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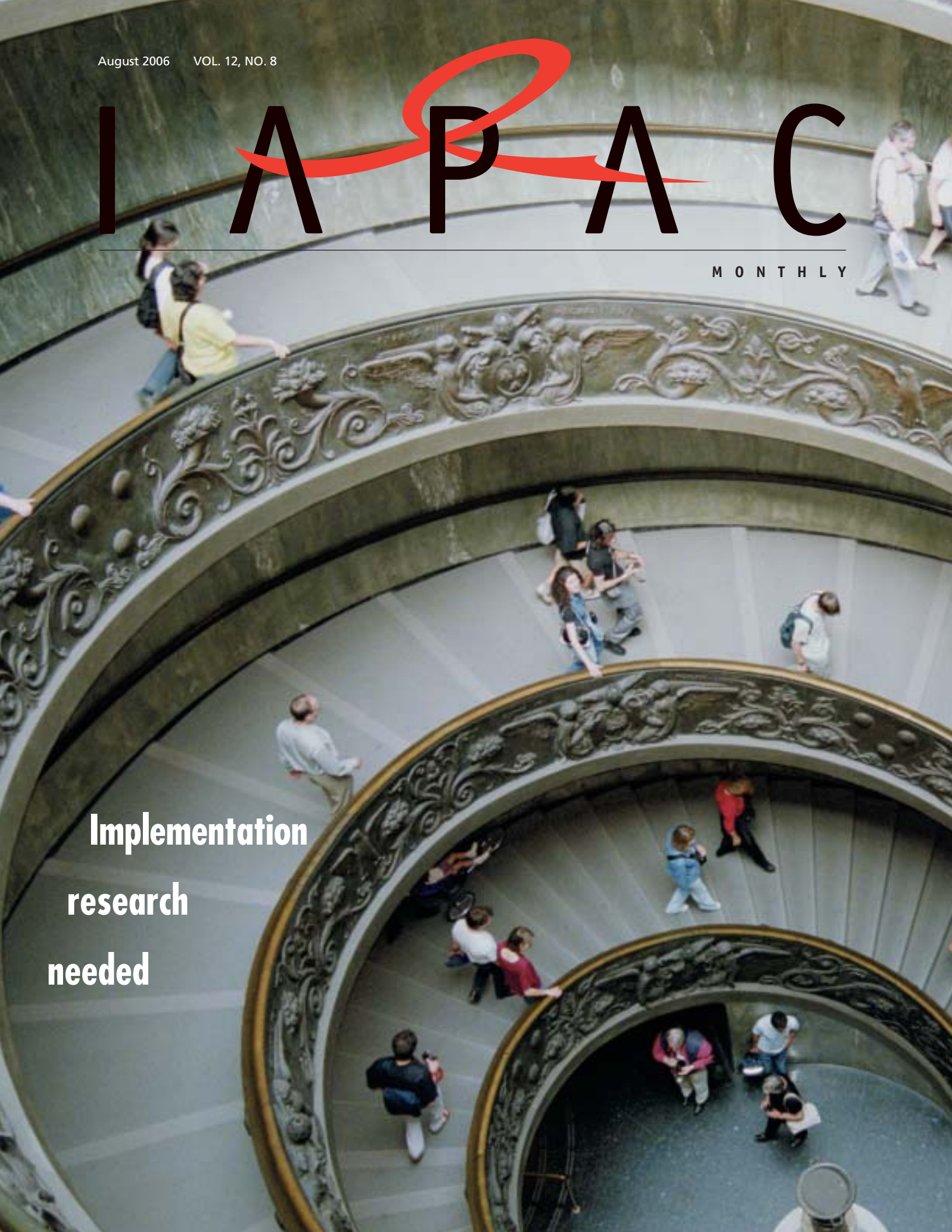

Implementation research needed

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David Sanders and Andy Haines

Health research needs to focus not just on the growing divide in health status between rich and poor countries, suggest the authors of this essay, but on the unacceptable gap between our unprecedented knowledge of diseases (including their control) and the implementation of that knowledge, especially in poor countries.

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REPORT FROM THE PRESIDENT

Reasons to hope...

José M. Zuniga

Given the security measures instituted following the news of the recent terrorist plot foiled by the British police, several colleagues and I, representing the International Association of Physicians in AIDS Care (IAPAC) at this month's XVI International AIDS Conference, decided to drive from Chicago to Toronto. We discussed myriad issues during the 12-hour drive, from the trivial to the profound. By far the most absorbing dialogue revolved around our own personal reasons for dedicating years of our life and labor to the fight against the human immunodeficiency virus, and our reflections on a 25-year-long battle to rout HIV—made "easier" by virtue of a decade-old medical breakthrough known as highly active antiretroviral therapy (HAART).

Throughout the conference, which attracted an estimated 24,000 delegates, my colleagues' comments mingled with my own and those of the IAPAC members with whom I chatted either in convenient hallway get-togethers or in scheduled meetings. The fact so many of us congregated in Toronto in the face of the global scourge AIDS represents is remarkable, because among the multitude of devastating catastrophes that occurred in the 20th century and continue to plague the 21st century, AIDS can sometimes seem like old news.

In the last century alone we have seen millions killed in senseless wars. We have witnessed deliberate programs of destruction and extermination. We see unnecessary suffering in the guise of poverty and malnutrition as well. Despite the existence of vast wealth and an overabundance of food production, much of the world lives in poverty. Internationally, 14% of the world's population is malnourished, and even in the United States there are those who will go to bed hungry tonight.

Twenty-five years ago, with the outbreak of the AIDS pandemic, we were forced to add to this litany of suffering a plague of world historical proportions. AIDS killed 3 million people last year. AIDS has killed over 25 million and infected 65 million people since its outbreak. And, according to a recent United Nations estimate, if drastic measures are not taken, AIDS will have killed 278 million people by the middle of the 21st century—and that is just in the 53 "most affected" countries of the world.

The devastating effect that this decimation would have on the world is even greater than these numbers alone might imply. For unlike many diseases, AIDS is primarily a killer of men, women, and children under 40 years of age. Moreover, HIV disease tends to be concentrated in developing countries. This means that national economies that are already in jeopardy face the added risk of losing a significant percentage of their workforce.

In other words, AIDS makes poor countries poorer and greatly contributes to the suffering of all citizens. Already experts predict that a current famine in southern Africa could be prolonged indefinitely because the agricultural workforce is too depleted to recover. The 12 million AIDS orphans living in sub-Saharan Africa may be just the beginning of a much larger disaster. Nevertheless, we do have reason to be hopeful. In fact, in the global struggle against AIDS, there are several factors on our side. With a deeply held resolve to do everything we can to fight this disease, I am confident that we can be victorious, despite difficult odds.

The first factor working in our favor is that HIV is not, relatively speaking, a highly communicable disease. It is not like influenza or severe acute respiratory syndrome (SARS), which are easily transmitted via airborne viruses; nor tuberculosis, whose bacterium is spread by aerosol droplets emitted by coughs; nor is it passed on as easily as malaria, a parasite which is efficiently spread via the bites of mosquitoes.

Of course, HIV is far more lethal than any of those diseases. And, despite great medical advances in AIDS treatment, there is no cure. Those are grim facts, but if such lethality and incurability were the characteristics of a disease that spread more efficiently, society as we know it would have long since come to a crashing halt.

