GMHC treatment ISSUES
NEWSLETTER OF CURRENT ISSUES IN HIV/AIDS
OCTOBER 2003 VOLUME 17, NUMBER 10

The Burden of Disease
HIV, TB, Malaria and Hepatitis

By Bob Huff

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The "S" in AIDS stands for "syndrome," which refers to a pattern of illness proceeding from the immune deficiency that develops in the years after a person becomes infected with HIV: the human immunodeficiency virus. Many people have pointed out the semantic illogic of "getting AIDS," that "you can't catch a syndrome," but, despite liberties taken with the name, the illnesses associated with HIV disease are real and deadly. In classical AIDS, the infections that began to appear in otherwise healthy gay men in 1980 were rare in Western medicine. Some, such as pneumocystis carinii pneumonia (PCP), a disease known to strike immune suppressed transplant patients, gave a clue to the underlying damage to immunity. A constellation of other runaway fungal and viral infections—opportunists that flourished when defenses were low—quickly joined the list of illnesses that defined the syndrome of acquired immunodeficiency.

For too many people in the world, the burden of disease they face is amplified by HIV.

The opportunistic infections of HIV disease were easy to recognize because they stood out so starkly against the typical health status of the young, productive middle-class persons who first came to the attention of doctors in California and New York. Eventually, the set of symptoms that prefigured AIDS became well known and the disease was understood to progress along a continuum from primary infection to a terminal stage.

But if AIDS had first appeared among people with poor health and many other problems (and there is evidence that it did) it would not have been so easily discerned. While AIDS allows a number of characteristic infections to cause disease, for most of the people in the world with HIV, these occur on top of endemic infections or health problems that can be deadly in themselves. For too many people in the world, the burden of disease they face is amplified by HIV.

HIV exists in a complex web of interactions with other infections and pathologies. Some venereal diseases, such as herpes and chlamydia, may enhance the likelihood of becoming infected through sexual contact. Other problems, such as addiction and mental illness, also increase the risk of acquiring HIV and other infections, and, for the infected, make care and treatment much more difficult. Chronic poverty, lack of education and inadequate infrastructure may also be considered pathologies that exacerbate and sustain poor health.

Worldwide, each year, about 20 percent of all deaths are caused by infectious disease, with the overwhelming majority of these occurring in resource-poor regions. And about half of these deaths in the developing world are due to tuberculosis, malaria, and HIV. These are diseases that strike poor people and young people

disproportionately and help perpetuate poverty by affecting people in the prime of their productive lives. The losses in lack of development, lost opportunities and lost lives due to preventable and curable infectious diseases are incalculable.

HIV is a transmissible infection acquired through sexual contact, during birth, or by contaminated blood, that depletes an individual's immune capacity to fight off deadly infections and some cancers. Nearly 50 million people may be infected with HIV, and HIV disease killed more than three million people last year, with this number set to rise dramatically in the coming decade. An estimated five million people will become newly infected this year, with rates of new infections poised to explode in Asia and Eastern Europe. Currently, about 70 percent of all people with HIV live in sub-Saharan Africa, where the disease mostly affects women, children and young people, most with few economic resources. Treatment is effective but out of reach for most who need it due to cost.

Selected Preventable Causes of Death

Cause of death	Deaths in 2001
HIV/AIDS	2,886,000
TB	1,664,000
Malaria	1,124,000
Diarrheal diseases	2,001,000
Perinatal conditions	2,504,000
Childhood diseases	1,318,000
Cirrhosis	796,000
Liver cancer	616,000
Lung cancer	1,213,000
Traffic accidents	1,194,000
Suicide	849,000
War	230,000

The World Health Report 2002, WHO

Tuberculosis is a contagious respiratory infection that follows poverty and urban crowding, infecting 30 million each year and killing 5,000 people every day. Worldwide, TB is the leading killer of people with HIV, and the course of both HIV and TB is much more rapid and deadly in persons with both infections. In Africa, half of all TB cases are associated with HIV, and although relatively rare in the U.S. due to robust prevention and treatment efforts, 10 to 20 percent of TB cases are associated with HIV.

Malaria is endemic in many resource-poor tropical and sub-tropical regions where the Anopheles mosquito thrives, particularly in Africa. Worldwide, as many as 500 million cases of clinical malaria occur each year and over 3000 people die each day—many of them children in Africa. For people with HIV, especially pregnant women, episodes of acute malaria are complicated and more serious.

Hepatitis B virus (HBV) is responsible for chronic liver infection in 350 million people around the world and is a major contributor to 1.4 million annual deaths from liver disease and cancer. Transmitted by sex, blood or at birth, chronic HBV infection is a long, slow illness that can produce serious liver damage later in life. In the developing world, particularly in Asia, most HBV infections occur in children, with from 50 to 90 percent of those exposed developing chronic infections. Individuals with chronic HBV infection from childhood have a 25 percent lifetime risk of dying from liver disease. In addition, persons with both HIV and Hepatitis B may be more likely to develop serious liver disease than those with HBV alone.

