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# IAPAC



MONTHLY

**A dearth of  
groundbreaking  
data at 14th  
international conclave  
of HIV medical community**



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**A dearth of groundbreaking data at 14th international conclave of HIV medical community**

*David S. MacDougall*

Although the XIV International AIDS Conference was calorie-packed with policy news, it was anemic in the sense that delegates missed the groundbreaking nature of data expected in the post-HAART era. Still, there were important insights into the expanding antiretroviral arsenal, resistance, and toxicities.



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**One step ahead of us**

*Carmen Retzlaff*

From the dramatic standpoint, Barcelona was no Durban... That said, the XIV International AIDS Conference served as a reminder of the enormous amount of work that remains to be done to redress the stigma and discrimination associated with HIV disease, as well as the inequities that exist in access to HIV/AIDS care.



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REPORT FROM THE PRESIDENT

## Taking stock of successes and challenges

*José M. Zuniga*

**W**ithout question, the global battle against HIV/AIDS can be daunting and spiritually depleting. So, while it is axiomatic that we must never let up in this struggle that is in many ways a race against time, it is nonetheless necessary and appropriate to take periodic stock of what we are doing right. Such assessments serve as a reminder that our efforts are not futile, and replenish our energy in order to push forward. Moreover, by examining our successes in one area of medical treatment, public health policy, or region of the world, we gain perspective and insight into corresponding areas in which we have so much more to accomplish.

As evidenced by the experience of the world's wealthiest countries, well planned, adequately funded programs for prevention and treatment are effective at slowing infection rates and greatly prolonging and improving the lives of people living with HIV/AIDS. We saw an example of this in statistics recently released by the US Centers for Disease Control and Prevention (CDC). These numbers show that, as with other resource-rich countries, the United States has enjoyed admirable success in curbing rates of incidence and in significantly reducing HIV-related morbidity and mortality over the past few years. This success hardly means HIV/AIDS has been defeated in the United States, but we must acknowledge progress that has been a long time coming, through much sweat and with much loss.

Yet, as we breathe a collective sigh of relief that our efforts have not been wasted, we must also commit to redoubling them. For, even in the midst of success, there is cause for further concern. In the United States, as in many of the other industrialized

countries of the North, there remain several sub-populations that indicate rates of incidence far above national averages. For example, rates of infection among Latinos and African Americans (most notably African-American women) in the United States have not been reduced and are, in fact, often on the rise. This unacceptable state of affairs reflects coincidental rates of poverty and social and cultural marginalization that must be addressed as part of our collective and comprehensive strategy to ensure the health of total populations.

More than anything on the US domestic level, however, the successes of some wealthier nations remind us how much more can be done in the less-developed countries and regions of our world. That Africans from the southern half of the continent alone account for 28.5 million of the world's 40 million HIV-infected people is relatively well known. But we cannot allow ourselves to become desensitized to such information; the danger is simply too great. The rate of infection in Botswana has reached a staggering 39 percent, for example, causing President Festus Mogae to remark of his nation's citizens, "We are threatened with extinction."

In other regions of the world, the rising number of HIV infections is at a critical stage as well. A United Nations Children's Fund (UNICEF) report released in September 2002 described the rapid movement of HIV/AIDS into Central and Eastern Europe and the former Soviet bloc states. The number of HIV-infected people in the region grew from 420,000 in 1998 to more than 1 million at the end of 2001, and the vast majority of newly infected people are younger than age 29, thus pointing to the potential for even more astronomical rates of increase in years to come. In China, there may be as

many as 1 million HIV-infected people in Henan Province alone, where unsanitary conditions in government-affiliated blood banks spread the disease during the 1990s.

Indeed, our worst fears may be surpassed in coming years. A report issued earlier this month by the National Intelligence Council, a federal group that advises the US Central Intelligence Agency (CIA), predicts a growth in HIV/AIDS infection higher than the most pessimistic calculations. According to the report, the five countries on which it focused could alone account for 75 million HIV-infected people by 2010, and its authors call the situation a security threat to the United States and several regions of the world. The report's authors maintain that within the next eight years China, India, Ethiopia, Nigeria, and Russia will have surpassed sub-Saharan Africa as the epicenter of the AIDS pandemic.

Faced with these terrible realities, let us remember the lessons that we can take from our successes: the spread of HIV is imminently preventable, and for those who have already been infected, treatment is highly effective if delivered within an adequate infrastructure by trained and supported healthcare professionals. Given these facts, we must continue to have the resolve to fight HIV disease, in all regions of the world, by advocating realistic and aggressive prevention methods and comprehensive HIV/AIDS care, to include antiretroviral treatment, for all, with a corresponding increase in clinical capacity necessary to prevent resistance. We know what is at stake. We have seen what we are able to accomplish. Thus, we must not settle for anything less. ■

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

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*Editor's Note: This article is Part 2 of a two-part series featuring clinical coverage and analysis of the XIV International AIDS Conference. The Editor wishes to gratefully acknowledge the contributions of Michelle E. Roland (University of California, San Francisco) and Mike Youle (Royal Free Center for HIV Medicine, London).*

*David S. MacDougall*

**A**lthough delegates to the XIV International AIDS Conference, held July 7-12, 2002, in Barcelona, were greeted with a healthy dose of encouraging news around clinical issues usually expected at this biennial conclave, there was in fact a dearth of the groundbreaking data to which many have

become accustomed in the post-highly active antiretroviral therapy (HAART) era. Still, what data were presented in this seaside Catalanian city are of significance as HIV/AIDS-treating physicians deal with how best to sequence antiretroviral agents in increasingly complicated regimens, emerging antiretroviral toxicities, as well as where new antiretroviral agents fit into an increasingly complex treatment equation.

#### **Treatment-experienced patients**

As the survival rate in HIV-positive populations increases, so too does the number of patients who are treatment-experienced. Hundreds of papers presented at the XIV International AIDS Conference addressed therapeutic options for patients with exposure to multiple antiretroviral agents who are failing their current therapeutic regimen. With relatively few newer agents on the

horizon, treatment strategies presented in Barcelona focused on the optimal use of existing agents and on recycling previously used agents based on phenotypic and genotypic resistance testing.

Franco Maggiolo and a team of his colleagues from the Ospedali Riuniti in Bergamo, Italy, presented on a treatment option called selective salvage therapy (SST), an innovative approach to the management of heavily pre-treated patients. SST is a genotype-driven antiretroviral treatment that is rapidly adjusted in response to the emergence of new viral populations so that continually adaptive selective pressure is applied. In a 24-month pilot study, 34 patients with extensive previous exposure to antiretroviral therapy underwent SST. Viral load was measured every two months, and the therapy was modified according to the findings of genotypic testing in patients with HIV RNA >10,000 copies/ml. Combination antiretroviral therapy was limited to four or fewer drugs.

The median HIV RNA was maintained between 3,560 and 10,787 copies/ml throughout the study. Therapeutic adjustments were made on an average of 3.0 occasions per patient, and each regimen was maintained for a mean of 6.1 months. Mean CD4 counts increased from 239 cells/mm<sup>3</sup> at baseline to 323 cells/mm<sup>3</sup> at 24 months ( $p < 0.02$ ). Only two patients experienced clinical progression of HIV disease, and nine patients experienced drug-related adverse events. SST tailored according to the predominant viral strain may be associated with favorable clinical and immunologic responses in heavily pretreated patients and may allow recycling of previously used drugs as major viral populations express mutations not previously observed.

Other studies presented in Barcelona provided evidence that the combination of lopinavir/ritonavir (LPV/r) is gaining popularity as a component of salvage therapy in heavily pretreated patients. In a study by Carmen de Mendoza and colleagues at Instituto de Salud Carlos III, Madrid, Spain, 137 patients with previous exposure to all three classes of antiretrovirals who were failing their current regimen were treated with LPV/r in combination with a nucleoside reverse transcriptase inhibitor (NRTI). The mean HIV RNA and CD4 count prior to the initiation of LPV/r was 4.04 log<sub>10</sub> copies/ml and 285 cells/mm<sup>3</sup>, respectively.

At six months, a significant virologic response—defined as >1 log reduction in HIV RNA and/or HIV RNA <500 copies/ml—was achieved in 61 percent of the patients. At nine months, 58 percent of the patients in the study had achieved a significant virologic response. The mean increase in CD4 cells at six and nine months was 75 and 85 cells/mm<sup>3</sup>, respectively. Triglyceride levels increased a mean of 70 mg/dl after the start of LPV/r but cholesterol levels remained stable. HIV RNA levels were held to less than 500 copies/ml in 88 percent of the patients with less than five protease inhibitor (PI) resistance mutations at baseline and in 48 percent of those with more than five PI mutations ( $p < 0.001$ ). Combination treatment with LPV/r was generally well tolerated.

Another presentation focused on the use of “mega-HAART,” a salvage regimen containing LPV/r + PI + two NRTIs with or without a non-nucleoside reverse transcriptase inhibitor (NNRTI). Miguel Torralba and his colleagues from the Palacio Hospital 12 de Octubre, Madrid, found that the addition of a second PI to LPV/r and an NRTI was associated with significant reductions in viral load and acceptable toxicity in patients who had already been heavily treated. In Torralba’s study, 25 highly antiretroviral-experienced patients with documented resistance to all three classes of antiretrovirals received a “mega-HAART” salvage regimen containing LPV/r + PI + two NRTIs with or without an NNRTI. The second PI was saquinavir (SQV) (60 percent), amprenavir (APV) (28 percent), or nelfinavir (NFV) (12 percent). Treatment was guided by prospective genotypic analysis at baseline in all patients. The median viral load and CD4 count at baseline was 16,180 copies/ml and 200 cells/mm<sup>3</sup>, respectively.

In an on-treatment analysis, 41 percent of the patients in the Madrid study achieved HIV RNA <50 copies/ml at 28 weeks. The median reduction in HIV RNA at 28 weeks was 0.80 log ( $p = 0.001$ ), and 64 percent of the patients showed less than a 0.5 log decrease in HIV RNA at 28 weeks. The median increase in CD4 count at 28 weeks was 64 cells/mm<sup>3</sup>. Toxicities requiring temporary cessation of therapy were observed in only two patients, and there were no significant increases in hepatic enzyme, triglyceride, or cholesterol levels.

A growing body of evidence suggests that phenotypic and genotypic testing are

critical adjuncts to the management of highly treatment-experienced patients, and presentations at Barcelona added to this evidence. Donna Mildvan and her colleagues at the Beth Israel Medical Center, New York, looked at 24 heavily pretreated patients who began taking abacavir (ABC) and at least one additional drug as part of a salvage regimen. The number of HIV protease and reverse transcriptase genotypic resistance mutations and phenotypic drug susceptibility scores (PSS) were measured retrospectively in plasma samples stored at baseline. At baseline, the mean HIV RNA was 5.38 log<sub>10</sub> copies/ml, and 20 patients had four or more resistance mutations.

