


IAPAC

MONTHLY

The background of the cover is a photograph of the Grote of Sint-Jacobskerk in Amsterdam, a Gothic church with two prominent brick towers and a central clock tower. The church is built of red brick with white stone accents. The towers have conical roofs. In the foreground, there is a wooden walkway with a black metal railing. The sky is a pale, overcast blue.

**HIV, HBV, and
HCV in Europe:
Border crossings
and buried bombs**

386



HIV, HBV, and HCV in Europe: Border crossings and buried bombs

Mark Mascolini

Although HIV has so far wreaked its worst havoc on Africa, Europe is struggling with the devastation HIV/AIDS has wrought on that more fortunate continent, which is driven not only by HIV transmission among native Europeans, but also by migration from other parts of the world. The IAPAC European Sessions 2005 limned the imprint of this nomadic retrovirus on a Europe that never wholly defused its own AIDS epidemic.

DEPARTMENTS

REPORT FROM THE PRESIDENT	379
TOP 10	385
ABSTRACTS	404
FOCUS ON HEPATITIS	406
IN THE LIFE	410
SAY ANYTHING	411



INTERNATIONAL ASSOCIATION OF PHYSICIANS IN AIDS CARE Headquarters Office Chicago, Illinois, USA

PRESIDENT/CEO José M. Zuniga
VICE PRESIDENT/EC Brian M. Hujdich

INTERNATIONAL ASSOCIATION OF PHYSICIANS IN AIDS CARE African Regional Office Johannesburg, South Africa

EXECUTIVE DIRECTOR Vacant
DEPUTY DIRECTOR Jaz Hughes

IAPAC MONTHLY

EDITOR-IN-CHIEF José M. Zuniga
MANAGING EDITOR Lisa McKamy
CREATIVE/DESIGN DIRECTOR Holly J. Emanuelson
ADVERTISING DIRECTOR Cathy Córdova
WRITER-AT-LARGE Mark Mascolini
CONTRIBUTING WRITERS
Liz Highleyman, Carrie Scharrer

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

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

Nonprofit postage paid at Kenosha, Wisconsin, and at additional mailing sites. Address all editorial, business, and production correspondence to *IAPAC Monthly*, 33 N. LaSalle, Suite 1700, Chicago, IL 60602-2601 USA. Those submitting manuscripts, photographs, artwork or other materials to *IAPAC Monthly* for consideration should not send originals unless specifically requested to do so by *IAPAC Monthly* in writing.

To order reprints (minimum order required: 250 copies) or request permission to publish an *IAPAC Monthly* article, please call (312) 795-4991 or e-mail monthly@iapac.org.

IAPAC Monthly © 2005, International Association of Physicians in AIDS Care. Reproduction of any part without written permission is prohibited. The information contained in *IAPAC Monthly* shall not, in whole or in part, be redistributed, reproduced, or entered into a computer without permission.

Accountability

José M. Zuniga

I have written this “Report from the President” column since 1999, and I always pray that I may, in the last issue of the year, report good news about the state of our world with respect to HIV/AIDS. Sadly, while I may report about good deeds performed by individuals and institutions in the trenches of our collective battle against this insidious disease, it is always punctuated by sobering yearend statistics generated by the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Organization (WHO). Regretfully, this year is no exception, as the UNAIDS/WHO “AIDS Epidemic Update: December 2005”¹ tells us that:

- the estimated total number of HIV-positive people worldwide has reached its highest level ever, increasing from 39.4 million in 2004 to 40.3 million in 2005;
- nearly five million new HIV cases occurred this year and about 3.1 million people died of AIDS-related illnesses in 2005, bringing the total number of deaths from HIV disease to more than 25 million since 1981; and
- of those who died this year, 500,000 were children and 2.4 million lived in sub-Saharan Africa.

Without question, 2005 has been a year of progress. There has been an unprecedented outpouring of money, significant advances in treatment, an accumulated understanding of how to deliver prevention as well as treatment and care services, along with growing political commitment to stop the spread of HIV disease. Yet, more people will have become infected with HIV and died from AIDS in 2005 than in any previous year.

This year’s World AIDS Day theme is

“Stop AIDS: Keep the Promise.” But just who is accountable when promises are not kept regarding treatment for HIV-positive patients and prevention of further spread of the disease? And for what and how are they accountable? Merriam-Webster’s dictionary defines accountability as the “obligation or willingness to accept responsibility or to account for one’s actions.” Simon Zadek, Chief Executive of the non-profit watchdog group AccountAbility, reminds us that, “Accountability is the stable core of civilized communities... The darker, sadder pockets of our past and present are often terrifying fragments of a world without accountability.”²

Rarely have individuals or institutions been willing to accept responsibility for missed opportunities to slow the spread of the AIDS pandemic and to ameliorate the suffering of those living with and affected by HIV disease. The WHO, on the other hand, has recently accepted responsibility for failing to have “moved quickly enough” to meet its target of placing 3 million people in the developing world on antiretroviral therapy by 2005. For so doing, the WHO’s self-awareness (sorely lacking in some bureaucracies) should be applauded.

That said, as I read a November 28, 2005, media report entitled, “WHO Sorry for Missing AIDS Target,”³ I was reminded of a fable used to great effect at a lecture I attended not long ago around the problem with utilizing overly simplistic metrics when dealing with complex, urgent, and sometimes long-standing public health emergencies.

Once upon a time in Wonderland, a prestigious national commission declared that the state of health care in that country was abominable. There were so many unhealthy people walking around that “the commission declared the nation “at risk” and called for sweeping reforms.

In response, a major hospital decided to measure doctors’ performance by patient outcomes and to tie decisions about patient treatment and dismissals to those measures.

The most widely used instrument for assessing health in Wonderland was a simple tool that produced a single score with proven reliability. That instrument, called a thermometer, had the added advantage of being easy to administer and record. No one had to spend a great deal of time trying to decipher doctors’ illegible handwriting or soliciting their subjective opinions about patient health. When doctors discovered that they would be held accountable for how many of their patients had thermometer scores above normal, some complained that it was not a comprehensive measure of health. Their complaints were dismissed as defensive and self-serving. The hospital administrators, to ensure that their efforts would not be subverted, then specified that subjective assessments would no longer be used in making decisions. Furthermore, medicines or treatment tools not directly related to thermometer scores would no longer be purchased.

After a year of operating under this new system, more patients were dismissed from the hospital with temperatures at or below normal. Aspirin prescriptions had skyrocketed and the use of other treatments had substantially declined. Some doctors also left the hospital arguing obtusely that their obligations to patients required them to pay attention to other things than to scores on the thermometer. Since thermometer scores were the only measure that could be used to ascertain patient health there was no way to argue whether they were right or wrong.

Some years later during the centennial Wonderland census, the census takers discovered that the population had declined dramatically and mortality rates increased.

As people in Wonderland were wont to do, they shook their heads and sighed, "Curiouser and curiouser..." They next appointed another commission.

The real work of battling HIV/AIDS is more difficult and complex than just setting targets and tracking statistics. As with any combat in the arena of infectious diseases, and HIV disease in particular, this global battle is about working and strategizing together as well as using our collective resources to employ the best, most efficient, and effective weapons with an ultimate aim of achieving the optimal outcome for the maximum number of people.

In every country I have visited this year, the myriad individuals and institutions needed to scale up access to antiretroviral therapy have made great strides in implementation of scale-up programs, even with human and organizational infrastructure challenges that have often threatened to cripple their efforts. Nonetheless, they are concerned about and frustrated by the lack of overall leadership required to answer a very basic question: "What next?"

There are numerous next steps around which we should be focusing our collective attention, including but not limited to:

- Increasing the number of people who are aware of their HIV status (which remains a major barrier to antiretroviral therapy scale-up when in some countries less than 10% of the general population is aware of its HIV status);
- Reassessing data analysis to confirm the estimated number of patients who are clinically eligible for antiretroviral therapy (as with any campaign, statistics evolve and may force course corrections);
- Augmenting the existing antiretroviral armamentarium to allow for more choices in first- and second-line as well as salvage antiretroviral regimens (this was an explicit goal when the WHO decided to recommend a limited menu of regimen options under the "public health emergency" rubric);
- Pushing brand-name and generic antiretroviral drug manufacturers, as well as diagnostic technology companies, to continue to reduce their prices and, as important, fulfill their responsibilities as corporate citizens by awarding grants in support of capacity-building activities (this is especially true of generic manufacturers,

many of which exhibit robust business acumen but anemic philanthropic leanings);

- Re-examining the way in which issues and logistics associated with providing effective antiretroviral therapy have been managed (what worked last year may not necessarily work next year);
- Tackling the thorny issue of which cadres of health care professionals may prescribe antiretroviral therapy and under what conditions (especially as the physician-to-patient ratio in many African countries continues its downward slide); and
- Integrating the work of traditional and biomedical health practitioners (in some countries, such as Botswana, there are approximately 100 times more traditional healers than physicians).

As important, these next steps must be better integrated—beyond "lip service"—into myriad other human development efforts ongoing worldwide. A renewed sense of accountability requires we consider the interconnected, trans-boundary nature of today's issues, impacts, and influences. Other endemic diseases, poverty, sanitation, and civil rights (eg, disability) can no longer be adequately addressed in isolation, as separate causes.

Now that the WHO and, by extension, all WHO partner-institutions, are assuming responsibility for not having done more to achieve the "3 by 5" goal, we must move forward and cease to dwell on the

"what ifs." Now that we have collectively affirmed that we are accountable not only to boards or governments, but also to the 40.3 million people living with HIV/AIDS, 6 million of whom are clinically eligible for antiretroviral therapy, we must accept responsibility for the next series of goals that will pave the way toward universal access to antiretroviral therapy.

Zadek argues that, "the increased interconnectedness of both accountability and solutions demands new ways of organizing, mobilizing, and learning. There is a need to join up the dots: to raise awareness of... how we may most effectively mobilize to shape societal outcomes."³ This argument is in line with the attitude we must all take as we enter the post-"3 by 5" era. Let us catch our breath, regroup, and address the challenges before us with renewed dedication and vigor. ■

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

Reference

1. Joint United Nations Programme on HIV/AIDS (UNAIDS), World Health Organization (WHO). *AIDS Epidemic Update: December 2005*. Geneva, Switzerland: UNAIDS; 2005.
2. Zadek, S. Reinventing Accountability for the 21st Century. September 12, 2005. http://www.opendemocracy.net/globalization-accountability/peer_to_peer_2823.jsp (Accessed December 7, 2005).
3. Reuters. WHO sorry for missing AIDS target. November 28, 2005. http://www.cnn.com/2005/HEALTH/conditions/11/28/who.aids.reut/?section=cnn_world (Accessed December 9, 2005).



Your connection
to AIDS thought
leaders: www.iapac.org

2005

TOP 10

10 Most Important Developments in HIV Medicine



1. Tipranavir, a protease inhibitor (PI), was approved by the US Food and Drug Administration (FDA).
2. The Joint United Nations Programme on AIDS (UNAIDS) issued the report *AIDS in Africa: Three Scenarios to 2025*, which included three case studies outlining possible outcomes of the AIDS epidemic in Africa over the next 20 years, based on different policy decisions made by the United Nations (UN) and by individual African governments.
3. The FDA issued its first tentative approval of a generic antiretroviral drug regimen (lamivudine [3TC]/zidovudine [ZDV] and nevirapine [NVP]) manufactured by a non-US company, Aspen Pharmacare of South Africa. Since the President's Emergency Plan for AIDS Relief (PEPFAR) rules would not allow funding for any antiretroviral drugs that did not have FDA approval, all PEPFAR-funded programs had been required to purchase more costly brand-name drugs.
4. The US Institute of Medicine (IOM) published the results of its extensive data review on the use of NVP for prevention of mother-to-child transmission (PMTCT) of HIV. The review confirmed that NVP was safe and effective for use in PMTCT, despite widespread reporting questioning the use of NVP in pregnant women.
5. Brazil rejected US\$40 million from PEPFAR because the United States required a declaration condemning prostitution.
6. The US patent expired for the nucleoside reverse transcriptase inhibitor (NRTI) ZDV. Four generic versions of ZDV were approved for sale within the United States.
7. The World Health Organization (WHO) released international treatment figures showing that the "3 by 5" initiative would most likely not achieve its goal of placing three million HIV-positive people in the developing world on antiretroviral therapy by the end of 2005. When the report was released in June 2005, the initiative had succeeded in placing 970,000 people on antiretroviral therapy, 1.6 million short of target.
8. Chinese officials announced that as many as 10 million Chinese may be infected with HIV by 2010, if effective prevention efforts are not immediately instituted. With appropriate funding and effective programs, Dai Zhicheng, Director of the Chinese Health Ministry's Committee of AIDS Experts, suggested that the number of HIV cases in that time period could be kept to below 1.5 million.
9. The *AIDS Epidemic Update: December 2005*, published by UNAIDS and the WHO, reported that the estimated number of people living with HIV/AIDS worldwide has reached its highest point yet: 40.3 million, up from 39.4 million in 2004. Nearly 5 million new cases of HIV and 3.1 million deaths due to HIV/AIDS occurred in 2005. Of the HIV-related deaths, 500,000 occurred in children, and 2.4 million occurred in sub-Saharan Africa.
10. Nelson Mandela announced that his eldest son, Makgatho, had died of AIDS at the age of 54.



References

1. US Food and Drug Administration, Center for Drug Evaluation and Research. A catalog of FDA approved drug products. <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm> (Accessed November 16, 2005).
2. New report presents three scenarios for AIDS in Africa by 2025. Scenarios look at how AIDS could shape Africa's future [press release]. Geneva, Switzerland: Joint United Nations Programme on AIDS, March 4, 2005.
3. US Food and Drug Administration. FDA grants tentative approval to generic AIDS drug regimen for potential purchase under the President's Emergency Plan for AIDS Relief. January 25, 2005. *FDA News*. <http://www.fda.gov/bbs/topics/news/2005/NEW01152.html> (Accessed November 16, 2005).
4. National Institute of Allergy and Infectious Disease. Questions and answers—the HIVNET 012 study and the safety and effectiveness of nevirapine in preventing mother-to-infant transmission of HIV. April 7, 2005. <http://www3.niaid.nih.gov/news/newsreleases/2005/hivnet012qa.htm> (Accessed November 16, 2005).
5. Boseley S, Goldenburg S. Brazil spurns US terms for AIDS help. *The Guardian*, May 4, 2005.
6. Kaisernetwork.org. FDA approves four generic forms of zidovudine for US sales after Retrovir's patent expires. September 21, 2005. http://www.kaisernetwork.org/daily_reports/rep_index.cfm?DR_ID=32663 (Accessed November 16, 2005).
7. Joint United Nations Programme on AIDS, World Health Organization. Progress on Global Access to HIV Antiretroviral Therapy. Geneva, Switzerland: World Health Organization, June 29, 2005.
8. Reuters. China could top 10 million HIV cases by 2010: State media projection echoes grim UN warning. October 24, 2005. http://today.reuters.com/news/newsArticle.aspx?type=healthNews&storyID=2005-10-24T150714Z_01_MOR420709_RTRUKOC_0_US-AIDS-CHINA.xml (Accessed November 16, 2005).
9. Joint United Nations Programme on HIV/AIDS (UNAIDS), World Health Organization (WHO). *AIDS Epidemic Update: December 2005*. Geneva, Switzerland: Joint United Nations Programme on HIV/AIDS; 2005.
10. BBC News. Mandela's eldest son dies of AIDS. January 6, 2005. <http://news.bbc.co.uk/1/hi/world/africa/4151159.stm> (Accessed November 16, 2005).



**HIV, HBV, and
HCV in Europe:
Border crossings
and buried bombs**

Mark Mascolini



Why did tiny Holland—tiny, resource-poor Holland—become a world power in the 17th century? How could a brand-new nation with only 200,000 citizens outmuscle

rivalrous world powers to dominate the trade wars while fostering peace, prosperity, and a cultural efflorescence at home?