Infection with another liver virus, hepatitis C (HCV) is nearly universal among injection drug users with HIV in the U.S. Worldwide, an estimated 170 million people are chronically infected with HCV. With a long, slow course of

The Top Ten Risk Factors for Disease and Injury throughout the World

In Developed Countries	In Developing Countries With Low Mortality	In Developing Countries With High Mortality
1. Tobacco	1. Alcohol	1. Underweight
2. Blood Pressure	2. Blood Pressure	2. Unsafe Sex
3. Alcohol	3. Tobacco	3. Unsafe Water, Sanitation, Hygiene
4. Cholesterol	4. Underweight	4. Indoor Smoke from Solid Fuels
5. Overweight	5. Overweight	5. Zinc Deficiency
6. Low Fruit and Vegetable Intake	6. Cholesterol	6. Iron Deficiency
7. Physical Inactivity	7. Low Fruit and Vegetable Intake	7. Vitamin A Deficiency
8. Illicit Drugs	8. Indoor Smoke from Solid Fuels	8. Blood Pressure
9. Unsafe Sex	9. Iron Deficiency	9. Tobacco
10. Iron Deficiency	10. Unsafe Water, Sanitation, Hygiene	10. Cholesterol

For the year 2000. The World Health Report 2002, WHO. Annex Table 14

progression, many people infected with HCV during the 1970s and 1980s are now experiencing serious liver disease, including cirrhosis and cancer. For those with HIV, liver damage may be more severe and treatment less successful. In the developed world, where death rates from AIDS have plummeted due to antiretroviral therapy, liver disease has emerged as one of the leading causes of mortality in people with HIV.

It's About Partnership

Collectively, these diseases may be responsible for over six million deaths per year, with many more trailing in their wake as the burden on economies and health care capacity becomes overwhelming. Increasingly, the fear that destabilized societies and economies may impact the security of Western nations has stimulated a great deal of rhetoric and an increasing amount of money dedicated to addressing the burden of disease in the world. Hopefully, several emerging global partnerships will be able to direct a coordinated and effective response to these threats as the promised resources become available.

Indeed, there are opportunities to be mined in these overlapping epidemics. Infrastructure in place to deliver TB treatment has been proposed as a platform on which to build a network to provide antiretroviral therapy. The high rate of antenatal clinic attendance in some parts of Africa gives an opportunity to detect HIV and sexually transmitted diseases, forestalling transmission to infants and preventing complications due to malaria.

The Global Fund for AIDS, Tuberculosis and Malaria (GFATM) was established to respond to these intertwining threats and has taken the first tentative steps towards underwriting expanded treatment programs on a country and regional basis. Although commitments to spend $2 billion by 2005 have been made, so far only $150 million has been disbursed. Despite the growing recognition that these diseases are a linked catastrophe, political will by the donor nations has lagged and the GFATM remains underfunded.

The Gates Foundation recently committed $168 million to fighting malaria and has issued challenges to develop affordable tests to diagnose infectious diseases and monitor therapy for HIV. The Grand Challenges in Global Health initiative is a $200 million partnership with the National Institutes of Health to get scientists to address open scientific questions in such fields as childhood vaccines, insect control, nutrition, and new treatments for debilitating latent infections that impede international development.

But the largest world body addressing the multiplicity of disease in the developing world is the World Health Organization (WHO), which, together with the UN's UNAIDS and other partners has launched an ambitious plan to bring HIV treatment to 3,000,000 people who need it over the next two years. While the thrust of this program is to procure drugs and diagnostics and establish guidelines for treating HIV with a restricted list of standard regimens, the necessary expansion of training and capacity improvement in the health care sector to allow ARV delivery is also expected to strengthen the ability to deliver a broader range of health services.

Success in rolling back malaria is seen as crucial for demonstrating that similar partnerships for TB and HIV are feasible.

Despite the existence of an effective vaccine for hepatitis B virus, few children in the world's poorest countries have been immunized. WHO is a leader in the Global Alliance for Vaccines and Immunization (GAVI), another broad-based partnership with the mission of vaccinating as many children as possible against preventable disease, such as hepatitis B.

WHO is also a leading agency in the Stop TB Partnership, a global association of all organizations and individuals working to control and eliminate TB in the world. Stop TB has set a goal of reducing the global burden of the disease by half by the year 2010. The means to accomplish this require a broad commitment from governments and NGOs to "ensure that every person with TB has access to a cure, that vulnerable populations are protected from infections, and that the social and economic damage of TB is minimized."

Roll Back Malaria is another WHO-founded global partnership with a goal of cutting the world's malaria burden in half by 2010. With a shorter treatment period, effective prevention technology and recent successes in fighting malaria in affected countries, this effort may have the best chance among the large-scale disease initiatives for hitting its marks Demonstrating success in rolling back malaria on a global scale is seen to be crucial for demonstrating that similar large partnerships for TB and HIV are feasible.

World Health Organization (WHO): www.who.int
UNAIDS: www.unaids.org
Global Fund for AIDS, TB & Malaria: www.theglobalfund.org
Global Alliance for Vaccines: www.vaccinealliance.org
Roll Back Malaria: mosquito.who.int
Stop TB Partnership: www.stoptb.org

TB Treatment Evolves

By Bob Huff

Over the past 50 years, and without any significant advances in the past 30 years, a number of fairly reliable medicines have been developed that effectively treat tuberculosis—as long as they are consistently and correctly taken. But simply knowing that there are drugs to treat TB is not enough, and much recent treatment research has focused on understanding the infrastructure and conditions that must be present to assure that courses of therapy are completed without interruption.

"Treatment of patients with tuberculosis is most successful within a comprehensive framework that addresses both clinical and social issues of relevance to the patient."

The Infectious Disease Society of America (IDSA), in association with the American Thoracic Society and the CDC has recently published updated guidelines for treating TB. The guidelines not only stress a provider's responsibility to prescribe appropriate regimens but also to assure that they are completed successfully. Directly observed therapy (DOT), which entails actually watching the patient swallow the mediation, is strongly recommended. Increasingly, this demands that providers embrace patient-centered case management to assure treatment adherence; it is not acceptable to simply prescribe drugs and send a patient home, or even to demand that patients show up at a prescribed time and place to take their pills. "Treatment of patients with tuberculosis is most successful within a comprehensive framework that addresses both clinical and social issues of relevance to the patient." Enhanced DOT may now include arranging for "social service support, treatment incentives and enablers, housing assistance, referral for treatment of substance abuse, and coordination of tuberculosis services with those of other providers." Studies have reported 91 percent treatment completion when enhanced DOT is used compared to 86 percent for DOT and 61 percent for unsupervised therapy. Adherence is measured by counting doses taken, and a complete course is accounted for down to the last pill. To do less has proven to yield suboptimal results.