When the baseline HIV RNA and number of resistance mutations were included in the predictive model, only the baseline HIV RNA predicted the viral load response at week 8 ( $p < 0.05$ ) and only the number of resistance mutations predicted the response at week 24 ( $p = 0.014$ ). When the baseline HIV RNA and PSS were included, each was predictive of the response at week 8 ( $p < 0.05$ ), but only the PSS predicted the response at week 24 ( $p = 0.043$ ). At week 24, HIV RNA was lower in patients whose antiretroviral therapy had been stopped for a mean of three months prior to the start of salvage therapy (mean: 3.18 log<sub>10</sub> copies/ml) than in those who were on treatment at the time of initiation of salvage therapy (mean: 4.77 log<sub>10</sub> copies/ml) ( $p = 0.05$ ).

Resistance to antiretroviral agents is a problem even when patients are good about taking their medications. Non-adherence to prescribed regimens increases the rate at which HAART is ineffective in HIV-infected patients. Providing a viable option in such situations, Hernando Knobel and his colleagues at the Hospital del Mar, Barcelona, found that a simplified salvage regimen containing three NRTIs produced favorable outcomes in a cohort of heavily non-adherent patients whose previous HAART regimen had failed. The study group was comprised of 50 patients considered severely non-adherent (by self-report, they had taken less than 50 percent of prescribed doses in the previous three months or withdrawn from therapy entirely) and who were failing HAART containing two NRTIs and a PI. All patients were switched to a combination of ABC and 3TC/ZDV (Combivir) twice daily and later switched to ABC/3TC/ZDV (Trizivir)

twice daily. All patients had HIV RNA >5,000 copies/ml and none of the patients had mutations associated with resistance to NRTI or PI at the start of salvage therapy.

At 24 weeks, the mean HIV RNA decreased 1.6 log<sub>10</sub> copies/ml and the mean CD4 count increased 124 cells/mm<sup>3</sup>. Overall, 66.5 percent of the patients achieved HIV RNA levels at less than 500 copies/ml in on-treatment analysis, as did 44 percent in intention-to-treat (ITT) analysis. Treatment-related adverse events were observed in 22 percent of the patients. Not surprisingly, adherence was greater with the salvage regimen than with previous HAART: 50 percent of the patients reported satisfactory adherence (taking more than 90 percent of prescribed drugs) with the twice-daily salvage regimen.

### Spare the PIs

The trend toward PI-sparing combination regimens for both initial therapy and switching in patients with lipid elevations or other adverse events during the course of treatment with PI-containing regimens, was demonstrated in Barcelona. It was shown that the potential advantages of PI-sparing regimens include increased tolerability, dosing convenience, and sparing of PI in patients with early HIV infection. However, the long-term efficacy and adequacy of PI-sparing regimens in patients in a more advanced stage of HIV-disease remain uncertain.

Two PI-sparing combination antiretroviral regimens were compared with a standard PI-containing regimen in a study led by Remko van Leeuwen at the International Antiviral Therapy Evaluation Center in Amsterdam. In this study, 298 antiretroviral-naïve patients were treated with stavudine (d4T) and didanosine (ddI) and either nevirapine (NVP), lamivudine (3TC), or indinavir (IDV). The median CD4 count and HIV RNA at baseline were 406 cells/mm<sup>3</sup> and 4.3 log<sub>10</sub> copies/ml, respectively.

After 48 weeks, the proportion of patients who showed <500 copies/ml of HIV RNA was just above half in each of the three treatment groups. Of patients taking NVP, 58.4 percent were at this level of HIV RNA per milliliter, while the number was 58.7 percent of those taking 3TC, and 57 percent of those on IDV. The proportion of patients with more than 49 copies/ml of HIV RNA was significantly less in the 3TC group (28.4 percent) than

in those treated with NVP (55.1 percent) or IDV (44.0 percent). Patients in the NVP group experienced a smaller increase in the absolute CD4 count than did those in the other two groups. The incidence of serious adverse events was similar in all three groups. High-density lipoprotein (HDL) cholesterol levels increased 40 percent in the NVP group, while the total HDL cholesterol ration decreased 6 percent in the NVP group and increased 25 percent in the IDV group.

Evidence of the long-term efficacy of triple NRTI therapy in severely immunosuppressed patients emerged in a study by Motoserrat Lonca and colleagues at the Gatell Hospital Clinic, Barcelona. In this study, 68 patients with CD4 counts <200 cells/mm<sup>3</sup> received triple therapy including two NRTIs and NVP or efavirenz (EFV). The study group included 23 patients (34 percent) with AIDS-defining illnesses, 38 (59 percent) with CD4 counts <100 cells/mm<sup>3</sup>, and 52 (76 percent) with HIV RNA appearing at a rate of 100,000 copies/ml. The time from the diagnosis of HIV infection to the beginning of antiretroviral therapy was less than 12 months in 22 patients (32 percent).

At 24 months, ITT analysis showed that 86 percent of the patients had CD4 counts that were >200 cells/mm<sup>3</sup> and all of the patients in the study had HIV RNA levels at <200 copies/ml. Similar trends in CD4 counts and HIV RNA levels were observed in the NVP and EFV groups. Only five patients (7 percent) discontinued NVP or EFV due to adverse effects.

EFV-based HAART proved comparable to PI-based HAART in severely immunocompromised patients in a study led by Federico Pulido of the Hospital La Paz, Madrid. The study tracked 214 treatment-naïve patients with advanced HIV infection and CD4 counts of <100 cells/mm<sup>3</sup> who underwent treatment with either EFV- or PI-based HAART. At 12 months, the proportion of patients who achieved CD4 counts <100 cells/mm<sup>3</sup> was 70 percent in the EFV group and 58 percent in the PI group, and the proportion who achieved HIV RNA levels <400 copies/ml was 78 percent in the EFV group and 55 percent in the PI group. After adjusting for baseline CD4 count, concurrent treatments, clinical status, and other variables, the use of EFV and PI was not associated with significantly different immunologic or virologic outcomes at 12 months. During the first year, EFV was discontinued in 13 patients

(14 percent) and PI was discontinued in 30 patients (24 percent) (p=0.09).

The long-term durability of the triple NRTI regimen ABC/3TC/ZDV was examined in a study by a team from the J.W. Goethe-Universitat in Frankfurt headed by Peter Gute. A group of 128 antiretroviral-naïve patients were started on triple combination therapy with ABC/3TC/ZDV and followed for a median of 20 months. Study endpoints included adding or switching to a different class of antiretroviral agent or to an NRTI regimen without ABC or treatment interruption without reinitiating a triple NRTI regimen containing ABC.

Overall, 83 patients (65 percent) were still on an ABC-containing triple NRTI regimen after a median of 20 months. Only 17 patients (13 percent) switched to a new class of antiretroviral agent and five patients (4 percent) switched to a different triple NRTI combination without ABC. A total of 23 patients (18 percent) stopped therapy after the initial regimen and did not restart treatment. Based on therapy changes, ABC/3TC/ZDV proved effective and well tolerated for long-term use in antiretroviral-naïve patients.

The ability to maintain virologic control while switching from PI- to either NVP- or EFV-based combination therapy was demonstrated in a study by Patricia Patterson and her colleagues at Cahn Fundacion Huesped, Capital Federal, Argentina. The study looked at 120 NNRTI-naïve patients who were switched from a PI-based regimen to an NVP- or EFV-based regimen without changing background NRTIs. All patients had evidenced HIV RNA counts at <50 copies/ml within six months of switching.

Patterson's presentation also showed that potential complications could be kept to a minimum over time. At 36 weeks, the proportion of patients who experienced virologic failure (two HIV RNA measurements >500 copies/ml) or treatment-limiting toxicity was 14 percent in the NVP group and 12 percent in the EFV group (p = NS). The median increase in CD4 count from baseline was 2 cells/mm<sup>3</sup> in the NVP group and 21 cells/mm<sup>3</sup> in the EFV group. Lipid profiles improved in the NVP group and remained unchanged in the EFV group.

### Emerging toxicities

The short-term toxicities of antiretroviral

therapy are widely known, but the adverse consequences of long-term HAART remain little understood. A number of studies presented in Barcelona characterized the emerging toxicities of HAART and examined the impact of antiretroviral-related adverse effects on physical and psychological health. These studies underscore the increasingly important role of the prevention and management of antiretroviral-related toxicities in patients receiving long-term HAART.

Bodily pain increases following the initiation of HAART and is related to immunologic and virologic parameters, reported Ségolène Duran and colleagues at INSERM U379, in Marseille, France. The finding was based on a study of 1,045 patients initiating PI-based HAART who completed standardized quality of life surveys at baseline and after 12 months of treatment. Treatment adherence was measured by self-report and by comparison of immunologic and virologic parameters determined at baseline and after 12 months.

Following the initiation of HAART, the mean score for bodily pain was the only component of the well-being survey to show significant deterioration ( $p=0.04$ ). In contrast, mean scores for physical functioning, general health perception, social functioning, role limitations due to physical and emotional problems, vitality, and general mental health improved significantly at one year after HAART initiation. In a multivariate analysis, mean changes in bodily pain scores were independently related to lower bodily pain scores at baseline. Higher levels of bodily pain at 12 months were associated with patients older than 35 years, baseline CD4 counts  $>200$  cells/mm<sup>3</sup>, female gender, lower baseline HIV RNA, loss of body weight, and self-reported non-adherence. The initiation of HAART may be associated with worsening of bodily pain in patients with favorable immunologic and virologic profiles at baseline.

Dyslipidemia is a frequent complication of HAART, but the incidence of coronary artery disease (CAD) and other cardiovascular complications in patients receiving HAART is unknown. In a study by Giorgio Barbarini and colleagues at the University of Pavia, Italy, 1,551 treatment-naïve patients started HAART with or without PI and were followed for up to three years. The study endpoint was the cumulative incidence of CAD in terms of recently

developed angina, unstable angina, and fatal or nonfatal myocardial infarction (MI).

Overall, 21 percent of the patients in the PI group and 3 percent of those in the non-PI group developed dyslipidemia and associated metabolic alterations during follow-up. The cumulative annual incidence of CAD was 9.8 per 1,000 in the PI group and 0.8 per 1,000 in the non-PI group ( $p<0.001$ ), and the cumulative annual incidence of MI was 5.1 per 1,000 in the PI group and 0.4 per 1,000 in the non-PI group ( $p<0.001$ ). Stepwise logistic regression analysis revealed that the incidence of CAD was primarily associated with dyslipidemia, lipodystrophy, and smoking and was independent of age, gender, and CD4 count.

Alterations in bone mineral density (BMD) are significantly more common in HIV-positive Caucasian women receiving HAART than in their HIV-negative counterparts, reported Barbara Smith who led a study at the University of Alabama at Birmingham, in the United States. A group of 20 HIV-positive women who received HAART for one year were compared with a matched control group of HIV-negative women. Study measurements included total fat mass, fat free mass, subcutaneous and visceral abdominal adipose tissue, and bone mineral content.

