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# IAPAC

MONTHLY

A close-up portrait of a young woman with a white headscarf. She has a female symbol tattoo on her forehead. The background is dark.

**'Feminizing' our  
response to AIDS**

340



**‘Feminizing’ our response to AIDS**

*José M. Zuniga*

In his monthly Report from the President, José M. Zuniga reflects on how the oppression of women in Africa can be considered a cultural vector fueling the spread of HIV on that continent at an alarming rate, and leading to a situation whereby in sub-Saharan Africa, for example, three women are infected with HIV for every two men.

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## 'Feminizing' our response to AIDS

*José M. Zuniga*

**T**hose of us who find ourselves on the road seemingly 99.9% of our professional lives, speaking out about the global AIDS pandemic and issuing calls to action, can at times find ourselves clicking into autopilot when delivering Power Point presentations laden with sobering statistics and motivational rhetoric. And so it seemed earlier this month, as I began to deliver a "State of the Global AIDS Pandemic" presentation to 800 delegates attending Kaiser Permanente's National Diversity Conference, held October 18-20, 2006, in Universal City, California. Within a period of 15 minutes, I traversed the globe from the United States (two slides) to The Ukraine (two slides), with stops in Brazil (two slides) and South Africa (four slides), telling the grim story of HIV's march across continents, wreaking death and destruction along its path.

It was not until I clicked to a slide entitled, "Feminizing the Response to AIDS," and looked directly in front of the lectern to a group of African-American women who began nodding in agreement with the words I was speaking, that I snapped back into the moment. Indeed, the devastating crisis that the AIDS pandemic represents worldwide for women is staggering in its proportion. Sub-Saharan Africa, for example, currently accounts for more than 60% of the world's HIV-positive population.<sup>1</sup> There are, of course, many factors that drive the explosive transmission of HIV, but in the tangled web that is the epidemic in Africa, many of these issues share a common thread. The oppression of women in Africa is the virus' cultural vector.

Women are rendered powerless in African societies, and existing gender inequalities are largely responsible for the



spread of HIV disease. The blatantly skewed distribution of power in African patriarchal societies makes women extremely vulnerable but has dangerous implications for all.

To examine the forces that steer the epidemic down its course, the epidemiology of HIV and AIDS in Africa must first be considered. More than 80% of all HIV infections in Africa are acquired through heterosexual contact.<sup>1</sup> This statistic is grossly out of balance with the 13% rate of infection through heterosexual contact in the United States.<sup>2</sup>

Vertical transmission from mother to child is the second most common route for the virus to take in Africa. These rates are generally much higher than in the United States and Western Europe, where the routine use of antiretroviral prophylaxis has drastically reduced mother-to-child transmission of HIV. This disparity is a direct result of differences in the nations' wealth. The Joint United Nations Programme on HIV/AIDS (UNAIDS) estimates that in sub-Saharan Africa fewer than 6% of

pregnant women in 2005 were offered services for the prevention of mother-to-child transmission of HIV.<sup>1</sup>

The continued transmission of HIV through contaminated blood during processes such as blood transfusions is another dismal consequence of poverty and inferior health services in many African countries. This is the third most important mode of transmission, one that has been virtually eradicated in many countries because the technology to prevent it is widely available.

Part of what makes the situation in Africa so devastating is that the primary roads the virus travels were shut down long ago in other countries. Much of the world's population already takes many of the roadblocks for granted. The transmission route of heterosexual contact is so heavily traveled in Africa that it demands an examination of sexual behavior.

Before delving into the workings of intimate relationships, however, the fine points of gender inequality in the public sphere merit examination. These social conditions spill over into every aspect of life, tainting women's casual and sexual relationships with men. Women are systematically disadvantaged in African society. Male bias in the structures of society is reflected in day-to-day behavior, embedded in legislation, policy, political and religious ideologies, and cultural conventions.<sup>3</sup>

Women's limited opportunities also translate into reduced access to education. Their lower levels of literacy contribute to their more limited access to information about sexually transmitted diseases, including HIV disease. Cultural conventions prevent them from asserting themselves in public, squelching any hope of improving their situation in this way. Since their work is confined to the domestic field, women's labor does not command market

value, leaving them dependent on those members of the household who operate in the cash economy. Economic need often drives women to enter into commercial sex work. The selling of sex, many argue, is often the only choice African women have between starvation and survival.

It is the link between women's position in wider society and their position in sexual relations that is crucial to understanding their vulnerability to the virus. The most recent "Report on the Global AIDS Epidemic" published earlier this year by UNAIDS reveals that in sub-Saharan Africa three women are infected with HIV for every two men.<sup>1</sup> Women have characteristically been viewed as responsible for transmitting the virus. Commercial sex workers are blamed for spreading HIV to clients, and mothers are blamed for passing it to their children. Females are thought to have a polluting influence and are treated as "vaginas or uteruses," "whores or mothers," and "vectors or vessels" as opposed to people.<sup>4</sup> Instead of regarding women as blameworthy for the severity of the AIDS epidemics in Africa (since there is no single "African" epidemic), they should be more accurately perceived as occupying a cultural niche in which they are highly vulnerable to contracting the virus.

Since women are forced to relinquish the driver's seat to males in the public sphere, they certainly have no say in the nature and timing of their sexual activity in the private sphere. Intimate relations revolve around the same "notions of personhood" that operate in the larger society.<sup>3</sup> The outcomes of these gender ideologies take form as sexual practices. Sexual norms prescribe relative passivity for females, while according sexual decision making to men.<sup>3</sup> Tolerance is expected for the greater sexual mobility of men. Female fidelity is usually viewed as necessary while male infidelity is consistent with the extension of the familial line.<sup>4</sup>

The double standard expectation is that women will enter into a marriage as virgins but men will not. In patriarchal, sub-Saharan African cultures, marriage can be defined as a legally and socially sanctioned relationship between a man and a woman within which procreation takes place. Women are viewed as the means by which to achieve an end. That end is the perpetuation of the family line.

This prime value on procreation presses young girls into risky, multiple-partner relationships long before they are psychologically or physically mature. Young women can neither refuse the sexual demands of older men nor bear the social stigma of being without a husband or children. Women are powerless within their relationships and have too little power outside of them to abandon partners that put them at risk.

How, then, do these social and sexual patterns account for the severity of the AIDS epidemics in Africa? Diane Russell, a US sociologist and recognized academic expert on the empirical study of sexual violence against women, bluntly states, "Those women who contract HIV/AIDS from their male partners because of their sexist attitudes and behavior, and/or because of their superior power and dominant status, are—when they die—victims of femicide."<sup>5</sup>

There are many examples of the manifestations of male domination that can be fatal for female partners. Male refusal to use condoms is perhaps the most critical of these behaviors. Utilization of condoms is the one factor that would undoubtedly reduce transmission rates drastically. Women are not even allowed to ask, "Can we have sex?" So it is even more difficult to bring up condom use. However, if a woman does find the courage to ask her male partner to use a condom, not only will he almost certainly refuse, he is likely to beat her. In conversing with a colleague about the theme of this Report from the President, she reminded me of a *TIME* magazine article published years ago relating the story of a nurse in Durban, South Africa, who, coming home from an HIV prevention training, suggested that her husband put on a condom before engaging in sexual intercourse.<sup>6</sup> The husband proceeded to grab a pot and bang on it loudly, attracting all the neighbors. He pointed a knife at her and demanded: "Where were you between 4 p.m. and now? Why are you suddenly suggesting that? What has changed after 20 years that you want a condom?"

Yet another expression of male dominance on which the virus thrives is the practice of female genital mutilation. This practice, which has roots in the patriarchal society, is defined by the WHO as the removal of part or all of the external female

genitalia and/or injury to the female genital organs for cultural or other non-therapeutic reasons.<sup>7</sup> It is designed to cater to men's sexual preferences and reinforce their control over women. The tendency of mutilated genitals to bleed, especially during intercourse, puts women at high risk for contracting HIV, as does the repeated use of the crude instruments used to perform these operations, which are often used on a number of girls on the same occasion. This practice is imposed on millions of girls in Africa. It is an attack not only on their bodies but also on their ability to protect themselves from a deadly disease.

Tolerance of male promiscuity is a further social construct that strips away females' autonomy with fatal consequences.<sup>3</sup> Many families' economic situations require that husbands are gone for months at a time in order to work, and they are certainly not expected to abstain from sexual activity during this time. Many women come to fear their husbands; they are worried their husbands may infect them with HIV. Their concerns are justified. When a wife suspects that her husband has many sexual partners outside the marriage, she is not entitled to refuse to engage in sex. "You are a wife, what can you do?" is the sad reality for most. Marriage is an institution of vulnerability for women in Africa with respect to HIV. In general, it is men who bring HIV into a marriage. Women can be infected, not through promiscuous activity on their own part, but as a consequence of being faithful to their husbands.

The prevalence of AIDS in Africa also transforms sexual assaulters into murderers. The problem of rape is especially highlighted in South Africa, where a woman is estimated to be five times more likely to be raped than a woman in the United States.<sup>5</sup> It is an extremely rare event that a rape is reported at all; 75% are believed to remain unreported.<sup>5</sup> And a bizarre, but nonetheless appalling, belief among many African men that sex with a virgin—even a child or baby—can cure HIV/AIDS is fuelling what is already one of the highest child sexual exploitation rates in the world.

An analysis of gender relations in Africa provides insight into how and why HIV spreads so efficiently. The question now becomes what should be done with this knowledge to generate prevention strategies. The first order of business

requires educating people about the role played by male domination in the spread of HIV, simultaneous with the development of policies to eliminate manifestations of patriarchy.<sup>5</sup> It is clear that education should focus more on gender issues than the need to avoid risky sexual behavior.

However, increased knowledge does not always translate into changed behavior. If economic dependence on men is a factor underlying women's vulnerability, greater economic security should serve to empower women.<sup>3</sup> For this to occur, women require higher levels of education. How men should be involved is another debatable issue. Male behaviors not only put their partners in danger, but themselves as well. Therefore, not only do men bear responsibility in this area, but it would be in their interest to assist in the process.

One truth above all else is clear: If AIDS is to become any less of a problem in Africa, women will have to be empowered. Though AIDS is certainly a virtually impossible fire to extinguish in any context, the patriarchal society and exploitation of women not only fuels the flames but turns a fire into an inferno. For millions of African women, this hell is their reality. Their inferior position in larger society renders them powerless in sexual relations. The manifestation of these social constructs emerges in sexual practices and behavior that not only allow HIV to transmit at alarming rates, but also are blatant violations of basic human rights. When African women are no longer denied these fundamental rights, a decrease in the severity of the AIDS epidemics in Africa will undoubtedly follow. ■

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

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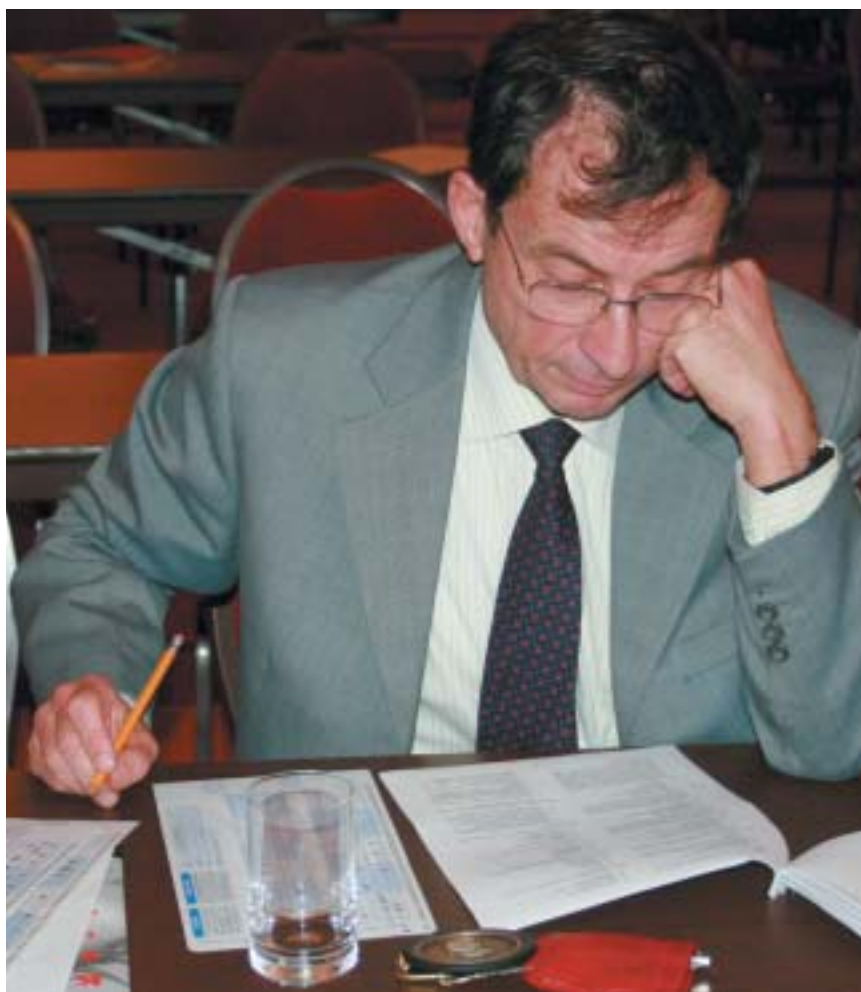


Photo: Aimee Clark

Swiss physician Bernard Hirshel writes the developed world GALEN Certification Examination during a beta-test in Budapest.

