EpidemicProportions

Johns Hopkins Undergraduate Public Health Journal
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Working Toward Global Health Solutions

RESEARCH *Narges Alipanah & Atieh Novin* explore the treatment outcome of TB patients diagnosed with HIV infection in Iran.

FEATURES *Linda Wan* helps build a sanitation system for Uduzhapa, Ecuador with Engineers Without Borders.

PERSPECTIVES *Dr. Alison Geyh* continues to investigate the health consequences of the Sept. 11th attacks in New York.

EDITORIAL *Liana Senaldi* discusses the ethical implications of recent advances in genetic testing for cancer susceptibility.

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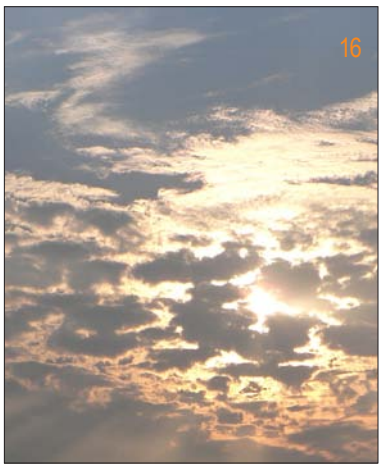
Confronting Challenges to Effective AIDS Treatment and Prevention

A Closer Look at the Air We Breathe

TB/HIV Co-infection: Changing Attitudes & Approaches

Dealing with Cancer Susceptibility: Research, Innovation, and Ethics

FEATURES



Front Cover: Two friends attempt to make the best of their surroundings in Stone Town, Zanzibar.
Back Cover: Group of children bathing and playing in the shadow of a *dhow*, a traditional Arab sailing vessel, off the coast of Tanzania.
Photos- Alex Wald

letter from the EDITORS

Dear Readers,

Welcome to the fourth issue of *Epidemic Proportions*, the Johns Hopkins undergraduate public health research journal. On behalf of the editorial staff, we are proud to present an issue that seeks to capture the breadth and depth of diverse public health experiences pursued by Hopkins students.

We are grateful to have the opportunity to highlight the work of our peers, individuals who have embarked upon innovative pursuits on the Homewood, Bloomberg, and JHMI campuses, as well as in Senegal, Iran, Sweden, India, Zambia, Ecuador, Argentina, South Africa, and the UK. The research will indeed take you around the world, across all disciplines and across all borders.

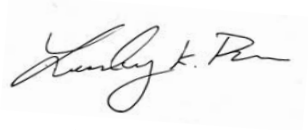
Our issue begins with a case study by Paul Sonenthal that explores how stigma associated with HIV/AIDS remains an overlooked barrier in effectively treating infected individuals. Staff members Ajay Gurbani and Atieh Novin draw on Paul's work to discuss how stigmatized individuals become excluded in their respective communities and call for a strategic advocacy framework to eliminate this discrimination.

Next, Amisha Patel's research compels us to take a closer look at the air we breathe, pointing out that endotoxins may pose a more serious health risk to humans than previously realized. Finally, we conclude this volume by following Teddy Holzer to the laboratory, where we learn how cancer screenings will continue to improve survival rates for patients. While this and other innovations in screening and detection technology may soon allow healthcare providers to better predict whether a person will develop cancerous mutations, staff members Liana Senaldi and Akash Bhatnagar use Holzer's work to discuss the ethical dilemma presented by this information and the context in which such knowledge should be used.

We hope to raise awareness, provoke thought, and create discussion. This issue of *Epidemic Proportions* is certainly a tribute to the countless professors and mentors here at Hopkins who have encouraged each and everyone of us to do well, to do more, and to do good. Most important, we would like to thank our staff for their hard work and dedication to the journal.

Scholarship through research has been the cornerstone of this university since its founding, and Johns Hopkins remains one of the world's leaders in the field of public health. We are proud to be able to continue in this vibrant tradition of combing the two and we look forward to doing so into the future. It is important to remember, however, that the research presented here is not an end in itself but rather a powerful instrument through which we can begin uncovering solutions to the world's most pressing public health challenges.

Sincerely,



Lindsay Brown
Editor-in-Chief

Rishi Mediratta
Editor-in-Chief

EpidemicProportions would like to thank the Public Health Studies Program, the Krieger School of Arts & Sciences, and the Johns Hopkins Bloomberg School of Public Health for making this journal possible. Producing this journal has been a true joy and a tribute to teamwork. Like any other student endeavor, it would not have been possible without the support of the Johns Hopkins community.

We would especially like to acknowledge:

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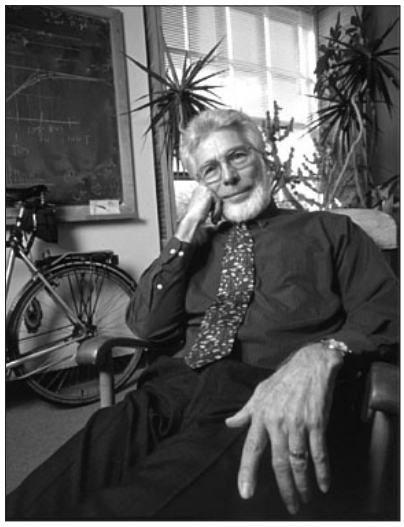
the staff of the Digital Media Center;
the faculty members and supporters of student research,
with special thanks to Dr. Susan Vazakas.

Back row: Rishi, Akash, Ajay, Teddy, Alex, James, Lindsay; **Middle:** Halshka, Samantha, Isabelle, Alyssa, Yogeeta, Nirosha, Maneesha, Atieh; **Front:** Jackie, Diana, Chandrani, Priyanka, Liana, Mehreen, Morgan; **Not pictured:** Hayley, Kristin, Farha, Annie, Jyoty

COVER LETTER

Richard Cone, PhD
Professor of Biophysics,
Professor of Biology,
Johns Hopkins University

Chair, Public Health Advisory Board



Public health combines elements of physical and biological sciences with social science and the humanities in order to address health and medical issues on a global scale — truly "epidemic proportions." My own research, for example, integrates biophysics — "bench science" — with the health of populations in every corner of the world. I work on vaginal microbicides designed to protect women against both pregnancy and sexually transmitted diseases, including AIDS.

New opportunities to integrate research science and the health of populations may be found in unsuspected places. One such place is the undergraduate classroom. While teaching physiology, I discovered that about 20% of Hopkins undergraduates had been told by their parents that their births were "accidents," conceptions despite the use of contraception. This fact, in addition to the knowledge I gained while spending a sabbatical year in 1979-1980 at the Bloomberg School of Public Health, were surprising catalysts which helped me realize the true potential my career in biophysics could have to change and improve the lives of millions.

While "the pill" is not yet 50 years old, the use of condoms dates back to ancient times. The technology has not been significantly improved since the invention of the latex condom over 130 years ago. Knowing this, I was left to wonder whether modern biotechnology could create something that would be more effective than the pill for reducing accidental pregnancies and more effective than condoms for preventing sexually transmitted diseases. I started developing methods would be more practical than the pill and would gain more acceptance and implementation than male condoms — vaginal microbicides which women could use for dual protection against disease and pregnancy.

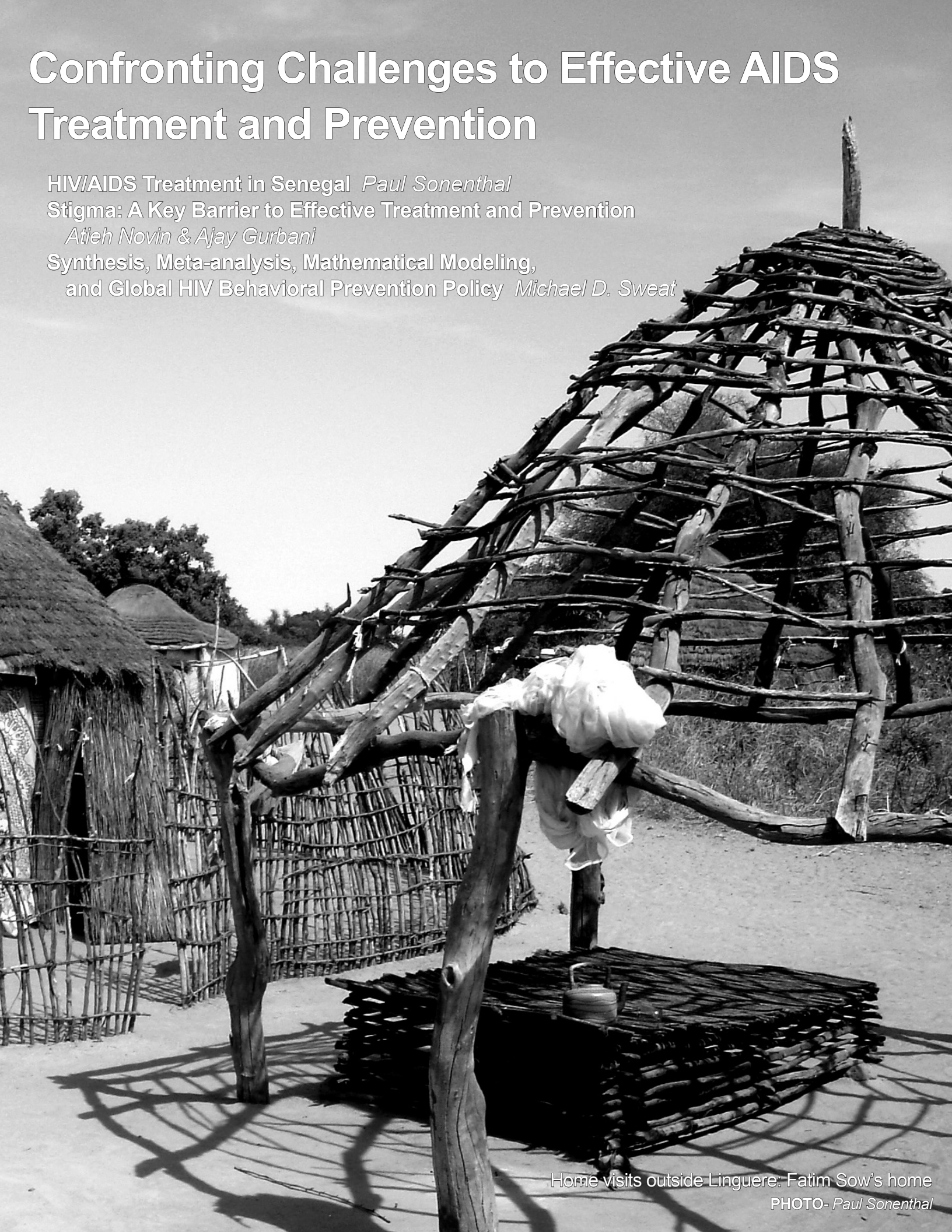
Today, many laboratories, including mine, are doing work at the core of public health: seeking methods that will help *prevent* diseases. One spermicidal microbicide, developed in my lab, BufferGel (ReProtect, Inc.), has recently been clinically proven as an effective contraceptive when used with a diaphragm. BufferGel is also one of five vaginal microbicides that are now in major Phase II and III clinical efficacy trials for preventing HIV infections.

The application of public health is necessary as well as universal. For instance, several epidemiologists uncovered the major public health implications of Bacterial Vaginosis (BV), a mild vaginal infection that markedly increases a woman's risk of acquiring HIV and other STDs, and also increases the risk of stillbirth and premature birth 5-10 fold. Also, epidemiological studies now reveal that circumcised men are less likely to acquire or transmit HIV infections. With the discovery of a practical health benefit of male circumcision, campaigns for the oft-questioned practice in adult male populations are underway in regions of high HIV prevalence.

Over the past 20 years, energetic and enthusiastic undergraduates, who see the potential for microbicides in reproductive health, have greatly contributed to the research in my lab. But there is much more to be done. I hope that students will be open to the many paths that the field of public health has to offer, and that those outside the field can benefit from and appreciate the far-reaching achievements in public health.

Photo courtesy of the Johns Hopkins Magazine.

Confronting Challenges to Effective AIDS Treatment and Prevention



Home visits outside Linguere: Fatim Sow's home
PHOTO- *Paul Sonenthal*

HIV/AIDS Treatment in Senegal

Decentralizing access to antiretrovirals through community involvement

Paul D. Sonenthal, Post-Baccalaureate

In this study, Highly Active Antiretroviral Therapy (HAART) is used to control the HIV/AIDS epidemic. Human Immunodeficiency Virus (HIV) is a retrovirus that weakens the body's immune system and causes Acquired Immunodeficiency Syndrome (AIDS). The success of HAART is dependent upon the reduction of social barriers such as stigma and decentralization. An analysis of the barriers surrounding the HAART was performed in a multitude of locations within Senegal. The results indicated that stigma and decentralization were in fact the principal barriers that prevented access and compliance to the HAART.

In the past eight years, more than 20 million people in the developing world have died as a result of HIV/AIDS. However, the increasing availability of antiretroviral (ARV) drugs, used in Highly Active Antiretroviral Therapy (HAART), has the potential to control HIV/AIDS in individuals and prevent many, if not most, future deaths. A massive worldwide effort is currently underway to provide HAART to millions of people living with HIV/AIDS (PLWHA). However, efforts to scale up treatment in resource-limited settings have encountered a number of barriers. Two concepts that are central to understanding the barriers discussed in this paper are "stigma" and "decentralization."

HIV/AIDS-related stigma is the association of HIV-positive status with some form of negative judgment. Culpability is often determined by a culture's values regarding sex. For example, Senegal is 94% Muslim.[1] "Islam and AIDS," a guide published by the Senegalese Ministry of Health to address the issue of religion and stigma, notes that there are numerous excerpts from the Koran condemning "fornication" as a sin.[2] PLWHA are often associated with promiscuity and high-risk behavior because HIV/AIDS can be transmitted through sexual contact. Therefore, in cultures with strong moral values regarding sex, the association of promiscuity with HIV/AIDS contributes to the stigmatization of PLWHA.

In most resource-limited settings (including Senegal), the scaling up of treatment follows a predictable pattern. First, treatment becomes available in the largest cities with the most medical infrastructure. Then, access slowly expands to the more rural areas. In Senegal, for instance, ARVs were first available in the capital city, Dakar. Now the country is in the process of expanding access from its urban centers to the rest of the country. This process is called "decentralization."

By balancing broad statistics and studies with anecdotal evidence, this paper will develop a clear picture of the barriers to effective treatment in Senegal and how best to deal with them. I argue that social factors, such as stigma and a paternalistic approach to health care, have presented barriers to effective distribution of ARVs. A potential solution to these problems is to augment the role of the community health worker. Providing specific ways for members of the community to take a more active role in the fight against HIV/AIDS creates an opportunity to address many of the problems hindering the process of decentralization.

The Senegalese initiative for access to antiretrovirals

Located on the tip of West Africa, Senegal is a country that, early on, recognized the threat posed by HIV/AIDS. Official estimates currently place Senegal's HIV prevalence rate at 0.9%, one of the lowest in Africa.[3] Senegal was also one of the first countries in Sub-Saharan Africa to address the issue of HIV/AIDS treatment. In January 2004, the Senegalese government committed to providing its citizens with access to ARVs free of charge.

By October 2005, it was estimated that the government-backed national treatment program, known as the Senegalese Initiative for Access to Antiretrovirals (ISAARV), was providing HAART to 3,500 patients.[4] However, by the fall of 2005 it was apparent that the scaling up of the ISAARV program had been hindered by a number of barriers.

The ISAARV is designed to function within Senegal's pre-existing health system, which is structured like a pyramid. At the very top of the pyramid are 17 hospitals. Below them are the 53 health centers, while at the base of the pyramid are 809 "health stations."[5]

Each level of the pyramid offers ISAARV patients a specific level of HIV/AIDS care. Health stations monitor patients' medication adherence and provide them with psychosocial care and symptomatic treatment with certain essential medicines (not including ARVs) for immunodepression. Health centers are equipped to diagnose signs of immunodepression, initiate HAART, and offer free HIV testing. At the very top of the pyramid, hospitals provide all of the services of a health center in addition to conducting biological tests to determine CD4 counts and viral loads.[5] In order to provide these services within the hospitals, the Senegalese government is working with the US Agency for International Development to build Centre Traitement Ambulatoires (CTAs). CTAs are specialized health centers located within hospitals that aim to centralize care in one area of the hospital. In October 2005, there were two operational CTAs in Senegal, located in Dakar and Ziguinchor.

The challenge of decentralization

The ISAARV was launched in 1998 as a pilot program in Senegal's capital city.

The pilot program was a success. Clinical and biological results from this trial were found to be similar to those in developed countries.[6] In order to build on this success and decentralize access to HAART, the program was expanded outside of Dakar with the objective of providing 7,000 patients with treatment by the end of 2006.[5] Halfway

One of the 809 health stations in Senegal. The room on the left is where local women give birth, and the room on the right is used for consultations. Photo- Paul Sonenthal

to the target in October of 2005, it was clear that the decentralization of the ISAARV had encountered a number of difficulties. Dr. Papa Salif Sow, head of Infectious Diseases at Fann Hospital in Dakar and the ISAARV national coordinator, characterized the issue of decentralization as the main challenge facing the ISAARV.[4]

Indeed, access to ARVs remains unequally centralized in Dakar. Although only 24% of the total population lives in Dakar, the city is home to roughly 68% of all patients on HAART in Senegal.[7] This imbalance cannot be explained by the fact that Dakar has a disproportionate number of patients. In fact, according to an HIV sentinel surveillance conducted in 2002, the median prevalence rate among pregnant women outside urban areas was higher than in urban areas.[8]

There is other evidence suggesting difficulties in expanding HAART access outside of Dakar. Adherence rates have dropped since the pilot program. According to a study of participants in the original pilot program, the adherence rate among ISAARV patients was 91%.[9] However, by October 2005, adherence for the entire program had dropped to just above 85%.[10]

Nevertheless, significant progress has been made towards decentralization. As of October 2005, there were 10 ARV distribution sites in Dakar and 22 sites throughout the rest of the country.[10] At the time, patients from all 11 regions of Senegal were enrolled in the ISAARV.

Culture and stigma

Cultural issues, including the stigmatization of PLWHA, present another barrier to effective treatment. Some cultural beliefs can lead to negative interpretations of the effects of HAART. For instance, a number of male patients in the pilot program complained of frequent erections and repeated wet dreams. The patients blamed these effects on Videx®, which has a milky appearance. Furthermore, the patients saw these side effects as a sign that HAART was diminishing their virility and masculinity. This interpretation is driven by a cultural belief of the Wolof, the main ethnic group in Senegal, that "sperm concentration [assures] masculine fertility."[11] Subsequently, some patients were unwilling to take the medication because they felt that their sperm concentration was at risk.

Although difficult to quantify, the negative impact of stigma is significant. The social exclusion that can result from stigmatization is particularly severe in Senegal because of the country's social structure. Senegalese culture is based around the extended family.

Children often live at home with their families until they are married or have a steady job. Even then, many Senegalese continue to live with their parents. Indeed, there are 10 people in the average rural Senegalese household and 8.5 in the average urban household.

Furthermore, the Senegalese depend on their extended family to provide an elaborate, and often essential, support system.

In a large initial study of the ISAARV, it was observed that most patients belonged to large households. Patients lived, on average, in households of 10 people, while only 1.5 people in each of these households had income and the majority of patients (54%) stayed with their families rent-free.[9] This dependence intensifies patients' fears of rejection.

Unfortunately, this fear is not always unfounded. In an initial study of the pilot program, one of the 26 patients included in the study was rejected by his family and subsequently thrown out of the house.[12] Familial rejection and abandonment would leave many patients destitute. Consequently, there are documented cases of PLWHA in Senegal who choose to disrupt their treatment rather than disclose their seropositive status to their families.[7]

There is a number of possible explanations for the stigmatization of PLWHA by their families. One possibility is that the family might associate seropositive status with immoral behavior and subsequently blame the patient. Furthermore, the family might fear that the greater community will blame them for the patient's seropositive status. As a result, the fear of stigmatization may extend beyond the patient to the entire family. Finally, unfounded fears of transmission of the virus through casual contact with the patient, such as hugging or sharing eating utensils, might incline members of the family to avoid all contact with the patient. All of these factors would prevent the patient from receiving support and care from their family.

Fear of stigmatization also creates a reluctance to accept homevisits from health workers.

Patients fear that having a health worker regularly visiting them at home would be highly conspicuous and make it virtually impossible to keep their seropositive status a secret from family and neighbors. For this reason, despite the opportunity to receive free food, counseling and support, patients often turn down homevisits from health workers.

Similarly, the stigmatization resulting from open association with HIV/AIDS discourages community mobilization. Associations of PLWHA find it difficult to recruit new members because many patients are afraid that by being identified as a member of an association of PLWHA, they will be stigmatized. Widespread stigma also discourages open discourse and the dissemination of information. Most important, stigma often deters people from getting tested for HIV.

Case study 1: Ziguinchor

In October 2005, the author traveled to the city of Ziguinchor to meet with doctors and staff at the CTA in Silence Hospital, and members of an association of PLWHA. Through these meetings and discussions, a more vivid picture of the specific problems confronting decentralization emerged.

Ziguinchor is located in the Casamance region of southern Senegal. According to sentinel surveillance in 2003, there is an HIV/AIDS prevalence rate of 2.3% among pregnant women in Ziguinchor, putting it above the national average of 1.2%.[8] In August 2004, Odette Coly founded the Casamance's first and only association of PLWHA, "Uribora, Sofora, and Wassora" (USWA), which translates roughly to "Togetherness, Solidarity and Sharing." The association is open to men and women who are HIV-positive. The association holds regular meetings at the CTA, including a communal meal on Saturdays.

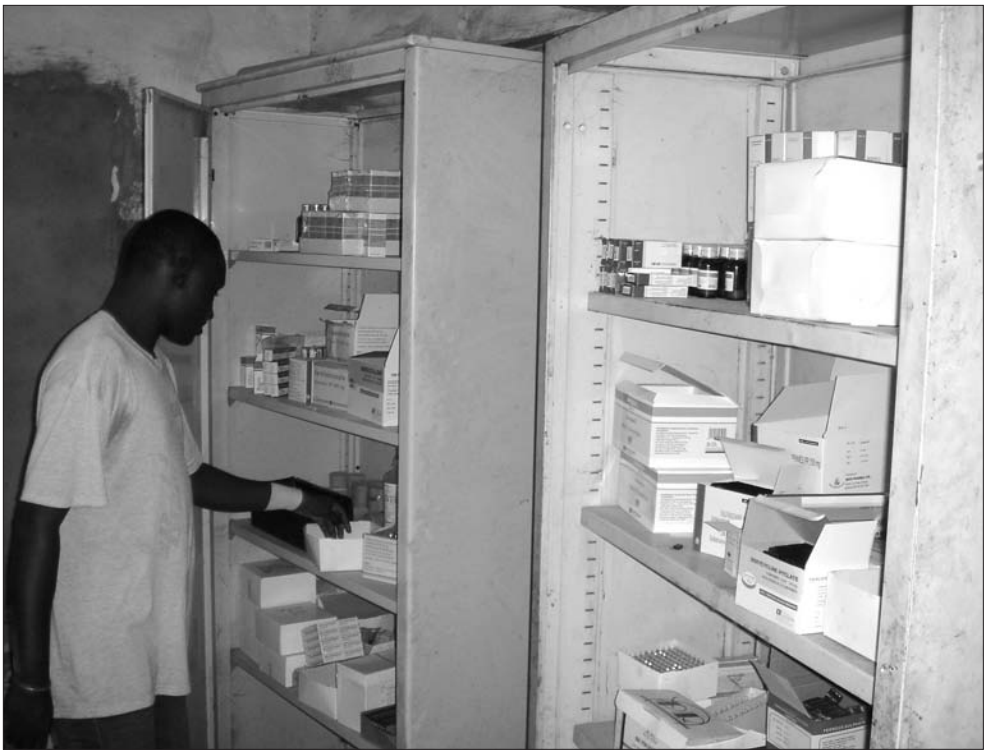
Through a series of discussions with patients, doctors, and other health officials, it was discovered that many infected individuals are not well informed about their drug regimens. In one meeting, patient A, a member of USWA, mentioned that he was taking bi-therapy. If true, his regimen would consist of two ARVs. By current standards, this is an inadequate method of treatment: all patients receiving HIV/AIDS treatment should be on a regimen of three ARVs. However, patient A might have been confused since some patients enrolled in the ISAARV are given Combivir®, a combination of two ARVs in one pill. When questioned further, he was not able to explain what was meant by "bi-therapy" or even name which ARVs he was prescribed. In fact, not a single member of USWA could name the medicines they were prescribed. This indicates a striking lack of knowledge concerning HAART, or treatment literacy, among patients in Ziguinchor.

Lack of treatment literacy is a serious problem for a number of reasons. First, it is important that patients feel involved in their treatment so that they develop a sense of responsibility for maintaining high levels of adherence. Increased treatment literacy would give patients a greater sense of involvement and empowerment, dispelling the notion that they are unable to participate directly in their treatment, and encouraging them to take a more active role in their health. A patient is more likely to maintain good adherence if he or she understands its importance.

Second, treatment literacy can serve as a mechanism for enforcing protocols by empowering individuals to monitor their own regimens. Well-informed patients who are given inadequate care, such as bi-therapy treatment, will be able to help recognize and deal with their problems.

There are several problems concerning patients' access to medicines in the Casamance. Patients enrolled in the ISAARV are required to travel to a hospital in order to obtain their ARVs. At the beginning of treatment, a patient must make the trip every two weeks. Eventually, with signs of good adherence, doctors are willing to give patients two months' worth of ARVs with every visit to the hospital, minimizing the patients' need to travel. Nevertheless, for many patients, travel to and from the hospital is time-consuming and costly. It is not unusual for patients to spend the entire day at the hospital waiting for their medicines.[13] Therefore, for patients with a job, the cost of a hospital visit can include losing an entire day's pay on top of transportation fees.

For patients with responsibilities at home, the burden of care falls on other members of the household due to the patient's absence. Furthermore, regular absences from the community and home leave patients open to scrutiny and suspicion. These hardships are exacerbated by logistical problems distributing ARVs to hospitals. Regional ARV distribution sites, including Ziguinchor, depend on regular deliveries of ARVs from Dakar. There are frequent delays in these ARV deliveries, which lead to shortages across administrative regions. During these shortages, hospitals issue patients only one week's supply of medicine per visit. This increases the burden on the patient by requiring more frequent visits to the hospital.[14]



The pharmacy at Silence Hospital, Ziguinchor. ARVs are kept elsewhere. Photo- Paul Sonenthal

For some patients, the cost of traveling to the hospital for care is simply too high. The voluntary counseling and testing (VCT) center at Silence Hospital in Ziguinchor offers free and anonymous HIV tests. Once a month, the VCT operates a mobile clinic in rural Casamance in order to provide HIV tests to people living in remote areas. When people test positive, the center sends them a

letter informing them of the test results and encouraging them to come to Ziguinchor to speak with doctors and counselors. However, the center cannot afford to cover the cost of a patient's transportation. If the patient is unable to come to Ziguinchor, then the center recommends that the patient visit a doctor located closer to his or her village. However, villagers consistently claim that financial constraints prevent them from ever making the journey to the hospital or local doctor. Therefore, every month, despite these measures taken by the VCT center, at least three villagers test positive and never receive any type of medical follow up.[15] Costs associated with travel to and from medical facilities is often a burden that patients simply cannot overcome.

Case study 2: Linguère

The story of one PLWHA, patient B, living in a small village in northeastern Senegal, provides an illuminating example of the way in which problems relating to access to medicine and treatment literacy exacerbate one another. Patient B lives in a small thatched roof hut about 50 kilometers from the nearest road. She has no access to electricity or running water. Fresh water is brought in daily on a donkey-drawn cart.

Every two months, in order to get her ARVs, she must travel two days to the nearest hospital distribution site. Often, when she arrives at the hospital, there is no doctor around to dispense her medicine. When this happens she must wait until the next day for her doctor to arrive. Because of these delays, she is forced to spend the night in a hospital bed, near other sick patients, which is dangerous for someone with a weak immune system.

Sometimes the hospital is running low on ARVs and she is only given enough pills to last for one week. Because she doesn't realize the importance of adherence and is unable to make a weekly trip to the hospital, she often conserves pills by taking only half of her prescribed doses. Thus, lack of treatment literacy and the inaccessibility of medication leads to poor adherence.

Engaging the community

At a conference on the social aspects of HIV/AIDS held in Dakar in October 2005, a large group composed of members from various regional associations of PLWHA marched and chanted in protest of their exclusion from meaningful participation in the conference. Although this incident was meant to highlight the lack of involvement of associations of PLWHA, it also offered a glimpse of the type of role that well-organized and effectively mobilized organizations can play. Associations of PLWHA can become powerful advocates for the rights and dignity of PLWHA and help ensure effective action from government and non-governmental organizations (NGOs).

With this in mind, it is unfortunate that there is not greater organization at the community level with regards to HIV/AIDS in Senegal. NGOs such as Family Health International (FHI), Association National Contre le SIDA (ANCS), and Africa Consultants International (ACI) recognize the importance of the role of community associations and are working to help strengthen and develop them. Common to many of these efforts is an underlying philosophy that the best catalysts for change come from within the relevant culture. All cultures, including Senegal's, have certain opinions and behaviors that increase vulnerability to HIV/AIDS. Therefore, working to change these attitudes is important in the fight against the disease.

One of the ISAARV's strategic errors has been an over-reliance on a hospital-based distribution system. This approach is symptomatic of an overly paternalistic view of health care. When the author asked one member of USWA which specific ARVs he was taking, he replied that it was not his job to know the details of his treatment. Rather, he said, it's his doctor's concern. This is exactly the type of attitude that needs to be dispelled: that most roles are better left to health professionals because the issues are too complicated or too technical. This view, held by people from remote rural villages all the way to the halls of government, is impeding the progress of decentralization. Communities must recognize that they have an important role to claim in the fight against AIDS.

Furthermore, the hospital-based approach places an excessive burden on a health system that does not have the capacity and infrastructure to meet the needs of PLWHA in rural areas. Broadening the role of local communities in the scaling up of treatment is an effective way of lessening the burden on pre-existing health infrastructure. This means informing patients about their regimens through treatment literacy campaigns, changing the doctor-patient relationship so that patients feel more comfortable asking questions, empowering local associations of PLWHA and community health workers to take a more active role in distributing ARVs and monitoring adherence. These measures are aimed at bringing about a more fundamental change in Senegal's treatment program. In short, the perceived barrier between the public health apparatus and the patient needs to be removed.

