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Building research capacity through programme development and research implementation in resource-limited settings - the Ipabalele study protocol: observational cohort studies determining the effect of HIV on the natural history of cervical cancer in Botswana

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ABSTRACT

Introduction The global burden of cancer continues to increase in low- and middle-income countries, particularly in sub-Saharan Africa (SSA). Botswana, a middle-income country in SSA, has the second highest prevalence of HIV worldwide and has seen an increase in human papillomavirus (HPV)-associated cervical cancer over the last decade in the setting of improved survival of HIV-infected women. There is an urgent need to understand more clearly the causes and consequences of HPV-associated cervical cancer in the setting of HIV infection. We initiated the Ipabalele ('take care of yourself' in Setswana) programme to address this need for new knowledge and to initiate long-term research programme capacity building in the region. In this manuscript, we describe the components of the programme, including three main research projects as well as a number of essential cores to support the activities of the programme.

Methods and procedures Our multidisciplinary approach aims to further current understanding of the problem by implementing three complementary studies aimed at identifying its molecular, behavioural and clinical determinants. Three participant cohorts were designed to represent the early, intermediate and late stages of the natural history of cervical cancer.
The functional structure of the programme is coordinated through programmatic cores. These allow for integration of each of the studies within the cohorts while providing support for pilot studies led by local junior investigators. Each project of the Ipabalele programme includes a built-in capacity building component, promoting the establishment of long-lasting infrastructure for future research activities.

Strengths and limitations of this study

► Protocols were designed by multidisciplinary teams including experts from both the US and Botswana.
► Investment in infrastructure and training was designed to not only facilitate this study but build capacity for future important research on HIV and malignancy in Botswana.
► Balancing and satisfying multiple international ethics boards provided a challenge, as reviewing bodies' recommendations and requirements could at times be discordant.

Ethics and dissemination Institutional review board approvals were granted by the University of Pennsylvania, University of Botswana and Ministry of Health and wellness of Botswana. Results will be disseminated via the participating institutions and with the help of the Community Advisory Committee, the project's Botswana advisory group.

BACKGROUND

Globally, cervical cancer is the fourth most common cancer in women, with an estimated 528000 new cases in 2012.[1] Around 85% of this disease burden falls on less developed countries, with sub-Saharan Africa (SSA) being one of the most dramatically affected regions.[1] Persistent infection with human papillomavirus (HPV) is the most important

risk factor for developing cervical cancer, and women co-infected with HIV are at greater risk of progressing to development of cervical cancer.[2 3]

Increased global access to antiretroviral therapy (ART) has led to the emergence of a maturing HIV-infected population worldwide.[4] In Botswana, with an HIV burden of approximately 18 per cent, implementation of a robust public ART programme has significantly reduced mortality due to AIDS-related infections.[5] Currently, cervical cancer rates in Botswana are increasing at a rate of 3% per year.[6] There remains a dearth in the literature, however, of research conducted in low- and middle-income countries (LMICs) concerning the populations and problems unique to those areas, such as the potential interplay and outcome of longstanding HPV and HIV coinfection.

One reason for this lack of research is the persistence of many barriers to clinical trial design and execution in LMICs.[7] Research studies designed for and carried out in the developed world may not successfully apply in other populations or settings. Further, research implemented in high-income countries (HIC) frequently excludes or underrepresents HIV-infected patients.[8–11] Thus, the creation of an innovative methodological design capable of effectively examining HIV-infected patients living in LMICs would be beneficial and necessary to answering these unresolved global questions.

Here we present the design and implementation of the Ipabalele Cervical Cancer Research Programme, a multi-disciplinary, multifaceted effort between a high-income institution and a middle-income institution, University of Pennsylvania (UPenn) and University of Botswana (UB). The aim of the Ipabalele programme is to determine the effect of HIV infection over the natural history of HPV-associated cervical cancer while increasing local research capacity via the establishment of physical infrastructure and research training. The increased research capacity creates an environment conducive to research implementation.

Overview

The overall objective of the Ipabalele (which means 'take care of yourself' in Setswana, the national language of Botswana) programme is to determine the epidemiology, pathogenesis and behavioural, clinical and immunological risk factors leading to progression towards cervical cancer among women with and without HIV infection, as well as determining optimal therapeutic approaches. An accompanying equally important focus is to develop a sustained, long-lasting research infrastructure in Botswana for the study of cervical cancer and other HIV-associated malignancies. A critical component of this is identifying and training local investigators who want to continue this work and form the nucleus for these programmatic efforts to continue long term.

STUDIES DESIGN AND PROCEDURES

In order to accomplish the programme's goals, we simultaneously implemented three complementary research projects across three cohorts of participants. The projects aim to:

1. Map the natural history and pathogenesis of HPV and other infectious agents and their role in mediating cervical cancers in HIV-infected patients. This will be examined through analysis of biological specimens from three unique cohorts of women representing different stages of disease progression.
2. Identify biological, behavioural, social, cultural and health system-related predictors of acquisition of HPV and HIV infection, as well as those related to screening, diagnosis, treatment and outcomes of HIV-uninfected and HIV-infected women with premalignant and malignant cervical lesions.
3. Determine whether immune reconstitution and low immune activation can improve tolerability and tumour response in women diagnosed with frank cervical cancer receiving chemoradiation therapy.

