Nevirapine misinformation:

Will it kill?
Nevirapine misinformation: Will it kill?

John S. James

Three Associated Press (AP) reports in mid-December 2004 created widespread doubts about nevirapine (NVP), the critically important drug that can prevent HIV in many of the 1,800 babies infected every day by their mothers in childbirth. Could these reports—and the emotions they stirred—result in many HIV-positive mothers receiving no treatment and unnecessarily infecting their children with HIV?
José M. Zuniga

As I write this Report from the President, I am visiting our association’s African Regional Office in Johannesburg. While here I have worked to re-tool the office in support of antiretroviral therapy scale-up efforts in the region, as well as visited regional stakeholders, including members of the International Association of Physicians in AIDS Care (IAPAC), allies, government officials, and donors. I have also, regrettably, witnessed an ongoing feud—unfolding on the front pages of major dailies—between South Africa’s government and the activist community.

Under sensationalist banner headlines such as, “AIDS activists threaten to sue ANC,” the South African Department of Health and Treatment Action Campaign (TAC) have engaged in a tit-for-tat around matters related more to institutional ego than the very real issues around addressing one of Africa’s most worrying AIDS epidemics; one in which an estimated 21.5 percent of adults are HIV-infected. Indeed, as of December 2004, an estimated 5.3 million South Africans are living with HIV/AIDS.

The relationship between the activist community—particularly TAC—and the Department of Health has gone as far as accusing TAC of serving as a mouthpiece for the brand-name pharmaceutical industry. And, TAC has long maintained the Department of Health’s complicity in the death of tens of thousands of South Africans lacking access to antiretroviral therapy. But no one can rightly believe that TAC is serving a marketing role promoting the use of brand-name antiretroviral drugs in South Africa. Similarly, it is unreasonable to suggest that the South African government wishes to witness scores of its citizens decimated by HIV/AIDS—even if its baby steps toward the expansion of access to antiretroviral therapy infuriate many within the activist community.

Perhaps even more disturbing than the ongoing feud between South Africa’s Department of Health and TAC was a controversy stirred by multiple Associated Press reports this month raising safety concerns about the use of nevirapine (NVP) for the prevention of mother-to-child transmission (PMTCT) of HIV—largely revolving around the conduct of the HIVNET 012 study in Uganda. Researchers and activists in the United States and elsewhere were quick to refute claims made by the Associated Press. But here, too, the media became complicit with governments of various countries, including South Africa, in fanning the fire around sensationalistic assertions about the use of NVP for PMTCT—so much so that experts worry that when the smoke clears NVP may be relegated to collecting dust in national medical store warehouses rather than serve its purpose of saving countless infants from HIV infection.

While we are publishing John S. James’s comprehensive report on the matter—“Nevirapine misinformation: Will it kill?”—in this issue of the IAPAC Monthly, I thought it wise to encapsulate in my Report from the President the thinking of a preeminent figure in the field of PMTCT. In a recent e-published editorial entitled, “Comments regarding recent media attention to the HIVNET 012 Uganda study” (excerpts from which are bulleted here), Art Amman, President of Global Strategies for HIV Prevention, lays out some basic facts about NVP’s history and the conduct of HIVNET 012, as well as refutes concerns about NVP-related resistance.

Out of the headlines

Just the facts

“In the context of these reports, it is important to recognize that recommendations for treatment with NVP for [PMTCT] remain valid. The reasons for this are discussed below.

• Questions regarding the conduct of HIVNET 012 are not new, and have been extensively addressed in the past. The initial intent of the study was not to obtain formal [US Food and Drug Administration (FDA)] approval for the use of NVP for PMTCT. (Nevirapine had already received approval for treatment of HIV infection in adults). Such a study would have required a greater stringency in quality control, monitoring, and data collection. Nevertheless, the result of the study, a 50 percent reduction in HIV transmission to infants, was considered by the scientific community to be of such great significance that recommendations could be made for the use of NVP for PMTCT while additional studies were being pursued to meet the formal requirements of FDA approval. Historically, this was in keeping with making life-saving drugs available while still under evaluation—a major objective of AIDS advocates and activists since the 1980s. Basically, it would have been unethical to withhold a treatment when the drug cost was less than US$1 and where effectiveness (infants would be spared a fatal HIV infection) outweighed any rare short-term risk that the study might have failed to identify.

• Current recommendations for the use of NVP for PMTCT are not based on the HIVNET 012 study alone. In fact, there are now 17 clinical trials throughout the world, conducted by multiple investigators, from many different countries, using...
T he 44th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), held October 30-November 1, 2004, in Washington, DC, offered unique perspectives on antiretroviral (ARV) drug resistance, as well as late-breaking news about Gilead’s newly approved fixed-dose combination, Truvada.

Detectable HIV and resistance


A retrospective study analyzed data from 79 patients who had two or more genotype assays while they had detectable HIV RNA and continued their antiretroviral therapy (ART). New, discrete mutations in the reverse transcriptase (RT) and protease (PRO) segments of the HIV genome were identified and resistance mutations were defined by the “Antiretroviral Drug Resistance in Adults with Human Immunodeficiency Virus Type 1: 2003 Recommendations of an International Panel.”

In the enrolled patients the baseline (BL) mean CD4 count was 337 cells/mm³ and median HIV RNA level was 10,600 copies/mL. All had received at least one nucleoside reverse transcriptase inhibitor (NRTI) with 12 on NRTIs only, 13 on NRTIs and nonnucleoside reverse transcriptase inhibitors (NNRTIs), 47 on NRTIs and protease inhibitors (PIs), and 12 on NRTIs, NNRTIs, and PIs. Mean time between genotypes was 314 days.

Eighty-seven new discrete mutations appeared in the RT (zero to 11 per patient) and 53 in PRO (zero to five). In univariate analyses the rate of accumulation of new mutations was higher in patients with BL viral load ≥10,000 copies/ml compared with those with lower viral loads (rate ratio 1.74 per 100 person-days, 95 percent CI 1.02, 2.96); in those with BL CD4 count ≤200 cells/mm³ compared to those with >200 cells/mm³ (1.89, 95 percent CI 1.01, 3.55); and in men compared to women (1.59, 95 percent CI 0.89, 2.84).

The authors conclude, “HIV-1 in patients who remain on stable ART in the face of viral replication evolve resistance-associated mutations over time. Rate of evolution appears to be influenced by HIV RNA level and CD4 cell count. Multivariate analyses including the effects of different drug classes on the mutation rate are ongoing.”

