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Evaluation of outcomes in patients with pancreatic cancer and Human Immunodeficiency Virus at Chris Hani Baragwanath Academic Hospital and the Donald Gordon Medical Centre, Johannesburg

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Evaluation of outcomes in patients with pancreatic cancer and Human Immunodeficiency Virus at Chris Hani Baragwanath Academic Hospital and the Donald Gordon Medical Centre, Johannesburg

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in fulfilment of the requirements for the degree of the Master of Medicine (MMed).

Johannesburg, 2022

Declaration

I, Jessica Roberta Wing, declare that this research report is my own unaided work which is submitted for the degree of Master of Medicine (in the submissible format with my protocol and extended literature review) at the University of the Witwatersrand, Johannesburg. This dissertation has not been submitted before for any other degree nor examination at any other university.

Dr Jessica Roberta Wing 
This day, 2022.11.29 , Johannesburg

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Abstract

Background:

Cancers which are not associated with Acquired Immune Deficiency Syndrome (AIDS) are increasing in incidence and mortality in the HIV-positive population. Pancreatic cancer (PC) is projected to be the second most common cause of cancer-related death by 2030. No literature exists on patients with PC and concomitant human immunodeficiency virus (HIV) infection in South Africa (SA), which has the highest number of HIV-positive people in the world.

Objectives:

To compare the demographics, stage, histological grade of disease, and survival outcomes of HIV-positive compared to HIV-negative patients diagnosed with PC.

Methods:

Records of patients diagnosed with PC were collected from Chris Hani Baragwanath Academic Hospital (CHBAH) and the Wits Donald Gordon Medical Centre (DGMC) from the 1st of January 2013 to the 31st of December 2018. A total of 240 patients' records were obtained. Demographic, clinical, and survival data were collected.

Results:

There were predominantly black Africans (64.6%) and males (54.6%) in the study. Although overall survival between the HIV-positive and negative patients did not differ (p=0.051), the median time of survival from presentation was significantly shorter in the HIV-positive compared to the HIV-negative patients (2.1 months; IQR 1.2-6.0 vs. 4.7 months; IQR 1.6-13.0; p=0.017). The HIV-positive cohort presented at a significantly younger age compared to the negative cohort (54.6; ±9.6 vs 62.4; ±11.1; p=0.0001) and at a more advanced stage of disease (72.2% vs. 43.1%; p=0.017). No difference was found between the histological grade of PC in both cohorts (p=0.298). The median survival time for HIV-positive patients on therapy at presentation was significantly longer compared to patients who were not (3.0; IQR 1.3-7.8 vs 1.1 months; IQR 0.9-1.9; p=0.037). Overall survival in patients who underwent pancreaticoduodenectomy at Wits DGMC was shown to be higher compared CHBAH

(41.7% vs. 12.5%; p=0.049). The majority of the patients presented with regionally advanced (30.6%) and metastatic (50.3%) disease.

Conclusion:

This is the first study in SA to provide insight into the clinical disease profile and survival outcomes of HIV-positive patients diagnosed with PC. This study has shown that HIV-infected patients with PC have a specific disease profile. Therefore, testing for HIV infection should be included in the management of all patients with PC, a higher index of suspicion for cancer should be maintained in younger HIV-positive patients and initiation of Antiretroviral treatment (ART) must be timeous.

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Abbreviations

ADCs	AIDS-defining cancers
AIDS	Acquired Immune Deficiency Syndrome
ASR	Age-standardised Incidence Rate
AJCC	American Joint Committee on Cancer
APCs	Annual percentage change
ART	Antiretroviral Treatment
CC	Cervical carcinoma
CD4	Cluster of Differentiation 4
CI	Confidence interval
CHBAH	Chris Hani Baragwanath Academic Hospital
CMV	Cytomegalovirus
DGMC	Donald Gordon Medical Centre
EBV	Epstein Barr virus
EPBCR	Ekurhuleni Population-Based Cancer Registry
ELISA	Enzyme-Linked Immunosorbent Assay
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human Immunodeficiency virus
HHV8	Human Herpes virus 8
HPV	Human Papilloma virus
IRIS	Immune reconstitution inflammatory syndrome
IQRs	Interquartile ranges
KS	Kaposi sarcoma
KZN	KwaZulu-Natal
MAC	Mycobacterium Avium Complex
MTB	Mycobacterium Tuberculosis
NADCs	Non-AIDS defining cancers
NHL	Non-Hodgkin lymphoma
NHLS	National Health Laboratory Service
NCR	National Cancer Registry
NSAID	Non-steroidal anti-inflammatory drug
PC	Pancreatic cancer
PD	Pancreaticoduodenectomy

PLWH	People living with HIV
RNA	Ribonucleic acid
SD	Standard deviation
SEER	Surveillance, Epidemiology, and End Results
SA	South Africa
TNM	Tumour, node, metastasis
UNAIDS	United Nations Program on HIV/AIDS
USA	United States of America
VL	Viral load
vs.	Versus
WHO	World Health Organization
Wits	University of the Witwatersrand

Chapter 1: Protocol with extended literature review

1. Introduction

The role of Human Immunodeficiency Virus (HIV) in malignancy is an intriguing topic that is continually being studied. Evidence has shown that malignancies in people living with HIV (PLWH) occur at an earlier age; have a higher tumour histological grade; are more aggressive and present at advanced stages of disease (1). This has a significant impact on clinical practice as patients have poorer outcomes with rapid progression; a worse response to treatment and a worse overall survival (2). A number of malignancies have been studied in relation to HIV. However, the existing literature on the impact of HIV on pancreatic cancer (PC) is very limited internationally and non-existent in South Africa (SA). Sub-Saharan Africa carries 64% of the global HIV burden (3), this provides a unique opportunity to assess and describe the demographic, disease profile and survival outcomes of HIV-positive patients with PC.

2. Background

2.1 The epidemiology of pancreatic cancer

2.1.1 Demographics of pancreatic cancer globally

PC is projected to be the second most common cause of cancer related death in the United States of America (USA) by 2030 (4). Men are noted to have an increased overall lifetime risk compared to women (5). In terms of ethnicity, the incidence is greater in people of African descent than in Caucasians with the highest incidence found among the Māori population in New Zealand, Hawaiians, and African Americans while the lowest incidences are reported in India and Nigeria (6, 7). The incidence of PC increases after the age of 45 years and before this, the disease is rare (8).

2.1.2 Demographics of pancreatic cancer in South Africa

In SA, data on PC is limited due to inadequate reporting. Available data comes from the Ekurhuleni Population-Based Cancer Registry (EPBCR) which is an urban population-based cancer surveillance site established by the National Cancer Registry (NCR). The latest EPBCR report is from the 1st of January 2018 to the 31st of

December 2018. According to this report, there were only 33 and 28 new cases of histologically confirmed PC in women and men respectively. Of note, PC was among the top ten cancers occurring in women with an Age-Standardised Incidence Rate (ASR) of 2.38/100 000, the highest in the 85 year and older age group. Men had an ASR of 1.76/100 000 with the highest in the 80- to 85-year-old age group. In terms of ethnicity, incidence was highest in Caucasians, followed by black Africans, people of mixed ethnicity and lastly by Asians (9).

2.2 Survival outcomes in pancreatic cancer

Pancreatic ductal adenocarcinoma is responsible for approximately 7% of cancer - related deaths worldwide and the prognosis remains poor with an overall 5-year survival rate below 10% (10, 11). Nodal status and radiological staging remain the most important prognostic factors in PC. This was reflected by a series of 8960 patients with resectable disease reported to the Surveillance, Epidemiology, and End Results (SEER) database between 2004 and 2013 demonstrating that a worse American Joint Committee on Cancer (AJCC) Tumour, node and Metastasis (TMN) stage of disease correlates with poorer overall survival (12). After a pancreaticoduodenectomy (PD), five-year survival in node negative disease is 30% and 10 % for node positive disease (13, 14). However, a concept known as “conditional survival” does exist which suggests that survival rates may improve overtime depending on the amount of time already survived post-PD. 60% and 80% of disease recurrence will occur post-PD at 2 and 3 years respectively. All patients that survive after the 3-year post-PD period are likely to achieve 5-year survival. The hazard of death due to PC-related death exceeded death due to other causes up until 8.75 years post diagnosis (15, 16).

The innate pathogenic factors of the adenocarcinoma also influence prognosis and mortality. These include histological grade, the presence of lymphovascular and perineural invasion, tumour location and unique oncogenetics of the tumour. Clinical factors including ongoing cigarette smoking, age, sex, weight loss and back pain also influence prognosis (17).

2.3 Risk Factors for pancreatic cancer

2.3.1 Environmental risk factors

Important environmental risk factors for PC such as cigarette smoking; obesity and physical inactivity (18); a high fat content diet (19); alcohol consumption (20) and impaired glycaemic control (21) will not be detailed as this data is not recorded consistently in our study populations' records and, as a result will not be used to achieve the objectives of this study.

2.3.2 Infections

Helicobacter pylori infection, Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV) infections have been considered potential risk factors for developing PC (22, 23). These infective agents may tie-in with one of the many oncogenic mechanisms of HIV infection.

2.3.3 Chronic pancreatitis

Chronic pancreatitis is considered to be a risk factor in developing PC (24). Antiretroviral Treatment (ART) regimens which include older drugs such as stavudine and didanosine may directly cause pancreatitis while hypertriglyceridemia caused by protease inhibitors which are used in current ART regimens may also contribute in developing acute pancreatitis. Certain opportunistic infections acquired in HIV-infected individuals such as Mycobacterium Tuberculosis (TB), Cytomegalovirus (CMV) and Mycobacterium Avium Complex (MAC) have also been associated with pancreatitis (25). However the above HIV-related causes of acute pancreatitis have not been shown to translate into chronic pancreatitis.

2.4.3 Genetic risk factors

Approximately 80% of PC cases occur sporadically but a small percentage are genetic. Germline mutations identified in known pancreatic susceptibility genes such as BRCA2, ATM, PALB2, CDKN2A and MLH1 are the basis for the molecular pathogenesis of PC (26, 27).The risk factors commented on above may contribute to acquiring these germline mutations. It is not known whether HIV specifically induces mutations in PC susceptibility genes.

2.5 Epidemiology of HIV

2.5.1 Epidemiology of HIV from a global perspective

At the end of 2016, there were 36.7 million PLWH worldwide, with 1.8 million people newly infected and 1 million people dying of Acquired Immune Deficiency Syndrome (AIDS). The overall prevalence of HIV has stabilised or has been noted to be increased in some countries, most likely as a result of increased life expectancy with the widespread use of ART. The global 2016 incidence of new HIV infections demonstrates a decline of 47% from 2001 (28).

