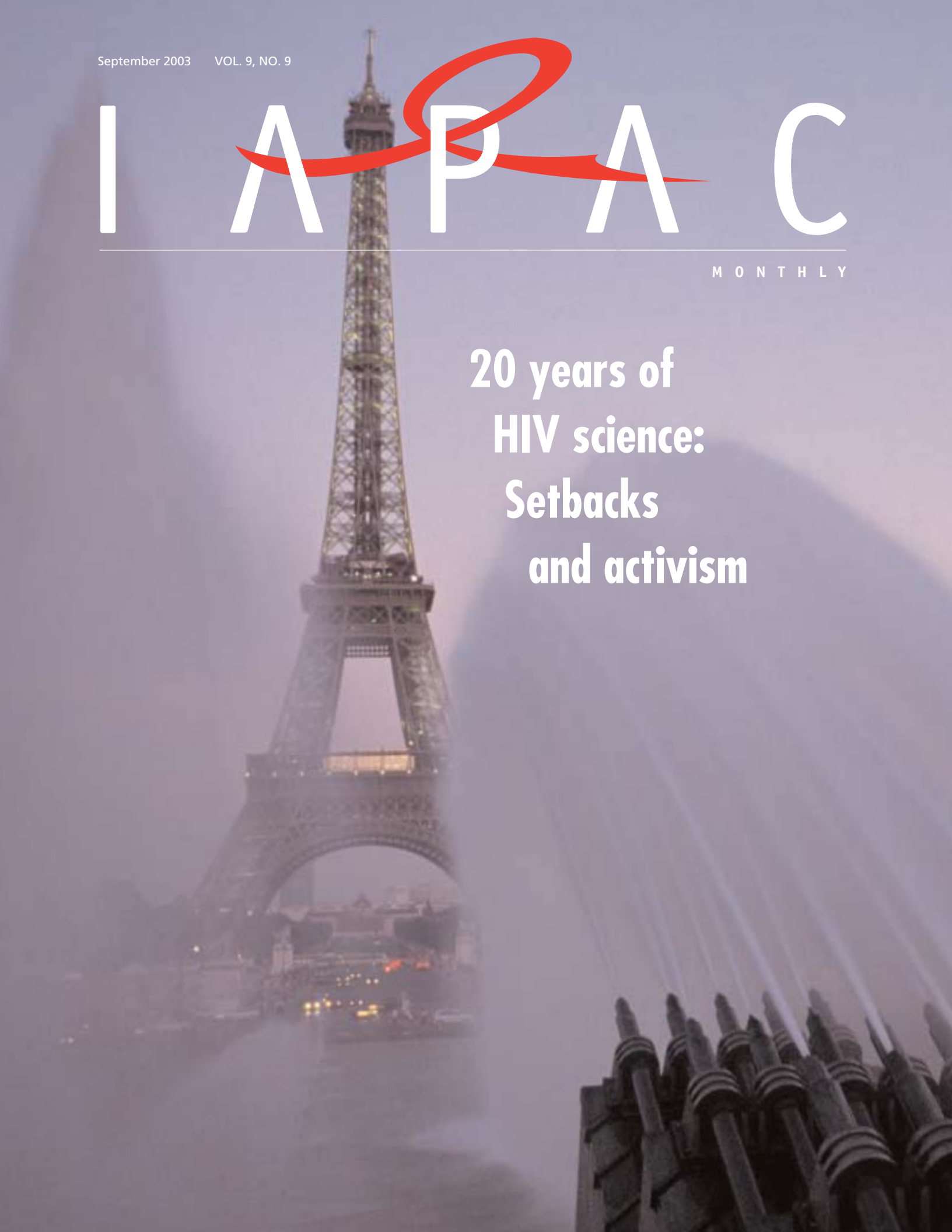


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I A P A C

M O N T H L Y

20 years of HIV science: Setbacks and activism



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20 years of HIV science: Setbacks and activism

Neil Osterweil

The 2nd IAS Conference on HIV Pathogenesis and Treatment provided a snapshot of HIV/AIDS research and treatment two decades into the history of the AIDS pandemic. The conference highlighted both the continuing advancement and refinement of antiretroviral therapy, and the continued resilience of HIV, which is leading to growing concerns about drug resistance.

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REPORT FROM THE PRESIDENT

GALEN moves forward

José M. Zuniga

I am pleased to report that the Global AIDS Learning & Evaluation Network (GALEN), an ambitious program launched by the International Association of Physicians in AIDS Care (IAPAC) in response to a growing need for HIV medicine capacity building, recently took a major step toward full implementation. Physicians from nine countries in the developing world field-tested the GALEN Certification Examination during the 2nd IAS Conference on HIV Pathogenesis and Treatment, held last month in Paris. Additional field-testing is scheduled for Brazil, South Africa, Thailand, and Uganda over the next several months.

Designed to assess the core knowledge of physicians at the front lines of the battle against HIV/AIDS, the proctored, 200-plus-question examination complements GALEN's primary component—a 15-module curriculum covering the gamut of HIV treatment and care issues. The curriculum and certification together constitute a comprehensive system of continuing medical education mechanisms for HIV-treating physicians in resource-limited settings. Physicians who work through the GALEN curriculum, either by participating in IAPAC-facilitated or -accredited training sessions or via self-study, will be designated "HIV Care Specialists" upon achieving a 70 percent or higher score on the GALEN Certification Examination. GALEN materials will be updated to incorporate changes to the state of the art, with those modules covering antiretroviral therapy re-evaluated biannually.

It is clear that there is a lot of work before us as IAPAC members and staff. I want to emphasize now, however, that



Frank Ekow Baiden of the Navrongo Health Research Centre in Navrongo, Ghana, field tests the GALEN Certification Examination. Additional field-testing will take place within the next several months in Brazil, South Africa, Thailand, and Zimbabwe.

the progress embodied in the July 2003 field test of the GALEN Certification Examination bespeaks years of work—and the commitment of men and women from around the world who are dedicated to innovative ways of strengthening local capacities to deliver optimal HIV/AIDS care. In developing GALEN, IAPAC convened two separate international committees to determine how best to enhance the capacity of countries to expand access to HIV/AIDS care, including antiretroviral therapy. Since these meetings, IAPAC

staff and smaller committees of HIV-treatment experts have worked tirelessly on the GALEN curriculum and certification components.

Many of these individuals will work with the data collected from the July 2003 field test and finalize the GALEN Certification Examination. Co-chaired by John G. Bartlett (Johns Hopkins University, Baltimore) and Peter Mugenyi (Joint Clinical Research Centre, Kampala, Uganda), the GALEN Certification Committee is composed of an international

panel of 32 clinicians who are leaders in the field of HIV medicine, balanced between those working in developed- and developing-world settings.

The GALEN Curriculum Committee—co-chaired by D. William Cameron (University of Ottawa, Canada) and Elly Katabira (Makerere University, Kampala, Uganda)—is equally dedicated in its mission and appropriately composed to represent a global cross-section. Thanks to their efforts, IAPAC has advanced in the development of materials to support the 15-module GALEN curriculum—including training modules and slide sets. Two anti-retroviral-specific modules are now being used in multiple countries in Africa, the Caribbean, and Central America. And, they have also recently been translated into Spanish through an arrangement with the Pan-American Health Organization (PAHO).

GALEN is already being recognized for its innovative approach to one of the most pressing challenges to the expansion of access to antiretroviral therapy in the developing world. A US-based organization of non-profit associations—the American Society of Association Executives (ASAE)—has bestowed upon IAPAC its highest award for the utilization of our membership to create and implement an initiative of such worldwide import. The ASAE Summit Award will be presented to IAPAC during an awards ceremony September 30, 2003, in Washington, DC.

More important than laurels, however, is the fact that physicians from developing world countries who are at the front lines of the battle against HIV/AIDS believe in GALEN—which was made abundantly clear during the Paris field test of the GALEN Certification Examination. Those physicians who sat the examination were eager participants, expressing their sense that formalizing HIV medicine would improve their practices and lead to better care for their patients. I was delighted to hear these reactions, but not entirely surprised. They speak to IAPAC's ongoing commitment to initiatives that are member-driven and address the needs of men and women charged with the day-to-day care of people living with HIV/AIDS. ■

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



A R V U P D A T E

BMS issues PK notice regarding ATV + TDF

Editor's Note: The following "Dear Healthcare Provider" letter was issued August 8, 2003, by Bristol-Myers Squibb through its Vice President for Virology Medical Affairs, Sally Hodder.

Bristol-Myers Squibb would like to make clinicians caring for HIV-infected patients aware of important new pharmacokinetic (PK) data concerning the co-administration of atazanavir (ATV) and tenofovir (TDF). Two studies have been conducted to evaluate the potential PK interaction between ATV and TDF, and an additional ongoing clinical study has provided preliminary data on the safety profile of this combination. Data from these trials are currently under review by the US Food and Drug Administration (FDA).

The following observations were made from these three trials:

- *Study AI454-181:* In healthy volunteers, ATV AUC and C_{min} were decreased by approximately 25 percent and 40 percent, respectively, when unboosted ATV 400 mg was co-administered with TDF 300 mg once daily (QD) as compared to ATV alone. In addition, an increase of approximately 24 percent in TDF's AUC was observed.
- *Puzzle 2 (ANRS 107) Study:* Atazanavir AUC and C_{min} were decreased by approximately 25 percent and 23 percent, respectively, when ATV 300 mg + ritonavir (RTV) 100 mg (boosted ATV) was co-administered with TDF 300 mg QD, as compared

to ATV 300 mg + RTV 100 mg administered without TDF to HIV-infected patients.

- For the combination of boosted ATV + TDF, the ATV AUC and C_{min} observed in the Puzzle 2 study were approximately 1.2- and 4-fold higher than the respective values observed for unboosted ATV 400 mg given alone to healthy volunteers in Study AI454-181.
- *Study AI424-045:* Interim safety data from an ongoing clinical trial suggest that the treatment of emergent adverse events of moderate or severe intensity is comparable for boosted ATV in treatment-experienced patients and for unboosted ATV-treated patients in other clinical trials.

Based on these results:

- Clinicians should use caution when administering unboosted ATV + TDF. Unboosted ATV may be less effective due to decreased ATV concentrations in patients taking ATV + TDF. As a result, the co-administration of unboosted ATV + TDF may lead to loss or lack of virologic response and possible resistance to ATV.
- If ATV is co-administered with TDF, consideration should be given to administering ATV 300 mg + RTV 100 mg + TDF 300 mg (all as a single daily dose with food), until additional data are obtained. Co-administration of ATV 300 mg + RTV 100 mg QD is currently under clinical investigation.
- The increase in TDF's AUC does not appear to be associated with increased toxicity over 24 weeks. ■

2ND INTERNATIONAL AIDS SOCIETY CONFERENCE
ON HIV PATHOGENESIS AND TREATMENT

JULY 12-16, 2003 - PARIS

20 years of HIV science: Setbacks and activism

It was billed as a scientific gathering intended to “provide new insights into HIV disease that can lead to new research directions, help speed translational research and move advances into clinical practice.” But in retrospect, the 2nd IAS Conference on HIV Pathogenesis and Treatment, held July 12-16, 2003, in Paris, said as much about the convergence of social and political concerns regarding the global HIV/AIDS pandemic as it did about the science.

Approximately 6,000 delegates from 120 countries filled the auditoriums, meeting rooms, and exhibit halls of Paris’s Palais des Congrès, where they shared insights into the molecular biology of HIV, clinical data on current and emerging antiretroviral therapies, the epidemiology of HIV infection and HIV disease, and strategies for providing optimum care in parts of the world where resources are severely limited.

Organizers framed this second annual IAS Conference to highlight HIV science two decades into the AIDS pandemic. Thus, the clinical and scientific sessions at the heart of the IAS Conference provided a snapshot of HIV/AIDS research and treatment two decades on. The sessions highlighted the continuing advancement and refinement of antiretroviral therapy, but also the continued resilience of HIV and growing concerns about containment, as evidenced by reports of the increasing prevalence of newly acquired antiretroviral drug-resistant HIV infections.

State-of-the-ART: New agents, old standbys

Three recently approved antiretroviral agents, including a new protease inhibitor (PI), a new nucleoside reverse transcriptase inhibitor (NRTI), and the first agent in a new class of drugs (fusion inhibitors), received a great deal of attention in clinical sessions at the IAS Conference.

Summaries of the presentations regarding these drugs are presented below in alphabetical order by generic name. These drugs are also discussed later in this article in sections focusing on salvage therapy and industry-sponsored satellite symposia.

Atazanavir

Atazanavir (ATV), a once-daily azapeptide PI that received US Food and Drug Administration (FDA) approval just a few days before the IAS Conference’s opening

ceremony, was the focus of numerous talks in clinical presentation and industry sponsored-symposia.

In a late-breaking oral presentation, Joseph G. Jemsek (Jemsek Clinic, Huntersville, North Carolina) reported data from the metabolic substudy of the BMS-034 trial, which compared ATV 400 mg once daily (QD) with efavirenz (EFV) 600 mg QD, each in combination with fixed dose zidovudine (ZDV) and lamivudine (3TC) twice daily (BID). The metabolic substudy looked at adipose tissue changes and metabolic parameter changes from baseline to 48 weeks. The researchers found that ATV and EFV produced comparable and proportional effects on body fat distribution at week 48. They also determined that the pattern of fat increase seen in patients was consistent with normal weight gain and not with patterns of central adiposity. In addition, whereas therapy with EFV raised total cholesterol, fasting LDL, HDL, and fasting triglycerides, ATV resulted in an 11 percent increase in HDL, but a 6 percent decrease in fasting triglycerides, and was essentially neutral in its effects on total cholesterol and fasting LDL.

Atazanavir’s reputation was further enhanced by a study indicating that the lipid benefits can be seen in antiretroviral-experienced patients who are switched to ATV-containing regimens. That conclusion was reported in a late-breaking poster session. Kenneth Lichtenstein *et al* (University of Colorado Health Sciences Center, Denver) evaluated serum lipid levels of patients in antiretroviral failure who were then switched to regimens containing ATV or lopinavir (LPV) boosted with ritonavir (RTV)—lopinavir/ritonavir (LPV/r). They looked at two open-label studies, one comparing ATV 400 mg QD to LPV/r BID plus two NRTIs, and the other comparing RTV-boosted ATV, ATV plus saquinavir (SQV) 1,200 mg QD and LPV/r BID each combined with tenofovir (TDF) and one NRTI. In the first study, they found that at 24 weeks, ATV lowered total cholesterol, fasting LDL and triglycerides by 2 percent, 6 percent and 2 percent from baseline, respectively. In contrast, LPV/r raised all three values 17 percent, 5 percent, and 55 percent, respectively.

