 (67.4)	40 (63.5)
Poor	34 (31.2)	14 (30.4)	20 (31.8)

Figure 5 illustrates the level of differentiation of the tumours in relation to the HIV status of the participants.

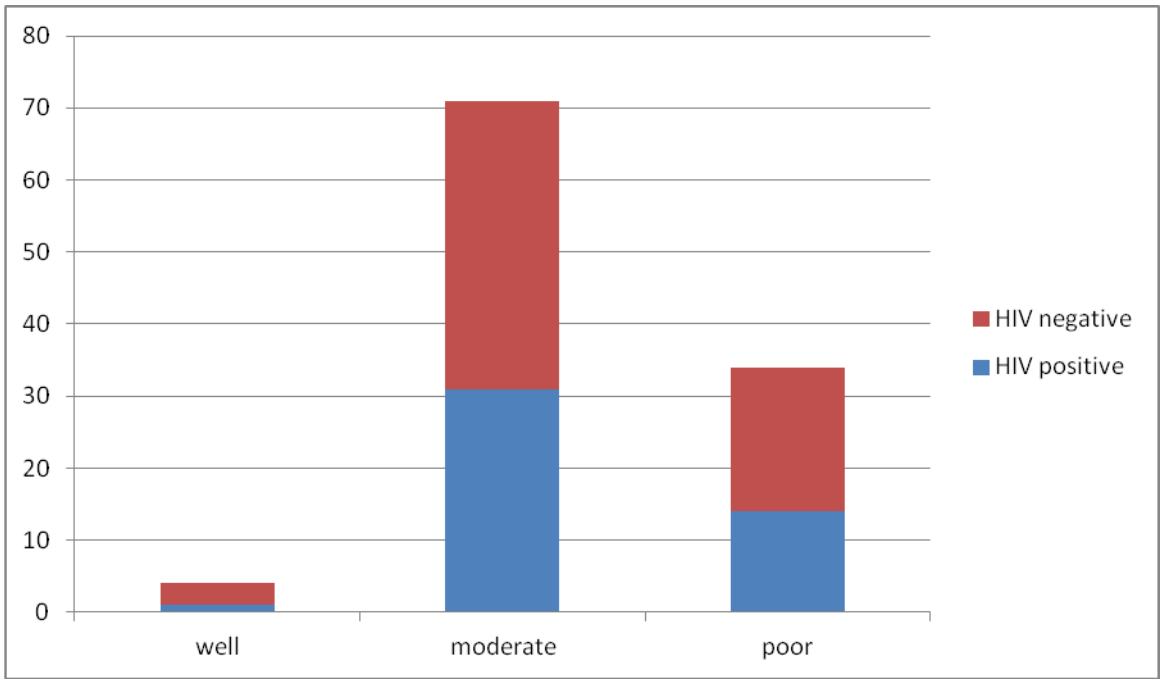

Figure 5: Level of differentiation of the tumours

The results show that 63% of HIV positive patients had CD4 cell counts greater than 350cells\ul, 28.3% had CD4 cell counts between 200 and 351 cell/ul and 8.7% had CD4 cell counts less than 200 cells/ul. Thirty-five(76.1%) of the HIV positive patients were on HAART while 11(23.9%) were not on HAART. The duration of HAART is shown below. Of the patients, 51.4% had been on HAART for 1-5 years, 37.1% for less than a year while 11.4% had been on HAART for between 5 and 10 years. This is illustrated in Figure 5 below.

