

Research Components of the Brown Kenya Program: A Personal and Professional Perspective

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INTRODUCTION

Research, whether basic science, implementation, operational, clinical or other, supports and promotes clinical care.¹⁻⁴ It generates and addresses hypotheses, informs programs and provides data that can be translated to care. Research is not trivial or easy. It is time consuming, requires much planning, mandates a detail-oriented approach, involves availability of, or time and capability to create infrastructure, includes access to relevant resources and facilities and mandates complete and full dedication of experienced and motivated personnel.

The Academic Model Providing Access to Healthcare (AMPATH) in western Kenya leads with care. It has provided clinical services to >130,000 of the country's 1.6 million HIV-infected people, reducing morbidity, mortality and the very high burden of this pandemic on the country (<http://www.unaids.org>).

The Brown Kenya Program also leads with care. The medical exchange program of students, residents, post-doctoral fellows and faculty is the mainstay of the program. Both programs are intertwined with research. In this paper I discuss the conduction of research in the Brown program with the support of the AMPATH infrastructure, from a programmatic as well as from a personal perspective.

The AMPATH Research Infrastructure

<http://www.ampathkenya.org>

Brown University is part of the AMPATH consortium, led by Indiana University and consisting of multiple North American universities, in addition to Moi University and Moi Teaching and Referral Hospital. The AMPATH Research Network has dedicated much effort towards a strong and sustainable infrastructure to allow research that can support clinical care. This infrastructure includes a research administration office in Kenya that oversees and coordinates research activities; a Research and Sponsored Programs Office (RSPO) that provides grants management and other financial and human resources services; an Institutional Review Ethics Committee (IREC) to ensure that proposed research is both ethical and culturally-appropriate; and advanced laboratory capacity to support research projects.

AMPATH's research program is organized into nine Working Groups (adult medicine, basic science, behavioral and social science, oncology, pediatrics, prevention of HIV mother-to-child transmission, public health and primary care, reproductive health, and tuberculosis) and seven Cores (operations, data management, biostatistics, clinical informatics, pharmacy, laboratory, and bioethics). Working Groups and Cores have frequent conference calls to discuss general operating procedure and specific projects. Each project, which must have both a North American and Kenyan principal investigator, is presented to and must be approved by the relevant research working group, with subsequent IREC approval. Prior to presentation or publication, abstract and papers are submitted to a publications committee, which has representatives from the various Working Groups and Cores, who review papers and provide input to authors.

A major infrastructure component of the research program is the use of an electronic medical record system throughout AMPATH.⁵ This uniform system is used in a well-organized manner, that includes specific forms filled out by clinicians throughout the network; quality controlled data entry into a carefully designed database; and a computer system that allows



Dr. Rami Kantor and his team in Kenya.

querying and efficient use of the electronic data. Such a system allows research diversity and flexibility such as patient identification for projects, provision and use of clinical data and storage of study data.

This excellent research infrastructure provides an engagement structure for efficient collaborations, maximizing capacity and expertise from all participants.

The Brown University – Kenya Program Research Scheme

<http://brownmedicine.org/kenya>

It all started with Dr. Jane Carter. Brown University was the first institution to join the Indiana University-led AMPATH consortium in 2001. Hence, tuberculosis, Dr. Carter's research focus, was the first to be incorporated into the research program. Over the years, Dr. Carter has mentored many students and faculty within the program, obtained various grants, overseen numerous research projects, collaborated with a variety of institutions and investigators and published abundant papers related to her research in Kenya (eg,⁶).

The infrastructure provided by the AMPATH consortium and Dr. Carter's vision allowed for the Brown-Kenya research program to flourish. Today, a growing number of Brown investigators and disciplines are actively involved with research in Kenya (*See Table*). Some examples include pulmonary medicine (eg, tuberculosis, household air pollution); HIV medicine (eg, HIV diversity and drug resistance); psychiatry (eg, mood disorders); nephrology (eg, genetic factors in disease); gynecology (eg, cervical cancer); pediatrics (eg, HIV and health in street kids); behavioral medicine (eg, alcohol effect on Kenyans); and biostatistics (eg, support to AMPATH's research and training a new generation of Kenyan biostatisticians).