2.5.2 Epidemiology of HIV in South Africa

Sub-Saharan Africa has been devastated by the HIV pandemic. Mortality related to HIV/AIDS is the primary cause of mortality in the region and has resulted in HIV infection in becoming one of the top ten causes of mortality globally (28). Sub-Saharan Africa constitutes 10% of the global population but has 64% of the world's HIV-infected population and of that, 25% are in SA (28). The pandemic in this region has declined by 29% from 2010 to 2016 but SA accounted for one third of all new infections in Sub-Saharan Africa in 2016 (28). In 2018, the estimated prevalence for adults (age group 15-49) in SA was 19.4% and incidence rate per 1000 uninfected population was 6.9 while the approximate number of adult deaths due to HIV/AIDS was 68 000 (29).

The epidemic in Sub-Saharan Africa is predominantly due to heterosexual transmission and disproportionately affects young women. In 2016, women accounted for 56% of the new HIV infections and there were an estimated 4.3 million women and girls living with HIV in that year. The HIV prevalence among females aged 15 to 19 is five times higher than that among males of the same age. Prevalence for HIV infection also peaks a decade earlier in South African women (20-29 age group) than in South African men (30-39 age group) (30, 31). In terms of ethnicity, the highest prevalence for HIV infection is found in black Africans (12.9%) followed by caucasians (6.2%), people of mixed-ethnicity (6.1%) and lastly by people of Asian descent (1.6%). Informal settlements in urban areas in South Africa have the highest prevalence of HIV infection when compared to urban formal, rural informal and rural formal areas (31). By the end of 2016, South Africa had approximately 7.1 million PLWH with 56% on ART and 45% achieving viral load (VL) suppression (3).

2.6 The impact of HIV on malignancy

2.6.1 Incidence of AIDS-defining cancers and Non-AIDS-defining cancers in high-income countries

Evidence from high-income countries has shown that the HIV-infected population is at an increased risk for malignancy. (32-34). Kaposi sarcoma (KS), Non-Hodgkin lymphoma (NHL) and cervical carcinoma (CC) are well documented AIDS-Defining Cancers (ADCs) which, with the widespread use of efficacious ART, have decreased markedly in their incidence. For example, an American study conducted from 1990-2002, showed that the absolute number of KS cases decreased from 3252 to 50 with the advent of ART. Similarly the absolute number of NHL cases decreased 1940 to 589 (35). Interestingly, there has been an increase in the incidence of malignancies known as non-AIDS-defining Cancers (NADCs) in the HIV-positive population when compared to the negative population (36). A large (9429 patients), Swiss HIV cohort study used three separate periods: 1985 to 1996 (pre-ART), 1997 to 2001 (early ART), and 2002 to 2006 (late ART) to analyse the change in incidence of ADCs and NADCs. In the pre-ART period, ADCs accounted for 88% of the total cancer burden while, in the early and late ART periods, the percentage of ADCs declined to 47% and 33 % respectively. The incidence of NADCs was noted to be mildly increased in the HIV-positive population compared to the HIV-negative population (37). Another prospective cohort study of 11,112 patients followed up in an HIV registry over a 25 year period, found that there were no significant increases in the incidence of NADCs before the introduction of ART but rather a significant increase in NADCs after the introduction of ART (38).

2.6.2 Incidence of AIDS-defining cancers and non-AIDS-defining cancers in low- and middle-income countries

A Brazilian study linked records from the “Population-Based Cancer Registry of São Paulo” and their AIDS notification database. In PLWH, 2,074 cancers were diagnosed, and cancer trends were assessed by annual percentage change (APCs). In both men and women, ADCs were the still the most frequent cancers (KS and NHL; CC and NHL respectively) but importantly the overall trend of ADCs was declining steadily for both sexes (-14.1%/year and -15.6%/year respectively). In the male cohort, the trend of all NADCs is increasing (7.4%/year) since the mid 2000s, mainly due to an increase in the incidence of anal (24.6%/year) and lung cancer (15.9%/year) in this population.

In contrast, these malignancies were on the decline in the HIV-negative male population. In the female cohort, there was a decline in both the APCs of ADCs and NADCs (39).

Interestingly in India, there appears to be a low prevalence of HIV infection in cancer patients and ,conversely, a low prevalence of cancer in HIV-infected patients at the time of diagnosis. A cross-sectional study in Northern India took place from July 2013-June 2016 which enrolled 999 patients from an ART centre who were screened for malignancy and 998 patients from a cancer centre who were screened for HIV infection. Within the HIV-positive patient cohort, 20 were diagnosed with cancer (2% prevalence) and 9 known cancer patients were diagnosed with HIV infection (0,9 % prevalence). Although the prevalence of HIV infection in patients with malignancy in this study was shown to be low, it was still four times the national prevalence of HIV infection of the general population (0.26%). AIDS-defining cancers were more common than NADCs with NHL and CC being the most common cancers (40).

A nationwide follow up study in China was conducted from January 2008 to June 2011 and analysed incidence of cancer among PLWH and showed a substantial ADC and NADC burden among adult PLWH. Their main outcome measures were gender-stratified, age-standardised incidence rates for China (ASIRC) and standardised incidence ratios (SIR) for all malignancy types. A total of 3,819 cases of cancer were identified. Overall, ASIRC was 776.4 per 100,000 for males and 486.5 per 100,000 for females. Malignancy types with highest ASIRC among males were lung, liver, and lymphoma. Among females, lung, lymphoma, stomach, and cervical cancers had the highest ASIRC. Overall SIR for males was 3.4 and for females was 2.6. The highest SIR was observed for Kaposi sarcoma (2,639.8 for males and 1,593.5 for females) and lymphoma (13.9 for males and 16.0 for females) (41).

The largest African study on the incidence of cancers in the ART-era (46,952 patient records) was from SA which used probabilistic record linkage to match cancer records from the National Cancer Registry (NCR) to HIV data from the National Health Laboratory Service (NHLS), found that the incidence of ADCs was consistently higher than NADCs throughout the study period of 2004-2014 but that the HIV-positive population was still at a higher risk for virally-mediated NADCS such as penile, liver,

oral cavity and vulval cancers (42). Another South African study in the ART-era used similar methodology to calculate cancer incidence rates in PLWH on ART (43) . A total of 448 cancers were identified, 82% (n = 367) were recorded in the cancer registry, 10% (n = 43) in the HIV cohort and 8% (n = 38) both in the HIV cohort and the cancer registry. Incidence rates (per 100 000 person-years) were still highest for ADCs: KS 432 (95% CI; 341-555) followed by invasive CC, 259 (95% CI; 179-390). The incidence rate for NADCs was 294/100 000 (95% CI 223-395), increasing and gained prominence over CC and NHL from the second year on ART (43). A Ugandan study found a more than two-times increase of overall NADCs among PLWH with a prominence of uterine, conjunctival, thyroid cancers (44). A Nigerian study, however, did not find any difference in incidence of NADCs in their HIV-positive compared to their negative cohorts (45). Overall, the above literature showed that the cancer-shift from ADCs to NADCs in HIV-positive populations, observed in high-income countries was not yet apparent in low and middle income countries.

2.6.3 Survival outcomes of Non-AIDS-defining cancers in people living with HIV

These NADCs have changed the spectrum of mortality in the HIV-infected population. Prior to the introduction of ART, malignancies were responsible for less than 10% of all deaths in the HIV-infected population (46) whereas, in a French study (n=64 000) conducted in 2000, death due to malignancy accounted for 28% of mortality in HIV-positive patients, of which 15% where due to ADCs and 13% where due to NADCs (47). The HIV-infected population has a higher cancer specific mortality rate as compared to the general population. This was demonstrated in a large American retrospective observational study conducted from 1996 to 2010 which reviewed over 1.8 million cancer patients and included 6,459 PLWH. This study concluded that overall cancer related mortality was significantly elevated in the HIV-infected population when compared to the HIV non-infected population independent of cancer stage and receipt of specific cancer therapy. Importantly, cancer specific mortality was significantly increased in 7 out of the 14 common malignancies studied and included: colorectal; pancreas; laryngeal; lung; melanoma; breast and prostate cancer. A notable sub-analysis which only included patients with locoregional disease also showed consistency in worse cancer survival and HIV-infection, particularly in PC and melanoma (48).

2.6.4 HIV infection and cancer risk

The increased incidence of malignancy in HIV-infected patients is multifactorial. Innate pathogenic effects of the HIV virus itself; profound immune suppression; increased co-infection with oncogenic viruses and bacteria; environmental factors ,co-morbidities, and perhaps but, unlikely, the use of ART may all contribute to cancer risk (34).

The Human Immunodeficiency virus itself provides a form of chronic antigenic stimulation and has direct effects on cellular processes including directly activating proto-oncogenes, causing changes in cell cycle regulation and inhibiting tumour suppressor genes (1). A study in the USA found a strong risk reduction for ADCs and a weaker risk reduction for virally-mediated NADCs with early and long-term HIV viral load (VL) suppression, which was defined as a VL below 500 RNA (ribonucleic acid) copies/mL. This finding, however, was not observed in NADCs which were not virally-mediated. Notably, long-term viral suppression still conferred excess cancer risk in HIV-positive patients compared to negative patients (49).

The hallmark of untreated HIV infection is progressive immunological deterioration, reflected by the decline in the Cluster of Differentiation 4 lymphocyte count (CD4) which paralleled with the increased incidence of ADCs such KS and NHL before the advent of ART (50). In an American study, an increase in a CD4 count by 100 cell/mm^3 at 6 months post-ART initiation or in the most current CD4 count independently reduced the incidence of virally-mediated NADCs by 29%and 30% respectively. The early CD4 count response at 6 months post-ART initiation was the strongest predictor for virally-mediated NADCs. In terms of NADCs which are not virally-mediated, no immunological measures were associated (51). Immune suppression also seems to play a role in the acceleration of malignancy as HIV-positive patients are diagnosed at earlier ages as compared to the general population, noted by the SEER database, where lung cancer and multiple myeloma were diagnosed at a median of 4 years earlier in the HIV-positive population compared to the negative population (52). This may be explained by accelerated aging linked with chronic immune activation which occurs in HIV infection (53).

Due to marked T-cell deficiency, people living with HIV are at increased risk of co-infection with viruses that are innately oncogenic. The clinical course of these viruses

is also accelerated in HIV-positive individuals. These oncogenic viruses include: Human Herpes Virus 8 (HHV-8), Human Papilloma Virus (HPV), Epstein-Barr Virus (EBV), HCV and HBV and Merkel Cell Polyomavirus (1).

The role of other well-known oncogenic environmental stimuli such as cigarette smoking seem to be enhanced in individuals infected with HIV as the virus itself may sensitise cells to oncogenic processes (1, 34). This is illustrated by a significant 3 fold higher risk of developing lung cancer in HIV-infected individuals as compared to the general population after adjusting for smoking status (54, 55).

