

# IAPAC

MONTHLY

*Switching  
antiretroviral  
therapy:*

*Why, when,  
and how*

## 220



### Switching antiretroviral therapy: Why, when, and how

*Timothy Wilkin, Marshall Glesby, and Roy M. Gulick*

Once antiretroviral therapy is initiated, patients generally remain on medications indefinitely. Timothy Wilkin, Marshall Glesby, and Roy M. Gulick describe the possibilities and hazards inherent in switching antiretroviral regimens in patients experiencing side effects and dealing with toxicities.

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## REPORT FROM THE PRESIDENT

# Pushing and pulling

José M. Zuniga

**P**ush-pull is a mode of operation for locomotive-hauled trains. A push-pull train has a locomotive at one end of the train and a vehicle equipped with a second control cab at the other end, allowing the train to be driven from either end. If the train is heading in the direction in which the locomotive end of the train is facing, this is considered “pulling.” If the train is heading in the opposite direction, this is considered “pushing.” Alternatively, a push-pull train, especially a long one, may have a locomotive on both ends so that there is always one locomotive pushing and one locomotive pulling.

For those readers worried that this month’s Report from the President will be a primer on locomotive dynamics, fear not. My description of push-pull train operations is an analogy for the different types of forward motion displayed by the various social groups—activists, medical professionals, governments, businesses, etc.—that struggle together against the HIV/AIDS pandemic. In this analogy, the part of the front locomotive is played by those segments of civil society that have determined the movement’s direction, pulled it along toward the desired ends, and lobbied other groups to join the fight. Those groups that were successfully lobbied—and that now contribute momentum and energy to this Herculean effort—are represented by the control cab, the responsibility and effort of which increases in proportion to the length and weight of the train.

As the XVI International AIDS Conference approaches next month in Toronto, it may be instructive to consider the state of the world with respect to the

AIDS pandemic—our present course, the stops and crossings along the way, and what we must do better to ensure that we reach our destination.

For many years following the advent of AIDS, there was a general lethargy; a feeling that the virus was out of control, but that little progress was possible against it given political, financial, and social constraints, as well as the nature of under-resourced and overburdened health care systems in developed and developing countries alike. During this time, the virus consolidated its hold, devastating sub-Saharan Africa and parts of the Caribbean, as well as gay communities and intravenous drug-using populations in the United States and Western Europe. And it gained a toehold, or more, in Asia, Eastern Europe, and Latin America.

Fifteen international AIDS conferences later, lethargy has been replaced by momentum as most everyone has come to grips with the reality that HIV prevalence and its accompanying (albeit avoidable) mortality can determine a country’s future, and influence the course of global events. That shift has not occurred overnight, and requires constant investment of time, energy, and resources to maintain, as well as constant vigilance lest we slip back into the blissful neglect (“out of sight, out of mind”) that has allowed for a world in which more than 40 million men, women, and children are living with HIV/AIDS.

But what exactly have we accomplished during the past 25 years?

We have demanded governments fund health initiatives at reasonable levels, to ensure that vital work can be completed by developing-country governments, non-governmental organizations, and research institutions; and in many cases, governments are starting to respond. Although govern-

ments have a long way to go, both in living up to their financial commitments and in allocating funds through mechanisms that are not unduly influenced by political or religious ideology, more money has been made available just in the last year for essential HIV prevention and treatment interventions than ever before.

We urged the private sector to step up to the challenges of a world, and a workforce, living with HIV/AIDS. And they have begun to do so; belatedly, but in some cases determinedly. According to *The State of Business and HIV/AIDS (2006): A Baseline Report*, a survey coordinated by Booz Allen Hamilton for the Global Business Coalition on HIV/AIDS (GBC), in high HIV prevalence African regions, more than 70% of companies surveyed are fully subsidizing staff access to HIV/AIDS treatment, including antiretroviral therapy. There is also an increasing global trend to expand access to treatment beyond individual employees: 36% of all companies surveyed are fully subsidizing treatment for direct employees, and 45% are providing treatment access for all dependents.<sup>1</sup>

We have called upon foundations to take the initiative, and the recent, well-publicized philanthropy of certain private individuals has also been gratifying. The efforts of the Bill & Melinda Gates Foundation, and Warren E. Buffett’s generous donation to it of US\$31 billion, are but two recent examples of individuals making a real difference in the lives of people living with HIV/AIDS and other diseases of poverty, including malaria and tuberculosis.

We have asked researchers for new pharmaceutical agents to combat HIV disease, and they have responded to this call with new antiretroviral drugs for first- and

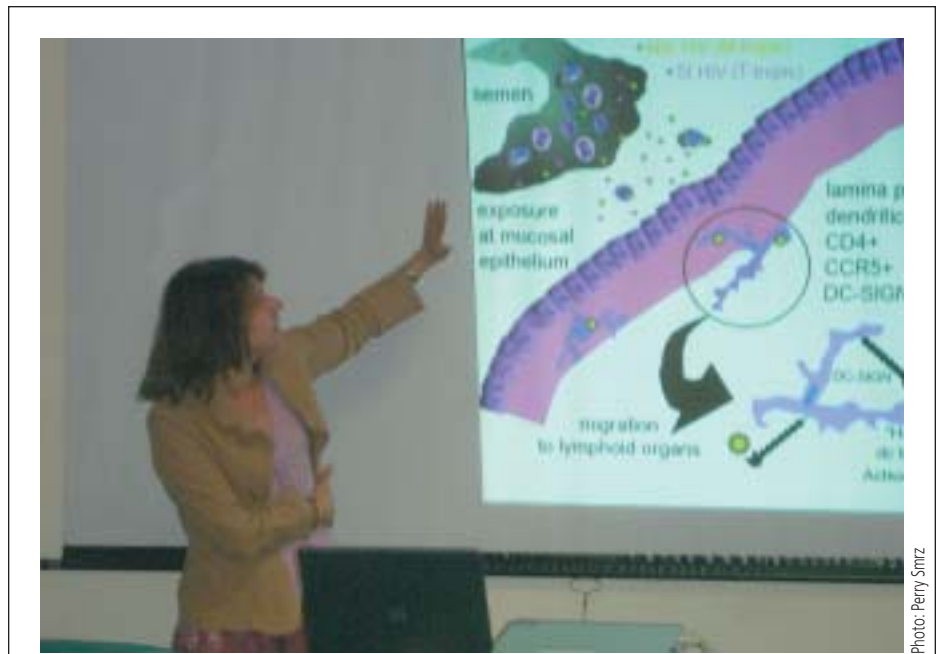
second-line and salvage therapy, as well as fixed-dosed combinations through which to promote improved adherence. They have also forged ahead with promising research that may someday lead to an AIDS vaccine, microbicides, and other pharmaceutical products to restore human health in people living with and affected by diseases of poverty.

We have encouraged developed-world physicians and other health care professionals to leave comfortable practices and well-funded research facilities to donate their time to train developing-country physicians, minister to patients, and conduct research in underserved areas; their response to this call has been inspiring. Within developing countries, local physicians and nurses are waging daily battle with the disease, often in conditions that would challenge the creativity and diligence of the most dedicated professional. They continue every day to rise to the challenge.

We have asked patients in both the developed and developing worlds to take risks: to be tested for HIV despite stigma, to hazard the potential side effects and toxicities of antiretroviral therapy, and to take part in clinical trials (many of which are for pharmaceutical products that would have taken many more years to pass muster, but which were desperately needed now to avoid hastened deaths). The response from patients and their families has been more than anyone could have hoped.

With this incredible response, why are HIV prevalence rates still increasing throughout the developing and in some communities of the developed world? Why are people still dying of AIDS-related complications in such devastating numbers? Because there is still so much more that needs to be done. Rather than succumb to fatigue or rejoice in what we have collectively accomplished, civil society must redouble its efforts to ensure that all this effort—these donations of money, time, talent, and enthusiasm; the momentum generated by political and societal commitment to the fight against HIV/AIDS; the sacrifices made by so many, but most especially by people living with HIV/AIDS—are not wasted. Every bit of value must be extracted to combat a disease that has had its way for far too long.

Referring back to the push-pull train analogy, the push-pull strategy often discussed in public policy circles



Vivian Black (University of the Witwatersrand, Johannesburg) delivers a presentation on acute HIV infection.

Photo: Perry Smrz

## IAPAC co-hosts SAHIVS branch meeting

The International Association of Physicians in AIDS Care (IAPAC) African Regional Office (AFRO) recently co-hosted a Southern African HIV Clinicians Society (SAHIVS) branch meeting in Vaal Triangle, South Africa. The branch meeting's theme was "Acute HIV Infection," and featured a clinical presentation by Vivian Black (University of the Witwatersrand, Johannesburg). Black, who has been heading the antiretroviral antenatal clinic at Johannesburg General Hospital for the past 20 months, is renowned for her work with HIV-positive pregnant women. ■

contends that program uptake by the desired audiences may be most efficiently ensured when services are both "pushed" to institutions that can effectively advertise and provide them, and marketed directly to consumers, who can "pull" toward them the services that they desire. For example, in terms of implementation of HIV prevention interventions and/or the delivery of care and support, the confluence of "push" and "pull" may be what is needed to allow affected communities to effectively utilize the resources now becoming available as well as to ensure sustainability of effort against a disease that exacts a lifetime toll on those infected and affected.

It is our responsibility, as members of global civil society, to ensure that momentum and enthusiasm, as well as financial and human resources, are not lost at this time of increased (though still insufficient) awareness. To make the most of this moment, perhaps we should consider our next steps in light of the push-pull strategy. How can we create appropriate and necessary goods and

services and offer them both to the organizations that can effectively "push" them toward their intended audiences and to the audience members themselves, who will "pull" toward them the services that are most appropriate for them?

The next five years may turn out to be pivotal; there is a chance for unprecedented progress, but the possibility of failure, whether because of fatigue, poor planning, or lack of will on the part of civil society, is always lurking. Let us use every tool available to make the most of this moment. For if we do not make the most of the vast resources that are beginning to become available, businesses, governments, and individuals will have no reason to continue to provide them. ■

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

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1. Booz Allen Hamilton. *The State of Business and HIV/AIDS (2006): A Baseline Report*. Available at: [www.businessfightsaids.org/site/pp.asp?c=gwKXUfNVJf&b=1716123](http://www.businessfightsaids.org/site/pp.asp?c=gwKXUfNVJf&b=1716123) (Accessed July 20, 2006).

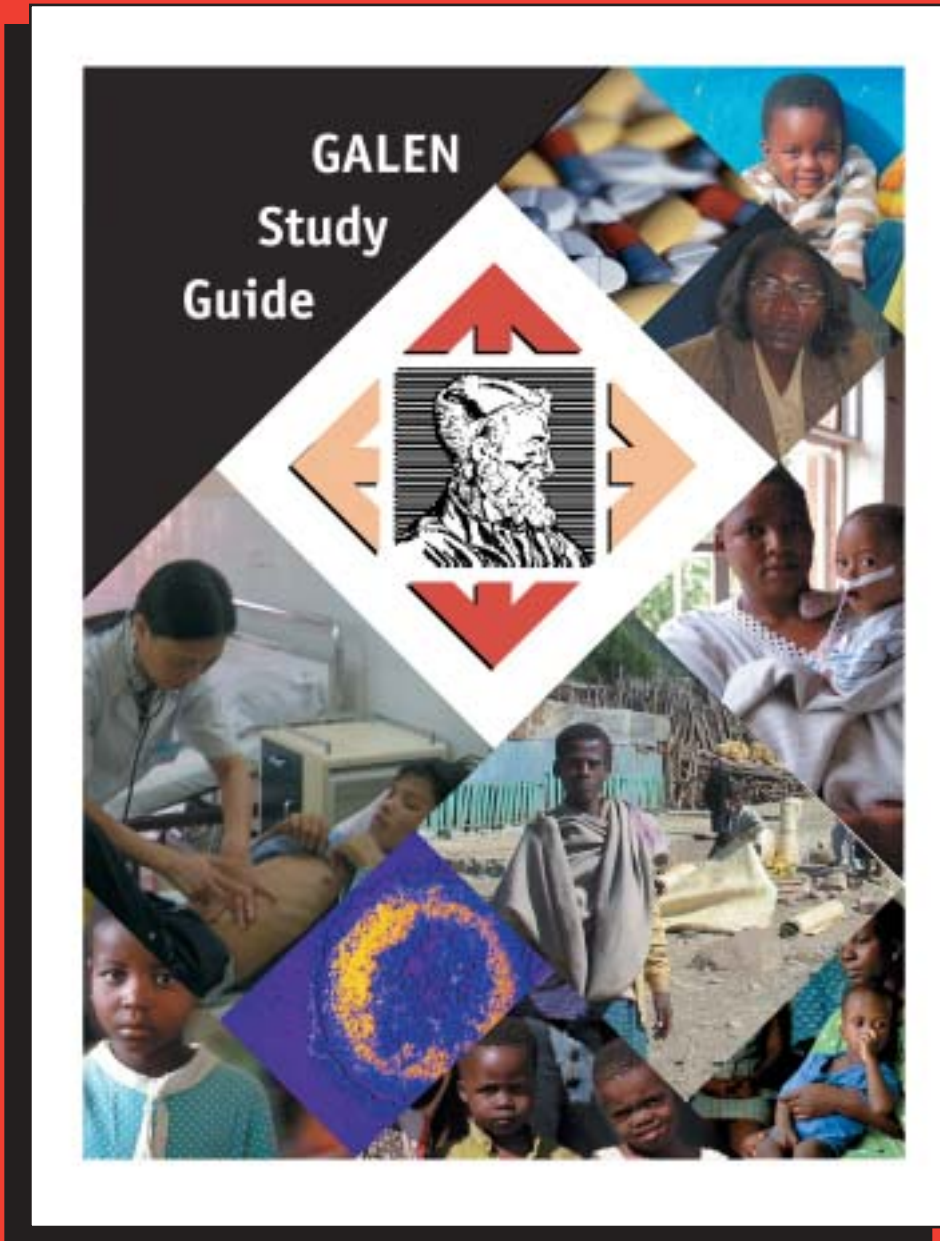


***Silence = complacency***

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## Fat loss prompts SA treatment switch

**F**at loss caused by the stavudine (d4T) component of triple antiretroviral therapy is beginning to trigger treatment changes among South African patients receiving treatment, according to doctors who presented their findings at last month's 2006 Implementers Meeting of the President's Emergency Plan for AIDS Relief (PEPFAR) in Durban. These data are the first substantial indicator from southern Africa that fat loss due to d4T is a problem for African patients.