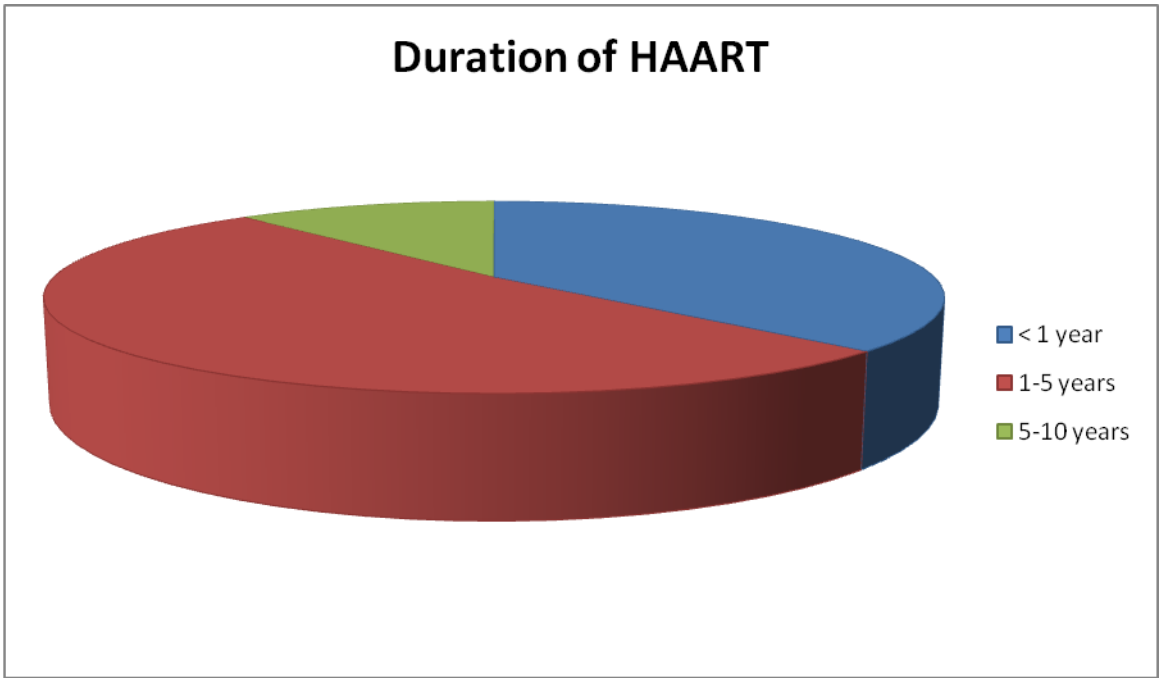

Figure 6: Duration of HAART of participants

The clinical staging of the group was as shown in Table 5 with 85.5% of participants having advanced disease (FIGO stage >/= 2b) and 14.5% having early disease.

Table 5: FIGO clinical staging of participants

	Total	HIV positive	HIV negative
1a	1	0	1
1bi	3	2	1
1bii	5	2	3
2a	7	2	5
2b	42	17	25
3a	9	3	6
3b	36	18	18
4a	6	2	4
4b	1	0	1
Total	110	46	64

The relative clinical staging of the participants is illustrated in Figure 7 overleaf.

