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Topics in HIV Medicine®

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Perspectives

The International AIDS Society–USA

About This Issue

This issue of *Topics in HIV Medicine* includes 3 *Perspectives* articles that address some of the most crucial clinical needs in resource-limited areas: the prevention of mother-to-child transmission of HIV, and the prevention and management of life-threatening opportunistic infections in HIV-infected individuals. Attention to some of these issues (eg, management of *Pneumocystis jiroveci* pneumonia, tuberculosis treatment, and so on) has decreased substantially in the developed world because of the availability of effective antiretroviral therapy. However, the articles in this issue focus on the pressing challenges of the epidemic in resource-poor areas, providing a review of these areas for clinicians who have not encountered these complications recently—but may in the future.

The first article highlights a talk given at an International AIDS Society–USA continuing medical education course by Sten H. Vermund, MD, PhD. Dr Vermund discussed preventing mother-to-child transmission of HIV in Africa, including risk factors, care of the mother, and the current research agenda.

The Caribbean Region has the highest HIV prevalence rate of any region of the world, outside of sub-Saharan Africa. The Caribbean HIV/AIDS Regional Training (CHART) initiative was started to address the shortage of health care personnel in the Caribbean region who have specialty training in HIV/AIDS, particularly in clinical management.

At the First CHART Caribbean Conference on the Clinical Management of HIV/AIDS, Jonathan E. Kaplan, MD, presented a review of the diagnosis and prevention of specific opportunistic infections that are common among HIV-infected patients in the Caribbean region. Jean William Pape, MD, discussed tuberculosis infection in particular. Both of these presentations are summarized in this issue.

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The Caribbean HIV/AIDS Regional Training (CHART) initiative and its first regional training in June 2004 were funded by the Centers for Disease Control and Prevention, the US Agency for International Development (USAID), Health Resources and Services Administration of the US Department of Health and Human Services, and UNAIDS, among others.

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Perspectives

Announcements

Perspective

Prevention of Mother-to-Child Transmission of HIV in Africa

HIV infection and mortality rates in African children are astoundingly high. Risk factors for mother-to-child transmission of HIV include maternal plasma viral load and breastfeeding. With regard to the latter, current data indicate that mixed feeding (breastfeeding with other oral foods and liquids) is associated with the greatest risk of transmission. Studies are under way to determine if exclusive breastfeeding with rapid early weaning can reduce transmission rates in the absence of exclusive formula feeding for all infants. Perinatal transmission rates have been dramatically reduced with the use of single-dose nevirapine, but this strategy protects only approximately 50% of infants, and more than 75% of women receiving nevirapine develop a major nevirapine resistance mutation. In developed areas of the world, antiretroviral therapy has reduced perinatal transmission by more than 90% compared with 1993 rates. Improved HIV-related care for HIV-infected women in Africa is needed to reduce rates of HIV infection in children and to prevent maternal mortality. This article summarizes a presentation by Sten H. Vermund, MD, PhD, at the International AIDS Society–USA course in Chicago in May 2004.

Since the finding in Pediatric AIDS Clinical Trials Group (PACTG) Study 076 (Connor et al, *New Engl J Med,* 1994) that zidovudine treatment for pregnant women decreased the rate of HIV transmission to the newborn from approximately 25% to 8%, the rate of perinatally acquired HIV infection in the United States has decreased more than 90%, to fewer than 50 per year (Figure 1). However, the situation in Africa and other locales worldwide is quite different. The Joint United Nations Program on HIV/AIDS (UNAIDS) estimates that the ratio of African children to North American children under 15 years of age with new HIV infection in 2002 was 3000 to 1, and the ratio of African children to North American children who died from HIV disease in 2002 was 10,000 to 1. This is in the context of a 2.6 population ratio for Africa and North America.

Risk Factors for Maternal Transmission

Risk factors for mother-to-child transmission include high plasma viral load in the mother; choriodecidual inflammation; obstetric factors, such as vaginal delivery (cesarean delivery is protective) and preterm delivery; and breastfeeding (Mofenson, *Semin Pediatr Infect Dis*, 2003). Mixed feeding (ie, breast milk plus other foods and liquids by mouth) appears to account for substantial transmission risk via this route in the first six months of life (Coutsoudis et al, *Lancet*, 2000).

Maternal Viral Load

The eminent preventability of perinatal transmission is indicated by Figure 2. Rates of transmission are under 2% when the infected mother receives potent antiretroviral therapy or when the mother's plasma HIV RNA level is below assay detection limits, but are as high as 50% in women with high HIV RNA levels who are receiving no antiretroviral therapy (Cooper et al, *J Acquir Immune Defic Syndr*, 2002).