The research studies above involve enrolment of three cohorts of participants; each cohort aims to represent progressive stages in the natural history of cervical cancer progression. Figure 1 outlines overall study design and highlights contribution of each of the cohorts to the three studies. Figure 2 outlines the study procedures of the three projects and the three cohorts. The cohorts are the following:

Cohort 1: early events

Participants: Female UB students, age >18, HPV-uninfected and HIV-uninfected, recruited during their first and second year entering university. The student body at UB represents the young population of Botswana well, as they come from diverse geographical and socioeconomic backgrounds due to UB being the only public university in Botswana. Attendance is free of cost to citizens of Botswana, and students are also provided a stipend for attending university. All undergraduates stay in the dorms at UB, and students typically begin to engage in high risk behaviours once they are away from home and residing in the dorms with their peers for the first time.

Setting: Participants are recruited and followed at the University of Botswana Health Clinic, a free on-campus clinic for university students. Of note, education and counselling regarding the prevention of acquisition of HPV and HIV are provided to all patients who are seen at the UB Health Clinic, regardless of whether or not they're enrolled in this study.

Data sources and sample collection: Baseline demographic data, qualitative surveys regarding health screening beliefs and sexual risk behaviours; urine sample, cervical swab and HIV test.

Sample size: 1000 women.

Enrolment dates: 13 September 2016 through 31 May 2019.

Cohort 2: intermediate events

Participants: Women diagnosed with cervical intraepithelial neoplasia, age >18, HIV-uninfected or HIV-infected.
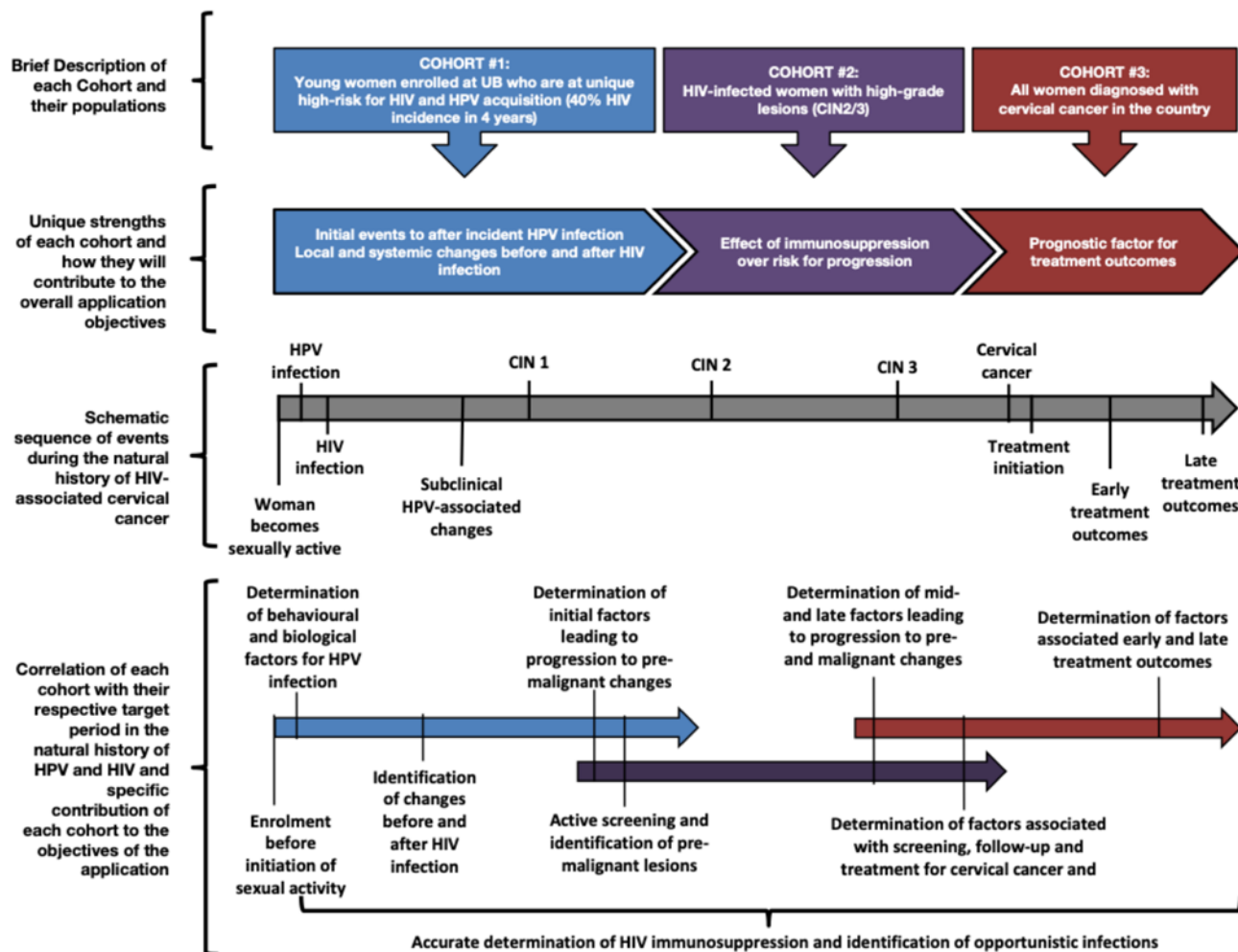
Figure 1 Overview of Ipabalele study design. CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; UB, University of Botswana.