These ongoing expansions allow involvement of students, staff and faculty in multidisciplinary areas of research, in a safe, productive and nurturing environment, supporting clinical care. This is how my personal research story in Kenya started.

HIV Drug Resistance and Patient Monitoring Research

In January of 2005, when I arrived at Brown, HIV drug resistance research was already my passion, particularly in international settings, and I wanted to continue this line of investigation. During my prior post-doctoral fellowship at Stanford I had already worked in Zimbabwe, South Africa, Thailand and India, where diverse HIV variants and resistance patterns exist, different than in the United States.⁷ A few weeks after my arrival, I learned about the Brown Kenya Program and was advised to set up a meeting

with Dr. Carter, the program's director. Our meeting went extremely well and I was very quickly introduced to the Indiana University and AMPATH leadership and to my Kenyan collaborators, and now friends, Dr. Lameck Diero, the Moi University chief of medicine, and Dr. Nathan Buziba, the AMPATH Reference Laboratory director. By April 2005 I submitted and was awarded my first Kenya grant, a Brown/Lifespan/Tufts Center for AIDS Research (CFAR) Developmental Award. This rapid turnaround, from idea to fact, opened the door of opportunity for me and would not have been possible without the amazing relationships and infrastructure that were already in place in Kenya.

In this first project, we conducted a feasibility study to investigate diversity and drug resistance in antiretroviral treatment naïve and experienced HIV-infected patients. Such research had never been done at AMPATH; circulating HIV subtypes were unknown and none of the 80,000 HIV infected patients enrolled at that time at AMPATH had ever undergone HIV drug resistance testing. We were able to enroll 120 patients and obtain blood samples using various novel analytes. We examined cheaper and simpler options for HIV viral load and resistance testing in resource limited settings. We conducted CD4 and viral load testing at the AMPATH laboratory. Further, we shipped samples of all analytes to my Brown laboratory for drug resistance testing. Study results of diversity (subtypes A, C, D and many recombinants) and low-transmitted and high-acquired drug resistance were original for the region and provided abundant data for continued research.

During this first project, an important thing happened. To examine HIV drug resistance, we first had to identify patients who were failing antiretroviral treatment. To do this, we used the World Health Organization (WHO) patient monitoring guidelines, practiced at AMPATH and in Kenya

Brown Investigators	Kenyan Investigators	Research Theme
J Carter, C Sherman, A Gardner	W Injera, N Buziba, D Menya, R Kosgei, N Kirui, L Diero, D Oyieng'o, A Siika, R Karwa, S Kimaiyo, F Ogaro	Pulmonary Medicine; Tuberculosis, Cookstove Household Air Pollution and Lung Disease
M Keller	Atwoli, E Omolo, R Songole	Psychiatry; Mood Disorders
S Winston	A Chirchir, D Ayuku	Pediatrics; Sexual Health Risks and HIV Prevalence in Street-Involved Youth
R Papas	B Gakinya, J Baliddawa	Behavioral Medicine, Alcohol research
L Brown	D Ayuku	Adolescent risk behavior research
T Montague	M Owiti	Nephrology; APOL1 as a Kidney Disease Risk Genetic Locus
S Cu-Uvin	H Mabeya, O Orangu, D Chumba, P Itsura, D Patel	Obstetrics-gynecology; Cervical Cancer in HIV-Infected Women
J Hogan	A Mwangi	Biostatistics
R Kantor	L Diero, N Buziba, S Kimaiyo	HIV Diversity, Drug Resistance and Treatment Monitoring in Adults and Children; Laboratory Assays Development

for clinical care. These guidelines are significantly different than those used in Western settings. The latter utilize HIV viral load testing every few months, whereas in resource limited settings CD4 and clinical criteria are used. Study viral load testing of enrolled patients who fit the WHO failure criteria quickly revealed that most patients actually had non-detectable HIV and thus were not failing their treatment regimens. Though it made our lives more difficult and patient enrollment much longer than anticipated, this research finding⁸ was important. With the existing AMPATH infrastructure it quickly led to clinical care change, and mandatory HIV viral load testing upon suspicion of treatment failure. Such change would avoid unnecessary switches to more advanced and costly antiretroviral therapy.