## Developed world physicians beta-test certification exam

In response to requests from physician-members in developed world countries, the International Association of Physicians in AIDS Care (IAPAC) is working with various physician-experts, including IAPAC Trustee John G. Bartlett (Johns Hopkins University, Baltimore), to build on the success of the GALEN Certification Examination's administration in sub-Saharan Africa by planning for its introduction in the developed world next year.

A developed world version of the proctored and secure GALEN Certification Examination, which will ultimately include 190 clinical practice questions, is currently undergoing beta-testing in various countries. The first beta-test took place August 18, 2006, during the 16th International AIDS Conference in Toronto. IAPAC

has also hosted beta-tests in San Francisco following the association's Decade of HAART conference last month, and in Budapest following this month's IAPAC European Sessions 2006. The purpose of the beta-tests is to facilitate psychometric analysis.

IAPAC President/CEO José M. Zuniga said outreach activities are ongoing to build consensus around the GALEN Certification Examination among key stakeholders, including national specialty societies. "We expect to make an announcement within the next several months about our plans to move forward in a collaborative fashion with the introduction of an alternative, but nonetheless credible, means of documenting core competencies among physicians who wish to specialize in HIV medicine."



## D for “diagnosis,” and E for “everything else”

**K**evin M. De Cock, a Belgian-born citizen of the United States, is an infectious disease specialist with expertise in HIV/AIDS, tuberculosis, and tropical diseases. He had served in senior public health posts, most recently as Director of the US Centers for Disease Control and Prevention (CDC) Division of HIV/AIDS Prevention from 1997 to 2000, and as Director of the CDC's activities in Kenya from 2000 to 2006. Earlier this year he was appointed Director of the World Health Organization (WHO) Department of HIV/AIDS.

In this interview, De Cock discusses new technologies to fight HIV/AIDS (eg, male circumcision, pre-exposure prophylaxis, microbicides, and vaccines), as well as the ethical issues that must be addressed as HIV testing is rolled out in developing countries. He also calls for better coordination of donor funds, given the new global target of universal access to prevention and treatment services by 2010.

**Q: Should health workers offer free HIV testing even if antiretroviral therapy (ART) is unavailable or unaffordable?**

**A:** Strong arguments can be made for free universal access to prevention, diagnosis, and treatment, since user fees impede access to these services and adherence to treatment. The absence of ART should not be an absolute impediment to the routine recommendation of HIV testing by health care providers because it is clear that a great deal can be done—even without

ART—in terms of providing life-prolonging care. Provider-initiated testing and counseling must, however, be scaled up in the context of national plans to expand access to treatment and care.

**Q: Is there a shift from voluntary HIV testing and counseling (VCT) to provider-initiated testing?**

**A:** The WHO believes that a diverse range of approaches is needed, including both VCT and provider-initiated testing and counseling. Provider-initiated testing and counseling refers to testing of patients who visit health care facilities or are visited by health workers. The process must remain voluntary and emphasize consent, confidentiality, counseling, and information. A key aspect of provider-initiated testing and counseling is to ensure informed consent by providing the patient with an opportunity to decline testing. The WHO and Joint United Nations Programme on HIV/AIDS (UNAIDS) also continue to strongly support client-initiated VCT, which occurs mainly outside health care settings for people who want to know their serostatus.

**Q: When will the WHO issue revised testing guidelines for HIV?**

**A:** The guidelines being discussed consider only provider-initiated testing in health care settings, a narrow focus. Following an international consultation in early July 2006, co-sponsored by WHO and UNAIDS, a further draft of the guidelines is being developed for public comment. The WHO and UNAIDS plan to issue the guidelines later this year.

**Q: Is it ethical to encourage self-testing in countries where counseling and treatment are not available?**

**A:** Self-testing is largely unexplored. The traditional view is that testing should not be done without counseling, but some of what is said about counseling is not evidence-based. With much more experience with testing, one has to ask whether the negative attitudes towards self- and home testing will not, in future, seem paternalistic and inappropriate. If we believe in self-empowerment and rights of the individual, why should self-testing not be allowed, when self-testing (diabetes, pregnancy) or self-examination (breast and testicular cancer) are actively promoted for other conditions? However, more work and reflection are required before offering specific advice, and some form of patient information and education will always be important.

**Q: How will testing be free and widely available in countries where HIV/AIDS prevalence is high?**

**A:** There has been a tremendous scale-up of HIV testing in developing countries, especially in Africa, mostly through VCT programs. There is increasing emphasis, for example, in Botswana, Kenya, and Malawi on the additional approach of provider-initiated testing and counseling in health care settings. In many settings testing is free, through the support of donor initiatives.

**Q: If home testing were widely available in developing countries, how would you counsel people on the implications of a positive or negative result?**

**A:** Self-testing would obviously need to be carefully handled, and protocols and standardized information will need to be developed and evaluated. Self-testing is not likely to become the dominant form of testing. We need to ask ourselves, however, whether universal knowledge of HIV serostatus in heavily affected countries is

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**Editor's Note:** Reprinted with permission from the Bulletin of the World Health Organization (Bull World Health Organ. 2006;84(10):765-840).

not a requirement if we are to achieve universal access to HIV/AIDS prevention, treatment, and care.

**Q: Is the WHO disappointed that the “3 by 5” campaign failed to achieve its stated goals?**

**A:** The “3 by 5” [campaign] was about more than a numeric target. This campaign fundamentally changed the landscape of how the world is addressing HIV/AIDS. Treatment and prevention are inseparable parts of the response and both are needed. Concerning treatment scale-up, we have learned many lessons as a result of “3 by 5.” For example, about health systems weaknesses, and that more focus is needed on previously underserved populations, such as children and injecting drug users.

**Q: South Africa attracted considerable criticism in Toronto. How do you view the situation?**

**A:** Clearly, there is much dissatisfaction with the official response to HIV/AIDS in South Africa. In my view, this has resulted in at least three important missed opportunities. First, South Africa, with its political and economic authority, could have been a leader in the fight against AIDS for the rest of the continent. Second, enormous international support, financial and technical assistance, and good will could have been mobilized if the unorthodox discussions and controversy had been avoided. Third, treatment and prevention scale-up could have occurred much faster and gone further. As it is, South Africa is not among the 20 or so low- and middle-income countries that have achieved 50% HIV/AIDS treatment coverage for those in need.

**Q: There is more donor money to fight HIV/AIDS than ever before, but is the money being spent in a coordinated way on evidence-based interventions?**

**A:** Coordination can always be improved and this is certainly necessary in the struggle against HIV/AIDS. The WHO and its partners are working to improve how we work together; for example, through implementation of the recommendations of the Global Task Team on Improving Coordination among Multilateral Institutions and International Donors. We do also need to do better in the use of evidence in the design of public health interventions; for example, on policies and practices concerning male

circumcision, isoniazid preventive therapy (for tuberculosis), post-exposure prophylaxis, and abstinence. It is part of the WHO’s role to synthesize existing knowledge, support operational research, and disseminate the evidence in support of different interventions and approaches. But decision-making will never be simply about evidence alone. Political choices obviously influence practice, such as restrictions on needle and syringe exchange in many countries. An emphasis on human rights also represents more of a value or moral judgment than an evidence-based one, but this judgment is essential.

**Q: Do some donors attach conditions to the use of funds for HIV/AIDS regarding sex workers, injecting drug users, and condoms, ignoring the scientific evidence?**

**A:** I assume you mean the US President’s Emergency Plan for AIDS Relief (PEPFAR) policies on ABC (abstinence, be faithful, condoms). The furious political debate around this, which is polarizing and often impedes genuine discussion, has generally been brought in by politicians or individuals with vested interests on both sides of the political spectrum, including in heavily affected African countries. I hope we can move beyond the ABC debate—there will not be a single magic bullet for HIV prevention, it is more complicated than fixating on the alphabet, and we also need D and E. D for diagnosis (HIV testing) and E for everything else!

**Q: Can such funds still be used in a constructive way?**

**A:** If certain programs indeed impede or do not fund certain initiatives—needle exchange, condoms, or whatever—there is nothing to stop other donors stepping in and filling the gap, or coordinating assistance. Why is this not done more? This again represents missed opportunities for collaboration and coordination.

**Q: The Bill and Melinda Gates Foundation is one of the biggest sponsors of public health programs, but could one argue that it is focusing on high-tech solutions while the technology to prevent, treat, and control HIV/AIDS is known and available but needs to be rolled out universally?**

**A:** I think the Gates Foundation is under some criticism for excessive emphasis on technologies and under-emphasizing basic programmatic work required to improve

global health. This was rather evident in Toronto with the great attention given to technological interventions such as pre-exposure prophylaxis. Understandably, the Gates Foundation does not want to take on “entitlement programs” without an end in sight. I think the Gates Foundation staff recognize the predicament and that it is the subject of intense discussion. Whether we have the knowledge and technology we need is an interesting question. Most of the world faces HIV epidemics concentrated in specific groups: men who have sex with men, sex workers, injecting drug users, sex partners of such persons, and their children. We have the knowledge and interventions to control these epidemics, and in some settings this has been done effectively. At the other extreme, we have generalized epidemics with very high rates of HIV infection in the general population; for example in southern Africa. Targeted interventions cannot control such situations, and we have not had the difficult discussions about what additional technological and social interventions are needed to turn such situations around. We have basically applied similar approaches to very different epidemiologic contexts and should not be surprised this is not successful.

**Q: There are technological developments that are keenly awaited. When will the world see these widely available?**

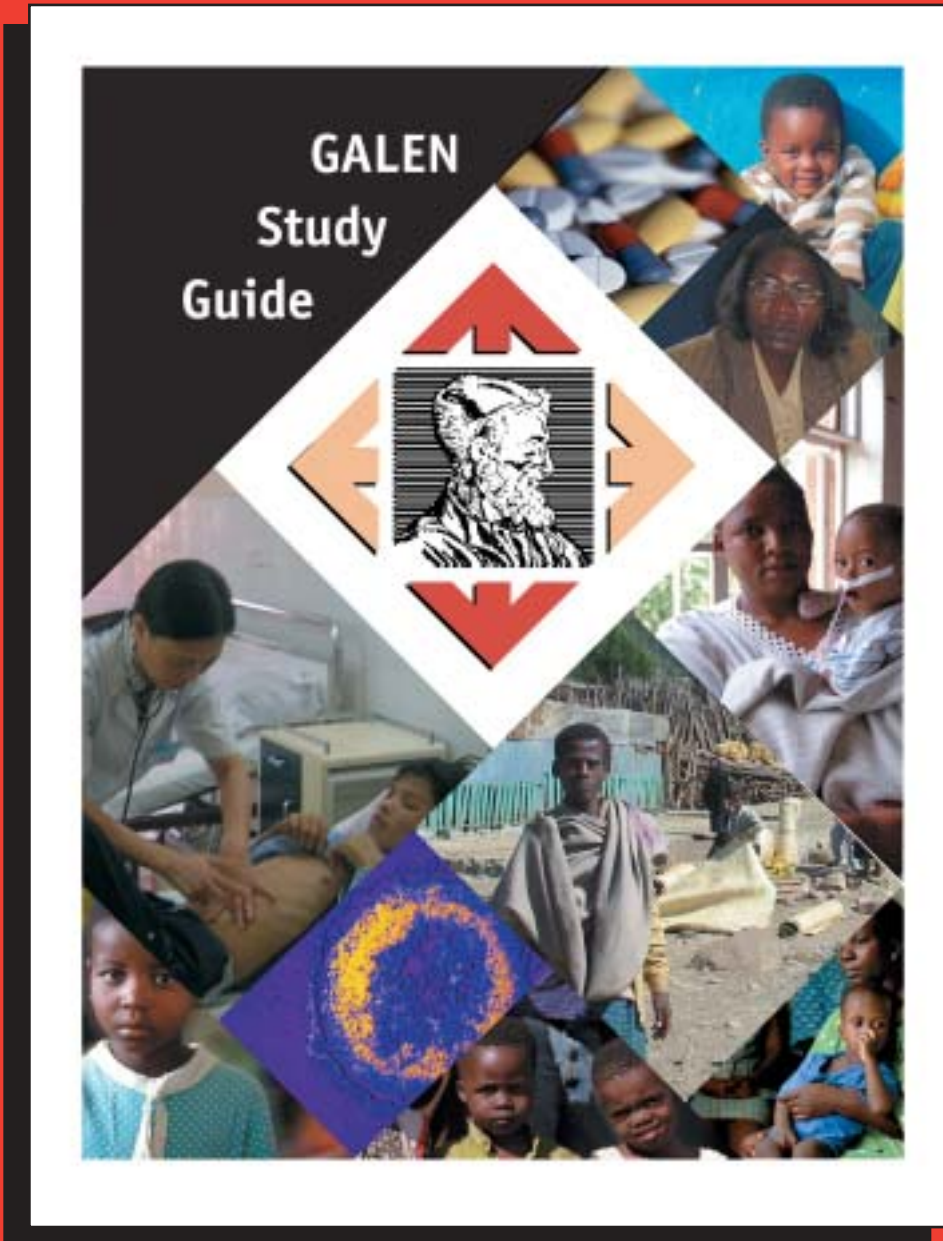
**A:** It is dangerous to predict how fast things will happen. In terms of new technologies, I think the likely order of more expanded use will be (1) male circumcision, (2) pre-exposure prophylaxis with ART, (3) microbicides, and (4) vaccines.

