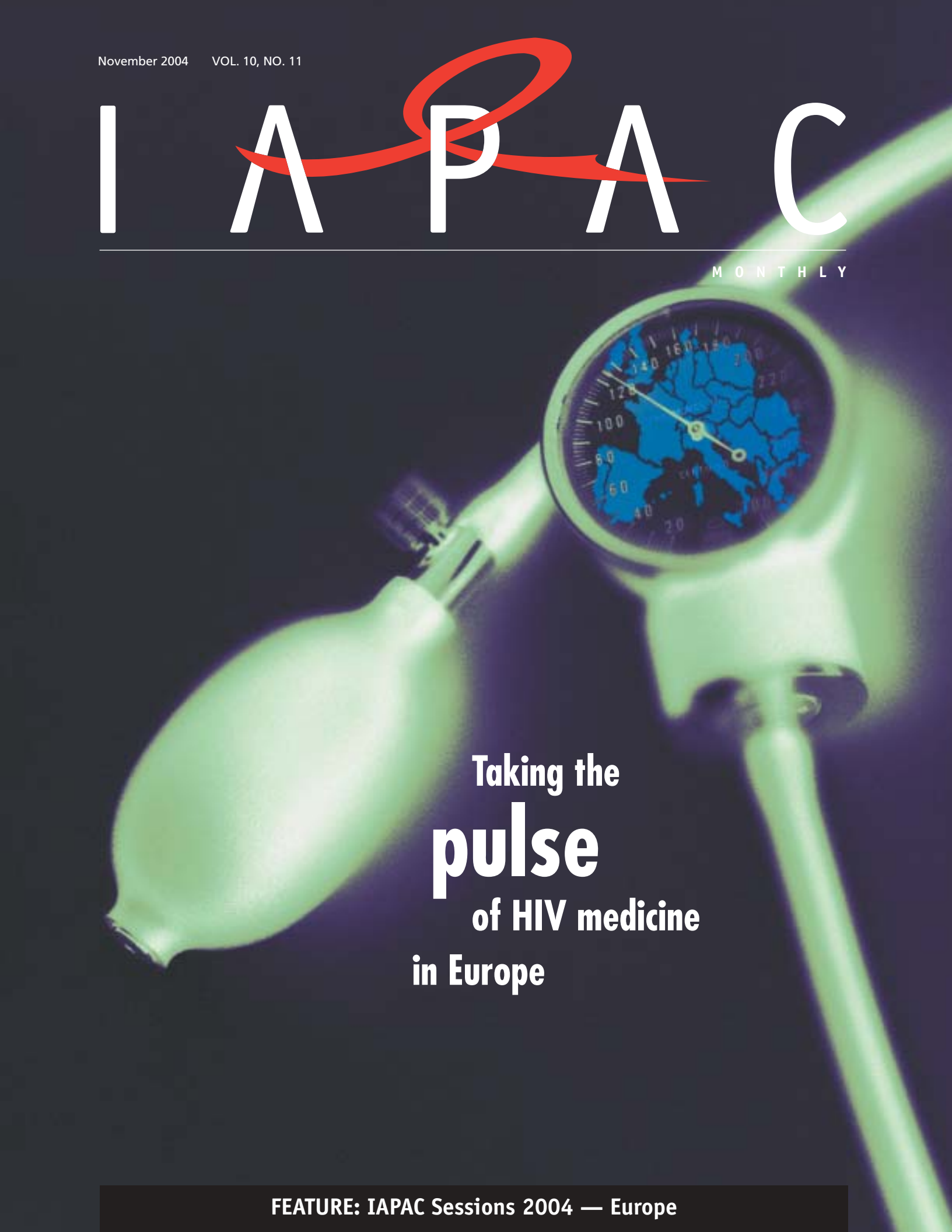
November 2004 VOL. 10, NO. 11

IAPAC

MONTHLY



Taking the pulse of HIV medicine in Europe

FEATURE: IAPAC Sessions 2004 — Europe

November 2004

IAPAC MONTHLY

Volume 10, Number 11

416

IAPAC Sessions 2004 – Europe
Taking the pulse of HIV medicine in Europe

Julian Meldrum

The International Association of Physicians in AIDS Care (IAPAC) convened European physicians in September 2004 to take the pulse of HIV medicine in Europe. From simplification of to management of toxicities related to antiretroviral therapy, the IAPAC Sessions 2004 - Europe served as a sounding board for recommendations around some of the most complex issues in HIV clinical management.

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IAPAC Monthly (ISSN 1545-1089) is published monthly by the International Association of Physicians in AIDS Care. All material published, including editorials and letters, represents the opinions of the authors and does not necessarily reflect the official policy of the International Association of Physicians in AIDS Care, or the institutions with which the authors are affiliated, unless otherwise noted.

IAPAC Monthly welcomes responses to the material presented. Letters should be sent to Letters to the Editor, *IAPAC Monthly*, 33 N. LaSalle, Suite 1700, Chicago, IL 60602-2601 USA.

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IAPAC welcomes new trustees

John G. Bartlett

Christine Katlama

José M. Zuniga

In addition to the privilege of hosting our annual Honoring Our Heroes tribute dinner earlier this month in Washington, DC, I had the honor of convening the annual general meeting of the Board of Trustees of the International Association of Physicians in AIDS Care (IAPAC). This august body—comprised of physician- and lay-activists representing vastly diverse geographical regions—bears fiduciary responsibility for IAPAC's affairs, as well as provides invaluable guidance to the association's management around policy and program activities.

I am pleased that one outcome of our November 2, 2004, meeting was the election of five new Trustees:

- John G. Bartlett (Johns Hopkins University, Baltimore);
- Melissa Fitzgerald (a star of NBC-TV's "The West Wing");
- Christine Katlama (Hôpital Pitié-Salpêtrière, Paris);
- Jean William Pape (Center GHESKIO, Port-au-Prince, Haiti); and
- Papa Salif Sow (University of Dakar, Senegal).

I also wish to recognize the ongoing contributions made by our veteran Trustees, including:

- Allen I. Freehling (Human Relations Commission, Los Angeles);
- Carol A. Harris (Albert Einstein College of Medicine, New York);
- Bernard Hirshel (University of Geneva, Switzerland);
- Elly Katabira (Makerere University, Kampala);
- Praphan Phanuphak (Thai Red Cross Society, Bangkok);
- Rubin Phillip (Diocese of KwaZulu-Natal, Durban, South Africa);
- Celso Ramos-Filho (Federal University of Rio de Janeiro); and
- Mike Youle (Royal Free Hospital, London).

As IAPAC winds down its first decade of existence and prepares for the next, I am confident that we count on the caliber of volunteer leaders who are willing to place their stock in an association founded on former United Nations Secretary-General Dag Hammarskjöld's principle that "to let oneself be guided by a duty from the moment you first see it approaching is part of the integrity that alone defines responsibility." ■

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

New fixed-dose once-a-day combinations

John S. James

The US Food and Drug Administration (FDA) recently approved two fixed-dose combinations of previously approved antiretroviral drugs; both are dosed for once-daily use by adults. The FDA said that these combinations should be used together with at least one other antiretroviral drug not in the nucleoside reverse transcriptase inhibitor (NRTI) class. In practice, they have been tested and used mostly with efavirenz (EFV), and with at least one ritonavir (RTV)-boosted protease inhibitor (PI).

The two new combinations are:

- Epzicom [abacavir (ABC) + lamivudine (3TC)]
- Truvada [tenofovir (TDF) + emtricitabine (FTC)]

Cal Cohen, Research Director of the Community Research Initiative of New England, answers questions about the new fixed-dose combinations.

The FDA recently approved two once-a-day fixed-dose combination pills: Epzicom and Truvada. How do you see their use for patients who are first starting antiretroviral therapy?

The fixed-dose combinations are primarily for convenience. The individual drugs were already approved in the United States, and there is no medical reason that they had to be put into one pill. So the first decision is whether these are the right medicines for the patient.

The importance of fixed-dose combinations, and the reason there are now two more of them, is that several years ago,

Cal Cohen

when zidovudine (ZDV) and 3TC were separate pills, [GlaxoSmithKline] asked clinicians what they thought about putting them into one pill. As I recall, most of the doctors said that was not a priority, that their patients did not mind taking the extra pill. When [GlaxoSmithKline] made Combivir anyway, its use was far greater than most physicians had predicted. Something about the simplicity was not anticipated, but was very important to many people taking these medicines. Maybe it was the one less co-pay, or one less bottle and refill to deal with. In any case the success of Combivir led to Trizivir (ABC + ZDV + 3TC), and now to these once-a-day combinations.

[The issues] of practicality and convenience [are] not to be minimized. But deciding which regimen you use is a choice of which meds you would pick, not just which fixed-dose combinations you would pick.

How do the once-a-day options compare with the twice-a-day antiretroviral regimens already in use?

A head-to-head comparison of Combivir versus the same drug combination as Epzicom, presented last year at the [43rd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC)], showed that the success of these regimens was spot-on identical. Efavirenz was the third drug in both cases.

The only differences were in side effects. With Epzicom, 5 to 7 or 8 percent of patients will have the hypersensitivity reaction to ABC; this won't happen [with] Combivir. But there were other toxicities in favor of the Epzicom arm. For example, the CD4 counts went up higher on that arm than on the ZDV-containing arm. There were fewer cases of nausea and vomiting, a well-known side effect of ZDV; and there was less anemia on Epzicom.

Surprisingly, there was a tiny bit more lipid increase on Epzicom than there was on Combivir. The significance of this difference is a subject of continued debate, but is just another factor to consider at this time.

So there are a series of tradeoffs—hypersensitivity in some cases with Epzicom, versus better CD4 counts and less hematologic toxicity than with Combivir.

What about Truvada?

In a statement on August 26, 2004, Gilead Sciences released early (24-week) results of a study comparing the Truvada drugs with Combivir (the other drug was EFV in both cases). That study showed a difference in the overall intent-to-treat response rate, giving an 8 percent advantage to Truvada over Combivir.