In clinical trials, a trade-off was seen between duration of treatment and adherence. While a 9-month course of treatment was proven effective, gains were undermined by poor adherence. It has always been a problem for TB treatment that patients will stop taking their drugs after symptoms resolve, well before the TB organism has been eradicated. Better adherence—and better overall outcomes—have been demonstrated by using a 6-month course of treatment that is strictly adhered to, hence the emphasis on DOT and dose counting.

Treatment is generally planned in two stages, a first intensive stage that may last two months, and, depending on the results of sputum culture test, a second phase that may last from 4 to 7 months. For adults with previously untreated TB, the initial two-month course of treatment will use a four-drug regimen of isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and ethambutol (EMB) given daily for at least the first two weeks. Modifications may be made depending on drug susceptibility results. If TB therapy is given at the same time that certain anti-HIV drugs are being taken, rifabutin may be substituted for rifampin to avoid potential drug interactions.

For people without HIV who respond to the initial stage, the continuation phase may be as simple as once-weekly DOT to complete the six months. But regimens for people with HIV are more stringent, because their response to TB therapy is often less certain, and daily therapy, or thrice weekly at a minimum, is continued throughout the second phase.

Many of the TB drugs can cause hepatitis, which may pose special problems for patients with preexisting viral hepatitis or for persons with HIV taking antiretroviral drugs such as nevirapine that can cause hepatic toxicity. In general, the guidelines recommend toughing it out, giving precedence to finishing the course of therapy. In some cases, regimen modifications can be made, such as removing one of the liver toxic TB drugs while extending the duration of therapy. In all cases, frequent and careful monitoring should be performed to detect drug-induced liver injury.

TB Treatment in Resource-poor Settings

The Guidelines discussed above are designed for the U.S. and appropriate for a setting with a low incidence of TB, a public health commitment to TB elimination, and the resources to accomplish this through comprehensive case management. But, what is appropriate in regions where TB is epidemic and these resources are not present? Given that most new TB cases in the U.S. occur in foreign-born individuals, the world TB problem is a persistent factor in any plan to eliminate TB domestically. The World Health Organization has developed guidelines for countries without recourse to sophisticated drug suscepti-

bility testing and exotic backup drugs. While there are some difference in available drugs and recommended regimens, the underlying goals are the same: to assure treatment adherence and completion of the course of therapy. The strategy WHO offers to accomplish this is based on the familiar DOT, but within a national case management context called DOTS, for directly observed therapy, short course. The principles of DOTS are: "1) government commitment to sustained tuberculosis control activities, 2) case detection by sputum smear microscopy among symptomatic patients self-reporting to health services, 3) a standardized treatment regimen of 6 to 8 months for at least all confirmed sputum smear-positive cases, with DOT for at least the initial 2 months, 4) a regular, uninterrupted supply of all essential antituberculosis drugs, and 5) a standardized recording and reporting system that enables assessment of treatment results for each patient and of the tuberculosis control program overall."

CDC. Recommendations and reports: Treatment of tuberculosis. MMWR, June 20, 2003 / 52(RR11);1-77
http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5211a1.htm

Targeting Persistence: The Next Frontier in TB Drug Development

The Global Alliance for TB Drug Development

As if it weren't bad enough that tuberculosis affects a third of the world's population, 99.5% of those cases, or roughly 1.8 billion people, exhibit no outward symptoms of infection. They have a latent form of the disease. It sounds almost benign, but the reality is that the bacterium that causes the active disease—Mycobacterium tuberculosis or M.Tb persists in their lungs, cleverly concealed and notoriously hard to detect.

The persistence of M.Tb helps explain why TB has been so difficult to treat effectively. Each year, 8 million people who carry "latent" disease will experience reactivation of their disease to full-blown pulmonary tuberculosis. Only 27% of the world's TB patients are fully and properly treated. Even if they are lucky enough to finish treatment, some 5-20% of these patients will go on to experience a reactivation of disease. Most people don't know that they are not completely "cured" and that persistent bacteria can linger even after treatment with current drugs. Due to the large number of latent cases, reactivation is one of the most common ways the disease spreads from one person to another.

Since M.Tb was first identified, scientists have wrestled with its unusual ability to persist in a non-replicating state. It creates a problem for traditional antibiotics and raises some vexing questions: What is the bug doing in a persistent state? What causes it to go "active"? How critical is the immune system response? Perhaps most importantly, how can we begin to answer these questions?

These questions underscore the need for more basic research to address the complex biology of persistent M.Tb during latent disease. At the same time, it's been noted that persistent bacteria seem to play a role in both active and latent disease. Most antibiotics only target bacteria inside the body that are actively replicating. With tuberculosis, however, the bulk of infecting bacteria persist without replicating and live inside the very cells designed to destroy the disease. That makes it difficult to determine whether a patient is free from the disease. Furthermore, if a particular patient suffers another bout of TB symptoms, one can't be sure if it's a reactivation of persistent bacteria or a wholly new infection.