Setting: Patients are recruited on their presentation to the 'Colposcopy and Treat' clinic at Princess Marina Hospital, the public hospital serving the region surrounding and including Gaborone. Many patients travel long distances to attend and are referred to this particular clinic as a consequence of having an abnormal pap smear or visual inspection with acetic acid found to be positive. Study staff screen patients on their presentation to the clinic, and eligible patients are approached and given the opportunity to provide informed consent and enrol. Any patients who enrol and are found to not have cervical intraepithelial neoplasia will be regarded as a screen fail and their enrolment in the study will cease.

Data sources and sample collection: Baseline demographic data, qualitative surveys regarding health seeking beliefs; cervical biopsy obtained as part of clinical care.

Sample size: 300 women.

Enrolment dates: 07 March 2017 through 07 March 2019.

Cohort 3: late events

Participants: Women with frank locally advanced cervical cancer, age >18, HIV-infected or HIV-uninfected, receiving curative chemoradiation. Cervical cancer specimens are staged by oncologists in Botswana using The

International Federation of Gynecology and Obstetrics (FIGO) 2008 guidelines.[12] Chest X-ray and abdominal ultrasound are done routinely for staging.

Setting: Participants are enrolled and seen for study visits at Princess Marina Hospital's women's health clinic and Gaborone Private Hospital, which is the main tertiary-level referral centre for cancer treatment in Botswana.

Data sources and sample collection: Baseline and follow-up patient and disease characteristics, treatment toxicities, qualitative surveys regarding treatment retention; cervical fluid, peripheral blood, cervical biopsy tissue obtained as part of clinical care.

Sample size: 450 women

Enrolment dates: 23 August 2016 through December 2019.

Patient and public involvement:

Patients were involved in the development of this study primarily through the formation of focus groups consisting of eligible and consented patients. By convening these groups early in the development of the projects, we were able to gear our research surveys used throughout the study towards the priorities and preferences of our patient populations. We will disseminate the results of
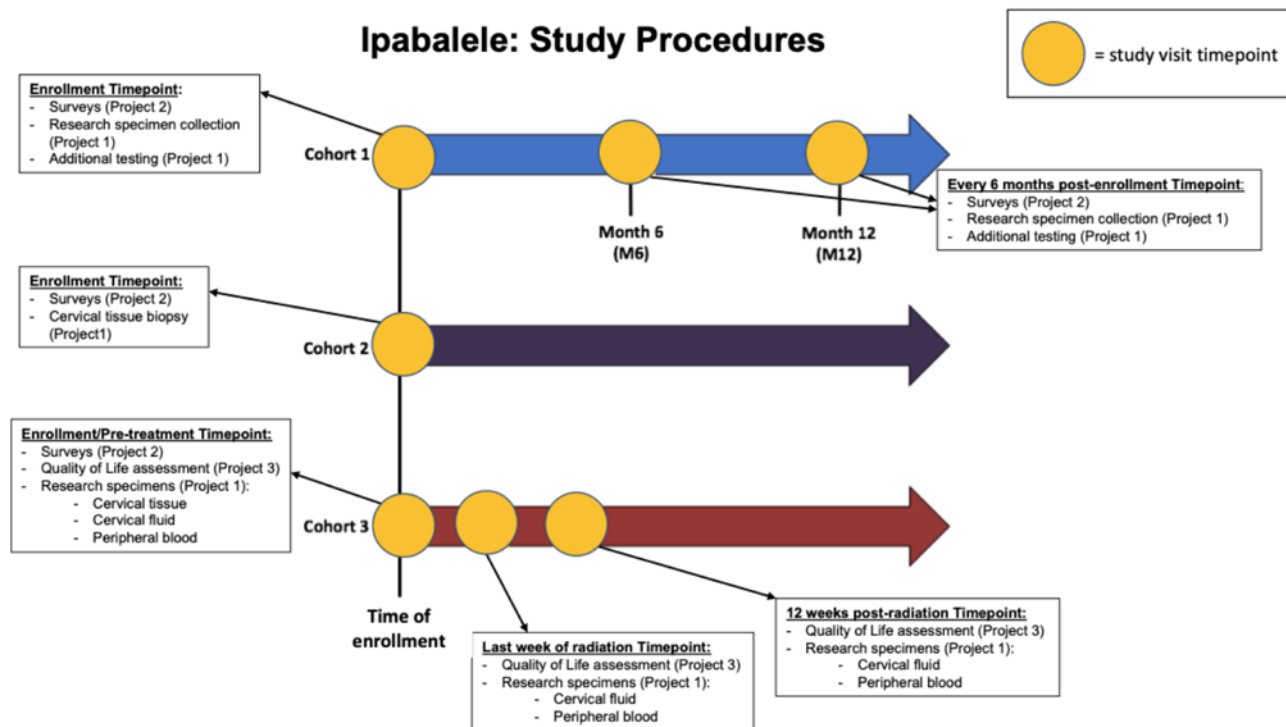
Figure 2 Overview of Ipabalele research procedures.

this study via the participating institutions, particularly the University of Botswana, Princess Marina Hospital and Gaborone Private Hospital, as well as with the help of our Community Advisory Committee, the project's Botswana advisory group, which has a strong link to patients in the surrounding Gaborone communities.