**Q: How would you define universal access to ART? When will this happen?**

**A:** In the speech Jong-wook Lee was to make to the 2006 World Health Assembly on the day he died, he wrote that universal access means that “no one should die because they [cannot] get drugs or there [are no] clinics.” He called for “a relentless push to make sure people know how to prevent HIV infection.” The WHO and UNAIDS are working with countries to convert a political and aspirational target into country-owned, specific targets that can be linked to programmatic work. Regardless of targets, the WHO is responsible for setting standards and norms and needs to provide guidance on what constitute acceptable levels of availability, coverage, and impact. ■

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A vibrant San Francisco street scene. In the foreground, a red and gold cable car is moving along the street. The cable car has a sign that reads "Van Ness Ave. California & Market Streets" and the number "59". A person in a light blue shirt and white pants is walking on the sidewalk next to the cable car. In the background, the Transamerica Pyramid is the most prominent building, with other skyscrapers and buildings visible. The sky is a clear, bright blue.

# After Toronto, 46th ICAAC offers back to basics

Keith Alcorn, Edwin J. Bernard,  
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Mark Mascolini, Derek Thaczuk

**A**fter the marathon-like challenge presented by the 16th International AIDS Conference held in Toronto a month prior—a challenge that tested the stamina of even the youngest and fittest of conference-goers—the 46th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), held September 27-30, 2006, in San Francisco, was a welcome relief in its staid and singular focus on the presentation of data offering insights into the challenges a variety of patients and their physicians are facing in the second decade of highly active antiretroviral therapy (HAART), as well as reviews of how to make optimal use of antiretroviral regimens constructed from within the existing HAART armamentarium. The big news at this year's ICAAC, however, was on the antiretroviral pipeline, with previews of how a new generation of drugs may help make the difference between life and death for countless millions of men, women, and children living with HIV/AIDS.

### On 'naive-te,' older age, and discordance

#### 16% of ART-naive entering GSK US studies resistant

Sixteen percent of antiretroviral therapy (ART)-naive patients enrolling in GlaxoSmithKline-sponsored clinical trials in the United States last year already had resistance to at least one antiretroviral drug, according to data presented by company researchers.<sup>1</sup> Furthermore, the frequency of resistance has almost tripled since 2000, and almost two-thirds of those with resistance in 2005 showed resistance to a nonnucleoside reverse transcriptase inhibitor (NNRTI), the backbone of first-line antiretroviral regimens for the majority of HIV-positive patients initiated on ART in the United States.

The study analyzed data from 2,035 ART-naive patients who enrolled in GSK-sponsored studies in the United States between 2000 and 2005. The recruited population was predominantly male (84%), 48% were white and 36% African American, with a median CD4 count of 252 cells/mm<sup>3</sup>. There was a slight disparity in recruitment

by year (less than 250 people were recruited to studies in 2000 and in 2005, but over 400 individuals entered studies in each of the other years). Exposure category data were available on 1,529 patients: 67% were gay men, 35% heterosexual, 5% had acquired HIV through injecting drug use, and 2% through blood transfusion.

The researchers used two different classification systems for resistance to analyse the prevalence of resistance: the International AIDS Society-USA (IAS-USA) definitions<sup>2</sup> and the Stanford University HIV Drug Resistance Database definitions.<sup>3</sup>

NNRTI resistance prevalence grew from 2% in 2000 to between 10% and 11% in 2005, while nucleoside reverse transcriptase inhibitor (NRTI) resistance prevalence grew from 4% to 5% in 2000 to 7% to 8% in 2005, depending upon which classification system was used. However, the two systems were in close agreement for all years and all drug categories regarding resistance prevalence. Protease inhibitor (PI) resistance showed less of a trend toward increase, and remained below 5% throughout the period.

In the multivariate analysis, the likelihood of participants having any resistance mutations significantly increased over time between 2000 and 2005, ( $P=0.0151$  IAS-USA definitions or  $P=0.0219$  Stanford University definitions, respectively). Similarly the likelihood of having either NRTI or NNRTI mutations significantly increased over time by either IAS definition ( $P=0.0419$ ,  $P=0.0109$ , respectively) or Stanford University definitions ( $P=0.0116$ ,  $P=0.0074$ , respectively).

When looking at specific demographics of study participants, multivariate analysis showed no significant difference between gay men and heterosexuals in the risk of resistance (although by using the Stanford University definitions, heterosexuals appeared to have a lower risk of acquiring PI resistance). The analysis also revealed a significantly lower risk of resistance overall among African-American men and women compared to whites (approximately 40% reduced risk), and a lower risk of NRTI (53% lower risk). The Stanford University and IAS-USA databases did not agree on whether a reduced risk of resistance for NNRTIs and PIs also applied to African Americans. In addition, a greater risk of resistance in later years among people with lower viral load (<100,000 copies/mL). Since higher CD4

count did not show a similar relationship, it is impossible to know whether this is a marker for more recent infection.

#### ART suppresses viral load in older patients, but CD4 cell recovery impaired

Individuals who are diagnosed with HIV aged 50 years and above have as good a response to ART as patients who are aged under 40 when they receive their HIV diagnosis.<sup>4</sup> However, researchers from [affiliation] found that even though older patients do well on ART, they are nevertheless more likely to progress to AIDS and die than do younger patients. In another study also looking at older patients, Spanish researchers found that although older age did not reduce the odds of a patient achieving and sustaining viral suppression with anti-HIV therapy, but it yielded lower increases in CD4 count for patients on ART as they aged.<sup>5</sup>

In the California study, researchers wished to gain a better understanding of the characteristics of HIV infection in older patients. For the purpose of the study, they defined "older" as 50 years of age or above at the time of HIV diagnosis. Over a six-year period (1998 to 2004), data were gathered on all new HIV diagnoses at 11 hospitals in California. Patients were divided into two groups on the basis of their age: the first group consisted of just under 500 patients who were aged 50 years or older at the time of their HIV diagnosis; the second group was composed of almost 4,000 patients aged between 18 and 40 years at the time of HIV diagnosis. Information was gathered for both groups of patients and compared regarding risk factors for HIV infection; baseline viral load and CD4 count; response to ART; progression to AIDS; and death.

Some significant differences existed between older and younger patients at the time of their HIV diagnosis (Table 1). Older patients were more likely to be male (84% versus 75%, younger patients,  $P<0.01$ ) and more likely to have been infected with HIV due to sex (52% versus 29% younger patients,  $P<0.01$ ). By contrast, younger patients were significantly more likely than older patients to be coinfecting with hepatitis C virus (HCV) at the time of HIV diagnosis (45% versus 14%,  $P<0.01$ ), suggesting higher levels of injecting drug use.

At the time of their HIV diagnosis, older patients had a median CD4 count of 229 cells/mm<sup>3</sup> compared to a median

count of 360 cells/mm<sup>3</sup> in younger patients. This difference was statistically different ( $P<0.01$ ), and also had important clinical implications as 35% of older patients had an AIDS-defining illness at the time of HIV diagnosis compared to 20% of younger patients. This difference was also statistically different ( $P<0.01$ ).

The researchers next compared how older and younger patients responded to ART. Both groups of patients had comparable viral load before treatment was initiated, but after six months of treatment significantly more older patients had a viral load below 500 copies/mL than did younger patients (85% versus 66%,  $P<0.01$ ). This difference was maintained a year after ART was initiated (86% versus 68%,  $P<0.01$ ), but after five years, although more older patients still had a viral load below 500 copies/mL, the difference between the two groups of patients had ceased to be statistically significant (81% versus 73%).

Despite having better virologic control of HIV, CD4 counts were lower among older patients than younger patients six and 12 months after starting ART by approximately 100 cells/mm<sup>3</sup> (313 cells/mm<sup>3</sup> versus 415 cells/mm<sup>3</sup>; 350 cells/mm<sup>3</sup> versus 449 cells/mm<sup>3</sup>). This difference was maintained five years after treatment was initiated (483 cells/mm<sup>3</sup> versus 547 cells/mm<sup>3</sup>). No tests for statistical significance were provided by the researchers, but at all time points measured after the initiation of ART, both younger and older patients had median CD4 counts high enough to suggest adequate protection against AIDS-defining illnesses.

Finally, the researchers compared outcome in their patients. They noted that older patients were significantly more likely to progress to AIDS ( $P<0.01$ ), were significantly more likely to die ( $P<0.01$ ), and had significantly shorter survival ( $P<0.01$ ). The only significant factor associated with an increased risk of AIDS and dying for older patients was AIDS at the time of HIV diagnosis. By contrast, multiple risk factors were significantly associated with disease progression and death for younger patients, including coinfection with hepatitis C virus ( $P=0.019$ ); AIDS at the time of HIV diagnosis ( $P=0.017$ ); and a baseline CD4 cell count below 200 cells/mm<sup>3</sup>.

The Spanish study produced broadly similar findings. It included 187 patients who had a CD4 count below 200 cells/mm<sup>3</sup> and were ART-naive when treatment was initiated. Although age had no effect on

**Table 1. Traits of older, younger individuals at HIV diagnosis**

	≥50 years (n=493) (n, %)	18 to 40 years (n=3,916) (n, %)	P
Male	416 (84.4)	2,926 (74.8)	<0.001
IDU	25 (5.2)	1,658 (43.3)	<0.001
Heterosexual	250 (52)	1,110 (29)	<0.001
MSM	132 (27.4)	894 (23.4)	0.047
MSMW	32 (6.7)	59 (1.5)	<0.001
AIDS at entry	188 (38.1)	270 (20.2)	<0.001
AIDS in 1st year of HIV	31 (6.4)	89 (26.3)	<0.001
HCV coinfection	55 (13.8)	1,451 (45.2)	<0.001
1st viral load <500 copies/mL	22 (5)	263 (9)	0.016
1st CD4 count <200	267 (57)	1,253 (35)	<0.001
1st CD4 count 200-350	93 (20)	751 (21)	<0.001

IDU = injecting drug user; MSM = men who have sex with men; MSMW = men who have sex with men and women

the likelihood of achieving and maintaining viral load for up to 18 months after starting antiretroviral drugs, each additional 10 years in age significantly reduced (by 90%) a patient's odds of achieving a CD4 count of 350 cells/mm<sup>3</sup> after 18 months of ART ( $P=0.02$ ).

#### **Immunologically discordant ART response, increased disease progression risk**

HIV-positive patients whose ART succeeds in suppressing viral load to undetectable levels, but who nevertheless fail to experience an increase in their CD4 count above 200 cells/mm<sup>3</sup>, remain at a high risk of experiencing progression to AIDS and death in the first year of treatment.<sup>6</sup>

The objective of ART is to suppress the replication of HIV in the blood to undetectable levels (below 50 copies/mL), thus allowing the immune system to strengthen and preventing the emergence of AIDS-defining infections and tumours. However some patients who commence ART experience an immunologically discordant response to their treatment. This means that although their viral load is suppressed to undetectable levels, their CD4 count fails to increase to above 200 cells/mm<sup>3</sup>.

Canadian researchers wished to determine if a failure to achieve a CD4 count above 200 cells/mm<sup>3</sup>, despite having an undetectable viral load, was associated with an increased risk of progression to AIDS and death. They therefore conducted a study involving 299 patients who started ART between 1996 and 2003.

To be included in the study, patients needed to have had two consecutive viral loads below 50 copies/mL. The researchers then divided patients into two groups according to their CD4 count response to

ART: patients whose CD4 count had increased to at least the target level of 200 cells/mm<sup>3</sup>, and those whose CD4 count had not. Rates of progression to AIDS and death were then compared between the two groups during the first year of ART. The median age of the study population at baseline was 42 years, 86% were male, 15% were (or had been) injecting drug users, 27% had been diagnosed with AIDS, and median CD4 count was 80 cells/mm<sup>3</sup>.

A total of 97 patients (32%) failed to experience an increase in their CD4 count during the first year of ART, despite having effective control of HIV. There were 21 new AIDS-defining events, and six deaths. When the researchers looked at the factors associated with an increased risk of HIV disease progression, they found that patients whose CD4 counts did not increase to at least 200 cells/mm<sup>3</sup> a year after commencing virologically effective ART had a hazard ratio of progression to AIDS or death of 3.94 compared to patients whose CD4 count increased to above 200 cells/mm<sup>3</sup>.

#### **HCV infection limits ART-associated cholesterol increases**

HIV-positive patients on ART who are also HCV-coinfected are less likely to have abnormally high levels of cholesterol or triglycerides.<sup>7</sup> Hyperlipidemia is a recognised complication of ART, but exactly how HIV, HCV, hepatitis B virus (HBV), and lipids interact is not fully understood.

Canadian researchers studied 729 HIV-monoinfected patients and compared their lipid levels with 305 HIV/HCV-coinfected patients. All were on ART and had their lipid levels checked at the beginning of

the study and again at six and 12 months. The differences between the two groups were marked and statistically significant.

For those only infected with HIV the total blood cholesterol levels rose by an average of 0.99 mmol/l at six months and by 1.43 mmol/l at 12 months. But in those with HIV/HCV coinfection cholesterol rose by only 0.16 ( $P<0.001$ ) and 0.01 mmol/l respectively ( $P<0.001$ ). Similar results were seen when the total cholesterol findings were broken down to look at low-density lipoprotein (LDL) and triglycerides.