The 24-week result was about 88 percent (on Truvada) versus 80 percent (on Combivir) of the volunteers having a viral load of fewer than 400 copies/ml. It seems that some if not most of this difference is explained by toxicity, as the researchers found more toxicity on the Combivir arm than on the Truvada arm. Drug discontinuation due to toxicity seems to be explaining most of the difference in the intent-to-treat analysis, but further details are needed to truly answer the question.

Truvada is better than Combivir in some ways, and you have other advantages with Epzicom. The head-to-head test of Truvada versus Epzicom has not yet been done; it is being planned through the government-funded AIDS Clinical Trials Group (ACTG) trials network.

So how do physicians choose between these two? Epzicom has a 5 percent to 8 percent chance of hypersensitivity, which, while certainly manageable, is an issue to be dealt with in those starting the treatment. Clinicians need to review the symptoms of hypersensitivity with anyone starting ABC in this or any combination, as it is not yet standard to try to predict who is in this 5 percent to 8 percent. This extra step will be a consideration in deciding when to use this treatment, for some clinicians at least.

Truvada has none of the hypersensitivity; it is a relatively easy drug. It is certainly well tolerated; very low rates of discontinuation have been seen fairly consistently with the Truvada regimen, as well as in all the studies of TDF and FTC separately. Those are both well-tolerated drugs, with very low rates of discontinuation for side effects or lab toxicity. And overall the virologic success rates have been excellent.

The few concerns about Truvada have been mainly issues around renal toxicity and dosing. These drugs are cleared by the kidneys, and for those with compromised kidney function, the doctor has to pay attention to accurate dosing, to not overdose the patient. And some people are asking, if these drugs are cleared by the kidneys, does that mean we will see more renal toxicity?

Several physicians have presented studies of large cohorts of patients in their clinics, and so far one can safely conclude that while there are case reports of people who have had laboratory changes and decreases in renal function on TDF-based regimens, some very large cohorts have reassured us that these changes are rare events, and we don't know how often they happen because of tenofovir, or at a rate different from other antiretrovirals. For example, in the head-to-head comparison of stavudine (d4T) versus TDF, there was a very low rate of grade 3 renal problems on the d4T arm – and yet people don't worry about d4T and renal toxicity. Just because there are case reports does not mean the TDF was involved. Most cohorts have been reassuring overall.

A statement on the labeling of TDF noted slightly increased bone loss, and suggested that supplementation with calcium and vitamin D might help.

There has been much discussion for at least five years on TDF and bone loss. In both arms of the study, d4T and TDF, there was evidence of bone loss in the first year. It was about 1 percent more on TDF than d4t, but it happened in both arms. We don't usually think of d4T, 3TC, and EFV [as causing] bone loss. It was almost identical for men on TDF and men on d4T—about 1 percent bone loss that stabilized after about one year. Only for women was the bone loss statistically worse for TDF.

So is this a TDF issue or an antiviral issue? The curves flatten out after a year—bone loss for the first year, and then there seems to be stabilization for about two years [beyond that we don't have much data]. If this were a drug toxicity, we would generally expect it to get worse over time, not get worse for a year and then stabilize.

Could HIV be contributing to the bone loss? Some data suggest that people with HIV have bone loss even without taking antiretrovirals. If we look at what happened in the year before antiretrovirals [were initiated], there are data to suggest bone loss from untreated HIV. So one possible explanation for what we are seeing is that the HIV-related bone loss may be continuing for the first year on treatment; not [until] year 2 is the control of HIV resulting in a slowing of bone loss. This does not explain the 1 percent difference in women on TDF versus d4T. There may be some contribution of drug toxicity and another effect of drug benefit, in terms of long-term stability.

Whether that initial difference between TDF and d4T would be reversed by calcium supplementation is completely unanswered, at least from any public data sets. I am not aware that the bone loss is caused by the drug blocking calcium absorption in the gut. It would be an interesting study to see if calcium mattered or not. But for now it may be too simple to say bone loss happens and therefore calcium is the answer.

What about drug resistance with the new combinations?

You don't have resistance too often with either of these starting regimens. But if you do, the choice is between TDF resistance and ABC resistance (the percent of people who develop 3TC/FTC resistance is likely to be the same, based on these studies). There is no right or wrong answer; you don't want resistance to either one. Ultimately it is a trade-off of other issues, since resistance to either ABC or TDF causes cross-resistance to other medications in this class, and neither is a clear "winner" in this regard.

If you look at the mutations, about 2 percent to 3 percent of patients who start treatment with TDF regimens will get the K65R mutation, and about the same percentage who start with ABC regimens will get the L74V mutation. Both these mutations can cause cross-resistance to other NRTIs.

One key issue that may be important in how often we see these mutations is how often people with very low CD4 counts were allowed in these studies. A fact some people are not aware of is that the Gilead trial did not have a lower CD4 cutoff—you could have zero [cells] and still be eligible. The ABC trials had a lower cutoff of 50 cells/mm^3. It turns out this matters in terms of resistance. Most of those who developed mutations in the Gilead study had low CD4 [counts] when they entered. In fact, the single best predictor of who would develop TDF resistance was the CD4 [count] at entry. The median CD4 count of [patients] who developed the K65R TDF mutation was around 25 cells/mm^3.

Therefore, you cannot directly compare these studies, because they did not enroll people at the same risk of resistance. If you look just at those entering with CD4 counts above 50 cells/mm^3, there were very few in the TDF study who developed resistance.

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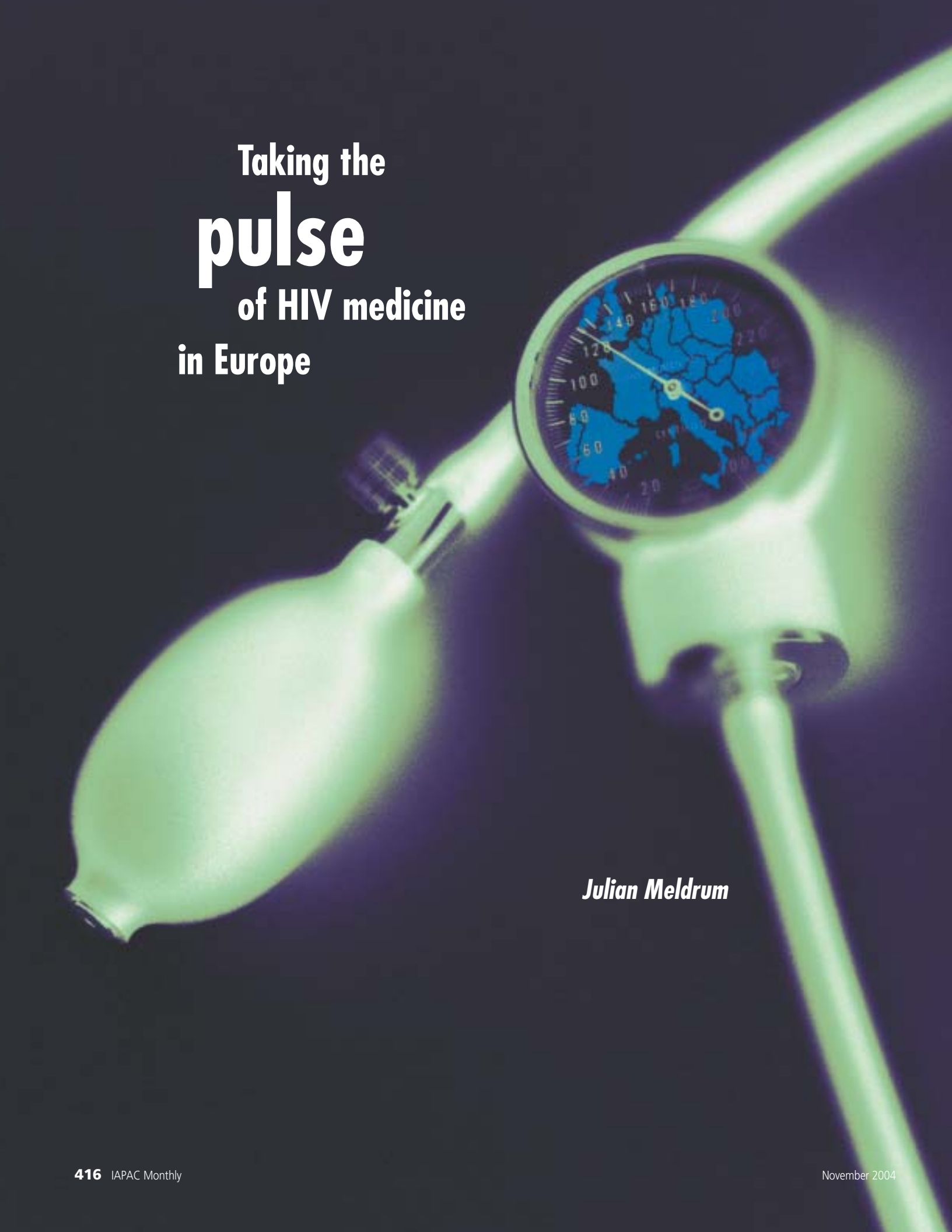
Taking the pulse of HIV medicine in Europe



Julian Meldrum

IAPAC SESSIONS 2004 — EUROPE
SEPTEMBER 23-24, 2004 · LONDON

A very English drizzle gave way to sunshine through the library windows of the Royal College of Physicians, bordering on Regent's Park in the center of London, as the IAPAC Sessions 2004 - Europe were inaugurated. The 14-member faculty included Co-Chairs Mike Youle (Royal Free Hospital, London) and Bernard Hirschel (University Hospital of Geneva), delegates representative of Eastern and Western Europe, and observers from UK-based AIDS service organizations as well as the World Health Organization (WHO).

José M. Zuniga, President/Chief Executive Officer of the International Association of Physicians in AIDS Care (IAPAC), welcomed delegates, observing that the toll of AIDS has diminished, but is far from gone, in western industrialized countries: 50,610 died in the United States in 1995; 16,371 in 2002, despite a growing prevalence of HIV in the population over that period. There had been a similar decline in Western Europe, but deaths were still occurring for a variety of reasons.

