Treat, train, retain
May 2006

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Treat, train, retain
José M. Zuniga

A little more than a week before his untimely demise, World Health Organization Director-General Lee Jong-wook called upon the HIV/AIDS movement to confront one of the most pressing challenges to each and every public health initiative devised to prolong and enhance human life free from disease: to bolster a global health workforce that is being decimated in the developing world by myriad forces.
José M. Zuniga

As far as World Health Organization (WHO) consultations go, the “Consultation on AIDS and Human Resources for Health” I participated in May 11-12, 2006, on behalf of the International Association of Physicians in AIDS Care (IAPAC) was exceptional. Greeting us in the WHO’s Executive Board Room was the WHO’s Director-General, Lee Jong-wook, accompanied by Tim Evans and Anarfi Asamoah-Baah, his Associate Director-Generals for the Evidence and Information for Policy (EIP) and HIV, Tuberculosis, and Malaria (HTM) clusters, respectively. Their individual remarks and collective message were spare and to the point — “We face a crisis in human resources. The solution is not straightforward, and there is no consensus on how to proceed. We need your help.”

For veterans of such technical consultations that typically focus narrowly on a topic du jour, whether convened by the WHO or other equally bureaucratic institutions, such statements are de rigueur, and are often followed by the introduction of a consensus document written well in advance of the “consultation” and to which all parties convened to offer technical assistance are expected to sign on in a show of solidarity. This particular consultation, however, was different because it covered a broad spectrum of challenges confronting the health workforce in developed and developing countries alike, was low on rhetoric (especially from the WHO), and engaged almost every individual in attendance.

As fate would have it, this consultation would be the second to last public event over which the WHO’s Director-General presided. His hectic schedule required the 61-year-old tuberculosis specialist to wear multiple hats in the global battles against avian flu, HIV/AIDS, malaria, obesity, tobacco, and tuberculosis, to name just a half dozen of the health woes facing humankind. He died May 22, 2006, from a stroke following emergency surgery to remove a blood clot in his brain [Editor’s Note: See “In Memoriam,” page 163.]. His untimely passing — sad as it is for his family, his colleagues, and the global health community — would be devastating to the HIV/AIDS movement were it not for his clear and unwavering leadership around and commitment to ensuring that the benefit of antiretroviral therapy (ART) now taken for granted in the developed world reaches many more men, women, and children living with HIV/AIDS in the developing world.

A man of few words, Lee preferred action. Upon his election in 2003, colleagues at the WHO described him to me as the antithesis of contrived momentum. In his years heading the WHO’s “Stop TB” program, for example, he brought new direction and marshaled resources in response to a growing epidemic of multiple drug resistant-tuberculosis. Whichever side of the argument one takes with respect to that program’s successes or failures, there is much to be said about steadfast, results-oriented leadership.

It was thus no surprise to those who knew and respected him that upon his election Lee staked his political clout on an initiative meant to offer access to ART to 3 million people living with HIV/AIDS in the developing world by 2005. The challenges were immense, the conditions not perfect, the resources not quite enough, the political will not quite hardened, yet the world faced a public health crisis in HIV/AIDS that required a public health solution — even if it represented a time-delimited goal that might not be met. In promoting the “3 by 5” initiative, he seemed to challenge the world with a simple question: Is it better to do nothing in the face of a modern-day plague, or to aim high and possibly miss the target but still save and enhance the lives of more than the few who today (then 2003) are alive and living more productive lives as a result of ART?

Those who regularly read my Report from the President in the IAPAC Monthly know that IAPAC was supportive of the “3 by 5” initiative. Our support was steadfast throughout its two-year run because it was in line with the ethical framework under which the association labors, based largely on former UN Secretary-General Dag Hammarskjöld’s doctrine that “to let oneself be bound by a duty from the moment you first see it approaching is part of the integrity that alone justifies responsibility.” In line with the initiative’s objectives, IAPAC scaled up its educational offerings in African, Eastern European, and Latin American countries, as well as China, through our Global AIDS Learning & Evaluation Network (GALEN). We also produced and distributed sets of GRIP Guides that graphically illustrate first- and second-line...
antiretroviral regimens recommended in the WHO’s “Scaling Up Antiretroviral Therapy in Resource-Limited Settings: Guidelines for a Public Health Approach.”

We were also at times highly critical of the “3 by 5” initiative. Our criticism (sometimes pointed) was meant to influence course corrections around such critical issues as the value of fully engaging strategic partners in various aspects of the initiative’s work, the need to rapidly scale up capacity-building efforts advanced by multiple interested parties, and the imperative to begin to redress years of health workforce neglect that threatened the initiative’s progress. In retrospect, ours was the desire to influence the initiative’s execution, rather than quibbling with its objectives—a distinction sometimes lost in translation.

Midway through the initiative, and certainly by December 2005, it was clear that the “3 by 5” initiative would miss its target. In the end, and purely from an empirical perspective, the initiative succeeded in ensuring that 1.3 million people were on ART by December 2005 (or 20% of the 6.5 million deemed clinically eligible for ART)—a significant increase from the 400,000 (a level of ART coverage just over 6%) who benefited from treatment at the initiative’s launch (210,000 of whom lived in the Latin American region, most in Brazil). In two years, the number of HIV-positive patients on ART in low- and middle-income countries tripled, and access to ART in sub-Saharan Africa increased by more than 800% (Table 1). Still, to many critics and skeptics, the inability to reach the target of 3 million signaled failure—even if it represented a global, collective failing. To Lee and his WHO colleagues, in league with other United Nations agencies and likeminded allies, missing the target represented a further opportunity—one he and others seized upon to declare a global mission to achieve universal access to ART by 2010.

