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Resistant to Treatment: AIDS, Science, and Power at the Dawn of Uganda's 'Treatment Era'

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Resistant to Treatment: AIDS, Science, and Power at the Dawn of Uganda's 'Treatment Era'

by

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DISSERTATION

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DEDICATION

For David, with gratitude and friendship

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ABSTRACT

Resistant to Treatment:
AIDS, Science, and Power at the Dawn of Uganda's 'Treatment Era'

Johanna Tayloe Crane

Drug resistance, which occurs when HIV mutates to render AIDS medications (antiretrovirals) ineffective, has been a highly politicized topic within international health. Fears of "antiretroviral anarchy" leading to widespread drug resistance have been cited as a reason to exercise caution in extending access to HIV medication in poor countries, particularly those in sub-Saharan Africa. Nonetheless, the exact definition, causes and consequences of drug resistance remain topics of uncertainty and debate within HIV science. This is especially true in relation to drug resistance in Africa, where studies of drug resistance are just beginning as HIV drugs become more widely available. Using ethnographic research conducted among North American and Ugandan HIV researchers, my dissertation asks the questions: *What* do we know about drug resistance in Africa, and—more importantly—*how* do we know it? This multi-sited project combines approaches from science and technology studies and critical medical anthropology to interrogate the political economy of transnational scientific research.

Resistant to Treatment examines the nexus of professional, economic, and ethical relations that is emerging between North American and Ugandan AIDS researchers in the context of multilateral efforts to provide widespread access to HIV drugs in sub-Saharan African countries. The immanent availability of these drugs has created research opportunities that are powerful both politically and professionally, and has resulted in an

influx of research funding to Uganda via American researchers seeking to collaborate with Ugandan physicians. I describe how these partnerships are fueled by humanitarian and professional ambitions on both sides, and how researchers must negotiate these sometimes competing goals in the context of a donor/recipient relationship in which collaboration includes (but is not limited to) a strategic exchange of American research funding for access to Ugandan patients. I argue that commensurability becomes a key issue in these collaborations, as the profound incommensurability of the Ugandan and American HIV epidemics must be at least partially reconciled in order to render U.S. scientific and ethical protocols operable in Uganda. In addition, I explore how Ugandan AIDS experts negotiate their position as enablers of and participants in these emerging research opportunities.

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INTRODUCTION

By the year 2000, the AIDS epidemic in wealthy industrialized nations had been transformed. Antiretroviral (ARV) medications capable of drastically reducing the replication of the HIV virus had been available since 1996 and, as a result, many patients in wealthy nations had seen their health radically improve. In the U.S., the annual number of deaths from AIDS dropped from over 50,000 in 1995 to less that 18,000 in 2000 (CDC HIV/AIDS Surveillance Report 2001, 2003). With our own epidemic coming under control, the eyes of the West began to look southward and eastward, and particularly towards sub-Saharan Africa where an estimated 70% of the world's people infected with HIV were living and dying. Here ARV medications remained largely unavailable, except to the wealthy and well-connected able to obtain "briefcase drugs" purchased by relatives working in Europe and brought into the country on airplane luggage. Activists around the world clamored for more equitable access to drugs, and clinicians and researchers began to join them.

As a result, by 2001, international health policymakers were having serious discussions about the possibility of expanding HIV treatment to the developing world. These discussions hinged on questions of feasibility at both a technical and a behavioral level. First, would it be technically feasible to safely and consistently administer high-cost, high-tech, multi-pill regimens in areas with limited physical and health infrastructure? And second, would patients with little education and few resources be willing and able to adhere to (i.e. "comply" with) the regimens? Concerns about consistent drug supply and adequate adherence were both rooted in the fear of drug

resistance—if patients missed doses, their HIV could easily mutate into a drug-resistant strain, rendering the drugs ineffective and, as one medical journal argued in 2002, "making the developing world a veritable 'petri dish' for new, treatment-resistant HIV strains" (Popp and Fisher 2002).

At times, little distinction was made between technical and behavioral feasibility, revealing much about the role occupied by Africa in the Western imagination. For example, in a 2001 interview with the *Boston Globe* Andrew Natsios, the Chief Administrator of the U.S. Agency for International Development (U.S.AID) told a reporter:

> Those who argue for treatment of AIDS in Africa "do not know the challenges we have with diseases that we have cures for. . . . We cannot get it done because of conflicts, because of lack of infrastructure, lack of doctors, lack of hospitals, lack of clinics, lack of electricity."…Many Africans "don't know what Western time is. You have to take these (AIDS) drugs a certain number of hours each day, or they don't work. Many people in Africa have never seen a clock or a watch their entire lives. And if you say, one o'clock in the afternoon, they do not know what you are talking about. They know morning, they know noon, they know evening, they know the darkness at night" (Donnelly 2001).

This dissertation project began as a response to this imaginary, as an effort to track how "Africa" has been constructed through Western scientific discourse about drug-resistant HIV. Through interviewing and observing North American scientists engaged in studying drug resistance, I have tried to document not only what we know about drug-resistant HIV in Africa, but also *how* we know what we know, and what the consequences of that knowledge have been for people in need of medication. However, this dissertation is not a straightforward story of Western medicine constructing the marginalized "other." Any account of scientific knowledge about HIV in Africa that did not include perspectives of scientists from that continent would not only be woefully

incomplete, but would participate in the same imaginary I seek to disassemble: that of "Africa" as by definition marginal, backward, helpless, and—by extension—unscientific.

Of the 54 countries on the African continent, many are fighting well-publicized battles with national AIDS epidemics that far exceed the scale of anything faced by wealthy countries. Among these, the small East African nation of Uganda has become particularly associated with AIDS in international public health discourse—a result of the government's proactive prevention efforts, friendliness toward international researchers, and the pivotal role played by Ugandan doctors in describing the early epidemiology of HIV in East Africa. It is for this reason, in part, that my effort to include African perspectives on the science and politics of HIV drug resistance focuses specifically on Uganda. Through interviewing and observing Ugandan physician-researchers in the HIV field, I sought to explore the roles played by these experts in the production of knowledge about HIV treatment and drug resistance in Africa and to describe the global webs of professional connection, obligation, mutual assistance, and competition that tie these Ugandan scientists to their North American colleagues.

Methods: a multi-sited ethnography

It is the in-between space of these webs, rather than the U.S. or Uganda specifically, that constitutes the primary "field site" of my research. Methodologically, I approached this arena in two ways: first, through participant-observation among a group of American HIV researchers studying questions of treatment access, adherence to medication, and drug resistance in Uganda; and secondly, through one-on-one interviewers with North American and Ugandan HIV researchers and clinicians. The participant-observation component of my research was greatly facilitated by my status as

a former research assistant with the group I observed, as I had worked with them for a period of over four years beginning in late 1999. The fact that I was well-known and friendly with the group and its principal investigator (known here by the pseudonym Dr. Jason Beale) provided a baseline of mutual trust and respect that allowed me to gather much of the material presented here, including accounts of the group's research meetings and informal, candid conversations with study staff. My first trip to Uganda during July and August of 2003 was as an employee of Dr. Beale's, charged with organizing a pilot qualitative study of patients' struggles to purchase HIV medications. It was this trip, combined with a growing interest in and awareness of the scientific controversies over HIV drug resistance, that set the stage for my subsequent dissertation research.

My affiliation with Dr. Beale also provided me with a certain kind of legitimacy that facilitated access to many of the scientists formally interviewed for this dissertation. Overall, I conducted 49 one-on-one, tape-recorded interviews with 48 researchers and physicians (2 individuals were interviewed twice). Of these, 22 were North American or European and 24 were Ugandan. The interviews with North American researchers were conducted over 12 months of fieldwork from September 2004 through August 2005. In March of 2005 I made a five-week trip to Uganda, during which I conducted the bulk of my interviews with Ugandan researchers (2 Ugandans were interviewed in the U.S. as well). During this trip, I also observed the training course designed to educate doctors from Uganda and other African countries in HIV treatment and management that is described in Chapter 5. The 2005 trip, as well as my earlier trip in 2003, provides the basis for my descriptions of HIV treatment and care in Uganda. Again, because my time in Uganda was brief by ethnographic standards, I will reiterate here that my field "site"

was not Uganda per se, but rather the transnational flow of knowledge, politics, research money, obligation, blood samples, viruses, drugs, and research personnel that constitute international scientific collaboration between the U.S. and Uganda.

The Science and Politics of Drug Resistance

This dissertation is an effort to describe the relationship between science and power in transnational HIV research, with a particular focus on the science of antiretroviral treatment and drug resistance. These two areas—treatment and resistance—are deeply intertwined socially, scientifically, and politically, which makes them a particularly rich arena for anthropological inquiry. A basic definition of "drug resistance" is "the ability of some disease-causing microorganisms…to adapt themselves, to grow, and to multiply even in the presence of drugs that usually kill them" (American Foundation for AIDS Research). The problem of drug resistance is not limited to the field of HIV medicine, rather, it is a challenge faced in the treatment of many infectious diseases. The reasons behind drug resistance are complex and vary across different contexts but are generally related to what doctors call "sub-optimal" treatment—for example, treatment that is too short in duration, too low in dosage, or does not adhere to current medical standards (i.e. includes older, less effective drugs or includes only one drug rather than a combination of drugs). Sub-optimal treatment fosters the development of drug-resistant pathogens: bacteria, viruses, and parasites that are no longer killed or held at bay by pharmaceutical intervention. In the U.S. this problem is most familiar in relation to antibiotics, as bacteria resistant to penicillin and related drugs have become the major cause of hospital-acquired infections and are beginning to be linked to significant numbers of infections outside health care settings as well. Several practices have been

blamed for this burgeoning public health problem: the overzealous prescription of antibiotics by physicians, the tendency of patients to stop taking their antibiotics once they feel better, and the heavy use of antibiotics by the meat and poultry industries.

Antibiotic-resistant infections, although sometimes serious and difficult to treat, are usually not life-threatening. In addition, their spread can often be limited through fairly simple hygienic measures such as regular hand-washing. In contrast, the case of drug-resistant tuberculosis (TB) has caused much greater public alarm, as it is both spread through the air and potentially fatal. In addition, unlike antibiotic resistance, TB resistance (like TB in general) is more likely to be found among the socially marginalized: recent immigrants, the poor, and the homeless. As I discuss in depth in Chapter 3, the rise of drug-resistant TB in the U.S. in the early 1990s thus cemented an association between drug resistance and poverty—and in particular, a fear among public health officials that poor people would develop resistance by not taking their medicine as prescribed. This fear would later play a major role in the politics of HIV treatment both domestically and globally.

In the U.S., this fear operated mostly at the level of the doctor-patient relationship, as some doctors hesitated to prescribe antiretrovirals to patients they felt were likely to miss doses such as the homeless, the mentally ill, and the drug addicted. Globally, this kind of selective exclusion occurred at the national and regional levels, as donor nations justified their reluctance to foster antiretroviral access in poor countries by arguing that poor adherence would generate widespread drug resistance, thus eliminating any long-term benefits treatment. This reasoning is particularly suspect in light of the fact that in the case of antiretroviral treatment, resistance is inevitable—all patients who

take HIV drugs develop resistance sooner or later, even if the medicines are taken religiously. However, in the context of an increasingly vocal treatment activist movement, this discourse managed to reframe the problem as the *presence* rather than the *absence* of drugs, and imagine the (continued) absence of treatment as ultimately beneficial to the public health even in the context of what was, in some countries, a massive die-out.

Difference and Inequality in Transnational HIV Science

In addition to being politically contentious, drug resistance is also controversial scientifically. My interest in the science of antiretroviral treatment arose out of the juxtaposition of two very different knowledge claims about HIV drug resistance. As I described above, the first claim was the assertion by certain international health experts and officials that Africans were likely to be poorly adherent to HIV medication and would cause widespread drug resistance. This scenario, they argued, would eliminate any benefits that treatment might have brought to the continent as well as initiate a global public health threat in the form of drug-resistant strains of the virus. The second, and contrasting, claim was posed by scientists studying drug resistance, who upset the conventional wisdom with evidence that poor adherence did *not* necessarily cause drug resistance, and that patients with drug resistant virus often continued to stay clinically well for extended periods of time.

My research began as an exploration of the gap between these two competing claims. This exploration has resulted in an anthropological account of how drug-resistant HIV is standardized and made legible in the laboratory, and how this standardization reflects a particular history of the epidemic as it happened in North America and Western

Europe. The result is a "molecular politics" in which global inequalities are played out in the laboratory at the level of the viral genome. Given the degree of speculation that had occurred about drug resistance in Africa in the absence of any data, I was also curious to understand what was involved in producing actual (non-speculative) data about these topics. To examine this question, I followed Dr. Beale's team of American researchers as they worked to establish a study of HIV treatment and drug resistance in Uganda in collaboration with Ugandan colleagues. This aspect of my research produced an ethnographic account of the nexus of professional, economic, and ethical relations that is emerging between North American and Ugandan AIDS researchers in the context of multilateral efforts to provide access to HIV drugs in sub-Saharan African countries.

As is often the case with anthropological fieldwork, my research sometimes led me in directions that I could not have predicted at the outset. In many ways, it is these unexpected pathways that have been the most exciting to explore (both ethnographically and theoretically) and that will provide a foundation for the research questions I pursue on this topic hereafter. One such pathway led me to consider the complex relationship between humanitarian and professional desires among HIV researchers. My interest in this subject arose out of my realization that the scale of the African AIDS epidemic combined with the sudden shift in international political will towards supporting antiretroviral access provided what North American HIV scientists saw as an incredible scientific opportunity to study the impact of effective HIV drugs on a very large and previously untreated patient population—an opportunity that had been "lost" in the U.S. The resulting rapid influx of Western research money to countries like Uganda also created significant professional opportunities for Ugandan researchers and doctors, who

had little local money available to them to engage in research and were often underpaid. Collaboration with North American colleagues thus allowed them opportunities for professional advancement, development, and remuneration that would have been unlikely in the absence of international connections.

At the same time, the researchers I spoke with described their research agendas as motivated by a desire to do good—in other words, to help alleviate the suffering caused by the epidemic. Dr. Beale's research, for example, was motivated by a desire to provide scientific evidence that Africans could indeed take HIV medicines properly, and that treatment access should be expanded on the continent. Similarly, many Ugandan researchers I spoke with framed their work in terms of helping fellow Africans—describing their research, for example, as something that "benefits our women and children." There are a number of factors that can complicate the relationship between these humanitarian urges and professional ambition—most obviously, the fact that science that is "good for the people" and science that is good for one's career are only sometimes aligned. In addition, what constitutes "good science" is also a contested question, and one that may be answered differently according to one's perspective as a North American, a Ugandan, an National Institutes of Health (NIH) regulator, a researcher, a clinic doctor, or a patient—to name a few. One of the most interesting ways in which this tension arose during my research was in the negotiation of the terms of collaboration between North American and Ugandan colleagues. North American researchers bring money, experience, and international connections to the table; Ugandan researchers bring local connections (important for getting approval for research), patients, and—when their names are appended to grant applications—the stamp of "African"

authenticity and legitimacy. However, most American researchers have significantly greater access to funding resources than do their Ugandan counterparts, and in many cases they also have greater research experience and training. For this reason, it is not surprising that American researchers sometimes see their work in Africa as a form of "capacity building" by which they are able to not only conduct interesting and important studies, but also transfer research infrastructure (like computer databases) and skills (like grant writing) to African institutions and colleagues. However, this imputation of humanitarian assistance to collaborative research projects can be problematic. One researcher posed the question to me this way: if a North American views his research as a charitable endeavor, is it possible for him to have an equitable relationship with his Ugandan "collaborator"?

A second unexpected trajectory that arose during my fieldwork was the importance of molecular knowledge within the axes of difference that demarcate HIV medicine in the U.S. from HIV medicine in Uganda. This question is dealt with most directly in Chapter 4, in which I describe the ways in which the gross inequalities that characterize the global AIDS epidemic become manifest at the most minute molecular level within the laboratory. Genetic differences in the subtypes of HIV that predominate in the Americas and Europe versus in Africa and Asia have long been known to HIV scientists, but these differences take on increased significance as North American researchers seek to transfer molecular diagnostics designed around one viral subtype to the African continent, where the viruses are genetically different. Furthermore, the importance of these molecular measures to American scientists—and the fact that their funding and their scientific legitimacy often depends upon the use of technology in their

research—marks another important difference between HIV medicine in the U.S. as compared to Uganda. The phenomenon of the "molecularization" of biomedicine has been much commented upon by social scientists, who describe how the genomic revolution has contributed to a situation in which medicine, disease, and the body are increasingly conceptualized in molecular terms—framed as a matter of genes and proteins. HIV medicine in the U.S. has become heavily molecularized in recent years, but in my observations this conceptualization often did not translate well to the context of Uganda, where a health care system ravaged first by the decade-long dictatorship of Idi Amin and subsequently by neo-liberal structural adjustment programs has scarce resources to allocate to basic medical supplies, much less expensive molecular diagnostics. Ugandan doctors' knowledge and experience of AIDS was instead deeply clinical, rooted in physical signs and hands-on assessment of patients' symptoms. Thus, North American and Ugandan researchers often brought very different forms of expertise to the table, and their collaboration forced a sometimes uneasy confrontation between technical versus clinical medicine. One aim of this ethnography is to show how the technical/clinical divide is both a product of global inequality and a perpetuator of it, as the valorization of technical over clinical expertise within the international scientific arena serves to reinforce "first world" medical science as the standard by which all other science is assessed.

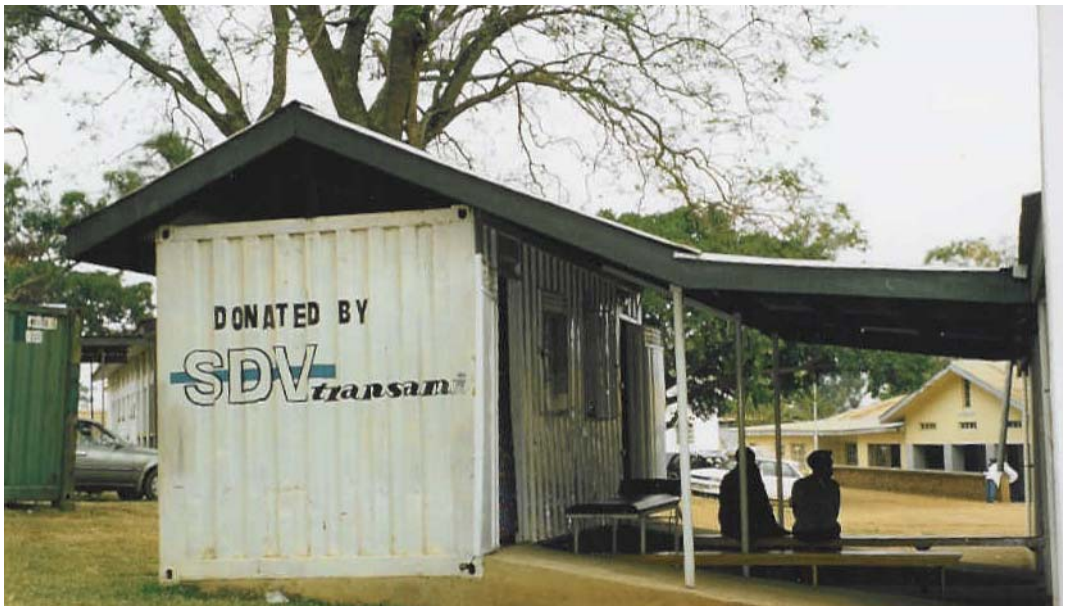
In sum, this dissertation is an effort to expand the traditional purview of science and technology studies (STS) beyond the borders of the industrialized West, and to join the contributions of STS with an attention to political economy. The result is a dissertation that attempts to meld a close reading of scientific knowledge, practice, and

relations with an interrogation of their social, political, and economic conditions of possibility. As such it is an effort to interweave the field of science and technology studies with critical medical anthropology, in order to describe the articulation of scientific knowledge and practice with structures of inequality.

Chapter One

THE TURN TOWARDS AFRICA

Mukwano[1] is a medium-sized town lying several hours to the southwest of Uganda's capital city, Kampala. It is located in a peaceful and fertile part of the country famous for its long-horned cattle. At one end of town is Mukwano University, a regional government-run university that includes a medical school and hospital on its campus. Clustered in one corner of the hospital grounds is a hodge-podge of small buildings—several made from donated shipping containers—that comprise the Infectious Disease Treatment Center (IDT Center).



Infectious Disease Treatment Center, Mukwano, 2003 (photo by J. Crane)

[1] Mukwano is a pseudonym. Throughout this dissertation I have changed the names of interviewees, places, and institutions in order to protect anonymity. Real names are used occasionally in reference to persons and events covered in the press.

The IDT Center was started by the university's Department of Medicine in 1998. The primary motivator behind its inception was Dr. Harry Salter, an American physician and missionary who had been stationed at the hospital by his Baptist mission organization two years earlier. Clean-cut and boyish in looks, Salter is dedicated to his faith and his patients. When I first met him in Mukwano in 2003 he was wearing a white medical coat embroidered on the breast with his name and, underneath it, the Biblical reference "John 14:6."[2] He is an unwavering advocate for better and more affordable HIV treatment in Mukwano. When I interviewed him in 2005, Salter told me that when he first arrived at the hospital in 1996 treating HIV patients was commonly regarded as a waste of scarce resources. Because no antiretroviral drugs were available, patients with AIDS were destined to die and physicians felt that the hospital's very limited budget was better spent treating those who might actually survive. Though the local grass-roots HIV support organization had a clinic nearby, many patients with HIV avoided seeking care there due to the stigma associated with the disease. Salter convinced his colleagues that these patients were worth treating, and as a result the university opened a clinic especially for them—though, because of stigma, "HIV" and "AIDS" were purposefully left out of the IDT Center's name. At first the clinic was held only one day a week, with Dr. Salter as its primary clinician. The center had no HIV drugs, but it was able to treat some AIDS-related infections with medicine donated by Salter's missionary organization. At the time, it was the only HIV clinic in all of southwestern Uganda.

By 2005, the IDT Center had acquired several more buildings, was open five days a week, and was serving a total of 5000 registered patients from the surrounding region.

[2] "Jesus saith unto him, I am the way, the truth, and the life: no man cometh unto the Father, but by me." (John 14:6, King James Bible)

Nearly half of those patients were new to the clinic within the last year, drawn there by the promise of free HIV drugs provided by international donor organizations—primarily the Global Fund to Fight AIDS, TB, and Malaria and the U.S. President's Emergency Plan for AIDS Relief (PEPFAR). Dr. Salter was still working there, but the clinic's director was now Dr. Iris Akiki, an ambitious young Ugandan doctor who had just finished her postgraduate medical degree at Mukwano University. Also staffing the clinic regularly were Dr. John Butembe, who had grown up locally and lost both his parents to AIDS, and several new Ugandan physicians paid through the PEPFAR program. Also new was a small, two-room building (made, like the original clinic, from a donated shipping container) that had been built by Dr. Jason Beale, an American doctor from California who brought the first international AIDS research project to the IDT Center.

Back home at Yerba Buena University, a large research university in the San Francisco Bay Area, Beale had made a name for himself in the late 1990's by championing the American epidemic's most marginalized patients: the HIV-positive homeless, who were having trouble getting access to the antiretroviral (ARV) drugs that had transformed the lives of many people with AIDS in the United States. Conventional medical wisdom held that missing even one dose of ARV medication could cause HIV to mutate into difficult-to-treat, drug-resistant strains (Chesney 2003), and some doctors were delaying treating homeless patients for fear that they would miss too many doses (Sontag and Richardson 1997). "Adherence" is the term doctors and researchers use to describe taking medication as prescribed, though in the past the word "compliance" was more commonly employed. Adherence includes a range of behaviors including taking

medicine on time and with or without food, but is most frequently used to refer to taking the number of doses prescribed. "Good adherence" implies few or no missed doses; "poor adherence" implies many missed doses, and is considered a predecessor to drug resistance.

A few years later, similar fears arose as international pressure grew to provide ARV drugs in sub-Saharan Africa. Beale, a secular doctor who nonetheless once described himself to me as something of a "missionary" for the treatment cause, began working in Uganda in 2002 out of a desire to prove the nay-sayers wrong. After documenting that patients in Kampala were taking over 95% of their medication (Oyugi et. al. 2004) he began a larger study in Mukwano in 2005. This location was both practical and strategic: Mukwano, unlike Kampala, was not crowded with Western research projects. In addition, its location 280 kilometers away from the capital city implied a "rural" setting, allowing Beale and his colleagues to respond to criticisms that their Kampala findings were not representative of a population that is overwhelmingly agrarian. (Though, by Ugandan standards, Mukwano town is still considered at least semi-urban. Nonetheless, the clinic does serve many patients from surrounding rural areas). In addition to tracking patients' adherence to antiretrovirals the study would also ship blood back to North America, where it would undergo genetic analysis ("genotyping") to determine whether patients were developing drug resistance.

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In *Laboratory Life,* their seminal work in science and technology studies, Bruno Latour and Steve Woolgar describe how laboratories serve to create order from disorder through a process they call "inscription." Through this process, material substances are

transformed into written or diagrammed "data," and are thus rendered usable to scientists (Latour and Woolgar 1979). In Latour and Woolgar's ethnography the process of inscription occurs mainly through various technological processes located within the walls of the laboratory, and does not travel outside this space until it is published in a scientific journal. They describe how rats become samples in tubes, which then become a sheet of figures; these figures become computer input and then a data sheet, which is distilled into "single elegant curve," and it is this curve that appears in the final published article (Latour and Woolgar 1979: 49-50).

Latour and Woolgar's concept of inscription provides a useful tool for describing the process of abstraction that is necessary in order for scientists like Dr. Beale and his colleagues to transform the blood of a heterogenous group of people with HIV into standardized, quantitative data on drug-resistant virus. However, doing so requires leaving the laboratory both spatially—because the blood itself travels across three continents during its process of transformation—and epistemologically, in that the transformation of blood into drug resistance data cannot be separated from a host of political, economic, and social forces that transcend the laboratory. Within the lab, we are able to see the technological processes—centrifuging, DNA extraction, PCR technology, and genotyping—that produce publishable data on drug-resistant HIV. However, it is only by leaving the lab that we can begin to discern the contingency of this knowledge upon broader political and economic phenomena such as international drug patenting laws, humanitarian and development agendas, the landscape of recognition and prestige in international research, and the complex and sometimes uncomfortable relationship between extreme poverty and scientific opportunity.

It seems logical to begin this dissertation with an account of the journey taken by the blood drawn from Mukwano's patients in its inscription into drug resistance data. HIV-positive men, women, and children come from all over southwestern Uganda to receive care at Mukwano hospital's IDT Center. The care is free and, increasingly, patients are able to get HIV drugs for free as well, though they must purchase most other medications at local pharmacies. In order to recruit participants for Dr. Beale's study of adherence and drug resistance, Ugandan research assistants approach clinic patients on the cusp of receiving their first HIV drugs and get their consent to enroll them in the project.[3] In medicine, such patients are described as "treatment-naïve," meaning they have never taken HIV medications before. They are particularly sought-after in research because they are imagined as something akin to a blank slate; without previous exposure to antiretrovirals, their virus has most likely not mutated to become drug-resistant and remains in what scientists call a "wild-type" state.

Patients who agree to be in the study often begin their participation the very same day that they start their antiretroviral drugs. Their blood is drawn in the morning, before they take their first dose of medication. After providing the study with 11 tubes of blood, they are given a hearty breakfast of meat and *matooke* (steamed green banana) at a nearby canteen on the hospital grounds.[4] After eating, they collect their first month's worth of medication from the clinic pharmacy and begin their journey home—usually by foot, bicycle, moped, or *matatu* (minibus taxi) for those living farther away. They will

[3] Although I will not go into an in-depth description of the consent process here, it is important to note that it is neither simple nor straightforward. To even begin approaching patients, the study had to first gain scientific and ethical approval from the Institutional Review Boards at both Yerba Buena and Mukwano universities, as well as by the Department and Faculty of Medicine at Mukwano. Participation necessitates blood draws of sometimes up to 12 tubes of blood, an unusually large amount that causes reluctance among many patients who fear that giving this amount of blood will make them sick.

[4] Unlike in the U.S., cash reimbursement for study participants is considered coercive and is not permitted. Provision of food, however, is often possible.

return to the clinic each month to renew their supply of pills. Every three months, the study staff will draw their blood again.

The blood they leave behind at the clinic is prepared for a separate journey that will take it across several continents and through various states of material transformation. The first step involves getting the blood from Mukwano to Kampala, as the laboratory in Mukwano does not have the facilities to process or store the samples. The trip takes between four and five hours on a two-lane asphalt road lined with the rolling green and brown countryside typical of southwestern Uganda. In between the small towns that straddle the road are long stretches of rural landscape, much of it cultivated by small farms and groves of banana trees. Occasionally, a large corporate farm will appear with a single crop—such as tea or sugarcane—stretching for miles.

The logistics of getting the samples to Kampala along this road are mainly handled by study staff, not by Dr. Beale himself. Eve Agalaba is Beale's project director in Mukwano. Born to a West African father and an American mother and raised and educated on both continents, she told me that she sees her "bicultural" perspective as indispensable to her job, much of which involves acting as a go-between between American and Ugandan colleagues. The following excerpt from a 2004 meeting demonstrates her role as intermediary, as well as the considerable complexity involved in simply moving the blood from Mukwano to Kampala. At the time of this meeting, the study was still in its "pilot" stage—a trial phase intended to work out the kinks before patients would be enrolled in large numbers. In this passage, Dr. Beale and his Yerba Buena-based colleagues (identified below by job title) question Agalaba—who had flown

in from Uganda for a series of meetings—on possible options for transporting the samples:

> Eve Agalaba: Shipping blood to Kampala remains a problem because we have to draw it by 9 or 10 in the morning [to get it to Kampala before the labs close].
>
> YBU epidemiologist: That limitation is due to the 4 ½ hour drive? Who's driving?
>
> Eve Agalaba: We're still going back and forth about that. World Courier is ridiculously expensive – $100 a day for one sample – and DHL doesn't have the same infrastructure and wants the samples by 9 or 10 am. … We could just hire someone to take the bus to Kampala every day. Bus fare is 7000 shillings [approx. $3.50]. Their salary would be 50 – 100,000 shillings a month [$25-50]. That's what a messenger makes.
>
> YBU epidemiologist: [shocked at the low cost] Fifty bucks!
>
> Dr. Jason Beale: I just talked to Mike [an American scientist based in Kampala] when I was in Kampala. He said it's ok for the blood to sit overnight, it just needs to be at the lab first thing in the morning. The tubes he uses allow the blood to sit overnight [without spoiling].
>
> Eve Agalaba: So where does the blood sit overnight?
>
> YBU study administrator: [laughing] Under his bed, in a cooler?
>
> Dr. Beale: It needs to be secure. The messenger could keep it, or it could go to Lincoln Towers [the Kampala high-rise where the study rents an office]. The labs don't have night drop-off. They won't take it then.
>
> Eve Agalaba: I'm sure we'll figure out a way. We could give the messenger a key to Lincoln Towers.
>
> Dr. Beale: Or set up a lock box at Lincoln Towers for samples.
>
> Eve Agalaba: Lincoln Towers is kind of funny about you using any space outside your office…. The labs won't stay open any later than 5 or 5:30….We could get a Corolla and a driver to deliver the blood.
>
> Dr. Beale: Then we'd have to pay for petrol. You can't drive to Kampala for 7000 shillings [U.S.$3.50][5]….I'm nervous about giving someone a key to Lincoln Towers. Security there is not as good as it was. But

[5] Gas in Uganda ran between $3 and $4 a gallon at the time.

> [reconsidering] — if we're trusting them with blood then we should trust them with a key to Lincoln Towers. The issue is finding that person.
>
> Eve Agalaba: We need to be able to recruit people later in the day than 9am. The people who come in that early to the clinic are often those who come from very far away and are ineligible for our study.
>
> YBU statistician: I don't know what the work rules are, but I can't imagine someone being able to do that [bus trip] five days a week.
>
> Eve Agalaba: There will be no problem finding someone who wants this kind of job. The issue is finding a secure place for the blood overnight.

This exchange shows the difficulty in transporting blood samples from outlying areas to Kampala, as well as the high value of these samples to scientists—as indicated by their concern that the blood remain "secure." Logistics that would be straightforward in the U.S. become much more complex when trying to negotiate an unfamiliar and often inadequate infrastructure halfway across the world. In this scenario, Agalaba's dual knowledge of the terrain in Uganda and the concerns of her U.S.-based colleagues was indispensable.

After the meeting, it was up to her to return to Mukwano and test out the different transport options. By the time the study was up and running in 2006, the issue was still being resolved. Agalaba had abandoned the idea of hiring someone to take the samples by bus after finding that the bus schedules were not as reliable as she had hoped. Next, she tried hiring a courier service to take the samples to Kampala. This was convenient because the couriers provided the dry ice needed to keep the samples cold, and packaged the blood themselves. However, they were also extremely expensive and sometimes arrived in Kampala late (because, she suspected, the couriers were taking the bus rather than driving, and pocketing the extra cash). In the end, she convinced Dr. Beale to

allocate funds to buy a car for the study and hire a private driver to take the samples—also expensive, but more reliable than contracting out to a courier. In order to do this, she had to figure out a way to obtain dry ice to keep the blood cold on its journey. After doing some research, she learned that all the dry ice in Uganda is sold in bulk to Ugandan courier services by vendors in Kenya. There was no way to purchase the small amount needed for an individual study. Thinking creatively, she paid a visit to the Coca-Cola bottling plant near Mukwano—one of two in the country—and convinced them to sell the study a small amount of their dry ice, "as a favor."[6] In addition, she and Beale decided to hire a night-time lab technician in Kampala, so that their samples could arrive later in the day and still be processed and stored immediately.

Upon arrival in Kampala, each patient's sample gets divided into three batches of blood. One batch of blood goes to the laboratory of a Kampala-based American colleague who is conducting an immunological study. The other two batches go to Kampala's Olusozi HIV Institute, which houses a state-of-the-art laboratory recently built by a large U.S. corporate donation and governed by a complex partnership of Ugandan and American academics (Olusozi is described in depth in Chapter 5). Moped couriers from DHL—the international shipping service—regularly visit the building, a testament to the constant transnational flow of materials and information circulating through the Institute. At Olusozi, one set of blood samples is tested for CD4 (t-cell) count and viral load and these results are sent back to Mukwano to be given to patients and their doctors and to be recorded in the study database. The remaining batch is stored at the institute

[6] Agalaba told me that she had already been asked for her contacts at Coke by several other researchers, but she had not given them out because "Coke doesn't want to be inundated by requests from researchers looking for a small amount of dry ice."

until it can be shipped to North America for drug resistance testing, which requires technology not available in Uganda.

Twice a year, the stored samples are sent from Kampala to North America at the cost of $2500 per shipment. For this, Dr. Beale's study purchased a special refrigerated shipping container that keeps the blood frozen on its international journey. One vial of each patient's blood is always retained in Kampala in case the shipment gets lost or damaged, or the shipping container gets stolen en route. This ensures that all the data from any given patient won't be lost in such an event. In order to ship blood out of Uganda, Eve Agalaba and Dr. Beale had to obtain a "Materials Transfer Agreement" (MTA) from the Uganda National Council on Science and Technology, the government body that oversees research conducted in Uganda. The agreement is essentially a contract stating that Mukwano University gives permission for biological samples to be "loaned" to Dr. Beale. These agreements are a relatively new phenomenon, Agalaba told me, and contain very specific language about who owns the blood—including the name of a specific Ugandan researcher who has rights to the samples and will be named as an author on any publication resulting from their analysis. In order for the blood to enter the U.S., Agalaba had to obtain a Permit to Import Infectious Agents from the U.S. Centers for Disease Control (CDC). This document is purely concerned with public health issues such as biohazard level, and contains none of the proprietary language that characterizes Uganda's Materials Transfer Agreement.

The blood travels from Kampala to San Francisco via London. From the San Francisco International Airport, it is brought to nearby Yerba Buena University where a portion of it is stored. Then the remaining tubes of blood complete the final leg of their

journey to Vancouver, Canada, to be tested for drug resistance. At approximately four hundred dollars per sample, resistance testing is expensive. Dr. Beale was able to strike a deal with a colleague in Vancouver who offered him a better price on the resistance testing than he was able to get locally at Yerba Buena. Once in the Vancouver lab, the sample is allowed to thaw and the HIV virus is separated out for genetic analysis (genotyping)—a process further described in Chapter 3. This is the final stage of inscription, in which each patient's invisible virus is rendered legible in the form of a genetic sequence. These sequences can then be analyzed for changes (mutations) that are known to indicate resistance to particular antiretroviral drugs. This data is then sent back to Dr. Beale in San Francisco.

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This intense scientific interest in Africa—and the willingness to confront the logistical challenges presented by conducting HIV research in a low-income country—is relatively new in American AIDS research. Although colonial powers have long engaged in medical research on the continent (Vaughan 1991), and African researchers have been conducting clinical and epidemiological studies of HIV locally since the epidemic began, the interest of North American researchers in AIDS in Africa is fairly recent.

"Africa is in vogue now," Dr. Beale told me in early 2005. "Three or four years ago, no one would mention it." His comment was not intended to be flip, rather, it was a joking acknowledgement of the way in which science is subject to its own form of trendiness that governs both interest in and funding of research projects. Beale is a warm and enthusiastic man, prone to mild exaggeration when trying to make a point, but

earnest and persuasive nonetheless. He is both extremely ambitious and morally driven—a combination that has served him well in advancing his research first in the U.S., and then in Uganda. To prove his point about the research trend, he urged me to search the abstracts of the last several years of the Conference on Retroviruses and Opportunistic Infections (CROI) –the U.S.'s most prestigious scientific AIDS conference—for the word "Africa." "It probably won't even be mentioned until 2002 or 2003," he told me. Beale's predication proved to be generally true, if somewhat overstated. A search of the abstracts for "Africa" shows a steady increase between 1997 and 2006, ranging from a low of 6 in 1998 to a high of 91 in 2005.[7]

Science studies scholars use the term "scientific bandwagon" to describe when a large number of "people, laboratories, and organizations commit their resources to one approach to a problem" (Fujimura 1988: 261). Bandwagons generate their own "snowball effect" whereby the effort of early adherents encourages other scientists to join, eventually making the scientific movement self-perpetuating. The turn towards Africa among North American AIDS researchers was in many ways a scientific bandwagon, with scientists, universities, and federal funding agencies such as the National Institutes of Health (NIH) collectively shifting their attention and resources southward. However, to understand *why* this happened we need to go beyond the concept of the bandwagon—or, at least, beyond Fujimura's classic definition of it. Fujimura is interested in the social organization of scientific work environments and the technological infrastructure that allows scientists to do their work. Her analysis focuses

[7] Because abstracts containing the word "African American" also appeared when searching under "Africa," I conducted searches under both terms and then subtracted the African American abstracts from the Africa abstracts to get a sense of how many papers were reporting on data collected on the African continent. The earliest year for which abstracts are available on line was 1997.

on how oncogene (cancer genetics) researchers developed approaches and technologies (a "theory-methods package") that were easily standardized and thus rapidly adopted by other laboratories, creating a bandwagon of interest in oncogenes within the broader field of cancer research. Once this field became "hot" it generated a snowball effect that attracted more and more researchers seeking to advance their careers.

Fujimura's description of the bandwagon must be expanded in several ways in order to adequately understand the turn towards Africa in American AIDS research. First, the Africa bandwagon must be understood in the context of events *outside* scientific workplaces as well as within them. While shifts within AIDS medicine and research definitely contributed to the growth in interest in Africa, these shifts are inseparable from national and international economic and political developments that brought attention—and, subsequently, low-cost HIV medications—to the continent. Second, Fujimura places great importance on the role of easily adaptable technologies in facilitating the oncogene bandwagon. In contrast, the African AIDS bandwagon faced a constant uphill battle with technology, as the scientific materials and tools that researchers took for granted in their well-funded U.S. labs were often difficult and sometimes impossible to come by in low-income countries like Uganda. Furthermore, these technologies had been designed to analyze the subtype of the virus that predominates in the U.S. and Europe and were sometimes unreliable when applied to other subtypes, as I describe in Chapter 4. Last, Fujimura spends little time addressing the humanitarian or altruistic motivation that scientists might have for their work, arguing that their primary concern was career success and that the possibility of curing cancer was only one of many secondary concerns. While I do not dispute that professional success is a major motivator for

scientific researchers, the spectacular nature of AIDS and suffering in sub-Saharan Africa—backlit by the spectacular success of AIDS treatment in wealthy nations—necessitates an analysis of how desires to "help" or "do good" play into scientific interest in AIDS in Africa.

This said, how *did* the turn towards Africa come about?

The Advent of the "Treatment Era"

Nineteen ninety-six was a landmark year in the history of the AIDS epidemic, because it marked the advent of effective anti-HIV medications. Previous antiretroviral therapy had consisted of treatment with one or sometimes two drugs that worked to inhibit the production of reverse transcriptase, an enzyme necessary for the virus to reproduce itself. These early reverse transcriptase inhibitors—still most commonly known by their experimental names: AZT, 3TC, and D4T—often caused severe side effects when taken as single drugs and offered little or no long-term benefit, as the virus rapidly mutated to become resistant to them. In late 1995, scientists announced the discovery of a new class of antiretroviral drug, one that acted on a different viral enzyme called protease. These new drugs, called protease inhibitors or PIs, proved extremely effective at blocking viral replication for extended periods of time when combined with 2 other drugs of the older type. The new approach to treatment came to be called by a number of names including "triple combination therapy," "highly active antiretroviral therapy" (or HAART), and—more colloquially—"the cocktail." Its success was attributed to the combination of three different drugs, each of which used a different mechanism to attack HIV and thus made it difficult for the virus to mutate into a strain resistant to all three medications.

The advent of combination therapy ushered in what HIV doctors and researchers call "the treatment era," and utterly transformed the epidemic in the wealthy parts of the world where these drugs were available. Often costing close to $1000 a month and sometimes requiring up to 20 pills a day, triple therapy nonetheless rapidly became the standard of care in countries that could pay for it. The result was a sharp decrease in deaths from AIDS and a growing sentiment that HIV was being transformed into a chronic manageable disease. In the U.S., the annual number of deaths from AIDS dropped by more than half in just two years, going from a high of over 50,000 in 1995 to 22,000 in 1997 (CDC 2000). In 2004, the latest year for which statistics are available, it dropped below 16,000 after having hovered in the 17,000 range for the several previous years (CDC 2004).

The drugs did not eradicate HIV from the body; in other words, they did not cure the disease. This is because the medications act only on HIV that is free-floating in the blood plasma,[8] not the viruses that have already infected blood cells or other cells in the body.[9] Once inside a cell, HIV can remain dormant indefinitely, constituting what researchers and clinicians call a "latent reservoir" of virus that prevents the infection from being cured. What the drugs are able to do is reduce the amount of HIV actively circulating in the plasma—known in medicine as the "viral load"—by interfering with the virus's ability to reproduce itself. This means that there are fewer viruses around to infect CD4 and other immunological cells, and patients' immune systems remain protected as long as the drugs continue to work.

[8] Plasma is the acellular component of blood. Whole blood consists of plasma, red and white blood cells, and platelets.

[9] Though HIV's most well-known target are CD4 cells or "t-cells" (a form of white blood cell), the virus can and does infect cells throughout the body, particularly in the brain and the gastrointestinal tract.

The advent of triple therapy radically altered the experience of treating HIV in the U.S. and other wealthy industrialized nations. Clinicians who had been focused primarily on staving off AIDS-related infections and providing a less painful death suddenly found themselves managing a complex pharmacopeia and its accompanying side-effects, some of which were life-threatening in their own right. Nonetheless, patients were now living—often for many years—rather than dying. For clinicians at large universities and teaching hospitals, where their professional duties were split between patient care and research, this shift also impacted their research agendas. Many researchers focused on tracking their patients' response to the new treatments by looking at factors like drug side effects, drug resistance, and long-term survival. In addition, once they no longer faced an acute crisis at home, some researchers began to turn their attention to the global epidemic.

Difference and Nostalgia in Transnational AIDS Research

Dr. Beale had never traveled to Africa until he began planning a research project in Uganda. This was not unusual among the American researchers I spoke with over the course of my fieldwork, and applied to myself as well. For him and for many others, the first trip was a confrontation with striking familiarity embedded in a context of profound difference. These differences ranged from the ordinary variation in language (though many Ugandans speak English), landscape, and culture encountered when traveling to any foreign country, to much starker contrasts of race and wealth. For example, "whiteness" was no longer the unmarked category it so often is in the U.S.; instead, white skin was highly conspicuous an overwhelmingly black- and brown-skinned nation, and

muzungu—the Luganda[10] word for "white person"—was often the first (and sometimes the only) local vocabulary that the predominantly white American researchers learned. This difference was further accentuated by the contrast between Uganda's poverty and America's wealth, and the realization that elements of daily living often taken for granted in the U.S—such electricity, public transit, bank machines, street addresses, and refrigeration—were suddenly unreliable, confusing, or non-existent. The reliance on a cash-based economy and the rarity of receipts was particularly vexing for Beale's grant manager at Yerba Buena University, who was constantly struggling to produce a paper trail showing how the project's funds were being spent in Uganda.

American researchers turning their attention to Africa were confronted with the social and logistical realities of what it means to conduct research in a "resource-poor country" or a "resource-limited setting"—the terms most commonly used in international HIV research to describe low-income countries like Uganda. Dr. Beale, having spent years working in New York and San Francisco's poorest county hospitals, was no stranger to poverty. However the signs of this poverty—young boys with bathroom scales on Kampala Road selling passers-by the opportunity to weigh themselves, women scavenging for wood to turn into charcoal they could sell, and the coffin shops lining the road between the airport and the capital city — were radically different from inner-city poverty in a "resource-rich" country. (This was further confirmed when Beale's Ugandan staff began visiting San Francisco, where they were utterly shocked by the sight of homeless people living and sleeping on the street).

[10] Luganda is the most common of the approximately 40 African languages spoken in Uganda. *Muzungu* is a word used for "white person" in many East African Bantu languages, including Swahili *(mzungu)*. English is Uganda's national language, a legacy of British colonialism, and is widely spoken among the educated classes.

Yet, within this world of difference, visiting American researchers encountered an eerie familiarity upon entering the inpatient wards of Kampala's hospitals, where they saw patients with AIDS dying from infections they had not encountered since the first days of the U.S. epidemic. The experience was particularly striking, Dr. Beale told me, for those coming from San Francisco—a city that was emblematic of the epidemic in the U.S. in the early 1980s much in the way that Uganda was to become emblematic of AIDS in Africa in the late 1980s. He described a senior colleague as getting "almost wistful" or "nostalgic" in Uganda's hospitals because he was reminded of his experience working in San Francisco in the 1980s. He also told me of a young, gay epidemiologist on his staff who began crying when he first walked through the inpatient wards in Kampala because it reminded him of the partner he had lost to AIDS, of his friends who had died, and of what Beale described as the "slaughter" that was San Francisco before treatment.