Disorders of the metabolism, such as high cholesterol levels, led 7% of HIV-monoinfected patients to stop or change their ART, compared to less than 1% of those who were HIV/HCV-coinfected. Twenty-two percent of HIV-infected patients went on to take a lipid-lowering drug, such as a statin, compared to just 4% of those with coinfection.

The researchers also looked at what happened when coinfecting patients were treated for their HCV infection using interferon (IFN). Intriguingly they found that successful treatment of HCV means that the protection against raised lipid levels with ART is lost. Total cholesterol rose by 0.85 mmol/l in coinfecting patients whose HCV levels dropped long-term after treatment with IFN. But the level was unchanged in patients who did not respond to IFN.

The researchers also looked at whether HBV infection had any effect on lipid levels but found nothing to suggest it did.

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### ATV/EFV NRTI-sparing regimen effective, raises lipid levels

Regimens that spare NRTIs and consist of ritonavir (RTV)-boosted atazanavir (ATV) plus efavirenz (EFV) demonstrate potent antiviral activity in treatment-naïve patients, but raise levels of triglycerides and both LDL and high-density lipoprotein (HDL) cholesterol.<sup>8</sup>

Given concerns about long-term side effects such as lipoatrophy and mitochondrial toxicity associated with certain NRTIs, researchers have explored the use of NRTI-sparing regimens that include only NNRTIs and protease inhibitors PIs. However, NRTI-sparing regimens may cause toxicities of their own, in particular elevated lipid levels. In studies to date,

ATV has been shown to cause fewer lipid abnormalities than other drugs in the PI class.

Bristol-Myers Squibb researchers presented data on one such regimen. In the multicenter, open-label BMS-121 study, 61 participants initiated on ART for the first time were randomized and began treatment with one of two doses of RTV-boosted ATV (300/100 mg or 400/100 mg once daily) plus 600 mg EFV for 48 weeks. No NRTIs were used.

Most participants were men (85%), nearly half (49%) were white, 43% were African American, and the mean age was 37 years. At study entry, participants had CD4 counts of at least 50 cells/mm<sup>3</sup> (median 305 cells/mm<sup>3</sup>), viral load levels of 1,000 copies/mL or higher (median 4.97 log<sub>10</sub> copies/mL), and fasting triglyceride levels below 200 mg/dL (considered the upper limit of normal).

Overall, viral load fell by a mean 3.24 log<sub>10</sub> copies/mL by Week 48. In an intention-to-treat analysis (drop-outs counted as failures), 75% of patients in the 300/100 mg ATV arm and 67% in the 400/100 mg ATV arm achieved viral suppression below 400 copies/mL; 63% and 61%, respectively, had viral loads below 50 copies/mL. Mean CD4 counts increased by 271 cells/mm<sup>3</sup> in the 300/100 mg group and 250 cells/mm<sup>3</sup> in the 400/100 mg arm.

In an observed/as-treated analysis (looking only at patients who successfully completed the study), 92% and 96% in the 300/100 mg and 400/100 mg arms, respectively, reached viral load levels below 400 copies/mL, while 77% and 87% had viral load below 50 copies/mL.

With regard to side effects, moderate to severe (grade 2 to 4) treatment-related adverse events were seen in nearly one-third of participants (26% in the 300/100 mg arm and 30% in the 400/100 mg arm), with the most common being insomnia, skin rash, diarrhea, and dizziness. A total of 12 patients stopped treatment prematurely, but only two discontinuations were due to adverse events.

Grade 3 to 4 bilirubin elevation was observed in 13% of patients in the 300/100 mg arm and 40% in the 400/100 mg arm, though none discontinued for this reason. For grade 3 to 4 liver enzyme elevations, the rates were 10% and 7%, respectively, for alanine aminotransferase (ALT), and 7% and 3% for aspartate aminotransferase (AST).

Looking at lipid changes, fasting triglyceride levels rose by 48% from baseline in

the 300/100 mg arm and by 63% in the 400/100 mg arm. These elevations were greater than those observed in most studies of ATV or EFV to date, although none were worse than grade 2.

Total cholesterol increased by 29% and 32% from baseline in the 300/100 mg and 400/100 mg arms, respectively. From a clinical perspective, it is more useful to consider the different types of cholesterol separately. Low-density lipoprotein is a risk factor for cardiovascular disease, while HDL has a protective effect. Low-density lipoprotein increased by 11% in the 300/100 mg arm and by 13% in the 400/100 mg arm, while HDL rose by 54% and 45%, respectively.

None of the total cholesterol or LDL elevations were considered severe (grade 3 to 4), while the HDL increases were greater than those observed in most previous studies of these drugs. Further, the ratios of total cholesterol to HDL and of LDL to HDL (TC:HDL and LDL:HDL) decreased in both dose arms, which is considered to be a more favorable.

The researchers concluded that both dosing regimens of ATV/r plus EFV “were generally safe, well-tolerated and demonstrated potent antiretroviral efficacy through 48 weeks.” They added that, “increases in triglycerides, total cholesterol, and LDL cholesterol were observed in both arms and were accompanied by robust increases in HDL cholesterol and decreases in TC:HDL and LDL:HDL ratios.” Because both potentially dangerous triglycerides and LDL and protective HDL increased simultaneously, the researchers acknowledged that the long-term implications for cardiovascular health could not be determined.

### Trizivir non-inferior to unboosted ATV in treatment-naïve

Trizivir is non-inferior to unboosted ATV plus Combivir as first-line ART.<sup>9</sup> After 48-weeks, 62% of participants on the triple-NRTI regimen achieved viral loads below 400 copies/mL compared with 59% on the unboosted PI, although important differences were seen in patients who initiated ART with viral loads above 100,000 copies/mL, leading researchers to conclude that Trizivir should only be considered as first-line ART in patients with viral loads below this threshold.

Current treatment guidelines from both the United States and the United Kingdom



do not recommend a triple-NRTI combination as first-line ART due to Trizivir's reduced potency compared with EFV.<sup>10,11</sup> Although unboosted ATV is recommended in the US guidelines as an option for first-line treatment,<sup>10</sup> the latest IAS-USA treatment guidelines only recommend the use of RTV-boosted ATV due to concerns over low trough levels of the unboosted drug that might lead to resistance.<sup>12</sup> Unboosted ATV is not approved in the Europe for similar reasons, and therefore, UK guidelines do not recommend its use in first-line therapy.<sup>11</sup>

However, the guidelines do state that there are situations when the triple-NRTI combination of zidovudine (ZDV)/lamivudine (3TC)/abacavir (ABC) could be considered as first-line ART—notably when NNRTI- or boosted PI-based ART cannot be used, for example when the concomitant treatment of a coinfection, in particular tuberculosis (TB), is warranted since TB treatment can interact with NNRTI- or boosted PI combinations.

The randomized, open-label ACTION study (or ESS100327) effectively compared ABC and unboosted ATV head-to-head, with a common background of ZDV and 3TC in both arms. Participants were randomized to receive one of two triple-drug antiretroviral regimens: ZDV plus 3TC plus ABC (taken as one Trizivir tablet twice daily) or ZDV plus 3TC plus ATV (taken as one Combivir pill twice daily, plus two 200 mg capsules of ATV once daily).

A switch to tenofovir (TDF) was allowed if participants taking ABC experienced a suspected hypersensitivity reaction. Similarly, a switch to unboosted fosamprenavir (FPV) was allowed if participants taking ATV experienced clinical manifestations of hyperbilirubinemia.

Virological failure was defined as viral load reduced less than 1 log from baseline by Week 12, viral load not below 400 copies/mL by Week 24, viral load previously below 50 copies/mL rebounding above 400 copies/mL prior to Week 24, confirmed viral load above 400 copies/mL after Week 24, or unconfirmed viral load above 400 copies/mL at Week 48. None of these definitions meet the current gold standard of a sustained viral load below 50 copies/mL at Week 48, however, which has been used in many recent studies, including those comparing currently recommended first-line antiretroviral regimens: boosted FPV with RTV-boosted LPV and EFV with LPV.

In total, 279 patients were enrolled in

the study, 139 were randomized to receive ABC and 140 received LPV. However, one patient in the ABC arm did not receive treatment and this led the researchers to provide a slightly modified intent-to-treat analysis, which they termed, “intent-to-treat exposed (ITT-E).”

Demographic, immunologic, and virologic characteristics were essentially similar in both arms. This was an ethnically varied group, with an average age of around 37 years; one-in-five were women. Baseline viral loads ranged between 5,000 copies/mL and 200,000 copies/mL, and the median baseline viral load was 66,000 copies/mL; median CD4 counts were at least 100 cells/mm<sup>3</sup>, and the median CD4 count was 268 cells/mm<sup>3</sup>.

The researchers first presented ITT-E data where switch *does not* equal failure. They found that overall both arms were similar in efficacy. At 48 weeks, 64% of participants initially randomized to the ABC arm and 63% of participants initially randomized to the ATV arm had sustained viral loads below 400 copies/mL. Both arms had a median CD4 count increase of 147 cells/mm<sup>3</sup> from baseline to week 48.

However, there were noticeable differences in efficacy at higher viral loads when the participants were stratified according to baseline viral load above and below 100,000 copies/mL. Only 39% of the 23 participants in the ABC arm with baseline viral loads above 100,000 copies/mL had sustained viral loads below 400 copies/mL at Week 48. In contrast, 64% of the 25 participants in the ATV arm with baseline viral loads above 100,000 copies/mL had sustained viral loads below 400 copies/mL after 48 weeks. However, due to the small number of participants in both arms, this only achieved borderline statistical significance.

During their summation, the researchers also presented more rigorous ITT-E data, in which switch equals failure, and found slightly reduced efficacy at 48 weeks in the study population as a whole: 62% in the ABC arm and 59% in the ATV arm. No CD4 count data were provided for this analysis.

Seventy-five percent, or a total of 103 out of the 138 who began treatment in the ABC arm completed the full 48 weeks, compared with 98 out of the 140 (70%) who began treatment with ATV. The differences were not statistically significant. The most common reason for not completing the study was virological failure. A total of 18 (13%) in the ABC arm and 17 (12%) in the ATV arm met one of the five definitions

of virological failure. There were no significant differences between the arms in terms of which of these five definitions they met.

Resistance profiles were somewhat similar between the two arms, with 10 participants in the ABC arm harboring resistant viruses, nine of whom had the M184V mutation (which confers resistance to 3TC and FTC), seven of whom had minor PI mutations. One individual had several thymidine analog mutations (TAMS) and one individual—strangely, and possibly due to baseline transmitted resistance—K103N, which confers resistance to NNRTIs. Eleven participants in the ATV arm had resistant virus, nine of whom also had the M184V mutation, six of whom harbored minor PI mutations, and again one had K103N.

Similar numbers in both arms experienced grade 2 to 4 adverse events. Notably 21% and 4% in the ATV arm experienced hyperbilirubinemia and yellowing of the whites of the eyes, respectively. The most commonly reported side effects in the ABC arm were nausea (11% versus 4% in the ATV arm) and fatigue (5% versus 2% in the ATV arm), and 5% had a suspected ABC hypersensitivity reaction.

Lipid profiles were comparable at week 48, with very slight increases of total cholesterol and very slight reductions in LDL in both arms. However, slightly higher increases were noted in triglycerides in participants in the ABC arm (+11% from baseline versus +5% in the ATV arm); and slightly higher increases were seen in HDL in the ATV arm (+21% versus +16% in the ABC arm).

The researchers concluded that although ABC-containing triple-NRTI regimens were non-inferior to ATV-containing PI-based regimens according to the study protocol, Trizivir “remains a viable option” for “select patients naive to therapy” with viral loads below 100,000 copies/mL. However, these data show that neither Trizivir nor unboosted ATV appear to be as potent as the currently recommended or alternative first-line antiretroviral regimens in the most recent treatment guidelines.

### **NVP hepatotoxicity after switch no more likely at higher CD4 counts**

Patients with undetectable viral load who switch from current treatment to nevirapine (NVP) when they have a CD4 count above the recommended threshold for starting the NNRTI are no more likely to develop

hepatotoxicity than women with CD4 counts below 250 cells/mm<sup>3</sup> or men with CD4 counts below 400 cells/mm<sup>3</sup>.<sup>13</sup>

Nevirapine has been shown to pose a risk for liver toxicity for treatment-naive patients who are starting their first antiretroviral regimen at relatively high CD4 counts. The degree of risk is different for men and women: men with CD4 counts above 400 cells/mm<sup>3</sup> and women with CD4s above 250 cells/mm<sup>3</sup> are most at risk for hepatotoxicity. However, the risk has been unclear for those who are already virologically suppressed on a non-NVP-containing regimen, who switch to one that contains NVP, and who have CD4 cell counts above these levels.

Spanish researchers conducted a meta-analysis that pooled the results of four existing studies. To be eligible for inclusion in the meta-analysis, studies had to have switched participants from a successful antiretroviral regimen to one containing NVP while the participant’s viral load was still undetectable, and then observed participants for at least three months after switching. The selected studies included a one-year study in patients who switched to NVP from a PI; a randomized study of prednisone as a preventive treatment against NVP-associated rash; a large randomized comparative study of switching from a PI to either NVP, ABC, or EFV; and a study of cetirizine as a preventive treatment against NVP-associated rash.