Potential difficulties and challenges to implementation:
We encountered a variety of challenges to successfully implementing this study. For example, adapting research approaches common in high-income countries to suit a low- or middle-income country setting included a large amount of collaboration with local investigators and stakeholders beginning in the earliest stages, as well as continuous surveillance and review to ensure that our methods and procedures were both appropriate and feasible for local participants and staff alike. Obtaining approvals from multiple institutionalreview boards (IRBs) in multiple counties was a massive challenge, as cultural expectations and departmental protocols sometimes conflicted or yielded differing recommendations. To work through this dilemma, we found it most helpful to ensure that a dialogue and familiarity was present between the various IRBs and their representatives so that collectively we could all work towards a fully-approved final project that was satisfactory and acceptable to all parties. We also encountered challenges stemming from the necessary front-heavy investment in training new local research professionals to build capacity, including both logistical issues and the delays that training a new team member or starting a new programme typically yield in a real-world setting.

Research study #1 focuses on the pathogenesis and biological determinants of cervical cancer
Objective
The objective of this research project is to study the natural history and pathogenesis of HPV and other infectious agents and their role in mediating cervical cancers in HIV-infected patients through the analysis of biological specimens.

Procedures
Samples from women in cohorts 1, 2 and 3 are collected, and microbiome and inflammatory response will be analysed.

Collection of biological specimens is specific for each cohort:
► Cohort 1:
  – Study visits occur at enrolment and every 6 months thereafter. At each study visit, a cervical swab and a urine sample are collected and a HIV test is performed. Cervical swab will be used for microbiome testing as well (which will include HPV subtyping as high risk and low risk). Real time Polymerase Chain Reaction (PCR) will be used in Botswana to detect presence or absence of HPV. Participants are provided results to the following tests at each visit: HIV, HPV, pregnancy (if done) and will also be provided with results of sexually transmitted disease tests when available. Infections tested in Botswana in addition to HPV and their corresponding diagnostic methods are as follows:
  – Gonorrhoea and chlamydia via urine sample.

- Bacterial vaginosis and trichomoniasis via wet mount from cervical swab.
- Vaginal candidiasis via potassium hydroxide preparation (KOH prep) from cervical swab.

Primary outcomes

▶ Microbiome signatures that contribute to HPV-associated dysplasia and cervical carcinomas in HIV-infected women with cervical cancer.
▶ Inflammatory markers associated with HPV and HIV infection between the three cohorts.

Laboratory analysis and samples

Microbiome analysis will be done at UPenn. However, laboratory infrastructure for HPV analysis has been established at the UB Faculty of Medicine through implementation of this project and support from UPenn. A graduate student and junior faculty member from UB have also worked with UPenn faculty and technical specialists during visits to the laboratory at UPenn to learn the techniques and methodologies associated with microbiome and HPV analysis.

Statistics
Sample size

Based on our estimates of the number of infectious agents associated with normal individuals we expect that an infectious agent contributing to the disease will be associated with 25% to 55% of cervical cancers. By looking at 100 samples from a homogeneous subtype, we would expect at least 25% of them to be associated with a particular infectious agent. If the normal tissues are less than 10% this strongly suggests a contributory role for an agent. We should keep in mind that this study will provide a broad and unbiased detection of infectious agents that may be contributing to cervical cancers. The 0.5% error rate reflects a Bonferroni adjustment since it is likely that multiple (~10) infectious agents will be compared between groups.

Data analysis

The primary objective of Project 1 is to determine the natural history and pathogenesis of HPV positive cervical cancer. To test the hypothesis that rates of expression of infectious agents will be high in cervical tissue in HPV infected women and low in cervical tissue in HPV uninfected women, we will perform group comparisons. Power to detect an association using a X^2 test at one-sided 0.5% significance level based on assumptions of >25% rate in HPV infected samples and <10% rate in normal HPV uninfected samples is shown below (table 1). The 0.5% error rate reflects a Bonferroni adjustment since it is likely that multiple (~10) infectious agents will be compared between groups.

Another sub-aim of Project 1 is to enrol a cohort of UB female students and follow them for HPV and HIV seroconversion and cervical cancer. This population will provide repeated cervical swabs at regular intervals over a period of 4 to 5 years during and following their university

Table 1 Power (for OR) to detect overexpression of infectious agents in HPV + samples

Rate of infectious agents in 100 normal cervical samples	Rate of infectious agents in 100 HPV⁺ cervical samples		
	25%	35%	45%
5%	92% (6.3)	99% (10.2)	99% (15.6)
7.5%	78% (4.1)	98% (6.6)	99% (10.1)
10%	58% (3.0)	95% (4.8)	99% (7.4)

HPV, human papillomavirus.

education. We will use longitudinal modelling to evaluate changes in infectious agents and inflammatory markers during follow-up. Data will be analysed by Stata statistical software or by employing commands in R.

