As we enter the tenth year of the HAART (highly active antiretroviral therapy) era, HIV-infected subjects can no longer be simply classified as treatment-naïve or treatment-experienced when considering therapy. Subjects infected with drug-resistant virus may have limited therapeutic options from the start. In the recently publicized New York City case of multidrug-resistant HIV, for example, only two active drugs are available for fighting the virus at the start of treatment. The resistance profile when considering therapy. Subjects infected with drug-resistant virus may have limited therapeutic options from the start. In the recently publicized New York City case of multidrug-resistant HIV, for example, only two active drugs are available for fighting the virus at the start of treatment. The resistance profile
Ask the Expert:

In Light of Recent Resistance Trends, How Should Clinicians Treat Antiretroviral-Drug-Resistant HIV-1?

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Investigators in New York City have recently reported a case of an individual who became infected with multidrug-resistant HIV and who subsequently progressed rapidly to AIDS. This case has generated widespread concern that a new, more virulent form of the virus may emerge with time, and that our current ability to treat the virus may be limited. While the answers to these questions remain to be determined, the New York City case clearly illustrates that despite aggressive treatment, many patients remain at risk for developing progressive immunodeficiency.

Unfortunately, resistance to one drug often confers cross-resistance to other drugs in the same therapeutic class.

Unless drug treatment completely inhibits viral replication, powerful selection pressure typically leads to the emergence of resistant variants of HIV-1. In untreated patients, HIV-1 replicates at a high rate, with at least 10^9 new virions produced and cleared per day. This high viral replication rate, coupled with high mutability and high plasticity, permits the virus to evolve rapidly in the presence of incompletely suppressive antiretroviral therapy.

Over the past few years, the proportion of patients newly infected with drug-resistant HIV-1 has risen dramatically. This trend is especially evident in the United States, where most studies suggest that the proportion of patients infected with drug-resistant HIV-1 has grown from less than 5% before 1996 to 10-22% in 1998-2000. Recent unpublished data from a number of U.S.-based cohorts suggest that these rates have stabilized in recent years. Although the transmission of resistance remains a concern, most drug resistance found in clinics is due to de novo generation in settings of poorly administered antiretroviral therapy, rather than transmission of resistant virus.

A limited number of prospective clinical trials comparing various treatment approaches for patients with drug-resistant HIV-1 have yielded consistent conclusions. First, higher viral suppression results when more antiretroviral drugs are used, especially when a new therapeutic class is employed. Second, patients with early-stage HIV-1 disease, lower viral loads, or both, have a better virological response to salvage therapy than do patients with later-stage disease.

Third, genotypic or phenotypic resistance is associated with poor virological response to subsequent salvage therapy. These data support the general recommendations that salvage therapy

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risk of pursuing an undetectable viral load becomes more murky. In these instances, how should clinicians treat motivated patients with multidrug-resistant HIV-1?

One approach is to administer as many drugs as possible, in the hope of achieving complete viral suppression. In a large salvage study, patients given a complex regimen of five drugs had more viral suppression than patients given a four-drug regimen. (6) Yet it is not clear whether such complex regimens should always be used; each additional drug brings with it higher financial costs and a higher risk of treatment-related adverse events, such as drug-associated toxicity.

The question of when to switch therapy in patients infected with multidrug-resistant HIV-1 remains controversial. On the one hand, modifying therapy at the first signs of virological failure risks the rapid exhaustion of all therapeutic classes. On the other, continuing the same therapy risks the accumulation of drug-resistance mutations and unpredictable immunological and clinical consequences. Clinical assays that measure viral replicative capacity might be useful in deciding whether a switch in treatments is necessary or whether the clinician can stay the course.

Drug-resistant HIV-1 is presumed to be more fit than the wild-type in the presence of the drug, but has a lower replicative capacity. When patients with drug-resistant HIV-1 infection stop antiretroviral therapy, the archived wild-type strain typically emerges and out-competes the drug-resistant variant. (11) In view of this finding, interrupting therapy in patients with incomplete viral suppression may help preserve future treatment options.