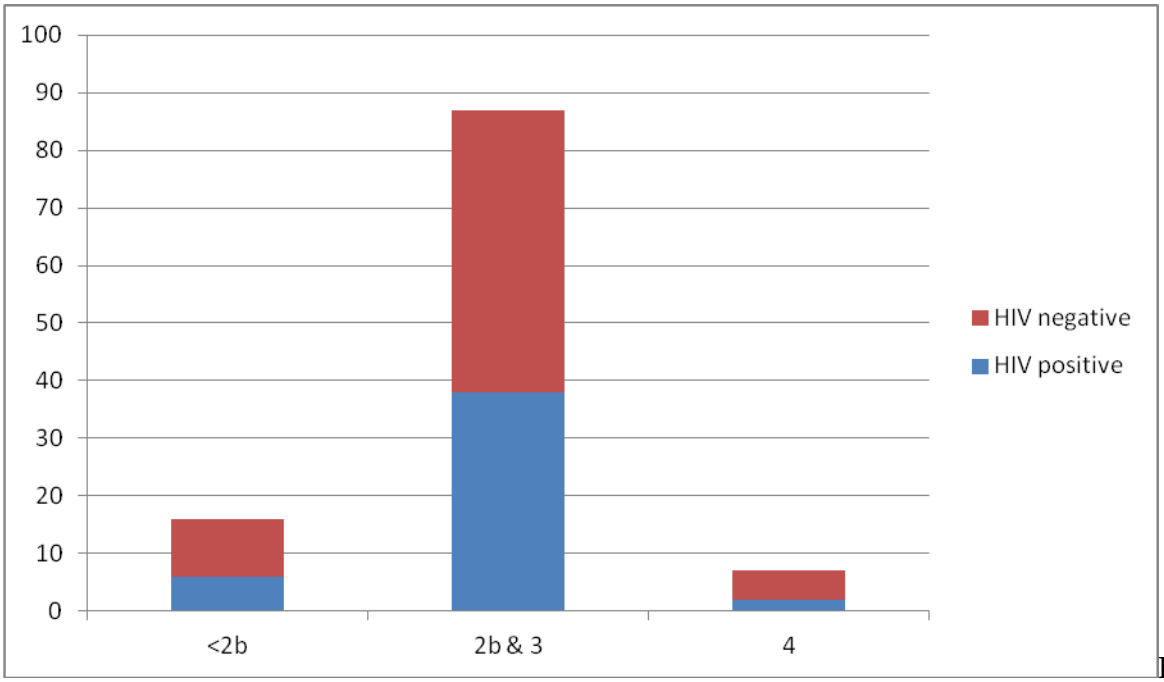

Figure 7: FIGO clinical staging of participants

Chapter 4

4.1: Discussion

This study confirmed that the mean age of HIV positive versus HIV negative participants of 10.3 years is similar to that reported by other studies(Gichangi, De Vuyst et al. 2002; Kahesa, Mwaiselage et al. 2008). The overall mean age of participants was 48.7 years which is similar to the reported mean age of 47(Chirenje, Rusakaniko et al. 2000) in a previous study and that of a meta-analysis of 12 studies which reported a mean age of 45 years for squamous cell carcinoma and 43 years for adenocarcinoma(International Collaboration of Epidimeological Studies of Cervical Cancer 2007).

The information of the reported income of participants is difficult to interpret as 51% of the participants could not quantify their income as they were either peasant farmers or reliant on inconsistent support from family members. However, the income of the 49% of participants who supplied a nominal value of their income, was below the poverty datum line(ZIMSAT and ICF International 2012) implying that ICC is indeed a disease associated with low socio-economic status. The majority of patients (57.3%), were also rural dwellers, similar to those in a previous local study which was carried out in the same two hospitals during 1998 where 63.3% of patients diagnosed with ICC were rural dwellers(Chirenje, Rusakaniko et al. 2000). The level of education of the majority (58%) of participants was primary education. This data may be considered in the design of materials to be used in prevention programmes so as to have maximum effect.

The sexual debut of the patients does not appear to be a significant risk factor because as compared to debut at age 21 or older, a debut from 18 to 20 years is associated with a 1.5-fold

increased risk of ICC and at less than 18, a two-fold increase(International Collaboration of Epidimeological Studies of Cervical Cancer 2007). None of the participants had reported a sexual debut of less than 18 years and 1.6% of participants had their sexual debut from 18 to 20 years of age. The other 98.4% had their sexual debut beyond 20 years of age, which is not significant as a risk factor. Six or more sexual partners are associated with a three-fold greater risk of ICC. Of the study participants, 0.9% reported a minimum of six partners, while 46.4% reported having two to five partners which is associated with a two-fold increased risk of ICC. However, the majority (52.7%) had one sexual partner, which is associated with baseline risk of ICC(International Collaboration of Epidimeological Studies of Cervical Cancer 2007).

