Botswana-UPenn Partnership
Annual Report for Calendar Year 2015

Sharing the expertise of a world-class university with our partners in Botswana to build capacity and excellence in clinical care, education, and research.

Summary

The University of Pennsylvania continues to optimize its strong and productive partnerships with Botswana's Ministry of Health and the University of Botswana to build health care capacity and improve the quality of care in Botswana. Our research directly addresses health care issues in Botswana and has been used to inform Ministry of Health Guidelines for HIV/AIDS, TB, cervical cancer, and other illnesses. The Botswana-UPenn Partnership involves multiple Schools at Penn, thereby using Penn's expertise to more deeply benefit Botswana's health care and economic development while providing rich global research and learning opportunities for Penn faculty and students.

Program Overview

The overall mission of the Botswana-UPenn Partnership (BUP) program is to help build capacity in health care in Botswana and to offer outstanding opportunities for global health experiences for Penn trainees. Penn was invited in 2001 by ACHAP (African Comprehensive AIDS Partnership, a collaboration involving the Bill and Melinda Gates Foundation, the Merck Foundation, and the Government of Botswana) to train health care workers on the management of HIV-infected patients in Botswana. Botswana has one of the highest HIV prevalence rates in the world with about 25% of adults (ages 15-49) or 390,000 people infected[1].

The BUP established formal working relationships through Memoranda of Agreements with the Ministry of Health (2004) and the University of Botswana (2006 and 2013) for joint projects aimed at improving health and healthcare education in Botswana. Country-based staff and faculty help Penn-based leaders fine-tune plans to fit local needs and navigate local requirements. The University of Pennsylvania through the Trustees registered the University of Pennsylvania operating as the Botswana-UPenn Partnership as an external company in Botswana in 2010. The program is led by Harvey Friedman at Penn and Doreen Ramogola-Masire in Botswana.

Current Programs & Initiatives

[1] Source: World Bank: http://data.worldbank.org/indicator/SH.DYN.AIDS.ZS

A. Clinical & Public Health:

Tuberculosis

The Partnership was awarded a new five-year PEPFAR grant "Botswana: Capacity Building through Training and Mentoring for Treatment, Care and Support" to continue to serve as technical advisers on Botswana's national tuberculosis program. The grant is under the leadership of Chawa Modongo MD, Head of the BUP TB Program with Nicola Zetola MD, MPH and Tonya Arscott-Mills MD, MPH as co-investigators. Tuberculosis (TB) is a common co-infection among HIV/AIDS patients and remains the leading cause of death in people living with HIV (40%) and is responsible for 13% of all adult deaths in Botswana. The BUP-TB program supports the Ministry of Health to achieve HIV and TB epidemic control by capacitating health care workers (Medical doctors, Nurses, Nursing assistants and Community TB volunteers) at the national, district, and health facility levels in 63 health facilities spread across 11 districts identified as having the highest volume of HIV patients. These districts are home to a majority of the Botswana population and home to 87% of the HIV infected population in Botswana. Through the new TB grant the BUP-TB program aims to screen 105,107 HIV infected people for TB, diagnose 7000 TB cases and ensure 100% of those who are HIV infected and have TB are initiated on ART in the 63 high volume health facilities.

Ongoing activities from 2015 include:

- Informing TB/HIV policies and guidelines for adult and pediatric TB at the national level
- Training and mentoring health care workers at the district and health facility level to increase TB case finding and case detection
- Identifying TB hotspots (within facility and community) using geospatial data
- Providing technical assistance in TB/HIV training to increase TB and HIV case detection in the entire population
- Assist MDR-TB outbreak investigations

Epidemiology & Biostatistics

BUP contributions in epidemiology and biostatistics include under the leadership of Ari Ho-Foster MPH and Joseph Jarvis MD, PhD:

- Providing mentorship and support to UB Department of Medicine, Pediatrics and Emergency Medicine residents completing MMED projects.
- Providing epidemiological and biostatistical support to UB.
- Supporting Botswana National TB Program's development of Monitoring & Evaluation framework.