In the second of the two studies looked at by Lichtenstein *et al*, both ATV combinations result in modest lowering of all lipid parameters, whereas LPV/r was asso-

ciated with a slight rise in total cholesterol, and a 31 percent jump in triglycerides, although fasting LDL was slightly decreased among LPV/r users in this study. The researchers concluded that: “in patients who have experienced virologic failure on other PI-containing [highly active antiretroviral therapy] HAART regimens, a switch to a HAART regimen containing ATV is associated with significantly greater improvements in lipid levels compared to a switch to a HAART regimen containing LPV/r.”

Emtricitabine

Emtricitabine (FTC), a new once-daily NRTI, showed promise in several studies. One such trial was the ALIZE-ANRS 99 study, a 48-week randomized prospective trial comparing FTC, didanosine (ddI), and EFV QD to a continued PI-based regimen in patients with undetectable HIV RNA plasma levels. The study researchers, led by Jean-Michel Molina (Hôpital Saint-Louis, Paris), found that the substitution of the once-daily combination maintained full control of HIV levels in plasma and was well tolerated.

In a second study, a double blind multicenter comparison of FTC QD to stavudine (d4T) BID in treatment-naïve HIV-infected patients, lead author Francois Raffi (CHU de Nantes, France) reported that once-daily FTC produced a higher rate of virologic success at 48 weeks (80 percent versus 62 percent for d4T), and that FTC continued to show “durable and superior virologic efficacy and tolerability” out to 60 weeks of follow-up.

Emtricitabine was also evaluated for its efficacy in patients with HIV and hepatitis B virus (HBV) co-infections. Raffi *et al* conducted three multicenter, 48-week studies to assess the following triple-drug regimens:

- FTC versus d4T (1:1) with ddI plus EFV (571 patients)
- FTC versus 3TC (1:1) with d4T plus EFV or NVP (468 patients)
- FTC plus d4T with either emivirine (an investigational NNRTI) or abacavir (ABC) (564 patients)

They found that “FTC as a component of HAART produced potent suppression of HBV DNA in co-infected patients with HIV RNA suppression.”

South African researchers also found that FTC provided significant efficacy

when included in an antiretroviral regimen given to treatment-naïve patients with high pre-treatment viral loads (>100,000 copies/ml).

Enfuvirtide

Enfuvirtide, also known as T-20, generated a considerable amount of buzz as the first agent in the new class of therapies known as fusion inhibitors. This agent has a novel mechanism of action, blocking gp41-mediated fusion of HIV-1 to host cells.

In an analysis of virological response of T-20 in the TORO 1 and TORO 2 trials, Julio Montaner (University of British Columbia, Vancouver) said that the virologic response to T-20 plus optimized background (OB) therapy is directly related to the activity of the background regimen itself.

A different analysis of the TORO 1 and TORO 2 data by researchers from Stanford University and Roche Pharmaceuticals found the combination of T-20 and an OB regimen increased the time to virological failure and the mean change in HIV-1 viral load and CD4 cell counts compared to the background regimen alone. Enfuvirtide administered to the patients with genotypic sensitivity scores of 1 to 2 or 3 to 4 provides a greater than 2.3-fold predicted benefit in mean overall survival compared with those with GSS scores of 0. When given to patients with baseline CD4 cell counts ≥ 100 cells/mm³, T-20 was predicted to result in increased mean overall survival of 2.4 years, compared with 0.9 years when given to patients with CD4 counts <100 cells/mm³. The researchers found that “the clinical prognosis was more favorable with [T-20] plus OB than with OB alone... [T-20] is expected to provide greater benefit in prognosis among patients in the higher [baseline] CD4 subgroup and those with remaining active antiretroviral therapy options (higher GSS).”

NRTIs: Three’s a crowd

Triple-NRTI therapy suffered some cruel blows, but other drugs fared considerably better in one of several scientific sessions on antiretroviral therapy.

In a 24-week study of an NRTI-sparing regimen combining RTV-boosted LPV and EFV, researchers from the BIKS study reported that the combination reduced HIV RNA levels to <50 copies/mL in 76 percent of treated patients. Virologic success (<400 copies/mL) was achieved in 67 of 72 patients treated (93 percent). The combination of LPV/r and EFV showed a similar efficacy to classic NRTI-based

regimens with “acceptable” tolerance. Most dropouts from the study for safety occurred in the early weeks of the study, and there was only one virologic failure.

In a study comparing an NRTI-sparing regimen of indinavir (IDV), RTV, and EFV with the same three drugs plus an NRTI (d4T), Michael Stek Jr. (Merck & Co.) reported that at 48 weeks the NRTI-sparing regimen was similar in both safety and efficacy to the NRTI-containing regimen.

But in a presentation that raised some eyebrows among conference delegates, Roy M. Gulick (Weill Medical College, Cornell University, New York) reported on results of the ACTG 5095 trial, comparing three PI-sparing antiretroviral regimens for the initial treatment of HIV. The trial compared Trizivir (ZDV/3TC/ABC) with Combivir (ZDV/3TC) plus EFV and with Trizivir plus EFV in more than 1,100 patients. The study was halted early due to the fact that the rates and time to failure among patients on the triple-NRTI arm was “demonstrably inferior to each of the two EFV-containing regimens,” Gulick said. Patients in the triple-NRTI arm were offered the chance to continue in the study with either of the two EFV-containing regimens.

In another study presented later in the same session, a triple-NRTI combination of ABC, 3TC, plus TDF also failed to make the grade, according to Charles Farthing (AIDS Healthcare Foundation, Los Angeles). He reported that of 19 patients in the study, 11 (58 percent) had virologic failures, and only five had a virologic response. “These preliminary results raise concerns about potency and efficacy of the once-daily combination in naïve patients. Until further data are available, this regimen, especially once-daily, should be avoided,” Farthing concluded.

Martin Markowitz (Aaron Diamond AIDS Research Center, New York) reported that a combination of Trizivir and EFV for induction in antiretroviral-naïve patients treated for 48 weeks produced viral RNA of <50 copies/mL in 61 percent of patients—90 percent in an intent-to-treat (ITT) analysis. There was a somewhat high dropout rate due to adverse events, however, with about 30 percent of patients quitting. Nonetheless, Markowitz said, the combination of Trizivir and EFV is a “compact and potent regimen that can effectively reduce viral RNA in patients with broad ranges of viral RNA and CD4 cell counts.”

Salvage therapy

New drugs in existing therapeutic classes and emerging drugs in new categories offer promise in the treatment of patients with multi-drug-resistant HIV infection or advanced, late-stage infection, according to speakers at a forum on salvage therapy regimens.

Each stage of virologic failure may require a different intervention strategy, said Schlomo Staszewski (J.W. Goethe University, Frankfurt am Main, Germany):

- Stage 1 – Viral replication without resistance: the physician can evaluate for low drug exposure, promote compliance with prescribed regimens, and boost PIs for higher dose levels.
- Stage 2 – Moderate resistance: This stage may be successfully managed with a resistance-based switch to avoid development of further mutations.
- Stage 3 – Significant level of resistance but still some treatment options available. Here, the current regimen may be continued as long as CD4 levels remain stable above nadir, or the patient may be switched to another regimen, if feasible, to maintain viral suppression.
- Stage 4 – No remaining treatment options, the current regimen can be continued as long as CD4 levels are stable, or the patient may qualify for an experimental regimen with a fusion inhibitor (T-20) with optimized background, or to a mega-drug regimen such as GIGHAART or MEGAHAART.

Robert L. Murphy (Northwestern University Medical School, Chicago) briefly discussed new and emerging antiretroviral agents as salvage therapy options, including T-20, ATV, and FTC.

“Atazanavir was developed for initial therapy but with a little RTV boosting it looks like it’s highly effective for salvage therapy as well,” Murphy said. He pointed to ATV’s potency, once-daily dosing, unique resistance profile, and good lipid profile versus a standard PI regimen (RTV-boosted LPV). He also touched on new drugs in development, including DPC 817 (an NNRTI), and T-1249 (a fusion inhibitor that is a follow-up to T-20). One old drug—MIV-310 (FLT) a thymidine analog that was abandoned due to toxicity—is being looked at in lower doses in new studies, which suggest that it may be effective in treating multi-drug resistant strains, at least *in vitro*, Murphy said.

Among emerging drug classes, Murphy mentioned integrase inhibitors, d-amino acid peptides, and TAT-TAR antagonists.

In a study comparing unboosted ATV with LPV/r in combination with two NRTIs in PI-experienced patients in virological failure, Calvin Cohen (Community Research Initiative of New England, Boston) reported that there were “robust increases” in CD4 cell counts and significant declines in HIV RNA in both treatment groups. Although the non-boosted ATV showed slightly less antiviral efficacy than LPV/r, ATV had a significantly more favorable lipid profile. He said that ATV might be a good therapeutic option for antiretroviral-experienced patients in whom lipid management is a priority. In a discussion at the end of the forum, he also suggested that boosting ATV with 100 mg RTV could make ATV-based regimens even more effective.

That last conclusion seems to have been borne out by a study pitting ATV/r or ATV in combination with SQV against LPV/r in combination with TDF, reported by Bonaventura Clotet (Retrovirology Laboratory and HIV Unit, Hospital Universitari Germans Trias I Pujol, Barcelona). In an interim analysis of the BMS AI424-045 study, the researchers found that the ATV/r regimen was comparable to LPV/r at viral load reduction. In contrast, the ATV-SQV combination was less effective than either of the two boosted regimens. ATV with either RTV or SQV was safe and well tolerated, and had a better lipid profile than LPV/r. ATV was associated with elevated bilirubin levels and a small number of cases of clinical jaundice, but these were not serious and did not lead to patient dropout. The LPV/r combination was associated with more frequent diarrhea.

The session also contained results of a subgroup analysis of the CPCRA 064 trial, which examined whether structured treatment interruption could benefit patients with advanced treatment failure. The analysis confirmed earlier results suggesting that treatment interruption does not confer any immunological or virological benefit, said Jody Lawrence (University of California, San Francisco).

Satellite symposia: New and up-and-coming PIs

“HAART in the new century”

In a satellite symposium sponsored by Bristol-Myers Squibb, which markets several anti-HIV agents (specifically ATV, EFV, d4T, and ddI), Giovanni di Peri (University of Torino, Turin, Italy) said that ATV is attractive as an antiretroviral because of its once-daily dosing, low pill burden, lack of cross resistance in PI-naïve patients, and favorable lipid profile. The availability of a once-daily PI may help to address non-compliance issues centered on regimen complexity and high pill burden.

Noting that patients must take 90 to 95 percent of their prescribed antiretroviral doses daily to optimize virologic suppression, di Peri suggested that anything that can be done to reduce pill burden and simplify dosing regimens would likely enhance compliance.

Kathleen Squires (University of Southern California, Los Angeles) described the use of ATV in PI-naïve patients, noting that the drug appears to be lipid neutral: “There is no negative impact in important metabolic parameters, including cholesterol, triglycerides, insulin, and glucose,” according to Squires. In a study comparing ATV with EFV, both in combination with ZDV and 3TC, the drugs were comparably effective and had similar lipid profiles. ATV was generally safe and well tolerated, with adverse events similar to those seen with EFV.

A similar experience was seen by Clotet, who reported that in a study of ATV in treatment-experienced patients who had failed at least two antiretroviral regimens (BMS-045), RTV-boosted ATV was comparably effective to RTV-boosted LPV, with undetectable viral loads (<400 copies/mL) occurring in 64 percent and 62 percent of patients, respectively. Both regimens were well tolerated, although diarrhea occurred three times more frequently with LPV/r than with ATV/r.

“What do we need a new PI for, anyway?” asked Cohen, tongue in cheek. He said that ATV “addresses and improves on several issues we’re seeing in the current standard of care.” The drug has established efficacy, a favorable lipid profile (in which lipid decreases are significant and sustained at more than two years), and a distinct resistance profile. Cohen noted that in treatment-naïve patients resistance is infrequent, and when it does occur, it has always been the 150L mutation, which does not confer cross-resistance to other PIs and has been associated with increased *in vitro* sensitivity to other PIs.

Cohen said that ATV has similar efficacy to standard-of-care regimens containing EFV in treatment-naïve patients, as demonstrated by similar mean declines in baseline HIV RNA levels at 48 weeks. In addition, ATV-containing regimens were associated with significantly greater increases in CD4 cell counts, he said. ATV-based therapy also maintained or improved virologic response in treatment-experienced patients switched. With RTV boosting at the 300 mg QD dosing level, ATV-based regimens were comparably efficacious to standard-of-care regimens containing LPV/r in patients with prior PI failure.

“New standards in HIV therapy”

A satellite symposium sponsored by Boehringer Ingelheim, which markets nevirapine (NVP) and is developing the investigational PI tipranavir (TPV), was marked as much by an unplanned event as by the scheduled program: the session was briefly interrupted by a handful of activists from ACT UP Paris, who took the stage to demand patient access to TPV. The protestors called for immediate access to TPV for patients with severe treatment failure, and relaxation of entry criteria to a planned compassionate-use program. Acting as spokesman for Boehringer Ingelheim, Douglas Mayers of the company’s international virologic therapies division, noted that TPV is in short supply, and that some of the drug was pulled from pivotal clinical trials in order to ensure adequate amounts for the compassionate-use program.

The clinical portion of the program focused on adverse events and new insights into therapy.

Although anti-HIV therapy is likely to result in an excess risk of coronary heart disease (CHD), the benefits of antiretroviral therapy clearly outweigh any possible risk, according to Jens D. Lundgren (Hvidovre University Hospital, Copenhagen). He noted, however, that most evidence to date for possible cardiovascular effects of antiretroviral therapies come from cohort studies, which by definition cannot define causality. Lundgren recommended cardiovascular risk assessment for all patients on antiretroviral therapy, both as a means of identifying those at risk and as a teaching tool. He said that a reasonable strategy for medical intervention might be when an individual’s 10-year risk for CHD is



By general consensus, the highlight of the 2nd IAS Conference on HIV Pathogenesis and Treatment was the extraordinary plenary session held on Bastille Day, July 14, 2003. The session—which took place as tanks rumbled, bands blared, and troops paraded down the nearby Champs d’Elysee in honor of France’s *Fête Nationale*—was co-chaired by Robert C. Gallo and Luc Montagnier, credited as co-discoverers of HIV as the pathogenic agent underlying AIDS. Both gave brief (and uninspired) remarks regarding the past, present, and future of HIV/AIDS research and treatment.