Currently, the notion that ART contributes to the development of NADCs is unclear, and further evidence is required (56). One postulation is that ART extends life expectancy in HIV-infected individuals and thus with aging, malignancy becomes more probable (34, 57). Effective ART readily increases the CD4 count but the normalisation of the CD4/CD8 (Cluster of differentiation 8 lymphocyte) ratio above 1 is slow, largely secondary to the persistence of increased CD8 lymphocytes, implying a chronic inflammatory state with immune activation and providing a possible mechanism for increased morbidity and mortality for patients on ART. However, a cohort study (n=11,485) noted that the onset of ADCs such as KS and NHL appeared to highest at within the first 6 months post ART initiation. This is probably attributed to severe immunosuppression present at the time of ART initiation resulting in an immune reconstitution inflammatory syndrome (IRIS) of subclinical malignant disease (58).

2.7 Previous literature on pancreatic cancer outcomes in HIV-positive patients

There is only one previous study specifically on outcomes of PC in the HIV-infected population. The Italian Cooperative Group on AIDS and Tumours identified 16 patients with who were HIV-positive and diagnosed with PC from April 1988 to June 2010. These patients were randomly matched with 32 HIV-negative patients (ratio 1:2). They found that the HIV-infected patients were diagnosed at a younger age and had a poorer Eastern Cooperative Oncology Group (ECOG) performance status (PS > 2) than the non-infected patients. A performance status of 2 or more and HIV infection were the only two variables which significantly reduced patient survival in PC and as

such the HIV-positive cohort showed shorter survival as compared to the HIV-negative cohort (59).

There is no current literature in SA which has been conducted exclusively on outcomes of patients with PC and who are concomitantly infected with HIV. Our study intends to elucidate on this.

3. Aims and objectives

3.1 Aim:

To determine and evaluate outcomes in HIV-positive patients diagnosed with PC in the South African setting.

3.2 Primary Objective:

To compare overall survival in patients with confirmed PC who are HIV-positive to patients with confirmed PC who are HIV-negative.

3.3. Secondary Objectives:

- To determine whether a relationship exists between VL, CD4 count and overall survival in patients with confirmed PC and who are HIV-positive.
- To compare the stage and the histological grade of PC at presentation in the HIV-positive to the HIV-negative patients.
- To assess and compare the demographics of patients diagnosed with PC and are HIV-positive with patients who are diagnosed with PC and are HIV-negative. These demographics will include age at presentation, ethnicity, and gender.

4. Methodology

4.1 Study Design

This study will be a retrospective observational study.

4.2 Study population

Sampling will be done from the admission records of all patients diagnosed with PC including those that undergo surgical resection and those that are managed

conservatively. The sample population will be from the hepatobiliary units at Chris Hani Baragwanath Academic hospital (CHBAH) and the University of Witwatersrand's (Wits) affiliated Donald Gordon Medical Centre (DGMC). Convenience sampling will be used whereby all patients admitted to these two hepatobiliary units from 01 January 2013 to 31 December 2018 will be included.

4.3 Data collection

Data will be extracted from the existing records of these two sites which include: patient demographics (age, gender, and ethnicity); disease stage and histology; patients' HIV status, viral load and CD4 count and overall patient survival as well as median survival time in months from presentation.

4.4 Statistical analysis

STATA® version 16 software will be used to analyse the data. All categorical variables which include: tumour histological grade and radiological stage; HIV sero-positivity or sero-negativity; patient ethnicity and gender will be presented as percentages. The continuous variables which include age and CD4 count will be presented by means and standard deviations (SDs) if nominally distributed and by medians and interquartile range (IQRs) if not nominally distributed. A regression model will be used to present VLs. Overall survival will be presented as median of time survived measured in months. A subgroup analysis comparing the outcomes in patients who underwent PD at CHBAH with those at Wits DGMC will also be done on request of the protocol assessors.

5. Ethical considerations

Ethics clearance will be obtained from the Wits Human Research Ethics Committee (medical). Permission to access patient records will be obtained from the head of medicine at CHBAH, along with the Chief Executive Officers of the respective institutions. In order to ensure patient confidentiality, each patient record will be allocated a study number at random. The primary investigator will only know which study number corresponds to a particular record. This information will be kept anonymous.

6. Timing

A Gantt chart illustrating the proposed timing of the study

	2018	2019	2019	2019	2019	2019	2019	2019	2019	2019	2019	2019	2019	2020
	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan
Literature Review														
Protocol Preparation														
Ethics Application														
Protocol Assessment														
Data Collection														
Write up														

7. Funding

As this is a retrospective observational study, no costs will be incurred upon the institutions in which this study will take place. Printing and stationary will be funded by the primary investigator.

8. Study limitations

Patients within the South African public health care system, namely, those referred to CHBAH have long delays to tertiary specialist care compared to patients attending private health care facilities such as DGMC. This may influence the stage of presentation and therefore outcomes of disease. Histology may not be present in all patients' records as those who score 3 or 4 on the ECOG functional scoring system or are diagnosed radiologically with advanced stage 4 disease will be palliated without a biopsy as per evidence-based clinical practice. Radiology records at CHBAH may be difficult to access. These obstacles, may underpower important intended objectives. Due to inconsistent record keeping at CHBAH valuable data for PC and HIV infection such as patients' social habits; body mass indices; diet; medical co-morbidities; previous admissions for pancreatitis; previous or concomitant infection with opportunistic infections; time from diagnosis of HIV infection and time on ART

cannot be extracted. The above limits this study in comprehensively describing the epidemiology of PC in both the HIV-positive and negative cohorts; in assessing possible factors contributing to mortality in both study groups and lastly in the potential to expand this study by exploring HIV as having a possible associative role in the development PC.

9. References

1. Deeken JF, Tjen-A-Looi A, Rudek MA, et al. 2012. The rising challenge of non-AIDS-defining cancers in HIV-infected patients. *Clin Infect Dis.* 55(9):1228-35.

2. Bower M, Collins S, Cottrill C,et al. 2008.British HIV Association guidelines for HIV-associated malignancies 2008. *HIV Med.* 9(6):336-88.

3. Joint United Nations Program on HIV/AIDS. UNAIDS Data 2017. Available: https://www.unaids.org/sites/default/files/media_asset/20170720_Data_book_2017_en.pdf. (Accessed 5.12.2019).

4. Rahib L, Smith BD, Aizenberg R, et al. 2014. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. *Cancer Res*.74(11):2913-21.

5. Ries LA, Wingo PA, Miller DS, et al. 2000.The annual report to the nation on the status of cancer, 1973-1997, with a special section on colorectal cancer. *Cancer*.88(10):2398-424.

6. Hariharan D, Saied A, Kocher HM. 2008. Analysis of mortality rates for pancreatic cancer across the world. *HPB (Oxford)*.10(1):58-62.

7. Boyle P, Hsieh CC, Maisonneuve P, et al. 1989. Epidemiology of pancreas cancer (1988). *Int J Pancreatol.*5(4):327-46.

8. Zhang J, Dhakal I, Ning B, Kesteloot H. 2008. Patterns and trends of pancreatic cancer mortality rates in Arkansas,1969-2002: a comparison with the US population. *Eur J Cancer Prev.*17(1):18-27.

9. South Africa. National Cancer Registry, National Health Laboratory Services. 2018. Ekurhuleni Population-based Cancer Registry Annual Report. Available: https://www.nicd.ac.za/wp-content/uploads/2020/04/EPBCR-2018-report-Final-report.pdf (Accessed 12.06.2021).

10. Ferrone CR, Brennan MF, Gonen M, et al. 2008. Pancreatic adenocarcinoma: the actual 5-year survivors. *J Gastrointest Surg.*12(4):701-6.

11. Siegel RL, Miller KD, Jemal A. 2019. Cancer statistics, 2019. *CA Cancer J Clin*.69(1):7-34.

12. Kamarajah SK, Frankel TL, Sonnenday C, et al. 2018. Critical evaluation of the American Joint Commission on Cancer (AJCC) 8th edition staging system for patients with Hepatocellular Carcinoma (HCC): A Surveillance, Epidemiology, End Results (SEER) analysis. *J Surg Oncol.*117(4):644-50.

13. Kang MJ, Jang JY, Chang YR, et al. 2014. Revisiting the concept of lymph node metastases of pancreatic head cancer: number of metastatic lymph nodes and lymph node ratio according to N stage. *Ann Surg Oncol.*21(5):1545-51.

14. Allen PJ, Kuk D, Castillo CF, et al. 2017. Multi-institutional Validation Study of the American Joint Commission on Cancer (8th Edition) Changes for T and N Staging in Patients With Pancreatic Adenocarcinoma. *Ann Surg.* 265(1):185-91.

15. Swords DS, Mulvihill SJ, Firpo MA, et al. 2018. Causes of Death and Conditional Survival Estimates of Medium- and Long-term Survivors of Pancreatic Adenocarcinoma. *JAMA Oncol.*4(8):1129-30.

16. Mayo SC, Nathan H, Cameron JL, et al. 2012 Conditional survival in patients with pancreatic ductal adenocarcinoma resected with curative intent. *Cancer.* 118(10):2674-81.

17. Brennan MF, Kattan MW, Klimstra D, et al. 2004. Prognostic nomogram for patients undergoing resection for adenocarcinoma of the pancreas. *Ann Surg*.240(2):293-8.

18. Michaud DS, Giovannucci E, Willett WC,et al. 2001. Physical activity, obesity, height, and the risk of pancreatic cancer. *JAMA*.286(8):921-9.

19. Arem H, Reedy J, Sampson J, et al. 2013. The Healthy Eating Index 2005 and risk for pancreatic cancer in the NIH-AARP study. *J Natl Cancer Inst*. 105(17):1298-305.

20. Michaud DS, Vrieling A, Jiao L, et al. 2010. Alcohol intake and pancreatic cancer: a pooled analysis from the pancreatic cancer cohort consortium (PanScan). *Cancer Causes Control*. 21(8):1213-25.

21. Batabyal P, Vander Hoorn S, Christophi C, et al. 2014. Association of diabetes mellitus and pancreatic adenocarcinoma: a meta-analysis of 88 studies. *Ann Surg Oncol.* 21(7):2453-62.

22. Trikudanathan G, Philip A, Dasanu CA, et al. 2011. Association between Helicobacter pylori infection and pancreatic cancer. A cumulative meta-analysis. *JOP.* 12(1):26-31.

23. Huang J, Magnusson M, Törner A, et al. 2013. Risk of pancreatic cancer among individuals with hepatitis C or hepatitis B virus infection: a nationwide study in Sweden. *Br J Cancer*. 109(11):2917-23.

24. Duell EJ, Lucenteforte E, Olson SH, et al. 2012. Pancreatitis and pancreatic cancer risk: a pooled analysis in the International Pancreatic Cancer Case-Control Consortium (PanC4). *Ann Oncol.* 23(11):2964-70.