Issues limiting the success of AIDS treatment prioritized by IAPAC members included: liver complications – where hepatitis C virus (HCV) coinfection increases death risk even with successful HIV treatment; poor adherence; late diagnosis and late presentation for treatment, even when people are aware of their HIV status; non-Hodgkin's lymphoma; and non-AIDS cancers.

Youle, who with Hirschel is also an IAPAC Trustee, said the top of his own list was for people with HIV to be diagnosed. In the United Kingdom, anonymized serosurvey data imply that 35 percent of people with HIV are still unaware of their status. He called for the current paradigm of voluntary counseling and testing (VCT) to be scrapped, and for HIV testing in public health settings to be put on the same routine basis as HCV and syphilis tests. Why, he reasoned, should a diabetic entering hospital care for the first time not be tested for HIV alongside other routine investigations?

Francois Raffi (Nantes Medical University, France) reviewed current antiretroviral therapy (ART) options and posed what he thought remained some unanswered questions for ART guidelines writers.

There are now many potent antiretroviral (ARV) regimens to choose from, even when limited to the 20 European Medicines Agency (EMEA)-licensed ARV drugs, but some are better than others. A non-nucleoside reverse transcriptase inhibitor (NNRTI) plus two nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs) is better than triple NRTIs; ritonavir (RTV)-boosted protease inhibitors (PIs) are better than unboosted PIs.

Growing experience with the use of ART may not have led to the inexorable rise of ARV drug resistance that was once feared, at least on the evidence of cross-sectional surveys in the United States. The durability of current regimens might be three to five years or longer, yet there is still no sign of a return to previous mortality rates.

On the other hand, treatment across the global genetic diversity of circulating HIV strains has shown that patterns of ARV drug resistance vary with subtype. For example, patients with subtype C—which is currently by far the most common—are more disposed to nelfinavir (NFV) failures with L90M than with D30N as in subtype B.

Continuing issues with current ARV regimens include their complexity, the ease with which viral drug resistance is selected, and both short-term and long-term toxicity.

Still unresolved strategic questions include the CD4 count at which ART is best initiated. Is a CD4 count less than 200 cells/mm^3 too late? Is a CD4 count greater than 350 cells/mm^3 too early? Should the decision be influenced by viral load? Is there a case for induction and maintenance phases of ART, starting with the most powerful inhibitors of viral replication and shifting to those with least toxicity? Is there a role for ARV regimens based on less than three drugs? Are structured treatment interruptions finished as a strategy?

Tuberculosis (TB) treatment, where active disease must be controlled but deferral of ART can also be deadly, remains a particular challenge. Many patients seen in Europe present with active TB.

Depression and other psychiatric illness still raise questions about choices of first-line ARV regimens, with or without efavirenz (EFV).

The safety and efficacy of drugs during pregnancy both for mother and baby is not easy to assess.

HIV/HCV coinfection—especially where there is liver fibrosis—raises questions about drug safety and possibly the need for drug level monitoring.

Hepatitis B virus (HBV) coinfection complicates treatment when specific drugs—lamivudine (3TC) and emtricitabine (FTC)—limit HBV viremia so their withdrawal risks viral rebound and immunological attack on the liver.

Questions about NRTIs include:

- Is there truly a long-term tolerability advantage for abacavir (ABC), tenofovir (TDF), 3TC, and FTC, or will this fade, especially in the case of TDF and FTC, with longer usage?
- Which backbone is best—Combivir (ZDV/3TC), TDF/FTC, or ABC/3TC?
- Does stavudine (d4T) still have a place in ART guidelines or should it be dropped?

In discussion, the case for first-line d4T in developing countries was argued on economic grounds, that for widespread treatment access its low cost from generic manufacturers is crucially important. Zidovudine (ZDV), the next most affordable drug, is not an easy alternative, as there have been deaths from anemia induced by ZDV in populations which are already anemic for other reasons, in settings where emergency treatment is harder to deliver than ART itself.

With respect to NNRTIs and PIs, there is still a question as to whether RTV-boosted PIs or NNRTIs are preferable for first-line ART. Is the hepatotoxicity risk of NNRTIs (NVP, especially) limited to identifiable populations of patients? Is there any role in treatment for unboosted PIs? What can or should be done when boosted PIs fail?

New ARV drugs are still needed. In particular, NRTIs are needed that are better tolerated and/or active against virus resistant to current ARV drugs. Similarly, we need NNRTIs that can be used in salvage therapy. New classes of drugs, especially oral CCR5 inhibitors, integrase inhibitors, and immunomodulators, remain highly desirable.

Are all antiretrovirals created equal?

Mike Youle
Royal Free Hospital, London

Youle agreed that all ARV drugs are not equal, although as they are used in combinations, it is the combinations that matter. The number of effective drugs available is now considerably greater than for many other conditions. Nonetheless, resistance is an increasing problem, with a growing prevalence of multi-class resistant viruses.

In the best case scenario of a 29-year-old gay man with a job, a supportive partner, good mental health, and wild-type HIV infection, prospects on starting ART are vastly better than they were 10 years ago. Such a man, seen recently in his own clinic, would take his pills and might outlive his physician.

Youle contrasted this with the case of a man with schizophrenia, who has been through multiple ARV regimens and would only take a tablet "if it is white." (He had finally managed to persuade his patient that lopinavir (LPV) was indeed very white, despite being surrounded by an orange protective coating!)

The flow of new drugs has not stopped, although there are problems that may limit their use. Enfuvirtide (ENF) has not sold as well as its manufacturer had hoped, contributing to the decision to drop a successor molecule. It is also getting difficult to recruit patients into clinical trials; Youle relayed his frustration with a patient who said he was "too busy" to help future patients. In addition, he said that plans in the United Kingdom for domestic implementation of legislation from the European Union on the regulation of clinical trials threatened to eliminate investigator-led research on the use of pharmaceuticals, by imposing conditions like those for initial drug registration, regardless of the nature and purpose of the study.

Popular medical and health beliefs could sometimes be in competition with ARV drugs—for example, a man with a CD4 count of 20 cells/mm^3 thought that because he took antioxidants, ARV drugs were irrelevant to his treatment.

It is unavoidably difficult to compare new drugs with established drugs, given the lack of long-term data. Newer drugs might have fewer long-term effects than older ones, but there was no way to know this in advance.

Drug tolerability is mediated by the way the physician works to support the patient, and apart from cases of severe allergic reaction, most ARV drugs can be made tolerable for most patients. That said, better formulations also helped, and the regulatory environment for approval of reformulations has greatly improved in recent years. However, manufacturing issues have sometimes been a problem. For example, d4T extended release (XR) has been a severe problem for Bristol-Myers Squibb; NFV's 625 mg formulation

had also been a problem for Roche Laboratories. Past problems with RTV—which forced patients to switch from pill to liquid formulation for several months—were matched by persistent delays in delivering and studying pediatric formulations of newer and much-needed ARV drugs for young children.

Discussing NRTIs, while the newer coformulated pairs—ABC/3TC and FTC/TDF –might be more potent and generally better tolerated than ZDV/3TC, there were no long-term data on their toxicities.

Considering FTC, there are no data yet on its durability as compared to 3TC. Will it give rise to peripheral neuropathy? Since this might be expected to take 18 months to emerge, Youle still did not know. There has been an unexpected problem with hyperpigmentation of the palms in African patients. How reversible is this side effect? We still do not know for certain.

Among other NRTIs in development, D-d4FC (DPC 817) may offer the best prospect of activity against virus with high-level resistance to NRTIs.

Turning to NNRTIs, it had taken cohort studies, not clinical trials, to link high CD4 counts to NVP-related liver toxicity. Men with a CD4 count over 400 cells/mm^3 and women with a CD4 count above 250 cells/mm^3 should not, he said, be started on NVP-based ART.

Despite the 2NN study (which suggested they were equivalent), the relative potency of NVP and EFV remains controversial. However, according to Youle, it is uncontroversial that the single mutation, K103N, still "blows your entire NNRTI options."

The most promising experimental NNRTI is Tibotec Virco's TMC 125, on which he commented that a compassionate access program is now needed for heavily ART pre-treated patients ineligible for current clinical trials. Treatment access has not disappeared as an issue, even in Europe.

In relation to PIs, he observed that the lipid abnormalities that had been associated with their use may be driven by NRTIs as much as by the PIs themselves. Preliminary studies of "monotherapy" with RTV-boosted LPV (LPV/r) had found lipid disturbance to be minimal compared to that seen when LPV/r is used with NRTIs.

Boosted PIs have been gaining on NNRTIs in popularity as first-line ART, if only in relatively high-resource settings. And PI reformulations to reduce pill count have reduced gastrointestinal side effects.

Twice-daily RTV-boosted fosamprenavir (FPV/r), appeared to be slightly less potent at 48 weeks than twice-daily LPV/r, though the difference was not statistically significant. The response did seem to be lower in a further group treated once daily, though this may be a useful option.

Once-daily atazanavir (ATV) 300 mg boosted with 100 mg RTV is being investigated as an option which appears to have greatly reduced impact on lipids compared to other PIs (though, as other contributors later stressed, it is not yet certain that this will translate into better performance in relation to lipodystrophy).

Tipranavir (TPV)—now in Phase III trials—seems to be more tolerable in earlier-stage HIV disease than it was in salvage settings, where there were particularly severe gastrointestinal effects.

Discussing new classes of investigational ARV drugs, Youle observed that recruiting ART-naive, relatively early-stage patients to clinical trials of CCR5 inhibitors may be problematic, since those patients who actually need treatment have well-established treatment options available to them already (and may not be particularly willing to commit to close monitoring in extended clinical trials).

Among the treatment strategies which are further from clinical use, short interfering RNAs (RNAi) stood out for him as the only conceivable prospect for eliminating HIV from the body, though this would depend on the ability to target conserved gene sequences and deliver the RNAi efficiently to all target (infected and susceptible) cells. So far, the concept has only been demonstrated in a mouse/herpes model and has years to go before it could enter clinical trials.

While treatment simplification is a worthy goal as a means to improve adherence, decrease pill burden, ameliorate toxicities, and reduce cost, as well as to preserve future treatment options, it is not an end in itself. And, according to Sharon Walmsley (University of Toronto), it should not be pursued at the expense of treatment efficacy, in particular.