The San Francisco-based AIDS researchers that I followed to Uganda often described the epidemic they saw there as resembling San Francisco in the pre-treatment era. They gave this description both with horror—over the extreme and unnecessary suffering caused by the lack of drugs – and with the "nostalgia" that Dr. Beale identified. For Beale himself, this nostalgia was for a time when he felt he was really a part of something: fighting a disease that no one understood, and caring for patients that had become social and medical pariahs in much of the rest of the country. The nostalgia was not about wishing the drugs did not exist—on the contrary, he has heavily advocated for expanded access to treatment throughout his career. Rather, it was about the kind of doctor he had been able to be in that era. "Right now," he told me, "HIV medicine is much more technical and much less human" than it used to be.

> In the 1980s, it was all human, because comfort and care were the only and the best thing you could provide. It was horrific, but it was also terrific because the staff was so close, and so dedicated. It was a very special relationship. Now, HIV medicine in the U.S. is much more frightening. It used to be about providing a painless and meaningful death. Now a death is a mistake. The cost of making an error is much higher, because the standard is that everyone lives. Now, making a technical error could have a major impact on patient survival. The weight of technical errors is much heavier now [when there are 20 drugs available] than in the '80s and early '90s when there were only 1 to 4 drugs and none of them worked very well. Then there were fewer mistakes to be made, and mistakes didn't impact the outcome anyway. In the 1980s, the human was the best you had.

Ten years have passed since the development of effective HIV drugs, and HIV medicine in the U.S. has changed drastically in this time. As Dr. Beale says, it has grown much more technical as clinicians must master a growing list of antiretroviral drugs and the ways in which they should and should not be combined. Once inevitable, "death is now a mistake." In addition, diagnostic technologies assessing a patient's CD4 count, viral load, and drug resistance genotype have all become routine aspects of HIV care in wealthy countries. Furthermore, these drugs and technologies have changed the disease itself—both how it manifests in patients, and how it is conceptualized in medicine. Once-common markers of "full-blown AIDS" such as Kaposi's sarcoma (KS), pneumocystis carinii pneumonia (PCP), and dementia have grown much rarer. Instead, the markers of AIDS in the U.S. are now often side effects of the drugs themselves: lipodystrophy (fat redistribution), metabolic disorders, anemia, and liver damage.

In Uganda, however, this shift is just beginning to happen as more and more people access free antiretroviral drugs. At the time of my research in 2005, most Ugandan physicians—though highly skilled in the clinical management of disease—had little experience with antiretroviral medications. The roll-out of free drugs brought with

it a need and demand for doctor training, as Ugandan physicians struggled to manage this newer, more "technical" HIV medicine.

Yet, it would be a gross oversimplification to say that AIDS in Uganda currently is simply a time-delayed version of what AIDS was in San Francisco in the 1980s. Despite any nostalgia that they may feel, when North American AIDS doctors travel to Uganda they encounter a disease which is—despite its eerie familiarity—fundamentally different in many ways than AIDS as they know it. While some of the visible manifestations of untreated HIV disease may remind them of their own past clinical experiences (the Kaposi's sarcoma, the wasting syndrome, the cryptococcal meningitis), other elements suggest an epidemic that is not commensurable with AIDS in the U.S.: the "background" of endemic malaria and malnutrition against which the infection plays out, additional "tropical" diseases not seen in the U.S., and the large numbers of women and children with HIV. There are less visible differences too—for example, the strains of HIV most prevalent in Uganda are of a different genetic sub-type than the HIV found in the U.S., the significance of which is still unknown.

The experiences of another San Francisco doctor highlight this tension between familiarity and difference that characterizes the turn towards Africa in American AIDS research. In the summer of 2005, I met with Dr. Richard Swan in his office at the Foundation for Global HIV/AIDS, which he directs. The foundation supports HIV clinics and treatment in Uganda as well as elsewhere in Africa, China, and the Caribbean. He had first encountered AIDS when working as a doctor at San Francisco General, the county's public hospital, when the epidemic hit in the 1980s. In the 1990s he went into health policy, and became a prominent member of the Clinton Administration and an

advocate for greater attention to the impact of the epidemic on African American communities. While working for the federal government in the late '90s he served as a representative to UNAIDS, the United Nations body dealing with the global AIDS epidemic. The UNAIDS meetings were often held in areas of the world heavily effected by HIV, and in traveling there Dr. Swan found himself immersed in an epidemic that both reminded him of his early days at San Francisco General Hospital and far exceeded anything he had witnessed in the U.S.:

> My travel in the developing world started around 1995 or 1996. I had to go to these quarterly meetings of UNAIDS which would be held in Lusaka in Zambia, in Kyelitsha in South Africa, in Durban in South Africa, in Zimbabwe. They put them in areas that were heavily impacted by HIV. And so through the course of that, I began to see all of these extraordinary things.
>
> For a clinician to walk into hospital after hospital where people are standing in the hallways, they're sleeping in the hallways, they're two people in the bed, one underneath the bed—you have these large open wards. I can remember being in Zambia about two hours outside of Lusaka, and we had been taken to this Salvation Army hospital that truly was out in nowhere, that was big—and in a ward of about 60 beds times three [3 times as many patients as beds] there were probably twenty people with grand mal seizures, seizing in the beds, just from untreated cryptococcal meningitis. And the standard of care there—this was '98 or maybe '97—drugs that we all knew how to use were not available. Diflucan [fluconazole] was out; amphotericin, which is the drug of choice [for cryptococcal meningitis] was absolutely available but [they] couldn't pay for it. It was really startling, and that was when my mind started to say, "The need that I'm seeing is extraordinary, and it's completely unmet and unaddressed." And I began to think about the ethics of ignoring it, and not being able to ignore it.
>
> …So I started realizing that the epidemic really wasn't happening in North America at all, and was happening elsewhere. And not only that, having been a pre-ARV clinician [in the U.S.], I realized that all of what I knew was directly applicable to what I was seeing. These were people who've never seen ARVs. These are people who are dealing with opportunistic infections, and that's what we did up until 1994 [sic], in the United States. Fifty percent of the gay men in San Francisco were infected when I was in San Francisco. We were *full* on the in-patient service at San Francisco General Hospital; 70-80% of the patients in the

> hospital, all services, were AIDS-related. The emergency room was full of people coming in with complaints of infections related to HIV.

While Swan never uses the word "nostalgia" to describe his experiences in Africa, what he saw in Zambia in the 1990s clearly brought back memories of working in San Francisco in the 1980s. In the above passage, his description of the crowded hospital and lack of medications in Zambia flows directly into a reminiscence of San Francisco General Hospital prior to the availability of effective treatment. As a clinician, he realized that having worked in the pre-treatment era in the U.S. had given him experience treating the kinds of infections he was now witnessing in Africa. Yet, this clinical familiarity was paired with differences in scale and economics that were shocking to a doctor accustomed to the health care system of a wealthy nation. This is evident in his description of the Zambian Salvation Army hospital—the open wards crowded to three times their capacity, 2 patients to each bed and a third on the floor, the simultaneous seizing of 20 patients from untreated meningitis—in which the epidemic takes on a level of spectacle unmatched at even the hardest-hit hospitals in the U.S. in the 1980s.

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Such images of suffering are powerful, but they are also complex. As a doctor and a policy-maker, what Dr. Swan saw in Zambia motivated him to take action that might alleviate the suffering he witnessed. At the same time, despite his humanitarian intentions, his description could easily be read as a modern affirmation of Africa as a diseased continent—a representation that has plagued it

since the colonial era and which was used by missionaries and colonial powers to justify their intervention (Vaughan 1991; Comaroff 1993; Butchart 1998).

In the colonial era, disease was often framed as an *environmental* hazard intrinsic to the tropics—linked more to the land and the climate than to the people themselves. This reflected the prominence of medical geography and other environmental models of illness in the era prior to the advent of germ theory. In this framework, European colonists' susceptibility to tropical illness was seen as evidence of bodies out of place, unsuited to and weakened by exposure to heat and humidity (Hannaway 1993; Anderson 1997). This began to change when germ theories of disease gained prominence in the West in the early 20th century. Within germ theory *bodies* rather than *places* were seen as the primary hosts of disease, resulting in new strategies of public health intervention.[11] In his work on Australian colonial history, Warwick Anderson argues that this shift to germ theory meant that ideas of disease and infection acquired a new mobility—no longer tied to certain landscapes, diseases were understood to move about freely between bodies. In Australia, this led to the pathologization of native bodies as vectors of disease, and the resultant exclusion of natives from portions of Australia targeted for white settlement. He describes this as shift from medical geography to "medical government" (Anderson 1997). In her work on colonial medicine East and Central Africa, Megan Vaughan describes how "medical discourse operated by locating differences and difference in the body, thereby not only pathologizing them but naturalizing them" first as inherent in race, and later

[11] It is important to note that germ theory did not displace environmental theories of disease, but rather co-existed with it in many instances (Valencius 2000).

in culture (Vaughan 1991: 13). Often, discourses about racial differences were also highly sexualized (Gilman 1985; Vaughan 1991; also see Magubane 2001 for an important corrective to Gilman).

AIDS provided a new context for this old project, in which sexual discipline in particular became a key public health objective as well as a sign of social responsibility. So-called "African sexuality" was widely pathologized as both deviant and promiscuous (sometimes even by African authors themselves—e.g. Serwadda et. al. 1985), while other routes of transmission such as the frequent re-use of syringes for medical injections were given much less attention (Packard and Epstein 1991). A 1989 article published by two sociobiologists in *Social Science and Medicine* is one of the more notorious examples of this. In this piece, the authors propose that different racial groups have evolved different reproductive strategies, resulting in a hierarchy of "sexual restraint" where Asians occupy the top position (i.e. show the most restraint), followed by whites, and lastly blacks. It is this lack of sexual restraint, they argue, that places blacks both in Africa and the diaspora at greater risk for HIV (Rushton and Bogaert 1989). The authors also implied that blacks were of lower intelligence than other racial groups. The representation of Africans as sexually undisciplined in publications such as Rushton & Bogaert's (as well as in other less overtly racist forums) also implied their social irresponsibility. In this reading African bodies, through their undisciplined behavior, posed an overt threat to public health.

This piece has since been excoriated as scientific racism (Leslie 1990) as well as "bad science," representing a scientific imaginary of Africa rooted in

Enlightenment ideas about white superiority and black inferiority (Bibeau and Pedersen 2002). However, anxiety about African bodies was a theme that reappeared several years later in relation to treatment and drug resistance, when a speculated lack of discipline around pill-taking was framed as posing a risk to the public health in the form of drug-resistant "doomsday" strains of the virus. Again, Vaughan's work provides a valuable historical perspective on this discourse, which echoed the concerns expressed in the 1940s by colonial health officials treating syphilis in East Africa (Vaughan 1991: 146).

This representation of Africa as continent of undisciplined bodies—what Briggs and Mantini-Briggs (2003) call "unhygienic subjects"—coexists with another powerful trope which positions Africa as a continent defined by suffering. Indeed, this is another lens through which Swan's description of the Zambian hospital ward can be refracted: Africa as a place of unmitigated, uncontrollable bodily suffering. Of course, the suffering that Swan witnessed is very real, as is the suffering caused by poverty and disease in many countries on the African continent and elsewhere. However, within anthropology a debate has arisen over the use and misuse of representations of suffering, and how they relate to humanitarian intervention. Are anthropologists' use of stories and images of suffering people a form of partnership with the poor, or a form of exploitation in the name of humanitarianism? Must they be one or the other?

In her critique of "human rights culture" (and in particular the book *Dying for Growth: Global Inequality and the Health of the Poor,* edited by the non-profit Partners In Health), anthropologist Leslie Butt argues that those on the "social justice bandwagon" use the stories of the poor to further their own agendas. In so doing, the personal

experiences of individuals become dehistoricized and rendered in "capsule format" to serve as "icons for a 'public' wracked by poverty and ill health" (Butt 2002a, 2002b). Butt calls this iconic representation "the suffering stranger" and argues that it actually serves to replicate the very inequality that humanitarians who employ it are arguing against. The editors of *Dying for Growth*, including physician-anthropologist Paul Farmer, respond to Butt's attack with the assertion that their use of human rights discourse is strategic rather than absolutist, and question her attempt to completely dismantle the intellectual foundations of social justice (Irwin et. al. 2002). My goal here is not to adjudicate this debate, but rather to point it out as yet another way in which the representation of Africa and African bodies is highly political and contested. This is relevant because it is within this volatile arena that transnational science is being carried out. In such a scenario, questions about illness, treatment, aid, and ethics are always bound up with political as well as scientific agendas.

Conclusion: Turning Towards "Africa"

The debate over the "suffering stranger" is not limited to the subject of disease. Rather, it can be seen as but one element of a kind of "'Africa' talk" that seems increasingly prevalent in the international arena. In his most recent book, James Ferguson describes this "'Africa' talk" as "full of anguished energy and (often vague) moral concern. When we hear about 'Africa' today, it is usually in urgent and troubled tones. It is never just Africa, but always the crisis in Africa, the problems of Africa, the failure of Africa, the moral challenge of Africa to the 'international community…" (Ferguson 2006: 2). This idea of "Africa" writ large (and more specifically, "Sub-Saharan Africa" as separate from "Middle Eastern" North Africa) is, Ferguson argues,

"as much a product of modern race thinking as it is an obvious cultural or historical unity" (2006: 1).

This imaginary of a singular "Africa" is highly problematic for anthropologists and others who seek to study the many specific and diverse peoples, places, and events on the continent. And yet, as Ferguson points out, the idea of "Africa" cannot be simply discarded because no matter how imaginary it is, its effects are nonetheless very real. Perceptions of "Africa" as a place defined by spectacular poverty and suffering "don't just misunderstand social reality, they also shape it" by warding off international investment on the continent and, in the case of my research, by initially discouraging the expansion of HIV treatment (2006: 7). For this reason, Ferguson argues, even if the notion of "Africa" is misguided, the fact that its effects are real means that we must account for this "Africa" in our research, even as we struggle to present more specific and historicized views of lives on the continent. He writes:

> My fundamental concern in this book is less with Africa as an empirical territory, culture region, or historical civilization than with "Africa" as a category through which the "world" is structured—a category that (like all categories) is historically and socially constructed (indeed, in some sense arbitrary), but also a category that is "real," that is imposed with force, that has a mandatory quality; a category within which, and according to which, people must live. I want to focus attention on how a vast, complicated, heterogenous region of the planet has come to occupy a place-in-the-world called "Africa" that is nowadays nearly synonymous with failure and poverty. I want to ask both how that place-in-the-world functions in a wider categorical system and what this means for the way we understand an increasingly transnational political, economic, and social "global order" (2006:5).

My research for this dissertation began with a concern over how notions of "Africa" in Ferguson's sense were playing out in international debates over antiretroviral access on the continent. At the same time, I wanted to explore how scientific knowledge

about ARVs in Africa was being generated at a particular place and time, in central and southern Uganda in the early 2000s. For this reason, throughout my dissertation my focus toggles back and forth between "Africa" as an imagined whole and the very specific arena of Ugandan HIV research and care. In reality, often these two "places" were inseparable, as the researchers and doctors I interviewed would invoke their specific experiences in Uganda as speaking to HIV treatment in Africa as a whole. Usually they did so in an attempt to challenge the idea of "Africa" as a place of failure—arguing, for example, that their studies of ARV adherence in Uganda proved that "Africans" can take HIV drugs properly, or that their program for treating pregnant women with HIV proved that HIV treatment was feasible "in Africa."

In the chapters that follow, I have done my best to represent the specificity of what I observed in Uganda while addressing the imaginary of "Africa" writ large. At times, like my scientist informants, I am sure that I nonetheless slip into the very discourse I seek to undermine, and employ "Uganda" as a proxy for "Africa"—or, as one American doctor phrased it—"the African context." I hope that these transgressions can be forgiven, both in light of my fairly recent transformation from an anthropologist of urban North America to what some would describe as an "Africanist"—a title that makes me uneasy—but also because, like Ferguson, I am trying to figure out the relationship between "Africa" and the lives and work of the American and Ugandan physician-researchers I studied.

Chapter Two

THE POLITICAL ECONOMY OF ANTIRETROVIRALS

Introduction: Economies of Life and Death

One of the central aims of this dissertation is to track the relationship between scientific knowledge and structural inequalities. Sociologists and anthropologists of science have long argued that "science" and "society" are not separate realms. In other words, it is not sufficient to argue that science is "influenced by" social context; this schema maintains both the scientific and the social as autonomous arenas that could ostensibly be purified of one another's influence. Rather, STS scholars argue that science and society are mutually constitutive or "co-constituted"—in other words, indivisible (Clarke and Fujimura 1992; Latour 1993; Shapin 1995; Clarke and Starr 2003).

This dissertation examines the production of scientific knowledge about HIV treatment, drug resistance, and "Africa" in an effort to describe how this knowledge is co-constituted with political economic structures of inequality. Much of what I discuss in later chapters hinges on the history of unequal access to antiretroviral drugs in Africa which, in turn, hinges on the political economy of the global pharmaceutical industry. It is this inequality that created the research and humanitarian opportunities that have drawn American researchers to countries like Uganda in large numbers, and that is shaping the trajectory of drug-resistant HIV in the region.

For these reasons, this chapter is devoted to an examination of the political economy of antiretrovirals—by which I mean the policies and markets governing the production, circulation and consumption of these drugs in a global capitalist system. I

undertake this examination at several scales. Part I of this chapter provides a brief overview of the scientific debates over HIV treatment and drug resistance in Africa, and how these debates helped frame the controversy as one over public health and safety rather than political economy and/or human rights. Part II examines antiretroviral access in relation to the global economy, and describes how patent law and international trade agreements have played a key role in drug pricing, manufacture, and availability. This section also describes the recent sea change in donor-country attitudes towards HIV treatment in Africa, and the birth of major unilateral and multilateral programs providing free antiretrovirals in low-income countries, including Uganda. In Part III of this chapter I take a more ethnographic approach, and provide a "snapshot" of the advent of free treatment in Uganda as of March 2005. The aim of this final section is to link earlier discussions of politics and economics to what actually unfolds "on the ground" in two Ugandan HIV clinics. In addition, it is an attempt to suggest some ways in which the advent of free drugs is altering the landscape of treatment access in Uganda by tracking the forms of inclusion and exclusion—or "governance"—that are emerging in relation to donor-funded antiretroviral programs.

As an "ethnography of capitalism," Kauchik Sunder-Rajan's book *Biocapital* provides a useful framework for understanding capitalism in terms of governance. Sunder Rajan brings a Marxian approach to global capitalism into dialogue with Michel Foucault's analyses of biopower and governmentality (see Foucault 1978, 1979). Foucault, he argues, tended to position biopolitical and governmental rationality in terms of the *state*; but in an increasingly globalized world, we need to think about the forms

that *global* governance is taking. In a passage particularly relevant to this chapter of my dissertation, Sunder Rajan writes:

> As we start thinking about governance in more global terms, it is not surprising that biopolitical regulation—the regulation, calculation, accounting for bodies, decisions about who lives and who dies—becomes central to the calculus of this new governmental rationality (Sunder Rajan 2006: 79).

This chapter is devoted to the political economy of antiretrovirals precisely because the valuation, production, circulation, and consumption of these drugs in the global economy are intimately related to the calculus of "who lives and who dies." And, as I hope this dissertation will show, science is not exempt from this calculus.

PART I: Antiretroviral Anarchy and Sanitary Citizenship

Adherence and Resistance

As described in the Introduction, policy debates over access to ARVs in Africa have been intimately related to scientific claims about *adherence*—the ability of patients to take drugs as prescribed—and its relationship to the development of drug resistance. The framing of pill-taking behavior in terms of "adherence" to a regimen is relatively new. In the past, the term "compliance" was more commonly used but with the shift in American medicine towards a less hierarchical patient-doctor relationship, this term has largely been replaced by "adherence" (Chesney 2000). When a patient is described as "poorly adherent," this usually means that he or she has been missing doses of medication—though it can also refer to not taking medicine according to instructions (such as with or without food, at a certain time of day, or at a particular dosage). Within medicine, adherence is most commonly understood in behaviorist terms—in other words,

as an individual behavior rooted in patient knowledge, health beliefs, and rational choice (see, for example, Eraker et. al. 1984; Gold and McClung 2006). In contrast, anthropologists and critical epidemiologists have argued that medication adherence must be understood in social context, and in particular in light of relations of stigma, power, and governance (Estroff 1981; Trostle 1988; Lerner et. al. 1998; Liu 2005).

Adherence to combination antiretroviral therapy has been a major concern among HIV doctors from the very beginning of the treatment era in 1996. All combination therapies include at least 3 drugs, and the earliest combinations were built around protease inhibitors—the powerful and expensive class of antiretrovirals that debuted in the mid-1990s and remain a keystone of many ARV regimens today, particularly in wealthy countries. The early regimens were difficult to take because they often required taking some medications with food and some without, a three-times daily dosing schedule, and consisted of a large number of pills. They also came with significant side effects (and still do). The regimens have grown progressively simpler over the years, but as with any medication—especially those that must be taken for life— achieving good adherence remains a challenge for many people. "Poor adherence" — missing doses — can have two major consequences. First, there is a clinical consequence: a patient's health may worsen as the virus resurges in the absence of adequate medication. Second, there is a public health consequence: missing doses can allow HIV to mutate into drug-resistant strains, which can then be passed on to others through all the usual routes of HIV transmission (blood and body fluids). These drug-resistant strains are harder and more expensive to treat successfully.

The Conventional Wisdom

In the late 1990s and early 2000s, when the movement to get antiretrovirals into Africa began to gain velocity, the conventional wisdom in HIV medicine was that preserving health and preventing drug resistance required near-perfect adherence to the drugs, upwards of 95%—in other words, missing no more than 5% of prescribed doses (Chesney 2003). (I will discuss recent scientific challenges to this conventional wisdom in detail in Chapter 3). There was much anecdotal evidence from both doctors and patients that adherence to these drugs was a struggle, but there was little systematic data on what average adherence rates to combination therapy actually were. The studies that did exist often used different methods to assess adherence, making it difficult to draw general conclusions.[12] Furthermore, data on adherence to antiretrovirals in Africa was effectively non-existent at this time, given that there were virtually no antiretrovirals in sub-Saharan Africa for patients to adhere to.

Despite this, there was significant speculation regarding what adherence to ARVs in Africa *would* be were medications to be provided on a large scale. Skeptics speculated that poverty, illiteracy, and poor health infrastructure made it likely that adherence in Africa would be poor, and some argued that it would be more cost-effective to direct AIDS relief funding towards preventing new infections rather than treating the HIV-positive. Poor adherence, they argued, would not only erase any benefit the treatment might have provided to individual patients, but might also generate a dangerous new public health threat in the form of drug-resistant virus.

[12] For example, a 1999 study was based on patients' estimates of their own adherence ("self-report") and found that the vast majority (89%) of the sample reported adherence rates of over 80% (Haubrich et. al. 1999). In contrast, a 2000 study using monthly pill counts to monitor adherence found a median adherence rate of 73%—meaning that half the patients fell below this rate and half above. This was lower than Haubrich's 1999 findings (Bangsberg et. al. 2000). Both of these studies were conducted in the U.S.

In the Introduction to this dissertation I describe the most notorious of these claims—the U.S.AID Chief Administrator's 2001 assertion that Africans would not be able to take HIV medicines accurately because they "don't understand Western time." In the medical literature, skepticism was usually expressed in the less inflammatory language of public health. For example, a British-led team in Malawi argued that "widespread, unregulated access to antiretroviral drugs in sub-Saharan Africa could lead to the rapid emergence of drug resistant viral strains, spelling doom for the individual, curtailing future treatment options, and leading to transmission of resistant virus" (Harries et. al. 2001, see also Stevens 2004). Reflecting these fears, these researchers argued that in order to prevent "antiretroviral anarchy," treatment should be delivered only in the context of highly structured programs designed to insure good adherence, such as "directly-observed therapy" (DOT) where health workers would watch as patients took their daily doses of medication.[13] This sentiment was echoed in a paper written by two health psychologists at the University of Connecticut, who argued that "without very substantial science-based interventions aimed at insuring adherence…Individual patients may not benefit, and developing countries could become a veritable 'petri dish' for new, treatment-resistant strains" (Popp and Fisher 2002).

Power Over Life: Death in the Name of Health

The choice of the term "antiretroviral anarchy" to describe chaotic medication use points to the important link between questions of adherence and forms of governance—both self-governance in the form of pill-taking, and governance by the state in the form of

[13] DOT emerged as a strategy for treating tuberculosis, which requires many months of antibiotic therapy. It has been suggested as a means of assuring adherence to antiretrovirals in poor countries. The efficacy of DOT in treating TB and its appropriateness for HIV therapy are both topics of debate (see Garrett 2001; Farmer et. al. 2001; Liechty and Bangsberg 2003; Harries 2004).

public health programs for HIV treatment. Both forms of governance can be understood as examples of what Michel Foucault called "biopower"—a specifically modern form of power which operates through the cultivation and administration of bodies and populations. In describing the shift between the Classical and Modern Ages in Europe, Foucault describes a transition in the major form of power from one that was "subtractive"—the power of the sovereign to take life (or let live)—to one that was "generative" in that it sought to order, administer, and foster (or disallow the fostering of) life (Foucault 1978: 136, 138). What prior to the Classical Age had been the sovereign's right to take the life of his subjects (the "right of death"), became the modern state's "power over life."

More recently, anthropologists have used Foucault's conceptualization to think through the state's response to epidemic disease and the ways in which questions of rights and citizenship are interwoven with questions of health, illness, and biology. In their book on Venezuela's cholera epidemic in the early 1990's, Charles Briggs and Clara Mantini-Briggs argue that the state response to cholera practiced a kind of "medical profiling" whereby certain groups were included in and excluded from public health services. Like its more familiar counterpart, racial profiling, medical profiling was deeply racialized as well as class-based, separating middle-class professional Venezuelans from the poor and indigenous into what the authors describe as "sanitary citizens" and "unsanitary subjects":

> *Sanitary citizenship* is one of the key mechanisms for deciding who is accorded substantive access to the civil and social rights of citizenship. Public health officials, physicians, politicians, and the press depict some individuals and communities as possessing modern medical understandings of the body, health, and illness, practicing hygiene, and depending on doctors and nurses when they are sick. These people

> become *sanitary citizens*. People who are judged to be incapable of adopting this modern medical relationship to the body, hygiene, illness, and healing—or who refuse to do so—become *unsanitary subjects*. …[B]ecoming infected with cholera became a key means of characterizing *indigenas* and other poor Venezuelans as unsanitary subjects. (Briggs and Mantini-Briggs 2003:10).

The authors rightly point out that these discourses about disease and citizenship are deeply linked to beliefs about "modernity" and peoples' relationship to it. Their description of "medical profiling" aptly describes the attitudes towards Africa held by the treatment skeptics I described earlier. How better to understand Andrew Natsios' claim that "Africans don't understand Western time" than as an assertion that Africans are "unsanitary subjects," "incapable of adopting this modern medical relationship to the body, hygiene, illness, and healing"?

Briggs and Mantini-Briggs' work dovetails with Joao Biehl's analysis of the Brazilian state's "activist" response to the AIDS epidemic. In defiance of both international political opinion and the multinational pharmaceutical industry, Brazil initiated a universal HIV treatment program very soon after the advent of triple-therapy by using domestically-manufactured generic antiretroviral drugs. This program had an immediate impact, reducing the number of AIDS cases in Brazil by as early as 1997. Nonetheless, Biehl points out that certain people—namely the poor—remained invisible to this otherwise model system and continued to die without treatment, often in the street. The reason for this, he argues, is that the Brazilian program works for those who assert themselves as "biomedical citizens" by identifying themselves as HIV-positive, seeking treatment, and advocating for their continued care in an overcrowded public health system (Biehl 2004). Very much like Briggs' and Mantini-Briggs' "hygienic citizens," the active pursuit of care by these biomedical citizens serves as proof of their worthiness

for treatment. Those who do not assert themselves fall through the cracks, a phenomenon that Biehl describes as a form of "social abandonment." The "abandoned" become visible to the public health system only through their deaths, when they are "traced as 'drug addicts,' 'robbers,' 'prostitutes,' or 'noncompliant,' practices and labels that allow them to be blamed for their dying."

Interestingly, Biehl sees this "abandonment" not as a form of exclusion, but as an "active capacity of the local state," a way of "letting die" in which the "poorest and marginal are socially included through a public dying, *as if their deaths had been self-generated"* (Biehl 2004: 120; emphasis added). This last phrase is important, as it echoes Briggs' and Mantini-Briggs' category "unsanitary subjects"—those whose inadequate self-regulation render them undeserving of treatment and thus justifiably allowed to die by the state. It was this same rhetoric that informed the debates over treatment access in Africa, in which Africans—both by way of their alleged misunderstanding of "Western time," and by way of their "anarchic" health care provision—figured as unsanitary subjects, inappropriate for treatment due to their likely noncompliance and the threat of drug resistance that this implied. The deaths that resulted, an estimated 2.1 million as of 2006 (UNAIDS 2006), can thus be seen as a result of a sanctioned abandonment, a biopolitical decision to "let die" justified in the name of public health.

PART II: Antiretroviral Economies

The scientific discourses outlined in Part I facilitated the obfuscation of the economic interests at stake in the controversy over treatment in Africa. Specifically, the framing of the debate as a public health issue directed attention away from the questions

of global trade policy, intellectual property law, and pharmaceutical market share. It was these political economic factors that were fundamentally determining who could and could not afford antiretroviral treatment.

Public Health and Private Property

The price of antiretroviral therapy is primarily determined by a combination of national laws and international trade agreements that define these drugs as the intellectual property of the corporations that develop them. In the U.S., developers of a new drug are granted 20 years of patent protection beginning at the time they submit a "New Drug Application" to the Food and Drug Administration (FDA). This protection forbids the manufacture and sale of the drug by any competitor for the duration of the patent, effectively allowing the patent owner to charge whatever the market will bear. Because New Drug Applications must be filed before clinical trials are initiated, many years usually pass between the submission of the application and the FDA's approval of the drug for marketing. Thus, manufacturers rarely get the full 20 years of market exclusivity granted by their patent protection. The rationale behind patent protection is that although these drugs are often cheap to manufacture, companies argue that they are expensive to develop, and patents allow corporations to recoup money invested in "R&D"—research and development. (Nonetheless, this rationale is undercut by the fact that a great deal of drug research is actually funded through federal research grants, not the companies themselves).

Colloquially, drugs manufactured and sold under patent protection in the U.S. are called "branded" drugs, and come to be known to the general public primarily by the trademark name under which they are marketed, rather than their generic name (e.g.

"Prozac" vs. "fluoxetine.")[14] However, once a patent expires, any company can legally manufacture and market a generic version of the drug. The regulations are similar in Western Europe. Globally, the situation is somewhat more complicated. Many countries—including Brazil, India, South Africa, and Thailand have domestic drug industries that make generic versions of drugs that are still under patent protection in the West. These drugs are far cheaper than their branded counterparts.

In 1997, one year after the debut of triple antiretroviral therapy in the West, the South African government passed a law called the Medicines and Related Substances Act which permitted the importation of drugs at the cheapest price available, regardless of patent status—a practice known as "gray market" or "parallel" importing. The law also authorized the government to engage in "compulsory licensing" in the case of a public health emergency, meaning the government could license local companies to manufacture generic versions of essential medicines still under patent. The branded pharmaceutical industry interpreted the law as a direct threat to their intellectual property and market share, predicting that the South African law would open the door to the widespread abrogation of patent protections and the parallel importation of cheap drugs into the U.S., where most of their market lay (Cooper 2001). Shortly after the passage of the Act, a group of 40 pharmaceutical companies filed a lawsuit against the South African government, arguing that the law was unconstitutional. The companies were led by a number of industry groups including the Pharmaceutical Manufacturers' Association

[14] This description of "branded" vs. "generic" reflects how these drugs are referred to the U.S., and in the international HIV debates that are the subject of my research. However, in places where the domestic pharmaceutical market is dominated by multiple competing generic manufacturers (each with its own distinctively-named version of a drug), the meaning of "branded" and "generic" can be different and much more complicated than what I have described here (see Hayden 2006).

of South Africa, and the Pharmaceutical Research and Manufacturers of America (PhRMA)—the largest pharmaceutical lobbying group in the U.S.

PhRMA has a website devoted to the issue of "health care in the developing world" which provides a useful window onto the industry's defense of its stance. Drawing on the scientific discourses I described in Part I of this chapter, PhRMA argues that the provision of antiretrovirals in poor countries poses a danger to public health. The PhRMA website devotes an entire page to the subject of drug resistance titled "DANGER AHEAD: Drug-Resistant Strains Show There Are No Simple Solutions." On this page, PhRMA includes a quote from a *New Republic* article written by a clinical fellow at Harvard Medical School asserting, "What the enthusiasts [of low drug prices in Third World countries] seem not to realize is that *without adequate health care networks to monitor their distribution, potent new medicines are worse than useless; they're dangerous"* (PhRMA 2006). In this way, PhRMA strategically employs quotes from authoritative sources to portray pharmaceutical access as a danger to public health in the developing world, and, in fact, makes frequent reference directly to Africa as a place where treatment is particularly unfeasible.[15]

The Clinton Administration initially supported the industry's lawsuit, and—at PhRMA's request—put pressure on South Africa by denying the government's request for trade preferences and putting the country on the U.S. Trade Office's "watch list" of

[15] The lobbying group repeatedly cites the poor state of health infrastructure as a reason for its concern. When I first accessed the site in 2003, it placed the blame for this squarely on the shoulders of African states. However, it is now widely agreed that the decline of public services across Africa since the 1970s is closely related to World Bank and International Monetary Fund "structural adjustment" policies, which required economic liberalization and divestment from the public sector as a condition of loan receipt and repayment. Nonetheless, in 2003, the PhRMA website described the deterioration of health care facilities in Africa as "a result of these governments' budget decisions" and, ironically, cited a World Bank survey of public hospitals in Kenya to back up this argument. The site no longer makes these claims.

countries in potential violation of intellectual property laws. However, this stance ultimately became an untenable public relations position for both the administration and the pharmaceutical industry. The Clinton government withdrew its support of the suit in June of 1999 after treatment activists staged a series of vocal demonstrations at Vice President Al Gore's presidential campaign events (Cooper 2001). In December of the same year, the lawsuit and the issue of treatment access were featured prominently in the massive protests that shut down the World Trade Organization's meeting in Seattle. Activists continued protesting against the lawsuit in the months that followed, and in April of 2001 it was dropped. The decision to end the suit was led by several major manufacturers of HIV drugs[16] in an attempt to remedy the significant damage to their public image that the lawsuit was causing (Kaiser Family Foundation: 2001).

Generic Drugs and the Rise of the Gray Market

The drug companies' 2001 decision to drop the lawsuit against the South African government marked the beginning of a significant shift in international attitudes toward pharmaceutical patent protections. Shortly after the lawsuit was dropped, the questions it had raised regarding the legality of parallel importation and compulsory licensing were revisited at the 2001 meetings of the World Trade Organization (WTO) in Doha, Qatar.

The WTO policy governing patent laws is called the Agreement on Trade-Related Aspects of Intellectual Property Rights, more commonly referred to as TRIPs. The TRIPs agreement required that countries joining the WTO recognize patent protections by 2006. Although the agreement contained language that seemed to permit parallel importing and compulsory licensing of drugs in the case of a public health emergency, at

[16] These companies were Merck & Co., GlaxoSmithKline, Bristol-Myers Squibb, Boehringer Ingelhiem and Roche (Kaiser Family Foundation: 2001).

the time of the Doha talks this provision was unclear and countries had been loathe to employ it, especially in light of the South African lawsuit. The Doha meetings clarified the agreement, and in a victory for low-income countries affirmed their right to both parallel importation and compulsory licensing of drugs. In addition, the poorest WTO member countries were given a 10-year extension on the 2006 deadline for enforcing patent laws (Avafia 2005).

In many ways, the Doha meetings gave official permission for a process that was already underway. Low-income countries were already exploring the manufacture and/or importation of generic antiretrovirals as a way to provide treatment access to a greater portion of their populations. In Uganda, importation of generic antiretroviral drugs from India began in October of 2000.[17] At this time, an estimated 1.4 million Ugandans were HIV-positive, of which 120,000 had a clinical AIDS diagnosis and were in immediate need of treatment (Uganda Ministry of Health 1999). An Indian company named Cipla was making a combination medicine under the name Triomune and selling it for $40 monthly. The importation of Triomune into Uganda resulted largely from the efforts of Dr. Peter Mugyenyi, the director of Kampala's Joint Clinical Research Center (JCRC). Established by the Ugandan government with funding from the U.S. Agency for International Development (U.S.AID) in 1990, the JCRC had long been an important center of HIV research and international collaboration. Dr. Mugyenyi was an outspoken advocate for increased access to antiretrovirals in Africa, and by purchasing the drugs from Cipla, the JCRC clinic was able to offer them to patients at cost. Triomune

[17] At the time, India's pharmaceutical industry was governed by the India Patents Act of 1970, which granted patents only for the method or process of drug manufacture, but not for the substance itself. Under this law, it was legal within India to make and sell versions of drugs that were still under patent in the West as long as the manufacturing process was not identical.

combined three drugs—nevirapine, staduvine (D4T) and lamivudine (3TC)—into a single pill to be taken twice daily.[18] At that time, the same three drugs cost $550 monthly in Uganda when purchased in branded form (Oxfam 2002).

Prior to this turn of events, only a small number of Ugandans had been able to access antiretrovirals. The wealthy and well-connected were able to buy the drugs through private doctors or by obtaining what one Ugandan doctor described to me as "briefcase drugs" purchased abroad by relatives living in Europe and brought to Uganda in their airplane luggage. In 1999, a UNAIDS pilot program called the Drug Access Initiative made discounted brand-name antiretrovirals available at selected clinics in Kampala, but the program—which relied on partnerships with multinational pharmaceutical manufacturers—offered a price reduction that was too insubstantial to make a difference to most Ugandans. A small number of patients were able to get antiretrovirals for free, either by qualifying for donor-funded research projects or through informal connections, often forged through working with AIDS service organizations that linked them to international humanitarian networks—what Vinh-Kim Nguyen calls "therapeutic citizenship." (Whyte et. al. 2004; Nguyen 2004). Although at the initial cost of $40 a month Triomune still exceeded the monthly earnings of many Ugandans, it was nonetheless significantly cheaper than the branded combination, and people began traveling to JCRC from all over the country to purchase it. Indeed, according to an Oxfam report, the number of patients receiving HIV drugs at JCRC increased by 200%

[18] Because Indian companies ignored patent protections, they were able to co-formulate three medications into one pill. In the U.S., such coformulations—called "fixed-dose combinations"—did not exist because each of the three components was owned by a separate company. Creating a combination pill would have required an alliance among competitors.

after generic drugs became available from 962 patients in 2000 to 3,000 in 2001 (Oxfam 2002).

As a result of the competition, branded drug manufacturers began discounting their drugs as well. When I asked an administrator at JCRC about this in 2005, he laughed, telling me how once the center began importing generics, the branded pharmaceutical companies "came running to us saying, 'we've been meaning to give you a discount!'" He then described playing the companies off each other: when the branded companies offered a price that undercut the generics, JCRC took that price back to the generic companies, and got them to lower the prices of the generic drugs as well. By the time I spoke with him in March 2005, the monthly cost of Triomune had fallen to $17.

The Global Fund and PEPFAR: The Free Treatment Era

However, the most significant change in the global treatment landscape came with the founding of two major programs providing free treatment in poor countries. The need for more funding to fight "neglected" diseases had been on the agenda at the 2000 G8 meetings in Okinawa, Japan, as well as at the African Summit on HIV/AIDS in Abuja, Nigeria, in April 2001. At the Abuja meeting, U.N. Secretary General Kofi Annan called for the establishment of a global trust fund to treat AIDS, tuberculosis, and malaria. One month later, U.S. President George W. Bush pledged the first donation of $200 million in a White House ceremony attended by Annan and Nigerian President Olusegun Obasanjo. European countries and the U.N. soon made additional pledges, and by July total committed donations reached $1.5 billion. The new organization was named the Global Fund to Fight AIDS, TB, and Malaria, and located its main office in Geneva, Switzerland. Though it would take several years for Global Fund to become fully

operational, its establishment made the expansion of antiretroviral treatment in Africa increasingly likely.

It was in reference to the fledgling Global Fund that U.S.AID chief Andrew Natsios made his comments about Africans' unsuitability for ARV treatment due to their lack of understanding of "Western time." Natsios was not the only one in the Bush Administration to openly express criticism. Even before Natsios' statements, the *New York Times* quoted an unnamed senior Treasury Department official expressing nearly identical concerns about the Global Fund. "The official," wrote the *Times*, "said Africa lacked the basic medical and physical infrastructure that would make it possible to deploy effectively the complex cocktail of drugs to fight AIDS. He said Africans lacked a requisite 'concept of time,' implying that they would not benefit from drugs that must be administered on tight time schedules" (Kahn 2001). Thus, it was surprising when a year and a half later, in January of 2003, the movement to expand treatment access was given another major boost from what seemed to many an unlikely source—the U.S. government. In his State of the Union address on January 23, President George W. Bush announced the advent of the President's Emergency Plan for AIDS Relief—or PEPFAR—a 5-year initiative aimed at providing AIDS services in 14 "focus" countries, mostly in sub-Saharan Africa and the Caribbean. At $15 billion, the program dwarfed the Global Fund. Much of this money was slated for antiretroviral treatment.

There has been a range of speculation regarding the motivation behind PEPFAR. Some have argued that the timing of the announcement was orchestrated to temper the advent of the U.S.-led war in Iraq, which was also announced during the same State of the Union address. Others have speculated that the program was aimed at stabilizing

African states weakened by AIDS in a post-9/11 effort to make these countries less hospitable to terrorist cells. More recently, Vinh-Kim Nguyen has taken this argument further, suggesting that PEPFAR's use of defense subcontractors such as Bechtel (which handles the information technology for some PEPFAR programs) raises the possibility of a neo-colonial "military-therapeutic complex" (Nguyen 2006). Lastly, some have suggested that PEPFAR was motivated by the President's evangelical Christian faith. Indeed, in his address, the President described the plan as "a work of mercy" (Behrman 2004) and has been criticized for using the program to direct funds to abstinence-oriented prevention programs (U.S. Government Accountability Office 2006). Regardless of the motivation behind the program, its impact has been significant. Currently, the program provides HIV treatment to more people than does the Global Fund, though in fewer countries (Global Fund 2005). Uganda receives drugs from both programs.

PART III: Rolling Out Antiretrovirals in Uganda

The PEPFAR and Global Fund programs have met with elements of both praise and criticism. My purpose in Part III of this chapter is not to evaluate these programs but rather to present a snapshot of how they played out "on the ground" at a particular time and place. This time and place was Uganda in March 2005, when I spent five weeks interviewing doctors in Kampala and the southern Ugandan town I call Mukwano about the impact of the free treatment "roll-out." At this time, free antiretrovirals from the Global Fund and PEPFAR had been available for approximately 8 months. My account is by no means intended to represent the impact of the roll-out in other countries, or even in other parts of Uganda. Rather, it is an effort to connect some of the macro-level

political and economic factors discussed in the first part of this chapter to the daily lives of physicians and patients at two specific clinics, and ultimately to the question of who lives and who dies.

I begin with an account of my first visit to Uganda in 2003, when most people accessing drugs were doing so by purchasing Triomune on a monthly basis, usually from JCRC. This account provides an important backdrop for my subsequent discussion of how the Global Fund and PEPFAR programs altered the landscape of medication access and HIV care in Uganda. My point in this section is to track how shifts in global pharmaceutical economies and the politics of international health altered the patterns of problems of antiretroviral access for Ugandan patients; how new forms of inclusion and exclusion were generated to cope with the limited supply of free drugs; and how the new, large, donor-funded programs brought the global politics of patent protection and generic drug manufacture into Ugandan clinics.

Before Free Treatment: The Price of Adherence[19]

I first traveled to Uganda in the summer of 2003. At that time, free treatment was not yet available, and most Ugandans accessing ARVs did so by paying for Triomune out of their own pockets. I came to Uganda by way of Dr. Beale, who had hired me to conduct qualitative interviews with the patients in his fledgling study of antiretroviral adherence in Kampala. Dr. Beale had begun working in Uganda in 2002. He was angered by skeptical attitudes towards antiretroviral treatment in Africa, having heard many of the same arguments made about poverty and adherence in the U.S. a few years earlier. In the late 1990s had used his research among the HIV-positive homeless to show

[19] I borrow the title of this sub-heading from an article I co-wrote in 2006 entitled "The Price of Adherence: qualitative findings from HIV positive individuals purchasing fixed-dose combination generic HIV antiretroviral therapy in Kampala, Uganda" (Crane et.al. 2006).

that adherence among the urban poor was not significantly less than among "average" Americans, findings that advocated more equitable access to treatment for the socially and economically marginal patients that were increasingly suffering the burden of HIV infection in the U.S. Now Beale wanted to conduct a study of adherence in Kampala.

Dr. Beale began working with a young Ugandan researcher named Joan Bingamu to document patients' adherence to the generic medications. For her Master's thesis in Pharmacy, Bingamu had surveyed over three hundred patients on Triomune and found that they reported extremely high levels of adherence despite having to pay for their medication (Byakika-Tusiime 2003). She had funded her research with her own money because of the lack of research funding available at the university.[20] Beale was excited by her findings, and began working with her to replicate his San Francisco-based study of adherence in Kampala. In addition to documenting patients' self-reported level of adherence as Bingamu had done, this study would use what was considered the more objective measure of monthly pill counts to account for missed doses. Their work, along with studies conducted by other research teams in South Africa and Senegal, eventually found some of the highest rates of adherence ever documented (over 95%), and significantly eroded the conventional wisdom about adherence being poor in Africa (Laurent et. al. 2002; Orrell et. al. 2003; Oygui et. al. 2004). By the time I traveled to Uganda in 2003 to assist Beale's team with the qualitative project, hegemonic discourses about adherence in Africa had shifted significantly—to the point where a senior

[20] In a 2006 paper, Josephine Beoku-Betts makes the important point that the self-funding of African women's scientific research often contributes to its marginalization by Western researchers, who see it as primarily as "baseline" data for their own projects rather than important in its own right (Beoku-Betts 2006).

American epidemiologist visiting Kampala told me that it was no longer acceptable to even discuss adherence in Africa as a potential problem anymore.

In the qualitative interviews we conducted that summer, HIV-positive men and women described challenges more properly seen as issues of *access* than of *adherence*. In 2003, a month's worth of Triomune cost about $30 (55,000 UGS), and it was this monthly expense that was most likely to cause patients to miss doses. Patients' ability to continue the medication from month to month often depended on complex and tenuous webs of assistance from family members, and regularly required the curtailing of other expenses—especially their childrens' school fees (Crane et. al. 2006).