Tolerance is one answer, proposed Joep MA Lange (Academic Medical Center, Amsterdam) in opening the International Association of Physicians in AIDS Care (IAPAC) European Sessions 2005. The plucky Dutch not only welcomed Sephardic Jews driven from Spain, they declined to kill Catholics and homosexuals, gave women unheard-of license, and revered children.¹

Not a bad recipe for success, it seems, but a rare one. Today many Dutch and more than a few of their European neighbors “take the opposite view” on immigrants, Lange noted. “But of course they have no sense of history.”

HIV has only a short history, but one already rife with anomie as parents, teachers, soldiers, and doctors die; as farms fail; workers quit; and barely nubile girls get HIV and pass it on. This tragedy may play to the last bloody act only in Africa—unless India or Russia, for example, teeters past the brink. But the sub-Saharan epidemic, and those in the Caribbean and beyond, already spark incendiary inroads through Western Europe and any other place AIDS-harried migrants can reach, legally or not.

In three insightful talks, IAPAC Sessions limned the imprint of this nomadic retrovirus on a Europe that never wholly defused its own epidemic. The balance of this two-day parlay also evinced a sure sense of history, invoking what’s known to envision what’s not about antiretroviral strategies, anti-retroviral side effects, and hepatitis virus coinfection.

Table 1. **Migrant populations in European Union countries**

	Migrants (%)	Migrants (n)	Estimated undocumented migrants (n)
Germany	9	7,366,000	2,000,000
Belgium	9	864,600	300,000
Austria	9	739,800	—
France	7	3,971,000	2,000,000
Sweden	6	532,000	—
Netherlands	4.4	662,400	600,000
United Kingdom	3.4	2,121,000	250,000
Italy	2.9	1,690,000	500,000
Spain	1.3	719,600	500,000



If you want to place blame for Europe’s cyclic struggle with contagion, blame civilization, contended Mark Nelson (Chelsea and Westminster Hospital, London). In antediluvian days our foot-loose forebears—living in small tribes that seldom crossed paths—worried about hunger and scavenging hyenas, but not about infectious disease. That changed for good, but perhaps for worse, when the sapient species set up cities, kept pets, bred animals, and built armies.

When 200,000 people holed up in Athens to avoid Sparta’s sword in 430 BCE, Nelson noted, the plague holed up too and killed a third of them. Roman legions returning from Syria in 166 CE brought buboes and pox back with them, slaughtering four million or more. Four years later “barbarian boils” came to China with northern marauders. Many died and the Han dynasty crumbled. Talk about anomie.

Columbus slew thousands, not with Spanish steel, but with flu, measles, small-pox, tuberculosis (TB), and gonorrhea. Perhaps not coincidentally, syphilis showed up in Europe at the same time, touching off fierce rounds of epidemiologic finger pointing. The French called it the Neapolitan disease, the Neapolitans called

it the German disease, the Germans called it the French disease, the Poles called it the German disease. And so on.

Migration mediates infection

If everyone stayed put in their place of birth, nascent epidemics—confined to their epicenters—would stay put too. But *Homo* has long been a migratory beast, probably since attaining *erectus* status. Except for the few who stayed forever in East Africa, we are all migrants—a point worth considering when xenophobic fustian tempts.

Perhaps 185 million migrants now roam the world, Nelson reported, 60 to 65 million seeking work, another 60 million following them, and another 15 million fleeing persecutors. One in 35 people—3% of the globe’s populace—can be called an international migrant. Nearly half are women. In Europe alone, added session chair Alberto Matteelli (Spedali Civili University Hospital, Brescia, Italy), 20 million people—5.2% of the population—live outside their country of citizenship. Nearly one in 10 residents of Austria, Belgium, and Germany are immigrants (Table 1).

Migrants from countries with runaway HIV epidemics account for two thirds of heterosexually acquired HIV infections in Western Europe.² In 2002, about three quarters of Britain’s heterosexually

acquired infections involved people from Africa, and in Germany most new HIV diagnoses are made in people born elsewhere.² More than 80% of Sweden's HIV infections happened outside Sweden, and nearly three quarters of Belgium's heterosexually acquired HIV infections involve migrants.²

The disproportionate HIV burden among migrants in Europe shows no sign of stabilizing. Today's 185 million international migrants will swell to 230 million by 2050, Nelson said. And research hints that HIV will not stay circumscribed in migrants' ethnic circles. Migrant men in The Netherlands, for example, reported that nearly half of their sexual liaisons involved partners of other ethnicities.³

If migrants from the epidemic's vortex do not bring HIV with them, they run a high risk of picking up the retrovirus in their new home or of getting a late diagnosis or poor treatment. Nelson and Matteelli spelled out several factors behind these trends:

- Vulnerability to sexual exploitation and harassment
- High HIV risk when visiting their native country
- Poor access to health care, including prevention services, counseling, and testing
- Work in an isolated environment (separated from families, communities, norms)
- Lack of legal protection

Late HIV diagnosis threatens not only the infected person, but also that person's sexual partners.

The risk of picking up HIV during visits home may be particularly acute for immigrants socially isolated in their adopted country. Among Africans living in London, Matteelli noted, 40% of men and 20% of women found a new sex partner when traveling abroad.⁴ Still unpublished research found that 47% of men and 11% of women who visit friends and relatives in Suriname or the Antilles after settling in Amsterdam meet a new sexual mate on their trip. HIV gene mapping shows that half of the HIV-infected from these lands now living in The Netherlands got infected in their homeland.⁵

HIV is hardly the only infectious disease immigrants bring to Europe or get once they settle there. In England and Wales, Nelson reported, migrants accounted for 73.1% of TB cases in 1999. That proportion

Table 2. People in Europe who need antiretroviral therapy

Region	People with HIV, 2004	People needing antiretroviral therapy, 2004	People getting antiretroviral therapy, 2004	People needing antiretroviral therapy, 2010
West	674,000	330,000	267,000	340,000 to 380,000
Center	49,000	13,500	9,300	12,000 to 20,000
East	1,222,000	105,000	3,900	230,000 to 600,000
Total	1,945,000	448,500	280,200	582,000 to 1,000,000

inched inexorably upward to 79.9% in 2000, 80.8% in 2001, 90.7% in 2002, and 90.9% in 2003. Foreign-born residents make up more than half of the TB case load in six Western European countries—Britain, Denmark, Luxembourg, The Netherlands, Norway, and Sweden—and about one third in Belgium, France, and Germany.

All these trends add up to one safe wager, according to the World Health Organization (WHO): The number of people needing antiretrovirals in Europe will climb sharply over the next five years (Table 2).

Caring for HIV-infected migrants

Migration surely does not completely explain recrudescing HIV incidence in Western Europe. But some see immigrants as an easy target of nationwide prevention tactics. Close the tap and cut the flow, this paralogism purports.

But it's not that simple, said Nelson and others at IAPAC Sessions. First, pre-departure HIV testing wafts an unethical fetor when done without consent, confidentiality, or counseling. Second, it doesn't work. People who have HIV or think they might will not roll up their sleeve for an HIV test when they want to get into another country. They'll try to get there illegally. If they succeed and if they have HIV, they will spread the virus.

Instead Nelson proposed strategies for educating migrant populations about sexually transmitted diseases and for managing HIV infection in those already infected. Education should have five goals, he suggested:

- Promoting HIV testing
- Offering sex education
- Promoting sexual health
- Destigmatizing HIV disease
- Destigmatizing routes of HIV infection

Nelson thinks family-focused clinics stand the best chance of stopping HIV among immigrants for three reasons:

Families have complex health needs including pediatric, adult, and pregnancy concerns. Family health problems go well beyond the skills of any one health worker. Families comprise discrete units that lend themselves to an all-embracing health care approach.

Besides offering the talents of many specialists, family clinics have some practical pluses for HIV-infected immigrants and their kin, including manageable appointments on the same day, and fewer appointments with less travel time and expense. The ideal HIV family clinic, Nelson proposed, would offer the following amenities:

- Regular meetings with a multidisciplinary team
- Weekly clinics with a pediatrician and adult disease specialist
- Shared clinics in the same room (although that may be impossible)
- All blood work done before the family visit
- Child space in the clinic

Nelson urged colleagues treating migrant populations to think carefully about the antiretrovirals they prescribe. Too often, he cautioned, clinics adopt a standard first regimen then prescribe it to all comers. At London's Chelsea and Westminster Hospital, for example, efavirenz (EFV) plus tenofovir (TDF) and emtricitabine (FTC) emerged as the preferred blend. But is it the right regimen for black Africans?

Africans often carry mutations in CYP2B, the enzyme that drives EFV metabolism. Those genetic wrinkles can boost EFV levels and spur early, intolerable side effects. Renal worries lead the short list of TDF toxicities, and Africans generally suffer more kidney disease than other groups. Emtricitabine has also proved a highly tolerable drug. But one of its side effects—hyperpigmentation—can leave blacks with an unwanted badge of HIV infection.

Plugging Holland's HIV dike

Frank de Wolf (HIV Monitoring Foundation, Amsterdam) has a solution to uncontrolled immigration of people with HIV that is more sublime and, on its face, simpler than Nelson's family clinic plan: Treat everyone who needs treatment before they leave home.

Though hardly cant, de Wolf's modest proposal will take decades to effect, and he realizes that as much as anyone. But HIV can't be kept out of Europe, he noted, with the handy finger-in-dike feat of Hans Brinker, the Dutch boy of (American) legend who saved Holland's sea-menaced polders by plugging a leak with a plump digit. North Sea swells would have whelmed Brinker—and Holland—if the bustling Dutch had not ringed lowlands with high dams in the first place. Years of planning and hard-headed mud molding kept Holland dry, not an expedient finger. It will take as much work to stop HIV.

And of course defusing immigration by treating everyone in their native land will do nothing about migrants already settled in other countries. But The Netherlands has long since figured out what to do about them: Treat everyone who needs treatment after they migrate.

De Wolf figures about 80% of people who need antiretrovirals in The Netherlands—including immigrants—get antiretrovirals. As a result HIV-related morbidity skidded from 15.4 cases per 100 person-years in 1996 to 1.43 per 100 person-years in 2004. Over the same years mortality among people with HIV plunged from 4.62 to 1.55 deaths per 100 person-years. A small mortality spurt marred this record in 2005, de Wolf noted, but so far this trickle lacks statistical significance.

These rates come from a cohort of 8,439 people—957 of them with AIDS—who deluged statisticians with 40,000 years of follow-up data. About 80% of treated people reached a viral load below 500 copies/mL in their first 48 weeks of therapy, and about 75% of them started with a load topping 100,000 copies/mL. Among people whose RNA tally exceeds 500 copies/mL, the average load lies 1.5 log copies/mL below pretreatment values after five years of follow-up. A lower nationwide viral load, de Wolf suggested, will slow the epidemic by cutting transmission risk.

As Netherlandish viral loads stay below sea level, CD4 counts continue to surge. Most CD4 subgroups in de Wolf's cohort

kept adding T cells through 240 weeks of follow-up. Only people who began treatment with more than 600 cells/mm³ hit a CD4 high-water mark—at a normal 800 cells/mm³.

Despite the clear impact of antiretrovirals, de Wolf warned, several factors could spur a rising tide of new HIV cases in The Netherlands:

- A growing contingent of relatively healthy people with HIV means a wider pool of potentially transmitted virus.
- As soon as HIV-infected people start feeling well, they start having sex—sometimes risky sex.
- A spurt in sexually transmitted diseases in The Netherlands reflects a national surge in condom-free intercourse.
- HIV will continue to arrive from abroad (Table 3).

Indeed The Netherlands began to see a rebound in HIV incidence after 2000. From 1996 through 2000, incidence had dropped steadily.

Today women and girls born outside The Netherlands account for 53.3% of the country's female HIV cases. In contrast, 65.7% of men and boys with HIV are Dutch. Among immigrants with HIV, women and girls outnumber men and boys in groups from sub-Saharan Africa, Ghana, and Thailand (Table 4). Males far outnumber females in HIV-infected cohorts from the Antilles and Suriname.

HIV diagnoses per year climbed precipitously from 1996 through 2005 for sub-Saharan Africans and Ethiopians living in The Netherlands. Diagnosis rates also rose, though less dramatically, among people from the Antilles, Ghana, Latin America, Suriname, and Thailand.

Immigrant groups get treated for HIV in The Netherlands as consistently as the native Dutch, de Wolf reported, and they respond as well on most measures. The exceptions involve slower CD4 gains among people from the Antilles, sub-Saharan Africa, and Suriname. Differences in adherence to therapy may contribute to those tardy responses, but that's a guess because de Wolf does not have adherence data on the cohort.

Co-Chair Joep Lange observed that some African populations have lower CD4 counts than Europeans regardless of HIV infection. Without more complete baseline numbers, he suggested, cross-ethnic CD4

Table 3. **Nonnative HIV cases in Europe through 2002**

Source	Percent with AIDS	Percent of new HIV diagnoses
Sub-Saharan Africa	13.3	18.6
Latin America, Caribbean	3.0	1.5
Another European country	2.2	3.4

gain comparisons remain tenuous.

Virologic responses in immigrant groups mirror responses in European natives: 65% to 85% of immigrants have RNA readings under 500 copies/mL 20 to 40 months after starting antiretrovirals. And non-Dutch groups stick with their first regimen as long as Dutch natives. But people from the Antilles, Ghana, and Suriname have faster rebounds than the Dutch.

Antiretroviral-treated immigrants do not differ from the Dutch in overall survival or, in an analysis adjusted for CD4 count, in AIDS-free survival.

Perhaps the most astonishing statistic from de Wolf's portfolio is the proportion of immigrants still free of AIDS symptoms when they get diagnosed with HIV: 70% to 80%. Those rates do not differ from the proportion of symptom-free HIV diagnoses among the Dutch.

British statisticians tell a different story, Nelson noted: 90% of immigrants in the United Kingdom have HIV symptoms when they get their first positive test. Indeed, most of them get tested *because* of their symptoms. Why the stark difference? Lange thinks two factors may explain early HIV diagnoses among immigrants in The Netherlands: Many groups have strong social networks that foster HIV education programs. And anyone coming to The Netherlands knows an HIV diagnosis and low CD4 count entitle them to free treatment.

Immigrants with HIV in Italy

Before 1994, native Italians accounted for more than 95% of HIV diagnoses in Italy and immigrants for fewer than 5%. The ratio has narrowed steadily ever since, Matteelli reported. According to the Italian National AIDS Registry, nonnatives first made up more than 10% of HIV diagnoses in 1998 and 1999. By 2004 they accounted for nearly 20%.

In Modena, a city southwest of Venice, 2.3% of new HIV diagnoses involved

immigrants in 1985. That rate rocketed to 32.1% in 2000. In Brescia, Matteelli's base in Lombardy, the Institute of Infectious and Tropical Diseases attributed 5% of incident HIV cases to foreign-born people in 1986 and 21% to nonnatives in 2003. At Italian sexually transmitted disease clinics, HIV prevalence drifted downward from about 7% in 1991 to 4% in 1996. From that point through 1999 it quadrupled.

A 2005 study of 465 illegal immigrants in Brescia confirmed active and often omniform sex lives. Among the 70% who reported sexual intercourse within the past year, 52% had a steady partner, 48% entertained casual partners, and 7% paid partners. In those three groups, 93% who paid for sex regularly used condoms. But only 51% with casual partners and 21% with regular partners routinely wore condoms.

As in Britain a whopping majority of HIV-diagnosed immigrants in Brescia already have symptoms when their test comes back positive (Table 5). In comparison only about one third of Italians have symptoms when diagnosed. A comparison of 1,904 native Italians and 215 immigrants found that 27.7% of Italians had a CD4 count under 200 cells/mm³ at diagnosis compared with 36.3% of immigrants. Late diagnosis, Matteelli reminded colleagues, qualifies as a transmission "risk behavior."