In his low-key but persuasive style, Lee and his colleagues reinvigorated the 100-plus individuals who participated in this month’s WHO consultation by calling upon us to confront one of the most pressing challenges to each and every public health initiative we might devise to prolong and enhance human life free from disease. The challenge is to bolster a global health workforce—an estimated 59.2 million dedicated men and women worldwide (including its invisible backbone, tens of thousands of health management and support workers)—who are mobilized to address specific health concerns, among them:

- The Millennium Development Goals (MDG) and their ambitious targets meant to alleviate the scourge of HIV disease, malaria, and tuberculosis;
- Chronic conditions such as cardiovascular disease, metabolic disorders, and cancers; and
- Health crises, whether posed by new epidemics (eg, avian flu), natural disasters (eg, tsunamis), or man-made conflicts (eg, Darfur).

Yet the very foundation of health systems globally has been undermined by draconian monetary policies and neglected by national governments spending less each year on health care would be necessary to alleviate the scourge of HIV disease, malaria, and tuberculosis; chronic conditions such as cardiovascular disease, metabolic disorders, and cancers; and health crises, whether posed by new epidemics (eg, avian flu), natural disasters (eg, tsunamis), or man-made conflicts (eg, Darfur).

If one looks at the issue of brain drain, while respecting the human right to migration, it would appear the primary culprits are developed world health systems dealing with their own health workforce shortages. Data compiled by affluent member-countries of the Organization for Economic Cooperation and Development

Table 1. Estimated ART coverage by geographical region (low- and middle-income countries)

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<tbody>
<tr>
<td>Sub-Saharan Africa</td>
<td>810,000</td>
<td>4,700,000</td>
<td>17%</td>
<td>100,000</td>
</tr>
<tr>
<td>Latin America and the Caribbean</td>
<td>315,000</td>
<td>465,000</td>
<td>68%</td>
<td>210,000</td>
</tr>
<tr>
<td>East, South, and SE Asia</td>
<td>180,000</td>
<td>1,100,000</td>
<td>16%</td>
<td>70,000</td>
</tr>
<tr>
<td>Europe and Central Asia</td>
<td>21,000</td>
<td>160,000</td>
<td>13%</td>
<td>15,000</td>
</tr>
<tr>
<td>North Africa and the Middle East</td>
<td>4,000</td>
<td>75,000</td>
<td>5%</td>
<td>1,000</td>
</tr>
<tr>
<td>TOTAL</td>
<td>1,330,000</td>
<td>6,500,000</td>
<td>20%</td>
<td>400,000</td>
</tr>
</tbody>
</table>


Table 2. Estimated shortages of physicians, nurses, and midwives

<table>
<thead>
<tr>
<th>Region</th>
<th>Countries with shortages</th>
<th>Estimated shortage</th>
<th>% increase needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>36</td>
<td>817,992</td>
<td>139%</td>
</tr>
<tr>
<td>Americas</td>
<td>5</td>
<td>37,886</td>
<td>40%</td>
</tr>
<tr>
<td>Southeast Asia</td>
<td>6</td>
<td>1,164,001</td>
<td>50%</td>
</tr>
<tr>
<td>Europe</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Eastern Mediterranean</td>
<td>7</td>
<td>306,031</td>
<td>98%</td>
</tr>
<tr>
<td>Western Pacific</td>
<td>3</td>
<td>32,560</td>
<td>119%</td>
</tr>
<tr>
<td>TOTAL</td>
<td>57</td>
<td>2,358,470</td>
<td>70%</td>
</tr>
</tbody>
</table>

(OECD) indicate that physicians and nurses trained abroad comprise a significant percentage of the total health workforce in most of them, but especially in English-speaking countries (e.g., 33% of physicians working in the United Kingdom were trained abroad). According to WHO estimates, physicians and nurses trained in sub-Saharan Africa and working in OECD member countries represent 23% and 5%, respectively, of the current physician and nurse workforce in those countries.

In geographical areas experiencing high HIV prevalence rates, attrition rates due to HIV-related morbidity and mortality have led to the alarming prediction that if HIV-positive health workers are left untreated, the proportion of those dying as a result of their HIV disease may reach 40% by 2010. Statistics compiled by its Ministry of Health reveal that in Zambia, AIDS-related deaths among female nurses in two public sector hospitals increased from two per 1,000 in 1980 to 26.7 per 1,000 in 2001. Another set of statistics demonstrates that Botswana lost 17% of its health workforce to AIDS between 1999 and 2005.

With respect to scaling up access to ART in developing countries, it was from within this long-neglected health workforce that the first pioneers started programs, which were initially small in scope and reach, but which offered access to ART to their HIV-positive patients, albeit mostly to society’s elite. Still neglected, the same health workforce rose to the challenge raised by the “3 by 5” initiative and can rightly claim credit for whatever success this initiative has achieved. Now that a global call for universal access to ART is on the lips of activists, donors, politicians, and patients, it is time to recognize that a health workforce decimated by years of neglect cannot fully rise to the challenge without a much-needed investment by all stakeholders responsible for promoting sound public health policy and strengthening health care delivery systems. Without such a recognition, and subsequent action, the imbalance between our expectations and the means that exist to realize them will grow—as will the historic and devastating deterioration of a health workforce we must all rely upon to meet our health needs and allow us to live healthy and productive lives.

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

Reference

The Open Society Institute (OSI) and the International Association of Physicians in AIDS Care (IAPAC) announced earlier this year that Bui Thi Bich Thuy, Chair of the Department of Infectious Disease at the Haiphong Medical School in Haiphong, Vietnam, has been awarded the inaugural “OSI-IAPAC International Fellowship in HIV/AIDS Palliative Care.” Her one-year fellowship will focus on pain management in intravenous drug-using HIV-positive patients in Vietnam. “Fifty to 70% of advanced HIV-positive patients suffer from moderate to severe pain which is often under-assessed and under-treated. Clinicians should not withhold treatment for pain because a patient has a history of substance use. Dr. Thuy’s fellowship will draw attention to the plight of this already stigmatized patient population, and demonstrate how effective pain management can be accomplished,” said Mary Callaway, Director of the OSI International Palliative Care Initiative.