Race, HIV risk factor, and resistance


To explore resistance patterns among ART-naive patients, HIV genotypic resistance-associated mutations (gMut) and phenotypic drug susceptibility (PS) were obtained from plasma of 317 HIV-infected, ART-naive subjects from 54 sites in 44 US cities.

Of the 317 patients, 73 (23 percent) had decreased PS to ≥ one drug, and 73 (23 percent) had an NRTI, NNRTI, or primary PI gMut. Further, 48 (15 percent) had NRTI gMut, 19 (6 percent) had NNRTI gMut, and 12 (4 percent) had primary PI gMut.

Decreased NRTI PS occurred in three (1 percent), with 58 (18 percent) for NNRTIs and 16 (6 percent) for PIs. By race, 27 percent of whites, 23 percent of blacks, and 6 percent of Hispanics had decreased PS to ≥ one drug (p = 0.022); however, GMut failed to show a significant difference. By sexual contact, 24 percent of homosexuals and 19 percent of heterosexuals had decreased PS to ≥ one drug (p = 0.354); however, homosexuals were less likely than heterosexuals to have a GMut.

The authors conclude, “In a large US cohort of ART-naive subjects, a prevalence rate of 23 percent for phenotypic resistance to ≥ one drug and a gMut prevalence rate of 23 percent was observed. Decreased PS to NNRTIs was more common than for NRTIs or PIs. Risk of having drug resistance to ≥ one drug prior to ART was significantly higher for white subjects, and subjects reporting primarily heterosexual contact were more likely to have gMut than those reporting homosexual contact.”

Fixed-dose TDF/FTC + EFV

Gazzard B, DeJesus E, Campo R, et al for the Gilead Study 934 Team. The combination of tenofovir (TDF), emtricitabine (FTC) and efavirenz (EFV) has significantly greater responses vs fixed dose zidovudine/ lamivudine (CBV) and EFV in antiretroviral naive patients: A 24-week preliminary analysis. [Abstract H-1137c]

Twenty-four week preliminary data from an ongoing study (Gilead Study 934) suggest that ART-naive patients receiving a once-daily regimen containing tenofovir (TDF) 300 mg + emtricitabine (FTC) 200 mg + efavirenz (EFV) 600 mg experienced fewer study discontinuations related to adverse effects than those patients receiving a regimen of twice-daily lamivudine (3TC) 150 mg/zidovudine (ZDV) 300 mg (aka Combivir) and once-daily EFV 600 mg. Brian Gazzard (Chelsea & Westminster Hospital, London) presented this interim data at an oral late breaker slide session at the 44th ICAAC.

Gilead Study 934 is an ongoing, open-label, Phase III clinical trial comparing a once-a-day regimen of TDF and FTC versus twice-daily Combivir, both in combination with once-daily EFV in more than 500 patients in the United States and Europe.
The study, which has a 48-week primary endpoint, was recently extended to 96 weeks in duration. The US Food and Drug Administration (FDA) recently granted accelerated marketing approval of Truvada, a fixed-dose combination of TDF and FTC, to be taken once a day in combination with other ARV drugs.

The primary endpoint of Gilead Study 934 is the proportion of patients achieving and maintaining viral load reductions to <400 copies/mL at week 48, using the Time to Loss of Virologic Response (TLOVR) algorithm, as specified in FDA guidance.

At study entry, no patients had previously received ART and all had a viral load >10,000 copies/mL. The median viral load at baseline was 100,000 copies/mL. There were no CD4 count restrictions for study participants. The median CD4 count at baseline was 237 cells/mm³ and 13 percent of patients entered the study with CD4 counts below 50 cells/mm³.

The 24-week interim data presented at the 44th ICAAC are based on analyses of the intent to treat (ITT) study population of 509 patients. This includes the pre-specified population of 487 patients described in Gilead’s preliminary 24-week data announcement, and an additional 22 patients with pre-existing nonnucleoside reverse transcriptase inhibitor (NNRTI)-associated mutations. Using the TLOVR algorithm, at 24 weeks, 87 percent of patients in the TDF/FTC arm (n = 255) achieved and maintained a reduction of viral load to <400 copies/mL compared to 78 percent of patients in the Combivir arm (n = 254) (p = 0.010; 95 percent CI, +1.9 percent to +14.9 percent). Similarly, 73 percent of patients in the TDF/FTC arm versus 65 percent in the Combivir arm achieved and maintained a reduction of viral load to <50 copies/mL, (p = 0.038; 95 percent CI, +0.5 percent to +16.2 percent). The mean increase in CD4 count for patients in the TDF/FTC arm was 129 cells/mm³ compared to 111 cells/mm³ in the Combivir arm.

The study regimen discontinuation rate due to adverse events was higher in the Combivir arm, with 9 percent of patients discontinuing from the study versus 3 percent in the TDF/FTC arm (p = 0.008). The most common adverse events leading to study discontinuation were anemia, nausea, fatigue, and vomiting.

Mutations associated with EFV resistance as well as 3TC and FTC resistance developed similarly in both arms, with no patients developing TDF-related K65R or thymidine analogue mutations (TAMS). The renal safety profile was similar in both arms.

**Report from the President**

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either single-dose NVP or combinations of other antiretroviral drugs along with single-dose NVP, to evaluate safety and effectiveness in PMTCT. Of the 17 clinical trials, the seven that have been completed show that single-dose NVP for mothers and infants or single-dose NVP in combination with other antiretroviral drugs, reduces HIV risk of transmission, in some instances by more than 90 percent.

- None of the 17 ongoing or completed clinical trials raise any major safety concern regarding the use of single-dose NVP for PMTCT. No fatalities have been attributed to single-dose NVP in any of these studies. Nevirapine can cause significant rash, liver disease, and occasional fatalities when used as chronic therapy (daily or twice-daily dosing over weeks or months) to treat HIV infection, especially in women... Healthcare workers have been aware of the potential liver toxicity of NVP for over five years.

**NVP resistance**

The issue of resistance to NVP and its impact on subsequent use in HIV-infected women has also been debated. Several important facts need to be considered:

- Nevirapine resistance occurs even with single-dose NVP given to mothers. This resistance is transient and there is no evidence that it prevents the effectiveness of NVP in subsequent pregnancies. Healthcare workers have known about NVP resistance for over five years and have taken this into consideration in making recommendations for PMTCT.

- The “threat of resistance” arguments are, in a sense, backwards. The greatest threat for the development of widespread NVP resistance is not from its use as single-dose NVP for PMTCT in hundreds of thousands of pregnant women. Rather, widespread NVP resistance is more likely to result from its use with combination drugs to treat millions of HIV-infected individuals worldwide and could jeopardize its use for PMTCT.

