A publication of The Center for AIDS Information & Advocacy

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Dear Reader,

The year 2006 marked the 25th anniversary of AIDS. In light of this event, The Center for AIDS (The CFA) dedicated 3 issues of Research Initiative/Treatment Action! (RITA!) to mark this anniversary: HAART at 10, AIDS at 25, and finally, AIDS at the Crossroads: Perspectives on Research, Treatment, and Advocacy. This current Crossroads issue is a compilation of essays that focus on future milestones we must cross to end the AIDS epidemic. As we complete a quarter century of HIV/AIDS, what keeps us from reaching a cure? We were pleased that so many involved in the fight against HIV/AIDS, including advocates, researchers, and physicians, contributed to this issue and shared their ideas.

As Tom Gegeny wrote in his farewell message, “Perhaps change is the only constant.” And there are many changes happening at The CFA. First, I would like to announce that I am stepping down as editor, though I will continue to be a contributing writer. Personal and family obligations (ie, taking care of 2 small children) prevent me from dedicating the time and energy that this position requires. I have been working with this wonderful organization since 2003 and hope to continue to do so.

However, I am thrilled to introduce (or re-introduce for those longtime RITA! readers) Donna Rochon, PhD, as editor of The CFA publications. Donna has spent the majority of her career in the field of HIV/AIDS, including being a past editor and writer for RITA!. She received her doctorate from the University of Texas School of Public Health in Houston, specializing in Behavioral Sciences. At UT, her research focused on the effects of health care workers’ attitudes toward pregnant, HIV-positive women. She currently works as a Research Associate in the Department of Family and Community Medicine at Baylor College of Medicine and will work as editor on a part-time basis.

Second, this is the final print issue of RITA! You will find future issues online, in pdf format, at www.centerforaids.org. (On a related note, The CFA’s website will soon undergo a massive redesign; we think you will enjoy visiting the new site.)

Finally, I am very happy to announce that Paul Simmons has joined The CFA as Co-Executive Director of Programs. Paul will be working with the Co-Executive Director of Operations, Sara Haynes, who has been with The CFA since 1996. Paul previously worked for The CFA from 1997 to 2001 and then worked as a nurse in the Texas Medical Center for the past 5 years. Paul’s health care experience and knowledge, combined with his previous science and advocacy experience at The CFA, make him an excellent addition to this organization, now well into its second decade of educating, advocating, and collaborating in the fight against AIDS.

Very truly yours,

Jennifer K. Newcomb-Fernandez, PhD
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Highly active antiretroviral therapy (HAART) has been tremendously successful in reducing mortality from HIV infection in the developed world and is beginning to reach needy persons in the developing world. Mortality in the US has decreased by about 75% from its peak in the mid-1990s. Survival of patients infected with HIV in the developed world is now estimated in some studies in decades rather than individual years. Potent drugs in existing classes and drugs from new classes are coming down the development pipeline. Given this success, it is tempting to believe that we have maximized care for HIV-infected individuals in the US and that we simply need to keep that stream of new drugs full for our patients who are gradually exhausting (or who have already exhausted) treatment options while we work towards a cure. That may be the case for some patients, but for most, there remains plenty of room for improvement.

For HIV care to be maximally effective, all persons with HIV infection must be diagnosed as infected and must enter and remain in care, while those persons with a clinical indication for HAART must receive it and, finally, must adhere to HAART. Failure at any one of these steps will adversely affect not only the individual’s but the public’s health as well.

Unfortunately, large portions of the population infected with HIV are under-treated, even in the US and other developed countries. In other words, even with no new drugs or treatment strategies, we can do far better at caring for persons infected with HIV. The US Centers for Disease Control and Prevention (CDC) estimates that 25% of persons with HIV infection are unaware of their infection. Once they become aware of their status, people reduce their risky behavior by about two-thirds, thus helping to limit transmission of the virus to others. Persons who are unaware of their status are estimated to be responsible for 50% to 70% of HIV transmission in the US. Clearly, any decrease in the proportion of persons unaware of their HIV infection could improve public health.

Further, almost half the persons who are diagnosed with HIV in the US are not diagnosed until their disease is advanced enough to adversely affect long-term prognosis. In urban hospitals throughout the country, people with previously undiagnosed HIV infection still present with and die from severe Pneumocystis pneumonia, toxoplasmosis, and cryptococcal meningitis. Recent research suggests that about 75% of patients ultimately diagnosed with advanced HIV infection have had previous encounters with the health care system, often in emergency departments, mostly without conditions that would trigger HIV testing. For these reasons and others, the CDC has released new guidelines for HIV testing that encourage widespread screening for infection and reduce the barriers to testing, while still maintaining that testing must be both voluntary and informed. These guidelines have the potential to reduce the number of persons newly infected with HIV and improve the prognosis of many who are infected. They should be carefully and conscientiously implemented.

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Once they are diagnosed with HIV infection, many people delay accessing health care. A number of studies have shown that delays can range from a few months to many years. Denial, stigma, fear, lack of health insurance, perceived lack of access to health care, substance use, and psychiatric illness all contribute to this problem. Often the site of diagnosis is not an HIV clinic so a “hand-off” must occur, sometimes not only from one provider to another, but from one health care system to another. Case management can be an effective tool for smoothing the transition into HIV care, but the patient still has to be linked to HIV case management. The burden is especially high on the uninsured, who must establish and then maintain eligibility for publicly funded programs. There is little research on how to best accomplish this difficult transition.

Once in care, patients must receive and then adhere to HAART. Recent deaths of patients on the AIDS Drug Assistance Program (ADAP) waiting lists in several states tragically demonstrate that even in the US, not all persons who need access to HIV medications can get them. Patients who do get HAART must then adhere to the treatment regimens. Reduced adherence to HAART contributes to earlier viral failure and faster disease progression leading to death. While adherence in clinical trials is often excellent, adherence in routine care is generally between 50% and 80%. Researchers are just beginning to develop some effective interventions to improve adherence, but there is no “magic bullet” that will work for every patient.

Remaining in care is challenging for patients with HIV infection. Providers often struggle to comprehend why a patient fails to remain in care when doing so means that the provider can give the patient medications at low cost that will turn this otherwise fatal infection into a manageable, chronic illness. From the patient’s standpoint, however, HIV infection is often only one threat of many to his or her health and welfare. The HIV-infected population is socioeconomically vulnerable, with about half the persons in care dependent on the Ryan White CARE Act or Medicaid/Medicare. Other common threats include substance use, psychiatric disease, and legal problems. A person who feels well but has unstable housing, no telephone, limited means of transportation, and a fixed, low income may have little drive to expend some of their limited resources on getting an appointment with a provider, having blood drawn for a laboratory assessment, and attending an appointment with a provider. Lapses in care are not uncommon—as any clinician can attest. Other reasons for lapses include problems navigating the health care system, logistical barriers (for example, limited clinic hours and difficulties maintaining eligibility for publicly funded services or health insurance coverage), denial, fear, and stigma.

These same factors contribute to poor adherence to HAART. Persons with poor clinic attendance generally have poor adherence to medications. However, poor adherence to HAART is not the only reason that retention in care is important.
Many persons with HIV infection do not die from HIV infection, they die with HIV infection. For example, substance use and psychiatric disease can lead to traumatic or accidental deaths, hepatitis C infection can lead to liver failure, and diabetes, hypertension, obesity, and smoking can lead to early heart disease. These comorbid medical conditions require active management. Poor retention in care may result in inadequate treatment of these and other serious conditions. While the Health Resources and Services Administration (HRSA) and the CDC have sponsored some research on retention in care, there remains much work to be done and much room for improvement. Innovative models of health care delivery, case management, and chronic disease management will likely be needed to maximize retention rates.

When examining the US health care system as a whole, it is clear that we are not succeeding at assisting a large proportion of patients in navigating all the steps of HIV care. The CDC estimates that about 50% of persons with HIV infection in the US are not presently in HIV care. Some are undiagnosed, some have not yet entered care, and others have fallen out of care. Many patients on HAART will have inadequate adherence to their medications. Many in care will only sporadically engage in care and as a result, will not be adequately treated for their HIV infection and for serious comorbid conditions. While new medications to treat HIV are certainly needed, significant improvements in viral, immunologic, and clinical outcomes could be achieved from improving timely diagnosis of HIV infection, and access to and retention in care, as well as adherence to HAART. There is no time for complacency in the US as we work towards a cure for HIV infection.

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New approaches and resolve may define the future of the global HIV pandemic

By Eric S. Daar, MD

More than 25 years since the first cases of AIDS were described, there continue to be grim reports of the growing global pandemic. These include an estimated 40 million HIV-infected people, with approximately 4 to 5 million new infections per year and little evidence of a decline in the rate of infection. In addition, despite ongoing research to define the immunopathogenesis of HIV disease, there remains little hope in the near future for the development of an effective preventative vaccine. On a more positive note, the year 2006 represented the 11th year in which potent combination antiretroviral therapy has been routinely used in the richest countries. Even more importantly, this past year may be remembered for pivotal events in research related to both treatment and prevention that may define the future of the HIV/AIDS epidemic for both rich and resource-limited parts of the world.

For the wealthy countries, antiretroviral therapy has continued to become increasingly well tolerated by patients, relatively easy to administer, and associated with virologic suppression in the overwhelming majority of individuals starting treatment for the first time. From a psychological and emotional perspective, the pinnacle of this success was the availability of a single pill: once-daily therapy given as the fixed-dose combination of tenofovir DF/emtricitabine/efavirenz. Despite this progress, there are still those who experience virologic failure and others who have been on treatment for many years with the emergence of highly drug-resistant HIV that limits their ability to achieve viral suppression. For these individuals, other new drugs have offered hope, particularly with regimens that include the fusion inhibitor enfuvirtide, which is the first available agent in a novel class since the development of protease inhibitors. Nevertheless, there remain many who cannot tolerate available treatments or have viruses so resistant that even these new advances are insufficient to allow for long-term virologic suppression.