A total of 410 trial participants were entered into the analysis. Of these, 277 were deemed eligible for the high-CD4 group: females with a CD4 count of 250 cells/mm<sup>3</sup> or higher, and men with CD4 count of 400 cells/mm<sup>3</sup> or higher. The remaining 133 participants were designated as the low-CD4 group.

Occurrences of liver toxicity (after the treatment switch) were then examined in both groups. The researchers defined hepatotoxicity as happening if: (a) liver enzymes (ALAT or ASAT) increased from normal levels to above 200 units/L, or (b) increased by a factor of three or more if they were abnormally high to begin with.

The study showed a 2% risk of hepatotoxicity in the low-CD4 group, and a 4% risk in the high-CD4 group. However, the statistical difference between the two groups was not significant, and the overall results showed essentially no difference in risk between the low- and high-CD4 groups. The only clear risk factor for

hepatotoxicity was having elevated liver enzymes at the beginning of the study. There were no deaths, and only a very few patients (1%) developed liver inflammation (hepatitis).

The researchers concluded that their analysis found no evidence of an increased risk of hepatotoxicity for women with CD4 counts above 250 cells/mm<sup>3</sup> or men with CD4 counts above 400 cells/mm<sup>3</sup> who switch to NVP when they already have undetectable viral load as a result of previous ART.

A second study, conducted at a single treatment center in Munich, Germany, looked at that center’s experience of hepatotoxicity in treatment-naive and -experienced patients from 1996 to 2005.<sup>14</sup> They defined hepatotoxicity as an ALT five times the upper limit of normal. Their analysis included 507 patients (397 male, 110 female) with a median baseline CD4 count of 219 cells/mm<sup>3</sup> in women and 270 cells/mm<sup>3</sup> in men. Forty percent of women had a CD4 count over 250 cells/mm<sup>3</sup> and 27% of men had a CD4 count over 400 cells/mm<sup>3</sup>.

The study evaluated 817 patient-years of NVP treatment with a median observation time on NVP of 21 months. At the time of analysis 58% had discontinued NVP treatment, 20% due to treatment failure, 6.7% due to rash, and 7.5% due to liver enzyme elevations. Other reasons for discontinuation were not stated. Of the 38 patients who discontinued due to liver enzyme elevations, 20 of 38 discontinued due to ALT more than five times the upper limit of normal, after a median of 3.6 months on nevirapine. Two patients had acute hepatitis A or B, while the remainder discontinued due to smaller liver enzyme increases.

Among men, 3.9% experienced grade 3 or 4 ALT elevations, compared to 6.3% of women. There was no significant difference by CD4 count in the risk of grade 3 or 4 ALT elevation for either men or women, and the only independent risk factors by multivariate analysis were HBV or HCV coinfection (odds ratio 3.92), or elevated ALT levels at baseline (OR 4.84). A prior AIDS diagnosis, a CD4 count above 250 cells/mm<sup>3</sup>, or being new to treatment did not increase the risk.

### **Two-drug ART with TDF/EFV less effective than triple-ART**

A team of French investigators has found a two-drug maintenance regimen of TDF/EFV to be less effective than a three-drug regimen containing the same two

drugs plus 3TC over 48 weeks of follow-up.<sup>15</sup> As a possible way of reducing long-term toxicities associated with NRTIs (eg, lipodystrophy), the COOL study specifically looked at the effectiveness and toxicity of 3TC as part of one specific antiretroviral drug regimen. In this study, researchers at various sites in France took participants already on successful ART, and switched them to either a standard three-drug regimen—TDF/3TC/EFV—or a simplified regimen of only TDF and EFV.

To enter the 48-week trial, patients needed to have already been on a stable treatment regimen for at least three months, with a viral load below 50 copies/mL, and no history of treatment failure. They needed to weigh over 45 kg, and to show no significant toxicities at the time of entering the trial. Since TDF may be toxic to the kidneys in people with reduced kidney function, laboratory markers of kidney health had to be normal (creatinine clearance over 60 ml per minute). There were no restrictions on CD4 count.

The COOL study enrolled 143 patients, who were randomized to receive either TDF/EFV/3TC, or TDF/EFV. Characteristics of the two groups were very similar, with the following overall average values: 40 years of age, 69kg, CD4 count of 473 cells/mm<sup>3</sup>, and 3.7 years on ART (43.5% NNRTI-based, 45.5% PI-based, 71% including ZDV/3TC). Twenty-eight percent of the participants were female.

Intent-to-treat (ITT) analysis included all 143 original participants; cases where data was missing for any reason (including those who dropped out of the study) were classified as treatment failures. Table 2 reflects results by both methods.

Six participants were “lost to follow-up” in the TDF/EFV arm, but only two in the TDF/EFV/3TC arm. Somewhat oddly, all four dropouts due to side effects were in the TDF/EFV arm. (No kidney toxicity or drop in blood phosphate levels was seen.)

All three of the virologic failures were also in the two-drug, TDF/EFV arm: all three of these patients acquired NNRTI resistance mutations. (One case was likely due to very poor treatment adherence, but the adherence levels for the other two were not known.) There was no explanation as to why more side effects and dropouts would be seen in the group taking fewer medications.

The researchers concluded that, “TDF/3TC/EFV demonstrates an optimal

**Table 2. Two- versus three-drug maintenance for 48 weeks**

	EFV/TDF (n = 72)	EFV/TDF/3TC (n = 71)	Difference
ITT <50 copies/mL	81.7%	97.2%	15.5% (upper bound of 95% CI 23.7%)
On-treatment copies <50 copies/mL	90%	100%	10% (upper bound of 95% CI 15.5%)

EFV = efavirenz; ITT = intent-to-treat; TDF = tenofovir; 3TC = lamivudine

success rate (97%) as a maintenance regimen when compared to TDF/EFV (82%). Switching to a ... [TDF]-based regimen can significantly improve lipid profile even when lipid [levels] are within the median normal range at baseline. Other improvements in biological parameters were observed following a switch from [twice-daily] HAART to TDF-based HAART.”

### Reduced LPV/r soft-gel capsule dose effective in Kaledose

French researchers conducting the Kaledose study have found that it may be possible to reduce the standard dosing of the LPV/r soft-gel capsule from three capsules twice daily to two capsules twice daily. However, viral load blips were frequently seen in patients taking the reduced dose, and therapeutic drug monitoring (TDM) is recommended.<sup>16</sup>

Although the new hard tablet formulation of LPV/r has recently become available in the United States and the European Union, the LPV/r soft-gel capsule is still being used elsewhere in the world until the new formulation becomes available. The drug’s manufacturer, Abbott Laboratories, has filed for registration of the new tablet formulation in countries in Africa, Asia and Latin America.

This trial only studied the soft-gel formulation of LPV/r, which contains 133.3 mg LPV and 33.3 mg RTV in each capsule. The standard dose is three capsules twice daily, providing 400 mg of LPV boosted with 100 mg of RTV twice a day. The Kaledose study examined two soft-gel capsules twice daily, providing 266.6mg of LPV and 66.6mg of RTV twice a day.

For treatment-naïve patients, the recommended LPV trough concentration (C<sub>min</sub>) is 3,000 ng/mL. Over half the patients in a database kept by the study investigators had LPV C<sub>min</sub> levels of 5,000 ng/mL or more. This led researchers to believe that lower doses of LPV/r might be safe and effective, and lead to fewer side effects.

The study group enrolled adults on an antiretroviral regimen that included LPV/r.

None had ever taken a PI. (Some had previously been on NNRTI-based regimens; none were taking NNRTIs during this study.) All had maintained an undetectable viral load (less than 50 copies/mL) for at least three months, and were tested to ensure they had LPV C<sub>min</sub> levels of more than 5,000 ng/mL. Average CD4 count was 346 cells/mm<sup>3</sup>, average age was 44.6 years, and patients had been HIV-infected an average of 5.2 years.

Out of 33 initial participants, five dropped out during the study, leaving a total of 28 at the 48-week endpoint. The reduced dose resulted in lower trough LPV concentrations—an average of 4,319 ng/mL, down from 7,363 ng/mL; with 1,427 ng/mL being the lowest level observed. At the end of the study, three out of the 28 participants had detectable viral loads (80 copies/mL, 160 copies/mL, and 1,842 copies/mL).

However, over the course of the study, the investigators reported that a proportion of participants experienced viral load blips that returned to below 50 copies/mL two weeks later. Unfortunately, the researchers’ report is inconsistent, and either eight out of the 28 participants experienced a total of 13 viral load blips, or 13 of the 28 participants experienced a total of 18 viral load blips. None of the blips were greater than 2,000 copies/mL, and the majority of the blips were between 51 and 100 copies/mL. The researchers state that they did not find any significant differences in LPV C<sub>min</sub> levels in the patients whose viral loads blipped; in fact, they were not able to find any specific factors that identified the patients at risk of blips.

Over the 48 weeks, blood triglyceride levels went significantly down (from an average of 1.73 mmol/L to less than 1.4 mmol/L). Two episodes of gastrointestinal problems were reported. A more detailed report on side effects and quality of life was not presented; the analysis is still ongoing.

The researchers concluded that, “a reduced dosing of LPV/r in patients without

previous failure of PI containing regimen[s] and with  $C_{\min} > 5,000$  ng/mL is associated with a sustained virological response. Nevertheless, this strategy is associated with episodes of [viral load blips]. Therapeutic drug monitoring and [viral load] control is recommended in this type of strategy.”

### Needle-free ENF administration ISRs

A small eight-week study of a needle-free injection device for enfuvirtide (ENF) has shown the device to be as effective as injection by needle, without causing as much pain, discomfort, and swelling.<sup>17</sup> Because ENF is composed of a very large drug molecule, it cannot be taken orally since the digestive system would break the drug down into smaller molecules that would not be effective against HIV. Until now, ENF has been taken by twice-daily subcutaneous injections that very frequently cause injection site reactions (ISRs).

The drug is prepared in the same way no matter which injection method is used—a prepared powder is dissolved in sterile water to produce an injectable liquid. When 27-gauge needles are used to inject the liquid subcutaneously, the entire dose forms a bubble below the skin surface, which tends to produce hard nodules at the injection site and prevents the site from being used again until the nodule has cleared.

Instead of needles, a hand-held needle-free injection device (NFID) called the Biojector B2000 can also be used to administer ENF. The needle-free injection device uses pressurised gas to blast the liquid below the skin surface, thus avoiding the need for needle punctures, and dispersing the drug more evenly over a larger area. While the Biojector B2000 has been in use for some time, it has not been well studied in randomized clinical trials.

The study used a crossover methodology to compare both injection methods for participants who were beginning ENF for the first time. Participants were randomized to begin with either the Biojector B2000, or standard 27-gauge needles. After four weeks, they switched over to the opposite method. All participants who completed the study had therefore tried both methods, and were able to compare their satisfaction levels, preference, and adherence. Minimum blood concentration levels were also monitored to ensure that effective ENF doses were being delivered.

Fifty-eight people were enrolled, about

Table 3. 24-week response to DRV/r after PI failure

	PI in failing regimen		
	TPV	LPV	FPV
n (%)	51 (11)	192 (42)	74 (16)
< 50 copies/mL (5)	44	40	42
≥ 1-log (10-fold) drop in viral load (5)	69	63	68
Viral load log change from baseline	-1.64	-1.72	-1.66

FPV = fosamprenavir; LPV = lopinavir; PI = protease inhibitor; TPV = tipranavir

half of whom were Caucasian and 85% of whom were white, an average of 43 years old, with a median of 203 CD4 cells/mm<sup>3</sup> and 4.6 log viral load. (Fifty-four percent had previous experience with self-injection.) Of these, 49 went on to actually start taking ENF; data on at least one dose was available for 48, and 39 completed the full eight-week study.

Drug concentration levels were similar for both methods, especially when non-adherent patients were left out of the comparison. The average minimum concentration of ENF achieved by the Biojector B2000 was 2,038 ng/mL, and 2,204 ng/mL by subcutaneous needles.

Although almost all participants had some degree of ISR no matter which method was used, the reactions were considerably less severe with the Biojector B2000. Participants overwhelmingly (84%) rated the Biojector B2000 as the preferable method. The researchers concluded that “[needle-free injection device] administration of [ENF] resulted in a substantially lower incidence of painful nodules... was preferred by most patients over standard [27-gauge needles], and is generally safe and well-tolerated.”

### Scoping out the newer ARVs on the block

#### No DRV response difference by prior PI use in POWER

The new boosted PI darunavir (DRV) has already proven to be more powerful than other boosted PIs when taken by highly ART-experienced patients. Combined results from three related clinical trials have now confirmed that DRV is equally effective, regardless of which PI has been used previously.<sup>18</sup>

Much of the data on DRV are drawn from several ongoing multi-site trials. For the purposes of this study, data from three

of these randomized trials – POWER 1, 2, and 3—was combined. These three trials all studied similar groups of people: participants were on failing regimens, with viral loads over 1,000 copies/mL. They also had experience with NRTIs, NNRTIs, and PIs, and had developed at least one PI resistance mutation. On starting the study, all participants received a background antiretroviral regimen that was optimized by resistance testing, plus 600 mg DRV and 100 mg RTV twice daily. The new combinations may or may not also have included ENF; none contained NNRTIs.

