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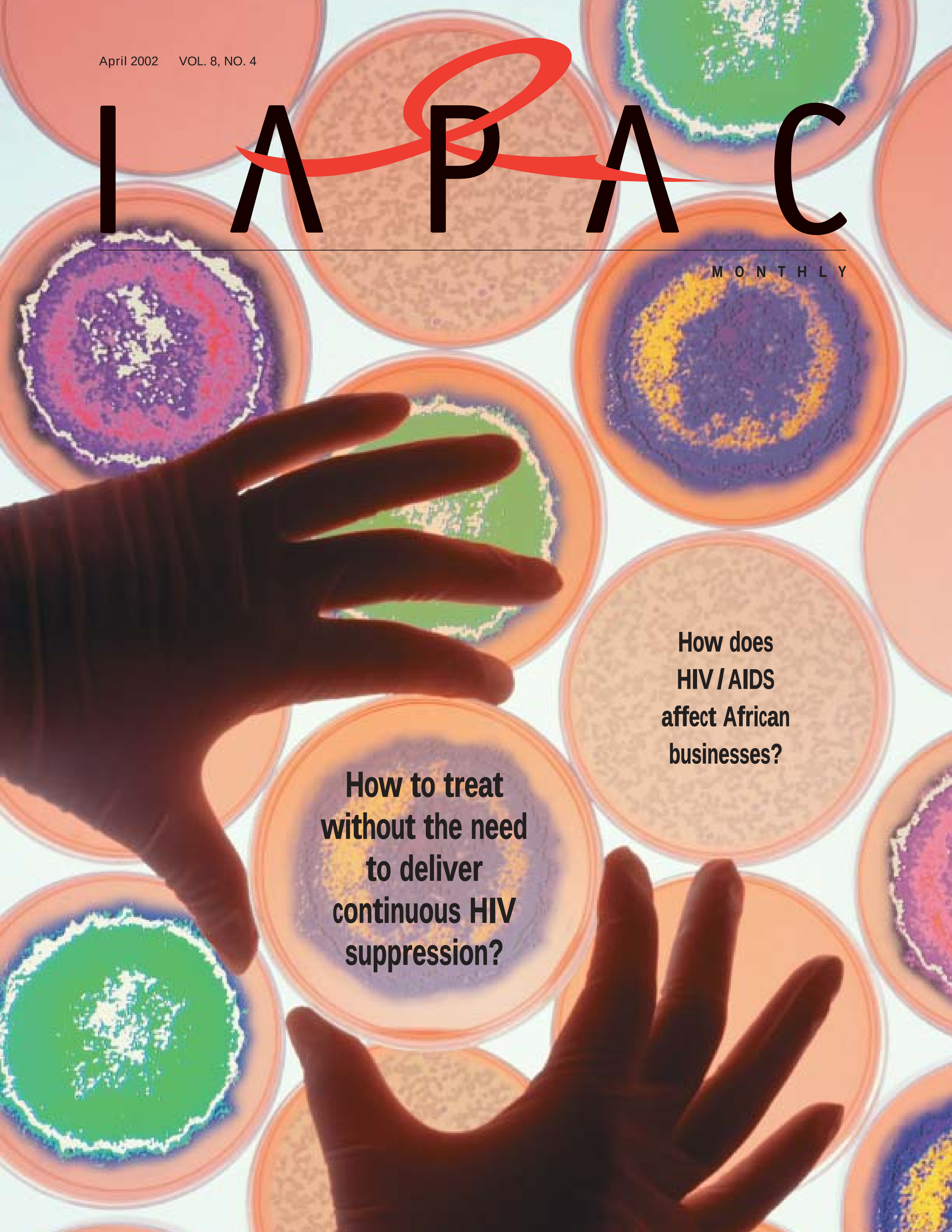

How does HIV / AIDS affect African businesses?

How to treat without the need to deliver continuous HIV suppression?

April 2002

IAPAC MONTHLY

Volume 8, Number 4

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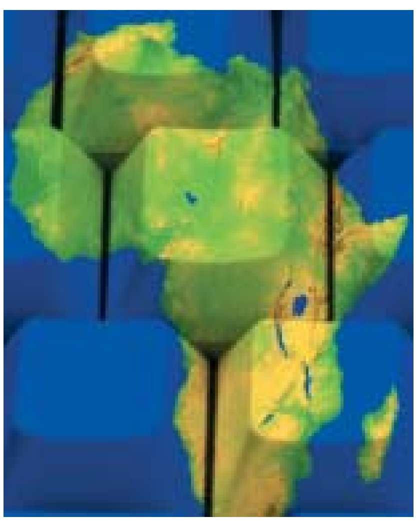
COVER STORY

How to treat without the need to deliver continuous HIV suppression?

Mike Youle

The potential for therapy breaks or the use of immune enhancement is always greeted with great enthusiasm—although, until recently, therapy breaks were not backed by hard evidence. There was plenty of news on this clinical front at the 9th Conference on Retroviruses and Opportunistic Infections, held February 24-28, 2002, in Seattle.



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How does HIV/AIDS affect African businesses?

African businesses have a potential competitive advantage over business in other regions of the world. However, the spread of HIV/AIDS has resulted in the loss of profitability among African businesses. What is the impact?

DEPARTMENTS

IAPAC

battling complacency
advancing commitment

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GALEN: Breathing life into healthcare capacity building

José M. Zuniga

Each day the HIV/AIDS pandemic deepens to the toll of an estimated 16,000 new infections. Roughly 95 percent of these infections, as well as AIDS-related deaths, occur in the least developed countries (LDCs) of the world, most notably those of sub-Saharan Africa and the Caribbean. Many of these countries, crippled by the double burden of HIV disease and staggering international financial debt, stand at a critical crossroads: that of potential recovery, health and prosperity down one path, or increased death and debilitation down the other. Not only do individual lives and vibrant cultures hang in the balance but so, too, is our very humanity called into question as this insidious disease continues to be visited upon our brothers and sisters in these resource-limited settings.

Throughout most of the world, physicians and allied health professionals work within a robust network of care providers, advocates, social activists, donors and policy makers whose collective energies have generally yielded strong policy and financial responses to HIV/AIDS. In the particular case of LDCs, however, massive inequities and widespread poverty have limited the capacity of governments and civil-society groups to buttress and support the healthcare system through such broad-based advocacy and policy measures; measures whose objectives would include redress of the numerous political, social, and economic factors that fuel the epidemic in these countries. The burden of responsibility for both prevention and treatment of HIV in resource-limited settings has and continues to fall, therefore, most heavily upon physicians and allied health professionals working within skeletal primary healthcare settings.

Although one of our primary goals must remain pursuit of a truly global commitment to addressing and redressing the global inequities that drive the pandemic, and to entrenching an understanding of HIV disease as related to broader issues of sustainable development, it is imperative that we attend equally to the practical needs of those very healthcare practitioners in resource-limited settings who are our greatest beacons of hope in these times. For those of us who have witnessed the far too common images of wasted bodies, orphaned children, and devastated families scattered throughout these countries—largely due to the lack of basic healthcare services and therapies—there is no question that we must act immediately to ensure quality care and treatment.

Among the more pressing needs of physicians providing HIV/AIDS care within resource-limited settings, are standardized HIV clinical management training, and media through which they may obtain updated information, accreditation, and continuing education. More than mere common sense, the potential impact of such training and accreditation is substantiated by way of literature from many areas of medicine, including HIV medicine, which has established that specialized education and level of experience among physicians predicts patient outcomes. Furthermore, medical fields with rapidly developing technology and an evolving standard of care are those in which specialized education and experience have the *most* profound impact on morbidity, mortality, and the use of healthcare resources. So, while there remain a plethora of macro-political and -economic questions that must be answered with a view to fully reversing HIV/AIDS trends, there *are* very concrete and immediate remedies available to us which may have a great impact in resource-limited settings, thus greatly reducing avoidable death and suffering.

The need for improved education in HIV clinical management is *especially* important and must be prioritized in sub-Saharan Africa. Deserving particular mention, in this regard, is our deepening appreciation of one very frightening possibility: that bank vaults of money which have been committed to HIV/AIDS programming by the global donor community and international lending institutions may very well fail, under current conditions, to achieve their intended impact.

This warning has come from a number of sources, among them Ebrahim Samba, World Health Organization (WHO) Regional Director for Africa. During a recent joint WHO/World Bank consultation, convened to address the dramatic shortage on the African continent of health sector staffing due both to poor training programs and healthcare worker migration, Samba reiterated that "there is a risk that the contributions soon to be committed in Africa by the new [Global Fund to Fight AIDS, Tuberculosis, and Malaria (GFATM)] will not even have a serious possibility of achieving their goals."

Foremost, during this February 2002 WHO/World Bank consultation, held in Addis Ababa, Ethiopia, delegates from 17 African nations agreed that the challenges posed by lagging infrastructure, lack of healthcare training, and migration have made Africa's healthcare facilities "barely able to function for lack of qualified, motivated doctors, nurses, and other health workers." Mirroring the thoughts of many others, Samba has, therefore, urged African health ministers to address these challenges in cooperation with other government leaders in their respective countries, professional associations, private sector healthcare providers, donor countries, and institutions.

In view of the critical shortage of adequate and standardized physician care in

LDCs, and the very practical and immediate impact that improved training in HIV care can yield, the International Association of Physicians in AIDS Care (IAPAC) has been embarked upon a journey to realize what will be known as the Global AIDS Learning & Evaluation Network (GALEN). In the not too distant future, GALEN, an HIV/AIDS care training program for physicians in resource-limited settings, will provide a means through which physicians may avail themselves of nationally administered, and WHO-endorsed training for certification as "HIV care specialists." We are convinced that this network of HIV care specialists will not only be a significant means of increasing and improving the quality of patient care and life, but will also assist in fostering further professional coordination and technical leadership within these beleaguered countries.

Aside from its ultimate goal of improving patient outcomes and strengthening healthcare delivery infrastructure, what particularly excites me about this network is that, in relative terms, it will not place a huge financial demand on governments, nor already strapped health systems, since extra burden can be ill-afforded. Rather, GALEN promises its outcomes most fully in consequence of the concerted and collective energies of IAPAC, the WHO, allied partners, and national health authorities to harmonize and clarify HIV clinical management education. As a result, GALEN will be highly cost-effective, and should yield further benefits for countries by both reducing the financial burden placed upon health systems and making for healthier, more productive populations.

In its design, content, and delivery, GALEN is intended to account for the particular challenges faced by physicians practicing in environments with limited physical infrastructure and reduced treatment options. This is critical to GALEN's ultimate success, and reflects the thinking of international bodies such as the Pan American Health Organization (PAHO), whose comprehensive care guidelines for persons living with HIV/AIDS make explicit that while there must be critical attention given to ensuring adequate healthcare infrastructure, "local standards should reflect the best care obtainable in current local circumstances."

Further in this regard, GALEN training will be tiered, in order to accommodate both those who require basic and advanced levels of training, and will be provided by a select group of locally trained, IAPAC-certified trainers. This first cohort of trainers, whose members will most likely act in a regional capacity as IAPAC-contracted trainers, will ensure that each locale, beginning in Southern Africa and then gradually spreading to other regions globally, will have local, certified trainers in place.

Evaluation of physicians receiving training will be conducted, in cooperation with local health authorities, through national and local boards, and in strict compliance with standards outlined in the GALEN protocols established by IAPAC, and endorsed by the WHO. It is perhaps this evaluation component that best distinguishes GALEN from numerous other training programs that exist for physicians in developing world settings. GALEN will ensure that through the examination and certification process, the core clinical competencies of physicians are evaluated and documented. This, in turn, will not only ensure that physicians are adequately and ethically prepared to provide basic and/or advanced HIV care, but will provide a means of determining GALEN's success and the need for revisions in the training regimen on an ongoing basis.

Ultimately, physicians certified as HIV care specialists in these resource-limited settings will have received highly standardized training. What is more, however, these physicians will then surely diffuse their knowledge and expertise throughout the vast system of healthcare providers working in the field of HIV/AIDS. It is my hope that this ripple effect will come to occupy an important place, on what we will eventually look back upon as the timeline along which the pandemic, in Africa and elsewhere, was brought to a halt. If we are to achieve this, of course, our collective effort is required. Toward this end, I welcome and look forward to establishing strong collaborative efforts and partnerships with nurses, community health workers, and other allied health personnel who have a vested interest in what GALEN offers.

GALEN's training curriculum, divided into basic and advanced components requiring either more basic or advanced instruction, includes information ranging from epidemiology and prevention of HIV, to best practices in diagnosis, screening, and treatment of patients across the range of important gender, age, and infection/co-infection categories faced by physicians in resource-limited settings. The core curriculum contains 14 learning modules, to which is appended a comprehensive train-the-trainer module, in further support of IAPAC-certified trainers and examiners (Figure 1).

While a program of GALEN's sort is long overdue, IAPAC has worked tirelessly to bring it to bear in the global arena. We have always seen ourselves as being strategically positioned to bring a global network of its desperately needed type to fruition. Most importantly, IAPAC is a catalyst for creating strong public-private health partnerships, having the flexibility to move quickly, as an honest broker between government agencies, nongovernmental organizations, and the private sector in order to create new working alliances to meet the challenges of HIV. We also bring to the mix the unparalleled energy, experience, and talent of our physician members, spread over 83 countries worldwide. I am thrilled to finally announce with certainty that GALEN will soon be a reality.

Of particular importance to GALEN's development have been the contributions of our various members and partners. The ongoing direction and guidance provided by GALEN Curriculum Committee Co-Chairs D. William Cameron (University of Ottawa, Ottawa, Ontario, Canada) and Elly Katabira (Makrere University, Kampala, Uganda), for example, has been of inestimable value. Equally deserving of mention is John G. Bartlett (Johns Hopkins University, Baltimore) who has provided both programmatic guidance and impressive authorship of two of GALEN's 14 learning modules. Looking to the future, GALEN will be guided through its final stage of development and implementation, by Scott Wolfe, IAPAC's Director of Communications and International Relations, who will coordinate the GALEN Curriculum Committee's efforts as well as communicate with academic institutions and health ministries throughout LDCs worldwide.

As I thank our staff and members who have been critical in breathing life into GALEN, it is also important for me to mention that GALEN, as it will be implemented in the not too distant future, will have benefited in its design and implementation, from multiple stages of peer review and assessment. Of greatest significance is the fact that GALEN will not only have been endorsed by the WHO,

Figure 1. **GALEN core curriculum**

Basic HIV medicine

1. History and epidemiology of HIV
    - Definition
    - History
    - Etiology
    - Epidemiology
        - — Global
        - — Regional
2. Ethical considerations in HIV management
    - Ethical precepts and community values
    - Confidentiality and duty to warn
    - International standards
3. Diagnosis of HIV infection
    - HIV structure and replication cycle
    - Tests for the detection of HIV infection
        - — Serologic assays
        - — ELISA
        - — Western blot
        - — p24 Antigen test
    - Indications for HIV testing
    - Clinical uses of HIV testing
        - — Primary HIV infection
        - — Pediatric HIV infection
        - — Established HIV infection in adults
    - Guidelines for voluntary counseling and testing
4. Mechanisms/prevention of HIV transmission
    - Modes of HIV transmission
        - — Sexual transmission
        - — Perinatal transmission
        - — Transmission by blood and other tissues
        - — Transmission of HIV in healthcare settings
    - Prevention of HIV transmission
        - — Prevention of sexual transmission
        - — Prevention of perinatal transmission
        - — Prevention of transmission by blood and other tissues
        - — Prevention of transmission of HIV in healthcare settings
5. Pathogenesis/immunology of HIV disease
    - Life cycle of HIV
        - — HIV-1
        - — HIV-2
    - Immune responses against HIV
        - — Humoral immune responses
        - — Cellular immune responses
        - — $CD4^+$ T-Cell response
    - Immune dysfunction during HIV infection
    - Cellular activation in pathogenesis of HIV
    - Cytokines and HIV disease
    - Long-term non-progressors and "exposed-uninfected" patients
6. Laboratory testing
    - Methodologies
    - Drug resistance assessment
    - Evaluation of immunologic status
    - Test interpretation
    - Sensitivity, specificity, and misleading test results
    - Recommendations
7. Management of sexually transmitted infections
    - Prospective monitoring
    - Spectrum of sexually transmitted infections
    - General principles of management

Advanced HIV medicine

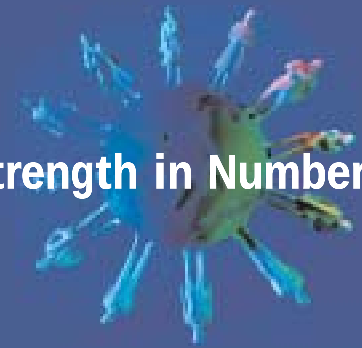
8. Introduction to antiretroviral therapies
    - Principles of antiretroviral therapy
        - — Rationale for viral suppression
        - — Therapeutic trial/cohort studies
        - — Goal of antiretroviral therapy
        - — Methods to suppress HIV
        - — Resistance
    - Challenges of access and adherence
    - Indications for antiretroviral therapy
        - — Patient criteria
        - — Systems criteria
    - Adverse reactions associated with antiretroviral therapy
    - Strategies for implementation of antiretroviral therapy
9. Recommendations for HIV treatment
    - Treatment planning
        - — Infrastructure
        - — Personnel
        - — Laboratory resources
        - — Subset analysis
        - — Sustainability
    - Antiretroviral therapy
        - — Indications
        - — Antiviral agents
        - — Initial therapy recommendations
        - — Preferred regimens
        - — "The third drug"
        - — Special populations
        - — Monitoring response
10. Management of HIV-infected pregnant women/ prophylaxis of perinatal HIV transmission
    - HIV infection of the genital tract
    - Preconceptional counseling
    - Counseling and testing HIV-infected pregnant women
    - Perinatal transmission
    - Prenatal care
    - Use of antiretroviral drugs as MTCT HIV prophylaxis
    - Intrapartum care
    - Postpartum care and follow-up
11. Prophylaxis and treatment of opportunistic infections
    - Prospective monitoring
    - Spectrum of opportunistic pathogens
    - General principles of management
    - Opportunistic infections
        - — Viral
        - — Bacterial
        - — Mycobacterial
        - — Fungal
        - — Parasitic
12. Prophylaxis and treatment of co-infectious diseases
    - Prospective monitoring
    - Spectrum of co-infectious diseases
    - Co-infectious diseases
        - — Tuberculosis
        - — Malaria
        - — Hepatitis
13. Pediatric AIDS infection
    - Natural history
    - Clinical features in children
    - Early diagnosis of HIV infection in children
    - Clinical management of the HIV-infected child
    - Psychosocial support for the HIV-infected child
14. Palliative care in HIV management
    - Principles of palliation
    - Palliative care for HIV-infected patients
        - — Pain management
        - — Treatment of diarrhea/constipation
        - — Treatment of nausea
        - — Treatment of dermatological complications
        - — Treatment of malaise/fatigue
        - — Psychological/spiritual support
    - End-of-life care
    - Special needs of children

but will have been presented to health authorities with the backing and approval of a truly international GALEN Curriculum Committee. Members of this committee reflect the collective experience of physicians at the vanguard of clinical HIV practice, as well as those best attuned to the challenges of preventing and managing HIV disease in resource-limited settings.