Preterm Delivery and Chorioamnionitis

Data showing markedly increased risk of maternal HIV transmission in infants born very prematurely (Figure 3; European Collaborative Study, *Lancet*, 1992) prompted Dr Robert Goldenberg and colleagues to perform a study in Zambia, Malawi, and Tanzania to determine if simple antibiotic therapy to reduce maternal bacterial infection during gestation might have an impact on reducing HIV transmission rates and perhaps on preventing preterm deliveries. The rationale for the intervention is that chorioamnionitis during pregnancy may result in increased white blood cell recruitment to the site, offering target cells for HIV (Goldenberg et al, *Lancet*, 1998). In this

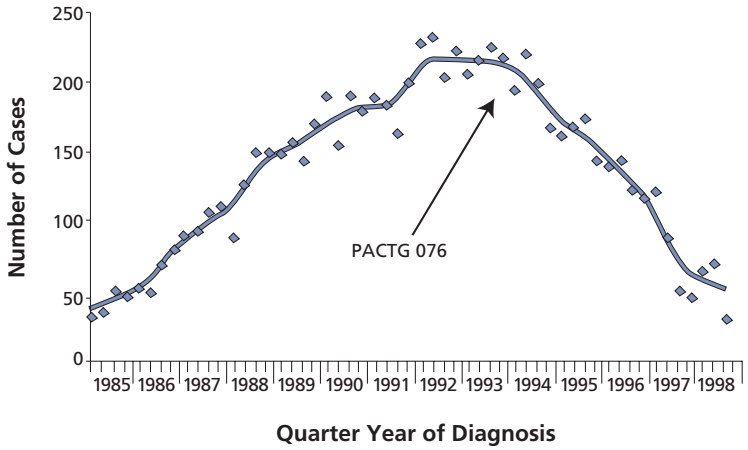

Figure **1.** Perinatally acquired AIDS cases in the United States, by quarter year, from 1985 to 1998. Cases are adjusted for reporting delays and redistribution of "no identified risk" cases into probable risk categories; data were reported through March 1999. Arrow indicates when the Pediatric AIDS Clinical Trials Group study 076 was reported in 1994. Adapted from Centers for Disease Control and Prevention, Pediatric HIV/AIDS surveillance slides at www.cdc.gov.

Dr Vermund is Professor of Medicine at The University of Alabama at Birmingham.

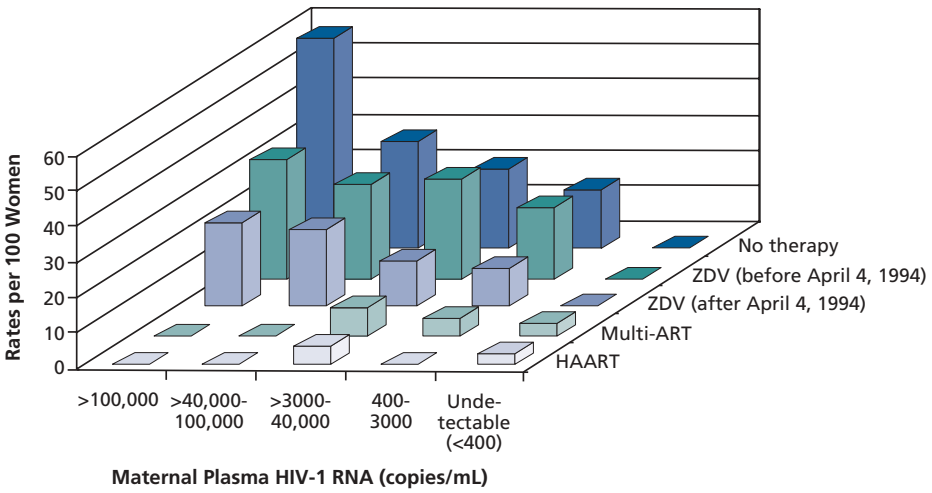

Figure **2.** Rates of perinatal HIV transmission according to maternal plasma viral load at delivery and type of antiretroviral treatment: No therapy, zidovudine monotherapy (ZDV) prior to or after reporting of Pediatric AIDS Clinical Trials Group study 076 in April 1994, combination antiretroviral therapy (multi-ART), or highly active antiretroviral therapy (HAART). Adapted from Cooper et al, *J Acquir Immune Defic Syndr*, 2002; and Mofenson of the National Institute of Child Health and Human Development.

study, HIV-infected pregnant women were randomized either to metronidazole and erythromycin during the second trimester and metronidazole and ampicillin at delivery, or to placebo. Interim analysis of data from the first approximately 1500 women suggests that antibiotic treatment of chorioamnionitis is not likely to be an effective intervention factor in this setting (Taha Taha and Goldenberg, unpublished data), and reemphasizes the need for improved antiretroviral coverage to prevent perinatal transmission.

Breastfeeding

In a study of infants born to HIV-infected women in South Africa, Coutsoudis and colleagues (*Lancet*, 1999; *Lancet,* 2000; XIIIth Int AIDS Conference, 2000) found that HIV infection was detected at 6 months in identical proportions of exclusively breastfed infants (19%) and never-breastfed infants (19%), and that infants who received mixed feeding had a higher rate of infection (26%; Figure 4). By 15 months, the infection rate was higher in exclusively breastfed children than in never-breastfed children, and the rate remained highest in children who received mixed feeding. The explanation for this finding may be the infant's immune response to novel foods, which results in recruitment of white blood cells into the gastrointestinal tract, providing additional targets for HIV infection. A strategy of feeding all infants born to HIV-infected mothers exclusively formula is, sadly, untenable in much of Africa and in other areas of the world, because the daily cost of formula exceeds the daily income of most individuals. Availability of safe drinking water to prepare infant formula is also a limiting factor. Approximately 20% of the human race lives on $1 per person per day and 50% lives on less than $2 per person per day. In this context, Donald Thea and colleagues currently are performing a study in Zambia assessing a strategy of exclusive breastfeeding with rapid weaning at 4 to 6 months versus normal weaning. The target population is 1600 HIV-infected mothers and their infants. Study outcomes include HIV infection status and growth of the child at 24 months, maternal satisfaction with and community acceptance of the rapid weaning approach (which is completely novel in this locale), and maternal morbidity and mortality (Thea et al, *Control Clin Trials*, 2004).