Both within HIV clinics and inpatient hospital wards (where the vast majority of patients were sick with HIV-related illness), the ability to pay for medication was a regular component of doctor-patient interaction. I witnessed this first-hand one day when I observed a doctor at work in Olusozi's HIV clinic. Dr. Helen Wamola was an East African raised by diplomat parents in the American suburbs. Having recently completed her medical residency at Yerba Buena University, she had been hired by Beale to manage the Kampala study. At the same time, she continued to see patients one day a week in the HIV clinic at Olusozi Hospital, Kampala's largest public facility. One Friday, I sat in:

> *I walked up to the 5th floor of Olusozi, which is where the Infectious Disease Clinic is. As I arrived on the 5th floor I saw a long line extending into the central hallway of the hospital. This line continued down the corridor to the clinic's reception area, where all the seats were full, and into the hallway leading to the doctors' rooms, which was lined with seats—all full. Dr. Wamola's "office" was a plywood cubicle with a curtain over the entrance. In the cubicle was a small wooden table with a wooden chair on either side, where she sat across from her patient, and an exam table. There was an extra plastic chair across from the exam table, which I sat in. The exam table was very simple—just a narrow, flat cushioned table covered with a Olusozi hospital sheet. No stirrups or any other adjustable components like exam tables in the U.S.. Also no paper. The same sheet remained on the table throughout clinic hours—it isn't changed between*

patients. She gave me a brief tour of the clinic and the other doctors' spaces were similar…

…A young male patient came in whose name I did not catch. He was a regular patient of Dr. Wamola's. Speaking in English, he told her he was "suffering a lot" with fever, pain, and "scratching in all parts of the body." Dr. Wamola asked him "What about the areas below?" and he said he had improved there. At one point, she asked him to undress so she could check "below" and I offered to step out but Helen the nurse said, no, it's ok, you're a medical person so you can stay. So Dr. Wamola checked his genitals and said that indeed it was much better than before—no new sores [syphilis?]. She tried to talk to him about his CD4 count, which is 17[21], but his English was limited and Dr. Wamola speaks Swahili, not Luganda, so Helen the nurse came in and helped translate. The doctor was trying to ascertain whether or not he was able to afford ARVs. He said right now he is not working, "there is no more work," but said he could get money from his family if she writes him a prescription. She explained that this medication is different than others, it's not like a medication for an infection that you only need to buy once and take for one week; you need to take it always for the rest of your life. Talking to Helen, she noted that DART—a research study offering free treatment[22]—probably wouldn't take him because "his number is too high." The DART study is prioritizing people based on the length of time they have been a registered patient at the Olusozi clinic; his registration number was one thousand seven hundred and something. While Dr. Wamola and Helen stepped out, I introduced myself and tried to talk with him a bit. I told him that I had come from the U.S. to do some research, and he said he has a sister in the U.S. who is a doctor. He wasn't sure the name of the place where she lives. I was surprised to hear this, and told Helen when she came back in, and she asked him in Luganda and he said the same thing. She asked if his sister might be able to help him pay for medication, but he said she doesn't know about his condition [that he is HIV-positive]. When Dr. Wamola returned, she encouraged him to tell his sister and ask her for help but emphasized that it would need to be sustained help—not just for a few months. For now, she won't prescribe him ARVs because he doesn't have the means to continue paying for them.

—Field notes, 7/4/2003

This discussion between Dr. Wamola, Helen the nurse, and their patient illustrates how the political economy of antiretrovirals could enter into clinician/patient negotiations in very explicit ways prior to the advent of free treatment. Here, Dr. Wamola and Helen do

[21] A normal CD4 count ranges between 500 and 1500.

[22] DART (Development of Antiretroviral Therapy in Africa) is a 5-year, 3000-patient study being conducted in Uganda and Zimbabwe. The study is funded by the Medical Research Council in the United Kingdom (http://www.ctu.mrc.ac.uk/dart).

not simply ask the patient whether or not he can afford the drugs; rather, they inquire about his employment situation, his family finances, and his possible overseas resources. In the end, Dr. Wamola decides against writing him a prescription, fearing that he will not be able to afford the drugs on a sustained basis.

Sometimes this kind of decision-making was much less explicit, as when doctors assessed a patient's class status—and thus their ability to pay for antiretrovirals—based on visual cues. Susan Reynolds Whyte and colleagues have described how doctors at Kampala's Mulago Hospital use the "blanket sign" to determine whether or not to raise the possibility of purchasing ARVs with a patient's family (Whyte et.al. 2004). Doctors examine the quality of a patient's bedding—whether their family has provided them with a substantial blanket, or merely a sheet—in deciding whether or not the patient might be able to afford treatment. This description of the blanket sign was also repeated to me, and to other members of Dr. Beale's research team, while visiting Olusozi. In Whyte et.al.'s piece, Dr. Harriet Mayanja, the head of Mulago's Department of Medicine, describes how and why doctors employ the "blanket sign:"

> 'Our patients bring their own bed linen. You check the blanket, the bed sheets, how the patient and family are dressed, whether they are wearing shoes or rubber slippers. Do they bring a nice thermos flask, a basket of food with a crocheted cover, a radio? Do they ask for a private room? Or is the patient using old sheets, or maybe a woman's gown because they can't afford a blanket. On the bedside table, is there only a plastic mug with the cold porridge provided by the hospital? It's not fair to suggest treatment costing 60,000 shillings [$30] a month to someone who has not been able to afford sheets at 8,000 shillings [$4] in the past five years.' (Whyte et.al. 2004).

Dr. Mayanja, as well as other clinicians quoted in Whyte et.al.'s article, describe their use of the "blanket sign" as an act of compassion—an effort to not further traumatize relatives of a sick patient by proposing a treatment they cannot afford. Discussing

antiretrovirals with these patients and their families, one nurse says, would be "cruel" (Whyte p. 19). Significantly, a piece written by one of Whyte's colleagues suggests that patients do not necessarily experience this behavior as compassionate. In a paper describing Ugandan patients' experiences in the health care system generally (not specifically HIV care), Hanne Morgensen quotes a patient whose words are remarkably similar to Dr. Mayanja's, yet, her experience is much different. The woman is a confidant of Morgensen's, and in the quote she explains why she refused to admit her son (sick with pneumonia) to the hospital, despite Morgensen's offer to pay:

> 'All the other people there just talk to each other and laugh and they look at you and think you are strange. And also, even if you had given me money for the fees and the medicine, then everybody could see that I was poor. When they see that you do not even come with your own flask for porridge and just a sheet, but not a blanket, then they just think that you are poor and ignorant and do not understand anything, and they will treat you as somebody primitive.' (Morgensen 2005, p. 224).

Here, Morgensen's confidant describes her own awareness of the significance of certain objects—a blanket and a thermos (or "flask")—as markers of class that will shape her hospital care. Her narrative points to the importance of class stratification even in societies often viewed as universally poor in Western terms, and suggests the existence of a gray zone in the hospital in which discrimination and compassion exist as two sides of the same coin. Whether compassionate or discriminatory, the use of the "blanket sign" as well as the more explicit discussion of income between Dr. Wamola and her patient were both born out of the reality of the antiretroviral market in Uganda at the time.

The Advent of Free Treatment: New Forms of Triage

In the summer of 2004, the first free HIV drugs from the Global Fund and PEPFAR became available to patients in Uganda. I returned to Uganda in the spring of

2005, about eight months into the treatment roll-out. Not surprisingly, clinics with antiretroviral programs had found themselves quickly overwhelmed by patients seeking treatment. In an interesting counterpoint to Harries' et.al.'s (2001) concern about "antiretroviral anarchy," treatment advocates described the advent of free antiretrovirals in Uganda as a time of "happy chaos" (Donnelly 2005). At Olusozi, the number of patients registered at the outpatient HIV clinic had soared to 8000 by March of 2005, compared to 5000 prior to free treatment. In Mukwano, the number of patients essentially doubled over the same period of time, from 2500 to 5000.

When I spoke with them in 2005, doctors at these clinics attributed the sharp rise both to the availability of free drugs and to recent changes in HIV testing. Whereas previously HIV testing had been conducted only in free-standing test centers, both Olusozi and Mukwano hospitals had recently initiated a policy of "routine counseling and testing" on the in-patient wards, meaning that patients would be offered the opportunity to test while hospitalized, rather than being referred out to a test center. This greater ease of testing, combined with the knowledge that free drugs were available should the test come back positive, was causing the clinics to become flooded with patients.

My interviews with Ugandan doctors at this time suggest that the initiation of free treatment programs shifted—but did not eliminate—patterns of inclusion and exclusion determining which patients got drugs and which did not.[23] In the early months of free treatment, clinics were granted only a limited number of treatment "slots" by the Global Fund and PEPFAR, with the intention of gradually increasing the number as these slots filled. In order to access ARVs, patients first had to meet clinical guidelines for eligibility—meaning their disease had to be sufficiently advanced to warrant treatment.

[23] The dynamics I describe here may have shifted since my 2005 observations.

Patients with late-stage disease were given first priority, followed by patients who were symptomatic.[24] However, many more patients met these clinical criteria than there were slots available, so the staff at both Olusozi and Mukwano clinics decided to establish additional guidelines by which they would prioritize patients—essentially a form of triage. At Mukwano, which was initially granted 50 treatment slots, the decision was made to prioritize widows with children and individuals who had been long-term patients at the clinic. By the time I visited in March 2005, the number of treatment slots had increased to over 1,000 (and was continuing to rise), and this system of prioritization was no longer needed.

At Olusozi, however, a form of triage was still in place in 2005. In a presentation given at Olusozi Medical School Barbara Zenti, an Italian doctor working at the hospital, outlined how and why the staff had developed their particular criteria. Olusozi had been granted its first allotment of free treatment nine months earlier in July of 2004. Zenti described the mixed emotions of the hospital staff at the time, telling the audience, "When we got the first doses, we were singing. But when we found ourselves with 100 doses and 5000 patients, we were stuck." It was at that time that the clinical staff met to hammer out their treatment eligibility criteria. In addition to clarifying who should get treated first, these guidelines were intended to help reduce pressure on health care workers who, she said, had begun receiving numerous personal requests for treatment once the word spread that free drugs were available.

After meeting the basic clinical criteria of a documented positive HIV test symptoms of later-stage disease, the next eligibility requirement Olusozi patients were required to meet was one of adherence. Zenti explained that patients were assessed for

[24] Footnote use of clinical staging vs. CD4, this will be discussed in detail in chap 5.

their likely adherence to ARVs based on their clinic attendance, and were required to keep a minimum of 80% of their clinic appointments over a period of 3-4 months in order to receive ARVs. Since patients seeking ARVs at Olusozi undergo an extensive counseling and education program carried out over three visits, it was attendance at these visits that often served as the means by which to measure adherence. Because a number of patients would travel long distances to access free treatment (often at significant cost to themselves), this measurement of clinic attendance served not only as a proxy for medication adherence, but also as an assessment of patients' ability to return to the clinic each month to obtain their medication. In this way, even though patients' financial resources were no longer an issue in terms of medication cost, access remained linked to income for those living at a distance from the clinic. It is important to point out that this kind of test of adherence was never a precondition of receiving antiretrovirals in the U.S.—a double-standard that Dr. Swan, the Clinton Administration's UNAIDS representative introduced in Chapter 1, described to me as "unethical."

During that first year of free treatment, one issue that caused consternation for doctors at both Olusozi and Mukwano was what to do about patients who had previously been buying their drugs out-of-pocket. Some of these patients were well-off, and those who were clearly able to continue purchasing their drugs were not put on free treatment in order to preserve the free slots for others. However, many patients had been impoverishing themselves in order to pay for their drugs, and the doctors I spoke with at both clinics felt that these people should be switched over to the free programs. Making such a switch was not always easy because both PEPFAR and the Ugandan Ministry of Health (which was the grantee for money from the Global Fund) had their own criteria

for treatment stating that patients who were “treatment-naïve” should be given priority. This meant that patients who had been buying their own ARVs were at a distinct disadvantage. Dr. Salter, the American missionary doctor who founded the Mukwano HIV clinic, explained:

> A number of our patients have been buying drugs for a year, two years, maybe longer than that. And they were asking us, "Can't we please be put on this free program? Because we've run out of money." You know, they've sold off land, their kids are not going to school because they need the money for drugs, they've sold cows—whatever their resources are—and have literally ended up with, are down to really nothing. They're down to buying drugs one week at a time because they don't have any other source of funds.

Fortunately the Ministry's policy prioritizing treatment-naïve patients was, in the words of the Mukwano clinic’s Dr. Butembe, a “soft” policy—meaning that when clinic representatives requested permission to enroll previously treated patients in the free drug program, the Ministry agreed. Doctors at Olusozi described a nearly identical story—they, too, were troubled by the exclusion of patients who had impoverished themselves purchasing drugs—and upon request were allowed by the Ministry of Health to put these patients on free treatment. The PEPFAR program, however, remained for treatment-naïve patients only at both sites. When I asked a senior doctor at Olusozi about this policy (which she disagreed with), she speculated that donors preferred to focus on treatment-naïve patients because “they are easier to start on treatment, and cheaper to treat.” Previously treated patients are more problematic because they may harbor drug resistance, and might need alternative, more expensive drugs. In addition, she said, the policy allowed the donor programs to cite higher numbers of patients treated in their results. Simply switching patients from paid to free treatment did not increase the overall number of patients receiving medication, but starting never-treated patients on drugs did.

Brand Loyalty? PEPFAR versus the Global Fund on the ground

This difference regarding the eligibility of previously-treated patients was just one of several differences between PEPFAR and Global Fund-funded programs. At a macro-level, these programs are very different politically, economically, and structurally. The Global Fund is a multi-lateral, independent, international foundation funded through donations primarily from the U.S., Western Europe, and Japan. It was born out of discussions in the U.N, the G8, and at a summit of African leaders. The Fund does not implement programs directly; rather, it acts something like a bank, providing grants to governments and non-governmental organizations (NGOs) which then develop their own treatment and prevention programs. Its policy is to fund the purchase of the cheapest drugs available, as long as they have been deemed safe and effective by the World Health Organization (WHO). This means that HIV treatment programs funded by the Global Fund usually provide generic antiretrovirals such as Triomune.

In contrast, PEPFAR is a unilateral, U.S.-funded program that was developed largely in secret at the upper levels of the Bush Administration (Behrman 2004). As such, its funds are available only to the 14 "focus countries" designated by the U.S. government, most of which are in sub-Saharan Africa or the Caribbean.[25] Though PEPFAR also works through local health care systems—often the same government hospitals and NGOs receiving Global Fund grants—it is more involved in program implementation than the Global Fund. Unlike the Global Fund, PEPFAR requires that patients receive a CD4 count before beginning treatment, and provides funding for this

[25] These countries are: Botswana, Cote d'Ivoire, Ethiopia, Guyana, Haiti, Kenya, Mozambique, Namibia, Nigeria, Rwanda, South Africa, Tanzania, Uganda, Vietnam and Zambia.

type of serological monitoring in its grants. It also provides funding for additional doctors in order to help clinics meet the demand of increasing numbers of patients. In addition, PEPFAR does its own drug procurement and supply-chain management through American corporate sub-contractors.

Lastly, PEPFAR will only fund generic antiretrovirals that have been approved by the U.S. Food and Drug Administration—which, at the time of the program's initiation, none had. This meant that PEPFAR programs initially provided only branded pharmaceuticals—as was the case during my 2005 fieldwork trip to Uganda. The Office of the Global AIDS Coordinator, which oversees PEPFAR, defended the decision by arguing that the intention was to provide the highest quality drugs and avoid drug resistance. Dr. Mark Dybul (then the Office's deputy chief medical officer, and now the head of PEPFAR) told the Washington Post, "If in two or three years we have drug resistance as a result of a therapy that we introduce, we will have lost the continent in terms of our ability to treat. 'Good drugs' isn't good enough. Because of the risk of resistance, we need the highest possible quality drugs to avert a disaster on the continent" (Brown 2004). This decision was criticized by treatment advocates, and fostered widespread suspicion among activists that the Office of the Global AIDS Coordinator (which was headed by former Eli Lilly CEO Randall Tobias) was in the pocket of the pharmaceutical industry (Lueck 2004).

Randall Tobias, as head of the Office of the Global AIDS Coordinator, rings the opening bell at the New York Stock Exchange on October 13, 2004. Tobias was "honoring private sector leaders in the fight against global HIV/AIDS" (New York Stock Exchange 2004).

However, in the last several years the FDA has approved over 20 generic antiretrovirals, and 14 of PEPFAR's 15 focus countries are purchasing some generic drugs through the program. In addition, PEPFAR recently announced that in the coming year, generics will comprise 70% of the drugs purchased for three focus countries: Nigeria, Zambia, and Haiti (Donnelly 2006). This recent turn of events suggests that Uganda's PEPFAR program might come to rely more heavily on generic drugs in the near future. During my 2005 visit, however, all the PEPFAR drugs were branded in the two clinics I visited.

The Olusozi and Mukwano HIV clinics receive funding from both PEPFAR and the Global Fund. The PEPFAR program has an internal system for managing its drug supply, while the Global Fund drugs are supplied through the Ugandan Ministry of Health. When I visited the pharmacy at the Mukwano clinic in 2005, this division between the two programs was clearly visible. The pharmacy occupied a single, small room. The Ministry of Health's generic drugs and patient records were stored on the left side of the room, and PEPFAR's branded drugs, patient records, and computer database were on the right. Anna and Nicholas, the two pharmacists on duty, each worked for a separate program. Anna, the pharmacist for the Ministry of Health/Global Fund program, showed me the large ledger books where she wrote down a record of each patient's name

and their antiretroviral regimen. Nicholas had an identical book for the PEPFAR clients, but, in addition he entered his patients' information into the computer database that PEPFAR had provided. Anna told me that the plan was for the Ministry of Health program to eventually share the computer with PEPFAR.

I was curious how clinic doctors made the decision as to whether a patient should be enrolled in the PEPFAR or the Global Fund/Ministry of Health (hereafter "Ministry of Health") treatment program. Was this decision a practical one, based on which program had slots available, or were there other factors shaping doctors' decisions? Furthermore, did the distinction between generic and branded drugs enter in to the equation? I began asking the Mukwano doctors about this during our interviews.

Firstly, they told me, because the programs offered different drug cocktails, there were sometimes clinical reasons for enrolling a patient in one program or the other.[26] If a patient had no medical contraindications, however, their placement was at the discretion of the prescribing physician. Often this decision was based on logistical factors related to obtaining a CD4 count, which PEPFAR required but the Ministry of Health did not. Though the Ministry of Health had provided Mukwano clinic with a CD4 machine, it was a source of annoyance for the clinic's doctors. The machine often lacked reagents, or faced problems due to sporadic electricity outages, meaning that it could not be relied upon to keep up with the demand of the growing number of patients in need of CD4 tests.

[26] The Ministry of Health program offered Triomune, a combination of nevirapine, D4T, and 3TC. Patients who were in need of TB treatment as well as ARV treatment could not receive this combination because rifampicin, a drug used against TB, lowered the effectiveness of nevirapine, putting patients at risk for disease progression and drug resistance. Thus, patients in need of TB treatment were automatically tracked into the PEPFAR program, which provided an antiretroviral cocktail of efavirenz, AZT, and 3TC. For patients who were pregnant or anemic, the opposite was true. AZT can cause severe anemia, and so patients with a low hemoglobin count were placed in the Ministry of Health program. Pregnant women were also placed on Triomune, because initial animal studies of efavirenz showed the drug poses a high risk of severe birth defects.

Patients who were willing to pay for a CD4 count were sent to the private lab in town, but those with late stage disease who could not afford this were simply started on Triomune without the test.

The PEPFAR program not only required a CD4 count, but for reasons of quality control it required that the test be done at the U.S.-run Centers for Disease control lab located outside Kampala, at the Uganda Virus Research Institute. Test results sent to Kampala sometimes took two or three weeks to return to Mukwano. For this reason, Dr. Butembe told me, he tended to put the sickest patients on the Ministry of Health drugs simply because it could be done more speedily—either with no CD4, or with a CD4 done locally. Furthermore, PEPFAR had other additional requirements: more paperwork, extra counseling visits, and the stipulation that patients bring a "treatment supporter" (a friend or family member willing to help them with adherence). These additional requirements also influenced some physicians' decisions. Dr. Norman Musingusi, a postgraduate medical student who did a weekly shift in the HIV clinic, confessed that he had little patience for the logistical requirements of PEPFAR:

> The Ministry of Health drugs, those are the ones I have been writing [prescriptions for]. The PEPFAR people have so many rules. They have to be counseled twice, they have to bring a treatment supporter—please, I am a simple man! [laughs]. Always I want simple things.

Dr. Rosa Kizito, another postgraduate medical student, also preferred to prescribe Triomune but for a different reason. She felt that Triomune was easier for patients to adhere to, because it required taking fewer pills.

More often, however, physicians expressed a preference for the branded PEPFAR drugs over the generics. I first learned of this when Dr. Butembe mentioned that HIV-positive staff at Mukwano hospital were enrolled in the PEPFAR program, even if they

were not treatment-naive. Staff were the only "treatment-experienced" people who were allowed to receive PEPFAR drugs, and this exception to the rule was based on a belief that the PEPFAR drugs were superior:

Dr. Butembe: The PEPFAR program, we are giving to naïve patients. Here, the non-naïve patients we have given the drugs are the staffs.

Johanna: The hospital staff?

Dr. Butembe: The hospital staffs only.

Johanna: Okay. Why is that?

Dr. Butembe: We have a belief that the drugs from the PEPFAR project are much better than the generics. And nobody would want to leave the staffs to continue taking the drugs that you are kind of thinking are not so good or whatever. Everybody wants to be much on the safer side of the drug that has been [around] for a long time and is from a good country and you are really convinced about its production.

Dr. Butembe was not the only doctor at Mukwano who expressed a preference for the PEPFAR drugs. For example, Dr. Solomon Ogola, who staffed Mukwano's pediatric AIDS clinic, initially told me that the combination of drugs offered by PEPFAR was more "potent" than Triomune, saying "it has been shown to help the patients better." Significantly, both doctors expressed this belief even though they were aware of studies showing the drugs to be equivalent. Shortly after making the claim that Triomune was a less potent drug, Dr. Ogola contradicted himself, saying:

> From my experience, I really don't see much difference [between the drugs]. And even some studies were done on Triomune some time ago in Olusozi and the findings that came out were that over 60% of those patients who were on Triomune received undetectable viral loads by six months. And that's what I think is important as far as I'm concerned.

Similarly, Dr. Butembe was well-aware of the research. He speculated that his preference for the PEPFAR drugs might be a "psychological thing:"

> I mean part of it could be psychological thinking, because like I'm saying, most of the studies show that the drugs work similarly. They have the same concentrations in the blood, they are the same drugs, and when you ask most of the researchers—like if you ask Jason [Beale] what's the difference—he would tell you there's no difference between the generics and the branded ones. But psychologically, people tend to think—the doctors and the patients—we tend to think that the branded drugs are much better. It's a kind of a psychological thing.

The ability of Dr. Butembe and others to simultaneously hold two contradictory views—that generics were equivalent to branded drugs and that they were inferior—points to what anthropologists have called the "social lives of medicines" (Whyte, Van der Geest and Hardon 2002). In other words, drugs carry meaning beyond their pharmaceutical properties. Thus, Dr. Butembe could know that PEPFAR and Ministry of Health drugs were equally efficacious, but for social reasons—the association of higher quality with Western manufacture, and the desire to give fellow clinicians the best possible treatment—he could also hold the view that the PEPFAR drugs were superior.

It was not only doctors who held this belief. Dr. Esther Were, whose position at the clinic was actually funded by PEPFAR, initially told me that it might be loyalty to her American employers that caused her to enroll more patients in the PEPFAR program than the Ministry of Health program. However, she continued, there was also a belief that the PEPFAR drugs were better, and when people requested them she liked to grant their request even though she was equally confident in the efficacy of Triomune:

> Some people come requesting particularly, 'This is my patient. Could you please put them on those PEPFAR drugs? It seems for them they are good.' And I do for them what they want. Maybe it's a doctor [who makes the request]. Maybe a nurse. Maybe a friend. I just do for them what – I put them on PEPFAR drugs because they're there. But even Triomune, I have no questions about. It's also raising people [up].

Ultimately, the preference for PEPFAR drugs seemed to be more about *trust* than about science or medicine. Doctors knew that Triomune worked well, as they had seen the results in their patients. And they knew that studies comparing Triomune to branded drugs had shown them to be of equal efficacy. But they also knew that the PEPFAR drugs were of Western manufacture—"from a good country," as Dr. Butembe put it. His colleague, Dr. Willa Balozi, explained "I have that attitude that drugs from UK or Europe are always very good quality."

Dr. Ida Kanogo explained that she had worked with Indian medicines before, and found their quality unreliable: "Initially it is good medicine but then along the way it is not exactly good." Even Dr. Musingusi, who preferred to prescribe Triomune, expressed caution about Indian drugs telling me, "Cipla is quite a reliable company. But there is a danger. There is a danger because I have seen drugs coming from India which have not been good." These fears are not unwarranted. The selling of counterfeit drugs is a very real problem, particularly in poorer countries, where it is estimated that up to 25% of medicines consumed are counterfeit and/or of inferior quality (WHO 2003). (Though, it should be noted, that inferior drugs may well be Western-manufactured medicines that are "dumped" in poor countries with incorrect or inadequate labeling; see Silverman, Lee and Lydecker 1982).

The origins of the generic drugs were not the only thing that made the Mukwano doctors wary. In addition, they were very familiar with the unreliability of the Ministry of Health's management of its drug supply. Prior to my visit, the doctors told me, the clinic had run out of Triomune and the Ministry of Health was not able to send them more for a period of two weeks. The doctors were forced to tell their patients on

Triomune that they had to pay for their own drugs until the new supply came in, which many could not afford to do. These patients simply went without, which put them at significant risk for developing drug resistance. PEPFAR, with its well-financed supply-chain managed by U.S. contractors, inspired more confidence in its reliability than the Ugandan Ministry of Health.

The Future of Free Treatment: "With a donation, you can't be sure."

Ultimately, what concerned doctors most was the future of these programs. Over and over again in our interviews, doctors at both Mukwano and Olusozi worried about the sustainability of both PEPFAR and the Global Fund treatment programs. They had witnessed the dramatic effect that antiretrovirals had had on the lives of their patients—a restoration of health so dramatic that it has come to be known as "the Lazarus effect" in HIV medicine, after the Biblical character who rose from the dead. What would happen, they wondered, if the political will behind these programs suddenly shifted? At the conclusion of our interview I asked Dr. Annette Abe, one of the Mukwano clinic's new full-time physicians, if there was anything important that she wanted to add before we finished. "Personally," she said, "I'm just concerned about the free ARVs and whether or not they will be sustained for the long term." Citing the recent shortage of Triomune at the clinic, when some patients had been forced to stop their medicine, she worried about the uncertainty that came with relying on donor programs: "This is basically a donation. And with donation, you can't be sure."

Doctors seemed very aware that the availability of the drugs depended upon international political factors largely out of their control, such as drug patenting policy in India and the attitude of the U.S. President towards the quasi-democratic Ugandan

government. For example, during my 2005 visit to Uganda, the Indian Parliament passed a an amendment to its Patent Act in order to bring it into compliance with WTO regulations. Whereas India had previously only recognized patents of *processes*, not *products*, the amendment did away with this caveat, bringing the country's patent laws more in line with American and European standards. This new recognition of product patents posed a direct threat to the production of the cheap, generic antiretrovirals purchased by the Global Fund and imported by Uganda and other low-income countries.[27] Mukwano's Dr. Musingusi referred to this news during our interview, telling me, "India has already said it is going to increase the price of these drugs. How are we going to continue having these ARVs? If they stop, what shall we do?"

AIDS activists march in Kampala to protest the proposed Indian patent law in March 2005 (photo by J. Crane)

Dr. Musingusi also worried about the continuance of the PEPFAR program. What if the U.S. President's good will towards Uganda shifted? This was a valid worry

[27] The final version of the law included a grandfather clause that allowed the continued production and sale of generics already on the market, such as Triomune. However, it may prevent the production of generic versions of future antiretrovirals needed for second- and third-line treatment (Halliburton 2006; Avafia 2005).

in light of the Ugandan President's controversial decision to attempt a run for a third term. President Yoweri Museveni had been in power since overthrowing dictator Milton Obote in 1986. Since then, he had been re-elected twice but was not allowed to run for a third term due to term limits. However, at the time of our interview, Museveni was pressing for *kisanja*—the repeal of term limits—so that he could run again. It was widely agreed that if allowed to run, he would win, as his government controlled the political purse strings in the country and was known for repressing political opposition. *Kisanja* was controversial among Ugandans. "What if the President goes for a third term and America does not agree with it?" Dr. Musingusi asked. "Will they be good enough and say even if the man is there for a third term let us give them [ARVs]? If another man goes in and he starts abusing them and they don't agree with him, will they continue the drugs?"[28]

As an American, some of the clinic doctors I interviewed assumed I was linked to PEPFAR, telling me that they were grateful for the program and asking me to pass on their thanks to PEPFAR. Others, such as Dr. Were, hoped I could give them answers about the future of the program:

> I don't know whether you have the answers. But I'm wondering—these drugs are coming here, but what is going to happen? I mean is it going to be consistent that every U.S. president [sustains this program] or what?...What worries me personally is that it raises some debates there [in the U.S.]: "Why do you go for these drugs? Why don't you go for those? Why should you give drugs anyway?" Something like that. And we get worried. If there is a rumble, if people are not agreeing, then what is our future?

[28] As it turned out, Museveni did succeed in running for a third term and, as predicted, he won the election. Uganda has remained a U.S. ally and PEPFAR recipient; in fact, it is sometimes cited as one of PEPFAR's biggest success stories. In contrast, Uganda's access to the Global Fund has been threatened by a corruption scandal that led to the temporary suspension of its Global Fund grants. Ministry of Health officials are currently on trial for mismanaging the funds (Kaiser Family Foundation 2006).

Alluding perhaps to some of the earlier skepticism expressed about antiretrovirals in Africa, as well as more recent controversies over the use of branded versus generic drugs, Were worried about the American public's willingness to continue supporting the programs in the event of a "rumble" or disagreement. Dr. Salter, an American himself, summed up the worries among his Ugandan colleagues: "All of us are concerned about the sustainability of these programs. And we know that PEPFAR is talking about five years, and Global Fund five years, maybe three years. What's going to happen beyond that?"

The goal of both PEPFAR and the Global Fund was to ultimately turn over their programs to local governments. However, in countries suffering from decades of divestiture from the health sector and ongoing "brain drain" of doctors and nurses to Europe, the feasibility of local control remained an open question. As much as they supported the continued roll-out of ARVs, the clinic doctors in particular felt the crushing weight of a demand that was rapidly outstripping the health care system's staffing and laboratory capacity. Dr. Ben Mana, a physician and lecturer at Mukwano's medical school, expressed frustration with the sometimes narrow vision of health development agencies and drug donation programs, arguing that a lack of a comprehensive approach set countries like his up for failure:

> The issue is that by going to look at drugs per se they will forget other programs that are supposed to be part and parcel of this, to make the antiretroviral program successful….Donations should not look at drugs only, but should also look at [other] areas, so they all move together. People get trained, counselors are in place, drugs are in place, laboratories are equipped. The question of whether Africa can take on drugs is no longer a question. It's that the drugs—it's just that now whatever support you give, you give to completion. It's not support in isolation. It's not one component of a package and then you blame that component and say,

> "you see? They have failed." …[For example] you give me a vehicle. But do not give me a vehicle without tires because I will not move. So give me the complete vehicle, with even the keys.
>
> This is a problem with this kind of donation, is singling out one thing out of this big component package and giving out one thing. You give drugs. Then they wonder why people say "You see? They have failed. We told you they were not ready." No! You have not helped me at all. You have caused more trouble. Give me a whole vehicle with keys. Don't only give me a vehicle and don't give me keys and say, "you move!" No. Give me everything, then I move. I'll move. That's what Africa needs now. I don't want a situation [like] "You see? We told you!"

Here Dr. Mana expresses some of the same concerns about health care infrastructure voiced by the treatment skeptics I described in the first part of this chapter. And, to its credit, PEPFAR has tried to address some of these problems by providing funding for additional staff and laboratory monitoring in its programs. At the same time, there is an active debate over whether or not PEPFAR is actually building local capacity through funding these services or causing the further divestiture of public health systems by setting up a separate, donor-funded and operated structure. Certainly the enthusiasm of PEPFAR and other donors (as well as research projects) to fund programs in Uganda has changed the landscape of medical careers in Uganda, as doctors leave their poorly-paid government jobs for much more lucrative jobs with donor programs. This can lead to a kind of internal brain-drain as clinicians hop from job opportunity to opportunity. Indeed, when I last saw Dr. Butembe when he visited San Francisco in the fall of 2006 he told me that the clinic staff in Mukwano had completely turned over since I had visited a year and a half earlier, and all the doctors I had interviewed had left for other jobs with the exception of himself (who was being paid through Dr. Beale's research project) and Dr. Salter, the American missionary.

Nonetheless, regardless of their worries about the capacity of their health system and the sustainability of the roll-out, the doctors I spoke with were resolutely in favor of continuing to expand access to treatment. In doing so, they were constantly balancing the needs of individual patients with public health concerns about antiretroviral resistance. Dr. Hilda Mulondo, a senior doctor in Olusozi's Department of Medicine, explained to me:

> There's a general problem. A public health problem as opposed to the individual problem. When you come to the individual level, what we did was right. Start ARVs, make sure you ensure adherence, keep training people, have continued information and training and try to look at ways of minimizing resistance. And that was a right decision. From the public health point of view, the right decision would have been no, wait. For the next five years, train everybody. Bring them up to speed and train the population, train the community and then when we are all ready, start ARVs. But you tell that to the individuals who come to Olusozi every day who are dying, who have children, who have families, that – "No-no. We can't start you on treatment now because we are waiting for proper training and proper readiness, adequate readiness."

However, Dr. Mulondo continued, taking the "public health" approach and waiting to roll out free antiretrovirals was simply not realistic—not only because it would require doctors to turn away dying patients but also because patients would seek to buy drugs out of their own pockets, which would likely lead to drug resistance anyway:

> What would their response have been? People would still continue buying ARVs. They would buy [them] if they have the money, when they have the money. The cost would continue coming down. At the end — let's say they cost $10 a month, nearly everybody would be able to afford ARVs. But as soon as I'm well, that $10 would go to food or other expenses. So in the end, you will have a situation that is worse. Where people start treatment, once they are better, they say "I can no longer afford the treatment," they go [off]—so either way we would still have got resistance. People wouldn't have sat back and waited, they'd have looked for ways of getting treatment.

For these reasons, Dr. Mulondo, as well as the other doctors I interviewed, continued to advocate for more treatment for their patients. Problems with the system, they argued, should be acknowledged, but were not a reason to stop the roll-out of drugs. Rather, they should be dealt with as they arise. Once again, Dr. Mulondo made this argument most eloquently:

> Despite the struggle, I need more ARVs in Olusozi. I need more patients to be started on treatment. When you go to the [in-patient] wards, it becomes a bit difficult to look at one patient—a 24-year-old woman not on ARVs—knowing well that if that woman was put on ARVs, she can go from a sick person back to that healthy person you saw….There will be problems. Let's face them as we go.

The Political Economy of Drug Resistance

The resolute support expressed by Dr. Mulondo and others for the continued expansion of treatment in Uganda did not mean that they did not also worry about drug resistance. In fact, when I asked both Ugandan and American researchers about the potential for drug resistance in Africa, they almost universally agreed that it would eventually become a problem. However, in contrast to the claims of the treatment skeptics, they did not see this eventuality as resulting from anything inherent to Africa—rather, they saw it as the inevitable outcome of antiretroviral treatment anywhere. Over time, everyone on antiretroviral therapy eventually develops some form of drug resistance; the only way to completely avoid it is not to treat.

Furthermore, the trajectory of drug resistance is fundamentally shaped by political economic parameters. This is true not only for poor countries like Uganda, where the high price of drugs put people at risk for missed doses and drug resistance, but also in wealthy countries like the U.S.—which, significantly, bear the burden of the lion's share of drug-resistant HIV world-wide. However, in the U.S., antiretroviral resistance has

been shaped by the *availability* of drugs rather than their unavailability. The U.S. is the biggest and most lucrative market for the multinational pharmaceutical market and, as a result, new drugs often become available to American patients first. Prior to the discovery of triple antiretroviral therapy, AIDS activists in the U.S. waged a highly successful campaign to gain access to experimental drugs that might prolong their lives. In the late 1980s and early 1990s, a series of antiretroviral drugs (most famously AZT) were made available to American patients in a step-wise fashion. Although they initially seemed promising, any boost in health they provided was rapidly undermined by the quick development of drug resistance, the result of being treated with a single agent ("monotherapy").

AZT, for example, was initially seen as a breakthrough drug when a 1989 study suggested that it slowed down the progress of AIDS (Volberding et.al. 1990). The FDA adopted new guidelines recommending patients be treated with AZT based on this study, and the stock of the drug's manufacturer, Burroughs-Wellcome, immediately skyrocketed (Epstein 1996). However, just three years later the findings of a longer and more comprehensive trial contradicted these results, showing no difference in the health or survival of patients treated with AZT versus those given a placebo (Aboulket and Swart 1993). Treatment with other single drugs resulted in similar results, until the development of protease inhibitors in 1996 and the discovery that successful treatment required a cocktail of at least three different drugs from two or more different classes. By that time, many patients had viruses that were resistant to one or more of the older drugs, a product of having been exposed to sequential monotherapy.

This history is important because it shows that the evolution of drug development and drug markets were fundamental in shaping the level of antiretroviral resistance in the U.S.—which was, by the early 2000s, present in half of people undergoing ARV treatment (Richman et al 2004 Jul 2 AIDS). Furthermore, contradicting earlier fears about poor adherence leading to an epidemic of resistant virus among the homeless and drug addicted, this resistance was found primarily in middle-class gay men who had in fact been highly adherent but had been treated in the early days of the epidemic with single drugs (Garrett 2001).

The political economy of the pharmaceutical industry is shaping the trajectory of drug resistance in African countries as well. As I described earlier, prior to the advent of free drugs the main reason for a missed dose in Uganda was the inability to pay for the next bottle of pills—a situation that likely caused some patients to become drug resistant. However, market factors also contribute to drug resistance in Uganda in less obvious ways. Understanding how requires a brief review of the pharmacology of antiretrovirals. There are three main classes of antiretroviral drugs: protease inhibitors (PIs), NNRTIs (non-nucleoside reverse transcriptase inhibitors, or "non-nucs," and NRTIs (nucleoside analog reverse transcriptase inhibitors, or "nucs"). Triple therapy usually consists of a "backbone" of either a protease inhibitor or a non-nuc paired with two other drugs, usually nucs. The vast majority of patients on treatment in Uganda take one of two cocktails: Triomune, which contains the drugs nevirapine, D4T, and 3TC; or the PEPFAR combination of efavirenz and Combivir (3TC and AZT). Both of these combinations pair a non-nuc backbone (nevirapine or efavirenz) with two nucs (3TC plus D4T or AZT). While these combinations are also commonly prescribed in the U.S., there

are also a huge number of Americans who take protease-inhibitor based regimens. By contrast, PI-based regimens are rare in Uganda. Protease inhibitors are much more expensive than non-nucs, and, as a result, donor-funded programs provide mainly NNRTI-based therapies so as to be able to treat the maximum number of patients.

In terms of efficacy, PIs and NNRTIs are equally good.[29] However, they differ significantly in their resistance patterns. As will be discussed in greater detail in Chapter 3, NNRTIs have what is called a "low genetic barrier" to resistance. This means that it takes only a single mutation to render a virus highly resistant to nevirapine or efavirenz. As a result, these drugs are very sensitive to gaps in adherence. A relatively minor decline in adherence—a small number of missed doses—can provide enough time for the virus to develop the one mutation it needs to become resistant. Resistance to PIs, on the other hand, requires numerous mutations and as a result is more difficult to develop (though it does eventually emerge). Because of this difference, doctors describe protease inhibitors as more "forgiving" of lapses in adherence than NNRTIs.

What this ultimately means is that the consequence of a missed dose is potentially much higher in Uganda than it is in the U.S. This is so not only because of the preponderance of NNRTI-based therapies, but also because there are many fewer options for drug resistant patients in Uganda than in the U.S. Although treating patients with antiretroviral resistance is complicated, it is routinely done successfully in the U.S. by changing drug regimens, often many times over the course of a patient's life. Patients in the U.S. have access to all the antiretrovirals available on the market, including a new

[29] This was not always the case. Protease inhibitors used to be less effective, before it was discovered that "boosting" them with a small dose of the drug ritonavir kept drug levels in the blood higher for a longer period of time. Now, these "boosted" PI regimens are the standard of care.

class of drugs called integrase inhibitors that can treat those who have become resistant to the other three drug classes.

In Uganda, the situation is very different. The drug combinations offered by the Global Fund and PEPFAR are similar enough that resistance to one often means cross-resistance to the other. Thus, patients who develop resistance to these "first-line" combinations must be switched to a "second-line" regimen containing a protease inhibitor. The donor programs do include a provision for one second-line combination (with a "backbone" of the protease inhibitor Kaletra) but availability is limited. Furthermore, because resistance is inevitable over time, long-term survival for people with AIDS often requires numerous changes in drug regimens over the years. Currently, there is no provision for patients in Uganda who develop resistance to the second-line combination. As Dr. Eunice at the Mukwano clinic told me, the "second line is our last at the moment."

Conclusion: Inclusion and Exclusion

Vinh-Kim Nguyen has written eloquently on strategies used by West African people with HIV to obtain antiretroviral drugs in the years preceding free treatment (Nguyen 2005). Focusing on Burkina Faso in the late 1990's, he describes how local AIDS service organizations were targeted by donor programs as a way to funnel their resources to communities. These local non-governmental organizations (NGOs) and community-based organizations (CBOs) did not offer antiretrovirals, but through their connections with donor programs abroad they were sometimes able to provide drugs for members of their staff or for volunteers. Thus, becoming involved with such an organization became an informal mechanism by which some people with HIV gained

access to the international "therapeutic economy" and got treatment for their disease. This kind of participation, Nguyen argues, is predicated on a certain kind of "self-fashioning"—a willingness to take on the identity of "HIV-positive" or "PLWHA" (Person Living With HIV/AIDS) in a public way, and embrace the self-help ethos of these AIDS service organizations aimed at promoting "living positively" (see also Kalafonos, n.d.). Nguyen describes this means of accessing drugs as an exercise in "therapeutic citizenship—a form of stateless citizenship whereby claims are made on a global order on the basis of one's biomedical condition, and responsibilities worked out in the context of local moral economies" (Nguyen 2005: 142). Although NGOs and CBOs were not the focus of my research, I saw signs of this kind of "therapeutic citizenship" in Uganda, such as the mention by one doctor that members of a local AIDS organization's "client council" were able to get treatment through the group, even before free drug programs had begun.[30]

Nguyen's analysis is a useful framework for understanding how, in the absence of a viable welfare state, individuals may seek to make claims for their care and rights on a more global order. What I hope this chapter has shown is that therapeutic citizenship is taking on new forms in the era of free treatment. This does not mean that the forms Nguyen describes are gone—I doubt this very strongly—rather, it means that new iterations are being added to the scenario he portrays. In Uganda, the state (in the form of the Ministry of Health) has become a significant player in the new donor-funded therapeutic economy, as has the U.S. government through PEPFAR. New forms of

[30] The group he was referring to was TASO, short for "The AIDS Service Organization," an organization that rose from Uganda's grass roots to become an internationally-known NGO. Since 1987, TASO has been providing support and services for HIV-positive Ugandans, as well as community outreach and HIV education, often through music and drama.

inclusion and exclusion from this economy have arisen both at a gross level—for example, in the selection of PEPFAR's 15 "focus countries"—and at the level of the everyday medical practice, in which decisions about who gets treated and how often hinge on otherwise mundane factors such as transportation, paperwork, and medical history as well as more abstract issues such as trust.

Thus far, the first two chapters of this dissertation have addressed broad, transnational questions regarding the advent of antiretroviral treatment in Uganda (as well as Africa in general) and the related shift in attention towards AIDS in Africa among North American HIV researchers. In these areas, the role of the political economy of antiretrovirals and structures of inclusion and exclusion such as "therapeutic citizenship" are often writ large. In my next two chapters I will focus on the much more narrow world of HIV laboratory science, for it is within the laboratories that understandings of HIV treatment and drug resistance are being worked out at the molecular level. While this focus on the relatively cloistered world of molecular biology may initially seem a far cry from the questions of life and death or inclusion and exclusion introduced in the first two chapters, I intend to show that they are in fact deeply related. The political economy of antiretrovirals, I will argue, is inherent within the tools of the laboratory, the tests use to assess drug resistance, and even within the design of the drugs themselves.

Chapter Three

FRAMING DRUG RESISTANCE

Introduction

Medical historian Charles Rosenberg uses the term "framing disease" to describe how we come to know a disease through processes of diagnosis, prognosis, illness experience, as well as our social, political, and institutional responses to it. "Disease," Rosenberg writes, "is at once a biological event, a generation-specific repertoire of verbal constructs reflecting medicine's intellectual and institutional history, an occasion of and potential legitimation for public policy, an aspect of social role and individual, intrapsychic, identity, a sanction for cultural values, and a structuring element in doctor and patient interactions. In some ways disease does not exist until we have agreed that it does, by *perceiving*, *naming*, and *responding* to it" (Rosenberg 1992: xiii, emphasis added). The previous chapter described how fears about the development of antiretroviral resistance in Africa came to be "framed" as a public health concern and how this framing legitimated a particular response to the epidemic in poor countries that prioritized prevention over treatment. This chapter will continue to explore the "framing" of HIV drug resistance through a critical examination of the *perceiving* and *naming* of resistance. I do so in order to show that the category of "resistant" HIV is, in fact, much more complicated and less straightforward than is often apparent in public scientific debates.

Rosenberg chooses the metaphor of "framing disease" in part as a corrective to the social constructionist literature of the 1970s and 1980s which, he argues, tends to be "overly functionalist" in its presentation of the construction of disease as a mechanism of

social control, as well as disproportionately concerned with "culturally resonant diagnoses…in which a biopathological mechanism is either unproven or unprovable" (hysteria, or homosexuality, for example). In this sense, his argument has some resonance with theoretical approaches from the field of science and technology studies, which—as described in Chapter 2—sees science and "society" as mutually or "co-" constituted and takes seriously the role played by non-human entities (disease organisms, machines, medicines, etc…) in this process (see Callon 1999, Star and Griesemer 1989, Clarke and Star 2003).