The study, reported by Jane Hampton (McCord Hospital, Durban) and colleagues, showed a switch rate of 73 cases per 1,000 patient-years of follow-up. Previous data from Cape Town, presented at the 13th Conference on Retroviruses and Opportunistic Infections (CROI) earlier this year, had suggested that switching from d4T-based treatment due to lipodystrophy was uncommon. The Durban data found an unexpectedly high incidence of lactic acidosis, especially among women with a higher body mass, and led in part to the publication of guidelines by the Southern African HIV Clinicians Society (SAHIVS) on monitoring and managing patients at risk of lactic acidosis.

The McCord Hospital study reported data from 2,323 patients who had initiated antiretroviral therapy at its Sinikithemba Clinic since 2004. Just over 8% had died after beginning treatment, 3.8% were lost to follow-up, and 8.9% had changed treatment centers. The predominant regimen prescribed was d4T, lamivudine (3TC), and efavirenz (EFV). The cohort had accumulated 1,204 patient-years of treatment with d4T, while 2,022 had received treatment with EFV, 290 with nevirapine (NVP), and 330 with

zidovudine (ZDV) in their first-line antiretroviral regimen.

The most common reason for a switch of treatment was peripheral neuropathy caused by d4T, which accounted for 160 switches (56% taking place between months six and 12 of treatment).

A total of 40 cases of lactate levels above 5 mmol/L were observed through March 2006. Twenty-six cases of hyperlactatemia were observed through July 2005 (two men, 24 women), leading to four deaths, an incidence rate of 37 per 1,000 patient-years of d4T treatment. This compares with an incidence rate of 15 cases per 1,000 patient-years of follow-up in the Cape Town cohort, although the two groups may not be strictly comparable.

No further deaths occurred after July 2005, when new treatment initiation guidelines were introduced. Women with a body mass index (BMI) above 28 (the highest risk group for developing lactic acidosis among South African patients) would henceforth start treatment with ZDV/3TC rather than a d4T-containing regimen, while women with a BMI above 28 already receiving d4T would be switched to ZDV and given dietary advice in a bid to reduce their weight. No cases of hyperlactatemia have occurred in those who previously received or switched to ZDV.

Ninety-seven patients switched from d4T due to lipodystrophy, a rate of 73 switches per 1,000 patient-years. Fat loss manifested more commonly in the buttocks and thighs than in the arms or face among women. Changes were a consequence not only of fat loss, but of fat accumulation. Twenty-three women who switched treatment experienced breast enlargement and 19 experienced abdominal fat accumulation, but no details were available regarding whether these women had received EFV-containing antiretroviral regimens.

The study's authors say that the documentation of side effects and reasons for switching treatment is necessary in order to inform policymakers, and that the choice of antiretroviral drugs presently used in South Africa will need to be reconsidered. ■

### Reference

Hampton J. ART side effects resulting in a change of regimen in a cohort of patients treated at McCord Hospital, Durban, KZN, South Africa. 2006 HIV/AIDS Implementers Meeting of the President's Emergency Plan for AIDS Relief. June 12-15, 2006. Durban. [Abstract 488]

## TPV warning issued

Tipranavir (TPV) may be associated with an increased risk of bleeding within the skull when boosted with low-dose ritonavir (RTV), according to a warning issued June 30, 2006, by its manufacturer, Boehringer Ingelheim.

Patients given TPV in clinical trials did not show any blood clotting abnormalities. However, some test-tube studies and animal experiments did find some reductions in the ability of blood clots to form. Boehringer Ingelheim is carrying out more investigations into the link between TPV and bleeding.

Boehringer Ingelheim's "Dear Healthcare Provider" letter explained that 14 cases of intracranial hemorrhage have been identified in 6,840 patients receiving TPV/r. Eight of the patients have died. Boehringer Ingelheim claims that most of the patients had other risk factors for intracranial hemorrhage. These include lesions in the brain, head injury, recent brain surgery, blood clotting disorders, high blood pressure, and alcohol abuse, as well as use of medications that can increase bleeding. However, it did not reveal how many of the patients did not have a known risk factor for bleeding. It took a median of 525 days from the start of treatment with TPV/r for the hemorrhage to occur.

The company has advised that patients who may be at risk of bleeding due to surgery, injury, other conditions, or other medications should use TPV/r with caution. ■ — *Chris Gadd*

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**Training and  
ART scale-up:  
Establishing an  
implementation  
research  
agenda**





Elizabeth A. McCarthy, Megan E. O'Brien, and William R. Rodriguez

**T**he provision of HIV treatment and care in resource-limited settings is expanding rapidly. Health worker training is one of many factors critical to the rapid scale-up of high-quality care.<sup>1-6</sup> Large numbers of health workers require HIV training, yet few countries have a comprehensive training plan, a clear assessment of ongoing training needs, a plan to operationalize training on a large scale, or adequate funds budgeted for training. In this setting, an extensive variety of HIV-related training programs have sprung up over the past few years. Unfortunately, there are limited data measuring their effectiveness, and there is no consensus about what constitutes effective training.

Underlying the looming challenge in health worker training, most resource-limited countries face a chronic shortage of trained health care providers; chronic understaffing impedes the ability to adequately train health workers in HIV care. First, removing clinicians and nurses from active clinics for training purposes intensifies the strain on

clinical care systems. Second, professional programs for physicians and other health workers are commonly lacking. For example, several countries in Africa and the Caribbean—including Botswana, Lesotho, and the Bahamas—do not have medical schools, and must send students outside of the country for basic professional training (Table 1). Finally, trained workers (and potential recruits) commonly leave the public health sector for the better compensation, benefits, working conditions, and job satisfaction found in other sectors and other countries—the “brain drain” phenomenon—further exacerbating the human resource crisis.<sup>7-12</sup>

Faced with these challenges, and with the rapid pace of HIV-treatment expansion, few resource-limited countries have sufficient internal resources to address their training needs. As a result, most countries have collaborated with external partners to develop training programs for health care workers, and/or to bring in expatriate specialists to provide training, at least in the initial phase of scale-up. Often, these training efforts are poorly coordinated with national training priorities, lack evidence to support their effectiveness, and are driven largely by foreign partners. As a result, many training redundancies exist alongside large, unmet training needs.

We gathered information on global HIV training through a thorough review of the

Table 1. Medical Schools in Selected Countries

Country	Number of medical schools
India	221
China	165
Dominican Republic	16
Tanzania	4
Haiti	3
Cambodia	2
Kenya	2
Jamaica	1
Mozambique	1
Rwanda	1
Bahamas	0
Botswana	0
Lesotho	0

From: McCarthy EA, O'Brien ME, Rodriguez WR (2006) Training and HIV-treatment scale-up: Establishing an implementation research agenda. *PLoS Med.* 3(7): e304.

published peer-reviewed literature, Internet sites, program reports related to training for HIV treatment in resource-limited countries, a survey of HIV training efforts in high-burden countries, and discussions with appropriate professionals in selected countries. Here, we review challenges and approaches to clinical HIV training, and suggest an agenda for implementation research—defined here as research into how proven interventions can be implemented to accelerate high-quality HIV-treatment scale-up—to address the question: what is the optimal approach to training the health workforce for an expanding HIV-treatment program in a resource-limited setting?

### Training appropriate to the model of care

The design of a national health worker training program to support the expansion of quality HIV treatment should be tightly linked to the way in which HIV care and treatment are delivered in the respective country. Many national programs, such as those of the Bahamas,<sup>4</sup> Botswana,<sup>5</sup> and Uganda,<sup>13</sup> initiated HIV treatment by following a “vertical” specialty HIV-clinic model in which the majority of HIV treatment is provided by HIV specialists. Training according to this approach targets the creation of multidisciplinary HIV-care teams who provide care predominantly, or exclusively, for patients with HIV.

At the other end of the spectrum is the public health model of care delivery,<sup>14-15</sup> where HIV care and treatment are provided

by primary health care providers who are trained in basic aspects of HIV care for adults and children and to recognize conditions that warrant referral to a specialized setting.<sup>16</sup> Training in advanced aspects of HIV care is reserved for a small cadre of specialists. A hybrid of these two models occurs when a national program starts its treatment program in the specialty model, but decentralizes HIV services to peripheral facilities. In this case, HIV care and treatment may be provided in a primary health care setting by primary health clinicians, or by an HIV-care specialist.

In the vertical model, training in HIV care relies on a highly centralized training program driven by a small group of expert trainers, with a core curriculum that can be quickly and easily updated to keep pace with changes to practice and guidelines, and short intensive trainings for small groups of trainees. Parallel systems are often established for training in laboratory methods, counseling and patient education, data collection, and pharmacy and supply management. As programs decentralize into a public health model, training decentralizes accordingly. Short, intensive trainings in a central setting become less practical. The cadre of trainers and curricula must be expanded, and systems must be implemented

**The HIV health workforce includes doctors, clinical officers, nurses, pharmacists, laboratory technicians, phlebotomists, counselors, program managers, data clerks, ancillary staff, and community health workers.**

**Table 2. Human resources per 100,000 people in selected countries**

Country	Physicians	Nurses	Pharmacists
United States	256	937	88
Dominican Republic	188	184	40
China	106	105	28
Bahamas	105	447	N/A
Jamaica	85	165	N/A
India	60	80	56
Botswana	40	265	19
Haiti	25	11	N/A
Cambodia	16	61	4
Kenya	14	118	10
Lesotho	5	62	3
Rwanda	5	42	3
Mozambique	3	21	3
Tanzania	2	37	1

Latest available data. Data are from the Global Health Atlas of the World Health Organization. Available at <http://globalatlas.who.int/> (Accessed July 24, 2006).

From: McCarthy EA, O'Brien ME, Rodriguez WR (2006) Training and HIV-treatment scale-up: Establishing an implementation research agenda. *PLoS Med.* 3(7): e304.

to allow for curricula review, updates, and distribution of continuing medical education (CME) materials.

### Training decisions amidst a crisis in human resources for health

The human-resources-for-health crisis in resource-limited countries is a substantial obstacle to scaling up HIV treatment programs and is directly relevant to health workforce training. Neither Mozambique, Rwanda, nor Tanzania, for example, has more than five physicians, 42 nurses, or three pharmacists for every 100,000 people (Table 2).<sup>17</sup> The United States, by comparison, has a density of 256 physicians, 937 nurses, and 88 pharmacists for every 100,000 people.<sup>17</sup> Lincoln Chen (Harvard University) and colleagues have linked low national staffing ratios to poorer health outcomes,<sup>18</sup> and it is likely that this link extends to HIV care.

The HIV health workforce includes doctors, clinical officers, nurses, pharmacists, laboratory technicians, phlebotomists, counselors, program managers, data clerks, ancillary staff, and community health workers. The function of each category of health worker depends on the local model of care delivery, and is influenced by tradition, legislation, and local regulations. Variation in health worker roles can be an obstacle to adapting generalized training tools and curricula to a specific setting. A recent study in the United States found that nurse

practitioners and physician assistants who specialize in HIV care provide better care than non-HIV expert physicians and comparable care to HIV-specialist physicians—a finding which could support the expanded role of nurses and clinical officers in HIV treatment in resource-limited settings.<sup>19</sup>

As noted, many countries lack adequate pre-service training institutions for health care workers, and must send clinicians outside of the country for professional training. Postgraduate migration to other countries is common, exacerbating the human resource crisis.<sup>7</sup> In a setting where the need for health workers outweighs the number of health workers who are available, it can be difficult to entice workers to staff underserved areas, such as rural sites.