The study looked at virological response to the new regimen after 24 weeks (Table 3). Specific comparisons were made between those whose previous (failing) regimen had contained tipranavir (TPV), LPV, and FPV.

Results were very similar for the study overall, and the three PI-specific groups. In the overall study (n=458), the average viral load drop was of 1.74 log and 42% became undetectable. The average viral load drop in the TPV group (n=51), LPV group (n=192), and FPV group (n=74) was 1.64 log, 1.72 log, and 1.66 log, respectively. Forty-four percent became undetectable in the TPV group, versus 40% and 42% in the LPV and FPV groups, respectively.

The study also compared the effectiveness of boosted DRV to other control PIs (CPIs). In the set of participants studied (131 on DRV-containing regimens, 124 on CPIs), 45% and 12%, respectively, achieved viral loads of less than 50 copies/mL after 24 weeks. Responses were better in those who showed genotypic susceptibility to at least one CPI at baseline (24% versus 7% in those resistant to all CPIs). Among the CPIs, FPV was the most successful, leading to undetectable viral loads in 16% of those on an FPV-containing regimen.

Researchers concluded that DRV “showed greater HIV RNA reductions and



**Table 4. Response to MK-0518 by baseline PSS**

	<400 copies/mL			
	PSS = 0*		PSS = 1-2*	
	n	% (95% CI)	n	% (95% CI)
MK-0518 200 mg BID	13	54 (25 to 81)	25	84 (64 to 95)
MK-0518 400 mg BID	13	69 (39-91)	26	77 (56 to 91)
MK-0518 600 mg BID	13	62 (32 to 88)	28	75 (55 to 89)
OB alone	11	0 (0 to 28)	27	19 (6 to 38)

\* Enfuvirtide counted as an active drug.

BID = twice daily; CI = confidence interval; OB = optimized background; PSS = phenotypic sensitivity score

CD4 count increases over the [control PIs (CPIs)] used by the control group, regardless of CPI used, type of boosting (single or double RTV-boosted PI regimen), and baseline susceptibility.” They added that, “the PI-based regimen at screening did not affect the subsequent virologic response to [DRV/RTV] 600/100 mg bid plus [an optimized background regimen] after 24 weeks of treatment.”

**MK-0518 stalls resistant HIV, causes no lipid increase at 24 weeks**

In heavily treatment-experienced patients with few—or no—antiretroviral drugs available as an option for a salvage regimen, the integrase inhibitor MK-0518 stalled HIV impressively.<sup>19</sup> The investigational drug worked even better when ENF-naïve patients could start it in combination with ENF. MK-0518 inhibits the activity of integrase, an HIV enzyme that allows the virus to insert its genetic material into the DNA of human T-cells.

Researchers from Europe and the United States randomized 178 treatment-experienced patients to 200 mg, 400 mg, or 600 mg of MK-0518 twice daily, or placebo, plus an optimized background regimen picked on the basis of resistance tests and treatment history. But the researchers could do little or nothing to optimize the new regimens of most study participants. About half of those enrolled had a phenotypic sensitivity score (PSS) of 0 to all antiretroviral drugs, meaning the Phenosense GT assay rated their virus resistant to every available drug except MK-0518. According to this same test, about 90% of study participants did not have a single active PI to put in their new regimen.

When patients signed up for the study, their viral loads averaged 40,000 copies/mL to 63,000 copies/mL across the study arms. Average CD4 counts stood at

200 cells/mm<sup>3</sup> to 245 cells/mm<sup>3</sup> in the three MK-0518 arms and at 274 in the placebo group.

By study week 24, 10 participants (23%) had quit the 200-mg arm, eight (18%) had left the 400-mg arm, eight (18%) the 600-mg arm (18%), and 31 (69%) the placebo arm. Three dropouts in the MK-0518 arms and 1 in the placebo arm resulted from clinical problems or side effects. Lack of efficacy caused the other 49 dropouts.

A 24-week noncompleter-equals-failure analysis figured that about 70% in all three MK-0518 groups had a viral load below 400 copies/mL, compared with fewer than 20% in the placebo group. While 57% to 67% in the MK-0518 arms had a 24-week load below 50 copies/mL, only 14% in the control arm hit that mark. About 80% taking MK-0518 at any dose had at least a 1-log (10-fold) viral load drop by week 24, compared with 18% in the placebo arm. Viral load declines averaged about 2 log (100-fold) with the integrase inhibitor and 0.4 log with placebo plus other background drugs. Among people who started the trial with a phenotypic sensitivity score of 0, 54% to 62% randomized to MK-0518 had a 24-week viral load under 400 copies/mL, while no one in the placebo group with a baseline score of 0 got below 400 copies (Table 4).

As in previous salvage therapy studies, including ENF in the regimen increased chances of virologic response. Among people in the placebo arm, the percentage with a 24-week viral load below 400 copies/mL rose from about 15% without ENF to about 30% with the injectable drug. In the MK-0518 arms the response rate climbed from about 60% without ENF to 90% or more with ENF. These findings underline the advantage of waiting until one has at least two potent antiretroviral

**Table 5. Lipid level after 24 weeks of MK-0518 or EFV**

Dose	n	Baseline cholesterol (mg/dL)	Change (mg/dL) (95% CI)	Baseline triglycerides (mg/dL)	Change (mg/dL) (95% CI)
MK-0518 100 mg BID	39	168	-7* (-14 to 0)	129	+2 (-22 to 26)
MK-0518 200 mg BID	34	161	-2* (-11 to 8)	110	-5 (-20 to 9)
MK-0518 400 mg BID	40	168	-7* (-15 to 2)	127	-2* (-23 to 18)
MK-0518 600 mg BID	35	162	-4* (-12 to 5)	155	-43* (-87 to 1)
EFV 600 mg QD	36	170	+19 (8 to 30)	128	+47 (-1 to 96)

\*  $P < 0.05$  versus EFV

BID = twice daily; CI = confidence interval; EFV = efavirenz; QD = once daily.

drugs for a salvage regimen—if at all possible—rather than adding new drugs one at a time to already enfeebled anti-retroviral drugs.

Grade 3 or 4 lab abnormalities proved uncommon and their rates were similar in the MK-0518 and placebo groups. The researchers reported four serious clinical setbacks: one stroke in the placebo group, one case of acute pancreatitis after two doses in the 200-mg MK-0518 group (attributed to the background regimen), one case of lipoatrophy, and one death from metabolic acidosis and renal insufficiency.

In a separate dose-ranging study with treatment-naïve patients, participants receiving MK-0518 experienced no significant increases in total cholesterol and triglycerides (Table 5).<sup>20</sup> The study compared four doses of MK-0518 with EFV in 184 treatment-naïve patients also receiving TDF and 3TC.

Baseline lipid levels were comparable across the five study arms, at around 160mg/mL for total cholesterol and between 110 mg/dL and 155 mg/dL for triglycerides. After 24 weeks on treatment, very slight declines in lipid levels were observed in the MK-0518 recipients at all doses (with the exception of HDL cholesterol), but in the EFV group all lipid levels rose. The only statistically significant difference was seen in LDL cholesterol, where the EFV group had an increase of approximately 5mg/dL while slight declines were seen at all MK-0518 doses ( $P < 0.05$ ).

### Plugging CCR5 with a monoclonal antibody

Most attention on blocking CCR5 coreceptors has focused on the CCR5 antagonists—aplaviroc (no longer being developed), maraviroc, and vicriviroc—and this year's ICAAC featured some

intriguing studies on all three of these investigational drugs. But a humanized IgG4 monoclonal antibody currently under study also keeps HIV off CCR5 receptors and boosts the power of traditional antiretroviral drugs.<sup>21</sup> Twenty-four weeks of serial passage pressure did not promote emergence of mutations conferring resistance to this agent, but that does not mean HIV cannot find a way to outmaneuver the monoclonal antibody. A disadvantage of this monoclonal antibody, still enigmatically tagged CCR5mAb004, is that it requires intravenous infusion.

Fifty-four ART-naïve patients with virus that homes exclusively to CCR5, viral loads of more than 5,000 copies/mL, CD4 counts of more than 250 cells/mm<sup>3</sup> were randomized to a single infusion of 0.4 mg/kg, 2 mg/kg, 8 mg/kg, 20 mg/kg, or 40 mg/kg of CCR5mAb004 or placebo. The 2-mg/kg-dose raised a moderately severe urticarial rash in two people. After that the researchers pre-treated people with oral diphenhydramine and no more rashes flared. No one experienced grade 3 or 4 treatment-related problems.

CCR5mAb004 has a slow onset of action—three to four days—while it coats CCR5 receptors. But one infusion lasts a long time. The monoclonal antibody eventually saturated more than 80% of receptors 14 to 28 days after infusion of 8 mg/kg or higher doses. The researchers calculated a five- to eight-day half-life for CCR5mAb004. Maximum concentration of the monoclonal antibody was dose-proportional (the higher the dose, the higher the concentration), and area under the concentration-time curve (AUC) was more than dose-proportional.

More than half of the participants who took the higher doses of CCR5mAb004 had at least a 1-log (10-fold) drop in viral

**Table 6. Day 14 response to an anti-CCR5 monoclonal antibody**

	Single infused dose of CC45mAb004		
	0.4 or 2 mg/kg	8 or 20 mg/kg	40 mg/kg
n	34	19	10
≥1-log drop at day 14 (ITT analysis)	0	11 (57.9%)	5 (50%)

ITT = intent-to-treat

load at day 14 (Table 6). Those who began therapy with a lower pre-treatment viral load had a better chance of knocking their viral load down farther: Pre-treatment loads averaged 4.0 log (10,000 copies/mL) in participants with more than a 1-log drop and 4.4 log (about 25,000 copies/mL) in those with less than a 1-log drop ( $P = 0.02$ ). The monoclonal antibody's 90% inhibitory concentration was significantly lower (better) in patients who had at least a 1-log viral load dip (31.3 ug/mL) than in those who did not (87.5 ug/mL) ( $P = 0.0388$ ).

Notably, HIV preference for CCR5 changed in five people after one day of treatment. Because the Monogram Biosciences assay used to determine coreceptor preference (tropism) still has shortcomings, it is impossible to say whether these coreceptor shifts resulted from infusion of the monoclonal antibody or whether they simply reflect the assay's inadequacies. Whatever the explanation, none of the five people with changing tropism had a good virologic response to CCR5mAb004, even though four of them got either the 20- or 40-mg/kg dose.

How this infused monoclonal antibody would be integrated into an oral antiretroviral regimen and whether it can compete with oral CCR5 antagonists remain to be determined. This year's ICCAC provided an insight into oral CCR5 antagonists—interestingly via results of a study of one CCR5 antagonist whose wings were clipped earlier this year. Development of the investigational CCR5 antagonist, aplaviroc, was suspended when a few patients in its study suffered severe liver toxicity. But an aplaviroc study may hold clues to the efficacy of the two remaining CCR5 antagonists: maraviroc and vicriviroc.

Data from the aplaviroc study indicated that resistance to aplaviroc in patients



Table 7. **CCR5 antagonist receptor affinity and disassociation**

	Receptor affinity (K <sub>d</sub> , nM)	Receptor dissociation (t <sub>1/2</sub> , h)
Vicriviroc	0.40 ± 0.02	12 ± 1.2
SCH-C	0.91 ± 0.10	3.2 ± 0.2
Aplaviroc	0.17 ± 0.03	24 ± 3.6
Maraviroc	0.18 ± 0.02	7.5 ± 0.7

with virologic failure could prove hard to spot with standard viral-population-based testing.<sup>22</sup> Clonal analysis—which looks at a wide array of clones created from HIV isolates—was conducted in 10 ART-naive patients who began treatment with aplaviroc plus LPV/r and endured virologic failure, defined as less than a 1-log (10-fold) drop in viral load by treatment week 4, a confirmed viral load above 400 copies/mL after a sub-400 copies/mL load, or more than a 0.5-log viral load climb from the lowest recorded load.

Testing on the population level detected no drop in susceptibility to either aplaviroc or LPV/r. But clonal analysis uncovered reduced susceptibility to aplaviroc in fewer than half of the clones derived from six of the 10 patients. The researchers also found shifts in coreceptor affinities from R5-only virus to R5/X4-mixed virus in two of these 10. But phylogenetic analysis suggested that one person had mixed-tropic virus before treatment began. The study did not turn up mutations in the viral envelope gene that correlate with reduced susceptibility to aplaviroc.

In another study, researchers reported cell study results gauging how avidly four CCR5 antagonists bind to their target receptor, and how long they stick to the target after binding.<sup>23</sup> Maraviroc and aplaviroc bound CCR5 more tightly than vicriviroc (Table 7). But vicriviroc clung to CCR5 almost twice as long as maraviroc. Aplaviroc won the durability contest, plugging CCR5 receptors twice as long as vicriviroc.

Vicriviroc's slow receptor dissociation rate supports its once-daily dosing schedule; ongoing maraviroc trials are testing both once- and twice-daily dosing. Whether this dissociation advantage and potential dosing plus for vicriviroc translate into a clinical edge can be determined only in a head-to-head comparison with maraviroc.