Once HIV-infected immigrants in Brescia start antiretrovirals, adherence can be iffy. Matteelli reported that more than half of the immigrant group interrupted therapy within 12 months of starting. Female gender, older age, and African origin boosted the risk of suspended therapy. Matteelli believes health workers caring for immigrants must work harder to explain the need for treatment, its impact on infection, and its potential side effects. At the same time they should discourage behavior that favors HIV transmission.

Matteelli echoed Lange's concern over an increasingly xenophobic mindset in Europe and elsewhere. He closed his talk with a comment made by Judith Kumin, the United Nations High Commissioner for Refugees regional representative in Belgium.

"Politicians across the globe have won elections by fueling nationalistic and xenophobic sentiments," Kumin said at the 2005 Caritas Europa 4th Migration Forum, "blaming a variety of ills—insecurity, unemployment, housing shortages, overcrowded classrooms—on immigrants,

Table 4. HIV rates in immigrants to The Netherlands and Dutch natives

	<i>n</i>	Percent of total	Percent male	Percent female
Sub-Saharan Africa	1,234	14.2	40.7	59.3
Ethiopia	125	1.5	57.6	42.4
Ghana	148	1.8	37.2	62.8
Thailand	125	1.5	33.6	66.4
Latin America	241	2.8	79.3	20.7
Suriname	373	4.3	67.0	33.0
Antilles	266	3.1	71.8	28.2
Turkey	54	0.7	88.9	11.1
Netherlands	5,025	57.8	88.4	11.6
Other	1,104	12.8	82.4	17.6

including refugees and asylum seekers." As with syphilis, of course, many blame foreigners for HIV.



BURIED BOMBS

Sessions organizers had to do some fast schedule shuffling on the meeting's first day because three speakers got stuck on their way to Amsterdam. The sticking point was a 500-pound World War II bomb discovered during digs at Schiphol Airport, which—along with a painterly fog—closed runways and snarled air traffic across the continent. The Royal Air Force dropped this particular payload, missing Germany by a wide mark. By the time authorities lugged away the widow-maker, airlines had cancelled two speakers' flights and delayed a third by half a day.

Bombs buried at international airports make headlines while making hash of schedules. But within 24 hours CNN's news cycle disgorges such fortuities and cybervillagers sit back to await the next tsunami, earthquake, or war. Something with at least a week's worth of round-the-clock video feeds.

Bombs latent in cryptic pathogens (and in their treatment) get less media play if they are not new (SARS), sanguinary (Ebola), or vaguely apocalyptic (bird flu). *Truly* apocalyptic infections—AIDS, TB, malaria—rarely breach the news cycle these days unless they seemingly threaten media capitals ("Super AIDS Bug in New York!"), perhaps because the yearly death of three million noncelebrities fast becomes tired copy, perhaps because the visuals lack drama. (Soweto clinics? Lesotho huts? Delhi hovels?)

Yet epidemic HIV surely hides countless buried bombs. How bad will it get in

China, Papua New Guinea, or Russia? How will cross-clade superinfection⁶ and recombination prod viral evolution? And—more immediately, if less spectacularly—what still-covert side effects lie in wait for the many fated to gulp antiretrovirals for 20, 30, 40 years? Though prescient experts such as Charles Flexner (Johns Hopkins University, Baltimore) registered early fears over the toxic potential of drugs studied fast in small groups, none could foresee the noxious fat fluxes attendant on therapy, and no one supposed heart attacks would kill middle-aged men with double-digit viral loads.

Opening the IAPAC Sessions review of antiretroviral side effects, Peter Reiss (Academic Medical Center, Amsterdam) warned that more toxic surprises may lurk "below the surface" surveyed in HIV's ample literature. Why do people with well-controlled replication complain of fatigue, flaccid sex drives, and borborygmic bowels? Probably not because they're whiners. Something must be going on.

Side effects session chair Nathan Clumeck (St. Pierre University Hospital, Brussels) reminded colleagues that it took years to pin down the toxic threats of stavudine (d4T). Even after several groups sounded the alarm in 1999, reasonable exculpatory arguments persisted more than a few months. In retrospect one easily forgets that d4T/lamivudine (3TC) became the anointed backbone because it seemed both potent *and* safe. That transient blindness fostered generic blends of the two nucleoside reverse transcriptase inhibitors (NRTIs) that now abound in poor countries struggling to slow HIV.

Is there a rich-poor double standard in d4T use, Clumeck asked Reiss. Yes, Reiss answered, though a choice between d4T/3TC regimens and no regimen remains an easy

Table 5. Time from HIV diagnosis to first HIV symptoms in Brescia

	Symptoms at diagnosis		Symptoms ≥ 6 months after diagnosis	
	n	Percent	n	Percent
Italian	6,418	35.9	11,457	64.1
Foreign	1,450	70.1	618	29.9

pick. Clinicians in AIDS-ridden countries do see lipoatrophy in people taking d4T, he added. Whether stigmatizing fat loss proves as frequent or bad there as it became in Europe—or worse—no one knows.

When Clumeck asked if zidovudine (AZT) should be “blacklisted” for its peripheral fat-depleting penchant, Reiss proposed that clinicians “can’t afford the luxury” of avoiding AZT. Although AZT thins subcutaneous fat more slowly than d4T, Reiss believes it does so inexorably. Yet research on AZT-induced lipoatrophy remains inconsistent. Analysis of the US Nutrition for Healthy Living Cohort correlated AZT with a 4.9% loss of arm and leg fat—and 10.8% loss of trunk fat—for every year of use.⁷ In this cohort, d4T looked blameless. But AIDS Clinical Trials Group (ACTG) investigators charted a small 64-week limb fat *gain* in people randomized to AZT/3TC (+4%) rather than didanosine (ddI)/d4T (-16.8%) in ACTG 384.⁸

Lange wondered whether only d4T and AZT, the thymidine analogs, deserve all the blame for lipoatrophy. Zalcitabine (ddC), he reminded colleagues, fell from favor because of its bleak toxicity record. Lange added that both ddC and ddI ranked poorly in early mitochondrial toxicity studies. But more recent work focused on fat cells found significantly less mitochondrial DNA depletion with abacavir (ABC) and nonthymidine analogs than with d4T or AZT.⁹

What other bombs lie buried? Lange noted that the general lack of systemic toxicities with enfuvirtide (ENF) does not mean such side effects will not crop up in people who take the injectable fusion inhibitor long enough. And despite TDF’s still glistening lipoatrophy record, Nelson warned that could change with longer use. What about long-term kidney toxicity with TDF? A year and a half of follow-up in the Johns Hopkins cohort did show significantly worse creatinine clearance with TDF than with other reverse transcriptase inhibitors,¹⁰ Nelson added. But long-term follow-up in the TDF-versus-d4T trial¹¹

and in Nelson’s Chelsea and Westminster cohort¹² did not flush out a latent risk of kidney toxicity with TDF.

HIV, lipids, and MI risk

Reiss assured IAPAC Sessions attendees that for people taking antiretrovirals “myocardial infarction [MI] is not a major health crisis—yet.” Although the latest results from the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study confirm a nearly linear jump in MI risk with each added year of antiretroviral therapy,¹³ “in absolute terms” the MI threat “remains a relatively minor problem” that does not add up to an antitherapeutic argument.

So should one bother taming unruly lipids? Yes, Reiss argued. The D:A:D study also found that out-of-line lipids modulate antiretroviral therapy’s impact on MI risk.¹³ A statistical model reckoning the cumulative yearly impact of therapy showed that each extra year of treatment boosted MI risk 17% (relative risk [RR] 1.17, 95% confidence interval [CI] 1.11 to 1.24). But in a model factoring in lipids and other variables, each extra year of therapy raised the risk 10% (RR 1.10, 95% CI 1.01 to 1.19, $P=0.03$). So high lipids must play some role in people with HIV. In the same analysis each log₂ mmol/L higher triglyceride reading jacked the MI risk 64% (RR 1.64, 95% CI 0.98 to 2.74, $P=0.06$), and each mmol/L higher total cholesterol value swelled the risk 15% (RR 1.15, 95% CI 1.06 to 1.25, $P=0.001$).

At the same time clinicians can’t ignore other tractable MI risk factors that abound in the D:A:D cohort and in most groups taking antiretrovirals—smoking (52% of the D:A:D cohort), hypertension (8.5%), body mass index above 30 kg/m² (3.5%), and diabetes (2.5%). Smoking drove up MI risk substantially more than each year of antiretrovirals in a model including both variables.

Stop the PI or start a lipid lowerer?

What’s the best way to rein in baneful lipids? Until a few months ago, Reiss preferred

switching people taking a protease inhibitor (PI) to a nonnucleoside reverse transcriptase inhibitor (NNRTI). But he started questioning that stance when Italian clinicians reported that mean total cholesterol dropped more over one year in people randomized to take pravastatin (-46%) or bezafibrate (-38%) than in those switched to nevirapine (NVP) (-27%) or EFV (-10%).¹⁴ People assigned to a lipid-lowerer also did better than the switch groups in easing low-density lipoprotein (LDL) cholesterol and triglycerides. Differences between the antilipid and switch groups were statistically significant.

Reiss noted, though, that these researchers signed up only about 30 people per treatment arm, so confirming work would be welcome. And on the other side of the equation, some evidence suggests lipid busters lack punch in people with HIV. In a 16-week trial that randomized people with triglycerides at or above 3 mmol/L to diet plus gemfibrozil or diet alone, gemfibrozil pushed triglycerides below 2 mmol/L in only one of 17 men.¹⁵ Gemfibrozil did not alter cholesterol levels or insulin resistance. And a 48-week ACTG study found that pravastatin and fenofibrate—first alone, then together—rarely brought boggled lipids back to National Cholesterol Education Program (NCEP) targets.¹⁶ But the combined drugs proved tolerable and did shove lipid readings in the right direction.

Trading a PI for an NNRTI—if it does not threaten viral control—has one clear advantage over prescribing antilipidemics: It often simplifies therapy rather than complicating it. And at this point few doubt that PIs drive lipids askew more than other antiretrovirals. Further D:A:D data show consistently higher triglycerides, LDL cholesterol, and total-to-high-density lipoprotein (HDL) cholesterol ratio in people taking one or two PIs than in treatment-naive people or those taking two NRTIs plus an NNRTI.¹⁷ And two PIs proved consistently worse than one PI. A similar analysis by Dutch and D:A:D researchers documented worse triglyceride, total cholesterol, and LDL cholesterol profiles in people taking a first-line PI than in those taking a first-line NNRTI.¹⁸

But Reiss cautioned that lipid differences between people starting treatment with PIs versus NNRTIs are subtle. In a Swiss cohort of 1,065 people primarily starting lopinavir (LPV)/ritonavir (RTV), indinavir (IDV)/RTV, nelfinavir (NFV), or EFV,

non-HDL cholesterol rose regardless of regimen.¹⁹ Triglycerides tended to climb with PIs (especially RTV-boosted PIs), to drop slightly with NVP, and to rise slightly with EFV. High-density lipoprotein cholesterol improved with NNRTI regimens. Among the most-prescribed PIs, NFV stirred lipids less than LPV/RTV or IDV/RTV.

The lipid lines that may separate EFV from NVP can be blurry, but the D:A:D cohort analysis¹⁷ echoes the Swiss HIV Cohort Study review¹⁹ in charting a higher prevalence of top-heavy triglycerides (2.3 mmol/L or more) with EFV than with NVP. In the D:A:D survey people taking EFV and NVP had nearly equivalent rates of low HDL cholesterol (at or under 0.9 mmol/L), and similar proportions in each group had a total-to-HDL cholesterol ratio at or above 6.5 mmol/L.

How did lipid quotients compare in treatment-naïve people randomized to EFV or NVP in the 2NN study? An analysis comparing 417 people who took NVP with 289 who took EFV for 48 weeks declared NVP the clear lipid winner²⁰ (Table 6). Nevirapine's handsomer lipid profile held true—or even improved—after statistical adjustment for changes in viral load and CD4 count. That finding, the 2NN team explained, indicates “an effect of the drugs on lipids over and above that which may be explained by suppression of HIV-1 infection.”

Finally, Reiss advised, clinicians must consider a person's fat abnormalities when deciding whether to swap a PI for NVP, EFV, or ABC. Those trades have a harder time righting unbalanced lipids in people with moderate to severe lipoatrophy or moderate to severe lipohypertrophy, results of a randomized trial suggest.²¹

Lipids look for pretreatment baseline

Reiss counseled colleagues to remember that HIV itself—before the body ever experiences antiretrovirals—upsets lipids. And the longer infection lasts, the farther those lipids stray. When treatment begins, at least some lipid flux reflects a *healthy* redialing to baseline lipid settings. People with more advanced disease when they start antiretrovirals spin the reset dial farther than people with milder HIV infection. Clinicians should invoke this rule of thumb when comparing lipid seesaws across trials because study populations often differ in disease progression.

Table 6. **Lipid comparison at 48 weeks in the 2NN study²⁰**

	Nevirapine (n = 417)	Efavirenz (n = 289)	P
HDL cholesterol	+42.5%	+33.7%	0.036
Total cholesterol	+26.9%	+31.1%	0.073
Total-to-HDL cholesterol ratio	-4.1%	+5.9%	<0.001
Non-HDL cholesterol	+24.7%	+33.6%	0.007
LDL cholesterol	+35.0%	+40.0%	0.378
Triglycerides	+20.1%	+49.0%	<0.001

Multicenter AIDS Cohort Study (MACS) researchers showed that total cholesterol (-30 mg/dL [-0.78 mmol/L]), HDL cholesterol (-12 mg/dL [-0.31 mmol/L]), and LDL cholesterol (-22 mg/dL [-0.57 mmol/L]) all dropped from pre-HIV values when men become infected.²² After treatment began the MACS team traced big rebounds in total cholesterol (+50 mg/dL [1.30 mmol/L]) and LDL cholesterol (+21 mg/dL [0.54 mmol/L]). Mean HDL cholesterol levels languished below baseline in the early months of antiretroviral therapy.

Whether interpreting trials or treating patients, clinicians must also consider two other factors when clocking lipid changes, Reiss added. First, treatment-induced body fat swings affect lipid levels. Research ties both lipohypertrophy and lipoatrophy to surging lipids.²³ Second, the NRTI in the regimen can drive lipids. The randomized comparison of TDF with d4T (plus 3TC and EFV) in treatment-naïve people found significantly higher triglycerides, total cholesterol, and directly measured LDL cholesterol after 144 weeks in the d4T group ($P < 0.001$ for all comparisons).²³ But people taking TDF gained significantly more “good” HDL cholesterol ($P = 0.003$).

Rating cardiovascular risk

Bundling advice from expert panels, Reiss advanced the following scheme for rating and tracking heart disease risk in people with HIV:

- Estimate overall cardiovascular risk
 - Gauge fasting measures before starting or switching antiretrovirals, then every three to six months afterwards, and finally once a year in people on a stable regimen

- Measure total, HDL, and LDL cholesterol, triglycerides, and glucose
- Give an oral glucose tolerance test at least to people at risk for type 2 diabetes or with severe lipodystrophy

- Assess *all* other modifiable cardiovascular risk factors, including:
 - Blood pressure
 - Smoking

This advice rests on algorithms devised for the general population, not for people with HIV infection. Ongoing mega-cohort work like the D:A:D study may eventually yield HIV-specific guidelines. But until then, Reiss assured colleagues, it looks like general models work for people with HIV. Applying the Framingham Heart Study risk equation to MI incidence in the D:A:D cohort plotted a near overlap between predicted and observed heart attacks through four years of potent antiretroviral therapy.²⁴ But Reiss warned that values derived from models such as Framingham may *underestimate* risk in people with HIV.