The past year will likely be remembered as one that ushered in an extraordinary array of novel therapeutics, including several in new classes. In fact, by the end of 2006 in the United States, there were 2 new drugs available in expanded access that offered options for treatment-experienced individuals, one of which was etravirine, a “second generation” non-nucleoside reverse transcriptase inhibitor, and the other MK0518, an integrase inhibitor. Integrase inhibitors are a new class of drugs that are expected to have activity against the virus of even the most treatment-experienced individuals. In addition, another agent in a new class, maraviroc, the chemokine receptor (CCR5) inhibitor, will be available through expanded access during the early part of 2007. There are also other drugs in the integrase and CCR5 inhibitor classes that are in development, and additional promising new classes, such as maturation inhibitors, are being actively evaluated in clinical trials. Assuming results from studies underway prove to be as promising as hoped, these advances may offer extraordinary opportunities for those in need of new treatment options. In fact, these drugs could make the goal of achieving full virologic suppression in previously difficult-to-treat individuals the norm, as it has become in those starting therapy for the first time.
“...the past year may forever be remembered as a time when epidemiologic observations of the...relationship between male circumcision and reduced risk of acquiring HIV infection were confirmed by randomized controlled trials.”

Another milestone during the last year was the unprecedented expansion of programs to roll out potent antiretroviral therapy to resource-limited settings. This advance has in part been made possible by dramatic reductions in the cost of treatment, as well as increased training of local health care providers. Furthermore, preliminary studies have demonstrated high levels of adherence amongst those who were first to access treatment in resource-limited countries, in addition to an associated decline in mortality mimicking that seen with the introduction of protease inhibitor-based regimens in the developed world. Only time will tell whether the world’s resolve will be sufficient to address the many challenges associated with treating millions of people in resource-limited settings, particularly in meeting the recently established goal of universal access to HIV care by 2010 as proposed at the 2006 G8 summit.

The alarming rate of new infections throughout the world remains an enormous problem that has been inconsistently addressed with current prevention programs such as voluntary counseling and testing and ABC (abstinence, be faithful, and condoms). Moreover, it is increasingly clear that a preventative vaccine is not on the immediate horizon. In 2006, the scientific community took major steps towards establishing novel prevention strategies that do not rely on changing behaviors or the development of a vaccine. Instead, the prevention field has re-evaluated the potential impact of pharmacologic and biologic strategies. After all, one of the greatest advances in the history of the epidemic is the ability to use antiretroviral therapy to prevent mother-to-child transmission. It has been suggested that the benefit associated with reducing maternal viral load and prophylaxing the baby with antiretroviral therapy to prevent maternal-fetal transmission could be used to prevent sexual transmission. This is supported by the observation that increased plasma HIV RNA is associated with the enhanced risk of transmission amongst serodiscordant couples. Together, these observations have led to studies assessing the impact antiretroviral therapy might have on sexual transmission. This includes studies of pre-exposure prophylaxis, a controversial yet innovative means of avoiding transmission by administering antiretroviral drugs to uninfected individuals prior to potential exposure. Even more intriguing is the possibility that sexual transmission of HIV might be reduced by increasing the number of individuals on treatment, a potential public health benefit of the global rollout of antiretroviral therapy. Needless to say, the benefits of such strategies might be countered by changes in risk-taking behavior, increased transmission of drug-resistant virus, and drug-related toxicity.

Since the stakes are high and outcomes unpredictable with all prevention strategies, it is exciting to note that the field is not resting its hopes on any one modality. Instead, several pharmacologic and biologic interventions are simultaneously being pursued with the hope that any one or several could impact the growing epidemic. Novel prevention strategies are attempting to exploit...
new technologies, as well as what we have learned about cofactors for transmission. For example, studies are evaluating the safety and efficacy of microbicides, perhaps more aptly referred to as agents that can prevent infection at the mucosal level during vaginal intercourse. If initial studies show promise, women would be empowered to protect themselves. Moreover, this modality could be extended to protect against transmission during anal intercourse. Other interventions focus on the relationship between HIV transmission and the presence of sexually transmitted diseases. In this case, studies can be designed to assess the benefit of more aggressive treatment and/or suppression of these infections.

Finally, the past year may forever be remembered as a time when epidemiologic observations of the biologically plausible relationship between male circumcision and reduced risk of acquiring HIV infection were confirmed by randomized controlled trials. One study was published and 2 others recently closed because of a marked reduction in heterosexual HIV acquisition by circumcised men compared to uncircumcised controls.10 Further study is still needed to determine whether male circumcision of an infected individual will reduce transmission to others, as well as whether such strategies can be safely implemented in resource-limited areas. Regardless, the outcomes of these studies represent a major advance towards curbing the spread of HIV around the world.

While major breakthroughs in our understanding of HIV immunopathogenesis and the development of treatments occurred during the first 25 years of the HIV epidemic, it also became clear that there were major obstacles towards achieving curative treatment and the development of a preventative vaccine. As we look to the future, it is satisfying to note that the field has moved forward with improved treatment modalities that are better tolerated and increasingly available at relatively low cost to many resource-limited countries. Moreover, prevention efforts have expanded to consider the potential impact that universal access to antiretroviral treatment might have on the global pandemic. In addition, novel pharmacologic and biologic prevention strategies are moving forward, some of which have already demonstrated great promise. For these reasons, there remains great hope that the next 10 years will redefine the global HIV pandemic.

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References
Politics underlie everything in life and HIV/AIDS research is no exception. It should therefore come as no surprise that how “science” is conducted in this country is strongly influenced by politics. The decision-making of what to explore, who should explore it, and what methods shall be utilized to conduct this exploration are all the result of political decisions and leadership preferences. When money (or lack thereof) is added to this equation, the outcome is sometimes unpredictable. One must never lose sight of the fact that the results of this process trickle down to the person living with HIV and have real-life consequences for that individual and his or her loved ones.

In light of this observation, the National Institutes of Health, National Institute of Allergy and Infectious Diseases (NIAID), Division of AIDS (DAIDS), is in the midst of a reorganization of its HIV clinical trials network. This network consists of 6 newly funded clinical trial networks, each with its own population expertise and approach (see studysource.org/networks for a brief explanation of the different networks). Although newly funded (with the exception of one network), the others have existed in previous machinations, several having up to a 15-year history of conducting clinical trials across the globe, serving tens of thousands of patient participants. These networks have also employed hundreds of researchers, clinical staff, and mid-level staff as well. Additionally, there have been countless community volunteers who have participated both as research subjects and on community advisory boards, giving their energy and time for this important work. However, several of these networks have grown very large and bureaucratic, rendering decision-making an arduous process at best.

The picture that I am trying to paint is one of a huge animal that slowly creeps over the landscape choosing specific low-lying vegetation to consume along the way and only responding noticeably to cataclysmic change. This cataclysmic change, in terms of the DAIDS funding world, has come in the form of diminishing funding resources.

In theory, the recent reorganization of all of the DAIDS networks was necessary and a long time in coming. The old system was unnecessarily complicated, expensive, and lacking transparent and consistently clear decision-making processes. Gathering input from each level within each of the networks into the decision-making process, while
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extremely helpful to the study design, slowed the entire process down, often making the questions being asked irrelevant by the time the studies were up and running. This made patient enrollment difficult, at best. Some studies had to be stopped prematurely as they just could not enroll or because the burden placed on patients was too unrealistic by the time the study was finalized.

It was thought that this reorganization would foster more collaboration and strengthen the partnership between DAIDS, the researchers, and the community members. One of the important goals/aims of the reorganization was to streamline resources at all levels, allowing for excesses and duplications to be eliminated. It was thought that the reorganization would strengthen the similarities of each network, while highlighting and respecting their differences. Though these are helpful and efficient aims, the community voice seems to be diminishing during this process. The recompetition has been a procedural nightmare and it is unclear how and what research will be supported in the future.

The reality is that there is an ever-growing need for more research to cover the entire continuum from prevention issues to problems that individuals face while living with HIV. Continued research into basic science and HIV pathogenesis are also needed. The challenge for us, as community advocates for people living and dying with HIV/AIDS, is to try to design a flexible research agenda that addresses the unique management problems at each point in the HIV disease spectrum: those who are at most risk of acquiring HIV, the newly infected, those experiencing drug-related side effects, those ill with AIDS, those with few treatment options, and those at the end of their lives. These issues are also true across the age-life cycle of individuals: fetus, neonate, children, adolescents, adults, and elderly people.

Advocates need to articulate what kind of research will be most helpful and then advocate for the kind of research questions we want answered. We need to advocate for research methods that adjust and grow and change, incorporating new creative approaches. For example, in rural geographic areas that do not have access to surrogate marker tests (such as viral load and CD4 tests), studies comparing established, but low-tech tests against the higher technology-based methods as indicators of disease progression, may be needed. Or, what about developing diagnostic tests for infants to measure disease progression because the use of dried blood indicates exposure but not infection status? We must support the establishment of infrastructure in geographic areas that have been unable to do so by themselves, as well as mentor and support researchers who live and work within their own communities because they understand their cultures and resource constraints.

HIV advocates have fought long and hard to establish credibility within the research structure so that the diversity of their voices and unique perspectives would be heard, acknowledged, and taken into account at crucial decision-making points. What is happening, though, through this reorganization, is that fewer HIV-infected people and their advocates are participating in the overall network decision-making processes. We are told that we need to streamline the process. But this “streamlining” creates an increasing sense of

“Politics underlie everything in life and HIV/AIDS research is no exception.”
alienation and decreasing contribution from those participants in the actual trials. The funding cuts across all of the networks and the establishment of a new cross-network community group has limited the amount of community input available within the networks. Each clinical trial network has been financially cut and is struggling to do what they can with limited funds. Instead of fostering cooperation, it appears to be increasing self-preservation, with the community getting hit the hardest. It is a situation of “robbing Peter to pay Paul.”

Although gathering community input is not an easy process, it is worthwhile. It is an additive process, not a reductive one. There is no single community voice, but rather there are as many voices as there are people who experience this disease. Sociologists have assigned individuals with certain attributes, such as socioeconomic status, ethnic background, and/or HIV risk behavior(s), into a less than perfect system. All of the facets of living with HIV must be recognized when developing strategies and priorities so that research questions bear directly on clinical relevance. Therefore, asking for one community voice is just as unreasonable and unfair as asking for one voice within a specific field of research. One expects researchers to have substantial differences of opinion, so why not community members?

I try to remain optimistic that the outcome of this reorganization and the millions of dollars that the United States taxpayers are spending to support it, will continue to ask and answer important HIV/AIDS research questions. The research focus seems to be shifting from what is needed here in the United States to what is needed abroad. Of course, there are overlapping research questions applicable across the globe, and there is also a need to expand research outside of the United States to successfully enroll the vast numbers of patients needed to assure statistical power within the trials. However, there already have been concerns that too much money has been taken from the United States and sent overseas when there are still tax-paying citizens failing their treatment regimens. Issues such as managing people beyond their initial 2 or 3 treatment regimens seem to have fallen far down the research priority list. The truth is that there are limitations to HAART (highly active antiretroviral therapy) and everyone with HIV will eventually develop drug resistance and run out of treatment options—whether as the result of burning through drug classes used as partially suppressive regimens or by staying on failing drugs while waiting for more choices or resources to come their way.