There are concrete steps that people can take to protect themselves from HIV infection, and as a global society, we can implement prevention strategies that can radically reduce incidence rates. In many locations around the world, from Las Vegas to Cambodia to Uganda, prevention strategies have successfully stemmed the incidence of HIV. That such strategies can be employed elsewhere, and it is clear that they can be, is a very tangible reason to hope.

The next cause for hope is HAART. Despite on-going medical complications associated with antiretroviral therapy, and the fact that, again, it is not a cure, the various drugs that when strategically combined comprise HAART are truly miraculous. They rescue patients from the brink of death, and offer them decades of life where in the past life expectancies were limited to one or two years after diagnosis.

We have many obstacles to overcome with antiretroviral drugs. These include developing effective techniques to limit the drugs' side effects and determining strategies to make these medications, and adequate medical infrastructure for their safe and effective use, available to millions in developing countries, particularly in sub-Saharan Africa. But we must certainly draw hope for the future from

our profound medical ability to prolong and enhance the lives of men, women, and children living with HIV.

The third cause for hope is, perhaps, counterintuitive, and may be the most debatable of the three factors that I see as working in our favor. In a word, that factor is globalization. The idea that globalization—by which I mean the growing interconnectedness of everything from business to culture to travel—could be a positive force in stemming the AIDS pandemic might be controversial for several reasons.

The first of these is that the increase in global exchanges of population is often cited as a reason that no nation or region can consider itself immune from an epidemic of HIV disease. Second, one might argue that some of the negative economic aspects of trade globalization contribute to the spread and destructive power of HIV.

These two potential pitfalls must be addressed, of course, but I remain convinced that globalization, taken as a whole and defined broadly, can be a positive force to marshal in our struggle against AIDS. We have never before been able to coordinate global efforts for any goal in the way that we can now. I was reminded of this by the SARS outbreak a few years back, when researchers sharing information around the world were able to identify the culprit virus with unprecedented speed. It took months to accomplish this for SARS in 2003 versus years for AIDS in the early 1980s. That represents true progress made possible by globalized medicine.

More radically, I believe there is a somewhat hidden but nonetheless real benefit in the fact that no country or region can suffer without the rest of the world suffering. Such is life in a globalizing world that we are all confronted with the plight of fellow world citizens on television and in other media.

Global well-being is jeopardized by the world-historical loss of life that HIV could cause, even if that loss of life is concentrated more in some regions of the world than in others. And every citizen of the world has both a humanitarian and a personal interest in fighting global HIV disease, even those who never become infected and live in countries with relatively low prevalence rates. For in a world of global economic interconnections, the ability of any one person to earn a living, provide for children, and enjoy life, is lessened when there is widespread illness and premature loss of life.

I believe that when there is a broader realization of this fact, the world will focus as it never has before on improving global health. And matched against the coordinated efforts of a world community so motivated, AIDS can be defeated. ■

José M. Zuniga is President/CEO of the International Association of Physicians in AIDS Care, and Editor-in-Chief of the IAPAC Monthly.

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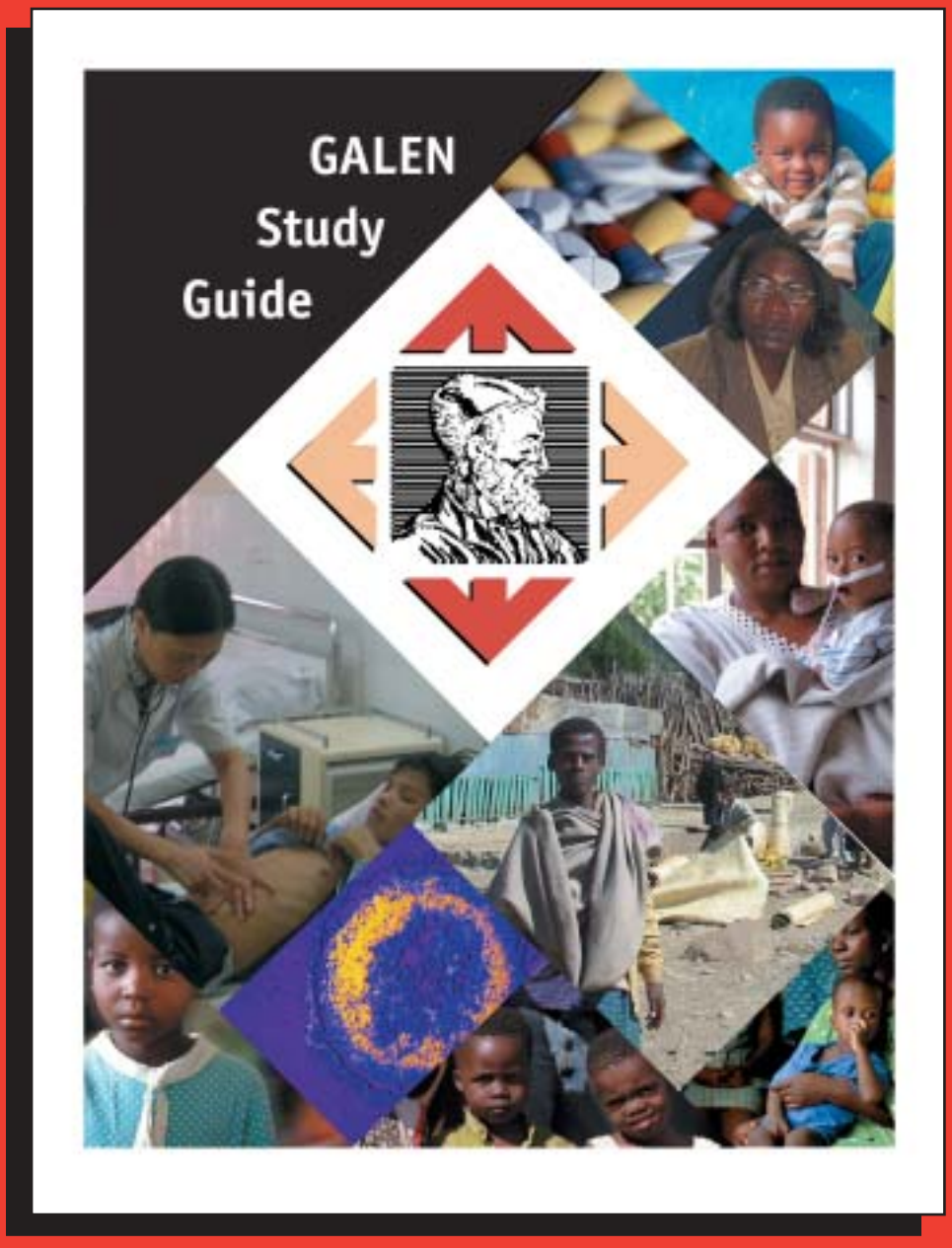

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Produced in collaboration with the US National Institutes of Health (NIH), the GALEN Study Guide is a useful tool to measure and strengthen clinicians' ability to pass the GALEN Certification Examination with a score of 70% or better. Visit www.iapac.org to order your GALEN Study Guide today!

ZDV link to early signs of CVD?

Edwin J. Bernard

Zidovudine (ZDV) alone and in combination with the protease inhibitor (PI) indinavir (IDV) directly causes damage to the lining of blood vessels, according to a study in rats published in the August 1, 2006, issue of the *Journal of Acquired Immune Deficiency Syndromes*.[1] This early sign of atherosclerosis suggests that certain nucleoside reverse transcriptase inhibitors (NRTIs) may directly contribute to the increased cardiovascular risk associated with PI therapy.

