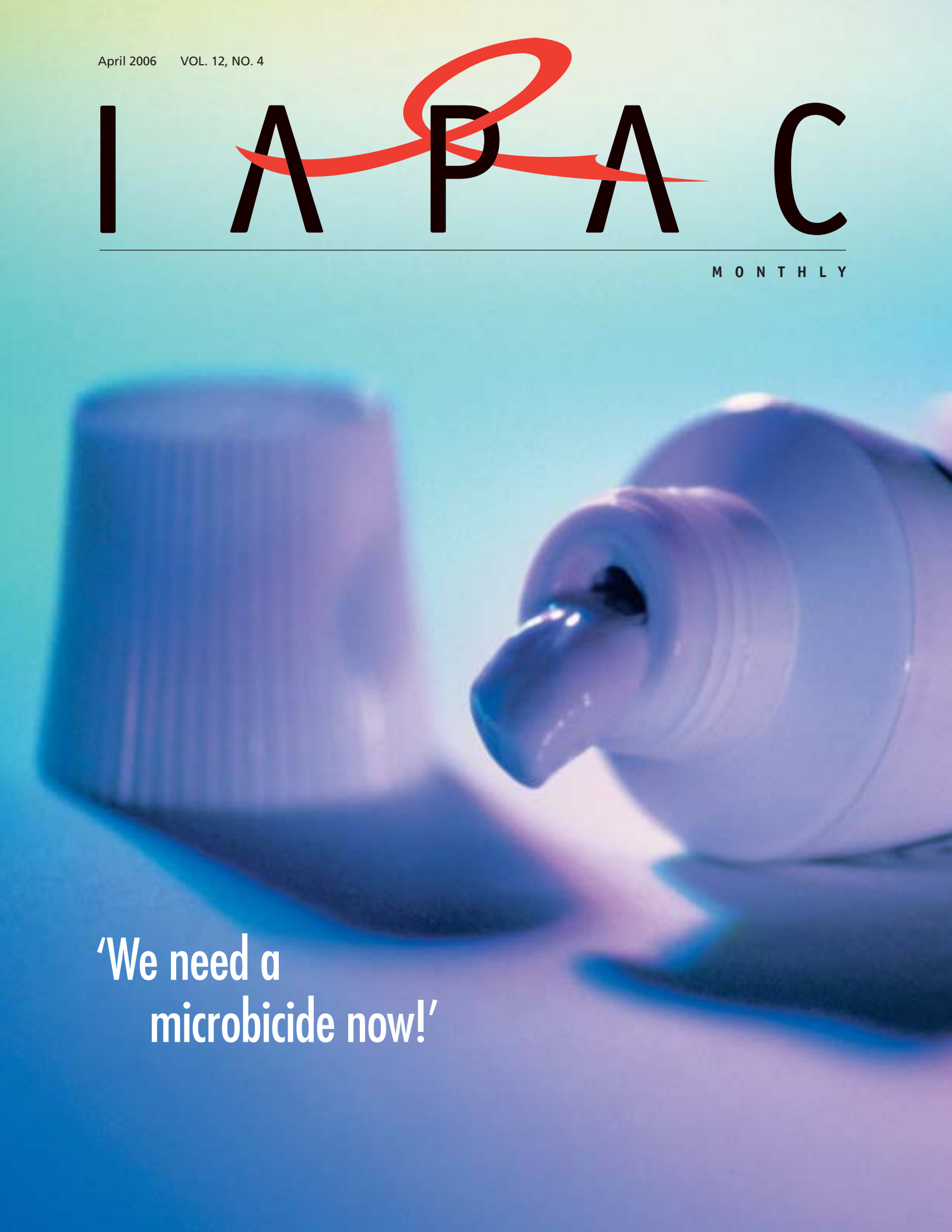


April 2006 VOL. 12, NO. 4

# IAPAC

MONTHLY



'We need a  
microbicide now!'

# 114



## 'We need a microbicide now!'

*Theo Smart*

Existing methods to prevent HIV infection in women are failing, especially in southern Africa. Attendees at the Microbicides 2006 Conference heard how the development and distribution of even a moderately effective microbicide could prevent 3.7 million HIV infections in women.

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## Of worms and quackery

José M. Zuniga

**A**IDS Worm Fury,” read the headline of an April 19, 2006, newspaper article prominently featured on the front page of *The Citizen*, one of South Africa’s wide-circulation dailies. The worm in question is *Imbrasia belina* (aka the “mopane worm”), a large edible caterpillar that forms the basis of a multimillion-dollar trade in South Africa’s Limpopo and Mpumalanga Provinces, as well as in Botswana and Zimbabwe. Why such fury around the mopane worm? Because elderly South African women are raking in cash by selling the worm as a cure for AIDS!

This is not the first time such claims have been made about the mopane worm—the first documented claim dates back at least a decade. And it is not the first time that so-called AIDS cures have stirred such an uproar in South Africa. In 1998, Virodene (which consisted largely of industrial solvent) was touted by then-Minister of Health Nkosazana Zuma as a potential AIDS cure. That country’s Medicines Control Council (MCC) determined Virodene likely killed a number of HIV-positive South Africans; but its retraction from the “market” came only after a pitched battle between the MCC and Zuma, leading to the resignation of the MCC’s longtime Chair, Peter Folb.

Almost a decade later, quackery in the global battle against HIV/AIDS is unabated. Considered by many an archaic term, “quackery” is most often used to denote the peddling of cures. Quackery can be found in any culture and in every medical tradition. Advertisements for “miracle cures” and “faith healing,” as well as many natural remedies, or certain diet and fitness regimes, are considered quackery by many conventional medical specialists. A variety of

medicines with heavy marketing campaigns also fall under the term “quackery.” Full-page ads in magazines are popular places to sell these products or services, as are Web sites featuring exaggerated medical claims. Indeed, most people with an e-mail account have experienced the marketing tactics of spamming; miraculous penis enlargement, weight-loss remedies, and unprescribed medicines of dubious quality sold on the Internet are perhaps the most common current form of quackery.

There are several reasons why quackery is accepted by patients (and, apparently, by some government officials) in spite of its lack of effectiveness:

- **Ignorance.** Those who perpetuate quackery may do so to take advantage of ignorance about conventional medical treatments.
- **The placebo effect.** Medicines or treatments known to have no effect on a disease can still affect an individual’s perception of his or her illness. People report reduced pain, increased well-being, improvement, or even total alleviation of symptoms. For some, the presence of a caring practitioner and the dispensation of medicine is curative in itself.
- **Side effects.** Pharmaceutical medications, including antiretroviral drugs, can have very distressing side effects, causing patients to shy away from these mainstream treatments.
- **Distrust.** Many people, for various reasons, distrust conventional medicines (or the regulating bodies responsible for their approval), and believe that alternative treatments are more trustworthy.
- **Cost.** There are some people who simply cannot afford conventional treatment, and seek out a cheaper alternative. Nonconventional practitioners can often dispense treatment at a much lower cost.

- **Desperation.** People with a serious or terminal disease, or who have been told by their health care practitioner that their condition is “untreatable,” may seek out unconventional treatment, disregarding the scientific proof of its ineffectiveness.
- **Pride.** Once a person has endorsed or defended a cure, or invested time and money in its procurement, they may be reluctant to admit its ineffectiveness, and therefore recommend the cure that did not work for them to others.
- **Fraud.** Some practitioners, fully aware of the ineffectiveness of their “medicine,” may intentionally produce fraudulent scientific studies and medical test results, thereby confusing potential consumers as to the effectiveness of the treatment.

Whatever the reason people believe in and subscribe to fraudulent treatments, governments have a responsibility to do more than issue public statements of condemnation against quacks. Declaring that claims such as those recently made about the mopane worm are “irresponsible and dangerous” does not mean much when government officials have, in the recent past, made similar claims about antiretroviral therapy, much to the detriment of scale-up efforts. As important, the World Health Organization (WHO) must do its part to safeguard the lives of vulnerable populations of people with limited health literacy. Let us encourage local and national governments, as well as the WHO, to discourage and punish quackery as quickly as possible, before the perpetrators steal their victims’ wealth and health. ■

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

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## 1 in 5 with low CD4 counts not on treatment

Edwin J. Bernard

**T**reatment guidelines that recommend antiretroviral therapy in all adults with CD4 counts below 200 cells/mm<sup>3</sup> are not being followed by one in five individuals with severe immunosuppression, according to data presented by the Health Protection Agency (HPA) at the 12th Annual Conference of the British HIV Association (BHIVA) last month. Of particular concern is that 70% were not due to late diagnosis, and there was much regional variation, with the highest proportion not on treatment in the northeast and southwest of England.

Since 2001, BHIVA treatment guidelines have recommended that highly active antiretroviral therapy (HAART) should be commenced prior to CD4 counts falling below 200 cells/mm<sup>3</sup>. Several large cohort studies have found that the short-term risk of illness or death is much greater at these lower CD4 counts, but a BHIVA re-audit examining patients starting therapy at UK clinics in 2004, presented at BHIVA's conference last autumn, found that 62% of patients commenced HAART once CD4 counts had fallen below 200 cells/mm<sup>3</sup>, including 22% who did not commence HAART until their CD4 counts had fallen below 50 cells/mm<sup>3</sup>. Starting HAART at low CD4 counts was associated with recent (ie, late) diagnosis.

The HPA collects demographic, immunologic, virologic, symptom, and treatment-related data on every diagnosed

HIV-positive individual seen for HIV-related treatment or care in England, Wales, and Northern Ireland. The Survey of Prevalent HIV Infections Diagnosed (SOPHID) data was used to determine the percentage of diagnosed HIV-positive individuals with CD4 counts below 200 cells/mm<sup>3</sup> who were not on HAART at one point in time in 2004, and to investigate possible reasons for this.

Out of 40,265 individuals reported to SOPHID in 2004, 35,242 (88%) adults aged over 15 had both CD4- and treatment-related data. Almost 5,000 (14%) had CD4 counts below 200 cells/mm<sup>3</sup>, of whom 950 (19%) were not receiving HAART.

In univariable analysis, age, clinical stage of HIV disease, and geographical region of care were associated with not being on treatment (all  $P < 0.01$ ). There was no association with route of infection (eg, sex between men, heterosexual sex, or injecting drug use), ethnicity, or gender.

Around 25% of all individuals between 15 and 34 years of age with CD4 counts below 200 cells/mm<sup>3</sup> were not on HAART, whereas about 15% of individuals with low CD4 counts aged over 44 were not on HAART.

Individuals who were asymptomatic were more likely not to be on treatment than those who were symptomatic and/or had an AIDS diagnosis. Although not all deaths were reported to SOPHID in 2004, more than 50% of individuals reported to have died in 2004 with CD4 counts below 200 cells/mm<sup>3</sup> were not on HAART.

There was significant variation between regions—from 36% and 30% not on therapy in the northeast and southwest of England, respectively, to 9% not on therapy in

Northern Ireland—and multivariable analysis did not find that these differences could be explained by a different case mix of patients.

The HPA also considered more comprehensive data from London in order to assess how many individuals were not on therapy due to recent (ie, late) diagnosis, and found that about 30% of individuals were diagnosed within three months. The HPA also compared their 2004 SOPHID data to their 2003 data and found that 53% of individuals with low CD4 counts who were not on HAART in 2004 had CD4 counts below 200 cells/mm<sup>3</sup> in 2003 and should, therefore, have been recommended therapy before 2004.

Timothy Chadborn (Health Protection Agency, Centre for Infections, London) concluded that one in five diagnosed HIV-positive individuals with CD4 counts below 200 cells/mm<sup>3</sup> were not on any HAART in 2004; that individuals with HIV-related symptoms and AIDS were more likely to be on antiretroviral drugs than asymptomatic individuals; that older individuals were more likely to be on treatment; and that differences in case mix between regions did not explain all of the differences in proportions with low CD4 counts not on treatment.