In addition, a more comprehensive understanding of the interactions between long-term drug therapy and developmental problems in HIV-infected children and adolescents is needed so that they can develop into fully functioning adults. We need to continue to develop strategies for holding treatment-experienced patients in a healthful place until there are new agents for them to use, while simultaneously better understanding how to administer these agents to the newly HIV-infected.

I am hopeful that there will remain in place mechanisms for meaningful community participation and dialogue in research, and that community members will be incorporated into the entire research process and seen as valuable assets. Historically, mistakes in the delivery of research have been corrected and improved by listening to the community. I remain optimistic that clinicians and researchers can form an even...continued
stronger partnership and address questions that are of importance to them as well as to all people living with this disease. Community is strong because it is diverse—we represent all voices of people across the globe who are concerned and care about those who are infected with HIV/AIDS.

The challenge is not to fight amongst ourselves for ever-shrinking dollars and programs, but rather to think creatively about what can be accomplished within the diverse populations and clinical research sites, with these shrinking dollars. We need to support the reduction of top-heavy bureaucracy and reduce waste within the firmly entrenched research system that we have created. We need proactive leadership at the top of the funding process. This research agenda should be developed in true partnership with community, researchers, DAIDS, and many other stakeholders across the globe. Most importantly, we must hold all people accountable for this research work and immediately address shortcomings and problems.

In other words, we need to step outside of our collective comfort zones and do what is best for those of us living with HIV across the globe.

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The potential of behavior-change interventions to improve the HIV/AIDS survivorship experience: The example of smoking cessation

By Damon J. Vidrine, DrPH

The concept of survivorship, generally defined as the physical, psychosocial, and economic impact of disease and treatment on an individual, is widely recognized as an important field of research. The focus on survivorship research is perhaps most visible within the oncology community. Government agencies, foundations, and advocacy groups frequently stress the importance of both a thorough consideration of the factors that can potentially influence the survivorship experience for individuals diagnosed with cancer, and the development and dissemination of interventions designed to improve that experience. While the term survivorship may not be commonly used in reference to persons living with HIV/AIDS, this perspective can help both clinicians and researchers identify areas in need of intervention. In addition, the significantly extended life expectancy made possible by highly active antiretroviral therapy (HAART) certainly brings the relevance of this perspective to the forefront.

It is from this standpoint that one can appreciate the importance of interventions addressing health-risk behaviors. Targeting of risky behaviors has a long history in the field of HIV research; the most common purpose of these behavioral interventions is to reduce the risk of primary or secondary HIV infection. While prevention is obviously still needed, behavioral interventions can also be used to improve the lives of persons already infected. For example, recent years have seen a growing number of interventions targeting diet and physical activity. This form of intervention has the potential to at least partially counter the increased risk of cardiovascular disease (CVD) seen in the HIV-positive population. Similarly, interventions designed to reduce illicit drug use and alcohol abuse can potentially lead to lower rates of secondary infection, improved medication adherence, and ultimately, to improved quality of life.

Cigarette smoking among individuals living with HIV/AIDS is a health-risk behavior that is of particular interest to me and has been a major focus of my research for the past 6 years. At the time that my colleagues, Roberto C. Arduino, MD, and Ellen R. Gritz, PhD, and I began our studies, very few research efforts had been made to understand the scope of the problem (ie, the prevalence of current smoking, interest in cessation treatment, and development of appropriate interventions). The existing literature, however, did clearly indicate that smokers with HIV/AIDS were at higher risk for numerous adverse outcomes, including pulmonary diseases, oral infections, and both AIDS- and non-AIDS-related malignancies. Thus, it seemed quite clear that efforts to target this population for smoking cessation treatment were warranted.

The reasons for the lack of published smoking cessation interventions involving the HIV-positive population were most likely driven by the historically poor prognosis. In fact, an all too common assumption from patients and health care providers alike has been that individuals living with HIV/AIDS were unlikely to survive long enough to be at risk for the diseases attributable to smoking. Other concerns included the possibility that over-burdening the population with a smoking cessation intervention might actually...continued
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detract from other important focuses, such as medication adherence and secondary prevention. A final concern stems from the belief of some smokers that cigarettes promote relaxation at stressful times. On the surface, this would suggest that cessation efforts may actually increase distress levels by eliminating an effective stress-management practice.

More recently published evidence clearly elucidates the deleterious relationship between smoking and HIV/AIDS. The increasing incidence of CVD within the HIV-positive population is particularly alarming. Whether this increasing risk is caused by the metabolic changes associated with long-term use of HAART, a consequence of disease progression now more apparent because of longer life expectancies, or a combination of these 2 factors is not clear. However, what is clear is the strong, independent CVD risk associated with smoking cigarettes. Therefore, it appears that cessation treatment could become a crucial component in the long-term management of HIV-positive patients to reduce the morbidity and mortality associated with CVD.

The morbidity and mortality associated with malignancy among persons living with HIV/AIDS has also received more attention in recent years. During the HAART era, the mortality rate attributable to several AIDS-defining cancers has decreased, but the proportion of deaths due to smoking-related cancers has increased. Also alarming is the increased risk of aerodigestive cancers (those affecting the organs of the respiratory and upper digestive tracts) observed in HIV-infected smokers compared to non-HIV-infected smokers, suggesting a synergistic relationship between smoking and HIV.

It is now evident that cigarette smoking is an important contributor to morbidity and mortality in the HIV-positive population and that reducing the prevalence of smoking would result in an improved survivorship experience characterized by better disease management, increased quality of life, and further improved survival rates. A demonstration of the effects of cigarettes can be observed in the recent findings from the Women’s Interagency HIV Study, where current smokers had significantly poorer response to HAART (both viral and immunologic) and higher death risk compared to nonsmokers. Perhaps based partly on these findings, the all-too-common reluctance to acknowledge the smoking problem within the HIV-positive population seems to be waning and the importance of introducing effective smoking cessation strategies into the HIV clinic seems to be far more accepted today.

Our first research efforts were descriptive and designed to gain a more complete picture of smoking behavior in this population. Our results, and those of several other groups conducting similar research across the country, indicated an alarmingly high prevalence of smoking. The proportion of individuals living with HIV/AIDS who are current smokers is estimated to be about 50%, which is more than double the proportion in the general US population—about 21%.

“The proportion of individuals living with HIV/AIDS who are current smokers is estimated to be about 50%, which is more than double the proportion in the general US population—about 21%.”
smoking are disproportionately observed in the HIV-positive population. Specifically, increased prevalence of negative affect, low socioeconomic status, illicit drug and alcohol use, and non-heterosexual orientation are all associated with both smoking status and HIV infection.

Additional research efforts helped us to identify potential barriers to more traditional cessation interventions. Many of the barriers are not necessarily associated with HIV status, but rather with socioeconomic status. For example, we found that the majority of the population reported several household moves in the past year, a reliance on public transportation, and inconsistent or no access to a working telephone. Other potential barriers included the burden of numerous medical care appointments and fears regarding side effects from additional medication. While our sample of participants was drawn from the Houston metropolitan area, these barriers are likely common across the nation.

Based on our findings, we developed an intervention approach designed to overcome these barriers to treatment. This approach involved the systematic screening of all patients attending a large, county-funded HIV clinic. Smokers were offered cessation treatment consisting of either a usual care approach (brief physician advice to quit and recommendation of nicotine-based replacement patches) or an enhanced care approach that supplemented the usual care elements with proactive counseling delivered via prepaid cell phones that we provided. Our results were encouraging. Interest in quitting was high among the individuals screened—about two-thirds of people enrolled in the study. We also found that the addition of the cell phone component tripled the smoking abstinence rates at the 3-month follow-up. Currently, a larger efficacy trial, with long-term follow-up, is being conducted. Additional analyses will also be conducted to compare changes in markers of disease progression and functional status domains between those who successfully quit smoking and those who continue to smoke.

The use of cell phone-delivered counseling is certainly not the only smoking cessation treatment option for the HIV-positive population. Additional assessments of both traditional and innovative cessation treatment approaches (eg, educational, behavioral, and pharmacologic) are needed. And, efforts to tailor treatment type and intensity to the individual smoker will improve the likelihood of successful cessation.

The significantly decreased death rate and reduced risk of AIDS-related diseases brought about by HAART has dramatically changed the lives of persons living with HIV/AIDS. This disease is now much more accurately viewed as a long-term, medically manageable condition, and thus, the effects of health behaviors are now more relevant than ever. Integrating careful tobacco-use screening and treatment into routine clinical practice could significantly improve a variety of health outcomes, ranging from perceived symptom burden to mortality risk. Such an approach also offers the very real potential of significantly improving the survivorship experience of this ever-growing population.

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References
Women and HIV: A population at risk

By Kathleen E. Squires, MD

In July 2006, a colleague called me to discuss a case that troubled him. He was following a young African-American woman, Gina, who had been diagnosed with pancytopenia (low red cells, white cells, and platelets) 1 year previously. He had undertaken an extensive evaluation at the time that did not yield a diagnosis. Her past medical history included a biopsy of an enlarged supraclavicular node, which was interpreted as hyperplastic on histology, and cervical dysplasia. Despite cytokine treatment, her cell counts remained low and a repeat bone marrow biopsy was non-diagnostic. A second round of evaluations included HIV testing, which was positive. He questioned the diagnosis of HIV infection and asked me to see the patient in consultation. The patient was not only surprised by the results but was also distraught. She could not understand how she had acquired this infection. She did not believe that she was at risk for HIV since she had never used drugs or “slept around.”

It is a little-remembered fact that the first cases of AIDS occurring in women were reported within months of the often cited initial 1981 Morbidity and Mortality Weekly Report (MMWR) publication detailing the presentation of Pneumocystis carinii pneumonia in gay men residing in Los Angeles. However, for much of the ensuing decade, homosexual activity and to a lesser extent, intravenous drug use, were the overriding and almost exclusive risk factors associated with transmission or acquisition of HIV/AIDS. When we thought about HIV and women, the discussion centered on women as transmitters of infection, either to their fetuses (mother-to-child transmission, MTCT) or their male partners. Gender-related research was pursued to define: 1) modalities to decrease MTCT and 2) risk factors associated with increased risk for heterosexual transmission primarily involving groups of commercial sex workers residing in international settings. In the early 1990s, when it became apparent that HIV was being diagnosed in increasing numbers of women in this country and around the world, there was a shift in gender- and sex-based research to define the natural history of HIV in women.