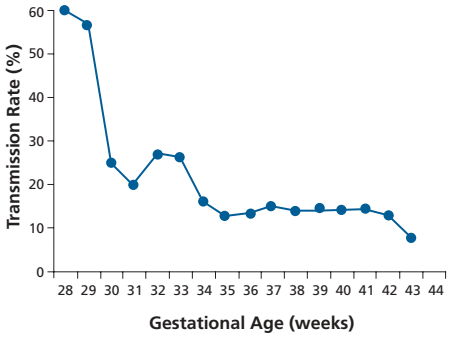

Figure **3.** Perinatal transmission by gestational age at delivery. Adapted from the European Collaborative Study, *Lancet*, 1992.

What About the Mothers?

A coherent public health approach must include upgrading maternal health in parallel with saving infants' lives. The good news in this regard is that there are a number of initiatives under way to improve pre- and postpartum HIV-related care for women, including Mother-to-Child Transmission (MTCT)-Plus, based at Columbia University in New York; the President's Emergency Plan for AIDS Relief (PEPFAR), which represents up to $15 billion over five years, $9 billion of it being new funding; and the Global Fund to Fight AIDS, Tuberculosis, and Malaria.

Efforts to bring adequate antiretroviral therapy to African nations are beginning to bear fruit. Figure 5 shows the decrease in cost of antiretroviral agents over the past several years (Vermund, *Clin Infect Dis*, 2003). Currently, US drugs can be obtained for as little as $600 per person per year, and generic drugs from India and elsewhere can be obtained for as little as $239 (zidovudine, lamivudine, nevirapine) or $132 (stavudine, lamivudine, nevirapine) per person per year when secured through the William Jefferson Clinton Presidential Foundation purchasing agreements (William R. Rodriguez, personal communication, December 2, 2004). However, tests for monitoring effects of antiretroviral therapy remain costly. One potential option for low-cost monitoring is indicated by findings among infected individuals in Tamil Nadu, India, showing a good correlation between increases in CD4+ cell counts and total lymphocyte counts in patients receiving antiretroviral therapy; decreases in CD4+ cell counts correlated less well with total lymphocyte counts (Figure 6; Kumarasamy, *J Acquir Immune Defic Syndr*, 2002; Kumarasamy et al, *Lancet Infect Dis*, 2002; Mahajan et al, *J Acquir Immune Defic Syndr*, 2004). Measurement of the total lymphocyte count is widely available and very inexpensive. Such data suggest the feasibility

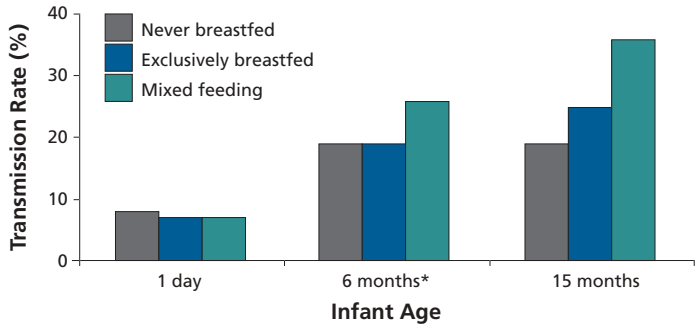

Figure **4.** HIV transmission rates in infants of HIV-infected mothers at 1 day, 6 months, and 15 months according to whether infants were exclusively breastfed (n=118), never breastfed (n=157), or had mixed feeding (n=276). *At 6 months: exclusive versus mixed relative risk=0.6 (range 0.3-1.0); exclusive versus never, 1.2 (0.6-2.2). Adapted with permission from Coutsoudis et al, XIIIth AIDS Conference, 2000.

of a strategy of performing a baseline CD4+ cell count at initiation of therapy and following patients with the total lymphocyte count. Although not ideal, this strategy may permit more money to be devoted to getting more infected individuals on appropriate antiretroviral therapy until cheaper CD4+ cell count and viral load technologies become available (Kent et al, *Clin Infect Dis*, 2003; Crowe et al, *Clin Infect Dis*, 2003).

Aspects of Current Perinatal Agenda

Zambia is a country roughly the size of Texas with a population of 10.2 million, of whom 50% live in urban areas. Lusaka, the capital city, has a population of approximately 2 million. In Lusaka, there are more than 50,000 live births per year occurring in public section birthing centers and the University Teaching Hospital. Infant mortality is at least 100 per 1000 live births. Putting this in context, infant mortality in the state of Illinois (the location of the talk upon which this article is based) is approximately 8 per 1000 live births. Maternal mortality in Lusaka is approximately 800 per 100,000 live births; maternal mortality in Illinois is approximately 1.5 per 100,000 live births.

The overall HIV prevalence in Lusaka is 25% among young adults, as estimated in the antenatal clinic population. Per capita annual income is $250 to $350. In 2002, the public health department of Lusaka had an annual budget of less than $200,000 to provide prenatal care and delivery services to 45,000 women and newborns (Moses Sinkala, personal communication). Although not all women come for antenatal services, those who do make an average of 5 visits (Robert MacDonald, unpublished data). At $0.50 per antenatal visit and $2 per delivery, the cost of delivery and antenatal care alone projected to the antenatal population exceeds the annual budget for care.