HIV Care & Support

The HIV Care & Support program began in 2003 to provide technical training support for the national rollout of antiretroviral therapy treatment for HIV infected citizens. Botswana with the help of key partners like the BUP has had tremendous success in treating HIV nationwide and is very close to reaching the 90-90-90 target[2] for testing, treatment and viral

[2] The 90-90-90 target set by UNAIDS encourages countries to aim to achieve: Diagnosis of 90% of people living with HIV by 2020; Initiation of treatment by 90% of diagnosed people by 2020; Viral suppression in 90% of people on treatment by 2020.

suppression of HIV and is ahead of the United States and most European countries in its efforts to improve treatment coverage.

BUP under the leadership of Miriam Haverkamp continues to work in the following HIV areas:

- Providing postgraduate medical education in HIV to local healthcare workers
- Assisting the MOH with the development of national treatment guidelines by serving on the Botswana national HIV treatment guidelines committee
- Serving on the Drug Costing Committee of the Ministry of Health
- Chairing the Antimicrobial Management Committee

Malaria

The malaria program is lead in country by Giacomo Paganotti, PhD

- Molecular detection of malaria in people and in mosquito vectors in Botswana and surveillance in mosquitoes for Zika virus in collaboration with the MOH
- Serving on the National Malaria Guidelines Writing Committee

mHealth & Telemedicine

Carrie Kovarik, MD, launched the BUP tele-dermatology program in 2007, which has expanded into a broad telemedicine and mobile health (mHealth) program that seeks to circumnavigate the use of unreliable, expensive landline IT infrastructure in the region and address the severe shortage of healthcare workers (particularly specialists) by harnessing readily available cellphone technology. Led in country by full-time staff director, Ryan Littman-Quinn, the program uses mobile devices (cell phones, tablets, etc.) and other electronic tools to transmit health information for education, diagnosis, and treatment. Current efforts include:

- Sponsoring and mentoring local citizens interested in medical informatics, telemedicine, and/or mHealth to pursue post graduate degrees
- Partnering with international and local public and private partners on national Youth mHealth Innovation Competitions and mentoring teams and winners to develop their innovations
- Supporting health informatics in UB Health Science's yearly curriculum
- Supporting the National eHealth Strategy with technical advice and participation in stakeholder workshops and committees.
- Spearheading Peek Vision Task Force to build capacity in MoH and MoE to conduct vision screenings at schools as part of their School Health campaigns. The Peek Vision Task Force is part of the Partnerships Subcommittee of the National Eye Health Committee.
- Serving as a member of the National Eye Health Committee.

Pediatric Advanced Lift Support and Pediatric Emergency Assessment Recognition and Stabilization Training

These training programs were led by Pete Meaney MD, MPH from CHOP:

- Over 300 doctors, nurses, midwives at UB and District Hospitals were trained in pediatric advanced life support techniques and approaches to emergency care.

Radiation Oncology

The Radiation Oncology program is lead in country by Surbhi Grover MD, MPH. Global cancer mortality is expected to double by the year 2030. The problem is magnified in Botswana, as HIV patients live longer with effective therapy, cancer cases are surging. More than 40% of new cancer cases in Botswana are due to HIV[3]. 2015 saw the addition of Surbhi Grover as a regular faculty member working on the ground in Botswana to address issues in cancer care including:

- Leading development of cancer treatment guidelines
- Participating in gynecological and head and neck multidisciplinary treatment clinics and new patient oncology clinics at Princess Marina Hospital
- Helping with chemo-stocking calculations

Women's Health: Cervical Cancer, Family Planning, Sexual and Reproductive Health

The BUP Cervical Cancer Screening Program led by BUP Country Director, Doreen Ramogola-Masire MD, was established in 2009 to prevent cervical cancer, which is the most common cause of cancer-related deaths among women in Botswana. About 60% of the cervical cancer patients are HIV positive; most present with advanced cervical disease. The program uses the "See & Treat" approach of acetic acid to help evaluate cervical lesions and determine treatment including perform cryotherapy, or refer to the Colposcopy Clinic for assessment and treatment with loop electrical excision procedure (LEEP) making significant improvements in the care of pre-invasive and invasive cervical cancer patients.