### Advantages and disadvantages of training methodologies

There is scant evidence to support the effectiveness of one training methodology over another. Advantages and disadvantages of the predominant training methodologies that have emerged *ad hoc* in the past few years are discussed below.

- **Pre-service education.** Adding or enhancing relevant coursework during pre-service education for health professionals (eg, medical schools, nursing schools) takes advantage of pre-existing programs without taking professionals away from the workplace as trainers or trainees.

## Sidebar 1. Implementation research

### Model of care

- What are the advantages and disadvantages of parallel systems of specialty HIV clinics and primary health care clinics?
- Does the most efficient model of HIV care delivery vary from urban to rural site?
- What is the optimal way to integrate HIV and other services (such as tuberculosis care, maternal and child health care, and HIV testing) to maximize patient capacity while minimizing resource needs?
- What is the impact on quality of care and cost if stable patients are managed by trained nurses, clinical officers, or generalist physicians instead of HIV-specialist physicians?
- What is the impact on quality of care and program scale-up rates if children with HIV are managed by doctors other than pediatricians?

### Human resources

- What is the optimal role for each health worker (ie, physician, nurse, clinical officer) to maximize the patient capacity given fixed resources?
- How many health workers of each category are needed for a program to scale up efficiently?
- Can existing health systems subsume HIV care and treatment without adding staff?

### Training delivery

- What is the ideal combination of training methodologies (didactic training, clerkship, onsite mentoring, ongoing consultation, Internet-based courses, etc) to prepare providers to offer HIV care and treatment services?
- What are the most effective ways to reinforce knowledge and skills gained in training (eg, CME, refresher courses, consultation)?
- Does inclusion of other causes of morbidity in HIV training, such as diabetes, tuberculosis, sexually transmitted infections, malaria, and other locally prevalent infections, lead to improved patient outcomes?
- Does inclusion of nutrition in HIV training lead to improved patient outcomes?
- What are the advantages and disadvantages of relying on local, national, or foreign HIV experts to provide HIV training?

It helps address health workforce needs, and ensures an adequate skill set among graduating professionals. However, it does not address the needs of those who have already completed their professional education, nor does it provide immediate solutions to urgent needs.

- **Didactic training.** Most training programs have emphasized centralized didactic training as the core training method. Didactic training, delivered as lectures in a classroom setting, is often used to

convey large amounts of information at one time. It is often delivered in a centralized location, typically lasts a week or two, and can accommodate large numbers of trainees—requiring fewer trainers and resources than other methods, and allowing for standardization of the training's content. The classroom style is a familiar approach for many trainees, yet the translation of classroom knowledge to clinical practice can be challenging, especially if the curriculum is divorced from practical circumstances facing trainees. Trainees may not retain knowledge if it is not immediately applied to clinical practice. And, like all methods that take trainees and trainers away from their workplace, didactic training can temporarily exacerbate the strain on clinical care.

- **Training of trainers.** A training-of-trainers methodology is generally implemented when programs wish to provide didactic training at decentralized sites. Groups of health professionals are trained as “experts,” and expected to lead or facilitate future trainings. This approach attempts to expand the pool of trainers and leverage resources to build training capacity. An important downside of this method is the potential distillation of information as trainers get further removed from the original trainer's expertise and information, which can impact the quality of training and the resulting clinical outcomes. Some trainers may require training in educational methods and pedagogy beyond training in the management of HIV infection.
- **Refresher course.** It can be difficult for trainees with limited experience to absorb information from a didactic training. Trainees often benefit from practical experience at their own sites, followed by a refresher course. This affords trainees an opportunity to develop skills before returning for ongoing training, which may add complexity and build on their classroom and practical experiences. It gives programs an opportunity to provide trainees with updated information, and affords trainees the opportunity to problem-solve with each other.

The classroom style is a familiar approach for many trainees, yet the translation of classroom knowledge to clinical practice can be challenging, especially if the curriculum is divorced from practical circumstances facing trainees.

- **Distance learning.** Using computer-based or video-based technology is another way to train health care workers in resource-limited settings. This approach allows trainees to remain at their workplace, and has the added advantage of reaching a wide, geographically disparate audience with simulated cases that allow providers to test their knowledge without negative consequences to patients. These courses are inherently technology- and resource-intensive and require a certain degree of comfort with technological applications, but they reduce the need for trainers and allow trainees to move at their own pace.

While some programs, such as those in Botswana,<sup>5</sup> Tanzania, and the Dominican Republic send multidisciplinary teams of health workers to didactic trainings, others focus didactic training exclusively on one discipline—such as physician trainings in Mozambique. Often, workers from one clinic who attend the training are expected to bring back the information to their clinic and train the remaining staff, although this is rarely operationalized.

- **Off-site clerkships.** Some programs, such as those in Botswana<sup>5</sup> and Kenya,<sup>6</sup> complement didactic courses with opportunities to shadow experienced providers. During these off-site clerkships or “attachments,” trainees spend a block of time with a mentor at the mentor's clinical facility, which, ideally, is similar to their home clinic. Trainees gradually assume clinical responsibilities under supervision. The mentored environment allows the trainee to practice a skill with the comfort of

having an experienced mentor to address questions and difficulties, and reinforces information provided during the didactic course. If the caseload and experience of the mentor are inadequate or if the attachment site differs significantly from the practice sites of the trainees, this type of training may be less relevant. Finally, attachments can take trainees away from their jobs for an extended period of time.

- **On-site mentoring.** Botswana and Lesotho are both implementing national on-site mentoring, or “preceptorship,” programs that send experienced HIV-treatment professionals (nationals and/or expatriate health professionals) to sites of less-experienced providers for an extended period of time (several days to several months) to offer on-site mentoring. In Botswana, the preceptorship program builds on didactic training and an attachment at one of the four initial national treatment sites,<sup>5</sup> while in Lesotho, the preceptorship program complements the decentralized trainings at antiretroviral treatment sites using World Health Organization (WHO) Integrated Management of Adult and Adolescent Illness (IMAI) materials,<sup>16</sup> which are tailored to the public health model of care delivery.

The preceptorship training methodology has the same advantages as attachments, and also offers training specifically tailored for the trainee’s work situation. Preceptorships can be particularly time-, labor-, and resource-intensive, and can require a large number of skilled mentors. While expatriate mentors are not always knowledgeable about local conditions, language, or policy, and may need to be

licensed and/or registered to work as mentors, national mentors are in very short supply because of the human resource crisis and the fledgling nature of treatment programs in resource-limited countries. Most countries currently rely heavily on expatriate preceptors.

- **Consultation.** Some programs have developed a consultation system that allows newly trained providers to ask questions of experienced providers through direct phone calls, e-mail, call centers, or frequent site visits by the mentor. Consultation systems provide a support network that builds the confidence of newly trained providers. In Uganda, for example, the AIDS Treatment Information Centre hosts a call-in center that responds to providers’ treatment questions. Similarly, the Prince Leopold Institute of Tropical Medicine has developed an Internet-based program, TELEmedicine, to enable their experienced providers to respond via e-mail to inquiries made by clinicians in resource-limited settings. One drawback to a telephone or e-mail system of consultation is its reliance on communication technology.
- **Case conferences.** Another way to train providers is through case conferences: regular meetings to discuss complex problems in HIV care and to provide updates on practices or guidelines. Case conferences encourage a team approach to HIV care, help establish a network of HIV care providers for informal consultation and/or referrals, and can reach a wide audience, especially with advanced Internet-based conferencing software, where it is available.
- **Twinning.** An established relationship between two institutions to share expertise, which can be North-South or South-South, is referred to as twinning. One example of this approach is the collaboration between the Moi University Faculty of Health Sciences in Kenya and both the Indiana University School of Medicine and the Brown University School of Medicine.<sup>6</sup> Twinning increases resources for individual in-country institutions by facilitating a flow of funds and an exchange of information and expertise from one institution to the other. There is, however, a limit to the number of available twinning programs, and trainers from foreign institutions are not always knowledgeable about local conditions, language, or policy.

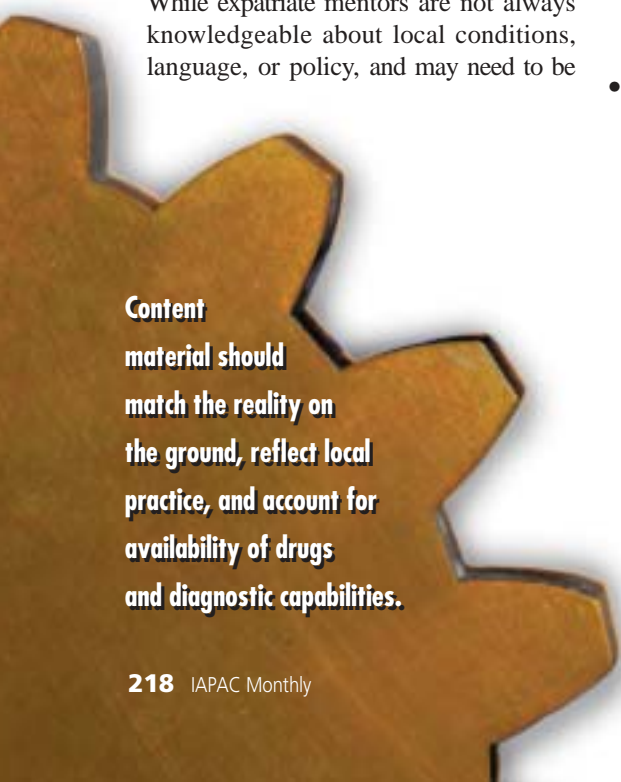
- **Certification.** Official recognition, or certification, of some degree of HIV treatment expertise for trainees who complete a training program can be an incentive for completion. If accompanied by testing, it can ensure a minimum level of knowledge, and can be used to evaluate the effectiveness of the training. Recertification can be the basis for a CME program. However, in addition to the potential for certification to increase bureaucracy and administrative costs, certification may be used by trainees to seek more lucrative positions outside of the country or with other organizations within the country.

- **CME programs.** These programs exist in countries with robust medical associations. Pre-existing CME systems can be used as a vehicle for HIV training, but are generally used to supplement a pre-existing knowledge base, not to train inexperienced providers.

### Establishing a national training plan

More data on the effectiveness and program costs of training are needed to help planners determine which options are optimal given a program’s unique circumstances, including the size of the population requiring treatment, the care delivery model, the extent of local expertise, the existing public health infrastructure, health worker/population ratios, political will, nongovernmental organization involvement, and resources. Training programs would also benefit greatly from accurate forecasts of the demand for health workers:<sup>4</sup> the number of necessary staff needed immediately, the number of staff needed over time as programs scale up treatment, site locations, and the optimal number and mix of staff at each site. Such forecasts allow planners to determine the extent to which an investment in hiring and training additional health workers would affect HIV care and the extent to which it is critical to budget and resource-allocation decisions.

Training plans should anticipate common experiences—such as the permanent loss of trained health workers who take more lucrative jobs or burn out, the temporary loss of health workers who take leave or attend trainings, and worker illness and death from HIV infection. Some programs have chosen to train two individuals for every position, assigning each to spend half of their time at the HIV clinic and



**Content material should match the reality on the ground, reflect local practice, and account for availability of drugs and diagnostic capabilities.**

half elsewhere in the hospital or clinic. This reduces reliance on one individual, allowing each to miss clinical time without significant disruption. Without a buffer system to replace trained individuals, or the flexibility to train additional staff quickly, unexpected staff shortages create bottlenecks in clinic operation, slowing down the flow of patients and straining other staff. A forward-thinking national training plan will not only anticipate job loss but will also incorporate ways to avoid it. Approaches might include augmented salary, recruitment of staff to work in their home districts, improved staff-to-patient ratio, and adequate supplies.