Earlier this year, at the 13th Conference on Retroviruses and Opportunistic Infections (CROI) in Denver, an analysis of the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study found that the 16% per-year increased risk of heart attack seen in patients on antiretroviral therapy is caused by PIs and not by nonnucleoside reverse transcriptase inhibitors (NNRTIs).

Although the D:A:D investigators did not determine the effect of the NRTI backbone taken by the patients in the study, they did find that that even after adjusting their analysis for lipid levels, there remained a residual risk that could not be accounted for by the PI class's effect on lipid levels alone.

Following initial test tube studies, investigators from Louisiana State University (LSU) hypothesized that some NRTIs may adversely affect vascular endothelium, leading to reduced flexibility in response to blood flow, even in the absence of lipid abnormalities. This endothelial dysfunction is an early indicator of atherosclerosis, one of the earliest detectable signs of the development of cardiovascular disease (CVD).

In order to test their hypothesis, the LSU investigators treated rats with a month of ZDV and/or IDV, achieving levels similar to those taken by humans. They then measured plasma lipids and looked for various signs of endothelial dysfunction. These included measuring the ability of the aorta to relax, as well as measuring endothelin-1 (ET-1) levels.

To test whether these antiretroviral drugs had a direct effect on the endothelium, the researchers used the drug acetylcholine, which relies on the presence and proper functioning of the endothelium to relax blood vessels. They found that the ability of the aorta to relax was dramatically impaired by ZDV as well as the combination of ZDV and IDV.

To confirm that the changes in aortic relaxation were indeed due to the antiretroviral drugs, the investigators also used the drug sodium nitroprusside. This drug stimulates the blood vessels to relax independently of the endothelial cells. Since this drug caused normal aortic relaxation, the investigators write that this suggests "that a specific impairment of vascular endothelial function was induced by treatment with [ZDV] or [ZDV] plus [IDV]."

The investigators also measured levels of ET-1, an amino acid peptide produced by the endothelium to make blood vessels contract. An increase in ET-1 levels indicates damage or injury to endothelial cells, and increases in ET-1 release have been shown to be correlated with atherosclerosis. They found significantly increased levels of ET-1 in the blood of the rats treated with ZDV and IDV in combination ($P < 0.05$) but not in those treated with either drug alone.

Since endothelial dysfunction and ET-1 levels can also be associated with increased plasma lipid levels, the investigators measured total cholesterol and triglyceride levels. They found that only IDV alone significantly increased total cholesterol levels, and that triglycerides were not significantly increased in the presence of either drug.

The investigators explain that since ET-1 levels are usually very low, and are difficult to detect, they were not surprised that differences in ET-1 levels could not be detected in the presence of ZDV or IDV alone. They suspect that the increased levels seen when the drugs are used in combination may confirm that ZDV's direct effects on endothelial function add to IDV's indirect effects through increasing blood cholesterol levels.

There are some limitations to this study. These experiments were carried out on rats, not in humans, and may not be reproducible or clinically relevant in humans. In addition, the investigators tested two antiretroviral drugs that are being used less often in affluent countries, although since it is now cheap and off-patent, ZDV may well continue to be used worldwide for many years to come, particularly in resource-limited countries. The investigators used ZDV and IDV because they had previously undertaken test-tube experiments with these two drugs (at a time when they were being used routinely in developed countries with access to antiretroviral therapy) and had found they induced endothelial cell toxicity *in vitro*.

Nevertheless, they write that their "data suggest that clinical treatment with [ZDV] may induce direct vascular endothelial damage," and that the likely mechanism is mitochondrial toxicity. They argue, therefore, that endothelial dysfunction may not be limited to ZDV but could also occur with any NRTI that causes mitochondrial toxicity, including didanosine (ddI) and stavudine (d4T).

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Although these drugs are also being used less often in the developed world because of their association with mitochondrial toxicity, d4T in particular is a common backbone drug in many antiretroviral regimens prescribed in resource-limited countries.

In summary, the investigators conclude that their data suggest that "in addition to the lipid disorders induced by [PIs]... [ZDV] and perhaps other NRTIs may contribute to the development of cardiovascular complications observed in HIV patients." They add they are undertaking further research to discover exactly how this happens. ■

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Implementation research needed

David Sanders
Andy Haines

Health research needs to focus not just on the growing divide in health status between the world's rich and poor but also on the unacceptable gap between our unprecedented knowledge of diseases (including their control) and the implementation of that knowledge, especially in poor countries. Directed and innovative research is needed to analyze the causes of this situation and to point toward solutions at the global and local levels, both within and outside the health sector—given that inequitable economic globalization is leading to greater disparities in wealth between and within countries.[1]

Because interventions directed at health improvement require, for optimal implementation, infrastructure, equipment, supplies, and competent personnel in adequate numbers, together with intersectoral actions to address the underlying determinants of health, the term "health systems" is increasingly used. Health systems can broadly be described as containing the following principal components: structures, equipment and supplies, policies (technical priorities, financing), people (their numbers, distribution, and skills mix), and processes (how people function within the system and in relation to other sectors). How these components articulate with one another and the communities in which they are based, their effectiveness, and opportunities for modification are also framed by the social and political context in which they have evolved.

This essay focuses on health systems research (HSR). It begins with an overview of the crisis in health, health systems, and HSR in low-income countries, with a special focus on Africa. Then, it discusses an issue that has come to be termed the "knowledge-implementation gap," focusing particularly on those types of HSR most concerned with implementation (Sidebar 1). Some of the key obstacles to correcting this gap are identified, and the essay concludes with some suggestions for actions that can be taken to increase the quantity and quality of HSR.

Weak health systems in poor countries

The gap in infant mortality and life expectancy between rich and poor countries is widening substantially. Sub-Saharan Africa is the starkest example of this growing divide. A combination of new and old infectious diseases (in particular HIV infection) and rising rates of injuries have resulted in the populations of countries such as Kenya, South Africa, Zambia, and Zimbabwe losing more than 10 years in life expectancy in a short period of time.[2] In many of these countries, this situation is exacerbated by public health services that have been seriously weakened by chronic underfunding and loss of personnel, with an accelerating "brain drain" that is reaching crisis proportions and raising ethical questions regarding recruitment by wealthy countries.[3,4] Health system dysfunction has been aggravated by ill-considered and inappropriate reforms in the health sector.[5] A stark reflection of these weakened health systems was the stagnation in immunization rates over the 1990s for the six basic childhood vaccines in many poor countries, despite impressive increases in coverage during the 1980s, the availability of more and improved vaccines, and the subsequent intensive World Health Organization (WHO)-driven campaigns for the eradication of polio and measles.[6]

These challenges will require the implementation of policies that ameliorate the above underlying factors. Research can assist in achieving this but should stress health determinants, population health perspectives, HSR with a focus on implementation, and studies of the effectiveness of strategies designed to bring about equitable social and economic change.