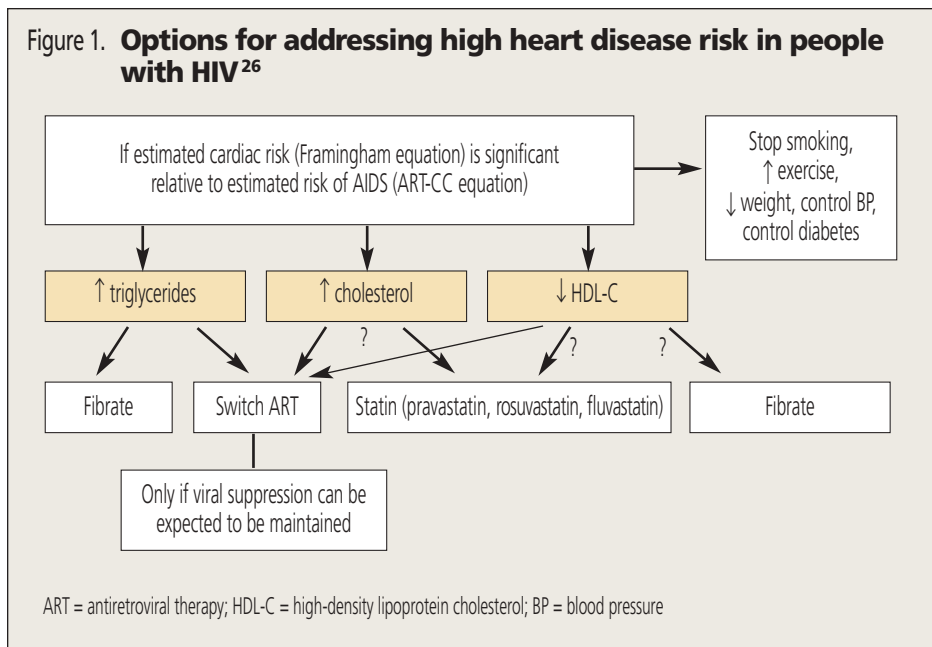
What should clinicians do if the heart disease risk looks high relative to the risk of AIDS (as defined by the ART Cohort Collaboration²⁵)? Reiss offered a management tree adapted from advice by Steven Grinspoon (Harvard Medical School, Boston) and Andrew Carr (St. Vincent's Hospital, Sydney)²⁶ (Figure 1).

Groping for lipodystrophy predictors

Understanding predictors—and possible remedies—for HIV-related body fat changes remains a tall order, conceded Esteban Martínez (Hospital Clinic, Barcelona). And that's not just because lipodystrophy is a new and motley syndrome. Environmental factors, genetics, HIV, and antiretrovirals all make their contribution (Figure 2). And scant data so far shed light on environmental or genetic variables. On top of that, unlike bad lipids, body fat abnormalities have no standard definition.

But research continues to etch out slow advances in understanding subcutaneous fat loss (lipoatrophy) and central fat buildups (lipohypertrophy). On the genetic front, for example, Simon Mallal (Centre for Clinical Immunology and Biomedical Statistics, Perth, Australia) and colleagues linked a gene flip in tumor necrosis factor- α (TNF- α) to a higher risk of lipoatrophy.²⁷

Figure 1. **Options for addressing high heart disease risk in people with HIV**²⁶



Though HIV clinicians aren't set to start probing for single nucleotide polymorphisms, they already routinely measure triglycerides, and pretreatment levels of those lipids also predicted lipoatrophy in people taking extended- or immediate-release d4T.²⁸ Pretreatment fasting triglycerides at or below 200 mg/dL independently predicted a lower risk of lipoatrophy after more than 100 weeks of follow-up, as did age under 40 years and d4T therapy. But this 877-person analysis could not tie a familiar array of variables to lipoatrophy—gender, race, baseline body mass index, fasting glucose, waist circumference, baseline CD4 count, and viral load.

A growing mound of evidence implicates HIV infection itself in lipoatrophy. A US study comparing HIV-infected people with a general population cohort clearly showed that men with HIV—though still naive to antiretrovirals—have a higher risk of fat atrophy than men in the non-HIV group ($P < 0.01$).²⁹ The HIV Outpatient Study (HOPS), which tracks people in several US HIV clinics, charted a growing incidence of lipoatrophy with each lower bracket of CD4 count nadirs.³⁰ Comparing 384 gay men with HIV and 314 without HIV, MACS researchers confirmed the rarity of lipoatrophy in uninfected people.³¹ While 20% of infected men taking antiretrovirals had subcutaneous fat wasting, only 1% of the HIV-uninfected group did.

Gender differences in lipodystrophy risk?

Several studies determined that women have a higher risk of lipodystrophy,

depending on how one defines the syndrome. If one uses the proposed case definition of a mixed syndrome³² and applies it to people in the Gilead Sciences trial of TDF versus d4T, women had a 3.71 times higher risk of lipodystrophy than men (95% CI 1.67 to 8.25) in a multivariate analysis ($P = 0.001$).³³

Two Italian studies found a higher risk of fat accumulation or mixed lipodystrophy in women than in men.^{34,35} But men and women had an equivalent risk of lipoatrophy,³⁴ which proved the predominant fat abnormality in men.³⁵ One of these studies also suggested that fat changes happen faster in women than in men with HIV.

What might explain this higher fat abnormality risk in women? One possibility may be that at least some nucleosides—including AZT—reach significantly higher triphosphate levels in women's cells than in men's.³⁶ As a result, Martínez suggested, some antiretrovirals may be more potent, and more toxic, in women. But that cannot be the whole explanation, he proposed, because research shows women also endure more side effects from other drugs, such as psychotropics. And if women specifically metabolize NRTIs better than men, one would expect more lipoatrophy in women, not more fat buildups.

Scarce remedies for lipodystrophy

Reversing lipodystrophy remains a mammoth challenge—especially when many still disagree on lipodystrophy's definition. In notes prepared for the IAPAC Sessions, Brian Gazzard (Chelsea and Westminster Hospital, London) squarely raised the most perplexing

question: Does lipohypertrophy exist?

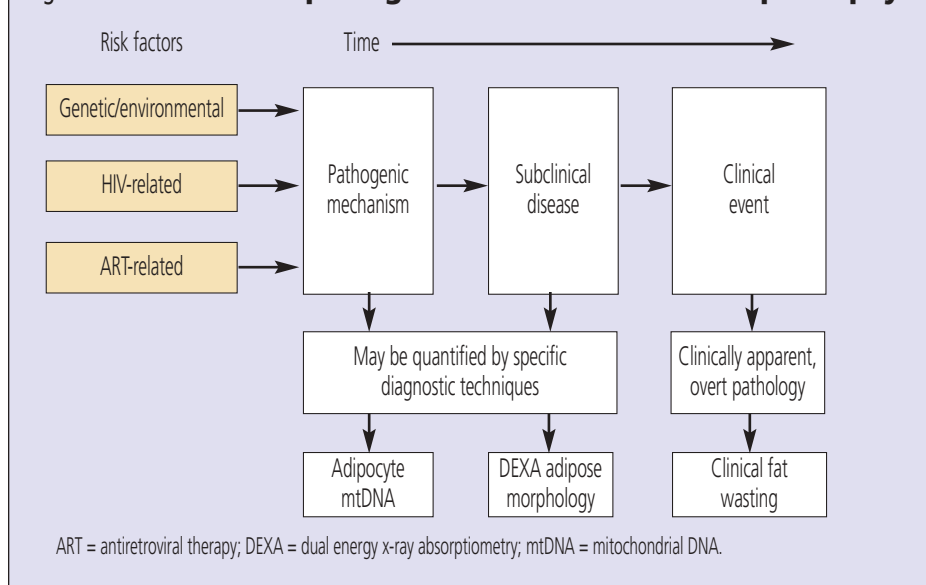
Lots of people with suddenly large bellies have one answer, but the Study of Fat Redistribution and Metabolic Change in HIV Infection (FRAM) famously posited data to the contrary. As sessions attendees pondered Gazzard's challenge, the FRAM team published their long-mulled findings.²⁹ Defining lipohypertrophy as agreement between a participant's report of fat buildup and physical exam evidence, FRAM found that men with HIV have a lower rate of central lipohypertrophy (40.2%) than do men of the same age from the general population (55.9%) ($P < 0.001$). FRAM data on women remain unpublished.

Nonetheless, Nelson (who presented Gazzard's talk because of the bomb-induced flight delay) concurred with legions of lipohypertrophic people that the problem does exist. But most agree it probably has nothing to do with lipoatrophy. Among HIV-infected FRAM men, hypertrophy did not correlate positively with atrophy (odds ratio [OR] 0.71, 95% CI 0.47 to 1.06, $P = 0.10$). In other words, HIV-infected men with lipohypertrophy were no more likely to have atrophy than were HIV-infected men without hypertrophy.

And stopping a PI does not make excess central fat melt away, as Martínez³⁷ and several other research groups showed in switching people from a PI to an NNRTI or ABC. But, Martínez explained, these findings do not vindicate PIs from a role in fat atrophy. The ACTG 384 statisticians proved that when they compared 64-week limb fat losses in treatment-naive people randomized to start the PI NFV or the NNRTI EFV.³⁸ In a subset of 157 people with fat changes measured by dual-energy x-ray absorptiometry (DEXA), those taking NFV had a median 13.1% limb fat loss while those taking EFV gained a median 1.8% ($P = 0.003$). In a logistic regression model adjusted for age, gender, race/ethnicity, baseline body mass index, viral load, CD4 count, and NRTIs used, taking NFV rather than EFV proved a nearly significant predictor of limb fat loss ($P = 0.06$).

Though ousting a PI may not reverse fat upsets, benching d4T and possibly AZT can add fat to skinny arms and legs. A thymidine analog tradeoff remains the longest-tested limb atrophy-reversing strategy, with follow-up to 104 weeks in the MITOX study.³⁹ But most people who could stop d4T did so long ago and, as

Figure 2. **Model for the pathogenesis and time course of lipotrophy**



Martínez noted, post-switch gains in subskin fat come so slowly that many feel disappointed.

People still taking 40 mg of d4T daily have three choices—live with the side effects, swap d4T for another drug, or lower the dose. A study that randomized people to continue 40 mg of d4T twice daily, trim back to 30 mg twice daily, or switch to TDF logged a significant six-month limb fat gain with TDF ($P=0.003$).⁴⁰ People who eased the d4T dose by 10 mg twice a day also gained limb fat, but not significantly more than people who stayed with 40 mg ($P=0.124$). Martínez said the difference between the 40-mg and 30-mg groups remained insignificant at 48 weeks.

If someone wants to trade d4T for another NRTI, what's the best choice? A randomized trial involving people who swapped d4T or AZT for ABC or TDF found equivalent 48-week limb fat gains in the two arms.⁴¹ But fat refills are not the only concern when replacing a thymidine analog. This study also found more toxicity dropouts in the ABC arm (six versus one) and significantly better lipid fixes with TDF.

What about trying drugs that tinker with purported lipodystrophy mechanics? The record here offers little grounds for optimism, Martínez argued (Table 7). Even if a metabolically aimed drug does patch one problem, it often provokes another. And any added drug may have unhappy interactions with antiretrovirals.

Although implants can remedy facial atrophy, Martínez listed several unknowns

or disadvantages with this approach: Long-term results remain unverified. No one knows which method works best for which person. All techniques require a trained professional. All are expensive. And most European countries won't pay the bill.

(At the 7th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, held a few weeks after IAPAC Sessions, researchers showed that uridine⁴² or pravastatin⁴³ reverses fat loss in anti-retroviral-treated people and that switching from d4T or AZT to TDF or ABC restores some facial fat.⁴⁴)

Antiretrovirals: One liver threat among many

All antiretroviral classes—even, we latterly learned, the entry inhibitors⁴⁵—may rock the liver. That's a threat to everyone who needs these drugs, but especially to people coinfecting with hepatitis B or C virus (HBV or HCV). And there are lots of them in Europe, reported Jürgen Rockstroh (University of Bonn, Germany), who chaired the IAPAC Sessions talks on hepatitis and HIV.

Among 5,883 members of the EuroSIDA cohort with a hepatitis B surface antigen (HBsAg) test at enrollment, 530 (9%) had a positive test. A similar HBV coinfection prevalence applies in the United States, Rockstroh noted. Hepatitis C prevalence stands even higher in EuroSIDA, at about 33% across the continent. Rates range from 19.6% in central Europe to 46.9% in eastern Europe. And HCV coinfection

prevalence will climb even higher in eastern countries, Rockstroh predicted, as HIV spreads among injecting drug users (IDUs).

Grade 4 adverse events—also known as really bad side effects—now outrank AIDS as complications of HIV infection.⁴⁶ And the most common egregious “events” involve the liver. A survey of severe side effects in 2,947 people at five US clinical trial sites counted 2.6 liver-related insults per 100 person-years, followed distantly by neutropenia (1.5 cases per 100 person-years), anemia (1.1 cases), cardiovascular disease (0.9 cases), and others.⁴⁶ Collating data from France, Italy, Spain, and the United States, José Arribas (Universidad Autónoma, Madrid) traced steep jumps in death due to HCV-related end-stage liver disease with the dawn of triple antiretroviral therapy:

- From 13% to 35% in Brescia
- From 11.5% to 50% in Boston
- From 4.8% to 45% in Madrid
- From 1.5% to 14% in France

These scary trends don't mean antiretrovirals suddenly started killing people with hepatitis coinfection in 1996. Relative leaps in liver-related deaths reflect lower mortality from opportunistic infections and cancers. And, of course, antiretrovirals remain only one of many liver threats in people with HIV. At the same time, Arribas explained, several factors complicate the understanding of liver toxicity in people taking antiretrovirals:

- Hepatotoxic injuries are poorly understood
- Multiple drugs are involved
- Cholestasis (hampered bile flow) is probably underreported
- Both cohort studies and randomized controlled trials have important methodologic shortcomings
- Long-term follow-up is rare

Complicating matters further, even liver experts don't really understand what elevated transaminases mean. They know even mild elevations forebode progressive liver fibrosis in people with HBV, HCV, and alcoholic and nonalcoholic fatty liver disease, Arribas said. But no one has long-term data on what drug-induced transaminase spurts portend. And most liver enzyme leaps—even five times a lab's upper limit of normal—may cause no symptoms. Antiretroviral toxicity

Table 7. Balance sheet on drug therapy for lipodystrophy

	<i>Lipids</i>	<i>Insulin resistance</i>	<i>Central obesity</i>	<i>Lipoatrophy</i>
Steroids	Worse	Worse	Little change	Little change/worse
Recombinant human growth hormone	Worse	Worse	Better	Little change
Metformin	Better	Better	Better	Worse
Glitazones	Little change/worse	Better	Little change	Little change/better

probably explains only a fraction of such flares, Arribas proposed. More can be traced to other drugs, infections, alcohol, immune reconstitution, or the chafing hum of “background noise.”

RTI-related liver toxicity

Nucleoside reverse transcriptase inhibitors probably rile the liver by depleting mitochondrial DNA, and the worst offenders are ddI and d4T, especially when combined.⁴⁷ Ribavirin (RBV), the anti-HCV drug, worsens NRTI-mediated mitochondrial mixups and should not be teamed with ddI. In the APRICOT trial of pegylated interferon (PEG-IFN) with or without RBV for HCV coinfection, ddI quadrupled the risk of hepatic decompensation.⁴⁸

Arribas listed four signals of NRTI-induced liver damage:

- Unspecific symptoms including abdominal pain, right upper quadrant pain, vomiting, and anorexia
- Hepatomegaly (enlarged liver)
- Mixed cholestatic-hepatocellular liver enzyme pattern: elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST), gamma-glutamyltransferase (GGT), and alkaline phosphatase (AP)
- Evidence of extrahepatic mitochondrial toxicity (metabolic acidosis, bicarbonate loss, abnormal amylase, lipase, creatine kinase, or lactates)

Abacavir appears to have a clean mitochondrial slate, but hypersensitivity reactions to this NRTI—and to the NNRTIs—threaten the liver. Pregnant women with HIV also run a risk of antiretroviral-related hepatotoxicity signaled by climbing transaminases, cholestasis of pregnancy, lactic acidosis with hepatic involvement, and the HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets). The US Food and Drug Administration (FDA) counted six liver-related deaths of antiretroviral-treated pregnant women from 1998 through 2003, three of them

taking NVP plus AZT/3TC, two taking NVP plus ddI/d4T, and one on NFV plus ddI/d4T.⁴⁹

In the randomized 2NN study comparing EFV, NVP once or twice daily, and EFV/NVP (all with d4T/3TC), rates of grade 3 or 4 liver toxicity proved much lower with EFV (4.5%) than with NVP twice daily (8.3%), EFV/NVP (9.1%), or NVP once daily (13.6%).⁵⁰ Researchers pinned two liver-related deaths on NVP.