“Dr. Thuy works in Vietnam’s third largest city and in the province with the second highest HIV prevalence in the country. Her dedication and commitment to the ever-increasing number of HIV-positive patients in Haiphong, most of whom are injection drug users, will greatly contribute to the success of the project she will advance through this one-year fellowship,” said IAPAC President/CEO, José M. Zuniga.
Workshop explores racial PK differences, TDF-PI interaction

Yasmin Halima

The 7th International Workshop on Clinical Pharmacology of HIV Therapy, held April 20-22, 2006, in Lisbon, once again reiterated the importance of taking into account and planning around pharmacological factors that could affect the therapeutic success or failure of antiretroviral therapy (ART). Among the many topics covered during this year’s workshop were the role that racial differences may play with respect to therapeutic response among African HIV-positive patients on ART, as well as new data on tenofovir (TDF)-related renal toxicities and interactions with protease inhibitors (PIs).

Racial differences in ART response
Racial differences in therapeutic responses have been reported previously in relation to efavirenz (EFV)-containing treatments in African-American patients correlated with polymorphic variants in CYP2B6. A collaborative study by Bichat-Claude Bernard Hospital in Paris, the Institut Pasteur, and Fann University Hospital in Dakar, Senegal, described the plasma concentrations of EFV in Senegalese patients. They observed plasma distribution and variability in 80 patients enrolled in two prospective pilot studies. The researchers administered 600 mg of EFV once a day (QD) plus two nucleoside reverse transcriptase inhibitors (NRTIs) comprising lamivudine (3TC), didanosine (ddI), or stavudine (d4T) to patients with CD4 cell counts of less than 350 cells/mm³ (baseline 143; range 93-213 cells/mm³) and viral load more than 30,000 copies/mL (5.6 log₁₀ copies/mL; range 5.2-5.8). Monitoring included monthly checks for clinical parameters, drug dispensing, and adherence and three-monthly checks for virological, biological, and immunological monitoring. Drug levels were observed at month one and again at month six using standard HPLC-UV techniques approximately 11.3 hours after the last drug intake.

At month six, CD4 cell count had increased by 113 (range 62-162) and viral load had dropped below 50 copies in 67% of patients. At month one and month six, EFV plasma concentrations were below 1,000 ng/mL (12% and 4%) and above 4,000 ng/mL (21% and 23%) respectively—the usual adequate therapeutic range is 1,000-4,000 ng/mL. Researchers reported consistent plasma levels between the first and sixth months on therapy, although a high degree of inter-individual variability was reported (107%). No significant differences were found between men and women in the studies but a number of discontinuations were reported, probably due to toxicities related to ddI and d4T. Reassuringly, these results confirm that around 70% of EFV plasma concentrations fall within the adequate range and demonstrate virological and immunological efficacy. Eighteen percent of patients, however, were found to be above the therapeutic plasma concentration range at both month one and month six. The researchers speculated whether the polymorphism previously described (CYP2B6) might explain the difference in over-exposure.

Following the presentation, Jonathan Schapiro (Stanford University) asked the critical question: “What are the appropriate drug levels for different population groups?” These levels have not yet been established. While 70% of the patients in this study achieved adequate plasma levels (and consequently, nearly a third did not reach adequate levels), the comparator reference continues to be therapeutic ranges determined in a very different population. To inform large-scale and long-term treatment programs, we need to define therapeutic drug levels that are better characterized in different population groups.

TDF and PIs
Interactions between TDF and PIs appear to be governed by a wider range of drug transporters than previously assumed, according to findings presented at the HIV Pharmacology Workshop in Lisbon, suggesting that drug interaction studies involving TDF will be essential in the development of all new PIs.

As the newest nucleotide reverse transcriptase inhibitor (NtRTI), there is still a need to better understand the pharmacokinetic profile of TDF, including intestinal absorption, potential for renal drug interactions, and impact on co-administered PIs. The prodrug form of tenofovir (tenofovir disoproxil fumarate [TDF]) is delivered through the gut wall. Tenofovir is cleared through the kidneys, but renal elimination of TDF has been shown to be affected by other drugs that are also renally excreted. The level of reduction in TDF clearance directly correlates with nephrotoxic effects.

Notably, coadministration of TDF with some PIs, such as atazanavir (ATV) and lopinavir (LPV), results in elevated TDF levels.

The interaction between PIs and TDF has been hypothesized to occur because some drug transporters mediated by PIs may affect TDF renal efflux, causing an
accumulation of TDF in proximal tubule cells, leading to nephrotoxic events.³

This means that some PIs are eliminated from the kidneys by the use of specific drug transporters such as P-glycoprotein (Pgp) or MRP2 or MRP4—the drug transporters most frequently associated with drug trafficking in and out of the kidney cells.

A study by scientists at Gilead Sciences demonstrated in vitro which drug transporters may be responsible for drug-drug interactions between TDF and ATV, LPV, and ritonavir (RTV).⁴ They found that Pgp and MRP2 are not substrates of TDF, but they did observe that TDF metabolites accumulated at five-fold lower levels in MRP4 over-expressing cells. The researchers did not correlate intracellular levels with cytotoxicity in MRP4 over-expressing cells.