A Drug Strategy for Latency

A drug that targets latent disease is critical to improved therapy, reducing the spread of disease, and ultimately reversing the TB epidemic. However, latent disease poses a number of challenges to scientists trying to develop new drugs. One possible approach to targeting the persistent bacteria—without waiting for the basic science to get up to speed— is to work on developing a new, faster-acting treatment for the latent bacteria in patients with active tuberculosis. Research to date suggests that persistent bacteria behave similarly in both active and latent cases. The hope is that drugs developed to fight persistent bacteria will ultimately prove effective in treating latent disease.

Another clue supporting the validity of this approach is that research suggests that drugs that most effectively shorten TB therapy are most effective at attacking persistent M.Tb. Faster-acting drugs will offer benefits far beyond pointing the way to therapies aimed at latent disease. Drugs that need to be taken for relatively short periods of time will also ensure that more patients receive proper treatment, while reducing the associated healthcare expenses by up to 65%. Equally important, the shorter treatment duration will make it easier for people to see therapy through to the end. This will increase the likelihood of full compliance, limiting the opportunity for the bacteria to evolve beyond antibiotics' reach.

The Global Alliance for TB Drug Development is building a portfolio of promising drug candidates and creating partnerships in order to deliver a new anti-tuberculosis drug in a decade. A key part of the R&D strategy of the TB Alliance is to promote a productive environment for new TB research and drug development. For more about the Alliance: www.tballiance.org

Vaccinate to Prevent Hepatitis B

By Bob Huff

Susan Goldstein and colleagues from the Centers for Disease Control (CDC) have projectedthat if everyone born in 2000 were considered as a single cohort, and none were vaccinated for HBV, over their lifetimes they would experience 64.8 million HBV infections resulting in 9.7 million chronic infections. In this imaginary cohort there would be 1.4 million deaths from chronic infection and 65,000 deaths due to acute hepatitis B. Perinatal infection would contribute 21 percent of these deaths, infections occurring between birth and age 5 would account for 48 percent, and infections acquired after the age of 5 would lead to 31 percent of the deaths. They estimate that HBV infection would be responsible for 1.3 percent of the deaths of all people born in 2000.

They then modeled the effect that vaccination would have on these estimates. Infant vaccination with 90 percent 3-dose coverage starting within 24 hours of birth could prevent 84 percent of these projected HBV-related deaths.

Preventable HBV in a U.S. Prison

Despite general agreement that healthcare in prison settings is terrible, remarkably little research appears at the major infectious disease conferences to document the results of treatment or the epidemiology of disease behind bars. William Bower, of the CDC in Atlanta, presented a poster at the IDSA conference in San Diego that tracked the molecular epidemiology of HBV transmission in a Georgia state prison. Prisons are prime settings for transmitting HBV through sexual activity, shared needles, shared tattooing equipment or in fights. The CDC recommends hepatitis B vaccination for all inmates in correctional facilities without evidence of immunity.

A baseline serologic survey was conducted in June of 2000 of 1,124 participating prisoners. Of these, 11 were found with acute HBV infection, 11 had chronic infection and 208 had a resolved infection for a total of 230 or 20.5 percent of the sample. This left 894 inmates susceptible to infection. A year later, in June of 2001, a second survey of the susceptible inmates was conducted with 653 of the 894 remaining at the facility. Of these, 503 of 653 (77 percent) consented to retesting. One year after the baseline survey, 18 new infections were detected, with one of these a chronic infection. This results in an annual infection rate of 3,579 per 100,000 persons in this prison.

DNA sequence analysis identified 11 different strains within three HBV genotypes. Eight of the chronically infected and one of the acutely infected inmates had unique strains. But ten of the sequences represented the other two strains, with one of those found in four inmates with chronic infection. The other shared strain was found in six inmates, two with chronic and four with acute infection. Three of these acute infections turned up in the June 2000 survey and one in 2001. Two inmates with acute infection reported having sex with one of the inmates with chronic infection.

This study is remarkable for a number of reasons. First, it documents the sexual transmission of disease within a correctional facility, a phenomenon that is rarely acknowledged by corrections officials who then deny the need for providing condoms inside. It also confirms that, with an annual incidence of HBV infection in this facility over 120 times that of the estimated national incidence, prisons are incubators of infectious disease. It also shows the role that an individual can play in sparking an epidemic. Finally it shows that a prison in Georgia, willing to collaborate with the CDC in its research, routinely ignores its recommendation that all inmates be vaccinated against hepatitis B.

