INTRODUCTION

Human Immunodeficiency Virus Type 1 (HIV) has pervaded New York City since the early days of the epidemic (see Figure 1). The peak of reported Acquired Immunodeficiency Syndrome cases occurred in the early 1990s; however, according to the NYC Department of Health and Mental Hygiene (NYC DHMH, 2005), the number of persons living with HIV/AIDS is steadily increasing because patients are living longer lives on combination therapy. HIV, therefore, remains a significant health concern for New Yorkers, especially since it is concentrated in the poorest neighborhoods, including the South Bronx.

Despite the fact that most individuals have a basic understanding of the modes of transmission of HIV, over 4,000 new cases were reported in 2003 in NYC, bringing the total to greater than 92,000 people living with HIV/AIDS throughout the city (NYC DHMH, 2005). Eighty-one percent of the newly diagnosed cases were in blacks and Hispanics. HIV is highly prevalent in the Bronx; it is present in 1.5% of the Bronx population. In fact, out of the five boroughs of NYC, the rate of new HIV diagnoses is highest in the Bronx (78.2 per 100,000) (NYC DHMH, 2005). Eighty-one percent of the newly diagnosed cases were in blacks and Hispanics. HIV is highly prevalent in the Bronx; it is present in 1.5% of the Bronx population. In fact, out of the five boroughs of NYC, the rate of new HIV diagnoses is highest in the Bronx (78.2 per 100,000) (NYC DHMH, 2005). For those who knew the mode of transmission by which they acquired the virus, approximately 10% contracted HIV from injection drug use. The majority of cases of HIV are sexually transmitted (63.5% in men; 40% in women) and perinatal transmission now only accounts for less than one percent of new cases of HIV (NYC DHMH, 2005). These statistics indicate that risky behaviors are still occurring to a large extent throughout NYC and are responsible for the majority of new cases of HIV.

This review provides a historical perspective on research performed at both the Albert Einstein College of Medicine (AECOM) and the Montefiore Medical Center (MMC). It discusses how the Center for AIDS Research (CFAR) has been an invaluable resource for the network of investigators at AECOM/MMC and it surveys the past and current HIV-related research projects in the Bronx and beyond.

HIV RESEARCH AT THE ALBERT EINSTEIN COLLEGE OF MEDICINE: THE EARLY YEARS

During the 1980s, the investigators of AECOM and MMC were on the front lines of the fight against HIV in terms of both research and patient care because the high rate of substance abuse in the Bronx facilitates HIV spread. Researchers sought to characterize the natural history of HIV infection and its modes of transmission. For example, Drs. Robert Klein and Ellie Schoenbaum searched for links with drug abuse and homosexuality (Moll et al., 1982; Small et al., 1983), while Dr. Arye Rubinstein described pediatric HIV/AIDS and compared it to adult forms (see Rubinstein, 1989 for review). Research at AECOM/MMC was also crucial in improving the understanding behind mother-to-child transmission of HIV (Kollmann et al., 1991; Soeiro et al., 1992) and the nature of opportunistic infections, such as tuberculosis and oral candidiasis (Klein et al., 1984; Selwyn, 1991). In 1985, researchers at the AECOM/MMC established a cohort called the HIV Epidemiological Research on Outcomes and they worked in collaboration with investigators who organized the Montefiore Substance Abuse Treatment Program. These programs provided large numbers of HIV-infected and substance abuse patients for clinical study.

The pioneering research that began at AECOM/MMC and the successful recruitment of HIV-infected patients in the Bronx into several clinical trials led to the initial
funding of the AECOM/MMC Center for AIDS Research (CFAR) by the National Institutes of Health (NIH) in 1988. The CFAR was spearheaded by Dr. Rubinstein, a prominent pediatrician. The AECOM/MMC CFAR was highly successful. It focused on clinical research, and expanded to foster relationships with the Mount Sinai Medical Center, Beth Israel Medical Center, and St. Luke's-Roosevelt Hospital Center. In parallel with continuing to characterize the natural history of HIV, investigation focused on the development and evaluation of new treatments, such as reverse transcriptase inhibitors and protease inhibitors, as they became widely available in the US and in NYC. The high prevalence of HIV infection in the Bronx provided AECOM/MMC physicians with ample research subjects, while CFAR investigators continued with their strong research programs. NIH funding for the multi-institutional CFAR continued through 1998.