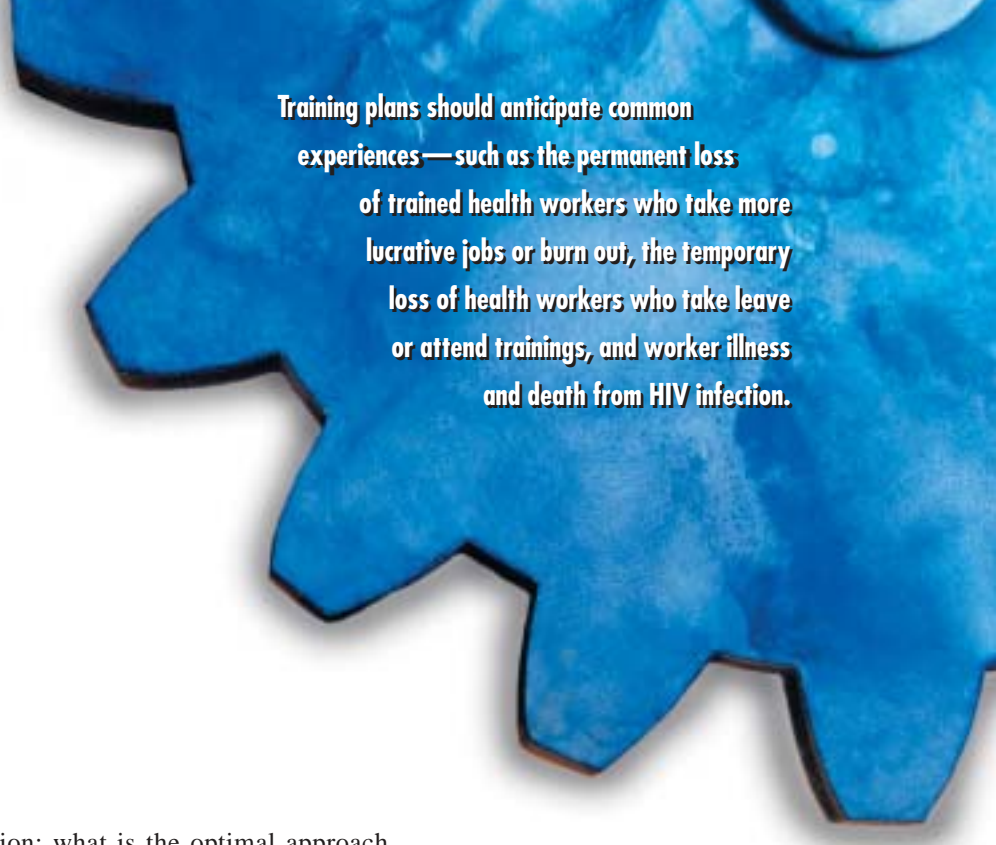
Other considerations to be addressed when designing a training plan include the site of training, target audience, and content material. Training plans need to consider the optimal components of a training site, eg, proximity to a health-care facility and an environment similar to what the trainee will experience at their home clinic. Training plans need to assess training previously received by workers, and decide whether to train one health cadre at a time or to train multidisciplinary teams together. Content material should match the reality on the ground, reflect local practice, and account for availability of drugs and diagnostic capabilities.

### Toward a more evidence-based training program

Decisions as to how best to train the health workforce in resource-limited countries are being made with limited data to support them. Few programs measure the impact of training on clinical outcomes. Critical questions that correspond to key topics are identified in Sidebar 1, page 217: that correspond to key topics: model of care, human resources, and training delivery. We recommend that an implementation research agenda be established to address these questions.

### Conclusions

Training a robust health workforce is critical for sustainable HIV treatment programs. The care delivery model, the roles played by different health workers, the number of workers needing training, resources available for training, and the phase of program development all significantly affect training design. Evidence to support these decisions must come from implementation research to answer the overarching



**Training plans should anticipate common experiences—such as the permanent loss of trained health workers who take more lucrative jobs or burn out, the temporary loss of health workers who take leave or attend trainings, and worker illness and death from HIV infection.**

question: what is the optimal approach to training the health workforce for an expanding HIV treatment program in a resource-limited setting? ■

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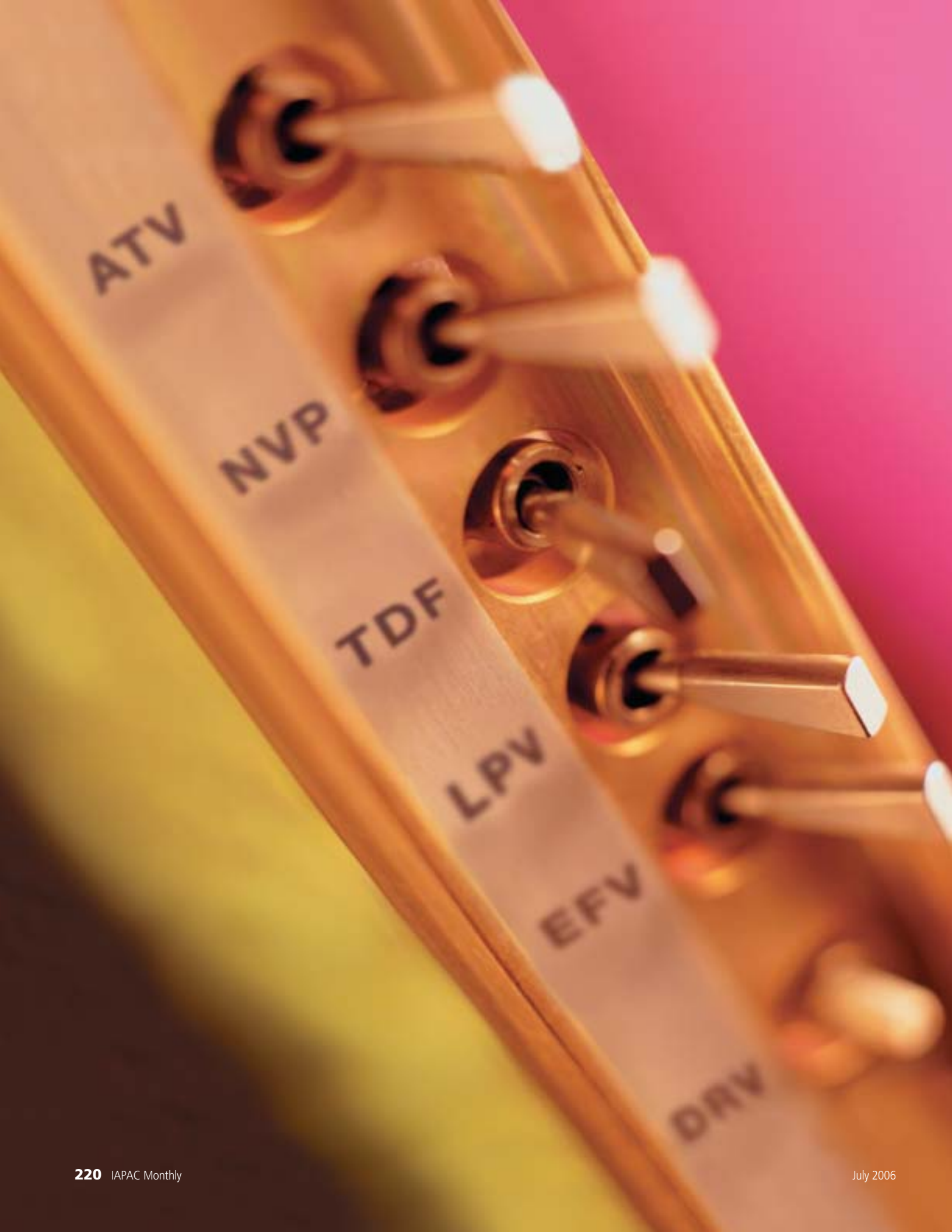
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# Switching antiretroviral therapy:

## Why, when, and how

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and Roy M. Gulick*



Once antiretroviral therapy (ART) is initiated, patients generally remain on medications indefinitely. A switch in the antiretroviral (ARV) regimen is often necessary because of both acute and chronic toxicities, concomitant clinical conditions, and development of virologic failure. The approach to patients who need to switch ART will differ depending on several issues, including the reason for change, the amount of previous ART experience, and the available treatment options. For example, when patients develop an adverse effect to a drug during their first ARV regimen, effective treatment may be easily accomplished by substituting another agent for the offending drug in the regimen. At the opposite end of the spectrum are patients with advanced HIV disease who have experienced toxicities, virologic failure,

and drug resistance during multiple past treatment regimens and thus require a new treatment regimen. This article reviews these circumstances and provides clinical evidence and strategies for switching ART.

### **Acute toxicities**

Toxicities from ART are common and may necessitate changes in medications (Table 1). These toxicities are typically not life threatening but can affect quality of life and negatively affect patients' willingness to adhere to their regimens. In fact, several cohort studies have suggested that toxic effects are a more common reason for switching ART than are virologic failures. A review of published cohort studies that examined modification of initial ART regimens found that antiretroviral intolerance and toxicity were the most common reasons for changing therapy in eight of 11 studies.

Gastrointestinal disturbance such as nausea, vomiting, and diarrhea was the most frequently cited toxicity leading to a change in an initial ARV regimen, and this has been confirmed in a separate cohort study. Most of the modifications due to intolerance in these studies occurred within three months of starting ART. The large majority of the patients in these cohort studies were taking protease inhibitor (PI)-based regimens.

Investigators monitoring an Italian cohort of HIV-infected patients examined the outcomes of patients whose first ARV regimens were based on nonnucleoside reverse transcriptase inhibitors (NNRTIs). They found that clinical drug toxicity, which occurred in 18% of patients starting a nevirapine (NVP)-based regimen and in 10% of patients starting an efavirenz (EFV)-based regimen, was the most common reason for switching an initial ARV regimen. In contrast to gastrointestinal disturbance with PI-based regimens, hypersensitivity (eg, rash and hepatitis) was the most common reason for discontinuing an NVP-based regimen (12%), and central nervous system toxicity was the most common reason for discontinuing an EFV-based regimen (5%). In addition to the toxicities mentioned above, rash, headache, fatigue, and abnormalities in hematologic and liver function tests are common toxic effects leading to a change in ART. In some resource-constrained settings, where ARV regimens usually consist of an NNRTI (typically NVP) in combination with either zidovudine (ZDV) or stavudine (d4T) plus a second nucleoside analogue, high rates of acute toxicities necessitating antiretroviral changes have been reported. These adverse effects include rash, hepatotoxicity, and anemia.

No absolute guidelines exist for determining when to change regimens if these toxicities occur. Given that many patients improve within a few weeks of starting ART, providers often attempt to control adverse effects with short-term palliative medicine (eg, loperamide for diarrhea and prochlorperazine or metoclopramide for nausea). Efavirenz-associated central nervous system toxicity often subsides within a few weeks after starting the medication and is usually managed by reassuring the patient. In the case of acute toxicity attributable to a specific antiretroviral drug, same-class substitution of a drug with a differing toxicity profile is accepted clinical practice, based largely on anecdotal experience and descriptive data from clinical trials (eg, abacavir

**Table 1. Common toxicities of antiretroviral drugs**

Antiretroviral drug	Toxicities
<b>Nucleoside (and nucleotide) reverse transcriptase inhibitors</b>	
<i>All NRTIs have been associated with lactic acidosis and hepatic steatosis, which can be fatal.</i>	
abacavir	Gastrointestinal disturbance, hypersensitivity (eg, abdominal pain, fatigue, fever, rash, respiratory symptoms), nausea
didanosine	Gastrointestinal disturbance, lipoatrophy, pancreatitis, peripheral neuropathy
lamivudine	Gastrointestinal disturbance, headache
stavudine	Hepatitis, lipoatrophy, pancreatitis, peripheral neuropathy
tenofovir	Gastrointestinal disturbance, nephrotoxicity
zidovudine	Anemia, fingernail discoloration, gastrointestinal disturbance, headache, lipoatrophy, neutropenia
<b>Nonnucleoside reverse transcriptase inhibitors</b>	
delavirdine	Hepatitis, rash
efavirenz	Central nervous system effects (eg, dizziness, sleep disturbance), hepatitis, rash
nevirapine	Hepatitis (more common in patients with higher CD4 counts at initiation of nevirapine), rash
<b>Protease inhibitors</b>	
atazanavir	Gastrointestinal disturbance, hyperbilirubinemia (not clinically significant)
fosamprenavir	Central fat accumulation, gastrointestinal disturbance, hyperlipidemia, insulin resistance
indinavir	Central fat accumulation, gastrointestinal disturbance, hyperbilirubinemia (not clinically significant), hyperlipidemia, insulin resistance, nephrolithiasis
lopinavir/ritonavir	Central fat accumulation, diarrhea, gastrointestinal disturbance, hyperlipidemia, insulin resistance
nelfinavir	Central fat accumulation, diarrhea, gastrointestinal disturbance, hyperlipidemia, insulin resistance
ritonavir	Central fat accumulation, circumoral paresthesias, gastrointestinal disturbance, hyperlipidemia, insulin resistance
saquinavir	Central fat accumulation, gastrointestinal disturbance, hyperlipidemia, insulin resistance
tipranavir	Hepatitis, gastrointestinal disturbance, rash, central fat accumulation, hyperlipidemia, insulin resistance
<b>Entry inhibitors</b>	
enfuvirtide	Injection-site reactions

(ABC) or tenofovir (TDF) for ZDV-related gastrointestinal intolerance). The decision to change antiretroviral medications is based on consideration of the severity of symptoms, efficacy of palliative medications, options for substitution, and risks associated with those options. The occurrence of adverse effects has been associated with reduced adherence, and providers generally should offer a change in medications for patients who report diminished adherence due to toxicity. Modification of ART because of toxicity in patients who are starting an initial ARV regimen does not seem to be associated with subsequent virologic failure.