Thus, the Mexico Statement from the Ministerial Summit on Health Research, which took place in Mexico City in November 2004, among other things calls on governments to allocate adequate funds to support HSR in order to address priority questions.[7]

Implementation research has been neglected

Health research of the types described above remains only a small fraction of global health research and a tiny proportion of expenditure on health in low-income settings. Recent estimates suggest that only about 0.017% of health expenditure in low- and middle-income countries (around US$134 million) is devoted to such research.[8]

In public health research, the focus has traditionally been predominantly on descriptive and analytic epidemiological research ("what," "why," "where," and "who"). There is growing funding for intervention research, particularly for drugs, vaccines, and other products that could benefit the poor through sources such as the Bill & Melinda Gates Foundation (http://www.gatesfoundation.org) and the European and Developing Country Clinical Trials Partnership (http://www.edctp.org). However, there is still little funding for, and, therefore, a relative dearth of implementation research, particularly in low-income settings (such research addresses the "how" of translating current research knowledge into practice within health and social systems).[9,10]

Gaps between knowledge and action

In developed countries, implementation research focuses particularly on how to promote the uptake of research findings—for example, by evaluating a variety of strategies to enhance the use of clinical guidelines. A recent overview[11] suggests that different approaches might affect different behaviors. For example, reminders may be particularly appropriate for improving preventive behaviors such as immunization and screening, feedback on performance may be effective for rationalizing the ordering of diagnostic tests, and financial interventions may be effective in promoting more rational prescribing. However, overall these effect sizes are modest, generally resulting in a less than 10% improvement in practice.

Sidebar 1.

What is implementation research?

Implementation research is that subset of HSR that focuses on how to promote the uptake and successful implementation of evidence-based interventions and policies that have, over the past decade, been identified through systematic reviews. Implementation research is used as a general term for research that focuses on the question "What is happening?" in the design, implementation, administration, operation, services, and outcomes of social programs; it also asks, "Is it what is expected or desired?" and "Why is it happening as it is?"*

In the health field, implementation research often encompasses "impact research," which includes both research aimed at understanding what is happening during the processes of implementing changes in policy or practice, and intervention studies that are designed to compare different approaches to implementing change. Implementation research is often multidisciplinary, encompassing both quantitative and qualitative approaches that require expertise in epidemiology, statistics, anthropology, sociology, health economics, political science, policy analysis, ethics, and other disciplines.

* Werner A. *A Guide to Implementation Research.* Chapter one. Washington DC: Urban Institute Press; 20005. Available: www.urban.org/pubs/implementationresearch/chapter1.html (Accessed July 12, 2006).

Combinations of a number of interventions appear to be no more effective than single interventions, perhaps because we still do not understand which combinations work best in which circumstances.[11] A recent review suggests that some approaches, such as supportive supervision and audit with feedback, may be effective in low-income settings, but more research is needed—not just on specific approaches to improving the quality of care, but also on the health systems environment that will sustain accessible and high-quality care over time.[12]

Health systems research remains marginalized and has been dominated in the past decade by cost-effectiveness studies that have been promoted by international institutions and incorporated by governments as components of their health sector reform and rationing policies. Such research needs to be complemented by a stronger focus on the development and functioning of health systems, using a combination of quantitative and qualitative methods, including the use of action research that involves practitioners in critical reflections on their own practice. In addition, detailed and comparative case studies of the results of long-term implementation of (especially complex) interventions are needed to identify those program and contextual factors that lead to success in health development. Health systems research has the powerful potential to bridge the implementation gap through testing and evaluating activities and systems while simultaneously enhancing the capacity of health staff to evaluate and improve their own performance.[13,14]

However, gaps between knowledge and action persist, with serious consequences for health. For example, full use of existing interventions would cut the more than 10 million annual child deaths that occur globally by more than 60%.[15] A high proportion of the half million or so maternal deaths that occur globally every year could also be prevented by promoting access to interventions and services of known efficacy.[16] While these problems are seen at their most extreme in low-income countries, they are certainly not restricted to such settings. Studies in Europe and North America show that between 30% and 60% of patients do not receive effective treatment for common conditions such as asthma, heart failure, and high blood pressure.[17,18]

The scope of health systems research

Since HSR constitutes a relatively new and underdeveloped field, it is important that its scope is defined and the factors inhibiting its development are identified and addressed. A WHO Task Force on HSR recently identified a number of topics for HSR (Sidebar 2) and made recommendations on how such research could be scaled up[19] (more detailed descriptions of each topic and the rationale for addressing them are given in Reference 20).

Sidebar 3 gives an example of HSR that took place in the impoverished former Transkei "homeland" in South Africa. This example includes aspects of a number of the HSR topics listed in Sidebar 2, such as human resources for health at the district level and below; equitable, effective, and efficient health care; and effective approaches for intersectoral engagement in health.

In some circumstances, health system interventions can be evaluated using randomized trials—particularly cluster trials, where the unit of randomization may be communities or health facilities. A recent example is a cluster trial of a participatory intervention with women's groups to improve maternal and neonatal mortality in Nepal.[21] Many research questions, however, cannot be addressed by randomized trials—for example, because they may be system-wide in scope. Other approaches need to be considered, such as controlled before-and-after studies and interrupted time-series analyses and process evaluations to better understand how and why interventions work or do not work as intended. Participatory action research, which is a family of research methodologies that pursue action (or change) and research (or understanding) at the same time,[22] has the potential to both elucidate constraints to the success of interventions and improve the performance of health staff (as described in Sidebar 3).[23]

Building HSR capacity

Health systems research capacity is as yet limited in almost all countries. It is an interdisciplinary endeavor that demands not only technical expertise but also expertise in relating to and working with policymakers and

Sidebar 2.

Suggested topics for HSR*

Financial and human resources:

- Community-based financing and national health insurance
- Human resources for health at the district level and below
- Human resources for health at the national level

Organization and delivery of health services:

- Community involvement
- Approaches to the organization of health services
- Equitable, effective, and efficient health care
- Drug and diagnostic policies

Governance, stewardship, and knowledge management:

- Governance and accountability
- Priority setting and evidence-informed policymaking
- Health information systems
- Effective approaches for intersectoral engagement in health

Global influences:

- Effects of global initiatives and policies (including trade, donors, and international agencies) on health systems

* Task Force on Health Systems Research. *The Millennium Development Goals Will Not Be Attained Without New Research Addressing Health System Constraints to Delivering Effective Interventions.* Geneva: World Health Organization; 2005. Available: www.who.int/rpc/summit/Task_Force_on_HSR_2.pdf (Accessed July 12, 2006).

other decision-makers in developing research agendas, conducting and interpreting research, and supporting action based on the findings. While training plays an important role in developing research capacity, expertise also has to be built "on the job," by doing research initially under supervision.

We need larger and more widely applicable research programs that compare policies and interventions in a range of settings, assess the impact of global factors, and build HSR capacity. These could all be more easily achieved through the development of multi-country collaborative HSR networks.

At a time when substantial sums are being made available for the purchase of efficacious interventions and the development of more effective drugs, vaccines, and other products, it is essential to channel more resources to address the preparedness of health systems for delivering these interventions.

The next steps

Health systems research is becoming recognized as a legitimate and indispensable part of health research. This has been acknowledged in, for example, the recent Mexico Summit statement.[7] But it is imperative to move beyond words. What, therefore, needs to happen—and who should be primarily responsible?

Educational and research institutions need to rapidly build capacity in this area of research, especially within the field of public health, since it is health systems that are the focus. These institutions need to be encouraged to do this by the creation of both financial and non-financial incentives. The latter come mainly from publication prestige (which, in some countries, is accompanied by financial reward to the institution or author)—hence, it is urgent that journals, especially those with high impact factors, encourage submission of articles in this area, and (where they meet the required standards) facilitate their expeditious publication. Unlike research leading to the development of pharmaceuticals, vaccines, or other health-related products, HSR has no substantial sponsorship from the private sector. Research bodies and donors can thus play an important role by calling for and funding HSR, and especially implementation research; the derisory amounts currently being spent on HSR need to rapidly increase if the benefits of much existing and new knowledge are to be realized.