Of concern, and requiring further investigation, he said, was the fact that more than half of diagnosed HIV-positive individuals with low CD4 cell counts in 2004 and not on treatment, who were also seen in 2003, had low CD4 counts in 2003 and should have already have been placed on therapy. ■

### Reference

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**Editor's Note:** Reprinted with permission from [www.aidsmap.com](http://www.aidsmap.com) (first e-published April 7, 2006).



## 'We need a microbicide now!'

Theo Smart

**T**he Microbicides 2006 Conference held April 23-26, 2006, in Cape Town, South Africa, maintained a consistent focus on the vulnerability to HIV infection of women in Africa (and elsewhere) and the need to find better ways for women to protect themselves.

"Asking women to simply abstain, be faithful, or use condoms is not practical. Nor is it enough, especially when... 75% of new infections are acquired from a spouse or regular partner," said Graça Machel, (Foundation for Community Development), who gave one of the conference's opening addresses (see "Microbicides 2006 Conference Opening Address," page 115).

Machel's long list of distinctions include Founder and President of the Foundation for Community Development, former Minister of Education and Culture, former First Lady of Mozambique, and current wife of former South African

President Nelson Mandela. She is also a renowned advocate for women's health and, more recently, for microbicide research.

Microbicides are products that could reduce the transmission of HIV and other sexually transmitted infections when used in the vagina or rectum. Microbicides can have a variety of formulations, such as gel, foam, cream, sponge, or intravaginal ring. Since microbicides can be applied by a woman before and, in some cases, even after sex, they are being touted as a female-controlled prevention method.

"Too many women, married or not, lack the social power to negotiate condom use with their partners or husbands," said Machel. "The development of vaginal microbicides is key to [preventing] more women [from] becoming infected with HIV. Whether it be a gel, or a cream, or an intravaginal ring... regardless of the type, we need a microbicide now!"

Nowhere is this more true than in southern Africa, where more than 60% of HIV-infected adults are women. One in four South African women aged 15 to 24 is infected with HIV, compared to one in 14 of young men of that age. But in some communities, the prevalence is much higher, with up to two thirds of pregnant

women aged 25 to 29 now HIV-infected. For Machel, this means the existing methods to prevent HIV infection in women are failing. "Despite the huge investment we have made [in] HIV prevention, little has changed," Machel said.

However, according to projections presented at Microbicides 2002 by Charlotte Church (London School of Hygiene and Tropical Medicine), if a microbicide that is 60% effective reaches the market, and is used consistently by 30% of women at risk, it could prevent 3.7 million HIV infections. Even a weakly effective microbicide could have similar effects if it reaches a higher percentage of women; and if it is affordable, would translate into substantial savings for Africa's overstretched public health systems.

As a result of such modeling (and the apparently poor prospects for an HIV vaccine) over the last several years, interest and funding for microbicide research has grown substantially. Currently, over six products are in advanced clinical studies in Africa, involving over 25,000 participants (five are being studied in South Africa in at least 12,000 women). If found to be at least partly effective, one of these products could move toward licensing as soon as 2010. ■

*Editor's Note: Reprinted with permission from [www.aidsmap.com](http://www.aidsmap.com) (first e-published April 26, 2006). Look to next month's issue of the IAPAC Monthly for clinical coverage of the Microbicides 2006 Conference.*

## Microbicides 2006 Conference Opening Address delivered by Graça Machel

*Good afternoon and welcome to Cape Town. I am delighted to be here with all of you today. I am especially pleased that [the] Microbicides 2006 [Conference] is, for the first time, taking place in Africa. We have the unenviable position of being the continent most affected by HIV/AIDS. And southern Africa is the epicenter of the pandemic. HIV/AIDS is having a devastating impact on society. The developmental gains we have made in Africa are being reversed, our economies are suffering, and communities are being shredded and destroyed. For me, what is most painful is to see what the pandemic is doing to women.*

*Globally, almost half of all people living with HIV are females. But nowhere is the “feminization” of the epidemic more acute than in Africa. Here, where women and girls make up almost two thirds of all people infected with HIV, and where 76% of those who are HIV-positive in the age group of 15- to 24-year-olds are young women, we are facing life-or-death situations. To some it may sound extreme to put it in such terms, but believe me ... it is not strong enough!*

*The vulnerability of women stems from their pervasive disempowerment. Many women have little capacity to say no to sex; they are unable to negotiate condom use in their relationships; they lack legal protections against abuse and sexual violence; and it is most often girls who are pulled out of school to take care of sick parents.*

*Poverty and food insecurity forces women to engage in “transactional” or “survival” sex, further exposing them to the virus. The vulnerability of women is further exacerbated by legal systems that deny them equal status. For too long, we have paid lip service to gender equality and have shown modest results. Our efforts have been insufficient and inefficient, and we have shown a lack of urgency in creating a more equal society, and this is coming back to haunt us now.*

*We have to drastically change a situation where women in Africa continue to bear the brunt of the HIV epidemic. Every statistic, every new report documenting the havoc wreaked by the pandemic, is a terrible reminder that we are failing to protect our mothers, sisters, and daughters. Two decades have elapsed since HIV/AIDS first came to light in the early 1980s. It is completely unacceptable that for over 20 years we have failed to provide women with the means to protect themselves against HIV infection. I see no pursuit*

*more worthwhile than the search for an effective microbicide, and that is why we are here.*

*Despite the huge investment we have made [in] HIV prevention, little has changed. The existing methods to prevent HIV infection are failing many women. Asking women to simply abstain, be faithful, or use condoms is not practical. Nor is it enough—especially when UNAIDS reports that 75% of new infections are acquired from a spouse or regular partner. Closer to home, in studies among young women in Harare, Durban, and Soweto, 66% of women said they have one life-time partner, and 79% said they had abstained from sex at least until the age of 17. Yet, 40% of these young women were HIV-positive. Marriage, or being in what a woman thinks is a monogamous, faithful relationship, is sadly, one of the biggest HIV risk factors for many young African women.*

*Condoms are important, but not enough. Too many women, married or not, lack the social power to negotiate condom use with their partners or husbands. But let me add that it is important that female condoms be readily available—and affordable—for women in Africa and worldwide.*

*Existing prevention methods are not working. They must be broadened and expanded—women must have access to education and information, sexual and reproductive health services, female-controlled prevention methods, and prevention of mother-to-child transmission (PMTCT) methods.*

*The development of vaginal microbicides is key to preventing more women becoming infected with HIV. Whether it be a gel, or a cream, or an intra-vaginal ring, whether it prevents HIV infection but allows for conception—an incredible scientific feat, I must say—regardless of the type, we need a microbicide now!*

*We must have and [we must] empower women with a range of approaches. Microbicide science is advancing rapidly, and current clinical trials provide hope that a microbicide could be available in five to seven years. We have microbicide candidates in large-scale efficacy trials and a new generation of microbicides already in safety studies. Five first-generation microbicide candidates have now entered large-scale efficacy trials around the developing world. I do understand the limitations of science, but we simply have to find ways to do this faster.*

*I am told that even if a microbicide were only 60% effective, it could prevent 3.7 million infections within three years if used by all women who are unable to use condoms. I am sure you all share my sense of urgency and are prepared to accept the challenge that we have to make such a product available now and not in a few years' time.*

*Clinical trials, a crucial component in the development of an effective product, are complex. There are issues of science, ethics, and advocacy that must be pondered and debated. Successful clinical trials require networking and institutional collaborations between research organizations, government and civil society, and knowledge transfer between institutions in the North and South. They require funds that are not readily available. They require facilities and staff development and training which can take several months. But most important of all, clinical trials require acceptance by the community and participation of women. To gain women's trust and collaboration, we have to be sensitive and ethical in our approach and have impeccable research methods.*

*We are attempting to do this in Mozambique. The government of Mozambique; Manhica Research Centre; the Foundation for Community Development (FDC), my foundation; and our UK and South African partners are currently in the process of setting up microbicide feasibility studies in the country. In a short six months, we have come a long way—in fact, I have no doubt that we are on our way to establishing a clinical site. Why? Because we have worked together to build on the strengths of each partner. Synergies are needed since none of us, be it the national or international partners, could have taken on this challenge alone.*

*If we are to have a microbicide that will be accessible and affordable for poor women in rural and urban areas, we need to embark on a truly global effort—with political leadership, financial resources, and community mobilization. We know all too well in this part of the world what happens when profits take precedence over lives. We do NOT want to repeat the struggles in the efforts to get affordable access to antiretroviral treatment to people living with AIDS.*

*From the pharmaceutical industry, we need their active participation in the discovery of effective microbicides. We also need increased investment from the business and corporate sector for the development and distribution of new preventive technologies. My primary concern is to save the lives of women, but I am convinced it makes good business sense to invest in microbicides.*

*Some companies might be unable to see the business case to*

*develop an effective microbicide since it poses scientific challenges, can take up a significant amount of time, and requires a series of large investments to research and develop a product. But what about those pharmaceutical companies that believe themselves to be industry leaders, innovators, and visionaries? Can you not see that the investment, risks, and costs you incur will be recouped through microbicide sales in developed and developing countries once the product is on the market? Can you not see that demand will also be constant? Can you not see that demand will be massive? We are talking of many millions of women in developing and developed countries that would buy microbicides to protect themselves from HIV infection and choose to buy your product rather than die of AIDS.*

*From developed countries, we need political leadership, continued support in research and development, and sustained financial support. We need to increase the efforts and commitments of scientific institutions and agencies. In 2004, US\$140 million was committed to microbicide research, development, and advocacy worldwide. However, if we are to ensure timely development of a safe and effective microbicide, annual investment will have to double to US\$280 million per year for the next five years ... and thereafter, it will have to remain at approximately US\$260 million per year until satisfactory microbicides are licensed.*

*At the G8 Summit last year, the leaders of the most powerful countries in the world reaffirmed their commitment to meet the development target of [donating] 0.7% of their [gross national product as] overseas development aid—a goal that was introduced a few decades ago, that has been affirmed over and over again. Now, a number of countries have set a deadline of 2015 to reach 0.7%. We must not let this become another empty promise.*

*G8 leaders also promised global AIDS treatment for all by 2010. I would like to have a similar commitment to protect women from HIV infection by 2010. Delivering on this will require generating increased resources, [investing in] scientific research, making drugs and microbicides accessible and affordable, and strengthening health systems. But in 2010 we have to be able to say, "We are protecting a significant number of women against HIV, and we are providing universal treatment to all." I expect our friends in donor countries to hold their governments accountable, so that the resources that are so desperately needed—for new preventive technologies and the response to HIV/AIDS—transpire.*

*From developing countries, we need to support efforts on*

the ground. That means building networks and engaging with communities; it means working with partners in clinical trials, and ensuring that women—and men—know about microbicides and the incredible potential they hold. We also need our leaders to prioritize the response to HIV/AIDS—with special focus on women and AIDS—in the work of government. Our weakened health care systems must be strengthened and improved, so that when a microbicide is [developed], it can get to the women who need it most.

And how are we going to reach these women? We need a strong women's movement to achieve this. My hope is that we use every opportunity we can—international meetings, in gatherings like this one, or simply in our daily interactions—to build a continent-wide women's movement. HIV/AIDS has the potential to wipe out an entire gender ... have we ever had a greater cause to mobilize and demand change?

In my lifetime, I have seen how a strong women's social movement can transform society. On this continent, we have fought and defeated colonialism, and apartheid. Now we must turn our efforts to the plight of women. We need women in all sectors—from business, to science, to government, parliament—to take up the issues that affect women with commitment and passion. But more than that, we need to challenge traditional practices that are harmful to women.

We can no longer remain silent when our sisters face sexual violence, rape, and female genital mutilation. We can no longer stand for discriminatory laws that deem women as minors. We must hold our governments and institutions accountable for the decisions they make—or fail to make—when it comes to women. When our governments sign and ratify international frameworks guaranteeing women equal status and a host of rights, we must insist that our national laws reflect the letter and spirit of these treaties. Signing a convention, enacting a law that looks good on paper and makes headlines is not enough!