### Chronic toxicities

Certain toxicities emerge months to years after the initiation of antiretroviral medications. These include neuropathy, changes in body composition (commonly termed lipodystrophy), and metabolic toxicities

(eg, dyslipidemia and insulin resistance) that are associated with an increased risk of cardiovascular events. Researchers have shown great interest in the strategy of changing antiretrovirals to manage these chronic toxicities. The presumed multifactorial etiology of such complications makes their study a challenge because more than one drug or class of drugs in a regimen may contribute pathogenetically to the toxicity. Nonetheless, investigators have addressed chronic toxicities by substituting drugs that have been linked epidemiologically to specific adverse effects.

### Lipoatrophy

Lipoatrophy (eg, loss of subcutaneous fat in the face, extremities, and buttocks) is a component of lipodystrophy. Thymidine analogue use has been associated with lipoatrophy, and, in particular, d4T use has been identified as a risk factor in several studies.

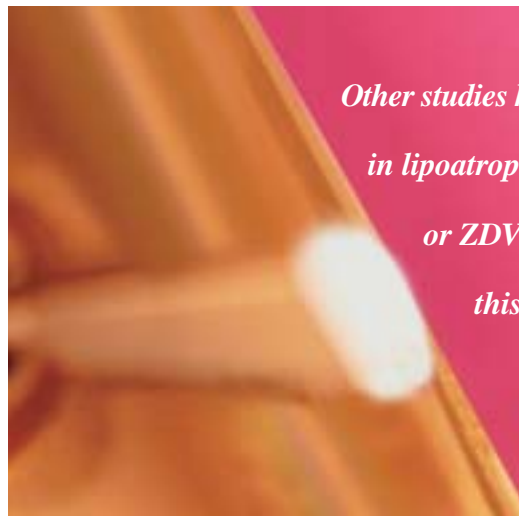
Although fat loss was once thought to be irreversible, small proof-of-concept studies have suggested that substituting ZDV or ABC for d4T was an approach worthy of further examination. In a landmark study, subjects with lipoatrophy were randomized to continue d4T or ZDV or to switch the thymidine analogue to ABC. Those who switched had statistically significant increases in both subcutaneous abdominal tissue volumes by computed tomography and peripheral fat mass by dual-energy X-ray absorptiometry (DEXA) scanning at 24 weeks of follow-up. Although these short-term changes were not clinically significant, further follow-up to two years demonstrated continued improvements in lipoatrophy. Other studies have demonstrated improvements in lipoatrophy after substituting ABC, TDF, or ZDV in place of d4T, suggesting that this approach may be reasonable to consider if a patient's treatment history permits safe substitution. A patient with a history of ABC hypersensitivity or documented resistance to ABC would not be an appropriate candidate for this switch. Similarly, a history of single or dual nucleoside analogue therapy is associated with an increased risk of virologic failure after changing to ABC, probably because of preexisting nucleoside resistance mutations, and precludes such a switch.

Observational data have suggested that PIs may act synergistically with nucleoside analogues in the development of lipoatrophy. Several small, randomized controlled studies in which a PI was switched to an alternative agent, however, have not shown objective improvements in lipoatrophy. For example, among 77 subjects randomized either to switch from a PI to NVP or EFV or to continue the PI, the 58 subjects with lipodystrophy at baseline showed no changes in body composition by DEXA or anthropometric measurements after one year of follow-up. Contrasting results came from a subgroup analysis of a larger trial in which eight subjects taking a regimen containing ZDV and a PI switched their PI for ABC. On average, these subjects gained small amounts of leg fat over 48 weeks, as assessed by DEXA, compared with seven control subjects who remained on a ZDV-based regimen that included a PI. Taken together, these data suggest that substituting another agent for a PI is not likely to have a clinically significant impact on lipoatrophy, at least in the short term.

### Central fat accumulation

Because increased truncal (visceral) fat has been linked epidemiologically to PI use, the effect on truncal fat of switching to regimens that do not contain a PI has been explored in several small studies, most of which have lacked a control group and objective endpoints. In one randomized study, subjects with increased visceral abdominal tissue volume at baseline had greater reductions after switching from a PI-containing regimen to ABC, NVP, adefovir (ADV), and hydroxyurea compared with controls who stayed on PI-containing regimens. Lipoatrophy, however, worsened in those randomized to the change in regimens. In a metabolic substudy of a large randomized trial, no significant improvement was found in body composition abnormalities 24 months after patients switched from a PI to ABC, NVP, or EFV. Overall, the approach of switching from PIs has not proven

successful and cannot be recommended as a strategy for addressing increased truncal fat. Specific therapies for this condition are an active area of research.



*Other studies have demonstrated improvements in lipoatrophy after substituting ABC, TDF, or ZDV in place of d4T, suggesting that this approach may be reasonable to consider if a patient's treatment history permits safe substitution.*

successful and cannot be recommended as a strategy for addressing increased truncal fat. Specific therapies for this condition are an active area of research.

### Dyslipidemia

Hypertriglyceridemia and hypercholesterolemia have been clearly associated with the use of specific PIs and may occur within weeks after initiation. These toxicities have been managed successfully by switching within the PI class or by switching to drugs from other antiretroviral classes. As an example of the first approach, replacing ritonavir (RTV) with nelfinavir (NFV) or NFV plus saquinavir (SQV) improved lipid profiles in a small, randomized study. Similarly, substituting atazanavir (ATV) for a PI improved lipid profiles in uncontrolled

have variable effects on low-density lipoprotein (LDL) cholesterol.

Nucleoside analogues also may contribute to dyslipidemia in HIV-infected patients. Stavudine has been associated with greater adverse lipid effects in two randomized, controlled studies when compared with ZDV or TDF, in conjunction with lamivudine (3TC) and EFV or NFV. Several studies have suggested that substituting TDF for d4T may improve total cholesterol and LDL cholesterol; the effect on triglyceride levels is less clear.

### Insulin resistance/diabetes mellitus

The effect of drug substitution has been characterized less well for insulin resistance than for dyslipidemia. Whereas indinavir (IDV) clearly causes decreased insulin

sensitivity when administered to healthy, HIV-uninfected volunteers, the relative effects of other PIs have not been clearly discerned *in vivo*. *In vitro* data concerning insulin resistance and diabetes mellitus associated with PI use, however, do suggest that certain other drugs within the class may induce insulin resistance directly or indirectly. Switching a PI to ABC, EFV, or NVP appears to have a favorable effect on insulin resistance; few data exist on the effect of substituting ATV for another PI. Substituting an alternative drug for a PI may therefore be a reasonable strategy for patients with other risk factors for diabetes mellitus, such as obesity and positive family history, although no data are available on the efficacy of such a strategy in preventing the development of diabetes mellitus. Because insulin resistance is associated with increased cardiovascular risk in the general population, reducing insulin resistance may have long-term benefits.

### Life-threatening toxicities

Life-threatening toxicities are rare, but remain an important reason for changing ART. Severe rash such as Stevens-Johnson syndrome or erythema multiforme is an indication to switch ART. These rashes have been reported most commonly with NNRTIs: delavirdine (DLV) (rarely), EFV (0.1%), and NVP (1%). Lactic acidosis is potentially fatal and is most commonly associated with d4T, but it has been reported with all nucleoside reverse transcriptase inhibitors (NRTIs). In the case of symptomatic hyperlactatemia or lactic acidosis, retrospective data suggest that it is generally safe to change the presumed offending agent (typically d4T or ddI) to an alternative nucleoside analogue considered to have similar virologic activity but less propensity to injure mitochondria (typically ABC, 3TC, or TDF). This substitution is generally made after a treatment interruption to allow resolution of the initial toxicity. Other potentially fatal toxicities include ddI-associated pancreatitis and ABC hypersensitivity. Rechallenge with the offending agent after the onset of any of these life-threatening toxicities should not be attempted.

### Adherence/quality of life

Much progress has been made in simplifying ART so that regimens are easier for patients to take in a consistent manner. In the mid-

Table 2. Recent improvements in antiretroviral drug formulations and new dosing options to improve adherence

Antiretroviral drug	Dosing
<b>Nucleoside analogue reverse transcriptase inhibitors</b>	
abacavir	600-mg once-daily dosing
abacavir/lamivudine	Fixed-dose combination, once-daily dosing
didanosine EC (enteric-coated formulation)	Once-daily dosing
lamivudine	300-mg once-daily dosing
tenofovir/emtricitabine	Fixed-dose combination, once-daily dosing
zidovudine/lamivudine	Fixed-dose combination, twice-daily dosing
zidovudine/lamivudine/abacavir	Fixed-dose combination, twice-daily dosing
<b>Nonnucleoside reverse transcriptase inhibitors</b>	
efavirenz	600-mg pill
nevirapine	400-mg once-daily dosing*
<b>Protease inhibitors</b>	
fosamprenavir	Prodrug of amprenavir; fewer pills
lopinavir/ritonavir	Fixed-dose combination, once-daily* or twice-daily dosing, 200/50-mg tablet
nelfinavir	625-mg pill
ritonavir	Pharmacokinetic enhancement for once-daily dosing of amprenavir, atazanavir, fosamprenavir, lopinavir*
saquinavir	Tablet formulation, 500 mg

\* Once-daily dosing is not approved by the US Food and Drug Administration.

to late 1990s, combination ART involved taking medications at least three times a day, often with food and water restrictions and high numbers of pills. These complex regimens are gradually giving way to simpler regimens involving fixed-dose combination pills, newer drugs or formulations that can be taken once daily, and the use of RTV for pharmacokinetic enhancement of other PIs (Table 2). Given these new options, many patients with stable virologic suppression on more difficult regimens can change to regimens with lower pill burdens and minimal dosing complexity, thus improving adherence and quality of life.

Investigators have studied many approaches to simplifying complex ARV regimens with the aim of improving adherence and quality of life, and thereby reducing rates of virologic failure. The most widely studied approach has been replacing a PI with NVP, EFV, or ABC in patients with full virologic suppression while taking a PI-based regimen. In two studies, adherence improved in subjects randomized to switch from a PI to EFV or to ABC compared with those who continued the PI-based regimen. In both studies, time to virologic failure was delayed in the switch

arms, suggesting that the improvement in adherence was clinically relevant. Other investigators have reported improvements in quality of life, as assessed by questionnaires, in two randomized studies in which PIs were switched to NVP or to either NVP or EFV compared with continuing the PI.

Clinicians who are contemplating changing an ARV regimen for quality-of-life considerations should keep in mind the potential for adverse effects of the new regimen. In a large, randomized study that assessed the efficacy of simplifying PI-based regimens by substitution with ABC, EFV, or NVP, approximately 50% of subjects had new adverse events, although few of those events resulted in discontinuation of the regimen. With the advent of several simpler PI regimens that include options for once-daily dosing with decreased pill burden and fewer adverse effects, clinicians may have less need for the strategy of replacing PIs merely for the purpose of simplification.

### Changing ART in patients with virologic suppression

When considering switching an ARV regimen for any of the reasons discussed above in

a patient with virologic suppression, it is critical to examine the patient's treatment history. Previous virologic failure on an NNRTI, whether or not resistance testing was performed, or documented resistance to this class of agents, is a contraindication to switching to NVP or EFV. Similarly, previous monotherapy or dual therapy with nucleoside analogues increases the risk of virologic failure when changing to ABC because of selected nucleoside resistance mutations. Of note, substituting ABC for a PI or NNRTI typically results in a triple nucleoside regimen, which has been shown to be virologically inferior to EFV-based regimens as initial therapy. Although switching a virologically suppressed patient to a triple-nucleoside regimen may differ from using such a regimen as initial treatment, a randomized simplification trial in which subjects on PIs were switched to ABC, NVP, or EFV showed a trend toward a greater rate of virologic failure in the ABC arm. Thus, drug substitution that results in a triple-nucleoside combination without additional drugs cannot be recommended for most patients.

#### Concomitant medical conditions

A patient's changing clinical status often mandates a change in ART. For example, certain antiretroviral medications are less favored in pregnancy. Efavirenz is teratogenic in animals and was linked to birth defects in several reported cases, so this agent should be substituted with NVP or an appropriate PI-based regimen in pregnant women. Caution should be used with NVP in pregnancy because it has been associated with an increased risk of fatal hepatitis in pregnant women, especially in women with higher CD4 counts; NVP generally should not be initiated in women whose CD4 count is  $>250$  cells/ $\mu$ L. The oral solution of amprenavir (APV) should not be used in pregnant women because of the high content of polyethylene glycol, and hyperbilirubinemia induced by ATV and IDV is a theoretical risk for the newborn.

Medications used to treat comorbid illnesses often interact with antiretroviral agents. A prime example is the interaction of rifampin, a first-line drug for the treatment of tuberculosis, with both NNRTIs and PIs. This interaction may be avoided by substitution of EFV for NVP, perhaps by dose adjustment of EFV, or by substitution of rifabutin for rifampin in the case of PIs.