Reduced dosing frequency is an advance, although the added benefit in switching from twice-daily to once-daily ART may be much smaller than the benefit of moving away from drugs that have to be taken three or four times a day.

On the other hand, pill or capsule size is definitely an obstacle to adherence: bigger and more numerous pills are harder to take.

An increasing number of drugs can be taken once daily, although there are suggestions that, in some cases, they are less potent or durable—or more likely to give rise to ARV drug resistance—than alternatives dosed more frequently. Where this balance of advantages and disadvantages rests will vary between patients.

For a patient to benefit from an ARV regimen, it clearly has to be acceptable to that patient at the time when they are taking it. Social and lifestyle factors may influence what is or is not acceptable, as well as likely medical benefits and risks.

For those who are able to stay on ART, LPV/r + d4T + 3TC has been very effective and durable, but over 250 weeks of an extended clinical trial (Study 720), as many as 30 percent have abandoned that particular regimen. LPV/r is still three tablets, twice a day, hopefully reducible

soon to two tablets, twice a day.

A trial in which LPV/r was combined with TDF/FTC and taken once daily gave comparable results to the same combination taken twice daily. However, taking more tablets at one time did seem to give rise to more diarrhea.

The OK study is now examining whether it is possible to simplify LPV/r-based ART by dropping the NRTI components of the regimen once viral load is controlled. A substudy among treatment-experienced patients has found some maintenance failures, though it remains possible that the main study—among treatment-naive patients—will be more successful. However, lipids did not seem better among those treated with fewer drugs.

Simplification to an NNRTI with two NRTIs, as in the 2NN study which compared NVP to EFV (and to the combination of both), shows that while these combinations may be simpler to take, they leave new toxicities and some treatment failures in their wake. Perfect adherence may be less important for virological control than with PIs, on account of the longer half-life of NNRTIs, but when failure occurs, the risk of selecting a resistance mutation that will preclude further use of NNRTIs is much higher.

Triple NRTI strategies once seemed to offer once-daily and extremely simple ARV regimens, but there have been unacceptably high rates of virologic failure with ABC + 3TC + TDF, with TDF + didanosine (ddI) + 3TC, and with ABC + ddI + d4T (which also carries toxicity risks that most would reject).

Trizivir (ABC/ZDV/3TC), although clearly less potent than standard ARV regimens, may still be slightly more respectable than some would allow, based on the argument that for a few patients it may be easier to take. Even when it fails, Walmsley argued that the virus remains more treatable than if they were failed by another "more powerful" combination. Most patients who fail on Trizivir have either M184V or wild-type HIV, so would still have multiple treatment options.

Switching from a PI-based regimen to one using an NNRTI or ABC with two NRTIs could be an option for some patients, provided they have been successful on their first regimen and do not have NRTI resistance mutations. Any history of suboptimal therapy with NRTIs should rule out this strategy.

Intermittent therapy could take multiple forms. The STACCATO trial set out to compare continuous therapy with CD4-guided treatment interruption and one week on, one week off intermittent therapy. The last of these arms was abandoned due to too many treatment failures, but the CD4-guided arm failed to show hoped-for improvements in terms of quality of life and unwanted effects.

Finally, Walmsley discussed the impact of the use of single-dose NVP given to a mother at the start of labor, to prevent HIV transmission to her baby, on the woman's subsequent ability to benefit from ART. There is now evidence that the resistance mutations frequently detectable following such a single treatment can indeed reduce the response to subsequent triple ART. There is, therefore, a strong argument to avoid this use of NVP on its own, and to explore strategies for combining it with other drugs to avoid the selection of NNRTI resistance.

In discussion, Hirschel observed that his clinic is now treating African women with PI-based first-line combinations. Youle reported that he was now carrying out ARV drug resistance tests before starting any African patients on ART, as there was a reluctance to disclose past histories of suboptimal ART.

Walmsley was asked whether stopping a triple ARV regimen might be just as likely to lead to NVP resistance as monotherapy, given the longer half-life of NVP compared to NRTIs. She replied that she is now conducting a study in which drugs are stopped at same time and there is intensive testing for resistance mutations.

Hirschel observed that when stopping triple ARV regimens in his clinic, he extends NRTI treatment to cover the period when NNRTI concentrations are declining.

The simplification and development of HIV diagnostics

George Janossy
Royal Free Hospital, London

Janossy was a recent recipient of an IAPAC Hero in Medicine award for his work with the AffordCD4 group, an international network of laboratory researchers determined to match expanded global access to ART with better and cheaper monitoring and diagnostics.

Over lunch, Janossy argued for flow cytometry over supposedly lower-tech alternative technologies, to obtain CD4 counts and CD4/CD8 ratios. The CD45 marker enables CD4 and/or CD8 cells to be enumerated as a proportion of all white blood cells, which can be counted accurately and inexpensively in a dual-platform system. Low-cost sample fixing reagents (TransFix), initially developed for quality assurance purposes, could extend sample life to five days without loss of assay reliability. Volumetric flow cytometry offers the prospect of accurate, high-speed, single-platform counts, subject to validation of particular systems.

He cautioned against other assays for CD4, which failed to distinguish properly between T cells and monocytes. Patients with active TB had large numbers of monocytes, which could be mistaken for CD4 T cells in systems that lyse cells before performing the assay. He also cautioned against manual counting systems such as DynaBeads, which are inappropriate for programs due for rapid scale-up.

He also strongly supported observations made by Anthony Fauci (US National Institutes of Health [NIH]) at the XV International AIDS Conference in Bangkok, highlighting the importance of CD8 activation in HIV pathogenesis. Flow cytometry can be used to monitor CD8 activation states, which may be as sensitive as viral

load as a marker of viral rebound, and have the potential to be cheaper, simpler and faster.

Specifically, this means using CD38 in conjunction with CD8, which can be offered at a price of US$3 to US$7 per test—substantially less than any viral load test in prospect.

It has been shown, using blood samples taken during the course of the QUEST study of treatment in primary HIV infection, that CD38 activation rises during primary HIV infection, falls when HIV is treated, and rises rapidly when treatment is discontinued, all correlating with viral load.

Translating this into standardized values which could be used in clinical guidelines clearly needs further research on clinical populations in the settings where these tests would be deployed. However, if it uses the same equipment deployed for CD4 counts, it is obvious that it could be made equally available.

Navigating HIV resistance and drug level monitoring

Mark Nelson
Chelsea and Westminster Hospital, London

Nelson said that for all the success of the treatments where patients are able to adhere to therapy for extended periods, a substantial proportion of patients are in fact unable to do so, as Walmsley previously observed. When treatment fails, major opportunistic infections, tumors, and deaths can still be seen. The reasons for failure may be attributed to factors related to the virus, the drug (potency or toxicity), or the patient's inability to take the drug consistently, but the impact is comparable whatever the reason(s).

More primary resistance is being seen in the United Kingdom, especially to NNRTIs—as, he observed, there has been a British "boycott" of PIs in first-line ART for some years. A study of 1,633 treatment-naive patients in Europe from 1998 to 2002 found a significantly higher rate of resistance mutations among those believed (on various grounds) to have been infected within the previous year compared to those believed infected earlier—10.9 percent versus 7.5 percent. Among patients actually on ART, the prevalence of at least one resistance mutation varied between 50 percent and 80 percent across three European and one Brazilian populations.

With respect to toxicities, nausea and diarrhea are probably the biggest everyday challenges to proper adherence. However, lipodystrophy as well as cardiovascular and cerebrovascular concerns are real, and may be joined by concerns over bone toxicity and renal toxicity.

When drugs fail, especially through nonadherence or poor drug efficacy, the outcome is likely to be viral resistance, which requires careful and expert evaluation.

It is obviously very unlikely that one dose of any of these ARV drugs will be ideal for all patients, so therapeutic drug-level monitoring may also have an important role to play in tailoring treatment to the patient.

Drug sequencing guided by resistance testing (Part 1)

Anna Maria Geretti
Royal Free Hospital, London

Geretti observed that there must be a relationship between viral fitness and drug resistance, given that heavily treated patients may have stable CD4 counts in the presence of detectable viral load. However, it is hard to see how to use this, as viral resistance pathways are unpredictable. Even for M184V with 3TC, it has been very hard to see a clinical benefit from keeping 3TC in the regimen to maintain this mutation.

Is there an advantage to using FTC instead of 3TC? *In vitro* studies imply that FTC selects for M184V more slowly than 3TC, but it is not clear if this will translate into greater clinical durability.

Is there an advantage to choosing TDF over ABC, aside from the ABC hypersensitivity issue? Her personal view was that ABC and TDF are equivalent, and equally likely to be active following treatment with ZDV.

The activity of ATV/r in the presence of PI-resistance mutations is not clear, though it seems ATV/r may be affected a little more than LPV/r or FPV/r.

In the event of treatment failure on a first-line ARV regimen, she would favor an early switch to try and avoid accumulating multiple mutations in the same viruses. With more highly experienced patients, it would be better to keep them on treatment and wait until multiple effective agents were available for a switch.

Asked about virtual phenotypes, Geretti observed that they inevitably do not work as well for newer ARV drugs as they do for older ones, given the relative lack of data to correlate phenotypes and resistance mutations. The way values are given to physicians—as X-fold reductions—needs careful interpretation for clinical relevance.

Drug sequencing guided by resistance testing (Part 2)

Saye Khoo
University of Liverpool

From reviewing clinical guidelines, therapeutic drug-level monitoring is (rightly) perceived as a niche procedure, to be reserved for circumstances where it is likely to be of most value. This is primarily in relation to PIs but also arguably for NNRTIs, especially EFV. A growing

prevalence of HCV-associated liver damage over time may also expand the role of therapeutic drug-level monitoring in ART.

Saye Khoo (University of Liverpool) reported recent findings on the pharmacokinetics of combining boosted PIs, which offer yet another level of complexity for ART, and may point to another potential growth area for therapeutic drug-level monitoring.