Despite similarities in age, race, body mass index, and menopausal status, HIV-positive women had nearly twice the amount of visceral abdominal adipose tissue (mean: 10,416 cm<sup>2</sup>) as the HIV-negative women (mean: 5,543 cm<sup>2</sup>) ( $p=0.0009$ ). The amount of subcutaneous abdominal adipose tissue was greater in the HIV-positive women than in the HIV-negative women, but the difference was not statistically significant. Among all patients, BMD as measured by dual energy x-ray absorptiometry was similar in both groups. Among Caucasian women, BMD was significantly lower in the HIV-positive group (mean: 2,178 g) than in the HIV-negative group (mean: 2,411 g) ( $p=0.03$ ).

Evan Collins and colleagues from the University of Toronto, Canada, examined lipodystrophy and its effects on health-related quality of life and treatment adherence. Lipodystrophy severity was assessed in 83 patients receiving HAART who completed standardized self-report measures for depression, anxiety, self-esteem, medication adherence, and overall symptoms. The mean duration since

diagnosis of HIV infection was 10 years, the mean duration of antiretroviral use was seven years, the mean HIV RNA was 8,600 copies/ml, and the mean CD4 count was 534 cells/mm<sup>3</sup>.

There were moderate correlations between lipodystrophy severity and quality of life measures related to physical and psychosocial functioning. In cross-sectional sampling, however, lipodystrophy severity had no apparent influence on depression, anxiety, self-esteem, or self-reported medication adherence. Hypertrophy was shown to have a more negative effect on patients; it was associated with psychological distress and worry. The impact of lipodystrophy severity on quality of life was greater in younger patients, suggesting that advanced age may mitigate some of the negative effects of lipodystrophy on quality of life. Patients' self-assessment of the severity of their lipodystrophy correlated well with clinician ratings.

The observation that patient characteristics may influence some of the effects of HIV-related lipodystrophy on quality of life was bolstered by the findings of a study by Jordi Blanch and other researchers at the Hospital Clinic Universitari, Barcelona. In comparison with a group of 66 HIV-positive patients without lipodystrophy, 84 patients with lipodystrophy were older, had received antiretroviral therapy for a longer period of time, and reported a poorer physical status. Surprisingly, lipodystrophy itself was not found to influence overall quality of life. In comparison with their counterparts without lipodystrophy, those with lipodystrophy who were homosexual, unemployed, or had a history of psychiatric illness showed greater impairment on quality of life subscales related to psychological well being.

Changes in body fat distribution after three years of HAART are similar in patients receiving NRTI-, NNRTI-, and PI-based combination therapy, reported Baiba Berzins and colleagues from the Northwestern University Medical School in Chicago. The unexpected finding emerged in an analysis of preliminary data from the Atlantic Study, an ongoing, prospective, randomized, international trial of d4T/ddI administered in combination with 3TC, NVP, or IDV in 298 treatment-naïve patients. Changes in body fat distribution were determined in a subgroup of 69 patients at baseline and every 24 weeks thereafter during treatment.

Accumulation of fat in the abdomen, neck, or breasts was observed in 23 percent, 9 percent, and 5 percent of those receiving 3TC, NVP, or IDV ( $p=0.15$ ), respectively. Loss of fat in the arms, legs, face, or buttocks was observed in 27 percent of patients in both the 3TC and NVP groups and in 19 percent of those taking IDV ( $p=0.78$ ). The mean ratios of visceral and subcutaneous to total adipose tissue were similar in patients with and without body fat redistribution. The results of abdominal CT and whole body DEXA scans revealed no significant differences in body fat between the groups.

### Resistance challenge

Infection rates with drug-resistant viral strains in Western countries are rising at an alarming rate. For example, various studies presented in Barcelona, including one published in the July 10, 2002, *Journal of the American Medical Association* (Grant R, et al. Time trends in primary HIV-1 drug resistance among recently infected persons. *JAMA* 2002;287:181-8), found that up to three-quarters of HIV-infected patients in the United States are resistant to at least one antiretroviral agent, with one in four new cases of HIV infection in San Francisco showing some resistance.

Given these statistics, it is no surprise that resistance was heavily discussed at the XIV International AIDS Conference (as well as at the preceding XI International HIV Drug Resistance Workshop held July 2-5, 2002, in Seville, Spain). In fact, there was a great amount of discussion about ways to improve our understanding how resistance impacts on the efficacy of antiretroviral agents.

Among the issues up for discussion in Barcelona was that of hypersusceptibility, a phenomenon where the acquisition of resistance appears to make the virus more, rather than less, susceptible to certain antiretroviral agents. Richard Haubrich and colleagues of the University of California, San Diego, examined the prevalence, associated factors, and clinical significance of NNRTI hypersusceptibility (NNRTI-HS). They enrolled 177 patients without prior NNRTI therapy who were failing (HIV RNA  $>400$  copies/ml) stable antiretroviral therapy and administered ViroLogic phenotype assay, HIV RNA, and CD4 counts before changing to a new NNRTI-containing regimen at baseline. NNRTI-HS was defined as a fold change

in  $IC_{50}$  of less than 0.4 (patient compared to reference control). The mean baseline HIV RNA was  $4.1 \log_{10}$ , the CD4 count was  $322 \text{ cells/mm}^3$ , and the patients had been treated for an average of 41 months. NNRTI-HS appeared to be common: EFV-HS was 24 percent, DLV-HS was 17.5 percent, and NVP-HS was 20 percent.

EFV-HS was associated with duration of previous NRTI use ( $p<.001$ ), number of NRTI agents ( $p=.002$ ), use of ZDV ( $p=0.04$ ), and reduced susceptibility to ZDV and ABC (fold change in  $IC_{50} >5.0$  compared to control) ( $p<.005$ ). The mean change in HIV RNA through six and 12 months after starting a new NNRTI-based regimen was greater in the 21 patients with NNRTI hypersusceptible virus compared to the 77 patients without HS (at month 12) ( $p=.023$ ). CD4 cell increases were also greater for patients with HS virus. Thus the phenomenon of hypersusceptibility appears to offer a significant advantage to the host.

In an attempt to evaluate the impact of combining both resistance assays in a single report (PhenoSense GT), genotype and phenotype tests were performed on approximately 200 patients participating in a pilot program. Genotypic interpretations were based on an updated algorithm reflecting state-of-the-art knowledge. Discordance was defined for drugs with a fold-change in  $IC_{50}$  over the PhenoSense HIV assay cut-off but scored as genotype sensitive (PR/GS), or vice versa (PS/GR). Within the cohort 85 percent of the patients had two or more treatment failures and PT/GT discordance was observed in 75, 54, 33, and 22 percent of samples for at least one, two, three, or four agents, respectively.

After accounting for mixtures at resistance-associated positions, only ddI (29 percent), ddC (20 percent), 3TC (14 percent), ABC (14 percent), and APV (11 percent) had discordance rates over 10 percent. The majority of samples showed PT/GT discordance for at least two of 15 drugs. This combination approach to resistance testing may hopefully expand the picture for clinicians while not increasing the complexity of interpreting test results.

Susan Sufka and colleagues at the Duke University Medical Center in Durham, North Carolina, examined replicative capacity in patients with discordant CD4 count and viral load responses. Nine of 30 HIV-infected patients on PI-based HAART who had viral load of 500 to 5,000

copies/ml, and CD4 count of  $>200 \text{ cells/mm}^3$  increasing over more than two years were compared with successfully treated patients (viral load  $<50$  copies/ml, CD4 count  $>200 \text{ cells/mm}^3$  increasing over more than two years). Despite high-level drug resistance, CD4 cells continued to increase in the discordant group and viral load remained partially controlled. Diminished HIV replicative capacity persisted. Evolution of viral and immunologic responses was observed during the additional year of follow-up suggesting that replicative capacity may be a major factor related to the success of a regimen in the face of persistent HIV viremia.

Two studies examined the relationship to virologic outcome of phenotypic resistance at baseline in subjects taking ritonavir boosted indinavir regimens. A research team from Stanford University, in Palo Alto, California, and the Kaiser Permanente Medical Center in Santa Clara, California, examined 88 subjects with a phenotype taken prior to commencing IDV/ritonavir (RTV). Median duration of prior antiretroviral therapy was 50 months, median number of prior PIs was two, median baseline CD4 count was  $184 \text{ cells/mm}^3$ , and the median baseline viral load was  $4.6 \log_{10} \text{ c/ml}$ . IDV/RTV doses were twice daily and varied IDV 400 to 800 mg and RTV 100 to 400 mg. The median and mean  $IC_{50}$  fold changes for IDV were 1.87 and 17.2, respectively (range 0.35 to  $>178$ ). Virologic responses by IDV fold change categories were calculated using available data through 24 weeks for all patients, and appeared to diminish with increasing baseline IDV phenotypic resistance, although some subjects appeared to respond even with baseline IDV phenotypes of up to 25 fold changes.

The second study from Rafael Campo of the University of Miami examined IDV  $IC_{50}$  of plasma viruses from 73 patients with PI failure (median two prior PIs) using the PhenoSense assay, and compared these with virologic responses to subsequent IDV/RTV (800 mg/200 mg twice daily)-containing regimens. Plasma HIV RNA suppression was scored at HIV RNA nadir and after 24 weeks of therapy. Adjusting for covariates that may have affected suppression did not change the relationship between baseline phenotype and outcome. IDV/RTV-based regimens achieved viral suppression in heavily pretreated patients with prior failure of multiple PIs, including

IDV. Baseline IDV “resistance” >2.5-fold or >5-fold was not associated with lessened suppression. Although proportionally fewer patients with >10-fold IDV resistance achieved suppression, the difference was not significant.

Zidovudine prophylaxis is recommended to prevent perinatal HIV-1 transmission. Limited data exist on the role of reduced susceptibility to antiretrovirals (viral “resistance”) in perinatal transmission. A study was presented in Barcelona that examined its association with reduced susceptibility to ZDV determined by genotypic and phenotypic methods and the agreement between these methods. Stored plasma from baseline and delivery was tested in 24 transmitting and 72 non-transmitting women matched for baseline HIV RNA in PACTG 185 (a 1993-1997 controlled trial of anti-HIV hyperimmune globulin to reduce perinatal transmission in women with CD4 count <500 cells/mm<sup>3</sup> on ZDV and given ZDV prophylaxis).

PCR amplifiable sequences of subtype B in 95 women and subtype A in one woman were obtained. ZDV resistance mutations were found in six (25 percent) transmitting and eight (11 percent) control women. Phenotypic ZDV resistance was found in six of 23 (26 percent) transmitters and nine (13 percent) controls. Overall agreement between genotypic and phenotypic methods was 97 percent for identification of presence or absence of ZDV resistance ( $p < 0.0001$ ). Reduced susceptibility to ZDV by either method was found twice as often in transmitting compared with non-transmitting women.