Gallo spoke of three now-absurd notions that prevailed in the medical community in the 1970s:

- that viruses did not cause cancer,
- that retroviruses did not exist, and
- that epidemics caused by microbial infections were no longer a serious threat to world health.

He noted that in the 1970s, US medical schools closed their Departments of Microbiology, and that the then-named US Centers for Disease Control (CDC) was “threatened with reduction or closure” in the then-common belief that major infectious diseases had been relegated to the medical history books.

Later in the program, Montagnier called for efforts to ensure access to medications in the developing world, as well as more coordinated surveillance, and, it goes without saying, research into new therapies and preventive vaccines.

“The greatest health crisis in human history”

It was clear to all present, however, that the star attraction of the session and indeed the highlight of the conference was the speech by Nelson Mandela, a champion of human rights, freedom, and dignity, and a tireless advocate for access to critical health services for all people in all nations.

The former President of South Africa and winner of the Nobel Peace Prize in 1993, looked frail as he was helped to the podium, leaning on a cane and on the arms of aides. Yet, as he spoke, his strength and passion were as great as they have ever been.

Mandela cited United Nations estimates that:

- About 45 million people are living with HIV
- 10,000 people die every day from AIDS-related causes
- 26 million people (95 percent of them in the developing world) have already died from the complications of AIDS

“These numbers are staggering—in fact incomprehensible,” Mandela said. “By all accounts we are dealing with the greatest health crisis in human history. By all measures we have failed in our quest to contain and treat this scourge. And the disparity between its impact in the developed world and the developing world is a shocking reality that we cannot hide from.”

Noting the devastating toll that AIDS has taken on impoverished nations, Mandela challenged the audience of scientists, clinicians, policy-makers and activists to “act for the sake of the world.”

“Why have we failed? What are we going to do? In the end it boils down to one inescapable fact—we have failed to translate our scientific progress into action where it is most needed—in the communities of the developing world, the poorest regions of the globe. This is a global injustice [that] cannot be tolerated. It is a travesty of human rights on a global scale.”

He called for dramatic expansion of prevention programs and access to treatment throughout the developing world. Noting the early promise of the Global Fund to Fight AIDS, Tuberculosis, and Malaria, Mandela mentioned the US\$1 billion the United States set aside for the fund. “We would like it to be more, but we believe that this is a floor from which to start,” Mandela commented. He also praised French President Jacques Chirac for committing France to a tripling of its investment in the fund, and called on the leaders of other European nations to substantially increase funding.

Mandela did not spare criticism for the leaders of nations at the center of the pandemic: “With regard to delivering effective HIV/AIDS responses on the ground, we must sadly point out that many of the countries that are most highly affected by HIV/AIDS have not done nearly enough to fight the epidemic—especially in sub-Saharan Africa. This is completely unacceptable. It too is a travesty of human rights. Yes, these countries are poor, but we know they have the capacity to do more—much more.”

However, Mandela did single out Botswana, Senegal, and Uganda as exemplars. “These are countries that have demonstrated leadership from the very top and have made remarkable progress in both prevention and care,” he said, noting that in Botswana, a relative latecomer to active intervention, more than 6,000 people are now receiving antiretroviral therapy.

He ended his remarks with an expression of “our very great concern about India, China, and Russia, which have rapidly evolving epidemics. If they follow the trends of Africa, the results will be calamitous, not only for the countries concerned, but for the whole world.”

20 years in 20 minutes...

The other featured speaker at the Bastille Day plenary session was Anthony Fauci, Director of the US National Institute of Allergy and Infectious Diseases (NIAID) and a pioneer in HIV/AIDS research. In a talk illustrated with images from the medical literature and popular culture, Fauci spoke of the earliest days of the epidemic, beginning with “the realization back in the summer of 1981 that we were dealing with a new disease, as shown by [the] original Morbidity and Mortality Weekly reports from the CDC. Over the ensuing months, it became very clear that we were dealing with something much more than just handfuls of gay men in New York and in San Francisco, as the epidemiology began to unfold involving hemophiliacs, infants, [and] sexual partners of infected individuals. And, in fact, what we see now in the year 2003, is most extraordinary and in many cases and in many senses, tragic.”

Fauci reviewed the rapid scientific progress in the field, including:

- The first inklings that the pathogen might be a retrovirus.
- The development of an HIV antibody test, allowing protection of the blood supply and early identification of asymptomatic individuals.
- The determination of the molecular biology of HIV, including the molecular cloning of the virus, determination of the nucleotide sequence, and molecular biology and molecular epidemiology pointing to the origins of the pathogen.
- Discovery of HIV/AIDS pathogenesis, including the identification of the CD4 receptor.
- The development and evolution of antiretroviral therapies, from monotherapy with azidothymidine (AZT) to today’s complex multi-drug antiretroviral regimens.
- The evolution of prevention as a science.

Challenges for the foreseeable future, Fauci said, include the development of an effective vaccine, based not solely on traditional antibody strategies, but on a combination of antibody-based and CD8-based approaches. “A safe and effective vaccine is absolutely critical and it is probably the most important and difficult scientific challenge in AIDS research,” he said.

Fauci also acknowledged the role that activists played, especially in the early years of the epidemic, in advancing the cause of HIV/AIDS research and treatment. “It was activism



that demanded that those who were infected with HIV, or who were at risk of infection, play a role in determining the nature of clinical trials and the access to drugs which could only be accessed through clinical trials, and it was more than a decade and a half ago that we decided to address that problem. We brought the activist to the table, and I can tell you from personal experience how the clinical trials process and the process of access is much the better for it," he said.

"A powerful and crafty scourge"

In remarks at the ceremony marking the official end of the IAS Conference and a parallel support conference for the Global Fund to Fight AIDS, Tuberculosis, and Malaria held July 16, 2003, France's President Chirac said that "AIDS is a powerful and crafty scourge which is shaking our societies to their core; powerfully spreading everywhere, with nothing, so far, able to stop it, craftily appearing where it is not expected and showing a remarkable ability to fight back when attacked."

Chirac, whose speech was briefly interrupted by demonstrators demanding increased funding for treatment, spoke of the devastating social and economic impacts of the HIV/AIDS pandemic, and praised the efforts of the medical communities, non-governmental organizations, and support groups who serve on the front lines of the crisis.

He called for increased coordinated global efforts to support research and treatment. "I wish, today, to issue a solemn appeal: an appeal to governments of donor countries all over the world to show more generosity, despite budgetary difficulties. This is not an act of charity; it is an act of shared responsibility in standing up to a global scourge. An appeal to the developing and transition countries to set the fight against AIDS as a national priority. An appeal to businesses, well-represented here, to do even more."

Chirac also warned against complacency: "In the developed countries the advent of multiple therapies and a certain weariness of complying with the discipline of prevention have prompted a renewed trend toward risky behavior. The critical importance of responsibility—both collective and individual—in dealing with this disease cannot be overstated." ■

—Neil Osterweil

greater than 10 percent. Interventions may include diet, exercise, and smoking cessation.

Joep MA Lange, representing the International Antiviral Therapy Evaluation Center (IATEC), reported on a study comparing antiretroviral regimens based on either NVP (QD or BID) or EFV or a combination (the 2NN study). The study showed that the dual NNRTI regimen was significantly less effective than either of the single NNRTI regimens, primarily due to toxicity-related dropouts. The study found that antiretroviral regimens based on either NVP or EFV had comparable immunological and virological efficacy. In terms of safety, there was a trend toward more liver enzyme elevation and skin rashes in NVP-treated patients, with EFV accounting for significantly more psychiatric and central nervous system (CNS) adverse events. Lange said that co-administration of NVP and EFV is not recommended due to safety concerns.

Changes in serum lipid profiles associated with PI-based antiretroviral regimens are greater than can be explained by the "return-to-normal" phenomenon associated with effective HIV suppression, according to Mark van der Valk (University of Amsterdam, The Netherlands). NNRTI-based regimens, in contrast, are associated with significant rises in HDL, and smaller increases in LDL and triglycerides, van der Valk said. He suggested that although antiviral efficacy is the primary concern, it might be appropriate to initiate or switch to NNRTI-based regimens in the treatment of patients with pre-existing cardiovascular risk factors.

Hepatotoxicity of antiretroviral regimens is a serious issue, but it may be confounded by issues such as co-infection with hepatitis B or C, use of other drugs, alcohol, or even over-the-counter herbal preparations, said Marion Peters (University of California, San Francisco). Peters said the majority of hepatotoxicity cases are mild and asymptomatic. "HIV patients have other reasons for abnormal liver tests," Peters said.

The session was concluded by Daniel R. Kuritzkes (Harvard Medical School and Brigham and Women's Hospital, Boston), who discussed current experience with RTV-boosted TPV. The drug is a non-peptide inhibitor of HIV-1 protease that has shown activity against viral isolates resistant to currently approved PI. In preliminary studies of patients failing a first PI, TPV/r achieved a median reduction in

viral load comparable to RTV-boosted SQV. More recently, the BI 1182.52 study looked at TPV/r in three dose combinations in patients infected with multiple-PI-resistant HIV. At two weeks, median change in viral load was $-0.9 \log_{10}$ copies/mL for a dose of TPV 500 mg plus RTV 100 mg; $-1.0 \log_{10}$ copies/mL for a 500 mg/200 mg dose; and $-1.2 \log_{10}$ copies/mL for a 750 mg/200 mg dose. Grade 3 or 4 adverse events trended toward more frequent with the higher dose ranges, and there was substantial loss of virologic response in patients with three or more mutations. Based on the results, Phase III trials using the TPV 500 mg plus RTV 200 mg dose are currently underway.

"Long-term management of HIV"

Choosing antiretroviral agents for initial therapy based on the assumption of ultimate failure may be a mistake, because long-term suppression of HIV without significant drug resistance is an attainable goal, according to Joel E. Gallant (Johns Hopkins University School of Medicine, Baltimore), speaking at this Abbot Laboratories-sponsored satellite symposium. Abbott Laboratories markets RTV and LPV.

With the advent of more potent antiretroviral therapy, the focus is turning from management of inevitable resistance to selection of therapeutic regimens that prevent failure in the first place, Gallant said. Although cross-trial comparisons are fraught with difficulties, a meta-analysis comparing antiretroviral trials suggested that newer regimens using more potent agents in more convenient and tolerable regimens can result in a greater number of participants achieving virologic suppression compared with earlier trials, Gallant noted.

Gallant said that the pendulum is swinging back toward the concept of "hit early and hit hard" to achieve maximum viral suppression at the earliest opportunity. He cited results from Study 720 of LPV/r indicating that a high percentage of patients had undetectable viral loads at four years. In a second trial (Study 863), there were no primary or active site mutations in HIV among 51 patients with a known genotype who received RTV-boosted LPV for up to 96 weeks; in contrast, 44 of 96 patients (46 percent) of those receiving nelfinavir (NLF) had mutations.

Kuritzkes discussed the concept of "viral fitness"—the ability of a virus to

replicate in a given environment, which is distinct from—but interrelated with—viral replication capacity and virulence. The overall potency of a regimen is important for determining rates of resistance, he explained, but it appears the combination of a genetic barrier to high-level resistance seen with PIs and the pharmacologic barriers thrown up by RTV boosting make patients on RTV-boosted PI regimens less likely to fail therapy than those on other antiretroviral regimens.

Keeping patients on antiretroviral regimens after they begin to experience significant side effects is a major challenge to continued success, said José R. Arribas (La Paz Hospital, Madrid). Arribas emphasized that survival benefits of antiretroviral therapy outweigh the modest increase in cardiovascular risk seen in some studies.

When it comes to antiretroviral therapy, more drugs may not necessarily be better, noted Mark Nelson (Chelsea and Westminster Hospital, London). He pointed to the so-called Treasure Coast cohort of 15 patients, 11 with prior PI exposure, who were switched to monotherapy with LPV/r because of either toxicity or virologic failure. Of this cohort, 12 patients had a viral load of less than 400 copies/mL, and nine of the 12 achieved a viral load of <50 copies/mL with a median of 34 weeks therapy.

The epidemiology of resistance

Among the most important clinical news stories to come out of the meeting was the release of data from the CATCH (Combined Analysis of resistance Transmission over time of Chronically and acute infected HIV patients in Europe) study.

The CATCH study looked at reverse transcriptase (RT) and protease sequence information from 1,633 newly diagnosed, recently and chronically infected patients from 17 European countries. The researchers looked at the prevalence of resistance from 1997 to 2002.

The researchers found that prevalence of primary drug resistance among people in Europe who are newly diagnosed with HIV is about 10 percent. The prevalence of resistance among infections with viral subtype B—the type most prevalent in Europe during the study period of 1996 to 2002—was about four times higher than in non-B subtypes, which are more commonly found in Africa, noted David van de Vijver

(University Medical Center Utrecht, The Netherlands), who presented the study. Transmission of drug-resistant non-type-B strains in Europe is also occurring, he noted.

Speaking at a press briefing before the session, Lange said that the study shows that when it comes to new infections with drug-resistant HIV strains, “we’re never going to be able to prevent it from happening.” Lange went on to say that, “the idea that we should not give HAART to people in developing countries to prevent the emergence of resistance is ridiculous. Nobody is asking us to stop giving drugs to patients in the United States and Europe.”

Overall, the researchers found that the following prevalence of any major resistance-related mutation during the study period was 11.6 percent. Resistance to at least one NRTI was 9.2 percent, while infections resistant to any NNRTI was 2.7 percent. Resistance to a PI was detected in 2.3 percent of all infections, and resistance to at least two antiretroviral drug classes was 1.8 percent.

The CATCH study researchers recommend that because of the high prevalence of resistance, baseline sequencing should be considered in newly diagnosed patients who became infected in Europe.