### **Novel NRTI active against HIV in monotherapy study**

The investigational NRTI elvucitabine demonstrated potent and prolonged anti-HIV activity in a seven-day monotherapy study.<sup>24</sup> Elvucitabine (also known as L-Fd4C) is an L-cytosine nucleoside analogue. A small study reported at last year's ICAAC showed that various doses of elvucitabine plus LPV/r suppressed HIV RNA by as much 2 log<sub>10</sub> copies/mL over 21 days. That study demonstrated the short-term safety of elvucitabine, but was not able to determine how much of the observed antiviral effect was attributable to the new drug and how much to LPV/r. Accordingly, researchers then carried out a study of elvucitabine used as monotherapy.

The present Phase II double-blind study presented on at this year's ICAAC included 24 HIV-positive participants who were randomly assigned to receive 10 mg once-daily elvucitabine or placebo. After seven days on elvucitabine monotherapy, these patients were given LPV/r for an additional 21 days in order to reduce the risk of resistance, since elvucitabine remains in the body for a prolonged period.

All participants but one were men, and all but one was white; the average age was about 40 years. The presenter noted that future multicenter trials would aim to enroll a more diverse study population. Baseline characteristics were generally similar in both arms, but participants randomized to the elvucitabine group had a slightly lower CD4 count than those in the placebo arm (mean 320 cells/mm<sup>3</sup> versus 403 cells/mm<sup>3</sup>). The mean viral load level was about 4.75 log<sub>10</sub> copies/mL. Patients had minimal previous ART experience, and genotypic testing showed that they did not have mutations associated with resistance to elvucitabine or LPV/r (M184V, M184I, D237E).

By Day 7, viral load declined by an average of 0.85 log<sub>10</sub> copies/mL from baseline in patients taking elvucitabine, compared with essentially no change in the placebo group (*P*<0.001). The mean CD4 count increases were 62 cells/mm<sup>3</sup> versus 9 cells/mm<sup>3</sup>, respectively. Viral load continued to decrease even after discontinued use of elvucitabine, but the decline became less pronounced as elvucitabine concentrations dropped. On Day 21 (14 days after the last elvucitabine

dose), the maximal viral load decrease was 1.73 log<sub>10</sub> copies/mL, before rising again.

Pharmacokinetic analyses showed that the overall half-life of elvucitabine was about 100 hours, and there were still detectable concentrations in plasma and peripheral blood mononuclear cells at Day 21. Maximum concentrations and maximum trough levels of plasma elvucitabine were attained on the final day of dosing, but concentrations remained above the IC<sub>50</sub> (the level at which viral replication is reduced by 50%) for up to 14 days after discontinuation.

Overall, elvucitabine was well tolerated. No major safety issues were identified, and the emergence of virus with resistance to elvucitabine or LPV/r was not observed. The researchers concluded that, “these results confirm that elvucitabine monotherapy demonstrates significant antiviral activity over seven days of dosing.” They added that the drug’s long plasma and intracellular half-life and concentration-dependent efficacy “may provide a better barrier to resistance than antiviral agents with short half-lives.”

### One-two punch from the DRV/TMC125 duo

Two single-center studies suggest that DRV and the investigational NNRTI etravirine (TMC125) could be a formidable duo for patients resistant to other drugs in those classes.<sup>25</sup> Thirteen of 15 patients in these small, nonrandomized studies—one presented at this year’s ICAAC, the other at the 16th International AIDS Conference—saw their viral loads dip under 50 copies/mL within 24 weeks of starting DRV and etravirine with a clutch of NRTIs and, sometimes, ENF.

British researchers paired DRV and etravirine in 12 patients with woeful resistance records. Two withdrew consent for personal reasons. Among the remaining 10, the median number of primary PI mutations stood at four (range 0 to five), the median number of NNRTI mutations at two (range 0 to six), and the median number of NRTI mutations at seven (range two to nine). Median fold-change in susceptibility to PIs ranged from 0.4 to 137.6 (1.25 for DRV) and to NNRTIs from 0.6 to 104.9 (1.25 for etravirine). Six of 10 participants had already tried TPV and emtricitabine (FTC); only two patients started FTC as a new drug in this

study. Everyone took 200 mg of etravirine twice daily, 600/100 mg of DRV/r twice daily, and two or more NRTIs.

After 24 weeks, nine of 10 participants had a viral load under the 50-copy/mL mark. The tenth had a viral load of 722 copies/mL, which dwindled to 59 copies/mL by week 32. Median drop in HIV RNA log copies/mL measured 2.7 (range 2.3 to 3.9), and median CD4 gain stood at 113 cells/mm<sup>3</sup> (range 41 cells/mm<sup>3</sup> to 268 cells/mm<sup>3</sup>). No one had a serious clinical setback or dangerous lab reading. Possible treatment-related side effects included mild diarrhea in one patient, headache in one, and rash in one. All problems resolved without a change in drugs or dosing. ■

*Editor’s Note: This article is compiled from various reports which have been adapted and reprinted with permission from [www.aidsmap.com](http://www.aidsmap.com) and [www.natap.org](http://www.natap.org).*

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## ABSTRACTS

### AIDS

#### Comparison of the risks of atherosclerotic events versus death from other causes associated with antiretroviral use

Kwong GP, Ghani AC, Rode RA, et al.

**BACKGROUND:** Studies considering the risk of atherosclerotic disease (AtD) associated with the use of highly active antiretroviral therapy (HAART) have reported inconsistent results. **METHODS:** Data on antiretroviral therapy (ART) and risk factors for cardiovascular disease (CVD), AtD, and death from other causes in 18,603 HIV-infected patients from two established cohorts were evaluated. The relative hazards of AtD and death from other causes were calculated using a proportional hazards competing risks framework. The impact of protease inhibitor (PI)-containing, nonnucleoside reverse transcriptase inhibitor (NNRTI)-containing or PI + NNRTI-containing regimens on these outcomes were compared to nucleoside reverse transcriptase inhibitor (NRTI)-only regimens or stopping therapy, adjusting for known CVD risk factors. **RESULTS:** In 77,480 person-years of follow-up (median duration 3.49 years) there were 318 AtD events, including 92 myocardial infarctions and 2,044 deaths. Older age, hypertension, diabetes mellitus, having smoked, and HIV disease stage were significantly associated with increased risk of AtD. Protease inhibitor- and NNRTI-containing regimens significantly reduced the joint risk of either AtD or death from other causes compared to NRTI-only or stopping therapy (hazard ratio [HR] for PI-containing ART 0.76, 95% confidence interval [CI] 0.73 to 0.78,  $P < 0.001$ ; NNRTI-containing ART 0.69, 95% CI 0.65 to 0.74;  $P < 0.001$ ). Protease inhibitor-containing ART was associated with a borderline significant increased risk of myocardial infarction (cause-specific HR for PI-containing ART 1.19, 95% CI 1.01 to 1.40,  $P = 0.04$ ) but not with increased risk of AtD compared to NRTI-only regimens or stopping therapy (cause-specific HR for PI-containing ART 1.03, 95% CI 0.95 to 1.13,  $P = 0.44$ ). **CONCLUSIONS:** Overall benefits of PI- and NNRTI-based ART in reducing mortality significantly outweigh any risks of AtD in the short-term follow-up of this study. Traditional cardiac risk factors play an important role in determining AtD risk status.

*AIDS*. 2006;20(15):1941-1950.

### Journal of Acquired Immune Deficiency Syndromes

#### Pregnant women with HIV infection can expect healthy survival: Three-year follow-up

Marin F, Navaratne L, Khan W, et al.

**OBJECTIVES:** To document postpartum disease-free survival of HIV-infected women taking antiretroviral therapy (ART) during pregnancy. **METHODS:** Laboratory and clinical data were collected on all HIV-infected pregnant women delivering from 1998 to 2002 and followed up until September 2004 at six

hospitals in London. Mothers were grouped according to receipt of zidovudine monotherapy (ZDVm), highly active antiretroviral therapy (HAART) given during and continued after pregnancy (cHAART), and short-term HAART given during pregnancy and discontinued on delivery (START). **RESULTS:** Eight-five women took ZDVm, 155 took cHAART, and 71 took START. The mean follow-up for all mothers was 33 months, with a total of 847 person-years. At the first antenatal clinic (ANC) visit, 72% of women were in Centers for Disease Control and Prevention (CDC) stage A, 85% were treatment-naive, and the ZDVm group had a median HIV viral load (VL) 10-fold less than those mothers who started HAART during pregnancy. At last follow-up, one patient had died and six (1.9%) had progressed to CDC stage C; 62% of all women, including a quarter of the ZDVm group, were receiving HAART for their own health; and 83% of all mothers had a VL  $< 50$  HIV RNA copies/mL in plasma regardless of whether or not they were on treatment. **CONCLUSIONS:** The median-term postpartum prognosis of HIV-infected pregnant women with access to HAART is good. Exposure to short-course ZDVm or START during pregnancy did not jeopardize their response to subsequent therapy.

*J Acquir Immune Defic Syndr*. 2006;43(2):186-192.

### Clinical Infectious Diseases

#### Symptomatic relapse of HIV-associated cryptococcal meningitis after initial fluconazole monotherapy: The role of fluconazole resistance and immune reconstitution

Bicanic T, Harrison T, Niepieklo A, Dyakopu N, Meintjes G.

**BACKGROUND:** Cryptococcal meningitis (CM) in South Africa is often treated with fluconazole as initial therapy. Surveillance data suggest that the prevalence of fluconazole-resistant CM is increasing, and expanding access to antiretroviral therapy is resulting in increasing recognition of immune reconstitution inflammatory syndrome. Therefore, we conducted a study to assess the contribution of these factors to CM relapse in this context. **METHODS:** Patients with symptomatic relapse of CM were prospectively identified at two hospitals in Cape Town, South Africa, during the period of 2003 to 2005. Patients met the following criteria: (1) a previous laboratory-confirmed episode of CM, with resolution of symptoms after treatment; (2) reported adherence to fluconazole treatment; (3) recurrence of typical CM symptoms; (4) cerebrospinal fluid antigen test and/or culture positive for *Cryptococcus neoformans*; and (5) no alternative diagnosis. Data on patients' human immunodeficiency virus (HIV) and CM infections and treatment were collected and analyzed. **RESULTS:** Thirty-two episodes of relapse occurred among 27 patients. Episodes were classified into three groups: culture-positive episodes in antiretroviral therapy-naive patients (six episodes), culture-positive episodes in patients receiving antiretroviral therapy (15 episodes), and culture-negative episodes in patients receiving antiretroviral therapy (11 episodes). Seventy-

six percent of culture-positive relapses were associated with isolates that had reduced susceptibility to fluconazole. Drug-resistant cases required prolonged intravenous therapy with amphotericin B, and despite this treatment, the mortality rate was high (54% at a median of six months of follow-up). Despite a long interval between initiation of antifungal therapy and initiation of antiretroviral therapy (median interval: 144 days), immune reconstitution inflammatory syndrome contributed to at least one third of relapses. **CONCLUSIONS:** After initial treatment with fluconazole, relapses of symptomatic CM are often associated with fluconazole resistance and immune reconstitution inflammatory syndrome. These data add to concern about the efficacy of fluconazole, compared with amphotericin B, for initial treatment of HIV-associated CM.

*Clin Infect Dis*. 2006;43(8):1069-1073.

### HIV Medicine

#### Transmitted drug-resistant HIV-1 in primary HIV-1 infection; incidence, evolution and impact on response to antiretroviral therapy

Fox J, Dustan S, McClure M, Weber J, Fidler S.

**OBJECTIVES:** The aim of the study was to determine the incidence and persistence of transmitted drug-resistant HIV-1 in an incident cohort between 2000 and 2004, and to investigate the impact of transmitted drug-resistant HIV-1 on the response to antiretroviral therapy (ART). **METHODS:** A prospective, nonrandomized study was carried out on 140 individuals identified with primary HIV-1 infection (PHI). Primary HIV-1 infection was defined as an HIV-positive antibody test with an HIV antibody-negative result in the prior six months ( $n = 69$ ); positive HIV DNA in the absence of antibody ( $n = 30$ ); an evolving titer-positive HIV antibody test ( $n = 23$ ), or an incident detuned assay (B clade viruses only) ( $n = 18$ ). Genotypic resistance testing was performed at baseline, following ART, and annually over a four-year period. **RESULTS:** The prevalence of transmitted drug-resistant HIV-1 infection between January 2000 and June 2004 was nine in 140 (6%), and the annual incidence was stable. Seven of these nine patients had a single point mutation conferring single-class drug resistance and the other two patients had multiple mutations conferring multiclass drug resistance (MDR). In eight of the nine cases, mutations conferring drug resistance persisted for more than 12 months off therapy. In contrast to transmitted MDR HIV-1, the virological response to initial ART and CD4 decline were comparable in those with wild-type virus, virus with polymorphisms (secondary mutations), and virus with single drug-resistance mutations. **CONCLUSIONS:** The incidence of transmitted drug-resistant HIV remained stable and low over a four-year period. Although MDR remains rare, its presence significantly affects the response to first-line ART, predisposes towards the accumulation of new resistance mutations, and is associated with a more rapid CD4 decline.

*HIV Med*. 2006;7(7):477.