There were new data presented in Barcelona with regard to genotypic resistance testing itself. Data presented included the NARVAL trial, an updated multivariable logistic regression model of predictors of virologic response or failure at 12 weeks. In the French trial, of 541 randomized patients, 39 percent achieved suppression of HIV RNA levels to <200 copies/ml. Among the factors that were significantly associated with virologic success was the prescription of EFV in NNRTI-naïve patients (OR 4.37) and randomization to the genotype group (OR 2.13).

The importance of using an NNRTI in salvage regimens in NNRTI-naïve patients is a recurring and very important theme. Not surprisingly, NNRTI use appears to play an even more significant role in virologic success than does access to a genotypic

resistance test. Nevertheless, this analysis does suggest that there is an additional benefit—beyond reminding clinicians to include an NNRTI—afforded by the resistance test itself. Factors associated with lack of virologic response included prescription of NFV in this highly PI-experienced population (OR 0.30), higher baseline viral load (OR 0.37), five or more PI-resistance mutations (OR 0.42), three or more NRTI mutations (OR 0.61), and PI exposure greater than 30 months (OR 0.64). In summary, the virologic benefit associated with the genotype test appears modest compared to the variables related to the extent of antiretroviral experience and the new drugs selected.

There were also data presented in which researchers compared genotyping and phenotyping. Among the two more prominent studies presented in Barcelona was VIHRES, a randomized study comparing the short-term virologic effects of genotypic versus phenotypic resistance testing. One hundred forty-four patients who had failed more than two HAART regimens and had HIV RNA levels >5,000 copies/ml were randomized to receive either a genotype test or a phenotype test, with results of both assessed by a committee of experts, prior to modification of their antiretroviral regimen. At 24 weeks, the proportions of subjects in the genotype and phenotype arms with HIV RNA <200 copies/ml were not statistically significantly different (50 percent and 40 percent, respectively) ( $p = 0.48$ ). Of note, this finding is different from that of the NARVAL study, where the genotype arm was superior to the phenotype arm. It also differs in that a “no-resistance test” control was not included.

The CERT trial compared the outcomes of patients randomized to receive a genotypic resistance test, a phenotypic resistance test, or no resistance test prior to modifications in antiretroviral therapy. No expert guidance was provided. The outcome variable in this study—time to persistent virologic failure despite a change in antiretroviral therapy—was different than in all previous studies. Virologic failure was defined as less than 1.0 log<sub>10</sub> copies/ml reduction in HIV RNA by four weeks, failure to achieve HIV RNA of <200 copies/ml four to six weeks after antiretroviral therapy change, an increase in HIV RNA to detectable levels in subjects with previously undetectable HIV RNA,

or greater than 0.5 log<sub>10</sub> copies/ml increase from nadir HIV RNA level. If subsequent antiretroviral changes resolved the virologic failure, the subject remained on the study without reaching an endpoint.

Among the 450 study subjects, the median CD4 count was 471 cells/mm<sup>3</sup> and the median HIV RNA level was 2.76 log<sub>10</sub> copies/ml. The median follow up was 525 days. Subjects in both the genotype and phenotype arms had a delayed time to virologic failure compared to the no resistance test arm (574 days for genotype, 521 days for phenotype and 478 days for no test); there was no difference in this respect between the genotype and phenotype groups.

Of particular interest is that the genotype interpretation methodology changed over the course of the CERT trial, which to some extent complicates the interpretation of data. Genotypes were initially interpreted with the commercially supplied, rules-based algorithm employed by Virco, and then with Virco’s Virtual Phenotype when it became commercially available. Thus, it is not clear if this study should be considered a comparison of genotype versus phenotype testing, or of Virtual Phenotype versus phenotype testing.

### On the horizon

Enfuvirtide (also known as T-20) is the first and most advanced of a new class of agents known as HIV fusion inhibitors. T-20, a synthetic peptide that corresponds to a peptide sequence of HIV gp41, blocks gp41-mediated fusion to host cells. The addition of enfuvirtide to optimized conventional therapy is expected to become a primary approach to the management of antiretroviral failure in treatment-experienced patients. The novel mode of action of enfuvirtide suggests that cross-resistance with other agents is unlikely.

Henry Keith and his colleagues at the Hennepin County Medical Center in Minneapolis presented in Barcelona findings from TORO 1 (T-20 vs. Optimized Regimen Only), a multicenter North American study of enfuvirtide in treatment-experienced patients. In this study, 491 patients who had more than six months experience with three classes of antiretroviral agents and HIV RNA measurements >5,000 copies/ml were randomized to optimized background (OB) therapy alone or in combination with enfuvirtide. OB consisted of three to five antiretroviral agents selected

on the basis of prior history and genotypic and phenotypic resistance testing. Twice daily doses of enfuvirtide were administered subcutaneously. The median baseline HIV RNA and CD4 count was 5.2 log<sub>10</sub> copies/ml and 80 cells/mm<sup>3</sup>, respectively

At 24 weeks, the mean decrease in HIV RNA was 1.70 log in the enfuvirtide group and 0.76 log in the OB group ( $p < 0.0001$ ). The proportion of patients with more than 400 HIV RNA copies/ml at 24 weeks was 37.1 percent in the enfuvirtide group and 16.4 percent in the OB group. The mean increase in CD4 counts at 24 weeks was 76 and 32 cells/mm<sup>3</sup> in the enfuvirtide and OB groups, respectively. Injection site reactions were experienced by 98 percent of the patients treated with enfuvirtide, but only 2.8 percent of these patients discontinued treatment for this reason. Of patients receiving enfuvirtide, 11.3 percent withdrew from the study. A similar percentage of patients receiving OB, 10.9 percent, also withdrew.

The second phase III study of enfuvirtide presented in Barcelona, TORO 2, was similar in design to TORO 1. Bonaventura Clotet and colleagues at the Hospital Germans Trias i Pujol in Barcelona offered the results of TORO 2. In this study, 504 patients recruited from 64 sites in Europe and Australia were randomized to enfuvirtide with or without OB. All patients had less than three months of experience with three classes of antiretroviral agents. The median baseline HIV RNA and CD4 count was 5.1 log<sub>10</sub> copies/ml and 98 cells/mm<sup>3</sup>, respectively. Almost all patients had HIV with five or more primary resistance mutations to the three classes of antiretroviral agents.

At 24 weeks, the mean decrease in HIV RNA was 1.43 log in the enfuvirtide group and 0.65 log in the OB group ( $p < 0.0001$ ). The proportion of patients with HIV RNA levels at <400 copies/ml at 24 weeks was 28.4 percent in the enfuvirtide group and 13.6 percent in the OB group. The mean increase in CD4 counts at 24 weeks was 65 and 38 cells/mm<sup>3</sup> in the enfuvirtide and OB groups, respectively. Aside from the injection site reactions, the adverse events profiles were similar in both groups.

Atazanavir (ATV) is a novel once-daily PI currently in phase III clinical development. Preliminary findings presented in Barcelona suggest that ATV may be associated with a low incidence of dyslipidemia and other metabolic abnormalities. A

group of 346 patients receiving NFV-based HAART were switched to ATV with d4T and 3TC in a study by Michelle Kiskorna and colleagues, Ingenix, Basking Ridge, New Jersey. At 12 weeks, significant reductions in total and LDL cholesterol and triglycerides and increases in HDL cholesterol were observed. The once-daily PI may be associated with decreased cardiovascular risk and provide a useful option for the simplification of combination antiretroviral therapy.

Extended-release d4T (d4T-XR) administered once daily is well tolerated and exhibits immunologic and virologic activity similar to that of twice-daily treatment with immediate-release stavudine (d4T-IR) when administered in combination with EFV and 3TC, reported Meredith Pugh of Medisolutions, New York. In a multinational, double-blind, placebo-controlled study, 797 treatment-naïve patients were randomized to d4T-XR or d4T-IR in combination with EFV and 3TC. The mean baseline HIV RNA and CD4 cell count was 4.8 log<sub>10</sub> copies/ml and 277 cells/mm<sup>3</sup>, respectively.

After 48 weeks, mean increases in CD4 counts were 187 and 181 cells/mm<sup>3</sup> in the d4T-XR and d4T-IR groups, respectively. Virologic responses were similar in both groups, and 4 percent of patients in each group discontinued treatment due to adverse effects. The rate of treatment-related peripheral neurologic symptoms was lower in the patients treated with d4T-XR than in those treated with d4T-IR.

Poly 1:poly C<sub>12</sub>U is a biological response modifier that has been shown to augment delayed-type hypersensitivity responses in HIV-infected patients. The mechanism of action of poly 1:poly C<sub>12</sub>U is activation of the intracellular antiviral mediators 2-5A synthetase/RNase L, and the compound is currently in phase II of clinical development. In a study reported by William Mitchell and colleagues, Hemispherx Biopharma in Philadelphia, eight treatment-naïve patients received poly 1:poly C<sub>12</sub>U (400 mg intravenous twice weekly) monotherapy and seven treatment-experienced patients received poly 1:poly C<sub>12</sub>U in combination with stable HAART. At study entry, HIV RNA and CD4 counts were greater than 4,000 copies/ml and 400 cells/mm<sup>3</sup>, respectively, in the treatment-naïve patients, and between 500 and 30,000 copies/ml and over 300 cells/mm<sup>3</sup>, respectively, in the treatment-experienced group.

After 24 weeks, patients receiving poly 1:poly C<sub>12</sub>U monotherapy experienced a 0.25 log<sub>10</sub> copies/ml decrease in HIV RNA ( $p = 0.04$ ). The treatment-experienced patients experienced a 0.50 log<sub>10</sub> copies/ml decrease in HIV RNA after a mean of 4.5 months. Adverse events in patients treated with poly 1:poly C<sub>12</sub>U were generally mild and self-limiting, and no adverse changes in blood lipid profiles or glucose metabolism were observed.

### Looking to 2004

As the XIV International AIDS Conference drew to a close, it became apparent that both the clinical and policy news that had generated so much excitement at previous conferences was missing in 2002. Excitement like that generated in 1996 at the XI International AIDS Conference in Vancouver, Canada, by reports of dramatic survival increases following the introduction of PI-based HAART was not to be found, nor was the mood precisely like that of the XIII International AIDS Conference two years ago in Durban, South Africa, during which conferees were presented with somber realities regarding access to care to both ponder and address in the new millennium. Perhaps what was missing was some evidence that the world, indeed, had learned sufficiently from the lessons of the past and was now adequately prepared to take appropriate action.

The global spread of HIV/AIDS is fueled by poverty, discrimination, and ignorance, but, sadly, even in the absence of major clinical findings that might warrant prioritization of the research agenda, it was unclear what the XIV International AIDS Conference achieved in harnessing greater global action to redress these ills. The foundation of a meaningful global response to the HIV/AIDS pandemic is a balanced approach to research, prevention, and care activities. Without the active involvement of governments and other organizations with the influence and resources to affect global change, what hope can be held for progress in slowing the spread of HIV/AIDS and providing adequate treatment to those already infected? The opportunity was missed in Barcelona, but perhaps the XV International AIDS Conference in Bangkok will be different. ■

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## One step ahead of us

*Carmen Retzlaff*

**D**ata presented at the XIV International AIDS Conference called to mind similarities between the disease's effect on the individual and the pandemic's effect on global society. African human rights activist Graça Machel pointed out this similarity in her plenary address to conference participants, assembled this year in Barcelona.