Some of these goals can be achieved by expanding the role of community health workers.

The first step would be to enable health workers currently conducting homevisits to deliver ARVs directly to the patient. During these visits, health workers could also begin treatment literacy education, as well as work with associations of PLWHA to promote treatment literacy. Through these initiatives, certain members of the associations of PLWHA can be identified and trained as community health workers. The result would be a gradual increase of communal knowledge and involvement regarding HAART and HIV/AIDS in general. The idea of enabling health workers to distribute ARVs in Senegal has previously been suggested by ISAARV's coordinator, Dr. Papa Salif Sow.[10]

There is evidence that these methods will improve treatment. In Uganda, a program called Reach Out recorded a 99.4% adherence rate among patients in the program. Reach Out enrolls patients in an initial treatment program in which community health workers conduct homevisits where they provide medication and counseling as well as monitor adherence. All services are free of charge. Patients who have maintained good adherence levels are then invited to train as community health workers.[16]

Conclusion

Senegal is an excellent example of the successes against the spread of HIV/AIDS as well as the barriers to further progress. Specifically, Senegal's HIV/AIDS treatment program has achieved remarkable results, but is struggling to decentralize. The community health worker system presents a formal mechanism for addressing the social factors of HIV/AIDS and encouraging the spread of positive attitudes and behavior throughout communities. The system could be adapted in Senegal to help strengthen associations of PLWHA, build the capacity of the rural health system, increase treatment literacy, and fight stigma.

Acknowledging that some patients are reluctant to accept homevisits because of fear of stigmatization, health workers will first restrict homevisits to patients less concerned about it. The aim then is to provide a positive example through outreach, which, over time, will encourage more patients to accept homevisits. As members of the community, health workers and members of associations of PLWHA can effectively address concerns based on cultural issues, such as the sexual side effects of HAART. Most important, by enabling community health workers to distribute ARVs during homevisits, a significant burden on the patient can be lifted.

1. Central Intelligence Agency. CIA- The World Fact Book Senegal <https://www.cia.gov/cia/publications/factbook/geos/sg.html>. Accessed November 20, 2006. Central Intelligence Agency, Washington D.C., 2006.
2. Seck E. Guide Islam Et SIDA. Dakar, Senegal: République Du Sénégal Ministère De la Santé Publique et De L'Action Sociale, 2003.
3. UNAIDS. 2006 Report on the Global AIDS Epidemic. Geneva, Switzerland: UNAIDS, May 2006.
4. Sow PS. Fann Hospital, Dakar, Senegal. Personal communication, September 19, 2005.
5. Ministère de la Santé et de la Prevention Médicale. Prise En Charge Médicale Des Patients Vivant Avec Le VIH/SIDA. Dakar, Senegal: Ministère de la Santé et de la Prevention Médicale, 2004.
6. Laurent C, Ngom Gueye NF, Diahakté N, Gueye PM, Diouf M, Lanièce I, Touré Kane NC, Vergne L, Ndir A, Liégeois F, Faye MA, Peeters M, Mboup M, Delaporte E, Ndoye I, Sow PS. Clinical and Biological Assessment of HAART in the ISAARV Programme. In: Desclaux A, Laniece I, Ndoye I, Taverne B (eds). The Senegalese Antiretroviral Drug Access Initiative. An Economic, Social, Behavioural and Biomedical Analysis. Paris, France: ANRS, UNAIDS, WHO, 2004:133.
7. Sow K, Desclaux A. Antiretroviral Treatment Adherence and its Determinants: A Qualitative Analysis. In: Desclaux A, Laniece I, Ndoye I, Taverne B (eds). The Senegalese Antiretroviral Drug Access Initiative. An Economic, Social, Behavioural, and Biomedical Analysis Paris, France: ANRS, UNAIDS, WHO, 2004:103.
8. UNAIDS. Epidemiological Fact Sheets on HIV/AIDS and Sexually Transmitted Infections: Senegal. Geneva, Switzerland: UNAIDS, 2004.
9. Lanièce I, Desclaux A, Sylla O, Taverne B, Ciss M. Terms of Selection and Patient Social Profile. In: Desclaux A, Laniece I, Ndoye I, Taverne B (eds). The Senegalese Antiretroviral Drug Access Initiative. An Economic, Social, Behavioural, and Biomedical Analysis. Paris, France: ANRS, UNAIDS, WHO, 2004:31.
10. Sow PS. Meridien Hotel, Dakar, Senegal. Personal communication, October 14, 2005.
11. Sow K, Desclaux A. Confidence in HAART. In: Desclaux A, Laniece I, Ndoye I, Taverne B (eds). The Senegalese Antiretroviral Drug Access Initiative. An Economic, Social, Behavioural and Biomedical Analysis. Paris, France: ANRS, UNAIDS, WHO, 2004:124.
12. Sow K, Desclaux A. Family Solidarity in Patient Treatment: Realities, Myths and Limits. In: Desclaux A, Laniece I, Ndoye I, Taverne B (eds). The Senegalese Antiretroviral Drug Access Initiative. an Economic, Social, Behavioural and Biomedical Analysis. Paris, France: ANRS, UNAIDS, WHO, 2004:79.
13. Members of USWA. Hopital Silence, Ziguinchor, Senegal. Personal communication, October 22, 2005.
14. Diatta JR. Ziguinchor, Senegal. Personal communication, October 21, 2005.
15. Dieme J. Hopital Silence, Ziguinchor, Senegal. Personal communication, October 21, 2005.
16. Alamo S. Dakar, Senegal, Meridien Hotel. Personal communication, October 10, 2005.

EDITORIALS

Stigma: A Key Barrier to Effective Treatment and Prevention

Influence of culture on disease

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Puja wakes up every morning not knowing how she is going to make it through another day with the responsibility of having to support her children and needing to go to work. Ever since her husband died, Puja has been left to maintain the family by herself without any government aid or outside help. Her children often go hungry, and she does not have the financial means to secure housing. Perhaps the worst part of Puja's dilemma is that she and her children have AIDS, and they cannot afford the treatment to fight it.

Although Puja is a fictional character, her story resembles those of thousands of widows in India who face a similar horror. Because of its association with sex, AIDS is considered taboo in much of Indian society, especially in the least urbanized areas. For this reason, it is often considered unthinkable for a fiancée to ask her future husband's sexual history and thus cannot obtain any knowledge of the likelihood of infection with AIDS. As a result, these women often enter marriages without awareness of their husbands' illnesses, and these diseases are in turn transmitted to them through unprotected sex. Even worse, in the cases where the wives get pregnant, their children are at risk of being born with the disease.

Once the husband dies, the widow is left to cope with her disease and to raise their children alone because typically the family, both her in-laws and her own, have abandoned her and the children as a result of the shame associated with AIDS. While the assistance of non-governmental organizations (NGOs) is helpful, it is simply too sparsely located geographically. Furthermore, the victims receive very little or no help from either the community or the state, and therefore are very much on their own in dealing with their plight.[1]

Ultimately, this means that the widow and her children have no realistic chance of ever leading normal lives.

Unfortunately, social stigmas toward disease exist throughout the world. In his book *Stigma: Notes on the Management of a Spoiled Identity*, sociologist Erving Goffman states that stigma "can arise of one possessing an attribute that makes that person different from others and of a less desirable kind." He further states that the victim is thus "reduced in our minds from a whole and usual person to a tainted, discounted one."[2] Stigma is a pervasive viewpoint that marginalizes and discredits a group of individuals due to cultural intolerance of their conditions. The cultural intolerance of AIDS patients results from two factors, namely lack of knowledge about the disease and religious convention. In an era in which the search for effective treatment and prevention methods has led to extensive work in sociology, anthropology, psychology, and numerous other fields, stigmatization tends to be the key barrier. This barrier, therefore, affects not only stigmatized individuals but the community as a whole.

It is important to understand some of the causes of cultural intolerance, which are the initiating factors of stigmatization. Sociologist Ann Swidler, in her publication *Culture in Action: Symbols and Strategies*, notes that culture "influences action not by providing the ultimate values toward which action is oriented," and states that this occurs "by shaping a repertoire or tool kit of habits, skills, and styles from which people construct strategies of action."[3] Culture, as a set of values and beliefs, must therefore be examined indirectly by studying behaviors and customs. The issue arises when essential contributors to culture such as religious and moral conventions build social boundaries leading to silence, denial, and ultimately stigma.

Perhaps one of the most significant and explicit examples of social stigma in relation to a disease are those that resulted in response to leprosy. In the past, the cultural shame and degradation associated with leprosy was extreme. As a result of the nonexistence of treatment, individuals with the disease were forced to live in colonies apart from the rest of society. As a study of the social reaction to leprosy in modern Nepal has indicated, social stigmatization toward the illness persists today, although to a relatively milder degree. Often, diseased individuals are not banished from the community but are forced to eat or sleep separately from family or live in a different part of the village. Despite the reduced nature of the stigmatization, victims may still think that they are being judged harshly for their sickness and will eventually be ostracized or expelled from their homes. This phenomenon is defined by experts as "perceived stigma," or the dishonor that is felt by an individual, whether or not such stigma truly exists. This is often compared to a variable labeled "enacted stigma," which is the visible, measurable amount of stigmatization seen in these cases.[4]

"Stigma is a pervasive viewpoint that marginalizes and discredits a group of individuals due to cultural intolerance of their condition."

This comparison between perceived and enacted stigma is one that reveals an important aspect of the social phenomenon behind disease. Many cases of cultural stigma toward a disease manifest themselves not through physical outcomes but rather through the mental effects that they have on the individuals with the illness. Frequently, these mental effects can be as strong as or even worse than the physical outcomes that result from enacted stigma. These effects include the development of psychosomatic conditions and can lead to serious depression due to feelings of isolation and hopelessness. Moreover, this trend becomes especially complicated when comparing perceived stigma with the condition of depression itself. A recent study Dr. Jeffrey Pyne et al. conducted in a Veterans Administration primary care clinic in Arkansas indicated that those who were receiving treatment for depression demonstrated a significantly increased degree of perceived further stigma. In addition, there was a correlation seen between the severity of depression and the level of stigmatization that was felt by the patient. As a result, stigma was considered a possible barrier to adequate treatment for these patients afflicted by depression.[5]

The "education vaccine" as the best available protection for many conditions including HIV is not always available.

One of the results of stigma as a treatment barrier is the discontinuation of treatment by stigmatized individuals. These individuals may delay or discontinue treatment or conceal their condition. A study by Lui et al. on stigma, delayed treatment, and spousal notification on sexually transmitted diseases (STDs) concluded that among 406 patients, 80% felt stigmatized, 28% sought treatment only after suffering symptoms for at least one week, and 40% reported continuing to have sex while having symptoms. Patients who felt stigmatized were less likely to agree to notify their spouses.[6] Through this study, stigma was clearly determined to be a barrier to notification. Concerns of confidentiality can also hinder individuals from soliciting counseling and testing services. The Centers for Disease Control and Prevention (CDC) estimates that as many as 300,000 persons living with HIV infection in the United States are unaware of their infection status. A broad range of studies has shown that, for some of these individuals, fear of receiving a positive test result remains a potent disincentive to seeking HIV testing.

Stigma as a barrier to prevention can lead to the silent spread of the stigmatized groups' conditions. A study in Zambia showed that HIV/AIDS-related stigma drives the epidemic underground and is one of the main reasons that people do not wish to know their HIV status.[7] Lack of knowledge due to stigmatization is another barrier to prevention measures. The "education vaccine" as the best available protection for many conditions including HIV is not always available.[8] The lack of education can make a person more vulnerable to disease. Studies of women as vulnerable groups indicate that nearly one in every two illiterate women does not know basic facts about HIV/AIDS, such as possible transmission methods, including sexual intercourse.[8] Their lack of minimum knowledge about AIDS is about five times higher than that for women with post-primary education. Among those with basic knowledge about the disease, illiterate women are three times more likely to think that a healthy-looking person cannot be HIV-positive. Their belief that there is no way to avoid AIDS is about four times higher compared with their educated counterparts. The proportion of women who do not know that HIV can be transmitted from mother to child is, on average, three times higher for uneducated women than for those with post-primary schooling.

Although stigmatized conditions disproportionately affect poor and illiterate people, social stigma does extend to countries and societies that are more developed. In the United States, social stigma against sexually transmitted infections has led to reluctance to seek treatment. For example, American teens often avoid seeking treatment for a perceived sexual illness due to the dishonor and embarrassment associated with such a visit to a doctor. Furthermore, there is apprehension that one's parents may discover knowledge of the

illness and, hence, of one's sexual behaviors. Another example of a social stigma leading to lack of treatment in an individual of higher socioeconomic status is the unwillingness of obese patients to make visits to the doctor. It has been reported that "patients may cancel physician appointments because of weight concerns, with cancellations increasing as weight increases."[9] Although stigma may most commonly affect the poor or illiterate, these instances clearly demonstrate cases where its effects extend to all individuals, regardless of class or economic barriers.

Stigma hurts not only individuals, but also entire communities. The fact that individuals with certain diseases are often ostracized from communities neither assists the community in preventing the spread of disease, nor eliminates the existence of certain conditions. The shift of an intolerant culture to a more accepting one is not impossible. The role of advocacy is vital for developing organizations and opportunities for people at risk and those living with them and ultimately building more tolerable cultures. Communities that are successful at reducing the spread of disease are those that work on public policy to eliminate discrimination. These communities can provide stigmatized individuals with adequate treatment and prevent silent spread of HIV by making education available to everyone regardless of gender or socioeconomic status. Challenges are omnipresent in the case of stigmatization. Strategic frameworks are necessary in order to eliminate stigma on the whole. These can include community participation; extensive research and data analysis of stigma; public education for children, youths, adults, and professionals; and law reforms. Many national and international policies are on their way to eliminate stigmatization and are not too far away from achieving their goals against these.

International cooperation to eliminate stigma and ensure better health care has extended to different areas of the world.[10] An important and successful example of such cooperation has been seen with the PolicyProject, established by the United States Agency for International Development (USAID). The project involves USAID working with government and private agencies to establish policies promoting greater understanding of stigma and greater access to health care for these populations. The newly created policies are then maintained within the existing system of the country, promoting a long term endorsement of social understanding as well as availability of treatment and prevention programs.[11] This project is one of the few ongoing developments of its kind. Although the expansion of such advancement is commendable, efforts towards policy change through both governments and non-governmental organizations need to be continued to win the fight against social stigma.

1. Cohen J. HIV/AIDS in India. Till death do us part. Science. 2004; 304(5670):513.
2. Goffman E. Stigma: Notes on the Management of a Spoiled Identity. New York, NY: Prentice-Hall, 1963.
3. Swidler A. Culture in action: Symbols and strategies. Am Sociol Rev. 1986; 58(April):273-286.
4. Heijnders ML. The dynamics of stigma in leprosy. Int J Lepr Other Mycobact Dis. 2004; 72(4):437-447.
5. Pyne JM, Kuc EJ, Schroeder PJ, Fortney JC, Edlund M, Sullivan G. Relationship between perceived stigma and depression severity. J Nerv Ment Dis. 2004; 192(4):278-283.
6. Liu H, Detels R, Li X, Ma E, Yin Y. Stigma, delayed treatment, and spousal notification among male patients with sexually transmitted disease in China. Sex Transm Dis. 2002; 29(6):335-343.
7. Bond V, Chase E, Aggleton P. Stigma, HIV/AIDS and prevention of mother-to-child transmission in Zambia. Eval Program Plann. 2002; 25(4):347-356.
8. Vandemoortele J, Delamonica E. The education vaccine against HIV. Current Issues in Comparative Education. 2002; 3(1):6-13.
9. The Beacon. Disease, Stigma, and the Reprecussions <http://www.babylonbeacon.com/News/2005/0204/Front_Page/040.html>. Accessed October 25, 2005. The Beacon, Babylon, New York, 2005.
10. USAID. U.S. Agency for International Development <http://www.usaid.gov/>. Accessed November 21, 2006. USAID, Washington D.C., 2006.
11. POLICY Project. POLICY Project <http://www.policyproject.com/index.cfm>. Accessed November 21, 2006. POLICY, Washington D.C., 2006.

PERSPECTIVE

Synthesis, Meta-analysis, Mathematical Modeling, and Global HIV Behavioral Prevention Policy

Behavioral preventions for HIV: evidence-based models that work

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What exactly is "evidence"? It is a term used frequently by scientists, policy makers, and political leaders in regards to health policy. The term "evidence" implies cold hard facts that give definitive answers to scientific questions – the answers which inform important health policy makers on the use of limited resources. However, in practice, evidence provided by scientific studies can be difficult to translate into metrics that are relevant to specific policy decisions, conflict across studies, or are overwhelming in the level of detail provided. This all can make translating science into effective health policy a difficult process. Perhaps worst of all, collecting evidence can also be used as a stalling tactic, allowing individuals to avoid taking action, or to simply ignore an issue on the basis of ideological grounds.

"...the literature on behavioral prevention science is composed of an overwhelming volume of studies ... many of which investigate the same research questions but yield conflicting results."

The global AIDS pandemic provides many examples of the challenges of translating scientific evidence into health policy. AIDS emerged as a global threat in the late 1980s and has since continued to grow at a dramatic pace. Laudably, many international donors have supported an enormous array of HIV behavioral prevention research studies over the years in an attempt to identify what works best in reducing risky behavior and what will hopefully slow the epidemic. Yet the literature on behavioral prevention science is composed of an overwhelming volume of studies in press, many of which investigate the same research questions but yield conflicting results. Compounding these challenges is a political environment where policies on which interventions have been supported have not been evidence-based – sometimes because the evidence has not been complied in a manner that is accessible and usable, and other times because the evidence has simply been ignored.

In an effort to try to organize and make sense of available evidence on the efficacy of HIV behavioral interventions in developing countries, our team in the Social and Behavioral Interventions Program has been working collaboratively with the World Health Organization on a project to conduct systematic reviews and meta-analysis on 16 major HIV behavioral intervention approaches. The project is funded by the US National Institute of Mental Health. We are also using data gleaned from the project to mathematically model the impact that behavioral interventions could have on AIDS epidemics, and using the results of these analyses to inform evidence-based policy decisions.

The project involves a series of careful steps taken to identify relevant and rigorous studies, and to extract data from the studies in a systematic manner. An overarching concept behind systematic review is to have written guidelines detailing how evaluations of scientific studies are made, and how various procedures are used to minimize bias in the interpretation of study results. For example, we search the literature and apply written rules to what constitutes a study that matches our inclusion criteria. Then two trained staff members independently extract key information from each study, and a third staff member compares the results and resolves differences in how the data were coded. This process is painstaking and tedious, but by extracting data systematically, we are able to harmonize the findings across studies into standard measures, allowing for comparisons to be made more efficiently. Moreover, we are then able to meta-analyze across studies. Meta-analysis is a statistical technique that combines results from different studies to see what the overall effect of an intervention is, and to identify how much variation there is across studies, population groups, and settings. This process whittles down the often overwhelming volume of research findings on the efficacy of an intervention into a concise and interpretable analysis that is much easier to understand.

One example of how we are now using the results from the study to inform rational policy-making on HIV prevention is our work on a recent initiative to establish a global standard of basic services, both medical and preventative, that HIV-infected persons in all countries should receive. The World Health Organization's Department of HIV/AIDS and the US Centers for Disease Control and Prevention cosponsored an international consensus meeting in Montreux, Switzerland in June of 2006 to review evidence on the efficacy of both biomedical and behavioral interventions for HIV-infected persons. Our project team from Hopkins was invited by the planning committee to prepare background materials and analysis for the conference addressing evidence of efficacy for behavioral

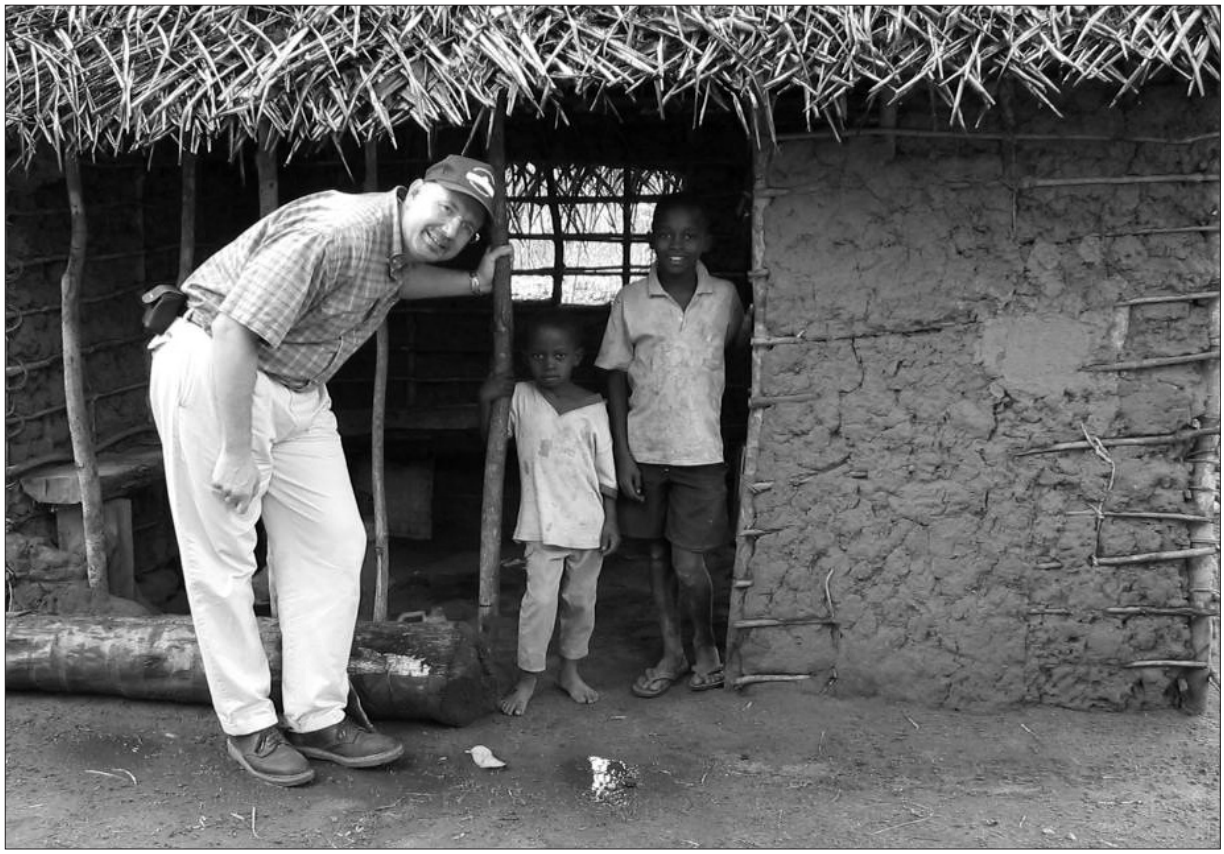
interventions, and a team from the University of California, San Francisco compiled summaries of evidence for the biomedical interventions.

Over 60 policy makers, scientists, donors, advocates, and representatives from communities affected by HIV came together from countries the over the world to attend the meeting. Sub-committees were established to review evidence for a wide range of biomedical and behavioral interventions, and a ranking was conducted to assign a score for the level of evidence supporting each intervention approach. This process involved reviews of summaries of evidence provided by Hopkins and UCSF, and iterations of discussion, voting, and ranking until a consensus was achieved.

"A synthesis and meta-analysis of abstinence-based interventions showed that there is actually weak evidence for their effectiveness in developing country settings."

In this meeting, several cases stood out in which the review of evidence led to recommendations that were at odds with current practices in many settings. For example, a synthesis and meta-analysis of abstinence-based interventions showed that there is actually weak evidence for their effectiveness in developing country settings. The few studies that have been implemented on the effectiveness of abstinence-based interventions were all conducted among in-school adolescents, and there were minimal effects on behavioral risk reduction. Likewise, a meta-analysis of needle exchange interventions for drug users in developing countries consistently showed the strong effects of reducing needle sharing across multiple settings, despite the fact that there has been virtually no policy or financial support for needle exchange programs for injecting drug users in many countries, including the United States.

The recommendations from the Montreux meeting are now being finalized by the WHO, with a final round of review and comments in process. Since the Montreux meeting, our team has also been awarded supplemental funds from the National Institute of Mental Health to conduct a special synthesis of behavioral interventions that have been targeted directly at HIV-infected populations. It has been very rewarding to see the results of our project directly contribute to the establishment of global health policy on topics that have been so hotly debated and often politicized without supporting data.



Dr. Michael Sweat with Tanzanian children. His research includes examining the efficacy of community-based HIV counseling and testing for HIV in Tanzania. Photo- Michael Sweat

A Closer Look at the Air We Breathe

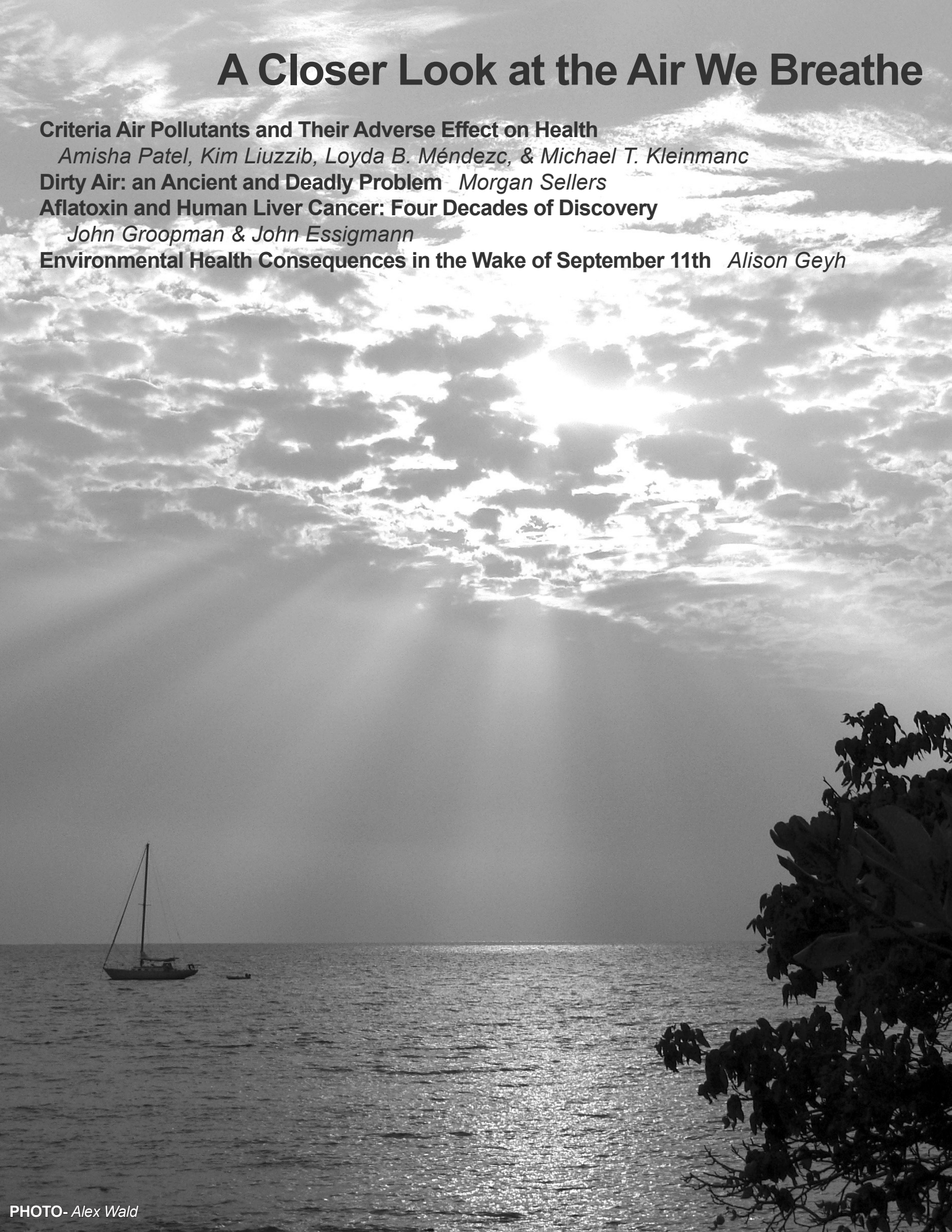


PHOTO- *Alex Wald*

Criteria Air Pollutants and Their Adverse Effect on Health

The role of endotoxin in macrophage responses to fine particulate matter

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Background: This study investigates the role of endotoxins in alveolar macrophage responses. Particulate matter has been shown to negatively affect the respiratory system. Endotoxins are found in conjunction with fine particulate matter. When inhaled, they may exacerbate conditions such as asthma.

Methods: Using various biological assays and quantitative measurements, this study determined the activity of particulate matter that was collected from a specific polluted site and calculated the effect of endotoxins on pro-inflammatory responses.

Results: This study showed that small amounts of endotoxins (0.67EU/mL) are responsible for the production of NO and pro-inflammatory cytokines by AM exposed to CAPS. Nevertheless, the generation of ROS was not associated with the presence of endotoxins.

Conclusions: The results demonstrated that endotoxins, a part of particulate matter, may aggravate chronic inflammatory diseases of the lungs.

Particulate matter (PM) such as asbestos, metals, combustion products, and dust is a "criteria air pollutant" that may have a harmful effect on the human respiratory system. In 1997, the US Environmental Protection Agency established new standards for particles of ≤2.5μm in diameter ($PM_{2.5}$) in response to epidemiological studies which revealed relationships between fine particulate matter ($PM_{2.5}$) exposure and adverse health effects. More important, these symptoms include the exacerbation of widespread chronic pulmonary diseases such as asthma.[1] However, the specific mechanisms by which fine PM causes adverse health effects remain unknown. The toxic effects of PM have been attributed to the different properties and compositions of the particles.[2, 3] Several studies recognize that biogenic compounds, including bacterial endotoxins, may contribute to the toxic effects of PM partly through their own toxicity and partly through a combination with other PM components.[4]

Endotoxins are found ubiquitously in the environment and are mainly associated with PM.[5-9] Evidence has shown that in occupational settings, the inhalation of organic dust containing endotoxin can cause respiratory distress symptoms such as airway inflammation, decreases in lung function, and hyperreactivity of the airways.[10] Furthermore, the presence of endotoxins in children's homes has been acknowledged as a factor in asthma exacerbation.[11] In-vitro studies with ambient coarse particles ($PM_{2.5-10}$) have identified endotoxins as important players in inflammatory responses to PM.[6, 12-14] However, the contribution of endotoxins in response to fine particles has only been studied on a superficial level and the ambient concentrations of endotoxins necessary to produce pulmonary responses are still not clear.[4]

Endotoxins, also known as lipopolysaccharides (LPS), is a part of the outer cell membrane of gram-negative bacteria. They act on cells of the respiratory system by binding to specific receptors that are mainly expressed on the surfaces of immune system cells. When these cells recognize endotoxins, they activate a signaling cascade that triggers the production of mediators which, in turn, induce an inflammatory response.[13]

Alveolar macrophages (AM) are key players in the orchestration of the innate immune response in the lungs. They are the first cell types in the airways to respond to inhaled particles. Upon particle uptake, activated AM release a myriad of mediators which include reactive oxygen species (ROS), reactive nitrogen species (RNS), pro-inflammatory cytokines such as interleukin 6 (IL-6) and tumor necrosis factor α (TNFα).[2] ROS, such as superoxide, hydrogen peroxide, and hydroxyl radicals, can directly damage lung epithelial cells upon binding to macromolecules (e.g., DNA, proteins, lipids).