With the addition of BUP faculty Chelsea Morroni MD, PhD, BUP programs in women's health have included:

- Providing technical assistance, mentorship and training for the national scale up of the "See & Treat" approach for cervical cancer prevention
- Training local nurses and doctors to become proficient providers of cervical cancer prevention services
- Reviewing national data collection tools, management algorithms as well as improvements in cervical cancer prevention program data quality
- Providing technical assistance to the MOH for women's health issues, including advising on national HIV issues, maternal mortality, and HPV vaccination
- Serving on the National HIV specialist committee providing consultant expert advice to doctors around the country in HIV-related issues for pregnant women
- Serving as a member of the HIV guideline development committee
- Serving as a member of Steering Committee for the National Cervical Cancer Prevention
- Serving as a member of the National Health Forum to advise MoH on important health related issues
- Contributing to the National 2036 Vision as part of the Botswana health care group
- Serving as special advisor to Family Planning Program in Sexual and Reproductive Health Department of MoH

[3] Source: Botswana Oncology Global Outreach - http://www.botsogo.org/

- Serving as lead advisor for introduction of the Contraceptive Implant into Botswana for the Health Department of MoH
- Starting and operating the only doctor referral Sexual and Reproductive Health clinic in Botswana
- Global contributions (Ramogola-Masire) include: Serving as vice president representing Southern Africa at the African Organization for Research and Training In Cancer (AORTIC); Serving as a member of the international Steering Committee for PEPFAR/NIH non-communicable disease project; Serving as member on the advisory board for the IARC/WHO HPV vaccine clinical trial in India for 20000 girls; Serving as member of the ASCO guideline group for secondary cervical cancer prevention

B. Research

With support from the CFAR international core, in 2015 BUP supported 19 grants in Botswana including 13 US government grants, 1 Gates Canada Grand Challenge grant, 2 UK grants, and 1 industry grant. In 2015, BUP-researchers in Botswana and at Penn published 29 peer-reviewed papers based on research in Botswana. In July 2015, Botswana Research Director Andrew Steenhoff, MD, moved to Philadelphia to become Director of the CHOP Global Health Program and Tonya Arscott-Mills, MD was appointed as Research Director. The laboratory director is Giacomo Paganotti, PhD. The lab is shared with and housed on the UB campus, and particularly well equipped for molecular biology and genetic studies.

Research Highlights of 2015:

- The International Core, in collaboration with the U54 Mentoring and Career Development Core held a 2-day workshop on August 12-13, 2015 in Botswana on the campus of the University of Botswana with a workshop on "Grant Writing and Research Training" that featured both UB and Penn faculty. 100 trainees and faculty from UB attended the workshop. Junior faculty members were encouraged to prepare pilot grant applications for submission by Nov. 2015. Two pilot grants were funded.
- Provided on-site scientific oversight of over 20 research projects
- Advised Penn/Botswana scientists on the feasibility of their proposed research studies
- Assisted over 20 investigators from Penn and Botswana in obtaining approval from the appropriate IRB regulatory committees in Botswana and at Penn
- Obtained a Cytoflex flow cytometer to facilitate HIV research in Botswana.
- Mentored 3 junior faculty from the University of Botswana in lab-based research and more than 10 MMED residents who must complete a thesis to qualify for the Masters in Medicine Degree.
- Examples of new inter-CFAR synergy include: A) Two CFAR supplements were awarded during the current year: i) A CFAR supplement was awarded to Harvard/UPenn/University of Botswana on the topic of HPV as a cause of penile cancers in Botswana; ii) A CFAR supplement was awarded to MD Anderson Cancer Center/UPenn/University of Botswana on the role of radiation therapy in treating cervical cancer in Botswana. B) NIH grants have been implemented in collaboration between Nicola Zetola from BUP with the UCLA and Duke CFARs: i) The Effect of mixed-strain M. tuberculosis infections on treatment outcomes. ii) Utility of deep sequencing for detecting heteroresistant mycobacterium tuberculosis infections among

HIV-infected persons. iii) Molecular epidemiology of nosocomial TB acquisition among HIV-infected patients; iv) Investigating the role of the nasopharyngeal microbiome in mediating the increased susceptibility of HIV-exposed, uninfected infants to Streptococcus pneumonia.