One of Rosenberg's complaints about social constructionism is that it loses track of the biological aspects of illness and, importantly, the process of disease definition and its consequences. Indeed, in my own research, I sometimes encountered skepticism from the HIV researchers I sought to interview, who—when I said I was interested in the "production" of knowledge about antiretroviral resistance—feared I was arguing that drug resistance did not, in fact, exist. As I explained to them, and as I elaborate in this chapter, my goal in interrogating the science of HIV drug resistance is not to prove that resistance does not exist but rather to describe the challenges, both biological and social, to its concise definition. The difficulty of defining drug resistance is important precisely because the term "resistant" is so often taken for granted in public discussions about the virus and its dangers. Taking resistance for granted is, in fact, crucial to maintaining the framing of drug-resistant HIV as a cause for major public health alarm—what I call its framing as a potential "super-bug." In exploring the complexity of what drug resistance actually is and what it means, I argue, alternative and more complex framings may emerge.

This chapter begins with the story of how drug-resistant HIV first came to be framed as a potential super-bug, as it is this framing that was initially so powerful in shaping public responses to the epidemic—and particularly to the international health debates around treatment access that were outlined in Chapter 2. Within this frame, the category of "drug resistant" went unquestioned; a "resistant" virus was taken at face value to mean a virus that could no longer be treated, and that through its spread posed a threat to the broader public health. I follow this story with a discussion of a series of recent scientific controversies surrounding HIV drug resistance; controversies which undermine the "super-bug" framing as well as complicate our understanding what "resistant" means. Lastly, the final section of this chapter goes on to give a detailed account of drug resistance testing, as it is through an examination of the laboratory assays designed to assess viral resistance that the slipperiness of its definition becomes most apparent. This slipperiness, I will argue, is in part a product of the gap between the growing prominence of molecular medicine (of which HIV drug resistance testing is a part) and older traditions of clinical medicine. This recent shift towards understanding disease and its treatment at the molecular level coincided with the emergence of the HIV epidemic, and, as a result, HIV medicine in wealthy industrialized countries became rapidly "molecularized." As I will describe in later chapters, this molecular framing of HIV presents problems both in the laboratory and at the clinic when the focus of American and European HIV research shifts towards poorer parts of the world.

Drug-resistant HIV: the making of a super-bug

Dr. Ron Aguila saw his first AIDS patients shortly after finishing his medical residency. At that time, in the early 1980's, the virus itself had not yet been identified.

Over the next twenty years he would make a name for himself in AIDS medicine, balancing continued work in the clinic with a prominent research career studying HIV drug resistance. By the time I met him in 2005, he was a nationally-recognized expert in the field. When we spoke, he surprised me by telling me that during the early years of the epidemic there was "huge skepticism" that HIV drug resistance would have any clinical relevance—i.e. that it would have any negative impact on patients. At that time the predominant view in medicine was that viruses, once they developed drug-resistant mutations, became too weak to replicate in the body and were thus unable to cause disease. This belief was based on clinical experience treating the herpes virus with the drug acyclovir. Dr. Aguila explained:

> At that point, there was huge skepticism that anti-viral resistance was at all relevant to the clinic. There was one experience with herpes simplex virus. It was common to find acyclovir-resistant virus, but acyclovir would still usually work. It was only in the rare case when it wouldn't work. And the reason for that, it was learned after a while, was that the acyclovir-resistant viruses didn't grow very well in the body. So even though they might be selected, they didn't really replicate well enough for it to cause any disease. And so that was the expectation for HIV resistance.

Aguila wanted to test this expectation, and made his mark in the field by putting together a group of doctors and virologists to study the impact of HIV drug resistance on patients. The team he organized analyzed the results of a large clinical trial conducted within the AIDS Clinical Trials Group (ACTG), a federally-funded program established in 1987 to support research in AIDS treatment. Their findings showed that drug-resistant HIV was in fact quite different from drug-resistant herpes. Drug-resistant HIV remained able to reproduce itself inside the body, and rendered AZT—the principle antiretroviral drug available at the time—useless in a matter of months:

> Dr. Aguila: So we did this big analysis of a large clinical trial within the ACTG. And basically we and subsequently many others showed that in fact people who had an AZT-resistant virus didn't respond to AZT and they didn't even respond all that well to related drugs. And all of our presentations were met with skepticism. I remember at the time, the guy who had just resigned from being the chair of the AIDS Clinical Trials Group, this big national research organization, challenged us when we presented our findings and said, "Well, this is just confounding. Everybody knows that drug resistance in viruses is meaningless. Go back and reanalyze your data. You've made a mistake somewhere." And we all said to him "no, we did it right! This is it!" And subsequently, we were proven right.

As it would turn out, Aguila's findings would coincide with historical events that rapidly caused the pendulum of scientific opinion to swing to the opposite extreme—a modern-day demonstration of Shapin and Schaffer's argument that the vindication of what is scientifically "right" is not inevitable, but rather an outcome contingent upon historical and social context (Shapin and Shaffer 1987).

The realization by Dr. Aguila and others that drug resistance was able to undermine any benefits offered by anti-HIV drugs came in the early 1990s, sharp on the heels of a well-publicized epidemic of drug-resistant tuberculosis in New York City. The timing of this outbreak and the public health alarm that it caused shifted the lens through which drug-resistant HIV was viewed. Rather than comparing HIV to drug-resistant herpes, it was likened to multi-drug resistant TB, which was potentially lethal and carried with it a particular image of danger marked by race and class (see also Bangsberg, Moss & Deeks 2004). Following the TB publicity, Aguila told me, the discourse "was very much the broad brushstroke that resistant HIV is not going to respond to anything." He was circumspect about this shift, laughing as he told me that "that's the pattern for much of HIV research. It's always from one extreme to the opposite extreme."

"A Loaded Gun"

In the late 1980s and early 1990s, tuberculosis in the U.S. began to climb at an alarming rate, spurred on by Reagan-era cuts in anti-tuberculosis programs and rising cases of HIV, which made infected individuals more susceptible to TB by weakening their immune systems. Significantly, however, the disease was relatively rare among the gay, white, middle-class patients who were the public face of AIDS activism in the U.S. Instead, TB appeared most commonly among HIV-positive Haitians (who were more likely to have been exposed to the disease in Haiti, where TB prevalence was high) and the HIV-positive homeless or incarcerated—as the overcrowding and poor ventilation common in both shelters and prisons facilitated TB transmission (Rosenthal 1990). The jump in tuberculosis was particularly acute in New York City, where the TB rate in 1991 topped 4000 for the first time since 1967 (Specter 1992). In addition, many more of these TB cases were drug-resistant than ever before. An outbreak of multi-drug resistant TB (MDR-TB) in a New York prison resulted in the deaths of 13 inmates in 1991 (McFadden 1991). Tuberculosis experts quoted in the press argued that resistant TB was on the rise because many patients were failing to complete the months-long regimen of antibiotics required to cure active tuberculosis, often because of mental illness, drug abuse, and/or homelessness.

Treatment of MDR-TB is possible but requires an even longer course of harsher drugs, and has a lower chance of succeeding. In addition, like drug-susceptible tuberculosis, MDR-TB can be transmitted from person to person through the air. Understandably, health officials were alarmed at the possibility of a growing epidemic of a microbe that was difficult to treat, easy to spread, and potentially lethal. As a result, the

city began the enforced hospitalization of tuberculosis patients who repeatedly failed to complete their treatment. These modern-day Typhoid Marys were most often African-Americans from the most marginal fringes of society—the addicted, the mentally ill, and the homeless.[31] Similar issues arose in other U.S. cities as they confronted their own growing rates of tuberculosis.

Gauging Threat of Recalcitrant TB Patients

By MIREYA NAVARRO

Milton A. Ellison is considered a walking public health threat.

A 34-year-old homeless man from New York City with tuberculosis, Mr. Ellison has repeatedly failed to take the medicine that he needs. So last month health officials took a step that they said was the only way to protect Mr. Ellison and the people around him: They detained him in Orange County and took him to a hospital where he was guarded by sheriff's deputies and shackled by wrist and ankle to his bed.

Mr. Ellison, who has a history of schizophrenia, raised questions in a rumbling one-hour interview a week and a half ago, shortly after his release from the hospital, about whether he had actually been sick with TB, much less contagious.

'I Couldn't Go Anywhere'

"They had me chained to the bed for three weeks," he said. "Why is that necessary? If I were ill, I couldn't go anywhere."

Increasingly, as tuberculosis has made a comeback, especially among homeless people and those infected with the virus that causes AIDS, states are grappling with ways to deal with problem patients like Mr. Ellison. Success in controlling the epidemic hinges on getting people to take their medicine, because those who do not complete treatment can develop drug-resistant strains of TB and infect others with it. In Orange County, Mr. Ellison was found to be resistant to one drug.

Cases like Mr. Ellison's are a minority among TB patients, health officials say. Although many patients are lax when it comes to completing therapy,

Alan Zale for The New York Times

Milton A. Ellison, at a bus stop after leaving a hospital in Orange County, N.Y., where he had been detained because of tuberculosis.

Front page, *New York Times*, April 14, 1992

Coverage of and response to the outbreak of MDR-TB in the U.S. established a clear discursive link between poor adherence and a threat to public health, with one expert going so far as to compare walking around with MDR-TB to walking around with "a loaded gun" (NYT 11/18/91). This link was also marked by race and class, as the majority of the most "recalcitrant" patients were black and poor.

[31] Of 33 tuberculosis patients detained by the NYC Public Health Dept. between January of 1988 and April of 1991, 79% were black, 79% were drug users, 49% were homeless, and 61% were men (NYT 3/10/93). Many were also mentally ill, and had been hospitalized for TB several times previously. Seventy-three percent had drug-resistant tuberculosis (Navarro 1992). The law under which tuberculosis patients were forcibly hospitalized dates from the era of Mary Mallon—"Typhoid Mary"—who was believed to have infected 50 people with typhoid fever prior to 1915 (Barbanel 1991).

This coding of incomplete adherence as a threat to not only one's own health but to the general public, as well as the media image of the poorly adherent patient as poor and black, would play a significant role in subsequent debates over the threat posed by drug-resistant HIV. Like TB, successful HIV treatment requires patients to take a combination of several drugs over an extended period of time. Understandably, adhering to such regimens is challenging for many patients—especially given that the treatment for HIV is indefinite, with no endpoint in sight. Having witnessed the recent upsurge of MDR-TB, many AIDS doctors feared the development of drug-resistant strains of HIV among their poorly-adherent patients. Clinicians had to weigh the individual benefit that their patients might receive from treatment—however partial—and the potential threat they could pose to public health as carriers and transmitters of drug-resistant viral strains. Some doctors delayed prescribing ARVs to patients they believed would be unable to adhere (Sontag and Richardson 1997**;** Gerbert et. al. 2000), though studies later showed that clinicians' estimates of who would and would not be adherent were no more accurate than random guessing (Tchetgen et. al. 2001; Paterson et. al. 2000). Often, these patients bore the same markers as many of the carriers of MDR-TB: poverty, drug addiction, homelessness, mental illness, and black skin.

Once pressure began to mount for antiretroviral treatment in Africa, a similar discourse resurfaced with a new international slant. While treatment skeptics did not make direct comparisons between the U.S. urban poor and patients in Africa, it seems noteworthy—as Dr. Beale told me, with intentional irony—that the targets of fear remained "poor black people." In addition, this discourse was remarkable not only for its invocation of the centuries-old trope of Africa as a "diseased continent" (Vaughn 1991;

Comaroff 1993), but also because it emerged despite great scientific uncertainty about the nature and consequences of drug-resistant HIV.

Drug Resistance Controversies: Technical, Political, Moral

Sociologist of science Dorothy Nelkin argues that scientific controversies often take the form of disputes over technical issues, but that they are in reality often debates over moral and political issues (Nelkin 1995). Steve Epstein's work on AIDS and controversy in the U.S. provides a good example of this. In controversies over HIV treatment in the late 1980s and early 1990s, Epstein describes how moral and political debates over patients' rights, gay rights, and who counted as a scientific "expert" were fought out in the form of largely technical arguments over the proper design of pharmaceutical clinical trials (Epstein 1996).

Likewise, in the case of HIV drug resistance, technical debates are never far from moral and political controversies. The framing of drug-resistant virus as a super-bug akin to MDR-TB (with similar racial and class overtones) is an example of how the political question of who *gets* treatment and the moral question of who *deserves* it were often articulated through the technical language of epidemiology and public health. Interestingly, it was from within these more technical domains that the frame of "super-bug" later confronted some of its biggest challenges. This happened when drug resistance researchers began to question both the relationship between adherence and resistance and the relationship of resistance to individual and public health.

Resistance and Adherence: when good patients get bad results

Based on previous experience with tuberculosis treatment, the belief that poor adherence would lead to drug resistance was widely accepted from early on in the field of AIDS medicine. Because of the virus's natural ability to mutate rapidly, patients were

warned of the danger of missing even one dose of their medications. In both the research literature and published treatment guidelines, the importance of assuring patient adherence continues to be stressed as a key tool for warding off the development of drug-resistant virus (Altice and Friedland 1998; Chesney et. al. 2000; Tchetgen et. al. 2001; Chesney 2003; DHHS 2003). A review article published by a leading AIDS prevention researcher argued that the prevention of HIV drug resistance required "near perfect" adherence to antiretrovirals, in the range of 95% or higher (Chesney 2003).

In 2002, some HIV researchers began to challenge this accepted wisdom, posing the provocative question, "Is average adherence to HIV antiretroviral therapy enough?" (Bangsberg and Deeks 2002). These researchers argued that the association between poor adherence and resistance to ARVs was based on inadequate research, and that recent studies suggested a more complex relationship between adherence and resistance that varied according to drug class. In their own research among the urban poor, they found that drug resistance was most concentrated among *highly* adherent patients, with nearly a quarter of resistance occurring in patients who took 92-100% of their medications (Bangsberg et. al. 2003). This relationship was particularly strong for protease inhibitors, but also held for NRTIs. (NNRTIs, by contrast, showed nearly the opposite relationship, with resistance emerging at low to moderate levels of adherence as the conventional wisdom would have predicted.)[32]

[32] Though initially counter-intuitive, these results make sense in light of the different genetic barriers to resistance that characterize different classes of antiretrovirals. Resistance occurs when there is viral replication in the presence of drug. As described in Chapter 2, protease inhibitors require many more mutations to become completely drug resistant than do NNRTIs. Patients who were poorly adherent to a PI-based regimen simply did not create enough drug pressure to cause the virus to mutate into a drug-resistant strain. But in patients who were highly—but not perfectly—adherent, significant drug pressure combined with continued viral replication to produce the multiple mutations necessary to generate PI-resistant virus.

Given the common belief that missing even one dose of ARVs could be dangerous, these findings were provocative. They also complicated the moral calculus established during the MDR-TB outbreak that linked poor adherence, "recalcitrant" patients, and dangerous, drug-resistant disease as suddenly it was the "good" patients who were developing drug resistance.

The Silver Lining of Drug Resistance

This controversy over the cause of drug resistance coincided with a related debate over the consequences of resistance. Physicians studying the management of patients with resistance to multiple HIV drugs began publishing data showing that many patients with drug resistance continued to do well clinically (Deeks et. al. 2000) In other words, even though testing showed them to be "resistant" to the drugs they were on, the drugs were continuing preserve their health. These patients' CD4 counts remained stable—meaning their immune systems continued to function—and the level of virus in their blood (their viral load) remained relatively low. The reason behind this, the researchers argued, was that resistance mutations weakened the virus. As a result, resistant viruses were less able to replicate efficiently, which ended up keeping viral loads low and preserving the health of the patient. Furthermore, these weaker viruses appeared to be more difficult to transmit to others, suggesting that drug-resistant HIV might be less of a public health threat than had been initially thought. This reduced "replicative capacity" or "viral fitness" was an unexpected benefit of many drug resistance mutations—a sort of a silver lining to an otherwise dark cloud. To recall Dr. Aguila's comparison, the findings suggested that drug-resistant HIV perhaps bore closer resemblance to drug resistant herpes than to drug-resistant TB after all.

Although they are now widely accepted, these studies were very controversial when first presented at scientific meetings. David Capelli, a young Ph.D. involved in the research on viral fitness, described scientific conference sessions that ended up in "shouting matches" over their data:

> I think people were very concerned about what the message of our work could be….We were—I think "accused" is the right word—of saying that we thought it was okay for people to have drug resistance. And that maybe it was even good news. You know, and I think even though we tried to very carefully deliver our message onto the broadest stages in the field, I think there was still active misinterpretation of that message. We were never trying to suggest that we thought drug resistance was okay.

Dr. Capelli's account of the controversy suggests that the debate over this research was moral as much as it was scientific. The implication that drug resistance might be "okay" was volatile. Just as the controversial findings about adherence and resistance had upset the moral equation of "bad" (non-adherent) patients to "bad" (drug-resistant) virus, the studies on viral fitness further complicated this calculus by suggesting that drug resistance might actually have some clinical benefits.

Indeed, the knowledge that certain resistance mutations might weaken the virus was useful to clinicians, especially in the treatment of patients who were resistant to most drugs and had few remaining treatment options. It meant that leaving these patients on their regimens might actually continue to do them some good even if they were technically resistant to the drugs. Signficantly, this knowledge was also useful to drug companies, as it provided an alternative, positive spin for resistance mutations that would otherwise be seen as a strike against their product.

For example, Dr. Aguila described being visited by a representative from GlaxoSmithKline, the manufacturer of 3TC, an NRTI used in many triple-drug regimens.

This drug commonly causes a resistance mutation referred to as M184V. In addition to causing 3TC resistance, M184V also significantly weakens the virus. Unaware that the Dr. Aguila was a leading drug resistance researcher in addition to being a clinician, the company representative showed him some drug product information that listed only the beneficial effects of the mutation, and not the fact that it also caused resistance. This was in contradiction to guidelines issued by the International AIDS Society-U.S.A (IAS-U.S.A), an independent body of experts, which listed M184V as resistance mutation.[33] Because Dr. Aguila was an expert on resistance, he recognized the omission. However, though the IAS-U.S.A guidelines are widely used and respected, there still exists no single standardized list of resistance mutations, making it easy for different bodies to compile lists that reflect their own interests. In this case, the drug company had been successfully marketing an alternative interpretation of the mutation directly to doctors. As Dr. Aguila told me:

> Three or four years ago, it was very common for doctors to believe that if you were on this drug and you developed this one particular resistance mutation, you didn't really need to stop the drug. You could keep the drug going. In vitro, it would look like the virus was resistant to the drug. But the drug was still providing benefit. …There may be some truth to it, but the reality is that you know it's a good way to sell the drug. You never have to stop using it. Just always keep using it. And so the drug company very early on recognized this as a good marketing tactic and very aggressively marketed the decreased fitness of the mutant [virus].

[33] In fact, Dr. Aguila explained to me, the IAS-U.S.A list was developed as an attempt to generate an objective list in the face of pressure from pharmaceutical interests. In his words: "Well, everybody recognized that there were different tables and lists out there. Some of them were being promoted heavily by some of the drug companies to say that, you know, 'oh, this mutation that's selected by my drug is really not a bad mutation, and it doesn't confer resistance.' So that was what really drove having an objective, standardized listing so physicians would be able to counter the drug detail men and say, 'Well, no. Here's what the IAS-U.S.A says. You're wrong.'"

In actuality, both interpretations of M184V are true—the mutation both reduces the drug's effectiveness *and* weakens the virus—but the company was seeking to highlight the latter while obscuring the former, essentially using the mutation as a selling point.

Companies use drug resistance as a marketing tool in other ways as well—for example, by arguing that their drug causes less resistance than those of competitors. This practice is facilitated by FDA regulations allowing drug companies to withhold their drug resistance data from the public as "proprietary" information (Shafer 2005). The result is that the company's interpretation of their drug's resistance profile is never subjected to independent scientific scrutiny outside the FDA. Dr. Aguila described how this secrecy led to a protracted controversy about the drug Kaletra (lopinavir/ritonavir), a commonly-used protease inhibitor manufactured by Abbott Laboratories. At the time, he was a member of the IAS-U.S.A sub-committee that wrote the group's guidelines on interpreting drug resistance mutations:

> The drug company had published that [Kaletra causes] "x" number of mutations. But there were data presented in lots of scientific meetings suggesting others. And the drug company kept saying, "No, no, no. In our data, we don't see that." And so we basically added mutations [to the IAS-U.S.A list] based on what was being presented in scientific meetings and had counter-letters and arguments from the drug company who said, "No, that's wrong. It's not a mutation." Well, it turned out a year or so later that four or five different groups all had independent data saying some additional mutations did cause resistance to Kaletra.

In other words, Abbot argued that the company's clinical trial data showed only a few mutations that caused resistance to their drug, in contradiction to other studies that showed several more. The company argued for the IAS-U.S.A to accept their findings as definitive, but because they were not required to make their resistance data public, the IAS-U.S.A was not able to scrutinize their results directly. Ultimately, the group rejected

Abbott's argument in light of contradictory findings by several independent studies. In the end, Aguila and the other scientists were left to wonder whether the company's data was simply incorrect, correct but mistakenly interpreted, or purposely misrepresented.

From "Super-Bug" to "Non-story"

These debates over viral fitness, mutation interpretation, and the relationship of adherence to resistance were sometimes heated, but they were largely limited to the scientific arena of conferences and medical journals. However, in February of 2005, HIV drug resistance burst into the mainstream news media when the New York City Department of Public Health held a press conference to announce the discovery of a man who appeared to have been infected by a "strain" of HIV that was both highly drug resistant and extremely aggressive. Given that most of the recent anxiety about resistant virus had been targeted at the developing world, the arrival of a candidate super-bug in the U.S. was somewhat ironic.

The patient, a gay man in his 40s, showed resistance to all three major classes of antiretrovirals (PIs, NNRTIs, and NRTIs) even though he had only recently tested HIV-positive and had never taken any antiretroviral drugs previously. Furthermore, his CD4 count was quite low (80 cells) and his disease had progressed to an AIDS diagnosis even though he was believed to have become infected only a few months earlier. It was this combination of multi-drug resistance and aggressive virulence that alarmed the New York City Department of Health and Mental Hygiene and led them to take the unusual step of holding a press conference to announce the finding. Although viruses with each of these characteristics had been identified before, it was uncommon to find them both in a single virus.

The health officials' concern over the virus was fueled by the patient's description of his sexual activity. In the department's press release, the infected man was described as a methamphetamine addict who regularly engaged in anonymous, unprotected anal sex with other men while high on crystal meth. Calling the case a "wake-up call" and citing rising rates of sexually transmitted disease among gay men, the New York City Health Commissioner urged the gay community to do more to stop the spread of HIV and methamphetamine use among its members (New York City Dept. of Health and Mental Hygiene 2005). The department also issued an alert to clinicians and hospitals, asking them to screen their HIV-positive patients for evidence of the resistant virus. This alarm was echoed in a case study of the infection published a month later in the medical journal the *Lancet*, in which a group of doctors at New York's prestigious Aaron Diamond AIDS Research Center asserted that the case had "great public health ramifications" (Markowitz et. al. 2005). The article carried particular weight because its senior author was Dr. David Ho, a pioneering AIDS researcher who had been named Man of the Year by *Time* Magazine in 1996 for his major contributions to the development of combination antiretroviral therapy.

The news media jumped on the story, producing multiple articles on the arrival of the potential "super bug" (Santora and Altman 2005a; Perez-Pena 2005; Edozien 2005; Honigsbaum 2005). Just as quickly, the Health Commissioner and the New York City Department of Health came under fire both from gay activists—who objected to the portrayal of gay men "as crazed drug addicts…wantonly spreading a killer bug"—and from fellow AIDS experts who felt that the alarm over the case was overly hasty (Santora and Altman 2005b). At a major scientific AIDS conference that was held

(coincidentally) just two weeks after news of the infection was made public, last-minute changes were made to the conference schedule in order to devote an entire session to discussion of the case (Conference on Retroviruses and Opportunistic Infections 2005). Opinions remained divided over whether the decision to publicize the case had been important to protect the public's health, or ill-informed fear-mongering.

In the end, some of the key assertions in the Health Department's press release proved to be overstated. Although the virus was in fact multi-drug resistant, it was not true—as the press release had reported—that it "did not respond to three classes of anti-retroviral medication." In fact, several months later the patient was reported to be doing well on therapy—perhaps another example of a technically "resistant" patient who was nonetheless able to benefit clinically from medication. In addition, the department's claim that the patient seemed to have progressed rapidly to AIDS—perhaps as quickly as "within two to three months" of becoming infected—was rejected by many experts, who thought it was more likely that he was infected closer to 20 months earlier, shortly after last testing HIV-negative in May 2003 (Volberding 2005). Because HIV infection often takes close to 10 years to progress to AIDS, 20 months was still unusually fast—though not unprecedented. However, these experts argued, the patient's rapid disease progression might have little to do with the virus itself, and could instead be the result of what they called "host factors"—in other words, characteristics of the patient's immune system, as well as his addiction—rather than a particularly aggressive virus. When I asked Dr. Aguila about the case four months after the initial publicity, he said that the scientific consensus was that the initial reaction to the infection had been "hyperbole." In his opinion, most experts agreed that "this was worrisome and needed investigation, but

it's a single case and not yet an epidemic." Dr. Paul Volberding, director of the Center for AIDS Research at the University of California San Francisco and a senior scientist in the field, was more blunt, telling the *New York Times*: "This is a non-story" (NYT 2/21/05).

Making Resistance: Genotyping and Phenotyping

Given these controversies over the causes and consequences of drug resistance—over its "framing"—it seems important to dig deeper and examine what drug resistance, in fact, *is*. What is antiretroviral resistance exactly, and how is it defined? This is in some ways an open question. The definition of resistance varies according to the specific antiretroviral medication in question and the tools used to measure it. Resistance is not a self-evident measurement, but rather the product of numerous social negotiations over the use and interpretation of technologies, the identification and categorization of genetic sequences, and the definition of drug susceptibility thresholds. Understanding this requires a close examination of the drug resistance assay.

Over the past decade, the complexity of both HIV treatment and drug resistance have become much better understood than during Dr. Aguila's early years in the clinic. Scientific understanding of drug-resistant HIV was shaped by the development of two different diagnostic "assays" (tests) designed to measure whether or not a patient's virus had developed resistance to antiretrovirals. Scholars in the anthropology and sociology of science have written extensively about the relationship between technology and the development of scientific knowledge. This body of work is useful for understanding the role played by drug resistance assays in the development of knowledge about HIV. In many ways, these tests act as "inscription devices" by transforming otherwise chaotic

information into concise, legible data usable by scientists and doctors (Latour and Woolgar 1986). As such, these scientific tools and the knowledge they generate "co-construct" one another (Clarke and Fujimura 1992). This means that drug resistance tests and drug resistance itself are mutually continuative, making the definition of drug resistance inseparable from the particular technologies used to measure it. It follows, then, that the two different assays currently in use imply somewhat different definitions of resistance.

The following examination of drug resistance assays is what STS scholar Bruno Latour would call "opening a black box"—subjecting a taken-for-granted scientific fact to a kind of intellectual surgery, whereby the inner workings that make it possible are revealed. Much of Latour's work revolves around calling these "black boxes" of science into question:

> The word **black box** is used by cyberneticians whenever a piece of machinery or a set of commands is too complex. In its place they draw a little box about which they need to know nothing but its input and output….That is, no matter how controversial their history, how complex their inner workings, how large the commercial or academic networks that hold him in place, only their input and output count (Latour 1987).

It is my argument that framing of drug-resistant HIV as a potential super-bug relies on the continued black-boxing of the category of "resistance" in order to maintain its coherence. However, both in the laboratory and in clinical practice, this category of resistance as well as the assays used to measure it manifest as complex and contingent entities. Exploring how resistance is actually "made" allows us to understand its inherently slippery, multiple, and often contradictory nature—an important counterpoint to the simplistic and monolithic way in which resistance is invoked as a threat in public debates.

Currently, there are two types of commercially available assays that are used to assess drug resistance in the HIV virus—the genotype and the phenotype. Phenotype assays work by exposing a sample of the patient's HIV to one or more antiretroviral drugs *in vitro*. Resistance is determined by measuring the ability of HIV to replicate in the presence of these drugs. Thus, phenotype assays provide a direct measure of the virus's susceptibility to drugs. However, these tests are both costly and time-consuming. Genotype assays are cheaper and faster. These tests detect mutations in viral genes that are believed to result in drug resistance. Thus, they are an indirect measure of resistance because they do not actually examine how the virus behaves in the presence of a drug. Because these assays are cheaper and faster than phenotype assays, they have gained rapid acceptance in HIV research and, more recently, clinical practice (see Hirsch et. al. 2000).

Genotyping: making sense of a "quasi-species"

Laboratory technician Angela Zamora explained to me that the genotype assay usually took her three days to run. If I wanted to observe the complete process, she said, I would have to return to the virology laboratory for three days in a row. I agreed, and arrived at the laboratory on the appointed day. The lab was affiliated with Yerba Buena University's teaching hospital, and provided genotyping for the hospital's HIV clinic as well as for university-based drug resistance research studies.

On the first day, Angela performed the "extraction." This initial step involved separating the viral RNA (i.e., the virus's genetic information) from patient blood samples that had been sent to the lab for testing. (Whereas most organisms carry their genetic information in the form of DNA, HIV belongs to a group of viruses known as

"retroviruses" which have the unusual characteristic of carrying their genetic information in the form of RNA). In layperson's terms, the extraction consisted of forcing patient plasma samples through tiny filters equipped with microscopic holes that would sift out the viral RNA. Next Angela used a technology called RT-PCR (reverse transcription-polymerase chain reaction) which converted the viral RNA to DNA form and rapidly generated millions of copies of it. This volume of DNA was necessary to perform the next step in the assay on the following day.

This next step involved separating out the segments of the viral DNA that were relevant for drug resistance testing. Currently, most antiretroviral drugs available act by interfering with one of two enzymes involved in viral replication: protease or reverse transcriptase. For this reason, genotype resistance assays typically examine only the parts of the viral DNA that code for these enzymes, as it is believed that any mutations responsible for drug resistance would most likely be located in these areas of the genome.

On the third day Angela performed the "analysis." She described this as the "best part" of the assay, because it involved less of the monotonous pipetting and centrifuging that had taken up the first two days, and more interpretive work in order to determine which mutations were present in the viral DNA. In order to perform the analysis, Angela took the samples she had prepared the previous day and subjected them to electrophoresis—an electric current—which caused the DNA segments to arrange themselves in such a way that they could be "read" by a computer. Sitting in front of the computer screen, Angela then engaged in the most interpretive aspect of her job by helping code the portions of the DNA that the computer found ambiguous.

It was during this process of analysis that the process of inscription—creating order from disorder—became most apparent. Due to its rapid mutation rate, HIV is an inherently chaotic object of study. Any given HIV-positive individual carries millions of copies of the virus that are each slightly genetically different from one another—a "population" of viruses, rather than identical copies of a single virus. As I describe further in chapter 4, scientists who study HIV at the genetic level must constantly work to generate coherence from this extremely diverse object of study. Genotype assays are useful because they are able to take the *population* of diverse viruses carried by any one patient and generate from this population a single, aggregate list of drug resistance mutations.

Angela brought up a window on the computer showing the progress of her first sample. The window showed a graph of four overlapping lines, each a different color, representing the four nucleic acid bases that are the basic building blocks of all DNA and RNA. Whatever line showed the highest peak at a given location reflected which nucleic acid base (adenine, guanine, cytosine, and thymine) occupied that space on the DNA in *most* of the patient's viral population. For purposes of comparison, this graph was juxtaposed next to a "reference sequence" taken from a drug-sensitive virus.

The "analysis" step in resistance genotyping, from the Trugene genotype assay (Bayer Healthcare Diagnostics).

Disagreements between the base sequence of the sample DNA and the reference sequence were highlighted in green by the computer. These disagreements indicated possible mutations in the patient's virus. Angela's job was to examine these sites more closely and decide whether a mutation was actually present, or whether the computer reading had merely been muddled due to "background activity" by other bases—"background," in this case, indicating the diversity of the patient's viral population. Angela told me that basically what she was doing was checking to see if the computer was right. She moved very quickly, able to take in all the information in the graphs and make a decision rapidly. Occasionally there would be a base that was difficult to interpret, and she'd leave it coded as a "mixture" of bases at that site—an indication that the patient's viral population was fairly equally divided between viruses that carried, for

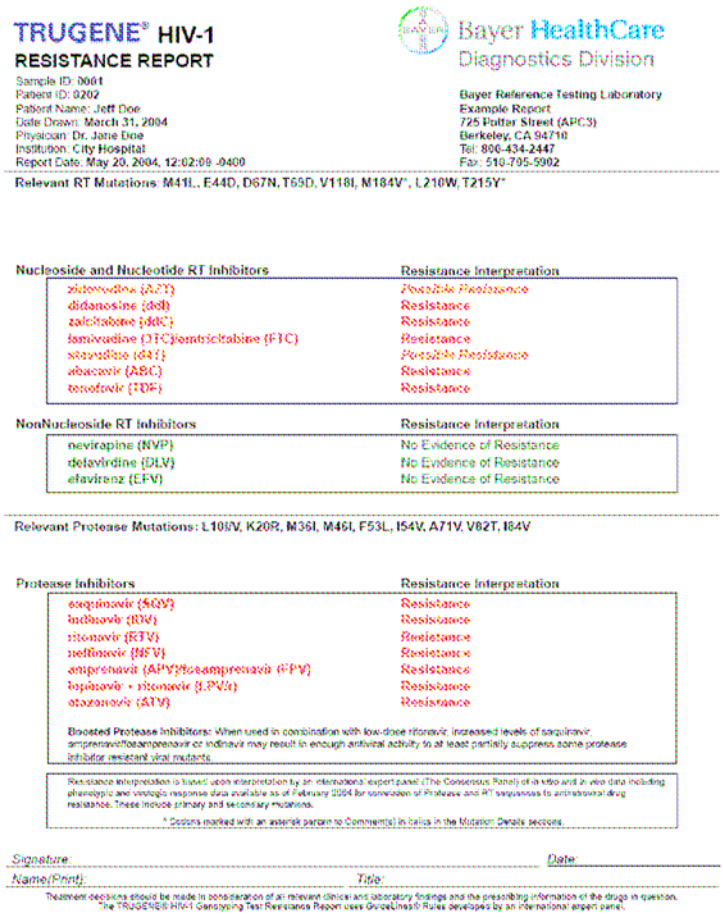
example, adenine (A) and thymine (T) at that location on the genome. There were also times when she just had to make her own call: "That looks like a T to me, I'm going to put a T…sometimes you just have to use your judgment….After a while you get used to it."

After completing the analysis of a patient's sample, Angela printed out two reports. One was the "mutation report," which listed *all* the mutations found in the sample, regardless of whether or not they were mutations that indicated drug resistance. The second report was the "resistance report," which listed the drugs to which the patient should be resistant, based on the mutations listed in the mutation report. Which mutations are considered "resistance mutations" is constantly evolving as new drugs and new studies of resistance emerge. Furthermore, there is no standardized algorithm correlating mutations and resistance shared by all scientists. In the case of the commercial genotype assay that Angela was using, the computer generated the resistance report based on the manufacturer's algorithm. Other researchers refer to the mutation lists published by the IAS-U.S.A or a similar European body. Still others consider a list put out by a group at Stanford University to be the "gold standard." Although none of these mutation lists are radically different, some do have the reputation of being more up-to-date than others.

For this reason, the mutation report is primarily used by researchers, and the resistance report by clinicians. Aware of the inconsistency of resistance interpretations, researchers prefer to report their data in the form of mutations (i.e., "we found patients on drug X developed mutation Y") rather than in the form of resistance ("we found patients on drug X developed resistance"). For example, in a meeting with his research team

about their drug resistance study in Uganda, Dr. Beale instructed his statistician and data manager on this point, telling them, "The problem is that mutations are fixed, but the resistance algorithms change. The definitions for resistance are published each year. We need a database that will be flexible enough to keep up with these changes. We'll never report resistance and [drug] sensitivity; we'll report the codon number and the mutation."

Clinicians, on the other hand, are less likely to be interested in specific mutations unless they are involved in drug resistance research. In making treatment decisions for their patients, it is more useful to be told what drugs the patient remains sensitive to rather than the viral mutations. Thus, in the end it was the resistance report—not the mutation report—that Angela would send back to the patient's physician.



TRUGENE® HIV-1
RESISTANCE REPORT

Sample ID: 0001
Patient ID: 0202
Patient Name: Jeff Doe
Date Drawn: March 31, 2004
Physician: Dr. Jane Doe
Institution: City Hospital
Report Date: May 20, 2004, 12:02:09 -0400

Bayer HealthCare
Diagnostics Division

Bayer Reference Testing Laboratory
Example Report
725 Potter Street (APC3)
Berkeley, CA 94710
Tel: 800-434-2447
Fax: 510-705-5902

Relevant RT Mutations: M41L, E44D, D67N, T69D, V118I, M184V*, L210W, T215Y*

Nucleoside and Nucleotide RT Inhibitors	Resistance Interpretation
zidovudine (AZT)	Possible Resistance
didanosine (ddI)	Resistance
zalcitabine (ddC)	Resistance
lamivudine (3TC)/emtricitabine (FTC)	Resistance
stavudine (d4T)	Possible Resistance
abacavir (ABC)	Resistance
tenofovir (TDF)	Resistance

NonNucleoside RT Inhibitors	Resistance Interpretation
nevirapine (NVP)	No Evidence of Resistance
delavirdine (DLV)	No Evidence of Resistance
efavirenz (EFV)	No Evidence of Resistance

Relevant Protease Mutations: L10I/V, K20R, M36I, M46I, F53L, I54V, A71V, V82T, I84V

Protease Inhibitors	Resistance Interpretation
saquinavir (SQV)	Resistance
indinavir (IDV)	Resistance
ritonavir (RTV)	Resistance
nelfinavir (NFV)	Resistance
amprenavir (APV)/fosamprenavir (FPV)	Resistance
lopinavir + ritonavir (LPV/r)	Resistance
atazanavir (ATV)	Resistance

Boosted Protease Inhibitors: When used in combination with low-dose ritonavir, increased levels of saquinavir, amprenavir/fosamprenavir or indinavir may result in enough antiviral activity to at least partially suppress some protease inhibitor resistant viral mutants.

Resistance interpretation is based upon interpretation by an international expert panel (The Consensus Panel) of in vitro and in vivo data including phenotypic and virologic response data available as of February 2004 for correlation of Protease and RT sequences to antiretroviral drug resistance. These include primary and secondary mutations.

* Codons marked with an asterisk pertain to Comment(s) in italics in the Mutation Details section.

Signature: Date:
Name(Print): Title:

Treatment decisions should be made in consideration of all relevant clinical and laboratory findings and the prescribing information of the drugs in question.
*The TRUGENE® HIV-1 Genotyping Test Resistance Report uses GuideLines® Rules developed by an international expert panel.

The Trugene Resistance Report

Both reports can be seen as the end-product of multiple inscriptions in the Latourian sense. First, a diverse population of millions of slightly different HIV viruses—what scientists call a "quasi-species"—were reduced to their genetic material. Next, this genetic material was further reduced to the specific segments of the genome that coded for the enzymes protease and reverse transcriptase. These segments—still representing millions of different viruses—were then read in aggregate form by the computer and, with Angela's assistance, transformed into a single list of mutations and printed in the form of the Mutation Report. Lastly, the Resistance Report was generated through one more round of inscription in which the meaning of these mutations was interpreted, further distilling the complexity of the patient's virus into three categories: "resistant," "possibly resistant," and "no evidence of resistance."

Phenotyping: the spectrum of resistance

The use of a genotype assay to determine drug resistance is a fairly new phenomenon. This molecular technique differs significantly from older methods of measuring drug resistance, which are still used to test for resistance to other drugs such as antibiotics. Put simply, the older method involves placing bacteria from a patient's infection in a petri dish, adding drugs, and seeing if the bacteria are able to grow. If the bacteria die, they are drug-susceptible; if they do not, they are drug-resistant.

Unlike bacteria, HIV can be difficult to grow in a laboratory—one reason why HIV resistance is most commonly measured using the genotype assay. However, a test analogous to this petri dish method does exist for HIV. This test, the phenotype resistance assay, is important for several reasons. First, genotype testing would not be possible without it, as genotypes provide only an indirect measure of resistance through

the detection of mutations. In order to know that these mutations do, in fact, cause a virus to become less susceptible to drugs, these mutations must be correlated with phenotype results in which mutated viruses were exposed directly to antiretrovirals. Secondly, and more relevant to my purposes in this chapter, the phenotype complicates the simplistic way in which drug resistance has been framed in public and international health debates over HIV treatment. It does so by revealing the way in which HIV drug resistance exists on a spectrum. Often, it is too simplistic to say that a virus "is" or "is not" drug resistant. A patient's virus may be more or less drug-resistant; in addition, it may be simultaneously resistant to some drugs in a regimen and hyper-susceptible to others.[34]

The market for phenotype assays is dominated by only a handful of companies world-wide, one of which is located in South San Francisco, a largely industrial suburb lying in between the city of San Francisco and the international airport. This company, Virologic, makes a phenotype test that is widely used in research, clinics, and industry. Virologic's lead researcher is Chris Petropoulos, a warm and friendly scientist who sports a graying ponytail and rides a motorcycle to work. He explained the science of the phenotype test to me while walking me through the company's laboratories. First, the virus's genetic material (RNA) is removed and spliced into a bacterium. This bacterium, which has been specially engineered for the job, then produces a high number of copies of the virus. (These viral copies or "clones" are non-infectious, making them safe for scientists to work with). In other words, when placed on a petri dish, these bacteria essentially act as miniature factories for the production of virus. To show me what he

[34] Again, as with the genotype, the phenotype is not measuring a single virus but rather the response of a *population* of viruses to a drug.

meant, he reached into one of the lab's trash bins and pulled out a discarded petri dish. Holding it up to the light, he pointed out the spots on the dish's surface that indicated growing colonies of cloned virus. It is these colonies that are collected and exposed to antiretroviral drugs to test for resistance.

Whether or not a virus is deemed resistant to a drug is determined by how well the antiretroviral is able to impede viral replication. If the drug stops the virus in its tracks, the virus is drug-susceptible (i.e., not resistant). If the virus replicates well despite the presence of an antiretroviral, it is resistant to that drug. Often, the result is somewhere in between, meaning the virus is only partially resistant.

The Cut-Off Question

Determining whether a virus is resistant is further complicated by the gap between how a virus acts in the lab and how it may act within a patient. Because phenotype assays measure resistance along a continuum, doctors and scientists must decide which points along this continuum constitute the line between "susceptible," "partially susceptible," and "resistant." These points, called "cut-offs," vary depending on which criteria are used. Initially, a *technical* cut-off was used, where the virus being tested was compared to a commonly-used laboratory reference strain of HIV (see chapter 4 for an in-depth exploration of the "reference strain"). However, the extreme diversity of HIV made this technical cut-off limited in applicability outside the laboratory. A move was made to use *biological* cut-offs, where resistance was based on a comparison to viruses taken from treatment-naïve patients. Still, this comparison was based on how these viruses responded to drugs in the lab, not in the human body, and—as one Yerba Buena

physician told me—"Clinicians are saying, 'yeah, that's great, that's what happens in the lab. But my patient's not a lab. What happens when I give it to my patient?'"

Currently, there is a push in HIV medicine for the development of *clinical* cut-offs, where resistance is defined according to when patients actually no longer benefit from a drug. The development of clinical cut-offs is labor-intensive because it requires the collection of large amounts of clinical trial data from patients on treatment. In addition, each antiretroviral drug—of which there are currently more than 20—has its own cut-off, i.e. a different point at which it ceases to provide any benefit to a patient. Because it is ineffective (and thus unethical) to treat an HIV patient with less than three drugs, teasing out the different cut-off of each drug in a three-drug combination from clinical trial data is a tricky business. Currently, most phenotype assays rely on a combination of biological and clinical cut-offs to demarcate drug resistance.

The Molecularization of HIV

The question "what happens when I give it to my patient?" points to the broader context in which these debates over the definition and measurement of resistance are being carried out. Specifically, it is critical to recognize that this proliferation of definitions of drug resistance (e.g. phenotypic, genotypic, technical, biological, clinical) is very much a consequence of the age of molecular medicine in which we now live. Medical history has shown us that models of the body and disease change and evolve over time—one need only remember the humoral system of medicine to see how radically different these models can be. More familiar is the 19th and 20th century model of the body as "a vital living system, or a system of systems" with a variety of associated organs, fluids, and functions (Rose 2001:13). And although this "system of systems" is

still relevant to the practice of medicine today, more often than not the body is now understood and intervened upon at a much smaller scale: the molecular scale—the level of genes, proteins, and amino acids. Sociologist Nik Rose writes that "in changing the scale on which the characteristic phenomena of life are studied, contemporary biology had adopted a new language" in which the body came to be understood in terms of information encoded in molecules. "Molecularization" is the term used by social scientists to describe the profound changes in medicine and the life sciences brought about by the genomic revolution.

HIV medicine and molecular medicine have been mutually influential on one another. The recognition of the HIV epidemic in the U.S. in the mid-1980s coincided with the development of the polymerase chain reaction (PCR), a cornerstone of modern molecular biology. PCR technology takes a small sample of DNA and multiplies it exponentially ("amplification") through a process that is both rapid and relatively cheap. The technology greatly facilitated the analysis of genetic material, which in turn influenced the study of disease and drug development and ushered in the era of molecular medicine. Two of the most important and abiding contributions of molecular biology to HIV medicine debuted in 1996, in the form of the viral load assay and protease inhibitor drugs. A third, the drug resistance assays described above, also emerged in the late 1990s. The development of these technologies reflected the emerging molecularization of medicine, as well as its increasing "personalization."

Molecular Medicine

Viral load refers to the quantity of HIV virus in a patient's blood. As HIV disease advances, the viral load climbs. The viral load assay uses PCR technology to measure

how much virus a patient is carrying. Ideally, a patient who is responding well to antiretroviral drugs will have a viral load that is "undetectable"—too low for the test to measure. Prior to viral load testing, the primary way of assessing the progression of HIV disease was through clinical symptoms and CD4 count. Although CD4 count provides an important measurement of the disease's *immunological* progress (damage to a patient's immune system), viral load testing allows the measurement of the disease's *virological* status by measuring blood levels of the virus itself. This is especially significant in monitoring a patient's HIV treatment, because a rising viral load is usually the first sign that a patient has become resistant to his or her medication. As a result, viral load testing rapidly became a key tool for assessing the efficacy of HIV therapy, at least in wealthy countries.