These results confound other studies that link TDF with nephrotoxicity as a result of interaction between TDF and PIs in over-expressing MRP2 kidney cells. This is a surprising result, since according to Gilead scientists, MRP2 over-expressing cells should have a minimal impact on possible interactions between TDF and PIs, given that MRP4 has been identified as the primary transporter of TDF out of the kidneys.

One such study linking MRP2 to TDF was the brecanavir/RTV interaction study presented by GlaxoSmithKline (GSK).⁵ Brecanavir/RTV is the new GSK PI boosted with low-dose RTV for treatment in PI-experienced patients. Ritonavir co-administered with other PIs is known to increase plasma concentration of TDF, and RTV is responsible for the inhibition of the MRP2 transporter. In this healthy adult study, 15 individuals were randomized to an open-label cross-over study to receive TDF 300 mg QD for seven days followed by brecanavir/RTV 300/100 mg every 12 hours (BID) plus TDF QD for another 14 days, with no washout periods in between. Blood and urine sampling took place at both time points. Tenofovir excretion, and renal and creatinine clearance were monitored.

Results following brecanavir/RTV 300/100 mg BID combined with TDF 300 mg QD relative to TDF QD:

- AUC (area under the curve): 1.32
- Cmax: 1.24
- Renal clearance: 0.70
- TDF plasma concentrations increase: 32%
- TDF renal clearance decrease: 30%
- Creatinine clearance: 13% (15.4 mL/min: from 119 mL/min to 103 mL/min)

These results are similar to those reported with concomitant use of other PIs, including ATV (with or without RTV boosting) or LPV/r, where 30% increases in plasma exposure of TFV were reported.

Reference
This is more than a survey

Questions
As a professional medical association dedicated to implementing education and advocacy activities through which to improve the quality of care for people living with HIV/AIDS, the International Association of Physicians in AIDS Care (IAPAC) is committed to conducting relevant HIV/AIDS-related research. As a result of this commitment, IAPAC recently completed the “IAPAC State of HIV Treatment Surveys,” two of the most comprehensive surveys of both HIV-positive patients and HIV-treating physicians ever conducted.

The national surveys, which were conducted through funding provided by Bristol-Myers Squibb, were developed as a tool to gain insight into the mindsets of people living with HIV/AIDS and HIV/AIDS-treating physicians on a variety of topics related to treatment, including:

- Definitions of successful treatment
- Impact of treatment on quality of life
- Relationships and interactions between patients and physicians

The ultimate goal of the surveys was to identify gaps in perceptions of treatment-related issues between patients and physicians, and promote dialogue to ultimately lessen those gaps and ensure successful treatment for all people living with HIV/AIDS.

**SURVEY METHODS**

Physicians and patients were surveyed at random, and therefore the patients surveyed may or may not have been under the care of the physicians surveyed.

**Patient population**

Three hundred ninety-nine HIV-positive patients participated in the patient survey. Of the total, 206 survey participants were recruited via a national online provider panel, and the remaining 193 were recruited via 13 clinics and AIDS service organizations nationwide.

**Physician population**

One hundred fifty-two physicians completed the physician survey. Most physician participants were IAPAC members. All physician participants had been treating HIV-positive patients for at least two years at the time of the survey, with 16 years being the average length of time. All physicians reported seeing at least one HIV-positive patient per week, and 47% of all participants reported seeing more than 20 HIV-positive patients per week.

**FINDINGS**

The surveys revealed several insights into patient and physician perspectives about HIV treatment. According to survey results, physicians and patients are in agreement on many treatment-related issues, including:

- It is an insight into patient and physician perspectives about HIV treatment.
- It is a guide showing where patient and physician dialogues could be stronger.

**399 HIV-positive patients**

**152 physicians**
HIV suppression being a top priority when making treatment decisions
Avoiding treatment side effects
Definitions of adherence to treatment regimens
Physicians’ willingness and commitment to listen to patients’ concerns and opinions

However, the surveys also uncovered many gaps in opinions between physicians and patients, among them:

• Concerns about the type and incidence of treatment side effects and adverse events
• Patient reluctance to begin treatment
• Assessment of patient levels of understanding about HIV and treatment-related issues

Goals of treatment
Among multiple treatment goals, more than two thirds of physicians (69%) and patients (68%) rated HIV suppression as extremely important — more than any other goal. Other high priorities for both patients and physicians included keeping patients feeling healthy (55% of physicians and 69% of patients), avoiding resistance to HIV (51% of physicians and 65% of patients), and keeping CD4 counts high (49% of physicians and 66% of patients).

Patient and physician viewpoints diverged when it came to keeping patients looking healthy, with patients (60%) being far more likely to rate this goal as extremely important than physicians (14%).

Patients and physicians were also questioned about their views on suppressing HIV versus preserving quality of life (physicians were asked about their typical approach to HIV treatment, while patients were queried about their priority for HIV treatment). Forty-three percent of patients and 44% of physicians reported that HIV suppression and preserving quality of life were equal priorities.

Current state of HIV treatment
When it came to describing feelings about current treatment regimens, 79% of both patients and physicians said they were somewhat or very satisfied with available treatment regimens. Both patients and physicians also indicated satisfaction with current treatment regimens as they relate to many treatment goals, including keeping viral loads low (90% of physicians reported being “somewhat” or “very” satisfied, as did 84% of patients), keeping CD4 counts high (81% of physicians and 77% of patients), and keeping patients feeling healthy (71% of physicians and 73% of patients).

Both patients and physicians expressed less satisfaction with current treatment regimens as they relate to side effects. Forty-five percent of physicians said they were somewhat or very satisfied with current treatment regimens in terms of avoiding short-term side effects, and 22% of physicians were satisfied in terms of avoiding long-term side effects. Fifty-two percent of on-treatment patients reported being satisfied with their treatment regimen in terms of side effects.