A second resistance project followed the 2007–2008 Kenya post-election violence. During this crisis multiple HIV-infected patients were displaced from their homes and had unplanned interruptions in their antiretroviral treatment. Having the collaborations and methods in place, we obtained funding to examine long-term outcomes of such treatment interruptions.⁹ Our findings, that patients with crisis-induced treatment interruptions were more likely to fail treatment compared to those with no interruption,¹⁰ are important for Kenya as well as for other resource-limited settings, where HIV prevalence is high and the likelihood for future political and other conflicts are unfortunately high as well.

In a third project we are examining treatment failure and drug resistance upon HIV second-line antiretroviral therapy, the last resort in such settings. As AMPATH, Kenya and other similar settings are programmatically preparing for third-line antiretroviral options, such data are essential. As this article is being written, results from this ongoing project, unique in Kenya, are being made available to the AMPATH leadership, and through them to the Kenya National AIDS and STI Control Program (<http://nascop.or.ke>) to plan for purchasing third-line medications and save the lives of patients who develop resistance to second-line medications.

Research projects like the three outlined above have many advantageous aspects in addition to their impact on clinical care. They allow me to mentor students and involve them in research; train, collaborate and develop friendships with Kenyan investigators; host them at Brown; incorporate Kenya into grants; increase research infrastructure; conduct resistance testing in my lab for AMPATH patients; work towards setting up a much-needed drug resistance laboratory at AMPATH; and develop multidisciplinary research collaborations at Brown (eg, Center for Statistical Sciences, Center



Dr. Rami Kantor and Kenyan medical trainee Millicent Orido, who spent six months in Dr. Kantor's lab to learn techniques in diagnosing HIV resistance mechanisms.

for Computational Molecular Biology and School of Engineering]. Every second of time spent in all these endeavors is worthwhile.

CHALLENGES

Conducting research in resource-limited settings can be different and challenging. Following is a short Swahili lesson to explain such potential differences. Anyone who has studied Swahili, whether with Wycliffe at the IU House in Eldoret or with anyone else, knows that the number 1 in Swahili is 'moja.' However, if you want to meet someone for dinner at 7 p.m., you tell them to meet you at 'moja', even though the number '7' is 'saba.' One reason for this, as Wycliffe carefully explains, is the history of time relatedness to sunrise (6 a.m.). So '7' becomes one (or 'moja') hour after 6, '8' becomes two, and so on. Google 'Swahili clock' and see for yourself.

This (perhaps confusing) example conveys the concept that details are sometimes not the same in different settings, affecting the ways things are processed, performed, executed and discussed. Issues like language, the concept of time, available resources, verbal and non-verbal communication, cultural norms and prior experience and exposures are key to essential parts of research. Typical research milestones like writing a grant, designing a protocol, executing a study, obtaining a consent form, enrolling patients, explaining an intervention or a laboratory test, quality controlling data, conducting data analyses and writing a paper collaboratively – all key for research, can be new experiences in new settings. Limited funding, long flight hours, price of phone bills and dusty shoes can all add to the burden. Addressing such challenges and learning from the experiences that this program provides offer endless opportunities.

CONCLUSIONS

Everyone who is involved with the Brown Kenya Program has their own story to tell and their own journey to travel. When people hear that I work in Kenya, their questions indicate that they're sure there is nothing there. After all, it's a developing country, with limited resources; what can possibly be accomplished there? In this article I tried to paint the picture, describe the grounds, and provide information on how far from the truth this notion is. I tried, partly through my own experience, to show what great work that answers important questions can be done through the Brown Kenya Program. I attempted to show that research helps build infrastructure and capacity to address important questions that can be translated to patient care.

This wonderful journey started with a quick meeting with Dr. Carter. It continued with the support of my superb research group including Leeann Schreier, Dr. Mia Coetzer and Dr. Austin Huang; the Brown/Lifespan/Tufts CFAR, the Brown Infectious Disease Division, and the Department of Medicine. Such an adventure is only possible due to the outstanding infrastructure that is in place through the Brown Kenya Program, which is a great testimony for the opportunities that lie ahead. ❖

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