Now, in 2007, HIV infection is a global disease, transmitted primarily by sexual activity and intravenous drug use. The burden of this disease affects both sexes; in many regions of the world, the number of cases in women exceeds those reported in men. The vast majority of girls and women acquire HIV through heterosexual activity. As compared to the late 1990s, the increase in new infections has disproportionately affected young women who are becoming infected as they become sexually active. There are biologic and societal reasons why young women are susceptible and more vulnerable to HIV infection. Biologically, the cervix of young women is immature, lined with columnar epithelium which is friable and easily disrupted during trauma, increasing the risk of HIV acquisition during coitus. Socially, the gender inequality that is the status quo in most areas of the world renders all women more vulnerable to HIV infection: lack of financial security, intimate-partner violence, male control in the woman’s current relationship, and lack of legal status. It is this last factor specifically that impedes our ability to significantly change the scope of the epidemic among women.
Strong, committed leadership on the part of governmental and medical authorities, together with a change in the legal and financial status of women in many parts of the world, are necessary and critical to empower women to exert control over factors that increase their risk of acquiring HIV. On a global basis, women and girls comprise more than 50% of individuals who are HIV-positive. It is critical for both public health officials, who work to craft and implement prevention strategies, and clinicians, who evaluate and manage HIV-infected persons, to recognize the unique impact of HIV infection on women.

Most HIV-infected women are of child-bearing potential. Therefore, issues of fertility, fertility potential, and MTCT are particularly germane to this patient population. It is not unusual for these very settings, it is of critical importance on a societal level for women to bear children; however, less than 10% of HIV-infected pregnant women receive therapy and most of them receive short-course, single-agent, single-dose regimens. A 50% reduction in HIV-transmission is achieved with this approach, but with the substantial risk of antiretroviral resistance and subsequent compromise of therapy when it is later indicated for these women.

A number of gynecologic conditions occur with increased frequency in HIV-infected women. For instance, genital HPV infection, a sexually transmitted disease that is caused by human papillomavirus, occurs with increased frequency in HIV-infected individuals; accelerated rates of progression or persistent infection are associated with women to receive their diagnosis of HIV infection while undergoing a prenatal evaluation. In addition, especially where antiretroviral therapy (ART) is widely available, women with an established diagnosis of HIV infection may choose to have children, reassured by statistics that suggest the risk of MTCT is 1% to 2% when taking ART. While pregnancy does not appear to have an impact on the progression of HIV disease, some studies have suggested that HIV may negatively affect fertility, primarily in women residing in resource-limited settings, suggesting that other factors such as nutritional status and routine access to health care may also be implicated. In more profound immunosuppression. Optimal management strategies for HIV-infected women must include routine gynecologic evaluation as part of a comprehensive treatment approach.

The preponderance of data from patient cohorts and clinical trials suggest that women and men derive equal benefit from ART. However in some studies, factors such as impaired access to health care, high rates of depression, substance use, and decreased rates of adherence have been associated with worse outcomes for women. Poor adherence has been linked in turn to increased rates of side effects and higher off-treatment rates for

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women. Women have experienced higher rates of virologic failure in a number of observational studies, although the causes for these results are not clear. In order to ensure maximal benefit of ART for women, studies to determine which drug regimens are best tolerated and most effective need to be undertaken.

Gina was indeed HIV-positive. Several factors in her presentation and past history strongly suggested HIV infection as an underlying, unifying diagnosis. Her sex was the confounding variable for the clinicians who saw her; they did not make the association between any one factor and HIV infection in this female patient. She did not see herself as being at increased risk of HIV infection; she was not aware of US demographics that indicate African-American women have a significantly increased risk of acquiring HIV infection. Gina has been in counseling, participates in regular group sessions, and has disclosed her status to her sister who is very supportive. She has responded well to ART and is working full-time.

Women acquire HIV infection primarily through heterosexual activity. They represent the fastest growing segment of the epidemic globally. Effective prevention of this infection in women requires a commitment to significantly improving their social and financial status, crafting and disseminating information about risk factors in a culturally sensitive format, and organizing comprehensive, specialized medical services that can be easily accessed. Ultimately, prevention measures that the woman can control will be most successful in reducing the impact of this virus on women. Although there is much interest and active research efforts in the area of microbicides and vaccines, women currently have few such methods available to them.

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HIV controllers: An untapped source of clues to overcoming HIV infection

By Bruce D. Walker, MD

The goal of developing an effective AIDS vaccine to provide sterilizing immunity remains elusive; protection from disease progression but not protection from infection has been achieved in animal models. Current AIDS vaccine strategies are thus focused on protection from disease progression as a goal for first-generation HIV vaccines for humans. As a strategy to curtail the global epidemic, there is reason to believe that the epidemic would start to decline even if immunized persons were to become infected, as long as viral load could be durably sustained at levels that would make HIV transmission and disease progression much less likely. A reasonable upper-limit target level of plasma viremia for such vaccines would be less than 2000 RNA copies/mL, a level at which the probability of transmission and disease progression is markedly reduced. Moreover, if one could use immune-based therapies to achieve this level of control in persons already infected, the same benefits would accrue on an individual and population level.

Remarkably, there exists a small group of individuals who appear to survive without any adverse consequences from their HIV infection. These persons, who have been given the rather unfortunate designation “elite controllers,” represent less than one-half of 1 percent of persons infected with HIV. They are able to keep the virus in near-total check, which means that they are still infected but the virus is somehow prevented from growing rapidly in their bodies and inflicting damage. How does this happen? We don’t know! As incredible as this seems, we still do not understand the most fundamental ways in which these persons are able to beat the odds and live for years—some now for more than 25 years and counting—without developing AIDS. And they do this without ever needing antiretroviral medications.

Understanding how viral control is achieved in these HIV controllers is likely to be critical to the process of vaccine development. And yet, it is poorly understood in part because of limitations in identifying sufficient subjects with sufficient volumes of samples to study, and in part because comprehensive studies of both the virus and the body’s immune response have not been performed on these same subjects. Becoming familiar with the mechanisms of durable viral control will require comprehensive viral and host genetic data in conjunction with functional data on the innate and adaptive immune responses, something that is yet to be attempted.

With substantial seed funding from the Mark and Lisa Schwartz Foundation, we have initiated a comprehensive and collaborative large-scale study to attempt to break the code of how this...continued
remarkable state of “elite control” is achieved, but this will require very large numbers of such individuals. Approximately 1 patient in 300 is an elite controller, able to control HIV-1 replication to less than 50 RNA copies/mL without the need for antiretroviral medications. Our data thus far indicate that host genes play an as yet poorly defined role. It also appears that preferentially targeting certain HIV proteins by the immune response may play a role. However, none of the parameters identified thus far has high predictive power for this outcome. Nevertheless, it is now possible to define the genetic basis of this outcome through new techniques that have been established in relation to the Human Genome Project, which allows for rapid and comprehensive identification of gene sequences that are associated with certain disease states.

To search for novel human genetic factors that influence HIV viral load, we will conduct what is called a “whole genome association scan” (WGAS) on persons at the extremes of the amount of HIV levels in the blood, under the hypothesis that host genetic factors influence immune responses and durable suppression of HIV infection. Such association studies, applied to other diseases such as macular degeneration, have successfully identified genes that have an important role in causing disease. Because the genetic screen is not biased towards any gene or pathway of known biologic function, this approach has the greatest opportunity of distinguishing factors previously unidentified as being important in viral control. Once a causal gene is identified, this information will provide immediate insight into host genetic factors and immunologic pathways that regulate HIV control.

The WGAS will use more than 650,000 genetic signatures called single-nucleotide polymorphisms (SNPs) in 1000 elite controllers, 1000 viremic controllers, and up to 3000 age/sex/ethnicity-matched control individuals with progressive viremic HIV-1 infection. Identification of a gene that influences host immune responses and viral load, as well as its mechanism of action, will have immediate practical applications not only for development of an effective AIDS vaccine but also for identification of potential new therapeutic targets.

The key to the success of this project is the ability to find the persons that fit these highly specific criteria. We are trying to locate at least 1000 elite controllers and 1000 viremic controllers—the latter with persistent viral loads (for greater than 1 year in the absence of therapy) of 50 to 2000 RNA copies/mL. Thus far, through collaboration with scientists, health care workers, AIDS service organizations such as The Center for AIDS Information & Advocacy, and patients themselves, we have identified more than 150 elite controllers and a similar number of viremic controllers. The success of this project will depend on our ability to find the additional necessary patients. If the true frequency is 1 in 300 and there are close to one million HIV-infected persons in the US, then there are at least 3000 persons that fit the elite controller category alone. Our challenge as a group is to recruit as many of these persons as possible, as they offer a unique and untapped resource that can provide critical clues to ending the HIV epidemic.

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Twenty-five years after its discovery, HIV has proven to be a problem that is truly exceptional, medically, socially, and politically. HIV has galvanised partnerships across public policy, human rights, and medicine—constituency collaborations that would have been previously inconceivable. This unprecedented attention has been largely matched by investment in clinical research. That there are 24 licensed antiretrovirals for the treatment of HIV infection from 4 different classes of drugs, presenting myriad therapeutic possibilities, is testament to the political and social tenacity of the response to the epidemic. No other medical discipline or disease can boast such tangible results. At the heart of this phenomenon is the remarkable legacy of AIDS activism.

Even after all of these years, it is sobering to consider how much we as an activist community have learned and adapted in our fight against AIDS. In this moment of introspection, not only should we reflect on what the next 25 years may bring, but more importantly, we should define our place in this future and whether we are motivated and equipped to adequately address the impending challenges of HIV treatment and prevention in the developing world. The gaping chasm of inequality that stares back at us from other continents should be evidence enough to mobilise us. Consider this perversive transposition—80% of people with HIV in the developed world have access to antiretroviral therapy, while slightly less than 80% of those living in poorer countries that need HIV treatment do not.1 And while the rest of this essay primarily addresses our advocacy efforts in the developing world, I accept as paramount and as a fundamental objective the necessity of working toward a “100% access” goal in our own developed countries.