Physicians also indicated less satisfaction with current antiretroviral regimens than patients in the areas of keeping patients looking healthy (40% of physicians “somewhat” or “very” satisfied versus 69% of patients “somewhat” or “very” satisfied), and avoiding resistance (31% of physicians versus 54% of on-treatment patients).

Despite physicians’ lack of satisfaction with current treatment side effects, most seemed to agree that the positives of efficacy outweighed the negatives of potential side effects. Seventy-six percent of physicians disagreed or disagreed strongly that the side effects of treatment were worse than the disease itself. Physicians also reported that they believe HIV is now a manageable disease (90% agree or agree strongly), and
that most patients can expect to live a normally long life as a result of currently available treatments (72% of physicians agreed or agreed strongly).

While patient attitudes mirrored the positive outlook of physicians, patients indicated less certainty, with 47% disagreeing or disagreeing strongly that the side effects of treatments were worse than the disease itself.

When asked about their biggest concerns with current antiretroviral regimens, side effects and the potential for developing resistance topped the list for both physicians and patients. Physicians, however, were more likely to be concerned about these issues than patients (side effects were the single biggest concern for 45% of physicians versus 17% of patients, followed by 28% of physicians citing resistance as their biggest concern, compared to 22% of patients). From the patient perspective, 51% of all patients expressed concern that taking medications is a daily reminder of having HIV.

When it comes to following US Department of Health and Human Services (DHHS) guidelines for the treatment of HIV, 45% of physicians indicated that they typically follow the guidelines “very closely” or “exactly.”

**Initiating, delaying and ending treatment**

When deciding when to begin patients on highly active antiretroviral therapy (HAART), physicians said they decide to delay treatment an average of 39% of the time. Similarly, 33% of patients who were currently on treatment at the time of the survey also said there was a period of time when they and/or their physician decided to delay treatment.

Most patients reported having discussed HIV treatment with their physicians, regardless of whether they were currently on a treatment regimen. In fact, 82% of treatment-naive patients said they have discussed taking HIV medication with their physician.

Sixty-six percent of patients currently on treatment, as well as 34% of treatment-naive patients, reported that it was solely their physician who initiated the conversation about beginning treatment.

Patients appeared to express more reluctance about beginning treatment than physicians reported: While 39% of patients currently on treatment said they were reluctant to begin treatment, physicians estimated 15% of their patients are reluctant to begin HAART.

In determining whether to delay treatment, 89% of physicians indicated a primary reason for doing so was that laboratory values did not mandate treatment. Physicians also cited patient desire to delay (85%) and lack of anticipated adherence (68%) as other predominant reasons for delaying treatment. The three reasons on-treatment patients most often cited for delaying treatment were to avoid side effects of treatment (44%), they were feeling healthy and experiencing no symptoms (38%), and their CD4 count and viral load did not mandate treatment (27%).

When it came to stopping treatment, 38% of off-treatment patients said they did not have a discussion with their physician before deciding to end treatment. Of off-treatment patients who did discuss stopping treatment with their physicians, 59% said they either initiated the conversation alone or equally with their physician. Of the same group of patients, 37% reported that they, their physicians, or both felt reluctant about ending treatment.

Consistent with physician results, off-treatment patients and treatment-naive patients focused on CD4 counts and viral loads as the primary reasons for delaying HAART (42% of off-treatment patients and 64% of treatment-naive patients).

**Side effects**

Side effects of treatment continued to be an issue for many HIV-positive patients and HIV-treating physicians. In a typical
week, physicians reported switching an average of 5% of their patients from one treatment regimen to another specifically because of side effects, and 68% of patients surveyed reported having switched treatment regimens due to side effects at least once. However, 82% of patients currently on treatment said their physician worked with them closely to help minimize treatment side effects.

The types and incidence of side effects varied between the patient and physician perspectives, with more patients reporting experiencing side effects than physicians reported. The gaps were largest when it came to reporting of sleep disturbances (73% of patients reported experiencing this side effect, but 20% of physicians reported their patients experienced the same side effect), fatigue (77% of patients versus 26% of physicians), and joint or muscle pain (63% of patients versus 11% of physicians).

There was also a gap between the side effects physicians were most concerned about and the side effects patients were most bothered by. Physicians noted patients’ lipid levels (76% of physicians were “very concerned” or “extremely concerned” versus 40% of patients who were bothered “very much” or “a great deal”), body shape changes (73% of physicians versus 53% of patients), and gastrointestinal problems (61% of physicians versus 54% of patients) as their top concerns. In comparison, on-treatment patients cited sleep disturbances (60% of on-treatment patients were bothered “very much” or “a great deal”), fatigue (59% of physicians versus 38% of patients), and depression/anxiety (56% of patients versus 32% of physicians) as the side effects they were most bothered by.

Twenty-one percent of physicians reported occasionally or very often helping their patients structure treatment interruptions due to side effects. Physicians also estimated about 16% of their patients are taking “drug holidays” due to treatment side effects. In comparison, 50% of all patients reported having stopped treatment because of side effects at least once.

**Adherence**

According to the surveys, 88% of physicians defined adherence as a patient taking his or her medication at least 90% of the time.

Eighty-four percent of patients currently on treatment indicated they considered themselves adherent to their treatment regimen; however, 76% of all on-treatment patients said they took their full dosage of medication in the seven days leading up to the survey. These results were consistent with physician estimates of their own patients’ levels of adherence—physicians reported that an average of 71% of their own patients were adherent.

These results are similar to findings from a separate medication adherence survey underwritten by Bristol-Myers Squibb, which found that 69% of patients reported themselves as being adherent to their treatment regimens. According to the DHHS, success with HAART can begin to diminish when patients are less than 95% compliant.