Eighty-one per cent of the participants had no reported history of STI treatment. However, this result must be interpreted with caution as it may reflect asymptomatic infection or low uptake of healthcare services in the participants. Circumcision of the male partner provides protection against ICC. However, in this study only 6.4% of participants reported that their partners were circumcised. The parity of the majority (80.9%) of the patients was three or more, which is associated with an increased risk of ICC. The risk factors included in this study showed no difference in terms of whether the histology was squamous or adenosquamous(International Collaboration of Epidimeological Studies of Cervical Cancer 2007).

In this study, 41.8% of participants were found to be HIV positive, a finding that is similar to that reported in another study in South Africa in 2006 for the age range 30-34 years(Nel CPG 2006), but not observed in other studies, which report a seroprevalence as low as 2% in their ICC patients in Nigeria at an HIV prevalence of 4%(Abdus-Salam, Ogunnorin et al. 2008), 7% in South Africa(Lomalisa P 2007), 16% in Kenya(Adjorlolo-Johnson, Unger et al. 2010), 31% in another Kenyan study(Gichangi, De Vuyst et al. 2002), 21% in Tanzania(Kahesa,

Mwaiselage et al. 2008) and a KwaZulu-Natal (South Africa) study(Moodley and Mould 2005). These differences are probably a result of differences in population prevalence and time points for availability of HAART.

Of the HIV positive patients 63% had CD4 counts greater than 350 cells/ul. This finding is similar to that of other studies which reported mean CD4 counts greater than 300cells/ul(Maiman 1994; Leitao, White et al. 2008). This disparity in immunological status and the presence of ICC brings into question whether ICC should be classified as an acquired immunodeficiency syndrome (AIDS) defining illness. Of the HIV positive patients, 76.1% of participants were on HAART. This implies that they were accessing healthcare services and would raise the questions whether they were offered screening; whether it was done and the reasons why or why not. These issues are important in a low-resource setting such as Zimbabwe where the major focus of cervical cancer control is preventative. This approach is cheaper and effectively reduces mortality(World Health Organisation 2006).

As expected, the majority (92.7%) of cancers were squamous cell carcinoma, followed by adenocarcinoma (6.4%) and then by adenosquamous carcinoma (0.9%) lesions. The HIV positive and negative groups had similar proportions of each.

HIV positive patients showed a trend towards more advanced disease, that is FIGO stage 2b or greater OR 1.23 (C.I 0.41-3.68). However, this did not reach statistical significance. Overall, 31.2% of tumours were poorly differentiated. HIV positive were less likely to have a poorly differentiated tumour as compared to HIV negative, OR 0.94 (C.I 0.41- 2.14). This also did not reach statistical significance.

The major limitation of this study was the design itself, as a case control study would provide more conclusive evidence. In addition, the use of convenience sampling also compromises the strength of the evidence. However, it still provides some insight into the magnitude of the problem of HIV and ICC in the patient population and brings to light potential possibilities for further research.

4.2: Conclusion

This article sought to report data that would provide a better understanding of the magnitude of the problem of ICC and HIV in Zimbabwe currently. This is important to identify further gaps in knowledge, possible intervention opportunities and to stimulate the medical community to take a closer look at this problem.

HAART availability and improved life expectancy in HIV positive individuals appears to be leading to an increase in the proportion of ICC patients with HIV disease. It seems that the initial lack of data demonstrating an increase in ICC despite increased HIV seroprevalence may be as a result of the time taken from HPV infection to manifestation of ICC. Larger longitudinal studies may confirm this theory. Women on HAART(76.1%), reported in this study or women who are accessing health care services for any reason provide an opportunity to offer screening services and it would be prudent to take advantage of this opportunity.

4.3: Recommendations

1. Further, more robust research should be conducted to confirm or refute the large proportion of HIV positive patients with ICC reported in this study

2. HIV positive patients should specifically be targeted for screening for pre-invasive cervical lesions and provision may be made for this within the setting of the Opportunistic Infections Clinics.