HIV activism has reached a critical hiatus. This is an opportune moment in which to evaluate priorities for the role of treatment activism in the global context, as decisions that we make now will shape our impact over the next 2 decades. What we have achieved is duly acknowledged, but the challenges that face us are uniquely different from those we have previously encountered. Two major challenges lie ahead: first, to continue with treatment and prevention activism, pushing forward the scientific agenda on which we have so ably delivered, and second, to ameliorate the conditions of those who suffer the multiple, compounding indignities of poverty, disease, and discrimination within our own research-rich nations and those distanced by geography and circumstance. The latter is a far more daunting challenge. In this regard and with some notable Non-Governmental Organization (NGO) exceptions, our interventions have been sorely inadequate.

At this historic juncture, I take this opportunity to share some perspectives from my personal experience as an AIDS activist, a member of both European and US advocate forums, and a community treatment journalist. My learning has also been shaped by professional networks in the HIV scientific, policy, and clinical communities, including my work with international NGOs. Physicians,
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scientists, governments, industry, and donors all have a uniquely nuanced role in the world of HIV, but I focus here on the Western activist community’s neglected potential for addressing issues critical to the developing world. In particular, there is a need to establish well-informed, responsible strategies for intervention that recognise the evolving new world order in which a few powerful individuals and non-governmental agencies have the potential to dominate the global public health agenda. As such, I propose a critical self-analysis in several important arenas: 1) the knowledge and skills needed for our constructive contribution; 2) the implications of the funding and political alliances we may deliberately or inadvertently cultivate; 3) the need for a coherent policy framework based on local realities of people with HIV in the developing world; and finally, 4) a shift from the established self- and individual-advocacy approaches to models that encompass broader public health perspectives.

Science and the activist
The HIV agenda embraced by Western activists over the past 2 decades has been predominately a clinical one, with a singular emphasis on pushing the best drugs rapidly through licensure, into the clinics and to the patient. To a great extent we have achieved our clinical goals. With so many drugs on the market, our emphasis now should be on fewer but better drugs with higher genetic barriers to viral resistance that help compose safer, simpler, and more tolerable regimens. Charles Boucher, a virologist from Utrecht Medical School in the Netherlands, charts a demographic chronology of the virus. He draws a distinction between 2 divergent populations affected by HIV. The first population encompasses those infected early in the pandemic and treated historically with suboptimal mono- and dual-therapies. These patients harbour multi-drug resistant viral strains less responsive to existing treatments; a constant supply of new treatments is essential to battle their rapidly resistant virus. For the second population—those newly-infected with either wild-type or a transmitted virus with low-level resistance that is increasingly detected at baseline by routine monitoring—the treatment needs are different from the drug-resistant patients. Yet despite the epidemiological evolution and success of antiretroviral therapies, we have yet to modify our activist approach. We demand drugs with novel mutational pathways and faster approval from FDA.

Safety, tolerability, and effectiveness of new regimens remain paramount, as does the need to improve investments in diagnostic technology. There is a special role for treatment activists who are highly research- and treatment-literate and therefore able to interface effectively with industry and investigators. We have learned that industry, and even the clinical community, perceive the needs of patients differently than we do as patient advocates. For this reason, scrutiny by informed activists who understand the complex language of viral resistance, pharmacokinetics, and chemokine receptors will continue to be important in bringing forward sustainable, effective therapies and prevention technologies to treat and prevent HIV.

In addition to continuing our inquisition of the science and trial designs put before us, we can also assume greater responsibilities in effecting change. Those in leadership positions at NGOs consistently reflect the structures of those in power in the US and Europe. Our focus should be the marginalised communities within our resource-rich countries, those communities who bear the disproportionate burden of HIV here are not yet strongly reflected in our activist circles, at scientific conferences, as speakers, or as community journalists. Advocates from these communities should be incorporated into our ranks.
Global health and the international activist

In UNICEF’s famous words, “there shall be no silent witnesses.” Yet we continue to be observers in the unfolding catastrophe of HIV in the developing world. Our success as activists in pushing forward HIV treatments in the developed world is unmatched by our actions to support the world’s most vulnerable populations. There are shining examples of agencies that have delivered exceptional results. Organisations such as Médecin Sans Frontières (Doctors Without Borders) have demonstrated a coterminous approach to activism and health service provision; by delivering health care in rural, isolated regions, they have only strengthened their contribution and credibility. But in large part, treatment advocates active in the Western hemisphere have failed to mobilise their skills, resources, and attention beyond our community sub-groups.

If we do decide that the developing world deserves our attention—and as yet there remain only a handful of organisations entering this global advocacy movement—we have a number of challenges with which to contend:

- Do we have an inherent moral imperative to intervene? If so, what is our role and with what legitimacy or authority do we deem to intervene?

- Do we have an accurate understanding of the situational realities of people living with HIV in the developing world?

- Without a coherent policy framework, how will we organise ourselves and take our place alongside our activist peers in the developing world?

- Can we make the transition from the well-rehearsed individual and self-advocacy paradigms to population, public health-focused advocacy that requires different knowledge, sensitivities, and world-view?

To intervene or not to intervene

Given our collective histories and the role that our respective governments and market dynamics have played in creating the vast disparities in health in the world, the moral imperative seems self-evident. However, this responsibility does not give us legitimacy. Indeed, our motive for intervening is, and should be, called into question. Sergio Haddad, President of the Brazilian Association of NGOs, states the problem as one of perception: “Northern partners view Southern social problems as charity issues,” he notes. He amongst others has called for greater scrutiny of funding sources that support NGOs. But more than that, he suggests that what is needed are coherent “principles to influence public policy” rather than the fragmented and self-indulgent agendas of individual agencies.

In an article titled Belligerent Funding, Hugo Slim, a Trustee of Oxfam and international adviser to the British Red Cross, contemplates the “‘moral implications’ of accepting (or not accepting) funding” from suspect sources. His own analysis explores actions by governments who pursue military intervention followed by the offer of subsequent relief, in this case by the British government. He concludes that in fact it may be immoral not to accept money from agents who have been instrumental in shaping the debilitated circumstances of war-torn, poverty-ravaged countries.

As we assume a role in international advocacy, it is not only funding that is relevant but also our offi-
cultural and informal alliances. In the fractured, ideologically nuanced world of international politics, we may struggle with our own cultural limitations and usefulness. In treading the tortuous path of intervening in other countries’ affairs, we must do so with clearly articulated motives, scrupulous principles, transparency in our governance and administrative systems and, above all, a constant reflexive awareness of our funding masters and their agenda. The “clientilistic” relationships that governments have formed with international NGOs are well-intentioned, and to some extent necessary, but they can be a relationship fraught with danger. Too easily, NGOs are perceived to have been co-opted to deliver the prevailing government agenda, whether by design or more often, by benevolent ignorance.

Arundhati Roy, in a vociferous critique of the role of NGOs, writes, “Though they may not be the same agencies (as those of Western governments), they are certainly part of the same political formation . . .” 4 She sees NGOs as an extension of the neo-liberal project, as mannequins of the state, motivated by guilt, animated by zeal, but ultimately serving to “. . . defuse political anger and dole out as aid or benevolence what people ought to have by right. They unwittingly reinforce racist stereotypes and reaffirm the achievements . . . the compassion—the tough love—of Western civilisation. They’re the secular missionaries of the modern world.”

Given this just critique, how do we counteract this? How do we take our place as responsible global citizens with skills, resources, and conviction, and do so in a manner that is fair and worthwhile? This brings us to a more sensitive introspection—is our intervention even wanted? Developing world NGOs have sometimes expressed the opinion that we may be interfering without adequate reference to local realities and due diligence. Witness the recent and very public clash between the Treatment Action Campaign (TAC) of South Africa and Act-UP Paris regarding conduct in the DART (Development of AntiRetroviral Therapy in Africa) trial in Africa.5 The issue became one about information and representation—whose priorities were being expressed, how these were formulated, and the terms of engagement for intervention.

But good intentions aside, such contretemps rest largely on the notion that organisations that intervene at arm’s length sometimes jeopardise the hard-earned investments or relationships cultivated by local NGOs. Advocates from developing countries sometimes receive external activist intervention with muted enthusiasm, perceiving us to be morally supervising, dictating terms from New York, London, or Paris, rather than participating as equal or advisory partners. Indeed, as individuals and agencies, we are rarely humbled by our outsider status, consistently refusing to accept that we will always know less about the local situation, all the while basking in the luxury that we can ultimately return to our comfortable existence.

And it’s not only Southern NGOs, but research and clinical colleagues from the developed world, who challenge our competency, legitimacy, and value. Professor Joep Lange, writing in PLOS Medicine, accuses us of “uninformed demagogy and intimidation.”6 When respected physicians such as Professor Lange feel this way, we have to strive even harder to develop our role as credible partners in the global health planning and negotiating arena.

**Our place in the new world order**

Beyond issues of legitimacy, there is a structural challenge that should immediately focus our efforts. It follows a famous maxim that the world
is made up of a hundred people; that is, our lives are shaped by the influences of a few very powerful individuals. In the field of HIV, I would argue that the world is getting smaller still, throwing into sharp relief the function and sustainability of historically established organisations endowed with the responsibility for global health. The Bill and Melinda Gates Foundation, one of the largest donors of research and capacity in resource-poor countries, has a commendable record of intervention on HIV and neglected diseases. Along with other giant donors, such as the Clinton Foundation and the Soros Foundation Network, they have the potential to influence the global public health agenda, in some ways distorting it. This has created a very real conundrum in modern public health. Given that these organisations invest unprecedented funds towards improving public health, and that they do so publicly, what implications are there for international health agencies tasked with planning and implementing global health? And how must activists seeking to engage with these charitable organisations define their contribution in this new world order?

Journalists Jon Cohen and Laurie Garrett call attention to the phenomenon. Writing in Science, Jon Cohen pronounces in “The New World of Global Health,” “A revolution is under way that is fundamentally altering the way the haves of the world assist the have-nots.”7 Laurie Garrett alerts us to the potential alarming consequences of individuals who bring so much resource to the negotiating table that any claim to an equal, empowered transaction is tendentious. “Gates’ money sets the agenda for a great deal of public health policy, but it’s important to remember what it isn’t doing and won’t do—the job of the World Health Organization (WHO) and the World Health Assembly . . .”8 Mark O’Keefe, writing in the San Francisco Chronicle, refers to the same issue, describing the “dangerous degree of influence” that these agencies can bring to bear.9

The fact that the Gates Foundation and others donate their personal wealth towards ameliorating global public health is commendable, but where is the accountability? It may be worth bearing in mind that, for all its faults, the WHO is a democratically-formed international agency made up of its member states, with established structures of global governance and accountability. In contrast, leaders of private donor agencies have responsibility only to the internal agenda of the foundation. It is imperative therefore, that NGOs themselves participate in the process of defining donor responsibilities to safeguard against any potential transgressions. And for this to be effective, NGOs will need greater transparency, accountability, and responsibilities. In this new world order where articulate, powerful donors sit alongside normative agencies, NGOs have a different but entirely legitimate contribution to make. In this situation, international HIV and public health advocates can define a new position, one in which we are tasked with keeping a check on the extent of powers of donor agencies, just as we would do with our own governments, international normative agencies, or industry representatives.