"HIV/AIDS has proven itself to be an incredibly aggressive and comprehensive virus," Machel said. "By undermining the immune system, the virus effectively attacks

the whole body. Then there is the social stigma attached to HIV/AIDS, the economic fallout from subsequent illness, and the lack of access to treatment and care that might minimize the effects of the virus. It attacks the human, the individual. And it attacks physically, emotionally, spiritually, in a very aggressive manner. And these individual effects and impacts are multiplied in our communities, our countries and our regions."

As many participants at Barcelona commented, it seems that both a medical solution to HIV disease and a coordinated public policy program that could stem the

global tide of infection and death are always just out of reach.

With respect to medical developments, researchers confirmed for conference-goers that an HIV vaccine and cure continue to remain elusive. Findings presented by Robert Siciliano (Johns Hopkins School of Medicine, Baltimore) suggest that current medications, while very effective at prolonging life, could never be developed into a cure. Siciliano noted, in this regard, that, "the latent reservoir for HIV in resting memory CD4 cells guarantees lifetime persistence of the virus and makes the disease intrinsically incurable with antiretroviral therapy alone."

Siciliano attempted to present a positive side to this grim news, however. "First, [this] fact is as powerful an argument for preventive efforts as we will ever find," he said. "And I believe that [highly active antiretroviral therapy (HAART)] can completely arrest virus evolution. In principle, this makes it possible to offer everyone with HIV infection the chance for a normal life."

Even the good news from medical researchers, however, turned bittersweet in light of information provided by epidemiologists on the spread of the disease and the very low numbers of HIV-infected people actually receiving the effective treatment antiretroviral drugs have made possible. First, the rate of infection exceeded predictions; more people than expected are infected in 2002. Second, in the developing world, where 95 percent of people living with HIV/AIDS live, fewer than 10 percent have access at all to antiretroviral drugs.

"It is now clear that the AIDS epidemic is still in its early stages," said Peter Piot, Executive Director of the Joint United Nations Programme on HIV/AIDS (UNAIDS), in the speech he made to open the conference. "And let's be equally clear: our fight back is at an even *earlier* stage." These were strong words and a challenge indeed to redouble our efforts.

But Piot lamented that no effort, even when largely successful, seemed to be quite enough. There are now many more mother-to-child transmission (MTCT) programs operating than there were two years ago, he reported. Nonetheless, the number of HIV-infected women who transmit the disease to their children remains quite high. "Why are three-quarters of a million babies born with HIV a year, when it is eminently preventable? Why have we failed to stop the dramatic expansion of HIV?"

### **HIV/AIDS linked to human rights and economic disparities**

The policy-related content at the Barcelona conference reiterated the fact that this disease is inextricably linked to economic disparity and human rights. HIV/AIDS disproportionately affects the poor and those who suffer discrimination on the basis of their race, sexuality, socioeconomic class, or other factors.

In fact, there is no global consensus that healthcare is a human right. Most of the featured speakers in this relatively liberal European setting, however, spoke as if

## **Spain as conference host encourages focus on Latin America and impact of injection drug use**

At the opening ceremony of the XIV International AIDS Conference in Barcelona, Conference Co-Chair Jordi Casabona gave a special welcome to participants from Latin America. Many times during the conference plenaries, Spanish hosts and dignitaries thanked attendees from the Spanish-speaking Americas for their participation. Casabona noted that the Barcelona conference was unique in its ability to welcome that delegation: "This is the first International AIDS Conference in a Spanish-speaking country."

Casabona also said in his opening remarks, "You will see that the city is full of other conference-related activities." A representative from RED 2002, a coalition of Spanish, community-based, non-governmental organizations, joined Casabona in the opening lineup, underscoring the participation of local AIDS organizations in the conference and related events. The mayor of Barcelona, Juan Klos, gave a trilingual welcome to participants (in Catalan, Spanish, and English), and boasted of Barcelona's longstanding commitment to public health and healthcare for the disadvantaged, and its interest in global activism on these issues and others, including equality for women. His speech was indicative of the influence of the host city on the conference: Barcelona is a liberal city with a strong socialist tradition, and it welcomed the conference and helped set the tone for open dialogue about the complex social issues surrounding HIV/AIDS.

The Spanish location also afforded an opportunity to highlight the impact of injection drug use on the epidemic. In the European setting, with a general level of primary healthcare available to the population, the continuing epidemic among injecting drug users (IDUs) exemplified how the disease continues to thrive among people who face societal discrimination, even in relatively affluent settings. A poster cited Spain as having the highest incidence of IDU-related HIV infection in Europe [WePeG6937]. The poster showcased the work of *Medicos del Mundo*, a harm reduction program in Madrid and six other Spanish communities. They described their population as 85 percent male, with a mean age of 31. Mean age of first injection was 20. Eighty percent had used heroin in the last month, with 59 percent injecting. Seventy-six percent had used cocaine in the last month, with 96 percent injecting. Poster authors stated that "the users of our services are more discriminated against now than 10 years ago."

At a press conference, one of the questions put to Richard Feachem, the newly-appointed Executive Director of the Global Fund to Fight AIDS, Tuberculosis, and Malaria, was whether the fund was going to consider funding needle exchange programs, and how it would interact with governments that did not want those programs. He said, "The Global Fund is already funding needle exchange programs. Yes, we're doing it, we will continue to do it." He went on to state that, beyond a system of country-specific planning processes and negotiations, the Global Fund is limited in that it can only make the funds available as a means of influencing sovereign states.

there were such a universal understanding (See "Spain as Host" sidebar). José María Mediluce, Chairman of the Green European Solidarity Foundation, stated in his opening ceremony speech that, "The fight against AIDS is a fight for human rights. And, among others, the rights to healthcare, sanitation, clean water, and generic medicines are basic to the rights of people affected by AIDS and all are part of the same reality."

Bill Clinton and Nelson Mandela, former presidents of the United States and the Republic of South Africa, respectively, each devoted considerable time in their addresses during the closing ceremonies of the conference to the issue of discrimination against people living with HIV/AIDS. "Many people who have AIDS are not killed by the disease itself. They are killed by the stigma suffered by everyone who has HIV/AIDS," said Mandela. He offered a moving story of his personal battle against the discrimination associated with HIV, describing how, while President, he traveled through the country inviting children with HIV/AIDS and physical disabilities to dine

with him. "The fact that the President of the country is sitting at the table with children with HIV/AIDS and those who are disabled, makes the parents less ashamed of their children," he said. He called on other world leaders to lead by such actions.

Clinton, in turn, cited a Human Rights Watch report that documented police brutality against AIDS activists in India, and said, "The government must stop this. And not just in India, but everywhere." He pointed to former US Senator Jesse Helms—who recently stated that instead of opposing AIDS funding during his tenure, he wished he had advocated for it—as a hopeful example that "anyone can have a change of heart."

### **Access to treatment the conference's focal issue**

Nowhere at the conference was the triangle linking discrimination, poverty, and HIV/AIDS more evident than in discussions around the most prominent, and contentious, policy issue discussed throughout: that of access to antiretroviral treatment.

Much of the contention surrounding patent rights for antiretroviral medications,

however, remained unvoiced at the conference. Many speakers made impassioned arguments for easing of patent restrictions, but those agreeing with the pharmaceutical industry and with concerns over inadequate infrastructure and risks of drug resistance, seemed more hesitant to make their opinions heard in conference plenaries or oral sessions, fearing the ire of activists and patient groups.

Among drug access advocates, many at the Barcelona conference held up Brazil and Thailand, with their local manufacturing programs for pharmaceuticals, as models of appropriate reform. Paolo Teixeira, Director of the Brazilian STD/AIDS Program, described his country's strategy of providing antiretroviral treatment in conjunction with a nationwide prevention program as more or less an obvious action. "There is no 'Brazilian Model,'" he told a plenary audience. "What we have been doing is to put into practice principles that have long been recognized by the international community. At their very core is the Universal Declaration of Human Rights, adopted more than 54 years ago." Brazil has documented significant reductions in HIV/AIDS incidence, including new cases, as well as a reduction in the number of deaths from AIDS.

"In Brazil," Teixeira added, "the average cost for patient per year in antiretroviral therapy decreased by half in the last years. This reduction occurred because of a combination of two concomitant factors. First, investments made by the Ministry of Health to set up domestic national laboratories. Currently, the Brazilian Ministry of Health distributes 15 antiretroviral drugs, of which eight are locally produced. Second: the effective negotiation, based on tiered or differentiated prices, with drug companies... National production under compulsory licensing has been a strong argument to push these companies to the negotiation table."

Teixeira concluded his remarks by reiterating Brazil's offer of technical assistance to other countries wishing to institute local production. However, he expressed Brazil's wish not to become an exporter of generic medications, saying that would "fundamentally alter the mission which the Brazilian public laboratories serve," namely, that of utilizing local manufacturing to regulate domestic prices.

At an oral session on strategies for lowering treatment prices, which drew an

attentive and vocal audience, K. Kraisintu presented the results of Thailand's manufacturing of generic medications. Thailand's Governmental Pharmaceutical Organization (GPO) produces more than 300 items, she said, including antiretroviral medications and drugs to treat opportunistic infections [MoOrG1038]. The Thai GPO introduced a lamivudine (3TC)/ nevirapine (NVP)/ stavudine (d4T) co-formulated drug in April 2002. "The reasons for doing this," she said, "are that we wanted to simplify treatment, we wanted to increase compliance, we wanted to reduce the resistance, and, most of all, we wanted to reduce the cost of treatment." Participant discussion included a comment that drugs are not the only patents driving treatment costs up. Kraisintu agreed that CD4 monitoring was a cost issue for her country, but that they planned to internally manufacture that technology as well: "Wait and see. I will make it lower!"

Presenters at the treatment pricing strategies session focused on local pharmaceutical production of essential anti-HIV medications in low-income countries, patent restrictions, and standardized price negotiations. AIDS drug activist Jamie Love advocated the creation of a "non-voluntary patent pool for interventions that address essential public health needs." Love would include on this list the most effective known antiretroviral treatments for HIV. During the same session, the issue of inflation of drug prices at the local retail level was raised by an audience member, who cited the doubling and tripling of prices at local pharmacies in southern Africa to demonstrate that prices charged by drug manufacturers were not the only factors driving up cost. Love agreed, saying that in Central America, as well, patents "are not really the issue," but that distribution systems increase drug costs in those countries.