NIH-funded actives studies in 2015 include the following:

- **D43 TW009781 (Robert Gross, PI): HIV Clinical Epidemiology Training for Botswana -** This NIH Fogarty grant is helping to train the future clinical research leaders in Botswana by providing training at Penn and in Botswana for a Masters of Science in Clinical Epidemiology (MSCE). In addition, an Associate Investigator certificate program was launched in July 2015. Approximately 30 applicants were accepted for training. In 2015 one student enrolled in the MSCE program in its first year. A total of 8 slots are available over a 5-year period. Two NIH supplemental awards were funded that are linked to Dr. Gross' D43 grant:
- **K23 MH095669 (Elizabeth Lowenthal, PI): Targeted Monitoring and Determinants of Adherence in Adolescents with HIV -** Dr. Lowenthal aims to identify successful interventions to promote adherence among HIV-infected adolescents, particularly in resource-limited settings. The research being done under this award is uncovering developmental and behavioral characteristics of adolescents associated with HIV treatment non-adherence.
- **R01 AI120821-01 (Greg Bisson, PI): Rapid Immune Restoration and Lung Injury in HIV/TB -** In pulmonary TB over half of patients have pulmonary function impairment despite achieving microbiologic cure. This proposal, which is set in South Africa yet based on preliminary data collected in Botswana, hypothesizes that in HIV/Pulmonary TB worsening of lung injury is an untoward and modifiable effect of rapid, treatment-related reversal of immunosuppression.
- **R01 GM113657-011 (Sarah Tishkoff, PI): Integrative Genomics of Body Size and Metabolism in Ethnically Diverse Africans -** The Tishkoff lab has genotyped 550 Botswana samples as part of a larger cohort of 1650 ethnically diverse Africans. They have used these samples for GWAS of a number of traits, including skin pigmentation, height, BMI, blood pressure, and biomarkers of lipid and glucose metabolism. They have completed an analysis of 16S RNA from fecal samples from 70 Botswana individuals to characterize microbiome diversity, and have initiated high coverage Illumina whole genome sequencing of 45 individuals from three ethnic groups in Botswana. These results will be useful for identifying population specific markers and local adaptation.
- **R01 AI097045-04 (Nicola Zetola, PI): Dynamics of TB and MDR TB Transmission in Areas with High HIV Prevalence -** This study combines traditional and molecular epidemiology approaches to determine the effects of HIV on TB transmission dynamics in two of the highest burden districts in Botswana. This is the largest TB transmission study conducted in a hyper-endemic area for TB and HIV to date. Over the last 3 years, close to 5,000 TB patients have been enrolled. Their primary residencies and areas of social aggregation have been mapped. TB transmission is determined by MTB genotyping analyses. Methods developed through the implementation of this study were the basis for the development of the Botswana National Guidelines for TB Case Finding and Contact Tracing and will be adopted in the revised Botswana National TB Guidelines. The preliminary results from the study have led to a pragmatic cluster

randomized trial to determine the best approaches for TB and HIV case finding and treatment delivery at the community level, currently being developed by Penn and the Ministry of Health nationwide.

- **R21 AI105611-02 (Nicola Zetola, PI): Determination of Exhaled Biomarkers for Low-Cost Diagnosis and Monitoring of TB -** This study has provided proof-of-concept for the use of breath samples for diagnosis and prognosis of MTB infection in HIV-infected and uninfected individuals. The approach allows the use of cheap, rapid non-invasive point-of-care diagnosis for MTB infection.
- **U54 CA190158 (Erle Robertson, PI): Botswana-UPenn Research Consortium of HPV-Related Cervical Cancer in HIV Patients -** In collaboration with UB, the PSOM under the departments of Radiation Oncology and Microbiology and the Botswana-UPenn Partnership, received a $3.5 million U54 grant over five years from the National Cancer Institute (NCI) to study cervical cancer in HIV Positive Women in Botswana. The purpose of the grant is to establish an inter-disciplinary research consortium between the UB and Penn. The consortium focuses on HPV-associated cervical cancer in HIV seropositive patents as well as building research capacity in Botswana through a strong emphasis on mentoring and education. The consortium focuses on three cohorts: co-infected women with no clinical signs of cervical cancer; women with precancerous lesions; and a third group who are being treated for cervical cancer. The overall goal is to translate the knowledge into effective prevention and treatment strategies that will lower the burden and associated illness and deaths from cervical cancer.