The activation of macrophages is also characterized by the production of nitric oxide (NO) and pro-inflammatory cytokines. NO plays an important role in inflammatory responses and can react with ROS to form potent RNS. RNS is toxic to lung cells. IL-6 and TNFα stimulate the airway epithelium and induce the recruitment and activation of inflammatory cells.[2, 15] Thus, the activation of AM and the subsequent release of pro-inflammatory mediators may cause damage to the lung epithelium and contribute to the exacerbation of chronic lung inflammatory diseases.

The objective of this study is to assess AM responses to concentrated ambient particles (CAPS) and to evaluate the contribution of particle-bound endotoxin in the activation of AM.

METHODS

Materials: Unless otherwise noted, all chemicals were purchased from Sigma (St. Louis, MO).

Sampling site: Air samples were collected

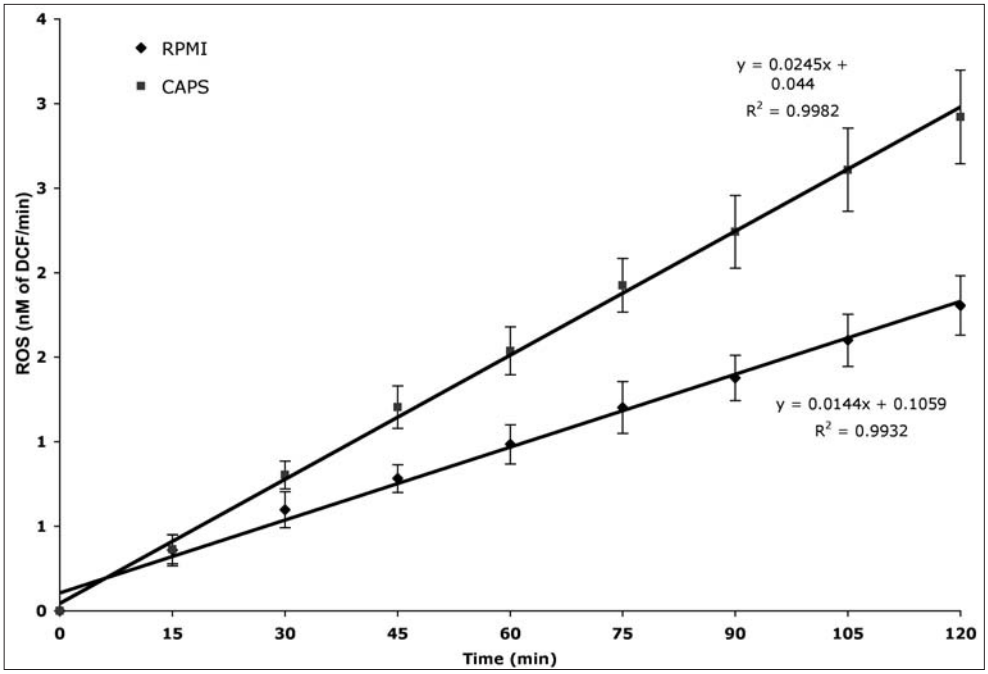

Figure 1. CAPS induce the generation of ROS in AM. AM were exposed for 2 hours to RPMI (diamonds) and CAPS (squares). The production of ROS was monitored every 15 min. Values represent the mean ± SE of 4 individual experiments.

Table 1. Rate of ROS fromation

Treatments	RPMI	CAPS
Control	0.014 ± 0.001	0.024 ± 0.002*
Polymixin B	0.014 ± 0.001	0.023 ± 0.001*
rENP	0.017 ± 0.000	0.024 ± 0.003*

*The rate of ROS formation is represented as nM of DCF/min. Both the medium (RPMI) and CAPS were treated with 10µg/mL of either polymixin B or rENP for 30 min prior to exposure. Values are expressed as the mean± SE (n=4).

at a fixed location in the agricultural station of the University of California, Riverside (UCR) located at the junction of Martin Luther King Boulevard and Canyon Crest Road in Riverside, CA. The site is adjacent to a Southern California Air Quality Management District facility. Samples were collected on August 18, 2006 for a period of 2 hours.

PM concentration and collection: Fine ambient particles were concentrated with a portable Versatile Aerosol Enrichment System (VACES) incorporated with a 2.5µm size-selective inlet.[16, 17] The VACES was installed inside a trailer located at the UCR agricultural station. Ambient air samples were drawn from the outside of the trailer, at a flow rate of 330 L/min, into the VACES via a duct made of aluminum in order to avoid particle losses due to electrostatic deposition. CAPS were collected in 10 mLs of endotoxin-free water (Cambrex, Walkersville, MD) with a swirling impinger (Biosampler; SKC, Eighty Four, PA) connected to the VACES at a flow rate of 5 L/min. The samples were stored at -20° C until they were needed for further analysis.

Endotoxin determination: Quantitative measurement of endotoxin present in the concentrated particles was determined with a kinetic chromogenic *Limulus* amebocyte lysate (LAL) assay (Pyrochrome; Associates of Cape Cod, Falmouth, MA) per the manufacturer's instructions. The detection limit for the assay was 0.005 Endotoxin Units/mL (EU/mL).

Cell preparation: Murine alveolar macrophages (MH-S; ATCC, Manassas, VA) were grown in RPMI-1640 medium supplemented with 10mM HEPES, 1 mM pyruvic acid, 4.5g/L of glucose, 1.5g/L of sodium bicarbonate, 0.05mM 2-mercaptoethanol and 10% Fetal Bovine Serum (Mediatech, Hermont, VA) which was prepared with endotoxin-free water. The serum contained less than 0.03ng/mL of endotoxin. Therefore, the concentration of endotoxin in the medium was less than 0.003ng/mL. The cells were maintained at 37°C in a humidified atmosphere of 5% CO_2.

Cell exposure: AM were seeded onto 96-well tissue culture plates (Costar, Corning, NY) at a density of 200,000 cells per well and incubated overnight. Attached cells were exposed for 4 hours to CAPS diluted in RPMI. Cell culture supernatants were collected 18 hours after stimulation and stored at -80°C until they were needed for further analysis. For endotoxin inhibition experiments, the particles were pre-incubated with 10µg/mL of either Polymixin B sulfate or recombinant Endotoxin Neutralizing Protein (rENP) (Association Cape Cod, Falmouth, MA) in a sonic water bath for 30 minutes prior to cell stimulation. Positive controls were exposed to 1µg/mL of LPS derived from *Eschericia coli*. Negative controls were exposed to media alone. For ROS experiments, cells were exposed for 2 hours to CAPS diluted in RPMI.

Cell viability: The viability of the cells was assessed with a Live/Dead viability/cytotoxicity kit from Molecular Probes (Eugene, OR). This assay simultaneously determines live and dead cells by measuring the fluorescence of two dyes. A final concentration of 1µM calcein and 2µM EthD-1 was used in the assay. Fluorescence was measured after 45 minutes of incubation using a FL600 microplate reader (Biotek). The fluorescence was measured at excitation/emission wavelengths of 485/530nm for live cells and at the wavelengths of 530/645nm for dead cells. The percentage of cell viability was calculated based on the intensity of fluorescence using standards of live and dead cells. Dead cell controls were killed by treatment with 0.1% saponin for 15 minutes.

Cytokine analysis: Levels of IL-6 and TNFα present in cell culture supernatants were quantified using a quantitative enzyme-linked immunosorbent assay (Quantikine, R&D Systems, Minneapolis, NY) according to the manufacturer's instructions. The absorbance was determined using a microplate reader set to a 450nm wavelength. The detection limit for the assay was 7.8pg/mL.

Nitric oxide (NO) production: NO production was assessed by measuring nitrite in cell culture supernatants. Nitrite concentrations were determined using the Griess reagent system (Promega, Madison, WI) per the manufacturer's instructions. The absorbance was measured at 520nm with a microplate reader. A standard curve (1.56 – 50µM) was prepared with sodium nitrite.

Reactive oxygen species (ROS) formation: ROS formation was determined using the

non-fluorescent dye 2,7 dichlorofluorescein diacetate (DCFH-DA, Molecular Probe, Eugene, OR). Upon formation of ROS, DCFH-DA is oxidized to its fluorescent form, 2,7 dichlorofluorescein (DCF). 20 µL of a 50µM DCFH-DA stock was added to each well prior to the addition of CAPS for a final concentration of 5µM DCFH-DA. A standard curve was prepared with DCF (2.5-50nM) to calculate the fluorescence formation. The rate of ROS formation was monitored for 2 hours by measuring fluorescence ($485_{ex}/530_{em}$) every 15 minutes using the FL600 microplate reader.

Statistical analysis: To assess differences between non-exposed and exposed groups, paired student's t-tests were performed. A one-way ANOVA followed by a Tukey test was performed for the endotoxin inhibition experiments. A p-value of less than or equal to 0.05 was considered significant and is represented in the figures and tables by an asterisk (*). Values are expressed as the mean ± standard error.

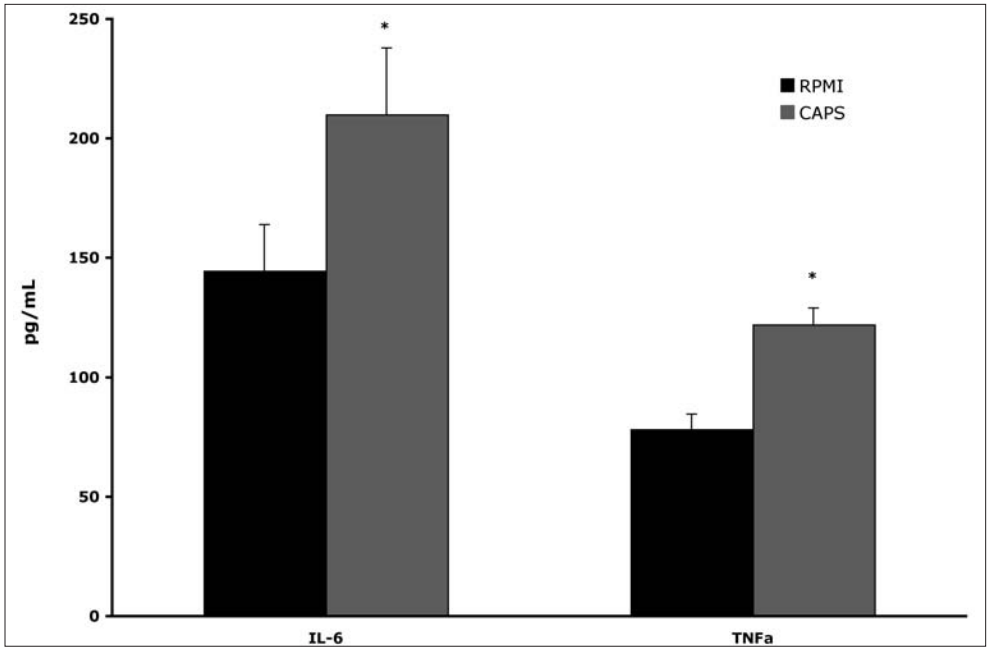

Figure 2. Cytokine induction by CAPS. AM were exposed with either medium (RPMI) or CAPS for 4 hours. IL-6 and TNFα levels in supernatants were determined 18 hours after stimulation. Values are expressed as the mean± SE (n=3).

RESULTS

The concentration of endotoxin present in CAPS was 2EU/mL. A pilot dose-response experiment revealed that the particles had a slight cytotoxic effect and that the CAPS dilution 1:2, which corresponds to approximately 1EU/mL, was optimal for the stimulation of ROS formation and IL-6 production. Similarly, a 1:3 dilution, which corresponds to about 0.67EU/mL, was found to be optimal for the induction of TNFα and NO. Therefore, the experiments were performed with either a 1:2 or a 1:3 CAPS dilution, depending on the endpoint to be measured.

To assess oxidative responses to CAPS by murine AM, the formation of ROS and the production of NO were measured. The generation of ROS was assessed indirectly through the oxidation of DCFH-DA to DCF, a fluorescent substrate. The emission of fluorescence was monitored for 2 hours during CAPS exposure. Addition of CAPS (1:2 dilution) resulted in an increase of free radical generation (Figure 1). The production of NO was measured for 18 hours after stimulation with CAPS. The concentration of nitrite, which is a product of NO breakdown, was significantly higher in AM exposed to CAPS (1:3 dilution).

To evaluate the generation of pro-inflammatory cytokines by AM, IL-6 and TNFα were measured in cell culture supernatants. The production of IL-6 and TNFα by AM was determined 18 hours after stimulation with CAPS. The levels of both cytokines were significantly higher in exposed AM (Figure 2). In summary, exposure to CAPS caused approximately a 15% increase in AM oxidative and inflammatory responses.

To demonstrate the involvement of endotoxin in oxidative and inflammatory responses to CAPS, the particles were treated with the endotoxin inhibitors, polymixin B, and rENP. Endotoxins were found to have no effect on ROS generation by AM (Table 1). However, the production of NO and TNFα was reduced to baseline levels when the particles were treated with both endotoxin inhibitors. IL-6 levels were significantly reduced when both the medium and CAPS were treated with polymixin B and rENP (data not shown), indicating that the media used for those experiments were contaminated with endotoxin.

DISCUSSION

The goal of this study was to screen the biological activities of fine particles collected from a highly polluted area and to evaluate the effect of endotoxin on the observed responses in an in-vitro system. Epidemiological data suggest that fine ambient particles may be more important than coarse particles in PM-associated adverse respiratory health effects. However, the specific mechanisms involved in PM toxicity are relatively unknown.[1, 15]

AM are targets of inhaled particles and key players in the initiation of the innate immune responses in the lungs. Therefore, it is particularly important to study the behavior of AM exposed to ambient PM. Since endotoxin is mainly associated with coarse particle fraction ($PM_{2.5-10}$), only a few studies have looked at the involvement of endotoxin in macrophage activation by fine particulate.[3, 15, 18] In addition, most studies do not report the concentrations of endotoxins in particles, thus making it difficult to interpret the concentration at which endotoxins begin to exert a toxic effect. The present study demonstrates that even small amounts of endotoxins (0.67EU/mL) are responsible for the production of NO and pro-inflammatory cytokines by AM exposed to CAPS. However, the generation of ROS was not associated with the presence of endotoxins. Several studies have attributed the generation of ROS to other components (e.g. organics and metals) of $PM_{2.5}$.[2, 15, 19] Thus, it appears that the pro-inflammatory and oxidant responses are driven by different components of PM. It is possible that endotoxins play a role in the cytokine-driven respiratory burst of AM, which releases ROS.[20]

Taken together, the data from the present study demonstrate that exposure to CAPS causes an increase in AM oxidative and pro-inflammatory responses, and that endotoxin might be one of the $PM_{2.5}$ components that contribute to the exacerbation of chronic inflammatory diseases of the lungs.

1. National Research Council. Immediate Priorities and a Long-Range Research Portfolio. Vol. 1 ed. Washington D.C.: National Academy Press, 1998.
2. Kleinman MT, Sioutas C, Chang MC, Boere AJ, Cassee FR. Ambient fine and coarse particle suppression of alveolar macrophage functions. Toxicol Lett. 2003; 137(3):151-158.
3. Becker S, Soukup JM, Sioutas C, Cassee FR. Response of human alveolar macrophages to ultrafine, fine, and coarse urban air pollution particles. Exp Lung Res. 2003; 29(1):29-44.
4. United States Environmental Protection Agency. Provisional Assessment of Recent Studies on Health Effects of Particulate Matter Exposure. Research Triangle Park, NC: United States Environmental Protection Agency, 2006.
5. Olenchock SA. Airborne Endotoxin. In: Hurst CJ, Knudsen GR, McInerney MJ, Stezenbach LD, Walters MV (eds). Manual of Environmental Microbiology. Washington D.C.: ASM Press, 1997:661-665.
6. Soukup JM, Becker S. Human alveolar macrophage responses to air pollution particulates are associated with insoluble components of coarse material, including particulate endotoxin. Toxicol Appl Pharmacol. 2001; 171(1):20-26.
7. Carty CL, Gehring U, Cyrys J, Bischof W, Heinrich J. Seasonal variability of endotoxin in ambient fine particulate matter. J Environ Monit. 2003; 5(6):953-958.
8. Heinrich J, Bischof W, Krug N, Borm P. Endotoxin in fine (PM2.5) and coarse (PM2.5-10) particle mass of ambient aerosols: A temporo-spatial analysis. Atmospherical Environment. 2003; (37):3659-3667.
9. Mueller-Anneling L, Avol E, Peters JM, Thorne PS. Ambient endotoxin concentrations in PM10 from southern california. Environ Health Perspect. 2004; 112(5):583-588.
10. Schwartz DA, Thorne PS, Yagla SJ, Burmeister LF, Olenchock SA, Watt JL, Quinn TJ. The role of endotoxin in grain dust-induced lung disease. Am J Respir Crit Care Med. 1995; 152(2):603-608.
11. Michel O, Kips J, Duchateau J, Vertongen F, Robert L, Collet H, Pauwels R, Sergysels R. Severity of asthma is related to endotoxin in house dust. Am J Respir Crit Care Med. 1996; 154(6 Pt 1):1641-1646.
12. Alexis NE, Lay JC, Zeman K, Bennett WE, Peden DB, Soukup JM, Devlin RB, Becker S. Biological material on inhaled coarse fraction particulate matter activates airway phagocytes in vivo in healthy volunteers. J Allergy Clin Immunol. 2006; 117(6):1396-1403.
13. Becker S, Fenton MJ, Soukup JM. Involvement of microbial components and toll-like receptors 2 and 4 in cytokine responses to air pollution particles. Am J Respir Cell Mol Biol. 2002; 27(5):611-618.
14. Becker S, Mundandhara S, Devlin RB, Madden M. Regulation of cytokine production in human alveolar macrophages and airway epithelial cells in response to ambient air pollution particles: Further mechanistic studies. Toxicol Appl Pharmacol. 2005; 207(2 Suppl):269-275.
15. Hetland RB, Cassee FR, Lag M, Refsnes M, Dybing E, Schwarze PE. Cytokine release from alveolar macrophages exposed to ambient particulate matter: Heterogeneity in relation to size, city and season. Part Fibre Toxicol. 2005; 2:4.
16. Kim S, Jaques PA, Chang M, Froines JR, Sioutas C. Versatile aerosol concentration enrichment system (VACES) for simultaneous in vivo and in vitro evaluation of toxic effects of ultrafine, fine and coarse ambient particles part I: Development and laboratory characterization. Journal of Aerosol Science. 2001/11; 32(11):1281-1297.
17. Kim S, Jaques PA, Chang M, Barone T, Xiong C, Friedlander SK, Sioutas C. Versatile aerosol concentration enrichment system (VACES) for simultaneous in vivo and in vitro evaluation of toxic effects of ultrafine, fine and coarse ambient particles part II: Field evaluation. Journal of Aerosol Science. 2001/11; 32(11):1299-1314.
18. Long CM, Suh HH, Kobzik L, Catalano PJ, Ning YY, Koutrakis P. A pilot investigation of the relative toxicity of indoor and outdoor fine particles: In vitro effects of endotoxin and other particulate properties. Environ Health Perspect. 2001; 109(10):1019-1026.
19. Zelikoff JT, Schermerhorn KR, Fang K, Cohen MD, Schlesinger RB. A role for associated transition metals in the immunotoxicity of inhaled ambient particulate matter. Environ Health Perspect. 2002; 110 Suppl 5:871-875.
20. William N. Rom, M.D., M.P.H. Environmental and occupational lung diseases; Molecular mechanisms of lung cancer; Tuberculosis (TB)/AIDS; Interferon-gamma therapy for TB, and TB vaccine and immune response; Environmental policy, wilderness preservation, and global warming <http://www.med.nyu.edu/environmental/faculty/RomW-med-res.html>. Accessed 11-17-06. Nelson Institute of Environmental Medicine, New York City, 1999.

EDITORIAL

Dirty Air: An Ancient and Deadly Problem

The politics and science of regulating particulate matter

Morgan Sellers, Post-Baccalaureate

Before the hole in the ozone layer. Before global warming. Even before the Industrial Revolution.

The health risks associated with particulate matter – small bits of material floating in the air generally caused by the combustion of solid carbon fuels – have existed since the discovery of fire. The particles, which are categorized as "coarse" particles (between 2.5 and 10 microns in diameter) and "fine" particles (less than 2.5 particles in diameter) in the 1990s, have been recognized as harmful to human health since the 1200s, when King Edward I of England unsuccessfully tried to ban the burning of sea coal. However, with no cheap alternative fuel available and coal rising in importance due to the industrialization of Europe, smoke-saturated "pea-soup" fog became trademark of London from the early 1800s through the 1950s. Finally, in 1956, four years after a days-long fog killed more than 4,000 people in the city due to heart-and-lung associated problems, Parliament passed the Clean Air Act, the first national legislation dealing with air pollution anywhere in the world.[1] In the United States, federal regulation started with the Clean Air Act of 1963, which was significantly rewritten as a much more stringent and ambitious set of regulations in 1970.[2]

Despite this long history, the actual biological mechanisms by which particulate matter (PM) affects human health are still being determined. Not until 1993 was the first long term study relating air quality to human health released, with the shocking news that up to 60,000 deaths in the United States were caused each year by fine particles, for the most part at levels well below the federal regulations at the time.[3] The composition of PM and the mechanism by which it endangers human health are still relatively unstudied.

As with most environmental issues, the regulation of PM has progressed slowly due to both scientific and political stumbling blocks. Under the United States' Clean Air Act of 1970, the US Environmental Protection Agency (EPA) is required to review air quality standards every five years. In fact, the standards have been updated on average once a decade (1987, 1996, and 2006), consequently, with the allowable limits for PM being decreased with each revision. In 1996, after extensive scientific research indicated that the major health problems

in the United States are predominantly caused by particles less than 2.5 microns in diameter (as opposed to any particles smaller than 10 microns in diameter), the EPA established separate standards for the two groups (designated as PM2.5 and PM10.) In September 2006, the newest revisions were published,[4] lowering the 24-hour maximum levels of PM2.5 to 35 μg/m^3 from the previous limit of 65 μg/m^3, set in 1996. However, the EPA left the annual average limit for PM2.5 unchanged at 15 μg/m^3, and left the daily maximum for PM10 also unchanged at 150 μg/m^3. It also entirely revoked the annual average limit for PM10.

The announcement immediately provoked attacks from health and environmental advocates on one side, and industry representatives on the other. Health and environmental organizations criticized Stephen Johnson, the administrator of the EPA, for ignoring the majority recommendation of the agency's Clean Air Scientific Advisory Council to lower the 24 hour PM2.5 limit to 13 or 14 μg/m^3, a modification that the agency estimated would result in an additional 24,000 lives saved each year. Both the American Medical Association and the American Lung Association had filed letters in support of the lower standard. Meanwhile, representatives from the electricity industry said the scientific evidence was inconclusive and called the costs of meeting the new annual limit on PM2.5 unjustified.[5] The EPA's estimated cost of meeting a 14 μg/m^3 limit compared with the 15 μg/m^3 limit was about $1.9 billion more per year, while the savings in areas such as healthcare costs and productivity was estimated to be between $4.3 billion and $51 billion per year.

How low are the limits? Based on published monitoring data from 2003-2005, 143 counties nationwide would fail to meet the revised limits, including 126 counties that exceed the 24-hour standard first introduced in 1996. Most of these counties are in southern California and the eastern corridor between Washington, DC and New York, with some scattered throughout the Midwest, South, and Pacific Northwest. The EPA predicts that approximately 48 of these counties will still be exceeding the limits by 2010.[6]

In comparison, the World Bank's modeled air pollution data for 1999 lists 20 countries with PM10 averages above 100 μg/m^3, and another 55 countries with averages between 50 and 100; 10 countries have averages less than 20. The United States is listed with an average of 25 μg/m^3, ranking 31st on the list.[7]

As is true with numerous environmental issues, problems with air pollution go hand-in-hand with traditional economic development and industrialization. In most of the countries that participated in the Industrial Revolution in the 19th century, air quality has actually improved in the past 50 years as regulations have strengthened. Now, the largest challenges are in developing nations where there is little regulation and often little or no monitoring. The World Health Organization (WHO) estimates that more than 2 million premature deaths each year can be attributed to air pollution, with more than half of these occurring in the developing world. In 2006, the WHO published global recommendations for particulate matter for the first time, with limits for PM10 set at an annual mean of 20 μg/m^3 and a 24-hour mean of 50 μg/m^3. Annual limits for PM2.5 were set at 10 μg/m^3 and 25 μg/m^3, respectively.[8]

These recommended limits are lower than average PM concentrations in all but a few countries, making it clear that the greatest risks to human health are occurring in developing nations that often lack the technological capabilities or political will to address this ancient yet deadly form of pollution. Thus, more attention is needed on the political and logistical challenges of regulating a clear and immediate danger in areas still struggling to catch up economically with the developed world.

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1. Browne A. London's air cleanest since 1585 <http://education.guardian.co.uk/higher/physicalscience/story/0,,505158,00.html>. Accessed November 2, 2006. The Observer, London, 2001.

2. U.S. Environmental Protection Agency. Basic Concepts in Environmental Sciences <http://www.epa.gov/eogapti1/module7/caa/caa.htm>. Accessed November 22, 2006. U.S. Environmental Protection Agency, Washington D.C., 2006.

3. Hilts PJ. Studies say soot kills up to 60,000 in U.S. each year <http://query.nytimes.com/gst/fullpage.html?sec=health&res=9F0CE2DC1F3BF93AA25754C0A965958260>. Accessed November 7, 2006. New York Times, New York, NY, 1993.

4. US EPA. PM Standards Revision - 2006 <http://epa.gov/pm/naaqsrev2006.html>. Accessed November 2, 2006. US EPA, Washington, DC, 2006.

5. Eilperin J. EPA cuts soot level allowable daily in air <http://www.washingtonpost.com/wp-dyn/content/article/2006/09/21/AR2006092101616.html>. Accessed November 7, 2006. The Washington Post Company, Washington, DC, 2006.

6. US EPA. Graphs and Maps. PM 2006 Standards <http://epa.gov/pm/pdfs/20061025_graphsmaps.pdf>. Accessed November 2, 2006. US EPA, Washington, DC, 2006.

7. Pandey KD, Wheeler D, Ostro B, Deichmann U, Hamilton K, Bolt K. *Ambient Particulate Matter Concentrations in Residential and Pollution Hotspot areas of World Cities: New Estimates based on the Global Model of Ambient Particulates (GMAPS).* Washington, DC: The World Bank, 2006.

8. The World Health Organization. WHO Air quality guidelines for particulate matter, ozone, nitrogen dioxide and sulfur dioxide, Global update 2005, Summary of risk assessment <http://www.who.int/entity/phe/air/aqg2006execsum.pdf>. Accessed November 2, 2006. WHO Press, Geneva, Switzerland, 2005.

Aflatoxin and Human Liver Cancer: Four Decades of Discovery

Public health repercussions of contaminated food

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In 1960 a ship named "Rossetti" delivered tons of a ground nut meal commonly called "peanut press cake" from Brazil to a port in the United Kingdom. Months later, between 100,000 and 200,000 turkeys had perished from acute hepatic poisoning. Thus began the 40-year saga that has identified and characterized one of the world's most interesting and important human toxins.

The toxicosis of 47 years ago in the British turkey poults was troubling for its obvious and huge economic impact on agriculture. In addition, the high protein content of peanut meal made it a practical and inexpensive human food, and it was fortunate that the Rossetti meal, as it later became known, had not found its way into the human food supply. A clue to the nature of the toxic substance was the presence of abundant fungal filaments in the meal (Figure 1). When the filaments or spores from the meal were grown on fresh microbiological media, the potent hepatotoxic properties of the contaminated meal were reproduced. Moreover, feeding Rossetti meal, or the toxin produced metabolically by the fungus, to ducks and rats revealed that short-and-long term exposure to the toxin resulted in the efficient induction of toxicity and liver cancer.

The fungus from Rossetti meal that produced the toxin was identified as Aspergillus flavus; the first four letters of the word "aflatoxin" link the chemical toxin with its biological parent. From extracts of mold cultures, supplemented by a quantity of extract provided by the US FDA laboratories, a small amount of a blue fluorescent compound, named aflatoxin B1 (B for its blue fluorescence under ultraviolet light and 1 for its chromatographic properties on TLC plates) was isolated. The compound was identified in 1963 as the molecule shown in Figure 2. The elucidation of the structure of this chemical is still considered a milestone in chemistry, as is the later chemical synthesis of the toxin, which established unequivocally that aflatoxin was indeed the chemical culprit responsible for the Rossetti poisonings. Knowledge of the structure of aflatoxin revealed its molecular weight and, with the availability of homogeneous natural or synthetic material, it was possible to quantitatively characterize just how potent the toxin is. The results were staggering— in most species it was, at the time, the most potent frequently occurring natural liver toxin and it was found to cause cancer with equal facility in many animal species at levels of parts per billion (concentrations that are easily achieved in the diets of people in many areas of the economically developing world.) Liver disease represents a major human public health problem in sub-Saharan Africa and all of Asia, where over 600,000 individuals die each year of hepatocellular carcinoma.

The availability of analytical procedures for quantitative analysis of the toxin made it possible to turn attention to the plausible link between the presence of the toxin in food and prevalence of human liver cancer, and acute hepatotoxicity. To conduct these studies, international health partnerships were necessary. The first such partnership was with the Kingdom of Thailand in the mid-1960s with the establishment of the "MIT-Thai Project," an epidemiological study supported by the US Agency for International Development and by the Rockefeller Foundation, to determine whether associations exist between the level of ingested aflatoxin and cancer registry data on local liver cancer incidence in human beings. The MIT-Thai Project started in 1967 and continued for about five years, establishing the definitive epidemiological link between aflatoxin with hepatocellular carcinoma. Other studies in Africa and in other parts of the world further strengthened the association. Indeed, aflatoxin was among the very first compounds explored in Volume 1 of the International Agency for Research on Cancer (IARC) monographs. In 1974, it was listed as a group 2A probable human carcinogen. Another 22 years would pass before it was reclassified as a Group 1 known human carcinogen.