Capacity building specific for this project

UPenn hosted graduate students for training in microbiome and HPV subtyping analysis. This project of Ipabalele is supporting UB students interested in a doctorate programme in the biomedical sciences, which is related to the aims of the study in all aspects of their project. This includes mentoring and training throughout their doctoral studies, resources to conduct their project and access to international meetings to present their work. Junior faculty identified through the Mentoring Core who are interested in research related to the aims of this project also have access to the data and laboratory facilities built through this project.

Research study #2 will focus on social, cultural and behavioural determinants
Objective

The overall objective of this project is to identify prospective predictors by:

▶ Screening for cervical cancer and acquisition of HPV and HIV infection (cohort 1).
▶ Tracking treatment seeking among women screened for cervical cancer (cohort 2).
▶ Monitoring retention into treatment of women diagnosed with frank cervical cancer (cohort 3).

Procedures

Initially, focus groups assessments and pilot studies were conducted to refine the procedures and the questionnaire. Information from the focus groups was then integrated within the theoretical framework, social cognitive theory and the reasoned action approach to tailor the questionnaire to the target population. Finalised web-based surveys using ACASI software are being used to evaluate patients in the three cohorts.

Examples of questions asked of the participants to assess social and cultural predictors are as follows (rated on a scale from disagree strongly to agree strongly):

▶ 'I feel under social pressure to go for cervical cancer screening.'

- 'My family would think it is a good idea to go for cervical cancer treatment.'
- 'Before we are ready to have sex, I can talk to the person with whom I have sex about using a condom.'

Health system predictors will include assessing if and how participants choose to seek treatment and/or gain access to medical care and treatment. Examples of questions used to assess this are as follows (rated on a scale from disagree strongly to agree strongly):

- 'Poor health practices in hospitals makes it hard for me to go for cervical cancer screening.'
- 'Knowing that cervical cancer screening is provided free in hospitals makes it easy for me to go for screening.'
- 'I can keep my cervical cancer treatment appointments even if the health clinic is far away.'

All three cohorts utilise a prospective design with data collection visits at varying schedules as detailed below:

- Cohort 1: After the first enrolment visit, participants are assessed every 6 months in follow-up throughout the duration of the study.
- Cohort 2: At the first visit/enrolment visit only.
- Cohort 3: After the first enrolment visit, participants are assessed at the final week of radiation and at 12 weeks post-chemoradiation.

Primary outcomes

- Cohort 1: The primary outcome is cervical cancer screening history and acquisition of HPV and/or HIV. Secondary outcome variables include number of sexual partners including circumcision status, partner's age, partner's number of prior sex partners and the length of time participant knew the partner before engaging in sexual intercourse.
- Cohort 2: The primary outcome is treatment-seeking history.
- Cohort 3: The primary outcome is treatment completion.

Statistics
Sample size

For Cohort 1, the primary outcome is adherence to the cervical cancer screening guideline of screening annually and acquisition of HPV, HIV or HPV/HIV co-infection. We performed a power analysis to calculate the sample size needed to detect a clinically important relation between baseline predictors and adherence to cancer screening guidelines. Previous studies in SSA have demonstrated a 90+% adherence rate. We will enrol approximately 1000 women in the study. Assuming a two-tailed test, alpha=0.05, 20% attrition and an effect size of OR=1.55, a total N of 1000 women enrolled will yield statistical power of 0.80. For Cohort 2, assuming the same effect size and attrition, statistical power will be the same, 0.80. For Cohort 3, the primary outcome is retention in treatment and quality of life. A total of 250 women will be enrolled. For this cohort, which has a smaller sample and a shorter follow-up period than Cohorts 1 and 2, we took the repeated measures into account in calculating sample size and statistical power. Based on previous studies, we estimate that the average pair-wise correlation between treatment retention at 6, 12, 18 and 24 month follow-up is r=0.25. Assuming a two-tailed test, alpha=0.05, r=0.25, 20% attrition and an effect size of OR=1.70, a total N of 250 patients enrolled will yield statistical power of 0.80.

Data analysis

Web-based surveys for the three cohorts were developed by investigators based on primary objectives after initial focus groups conducted in the three different cohorts. Qualitative and quantitative analysis correlating behaviour and clinical data is led by investigators and completed at UB with the Biostatistics and Data Management Core. HPV, HIV and sexually transmitted infection (STI) analysis is done at UB with the laboratory infrastructure established by the Ipabalele study. UB staff are trained and supervised by experienced investigators who are skilled in the technologies implemented.

Capacity building specific for this project

Graduate students at UB focusing their studies on cervical cancer and behavioural science are supported through this project with mentoring and analyses of the data generated from their graduate programme studies. Junior faculty identified through the Mentoring Core who are interested in research related to the aims of this project have access to the data and laboratory facilities built through this project. They are matched with experienced mentors at UPenn and UB so that their possibility of success will be enhanced.

Research study #3 will focus on clinical determinants for progression to cancer and the response to treatment with chemoradiation
Objective

The long-term goal of this project is to examine tumour response, treatment tolerability and acute toxicity rates among HIV-infected and HIV-uninfected women enrolled in cohort 3. We will also assess if immune reconstitution and lower immune activation may be associated with improved treatment tolerability as well as tumour response.