At another session on the cost of drug access expansion, a South African study presented by Andrew Boule on cost-effectiveness of antiretroviral treatment [TuOrG1248] was greeted with praise from a large audience, primarily composed of activists and economists. Boule made two arguments to support his conclusion that the South African government could feasibly begin widespread provision of HAART in the near future. First, he noted that, in cost analyses, "HAART is often described as a uniform entity," and that the costs of different implementation

scenarios were not taken into account. His analysis included variables such as provision of only one drug regimen option versus making available a second more costly option if the first failed; different staffing options in service delivery (eg, employing allied health professionals for services that do not require a physician, such as counseling); and the use of generic medications.

Secondly, Boule argued that determining the feasibility of supplying HAART need not reflect provision of treatment to all infected persons in a given country. The study authors pointed out that the numbers treated would be limited by human resources and other factors, just as all healthcare provision in poor countries is limited. "In resource-poor settings, there is implicit rationing anyway," he said. Moreover, Boule suggested that if governments invest at least a portion of their HIV care expenditure in HAART, they will show commitment that might leverage resources from other players.

### **The complex capacity issue**

Though patent rights, generic manufacturing, and economic support by the richest countries were the hot button issues, all parties acknowledged that these were not the only barriers to HIV/AIDS treatment access in low-income settings. Lack of infrastructure and problems with distribution systems were also cited as important obstacles. While proponents of universal access to antiretroviral treatment warned donors and drug companies not to inflate these issues to deflect human rights discussions, all sides agreed on the need for constructive ideas and action to actually deliver care to those in need.

At a press conference in Barcelona, the International Association of Physicians in AIDS Care (IAPAC) announced two initiatives designed to address capacity issues in countries with limited resources. The Global AIDS Learning & Evaluation Network (GALEN), and the Joint HIV/AIDS Care Initiative (JHACI) will provide much needed medical education to HIV care providers and ensure the ability of clinicians in resource-limited countries to administer effective antiretroviral treatment as drugs are made available and scaled up. Both initiatives are driven by the very practical strategy to ensure that infrastructure concerns precede, or at least accompany, the introduction of antiretroviral drugs into settings that can ill-afford their mismanagement.

## IAPAC unveils new initiatives at Barcelona conference

IAPAC's new capacity-building initiative, the Global AIDS Learning & Evaluation Network (GALEN), will provide training and certification of "HIV Care Specialists" in low-income countries. "GALEN will ensure that HIV/AIDS-treating physicians will have the core clinical competencies to provide appropriate HIV patient care through its critical evaluation and certification components," said IAPAC President/CEO José M. Zuniga.

IAPAC members will work in partnership with the World Health Organization, Pan American Health Organization, and local partners to provide intensive face-to-face clinical education to physicians and allied healthcare providers, and evaluate their knowledge and progress through written and oral examinations and clinical observations leading to certification of HIV specialist practitioners. The curriculum design is intended to be adaptable to address specific regional needs. "We expect GALEN will evolve through contributions from the programs where it is implemented," said D. William Cameron (University of Ottawa, Canada), Co-Chair of the GALEN Curriculum Committee. He also commented, "I've been with IAPAC for many years, and I believe GALEN is one of [IAPAC's] most important undertakings, to say nothing of its being one of the more promising capacity-building interventions that I am aware of."

A second initiative is the Joint HIV/AIDS Care Initiative (JHACI). Five academic and research institutions will partner with IAPAC to provide operational expenses, medical education (through GALEN), medical exchange opportunities, and increased access to advanced HIV treatment to five rural HIV clinics in Brazil, Haiti, Jamaica, South Africa, and Thailand. "This approach will ensure that access to global funds and treatments are accompanied by access for healthcare providers and patients to appropriate medical education and knowledge, and that the potential clinical, ethical, and economic consequences of providing funds and drugs without equal attention to medical education and capacity building are prevented," said Zuniga.

Participating educational institutions are: University of Ottawa Medical School, Ottawa, Canada; Albert Einstein College of Medicine, New York; Makerere University School of Medicine, Kampala, Uganda; Thai Red Cross AIDS Research Centre, Bangkok, Thailand; the Royal Free Centre for HIV Medicine, London, UK; and the Federal University of Rio de Janeiro School of Medicine, Rio de Janeiro, Brazil. Mike Youle, Director of HIV Clinical Research at the Royal Free Centre for HIV Medicine pointed out, "This is a very practical initiative," acknowledging that the first step in the capacity-building process is implementing projects such as JHACI. "If we don't do anything, we won't get anywhere," he said. This logic, straight and to the point, is the driving force behind both initiatives; empowering physicians and allied health professionals to care for their patients from within locally and nationally sustained infrastructure.

In further support of this strategy, and opening an oral session dedicated to the issues of capacity and policy prerequisites for antiretroviral access, Joseph Saba of Ireland advocated encouraging resource-challenged countries to establish sound policies that would enable them to effectively administer antiretroviral distribution. He pointed out that increasing capacity to provide antiretroviral treatment increases the capacity of the entire HIV care system and, indeed, the country's whole healthcare system. He stated that he believed the lack of sound policies in many countries was a "lack of will" on the part of some governments, challenging them with the task at hand: "It is not very expensive to improve policy." He listed training guidelines, policies on pricing and procuring supply, and accounting mechanisms as examples of the types of measures he felt countries considering antiretroviral provision should prioritize.

Making specific country references were Kriengkrai Srithanaviboochai, who presented an example of capacity-building efforts being undertaken by the government of Thailand in preparation for implementation of HAART, at no out-of-pocket expense to the patient [TuOrG1246], and Paul Farmer, who presented a case study from Haiti. The process of integrating

HAART into the current healthcare system in Thailand, as Srithanaviboochai told the audience, included active participation by community advisory boards. The advisory boards developed selection criteria, to determine which patients would receive the medications, and guidelines for distribution, ensuring continuous adequate supply at each site. A "focus person" was assigned at each of 54 participating hospitals, and each focus person led a HAART team that included a minimum of five specially trained professionals: a physician, a nurse, a pharmacist, an HIV counselor, and a lab technician.

Paul Farmer of Harvard Medical School related experiences of a rural study in Haiti, intended to demonstrate the feasibility of antiretroviral treatment in even the poorest of settings. "No one seems to have actually done such projects in the world's poorest communities, although HIV is now the leading cause of young-adult death in almost all of them. There's thus a lack of know-how regarding who should receive HAART, what the enrollment criteria would be, how to manage the drug supply, and how best to monitor therapy in resource-poor settings. There is much speculation but little experience in linking prevention to care in the poorest communities." Farmer said that recruiting

major institutional donors for a treatment pilot project had been difficult.

This Haiti project, termed the "HIV Equity Initiative," complemented ongoing prevention efforts with "antiretroviral treatments for those patients in greatest need and who were soon to die, in our opinion, without these drugs," said Farmer. Ten to 12 percent of the over 2,000 HIV-infected patients examined in the clinic are now receiving antiretroviral treatment, and the project relies heavily on therapy methods borrowed from an earlier tuberculosis/HIV program, as well as on community health workers who deliver domiciliary care.

Farmer and colleagues concluded that antiretroviral treatment in rural Haiti was possible and effective, although Farmer stated that effectiveness was hard to measure using traditional evaluation criteria. "The gold standards for assessing efficacy of AIDS prevention and care are quite different, and both are largely beyond the reach of healthcare facilities in regions most affected by HIV. In Haiti or comparably poor countries in Africa, even university-affiliated projects would have as much or more difficulty measuring HIV incidence as they would measuring viral load." Farmer suggested biosocial measures of success, including patient outcomes (such as body weight) and chart review; reduced rates of hospitalization; and increased demand for voluntary counseling and testing.

In all, these various capacity-building initiatives were heralded as critical and irreplaceable elements in the strategy necessary to ensure that more positive news regarding treatment and survival rates would be possible two years from now at the XV International AIDS Conference in Bangkok.

### Donor contributions and the global fund

The Global Fund to Fight AIDS, Tuberculosis, and Malaria was established in June 2001 and awarded its first round of grants in April 2002. However, national donations to the Global Fund have not met the hopes of its creators and proponents. The June 2002 Global Update by the International Council of AIDS Services Organizations (ICASO) states that pledges as of May 2002 totaled US\$1.922 billion, far short of the US\$10 billion originally called for by the Global Fund's founders.

## Should the US response be an international model?

A forum on US domestic policy packed the hall one evening of the XIV International AIDS Conference, in Barcelona. The standing-room only event was convened by Washington, DC-based policy group AIDS Action.

A panel of representatives from large, long-running AIDS programs gave their perspectives on the history of the epidemic and community response in the United States. Their testimonies highlighted the role of discrimination and activism in that history.

Ana Alvera of the Gay Men's Health Crisis (GMHC) in New York, said, "From the very beginning, the gay community—and its allies—was way more diverse than we tend to give it credit for being. And also the clients—it was never all white men. I'm saying this because I think it is very important for us not to perpetrate the invisibility of women in the epidemic and people of color in the epidemic and poor people in the epidemic since the very beginning. We have many epidemics. We have an epidemic that has moved very fast into vulnerable communities. Does this mean the epidemic has left the gay community? It hasn't left the gay community. It has expanded to other communities...It is almost as if, when we say, 'gay community,' we mean 'gay white men.' And when we say 'communities of color,' we mean 'everyone's straight.'"

GMHC started with a hotline and buddy program in 1981, recounted Alvera, when a "gay disease" had been identified. Today GMHC provides three types of services: clinical, prevention, and public advocacy. The agency now serves a clientele that is 25 percent female. "These women are poor women of color, 60 percent black and 40 percent Latina, and are heads of households," said Alvera. "Women choose to come to GMHC because we offer a continuum of services from prevention to longer-term care in one place. Women also tell me, 'I go there and men don't bother me.' I think that is about the history of sexual violence that women living with HIV/AIDS carry with them. Also, we have a family program, and they can bring their children with them."

The San Francisco AIDS Foundation (SFAF) also has a history of providing both prevention and care services, as well as activism. "From the beginning," said SFAF's Fred Dillon, "our epidemic, comprised heavily of gay men and

drug users, was considered our problem by US policy makers." He gave credit to early activists. In San Francisco and the [rest of the] United States, he said, activists showed that "a relatively small group of committed and active citizens can make a difference and can make a government that doesn't want to, listen."

Craig Thompson of AIDS Project Los Angeles (APLA) has been living with HIV since 1984. "When I look at the AIDS epidemic and what we did right and what we did wrong and what we could learn from what we've done," he said, "it is hard to separate it from the personal experience." Thompson said that early activists, including himself, were not always motivated by purely altruistic feelings. "Many activists thought they'd get better information inside the movement," he said. "Also, there was a feeling of prestige working in AIDS. There is no prestige anymore."

Though APLA started with a slate of services similar to the other longstanding programs, Thompson said that he thought a strength of the early movement was the diversity of efforts. "From the beginning," he said, "we created strong, local, vibrant community responses." He noted that the commonly cited shift of the US epidemic to minority communities is not a recent phenomenon in Los Angeles. "Ten years ago, in 1992, the majority of APLA clients were poor people of color," he added.