HBV in EuroSIDA

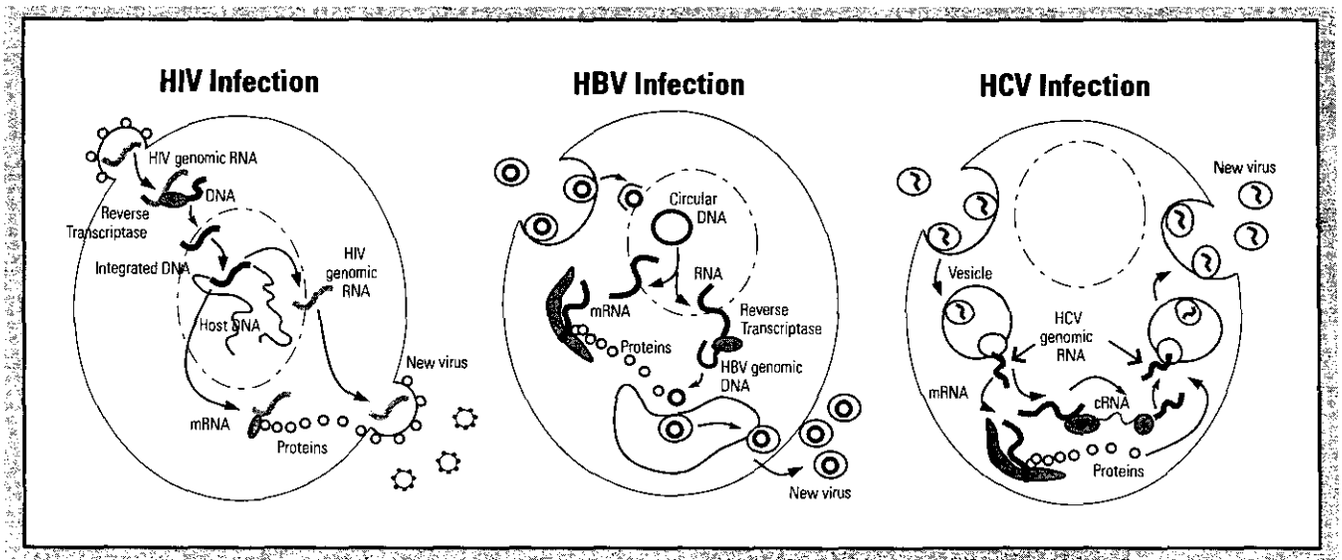
The EuroSIDA cohort reported on the impact that chronic HBV infection has on AIDS progression and response to antiretroviral therapy. Of 5,833 individuals in EuroSIDS tested for HBV surface antigen, 530 (9%) were found positive. The incidence of all-cause and liver-related death was greater in those with chronic HBV than in others (12 vs. 2.6 and 0.5 vs. 0.2/100 patient years, respectively). The authors conclude that HBV antigen status did not impact virological or immunological response in 1752 patients receiving HAART. This confirms previous reports that, although HBV may not make HIV worse, coinfection with HBV increases the risk of dying from liver disease in people with HIV.

Goldstein S, et al. Hepatitis disease burden: global estimates and reduction from vaccination. 41st IDSA, 2003, San Diego.. Abstract 583.

Bower W, et al. Molecular epidemiology of hepatitis B virus transmission in a United States correctional facility. 41st IDSA, 2003, San Diego.Abstract 585.

Konopnicki D, et al. Hepatitis B (HBV) in the EuroSIDA Cohort: prevalence and impact on mortality, AIDS progression and response to HAART. 9th European AIDS Conference,Warsaw, Poland. Abstract F9/3.

	HIV	HBV	HCV
EPI	Slowly progressing disease, with ~10 years to life threatening stage. High mortality if untreated. Transmitted by blood, sex, and from mother to child. Not easy to transmit	Slowly progressing disease with ~40 years to life threatening stage. 5% to 25% mortality if untreated. Transmitted by blood, sex, and from mother to child. Extremely easy to transmit	Slowly progressing disease with ~20 years to life threatening stage. Uncertain mortality if untreated. Transmitted by blood, sex, and from mother to child. Easy to transmit
THERAPY	No vaccine available. Viral eradication not possible.	Effective vaccine is available. Eradication is unlikely.	No vaccine available. Viral eradication is possible.
	Lifetime therapy required.	Lifetime therapy required to control chronic, replicating disease.	Duration of therapy ranges from 6 months to 1 year for ~50% success rate.
	Viral suppression with therapy offers clinical benefits. Immune recovery is possible.	Therapy may offer clinical benefits. Recovery from liver damage is possible. Conversion from chronic replicating to inactive state is possible.	Therapy may offer clinical benefits despite failure to eradicate. Recovery from liver damage is possible.
	Disease progresses if therapy is halted.	Life-threatening flares are possible if therapy is halted.	Disease progression is possible if therapy is halted.



VIROLOGY	**Retrovirus** Contains 2 strands of RNA.	**Hepadnavirus** Usually contains 2 circular strands of DNA.	**Flaviviridae virus** Contains 1 strand of RNA.
	Infects immune cells using CD4 receptors by fusion with cell membrane.	Infects liver cells using an uncertain receptor. Cell membrane fusion is likely.	Infects liver cells using uncertain receptors. Fusion occurs within a vesicle.
	The genetic material (RNA) is uncoated in the cytoplasm. DNA is transrcibed by RT in the cytoplasm then delivered to the nucleus and integrated into the nuclear DNA.	The genetic material (DNA) is delivered directly into the nucleus where it resides as circular DNA. Pre-genomic RNA is exported to the cytoplasm and reverse transcribed to genomic DNA.	The genetic material (RNA) is uncoated in the cytoplasm and never enters the nucleus. Templates for the genomic RNA are produced in the cytoplasm.
	New virus is produced when the cell divides.	New virus is produced when the cell divides.	New virus production is stimulated by infection.
	RNA exported from the nucleus and viral proteins produced in the cytoplasm are packaged using cellular membrane.	Viral proteins are produced in the ER and packaged with genomic DNA in the Golgi.	Viral proteins are produced and packaged with genomic RNA in the cytoplasm using vesicle membranes.

The Ecology of Drug Resistance

By Bob Huff

The perils of prophylaxing against one disease only to introduce drug-resistant strains of another bug were the topic of a poster at the annual conference of the Infectious Disease Society of America (IDSA) in San Diego.

Researchers from the Universities of Maryland and Malawi joined forces to find out which opportunistic infections were striking people with HIV in Malawi and what drugs would be useful for treating and preventing those infections. This was done in preparation for a clinical trial of trimethoprim-sulfamethoxazole (TS, Bactrim) to be used as prophylaxis against salmonella and streptococcus, two pathogens that cause serious intestinal and respiratory disease in Africans with HIV. Yet there is a concern that, in Malawi at least, these organisms may have developed resistance to TS. A further concern is that widespread use of TS will produce cross-resistance to one of the only affordable drugs left to treat malaria in the region, sulfadoxine-pyrimethamine (SP). TS acts in a way similar to SP, but it has far less activity against malaria.