- Withholding NVP, on the theoretical basis of blunting a subsequent response if used in combination therapy to treat HIV infection, would result in HIV infection and subsequent death of hundreds of thousands of infants for whom no other options are available. In contrast, more than 17 antiretroviral drugs are available which can be used in various combinations to treat HIV infection if resistance occurs. In most resource-poor countries the only option for preventing HIV-infected babies is single-dose NVP.

It is of the utmost urgency that PMTCT programs move forward to save the lives of infants from fatal HIV infection.”

Indeed, rather than waging war on the front pages of newspapers, or using sensationalized media reports to jeopardize the success of ongoing interventions, and given the public health emergency against which we are faced, perhaps it would be wise for us all to step back and with humility in our hearts recite the following prayer:

*Give me the insight to think in new ways, the confidence to trust my instincts, the humility to learn from those around me—even those with whom I may disagree. May I find the courage to stand up for that in which I believe. May I never compromise my integrity. Remind me to treat everyone around me with patience, kindness, and respect. Give me the strength to overcome the ill will that could poison my soul and my relationships. But, most of all, I pray that my work may help to bring goodness into the world.*

Let us always remember that, despite our disagreements, we are all in this great battle together. Our enemy—HIV—is much too formidable for us to cede ground.

José M. Zuniga is President/CEO of the International Association of Physicians in AIDS Care (IAPAC), and Editor-in-Chief of the IAPAC Monthly.
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Nevirapine misinformation: Will it kill?
Three Associated Press (AP) reports in mid-December 2004 created widespread doubts about nevirapine (NVP), the critically important drug that can prevent HIV in many of the 1,800 babies infected every day by their mothers in childbirth. The media allegations that circulated around the world grew out of a bitter personal and personnel dispute between two employees at the US National Institutes of Health (NIH) about the conduct of the HIVNET 012 trial in Uganda from 1997 to 1999. No new information was released about NVP; indeed, following publication of the AP reports, physicians know that NVP still has the same risks and benefits as before. But many experts fear that the emotions stirred by the misinformation disseminated worldwide will result in many HIV-positive mothers receiving no treatment and unnecessarily infecting their children with HIV. This article offers background that has been missing in many news reports.

John S. James

The AP touched off a media firestorm in mid-December 2004 with reports charging that side effects of single-dose NVP (to prevent mothers with HIV from infecting their babies during childbirth) had been covered up. The next day the AP reported on the August 2003 death of a woman in a US clinical trial of continued treatment with NVP (not single dose) due to a rare liver failure probably caused by the drug, after an abnormal blood test result was not noticed in time. The AP later quoted responses—one comparing NVP’s distribution in Africa to the notorious Tuskegee Experiment, another charging that Africans were treated like guinea pigs. In fact there never was any evidence of a significant risk of side effects from only a single dose of NVP. There is a risk of HIV drug resistance, but this is well known to all AIDS-treating physicians and has never been covered up.

Editor’s Note: This article was first e-published December 31, 2004, and is reprinted here with permission from AIDS Treatment News.

Every day about 1,800 babies are born with HIV, mostly to women who have no treatment options either for themselves or to prevent the infection of their child. There is no reason to doubt that single-dose NVP works and could prevent about half of these infections. Because of the resistance problem, single-dose NVP is not the first choice—but sometimes it is the only choice possible.

The brief media storm that still threatens the lives of thousands of children grew out of a bitter dispute between two NIH officials—Jonathan M. Fishbein, a physician with clinical trials monitoring expertise; and his supervisor, Edmund Tramont, Director of the Division of AIDS at the US National Institute of Allergy and Infectious Diseases (NIAID). The falling out happened rapidly; Fishbein was hired by the NIH in July 2003, and notified in February 2004 that he would be fired. Fishbein sought whistle-blower status and released documents to the US Congress that he said showed “scientific and professional misconduct” at the NIAID. The AP published selected internal NIAID emails, memos, and reports—including a damaging email containing Tramont’s response to concerns related to the re-opening of the HIVNET 012...
site in Kampala, Uganda (Figure 1). Fishbein, still a federal employee as of December 2004, set up a Web site—www.honestdoctor.org—which alleges wrongdoing by NIAID officials and provides documents that had been released elsewhere; he “did not provide non-public documents to the [AP],” according to a statement from his attorney.

The danger now is that misleading NVP stories published around the world will cause patients, physicians, or even governments to reject single-dose NVP to prevent mother-to-child HIV transmission in cases when no other treatment is possible.

**NVP for PMTCT**

The US Food and Drug Administration (FDA) approved NVP in June 1996 for use in combination with other antiretroviral drugs for treating HIV. For this use it is taken twice a day for as long as the virus is under control.

A year later HIVNET 012, a study conducted from 1997 to 1999 in Uganda, found that a single dose of NVP given to the mother and a single dose to the infant reduced HIV transmission (from childbirth or breastfeeding) during the first 14 to 16 weeks of life by about half, compared to a very short course of zidovudine (ZDV). This NIH-funded study in 645 mother-infant pairs—conducted jointly by researchers from Johns Hopkins University in Baltimore and Makerere University in Uganda—was published in September 1999. It showed that HIV transmission at childbirth could be greatly reduced by a very inexpensive and easy regimen, even when the mother had little or no prenatal care. It is rightly considered one of the great successes in HIV prevention.

Nevirapine alone is not the best antiretroviral regimen, however. Later it was learned from the same study that even the single dose sometimes selects for resistance mutations in the mother’s HIV—a serious problem because it could make her treatment more difficult in the future. This can be prevented by treating the mother’s HIV if she needs antiretroviral therapy, which of course should be done anyway—or by using a much more difficult regimen of ZDV to prevent transmission—or by adding other drugs (usually ZDV plus lamivudine [3TC]) to suppress the virus while the NVP is slowly eliminated from the body. But still today the great majority of women with HIV do not have access to any antiretroviral therapy.

Single-dose NVP is inexpensive and easy to use—and in some areas many women will not accept a longer course of medication, because they are afraid of the consequences if people around them learn about or suspect their HIV serostatus.

**The recent controversy**

The December 2004 controversy developed because an NIH audit conducted after the HIVNET 012 study had been published found that the Ugandan research staff had not reported data about possible side effects. This problem in one trial did not change the known safety of single-dose NVP—which has been tested in many other clinical trials and widely used to prevent maternal transmission, without side effects. In continuous, long-term use in HIV treatment, serious or fatal side effects can occur, as with any antiretroviral drug. But these are rare, they can be prevented with proper medical care, and they do not happen with one dose. Aside from the HIV resistance problem, there is no evidence of any significant safety risk from a single dose of NVP.