Procedure
Primary population (all Cohort 3 participants):

- Data collected at initial visit: patient demographics, tumor-related and patient-related characteristics including presenting symptomatology and staging information, HIV status, if HIV-infected then history of HIV infection and data on ART regimens and complete medication list, HIV viral load and cluster of differentiation 4 (CD4) count, squamous cell carcinoma antigen (SCCAg), HIV test if HIV-uninfected and no test has been performed in the prior 6 months, baseline weight, baseline complete blood count and creatinine. The only tests that are not standard

practice currently for clinical care are CD4, viral load and SCCAg.

► Data collected weekly during treatment: toxicity data, laboratory investigations, documentation of ART regimen adherence.

► Health related quality of life assessments are administered at baseline, at the last week of radiotherapy and 12 weeks post-chemoradiotherapy.

► At the end of chemoradiation, approximately 12 weeks post-chemoradiotherapy SCCAg is obtained to assess tumour response.

Nested cohort with tissue specimens (subset of cohort 3):

To address our tissue-based objectives, patients will be asked to separately consent to researchers obtaining peripheral blood and cervical samples (cervical biopsy and/or fluid) as follows:

► Prior to (and within 3 months of) initiation of treatment: Peripheral blood, cervical biopsy and cervical fluid will be collected.

► Last week of treatment: Peripheral blood only will be collected.

► 12 weeks post-treatment completion: Peripheral blood and cervical fluid will be collected.

Primary outcomes

► Tumour response as defined as normalisation of squamous cell carcinoma antigen (value <2.2 ng/mL) at 12 weeks post-chemoradiotherapy will be assessed.

► Standard immunologic variables, including but not limited to: baseline CD4 count, pre/post treatment per cent change in CD4 count and viral load suppression (absent/present).

► Histopathology (ie, grade) and peripheral blood-based and tissue-based immunological variables, including but not limited to T-cell subsets and their activation phenotypes and functions.

Laboratory analysis and samples

Extraction of peripheral blood mononuclear cells (PBMCs) from peripheral blood and flow cytometry for immune marker analysis will be performed at UB with technical training from UPenn investigators. Quantitative data analysis will be led by UPenn and UB faculty and will be conducted at UB within the Biostatistics and Data Management Core.

Statistics

Sample size/power

From our pilot study, 67% of cervical cancer patients enrolled for chemoradiotherapy were HIV-infected,[13] thus with 450 patients enrolled, we expect approximately 275 to be HIV-infected. All 450 patients who initially enrol to the study (as part of Cohort 3) will be tracked for adherence and acute toxicity while on treatment. We expect that due to geographical considerations, there will be 10% loss to follow-up for tumour assessment at 12 weeks based on peripheral blood SCCAg. Thus, we expect approximately 400 patients (250 HIV-infected and 150

HIV-uninfected) will be available for tumour response assessment. We would estimate the tumour response rate as defined by normalisation of SCCAg after standard chemoradiotherapy to be approximately 75% for HIV-uninfected cervical patients. For our primary analysis, with 250 HIV-infected and 150 HIV-uninfected cervical cancer patients, we will have 87% power at two-sided 5% type I error rate to detect a difference in tumour response of 15% (75% in HIV-uninfected vs 60% in HIV-infected patients) using a X^2 test. High power will be maintained in the planned multivariable analysis that will adjust for several (up to six) baseline clinical and standard immunological variables.

Data analysis

For our primary endpoint: Tolerability, acute toxicity rates and tumour response (at 95% CIs) will be calculated and compared between HIV-infected and HIV-uninfected groups and among HIV-infected high CD4, HIV-infected low CD4 and HIV-uninfected groups by X^2 test. Multivariable logistic regression will then test the association between acute toxicity and HIV status as well as tumour response and HIV status, controlling for baseline CD4 count and standard clinical variables (haemoglobin, stage, overall treatment time).

For our secondary endpoint: To determine associations between clinical parameters, immune activation markers, treatment tolerability and tumour response in the subset of women who are HIV-infected, we will compare baseline HIV status (CD4 count, viral load), clinical parameters and immune activation markers (~5 variables) in HIV-infected women with cervical cancer receiving chemoradiation between groups defined by tolerability and tumour response at 12 weeks post-treatment. We will model the associations between tumour response and multiple independent predictors. The distributions (ie, mean, SD, range) of baseline CD4 count, CD4 recovery and immune markers will be summarised for each tumour response group and compared by Student's t-test or non-parametric Wilcoxon rank sum test as necessary. Bonferroni adjustment will be used to account for multiple testing. Multivariable logistic regression will then test the association between tumour response and baseline CD4 count, CD4 recovery and immune markers controlling for known predictive factors such as stage, haemoglobin and treatment duration.

Capacity building specific for this project

Through this project, infrastructure for collection of PBMCs from peripheral blood and flow cytometry for immune marker analysis has been established. The cytoflow machine was donated by Boitumelo Foundation to UB through a request made by UPenn. Junior investigators identified through the Mentoring Core who are interested in HIV and cancer research have full access to the flow cytometer for their pilot studies. Graduate students at UB interested in pursuing doctorate training related to the aims of the study have access to the data

and samples for their projects and are provided support including mentorship and training through this project.

FUNCTIONAL AND PHYSICAL STRUCTURE OF THE PROGRAM: PROGRAM CORES

The complexities intrinsic to the simultaneous implementation of three complementary studies across three cohorts required the development of functional cores to centralise activities common to all studies. In addition, the development of these cores is aimed to provide long-lasting resources within UB for the support of junior researchers and future research efforts regarding HIV-related malignancies. Concomitantly, the following cores have been developed and fully integrated into the UB academical and physical infrastructure.