25. Maartens G, Meintjies G, Mendelson M, et al. Managing drug toxicity. Pancreatitis. In: Aids for Aids: Clinical Guidelines 11th edition, ed. by L R, Dunn L, Maharaj S. Pinelands, South Africa:AFA management, 2016. pp. 95.

26. Grant RC, Selander I, Connor AA, et al. 2015. Prevalence of germline mutations in cancer predisposition genes in patients with pancreatic cancer. *Gastroenterology*. 148(3):556-64.

28. Frank DT, Carter A, Jahagirdar D, et al. 2019. Global, regional, and national incidence, prevalence, and mortality of HIV, 1980-2017, and forecasts to 2030, for 195 countries and territories: a systematic analysis for the Global Burden of Diseases, Injuries, and Risk Factors Study 2017. *Lancet HIV.*6(12):831

27. Shindo K, Yu J, Suenaga M, et al. 2017. Deleterious Germline Mutations in Patients With Apparently Sporadic Pancreatic Adenocarcinoma. *J Clin Oncol*.35(30):3382-90.

29. Joint United Nations Program on HIV/AIDS. UNAIDS Data 2019. Available: https://www.unaids.org/sites/default/files/media_asset/2019-UNAIDS-data_en.pdf. (Accessed on 03.10.2020).

30. Joint United Nations Program on HIV/AIDS. Women and Girls and HIV 2018. Available: https://www.unaids.org/sites/default/files/media_asset/women_girls_hiv_en.pdf.(Accessed on 10.10.2020).

31. Connolly C, Shisana O, Shishana O, et al. 2004. Epidemiology of HIV in South Africa-results of a national, community-based survey. *S Afr Med J*.94(9):776-81.

32. Rubinstein PG, Aboulafia DM, Zloza A. 2014. Malignancies in HIV/AIDS: from epidemiology to therapeutic challenges. *AIDS.*28(4):453-65.

33. Reid E, Suneja G, Ambinder RF, et al. Cancer in People Living With HIV, Version 1. 2018,NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw.* 2018;16(8):986-1017.

34. Chiao EY, Coghill A, Kizub D, et al. 2021. The effect of non-AIDS-defining cancers on people living with HIV. *Lancet Oncol.* 22(6):240-53.
35. Biggar RJ, Chaturvedi AK, Goedert JJ, et al. 2007.AIDS-related cancer and severity of immunosuppression in persons with AIDS*. J Natl Cancer Inst*.99(12):962-72.

36. Engels EA, Biggar RJ, Hall HI, et al. 2008. Cancer risk in people infected with human immunodeficiency virus in the United States*. Int J Cancer.*123(1):187-94.

37. Franceschi S, Lise M, Clifford GM, et al. 2010. Changing patterns of cancer incidence in the early- and late-HAART periods: the Swiss HIV Cohort Study. *Br J Cancer*.103(3):416-22.

38. Powles T, Robinson D, Stebbing, et al. 2009. Highly active antiretroviral therapy and the incidence of non-AIDS-defining cancers in people with HIV infection. *J Clin Oncol*. 27(6):884-90.

39. Tanaka LF, Latorre MDRD, Gutierrez EB, et al. 2017. Trends in the incidence of AIDS-defining and non-AIDS-defining cancers in people living with AIDS: a population-based study from São Paulo, Brazil. *Int J STD AIDS.*28(12):1190-8.

41. Zhu W, Mao Y, Tang H, et al. 2019. Spectrum of malignancies among the population of adults living with HIV infection in China: A nationwide follow-up study, 2008-2011. *PLoS One.*14(7):e0219766.

42.Dhokotera T, Bohlius J, Spoerri A, et al. 2019. The burden of cancers associated with HIV in the South African public health sector, 2004-2014: a record linkage study.

43. Sengayi M, Spoerri A, Egger M, et al. 2016. Record linkage to correct under-ascertainment of cancers in HIV cohorts: The Sinikithemba HIV clinic linkage project. *Int J Cancer.*139(6):1209-16.

44. Mbulaiteye SM, Katabira ET, Wabinga H, et al. 2006. Spectrum of cancers among HIV-infected persons in Africa: the Uganda AIDS-Cancer Registry Match Study. *Int J Cancer*. 118(4):985-90.

45. Akarolo-Anthony SN, Maso LD, Igbinoba F, et al. 2014. Cancer burden among HIV-positive persons in Nigeria: preliminary findings from the Nigerian AIDS-cancer match study. *Infect Agent Cancer.* 9(1):1.

46. Kravcik S, Hawley-Foss N, Victor G, et al. 1997. Causes of death of HIV-infected persons in Ottawa, Ontario, 1984-1995. *Arch Intern Med.*157(18):2069-73.

47. Bonnet F, Lewden C, May T, et al. 2004.Malignancy-related causes of death in human immunodeficiency virus-infected patients in the era of highly active antiretroviral therapy. *Cancer.*101(2):317-24.

48. Coghill AE, Han X, Suneja G, et al. 2019. Advanced stage at diagnosis and elevated mortality among US patients with cancer infected with HIV in the National Cancer Data Base. *Cancer*. 125(16):2868-76.

49. Park LS, Tate JP, Sigel K, et al. 2018. Association of Viral Suppression With Lower AIDS-Defining and Non-AIDS-Defining Cancer Incidence in HIV-Infected Veterans: A Prospective Cohort Study*. Ann Intern Med*.169(2):87-96.

50. Carbone A, Gloghini A. 2005. AIDS-related lymphomas: from pathogenesis to pathology. *Br J Haematol.*130(5):662-70.

51. Yanik EL, Napravnik S, Cole SR, et al. 2014.Relationship of immunologic response to antiretroviral therapy with non-AIDS defining cancer incidence. *AIDS*.28(7):979-87.

52. Shiels MS, Althoff KN, Pfeiffer RM, et al. 2017. HIV Infection, Immunosuppression, and Age at Diagnosis of Non-AIDS-Defining Cancers. *Clin Infect Dis*.64(4):468-75.

53. Appay V, Sauce D. 2008. Immune activation and inflammation in HIV-1 infection: causes and consequences. *J Pathol.*214(2):231-41.

54. Kirk GD, Merlo C, O' Driscoll P, et al. 2007. HIV infection is associated with an increased risk for lung cancer, independent of smoking. *Clin Infect Dis*.45(1):103-10.

55. Simard EP, Engels EA. 2010. Cancer as a cause of death among people with AIDS in the United States. *Clin Infect Dis*.51(8):957-62.

56.Bruyand M, Ryom L, Shepherd L, et al. 2015. Cancer risk and use of protease inhibitor or nonnucleoside reverse transcriptase inhibitor-based combination antiretroviral therapy: the D: A: D study. *J Acquir Immune Defic Syndr.* 68(5):568-77.

57. Silverberg MJ, Lau B, Achenbach CJ, et al. 2015.Cumulative Incidence of Cancer Among Persons With HIV in North America: A Cohort Study. *Ann Intern Med.*163(7):507-18.

58. Yanik EL, Napravnik S, Cole SR, et al. 2013. Incidence and timing of cancer in HIV-infected individuals following initiation of combination antiretroviral therapy. *Clin Infect Dis*. 57(5):756-64.

59. Zanet E, Berretta M, Benedetto FD,et al. 2012. Pancreatic cancer in HIV-positive patients: a clinical case-control study. *Pancreas.* 41(8):1331-5.

Chapter 2: Submissible article

Title: Evaluation of outcomes in patients with pancreatic cancer and Human Immunodeficiency Virus at Chris Hani Baragwanath Academic Hospital and the Donald Gordon Medical Centre, Johannesburg, South Africa.

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Abstract

Background:

Non-AIDS-defining Cancers are increasing in incidence and mortality in the HIV-positive population. Pancreatic cancer (PC) is projected to be the second cause of cancer-related death by 2030. No literature exists on patients with PC and concomitant human immunodeficiency virus (HIV) infection in South Africa, which has the highest number of HIV-positive people in the world.

Objectives:

To compare the demographics, stage, histological grade of disease, and survival outcomes of HIV-positive compared to HIV-negative patients diagnosed with PC.

Methods:

Patient records with PC were collected from Chris Hani Baragwanath Academic Hospital (CHBAH) and the Wits Donald Gordon Medical Centre (DGMC) from the 1st of January 2013 to the 31st of December 2018. A total of 240 patients' records were obtained. Demographic, clinical, and survival data were collected.

Results:

There were predominantly black Africans (64.6%) and males (54.6%) in the study. Although overall survival between the HIV-positive and negative patients did not differ (p=0.051), the median time of survival from presentation was significantly shorter in the HIV-positive compared to the HIV-negative patients (2.1 months; IQR 1.2-6.0 vs. 4.7 months; IQR 1.6-13.0; p=0.017). The HIV-positive cohort presented at a significantly younger age compared to the negative cohort (54.6; ±9.6 vs 62.4; ±11.1; p=0.0001) and at a more advanced stage of disease (72.2% vs. 43.1%; p=0.017). No difference was found between the histological grade of PC in both cohorts (p=0.298). The median survival time for HIV-positive patients on therapy at presentation was significantly longer compared to patients who were not (3.0; IQR 1.3-7.8 vs 1.1 months; IQR 0.9-1.9; p=0.037). Overall survival in patients who underwent PD at Wits DGMC was shown to be higher compared CHBAH (41.7%vs. 12.5%; p=0.049). The

majority of the patients presented with regionally advanced (30.6%) and metastatic disease (50.3%).

Conclusion:

This is the first study in South Africa to provide insight into the clinical disease profile and survival outcomes of HIV-positive patients diagnosed with PC. This study has shown that HIV-infected patients with PC have a specific disease profile. Therefore, testing for HIV infection should be included in the management of all patients with PC, a higher index of suspicion for cancer should be maintained in younger HIV-positive patients; and initiation of ART must be timeous.

Introduction

South Africa (SA) carries 64% of the global HIV burden (1). People living with HIV (PLWH) are at increased risk for developing AIDS Defining Cancers (ADCs): Kaposi Sarcoma (KS), Non-Hodgkin lymphoma (NHL) and Cervical Carcinoma (CC). These cancers have decreased significantly with the advent of Antiretroviral treatment (ART) (2). However, the incidence of Non-AIDS-defining Cancers (NADCs) has increased even after controlling for known cancer risk factors (3). Studies from developed countries have described the epidemiology and survival outcomes of NADCs but there is limited literature on Pancreatic Cancer (PC) and survival outcomes in the HIV-positive population.

The global incidence of HIV infections has demonstrated a decline of 47% from 2001 to 2016 but prevalence has stabilised or increased in some countries (1). This reflects an increased life expectancy with ART and an aging HIV population which account for the observed increased incidence of NADCs and cancer-related mortality (4, 5). Before the ART era, cancers accounted for less than 10% of mortality in PLWH (6) whereas, in the era of ART, cancers accounted for 28% of mortality in a French study with a large (n=64,000) HIV-positive population (7). Another (n=6,459) retrospective observational study, found overall cancer-related mortality, independent of cancer stage and receipt of therapy was significantly increased in the HIV-infected compared to the non-infected population. Of note, mortality was significantly increased in colorectal, pancreas, laryngeal, lung, melanoma, breast and prostate cancer (5).