Figure 1. Rossetti meal - this shows the ground nut meal from the ship, "Rossetti" labeled as "British Cake and Oil Mills, Ltd." of London, England. This is a sample of the meal that was toxic due to its contamination with aflatoxin. Photo Courtesy of Dr. John Groopman.

During the 1970s and 1980s, detailed studies of

the mechanism of action of aflatoxin were conducted. It was suspected that the binding of the toxin to DNA could result in the formation of DNA adducts that could force replication errors, or mutations. One, or more likely, a series of such genetic changes ultimately could result in the conversion of normal liver cells into cancer cells, which would then outgrow into a tumor. The challenge stemmed from the need to identify infinitesimal amounts of the putative aflatoxin-DNA adducts. The project pushed the analytical technology of the day to its limits; yet, in the final analysis, the structures of the DNA adducts were revealed. The work on these DNA adducts was translated to human epidemiologic studies and over a 15 year period there was a rapid translation of the analytical strategies to cohort studies in China. This work established that aflatoxin synergized with hepatitis B virus infection, and possibly other infectious agents, as co-risk factors for liver cancer. In the early 1990s it further became evident that the magnitude of this synergy is very large. Relative risks of liver cancer are elevated by 60-to-100 fold in hepatitis B carriers who are exposed to aflatoxin. The mechanistic basis of this powerful toxicological synergy remains a mystery. However, the knowledge of these DNA adducts has become an important biomarker for use in prevention trials in high-risk populations in Asia and Africa. A number of synthetic and natural compounds have been found that block aflatoxin cancer-causing properties in experimental models, and these agents have been used to demonstrate that aflatoxin-induced DNA damage in people can also be reduced. Thus, the next decade portends major opportunities to reduce the burden of this carcinogen in high-risk people who live in economically disadvantaged regions where there are few resources for contaminate reduction.

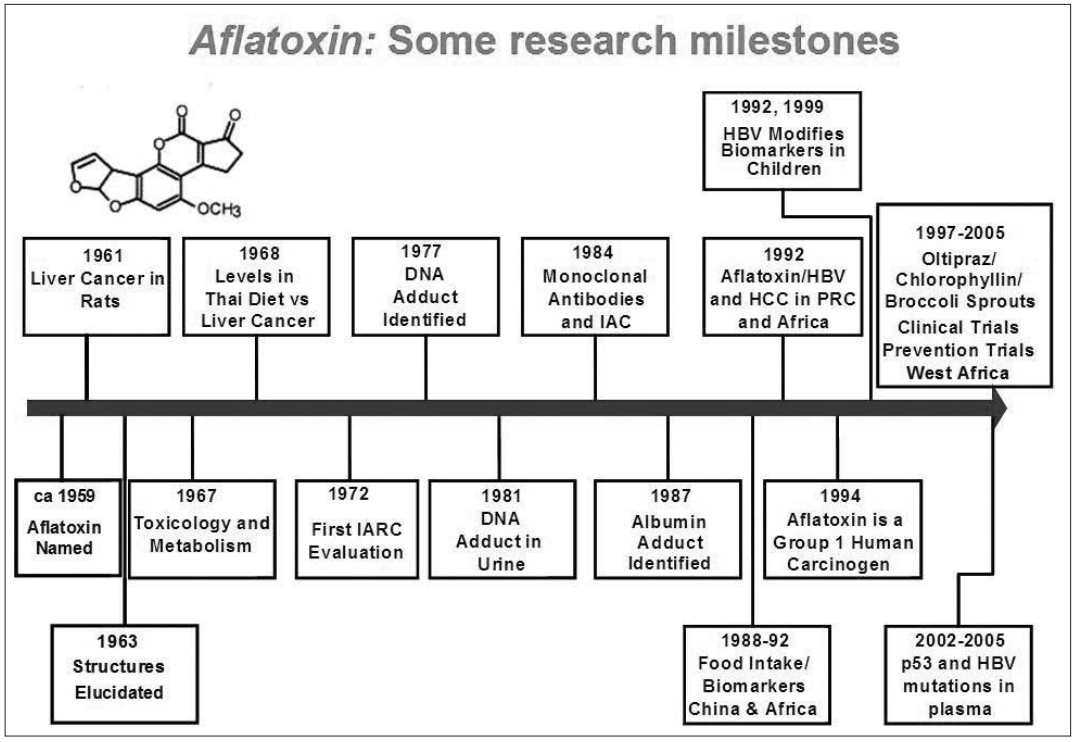

Figure 2. The structure of aflatoxin B1, the most biologically potent of the aflatoxin family of mycotoxins, is shown to the upper left. This figure summarizes milestones during the nearly 50-year history of research on aflatoxin. Courtesy of Dr. John Groopman.

Environmental Health Consequences in the Wake of September 11th

The collapse of the World Trade Center – an environmental disaster

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The September 11th, 2001 attack on the World Trade Center (WTC) was immediately identifiable as a national tragedy with psychological, political, and economic impacts that were far-reaching and are still unfolding.

It was also a major environmental disaster. The particles and gases generated from the crush of buildings and burning debris resulted in a complex mixture, raising the potential for an unprecedented human exposure that could lead to serious adverse health effects. The popular press has recently reported that some people exposed to

the dust and debris are now suffering debilitating respiratory problems that they feel have resulted from their exposure. In addition, the cause of death for at least two people who worked hundreds of hours at the disaster site has been connected to the exposure to contaminants from the WTC. A recently released report summarizing information obtained through the "World Trade Center Worker and Volunteer Medical Screen Program," conducted by the Mount Sinai Medical School, indicates that a significant proportion of the people who took advantage of the program were having health problems one to three years after working at the disaster site. Still, more than five years later, we do not have a good understanding of the risk to health from being exposed to WTC contaminants.

During the first days after the attacks, hundreds, if not thousands, of people came to the disaster site to help with rescue and recovery. The clean-up effort formally began about three weeks later, bringing more people in direct contact with the rubble and crushed debris. With the return to lower Manhattan of office workers to their jobs and residents to their apartments, the number of people potentially exposed to contaminants from the WTC grew.

What were they exposed to? When the buildings were destroyed, they included materials found in any modern city. The material inventory that contributed to the complex debris matrix likely included concrete, metals, asbestos, plastics, foams, fuels, solvents, electronic devices, insulating materials, glass, and more. The fires, which were ignited from the burning jet fuel and the compaction energy from the collapsing buildings, had the potential for producing dangerous gases and volatile organic compounds. In addition, there was the presence of human remains. Together, this extraordinarily complex mixture of materials and the number of people potentially exposed raised very large concerns about health effects, presenting a challenge that the environmental health community struggled to meet.

To understand the environmental health consequences of the WTC event, a comprehensive application of environmental, occupational, and disaster epidemiological methods was needed. Environmental (and occupational) epidemiology identifies and measures the influence of factors—physical, chemical, and biological—on human illness and injury in a community or in the workplace. A disaster can be thought of as a special circumstance of an extreme environmental event, where the disaster may result in environmental exposures that cause excess morbidity and mortality. Under the conditions of a disaster the opportunity for extensive planning does not exist.

The unprecedented nature of this event resulted in a response that was in many cases largely uncoordinated and often chaotic, including the response of the environmental health community. Several groups from federal, state and local government agencies, private organizations, and universities sent environmental scientists to the site. There was no coordination among these efforts. Over the course of the clean up and recovery effort, which ran until June 2002, thousands of measurements were made in, and around the disaster site. There was a special emphasis on some contaminants such as asbestos, but less focus on contaminants that should have been of equal concern. For example, only limited monitoring was conducted for airborne particle concentrations directly within the debris pile and at the perimeter. The community monitoring that was done has turned out to be very uninformative about particle concentrations immediately on site. Complete information regarding the contents of the particle mixture is available only for the dust that was found on the ground, but not the dust that was airborne. Other airborne contaminants such as dioxins were detected on the site, but sampling was limited. Health studies that have been implemented throughout the last five years are finding the data set of environmental contaminant measurements to be of limited value for understanding health effects that may have resulted from exposure. Because the majority of the environmental monitoring was done without considering how the data would be used in the context of answering concerns about health, the question "was exposure to the dust and debris from the WTC disaster site harmful to health, and if so, how?" is turning out to be alarmingly difficult to answer. Because we do not have a good understanding of how people may have been harmed, we cannot give them advice on how to seek care and what the appropriate care might be. We cannot give them advice on how to explain their condition to their doctors, insurance companies, and employers.

"Because we do not have a good understanding of how people may have been harmed, we cannot give them advice on how to seek care and what the appropriate care might be."

This disaster was a shock to the nation and the response that was launched was impressive in its magnitude and passion. There are many good reasons why the response by the environmental health community was incomplete. Lack of time to plan, limited financial resources and equipment, and difficulty in identifying personnel with the right expertise and the time to commit to the disaster response resulted in gaps in our knowledge which is impacting our ability to understand and explain how health was damaged as a result of exposure to WTC contaminants.

It is likely to be true that in any disaster, whether man-made or natural, people responding will be put at risk for injury to their health. Our governmental representatives need to make a commitment now to ensure that the right people are in place immediately with appropriate resources and high-level support to carry out the environmental health work that must be done alongside the rescue, recovery, and clean-up effort.

Two women walking past homes in Dar es Salaam, Tanzania. Photo- Alex Wald

FEATURES

Health Locus of Control and the Promotion of Breast Cancer Screening Practices

Lindsay Brown, Public Health Studies 2008

When I was given the opportunity to spend the summer working on a breast cancer research project in Sweden, I quickly realized that I knew more about breast cancer than I did about Sweden. I hate to admit this but I had to check on a map to see which of the three "fingers" of Scandinavia Sweden comprises. Wanting to remedy this unfortunate gap in knowledge, I spent several days in the library reading whatever I could find about the country sandwiched between Norway and Finland in the heart of Scandinavia. As little as I knew about Sweden, I knew even less about the Swedish healthcare system—all I had was a vague idea that healthcare is available to all citizens at a very low cost.

Over the course of the summer, I was able to spend a great deal of time in Swedish hospitals, research institutions, and, of course, talking with Swedes themselves, including many healthcare workers, researchers, and students. Through this interaction, I discovered that the Swedes are incredibly proud of their country and their healthcare system, a system which is successfully tackling many of the same problems that face America today. This resonated particularly with the research project I was involved with—an undertaking designed by two Swedish researchers to better understand the experience a woman goes through during the first 12 months diagnosis with breast cancer. Within the larger scope of the study, the two researchers, Dr. Marianne Gustafsson and Dr. Ulla Svantesson, have launched an initiative to gain insight regarding what factors may hinder a woman from taking advantage of breast cancer screening—currently the only widely available weapon against the disease.

Of all places, how did I end up in Sweden? I was chosen as the undergraduate fellow from Hopkins to participate in the 2006 Minority Global Health Disparities Research Program (MHIRT), run by Dr. Fannie Gaston-Johansson of Johns Hopkins University and funded by the National Institutes of Health. The MHIRT program provides the opportunity for one undergraduate from Hopkins, several Hopkins graduate or medical students, two undergraduates from Brown University, and two students from schools in North Carolina to spend the summer working under the mentorship of an internationally recognized researcher at one of five sites. The MHIRT program provides a variety of projects in several countries, including "The Biology of Stress" in Australia, "HIV/AIDS and Adolescent Health" in South Africa, "Violence Against Women and Women's Health" in South Africa, and "Cardiovascular Health Promotion" in South Korea. Once accepted to the program, students are placed at one of the five sites based on previous research experience and interest. Having experienced the loss of both my own mother and aunt to breast cancer, I have always had a strong interest in breast cancer prevention and research. Considering this interest, work on Drs. Gustafsson and Svantesson's project at Shalgrenska Academy in Sweden was an extremely rewarding endeavour.

According to the WHO, cancer is the highest cause of mortality in Sweden, accounting for 26% of deaths and 15-16% of the disease burden represented as DALYs. Photo- Lindsay Brown

Swedish healthcare strives to keep citizens in good health through the institution of a clear, comprehensive, and admirable strategy that focuses on disease prevention through both research and public advocacy. The initiative I was involved with was one of many going on within the academic circles of Gothenburg alone. In addition, public advocacy campaigns are instituted on a scale simply not seen in the United States. For example, over the course of the summer, I notices that every single television channel ran an advertisement promoting breast cancer screening practices—*every single commercial break.*

According to the American Cancer Society, there are over 2 million women living in the United States who have been treated for breast cancer, and a woman's chance of getting invasive breast cancer over the course of her life is roughly 1 in 8.[1] The World Health Organization projects that over 1.2 million women will be diagnosed with breast cancer this year, the majority of whom reside in the developed world.[2] While not a single method of preventing breast cancer is known, the earlier cancer is detected, the easier it

Gothenburg is home to Sahlgrenska Universitetssjukhuset, a university hospital system formed in 1997 by integrating the three hospitals Sahlgrenska Sjukhuset, Östra Sjukhuset and Mölndals Sjukhus. With 1,500 researchers, 4,000 students, and 17,000 staff members the hospital is now the largest hospital in Northern Europe. Photo- Lindsay Brown

may be to treat—reducing the overall morbidity and mortality of the disease.[3]

Since mammography, breast self-examinations (BSE), and clinician breast examinations (CBE) are currently the only widely available weapons against breast cancer, it is undeniably important that the scientific community gains as much knowledge as possible about obstacles women face in undergoing any of these three screening procedures.[4] Despite the fact that routine mammography has been shown to reduce mortality, the use of mammography screening continues to remain well below national goals in both Sweden and the United States. In addition, results have indicated that as many as 67% of American women fail to follow the American Cancer Society recommendations and do not report practicing monthly BSE.[5] Evidence suggests that even the campaigns designed to promote these practices have only been partially successful,[6] adding urgency to the need to find a successful method to promote breast cancer screening practices.

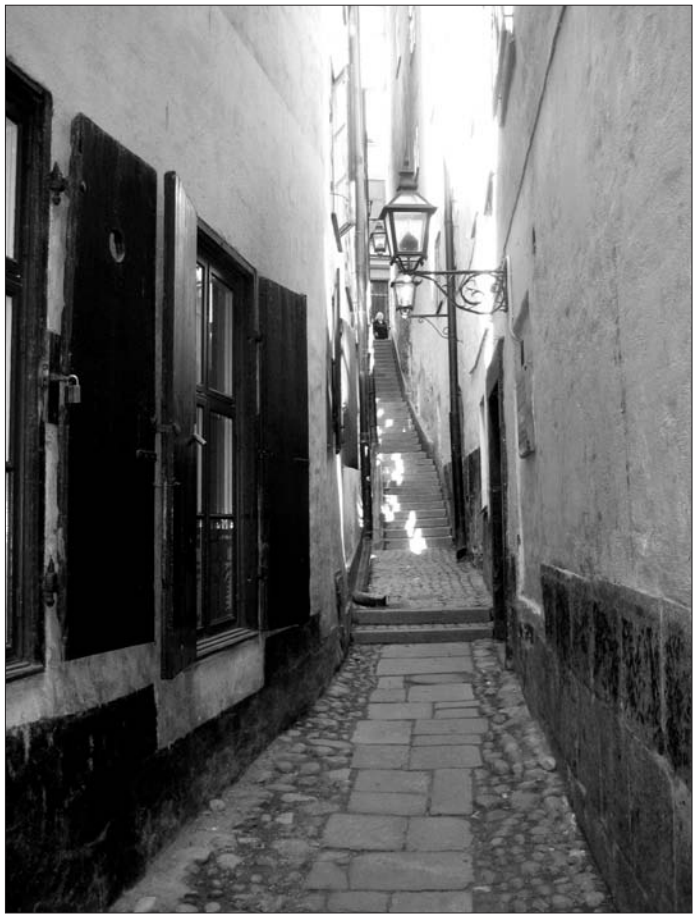
The Swedish health care system is publicly operated and taxed based. In 2002, health expenditures accounted for 9.2% of its GDP (WHO). Photo- Lindsay Brown

Understanding people's beliefs about what factors play a role in health related outcomes may assist in understanding people's health related behaviors.[7] That is, it is necessary for healthcare providers to understand how patients think before fully understanding how to help them. To effectively decrease mortality through these early detection methods and to make future screening methods more successful, it is vitally important to accumulate new data and examine the current state of knowledge regarding a woman's outlook towards her personal control over her own health, an important factor that may indeed influence a woman's interest in seeking out mammography, BSE and CBE. My niché within the scope of Drs. Gustafsson and Svantesson's project was to investigate just that: is there conclusive evidence that the degree to which a woman feels that she is in charge of her own health can be used as a predictor of her level of participation in preventive screening practices?

Health locus of control is a framework that is commonly used to examine the effect of a woman's perspective regarding her degree of control over personal health and behaviors.[8] Although many health loci of control models exist, the most common is the Multidimenional Health Locus of Control (MHLC) scales developed by Wallston, Wallston, and DeVellis in 1978. The MHLC model

is based on the theory that individuals attribute variations in the amount of control they exhibit over their health to three factors: self, powerful others, and chance.[9] Individuals who believe they control their own health and health outcomes are labeled "internals." Individuals who believe chance or powerful others control their health and health outcomes are labeled "externals." The group defined as "powerful others" can include individuals (such as a doctor) or other beings (such as God) whom an individual believes have power over his or her state of wellness. The MHLC model derives from Rotter's 1954 Social Learning Theory.[6] According to Rotter's Social Learning Theory, the potential of a specific behavior occurring in a certain situation is a function of the expectancy that the behavior will lead to reinforcement and value of reinforcement.[6] The theory grew in popularity within the scientific community in conjunction with the development of a measure of generalized expectancy for internal and external control of reinforcement; that is, the I-E scale.[6] The first health-specific version of this scale, known as the Health Locus of Control (HLC) scale, was developed by Wallston, Wallston, and Maides in 1976. The scale was one-dimensional, with externals on one end and internals on the opposite end. Wallston, Wallston, and DeVellis revised the scale in 1978 in light of criticism directed toward the one-dimensional nature of the instrument.

By incorporating a patient's responses to MHLC items into an abridged version of the scale, a physician or healthcare provider may be able to identify the patient's pattern of orientation as being related either more strongly to belief in internal control or to control by powerful others.[7] Using this information as a guideline, the physician could present advice about screening behaviors that are in line with the patient's existing MHLC orientations.[7] For example, this might involve stressing the self-initiating nature of BSE and appointment-setting to patients high in internal control, and advising such patients to follow information provided in pamphlets.[7] However, although providing information is crucial, information alone generally has not been shown to lead to increased frequency or quality of breast self-examination performance, making an emphasis on self-initiated prevention tremendously important.[10]



In 2003, 83% of Sweden's 8.9 million people lived in urban areas (WHO). Consistent with the trend in developed counties, its population of elderly people is increasing rapidly, in fact the ederly are expected to represent 25% of the population by 2030 (WHO). Photos- Lindsay Brown

For women who score highly on the externality/powerful others dimension, the physician may be able to increase the extent to which women perform necessary medical screening by stressing compliance with physician recommendations as an important component of the physician-patient relationship.[7] It is also necessary that health professionals empower women who score on the lower end of the scale by illustrating that they do indeed have control over their own health, and that by taking advantage of that control through preventative screening practices, breast cancer can become a less frightening and perhaps less deadly disease.

The bottom line is that it is possible and necessary for health care professionals to encourage all women to seek and to practice preventive care, no matter which HLC they display. Incorporating the MHLC construct into clinical intake proceedings, an innovative idea in that it will afford an individual patient a message targeted to her personal belief system, may prove extremely promising in catching cancer as early as possible in as many women as possible.

I am grateful for my time in Sweden and the opportunity to have worked as a member of a unique and very advanced healthcare system. In an age where information is transmitted across the globe in an instant, the future of transnational collaboration is both extremely promising and absolutely necessary. I thank the MHIRT program for helping me reach greater degree of professional and cultural competence. The program also showed me the need to fight public health battles outside of rigid boundaries that constrict nations in an ever-shrinking world. United we stand, or divided we'll fall—globally. By supporting fluidity in our own healthcare system and learning from the priorities and innovations of other societies, such as Sweden's, perhaps we too can provide the encouragement and means through which to lessen the devastation of breast cancer in our own society.

1. American Cancer Society. How Many Women Get Breast Cancer <http://www.cancer.org/docroot/CRI/content/CRI_2_2_1X_How_many_people_get_breast_cancer_5.asp?sitearea=>. Accessed 11/20/2006. American Cancer Society, 09/26/2006.
2. Anonymous <http://www.imaginis.com/breasthealth/breast_cancer2.asp>. Accessed 11/20/06. Imaginis Corporation, May 2006.
3. National Cancer Institute, National Institute of Health. Breast Cancer (PDQ): Breast Cancer Screening <www.cancer.gov/cancertopics/pdq/screening/breast/patient>. Accessed 11/20. National Cancer Institute, 2006.
4. Miller LY, Hailey BJ. Cancer anxiety and breast cancer screening in african-american women: A preliminary study. Womens Health Issues. 1994; 4(3):170-174.
5. Nemcek MA. Factors influencing black women's breast self-examination practice. Cancer Nurs. 1989; 12(6):339-343.
6. Murray M, McMillan C. Health beliefs, locus of control, emotional control and women's cancer screening behaviour. Br J Clin Psychol. 1993; 32 (Pt 1)(Pt 1):87-100.
7. Bundek NI, Marks G, Richardson JL. Role of health locus of control beliefs in cancer screening of elderly hispanic women. Health Psychol. 1993; 12(3):193-199.
8. Holm CJ, Frank DI, Curtin J. Health beliefs, health locus of control, and women's mammography behavior. Cancer Nurs. 1999; 22(2):149-156.
9. Borrayo EA, Guarnaccia CA. Differences in mexican-born and U.S.-born women of mexican descent regarding factors related to breast cancer screening behaviors. Health Care Women Int. 2000; 21(7):599-613.
10. Redeker NS. Health beliefs, health locus of control, and the frequency of practice of breast self-examination in women. J Obstet Gynecol Neonatal Nurs. 1989; 18(1):45-51.

The Gothenburg tram is the largest tram/light rail network in all of Northern Europe, a network comprised of over 200 trams which travel 30,000 kilometers each day. Photo- Lindsay Brown

Fighting Fire Without Water: HIV in Lusaka, Zambia

Brian Kalish, Public Health Studies 2008

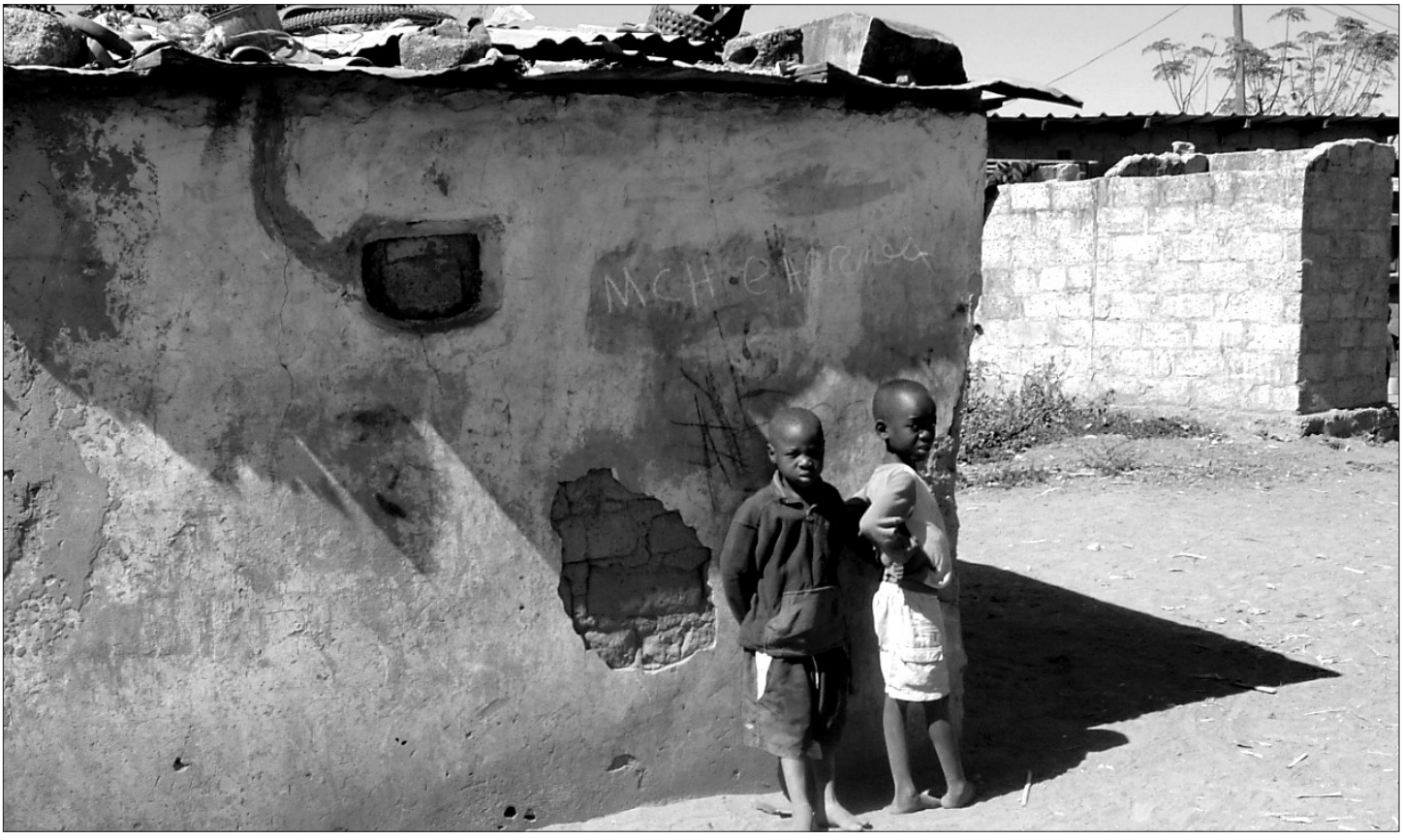
"Bwana, do you mind if I turn on the radio?" The Lusaka news station came on before I had a chance to answer.

I looked out the taxi window, the dense darkness encroaching upon the unlit, pot-holed road. I knew from daylight excursions to this area that cinderblock houses lined the edge of the road, but only the outlines were visible at night when they were lit faintly by the occasional light bulb or fire.

"Hey boss, listen to this." The taxi driver turned up the radio. The newscaster was reporting on a fire in downtown Lusaka, the capital of Zambia. The fire had consumed several shops along Cairo Road, which was the boisterous market thoroughfare there. The newscaster said that local residents had attempted to extinguish the fire, but they had run out of water. Lusaka firefighters responded to the fire, but they too ran out of water. As a last resort, the firefighters from Lusaka International Airport attempted to fight the fire, but alas, they ran out of water as well. The newscaster reported that the fire was still burning three hours after it began and that officials had said that the fire showed no signs of stopping. The fire was allowed to burn itself out.

I had been in Lusaka for three weeks and was still struggling to keep up with the learning curve. Nonetheless, the news report had really caught my attention because the fire seemed all-too-applicable as a metaphor for Zambia's predicament; the onset of problems seems to be outpacing the development of plausible solutions and mechanisms of prevention. Lusaka is one of the fastest-growing cities in Africa, but amenities like proper sanitation and waste disposal are nonexistent. Health crises compound these infrastructure problems; Zambia is one of the few countries where the under-five-years mortality rate has increased in the past few decades. The number of inextinguishable fires is multiplying with only a few signs of letting up.

My perceptions of the plight of urban Zambians comes from the six weeks I spent in Lusaka during the summer of 2006 working on a child health survey with Dr. Bill Moss, a pediatric infectious disease specialist and Bloomberg School of Public Health faculty member, and Sara Lowther, a PhD candidate in epidemiology. The study, a cross-sectional survey of about 1000 children in the Chawama district of Lusaka, had two main objectives. The first was to assess the proportion of children in the population with antibodies to measles and/or HIV-1. The second objective of the study was to investigate risk factors that decreased the probability of acquiring measles immunity through vaccination. We focused on two risk



Two children outside of their home in the Chawama district of Lusaka, Zambia. Photo- Brian Kalish

A girl in the market area of the Chuwama district, where the average household does not have running water. Photo - Brian Kalish

factors in particular: the failure of children to be vaccinated and infection with HIV. The latter is a concern because HIV infection can lower immunity to secondary infectious diseases like measles because of the detrimental effect of the virus on the immune system. Failure of HIV-positive children to be immunized may be the product of numerous sociocultural factors, many of which we hope will be be elucidated by the results of this study.

The protection of HIV-positive children against measles is of the utmost importance because such an infection can prove to be more serious in immune-compromised individuals than would be expected in HIV-negative individuals. Results of the study will allow investigators to decide whether the Zambia Mass Measles Immunization Campaign in 2003 was effective enough to prevent continued endemic measles infection, and will also aid in creating successful vaccine strategies in regions with high HIV prevalence.

The study hinged on the collection of oral fluid samples, which was done by swabbing the inside of the child's mouth for one minute. My main role in the study was to test the oral fluid samples collected from each study participant for HIV and measles antibodies. Local biomedical students conducted the actual on-the-ground collection of data, so I also assisted in preparing the students before each survey day. In addition to these tasks, I conducted quality control overview of the survey results and gave feedback to the survey team members.

My experience in Zambia was more than a rigorous crash-course in international health; it was an opportunity for me to gain insight into the lives of people of whom I would have otherwise been ignorant. The project used a local theater group to raise awareness about the study and quell any suspicions of satanism. Many outside-run health projects that involve the collection of bodily fluids face the risk of being stigmatized as satanic, which, in many cases, leads to the community refusing to participate. The theater group attempted with much success to answer any lingering questions about the study. I was able to venture into the communities with the theater group and directly witness the conditions that I had seen glimpses of from the side of the road. The prevalence of cell phones and western clothing presented a striking contrast to the one-room, concrete-floored houses, many of which lacked indoor plumbing or electricity. I immediately noticed the ubiquity of coffin-makers, which to me was a conspicuous sign of the devastatingly poor health in these urban neighborhoods. The enormity of Zambia's public health issues was further impressed upon me when I was given a tour of the University Teaching Hospital, where I tested the oral fluid samples. The notion of whole wards devoted to diarrhoeal disease, tuberculosis, and measles graphically demonstrated the reason I was in Zambia.