We must move from rhetoric to action. We must demand the enforcement of laws that protect women. We must say, individually and collectively, enough is enough ... Our sisters and daughters are dying .... and we will not stand for this any longer! Women must be at the forefront of every decision that is taken about their lives—whether it is in the halls of parliament, or in their own homes. I must say I am impatient for change.

Last year, during a session on microbicides in Maputo, after the formal proceedings, the discussion was opened up for questions. The first question came from an activist from Swaziland. She asked, "Where do women living with AIDS

fit into this plan? What about those of us who are already positive?" Nobody could give a satisfactory response to her question. Our slowness to act, our inadequate response to the pandemic, has resulted in the loss of millions of lives. Let me repeat that ... it has resulted in the loss of MILLIONS of lives. We cannot allow another generation of women to live in a world that does not offer them options to protect their health, their future, and save their lives!

I would like to praise women living with HIV who acknowledge their HIV-positive status openly and in public forums. Given the stigma and discrimination they know they will face from their family, community, peers, and society, it takes huge amounts of courage and determination to disclose their HIV status. I praise these women because they have become advocacy agents. I praise these women because they are educating other women and all of society. I also praise them because they are changing our mindset and demanding results ... But most of all I praise them because despite the personal price they pay they are indeed our conscience.

Every single one of us in southern Africa is personally affected by the AIDS pandemic. I often wonder how we shall turn things around. Will we one day find ourselves in a world where AIDS is curable, or will it continue to spread and ravage our societies, our communities, and our families? Some people say that we will always be running to "catch up"; that the virus is too strong, too fast, and too clever ... others say that only with the discovery of a vaccine will we see the end of the pandemic.

I cannot predict the future. But I believe that it will not be one thing that changes the trajectory of AIDS—we will need a host of methods, responses, and tools to make the change. We cannot set up false dichotomies—it is not about choosing one thing over another. It is not that we need investment in preventive technologies, or in treatment. Or that we should focus on one group over another. No! We need resources for microbicides and vaccines and new medicines for second- and third-line regimens. We need a holistic approach, and our action must lead by a sense of urgency.

The work that each and every one of you is doing, whether in research, in advocacy, or in the community—what you are engaged with ... that is finding a tool that will allow women to prevent HIV infection and empower them... well, I cannot think of a more worthy cause. Your work is invaluable and urgently needed. A future of a generation of African women depends on it. ■



# Serious bacterial infections in children with HIV

*Shirley Jankelevich*

## **Introduction**

**H**IV-infected children have an exceptional vulnerability to invasive bacterial infections that is much greater than that seen in immunocompetent, HIV-uninfected children and HIV-infected adults. Because of this increased risk, the US Centers for Disease Control and Prevention (CDC) added a new category of invasive bacterial infections to the list of pediatric AIDS-defining illnesses in 1987.<sup>1</sup>

Numerous defects in the immunologic system are responsible for the increased vulnerability of HIV-infected children to serious bacterial illness. These include defects in the cell-mediated (T-cell) and the humoral (B-cell) arms of the immune system; phagocytic abnormalities including decreases in neutrophil number, multiple defects in neutrophil function, and impairment in macrophage and monocyte function;<sup>2</sup> functional asplenia;<sup>3</sup> and defects in three components of complement.<sup>3</sup> These defects become more severe as the child's HIV disease progresses. Extrinsic factors in industrialized countries that increase susceptibility to infection in HIV-infected children include frequent use of broad-spectrum antibiotics, frequent hospitalizations, and the use of indwelling intravascular catheters that disrupt the integrity of skin. Major factors in developing countries include malnutrition, micronutrient deficiencies, and lack of adequate medical care. The results of these defects are increased susceptibility to infection with encapsulated bacteria beyond age two years,<sup>4</sup> increased nasopharyngeal colonization rates for *Streptococcus pneumoniae* and *Haemophilus influenzae*,<sup>5</sup> recurrent infections with the same bacterial species, increased susceptibility to infections with bacteria unusual in immunocompetent hosts, and increased morbidity and mortality.

Vaccines against bacterial agents or their toxins administered to HIV-infected children who do not receive treatment with effective antiretroviral therapy (ART) may not be protective because they often produce antibody titers that are lower and less persistent than those seen in HIV-uninfected children. These include *H. influenzae* type B polysaccharide conjugate vaccine,<sup>6</sup> pneumococcal polysaccharide vaccine,<sup>6</sup> pneumococcal conjugate vaccine,<sup>7,8</sup> and pertussis vaccine,<sup>9</sup> as well as diphtheria and tetanus toxoids.<sup>10,11</sup> A recent double-blind randomized trial examined the efficacy of a 9-valent pneumococcal vaccine in HIV-uninfected and HIV-infected children who were not treated with ART.<sup>12</sup> This vaccine reduced the incidence of a first episode of invasive pneumococcal disease due to vaccine serotypes by 83% and 65% in HIV-uninfected and HIV-infected children, respectively. Although the vaccine reduced the incidence of a first episode of radiologically confirmed pneumonia in the HIV-uninfected children, it had little effect on pneumonia in HIV-infected children.

Successful treatment of HIV-infected children with ART may result in improved antibody responses to measles, tetanus, and *H. influenzae* type B vaccines following reimmunization.<sup>13</sup> However, the degree and persistence of these responses may be less robust than those in HIV-uninfected children.

The availability of effective ART in resource-rich nations has had a major impact on HIV-associated mortality in children. In the United States, prior to the widespread use of ART in children, the mortality rate of HIV-infected children six and nine years of age was approximately 25% and 50%, respectively. The current use of combination ART, however, has slowed the progression of HIV disease in many children, resulting in fewer bacterial and other opportunistic infections and decreases in mortality.

Morbidity and mortality at unprecedented levels, however, currently are seen in HIV-infected children in many developing nations where there is malnutrition, difficulty in supplying adequate medical care, and an increased incidence of coinfection with organisms such as tuberculosis, cytomegalovirus (CMV), and syphilis.<sup>14</sup> The mortality rate in these nations is much greater than that seen in the United States, even before the availability of ART. The mortality rate of HIV-infected infants when compared with HIV-uninfected infants at one year of age in Rwanda was estimated to be 26% versus 2%, respectively.<sup>15</sup> Data from the clinical trial DITRAME ANRS 049a, conducted in Abidjan, Côte d'Ivoire, revealed a mortality rate by one year of age of approximately 50% and 5% for HIV-infected and HIV-uninfected infants, respectively.<sup>15</sup> Similar statistics were seen in Malawi and Uganda, where the median survival of HIV-infected children by three years of age in two pediatric cohorts was only 34%.<sup>15</sup> These deaths were due primarily to pulmonary infections, diarrhea, and malnutrition.

## Serious bacterial infections

Serious bacterial infections occur more frequently in HIV-infected children than in HIV-uninfected children in resource-rich as well as resource-poor countries. In one large natural history study in which a cohort of 3,331 HIV-infected children was followed in the United States, the rate of serious bacterial infections in children between the ages of 0.1 and 20.9 years was 15.1 per 100 person-years.<sup>16</sup> The median age, CD4 count, and CD4 percentage for

these children was 3.8 years, 420 cells/ $\mu$ L, and 17%, respectively, whereas those children who developed *Pneumocystis jiroveci* pneumonia (PCP) had a median age, CD4 count, and CD4 percentage of 3.9 years, 42 cells/ $\mu$ L, and 6%, respectively. These data indicate that serious bacterial infections may occur at CD4 counts and percentages that are much higher than those at which PCP occurs. The majority of these infections, however, occurred in children with CD4 percentages less than 15%, consistent with the findings of other studies in which bacterial illnesses occurred at a greater frequency in children with CD4 counts under 200 cells/ $\mu$ L.<sup>17,18</sup> The most common clinical syndromes due to bacteria and their event rates were pneumonia (11.1 per 100 person-years), bacteremia (3.3 per 100 person-years), and urinary tract infection (1.6 per 100 person-years).<sup>16</sup> The clinical syndromes of osteomyelitis, meningitis, abscess, and septic arthritis had event rates of less than 0.2 per 100 person-years. In another large study that followed 2,167 perinatally HIV-infected children in the United States,<sup>4</sup> the most common serious bacterial infections were sepsis (56%) and pneumonia (25%). Less common infections were cellulitis (6.4%), meningitis (4.2%), sinusitis (3.1%), and adenitis (2.1%). Mastoiditis, internal organ abscess, osteomyelitis, and septic arthritis occurred at frequencies of less than 2%. In that study, serious bacterial infections occurred most frequently in children under one year of age (21.5 episodes per 100 person-years), whereas, in children of one and two years of age, the rates decreased to 14.3 and 11.2 episodes per 100 person-years, respectively. The rate of these infections continued to decrease with increasing age so that, by 10 years of age, the estimated rate decreased to 3.3 episodes per 100 person-years.

*S. pneumoniae* is the most common pathogen causing invasive bacterial infections in HIV-infected children in the United States.<sup>4</sup> An incidence of 6.1 serious bacterial illnesses due to *S. pneumoniae* per 100 person-years for children through age seven years was seen,<sup>19</sup> and was similar to that seen in children with sickle cell disease through age six years. This rate was 100- to 300-fold the rates seen in immunocompetent, HIV-uninfected children in the United States and several other industrialized countries. Data presented at a 2003 World Health Organization (WHO) conference showed that pneumonia in HIV-infected

children under five years of age was the leading cause of hospital admission and the most frequent cause of death in the six participating African countries.<sup>20</sup> Although PCP was the most important cause of pneumonia rated “severe” or “very severe,” bacteria were the most common cause of pneumonia overall.

Acute lower respiratory tract infection (LRTI), diarrhea, and bacteremia accounted for the majority of infections in 108 hospitalized HIV-infected children in Cape Town, South Africa.<sup>21</sup> In this study, none of the children received pneumococcal or *H. influenzae* vaccines, intravenous gamma globulin, or ART. The children, whose median age was 61 months (1.5 to 214 months), had 136 episodes of serious bacterial infection; 85% of infections occurred in children under two years of age and 40% of the children had two or more clinical syndromes. The most frequent syndromes were acute LRTI (44%), diarrhea (29%), septicemia (17%), and skin infections (5%). All other syndromes, including meningitis and urinary tract infection, accounted for less than 2% of infections. Bacterial cultures were positive in 24%, 18%, and 45% of children with acute LRTI, diarrhea, and septicemia, respectively. *S. pneumoniae*, *Campylobacter* spp, and gram-negative bacilli accounted for the majority of the isolates in patients with acute LRTI, diarrhea, and septicemia, respectively. Of note, 33% of these episodes occurred in patients receiving cotrimoxazole (TMP/SMX) three times a week. In a recent surveillance study conducted in Malawi, the most frequently isolated bacteria in blood taken from 208 acutely ill HIV-infected children were nontyphoidal *Salmonella* spp and *Escherichia coli*; there were no isolates of *S. pneumoniae*.<sup>22</sup> Of note, *Salmonella* spp are the most frequently isolated pathogen in HIV-infected children in areas of high malaria activity.<sup>23</sup>

HIV-infected children who are not severely immunocompromised and do not have neutropenia are most likely to respond to the age-appropriate antimicrobial regimens used in the treatment of many bacterial infections in HIV-uninfected children. The duration of therapy, however, often is greater and should be based in large part on the clinical course of the child. Lack of response to a regimen of appropriate duration and targeted to the pathogen(s) isolated should prompt a reevaluation of the child, as coinfection with several types of pathogens or infection with resistant bacteria may be present.

This paper recommends diagnostic procedures and antibiotic treatment for serious infections in HIV-infected children based on current practices in health care institutions in resource-rich countries. In most cases, the severity of infection will require hospitalization of the child. The procedures and the antibiotics chosen should be used in accordance with the capabilities and limitations of the health care institutions providing treatment for these children. In addition, the type and prevalence of antibiotic resistance in each geographic region must be considered when choosing treatment.