“The inevitable consequence of failure”

Other presentations at the IAS Conference focused on the mechanisms of resistance. According to Kuritzkes, the prevalence of infection with HIV-1 strains that are resistant to at least two classes of drugs now exceeds 1 percent and is creeping up toward 2 percent.

Calling drug resistance “the inevitable consequence of our failure to fully suppress the virus,” Kurtzkes noted that the benefits of continued drug therapy on morbidity and mortality of infection persist despite the emergence of drug resistance, and that the benefits continue until the highest levels of viral drug resistance are reached. He said that resistance testing is recommended in acute or recent HIV infections, before initiation of antiretroviral therapy in established HIV infections, following first regimen or multiple regimen failure, and in pregnancy if the mother has detectable plasma levels of HIV-1 RNA.

Boehringer Ingelheim’s Mayers discussed results from the BI 1182.52 study looking at the inhibitory quotient (IQ) of RTV-boosted TPV. The IQ, which is the ratio of trough plasma concentration of a drug to the protein-adjusted viral IC₅₀, is a

good measure of the potential therapeutic margin of antiretroviral therapies. In a trial comparing three doses of TPV/r twice daily in patients with triple antiretroviral drug class experience, the IQ of TPV/r compared favorably with IQ data for other PIs given to treatment-naïve patients. This finding “suggests that TPV/r may provide antiviral activity in the majority of highly treatment-experienced HIV-positive patients,” he said.

In other news, researchers from the ERA trial comparing phenotypic resistance testing added to genotypic resistance versus genotypic testing alone, found that testers could probably save money by skipping the phenotypic part. The trial result showed no significant differences in terms of virologic and immunologic response between therapy guided by genotype testing alone or genotype-plus-phenotype. The researchers also found that access to phenotypic resistance testing did not significantly alter the composition of new drug regimens.

Means for coping with drug resistance and adverse events in HIV-1 were also the subject of a separate oral abstracts session on resistance and pharmacology.

Anders Malmsten (Uppsala University, Sweden) reported on a simple assay that combines viral load and phenotypic drug susceptibility testing by measuring virion-associated reverse transcriptase activity. The assay, which can detect activity down to a few thousand particles, correlates well with a standard, commercially available viral load assay, Malmsten said. He noted that the assay might be helpful for managing drug therapy in regions where healthcare resources are limited.

Such an assay could be of benefit in countries such as Cameroon, where a study monitoring the prevalence of antiretroviral-resistant HIV-1 strains in patients receiving either antiretroviral therapy or single-dose NVP to prevent mother-to-child HIV transmission found a high rate of mutations in treated patients. In an analysis of PCR-amplified samples, researchers from Hopital du Jour HCY, BP81 in Yaoundé, Cameroon, and other African colleagues found resistance mutations in 19 of 34 samples, including high-level resistance to three antiretroviral classes in some patients. They concluded that antiretroviral therapy guidelines and biological monitoring must be implemented in Africa to prevent rapid selection of resistance.

Circumstances are considerably different in France, where a study of genotypic drug resistance mutations in 2001 to 2002 showed no significant changes in frequency of resistant virus from 1996 to 2000. The researchers—from ANRS and the PRIM, INTERPRIM, and PRIMSTOP study groups—did find an increasing trend in the frequency of non-B subtype strains, from 19 percent in 1999 to 2000 to 24 percent in 2001 to 2002.

Another French study looked at the efficacy of an RTV-boosted amprenavir (APV) combination in PI-experienced (but APV-naïve) patients in virological failure and found that treatment with APV 600 mg plus RTV 100 mg led to a median viral load decrease of -1.32 log by week 12, and -1.46 by week 24.

In other therapeutic news...

In a meta-analysis of published clinical trials, researchers from France and Switzerland determined that in NRTI-experienced patients with advanced infections, PI-based triple regimens appear to be superior to regimens based on the NNRTIs NVP or DLV.

In a study that spanned the globe from Switzerland, to Thailand, to Australia, researchers found that in a planned treatment interruption strategy of one week on, one week off, 19 of 36 (53 percent) of evaluable patients had two successive HIV RNA concentrations above 500 copies/mL at the end of the week off therapy, and were classified as virologic failures. This arm of the study was halted.

Better results were seen in a study of the use of antiretroviral prophylaxis to reduce the risk of HIV transmission from mother to child during breast-feeding (the SIMBA study). Joseph Vyankandondera (Centre Hospitalier de Kigali, Kigali, Rwanda) reported that in a trial of 397 infants of HIV-positive women in Uganda and Rwanda, a combination of antiretroviral prophylaxis (with either NVP or 3TC) and counseling to the mothers on breastfeeding practices kept late postnatal transmission of infection (out to six months) to 1.1 percent of infants receiving 3TC, and just 0.6 percent of those receiving NVP.

A rather different study out of the Hospital La Paz in Madrid looked at the use of ambulatory EEG and therapeutic drug monitoring of patients on EFV who experience sleep abnormalities. The researchers found a dose-related correlation,

with sleep problems tending to occur at plasma drug levels of about 4 ng/l or higher. They found that dose adjustment appeared to resolve or ameliorate problems in most patients.

Toxicity mechanisms of ART

When it comes to mechanisms of toxicity of antiretroviral drugs, there is plenty of blame to go around, suggested researchers presenting data at an oral abstract session.

Protease inhibitors and NRTIs can exert negative effects on various organ systems, including the liver, muscle, pancreas, bone and CNS, said Jacqueline Capeau (Hôpital Ste. Antoine, Paris). She noted that lipodystrophy and metabolic changes might be linked to hepatotoxicity and alteration of glucose metabolism mechanisms. Drug effects may also be influenced by co-infection with hepatitis B virus or hepatitis C virus.

Morris Schambelan (University of California, San Francisco) discussed possible approaches to treating lipodystrophy and metabolic changes using thiazolidinediones. He cited two studies looking at the use of rosiglitazone 8 mg/day (one for 12 weeks and the other for 24 weeks), in which use of the drugs significantly resulted in improved insulin resistance profiles, decreased visceral adipose tissue, and increased subcutaneous abdominal tissue. He also briefly described pilot studies using recombinant humanized leptin to treat acquired generalized lipodystrophy. In one case, administration of leptin to a woman with a massively steatotic liver caused a loss of about 2 kg of intrahepatic fat.

In an *in vitro* study, Capeau *et al* looked at the effects of five NRTIs on adipose cell differentiation, insulin sensitivity, and cell survival. They found that three of the NRTIs tested (ABC, ddI, and 3TC) did not modify adipose cell functions. In contrast, d4T and ZDV decreased cell lipid content and mildly increased apoptosis and ZDV also induced insulin resistance. They conclude that the thymidine analogues, but not the other NRTIs, exerted adverse effects in cultured adipocytes.

Researchers from the Laboratory for AIDS Virus Research at Weill Medical College of Cornell University in New York looked at factors that might affect bone formation or retention in people with HIV who are both treatment-naïve and antiretroviral-experienced. They com-

pared the expression and biological activity of the primary cytokine responsible for osteoclast differentiation and bone resorption, receptor activator of nuclear factor kB ligand (RANKL). They found upregulation of the cytokine, and that pharmacologic levels of RTV and SQV, which have linked to osteopenia alter RANKL activity. In contrast, IDV had no effect.

Ulrich Walker *et al* (Medizinische Universitätsklinik, Freiburg, Germany) investigated whether mitochondrial DNA is depleted in the livers of people receiving NRTIs. They found that current treatment with ddI, d4T, or ddC is associated with decreased mitochondrial DNA in the liver without regard to liver cirrhosis or inflammation.

Mitochondrial toxicity was also seen in a study by researchers from Hôpital Avicenne, Université Paris-Nord, Bobigny, France, who looked at patients with long-term exposure to NRTIs. They found that chronic exposure to NRTIs produced a loss of responsiveness of capsaicin-sensitive nociceptors, suggesting that the drugs may produce alterations in small peripheral nerve fibers that may be linked to mitochondrial toxicity.

FRAM study: The skinny on lipodystrophy

The term “fat redistribution syndrome” should be retired, because lipoatrophy and lipohypertrophy that occur in people who are HIV positive may not be directly related to one another, even when they occur simultaneously in the same person, according to researchers from the NIH-sponsored Fat Redistribution and Metabolic Change in HIV Study (FRAM). They reported findings of the fat redistribution and metabolic change portions of the study at an institutional symposium.

“Forget about ‘fat redistribution,’ because it ain’t moving,” said Charles M. van der Horst (University of North Carolina, Chapel Hill).

The FRAM study was a cross-sectional population-based study looking at lipid, metabolic, and adipose tissue changes in people who are HIV positive and in controls (HIV-negative individuals enrolled in the CARDIA study). The researchers had “no a priori assumption of what constitutes the HIV lipodystrophy syndrome,” said co-principal investigator Carl Grunfeld (University of California, San Francisco). *Continued on page 227*



A B S T R A C T S



Editor's Note: Following are selected abstracts from the 2nd IAS Conference on HIV Pathogenesis and Treatment, held July 13-16, 2003, in Paris.

HIV Drug Resistance

Abstract 9: The inhibitory quotient (IQ) of tipranavir/ritonavir (TPV/r) in triple-class-experienced HIV-positive patients: Results from BI 1182.52

DL Mayers *et al.*

PURPOSE: A high IQ—the ratio of trough plasma drug concentration to the protein-adjusted viral IC_{50} —is a useful indicator of the potential therapeutic margin of antiretroviral (ARV) drugs. The IQ data for most ARV drugs was obtained in studies of treatment-naïve patients. TPV is a non-peptidic protease inhibitor (NPI) that has demonstrated sustained viral load (VL) response during up to 80 weeks of treatment in multiple-protease inhibitor (PI)-experienced patients. The BI 1182.52 phase II study allowed evaluation of the IQ breakpoint for successful viral suppression using TPV in highly treatment-experienced (HTE) patients. **METHODS:** BI 1182.52 was an international, randomized, double-blinded trial of three doses (500 mg/100 mg; 500 mg/200 mg; and 750 mg/200 mg) of TPV/r given BID in HIV-positive patients. Patients were triple-class-experienced, and had detectable plasma virus on their >second PI-based regimen. IQ was calculated using the trough plasma TPV concentration at 14 days after starting TPV/r, divided by the protein-adjusted viral IC_{50} . The protein adjustment factor was 3.75. TPV IQ was related to the change in VL during two weeks of functional monotherapy with TPV/r in these HTE patients. **RESULTS:** 216 HIV-positive patients with a median baseline VL of 4.5 \log_{10} copies/ml and CD4 cell counts of 153 cells/mm³ were enrolled. 157 patients from all three [of the] study arms were included in the IQ analysis. The median VL responses after two weeks of functional TPV/r monotherapy for IQs <5, >5-25, >25-50, >50-100, >100-150 and >150 were -0.19, -0.35, -0.82, -1.31, -0.96, and -1.23 respectively. This result suggests that there is an apparent IQ breakpoint of roughly 50 in HTE patients below which there is a decrease in antiviral response. 67 percent of patients in this study reached this IQ threshold >50. **CONCLUSION:** The IQ of TPV observed in this trial of HTE triple-class-experienced patients compares favorably

to IQ data for other PIs obtained from treatment-naïve patients. This high IQ, coupled with the need for multiple protease gene mutations in most HIV isolates that show decreased susceptibility to TPV, suggests that TPV/r may provide antiviral activity in the majority of HTE HIV-positive patients.

Abstract 10: A randomized controlled trial of phenotypic resistance testing in addition to genotypic resistance testing: The ERA trial

C Loveday *et al.*

BACKGROUND: Although clinical guidelines recommend the routine use of HIV drug resistance testing, they are not prescriptive on the choice between genotypic and phenotypic testing. We report on the clinical utility of phenotypic resistance testing in addition to genotypic resistance testing in patients with limited therapeutic options. **METHODS:** In the ERA (Evaluation of Resistance Assays) trial, patients in whom therapy was failing were randomized to one of two parts depending on whether the clinician considered that a resistance test was essential for selecting the new regimen. In Part B (test was considered essential), all subjects had access to genotypic testing with rules-based interpretation (VIRCOGEN) at baseline and during follow-up and were randomized to have or not have access to phenotypic testing (ANTIVIROGRAM prior to the introduction of drug-specific cutoffs). The primary endpoint was change in plasma HIV RNA viral load (VL) between randomization and 12 months by an intent-to-treat analysis. **RESULTS:** 311 patients were enrolled in Part B, of whom 152 were allocated to genotypic testing alone (G arm) and 159 to genotypic plus phenotypic testing (G+P arm). At baseline, mean VL was 4.23 \log_{10} copies/ml, mean CD4 count was 275 cells/mm³, and subjects had previous exposure to a mean of 7.7 antiretroviral drugs. The primary endpoint was evaluable in 283 (91 percent) subjects; the main reason for being missing was non-attendance at the clinic around 12 months. The mean reduction in plasma VL at 12 months was similar in the two arms (G: 1.37 \log_{10} reduction; G+P: 1.28 \log_{10} reduction; difference = 0.08, SE = 0.27, P = 0.77); 35 percent of subjects in the G arm and 27 percent in the G+P arm had a VL of less than 50 copies/ml. There was no appreciable difference between the study arms in

terms of the number of drugs, the number of "active" drugs (as assessed by genotypic resistance) or the individual prescribed drugs following the initial test. **CONCLUSION:** The ERA trial found no clear evidence of added value (in terms of virological response) of phenotypic resistance testing against a background of genotypic resistance testing in patients with limited therapeutic options.