Further to this, a short-course GALEN package will soon undergo piloting in South Africa in order to provide a first assessment of its reception by practicing physicians and its amenability to the protocols and capacity of health authorities and professional associations. The level of cooperation, consensus, and support that GALEN will ultimately have, therefore, is truly remarkable and gives us ample reason to be enthusiastic.

As IAPAC embarks upon the next stages of our journey to realize GALEN, I wish to offer up the following reminder and message of appreciation and collegiality to our membership, partners, colleagues, and friends: GALEN does not exclusively represent the vision and commitment of IAPAC. Rather, this critical program reflects the cumulative effort and energies of disparate individuals, groups and agencies who, over the past 20 years, have struggled to foster harmonization and cooperation among global actors working in the HIV/AIDS care field. Where so often our hope for the future prospect of reversing the global pandemic is outweighed by apprehension and dread, GALEN offers a much-needed boost and reason to redouble our efforts. ■

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



[Strength in Numbers]

[IAPAC Welcomes New and Renewing Members]

In March 2002, the International Association of Physicians in AIDS Care (IAPAC) welcomed 35 new and renewing dues-paying physician members and three allied health professional members from six countries. IAPAC thanks the following individuals for their support of the association's mission to improve the quality of care provided to all men, women, and children living with HIV/AIDS.

Jamila Aboobaker, *South Africa*
Adam Abramowitz, *USA*
Orlando Alonso, *USA*
Susan Ball, *USA*
Joseph Baran Jr., *USA*
Paul Bellman, *USA*
Ellen Birenbaum, *USA*
John Black, *USA*
Bob Colebunders, *Belgium*
Rod Felber, *USA*
Manfred Forstenlehner, *Austria*
Donna Futterman, *USA*
Carol Harris, *USA*
Andrew Helfgott, *USA*
José Hernandez, *USA*
Clair Hicks, *USA*
Ronald Hirsch, *USA*
Joseph John Jr., *USA*
Jeffery Kirchner, *USA*
Jeffery Klausner, *USA*
Patricia Kloser, *USA*
Steve Kravick, *Canada*
Theodore Lenox, *USA*
Nathan Linsk, *USA*
Debapriya Mallick, *India*
Joseph Marzouk, *USA*
Julio Montaner, *Canada*
Amar Munsiff, *USA*
L. Murray-Bookhardt, *USA*
Peggy Parsons, *USA*
John Post, *USA*
Wendee Rogerson, *USA*
James Sosman, *USA*
Greta Stiebel-Chin, *USA*
Donna Sweet, *USA*
Lorraine Tosiello, *USA*
Quy Vihn, *USA*
Robert Wallace, *USA*
Athol Ware, *USA*

In addition, one corporation renewed its IAPAC corporate partners membership in March 2002. As part of its corporate partners contribution, Gilead Sciences is subsidizing 10 developing world IAPAC physician memberships for a year. IAPAC thanks Gilead Sciences for its support.

To learn more about IAPAC individual and/or corporate partners membership, please contact Joey Atwell, Director of Membership, at (312) 795-4941 or jatwell@iapac.org.

[Recruit and Win]

Do you wish to strengthen the profession, enhance your colleagues' work, and win a prize? Your recruitment effort will not go unrecognized. Each time you recruit a new member, your name will be entered into a drawing to win one of the following prizes:

- One roundtrip, upgradeable, tourist class ticket anywhere United Airlines flies in the United States.
- One roundtrip, upgradeable, tourist class ticket anywhere United Airlines flies in Europe.

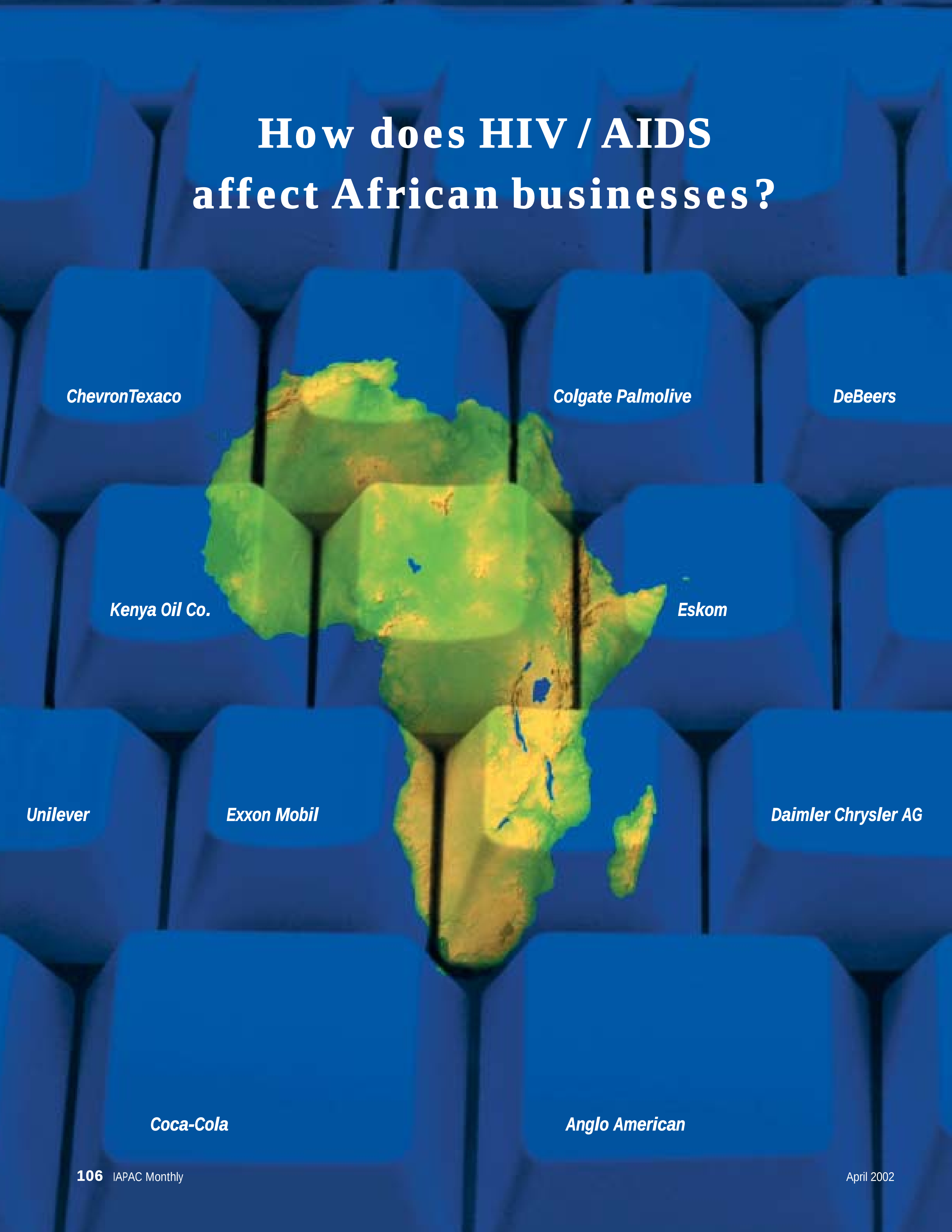
From March 1, 2002, to December 15, 2002, the more new members you recruit, the greater your chances of winning! Plus, you will receive recognition in the *IAPAC Monthly*.

Whether you sponsor one or 100 new members, you will receive a gift as recognition of your contribution to the success of this IAPAC membership campaign. There are four sponsorship levels; at the end of the campaign, you will receive a prize for the recruitment level you have met.

- Level 1 – Recruit one to four new members between March 1, 2002, and December 15, 2002, and receive an IAPAC lapel pin.
- Level 2 – Recruit five or more new members between March 1, 2002, and December 15, 2002, and receive an IAPAC lapel pin and a custom-designed plaque recognizing your commitment to IAPAC.
- Level 3 – Recruit 20 or more new members between March 1, 2002, and December 15, 2002, and receive Level 1 and 2 gifts and a 12-month complimentary extension of your IAPAC membership.
- Level 4 – Recruit 75 or more new members between March 1, 2002, and December 15, 2002, you may show off your accomplishment with a 10k yellow gold IAPAC lapel pin (and receive Level 2 and 3 gifts).

There is *Strength in Numbers*—encourage others to become IAPAC members. It is easy. To learn how easy, contact IAPAC's Membership Department at (312) 795-4941 or e-mail membership@iapac.org.

How does HIV / AIDS affect African businesses?



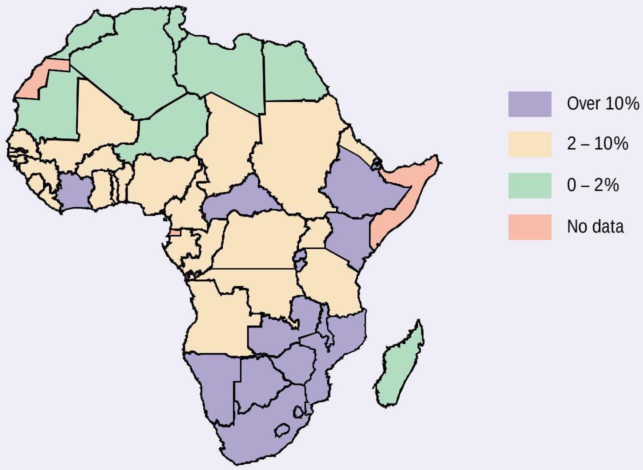
For African businesses to attract new investors, they must demonstrate a competitive advantage. In much of Africa, businesses already have a competitive advantage because labor is abundant, affordable, and productive. Countries inevitably compete against one another to attract investors. In turn, investors seek to locate their businesses in a country that has the most productive, lowest-cost workforce.

There are several mechanisms by which HIV/AIDS affects the international competitiveness of African businesses:

- **Labor supply.** AIDS deaths lead directly to a reduction in the number of available workers. These deaths occur predominantly among workers in their most productive years. As younger, less experienced workers replace experienced workers, worker productivity is reduced, which in turn results in a decline in international competitiveness.
- **Profitability.** AIDS reduces the profitability of African businesses by both increasing the cost of production and decreasing the productivity of African workers. The loss of profitability clearly will reduce Africa's competitive advantage.
- **Other impacts.** AIDS can also affect African businesses in many ways that are difficult to quantify but that nonetheless can significantly affect competitiveness. For example, AIDS affects worker morale, labor relations, demand for output, and so forth.

Each of these impacts is discussed in greater detail on the following pages.

Figure 1. **Percent of adults infected with HIV in Africa, 1999**



Source: UNAIDS, 2000

How does HIV / AIDS affect the labor supply?

As already indicated, the objectives of promoting trade and increasing investment in Africa can be reached only if African businesses have an adequate supply of trained workers.

Figure 1 shows the percent of adults in Africa infected with HIV. It is currently estimated that at least one in 12 workers in sub-Saharan Africa is infected; for some African businesses, the ratio is as high as one in three. Most infected workers will become ill and die within seven to 10 years of becoming infected. The impact from losing so many workers will vary greatly as will the response of companies with several infected workers.

Most African businesses that have more than 10 employees have already seen at least one employee die of HIV/AIDS or currently employ infected workers. In some countries, the number of HIV infected employees has been devastating.

For example,

- In a sugar mill in South Africa, 26 percent of all tested workers were infected with HIV. Infected workers incurred, on average, 55 additional days of sick leave during the last two years of their life.[1]
- In Botswana, it has been estimated that 35 to 40 percent of all teachers are infected with HIV.[2]
- One study in Kenya on a sugar estate found that 25 percent of the estate's workforce was infected with HIV.[3]
- Even in countries such as Ghana, which has a more moderate prevalence of HIV, businesses report significant numbers of both AIDS deaths and known HIV infections.[4]

If businesses are to succeed financially, they require a steady supply of adequately skilled labor. For companies requiring skilled workers, it is likely that HIV/AIDS will present a particularly significant problem. Professionals are in short supply, and the costs required to train a new worker are often significant. One study demonstrated that firms took, on average, eight times longer to replace a deceased professional than a skilled worker.[5]

Figure 2 illustrates the average age and sex of persons infected with HIV in Rwanda. This shows that the bulk of infections are occurring among young people who are just entering the workforce. This should be particularly worrisome to African businesses, as it demonstrates that the future supply of laborers and managers are likely to be the ones most affected by HIV/AIDS. At the same time, this figure shows the critical importance of spending money on HIV/AIDS prevention among young people. In order to safeguard the future labor supply, it is necessary to stress prevention programs for youth today.

How does HIV / AIDS affect profitability?

HIV/AIDS can affect a company's profitability by either increasing expenditures or decreasing revenues. During the early stages of infection, managers may observe an unexplained increase in the number of sick days taken. The employee, his or her spouse, and children may incur higher healthcare costs, many of which are reimbursed by the employer. The productivity of the worker may decline, particularly when opportunistic infections such as tuberculosis (TB) become more common.

As the epidemic progresses, managers may observe within their workforce an increase of diseases, such as TB, sexually transmitted infections (STIs), skin rashes, diarrhea, and possibly even malaria. (Some evidence suggests that HIV-infected individuals are much more susceptible to serious bouts of malaria as a consequence of their suppressed immune system.) There is likely to be a corresponding increase in healthcare costs and sick days. Employees who are identified as being infected may be retained, moved to a less demanding position in the company, or fired outright (with or without compensation) depending on corporate policy.

Figure 2. **HIV prevalence by age and sex (Rwanda, 1997)**

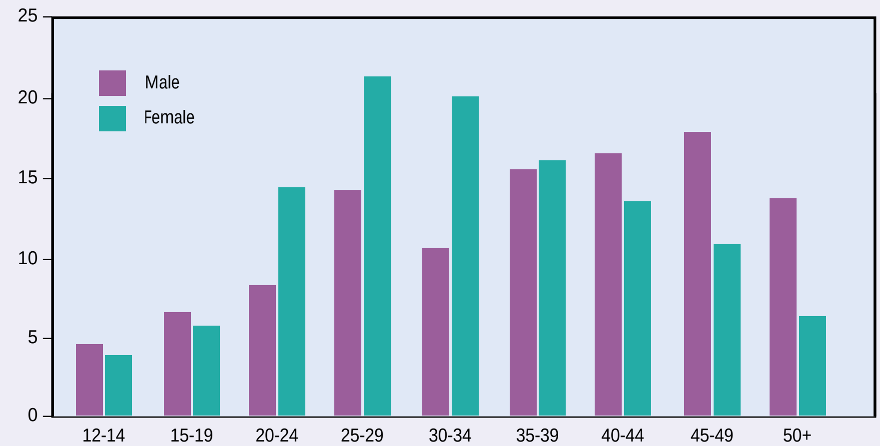


Table 1. **Expenditure/revenue**

Factors leading to increased expenditures

- Healthcare costs
- Burial fees
- Training and recruitment

Factors leading to decreased revenue

- Absenteeism due to illness
- Time off to attend funerals
- Time spent on training
- Labor turnover
- Reduced worker productivity

"NamWater, the largest water purification company in Namibia, announced recently that HIV/AIDS is 'crippling' its operations. They report high staff turnover due to AIDS-related deaths, increasing absenteeism, and a general loss of productive hours. The firm plans on examining the impact of the epidemic through a survey, and then designing further policies to mitigate the impact. The company already distributes condoms to their workforce and has trained 60 peer educators."[6]

A loss in revenues attributable to HIV/AIDS can occur when infected workers take leave due to illness, the need to care for other infected family members, or the need to attend the funerals of coworkers or loved ones—in north central Namibia, for example, it has been estimated that extension staff spend at least 10 percent of their time attending funerals.[7] Productivity can also decline when workers in poor health come to work but are unable to produce at their normal levels.