3. Research to establish HPV serotypes present in ICC specimens of HIV positive patients should be conducted in order to inform policy on the use of the HPV vaccine in these patients.

Invasive cervical cancer is a disease for which proof of effectiveness of screening in reducing mortality is abundant(Peto, Gilham et al. 2004). Identification of groups at particular risk will assist in this effort in order to reduce the morbidity and mortality related to the condition. “Prevention is better than cure”, is a cliché but undeniably true …

Chapter 5

Appendix 1: PARTICIPANT CONSENT FORM ENGLISH

PROTOCOL TITLE : The Association of HIV with Invasive Cervical Cancer in Harare's Central Hospitals

NAME OF RESEARCHER: Dr Takudzwa L.P Chiwanga

PHONE : +263 772 908 861

E-MAIL : takuloraine@yahoo.co.uk

Purpose of the study

This study will aim at assessing the proportion of patients diagnosed with invasive cervical cancer who are also HIV positive at Harare's Central Hospitals and to see how those patients may differ from HIV negative patients with the same diagnosis.

This knowledge will help us better anticipate the health needs of our patients with Invasive Cervical Cancer.

Your Rights

Before you decide whether or not to agree to participate in the study, you must understand its purpose, how it may help you, the risks to you and what is expected of you. This process is called informed consent.

What is involved if you choose to participate

Should you choose to participate in the study, I will ask you questions from my questionnaire, some of which are of a sexual nature under strict confidentiality. I will also obtain information about your diagnosis and investigations from your hospital notes.

Risks, stress or discomfort

The interview is expected to take about 10 minutes of your time and there is a small risk of confidentiality being breeched as a result of your participation Though every effort will be made to ensure confidentiality as specified below.

Potential Benefits/ Incentives

There are no monetary gains as a result of participation in this study. But I would like to make myself available to answer any questions you may have concerning your diagnosis and treatment at the end of the interview.

Study withdrawal

Participation in this study is voluntary.

You may choose not to participate in this study and this choice will not affect your management in any way.

You may withdraw from the study at any time without penalty or loss to benefits to which you are otherwise entitled.

Confidentiality of records

Information about you is confidential. I will assign you a study number which will appear on my data collection sheet with your study responses and medical information. The link between your name and the study number will be kept separately in a secure location.

……

PRINTED NAME OF STUDY STAFF OBTAINING CONSENT

…… ……

SIGNATURE DATE

Participant's Statement

This study has been explained to me, and I voluntarily consent to participate. I have had an opportunity to ask questions. If I have questions about the research, I can ask the researcher with above details provided. If I have questions about my rights as a research participant, I may call the Medical Research Council of Zimbabwe on telephone 04 791792 or 04 791193. I give the researcher permission to use my medical records as described in this consent form.

……

PRINTED NAME OF PARTICIPANT

…… …….

SIGNATURE OF PARTICIPANT DATE

OR AUTHORIZED REPRESENTATIVE

APPENDIX 2 PATIENT CONSENT FORM, SHONA

GWARO RETENDERANO

PROTOCOL TITLE: The HIV profile of patients with Invasive cervical cancer at Harare's central hospitals.

ZITA REMUONGORORI: Dr Takudzwa L.P Chiwanga

NUMBER DZERUNHARE : +263 772 908 861

E-MAIL : takuloraine@yahoo.co.uk

Chinangwa Chechirongwa

Chirongwa ichi chiri kuda kuongorora huwandu hwemadzimai vanenge vaonekwa vaine gomarara repamuromo wechibereko uyezve vaine hutachiwana hwe HIV pazvipatara zvikuru zvemu Harare. Chinodazve kuona kuti pane musiyano here pakati pemadzimai vanegomarara repamuromo we chibereko vaine hutachiwana hwe HIV ne vanenge vanegomarara repamuromo wechibereko asi vasina hutachiwana hwe HIV. Ruzivo rwatichawana ruchatibatsira pakurapwa kwemadzimai vane gomarara repamuromo wechibereko.