- LPV/r in combination with either amprenavir (APV) or FPV is problematic. Both PIs are reduced, APV or FPV more so than LPV.
- FPV/r with saquinavir (SQV) may reduce SQV levels, especially when SQV is given once daily, requiring either more RTV or more SQV to compensate.
- ATV/r with SQV boosts exposure to SQV.
- LPV/r with either SQV or indinavir (IDV) appears neutral, not affecting the concentration of these drugs.

The window in which clinical trials to test the value of therapeutic drug-level monitoring might have been possible has probably now closed. To prove added clinical value from using therapeutic drug-level monitoring—especially when combined with the use of resistance tests—would now require impossibly large numbers of patients.

Finding that a drug level is within a target range can sometimes be very useful; for example, in establishing that a particular drug interaction with a long-term non-HIV medication, such as an anticonvulsant, is not problematic (so that is one less issue to worry about) or in directing attention to another area of concern.

Inhibitory quotients (IQs) may be of additional value in individualizing ART, although there is a long way to go before these tests are standardized and validated.

The ideal for an IQ is to compare the trough concentration of the drug in a patient (C_{min}) with the IC_{50} value for the patient's own virus (eg, the phenotypically determined susceptibility of the virus to the drug). In practice, cost dictates that genotypic surrogates must be used. A further refinement is normalization, comparing individual values to those for a population treated with that drug.

Studies using IQs have so far been small, mostly with LPV/r, some with APV. Follow-up has often been too short—this should be 24 weeks to 48 weeks for any meaningful results.

He argued that while this might be a helpful guide to dosage for a particular drug in a particular patient, claims that one ARV drug is superior to another based on comparisons of IQ data should not be taken seriously. Also, in isolating one component of an ARV regimen, its clinical meaning is inevitably restricted.

Costs of therapeutic drug-level monitoring in the United Kingdom, offered nationally by the University of Liverpool, are largely defrayed by a consortium of ARV manufacturers: a charge just over US$100 is levied for each drug assayed.

Khoo was asked how to respond to high serum levels of EFV; for example, five times over target, associated with central nervous system side effects. As the dose relationship is nonlinear, he would advise a limited dose reduction (eg, from 600 mg to 400 mg) followed by retesting.

Managing metabolic and morphologic complications

Stefan Mauss
Center for HIV and Hepatogastroenterology, Düsseldorf

Opening the second day of the meeting, Stefan Mauss (Center for HIV and Hepatogastroenterology, Düsseldorf) observed that it is a big step forward to be aiming for quality of life rather than fighting death and prolonging survival.

Lipodystrophy is a problem for patients because it is stigmatizing, and has social implications that take it to the top of the list of many patients' concerns. However, research in this area continues to be hampered by the lack of a workable and accepted case definition, and the limitations of available scanning methods. Among those limitations are the fact that scan results are highly sensitive to alignment between the patient's body and the equipment, creating problems with repeatability over time and standardization between centers.

In many cases, facial wasting can be successfully addressed cosmetically with fillers, though there were continuing difficulties in a number of countries in getting reimbursement from healthcare systems. In a minority of cases where the primary problem was a substantial accumulation of visceral fat, recombinant human growth hormone (rHGH) could help correct the problem, at the price of some small additional loss of peripheral fat—and, again, considerable financial cost.

How real and substantial is the cardiovascular risk of ART? Mauss argued that the signals from large cohort studies are still weak, with small numbers of events in the relatively young treated populations, and methodological limitations due to incomplete and biased data. Nonetheless, patients should be assessed individually for their cardiovascular risks.

Using data from large studies of cardiovascular risk factors in HIV-negative populations, what becomes clear is that these interact in ways that give elevated low-density lipoprotein (LDL) cholesterol a very different significance for some patients than for others. In an older male smoker with a positive family history, it becomes far more important than it would be for a younger non-smoking woman.

There is evidence that different ARV regimens have different implications for lipids, but some patients may have their choice restricted for other reasons, so this probably cannot be the sole basis for choosing between regimens. His take-home message for those of his patients who smoke: "You can stop smoking, but you cannot stop being HIV positive!"

HAART to heart

Devaki Nair
Royal Free Hospital, London

Devaki Nair (Royal Free Hospital, London) is a lipidologist now working with an HIV clinic, in which, as she explained in discussion, she saw her role as strictly limited to treating the lipid problems that were brought to her attention. It was for her HIV specialist colleagues, and not for her, to advise the patient on which ARV drugs they should be taking. When she started the clinic three years ago, Nair said she felt inadequate because the patients expected her to be a "lipodystrophyologist." This highlights one of the key issues in the current management of HIV/AIDS, which is that patients' concerns are not always the same as those of treating physicians.

Changes in lipid metabolism are common in the context of HIV disease and of its treatment, in ways that are likely to increase the risk of ischemic heart disease (IHD), diabetes, and pancreatitis. However, the significance of these changes and the need to treat them must be considered for each patient individually, taking into account "conventional" risk factors for cardiovascular disease. Some of these—such as smoking and excessive salt intake—can be modified, whereas HIV status and the need for treatment cannot.

During HIV infection, there are a number of lipid changes that are typical of ANY acute infection, not just HIV. These include:

- Triglycerides (TG) increase
- High density lipoprotein-cholesterol (HDL-C) decrease
- Low density lipoprotein-cholesterol (LDL-C) decrease
- Very low density lipoprotein (VLDL) increase
- Insulin sensitivity increases
- Insulin levels are lower than in control populations
- Glucose levels are either stable or lower than in controls

While a number of mechanisms have been proposed for changes linked to disease and also for changes linked to treatment, she regarded all of them as speculative with no conclusive evidence to identify those of clinical importance.

Serum cholesterol in itself is not a major problem, but does become so when combined with other risk factors for cardiovascular disease.

On assessment of patients, the first priority is therefore to identify potential therapeutic lifestyle changes that can reduce risks without additional medication. For example, smoking cessation, increased exercise, and reduced dietary salt intake.

The primary aim of treatment is to reduce LDL-C, and the most effective drugs for this purpose are statins, which are well tolerated by 90 percent to 95 percent of HIV-positive patients for whom they are prescribed. A secondary aim is to reduce all non-HDL-C lipids, which includes a reduction in TG where these are elevated. This may be achievable with statins alone or may require specific drugs to lower TGs.

In discussion, Nair confirmed that when a patient is offered treatment with a statin, on account of raised cholesterol and other risk factors for heart disease, they would also be offered low-dose aspirin.

The choice of statins is influenced for HIV-positive patients by interactions with the cytochrome P450 system. This means, on the basis of pharmacokinetic studies carried out in AIDS Clinical Trials Group (ACTG) study 5047 with RTV/SQV, that simvastatin and lovastatin should not be used. Pravastatin has no interaction with these PIs, and atorvastatin should start at the lowest recommended dose (10 mg).

Triglycerides raise two concerns. Cardiovascular risk is elevated with moderate elevation of TG (peaking at 4.6 to 8 mmol/l) but actually falls with the highest levels of TG observed. Very high levels of TG probably reflect a different disease process and should be treated on account of the increased risk of pancreatitis, not for the risk of heart disease. There may be different classes of TG with differing effects, just as there are different classes of cholesterol.

High levels of TG also complicate the measurement of cholesterol levels and block the measurement of LDL-C in particular; though it may be assumed that elevation is likely whenever high levels of TG are observed.

Fish-oil supplements would be the initial treatment for high TG, preferred for lack of any interactions with other medications. Supplements are needed to deliver dosages that would be difficult to achieve by eating fish.

Niaspan (nicotinic acid slow release formulation) is better tolerated than in the general population, perhaps because the side effects are moderate compared to those to which HIV-positive patients on ART may be accustomed. And, bile acids have no place in treating people with HIV because of their complex dosing schedules.

In relation to ethnicity, Nair observed that high blood pressure, stroke risk, and diabetes are more common in African populations than among ethnic Europeans. This would argue for increased importance of treating high lipids in those populations.

Current management of body shape changes

Peter Reiss
University of Amsterdam

Changes in body shape through peripheral fat loss and gains in visceral fat are distressing and may be stigmatizing for people living with HIV/AIDS. These are definitely associated with ART, although the linkage is complex and varies between patients as well as between different ARV

regimens. There is limited scope for reversing or cosmetically correcting these changes, thus prevention is an inherently more desirable objective. In fact, polylactic acid (New Fill) has been successful in correcting facial wasting, although longer follow-up remains desirable.

Peter Reiss (University of Amsterdam) discussed a number of approaches to treatment, all of which are still experimental.

Recombinant Human Growth Hormone (rHGH) is expensive and is "not a clean drug." The most convincing results have been in reducing excessive visceral fat accumulation, although some loss of peripheral fat was seen at the same time.

Metformin is far cheaper than rHGH and shows some efficacy in reducing fat accumulation, compared to placebo, when taken 500 mg twice daily by 14 patients for 12 weeks. There was decreased weight and waist circumference, but only borderline difference in visceral adipose tissue. There was also some reduction in subcutaneous adipose tissue, which is a concern. A lactate problem seen with metformin treatment for diabetes was not seen here, probably because of the lower dose used. The mechanism by which metformin raises lactate levels is unrelated to mitochondrial function and is therefore unlikely to compound the risks associated with NRTIs.

Rosiglitazone can protect liposomes from PI or NRTI damage *in vitro*, but the largest clinical trial so far, which evaluated limb fat by DEXA at baseline, 24 weeks, and 48 weeks found no overall difference from placebo. Other studies have also failed to show any consistent gain in peripheral fat, though there may be some evidence for improvements in insulin sensitivity.

NRTI comparative and switching studies do support the idea that some NRTIs are more, and others less, damaging in terms of lipoatrophy. ACTG 384 showed that limb fat declined more rapidly in a group treated with ddI/d4T than in a comparison group with ZDV/3TC.

In discussion, the consensus seemed to be that switching d4T for ZDV would not generally be expected to reverse lipoatrophy but at best to slow the rate of decline.

On the other hand, the MITOX study showed that switching from ZDV or d4T to ABC could lead to some reversal of lipoatrophy, and when ABC was used in place of ZDV or d4T from the outset, limb fat increased through 72 weeks rather than first rising and then declining.