Treatment for severe malaria in Africa is approaching a crisis point. The global burden of malaria is worsening due to drug resistance, with mortality increasing as resistance spreads.

The researchers enrolled 548 HIV-positive adults and children with a mean CD4 count of 247 cells/mm^3. More than half of the participants were women. The rates of hospitalization and death, not surprisingly, were increased in those with lower CD4 counts.

The most common diagnoses in this group during 2537 person months of observation were:

uncomplicated malaria (84 events);
non-specific diarrhea (69);
unspecified respiratory illness (60);
bacterial pneumonia (52);
fever of unknown origin (49);
oral candidiasis (48);
bacterial sepsis (38);
pulmonary TB (21); and
PCP (5).

One striking finding in this population is the low frequency of PCP, the signature infection of the AIDS epidemic in the U.S. and the rationale for TS prophylaxis in developed countries for persons with fewer than 200 T-cells.

Bacterial samples (62) were collected and analyzed by disc diffusion for antibiotic susceptibility. *Salmonella typhimurium* represented 52% of the pathogens, with 90% of those isolates having resistance to TS and 46% with resistance to azithromycin. *Streptococcus pneumoniae* accounted for 17% of the pathogens, with 91% of isolates resistant to TS, but all isolates retaining susceptibility to azithromycin. All other gram negative rods (*E. coli* and *Klebsiella*) were resistant to TS; 25% retained susceptibility to azithromycin.

Since most of the pathogens isolated were resistant to TS, the authors question the efficacy of TS as prophylaxis in the region. Any potentially effective prophylactic agent would have to prevent non-typhi *Salmonella* and *Streptococcus pneumoniae* and have broad-spectrum activity against respiratory and enteric pathogens. Such antibiotics, like azithromycin or ciprofloxacin, would likely be unaffordable. While the introduction of TS prophylaxis may not be very effective, the greater concern is the potential for harm if the prevalence of SP-resistant malaria in the region were to increase as an unintened result.

Coming Crisis in Malaria Treatment

Treatment for severe malaria in Africa is approaching a crisis point. The global burden of malaria is worsening due to drug resistance, with mortality increasing as resistance spreads. Resistance to chloroquine, a cheap drug that had been used for years, is now nearly universal. Its replacement, sulfadoxine-pyrimethamine (SP) is also cheap and effective, but its days are numbered as resistance spreads.

Resistance to SP originated in Asia, appeared in South America, and is rapidly spreading through Africa. The development of SP resistance may owe its origins to the earlier, widespread use of pyrimethamine by itself. SP resistance is now so common in South Africa that the drug is no longer used there. Resistance has gradually spread north to Mozambique, probably carried by mosquitoes. Although resistance to SP has been reported in many other African countries, including Kenya, Malawi and Tanzania, many outbreaks of malaria can still be treated by SP. However, if drug resistance against SP continues spread, the region will be left without an affordable weapon against this deadly infection.

When SP is no longer an option, the next alternative will cost 10 times as much, rendering it virtually unobtainable in most malarious regions. With no likely vaccine candidate on the horizon for at least 10 years, a new drug—and a new approach—for treating severe malaria in Africa is needed. And while there is no obvious

successor to SP, in the future it seems certain that combination therapy—the norm for treating TB and HIV—will have to be adopted for malaria if the tide of drug resistance is to be stopped and malaria rolled back.

One of the most promising candidates for the next generation of malaria drugs is arteminisin, a plant-derived compound that originated in China. References to the plant as a malaria treatment have been found in documents dating back 1700 years, yet its activity was only rediscovered in 1972. Arteminisin is one of the most potent and fast acting malaria treatments available, killing up to 99.99 percent of parasites. In killing a young form of the parasite, it acts earlier during the 48 hour cycle of an episode of severe malaria than conventional drugs.

Thailand leads the world in drug-resistant malaria. After SP ceased to be effective there, mefloquine was introduced in 1984, yet resistance to it developed within 6 years. Faced with untreatable malaria, a combination of mefloquine with artesunate was attempted, which proved successful, producing sustained levels of efficacy greater than 95 percent. There was a reduction in the incidence of malaria and parasites were less mefloquine-resistant than before combination therapy was introduced. Transmissibility also seemed to be reduced. With this success, randomized trials of artesunate plus existing drugs were conducted in Africa. Although the existing drugs at that point were mostly worthless, the combinations had better efficacy than either drug alone. This led to a program in KwaZulu Natal in South Africa that employed mosquito control along with a fixed-dose combination of artesunate plus mefloquine as therapy. The result was virtual eradication of malaria in the region. This plan is now being replicated in Mozambique.

Artemether, another arteminisin derivitive, is an oil-based compound that requires intramuscular injection. A 1,900-person randomized trial of artemether versus quinine to treat severe malaria reported fewer deaths with the new drug, although marginal statistical significance has limited the impact of the study. Although this form of the drug is unlikely to be well absorbed, which may have limited its efficacy, it was shown to be safe, with the neurotoxicity seen in animals not observed in humans. Artesunate, a water-based compound, is now being manufactured, but current supply sources do not meet FDA approved manufacturing standards, and it could years before an acceptable formulation appears. One practical formulation of artesunate for the tropics may be a rectal suppository that the WHO is now assessing.

Artesunate champion Nicholas John White argues that a crucial principle for the success of new treatment campaigns will be to make the drugs available for free. In markets where ineffective drugs are common and inexpensive, the only way to introduce an effective drug is to outcompete the ones that don't work. Free drugs will forestall an influx of counterfeit artesunate as was seen in Cambodia two years ago.