The Child and Adolescent Health and Development (CAH) division of the WHO has developed the Integrated Management of Childhood Illness (IMCI) guidelines for the care and treatment of many diseases affecting children, including HIV-infected children, in many resource-poor countries.<sup>24</sup> The WHO also has published the *Pocket Book of Hospital Care for Children: Guidelines for the Management of Common Illness with Limited Resources*, which is updated frequently, accessible via the World Wide Web, and recommended highly to health care workers in resource-limited settings as an aid in selecting antibiotic regimens.<sup>25</sup>

Although this paper provides a general overview of serious bacterial infections, it is important for the practitioner to have a low threshold for consulting experts in the care of immunosuppressed patients and for expanding the differential diagnosis, diagnostic work-up, and therapeutic coverage to include other pathogens likely to cause disease in HIV-infected children.

Guidelines for the use of TMP/SMX as prophylaxis for opportunistic infections in resource-poor nations have been established by the WHO and the Joint United Nations Programme on HIV/AIDS (UNAIDS),<sup>26</sup> and are similar to previously developed US guidelines.<sup>27</sup> It is highly recommended that these guidelines be followed. Recently, the combination of atovaquone and azithromycin was shown to be as effective as TMP/SMX for prophylaxis of opportunistic infections in children with HIV.<sup>28</sup>

## Clinical syndromes

### Pneumonia

#### Epidemiology

Acute LRTI is a major cause of morbidity and mortality in HIV-infected children in

resource-limited and resource-rich countries and may be due to a single pathogen or a combination of bacterial, viral, or fungal pathogens.<sup>4,29</sup> Children with lower CD4 T-cell counts generally have a higher incidence of bacterial pneumonia.<sup>16</sup> The spectrum of bacteria associated with pneumonia in HIV-infected children is wide. The pathogens most commonly seen include *S. pneumoniae*, *H. influenzae* type B, *Staphylococcus aureus*, and *E. coli*. Other pathogens less commonly observed are *Streptococcus viridans*, *Streptococcus pyogenes*, *Moraxella catarrhalis*, *Bordetella pertussis*, *Klebsiella pneumoniae*, *Salmonella* spp, *Pseudomonas aeruginosa*, *Legionella* spp, and *Nocardia* spp.

Bronchiectasis may occur in HIV-infected children as a result of severe, unresolving, or recurrent pulmonary infections.<sup>30</sup> Of 164 HIV-infected children with “respiratory problems” in one study, 26 (15.8%) had bronchiectasis. Sixteen children had lymphoid interstitial pneumonia, three were found to have recurrent pneumonia, and five had unresolving pneumonia. Of the 12 children that had bronchoalveolar lavage, seven had bacteria isolated and six of these seven children had mixed infections of up to four organisms with various combinations of *P. aeruginosa*, *S. aureus*, *Candida albicans*, *Mycobacterium avium* complex, *S. viridans*, *B. pertussis*, chlamydia, multidrug-resistant *Mycobacterium tuberculosis*, and *Corynebacterium* spp.

Pneumonia due to *Pseudomonas* spp is infrequent but particularly problematic because it results in a necrotizing infection and may respond poorly to antibiotic treatment.<sup>31</sup> *Pseudomonas* pneumonia usually is acquired nosocomially, but it also can present as a community-acquired infection in HIV-infected patients, a mode of acquisition that is rare in HIV-uninfected individuals. *Pseudomonas* pneumonia may present as a fulminant infection with bacteremia, or may have a chronic or subacute course. Unlike pneumonia due to *S. pneumoniae*, *Pseudomonas* infection usually is associated with a CD4 count less than 50 cells/ $\mu$ L. Multiple relapses are common and may occur despite an intravenous antibiotic course of 14 days.<sup>32</sup> Risk factors for *Pseudomonas* pneumonia include lung injury caused by prior opportunistic infections, bronchiectasis, chronic sinusitis, and repeated courses of broad-spectrum antibiotics that predispose patients to colonization.

Pneumonia is the predominant bacterial clinical syndrome in HIV-infected children in Africa. Because the etiologies of bacterial pneumonia in studies of HIV-infected children have been determined primarily by blood culture isolates from these patients, it is possible that the reported frequencies of bacterial pneumonia in developing countries represent underestimates. The pattern of respiratory infections in HIV-infected children in Africa is similar to that seen in resource-rich nations prior to the use of ART, with the exception of tuberculosis, which is uncommon in resource-rich nations.<sup>29</sup> Common nonbacterial pathogens are *P. jiroveci*, *Mycobacterium tuberculosis*, and CMV.<sup>20</sup> The difficulty in differentiating the various etiologies of pneumonia is a major obstacle to appropriate therapy.<sup>20</sup>

In Soweto, South Africa, HIV-infected and HIV-uninfected children hospitalized with LRTI were studied. Lower respiratory tract infection was found to be the most common cause of hospitalization and mortality in all children aged two to 60 months, regardless of HIV status.<sup>33</sup> However, HIV-infected children had a significant increase in bacteremic LRTI relative to uninfected children and a higher case-mortality rate. Frequently encountered pathogens were *S. pneumoniae*, *H. influenzae* type B, *S. aureus*, and *Salmonella* spp. Lower respiratory tract infection due to *E. coli* was significantly more common in HIV-infected children than in HIV-uninfected children. In HIV-infected and HIV-uninfected children aged two to 24 months, *S. pneumoniae* was the most frequently isolated pathogen. The relative risk of pneumonia due to *S. pneumoniae* was 43 for these younger HIV-infected children compared with HIV-uninfected children. In this same age group, HIV-infected children had relative risks of 21, 98, 49, and 13 for pneumonia due to *H. influenzae* type B, *E. coli*, *S. aureus*, and *Salmonella* spp, respectively, compared with HIV-uninfected children. In children aged over 24 months, *S. pneumoniae* was found in 37% of those infected with HIV but in only 20% of HIV-uninfected children with LRTI.

In Cape Town, South Africa, LRTI accounted for 44% of 136 episodes of severe infection in HIV-infected children who required hospitalization or were hospitalized concurrently.<sup>21</sup> Blood cultures were positive in 24% of these cases and the predominant bacterial isolates, in order of frequency, were *S. pneumoniae*,

*S. aureus*, *H. influenzae*, and *E. coli*. Notably, 31% of the *S. pneumoniae* isolates were penicillin-resistant, and 33% of LRTI occurred in children receiving TMP/SMX three times weekly.<sup>21</sup>

### Diagnosis

The differential diagnosis of fever, tachypnea, and hypoxia in an HIV-infected child is extensive and includes bacterial, viral, and fungal pneumonias. The ability to determine the cause of pneumonia often is limited because infected material cannot be obtained for culture without performing an invasive procedure. Chest X rays, blood cultures, and sputum gram stains and cultures are essential components of the diagnostic workup and will help determine the etiology. However, the absence or presence of alveolar consolidation on chest X ray may not help in distinguishing pneumonia due to bacteria from that due to viral pathogens or *P. jiroveci*.<sup>33</sup> For example, radiographic patterns with PCP may have the appearance of a bacterial pneumonia. Chest X rays of children with *H. influenzae* (type B and nontypeable) pneumonia will show consolidated areas in some cases, but diffuse bilateral infiltrates may be seen in others.<sup>34</sup> The appearance of *Pseudomonas* pneumonia on chest X ray may be that of a lobar infiltrate, or, less commonly, diffuse interstitial disease and cavitary lesions.<sup>34</sup> The most sensitive diagnostic techniques are bronchoscopy with bronchoalveolar lavage and/or lung biopsy. However, if these procedures cannot be done, induced sputum may yield clues to the etiology. If empyema is present, a specimen should be obtained for microbiologic evaluation.

### Initial treatment

Initial treatment should target the most likely pathogens based on the age of the child and the level of immunosuppression. *S. pneumoniae* is the most common cause of bacterial pneumonia after the neonatal period. Therefore, initial treatment for children under one month of age should provide coverage for this organism unless there is compelling evidence that the infection is not caused by *S. pneumoniae*. Because of the high prevalence of penicillin resistance in pneumococcus and many other respiratory pathogens in resource-rich nations, the initial antibiotic regimen for an HIV-infected child should consist of a second-generation cephalosporin

(eg, cefuroxime) or a third-generation cephalosporin (eg, cefotaxime or ceftriaxone). Neutropenic patients also should be treated with an antipseudomonal drug such as ceftazidime to provide activity against *Pseudomonas* spp. If *S. aureus* is suspected and there is a prevalence of community-acquired methicillin-resistant *S. aureus* (CA-MRSA) of greater than 10%, vancomycin should be added to the antibiotic regimen.

The type of bacteria isolated and the antibiotic susceptibility pattern should then guide changes in the antibiotic regimen. Because slower responses to antibiotic treatment or relapses may occur in HIV-infected children,<sup>34</sup> careful monitoring is required. Prolonged antibiotic therapy may be necessary in many cases.

### Bacteremia

HIV-infected children, especially those less than two years of age, have an increased risk of bacteremia relative to uninfected, immunocompetent children. In the CDC Pediatric Spectrum of Disease project, sepsis was diagnosed in 401 of 714 HIV-infected children with bacterial infections in the United States,<sup>4</sup> whereas the incidence of bacteremia in study participants of the Pediatric AIDS Clinical Trials Group (PACTG) was 3.3 per 100 person-years.<sup>16</sup> In South Africa, the relative risk of bacteremia secondary to *S. pneumoniae* pneumonia in HIV-infected children under two years of age was 50 times that of uninfected children.<sup>35</sup> An odds ratio of 2.68 for bacteremia in HIV-infected children relative to uninfected children was seen in Zimbabwe.<sup>36</sup> The incidence of bacteremia also increases as the CD4 count decreases.<sup>37</sup> Bacteremia often occurs secondary to infection of the lung, gastrointestinal tract, vascular catheters, and skin and soft tissue<sup>38</sup> as well as other sites, including the ear, sinuses, and urinary tract. Bacteremia without an identifiable focus may occur, especially with *S. pneumoniae*. In a study of pneumococcal bacteremia in the United States, a focus of infection could not be found in 10 of 54 bacteremic children.<sup>39</sup>

Many of the bacterial pathogens that infect HIV-infected children are those that also infect HIV-uninfected, immunocompetent children. *S. pneumoniae* is most frequently isolated, but in children with advanced HIV disease, bacteremia may be caused by other bacterial species less commonly seen in immunocompetent children. These include nontypoidal

*Salmonella* spp, *Pseudomonas* spp, *E. coli*, *Campylobacter jejuni*, *Listeria monocytogenes*, *Citrobacter* spp, *Enterobacter* spp, *Klebsiella* spp, *Rhodococcus equi*, and *Actinomyces israelii*.<sup>40-42</sup> Prior to 1990, *H. influenzae* bacteremia accounted for 12.5% of gram-negative bacteremia in HIV-infected children in the United States but was not seen after that time.<sup>42</sup> This decrease may be related to the widespread use of the *H. influenzae* type B conjugate vaccine. In Zimbabwe, gram-positive pathogens isolated from blood cultures of children with HIV, in order of frequency, were coagulase-negative staphylococci, *S. pneumoniae*, *S. aureus*, *R. equi*, and *A. israelii*.<sup>36</sup> Gram-negative pathogens isolated in this study were *S. enteritidis*, *E. coli*, and *K. pneumoniae*.<sup>36</sup>

A retrospective study that analyzed the impact of central venous catheters (CVC) on bacterial infection in HIV-infected children showed that HIV-infected children under six years of age had an increased frequency of CVC-related bacterial infections relative to older HIV-infected children.<sup>37</sup> Bacteria associated with CVC infections included *S. aureus*, *S. epidermidis*, *Enterococcus* spp, *Pseudomonas* spp, *Acinetobacter* spp, and other gram-negative rods,<sup>37</sup> as well as *Bacillus cereus*.<sup>43</sup>

Recurrent bacteremia and polymicrobial bacteremia are not uncommon infections in HIV-infected children. Complications of bacteremia include septic shock, disseminated intravascular coagulation, and seeding of the pathogens to multiple organs. Bacteremia due to *Salmonella* spp has very high rates of relapse following completion of a short course of antibiotic treatment.<sup>2,38,44,45</sup> Metastatic complications may occur and result in osteomyelitis, meningitis, pneumonia, endocarditis, and pyelonephritis.<sup>38</sup> *S. aureus* bacteremia frequently results in dissemination of infection to multiple sites.