Administrative core

The main purpose of the Administrative Core is to provide an organisational framework that facilitates communication and oversees all research collaborations to keep the effort as a whole centred on the research and mentoring themes of the consortium.

The size and scope of this programme, particularly the distance between UB and UPenn, makes formalised organisation and structure absolutely essential. It creates the tone for all research and mentoring efforts and is therefore a significant driving force for achieving the project's goals. The Administrative Core provides administrative fiscal oversight and management to the project, organises and leads the project's governance and advisory committees, and creates, modifies, oversees and (when necessary) facilitates changes in mentoring/research plans.

This Core includes: (1) an **Executive Committee**, the Consortium's governing and principal decision-making and policymaking body; (2) an **Internal Advisory Committee** consisting of senior UPenn and UB academic thought leaders with interest in HIV/HPV cancer-related issues and who have extensive experience with mentoring of junior faculty, students and residents; (3) an **External Advisory Committee** consisting of internationally recognised senior HIV/HPV cancer investigators outside the participating institutions that provides input into the major questions and current activities in the field as well as honest scientific and administrative feedback (4) and a **Community Advisory Committee,** the project's Botswana advisory group, that provides input and implementation of activities in the surrounding Gaborone communities.

Shared resources core

The overall objective of this Core is to reconcile the needs and research approaches of all research projects in order to ensure high-quality, uniform processes and tools for data and specimen collection. The multidisciplinary and comprehensive evaluation of HIV-infected women at different stages of the natural history of HPV-associated cervical cancer requires the simultaneous assessment of a wide variety of behavioural and biological factors. To maximise the cost-effectiveness of this process and ensure complete homogeneity in all logical procedures, the Shared Resources Core (SRC) is in charge of all aspects related to: (1) participant outreach, screening, enrolment and follow-up; (2) data collection, processing and cleaning as well as maintenance of the study database and production of periodic reports and (3) collection, initial processing and, when appropriate, shipment of participant samples. Accordingly, the SRC is subdivided into three operational divisions: clinical, data management and laboratory. Figure 3 details overall structure of SRC. As the main logistical core, the SRC maintains close and dynamical interactions with all other cores. In order to allow for a complete transfer of skills and sustainability beyond the duration of this programme, the SRC is fully housed within UB.
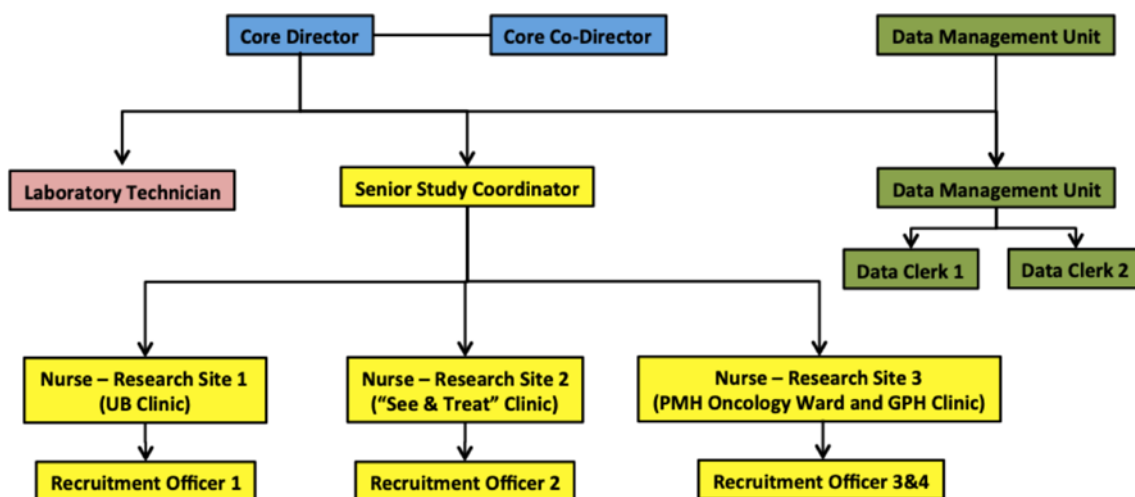