Much progress stands to be made in rolling back malaria and the tools, spraying, bed nets and treatment, are available and affordable. Dr. White argues that it is important to prove that progress can be made while the interest of funders is high. Malaria offers a more tractable problem than treating HIV or TB in the short run, yet the gains made in malaria would help the situation with those diseases as well. With effective drug combinations, eradication could be achieved with an investment of between $1 billion to $2 billion a year, and countries could see results within 5 years.

Yet there is much education and convincing to be done. Most proposals submitted to the Global Fund for malaria treatment rely on chloroquine and SP. Dr. White responded, "Countries are asking for drugs that don't work. We have to provide an incentive for them to ask for drugs that do work. It may be best to argue from an economic perspective; that it makes economic sense to ask for effective treatments."

MSF Supports ACT

The Campaign for Access to Essential Medicines organized by Medicins sans Frontieres (MSF) has issued a call to support artemisinin-based combination therapy (ACT) for malaria treatment in African countries facing resistance to classical antimalarials. In 2002, "after extensively documenting resistance to current treatments in MSF projects and carefully considering data gathered by ministries of health in endemic countries," MSF decided to switch to ACT in all its programs.

MSF produced a report that criticised some international donors for supporting a "leave it alone" policy that doesn't press endemic countries to break away from failing past practices and programs that depend on single-drug, resistance-prone drugs. Financial and technical support is needed to help these countries implement more effective strategies.

Next on the agenda is a movement to get WHO to push harder for implementation of its own recommendation that malaria treatment programs get their ACT together.

www.accessmed-msf.org

HCV Snapshots: Macro to Micro

By Bob Huff

HCV Prevalence in Europe Tracked

The enormously productive EuroSIDA study has reported on the prevalence of HCV in the cohort and on the effect that hepatitis C infection has on response to HAART. At the 9th European AIDS Conference in Warsaw, Poland, Jurgen Rockstroh, from Bonn, presented an evaluation of 4,957 members (50.6%) of the large cohort who have had an HCV antibody test. About a third (1685) were HCV positive. In general, coinfected persons were slightly more likely to be female and to be Caucasian. Not surprisingly, 75% of those with HCV had used IV drugs compared to less than 4 percent of those without HCV. Ominously, the median age of coinfected persons (34.2 years) was about 3 years younger than people with HIV alone, which suggests ongoing and recent infections. In the U.S. the median age of HIV-positive people with HCV would likely be several years older. An explanation might be the nearly 50 percent prevalence found in individuals from Eastern Europe, on the borders of states of the former Soviet Union where injection drug use, and HIV incidence is exploding. In central and northern Europe the prevalence was less than 25 percent.

At long last a few studies are starting to investigate the impact that having hepatitis may have on blood levels of some of the most commonly used antiretroviral drugs.

Fewer coinfected individuals were receiving HAART, and fewer had an AIDS diagnosis, although median viral load and CD4 counts were not dramatically different between the groups. About 11.5 percent of HCV-infected individuals also had hepatitis B antigen, meaning that they were triply infected. The prevalence of chronic HBV in the non-HCV group was 5.8 percent.

In a multivariate analysis, and after controlling for other factors, there was no correlation between HCV status and progressing to an AIDS diagnosis or dying of any cause. However, those with HCV had a significantly higher relative risk (HR=3.8) for dying of a liver-related illness. The rate of liver-related death (n=53) was 0.5 per 100 patient years in the HCV-positive group and 0.1/100 per 100 patient years in HCV-negative persons.

In this cohort, no impact of HCV on HIV progression for individuals on HIV therapy was apparent. Within 12 months of starting HAART, the time to virological failure (<400 copies/mL) was about the same for both groups (p=0.77). Similarly, within 12 months of starting HAART, the time to achieve a 50 percent increase in CD4 counts was not significantly different between the groups (p= 0.3).

While there are other issues to consider (see the effect of hepatic impairment on Kaletra blood levels reported below), these findings may give some guidance to clinicians deciding whether to treat HCV before HIV in coinfected persons. If the liver disease is not serious, and if there are immunological gains to be made by starting HAART, then there seems to be little reason to expect that response to HIV therapy should be unsatisfactory.

Sexually Transmitted HCV in London

Also at the European meeting, Brian Gazzard of Chelsea and Westminister Hospital in London, reported on an epidemic of acute HCV infection in HIV-positive gay men presenting in their clinic over the past two years. Men with elevated ALT or reported contact with other HCV-positive men are now routinely screened for hepatitis C.

Of the 49 men who seroconverted, 24 were given treatment, and of the 15 who have completed therapy, 10 have become HCV antigen negative, a relatively good showing compared to treatment results in HIV-positive people with chronic HCV. Also encouraging was that 12 individuals who were not treated have had spontaneous clearance of HCV antigen. These tended to be people with higher CD4 counts and higher ALT levels. In the future the clinic will recommend waiting 12 weeks after seroconversion before initiating treatment to allow time for spontaneous clearance to occur. Five treatment failures were reported, including one discontinuation due to toxicity.

Anecdotely, Gazzard commented, he thought nearly all the men had been passive anal sex partners and that many had participated in fisting. About half the men had a recent diagnosis of syphilis. Future reseach plans include genetic fingerprinting of the HCV strains, which will allow drawing a map of the social path this epidemic has followed.