As the main modes of transmission became defined and the etiological cause of AIDS was identified and characterized, the focus of national research shifted towards ways to control the infection in individuals and impede its spread in populations. Several reasons contributed to the unsuccessful applications to the NIH for refunding the CFAR, including its heavy emphasis on clinical research, and the complex logistical issues related to the overwhelmingly large structure of the multi-institutional CFAR. Therefore, the AECOM/MMC CFAR was revamped to focus solely on AECOM/MMC investigators and to concentrate on a translational approach, linking clinical and basic science research under the leadership of Dr. Harris Goldstein, who previously served as the Director of the SCID-hu mouse core. The CFAR was funded by the NIH in 2003 and was inaugurated with a ceremony at which one of the world’s leading AIDS investigators, Dr. Anthony Fauci, Director of the National Institute of Allergy and Infectious Diseases (and Dr. Goldstein’s former mentor) gave the invited lecture.

**MAKING CHANGES FOR THE FUTURE: THE CENTER FOR AIDS RESEARCH IS REDESIGNED**

With the new leadership of the AECOM/MMC CFAR came a reorganization of its structure. The current CFAR is divided into cores with specific purposes (see

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**FIGURE 1:** The effect of the HIV epidemic in New York and clinical milestones in the field of HIV medicine. This figure is reprinted with the permission of the New York City Department of Health Mental Hygiene (New York City Department of Health Mental Hygiene, 2005).
Treating HIV in the Bronx and Beyond

| TABLE 1: THE STRUCTURE AND FUNCTIONS OF THE CORE FACILITIES OF THE AECOM/MMC CFAR |
|---------------------------------|---------------------------------|
| **CORE**                        | **FUNCTIONS**                   |
| **Administrative**              | • To provide guidance for the AECOM/MMC CFAR |
| Director: Harris Goldstein      | • To oversee the functioning of individual cores |
| Co-Director: William Jacobs, Jr. | • To devise a strategic plan for long-term future goals |
| **Basic Science: Animal Biohazard** | • To provide biosafety level 3 housing for mouse models of HIV and opportunistic pathogens |
| Director: John Chan             | • To supply HIV transgenic and SCID-hu mice |
| Co-director: Larry Herbst       | • To contain a virus repository of clinical isolates and laboratory derived strains |
| **Basic Science: Clinical Virology** | • To analyze HIV specific RNA and DNA |
| Director: Harris Goldstein      | • To prepare viral constructs or retroviral expression vectors |
| Co-director: Tanya Dragic       | • To analyze HIV-specific immune responses |
| **Basic Science: Flow Cytometry** | • To perform phenotypic analysis, tetramer analysis and flow cytometric sorting of human or mouse cells |
| Director: Stephen Porcelli     | • To perform magnetic cell separation of cell populations |
| **Immunology/Pathology**        | • To perform RNA and protein analysis as well as experimental cellular immunology |
| Director: Joan Berman           | • To perform histopathological analysis of tissue samples |
| Director: Sunhee Lee            | • To be a resource for clinical samples. |
| **Clinical Investigation**      | • To facilitate epidemiological studies of HIV in the Bronx and abroad |
| Director: Robert Klein          | • To explore behavioral interventions to inhibit the spread of HIV |
| **Developmental**               | • To provide CFAR members with databases containing demographic, clinical and research data related to individuals with or at risk for HIV infection |
| Director: Vinayaka Prasad      | • To support collaborative and translational research by funding pilot projects |
|                                 | • To stimulate and support interactions among research at the AECOM/MMC |
|                                 | • To facilitate communication within the CFAR |