The consequences for quality of care are illustrated by the following scenario. A 1998 to 1999 chart review of 600 antenatal care clinic clients showed that 44 had positive rapid plasma reagin (RPR) testing, indicating exposure to syphilis, and only 2 had documented penicillin treatment (MacDonald, unpublished data). The RPR test kits had been donated by a foreign government; the penicillin was to have been provided by the Zambian Ministry of Health, but no shipments had been made in 3 years (Sinkala, personal communication). The untreated RPR-positive clients were written prescriptions to be filled outside the clinic, a virtual impossibility, given the financial status of these individuals. It is within this health care setting, with profound resource limitations, that both infant and maternal health programs must attempt to improve health care.

As reported by Guay and colleagues in 1999, the HIVNET 012 study in Uganda showed that voluntary counseling and testing, and a single nevirapine dose given to HIV-seropositive mothers at the beginning of labor plus 1 dose of nevirapine syrup given to the newborn in the first 72 hours reduced HIV transmission by 49%, compared with short-course zidovudine treatment (*Lancet*, 1999). A 2003 update of HIVNET 012 indicates that the benefits of nevirapine versus zidovudine treatment are maintained over 18 months of follow-up, with no diminution in protective benefit as a result of potential breastfeeding transmission (Jackson, *Lancet*, 2003). This study has had a profound effect on prevention of perinatal transmission on a global level. Within 2 years of the report's initial publication, the Elizabeth Glaser Pediatric AIDS Foundation, with funding from the Gates Foundation, had instituted its Call to Action program in 17 countries, and tens of thousands of women were receiving nevirapine shortly thereafter.

The advantages of the nevirapine approach are that it is effective, safe, simple (apart from administrative issues), convenient, and affordable. The drug actually costs less than $4 per dose, but it is provided free by the manufacturer to developing country programs through the Axios Foundation in Ireland. One disadvantage of the nevirapine approach is that it still protects only 50% of infants from HIV transmission; potent triple-drug antiretroviral therapy reduces the perinatal transmission rate to less than 2%. Further, more than 75% of women receiving nevirapine exhibit a major nevirapine resistance mutation that may

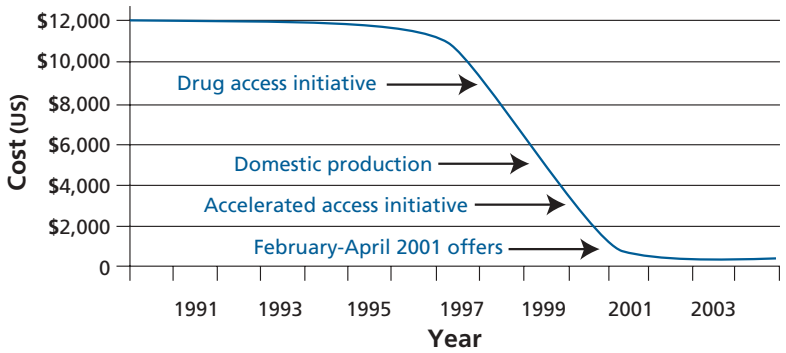

Figure **5.** Annual cost (in US dollars) per person for triple-drug antiretroviral therapy in Africa. The annual costs have declined from approximately $12,000 a year to $300. Data from UNAIDS.

compromise nevirapine use in subsequent pregnancy and use of other nonnucleoside reverse transcriptase inhibitors (NNRTIs) in potent antiretroviral therapy. About 6 to 12 months after this short treatment course, the proportion of nevirapine-resistant virus is dramatically reduced, but the resistant variants may emerge rapidly with reexposure to NNRTIs. A recent publication from Thailand suggests that women who received a single intrapartum nevirapine dose were less likely to have virologic suppression after 6 months of a nevirapine-containing triple-therapy antiretroviral regimen (Jourdain et al, *N Engl J Med*, 2004). Finally, although the nevirapine therapy itself is simple, voluntary counseling and testing programs and nevirapine programs are costly and complex at a national level.

From the point of view of care in Lusaka, Zambia, nevirapine treatment of mothers and newborns can save more than 2400 infants per year, or 50 per 1000 live births, from transmitted HIV infection. No other single intervention of an obstetrics or pediatrics provider will have nearly this magnitude of impact on childhood survival. Yet, much more needs to be done in parallel with a nevirapine program. Other key interventions include training midwives to perform appropriate obstetric services; upgrading infrastructure for providing and accessing consumables such as RPR test kits, penicillin, vitamins, gloves, antituberculosis drugs, and other antibiotics; determining the most effective ways to test pregnant women for HIV and to provide antiretroviral therapy; finding the resources to carry out and sustain current programs, such as Call to Action, PEPFAR, and the Global Fund to Fight AIDS, Tuberculosis, and Malaria; providing HIV test kits and additional antiretrovirals that could reduce mother-to-child transmission much more than 50% with full adherence; and using programs for prevention of mother-to-child transmission as bridges to potent antiretroviral therapy for HIV-infected women and infected family members (eg, by maintaining current efforts of such programs as MTCT-Plus and PEPFAR; Goldenberg et al, *J Matern Fetal Neonatal Med*, 2002).