The NIAID hired Fishbein in July 2003 to help correct the types of deficiencies that had been found in the Uganda study. A key disagreement seems to be whether the reporting problems should invalidate the conclusion from that study that single-dose NVP is safe and effective for preventing maternal-infant transmission of HIV.

**Commentary**

This whole dispute concerns an NVP trial that was completed and published more than five years ago, and recent disagreements over how to report flaws in the research that were discovered after publication of the HIVNET 012 data. These flaws are universally acknowledged and were being addressed well before Fishbein arrived at the NIH. They almost certainly do not affect our current understanding of the risks and benefits of NVP.

We looked through all the documents on www.honestdoctor.org as of December 22, 2004, including those on the AP Web site, and found nothing there that raised any new doubt about single-dose NVP—now established by much more than the one trial in Uganda. Instead, the documents on that site show the extensive work that the NIH and others were doing, both before and after Fishbein was hired, to correct universally acknowledged reporting problems. The goal was and is to reanalyze HIVNET 012 in the light of all available information, both to re-check its conclusions when possible, and also to improve clinical research in the future, particularly in developing countries, which often have a steep learning curve in applying standards created for pharmaceutical company-sponsored research at sites with far more resources. We do not know why Fishbein alleged “widespread scientific and professional misconduct at the NIH Division of AIDS,” as quoted on his Web site.

The biggest public controversy concerned the rewritten safety report that was the subject of the second AP report filed December 14, 2004.
We do not know NIH rules and procedures, but it is our understanding that Tramont was responsible for that report, not the team as a whole. Tramont’s version provided more overview, while the previous version more deeply analyzed the problems and was repeatedly critical of management decisions not to investigate certain problems further. Tramont’s report also differed in noting something the study did right:

“These health visitors [who assisted in the trial in Uganda] knew each patient individually and used culturally sensitive methods of making the contact. As a result of their efforts, maternal and infant follow-up overall for the first six weeks of the study was 97.4 [percent] for those who received ZDV and 98 [percent] for those in the NVP group. The 18-month follow-up of the study was also high, 93.8 [percent] for the ZDV group and 96.1 [percent] for the NVP group.”

A separate issue, not part of the public controversy but being discussed among some activists and researchers, is whether the FDA’s current Good Clinical Practice research standards (which were required but not always followed in
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A strong case could be made that imposing the same research requirements regardless of infrastructure and environment can result in second-class standards for developing countries, since there was little or no attempt to make the standards they must use appropriate and workable for them—while there was such flexibility in the United States and other [affluent] countries where the standards were developed. Instead of fighting over how strictly to enforce rules that are sometimes unworkable, why not design rules that will better protect people and data, while helping staff get their work done correctly?

Despite the problems in this trial five years ago in Uganda, there is no reason to doubt that single-dose NVP works and reduces HIV transmission to about half of what it would be without treatment. (It may do better than that, since the comparison group was not a placebo but a very short course of ZDV, which may have had fewer HIV transmissions than placebo would have.)

The management team at the NIAID Division of AIDS, like almost all other AIDS experts, wants to focus on public-health efforts to make preventive and other treatment available, and not derail these efforts by fighting over technical problems in a trial that ended five years ago, when the medical and scientific results of that trial remain firmly established regardless. This is not “scientific and professional misconduct.”

Lesson learned

This is not the last time the AIDS world will face mass media storms that carry serious misinformation throughout the world. What can we do to prevent this in the future?

AIDS needs a major organization dedicated to consensus development, which is able to offer reporters a single entry point to learn what credible consensus exists on almost any AIDS issue. No position will speak for everybody, but the process should be open to hearing and understanding all dissenting views. Two or more incompatible consensus clusters could emerge and they would need to be represented by different organizations. But reporters could immediately find broadly credible statements, and talk with experts about them. They might still publish misinformation, but at least an answer could go out with it—or be clearly missing from their story.

Years ago AIDS had more influence through policy organizations in Washington, DC, than it does now. Often these organizations represented insiders with their own interests more than a national or world community; for example, treatment and international issues were mostly locked out for years, and usually the only way to have a voice was to be part of the Washington, DC, scene, to be at the right meetings and dinners. Groups such as the AIDS Action Council became insiders with their own interests more than a policy organizations in Washington, DC, than it does now. Often these organizations represented insiders with their own interests more than a national or world community; for example, treatment and international issues were mostly locked out for years, and usually the only way to have a voice was to be part of the Washington, DC, scene, to be at the right meetings and dinners. Groups such as the AIDS Action Council became trade associations, only without admitting it—and with a deep fear of grassroots activity, and no way for non-specialists to get involved. Still they served an important purpose in providing reporters a single entry point to learn what credible consensus exists on almost any AIDS issue. No position will speak for everybody, but the process should be open to hearing and understanding all dissenting views. Two or more incompatible consensus clusters could emerge and they would need to be represented by different organizations. But reporters could immediately find broadly credible statements, and talk with experts about them. They might still publish misinformation, but at least an answer could go out with it—or be clearly missing from their story.

Now we need a new kind of organization that prides itself on listening and learning from different people (almost like social scientists exploring what is out there instead of imposing their own view)—but then finds and suggests practical, creative ways these views and movements can work together in a larger whole. And, we need funded, top-quality media outreach that reflects consensus of those working on the epidemic, is on duty at all times, and can answer misinformation immediately.

John S. James is Editor of AIDS Treatment News.
Medical Care

A national study of the relationship of care site HIV specialization to early adoption of highly active antiretroviral therapy

Wilson IB, Landon BE, Dong L, et al.

BACKGROUND: Little is known about characteristics of organizations that predict early adoption of highly active antiretroviral therapy (HAART) for persons with HIV infection. OBJECTIVES: To describe characteristics of sites where HIV care is provided and to assess site characteristics that predict early adoption of HAART. DESIGN: Cross-sectional analysis of survey data from patients, HIV physicians, and medical directors. PATIENTS AND SETTING: Participants in the HIV Cost and Services Utilization Study, a national probability sample of persons with HIV who received outpatient care in the continental United States during 1996. MAIN OUTCOME MEASURE: Rates of exposure to HAART by December 1996. RESULTS: Nationally, 79 percent of patients were treated at sites specializing in HIV care (HIV sites). Over 90 percent of patients were cared for by physicians who were experts in HIV care, either infectious disease specialists (46 percent) or general medicine experts (45 percent). Adjusted rates of exposure to HAART by December 1996 varied from 0.02 to 0.79 across sites (mean rate, 0.33). In multivariable models, HIV specialization (odds ratio [OR], 3.6; P < 0.001), total patient volume of more than 20,000 visits a year (OR, 2.1; P < 0.01), and educational level of the zip code in which the site was located (OR, 1.2 for each 10 percent increase in college education) were associated with higher rates of exposure to HAART. These effects persisted after adjustment for physician HIV expertise. Site effects were more important than physician effects in explaining rates of exposure to HAART. CONCLUSION: In 1996 there were wide variations in rates of HAART use by site of care. Low-volume sites that do not specialize in HIV care should take measures to ensure that HIV expertise is available to their patients.