One image that is burned into my mind's eye is that of several middle-aged and elderly women seated on the side of the road making small gravel-sized rocks from larger blocks, presumably for the production of concrete. This menial operation took place next door to a fenced-in Mercedes Benz dealership. I passed this remarkable irony on my way to the Chawama clinic each day, where the study was conducted. Pregnant women would be miled about outside the clinic awaiting free antenatal care, and individuals with various other ailments would sat waiting in crowded rooms to see the one health officer. I was reminded daily of the prevalence of preventable illness, especially in children under five. The dichotomy between these hardships and the isolated islands of wealth made me realize that public health problems had to be contextualized within the broader economic and political conditions in Zambia, and that the work to address these issues had only just begun.

I could not have imagined a better way to understand the extent of the public health crisis in Zambia than to experience for myself the excitement, frustration, hope, and fulfillment of working with and befriending the people themselves. The stoic suffering captured my heart, and the direction of my aspirations will forever reflect my time spent in Lusaka.

HIV/AIDS Research in Pune, India

Vivek Murthy, Public Health Studies 2008

India has a population of 1.1 billion, over three times that of the United States, yet spread over an area one-third its size. There are 28 states, 19 official languages, and 4 major religions. Although marginal, the caste system endures today. These factors all lend to a diversity that complicates the implementation of macroscopic health initiatives. The country's health infrastructure also must cope with periodic surges in tropical disease, which are punctuated by the seasonal monsoon rains.[1] In recent months, flare-ups of chicken guinea and dengue fever in major urban centers have emerged as new symptoms of this chronic burden.

However, one of the country's most dire health concerns is not a periodic phenomenon, but rather a permanent and eclipsing aspect of the lives of 5.2 million Indians.[2] HIV/AIDS is proliferating, challenging the country's economic resources, and testing its political expediency on health matters. Moreover, it is catalyzing a public dialogue on sexual behavior. And the staggering reality of HIV/AIDS in India is that of the 5.2 million individuals estimated to be living with the disease, only 125,000 have been identified thus far[3].

My interest in the HIV/AIDS epidemic in India began at the age of 16, when I spent a summer working with a counseling and prevention program in the slums of Bangalore. At that age I was too young to understand the overall scope of the project, but I was certainly old enough to perceive the tragedy of the lives consumed by the disease. This past summer, four years and four visits later, I was given the opportunity to return to India under the Merck Scholars in Global Health sponsorship and make a difference.

My project took me to Pune, the second largest city in the western state of Maharashtra, which is often called the "Oxford of the East" for its abundance of educational institutions. I spent the summer at Byramjee Jeejeebhoy Medical College (BJMC) helping to create a database for blood samples under the supervision of Dr. Nikhil Gupte, the head biostatistician for the project. My participation took place in the larger context of a Johns Hopkins-BJMC study of the drug nevirapine, which has proven effective in reducing mother-to-infant transmission (MIT) rates of HIV when administered to the infant after birth. The primary goal of this ongoing study is to determine wheather extended nevirapine treatment is more effective than a single dose in reducing transmission rates. The protocol calls for all infants born to HIV-infected mothers to receive nevirapine within 48 hours of delivery, but randomization into study groups is done one week afterwards. One group of infants is placed on a regimen of only multivitamins, another receives multivitamins and nevirapine, and a third group receives multivitamins and a higher dose of nevirapine. The infants are monitored and tested for HIV at set dates following the initial dose of the drug. The database I worked on contains the data for these tests, but was complicated by the fact that the blood samples were separated into many parts (whole blood, plasma, etc.) and analyzed at both BJMC and the National AIDS Research Institute (NARI).

Top: Front entrance to BJMC, an undergraduate medical institution in Pune which operates HIV/AIDS drug studies in collaboration with Johns Hopkins University.
Bottom: This billboard, and many others like it outside of BJMC, encourage women to play active roles in maintaining their well-being. Photos- Vivek Murthy

Working with the data of a MIT drug trial was a particularly edifying experience, because mother-to-infant transmission of HIV accounts for thousands of reported cases in India, and drugs like nevirapine offer practical hope for effective disease management today and in the future. The culmination of this study could produce knowledge applicable to MIT prevention regimens worldwide.

In addition to preparing the database, I was able to witness Johns Hopkins and BJMC scientists operating in collaboration. I worked primarily out of the Adverse Events Reporting Office, set up in the medical school's pathology museum, and there I had the chance to interact with researchers examining deviations from protocol and unexpected events during the infant observation period. I learned about the degree of microscopic detail paid to individual subjects and the scrupulousness with which every deviation from protocol was submitted for evaluation to the JHU Review Board and the Indian equivalent. One thing that particularly struck me was the complex effort taken to ensure patient privacy (by removing protected health information) while simultaneously allowing subjects to remain separate and unique.

I also learned from my mentor, Dr. Gupte, who patiently explained several of the projects he was involved with. One of these was utilizing statistical models to reconsider the standard HIV seroconversion window (the time between the first exposure and when a test can detect the related infection) used in India. Individuals exposed to HIV through risky sexual behavior or intravenous drug use were perhaps classified as infection-free prematurely, possibly contributing to the underestimation of HIV/AIDS statistics in India. This was one of the first projects Dr. Gupte discussed with me and I was impressed by the immediate relevance of his work.

Along with research on the nature of the disease and treatment drugs, India has been taking several other steps to manage HIV/AIDS. The National AIDS Control Organization in New Dehli, tasked by the government with the containment of the epidemic in 1986, has taken widespread initiative to educate Indians in rural and urban settings on responsible sexual behavior and the importance of abstinence before marriage and faithfulness thereafter.[3] Additionally, more than 1,200 non-governmental organizations (NGOs) have moved into the most affected areas and have counseled commercial sex workers, migrant laborers, and other high-risk individuals. Over 900 Integrated Counseling and Treatment Centers have been set up in the country and continue to provide comprehensive and region-specific care for those in need. But these organizations face obstacles older than the HIV/AIDS pandemic itself: the reluctance of a society to discuss sexuality and the habits of reproduction.[4] In some cases, this reluctance has manifested itself in the harassment of NGO employees by police officers, but in the larger context this has meant that the overwhelming majority of HIV/AIDS cases in the country have not yet even been identified.

My experience this past summer was invaluable, because it allowed me to learn from dedicated scientists fighting the spread of HIV/AIDS in India, one of the most beleaguered fronts in the global war. It also sensitized me to the plight of thousands of children in the country who have been born with the disease, and familiarized me with the hard work of many to change this staggering reality into a tragedy of the past. I am grateful for having had the opportunity to learn from those dedicated to the project's success.

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1. "India." The CIA World Factbook Online. 17 October 2006. 20 October 2006. <http://www.cia.gov/cia/publications/factbook/geos/in.html>.
2. "2006 Report on the Global AIDS Epidemic." UNAIDS website. May 2006. 19 October 2006. <http://www.unaids.org/en/HIV_data/2006GlobalReport/default.asp>.
3. "Facts and Figures." India National AIDS Control Organization website. 22 August 2006. 19 October 2006. <http://www.nacoonline.org/facts_reportaug.htm>.
4. "India's Minister of Health Talks about the Control of HIV/AIDS." Johns Hopkins Bloomberg School of Public Health website. 29 June 2006. 19 October 2006. <http://www.jhsph.edu/publichealthnews/articles/2006/Ramadoss/ramadoss.html>.

The BJMC pathology museum, where the Adverse Events Reporting Office was located along with several other administrative offices for the nevirapine study. Photo- Vivek Murthy

EWB Mission: Building a Sanitation System for Uduzhapa, Ecuador

Linda Wan, Civil Engineering 2009

Engineering and public health are interdisciplinary arts to a greater degree than one might think. In summer 2006, I traveled to Ecuador with the Engineers without Borders (EWB) chapter from University of Maryland at College Park. For three weeks, I worked to implement a sanitation system for the rural community of Uduzhapa. During this time, I worked together with members of the local community, fellow project teammates, and professional engineers to meet the ambitious goal of constructing 40 latrines, despite the presence of personality conflicts and cultural differences such as language and customs.

Engineers without Borders is a non-profit organization that operates beyond that of an average non-profit organization. Like most non-profit organizations and non-governmental organizations (NGOs), EWB's mission is to partner with disadvantaged communities to improve their quality of life. However, what sets EWB apart from other organizations is the fact that it emphasizes the environmental and economic sustainability of its engineering projects, while also fostering internationally responsible engineering students. EWB also provides education regarding the maintenance of projects or processes vital for sustainability. Engineers without Borders' principle goal, underlying all of its projects, is to establish a relationship with the target community and resolve the problem in a holistic fashion. EWB analyzes problems using a multi-pronged approach, which often includes tools related to the study of public health. We ask the community questions such as what resources the area lacks, what the subsequent adverse effects are, and how one might employ some changes beneficial to the community. Seeking answers to these questions is beneficial in assessing the problem and deciding what needs to be implemented in the target community.

Uduzhapa, the 180-resident community that I worked in, is located in the Azuay province of Ecuador in the Andes Mountains region. In Uduzhapa, the only source of drinking water was open irrigation channels, which had become contaminated over the years by the runoff of excretion of human and animal waste nearby.

This problem adversely affected the health of the residents. In the county of Cochapata, where Uduzhapa is located, nine out of ten individuals do not have access to adequate sanitation or water services. Gastrointestinal illnesses are among the main illnesses reported at the three health centers of Cochapata. The most prevalent diseases among children under five years old are severe dysentery, malnutrition, and parasitic infection. At the time of my visit, a local government agency, Fondo de Inversion Social de Emergencia (FISE), was planning to provide a clean water supply system for this community. Introduction of potable water and a sanitation system, they argued, would change the water usage and waste water generation patterns of the future. However, such an increase in waste water production would demand a suitable sanitation system to mitigate the potential spread of pollution and

All 40 of the latrines used the same basic design with modifications according to the preferences of the owner. Photos- Linda Wan

Buildings in the village are spread far apart from each other, making traditional sewer systems expensive and impractical.
Photo- Linda Wan

disease. Without any form of containment, runoff would most certainly enter the irrigation channels, contaminate the fields, increase human contact with waste, and provide a route for the transmission of disease, thus making existing health conditions even worse.

Engineers without Borders – University of Maryland at College Park (EWB-UMCP) had been exploring the opportunity to design and implement a sanitation system for the community, particularly for the school located in Uduzhapa. All design possibilities from latrines to septic tanks and facultative ponds were considered. Ultimately, EWB-UMCP decided to build 40 latrines, one for each household, in order to solve the confounded problem of the fecal contamination of potable water and crops.

My experience in Uduzhapa was completely immersive. I lived and worked in cultural setting away from the spoiled human comforts of television, malls, heating and air conditioning, electricity, and even hot showers. Nonetheless, my experience was altogether positive. On this trip, I learned how to mix concrete not by machine but by hand, filling a 2 x 2 square-meter foundation for the latrine superstructure and two 120 x 60 centimeter pit covers. Initially, our group had been mixing the sand, gravel, and cement powder in an inefficient way. However, with the assistance of several skilled laborers from the community, we were shown the local, efficient way of mixing concrete. These skilled laborers illustrated the effectiveness of mixing one element of the concrete before the other, as well as when and how much water to add. This entire process was beautifully demonstrated to us, encouraging the exchange of ideas and marking the establishment of a trust-filled relationship.

On this trip, I learned two fundamental principles of engineering: adaptation and efficiency. While the codes and regulations we used for construction were based on United States standards, working in a different country means being culturally aware and having the ability to adapt to local methods of efficient production. I learned that despite being a United States resident working abroad, I was responsible for adapting to local conditions and learning as much as I could in order to achieve high results. By joining EWB on this project, not only did I get to travel abroad and impact an international community, I also gained the opportunity to learn valuable professional skills such as fundraising, presenting, organizing, and working in teams, all of which were critical for this project. I also had the opportunity to work with the professional engineers to gain insight on designing the structure.

For the academic year of 2006-2007, EWB at Johns Hopkins University has taken initiative to start our very own Ecuador Project. We will be traveling to Santa Rosa de Ayora, a very remote and poor community, located an hour outside of the capital, Quito. In Santa Rosa de Ayora, most of the parents are working demanding schedules and leaving their young children behind in the homes alone. Our proposed solution to this problem is to build a seismic-safe nursery for the children where a responsible adult can watch over the young children of the community.

In conclusion, as one professor involved with Engineers without Borders at Columbia University mentioned, engineering projects are commonly the solution to public health problems. Moreover, I know that the EWB implementation in Uduzhapa, Ecuador was successful, especially since I will be able to return the following year and see healthier residents, one of the direct results of the implementation of the sanitation system in Uduzhapa.

Sexual Health Education in Low-income Areas of the Buenos Aires Province

Jana Freeman, Post-Baccaleurate

Condom balloons and hand-cut chain links of colored paper swung from the wood scaffolding. Dozens of Argentine sweets—*pan dulce* and *medialunas*— were scattered across the long, wooden table in the middle of the room. I stood in the doorway, marveling at the creative handiwork of the 20 women participating in our HIV/AIDS prevention workshop; with neither the time nor the money to spare, they had completely transformed the humble room where we held our weekly sessions. The women stood proudly amongst their decorations and smiled as I entered the room, anxious to kiss me hello and goodbye. On the final day of our HIV/AIDS workshop, we celebrated both the culmination of their training as community health promoters and my last day of work in Argentina.

As a senior at Yale University in 2005, I hoped to pursue a post-graduate work experience which combined my evolving interests in epidemic disease, women's health, and the Spanish language. The Parker Huang Travel Fellowship allowed me to do so by funding my internship at the Epidemiology and Prevention Department of Fundación Huésped, an active HIV/AIDS Non-Governmental Organization (NGO) in Buenos Aires, Argentina. This is how I arrived in Guernica, a suburban neighborhood of Buenos Aires, a participant in one of Fundacion Huesped's workshops: Sexuality, Pregnancy, and Vertical Transmission of HIV among Women Living with HIV/AIDS.

Workshops like the one in Guernica are part of Fundación Huésped's broader campaign to promote health education for women and youth in low-income areas of the Buenos Aires Province. Fundación Huésped's Prevention Department focuses on the struggle against HIV/AIDS as both a biological disease and a social problem encompassing issues of discrimination, politics, and economics. With an estimated 130,000 people living with HIV/AIDS in 2005, Argentina's 0.6% rate of HIV infection is among the highest rates in Latin America, second only to Brazil. Perhaps the most striking facet of Argentina's current situation is the significant increase of incidence among women; while the number of reported HIV/AIDS cases has risen over the past two decades, the male-to-female ratio has decreased from 15:1 in 1988 to 3:1 in 2004. This trend reflects the fact that unprotected heterosexual sex has become a primary mode of transmission in Argentina, increasingly and disproportionately affecting young, poor women.

To address these issues, Fundación Huésped directs much of their prevention initiatives toward youth and women of fertile age in low-income areas of the Buenos Aires province, where 75% of the national HIV/AIDS cases occur and 50% of the young population lives below the poverty line. As part of Fundación Huésped's effort to support the development of local health organizations in these areas, my co-worker, Lucila Falcone, and I traveled to Guernica each week to provide technical support to *Gente en Movimiento*, a smaller NGO promoting community health in the surrounding neighborhoods of Guernica. While this particular workshop concentrated on sexuality, pregnancy, and the vertical transmission of HIV/AIDS, other workshops organized by Fundación Huésped pertain to human rights and discrimination, gender equality, adolescent health, and the development of community prevention strategies.

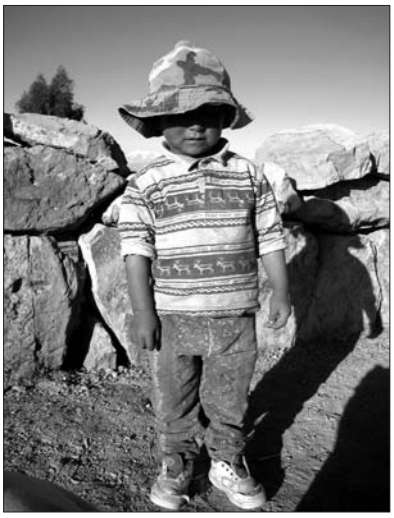
Women participating in a HIV/AIDS prevention workshop in Guernica, Argentina. Photo- Jana Freeman

Fundación Huésped's prevention workshops, geared toward youth, integrate cultural activities and promote peer health education. Cultural workshops train young peer educators who, in the process of learning about HIV/AIDS and other health subjects, produce prevention messages for their peers in a variety of formats, including theater, music, videos, comic strips, and magazines.[1] Proactively involving youth in learning about HIV/AIDS and sexually transmitted diseases both increase access to health information and facilitates communication among youth.

Throughout my internship, I helped monitor and coordinate a workshop for adolescents in San Fernando, a poor neighborhood in the Buenos Aires province. This workshop educates youth about sexual and reproductive health and promotes healthy lifestyles for a group of adolescents who have formed a volleyball team. As part of the development of this workshop, the group has produced two editions of their prevention magazine, *Mundo Tigresas,* to educate their peers about health, adolescence, drug use, and sexually transmitted disease.

On my last day of work in Guernica, the women participating in our HIV/AIDS workshop sent me home with Argentine *mate* cups, signed posters, and a great sense of accomplishment. While the return to the United States would be bittersweet, I knew that these women possessed the tools to continue their work as community health promoters, and that this experience had given me a renewed motivation to pursue a career in medicine. I have since begun the Post-Baccalaureate Pre-Medical Program here at Johns Hopkins, and I am forever grateful for my time and work in Argentina. Clarifying my passion for public health, my experience at Fundación Huésped will contribute to my life as a physician and a US citizen in our global community. As an American living abroad, I gained the ability to view the consequences of US international activity with an international perspective, especially toward our relations with third-world countries. For me, this fellowship highlighted the importance of international public health collaboration; after all, the HIV/AIDS pandemic and consequent health issues are global concerns that transcend social and political boundaries.

1. Vazquez M, Cosovschi A, Gras C, et al. Culture and Health: promotion of sexual and reproductive health and prevention of HIV/AIDS among youth in low-income areas of Buenos Aires province, Argentina.(2006). 2006, November 13, 2006.



Children of Argentina and Peru: 99% of children in Argentina are immunized against measles, whereas 80% of their Peruvian counterparts are immunized against the same disease. Photos- Jana Freeman

Setting Up an Adolescent HIV Clinic in Cape Town, South Africa

Andrew Telzak, Public Health Studies 2008

South Africa has one of the world's worst HIV problems, with approximately 1,000 deaths due to HIV/AIDS every day. It is impossible to be in the country without seeing the effects of the devastation this epidemic causes. Even in conversations on the street, there is no way to avoid the subject. Taking a mini-bus (the cheap public means of transportation) into the center of Cape Town one day, I began talking with the fare collector. The conversation turned to my business in Cape Town, to which I told him about the HIV clinic at Groote Schuur Hospital. 'Oh, really?' he remarked, with a slight grin on his face. Whenever I mentioned HIV around people in Cape Town, I was almost always met with a defeatist and slightly amused attitude, as if I were just another idealistic foreigner trying to come in and solve the big "AIDS in Africa" problem, because obviously the Africans did not know how to deal with it themselves. He then proceeded to tell me "my boy over here has the HIV," gesturing over to his friend, the driver of the mini-bus. Laughing, he continued. "He doesn't like using condoms. He polishes his shoes with them instead!" He apparently found this very amusing, and continued chuckling about it for a little while thereafter, I sat there, a little shocked, although somewhat intrigued as to how much of a common joke HIV had become in South Africa. The gravity of the illness had been lost here in the widening niche it had dug itself in society.

On my first day in Cape Town, I walked into the hospital, ready to tackle one of the toughest challenges facing South African society today, as only an overly optimistic, naïve American college student could. As I slowly adjusted myself to life in South Africa, however, I became more aware of the magnitude of the HIV crisis. Initial aspirations slowly gave way to more realistic goals for making some contribution in my brief time there. While it seemed fairly easy to stand back and point out the problems in the healthcare system, I came to appreciate the complexity of the problems and realized how an outsider's view on what and how things should be changed should be taken as exactly that: an outsider's view, without a real grasp of the constructs surrounding and defining the system.

During summer 2006, I was presented with the opportunity to live in Cape Town, South Africa, underwritten by a Merck Scholars in Global Health grant. My work in Cape Town was based at Groote Schuur Hospital, a public hospital with a focus on the two biggest public health issues in Cape Town: trauma and HIV. The G25 ward of Groote Schuur Hospital is a pediatric ward with mostly HIV-positive patients. Two days a week, there is also a clinic that is run out of G25 for vertically infected (mother to child) HIV-positive children, with ages ranging from newborn infants to 16- and 17-year-old teenagers. The services offered at the clinic include doctor visits as well as individual counseling sessions for the children and their caregivers. As the children mature into adolescents, a whole host of new issues arise that transcend the scope of the medical community. In this time of enormous emotional, intellectual, and physical change, problems that cannot be answered simply by prescribing a pill or a cream arise. A multifaceted approach combining medicine, counseling, and education seemed to be the most effective way of addressing these issues.

The clinical aspect of my work experience involved working in the ward in G25, as well as in clinics in Gugulethu and Nolungile, both townships outside of Cape Town. Private donations through KidsPositive, a non-profit initiative that generates income for caregivers of the children in G25, funded these projects. While waiting for the children's appointments, caregivers are trained in making beadwork that is then sold. The caregivers are given the raw materials and are paid for their efforts. The project goal is to provide a sustainable self-help industry to support HIV-affected families. Most of the children coming into the ward were from the townships outside of Cape Town, where the majority of families were living off of meager government grants, with no consistent employment income from any family member. It was in these townships that I was able to see the continuing legacy of the

Graffiti across the street from Groote Schuur Hospital testifies to South Africa's anit-apartheid movement. Photo - Andrew Telzak

Empty ARV bottles in the clinic. Patients are required to return empty bottles to the clinic as a proof of compliance. Photo- Andrew Telzak

apartheid government in the broken-down shacks crammed one on top of another.

In addition to my clinic work, I was put in charge of creating an "adolescent clinic" within the already existing infrastructure of G25, under the supervision of Dr. Heather Jaspan, the consulting physician in the ward, and Dr. Paul Roux, the head of the Department of Pediatrics and the founder of *KidsPositive*. When I first began to address my task of creating this clinic, doing a literature search for other adolescent clinics seemed to be the obvious starting point. However, only after exhausting journal after website after search engine did I finally realize that although there were many adolescent clinics already in existence, none of them was in South Africa, and few of them seemed to have anything culturally appropriate to include in this adolescent clinic. The framework for this clinic, therefore, had to be built from the ground up, with only vague, culturally inappropriate resources to draw from.

HIV status disclosure (with those adolescents that did not know their status), as well as adherence to antiretrovirals (ARV) were the main issues we hoped to address in this clinic. These seemed to be the two largest issues facing our targeted demographic group. The clinic was intended to be a transition into adult care, teaching the adolescents the necessary skills to care for themselves as they mature.

Moving past the theoretical thinking of the clinic and on to organizing its logistics became somewhat of a large task. The initial question I had to ask was "who are these 'adolescents' we are trying to target?" After deciding on the age group of roughly 10-17 year olds, I began the task of collecting the vital information on approximately 70 adolescents. Having only one doctor forced us to determine which adolescents would go to different clinics and to develop a grouping system to accommodate the large number of patients.

Two distinct groups were initially created: one group that knew their HIV status (disclosed), and the other group that did not know their HIV status (undisclosed). From there, as the clinic grew, we divided the groups by age and even language.

The clinic with the undisclosed adolescents was different from the already disclosed clinic in that the caregivers of undisclosed adolescents received a counseling session. This session offered caregivers the opportunity to talk about the difficulties and strategies of a disclosure. It also hopefully encouraged them to disclose to the adolescent as soon as they were ready, so that the adolescent could join the clinic for the disclosed group. While these counseling sessions took place, the adolescents were doing various other things, from life skills education to talking about HIV/AIDS (but not specifically abut whether or not they have it).

After the logistics of the clinic were decided upon, the next big task was to decide what our actual goals were for the clinic and how we would implement them. The focus of the clinic was not entirely fixed when I left, wavering somewhere in between family planning and life skills, and HIV education. It was decided to allow the clinic's participants to determine what the focus of the clinic would be. Theorizing over the direction of the program before analyzing the responses was one of the most important lessons I learned *not* to do with this project. In order to involve the adolescents as much as possible in the shaping of the clinic, we brainstormed with them and came up with a list of different topics and activities that they chose from week to week as the topic of the next clinic/support group. It was very important to make sure the adolescents knew that this was their clinic, and that any input they had was much more important than anything I, or anyone else working there, would suggest.

One of the main goals of the clinic was to create a comfort zone for the adolescents, in which they would feel welcome and able to talk about such a sensitive issue as their HIV status. Having to deal with HIV as a teenager is a very challenging and isolating experience. Knowing that there are other kids who seem just as normal and are facing a similar situation is enough to motivate an adolescent to learn more about his/her illness, how to take the medication, and how to stay healthy.

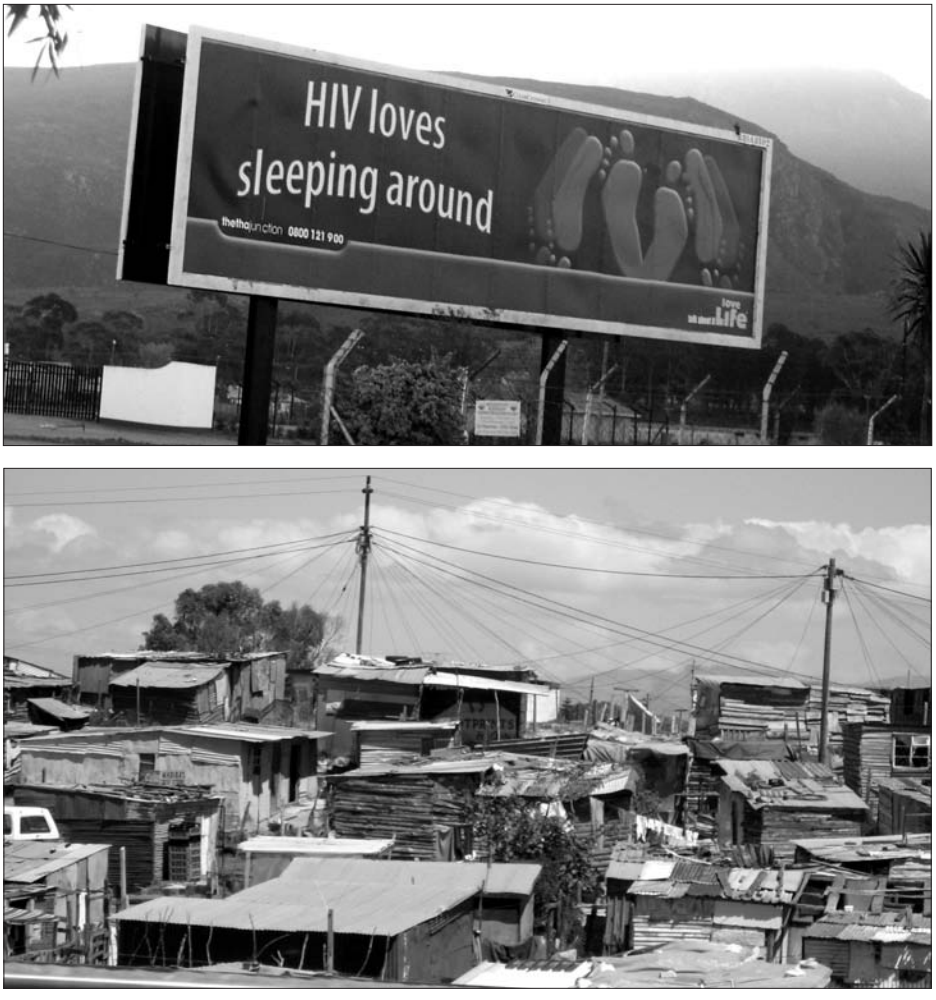
Aside from my work in the clinics, living in Cape Town was an experience unlike any other. Everything from the intensely charged political atmosphere, to the incredible racial integration and tolerance (of the younger generation, at least), to the month-long frenzy over the World Cup, are all things I have definitely not been able to find in the United States. Although the Merck grant gave me the opportunity to go abroad and do public work, the experience I got out of it was so much more than that. I realized from the very beginning that working in a clinic abroad required much more than general science or public health knowledge. In order to really understand the issues at hand, I needed to understand the culture and general atmosphere of South Africa. My learning within the walls of the hospital in more than two months paled in comparison to the amount I would learn in one afternoon of walking around a market, or talking to a street vendor. I would cherish the times I could spend simply wandering around the city, speaking to whomever would listen, and trying to get a feel for the South Africa only to be had by experiencing it first hand.

I would like to end this narrative with two brief anecdotes that I feel really sum up my personal experience working in Cape Town, and have taught me a tremendous amount about the general attitude towards HIV and ARVs among adolescents. Allow me to preface these anecdotes by saying that one of the main things that I learned in developing this clinic was that the program was not going to be perfect from the beginning. Such endeavors almost always tend to start off slowly and grow gradually in small intervals.

While speaking with Nokutula (one of the adolescents attending the clinic) about the clinic, she and her mother shared an interesting story with me about their experience with HIV disclosure. Nokutula had been coming to the HIV clinic in G25 for a few years, being seen by the doctor and getting ARVs each time. Her mother never told her what the medication was for or why she had to go to the doctor more often than a normal child of her age. She knew that her mother was HIV positive but had never questioned whether she was as well. While watching television one day, Nokutula realized that the medication in a commercial for ARVs was the same medication that she had been taking for a long time. She asked her mother whether her medication was for HIV and her mother replied that the medication was just for sick people to help their immune systems, and every sick person took the medication. Nokutula's mother was scared of disclosing her daughter's status, not knowing how she would respond. Nokutula recalled that she believed her mother at the time, but when her mother was finally ready to reveal "her secret," she was not surprised, or even upset, but glad that her mother told her, and that they could now fight the condition together.