In the IDU-rich Johns Hopkins HIV cohort, grade 3 or 4 hepatotoxicity affected 15.6% taking NVP versus 8.0% taking EFV.⁵¹ Of the 564 people studied, 43% had HCV coinfection and 8% HBV coinfection. Coinfected people had a higher risk of liver toxicity, as did people combining an NNRTI with a PI.

A cross-sectional study of 152 HCV-coinfected people in Seville, Spain, charted a 2.56 times higher RR of stage 3 or 4 liver fibrosis with NVP, compared with lower risks among people taking EFV (RR 0.7) or a PI (RR 0.39) and among people younger than 21 years old (RR 0.39).⁵²

PIs' impact on hepatotoxicity

Ritonavir-boosted PI therapy does heighten the risk of liver toxicity, but the risk appears to depend on what PI gets boosted. That conclusion emerged from a 1,001-person prospective study of people with or without HCV coinfection in a US cohort.⁵³ After tracking hepatotoxicity for up to 60 months, Johns Hopkins researchers found no higher risk of severe toxicity (AST or ALT more than five times the upper limit of normal) with LPV/RTV or with unboosted NFV. But people taking IDV/RTV had a 2.97 times higher risk of liver trouble and those taking 400/400 mg SQV/RTV twice daily had a 2.41 times higher risk. Coinfection with HCV upped the odds of severe liver toxicity 1.82 times, a viral load above 10,000 copies/mL raised the risk 4.77 times, and a CD4 count above 200 cells/mm³ halved the risk.

Notably, 83% of people with HCV

coinfection in this cohort did not suffer antiretroviral-induced liver injury. But coinfection approximately doubled the risk of severe liver toxicity among people taking SQV/RTV, LPV/RTV, or NFV, but not IDV/RTV (Figure 3).

A retrospective analysis of 560 Dutch people taking antiretrovirals found that full-dose RTV quintupled the risk of grade 4 liver enzyme leaps.⁵⁴ But a boosting RTV dose of 200 mg twice daily or less did not inflate toxic markers in this cohort. All told, this study picked out seven independent predictors of grade 4 AST or ALT (at the following hazard ratios [HR] and 95% CIs):

- Female gender: HR 2.8 (1.3 to 5.8)
- Baseline ALT (per 10 U/L increase): HR 1.05 (1.01 to 1.11)
- Chronic HCV infection: HR 5.0 (2.3 to 10.7)
- Chronic HBV infection: HR 9.2 (4.1 to 20.6)
- Recent discontinuation of 3TC: HR 6.8 (2.1 to 22.7)
- Starting NVP in past 12 weeks: HR 9.6 (3.2 to 28.3)
- Starting full-dose RTV in past 12 weeks: HR 4.9 (2.0 to 12.1)

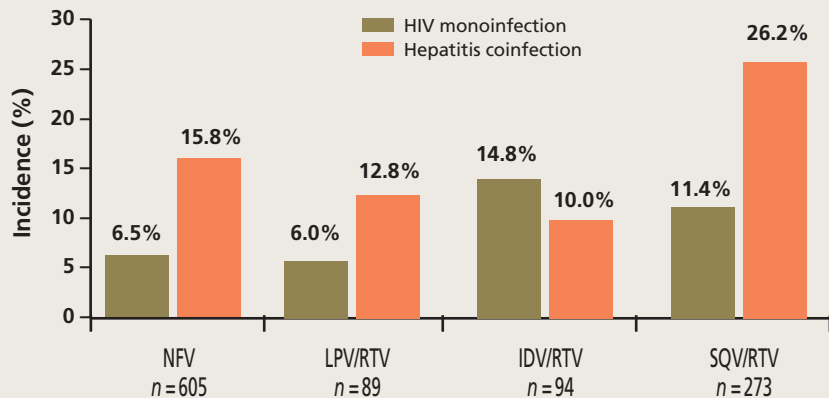
Arribas reminded colleagues that both IDV and atazanavir (ATV) can cause unconjugated hyperbilirubinemia, and the risk is higher in people with hepatitis, added Rockstroh. He avoids ATV after liver transplants or in people with hepatic decompensation—not because of toxicity but because the high bilirubins complicate clinical management. Stefan Mauss (Center for HIV and Hepatogastroenterology, Düsseldorf) noted that coinfecting people take a dim view of ATV-induced yellow eyes because it signals their liver disease to others.

Preventing and managing liver toxicity

Clinicians can take several steps to lower the risk of hepatotoxicity in people with HIV, Arribas proposed, starting with remembering that the risk is higher in women, people with an earlier episode of liver toxicity, obese patients, and of course those with hepatitis coinfection. He suggested the following protocol when sizing up a person's liver toxicity risk:

- Carefully check all baseline characteristics
- Measure aminotransferase levels

Figure 3. Incidence of severe hepatotoxicity with different PIs⁵³



- Establish a history of preexisting liver disease
- Consider
 - Concomitant medication and over-the-counter products
 - Alcohol consumption
 - Potential for drug abuse
 - Vaccination against hepatitis A virus (HAV) and HBV

For people who run a higher risk of liver toxicity, pick antiretrovirals that do not swell that risk—AZT, 3TC, ABC, TDF, and FTC among the NRTIs; NFV and LPV/RTV among the PIs; and EFV if considering NNRTI therapy. Current guidelines spell out dosing advice for certain antiretrovirals given to people with hepatic insufficiency (Table 8).

Arribas recommended checking aminotransferase levels two, four, and 12 weeks after starting a new regimen in people without liver disease. If levels are stable at those points, recheck every three months. In people who have liver disease when they start antiretrovirals, check aminotransferases every two weeks during the first three months of a new regimen, then every three months if stable. Skin rash at any point should signal ALT and AST readings.

What should you do if liver enzymes do rise? Jumps below five times the upper limit of normal are generally safe to tolerate—if they're asymptomatic and you exclude hypersensitivity reaction. Arribas listed three reasons to stop antiretrovirals: symptoms of liver disease, escalating lactates, and evidence of severe liver dysfunction such as coagulopathy or encephalopathy.

Severe liver injury should prompt a search for a cause other than antiretroviral therapy.

Treatment options for HBV and HCV

With HIV, seroconversion is a bad thing. But with HBV, hepatitis B e antigen (HBeAg) seroconversion is a very good thing, linked as it is to longer survival.⁵⁶ Yet studies across Europe, reported Mauss, show that HBeAg-negative (“precore mutant”) chronic HBV infection has become more prevalent. That’s bad news because HBeAg-negative HBV carries with it a higher risk of cirrhosis than HBeAg-positive infection. Hepatitis textbooks, Mauss cautioned, have yet to reflect this change.

Treatment options for chronic HBV fall into two bins—PEG-IFN and HBV polymerase inhibitors, which often double as nucleoside or nucleotide inhibitors of HIV reverse transcriptase. Interferon, Mauss explained, is an option only for HBeAg-positive people without marked cellular immunosuppression (Table 9). Because polymerase inhibitors act independently of cellular immune status, they are the choice after cellular immunosuppression sets in.

Lamivudine, the prototype polymerase inhibitor, boasts a long ledger of success in controlling HBV. But rapid evolution of HBV resistance to this drug limits its value as monotherapy. Resistance emerges more slowly to adefovir, but some people may not respond to the drug, and resistance to adefovir seems likely to confer cross-resistance to more potent polymerase inhibitors.

Tenofovir ranks as one of those more

potent polymerase stifiers, and resistance emerges slowly to this drug. A placebo-controlled trial comparing TDF with adefovir in HIV/HBV-coinfected people yielded 48-week evidence favoring TDF.⁵⁷ Entecavir, Mauss predicted, will become an option for people who need no anti-retrovirals. But entecavir does a poor job of controlling lamivudine-resistant virus.

Emtricitabine, licensed for HIV infection, has activity against HBV. Other polymerase inhibitors in development are telbivudine (LdT), clevudine (L-FMAU), elvucitabine (LFd4C), valtorcitabine (Val-LdC), and amdoxovir (DAPD).

Reverse transcriptase inhibitor monotherapy proved fruitless—even disastrous—against HIV. What’s keeping HBV experts from taking a harder look at polymerase inhibitor combos? So far, Mauss explained, research on anti-HBV combinations has turned up scant evidence supporting this strategy, though the superior efficacy of multidrug regimens remains “theoretically convincing.”

A trial of lamivudine plus adefovir versus lamivudine alone in HBeAg-positive treatment-naïve people without HIV discerned no HBV DNA load difference between the regimens after 52 weeks. Resistant virus did emerge more slowly in the two-drug group (2%) than in the lamivudine monotherapy group (20%). Perhaps because of overlapping resistance profiles between lamivudine and LdT, combining the drugs in another study did not lower HBV DNA more than LdT alone. And in a third study solo TDF could not outdo TDF plus lamivudine in lowering DNA load or calming liver enzymes.

How these lackluster results will shape the future of anti-HBV therapy is hard to say. What would have happened to antiretroviral planning, for example, if three successive randomized trials failed to demonstrate the inferiority of AZT monotherapy?

In contrast, combination therapy with IFN and RBV has nailed down a standard-of-care slot for HCV infection, regardless of coinfection with HIV. When completed, the AIDS Pegasys Ribavirin International Coinfection Trial (APRICOT) trial of PEG-IFN plus RBV in coinfecting people yielded the best sustained virologic response (SVR), 40%, in any study of people burdened by both viruses—even though the RBV dose (800 mg daily) was low according to current thinking.⁵⁸

Yet this SVR lags those evoked in people

Table 8. Antiretroviral advice for people with hepatic insufficiency⁵⁵

Antiretroviral	Daily dose	Dosing in hepatic impairment
Amprenavir	1,200 mg twice daily Note: oral solution not recommended in patients with renal or hepatic failure	<ul style="list-style-type: none"> • Child-Pugh score 5-8: 450 mg twice daily • Child-Pugh score 9-12: 300 mg twice daily
Atazanavir	400 mg once daily	<ul style="list-style-type: none"> • Child-Pugh score 7-9: 300 mg once daily • Child-Pugh score >9: not recommended
Fosamprenavir	1,400 mg twice daily	<ul style="list-style-type: none"> • Child-Pugh score 5-8: 700 mg twice daily • Child-Pugh score 9-12: not recommended • Ritonavir boosting should not be used in patients with hepatic impairment
Indinavir	800 mg every 8 hours	<ul style="list-style-type: none"> • Mild to moderate hepatic insufficiency due to cirrhosis: 600 mg q8h
Lopinavir/ritonavir	400 mg/100 mg twice daily or 800 mg/200 mg once daily (once-daily dosing only for treatment-naive patients)	<ul style="list-style-type: none"> • No dosage recommendation; use with caution in patients with hepatic impairment
Nelfinavir	1,250 mg twice daily	<ul style="list-style-type: none"> • No dosage recommendation; use with caution in patients with hepatic impairment
Saquinavir soft-gel cap	1,200 mg three times daily	<ul style="list-style-type: none"> • No dosage recommendation; use with caution in patients with hepatic impairment
Tipranavir	500 mg twice daily with ritonavir 200 mg twice daily	<ul style="list-style-type: none"> • No dosage recommendation; use with caution in patients with hepatic impairment; TPV/RTV is contraindicated in patients with moderate to severe (Child-Pugh class B and C) hepatic insufficiency

without HIV infection, and only 29% of coinfecting people with HCV genotype 1 managed a sustained response. In a later and much smaller study of PEG-IFN plus a weight-adjusted RBV dose of 800 to 1,200 mg daily, the SVR came close to 40% in people with genotype 1 or 4 and exceeded 50% in those with genotype 2 or 3. Mauss argued that this weight-tempered RBV dose should be the standard of care in HIV/HCV-coinfecting people. He also cited histologic improvement in APRICOT enrollees without an SVR to argue that it may be unethical to withhold anti-HCV therapy from coinfecting people with early cirrhosis, because they may stand to gain the most from treatment.

The APRICOT trial also showed that clinicians can predict failure to attain an SVR with PEG-IFN plus RBV after only three months of treatment. Among people randomized to those drugs, 85 (29%) did not have an early virologic response. Of those early nonresponders, only two (2%) went on to notch an SVR. The financial and toxic costs of this regimen are probably too high for early nonresponders.

Is PEG-IFN/RBV a feasible regimen for people on opioid maintenance therapy?

Results of the first controlled trial of this strategy in people with chronic HCV infection (but not HIV) suggests the answer is yes.⁵⁹ Mauss and colleagues recruited 50 people on methadone maintenance for at least six months and 50 with no injecting drug use or opioid maintenance for at least five years. They matched the groups for gender, age, HCV genotype, and HCV RNA load. People with genotype 2 or 3 got 1.5 µg/kg of PEG-IFN alfa-2b weekly plus 1,000 to 1,200 mg of RBV daily for 24 weeks. Those with genotype 1 or 4 took the same regimen for 48 weeks.

Although the end-of-treatment response proved significantly better in the nonopioid control arm, the groups did not differ in SVR (Table 10). A substantially higher proportion of people in the methadone maintenance arm (about 50%) than in the control arm (about 20%) did stop antiviral therapy. But methadone maintenance enrollees with an SVR managed to lower their methadone dose during the trial.

Mauss concluded that careful selection of HCV-infected people for PEG-IFN therapy and active management of side effects will maximize the impact of treatment.

Table 9. Variables favoring HBV response to IFN-α

- Short-course infection
- Elevated liver enzymes (ALT >100 U/L)
- Moderately elevated HBV DNA
- History of inflammation
- Female gender
- Infection as an adult
- Genotype A > B and C
- HBeAg positive

New antiretrovirals, new targets

Compared with clinicians treating HBV and HCV, those focused solely on HIV hold a royal flush of treatment options. For people just starting antiretroviral therapy, that has made life easier, and longer, but nonetheless more vexing than it would be without a retrovirus locked forever in their T cells. As Clumeck opined when opening the IAPAC Sessions talk on side effects, the key to any new antiretroviral may now be durable *tolerability*.

But for people with plenty of resistant virus immured in mononuclear vaults, priorities change. They need a drug that reins in that resistant virus, and they need one or two more drugs to harness other strains in their dodgy quasispecies. Drug developers do their best to fashion physics for resistant virus, but these new meds have their limits. Lange—pressed into service when air delays grounded the designated speaker, Schlomo Staszewski (JW Goethe University, Frankfurt)—cited tipranavir (TPV) and TMC 114 as PIs that parry resistant virus well. But once a handful of mutations pile up, these PIs' potency fades. And they carry toxic baggage that few would tolerate in a first-line drug.

Meanwhile, the hunt for agents that hit new targets shows few signs of slowing—despite the chancy odds on devising peppy and more-or-less palatable drugs to fit a narrow niche. Inhibitors of viral attachment, entry, integration, and maturation all vie for the attention of investors, reporters, and—perhaps one day—clinicians. But the urgent need for such remedies has barely shortened their road to approval.