When assessing a patient’s potential
adherence, physicians indicated they focus primarily on recreational drug/alcohol use (80%) and a patient’s social support network (78%) as primary indicators of whether a person will adhere to his or her treatment regimen.

Patient quality of life
In order to better understand the various quality of life issues facing people living with HIV/AIDS, patient survey participants were asked to define how much having HIV affects their lives in a variety of areas. Patients indicated that having HIV most affects their financial security (69% of patients report their life being affected “somewhat” or “very much”), emotional well-being (69%), and their ability to work (57%).

Patient knowledge of treatment issues
Sixty-four percent of patients reported feeling very or extremely well-informed about HIV treatments, and 88% agreed or strongly agreed they took their medications because they understood the pros and cons of taking it or not taking it. However, 69% of patients also agreed or strongly agreed that they took their medications because they had been directed by their physician to do so, and 84% of patients agreed or strongly agreed that they took their medication because they were afraid of the consequences of not doing so.

Ninety-three percent of patients surveyed said they were familiar with their treatment regimens, and more than half (54%) knew the classes of drugs they were currently taking. Seventy-two percent of on-treatment patients who knew what classes of drugs they were taking reported taking a protease inhibitor (PI), while 56% reported taking a nucleoside reverse transcriptase inhibitor (NRTI), and 34% reported taking a non-nucleoside reverse transcriptase inhibitor (NNRTI). In comparison, 62% of physicians reported most often prescribing NRTI(s) plus an NNRTI for their patients, followed by NRTI(s) plus PI(s) (28%), PI(s) plus NNRTI(s) (8%), and triple NRTIs (2%).

In terms of specific treatment issues, physicians reported their patients were generally best informed about the importance of adherence (51% of physicians) and side effects (31% of physicians), while their patients were least informed about drug resistance issues (65% of physicians). Seventy-five percent of physicians said they believed “more than half” or “almost all” of their patients had unrealistic expectations about HIV treatments.

When it came to specific sources of information, 83% of patients reported that their physicians were a primary source of HIV treatment information, and 74% of all patients said they believed their physicians were doing very well or extremely well at keeping them informed of treatment-related issues. Other sources for patients to gain information about HIV included HIV-related magazines (41%), physicians’ support staff (36%), and HIV treatment Web sites (35%).

Physician-patient relationship
Views varied when it came to the level of equality within the physician-patient relationship, particularly as it related to the treatment decision-making process. While 65% of patients reported having (and 74% reported that they prefer) an equal partnership with their physician when making treatment decisions, 44% of physicians reported an equal partnership, and 47% said they most often make most of the treatment decisions on their own.

Eighty-seven percent of physicians reported having discussions with patients “very often” or “all the time” about treatment objectives and the trade-offs of each, compared to 50% of patients who said their physicians “very often” or “always” discussed these issues. However, both patients and physicians agreed that physicians listened to and took into consideration patients’ expressed objectives (71% of patients said their physician “very often” or “always” listened to their opinion, and 77% of physicians reported taking into account patients’ treatment objectives “a great deal”).

Beyond treatment options and side effects, surveyed physicians reported “very often” or “all the time” discussing issues such as diet and physical activities (78% of physicians), safer sex (73%), and overall quality of life issues (70%). But while fewer patients said their physicians very often discuss these topics with them (53% of patients reported “very often” or “all the time”) discussing issues about diet and physical activities, 40% safer sex and 46% how their everyday life is affected by HIV and HIV treatments, 41% of patients who do not always discuss these topics with their physicians reported they would prefer more conversations, and 44% reported they would not.

While 95% of physicians reported that half or fewer of their patients typically understand what is told to them, 66% of all patients said they almost always understand their conversations with their physicians. Similarly, physicians reported that an average of 49% of their patients were very well-informed about HIV treatment issues, while 64% of patients surveyed said they were very or extremely well-informed.

For more information
If you would like more information about these surveys, or to obtain copies of the survey results, please visit www.iapac.org.
A randomized trial of directly administered antiretroviral therapy and adherence case management intervention


BACKGROUND: A randomized, controlled trial was conducted to evaluate the impact of a directly administered antiretroviral therapy program (DAART) and intensive adherence case management (IACM) intervention on virologic and immunologic response to highly active antiretroviral therapy (HAART) among patients at three HIV clinics in Los Angeles County, California. METHODS: Participants included 250 treatment-naive and treatment-experienced persons for whom no more than one prior HAART regimen had failed. Five days per week for six months, a community worker delivered one HAART dose to DAART participants and observed the participant take it. Intensive adherence case management participants met weekly with a case manager to overcome barriers to HAART adherence. A control group (the standard of care [SOC] group) received the usual care. RESULTS: The majority of patients were Latino (64%) or African-American (24%); 57% were monolingual Spanish speakers. Seventy-five percent of the patients were male, and 64% reported an annual income of under US$10,000. In an intent-to-treat analysis, no statistical differences were observed in the percentage of patients with an undetectable viral load (ie, under 400 copies/mL) at six months between the DAART group (54%), IACM group (60%), and SOC group (54%; P > 0.05). An on-treatment analysis determined that there were no statistical differences in the percentage of patients with an undetectable viral load at six months between the DAART group (71%), IACM group (80%), and SOC group (74%; P > 0.05). Additionally, there were no statistical differences in six-month changes in the CD4 count or in self-reported adherence to therapy. CONCLUSIONS: Among patients with limited prior HAART experience and adherence barriers that had not been assessed before randomization, no differences were found in virologic or immunologic response for DAART or IACM, compared with SOC, at six months. Directly administered antiretroviral therapy and IACM did not improve short-term outcomes when SOC included other means of adherence support that were not controlled for by the study design.
HIV/HCV coinfection and ART

Michael Carter

HIV-positive individuals who are coinfected with hepatitis C virus (HCV) have poorer outcomes after starting antiretroviral therapy (ART) than patients who are only infected with HIV, according to a nationwide Danish study published in the May 15, 2006, edition of Clinical Infectious Diseases. The investigators established that HIV/HCV-coinfected individuals had a higher risk of dying than HIV-monoinfected patients, and less pronounced increases in their CD4 counts.