Table 1). The AECOM/MMC CFAR functions on multiple levels to provide resources to HIV investigators and to coordinate basic and clinical research projects. Its goals are (1) to provide an institutional infrastructure to facilitate collaborative research; (2) to establish and maintain core facilities; (3) to provide scientific leadership as well as intellectual and financial support for HIV research; and (4) to educate the medical community as well as the general population about HIV transmission, prevention, and therapies. The AIDS research effort is one of the major focuses of AECOM/MMC research overall, with investigators receiving over 27 million dollars/year of NIH funding for their individual HIV research programs. Some trainees (postdoctoral fellows and graduate students) are sponsored by other NIH-funded programs, including the NIH AIDS Training Program for Pre- and Postdoctoral Fellows, and the NIH Experimental Neuropathology Training Grant.

When the AECOM/MMC CFAR was newly funded, additional space was provided for Core Laboratories. There are over 50 AECOM/MMC faculty participants in the CFAR, many of whom use the specialized techniques provided by the CFAR Core laboratories to support
their research efforts. The investigators of the AECOM/MMC CFAR are grouped into general programs based on their research interests. These include the studies of developmental therapeutics, epidemiology, HIV-associated pathogens, immunology, substance abuse and behavior, and viral pathogenesis. More information about individual laboratories and Core services can be found on the AECOM/MMC CFAR’s homepage (http://www.aecom.yu.edu/home/cfar/).

The CFAR promotes interactions among its investigators through the presentation of a bi-monthly AIDS Club Seminar, where basic researchers and/or clinical investigators who are members of the CFAR present their latest findings to the AECOM/MMC communities. The communication and interactions between clinicians and basic scientists has greatly improved. New collaborations between physician scientists and basic scientists have been initiated. For example, one project is studying cytokine levels in HIV-infected patients, and a second collaboration examines potential activation markers in HIV-infected patients. In addition, the AECOM/MMC CFAR held its first annual retreat in 2004 where members helped to educate one another about the services provided by the individual Core laboratories. One of the outcomes of the retreat was the development of a mentorship program for junior clinical investigators led by Dr. Julia Arnsten. Dr. Arnsten organizes monthly meetings that provide a forum where junior clinicians can present their research proposals to senior faculty, and they receive critical feedback before submission of their formal proposals.

The AECOM/MMC CFAR also fosters the research careers of junior investigators by funding pilot projects through the Developmental Core. In the past several

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<tr>
<th>Investigator</th>
<th>Potential Therapeutic</th>
<th>Details or Potential Mechanism</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Tanya Dragic, Ph.D.</td>
<td>Small-molecule CCR5 antagonists (i.e., SCH-351125/AD101)</td>
<td>Inhibition of HIV replication and viral entry</td>
<td>Tsamis et al., 2003</td>
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<tr>
<td>Sunee Lee, M.D.</td>
<td>Anti-HIV activity of the antibiotic minocycline</td>
<td>Inhibition of HIV replication at the transcriptional level</td>
<td>Si et al., 2004</td>
</tr>
<tr>
<td>Vinayaka Prasad, Ph.D.</td>
<td>Small nucleic acid molecules isolated from combinatorial libraries by systematic evolution of ligands by exponential enrichment (Aptamers)</td>
<td>Inhibition of HIV protein (i.e., reverse transcriptase) activity</td>
<td>Joshi and Prasad, 2002</td>
</tr>
<tr>
<td>Arturo Casadevall, M.D. Ekaterina Dadachova, M.D.</td>
<td>Fungal-binding monoclonal antibodies against Cryptococcus neoformans</td>
<td>Conjugation of a radioactive isotope to a fungal-specific antibody converts immunoglobulin into a microbicidal molecule</td>
<td>Dadachova et al., 2003</td>
</tr>
<tr>
<td>Joshua Nosanchuk, M.D.</td>
<td>Voriconazole is fungicidal against Cryptococcus neoformans</td>
<td>High activity against both melanized and nonmelanized cells</td>
<td>van Duin et al., 2004</td>
</tr>
<tr>
<td>Robert Burk, M.D. Mark Einstein, M.D. Anna Kadish, M.D.</td>
<td>Vaccine strategies for management of Human Papilloma Virus-induced neoplasia</td>
<td>Immunotherapy with vaccines offer both prevention and therapy for Human Papilloma Virus</td>
<td>Kadish and Einstein, 2005</td>
</tr>
<tr>
<td>William Jacobs, Jr., Ph.D.</td>
<td>Novel vaccine strategies as prophylaxis for Micobacterium tuberculosis</td>
<td>Double lysine and pantothenate auxotrophs are safe and effective</td>
<td>Sambandamurthy VK et al., 2005 Sambandamurthy and Jacobs, 2005</td>
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years, the Developmental Core has funded more than eleven pilot projects for junior investigators, ranging from studies investigating HIV pathogenesis to studies examining HIV transmission in developing nations.