HIV integrase inhibitors have tantalized drug makers since scientists crystallized the enzyme's structure over a decade ago. Because the current crop of candidates inhibits DNA strand transfer, Lange noted, they may be called STIs. That

Table 10. Chronic HCV response to PEG-IFN/RBV during methadone maintenance

	Methadone maintenance (n = 50)	Non-IDU control (n = 50)
Median age (y)	35	40
Median baseline HCV RNA (copies/mL)	556,000	708,000
End-of-treatment response (%)	50	76 (P < 0.05)
Sustained virologic response (%)	42	56 (not significant)

Table 11. How R5 and X4 viral populations differ

CCR5-tropic virus	CXCR4-tropic virus
<ul style="list-style-type: none"> • Nonsyncytium-inducing (NSI) virus • Macrophage-tropic • Lower replication capacity • Small target cell range (mostly activated T cells) • Low immunogenicity • More common in transmission, early infection • Delta 32 deletion in CCR5 slows progression; homozygosity for this deletion prevents infection with R5 virus 	<ul style="list-style-type: none"> • Syncytium-inducing (SI) virus • Linked to CD4-cell decline • Higher replication capacity • Broader target cell range (but mainly naive resting memory T cells) • More common in late-stage disease

acronym seems certain to foment further confusion in headlines on structured treatment interruptions and sexually transmitted infections. But it would be nice if that were the biggest worry about this problem-plagued class. The long-suffering Merck and Company team did midwife an integrase inhibitor that knocked down viral loads 1.7 log copies/mL—all by itself—in treatment-naïve or currently untreated people. But Merck had to abandon this prodigy because of toxic threats. (A few weeks after IAPAC Sessions, the same team unveiled data showing 2-log [100-fold] drops after 10 days of monotherapy with its newest integrase inhibitor, MK-0518.⁶⁰)

Maturation inhibitors do the same thing PIs do, Lange explained, preventing viral bits and pieces from melding into mature virions. But they do so at a different step in HIV’s Homeric life cycle. The maturation muffler PA-457 looked good in a 10-day placebo-controlled monotherapy study, trimming viral loads in eight of 12 people who took the drug.⁶¹ But toxicity studies in animals have been hard to mount.

TNX-355, a monoclonal antibody that smotheres CD4 receptors, garnered interest when a 10-mg/kg dose lopped a median 1.5 log copies/mL off the viral loads of treatment-experienced people in a phase 1 dose-finding study.⁶² The drug is a humanized monoclonal antibody with a long half-life. Viral loads in the 10-mg/kg

group kept going down for 14 days after a single injection.

Coreceptor rejector conundrums

The front-running CXCR4 coreceptor antagonist appears to be AMD 070, tested in humans at 50, 100, 200, and 400 mg. But Staszewski and Lange noted several potential drawbacks to drugs that target the X4 coreceptor:

- X4-tropic virus surfaces mainly in people with advanced infection.
- Most people with X4 virus have a mixed viral population that includes R5-tropic HIV.
- Clinical benefits of inhibiting X4 virus alone remain unknown.
- The safety of X4 antagonists has not been verified.

The viral population never shifts from R5 to X4 virus in about half of all people infected with HIV-1 subtype B. X4 virus hardly ever crops up in people infected with the globally dominant HIV-1 subtype C, Lange noted. In Chelsea and Westminster Hospital’s London cohort—19% of whose members carry non-B virus—HIV-1 subtype did not influence coreceptor use.⁶³ Multivariate analysis in this study linked higher CD4 count, higher natural killer cell count, and lower viral load to R5 tropism.

Lange warned that discussion of viral coreceptor tropism often gets fuzzy

because many misuse the term “dual tropic.” Strictly speaking, dual-tropic virus can grasp either X4 or R5 coreceptors (Figure 4). But when speakers say “dual tropic” they often mean a “mixed-tropic” viral population—that is, an ensemble of *single-tropic* X4 and R5 viruses. Research shows clear distinctions between virus that prefers the X4 coreceptor and virus that fancies R5 (Table 11).

Lange noted that AZT preferentially phosphorylates to its active metabolite in activated T cells. In other words, the drug works mainly against R5-tropic HIV. Zidovudine monotherapy studies showed that the NRTI can push the viral population from preferring R5 to preferring X4. On the other hand, ddI phosphorylates mainly in resting T cells and so exerts most of its antiviral activity there. It can push an X4 population back toward R5.

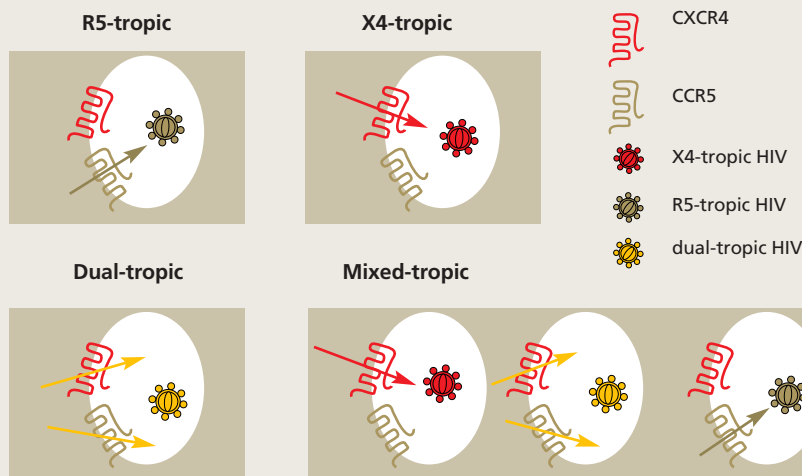
Traits such as these, Lange argued, could help pick the best partners for CCR5 antagonists. For example, AZT may prove a less desirable partner for CCR5 antagonists because both drugs could egg an R5 viral population toward a possibly more dangerous X4 tropism. Such fateful synergies remain to be explored, even as CCR5 antagonists thrum through phase 2 and 3 trials.

Getting a handle on how antiretrovirals drive tropism remains difficult, though, because tropism assays remain rudimentary. Staszewski listed these limitations:

- Tropism assays do not distinguish between dual-tropic and mixed-tropic viral populations.
- Tropism assays do not measure the *quantity* of virus that has a particular tropism.
- Tropism assays may fail to phenotype 5% to 10% of viral samples.
- Assay failure to detect X4- or R5-tropic virus in plasma does not preclude existence of such virus below the limit of detection *or* in other anatomical compartments.

Meanwhile, development of CCR5 antagonists proceeds in the face of apparent irony, Lange suggested. Everyone knows that CCR5-tropic virus dominates the viral population from the day of infection throughout its early course. Yet the primary market for these agents consists of people with multidrug-resistant virus—in other words, people with more advanced HIV infection and thus most likely to have X4-tropic virus. Yet because viral populations

Figure 4. **The difference between dual-tropic and mixed-tropic HIV populations**



Source: Schlomo Staszewski.

in late infection rarely, if ever, use only the X4 receptor, CCR5 antagonists could corral at least part of that population. But the rest of the regimen better bridle X4-tropic virus.

This irony grew richer in recent months when GlaxoSmithKline halted a phase 2 study of its CCR5 candidate in previously untreated people because of acute liver toxicity.⁴⁵ Then the company pulled the plug on all development—and started shifting trial participants to other antiretrovirals—after liver enzymes and bilirubin spiked in a treatment-experienced person taking the drug.

Weeks after IAPAC Sessions, Pfizer announced a solitary case of liver toxicity in the nearly 1,000 people exposed to maraviroc. The case involved a person already taking isoniazid and cotrimoxazole before starting maraviroc. Independent safety reviewers believe any of these drugs, alone or together, could have caused the severe liver toxicity, which required transplantation (see note 45). So far Schering-Plough has seen no liver snags in trials of their CCR5 drug, vicriviroc. But Schering-Plough had to shutter a study of treatment-naïve people when vicriviroc plus AZT/3TC proved virologically inferior to EFV plus AZT/3TC.⁶⁴ The company says it will continue testing its CCR5 antagonist—with backbones other than AZT/3TC—in antiretroviral neophytes.

As in other antiretroviral classes, cross-resistance threatens CCR5 antagonists. But work so far suggests class resistance emerges only when a triazole antagonist

fails. Maraviroc, the CCR5 blocker from Pfizer, is not a triazole drug. Viral clones resistant to maraviroc remained sensitive to other agents in this class.⁶⁵

Adherence, toxicity, and adherence

The meeting organizers recruited the always-provocative Brian Gazzard to share his insights on “maximizing highly active antiretroviral therapy (HAART).” But the World War II bomb unearthed at Schiphol (see above) kept him in London, so attendees saw his slides filtered through his equally piquant colleague, Mark Nelson.

Both see efficacy as a nearly eclipsed issue in antiretroviral development of first-line regimens. Hefty majorities of people starting medleys such as EFV, 3TC, and TDF in clinical trials promptly push their viral load under 50 copies/mL and keep it there. Nelson maintained that good physicians should no longer see new patients slip into triple-class failure. Chelsea and Westminster Hospital arithmeticians count only 100 triple failures in a 4,000-person cohort, though that sterling record owes something, he conceded, to an early preference for later antiretroviral intervention. That policy let Nelson and confreres learn from others’ mistakes.

So dogged adherence becomes issue number one, and nothing undoes doggedness like side effects. Echoing other speakers, Nelson splayed side effects into two species—those we know now, and those we’ll learn about later (the buried bombs). Adherence depends partly on a gamut of flexible factors including pill burden, food

requirements, day-to-day toxicity, and long-term toxicity—and partly on more unvarying variables such as a person’s behavior and beliefs about health.

But besides a certain antiretroviral’s pill tally and tolerability, Gazzard and Nelson noted, clinicians must also weigh the “forgiveness” factor when deciding what to prescribe. Non-nucleosides proved more “forgiving” than PIs because their long half-lives mean one missed dose does not spell rebound doom. But the equation is not that simple, Nelson added, because loss of viral control evokes NNRTI-resistant virus much more readily than PI-resistant virus. So if you suspect shaky adherence in someone starting therapy, do you prescribe an NNRTI because it is more “forgiving,” or a boosted PI because it provokes resistance less often in early rebounds? He did not answer that question.

Is today’s guideline-favored NNRTI, EFV, better than the guideline-favored PI, LPV/RTV? Gazzard raised that possibility, citing the modest 53% sub-50-copy rate in a 96-week noncompleter-equals-failure analysis comparing twice-daily with once-daily LPV/RTV (plus TDF/FTC).⁶⁶ Nelson added that the disappointing response reflects high dropout rates in both the once-daily arm (37%) and the twice-daily arm (39%), and that toxicity explained about half the dropouts. But toxicity—Gazzard and Nelson agree—must rank as a primary concern in treatment planning.

For treatment-naïve people, picking between a PI and an NNRTI is only the first hurdle, Nelson reminded colleagues. Among the many gems mined from ACTG 384 was the clearly superior potency of EFV when backed by AZT/3TC instead of ddI/d4T.⁶⁷ Sinking virologic response curves for EFV plus ddI/d4T overlapped those for NFV plus either ddI/d4T or AZT/3TC, with the response to EFV/AZT/3TC remaining significantly better. One could quibble that ddI/d4T looks like a straw man backbone in hindsight. But a more recent contest between AZT/3TC and TDF/FTC, again with EFV, clearly showed the newer duo’s superiority.⁶⁸ Better backbones make better third drugs better.

Gazzard and Nelson discriminated between finding a potent, tolerable regimen and finding an “easy” regimen. The ACTG A5095 protocol⁶⁹—and a raft of

other studies—proved that point to the dismay of many. Triple-NRTI regimens, despite their convenience and other, theoretical, attributes, came up short against EFV-based combos in trial after trial. “You can’t be *too* patient oriented,” Nelson cautioned.

These studies make a larger point than the relative frailty of triple nukes: Good-looking but untested regimens of any ilk—EFV plus ddI/TDF comes to mind—carry the risk of rude surprise.

Adherence remains the most-touted but least-tested element of antiretroviral planning. Gazzard stressed the need for *continued* reinforcement even in prize adherence pupils. Nelson vouched for the value of enlisting nurses and pharmacists in this enterprise.

Although it is politically correct to say physicians cannot predict good adherence, Gazzard counseled, in reality all physicians see more than a few people with “very disturbed behavior.” Forcing them into therapy on the grounds that adherence can be taught may be the first knot in a string of failures. ■

Mark Mascolini writes about HIV infection (markmascolini@earthlink.net).