Five-year Funding Summary from Extramural and Intramural Sources

Funding	FY12	FY13	FY14	FY15	FY16 (estimate)	Total
Direct costs: grants	$5,281,912	$6,245,147	$4,764,721	$7,521,966	$ 8,429,350	$32,243,096
Indirect costs: grants	$915,060	$520,532	$ 685,645	$1,180,267	$ 879,985	$3,301,504
Institutional support	$643,000	$663,283	$ 686,090	$ 650,000	$ 789,650	$2,642,373
Total costs	**$6,839,972**	**$7,428,962**	**$6,136,456**	**$9,352,233**	**$10,098,985**	**$38,186,973**

C. Educational Programs & Initiatives and Global Health Experiences
Global Experience for Penn Students and Trainees: Total Penn Travelers: 2002-2015

YEAR	Penn Faculty	Penn Fellows & Residents	Penn Dental Students	Penn Medicine1 Students	Penn Nursing Students	Penn Other2 Students	Penn Summer Intern Students	Penn Other (Staff, Alumni, Doris Duke)	Non Penn Fellows & Residents3	Other NON Penn	TOTAL
2002-2004	N/A	1	0	6	0	N/A	0	N/A	0	N/A	**7**
2005	N/A	29	0	24	0	N/A	0	N/A	0	N/A	**53**
2006	N/A	22	0	25	0	N/A	0	N/A	3	3	**53**
2007	N/A	15	0	52	0	N/A	N/A	N/A	1	4	**72**
2008	14	26	0	21	9	N/A	14	6	14	32	**136**
2009	32	40	2	30	8	N/A	14	19	15	4	**164**
2010	19	33	6	31	9	N/A	14	17	13	9	**151**
2011	19	33	6	33	12	N/A	14	29	18	13	**177**
2012	21	34	2	31	7	N/A	10	12	14	14	**145**
2013	13	34	2	36	0	N/A	14	13	16	3	**131**
2014	15	22	2	30	8	14	9	9	20	0	**129**
2015	17	25	1	24	7	1	6	5	17	5	**108**
TOTAL	**150**	**314**	**21**	**343**	**60**	**15**	**95**	**110**	**131**	**87**	**1326**

1= Medicine includes MPH students. 2 in 2014 1 in 2015.

2= Other student groups. 9 School of Design students, 2 Wharton Social Impact, 2 Fox Leadership and 1 self-funded in 2014. 1 Fulbright in 2015.

3= Note that there are 12 non-Penn dermatatologists who travel to Botswana under AAD annually. Plus CHOP residents.

Description of Programs listed in Table:

1. Penn Faculty

Most faculty members who travel to Botswana are doing so to explore new opportunities for global programs or research, establish research collaborations, or to further develop already established programs. Faculty involvement includes many Penn Schools.

- SAS: Faculty trip by Carol Muller from the Dept. of Music
- SP2: Faculty & Staff Trip to look for collaborations and opportunities for SP2 involvement in Botswana.
- Wharton: Faculty trip by Witold Henisz to do fieldwork on a grocery store chain headquartered in Botswana for a management course case study

2. Penn Residents/Fellows

- Residents in Internal Medicine: The Botswana Elective is a 4-week experience at PMH working on a medical firm as a senior resident co-running ward rounds with Medical Officers from the MOH or UB residents and teaching UB medical students.
- Residents Global Health Track in Internal Medicine for PGY2 & PGY3: 4 weeks working abroad as PGY2 and PGY3. The PGY3 focus is on outpatient and community outreach.
- Residents in Dermatology: From Penn and other institutions participate in the Botswana elective in a 4-week dermatology elective in Botswana. Two residents a year are from

Penn and 12 from outside institutions.

- Residents in OBGYN: A 4-week experience offered to 1-2 residents per year to work in the BUP Women's Health Clinic.
- Residents Pediatrics: The CHOP Global Health rotation to Botswana affords a 4-week experience of in-patient pediatrics for pediatric residents at PMH.
- Residents Surgery: 2 residents annually supervised by an adjunct Penn faculty member.
- Residents from radiology, radiation oncology, and psychiatry participate in rotations to Botswana for four weeks.

3. Students – Dental

Penn Dental students spend 4 weeks in Botswana serving as dental assistants and working under the tutelage of an oral surgeon.