Antiretroviral Therapy

Abstract 36: BIKS Study (lopinavir/ritonavir/efavirenz combination): Complete 24-week results

V Ferré *et al.*

BACKGROUND: Nucleoside reverse transcriptase inhibitors (NRTIs) are associated with significant long-term toxicities and cross-resistance. NRTI-sparing regimens need to be assessed as alternative antiretroviral (ARV) regimens. **METHODS:** The BIKS Study is an ongoing multicenter, open-label, controlled trial to assess the combination of LPV/r (533.3/133.3 mg) BID and EFV 600 mg QD in HIV-infected patients. Patients have to be non-nucleoside reverse transcriptase inhibitor- (NNRTI) naïve and, if PI experienced, have less than five LPV-associated mutations (2001 ANRS algorithm) in the protease gene. **RESULTS:** 86 patients have been enrolled, with the following baseline characteristics: 65 ARV-naïve/21 ARV-experienced (12 PI-naïve), mean CD4 count 307 cells/mm³, mean HIV RNA: 4.84 \log_{10} copies/ml (>5 \log_{10} copies/ml in 42 percent of the patients). After median follow-up of 36 weeks, premature discontinuation occurred in 14 patients, due to CNS side effect (n=3), cutaneous rash (n=3), non-compliance or lost to follow-up (n=3), others (n=5). From baseline to week 24, the mean HIV RNA decrease was -3 \log_{10} copies/ml. Plasma HIV RNA was <400 copies/ml in 92 percent of the patients and <50 copies/ml in 76 percent of the patients at week 24 (on-treatment analysis). The mean increase in CD4 (cells/mm³) was +162 at week 24. On intent-to-treat analysis, 87 percent of the patients had HIV RNA <400 copies/ml at week 24. Viral rebound occurred in four patients: two patients had blips (HIV RNA <400 copies/ml on subsequent control), one was not compliant and one had confirmed virologic failure. Grade 3/4 clinically

relevant adverse events have been noted in 34 patients (40 percent) including CNS symptoms (n=17), diarrhea (n=11), cutaneous rash (n=4). Grade 3/4 hypercholesterolaemia, hypertriglyceridaemia, and asymptomatic hepatic cytolysis have been observed in 29, 13, and three patients, respectively. After an initial increase between baseline and week 4, the median change in fasting triglycerides and total cholesterol at week 24 was +0.88 and +0.62 g/l, respectively. Median increase in LDL/HDL ratio was +0.27 at week 24. **CONCLUSION:** The dual combination of LPV/r-EFV shows a similar immunovirological efficacy to NRTI-based ARV regimen with an acceptable tolerability. Durability of antiviral effect will be assessed at week 48 of follow-up.

Abstract 38: A randomized, double-blind, multicenter comparison of emtricitabine QD to stavudine QD in treatment-naïve HIV-infected patients

F Raffi et al.

BACKGROUND: Emtricitabine (FTC) is a new once daily (QD) NRTI in development with potent activity against hepatitis B virus (HBV) and HIV. Stavudine (d4T) is a frequently used nucleoside reverse transcriptase inhibitor (NRTI) for the treatment of HIV infection. **METHODS:** Antiretroviral-naïve patients with screening plasma HIV-1 RNA (VL) >5,000 copies/ml were randomized in a 1:1 ratio to 200 mg FTC QD or d4T BID at standard doses. All patients also received open-label didanosine (ddI) QD and efavirenz (EFV) QD and were evaluated at baseline (BL), every four weeks to week 48 and then every 12 weeks. Virologic failure (VF) was defined as never achieving VL <400 copies/ml, or two consecutive visits >400 copies/ml after achieving <400 copies/ml. Efficacy failure (EF) was defined as VF, new CDC class C progression event, or loss to follow-up. Tolerability failure (TF) was defined as permanent discontinuation of blinded study medication due to AE. The Kaplan-Meier (KM) probability of failure was compared between treatment arms using a log-rank test. Absolute CD4+ and CD4 percent change from BL were compared between treatment arms at week 60. **RESULTS:** A total of 571 (285 d4T, 286 FTC) patients were enrolled. The median BL VL was 4.9 log₁₀ and the median BL CD4+ was 288 cells/mm³. The majority of patients were male (85 percent) and Caucasian (52 percent). The median duration of follow-up was 60 weeks. BL characteristics were comparable between the two arms. The KM probabilities at week 60 were: VF, 15.3 percent for d4T and 7.4 percent for FTC (P=0.001); EF, 22.0 percent for d4T and 12.5 percent for FTC (P=0.002); and TF, 16.6 percent for d4T and 7.4 percent for FTC (P=0.003). Mean increase from BL at week 60 in absolute CD4+ was 163 cells/mm³ (FTC) and 137 cells/mm³ (d4T); mean increase from BL in CD4 percent was 8.6 percent (FTC) and 5.1 percent (d4T). The majority of adverse events in both treatment arms were mild or moderate in severity. **CONCLUSION:** Once-daily FTC demonstrated durable and superior virologic efficacy and tolerability through 60 weeks of follow-up compared to twice-daily d4T when used with once-daily ddI and EFV.

Abstract 41: ACTG 5095: A comparative study of three protease inhibitor-sparing antiretroviral regimens for initial treatment of HIV infection

RM Gulick et al.

OBJECTIVE: To compare safety/antiviral activity of three regimens for initial HIV treatment: zidovudine (ZDV)/lamivudine (3TC)/abacavir (ABC); ZDV/3TC efavirenz (EFV); ZDV/3TC/ABC+EFV. **METHODS:** Phase III, randomized, double-blind, placebo-controlled study of treatment-naïve HIV-infected patients with HIV RNA (VL) >400 copies/ml. Patients were randomized 1:1:1 to ZDV/3TC/ABC (fixed dose combination, FDC); ZDV/3TC (FDC) + EFV; or ZDV/3TC/ABC (FDC) + EFV and followed for safety/virologic responses. Virologic failure (VF) was defined as confirmed VL >200 copies/ml >16 weeks after randomization. VL data are presented as intent-to-treat with VF time distributions estimated using Kaplan-Meier methods. Based on a planned interim review, the NIAID Data and Safety Monitoring Board (DSMB) recommended termination of the ZDV/3TC/ABC arm; EFV-containing arms continue blinded treatment. Data are presented as ZDV/3TC/ABC versus pooled EFV-containing arms as recommended by the DSMB. **RESULTS:** 1,147 patients were enrolled: 19 percent women, 60 percent non-white, 11 percent injection drug users. Baseline (BL) mean VL 4.9 log copies/ml (43 percent >100,000 copies/ml) and CD4 238 cells/mm³. BL characteristics were comparable across study arms. After a median 32 wks of follow-up, 93 percent of patients continued on study and 91 percent continued study drugs. Grade 3 and 4 signs/symptoms occurred in 12 percent and 2 percent, with comparable proportions across study arms. 167 patients reached protocol-defined VF: 82 (21 percent) on ZDV/3TC/ABC and 85 (10 percent) on pooled EFV arms. Time to VF was shorter with ZDV/3TC/ABC compared to pooled EFV arms (P<0.001). This was true with BL VL > or <100,000 copies/ml (P<0.001 for each). The proportion of patients with VL <200 copies/ml at week 48 was 74 percent (ZDV/3TC/ABC) versus 89 percent (pooled EFV). In a post-hoc analysis of patients with at least one VL <200 copies/ml, time to VF also was shorter with ZDV/3TC/ABC than in pooled EFV arms (P<0.001). **CONCLUSIONS:** In treatment-naïve patients, ZDV/3TC/ABC was inferior to EFV-containing treatment in terms of rates and time to virologic failure.

Complications of Antiretroviral Therapy

Abstract 52: Risks of cardiovascular disease associated with highly active antiretroviral therapy among persons treated for HIV/AIDS

AR Levy et al.

BACKGROUND: Although abnormal lipid profiles have been reported among persons treated with highly active antiretroviral therapy, the evidence regarding the risk of cardiovascular disease has been equivocal. **OBJECTIVE:** To estimate the association between use of protease inhibitors (PIs), and non-nucleoside reverse transcriptase inhibitors (NNRTIs) and the risk of hospitalization or death from cardiovascular disease, in a population-based cohort. **METHODS:** We included all antiretroviral-naïve HIV-infected persons in British Columbia, Canada, who initiated triple therapy after August 1, 1996. Subjects were followed until March 31, 2001, for a hospitalization record or death certificate with a diagnostic code for myocardial infarction, stable or unstable angina or cardiovascular disease. Information was linked on use of antiretroviral medications and all hospitalizations and deaths in the

cohort using administrative data sources. Use of PIs and NNRTIs were treated as time-dependent covariate in a Cox proportional hazards model, after adjusting for age, sex, baseline CD4 count, year of entry, and prior cardiovascular disease. 90 percent confidence intervals (CI) are presented due to the exploratory nature of these analyses. **RESULTS:** All 2,616 subjects in the cohort received nucleoside reverse transcriptase inhibitors (NRTI); of these, 10 percent received only a nucleoside analogue, 40 percent also received PI, 24 percent also received NNRTI and 26 percent also received both PI and NNRTI. Over a mean of 3.0 years of follow-up, 24 subjects were hospitalized or died with evidence of cardiovascular disease. After adjusting for covariates, the hazard ratio (HR) during periods of exposure to PIs alone was 3.9 (90 percent CI: 1.0, 15.2), during periods with exposure to NNRTIs alone 1.6 (90 percent CI: 0.3, 10.5), and periods with both PI and NNRTI exposure, 2.2 (90 percent CI: 0.5, 9.6). **CONCLUSIONS:** This population-based analysis showed that the risk of cardiovascular disease may be increased when HIV-infected subjects were using PIs. The true association is likely to be stronger than shown here because misclassification of exposure likely reduced the magnitude of the association.

Abstract 54: ACTG 5097s: Impact of efavirenz (EFV) on neuropsychological performance, mood, and sleep behavior in HIV-positive individuals

DB Clifford et al.

OBJECTIVE: To characterize the efavirenz- (EFV) associated neurological symptoms in a controlled treatment initiation protocol. **METHODS:** A5097 is a substudy of A5095, a phase III, randomized, double-blind, active controlled comparison of three antiretroviral regimens: two are EFV-based and one is abacavir- (ABC) based. Neuropsychological performance was summarized as Z-scores of Digit Symbol Substitution and Trailmaking A and B, (NPZ3). Additional measures were Pittsburgh Sleep Quality Index (PSQI), Center for Epidemiologic Studies-Depression (CES-D), Spielberger State-Trait Anxiety Inventory (STAI), EFV serum levels and a symptom list. Measures were made at baseline, week 1, 4, 12, and 24. Changes in test parameters over time were compared in EFV-containing and sparing arms. **RESULTS:** 303 subjects were randomized (200 EFV-treated). Randomization balanced baseline characteristics. No significant differences in changes of NPZ3 between the EFV and EFV-free arms were seen, nor of the proportion of subjects with neurological deficit. The symptom questionnaire detected significant increases in neurological symptoms at week 1 (P<0.001), but not at week 4, 12, or 24. Similarly, the PSQI revealed more "bad dreams" at week 1 in EFV-treated subjects (P=0.038). However, better global PSQI scores and "sleep quality" were found in the EFV-containing arm at week 4. No significant differences in changes in total depressed mood (CES-D) or anxiety (STAI) were noted, nor in the proportion of subjects with clinically significant anxiety or high levels of depressive symptoms. Small negative significant correlations between EFV levels and NPZ3 persisted over time [range of r=(-0.15, -0.25)] but there was no correlation of EFV level and mood. **CONCLUSIONS:** In a large active-controlled trial, early neurologic symptoms distinct from depression or anxiety were associated with EFV use, and resolved by week 4. Improvement in neuropsychological performance was comparable in EFV and non-EFV-treated subjects.

Abstract 60: Factors associated with perinatal HIV-1 transmission in mothers and non-breastfed infants receiving zidovudine (ZDV) prophylaxis

G Jourdain et al.

PURPOSE: HIV perinatal transmission-associated factors in mothers and non-breastfed infants receiving ZDV have been studied in clinical trials with relatively low sample size. **METHODS:** PHPT-1 was a multicenter, randomized, controlled trial in Thailand, with a factorial design: maternal ZDV starting at 28 or 35 weeks' gestation, 6 weeks or 3 days ZDV in formula-fed infants (*N Engl J Med* 2000; 343). Out of 1,409 infants born to 1,437 women, HIV status by Roche Amplicor 1.5 DNA PCR was available for 1,386 infants (98.4 percent). There were 97 HIV transmissions: 42 percent "early" (ie, PCR+ within 1 week of birth), and 58 percent "late" (ie, PCR+ after PCR- in the first week). Analyses were adjusted on maternal/child treatment assignment (including interaction). P value for factor selection was <0.05. **RESULTS:** Overall transmission was associated with baseline viral load (VL) >10,000 copies/ml, baseline maternal creatinine >1 mg/dL, pregnancy complications, labor >24 h, prematurity (Ballard score), and birth weight <2,500 g (LBW). Early transmission was associated with VL >10,000 copies/ml, creatinine >1 mg/dL, pregnancy complications, labor >24 h, prematurity, and LBW. Late transmission was associated with VL >10,000 copies/ml and CD4 <200 cells/mm³ (versus >350 cells/mm³). Upon multiple logistic regression, VL >10,000 copies/ml (OR: 3.2; 95 percent CI=1.9-5.3), creatinine >1 mg/dL (OR=2.5; 1.2-5.2), low birth weight (OR: 2.1; 1.2-3.7), and labor >24 h (OR: 3.6; 1.1-11.4) remained independently associated with overall transmission; labor >24 h (OR: 5.6; 1.5-21.0), low birth weight (OR: 2.8; .3-6.3) and creatinine >1 mg/dL (OR=2.9; 1.1-8.0) with early infection, and only VL >10,000 copies/ml with late transmission (OR=4.7; 2.3-9.4). **CONCLUSION:** Factors independently associated with early and late transmission despite ZDV may give insight on the mechanisms of transmission or of ZDV prophylaxis failure. The pathogenesis significance of elevated creatinine in relation to transmission needs to be investigated.

Abstract 62: Multicenter, randomized controlled trial assessing the safety and efficacy of nevirapine in addition to zidovudine for the prevention of perinatal HIV in Thailand: PHPT-2 update

M Lallemand et al.