References and Notes

- Schama S. *The Embarrassment of Riches*. New York: Vintage Books; 1987.
- Hamers FF, Downs AM. The changing face of the HIV epidemic in western Europe: what are the implications for public health policies? *Lancet*. 2004;364:83-94.
- Gras MJ, Weide JF, Langendam MW, et al. HIV prevalence, sexual risk behaviour and sexual mixing patterns among migrants in Amsterdam, The Netherlands. *AIDS*. 1999;13:1953-1962.
- Fenton KA, Chinouya M, Davidson O, Copas A. HIV transmission risk among sub-Saharan Africans in London travelling to their countries of origin. *AIDS*. 2001;15:1442-1445.
- Op de Coul ELM, Coutinho RA, van der Schoot A, et al. The impact of immigration on env HIV-1 subtype distribution among heterosexuals in the Netherlands: influx of subtype B and non-B strains. *AIDS*. 2001;15:2277-2286.
- Chohan B, Lavreys L, Rainwater SM, Overbaugh J. Evidence for frequent reinfection with human immunodeficiency virus type 1 of a different subtype. *J Virol*. 2005;79:10701-10708.
- McDermott AY, Terrin N, Wanke C, et al. CD4+ cell count, viral load, and highly active antiretroviral therapy use are independent predictors of body composition alterations in HIV-infected adults: a longitudinal study. *Clin Infect Dis*. 2005;41:1662-1670.
- Dubé MP, Parker RA, Tebas P, et al. Glucose metabolism, lipid, and body fat changes in antiretroviral-naive subjects randomized to nelfinavir or efavirenz plus dual nucleosides. *AIDS*. 2005;19:1807-1818.
- Hammond E, Nolan D, McKinnon E, et al. Differential effects of nucleoside reverse transcriptase inhibitor regimens on adipocyte mitochondrial DNA depletion in HIV-infected subjects. 6th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV. October 25-28, 2004. Washington, DC. [Abstract 16]
- Gallant JE, Parish MA, Keruly JC, Moore RD. Changes in renal function associated with tenofovir disoproxil fumarate treatment, compared with nucleoside reverse-transcriptase inhibitor treatment. *Clin Infect Dis*. 2005;40:1194-1198.
- Izzedine H, Hulot JS, Vittecoq D, et al. Long-term renal safety of tenofovir disoproxil fumarate in antiretroviral-naive HIV-1-infected patients. Data from a double-blind randomized active-controlled multicentre study. *Nephrol Dial Transplant*. 2005;20:743-746.
- Jones R, Stebbing J, Nelson M, et al. Renal dysfunction with tenofovir disoproxil fumarate-containing highly active antiretroviral therapy regimens is not observed more frequently: a cohort and case-control study. *J Acquir Immune Defic Syndr*. 2004;37:1489-1495.
- El-Sadr W, Reiss P, De Wit S, et al. Relationship between prolonged exposure to combination ART and myocardial infarction: effect of sex, age, and lipid changes. 12th Conference on Retroviruses and Opportunistic Infections. February 22-25, 2005. Boston. [Abstract 42]
- Calza L, Manfredi R, Colanelli V, et al. Substitution of nevirapine or efavirenz for protease inhibitor versus lipid-lowering therapy for the management of dyslipidaemia. *AIDS*. 2005;19:1051-1058.
- Miller J, Brown D, Amin J, et al. A randomized, double-blind study of gemfibrozil for the treatment of protease inhibitor-associated hypertriglyceridaemia. *AIDS*. 2002;16:2195-2200.
- Aberg JA, Zackin RA, Brobst SW, et al. A randomized trial of the efficacy and safety of fenofibrate versus pravastatin in HIV-infected subjects with lipid abnormalities: AIDS Clinical Trials Group Study 5087. *AIDS Res Hum Retroviruses*. 2005; 21:757-767.
- Fontas E, van Leth F, Sabin CA, et al. Lipid profiles in HIV-infected patients receiving combination antiretroviral therapy: are different antiretroviral drugs associated with different lipid profiles? *J Infect Dis*. 2004; 189:1056-1074.
- van Leth F, Friis-Møller N, Weber R, et al. Distinguishable lipid profiles between PI- and NNRTI therapy may carry different risk of cardiovascular disease. 9th Conference on Retroviruses and Opportunistic Infections. February 24-28, 2002. Seattle. [Abstract 34]
- Young J, Weber R, Rickenbach M, et al. Lipid profiles for antiretroviral-naive patients starting PI- and NNRTI-based therapy in the Swiss HIV cohort study. *Antivir Ther*. 2005;10:585-591.
- van Leth F, Phanuphak P, Stroes E, et al. Nevirapine and efavirenz elicit different changes in lipid profiles in antiretroviral-therapy-naive patients infected with HIV-1. *PLoS Med*. 2004;1(1):e19.
- Fisac C, Fumero E, Crespo M, et al. Metabolic benefits 24 months after replacing a protease inhibitor with abacavir, efavirenz or nevirapine. *AIDS*. 2005;19:917-925.
- Riddler SA, Smit E, Cole SR, et al. Impact of HIV infection and HAART on serum lipids in men. *JAMA*. 2003;289:2978-2982.
- Gallant JE, Staszewski S, Pozniak AL, et al. Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naive patients: a 3-year randomized trial. *JAMA*. 2004;292:191-201.
- Law MG, D’Arminio Monforte A, Friis-Møller N, et al. Cardio- and cerebrovascular events and predicted rates of myocardial infarction in the D:A:D study. 11th Conference on Retroviruses and Opportunistic Infections. February 8-11, 2004. San Francisco. [Abstract 737]
- ART Cohort Collaboration. Defining prognosis in the era of potent antiretroviral therapy. <http://www.art-cohort-collaboration.org>. Last updated June 13, 2005. (Accessed November 22, 2005)
- Grinspoon S, Carr A. Cardiovascular risk and body fat abnormalities in HIV-infected adults. *N Engl J Med*. 2005;352:48-62.
- Nolan D, Moore C, Castley A, et al. Tumour necrosis factor-alpha gene -238G/A promoter polymorphism associated with a more rapid onset of lipodystrophy. *AIDS*. 2003;17:121-123.
- Noor M, Deziel C, McLaren C, et al. Baseline triglyceride levels predict development of lipodystrophy in patients treated with stavudine extended-release/prolonged-release capsules or stavudine immediate-release. 11th Conference on Retroviruses and Opportunistic Infections. February 8-11, 2004. San Francisco. [Abstract 722]
- Study of Fat Redistribution and Metabolic Change in HIV Infection (FRAM). Fat distribution in men with HIV infection. *J Acquir Immune Defic Syndr*. 2005;40:121-131.
- Lichtenstein KA, Delaney KM, Armon C, et al. Incidence of and risk factors for lipodystrophy (abnormal fat loss) in ambulatory HIV-1-infected patients. *J Acquir Immune Defic Syndr*. 2003;32:48-56.
- Pallela FJ Jr, Cole SR, Chmiel JS, et al. Anthropometrics and examiner-reported body habitus abnormalities in the multicenter AIDS cohort study. *Clin Infect Dis*. 2004;38:903-907.
- Carr A, Emery S, Law M, et al. An objective case definition of lipodystrophy in HIV-infected adults: a case-control study. *Lancet*. 2003;361:726-735.
- Law MG, Cheng A, Cooper DA, Carr A. Objective evaluation of HIV lipodystrophy case definition in a randomized 96 week clinical trial. 6th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV. October 25-28, 2004. Washington, DC. [Abstract 11]
- Galli M, Veglia F, Angarano G, et al. Gender differences in antiretroviral drug-related adipose tissue alterations: women are at higher risk than men and develop particular lipodystrophy patterns. *J Acquir Immune Defic Syndr*. 2003;34:58-61.
- Galli M, Ridolfo AL, Adorni F, et al. Body habitus changes and metabolic alterations in protease inhibitor-naive HIV-1-infected patients treated with two nucleoside reverse transcriptase inhibitors. *J Acquir Immune Defic Syndr*. 2002;29:21-31.
- Anderson PL, Kakuda TN, Kawle SP, Fletcher CV. Antiviral dynamics and sex differences of zidovudine and lamivudine triphosphate concentrations in HIV-infected individuals. *AIDS*. 2003;17:2159-2168.
- Martínez E, Arnaiz JA, Podzamczar D, et al. Substitution of nevirapine, efavirenz, or abacavir for protease inhibitors in patients with human immunodeficiency virus infection. *N Engl J Med*. 2003;349:1036-1046.
- Dubé MP, Parker RA, Tebas P, et al. Glucose metabolism, lipid, and body fat changes in antiretroviral-naive subjects randomized to nelfinavir or efavirenz plus dual nucleosides. *AIDS*. 2005;19:1807-1818.
- Martin A, Smith DE, Carr A, et al. Reversibility of lipodystrophy in HIV-infected patients 2 years after switching from a thymidine analogue to abacavir: the MITOX Extension Study. *AIDS*. 2004;18:1029-1036.
- Milinkovic A, Lopez S, Vidal S, et al. A randomized open study comparing the effect of reducing stavudine dose vs switching to tenofovir on mitochondrial function, metabolic parameters, and subcutaneous fat in HIV-infected patients receiving antiretroviral therapy containing stavudine. 12th Conference on Retroviruses and Opportunistic Infections. February 22-25, 2005. Boston. [Abstract 857]
- Moyle G, Sabin C, Cartledge J. A 48-week, randomized, open-label comparative study of tenofovir DF vs abacavir as substitutes for a thymidine analog in persons with lipodystrophy and sustained virological suppression on HAART. 12th Conference on Retroviruses and Opportunistic Infections. February 22-25, 2005. Boston. [Abstract 44LB]
- Sutinen J, Walker UA, Sevastianova K, et al. Uridine supplementation increased subcutaneous fat in patients with HAART-associated lipodystrophy: a randomized, placebo-controlled trial. 7th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV. November 13-16, 2005. Dublin. [Abstract 7]
- Mallon PWG, Miller J, Kovacic J, et al. Changes in body composition and cardiovascular measures in hypercholesterolaemic HIV-infected men treated with pravastatin: a randomized placebo-controlled trial. 7th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV. November 13-16, 2005. Dublin. [Abstract 23]
- Benn P, Sauret V, Cartledge J, et al. Improvements in facial lipodystrophy at 48 weeks following substitution of a thymidine analogue with tenofovir or abacavir: a randomized, open-label study in people with lipodystrophy and virological suppression on HAART. 7th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV. November 13-16, 2005. Dublin. [Abstract 8]
- GlaxoSmithKline terminates patient enrollment for phase 3 studies of investigational HIV entry inhibitor aplaviroc (GW873140) [press release]. London, UK: GlaxoSmithKline. October 25, 2005. Four cases of liver toxicity stopped all trials of Glaxo’s CCR5 antagonist, and Pfizer reported one such case with maraviroc on November 19, 2005, at the European AIDS Conference in Dublin. The Pfizer announcement raised concern that liver toxicity may be a CCR5 antagonist class effect. So far Schering-Plough has reported no liver toxicity with vicriviroc.
- Reisler RB, Han C, Burman WJ, et al. Grade 4 events are as important as AIDS events in the era of HAART. *J Acquir Immune Defic Syndr*. 2003;34:379-386.
- Fleischer R, Boxwell D, Sherman KE. Nucleoside analogues and mitochondrial toxicity. *Clin Infect Dis*. 2004;38:e79-e80.
- Mauss S, Valenti W, DePamphilis J, et al. Risk factors for hepatic decompensation in patients with HIV/HCV coinfection and liver cirrhosis during interferon-based therapy. *AIDS*. 2004;18:F21-F25.
- Baylor M, Truffa M, Gibbs N. Hepatic toxicity of antiretrovirals in HIV-infected pregnant women: a review of the FDA’s adverse event reporting system. 11th Conference on Retroviruses and Opportunistic Infections. February 8-11, 2004. San Francisco. [Abstract 944]
- van Leth F, Phanuphak P, Ruxrungtham K, et al. Comparison of first-line antiretroviral therapy with regimens including nevirapine, efavirenz, or both drugs, plus stavudine and lamivudine: a randomised open-label trial, the 2NN Study. *Lancet*. 2004;363:1253-1263.
- Sulkowski M, Thomas DL, Mehta SH, et al. Hepatotoxicity associated with nevirapine or efavirenz-containing antiretroviral therapy: role of hepatitis C and B infections. *Hepatology*. 2002;35:182-189.
- Macias J, Castellano V, Merchante N, et al. Effect of antiretroviral drugs on liver fibrosis in HIV-infected patients with chronic hepatitis C: harmful impact of nevirapine. *AIDS*. 2004;18:767-774.
- Sulkowski MS, Mehta SH, Chaisson RE, et al. Hepatotoxicity associated with protease inhibitor-based antiretroviral regimens with or without concurrent ritonavir. *AIDS*. 2004;18:2277-2284.
- Wit FW, Weverling GJ, Weel J, et al. Incidence of and risk factors for severe hepatotoxicity associated with antiretroviral combination therapy. *J Infect Dis*. 2002;186:23-31.

55. US Department of Health and Human Services Panel on Clinical Practices for Treatment of HIV Infection. *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*. April 7, 2005.
56. Niederau C, Heintges T, Lange S, et al. Long-term follow-up of HBeAg-positive patients treated with interferon alfa for chronic hepatitis B. *N Engl J Med*. 1996;334:1422-1427.
57. Peters M, Anderson J, Lynch P, et al. Tenofovir disoproxil fumarate is not inferior to adefovir dipivoxil for the treatment of hepatitis B virus in subjects who are co-infected with HIV: results of ACTG A5127. 12th Conference on Retroviruses and Opportunistic Infections. February 22-25, 2005. Boston. [Abstract 124]
58. Torriani FJ, Rodriguez-Torres M, Rockstroh JH, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C infection in HIV-infected patients. *N Engl J Med*. 2004;351:438-450.
59. Mauss S, Berger F, Goelz J, et al. A prospective controlled study of interferon-based therapy of chronic hepatitis C in patients on methadone maintenance. *Hepatology*. 2004;40:120-124.
60. Morales-Ramirez JO, Teppler H, Kovacs C, et al. Antiretroviral effect of MK-0518, a novel HIV-1 integrase inhibitor, in ART-naive HIV-1 infected patients. 10th European AIDS Conference. November 17-20, 2005. Dublin. [Abstract LBPS1/6]
61. Martin D, Jacobson J, D Schurmann D, et al. PA-457, the first-in-class maturation inhibitor, exhibits antiviral activity following a single oral dose in HIV-1-infected patients. 12th Conference on Retroviruses and Opportunistic Infections. February 22-25, 2005. Boston. [Abstract 159]
62. Kuritzkes DR, Jacobson J, Powderly WG, et al. Antiretroviral activity of the anti-CD4 monoclonal antibody TNX-355 in patients infected with HIV type 1. *J Infect Dis*. 2004;189:286-291.
63. Moyle GJ, Wildfire A, Mandalia S, et al. Epidemiology and predictive factors for chemokine receptor use in HIV-1 infection. *J Infect Dis*. 2005;191:866-872.
64. Schering-Plough discontinues phase II study of vicriviroc in treatment-naive HIV patients, continues phase II study in treatment-experienced HIV patients [press release]. Kenilworth, New Jersey: Schering-Plough. October 27, 2005.
65. Westby M, Mori J, Smith-Burchnell C, et al. Maraviroc (UK-427,857)-resistant HIV-1 variants, selected by serial passage, are sensitive to CCR5 antagonists and T-20. XIV International HIV Drug Resistance Workshop. June 7-11, 2005. Québec City. [Abstract 65]
66. Molina JM, Wilkin A, Domingo P, et al. Once-daily vs. twice-daily lopinavir/ritonavir in antiretroviral-naive patients: 96-week results. 3rd IAS Conference on HIV Pathogenesis and Treatment. July 24-27, 2005. Rio de Janeiro. [Abstract WePe12.3C.12]
67. Robbins GK, De Gruttola V, Shafer RW, et al. Comparison of sequential three-drug regimens as initial therapy for HIV-1 infection. *N Engl J Med*. 2003;349:2293-2303.
68. Pozniak AL, Gallant JE, DeJesus E, et al. Superior outcome for tenofovir DF (TDF), emtricitabine (FTC) and efavirenz (EFV) compared to fixed dose zidovudine/lamivudine (CBV) and EFV in antiretroviral naive patients. 3rd IAS Conference on HIV Pathogenesis and Treatment. July 24-27, 2005. Rio de Janeiro. [Abstract WeOa0202]
69. Gulick RM, Ribaldo HJ, Shikuma CM, et al. Triple-nucleoside regimens versus efavirenz-containing regimens for the initial treatment of HIV-1 infection. *N Engl J Med*. 2004;350:1850-1861.

You're Invited! Honoring Our Heroes



**February 8, 2006
Denver, Colorado**



battling complacency
advancing commitment

**Colorado
Convention Center**



ABSTRACTS

Clinical Infectious Diseases

Incidence of tuberculosis among HIV-infected patients receiving highly active antiretroviral therapy in Europe and North America

The Antiretroviral Therapy Cohort Collaboration.

BACKGROUND: We obtained estimates of the incidence of tuberculosis (TB) among patients receiving highly active antiretroviral therapy (HAART) and identified determinants of the incidence. **METHODS:** We analyzed the incidence of TB during the first three years after initiation of HAART among 17,142 treatment-naïve, AIDS-free persons starting HAART who were enrolled in 12 cohorts from Europe and North America. We used univariable and multivariable Poisson regression models to identify factors associated with the incidence. **RESULTS:** During the first three years (36,906 person-years), 173 patients developed TB (incidence, 4.69 cases per 1,000 person-years). In multivariable analysis, the incidence rate was lower for men who have sex with men, compared with injection drug users (relative rate, 2.46; 95% confidence interval [CI], 1.51-4.01), heterosexuals (relative rate, 2.42; 95% CI, 1.64-3.59), those with other suspected modes of transmission (relative rate, 1.66; 95% CI, 0.91-3.06), and those with a higher CD4 count at the time of HAART initiation (relative rate per \log_2 cells/ μ L, 0.87; 95% CI, 0.84-0.91). During 28,846 person-years of follow-up after the first six months of HAART, 88 patients developed TB (incidence, 3.1 cases per 1,000 person-years of follow-up). In multivariable analysis, a low baseline CD4 count (relative rate per \log_2 cells/ μ L, 0.89; 95% CI, 0.83-0.96), six-month CD4 count (relative rate per \log_2 cells/ μ L, 0.90; 95% CI, 0.81-0.99), and a six-month HIV RNA level >400 copies/mL (relative rate, 2.21; 95% CI, 1.33-3.67) were significantly associated with the risk of acquiring TB after six months of HAART. **CONCLUSION:** The level of immunodeficiency at which HAART is initiated and the response to HAART are important determinants of the risk of TB. However, this risk remains appreciable even among those with a good response to HAART, suggesting that other interventions may be needed to control the TB epidemic in the HIV-infected population.

Clin Infect Dis. 2005;41(12):1772-1782.

HIV Medicine

Carotid intima-media thickness is slightly increased over time in HIV-1-infected patients

Mercie P, Thiebaut R, Aurillac-Lavignolle V, et al, on behalf of the Groupe d'Epidemiologie Clinique du Sida en Aquitaine (GECSA).