The mortality rate from bacteremia is dependent on multiple factors including the type of pathogen, presence of metastatic lesions, immune status, age, nutrition, and availability of medical care. In the United States, of 54 HIV-infected children who presented with *S. pneumoniae* bacteremia, death occurred in only two children who had associated meningitis.<sup>39</sup> However, in Zimbabwe, death occurred in 20 of 67 HIV-infected bacteremic children who were infected with a variety of pathogens.

The highest mortality occurred in children less than 18 months of age.<sup>36</sup> Gram-negative bacteremia generally carries a higher mortality than does bacteremia due to most gram-positive bacteria. In HIV-infected children in the United States, the case-fatality rate for *Klebsiella* spp, *E. coli*, and *P. aeruginosa* was 57.1%, 54.5%, and 52.6%, respectively.<sup>42</sup> Mortality due to *S. aureus* infections without endocarditis varies from 2.6% to 19%, with a significantly higher mortality if *S. aureus* endocarditis is present.

Predisposing, but not essential, conditions that favor *Pseudomonas* bacteremia are a low CD4 count, neutropenia, and the presence of a CVC. *Pseudomonas* may be community acquired or nosocomially acquired, with the urinary tract, upper and lower respiratory tracts, and CVCs serving as the primary sources. Bacteremia with *Pseudomonas* may be associated with several different types of skin lesions that include tender, red papular lesions and ecthyma gangrenosum. Hypotension and other signs of sepsis often accompany *Pseudomonas* bacteremia. Because bacteremia due to *Pseudomonas* spp, predominantly *P. aeruginosa*,<sup>46</sup> has a high mortality rate, especially in the presence of CD4 count under 100 cells/ $\mu$ L and neutropenia,<sup>47</sup> aggressive and prolonged treatment is needed.

#### **Initial treatment**

Initial treatment should provide antibacterial coverage for the most likely pathogens. Ill-appearing children with *S. pneumoniae* bacteremia in regions with significant rates of penicillin-resistant pneumococcus should be treated initially with a third-generation cephalosporin plus vancomycin until the susceptibility of the isolate is known. Vancomycin should be discontinued once the isolate is shown to be susceptible to penicillin or a cephalosporin. Vancomycin may be used in cases of hypersensitivity to beta-lactam antibiotics. Treatment with appropriate antibiotics for 10 to 14 days generally is sufficient. The child who clears bacteremia within a day and appears well may be able to complete antibiotic therapy as an outpatient.

Where penicillin-resistant, gram-positive bacteria are not suspected, a child who has a CD4 count over 200 cells/ $\mu$ L and an absolute neutrophil count (ANC) greater than 500 cells/ $\mu$ L, and who does not have a CVC, can be treated initially with ceftriaxone or cefotaxime until culture results are

available. Following isolation of an organism, antibiotic therapy should be modified appropriately. Broad-spectrum antibiotics should be considered with severely immunosuppressed children until culture results are available. For children with an ANC less than 500 cells/ $\mu$ L, treatment with ceftazidime to provide coverage for *Pseudomonas* spp should be considered until culture results are available. Vancomycin should be part of an antibacterial regimen if *S. aureus* is suspected and there is a 10% or greater prevalence of methicillin-resistant *S. aureus* (MRSA) in the community.<sup>48</sup>

#### **Treatment of specific pathogens**

Catheter-related bacteremia can be treated with ceftazidime and vancomycin to cover *Pseudomonas* and MRSA, respectively. Once the bacterial pathogen(s) are identified, a decision can be made regarding catheter removal. For certain species of bacteria (eg, *S. epidermidis*), catheter-associated bacteremia can often be treated with antibiotics alone without catheter removal, if the patient is stable and the blood cultures rapidly become sterile.<sup>37</sup> Treatment involves approximately 14 days of appropriate antibiotics, followed by observation for recurrence. Certain bacteria, such as *Bacillus* spp, cannot be eradicated without catheter removal.<sup>43</sup> In these cases, a shorter course of approximately seven days of antibiotics may be given following catheter removal.

Treatment of nontyphoidal *Salmonella* with ampicillin, TMP/SMX, ceftriaxone, cefotaxime, or chloramphenicol should be instituted until susceptibility is known.<sup>27</sup> Treatment duration of four to six weeks is necessary to prevent relapse.

Methicillin or oxacillin should be used for susceptible strains of *S. aureus*. In regions with a high incidence of CA-MRSA, alternative therapy such as clindamycin or vancomycin should be considered. Vancomycin or linezolid should be considered for nosocomially acquired *S. aureus*, as these organisms are likely to be methicillin-resistant. Length of treatment in the absence of metastatic foci is approximately 21 days. If the patient remains bacteremic for more than three days after beginning adequate therapy, a thorough evaluation for sites of dissemination, such as lungs, heart valves, bones, and central nervous system (CNS), should be considered.

Treatment of bacteremia due to *Pseudomonas* spp includes intensive clinical support and a combination of two antipseudomonal agents<sup>47</sup> such as ceftazidime or imipenem plus an aminoglycoside or a quinolone (quinolones are not recommended for children under 18 years of age), for a minimum of two weeks. Antibiotic therapy should be adjusted based on the results of susceptibility tests. The sources and metastatic foci of infection (lungs, skin infection, urinary tract infection, sinuses, CVC) must be determined and treated surgically when appropriate. If a CVC is infected, it may be possible to eradicate the infection without catheter removal in approximately 65% of cases.<sup>31</sup> If infection persists or recurs, catheter removal will be necessary.

If *Campylobacter jejuni* is suspected, both blood and stool cultures should be obtained. No studies have established the optimal treatment of *Campylobacter* bacteremia. Two weeks of intravenous therapy with cefotaxime, imipenem, gentamicin, chloramphenicol, or erythromycin will most likely provide adequate treatment.

Invasive, nonmeningeal *Listeria* infection may be treated with ampicillin plus an aminoglycoside, or with intravenous TMP/SMX alone, if penicillin-allergic, for 10 to 14 days.<sup>49</sup> The treatment course for *Listeria* meningitis should be no shorter than 14 to 21 days.

## Meningitis

Although *S. pneumoniae* is the most common cause of acute bacterial meningitis in HIV-infected children, many other bacterial pathogens, including *Neisseria meningitidis*, *H. influenzae*, *Salmonella* spp, and *L. monocytogenes*, must be included in the differential diagnosis. The diagnostic workup should include a lumbar puncture (LP). Appropriate studies, including stains and cultures for bacteria, fungi, and acid-fast bacilli, and rapid antigen tests for bacteria and cryptococcus should be performed on the cerebrospinal fluid (CSF).

For children over one month of age, initial treatment should include a third-generation cephalosporin and vancomycin if purulent CSF is obtained upon LP or if an etiologic agent cannot be identified. In the absence of specific recommendations for HIV-infected children less than one month of age, initial treatment with standard empiric treatment for meningitis (consisting of ampicillin and cefotaxime) is reasonable.

Dexamethasone may be used to reduce the effects of CNS inflammation, although

concomitant administration of dexamethasone decreased the penetration of vancomycin into the CSF in animal studies.<sup>50</sup> For the child with a CSF shunt and meningitis, initial therapy should include vancomycin and ceftazidime. Following isolation of an organism, treatment should be modified depending on the bacteria identified and its resistance pattern. Repeat LP may be needed in some children if the treatment response is not satisfactory, if the etiologic agent is penicillin-resistant *S. pneumoniae* and results from cefotaxime and ceftriaxone resistance testing are not yet available, if dexamethasone was administered,<sup>49</sup> or if gram-negative organisms are isolated. Therapy may need to be prolonged, depending on the response and the resistance pattern of the bacterial isolates.

### Initial treatment

Initial treatment of suspected bacterial meningitis beyond the neonatal period should always include coverage for *S. pneumoniae* unless specific information suggesting a different pathogen is available, such as the findings on gram stain of the CSF. A combination regimen of vancomycin and either cefotaxime or ceftriaxone should be used in children beyond the neonatal period until a pathogen and antibiotic susceptibilities are known.

### Treatment of specific pathogens

Meningitis due to penicillin-susceptible pneumococcus should be treated with meningitis-level doses of penicillin, ampicillin, cefotaxime, or ceftriaxone. The combination of vancomycin and rifampin may be used for children with hypersensitivity to penicillins and cephalosporins.

The high prevalence of antibiotic resistance in *S. pneumoniae* has made the treatment of pneumococcal meningitis complex. Treatment of penicillin-nonsusceptible and cephalosporin-nonsusceptible pneumococcus is problematic mainly because concentrations of penicillins and cephalosporins in the CSF usually are not high enough to achieve prompt eradication of some intermediately resistant and most highly resistant pneumococcal strains. Therefore, meningitis due to strains of pneumococci with intermediate-level or high-level resistance to only penicillins can be treated with either ceftriaxone or cefotaxime alone. However, meningitis due to strains of pneumococci that are nonsusceptible to both penicillins and

cephalosporins should be treated with a combination of vancomycin plus either ceftriaxone or cefotaxime. The combination of vancomycin plus either ceftriaxone or cefotaxime is recommended because clinical experience to support the use of vancomycin alone for the treatment of pneumococcal meningitis is insufficient.<sup>49</sup> Rifampin should be added to this regimen after 24 to 48 hours if the isolate is susceptible to rifampin and the patient has clinical deterioration, if repeat LP fails to show eradication of the bacteria, or if the isolate has high-level resistance (minimal inhibitory concentration [MIC]  $\geq 4$   $\mu\text{g/mL}$ ) to ceftriaxone or cefotaxime.<sup>49</sup>

Meropenem, a carbapenem-class antibiotic approved for children over three months of age with meningitis, was shown to have very good activity against penicillin-susceptible pneumococcus and was a very promising agent for the treatment of meningitis due to penicillin-resistant pneumococcus. However, because a recent study revealed that 49% of 59 isolates with either intermediate-level or high-level resistance to penicillin also had meropenem resistance, meropenem is not recommended for the treatment of meningitis caused by intermediately or highly resistant pneumococcus.<sup>49</sup>

Meningitis due to *Salmonella* spp should be treated with ceftriaxone or cefotaxime for no less than four weeks.<sup>49</sup> *H. influenzae* meningitis can be treated with ceftriaxone or cefotaxime or the combination of ampicillin and chloramphenicol<sup>49</sup> for at least 10 days. *Listeria* meningitis may be treated with ampicillin plus an aminoglycoside for a minimum of 14 to 21 days.<sup>49</sup>

## Gastroenteritis

Bacteria associated with gastroenteritis in HIV-infected patients include *Salmonella* spp, *Shigella* spp, *Campylobacter* spp, *Aeromonas hydrophila*, *Vibrio* spp, *Clostridium difficile*, and enterotoxigenic, enterohemorrhagic, enteropathogenic, or enteroinvasive *E. coli*. *Salmonella* spp, *Shigella* spp, and *Campylobacter* spp may disseminate and cause widespread serious infection. The presence of white blood cells, blood, parasites, and *C difficile* toxin in stool samples should be determined, and bacterial culture should be performed. Special tests must be performed to determine the presence of disease-causing *E. coli*. If the infection is due to *Salmonella* spp or *Shigella* spp, treatment with ampicillin, TMP/SMX, cefotaxime, or ceftriaxone should be initiated. Treatment

for *Campylobacter* spp infection includes erythromycin or azithromycin. Bacterial isolates should be tested for antibiotic susceptibility and the antibiotic regimen should be adjusted accordingly.