BACKGROUND: Zidovudine (ZDV) starting at 28 weeks' gestation decreases *in utero* transmission to 1 to 2 percent, yet 4 to 5 percent intrapartum transmission still occurs. Adding nevirapine (NVP) to ZDV during labor and in neonates may further reduce intrapartum transmission. **METHODS: Eligibility:** ZDV prophylaxis as soon as possible after 28 weeks' gestation (>2 weeks), labor oral loading dose and 1 week for infants (6 weeks if mother <4 weeks); formula feeding. Three arms: 1) NVP + ZDV mother/NVP + ZDV infant; 2) NVP + ZDV mother/placebo + ZDV infant; 3) placebo + ZDV mother/placebo + ZDV infant. Dosing: NVP mother 200 mg po at onset of labor, NVP infant 6 mg po 48-72 hours after birth. **Endpoint:** HIV-infected infants (two PCR+ on two samples) versus uninfected (two PCR after one

month). After the first interim analysis based on 629 outcomes, the ZDV alone arm was discontinued as HIV transmission was higher than in the NVP + ZDV mother/NVP + ZDV infant arm (P≤0.00036). **RESULTS:** As of March 5, 2003, 1,833 women (antiretroviral-naive: 99 percent) have been enrolled and 1,726 have delivered. Median baseline CD4 count: 370 cells/mm³ (18 percent <200); log viral load: 3.94 copies/ml; delay between study treatment intake and delivery: 6.7 hours (13 percent <2 hrs; 26 percent <3 hrs); non-elective C-sections: 21 percent. **Infants:** Median delay from birth to study treatment intake: 48.5 hrs (98 percent <72 hrs). The second interim analysis in February 2003 did not raise safety concerns and confirmed the first analysis results. Enrollment was stopped March 1, 2003, as the planned sample size for non-inferiority comparison of NVP + ZDV mother/placebo + ZDV infant with NVP + ZDV mother/NVP + ZDV infant (delta 2.5 percent, power 80 percent) had been reached. **CONCLUSION:** While adding NVP during labor and in the neonate to oral ZDV prophylaxis significantly decreases HIV transmission, the need for the infant NVP dose still needs to be established.

Scaling Up Antiretroviral Therapy in Developing Countries

Abstract 110: Safety and immunological effectiveness of simplified fixed-dose combination of nevirapine-based HAART among Indian patients: Extended follow-up data

S Pujari et al.

OBJECTIVE: To determine the safety and immunological effectiveness of simplified fixed dose combination (FDC) of nevirapine- (NVP) based HAART amongst HIV-infected patients in India. **DESIGN:** Longitudinal study. **METHODS:** Antiretroviral-naive patients initiating NVP-based HAART were recruited consecutively and followed up at two HIV clinics in Ahmedabad and Pune. After the lead-in dose patients were initiated on fixed dose combination of d4T/3TC/NVP (n=659) or AZT/3TC/NVP (n=335). Patients were followed up clinically monthly and with CD4 counts every three to six months. Adherence was assessed by self-report. CD4 counts were estimated by FACS count. Adverse events (AE) were defined as any event judged by the investigator to be definitely, probably or possibly related to NVP. Logistic regression analyses were done to assess risk of adverse events by age, gender, baseline CD4 counts, and concomitant TMP-SMX. Paired t tests were used to assess improvement in CD4 counts. Results of as-treated analysis are described here. **RESULTS:** Out of 994 patients studied, 726 (78.3 percent male and 21.7 percent female) who had completed minimum of three months were evaluable. 15.8 percent patients were lost to follow-up or had CD4 decline after three months. Adverse events were documented in 23.2 percent, usually occurring within the first 12 weeks of initiating therapy. Rash was documented in 6.9 percent (10; 9 SJS and 1 fatal), GI disturbances in 15.6 percent and hepatitis (symptomatic, clinical) in 3.3 percent. Female gender was significantly associated with development of AE, however age, baseline CD4 counts and concomitant TMP-SMX were not. Mean CD4 counts at baseline, three months, six months, nine months, 12 months, 18 months, and 24 months were 125.6 cells/mm³ (119.8-131.3, n=726), 281.2 cells/mm³ (270.5-291.8, n=726), 310.8 cells/mm³ (298.1-323.5, n=619), 349.9 cells/mm³ (328.5-371.2, n=256), 380.6 cells/mm³ (358.4-402.9, n=332), 422.8

cells/mm³ (380.3-465.3, n=124) and 403.8 cells/mm³ (326.6-481.1, n=33), respectively. In patients showing improvement, more than 95 percent of the doses were taken regularly. **CONCLUSION:** The fixed dose combination of NVP-based HAART showed good safety and durable immunological improvement in this largest observational study to date from India. Simplifying therapy may be one of the reasons [behind] this remarkable success.

Abstract 111: What happens when a research project closes: HIV incidence, mortality, and perceptions in a couples' cohort in Lusaka, Zambia

E Shutes and the Rwanda/Zambia HIV Research Group

OBJECTIVE: HIV research projects in developing countries often provide services to study participants. When research is concluded, participants are left without the support they have come to depend on. The impact of a seven-month closure of an HIV research study in Lusaka, Zambia, is examined. **METHODS:** Eligible couples were enrolled and followed every three months between May 1995 and April 2002. Primary healthcare was provided at the research clinic. The project was closed between December 1998 and June 1999. HIV and syphilis seroprevalence and mortality rates are compared before, during, and after the closure. Between August 1999 and January 2000, 531 returned study participants answered a two-page questionnaire regarding their experience during the closure. **RESULTS:** Couples that returned (75 percent of those that were actively enrolled at the time the project was closed) were not demographically different from couples that did not. The majority (82 percent) of respondents reported continued condom use and the incidence of syphilis and HIV was not significantly different during the closure compared with before and after. 84 percent of respondents reported that the project closure had a negative impact on them, 87 percent of whom rated lack of medical care as the main reason. The mortality rate among HIV-positive participants doubled from 6.7/100 PY (95 percent CI 5.3-8.3) before to 12.4/100 PY (8.1-18.1) during closure, and decreased again to 7.5/100 PY (5.7-9.7) after the project re-opened. **DISCUSSION:** Self-reported and objective data confirmed that risk reduction was maintained in the absence of regular follow-up. The most negative perceived impact on study participants was the loss of healthcare, which coincided with an increase in mortality rates. HIV research projects should make transition plans and establish functional health referral mechanisms for study participants when research funding ends.

Salvage Therapy

Abstract 116: Analysis of virological response to enfuvirtide in TORO: Implications for patient management

J Montaner et al.

BACKGROUND: Enfuvirtide (ENF) is an HIV-1 fusion inhibitor, a new class of approved antiretroviral (ARV) that targets HIV-1 gp41 thereby inhibiting HIV fusion to the host cell. The safety and efficacy of ENF plus an optimized background (OB) regimen through 24 weeks of treatment has been established in two pivotal studies, TORO 1 and TORO 2. We evaluated virological response with the objective of providing guidance for clinical practitioners on the effective use of ENF + OB. **METHODS:** Triple-class-

experienced patients with plasma HIV-1 RNA >5,000 copies/ml selected an OB regimen of three to five antiretrovirals based on prior history and baseline (BL) genotypic and phenotypic resistance. The percentages of patients with plasma HIV-1 RNA <50 and <400 copies/ml were summarized by randomized treatment arm. Exploratory multiple logistic regression analyses were used to assess the prognostic value of baseline and treatment factors on virological response, and subgroup analyses were performed to confirm the findings. **RESULTS:** 995 patients (ENF + OB: 661; OB: 334) were included in the ITT population (defined as randomized, received at least one dose of study drug and had at least one post-baseline assessment). At 24 weeks, the percentage of patients with plasma HIV-1 RNA <50 and <400 copies/ml were 22.8 percent and 37.4 percent for ENF + OB versus 9.0 percent and 16.2 percent for OB, respectively. The likelihood of virological suppression <400 copies/ml was higher for ENF + OB patients that were: healthier [CD4 count >100 cells/mm³ versus <100 cells/mm³; OR=3.0, 95 percent CI=(2.1, 4.2)]; less antiretroviral experience [<10 prior antiretrovirals versus >10 antiretrovirals; OR=1.8, 95 percent CI=(1.2, 2.7)]; and had more active drugs in their OB (>2 versus <2; OR=2.6, 95 percent CI=(1.8, 3.7)). **CONCLUSION:** While the comparative efficacy of ENF + OB over OB alone has previously been established, these results suggest that the virological response to ENF + OB therapy is directly related to the activity of the background regimen and improved responses were observed in less-advanced and less-experienced patients.

Abstract 118: Efficacy and safety of atazanavir (ATV) with ritonavir (RTV) or saquinavir (SQV) versus lopinavir/ritonavir (LPV/RTV) in combination with tenofovir (TFV) and one NRTI in patients who have experienced virologic failure to multiple HAART regimens: 16-week results from BMS A1424-045

R Badaro et al.

BACKGROUND: Atazanavir (ATV) is a potent once-daily azapeptide PI with a distinct resistance profile, demonstrated safety and efficacy in naive and experienced patients, and a lipid profile superior to marketed PIs. ATV C_{min} levels are boosted 5 to 8 fold by co-administration of ritonavir (RTV). **OBJECTIVE:** Compare the efficacy and safety of ATV/RTV and ATV/SQV to LPV/RTV in patients who have failed multiple HAART regimens. **METHODS:** Ongoing, multinational, open-label, three-arm study in HAART failure patients randomized (1:1:1) to ATV (300 mg)/RTV (100 mg) QD, ATV (400 mg)/SQV (1200 mg) QD, or LPV (400 mg)/RTV (100 mg) BID, each combined with TFV (300 mg) and one NRTI. Results: Three hundred fifty-eight patients randomized; 347 treated. At week 16 similar efficacy was observed between ATV/RTV and LPV/RTV, with ATV/SQV having lower efficacy versus LPV/RTV [mean changes from baseline, HIV RNA (log₁₀ copies/ml) -1.85, -1.61, -2.00; CD4 (cells/mm³) 84, 55, 110; proportion of patients with HIV RNA <400 copies/ml, 64 percent, 48 percent, 65 percent]. Mean total cholesterol and triglyceride changes from baseline were favorable for both ATV regimens versus LPV/RTV (cholesterol: -7 percent, -10 percent, +5 percent; triglyceride: +2 percent, -15 percent, +34 percent, respectively). Adverse events (AEs) were comparable among all regimens and were consistent with known safety profiles of study drugs. Serious AEs were infrequent. **CONCLUSION:** In

this highly ARV-experienced population, the efficacy of ATV/RTV QD is similar to LPV/RTV BID through 16 weeks. ATV, when boosted with RTV or combined with SQV, is safe, well tolerated and with a more favorable lipid profile than LPV/RTV.

Abstract 119: Failure of structured treatment interruption (STI) to confer benefit in the setting of treatment failure: CPCRA 064 results by baseline CD4 count and phenotypic sensitivity score (PSS) subgroups

J Lawrence et al.

PURPOSE: CPCRA 064 is a randomized study (n=270) for HIV-infected people with treatment failure (HIV-RNA >5,000 copies/ml) and multidrug resistant HIV to test whether using an STI prior to changing therapy (STI arm) leads to an improved response compared with immediately changing therapy (no-STI arm). Shown previously, the STI arm had decreased CD4 count, increased clinical events and no benefit in virological response compared to the no-STI arm. These analyses are to determine if there are differential responses by subgroups. **METHODS:** Subgroups are defined by baseline CD4 count (CD4 <100, n=108; CD4 >100, n=162) and PSS for the first antiretroviral regimen after randomization (PSS=0, n=27; PSS=1, n=43; PSS >1, n=131). All analyses of change in CD4 count and log HIV RNA are intent-to-treat longitudinal regression models. **RESULTS:** For all subgroups (CD4 and PSS), the STI arm has a poorer mean CD4 count response than the no-STI arm through follow-up (up to 12 months), while the differences in mean HIV RNA are not significant after the STI period. For the CD4 <100 cells/mm³ subgroup, the maximum HIV RNA mean change is -0.5 in the STI arm and -0.6 in the no-STI arm. At months 8 and 12, the mean changes in HIV RNA are -0.5 and -0.4 in the STI arm and -0.3 and -0.5 in the no-STI arm. For the CD4 >100 cells/mm³ subgroup, the maximum HIV RNA mean change is -1.0 in the STI arm and -1.2 in the no-STI arm. At months 8 and 12, the mean changes in HIV RNA are -1.0 and -0.9 in the STI arm and -0.7 and -0.8 in the no-STI arm. **CONCLUSION:** Subgroup analyses by baseline CD4 count and PSS show similar results to the full cohort, suggesting that STI in these subpopulations does not confer immunological or virological benefit.

Resistance and Pharmacology

Abstract 163: HIV-1 genotypic resistance to antiretroviral treatment in Cameroon in populations treated by HAART and by single-dose nevirapine to prevent MTCT

C Kouanfack et al.

OBJECTIVES: To monitor the prevalence of antiretroviral-resistant HIV-1 strains in patients followed at the Central Hospital in Yaoundé, Cameroon, and to document genotypic resistance patterns in non-B subtypes. **METHODS:** Two populations were studied in 2002. The first one included 93 patients under HAART, with a median treatment time of 8 months (IQR, 3 to 55). The second one included 24 ART-naïve pregnant women who received one single dose of nevirapine to prevent mother-to-child transmission (MTCT population). Since viral loads were not available, PCR attempts were done on all samples to amplify protease and RT genes. All amplified fragments were sequenced and analyzed for resistance mutations and subtype identification. **RESULTS:** 34 of the 93

samples from patients under HAART (36.6 percent) could be amplified, suggesting a viral load below 1,000 copies/ml and an effective treatment in the remaining 59 samples. Among the 34 samples, the subtype distribution was as follows: CRF02 (64.7 percent), D (8.8 percent), group O (5.9 percent), F2 (5.9 percent), A (5.9 percent), CRF02/F (5.9 percent) and CRF13 (2.9 percent). The patients presenting resistance mutations (19/34) had received treatment for a longer period (10 months, IQR 5 to 55) than those without resistance (7 months, IQR 3 to 31), P<0.005. The resistance patterns were as follows: NNRTIs (n=4); NNRTIs + 3TC (n=4); 3TC (n=3); NNRTIs + NRTIs + PIs (n=2); NNRTIs + NRTIs (n=2); NFV + NRTIs (n=1); IDV + NFV + RTV (n=1); IDV (n=1); NNRTIs + 3TC + AZT + ddI + (d4T) (n=1). In the MTCT population, 20/24 samples (83.3 percent) were amplified: CRF02 (75 percent), A (15 percent), CRF02/F (10 percent). Only one woman developed a resistance to NNRTIs (K103N). **CONCLUSION:** This Cameroonian experience shows that HAART selected numerous mutations conferring high-level resistance to three antiretroviral classes, notably cross-resistance involving a limited alternative therapeutic choice. It is necessary to implement antiretroviral therapy guidelines and biological monitoring in Africa to avoid rapid selection of resistance.

Abstract 164: Stable prevalence of genotypic drug resistance mutations but increase in non-B virus among patients with HIV-1 primary infection in France in 2001-2002 compared to previous years

ML Chaix et al.