We have yet to fully develop our role in this respect, but the need for vigilance is becoming increasingly vital. As community-informed representatives, we can establish both legitimacy and practical usefulness with the advocacy and concil-
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...emergency skills we bring to help balance the differentials of power that influence North-South negotiations. Inherent in these different perspectives of agency responsibilities is the potential for both danger and opportunities for global public health. Certainly the challenge of meeting the burgeoning health needs of developing countries will require a multiplicity of partnerships and approaches, as well as a stringent critique of political motivations.

An end and a beginning

The treatment activist community in the West has been at the forefront of scientific and clinical advances in HIV. Less certain is the impact we have made on the global epidemiology of HIV. The potential for activist contribution on the global scene is matched only by the need and urgency for informed and conscientious intervention that addresses the escalating devastation inflicted by HIV disease. The emergence of big, powerful donors within global health has raised an intriguing spectre, introducing and reconfiguring key players around the public health agenda-setting table. With their insight, advocacy skills, and convictions to direct resources and energies towards those most vulnerable, HIV activists have a critical and much-needed contribution to make in this dialogue. How we fashion that role will require us to ask some important, if uncomfortable, questions as we take our role alongside activist comrades in the developing world. Only then can we hope to improve the conditions for the millions living with HIV, to realise our potential, and ultimately, to define our own place in the global community.

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HIV vaccines: The future looks promising

By Dorothy E. Lewis, PhD

If I had a dollar for every time a person asked me despairingly, “How come no HIV vaccine?” I’d be rich and eating bonbons in Tahiti. But I’d rather forgo the prospect of riches and additional pounds and actually have an effective and broadly used HIV vaccine.

There are several major reasons why we don’t yet have a vaccine that meets our needs. The most basic reason is that HIV is a wily pathogen, with surprises at every turn. The genetic diversity of HIV is a big problem. HIV also conceals important regions in its proteins that would normally elicit a robust immune response. This concealment leads to a key problem in the development of neutralizing antibodies, both in infected human beings and in animal models of HIV.\(^1\)

What are neutralizing antibodies? These are antibodies that develop in the body after exposure to an organism and actually prevent infection by “neutralizing” the agent in question via a number of mechanisms. The questions are: How do we create these for HIV? and How can we get humans to make such antibodies?

To even begin to address these questions, a broad review of how vaccines are made and delivered to humans is necessary. When the average person thinks of vaccines, they might think of the polio or smallpox vaccines, which are vaccines against diseases that have been conquered. The advantage of these vaccines is that they are live but attenuated (see Table 1). That is, the organism used as a vaccine is a less pathogenic form, but nevertheless causes infection and hence induces great long-lasting protective immunity. However, the downside is that in some cases, both the smallpox vaccine and the oral polio vaccine can cause disease, which, of course, is undesirable.\(^2\)

A live, attenuated vaccine is unlikely to be made against HIV because of worries about in vivo mutations and the fact that HIV integrates into cellular DNA. This means that once it’s there, it’s in the DNA for the life of the cell. The principle protective mechanism for live, attenuated vaccines is thought to be production of neutralizing antibodies. Unfortunately, the reality is that the actual mechanism of protection for any vaccine is seldom completely understood. Indeed, this is a crucial issue for the design of any vaccine. How do you know if you have the right antigen? How do you know if the immune responses you can easily measure are protective? Having a “challenge” animal model to test these ideas is extremely important. At this juncture, most agree that targeting both envelope and structural proteins from the virus will be necessary for an effective vaccine against HIV. Sterilizing immunity, however, has only been observed with antibodies given before or at the time of challenge with Simian Immunodeficiency Virus (SIV).\(^3\) T-cell vaccines induce good T-cell responses, but of course the animals still get infected with SIV. Thus far, the best control of virus replication occurred using an MVA (modified vaccinia virus Ankara) DNA prime/boost method.\(^2\)

Most of the other vaccines used to immunize humans are killed agents, or proteins, or subunit vaccines—those made from components of an
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organism, sometimes against a single protein, as is the case for Hepatitis B vaccine. But, get real! Preventive and/or protective immunity induced by immunization with a single protein is rare. For HIV, it is likely that responses to multiple proteins will be required.

The modern age of vaccine design is centered around immunizing by delivery methods using viral vectors that are either replication competent (meaning alive) or replication defective (meaning dead). None of these is really in use yet, although a Phase I study was recently published.4

The replication-competent vaccines are most like the live, attenuated vaccines mentioned above. They usually use other viral agents, which have been genetically engineered to contain HIV proteins. However, they do have the potential to revert (similar to live, attenuated vaccines).

A key issue with replication-defective vectors is that there may be pre-existing immunity to the vector, such as with adenovirus. Most of us have had various infections caused by this organism in our lives, so that when our immune system sees this virus again, there will be a memory response that will reduce the effectiveness of the responses against HIV proteins the vector is carrying. Naked DNA-encoding proteins from various organisms have also been found to induce immunity, especially cellular responses by T cells.

Both of these strategies—virus-based vectors and naked DNA-based vectors—are under evaluation for HIV vaccines. The virus-based vectors include those that are based on adenovirus and pox virus, both of which are being studied in advanced clinical trials. Several other formulations of vaccines are in advanced trials based on adeno-associated virus vectors or the use of HIV peptides mixed with lipids. These later vaccines primarily elicit cellular immunity. In addition, an HIV multiclade DNA vaccine and an adenovirus vaccine have induced antibodies. Now these 2 vaccines will be used together to elicit an optimal response.4,5

The current strategy of choice, arising from multiple preclinical trials, is called prime/boost, meaning priming with DNA (for example), then following with a boost from a vectored vaccine for the same organism. This primarily results in the generation of CD8 T cells, which are key in antiviral immunity. Variables important in generating good CD8 T-cell responses include the way vaccine is given (subcutaneous is best), the dosage, and the type of delivery vector.6,7

However, one thing should be made clear. No one believes that CD8 T cells by themselves can result in sterilizing immunity to HIV (ie, no infection at all). Rather, a good CD8 response typically contains the pathogen through the elimination of infected cells, but does not eliminate the pathogen per se. To eliminate or prevent infection, antibodies that are broadly neutralizing are needed and should be reactive with many of the HIV envelope proteins and other HIV proteins found in human populations.

So why don’t we just take a bunch of different envelopes from different HIV groups and create a vaccine from them? The answer is that HIV has “unprecedented mechanisms for evading the host antibody response.”1 Plus, a key problem discovered in the last few years concerns how HIV gets into susceptible cells. The viral envelope is a trimer of glycoprotein (gp): gp120-gp41. The gp120 binds to CD4, which induces a conforma-
tional change, exposing a region that then binds to a chemokine receptor on the T cell. After this binding, another conformational change allows gp41 to facilitate entry of HIV RNA into the cell. However, much of the HIV surface of the envelope has N-linked sugars, which actually come from the host cells that HIV buds from; hence much of the gp120, which is highly immunogenic without the sugars (for both mice and humans), is cloaked in carbohydrates!^{8,9}

On the other hand, as we have learned more about the structure of HIV, we also have learned that neutralization by antibodies is possible! That is, through the work of a few diligent investigators in the 1990s, and the screening of many thousands of human antibodies, a few neutralizing antibodies were found that came from a few rare HIV-infected people. The fact that these antibodies exist offers proof that, although rare, humans can make neutralizing antibodies to HIV. The best studied antibodies (4 of them) indicate that they work by recognizing physically conserved areas exposed on the gp120 molecule that have conformational restraints and are thus important in allowing HIV to enter cells.\(^1,8\)

Many investigators, especially organic chemists, are now at work trying to “mimic” these regions, so that an ordinary host immune system could be induced to respond reliably. Thus, there is real hope on this front.

Another recent area of promise in vaccine research uses virus-like particles or VLPs. These particles consist of various HIV proteins that can self-assemble without the infectious RNA. A key advantage of these particles is that they induce high levels of both T cells and antibody, most likely because these particles are so structurally similar to the real HIV.\(^10\) A key disadvantage is that

### Table 1. Types of vaccines

<table>
<thead>
<tr>
<th>Type</th>
<th>Examples</th>
<th>Immunity due to:</th>
<th>Risks/Problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Live, attenuated</td>
<td>Smallpox</td>
<td>Antibodies</td>
<td>Reversion to pathogenic</td>
</tr>
<tr>
<td></td>
<td>Oral polio</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heat killed: protein or subunit</td>
<td>Polio</td>
<td>Antibodies</td>
<td>Not very diverse, not as effective</td>
</tr>
<tr>
<td></td>
<td>Hepatitis B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Replication competent</td>
<td>Yellow fever</td>
<td>Antibodies</td>
<td>Reversion</td>
</tr>
<tr>
<td>Replication defective</td>
<td>Adenovirus 5</td>
<td>Cellular immunity</td>
<td>Pre-existing immunity</td>
</tr>
<tr>
<td>DNA</td>
<td>Many in development</td>
<td>Cellular immunity</td>
<td>No antibodies</td>
</tr>
<tr>
<td>Prime/Boost</td>
<td>Optimized strategy for HIV</td>
<td>Both antibodies and cellular immunity</td>
<td>Complicated, expensive</td>
</tr>
<tr>
<td>Virus-like particles (VLPs)</td>
<td>Many in development</td>
<td>Both antibodies and cellular immunity</td>
<td>Expensive to produce, unstable</td>
</tr>
</tbody>
</table>
continued from page 31...

they are very expensive to make and their stability is questionable, so future work is necessary. So far, this article has focused on prophylactic vaccines. What about vaccines for those already infected? The good news is that if the immune system is intact enough to respond, several strategies can be used to boost immunity and better suppress HIV or SIV. Moreover, even if a vaccine did not protect against infection, a recent study showed that vaccination before viral challenge could protect memory cells from dying during infection, allowing the immune system to remain intact.12 Another strategy using a canary pox virus vaccine and interleukin-2 (IL-2) in HIV-infected patients resulted in increased CD4 T cells (because of the IL-2), but did not control viral rebound.13 There is some indication that the timing of immune intervention is likely to be critical for a therapeutic vaccine to be effective.14 In summary, there has been real progress conceptually in HIV vaccine design in the last 5 years, as well as new approaches that remain to be tested clinically—the future of HIV vaccines looks promising.