### Urinary tract infection

HIV-infected children have an increased incidence of urinary tract infection.<sup>37,44,51</sup> The most common bacterial isolate is *E. coli*.<sup>51,52</sup> *Klebsiella* spp, *Enterobacter* spp, *Enterococcus* spp, *Pseudomonas* spp, *Proteus* spp, and *Morganella* spp or mixtures of organisms also can cause urinary tract infection. A urine specimen obtained by sterile technique should be examined for white cells and bacteria, and cultured. Blood cultures and appropriate renal studies should be obtained on patients with fever and evidence of pyelonephritis. Because of the elevated relative risk of bacteremia associated with urinary tract infection in this population, aggressive intravenous antibiotic treatment is required in patients with suspected pyelonephritis or constitutional symptoms such as fever. Antibiotic treatment should be guided by the susceptibilities of the bacterial isolates. Although cystitis often can be treated with a relatively short course of therapy, pyelonephritis usually requires a minimum of two weeks of therapy.

### Skin and soft tissue infections

Bacterial skin and soft tissue infections (SSTIs) are seen frequently in HIV-infected children. Skin infections are associated more commonly with *S. aureus* than with other bacteria, partly due to the increased nasal carriage of both methicillin-sensitive and methicillin-resistant *S. aureus* in HIV-infected patients.<sup>53,54</sup> A variety of other organisms, including *Pseudomonas* spp, can also cause SSTIs in certain clinical situations.

Community-acquired methicillin-resistant *S. aureus* is causing SSTIs with increasing frequency.<sup>55</sup> The appearance of these isolates is concerning because oxacillin and cephalosporins are not active against them. Though CA-MRSA usually causes minor SSTIs, in other cases it can progress rapidly to serious and life-threatening infections, including necrotizing fasciitis, pneumonia, osteomyelitis, and bacteremia in children as well as adults.<sup>56,57</sup>

As in all infections, identification of the organism, antibiotic susceptibility results, and careful monitoring of clinical response should guide further treatment.

Blood cultures and gram stain and culture of infected material should be performed, especially if CA-MRSA is prevalent in the community or if an unusual pathogen is suspected. If lesions are thought to be due to disseminated infection, a thorough workup for metastatic foci of infection should be performed. An aspirate or biopsy of an infected lymph node may be necessary, especially for those not responsive to antibiotics that are active against methicillin-susceptible *S. aureus* and group A streptococci, in order to rule out MRSA, cat-scratch disease, mycobacterial infection, and malignancy. Rectal exam usually is sufficient to detect a perianal abscess, although computed tomography (CT) imaging may be needed in systemically ill children who are thought to have deep abscesses. Infected material obtained at the time of perianal abscess drainage should be sent for microbiologic evaluation.

### Types of skin and soft tissue infections

#### Cellulitis

Cellulitis may be caused by *S. aureus*, group A streptococci, *H. influenzae* type B, group B streptococci, and *P. aeruginosa*. For facial cellulitis, if the patient is ill, or if the cellulitic area has a purplish hue, ceftriaxone or cefotaxime should be used to provide coverage for *H. influenzae* type B. For severely immunocompromised or gravely ill patients, antibiotic coverage should be extended to include gram-negative enteric bacteria and *P. aeruginosa*. Leading-edge cultures from cellulitic areas may help in making the microbiologic diagnosis. Following isolation of an organism, therapy should be tailored accordingly.

#### Catheter-related soft tissue infections

Two types of central catheter-related soft tissue infections occur: exit site infections and tunnel infections. Exit site infections are superficial infections around the catheter site with erythema and tenderness, and, occasionally, discharge. A tunnel infection is an infection that extends along the tunnel through which the CVC has been inserted. Erythema is present at the exit site and tenderness on palpation can be found over the entire catheter tunnel. Discharge often can be expressed from the exit site. Although the most common bacteria causing these two types of infections are *S. aureus* and *S. epidermidis*, a wide variety of gram-positive cocci and gram-negative bacilli also can cause these infections.

Exit site infections often may be treated with antibiotic therapy alone. Initial treatment with vancomycin will provide coverage for *S. aureus* and *S. epidermidis*. If *S. aureus* or *S. epidermidis* is isolated and shown to be susceptible to oxacillin (or nafcillin), vancomycin should be stopped and oxacillin (or nafcillin) therapy instituted. Antibiotics should be tailored to bacteria isolated from the exit site. Often, seven to 14 days of antibiotic treatment is necessary for bacterial eradication. Catheter removal, however, is necessary for bacterial eradication in cases of catheter tunnel infections. Initial antibiotic therapy should include vancomycin and then be directed toward the bacteria isolated from the infected site and catheter tip. Because the infection is deep-seated, antibiotic treatment often must be continued for at least seven days following catheter removal.

#### Skin lesions of *P. aeruginosa* infection

Skin lesions caused by *P. aeruginosa* infection are more common in advanced stages of HIV infection, and include ecthyma gangrenosum, erythematous macular or maculopapular lesions, and violaceous nodules.<sup>46</sup> *P. aeruginosa* can be cultured from these lesions and, often, from the blood. Ecthyma gangrenosum is a painless, round, indurated, ulcerated lesion containing a central black eschar. It usually occurs during *P. aeruginosa* bacteremia, but may occur following infection of hair follicles. The erythematous and macular, maculopapular, or nodular lesions occur following disseminated *P. aeruginosa* infection.<sup>46</sup> Treatment with two antipseudomonal antibiotics for at least two weeks should be instituted.

#### Lymphadenitis

Adenitis may be caused by typical bacterial pathogens, such as *S. aureus* and group A streptococci, but also may involve bacteria such as *S. viridans*, *Enterobacter* spp, and *S. epidermidis*.<sup>51</sup> The etiologic agent of cat-scratch disease, *Bartonella henselae*, also should be considered in the diagnosis. Initial treatment should be directed against *S. aureus* and group A streptococci and then changed if necessary to antibiotics that are active against the isolated bacteria.

#### Perirectal abscess

Perirectal abscesses are seen more frequently in immunosuppressed patients, especially those with neutropenia.<sup>58</sup> The most frequently isolated bacteria include

*Bacteroides* spp, *Prevotella melaninogenica*, *Peptostreptococcus* spp, *E. coli*, *K. pneumoniae*, and *S. aureus*. In addition, *Enterococcus* spp and *Acinetobacter* spp have been reported in HIV-infected children.<sup>51</sup> A combination of clindamycin or metronidazole plus an aminoglycoside, ceftriaxone, or cefotaxime will be active against most of the bacteria associated with these infections. The nonneutropenic child should have prompt surgical drainage or aspiration of the abscess, even if local fluctuance is not palpable.<sup>58,59</sup> Material obtained from drainage or aspiration of the abscess should be sent for gram stain and aerobic and anaerobic culture. Antibiotics should be tailored to the bacterial isolates obtained from the infected material. In an HIV-infected child with severe neutropenia, drainage often is not attempted because of the lack of pus formation. In these cases, intravenous antibiotics are given for two to three weeks. Surgical drainage or aspiration then can be performed if there is disease progression with abscess formation.

## Bone and joint infections

### Septic arthritis

Hematogenous septic arthritis is thought to occur following bleeding into a joint with secondary seeding by bacteria from another site.<sup>60</sup> A number of cases of septic arthritis have been reported in patients with hemophilia and HIV infection.<sup>60</sup> Development of hematogenous septic arthritis was associated with lower CD4 counts. Although fever, increased white blood cell count, and elevated erythrocyte sedimentation rate often were present, the classic signs of joint swelling, pain, redness, and warmth usually were modified. Joint aspiration with appropriate chemistries, cell counts, and microbiologic studies should be performed. The predominant bacteria isolated from infected joints are *S. pneumoniae*, *S. aureus*, *S. viridans*, *S. pyogenes*, *H. influenzae*, *Salmonella* spp, and *Klebsiella* spp.<sup>17</sup> Treatment consists of intravenous antibiotics targeted against the isolated bacteria for at least three weeks. Arthrotomy, arthroscopic lavage, or repeated aspiration may be needed as adjunctive therapy to decrease joint cartilage destruction by proteolytic enzymes that accumulate in the infected joint.

### Osteomyelitis

Although osteomyelitis occurs in HIV-infected children,<sup>17,37</sup> it is seen less frequently

than other types of serious bacterial infection in HIV-infected patients. A variety of organisms have been reported in HIV-infected patients, including *S. aureus*, *S. pyogenes*, nontyphoidal *Salmonella* spp, *H. influenzae*, and *M. catarrhalis*. Occasionally, mixed infection may be seen. Diagnosis involves appropriate radiographic studies and culture of blood and material obtained from infected bone by needle aspirate or biopsy. Treatment requires prolonged intravenous therapy with antibiotics that achieve high bone penetration and are directed against the identified or presumed causative bacteria. In some instances, blood and/or bone cultures may not identify an organism. In such cases, patients are treated with antibiotics empirically chosen in consultation with a specialist.

## Problems due to resistance of bacterial pathogens

Resistance of numerous bacterial pathogens to many antibacterial agents continues to increase globally. Frequencies, patterns, and distributions of resistant bacteria vary significantly with geographic regions and often reflect the usage patterns of antibiotics. Factors that increase antibiotic resistance in resource-poor and resource-rich nations include total antibiotic consumption as well as underuse through lack of access, inadequate dosing, poor adherence, and substandard antimicrobial usage.<sup>18</sup>

These increases in bacterial resistance create barriers to treatment of severe and recurrent infections in HIV-infected children and adults, especially in resource-poor countries, because of increased treatment complexity and the need for expensive and often unavailable antibiotics for appropriate treatment.

The treatment of infection due to *S. pneumoniae* has been problematic because of increasing resistance to many available antibiotics. The CDC's Active Bacterial Core Surveillance Report for 2004 showed that, in the United States, 8.4% of *S. pneumoniae* isolates had high-level resistance to penicillin (MIC  $\geq 2$   $\mu\text{g/mL}$ ) and 13% had intermediate-level resistance (MIC  $\geq 0.12$   $\mu\text{g/mL}$ ).<sup>61</sup> In addition, erythromycin, TMP/SMX, and tetracycline resistance were found in 17.4%, 15%, and 7.2%, respectively.

Further complicating the treatment of *S. pneumoniae* is the fact that penicillin-resistant strains often have some degree

of cross-resistance among penicillins, cephalosporins, and carbapenems. In addition, vancomycin tolerance (the ability of *S. pneumoniae* to escape lysis and killing by vancomycin) was found in 3% of 116 clinical isolates of pneumococci in a study in the United States. Such resistance may result in treatment failure, particularly in cases of meningitis in which bactericidal activity is critical for eradication.<sup>62</sup>

Mortality rates due to infection with penicillin-resistant pneumococcus may be increased among HIV-infected persons. In San Francisco, the mortality rate of HIV-infected adults infected with high-level penicillin-resistant pneumococcus was 7.8 times higher than that of the same population infected with susceptible or intermediate-level resistant pneumococcus.<sup>63</sup> Although comparative studies have not been done for HIV-infected children, in HIV-uninfected children non-CNS-invasive infections due to *S. pneumoniae* with intermediate resistance to penicillin resulted in a significant increase in length of hospitalization and in time to defervescence (but not in a higher mortality rate) compared with infections due to penicillin-sensitive *S. pneumoniae*.<sup>64</sup>

Surveillance studies of antimicrobial resistance have shown that bacterial resistance also has been increasing in many nosocomial pathogens in the United States.<sup>65</sup> The prevalence of resistance in many bacterial isolates from sites participating in the CDC's National Nosocomial Infections Surveillance increased from 1998 to 2002. Vancomycin-resistant enterococci increased in prevalence to 28.5% of reported clinical enterococcal isolates, whereas MRSA had increased to 59.5% of *S. aureus* isolates. Resistance of *K. pneumoniae* and *Enterobacter* spp to third-generation cephalosporins increased to 20.6% and 31.1%, respectively. Resistance of *P. aeruginosa* to imipenem, quinolones, and third-generation cephalosporins increased to 21.1%, 29.5%, and 31.9%, respectively.