Pediatric Infectious Disease Journal

Pharmacokinetics of enfuvirtide in pediatric human immunodeficiency virus 1-infected patients receiving combination therapy


BACKGROUND: Enfuvirtide is the first of a new class of antiretroviral agents, the fusion inhibitors. OBJECTIVES: The primary objective of this analysis was to evaluate the pharmacokinetics of 2.0 mg/kg enfuvirtide in human immunodeficiency virus 1 (HIV-1)-infected children and adolescents when administered in combination with at least three other antiretrovirals. METHODS: Twenty-five HIV-1-infected pediatric patients (five to 16 years of age) enrolled in an ongoing phase I/Ii study were included in this analysis. Patients received enfuvirtide 2.0 mg/kg sc twice daily (bid) for at least seven days. Blood samples were collected on day 7, and plasma concentrations of enfuvirtide and its metabolite were measured by a validated liquid chromatography-tandem mass spectrometry method. Pharmacokinetics measures [Cmax, Cmax, C trough, and area under the concentration time curve time 0 to 12 hours (AUC12 hours)] were calculated from plasma concentration-time data by standard non-compartmental methods. RESULTS: There was no significant difference between children and adolescents for enfuvirtide Cmax (6.43 versus 5.88 µg/mL), C trough (2.87 versus 2.98 µg/mL) and AUC12 hours (56.1 versus 52.7 µg·h/mL). Similarly no significant differences were found when the pharmacokinetic measures were compared based on sexual maturity stages. A post hoc regression analysis based on AUC12 hours showed that body weight-adjusted dosing of enfuvirtide provides drug exposure that is independent of age group, body weight and body surface area. CONCLUSIONS: Body weight-adjusted dosing of enfuvirtide at a dose of 2.0 mg/kg sc bid, in HIV-1-infected pediatric patients at least five years of age, provides drug exposure comparable with that previously observed in HIV-1-infected adults after 90 mg sc bid dosing. Drug exposure in children and adolescents is independent of age group, body weight, body surface area, and sexual maturity stage.

Pediatric Infectious Disease Journal

AIDS

Prognostic value of plasma HIV RNA among highly active antiretroviral therapy users

Tarwater PM, Gallant JE, Mellors JW, et al.

BACKGROUND: The study objective was to compare the prognostic value of plasma HIV RNA and CD4 cell count at baseline and as time-updated variables in highly active antiretroviral therapy (HAART) users for two outcomes: development of AIDS and change in CD4 cell count. METHODS: The study population comprised 387 men enrolled in the Multicenter AIDS Cohort Study who were AIDS-free and initiated HAART between 1996 and 2001. Follow-up until AIDS diagnosis (n = 36, 9 percent) or the last AIDS-free visit was included. To determine the predictive value of combining HIV RNA and CD4 cell count, regression tree methods using recursive partitioning at pre-specified cut points for both variables were used. RESULTS: Low CD4 cell count was a strong predictor of AIDS among HAART users. However, HIV RNA showed strong prognostic value for AIDS development among those with CD4 cell counts >250 x 10 cells/L, in whom an HIV RNA level >1,000 copies/ml carried a 4.6-fold greater risk of developing AIDS. HIV RNA >5,000 copies/ml was also predictive of subsequent increase in CD4 cell count with significantly higher increases among those with initial CD4 counts >300 x 10 cells/L. CONCLUSION: Although, in HAART users, CD4 cell count was the primordial prognostic marker, an HIV RNA >1,000 copies/ml attained after HAART initiation was a strong predictor of the rate of subsequent CD4 cell count increase and of developing AIDS in patients whose CD4 cell counts were >250 x 10 cells/L.

Neurology

Disease burden in HIV-associated cognitive impairment: A study of whole-brain imaging measures


OBJECTIVE: To study whole-brain MR measures derived from diffusion tensor imaging and magnetization transfer imaging (MTI) for the in vivo assessment of cumulative neuropathologic changes in HIV and to evaluate the quantitative imaging strategies with respect to cognitive status measures including the severity of dementia and the degree of impairment in specific cognitive domains including attention, memory, constructional abilities, and motor speed. METHODS: Quantitative whole-brain measurements, including fractional anisotropy (FA), apparent diffusion coefficient (ADC), and magnetization transfer ratio (MTR), were derived from histograms and compared in HIV and control participants. Relationships between the MR and cognitive status measures were examined. RESULTS: Whole-brain FA and MTR were reduced in patients with HIV and correlated with dementia severity. Whole-brain MTR and ADC were correlated with psychomotor deficits. Evaluation of relationships between the studied MR measures indicated a correlation between ADC and MTR. FA was not correlated with either ADC or MTR. CONCLUSIONS: Findings from this investigation support the use of quantitative whole-brain MR measures for evaluation of disease burden in HIV. Reductions in whole-brain fractional anisotropy and magnetization transfer ratio (MTR) distinguished HIV and control subjects, and these measures were associated with dementia severity. Relationships were identified between whole-brain MTR and apparent diffusion coefficient and psychomotor deficits. Combining these quantitative strategies in neuroimaging examinations may provide more comprehensive information concerning ongoing changes in the brains of HIV patients.

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Focus on Hepatitis

Workshop convened on HIV/hepatitis coinfection

Marina Núñez

IV and hepatitis coinfection is a growing and rapidly evolving field that is increasingly attracting the attention of HIV healthcare providers. So much so that a group of experts convened December 2-4, 2004, in Amsterdam for the 1st International Workshop on HIV and Hepatitis Coinfection. In addition to covering the most important aspects of these infections, the workshop also served as a venue for the presentation of new research around issues ranging from epidemiology to the treatment of mono-, dual and tri-infection.

Epidemiology

Mark Sulkowski (Johns Hopkins University, Baltimore) presented an overview of the epidemiology of hepatitis B virus (HBV) and hepatitis C virus (HCV) coinfections in HIV-positive patients.