The role of ART and the importance of immunological and virological status in ADCs is clear but is less uniform for NADCs. One study showed that a Cluster of Differentiation 4 (CD4) lymphocyte count of less than 200 cell/mm^3 and plasma viral load (VL) levels of more than 500 copies/mL were independently associated with an increased risk for ADCs, while each additional year of ART use was associated with a reduced risk. A higher risk for NADCs was independently associated with a CD4 count of less than 200 cells/mm^3 but VL and ART use did not confer a risk (8). A more recent American study, however, found risk reduction for virally-mediated NADCs with early and long-term VL suppression. This finding was not observed in non-virally mediated

NADCs. Notably, long-term viral suppression still conferred excess cancer risk in HIV-infected patients compared to non-infected patients (9).

The largest study on the incidence of cancers in the ART-era in Africa (n=46, 952), from SA, found the incidence of ADCs was consistently higher than NADCs throughout the study period 2004-2014 but that the HIV-positive population was still at a higher risk for virus-related NADCs such as penile, liver, oral cavity and vulval cancers (10). Another South African study conducted in the ART-era, showed that KS and invasive CC still had the highest incidence but that the incidence of NADCs was on the rise and gained prominence over CC and NHL from the second year on ART (11). This demonstrates that the cancer-shift from ADCs to NADCs in HIV-positive populations observed in high-income countries was not yet apparent in SA. This is possibly before the test and treat strategy was implemented in SA where a CD4 count threshold was required before ART could be initiated (10). However, existing literature from countries who had comparable socioeconomic statuses to SA at the time of this study, such as the BRIC (Brazil, India, and China) nations also showed that the incidence of ADCs was also still more frequent than NADCs in their respective HIV-positive populations (12-14).

Pancreatic cancer accounts for 3.2% of all new cancers with an incidence that has been increasing between 0.5% to 1% per year (15) and is responsible for approximately 7% of deaths globally with an overall 5-year survival rate below 10% (16, 17). Men have an increased overall lifetime risk compared to women (18) and the highest incidence is found among African Americans and the Māori population in New Zealand (19, 20). The incidence of PC increases after the age of 45 years and before this, the disease frequency is low (21). In SA, existing literature on the epidemiology of PC is limited due to inadequate reporting. Data published in the Ekurhuleni Population-Based Cancer Registry (EPBCR) 2018 report showed that over one year, there were 33 and 28 new cases of histologically confirmed PC in women and men with known ages respectively and 61 new cases that were morphologically verified or diagnosed clinically or by death certificate only. PC was among the top ten cancers occurring in women with an age-standardised incidence rate (ASR) of 2.38/100 000 person-years with the highest ASR in the 85 and older age group. Men had an ASR of 1.76/100 000 person-years with the highest ASR in the age group of 80 to 85.The

incidence was highest in caucasians, followed by black Africans, people of mixed ethnicity and lastly by asians (22).

There is only one previously published study on survival outcomes of PC in HIV-positive patients. The Italian Cooperative Group on AIDS and Tumours found that HIV-positive patients presented at a younger age and had a poorer performance status (PS > 2) than the negative patients. Performance status of 2 or more and HIV infection were the only two factors which significantly reduced patient survival in PC (23). This is concerning as the HIV epidemic still poses a significant burden on the South African population. An aging HIV-positive population along with age-related diseases such as PC is on the rise (24-26). This prompted a collection of data on HIV-positive patients diagnosed with PC at two tertiary hospitals in Johannesburg to describe demographics, the clinical disease profile and survival outcomes.

Methodology

Study design and setting

This was a retrospective observational study conducted at Chris Hani Baragwanath Academic Hospital (CHBAH) and the Wits affiliated Donald Gordon Medical Centre (DGMC). CHBAH is the largest tertiary hospital in Africa and provides health care to an extensive area within the largely urban southern region of Johannesburg and parts of Gauteng. Wits DGMC is a smaller and private tertiary hospital in central Johannesburg.

Ethics

Ethics to conduct this study was obtained from the University of Witwatersrand Human Research Ethics Committee (HREC) before its commencement (M190704).

Data collection

A total of 449 patient records with the diagnosis of PC from 01 January 2013 to 31 December 2018 were obtained. Data on patient demographics (age, sex, ethnicity); clinical and laboratory disease parameters (whether pancreaticoduodenectomy (PD) was undertaken or not; ART use; stage of disease, histological grade of disease; CD4

counts, VLs and survival outcomes) were retrospectively collected. Data collection and analysis on survival outcomes after PD was also done. A total of 129 patient records proved to have benign disease or malignancy other than PC on retrieval of histology were excluded. If the date of death was not documented in the patients' records, active follow-up was made to verify the vital status and to obtain the official date of death by contacting patients' next of kin using contact numbers provided in their respective original records. Data from a final population sample of 240 patients were analysed (figure 2).

Definitions

Pancreatic cancer was staged according to the 8th edition of the American Joint Committee on Cancer Tumour Node and Metastasis (AJCC TNM) system using radiological cross-sectional imaging (27). Virological and immunological incompetence were defined as VLs above 400 RNA copies/mL and CD4 counts below 200 cells/mm^3 respectively, based on existing literature on using CD4 count and VL as parameters within the context of malignancies (8, 9, 28). Patient records were assigned to a suppressed group and a non-suppressed group based on a VL less than or greater than 400 RNA copies/mL respectively. Similarly, patients were assigned to immune-competent and immune-suppressed groups based on a CD4 count of greater than or less than 200 cells/mm^3.

Statistical analysis

STATA® version 16 software was used to analyse the data. The distribution of continuous data such as age, CD4 counts, and VL, was determined using the Shapiro-Wilk test and differences between the HIV-negative and HIV-positive cohort were tested using the Two-sample t-test with equal variances for normally distributed data or the Mann-Whitney U test for non-parametric data. Propensity match scoring was also done. Differences between categorical variables were determined using the Pearson's Chi-squared test or two-sided Fisher's exact test, as appropriate. Survival was recorded as the median time of survival in months and the 1st of May 2020 was used as the date to categorize vitality status as the international average for overall survival in patients with PC undergoing PD and receiving adjuvant chemotherapy (the

best case scenario) at the time of this study's conception was 28 months (29). The survival analysis was measured from the date of presentation to the date of death using the Kaplan-Meier survival method. Differences in survival probability between the HIV-infected and non-infected cohorts were tested using the Mann-Whitney test. Statistical significance was claimed as $P<0.05$.

Results

Baseline characteristics of the study population

A total of 240 patients had a documented formal HIV Enzyme-Linked Immunosorbent Assay (ELISA) test done and of that 15% (n=36) of patients with PC were confirmed to be HIV-positive. The majority of the HIV-infected patients were on ART (75%; n%; n=27), immune-competent, and virally suppressed (65.6%; n%; n=11). Table 1 shows the characteristics of the patient and the disease profiles as well as survival data in both the HIV-positive and negative cohorts. Table 2 shows ART use, the CD4 counts and VLs of the HIV-positive patients.

Overall, the mean age (±SD) was 61.2 (±11.2) years of age. HIV-positive patients presented at a significantly younger mean age than their seronegative counterparts (54.6;±9.6 vs 62.4; ±11.1; p=0.0001). Furthermore, as noted in Table 2, HIV-positive patients presented a decade earlier in the age category than the HIV-negative patients (p=0.05).

The overall cohort of patients comprised predominantly (64.6%;n=155) black Africans, followed by Caucasians (25.4%;n=61). Asian and patients of mixed-ethnicity accounted for a minority of the population sample. Black African patients and patients of mixed-ethnicity accounted for 94.4%(n=34) and 5.6%(n=5.6) of the HIV-positive cohort, respectively. No Caucasian or Asian patients were confirmed as being HIV-positive.

The majority of the total population sample were male (54.6% n=131) and the HIV-positive cohort showed a male predominance (63.9%;n=23). There was no statistically

significant difference in terms of gender between the HIV-negative and positive groups (p=0.224).

Stage of disease and histological grade of disease

The vast majority of the overall patient cohort presented with regionally advanced (30.6%; n=98) and metastatic disease (50.3%;n=161). Notably, in the HIV-positive cohort, no patients presented with stage 1 disease and only (8.3%;n=3) presented with early and potentially resectable stage 2 tumours. The HIV-positive patients had significantly more advanced and metastatic disease at presentation than the HIV-negative patients (72.2%;n=26 versus 43.1%;n=88 respectively; p= 0.017).

Overall, less than half (45.8%;n=110) of the population sample had formal histology obtained, of which the majority were moderately-differentiated (57.3%;n=63) and poorly-differentiated (27.3%;n=30) tumours. There was a strong and directly proportional relationship between the stage of disease at presentation and the grade of the tumour. There was no difference found in the grade of the pancreatic adenocarcinomas between the HIV-positive and negative-cohort (p =0.298).

Survival

A striking 91.2% (n=219) demised and had a median survival time of 3.6 months from presentation (IQR 1.3-10.5). Of those who demised, a clear majority (84.1%; n=184) had loco-regional and metastatic disease at presentation. This demonstrated an expected finding between the stage of disease at presentation and prognosis (p=<0.0001). There was no significant difference found between survival and the histological grade of the tumour (p =0.075). Although overall survival between the HIV-positive and negative patient cohorts did not differ (p=0.051), the median time of survival from presentation was significantly reduced in the HIV-positive patients when compared to the HIV-negative patients (2.1 months; IQR 1.2-6.0 versus 4.7 months IQR 1.6-13.0; p=0.017). Moreover, the Kaplan-Meier survival curve (Figure 1) shows that all the HIV-positive patients compared to 87.3% of the HIV-negative patients had demised by 28 months. Although inferences cannot be made as statistical significance was not reached, it is striking that only 3 patients (8.3%) in the HIV-positive cohort underwent PD with 100% (n=3) dying compared to 45 patients (22.1%) who underwent PD with 71.1% (n=32) dying in the HIV-negative cohort (p=0.553). There was no

significant difference found between VL suppression, CD4 count, and survival outcomes in the HIV-positive patients (p=0.293;p=0.967) but the median survival time for patients on ART at presentation was significantly longer compared to patients not on ART (3.0; IQR 1.3-7.8 vs 1.1 months; IQR 0.9-1.9; p=0.037).