The extent to which people living with HIV/AIDS will continue to be employed depends on the type of work performed and the existing policies of the relevant company. Presumably, employees involved in heavy manual labor will be less likely than desk workers to maintain their jobs when they become infected. Certain companies are required (by government mandate or union contract) to continue offering benefits. However, other companies are able to shift the burden to the government or the families of the employee living with HIV/AIDS.

There are various ways in which expenditures are likely to increase when African businesses are affected by HIV/AIDS. An increase in healthcare costs is likely to be one sign that a company is experiencing the effects of the epidemic. Companies with private health insurance policies may find that their premiums are increasing. Other companies with inhouse healthcare services may find an increased need for services that may not immediately be identified as HIV-related (Table 1).

Figure 3 indicates how quickly the number of AIDS-related deaths can increase. As more workers die of AIDS, it is likely that the private sector in Africa will observe increased costs in terms of death benefits. When a worker dies, many larger African companies offer a death benefit to the surviving family. In some cases, these death benefits equate to as much as three years of salary plus funeral-related expenses. Some companies also pay workers a death benefit if their spouse or children die. With the advent of the HIV/AIDS epidemic, companies have tried to mitigate the impact of benefit costs in various ways. For example, some African companies have reduced the amount of their contribution to funerals. Other companies have required funerals to be conducted on weekends to minimize the disruption to work.

The cost of recruiting and training new workers may also be substantial. The cost of replacing unskilled workers may be small, particularly when the rate of unemployment in the community that houses the business is high. As a result, most unskilled workers can be replaced within a week with little or no cost of recruitment. However, many African countries have a shortage of experienced senior managers. In this case, positions may be left unfilled for months or even years, which represents a significant cost to the company. Some companies even have had to resort to hiring highly paid expatriates following the death of senior managers.

As with recruiting, the cost of training and of general human resource development depends on the education and skill level required for the position as well as on the capacity of the pool of available workers. Training of unskilled workers often occurs over a period of a few days and does not generally represent a high cost to the company. The costs involved in training a director of finance, marketing, accounting, or sales, however, can be significant, particularly as such training is typically performed overseas. One international company, for example, trains its African senior managers in Europe over a period of four weeks. That same company indicated that when a managing director is lost due to AIDS or other reasons, the company incurs costs of US$100,000 to recruit and train a replacement.

In the end, HIV/AIDS is likely to have a variable impact on expenditures depending on the

- prevalence of HIV;
- cost of training and providing benefits;
- availability of prevention activities; and
- extent to which the company can shift the economic burden of the disease from itself to workers, their families, and the public sector.

It should be noted that the data on the extent of the impact of HIV/AIDS on profitability remain controversial. Studies completed in South Africa[1] and Kenya[3] suggest that the economic impact of HIV/AIDS on profitability is likely to be substantial. Studies in Zambia,[8] Malawi,[9]

Figure 3. **Death rate on a sugar estate in Swaziland**

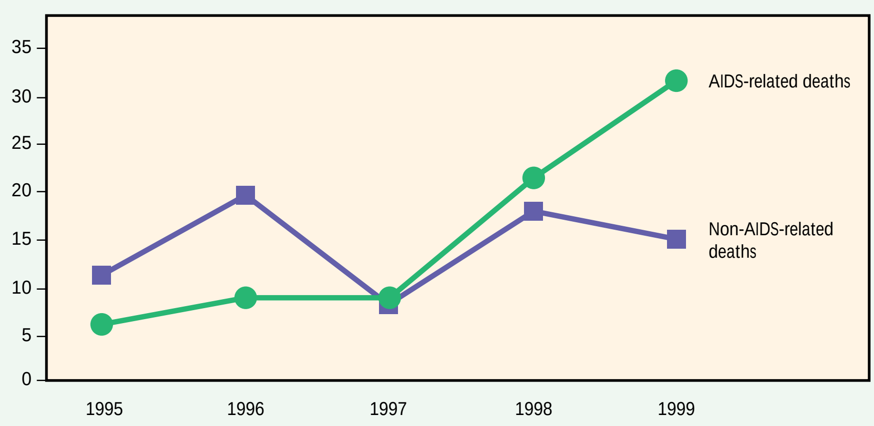


Table 2. **Investment/trade**

Impact on investment

- Uncertainty over the impact of HIV/AIDS causes investor reluctance
- Decrease in the pool of national entrepreneurs
- General economic picture

Impact on trade

- Reduced production due to increased costs to firms
- Decrease in workers with experience in export markets
- Transport of export products to marketplace

and Botswana,[10] however, indicate that the impact of HIV/AIDS on profitability was not substantial at the time those studies were carried out. Nonetheless, the loss of profits due to HIV/AIDS may be substantial for some African business. Therefore, it is critical that businesses become aware of the HIV/AIDS problem and take immediate steps to mitigate its impact. Such steps should include workplace peer education programs, condom distribution, voluntary counseling and testing, STI treatment, and treatment for HIV-related opportunistic infections.

What other impacts does HIV/AIDS produce?

The indirect impacts associated with HIV/AIDS are much more difficult to quantify but can nonetheless be an important factor in influencing investment decisions. The indirect impact incurred by African businesses refers to those outcomes that cannot be directly attributable to an increase in revenues or a loss in expenditures over the short term, but that still can create a significant burden for a company. For example, HIV/AIDS can result in a substantial decline in morale among workers. As employees watch many of their co-workers die of AIDS, they may adopt a generally fatalistic attitude toward life and work.

One indirect effect of absenteeism is that it results in extra work for other healthy employees who have to stand in for sick colleagues. In some companies, healthy employees were increasingly working extra hours to compensate for the time lost by their absent (sick) colleagues. In so doing, not only did companies pay more in terms of overtime, but interviewed workers also pointed out that they were overworked and exhausted. According to the engineering manager of one of the companies, working longer hours produced stress among employees and was responsible for a decline in both the quantity and quality of the final product (sugar). The spread of the epidemic can also contribute to worsening labor relations. If employees do not feel that their employers are providing adequate prevention or care services, the relationship may degenerate. In some cases, workers demand the dismissal of their colleagues when learning of their colleagues' illness.

"…*Knowledge or even suspicion that one of their colleagues has HIV/AIDS is likely to trigger certain negative attitudes and behavioural responses towards that individual and how they perform their own tasks.*"[11]

Managers may not always be aware of the ways in which HIV/AIDS is affecting their business. One way to address the indirect effects of HIV/AIDS is to establish a workplace policy that explains how the needs of infected workers should be addressed. Such a policy should promote a positive relationship among infected workers, their employer, and their colleagues.

HIV/AIDS can also result in a significant decline in the demand for some products. HIV/AIDS is known to be a disease that tends to impoverish families, particularly because infected individuals are often the main income earners in the household. As a result, families end up earning less but spending more on healthcare, leaving few resources available to purchase other goods. Thus, most businesses are likely to observe at least some decline in demand for their products, especially the "luxury" goods that consumers can forego during difficult economic times. An article by Alan Whiteside, for example, noted that a South African furniture manufacturer (JD Group) projected an 18 percent reduction in its customer base as a result of HIV/AIDS. The study went on to conclude that consumers would incur a significant decrease in demand for furniture due to HIV/AIDS and its corresponding impact on household consumption.[12]

How does HIV/AIDS affect African economies?

In addition to the impact of HIV/AIDS on particular businesses, HIV/AIDS can influence national economies. Such an impact can be particularly devastating to the objective of increasing investment, for investors seldom invest in countries with declining economies (Table 2).

Various methodological issues and features of developing country economies make detection of macroeconomic impacts difficult. Initial studies regarding the potential impact of HIV/AIDS on macroeconomic growth have generally not been conclusive, with some studies in Botswana[13] and Tanzania[14] showing that the change in per capita income would be minor.

However, as the epidemic has progressed, economists have tended again to raise questions about the potential macroeconomic impacts of HIV/AIDS. A Kenyan analysis indicated that HIV/AIDS would produce a significant impact, with predictions that HIV/AIDS would leave the Kenyan

African nations have a potential competitive advantage over other regions of the world. Businesses and governments must protect the vast majority of workers who are uninfected, offer appropriate support and services to those who are infected, and ensure that the impact of HIV / AIDS is mitigated.

economy one-sixth smaller than it would have been in the absence of HIV/ AIDS.[15] A study of African countries in 2000 suggests that HIV/AIDS has reduced the growth of per capita income by 0.7 percent per year; in malarial countries, the rate of growth was further lowered by 0.3 percent. For countries with HIV/AIDS prevalence levels above 20 percent, GDP is estimated to be 2.6 percentage points less per year. The most recent economic analyses have therefore indicated that the epidemic may be affecting growth to a much greater extent than earlier predicted.[16] A recent study found that the impact of the AIDS epidemic in South Africa could be "substantial." By the year 2010, the level of GDP could be lower by 17 percent due to HIV/AIDS while the level of per capita GDP could be lower by 7 percent. About half of the decline is attributable to the increase in current government spending to pay for healthcare associated with the epidemic; another third of the decline is attributable to lower productivity.[17]

It appears that many African economies are already being affected by HIV/AIDS. Decision makers must be prepared to pursue policies at the national level that can mitigate social and economic impacts. This may include promoting policies that increase savings and encourage investment in specific types of human capital that might be in short supply (eg, teachers, doctors, and so forth).

Conclusion

African nations have a potential competitive advantage over other regions of the world. Businesses and governments must protect the vast majority of workers who are uninfected, offer appropriate support and services to those who are infected, and ensure that the impact of HIV/AIDS is mitigated.

Since HIV/AIDS tends to affect people in their prime working ages, the spread of the disease can prevent some nations from meeting their labor needs, particularly for businesses that require workers with significant training or work experience. The loss to HIV/AIDS of even one critical employee can cause a business to lose its competitiveness.

The spread of HIV/AIDS has resulted in the loss of profitability among African companies. This loss is attributable to increased expenditures on benefits such as healthcare, sick leave, and death benefits as well as to the additional cost of retraining new employees. In turn, revenues have been shown to decline when many workers become infected and their productivity declines. African businesses have also been affected more indirectly as a result of HIV/AIDS. For example, as workers become ill, companies have experienced a decline in morale, labor relations, and demand for the company's products. Lost profitability among African businesses may already be thwarting efforts to encourage foreign businesses to invest new money in the African continent.

Strong macroeconomic prospects are particularly important to investors who want assurance that they are investing in a country with a stable currency and a growing demand for their products. The most recent economic studies indicate that HIV/AIDS can negatively affect a nation's overall economic growth, which in turn is likely to hinder the success of trade and investment initiatives by limiting the number of businesses that are willing to invest in Africa.

To conclude, it is imperative to recognize that in most African countries, more than 90 percent of workers are not infected with HIV. In other words, despite the potentially dire consequences of HIV/AIDS, in most countries there is still time to prevent and to mitigate the impact of the epidemic. Also, we now know what works in terms of HIV/AIDS prevention. In countries such as Uganda and Senegal, prevention programs have succeeded in significantly reducing or limiting the spread of HIV infection. Finally, there are now unprecedented levels of commitment globally to addressing the issue of HIV/AIDS. ■

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How to treat without the need to deliver continuous HIV suppression?

Mike Youle

In his seminal work, *A Brief History of Time*, Cambridge University theoretical physicist Stephen Hawking examines the relationship between space and time with regard to the universe. At one point, he describes the thermodynamic arrow of time that relates to the Second Law of Thermodynamics. The latter states that in any closed system disorder increases with time, a form of Murphy's law (read: things always seem to go wrong). Hawking goes on to relate the thermodynamic arrow of time to the psychological arrow of time (in that we remember the past but not the future) and the cosmological arrow of time, which states that the universe is expanding. These ideas are used to explain or attempt to evaluate the relationship between time and motion. Hawking concludes that human beings can only exist in an expanding universe. We expend more energy than we create to exist. Indeed, the mere reading of this article in the *IAPAC Monthly* will use up far more energy in living than you can ever conserve by the creation of order in your brain.

There is a fascinating cyclical, but ultimately progressive direction that appears to exist in science and clinical medicine. We approach each new area of interest by forays into unknown territory followed by returns to a more normative stance, a pendulum of advancement. The tides of HIV research are like waves on a beach with the occasional high tide that changes the topography forever. What we witnessed at the 9th Conference on Retroviruses and Opportunistic Infections (CROI), held February 24-28, 2002, in Seattle, was yet another backwash of information that increased our knowledge in some of the multifarious areas pertaining to HIV and associated conditions while leaving others static with no obvious advances.

This article focuses partially on the dilemma of how to treat without the need to deliver continuous suppression of HIV, which, with current therapies, ultimately results in some treatment-related toxicity. As physicians are taught, *primum no nocere* (first, do no harm), so the potential for therapy breaks or the use of immune enhancement is always greeted with enthusiasm—although, until recently, these therapy breaks had not been backed up by hard evidence of utility. However, first we go to the 9th CROI's opening ceremony and the stage setting for a variety of perspectives on the epidemic and its impact.

Beatrice Hahn (University of Alabama, Birmingham) first made reference to the association of this once quiet West Coast city with the booming software industry. When her slides appeared rather hesitantly, she remarked that her sin was to use a Mac computer—considered a sin because Seattle is largely non-Mac country. In delivering the Bernard Fields Memorial Lecture, she eloquently updated her previous presentations on the human zoonotic risk from the SIV reservoir.[1] Like an orator of old, Hahn declared we were "in for a journey *Back to the Future*," and over the next 30 minutes told her story: 30 primate species that harbor retroviruses, at least 10 separate cross-species transmissions into humans, and the potential *of course* of further new transmissions.

For another exquisite description of this area, and of the impact HIV has on the potential pathogenicity of other organisms, one need only refer to articles by Robin Weiss (University College, London) and colleagues.[2] She had recently, with a large group of collaborators, shown that where there is a will there is a way. First, Weiss's work revealed from captured animals and bushmeat (killed wild animals for the meat trade) that between 5 percent and 40 percent of West African animals were infected with a range of different simian retroviruses (SIV), with older animals more likely to be infected—suggesting sexual transmission. She then moved her focus to examining the chimpanzee populations that existed in the wild to establish if there was a reservoir within this species.

Her co-worker Mario Santiago (University of Alabama, Birmingham) developed non-invasive methods to evaluate the rate of infection in the wild by collection and examination of feces and urine by a remarkable set of co-workers in the bush of several African countries. When these biological samples were evaluated using an RT-PCR method to detect virus, only a very few animals could be found in the wild in which there was evidence of SIV infection. Weiss surmised that the spread of these viruses had occurred in the last 1,000 years from West Africa from a variety of monkey hosts into the chimpanzee population at several time-points and thence into man, although the epidemiology suggested that cross species transmission was a rare event. We await the sequel to this story since it is likely that since at least some animals appear to be able to live in harmony with HIV there are some answers hidden here that may allow us to do the same.

Next came a strangely emotive piece by journalist and photographer Andrew Petkin (Humanitarian Endeavors, Southlake, Texas), which one must assume was designed for those who do not work at the coalface of HIV. He showed numerous pictures of the heartache of HIV/AIDS, in Africa specifically, with barely a mention of the rest of the world. He used descriptions such as the "tidal wave—leaving in its wake a perverse population of orphans and old people" and observations such as "statistics are merely people with the tears removed." This and other text helped to create a number of images of the horror and scale of the African epidemic.

However, in the cathedral-like environment of the Washington State Convention and Trade Center, his presentation strangely evoked theological aspects of the crucifixion being discussed 2,000 years later, an academic observation of a human trauma. Perhaps Petkin's words did help those delegates who have had little contact with the everyday uncertainty and fears of HIV.

And, undoubtedly, the presentation did reveal the problems of Africa as a melange of social, anthropological, economic, and above all political issues which medicine and science alone cannot turn around.

Finally, it was the turn of computer magnate turned philanthropist Bill Gates to discuss the "Role of Philanthropy in Fighting AIDS and Improving Global Health." After describing what we may have in the way of high tech tools for the next few years (at least from his Microsoft Corp.), Gates went on to explain how his business philosophy has drawn him to help and support health-related projects in a number of areas, including AIDS.

While understanding his willingness and eagerness to rapidly change the terrible circumstances under which billions of people live worldwide, it was also clear that Gates understood, to a degree, that money for HIV/AIDS care alone is not helpful. Supporting research in the underlying science is also required to create the huge advances that have already been made and need to be made if we are to avoid being engulfed by this and the next wave of epidemics "designed" to reduce the human population.

It was fitting that the first two plenary talks at the 9th CROI dealt with different aspects of the immune system and how they may play a role in HIV entering the body and in its control once there. Melissa Pope (Population Council, New York) gave a clear explanation of the types and roles of dendritic cells that play a vital role in the orchestration of the immune response to external antigen (foreign material).[3] These cells take up antigen and then move it around the body and present it to the body for recognition and destruction.

With HIV, these cells act as a "Trojan Horse," allowing HIV to gain access to the very heart of the immune system. Since this process is vital for the spread of HIV away from the local infection site, it is a potential target for development of anti-HIV agents to prevent this process. Microbicides would be potential agents to block the interplay between dendritic cells and HIV and thereby limit the incursion of the virus into the body. Of course as yet it is unclear to what degree this is the major route of entry of the virus.