Although HBV is more effectively transmitted than HCV, the prevalence of HCV coinfection is much higher than that of HBV coinfection in developed areas of the world. The HIV/HCV-coinfected population consists primarily of individuals who have been infected through intravenous drug use. However, investigators from London, Germany, and the United States have recently reported an increase in the incidence of acute HCV infection among homosexuals.1

Andrew Phillips (Royal Free Hospital, London) addressed some of the methodological caveats commonly seen in clinical research on HIV/hepatitis coinfection. To evaluate the impact of highly active antiretroviral therapy (HAART) on deaths from liver disease, not only the people who died, but the whole population at risk should be analyzed.

In addition, bias must be considered, as some patients may not be tested for HCV and HBV infections. Phillips also pointed out several common sources of bias in investigations of HAART-related hepatotoxicity: different definitions across studies, spontaneous variability in transaminase levels over time in hepatitis-coinfected patients, and lack of stratification by HCV serostatus when the hepatotoxicity of a particular antiretroviral drug is analyzed.

It is also difficult to assess the effects of alcohol and HCV infection on the liver. These two factors often coexist. Information on alcohol use relies on self-reporting, and therefore is an underestimated phenomenon that leads to misinterpretations of the impact of HCV infection on liver disease.

Finally, regarding the effect of HCV on the development of AIDS and death, active drug use acts as a confounding factor, and the timing of HCV testing also may introduce bias if we include patients who were not tested at baseline but during follow-up.

HAART and the natural course of hepatitis coinfection

Paula Braithstein and colleagues (British Columbia Center for Excellence in HIV, Vancouver) presented data on the impact of HCV infection on CD4 recovery in patients on HAART.2 The researchers analyzed 1,186 patients taking either protease inhibitor (PI)- or nonnucleoside analogue reverse transcriptase inhibitor (NNRTI)-based regimens. Anti-HCV antibody-positive individuals gained significantly fewer CD4 cells within 48 weeks of HAART, but there were no differences in the CD4 percentage, compared to those with negative anti-HCV antibody.

However, it is unknown how the difference in the baseline CD4 fraction (higher among HCV-positive subjects) might have impacted the results of this interesting study. In addition, since HCV status was based on anti-HCV antibody, a bias could have been introduced, as approximately 14 percent of anti-HCV antibody-positive HIV-infected patients have no active HCV replication.

A multicenter team from Boston, Baltimore, New York, and Paris assessed the natural history of HIV/HCV-coinfected patients in the HAART era.3 Their analysis was based on 12,574 HIV-infected patients initiating HAART, and liver biopsies from 2,313 untreated HCV-monoinfected individuals.

They developed a Markov model to predict the outcome of HIV/HCV-coinfected subjects, based on Cox models for hepatitis C fibrosis progression and recent United Network for Organ Sharing (UNOS); Surveillance, Epidemiology, and End Results (SEER); US National Institutes of Health (NIH), and meta-analysis data. From the onset of HIV infection, projected life expectancy was 29 years with HAART, compared to nine years pre-HAART (normal life expectancy, 41 years).

In the absence of HAART, life expectancy was similar in HIV-monoinfected and HIV/HCV-coinfected patients, but it was shortened by nine years in coinfected subjects receiving HAART who had CD4 counts between 200 cells/mm3 and 350 cells/mm3, and by three years in those with <200 cells/mm3 (Table 1).

In a round table discussion, Juergen Rockstroh (University of Bonn, Germany) reviewed recent studies reporting a beneficial effect of HAART on the outcome of HIV/HCV-coinfected patients. Thus, both slower progression of liver fibrosis and a decrease in mortality due to hepatic diseases among patients taking HAART have been reported.4,8 The panel highlighted the problems in...
accurately assessing the influence of HAART on the outcome of viral hepatitis disease. Relevant differences are found in the characteristics of the main cohorts studied so far—Johns Hopkins, Swiss, and EuroSIDA—which may explain the different results.

It is difficult to evaluate HAART-induced immune recovery, which may not be homogeneous over time, and may be better quantified by percent than by absolute CD4 counts.

Regarding the assessment of liver fibrosis, prospective studies are needed, but biopsy also has its limitations and is not the perfect tool to prove the amelioration of liver fibrosis. Finally, the negative impact of HAART on the liver was mentioned, with “d-drugs” and PI use favoring hepatic steatosis.

Regarding HBV, Chloe Thio (Johns Hopkins University, Baltimore) commented on a recent report presented at the 55th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD) in which anti-HBe seroconversion was associated with control of HIV infection.

### Diagnostics

Hot debate but little agreement on the need of performance of liver biopsy as part of the pre-anti-HCV therapy assessment was the bottom line in a panel discussion conducted by Jean-Michel Pawlotsky (Hôpital Henri Mondor, France). While experts in the field of hepatitis C either support or argue against the use of pretherapy liver biopsy, non-invasive tests are rapidly emerging, raising doubts about the appropriateness of liver biopsy as the gold standard of fibrosis assessment.

In that regard, data on the performance of FibroScan, a new non-invasive method of liver fibrosis assessment which is based on its good correlation with stiffness of the tissue, were presented by Victor de Lédinghen (Hôpital du Haut-Lévêque, Pessac, France). Results obtained in 711 patients with chronic liver disease including 24 HIV/HCV-coinfected subjects were reported. They identified the value of 17.6 kPa as the cut-off for prediction of cirrhosis (positive predictive value [PPV] and negative predictive value [NPV] = 90 percent). The performance of this technique is best for advanced stages of liver disease.

Thierry Poynard (Hôpital Pitié-Salpétrière, Paris) presented results on 1,570 subjects assessed with the FibroTest, a diagnostic test based on serum markers. Although it better discriminated higher degrees of fibrosis, it was also able to detect early fibrosis (F0 to F1). Poynard pointed out that whenever there was discordance between the results of FibroTest/ActiTest and of the biopsy, it was most often due to errors in the biopsy (18 percent versus 2 percent; p < 0.001).

A combination of FibroScan and tests based on serum markers might improve the efficacy of each of the two techniques, leaving the biopsy for cases of discordance.

Marion Peters (University of California, San Francisco) summarized the characteristics of an ideal assay informing of liver tissue status (Table 2). She also mentioned that it would be desirable not only to have the static picture of fibrosis present in the liver, but information on the current fibrogenesis process.

Geoffrey Dusheiko (Royal Free Hospital, London) gave an overview of virological methodologies. Regarding HBV, much more sensitive HBsAg assays are available now, which may make it unnecessary to measure HBV DNA for screening of blood donation.