A sub-analysis was done to compare survival outcomes in patients who underwent PD at CHBAH and Wits DGMC. Although a minority of patients from both study sites' cohorts underwent PD, a significantly larger proportion of patients diagnosed with PC at Wits DGMC underwent PD when compared to CHBAH (14.6%;n=24 versus 32%;n=24; p=0.003). The majority of patients who underwent PD from both study sites demised, which is consistent with global literature on PC, however, overall survival in patients with PC who underwent PD at Wits DGMC was shown to be significantly higher when compared to those who underwent the surgery at CHBAH (41.7%;n=10 versus 12.5%;n=6; p=0.049).

Discussion

This is the first observational study in SA which has evaluated the demographic and disease profiles as well as survival outcomes in patients with PC and HIV infection.

The mean age of HIV-positive patients with PC was 54 years of age, which reflects the current international epidemiological literature on PC (21), however, the HIV-positive patients still presented at a significantly younger mean age compared to their negative counterparts (54 versus 62 years, respectively p=0.0001). A minority of the HIV-positive patients were in the 70-89 age group category when compared to the HIV-negative patients. Conversely, a larger percentage of HIV-positive than HIV-negative patients were in the 23-39 age group category. A possible explanation for this could be that the peak incidence of HIV infection in SA is in the age group of 20-29 for women and 30-39 for men respectively (30). HIV-positive patients with cancer experience a more aggressive and rapid clinical disease course due to accelerated aging linked with chronic immune activation in HIV infection (31) and this may be another contributing factor for earlier health-seeking behaviour and thus a younger age at first presentation than HIV-negative patients. This is important as treating

clinicians need to have a higher index of suspicion for malignancy in patients who are HIV-positive and younger than the typical age demographic for PC.

The demographic of the HIV-positive patients in a previous Italian study consisted mostly of intravenous drug-users and homosexual men (23). While the HIV epidemic in SA is starkly different and is dominated by heterosexual transmission which disproportionally and affects young women (30, 32), our findings were consistent with the Italian study in terms of gender and demonstrated that the majority of the HIV-positive cohort was male. There was no significant difference observed when comparing gender in patients with PC against HIV seropositivity or seronegativity (p=0.150). This is explained by the nature of PC itself where men are known to have an increased overall lifetime risk as compared to women and is consistent with our study's findings of a clear male predominance in both the HIV-positive and negative cohorts (18).

In terms of ethnicity, black Africans made up the majority of the total population sample, followed by caucasians, people of mixed-ethnicity, and lastly by Asians. This is in keeping with international literature on PC where incidence is highest in black people (19). Our findings, however, were inconsistent with local data from the EPBCR 2018 report where incidence was highest in caucasians, followed by black Africans, people of mixed ethnicity, and lastly by Asians (22). These discordant findings may be explained by a delay and underreporting of PC to the National Cancer Registry (NCR) as well as by bias of the sites reporting. Black Africans and people of mixed-ethnicity accounted for 94.4% and 5.6% of the HIV-positive cohort respectively (p=0.000), reflective of the epidemiology of the HIV-epidemic in SA (10, 30). Although no caucasians tested positive for HIV infection, the prevalence for HIV infection among caucasian South Africans is the highest documented population-level prevalence in the world (30). The above explains the increased incidence of PC and HIV infection in black South Africans and highlights the need for HIV status to be included in the South African NCR to improve insight into and facilitate research in this specific population.

Consistent with global data on PC, 47.5% of all patients diagnosed with PC presented with the AJCC TMN staging criteria for metastatic disease; 32.1% with locally advanced disease and 20.4% with resectable disease. This speaks to the inherent

insidious nature and clinical onset of PC itself but also may be explained in part by the delayed presentation of South Africa's general patient population to a tertiary health care facility. Importantly, a minority of HIV-positive patients (8.3%) had resectable disease. Patients with PC and concomitant HIV infection had significantly more advanced (p= 0.017) and metastatic disease (p=0.002) at index presentation when compared to non-infected patients. This emphasises the importance of expediting and completing the workup for malignancy timeously to curb accelerated disease progression and halt metastasis in HIV-positive patients with PC. Perhaps due to a small sample size of available formal histology, there was no significant difference in the histological grade of pancreatic adenocarcinomas between the HIV-positive and negative patients (p=0.298). Immune escape mechanisms, which may also contribute to accelerated disease progression have been noted in PC, particularly in tumours with BRCA2 mutations, however, no work has been done in the HIV-positive population (31).

Overall survival in both HIV-positive and negative patients with PC was low (91.3%) with a median time of survival from presentation of 3.6 months (IQR 1.3-10.3), consistent with global and current literature on PC where 5-year survival is below 10% (16). This is largely due to the stage of disease at presentation where approximately half (47.5%) of the total patient cohort presented with metastatic disease. Although statistical significance was not reached for overall survival in HIV-positive patients compared to HIV-negative patients with PC (p=0.051), a significant reduction in a median time of survival in months from the time of presentation in the HIV-positive cohort as compared to the negative cohort was found (2.1; IQR 1.2-6.0 vs 4.7; IQR 1.6-13.0 vs. 2.1; p= 0.017). This is predominantly related to the HIV-positive cohort presenting at a more advanced stage with a higher likelihood of having metastasis, thus portending a poorer prognosis. Importantly, the vast majority (91.7%) of the HIV-positive patients did not undergo PD, further contributing to a reduced survival time as long-term survival in PC is only achieved with complete surgical resection with both negative margins and node-negative disease (16, 33). The majority of the HIV-infected patients were immune-competent (75.8%) and virally suppressed (65.6%) but immunological competence and virological suppression did not affect survival outcomes (p=0.967;p= 0.293), consistent with the findings of the previous Italian study and other international literature on NADCs (8, 23). Although this could be skewed by

a low sample size of HIV-positive patients with documented CD4 counts and viral loads, this suggests that factors other than immunosuppression present in the HIV-positive cohort may be contributing to reduced survival time. These factors may include: patients present at advanced stages of disease; have a more aggressive clinical course; have frequent treatment failure, high rates of recurrence (25, 34-36); are less likely to receive cancer-specific treatment (37); frequently have co-morbidities and poor performance statuses and are less likely to be surgical candidates due to increased risk for post-operative infections (38). Furthermore, there is poor understanding of NADCs in HIV-positive patients which are not known to be mediated by an oncogenic virus, such as PC (5, 25, 26). Cancer-specific treatment disparities between HIV-positive and negative patients exist, resulting in substandard management. The National Comprehensive Cancer Network has begun to remedy this by creating guidelines and providing health care worker education (26). Paradoxically in our study, ART use at presentation significantly improved overall mortality with a median survival time of 3.0 (IQR 1.3-7.8) compared to 1.1 (IQR 0.9-1.9) months in HIV-positive patients who were not on ART (p=0.037). This may be due to patients on ART having more contact with the healthcare system in general, decreased risk of opportunistic infections and less immune dysregulation which uncontrolled HIV infection confers (39). This emphasises that HIV infection carries a significant worse prognosis in PC and thus HIV testing should be included in the management of all patients diagnosed with PC and importantly, effective ART should be initiated timeously. Furthermore, treating health professionals should adhere to established national cancer screening guidelines and appropriately manage co-morbidities in the HIV-infected patients.

Lastly, a significant difference in overall survival after PD between the study sites (p=0.049), can be explained by earlier and direct access to tertiary facilities by privately funded patients compared to patients who utilise public health care.

Limitations

Limitations to these findings mainly arise from our study's retrospective design, nonetheless, it provides an important foundation for the evaluation of the clinical

disease profile and survival outcomes of HIV-positive patients with PC. This foundation provides an opportunity to expand the study in exploring a possible associative relationship between HIV infection and PC. Due to the study's retrospective design, 80 patient records were excluded as these did not contain a documented HIV result, resulting in potential bias as a relatively large number of records could not be assessed. Data relating to PC risk factors; patient performance status, follow up and co-morbidities as well as data relating to HIV infection such as the duration of ART use were not originally documented in patient hospital records. These retrospective design issues, limit a more comprehensive description of PC in SA's HIV-positive population and in assessing possible factors contributing to a shorter survival time. Other limitations can be attributed to natural history PC itself: the majority of our cohort presented with advanced disease and as such, a significant proportion of patients received palliative care and did undergo a diagnostic procedure to procure histology as per standard clinical practice, limiting the sample size of available histology from the HIV-infected patient cohort.

Conclusion

This study has provided new insight into the clinical disease profile and survival outcomes of South African HIV-positive patients diagnosed with PC. The patient demographics in HIV-positive patients with PC in SA are similar to HIV-negative patients described in international literature in terms of gender and ethnicity. Namely, the highest incidence of PC is found in black males. However, South African HIV-infected patients with PC have a unique disease phenotype and course in that they present at a significantly younger age, with more advanced disease, and have a shorter median time of survival in months from their index presentation when compared to their non-infected counterparts.

Tables and figures

Table 1: Clinical characteristics, stage, histology and survival outcomes of 240 patients with pancreatic cancer according to HIV infection status

Parameters	HIV-Negative		HIV-Positive		Total		p-value
	N	%	N	%	N	%	
Total number (N)	204	85.0	36	15.0	240	100	
Age at presentation							
Mean age (±SD), years	62.4 (11.1)		54.6 (9.6)		61.2 (11.2)		0.0001
23-39	5	2.5	3	8.3	8	3.3	0.005
40-49	17	8.3	7	19.4	24	10.0	
50-59	59	28.9	15	41.7	74	30.8	
60-69	75	36.8	10	27.8	85	35.4	
70-79	40	19.6	1	2.8	41	17.1	
80-89	8	3.9	0	0.0	8	3.3	
Total	204	100.0	36	100.0	240	100.0	
Ethnicity							<0.0001
Black African	121	59.3	34	94.4	155	64.6	
Mixed ethnicity	12	5.9	2	5.6	14	5.8	
Caucasian	61	29.9	0	0.0	61	25.4	
Asian	10	4.9	0	0.0	10	4.2	
Total	204	100.0	36	100.0	240	100.0	
Gender							0.277
Female	96	47.1	13	36.11	109	45.4	
Male	108	52.9	23	63.9	131	54.6	
Total	204	100.0	36	100.00	240	100.0	
Histology							0.298
Well differentiated	15	16.5	2	10.5	17	15.5	
Moderately differentiated	54	59.3	9	47.4	63	57.3	
Poorly differentiated	22	24.2	8	42.1	30	27.3	
Total	91	100.0	19	100.0	110	100.00	