Other important drug interactions include cholesterol-lowering "statins" with PIs, oral contraceptives with NNRTIs or PIs, and ergot derivatives with PIs. The activity of TDF, emtricitabine (FTC), and 3TC against hepatitis B has encouraged many providers to include these drugs in the ARV regimens of patients with chronic hepatitis B.

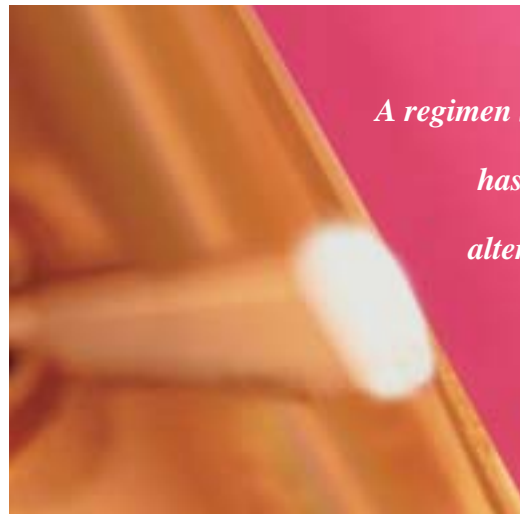
#### Suboptimal immunologic response

Patients starting ART may fail to have a significant increase in CD4 cells despite control of viral replication. Investigators from the Swiss HIV Cohort Study reported that 38% of patients with stable suppression of HIV during ART for more than five years failed to reach a CD4 count of at least 500 cells/ $\mu$ L. In some cases, the particular ARV regimen may be problematic; several studies have shown suboptimal increases,

with subcutaneous interleukin-2 versus placebo in patients taking ART. However, this study is limited to individuals who have CD4 counts  $>300$  cells/ $\mu$ L at baseline. Without additional data, the best strategy for patients with virologic suppression and suboptimal immunologic response is probably to continue their current regimens.

#### HIV-related clinical events

Clinical events such as opportunistic infections or AIDS-associated malignancies are uncommon in patients with virologic suppression during ART. The ART Cohort Collaboration, involving 13 cohort studies of patients starting a first ARV regimen, estimated the risk of an AIDS-defining illness or death within three years of starting ART. Among those patients with virologic suppression six months after



*A regimen should be changed if the patient has detectable viremia and if viable alternatives exist to ensure maximal suppression of HIV and to enhance immune reconstitution.*

or even decreases, in the CD4 count in patients treated with virologically suppressive ARV regimens that include the combination of ddI and TDF. Generally, however, the causes and clinical significance of this phenomenon are unclear, but remain a concern for both patient and provider. Treatment intensification (supplementing an existing regimen with additional antiretroviral drugs) in the setting of poor CD4 recovery has not been shown to increase the CD4 count. Interleukin-2 has been shown to increase CD4 cells, but its relationship to clinical outcomes has been lacking, and adverse effects are common. The Evaluation of Subcutaneous Proleukin in a Randomized International Trial (ESPRIT) study is a large ongoing trial that is assessing clinical endpoints (eg, death, new opportunistic infections)

starting ART, the estimate of risk ranged from 14% for those with a six-month CD4 count of  $<25$  cells/ $\mu$ L to 2% for those with a six-month CD4 count of  $>350$  cells/ $\mu$ L. Limited data are available on whether to change ART for patients who develop AIDS-defining illnesses. Certainly, a regimen should be changed if the patient has detectable viremia and if viable alternatives exist to ensure maximal suppression of HIV and to enhance immune reconstitution. Other infections such as herpes simplex virus reactivation, herpes zoster, pneumonia, and human papillomavirus-associated squamous intraepithelial lesions (eg, cervical and anal dysplasia) can occur in patients with stable virologic suppression during ART and do not indicate a need for changing ART.

Caution should be used in interpreting clinical events that occur soon after the initiation of ART (eg, within three months). During this period, patients starting ART with lower CD4 counts, especially <100 cells/ $\mu$ L, can experience an immune reconstitution syndrome consisting of unusual manifestations of opportunistic infections such as *Mycobacterium avium* complex, cytomegalovirus, and progressive multifocal leukoencephalopathy. These events result from an improved immune response to ongoing infection; they do not

explored. If adherence, toxicity, and pharmacokinetic reasons can be excluded, then virologic failure of the current regimen has been established. The initial approach to treatment failure is to carefully review the patient's antiretroviral history, including each specific drug (noting the formulation) and each previous regimen, the duration of each regimen, any adverse effects or toxicities, and the response in HIV RNA levels and CD4 counts (if known). This information is essential for assessing the likelihood of archived resistance mutations

testing in the management of antiretroviral failure, it is not clear whether the optimal test is a genotype, a phenotype, or both. Used together, a careful ART history and resistance testing yield the most complete assessment of both archived and present resistance mutations, and this strategy optimizes selection of the next ARV regimen.


### Expert advice

Evaluation and management of antiretroviral-experienced patients are complicated. Because HIV clinicians may have limited knowledge about resistance testing, expert advice is recommended. In the Havana study, resistance testing and expert advice for selecting subsequent ARV regimens were each associated with improved virologic responses. Current guidelines suggest obtaining expert advice when managing treatment-experienced patients.

### Pharmacokinetics

Drug concentrations are associated with virologic responses in treatment-experienced patients. For example, as part of the Viradapt study, PI concentrations were measured in patients taking combination regimens and were assessed as optimal or suboptimal (less than two-fold of the 95% inhibitory concentration [IC]). The reduction in HIV RNA was superior in the optimal concentration group ( $-1.3 \log_{10}$  copies/mL) compared with the suboptimal group ( $-0.4 \log_{10}$  copies/mL), and drug concentration was an independent predictor of virologic response. In the Genotypic Antiretroviral Resistance Testing (GART) study, patients taking two nucleoside analogues and a PI who experienced virologic failure were enrolled and underwent both genotypic and phenotypic resistance testing and evaluation of drug concentrations. The investigators found that a greater number of active drugs (based on resistance testing) and higher plasma drug concentrations were both associated with a better virologic response. Current treatment guidelines do not recommend routine measurement of antiretroviral drug concentrations, although controversy exists and prospective studies are in progress.

Antiretroviral drug concentrations, particularly those of the PIs, may be manipulated even without formal use of therapeutic drug monitoring. As a potent inhibitor of the hepatic cytochrome P450 system, which metabolizes PIs, RTV in low doses can enhance (or "boost") the



*Once a patient has experienced virologic failure, the cause of the failure should be explored. If adherence, toxicity, and pharmacokinetic reasons can be excluded, then virologic failure of the current regimen has been established.*

represent failure of the chosen regimen and do not mandate a change in therapy. Treatment should be directed at the opportunistic pathogen and at symptomatic relief (ie, with anti-inflammatory agents or corticosteroids) if indicated.

### Changing ART for virologic failure

The treatment guidelines of the US Department of Health and Human Services suggest criteria for assessing virologic failure: HIV RNA >400 copies/mL at 24 weeks of therapy, HIV RNA >50 copies/mL by 48 weeks of ART, or repeated detection of viremia after virologic suppression. A single elevated HIV RNA level should be confirmed with a second measurement because an isolated increase ("blip") in HIV RNA may occur in up to 40% of patients and is not associated with virologic failure. However, repeated or sustained increases in HIV RNA levels are associated with an increased risk of virologic failure.

### Cause of failure

Once a patient has experienced virologic failure, the cause of the failure should be

explored. If adherence, toxicity, and pharmacokinetic reasons can be excluded, then virologic failure of the current regimen has been established. The initial approach to treatment failure is to carefully review the patient's antiretroviral history, including each specific drug (noting the formulation) and each previous regimen, the duration of each regimen, any adverse effects or toxicities, and the response in HIV RNA levels and CD4 counts (if known). This information is essential for assessing the likelihood of archived resistance mutations

### Resistance testing

Resistance testing gives information only about the most prevalent viral strain circulating at the time the blood specimen is obtained. Therefore, resistance testing should be performed while the patient is taking the failing treatment regimen, because virus that harbors resistance mutations may not be detected readily after the selective pressure of drug is removed, but nevertheless will remain archived in tissue reservoirs. In separate studies, both genotypic testing and phenotypic testing led to significantly improved virologic responses with the subsequent ARV regimen as compared with the strategy of using the antiretroviral history alone in selecting the regimen. Although current guidelines recommend the use of resistance

Table 3. **Investigational agents 2006 (partial list)**

**Nucleoside analogue reverse transcriptase inhibitors**

alovudine (FLT, MIV-310)  
elvucitabine

**Nonnucleoside reverse transcriptase inhibitors**

capravirine  
etravirine (TMC-125)  
TMC 278

**Protease inhibitors**

brecanavir  
P-1946

**Entry inhibitors**

CD4 attachment inhibitors  
(BMS 378806; TNX-355)  
chemokine receptor inhibitors (CCR5)  
(PRO 140; Maraviroc UK-427,857)  
chemokine receptor inhibitors  
(CXCR4) (AMD070)

**Integrase inhibitors**

L-870810  
MK-0518  
GS-9137

**Maturation inhibitors**

bevirimat (PA-457)

concentrations of APV, ATV, fosamprenavir (FPV), IDV, LPV, SQV, tipranavir (TPV), and investigational PIs. Because drug resistance is relative, enhanced drug concentrations may overcome partial drug resistance. For example, in a study of 37 subjects with detectable viremia while taking a standard three-times-daily IDV-based regimen, the substitution of IDV/r resulted in a six-fold increase in IDV trough plasma concentrations, and 58% of the subjects (21 of 36) had a decrease in HIV RNA level of at least 0.5 log<sub>10</sub> copies/mL or to <50 copies/mL three weeks after the change. The authors suggested that, in this study, RTV enhancement of IDV concentrations overcame some degree of IDV resistance.

A parameter that incorporates both drug exposure and drug susceptibility of a viral isolate is the inhibitory quotient (IQ). The IQ is a ratio of drug concentration (eg, trough level of a PI in a given patient) to drug susceptibility (eg, 50% IC of the PI for that patient's viral isolate). Several retrospective studies in treatment-

experienced patients have shown that a higher IQ was associated with virologic response and was a better predictor than either drug concentration or drug resistance information alone for regimens containing APV/r, IDV/r, and LPV/r. Prospective studies that evaluate a baseline IQ and then recommend a change in PI dose (to achieve a higher concentration) are in progress.

### Selecting the next regimen

For a patient experiencing virologic failure, how is the next ARV regimen optimally designed? The initial approach was simply to use drugs that the patient had not yet taken, but in early clinical studies such as AIDS Clinical Trials Group (ACTG) studies 359 and 398, this strategy achieved maximal virologic suppression in only about 30% of patients. However, these early studies did suggest factors that were associated with better virologic responses, including a lower baseline HIV RNA level at the time of regimen change; use of two PIs, rather than one, in the next regimen; and use of a new class of agents (eg, NNRTIs). The initial studies of resistance testing also led to the recommendation that the new ARV regimen for a patient experiencing virologic failure should contain at least three active (on the basis of resistance testing) antiretroviral agents to achieve an optimal virologic response.

One study incorporated several of these factors in its design by enrolling 70 patients who had experienced failure of only one PI, had not taken NNRTIs, and had HIV RNA levels ranging from 1,000 copies/mL to 100,000 copies/mL. The subjects substituted LPV/r (at either of two randomly assigned doses) for their current PI and also added NVP (introducing a new drug class for these subjects) and at least one new nucleoside analogue. At 48 weeks in an intent-to-treat analysis, 70% of subjects had HIV RNA levels <400 copies/mL, and 60% had levels <50 copies/mL. Several factors led to the high response rates: Subjects had limited prior exposure to PIs and lower HIV RNA levels at the time of regimen change; a new drug class (NNRTI) was added; and LPV/r was used, establishing a regimen of three active drugs in many of the subjects.

Antiretroviral drugs with novel resistance patterns are currently in preclinical or clinical development. These drugs include both the current classes (nucleoside,

nucleotide, and nonnucleoside reverse transcriptase inhibitors; PIs; and the newest approved drug class, HIV entry inhibitors) and newer drug classes. The HIV entry inhibitors comprise three distinct groups classified by mechanism of action: CD4 receptor attachment inhibitors, CCR5 and CXCR4 chemokine receptor inhibitors, and fusion inhibitors. Other investigational antiretroviral classes include HIV integrase inhibitors and HIV maturation inhibitors (Table 3).

With newer antiretroviral agents in development, the best strategy to regain virologic control is to optimize the background ARV regimen based on the patient's history, resistance testing, and the addition of one or more new active agents. Recently, the TORO 1 and TORO 2 (T20 versus Optimized Regimen Only) studies incorporated these strategies in heavily treatment-experienced patients. TORO 1 was a study of 501 patients with heavy treatment experience who underwent resistance testing to help select an optimal background ARV regimen; they were randomized to add or not add the HIV entry inhibitor enfuvirtide (ENF) to their regimen. At 24 weeks, the mean change in HIV RNA level was -1.6 log<sub>10</sub> copies/mL in the ENF group versus -0.8 log<sub>10</sub> copies/mL in the control group (*P* < 0.001). The TORO 2 study showed similar results, and both studies demonstrated durable virologic responses through 96 weeks of follow-up. The TORO trials and subsequent studies of the newer PIs TPV and darunavir (TMC-114) have demonstrated the benefit of using treatment history and resistance testing to select an optimal regimen for heavily treatment-experienced patients, and the additional benefit of adding an antiretroviral agent with a novel mechanism of action.