HBeAg seems to correlate with HBV DNA plasma levels, and among HBV DNA quantification assays the TaqMan is more sensitive than other tests. In HCV, the measure of HCV RNA levels is critical to monitor response to treatment. Therefore, it is important to use appropriate assays with high enough upper limits of detection.

A study performed by Mauricio Bonacini and colleagues (California Pacific Medical Center, San Francisco) analyzed the presence of multiple HCV genotypes by performing an extended PCR of 45 cycles (45X PCR) in 12 HIV/HCV-coinfected subjects treated with interferon (IFN) and ribavirin (RBV). The 45X PCR was able to detect HCV genotype 1 combined with genotypes 2/3 at baseline in four patients, while the 30X PCR had detected only the more favorable genotypes.

Interestingly, three of the four patients relapsed after discontinuation of therapy. If this is one of the reasons for failures of anti-HCV therapy, especially in cases of relapse, it needs to be confirmed by further studies.

### Treatment for HCV and HBV coinfection with HIV

Vincent Soriano (Hospital Carlos III, Madrid) addressed the treatment of HCV coinfection. He emphasized how several strategies might help to improve the efficacy of IFN-based therapies, limited in these coinfected subjects. A good selection of candidates, close and individualized follow-up by experts, and optimization of RBV dosages and of duration of therapy could be the pillars for a successful treatment in HIV/HCV-coinfected subjects.

Christian Perronne (CHU Raymond-Poincaré, Garches, France) commented on some data on the RIBAVIC study, presented earlier this year at the 11th Conference on Retroviruses and Opportunistic Infections (CROI). Both a relatively high proportion of cirrhotic patients and a high number of drop-outs could account for the poor response to therapy (end of treatment response [ETR] 35 percent and sustained virological response [SVR] 27 percent in the pegylated IFN-alfa 2b + RBV, and ETR 21 percent and 20 percent SVR in the pegylated IFN-alfa 2b arms, respectively). Response was favored by genotypes 2/3 (OR = 6.6), age < 40 (OR = 1.8), and baseline ALT levels above three times the limit of normal (OR = 1.9).

Soriano and colleagues studied the response of HCV genotype 4. Interferon-based treatments, ranging from standard
IFN monotherapy to pegylated IFN + RBV combinations were given to 42 patients with HCV-4 over the years. Sustained virological response was 16.7 percent for these patients, significantly lower than responses of subjects with HCV-2/3 (40.4 percent) and comparable to that of HCV-1-infected patients (11.2 percent). Thus, this subset of patients should be considered difficult to treat and the strategies for their treatment optimized.

Several of the posters focused on anti-HCV therapy. Portuguese investigators analyzed the use of regular doses of pegylated IFN-alfa 2b (1.5 mg/kg) during the first month of treatment followed by lower doses (1.0 mg/kg) until the end, always combined with weight-adjusted RBV, in an attempt to improve tolerance.18

Based on their results, the approach may work for 71 percent of HIV-infected patients with HCV genotypes 2/3 completing treatment, but not for the majority of subjects with less favorable HCV genotypes. Interestingly, despite directly observed therapy, 17 percent of HIV-coinfected subjects discontinued therapy, compared to 5 percent of HCV-monoinfected patients.

A high proportion of discontinuations was observed in an Italian multicenter randomized study presented by Antonietta Cargnel (Ospedale L. Sacco, Milan) in which pegylated IFN-alfa 2b + 800 mg RBV (n = 69) was compared to pegylated IFN-alfa 2b (n = 66).19

In an analysis of early HCV kinetics, the investigators found an 86 percent negative predictive value (of SVR) for a decline in HCV load of at least 2 log_{10} at week 8 of therapy. However, the sample is small, and it is desirable that the negative predictive value of a tool guiding premature interruption of anti-HCV therapy be close to 100 percent. Otherwise, we might lose the chance of a response in some patients.

Two studies reported results of treatment of acute HCV infection in HIV-infected subjects. In one of them, performed in Germany, 17 patients were treated with pegylated IFN over 24 weeks, alone or with RBV (five subjects).20 The end-of-treatment response was similar for HCV genotypes 1/4 (9/11) and HCV-2/3 (4/6), while there was no apparent additional benefit from receiving RBV.

In the French study, 14 homosexual men received pegylated IFN and RBV (except for one treated with monotherapy) after a median follow-up period of 14 weeks.21 In accordance with the results of other authors, response was comparable across HCV genotypes. End-of-treatment response was 90 percent and sustained response 87 percent. Since the exact date of infection is unknown, it is not clear if spontaneous clearance could account, at least in part, for the good results.

An American-German group of researchers examined the GB virus-C (GBV-C), claimed by some to have a beneficial effect on the course of HIV infection.22 GB-C viremia was retrospectively measured in 130 HIV/HCV-coinfected subjects who had received IFN and RBV. GBV-C clearance was observed in 45 percent of patients with GB-C viremia at baseline (111), while no changes were observed in HIV RNA plasma levels.

In his review on treatment of HBV coinfection, Yves Benhamou (Hôpital Pitié-Salpêtrière, Paris) showed data on the performance of emtricitabine (FTC), the last NRTI approved for HIV, which also has anti-HBV activity. A median decrease of around 3 log_{10} in HBV DNA levels from baseline was seen at week 36 both in HIV-coinfected and in non-HIV patients in the FTCB-102 study. Similar to lamivudine (3TC), the main limitation of this drug is the selection of resistance mutations. After 96 weeks of therapy with 200 mg FTC, HBV was resistant in almost 20 percent of non-HIV patients.

Oliver Schildgen (University of Bonn, Germany) reported data from a German multicenter study evaluating HBV mutations in three patients previously treated with 3TC who had also failed adefovir (ADV).23 Common to the three patients were infection with HBV genotype A, presence of the L180M 3TC-resistance mutation at baseline, and mutation at position aa 217 within the polymerase region at the time of failure to ADV. Interestingly, the switch to tenofovir (TDF) was followed by a substantial decrease in HBV DNA levels.

**HBV-related issues**

In a retrospective study from the Italian study group IcoNA, the clinical outcome of HBV-coinfected patients was analyzed comparing those subjects who received 3TC-containing HAART with those treated with HAART, but not receiving 3TC.24 There was a significant reduction difference in the risk of liver-related morbidity/mortality among those patients receiving 3TC (RH = 0.07; 95 percent CI: 0.01-0.38; p = 0.002).