There is also promising preliminary evidence that TDF + 3TC + EFV is substantially better than d4T + 3TC + EFV in terms of loss of limb fat.

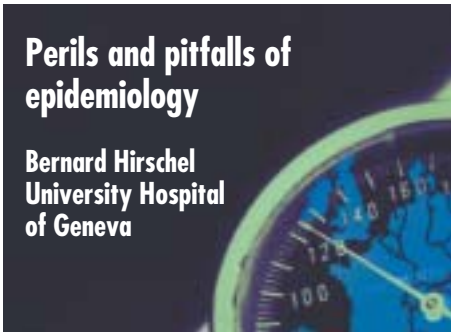
As for ATV/r, although there is evidence that this is superior to other PIs in relation to lipid metabolism, it is still unclear if this will translate into better performance in regard to lipodystrophy. The problem in assessing this, despite three-year follow-up in clinical trials, is that trials have often combined ATV/r with d4T.

The continuing lack of simple and practical methods for assessing fat loss and inability to agree on definitive clinical case definitions for lipodystrophy has limited data collection in trials. Even Gilead's TDF trials have only included DEXA scans relatively late. DEXA scans, while arguably among the better measures available, are still sensitive to orientation and fail to measure socially vital facial wasting. Trials are geared to 48-week data for drug approval, which may not be long enough to see differences in lipoatrophy.

The long-promised d4T extended release formulation should be evaluated for lipodystrophy from the outset of clinical trials, Reiss observed.

Asked about studies of dose reductions of d4T and other drugs as a strategy to limit lipodystrophy, he argued that it was hard to justify such studies.

In discussion, a North-South split emerged. Hirschel said that as d4T is "pretty dead" in Western Europe and North America, there was no rationale for Bristol-Myers Squibb to invest in further studies. Reiss would prefer mass access to better drugs such as TDF, but others observed that cost constraints will continue to ensure that d4T is widely used. In Thailand, for example, switching from d4T to ZDV in combination with 3TC and NVP increases the daily cost of treatment from US$1 to US$1.50. In Botswana, where ZDV/3TC is the first-line option (combined with NVP or EFV) there have been deaths from anemia. However, concerns over d4T-related lipoatrophy are just as high as in Europe or North America.



Recent claims of an increase in HIV cases in Britain and Switzerland need to be treated with more caution than has too often been the case. The impression given to the public of a rising threat has sometimes been misleading.

In 2003, the Stop AIDS Campaign ran an advertising campaign saying "a 25 percent increase in cases of HIV last year: Is that reason enough for the Swiss to start taking AIDS seriously again?"

Hirschel argued that although there are very good reasons to take AIDS seriously, this may not have been one of them, and identified a series of "traps" into which researchers, HIV agencies, the media and public could fall.

1. Vocabulary and definitions: An "epidemic" means something different to an epidemiologist and to the general public—and is far more alarming to the latter.
2. The case count depends on more than actual prevalence. In particular, with diseases that are often asymptomatic, it depends heavily on screening frequency and methods. For example, the impression of a chlamydia "epidemic" in the United States and other countries had been created through technical improvements in diagnosis and changes in legal reporting requirements. At the same time, prevalence has actually declined in areas where large-scale screening has been repeated!

3. New diagnoses of HIV are not necessarily new infections. So current prevalence may be a reflection of what was happening ten years ago, and possibly even in another country. Another time factor is the delay in collecting many statistics, especially for diseases that have lower priority than HIV. For example, the latest statistics for gonorrhea in Scotland seemed to relate to the year 2000!
4. Public alarms "cause" epidemics through enhanced surveillance. A good example of this was increased attention to syphilis among Parisian gay men leading to an escalation of testing and syphilis case finding, at the same time as rates of gonorrhea in the same population were actually stable or declining.
5. For those closest to a problem, it is bigger than it may be from a wider perspective. For example, a series of local "epidemics" of syphilis have been reported from US cities at the same time as national incidence has remained absolutely level for a number of years.
6. Neither syphilis nor gonorrhea are HIV. While new cases of these diseases among HIV-positive people do imply sexual risk-taking, they do not necessarily say anything about the risk of HIV transmission, which depends on serodiscordance, and likely on the transmitter's viral load. For example, between 1998 and 2002, a dramatic local rise in syphilis among HIV-positive gay men in San Francisco coincided with a reduction in incidence of HIV at two of the same sites in the same city.
7. Everyone loves an epidemic: "Alarmism is politically correct, keeping things in proportion is suspect, and denying a danger which turns out to be real is criminal." To be on the safe side, people inflate risks.
8. Experts have a vested interest in talking up the importance of a problem, as do journalists who want to sell newspapers.
9. Failure to distinguish between unlike cases, put together in the statistics.
10. Hidden moral, social, and political agendas—which are much easier to see in materials from earlier times than in our own…
11. Choice of time periods—both the starting point for statistics, and the time at which reporting finishes. For example, a supposed "highest ever" rate of gonorrhea in the United Kingdom could not be sustained when the time frame extended back to the 1940s and 1970s, rather than being started at a low-point in the mid-1990s. When there is a sudden rise in cases, this is newsworthy; a subsequent drop in cases is less often reported.

In conclusion, while there is some evidence of an upturn in diagnoses of sexually transmitted infections in the United Kingdom between 1990 and 2003, and of an increase in HIV diagnoses, especially since 1998 (though this does include some "old" infections), there is next to no evidence for an ongoing rise in HIV in Switzerland. In fact, the number of cases reported in 2003 was below the number in 2002—but this received no coverage.

Renato Maserati (University of Pavia) reviewed the meaning of disease prevention in relation to HIV, beginning with HIV transmission. While a vaccine remains elusive, treatment that suppresses viral load is likely to limit transmission by sexual routes as well as from mothers to infants. There is limited evidence for superinfection with HIV, although the number of reported cases has been sufficient for some to argue for sustaining safer sex among HIV-positive people, on or off ART.

Looking at reasons given for not using condoms in a recent telephone survey of adults, cost was rarely cited. Yet in Louisiana, the introduction in 1996-1997 of a charge of 25 [US] cents each to buy condoms that had been distributed freely for the previous three years, led to a 98 percent reduction in usage. Maserati argued that even in the world's richest country, the correct price for condoms is "free."

While he was skeptical about the existence of a separate compartment for the virus in genital secretions as distinct from plasma, the potential value of treatment in controlling transmission was limited by misperceptions of their own viral load by people living with HIV/AIDS, and a continuing tendency for condom use to be less frequent or consistent in regular ongoing relationships than with "casual partners."

Globally, HCV has an estimated prevalence of more than 170 million, compared to some 35 million or more people living with HIV. Yet there are only two licensed drugs for HCV treatment.

HCV infection rates among people with HIV vary across Europe, being highest in Southern Europe and Eastern Europe, where the HIV epidemic is most strongly driven by transmission among injecting drug users. HIV coinfection appears to accelerate fibrosis and cirrhosis among people with HCV. Fibrosis is influenced by CD4 count (below or above 200 cells/mm^3), age at infection (below or above 25 years), male sex, and alcohol consumption (below or above 50g/day).

As overall mortality rates among people with HIV decline, so the proportion due to liver disease associated with HCV increases.

Some studies—such as the Swiss cohort study—but by no means all, find accelerated HIV progression in coinfected populations.

While it is possible that effective HIV

treatment will lead to improved immune control over HCV, it is abundantly clear that ART-associated hepatotoxicity is greater in coinfected people. Similar issues arise for isoniazid and rifampicin in TB treatment.

Before the mid-1980s, HCV was widely transmitted through blood and pooled blood products. Effectively, every person with hemophilia treated with factor VIII before 1985 is now HCV positive.

Other transmission routes have included tattoo parlors, especially in the 1970s and 1980s; medical treatment with intramuscular injections for bilharzia in Egypt; possibly intranasal drug use; and some cases of household transmission, and through other routes such as poor hygiene in barber shops.

More unusual possibilities, which had given rise to either HBV or HCV outbreaks, included "alternative therapy" (an "ozone clinic" which gave rise to 150 cases of HBV) and 10 cases of HBV among gay men in Brighton who had shared a needle at a sex party to administer Caverject.

A striking rise in new cases of HCV infection has been seen between 2001 and 2004 among HIV-positive gay men in London and Brighton, in particular. It is particularly striking as a large-scale anonymized serosurvey of patients at 14 genitourinary medicine clinics in the United Kingdom found an HCV antibody prevalence below 1 percent among patients who did not report injecting drug use.

All of the men included in these reports have previously tested HCV negative, arguing against an epidemic driven purely by screening. Fifty-two new cases had been seen among 1,200 gay men treated at the Royal Free Hospital's clinic, with comparable numbers at two other London clinics and one in Brighton, on the South Coast (a city with a large gay male population and an HIV prevalence rate comparable to London).

There was a strong association between HCV transmission and "fisting"—which was reported in all of the cases seen at the Royal Free Hospital. Unprotected anal intercourse was also very common and many men reported intranasal use of cocaine and/or ketamine, which could take the form of "bullets" passed from one person to another. A small minority, between 2 percent and 5 percent, reported injecting drug use.

Sanjay Rasiklal Bhagani (Royal Free Hospital, London) gave an interim report of an ongoing study of response to treatment in this population. The majority of cases were genotype 1, none were genotype 2, and there were equal numbers that could not be typed, or were genotype 3 or 4. Some 25 percent spontaneously cleared HCV, as detected by repeatedly undetectable viral load (using bDNA assays with a 50-copy threshold). Among 15 who started treatment, with pegylated IFNa 2B and ribavirin, 71 percent (7/9) had undetectable viral load at end of therapy (48 weeks), implying clearance. One patient was lost to follow-up, one stopped due to drug intolerance, and three stopped due to depression. Other adverse events reported included anemia (no treatment or dose changes needed), a transient decline in CD4 counts (by a median of 128 cells per microlitre), and neutropenia (18 percent of patients requiring intermittent G-CSF treatment). HIV viral load was not affected. ■

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HIV Medicine

Symptomatic bone disorders in HIV-infected patients: Incidence in the Aquitaine cohort (1999-2002)

Martin K, Lawson-Ayayi S, Miremont-Salame G, et al.