Differentiated	69	75.8	11	57.9	80	72.7	0.155
Undifferentiated	22	24.2	8	42.1	30	27.3	
Total	91	100.0	19	100.0	110	100.0	
Stage at presentation							
1	10	4.9	0	0.0	10	4.2	
2	36	17.7	3	8.3	39	16.3	
3	70	34.3	7	19.4	77	32.1	0.017
4	88	43.1	26	72.2	114	47.5	
Total	204	100.0	36	100.0	240	100.0	
Metastatic disease at presentation							
Locoregional	116	56.9	10	27.8	126	52.5	
Metastatic	88	43.1	26	72.2	114	47.5	0.002
Total	204	100.0	36	100.0	240	100.0	
Pancreaticoduodenectomy							
Yes	45	22.1	3	8.3	48	20.0	
No	159	77.9	33	91.7	192	80.0	0.070
Total	204	100.0	36	100.0	240	100.0	
Survival post-PD							
Demised	32	71.1	3	100.0	35	72.9	0.553
Still Alive	13	28.9	0	0.0	13	27.1	
Total	45	100.0	3	100.0	48	100.0	
Overall Survival							
Demised	183	89.7	36	100.0	219	91.2	0.051
Still alive	21	10.3	0	0.00	21	8.8	
Total	204	100.0	36	100.0	240	100.0	

Table 2 : CD4 cell counts, VLs and ART use in 36 HIV-positive patients with pancreatic cancer

Parameter	N	%	Median	IQR
CD 4 count at presentation (mm^3)	33	100.0	302	213-420
>200	25	75.8		
<200	8	24.2		
VL at presentation (RNA copies/mL)	32	100.0	50	50-3005
<400	21	65.6		
>400	11	34.4		
Anti-retroviral therapy use	36	100.0		
Yes	27	75.0		
No	9	25.0		

Table 3: Median time of survival in months from presentation according to HIV infection status, CD4 count and viral load

Category	N	%	Survival (median time in months)	IQR	p-value
Alive	21	8.8	23.8	14.1-32.5	
Demised	219	91.2	3.6	1.3-10.3	<0.001
Total	240	100.0	4.2 (IQR 1.4-12.1)		
HIV +	36	15.0	2.1	1.2-6.0	
HIV-	204	75.0	4.7	1.6-13.0	0.017
Total	240	100.0	4.2 (IQR1.4-12.1)		
CD4>200/mm3	25	75.8	1.9	1.1-5.9	
CD4<200/mm3	8	24.2	1.9	1.1-6.1	0.967
Total	33	100.0			

VL>400 copies/mL	11	34.4	1.6	1.1-4.5	0.293
VL<400 copies/mL	21	65.6	2.9	1.3-7.8	
Total	32	100.0			
On ART	27	75.0	3.0	1.3-7.8	0.037
Not on ART	9	15.0	1.1	0.9-1.9	
Total	36	100.0	2.1 (IQR 1.2-6.0)		
CD4 <200/mm3 & VL>400 copies/mL	16	51.6	2.4	1.3-6.0	0.707
CD4>200/mm3 & VL<400 copies/mL	15	48.4	2.3	1.1-6.6	
Total	31	100.0			
Pancreaticoduodenectomy					0.048
Demised	35	72.9	12.8	6.0-22.9	
Survived	13	27.1	24.7	14.1-34.0	
Total	48	100.0	15.2	7.6-31.3	

Table 4: Survival outcomes in patients after pancreaticoduodenectomy (PD) at CHBAH compared to Wits DGMC

	CHBAH		WDGMC		Total		p-value
	N	%	N	%	N	%	
Total	165	68.8	75	31.3	240	100	

Pancreaticoduodenectomy							
Yes	24	14.6	24	32.0	48	20.0	
No	141	85.5	51	68.0	192	80.0	0.003
Total	165	100.0	75	100.0	240	100.0	
Post-PD							
Demised	21	87.5	14	58.3	35	72.9	
Still alive	3	12.5	10	41.7	13	27.1	0.049
Total	24	100.0	24	100.0	48	100.0	
Overall Survival							
Demised	159	96.4	60	80.0	219	91.3	
Still alive	6	3.6	15	20.0	21	8.8	0.000
Total	165	100.0	75	100.0	240	100.0	

Figure 1: Kaplan-Meier estimates comparing overall survival between HIV-positive (HIV revised=1) and HIV-negative (HIV revised=0) patients diagnosed with pancreatic cancer

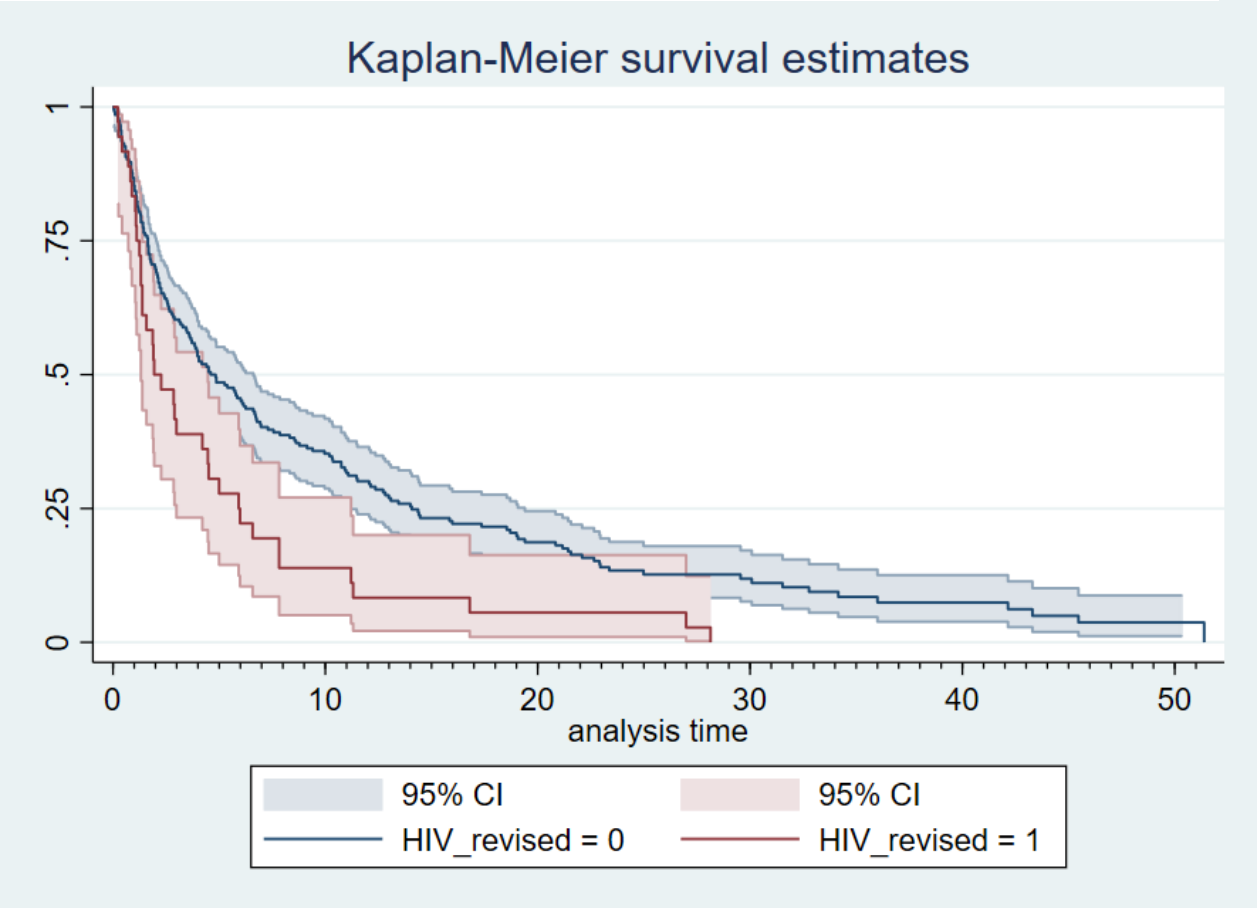
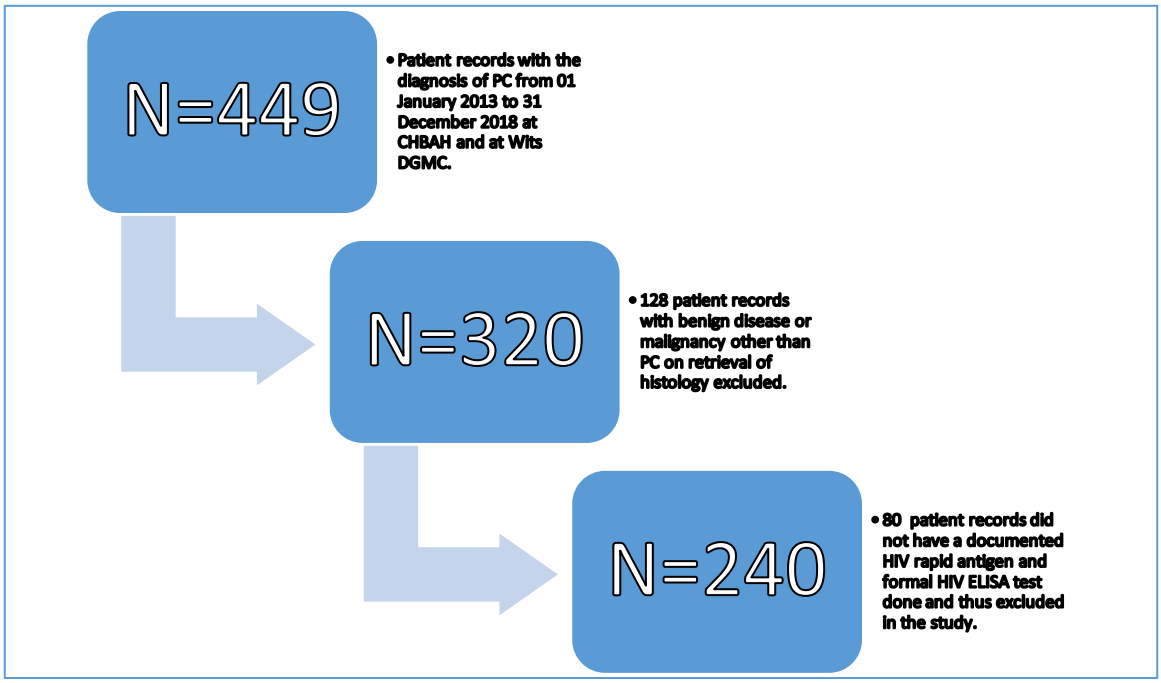


Figure 2: Flow chart illustrating the derivation of the final population sample size



References

1. Joint United Nations Program on HIV/AIDS. UNAIDS Data 2017. Available: https://www.unaids.org/sites/default/files/media_asset/20170720_Data_book_2017_en.pdf. (Accessed 5.12.2019).

2. Biggar RJ, Chaturvedi AK, Goedert JJ, et al. 2007.AIDS-related cancer and severity of immunosuppression in persons with AIDS. *J Natl Cancer Inst*.99(12):962-72.

3. Engels EA, Biggar RJ, Hall HI, et al. 2008. Cancer risk in people infected with human immunodeficiency virus in the United States. *Int J Cancer.*123(1):187-94.