Kodzero dzenyu

Musati maita sarudzo yekupinda muchirongwa chino munofanira kunzwisisa chinangwa chechirongwa, zvamungangowana kana zvakaipa zvingangoitika nekuve muchirongwa uye nezvinotarisirwa kwamuri. Ndizvo zvinonzi "Informed consent" muchirungu

Zvichaitwa kana maita sarudzo yekupinda muchirongwa

Kana maita sarudzo yekupinda muchirongwa ndinokubvunzai mibvunzo, imwe yacho yakanangana nezvekusangana pabonde. Zvese zvamunonditaurira zvinochengetedzwa zvakavanzika. Ndichatora zvinyorwa zvakanangana nezveurwere hwenyu, marapirwe enyu uye neongororo dzose dzakaitwa kubva muzvinyorwa zvenyu zvemuchipatara.

Kusagadzikana kana njodzi

Hapana njodzi inotarisirwa nekuve kwenyu muchirongwa chino. Ndichaedza nepose pandinokwanisa kuti zvinhu zvese zvichengetedzwe pakavanzika.

Zvamungangowana

Hapana mibhadharo yamunowana nokuti mapinda muchirongwa chino.

Kubuda muchirongwa

Kuve muchirongwa isarudzo yenyu iri pachena.Munogona kuita sarudzo yekusapinda muchirongwa kana kubuda muchirongwa panguva ipi zvayo musingarasikirwe nezvamanga muchawana pakurapwa kwenyu.

Zvakavanzika

Zvinyorwa zvenyu zvese zvemuchirongwa zvichachengetedzwa pakavanzika.Muchapihwa nhamba inenge ichizoshandiswa pazvinyorwa zvenyu zvemuchirongwa. Izvo zvinoita kuti pave nekuzivikana pakati pezita renyu nenhamba yenyu yemuchirongwa zvichachengetedzwa pazvo zvega panzvimbo yakavandika.

……

ZITA REMUONGORORI ARIKUPIHWA MVUMO

…… ……

SAINECHA Zuva

Mhiko yemunhu anopinda muchirongwa

Ndatsanangurirwa nezvechirongwa chino uye ndinoita sarudzo yekupinda muchirongwa. Ndapihwamukana wokubvunza mibvunzo. Kana ndine mibvunzo maererano nechirongwa ndinokwanisa kubvunza muongorori akanyorwa pabepa rino. Kana ndine mibvunzo maererano nekodzero dzangu senhengo yechirongwa ndinokwanisa kuridza runhare ku Medical Research Council ye Zimbabwe(MRCZ) panhamba 04 791 792 kana 791193. Ndinopa mvumo kune muongorori yekushandisa zvinyorwa zvangu zvemuchipatara maererano netsanangudzo iri mugwaro retenderano iri.

……

ZITA REMUNHU ARIKUPA MVUMO

…… ……

SAINECHA YAKE KANA AKAMUMIRIRA ZUVA

APPENDIX 3: DATA COLLECTION SHEET ENGLISH

Participant Number ☐

1. Age ☐
2. Parity ☐
3. Level of education Grade 7 ☐ O' level ☐ A' level ☐ Tertiary ☐
4. Residence Urban ☐ Rural ☐
5. Monthly income (U.S. $) …….
6. How many people are dependent on the above income? …….
7. Sexual debut ☐
8. Number of sexual partners ☐
9. Partner circumcised Yes ☐ No ☐
10. History of STI treatment Yes ☐ No ☐
11. HIV Status Positive ☐ Negative ☐
12. Date of diagnosis ☐
13. CD4 Count at diagnosis of HIV ☐
14. CD4 Count at diagnosis of ICC ☐ 0-200 ☐ 201-350 ☐ >350 ☐
15. On HAART Yes ☐ No ☐
16. Duration of HAART ☐
17. Histological Diagnosis ☐
18. Date of Diagnosis of Cervical Cancer ☐
19. Level of differentiation Well ☐ Moderate ☐ Poor ☐