"If there is one lesson it is important to remember today," concluded Thompson, "it is that we've got to continue to acknowledge the role that sex between men plays in this epidemic. And a lot of the work we still do is gay rights work. It is helping men acknowledge their behaviors. I honestly don't think we're going to be able to design good prevention efforts until we understand who is having sex with whom. And help them come to terms with that."

Cornelius Baker of the Whitman-Walker Clinic in Washington, DC, stated that, "We have the highest HIV rate per capita in the country. One in 20 of the population is infected. When you talk about sub-populations, like black men, you get one in 10."

"Whitman-Walker started in 1973 as a gay men's STD clinic," he said. "We knew immediately that black gay men would be infected." He continued, "If AIDS is really about racism, homophobia and poverty, then it's really important for us to lead this conversation about power. Without erecting a structure where people can access healthcare from birth,

people aren't going to be able to maintain good health."

Chris Bates, of the US Department of Health and Human Services, moderated a government panel, recalling his disappointment when it was discovered that the disease was not propagated by the use of "poppers," a drug commonly used by gay men at that time. "I was very sad to realize it wasn't that," he said, "that it was far more complicated... It is important to remember that this thing we now call HIV/AIDS came out of people trying to find love. Men who were trying to find intimacy in a world that didn't value them."

"There are still many people in the United States who don't have access to HIV care," commented Ron Valdeseri, of the US Centers for Disease Control and Prevention (CDC). "We estimate that as many as 224,000 Americans are diagnosed with HIV and don't have care." He presented statistics on the current face of the spread of HIV in the United States, giving a figure of approximately 40,000 new infections per year. Of those, Valdeseri said, 30 percent are women. Of that 30 percent, 75 percent are thought to be heterosexual transmissions, and 25 percent from injecting drug use. Of the 70 percent of annual US infections attributed to men, 60 percent are estimated to be in men who have sex with men, 25 percent injecting drug users, and 15 percent men who contracted the virus through heterosexual contact. "Thirty-two percent of African-American young men in one [CDC] study were infected with HIV. These are rates you hear people talk about when they talk about Botswana," he said.

Charles Henry of the Los Angeles County Health Department pointed out an immediate link to US HIV/AIDS policies and the worldwide response. "For those of us in large US cities," he said, "with business and personal travel of our citizens and immigration patterns, the international epidemic is also the local epidemic."

Should the US response to HIV/AIDS be a model for addressing the epidemic in other parts of the world? This discussion, held an ocean away from home, indicated that the US experience might serve as a reminder to other nations that a response to this disease is inseparable from a society's responsibility to its marginalized populations.

Many speakers at the Barcelona conference expressed frustration with wealthy countries that have not met their pledges. Graça Machel, advocate for children's rights, commended "the sterling efforts of Sweden, Norway, Denmark, and the Netherlands, the only countries to regularly meet the [promised] 0.7 percent mark," contrasting them to the United States and the rest of Western Europe, which linger far short of promised contribution levels. In recognition of this failure to pay promised dues, activist Terje Anderson of the United States said, "We have heard a lot about which countries are shouldering

their share of the burden for the response to this crisis, and which countries, like my own, are not." Brazil's Paolo Teixeira admonished wealthy countries in his plenary address: "We need the United States, along with Japan and Western Europe, to assume, at last, their responsibility in changing, or not, this dramatic situation."

On the same topic, Julio Frenk, Mexico's Minister of Health, said, "It is important that we make this fund truly global. Middle-income countries that can afford to contribute to the fund must make that contribution. My country, Mexico, will make a contribution." He

explained that even if the contribution is symbolic, it is important that the Global Fund not become another model of the richest helping the poorest. ICASO reports that of the 48 countries determined to have a high human development index, 28 have made no contribution to the Global Fund. Most agreed that this is unacceptable, given that the disease amounts to such a great collective burden. ■

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## A B S T R A C T S

### AIDS

#### In patients on prolonged HAART, a significant pool of HIV-infected CD4 T cells are HIV-specific

A Demoustier et al.

**Objective:** To examine the antigen specificities of HIV reservoir CD4 T cells in patients on prolonged and effective highly active antiretroviral therapy (HAART). **Design:** Five HIV-infected patients, who were highly adherent to antiretroviral treatment, were selected on the basis of long-term undetectable plasma viral RNA on unmodified HAART. To investigate the antigen specificities of infected memory CD4 T cells, we examined the capacity of recall antigens, including HIV antigens, to induce virus production by peripheral blood mononuclear cells (PBMC). **Methods:** To quantify CD4 T cells infected by replication-competent virus, and to determine their antigen specificities, we used a limited dilution-based culture assay. CD8 T cell-depleted PBMC at several cell densities were activated by using Tuberculin purified protein derivative, Cytomegalovirus, or HIV-1 p24 with and without HIV-1 Nef. **Results:** We found that the pool of infected CD4 T cells includes HIV-specific cells with apparent frequencies between 5- and 100-fold higher than those of the common specificities for Cytomegalovirus or Tuberculin. **Conclusion:** Our findings suggest that a significant proportion of replication-competent HIV-infected CD4 T cells in these patients are memory cells directed against HIV determinants. This may provide a rationale for the therapeutic use of recombinant HIV antigens to reduce the pool of HIV-reservoir cells.

AIDS 2002;16:1749-1754.

### Clinical Pharmacology & Therapeutics

#### Low-dose ritonavir moderately enhances nelfinavir exposure

M Kurowski et al.

**Background:** The protease inhibitor ritonavir is increasingly administered at subtherapeutic doses in highly active antiretroviral treatment, to utilize its potential for drug interactions and to enhance the plasma concentrations of other concomitantly prescribed protease inhibitors. The addition of low doses of ritonavir to nelfinavir was investigated to describe the extent of pharmacokinetic interaction. **Methods:** In this randomized, open-label, one-sequence crossover study, nelfinavir 1,250 mg twice a day was dosed for 17 days, followed by 14 days of nelfinavir 1,250 mg twice a day plus low doses of ritonavir of either 100 mg or 200 mg orally. Twenty-four healthy volunteers were evaluated for pharmacokinetics of nelfinavir, its metabolite M8, and ritonavir. Plasma concentrations were measured up to 12 hours after morning and evening dosing, respectively, on days 14 and 31. **Results:** Ritonavir increased the area under the plasma concentration-time curve (AUC) of nelfinavir by 20 percent ( $p=.024$ ) and 39 percent ( $p=.001$ ) after morning and evening

administration, respectively. The AUC of nelfinavir metabolite M8 was increased by 74 percent and 86 percent after morning and evening dosing ( $p<.001$  for both). **Conclusion:** During ritonavir combination therapy a clear although minor drug effect on nelfinavir pharmacokinetics was demonstrated but no dose effect was shown.

Clin Pharmacol Ther 2002 Aug;72:123-32.

### Chest

#### Clinical presentation of pulmonary mycetoma in HIV-infected patients

AK Greenberg et al.

**Study Objective:** Although pulmonary mycetoma has been well described in immunocompetent hosts, the only description in HIV-infected patients has been of 10 patients from our institution, from 1992 to 1995. To further investigate the impact of HIV status on the presentation and course of pulmonary mycetoma, we conducted a follow-up study. **Design:** Retrospective review of all cases of pulmonary mycetoma at Bellevue Hospital from 1992 to 1999. **Setting:** Patients were evaluated on the inpatient chest service and in the outpatient chest and HIV clinics of Bellevue Hospital in New York City. **Patients:** We identified 74 patients with pulmonary mycetoma; 20 of them were HIV-infected (27 percent). **Interventions:** The 20 HIV-infected patients were treated with antiretroviral and/or antifungal therapy. Measurements and results: Predisposing diseases were pulmonary tuberculosis (TB), *Pneumocystis carinii* pneumonia (PCP), or both TB and PCP. Seventeen patients had a CD4 cell count of  $<100$  cells/mL at presentation. Hemoptysis was present in 13 patients, but was massive in only one patient. Cough was common. Of the 18 patients for whom follow-up was available, 11 received antifungal treatment and seven were observed without therapy. Six patients received both antiretroviral and antifungal therapy. Disease progression occurred in 50 percent. Only five patients exhibited radiographic or clinical improvement. All five were treated with both antiretroviral and antifungal therapy. **Conclusions:** PCP is a risk factor for pulmonary mycetoma in the HIV-infected individual. HIV-infected patients with mycetomas have a significant rate of disease progression, although they rarely have life-threatening hemoptysis. A combination of antifungal and antiretroviral therapy may improve the clinical outcome in HIV-infected patients with pulmonary mycetoma.

Chest 2002;122(3):886-92.

### Medical Care

#### Improving informed consent: Insights from behavioral decision research

M Holmes-Rovner and CE Willis

**Background:** With publication of The Belmont Report concerning ethical principles, informed

consent gained explicit guidelines for the protection of human subjects of research. However, there is still little evidence about how well informed consent works to assist patients to reach informed decisions about research participation. **Objective:** To review behavioral decision theory and research to identify implications for informed consent. **Research Design:** Traditional literature review and hand search of literature were used. **Results:** Psychological research on biases and heuristics identifies cognitive biases in information processing (selection and interpretation of risks and benefits) that have implications for improving the informing process. A growing literature on patient decision aids provides evidence for the feasibility of more fully informing patients, and includes examples of "de-biasing" procedures (to improve information comprehension and consent). **Conclusions:** Informing and consenting involve conceptually different challenges concerning effectiveness versus values. De-biasing techniques need to be developed and empirically tested to determine their effectiveness in informing patients. Consenting involves both social and individual values. Appealing to altruism when summarizing the goals of research may increase research participation and does not necessarily violate voluntariness of informed consent.

Med Care 2002 Sep;40(9 Suppl):V-V308

### Journal of Pediatrics

#### Incidence of cardiac abnormalities in children with human immunodeficiency virus infection

TJ Starc et al.

**Objective:** To describe the five-year cumulative incidence of cardiac dysfunction in human immunodeficiency virus (HIV)-infected children. **Study design:** We used a prospective cohort design, enrolling children at 10 hospitals. Group I included 205 vertically HIV-infected children enrolled at a median age of 1.9 years. Group II consisted of 600 HIV-exposed children enrolled prenatally or as neonates, of whom 93 were ultimately HIV-infected. The main outcome measures were echocardiographic indexes of left ventricular dysfunction. **Results:** In Group I, the five-year cumulative incidence of left ventricular fractional shortening  $\leq 25$  percent was 28 percent. The five-year incidence of left ventricular end-diastolic dilatation was 21.7 percent, and heart failure and/or the use of cardiac medications 28.8 percent. The mortality rate one year after the diagnosis of heart failure was 52.5 percent [95 percent CI, 30.5-74.5]. Within Group II, the five-year cumulative incidence of decreased fractional shortening was 10.7 percent in the HIV-infected compared with 3.1 percent in the HIV-uninfected children ( $p=.01$ ). Left ventricular dilation, heart failure, and/or the use of cardiac medications were more common in infected compared with uninfected children. **Conclusions:** During five years of follow-up, cardiac dysfunction occurred in 18 percent to 39 percent of HIV-infected children and was associated with an increased risk of death.