A nevirapine program seems simple. In practice, it is not (Stringer, *AIDS*, 2003; Temmerman, *AIDS*, 2003). To maximize population coverage of such a program, pregnant women must have access to antenatal care. For women who do not come into the clinic for delivery or antenatal care, traditional birth attendants must be involved. Once a woman is within the care structure, she needs to be offered the intervention; thus, a voluntary counseling and testing program must be available, along with access to nevirapine treatment. A woman has to accept the counseling and testing and the nevirapine treatment; it should be noted that some 20% to 50% of women in Call to Action sites around the world refuse testing with such statements as: "I know I'm positive," "I don't need to know," "I don't want to know," "I have to ask my husband. He'll say no," or "If I'm infected, what is the sense of saving my baby, because I will die and there will be no one to take care of him." Once a woman who is giving birth at home has accepted participation in the intervention, support from the family or nurse-midwife is needed to carry through the intervention, including ensuring that she takes her nevirapine dose at the onset of labor and providing the nevirapine dose to the newborn.

In the initial experience of Dr Jeffrey Stringer and colleagues with trained midwives in Lusaka, it was found that the dose for the newborn was frequently omitted. The difficulties inherent in carrying out such a program are reflected in the fact that in their first year of operating the program in Lusaka, only 30% of eligible pregnant HIV-positive women received the complete nevirapine treatment, as assessed by directly observed therapy for the infant and measurement of nevirapine levels in cord blood. In the following year, the rate of successfully delivered treatment increased to 40% (Stringer, unpublished data).

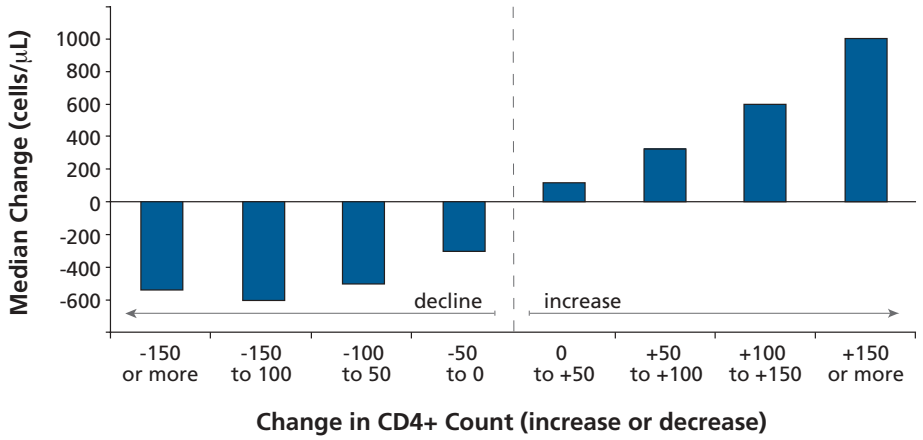

Figure **6.** Median change in total lymphocyte count by change in CD4+ cell count from baseline in patients receiving antiretroviral therapy. Adapted from data published in Kumarasamy, *J Acquir Immune Defic Syndr*, 2002, and Kumarasamy, *Lancet Infect Dis*, 2002.

Challenges

The prevention of mother-to-child transmission of HIV in Zambia and elsewhere requires novel antiretroviral regimens that are as "simple" as but more effective than single-dose nevirapine and that do not induce high-level drug resistance in the mother. Improved strategies for preventing HIV transmission through breastfeeding are also needed. Of course, from a societal perspective, great improvements are needed in efficient delivery of antiretroviral therapy for all who are HIV-infected, along with access to low-cost diagnostics and monitoring, improved training for health services personnel, and general health services improvements. HIV-related care must not come at the expense of deteriorations in other aspects of public health; this has been observed in some locales, in which funding for tuberculosis treatment and prevention programs has been diverted to HIV programs, with a resultant increase in tuberculosis rates. In short, effective delivery of HIV-related care in places such as Zambia ultimately will require sustainable programs that address all of the issues raised in providing care in industrialized countries, as well as issues related to implementing such programs across great financial and cultural divides.

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Suggested Reading

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Perspective

Diagnosis, Treatment, and Prevention of Selected Common HIV-Related Opportunistic Infections in the Caribbean Region

The Caribbean region, like other resource-limited areas, lacks many of the diagnostic and treatment modalities taken for granted in richer areas of the world. The Caribbean Guidelines for the Treatment of Opportunistic Infections in Adults and Adolescents Infected With the Human Immunodeficiency Virus *provides guidelines for the region for preventing and treating more than 20 opportunistic diseases reflecting the variable availability of diagnostic and treatment resources. Elements of diagnosis and prevention of tuberculosis,* Pneumocystis jiroveci *pneumonia, and other common opportunistic conditions in this resource-limited setting were discussed by Jonathan E. Kaplan, MD, at the first CHART Caribbean Conference on the Clinical Management of HIV/AIDS in Montego Bay, Jamaica, in June 2004.*

The Caribbean region, like other resource-limited areas, lacks many of the diagnostic and treatment modalities taken for granted in richer areas of the world. Polling of the attendees at the first CHART Caribbean Conference on the Clinical Management of HIV/AIDS (almost 350 HIV clinicians from 29 countries in the Caribbean region) indicated that approximately one third had access to both computed tomography (CT) and magnetic resonance imaging (MRI), whereas approximately one third had neither; only 10% had access to cryptococcal antigen testing; approximately one fifth reported having the ability to diagnose *Pneumocystis jiroveci* (formerly *carinii*) pneumonia (PCP), which requires induced sputum collection or bronchoscopy to obtain bronchioalveolar lavage specimens, as well as appropriate laboratory staining techniques; and approximately one half did not have access to CD4 + cell count testing.