Studies looking at the influence of HCV coinfection on responses to ART have produced conflicting results, and have often been limited by the size of their sample or a short period of follow-up. Accordingly, Danish investigators conducted a prospective cohort study involving 2,734 HIV-positive patients who started ART between 1995 and early 2004 at Denmark’s 12 HIV treatment centers to establish whether HIV/HCV-coinfected patients had a poorer outcome after starting ART than individuals who had only HIV.

Outcomes assessed were the proportion of patients with a viral load below 500 copies/mL and changes in absolute CD4 count. Data were also gathered on death and causes of death. Of the 2,734 individuals included in the investigators’ analysis, 443 (16%) were HIV/HCV-coinfected. A total of 12,356 person-years of follow-up were available for analysis, with the median duration of follow-up being 4.7 years.

Individuals who were coinfected with HCV started ART at a median CD4 count similar to patients who only had HIV. Median viral load at this point was also comparable, as was prior experience of ART and the proportion of patients who had been previously diagnosed with AIDS.

However, the investigators noted that coinfected patients were 34% less likely to start taking ART than patients who only had HIV. They also noticed that once ART was started, patients who were HCV-coinfected were significantly more likely to interrupt treatment for 90 days or longer (30% of coinfected patients versus 14% of patients with HIV only). In addition, patients with HCV were three times more likely to interrupt treatment for three months or more because of gastrointestinal problems, including liver-related toxicities, than patients who only had HIV (4.5% versus 1.5%).

At all time points after the commencement of ART, fewer HCV-positive patients achieved an HIV viral load below 500 copies/mL than did HCV-negative patients. However, when the investigators excluded injecting drug users from their analysis, they observed that the odds of an HCV-infected patient achieving a viral load below 500 copies/mL ceased to be worse than those of an HCV-negative patient at weeks 144 and 288. In addition, the investigators noted that the increased prevalence of lengthy treatment interruptions among the coinfected patients appeared to be driving the poorer virological response to ART seen among this group of patients.

Attention was then turned to changes in CD4 count after the commencement of ART. Once again, at all time points coinfected patients had a poorer response to treatment than patients who only had HIV. By week 300, the median CD4 count in coinfected patients was approximately 350 cells/mm³ but was over 450 cells/mm³ among HCV-negative individuals.

A total of 370 deaths occurred, the mortality rate being 63 deaths per 1,000 patient-years among coinfected patients and 28 deaths per 1,000 patient-years among individuals who had only HIV. The investigators calculated that the overall risk of death was 140% higher among coinfected patients.

The investigators next looked at causes of death. Liver-related deaths were much more common among HCV-infected patients than HCV-negative individuals (14 per 1,000 patient-years versus 1 per 1,000 patient-years). AIDS-related mortality was higher among HIV/HCV-coinfected patients than among patients who had HIV only (17 per 1,000 patient-years versus 11 per 1,000 patient-years), and coinfected patients were also more likely to die with a CD4 count above 100 cells/mm³ (33 deaths per 1,000 patient-years versus 13 per 1,000 patient-years).

“We found that [HCV]/HIV-coinfected patients had a weaker response to [ART] in terms of viral load suppression and improvement of CD4 counts, compared to patients who only had HIV,” comment the investigators, adding that, “the viral load findings are explained by differences in covariates, mainly injection drug use and compliance with therapy.”

Reference

On the decade anniversary of HAART, the International Association of Physicians in AIDS Care (IAPAC) is convening an historic meeting to review our collective progress, discuss obstacles faced and overcome, lessons learned, and challenges that lie ahead. Registration is limited. Visit www.iapac.org to view the meeting program and to register online!
### Co-Chairs

| John G. Bartlett | Joep MA Lange |

### Featured Speakers*

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*Visit www.iapac.org to view the complete faculty roster.*

This activity is jointly sponsored by the University of Medicine & Dentistry of New Jersey (UMDNJ) and International Association of Physicians in AIDS Care (IAPAC), and has been approved for 18.0 AMA PRA Category 1 Credits™.
What proverb, colloquial expression, or quote best describes how you view the world and yourself in it?
The world is a global thing; I am inside it, interacting with its components.

What activities, avocations, or hobbies interest you? Do you have a hidden talent?
My activities and hobbies are research and football.

If you could live anywhere in the world, where would it be?
I would live in South Africa.

Who are your mentors or real life heroes?
Nelson Mandela.

With what historical figure do you most identify?
I identify with Nelson Mandela, who went from prison to president through the strength of his determination.

Who are your favorite authors, painters, and/or composers?
My favorite actress is Genevieve Nnaji.

If you could have chosen to live during any time period in human history, which would it be?
I would choose to live in the primitive era.

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

In your opinion, what are the greatest achievements and failures of humanity?
Greatest failure: Humankind’s insatiability for wealth.

What is your prediction as to the future of our planet one full decade from present day?
Every country in the planet will be united.
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Journal of the International Association of Physicians in AIDS Care (JIAPAC) a quarterly, peer-reviewed journal, presents original research, research reviews, case studies, and clinical perspectives on the treatment of AIDS around the globe. A primary information resource for both developed and developing regions, JIAPAC explores the following topics and more in a variety of care settings: pathology, co-infections, clinical pharmacotherapeutics, diagnostic testing, epidemiology, health services, and cultural and behavioral influences on AIDS and its treatment.