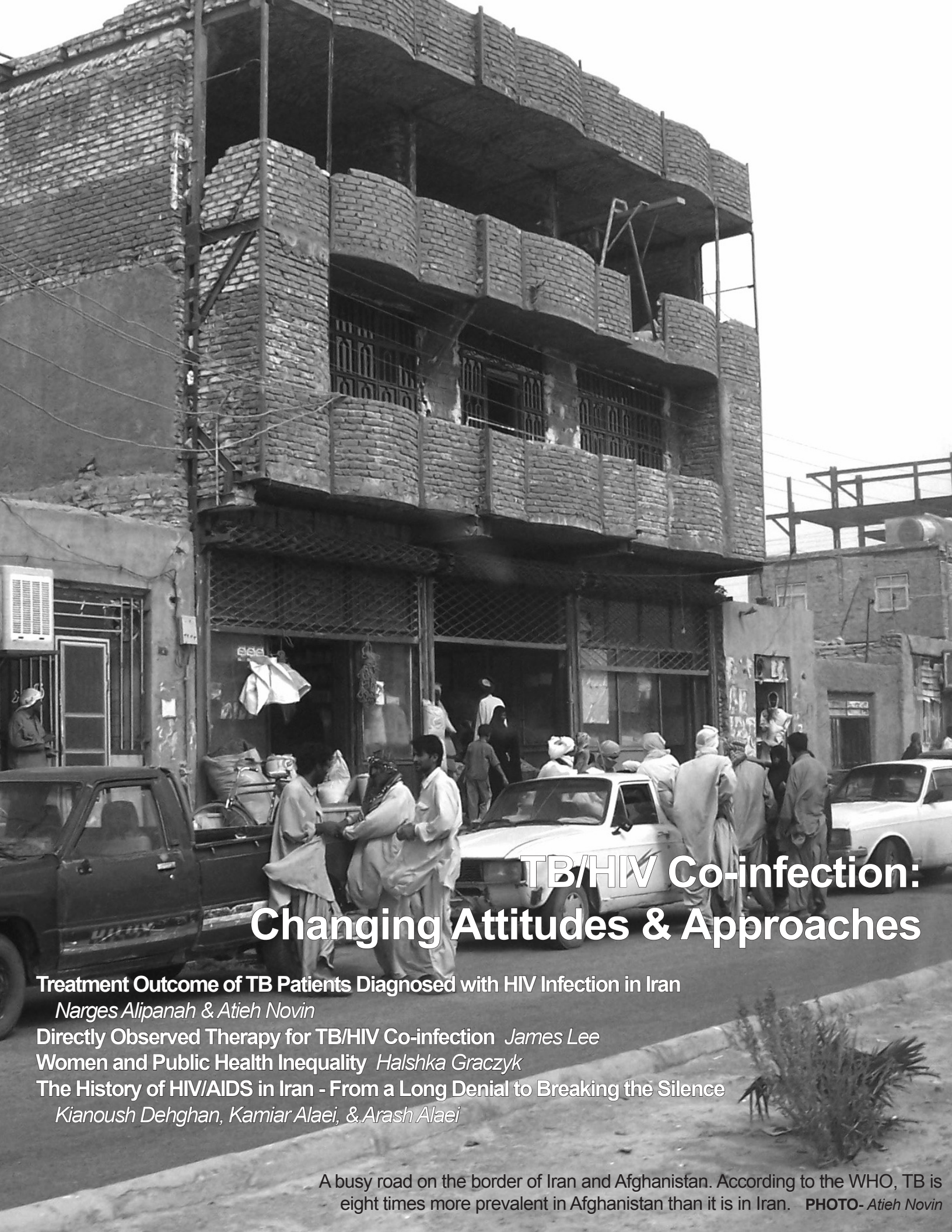
Nazareth House is an orphanage for HIV positive children, with individual cottages housing four or five children each. In one of the cottages, all the children except one of the girls, Patricia, are taking ARVs. They all know that they are HIV-positive, and regularly take their medication. As a result, Patricia constantly feels left out. Every time Patricia goes to the clinic, the doctor tells her that her CD4 count is still high and that she doesn't need to start HAART (Highly Active Antiretroviral Therapy) yet. This good news is almost always met with a look of disappointment on Patricia's face at not being allowed to take the same medication as the other girls in her house.

My brief period of time here was definitely not enough to fully see what this clinic would become, and accepting slow progress in the small time frame I had proved to be a difficult thing. However, I feel that I was able to make a contribution, no matter how small, to the broadening effort to fight HIV/AIDS.



Top: Billboard outside of Cape Town is part of an awareness campaign sponsored by LoveLife, one of South Africa's national HIV prevention programs targeting youths.
Bottom: Khayelitsha, one of the townships outside Cape Town that were created during the Apartheid regime, which prohibited blacks from living within city limits of Cape Town. Today, this is home of the majority of the adolescent patients at the clinic.

Photos- Andrew Telzak



TB/HIV Co-infection: Changing Attitudes & Approaches

A busy road on the border of Iran and Afghanistan. According to the WHO, TB is eight times more prevalent in Afghanistan than it is in Iran. **PHOTO-** *Atieh Novin*

Treatment Outcome of Tuberculosis Patients Diagnosed with HIV Infection in Iran

Early HAART for TB/HIV patients decreases the rate of mortality

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Background: The concomitant treatment of tuberculosis (TB) and human immunodeficiency virus (HIV) poses many problems due to pill burden, drug interactions, and toxicity. No reports have been made on the treatment outcome of TB/HIV patients in Iran. This study aims to evaluate the outcome of treatment at the Masih Daneshvari Hospital and the National Referral Center for Tuberculosis and Lung Diseases in Tehran, as well as assess the administration of highly active antiretroviral therapy (HAART) during the treatment of tuberculosis.

Methods: TB patients who tested positive for HIV and who were admitted to the hospital between 2002 and 2004 were included in the study. Sixty-one variables were chosen for comparison. All analysis was done using SPSS and significance was deduced via chi-square testing.

Results: Fifty-six patients were included in the study. A Kaplan-Meier analysis that provided an estimate of the survival function from life-time data revealed that 50% of deaths occur in the first four months of TB treatment. Comparison of patients who were receiving highly active antiretroviral therapy (HAART) and mortality did not yield significant results.

Conclusions: Even though the sample size of this study was limited, it can be suggested that starting HAART early for TB/HIV patients whose CD4-cell count is less than 130 can reduce the rate of mortality.

TB/HIV co-infection poses a dilemma to the medical community: there are half a million cases worldwide and it causes 10% of all adult AIDS-related deaths each year.[1] In the 1980s, the incidence of tuberculosis significantly decreased worldwide; however, with the emergence of HIV as a prominent infection, TB incidence has risen once again. Thus, it is suggested that HIV infection may have an indirect effect on the incidence of TB by increasing the rate of transmission of *Mycobacterium tuberculosis*.[2-4]

Concomitant treatment of TB/HIV patients is burdened with difficulties.[5, 6] At low CD4 counts, these patients are at an increased risk of progression and mortality in addition to an increased susceptibility to side effects from therapy. The occurrence of TB in HIV-positive patients also increases the risk of acquiring further opportunistic infections and thus contributes to the high mortality rate among these patients.[7, 8]

The use of Highly Active Antiretroviral Treatment (HAART) on HIV patients causes significant reductions in viral load, AIDS defining illness (ADI), and mortality, as well as decreasing the risk of developing TB by 70-90%.[9, 10] Many studies have suggested an appropriate time to start treatment of HIV in co-infection cases, yet there are no studies done in Iran to evaluate the optimal time to commence HAART. The present research was conducted as a retrospective cohort study on TB/HIV cases admitted to the Masih Daneshvari Hospital and the National Referral Center for Tuberculosis and Lung Diseases. The patients were admitted between the years 2002 and 2004 and had a yearly follow-up. The purpose of this study is to describe the survival of TB/HIV patients, evaluate the concomitant treatments, and to assess the treatment outcome in TB/HIV cases at the hospital.

METHODS

Setting: The Masih Daneshvari Hospital, the National Referral Center for Tuberculosis and Lung Diseases, in Tehran, Iran

Inclusion criteria: All 1,050 TB patients who were admitted to the hospital during the years 2002-2004 were tested for HIV infection using Enzyme-Linked Immuno Sorbent Assays (ELISA) and Western Blots. Of these, 56 patients were HIV-positive and were included in the study.

Procedures: Sixty-one factors that were deemed significant in the treatment outcome of the TB/HIV patients, such as age, sex, drug and opium use, method of transmission, incarceration, adverse effects, and AIDS defining illnesses (ADI), were chosen for analysis. The treatment outcomes were divided into three categories: cured, death, and absent. ADI consisted of Cerebral Toxoplasmosis, CMV Retinitis, CMV Pneumonitis, Cryptococal Meningitis, and Pneumocystis Carini Pneumonia. Since oral candidiasis is a sign of severe immune deficiency, physicians at this hospital start HAART for a patient upon detection of this illness; therefore, for the purpose of this study, oral candidiasis is also categorized as an ADI. The information needed was procured from the files of these patients at the hospital.

Hepatitis B and C serological tests, VDRL, serology of toxoplasmosis (IgM, IgG), sputum smears and cultures, antibiograms, and stool exams (S/E) were performed on these patients. When necessary, brain and lung CT scans, retinoscopies, and CSF analyses were also done for the patients. The CD4 counts of the 56 patients were measured and a chest x-ray was taken from each patient.

The standard TB regimen, which is treatment with Isoniazid, Rifampin, Pyrazinamide, Ethamutol, and vitamin B6, was administered to all these patients. The pa-

Table 1. Clinical and demographic information of TB-HIV patients

	Frequency *(n)*	Percent *(%)*
Method of transmission		
heterosexual intercourse	4	7.1
homosexual intercourse	1	1.8
IVDU	42	75.0
transfusion	9	16.1
Smoking		
yes	54	96.4
no	2	3.6
Opium use		
yes	51	91.1
no	5	8.9
Alcohol use		
yes	32	57.1
no	24	42.9
Prison		
yes	50	89.3
no	6	10.7
Total	**56**	**100.0**

Table 2. Tuberculosis characteristics in TB/HIV patients

	Frequency *(n)*	Percent *(%)*
Type of TB		
pulmonary	32	57.1
pleural	6	10.7
PTB + EPTB	18	32.1
Smear		
positive	39	69.6
negative	17	26.8
missing		3.6
Culture		
positive	33	58.9
negative	19	33.9
missing	4	7.1
Total	**56**	**100.0**

tients who developed adverse effects due to treatment received a modified treatment regimen with an extended duration of up to one year. The patients who were not injection drug users (IVDU), had good compliance, and had a CD4 count of less than 200 were administered HAART starting from the fourth to eighth week of TB treatment. HAART regimen consisted of Zidovudine, Lamivodine, and Nelfinavir. The patients for whom HAART was necessary, based on the mentioned criteria, received Rifabutin (150 mg/day) instead of Rifampin two weeks prior to initiating HAART.

All analysis in this study was done via SPSS. Chi-square tests were used in order to evaluate the significance of variables while survival was examined using the Kaplan-Meier Estimator.

RESULTS

Baseline characteristics: Of the 56 TB/HIV patients included in the study, 53 were male while only three were female. 89.3% of the patients did not know that they were HIV-positive until tested in the hospital. The mean age of the patients was 37 $\pm$ 8 years. Injection drug use was the most common method of HIV transmission (75%), while 96.4% were regular smokers, and 91.1% consumed opium (oral and inhaled). Fifty patients (89.3%) had a history of incarceration (Table 1). Of the 56 patients in the sample, 57.1% had pulmonary TB, 10.7% had pleural TB, and 32.1% patients had both pulmonary and extrapulmonary TB (4 lymph nodes, 8 pleural, 1 anal, 2 picarditis, 1 liver, and 1 abdominal) (Table 2).

Sputum smear results were positive in 39 cases (69.6%) while culture results were positive in 33 cases (58.9%). Thirteen patients (23.2%) were receiving HAART. For the purpose of analysis, CD4 count was divided into two categories of less than 100 and greater than or equal to 100: 19 cases (33.9%) belonged to the former while the rest (53.6%) belonged to the latter. Hepatitis B (HBV) was detected in 4 cases (7.1%) while 45 cases (85.4%) had hepatitis C (HCV) infections.

AIDS defining illnesses (ADI): thirty seven patients from the sample (66.1%) had ADI. The most common illness was oral candidiasis, which was detected in 34 cases (60.7%). Toxoplasmosis was the second most frequent ADI, which was detected in 5 cases (8.9%). Two cases were diagnosed with CMV retinitis while 1 case had CMV pneumonitis. PCP was found in one case and crypotococcal infection in 2 cases. There were also two cases of herpes (HSV).

Outcome of treatment: 50% of the cases were cured while mortality occurred in 15 cases (26.8%). Thirteen cases (23.2%) were lost in follow-up. Six patients died in the first two months of TB treatment (10.7%) while three died (5.4%) between (two to six months). Three other cases died after six months of treatment with one death (1.8%) occurring at the 12th month of follow-up.

Adverse effects (AE): Thirteen (23.2%) patients developed adverse effects. Hepatitis was the most common AE, which was detected in eight cases followed by skin rash in five cases, and central nervous system and hematological problems each in one case. An analysis of the rate of mortality in patients who developed AE showed that a higher percentage of patients who had AE died (38.5%) than the patients who did not have them (23.3%), yet this result was not significant (p-value 0.278).

Survival: The rate of mortality was higher in cases that demonstrated ADI: 35.1% mor-

tality in the ADI group as opposed to 10.5% in the non-ADI group (p-value 0.049). The two CD4 groups (<100 and ≥100) also generated significant results when cross-tabulated with mortality (p-value 0.049) such that death was more frequent in the first group (42.1%) in contrast to the second group (16.7%). An error bar graph of the patients' CD4 count with 95% CI versus mortality depicted 100% death in CD4 counts below 153 (Figure 1). The mean CD4 count was 193 ± 181 and the median was 128, while the average CD4 count at which death occurred was 128 ± 41. A graph of mortality versus the follow-up period revealed 50% of deaths occurring during the first four months of treatment with the mean at 6.11 months (Figure 2).

In order to cross-tabulate CD4 count and ADI, CD4 was divided into two categories of less than 200 and greater than or equal to 200. The analysis was significant (p-value 0.046) and demonstrated that for CD4 counts less than 200, the number of ADI cases is significantly higher than that for CD4 counts greater or equal to 200 (80.8% as opposed to 19.2%).

A cross-tabulation of HAART and mortality did not yield significant results (p-value 0.730). The same was true of the comparison of AE and mortality (p-value 0.278); however, it differed in that it showed that mortality in patients who developed AE was higher (38.8% as opposed to 23.3%).

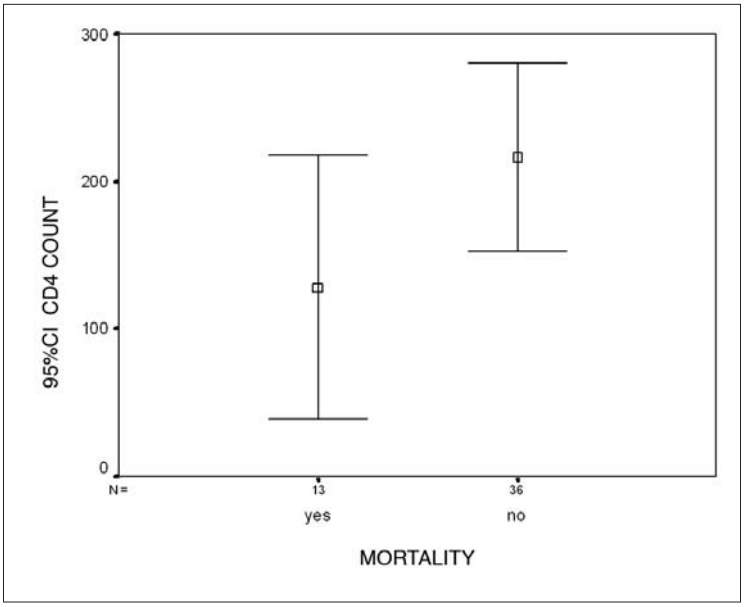

Figure 1. Error bar graph of CD4 count vs. mortality.

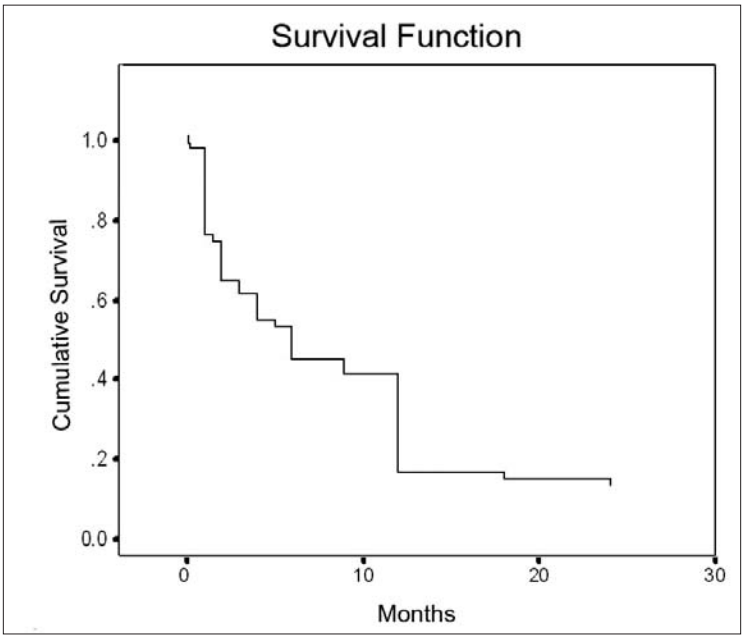

Figure 2. Kaplan-Meier analysis of survival versus followup time.

DISCUSSION

This study is the first report on the outcome of treatment of TB/HIV patients in Iran. Studies show that HIV-infected patients experience high mortality during and following treatment with two-thirds of deaths in TB/HIV patients occurring four years after the initial diagnosis of TB;[11] however, in this study, 50% of deaths occurred in the first four months of TB treatment, which is equivalent to 13.4% of all TB/HIV patients in the study. A total of 26.8% of the cases in the present study died at the end of the treatment period. A factor that could account for the difference in the rate of mortality of this study and that of the aforementioned study is the shorter follow-up period in this study (one year as opposed to four years). As other studies have shown that the use of HAART on TB/HIV patients causes significant reductions in mortality, it can be suggested that starting HAART early on patients can reduce the number of deaths[7, 8, 12-16] by increasing the capacity of the immune system and decreasing the risk of acquiring opportunistic infections.[17-19] Yet other reports have mentioned that if HAART is started at low CD4 counts, patients co-infected with HIV and TB may show minimal recovery of in vitro immunity to TB.[20]

In an unpublished two year follow-up study in Iran, the rate of mortality in new case, non-HIV patients was reported to be 3.5%, significantly less than the 26.8% mortality rate in the TB/HIV group of the present study. Some studies have stated that most of the deaths in TB/HIV cases occur in patients who have never received HAART or who have started it a few months prior to death.[21] The present study also confirmed this since the 13 cases who were receiving HAART had started treatment so late, it did not affect their rate of survival. The mean CD4 count at which patients started HAART was 137 ± 32 while the median was 120.

The median survival in this study was four months, significantly less than the median survival in a rural Ugandan cohort (4.5 years to 1.1 year)[22] and in Zaire (5.8 months),[21] yet it was higher than in Tanzania (less than three months).[23] Moreover, in the present study, 16.1% of patients died before the standard TB regimen period of six months concluded; however, in the study done by Dean et al., only 8.5% of their cases resulted

in death prior to successful completion of TB treatment.[24] It should be noted that many patients in the present study had progressive immunodeficiency and several simultaneous ADI. It should also be taken into consideration that this study was conducted in a referral center. This could result in a less representative sample with patients that have more chronic conditions. The same trend was observed in the study by Dean et al. where in CD4 counts less than 100, a higher percentage of patients developed a further ADI.[24]

Although we found that the rate of mortality was higher among patients who had AE, this result was not statistically significant. Yet other studies have also demonstrated similar results in HIV-positive patients (18-39%).[25] Moreover, some of these adverse effects could affect adherence, an essential factor in the treatment of HIV. The most common adverse effect observed in the study sample was hepatitis (14.3%), which can be explained as a side effect of the antiretroviral and antituberculosis drugs.

Even though the small sample size of this study has left many insignificant variables, such as ADI, and the study was conducted in only one referral center, it can still be concluded that starting HAART early for TB/HIV patients who have developed various ADI is essential. Furthermore, since 50% of deaths in the study sample occurred in the first four months of treatment, and the average CD4 count at which death occurred is 128 ± 41, it can be suggested that starting HAART early for TB/HIV patients whose CD4 count is less than 130 can decrease the rate of mortality.

1. Corbett EL, Watt CJ, Walker N Maher D, Williams BG, Raviglione MC, Dye C.. The growing burden of tuberculosis: Global trends and interactions with the HIV epidemic. Arch Intern Med. 2003; 163(9):1009-1021.

2. Sonnenberg P, Glynn JR, Fielding K, Murray J, Godfrey-Faussett P, Shearer S. HIV and pulmonary tuberculosis: The impact goes beyond those infected with HIV. AIDS. 2004; 18(4):657-662.

3. Lange C, Schaaf B, Dalhoff K. HIV and lung. Pneumologie. 2004; 58(6):416-427.

4. Marquardt T, Jablonowski H. Opportunistic diseases-current aspects in 2004. MMW Fortschr Med. 2004; 146 Spec No 1:34-6, 38.

5. Jones JL, Hanson DL, Dworkin MS, Alderton DL, Fleming PL, Kaplan JE, Ward J. Surveillance for AIDS-defining opportunistic illnesses, 1992-1997. MMWR CDC Surveill Summ. 1999; 48(2):1-22.

6. Fauci AS. The AIDS epidemic--considerations for the 21st century. N Engl J Med. 1999; 341(14):1046-1050.

7. Munsiff SS, Alpert PL, Gourevitch MN, Chang CJ, Klein RS. A prospective study of tuberculosis and HIV disease progression. J Acquir Immune Defic Syndr Hum Retrovirol. 1998; 19(4):361-366.

8. Pernerger TV, Sudre P, Lundgren JD, Hirschel B. Does the onset of tuberculosis in AIDS predict shorter survival? Results of a cohort study in 17 European countries over 13 years. BMJ. 1995; 311:1468-1471.

9. Jones JL, Hanson DL, Dworkin MS, DeCock KM, Adult/Adolescent Spectrum of HIV Disease Group. HIV-associated tuberculosis in the era of highly active antiretroviral therapy. The Adult/Adolescent spectrum of HIV disease group. Int J Tuberc Lung Dis. 2000;4(11):1026-1031.

10. Badri M, Wilson D, Wood R. Effect of highly active antiretroviral therapy on incidence of tuberculosis in South Africa: A cohort study. Lancet. 2002; 359(9323):2059-2064.

11. Van den Broek J, Mfinanga S, Moshiro C, O'Brien R, Mugomela A, Lefi M. Impact of human immunodeficiency virus infection on the outcome of treatment and survival of tuberculosis patients in Mwanza, Tanzania. Int J Tuberc Lung Dis. 1998; 2(7):547-552.

12. Sterling TR, Chaisson RE, Keruly J, Moore RD. Improved outcomes with earlier initiation of highly active antiretroviral therapy among human immunodeficiency virus-infected patients who achieve durable virologic suppression: Longer follow-up of an observational cohort study. J Infect Dis. 2003;188(11):1659-1665.

13. Ahdieh-Grant L, Yamashita TE, Phair JP, Detels, R, Wolinsky, SM, Margolick, JB, Rinaldo, CR, and Jacobson, LP. When to initiate highly active antiretroviral therapy: A cohort approach. Am J Epidemiol. 2003; 157(8):738-746.

14. Wood E, Hogg RS, Yip B, Harrigan PR, Montaner JS. Using baseline CD4 cell count and plasma HIV RNA to guide the initiation of highly active antiretroviral therapy. Rev Invest Clin. 2004; 56(2):232-236.

15. Hogg RS, Yip B, Chan KJ, Wood E, Craib KJ, O'Shaughnessy MV, Montaner JS. Rates of disease progression by baseline CD4 cell count and viral load after initiating triple-drug therapy. JAMA. 2001;286(20):2568-2577.

16. Phillips AN, Staszewski S, Weber R, Kirk O, Francioli P, Miller V, Vernazza P, Lundgren JD, Ledergerber B; Swiss HIV Cohort Study; Frakfurt HIV Clinic Cohort; EuroSIDA Study Group. HIV viral load response to antiretroviral therapy according to the baseline CD4 cell count and viral load. JAMA.2001;286(20):2560-2567.

17. Mocroft A, Katlama C, Johnson AM, Pradier C, Antunes F, Mulcahy F, Chiesi A, Phillips AN, Kirk O, Lundgren JD. AIDS across Europe, 1994-98: The EuroSIDA study. Lancet. 2000; 356(9226):291-296.

18. Palella FJ,Jr, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, Aschman DJ, Holmberg SD. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV outpatient study investigators. N Engl J Med. 1998; 338(13):853-860.

19. Ledergerber B, Egger M, Erard V, Weber R, Hirschel B, Furrer H, Battegay M, Vernazza P, Bernasconi E, Opravil M, Kaufmann D,Sudre P, Francioli P, Telenti A. AIDS-related opportunistic illnesses occurring after initiation of potent antiretroviral therapy: The Swiss HIV cohort study. JAMA. 1999; 282(23):2220-2226.

20. Hsieh SM, Hung CC, Pan SC,, Wang, JT, Tsai, HC, Chen, MY, Chang, SC. Restoration of cellular immunity against tuberculosis in patients coinfected with HIV-1 and tuberculosis with effective antiretroviral therapy: Assessment by determination of CD69 expression on T cells after tuberculin stimulation. J Acquir Immune Defic Syndr. 2000; 25(3):212-220.

21. Salinari RK, Filippo C, Claudio C. Preliminary survival analysis of AIDS data from Goma, Zaire. Trop Doct. 1990; 20(4):169-170.

22. Morgan D, Malamba S, Okongo M, Mayanja B, Maude G, Whitworth J. HIV Disease Progression and Median Survival Times in a Rural Ugandan Cohort. Int Conf AIDS. 1996 Jul 7-12; 11(235 abstract no. Tu.B.310)

23. Mbaga JM, Pallangyo KJ, Bakari M, Aris EA. Survival time of patients with acquired immune deficiency syndrome: Experience with 274 patients in Dar-es-Salaam. East Afr Med J. 1990; 67(2):95-99.

24. Dean GL, Edwards SG, Ives NJ, Matthews G, Fox EF, Navaratne L, Fisher M, Taylor GP, Miller R, Taylor CB, de Ruiter A, Pozniak AL. Treatment of tuberculosis in HIV-infected persons in the era of highly active antiretroviral therapy. AIDS. 2002; 16(1):75-83.

25. Pozniak AL, Miller R, Ormerod LP. The treatment of tuberculosis in HIV-infected persons. AIDS. 1999; 13(4):435-445.

Applying Directly Observed Therapy for TB/HIV Co-infections

The next logical step?

James Lee, Public Health Studies & Economics 2009

The co-epidemic of *Mycobacterium tuberculosis* (TB) and human immunodeficiency virus (HIV) remains an enormous and growing burden today. Of the 8.9 million new cases of TB worldwide, 13% of all new adult TB cases occurred in HIV-positive persons, with 11% of all new TB cases directly attributed to HIV.[1] The situation is especially alarming in Africa, where HIV is prevalent in 33% of new TB cases.[1]

While Alipanah and Novin's study published in this issue of *Epidemic Proportions* has recommended initiating Highly Active Antiretroviral Therapy (HAART) early for TB/HIV patients with T helper cell (CD4) counts of < 130/µl to reduce mortality, current guidelines by the American Thoracic Society, the Centers for Disease Control and Prevention, and the Infectious Diseases Society of America suggest delaying antiretroviral therapy until 4-8 weeks after starting anti-tuberculosis therapy for patients with CD4 cell counts of > 100/µl. HAART is only recommended for TB patients with CD4 counts of < 100/µl due to the advanced progression of HIV.[2] This recommendation was based on a study by Dean et al. in which overlapping drug toxicities, unfavorable drug-drug interactions, and high pill burden led to discontinuations and poor adherence in patients.[3] Thus, the decision of when to initiate HAART would ultimately reflect a balance between the risk of HIV progression, drug toxicity, and patient compliance.[4]

The clinical aspects of drug toxicity and HIV progression are beyond the scope of this journal. However, the most apparent tool to increase patient adherence in treating TB/HIV co-infections would be the use of directly observed therapy (DOT) for HAART as well as the TB treatment regimen. In the case of TB, DOT has been credited with improved outcomes and preventing drug resistance among its subjects and is currently the gold standard for TB treatment worldwide.[5] Current studies on DOT-TB in HIV-infected patients have demonstrated considerable evidence in its ability to cure TB and prevent relapse even without the use of antiretrovirals.[6, 7] But as Alipanah and Novin's study has confirmed, in the absence of antiretroviral therapy, mortality is substantially increased even after a successful DOT-TB course due to HIV-related diseases.[7]

"Published data on a combined DOT-TB/HAART course is non-existent to date."

In a recent literature review, Kwara et al. have argued that concurrent HAART and TB therapy is feasible though challenging.[4] Meanwhile, pilot studies on applying the DOT model to HIV treatment have provided encouraging signs for the DOT-HAART case in TB patients.[6, 8, 9] In these studies, directly observed therapy produced significant improvements in HIV treatment outcomes. However, due to major differences between the regimen for HIV and TB treatment, it is not a forgone conclusion that DOT-TB/HAART is an effective or even feasible course. HIV medications require daily or thrice-daily administrations, as opposed to the twice or thrice weekly doses of TB medications.[10] Also, the treatment of HIV as a chronic disease lasting a lifetime makes it significantly different from the six to nine month course of TB treatment.

Published data on a combined DOT-TB/HAART course is non-existent to date.[4] But, as its various components have been demonstrated to be practical (DOT-TB, DOT-HIV, concurrent HAART and TB-treatment), a strong case could be made for further, more rigorous studies in this course of treatment.

"... evaluations of cost-effectiveness and population benefits should be included ... expenditure in treating TB/HIV often represent tradeoffs in other programs – primary care, reproductive health, or even education."

In terms of patient mortality, DOT-TB/HAART could be expected to produce significant benefits by halting HIV progression while treating for TB. Given an effective DOT-TB/HAART program, HAART can thus be initiated earlier, as Alipanah and Novin suggested in their study. Improved patient compliance would be the most direct benefit derived from this course. An effective DOT-TB/HAART program could also significantly improve surveillance and response to drug toxicity and HIV progression, making the complications of concurrent regimens more manageable.

Indirect benefits and region-specific demands associated with DOT are also of significance here. Well-run DOT programs have frequently produced payoffs in the form of social support, reducing disease stigma, and providing connections to other needed social services and medical care. Furthermore, DOT has been demonstrated to be especially effective in reaching marginalized populations that otherwise would not receive care. In the Alipanah and Novin study where most HIV patients were intravenous drug users, a DOT course could produce substantial improvements in treatment outcomes.