Figure 3 Shared resources core organisational chart. GPH,Gaborone Private Hospital;PMH, Princess MarinaHospital; UB, Universityof Botswana.
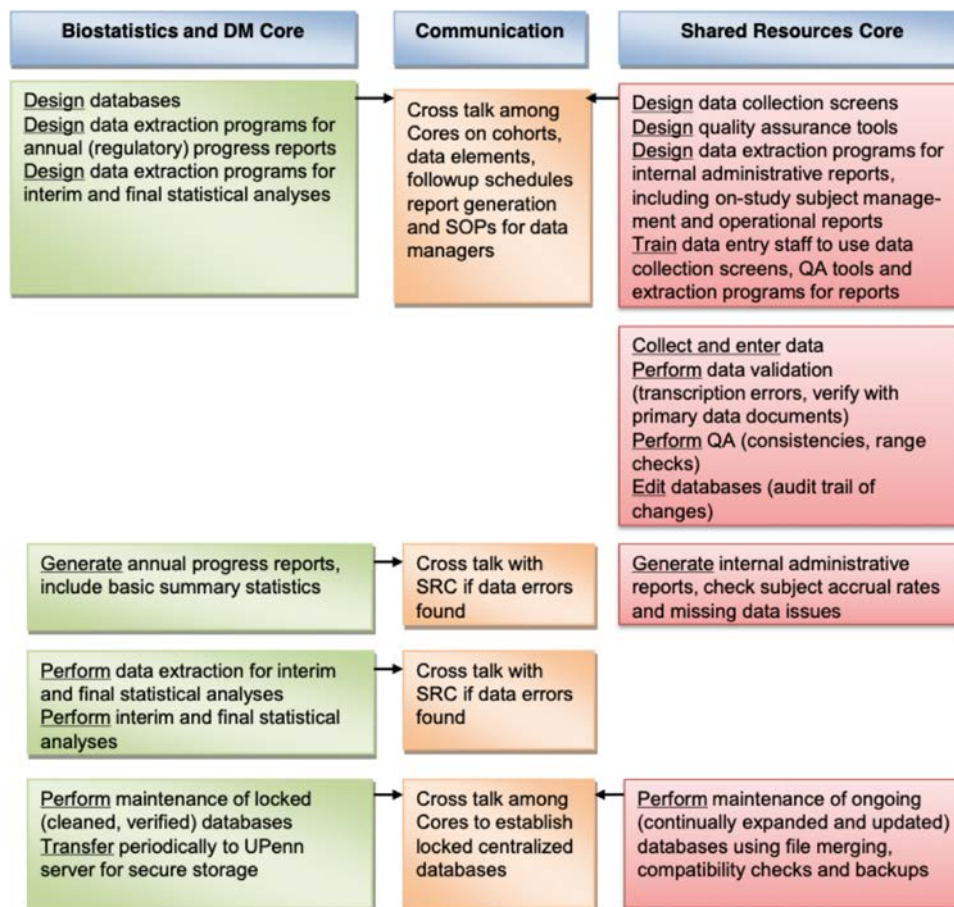
Figure 4 Communication between shared resources core and biostatistics and data management core. SOP, standard operating procedures; SRC, Shared Resources Core; UPenn, University of Pennsylvania; QA, quality assurance.

Biostatistics and data management core

This Core is providing crucial shared resources for biostatistical expertise in the design, conduct and statistical analysis of research projects generated in the Consortium. The Biostatistics and Data Management (BDM) Core enhances the productivity of Ipabalele investigators by providing them with access to a statistical/data management team who possess expertise in study design, conduct and statistical analysis in HIV/AIDS and cancer research.

Timely and in-depth collaboration will ensure that Ipabalele studies are designed, managed and analysed to the highest standard and will provide valid and robust answers to the scientific questions of interest. Interaction with the database programmer will ensure that accurate and analysable data are collected and managed appropriately.

Activities of this Core are complementary to those of the SRC. Crosstalk between the SRC and the BDM Core focuses on standardisation of data elements, data coding and quality assurance (QA) procedures and generation of standardised reports and analysable data sets. Figure 4 details overall interaction and communication between SRC and BDM Core.

Mentoring core

The overall objective of this Core is to help build the research careers of junior faculty at UB. The Ministry of Health, UB and UPenn have worked together for 18 years to build capacity in healthcare, education and research in Botswana. Through this Core, we hold an annual course on research methodology taught at UB by faculty from UPenn and UB. As part of the course, UPenn and UB faculty provide mentorship to prospective UB pilot grant principle investigators (PIs) helping them to develop the first draft of their Specific Aims on topics related to HIV and cancer. After completion of the 2 day course, UPenn and UB faculty continue to mentor UB PIs from a distance over 3 months as they complete a three-page pilot grant scientific application and a one-page mentoring plan. The grants are reviewed by research scientists at UPenn and UB and scored using National Institutes of Health (NIH) criteria. Written feedback is provided to each PI. Two 1 year pilot grants submitted by junior UB faculty are funded annually. The UPenn and UB mentors offer ongoing support to PIs of unsuccessful applications in an effort to improve the proposal for future submissions. For successful applications, the UPenn and UB mentors continue to work with the UB PIs to assist with IRB submissions, study implementation and completion of their first-author manuscript.

Ethics and dissmenination

Institutional review board approvals were sought and granted from the University of Pennsylvania, the University of Botswana and the Ministry of Health and Wellness of Botswana. These approvals remain active for each of the three projects for the duration of the study and are reviewed annually for re-approval by each reviewing body. All modifications to study protocol are submitted to all three review boards for review and approval prior to those modifications taking effect. Results will be disseminated via the participating institutions and with the help of the Community Advisory Committee, the project's Botswana advisory group, Ministry of Health and Wellness of Botswana as well as national and international meetings.

SUMMARY

With the rising burden of cancer in LMICs, it is imperative to conduct cancer research in LMIC settings. A collaborative model for research between institutions in HICs and LMICs is needed to build research capacity in LMICs and answer questions relevant to the LMIC context. Here we provide a collaborative study model, Ipabalele study, between UB and UPenn focusing on natural history of cervical cancer, mentorship and research capacity building in LMICs.

Study status

In progress (active recruitment expected to conclude December 2019).

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