The journal publishes original research and research reviews and includes the following regular sections:

- **Pharma Reviews**: Descriptions of specific drug actions, indications, contraindications, and so forth
- **Diagnostic Test Reviews**: Descriptions of new testing procedures for identifying HIV/AIDS
- **Country Profiles**: Overviews of how individual nations and their governments are addressing the AIDS epidemic
- **Program Reviews and Evaluations**: Review and analysis of a specific program (at any level) for AIDS health prevention, education, or treatment
Soon, the Vatican will issue a document about the use of condoms by persons who have grave diseases, starting with AIDS.
Cardinal Javier Lozano Barragán, President of the Pontifical Council for Pastoral Assistance to Health Care Workers, in an April 24, 2006, article in The Guardian discussing a directive Pope Benedict XVI issued to senior theologians and scientists to examine the use of condoms to prevent the transmission of HIV. Though the Roman Catholic Church currently opposes condom use in any situation, the issue of condom use in the specific context of HIV transmission in the developing world has divided church officials. The directive came only days after a contender in last year’s papal elections—Carlo Maria Martini—challenged the church’s official position on condoms, suggesting that condom use was the “lesser evil” in combating AIDS.

We have now agreed that we are going to have universal access. Universal access is not talking of 80%, not even 90%. It’s 100% access to preventive and treatment services.
Nigerian President Olusengun Obasanjo in a May 5, 2006, Agence France Presse report regarding the conclusion of a summit in Abuja, Nigeria, during which African leaders reaffirmed their commitment to providing their citizens universal access to drugs for HIV disease, malaria, and tuberculosis. The leaders also vowed to marshal local resources, negotiate for debt cancellation, and seek grants targeting the three diseases of poverty. In addition, the summit agreed on a common African position for next month’s United Nations General Assembly Special Session on AIDS (UNGASS), and on coordinating members’ approaches to the rights of HIV-positive Africans.

There was a strong agreement that given the commitments made to reach global health targets, and given the urgent needs out there, it would be ethically impossible to not launch Round 6.
Jon Liden, spokesperson for the Global Fund to Fight AIDS, TB and Malaria (Global Fund), in an April 28, 2006, Reuters report about the decision to launch a new round of grants though the Global Fund has not received sufficient pledges from donors to cover the grants. The new round of grants will cost up to US$1 billion, though the final amount will not be determined until the November 2006 meeting of the Global Fund’s Board of Directors, at which time proposals for specific projects will be approved. Carol Jacobs, the Board of Director’s Chair, stated, “We know that countries and vulnerable populations are depending on it and we must not fail them.”

When I reviewed testing records earlier this year I was shocked to see a substantial proportion of people were not testing for bureaucratic reasons.
Jeffrey Klausner, Director of San Francisco’s STD Prevention and Control Department in a May 18, 2006, San Francisco Chronicle article about a new policy through which that city’s public clinics and hospitals will streamline HIV testing procedures to remove “[t]he several layers of paperwork” that Klausner believes are a barrier to screening. In March 2006, the US Centers for Disease Control and Prevention (CDC) proposed a similar approach to testing as a means of reaching the more than 20% of HIV-infected people in the United States who do not know their serostatus and thus may transmit the virus.

Women beaten upon disclosure are most likely to be in an existing violent relationship.
Lori Heise, Director of the Global Campaign for Microbicides, in an April 25, 2006, article in The Herald describing a study which concluded that women who disclose their HIV status to a partner are not more likely to be beaten than if they do not disclose their status. Nevertheless, women still believe that disclosure will lead to violence. In developing countries, only 52% of women would tell their partner if they tested HIV-positive, as compared to 71% in developed countries. The study also found that “men who are violent are also more likely to have outside partners,” linking the risk of HIV acquisition to a violent partner.

The new data build on those reported previously to paint a vivid portrait of hepatitis C in the [United States]. A self-limited epidemic of injection drug use over several decades amplified the transmission of HCV, and we are now seeing the delayed, bitter harvest of chronic liver disease.
Excerpt from an editorial by Jules L. Dienstag of the Harvard Medical School which accompanied a May 2006 report in the Annals of Internal Medicine indicating that, based on a nationwide survey, 4.1 million Americans are infected with hepatitis C (HCV), and many of these patients have chronic infection, the leading reason for liver transplantation. About 5% of people with chronic HCV will die. The survey results were derived from analyzed data for 15,079 participants in the National Health and Nutrition Examination Survey (NHANES) from 1999 to 2002. Injection drug use was the biggest risk factor for HCV infection, with almost half of infected participants reporting having injected drugs. Other significant risk factors included blood transfusion before 1992, and having 20 or more lifetime sexual partners.
Lee Jong-wook, Director-General of the World Health Organization (WHO), whose gamble to greatly expand AIDS treatment to the poor around the world helped give new life to hundreds of thousands of people, died suddenly May 22, 2006, two days after emergency surgery to remove a blood clot in his brain. He was 61. Lee served less than three years of a five-year term as the WHO’s Director-General, where he faced challenges including SARS, avian influenza, preparation for a possible human influenza pandemic, tobacco control, and childhood immunization. But his decision after taking office in 2003 to set a goal of providing antiretroviral therapy to 3 million people in the developing world by December 2005 will be his greatest legacy. While the WHO fell short of the target—roughly 1.3 million people in developing countries were receiving antiretroviral therapy by the end of 2005, an increase of 1 million people in two years—the bold announcement created an environment of urgency, helping to accelerate the scale-up of access to antiretroviral therapy. Africa, the epicenter of the AIDS pandemic, increased treatment numbers eight-fold from 2003 to 2005.
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