Advocacy for HSR in general, and implementation research specifically, also needs to be strengthened. Policymakers can play an important role, both by demanding such research and by ensuring that health-service managers and practitioners see the value of evidence regarding the effectiveness of their activities and even acquire some skills in HSR themselves. The ongoing evaluation of the Integrated Management of Childhood Illness program offers an indication of the potential benefits of evaluating a major international health program that aims to promote the uptake of high-quality care based on research evidence.[24,25] Such evaluations can both demonstrate the positive impacts of such programs and highlight aspects that require further development if their full benefits are to be achieved, such as low rates of referral among children with severe illness. Presently, civil society organizations and selected research alliances are taking a lead in advocating more research in this area.[26] But until mainstream research organizations actively promote such research, and policymakers demand that the implementation of interventions and programs is rigorously evaluated, the unconscionable gap between knowledge and its implementation will persist in the health field. ■

Sidebar 3.

Participatory HSR addresses primary health care needs: Rural hospitals, malnutrition, and household food security

Research and development activities to improve the management of severe childhood malnutrition in rural hospitals have been continuing since 1998 in the impoverished former Transkei "homeland" in South Africa. The research has involved detailed situational assessments and analyses—by pediatric ward staff, together with an outside research team—of the processes and outcomes in children admitted with a diagnosis of severe malnutrition.

The research showed unacceptably high fatality rates and serious deviations from the WHO management protocol, caused by knowledge and skills deficits, inadequate resources and staff, and poor supervision and support from managers. Responses included additional resources (drugs, micronutrients, testing equipment, ingredients for special feeds, and extra night staff) and sustained training and supportive supervision, together with ongoing monitoring that is now a routine activity. This process has been successful in reducing case-fatality rates by, on average, 33% across 11 district hospitals. There is ongoing research to elucidate why some hospitals perform consistently better than others with equivalent infrastructure and resources, which indicates that differences in management and leadership are key explanatory factors.

Follow-up research on the children who were successfully treated in hospital showed that they returned to food-insecure homes, and although all households qualified for a government welfare provision to poor families (the Child Support Grant), none was receiving it, despite strenuous efforts on the part of most caregivers. Their testimony and these research findings were used in an advocacy campaign comprising formal submissions to government, newspaper articles prompting questions in parliament, and a prime-time television documentary that prompted immediate intervention by the Minister of Social Development. This, and continuing advocacy efforts in collaboration with an alliance of child-welfare nongovernmental organizations, has resulted in a sharp and sustained increase in Child Support Grant distribution and greater attention to the role of household food insecurity as a causal factor in malnutrition, although much work remains to be done.

This research illustrates the powerful potential of implementation research in developing capacity for self-evaluation—the first step in improving quality of care and in providing evidence for advocacy.*†

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AIDS at 25

Celso Ferreira Ramos-Filho

Federal University of Rio de Janeiro, Brazil

In the late 1980s, care for Brazilian AIDS patients was extremely poor. Zidovudine (ZDV) monotherapy was, of course, only partially effective, and drugs for opportunistic infections were either unavailable or very expensive. This situation made administrators rather reluctant to admit AIDS patients to public hospital facilities, since fees received would not cover costs incurred. University hospitals were less liable to such losses, and naturally stepped forward in most cities and states with some notable exceptions, especially in São Paulo. The situation in the private health market was also somber; insurance companies would balk at covering similar costs, arguing that epidemics were excluded from their contracts.

Happily, I took part in measures to correct both situations. In 1991, the Rio de Janeiro State Medical Council issued Resolution 35, based on a formal document written by its Technical Chamber on AIDS, of which I was then Coordinator. This legally binding document ruled that it was unethical for hospitals and physicians to refuse care to HIV or AIDS patients, and for health insurance companies to deny payment for their medical expenses. However, Resolution 35 was only binding in Rio de Janeiro, and the situation in other states was not greatly influenced.

In June 1992, the Ministry of Health issued Decree 197, regulating payment for AIDS and related conditions in the Unified (ie, Public) Health System. I was then Deputy Director of the National AIDS Program, and I conducted the studies that established the basis for its issuance. This measure made it possible for public hospitals to accept AIDS patients, since the fees were then considered sufficient.

In 1991, in a surprising move, the Ministry of Health had started a countrywide (albeit timid) program of free distribution of ZDV, and of drugs for the treatment of opportunistic infections. It was rumored that this was motivated by an interest in improving the AIDS surveillance system, which was failing after Lair Guerra's dismissal from the National AIDS Program the year before. She was reinstated in 1992, and she invited me to join her. We could find no trace of any administrative measures taken to assure the continuity of the program; nevertheless, we were able to expand the number of drugs being offered, but at great cost. For this reason, the Minister of Health, Adib Jatene (then in his first term in office) commanded me to find cheaper sources for drugs, especially ZDV. It should be noted that, at that time, patents on pharmaceutical drugs were not recognized in Brazil. The program was much improved in the following years, after I had left, and in November 1995 the National AIDS Committee decided to include double nucleoside reverse transcriptase inhibitors (NRTIs) (already primarily obtained as generics) as an acceptable therapy, following the preliminary results of AIDS Clinical Trials Group (ACTG) 175, presented at that year's Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC).

In March 1996, the National AIDS Program convened in Brasília a meeting of almost 100 physicians to try to create a consensus on how protease inhibitors (PIs) would be used in Brazil. Conveners and chairs of the various groups agreed to disallow discussion on economic and financial aspects of PI use, as this would impede consensus and would certainly jeopardize the attainment of the meeting's objectives. We did not at that time envisage distribution of PIs by the government, because of their great cost. After a visit by Jatene, then (and for a short while) again Minister of Health, Guerra unexpectedly announced that Jatene had ordered her to acquire PIs and other antiretrovirals for distribution free of charge. This was solely Jatene's decision, as he confirmed to me in a recent interview.

In November of that year, he was again out of office, and Congress Law 9.313 was sanctioned by the President of Brazil, obviating any doubts and uncertainties regarding the country's resolve to provide its citizens with adequate treatment for HIV and AIDS.

Editor's Note: *This is the third of six vignettes the IAPAC Monthly will publish this year to commemorate the 25th anniversary of the first report describing a lethal new virus terrorizing the US gay community. That virus—the human immunodeficiency virus (HIV)—today affects more than 40 million men, women, and children worldwide, and in the past quarter century has claimed some 25 million lives.*

ABSTRACTS

Journal of Acquired Immune Deficiency Syndromes

Predictors for lower quality of life in the HAART era among HIV-infected men

Liu C, Johnson L, Ostrow D, et al.

BACKGROUND: In the era of highly active antiretroviral therapy (HAART), maximizing health-related quality of life (QOL) has become a high priority of long-term management of HIV-infected individuals. Modifiable determinants of lower QOL should be identified for interventions specifically targeted to HAART-using individuals to improve their QOL. *OBJECTIVE:* To identify the predictors for lower QOL among HAART-using study participants in the Multicenter AIDS Cohort Study (MACS), a longitudinal study of HIV infection among homosexual and bisexual men in four cities. *METHODS:* In the MACS, 636 HAART-using subjects had QOL data before and at least two consecutive QOL measurements after HAART initiation to visit 40 (April 2004). Variables of sociodemographics, individual risk behaviors, social support, biological markers, HIV-related medication use and clinical outcome indicators preceding the study outcomes, the physical health summary score, and the mental health summary score derived from the standard SF-36 QOL form were assessed as possible predictors using random-effects mixed models. *RESULTS:* Quality of life before HAART initiation was a strong predictor of QOL subsequent to HAART initiation. Older age, lower socioeconomic status, fewer male sexual partners, no alcohol drinking, and more advanced HIV disease stage were significant predictors for a lower physical health summary score. In addition, more outpatient visits, depression, amprenavir use, antiretroviral drug interruption, recreational drug use, and less social support were significantly associated with a lower mental health summary score.