**BASIC SCIENCE RESEARCH AT THE ALBERT EINSTEIN COLLEGE OF MEDICINE**

Clinical HIV research was the main focus of the original multi-institutional CFAR; however, the newly designed AECOM/MMC CFAR targets translational research as well as basic science. HIV is one of the best-studied viruses, and recent research at AECOM has helped to better our understanding of its life cycle at the molecular level, with the hopes of finding some weakness that can be exploited for therapy. Basic scientists are exploring such topics as (1) the molecular interactions between HIV proteins and host proteins (see the review by Sorin and Kalpana, p. 10), (2) animal and cell culture models of infection, (3) cytokine/chemokine production and regulation, (4) virulence factors controlling co-infectious pathogens, and (5) potential therapeutics for HIV as a primary infection and its affiliated secondary infections. A sampling of completed and ongoing projects and their relation to potential therapeutics for HIV and related pathogens can be found in Table 2, and some will be highlighted in the text below.

Since HIV is specific to humans, it is difficult finding an inexpensive animal model in which to test various potential therapies. Dr. Goldstein’s laboratory has been committed to outlining the blocks to HIV infection in mice and has characterized various mouse models of HIV infection. The blocks to HIV infection in mice occur at various points in the viral life cycle, including the steps of entry, transcription, and budding. One transgenic mouse generated in Dr. Goldstein’s laboratory contains human-derived receptors for HIV (Browning et al., 1997), and another contains an intact HIV genome in the proviral form incorporated into the murine DNA (Wang et al., 2002). The latter mouse bypasses the need for the entry and integration of HIV and can be used to analyze post-integration phases of the life cycle. A third animal model has proven useful for testing disseminated infection and can potentially be used to screen new pharmacological therapies (Pettettelo-Mantovani et al., 1997).

Despite the advances with Highly Active Antiretroviral Therapy (HAART) for HIV-infected patients, the brain remains the second most targeted organ, after the lungs. Another area of interest at AECOM has been central nervous system HIV pathology, which can clinically manifest as HIV-associated dementia. Several investigators characterized the natural history and prevalence of HIV-associated dementia and the associated pathology, HIV encephalitis, including Drs. Dennis Dickson, William Lyman and Karen Weidenheim (Kure et al., 1989; Kure et al., 1990, Kure et al., 1991). They established an in vitro system of HIV-infected microglial cells that is an excellent model for HIV brain infection (Lee et al., 1993). The model has become invaluable for studying the neuroimmunological mechanisms that contribute to HIV encephalitis. Activation of glial cells, as studied by Dr. Sunhee C. Lee, indirectly contributes to HIV encephalitis (see Lee and Dickson, 2005 for review), but HIV and its component proteins can also directly incite damage. Using the same type of culture model developed by Dr. Dickson and colleagues, Dr. Joan Berman’s laboratory is probing into the potential neurotoxic effects of the HIV protein tat, and how the toxicity can be modulated by endogenous chemokines (Eugenin et al., 2003).