Brigitte Autran (Hôpital Pitié-Salpétrière, Paris) then took up the mantle of explaining the action of the immune system to attempt to control the damage HIV causes and the opportunities that are afforded by the use of highly active antiretroviral medication.[4] She noted "the powerful capacity of antiretrovirals to reconstitute the immune system." The major dilemma occurs from the fact that during primary HIV infection cytotoxic T-lymphocytes (CTLs) recognize cells that are actively producing HIV and target them for attack whereas later in infection this capacity is lost. Tests such as the EliSpot show that these HIV-specific CTLs are present in low numbers since there is a decrease in antigen and perhaps defective dendritic cell activity due to the effectiveness of HIV treatment.

> **...[S]topping therapy pro-term and fixed period intermittent on-off therapy schedules have all been proposed, discussed and to some degree studied over the past couple of years.**

Autran noted that treatment interruptions are problematic in that they cause rapid antigen exposure but also result in a viral load rise that causes total CD4 cell decline. Therefore, her conclusion was that therapeutic vaccination was likely to hold out some degree of hope to allow immune reconstitution to maximally occur with HIV-specific cells as a large proportion of the response. Then and only then, Autran suggested, is it possible that interruption of treatment would result in a sustained low viral load and prolongation of good health.

In terms of primary HIV infection, following from the work of Eric Rosenberg (Massachusetts General Hospital, Boston) et al, the early results of the PRIMSTOP pilot trial (ANRS 100) show some promise.[5] In this multicenter prospective trial, 29 subjects at an early stage after seroconversion were treated with a combination of stavudine, didanosine, nelfinavir and hydroxyurea for approximately nine months, followed by a series of treatment interruptions at three monthly intervals, which increase, from two weeks to four weeks and then to six weeks. Although the patients were later in their infection than those studied by Rosenberg, the outcomes seemed to indicate in the first group of 12 subjects to have had three breaks that eight subjects had controlled virus to a load <10,000copies/mL and five subjects were below 1,000 copies/mL. Whether this was due to the use of hydroxyurea alone, which limits target cell activation in HIV, or hydroxyurea combined with the treatment interruptions is uncertain. However, if these results could be replicated in a randomized controlled study a new treatment modality would be available for those few individuals who are seen at the time of seroconversion.

Further along in HIV disease from initial infection treatment interruption, stopping therapy pro-term and fixed period intermittent on-off therapy schedules have all been proposed, discussed and to some degree studied over the past couple of years. A number of "facts" about these strategies are clear, much more is less so. When treatment is stopped viral load rebounds usually to around the pre-treatment level, and over the next few months CD4 cell counts decline at a variable rate that appears to have little predictability. Some small studies (none randomized) have hinted that this strategy is more successful in those people who were treated at seroconversion, and that the further along in HIV disease you go the more risky will be interrupting therapy that has suppressed HIV.

Tantalizing data, first shown at the 8th European Conference on Clinical Aspects and Therapy in HIV (October 2002, Athens), appeared in the Giga-HAART study, from Christine Katlama (Hôpital Pitié-Salpétrière, Paris) and her group. This was the first controlled data to build on work by the Royal Free Hospital group in London, that of Steve Deeks (University of California, San Francisco), and of Veronica Miller (formerly of JW Goethe Institut, Universität, Frankfurt) showing that potential benefits existed in short-term treatment interruptions in salvage patients who then recommenced a new regimen.

Thus, the 9th CROI was a forum for synthesizing new data into the idea that interruption of antiviral suppression may be a double-edged sword. What you gain by lower toxicity and lack of pills may be offset by physical and laboratory changes showing that HIV was once more attacking the immune system. Of course, the fundamental question remains: do you gain any delay in disease progression by treatment that is not available if you delay treatment until the risk of disease occurrence is higher?

The "treat now, or treat later" discussion is intricately linked to the question of treatment interruption. In addition, there is now a large clinical endpoint study called Optima that will examine 1,300 patients who are three-drug class failures and who will be randomized to have a 3- to 6-month treatment interruption versus immediate switch to a salvage regimen. These patients will also be randomized to take a standard three-drug optimized HAART regimen or a Mega-HAART five or more drug regimen. This trial, which is now open to recruitment in the United States (through Veterans Affairs hospitals), across Canada, and the United Kingdom, should provide some more definitive answer as to the utility of this approach in later stage disease.

Overall, there were 26 presentations on this topic at the 9th CROI, including two late-breakers. They fell into a number of subject groups. The first were those that examined the effects on the viral populations and immune function in different tissues when treatment was ceased. Andrew Leigh Brown (University of Edinburgh, Scotland) worked with a group from the University of California, San Diego, led by R. J. Ellis, to examine the dynamics of viral rebound in the cerebrospinal fluid (CSF).[6,7] In two of nine patients studied where sufficient data points were available (understandably, repeat lumbar punctures are not popular with patients), there was a difference between CSF and plasma viral kinetics. A rise in white cells (pleocytosis) in four subjects was seen following the viral burst in the CSF suggesting that this is a response rather than a cause of viral turnover in the central nervous system. This work also appears to shed light on the issue that reducing viraemia systemically may limit the entry of lymphocytes and linked virus into the CSF.

Further work to evaluate the source of virus when treatment is suspended came from the group of Lydia Ruiz and J. Martinez-Picardo (irisCaixa Foundation, Badalona, Spain). They extensively examined the env sequences for 12 subjects over up to four sequential structured treatment interruptions (SSTI).[8] Genetic analysis was performed for stretches of the genome for the envelope of the virus in DNA, plasma RNA and PBMCs. In some patients there was little shift in the genetic structure of emerging populations whilst in others there was a marked alteration. This may limit the ability of treatment interruptions to strengthen the HIV-specific cell-mediated immune responses since the exposed viral antigens keep changing during each SSTI. A single subject was more extensively studied and examination of plasma samples revealed that the HIV populations that emerged over successive interruptions probably reflect a combination of reactivation of archived populations and ongoing selection due to the effect of cytotoxic T-lymphocyte responses.[9]

The role of neutralizing antibodies in treatment interruptions was examined by a group of investigators working on the Swiss Spanish Intermittent Therapy Trial, where subjects had four cycles of two weeks off/eight weeks on therapy.[10] In 10 subjects at week 2 and 25 subjects after week 42, virus was isolated from PBMCs and examined for replicative capacity and for neutralizing antibodies. Although neutralizing antibody levels did not increase over the cycles of the study during the 4-6 treatment free period, after the 4 cycles there was a significant increase in these antibodies (90 percent inhibition titre >1/1000). This occurred especially in the subgroup of subjects who had maintained control of viremia throughout the study.

Next were those studies that evaluated the effects of treatment interruption on the progression of disease in prospective studies. The largest of these came from the EuroSIDA cohort that represents large clinical centers across Europe and is a long established study that has been prospectively followed for many years.[11] Jens Lundgren (D:A:D Coordinating Center, Copenhagen) presented data on 565 (16 percent) subjects who interrupted therapy in a cohort of 3,610 representing 7,328 person years of follow-up after commencing HAART. Median CD4 cell count at interruption and nadir were 242/µL and 130/µL respectively. Of these patients, 290 developed new AIDS-defining illnesses or died during follow-up and 45 percent restarted treatment. In subjects with the latest T4<200/µL there were 25 clinical events in 48 person years (0.52 per PY) whereas in those with a latest T4>200/µL there were three events in 92 person-years (0.03 per PY). This suggests that absolute risk of illness still depends highly on the T4 level to which patients sink.

F. Lampe and co-workers (Royal Free Hospital Clinic, London) followed all 237 patients from their clinic who were naïve to antiretrovirals when they started a HAART regimen and who reached a viral load <400 copies/mL (within 32 weeks) or who reached a viral load <50 copies/ml without viral rebound.[12] Twenty-one percent of subjects were female; main HIV exposures were homosexual (60 percent) and heterosexual (34 percent) sex. The median age at start of HAART was 35 years. HAART was started on a median date of December 1998 (IQR September 1996 - November 2000). Baseline median (IQR) viral load was 5.3 (4.8–5.7) log copies/mL and CD4 count 193 (75–302)/mm^3. Nucleoside drugs in the initial regimen were zidovudine/lamivudine 126 (53 percent), stavudine/lamivudine 76 (32 percent) and other 35 (15 percent). Other drugs were nevirapine 58 (25 percent), efavirenz 44 (19 percent), indinavir 56 (24 percent), ritonavir 21 (9 percent), nelfinavir 50 (21 percent), and ritonavir boosted protease inhibitor 29 (12 percent).

Median time from start of HAART to first measured value of 50 copies/ml was 180 days; with 1,342 viral load measures made over a total 347 person-years of follow-up after the first viral load <50 copies/ml—a median of one measure per 13.5 weeks (median over all patients of 3.8 per year). Maximum follow-up was 4.4 years. Overall 13 people (5.4 percent) experienced viral rebound (breakthrough) on therapy (rate 0.037 per person-year) representing one person with viral rebound per 26.7 person-years of follow-up. There was a (non-significant) trend towards lower rebound rate with increasing time from start of HAART.

The Badalona group also presented a prospective study. Subjects with multiple exposure to antiretrovirals were randomized to a three-month treatment interruption or an immediate switch to a new salvage regimen that consisted of lopinavir/ritonavir plus saquinavir soft-gel, lamivudine, didanosine and abacavir.[13] In the 22 subjects who had the treatment interruption (Group A), 13 (64 percent) showed a reversion to wild-type virus during this period, perhaps raising the question as to whether the period off treatment was long enough. The outcomes, in this group, were compared to the 24 subjects from Group B who had an immediate switch to the salvage regimen. They showed no significant differences although a trend was seen to better response in Group A with a CD4 cell rise of 144 compared to 80 cells/µL and a viral load drop to less than detectable level in 47 percent compared to 36 percent in Group B.

Longer-term follow-up in greater numbers of patients may however be required to show such differences. The other major Catalan research group of José Gatell (Hospital Clinic-IDIBAPS, University of Barcelona, Spain) evaluated the use of mycophenalate mofetil (MMF) and the cytostatic drug hydroxyurea in groups of patients who had started HAART close to seroconversion.[14,15] These were small studies, 15 and 20 patients, respectively, but they did show that blunting of viral load rebound occurred under both agents that appeared not to be related to decrease in cell turnover or from increase in apoptosis. Further larger studies would be valuable for each of these agents, perhaps combined with another approach.

Therapeutic vaccination to maintain the benefits accrued during antiretroviral therapy has become an area of intense interest with several studies currently reaching a degree of fruition. For instance, the Quest study is currently evaluating the utility of a Canarypox vaccine, Remune, or both prior to cessation of HAART in subjects who have been treated just after seroconversion. The group of Franco Lori and Juliana Lisziewicz (RIGHT, Washington, DC) presented data evaluating the utility of a novel topical DNA immunization (DermaVir) in preventing viral rebound during treatment interruptions in macaques.[16] Ten animals with late-stage AIDS were studied and randomized to continuous HAART, STI-HAART (three weeks on, three weeks off) and after six cycles were also given DermaVir (a composition of HIV DNA plus Langerhans cell stimulant called polyethylenimine-mannose designed to stimulate recognition of the DNA by the animals' immune system). All the macaques on HAART alone were dead by month seven whereas only one on STI-HAART had succumbed. Of the three monkeys who were then treated with DermaVir, median viral load decrease during each subsequent interruption occurred until control at <200copies/mL was achieved. Clearly if this outcome were possible to replicate in humans it would be highly significant and could open the door to combination HAART and immunotherapy combination studies.

Other studies also seemed to suggest this trend with different vaccinations. A US National Institutes of Health (NIH) study using NYVAC-SIV in macaques showed similar blunting of viral rebound in immunized animals versus controls.[17] A pilot study nested within a Remune protocol evaluated the rise in viral RNA in subjects who stopped therapy for six weeks after suppressing to undetectable for at least six months.[18] In the 20 Remune patients, the slope of the rise was 0.16 $\log_{10}$ copies/mL versus 0.21 in the eight control subjects who were only treated with the adjuvant IFA ($p<0.05$). The difference in the post interruption viral load level between the groups was not significant but the numbers of patients in the study precluded this being properly evaluated.

So many approaches are being currently undertaken, or are planned, to the "Treatment Interruption" scenario, using HAART, immunotherapy, cytostatic treatments and immune enhancing agents. This once again suggests that a combination of different interventions may be the best way to continue to support the inherent immune response to HIV. Only the future will tell us if we are traveling toward a more effective period of HIV treatment. What is clear is that as entropy increases so the HIV epidemic appears to be little affected as yet by the therapeutic interventions that we have and even now it continues to threaten the very global infrastructure, a fact clearly not understood by many. ■

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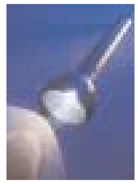

A B S T R A C T S

SELECTED ABSTRACTS FROM THE 9TH CONFERENCE ON RETROVIRUSES AND OPPORTUNISTIC INFECTIONS

FEBRUARY 24-28, 2002 — SEATTLE

Oral Abstracts

Abstract 14
Deaths from Non-AIDS Related Diseases Have Increased as a Proportion of Deaths of HIV-Infected Persons Since the Advent of HAART

M.I. Wolfe, D.L. Hanson, R. Selik, and D.L. Swerdlow

Background: In HIV-infected persons, the proportions of death due to many AIDS-related conditions have decreased since the advent of HAART therapy. There is concern that deaths from some non-AIDS-related causes are increasing as adverse outcomes from therapy or because people are living longer with HIV infection. We examined diagnoses present at death to determine trends in causes of death since the advent of HAART therapy.

Methods: Data were obtained from the Adult and Adolescent Spectrum of HIV disease (ASD) study, an ongoing medical record-review observational cohort study in 11 US cities that has followed over 54,000 HIV-infected persons since 1990. We analyzed data from persons who died in 1992-2000, comparing diagnosis rates during 1992-1995 (pre-HAART) with those in 1996-2000 (HAART). We restricted analysis to six sites that collected death certificate cause-of-death data. We compared the proportions of death diagnoses for the two periods using stratified Cochran-Mantel-Haenszel statistics and controlling for age, sex, race/ethnicity, HIV transmission mode, and study site.

Results: From 1992 through 2000, we observed a total of 7,188 deaths, 4,870 (68%) during the pre-HAART period, and 2,318 (32%) during the HAART period. Compared with the pre-HAART period, proportions of deaths with the following conditions decreased for tuberculosis (TB) (OR 0.41; CI 0.3-0.6), non-TB mycobacterial infections (OR 0.7; CI 0.6-0.8), pneumocystis pneumonia (OR 0.7; CI 0.6-0.9), and toxoplasmosis (OR 0.7; CI 0.6-0.9). Proportions of deaths increased for liver disease (odds ratio [OR] 1.7; 95% CI 1.4-2.1), non-Hodgkins lymphoma (OR 1.5; CI 1.2-2.0), cachexia/wasting (OR 1.3; CI 1.1-1.6), kidney disease (OR 1.3; CI 1.1-1.5), and sepsis (OR 1.2; CI 1.1-1.4). Although not reaching statistical significance, the trend for ischemic heart disease (OR 1.9; CI 0.99-3.62) was suggestive of an increase in proportion of deaths.

Conclusions: This study demonstrates that since the advent of HAART there have been declines in proportions of deaths from some AIDS-related causes, likely due to both improved treatment and prophylaxis. However, this study shows that there have been increasing proportions of some deaths from non-AIDS-related causes including liver and kidney disease, and possibly ischemic heart disease. While these results may be partially explained simply by the declines in AIDS-related causes, data from this analysis should be used to guide research into the question of whether some of these increases may be due to adverse outcomes from HAART or due to the aging population of persons infected with HIV.

Abstract 18
Tracking the Worldwide Subtype C Epidemic

C. Kuiken, U.R. Smith, D. Lang, and T. Bhattacharya

Background: The subtype C epidemic is the fastest-growing and for that reason the most dangerous sub-epidemic of HIV-1. Tracing its spread around the world can help decide which vaccine best suits which region.

Methods: Phylogenetic trees were used to analyze the evolution of the subtype C epidemic. The year of origin of the African and Indian subtype C epidemics were estimated using methods refined by Korber et al.

Results: Only a few African subtype C form clear subclusters and few inferences can be made from them. However, in Ethiopia the availability of a large number (>250) of samples from several cities has led to the identification of a distinct local subtype C sub-clade. The introduction of subtype C into Ethiopia was dated to the early 1980s, concordant with epidemiological data. The recent origin of this sub-epidemic may have contributed to the ease with which the Ethiopian sub-epidemic could be traced. In Asia, the subtype C epidemic shows clear epidemiological patterns. The variant that is spreading in India is distinct from all African sequences. Another sub-epidemic is seen in south-central China, driven by drug use and drug trafficking. A third distinct sub-epidemic, clearly branching off from the Indian subtype C, is currently invading Nepal. Reports of subtype C infections emanate from the other countries surrounding the Golden Triangle (Myanmar, Vietnam, Thailand, Cambodia), but few subtype C sequences are available from those regions. Our estimate for the beginning of the Indian subtype C sub-epidemic is 1986 (95% CI 1973-1988), which is consistent with epidemiological data. The best estimate for the origin of subtype C in Africa (1933, 95% CI 1571-1967) is more problematic, because due to the scarcity of longer sequences from early strains it is heavily influenced by a few data points. More early samples are needed before a more stable estimate can be obtained.

Conclusions: While in Africa the overall pattern in the subtype C epidemic appears to be chaotic, there are regions where distinct sub-epidemics can be identified. It is possible that patterns will emerge when the sampling density increases. The Asian epidemic is probably much younger (dating from the mid-1980s) and tracing the spread of the virus here appears to be very feasible. While the number of well-annotated sequences is small, increased awareness and interest in designing an appropriate vaccine should lead to a rapid accumulation of data.