J Acquir Immune Defic Syndr. 2006;42(4):470-477.

Acquired Immune Deficiency Syndromes

Diagnostic accuracy of CD4 cell count increase for virologic response after initiating highly active antiretroviral therapy

Bisson GP, Gross R, Strom JB, et al.

OBJECTIVE: To derive and internally validate a clinical prediction rule for virologic response based on CD4 count increase after initiation of HAART in a resource-limited setting. *DESIGN/METHODS:* A retrospective cohort study at two HIV care clinics in Gaborone, Botswana. The participants were previously treatment-naive HIV-1-infected individuals initiating HAART. The main outcome measure was a plasma HIV-1 RNA level (viral load) ≤400 copies/mL (ie, undetectable) six months after initiating HAART. *RESULTS:* The ability of CD4 count increase to predict an undetectable viral load was significantly better in those with baseline CD4 cell counts ≤100 cells/μL (area under the ROC curve [AUC], 0.78; 95% confidence interval (CI), 0.67 to 0.89; versus AUC, 0.60; 95% CI, 0.48 to 0.71; $P = 0.018$). The sensitivity, specificity, and positive and negative predictive values of a CD4 count increase of ≥50 cells/μL for an undetectable viral load in those with baseline CD4 counts ≤100 cells/μL were 93.1%, 61.3%, 92.5%, and 63.3%, respectively. Alternatively, these values were 47.8%, 87.1%, 95%, and 24.5%, respectively, if an increase in CD4 count of ≥150 cells/μL was used. *CONCLUSIONS:* CD4 count increase after initiating HAART has only moderate discriminative ability in identifying patients with an undetectable viral load, and the predictive ability is lower in patients with lower baseline CD4 counts. Although HIV treatment programs in resource-constrained settings could consider the use of CD4 count increases to triage viral load testing, more accurate approaches to monitoring virologic failure are urgently needed.

AIDS. 2006;20(12):1613-1619.

Neurology

Immune reconstitution inflammatory syndrome in the CNS of HIV-infected patients

Venkataramana A, Pardo CA, McArthur JC, et al.

OBJECTIVE: To describe challenges in diagnosis and management of patients with clinical syndromes of immune reconstitution inflammatory syndrome (IRIS) involving the central nervous system (CNS). *METHODS:* The authors describe three HIV-infected patients with clinically distinct neurologic manifestations of IRIS who presented as diagnostic and therapeutic challenges. *RESULTS:* One patient with cryptococcal meningitis developed acute cerebellitis with mass effect and brainstem compression. Corticosteroid therapy was associated with complete resolution of the cerebellar lesion, but the patient developed varicella-zoster virus (VZV) encephalitis. Another patient with progressive multifocal leukoencephalopathy developed subacute progression of focal neurologic deficits associated with contrast-enhancing lesions on brain MRI. This patient had spontaneous resolution of the lesion but was left with residual deficits. One patient developed a progressive dementing syndrome and deterioration over several months, resulting in coma, during combination antiretroviral therapy. A brain biopsy in this latter patient showed massive infiltration of T lymphocytes predominantly of the CD8 subtype. This patient had a significant improvement with corticosteroids and a change in antiretroviral regimen, although she was left with residual cognitive impairment. *CONCLUSIONS:* Immune reconstitution inflammatory syndrome should be suspected in patients who show clinical or radiologic deterioration following initiation of antiretroviral therapy accompanied with improvement in CD4 count and viral load. Some patients may respond to a brief course of treatment with corticosteroids.

Neurology. 2006;67(3):383-388.

The Lancet

Durable efficacy of tipranavir-ritonavir in combination with an optimized background regimen of antiretroviral drugs for treatment-experienced HIV-1-infected patients at 48 weeks in the Randomized Evaluation of Strategic Intervention in multi-drug reSistant patients with Tipranavir (RESIST) studies: An analysis of combined data from two randomized open-label trials

Hicks CB, Cahn P, Cooper DA, et al., and the RESIST investigator group.

BACKGROUND: Treatment options for HIV-1 infected individuals who have received extensive previous antiretroviral therapy are limited. We compared efficacy and safety of the novel non-peptidic protease inhibitor (PI) tipranavir (TPV) co-administered with ritonavir (RTV) plus an optimized background regimen with that of an investigator-selected RTV-boosted comparator PI (CPI-RTV) in such patients. *METHODS:* We did a combined analysis of 48-week data from two ongoing, randomized, open-label, multinational, phase 3, RESIST studies. HIV-1-infected adults with three months or longer previous triple antiretroviral class experience, two or more previous PI regimens, HIV-1 RNA 1,000 copies/mL or greater, and genotypically demonstrated primary resistance to PIs were eligible. Primary endpoints were proportion of treatment responders (with reduction in viral load of 1 $\log_{10}$ copies/mL or greater below baseline without treatment change) at 48 weeks and time to treatment failure through 48 weeks (intention-to-treat analysis). The RESIST studies are registered with ClinicalTrials.gov, numbers NCT00054717 (RESIST-1) and NCT00144170 (RESIST-2). *FINDINGS:* Of 3,324 patients screened, 746 received TPV/RTV and 737 CPI-RTV. Four hundred eighty-six (65.1%) patients on TPV/RTV and 192 (26.1%) on CPI-RTV remained on assigned treatment until week 48. At week 48, more patients achieved and maintained treatment response in the TPV/RTV group than in the CPI-RTV group (251 [33.6%] versus 113 [15.3%]; $P < 0.0001$). Median time to treatment failure was significantly longer in the TPV/RTV group than in the CPI-RTV group (113 days versus 0 days; $P < 0.0001$). Gastrointestinal system disorders and raised transaminase, cholesterol, and triglycerides were more frequent in the TPV/RTV group than in the CPI-RTV group. *INTERPRETATION:* Compared with CPI-RTV, TPV/RTV with an optimized background regimen provides better virological and immunological responses over 48 weeks in patients who have received extensive previous antiretroviral treatment.

Lancet. 2006;368(9534):466-475.

Low CD4 count + HCV coinfection = acute kidney failure?

Michael Carter

HIV-positive patients who are on antiretroviral therapy (ART) have an increased risk of experiencing acute kidney failure if they have a low CD4 count, US investigators report in the July 2006 edition of the *Journal of Acquired Immune Deficiency Syndromes*.[1] The investigators further found that patients who were coinfected with hepatitis C virus (HCV) had particularly elevated rates of acute kidney failure.

In the period before ART became available, severe immune suppression and AIDS-defining opportunistic infections were associated with acute renal failure in HIV-positive patients. Although ART can improve the immune function of HIV-positive patients, reducing the incidence of opportunistic infections, many patients may remain vulnerable to acute kidney failure because of coinfections, drug toxicities, lifestyle factors, and continuing susceptibility to some infections.

Researchers at the University of North Carolina's Center for AIDS Research conducted an observational study involving 705 HIV-positive patients between 2000 and 2002. Their primary aim was to assess the effect of a low CD4 count on the incidence of acute renal failure. Acute renal failure was defined as an increase in serum creatinine for at least two days of 0.5 mg/dL in individuals whose baseline level was less than 2 mg/dL; 1 mg/dL for patients whose baseline creatinine was between 2 mg/dL and 5 mg/dL; and 1.5 mg/dL for those with a baseline creatinine level of 5 mg/dL or higher.