Given the continued dilemmas in HIV-1 treatment, there is an urgent need for agents that target novel aspects of the viral life cycle. Perhaps the most compelling question today is how best to use new therapeutic drug classes as they become available. In the absence of controlled data, such decisions must be made on a case-by-case basis, taking into account the patient’s immediate risk of disease progression and the predicted interval before other potentially effective therapies become available. The recent New York City case notwithstanding, there is still only limited evidence that virological failure and the emergence of drug resistance leads to rapid clinical progression. The factors associated with rapid disease progression in the setting of chronic disease remain to be defined.

References:

Q: If resistance to trimethoprim-sulfa rises, what would be the public health consequences?

A: It would be disastrous. We give trimethoprim-sulfa globally. It’s used relatively early in HIV disease. And it’s been shown to have an impact in many developing countries in Africa and Asia in decreasing the morbidity and mortality associated with HIV/AIDS.

The amazing thing about trimethoprim-sulfa is that it has multiple actions. You’re protecting against *Pneumocystis carinii* — which in the developed world is the most common opportunistic infection. You’re protecting against pneumococcus. You’re probably protecting against more enteropathogens. Some people think trimethoprim-sulfa, although it’s not a great anti-TB drug, might make it harder for TB to reactivate. And there’s a protozoan that trimethoprim-sulfa works against that causes bad diarrhea in developing nations, called *Isospora belli*.

The next-line drugs are not as broad-spectrum. You can use Dapsone, but it’s probably not going to work, depending on the level and the type of resistance; if you have sulfa resistance, you’ll have sulfone resistance. If you don’t use Dapsone, then you’re stuck with an agent like atavoquone, which is even narrower spectrum and much more expensive.

Q: Are *Salmonella* and *Shigella* becoming resistant to TMP-SMX in HIV/AIDS patients?

A: There have been case reports. But there’s not a lot of good data to make a definitive comment — given that we have more than 40 million HIV infected people in the world and 20 million who have died. We know that it’s happened, and we know that we have to continue surveillance, because these are potential problems. Monitoring surveillance is the kind of thing that APUA has been very good at.

Q: Isn’t another bacterial infection — tuberculosis — the biggest proximate killer of people with HIV/AIDS?

A: It’s thought to be, in terms of infectious causes. Some people call TB an opportunistic infection. But it’s an atypical opportunistic infection, because TB is pervasive in the parts of the world where the HIV epidemic is spreading widely. We know that HIV contributes, but it’s not the only factor in that environment. If you didn’t have an HIV epidemic, these areas would still be highly endemic for tuberculosis.

Q: The HIV pandemic has coincided with the worldwide epidemic of antimicrobial resistance. What do you fear about these overlapping scourges?

A: It’s a big concern. In the HIV epidemic, you have so many immunocompromised people — five million new HIV infections every year — it has great potential to exacerbate the antibiotic resistance epidemic. The increased need to use trimethoprim-sulfa in immunocompromised hosts can’t be a good thing. Nor is the massive increase in the need for anti-tuberculosis therapy.

Q: Are you concerned that antibiotic-resistant bacterial infections in HIV/AIDS patients could spread to the wider community?

A: “Those concerns deserve further study. The use of long-term trimethoprim-sulfa, the propensity for recurrent pneumococcal infections, co-infection with tuberculosis — all these factors, in the setting of chronic immunosuppression among millions of patients who do not have access to highly active antiretroviral therapy, raise the specter of wider dissemination of multidrug-resistant infections in other community members. Recent reports of MRSA-related soft tissue infections in the community have noted a disproportionate level of HIV co-infection — in fact, these may be an example of the spread of multidrug-resistant community-acquired infections from HIV-infected people to close contacts who are HIV-uninfected.

Q: Could we someday see a single massive wave of drug resistance from these two overlapping epidemics?

A: With HIV, a lot of things are contextual. Rather than one mass of drug resistance, you’ll see lots of different local epidemics where HIV is one factor exacerbating the underlying drug resistance problems.

Q: Do bacterial infections take a worse course in patients with HIV/AIDS?

A: Yes. Particularly with pneumococcus, the prevalence of pneumococcal bacteremia is much higher. There’s a good number of people who have fairly intact immune systems who may develop a pneumococcal infection, walk around with it, and get oral antibiotics and even respond to them, or get sick with pneumococcal pneumonia, but aren’t going to get bacteremic. But in people with HIV, the threshold to go from pneumococcal colonization and initial bacterial pneumonia to bacteremia is much lower. We also see more extra-pulmonary TB in people with HIV — and so, more dissemination of tuberculosis and more reactivation of TB after completing what might be considered adequate courses of antituberculosis chemotherapy.