Protease inhibitors were also a product of molecular medicine. Traditionally, drugs are developed through a fairly laborious hit-or-miss process in which thousands of compounds are screened for possible pharmacological activity against a disease. This technique, called "high-throughput screening" is what led to the discovery that AZT—originally developed as a cancer drug—had some efficacy against HIV. The development of all the NRTIs and NNRTIs basically followed this traditional model. Protease inhibitors, on the other hand, were one of the very first fruits of "structure-based drug design," in which candidate drug compounds were specifically engineered based on a molecular model of the drug target. One virologist explained it to me as follows:

> So I think molecular biology and biochemistry have played a major role in the therapeutic progress made with HIV. In general, drug development usually proceeded through a very empirical mechanism. For example, an enzyme would be identified as important—for example, reverse transcriptase [the viral enzyme targeted by NNRTIs and NRTIs]. And then a screen would be set up and high throughput screening would be

> done where you screen millions of compounds for their ability to inhibit that enzyme. HIV actually formed the first departure from that tried and true mechanism of drug discovery. For example, with the HIV protease, the protease enzyme is crystallized, its active site defined, and then based on that active site, specific inhibitors were prepared that would occupy and inhibit that active site. So this was the first example of rational drug design as opposed to kind of throwing the kitchen sink at a particular assay.

What this scientist describes is the engineering of a drug at a molecular level. Protease is an enzyme manufactured by the HIV virus, and it plays a key role in viral replication. Blocking or "inhibiting" the enzyme with a drug thus prevents the virus from duplicating itself effectively. In order for protease inhibitor drugs to be developed, scientists first created a 3-D visual image of the physical form of the protease molecule. On this form, they were then able to identify the enzyme's "active site"—in this case, the physical location on the molecule that was most crucial to viral replication. Then they engineered a drug with a molecular structure that would bind to and "occupy" that active site, blocking it from action. Structure-based drug design is now used in the development of drugs for many diseases, particularly cancer, but this move was spearheaded by HIV medicine and the engineering of protease inhibitor therapy.

Personalized Medicine

Molecular medicine is, in turn, closely associated with what is often called "personalized" or "individualized" medicine, which refers to medicine that is tailored to an individual's genetics. The more technical name for "personalized medicine" is pharmacogenomics, an emerging field of scientific research seeking to understand the role played by genetics in a patient's response to drugs. Sometimes the genetic information in question is that of the *patient*, as when an individual is screened to see if

he or she possesses the gene necessary to metabolize a certain drug. In other cases, the genetic information of the *disease* organism (or, in the case of cancer, the tumor) is screened, in an effort to determine which treatments might be most effective against it. HIV resistance testing is an early example of the use of molecular diagnostic technologies to design individually tailored drug regimens. Significantly, ViroLogic, the HIV phenotyping company, describes itself as a company dedicated to "advancing individualized medicine." As a reflection of this emphasis, the company recently expanded its research to include cancer diagnostics and changed its name to Monogram Biosciences. On its company website ViroLogic/Monogram Bioscience posits that "the goal of individualized medicine is to move from a 'one drug suits all' approach to providing the right treatment to the right patient at the right time."

Although the clinical applicability of HIV resistance testing was initially uncertain, in recent years the use of resistance assays (and particularly genotyping) has become increasingly integrated into HIV patient care. Once reserved primarily for research purposes, genotype testing is now recommended for most patients initiating or switching HIV treatments in order to prevent the prescription of any drugs to which the patient might already be resistant (Hirsch et.al. 2003). In wealthy countries, where many HIV patients have been exposed to 10 or more years of antiretroviral therapy, resistance testing is crucial to identifying combination regimens that will be effective for patients with resistance to multiple drugs.

It is this clinical application of HIV resistance genotyping that best exemplifies the promise of personalized medicine: medication regimens individually tailored to a patient's disease. Yet, as I hope my discussion of genotyping and phenotyping

exemplified, there is often a gap between medicine *in vitro* and medicine *in vivo*—in other words, between a molecular and a clinical diagnosis. The drug resistance mutations detected by genotype assays do not always reflect clinical resistance (Tamalet 2000; Flexner 2000), and the biological cut-offs used to demarcate phenotypic resistance are only rough estimates of when a patient might stop benefiting from a drug.

This tension between "objective" genetic measures and "subjective" clinical indicators of resistance reflects a larger shift in the relationship of the laboratory to the clinic. Increasingly laboratory methods are being adopted in the clinic, resulting in a "culture of clinical experimentation" linking spaces of patient care to molecular and virology labs, and ultimately to processes of pharmaceutical production (Löwy 2000: 68). In this era of molecular medicine, the ability to integrate molecular measures into patient care is increasingly central to clinical practice. For example, when I asked one American HIV clinician and drug resistance researcher about the complexity of applying HIV genotyping to patient care he responded, "that's the art of medicine." In turn, molecular information collected through clinical care may also feed back into laboratory research and into industry, as in the proprietary HIV sequence database maintained by ViroLogic/Monogram. By recording and storing the genetic sequences of the viruses it receives for resistance testing, the company has built a valuable database of resistant HIV sequences to which it sells access—often to drug companies, who use the information in their drug development process.

However, this feedback loop between clinic, lab, and industry is profoundly shaped by geography, as my next three chapters will show. In Uganda, doctors have a very limited choice of antiretrovirals, are rarely able to test for viral load, are often unable

to get a CD4 count, and never have access to genotyping except in a few very rare research contexts. By contrast, in the U.S., doctors can choose from over 20 drugs and 4 (soon to be six) different drug classes as well as all available diagnostics, including two new tests designed to detect resistance to 2 newest classes of drugs. Outside wealthy industrialized nations, HIV medicine is much less molecularized and personalized. In fact, while individually *tailored* regimens based on genotype testing have become the norm in the U.S., discussions in international health focus on the development of *standardized* HIV regimens for use in low-income settings (Weidle 2002)—in other words, "one drug suits all."

Conclusion: towards a molecular politics

The certainty of what drug resistance *is* destabilizes once we start opening up scientific black boxes and getting closer to understanding the means by which drug resistance is *produced* as a scientific fact. Upon close examination, the definition of "resistance" grows fuzzy in light of the malleability of genotype resistance algorithms and the continuum of resistance revealed by the phenotype assay. Furthermore, the moral link between poor adherence and drug resistance breaks down, as does the framing of resistant HIV as a "super-bug." A significant theme that emerges from this close study of the science of antiretroviral resistance is the gap between the lab and the clinic; in other words, the ways in which laboratory-based technologies are limited in their ability to represent the course of disease within the environment of the human body. Though the gap between *in vitro* and *in vivo* results is nothing new in medical science, the rise of molecular medicine may raise new questions for this age-old quandary.

What is gained from the molecular understanding of disease, and what is lost? Do differences at the molecular level really matter at the clinical level? And, most significantly for this project, what are the political economic implications of the molecularization of HIV? In conceiving of the body as a space of interaction between genes and highly commercialized pharmaceutical and diagnostic products, "molecular," "pharmacogenomic" and "individualized" medicine imply a particular relationship between biologies and markets. In the global AIDS epidemic, what practices and discourses determine whose bodies and which biologies will constitute this marketplace? These are the questions that shape chapter 4, which examines the "molecular politics" of HIV science.

Chapter Four

THE MOLECULAR POLITICS OF HIV

"Biopolitics now addresses human existence at the molecular level: it is waged about molecules, amongst molecules, and where the molecules themselves are at stake." –Nikolas Rose 2001

More often than not, molecular medicine involves some form of genetic mapping. This is certainly the case in HIV medicine, where diagnostics (viral load tests, genotype assays) and therapeutics (antiretrovirals) are engineered based on very detailed, codon-by-codon[35] knowledge of the nine genes that constitute the HIV virus. The use of the term "mapping" to describe this kind of genetic knowledge and practice is more than metaphorical, as the knowledge that is generated by genetic sequencing is essentially spatial, telling scientists the order and location of the amino acids that make up the viral genome. In addition, mapping genes and mapping territory serve many of the same purposes: both provide a means of orienting one's self, a way of generating coherence, and a way to establish relationships between things (Rheinberger and Gaudilliere 2004). Critical geographers have long argued against "representationalism," in which maps are accepted as objective and straightforward depictions of space. Rather, as David Turnbull argues, maps should be examined as expressions of power (Turnbull 2004). In this chapter, I aim to show that this argument holds for genetic maps as well.

In his study of the colonial mapping of India, geographer Matthew Edney describes how map-making allowed the British to transform a disparate collection of empires and territories into the single, coherent entity of "British India" (Edney 1997). These maps then became rapidly naturalized, rendering the exclusions involved in

[35] A codon is a group of three adjacent bases in a strand of DNA or RNA. Codons provide genetic code information for particular amino acids.

constructing British India invisible. The representation of the territory as it appeared on colonial maps thus became taken-for-granted, and unquestioned—the map and the territory became synonymous. Turnbull makes a direct link between cartographic and scientific knowledge, arguing that maps are "an apt metaphor for scientific discourse. Scientific representations of the phenomenal world are, like maps, laden with conventions, which are kept as transparent, as inconspicuous as possible" (Turnbull 1989: 9).

If we interrogate how a map is constructed, we are able to understand the partiality and contingency of its representation. We are able to understand how the map is *productive* of certain possibilities—certain forms of understanding—and better able see what was necessarily included and excluded in order to produce a coherent entity. In Edney's analysis, this coherent entity was British India. In my analysis, I aim to show what was excluded in order to create a coherent map of the HIV virus. My point is that the generation of coherence has resulted in a situation in which the viral sequences (the genetic maps) of a particular strain of HIV—a strain found mainly in the U.S. and Europe—now serves as the common template for understanding and studying HIV worldwide. In this chapter, I want to raise questions about the scientific, clinical and political consequences of such a mapping.

Rethinking Laboratory Studies

In addition to attempting to bring the insights of critical geography to the study of science, this chapter is also an intervention into "laboratory studies," the sub-field of science and technology studies that takes the scientific laboratory as its object of study. One of the first and best-known examples of this is Latour and Woolgar's 1979 book

Laboratory Life. This ethnographic examination of a laboratory at the Salk Institute of Biological Sciences was revolutionary in its application of anthropological methods to Western science, and established the laboratory as a legitimate field site for social science researchers.

In her 1995 review of the field of laboratory studies, sociologist Karin Knorr-Cetina describes labs as "fact factories" where one can study the production of knowledge. For Knorr Cetina, laboratory studies are important because they "fly in the face of received interpretations according to which claims and procedures in science are standardized and universal" by describing the production of scientific knowledge as a product of the "local" practices and constraints of the laboratory. Thus, for her, "the power of the laboratory is the power of locales" (Knorr Cetina 1995: 157). Given her emphasis on the local, it is perhaps not surprising that her analysis of "the space of knowledge production" is generally focused on the practices taking place within the four walls of the laboratory. As she acknowledges in her review, a legitimate criticism of the field of laboratory studies is that this extreme focus on the microsocial environment of the laboratory often leaves out "the societal context in which laboratories operate as well as the political aspects of science" (Knorr-Cetina 1995: 162).

After co-authoring *Laboratory Life* Bruno Latour took a partial detour from the field of laboratory studies as Knorr-Cetina describes it. His subsequent analyses of the laboratory worked to explode the distinction of what constitutes the "inside" versus the "outside" of the lab by arguing that science works by extending the laboratory beyond its walls. In Latour's view, "the very difference between the 'inside' and the 'outside', and the difference of scale between 'micro' and 'macro' levels, is precisely what laboratories

are built to destabilize or undo" (Latour 1999). Using the example of Louis Pasteur's development of the anthrax vaccine, Latour describes the extension of bacteriological analysis into the French countryside and beyond as the development of a scientific "network" that transcends the space of the laboratory. Such a network, he argues, is essential for the circulation of scientific facts produced by the laboratory, and it is through the extension of such networks that society is ultimately transformed into a giant laboratory (Latour 1999).

My own point is somewhat different. I agree that the traditional, microsocial focus of laboratory studies described by Knorr-Cetina is far too narrow, and can end up producing a sociology/anthropology of science that fails to account for the political, historical, and economic basis of scientific knowledge production. The result is an analysis that separates the scientific from the social, and thus reproduces the very dichotomy that the social studies of science seeks to undo. In this sense, I am in line with Latour's take on the indivisibility of the laboratory and society. However, where Latour's analysis describes the extension of the laboratory across France, my analysis is concerned with the reverse: the manifestation of certain geographies and geopolitics *within* the laboratory. In other words, where Latour goes from the small-scale (the lab) to the large-scale (France), I aim to go from the large-scale back to the small-scale. I will do so by describing how the geopolitics of the AIDS epidemic is visible at the molecular level, in the laboratories where our knowledge about the molecular biology of HIV and antiretrovirals is produced. The result is a kind of "molecular politics" (Rose 2001) in which the global inequalities of the AIDS epidemic are manifest at the most minute scale, embedded within the materials scientists use to study HIV. My point is that even if we

do not go beyond the four walls of the laboratory—even if we do not go out into the fields as Pasteur did, but stay "inside" as laboratory studies has been criticized for doing—this is no excuse for not engaging the social and political conditions that make scientific knowledge possible. Rather, these conditions can be found *inside* the "locale" of the lab. The rest of this chapter will demonstrate how.

HIV Subtyping and the Production of Coherence

HIV is highly error-prone in its replication process, meaning that the virus mutates rapidly and constantly. Each viral offspring differs slightly from its parent by several mutations. This means that any given individual infected with HIV is carrying not many copies of a single virus but rather a *population* of related viruses. For this reason the scientific literature refers to HIV as a "quasispecies," meaning a mixture of genetic variants of a virus as opposed to a single virus with a consistent genome. This extreme diversity means that generating coherence is one of the key challenges involved in working with HIV in the laboratory.

However, despite this diversity, some viruses are more similar than others. The relatedness—or phylogeny—of HIV viruses is based on genetics. Viruses are mapped and grouped according to the similarity of their genetic material, which is understood to reflect their evolutionary proximity. The basic phylogeny of HIV is depicted in the figure below, showing both HIV-1 (the most common virus) and HIV-2 (found in West Africa), as well as various groups and subtypes of HIV-1. When most people refer to "HIV" they are actually referring to HIV-1 Group M, which accounts for 99% of the world's infections.

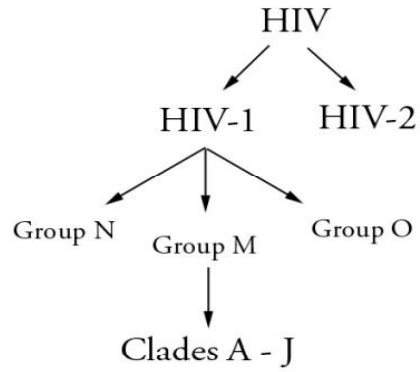
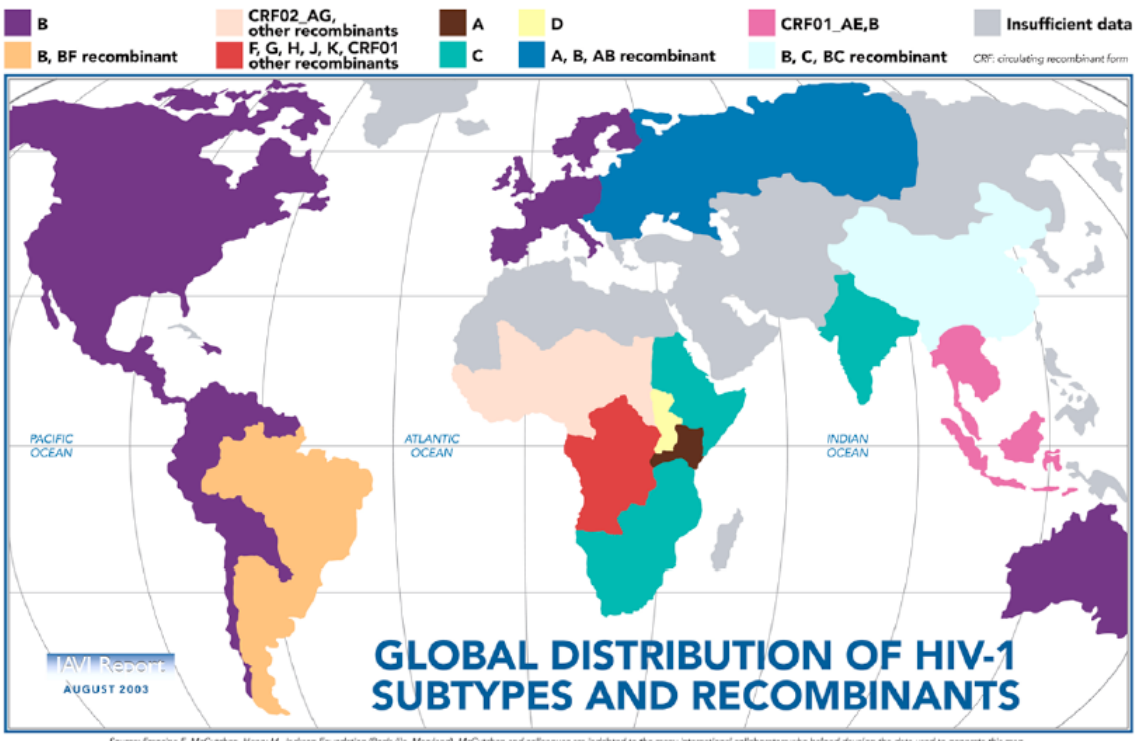


Figure II: Breakdown of classifications of human immunodeficiency virus according to sequence variation

(Source: Haeusser 2001)

There are currently 9 identified genetic subtypes of HIV-1 group M, each labeled by a different letter of the alphabet. In addition, there are several "recombinant" viruses that are mixtures of more than one subtype. The prevalence of these subtypes, also called "clades," varies geographically, as shown in the map below.



(source: Kahn 2003)

In the U.S., Western Europe, Australia, and parts of Latin America, the vast majority of infections are subtype B infections (represented on the map above in purple). In sub-Saharan Africa there is a much greater diversity of different subtypes, with the most common being C and A. Worldwide, the most prevalent subtype is type C (aqua green on the map above) which accounts for 47% of infections globally. This is because type C predominates in the areas of the world that bear the greatest burden of infection—particularly southern and eastern Africa, and India.

The map below shows another way of looking at the same phenomenon. Here the grayscale shows HIV prevalence, with the darkest areas being those with the highest numbers of infections. These hardest-hit regions are also the geographic areas where subtype C predominates.

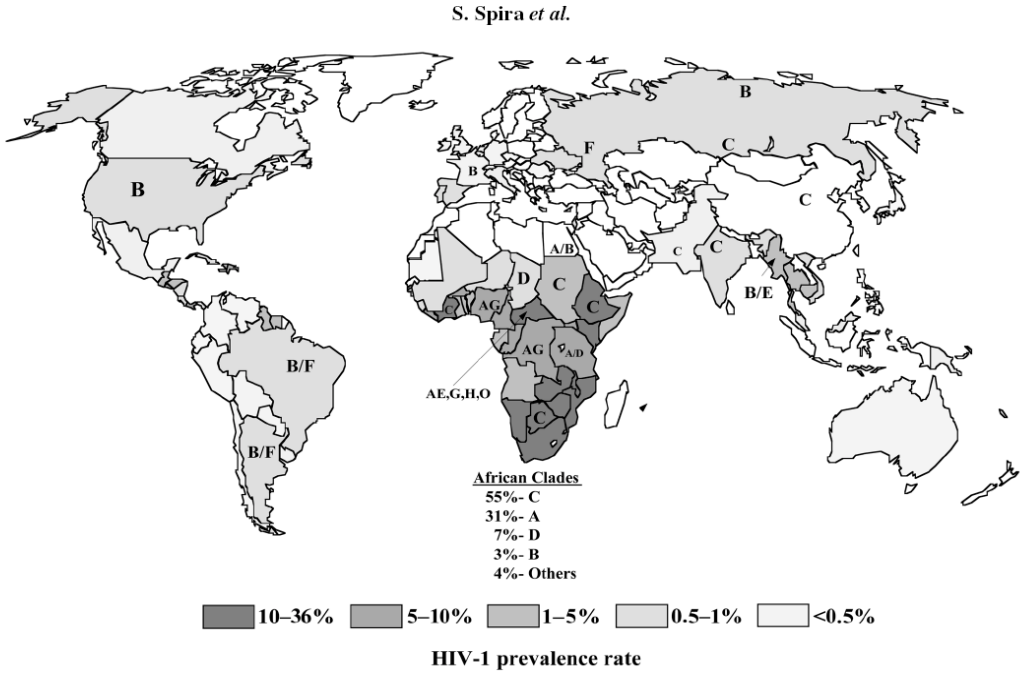


Figure 1. Subtype diversity of HIV-1 infections prevalent worldwide.

(Source: Spira et. al. 2003)

The ability to understand HIV at the molecular level—to literally make the genomics of the virus legible codon by codon—is what has allowed scientists to understand the breadth of the virus's diversity. However, this exquisite familiarity with the details of HIV genomics also creates certain tensions in relation to generating knowledge about the virus. Specifically, scientists confront the fact that there is no single viral sequence that represents HIV. There is no unity to HIV, no coherence. This presents problems: If all viruses are different, which virus should you use in your research? Which should you use to develop drugs, and diagnostic tests? Furthermore, this viral diversity presents problems of comparison—a particularly important element in the assessment of drug resistance. How, for example, how do you assess whether or not a virus has developed a resistance mutation? You must compare that virus to a virus known to be drug-sensitive. This drug-sensitive virus then serves as a "reference strain" to which a patient's virus can be compared and assessed for drug resistance mutations. But given the incredible diversity of HIV—the virtually infinite number of drug-sensitive viruses in existence—how do you choose just one to serve as a reference strain?

The Contingency of the Arbitrary

In choosing a reference strain to work with, scientists selected from viruses already available to them in their laboratories. In the U.S. and Europe these viruses were all of the subtype B variety, as this was the strain infecting local patient populations. Worldwide this subtype represents 12% of total infections (Kantor and Katzenstein 2004). When I asked David Capelli, the viral fitness researcher introduced in Chapter 3, about this he told me that the choice of a reference strain was "somewhat arbitrary." "In fact," he continued, "the idea that there was a normal strain of HIV is sort of strange to

begin with. There really is not. It exists as a population. It's sort of like saying, 'what is the representative American?' Well, I don't know. It's a highly diverse country."

Far from being a calculated effort to exclude strains from other parts of the world, researchers chose a reference strain was based on what was available at the time, among their own patients. However, it is important to recognize this "arbitrary" choice as both historically specific and socially contingent. The selection of subtype B viruses as the basis for HIV laboratory research and technology development was not random, but reflects the fact that the great majority of both research funding and infrastructure are located squarely in the U.S. and Western Europe, where subtype B predominates. Many HIV researchers are physicians who first encountered the virus in their medical practice. As such, the choice to focus their research on subtype B virus reflected both its convenient availability and the desire to work on the strain that was infecting the patients under their care.

Interestingly, convenience shaped not only the choice of subtype B virus as the reference strain, but a very specific virus within this subtype. The most commonly used reference strains are closely related and go by a number of names including NL4-3, HXB2, and LAI. This proliferation of names is a product of the complex and contentious history of the virus's discovery. Capelli explained it to me as follows:

> So its full name is pNL4-3. And you mention that to basically any lab scientist who works with HIV-1 and they go, "Oh, L4-3." It probably is the basic reference virus used in North America. It's a well characterized strain and people understand it…The history on this — this would be I think a good thing to look into. Basically, these are some of the earliest isolates that were grown in the 1980s. And they were some of the earliest variants. So as you know, in the very early stages of the epidemic there was (A) some confusion over what was the causative agent and then, (B) once it was determined that it was HIV-1, there was a great deal of energy put into determining how to appropriately grow and sustain these viruses.

> And some viruses grow better in culture than others. And NL4-3 was one that did. They also called it HXB2 or LAI…And my understanding is that these viruses are all highly related and came from a handful of labs in the 1980s.

The labs that Capelli refers to are those of Luc Montagnier and Robert Gallo. In the early 1980's, these two scientists emerged at the forefront of the search for the agent that caused AIDS: Montagnier at the Pasteur Institute in Paris, and Gallo at the National Cancer Institute in Bethesda, Maryland.[36] Both scientists were specialists in the study of retroviruses, and both thought that a retrovirus could be the cause of AIDS (a hypothesis that turned out to be correct). In the early 1980's, both labs worked trying to isolate a retrovirus from patients who were suffering from AIDS. The relationship between the labs was competitive, but they nonetheless exchanged samples according to common scientific etiquette.

In 1983, Montagnier's lab isolated a previously undocumented virus from a patient with lymphadenopathy, the swollen lymph nodes that are one of the hallmarks of AIDS. He named the virus "lymphadenopathy-associated virus" or LAV. Soon thereafter, his team isolated similar viruses from patients with more advanced disease. One of these viruses—from a patient identified only by the initials "LAI"—was particularly fast-growing and aggressive. However, attempts to describe the virus in greater detail was stymied by the difficulty of culturing it in the lab. The virus was difficult to grow because it killed all the cells used to culture it within a matter of days, and once the cells were dead, the viruses died too. After much trial-and-error, the French scientists developed a technique of transferring the viral cultures to fresh cells every three

[36] It was not at all obvious that AIDS had a viral cause, and during the early years of the epidemic a wide variety of other causes were considered (see Epstein 1996).

days over the course of several weeks, a laborious process that would eventually yield enough virus for further laboratory studies (Garrett 1994).

Shortly after Montagnier's discovery, Gallo's lab also isolated a virus from a patient with AIDS. They named the virus HTLV-III, believing it to be related to a group of human t-cell lymphotropic viruses (HTLVs) that Gallo had discovered in the late 1970s. The American and French groups agreed to compare their viruses and, if they were found to be the same, to hold a joint press conference in which they would co-announce the discovery of the virus that caused AIDS (Gallo 2002; Rainey 2006).

What happened next initiated a controversy that would drag on for nearly a decade. Before the viruses could be compared, Margaret Heckler, the U.S. Secretary of Health and Human Services, held a press conference to announce that the AIDS virus had been discovered. At the conference, Gallo was heralded as the discoverer of the AIDS virus, a title he embraced. Montagnier's team was not invited to the press conference, nor was their work cited. Gallo did not dispute that Montagnier had isolated a virus earlier than he had isolated HTLV-III. Rather, he defended himself as the discoverer of the AIDS virus by arguing that it was on the basis of his HTLV-III research that the definitive causal link between the virus and the syndrome was established, and that a blood test could be developed. Gallo's claim was boosted by his team's development of an "immortalized" cell line that did not die when cultured with the virus, eliminating the tedious culturing process used at the Pasteur Institute and providing a technology key to the development of the AIDS antibody test (Garrett 1992). Gallo filed a U.S. patent application for a blood test that would identify infection with the virus on the same day that the press conference was held. The U.S. government granted him the patent—worth

$100 million annually in sales and $100,000 to Gallo personally—and denied a patent to the French (Rainey 2006).

Montagnier and the Pasteur Institute challenged the patent, beginning a protracted struggle between the French and the Americans that would last nearly a decade and eventually involve both heads of state. Gallo continued to assert that HTLV-III was the virus that caused AIDS, and opposed the renaming of the virus "HIV" (human immunodeficiency virus) in 1986 by the International Committee on the Taxonomy of Viruses (Epstein 1996: 77). However, a genetic analysis of both viruses later revealed that they were essentially identical—confirming long-held suspicions on the French side that the isolate that Gallo had "discovered" was actually derived from LAV/LAI—the highly aggressive virus that had been isolated by Montagnier—which is now believed to have contaminated Gallo's samples as well as those in a number of other labs with which Montagnier had shared cultures (Montagnier 2002; Gallo 2002). Eventually, the two scientists agreed to share credit and split the patent proceeds. Today, Montagnier is generally recognized as the first to identify the virus, while Gallo is credited with solidifying the link between the virus and AIDS and developing the technology that made the AIDS antibody test possible (Rainey 2006; Stine 2004).

It was the LAI isolate of the virus and its derivatives that would go on to become one of the most commonly used viruses in HIV research. Interestingly, LAI was not selected on the basis of its representativeness. In fact, most scientists I spoke with readily agreed that the reference strain they used was not all that similar to the type B viruses found in patients (much less to the other non-B subtypes). Rather, these strains were used because they grew well under laboratory conditions. Having undergone genetic

changes over the course of numerous manipulations in Paris and Bethesda, these viruses were now what scientists call "lab-adapted." Dr. Paula Leigh, a virologist and the Associate Director of the Yerba Buena lab where I observed the genotype assay, explained it to me as follows:

> Whatever the first virus that Gallo or Montagnier isolated, that's a lab-adapted strain. And it was grown out in the laboratory in vitro and propagated. And maybe even cloned out. And those are viruses that generally replicate very, very easily. You can grow them easily, that's how they found them in the first place. And they might actually be quite different from what is actually growing in people.

Leigh went on to give her understanding of the complex nomenclature behind the reference strains:

> LAV is the original virus that they isolated. And they call it different things depending where in the world you are—LAV, LAI, BRU, HTLV-III. And then there's another reference strain called NL43 which actually a hybrid virus from two patients [that somebody] isolated and they spliced together and it's just used as a reference virus because it grows very well in tissue culture….[And] there's another one, HXB2. It's often used as a reference strain and that is just like LAI I think but there's a slight difference from it.

Likewise**,** Ralph Ernst**,** a Swiss scientist working at Yerba Buena's blood bank, echoed Leigh's assessment that the reference strains were "different from what is actually growing in people." He told me, "Not only did people use subtype B, they probably used the wrong subtype B. People basically used what they had. And the first thing they had was the cloned viruses—the one that Gallo/Montagnier isolated, HXB2. So everybody kind of uses a very limited set of the oldest virus. Why?" He then answered his own question, "Because they're convenient. Everybody's got it. You can compare data across labs."

It was this ease of use, rather than the virus's representativeness, that made the LAI virus "the right tool for the job" for these scientists (Clarke and Fujimura 1992). Representativeness, in this context, was less important than availability and adaptivity to laboratory conditions. A virus that was more genetically similar to the viruses circulating among patients could have been initially selected as a referent, but might have been difficult to grow in the lab, which would make working with it more trouble than it was worth. In addition, one the LAI strain and its cousins had become the common currency of lab work, switching to a different reference strain was impractical because it would impede the comparison of data between laboratories. Jim Greene, the virologist in charge of Yerba Buena's virology lab, put it most succinctly when he told me that "this is an example where consistency is more important than being right." After all, he continued, "there is no way to be right." In his view, it was more important for scientists to be explicit about which reference strain they were using, and to be consistent in this choice, than to use a reference strain that more closely resembled patient viruses.

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In its role as reference strain, subtype B virus (and specifically the LAI-related strains) has come to serve as a proxy for the otherwise highly diverse HIV genome. As such, it provides a standardized map of the virus—an extremely useful scientific tool for navigating a microbe notorious for its powers of rapid mutation. Consequently, subtype B became the template upon which nearly all the laboratory and much of the clinical knowledge about HIV has been based. This includes everything from the molecular models scientists have developed to understand the virus's structure to the antiretroviral drugs that have transformed the lives of patients able to access them. It also includes

knowledge about drug resistance, which is defined according to mutations found in subtype B viruses.

Indeed, I first learned about the significance of subtype in a discussion with Dr. Eileen Jacobs, an industry scientist who was working on developing a new genotype resistance assay. The molecular diagnostics company she worked for was already a dominant manufacturer of viral load tests, and was looking to expand into the market for genotyping. Her interview was one of the first I conducted during my fieldwork, and my understanding of the science behind genotype testing was still very limited at the time. Assuming that the technical challenge in genotyping had to do with the large number of antiretrovirals in use, I asked her if it was difficult to develop a test that could detect resistance to numerous different drugs. Her answer surprised me. The challenge lay not in tailoring the test to the drugs, she told me, but in tailoring it to the virus.

As I described in chapter 3, a key element of the genotype assay is the amplification of the virus using PCR technology. PCR works through the use of what are called "primers"—genetic sequences that attach to the beginning and end of a targeted region of DNA (in this case, viral DNA), marking the portion to be copied. These primers, Jacobs told me, were all initially designed based on a subtype B reference strain. As a result, they were sometimes less effective in attaching to and amplifying viruses of other subtypes. In the past, this had caused problems for the company's viral load test, which also uses PCR and was initially not very good at detecting non-B subtypes. The company had successfully reworked the primers used in the viral load assay to make it work with multiple clades, and was now trying to do the same for a genotype test. Jacobs explained:

E. Jacobs: So clade B is most common in this country. And so originally we knew most about that clade because that's where we could get our sequence information, that's where we could do the testing. So that's where the primers have been designed towards. So it's easy to amplify Clade B. It's more difficult to amplify every clade.

J. Crane: So is it — are the primers that are used generally the ones that were developed for Clade B?

E. Jacobs: Yes. Right. So all the commercial tests have been developed for Clade B.

In order to develop the multi-clade genotype test, Jacobs's company needed to provide its scientists with non-B viruses to work with. Because the corporation was not involved in any significant international collaborations, these viruses were not so easy to come by and had to actually be purchased from a biological supply company based in Miami. The fact that non-B viruses have achieved commodity status seems counterintuitive for a number of reasons. First, these viruses are hardly a scarcity, as they account for 88% of the world's infections. Moreover, the company's willingness to pay for such viruses seems ironic given the multinational pharmaceutical and biotech industries' long history of indifference towards the epidemic in developing countries. The recent industry interest in re-tooling their technologies for use outside the West (an interest also expressed by ViroLogic/Monogram, the phenotype manufacturer) is likely another offshoot of the turn towards Africa among American AIDS scientists, who rely on molecular diagnostic technologies for their research and who, unlike African clinics, can afford to pay for them.

Subtype B: A Colonial Language?

Although the North American AIDS researchers I spoke with described the field's reliance on subtype B HIV as essentially benign—a "historical fluke" and an issue of convenience, *not* favoritism—some also acknowledged that at a higher level, market

forces were at play. James Briswell, an expert in the study of non-B viruses, described the situation in terms reflecting the political economy of the global pharmaceutical market:

> Well I think there are two reasons [why subtype B has been used]. I think one is just that it was the most convenient. People had all those subtype B samples available. And all the studies were done with B because it's in the United States and Europe. So that's more of a benign explanation. But there's no question that a lot of drug development is targeted to parts of the world where you know people are more likely to be able to pay for drugs. There could have been a lot of work done with tuberculosis and malaria, and many new drugs developed during the same time period. But they weren't because it just wasn't considered a high enough priority on the part of some of the pharmaceutical companies from their – you know, people who are looking at their bottom line.
>
> So I think it's a combination. It's just that all the strains that people had in the labs were subtype B, and I think a lot of researchers just tend to work with the same strains. They're not always aware of the variability. But I think there's also an element of companies targeting the strains that infect the people in the parts of the world that have the most money.

Whether or not the *initial* choice of these subtype B viruses for laboratory research was a matter of convenience, they are now chosen by necessity. These lab-adapted strains have become established as the common referent or template for HIV research, and to change the template (by, for example, choosing a subtype C reference strain) would make it impossible to communicate with other laboratories or to compare data. It would make science "too chaotic" in the words Briswell, who told me that even researchers in the developing world—where subtype B is rare—speak in terms of subtype B:

> [Y]ou almost need a common frame of reference to describe things. Even if it's arbitrary…just to facilitate communication. So it has nothing to do with favoring one subtype over another. It's really just a matter of convenience that a lot of the people in the field – you have to pick something as a reference. And in the future you know maybe things will

> change. But people are used to speaking in terms of subtype B. *No matter where you go in the world, even if they have all subtype C, they're used to speaking in terms of subtype B*, from the literature, you know…. I don't think that's detrimental in any way. Because if you had people using different reference strains it would just be too chaotic (emphasis added).

Thus, subtype B has become not only the molecular template upon which all HIV medications and diagnostic technologies are based, but also the lingua franca of AIDS research globally—even though other strains are much more prevalent. In this way subtype B operates almost like a colonial language, allowing communication across different groups and across geography, but also reflecting a very specific and unequal arrangement of power.

Consequences: Clinical and Political

The fact that virtually all molecular knowledge about HIV is based on the "Western" subtype is significant both politically and theoretically as an example of how the geopolitical inequalities that characterize the AIDS epidemic can be found even at the most minute and technical levels of scientific research. However, ultimately, the more important question is: does all of this matter clinically? This is not a question that can be answered definitively, as researchers have only recently begun turning their attention towards it. Nonetheless, there are some important findings thus far. For example, some studies have shown that some subtypes may be more aggressive than others, leading to a quicker death (in the absence of treatment).[37] Below, I examine three areas of research

[37] One such study was conducted in Uganda, where most infections are either subtype A or subtype D. Researchers found that patients with subtype D infections died faster than those with subtype A, and that subtype was actually a better predictor of the speed of death than viral load. The study was reported in Uganda's major daily paper under the headline "HIV Type Determines How Fast You Die" (*New Vision*. 2006).

on the clinical implications of subtype diversity: response to HIV treatment, HIV vaccine development, and HIV drug resistance.

Response to HIV Treatment

Does the fact that many antiretrovirals are the product of structure-based drug design based on subtype B viruses make them any less effective at treating other viral clades? Fortunately the answer so far seems to be no. As treatment is rolled out in low-income countries, people with non-B virus seem to be responding to and benefiting from antiretroviral drugs just as well as people in the U.S. and Western Europe have (Braitstein 2006; Kantor 2006)—a result that James Briswell described to me as "lucky." This is good news, but raises the question: should the universal efficacy of HIV drugs be a question of luck? Furthermore, will this same luck apply to newer HIV drugs?

Now that effective first-line drugs are well-established and increasingly available in generic forms to poor countries, the HIV drug development efforts of multinational pharmaceutical companies are largely devoted to second- and third-line drugs for patients that have developed resistance to earlier regimens. This research has led to three entirely new classes of antiretrovirals designed to treat patients with multiple drug resistance: integrase and CCR5 inhibitors (still in the experimental phase), and an injectable entry inhibitor called Fuzeon (known generically as enfurvitide or T-20) that was approved by the FDA in 2003. At $20,000 a year, drugs like Fuzeon are unaffordable for many of the American and European patients to which they are marketed, much less to patients in Africa. To be fair, such a drug is not yet needed by most Africans with HIV, as patients are only beginning to develop resistance to first-line drugs and have not yet reached the point of multiple drug resistance that Fuzeon was designed to treat. But because drug

resistance is inevitable over time, African patients will need new drugs eventually. The most obvious barrier to obtaining them will be the cost—but, if this barrier is overcome as it has been with first-line drugs, the question of efficacy across subtype could become a real issue.

Thus far, there is evidence that Fuzeon works well against non-B subtypes (Fleury et. al. 2006), but the effectiveness of the newer classes of drugs under development is uncertain. This question came up at a 2004 conference presentation given by Francoise Brun-Vezinet, a French AIDS expert known for her work with Luc Montagnier on the discovery of HIV. Brun-Vezinet delivered a well-attended talk on drug resistance in non-B viruses at the 2004 Interscience Conference on Antimicrobial Agents and Chemotherapies (ICAAC), a major infectious disease conference held annually in the U.S. During the question-and-answer period, someone from the audience of physicians and scientists asked her whether anything was known about the efficacy of the newer classes of drugs in treating non-B infections. She told the audience that although there had been initial skepticism that Fuzeon worked against non-B viruses, a recent study had proved that it was indeed effective. But, she added, for the other new drugs [referring to the new classes under development] "I'm afraid that subtype will affect it very much" (Brun-Vezinet 2004).

HIV Vaccine Development

Historically, the clinical arena in which viral subtype has drawn the most attention is in vaccine development. When they announced the "discovery" of the AIDS virus in 1984, Robert Gallo and HSS chief Margaret Heckler made the optimistic prediction that a vaccine would be available within two to five years. This prediction proved to be

dramatically inaccurate, and 25 years into the epidemic an effective vaccine remains a long way off, and perhaps impossible. HIV clades have been a source of controversy in vaccine science, as there is evidence that vaccines designed using one subtype may not work (or will work less well) against other subtypes.[38] The earliest attempts at vaccines were indeed subtype-B specific, leading to politically and ethically volatile situations when they were brought to non-B developing countries for clinical trials. Ralph Ernst, the virologist, warned me about this after I posed several questions to him regarding subtype:

> [Y]ou've got to be careful [about] the political aspect of the whole trend of your research. Because there was a big concern from Africans that 'oh, you guys in the developed world, you're going to make a vaccine against subtype B and it's not going to work for us. So you're not thinking about us.' You know, they have a point. Now people will make a vaccine against subtype B because that's where the money is. Sadly enough.

Uganda was one site where early vaccine research caused controversy. The country hosted the first vaccine trial in Africa in 1999, a Phase I study of a clade B vaccine.[39] Because Uganda's epidemic is comprised of primarily subtypes A and D, this caused some concern that Ugandans were being used as 'guinea pigs' for a vaccine that might not benefit them.[40] However, this controversy was ultimately overshadowed by another:

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[38] The relationship between HIV subtype and vaccine development is highly complex and varies depending upon the type of vaccine under consideration. Different vaccines target different areas of the virus, some of which vary greatly across subtype and some of which do not. In addition, subtyping is based on viral genetic sequences, which do not necessarily correspond to the immune properties of the virus, which is what ultimately matters in vaccine development (Kahn 2003). For these reasons, my coverage of subtype issues in vaccine research is necessarily partial and incomplete.

[39] There are 3 main phases in the testing of any candidate vaccine or drug. Phase I clinical trials test for safety only, not efficacy.

[40] It is important to note that in many instances, this kind of cross-clade vaccine testing is actually a good thing. In fact, testing candidate vaccines against "unmatched" strains is crucial to determining the extent to which subtype impacts vaccine efficacy, an important issue in the development of a broadly effective vaccine (Kahn 2003). What is problematic is the fact that clade B vaccines dominated these early efforts, when B virus accounts for only 12% of worldwide infections. A more justifiable trial, for example, might

widespread fears (based on misinformation) that exposure to the vaccine would cause study participants to become infected with HIV (Kaleebu 2005). In part as a result of these early controversies, there is now a greater emphasis on the design of non-B vaccines and "multi-clade" vaccines designed to work against multiple subtypes, and the number of non-B vaccines in development now greatly exceeds those based on subtype B (Kahn 2003).

In addition, African countries have become increasingly involved in vaccine trials. In 2000, a group of African AIDS experts convened in Kenya and adopted "The Nairobi Declaration: An African Appeal for an AIDS Vaccine." This document pledged support for increased African involvement in vaccine development and urged industrialized countries and international donor organizations to increase their financial and technical contributions towards vaccine research for Africa, "paying particular attention to the variability of HIV strains between different regions of the world" (AfriCASO 2000). Under the auspices of the WHO, the group established the African AIDS Vaccine Programme to further promote and support the development of African vaccine research.

A few of the Ugandan researchers I interviewed were involved in vaccine studies, some for clade B vaccines and some for multi-clade vaccines. Dr. Ronald Wetege, a leading Ugandan researcher responsible for some of the first studies of the epidemic in his country, was circumspect about the issue of subtype. "The knowledge we have now is that really a vaccine is likely to be successful if it is tailored to the circulating subtype in the population as much as possible," he told me. At the same time, he said, it is

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have tested a clade C vaccine against Uganda's A and D subtypes (as is currently underway), but at the time, clade B vaccines were the only vaccines under development.

understandable that Western companies working on vaccine development would work on the subtype that prevailed in their countries. "One has to go to look at the other side," he told me, "and say look, most of these companies which have invested billions and billions are operating in countries where there's only basically one subtype. So they are in a dilemma." For Wetege, even a subtype B vaccine study could be beneficial for Uganda, providing an opportunity to build research infrastructure and train local scientists:

> I mean we did a study which was based on subtype B and I know we heard a lot of arguments like that—"Why is it a subtype which is not [here]?" But we told them, "Look, there's something we can benefit. We can build infrastructure. We can train people. And as technology moves, we'll get vaccines based on our subtypes."

In this way, Wetege points out an interesting and important connection between research and development in Uganda. I refer here not to the "R&D" of the pharmaceutical industry, but rather development as in "developing countries"—"development" that operates in the name of advancing the social and economic lot of poor nations, or, as James Ferguson writes, the "dominant problematic or interpretive grid through which the impoverished regions of the world are known to us" (Ferguson 1994: xiii). What Wetege implies is that a vaccine study was not just a vaccine study, but also a means by which to improve laboratory infrastructure, train researchers, and establish links with Western colleagues and funding bodies. In light of these tangible forms of development—or "capacity-building" as it is often referred to these days—the issue of subtype matching seems less important, especially given that clinical benefits are unlikely at the current stage of vaccine research anyway.

HIV Drug Resistance

A great deal of this dissertation circulates around the politics of drug resistance. How does the issue of subtype enter into these politics? Is it accurate to measure drug resistance in, for example, Uganda (where people are infected mainly with subtypes A and D) using a genetic map of resistance constructed using subtype B? Scientifically, this is still an open question that a number of the scientists interviewed for this dissertation are actively grappling with. Their research is ongoing, and has evolved in the period between my fieldwork and this writing. Thus far, there is no evidence that the *interpretation* of any given resistance mutation differs across subtype: in other words, an M184V mutation causes nevirapine resistance in a clade C virus just as it does in a clade B virus. Where differences do exist is in the patterns of mutations across subtype, meaning that some resistance mutations are more common in some subtypes than in others, and that some resistance mutations may be unique to a particular subtype. In addition, because resistance often develops through the accumulation of multiple mutations, the "pathway" of mutations that a virus takes towards drug resistance can be different in different clades (Kantor 2006). In sum, though there is no smoking gun showing radical differences in drug resistance across subtype, differences are "increasingly emerging" as research evolves, and further studies of non-B subtypes are considered an important priority within the field (Kantor 2006: 594). "The data," Ralph Ernst reminded me in 2005, is still "so slim. People don't do serious drug resistance studies in non-B countries or they're done very few of them."

It seems important to juxtapose the "slimness" of this data with the broadly stated conjectures (bordering on fear-mongering) about HIV drug resistance in Africa mentioned in the introduction of this paper. Those conjectures were made in the absence

of any data on drug resistance in Africa, yet they played significantly in policy debates over whether or not treatment should be expanded in Africa. And, significantly, these debates continue to haunt the field, as James Briswell made clear to me:

J. Briswell: I think a lot of people who are involved in this drug resistance research in Africa and Asia, like I am, are concerned that [the research] will be taken out of context, and people would exaggerate this fear [of resistance] and use it as a reason not to give therapy.

J. Crane: Is that a concern of yours, or in the field?

J. Briswell: Yeah, that's a major concern among experts in drug resistance—that fears of resistance not be blown out of proportion, so that they're not looked at as a reason not to give therapy.

Scientists are in agreement that the data on non-B drug resistance is scant, and needs to be increased. There are an increasing number of researchers committed to this project, yet, as Briswell describes, they conduct their inquiries with the fear that the data that they are beginning to collect may be interpreted as a reason not to expand treatment in poor countries—an expansion which they greatly support. This fear seems to indicate that despite the major shift in international will towards support of antiretroviral treatment in Africa, fear of drug resistance has retained a powerful political valence.