BACKGROUND: Since the inception of highly active antiretroviral therapy (HAART), mortality among HIV-infected patients has decreased, but this has been accompanied by the appearance of several complications. *OBJECTIVES:* To estimate the incidence of symptomatic bone disorders in HIV-infected patients of the Aquitaine cohort (from southwest France) for the period 1999-2002, and to describe cases. *METHODS:* We retrospectively studied the records of 2,700 patients of the Aquitaine cohort, which was derived from a hospital-based surveillance system of HIV infection in France. All cases of symptomatic bone disorders diagnosed from 1 January 1999 to 30 June 2002 were reviewed. *RESULTS:* Fourteen cases of bone disorders were diagnosed; eight cases of aseptic osteonecrosis and six cases of severe osteoporosis, representing incidences of 0.3/1,000 patient-years [95 percent confidence interval (CI): 0.14-0.62] and 0.22/1,000 patient-years (95 percent CI: 0.09-0.52), respectively. All patients with aseptic osteonecrosis were male, while all but one with osteoporosis were female. The ages of patients ranged from 36 to 54 years for osteonecrosis and from 39 to 50 for severe osteoporosis. At the time of clinical diagnosis, all patients were treated with nucleoside reverse transcriptase inhibitors (duration of treatment ranging from 19 to 123 months for osteonecrosis and from 46 to 132 months for severe osteoporosis). Ten patients were treated with nonnucleoside reverse transcriptase inhibitors [duration of treatment ranging from six to 31 months for osteonecrosis (n=6) and from four to 29 months for severe osteoporosis (n=4)]. Thirteen patients were treated with protease inhibitors [duration of treatment ranging from 12 to 62 months for osteonecrosis (n=8) and from 3 to 44 months for severe osteoporosis (n=5)]. All osteonecrosis and five osteoporosis patients had at least one known risk factor or comorbidity associated with the bone disorder occurrence. *CONCLUSIONS:* In our study, the etiology of clinical bone disorders seemed to be multifactorial, as almost all the patients had at least one possible risk factor in addition to HAART exposure.

HIV Med 2004;5(6):421-426.

American Journal of Independent Medicine

Blood and body fluid exposure risks among health care workers: Results from the Duke Health and Safety Surveillance System

Dement JM, Epling C, Ostbye T, et al.

BACKGROUND: Healthcare workers (HCWs) are at risk of exposure to human blood and body fluids (BBF). Needlestick injuries and splashes place HCWs at risk for numerous blood-borne infections, including human immunodeficiency virus (HIV), hepatitis B (HBV), and hepatitis C (HCV). Utilizing a new comprehensive occupational health surveillance system, the objective of this research was to better define the BBF exposure risk and risk factors among employees of a large tertiary medical center. *METHODS:* A population of 24,425 HCWs employed in jobs with potential BBF exposure was followed for BBF exposure events from 1998 to 2002. BBF exposure rates were calculated for strata defined by age, race, gender, occupation, work location, and duration of employment. Poisson regression was used for detailed analyses of risk factors for BBF exposure. *RESULTS:* The study population reported 2,730 BBF exposures during the study period, resulting in an overall annual rate of 5.5 events/100 FTEs and a rate of 3.9 for percutaneous exposures. Higher rates were observed for males, persons employed less than four years, Hispanic employees, and persons less than 45 years of age. Much higher rates were observed for house staff, nurse anesthetists, inpatient nurses, phlebotomists, and surgical/operating room technicians. Poisson regression results strengthened and extended results from stratified analyses. Rates of percutaneous exposures from hollow needles were found to decrease over the study period; however, exposure rates from suture needles appear to be increasing. *CONCLUSION:* While continued training efforts need to be directed toward new HCWs, our data also suggest that employees who have been in their job one to four years continue to be at higher risk of BBF exposures. This research also points to the need for better safety devices/products and work practices to reduce suture-related injuries.

Am J Ind Med 2004;46:637-648.

Clinical Infectious Diseases

Hepatitis C virus coinfection increases mortality in HIV-infected patients in the highly active antiretroviral therapy era: Data from the HIV Atlanta VA Cohort Study

Anderson KB, Guest JL, Rimland D.

BACKGROUND: We compared survival among patients coinfected with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) with that among patients infected solely with HIV. *METHODS:* Descriptive, bivariate, and survival analyses were conducted using data for all HIV-positive patients who were seen during the period of January 1997 through May 2001 in the HIV Atlanta VA Cohort Study (HAVACS) and who had been tested for HCV antibody since 1992 (n=970). *RESULTS:* The prevalence of HCV coinfection was 31.6 percent, and coinfected patients were significantly more likely to be older, black, and injection drug users. In multivariate analysis, the duration of survival from the time of diagnosis of acquired immunodeficiency syndrome (AIDS) was significantly shortened for HIV/HCV-coinfected patients (hazard ratio [HR]: 1.84; 95 percent confidence interval [CI]: 1.09-3.10), as was time from HIV diagnosis to death (HR: 2.47; 95 percent CI: 1.26-4.82). Recovery of CD4(+) cell count from the time of initiation of HAART did not differ significantly by coinfection status. *CONCLUSIONS:* HCV coinfection is common in this HIV-infected population and negatively affects survival from the time of both HIV and AIDS diagnoses, although this is apparently not associated with a difference in CD4(+) cell recovery while receiving HAART. These findings differ from those of a previous study that was conducted in this cohort in the pre-HAART era, which found no association between HIV/HCV coinfection and HIV disease progression.

Clin Infect Dis 2004;39(10):1507-13.

Annals of Oncology

Effect of highly active antiretroviral therapy (HAART) on pharmacokinetics and pharmacodynamics of doxorubicin in patients with HIV-associated non-Hodgkin's lymphoma

Toffoli G, Corona G, Cattarossi G, et al.

BACKGROUND: We demonstrated that highly active antiretroviral therapy (HAART) increases the toxic effect of cyclophosphamide, vincristine, doxorubicin (DOX), and prednisone (CHOP) in HIV patients with non-Hodgkin's lymphoma (NHL). To ascertain the cause of increased toxicity, we investigated the pharmacokinetics of DOX in HIV patients with NHL treated with CHOP with and without HAART. *METHODS:* Complete pharmacokinetics and pharmacodynamic analysis was determined in 19 patients during 38 cycles of chemotherapy: 19 cycles with CHOP and 19 CHOP + HAART in a crossover-designed study. HAART included protease inhibitors indinavir (IDV) in nine patients, saquinavir (SQV) hard gel in six patients, and nelfinavir (NFV) in four patients. *RESULTS:* No significant effects of HAART on pharmacokinetics parameters of DOX were observed. Similarly, no differential effect on DOX pharmacokinetics among IDV, SQV, and NFV was evidenced. Significant associations (P=0.012) were observed between DOX AUC (0-infinity) (area under the concentration curve) and G3-G4 WHO hematologic toxicity in patients treated with CHOP alone, but not in those treated with CHOP + HAART (P = not significant). *CONCLUSION:* We demonstrated that HAART therapy has no significant effect on DOX pharmacokinetics. DOX AUC appears to be a predictor of toxicity only in patients treated with CHOP alone. Other factors besides DOX plasma levels are detrimental for toxicity after CHOP + HAART. Therefore, pharmacodynamic interactions between HAART and DOX should be considered.

Ann Oncol 2004;15(12):1805-1809.

New fixed-dose...

Continued from page 415

Whether the correlation with CD4 [count] at entry is medical or behavioral is hard to say. It could be behavioral—if people who show up with that low a CD4 count are worse pill takers. Showing up with a CD4 count of 25 cells/mm^3 suggests that you are not actively pursuing healthcare in a preventive way. But it could also mean that the regimens may not be as protective at low CD4 [counts] as they are with less advanced disease, for biological reasons. We don't know the answer. We can observe that drugs work less well at very low CD4 counts, but don't know what explains this.

With these caveats, we now have a lot of confidence in EFV and two NRTIs. We have some differences in these regimens, and many similarities. Physicians are now gearing up to pick the one they think is best, given that treatment of HIV, at least in the United States and Europe, can be two pills once a day, with either fixed-dose combination you prefer. Overall I think that is wonderful.

The shorthand summary on which regimen [to select] (if one chooses one of these two once-a-day options) is that for some clinicians, it is a choice between the ABC hypersensitivity story up front or not; they see this as a conversation that may leave patients feeling concerned about starting a medication that has that issue, rather than starting one that does not. That doesn't mean they won't use it. [Efavirenz's] side effects, including vivid dreams and mood changes in many patients, have to be explained in either case. We are used to explaining the side effects of pills, but Truvada may have an easier starting conversation than Epzicom. ■

Editor's note: *The studies cited above did not use Epzicom or Truvada because they were not FDA-approved at the time; thus the studies used the two separate drugs in the same doses.*

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Gilead Sciences press release. August 26, 2004. Gilead announces preliminary 24-week data from study 934 comparing Viread and Emtriva to Combivir both in combination with efavirenz in patients with HIV.

HCV coinfection hastens HIV disease progression

Michael Carter

HIV-positive patients who are coinfected with hepatitis C virus (HCV) have a shorter survival time than those who are only infected with HIV, according to results of a US study published in the November 15, 2004, edition of *Clinical Infectious Diseases*. This finding is in contrast to a study published in 1999 involving the same study population, which found that HIV-positive patients coinfected with HCV did not have poorer survival.

Investigators from the HIV Atlanta Cohort Study (HAVACS) conducted research involving a cohort of HIV-positive patients in 1999 that found no connection between HIV/HCV coinfection and HIV disease progression. Much of the data for this study were obtained in the pre-antiretroviral therapy era. The investigators speculated that the increased survival of HIV-positive patients since effective antiretroviral therapy became available, and the potential for anti-HIV drugs to cause hepatotoxicity might now yield different results.

Accordingly, investigators conducted a retrospective review of the records of their cohort comparing survival time since HIV diagnosis and progression to AIDS, and CD4 count gain after starting antiretroviral therapy in HIV/HCV-coinfected patients and patients who were only infected with HIV.