Q: Is it true that HIV patients, even with correct doses of the proper antibiotics, may still experience a relapse of bacterial disease?

A: Yes. The problem is that if you’re severely immunocompromised with HIV, and you’re not on effective antiretroviral therapy, the CD4 cells orchestrate a number of immune responses, and some of them are related to B lymphocyte function and antibody function. So while people with HIV may have very high titers of specific antibodies, some of the cells that the antibodies are helping in the process of killing aren’t working so well. With profound HIV disease, you have an antibacterial killing defect.

Dr. Mayer spoke with Associate Editor Madeline Drexler.
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upon failure thus becomes an increasingly important factor for evaluating the long-term benefit of antiretroviral treatments.

For many HIV-infected patients, HAART fails to bring about complete viral suppression. The reasons for this failure may include nonadherence, use of suboptimal regimens, infection with drug-resistant strains of the virus, and severe immunodeficiency. (1) Unfortunately, many patients for whom an initial regimen fails are unable to achieve a durable response to a subsequent “salvage” therapy. Indeed, high virologic failure rates can follow the use of new therapeutic classes in HAART-experienced patients. (2)

While drug resistance leads to loss of antivirologic activity and increasing levels of viremia, patients often continue to experience immunologic and clinical benefits from treatment, even after highly resistant variants emerge (as long as therapy continues). (3) Many patients continue to receive stable therapy despite detectable viral replication because of the continued benefit conferred by partially effective therapy regimens and the risk of exhausting therapeutic options too soon when aggressive switch strategies are used. It is difficult to measure how much the chances of achieving virus suppression (resistance cost) are reduced, however, because no standard methodology exists for quantifying the impact of resistance mutations on future therapeutic options. Resistance cost evaluation for treatment strategies is even more important in resource-poor regions.

Given these dilemmas, simple and effective strategies to spare therapy options are vital. Needed is a metric that quantifies the number of antiretroviral drugs likely to be effective, based on genotypic and/or phenotypic resistance measurements at specified time points. In this regard, two related measures of future drug options (FDOs) may be useful, both in clinical and research settings. (4)

The first potential measure (FDO1) evaluates the number of drug classes to which a virus strain is sensitive and assigns extra value to full-class susceptibility to the nucleoside/nucleotide reverse-transcriptase inhibitor (NRTI) or protease inhibitor (PI) classes. On the basis of the viral genotype, a patient’s virus is scored as susceptible or resistant to each antiretroviral drug by use of a genotypic-interpretation system. The number of drug classes that include at least one drug to which the patient’s virus is susceptible is then determined. The final value of FDO1 is determined by further adding extra value if full-class susceptibility to NRTI or PI classes is observed.

A second measure of future drug options (FDO2) is determined by the number of drug classes that include at least one drug to which the patient’s virus is susceptible and the total number of effective drugs within each class. In determining the order of FDO2, the first component is deemed to be more important than the second.

The proposed FDO metrics are flexible enough to include new classes of drugs as they become available. Using such FDO metrics, the impact of therapy on resistance over a fixed period of time may be evaluated by measuring FDO end points at the beginning and end of the period. Resistance cost is defined as the difference in FDO end points at those two time points. Average resistance costs of therapies over variable periods of time can also be compared—for example, from the start of therapy to virologic failure.

The FDO approach may be a valuable addition to current approaches for assessing optimal treatments. Traditionally, surrogate markers have been used to determine optimal therapy strategies. Accepted surrogate markers include plasma HIV RNA levels and CD4+ T cell counts. With the FDO metric included as a therapy outcome, individual drug regimens demonstrating unique patterns of drug resistance (and cross-resistance) may be compared in terms of their impacts on future drug options.