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References
Twenty-five years of the HIV/AIDS epidemic has revealed nothing more certain than that it thrives at the crossroads of our shortcomings. Poverty, inequality, discrimination—find the intersection of these in any community and there also lies HIV.

Of the people who live in abject poverty, nearly 70% are women. Women perform two-thirds of the world’s work, earn less than 5% of its income, and own less than 1% of its property. Three of every 4 illiterate adults are women and two-thirds of children denied primary education are girls.¹

In areas where HIV/AIDS has hit the hardest, its burden has fallen most heavily on women and girls. In sub-Saharan Africa, there are 14 women living with HIV/AIDS for ever 10 men,² and a young woman is 3 times more likely to get infected with HIV than a young man.³

Globally, more adult women are living with HIV than ever before. In the United States, with its incomparable resources for disease prevention, AIDS cases among women rose from 8% in 1986 to 26% in 2001. Between 2001 to 2004, HIV infections increased 15% among women compared to 2% among men.⁴

A woman’s vulnerability to HIV infection is in direct proportion to her lack of control over the risks of infection. For the HIV epidemic to move off its current course of increasingly and disproportionately impacting women, the world in which women live must change. In the words of Peter Piot, Executive Director of UNAIDS, “The best way to prevent HIV is to raise the status of women.”

Women must be in control of their lives and bodies.

Women don’t need to be empowered. To empower is to give power or authority to someone. What women need cannot be passively received like a gift from a benefactor. They need economic opportunity, education, control over their sexual health, and access to health care and information. Women and girls need the tools of power that boys and men take for granted.

Women need to be in charge of the decisions in their lives, from their private choices to public laws. Globally, women remain under-represented in the governments that make policies affecting every aspect of their lives. In the United States, women make up just 23% of the state legislature and 15% of the Congress. Women living with HIV/AIDS have token participation with plenty of organizations that claim their cause, but authentic involvement of and direction by affected women is the only way to fully understand the issue and create a meaningful response.

In their intimate lives, women most often must rely on sexual protections that require the consent of men. Beyond female-controlled prevention tools like microbicides and readily available contraceptive options, women must also have access to safe and legal abortion. It is estimated that 68,000 women die each year from unsafe
aborted and at least 5 million more are hospitalized because of infection or other complications. In the absence of improved contraceptive options for women and legal endorsement of a woman’s right to possess her own body, these eminently preventable injuries and deaths are, for all intents and purposes, condoned.

Weakening the lack of authentic control women have over their bodies is how they are commonly infantilized and grotesquely objectified in many cultures, often with their presumed consent and under the guise of sexual liberation. In other cultures, young girls are forced into adult sexual situations for a host of reasons, effectively robbing them of their right to be girls.

**Women make up half of the world’s population. They are not extensions of men or a means of reproduction.**

Women are not victims. There is nothing inherently weak about women. What makes women vulnerable to harm and violence is the inherent injustice of a society, like that of so many countries too numerous to list, which systematically devalues the contributions of women and fails to recognize the resilience of women as a strength upon which families rely and communities are built. We would do well to take our cue from Cynthia Leshomo, Botswana’s Miss HIV Stigma Free of 2005, who said, “I am not a victim, because a victim is powerless. I am not a sufferer because suffering is nothing but a helpless prayer. . . I am a human being with flesh and breath.”

The great success story of mother-to-child prevention of HIV has never actually recognized the health of the mother as equally important in the equation of success. Countless mothers have risked their own future treatment options with single-dose nevirapine to spare their babies from HIV infection at birth. However, how many of those babies will successfully run the gauntlet of HIV risks into adulthood? Undeniably, the best protection for any baby is a healthy mother. Is this not true for HIV-positive mothers, too?

*“Instructions to abstain or to be faithful or to wear a condom don’t work in the growing number of places where the single greatest risk of HIV infection is to be a married, monogamous woman.”*

Despite the reality that more than half of all people living with HIV are women and that biologic differences are known to exist based on sex, women are treated according to guidelines that still extrapolate treatment data from studies of (White) men. Women have been dying of AIDS for as long as AIDS has existed. Still, in the shrug of the research community at the abysmal numbers of women in clinical trials, there is a sense that women are a foreign species whose lack of participation in research is shrouded in mystery. In truth, research has long been geared to address the needs of men, not the needs of people.

Further, there has never even been a prevention message for women. Instructions to abstain or to be faithful or to wear a condom don’t work in the growing number of places where the single greatest risk of HIV infection is to be a married, monogamous woman. These instructions speak to the realities of most men’s lives and, in fact, require their consent. There is virtually nowhere on the planet that a woman’s right to safe sex and
autonomous decision-making over sexuality are as respected as those of men, if at all.

**HIV/AIDS is not a crime or a sin.**
**HIV/AIDS is a health condition.**

When it comes to HIV/AIDS, there is no first world or third world. There is one global pandemic that requires a commitment to science-based methods to address the biologic process of infection and disease. Still, the United States leadership promotes abstinence as prevention, has refused to provide accurate information to the public about condoms in violation of its own federal laws, and openly opposes the right to safe and legal abortion. Compounding the misdirected prevention efforts of the current administration, the United States and other wealthy nations have shortchanged the Global Fund To Fight AIDS, Tuberculosis and Malaria and its efforts to mount a unified and community-based approach to combating HIV/AIDS.

For 18 years, the United States has banned federal funding for syringe exchange programs, the most effective tool that exists for HIV prevention. The government has stalled funding HIV services in favor of war and has allowed the epidemic to sweep into its communities of color, who now bear exponential risk of HIV infection compared to White Americans. With all the means to end the domestic epidemic, how could it be that African American and Latina women, who represent less than 25% of all women in the United States, comprise more than 79% of AIDS cases in women?  

Treatment is prevention. The distribution of antiretrovirals to a million-plus people in the developing world has not dented the death rates. Access to treatment must be universal. The US Centers for Disease Control and Prevention has recommended that HIV testing be routinely performed as a means to identify those who are currently undiagnosed. However, what purpose will knowing one’s HIV status serve if people with AIDS continue to die even while, in the wealthiest nation in the world, their names remain on waiting lists for antiretroviral drugs?

There is no mistaking the enormous challenges to facing down the HIV/AIDS epidemic in women in order to win the fight. The most encouraging truth is that we have available to us—all of us—the means to prevent infection and manage it. The steps that remain are the ones that not only move us toward a world in which women live outside the shadow of AIDS, but one in which women live in full possession of their lives and bodies.

**Heidi M. Nass** is with the Treatment Support & Education Program at the University of Wisconsin Hospitals & Clinics HIV Care Program in Madison, Wisconsin.

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1. milleniumcampaign.org (United Nations)
Plumbing HIV pathogenesis
By Richard Jefferys

More than 25 years have passed since the first cases of AIDS were reported, and from the very beginning the pathogenesis of the disease has presented scientists with a paradox: HIV infection is associated with the persistent activation (revving up) of the immune system, and yet also with eventual immune deficiency. Immune activation was described in the earliest cases based on swollen lymph nodes, or “lymphadenopathy,” something typically associated with activation of the immune system that occurs just transiently during acute infections (with the flu or the measles, for example). But in HIV infection, research has shown that such immune activation does not resolve, but rather persists after the acute stage of infection. This prolonged, low-level activation of the immune system is associated with a gradual decline in the numbers of CD4 T cells measurable in the blood and a spreading dysfunction among remaining CD4 T cells. This ultimately renders these vital immune system components unable to coordinate the suppression of pathogens (such as Cytomegalovirus, Mycobacterium avium complex, toxoplasmosis, etc) that are easily kept in check in healthy people.

Unraveling the mechanisms by which these phenomena occur is vital to gaining a full understanding of AIDS pathogenesis and, by extension, designing therapies that might ameliorate HIV’s harmful effects on the immune system (immunobased therapies). But the human immune system is vast and dauntingly complex, and this complexity presents an enormous challenge to those scientists who are working in the field. It also presents a challenge to anyone seeking to explain where pathogenesis research stands at the end of 2006! Nevertheless, it is well worth surveying the current terrain, highlighting the areas of consensus and controversy among researchers and the key questions that must be answered to gain a fuller understanding of the disease.

Taps and Drains
The first widely publicized theory that attempted to resolve the immune activation/immune deficiency conundrum was David Ho’s “tap and drain” model of pathogenesis, published in the journal Nature in 1995. In this relatively simple formulation, immune activation simply reflected the body’s attempt to generate new CD4 T cells (“tap”) to replace those that HIV was assumed to be killing (“drain”). The fact that this idea was relatively easy to grasp made it very seductive and even in 2006, it is possible to find information on HIV/AIDS that treats the tap and drain model as the leading theory of pathogenesis.

However, few immunologists were convinced by the simple plumbing scheme that Ho invoked. Several leading immunology researchers wrote to Nature to point out obvious flaws in this theory as soon as it was published, but their correspondence received little media attention. Over time, the dissenters in the immunology community produced data conclusively rejecting Ho’s theory. The increase in CD4 T-cell counts that occurs immediately after initiation of antiretroviral therapy (ART) was shown to primarily reflect the redistribution into the blood of CD4 T cells that had been trapped in the lymph nodes and other tissues; the initial rise in CD4 T cells did not signify the production of new cells as Ho’s model predicted. Also, it had already been reported (by the
late Janis Giorgi at UCLA) that immune activation markers on CD8 T cells were elevated and correlated with disease progression. And yet, CD8 T cells are not depleted by HIV. Subsequent sophisticated analyses of T-cell activation and proliferation in people with HIV showed that CD4 and CD8 T-cell activations are tightly correlated, confirming that immune activation does not reflect an attempt by the immune system to replace CD4 T cells killed by HIV. A number of studies have also reported that markers of immune activation correlate better with disease progression than viral load. Taken together, these data have led to a near total consensus in the scientific community that immune activation plays a critical causative role in HIV pathogenesis.