The *Caribbean Guidelines for the Treatment of Opportunistic Infections in Adults and Adolescents Infected with the Human Immunodeficiency Virus*, presented at the conference, represents a prodigious effort on the part of the Caribbean HIV-care community and offers invaluable regional guidelines for preventing and treating more than 20 opportunistic infections (OIs). The guidelines are oriented toward diagnosis and treatment of specific OIs. However, a syndromic approach to diagnosis and treatment of OIs is critical in assessing HIV-infected patients in settings in which laboratory diagnostics are lacking. Many of the OIs occurring in HIV-infected individuals are signaled by symptoms or signs that should prompt suspicion for specific conditions. The syndromic approach is represented in the acute care module of the World Health Organization (WHO) Integrated Management of Adolescent and Adult Illness modules. (The 4 modules of this program—acute care, chronic HIV care with antiretroviral treatment, general principles of good chronic care, and palliative care—are available at www.who.int/3by5/publications/documents/imai/en/.) The acute care module covers all common illnesses, but gives particular attention to those associated with HIV infection. It was specifically prepared to be used in peripheral health centers with limited or no laboratory diagnostics and where care may be provided by nurses and physician assistants.

Diagnosis of Opportunistic Infections

Tuberculosis

The natural history of HIV disease is such that most OIs occur after the CD4 + cell count has decreased to below 200/µL (Figure 1). Tuberculosis (TB) can occur at any CD4 + cell count. The pres-

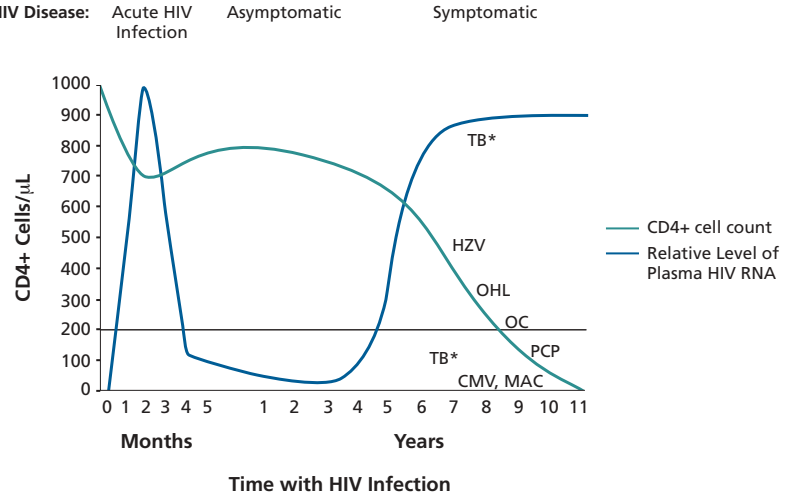

Figure **1.** Natural history of HIV infection and common complications. TB indicates tuberculosis (*can occur at any CD4+ cell count); HZV, herpes zoster virus; OHL, oral hairy leukoplakia; OC, oral candidiasis; PCP, *Pneumocystis jiroveci* pneumonia; CMV, cytomegalovirus; MAC, *Mycobacterium avium* complex.

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ence of oral candidiasis is clinically correlated with CD4+ cell counts of 200/µL or less, and infections such as PCP, cytomegalovirus infection, and disseminated *Mycobacterium avium* complex (MAC) disease are seen with progressively lower CD4+ cell counts. There is very little published information regarding the prevalence of opportunistic illnesses in HIV-infected populations in the Caribbean. One published report in a small number of patients from Haiti indicated that TB was the most common AIDS-defining condition, having been the index diagnosis in 39% of patients (Table 1).

Table **1**. Prevalence of AIDS-Defining Conditions Among 23 Persons with AIDS in Haiti

	Prevalence
Tuberculosis	39%
Wasting syndrome	31%
CD4+ count <200 cells/µL	10%
Cryptosporidiosis	4%
Cyclospora diarrhea	4%
Cryptococcal meningitis	4%
Candida esophagitis	4%
Toxoplasmosis	4%

Data from Deschamps, *AIDS,* 2000.

Figure 2 (color figures appear on pages 138 and 139) shows the x-ray of a young HIV-seropositive man who presented with fever and cough of 4 weeks' duration. The x-ray findings illustrate the atypical presentation of TB in HIV-infected individuals compared with that in HIV-uninfected individuals. The apical infiltrates or cavitation characteristic of TB in nonimmunosuppressed patients frequently are absent in HIV-infected patients, in whom the chest radiographic findings may be quite variable. The diagnostic sputum acid-fast smear showing tubercle bacilli is shown in Figure 2.