The potential utility of the FDO endpoint is illustrated by considering the therapy outcomes observed in AIDS Clinical Trials Group (ACTG) 364, a randomized, multicenter, three-arm clinical trial comparing PI nelfinavir and/or the NNRTI efavirenz in combination with two nucleoside analogs in HIV-infected patients with prolonged, but exclusive, NRTI exposure (Table 1). The proportion of patients who maintained virus load suppression throughout the study was greatest in those receiving nelfinavir plus efavirenz, intermediate in those receiving efavirenz, and lowest in those receiving anti-retroviral therapy continued on next page
Cars Joins Scientific Advisory Board

APUA welcomes to its Scientific Advisory Board Otto Cars, M.D., Ph.D., APUA-Sweden chapter leader. Dr. Cars is Professor of Infectious Diseases at Uppsala University, Sweden, and Consultant Physician at the Swedish Institute for Infectious Disease Control. He is a board member of the Swedish Reference Group for Antibiotics (which he chaired from 1994 to 1998), and has served as chairman of the Swedish Strategic Programme for the Rational Use of Antimicrobial Agents and Surveillance of Resistance (STRAMA) since its inception in 1995. Professor Cars’ main scientific interests include pharmacokinetics and pharmacodynamics of antibiotics, optimal dosing regimens, and the epidemiology and prevention of antibiotic resistance.

GAARD

The 2005 Global Advisory on Antibiotic Resistance Data (GAARD) Report — “Global Antimicrobial Resistance Alerts and Public Health Implications” — has been accepted for September publication by Clinical Infectious Diseases. The landmark report provides a comprehensive view of drug resistance patterns across the world’s major infectious diseases, synthesizing findings from diverse surveillance systems run by the world’s leading infectious disease experts. Among the infectious disease threats discussed are HIV/AIDS, tuberculosis, malaria, gonorrhea, pneumonia, and hospital-associated infections. (See Executive Summary at www.apua.org.)

ROAR Databases Improved

APUA’s ROAR (Reservoirs of Antibiotic Resistance) project website has recently been improved to include the ROAR Isolate and Literature Databases (http://db.roarproject.org). The ROAR Literature Database is a fully searchable annotated bibliography of publications relevant to the study of resistance in commensal bacteria, while the Isolate Database is a searchable collection of raw commensal isolate datasets generated and provided to ROAR by investigators in the ROAR scientific network. As these data are expanded and refined, they can be used for meta-analysis by investigators to test the ROAR hypothesis that resistance determinants flow from commensal to pathogenic bacterial populations. The improved website includes features to facilitate the analysis of ROAR data, such as customized data downloading capability, as well as updated general information about the ROAR project.

ROAR is a five-year effort funded by the National Institute of Allergy and Infectious Diseases and coordinated by APUA. The project’s objective is to define the role of commensal organisms as reservoirs of antibiotic resistance determinants that may be transferred to pathogenic organisms.

ROAR Symposium at ASM

ROAR will host an APUA-coordinated symposium, “Commensal Reservoirs of Antibiotic Resistance,” on Tuesday, June 7, 2005, at the 105th General Meeting of the American Society for Microbiology in Atlanta, Georgia. Speakers include Marilyn Roberts, James Tiedje, and convenor and APUA President Dr. Stuart Levy. The annual ROAR Steering Committee meeting will also take place during the ASM General Meeting. To learn more about ROAR meetings or the ROAR Databases, or to join the ROAR Network of scientists, please see www.ROARProject.org, or contact Amelie Peryea at amelie.peryea@tufts.edu.

For clinicians, the FDO approach may offer a method to synthesize resistance information, thus optimizing sequential drug regimens in the long-term therapy of HIV infection. Clinicians need to be aware that when treating patients infected with multidrug-resistant virus, some treatment options may have already been lost — even before the patient has been exposed to any antiretroviral treatment.

References:
APUA-India

APUA-India co-sponsored the National Symposium on Use of Antibiotics in Medical Practice on January 29, 2005 at Jaipur. Speakers stressed the need for an essential drug list to guide prescriptions, preserve the power of antimicrobials, and reduce costs. Professor Ranjit Roy Chaudhury of UNESCO presented.

APUA-Philippines

APUA-Philippines held its meeting and symposium on February 23, 2005 during the 12th annual convention of the Pediatric Infectious Disease Society of the Philippines (PIDSP). The meeting focused on the microbiology and treatment of urinary tract infections. Among the speakers were Dr. Celia Carlos, chapter coordinator, and Dr. Benjamin Co, associate professor at the University of Santo Tomas.