4. Silverberg MJ, Lau B, Achenbach CJ, et al. 2015.Cumulative Incidence of Cancer Among Persons With HIV in North America: A Cohort Study. *Ann Intern Med.*163(7):507-18.

5.Coghill AE, Han X, Suneja G, et al. 2019. Advanced stage at diagnosis and elevated mortality among US patients with cancer infected with HIV in the National Cancer Data Base. *Cancer*. 125(16):2868-76.

6. Kravcik S, Hawley-Foss N, Victor G, et al. 1997. Causes of death of HIV-infected persons in Ottawa, Ontario, 1984-1995. *Arch Intern Med.*157(18):2069-73.

7. Bonnet F, Lewden C, May T, et al. 2004.Malignancy-related causes of death in human immunodeficiency virus-infected patients in the era of highly active antiretroviral therapy. *Cancer.*101(2):317-24.

8. Bruyand M, Thiébaut R, Lawson-Ayayi S, et al. 2009. Role of uncontrolled HIV RNA level and immunodeficiency in the occurrence of malignancy in HIV-infected patients during the combination antiretroviral therapy era: Agence Nationale de Recherche sur le Sida (ANRS) CO3 Aquitaine Cohort. *Clin Infect Dis.*49(7):1109-16.

9. Park LS, Tate JP, Sigel K, et al. 2018. Association of Viral Suppression With Lower AIDS-Defining and Non-AIDS-Defining Cancer Incidence in HIV-Infected Veterans: A Prospective Cohort Study. *Ann Intern Med*.169(2):87-96.

10. Dhokotera T, Bohlius J, Spoerri A, et al. 2019. The burden of cancers associated with HIV in the South African public health sector, 2004-2014: a record linkage study.

11. Sengayi M, Spoerri A, Egger M, et al. 2016. Record linkage to correct under-ascertainment of cancers in HIV cohorts: The Sinikithemba HIV clinic linkage project. *Int J Cancer.*139(6):1209-16.

12. Tanaka LF, Latorre MDRD, Gutierrez EB, et al. 2017. Trends in the incidence of AIDS-defining and non-AIDS-defining cancers in people living with AIDS: a population-based study from São Paulo, Brazil. *Int J STD AIDS.*28(12):1190-8.

13. Sinha S, Agarwal A, Gupta K, et al. 2018. Prevalence of HIV in Patients with Malignancy and of Malignancy in HIV Patients in a Tertiary Care Center from North India. *Curr HIV Res*.16(4):315-20.

14. Zhu W, Mao Y, Tang H, et al. 2019. Spectrum of malignancies among the population of adults living with HIV infection in China: A nationwide follow-up study, 2008-2011. *PLoS One.*14(7):e0219766.

15. Von Hoff D. Pancreatic Cancer.Ch.79. In: Harrison's principles of internal medicine 20th edition,ed. by J.L. Jameson, A.S. Fauci, D.L. Kasper et al. New York: McGraw-Hill Education, 2018, pp. 591-595.

16. Ferrone CR, Brennan MF, Gonen M, et al. 2008. Pancreatic adenocarcinoma: the actual 5-year survivors. *J Gastrointest Surg.*12(4):701-6.

17. Siegel RL, Miller KD, Jemal A. 2019. Cancer statistics, 2019. *CA Cancer J Clin*.69(1):7-34.

18. Ries LA, Wingo PA, Miller DS, et al. 2000.The annual report to the nation on the status of cancer, 1973-1997, with a special section on colorectal cancer. *Cancer*.88(10):2398-424.

19. Boyle P, Hsieh CC, Maisonneuve P, et al. 1989. Epidemiology of pancreas cancer (1988). *Int J Pancreatol.*5(4):327-46.

20. Hariharan D, Saied A, Kocher HM. 2008. Analysis of mortality rates for pancreatic cancer across the world. *HPB (Oxford)*.10(1):58-62.

21. Zhang J, Dhakal I, Ning B, Kesteloot H. 2008. Patterns and trends of pancreatic cancer mortality rates in Arkansas,1969-2002: a comparison with the US population. *Eur J Cancer Prev.*17(1):18-27.

22. South Africa. National Cancer Registry, National Health Laboratory Services. 2018. Ekurhuleni Population-based Cancer Registry Annual Report. Available:https://www.nicd.ac.za/wpcontent/uploads/2020/04/EPBCR-2018-report-Final-report.pdf. (Accessed 12.06.2021).

23. Zanet E, Berretta M, Benedetto FD,et al. 2012. Pancreatic cancer in HIV-positive patients: a clinical case-control study. *Pancreas.*41(8):1331-5.

24. Rahib L, Smith BD, Aizenberg R, et al. 2014. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. *Cancer Res*.74(11):2913-21.

25. Chiao EY, Coghill A, Kizub D, et al. 2021. The effect of non-AIDS-defining cancers on people living with HIV. *Lancet Oncol.* 22(6):240-53.

26. Reid E, Suneja G, Ambinder RF, et al. Cancer in People Living With HIV, Version 1. 2018,NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw.* 2018;16(8):986-1017.

27. Kamarajah SK, Frankel TL, Sonnenday C, et al. 2018. Critical evaluation of the American Joint Commission on Cancer (AJCC) 8th edition staging system for patients with Hepatocellular Carcinoma (HCC): A Surveillance, Epidemiology, End Results (SEER) analysis. *J Surg Oncol.*117(4):644-50.

28. Yanik EL, Napravnik S, Cole SR, et al. 2014.Relationship of immunologic response to antiretroviral therapy with non-AIDS defining cancer incidence. *AIDS*.28(7):979-87.

29. Neoptolemos JP, Palmer DH, Ghaneh P, et al. 2017.Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. *Lancet.* 389(10073):1011-24.

30. Connolly C, Shisana O, Shishana O, et. al. 2004. Epidemiology of HIV in South Africa-results of a national, community-based survey. *S Afr Med J*.94(9):776-81.

31. Appay V, Sauce D. 2008. Immune activation and inflammation in HIV-1 infection: causes and consequences. *J Pathol.*214(2):231-41.

32. Joint United Nations Program on HIV/AIDS. Women and Girls and HIV 2018.Available: https://www.unaids.org/sites/default/files/media_asset/women_girls_hiv_en.pdf.(Accessed on 10.10.2020)

33. Zervos EE, Rosemurgy AS, Al-Saif O, Durkin AJ. 2004.Surgical management of early-stage pancreatic cancer. *Cancer Control.*11(1):23-31. doi:10.1177/107327480401100104.

34. Deeken JF, Tjen-A-Looi A, Rudek MA, et al. 2012. The rising challenge of non-AIDS-defining cancers in HIV-infected patients. *Clin Infect Dis.* 55(9):1228-35.

35. Bower M, Collins S, Cottrill C, Cwynarski K,et al. 2008.British HIV Association guidelines for HIV-associated malignancies 2008. *HIV Med.* 9(6):336-88.

36. Rubinstein PG, Aboulafia DM, Zloza A. 2014. Malignancies in HIV/AIDS: from epidemiology to therapeutic challenges. *AIDS.*28(4):453-65.

37. Suneja G, Shiels MS, Angulo R,et al. 2014. Cancer treatment disparities in HIV-infected individuals in the United States. *J Clin Oncol*.32(22):2344-50.

38. Nelson L, Fried M, Stewart K. 2007. The risks of surgery in HIV-infected patients. *J Perioper Pract.* 17(10):470, 472-475, 478.

39. Deeken JF, Tjen-A-Looi A, Rudek MA, et al. 2012. The rising challenge of non-AIDS-defining cancers in HIV-infected patients. *Clin Infect Dis.* 55(9):1228-35.

Chapter 3: Appendices

Appendix A: Data collection sheet for Chris Hani Baragwanath Academic Hospital

Appendix A: Data collection sheet for Chris Hani Baragwanath Academic Hospital

Study Number	Admission date	Age	Gender (F/M)	Ethnicity (A/C/M/As)	HIV Status (+/-)	CD4 Count (cells/mm^3)	Viral Load (copies/ml)	Stage of disease (1/2/3/4)	Histological grade (WD,MD,PD)	Date of death	Time of survival post presentation (months)	PD (Yes/No)

Key	
HIV status	
+	HIV seropositive
-	HIV seronegative
Gender	
F	Female
M	Male
Ethnicity	
A	African
C	Caucasian
M	Mixed-race
As	Asian
Histological grade	
WD	Well differentiated
MD	Moderately differentiated
PD	Poorly differentiated
Stage	American Joint Committee on Cancer stages (1-4)
Surgical treatment	
PD	Pancreaticoduodenectomy
Y	Underwent Pancreaticoduodenectomy
N	Did not undergo Pancreaticoduodenectomy

Appendix B: Data collection sheet for Wits Donald Gordon Medical Centre

Study Number	Admission date	Age	Gender (F/M)	Ethnicity (A/C/M/As)	HIV Status (+/-)	CD4 Count (cells/mm^3)	Viral Load (copies/ml)	Stage of disease (1/2/3/4)	Histology grade (WD,MD,PD)	Date of Death	Time of survival post presentation (months)	PD (Yes/No)

Key	
HIV status	
+	HIV seropositive
-	HIV seronegative
Gender	
F	Female
M	Male
Ethnicity	
A	African
C	Caucasian
M	Mixed-race
As	Asian
Histological grade	
WD	Well differentiated
MD	Moderately differentiated
PD	Poorly differentiated
Stage	American Joint Committee on Cancer stages (1-4)
Surgical treatment	
PD	Pancreaticoduodenectomy
Y	Underwent Pancreaticoduodenectomy
N	Did not undergo Pancreaticoduodenectomy

Appendix C: Human Research and Ethics Committee approval certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr JR Wing

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M190704

NAME: (Principal Investigator)	Dr JR Wing
DEPARTMENT:	School of Clinical Medicine Department of Medicine Division of Internal Medicine Medical School University
PROJECT TITLE:	Evaluation of outcomes in patients with pancreatic cancer and Human Immunodeficiency Virus at Chris Hani Baragwanath Academic Hospital and the Donald Gordon Medical Centre, Johannesburg, South Africa
DATE CONSIDERED:	2019/07/26
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Professor C Menezes; Dr J Devar
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2019/11/08

This clearance certificate is valid for 5 years from the date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the 3rd Floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **July** and will therefore reports and re-certification will be due early in the month of **July** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

2019.07.16
Date

Appendix D: Turnitin originality report

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ORIGINALITY REPORT

12%	6%	11%	2%
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PRIMARY SOURCES

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2	Submitted to University of Stellenbosch, South Africa Student Paper	1%
3	Ernesto Zanet, Massimiliano Berretta, Fabrizio Di Benedetto, Renato Talamini et al. "Pancreatic Cancer in HIV-Positive Patients", Pancreas, 2012 Publication	1%
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UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I Jessica Roberta Wing (Student number: 362003) am a student registered for the degree of Master of Medicine in the academic year 4.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

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