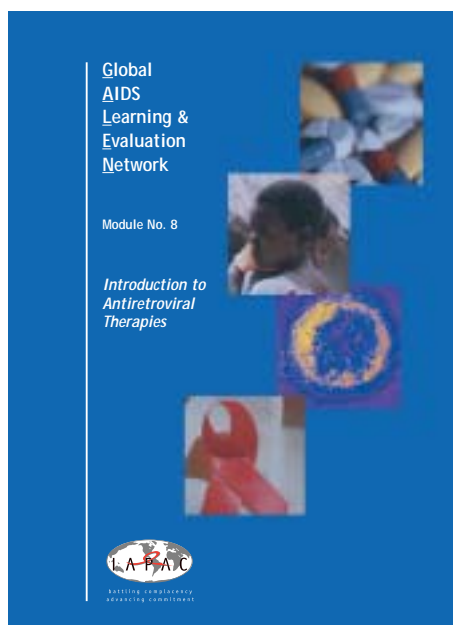
J Pediatr 2002 Sep;141(3):327-34

## GALEN in action

The International Association of Physicians in AIDS Care (IAPAC) has long argued that in order for antiretroviral therapies to be properly introduced and scaled up in resource-limited settings, increased attention must be paid to ensuring that physicians and allied health professionals are equipped with a core of knowledge and the minimum infrastructure required to effectively and ethically administer them. From IAPAC's perspective, this would include the guarantee of core clinical competencies via an explicit certification process to accompany HIV management training. Until very recently, this critical rationale—which lies at the core of IAPAC's Global AIDS Learning & Evaluation Network (GALEN)—had been most often neglected in global HIV care and drug access planning.

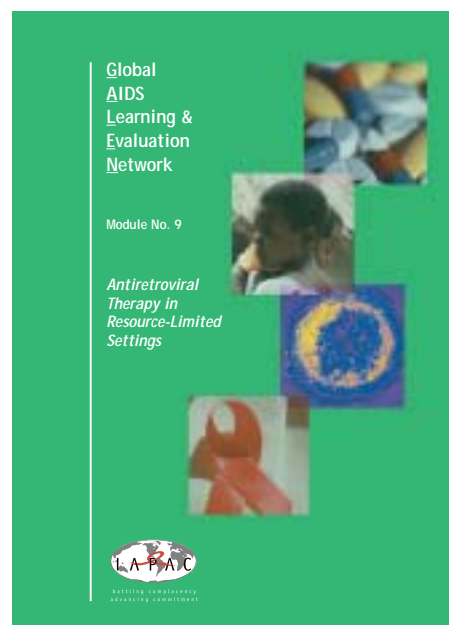
In October 2002, IAPAC made available to key international partners, including the World Health Organization (WHO), the Pan American Health Organization (PAHO), and other international HIV-focused organizations, the first two published modules from within the comprehensive, 15-module GALEN curriculum. In combination, these two modules provide an introduction to antiretroviral therapies, and guidelines and recommendations for their appropriate administration in resource-limited settings. They also provide a framework through which physicians may immediately enhance existing HIV clinical management knowledge.

IAPAC's Southern Africa Regional Office (IAPAC-SARO) this month began to field test the two modules throughout southern Africa, as an appendage to the association's ongoing training of healthcare professionals via the Diflucan Partnership Program. Further, the first two GALEN modules will be incorporated into a comprehensive training partnership program that in November 2002 will see Carol



Harris, Director of the Albert Einstein College of Medicine's Global Institute for HIV Medicine (New York, USA), provide two weeks of HIV management training to a select cohort of healthcare professionals in Addis Ababa and Gondar, Ethiopia, at the request and facilitation of the Ethiopian Ministry of Health. Through these various training sessions, IAPAC will be able to determine how best to roll out full-scale training and certification as the entire series of GALEN modules becomes available by year's end.

Of additional significance, IAPAC was recently able to gain important feedback and support from key clinical and policy peers during a WHO consultation convened October 1-2, 2002, in Geneva. The consultation, which explored international strategies and partnerships for scale-up of access to antiretroviral drugs for 3 million people by 2005, was an encouraging sign of positive things to come. As a result of both the serious interest expressed in the field test stage of GALEN and during the course of these and other WHO consultations,



IAPAC has reconfirmed commitment to implementing GALEN training and certification on a global scale as soon as remaining materials are finalized. The association continues to welcome and encourage the support and feedback of international partners allied in this struggle to ensure that the laudable goal of scale-up of antiretroviral therapy, as advocated by the WHO, will be achieved.

Development of GALEN materials continues at a quick pace, with additional modules to be made available incrementally over the next three months, following peer-review. Of note, translation of GALEN training modules into Spanish is already underway courtesy of PAHO. As the next few months unfold, IAPAC looks forward to further strengthening its alliances with committed national health authorities, training institutions, global partner organizations, funding agencies, and local care providers in order to quickly empower health professionals who continue to express their collective desire for expanded HIV medical education. ■



## I N T H E L I F E



### Rodica Matusa

*Vanity Fair* readers have every month since 1993 enjoyed *The Proust Questionnaire*, a series of questions posed to celebrities and other famous subjects. The *Vanity Fair* questionnaire—modeled after a questionnaire Marcel Proust was asked to fill out in the late 1800s—reveals much about the respondents' lives, thoughts, values, and experiences. In May 2002, *IAPAC Monthly* introduced "In the Life," through which IAPAC will feature members who have been asked to bare their souls through their answers to ten questions.

This month, *IAPAC Monthly* is proud to feature Rodica Matusa, who is Director of the Pediatric AIDS Ward at the Constanta Municipal Hospital in Romania.

**What proverb, colloquial expression, or quote best describes how you view the world and yourself in it?**

"For everyone there is a place in this world, and everyone has a destiny."

**What activities, avocations, or hobbies interest you?**

Travel.

**If you could live anywhere in the world, where would it be?**

I could not live in another place.

**Who are your mentors or real life heroes?**

My mother, whose goodness and wish for perfection characterized her.

**With what historical figure do you most identify?**

I do not identify with any historical figure.

**Who are your favorite authors, painters, and/or composers?**

Painter: Vincent Van Gogh; Composer: Beethoven

**If you could have chosen to live during any time period in human history, which would it be?**

The period between the two World Wars—1920-1940.

**If you did not have the option of becoming a physician, what would you have likely become given the opportunity?**

A diplomat.

**What is your prediction as to the future of our planet one full decade from present day?**

Within the next decade, I predict life will be approximately the same as today. After another decade, I predict an extra-planetary civilization. ■



## SAY ANYTHING

*e*  
**We are strictly adhering to patent law and will continue to do so in the future.**

*Qi Xiaoqiu, Director-General of the Chinese Ministry of Health's Department of Disease Control, quoted in a September 9, 2002, Associated Press report entitled, "China Denies Plans to Make AIDS Drugs." Qi denied news reports that he had suggested China violate patents if foreign companies did not offer discounted antiretroviral drugs. According to the Associated Press, China has begun treating patients with a domestically produced version of zidovudine (ZDV), for which patents recently expired. Qi said that 10 more Chinese firms have applied for permission to manufacture generic versions of AIDS drugs with expired patents, and might be producing them by year's end.*

*e*  
**We are tired of being thrown in the bush *re sena go jewa ke batho* [after sex]. Even the police rape us or threaten us with prison if we refuse sex. They do this knowing we have no place to run to.**

*An anonymous Botswanan commercial sex worker in a September 9, 2002, Inter Press Service article, "Reaching Young People to Beat AIDS." The article cited results from a survey of commercial sex workers in the Broadhurst, Bontleng, and Old Naledi townships of Gaborone, Botswana. On average, the women reported having three clients a night, and up to six around payday. The price they are paid for their services ranges from US\$8 to US\$33. Clients pay less for sex with a condom. Most prefer sex without a condom. Of the commercial sex workers interviewed, half were aged 15 to 24 and*

*a quarter were aged 12 to 14. Most were recruited into this work by friends or family, some as young as nine years old. Botswana, with a population of 1.5 million, has the world's highest rates of HIV infection, with 40 percent of adults infected. The United Nations Foundation (UNF) is sponsoring a US\$1.8 million, three-year AIDS awareness project targeting at-risk youth, including commercial sex workers, in poor Gaborone townships. The Urban Youth Project (UYP) is part of Telling the Story, a UNF-sponsored program to improve AIDS awareness among youth in seven Southern African countries.*

*e*  
**And thus it begins to develop according to the African scenario, where the majority of the HIV patients contracted it heterosexually... This will be very grave for the country's demographics, because 80 percent of the infected people are between 15 and 30. They will die, and they will not produce children.**

*Vadim Pokrovsky, Director of Russia's Federal AIDS Center, argued in a September 9, 2002, Los Angeles Times article that although the number of newly registered HIV cases has been dropping in the last year, the drop-off makes the situation no less alarming. Pokrovsky explained that the coming together of a poor economy, a burgeoning plague of intravenous drug use, and an overreaction to the country's new freedoms, has landed Russia on the cusp of an epidemic. At least 201,000 Russians are reportedly HIV-infected (although it is estimated the actual number is four to six times higher). According to UNAIDS, there are more than 1 million cases of HIV infection across the former Soviet Union. Pokrovsky worries that the number of new cases in*

*which HIV was transmitted heterosexually rose to 7 percent compared with 4.3 percent last year. Russia's leading AIDS official stated that if just half of the HIV-infected population transmits HIV to one sexual partner per year – which Pokrovsky considers conservative based on the African experience – Russia could have as many as 5 million HIV cases by 2010.*

*e*  
**With the advent of life-prolonging HIV treatment, and price barriers falling, access to treatment is now at the heart of realizing the human rights of people living with HIV/AIDS.**

*UNAIDS Executive Director Peter Piot in a September 10, 2002, statement regarding a joint announcement by UNAIDS and the Office of the High Commissioner for Human Rights that they have updated Guideline 6 of the International Guidelines on HIV/AIDS and Human Rights to highlight the need for better access to HIV/AIDS treatment. In Guideline 6, the UN agencies stress that people with HIV/AIDS must have access to medicine and other forms of treatment and call for international cooperation in providing access. According to the two agencies, the revised guideline breaks new ground by calling for specific actions on the part of governments, including the creation of national treatment plans, with specific resources committed and timetables established, leading to universal access; ensuring "vulnerable populations" have access; setting up mechanisms whereby people with HIV/AIDS can "challenge inequalities and discrimination" in treatment provision; ensuring quality control; and supporting the Global Fund to Fight AIDS, Tuberculosis, and Malaria.*