Abstract 31
An Objective Case Definition of HIV Lipodystrophy

A. Carr for the HIV Lipodystrophy Case Definition Study Group

Background: There is no objective, validated, sensitive, specific, and readily applicable case definition of HIV lipodystrophy (LD).

Methods: A European Medicines Evaluation Agency-initiated and industry-sponsored study was performed at 32 sites in the Americas (n=15), Europe (n=11), and Australasia (n=6) using a case control methodology for identifying clinical, laboratory, and imaging features that independently discriminate LD cases. Recruitment was of consecutive HIV-infected adults free of active AIDS, with equal numbers of patients (and of cases and controls) recruited at each site. 1,081 patients (15% female) were recruited: 417 cases (at least 1 moderate or severe LD feature identified by doctor and patient, except isolated abdominal obesity); 371 controls (no LD identified by doctor or patient, and no significant weight change since HIV diagnosis); and 288 non-assigned (neither case nor control). Cases and controls completed all assessments (demographics, antiretroviral and metabolic drug history, HIV disease, fasting metabolic bloods, and DEXA and abdominal CT). Models were generated from 504 randomly selected cases and controls by stepwise forward logistic regression of all parameters (excepting patient and physician LD assessments and antiretroviral history) significantly different between cases and controls on univariate analysis. Models were then validated in the remaining cases and controls.

Results: A model including low trunk:peripheral fat ratio (DEXA), report of abdominal bloating, low leg fat % (DEXA), lower alcohol consumption, higher waist:hip ratio, higher total:HDL cholesterol ratio, higher anion gap, report of increased bleeding tendency, higher VAT:SAT ratio (CT), and greater age had sensitivity of 84.4% and specificity of 81.4%.

Conclusions: This model can diagnose HIV lipodystrophy objectively and relatively simply.

Abstract 48

Interruption/Stopping Antiretroviral Therapy and the Risk of Clinical Disease: Results from the EuroSIDA Study

J.D. Lundgren, S. Vella, L. Paddam, A. Blaxhult, N. Vetter, N. Clumeck, G. Panos, M. Fisher, C. Katlama, A.N. Phillips

Background: Reports suggest that it has been relatively common for people to interrupt (or stop altogether) antiretroviral therapy.

Methods: We studied 3,610 people within the EuroSIDA study who started a HAART regimen (three drugs taken simultaneously). We assessed the tendency for therapy interruption and evaluated the relative hazard of a new AIDS-defining event (ADE) or death associated with therapy interruption/stopping using a Cox model. To minimize bias caused by stopping induced by terminal disease we assessed the risk associated with interruption for at least three months.

Results: At start of HAART median CD4 count was 214/mm^3, median viral load 25,000 copies/mL, 6% had a previous AIDS diagnosis. There was a total 7,328 person-years (median 3.2 years) after start of HAART. 565 (16%) interrupted HAART. Median (IQR) CD4 count at interruption and nadir were 242 and 130/mm^3, respectively. Median (IQR) viral load at interruption was 3,000 copies/mL (<400-45,000). 274 of the 565 (49%) have so far since restarted therapy. 290 developed a new ADE or died, incidence rate: 0.04 per person-year). After adjustment for demographic variables and previous ADE before HAART the relative hazard of new ADE/death associated with having been off therapy for at least the past three months was 6.0 (95% CI 4.0-8.9; p=0.0001). This changed to 2.4 (95% CI 1.6-3.6; p=0.0001) after adjustment for the latest CD4 count and viral load (known within at most the past three months). In those interrupting there were 25 clinical events in 48 person-years (0.52 per person-years) in people with latest CD4 count <200/mm^3 compared with three clinical events in 92 person-years (0.03 per person-year) in people with the latest CD4 count >200/mm^3. When six months was used instead of three months as a lag-time the adjusted relative hazard was unchanged at 2.4. Further, consistent results were obtained when we considered the relative hazard associated with therapy interruption (ie, people subsequently restarted therapy).

Conclusions: These data indicate that risk of AIDS and death increases several-fold upon therapy interruption/stopping. The absolute risk remains closely linked to the latest CD4 count and was higher among patients with a latest CD4 count below 200/mm^3.

Abstract 95

Persistence of Transmitted Drug Resistance among Subjects with Primary HIV Infection not Receiving Antiretroviral Therapy

S.J. Little, E.S. Daar, S. Holte, S. Frost, J.P. Routy, M. Markowitz, A.C. Collier, J.B. Margolick, R.A. Koup, B.Conway, E. Connick, M. Kilby, T. Wrin, C.J. Petropoulos, N.S. Hellmann, and D.D. Richman

Purpose: To evaluate the persistence and altered replication capacity (fitness) of transmitted antiretroviral (ARV) resistant variants among untreated subjects with primary HIV infection.

Methods: ARV drug susceptibility and replication capacity were measured using a single replication cycle assay (ViroLogic). ABI sequence analysis of *pol* was used to identify drug resistant mutations. Clonal analysis is in progress to evaluate the rate of reversion to wild type in these patients.

Results: Baseline antiretroviral susceptibility results have been previously reported for 412 subjects from North America with primary HIV infection (8th CROI). Pretreatment susceptibility testing was performed a mean of 79 days after the estimated date of infection. The prevalence of >10-fold reduced susceptibility to one or more ARV did not differ among patients relative to elapsed time from infection (0-147 days). Longitudinal samples were analyzed from 6 subjects, identified a mean of 60 days post infection, with >10-fold reduced susceptibility at baseline who deferred ARV therapy during follow-up. In the six patients, the presence of >10-fold reduced susceptibility to one or more NNRTI at baseline was associated with the detection of K103N with or without Y181C. The median baseline viral load was 5.6 $\log_{10}$ copies/mL (range 4.9-6.2). Reversion of the K103N mutation was observed in only one subject (>117 days after baseline), while persistence of the K103N mutation was observed in the other five subjects during a median follow-up of 140 days (and 77, 130, 200, 242, and 296 days post infection). Mixtures of wild type (WT) and drug-resistant (R) strains at positions K103 and Y181 in reverse transcriptase were detected in two of the five patients at days 119 and 182 with an associated increase in NNRTI drug susceptibility. The replication capacity was reduced in five of the six subjects (approximately 50% of WT replication capacity) and did not improve significantly after detection of the WT/R mixture in two subjects.

Conclusions: Transmitted K103N and Y181C drug resistance mutations are associated with reduced drug susceptibility and replication capacity. Transmitted NNRTI drug resistance in newly infected patients does not rapidly become undetectable in untreated patients, in contrast to the rapid reversion to WT virus described in patients with treatment-associated secondary drug resistance.

Abstract 96

Mixed Infection with Multidrug Resistant (MDR) and Wild Type HIV Strains in Primary HIV Infection (PHI): Early Viral Rebound Suggests Loss of Immune Control

E.S. Daar, S. D. Frost, J.K. Wong, N.S. Hellmann, T. Wrin, C.J. Petropoulos, D.D. Richman, J.A. Pitt1, S.J. Little, and A.J. Leigh Brown

Background: We described a patient with PHI with an MDR virus, who without receiving therapy precipitously lost all evidence of resistance in conjunction with an increase in viral load. Initial sequence analysis revealed many changes between resistant (strain 1) and susceptible (strain 2) variants raising the possibility of superinfection. We have used phylogenetic analysis and estimates of *in vivo* and *in vitro* fitness to address this issue.

Methods: Direct consensus PCR-sequencing of *pol* was performed on serial samples. Replication capacity (RC) was measured using a single-cycle assay based on the same amplicon. Motifscan was used to screen for potential CTL epitopes.

Results: Plasma viral load (pVL) was initially 5.5 $\log_{10}$, declining to 3.0 $\log_{10}$ by day 30. It remained stable until day 110, then increased to 4.5 $\log_{10}$ by day 173, when the switch in phenotype occurred. Phylogenetic analyses on all 1,200 nucleotides, or on third base positions alone, confirmed the two viral strains cluster separately among strains from other PHI patients, indicating co-infection with two independent virus strains. *In vitro* RC assays revealed strain one had a 4-fold higher fitness *in vitro* than strain 2. This fitness advantage is consistent with the success of strain 1 immediately after infection, but outgrowth of strain 2 after day 110 is inconsistent with the RC data. From its rate of increase in frequency, we estimate the fitness of strain 2 *in vivo* is at least 5% higher than strain 1 at day 110, implying a significant difference between strains in a fitness component not represented in the *in vitro* RC assay. We hypothesized that this outgrowth represented escape from immune control. Class 1 HLA typing (A3,24; B35,40) permitted screening of sequences from strains 1 and 2 for HLA-matched CTL epitopes. 18 potential A3- restricted epitopes were identified, two of which were present in the initial sample and missing from the later sequence and could represent the escape mutations.

Conclusions: We propose that the patient was co-infected with a drug susceptible strain and a more fit MDR strain, an effective immune response was elicited but the susceptible strain subsequently suffered a mutation in a critical CTL epitope, permitting outgrowth after day 110.

Abstract 121

Early HCV Viral Dynamics in HIV/HCV-Infected Patients on HCV Treatment

F.J. Torriani, R.M. Ribeiro, T.L. Gilbert, U.M. Schrenk, M. Clauson, D.M. Pacheco, and A.S. Perelson

Background: On daily interferon (5-15 mIU), plasma HCV RNA follows a biphasic viral decay curve, with a HCV viral half-life of 2.7 hours. If HCV clearance is slower in HIV/HCV patients, longer treatment may be required to ensure sustained response rates similar to those seen in HCV monoinfection. We characterized the early HCV viral dynamics in 10 subjects naive to HCV therapy and enrolling in a large randomized, partially blinded trial of pegylated interferon-2α (PEG) + ribavirin/placebo (+RIB) vs interferon-2α (IFN) + RIB. The infected cell death rate was also compared to the decline in ALT levels over the initial four weeks of therapy.

Methods: Plasma HCV RNA IU/mL and HIV RNA copies/mL were measured before starting HCV treatment (BSL), 6, 8, 12, 24, 32, 48 hours and 3, 4, 7, 9, 11, 14, 21, and 28 (W4) days (D) after BSL. CD4 counts were measured at BSL, ALT levels at BSL, D7, D14, W4. Non-linear least squares were used to fit a model of HCV therapy, which allowed calculating the parameters of viral decay and early antiviral efficacy. Results are in mean +SE.

Results: Eight of 10 subjects completed 24 weeks of study. Subjects were middle-aged men, infected with HCV genotype 1, 4 randomized to PEG+RIB and 4 to IFN+RIB. HAI and fibrosis scores were 6.4+0.7 and 2.3+0.5, respectively, and one subject had compensated cirrhosis. At BSL, HCV RNA, HIV RNA, absolute and % CD4 counts, and ALT were 5.4 + 0.4 $\log_{10}$ IU/mL, 2.2 + 0.4 $\log_{10}$ copies/mL, 625 + 93 cells/mm^3, 30 + 4% and 120 +20 IU/mL, respectively. HCV RNA became undetectable in <5 days in two subjects and in 28 days in a third. HCV RNA levels decreased slightly and transiently in three subjects and were overall unchanged in one. In the remaining patient, HCV RNA was not detected at BSL, but only six and 12 hours post-treatment. In the five subjects with HCV RNA decline, the HCV virion half-life was of 7.0 + 1.0 hours and the early antiviral efficacy was 78 + 9%. ALT decline paralleled plasma HCV RNA decline in the three subjects exhibiting a virologic response at 24 weeks.

Conclusions: The estimated HCV virion half life was longer in this small cohort of HIV/HCV infected patients on HCV treatment than that observed in patients infected with HCV alone receiving daily interferon, suggesting that HIV co-infection may be contributing to a slower clearance rate of HCV.

Invited Abstracts

Abstract S8

Managing HIV and Tuberculosis in Sub-Saharan Africa

G. Maartens

Background: Tuberculosis (TB) is the major cause of morbidity and mortality in HIV-infected patients in sub-Saharan Africa. The region has experienced a 20% increase in TB from 1997-1999, even in countries with well-functioning TB-control programs. HIV increases sputum smear-negative disease, which is difficult to diagnose in resource-poor settings with limited access to Mycobacterial culture. Smear-negative TB in many areas is treated with regimens that contain limited or no rifampin. Outcome studies show high mortality in these patients. Rifampin access is fortunately increasing. Innovative methods of directly observing therapy have been developed, including patient-nominated guardians and lay supervisors. Cotrimoxazole has been shown to improve mortality and morbidity in HIV-infected patients with TB, but this affordable intervention is still not being widely applied. There is increasing access to antiretroviral therapy (ART), particularly for private patients.

Conclusions: Suggestions have been made that public sector access to ART could be carried out using the infrastructure of the TB clinics. Pharmacokinetic interactions between rifampin and ART are well known. Rifabutin interacts to a lesser extent, but is not an option in most African settings as it is too expensive—thus ART must be tailored to be used with rifampin wherever possible. ART is often delayed until after TB therapy, especially if the CD4 count is >200, which is the case in about two-thirds of cases.

Abstract S17

When to Start Antiretroviral Therapy?

R.E. Chaisson

Background: Treatment guidelines for HIV infection have changed substantially in the past several years. Earlier guidelines endorsed beginning treatment early, based on the assumptions that infection might be eradicated, that response would be better in less advanced disease, and that adverse reactions would be less common than in later stage disease. Earlier criteria for starting therapy included CD4 count <500 and viral load >25-40,000. It is now apparent that HIV infection cannot be eradicated from cellular reservoirs with current therapy. In addition, data from observational cohorts demonstrate that patients started on therapy with CD4 counts as low as 200 respond as well as those started earlier in terms of immune reconstitution, reduction of disease risk, and survival, while those started with CD4 counts <200 are at higher risk of disease progression.

Conclusions: Delaying treatment in patients with CD4 counts >200 does not appear to increase risk of progression. Viral load, while highly predictive of progression in untreated HIV disease, does not predict clinical response to antiretroviral therapy. Patients started on antiretroviral therapy with CD4 counts >350 are likely to experience considerable toxicity as well as emergence of drug-resistant virus in the absence of a compelling clinical benefit. Initiation of therapy should be based on CD4 count and the patient's ability to comply with complex and potentially toxic regimens.

Abstract S18

Strategic Treatment Interruptions: Where Are We?

B. Hirschel

Background: Highly active antiretroviral therapies (HAART) lower mobility and mortality of HIV infection, but are unable to eradicate HIV and may cause side-effects. Strategic (also called planned or structured) treatment interruptions are studied for three reasons: to stimulate the anti-HIV immune response after viremia has been suppressed by treatment (autovaccination), to increase time off drug, in order to improve quality of life and diminish side effects, as well as costs, and, among individuals whose virus has become resistant to treatment, to induce reversion of resistance to wild-type and therefore to improve the success of subsequent salvage therapy. Regarding autovaccination, the most promising results come from the rare patients who started HAART during primary HIV infection. Up to 60% have controlled viremia below 5,000 copies m/L, for up to one year without HAART. *In vitro*, there is evidence for enhancement of CD4- and CD8-cell HIV-specific immune response. In the majority of patients who started HAART later, 17% (CI 11-25%) of patients remained with a viremia <5000 after 4 off-on cycles (two weeks on, eight weeks off) followed by 12 weeks' treatment interruption. *In vitro* tests also show stimulation of HIV-specific cytotoxic lymphocyte responses (CTL). However, such stimulation did not predict a state of low viremia without therapy; to the contrary, patients with higher rebounds tended to have more active CTL. In this population, additional immune stimulatory manoeuvres are being planned, such as administration of cytokines, or specific immune treatment by anti-HIV vaccines (therapeutic vaccination).

Conclusions: Intermittent HIV therapies also hold out the promise of fewer side effects, and of a more favourable cost/benefit ratio for HAART; in this, they are particularly interesting for developing countries. Risks (such as selection of resistant quasispecies and increase in HIV infectiousness during rebounds) and benefits still have to be compared in large clinical trials which are currently in the planning stage. Many types of treatment interruptions are being planned: Long interruptions. Start and stop of treatment may be guided by the calendar (eg, two months on, two months off), or by the CD4 count (eg, suspend treatment each time the CD4 count >350/uL). Rebounds of viremia and falls in CD4 counts are to be expected. Short interruptions. A pilot study has shown that in patients treated with ritonavir-boosted indinavir, stavudine, and lamivudine, no rebounds were observed on a schedule of one week on, one week off therapy. Potential advantages to this approach are steady CD4 cell counts, and lesser contagiousness. When treatment is interrupted in patients who fail HAART and who have drug-resistant HIV, the drug-sensitive wild-type replaces the resistant quasi-species in 30-60%. In a recently completed randomized study, the viral load response to salvage therapy with six to nine drugs was better in patients who were randomized to a drug holiday before salvage. However, the drop in CD4 counts during treatment interruption is of concern, as these patients are often immunosuppressed and therefore vulnerable to opportunistic infections.