OBJECTIVE: To evaluate the frequency of virus with genotypic antiretroviral resistance and the evolution of the molecular epidemiology during 2001, 2002. **METHODS:** Pre-treatment plasma samples were tested for genotypic resistance at the time of acute infection in 264 patients recruited all over France in the PRIMO Cohort study (n=125), in different laboratories of the AC11 Resistance group (n=108), in the INTERPRIM study (n=20) and in the PRIMSTOP study (n=11). **RESULTS:** The risk factors for infection were homosexual/bisexual contact for 64 percent of the patients, heterosexual contact for 29 percent, IVDU for 0.5 percent. Median HIV RNA and median CD4 at inclusion were 5.3 log copies/ml (1.7-7.57) and 503 cells/mm³ (38-1,516), respectively. 12 percent of patients (29/250, 95 percent CI: 8 to 16) presented with mutations associated with resistance to at least one antiretroviral drug. For patients with resistance mutations to 1 class of antiretroviral drug, the distribution was as follows: to NRTIs in 13/250 (5 percent, 95 percent CI: 3 to 9), to NNRTIs in 7/250 (3 percent, 95 percent CI: 1-6) and to PIs in 4/250 (2 percent, 95 percent CI: 0-4). Five patients (2 percent, 95 percent CI: 1-5) presented with virus mutations associated with multidrug resistance to two or three classes of antiretroviral drugs. Median plasma viral load was significantly lower in patients with one or more key mutations than in patients without mutations (4.62 versus 5.39 log, P=0.05) and CD4 cell count was higher (697 versus 487). No significant difference in the prevalence of resistance mutations was found according to HIV exposure group (11 percent homosexual/bisexual versus 9 percent heterosexual). Phylogenetic analysis based on 125 sequences of reverse transcriptase genes revealed that 24 percent of patients harbored non-B subtype strains (30/125). **CONCLUSION:** During 2001-2002, there was no significant evolution of the frequency of resistant virus compared to previous results from 1996 to

2000. We noted, however, an increasing trend in the frequency of non-B subtype strains (19 percent in 1999 to 2000 versus 24 percent in 2001 to 2002).

Abstract 165: Efficacy of ritonavir/amprenavir-containing regimen in HIV-1 protease inhibitor-experienced patients and predictivity of the delta viral load values up to week 24 using genotypic inhibitory quotient

AG Marcelin et al.

OBJECTIVE: To evaluate the efficacy of a ritonavir (RTV) plus amprenavir- (APV) containing regimen in HIV-1 protease inhibitor- (PI) experienced patients and the predictivity of a genotypic inhibitory quotient (GIQ) on the virological response at week 24 (W24). **METHODS:** Forty-nine PI-experienced but APV-naïve patients experiencing virological failure were treated with RTV (100 mg bid) plus APV (600 mg bid). We evaluated the parameters associated to the virological response at week 24. **RESULTS:** The genotypic resistance testing showed at baseline a median of two major and four minor PI resistance mutations (among IAS list). Patients responded to therapy with a median viral load (VL) decrease of -1.32 log by week 12 (W12) and -1.46 by week 24 (by intent-to-treat analysis). Baseline PI resistance mutations (L10F/I/V, K20M/R, E35D, R41K, I54V, L63P, V82A/F/T/S, I84V) identified in univariate analysis and included in a genotypic score and APV C_{min} at week 8 were predictive of the virological response at W12. GIQ calculated as ratio of APV C_{min} to number of HIV-1 protease mutations was a better predictor of the magnitude of VL decrease at week 12 but also at week 24 than the virological or pharmacological variables used alone. Among patients with a detectable VL (>200 copies/ml) at week 24, the patients who failed without any acquisition of PI resistance mutations harbored APV week 24 C_{min} higher than in those who failed selecting new PI mutations. **CONCLUSION:** This study shows a sustained efficacy of r/APV-containing regimen in PI-experienced patients up to week 24 and suggests that GIQ could be used in therapeutic drug monitoring. This approach could help to define plasma concentrations needed to control replication of viruses with different levels of PI resistance measured by the number of PI resistance mutations.

Coinfection with Hepatitis Viruses

Abstract 214: The impact of the hepatitis C virus (HCV) on CD4 response post initiation of HAART among a population-based HIV treatment cohort

P Bratstein et al.

OBJECTIVE: To characterize the impact of HCV on CD4 response to initiation of HAART in a population-based HIV/AIDS treatment cohort. **METHODS:** The HIV/AIDS Treatment Programme distributes, at no cost, all antiretrovirals in British Columbia, Canada. Eligible individuals were those whose first ever antiretroviral therapy was two NRTIs plus a PI or an NNRTI, and who had documented HCV serology. All available CD4 responses post initiation of HAART were examined. Adherence was measured through prescription refills. Statistical analyses used non-parametric methods and linear regression; mixed effect models were used to determine factors independently associated with CD4 increases over

time. **RESULTS:** Of the 1,416 ART-naïve individuals who initiated triple-combination therapy, 552 (39 percent) had recorded HCV-Ab test results, of whom 235 (43 percent) were HCV-antibody positive, and 317 (57 percent) were HCV-antibody negative. There were significant differences in median baseline values (HCV-negative: 240 cells/mm³ versus HCV-positive: 280 cells/mm³, $P < 0.001$). Using linear regression, a statistically significant increase in CD4 over time was found for HCV-negatives ($p = 0.008$), but not for HCV-positives ($P = 0.122$). These trends were maintained even among individuals who were >95 percent adherent (HCV-negative $P = 0.004$; HCV-positive $P = 0.162$). Mixed effect modeling found that factors independently predicting CD4 increase were HCV-serostatus ($P < 0.001$), time ($P < 0.001$), being >95 percent adherent ($P < 0.001$), and baseline CD4 ($P < 0.001$). Non-significant variables tested were gender, age, and baseline viral load. After adjustment for potential confounders, HCV-negative individuals gained an average of 33.5 CD4 cells per day, whereas HCV-positive individuals lost an average of 5.3 cells per day ($P < 0.001$). **CONCLUSION:** There appears to be an altered CD4 response over time among HCV-positive individuals following initiation of HAART, even after controlling for adherence. The clinical significance of these differences remains to be determined.

Abstract 215: Anti-HBV activity of emtricitabine (FTC) in patients co-infected with HIV and hepatitis B virus

F Raffi et al.

BACKGROUND: Co-infection with HBV occurs in 5 percent to 8 percent of patients with HIV infection. FTC is a novel, potent, QD NRTI with clinically demonstrated activity against HIV and chronic HBV infection (CHB) in HIV patients. HBV DNA was analyzed in HBsAg+, HIV coinfecting patients followed up (6 months in FTC Phase III HIV clinical trials). **METHODS:** The three multicenter, 48-week studies evaluated the following triple-drug regimens: FTC versus d4T (1:1) with ddI plus EFV ($n = 571$); FTC versus 3TC (1:1) with d4T plus efavirenz or nevirapine ($n = 468$); FTC plus d4T with either emivirine (an investigational NNRTI) or abacavir ($n = 564$). A subset of patients with HIV RNA ≤ 400 copies/ml at week 24 is included in this preliminary analysis. HBV DNA was measured in stored plasma at baseline (BL) and Q12 weeks through week 48 using the Digene HBV Hybrid Capture II assay (LOD 4,700 copies/ml). **RESULTS:** 52 HbsAg-positive patients received FTC. Of these, 34 have samples currently available. At BL, 12 patients had HBV DNA 4,700 copies/ml. Among the remaining 22 patients, median BL HBV DNA was 8.75 log₁₀ copies/ml and median HBV DNA change from baseline (CFB) was -2.26, -2.44, 3.13, and 2.75 log₁₀ copies/ml at 12, 24, 36, and 48 weeks. For the inactive d4T control group ($n = 10$), the median change in HBV DNA was -0.05, -0.21, -0.60, and +0.02 log₁₀ copies/ml ($P \leq 0.009$ compared with FTC). Among FTC-treated patients, 7/19 (37 percent), 8/19 (42 percent), 11/18 (61 percent), and 9/16 (56 percent) had HBV DNA <LOD, respectively. The most common adverse events (frequency >20 percent) were infection, headache, dizziness, nausea, diarrhea, and flu, which were similar in frequency among HbsAg-negative patients. The most frequent laboratory abnormalities that were of \geq Grade 3 severity were elevations of ALT (29 percent), AST (29 percent), and CK (25 percent). **CONCLUSION:** FTC as a component of HAART produced potent suppression of HBV DNA in co-infected patients with HIV RNA suppression.

Clinical Trials of New Drugs/Pro-Drugs

Abstract 543: 48-week results of an atazanavir-based QD regimen in patients switching from BID PI-based HAART

M Markowitz et al.

BACKGROUND: QD therapy with ATZ could result in control of viral replication and improved lipid profiles in HAART-treated individuals on PI-containing regimens. Furthermore if adherence were an obstacle to complete virologic suppression then QD therapy could result in accelerated proviral DNA decay (ie, decay $T_{1/2} \leq 6$ months). **METHODS:** 22 well-suppressed subjects treated with PI-based HAART for ~3 to 5 years were switched to QD therapy with ATZ 400 mg, 3TC 300 mg, and D4T XR 100 mg. Patients were monitored monthly. Provirial DNA levels were measured using a modification of the Roche Amplicor HIV-1 RNA assay at baseline, week 24 and week 48. **RESULTS:** 18 of 22 subjects completed 48 weeks of therapy. Of the noncompleters, one subject failed with M184V in RT (had previous therapy with NRTI bi-therapy including 3TC), one subject developed worsening lipatrophy, one moved out of state and one failed to return post-angioplasty for CAD. There were two Grade 4 elevations of bilirubin. Adherence was excellent with 15/22 subjects reporting missing no dosings and 5/22 reporting missing no more than one dosing per month. Two subjects missed more than one dose in any given 30-day period. While maintaining virologic suppression (all completers <50 copies/ml), mean CD4 cell counts increased 86 cells/mm³ ($P = 0.4$). Mean total cholesterol levels fell significantly from 215 mg/dl to 201 mg/dl at week 24 ($P = 0.02$) and mean triglyceride levels were also significantly less, falling from 203 mg/dl to 134 mg/dl at week 24 ($P = 0.03$). Provirial DNA decay in 12 subjects selected for the absence of intermittent viremia, no interruption in therapy, and 100 percent adherence by history was either absent ($n = 6$) or averaged 117 weeks (range: 44 to 196). **CONCLUSION:** ATZ-based therapy can maintain virologic suppression and allow for improvement in lipid profiles in PI-treated subjects. However once-daily therapy does not appear to result in substantially accelerated decay of the pool of cells harboring HIV-1 provirus.

Initiation of Therapy

Abstract 560: Efficacy and safety of ritonavir/indinavir 100/400 mg BID in combination with two NRTIs in antiretroviral treatment-naïve HIV-infected individuals

C Katlama et al.

OBJECTIVE: To evaluate the efficacy and tolerance of ritonavir/indinavir (RTV/IDV) 100/400 mg twice daily in combination with two NRTIs in antiretroviral- (ARV) naïve patients. **METHODS:** Pilot, single-arm study, including untreated patients with plasma HIV RNA (VL) >5,000 copies/ml. CD4 counts and VL were evaluated at weeks 4, 12, 24, and every 3 months until week 48. The primary endpoint was the proportion of patients with VL <400 copies/ml at week 48. Intent-to-treat (ITT) (missing values or change in treatment as failure) and on treatment (OT) analyses were performed. **RESULTS:** 40 patients (26 males/14 females) were enrolled. Seventeen patients were from sub-Saharan Africa (42.5 percent). Baseline median VL was 5.36 log₁₀ copies/ml, CD4 count was 84 cells/mm³ and 33 percent of the patients were in CDC stage C. At week 48, by

ITT, the proportion of patients with VL <400 copies/ml was 65 percent (26/40; 95 percent CI, 48 to 79 percent) and 50 percent with VL <50 copies/ml. By OT, the proportion of patients with VL <400 copies/ml was 96 percent (26/27; 95 percent CI, 81 to 100 percent) and 74 percent with VL <50 copies/ml. The median decrease in VL was $-3.79 \log_{10}$ copies/ml and the median increase in CD4 was $+164$ cells/mm³. Discontinuation before week 48 occurred in 13 patients: eight patients (22 percent) for drug-related adverse events, one patient's will, one patient for simplification after week 24, and three patients (7.5 percent) were lost to follow-up. IDV and RTV plasma trough concentrations (C_{min}) were performed in 31/40 patients, with 90 percent of patients having an adequate level as defined by IDV $C_{min} >150$ ng/ml. Median C_{min} at week 4 for IDV and for RTV, respectively was 429 ng/ml (5-2,662 ng/ml) and 431 ng/ml (30-3,165 ng/ml). **CONCLUSION:** RTV/IDV 100 mg/400 mg bid is an effective and safe first-line antiretroviral therapy in combination with two NRTIs. The simplicity and low cost of RTV/IDV is of major interest particularly in countries with limited resources.

Abstract 562: Favorable metabolic profile for tenofovir disoproxil fumarate (TDF) versus stavudine (d4T) when used in combination with lamivudine and efavirenz in antiretroviral-naïve patients: 96-week interim results

S Staszewski et al.

PURPOSE: To examine the metabolic profile of patients in Study 903, which was designed to evaluate the efficacy and safety of TDF as part of a fixed ART regimen in antiretroviral-naïve patients over 144 weeks. **METHODS:** Phase III, multicenter, randomized, double-blind, active-controlled trial in patients with HIV-1 RNA >5,000 copies/ml with no minimum entry requirement for CD4 count. Patients were randomized to receive either TDF or d4T plus 3TC and EFV. Patients randomized to TDF received d4T placebo bid while those randomized to d4T received TDF placebo once daily. **RESULTS:** The intent-to-treat (ITT) population included 600 patients with the following baseline characteristics: mean age 36 years, 26 percent female, 36 percent non-Caucasian, mean HIV-1 RNA $4.9 \log_{10}$ copies/ml; mean CD4 count 279 cells/mm³. At week 96, the change in CD4 cell counts (TDF 261, d4T 266), proportion of patients achieving <400 copies/ml (TDF 82 percent, d4T 78 percent) and <50 copies/ml (TDF 78 percent, d4T 74 percent) was similar in both arms. The incidence of grade 3 and 4 laboratory abnormalities and adverse events was also similar. With similar baseline fasting lipid parameters, a significantly more favorable fasting lipid profile was noted for TDF at week 96 (mean increase from baseline, in mg/dl) triglycerides (TDF +5, d4T +103), total cholesterol (TDF +30, d4T +51), LDL (TDF +11, d4T +20) and HDL (TDF +9, d4T +7). With similar mean weight at baseline, the TDF group demonstrated a significant weight gain through week 96 (in lbs, TDF +6.1, d4T +0.8, $P=0.002$). At week 96, the TDF group also demonstrated significantly more total limb fat, determined by whole body DXA scans, compared to the d4T arm (in lbs, TDF 17.6, d4T 10.9, $P<0.001$). **CONCLUSION:** Both arms showed similar efficacy but patients in the TDF arm had favorable differences compared to the d4T arm in cholesterol (total, LDL and HDL) and triglycerides, total limb fat and weight change. These differences were statistically significant.