### Conclusions

Changing an ARV regimen is common in clinical practice for patients with either suppressed virologic replication or virologic failure. Those with virologic suppression usually have changes in ART in an attempt to alleviate acute toxicities, control chronic toxicities, or improve quality of life. This strategy generally appears safe as long as relevant issues such as previous ART use are considered. The benefits of changing ART must be weighed against the possibilities of encountering new toxicities and increasing the risk of virologic failure.

The management of virologic failure among treatment-experienced patients has improved over the last several years. The establishment of clear criteria for assessing virologic failure, the development and availability of HIV resistance testing, the identification of factors leading to improved virologic responses in subsequent regimens (eg, three active drugs in the regimen), the development of new antiretroviral agents with activity against resistant virus, and the exploration of therapeutic drug monitoring have contributed to progress in the field. ■

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# AIDS at 25

Suniti Solomon

YR Gaitonde Centre for AIDS Research and Education  
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It is exactly 20 years since my team documented the first cases of HIV infection in India at the Madras Medical College in 1986. The news that six of the 90 samples we had taken from female sex workers were positive for HIV infection was received with unexpected shock and disbelief all over the country. India today, with an estimated 5.7 million infections, has more people living with HIV and AIDS than any other country in the world. The epidemic, which was initially restricted to sex workers and intravenous drug users, has now spread to the general population. The monogamous housewife is becoming the new face of the epidemic at an alarming pace.

I still remember the day we identified our first infection in a housewife. Her name was "Malar," which means "flower" in Tamil. She was thrown out of the hospital where she was going to deliver her baby after she was tested for HIV without her consent and found to be seropositive. We took her into the little 10-bed hospital we had in 1996. Unfortunately, we did not have an obstetrician. With great difficulty I managed to find one obstetrician who agreed to deliver the baby. But when the time came for Malar to deliver her baby, our obstetrician was on a "holiday," or so we were told. My nurse and I took Malar, who was in labor, from one hospital to a hospital without revealing her HIV status. This is, to date, probably the biggest obstacle in curbing the epidemic in India. HIV-infected individuals are subject to high levels of discrimination and inhuman treatment from the very people who are supposed to care for them—the medical community. Fortunately, these levels are significantly lower today than they were 20 years ago.

The YR Gaitonde Centre for AIDS Research and Education (YRGCARE), the nongovernmental organization (NGO) I founded in 1993, has networked with a group of hospitals that are willing to manage HIV-positive people who need specialized care. The last 76 babies we delivered through our network hospital are all HIV-negative. The fight to achieve this was a long and hard struggle but it was worth every moment. I still dream of the day when an HIV-positive "Malar" could walk into any hospital in India, state that she is HIV-positive, and receive the same level of care an HIV-negative "Malar" would receive. That will be the day India will finally beat the epidemic!

**Editor's Note:** This is the second of six vignettes the IAPAC Monthly will publish this year to commemorate the 25th anniversary of the first report describing a lethal new virus terrorizing the US gay community. That virus—the human immunodeficiency virus (HIV)—today affects more than 40 million men, women, and children worldwide, and in the past quarter century has claimed some 25 million lives.



## A B S T R A C T S

### AIDS

#### Cognitive-behavioral intervention to enhance adherence to antiretroviral therapy: A randomized controlled trial (CTG 578)

Wagner GJ, Kanouse DE, Golinelli D, et al for the California Collaborative Treatment Group (CCTG).

**OBJECTIVE:** We conducted a randomized, multi-site, controlled trial of a cognitive-behavioral adherence intervention for patients initiating or changing an antiretroviral (ART) regimen. **DESIGN:** A 3 x 2 factorial design was used with the primary randomization assigning patients (1:1) to one of two adherence interventions or usual care. **METHODS:** The five-session adherence interventions consisted of cognitive-behavioral and motivational components, with or without a two-week pre-treatment placebo practice trial. Intent-to-treat analysis used probability weights and regression tree analysis to account for missing data. **RESULTS:** A total of 230 patients were randomized; 199 started ART, of whom 74% completed the 48-week study. Electronic monitored adherence outcomes between the two intervention groups did not differ significantly, and were thus pooled in analyses. At week four, 82% of intervention patients had taken at least 90% of their prescribed ART doses, compared with 65% of controls ( $P < 0.01$ ); this group difference dropped to 12% at week 12 (72% versus 60%;  $P = 0.15$ ) and 11% at week 24 (66% versus 55%;  $P = 0.28$ ). Mean adherence in the intervention group was significantly higher than the control group at week 24 (89% versus 81%;  $P < 0.05$ ) only. There were no group differences with respect to HIV-1 RNA throughout the study. **CONCLUSIONS:** The effects of the cognitive-behavioral intervention on adherence were modest and transient, and no effects were observed on viral load or CD4 count. More robust effects may require a more intense intervention that combines ongoing adherence monitoring and individualized intervention "dosage" that matches the need and performance of each patient.

AIDS. 2006;20(9):1295-1302.

### Salud Pública de México

#### Hyperlipidemia and glucose intolerance in patients with HIV infection receiving antiretroviral therapy

Castro-Sansores CJ, Santos-Rivero A, Lara-Perera D, et al.

**OBJECTIVE:** To determine the prevalence of secondary effects on lipid metabolism as a result of highly active antiretroviral therapy (HAART), as well as the impact of different types of antiretroviral regimens on lipids and glucose in a group of patients in Yucatan, Mexico. **METHODS:** A cross-sectional study was conducted. A questionnaire created for this study was administered to each patient and total cholesterol, triglycerides, and fasting glucose values were determined. The presence of hyperlipidemia and alterations in glucose were determined as well as their relation to the epidemiological variables

obtained from the questionnaire. **RESULTS:** A total of 211 subjects were studied [36 (17%) of which were women and 175 (83%) men]. Ninety-two patients (44%) were found to have hyperlipidemia. Of these, 43 (20%) had hypercholesterolemia (HC) and 82 (39%) hypertriglyceridemia (HT). The presence of combined HC and HT was observed in 30 (14%) patients. Nineteen (9%) patients had alterations in glucose, six (3%) diabetes mellitus, and 13 (6%) impaired glucose tolerance. The variables associated with the presence of hyperlipidemia were: levels of lymphocyte CD4  $> 350$  cells/microL (odds ratio [OR]=2.79, confidence interval [CI]=1.08 to 7.27,  $P = 0.03$ ), male gender (OR = 3.6, CI = 1.4 to 9.12,  $P = 0.006$ ) and the use of nucleoside reverse transcriptase inhibitors (NRTIs) (OR = 3.1, CI = 1.2 to 8.1,  $P = 0.01$ ). **CONCLUSIONS:** Patients with HIV infection who receive HAART have an increased risk of presenting with hyperlipidemia. In this group of patients, the presence of hyperlipidemia and impaired glucose tolerance was significant. Unlike what has been indicated in most published reports, the alterations of lipids were associated more frequently with NRTI use, from which it is concluded that the pathogeny of these alterations is not unique, that it is probable that concurrent effects exist between different antiretroviral drug families, and that other host factors are involved in the pathogenic mechanism of these alterations.

Salud Publica Mex. 2006;48(3):193-199.

### Journal of Acquired Immune Deficiency Syndromes

#### Predictors for lower quality of life in the HAART era among HIV-infected men

Liu C, Johnson L, Ostrow D, et al.

**BACKGROUND:** In the era of highly active antiretroviral therapy (HAART), maximizing health-related quality of life (QOL) has become a high priority of long-term management of HIV-infected individuals. Modifiable determinants of lower QOL should be identified for interventions specifically targeted to HAART-using individuals to improve their QOL. **OBJECTIVE:** To identify the predictors for lower QOL among HAART-using study participants in the Multicenter AIDS Cohort Study (MACS), a longitudinal study of HIV infection among homosexual and bisexual men in four cities. **METHODS:** In the MACS, 636 HAART-using subjects had QOL data before HAART initiation and at least two consecutive QOL measurements after HAART initiation through visit 40 (April 2004). Variables of sociodemographics, individual risk behaviors, social support, biological markers, HIV-related medication use and clinical outcome indicators preceding the study outcomes, the physical health summary score, and the mental health summary score derived from the standard SF-36 QOL form, were assessed as possible predictors using random-effects mixed models. **RESULTS:** Quality of life before HAART initiation was a strong predictor of QOL subsequent to HAART initiation. Older age, lower socioeconomic status, less male sexual partners, no alcohol drinking, and more advanced HIV disease stage were significant predictors

for a lower physical health summary score. In addition, more outpatient visits, depression, amprenavir use, antiretroviral drug interruption, recreational drug use, and less social support were significantly associated with a lower mental health summary score. **DISCUSSION:** Many predictors of lower QOL are alterable risk factors that can be effectively targeted for interventions to maximize patients' QOL. With appropriate treatment and management of HIV disease and depression, clinicians can help improve the QOL of their patients. Through modification of individual risk behaviors, HIV-infected individuals can enhance their own QOL with support from clinicians and the community. In addition, active social support can also be an effective way to improve the mental health of infected persons.

J Acquir Immune Defic Syndr. 2006;42(4):470-477.

### HIV Medicine

#### The impact of malnutrition on survival and the CD4 count response in HIV-infected patients starting antiretroviral therapy

Paton NI, Sangeetha S, Earnest A, Bellamy R.

**BACKGROUND:** The impact that malnutrition at the time of starting antiretroviral therapy (ART) has on survival and the CD4 count response is not known. **METHODS:** A retrospective cohort study was carried out of patients attending the national HIV referral center in Singapore who had a CD4 count less than 250 cells/ $\mu$ L and a measurement of body weight performed at the time of starting ART. Demographic and clinical variables were extracted from an existing database. Body mass index (BMI) was calculated from the weight in kilograms divided by the square of the height in meters. Moderate to severe malnutrition was defined as BMI less than 17 kg/m<sup>2</sup>. Intent-to-treat Cox models were used to determine the predictors of survival. **RESULTS:** A total of 394 patients were included in the analysis, of whom 79 died during a median study follow-up of 2.4 years. Moderate to severe malnutrition was present in 16% of patients at the time of starting ART, and was found to be a significant independent predictor of death (hazard ratio [HR] 2.19, 95% confidence interval [CI] 1.29 to 3.73,  $P = 0.004$  for those with BMI  $< 17$  compared with those with BMI  $> 18.5$ ) as were stage of disease (HR 2.47, 95% CI 1.20 to 5.07,  $P = 0.014$  for those who were at stage C compared with those at stage A) and the type of ART (HR 0.50, 95% CI 0.27 to 0.93,  $P = 0.03$  for highly active antiretroviral therapy [HAART] compared with non-HAART treatment). Malnutrition did not impair the magnitude of the increase in CD4 count at six or 12 months. **CONCLUSIONS:** Malnutrition at the time of starting ART was significantly associated with decreased survival, but the effect appeared not to be mediated by impaired immune reconstitution. Given the increasing access to ART in developing countries and the high frequency of HIV-associated wasting, studies of nutritional therapy as an adjunct to the initiation of HAART are urgently needed.

HIV Medicine. 2006;7(5):323-330.

## Hepatic steatosis and ddI, d4T use

Edwin J. Bernard

**P**atients coinfecting with HIV and hepatitis C virus (HCV) should use didanosine (ddI) and stavudine (d4T) with caution, according to an editorial commenting on the results of the largest study so far to report on factors associated with hepatic steatosis in HIV/HCV-coinfecting patients.<sup>1</sup> The study, to be published in the August 1, 2006, issue of *Clinical Infectious Diseases*, found that 69% of coinfecting patients had steatosis, and that the use of ddI or d4T increased the risk of steatosis almost five-fold.

Hepatic steatosis is frequently a consequence of obesity, high alcohol consumption, and metabolic syndrome. It affects almost one third of the United States population, although it is usually a benign condition. However, previous studies in HCV-monoinfecting patients have shown that hepatic steatosis can result in accelerated progression of liver disease. Due to the body-shape changes and metabolic abnormalities that occur in HIV-associated lipodystrophy syndrome, patients who are coinfecting with HIV and HCV may be at increased risk of developing steatosis.

Researchers from the Johns Hopkins University School of Medicine last year found that hepatic steatosis was present in 40% of a cohort of 112 coinfecting patients. They also found that the risk of hepatic steatosis was greatest in those receiving treatment with d4T.