**Leaks and Patches**

The widespread agreement about the importance of immune activation reflects progress in the study of HIV pathogenesis, but it still leaves many questions to be addressed. Examples include:

- What is causing immune activation in HIV infection?
- Why and how does immune activation persist?
- Why are peripheral blood CD4 T-cell counts more affected than peripheral blood CD8 T-cell counts?
- How does immune activation lead to the eventual development of immunodeficiency?

A number of theories are emerging that go some way towards suggesting answers to these questions, but controversies remain. A recently popularized theory posits that HIV does most of its damage very early, by decimating the memory CD4 T-cell population in the gut within weeks of infection. However, skeptics point out that gut CD4 T cells have distinct properties that may make them unrepresentative of the CD4 T-cell population as a whole, and that the proportion of CD4 T cells that reside in the gut—often incorrectly said to be more than half of the total—has been overestimated.

An additional provocative suggestion associated with the gut CD4 T-cell depletion theory is that HIV’s early impact on the gut compromises the integrity of the gut surface, allowing the “friendly” bacteria that aid digestion to leak into the system, thereby provoking an immune response and causing systemic immune activation. Some preliminary evidence has recently been published in support of this notion, but it remains unproven and controversial.

Another line of reasoning posits that HIV has the ability to alter the behavior of CD4 T cells by binding to CD4 and CCR5, potentially inducing activation, affecting immune trafficking patterns, and/or triggering cell death. Other researchers are looking at HIV’s early impact on the development of the CD4 T-cell response to the virus itself.

“A full understanding of HIV pathogenesis would represent a colossal milestone on the road towards a cure for AIDS, but the opacity of the human immune system remains a stern challenge to researchers pursuing this goal.”
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(the HIV-specific CD4 T-cell response) as potentially setting the stage for the failure of the immune system to control HIV replication over the long term.

One research collaboration that is attempting to address a broad array of pathogenesis questions is the Cleveland Immunopathogenesis Consortium, headed by Mike Lederman from Case Western Reserve University. Lederman and a diverse group of colleagues have drawn up a plan to conduct small trials of a variety of potential immune-based therapies, with the goal of both assessing their potential and examining whether the effects of the therapies can shed light on the veracity of current pathogenesis theories.

**The Pipeline**

A full understanding of HIV pathogenesis would represent a colossal milestone on the road towards a cure for AIDS, but the opacity of the human immune system remains a stern challenge to researchers pursuing this goal. It’s also important to recognize that this pursuit is occurring in an increasingly challenging funding environment; the number of government grants to new investigators is dwindling and the era of large increases to the National Institutes of Health’s budget appears to be over. For community activists, the issues involved in HIV pathogenesis research can seem overwhelmingly complex. However, it is crucial for us to support scientists working in this area and to advocate for appropriate funding for not just HIV research, but for basic immunology research that will enable us to understand the complex milieu in which the virus is operating.

**Richard Jefferys** is Coordinator at the Michael Palm Basic Science, Vaccines & Prevention Project at Treatment Action Group in New York City.

**Suggested resources:**

- The Project Inform’s Immune Restoration Think Tank website at project inform.org/fs/prx.html.

**Recent pathogenesis reviews:**

The medical fight against HIV is now well into its third decade. Following the discovery of HIV and proof of its causative role in AIDS, the focus of much AIDS research has been on finding ways to suppress the replication of the virus once it has infected the human host. While this has been a daunting task because of the way HIV integrates itself into cells of the human immune system, science has succeeded grandly in slowing the growth of the virus and the damage it does within the body. This success didn’t come in a single leap, however, and many people who receive treatment still suffer today, both from the effects of HIV infection before they began treatment (common in the earlier days of the epidemic but still seen today) as well as from the side effects of many of the drugs used to treat HIV. But particularly for those infected recently who have access to good medical care and the best of the drugs, the ability to manage HIV disease is all but taken for granted. Even for those who were infected long ago and developed resistance to a series of the earlier generations of medications, the options for effective treatment today are striking. The biggest problems in confronting HIV disease today are more political than scientific in nature. If only we could be as successful in providing access to care and treatment as we have been at suppressing the virus itself.

So what do we have to complain about, some ask? On a purely medical or scientific basis, managing a disease, even if it can be done for decades, is not the same thing as curing it. People with HIV are grateful to be able to live longer lives today, but those lives are still dominated by the presence and effects of HIV. Coping with the virus still greatly complicates every aspect of their lives. It still makes those living with HIV dependent on a lifelong regimen of medication, daily dosing requirements, and possible drug side effects. It is not unreasonable for people with HIV to ask for, or even demand, an outright cure for the disease. There are few other illnesses in which society is content to settle for a lifetime of disease management based on the use of wildly expensive drugs and the acceptance of significant drug side effects. A true cure, and nothing less, must always be the goal of treatment activism.

As obvious as this seems, there is in fact little talk of “a cure” at most activist gatherings, AIDS service organizations, and research meetings. Talking about a cure is often considered a false hope or waste of time. The great majority of researchers do not believe that a cure will be possible in the foreseeable future, if ever. Of course, it’s hard to forget that similar attitudes were voiced about the possibility of even treating the disease back in the mid-1980s. Such pessimism was proven wrong then, and there is every reason to expect that it will be proven wrong again.

How do we get from disease management to cure? What will it take to change the current expectation of life-long disease management into the demand for a cure? First and foremost, what is required is a change of attitude. It is one thing, after 6 months or even a few years of research, to celebrate today’s new drugs that are more potent, last longer, and appear to have fewer side effects. It is quite another to contemplate how people will...continued
fare when they must use such drugs for 40 or 50 years. It is wonderful to see the US and other Western governments commit billions of dollars to fund treatment for a million or more people in resource-poor nations. It is quite another thing to contemplate whether the nations of the world are prepared to provide treatment for 40 to 100 million people for the length of their lives.

As activists and people living with HIV, we must remember how we reached the state of successful disease management we are so proud of today. We got there by demanding it. We raised our voices and made it clear to government, scientists, and private industry that we would not accept the status quo, which in the early days was simply a matter of going to an early grave. Over time, we generated enough pressure, and found enough allies in government, media, academia, and private industry to make AIDS research a real priority. That pressure, and the commitments it created, led to breakthroughs in biology, chemistry, immunology, and drug development. Sufficiently prodded, there is no known limit to what mankind can achieve.

So as a first step, we must put the concept of a cure back on the map. We must seek consensus that developing a real cure is as important as creating a vaccine, and perhaps more important than creating an endless string of slightly different drugs that suppress the virus. We don’t need countless new drugs of the same kinds, with the same limitations. We need a limited number of very good ones and we are very close to achieving that goal. Yet all but a small percentage of the investment in AIDS treatment research is directed toward finding more drugs to manage disease and endlessly fine-tuning their use. In contrast, the amount spent on developing a potential cure is so small as to be immeasurable. The hope that simply adding more or better antivirals alone will lead to eradication of HIV has withered. Finding a cure requires a different kind of research and different approaches to treatment. To get beyond this roadblock, the once loud voices of people with HIV and their advocates must once again be heard demanding action. Complacency with long-term disease management is not a solution.

Secondly, we must aggressively support research that offers the potential to move beyond disease management. Today, only a handful of scientists are openly working on a cure for HIV disease, and they are often chastised whenever they make public statements about such work. We must be quick to defend them whenever appropriate. This is equally true of the pharmaceutical industry. To the best of my knowledge, only 2 pharmaceutical companies are investing in research that even remotely offers the potential for a cure.

One of these is Tibotec Pharmaceuticals, which also makes the new protease inhibitor Prezista. While Prezista may be one of the best drugs of its type, like other antivirals it cannot cure the dis-

“We must seek consensus that developing a real cure is as important as creating a vaccine, and perhaps more important than creating an endless string of slightly different drugs that suppress the virus.”
ease. But Tibotec is also funding an innovative gene therapy experiment with the hope of creating a new line of immune cells that are essentially themselves immune to the effects of HIV and cannot be infected by it. This general approach has been discussed for more than 15 years, but this is the most advanced study actively testing it.

A second approach is under study at Merck, which makes the new integrase inhibitor MK-0518. As good as it appears to be, the integrase inhibitor is unlikely to lead to a cure. Other research at the company, however, points in that direction. It is widely believed that the biggest obstacle to eliminating HIV from the body is the way in which the virus creates reservoirs of infected cells that are protected from even the best antiviral drugs, as well as from the immune system itself. These reservoirs of infection remain in the body, always ready to maintain the presence of HIV. There are a number of possible ways of reducing or eliminating these reservoirs. Merck is the only company we are aware of that funds both internal research efforts and helps support external research on methods to reduce or eliminate these critical reservoirs of infection.

Both these efforts are surprising developments because it is easy to assume that pharmaceutical companies would not be interested in conducting research that offers the hope not only of curing the disease, but in turn eliminating the market for expensive HIV drugs. The work of these companies, and perhaps others we are not aware of, must be applauded publicly. It is a very good thing that they are doing this. We must encourage them, and encourage other companies to follow their example. If a cure is developed for HIV, there will always be plenty of other illnesses that companies can focus on. The future of the pharmaceutical industry does not depend upon the sale of HIV. But the lives of tens of millions of people do indeed depend on finding a real cure for AIDS.

Thirdly, we must demand that a significant portion of federal research dollars be spent on research seeking a cure. Today, it is difficult to say that any federal research efforts have such a direct focus. The Office of AIDS Research and the National Institute of Allergy and Infectious Diseases (NIAID) Division of AIDS must put such research on the federal agenda or use some of their modest discretionary funds to help kick-start a program of this type. NIAID has conducted internal research programs of this type but hasn’t developed programs to support outside researchers. Recently, the American Foundation for AIDS Research (AmFAR) took on this charge and invited grant applications from researchers who wished to work on reducing the reservoirs of HIV. It funded several such applications, and AmFAR should be acknowledged for this important effort. If AmFAR, with its far smaller research budget than NIAID, can direct funds toward seeking a cure, surely the federal government can do a great deal more.

Fourth, and perhaps finally, if we wish to get on the road towards a cure, we must believe in it ourselves. Far too many people with HIV, as well as their doctors, have accepted the notion that a cure is not likely. No one can be certain that a cure will be found. No one can predict the future. But one thing is certain: if we allow pessimism about a cure to dominate our thinking, we surely won’t get one. We get only what we demand, and we demand what we need. The current complacency about HIV is a very dangerous thing. It puts the lives of millions of people in needless jeopardy. We must restore our belief in a cure and make it one of the central demands of our activism.

*Martin Delaney* is Founding Director of Project Inform, an HIV/AIDS non-profit organization located in San Francisco.
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