Stefan Mauss and colleagues (Center for HIV and Hepatogastroenterology, Düsseldorf) analyzed HIV-coinfected patients with highly replicative chronic hepatitis B.25 Six patients, naive for anti-HBV treatment, initiated 3TC and TDF, and five patients failing 3TC were switched to TDF. After 12 months of therapy, median HBV DNA levels were comparable for both groups of patients.

The researchers noticed that after a period of follow-up of at least 18 months, all patients (except for one lost to follow-up) had undetectable HBV DNA, and suggested that the combination of 3TC with TDF does not seem to add further benefit to the action of TDF.

However, we have to be cautious at drawing conclusions since the sample is small and the scenarios of each group of patients are completely different. We cannot rule out hypersensitivity to TDF of 3TC-resistant HBV mutants in the group of 3TC failing patients, for example.

Angeline Bartholomeusz (Victorian Infectious Diseases Reference Laboratory, North Melbourne, Australia) presented an Australian-American collaborative study in which the reverse transcriptase and the envelope genome was sequenced in 63 HBV viremic HBV-coinfected patients, predominantly with HBV genotype A.26 Lamivudine resistance mutations were identified in 62 percent of them. Unique polymerase mutations were detected accompanying the classic 180 and 204 mutations. Thus, the triple combination rtV173L + rtL180M + rtM204V was present in 23 percent of the mutants. The implications of this particular pattern rely on the fact that it alters the envelope, resulting in sD164E and sI195M mutations, reducing the ability to bind the anti-HBs antibody, in a similar way to an HBV vaccine escape mutant.

A research group from Munich retrospectively examined responses to anti-HBV vaccination among 41 HIV-infected subjects.27 Response, defined as the achievement of anti-HBs titers of at least 100 IU/L, was obtained only in 37 percent of individuals, a much poorer result than that obtained in non-HIV patients. CD4 counts >500 cells/mL, HBV RNA levels <1,000 copies/ml, and HAART use, were
identified as independent predictor factors of response to vaccination.

**Therapeutic drug monitoring**

Ana Rendón (Hospital Carlos III, Madrid, Spain) investigated the role of early monitoring of RBV plasma levels during the course of anti-HCV treatment. Both the development of anemia and early virological response (defined as >2-log drop in HCV RNA levels) positively correlated with RBV plasma levels at weeks 4 and 12 of pegylated IFN-alfa 2a + RBV therapy (Figure 1). Use of zidovudine (ZDV) was also independently associated with anemia. Moreover, RBV plasma levels were higher among ZDV users (3.28 mg/kg) compared to patients not taking ZDV (2.51 mg/kg) at week 4 of anti-HCV treatment.

Stefanie Domínguez (Hôpital Pitié-Salpêtrière, Paris, France) presented a pharmacokinetic study comparing levels of several PIs and NNRTIs between 66 HIV-coinfected and 73 HCV/HIV-coinfected individuals. Around 20 percent of patients with HCV had a fibrosis score by Fibrotest of F4. Contrary to previously reported data, they found significantly higher lopinavir and efavirenz plasma levels among HIV/HCV-coinfected individuals. The management of antiretroviral and immune suppressive drugs was challenging due to frequent drug-drug interactions, especially when PIs were used. It was pointed out that daily monitoring of drug levels may be required in the post-OLT period. During the discussion, the issue of the timing of HAART post-OLT came up. The expert panel stated that HAART was usually initiated three to seven days after transplantation.

Peter Stock (University of California, San Francisco) showed data on 11 patients receiving OLT at UCSF, 91 percent of whom have survived so far. Five of them had chronic hepatitis B, and were managed with 3TC and either ADV or TDF, along with monthly immunoglobulin.

The third OLT series, which included seven liver transplants performed between 1997 and 2004, was presented by Martin Vogel (University of Bonn, Germany). The patients were either hemophiliacs or homosexuals. Like the study from the University of California, San Francisco, and contrary to the Spanish study, 40 percent of this cohort made up of HBV-infected patients. The survival rate was similar (86 percent) after a median follow-up of 20 months.

Besides the interactions between antiretroviral and immunosuppressive drugs, which cause a high number of episodes of graft rejection and increased toxicity, OLT in HIV-infected patients poses several other problems. Thus, several issues are of relevance, such as overlapping chronic toxicity (eg, diabetes mellitus, dyslipidemia, osteoporosis), the high pill burden (eg, HAART, immunosuppressive drugs, prophylaxis for opportunistic infections, methadone in ex-drug users), and HCV reinfection.

The latter is of special concern, due to its rapid progression and to the poor efficacy and tolerance of anti-HCV therapy (frequent need for erythropoietin and/or GCSF use). Other areas of uncertainty include the unknown impact of OLT and immune suppression on HIV progression, and of HIV infection on the long-term survival of patients who had HCC.
Hepatitis Coinfection.

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For additional information on how you can make a difference, contact Joey Atwell, Director of Membership, at (312) 795-4941 or jatwell@iapac.org, or complete and submit an on-line application at www.iapac.org.
Nicholas C. Bellos

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

This month, IAPAC Monthly is proud to feature Nicholas C. Bellos, who is President of the Southwest Infectious Diseases Association in Dallas.

If you could live anywhere in the world, where would it be?
Here in Dallas. My second favorite place would be on a Greek island (as a first-generation Greek, I love the country, especially the islands).

Who are your mentors or real life heroes?
Barbara Hanna, my mentor and the reason I chose infectious diseases and HIV medicine as a subspecialty.

With what historical figure do you most identify?
John F. Kennedy. He was an agent for social change and equality.

Who are your favorite authors, painters, and/or composers?
Authors: Tom Clancy, Patricia Cornwell, and Robert Ludlam; painters: Monet, Pizzaro, and Picasso.

If you could have chosen to live during any time period in human history, which would it be?
I would choose to live at no other time. I have been involved in the evolution of one of the most fascinating medical challenges in history—HIV disease—from its discovery and have enjoyed being part of crafting creative care models and treating patients. The period of the 1940s is also one of my favorite time periods because of the innocence of that time.

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

In your opinion, what are the greatest achievements and failures of humanity?
Our inability to tolerate cultural and personal differences allowing others to live according to their belief systems is our greatest failure. Our scientific and technological advances are our greatest achievements.

What is your prediction as to the future of our planet one full decade from present day?
I would predict that we will live in a more tolerant world where individual and cultural differences will be celebrated and not ostracized. I would also predict that our technologies will make life much easier and that we will have more global resources to deal with health and social issues.
As 2004 comes to a close, and lest we forget why we are so heavily invested in the global battle against HIV/AIDS, a collage of suffering and survival as it affects AIDS-ravaged Africa.
WHY DOES ALAN CUMMING WEAR THE BRACELET?

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