In addition, it is important to note that the research into non-B drug resistance is still centered in the West, where the technology exists to conduct the molecular analyses involved in drug resistance research. As I pointed out in Chapter 3, the molecularization of medicine—including medical research—is a phenomenon that is largely confined to wealthy countries. Uganda, despite its prominence in other areas of AIDS research such as epidemiology, is "rather thin" in the field of biological research, as one Ugandan epidemiologist put it to me. Training more Ugandan molecular biologists, he thought, would lead to more drug resistance research on Ugandan HIV clades:

> Molecular biology is rather thin. I was talking to somebody who was trying to pursue a career in the laboratory sciences and I said, "Just go for molecular biology." [In] the epidemiological sciences, I think we have trained sufficient number of epidemiologists. Behavioral scientists are being trained. Laboratory scientists are being trained. But molecular biologists and virologists, immunologists, those are in short demand. So, the only way we could develop, [that] we could study drug resistance working on our clades is by developing the capacity ourselves. I think that will be easier.

Like Wetege, this scientist makes a link between research and capacity-building. If Uganda had more molecular biologists, he argues, more research on clades relevant to Uganda would be done. This seems a fair prediction, given that the large number of molecular biologists in the U.S. and Europe produced a large amount of research on the subtype relevant to their parts of the world. It also raises the interesting question of how molecular knowledge about the virus might have evolved very differently had the scientific centers of power laid elsewhere.

Conclusion: At the Margins of the Center

Not only is scientific knowledge about HIV in Africa limited, but most of the knowledge that exists has been gleaned using tools designed around a strain of the virus rarely found in Africa. It is *within* these tools that the geographic and economic inequalities of the global epidemic have become embedded at the molecular level, in technologies that *always* refer back to the West—Western viruses, Western research capacity, and Western markets. In the beginning of this chapter I talked about cartography, and I described how maps are socially constructed representations of a territory, based on the specific inclusion and exclusion of different types of information, which later becomes naturalized, unquestioned, and taken-for-granted. This is the same thing that has happened with the genetic mapping of HIV: the drugs built to fight the

virus and the tools built to study it are based on a very partial and contingent map of the virus, yet, this map is rarely questioned.

Whether or not these tools are able to accurately monitor non-B ("African") viruses in scientific terms is a question that scientists are currently grappling with. Ultimately, my argument is that regardless of the scientific outcomes, it is *politically* urgent to bring attention to the willingness with which some Western experts made very consequential knowledge claims about HIV in Africa—and particularly drug resistance—despite the fact that there has been very little research done on drug resistance in Africa. Furthermore, the research that has been carried out has relied on a template of HIV created from the strain found in wealthy industrialized countries, rather than the much more common subtypes found across the African continent. This positioning of African HIV subtypes as the exceptions—the different or deviate viruses—and the Euro-American subtype as the universal standard fits what anthropologist Stacy Pigg has called "the definition of marginality: to be positioned as the exception, the deviate, the parochial, or the merely local in the face of the universal*"* (Pigg 2001: 510).

And yet, as I described in my introductory chapter, Africa is increasingly central to the most cutting-edge international HIV research. What does it mean to be both simultaneously marginal and central to scientific knowledge production? This tension between marginality and centrality is a key theme in my final two chapters, which will explore how Ugandan doctors and researchers and their American colleagues negotiate knowledge and power within the increasingly transnational field of HIV medicine.

Chapter Five

A DIFFERENT DISEASE?

A low-income country meets high-technology HIV medicine

Introduction

In 1985 the *Lancet* published an article by a team of Ugandan and British researchers working in the Rakai district near Uganda's southwestern border with Tanzania. The article described a "new disease" that people in Rakai were calling *slim* because of the severe weight loss it brought on. The authors claimed that "although slim disease resembles AIDS in many ways, it seems to be a new entity." The basis of their argument was that slim and AIDS looked different clinically: AIDS was found mainly in "Western homosexual patients" whose chief symptoms were often Kaposi's sarcoma (KS) and swollen lymph nodes (lymphadenopathy). Slim, in contrast, was found "primarily in the heterosexually promiscuous population," and had diarrhea and severe weight loss as its primary markers (Serwadda et.al. 1985).

The article on slim was published at a moment in history when AIDS and its causative agent were still entities under construction, as was the relationship between the two. The name "AIDS" (Acquired Immune Deficiency Syndrome) had replaced "GRID" (Gay-Related Immuno-Deficiency) less than three years previously, and knowledge that is now fundamental and taken-for-granted in the field of AIDS medicine was just being established. At the time that the article on slim was written, the exact link between the virus and the syndrome was still fuzzy. In Rakai, most—but not all—of the patients who had the symptoms of slim also tested positive for the virus that at that time was still being called HTLV-III. However, because the nature of the relationship between the virus and

the syndrome was still uncertain, it was scientifically viable for the authors to make the claim that slim was *associated with* the virus but was nevertheless *not the same* as AIDS.

Within months the *Lancet* article's claim that slim was "new" was contested, as it became apparent that many Ugandans with slim did indeed suffer from Kaposi's sarcoma, and many Westerners with AIDS developed severe wasting, making AIDS and slim more similar than different. However, for a time, a tacit acknowledgement of difference persisted in the medical literature—the equation of "slim" with "AIDS" was initially qualified by a reference to Africa: slim was "identical" not to AIDS but to "African AIDS" or to "AIDS as seen in Africa" (Kamradt et.al. 1985).

Although the idea that slim and AIDS were different diseases was short-lived, it is nonetheless an instructive example of the difficulty of establishing a universal definition of a syndrome made up of an assortment of diseases whose manifestation varies across geography and patient populations. Furthermore, it shows how Euro-American definitions of what constitutes "AIDS" have dominated the field from the very beginning. The vast majority of published papers describing AIDS at this time were based on research conducted among gay men in the U.S. and Europe. Thus, "AIDS" with no qualifier implied Euro-American AIDS, and this was the reference point against which other (qualified or marked) manifestations of the disease—such as "African AIDS"—were compared.

These qualifiers are now long-gone from the medical literature, but the issue of difference remains a challenge in international HIV medicine. As described in my introductory chapter, the upsurge of interest in AIDS in Africa among Western donor agencies and medical researchers has brought an increasing number of North American

and European doctors into professional relationships with their sub-Saharan colleagues through the establishment of Western-funded treatment programs, HIV training workshops for African doctors, and research collaborations based on the continent. This chapter uses observations from an HIV medicine training program located in Kampala, Uganda, and interviews conducted with Ugandan and North American doctors involved in training efforts to highlight some of the ways in which AIDS in Uganda remains a different disease from AIDS in the United States, and to raise questions about the nature and implications of this difference. I will argue that the fact of this difference generates both barriers to and opportunities for collaboration and knowledge exchange between the two countries. Barriers include the difficulty of communicating across this difference despite the common biomedical epistemology shared by North American and East African physicians. Opportunities include the chance for a reverse-exchange, when Western medical students trained in technical medicine are able to gain clinical experiences in Uganda that are no longer available to them at home.

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The Olusozi Hospital complex sprawls out across the slopes of one of Kampala's seven hills. As a national referral hospital, it is one of the country's largest health care facilities, and "free" to the public in that no official fees are charged to see a doctor. It is made up of a network of small, one-story concrete buildings linked together by a web of pathways—some paved, and some worn in the red dirt by foot traffic. In the open spaces between the buildings, women lay laundry out to dry on the green grass that covers the hillside. These women are the mothers, sisters, and aunties of bedridden patients who

have come to launder the sheets and blankets they have provided for their hospitalized relatives.

Drying laundry at Olusozi Hospital, March 2005 (photo by J. Crane)

At the bottom of the hill the pathways converge at the main hospital building, built by the British colonial government in 1962 just prior to Uganda's independence. With seven stories and 900 of the hospital's 1500 beds, it is the largest building in the complex, and newer than most. Prior to the 1970's Olusozi was the premier teaching hospital in East Africa, but its prestige was destroyed when many doctors were expelled or fled the country during the despotic regime of Idi Amin (1971-79). As the economy fell apart under Amin so did the hospital, to the point where it was left without running

water for ten years beginning in 1974 (Iliffe 2002). The facilities have improved since, but remain underfunded with patients frequently left responsible for providing their own bedding and food as well as purchasing their own medical supplies such as syringes and IV tubing.

There are two ways into the hospital grounds. The back way takes you up the far side of the hill, past a man selling coffins by the roadside.

Coffins for sale near Olusozi Hospital, July 2003 (photo by J. Crane)

More heavily trafficked is the front entrance where, on one side of the street, the "special hire" taxi drivers wait for fares under the shade of a large tree, their white Corollas parked nearby. On the other side the *bodaboda* men and their moped taxis wait in the sun. Just after the taxi drivers, you reach the main gate where an armed guard ushers you through. If you arrive by car the guards will sometimes ask you to open the trunk for inspection, though this request is more often made as cars depart the hospital in an

attempt to prevent the theft of drugs and medical supplies. A hundred yards further, the road dead-ends in between two buildings. On the left is the sooty, weathered façade of the main hospital. On the right is the smaller but much shinier Olusozi HIV Institute—the newest building in the hospital's complex, and a testament to the special access to donor money that HIV holds above other afflictions.

When I visited Kampala in the summer of 2003, the Institute building was still in the midst of construction, though several of the programs it was to house were already in existence. The Olusozi HIV Care Clinic that would come to occupy the ground floor of the Institute was located in the main hospital building across the street, where patients lined up beginning at 6 a.m. in hopes of being seen that day. The Institute's HIV Medicine Training Program—designed to provide intensive, "state-of-the-art" instruction to doctors in Africa—was also already up and running in one of the older single-story buildings on the hospital's campus, where it would remain until the new building was ready.

The Institute was the brain child of Max Edwards, an American infectious disease doctor who—like many senior AIDS researchers in the U.S.—made a name for himself treating and researching AIDS in San Francisco during the first years of the epidemic. He began working in Uganda in 1989, as part of a U.S.-funded study of heterosexual transmission of HIV. At this time, epidemiologists knew little about transmission of the virus between women and men because most research on HIV transmission had been done in the U.S. and Europe, where it was overwhelmingly focused on sexual transmission between men. Over the years he has held a number of prestigious positions in academic medicine, and currently chairs the department of internal medicine at a

university in the American southwest. In addition to his career in academia, Dr. Edwards has also spent 17 years as a member of the scientific advisory board of Medica Therapeutics, one of the most profitable pharmaceutical manufacturers in the world.

Still prominent in the field of clinical HIV research, Edwards is notorious among his university colleagues for his sociability and powers of persuasion. Thus it was not as surprising as it might have been when, over dinner in 2001, he managed to parlay his friendship with the CEO of Medica into a five million dollar grant from the company's philanthropic foundation to support the building of the Olusozi HIV Institute. In addition to providing a new space for the HIV Care Clinic and the training program, the Institute would also include a state-of-the-art research laboratory.

In 2004, the building was completed and christened with a gala grand opening celebration presided over by Ugandan President Yoweri Museveni. The guests at the celebration represented the numerous stakeholders in the Institute, and spoke to the complex web of alliances and jockeying for power that characterizes the Institute's administration. The most prominent guest other than Museveni himself was the CEO of Medica, who, according to one researcher I spoke with, had an armed security contingent that rivaled that of the President's. Also in attendance were numerous members of a group called the Physicians' Partnership, a loose collaboration of North American and Ugandan HIV physician-researchers organized by Max Edwards to oversee and staff the Institute's HIV Medicine Training Program. Two other groups of North Americans also participated in the grand opening: researchers who had ongoing studies based at Olusozi, and representatives of the Global AIDS Foundation, Dr. Richard Swan's San Francisco-

based foundation (see Chapter 1) which was the fiscal agent for Medica's donation and had overseen the construction of the Institute's building.

All three of the entities that the new building would house—the HIV Care Clinic, the HIV Medicine Training Program, and the research laboratory—already existed in some form at Olusozi Hospital prior to the construction of the Institute. In other words, the Institute's construction was not necessary to make these programs happen—although it did provide them all with substantially improved facilities. The rationale for building the Institute varies according to different stakeholders, as do feelings about its appropriateness. Its boosters describe the building as a way to leave something tangible to benefit the hospital and the medical school, and repeatedly point out that it is the first building to be built on the teaching hospital's campus in 37 years. It is also true, of course, that the building provides a very visible example of Medica's corporate philanthropy, one which has helped the company promote itself as humanitarian even as it lobbies in defense of the drug patenting laws that put many basic medicines out of reach in Uganda.

The relative importance of the three programs (the clinic, the training, and the laboratory) to the purpose and functioning of the Institute is a source of debate among those involved. Publicly, the HIV Medicine Training Program has been promoted as the Institute's primary raison d'etre, and this sentiment was echoed by Max Edwards in his interview with me. Privately, some stakeholders—including representatives of the Global AIDS Foundation and a few North American researchers—suggested to me that the Institute's state-of-the-art, U.S.-certified laboratory was actually the jewel in the crown, built to attract more Western-funded research projects and to benefit the research

of North American members of the Physicians' Partnership. Furthermore, opinions about the appropriateness of the training program also varied. Whereas Dr. Swan of the Global AIDS Foundation told me the training was "not a model that's reproducible, nor, in my opinion, sustainable," a board member at the same foundation argued that despite the program's expense, it was "a spectacular model" for "people who are going to go back to their communities, and really have a leadership role in the antiretroviral roll-out."

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Every other month, a group of 25 physicians from Uganda and other east African countries comes to the Olusozi Institute for 4 weeks to participate in its HIV Medicine Training Program, described by the Institute as a "state-of-the-art" training course in HIV care designed for doctors in Africa. They come to learn about the free antiretroviral medications that have recently become available at their clinics through international initiatives such as the Global Fund to Fight AIDS, TB, and Malaria and PEPFAR. Since the advent of these free programs, clinics in many cities and towns have become overwhelmed with patients seeking free drugs. As a result, clinics are scrambling for doctors educated in the complexities of HIV medications.

I spent March of 2005 among a class of trainees at the Olusozi Institute as we were schooled in the vocabulary of antiretroviral treatment as it exists in North America—terms like "CD4 nadir," "viral load blip," and "ritonavir boosting." Over the course of the training, however, I became aware of an alternate vocabulary coming from the trainees—terms like "WHO stage IV," "immune reconstitution syndrome," and "Triomune-40"—that reflected the specificity of HIV care in what the medical literature

refers to as a "resource-limited setting." The significance of these vocabularies, as I hope my argument will show, is that they suggest two different ways of knowing HIV/AIDS.

Economic inequality shapes health and medicine in numerous and complex ways, but for the purposes of this chapter I want to focus specifically on the role technology plays in this equation. Social scientists have described the role played by medical technologies in defining and giving meaning to health and disease (Clarke and Fujimura 1992, Fleck 1979, Wailoo 1997). They argue that diseases and technologies "co-constitute" one another—that one cannot be defined or understood without the other. In other words, disease as we know it does not exist independently of the tools we use to assess it: for example, the definition of epilepsy depends on the EEG, heart disease is defined according to EKG, cervical dysplasia is defined by the pap test, and—most relevant to my topic—the definition of AIDS increasingly depends upon the CD4 count and viral load tests.

Both CD4 and viral load tests constitute "surrogate markers"—measurements that provide an indirect assessment of the progression of HIV. CD4 cells are disease-fighting cells of the human immune system, and a major target of the HIV virus. Because of the destruction of these and other cells, people with HIV become vulnerable to illnesses that would not endanger people with healthy immune systems. Measuring an individual's CD4 count is a way of assessing damage to the immune system and, by extension, the advancement of HIV disease. Viral load testing measures the concentration of HIV in the blood. Ideally, viral load is "undetectable," meaning it falls below the ability of the test to measure it. A high viral load—especially in combination with a falling CD4 count—is another indication that an HIV-positive person's condition is worsening.

In addition to serving as an indication of disease progression for doctors and their patients, these surrogate markers provide the biological yardstick by which the key distinction between "HIV" and "AIDS" is demarcated. At the most basic level, HIV—human immunodeficiency *virus*—refers to the virus itself, an isolable microorganism. HIV belongs to a family of viruses known as lentiviruses, or "slow" viruses. The slow action of the virus means that even without antiretroviral medication a person may not become sick until years after infection.[41] AIDS (acquired immunodeficiency *syndrome*) is the name given to this state of being sick. In between these two categories—HIV and AIDS; being infected and being sick—lies the more nebulous state of *becoming* sick, sometimes referred to as "HIV disease" or "symptomatic HIV."

As HIV destroys the body's disease-fighting CD4 cells over time, people with the virus become vulnerable to infections and other illnesses that a healthy immune system is able to fight off. Microbes such as yeast, which are normally kept at bay by the immune system, begin to grow out of control and cause chronic infection. Similarly, bacteria lying dormant and harmless in the body can become active and disease-causing—as is often the case with tuberculosis.[42] These HIV-related illnesses are called "opportunistic infections" (OIs) because they take advantage of weakened immunity. Certain cancers, such as Kaposi's sarcoma and cervical cancer, also flourish in this state of immunodeficiency and are often referred to as OIs even though they are not technically infections.

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[41] Untreated adults infected with HIV may remain asymptomatic for 10 years or more. In children, this phase is usually much shorter. Most untreated African children born with HIV die before their third birthday (Chakraborty 2005).

[42] Approximately one-third of the world's population is infected with the tuberculosis (TB) bacillus, but only a small percentage will actually become sick with active TB because a healthy immune system is usually able to keep the disease at bay. People with HIV, if infected with tuberculosis, are much more likely to develop active disease because of the damage to their immune systems.

The tipping point at which HIV infection becomes AIDS is not a biological given; rather, it is a demarcation that has been constructed for both medical and social purposes. Initially, AIDS was defined by the U.S. government's Centers for Disease Control according to the number and severity of opportunistic infections an HIV-positive person had experienced. In the early 1990s, this list of "AIDS-defining illnesses" was revised and the criteria for an AIDS diagnosis were expanded to include people whose CD4 count had fallen below 200 (a normal count is between 500 and 1500). Within medicine, the distinction between HIV and AIDS initially served simply as a way for doctors and patients to put a name to the different stages of disease that they were witnessing or experiencing. In the realm of U.S. policy, however, these categories were linked to access to resources, as a diagnosis of AIDS qualified an individual to receive social security disability benefits, but HIV infection alone did not. Similarly, many AIDS service organizations made an AIDS diagnosis part of the eligibility criteria for receiving services such as food, housing, and financial assistance thus further "commodifying" the diagnosis (Crane, Quirk and van der Straten 2000; see also Leclerc-Madlala 2005 on the recent emergence of similar policies in South Africa).

With the advent of effective antiretroviral drugs in 1996, CD4 and viral load testing took on added importance in medicine as they became integrated into treatment guidelines specifying when a person should be started on medication.[43] Furthermore, by improving patients' CD4 counts and viral loads, antiretroviral drugs complicated the relationship between HIV and AIDS by making it possible for patients to develop AIDS

[43] Treatment guidelines are not standardized, but the two widely used guidelines in the U.S. recommend that any patient with a CD4 count of under 200 be put on antiretroviral treatment, and that treatment be considered for patients with a CD4 of under 350 and a viral load of over 50,000 (DHHS 2005; Yeni et. al. 2004).

and then become "well" again, such that they no longer met the criteria of an AIDS diagnosis. These changes, however, were largely limited to the industrialized West where both antiretroviral drugs and diagnostic technologies were available to most patients.

Indeed, in wealthy countries, the technologies of CD4 count and viral load measurements have become inextricably bound to the way that HIV and AIDS are medically conceptualized, studied, and treated. As a result, in a North American context, it is nearly impossible to have a professional discussion about HIV without referring to CD4 count and viral load. The same applies to the arena of international HIV research, where these numbers serve as a common vocabulary shared among elite researchers from around the world. More recently, as increasing numbers of patients in the U.S. and Western Europe have developed drug-resistant HIV, genotype resistance testing has become integrated into this medical lexicon. In contrast, the trainees at Olusozi—who were clinic doctors, not elite researchers—were accustomed to relying heavily on physical signs and symptoms to assess their patients' health. They were well-versed in the WHO's "clinical staging" system for HIV—basically a standardized categorization of progression towards death based on weight loss and infections, where stage I is asymptomatic and stage IV (the final stage) is advanced, bedridden illness. Only about half the group had access to CD4 tests, very few had access to viral load testing (this was limited to those with patients enrolled in internationally-funded research studies), and none had access to resistance testing. This disparity in access to technologies is of course, at is root, economic. At over $100 per test, viral loads are simply too expensive for the Ugandan health care system. Resistance testing is even more out of reach, costing

several hundred dollars per test. CD4 counts are cheaper ($15) and are, as a result, somewhat more widely available. However, most labs with the ability to do CD4 testing are located in cities and large towns which, in a country where over 80% of the population lives in rural areas, puts this technology out of reach for many. Furthermore, the choice of antiretrovirals in Uganda is much more narrow than the 20 different drugs available in the U.S., also a reflection of global economic inequality and Uganda's dependence on the limited selection made available by Western donor programs.

This begs the question: what constitutes HIV disease and AIDS in a place where CD4 and viral load testing are not readily available? Furthermore, what is antiretroviral "management" in a place where there are only 2 drug regimens to choose from? And what defines HIV drug resistance when there is no resistance testing to confirm it? These were questions that arose both explicitly and implicitly during the course of the Olusozi HIV Medicine Training Program. Charged with providing a state-of-the-art course in HIV medicine, the trainers had to constantly negotiate between what was *known* about HIV in the West and what was *possible* in the "resource-limited" context of Uganda. Trainees had to negotiate this as well, and try to map their existing clinical knowledge of HIV onto categorizations of the disease based on CD4, viral load, and other diagnostic technologies.

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The training room at the Olusozi Institute is furnished with rows of new desks and comfortable, swiveling office chairs, all facing towards a projection screen at the front. There is an LCD projector for presentations, and fans in the windows to keep the room cool. Down the hall is a computer lab where trainees learn how to search on-line medical

literature databases and create Power Point slides. During the training lectures, I joined them at an empty desk. Most were young Ugandan doctors from Kampala and other large towns, though there were a few from more rural areas. Six of them practiced at Olusozi Hospital, which uses the Institute to supplement the training of its medical residents. There was only one doctor from northern Uganda, which after 18 years of civil war has come to be regarded almost as a separate country from the more stable and wealthy south. A few of the trainees came from neighboring East African countries: Kenya, Tanzania, Ethiopia, and Zimbabwe. The training is not free, and so those who attended either had the means to pay or to obtained sponsorship to cover their fees. The training was conducted entirely in English, which is the colonial language of Uganda and also its official language, though fluency is limited to those with higher education. The training curriculum and lectures were designed by the North American Infectious Disease Association, a professional organization of infectious disease doctors formerly headed by Max Edwards that also contributes two North American trainers to each month-long training session. Many of the lectures were also given by internationally-recognized Ugandan AIDS experts affiliated with the Institute.

Over the course of the training, the lecturers regularly stumbled over the reality of the low-tech clinics in which many of the trainees practiced—particularly the North American trainers, who unlike their Ugandan counterparts, had had access to CD4 testing since the advent of the epidemic, and viral load testing since the technology was first developed in 1996. For example, one week into the training, there was a lecture describing when patients should be started on antiretroviral medications. Unlike many other diseases, HIV infection is not treated right away due to the toxic effects of long-

term antiretroviral therapy. Most doctors wait until their patients have experienced some decline in their immune system before beginning treatment, but the ideal timing of when to start has been a topic of debate over the years. The training lecture on when to begin medication was given by Peter Humphries, an American physician-researcher affiliated with the North American Infectious Disease Association.

Like all the lectures in the training, it was very much in the style of a typical presentation at a medical school or conference in the U.S.—relying heavily on Power Point slides and data published in leading medical journals such as the *Journal of the American Medical Association* and the *Lancet*. In teaching the group when to start a patient on drugs, Dr. Humphries had to toggle back and forth between the state-of-the-art guidelines (written in the U.S. and based on CD4 and viral load) and alternate guidelines designed for use in the absence of these technologies.

After describing the history of controversies within medicine over when HIV drugs should be started, Humphries showed us a Power Point slide outlining the current guidelines published by the U.S. Department of Health and Human Services (DHHS):

CD4<200	*treat with ARVs*
CD4<350	*offer treatment*
CD4>350	*consider treatment if viral load >55,000*

However, in "resource-limited settings," Humphries explained, the guidelines for antiretroviral use are different. Published by the World Health Organization, these guidelines assume that viral load testing is not possible, and that CD4 testing may or may

not be.[44] Explaining the guidelines, Dr. Humphries told us, "If you can do a CD4, treat anyone who is WHO stage IV [advanced disease] and those in stage III [symptomatic disease] with a CD4 of less than 200." Those without CD4 testing were encouraged to use a patient's total lymphocyte [white blood cell] count as an alternate measurement. This is a test that is more commonly available in low-income countries and roughly approximates CD4 levels. Then Humphries asked the class: "How many of you don't have a CD4 count available?" Half the trainees raised their hands.

This phenomenon—the description of some aspect of HIV/AIDS based on diagnostic technologies, followed by the question "how many of you have access to this technology?"—was a regular occurrence during lectures. Sometimes this would be followed by a discussion of alternate means of monitoring the disease, such as Dr. Humphries' suggestion that trainees rely on total white blood cell count to estimate a patient's CD4 count. At other times, however, trainers were at a loss to recommend alternate strategies, as when Dr. Humphries realized that most of the trainees had neither the medical facilities needed to perform kidney biopsies nor the technology necessary for dialysis—both key tools in the diagnosis and treatment of HIV-related kidney disease. "So," he told the class, "these patients will do poorly." As dialysis and transplant are the

[44] The WHO uses clinical symptoms to divide HIV/AIDS into four stages of increasing severity:
Stage I: Asymptomatic; Persistent generalized lymphadenopathy (PGL).
Stage II: Moderate unexplained weight loss; Recurrent respiratory tract infections; Herpes zoster; Angular cheilitis; Recurrent oral ulcerations; Papular pruritic eruptions; Seborrhoeic dermatitis; Fungal nail infections of fingers.
Stage III: Severe weight loss; Unexplained chronic diarrhoea; Unexplained persistent fever; Oral candidiasis; Oral hairy leukoplakia; Pulmonary tuberculosis; Severe presumed bacterial infections; Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis; Anaemia, neutropenia, or thrombocytopenia for more than one month.
Stage IV: HIV wasting syndrome; Pneumocystis pneumonia; Recurrent severe bacterial pneumonia; Chronic herpes simplex infection; Oesophageal candidiasis; Extrapulmonary TB; Kaposi's sarcoma; Toxoplasmosis; HIV encephalopathy; Cryptococcal meningitis; Disseminated non-tuberculous mycobacteria infection; Progressive multifocal leukoencephalopathy (PML); Candida of trachea, bronchi or lungs; Cryptosporidiosis; Isosporiasis; Visceral herpes simplex infection; Cytomegalovirus (CMV) infection; Any disseminated mycosis; Recurrent non-typhoidal salmonella septicaemia; Lymphoma; Invasive cervical carcinoma; Visceral leishmaniasis (WHO 2005a).

only effective treatments for advanced kidney disease, there was little that Humphries could do other than simply state the obvious and move on.

North American trainers were not the only ones to teach the trainees about technologies unavailable to most of them. The Ugandan trainers engaged in a similar kind of back-and-forth between what was known about HIV and what possible in the context of Uganda. Sometimes they acknowledged this disparity up front, as one pediatric AIDS specialist did in her lecture on antiretroviral treatment in children. She told the class that it is recommended that children be started on drugs if their viral load goes over 100,000, but immediately acknowledged that "we don't have that luxury, so we must use clinical symptoms." Other times, it was the students who raised the subject. This is what happened following a separate lecture on pediatric AIDS in which the trainer, a Ugandan pediatrician based at a private clinic in Kampala, relied heavily on CD4 and viral load. During the question-and-answer session, a question about CD4 came up and one of the trainees pointed out that that "in most of our settings we have no CD4 machine." The doctor responded that in such cases, clinical monitoring should be used.

"Clinical monitoring" is perhaps best explained as hands-on doctoring: assessing the patient's condition primarily through physical examination, supplemented by very basic laboratory tests when available. Clinical monitoring relies on physical examination: feeling the texture of the patient's hair and the condition of his or her skin, testing the firmness of the abdomen and the lymph nodes. It involves visual inspection for rash, thrush, lesions, clubbing of the fingertips—all indicators of possible AIDS-related illnesses. It requires noticing if a patient is losing weight or seems dehydrated, or if one side of the chest is rising more than the other when they breathe. And it

necessitates listening closely to the lungs for sounds that might warn of pneumonia or tuberculosis. These clinical abilities were well-respected by the North Americans I met working in Uganda, some of whom felt that these skills had eroded among doctors at home because of the reliance on diagnostic technologies. Alex Oliveira, an American surgical resident who had worked in Uganda, told me that working there had allowed him to practice the kind of "laying on of hands" that had been emphasized in his early years in medical school. At home, in contrast, he and his fellow residents would joke that instead of examining their patients, they should just send them through the CT scan and operate based on what the machine told them.

At the same time, this respect for the Ugandans' clinical expertise was often paired with an uneasiness about the accuracy of diagnosis based on clinical symptoms. One day during the daily "tea break" between morning training lectures at the Olusozi institute, I asked George Avery, a trainer from Canada, to reflect on the low-tech environment in which most of the trainees were working. As we snacked on hot tea, samosas, and boiled eggs that had been brought up for the class from the Institute's canteen, he told me that the trainees had very good clinical skills "because they don't have the diagnostics to fall back on the way Western doctors do." Then he told me the story of a Ugandan doctor he had observed evaluating a patient. The doctor's clinical examination suggested one diagnosis but the chest x-ray suggested another, and he had told his colleagues that he wasn't sure which he should trust. "In the West," Dr. Avery continued, "there would be no question—you would go with the x-ray." But in Uganda, he said, doctors are so confident in their clinical findings that it can actually lead them to doubt the diagnostics. He told this story with both a sense of awe for the clinical skills of

the Ugandan physician, but also a sense of disbelief and discomfort with the questioning of the x-ray's results.

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One of the tricky aspects of treating HIV is that many of the side effects of antiretroviral medications closely resemble symptoms of AIDS-related illnesses. Diarrhea, changes in body fat (lipodystrophy), pain in the extremities (peripheral neuropathy), and rash are all potential antiretroviral side effects that can also be signs of AIDS. For this reason, CD4 count and viral load have become even more important in HIV medicine since the advent of effective treatment, because they provide a non-clinical indicator of whether a patient's disease is progressing or improving. Without these diagnostics, the trainees at Olusozi sometimes struggled with how to interpret their patients' symptoms.

This struggle was most apparent in the training sessions where doctors were taught how to deal with treatment failure. "Treatment failure" is the term AIDS researchers and clinicians use when a patient has a "suboptimal response" to antiretroviral drugs – in other words, when the patient does not seem to be benefiting from treatment (DHHS 2005). Sometimes a person "fails" treatment from the very beginning. Other times, a person benefits from the medications for a period of time but then stops responding to them. Often this means that the patient's virus has developed drug resistance, but it can also indicate that a person isn't getting a strong enough dose of medicine—either because they are skipping doses, they are having problems metabolizing the drug, or the combination of drugs they are on is not as potent as it should be (DHHS 2005).

Treatment failure is a general term that includes the more specific categories "virologic failure," "immunologic failure" and "clinical failure." Doctors define virologic failure as when a patient's viral load continues to be detectable (or rises) despite antiretroviral treatment. It usually precedes immunologic failure, defined as when a patient's CD4 count either does not improve or drops down to below pre-treatment levels. Immunologic failure can be followed by clinical failure, when a person becomes sick with AIDS-related illnesses. In the U.S., viral loads and CD4 counts are essential tools in determining whether treatment failure is occurring and whether or not a patient should switch to a different drug regimen.

Without CD4 and viral load information, doctors at the Olusozi training sometimes had trouble deciding whether a patient's symptoms were a sign that the drugs weren't working ("treatment failure"), or were simply side effects of the medications themselves ("drug toxicity"). During one lecture a trainee named Dr. Aguma—a young, genial physician working in rural western Uganda—asked for advice on how he should have managed a difficult case of possible treatment failure in one of his patients. The patient came to his clinic with a swollen liver and spleen, lipodystrophy (body fat redistribution), and tuberculosis. She had begun antiretrovirals some time before by making monthly 100-kilometer journeys to Mukwano, the nearest large town, and purchasing them herself with money provided by her brother. She was taking Triomune—the generic combination of three antiretroviral drugs manufactured in India (see Chapter 2). But her brother had other financial obligations and was not always able to provide her with money to buy the pills, so she periodically missed doses when she couldn't afford to buy more. Eventually, however, she was able to enroll in a free

treatment program. Nonetheless, when she arrived at Dr. Aguma's clinic she was quite ill. What was difficult to know was whether she was ill with AIDS—meaning her drugs were no longer working—or if she was ill from side effects brought on by the medications, in which case the virus itself was still under control.

If this patient had been in a city like San Francisco, doctors would have solved this puzzle by ordering a viral load test and CD4 count. An increase in viral load and decline in t-cells (CD4) would indicate that the patient's drugs were not working, and that she was suffering from AIDS. A low or undetectable viral load and high CD4 count, on the other hand, would suggest that her symptoms might simply be side effects of the medications themselves and not a sign of disease progression. However, like most clinics in Uganda, Dr. Aguma's clinic could not provide viral load testing. He could have gotten a t-cell count by sending a blood sample to a lab in Mukwano, but only if the patient would pay for it—a cost of $35 (68,000 Ugandan shillings) not including transport (the average monthly income in Uganda is approximately $30). Furthermore, in order to see if her t-cell count was falling, he would need to not only get her current CD4, but have a previous CD4 count to compare it to. She said she had had one done at the Mukwano clinic when she began treatment, but did not remember what it was. Following the Ministry of Health's treatment guidelines, Dr. Aguma decided to switch two of the three drugs in her drug regimen. Although this combination included two new drugs, both were in the same classes as the old drugs, meaning that the patient might already be resistant to them nonetheless. However, these were the only antiretrovirals available for free at Dr. Aguma's clinic other than the ones the patient was already on.

In the end, the patient died. Dr. Aguma wondered if she had been experiencing treatment failure—possibly due to drug resistance—or if her symptoms were simply side effects of the drugs she was on. Was switching her drugs the right decision, or should they have stopped treatment for a month or two to see if her symptoms diminished? The trainer, an American, did not have an answer. He acknowledged it was a difficult case, and moved on.

The same issue came up again during the second week of the training in a clinical case presentation made by a Ugandan trainer named Dr. Katerwe. He described two patients who had sought treatment recently at Olusozi's HIV Clinic. Both were women who had been on antiretrovirals for several years, but were nonetheless losing weight. In particular, both were suffering from "facial wasting"—the loss of subcutaneous fat in the face, leaving them with sunken cheekbones. This condition can be a side effect of D4T, an antiretroviral drug that both patients were on, but it can also be a symptom of AIDS. The cosmetic effects were of great concern to the patients because they were stigmatizing, as they mimicked the physical wasting associated with AIDS. Before they developed the facial wasting one of the benefits that treatment had held for these women was restoring not just their actual health, but also the physical appearance of health, which prevented them from being easily identifiable as someone with the stigmatized virus. The problem now was that even though their health might actually be improved, they *looked* sick nonetheless.

Because these patients were being seen at Olusozi—which, as a national referral hospital, has better access to more diagnostic technologies than most other health care facilities in the country—they were able to get CD4 tests done, which showed that their t-

cell counts were improving. This meant that it was likely that the facial wasting was the result of D4T treatment rather than a form of wasting associated with AIDS itself. However, during the discussion that followed Dr. Dumont—a Belgian doctor affiliated with the Institute—emphasized that this was a very important presentation, because in clinics where CD4 and viral load were not available, facial wasting caused by D4T could look very much like AIDS. In other words, it could be very difficult to tell if a patient was losing body fat *despite* antiretroviral treatment or *because* of it.

Equally difficult was the task of distinguishing AIDS-related illnesses from what might be called "recovery-related" illnesses in the absence of laboratory diagnostics. What I mean by "recovery-related" illnesses are symptoms brought on by the reactivation of a patient's immune system after starting antiretroviral drugs. The technical name for this is "immune reconstitution inflammatory syndrome," abbreviated as IRIS. IRIS is essentially a paradoxical reaction to antiretroviral treatment in which patients suffer symptoms of AIDS-related illnesses even as their health improves according to CD4 and viral load measures. In patients with very low t-cell counts, the body's normal reaction to AIDS-related infections—fever, rash, itching, pain, inflammation, etc.—may not occur because the immune system is simply too weak to launch a response. However once antiretroviral drugs begin to raise a patient's t-cells, the immune response kicks in (Chenois 2004). Suddenly, the patient displays symptoms of numerous infections, but these symptoms are actually a sign that the treatment is *working*, not that it has failed. As antiretroviral drugs continue to rebuild the immune system, the symptoms of immune reconstitution syndrome generally recede, though acute cases can be life-threatening.

During my visit to the Olusozi training, the North American trainers told me that there was much more focus on immune reconstitution in Uganda than there was in North America. This is because the syndrome usually occurs among people who begin treatment with very low CD4 counts—something that rarely happens in the U.S. but is quite common in Uganda where geographic, financial, and other barriers to drug access mean that patients often start treatment much later than they would in the U.S. In this way, immune reconstitution syndrome is just one of the many biological consequences of economic inequality.

In a case presentation to the class, a Ugandan trainee named Dr. Odong described a possible case of immune reconstitution in one of his patients. The patient began antiretroviral medications when her CD4 count was only 49 – much lower than the starting point of 200-350 that is recommended in U.S. guidelines. After 14 months of treatment she began complaining of severe headaches, and a few months later she started having convulsions. Because she was being treated at Olusozi, she was able to get another CD4 test, showing that her count had climbed to 244. She further benefited from the fact that her family was unusual in their ability to pay for a CT scan, which revealed that she had some lesions in her brain. Dr. Odong thought it was possible that these lesions were signs of toxoplasmosis—a common cause of brain infection in people with AIDS—but they also could have been a symptom of immune reconstitution syndrome. He treated the woman with anticonvulsant medication, and her health improved.

Dr. Odong wanted to know what had caused his patient's condition. Was she suffering from AIDS-related toxoplasmosis, or was she experiencing immune reconstitution? Or, did the brain lesions have some other unrelated cause? The trainers

at the session—a Ugandan, a Belgian, and an American—debated the possibilities but could not come to a conclusion. The mystery of the patient's illness was left unresolved, though the patient's climbing CD4 count put most of the doctors at ease that she was not in any imminent danger of succumbing to AIDS.

The consequences of mistaking immune reconstitution for AIDS or vice-versa are significant, as immune reconstitution syndrome indicates that the drugs are working and should be continued, where AIDS suggests that they are not working and should be switched, if possible. WHO treatment guidelines for "resource-poor" countries caution against confusing the two, but give little in the way of concrete criteria by which to draw a distinction in the absence of a CD4 count, other than that immune reconstitution tends to occur within the first three months of antiretroviral treatment (although this 3-month timeline is also contested). In reality, as Dr. Humphries told me during a break between lectures, "not much is known about immune reconstitution because it doesn't happen in the West anymore."

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One of the things at stake in teasing out the effects of treatment from the failure of treatment is the possibility of drug resistance. The genotype technology used to assess resistance in the U.S. was not available to any of the Olusozi trainees. The use of genotype testing was, however, covered in the Olusozi training—perhaps because of an overly optimistic view that such testing might be available locally in the future, but also to familiarize trainees with a technology that they were certain to encounter in the medical literature, which largely reflected Western-funded research. The training lecture on drug resistance was given by Dr. Avery, the Canadian who had served as a trainer

once two years earlier. He began by acknowledging that the "gold standard" of genotype resistance testing was "unfortunately not available to any of you" and then went on to describe how to use viral load and CD4 testing to determine if a patient had become drug-resistant. Those without even a CD4 count, he told us, would be left no choice but to assess resistance clinically. Clinical resistance is defined by the WHO as the development of AIDS-related illnesses after 6 months or more of treatment with antiretroviral drugs. But in order to determine whether this resurgence of disease was due to drug resistance, both drug toxicity (side effects) and immune reconstitution had to be ruled out—a process which, as I hope previous sections of this chapter have shown, is far from straightforward. Dr. Avery then went on to explain different types of drug resistance testing, acknowledging a second time that none of the group would have access to such tests, but telling us that "there are some things to be learned from it anyway—you'll see these tests in the literature."

What went unspoken was the lack of applicability of much of the literature to treating AIDS in Uganda. This was made evidently clear in a case presentation by one trainee when he recommended—based on a review of medical literature—that one of his patients who was failing treatment undergo phenotype testing for resistance and, based on the phenotype results, be treated with a "mega-HAART" combination of six antiretroviral drugs. The other trainees erupted into laughter at this proposal. This situation speaks to one of the quandaries faced by East African doctors, particularly those who aspire to engage in research or work in international health: they must be up-to-date on the current medical literature in order to advance their careers, but the recommendations made therein may be impossible to apply in their own poorly-funded clinics. In such a context,

then, teaching "state-of-the-art" medicine may have more to do with preparing trainees to engage in a set of scientific conversations underwritten by the West than in providing them with information that could assist them in diagnosing and treating their patients.

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The global political economy of research funding shapes what questions get asked in HIV science—questions which, in turn, shape how the disease comes to be known and defined. These issues will be addressed in detail in the following chapter. At the same time, however, it is important to recognize that even as the differences between AIDS in Uganda and AIDS in North America discourage certain lines of scientific inquiry, these differences also produce certain opportunities for study. Specifically, the existence of large numbers of men, women, and children with HIV in the context of very limited access to antiretroviral treatment provides doctors and medical students from Western Europe and North America with the opportunity to see AIDS as it rarely appears anymore in their home countries.

In wealthy countries, ten years of effective antiretroviral treatment have changed the nature of the disease, transforming it into a chronic, manageable condition in many patients. Many people no longer die from AIDS per se but rather from other conditions such as hepatitis, heart disease, cancer, or drug addiction. Others die simply from old age. Of course, disparities within the industrialized West have also maintained pockets of people who, for reasons often linked to economic, racial, and geographic marginalization, do not get adequate medical care and die of AIDS having received little or no antiretroviral treatment (see Levenson 2004). However, the scale of this inequality and of the epidemic itself is several orders of magnitude less than the difference between,

for example, the U.S. and Uganda. In Uganda, it is estimated that only 35 to 43 percent of people in need of HIV drugs are getting them, a figure which despite its lowness far exceeds the percentages of patients accessing treatment in surrounding countries (WHO 2005b). In this way, the economic inequalities that impede access to treatment become biologized in the form of people who are not only sick, but sick in a very specific way: with the opportunistic infections and other AIDS-defining illnesses that are becoming increasingly scarce in wealthy countries like the U.S.

As a result, North American doctors and medical students may turn towards Africa as a way of studying AIDS as it rarely appears at home. Furthermore, they stand to gain a type of clinical experience in these low-tech settings that is often no longer possible in the highly technologically-mediated medicine practiced in the industrialized West. To describe this as a form of parasitism would be overly simplistic, and would do a disservice to those medical students and doctors who elect to complete a clinical rotation or a fellowship in a Ugandan hospital. On the contrary, the doctors and students who travel to countries like Uganda are often motivated by humanitarian concerns, and aim to use the knowledge and skills they gain to work towards the betterment of health in low-income countries. My goal is not to criticize this form of study, rather, it is to be specific about its conditions of possibility. Doing so requires the recognition that even those who decry the global inequalities of the epidemic stand to benefit from the opportunities for knowledge production that these very same disparities have made possible—myself (and this dissertation project) included.

Over the course of my fieldwork, the "opportunities" offered by Uganda were perhaps most eloquently articulated by Dr. Joseph Tabula, a professor at Olusozi medical

school and founder of a medical journal focusing on East Africa. Although not involved in the Institute's training program, he had conducted trainings for doctors in South Africa as well as for African doctors studying in Norway. In an interview in his office, I asked him if he felt there was a tension between providing high-tech, state-of-the-art information and the reality of the low-tech environment in which many African doctors practice. In the course of answering my question, he turned my assumption about what constitutes "state-of-the-art" on its head, and described very plainly the opportunities afforded by study in a setting like Uganda:

> *Prof. Tabula*: For me, the state of the art means finding your niche where you are best and excelling in it. So if you want clinical care of HIV infected children, the place to go is Uganda….If I go to Norway, they don't even have patients. There's not even one child with HIV anymore in Norway. There's not even one child. So they should be sending their students here to see the patients, and to know this is how we deal with them here….That's where we excel. We have clinical patients. We have loads and loads of patients. Other people don't have patients! They are training doctors under video – I saw it in Norway. They have never touched patients!
>
> *J. Crane*: They're training doctors on video?
>
> *Prof. Tabula*: Doctors! Yeah! They are operating in a theater there, carrying out an operation. The students are watching on the video. I said what is this?! What type doctors are you going to produce? They have never touched a patient! You work for us, our doctors, if there is an operation, the students go there. And they feel, they assist, they touch. And that's the excellence we want. Molecules and things they are very important, but at the end of the day — it's the person that matters, in my view.

His sentiments were echoed by Alex Oliveira, the American surgical resident mentioned earlier, who had worked in Uganda. When I met him in San Francisco, he was in the process of instituting a training program for his fellow American surgical residents at Olusozi hospital. The son of Brazilian immigrants, he said that his roots in a developing

country were one of the motivating factors behind his interest in international health. He felt strongly that medical training should not be looked at as a one-way street, with knowledge traveling from the global North to poor countries in the South. Americans, he told me, can learn a lot from working in Africa and from the clinical expertise of doctors there. Clarifying, he said, "I'm not trying to glamorize the lack of technology in Africa—they *should* have what we have. But they also have lots that we don't have: the resource-limited environment, the pathology, and the culture all make it a very rich learning environment." Here poverty, disease, and difference are reworked into a certain form of "richness" available to students willing and able to take advantage of it.

Conclusion

This chapter has described the ways in which economic inequalities govern access to medical technologies and how these technologies (or lack thereof), in turn, shape how HIV and AIDS come to be known and defined in North America and Uganda. What is interesting from a medical anthropological perspective is that these different ways of knowing HIV/AIDS emerge in the context of an otherwise shared epistemology of biomedicine. This differs from the kind of incommensurability (Pigg 2001) that has been described by anthropologists who study indigenous medical systems. For example, Julie Livingston's recent ethnography *Debility and the Moral Imagination in Botswana* (2005) juxtaposes Tswana medicine and biomedicine, and describes how their differing approaches to disability, chronic illness, and aging are rooted in "two radically different ontological regimes" (Livingston 2005: 162).