20 years of HIV science...

Continued from page 221

The results presented here did not include data on the effects of drug therapy; those data will be presented at a later meeting, the researchers said.

Self-reports of fat loss among both men and women in the study correlated closely with objective measures, a fact that several researchers reported to be "highly reassuring."

Among the most interesting study findings was that in HIV-positive men and women central lipohypertrophy was not associated with peripheral lipoatrophy, although peripheral and central lipoatrophy in the same individual were associated, said Michael Saag (University of Alabama, Birmingham). "There's no evidence that people who gained weight in the belly lost weight in the periphery," Saag remarked.

Among men, there was significantly greater peripheral fat loss in all body areas in those who were HIV positive versus controls. Men with HIV also reported, and exams confirmed, less central fat gain.

In an analysis of data on women enrolled in the study, the researchers found an inverse association between central lipohypertrophy and peripheral lipoatrophy. In general, women who were HIV positive experienced little overall change in body fat distribution, said Abby Shevitz (Tufts University School of Medicine, Boston).

In both men and women, HIV positivity was associated with either significant changes or trends toward decline in both LDL and HDL cholesterol, and increase in triglycerides, as well as unfavorable changes in insulin and glucose parameters, suggesting that HIV infection increases risk of cardiovascular problems, said Judith Currier (University of California, Los Angeles).

ART for opportunistic infections

The most effective approach to treating tuberculosis co-infections in patients with HIV/AIDS in the developing world is with antiretroviral therapy, according to Peter Mugenyi (Joint Clinical Research Centre (JCRC), Kampala, Uganda), at a session on opportunistic infections in resource-limited settings.

Mugenyi said that the patients who present to the JCRC tend to come in with advanced, late-stage disease, noting that about half of all patients present with CD4 cell counts below 100 cells/mm³ at

first admission. Tuberculosis is the leading cause of death, accounting for 40 percent of all mortality at the center, he said. Other common opportunistic infections include all the usual suspects, including toxoplasmosis, *Pneumocystis carinii* pneumonia (PCP), and cryptococcosis, all of which are almost uniformly fatal. He pointed out that the average life expectancy is 87 years in Japan versus 33 years in Zambia.

Mugenyi also spoke of a cruel irony or "evil convocation" resulting from the success of Uganda's HIV-prevention efforts: there is decreased HIV prevalence, but increased incidence of both AIDS and opportunistic infections.

The good news, said Mugenyi, is that antiretroviral therapy reduces the incidence of tuberculosis by about 80 percent in HIV-positive people, and that antiretroviral therapy is the ideal form of prophylaxis for opportunistic infections. He compared the costs of various forms of therapy for two weeks of therapy for opportunistic infections, noting that treatment of PCP and toxoplasmosis infection cost more than US\$100, tuberculosis therapy costs about US\$40 for the same period, but antiretroviral therapy, using generic drugs, costs only US\$12.

In the same session, Kevin DeCock (US Centers for Disease Control and Prevention, Nairobi) reported that there are 8 million new cases of tuberculosis per year, and 1 million deaths. In addition, there are 11.4 million people with HIV/tuberculosis co-infection, two thirds of whom are in sub-Saharan Africa.

DeCock said that most cases of tuberculosis occur in HIV-positive patients, but are transmitted primarily from those who are HIV-negative. He agreed with Mugenyi that antiretroviral therapy is the most effective means of tuberculosis prevention and treatment in the developing world, pointing out that it reduces the incidence of the disease by about 80 percent in HIV-positive patients, although they still remain at higher risk than those who are not infected.

He cautioned, however, against half measures, saying that "a bad tuberculosis program is worse than no program at all," and that widespread, poorly implemented antiretroviral therapy can do more harm than good. ■

Neil Osterweil is a medical writer with Osterweil & Baron Communications in Holliston, Massachusetts.



I N T H E L I F E



David Wheeler

Vanity Fair readers have every month since 1993 enjoyed *The Proust Questionnaire*, a series of questions posed to celebrities and other famous subjects. In June 2002, *IAPAC Monthly* introduced "In the Life," through which IAPAC members are asked to bare their souls.

This month, *IAPAC Monthly* is proud to feature David Wheeler, who is Clinical Assistant Professor of Medicine at Georgetown University, Washington, DC.

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

More than any single line of prose, the first of Bach's Goldberg variations, when heard after the prelude, reminds me that if my heart is in the right place and I work hard, I can achieve anything.

What activities, avocations, or hobbies interest you? Do you have a hidden talent?

Squash, snowboarding, classical music, contemporary fiction, Sunday night chili dinners with my family, and travel to Latin America. I can still do a 2 1/2 off the high dive.

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

I would live near the water—for now, one of the tributaries of the Chesapeake Bay.

Who are your mentors or real life heroes?

Although neither of them realizes it, John G. Bartlett has been my mentor, and my parish priest, Richard Martin, is my real-life hero. John was supportive of me during the seven years we worked across town. Although I tried, I just never managed to get up quite as early as he did. Father Martin continues to inspire me by his focus on people in an environment focused on rules.

With what historical figure do you most identify?

As a graduate of the University of Virginia, I confess I'd like to be a little more like Thomas Jefferson.

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

John Irving, Pat Conroy, Michael Ondaatje, Margaret Atwood, and Boris Pasternak; most of the Pre-Raphaelites and Gustav Klimt; Bach, Vivaldi, Mozart and anything played by Anne-Sophie Mutter or sung by Cecilia Bartoli.

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

It would be interesting to have lived in late 18th century America (North or South) to participate in the creation of new societies.

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

A geography teacher or an ambassador.

In your opinion, what are the greatest achievements and failures of humanity?

Achievement: separation of church and state. Failure: institutionalized subjugation of women.

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

Ten years: Against a background of sharper divisions between rich and poor countries, many underdeveloped countries will have been decimated by the HIV epidemic and exist at the brink of chaos. Twenty years: A limited number of mainstream religious and political leaders in the developed and underdeveloped world will have accepted their responsibility to prevent and treat HIV infection. Combined with an effective vaccine, these efforts will be successful in controlling the epidemic and averting a return to another "Dark Ages." ■



[Strength in Numbers]

[IAPAC Welcomes New and Renewing Members]

In August 2003, the International Association of Physicians in AIDS Care (IAPAC) welcomed 19 new and renewing dues-paying members from five countries. IAPAC thanks the following physicians and allied health workers for their support of the association's mission to improve the quality of care provided to men, women, and children who are living with HIV/AIDS.

Thomas Deetz, *USA*
Jack DeHovitz, *USA*
Milton Estes, *USA*
Martin Fenstersheib, *USA*

Wolfgang Guthoff, *Germany*
James Hinrichs, *USA*
Sandra Johnson, *USA*
Patrice Joseph, *West Indies*
Donald Kaminsky, *USA*
Bernadette Lactouock, *Cameroon*
Bryan Lipman, *USA*
Gregory Loomer, *USA*
Anil Mangla, *USA*
Rodica Matusa, *Romania*
George McSherry, *USA*
Judy Morrissey, *USA*
Peter Selwyn, *USA*
Steven Tay, *USA*
John Wiecha, *USA*

Also, the following are new and renewing institutional members: AIDS Community Alliance, Boulder County AIDS Project, Florida AIDS Action Foundation, Fredericksburg Area HIV/AIDS Support Service, Gay Men's Health Crisis, Harlem United Community AIDS Center, and Tarzana Treatment Centers.

To learn more about professional and institutional memberships, call (312) 795-4935 or send an e-mail to member@iapac.org. For more information regarding Corporate Partner opportunities, call (312) 795-4941 or send an e-mail to partner@iapac.org.

[Recruit your colleagues to join IAPAC]

Health professionals who join the International Association of Physicians in AIDS Care (IAPAC) benefit from the research and expertise disseminated through the association's journals, Web site, care tools, and annual symposia. Greater membership in IAPAC also means more support for the association's training programs. These programs are making great strides in helping professionals learn best practice care techniques in the developing world, where the pandemic is taking its heaviest toll. Finally, as IAPAC continues to find strength in numbers, and represent more and more of the

world's health professionals, expanded membership means a more powerful voice in discussions that can lead to increased funding for medications, more effective inter-organizational cooperation, and simply better quality of life for those living with HIV disease.

These reasons should be more than enough to encourage you to recruit colleagues to join IAPAC. Nonetheless, we want to provide you with personal rewards for your recruitment efforts.

Through the end of 2003, every new recruit who lists you as the member who referred him/her to IAPAC brings you

closer to winning free travel and/or a complimentary membership extension. For each member you recruit, your name will be entered in a drawing for one roundtrip airline ticket within your continent or region of the world. If you recruit five new members before the end of the year, you will receive 12 months of dues-free membership.

Battling complacency and advancing commitment in the international struggle against HIV/AIDS requires a strong, coordinated effort. Encourage your colleagues to join that effort as members of IAPAC.



SAY ANYTHING



The harassment of people with HIV/AIDS and their advocates diminishes China's ability to halt its AIDS epidemic.

An excerpt from a letter to Chinese Premier Wen Jiabo as quoted in an August 3, 2003, Newsday article entitled, "AIDS Violence Flares in China." The letter was sent by a coalition of leading HIV scientists and AIDS luminaries reacting to several human rights violations perpetrated in the past few months against Chinese people living with HIV/AIDS, including: beatings, arrests, harassment and denial of life-saving medicines. According to Chinese human rights activists, violence has flared in recent weeks, particularly in China's Henan province, where an estimated 1 million peasants became infected with HIV during the 1990s after selling their plasma to government-run clinics and then being transfused with pooled, contaminated blood.



People need to realize there's still no cure and no vaccine. Our greatest enemy in HIV prevention is...complacency about our epidemic here.

James Curran, Dean of Emory University's Rollins School of Public Health and a former Acting Director of the US Centers for Disease Control and Prevention (CDC) Division of HIV/AIDS Prevention, quoted in an August 3, 2003, Associated Press report about how AIDS diagnoses in the United States have increased for the first time in 10 years. The increase is attributed to a new generation of gay men who entered their 20s without the memory of the early days of AIDS devastation. According to Curran, believing that HIV disease was under control, many gay men have been lulled into a sense of complacency that has led to new HIV infections among gay men in large cities.



Photo: Patricia Hagen, *The Mercury*.

Zackie Achmat, head of South Africa's Treatment Action Campaign (TAC), and Louisa Hobson, whose activist daughter Charlene Wilson died of AIDS-related complications, taking a break following an April 2003 TAC protest march in Pretoria.

I am not going to die because they want us to die.

Zackie Achmat, head of the Treatment Action Campaign, in an August 5, 2003, speech delivered to a cheering crowd of activists congregated for the 1st South African AIDS Conference held in Durban, South Africa. Achmat, who is HIV-positive and had pledged not to take antiretroviral drugs until his government offered antiretroviral therapy to poor HIV-infected South Africans, decided to abandon his pledge in order to continue his advocacy. According to an Associated Press report, Achmat will begin taking generic versions of antiretroviral drugs—considered a symbolic nod to efforts to reduce the cost of antiretroviral therapy.



Somebody said, "Why are we helping addicts?" The question is: "Why shouldn't we? Are we only supposed to help heart patients?"

Viviana Zanocco, a spokeswoman for the Vancouver Coastal Health Authority, quoted in an August 2, 2003, Washington Post article entitled, "With Injection Sites, Canadian Drug Policy Seeks a Fix." Canada shifted its approach to drug users in the past year—from punishment to a policy of harm reduction. Accordingly, the Dr. Peter Center in Vancouver is one of the first "safe injection" sites in North America. Addicts who test HIV-positive can shoot up safely, under nurses' supervision. Safe injection sites provide clean needles, sterile water, cotton, and rubber tubing. Although the provincial and federal governments have yet to sanction the policy through law, police are allowing the clinics to operate without interference. The Bush Administration has criticized the Canadian policy.



In Africa, the United States has a chance to make a dent in a catastrophic problem. But if anyone thinks that the US effort can eliminate AIDS in Africa or worldwide, then he hasn't had a good look at the statistics.

Dan Rather, CBS Evening News anchor, in an August 2, 2003, Houston Chronicle editorial entitled, "Consider Bush's AIDS commitment a first step." While acknowledging criticism of the HIV prevention aspects of the Emergency Plan for AIDS Relief (ie, abstinence education), Rather praised US President George W. Bush for his pledge of US\$15 billion over the next five years to combat HIV/AIDS in 12 African and two Caribbean countries. Of note, the US Congress appropriation for the plan's first year was about US\$1 billion less than Bush had asked for—a shortfall that activists are calling for the Bush Administration to address by pressing for a supplemental appropriation.



IAPAC, with its broad mission to improve the healthcare of all who have been affected by the AIDS pandemic, is working to ease suffering and to ensure that persons living with HIV/AIDS are able to live productive lives. Though the battle ahead is one requiring the greatest of global commitments, even small donations from concerned world citizens with the means to provide a small amount of financial assistance can make a notable impact.

The same poverty that engenders higher infection rates in the developing world also means an inadequacy of healthcare infrastructure and, often, the inability of physicians and allied health professionals to access the training and information that they require to effectively treat those in their care.

With your donation of US\$60 (or more), you can help IAPAC in its mission as an agent of change. For only US\$60, IAPAC can sustain the cost of an annual membership for a physician in the developing world, thus enabling physicians in the regions most heavily burdened by HIV disease to gain greater access to critical clinical and policy information and to more fully partake of specialized HIV/AIDS medical training provided in the countries where it is most needed.

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.



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