Resistance of the bacterial pathogens associated with diarrhea (*Shigella* spp, nontyphoidal *Salmonella* spp, and *Campylobacter* spp) to numerous antibiotics has been increasing in the United States. In 2002, 92% of *Shigella* isolates were resistant to one or more antibiotics and 58% were multidrug-resistant. The most common antibiotics to which

resistance was found and the associated frequencies of resistance were: ampicillin (77%), streptomycin (54%), TMP/SMX (37%), sulfamethoxazole (32%), and tetracycline (31%).<sup>66</sup> Twenty-one percent of nontyphoidal *Salmonella* isolates were resistant to one or more antibiotics, 16% were resistant to two or more antibiotics, and 9% were resistant to five or more antibiotics. The highest prevalence of resistance in nontyphoidal *Salmonella* was to tetracycline (15%), streptomycin (13%), ampicillin (13%), and sulfamethoxazole (13%). Resistance of *Campylobacter* spp to at least two different antibiotics was found in 51% of isolates. The highest frequencies of resistance were to tetracycline (40%), nalidixic acid (21%), and ciprofloxacin (20%).

### Antibiotic resistance globally

Antibiotic resistance of *S. pneumoniae* to several antibiotics is increasing globally.<sup>67</sup> Rates of penicillin resistance range from 2.4% in Germany to 50.1% in South Africa.<sup>67</sup> Antibiotic-resistant *S. pneumoniae* has been seen with increasing frequency in HIV-infected patients in South Africa, Kenya, and Zimbabwe and may be due, in part, to increased use of antibiotics.<sup>68-70</sup> Rates of macrolide resistance range from 14.7% in Canada to 88.3% in Vietnam.<sup>67</sup> In private health care settings in South Africa where macrolides are available, an increase in resistance of *S. pneumoniae* to macrolides has been documented.<sup>69</sup> Macrolide resistance increased from 1% to 21% in *S. pneumoniae* isolates two months after initiation of a mass azithromycin prophylaxis campaign to eradicate trachoma in an aboriginal village in Australia.<sup>71</sup> Resistance of *S. pneumoniae* to fluoroquinolones is also increasing, with local frequencies ranging from 1% to 18%.<sup>67</sup>

Resistance to several antibiotics is also being seen in *H. influenzae* (B and non-B serotypes) globally.<sup>67</sup> Data from the LIBRA TARGETed surveillance program show that ampicillin resistance ranged from 6.4% in South Africa to 43% in France.<sup>72</sup> Although clarithromycin resistance ranged from 9% to 19%, most isolates were susceptible to azithromycin, amoxicillin-clavulanate, and quinolones.

The prevalence of resistance in *S. aureus* is also increasing globally.<sup>73</sup> A survey of MRSA isolates from eight large hospitals (>500 beds) in Africa and Malta

from 1996 to 1997 showed that 15% of the 1,440 isolates of *S. aureus* tested were methicillin-resistant.<sup>74</sup> The prevalence of MRSA ranged from 21% to 30% in Nigeria, Kenya, and Cameroon and less than 10% in Tunisia, Malta, and Algeria. All MRSA isolates were susceptible to vancomycin, with MICs  $\leq 4$  mg/L. The majority (more than 60%) of MRSA strains were multidrug-resistant. The SENTRY Antimicrobial Surveillance Program has shown that South Africa also has a high prevalence of MRSA (41.5% methicillin resistance in a sample of 94 clinical isolates from 1998 to 1999).<sup>75</sup> Of special note is that MRSA was found to be more common in HIV-infected children than in uninfected children in South Africa.<sup>76</sup> Knowledge of the incidence of MRSA in the community should be a factor in deciding whether oxacillin or a cephalosporin can be used to treat a staphylococcal infection. It is recommended that in areas where CA-MRSA causes more than 10% of *S. aureus* infections, antibiotics such as TMP/SMX, doxycycline, clindamycin, linezolid, and vancomycin should be considered as initial therapy, depending on the availability of the antibiotic and the severity of infection; an oral antibiotic should not be used to treat severe infections.

High levels of resistance to multiple antibiotics were found in many areas of the developing world in the major bacterial pathogens associated with diarrhea (*Shigella* spp, *Campylobacter* spp, nontyphoidal *Salmonella*, and *Vibrio cholerae*).<sup>77</sup> In Kenya, 90% of such primary isolates tested had resistance to one or more antibiotics, and 74% had resistance to three or more antibiotics. All isolates of *Shigella dysenteriae* type 1 tested were resistant to at least six antibiotics.<sup>78</sup>

Resistance of bacterial pathogens to TMP/SMX is increasing and is of particular concern because cotrimoxazole is the least expensive and one of the most frequently used antimicrobial agents. Cotrimoxazole resistance may be linked to the widespread use of TMP/SMX for prophylaxis of PCP and treatment of bacterial infections, and to the use of sulfadoxine-pyrimethamine to treat patients with chloroquine-resistant malaria.<sup>79</sup> That selection pressure on bacteria results from prolonged use of TMP/SMX for the prophylaxis of PCP has been demonstrated by the increase of TMP/SMX resistance in *E. coli* isolated from HIV-infected adults in HIV units at

San Francisco General Hospital (from 24% of isolates in 1988 to 74% in 1995).<sup>80</sup> Significant TMP/SMX resistance in clinically important bacteria has also been reported in South Africa,<sup>81</sup> Malawi,<sup>79</sup> and Zimbabwe.<sup>68</sup> Bacterial resistance leading to decreased effectiveness of TMP/SMX was demonstrated by a study in which women with either cystitis or uncomplicated pyelonephritis were treated with TMP/SMX. Those women who had infections due to TMP/SMX-resistant *E. coli* had poorer bacteriological and clinical outcomes than those who had TMP/SMX-susceptible *E. coli*.<sup>82</sup> Of concern is that increasing resistance to TMP/SMX may develop not only in bacterial pathogens but may also lead to decreased efficacy in prophylaxis and treatment of PCP, and in the use of sulfadoxine-pyrimethamine against *P. falciparum*. ■

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## A B S T R A C T S

### AIDS

#### Effect of long-cycle structured intermittent versus continuous HAART on quality of life in patients with chronic HIV infection

Powers AE, Marden SF, McConnell LR, et al.

**OBJECTIVE:** To examine the effect of repeated, long-cycle structured intermittent versus continuous HAART on health-related quality of life (HRQL) and symptom distress in patients with chronic HIV infection and plasma HIV RNA of less than 50 copies/mL. **DESIGN:** Prospective survey of adult patients ( $n = 46$ ) enrolled in a randomized clinical trial evaluating intermittent versus continuous HAART on immunological and virologic parameters. Patients ( $n=23$ ) randomized to structured intermittent therapy received serial cycles of four weeks on/eight weeks off HAART. **OUTCOME MEASURES:** Health-related quality of life was measured by the physical and mental health summary scores of the Medical Outcomes Study HIV Health Survey (MOS-HIV). Symptom distress was measured by the Symptom Distress Scale. Patients completed initial questionnaires prior to randomization and at weeks 4, 12, and 40 of the trial via a touch-screen computer in an outpatient clinic. **RESULTS:** Baseline demographic and clinical characteristics were equivalent in both treatment groups. Although the mental health summary score declined significantly over time for the structured intermittent group, linear mixed modeling ANOVA indicated no significant difference across time for MOS-HIV summary and Symptom Distress Scale scores between the two treatment arms. **CONCLUSION:** In this small sample, repeated long-cycle structured intermittent therapy may not provide HRQL or symptom distress advantage compared to continuous HAART in patients with chronic HIV infection over 10 months of treatment. Further research in a heterogeneous chronic HIV population and longer follow-up period is warranted.

AIDS. 2006;20(6):837-845.

### Journal of Clinical Oncology

#### Elevated incidence of lung cancer among HIV-infected individuals

Engels EA, Brock MV, Chen J, et al.

**PURPOSE:** People with HIV infection in the United States frequently smoke tobacco. We sought to characterize lung cancer incidence among HIV-infected individuals, examine whether cancer risk was related to HIV-induced immunosuppression, and assess whether the high prevalence of smoking explained elevated risk. **METHODS:** We conducted a retrospective cohort study at an HIV specialty clinic in Baltimore, MD (1989-2003). Incident lung cancers were identified using hospital records. We used negative binomial regression to compare incidence

across subgroups defined by demographics, use of highly active antiretroviral therapy (HAART), and HIV markers. Standardized incidence ratios (SIRs) compared incidence with an urban reference population (Detroit, MI). We adjusted SIRs for the effect of smoking, using smoking prevalences estimated from part of the cohort and the general population. Ninety-five percent confidence intervals (CIs) and  $P$  values were two sided. **RESULTS:** Thirty-three lung cancers were observed among 5,238 HIV-infected patients (incidence: 170 per 100,000 person-years). Incidence increased with age ( $P<0.0001$ ), but did not differ by sex, race, or CD4 count. Incidence tended to increase with calendar year ( $P=0.09$ ) and HAART use ( $P=0.10$ ), and was inversely related to HIV viral load ( $P=0.03$ ), but these associations were attenuated with age adjustment. The SIR was 4.7 (95% CI, 3.2 to 6.5) versus the general population. Twenty-eight lung cancer patients (85%) and 69% of the cohort were smokers. After smoking adjustment, risk remained elevated (SIR, 2.5; 95% CI, 1.6 to 3.5). **CONCLUSION:** Lung cancer risk was substantially elevated in HIV-infected individuals. Incidence was unrelated to HIV-induced immunosuppression. Notably, incidence remained high after adjustment for smoking, suggesting the involvement of additional factors.

J Clin Oncol. 2006;24(9):1383-1388.

### Clinical Endocrinology

#### Thyroid function in human immunodeficiency virus patients treated with highly active antiretroviral therapy (HAART): A longitudinal study

Madeddu G, Spanu A, Chessa F, et al.

**OBJECTIVE:** Given that few and controversial data have been reported on thyroid function in human immunodeficiency virus (HIV)-infected patients on highly active antiretroviral therapy (HAART), we further investigated whether HAART affects thyroid hormones. **DESIGN:** Two hundred two consecutive adult HIV patients in stable clinical condition were enrolled, 182 on HAART and 20 naive; 128 were rechecked during follow-up. Body mass index (BMI), CD4 cell count, HIV RNA, hepatitis C and B virus status, and infection duration were determined in all HIV patients, and HAART duration in treated patients. In all patients and in 60 controls, the following were measured: FT4 and FT3 by radioimmunoassay; thyroid-stimulating hormone (TSH), antithyroid peroxidase (TPO), and antithyroglobulin (TG) antibodies by immunoradiometric assay. **RESULTS:** Abnormalities in thyroid function tests were found in 23/182 (12.6%) HAART patients, but not in naive patients. Most abnormalities were subclinical hypothyroidism, with mean FT4 and TSH levels lower and higher, respectively, in HAART patients compared to naive patients and

controls, FT4 levels being significantly lower than nadir and positively with HAART duration. During follow-up, FT4 and FT3 significantly decreased and TSH increased in patients continuing HAART, whereas CD4 counts were unmodified; subclinical hypothyroid conditions persisted and further cases occurred, whereas the only hypothyroid patient who interrupted HAART shows a normalization of thyroid tests. Patients on stavudine, included in most hypothyroid patient protocols, had significantly lower FT4 levels with prolonged treatment. **CONCLUSIONS:** HAART, particularly stavudine, is associated with a high prevalence of subclinical hypothyroidism. Hypotheses are made regarding responsible mechanisms and risk factors. Thyroid function should be tested and sequentially rechecked in HAART patients.

Clin Endocrinol (Oxf). 2006;64(4):375-383.

### Journal of Infectious Diseases

#### HIV infection and antiretroviral therapy: Effect on hepatitis C virus quasispecies variability

Shuhart MC, Sullivan DG, Bekele K, et al.