However the situation I describe in this chapter is different from the kind of comparison that Livingston makes, because it demonstrates that incommensurable—or, at

least, only partially commensurable—understandings of AIDS may co-exist *despite* a shared biomedical framework. In other words, though I'm proposing that the doctors I observed had different ways of knowing HIV, I am not attributing this difference to culturally divergent models of medicine, illness, or the body. Nor am I arguing that national origin determined how these doctors approached the disease: there were internationally-trained Ugandan lecturers who relied on CD4 and viral load-based descriptions as much as the North American trainers did; and there were American and European trainers who had long worked in Africa who pushed for discussion of what could be done without these technologies. Rather, I hope this chapter highlighted the heterogeneity that can exist within biomedicine—particularly between "resource-rich" and "resource-poor" settings—and how technological differences rooted in economic inequality shape medical knowledge and practice. International collaborations in medical education such as those described above are an arena in which both the challenges and opportunities generated by this difference become manifest, blurring the lines between humanitarianism and self-interest and raising difficult questions about the relationship between technology, disease, and the amelioration of the AIDS epidemic in East Africa.

The question remains: what can be done? The answer is more complicated than a simple technological fix. The inequalities between HIV care in the U.S. and Uganda are rooted in much deeper economic inequalities that stymie efforts to equalize medical infrastructure. Efforts are being made to improve access to technologies such as CD4 testing machines to Uganda and other low-income countries. However, often well-intentioned donations of laboratory equipment bring only temporary benefit as the donations do not provide training in how to fix the machines once they break or are

damaged by power outages, nor do donors assure a reliable supply of the chemical reagents necessary to perform the assays. And access to HIV pharmaceuticals, though greatly improved since 2003, remains years behind the U.S. in terms of the number of drugs available. On a more optimistic note, access to HIV-related medical technologies is improving in Uganda, albeit slowly. Furthermore, there is a growing interest in inventing or redesigning technologies to be more compatible with a "resource-poor" environment in which refrigeration, transportation, and electricity are not as available as they are in the industrialized West. In the meantime, Ugandan doctors must continue to straddle the line between what is *known* in HIV medicine and what is *possible* in their clinics.

I asked one of the Ugandan trainers at Olusozi to reflect on this. Elijah Kagwa is a young, articulate Ugandan doctor who had been described to me by my American informants as a rising star in the field of international HIV research. He got his medical degree at Olusozi, where he now runs the HIV Care Clinic, and holds a Master's in Public Health from UC Berkeley. In addition, he is a collaborator on several Uganda-based research projects with colleagues at prestigious medical schools in the U.S. and is a member of the Physician's Partnership. Despite his busy schedule, we managed to sit down for an interview in his office at the medical school one afternoon. I asked him about the challenges of providing a state-of-the-art training program for doctors without reliable access to state-of-the-art technologies, such as CD4 and viral load testing. Laughing, he responded that "even in our medical schools, we teach a lot of things that are not out there — I mean when people go out in the field, then the limitations face them immediately. We teach them anyway. For me, my opinion is that people should know the

ideal and then should know what they can do when they are short of what the ideal is." The key, he told me, was balancing between the two. "It does no harm to know what's ideal and what the actual is. But balancing the two is a delicate affair."

Chapter Six

RESOURCE-POOR BUT PATIENT-RICH

Expertise, Opportunity, and Ethics in Ugandan HIV Research

"Resource-poor" but patient-rich: the turn towards the global South

North American HIV researchers have become increasingly interested in countries like Uganda for both humanitarian and professional reasons. Indeed, my own interest in Uganda—and the opportunity to travel there—arose from my involvement with a team of U.S. epidemiologists who shifted the focus of their HIV research from the U.S. urban poor to urban and semi-rural patients in Uganda. As effective HIV therapies became widely available to even the poorest patients in the U.S., these researchers felt a moral imperative to use their work to try to mitigate the disastrous impact that the epidemic was having in sub-Saharan Africa. In addition, their attention was drawn southward by the research opportunity that Africa presented: access to high numbers of patients who were on the cusp of receiving their first antiretroviral treatment through the free programs underwritten by the Global Fund and PEPFAR.

A vignette from my participant-observation among a team of American epidemiologists illustrates the importance of "Africa" as a research opportunity. In February of 2005, I sat in on a meeting attended by 8 researchers at Yerba Buena University where the agenda was to design a research protocol that could be used across the university's growing number of HIV studies being conducted in Africa. The goal was to develop a standardized way of collecting social, behavioral, and biological information from African HIV patients participating in research, so that the data could then be

"pooled" across studies conducted in different countries, creating larger and more powerful data sets for researchers to work with. Data regarding the advent of antiretroviral treatment in Africa was of particular interest because it provided a second chance to study the impact of HIV drugs on a large population of previously untreated people—a research opportunity that had been, in the words of the meeting's organizer, "lost" in the U.S. As the group discussed how large a blood sample would be necessary in order to obtain the desired biological data, the researcher leading the meeting suggested that the African study participants have their blood drawn twice, arguing, "I can't emphasize this enough – a biological specimen in the pre-treatment era is just golden to us. And 7mls of blood just isn't enough."

Afterwards I asked Dr. Beale, who had been in attendance, what the meeting's organizer had meant when he said a research opportunity had been "lost" in the U.S. What Africa offered, Dr. Beale told me, was the possibility of studying the virus as it evolved in relation to exposure to drugs. The Yerba Buena researchers believed that knowledge about this evolution could provide useful information about both the pathophysiology and treatment of HIV. The opportunity to conduct such a study was lost in the U.S. because effective drugs became available here much earlier in the epidemic, before researchers realized what Beale called the "scientific value" of such a project. This recognition of scientific value would come later, after the development of viral load and drug resistance tests that allowed researchers to study the impact of antiretroviral drugs at the molecular level, rather than simply at the level of the patient's body (the clinical level). As a result, researchers did not begin to study the impact of treatment in this way until after drugs had been available for several years, and most U.S. patients had

already been exposed to HIV medications. Thus, the opportunity to study the impact of HIV drugs on a large number of previously untreated patients in the U.S. was seen as "lost." This was precisely the opportunity that Africa now offered.

In other words, "resource-poor" countries like Uganda are rich in untreated patients—a valuable commodity in the research field (Petryna 2005). In medical lingo, patients not exposed to drugs are referred to as "treatment-naïve." The etymology of "naïve" comes from the Old French *naïf* meaning "natural" or "just born" and the Latin *nativus*, meaning "not artificial" or "native." One way to frame this usage is that treatment-naïve patients carry viruses that are "natural" or "native" in that they have not mutated or evolved through exposure to drugs. Indeed, the scientific literature refers to these unexposed viral strains as "wild-type" HIV.

In light of this terminology, it must be said that sub-Saharan Africa is rich in "naïve" patients and "wild-type" viruses not for reasons of nature, but for political-economic reasons. Drugs costing $1000 a month per patient are far beyond the reach of many Africans and their governments, and, as I described in Chapter 2, the efforts of the pharmaceutical industry to protect their patents prevented the manufacture of cheaper versions of these drugs for many years. The lack of purchasing power for HIV drugs in sub-Saharan Africa thus created another kind of market—one of research subjects. In this way, poverty enabled a certain kind of opportunity for the production of knowledge. At the same time, it offered a humanitarian opportunity for American doctors and researchers looking to put the skills and knowledge they gained from the U.S. epidemic to work in a place lacking not only the medications themselves, but the laboratory

technologies to monitor their effects and physicians knowledgeable in their prescription and management.

Expertise on the periphery: locating Ugandan scientists

Ugandan AIDS researchers published some of the earliest and most important papers on AIDS in East Africa and on the heterosexual epidemiology of the virus (Serwadda et.al. 1985, Sewankambo et.al. 1987). Because there are very few local sources of research money, most Ugandan scientists rely on collaborations with American and European universities in order to secure funding for their projects. A number of top U.S. medical schools including Johns Hopkins and Case Western have long-standing research partnerships with professors at Uganda's medical schools and research centers.

Following Stacy Pigg's work on "peripheral publics," this chapter is an effort to begin describing some of these transnational scientific relations, with a particular emphasis on the position occupied by what I am calling the "peripheral expert"—that is, Ugandan AIDS researchers located at the periphery of Western knowledge institutions and funding mechanisms, but at the center of the epidemic. I argue that we must expand our accounts of expertise to include "peripheral experts," and I situate this argument as part of the effort to get around a tendency to see science in the developing world in polarizing terms—either as entirely beneficent ("science-as-life-saving knowledge") *or* entirely malevolent ("science-as-epistemological-colonization") (Pigg 2001). In terms of AIDS in Africa, one example of this polarity would be the tendency to see Western-funded HIV research as either essentially humanitarian in nature, or as a neo-colonial plot to use Africans as "guinea pigs." In reality, the relationship between disaster, assistance,

and opportunity is much more complex. Like Pigg, I want to engage in "a discussion of processes and relations that *begins* by asking how ideas and technologies travel" (Pigg 2001: 525). At the same time, I want to problematize the center/periphery divide by showing how some of the institutional structures currently governing international research may serve to reinscribe inequalities between wealthy and poor nations attempting to engage in collaborative science.

This chapter begins with an examination of the landscape of power relations that Ugandan and North American researchers negotiate as part and parcel of their joint scientific endeavors. In Part I, I describe two aspects of peripheral expertise that I observed during my fieldwork. The first is what I call *translatability,* which refers to the imperative that research conducted in Uganda be translatable to the scientific language of the industrialized world. To clarify, I am not invoking Bruno Latour's concept of "translation" here, whereby scientists strategically mobilize others to view their interests in the scientists' terms (Latour 1999). Rather, I refer to translation in the more traditional linguistic sense—making the language of one group comprehensible to another group. In international HIV research, translatability depends upon the ability to render data in a form considered scientific by Western funders, which in turn requires a laboratory. Access to laboratories thus becomes a key issue in negotiating international research. The imperative of translatability has a number of consequences: first, it means that it can be harder to get funding to answer research questions that actually reflect the reality of managing HIV in a low-income country like Uganda, such as: What is the best way to monitor HIV patients without access to t-cell counts? This, in turn, raises further questions about the translatability of research ethics between rich and poor settings.

Answering such a research question might require a study that compared the outcomes of patients who did and did not receive t-cell count monitoring over the course of their disease. Although such trials have been conducted, a certain ethical stickiness arises when Western funders underwrite research that would be considered malpractice according to the standard-of-care in their home country—a topic I will address in Part II of this chapter.

The demand for laboratory space and the need to pass ethical review boards points to a second aspect of peripheral expertise, which I call "gatekeeping." Gatekeeping refers to the ways in which Ugandan experts are able to exert power through controlling access to laboratories and other research facilities, as well as to their patients. In order to conduct research in Uganda, American investigators must establish working relationships with Ugandan colleagues who have the power to submit their studies for approval to local review boards and grant them access to research facilities and patient populations. This provides Ugandan researchers with some power, albeit limited, in a context in which they are usually dependent upon their American colleagues for research funds.

Part II of this chapter focuses on the question of translatability as it relates to research ethics, through an in-depth examination of recent debates over HIVNET 012, a U.S.-funded study conducted in Uganda on the use of the drug nevirapine to prevent mother-to-child transmission of HIV. The case of HIVNET 012 highlights many of the difficult questions that arise in trying to translate ethical codes designed in the U.S. to research conducted in Uganda. Is it ethical to conduct a trial in Uganda that would not be done in the U.S.? Should the intervention being tested be compared to the "standard of

care" in the U.S. or in Uganda? And, crucially, who speaks for Uganda in deciding these questions?

PART I: Translatability and Gatekeeping

In order to produce knowledge accepted as viable and relevant per standards set by the NIH and similar funding bodies, information gleaned from patients must be abstracted into biological data. In the field of HIV research this process involves the transformation of bodily substance (blood) into "results" in the form of numbers (CD4 count, viral load) and mutations (resistance genotype) that can then be published in medical journals and circulated throughout a larger scientific community. This transformation would be impossible without a laboratory.

As described in the preceding chapter, the Olusozi HIV Institute in Kampala comprises a clinic, a training program, and a laboratory and is governed by a concatenation of North American and Ugandan public and private interests. The primary purpose of the Institute was a source of debate among its major stakeholders. Some, including its founder Max Edwards, described the HIV Medicine Training Program and the HIV Care Clinic the most important components of the Institute. The lab, in his view, existed to attract research investment that could then be used to support the costs of both the training program and the clinic. Others saw the training and clinic as of secondary importance to the research conducted in the laboratory. Regardless, all involved saw the laboratory as essential to attracting funded research projects from Europe and North America. What they disagreed upon was whether this was a means to an end or an end in itself.

Laboratories are important to international HIV research projects because they provide the infrastructure necessary to monitor the t-cell counts and viral loads of patients enrolled in studies. As discussed in the previous chapter, in North America and Western Europe these tests are the very foundation of both patient care and research. The kinds of clinical markers most Ugandan doctors rely on to monitor AIDS in their patients are no longer the language of Western research—they can't be standardized, and they can't be compared to data collected in wealthy countries, where everything is framed in terms of the numbers.[45] Thus, obtaining funding for clinical research in Uganda from an institution like the U.S. National Institutes of Health (NIH) usually requires access to facilities where reliable CD4 and viral load testing can be done. This is because without measurements of t-cells and viral load, HIV research conducted in Uganda is simply *not translatable* to a U.S. context, where these surrogate markers of disease progression form the basis of any clinical or scientific conversation about the virus.

The Olusozi laboratory made this translation possible, and, as such, made possible the influx of research money from the NIH. The ability of such a facility to attract high-profile American AIDS researchers was made clear to me by Karl da Silva, the director of a prominent, non-profit California virology center who had recently become involved with the Olusozi Institute when we spoke in 2004. Da Silva was spearheading what was viewed in the field as some of the most exciting and promising research on the molecular biology of HIV—research that could lead to entirely new ways of treating the disease. At

[45] This difference in access to diagnostic technologies makes it difficult to compare patients in wealthy countries to those in poor countries. For example, a team of researchers based in Switzerland is in the process of attempting a wide-scale comparison of response to HIV medications in low-income versus high-income countries. One of their key points of comparison is looking at how much the CD4 counts of each group rise after beginning antiretroviral therapy. A challenge of their project is finding enough cohorts of patients in low-income countries who have received a CD4 count at baseline—in other words, before starting HIV drugs (Braitstein et. al. 2006).

the time I interviewed him, his virology center had just moved into a gleaming new building in a formerly industrial part of the city now being redeveloped into scientific research campus. His office offered an expansive view of the surrounding area and the assortment of corporate and university research facilities being built through the city's public/private redevelopment initiative.

Da Silva was avuncular, encouraging me in my graduate studies, and enthusiastic but humble about his own research. He had just returned from Kampala, where he had attended the dedication ceremony for the Olusozi HIV Institute building. It had been his first trip to the African continent and he spoke like a converted man, decrying the lack of adequate medical treatment, the under-equipped hospital, and an average life span nearly cut in half. "The scope of the problem," he told me, "is *immense*." As a result of his trip, he said, he was determined to start a research project of his own in Uganda. This determination was made feasible by the new laboratory housed by the Institute. Though not the only research lab in Kampala, among the researchers I spoke with it was regarded as the best. I was told several times that it was the only laboratory in East Africa—and one of the few on the continent—to be certified by the American College of Pathologists. This certification meant that the tests conducted there were quality controlled, audited on a regular basis, and were acceptable for clinical trials and the registration of new drugs. As such, it was preferred by major funding agencies such as the NIH and its British equivalent, the Medical Research Council (MRC), as well as by drug companies.

For Da Silva, the lab made it possible to carry out biological analyses in Kampala, rather than dealing with the complicated shipment of perishable biological materials across several continents to a U.S. lab:

> It becomes a bit problematic to be trying to send cells from Uganda to here [California]. A lot of times they get stuck in customs in some country or they get lost. Or they thaw, and valuable samples are lost. The Olusozi Institute offers the opportunity to actually be able to do a lot of the analysis right there, from fresh samples, which is far better.

Da Silva's statement demonstrates how the imperative to generate translatable data also means that all research roads in Uganda lead to Kampala, where the best laboratories are located. In addition, Kampala is home to Olusozi Medical School, which despite the devastation it suffered under the Amin dictatorship remains the oldest and most prominent medical education institution in East Africa. As a result, there is a community of elite, internationally-recognized Ugandan AIDS researchers in Kampala who have relationships with their Western colleagues that are in many ways equitable. The presence of these researchers is yet another factor that draws North American and European collaborators to Kampala.

The geography of power: up-country "blood senders"

Ugandan doctors and aspiring researchers working "up-country," away from Kampala, have considerably fewer opportunities to collaborate with international projects. Up-country, viral load testing is completely unavailable and t-cell testing, when available at all, may not be up to the laboratory standards of American or European funders. As a result, researchers conducting HIV studies outside Kampala must often ship their blood samples to the capital if they want to collect biological data acceptable by U.S. research standards. Shipping blood can be a double-edged sword. On the one hand, it provides access to useful tests that might have otherwise been unavailable to local patients. For example, the arrival of Dr. Jason Beale's research study at Mukwano Hospital in Uganda's southwestern countryside meant that there was money to ship blood

280 kilometers to Kampala, giving Mukwano patients access to tests they might otherwise have gone without as the Mukwano clinic's own CD4 machine was often out of order or unusable due to a lack of reagents. In fact, this kind of testing provided a significant motivator for patients to enroll in studies.

However, this dependence on Kampala laboratories can also create a barrier for up-country doctors hoping to gain more equal participation in research by relegating them to the role "blood senders" (Fullwiley 2002). One doctor from war-torn northern Uganda complained to me that his collaborators (also Ugandan, but based in Kampala) required that all his blood samples be sent to their lab in the capital, even though he had a CD4 machine at his hospital in the northern city of Gulu. I asked him if he felt like a "blood sender" he responded "That's what I am describing. We're just a blood sender. And we shall not be quoted into their results if they come out." In other words, he and his local colleagues would not be included as authors—thus denied the professional recognition and social capital that comes with publication, while supplying the raw materials (samples) for research.

Helicopters and Parachutes

In thinking about initiating a research project in Uganda, Karl da Silva, the San Francisco virologist, was aware that collaborating with Ugandan researchers and institutions required the negotiation of issues of power and equity. The Olusozi Institute was allowing "whole new sets of partnerships" that he wanted to be attentive to. "You can imagine," he told me, "the Africans are not interested in North American scientists coming over and doing research and leaving, you know, exploiting the fact that the

epidemic is raging. It's got to be a 'win-win' situation – it's got to be of mutual benefit for the Ugandans, and the Ugandan people will have to see benefit from this."

Teasing out the benefits of such a laboratory "for the Ugandans" is a complicated matter, and depends upon which Ugandans and what kind of benefits are under discussion. The vast majority of the Ugandan researchers I interviewed spoke favorably about the opportunities offered by collaborating with Western colleagues. These collaborations offered valuable opportunities to answer important medical questions, hone their research experience, provide their patients with access to tests that might otherwise not have been available, and earn a better salary in what is often a poorly-paid profession.[46] In other words, their reasons for participating were both humanitarian and self-interested. The same can be said for their American colleagues, who saw collaboration with Ugandans as both a social good that built local research capacity and improved health infrastructure, and as a professional boon allowing them to conduct international research that could further their careers and improve their chances of winning future grants.

In California, anxieties about being accused of exploitative research surfaced regularly in discussions about international collaboration. At a day-long workshop titled "Conducting Research in Resource-Poor Countries" sponsored by Yerba Buena University's Center for AIDS Research, speakers warned about the history of "helicopter research"—where Western experts landed, collected their data, and then returned home leaving nothing behind—and spoke of the need to forge "true partnerships" with foreign

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[46] The low pay given to doctors in Uganda has led many to set up private clinics and pharmacies to supplement their incomes (Whyte, Van der Geest and Hardon 2002). In addition, across sub-Saharan Africa there is a problem with "brain drain", where doctors leave their countries for more lucrative positions in the U.S. and Europe (Hagopian 2004; Dovlo 2005).

researchers and institutions. Later, Dr. Beale told me that the same issue was causing conflict between his research project based in Mukwano and another American group working in Uganda. Dr. Beale's group was having the data collected by Ugandan interviewers scanned into a computer and sent back to California for "cleaning" and analysis. The data was then made available to Ugandan colleagues via the web. The other group, who was keeping their data on a computer in Uganda, was accusing him of "parachute research" for basing his data management in the U.S. instead of in Uganda. Dr. Beale countered that their accusations revealed a misrecognition of the true locus of power in international research. Power, he asserted, does not lie in where the computer is located. It lies in who gets first authorship on publications and who controls the grant money. His project, he argued, had given two Ugandan researchers Principal Investigator status, granting them control over portions of grant money, and had published significantly more articles with Ugandan first authors than the other group. This kind of power sharing, he said, was more meaningful than the location of data.

The Gatekeepers: Peripheral Experts as Obligatory Passage Points

At the same time, Ugandan researchers I interviewed also spoke of the risk of being excluded by supposed collaborators, and some described having experienced such a dynamic in the past. One way in which the Ugandans were able to leverage some power was in the form of what I call "gatekeeping"—their ability to grant or deny access to valuable research facilities and patient cohorts. In fact, the Olusozi Institute itself became the object of such a power struggle. The construction of the new Institute building had been partially motivated, according to Max Edwards, by a desire to have a "lasting impact" on the medical school and hospital at Olusozi. However, once it was

built, some North American members of the governing Physician's Partnership were reluctant to cede its control to Olusozi University, as had been previously agreed. The Global AIDS Foundation, as the fiscal agent and official owner of the building, had the final say and turned the Institute over to Olusozi medical school. As a result, American researchers who had had very easy access to research opportunities through the Institute now had to lobby for attention, "because," as Richard Swan put it, "now [the Ugandans] can decide not to use them." In other words, by gaining control of the Institute, the Ugandan faculty had maximized the power of their gatekeeping position.

In addition to governing access to laboratory space, Ugandan scientists and university officials also control the use of office space and rooms for interviewing research participants. Most significantly, however, they govern access to their key resource: patients. As in the U.S., both Olusozi University and Mukwano University in Uganda require that international research projects gain scientific and ethical approval from their local Institutional Review Boards (IRBs) in order to use their patients as study subjects. To gain this permission, they must have a local, Ugandan applicant submit the project to the board. At a large university with internationally-recognized faculty—such as Olusozi—the power of such a gatekeeping function can be quite substantial. However, at a smaller less prominent university, the process may be mainly bureaucratic in nature. This was the case at Mukwano's medical school, which because of its smaller size and more remote location had gotten little attention from international researchers prior to Dr. Beale's project. When the researchers I worked with decided to move their project there from Kampala, they did so easily with the help of Dr. Butembe, a young and relatively low-ranking doctor in Mukwano's HIV clinic:

> So when they came to Mukwano, they found me. I was the only person who was working in the clinic full-time and I am the person who had the data. And so they found I was the most resourceful person that they would need to help them to do the research. ….I am the main applicant for the protocol within Mukwano University, because the university has a policy that when people come from outside and they want to do research within the university, there must be one person on the academic staff within the university to be able to apply for the research. So for people to do research within our university, they must be linked somebody who is based locally within the system.

In this way, Dr. Butembe served as an important conduit for the U.S.-based research team, giving them the opportunity to access the patients at his clinic. He was what science studies scholars Bruno Latour and Michel Callon have called an "obligatory passage point"—a station through which others must pass in order to get their goals met (Callon 1999). In addition, the study offered him a valuable opportunity to gain research experience, earn a higher salary, and provide his patients with access to the t-cell counts and viral loads offered by the research study. He also got the opportunity to travel outside of Africa for the first time when his American collaborators paid for him to attend a 6-week summer course on clinical research methods in California. Furthermore, as the study got up and running, it provided jobs for several other clinical and non-clinical staff as well as a computerized database of patient records for the clinic. In this sense, such collaborations can provide benefits to experts from both wealthy and poor countries. However, just because Dr. Butembe's role was "obligatory" does not mean that it was necessarily equal—in other words, the status of "obligatory passage point" does not guarantee equal participation in research, and some Ugandan researchers I spoke with were critical of this. One high-ranking researcher in Kampala told me, "basically what happens is that you have a Western researcher who develops an idea and an interest and

then he comes to Uganda and starts knocking at doors, asking people, 'Who is working on this one? Who is working on this one?' And then he starts looking for good people and sells them the idea."

This suggests that the power gained from gatekeeping may be very limited in nature, given that control over money and publication remains primarily in North American hands. This is in many ways a structural problem, embedded both formally and informally into the bureaucracy of U.S. federal research funding. It is difficult for a foreign scientist to be listed as the Principal Investigator on an NIH grant, and holding this status is key to controlling how research funds are used. Nonetheless, Dr. Beale and others told me, the NIH looks very favorably at grants that include African names among the applicants as they see this as an indication of collaboration. This type of arrangement seems to encourage nominal African participation in research while at the same time relegating African scientists to permanent marginality by denying them Principal Investigator status. The result is a kind of a transnational glass ceiling that limits the power of African scientists to roles like gatekeeping and effectively preserves leadership positions for American researchers.

PART II: Experts and Ethics on the Periphery

The imperative to make data *translatable* described in Part I of this chapter points to the durability of institutional bureaucracies across national and economic borders. By this I mean that part of understanding how science travels between North America and East Africa is understanding how structures of bureaucracy housed in funding bodies like the NIH travel across continents, and how these bureaucratic structures are managed in practice by teams of Ugandan and American researchers. The imperative to make data

translatable to Western standards points to the ways in which these institutions govern what is recognized as legitimate science.

The issue of translatability rises again—and much more contentiously—around the question of what is considered *ethical* science. A number of issues are at play here: first, the economic and power disparities between a country like the U.S. and a country like Uganda makes the threat of exploitation very real. This threat is bolstered by medicine's historical willingness to utilize marginalized populations—especially poor blacks—as subjects in research projects that are ethically questionable or, simply blatantly unethical. This was certainly the case with the Tuskegee Syphilis Study which, although not an international project, remains the classic example of a project that exploited race and class inequalities to conduct a study that would never have been tolerated had the subjects been white, middle-class Americans. This threat is not relegated to the past. For example, anthropologist Adriana Petryna's work shows how multinational pharmaceutical companies frequently off-shore their clinical trials, in part to avoid the more stringent ethical codes that govern drug research in North America and Western Europe (Petryna 2005).

Though the risk of exploitation is very real, determining what is "ethical" in international HIV research is very complex. Concerns about ethics, fairness, and the protection of research subjects cannot be separated from the very disparate economic, political and cultural terrains across which transnational research collaborations are conducted. I will use the remainder of this chapter to examine this complex assemblage through the lens of HIVNET 012, a clinical trial conducted in Kampala by U.S. and Ugandan researchers that studied a novel way to prevent mother-to-child transmission of

HIV. This analysis of HIVNET 012 will show how a debate that was framed primarily as being about ethics was, in fact, also about economics, politics, race, and inequality. It will also demonstrate a central quandary in international research collaborations: the very thing that makes countries like Uganda attractive to Western researchers (large numbers of untreated patients and a lower standard-of-care) creates a significant stumbling block in designing studies that are accepted as ethical.

Case Study: HIVNET 012

In 1997, researchers in the Department of Pediatrics at Kampala's Makerere Medical School partnered with American researchers from Johns Hopkins University in Baltimore to evaluate the use of an antiretroviral drug called nevirapine in preventing the transmission of HIV from mother to child during birth. The NIH-funded trial was called HIVNET 012,[47] and was conducted in Kampala. Previous studies had already established the effectiveness of a 6-week course of another drug, AZT (zidovudine), in protecting babies born to HIV-infected mothers but nevirapine presented the advantage of requiring only a single dose—one to the mother during labor, and one to the baby after birth—meaning that it could be given to the many women who did not access medical care until they began labor. With no medication, the likelihood of transmission of HIV during childbirth has been calculated to be between 14 and 32% among non-breastfeeding mothers in industrialized countries, and between 25 and 48% among breastfeeding mothers in low-income countries (Wiktor 1997; DeCock 2000). The trial concluded that nevirapine reduced the risk of transmission to newborns to 8.2%, a slightly better

[47] HIVNET stands for HIV Network for Prevention Trials. It was established in 1993 by the National Institute of Allergy and Infectious Diseases (NIAID) and the Division of AIDS (DAIDS), both of which fall under the National Institutes of Health (NIH).

outcome than the AZT course (10.4%) (Guay et. al. 1999). Later studies would confirm these findings (McIntyre 2005).

In 2002 an NIH audit of HIVNET 012 raised concerns about incomplete reporting of participant illnesses and deaths, dosing inaccuracies, and unapproved changes made to the study. The NIH halted the trial for 15 months to investigate. Upon reviewing the study, however, the agency found that despite some problems the scientific findings about the safety and efficacy of single-dose nevirapine were solid. The results of the trial formed the basis for the initiation of large-scale programs providing the drug to HIV-positive pregnant women in low-income countries.

In late 2004, an Associated Press reporter published an exposé of HIVNET 012 that was carried in major newspapers in both the U.S. and Africa. By this time, single-dose nevirapine was the foundation of Prevention of Mother-to-Child Transmission (PMTCT) programs in Uganda and many other African countries, many of which were funded by the Bush Administration's AIDS initiative. The articles charged that the NIH's AIDS Research Chief, Edmund Tramont, had covered up flaws in the HIVNET 012 trial by re-writing an internal NIH report that expressed safety concerns about the trial. According to the reporter, the study "may have underreported thousands of severe reactions, including deaths" (Solomon 2004a). The articles were based on documents released by Dr. Jonathan Fishbein, who had been hired by the NIH to review the safety of the nevirapine trial during the study's 15 month hiatus.

The reports had a wide impact. In Uganda, a version of the Associated Press coverage was reprinted in a local weekly paper under the headline, "Flawed Uganda AIDS Research Misleads World" (*Weekly Observer* 2004). In South Africa, the

governing African National Congress—long skeptical of antiretrovirals in general—accused the NIH of using Africans as "guinea pigs" and of entering "into a conspiracy with a pharmaceutical company to tell lies to promote the sales of nevirapine in Africa, with absolutely no consideration of the health impact of those lies on the lives of millions of Africans" (African National Congress 2004). And in the U.S., Jesse Jackson accused the Bush Administration of financing "a crime against humanity" by funding nevirapine-based Prevention of Mother to Child Transmission programs in Africa (McNeill 2004).

In response to the publicity, Tramont admitted to changing a report warning that safety conclusions drawn from HIVNET 012 should be "very conservative" due to "incomplete or inadequate safety reporting" and record-keeping that was "below the expected standards of clinical research" (Solomon, 2004b). But he justified his removal of this negative language by arguing that the safety monitors did not adequately understand AIDS, the findings of the study were too important[48] to be jeopardized by the largely bureaucratic flaws cited in the safety report, and that African investigators should be granted some leniency in meeting U.S. research standards. His stance in favor of nevirapine was widely supported by AIDS experts in the U.S. and elsewhere. The controversy spurred a re-review of HIVNET 012 by the Institute of Medicine, which in 2005 re-affirmed that although the study had problems with record-keeping, its scientific findings regarding the safety and efficacy of nevirapine for the prevention of mother-to-child transmission were not in question.[49]

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[48] The study was very important symbolically, one American researcher told me, because it proved that providing antiretrovirals in Africa was feasible, and thus lay the ground for making triple-combination therapy more widely funded and accessible.

[49] The debate over the safety of nevirapine was recently revived in *Harper's* magazine, where journalist Celia Farber questioned the credibility of the IOM review of HIVNET 012. However, her treatment of HIVNET 012 was largely overshadowed by the attention the article gave to Peter Duesberg, the biologist who has long claimed that HIV does not cause AIDS. Farber was widely criticized for treating Duesberg as

Ethical Translatability

Upon close examination, it becomes clear that one of the key issues at stake in the HIVNET 012 controversy was translatability. An important component of any clinical trial is the documentation of any "adverse events" that occur during the study. The *AP* exposé accused the researchers of failing to report "thousands of severe reactions, including deaths" (Solomon 2004a). The NIH-approved research protocol for HIVNET 012 used the U.S. Dept. of Health and Human Services' (DHHS) definition of "adverse event" and "serious adverse event":

> An adverse event (AE) is defined as any health-related reaction, effect, toxicity or abnormal laboratory result that a participant experiences during the course of a study *irrespective of relationship to study treatment*… A serious adverse event is defined as any experience that is fatal or life-threatening, permanently disabling, requires in-patient hospitalization, is a congenital anomaly, cancer or overdose or is otherwise judged to be serious by the on-site clinician (approved HIVNET 012 protocol, cited in McNeilly 2002).

However, on the ground, the American and Ugandan investigators found these definitions unrealistic for a study population that already suffered from a high rate of illness and malnutrition—particularly since "adverse events" include *all* health problems experienced by study participants, including those unrelated to nevirapine. In Uganda, the infant mortality rate averages 138 deaths per 1000 births, versus 7.5 per 1000 in the U.S. The average life expectancy in Uganda is 49.5 years, compared to 77.5 years in the U.S. (WHO 2006). A "health-related reaction" or "abnormal laboratory result" that might count as an adverse event in the U.S. might be quite common among patients in

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a credible researcher and a victim of scientific ostracism. Farber's assertions about nevirapine and HIVNET 012 were also highly questionable, though these received much less attention. Significantly, though Farber argues that HIVNET 012 was "out of control" and "a story with eerie echoes of *The Constant Gardener*" she did not interview a single Ugandan scientist or patient for her story (Farber 2006).

Uganda. In a 2002 report the investigators explained that they had employed alternate criteria for categorizing serious adverse events, arguing:

> Due to the nature of the underlying health and nutritional status of the study population, some illnesses or laboratory abnormalities that *under normal circumstances* may be life threatening (Grade 3-4 on toxicity tables) were not considered as such….The main determination of seriousness was whether the illness was serious enough to require hospitalization….Given the very high rates of illness in this population, some differentiation was needed in order to identify children with the most severe illnesses. Children with illnesses that could be managed at home were not considered serious. High grade laboratory toxicities alone were not considered serious unless they were accompanied by symptoms of the same magnitude. (HIVNET 012 4/12/02 Report, cited in McNeilly 2002, emphasis added).

This revision reveals how NIH and DHHS definitions of "normal" are in fact socially and economically specific to wealthy, industrialized countries like the U.S. This presented a challenge to study investigators, who were faced with the normality of the abnormal in Uganda: what "under normal circumstances" (presumably, in the U.S.) would be considered a life-threatening condition was not always considered as such in Uganda. This assertion can be interpreted in two ways: that such conditions were not actually as life-threatening to Ugandans as they might be to Americans (perhaps due to locally-developed immunity, as is sometimes the case with malaria); or, more likely, that in Uganda the condition of being life-threateningly ill was so "normal" that the researchers needed to develop alternate criteria for what constituted severe illness (in this case, hospitalization). Either interpretation points to the way in which the deep social and economic inequalities that distinguish the U.S. from Uganda may actually become biologized in the form of malnutrition, disease, and the normality of "abnormal" lab results. This phenomenon was described most succinctly by Francis Mmiro, a lead Ugandan investigator on the HIVNET 012 trial, who defended the study to reporters by

arguing, "What you may call a serious side effect in the U.S. is not a serious side effect in Kampala" (Solomon 2004a).

Another way of phrasing Mmiro's assertion is to say that the category of "severe adverse event" was not directly translatable from the U.S. to Uganda. Instead, translation required some alteration of the category's definition. Although this change in definition was understood and supported by the U.S. researchers working in direct collaboration with the Ugandans, it was frowned upon by NIH regulators in Bethesda who saw it as a failure to adhere to required research standards.

In Kampala, I spoke with Ugandan investigators involved with HIVNET 012 about the controversy. Dr. Tabitha Mugombe met with me in her large office at Makerere Medical School. Poised and extremely articulate, Mugombe is one of the younger generation of researchers at Makerere who has risen to international prominence for her work on pediatric AIDS. I asked her whether she thought that U.S. regulators at the NIH had trouble understanding the realities of conducting medical research in impoverished countries like Uganda:

> I think they do because most of them are not in a resource-poor setting, and they've never been to a resource-poor setting. So we're not saying that the regulations should be different for Africa, but they have to put everything in context. … Many times, the answers are not so straightforward. … Many of the people in the regulatory divisions in the U.S. or the West have really conducted trials *in the West*. And they're very good, but in resource-limited settings, they actually sometimes don't understand the context of the patients being very sick, you as a researcher being their primary clinician so you're dealing not only with the study component, but you're also providing care and treatment. And so there are a lot more visits that go beyond the study visits that you have to take care of as a researcher. So there are a lot of severe, adverse events that are not related to the drug, but actually are severe, adverse events that are part and parcel of a child growing up in Africa with a high infant mortality rate, a lot of malaria and pneumonia, diarrhea. Just the common illnesses that all need to be reported as serious adverse events. You know, we're not denying that they should be reported, but there is a heavy

> load on the staff that are doing the studies. It's much harder than seeing a patient every two months and having a primary care physician who does their primary care.

Mugombe argues that not only do many Western regulators and researchers not understand the higher burden of disease in Africa, but they also do not understand the extra burdens born by clinician-researchers working in a health care system that has an annual government per capita expenditure of only $6 per patient, compared to the $2725 spent in the U.S. (WHO 2004).[50] Regulators, she argues, need to "put everything in context" in order to understand how Ugandan investigators face limitations and challenges that are different from those faced by researchers in the U.S. However, at the same time, she states that "we're not saying that the regulations should be different for Africa."

One way to read Mugombe's comments is as an example of the tension between difference and sameness that must be negotiated by experts on the periphery (see also Stepan 1986). On one hand, there are clear and important differences between conducting health research in a wealthy country versus a low-income country. On the other hand, because of their peripheral location, experts from countries like Uganda are always at risk of having their research discounted by the Western scientific establishment on grounds that it is either irrelevant or not up to Western standards. Thus, the assertion of difference also carries with it the risk of marginalization. As a result, peripheral

[50] Unlike their American and European colleagues, most Ugandan researchers do not have administrative support staff to help manage their research, and they a much heavier work-load of patient care as well. Her assertion that many Westerners don't understand the work constraints faced by their counterparts in low-income countries was confirmed for me when, in a Yerba Buena University workshop on international research ethics, a senior researcher described the different "culture of organization" she confronted in her international work. This "cultural" difference regarding organization and record-keeping was "a battle" for her every time she worked overseas. "You are like from outer space to them….It's very awkward. You have to be very forceful in saying, 'this trial is funded by so-and-so and we have to follow their rules, or the study will be stopped.'"

experts must balance these assertions of difference—the need to "put everything in context"—with assertions of sameness: "we're not saying that the regulations should be different for Africa."

Again, this quandary can be seen as a problem of translation: how do Ugandan investigators translate research protocols (both scientific and ethical) designed for countries where adequate health infrastructure, research support staffing, and a basic level of patient wellness are taken for granted, to their own country where health facilities are much more rudimentary, the clinical work load is much heavier, there is much less support staff to assist with research administration, and patients come to them much sicker than in the U.S.? Furthermore, how do they make this translation without undermining the integrity and credibility of their science?

Defending Peripheral Expertise: Who Speaks for Africa?

In March of 2005, I interviewed Professor Ezra Mkasa in his office in the MU-JHU (Makerere University-Johns Hopkins University) building that houses the long-standing collaboration between the two universities. MU-JHU houses the hospital's Prevention of Mother to Child Transmission clinic on its ground floor. Professor Mkasa is one of the lead investigators of HIVNET 012.

When I arrived for my interview, the clinic waiting room was full of women and children. A number of toddlers were playing on the floor with toys provided by the clinic. Dr. Mkasa's office was located upstairs. Mkasa was an older man, small and weathered, with thick glasses, a thick accent, and a biting sense of humor that he punctuated with a rasping laugh. I asked him for his opinion on the recent controversy over his study:

> The man who is accusing us of so many things has never stepped a foot in Africa. He doesn't know that the people who carried on this study are professors—people who have been in the field of medicine for longer than even before he was born, or before he ever got his degree [laughs]. Who have experience he will never have in his own lifetime. Because his experience is limited to a small area. African doctors have experience that is widespread. Because they are the only people who are there and they will be able to look at everything, in totality, everything…. In Uganda here probably more than 8000 women have taken [nevirapine]. And somebody who has never even been in Africa [laughing]—thinking he knows more of what is happening than the people who have done it. And the people who have done this are Africans. Pure, simple, African. Remember, and I'm interested in the survival of the African [laughs]. And with that interest, do you think I would do anything that would in any way interfere with the survival of the African?

Here Mkasa defends the study by referring to the qualifications of its investigators as both professors and as Africans. Tabitha Mugombe also defended the study by referring to African identity, telling me "many people in the West actually said they're using Africans as guinea pigs, which is not true. The study was conducted by Ugandan investigators to try and benefit our women. And it has benefited our women and children." In a sense, both Mkasa and Mugombe present themselves as authentic spokespersons for Africa and Africans. In doing so, they draw on a resource held by peripheral experts—the resource of authentic identity. On one hand, speaking out as African scientists is an important corrective to a Western imaginary of Africa that tends to see the continent as inherently unscientific, and thus always exploited by science rather than productive of scientific knowledge. On the other hand, however, this recourse to African identity as proof of good intentions obscures the many fault lines (class, gender, culture, ethnicity, etc.) that exist within the category of "African" or even of "Ugandan." It also may obscure a more fundamental discomfort with scientific experimentation (particularly on human subjects) that cuts across communities worldwide.

Ethical Translatability and Ethical Imperialism

Interestingly, the HIVNET 012 study was not the first or even the most controversial clinical trial testing methods of prevention of mother-to-child transmission in Africa. In 1994 the AIDS Clinical Trials Group (ACTG) conducted a study in France and the U.S. showing that giving AZT to HIV-positive women during pregnancy and childbirth dramatically reduced the transmission of the virus to their babies. This trial, named ACTG 076, was the first to establish an effective means of preventing mother-to-child transmission. The regimen it tested—which involved five doses of AZT per day beginning during the second trimester of pregnancy, and intravenous AZT during labor and birth—rapidly became the standard of care for HIV-positive pregnant women in North America and Western Europe.

However, the regimen was considered too complicated and expensive for widespread use in low-income, sub-Saharan African countries where many women either gave birth at home or did not come into contact with the health care system until they went into labor. Yet, mother-to-child transmission was a huge problem in Africa where the epidemic was both much larger and much more female than in the U.S. and Europe. Researchers decided to investigate the efficacy of a shorter, simpler regimen of AZT in hopes that it might be more feasible for use in Africa. Controversy erupted when the investigators opted to test the shorter AZT regimen against a placebo group that would receive no treatment, rather than against the longer regimen that had already been established as effective and was the standard of care in wealthy nations.

Critics of the study—most notably the editor-in-chief of the *New England Journal of Medicine*— accused the researchers of embarking on an unethical, Tuskegee-like

experiment that exploited African study participants and caused the unnecessary infection and subsequent deaths of infants in the placebo arm who were born with HIV (Angell 1997). They argued that that African study subjects should receive the same standard-of-care as study subjects in the West, and that the ethical thing to do was to test the short course of AZT against the long course, not a placebo. Advocates of the study argued that no treatment (i.e. a placebo) was the standard of care in Africa, and that a placebo-controlled trial allowed for the study to be done more quickly and with stronger results. The result, they argued, was that they were able to establish the efficacy of the short course rapidly and make the treatment available to women more quickly than if they had tested it against the longer regimen.

Ultimately, the debate came down to whether or not it was ethical to have different standards of care in wealthy versus poor nations. Critics argued that it was unethical, and that it was not acceptable for researchers to conduct studies in developing nations that would not pass ethical standards in their own countries. Defenders countered that studies needed to reflect the reality of "local" standards-of-care. Interestingly, American and African researchers did not line up neatly on opposite sides of the controversy. Rather, there were Americans and Africans who spoke out publicly both for and against the study. Like the HIVNET 012 trial, one of the issues at stake was: who speaks for Africa? While one of the AZT study's most vocal American critics, Peter Lurie, decried the exploitation of African subjects, a leading Ugandan oncologist named Edward Mbidde accused Lurie and his supporters of practicing "ethical imperialism" by presuming that they, as Westerners, had the authority to decide what was ethical in Africa (Lurie 1997; Varmus and Satcher 1997).

The issue of standard of care remains contentious in international HIV research, and North American and African researchers continue to fall on both sides of the debate. In Kampala I asked Dr. Elijah Kagwa, a Ugandan researcher at Olusozi, for his opinion on the issue:

> Somehow the ethics and the conduct of research is driven by the standards of the West [laughs]. I mean that continues to be true….My opinion is that we should use the standard of care here. Because it makes more sense if you are investigating whether something is useful, you should compare it with what is being done here rather than what is being done in the U.S., which will take a long time actually to be done here. I think the standard of care should really be the one we use because, you know, we might never achieve the standard of care in the West. We might never achieve it. I mean these are developing countries.

Kagwa's comments point to the way in which the standard-of-care debate is essentially a debate about how to redress inequality. In his view, testing a useful treatment against a treatment that might never be available in Uganda only exacerbates already existing inequalities between Uganda and the industrialized West. It requires the imposition of ethical standards designed in the West that do not reflect the reality of health care in Uganda.

Hilda Mulondo, Chair of the Department of Obstetrics and Gynecology, expressed similar views when I spoke with her in her large office within Olusozi Hospital's OB/GYN wing. She described getting pressure from international collaborators to use the standard of care employed in their home countries, rather than in Uganda. "I should do the best that's available in my country," she told me, "but not to a level of having an island of excellent investigation where that's not your standard of care." Professor Mulondo, like Elijah Kagwa, felt that using the standard-of-care of wealthy countries worsened rather than redressed health inequalities by creating an

"island" of high-level care that only a few patients would have access to. Of course, many research studies create such "islands" anyway, because even the basic tests they conduct for data collection are more than what is commonly available to patients in Uganda. This is certainly true for many HIV studies, where, as I described earlier, the need to produce data that is translatable to Western research standards requires CD4 and viral load testing—currently otherwise unavailable to patients throughout much of the country.

There is heterogeneity in how researchers view this debate over standard of care, and the debates are further complicated by concerns about producing "good" data. Studies comparing an experimental treatment to no treatment are easier and quicker to conduct, they require fewer participants, and are more likely to produce statistically significant results. This is because the difference between treated and non-treated patients is likely to be greater than any differences between two groups of differently treated patients. Dr. Joseph Tabula, the Olusozi professor and journal editor introduced in the previous chapter, described to me how he confronted this issue while sitting on an ethics committee that reviewed a proposal submitted by Dutch researchers. The Dutch-funded group wanted to test whether providing newborns with combination antiretroviral treatment starting at birth would lessen their risk of being infected through breastfeeding. They wanted to test the treatment group against a placebo control group, meaning that the newborns in the control group would not receive any treatment—not even the single-dose nevirapine that HIVNET 012 had already proved effective.

Prof. Tabula: I said to them, "this is very good, but why are you giving a placebo to this other group? Do you know that the transmission is obviously proven. It's there. So, can you really give placebo to this group?" They said, "Yeah. But you know, in as far as we are

concerned, there is no other study regarding this so we really want to give placebo to prove it." I said, "No way! There's no way! You know that these mothers are at a disadvantage. The children are at a disadvantage. How do you say you are going to give placebo? You are deliberately infecting those children!" Right? So we refused and that group was given nevirapine and this other group received the new drugs.