4. Students – Medicine

- Medicine – MS4: The experience is 7 weeks and provides students with an Orientation & Didactics Week (Intro to Setswana/ HIV/ TB/ Opportunistic Infections/ basic medicine and pediatrics in Botswana) followed by inpatient medicine at PMH for 2 weeks and 4 weeks at a District Hospital. Students earn 4 weeks of credit from Penn.
- Students – MS1 Research Elective: Research internships for rising first year medical students to participate in research in Botswana during the summer break. Opportunities are for 6-8 weeks.
- Students – MS3/4, Clinical Elective in Dermatology: Students rotate on the dermatology service in Botswana working with senior dermatology residents and the local dermatologist.
- Students – MPH, Summer Internship / Research: Students work in supervised internships with local NGOs, or under the supervision of UB or BUP faculty on research projects. Research in Botswana may count towards the Capstone project.

5. Students – Nursing

Nursing 341 (Nursing in the Community: Clinical, since 2008): Second Degree nursing students submit an application to complete their Community Heath clinical rotation in Gaborone, Botswana during the Penn summer term in August. Students have regularly-scheduled and supervised clinical practice in government community health clinics.

6. Penn Summer Intern Students (College, GSE, Law, SEAS, SP2, Vet, Wharton)

International Internship Program (IIP): BUP offers 10-week summer internships in Botswana from late May until late July for Penn students across various schools at Penn. The Internship provides an opportunity for Penn students outside of the health sciences to experience life in Botswana and obtain practical work experience in a developing country.

C. Facilities & Equipment

- Housing for Penn Trainees, Pilane Court: A gated 3-flat complex, each flat with 3 bedrooms. The complex includes a lounge/library, outdoor eating area, pool and garden. The flats can house up to 25 people and is walking distance to PMH.
- Research office space near center city: Office building at 214 Independence Ave that has 6 offices and a large open area with work cubicles. On the property there is

a portacabin (owned by BUP) with a research office and a pharmacy accredited for clinical trials and a converted garage that has a conference room and an office.

- Research office space on UB campus: A portacabin with 16 offices and a conference room.
- Faculty and administrative office space on UB campus: There are 16 offices and a conference room for our administrative and clinical faculty.
- Portacabins for enrolling patients into TB trials (owned by BUP): There are 5 1-room portacabins located adjacent to MOH Health Clinics that we use to enroll subjects into TB research studies..
- Lab research space at the National Health Lab (space provided by MOH): BUP has a lab of 500 NSF at the MOH National Health Lab near PMH. The lab is used to process clinical research samples and contains laminar airflow hoods, -80C freezer, -20C freezer, centrifuges and a PCR machine.
- Lab research space at the Faculty of Health Sciences Building at UB (space provided by UB): BUP shares a large lab, approximately 1800 NSF with the UB Faculty of Health Sciences. BUP provided equipment purchased with MEPI funds (approximately $200,000).
- Research Clinical Trials Pharmacy: The BUP runs a Research Pharmacy located in the research portacabin at BUP's 214 Independence Ave offices.
- Other assets: BUP owns 18 cars that are used for research and administrative purposes. Cars were purchased (one was donated as a gift) either using grant or SOM/UPHS funds.

D. Training Opportunities for UB trainees, Staff and Faculty at Penn

- Upper-year UB medical students are supported by BUP to do clinical electives at Penn: In 2016 two UB medical students will travel to Penn for clinical electives with funding provided by BUP and CHOP.

Changes in 2015

There was a significant shift in the grant funding support for BUP in 2015 as a result of the end of PEPFAR funding in three of four clinical areas. Additionally, the MEPI grant ended in August 2015. In looking ahead the BUP seeks continue its mission of building health care capacity by seeking to do the following:

- Partner with MOH on Clinical Staff – An important direction is a partnership with the MOH to jointly hire key physicians that are needed in the public sector but that the MOH has not been able to attract. The agreement is to have the MOH pay the standard salary offered for such positions and BUP will supplement the recruitment package by offering benefits that are important to the recruits, such as US healthcare. This approach will enable BUP to maintain a strong clinical presence.
- Establish joint appointments at UB: Several of our BUP faculty members have honorary appointments at UB. These appointments enable us to apply for grants that can only be awarded to African institutions. We are also looking to hire faculty who have joint appointments at UB and Penn that are supported along the lines described above for partnerships with the MOH.
- Expand clinical trials: Expand BUP clinical trials infrastructure in Botswana with the intent of attracting pharmaceutical support for clinical trials research.

Organizational Chart for the Botswana-UPenn Partnership