TB causes 11% of HIV-related deaths worldwide. As noted, it can occur at any CD4+ cell count. The clinical presentation of the disease becomes increasingly atypical as CD4+ cell count declines, with the x-ray picture becoming increasingly difficult to distinguish from that of other pulmonary conditions, and extrapulmonary manifestations of infection becoming more common. In resource-limited areas, a significant percentage of newly diagnosed HIV-infected individuals are found to have active TB. There are some data from Africa indicating that 5% to 10% of patients have active TB at the time of diagnosis of HIV infection. *TB should always be considered in an HIV-infected person with a pulmonary infiltrate.*

PCP

Figure 3 shows the x-ray of another young man with HIV infection who presented with fever and a nonproductive cough of 2 to 3 weeks' duration. The bilateral interstitial infiltrates shown are indicative of PCP; the organism is shown using methenamine silver stain of a bronchioalveolar lavage specimen. PCP is characterized by subacute onset (days to weeks) of shortness of breath, dry cough, and fever. The shortness of breath can be quite marked and may appear to be inconsistent with the findings on chest x-ray. Physical examination shows tachypnea and frequently hypoxemia, although the chest exam may reveal no adventitious sounds (rales or rhonchi). As noted, chest x–rays show bilateral, diffuse, interstitial pulmonary infiltrates. Diagnosis in resource-limited areas is difficult since it requires bronchoscopy or induced sputum and special stains that are not available in most laboratories. A normal sputum specimen is not sufficient for diagnosis. Treatment of choice is trimethoprim/sulfamethoxazole 15 to 20 mg/kg/ day for 3 weeks. In severe cases, prednisone 40 mg twice a day with dose tapering over 3 weeks can be given. However, use of prednisone is highly problematic in areas in which a definitive diagnosis of PCP cannot be made, since TB should be suspected in all patients with pulmonary infiltrates and prednisone should not be given to individuals with active TB. After successful initial treatment, chronic maintenance therapy is required, usually consisting of trimethoprim/sulfamethoxazole 160/800 mg/day.

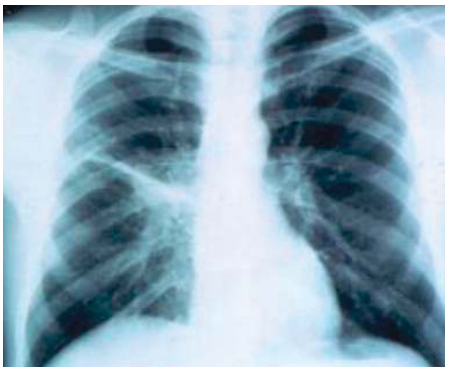
Bacterial Pneumonia

Figure 4 shows the lobar infiltrate characteristic of acute bacterial pneumonia and the sputum gram stain showing polymorphonuclear leukocytes and gram-positive diplococci. Onset of acute bacterial pneumonia is rapid (1 to a few days) and features fever and productive cough. It is important to recognize that bacterial pneumonias are about 8 times more common in HIV-infected persons than in HIV-uninfected persons, with pneumococcal bacteremia about 100 times more common. Bacterial pneumonia can occur at any CD4+ cell count, with common causative agents including *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*. Treatment consists of penicillin/ampicillin with or without an aminoglycoside or a third-generation cephalosporin.

Cryptococcal Meningitis

Figure 5 is an India ink preparation of spinal fluid showing the yeast form of *Cryptococcus neoformans* with the characteristic capsule around the organism. The sample was from a patient who presented with fever and complained of a progressively increasing headache over 2 weeks, which was described as extremely severe. This is a typical physical presentation of cryptococcal meningitis, with patients often describing the headache as the worst they have ever experienced. Mental disturbance is frequently present and increases in degree as disease worsens. As with other forms of meningitis, there generally are no focal neurologic signs on physical exam, allowing some degree of differentiation from conditions associated with focal abnormalities, such as toxoplasmic encephalitis and non-Hodgkin's lymphoma. The differential diagnosis principally involves bacterial meningitis and tuberculous meningitis. Lumbar puncture typically shows high opening pressure, and reducing the increased intracranial pressure constitutes an important aspect of managing patients with this infection. Protein levels are usually elevated, and approximately half of patients have low glucose levels.

The causative organisms can be isolated from the spinal fluid. Traditionally, the India ink method has been considered somewhat insensitive, with diagnosis relying on cryptococcal antigen testing; however, the sensitivity of the India ink method is likely markedly increased in patients with AIDS, who typically have large numbers of organisms, and the method is both relatively inexpensive



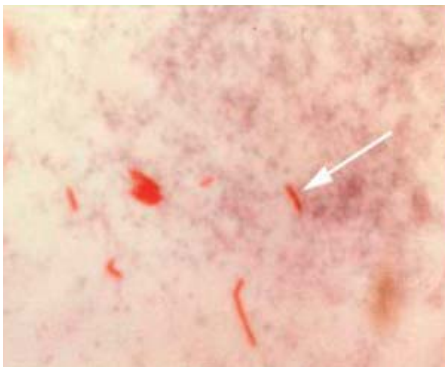


Figure **2.** Chest x-ray in a patient presenting with fever and cough of 4 weeks' duration (left). Acid-fast smear of sputum shows tubercle bacilli (right). This x-ray is illustrative of atypical findings of pulmonary tuberculosis in HIV-infected individuals.