OBJECTIVES: HIV-infected patients are at risk of atherosclerosis and cardiovascular diseases. In a 12-month follow-up study, we aimed to investigate changes in carotid intima-media thickness (IMT),

a surrogate marker of atherosclerosis, and its determinants in HIV-1-infected patients. **METHODS:** Our multicenter prospective longitudinal cohort study included 346 HIV-infected patients, for each of whom two IMT measurements were taken by B-mode ultrasonography at baseline (M0) and one year later (M12). **RESULTS:** We observed a significant but moderate increase in the common carotid artery (CCA) median IMT, from 0.54 to 0.56 mm ($P < 10^{-4}$), ie, an increase of 0.020 mm (95% confidence interval [CI] 0.012-0.029). There was a significant association between cross-sectional CCA IMT measures at M12 and conventional cardiovascular risk factors (higher CCA IMT with older age, $P < 10^{-4}$; male gender, $P = 0.02$; tobacco consumption, $P = 0.05$), as well as higher CD4 cell count at M12 ($>$ median 455 cells/ μ L, $P = 0.01$). Only CD4 cell count at M0 was strongly and positively associated with the variation in IMT between M0 and M12 ($P = 4 \times 10^{-3}$). Intima-media thickness progression was +0.0020 mm for the lowest quartile of CD4 cell count distribution at M0, ie, 3 to 253 cells/ μ L, +0.010 mm for 253 to 402 cells/ μ L, +0.043 mm for 402 to 590 cells/ μ L, and +0.028 mm for 590 to 2,270 cells/ μ L. No association was found with type or duration of antiretroviral exposure. **CONCLUSIONS:** Conventional cardiovascular risk factors are major determinants of IMT evolution. The link between immunological status and carotid IMT requires further study.

HIV Med. 2005;6(6):380-387.

Journal of Infectious Diseases

Histological findings and clinical characteristics associated with hepatic steatosis in patients coinfecting with HIV and hepatitis C virus

Marks KM, Petrovic LM, Talal AH, et al.

BACKGROUND: Hepatic steatosis, a common histological finding in hepatitis C virus (HCV)-infected patients, is associated with severity of fibrosis. The prevalence and significance of steatosis in patients coinfecting with HIV and HCV are not well characterized. **METHODS:** To determine the prevalence and severity of steatosis, a single pathologist evaluated liver-biopsy samples from 106 patients coinfecting with HIV and HCV but without hepatitis B infection (negative results for hepatitis B surface antigen) for findings associated with steatosis or steatohepatitis and viral hepatitis. Medical records were reviewed retrospectively to elucidate risk factors for steatosis. **RESULTS:** Steatosis was present in 56% of biopsy samples, with moderate to severe grades in 9%. Severity of steatosis was associated with fibrosis (odds ratio [OR], 1.84; 95% confidence interval [CI], 1.06-3.20; $P = 0.03$) but not with necroinflammation. In multivariate analysis, the severity of steatosis was associated with lower levels of high-density lipoprotein cholesterol (OR, 0.71 per 10-mg/dL increase; 95% CI, 0.52-0.95; $P = 0.02$),

higher body-mass index (OR, 1.30 per kg/m^2 increase; 95% CI, 1.13-1.49; $P < 0.001$), and the presence of lipodystrophy (OR, 3.82; 95% CI, 1.13-12.88; $P = 0.03$). There was a trend toward an association between the severity of steatosis and fibrosis in multivariate analysis (OR, 1.69; 95% CI, 0.91-3.16; $P = 0.10$). **CONCLUSIONS:** In patients coinfecting with HIV and HCV, hepatic steatosis is common and associated with more advanced fibrosis. Lower levels of high-density lipoprotein cholesterol, higher body-mass index, and lipodystrophy are potentially modifiable risk factors associated with the severity of steatosis.

J Infect Dis. 2005;192(11):1943-1949.

Journal of Acquired Immune Deficiency Syndromes

High maternal HIV-1 viral load during pregnancy is associated with reduced placental transfer of measles IgG antibody

Faruqhar C, Nduati R, Haigwood N, et al.

BACKGROUND: Studies among HIV-1-infected women have demonstrated reduced placental transfer of IgG antibodies against measles and other pathogens. As a result, infants born to women with HIV-1 infection may not acquire adequate passive immunity *in utero* and this could contribute to high infant morbidity and mortality in this vulnerable population. **METHODS:** To determine factors associated with decreased placental transfer of measles IgG, 55 HIV-1-infected pregnant women who were enrolled in a Nairobi perinatal HIV-1 transmission study were followed. Maternal CD4 count, HIV-1 viral load, and HIV-1-specific gp41 antibody concentrations were measured antenatally and at delivery. Measles IgG concentrations were assayed in maternal blood and infant cord blood obtained during delivery to calculate placental antibody transfer. **RESULTS:** Among 40 women (73%) with positive measles titers, 30 (75%) were found to have abnormally low levels of maternofetal IgG transfer ($<95\%$). High maternal HIV-1 viral load at 32 weeks gestation and at delivery was associated with reductions in placental transfer ($P < 0.0001$ and $P = 0.0056$, respectively) and infant measles IgG concentrations in cord blood ($P < 0.0001$ and $P = 0.0073$, respectively). High maternal HIV-1-specific gp41 antibody titer was also highly correlated with both decreased placental transfer ($P = 0.0080$) and decreased infant IgG ($P < 0.0001$). **CONCLUSIONS:** This is the first study to evaluate the relationship between maternal HIV-1 viremia, maternal HIV-1 antibody concentrations, and passive immunity among HIV-1-exposed infants. These data support the hypothesis that high HIV-1 viral load during the last trimester may impair maternofetal transfer of IgG and increase risk of measles and other serious infections among HIV-1-exposed infants.

J Acquir Immune Defic Syndr. 2005;40(4):494-497.

More on the link between HCV, drugs, unprotected sex

Liz Highleyman

A variety of factors related to sexual activity and drug use have contributed to an outbreak of hepatitis C among HIV-positive gay men in southeast England in recent years, according to a presentation by Mark Danta (Royal Free and University College Medical School, London) at the American Association for the Study of Liver Diseases (AASLD) annual meeting held November 11-15, 2005, in San Francisco, California.

More than 200 cases of acute hepatitis C virus (HCV) infection have been diagnosed in HIV-positive gay men seen at the Royal Free Hospital, Chelsea and Westminster Hospital, and University College Hospital in London; an additional 12 cases have been detected in Brighton.

The current study aimed to characterize the mode of HCV transmission, using both molecular analysis and a case-control examination of risk factors. The study included 111 HIV-positive gay men with acute hepatitis C recruited since 2002 from HIV units at Chelsea and Westminster (50 cases), Royal Free Hospital (50 cases), and Brighton Hospital (11 cases). The median age was 36 years, 65% were on antiretroviral therapy (ART), and the mean CD4 count at diagnosis was 552 cells/mm³. Most of the men (88%) had hepatitis C genotype 1, 8% had genotype 3, and 4% had genotype 4. About one third (30%) had been diagnosed with syphilis within the year prior to contracting hepatitis C.

In the molecular analysis, the researchers constructed phylogenetic trees using the E1/E2 sequence of the HCV genome to illustrate the relatedness between the men's specific viral variants. The genome patterns clustered into several distinct monophyletic "clades," or lineages, providing strong evidence for common sources of HCV

transmission. Because the clusters crossed subtypes and genotypes, the analysis suggested that "this epidemic is not due to a hepatitis C viral change, but rather behavioral and/or environmental factors," Danta reported.

In the epidemiological study, 60 patients with acute HCV and 130 matched HIV-positive/HCV-negative controls completed questionnaires about their risk factors over the 12 months preceding HCV diagnosis. Baseline characteristics were similar in both groups, although the case patients were less likely than the controls to be on ART.

In terms of risk factors, men with acute hepatitis C were more than twice as likely than control subjects to be injecting drug users (17% versus 7%; $P=0.08$), although the overall rate was low compared to other HCV-infected populations. Cases were also somewhat more likely to have tattoos (60% versus 44%), piercings (70% versus 52%; $P=0.03$), and a history of blood transfusion (17% versus 8%). Because most tattooing and piercing was done under sterile conditions, however, Danta suggested that HCV infection was "not really attributable" to these factors.

Similar percentages of men in both groups met sex partners in bars or clubs, at private parties, or in public cruising areas. But men with acute hepatitis C were significantly more likely to meet partners in sex clubs/bathhouses/saunas (approximately 4% versus 1%; $P=0.01$) or on the Internet (approximately 49% versus 8%; $P=0.003$). The HCV-infected men had a median 30 sex partners in the past year, compared with 10 for controls ($P=0.001$); in both groups, a majority of these partners were "one-night stands."

Looking at specific sexual practices, HCV-infected men were significantly more likely than control subjects to have engaged in unprotected receptive or insertive anal intercourse ($P<0.001$), receptive or insertive fisting ($P<0.001$), use of sex toys ($P<0.001$), receptive or active anilingus ("rimming"), and sado-masochism and group sex; rates of protected

receptive and insertive anal intercourse were similar in both groups. The largest difference was seen in the rates of insertive fisting (about three times higher among the HCV-infected men) and receptive fisting (about four times higher).

Men with acute hepatitis C were significantly more likely to have ever had syphilis, gonorrhea, and non-specific urethritis (all $P<0.01$). But overall, most men in both groups had a history of any sexually transmitted infection: 92% for the HCV-infected men and 78% for the control subjects ($P<0.01$).

The HCV-infected men were significantly more likely to have had sex under the influence of drugs (92% versus 62%; $P<0.001$). Use of various "club drugs" including crystal methamphetamine, ketamine, Gamma hydroxybutyrate (GHB), and Ecstasy was significantly more common among men with acute hepatitis C ($P\leq 0.006$). While injecting drug use was uncommon in both groups, HCV-infected men were significantly more likely to have shared paraphernalia for intranasal drug use (approximately 79% versus 49%; $P<0.001$).

Summarizing these findings, Danta concluded that various high-risk sexual practices, meeting partners online, the use of "club drugs," and sharing equipment for intranasal drug use are all linked to HCV transmission among HIV-positive gay men. However, because there is considerable overlap among these factors, it is difficult to tease out their relative contributions. Since high-risk sexual and drug use practices appear to be driving this epidemic—as opposed to traditional parenteral risk factors—he recommended that education about safe sex and drug-sharing practices should be the focus of preventive public health interventions. ■

Reference

1. Danta M, Brown D, Pybus O, et al. Evidence for sexual transmission of HCV in recent epidemic in HIV-infected men in South-East England. 56th Annual Meeting of the American Association for the Study of Liver Diseases. November 11-15, 2005. San Francisco. [Abstract 67040]

Editor's Note: Reprinted with permission from www.aidsmap.com (first e-published November 14, 2005).



IN THE LIFE



Albrecht Ulmer

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 Albrecht Ulmer, physician in private HIV practice with Bernhard Frietsch and Markus Mueller in Stuttgart, Germany.

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

Very, very small, but observable.

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

I enjoy music, playing piano, a little bit of classical composing.

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

Everywhere the sun shines enough, and the people are so friendly that I could live in freedom.

Who are your mentors or real life heroes?

Robert Newman of New York, and Frère Roger of Taizé, and many, many others whom I admire and from whom I learn, including patients.

With what historical figure do you most identify?

I never did. But I feel some closeness to the people who had to go to concentration camps or died for their convictions.

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

Painters: Vincent van Gogh, Edward Munch. Composers: Ludwig van Beethoven, Wolfgang Amadeus Mozart, Giacomo Puccini, Johannes Brahms, and others. Architect: Dominikus Zimmermann.

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

I don't know; perhaps during the years 1700-1770.

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

A pianist, composer, or archaeologist.

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

Achievements: Some compositions of my favorite composers, the life of Mahatma Gandhi. Failures: Hitler and others like him. Medical failures: That there is not enough interest in inexpensive solutions.

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

We have to reduce the danger of humans for humans. Life, and especially each human being, is an unbelievable miracle. ■



SAY ANYTHING



In 10 to 20 years' time about 50% of the population is going to be affected by HIV.

Alphonse Tay, Chief of Port Moresby General Hospital, Port Moresby, Papua New Guinea, in a November 4, 2005, Reuters report about this oceanic country's HIV epidemic. The number of known HIV-positive Papuans is around 12,000, but the number of people infected is believed to be closer to 80,000 to 120,000. Combatting HIV in Papua New Guinea is complicated by the fact that some residents believe HIV is connected to sorcery, and thus shun or actively harm people believed to be HIV-infected. Police have also been implicated in a human rights report of participating in gang rapes, and of beating people who are found to be carrying condoms.



I feel truly special and lucky. All the doctors have told me it is a medical miracle that I am clear.

Andrew Stimpson, an HIV-positive British man as quoted in a November 20, 2005, News of the World article, entitled, "I'm First in World to be Cured of HIV." The tabloid article claimed that the 25-year-old man had been diagnosed as HIV-positive in 2002 only to "learn" last year that he is now HIV-negative. Although the tabloid described Stimpson's case as miraculous, British AIDS advocates are concerned about widespread media misreporting of the details of the case. HIV prevention experts point out that although many media reports treat Stimpson's claims with caution, others have taken them at face value, which may lead to a belief that HIV can be "cured" spontaneously. They warn that until further scientific details can be reported, this anecdotal report is fascinating but unsubstantiated.



It's unacceptable that most patients must become disabled before they can qualify for Medicaid coverage.

Gordon Smith, Republican US Senator from Oregon, in a November 10, 2005, Bay Area Reporter article about the Early Treatment for HIV Act, which the US Senate approved November 3, 2005. The five-year, US\$450 million demonstration project would provide HIV-positive patients earlier access to Medicaid by enhancing federal matching funds for states that provide Medicaid benefits to low-income HIV-positive patients. Currently, to receive Medicaid coverage for antiretroviral drugs, patients must be diagnosed with an AIDS-defining condition. Under the act, patients would be provided treatment when guidelines state that it should be started.



If you protect women's legal rights, you go a long way towards protecting them from HIV.

Marina Mahathir, President of the Malaysian AIDS Council and daughter of Malaysia's former Premier, in a November 9, 2005, Agence France-Presse report covering the International Federation Of Women Lawyers (FIDA) XXXII International Conference, held November 7-11, 2005, in Kuala Lumpur. Speakers at the conference said that widespread failure to protect the legal and property rights of women and children has caused those populations to be at a higher risk of HIV/AIDS. "In most parts of Africa, girls and women face particular risks of HIV infection due to their disadvantaged physical, economic, and legal positions, and social status," said Victoria Awomolo, a Nigerian lawyer. "Women cannot negotiate for safe sex or say no to unfaithful partners. Monogamous married women are powerless

against infection by husbands with outside partners. To worsen the situation, economic dependency prevents women from leaving unsafe sexual relationships."



The normative framework in which we define HIV and AIDS in the [United States] is outdated. It does not match the current epidemiology and is based on social and political beliefs that no longer hold true. [T]he virus has changed dramatically, treatments have changed, the communities most affected have changed, but the way we fund and care for people has not.

Rebecca Haag, Executive Director of AIDS Action Committee (AAC), at the AAC's annual meeting, held November 1, 2005, in Boston, as reported in a November 3, 2005, Bay Windows article. Haag announced at the meeting that her agency and other AIDS organizations throughout the United States are creating a coalition to advocate "bold thinking and a new innovative approach" to ending the AIDS epidemic. According to Haag, the effort will create "a national 10-year plan to stop this epidemic."



One of the worst consequences of the AIDS epidemic is the discrimination. Without a doubt this violates people's dignity and impoverishes society.

Tony Saca, President of El Salvador, at an AIDS conference in San Salvador, as reported November 9, 2005, by the Associated Press. Saca stated that HIV prevention and treatment "should be at the top of our political agenda." AIDS activists hope that the meeting will spur representatives of Latin American governments to sign commitments to make anti-retroviral therapy more available in their respective countries.



**2006 NIMH/IAPAC
International Conference on
HIV Treatment Adherence**

March 8-10, 2006

**Hyatt Regency Hotel
Jersey City, New Jersey**

Visit www.hivadherenceconference.com for program and other information.