APUA African Initiative

Zambia

APUA’s International Program Director traveled to Zambia February 12-19, 2005 to provide technical assistance to the APUA-Zambia chapter. Chapter members will be conducting a small research project, “Knowledge, attitudes and behaviors of prescribers in Lusaka.” During his visit, Dr. Anibal Sosa reviewed the President’s Emergency Plan for AIDS Relief (PEPFAR) country initiative to scale up HIV treatment. In an effort to strengthen collaboration, Dr. Sosa and the Zambian chapter leadership also met with the Linkages Program/AED, Health Services and Systems Program, The University of Lusaka School of Medicine, Care International-Zambia, the Centre for Infectious Disease Research in Zambia, Family Health International, the SHARE Program/JSI, the International HIV/AIDS Alliance, JHPIEGO, the National HIV/AIDS/STI/TB Council, the Society for Family Health and the USAID-Zambia mission. This trip report can be seen at: http://www.tufts.edu/med/apua/Chapters/chapters.html.

South Africa

On March 15, 2005, Dr. Sosa visited the African Centre for Health and Population Studies (http://www.africacentre.org.za/) in Mtubatuba; the center operates under the direction of Dr. Michael Bennish, a Tufts University Professor and APUA Scientific Advisory Board member. The center serves the people of the Umkhanyakude District in rural KwaZulu-Natal on South Africa’s east coast, in the heartland of the Zulu people. Dr. Sosa met with staff and learned about several ongoing research initiatives, including the A.C. Demographic Information System (ACDIS), the HIV-1 genotyping project, the Migration Project, the Maternal Nutritional Assessment Project, the Traditional Healers Project, the Verbal Autopsies Project, the Vertical Transmission Project (Mamanengane), the Micronutrients Study and the Microbicide Development Project designed to inhibit HIV and STD transmission. Photos at: http://www.tufts.edu/med/apua/chapters/southafrica.html.

Namibia

On March 20, 2005, Dr. Sosa visited Namibia to meet with Ministry of Health and Social Services officials, the National Institute of Pathology, the Management Sciences for Health/RPM Plus program, Family Health International, Catholic AIDS Association, WHO Namibia, Red Cross Namibia, Medical Association of Namibia, University Research Corporation and the USAID-Namibia mission. During the visit, Dr. Sosa explored a possible collaboration with PEPFAR, and initiated steps for establishing a new APUA chapter in Namibia.

APUA-Colombia

The APUA-Colombia chapter reports a recently passed law in the nation which makes it illegal for pharmacies and drug vendors to sell antibiotics to patients without valid prescriptions or to sell incomplete doses or treatments. Noncompliance leads to vendor fines. The goal of the new law is to reduce infection, antimicrobial resistance, and the cultural acceptance of self-medication. While the law represents an important step forward, enforcement will be a challenge, since an estimated 49% of Colombians do not have access to a medical doctor.

APUA-UK

Professor Peter Davey, APUA-UK chapter coordinator, is chairing The 2015 Club, a small debating society that is examining the question of whether antibiotics will be redundant by 2015. According to Professor Davey, “The 2015 Club is a unique opportunity for an experienced multi-disciplinary team to look at challenges posed by infection today, and to consider what we have to do now to ensure that we are in good shape in ten years’ time.”

APUA Chapter Leaders Honored

APUA-Italy chapter coordinator Dr. Giuseppe Cornaglia has been named President-Elect of the European Society for Clinical Microbiology and Infectious Diseases (ESCMID). His two-year term begins in 2007. APUA-Spain chapter coordinator Dr. Fernando Baquero received the ESCMID Award for Excellence as a tribute to his scientific achievements and organizational leadership.

Please send information about upcoming chapter events — including date, time, location, content, and sponsor — to flora.traub@tufts.edu, for posting on the APUA website. To view upcoming international chapter events, please go to: http://www.tufts.edu/med/apua/intl/events.html.
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... containing global antibiotic resistance through local action

Founded in 1981 as a nonprofit organization, APUA is the only organization in the world solely dedicated to strengthening society’s defenses against infectious diseases through research and education on antibiotic use and antibiotic resistance. APUA’s mission is to improve infectious disease treatment and control worldwide through promoting appropriate antibiotic access and use and reducing antibiotic resistance. With members in over 100 countries and numerous foreign affiliated chapters, APUA provides a unique network to support country-based activities and facilitate international planning and communication. APUA’s resources include an international scientific advisory board with members of national academies of medicine and science and a professional staff with specialized expertise. APUA’s global network of affiliated chapters serves to tailor interventions to local customs and practices.

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