Abstract S20

The Role of Therapeutic Drug Monitoring (TDM) in Clinical Practice

D. Back, S. Khoo, and S. Gibbons

Background: The goal is always to improve clinical outcome. We need to do this since a significant proportion of patients on HAART never achieve optimal viral suppression or may experience viral rebound within a short space of time. One approach to optimize therapy is therapeutic drug monitoring (TDM). This strategy can be applied to patient care if there is a well-defined relationship between the exposure to a drug and its efficacy or toxicity (PK-PD), a large inter-individual variability in drug exposure, and a relatively narrow therapeutic window. PIs and NNRTIs are candidates for TDM. Optimally we need to relate drug levels to virus phenotype (actual or virtual) and generate inhibitory quotients (IQs or virtual IQs or normalized IQs). However, a minimalist approach is to have a trough plasma concentration (C_{trough}) above a critical value, which is based on a protein-corrected IC_{50} or EC_{50} of WT virus. Furthermore, the minimalist approach is to consider dose reduction in the face of drug-related toxicity. The ATHENA study has clearly shown that TDM of IDV and NFV in treatment-naive patients improved outcome after 12 months' follow-up. For IDV the difference was mainly driven by a lower rate of discontinuation for toxicity in the TDM group. For NFV, the difference was mainly due to a lower rate of discontinuation because of virological failure. Data from this study therefore give encouragement that TDM is a realistic approach. But again there is the need to stress that TDM in isolation from knowledge of resistance is only half a story. So the question then becomes, Can we use IQ to improve patient care? In one sense, IQ is still a research tool and there are numerous confounders in calculating the final number. However, the evidence of presentations at this meeting is that IQ (or vIQ or nIQ) is more predictive of virologic response than either resistance testing or drug exposure alone at lest for some drugs.

Conclusions: Numerous arguments against TDM have been put forward (ie, low plasma levels simply reflect adherence problems; effect of protein binding not adequately understood; what is the *in vivo* therapeutic index of each drug; logistics-yet another test!; expert interpretation, etc.). But if, as the U.K. experience shows, patients benefit from a relatively straightforward, cheap test, then we should at least be open to consider implementation.

Abstract L7

Treatment of Patients with Drug Resistant Virus

A. Collier

Background: The high prevalence of patients with drug-resistant HIV underscores the importance of understanding the issues that lead to this condition, in order to optimize its management. Insufficient drug exposure to prevent emergence of resistant virus may result from the use of regimens with inadequate potency, and pharmacokinetics, adverse drug-drug interactions, poor adherence, or lack of penetration into viral reservoirs. Management approaches and treatment goals differ for patients with limited drug resistance compared with patients with multi-class resistant HIV. Maximizing viral suppression with a regimen that is well tolerated is a reasonable goal for patients with limited viral resistance. Achieving partial viral suppression with a goal of maintaining $CD4^{+}$ T-lymphocyte counts and preventing opportunistic complications is a more realistic goal in many patients with highly resistant virus. Use of resistance testing, measurement of drug concentrations, and methods to assess and enhance adherence are important management tools, although the strength of data supporting their clinical utility varies. In patients with limited viral resistance, several approaches may be successful, including intensification of therapy or switching to regimens that include a new drug class. In patients with highly resistant virus, fewer treatment options have been demonstrated to result in long-term success. Regimens that include a new drug class, the entry inhibitors, have shown great promise but such compounds are not yet widely available. Use of second-generation non nucleoside reverse transcripts inhibitors, protease inhibitors with limited cross-resistance, and ritonavir-enhanced protease inhibitors are also promising approaches. Drug directed against other viral or host targets are eagerly awaited. Other options for selected patients include short-term structured treatment interruption with the rationale of enhancing responses to salvage regimens, multi-drug rescue therapy, use of drugs which might impact viral fitness, and adjunctive therapies.

Conclusions: Individualizing the approach for patients with drug resistant virus will ensure therapy minimizes the downsides and maximizes the benefits. This difficult management dilemma challenges all HIV laboratory scientists, clinical researchers, treatment advocates, and care providers to continue the quest to improve therapy and access to therapy for all persons with HIV.

Abstract S26

Prevention of Mother-to-Child Transmission: Implementation, Programs, and Treatment of Mothers and Children

C.M. Wilfert

Background: In 1994, PACTG trial 076 demonstrated for the first time the ability of an antiretroviral drug (AZT) to diminish transmission of HIV-1 from mothers to their infants. The ensuing years in the United States have documented a decrease of 80% in the number of infants with reported perinatal AIDS. In 1998, a 2-dose regimen of nevirapine was demonstrated to reduce perinatal HIV transmission by 47% in Ugandan women. Currently this regimen is feasible for implementation in the developing world.

Methods: In September 1999, a Call To Action was issued at the Global Strategies Meeting, and the Elizabeth Glaser Pediatric AIDS Foundation (EGPAF) developed an international program to provide resources for the implementation of prevention of mother-to-child HIV transmission. In the subsequent two years, projects in 11 sub-Saharan African countries and Thailand have been supported. The African countries are: Angola, Cameroon, Democratic Republic of the Congo, Kenya, Malawi, Rwanda, South Africa, Tanzania, Uganda, Zambia, and Zimbabwe. The projects include 70 clinics/hospitals and counseling for an estimated 41,852 women in antenatal care, with an overall HIV seroprevalence of 15% (5-45%). The clinics vary from public to private not-for-profit, rural to urban, large (25,000-30,000 deliveries per year) to small (1,000). Provision of counseling, HIV testing, and nevirapine as decided by the individual site occurs within the existing maternal child health clinics. Uptake of testing is variable in individual clinics with a reported low of 26% in a newly functioning setting, but with multiple clinics achieving rates >90%. Expansion of the program to additional hospitals/clinics has occurred and national programs are evolving in several countries. Additional interval and cumulative data on these projects through December 2001 will be presented.

Results: Establishment of voluntary counseling and testing in these clinics provides an opportunity for expansion of the availability of counseling, increased acceptance of knowledge of HIV status, laboratory testing with rapid tests, and identification of a population of HIV infected persons to benefit from treatment.

Conclusions: This is a stepping-stone to provision of additional care and support of HIV-infected women, children, and household members. A program entitled MTCT+ has been announced and funds secured to add additional care, including prophylaxis and treatment of OIs and treatment with antiretroviral drugs.

Abstract S28

Potential Antiretroviral Drug Resistance in Developing Countries: The Thailand Experience

P. Phanuphak

Background: Antiretroviral (ARV) therapy exert selective pressure for ARV resistance if the existing regimen is not fully suppressive. In the poorest countries where ARV will never be considered for large-scale use, ARV resistance will be less a problem. However, in countries with some resources, such as Thailand, ARV resistance can be a serious problem if sub-optimal regimens are being used. Although HAART is ideal, it is largely unaffordable. Physicians in many developing countries are forced by their dying patients to prescribe sub-optimal but affordable therapy because they realize that some ARV is better than no ARV. AZT and ddI were the two nucleosides most commonly used in Thailand since they were the first to come out, relatively cheap, and generic drugs were widely available. For the same financial reason, viral load is rarely used to measure therapeutic response. Immunological (CD4) failure was usually used to determine treatment failure. Even when treatment failure was evident, the patient had to be kept on the same regimen since the second-line regimen such as d4T/3TC after AZT/ddI failure was three times more expensive. As a result, thousands of patients in Thailand were maintained on AZT/ddI for as long as six to eight years or until they died of AIDS.

Methods: Genotype resistance data were obtained from 30 Thai patients failing prolonged AZT/ddI use.

Results: AZT resistance was found in all cases whereas ddI resistance was found in only one. Interestingly, 3TC resistance was found in eight, d4T resistance in two, ddC resistance in two, NNRTI resistance in one, and multi-drug resistance in two. These patients had never been exposed to any other NRTI or NNRTI besides AZT/ddI. Cross-resistance within the class of NRTI was also seen in non-suppressive d4T/ddI use. In a cohort of patients receiving low- and high-dose combinations of d4T/ddI for 48-96 weeks, we observed four cases of thymidine analogue mutations (TAM) and four cases of Q151M multi-drug resistance mutation out of 25 patients who had viral load over 1,000 copies/mL. Our data and data from others confirm that intra-class cross-resistance (between NRTI and NNRTI) as observed in one of our patients, if confirmed, will be more alarming. The risk of ARV resistance is of particular concern for countries with limited resources, since long-term sub-optimal therapy is common. Interrupted therapy is frequent due to financial constraint, inconsistent medical supply and poor compliance, viral load and resistance assays are not readily available and option for salvage regimens is limited. Single ARV such as AZT and nevirapine (NVP) is still being used in developing countries to prevent mother-to-child transmission of HIV. Fortunately, the course of treatment is short, but NVP resistance has been observed even with a single dose. In Thailand, single-dose NVP has been added to some of the existing regimens of AZT with the hope to enhance the protective efficacy. How this combined regimen will affect the outcome of AZT and NVP resistance remains to be seen.

Conclusions: Public health implications of ARV resistance are many. Transmission of resistant virus is the obvious concern. Although we could not find any baseline resistance in the RT genes in the patients enrolling in ARV trials during 1997-1998, periodic surveillance is needed. At the same time, prevention effort has to go hand in hand with ARV use. Conventional simple ARV regimens to prevent mother-to-child transmission or accidental needle stick injury may become ineffective if ARV resistance becomes widespread. Scarcity of effective salvage regimens is a threat of cross-resistance. Measures to minimize ARV resistance in developing countries are definitely needed. Maximally suppressive ARV regimens should be the goal. This goal requires drastic reduction in ARV price, government and international funding agencies commitment to care, as well as training of ARV prescribers. Adherence to ARV regimens must be stressed. Viral load and resistance assays as well as therapeutic drug monitoring should be made available, again with a much lower price. Uninterrupted supply of ARV must be ensured as well as the potency of ARV, especially if generic drugs are used. Alternative regimens for intolerance or treatment failure must also be available. Regular national surveillance for ARV resistance is required for constant update of national guidelines for first-line therapy, for prevention of mother-to-child transmission and for prevention of needle stick injury. Last but not least is to maintain a strong prevention program in order to prevent the transmission of resistant virus. The task is tremendous even for developed countries. Is it realistic for developing countries? No matter what the answer is, the concern of ARV resistance should not delay the political decision to start up a large-scale ARV use in developing countries.

Abstract S23

Viral and Host Factors in HIV-1 Transmission and Pathogenesis

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Background: Approximately half of HIV-1-infected adults are women, and the majority of the affected women are in sub-Saharan Africa.

Methods: We have been studying HIV-1 infection and pathogenesis in several cohorts of HIV-1-infected women in Kenya, including women who are identified near the time of seroconversion.

Results: Women who were using hormonal contraceptives near the time of their HIV-1 acquisition were more likely to be infected by multiple HIV-1 genotypes, and these women have higher plasma viral RNA set-point levels. In an earlier cross-sectional study, hormonal contraceptives were shown to increase viral shedding in the female genital tract, suggesting that hormones may also influence virus replication in the genital mucosa. Analyses of viral RNA levels in chronically infected women suggest that hormone changes that occur over the course of the menstrual cycle affect the level of genital virus, but not plasma virus.

Conclusions: Both endogenous and exogenous hormones may impact HIV-1 infection and replication in women.

Abstract 409-W

Once-Daily vs Twice-Daily Kaletra (Lopinavir / Ritonavir) in Antiretroviral-Naïve HIV + Patients: 48-Week Follow-Up

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Background: Kaletra is a coformulation of lopinavir (LPV), an HIV protease inhibitor, and ritonavir (r), which inhibits CYP3A, providing increased plasma levels of LPV. Clinical trials of LPV/r are ongoing in HIV patients with various levels of prior treatment experience.

Methods: 38 antiretroviral-naïve patients were randomized equally to receive LPV/r 800/200 mg qd or 400/100 mg BID with d4T/3TC BID. Steady-state plasma concentrations of LPV were measured throughout a dosing interval; troughs were measured at weeks 3, 8, 16, 24, and 48.

Results: Median baseline viral load (VL) and CD4 cell count were 4.7 $\log_{10}$ copies/mL and 264 cells/mm^3. LPV AUC and C_{max} were similar for the qd and BID regimens; overall median C_{trough}/IC_{50} (protein binding-adjusted) was 40 (range 3.6-220) for qd and 84 (range 36-174) for BID regimens. At week 48, 74% and 79% of patients in the qd and BID groups, respectively, had VL <50 copies/mL by intent-to-treat (missing=failure) analysis. No relationship between trough drug levels and antiviral activity was observed. Adherence to LPV/r, measured MEMS caps, was similar for the qd and the BID regimens. The most frequency across treatment groups and infrequency led to drug interruption or study discontinuation. Among the 38 study participants, grade 3 triglyceride or cholesterol elevations occurred in 3 and 2 patients, respectively.

Conclusions: Lower and more variable LPV trough concentrations were observed for the qd group vs the BID group. However, efficacy and safety results were similar through 48 weeks. The lack of association between trough drug levels and response may reflect, in part, the relatively high drug concentrations achieved. Side effects were similar to those in other studies of LPV/r in ARV-naïve patients.

Abstract 411-W

Stavudine XR vs Stavudine IR as Part of Potent Antiretroviral Combination Therapy: 24-Week Safety and Antiviral Efficacy

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Background: This multinational, prospective, randomized, double-blind, double-dummy study was designed to evaluate the antiviral activity, safety, and tolerability of once-daily d4T extended-release (XR) compared to the currently available twice-daily formulation of d4T immediate release (IR) when each is combined in a standard HAART regimen in antiretroviral naïve HIV-infected subjects.

Methods: Adult subjects with CD4 ≥100 cells/µL (copies/mL) (≥75 copies/µL if no prior clinical AIDS event) and a plasma HIV RNA ≥2,000 copies/mL were randomized to receive either d4T XR or d4T IR in combination with 3TC + EFV (standard doses) for a 48 week dosing period. The study had 90% power to demonstrate that the antiviral activity of d4T XR is not inferior (lower acceptance limit of -12%, d4T XR -d4T IR regimen) to that of d4T IR as determined by the primary outcome of HIV RNA <400 copies/mL. Analyses for the primary outcome as well as secondary outcomes (change in HIV RNA and CD4 cell count) were planned at 24 and 48 weeks. Results from the week 24 analysis are presented here.

Results: Of 797 randomized subjects, 783 started treatment. Most were non-white (58%) and male (69%). Median baseline HIV RNA and CD4 were 4.8 $\log_{10}$ copies/mL and 277 copies/µL, respectively. At the time of this analysis all subjects have reached the 24 week timepoint (37 weeks on-study median). 2 virologic response (VR) analyses for LOQ <400 copies/mL support similarity: VR-treated (VR-T, an ITT analysis for all treated subjects), XR 80% vs IR 82% (XR-IR difference, -1.5, 95% CI -7.0, 4.0); VR-observed cases (VR-OC, an observed completers analysis), 86% XR vs 89% IR (XR-IR difference, -2.9, 95%CI -7.7, 1.9). All analyses of VR for LOQ <50 copies/mL also demonstrated similarity: VR-T, XR 55% vs IR 55% (XR-IR difference, 0.3, 95% CI -6.6, 7.3); VR-OC, XR 59% vs IR 59% (XR-IR difference, -0.6, 95%CI -7.6, 6.5). Mean decrease in HIV RNA was identical in both groups (2.79 $\log_{10}$). Mean increase in CD4 was comparable: XR, 142 vs IR, 136 copies/µL. Safety and tolerability of the d4T XR regimen appear comparable to that of the IR regimen. At 24 weeks, 3% of subjects discontinued therapy in each group due to an AE. Grade 3/4 clinical AEs were comparable between treatments: 38 (10%) for XR and 29 (7%) for IR. Clinical syndromes involving one or more metabolic events (hepatotoxicity, pancreatitis, and lactic acidosis syndrome) occurred in 2 (1%) XR vs 2 (1%) IR subjects. Peripheral neurologic symptoms were reported at an identical rate (16%) in each group.

Conclusion: Therapy with d4T XR is well tolerated and exhibits a safety and antiviral profile comparable to that of d4T IR over 24 weeks of dosing when used as part of potent antiretroviral combination therapy in antiretroviral naïve subjects. A final analysis will be completed once all patients reach 48 weeks.

Abstract 412-W

Antiviral and Immunological Effects of Hydroxyurea (HU) plus HAART vs HAART Alone in Peripheral Blood and Lymphoid Tissue

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Background: Hydroxyurea (HU) could have the potential of decreasing the number of target cells for HIV replication and reducing viral integration. We tried to further characterize its effects on CD4$^+$ T-cell activation, CCR-5 expression, and proliferation in peripheral blood and lymphoid tissue as well as on productive and latent HIV infection.

Methods: 28 asymptomatic, unpretreated HIV+ patients were treated with stavudine, didanosine, and nelfinavir with (n=15) or without (n=13) additional HU (500 mg BID, given for the first six months) in a controlled, randomized, prospective trial (ARCHY). Mononuclear cells were obtained from peripheral blood monthly (all patients) and from lymph node biopsies at baseline and after six months (n=18). Plasma viremia (PCR), Lymphocyte subsets (+activation markers, Ki-67 and CCR-5 expression) were determined by 4-colour flow cytometry, and total proviral DNA was measured by PCR in PBMC and LNMC. Values were analyzed correcting for CD4$^+$ T-cell percentage. Treatment was discontinued temporarily after 12 months in five HU patients. Data were analyzed by Student's t-test, Mann-Whitney U test, and MANOVA, where appropriate.