Kaletra PK with Hepatic Impairment

At long last a few studies are starting to investigate the impact that having hepatitis may

have on blood levels of some of the most commonly used antiretroviral drugs. Jose Arribas, from Hospital La Paz in Madrid, Spain, presented a report in Warsaw about the effect of mild or moderate hepatic impairment in people with HCV and HIV on the pharmacokinetics of Kaletra (lopinavir/ritonavir). He took six patients with mild hepatic impairment (Child Pugh score 5–6), six with moderate impairment (scores of 7-9) and matched them with 12 HIV-positive, but HCV-negative controls. Everyone received lopinavir/ritonavir (400/100mg) twice-daily for 14 days, when they underwent intensive 24-hour pharmacokinetic testing.

They found that lopinavir levels were increased to a similar degree in people with both mild and moderate hepatic insufficiency. At 12 hours after a dose, the total exposure (AUC) to lopinavir was about 30 percent higher in the HCV patients than in the controls. However, ritonavir levels were increased to a greater extent in those with moderate hepatic insufficiency than in those with mild impairment. The authors recommend caution when administering Kaletra to persons with either mild or moderate hepatic impairment. With the ever-increasing number of drugs and combinations, the potential for unexpected pharmacokinetic interactions increases, especially in persons with coinfections or taking concomitant medications. Hopefully, more of these small but important studies will continue to fill in the blanks about how to use these drugs in the variety of patients who are out there.

Abnormalities in Liver Mitochondria

An interesting study presented at the European Conference by Leonardo Calza and colleagues from Bologna, Italy looked carefully and closely at the differences in liver cell mitochondria between people with HIV/HCV coinfection and people with HCV alone. Past studies have described ultrastructural mitochondrial abnormalities in HCV-positive persons both with and without HIV, although some studies found a stronger association in those receiving antiretroviral therapy.

Calza obtained liver biopsies from 68 patients and prepared two samples, one for examination by electron microscopy and the other for conventional histologic examination. Persons in Group A (n=40) were coinfected with HIV/HCV. Those in Group B (n=28) had HCV alone. The only significant differences between the groups were increased triglycerides and higher HCV RNA in Group A. Most of those in Group A were on HAART, with half receiving a PI-based regimen.

The histological examination reported more severe disease in Group A (33% vs 12%). Microvesicular liver steatosis was also more common in Group A (97% vs. 63%) as were moderate to severe ultrastructural abnormalities (55% vs. 30%). Intramitochondrial inclusions or crystals were twice as common in Group A (35.9% vs. 17.9%) but universal in persons with HCV genotype 1b (100%). Differences were apparent between these groups, yet it can't be said if these were due to the impact of HIV on HCV disease or due to the mitochondrial toxicity of the HIV drugs that most of the coinfected patients were taking.

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GMHC Treatment Issues is published twelve times yearly by GMHC, Inc.

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The Tisch Building
119 West 24 Street, New York, NY 10011
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TB is About People

By Winstone Zulu

Remarks at the opening plenary of the 34th World Conference of the International Union Against Tuberculosis and Lung Disease (IUATL), Paris, 2003.

I've been an HIV/AIDS activist for the past ten years. Although I knew that I was going to die of AIDS, no one specified exactly what that really meant in terms of the opportunistic infection that would take me. In my life as a person living with HIV, the nearest that I came to actually dying was when I had tuberculosis. And if I had died of tuberculosis, I would have been one of the AIDS statistics. Everybody, because they know I am HIV-positive, would have said I died of AIDS. Now technically, that would probably be true, because the underlying cause would have been HIV. But the fact that I took the TB medicines and got well shows that something is missing—that in our fight against AIDS, we are not looking at the individual opportunistic infections that can be cured. I'm HIV positive. I took the TB drugs when I had TB and I am here speaking to you today. My brothers were HIV-positive too. They had tuberculosis but they didn't take the TB drugs because they were not available, and they are no longer here.

In my recent travels, I found that this gives a different perspective to people. When you go to countries like France or the U.S.; when you talk about 50 million people living with HIV in Africa, many people just want to look away because the problem looks so insurmountable. They think, how can we deal with this? And the fact is that AIDS is known as an incurable disease. So when you say, "50 million people living with HIV in Africa," people then make the equation: HIV is equal to AIDS and AIDS is equal to death; there's no cure. But if you say, hey wait: the biggest killer of people living with HIV in Africa and many other developing countries is tuberculosis — and if you give them drugs that cost ten dollars, you can save someone's life—and you can avoid having more orphans... then people see it differently. In place after place that I recently visited people said, well, this gives some hope.

We all know that antiretrovirals are ultimately what we need. They are medications that are available now that have shown they can prolong life and improve the quality of life. But for many of us the dream of getting antiretrovirals is much more farfetched than the dream of getting drugs for ten dollars that can cure you of your disease. Even to me, who has been an AIDS activist for a long time, this is a new way of looking at things. And now when I see someone living with HIV, I say, well, if you don't have antiretrovirals now, you should go and get checked for tuberculosis. If you have tuberculosis, it can be cured. Now, I know there are difficulties in case finding, the diagnostics are very old, the drugs are difficult to take—six months is too long to take drugs—and there needs to be research and drug development around tuberculosis. But if you have TB, you can take these drugs we have and be cured.

I'm very encouraged that the organizers of this conference have invited, not only scientists, but also people living with tuberculosis and people living with HIV. I think this conference needs to have a community component so that you can actually see the people that you are talking about. It's not only about the germs and the pills, but also about the people under the microscopes and behind PowerPoint presentations. I'm also very glad that the WHO is now looking into social and community mobilization around the issues of tuberculosis. I believe that tuberculosis cannot be fought in the labs alone, and I think this is what has been missing. TB is about people; it is about our relatives, our friends; it's about people who are actually living with this disease.

Winstone Zulu is founding member of the Zambian Network of People Living with HIV.