While concerns over the long-term feasibility and outcomes of DOT-HIV remain valid despite the above-mentioned benefits, the option of DOT-TB/HAART for the 6 – 9 month period of TB treatment is worth exploring.

Lastly, evaluations of cost effectiveness and population benefits should be included in future considerations of DOT-TB/HAART courses. In resource-poor countries where TB/HIV co-infections are prevalent, expenditure in treating TB/HIV often represent tradeoffs in other programs – primary care, reproductive health, or even education. Concurrent HAART during TB treatment is especially costly

due to the high cost of protease inhibitors used in most clinical courses as well as the unavailability of selected antibiotics in certain countries. Potentially, the higher cost could be balanced by the economic benefits produced, such as the reduction of TB/HIV transmission, prevention of TB/HIV drug resistance, and other indirect benefits; however, this must be determined by future studies.

1. World Health Organization. WHO Report 2006 Global Tuberculosis Control Surveillance, Planning, Financing <http://www.who.int/tb/publications/global_report/2006/download_centre/en/index.html>. Accessed November 20, 2006. World Health Organization, Geneva, Switzerland, 2006.
2. American Thoracic Society, CDC, Infectious Diseases Society of America. Treatment of Tuberculosis <http://www.cdc.gov/MMWR/preview/mmwrhtml/rr5211a1.htm>. Accessed November 20, 2006. Centers for Disease Control and Prevention, Atlanta, GA, 2003.
3. Dean GL, Edwards SG, Ives NJ, Matthews G, Fox EF, Navaratne L, Fisher M, Taylor GP, Miller R, Taylor CB, de Ruiter A, Pozniak AL. Treatment of tuberculosis in HIV-infected persons in the era of highly active antiretroviral therapy. AIDS. 2002; 16(1):75-83.
4. Kwara A, Flanigan TP, Carter EJ. Highly active antiretroviral therapy (HAART) in adults with tuberculosis: Current status. Int J Tuberc Lung Dis. 2005; 9(3):248-257.
5. Weis SE, Slocum PC, Blais FX, King B, Nunn M, Matney GB, Gomez E, Foresman BH. The effect of directly observed therapy on the rates of drug resistance and relapse in tuberculosis. N Engl J Med. 1994; 330(17):1179-1184.
6. Farmer P, Leandre F, Mukherjee J, Gupta R, Tarter L, Kim JY. Community-based treatment of advanced HIV disease: Introducing DOT-HAART (directly observed therapy with highly active antiretroviral therapy). Bull World Health Organ. 2001; 79(12):1145-1151.
7. Connolly C, Reid A, Davies G, Sturm W, McAdam KP, Wilkinson D. Relapse and mortality among HIV-infected and uninfected patients with tuberculosis successfully treated with twice weekly directly observed therapy in rural South Africa. AIDS. 1999; 13(12):1543-1547.
8. Fischl M, Rodriguez A, Scerpella E, Mondroig R, Thompson L, Rechtine D. Impact of Directly Observed Therapy on Outcomes in HIV Clinical Trials. 7th Conf Retrovir Opportunistic Infect. 2000; 7(71):89.
9. Farmer P, Leandre F, Mukherjee JS, Claude M, Nevil P, Smith-Fawzi MC, Koenig SP, Castro A, Becerra MC, Sachs J, Attaran A, Kim JY. Community-based approaches to HIV treatment in resource-poor settings. Lancet. 2001; 358(9279):404-409.
10. Mitty JA, Stone VE, Sands M, Macalino G, Flanigan T. Directly observed therapy for the treatment of people with human immunodeficiency virus infection: A work in progress. Clin Infect Dis. 2002; 34(7):984-990.

Women and Public Health Inequality

Disproportionate susceptibility to TB/HIV co-infection

Halshka Graczyk, Public Health Studies 2010

Tuberculosis (TB) is the greatest curable infectious killer of women worldwide.[1] With 900 million women infected with TB, the disease remains responsible for 9% of female deaths worldwide between the ages of 15 and 44.[2] The greatest obstacle in eliminating TB globally lies in the high rate of co-infection with HIV. The synergistic effect of biological predispositions, cultural beliefs, and socio-economic burdens increases women's susceptibility to contract HIV, which provokes the rapid transmission and fatal progression of TB. Unfortunately, women experience a disproportionate burden of TB/HIV co-infection. With 14 million people co-infected and TB now remaining the leading killer of patients with HIV, innovative treatment initiatives are needed now more than ever to combat both of these deadly diseases.[3]

"With 14 million people co-infected and TB now remaining the leading killer of patients with HIV, innovative treatment initiatives are needed now more than ever to combat these deadly diseases."

Female susceptibility to co-infection defines itself through biological differences between male and female physiology and nutritional standards, which are further intensified through social constructs of third-world nations, such as widespread prostitution and the dynamics of refugee communities.

Anatomically, women are more vulnerable than men to HIV, regardless of their place of living or socio-economic status. Increased susceptibility to HIV in women is the result of larger genital tracts, especially in young girls whose reproductive tracts have not fully matured. A larger mucosal area exposed to various infectious agents during sexual intercourse allows for more efficient transmission of pathogens. In fact, due to an increased genital surface area**,** a woman remains more than twice as likely to be infected by an HIV-positive man as a man to be infected by an HIV-positive woman.[4] The immune systems of women living with HIV/AIDS become suppressed, which leaves them more vulnerable to highly opportunistic infections, such as TB. Thus, women between the ages of 15 and 24 are more likely to acquire tuberculosis than their counterparts, leaving them at a double disadvantage for co-infection of TB/HIV.[3] Physiologically and anatomically, women experience a burden of heightened vulnerability to sexually transmitted disease, thereby increasing their chances of co-infection due to immune suppression.

In addition to structural differences of the female body, the nutritional status of women remains inadequate in developing nations where malnutrition and starvation remain widespread, increasing the risk to develop TB. As frequent pregnancies place acute stress on the immune system, many impoverished women develop infectious diseases due to lack of nutrients during pregnancy and childbirth. Furthermore, studies have shown that the development of active TB disease from latent infection occurs more frequently in women than in men.[5] Women with nutritional deficiencies in vitamin D, iron, and zinc become more vulnerable in the progression of TB from infection.[6] Consequently, women in developing nations, prone to low body mass and malnutrition, are at a greater risk of transition from latent to infectious TB-poor nutritional status has been linked with the progression from tuberculosis infection to disease.

The main causes for increased female vulnerability to concomitant TB and HIV infection are disproportionately magnified because women in developing nations prove to be poor, less-educated, low-skilled, and unemployed. Women, in fact, represent 70% of the 1.3

billion people living in absolute poverty.[7] Many, desperate to earn a living, find no other choice than to engage in risky sexual behaviors, such as prostitution, in order to survive.[8] These social and cultural perceptions increase women's vulnerability to co-infection and risk of infectious diseases through silent coercion of unsafe behaviors. For example, a study carried out in India found 69% of females infected with TB would not discuss their disease with neighbors, while 15% of women reported they would face rejection by their families if their TB status was known.[7] These cultural stigmas keep women away from treatment facilities and greatly increase their risk of morbidity and mortality. A study in Vietnam determined that after recognizing TB-related symptoms, a woman's treatment was on average, delayed for two weeks than men's treatment.[9] When women do decide to receive treatment, sexual discrimination proves widespread since TB is perceived as largely a male disease.

"Female inequity in the public health world not only affects social practices or economic discrepancies, but also biological weakness, distinguishing HIV and TB co-infection as a blatantly sexist infectious duo."

In addition to forced prostitution and cultural stigmatization in the third world, women are uniquely affected by world conflict and feel the greatest impact from global health threats. Women suffer from unique health and emotional threats as a consequence of domestic wars and conflict. They often lose their home and family; are subject to gender-based violence including rape and sexual assault; sexual slavery; and chronic malnutrition. In a global society heavily affected by debilitating wars and racial conflict, refugees develop into a new and distinct group of people, burdened by their own hardships and individual struggles. Female refugees, who make up about 80% of the world's 37 million refugees, are much more susceptible to HIV/AIDS and other infectious diseases in such hostile environments.[10] For example, a United Nations study of Liberian refugee women residing in a Nigerian refugee camp demonstrated that forced migration contributes to increased incidence of both communicable and non-communicable diseases.[11] The forced proximity of refugees in camps potentially increases the transmission of TB. In addition, the absence of family in refugee camps forces women to depend on men, which can lead to rape, unwanted marriage or pregnancy, and forced prostitution, thereby increasing the risk of HIV and other sexually transmitted infections in women.

Where do we go from here? With this co-epidemic of HIV and TB on the rise, it is imperative that women's susceptibility to disease be addressed and mitigated. Unfortunately, cultural barriers mostly preclude the empowerment of women in developing nations, and we must realize that these cultural barriers will continue to exist in the future. What we *can* strive for are inclusive programs designed for the special health needs of and prevention strategies for girls and women. These programs, designed to promote gender equality, would provide adequate nutritional supplementation during treatment as well as preventive education in a stigma-free environment. As HIV infection is difficult to detect in women, many cases are only diagnosed at pregnancy or childbirth leaving women in the dark about their positive status.[10]

There is a need for increased awareness of women's increased susceptibility. In addition to readily available information and education regarding the prevention and supportive treatment of HIV and TB, efforts must be made to address the individual woman as the master of her destiny- to grant her the self-esteem that social inequities have stolen away. These programs should also offer support and therapy to enlighten women about their role in condom use, labor outside of the sexual trade, and empowerment in the acquisition of self-worth.

The brusque truth remains that women are at greater risk for co-infection with HIV and TB, and preventive measures must be taken to alleviate this disproportionate burden. Female inequity in the public health world not only affects social practices or economic discrepancies, but also biological weakness, distinguishing HIV and TB co-infection as a blatantly sexist infectious duo. Our next steps in the global battle of TB eradication must focus on the vulnerability of women in order to provide them with equality on the public health playing field.

1. World Health Organization. Tuberculosis (fact sheet) <http://www.who.int/mediacentre/factsheets/fs104/en/>. Last revised March 2006. Accessed December 1, 2006. World Health Organization, Geneva, 2006.
2. RESULTS. TB — A Leading Killer of Women <http://www.results.org/website/article.asp?id=2090>. Accessed October 21, 2006. 2006.
3. Stop TB Partnership. Women, TB and HIV <http://www.stoptb.org/news/archives/iacxv/assets/InfoPack/6GB.pdf>. Accessed October 20, 2006.
4. Ackermann L, de K. Social factors that make South African women vulnerable to HIV infection. Health Care Women Int. 2002; 23(2):163-172.
5. Holmes CB, Hausler H, Nunn P. A review of sex differences in the epidemiology of tuberculosis. Int J Tuberc Lung Dis. 1998; 2(2):96-104.
6. Bates I, Fenton C, Gruber J, Laloo D, Lara AM, Squire SB, Theobald S, Thomson R, Tolhurst R. Vulnerability to malaria, tuberculosis, and HIV/AIDS infection and disease. part II: Determinants operating at environmental and institutional level. Lancet Infect Dis. 2004; 4(6):368-375.
7. Glynn JR, Carael M, Auvert B, Kahindo M, Chege J, Musonda R, Kaona F, Buve A. Why do young women have a much higher prevalence of HIV than young men? A study in Kisumu, Kenya and Ndola, Zambia. AIDS. 2001; 15 Suppl 4:S51-60.
8. Twigg J, Bhatt M. Understanding vulnerability: An introduction. Understanding Vulnerability: South Asian Perspectives. 1998.
9. Long NH, Johansson E, Diwan VK, Winkvist A. Different tuberculosis in men and women: Beliefs from focus groups in Vietnam. Soc Sci Med. 1999; 49(6):815-822.
10. Farmer P. Infections and Inequalities: The Modern Plagues. Berkeley, CA: University of California Press, 1999.
11. Bennett T, Bartlett L, Adewumi O, Amowitz L. Refugees, forced displacement, and war. Emerg Infect Dis. 2004; 10(11):2034-2035.

The History of HIV/AIDS in Iran: from a Long Denial to Breaking the Silence

Pioneering HIV/AIDS awareness and prevention in Iran

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The clear beginning of HIV/AIDS history in Iran is unknown. In this paper, we will detail the evolution of HIV/AIDS recognition in Iran, from the cells of Kermanshah's prison, in Western Iran.

Iran is a Middle-Eastern country in southwest Asia with a population of 68,000,000. The great majority of Iranians are Muslims, and 89% belong to the Shi'a branch of Islam. Iran has a young population with greater than 70% under the age of 30. Iran is a major transit route for opiates harvested in neighboring Afghanistan. Consequently, opiate (mainly opium and heroin) addiction has long historical roots in Iran. According to the latest figures, at least four million of the population are opiate users, the highest number in any country in the world. Among the intravenous (IV) heroin users in Iran, needle exchange is notoriously common, and consequently, infections transmitted via dirty needle exchange, including HIV and hepatitis, are expected to be highly prevalent in this population.

> "When the rest of the world was struggling with the threats posed by the newly discovered virus in the late eighties and the early nineties, Iranian officials associated the infection with tainted blood that was imported from the 'sinful' West."

Like in most Muslim, Middle Eastern countries, HIV/AIDS topics were long taboo and disregarded in Iran. When the rest of the world was struggling with the threats posed by the newly discovered virus in the late 1980s and the early 1990s, Iranian officials associated the infection with tainted blood that was imported from the "sinful" West. In fact, during this era, the only publicized HIV/AIDS cases in Iran were known to be patients, mainly with blood dyscrasias, who had received HIV infected blood transfusions.

Eventually, in 1995, a group of scientific experts, considering the new international discoveries regarding HIV transmission modes and the already known high prevalence of IV drug use and needle exchange in Iranian prisons, asked the permission of state officials to perform a random HIV screening in various prisons in the country. The experts were shocked by the high prevalence of HIV infection they discovered in the prisons. One of the prisons chosen for the random screening was the Kermanshah's prison. Alarmed by the high prevalence of HIV in this prison, one member of Kermanshah's provincial parliament proposed the establishment of the first comprehensive HIV/AIDS hospital to the Iranian National Parliament (Majlis). Soon after the public announcement of his proposal, the streets of Kermanshah were flooded with angry demonstrators protesting the establishment of such hospital in their home province, fearing the transformation of Kermanshah into the home for "AIDS people." As a political consequence of his call for action, the said member of the parliament was not re-elected for office. After the public reaction in Kermanshah, the HIV/AIDS dilemma in prisons were again ignored for a few more years.

In 1999, two recent medical graduates from Isfahan and Shahid Beheshti Universities in Tehran convinced the Ministry of Health to allow them to complete their compulsory rural internship on HIV/AIDS in the province of Kermanshah. Arash and Kamiar Alaei were natives of Kermanshah, and through working with an infection disease specialist in Tehran, had become interested in HIV/AIDS. Furthermore, they were aware of the HIV screening results in Kermanshah's prison. Once in Kermanshah, Arash and Kamiar asked the Director of Public Health of Kermanshah to lend them a small room in a busy polyclinic affiliated with the University of Kermanshah, in the provincial capital. There, they established the first multidimensional clinic for HIV/AIDS in Iran with the contribution of Kermanshah Department of Health. At the beginning, while actively recruiting patients from the prison, the volunteer medical doctors found out that the number one cause of death amongst HIV positive patients in their home province was suicide within a year after diagnosis. The high suicide rate was attributable to the enormous sense of helplessness, fear of social stigmatization, and social isolation that these patients experienced shortly after their diagnosis. In an attempt to prioritize "need-based" services at their clinic, the two doctors started to offer psychosocial and educational counseling to HIV patients and their families, at the clinic during the day and at patients' houses at night. After six months, the reputation of their clinic became widespread and they had about 80 patients a day at the clinic. At this time, the health officials of the province became aware of a "popular" HIV counseling clinic, affiliated with the

University of Kermanshah. The provincial director of the Center for Disease Management provided their clinic with a financial grant and a fixed supply of general medications, as an incentive for their positive local impact. Using additional charitable funds, the doctors were able to expand their services from education and counseling to general medical care of HIV patients, including mother and child HIV screening and general care. The young doctors further lobbied for the support of provincial policy makers and religious authorities to upgrade their local pilot program for HIV patients to the provincial level, including the introduction of far-reaching HIV "harm reduction" strategies (mainly for IV drug users). Their lobbying efforts, eventually, resulted in the establishment of the first "triangular HIV clinic" in Kermanshah's prison, focusing on drug addiction, HIV/AIDS, and other sexually transmitted infections (STIs). The immediate and successful achievements of this newly established "triangular HIV" clinic in Kermanshah's prison were presented by the Iranian Minister of Health at the Middle Eastern AIDS Conference in Beirut in 2000. The policy makers from the Middle East region appeared impressed by Iran's pioneering HIV harm reduction strategies in the region, and congratulated the Health Minister. Shortly after this international encouragement, the Iranian Ministry of Health collaborated with the two doctors to expand the triangular clinics to prisons across Iran. As a result, to this day, there are 45 functional prison triangular clinics, nationwide. Moreover, as the HIV/AIDS "role model" in the region of Central Asia and the Middle East, Iran sponsors complimentary HIV training courses for healthcare professionals from the region.

The latest breakthrough in the ever-evolving journey of Iran with respect to HIV/AIDS has been the active engagement of the country's conservative judicial branch to amend the current laws which criminalize drug-users. Such amendments are hoped to facilitate the provision of HIV/AIDS education, counseling, and medical care for the vulnerable drug users, outside the prisons.

Iran, indeed, has become an exemplary country in the Middle East and Central Asia in providing HIV/AIDS services for the prisoners and the drug-addicted population. Still, the country has a long way to go to assure comprehensive and right-based HIV/AIDS care for all its citizens, especially the vulnerable and the historically marginalized. As noted in the brief summary presented, active involvement of policy makers, religious authorities, healthcare workers, and most importantly, "real" people in the society, is essential in securing current developments and ensuring further achievements in the field.

We should acknowledge the great help and support of our colleagues in Triangular clinic in Kermanshah who helped us to establish and promote the first Triangular clinic in Iran, documented by WHO/EMRO as "Best Practice Model."

With special thanks to Kianoush Dehghan, MD, MPH.

Dealing with Cancer Susceptibility: Research, Innovation, and Ethics

A case manager examines a mammogram.
PHOTO- *Courtesy of Dr. Helzlsouer*

Gauging Cancer Susceptibility

The effect of topoisomerase II on human lymphocyte radiosensitivity

Teddy Holzer, Post-Baccalaureate

Background: Cancer is characterized by uncontrolled cell division, which can lead to benign or malignant tumor growth. The topoisomerase proteins (I and II) are essential in the process of transcription. Transcription describes the process in which DNA is transformed into mRNA, which leads to the formation of proteins.

Methods: In this study, the effect of topoisomerase, a protein necessary for proper replication of DNA, was examined by exposing the Topo cell lines to irradiation and quantifying the aberrations induced by a micronucleus assay.

Results: The results of this study indicate that topoisomerase II activity affects the induction of chromosomal aberrations, which in turn, can lead to cancer.

Conclusions: Damage to DNA, the hereditary molecule, which carries genetic information, is directly linked to cancer susceptibility.

According to statistics published by the American Cancer Society, over half a million people will die of cancer this year in the US alone, and another 1.4 million will develop the disease.[1] While certainly dismaying, these statistics actually represent an almost rosy picture compared to that of 25 years ago. Since then, average cancer survival rates have increased from 51 to 66%, with statistically significant improvements for nearly every type of tumor.[1] The five-year survival rate for prostate cancer, for example, is now approaching 100% for early-and mid-stage tumors.

So what have we been doing right, and how can we ensure that positive trends continue over the next quarter of a century? The improvements seen to date are a direct result of advances in cancer detection and treatment. Technologies such as magnetic resonance imaging (MRI) have revolutionized the way cancers are observed, leading to earlier detection and better surgical outcomes. Increased public awareness has made screening programs more effective, while new chemotherapy drugs, aimed at biochemical targets specific to cancer cells, are better able to shrink tumors with fewer intolerable or life-altering side effects.

Nevertheless, these factors alone will not be sufficient to eradicate cancer as a major cause of death in the developed world. One reason is that the costs of the technologies described above are already straining the health system. The National Institutes of Health (NIH) estimate that the total monetary cost of cancer in the US reached $210 billion in 2005, with over $50 billion of that spent on treatment. Unchecked demand for cancer drugs, combined with aggressive pricing by pharmaceutical and biotech companies, ensures that the cost of new treatments increases exponentially (some cancer drugs, such as Genetech's Avastin, already cost $100,000 per patient per year). The result is that Americans are now paying heavily for drugs that are often only marginally better than old ones.

Given the fact that over 40 million Americans are already without health insurance, and that the cost of coverage is rising at nearly double the rate of inflation,[2] there is a serious possibility that many individuals will not be able to afford new therapies. Thus, in order to ensure that the rate of cancer deaths continue to decline, it is necessary to improve prevention alongside detection and treatment. To date, preventive measures have been predominately limited to public awareness campaigns against a known carcinogen. The reduction in smoking and the associated reduction in lung cancer rates in the US stand as an obvious success story.

Besides preventive measures, more information is needed regarding genetic predispositions to cancer. We can currently tell a patient with a family history of breast or prostate cancer a risk factor for developing that disease. We can even tell a patient the risk factor associated with a certain mutation or genetic variation. What we cannot do is look at a patient's genome and predict with any degree of accuracy the probability that he or she will develop new mutations that might lead to cancer.

Yet, in the not-too-distant future, it may be possible to do just that. One study indicated that 40% of breast cancer patients show elevated sensitivity to irradiation.[3] These patients also displayed an abnormally high level of macroscopic chromosomal aberrations, which presumably increase the probability of a cancerous mutation. If we can discover the mechanism behind this elevated sensitivity, it might be possible to find genes that contribute to these mutations.

Cancers result from a breakdown in the normal balance between cell growth and cell death. We know that genetic alterations that 'turn on' cancerous genes and 'turn off' helpful ones are the underlying cause of this breakdown. These alterations can include local errors such as point mutations, base substitutions, and base deletions, or may include larger alterations at the level of the chromosome or chromosome structure. Chromosomal aberrations, as they are known, result from DNA double-strand breaks (DSBs) that may be induced by irradiation or DNA-damaging chemical agents (in fact, many chemotherapeutic agents work by preferentially inducing DSBs in cancer cells).

If these DSBs are not quickly repaired, they can go on to form aberrations in which DNA from one region reattaches to DNA from another region, resulting in the translocation of genetic material or the formation of chromosome rings. Since the initial discovery and classification of these mutations in the 1930s,[4] it was assumed that this process occurred according to a simple 'breakage and mis-reunion' model. According to this model, four chromosome ends resulting from two DNA breaks are rejoined incorrectly, resulting in the migration of genetic material.

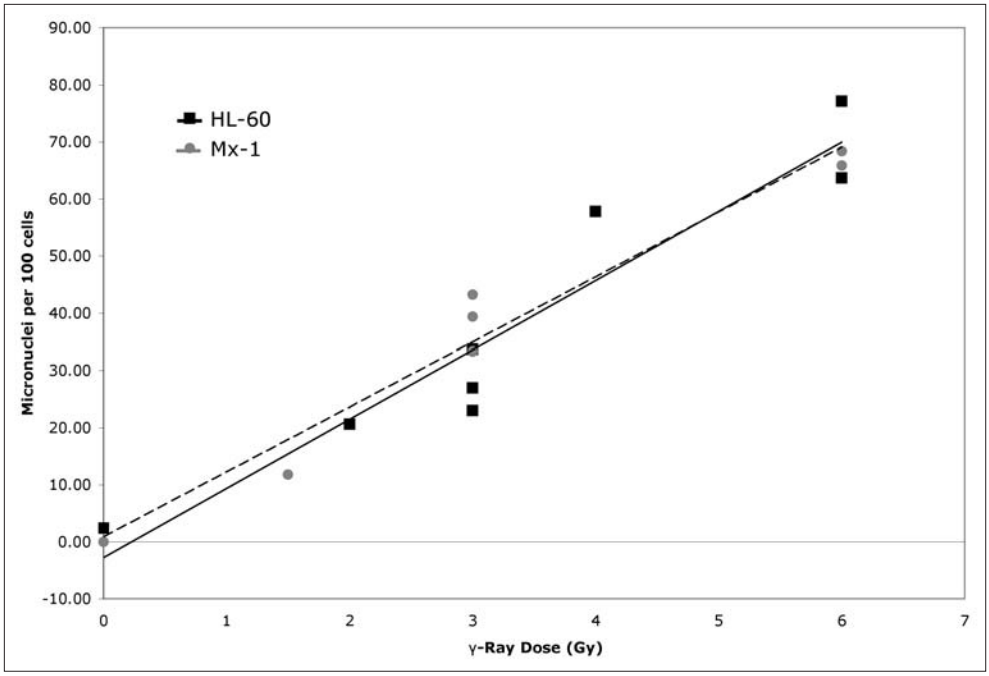

Figure 1. Micronucleus frequency graphed against gamma-ray dose for HL-60 (SHAPE) and Mx-1 (SHAPE) cells. Both cell lines show a positive dose-response, with more micronuclei at higher doses. R^2 values for the HL-60 (0.91) and Mx-1 (0.96) trendlines indicate that this dose-response is linear, and the trendlines are accurate. The HL-60 and Mx-1 trendlines have similar slopes (12.1 and 11.4, respectively), indicating a roughly equal sensitivity to IR-induced micronuclei.

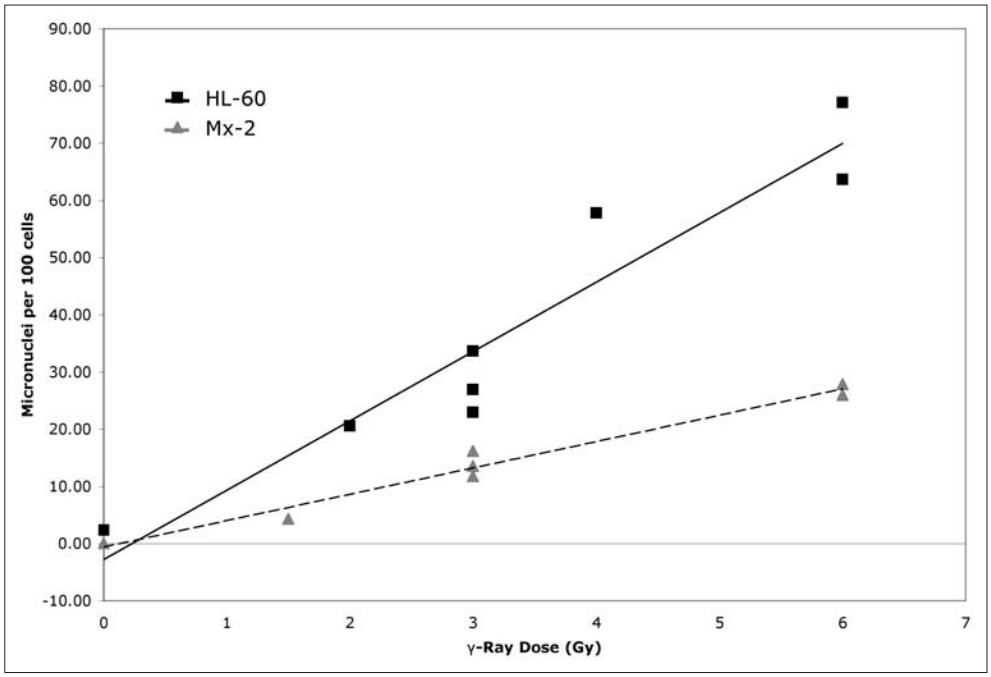

Figure 2. Micronucleus freqency graphed against gamma-ray dose for HL-60 (SHAPE) and Mx-2 (SHAPE) cells. Again, both cell lines show a linear dose-response (R2 values of 0.91 and 0.97, respectively). However, the Mx-2 dose-response curve has a lower slope compared to the parent HL-60 cell line (4.61 and 12.1, respectively). Thus, Mx-2 shows a more than 2-fold lower sensitivity to IR induced micronuclei.

There is increasing evidence, however, that this model does not accurately describe the induction of aberrations.[5,6] The preponderance of data suggests that one, not two, DNA breaks are sufficient to induce chromosome aberrations. As a result, a number of competing mechanisms have been proposed to describe aberration induction.[7-9] Each of these models makes predictions about the type and frequency of aberrations under varying conditions.

Radford's 'transcription-based' model represents one such attempt to explain aberration induction. It suggests that two proteins, topoisomerase I and II (topo-I and topo-II) play important roles. Topo-I and topo-II are proteins with numerous functions that are essential to the survival of almost every living cell. In short, they serve to 'untangle' DNA, facilitating the transcription of mRNA and maintaining a usable chromosome structure. In Radford's model, topo-I catalyses the formation of chromosome aberrations directly, while topo-II has a more indirect role via its function in mRNA transcription.

Thus, it should be possible to confirm or deny Radford's proposed model by examining the effect of varying topo-I and topo-II levels on aberration formation. Here, we assess aberration formation in cell lines with differential topo-II activity. The results will then be discussed within the context of cancer susceptibility and individual variations in radiosensitivity, with an aim toward identifying future areas of promising research.

METHODS

In order to examine the effect of topo-II on the induction of chromosome aberrations, we exposed three topo-II-variant cell lines to doses of γ-irradiation (measured in Greys, abbreviated Gy). The parent Human Leukemia cell line (HL-60) displays normal topo-II activity, while the derived Mx-1 and Mx-2 cell lines display markedly reduced topo-II activity. (The Mx-1 and Mx-2 cell lines were created in the 1980s by exposing HL-60 cell lines to mitoxantrone, a chemotherapy drug that kills cells via topoisomerase, and selecting for resistant cells).[10]

If topo-II is involved in the formation of chromosome aberrations, then the Mx-1 and Mx-2 cell lines should show fewer irradiation-induced aberrations than the HL-60 control line. To quantify the number of induced aberrations, we used a micronucleus assay.[11] Micronuclei, formed when a large portion of DNA (in this case the chromosome aberration) 'breaks off' from the chromosome and is enveloped by a nuclear membrane, prove to be directly proportional to the number of chromosome aberrations.

However, the formation of micronuclei remains dependent upon passage through mitosis, which may lead to an inaccurate picture of aberration formation, as the differential rate of division between two cell lines could give a false positive result. It is therefore necessary to count micronuclei either in qui-

escent cells or in cells that have undergone a known number of divisions post-irradiation.