Editor's Note: *Reprinted with permission from www.aidsmap.com (first e-published July 19, 2006).*

CD4 counts were measured at least three months before entry to the study and at regular intervals thereafter. Patients were also tested for infection with HCV and hepatitis B virus (HBV), and the investigators gathered data on the patients' age, race, sex, previous AIDS-defining illnesses, blood pressure, prevalence of diabetes, and history of injecting drug use. These were included in later statistical analyses.

Median age of the patients included in the study was 40 years, 69% were male, and 61% were African-American. Baseline CD4 count was 352 cells/mm^3, and approximately one third of patients had a CD4 count below 200 cells/mm^3, indicating an increased susceptibility to opportunistic infections. Baseline median creatinine was 0.7 mg/dL and did not differ by CD4 count. Approximately 25% of patients were HCV-coinfected, 17% had chronic high blood pressure, and 6% had diabetes.

Antiretroviral therapy was used to treat 93% of patients by the end of follow-up; the median duration of exposure to antiretroviral drugs was 5.5 years. The median number of antiretroviral drugs used was five. Only 38% of patients had a viral load below 400 copies/mL.

A total of 109 instances of acute kidney failure were observed in 69 patients during the two-year period of the study, providing an overall unadjusted incidence rate of 6.4 per 100 patient-years. Acute renal failure was associated with a low CD4 count: the unadjusted incidence rate being 15 per 100 patient-years for patients with a CD4 count below 100 cells/mm^3 compared to one per 100 patient-years among patients with a CD4 count of 500 cells/mm^3 or higher.

An even higher rate of acute renal failure was seen among HCV-coinfected patients, the unadjusted incidence rate being 25 per 100 patient-years for patients with a CD4 count below 100 cells/mm^3. Moreover, in their adjusted analysis the researchers noted very similar, and significantly elevated, incidence rates of kidney failure in coinfected patients with CD4 counts above and below 200 cells/mm^3 (4.3 per 100 person-years versus 3.7 per 100 person-years).

Patients in their first year of ART had the highest incidence of acute kidney failure (19 per 100 person-years versus three per 100 person-years for subsequent years of therapy). The researchers therefore recommend that kidney function be intensively monitored during the first 12 months of ART.

The researchers repeated their statistical analysis, adjusting it for possible confounding factors. They found that a low CD4 count ($P < 0.001$); number of years of previous ART, an indicator of long-term HIV infection and immune suppression ($P < 0.001$); and HCV coinfection ($P = 0.02$) were all significantly associated with an increased risk of kidney failure.

"A low CD4 count is… a strong predictor for experiencing an incident acute renal failure event," write the researchers, adding that, "we observed that increased acute renal failure incidence rates may be a more substantial concern for patients with relatively preserved immune function. These findings have clinical implications for the care of HIV-1-infected individuals, because acute renal failure by itself is associated with increased morbidity and mortality." ■

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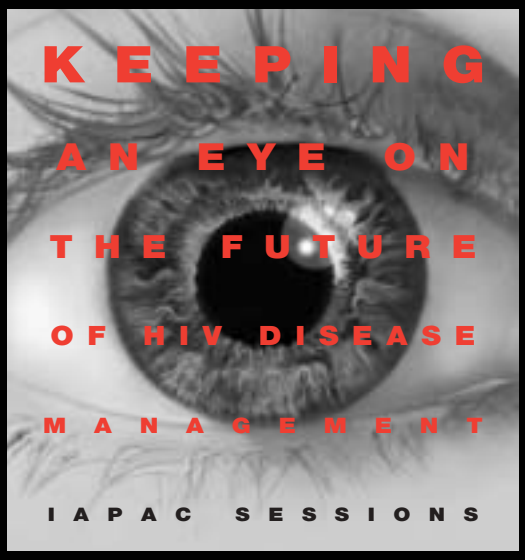

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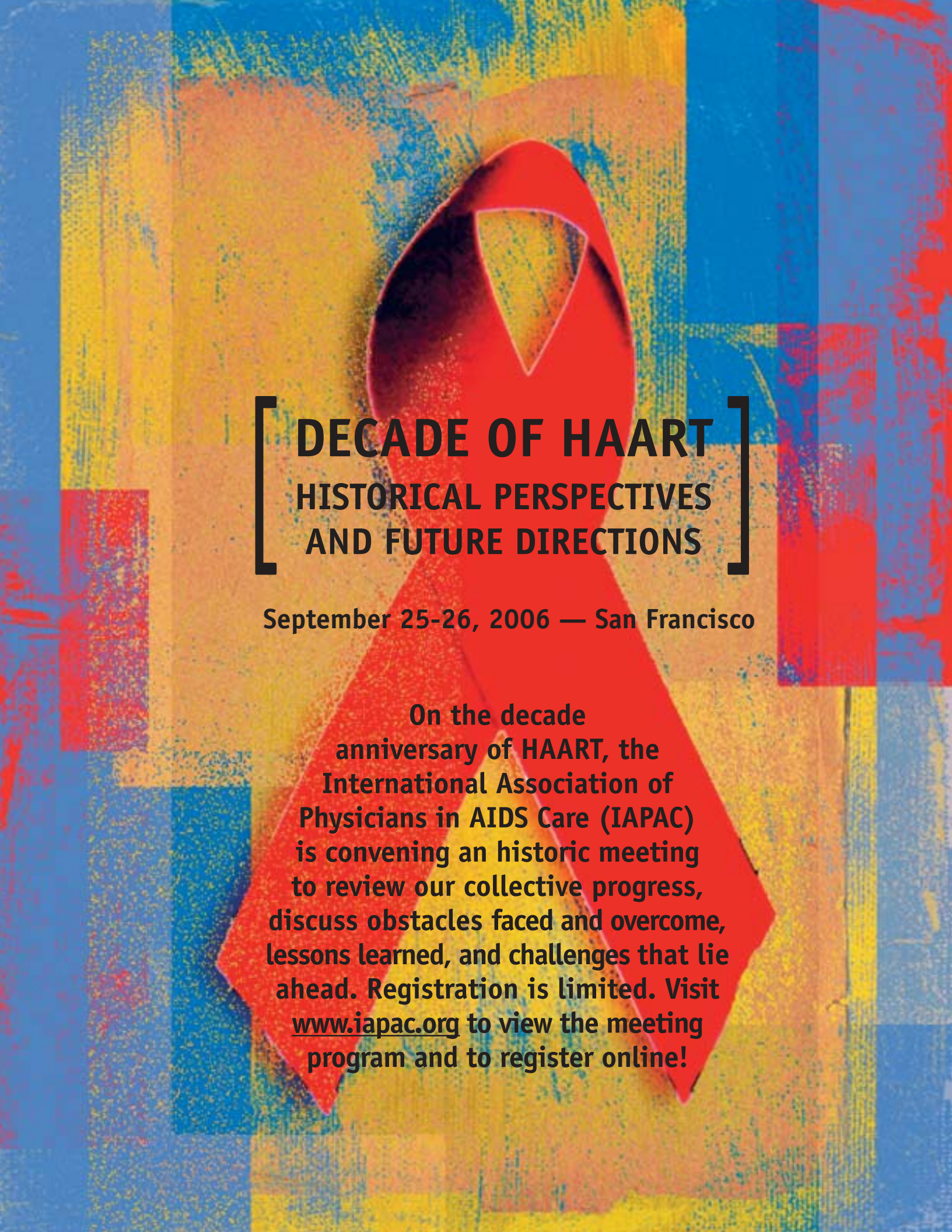
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Ralph Rynes

For more than three years the *IAPAC Monthly* has featured members of the International Association of Physicians in AIDS Care (IAPAC), who are asked to bare their souls by answering a series of questions similar in nature to those asked in the famous *Proust Questionnaire*.