In total, 970 patients were included in the investigators' analysis. The prevalence of HCV coinfection was high, at 32 percent. Seventy-six percent of patients received antiretroviral therapy at some time during the study period, and 67 percent of patients had been diagnosed with AIDS. Sex between men was the most common HIV risk group (48 percent), followed by injecting drug use (24 percent). The majority of the cohort was black (73 percent). Patients who were coinfected with HCV were significantly more likely to be older, have a history of injecting drug use, and to have never taken antiretroviral therapy ($p < 0.001$ for all factors).

The investigators found that coinfected patients had shorter survival after their HIV diagnosis than did patients only infected with HIV ($p = 0.009$). Furthermore, the time from receiving an AIDS diagnosis to death was also shorter for patients coinfected with HIV and HCV than for patients who only had HIV infection ($p = 0.022$). However, the investigators found no difference between coinfected patients and patients who only had HIV infection in the time it took to progress to AIDS.

After starting antiretroviral therapy, both coinfected and HIV-monoinfected patients experienced a similar recovery in CD4 count by month 6. However, injecting drug use was independently associated with decreased CD4 T-cell gain.

A longer-term model considering CD4 count gain from the initiation of antiretroviral therapy to the last follow-up visit found no difference between the coinfected patients and the HIV-monoinfected patients.

The investigators believe that their study has four clinically relevant findings:

- There is a high prevalence of HCV coinfection in their HIV-positive cohort.
- Patients with HCV coinfection are less likely to receive antiretroviral therapy.
- Coinfection with HCV results in markedly reduced survival from the time of diagnosis with HIV and the time of first AIDS diagnosis.
- HCV coinfection does not affect short- or longer-term CD4 count recovery after starting antiretroviral therapy.

According to the investigators, "These findings demonstrate a shift in the effect of [HCV] coinfection from the pre-[antiretroviral therapy] era to the [antiretroviral therapy] era. A previous evaluation of survival in the HAVACS cohort found [HCV] infection had little effect on progression of HIV infection."

Possible reasons for this change suggested by the investigators include:

- The hepatic side effects of antiretroviral therapy.
- More patients being tested for HCV, correcting a selection bias.
- The longer duration of follow-up allowed more time for the development of serious hepatic events. However, this is unlikely as there was no significant increase in mortality rates for liver disease after 1997. ■

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Testing for hepatitis C virus infection should be routine for persons at increased risk for infection

Alter MJ, Seef LB, Bacon BR, et al.

In the United States, chronic hepatitis C virus (HCV) infection affects an estimated 3 million persons, most younger than 50 years of age. It is one of the leading causes of chronic liver disease morbidity and mortality and the most common indication for liver transplantation. Effective treatment can eradicate the virus and eliminate or reduce liver inflammation and fibrosis, and counseling and immunization can modify or prevent the adverse effect of cofactors (for example, alcohol consumption or coinfections) on disease progression. However, controversy surrounds the need to routinely identify asymptomatic HCV-infected persons. Because no data currently demonstrate that treatment or other interventions will reduce future cases of HCV-related chronic disease and deaths, the US Preventive Services Task Force found insufficient evidence to recommend for or against routine screening for HCV infection in adults at high risk. Chronic hepatitis C would require many years of follow-up to determine the incidence of complication after treatment of or other interventions in asymptomatic persons. It seems inappropriate to wait several decades to measure the impact of early identification of this viral infection when current data support a positive therapeutic effect that points to long-term benefits. In addition, treatment and other interventions must be provided before cirrhosis or liver failure occurs. Therefore, medical and public health professionals should continue the practice of screening persons for risk factors; offering testing to those at increased risk for HCV infection; and providing infected persons with appropriate counseling, medical evaluation, and treatment.

Annals 2004;141(9):715-717.

Roberto Gutierrez Gonzalez

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

This month, *IAPAC Monthly* is proud to feature Roberto Gutierrez Gonzalez, who is a psychologist at the HIV/AIDS Clinic of the Hospital Dr. R.A. Calderon Guardia in San José, Costa Rica.

What proverb, colloquial expression, or quote best describes how you view the world and yourself in it?
"Do not cry if you do not see the sun, because the tears do not let you see the stars." This is a phrase that allows us to have a positive mindset and the strength to fight against the adversities.

What activities, avocations, or hobbies interest you?
I like to read drama, as well as biographies of important persons who made big changes in the world that affect humanity. I also like outdoor activities such as relaxing and reflection, and I have drawing abilities.

If you could live anywhere in the world, where would it be?
I would like to live in a country with coasts, or in a big city where I can develop my specialty.

Who are your mentors or real life heroes?
I like Mahatma Gandhi's ideals, such as "no violence." He succeeded in delivering his message throughout the world, challenging people to think about the harmony between countries.

With what historical figure do you most identify?
Any human being who has had to fight battles in which nobody believed and decided to continue. I think it is a good idea to reflect and admire these persons.

Who are your favorite authors, painters, and/or composers?
Rafael Sanzio, the Renaissance painter, who found the capacity to capture the essence of life; and Franz Liszt, whose compositions capture all the pain, color, and feelings of life.

If you could have chosen to live during any time period in human history, which would it be?
The Medieval Age is a very exciting period, because in this time many big changes occurred, most to the benefit of humanity.

If you did not have the option of becoming a physician, what would you have likely become, given the opportunity?
A lawyer, so that I could use the law to make positive changes.

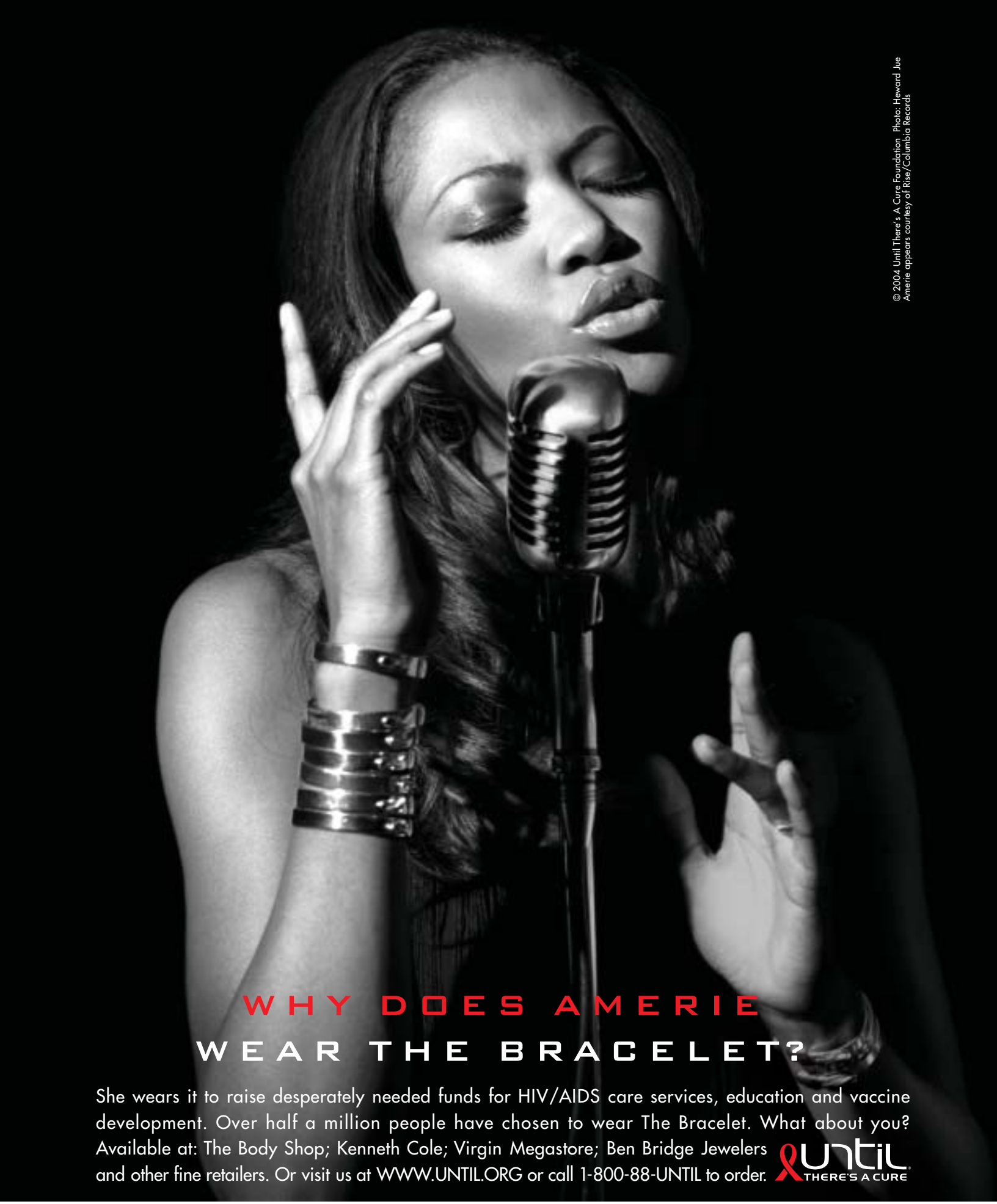
In your opinion, what are the greatest achievements and failures of humanity?
The beginning of the arts and sciences, with their achievements and failures.

What is your prediction as to the future of our planet one full decade from present day?
We have to mend our ways and begin thinking like rational human beings about all the destruction and violence around us. This is the moment to turn our attention to being better people and having a better life. ■

SAY ANYTHING

Photo: Brian Hujdich

Two hundred people joined the International Association of Physicians in AIDS Care (IAPAC) for its Honoring Our Heroes tribute dinner, held November 1, 2004, in Washington, DC. Among this year's honorees was Ethan Zohn (center) who was honored for using his US$1 million winnings from "Survivor: Africa" to launch Grassroots Soccer, an organization devoted to educating youth about HIV/AIDS with prevention messages delivered by African soccer players. Zohn is pictured with his girlfriend, Jennifer Morasca (left), who won "Survivor: The Amazon," and newly elected IAPAC Trustee Melissa Fitzgerald, a star of NBC-TV's "The West Wing."



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