This task, achieved by adding cytochalasin B at the time of irradiation, inhibits the separation of the two daughter nuclei formed during mitosis, resulting in one anucleate cell and one binucleate cell. When the binucleate cell passes through mitosis again, the two nuclei divide to form a cell with four nuclei, making it possible to visually 'count' cell divisions under the microscope. By counting micronuclei only in binucleate cells, it is possible to eliminate cell-cycle time as a cause of variations in micronuclei frequency.

Each of the three cell lines was exposed to increasing doses of γ-irradiation and the resulting frequency of micronuclei scored using a rigid set of criteria (the criteria are meant to unambiguously define what can be classified as a micronucleus. The criteria used in this study may be different from those used in other micronucleus assays, and thus data from other research are not directly comparable with data presented here). Multiple doses of irradiation allowed for the production of dose-response curves, presented in Figures 1 and 2.

RESULTS

Exposure to varying doses of γ-irradiation yielded linear dose-response curves for each cell line. While the dose-response curves for Mx-1 and the control line HL-60 were statistically identical, the slope of the Mx-1 curve was half that of Mx-1 and HL-60. This difference indicates that Mx-2 cells are resistant to irradiation-induced aberration formation.

To further quantify the significance of the observed differences in radiosensitivity, a two-sample t-test was performed on the data. The datasets from all three cell lines showed a normal distribution and approximately equal variances, allowing for the application of the t-test. At 3 Gy, the t-test found no significant difference between the frequency of HL-60 and Mx-1 micronuclei ($P = 0.064$, $P > 0.05$). However, at this dose, a significant difference was observed between HL-60 and Mx-2 ($P = 0.014$, $P < 0.05$). Thus, the data support a reduced sensitivity to chromosome aberrations in the topoisomerase variant Mx-2 cell line.

In addition, several other differences (not presented or discussed here) were observed in the response to irradiation by the three cell lines. Mx-1 and Mx-2 cells displayed significantly reduced levels of basal apoptosis as well as irradiation-induced apoptosis. Furthermore, while all three cell lines showed increased cell-cycle transit time following irradiation, this effect was more substantial for the Mx-1 and Mx-2 cells.

DISCUSSION

The results of the micronucleus assay performed on HL-60, Mx-1, and Mx-2 cells indicate that topoisomerase II may play a significant role in the cellular response to irradiation. As mentioned, Radford's transcription-based model for the induction of chromosome aberrations suggests that topoisomerase activity may affect the frequency of these irradiation-induced aberrations.[9] The model predicts a specific role for topo I in the formation of DNA double-strand breaks (DSBs), the lesions that mediate the mutagenic effects of irradiation.[9] These DSBs would then be converted into the observed large-scale chromosomal perturbations during mRNA transcription. As topo II is known to facilitate transcription,[9, 12] it is likely that the level of topo-II activity in a cell would affect the number of 'Radford-like' chromosomal events.

Thus, the reduction in aberrations observed following irradiation of Mx-2 cells may support a transcriptionally based mechanism such as Radford's, though it must be noted that while the data suggest aberration formation is linked to transcription, the data do not support Radford's model in its entirety. The model requires that topoisomerase I catalyzes the conversion of a single DSB into the macroscopic chromosome aberrations observed in irradiated cells, though the three cell lines display equivalent topo-I activity.[10] Therefore, this aspect of Radford's model cannot be studied in this context.

Before accepting the data presented here as evidence for topo-II's role in chromosome aberration formation, it is necessary to explain the fact that a significant reduction in aberration induction was observed in Mx-2 but not in Mx-1 cells. Both cell lines show reduced topo-II activity and would be expected to yield fewer aberrations if induction is linked to transcription. This differential induction of aberrations in Mx-1 and Mx-2 cells could be a reflection of the different topoisomerase variations characteristic of the two lines (the ratio of topo-II α and ß subtypes, as well as the timing of topo-II expression are different in each cell line).[10] It could also indicate, however, that the observed differences in aberrations are the result of other, non-topo-II- related differences between the cell lines. Indeed, the manner in which the cell lines were derived by selection for resistance to topo-II poisons suggests the possibility that yet uncharacterized mutations in Mx-2 caused the reduction in observed aberrations.

To eliminate this potential explanation for reduced Mx-2 radiosensitivity, a more targeted reduction in topo-II levels may be needed (e.g. by siRNA knockdown). In addition, exposing the three cell-lines to low doses of α-amantin, which is a compound isolated from poisonous mushrooms that inhibits transcription, could test whether reduced transcription is in fact responsible for the observed reduction in aberration induction.

If these experiments confirm the hypothesis presented here, suggesting that topoisomerase affects the induction of aberrations via transcription, it may be possible to develop cancer susceptibility assays based on the genes involved in this process. As mentioned above, recent studies indicate that 40% of breast cancer patients display elevated radiosensitivity.[3] The authors of this study also suggest that the reason the genes responsible have not yet been linked to cancer is that there are many genes acting in sum to alter the frequency of aberration induction in these cancer patients. Each gene has only a small affect on cancer susceptibility, making them difficult to find by whole-genome studies. Therefore, a better understanding of the mechanisms by which aberrations are induced will be necessary to guide research toward genes likely to affect the formation of cancer-causing mutations.

Indeed, knowledge of these mechanisms may have other benefits in the fight against cancer. Even if we cannot develop accurate cancer susceptibility assays, it may be possible to reduce the induction of aberrations in patients with other known risk factors, or to differentially affect aberration induction in tumor and host cells during radiation therapy. This would serve to increase the death of cancer cells while reducing that of host cells. In addition, a better understanding of aberration induction may lead to better radiosensitivity assays which could in turn predict which patients would experience adverse reactions to radiation treatment before treatment commences.

Thus, the effect of topoisomerase II on the induction of chromosome aberrations described here, in coordination with further research into the mechanisms of aberration induction, provide excellent opportunities for improvements in both cancer prevention and treatment.

1. American Cancer Society. Cancer Facts and Figures 2006. Atlanta, GA: American Cancer Society, 2006.
2. The Kaiser Family Foundation. <www.kff.org/uninsured/kcmu101906pkg.cfm>. Accessed November 7, 2006. The Kaiser Family Foundation, Menlo Park, CA, 2006.
3. Scott D, Barber JB, Spreadborough AR, Burrill W, Roberts SA. Increased chromosomal radiosensitivity in breast cancer patients: A comparison of two assays. Int J Radiat Biol. 1999; 75(1):1-10.
4. Sax K. An analysis of X-ray induced chromosomal aberrations in tradescantia. Genetics. 1940; 25(1):41-68.
5. Rogers-Bald M, Sargent RG, Bryant PE. Production of chromatid breaks by single dsb: Evidence supporting the signal model. Int J Radiat Biol. 2000; 76(1):23-29.
6. Thacker J, Wilkinson RE, Goodhead DT. The induction of chromosome exchange aberrations by carbon ultrasoft X-rays in V79 hamster cells. Int J Radiat Biol Relat Stud Phys Chem Med. 1986; 49(4):645-656.
7. Chadwick KH, Leenhouts HP. The rejoining of DNA double-strand breaks and a model for the formation of chromosomal rearrangements. Int J Radiat Biol Relat Stud Phys Chem Med. 1978; 33(6):517-529.
8. Bryant PE. The signal model: A possible explanation for the conversion of DNA double-strand breaks into chromatid breaks. Int J Radiat Biol. 1998; 73(3):243-251.
9. Radford IR. Transcription-based model for the induction of interchromosomal exchange events by ionizing irradiation in mammalian cell lines that undergo necrosis. Int J Radiat Biol. 2002; 78(12):1081-1093.
10. Harker WG, Slade DL, Drake FH, Parr RL. Mitoxantrone resistance in HL-60 leukemia cells: Reduced nuclear topoisomerase II catalytic activity and drug-induced DNA cleavage in association with reduced expression of the topoisomerase II beta isoform. Biochemistry. 1991; 30(41):9953-9961.
11. Kirsch-Volders M, Elhajouji A, Cundari E, Van Hummelen P. The in vitro micronucleus test: A multi-endpoint assay to detect simultaneously mitotic delay, apoptosis, chromosomal breakage, chromosome loss and non disjunction. Mutat Res. 1997; 392(1):19-30.
12. Zini N, Martelli AM, Sabatelli P, Santi S, Negri C, Astaldi Ricotti GC, Maraldi NM. The 180-kDa isoform of topoisomerase II is localized in the nucleolus and belongs to the structural elements of the nucleolar remnant. Exp Cell Res. 1992; 200(2):460-466

EDITORIALS

Genetic Testing
Is it everyone's crystal ball?

Liana Senaldi, Public Health Studies & Spanish 2010

Unraveling a patient's genetic information offers opportunities to predict, diagnose, treat, and prevent disease in ways never before imagined. Genetic testing has the potential to radically change the way our healthcare system works. Doctors would be able to start predicting and preventing diseases instead of waiting until the onset of disease to treat a patient. But the real questions are what would the patient want, and what would they do? How would people react emotionally if they were to know years in advance they were at risk for a deadly or debilitating illness?

A Harris Poll, an independent opinion poll established by Harris Interactive, conducted among a national cross section of 1,013 adults found that people's interest in having genetic testing varies substantially depending on whether there is a treatment or strategy of prevention available for the disease.[1] Among those who were interested in being screened for a serious disease, participants said they would be willing to spend a median price of $300, given an available and effective treatment.[1]

Although genetic testing can benefit the individual and society by determining genetic predispositions to diseases, it also has the precarious capability to lessen the personal quality of life through stress and depression. It may also expose the individual to discrimination through the invasion of privacy. Fears of genetic testing have been expressed by some people for several years; a case in point is testing for rare genetic diseases like Huntington's disease. A parent who suffers from Huntington's disease, a degenerative disorder of the nervous system, has a 50% chance of passing the deadly gene to his or her offspring. Researchers at Johns Hopkins University have found that people rarely seek testing, since there is no definitive treatment for the disease.[2] Positive test results have been found to lead to major depression among adults.

While Huntington's disease is confined to families with a history of the condition, cystic fibrosis (CF) can occur in persons with no CF in their pedigree. When a genetic test for CF became available in 1989, studies were proposed to look at its acceptance among both afflicted families and the general public before the test was widely offered. The screening procedure involved testing a population to select people at risk for an unfavorable health outcome.[2] Such individuals would undergo further investigation, monitoring, and treatment. Results indicated that people did not readily take advantage of their opportunity to be tested for cystic fibrosis.[2]

> "Insurance companies and HMOs would be very interested in knowing the risk factors of a potential enrollee. If the medical provider determines that a person is at high risk for a disorder, that person would be considered a 'bad bet.'"

Although people may have mixed emotions about testing for genetic predispositions, there are other entities interested in knowing this information. Insurance companies and HMOs would be very interested in knowing the risk factors of a potential enrollee. If the medical provider determines that a person is at high risk for a disorder, that person would be considered a "bad bet." The provider would not cover that person, or if they were already insured, the payments could become excessive. Alternatively, the provider may disallow the potential disease from coverage.

An example of financial versus medical decisions, inherent in a third party payer system, is the scenario encountered by a woman who was tested for genetic breast cancer mutations.[3] Testing indicated that she had a 90% chance of developing breast cancer. The

woman wanted both of her breasts removed immediately. Before she had the operation, she submitted a claim to her insurance company, not disclosing that she had the mutations, but reporting that there was a strong family history of breast cancer. The insurance company turned her down on the grounds that it did not pay for preventive medicine and it would not pay for the surgery because, "she had a pre-existing condition—a genetic defect—when she took out her health policy." The woman had the surgery anyway. When the pathologists examined the woman's breast tissue, they found a cancerous tumor, which had been missed by mammograms.[3] Cases like this and fears of similar treatment by insurance companies are convincing some women and researchers that it might be too dangerous to put testing results on medical charts and in clinical records, where privacy cannot be assured. The Health Insurance Portability and Accountability Act (HIPAA) provides some protection from discrimination. However, gaps remain in the current system, which does not explicitly prohibit the use of genetic information as a basis for charging a group more money for health insurance. Also, the act does not limit the disclosure of genetic information by insurers.

Information discovered through genetic tests could also lead to discrimination in the workplace. If an employer, who is paying health benefits for workers, discovers that a potential candidate may be subject to developing a disease, the employer may be less likely to hire that worker. That individual may increase the employer's premiums and may also raise those of the other existing employees. In addition, the employer may not want to invest in employee training for complex employment functions if the employee is at risk of developing a disease like Huntington's disease.

Another group within society that has an interest in this issue is the patient's family. Genetic testing may have implications for other members of the family. One of the most controversial issues is the duty to inform. What happens if a patient does not want to tell his or her family about a diagnosis? Does the patient have an obligation to do so? Does the fear of being personally ostracized outweigh the potential prevention of disease in other family members?

Witness the issues surrounding HIV testing in the mid 1980s. At that time, when AIDS became part of the national consciousness, it was considered a disease of bathhouses and crack dens—which quickly became labeled a "gay disease" or a "junkie problem."[4] Consequently, once the test for HIV became available, many people didn't want to be tested because if they were found to be positive, public health officials would dictate that they notify all sexual partners. This could easily be problematic. For example, a man who is married and becomes HIV-positive after having an affair would not want to tell his wife about the affair out of shame and embarrassment. It is likely that he would not want to be tested, even though he knows he is potentially putting his wife at risk.

A traditional public health approach to screening regards the population benefits of reduced morbidity and mortality as inherent.[3] However, the new advances in science and biotechnology are raising many ethical and moral dilemmas for everyone. Do society's rights outweigh those of the patient? Do patients have an obligation to practice modes of disease prevention once they know they are at risk? If they don't, does society have to pay for treatment? Unfortunately, genetic testing isn't as easy as gazing into a crystal ball. Genetic testing may provide information about a biological condition, but it can also lead to emotional and financial consequences, as well as discrimination. It is important that any person who is considering genetic testing understand and weigh these factors before making a decision.

1. Taylor H, Leitman R. If genetic tests were available for diseases which could be treated or prevented, many people would pay to have them: But what about privacy? and the cost of treatment? The Harris Poll. 2002; 2:1-5.
2. Lehmann L, Weeks JC, Klar H, Biener L, Garber JE. Disclosure of familial genetic information: Perceptions of the duty to inform. The American Journal of Medicine. 2000; 109:705-711.
3. Broesskamp-Stonek U, Plunger P. Track 4: Workshop: Positioning health promotion and prevention within public health-challenges and pitfalls. European Journal of Public Health. 2005; 15:63-64.
4. Pennington R. AIDS: The Epidemic in Alabama <http://www.wbhm.org/News/2006/AIDS_The_Epidemic_in_Alabama.html>. Accessed October 23, 2006. 2006.

A Physician's Dilemma

How to diagnose patients and tell them they have cancer

Akash Bhatnagar, Public Health Studies 2008

The patient is a young 16-year-old girl who has just undergone screening for skin cancer by you, her doctor. From the positive results of the screening test, you conclude that the teenager has stage III melanoma and is slowly advancing to stage IV. The five-year survival rates of stage III and IV melanoma are below 30%.[1] The parents demand that their child should not be told of her diagnosis, claiming that she would be overwhelmed with distress and sorrow. Does your responsibility lie with your patient, or are you obliged to follow the instructions of her parents? What would you do?

Ethical dilemmas occur frequently in medical situations, especially when the diagnosis is cancer. Cancer is unique because it is often difficult to detect and, many times, it is detected in its late stages, which leaves physicians with a limited number of options to treat the disease. From the moment the physician receives the results of the test, she is burdened with several ethical dilemmas. These dilemmas include the use of cancer screening and risk assessment tests, the decision of whether to tell the patient she has cancer, and how to do so.

A patient's life with cancer begins with its detection. With the advancements of cancer screening and risk assessment technologies, the ability to detect cancer, provide an accurate diagnosis, and discuss appropriate methods to treat cancer has increased. Ultimately, advances in technology have increased the chances of survival for patients. However, with the expanded ability to detect cancer or the risk of cancer, new ethical concerns have emerged.

Cancer screening is used specifically to detect seemingly healthy people who are at increased risk of having cancer. Screening for can-

cer can lead to an early detection, which is essential in defeating the disease. However, certain cancer screening tests are controversial because it is not always clear that the tests will benefit the patient. Screening for prostate cancer by tests such as the prostate-specific antigen blood test or digital rectal exam, has a chance of over-diagnosis. This is when the doctor detects asymptomatic legions that do not have the chance of becoming symptomatic, which may lead to unnecessary interventions.[2]

In general, the effectiveness of any type of cancer screening depends on its positive predictive value. The positive predictive value is the likelihood of a positive screening test giving a correct result. If the prevalence of the cancer being tested is low, then the correct detection of the disease by the screening test is extremely difficult. This may lead to the chance of a false-positive result causing unnecessary panic, fear, or unnecessary life decisions. Furthermore, the false-positive result can lead to further unnecessary medical procedures that are used to confirm the diagnosis.[3]

Even worse, a false-negative outcome can result from the test. A false-negative result has obvious extreme negative effects if the patient continues his or her life believing that he or she is cancer-free. The sense of security due to the incorrect negative result may lead the patient to ignore other signs of disease.[3]

"Some physicians believe that the parents know their child the best and only ask for what is in the best interest of their child. They want to let their child enjoy the time she has left and the physician is in no position to decide otherwise."

It is the physician's burden to consider whether the need to use screening tests is justified, in light of the possible consequences. Some patients may feel that it is unethical for a physician to withhold the option of using cancer screening tests despite the possible adverse outcomes. Other patients may decline the option of using cancer screening tests to determine their susceptibility. This will force the physician to investigate other options in order to diagnose their patient.

Once the results of either cancer screening or other detection tests are obtained, the physician is in a position to decide whether to divulge to the patient the truth about her diagnosis. It is commonly believed that the physician is obligated to tell the truth of her patient's diagnosis; however, there are several factors that must be taken into account before a physician can provide the patient's diagnosis. These factors are discussed in a research study entitled, "Ethical decision making on truth telling in terminal cancer: medical students' choices between patient autonomy and family paternalism." The study specifically discusses the influence of the family of a terminally ill cancer patient namely in Taiwan as being a major factor in the decision of the physician to disclose the diagnosis to her patient.

In cultures similar to the culture in Taiwan, the "safeguarding of vulnerable patients" takes precedence over the value of patient autonomy. Medical students who participated in the study stated, "In the traditional view, cancer is regarded as untreatable. In addition, some patients are more pessimistic or anxious by nature. If we disclose the truth to this group of patients presumptuously, they might feel hopeless and decline any treatment. This is something we really do not want to see."[4]

Other students said, "Asking a patient who has not much knowledge about the disease and [who is] emotionally vulnerable to make decisions on treatment may make the patient depressed and the family would complain about the doctor's imprudent act."[4]

As with the earlier example of the 16-year-old girl, physicians have varying opinions toward withholding information from patients. Physicians may answer the hypothetical situation by responding that it is her right to know. Physicians who believe this way feel that the patient is capable and competent enough to know her state of health and will ask questions about her situation; therefore, the patient should be told the truth. In addition, the physician may believe that she has an obligation to her patient. If this is so, it is the physician's duty to disclose her diagnosis. The physician may believe that her patient will understand the possibility of death and that it would be unfair to restrict this type of information from her. If the patient realizes, without the tests, that she is dying, the physician is obliged to confirm her thoughts, because if she did not, the patient would lose all faith and trust in the doctor. This could possibly damage their relationship and cause further harm.

The physician who decided to follow the parents' decision to withhold their daughter's diagnosis from her reasoned that her parents are in the best position to judge the reaction of the patient and understand the implications of explaining the diagnosis to her. Some physicians believe that the parents know their child the best and only ask for what is in the best interest of their child. They want to let their child enjoy the time she has left and the physician is in no position to decide otherwise.

Finally, some physicians believe that even though parents have the legal consent over their children, the physician is obligated to truthfully tell the patient about his or her diagnosis if the patient asks directly.

The decision about how to disclose a patient's diagnosis must also be made with care. The doctor-patient relationship varies with each patient, and certain patients expect their physician to act strictly as a source of information and statistics. One patient sees her doctor as only a technical aid and prefers to make her decision without any influence from the doctor.[5] Other patients expect their physician to instruct them in the treatment that the physician thinks is best. These patients rely heavily on their physician's opinions rather than researching on their own. A third type of patient is a combination of these two, and believes that it is the doctor's duty to provide her with information and treatment that is in accordance with the values and lifestyle of the patient. The doctor is neither strictly a source of numbers and definitions nor a decision maker, but an advisor who helps her patient make the best decision based on the patient's needs.

When disclosing information about a patient's diagnosis, physicians must recognize what type of patient they are dealing with. If a patient sees his or her physician only as a source of technical information, then she would not welcome significant influence by the physician. The same dilemmas would occur with the other two patient types if the physician did not recognize and adapt to the type of patient she was dealing with.

It is obvious to see that the role of a physician, when it comes to cancer, goes further than just providing medical treatment. The ethical dilemmas posed by cancer force the physicians to establish an integral relationship with the patient. A diagnosis of cancer requires a patient to contemplate her present and future lifestyles. Therefore, a doctor must treat the cancer patients on a unique, case-by-case basis to avoid falling into ethical predicaments.

1. American Cancer Society. How is Melanoma Staged? <http://www.cancer.org/docroot/cri/content/cri_2_4_3x_how_is_melanoma_staged_50.asp>. Accessed October 23 2006. American Cancer Society, Atlanta, GA, 2006.
2. National Cancer Institute. Cancer Screening Overview <http://www.cancer.gov/cancertopics/pdq/screening/overview/healthprofessional>. Accessed October 23 2006. U.S. National Institute of Health, Bethesda, MD, 2006.
3. Ustun C, Ceber E. Ethical issues for cancer screenings. Five Countries--Four Types of Cancer. Prev Med. 2004; 39(2):223-229.
4. Sheu SJ, Huang SH, Tang FI, Huang SL. Ethical decision making on truth telling in terminal cancer: Medical students' choices between patient autonomy and family paternalism. Med Educ. 2006; 40(6):590-598.
5. Bergsma J. Cancer and autonomy. Patient Educ Couns. 2002; 47(3):205-212.

PERSPECTIVE

The Rewards of Clinical Research

Cancer research at Mercy Medical Center

Kathy J. Helzlsouer, MD, MHS.
Director of the Prevention and Research Center
Mercy Medical Center

I have experienced the best of several worlds— that of the clinician, the researcher, and the teacher. As Director of the Prevention and Research Center at Mercy Medical Center in Batimore, I have the rewards that come from individual patient interactions as well as those that come from research that will help more broadly to improve patient care. At the Center, we conduct translational research in the truest sense of the word – integrating research activities seamlessly into patient care and then, when benefit is demonstrated, translating those findings into clinical practice.

Research ideas themselves come from many sources, but a vital resource remains the patient. Patient complaints or questions can spark excellent research ideas. My concern for my patients also fuels my drive and passion to find the answers to their problems and questions. It has compelled me to embark on a new aspect of research— evaluating the impact of mind-body interventions on symptoms and quality of life. The needs of patients are great and our health-care delivery system in the United States—especially supportive care—has failed to adequately meet those needs.

> "The needs of patients are great and our healthcare delivery system in the U.S. ... has failed to meet those needs."

Since its inception in 2004, the Prevention and Research Center has established three ongoing investigator-initiated research studies; we have several grants pending review and more ideas than we can keep up with. Our research has a special, but not exclusive, focus on women's health issues because the Prevention and Research Center is housed in Mercy's Weinberg Center for Women's Health and Medicine. Our current studies are focused on addressing health issues in breast cancer survivors including etiologic and intervention research studies. As a medical oncologist and epidemiologist, and as part of a Women's Center with a major clinical focus on breast and gynecologic cancers, I found that studying these cancers was a natural place to start. In addition to our initial "home-grown" research studies, we have expanded the cancer clinical trials program at Mercy.

The approach in forming our research agenda has been to fill the gaps in knowledge and address common issues in medical care where little work has been done. A critical area of research is finding ways to prevent or treat the long-term problems that often result from cancer treatment. Many survivors experience long-term effects from treatment such as persistent fatigue, neuropathy and arthritis, cognitive dysfunction (commonly called "chemo brain,") and increased risk of other diseases such as heart disease. Studies have documented these problems, but little has been done to evaluate what may prevent or ameliorate these debilitating conditions. We are in the midst of a trial to evaluate the efficacy of a mind-body medicine group to reduce symptoms of chronic fatigue among survivors of breast cancer. Another study is searching for clues to help treat the arthritis and arthralgias that sometimes results from hormone therapy in breast cancer treatment. We are planning studies to evaluate disparities in the side effects of treatment as well as intervention studies for cognitive dysfunction and lymphedema. Being close to the patient has reinforced the need to assess and address these common complications that present major impediments to achieving full recovery after treatment for cancer. They are often not adequately addressed in patients' on-going care.

In the last 10 to 20 years, there has been remarkable progress in cancer research with the introduction of improved and targeted therapies, better tools to predict risk and prognosis, and the promise of genomic sequencing. However, amid the huge emphasis on technology, we have lost sight of the value of addressing the human aspects of cancer and the total needs of the patient, both physical

and psychological. My personal experience with cancer, as well as my background as a clinician, has made me sensitive to the whole needs of the patient and has also made me realize that that we all too often fail in addressing issues that may have the largest impact on his/her quality of life. A major failure is the lack of adequate reimbursement for psychological support for patients and their families. The hope is that as evidence for the benefit of these services accumulates, reimbursement by insurers will follow.

"... amid the huge emphasis on technology, we have sometimes lost sight of the value of addressing the human aspects of cancer and the total needs of the patient, both physical and psychological."

The current funding environment presents challenges for us, as it does for all researchers, as there is often a lack of funding to support our ideas. Difficult choices need to be made regarding how to distribute limited funds. Basic science fuels new discoveries. Nonetheless, we cannot abandon the more immediate needs of the population. We must ensure that proven interventions are translated to the clinical setting. In the area of etiologic and clinical research, we must become more adept at efficiently answering research questions and avoid the problem of "circular epidemiology," a term coined by Dr. Lewis H. Kuller, a prominent cardiovascular epidemiologist. For example, we do not need more studies to examine the association between obesity and diabetes, or obesity and breast cancer. On the contrary, we need more studies to determine how to intervene and assist in weight loss, or better yet, prevent obesity. The epidemic of obesity in the United States has broken out on our watch. It is an enormous public health problem for both children and adults. The solutions to these public health problems will not come from the latest genome wide scan. As a clinician and researcher, I see that we are failing to address the problems with the most widespread and immediate impact on health. Achieving the right balance in what research is funded is a major challenge facing us.

The Prevention and Research Center at Mercy is a new and exciting endeavor. Our plans for future research include, but go far beyond, improving our knowledge of cancer and cancer treatment. The work we are doing at the Prevention and Research Center makes a difference and I can see its immediate impact on the patients I interact with on a daily basis. As with all serious clinical research, our findings will have a broader impact as we disseminate them. There is something remarkable about watching new ideas immediately improve the health and quality of life for the patients that I see. It is a creative, collaborative process that gets to the essence of why one might become both a medical doctor and a medical researcher. I feel fortunate to have found such a perfect balance.

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This issue of EP was made from contributions of Johns Hopkins students and faculty.

All of it ORIGINAL. See yourself here: ep@jhu.edu

Traffic Tickets to Survival in Uganda

David Bishai, MD, PhD, Department of Population and Family Health Sciences, JHSPH

Newly acquired traffic patrol cars are saving lives in Uganda. Photo- David Bishai

Road crashes kill 1.2 million people every year. The rising number of deaths is attributed to more cars on the road. Though it is true that traffic volume is increasing throughout the world, death rates in wealthy countries are falling, while death rates in poor countries continue to rise. Some of the things responsible for lowering death rates in rich countries, such as speed cameras, ambulances, modern trauma centers, and airbags, will be too costly for quite some time to come in countries where the population lives on $1 per day.

In 2003, my colleague Adnan Hyder and I developed models to identify road safety interventions that were both affordable and cost-effective in low-income countries. Results suggested that improved traffic safety enforcement offered the greatest promise. After reviewing budgets for spending on traffic safety in Pakistan and Uganda, we found that these countries spent less than 1 cent per person per day on traffic safety.

One of the obstacles to improving traffic patrols was the belief held by many policymakers that improving law enforcement would cost poor countries too much money. Unable to find any estimates of what it would really cost to enforce traffic laws, I set out on my own to find out.

With seed funding from the Johns Hopkins Center for Injury Research and Policy, I teamed up with Professor William Bazeyo and Dr. Brian Asiimwe of Makerere University to study the costs of traffic enforcement in Kampala, the largest city in Uganda. Following a visit to the police station in September 2005, and upon interviewing the police chief, we realized that we had stumbled upon a tremendous research opportunity. It so happened that the Kampala police department had just rolled out a major initiative in traffic enforcement.

Prior to 2004, Kampala's traffic enforcement had been limited to the stationing of foot patrols on traffic islands in busy intersections. In 2004 the police department acquired four patrol cars and had equipped them with radar guns. They hired and trained 20 traffic patrols to be deployed in mobile teams. Starting in October of 2004, they began daily surveillance of traffic on the four main roads leading into Kampala. In an effort to combine resources, we helped the police digitize their monthly crash statistics from 2001 to 2005, together dissecting the effects of the newly implemented safety enforcement.

The monthly data on the four roads leading into Uganda revealed an average of 408 deaths per year prior to the intervention, and 372 deaths per year after the intervention. This was a statistically significant difference that we confirmed with time series regression models that could control for the rising volume of traffic and any secular trends. The enforcement interventions cost $71,000 for the patrol cars, radar guns and staff salaries. In cost-effectiveness terms, traffic enforcement in Uganda cost less than $2,000 per life saved, demonstrating it to be more cost effective than many other public investments in the country.

From the government's perspective the intervention actually made money, as over $300,000 in fines were levied on motorists. Although the motorists resent such fines, viewed in the light of our research, the Ugandan traffic tickets are tickets to survival.

VISIONS
in public health

Photo- Alex Wald

Between the gaps of these prayer wheels, Tibet is changing.

Over the past decades, Tibet has changed under the rule of an oppressive government and by the influx of tourists and immigrants. Recently, the Tibet-Qinghai railway has brought the region into the fold of global industry, carrying passengers, consumer goods, minerals, and much more to and from the roof of the world. Passengers carry diseases; minerals come from mines; the production and consumption of new goods bring dramatic changes to diet and life.

While the impact of globalization can be debated in countless ways, in terms of public health, many of its challenges and opportunities presented here are obvious and specific. For workers and researchers in public health, the changes in a region are not simply documented and studied; rather, changes and interventions occur in real time,

improving the wellness of the population.