So they did the study. Unfortunately for them, they didn't have enough sample size so the power was very low so they couldn't demonstrate any effect. But even though they didn't demonstrate much effect, they still published the work at a conference in Paris where I was present. And the western researchers — my colleagues — said, "This study — they should have been allowed to give placebo! If they had given a placebo they would have demonstrated a difference." So I got up and I said, "It's the science and the ethics. Tell me in Sweden, in the States, in Canada, in France, would this research pass the ethics committee? Would children — American children, Canadian children, Swedish children, French, Norwegian children be deliberately exposed to milk that was HIV-infected and be given placebo? And compare with a group that was receiving anti-retroviral drugs? Would that pass your ethics committee?"

J. Crane: And what did they say?

Prof. Tabula: [whispers] There was silence.

In this case, the placebo-control group became something of a "boundary object" standing between Professor Tabula and the Dutch applicants. Leigh Star and James Griesemer coined this term to describe objects or entities existing at points of intersection and struggle between different groups and their competing visions of reality. Each group defines the boundary object differently, according to its interests (Star and Griesemer 1999). In this case, the Dutch saw using a placebo control group as a question of good research design because comparing treated to untreated infants would allow them to better demonstrate whether combination therapy effectively reduced the risk of infection through breastfeeding. If it did, application of these findings could potentially prevent

many babies from being infected through breast milk in the future. On the other hand, Professor Tabula saw the placebo group first and foremost as an ethical question: were children in the study being unnecessarily put at risk and potentially harmed? The answer was yes, because they were being denied access to a treatment (single-dose nevirapine) that had already proven effective at reducing their likelihood of infection, and he was unwilling to sacrifice their health for the sake of answering a question that might benefit others down the road.

Debates like the one described by Professor Tabula are echoed in the drafting and re-drafting of international guidelines for ethical research. For example, the World Medical Association's *Declaration of Helsinki: Ethical Principals for Medical Research Involving Human Subjects*, first drafted in 1964, has gone through numerous revisions of its paragraph #29, which governs the treatment of control groups. In 2000, the paragraph was revised to say that control groups must receive the best current treatment, not the best "attainable" treatment in that context—thus rejecting many placebo-controlled trials and the argument that treatments should be compared to the local, rather than international, standard-of-care. Two years later, after urging from the U.S. National Bioethics Advisory Committee, paragraph 29 was footnoted to allow the use of placebo-control groups, "Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method" (World Medical Association 2004).

Further Complications: drug resistance and the political economy of nevirapine

Often overshadowed in the sometimes-hyperbolic debates over HIVNET012 is that the fact that the trial was conducted at all acknowledges a different standard of care

for the U.S. versus Uganda. In Uganda—where both prenatal care and triple-antiretroviral therapy are available on only a limited basis—the possibility that one dose of a drug could prevent transmission of HIV to newborns was incredibly promising. However, in the U.S. the same intervention would be considered "malpractice," according to one American HIV doctor I spoke with. This is because antiretrovirals are readily available and many women receive prenatal medical care. Treatment guidelines instruct doctors to put women on full, triple-combination antiretroviral therapy early in their pregnancies as a strategy for preventing transmission of HIV to the baby. Offering only a single dose of nevirapine during labor would thus be sub-standard care.

Furthermore, a few years after the initial findings of HIVNET 012 were published, evidence emerged showing that many pregnant women who took a single dose of nevirapine developed nevirapine-resistant strains of HIV (Flys 2005, Hammer 2005, Eshleman 2005; Johnson 2005). This did not alter the efficacy of the drug in reducing transmission of HIV from mother to baby, but it did present the possibility that these women and (and those babies who were born infected, despite nevirapine treatment) would not benefit from combination HIV therapy—which in Uganda, like in many poor countries, is nevirapine-based. This data raises yet another slippery ethical question: is it right to provide a woman with a drug that may protect her child from becoming HIV-infected, but reduce her own ability to benefit from HIV drugs in the future?

Again, this ethical question has economics at its root. The reason treatment is nevirapine-based in Uganda is because the drug is chemically simple, making it easier and cheaper to copy. Generic drug manufacturers, particularly those based in India, took advantage of this when they ignored patent protection laws and began making and selling

generic, nevirapine-based combination therapy in the late 1990s. It was these generic drugs that were the first antiretrovirals to be imported into Uganda en masse and sold to patients for the initial price of $40 a month (versus the $1000 that a month's worth of antiretrovirals often cost in the U.S.). Since then, the price of these drugs has fallen even further to under $20 per month. Because of their cost-effectiveness, the generics are also the primary drugs supplied by the Global Fund's free treatment programs in Uganda. Although the generics are equally effective as branded drugs, this effectiveness could be compromised if widespread use of single-dose nevirapine during childbirth is indeed causing mothers to develop drug-resistant virus.

Whether or not this is the case is still a source of debate, because—as described in Chapter 3—resistance at the molecular level does not necessarily mean that a patient no longer benefits from drugs. Although studies have shown that women treated with single-dose nevirapine develop resistance *mutations* to the drug, other work suggests that they do not actually develop *clinical* resistance—in other words, the drug may still work despite the mutation (Chi et. al. 2006). Regardless, the fact remains that this is fundamentally an economic problem. Nevirapine is the backbone of both mother-to-child prevention programs and ongoing antiretroviral treatment in Uganda because it is cheap. Different drugs could be used—and are used in wealthy countries where choices are not limited by cost. If Ugandan women had these same options, nevirapine resistance would have a very different meaning: instead of signaling the end of treatment, it would merely indicate the need to switch regimens, as it does in the U.S. Thus, if nevirapine poses a danger to African women, it is the danger of resistance—a threat that researchers are

well-aware of but which is often lost in polemical debates over whether studies like HIVNET 012 are using Africans as "guinea pigs."

Conclusion: Ethical translatability and variability

In a 2005 article, Adriana Petryna critiques the phenomenon of "ethical variability" that facilitates the conduct of corporate clinical trials in low-income countries around the world. She describes how recourse to "local" standards-of-care allow for-profit contract research organizations (CROs) hired by pharmaceutical firms to finesse international ethics codes that protect human research subjects. Petryna makes the important point that it is the condition of "crisis"—for example, the African AIDS crisis—that not only legitimates clinical trials that might be deemed unethical in the global North, but also positions this experimentation as humanitarian by bringing medicine to needy people.

In many ways, Petryna's analysis describes the issues raised by HIVNET 012. The widespread transmission of HIV to newborn babies in Uganda constituted a crisis. In this context, the HIVNET 012 study was seen not simply as research but as humanitarian intervention. It was this elevated status that made it possible for Edmund Tramont, the NIH's AIDS Research Chief, to justify his alteration of the study's safety report in order to allow the project to continue. Nonetheless, I hope this chapter has shown that it would be incorrect to dismiss the HIVNET 012 trial as simply an exploitation of ethical variability. Petryna's piece focuses on corporate-funded, profit-driven drug research conducted in middle-income countries wealthy enough to have an adequate research infrastructure but too poor to be likely to afford the drugs they are testing. In contrast, HIVNET 012 was federally funded and generated findings that were

specifically relevant to the host country rather than the donor nation. Though the study did receive donations of nevirapine from its manufacturer, pharmaceutical multinational Boeringher-Ingelheim, the fact that the company donates all nevirapine used for prevention of mother-to-child transmission in poor countries suggests that corporate involvement in this case is driven more by "corporate citizenship" and public image concerns than by profit motivation.

More importantly, the case of HIVNET 012 forces us to raise the question of whether "ethical variability" should be inherently suspect. Though international variability in ethical standards may enable the kind of exploitation Petryna documents, universal ethical standards may also reinforce certain kinds of inequality by erasing the medical and economic realities faced by doctors and patients in poor countries. Does requiring that study participants in Uganda receive the same standard of care available to patients in the U.S. make research more equitable, or simply localize international inequality by creating "islands" of high-level, U.S.-funded care within an otherwise impoverished public health system? Furthermore, does the imperative that research ethics be translatable to a "first-world" context discourage research that is relevant to poor countries, but might be considered malpractice in the U.S.? Though ethical variability certainly opens a window to exploitation, is ethical universalism the answer? In the case of HIVNET 012, the attempt to apply American ethical standards to the Ugandan health care system can be read as an effort to force commensurability between two fundamentally incommensurable contexts. The question remains: is it possible to design research that is both ethical by international standards and answerable to local concerns?

CONCLUSION

When asked, I often tell people that I came into my dissertation research "sideways." I was a self-identified anthropologist of urban North America, with a great deal of experience in the world of domestic AIDS research but none in the study of Africa or global health. In many ways, my dissertation reflects these sub-disciplinary origins, as it takes a particular group of urban North American scientists as its primary anthropological object. Fortunately for me, the "population" I chose to study was highly mobile, giving me the opportunity to conduct some of my research in Uganda where increasing numbers of American AIDS researchers were initiating studies. While in Uganda, I gained a great deal of insight into the limits of biomedicine as a universal language—even among medical doctors—as I encountered the differences and inequalities that form the uneven terrain upon which transnational science is forged.

When I chose my dissertation topic, I was warned by an advisor of the challenges of doing a project on AIDS. The field moves so fast, she cautioned, that the work can rapidly become historical. As I attempt to conclude this project I can see that she was right, as a great deal of what I describe here is "old news" in the field of AIDS research. The "resistance to treatment" alluded to in my title—namely, the vocal opposition of some international health officials and policymakers to ARV treatment in Africa—has been rendered largely mute by the massive outpouring of donor funding for antiretrovirals on the continent in recent years. In addition, the scientific controversies over the causes and consequences of drug resistance that initially drew me towards this topic are no longer the source of much debate in AIDS science, as most researchers now

agree that the relationship between adherence and resistance is more complex than was originally thought, and that drug resistance does not necessarily lead to rapid clinical decline.

However, to describe these findings as "historical" is not to discount them—rather, it is my belief that they provide an important supplement to the ongoing documentation of an epidemic that has in many ways defined my generation. At the same time, I think this dissertation makes contributions that go beyond historical documentation as well as beyond the field of AIDS, and may offer some important directions for future work. In particular, given the current enthusiasm for the study of molecular medicine and "molecularization" in the biological and social sciences respectively, it is crucial to recognize the ways in which molecular medicine intersects with and potentially exacerbates global health inequalities. My work has documented the "molecular politics" inherent in HIV laboratory research, and has also described some of the tensions that arise when "state-of-the-art," highly molecularized AIDS medicine is confronted by the clinical reality and expertise of AIDS medicine in Uganda. It seems very likely that the issues I describe here—the use of "Western" molecular templates in the lab and the irrelevance of molecular medicine to clinical care in low-income countries—apply not just to HIV/AIDS but to the field of international health (or, as is now fashionable, "global health sciences") more broadly.

Despite the economic bust of the biotech industry in the early 2000s, the molecular medicine juggernaut continues forward both domestically and internationally. In the U.S., there is great scientific excitement over the advent of "whole genome analysis"—a technology allowing the entire genome of an individual to be analyzed for

the purposes of identifying disease risks. This excitement appears to be dovetailing with the American recent enthusiasm for aid to Africa in interesting ways. Last year, Dr. Beale told me that Genome Technologies—a multinational biotech company based in the Bay Area—was interested in funding an endowed Chair at Mukwano University. Furthermore, Dr. Beale himself was pitching the idea of a genomics research program based out of Mukwano to several American universities.

These developments may be greeted with some ambivalence by Ugandan researchers. On the one had, money for genomics research—like money for AIDS research—can provide infrastructural improvements and career opportunities that would have been unavailable otherwise. On the other hand, it is unclear whether genomics research holds any tangible benefit for Ugandan public health. This is already an issue within HIV research, as studies become increasingly focused on the molecular basis of disease pathogenesis, treatment response, and drug resistance. Recently, a Ugandan colleague told me she was concerned about this. As an employee of a U.S.-funded study of HIV treatment in Uganda, she had watched as the study shifted from an early focus on questions of drug access and adherence to a more recent concern with the molecular mechanisms of immune response, pharmacokinetics, and drug resistance. She characterized this shift as a move away from the basic public health issues relevant "to the people," to a more highly technical focus that was unlikely to benefit average Ugandans. Indeed—given the lack of clinically relevant discoveries thus far—it remains to be seen whether the promises of molecular medicine will bear fruit for the average person in wealthy countries, much less for those in Uganda and other low-income regions of the world.

Thus, I will conclude on a cautionary note. In the U.S., a growing emphasis within medical schools on "global health sciences" has coincided with the increasing molecularization of disease and its treatment. It appears that one result of this coincidence is a growing interest in applying molecular techniques to the study of HIV and other diseases in the developing world. While I appreciate that this type of research may be a useful and strategic means by which to route beneficial funding to universities and scientists in low-income countries—thus theoretically mitigating some of the global inequalities in research opportunities—it is important to recognize that this move may simultaneously exacerbate existing disparities by promoting a research agenda that has little relevance to the improvement of local public health. Of course, this is not a new problem, but rather points to a long-standing split between "basic" versus "applied" science. An important question for further research and attention is how this split operates in an increasingly globalized scientific arena.

REFERENCES

_____. Flawed Uganda AIDS research misleads world. (2004). *The Weekly Observer,* Dec. 16-22. Kampala, Uganda.

_____. HIV type determines how fast you die.(2006) *The New Vision,* March 1.

Aboulker, J. P., & Swart, A. M. (1993). Preliminary analysis of the Concorde trial.. *Lancet, 341*(8849), 889-890.

Afavia, T. (2005). TRIPs flexibilities and access to ARVs: Overview for international development. *International Conference on AIDS and STIs in Africa,* Abuja, Nigeria.

African National Congress. (2004). Nevirapine, drugs, and African guinea pigs. *ANC Today, 4*(50).

AfriCASO (African Council of AIDS Service Organizations). *The Nairobi Declaration: An African Appeal for an AIDS Vaccine*, (adopted June 14, 2000).

American Foundation for AIDS Research (AmFAR). (2007). www.amfar.org/cgi-bin/iowa/bridge.html.

Anderson, W. (1997). Geography, race, and nation: Remapping 'tropical' Australia, 1890-1930. *Historical Records of Australian Science, 11*(4), 457-468.

Angell, M. (1997). The ethics of clinical research in the third world. *New England journal of medicine, 337*(12), 847-849.

Bangsberg, D. R., Charlebois, E. D., Grant, R. M., Holodniy, M., Deeks, S. G., Perry, S., et al. (2003). High levels of adherence do not prevent accumulation of HIV drug resistance mutations. *AIDS (London, England), 17*(13), 1925-1932.

Bangsberg, D. R., & Deeks, S. G. (2002). Is average adherence to HIV antiretroviral therapy enough? *Journal of general internal medicine, 17*(10), 812-813.

Bangsberg, D. R., Hecht, F. M., Charlebois, E. D., Zolopa, A. R., Holodniy, M., Sheiner, L., et al. (2000). Adherence to protease inhibitors, HIV-1 viral load, and development of drug resistance in an indigent population. *AIDS (London, England), 14*(4), 357-366.

Bangsberg, D. R., Moss, A. R., & Deeks, S. G. (2004). Paradoxes of adherence and drug resistance to HIV antiretroviral therapy. *Journal of antimicrobial chemotherapy, 53*(5), 696-699.

Barbanel, J. (1991). Rise in tubuerculosis forces review of dated methods. *New York Times* (July 7).

Behrman, G. (2004). *The invisible people*. New York: Free Press.

Belkin, L. (1991). Top TB peril: Not taking the medicine. *New York Times,* November 18 pp. B1.

Beoku-Betts, J. (2006). Global science and the development of the nation. *Annual Meeting for the Society for the Social Study of Science,* Vancouver, B.C. November 1-5.

Bibeau, G., & Pedersen, D. (2002). A return to scientific racism in medical social sciences: The case of sexuality and the AIDS epidemic in Africa. In M. Nichter, & M. Lock (Eds.), *New horizons in medical anthropology: Essays in honour of Charles Leslie* (pp. 141-171). London; New York: Routledge.

Biehl, J. (2004). The activist state: Global pharmaceuticals, AIDS, and citizenship in Brazil. *Social Text, 22*(3), 105-132.

Braitstein, P., Brinkhof, M. W., Dabis, F., Schechter, M., Boulle, A., Miotti, P., et al. (2006). Mortality of HIV-1-infected patients in the first year of antiretroviral therapy: Comparison between low-income and high-income countries. *Lancet, 367*(9513), 817-824.

Briggs, C., & Mantini-Briggs, C. (2003). *Stories in the time of cholera*. Berkeley: University of California Press.

Brown, D. (2004) Bush AIDS program's drug limits. *San Francisco Chronicle,* March 27, pp. 3.

Brun-Venzinet, F. (2004). Genetic pathways of resistance among HIV subtypes. *Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC),* Washington, D.C. Oct. 30 – Nov. 2.

Butchart, A. (1998). *The anatomy of power: European constructions of the African body*. London; New York: Zed Books.

Butt, L. (2002a). The suffering stranger: Medical anthropology and international morality. *Medical Anthropology, 21*, 1-24.

Butt, L. (2002b). Reply to Alec Irwin, Joyce Millen, Jim, Kim, John Gershmen, Brooke G. Schoepf, and Paul Farmer. *Medical Anthropology, 21*, 31-33.

Byakika-Tusiime, J., Oyugi, J. H., Tumwikirize, W. A., Katabira, E. T., Mugyenyi, P. N., & Bangsberg, D. R. (2003). Ability to purchase and secure stable therapy are

significant predictors of non-adherence in Kampala, Uganda. (Abstract 170) Conference on Retroviruses and Opportunistic Infections (CROI). Boston, Mass. Feb. 10-14.

Callon, M. (1999). Some elements of a sociology of translation: Domestication of the scallops and the fishermen of St. Brieuc bay. In M. Biagioli (Ed.), *The science studies reader* (pp. 67-83). New York: Routledge.

Centers for Disease Control and Prevention (CDC). (2000). *HIV/AIDS surveillance report,* No. 12.

Centers for Disease Control and Prevention (CDC). (2001). *HIV/AIDS surveillance report,* No. 13.

Centers for Disease Control and Prevention (CDC). (2003). *HIV/AIDS surveillance report,* No. 15.

Centers for Disease Control and Prevention (CDC). (2004). *HIV/AIDS surveillance report,* No. 16.

Chakraborty, R. (2005). "HIV-1 infection in children: A clinical and immunologic overview." *Current HIV Research, 3*(1), 31-41.

Cheonis, N. (2004). Immune reconstitution syndrome. *Bulletin of Experimental Treatments for AIDS* (Winter 2004/2005).

Chesney, M. (2003). Adherence to HAART regimens. *AIDS Patient Care and STDs, 17*(4), 169-177.

Chesney, M. (2003). Adherence to HAART regimens. *AIDS Patient Care and STDs, 17*(4), 169-177.

Chesney, M. A. (2000). Factors affecting adherence to antiretroviral therapy. *Clinical infectious diseases, 30 Suppl 2*, S171-6.

Chi, B., Sinkala, M., Levy, J., Cantrell, R., Stringer, E., Bulterys, M. (2006). Maternal immune response and clinical outcomes on NNRTI-based antiretroviral therapy (ART) following exposure to single-dose nevirapine (NVP) for prevention of mother-to-child HIV transmission (PMTCT). (Abstract WEAB0104) *XVI International AIDS Conference,* Toronto, Canada. Aug. 13-18.

Clarke, A., & Fujimura, J. (1992). What tools? which jobs? why right? In A. Clarke, & J. Fujimura (Eds.), *The right tools for the job: At work in the 20th century life sciences*. Princeton: Princeton University Press.

Clarke, A., & Star, S. L. (2003). Symbolic interactionist science, technology, information, and medicine studies. In L. Reynolds, & N. J. Herman-Kinney (Eds.), *Handbook of symbolic interactionism*. Walnut Creek, CA: Alta Mira Press.

Comaroff, J. (1993). The diseased heart of Africa: Medicine, colonialism, and the black body. In S. Lindenbaum, & M. Lock (Eds.), *Knowledge, power, and practice: The anthropology of medicine and everyday life* (pp. 305-329). Berkeley: University of California Press.

Conference on Retroviruses and Opportunistic Infections (CROI). (2005). Special symposium: Transmitted HIV-1 drug resistance and rapid disease progression. Boston, MA. Feb. 22-25.

Cooper, H., Zimmerman, R., & McGinley, L. (2001). Patents pending: AIDS epidemic traps drug firms in a vise. *Wall Street Journal*, March 2, pp. A1.

Crane, J.T., Quirk, K., & Van der Straten, Ariane. (2000). 'Come back when you're dying:' the commodification of AIDS among California's urban poor. *Social Science and Medicine, 55*(7), 1115-1127.

Crane, J. T., Kawuma, A., Oyugi, J. H., Byakika, J. T., Moss, A., Bourgois, P., Bangsberg, D.R. (2006). The price of adherence: Qualitative findings from HIV positive individuals purchasing fixed-dose combination generic HIV antiretroviral therapy in kampala, uganda. *AIDS and behavior, 10*(4), 437-442.

De Cock, K. M., Fowler, M. G., Mercier, E., de Vincenzi, I., Saba, J., Hoff, E., Alnwick,D.J., Rogers,M., & Shaffer,N. (2000). Prevention of mother-to-child HIV transmission in resource-poor countries: Translating research into policy and practice. *JAMA, 283*(9), 1175-1182.

Deeks, S. G., Barbour, J. D., Martin, J. N., Swanson, M. S., & Grant, R. M. (2000). Sustained CD4+ T cell response after virologic failure of protease inhibitor-based regimens in patients with human immunodeficiency virus infection. *Journal of infectious diseases, 181*(3), 946-953.

DHHS (U.S. Department of Health and Human Services). (2003). *Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents*.

DHHS (U.S. Department of Health and Human Services). (2005). *Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents*.

DHHS (U.S. Department of Health and Human Services). (2006). *Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents.* http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf

Donnelly, J. (2001). Prevention urged in AIDS fight. *Boston Globe,* pp. A8.

Donnelly, J. (2005). AIDS overwhlems African health systems. *International Herald Tribune,* Feb. 25.

Donnelly, J. (2006). U.S. buying more generic AIDS drugs. *Boston Globe,* Nov. 12.

Dovlo, D. Taking more than a fair share? The migration of health professionals from poor to rich countries. *PLoS Medicine, 2*(5): e109.

Edney, M. (1997). *Mapping an empire: The geographical construction of British India, 1765-1843*. Chicago: University of Chicago Press.

Edozien, F. (2005). New AIDS super bug -- nightmare strain shows up in city. *New York Post,* Feb. 12, pp. 1.

Epstein, S. (1996). *Impure science: AIDS, activism, and the politics of knowledge*. Berkeley, CA: University of California Press.

Eraker, S A Kirscht, J P Becker,M H. (1984). Understanding and improving patient compliance. *Annals of internal medicine, 100*(2), 258.

Eshleman, S. H., Hoover, D. R., Chen, S., Hudelson, S. E., Guay, L. A., Mwatha, A., et al. (2005). Nevirapine (NVP) resistance in women with HIV-1 subtype C, compared with subtypes A and D, after the administration of single-dose NVP. *Journal of infectious diseases, 192*(1), 30-36.

Estroff, S. (1981). *Making it crazy: An ethnography of psychiatric clients in an American community*. Berkeley, CA: University of California Press.

Farber, C. (2006). Out of control: AIDS and the corruption of medical science. *Harper's Magazine* (March).

Farmer, P., Léandre, F., Mukherjee, J., Gupta, R., Tarter, L., & Kim, J. Y. (2001). Community-based treatment of advanced HIV disease: Introducing DOT-HAART (directly observed therapy with highly active antiretroviral therapy). *Bulletin of the World Health Organization, 79*(12), 1145.

Ferguson, J. (1994). *The anti-politics machine: "development," depoliticization, and bureaucratic power in Lesotho*. Minneapolis: University of Minnesota Press.

Ferguson, J. (2006). *Global shadows: Africa in the neoliberal world order*. Durham, NC: Duke University Press.

Fleck, L. (1979). *Genesis and development of a scientific fact*. Chicago: University of Chicago Press.

Fleury, H. J., Toni, T., Lan, N. T., Hung, P. V., Deshpande, A., Recordon-Pinson, P., et al. (2006). Susceptibility to antiretroviral drugs of CRF01_AE, CRF02_AG, and subtype C viruses from untreated patients of Africa and Asia: Comparative genotypic and phenotypic data. *AIDS Research and Human Retroviruses, 22*(4), 357-366.

Flexner, C. (2000). HIV genotype and phenotype--arresting resistance? *JAMA, 283*(18), 2442-2444.

Flys, T., Nissley, D. V., Claasen, C. W., Jones, D., Shi, C., Guay, L. A., et al. (2005). Sensitive drug-resistance assays reveal long-term persistence of HIV-1 variants with the K103N nevirapine (NVP) resistance mutation in some women and infants after the administration of single-dose NVP: HIVNET 012. *Journal of infectious diseases, 192*(1), 24-29.

Foucault, M. (1978). *The history of sexuality, vol. 1*. New York: Random House.

Foucault, M. (1979). On governmentality. *Ideology and Consciousness, 6 (Autumn)*, 5-22.

Fujimura, J. (1998). Authorizing knowledge in science and anthropology. *American Anthropologist, 100*(2), 347-360.

Fullwiley, D. (2002). Life, ethics, and sickle-cell anemia: A single-gene disorder in a contingent world. (Doctoral Dissertation, Medical Anthropology, University of California, Berkeley and San Francisco).

Gallo, R. C. (2002). Historical essay: The early years of HIV/AIDS. *Science (New York, N.Y.), 298*(5599), 1728-1730.

Garret, L. (1994). *The coming plague: Newly emerging diseases in a world out of balance*. New York: Farrar, Strauss, and Giroux.

Garret, L. (2001). Harvard urges AIDS trust fund. *Newsday,* April 5.

Gerbert, B., Bronstone, A., Clanon, K., Abercrombie, P., & Bangsberg, D. (2000). Combination antiretroviral therapy: Health care providers confront emerging dilemmas. *AIDS Care, 12*(4), 409-421.

Gilman, S. (1985). *Difference and pathology: Stereotypes of sexuality, race, and madness*. Ithaca, NY: Cornell University Press.

Global Fund to Fight AIDS, TB, and Malaria. (2005). *Global fund ARV fact sheet, December 1, 2005.* www.theglobalfund.org/en/files/publications/factsheets/aids/ARV_Factsheet_2006.pdf. Retrieved 2/2007.

Gold, D. T., & McClung, B. (2006). Approaches to patient education: Emphasizing the long-term value of compliance and persistence. *American Journal of Medicine, 119*(4, Supplement 1), S32-S37.

Guay, L. A., Musoke, P., Fleming, T., Bagenda, D., Allen, M., Nakabiito, C., et al. (1999). Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial. *Lancet, 354*(9181), 795-802.

Haeusser, D. (2001). HIV in southern Africa: A need for the development of a vaccine with cross-clade activity. *Journal of Young Investigators, 4*(1).

Hagopian, A., Thompson, M., Fordyce, M., Johnson, K., & Hart, G. L. (2004). The migration of physicians from sub-Saharan Africa to the United States of America: Measures of the African brain drain. *Human Resources for Health, 2*(17)

Hammer, S. M. (2005). Single-dose nevirapine and drug resistance: The more you look, the more you find. *Journal of infectious diseases, 192*(1), 1-3.

Hannaway, C. (1993). Environment and miasmata. In W. F. Bynum, & R. Porter (Eds.), *Companion encyclopedia of the history of medicine* (pp. 292-308). London and New York: Routledge.

Harries, A. D., Nyangulu, D. S., Hargreaves, N. J., Kaluwa, O., & Salaniponi, F. M. (2001). Preventing antiretroviral anarchy in sub-saharan Africa. *Lancet, 358*(9279), 410-414.

Harries, A. D. (2004). 'DOTS' and 'DOT' for delivering antiretroviral therapy in resource-poor countries. *AIDS (London, England), 18*(5), 830-1; author reply 831-2.

Haubrich, R. H., Little, S. J., Currier, J. S., Forthal, D. N., Kemper, C. A., Beall, G. N., et al. (1999). The value of patient-reported adherence to antiretroviral therapy in predicting virologic and immunologic response. california collaborative treatment group. *AIDS (London, England), 13*(9), 1099-1107.

Hirsch, M. S., Brun-Vezinet, F., Clotet, B., Conway, B., Kuritzkes, D. R., D'Aquila, R. T., et al. (2003). Antiretroviral drug resistance testing in adults infected with human immunodeficiency virus type 1: 2003 recommendations of an international AIDS society-USA panel. *Clinical infectious diseases, 37*(1), 113-128.

Hirsch, M. S., Brun-Vezinet, F., D'Aquila, R. T., Hammer, S. M., Johnson, V. A., Kuritzkes, D. R., et al. (2000). Antiretroviral drug resistance testing in adult HIV-1 infection: Recommendations of an international AIDS society-USA panel. *JAMA, 283*(18), 2417-2426.

Honigsbaum, M. (2005, West side story: A tale of unprotected sex which could be link to new HIV superbug. *The Guardian,* March 26.

Iliffe, J. (2002). *East African doctors: A history of the modern profession*. Kampala, Uganda: Fountain Publishers.

Irwin, A., Millen, J., Kim, J., Gershman, J., Schoepf, B., & Farmer, P. (2002). Suffering, moral claims, and scholarly responsibility: A response to Leslie Butt. *Medical Anthropology, 21*, 25-30.

Johnson, V. A., Brun-Vezinet, F., Clotet, B., Conway, B., Kuritzkes, D. R., Pillay, D., et al. (2005). Update of the drug resistance mutations in HIV-1: 2005. *Topics in HIV medicine : a publication of the International AIDS Society, USA, 13*(1), 51-57.

Kahn, J. (2001, Rich nations consider fund of billions to fight AIDS. *New York Times,* April 29, pp. A10.

Kahn, P. (2003). Do clades matter for HIV vaccines? *International AIDS Vaccine Initiative Report* (May/August).

Kaiser Family Foundation. (2006). Inquiry into alleged mismanagement of ugandan global fund grants has revealed 'pile of filth,' commission head says. *Kaiser Daily HIV/AIDS Report* (April 4).

Kaiser Family Foundation (2001). Drug companies withdraw lawsuit against South Africa. *Kaiser Daily HIV/AIDS Report* (April 19).

Kalafonos, I. (n.d.). *Treating AIDS in central Mozambique: Antiretrovirals, activists, and A vita positiva.* Unpublished dissertation in Medical Anthropology, University of California, San Francisco and Berkeley.

Kaleebu, P. (2005). HIV trials in Uganda. In P. Kahn (Ed.), *AIDS vaccine handbook: Global perspectives* (pp. 145-152). New York: AIDS Vaccine Advocacy Coalition.

Kamradt, T., Niese, D., & Vogel, F. (1985). Slim disease (AIDS). *Lancet, Dec 21-28*(2), 1425.

Kantor, R. (2006). Impact of HIV-1 pol diversity on drug resistance and its clinical implications. *Current opinion in infectious diseases, 19*(6), 594-606.

Kantor, R., & Katzenstein, D. (2004). Drug resistance in non-subtype B HIV-1. *Journal of clinical virology, 29*(3), 152-159.

Knorr-Cetina, K. (1995). Laboratory studies: The cultural approach to the study of science. In S. Jasanoff, G. Markle, J. Petersen & T. Pinch (Eds.), *Handbook of*

science and technology studies (pp. 140-166). Thousand Oaks, Ca: Sage Publications.

Latour, B. (1987). *Science in action*. Cambridge, MA: Harvard University Press.

Latour, B. (1993). *We have never been modern*. Cambridge, MA: Harvard University Press.

Latour, B. (1999). Give me a laboratory and I will raise the world. In M. Biagioli (Ed.), *The science studies reader* (pp. 258-275). New York: Routledge.

Latour, B., & Woolgar, S. (1979). *Laboratory life: The construction of scientific facts*. Princeton, NJ: Princeton University Press.

Laurent, C., Diakhate, N., Gueye, N. F., Toure, M. A., Sow, P. S., Faye, M. A., et al. (2002). The Senegalese government's highly active antiretroviral therapy initiative: An 18-month follow-up study. *AIDS (London, England), 16*(10), 1363-1370.

Leclerc-Madlala, S. (2005). Juggling AIDS, grants and treatment in South Africa: Predicaments of second phase HIV/AIDS. *Continuity, Change and Transformation: Anthropology in the 21St Century (Anthropology of Southern Africa Conference),* University of KwaZulu-Natal.

Liechty, C. A., & Bangsberg, D. R. (2003). Doubts about DOT: Antiretroviral therapy for resource-poor countries. *AIDS (London, England), 17*(9), 1383-1387.

Lerner, B. H., Gulick, R. M., & Dubler, N. N. (1998). Rethinking nonadherence: Historical perspectives on triple-drug therapy for HIV disease. *Annals of Internal Medicine, 129*(7), 573-578.

Leslie, C. (1990). Scientific racism: Reflections on peer review, science and ideology. *Social science & medicine (1982), 31*(8), 891-905; discussion 905-12.

Leuck, S. (2004). White House gets pressure on AIDS plan. *Wall Street Journal,* March 25.

Levenson, J. (2004). *The secret epidemic: The story of AIDS and black America*. New York: Pantheon Books.

Liu, J. (2005). Governing adherence: Medications, HIV, and power. *Unpublished manuscript.* (Winner, Hughes Paper Prize, Society for Medical Anthropology).

Livingston, J. (2005). *Debility and the moral imagination in Botswana*. Bloomington, IN: Indiana University Press.

Lurie, P., & Wolfe, S. M. (1997). Unethical trials of interventions to reduce perinatal transmission of the human immunodeficiency virus in developing countries. *New England journal of medicine, 337*(12), 853-856.

Magubane, Z. (2001). Which bodies matter? feminist post-structuralism, race, and the curious theoretical odyssey of the hottentot venus. *Gender and Society, 15*(6), 816-834.

Markowitz, M., Mohri, H., Mehandru, S., Shet, A., Berry, L., Kalyanaraman, R., et al. (2005). Infection with multidrug resistant, dual-tropic HIV-1 and rapid progression to AIDS: A case report. *Lancet, 365*(9464), 1031-1038.

McFadden, R. (1991). A drug-resistant TB results in 13 deaths in New York prisons. *New York Times,* Nov. 16.

McNeill, D. (2004, Furor in Africa over drug for women with HIV. *New York Times,* Dec. 21.

McNeilly, P. (2002). *RE: Human research subject protections under federalwide assurance (FWA) 00001293, single project assurances (SPA) S-6233 and S-6234, and cooperative project assurances (CPA) T-5124 and T-5125.* [Letter to Zerababel M. Nyiira and Nelson K. Sewankambo]. July 16. Office for Human Research Protections, U.S. Department of Health and Human Services.

Montagnier, L. (2002). Historical essay:A history of HIV discovery. *Science (New York, N.Y.), 298*(5599), 1727-1728.

Morgensen, H. O. (2005). Finding a path through the health unit: Practical experience of Ugandan patients. *Medical Anthropology,* (24), 209-236.

Navarro, M. (1992). Gauging threat of recalcitrant TB patients. *New York Times,* (April 14).

Nelkin, D. (1995). Science controversies: The dynamics of public disputes in the United States. In S. Jasanoff, G. Markle, J. Petersen & T. Pinch (Eds.), *Handbook of science and technology studies* (pp. 444-456). Thousand Oaks, CA: Sage Publications.

New York City Department of Health and Mental Hygiene. (2005). New York City resident diagnosed with rare strain of multi-drug resistant HIV that rapidly progresses to AIDS. *Press Release #016-05,* Feb. 11. http://www.nyc.gov/html/doh/html/pr/pr016-05.shtml

New York Stock Exchange. (2004). *Ambassador Randall Tobias visits the NYSE.* Oct. 13. http://www.nyse.com/events/Cal_1049657942330.html (Last accessed Jun. 11, 2007).

Nguyen, V. (2005). Antiretroviral globalism, biopolitics, and therapeutic citizenship. In A. Ong, & S. J. Collier (Eds.), *Global assemblages*. Malden, MA: Blackwell Publishers.

Nguyen, V. (2006). *Therapeutic citizenship in the era of global antiretrovirals: Emerging issues and research challenges for medical anthroplogy.* Paper given at the UCSF Department of Anthropology, History and Society Medicine; Medical Anthropology Colloquium, Sept. 13. San Francisco, CA.

Orrell, C., Bangsberg, D. R., Badri, M., & Wood, R. (2003). Adherence is not a barrier to successful antiretroviral therapy in South Africa. *AIDS (London, England), 17*(9), 1369-1375.

Oxfam. (2002). *Access to antiretroviral therapy in Uganda, June 2002.* http://www.oxfam.org.uk/what_we_do/issues/hivaids/downloads/arvaccessuganda.pdf.

Oyugi, J. H., Byakika-Tusiime, J., Charlebois, E. D., Kityo, C., Mugerwa, R., Mugyenyi, P., et al. (2004). Multiple validated measures of adherence indicate high levels of adherence to generic HIV antiretroviral therapy in a resource-limited setting. *Journal of acquired immune deficiency syndromes (1999), 36*(5), 1100-1102.

Packard, R. M., & Epstein, P. (1991). Epidemiologists, social scientists, and the structure of medical research on AIDS in Africa. *Social science & medicine (1982), 33*(7), 771-83; discussion 783-94.

Paterson, D. L., Swindells, S., Mohr, J., Brester, M., Vergis, E. N., Squier, C., et al. (2000). Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Annals of Internal Medicine, 133*(1), 21-30.

Perez-Pena, R. (2005). Chilled by findings, investigators dreaded the mounting evidence. *New York Times,* Feb. 12.

Petryna, A. (2005). Ethical variability: Drug development and globalizing clinical trials. *American Ethnologist, 32*(2), 183-197.

PhRMA. (2006). *Danger ahead: Drug resistant strains show there are no simple solutions.* http://world.phrma.org/challenges.drug.resistance.html.html (Last accessed June 11, 2007).

Pigg, S. L. (2001). Languages of sex and AIDS in nepal: Notes on the social production of commensurability. *Cultural Anthropology, 16*(4), 481-541.

Popp, D., & Fisher, J. D. (2002). First, do no harm: A call for emphasizing adherence and HIV prevention interventions in active antiretroviral therapy programs in the developing world. *AIDS (London, England), 16*(4), 676-678.

Rainey, L. (2006). Who discovered HIV: Gallo, Montagnier or both? *Dallas Voice,* July 7.

Rheinberger, H., & Gaudilliere, J. (2004). Introduction. In H. Rheinberger, & J. Gaudilliere (Eds.), *Classical genetics research and its legacy: The mapping cultures of 20th century genetics* (pp. 1-7). London; New York: Routledge.

Richman, D. D., Morton, S. C., Wrin, T., Hellmann, N., Berry, S., Shapiro, M. F., et al. (2004). The prevalence of antiretroviral drug resistance in the United States. *AIDS (London, England), 18*(10), 1393-1401.

Rose, N. (2001). The politics of life itself. *Theory, Culture and Society, 18*(6), 1-30.

Rosenberg, C. (1992). Framing disease: Illness, society, and history. In C. Rosenberg, & J. Golden (Eds.), *Framing disease: Studies in cultural history* (pp. xiii). New Brunswick, NJ: Rutgers University Press.

Rosenthal, E. (1990). The return of TB: A special report. *New York Times,* July 15.

Rushton, J. P., & Bogaert, A. F. (1989). Population differences in susceptibility to AIDS: An evolutionary analysis. *Social science & medicine (1982), 28*(12), 1211-1220.

Santora, M., & Altman, L. (2005a). Rare and aggressive HIV reported in New York. *New York Times,* Feb. 12.

Santora, M., & Altman, L. (2005b) Alarm over single AIDS case is challenged by questioners. *New York Times,* Feb. 21.

Serwadda, D., Mugerwa, R. D., Sewankambo, N. K., Lwegaba, A., Carswell, J. W., Kirya, G. B., et al. (1985). Slim disease: A new disease in Uganda and its association with HTLV-III infection. *Lancet, 2*(8460), 849-852.

Sewankambo, N. K., Carswell, J. W., Mugerwa, R. D., Lloyd, G., Kataaha, P., Downing, R. G., et al. (1987). HIV infection through normal heterosexual contact in Uganda. *AIDS (London, England), 1*(2), 113-116.

Shafer, R. (2005). RE: Comments and suggestions regarding the draft guidance document entitled "Guidance for Industry Role of HIV Drug Resistance Testing in Antiretroviral Drug Development (Docket number 2004D-0484). [Letter to the Food and Drug Administration]. Feb. 25.

Shapin, S. (1995). Here, and everywhere: Sociology of scientific knowledge. *Annual Review of Sociology,* (21), 289-321.

Shapin, S., & Schaffer, S. (1987). *Leviathan and the air pump: Hobbes, Boyle, and the experimental life*. Princeton, NJ: Princeton University Press.

Silverman, M., Lee, P. R., Lydecker, M. (1982). The drugging of the third world. *International journal of health services, 12*(4), 585.

Solomon, J. (2004a). U.S. officials knew of AIDS drug risks. *Washington Post,* Dec. 13.

Solomon, J. (2004b). AIDS chief says he rewrote safety report. *New York Times,* Dec. 15.

Sontag, D., & Richardson, L. (1997). Doctors withhold H.I.V. pill regimen from some. *New York Times,* March 2, pp. 1.

Specter, M. (1992). Neglected for years, TB is back with strains that are deadlier. *New York Times,* October 11. pp. A1.

Spira, S., Wainberg, M. A., Loemba, H., Turner, D., & Brenner, B. G. (2003). Impact of clade diversity on HIV-1 virulence, antiretroviral drug sensitivity and drug resistance. *The Journal of antimicrobial chemotherapy, 51*(2), 229-240.

Star, S. L., & Griesemer, J. (1999). Institutional ecology, 'Translations' and boundary objects: Amateurs and professionals in Berkeley's museum of vertebrate zoology, 1907-1939. In M. Biagioli (Ed.), *The science studies reader* (pp. 505-524). New York: Routledge.

Stepan, N. L. (1996). Race and gender: The role of analogy in science. *Isis, 77*(2)

Stevens, W., Kaye, S., & Corrah, T. (2004). Antiretroviral therapy in Africa. *BMJ (Clinical research ed.), 328*(7434), 280-282.

Stine, G. (2004). *AIDS update*. Englewood Cliffs, NJ: Prentice Hall.

Sunder Rajan, K. (2006). *Biocapital: The constitution of post-genomic life*. Durham, NC: Duke University Press.

Tamalet, C., Pasquier, C., Yahi, N., Colson, P., Poizot-Martin, I., Lepeu, G., et al. (2000). Prevalence of drug resistant mutants and virological response to combination therapy in patients with primary HIV-1 infection. *Journal of medical virology, 61*(2), 181-186.

Tchetgen, E., Kaplan, E. H., & Friedland, G. H. (2001). Public health consequences of screening patients for adherence to highly active antiretroviral therapy. *Journal of acquired immune deficiency syndromes (1999), 26*(2), 118-129.

Trostle, J. A. (1988). Medical compliance as an ideology. *Social science & medicine (1982), 27*(12), 1299-1308.

Turnbull, D. (1989). *Maps are territories, science is an atlas*. Chicago: University of Chicago Press.

Turnbull, D. (2004). Genetic mapping: Approaches to the spatial topography of genetics. In H. Rheinberger, & J. Gaudilliere (Eds.), *Classical genetics research and its legacy: The mapping cultures of 20th century genetics* (pp. 207-219). London; New York: Routledge.

U.S. Government Accountability Office. (2006). *Global health: Spending requirement presents challenges for allocating prevention funding under the president's emergency plan for AIDS relief* (No. GAO-06395). Washington, D.C.: U.S. GAO.

Uganda Ministry of Health. (1999). *An overview of HIV/AIDS in Uganda*, accessed 2/2007, from http://www.health.go.ug/docs/HIVinUganda.pdf

UNAIDS. (2006). *Report on the global AIDS epidemic.* Joint United Nations Program on AIDS (UNAIDS).

Varmus, H., & Satcher, D. (1997). Ethical complexities of conducting research in developing countries. *New England journal of medicine, 337*(14), 1003-1005.

Vaughan, M. (1991). *Curing their ills: Colonial power and African illness*. Stanford, CA: Stanford University Press.

Volberding, P. A. (2005). The New York case: Lessons being learned. *Annals of Internal Medicine, 142*(10), 866-868.

Volberding, P. A., Lagakos, S. W., Koch, M. A., Pettinelli, C., Myers, M. W., Booth, D. K., et al. (1990). Zidovudine in asymptomatic human immunodeficiency virus infection: A controlled trial in persons with fewer than 500 CD4-positive cells per cubic millimeter. *New England journal of medicine, 322*(14), 941-949.

Wailoo, K. (1997). *Drawing blood: Technology and disease identity in twentieth-century america*. Baltimore: Johns Hopkins University Press.

Weidle, P. J., Mastro, T. D., Grant, A. D., Nkengasong, J., & Macharia, D. (2002). HIV/AIDS treatment and HIV vaccines for Africa. *Lancet, 359*(9325), 2261-2267.

Whyte, S. R., Van der Geest, Sjaak, & Hardon, A. (2002). *Social lives of medicines*. Cambridge, UK; New York: Cambridge University Press.

Whyte, S. R., Whyte, M. A., & Meinert, L.: Kyaddondo, B. (2004). Treating AIDS: Dilemmas of unequal access in Uganda. *Journal of Social Aspects of HIV/AIDS Research Alliance, 1*(1), 14-26.

Wiktor, S. Z., Ekpini, E., & Nduati, R. W. (1997). Prevention of mother-to-child transmission of HIV-1 in Africa. *AIDS (London, England), 11 Suppl B*, S79-87.

World Health Organization (WHO). (2003). *Substandard and counterfeit medicines (fact sheet #275).*, accessed 2/2007, from http://www.who.int/mediacentre/factsheets/2003/fs275/en/print.html

World Health Organization (WHO). (2004). *WHO statistical information system: Core health indicators,* accessed 6/2007, from http://www.who.int/whosis/database/core/core_select_process.cfm?countries=all&indicators=nha

World Health Organization (WHO). (2005a). *Interim WHO clinical staging of HIV/AIDS and HIV/AIDS case definitions for surveillance, African region.* Retrieved 10/13, 2006, from http://www.who.int/hiv/pub/guidelines/casedefinitions/en/index.html

World Health Organization (WHO). (2005b). *Estimated number of people receiving ARV therapy and percentage coverage in 20 countries with the highest unmet need, June 2005.* Retrieved 10/13, 2006, from http://www.who.int/hiv/facts/20UNMETNEEDweb.jpg

World Medical Association. *Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects*, (Adopted 1964; Notes of Clarification added 2002, 2004).

Yeni, Patrick, et. al. (2004). Treatment for adult HIV infection: Recommendations of the international AIDS society-USA panel. *JAMA, 292*(2), 251-265.

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