This month, *IAPAC Monthly* is proud to feature Ralph Rynes, HIV/AIDS Program Director and Treatment Consultant at LRADAC/University of South Carolina School of Medicine in Columbia, South Carolina.

What proverb, colloquial expression, or quote best describes how you view the world and yourself in it?
I can't sum it up any better than Nkosi Johnson, a South African native born with HIV, who died at age 12. "Do all you can with what you have in the time you have in the place you are."

What activities, avocations, or hobbies interest you? Do you have a hidden talent?
My hobbies are research, cars, classical music, and going to recitals and concerts, particularly piano concerts. My hidden talent is that I seem to have a knack for learning foreign languages.

If you could live anywhere in the world, where would it be?
Probably Paris. I studied and interned there, and loved it.

Who are your mentors or real life heroes?
My mentors are my first language teacher, who taught that learning languages should be interesting and fun; David Ho; Stanley Prusiner, who has done so much groundbreaking work on transmissible spongiform encephalopathy (TSE); and many of my colleagues from whom I learn so much every day. My real life hero is my young friend Brandon Fornwalt, because of his ferocious intellect, enormously kind heart, and wisdom far beyond his years. He will soon be a major credit to medicine.

With what historical figure do you most identify?
Leonardo da Vinci, certainly not because my talents or intellect are comparable to his, but because my interests are all over the place, as were his.

Who are your favorite authors, painters, and/or composers?
My favorite author is Emily Dickinson. My favorite painters are Gustave Caillebotte, Joseph Hirsch, Chet Goff, and Steve Huston. My favorite composers are Alexander Scriabin and Frédéric Chopin. My favorite pianist is Marina Lomazov.

If you could have chosen to live during any time period in human history, which would it be?
Although there are many periods in history that fascinate me, I am glad to live now, because of all the incredible advances we are making in science.

If you did not have the option of becoming a physician, what would you have likely become, given the opportunity?
I would have become a language instructor.

In your opinion, what are the greatest achievements and failures of humanity?
Our greatest achievements are the amazing scientific advances made in the last 100 years. Our greatest failures have been our continued inability to cultivate tolerance, unite in peace, and take proactive steps to mitigate global warming.

What is your prediction as to the future of our planet one full decade from present day?
We will continue to advance medical research, but I do not think a preventive vaccine for HIV will be developed in the near future. In the United States, our conservative religious values will continue to limit stem cell research which might unlock the secrets to revolutionary treatments of many conditions that stymie us at present. Our dependence on fossil fuel will continue to diminish, but it will be too little, too late to stop the global warming cycle that is already underway. ■

SAY ANYTHING

Journalists have a central role to play in explaining why HIV/AIDS is on the rise. Simply put, lives depend on it.

Emma Walters, an Australian International Federation of Journalists (IFJ) representative, in a July 25, 2006, Deutsche Presse-Agentur report about a meeting held in Phnom Penh for African and Asian IFJ members. The meeting included discussions about the role of journalism in reducing stigma and combating myths about HIV, and in the process helping to arrest the epidemic. Khieu Kanharith, a former journalist, discussed journalism's role in changing the perceptions of readers. "Twenty years ago, when people spoke about HIV/AIDS they asked 'Who, who is to blame?' Now they ask, 'How, how to evolve, understand, and fight [this problem] better together?'"

I am not working, I live in the slums, and if coming up with rent is a problem for me, how will I live if I have to pay for drugs for myself and my baby?

Susan Atieno, one of hundreds of Kenyans protesting a bill requiring the Kenyan government to obtain permission from pharmaceutical companies holding patents for antiretroviral drugs before purchasing generic drug equivalents, in a July 25, 2006, Reuters report. Ignatius Kibe, one of the protest organizers, stated, "Kenya will witness a drastic increase in prices for various drugs, making medicines far out of the reach of [the] majority of Kenyans." As an example, Kibe cited nevirapine (NVP), which is used to prevent mother-to-child HIV transmission. A dose of brand-name NVP costs US$14.44 per dose; the generic version costs US$2.05. The bill would impact the purchase of generic drugs for malaria and tuberculosis, as well as HIV, and according to activists would imperil President Mwai Kibaki's promise, made in July 2006, of free antiretroviral drugs for government hospitals and health centers.

At first, I was very hesitant. The more I got to know the people, the less afraid I got and the more comfortable I got. Even just a tight squeeze makes a big difference for them because many people won't touch them.

Aisha Khatib, second-year medical student at the University of Alberta, in a July 26, 2006, Edmonton Journal *article about Khatib's summer spent working for the Deep Griha Society as an HIV/AIDS educator and a hospice administrator in Pune, India. Khatib discussed her own fear of contracting HIV or tuberculosis, and described bringing breathing masks and plastic gloves for protection. However, she stopped using them as she became more comfortable working with the patients. Khatib and fellow student Kim Dary distributed condoms, discussed methods of transmission, and worked to dispel harmful myths about HIV.*

We're going to make the public in Toronto aware that there's a lot more going on in preventing AIDS than abstinence and being faithful, which are the answers most promoted by the US government.

Judy Auerbach, Vice President for Public Policy and Program Development for the Foundation for AIDS Research (amfAR), in a July 22, 2006, Toronto Star *article detailing plans by the Caucus for Evidence-Based Prevention to present at the XVI International AIDS Conference alternatives to US policies that it says are ideologically driven. The caucus is an* ad hoc *coalition of over three dozen US and international organizations; amfAR, Population Action International, and the Sexuality and Education Council of the United States are the main partners. Mark Wainberg, Co-Chair of the XVI International AIDS Conference, said many scientists at US governmental health organizations who wanted to attend the conference were prevented by a federal quota on the number of federally funded scientists allowed to attend. Wainberg reported that many scientists said off the record that the quota was imposed for political reasons, allowing bureaucrats to decide which researchers would attend and thus which presentations would be made at the conference. According to the White House, the quota is an attempt to cut costs associated with attendance at international conferences.*

We need business to see HIV as more than a bottom line issue. It's also [their] social responsibility.

Ivan Toms, Health Director of Cape Town, South Africa, in a July 27, 2006, Johannesburg Business Day *article detailing the launch of the Western Cape chapter of the South African Business Coalition on HIV/AIDS. Speaking at the launch, Brad Mears, the coalition's CEO, said that businesses need to make a greater investment in fighting the epidemic, and suggested that business leaders create partnerships with local and provincial health department officials. Treatment Action Campaign (TAC) Secretary-General Sipho Mthathi urged businesses to demand stronger leadership on HIV/AIDS from the national government, and said the role of drug abuse in the HIV epidemic, including increasing methamphetamine use, must be addressed.*

Purchasing a UTAC bracelet contributes directly to the International Association of Physicians in AIDS Care (IAPAC) and its mission to improve access to quality treatment for all people living with HIV/AIDS. A full 25 percent of the price of each bracelet goes directly to IAPAC programming. Please be sure to mention IAPAC when shopping at www.until.org.