## Baseline HCV VL, CD4 percentage predict HCV treatment response

Liz Highleyman

**H**igher baseline hepatitis C virus (HCV) RNA levels predicted better sustained response to hepatitis C therapy in HIV-positive patients with HCV genotype 1 coinfection in the APRICOT trial, and pre-treatment CD4 cell percentage had a slight effect, according to two posters presented at the 46th Interscience Conference on Antiretroviral Agents and Chemotherapy (ICAAC) held September 27-30, 2006, in San Francisco.<sup>1,2</sup>

APRICOT was an international trial in which 860 HIV/HCV-coinfected participants who had not previously received interferon (IFN)-based therapy were randomly assigned to receive either 3 million IU conventional IFN- $\alpha$ -2a three times weekly plus 800 mg daily ribavirin (RBV); 180 mg pegylated interferon- $\alpha$ -2a (PEG-IFN- $\alpha$ -2a) monotherapy; or the same doses of PEG-IFN plus RBV, all for 48 weeks.

Baseline characteristics were similar across all three arms. Eighty-one percent of participants were men, with a mean age of 40 years; 79% were white and 11% were black. Sixty-one percent had HCV genotype 1, 5% had genotype 2, 27% had genotype 3, and 7% had genotype 4. All had detectable HCV RNA ( $>600$  IU/mL) and elevated alanine aminotransferase levels at baseline. Participants overall had stable HIV disease; the mean CD4 count was 530 cells/mm<sup>3</sup>, 85% were on antiretroviral therapy, and 60% had HIV viral loads below 50 copies/mL.

Final results from APRICOT were published in the July 29, 2004, edition of the *New England Journal of Medicine*.<sup>3</sup> In an intent-to-treat analysis at 48 weeks, 40% of patients treated with PEG-IFN plus RBV achieved sustained virological response (SVR), compared with 20% in

the PEG-IFN monotherapy arm, and 12% in the conventional IFN plus RBV arm. Among patients with HCV genotype 2 or 3, the corresponding SVR rates were 62%, 36%, and 20%, while in genotype 1 patients, SVR was observed in 29%, 14%, and 7%, respectively.

### Baseline HCV viral load

In the present analyses, researchers looked in more detail at factors that predicted sustained response. The APRICOT trial found that among patients with HCV viral loads below 800,000 IU/mL, SVR rates were lower in participants with higher baseline HCV RNA. To assist in the management of HIV/HCV-coinfected patients by defining “easier” and “difficult-to-cure” subgroups, Maribel Rodriguez-Torres (Ponce School of Medicine, Sancture, Puerto Rico) and colleagues sought to determine which baseline HCV RNA values best predicted who was most and least likely to achieve SVR.

This analysis included 271 participants in the PEG-IFN plus RBV arm (176 with genotype 1; 95 with genotype 2 or 3); baseline characteristics were similar to those of the trial population as a whole.

Sustained virological response rates were consistently above 70% in participants with baseline HCV RNA below 100,000 IU/mL, but declined to less than 20% in those with more than 2,000,000 IU/mL. The researchers determined that the HIV RNA cut-off that most effectively identified patients likely to achieve SVR was 400,000 IU/mL, or 5.6 log<sub>10</sub>. Among patients with HCV viral load levels below 400,000 IU/mL, sustained response rates were high regardless of genotype.

Among participants with HCV genotype 1, the SVR rate was “markedly lower” in those with baseline HCV RNA levels of 400,000 IU/mL or more compared to those with lower HCV viral loads (20% versus 71%). Among patients with genotype 2 or 3, a similar pattern was observed, but

the difference was “slight” (SVR rates of 59% versus 74%, respectively).

The researchers concluded that, “If baseline HCV RNA is to be used in clinical decisions, these analyses suggest the most appropriate HCV RNA cut-point with clinical relevance is 400,000 IU/mL.” They added that, “Use of this cut-point may allow further optimization” of therapy with [PEG-IFN] plus [RBV] in coinfecting patients.

They emphasized, however, that for any specific individual, the outcome of hepatitis C treatment cannot be predicted in advance based on HCV RNA levels. Thus, “all patients should be treated and evaluated at weeks four and 12 of therapy.”

### Baseline CD4 percentage

In APRICOT, a higher absolute CD4 count was associated with a higher rate of SVR among participants with HCV genotype 1, but not in those with genotypes 2 or 3; however, the number of patients with CD4 counts below 200 cells/mm<sup>3</sup> was small.

In the second analysis presented at ICAAC, Douglas Dieterich (Mount Sinai School of Medicine, New York) and colleagues explored the effect of baseline CD4 percentage on sustained response. Data on CD4 percentage were available for 705 patients. The median baseline CD4 percentage was 25%, with a range of 2.5% to 69.3%.

Across all CD4 percentage quartiles, SVR rates were higher in the group that received PEG-IFN plus RBV than in either of the other two treatment arms. Analysis of SVR rates according to CD4 percentage showed a “trend” toward greater virological response as baseline CD4 percentage increased. Looking only at patients in the two arms that received ribavirin, the researchers found that SVR rates “tended to improve” as baseline CD4 percentage rose, although the relationship was not consistent across genotypes or treatment regimens (Table 1).

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**Table 1. Effect of baseline CD4 percentage on SVR**

Baseline CD4% (quartiles)	SVR rate (%)								
	All patients (n = 705)*			HCV genotype 1 (n = 427)			HCV genotypes 2/3 (n = 226)		
	IFN + RBV (n = 222)	PEG-IFN + placebo (n = 231)	PEG-IFN + RBV (n = 242)	IFN + RBV (n = 138)	PEG-IFN + placebo (n = 139)	PEG-IFN + RBV (n = 150)	IFN + RBV (n = 75)	PEG-IFN + placebo (n = 73)	PEG-IFN + RBV (n = 78)
Q1 (2.5-19.1%)	4	20	33	3	13	16	6	40	62
Q2 (19.1-25.0%)	15	21	36	9	21	29	24	28	47
Q3 (25.0-32.1%)	14	18	41	12	14	34	24	44	73
Q4 (32.1-69.3%)	13	17	47	5	6	27	24	23	69

\*155 pts from APRICOT ITT population excluded due to missing CD4 percentage data

SVR = sustained virological response; IFN = conventional interferon; PEG-IFN = pegylated interferon-alfa-2a; RBV = ribavirin; ITT = intent-to-treat analysis

When broken down by genotype, the effect of CD4 percentage was most pronounced among patients with genotype 1, with the lowest rate of HCV clearance observed in the lowest quartile of CD4 percentage scores. Among patients with genotypes 2 or 3, in contrast, sustained response rates showed “no obvious trend” in relation to CD4 percentage.

Overall safety and tolerability of therapy did not appear to vary according to baseline CD4 count or CD4 percentage, though some adverse events and laboratory abnormalities were more common among

patients with the lowest CD4 counts (below 200 cells/mm<sup>3</sup>).

During therapy, patients experienced a “slight” (less than 10%) increase in CD4 percentage relative to the total number of T lymphocytes, which returned to baseline after completion of treatment. Decreased white blood count is a known side effect of IFN, but typically various types of cells decline by similar amounts, leaving percentages relatively stable.

The researchers concluded that among patients treated with conventional IFN or PEG-IFN plus RBV, SVR rates improved

with higher baseline CD4 percentage in genotype 1 patients, but not in those with genotype 2 or 3.

“Although analysis by baseline CD4 percentage quartiles did not reveal any strong influence on virological response rates from baseline, a slight trend toward an earlier and possibly a slightly more sustained response was seen in those with higher baseline CD4 percentage,” the investigators wrote.

The investigators concluded that while prospective studies in a larger number of severely immunocompromised patients are awaited, “our findings suggest that the benefits of treating HCV among immunocompromised patients with HIV infection outweigh the potential risks.” ■

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## I N T H E L I F E



### Jens D. Lundgren

For more than three 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 Jens D. Lundgren, who is Professor of Medicine and Director of the Copenhagen HIV Programme (CHIP) at the University of Copenhagen, in Denmark.

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

English is not my first language, but I guess it goes like something this: "We need international collegial dialogue to address the key issues we—as a globe—are confronting, including how to best fight the HIV epidemic. I am happy dedicate significant time for this to happen."

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

Running (the best anti-stress activity), and reading fiction. I played cello in my youth, still have the instrument, and would very much like to re-engage when time permits.

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

Where the climate is warmer and the sun is seen for extended periods of time. The climate in Denmark in the winter is around freezing temperature, and there is usually a westerly wind and sleet. Further, daylight emerges after I go to work and it is gone when I return home.

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

Many, many folks, but especially colleagues who unselfishly dedicate their time for a higher aim than personal (and national) interests; they do not take advantage of political arguments as the key to move science forward, but rather work to ensure that the best possible science is being advanced. In my professional life, I have been privileged to meet many who fulfill those criteria. They are my mentors and heroes.

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

The historical figures I most admire are Lars von Trier (Danish movie instructor) and the creators of Monty Python's Flying Circus (including John Cleese), although I would never dream of identifying myself with any of them. They are in a league of their own.

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

Musicians: Beatles (especially John Lennon), Billie Holiday (the most romantic singer I know). I also have a weak spot for Jim Morrison and The Doors. Painters: The post-Impressionists (eg, Claude Monet, Auguste Renoir, Paul Cézanne, Asger Jorn), because they painted surreal images that grab you and let you drift away.

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

We live now and have to focus on getting the best out of the moment.

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

No idea.

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

Achievements: Ability to evolve and exploit new opportunities, and being incredibly creative. Failures: We over-react and overdo the opportunities, and many times we lose the "style" of decent behavior.

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

The global population has grown, the trend of globalization has continued, and the religious frictions continue to dominate the international political scene. HIV remains out of control because the public misconception remains that we can only deal with this problem by developing medicine, whereas the obvious (using condoms and clean needles) remains neglected. ■



## SAY ANYTHING

*e*  
**Only an HIV-positive person can understand and respect my status. We are all living with uncertainty every minute. Let us try and enjoy every bit of life with a companion.**

*Sanjay Joshi, a 32-year-old Indian engineer whose wife died of AIDS-related complications four years ago, quoted in an October 2, 2006, Reuters report. People living with HIV/AIDS in India often face stigma due to lack of HIV/AIDS awareness and disease myths. To battle social isolation, the volunteer Network of Surat People Living with HIV+ recently organized a session where HIV-positive men and women could meet and perhaps find a partner to marry. About 30 people from across the country attended the event, during which participants discussed their families, medical histories, and professions. Some introduced their prospective partners to family members before agreeing to marriage.*

*e*  
**It's the first formal way to track HIV/AIDS treatments and outcomes on a broad, comprehensive scale and in real time.**

*Michael Saag, Director of the University of Alabama-Birmingham's Center for AIDS Research, in an October 10, 2006, New York Times article announcing a \$2.45 million grant that will help seven US centers monitor antiretroviral therapy outcomes among 15,000 HIV-positive patients within a shared data framework. The framework is meant to allow longer-term research and comparison of treatment benefits and dangers. Typical clinical trials are often short-term evaluations lasting weeks or months. Saag, who will direct the effort, said that to refine and improve*

*patients' treatment options, researchers need more data that accurately reflect the patient population.*

*e*  
**I would predict that if some of these countries suddenly turn, that a very rapid spread in [injecting drug users] would be the likeliest scenario.**

*Kevin M. De Cock, Director of the World Health Organization's Department of HIV/AIDS, in an October 10, 2006, Associated Press report about his two-day fact-finding mission in Vietnam. He called on Asia-Pacific nations to focus more prevention efforts on injecting drug users (IDUs) and men who have sex with men. De Cock predicted HIV could spread quickly, even in countries with very low rates, such as the Philippines, if there is a rise in drug injecting. In 2005, the Asia-Pacific region had an estimated 8.3 million HIV/AIDS cases. In much of the region, the disease is concentrated within high-risk groups such as commercial sex workers and IDUs.*

*e*  
**The drug resistance that we are seeing now is without doubt the most alarming [tuberculosis] situation on the continent since World War II.**


*Markku Niskala, Secretary-General of the International Federation of Red Cross and Red Crescent Societies, in an October 9, 2006, statement urging European Union leaders to, "Wake up, do not delay, do not let this problem get further out of hand." The International Federation of Red Cross and Red Crescent Societies estimate that approximately 450,000 people become infected with tuberculosis (TB) annually, and nearly 70,000 people die from the disease*

*in the European region each year. Globally, 14 of the 20 countries with the highest rates of multi drug-resistant TB are in Europe and Central Asia. According to Niskala, the majority of technical assistance for controlling TB in the European region, which encompasses Eastern Europe and Central Asia, is currently provided by the United States. The World Health Organization (WHO), International Federation of Red Cross and Red Crescent Societies, and 20 other agencies and non-governmental organizations are thus forming an alliance to press European Union governments to tackle dangerous levels of drug-resistant TB in Eastern Europe.*

*e*  
**I think people haven't made a newsworthy piece of it because people assumed it was true. I think people have a right to know that; it might have some impact in people's decision-making.**

*Steven Tierney, Executive Director of the San Francisco AIDS Foundation, in an October 5, 2006, Bay Area Reporter article reporting that, despite the 1996 advent of highly active antiretroviral therapy, AIDS remains the No. 1 cause of death for men ages 15 to 54 in San Francisco. According to a San Francisco Department of Public Health epidemiologist, the numbers translate to 52 AIDS-related deaths per 100,000 male residents in the 15- to 54-age group. In the state and nationally, AIDS is about the sixth-ranking cause of death for males ages 15 to 54. During 2000 to 2003, non-AIDS cancers (6.7%), and heart and liver disease (5.2% and 2.3%, respectively) increased as a proportion of causes of mortality among people living with HIV/AIDS.*

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