Results: Mean CD4$^+$ T-cell count at baseline was 431 and 436 in the HU and non-HU group, respectively. Mean HIV RNA was 4.5 vs 4.9 log (p=n.s.). During HU, HIV RNA suppression was superior in the HU group as compared with the controls. HU led to a delayed increase in CD4$^+$ T cell numbers. 21 patients have currently finished a follow-up of 12 months. In these, the expression of activation markers (HLA-DR, CD69, CD25) on CD4$^+$ and CD8$^+$ and of CCR-5 on CD4$^+$ lymphocytes in peripheral blood and lymph node was reduced during HAART and did not differ significantly between the two groups. HU reduced absolute numbers but not percentages of proliferating CD4$^+$ T cells in PB and LN. Pro-viral DNA in LN and PB of nine patients analyzed to date showed a significant decrease during therapy, but no difference between the treatment arms. All patients discontinuing therapy had a rebound to pretreatment levels of plasma viremia.

Conclusions: HU reduces numbers of proliferating CD4$^+$ T lymphocytes and delays the increase in CD4$^+$ T-cell numbers. Preliminary data suggests that it does not reduce total proviral DNA to a greater extent than HAART alone in blood and lymphoid tissue within six months, and that virus containment after treatment discontinuation is not influenced positively in this setting.

Abstract 414-W

Final 48-Week Genotypic and Phenotypic Analyses of Study 907: Tenofovir DF (TDF) Added to Stable Background Regimens

N. A. Margot, A. Johnson, A. Cheng, D. F. Coakley, and M. D. Miller

Background: Study 907 was a phase III study evaluating TDF when added to stable background regimens in treatment-experienced patients. The first 24 weeks were placebo-controlled (2:1), followed by 24 weeks of open-label TDF. 94% of patients had baseline NRTI resistance mutations. At week 24, there was a significant mean HIV RNA $\log_{10}$ reduction of -0.61 relative to placebo that was durable through week 48.

Methods: 274/552 patients were randomly assigned to a virology substudy. Plasma HIV RT and protease were genotyped and phenotyped (Virco) at baseline, week 24, and week 48.

Results: Week 48 genotypic results were obtained for 145/274 patients (53%). 58 patients (21%) developed ≥1 NRTI mutation; 47 of whom developed thymidine analog mutations (TAMs). Mutation development during the open-label phase was similar to placebo during the first 24 weeks (22%), suggesting that most mutations resulted from background therapy. As a group, patients who developed NRTI mutations showed continued viral load suppression (mean -0.56 log10 DAVG48). 8 patients (3%) developed the tenofovir-associated K65R mutation (5 prior, 3 after week 24). Patients developing K65R showed a wide range of responses with three patients maintaining viral load suppression. Week 48 phenotypic analyses showed HIV from K65R patients remained fully susceptible to AZT and d4T and had variable susceptibility to other drugs. Phenotypic data reflecting TDF exposure of 24 (n=12) to 48 (n=47) weeks were analyzed. Overall, the mean change in TDF susceptibility was 1.3-fold from baseline. 4/59 patients showed ≥3-fold decreased TDF susceptibility: 3 of these remained within normal TDF range (3-fold of wild-type) due to baseline TDF hypersusceptibility and 1 had reduced TDF susceptibility along with K65R. 8 of 41 substudy patients who entered the open-label phase with HIV RNA <50 copies/mL were >500 copies/mL at week 48. Most showed genotypic resistance to agents in their regimen but none developed K65R and no phenotypic resistance to TDF was observed.

Conclusions: Development of most NRTI mutations in patients adding TDF to their background regimen is due to the background regimen and not associated with loss of HIV RNA suppression. The incidence of K65R through week 48 remained low (3%) and does not correlate with treatment failure. Treatment failure was associated with resistance to other agents in the regimen. Reduction in TDF susceptibility was rare in patients with up to 48 weeks of TDF exposure.

Abstract 419-W

The Effect of Different HAART Regimens on Slope of Viral Rebound in HIV-Infected Patients Failing Therapy

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Background: The purpose of this study was to compare the characteristics of virologic rebounds in HIV-1-infected patients on various HAART regimens.

Methods: Individual patient data were compared from the triple regimen arms of 4 completed clinical trials (INCAS: AZT/ddI/NVP, n=51; AVANTI-2: AZT/3TC/IND, n=52; AVANTI-3: AZT/3TC/NFV, n=53; and CNAAB3005: AZT/3TC/ABC, n=262). HIV-1 RNA levels were performed in prospectively collected samples after completion of each trial, and thus were not available for use in patient management. Rebound was defined in patients who achieved viral suppression as 2 consecutive HIV-1 RNA values above the lower limit of quantification (LLOQ for INCAS, AVANTI-2, AVANTI-3 was 50 copies/mL, and for CNAAB3005 was 400 copies/mL). The triple drug regimens from the 4 clinical trials were compared for predictors of rebound, time to rebound and slope of rebound, using a logistic regression model, Cox proportional-hazards model and linear regression model, respectively.

Results: The NVP-containing regimen had the steepest slope of viral rebound (p=0.006) using the LLOQ of each trial. Even when 400 copies/mL was used as the LLOQ for all the trials, the NVP-containing regimen maintained a trend for steepest slope of rebound (p=0.065). A NVP-containing regimen did not influence time to rebound (p=0.63). Non-adherence was a predictor of viral rebound (OR 3.1, p=0.0001), a shorter time to rebound (RR 3.66, p=0.0001), and a steeper slope of rebound (p=0.04). Occurrence of a single detectable HIV-1 RNA (blip), baseline CD4 count and baseline viral load were not predictive of rate of viral rebound or slope of rebound.

Conclusions: Patients taking NVP-containing regimens showed a steeper slope of rebound than patients taking PI or ABC-containing regimens. The non-NVP regimens all contained 3TC, hence differences in early virologic rebound could be related to the emergence of the M184V mutation vs the K103N or Y181C mutation in the NVP regimen.

Abstract 421-W

Virological and Immunological Benefit of a Salvage Therapy that Includes Kaletra plus Fortovase Preceded or not by Antiretroviral Therapy Interruption (TI) in Advanced HIV-Infected Patients (6-Month-Follow-up)

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Objective: Our objective was to assess in a prospective, open, randomised study the virological efficacy of a Mega-HAART salvage therapy which includes Kaletra+Fortovase+3TC+ABC+ddI, preceded (group A) or not (group B) by a 3-month antiretroviral TI in HIV-infected patients with virological failure.

Methods: Patients with plasma viral load (pVL) >1000 copies/mL (twice consecutively), virological failure to more than 2 HAARTs and resistant mutations to all 3 classes of drugs prior to study entry were eligible. pVL and CD4 were determined in group A monthly during off therapy and every three months thereafter, whereas in group B these parameters were measured every three months. Genotypic testing was performed at the study entry in both groups and at the start of ST in group A by using Trugene HIV-Kit in RNA.

Results: A total of 46 patients (22 in group A and 24 in group B) were included into the study. Clinical complications were not observed. The mean number of drugs previously received was of 8 (5 - 13) for a median time of 5.7 years (2.8 - 14). Mean pVL was of 4.3±0.6 log10 in group A and of 4.3±0.7 $\log_{10}$ in group B at baseline. CD4 counts were of 396±189 cells/mm^3 and 322±165 cells/mm^3 in group A and group B, respectively. pVL increased a mean of 0.9 $\log_{10}$ copies/mL and CD4 decreased 131 cells/mm^3 after three months off therapy in group A. The mean number of drug-resistance mutations were 10.8±4.8 group A and 9.7± 5.4 (group B). The number of drug-resistance mutations at the start of ST decreased to 3.8±4.2 in group A. Results at 24 weeks: ST was well tolerated. A mean increase of 144 and 80 cells/mm^3 were produced in group A and group B, respectively. 47% of the patients in group A and 36% in group B reached a pVL <80 copies/mL (p=NS). Patients with pVL<20,000 copies/mL at baseline had a better response (<80 copies/mL) than those with pVL above this limit (p=0.016). In group A, the mutant virus population of 64% (13/20) of the patients interruptienting therapy complete or partially reverted to WT according to the genotype analysis. Overall, the number of prior regimens, CD4, or number of drug-resistance mutations at baseline were not associated with a better virological response. In a multivariate analysis the presence of L10I/V in the protease gene was the only factor associated with a poorer response (p=0.02).

Conclusions: Dual PI salvage therapy including Kaletra+Fortovase appears to be active in heavily pretreated patients at week 24. A prior three months of therapy discontinuation does not seem to affect the virological and immunological outcome in heavily treated HIV-infected patients.

Abstract 422-W

Indinavir TID vs Indinavir / Ritonavir BID in Combination with AZT / 3TC for HIV Infection in Nucleoside Pretreated Patients: HIV-NAT 005 76-Week Follow Up

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Background: Use of IDV may be simplified by addition of RTV. This permits BID dosing and removes need for dietary restrictions. There are limited randomised data on IDV/RTV BID compared to TID dosing.

Methods: In this ongoing, prospective, randomised, open label study 106 patients were randomised to either IDV 800 mg (TID) or IDV 800 mg/RTV 100 mg (BID) in combination with AZT/3TC. All patients had at least three months AZT before entry. Efficacy was determined by HIV RNA and CD4 response (median and [IQR]). Safety and tolerability were assessed. Analysis is by intention to treat. Mann-Whitney, Student's t and chi^2 tests tested differences between groups.

Results: This study enrolled 104 patients (54 TID vs 50 BID; 67 males, 37 females). Arms were well balanced at baseline with a median $\log_{10}$ HIV RNA of 4.0 (3.3-4.5) and CD4 of 168 (40-319) cells/mm^3. At week 76 no significant differences were found in the decrease of $\log_{10}$ HIV RNA from baseline (1.6 [-2.72 to -0.36] TID, -1.8 [-2.43 to -0.18] BID), percentage of patients with VL < 50 copies/mL (69% TID, 66% BID), or median increase in CD4 cells from baseline (128 [11-204] TID, 101 [-4 - 156] BID). 20 patients permanently discontinued therapy (8 TID, 12 BID; p > 0.1). Drug interruptions/dose reductions occurred in 39 patients (30% TID, 48% BID; p=0.05). Grade 3/4 adverse events related to study medication occurred in 43 patients (38% TID, 48% BID; p >0.1). Hyperbilirubinaemia (>2.5xULN) occurred in 31 patients (24% TID, 36% BID; p >0.1). Total cholesterol > 240 mg/dL was seen in 14 patients (5% TID and 22% BID; p > 0.1). Clinical nephrolithiasis was seen in 22 patients (17% TID, 26% BID; p >0.1).

Conclusions: After 76 weeks of therapy IDV/RTV twice a day remains as effective as the 3 times a day regimen. Both regimens are reasonably well tolerated, although there is a trend towards more adverse events, drug interruptions/dose reductions, study discontinuations and hyperlipidemia in the BID arm.

Abstract 425-W

ACTG 364: Efficacy of Nelfinavir (NFV) and / or Efavirenz (EFV) in Combination with New NRTIs in Nucleoside Experienced Subjects: Week-144 Results

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Background: The optimal alternative therapy for subjects with NRTI experience who develop viral rebound remains uncertain. ACTG 364 examined long-term virologic and immune responses of quadruple vs triple antiretroviral therapy (ART) regimens in exclusively NRTI-treated subjects. This was a randomized, partially blind trial for ACTG 302/303 highly nucleoside-experienced subjects receiving d4T alone or new NRTI combinations who remained on same treatment at entry into ACTG 364.

Methods: 196 subjects with screening HIV RNA ≥500 copies/mL were randomized to 1 of 3 arms: NFV, EFV placebo, + NRTIs; EFV, NFV placebo, + NRTIs; or NFV, EFV, + NRTIs. Open-label nucleoside therapy was assigned with at least 1 or 2 new NRTIs (ddI+d4T, ddI+3TC, or d4T+3TC). Plasma HIV RNA (Roche Ultrasensitive assay) and CD4 counts were monitored through week 144.

Results: 195 subjects were evaluable. The study was blinded through week 48. Baseline (BL) characteristics: median CD4 count and HIV RNA levels were 350 cells/mm^3 and 7,776 c/mL, respectively. By intent-to-treat analysis, 79 (59%) of 134 subjects with 71% (30/42), 58% (28/48), and 48% (21/44) of subjects in the NFV+EFV, EFV, and NFV arms, respectively, achieved HIV RNA <50 copies/mL at week 144 (3-way p=0.045). The NFV+EFV arm demonstrated superior viral suppression compared to the NFV arm (pairwise p=0.016) at week 144; the other pairwise comparisons were not significant. In time to virologic failure (confirmed HIV RNA ≥200 copies/mL at week 16 or later) analyses, a highly significant difference among the three study arms (p<0.001) was seen. In pairwise comparisons, the quadruple- and EFV-triple arms required a longer time to reach virologic failure compared to the NFV arm: p<0.001 and p=0.028, respectively; quadruple therapy arm vs EFV arm (p=0.003). At week 144, a median CD4 increase of 171 cells/mm^3 from baseline was seen.

Conclusions: In nucleoside-experienced subjects with virologic failure, alternative therapy with at least 2 new potent ART drugs in combination with new NRTIs provides a greater likelihood of achieving durable virologic suppression.

Abstract 426-W

Virologic Activity of Efavirenz in Subjects who Experienced Virological Failure with Emivirine (EMV, MKC-442)

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Background: *In vitro* resistance studies have shown that HIV containing non-nucleoside reverse transcriptase (NNRTI) mutations other than K103N are sensitive to inhibition by efavirenz (EFV). Emivirine is a potent NNRTI that has a low incidence of K103N mutation when given in combination with lamivudine.

Methods: Therapy-naïve subjects were enrolled in a randomized, open label study (MKC-401) to compare EMV vs abacavir (ABC) in the background of stavudine/emtricitabine (d4T/FTC). HIV RNA viral load (VL) was measured at baseline and every 12 weeks thereafter. Subjects who experienced virologic failure (VF) in the emivirine arm were allowed to switch to EFV and ABC + d4T. To determine if antiviral drug resistance was associated with therapy failure, genotypic analysis was performed at the time of a protocol-defined VF.

Results: To date, 45 subjects in MKC-401 have switched to EFV + ABC + d4T. Genotypic analysis was available for 36 of the 45 subjects. NNRTI mutations were observed in 14/36 (39%) of these subjects, with 8/14 having single NNRTI mutations and 6/14 with multiple NNRTI mutations. The NNRTI mutations observed were: E138K (7/36), K103N (6/36), V108I (4/36), K101E/Q (2/36), K103T (2/36), and Y188C (1/36). 21 of the 36 (58%) subjects remained wild type at time of failure, and one subject developed NRTI associated mutations only. VL analysis of the subjects by week 12 following switch to EFV indicated that 25/34 (74%) of the subjects had <400 copies/mL and 50% of these subjects had <50 copies/mL. The patients with wild type virus at failure had VL measurements post switch. 18 of the 20 subjects achieved a VL <400 copies/mL and 15/20 subjects (75%) achieved <50 copies/mL. For subjects who failed with a NNRTI mutation but did not have a K103N, 7/8 (87.5%) had VL <50 copies/mL following 4-84 weeks on efavirenz. Data available for 5 of the 6 subjects with the K103N showed that 40% were able to achieve a transient decrease in VL to <50 copies/mL prior to discontinuing therapy. Of the 16 subjects who have discontinued alternate therapy, 3 discontinued due to VF, 4 due to AE, 2 lost to follow-up, and 7 due to other reasons (withdrew consent, pregnancy, etc.).

Conclusions: These results show that subjects who fail an EMV-containing regimen subsequently achieved suppression of viral load to <50 copies/mL following rollover to an EFV-containing regimen.

Abstract 428-W

Racial Differences in Clinical Efficacy of Efavirenz-Based Antiretroviral Therapy

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Background: Different cytochrome P450 (CYP) 2D6 genotypes have been shown to predict marked difference in efavirenz (EFV) trough levels. CYP genotypes have different frequencies in different ethnic and racial groups. We sought to assess the relative clinical response duration in African American (AA) and Caucasian (C) HIV-1-infected subjects treated with EFV-based therapy, and to determine if differences could be explained by CYP genotype.

Methods: 450 HIV-1-infected US Department of Defense beneficiaries on 3 or more antiretroviral drugs including at least one NNRTI or PI were enrolled in a long-term study to assess the efficacy of resistance testing. Virologic failure was defined as either a rise in plasma viral load (VL) to >3 logs in a subject with previously undetectable viral load, or a failure to suppress VL to <3 logs by 16 weeks. 99 subjects (56 AA and 43 C) on efavirenz at enrollment were analyzed. Primary endpoint was time to virologic failure. 102 subjects who were on indinavir and 172 subjects on nelfinavir at time of enrollment were analyzed for comparison.

Results: There were no differences in age, CD4 count, number of previous antiretroviral drugs, or number of previous NNRTI between racial groups at baseline. There were no differences in time to virologic failure between racial groups for subjects on nelfinavir (NLV) or indinavir (IDV) at enrollment. For AA subjects on efavirenz, median time to failure was reached at 422 days. For C subjects, median was not reached at 1,400 days (Cox proportional hazard model risk ratio=2.42 (95% CI 1.35-4.57) p=.0027). No differences were observed between groups in mean fold resistance to efavirenz at failure. There were differences in CYP 2D6 genotypes between AA and C subjects, but these did not correlate with outcome.

Conclusion: In our cohort of HIV-1-infected military health care beneficiaries with uniform access to healthcare, we have observed significant racial differences in time to virologic failure that appear to be specific for efavirenz-based therapy. These differences could not be explained by CYP 2D6 genotype. Absence of time-to-failure differences in groups treated with IDV and NLV suggest that there are not race-based differences in adherence in this cohort. Further pharmacokinetic analysis is planned.