In addition to research focusing directly on HIV, a number of laboratories at AECOM investigate the pathology and molecular biology of AIDS-associated pathogens. For example, Drs. Arturo Casadevall, Lisanne Pirofski, and Marta Feldmesser investigate the virulence factors of and immune responses to the pathogenic fungi *Cryptococcus neoformans* and *Aspergillus fumigatus*, which cause cryptococcosis and aspergillosis, respectively, in immunocompromised individuals. In collaboration with Drs. Aharon Glatman-Freedman and Ekaterina Datachova, Dr. Casadevall studies the potential benefits of using protective monoclonal antibodies to alter the outcome of diseases such as cryptococcosis and tuberculosis (TB). Dr. William Jacobs Jr. and colleagues also study *Mycobacterium tuberculosis*, which, according to the World Health Organization (WHO), caused 1.75 million deaths in 2003, and causes 13% of all AIDS deaths worldwide (WHO, 2005a). TB has become a major problem in developing nations, especially due to its drug resistance. Dr. Jacobs’ laboratory performs genetic analysis on *M. tuberculosis* in order to study the genes that cause virulence and drug resistance, and to identify new drug targets and prepare novel vaccine formulations.

Other researchers at AECOM study viral and protist pathogens. Dr. Tanya Dragic, who has studied the structure of HIV glycoproteins that mediate viral entry, is beginning to investigate the receptors that mediate Hepatitis C virus entry. Drs. Anna Kadish, Robert Burk and Mark Einstein study the pathogenesis of Human papilloma virus-induced cervical cancer and are evaluating a new vaccine as a prevention strategy. Protrist pathogens, including *Toxoplasma gondii*, microsporidia and *Plasmodium falciparum* (which cause toxoplasmosis, microsporidiosis and malaria) are currently being examined in multiple laboratories, including those of Drs. Kami Kim and Louis Weiss. These examples of basic science research at AECOM have allowed for a better understanding of the pathology and consequences of HIV infection at molecular and cellular levels, as well as at the level of the patient. Hopefully, they will provide clues for adjunct therapies to treat HIV and its confounding infections.
CLINICAL RESEARCH AT THE MONTEFIORE MEDICAL CENTER

In the days of the multi-institutional CFAR, clinical researchers at MMC recruited a large number of HIV-infected patients and they formed a large research support system. Many clinicians at the MMC continue to study the substance abuse population of the Bronx, including how substance abuse promotes HIV spread. For example, Dr. Arnsten examines the relationship between drug and alcohol use and non-adherence to combination therapy (see Ramaswamy et al., p. 41 for review and Howard et al., 2002), while Dr. Klein investigates the prevalence of opportunistic diseases in past and present substance abusers. Furthermore, Dr. Andrea Howard studies the abnormal glucose metabolism in HIV-infected drug users (Howard et al., 2003). Patients on HAART now have a chronic form of HIV and they are living longer with the disease. Dr. Schoenbaum’s interests lie with the natural history of menopause in HIV-infected women (Miller et al., 2005), and a companion study of hormone levels in HIV-infected men is also being performed. Behavioral interventions are currently being investigated in a number of distinct projects. Dr. Laure Bauman heads “Primary Care,” which involves custody planning intervention for children of AIDS-afflicted mothers (Silver et al., 2003). She also examines the extent to which children are caring for their HIV-infected parents. Furthermore, she targets Bronx adolescents aged 14-17 in “Generation Safe,” an HIV, drug and alcohol prevention program.

GOING BEYOND THE BRONX: INTERNATIONAL RESEARCH AND OUTREACH EFFORTS

While there is no cure for HIV/AIDS, it is highly treatable with combination therapy in the developed world, where countries are affluent and have access to costly antiretroviral medications. Many low- and middle-income nations are poverty-stricken and do not have the resources to control the spread of HIV effectively (see Harris et al. for review, p. 25). The prevalence of HIV in developing nations is estimated by the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the WHO (see www.UNAIDS.org and www.WHO.org for more information). A number of United Nations-funded programs have been initiated, most notably the “3 by 5” target program, whose goals are to treat three million HIV-infected people in low- and middle-income countries with antiretroviral drugs by the end of 2005. WHO estimates that only 970,000 HIV-infected people of the six and a half million who need antiretroviral therapy in low- and middle-income countries had access to the drugs by June 2005 (WHO, 2005b). Although the “3 by 5” program might be falling short of its target goal, the number of people receiving therapy has steadily increased in the past year. For example, the number of people receiving therapy has tripled in Sub-Saharan Africa, reaching 500,000 (WHO, 2005b).