To further evaluate the prevalence of hepatic steatosis and its relationship to liver fibrosis, investigators from four New England HIV clinics undertook a retrospective chart review of all HIV/HCV-coinfecting patients who had undergone

liver biopsy between January 2000 and December 2003.

A total of 260 patients were evaluated, of whom 193 were eligible. Exclusion criteria included hepatitis B virus (HBV) coinfection, history of steatosis-associated drug use, and cirrhosis. A further 10 patients had inadequate biopsy specimens, resulting in a study population of 183 (median age 43 years; 79% male; 50% white, 27% Hispanic, 24% African-American; 83% injection drug use history, with a median 23 years HCV infection). The majority (60%) were infected with HCV genotype 1, 8% had genotype 2, 16% had genotype 3, and 4% had genotype 4. At the time of the liver biopsy, 55 patients (30%) were not taking antiretroviral therapy.

The investigators found steatosis in 69% of the biopsy specimens (minimal 31%, mild 27%, moderate 18%, severe 1%). They explain the higher prevalence of steatosis in their cohort compared to the Johns Hopkins cohort as due to a higher proportion of non-African Americans in their cohort. Previous studies have found that African-American patients with HCV monoinfection are at lower risk of steatosis than are white patients.

In univariate analysis, presence of steatosis was associated with greater weight ( $P=0.011$ ) and an undetectable viral load ( $P=0.019$ ). There was a trend toward significance with a higher body mass index, and HCV genotype 3 infection and glucose and triglyceride levels were found to be of borderline significance.

The greatest odds of steatosis, however, were associated with the use of any antiretroviral drug (odds ratio [OR], 1.99;  $P=0.043$ ) and any nucleoside analogue (OR, 2.14;  $P=0.024$ ). When types of nucleoside analogues were divided into dideoxynucleoside analogues (the D drugs, or ddI and d4T) and non-dideoxynucleoside analogues, the risk of

steatosis increased with the D drugs (OR, 2.63 versus 1.78;  $P=0.05$ ). Use of ddI and d4T together increased the odds even further (OR, 3.38; 95% confidence interval [CI], 0.67 to 17.07).

Adding to the weight of the association with the nucleoside analogue class was the finding that although only 21 patients were taking triple nucleoside analogue therapy, 19 had evidence of hepatic steatosis (OR, 7.13; 95% CI, 1.51 to 33.57).

In multivariate analysis, only nucleoside analogue use was significantly associated with hepatic steatosis. Although the use of nucleoside analogues that were not D drugs was still associated with an increased risk of steatosis compared with no nucleoside analogue use, there was a wide confidence interval, making it of borderline significance. (OR, 2.65; 95% CI, 0.95 to 7.41;  $P=0.062$ ).

However, when the investigators compared D-drug use with no nucleoside analogue use, the increased risk was almost five-fold (OR, 4.63; 95% CI, 1.55 to 13.8;  $P=0.006$ ). "This clinical observation is supported by *in vitro* and *in vivo* data that suggest that [ddI] and [d4T] have significant mitochondrial toxicity that exceeds that of other drugs," the investigators concluded.

Nevertheless, they note that the limitations of their cross-sectional study design should be taken into consideration, and add that "any association between steatosis and dideoxynucleoside use will need to be confirmed by longitudinal prospective studies. The impact of prior or cumulative NRTI exposure could not be evaluated in our study and was likely important."

The investigators also found that steatosis was associated with stage of liver fibrosis (univariate OR, 1.37; 95% CI, 1.03 to 1.81;  $P=0.029$ ). "These data are of vital clinical importance," they write, "because fibrosis progression occurs faster in HIV/HCV-coinfecting patients than in patients with HCV infection alone."

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They conclude by suggesting that “administration of antiretroviral [drugs] with little or no mitochondrial toxicity (eg, tenofovir [TDF], lamivudine [3TC], emtricitabine [FTC], or abacavir [ABC]) may be preferred over other NRTIs whenever possible.” This recommendation is echoed and amplified in an accompanying editorial by Marija Zeremski and Andrew Talal (Weill Medical College, Cornell University, New York).<sup>2</sup>

They write that although “an association between antiretroviral therapy and steatosis in HIV/HCV-coinfected patients has not been a universal finding among the studies that have been performed to date, a connection between antiretroviral therapy and steatosis is becoming increasingly apparent.”

Although the mechanism of NRTI-induced steatosis “remains obscure,” they add, “mitochondrial toxicity is likely responsible for [the] harmful effects” and D drugs are “the antiretroviral therapy agents with the strongest capacity to deplete mtDNA through the interaction with DNA polymerase- $\gamma$ .” They suggest that in addition to the direct effects of NRTIs on the development of steatosis, the indirect effects of the thymidine analogue d4T may also play a role, due to its association with lipotrophy, insulin resistance, and hyperlipidemia.

They point out that Barbara McGovern (Tufts University) and colleagues observed microvesicular steatosis (or small fat droplets of fatty infiltration) in the vast majority of cases (19% pure microvesicular; 50% mixed microvesicular and macrovesicular). “Because both microvesicular steatosis and use of NRTIs are implicated in mitochondrial toxicity, these observations support the role of NRTIs in the development of hepatic steatosis,” they argue.

They conclude by saying that “in the clinical treatment of HIV/HCV-coinfected patients, and especially for those with steatosis, the D drugs should be used cautiously.” ■

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## Questions?

Contact Aimee Clark at +(312) 795-4934 or [aclark@iapac.org](mailto:aclark@iapac.org).

## Co-Hosts:

International Association of Physicians in AIDS Care *and* European AIDS Clinical Society





**[ DECADE OF HAART ]  
HISTORICAL PERSPECTIVES  
AND FUTURE DIRECTIONS**

**September 25-26, 2006 — San Francisco**

**On the decade anniversary of HAART, the International Association of Physicians in AIDS Care (IAPAC) is convening an historic meeting to review our collective progress, discuss obstacles faced and overcome, lessons learned, and challenges that lie ahead. Registration is limited. Visit [www.iapac.org](http://www.iapac.org) to view the meeting program and to register online!**

**Co-Chairs**



John G. Bartlett



Joep MA Lange

**Featured Speakers\***



Samuel Bozzette



David A. Cooper



Martin Delaney



Anthony Fauci



José M. Gatell



Brian Gazzard



Elly Katabira



Christine Katlama



Jens D. Lundgren



John W. Mellors



Julio SG Montaner



Graeme Moyle



Paul Palumbo



John Phair



Praphan Phanuphak



Mark Wainberg

\*Visit [www.iapac.org](http://www.iapac.org) to view the complete faculty roster.



This activity is jointly sponsored by the University of Medicine & Dentistry of New Jersey (UMDNJ) and International Association of Physicians in AIDS Care (IAPAC), and has been approved for 18.0 AMA PRA Category 1 Credits™.





## IN THE LIFE



### Carlos del Rio

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

This month, *IAPAC Monthly* is proud to feature Carlos del Rio, Professor of Medicine (Infectious Diseases) and Vice Chair for Grady Affairs in the Department of Medicine of Emory University; Director for Clinical Sciences and International Research for the Emory Center for AIDS Research; and Director of the Emory AIDS International Training and Research Program at Grady Memorial Hospital in Atlanta.

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

Every day you may make progress. Every step may be fruitful. Yet there will stretch out before you an ever-lengthening, ever-ascending, ever-improving path. You know you will never get to the end of the journey. But this, far from discouraging, only adds to the joy and glory of the climb. — Sir Winston Churchill

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

I like to read novels, especially mystery novels and history books. I also love opera.

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

I would live in Paris.

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

My real life heroes are Jonas A. (“Jack”) Shulman and Paul Farmer.

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

I most identify with Sir William Osler.

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

My favorite author is Juan Rulfo; my favorite painter is Vincent van Gogh; and my favorite composer is Ludwig van Beethoven.

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

I would choose to live in the Renaissance.

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

A pilot.

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

The advances that have led to improvements in health are the major achievements; for example, the discovery of penicillin and the microscope, and increased understanding of human anatomy. The major failures of humanity are clearly the lack of understanding of diversity and of the importance of tolerance. Most wars have been senseless and are the products of greed, need for power, or the need to get rid of someone who is “different.”

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

I have great confidence, maybe a little too much, in the human race and the intelligence of men. I hope that we will eventually be able to work together, to help those in greater need and who are not as fortunate, and to eliminate the differences that divide us. ■



## SAY ANYTHING

*e*

### **It's the one true way you're going to know your status. You can't detect it by looking in the mirror.**

*Peggy Rivera, HIV Education and Program Coordinator for Planned Parenthood, in a June 28, 2006, Newsday article about the unveiling of Planned Parenthood's new 27-foot van in conjunction with National HIV Testing Day. The van will be used to travel to locations such as shopping malls and beaches, and will also concentrate on areas with high minority populations, given the increased risk of HIV infections among minorities. Planned Parenthood will offer counseling from adults and teenagers, and quick HIV testing using the OraSure method, in which results can be available in 20 minutes.*

*e*

### **Getting money out of even the richest governments in the world is not an easy task.**

*Jon Liden, Communication Director for the Global Fund to Fight AIDS, Tuberculosis, and Malaria (Global Fund), in a June 29, 2006, Reuters report about a Global Fund paper that states that the funding agency needs to acquire nearly US\$1 billion to meet its current commitments. Although the Global Fund says that it can demonstrate the effectiveness of the interventions it has funded, it is still struggling to meet its financial obligations. Brian Brink, an alternate board member of the Global Fund and Chief Medical Officer at Anglo American, the South African mining firm, stated that he believed that large corporations should be solicited for funds.*

*e*

### **We need to achieve a critical mass in order to make a difference. And not only do we need to reach this critical mass, but we need to do that very quickly, within the next three to five years.**

*Guillaume Le Hegarat, Task Force Coordinator for the UN Office on Drugs and Crime, in a July 5, 2006, Agence France-Presse report about the AIDS epidemic in Asia. Gary Lewis, the South Asia Representative, stated that since the epidemic in some Asian countries, such as Bangladesh, Malaysia, Nepal, and Vietnam is currently contained within high-risk groups, such as injection drug users, there is a narrow "window of opportunity" which may allow countries "to contain the spread of [HIV] into the general population." Le Hegarat stated: "Unless we are able to reach at least [50%] to 80% of the drug user population with these comprehensive services we will have saved lives, but we will not have made a difference in containing and reversing the HIV epidemic." Current programs reach less than 5% of injection drug users in these countries.*

*e*

### **Everyone would like to see more patients on treatment... In this country, a lot of credit goes to the activists.**

*Bill Gates, Microsoft Chair and Co-Chair of the Bill & Melinda Gates Foundation, in a July 11, 2006, article in the Johannesburg Business Day, speaking of the AIDS epidemic in South Africa. Though Gates suggested that the lack of progress against the epidemic has been frustrating, his wife, Melinda Gates, did mention that the country's reduction in mother-to-child HIV transmission was a positive factor. Gates planned to meet with Deputy President Phumzile Mlambo-Ncguka and with President Thabo Mbeki, to discuss issues including health topics. "Any ideas we have about the way things can improve we'll share—when a government wants to do something we're there to help," Gates said.*

*e*

### **This is like signing a death warrant for the remaining people who are in need of the drugs.**

*Mary Manyasa, Board Member of the National AIDS Commission of Malawi, in a July 11, 2006, article in the Malawi Nation about a new national organization of women living with HIV/AIDS that was formed at a two-day women's conference in Lilongwe. The meeting included discussions about access to care, lack of counseling for patients about antiretroviral drug side effects, and prevention of mother-to-child HIV transmission. Conference participants called on government and nongovernmental organizations to make every effort to ensure an uninterrupted supply of antiretroviral drugs and to train health workers to adequately educate patients in their use. Of the nation's 170,000 HIV-positive patients, only 45,000 are on antiretroviral therapy.*

*e*

### **The way it is being taught lacks the reverence, the refinement that the subject matter demands.**

*Jo Imbong, Legal Officer of the Catholic Bishops Conference of the Philippines, in a July 12, 2006, article in the Deutsche Presse-Agentur about the educational module entitled "Adolescent Sexual Health," which was beginning to be released to high schools in the Philippines. Education officials have already pulled the educational modules from schools "for further communications among stakeholders." The module will be edited before being re-released, and the section that discusses safe sex will be rewritten, according to Lolita Andrada, the module's editor and the Director of the Bureau of Secondary Education. Surveys have shown that the 15 to 24 age group has experienced an increased prevalence of pre-marital sex, induced abortion, and high-risk sexual activities.*

## WHY DOES ANASTACIA WEAR THE BRACELET?

She wears it to raise desperately needed funds for HIV/AIDS care services, education and vaccine development. Over half a million people have chosen to wear The Bracelet. What about you? Available at: The Body Shop; Kenneth Cole; Virgin Megastore; Ben Bridge Jewelers and other fine retailers. Or visit us at [WWW.UNTIL.ORG](http://WWW.UNTIL.ORG) or call 1-800-88-UNTIL to order. 

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