Abstract 435-W

Evidence of Systemic P-Glycoprotein (P-gp) Inhibitory Activity in Patients Receiving Twice-Daily Nelfinavir (Viracept)

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Background: Cellular P-gp effluxes HIV protease inhibitors (PIs) out of cells and some tissues (eg, the brain). $CD4^+$ and $CD8^+$ T cells express P-gp. Although high PI concentrations inhibit P-gp activity *in vitro*, it is unclear whether this occurs *in vivo*. Nucleoside reverse transcriptase inhibitors (NRTIs) do not inhibit P-gp. We measured the effect of patient plasma (obtained during steady state nelfinavir (NFV) dosing) on healthy volunteer lymphocyte P-gp activity.

Methods: One plasma sample was obtained from each of 17 adults during clinic visits (population sampling approach). Subjects were receiving NFV (1,250 mg q12-h) plus NRTIs, but no other PI or non-NRTI. Time of last dose was by patient report. Dye efflux inhibition (DEI) assays were performed by incubating HIV-negative donor whole blood cells with the P-gp substrate $DiOC_2(3)$. Cells were washed, then incubated at 37°C with 90% patient plasma (with 5% 1M HEPES, pH 7.4). Mean fluorescence intensity (MFI) was quantified by flow cytometry.

Results: The 17 patients included 5 (29%) women, 4 (22%) African Americans, HIV-1 RNA was below limits of quantitation in 8 (47%), $CD4^+$ T cells ranged from 175 to 819 cells/mm^3, and sampling times from 0.5-9 hours post-dose. Some samples modestly inhibited $CD4^+$ and $CD8^+$ T cell P-gp. Samples from 2-6 hours post-dose inhibited $CD4^+$ T P-gp (MFI 18.7±0.52) more than those from other times (MFI 16.6±0.61, p = 0.02), and inhibited $CD8^+$ P-gp (MFI 15.0±0.65) more than other samples (MFI 12.6±0.40, p=0.009). Inhibitory activity did not correlate with $CD4^+$ T cell count, viral load, or demographics.

Conclusions: Twice-daily NFV is associated with time-dependent variability in plasma P-gp inhibitory activity. Times of increased activity likely correlate with peak NFV and/or M8 metabolite concentrations. The relevance of modest P-gp inhibition during NFV therapy is uncertain. Ongoing studies are comparing P-gp inhibitory activity with NFV and M8 concentrations in these and additional patients.

Abstract 456-W

Total Lymphocyte Count (TLC) as a Surrogate for CD4 Count to Initiate and Monitor HAART in Resource-Limited Countries

T. Flanigan, A. Mahajan , N. Kumarasamy, K. Mayer, C. Carpenter, and S. Solomon

Background: Due to the prohibitively high cost of plasma viral load in resource-limited countries, monitoring of HIV progression and response to HAART largely depends on CD4 count. However, the routine use of CD4 count in management has also been hampered by high price per test. The cost of a single CD4 count in resource limited setting ranges from $25 to $100. In this era of large price reductions in triple antiretroviral drug regimens that are increasing access to treatment in developing countries, more affordable surrogate markers for evaluation, such as total lymphocyte count (TLC) are needed if therapy is to be routinely monitored.

Methods: The correlation of TLC to CD4 count was analyzed in 405 HIV-positive patients attending YRG CARE in Chennai, India from 1997-2000. TLC ranges that predict CD4 count <200 and <350 cells/mm3 were identified. Also, retrospective review of patients with CD4 <350 starting dual nucleoside therapy at YRG CARE and retrospective review of patients with CD4 <350 starting triple drug regimen at Brown University was conducted to determine if changes in TLC correspond to changes in CD4 count.

Results: The Spearman's correlation for 650 paired CD4 and TLC from 405 YRG Care patients was 0.74. The positive predictive value and sensitivity of TLC <1250 for CD4 <200 was 80% and 68%, respectively. Both the positive predictive value and sensitivity of TLC <2,000 for CD4 <350 was 79%. At three months, YRG patients starting dual nucleoside therapy with a statistically significant rise in mean CD4 count also had a rise in mean TLC (p < 0.001). At six months, Brown University patients starting a triple regimen with a statistically significant rise in mean CD4 count also had a rise in mean TLC (p < 0.001).

Conclusions: Since cost of monitoring remains significantly high relative to proposed prices of antiretroviral regimens, it is unrealistic to expect that patients from resource limited countries will be able to afford regular CD4 counts while on therapy. TLC may be used as a surrogate for or in combination with CD4 count to determine when to start therapy and to enable routine monitoring.

Abstract 457-W

Review of Antiretroviral Therapy in the Private Sector in Nairobi, Kenya

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Background: Though the majority of the HIV-infected Africans who are aware of their HIV status and for whom antiretroviral (ARV) medications are clinically indicated cannot afford them, some can obtain drugs through the private sector.

Methods: We reviewed charts of patients who received ARVs from five private physicians in Nairobi, Kenya since October 1996. We analyzed prescribing practices, sustainability, and virologic response to ARV therapy. Patient status as of June 15, 2001, was recorded as: active in care; died; lost to follow-up; transferred care; stopped ARV; or moved. For analysis of sustainability of remaining on ARV therapy, patients were considered on therapy until their last visit to the physician or death unless they had stopped ARV therapy or were lost to follow-up. HAART was defined according to US DHHS guidelines (April 23, 2001).

Results: We reviewed charts of 300 patients (41% women)—median age of 38 years (range 5-65 yrs), baseline $CD4^+$ count of 89 cells/mm^3 and viral load of 116,652 copies/mL,—who received ARVs for a median of 8.2 months (IQR 2.8-2). Of these, 217 (72%) were started on HAART. The number started on a HAART regimen from October 1 - December 31, 1996 was 3 (30%) of 10; in 1997, 22 (43%) of 51; in 1998, 35 (58%) of 60; in 1999, 45 (69%) of 65; in 2000, 48 (96%) of 50; and January 1 - June 15, 2001 was 64 (100%) of 64 (chi^2 for trend, p<0.001). For the 83 patients not started on HAART, reasons were financial for 27, drug interaction with rifampin for 21, HAART not yet widely available for 15, other for 20. As of June 15, 2001, 159 (53%) patients were active in care, 45 (15%) lost to follow-up, 34 (11%) known to have died, 27 (9%) transferred care, 23 (8%) stopped ARV, and 12 (4%) moved. The probability of remaining on ARV therapy at one year was 0.78 (number under observation = 124) and at two years was 0.66 (number under observation = 66). Viral load was <400 copies/mL between 1-6 months for 45 (59%) of 76, 6-12 months for 26 (47%) of 55, 12-18 months for 20 (49%) of 41, and 18-24 months for 10 (32%) of 31.

Conclusions: ARV prescribing in these private practices in Nairobi were consistent with international standards. Patients were treated with ARVs for an extended period of time and had demonstrable virologic responses. Efforts to train more practitioners, develop cheaper monitoring tests, and further reduce prices for drugs could increase the number of persons treated in the private sector in Kenya.

Abstract 462-W

Survival of Persons with HIV Disease following Antiretroviral Therapy in Southern India

N. Kumarasamy, K. Mayer, T. Flanigan, R. Hemalatha, C. Carpenter, S. P. Thyagarajan, and S. Solomon

Background: There are very few reports on the beneficial effects of antiretroviral therapy (ART) from developing countries. Here we report the survival time and adverse effects of persons who received antiretroviral therapy in a clinic-based population in Southern India.

Methods: This study was a retrospective analysis of 287 persons with HIV and with CD4 cell count less than 350 cells/muL and being followed up in a tertiary referral HIV care center in Chennai, India between June 1996 and June 2001 for a mean of 155.4/100 person years. The study subjects were divided into 4 groups based on their CD4 cell count and initiation of ART. Group 1: Patients started on ART when the CD4 cell count was less than 200 (n=141); group 2: Patients initiated ART when the CD4 cell was between 200 and 350 (n=35); group 3: Patients with CD4 <200 and not on ART (n=72), and group 4: Patients with CD4 between 200 and 350 and not on ART (n=39). Survival analyses were performed to determine mean survival times in patients stratified by baseline CD4 and Kaplan Meir curves were utilized to demonstrate the rates of disease progression.

Results: The mean survival of persons who initiated ART when the CD4 cell count <200 was 46 months (group 1) and the mean survival of persons who initiated ART when the CD4 cell between 200 and 350 was 78 months (group 2) (p<0.001). The mean survival of persons who were not on ART was 27 months in the group 3 and 73 months in the group 4 (p<0.001). 55 (31.3%) individuals reported adverse effects of ART. Among the adverse effects, the predominant one was peripheral neuropathy (21.8%), followed by anemia (16.4%), blue coloration of nails (10.9%), nausea/vomiting (9.1%), hepatitis (7.3%), skin rash (5.5%), and diarrhea (1.8%). Immune reconstitution syndrome was seen in 13 (7.4%) individuals who received ART. Lymphadenitis due to tuberculosis flared up following ART in 12 individuals and 1 had immune recovery vitritis.

Conclusions: Antiretroviral therapy in advanced HIV+ patients is beneficial in the developing world but the high co-prevalence of TB must alert clinicians to immune reconstitution syndrome.

Abstract 459-W

First Evaluation of d4T, ddI, and Efavirenz in Antiretroviral-Naïve Patients in Senegal: ANRS 12-06 / IMEA 012 Study

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Background: To assess the feasibility, efficacy and tolerance of the antiretroviral regimen combining stavudine (d4T), didanosine EC (ddI), and efavirenz (EFV) in patients with advanced immune deficiency in Senegal.

Methods: Multicenter, 18-month pilot trial in 40 HIV-1-infected patients. Biological, virological, and immunological parameters were evaluated every three months. Intent to treat analysis. Inclusion criteria: CD4 <350 cells/mm^3, plasma HIV1-RNA >30,000 copies/mL. d4T (30/40 mg BID), EFV and ddI were taken at bedtime (ddI 250/400 mg and EFV 600 mg qd).

Results: Inclusion characteristics: 23 women, 17 men; mean age (±SD) was 36±7 years; 47.5%, 52.5% were CDC stage B and C, respectively. Mean CD4 cell count was 133±92 cells/mm^3 and mean plasma HIV1-RNA was 5.5±0.4 $\log_{10}$ copies/mL (Roche, Amplicor) at baseline. Mean increase in CD4 cell count was 110±121 cells /mm^3 (n= 38 patients) and 105±120 cells /mm^3 (n=35 patients) at M3 and M6 respectively. Mean decrease in plasma HIV1-RNA was 3.4±0.7 log and 3.2±1.1 log (n=35 patients) at M3 and M6, respectively. Plasma HIV1-RNA <500 copies/ml: 91% and 77% of patients at M3 and M6 compare to baseline respectively. Plasma HIV1-RNA <50 copies/mL: 40% and 51% of patients at M3 and M6 compare to baseline respectively. Adverse events: peripheral neuropathy grade 1-2 (n=4), grade 3 (n=2) with interruption of d4T and ddI, dizziness (n=11) occurring during the first month of treatment and leading to transitory discontinuation in only 1 case. Kaposi's sarcoma worsened in one patient at M3. Four deaths related to reactivation of atypical mycobacteria disease at M2 (n=1), diarrhoea with septicemia at M4 and M6 (n=2), encephalopathy with fever in an alcoholic non-compliant patient.

Conclusions: These results indicate: peripheral neuropathy may be a treatment limitation for d4T and ddI combination in this population and despite HAART regimen, 10% case-fatality rate was observed mainly in patients with low CD4 cells at baseline (3 patients/4 <50/ mm^3); these interim results show a similar rate of undetectable viral load as compared to other HAART regimen even in symptomatic patients with low CD4 cells (30% of patients <50/mm^3) and high viral load at baseline.

Abstract 461-W

Genotypic and Phenotypic Analyses of Drug Susceptibility in HIV-1 Isolates from Drug-Naïve Patients in Nigeria

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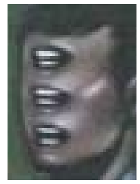
Background: One of the major concerns in the AIDS pandemic is the extensive genetic variability of HIV-1. This affects the development of candidate vaccines and may impact antiretroviral therapy.

Methods: *Env* subtype was determined using a modified *gp41*-based heteroduplex mobility assay. A 1.2-KB fragment in the pol gene (spanning the entire protease [PR] region and most of the reverse transcriptase [RT] region) were isolated and cloned into retroviral expression vectors. The sensitivity of the resultant PR and RT proteins to all available antiretroviral drugs was assayed using a version of Virologic's PhenoSense HIV assay modified for assaying non-B subtypes.

Results: Analysis of HIV-1 PR and RT positions associated with mutations conferring resistance to antiretroviral drugs revealed no known primary resistance-associated mutations. For example, compared with the NL4_3 consesus sequence, we found between 9 and 17 amino acid substitutions within the protease region, all of which would be classified as secondary mutations or polymorphisms. All but one isolate were susceptible to all of the 15 drugs analyzed. This isolate exhibited low-level reductions in susceptibility to nelfinavir (3.8-fold) and ritonavir (3.4-fold) relative to the drug-sensitive control. Relative to our NL4_3-based reference, this isolate exhibited the following PR genotype: L10I, I13V, K14R, I15I/V, K20I, E35Q, M36I, N37D, R41K, R57K, L63L/P, I64I/M, C67E, H69K, T74T/S, V82I, and L89M. From the *gp41*-based heteroduplex assay, 17 of the 18 patients were infected with subtype G, and one patient was infected with subtype A. From phylogenetic analyses of 1212 nucleotides of *pol*, 13 of the 17 isolates were strongly grouped with other subtype G reference strains throughout PR and RT regions. One of these was more distinct from the rest, although it is more closely related to subtype G strains than to any other subtypes. Of the remaining 4 samples, 1 most closely resembled CRF_02_AG, while the 3 others (including the 1 sample with a subtype A *env* designation) were sister taxa to the CRF_02_AG clade. These 3 isolates are recombinants with varying degrees of G and A subtype fragments within PR and RT.

Conclusions: Based on our analyses, subtype G and CRF_02_AG were susceptible to all classes of antiretroviral drugs and should respond to HAART regimens. ■

Editor's Note: All abstracts from the 9th Conference on Retroviruses and Opportunistic Infections may be found at www.retroconference.org. Selected abstracts published in the IAPAC Monthly *(Vol. 8, No. 4, pp. 119-126), © 9th Conference on Retroviruses and Opportunistic Infections.*



For the poorest of the poor, the onset of HIV/AIDS for the chief income earner can shatter the entire family unit. Properly targeted, food aid for them would be a life-saving tool. Food aid would guarantee good quality nourishment for the AIDS patient and it would reduce malnutrition among the family members.

John Powell, Director of the World Food Program's Asia Regional Bureau, in a March 4, 2002, announcement of the first major campaign using food aid to assist people living with HIV/AIDS and their families, particularly in Southeast Asia and East Africa. Powell said such relief may also serve as the financial glue to keep the family intact while fallback mechanisms are put in place.

Armies in Africa have traditionally been terrible breeding grounds for AIDS. Soldiers turn to prostitutes, [and] then carry the virus to every corner of the country after their service. But in Ethiopia, the opposite is happening: Soldiers have become safe-sex practitioners and peer educators.

Emelia Timpo, a UNAIDS representative in Ethiopia, as quoted in a March 5, 2002, Baltimore Sun *article entitled, "Ethiopia Strives to Control HIV/AIDS." According to the article, the Ethiopian army has broadened its partnership with DKT International, a US-based nonprofit organization, to conduct HIV prevention interventions. The Ethiopian army's infection rate is 5 percent—two percentage points lower than the rate of the country's civilian adult population. The seeds of this success began in 1997 when the Ethiopian army began buying millions of condoms from DKT International to stem new HIV infections and promote family planning. Today, soldiers receive 20 or more condoms with each monthly paycheck and are strictly prohibited from leaving military bases unless carrying condoms. The result, says UNAIDS, is a condom user rate of about 85 percent.*

People who want to consult doctors or any other person whom they think can give them a drug [that] is going to be useful... must be free to do so because otherwise the impression is going to continue that we don't care for people who are dying.

Former South African President Nelson Mandela at a March 3, 2002, news conference during which he attempted to clarify his seemingly contradictory statements about the South African government's policy responses. According to an Associated Press report, Mandela suggested that AIDS drugs should be made accessible to all South Africans who need them, but added that he did not intend to contradict official government policy. In a speech last month, Mandela said that prophylaxis against mother-to-child HIV transmission must be an integral component of the government's efforts to stem the spread of HIV disease. The next day, after meeting with the ruling African National Congress, Mandela called the government's AIDS program the best in the world.

M. Joycelyn Elders

We are spending a quarter of a billion dollars for abstinence education in our schools, when there is no scientific basis that abstinence-only education is effective. Abstinence education as it is presently taught does not allow our educators to tell young people anything about contraception or disease prevention... There are about 12 million problems with this approach—12 million being the number of sexually active teens in this country who are 19 or younger.

M. Joycelyn Elders, Professor Emeritus at the University of Arkansas and former US Surgeon General during the Clinton Administration, in a Newsday *editorial entitled, "Kids Need Straight Talk About Sex." Elders defended US Secretary of State Colin Powell who, in responding to questions about HIV during a recent MTV forum, affirmed that in his judgment, condoms are a tool to prevent HIV infection. Abstinence-only proponents attacked Powell's comment, citing that condoms do not protect against all sexually transmitted diseases. While serving as US Surgeon General, Elders' advocacy of sex education and condom distribution prompted some conservatives to refer to her as the "Condom Queen."*