Nations in Africa would benefit from additional financial support, but aid groups were unhappy about the proposed pledges from the world’s economic leaders at this year’s G8 summit, stating that Africa has been “shortchanged.” (Associated Press, 2005).

Despite all of the obstacles, researchers from AECOM/MMC are doing their part to study HIV in developing nations and are even trying to help relieve some of the burden of getting antiretroviral drugs to the places that need it most. Dr. Nina Cooperman has studied the effects of HIV on women in NYC (Cooperman and Simoni, 2005) and she has extended her work to Mumbai, India, where she plans to examine HIV in sex workers and housewives. The NIH also supports an international training program (directed by Dr. Vinayaka Prasad) centered on AIDS and tuberculosis prevention research. The goals of this training grant are to supply Indian and Eritrean scientists with a place to perform biomedical and clinical research, including behavioral and epidemiological studies. In India, HIV-1 subtype C is more prevalent than subtype B forms typical of Western countries. In collaboration with Dr. William Tyor at the Medical University of South Carolina, Dr. Prasad is studying the molecular characteristics of HIV that may control the difference in the prevalence of HIV-associated dementia between subtype C and subtype B. They are using the mouse model of HIV encephalitis described in this issue (see the article by Cook and Tyor, p. 32). Moreover, AECOM/MMC researchers are also working in South America. One study described in this issue was performed by Samayoa et al. (p. 49) and involved the potential risk to health care workers of contracting HIV from potentially infectious substances in Guatemala.

Africa is by far the most severely affected continent in terms of the HIV pandemic and several AECOM/MMC researchers are conducting research in various regions of Africa. In this issue, Langman et al. (p. 53) discuss their work performed in Kumba, Cameroon. In affiliation with Dr. Ernest Drucker of the MMC and Dr. Preston Marx of Tulane University, Dr. Yaron Langman investigated the contribution of blood transfusions to the HIV epidemic. Furthermore, Dr. Donna Futterman has initiated a program in South Africa for the prevention of vertical transmission of HIV. Additionally, Dr. Carol Harris established the Global Institute of HIV Medicine in 2001. The goals of the institute are (1) to teach state-of-the-art HIV medicine; (2) to understand and describe the cultural, economic and political barriers impeding the implementation of frontline programs; and (3) to act as a force for advice and change, and to enhance initiatives for the prevention and treatment of AIDS (Harris, 2005a). Dr. Harris has a pilot grant from the AECOM/MMC CFAR to determine the response to antiretroviral therapy in the Democratic Republic of Ethiopia. Dr. Harris also plays an
important role in training physicians locally and abroad. When she became aware of the dearth in knowledge regarding HIV management that existed on the home front, she established “HIV Management—the New York Course,” in collaboration with Dr. Klein and Mindy Cimino (HIV Management, 2005). This course conveys up-to-date comprehensive HIV management information for New York physicians. Dr. Harris assists in training physicians around the world about HIV management through the Global AIDS Learning and Evaluation Network, whose modules have been used in Africa, the Caribbean, Eastern Europe, and China (Harris, 2005b).

CONCLUSION

The CFAR of the AECOM/MMC has fostered HIV/AIDS research for almost 20 years and it is currently going strong. The projects it funds are clinical, basic science, and translational in nature. HAART has drastically altered the course of HIV infection in patients and AECOM/MMC clinicians continue to study it in the Bronx population. In addition, basic scientists explore the intricacies of the HIV life cycle so that we may have a better understanding of how to manipulate it to our advantage. The CFAR’s support is playing an important role in coordinating HIV research within the AECOM/MMC and abroad. With their knowledge, investigators have branched out to fight the HIV pandemic across several continents; and, with their research, they may one day find a novel therapy or a vaccine for one of history’s most devastating diseases.

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