20. Clinical staging 1a ☐ 1bi ☐ 1bii ☐ 2a ☐ 2b ☐

3a ☐ 3b ☐ 4a ☐ 4b ☐

APPENDIX 4:DATA COLLECTION SHEET SHONA

Number yemuchirongwa ☐

1. Mune makore mangani? ☐
2. Makasununguka vana vangani? ☐
3. Pamakasvika nedzidzo yenyu Grade 7 ☐ O' level ☐ A' level ☐ Tertiary ☐
4. Munogara kupi? Urban ☐ Rural ☐
5. Munowana marii pamwedzi? (U.S. $) ……..
6. Mari iyi inoriritira vanhu vangani? …….
7. Makatanga kusangana pabonde mune makore mangani? ☐
8. Makasangana nevarume vangani pabonde? ☐
9. Shamwari yepabonde taka checheudzwa here? Hongu ☐ Kwete ☐
10. Makamborapwa zvirwere zvinotaputitwa pabonde here? Hongu ☐ Kwete ☐
11. HIV Status Positive ☐ Negative ☐
12. Date of diagnosis ☐
13. CD4 Count at diagnosis of HIV ☐
14. CD4 Count at diagnosis of ICC ☐ 0-200 ☐ 201-350 ☐ >350 ☐
15. On HAART Yes ☐ No ☐
16. Duration of HAART ☐
17. Histological Diagnosis ☐
18. Date of Diagnosis of Cervical Cancer ☐
19. Level of differentiation Well ☐ Moderate ☐ Poor ☐

20. Clinical staging 1a ☐ 1bi ☐ 1bii ☐ 2a ☐ 2b ☐

3a ☐ 3b ☐ 4a ☐ 4b ☐

Appendix 5 FIGO clinical staging for cancer of the cervix(Pecorelli, Zigliani et al. 2009; National Cancer Institute 2014)

Stage	
I	The carcinoma is strictly confined to the cervix (extension to the corpus would be disregarded).
IA	Invasive carcinoma, which can be diagnosed only by microscopy with deepest invasion ≤5 mm and largest extension ≥7 mm.
IA1	Measured stromal invasion of ≤3.0 mm in depth and extension of ≤7.0 mm.
IA2	Measured stromal invasion of >3.0 mm and not >5.0 mm with an extension of not >7.0 mm.
IB	Clinically visible lesions limited to the cervix uteri or preclinical cancers greater than stage IA.[b]
IB1	Clinically visible lesion ≤4.0 cm in greatest dimension.
IB2	Clinically visible lesion >4.0 cm in greatest dimension.
II	Cervical carcinoma invades beyond the uterus but not to the pelvic wall or to the lower third of the vagina.
IIA	Without parametrial invasion.
IIA1	Clinically visible lesion ≤4.0 cm in greatest dimension.
IIA2	Clinically visible lesion >4.0 cm in greatest dimension.
IIB	With obvious parametrial invasion.
III	The tumor extends to the pelvic wall and/or involves lower third of the vagina and/or causes hydronephrosis or nonfunctioning kidney.[c]
IIIA	Tumor involves lower third of the vagina with no extension to the pelvic wall.
IIIB	Extension to the pelvic wall and/or hydronephrosis or nonfunctioning kidney.
IV	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the

Stage	
	bladder or rectum. A bullous edema, as such, does not permit a case to be allotted to stage IV.
IVA	Spread of the growth to adjacent organs.
IVB	Spread to distant organs.

Appendix 6: 5 year survival by FIGO clinical stage(World Health Organisation 2006)

FIGO Clinical Stage	Approximate 5 year survival(%)
1A1	98
1A2	95
1B1	85
1B2	75
11A	75
11B	65
111A	30
111B	30
1VA	10
1VB	<5

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