**BACKGROUND:** Hepatitis C virus (HCV) quasispecies variability has been associated with liver disease progression. The effects of human immunodeficiency virus (HIV) coinfection and highly active antiretroviral therapy (HAART) on HCV quasispecies variability have not been firmly established. **METHODS:** We determined HCV quasispecies complexity and diversity in 69 subjects, 28 of whom were HIV-infected, using clonal frequency analysis via heteroduplex mobility analysis of the second envelope gene hypervariable region. Nucleotide sequencing was performed for a small subset of subjects. **RESULTS:** HIV-positive, HAART-naive subjects had significantly lower HCV quasispecies complexity and diversity than did both HIV-negative and HIV-positive HAART-treated subjects. In multivariate analysis, HIV infection predicted decreased complexity ( $P<0.0001$ ) and diversity ( $P=0.001$ ) of HCV quasispecies, whereas HAART predicted increased complexity ( $P=0.013$ ) and diversity ( $P=0.026$ ). For four of six patients, sequence analysis yielded data supporting the model that positive host pressure drives HCV quasispecies heterogeneity, although data favoring the hypothesis of selective outgrowth of the most fit variants were also observed. **CONCLUSION:** HIV coinfection is associated with decreased HCV quasispecies variability, which appears to be reversed by effective HAART. Although HIV- and HAART-related effects on host immune pressure are likely to play a role in the observed differences in HCV genetic heterogeneity, other mechanisms may be operative.

J Infect Dis. 2006;193(9):1211-1218.

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# HIV/HCV-coinfected may have worse survival

Michael Carter

**H**IV-positive individuals who are coinfecting with the hepatitis C virus (HCV) appear to have slightly worse survival than patients who are infected with HIV alone, according to data from a study involving HIV-positive patients taking antiretroviral salvage regimens presented at last month's 12th Annual Conference of the British HIV Association (BHIVA). A separate study also presented to the conference revealed that an increasing proportion of HIV-positive patients in the United Kingdom are being tested for HCV and that injecting drug users were more likely to test positive for HCV.

Studies looking at the effect of HCV on the prognosis of individuals with HIV have yielded conflicting results. Investigators from the Options in Management with Antiretrovirals (OPTIMA) study, which is exploring various treatment strategies for patients with limited options, decided to look at the effect of HCV on the incidence of new AIDS events and survival in patients enrolled in their study. The OPTIMA study includes patients receiving care in Canada, the United Kingdom, and the United States.

A total of 311 individuals were included in the investigators' analysis. Of these, 72 individuals (23%) were infected with HCV. Over a median of two years of follow-up, 25% of patients coinfecting with HCV died compared to 16% of individuals who were infected with HIV only, meaning that patients coinfecting with HCV were 79% more likely to die than those who were HCV-negative, a statistically significant difference ( $P=0.05$ ).

The investigators then looked at how patients had acquired their infection with

HIV and HCV. They established that 74% of individuals coinfecting with HIV and HCV reported injecting drug use, compared to only 24% of patients who were HIV-monoinfected. When the investigators controlled for mode of transmission, they found that the effect of HCV on survival ceased to be significant ( $P=0.13$ ).

Attention was then turned to how many antiretroviral drugs HCV-infected and HCV-negative patients used. After controlling for this, the investigators found that patients coinfecting with HCV were 37% more likely to die than patients who had only HIV, but once again, this difference was not statistically significant ( $P=0.39$ ).

The durability of antiretroviral therapy in HIV-positive and HIV/HCV-coinfected patients was then examined by the researchers. The median duration of the first OPTIMA study regimen was four months for coinfecting patients and seven months for HCV-negative individuals.

Finally, the incidence of new AIDS-defining events was examined in the two groups of patients. During follow-up, 25% of individuals who were monoinfected with HIV developed a new AIDS-defining condition, compared to 23% of coinfecting patients. This difference was not statistically significant.

The investigators conclude, "coinfection with [HCV] appears to increase the risk of mortality, but this effect might be partly explained by a shorter time to switching/stopping antiretroviral therapy. One possible reason could be that [HCV]-infected patients are less able to tolerate antiretroviral [drugs]."

## HCV prevalence

A separate study presented to the conference described the prevalence of HCV coinfection in the UK Collaborative HIV Cohort (UK CHIC). Data from seven HIV clinics treating 21,250 patients from

1996 onwards were included in the investigators' analysis.

A total of 11,357 individuals had had at least one HCV antibody test with 1,045 (9%) testing HCV-positive.

Since 2004, the BHIVA treatment guidelines have recommended that all HIV-positive patients be tested for HCV soon after they are diagnosed HIV-positive, and at intervals thereafter if they have ongoing risk factors for the acquisition of HCV infection. The investigators presented evidence showing that there was a trend for more HCV testing over time: in 1995 only 7% of HIV-positive patients, nearly all of whom were injecting drug users, had been tested for HCV infection, but this had increased to 72% by 2003 with individuals being tested for the infection regardless of their HIV risk factors.

As a result of more widespread and less targeted testing, the proportion of patients who tested positive actually fell over time. In 1995, 26% of the 369 patients tested for HCV antibodies were HCV-positive. This fell to 13% of 2,861 individuals in 2000 and 8% of 8,033 patients in 2004.

HIV risk group was significantly associated with the likelihood of infection with HCV, with current or past injecting drug users ( $P<0.001$ ) and heterosexuals ( $P<0.001$ ) having a significantly increased risk compared to other risk groups. Gay men were not a risk group associated with an increased risk of HCV, despite recent studies from London and Brighton showing sexual transmission of HCV. ■

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**Editor's Note:** Reprinted with permission from [www.aidsmap.com](http://www.aidsmap.com) (first e-published April 4, 2006).



## IN THE LIFE



### Nnamdi Obidma Ndubuka

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 Nnamdi Obidma Ndubuka, a physician at the Masunga Primary Hospital in Masunga, Botswana.

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

The world is a global village filled with humans as political animals.

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

My activities and hobbies are conducting research and watching soccer. My hidden talent is making speeches.

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

I would live in Abuja, Nigeria.

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

My real life heroes are Nelson Mandela and Martin Luther King Jr.

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

Alexander the Great.

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

My favorite actors are Denzel Washington and Richard Mofe Damijo.

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

I would choose to live in the 20th century.

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

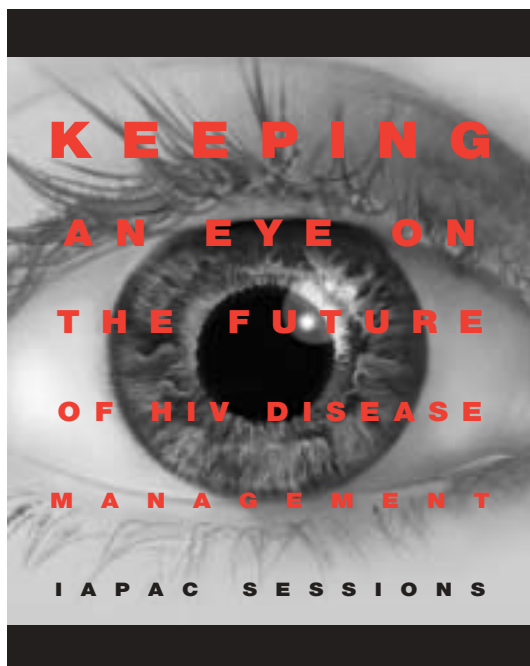
A politician.

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

Greatest achievement: the discovery of the human immunodeficiency virus. Greatest failure: our inability to discover a cure for HIV/AIDS.

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

The depletion of the ozone layer and the effects of global warming may adversely affect the lives of humans and other inhabitants of the earth. ■



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**Questions?**

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



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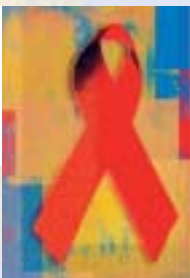


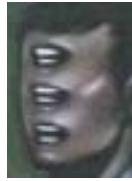
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## SAY ANYTHING



**If people want to work in the army and they are in good physical condition, it is simply not ethical to say they should be left out.**

*Robert Mkabala of Uganda's AIDS Support Organization, quoted in an April 4, 2006, Associated Press report in reaction to an announcement by that country's military that HIV-positive soldiers will be excluded from strenuous training. According to the report, the Ugandan Army's Chief of Operations and Training, Brig. Silver Moses Kayemba, announced that HIV-positive soldiers will only be allowed to participate in administration, finance, intelligence, and medical corps training.*



**...a time bomb waiting to explode...**

*Excerpt from the Pakistan Medical Association's 2006 Annual Report released April 3, 2006, predicting dire circumstances should the Pakistani government fail to take drastic measures to address hepatitis B virus (HBV) and hepatitis C virus (HCV) epidemics. Almost 10% of the country's 155 million people are infected with hepatitis, according to the report, and life expectancy has declined from 63 to 60 years. In addition, the report warned about the country's inadequate health care infrastructure, which facilitates the operation of people who offer fraudulent cures for HBV, HCV, cancer, and kidney disease.*



**Most of the 20 PEPFAR teams reported that fulfilling [the spending target] presents challenges to their ability to respond to the local epidemiology and cultural and social norms.**

*Excerpt from a US Government Accountability Office (GAO) report of US-funded HIV/AIDS programs in 20 countries,*

*as quoted in an April 5, 2006, Washington Post article. Included in the 20 countries are 15 countries in which the US President's Emergency Plan for AIDS Relief (PEPFAR) operates. According to the GAO report, HIV prevention spending quotas targeting abstinence make PEPFAR-funded programs unable to respond flexibly to local epidemics. Of the funding set aside for HIV prevention, half must be spent to prevent sexual transmission, of which two thirds must be used to promote abstinence. In nine PEPFAR countries, mandated abstinence targets led to reduced 2006 funding for programs preventing mother-to-child HIV transmission.*



**There are two things that make us worry. If you plot the number of cases reported to the Ministry of Health, it's quite a steep rise. The other thing is that we don't know what the situation is among the most vulnerable groups.**

*Maha Aon of the Joint United Nations Programme on HIV/AIDS (UNAIDS) in an April 3, 2006, Reuters report about efforts to recruit Islamic religious leaders to help Egyptians combat HIV/AIDS. The report described a recent United Nations Development Programme (UNDP) workshop on spreading HIV/AIDS awareness through local religious leaders in Cairo. In 2004, senior Islamic leaders publicly endorsed efforts to prevent HIV transmission and end discrimination against those infected. That same year, a study found most Egyptian health workers surveyed believed people living with HIV/AIDS should be removed from society. The UNDP's efforts include information packets demonstrating Islam's willingness to tackle sexual topics, as well as quotes from the Prophet Mohammad urging compassion and care for the well-being of others.*



**We were stunned – amazed – that nobody's looked at this before.**

*Stephen Simon, Los Angeles' AIDS Coordinator, quoted in an April 5, 2006, Los Angeles Times article about results of a study warning that gang members are particularly susceptible to HIV not only because of high-risk behavior, but also because of stigma and erroneous beliefs about AIDS. The study surveyed 300 gang members. About half agreed to be tested for HIV; one person tested HIV-positive. Among those surveyed almost 90% said they had engaged in unprotected sex in the previous 12 months; 31% believed a vaccine to prevent HIV infection had recently been developed; 54% said their friends would avoid them if they were HIV-infected; and 91% said their communities need more knowledge about HIV.*



**ADAPs will continue to have to make difficult trade-off decisions between serving more people with less services or serving less people with more services.**

*From a joint study conducted by the Kaiser Family Foundation (KFF) and the National Association of State and Territorial AIDS Directors (NASTAD) as quoted in a March 30, 2006, Reuters report. The KFF/NASTAD study revealed that 791 people are on AIDS Drug Assistance Program (ADAP) waiting lists in Alabama, Alaska, Arkansas, Idaho, Indiana, Kentucky, Montana, Nebraska, and West Virginia. In addition, cost-saving measures have been implemented in several states. For example, as of September 2005, only 35 states' formularies offer all currently approved antiretroviral drugs, with several state ADAPs having reduced the number of drugs offered.*