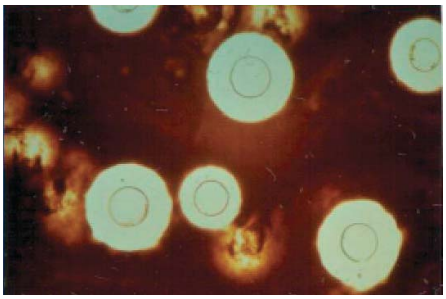
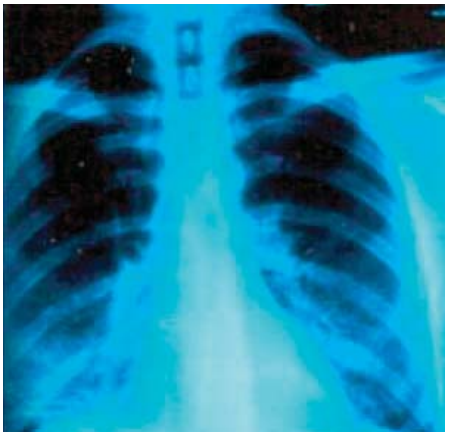


Figure **5.** India ink preparation of spinal fluid showing the yeast form of *Cryptococcus neoformans* with the characteristic capsule around the organism. Organisms were observed in a patient with cryptococcal meningitis who presented with fever, increasingly severe headache, and no focal neurologic signs.



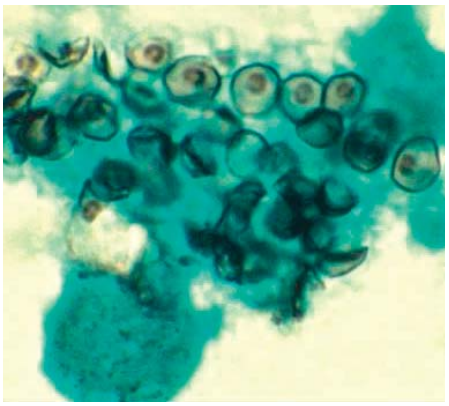
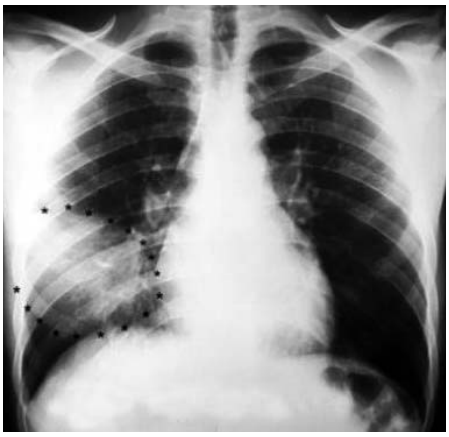


Figure **3.** Chest x-ray in a patient presenting with fever and nonproductive cough (top). Methenamine silver staining of a bronchioalveolar lavage specimen shows *Pneumocystis jiroveci* (PCP) (bottom). X-ray findings in PCP characteristically consist of bilateral, diffuse, interstitial pulmonary infiltrates.



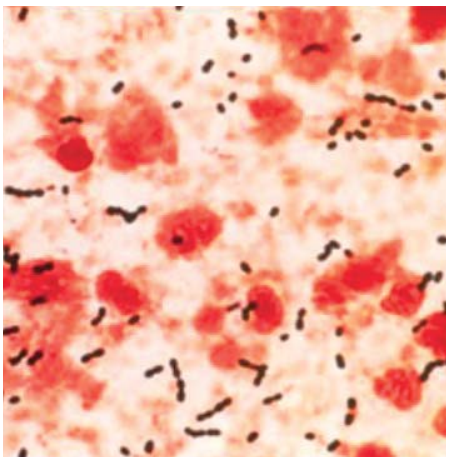


Figure **4.** Chest x-ray shows the lobar infiltrate characteristic of acute bacterial pneumonia (top), with sputum gram stain showing polymorphonuclear leukocytes and gram-positive diplococci (bottom).

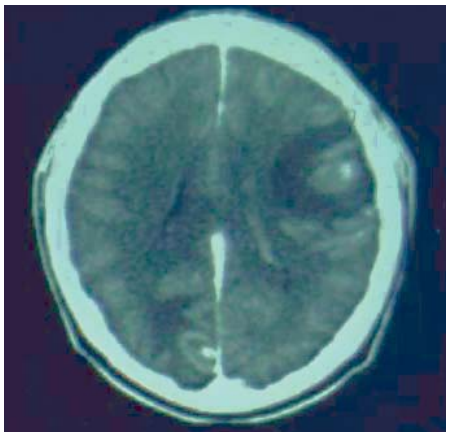


Figure **6.** Computed tomography scan of patient presenting with fever, headache, motor weakness, and recent seizure—a presentation suggestive of a focal neurologic lesion. The blank area around the lesion is edema. Multiple focal lesions are characteristic of cerebral toxoplasmosis.

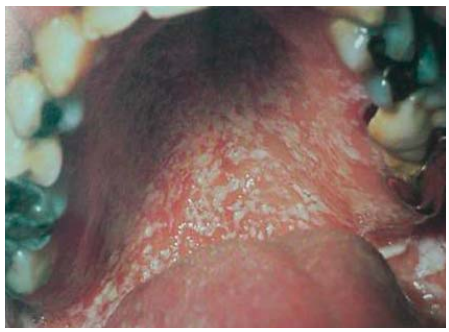


Figure **7.** Oral candidiasis (thrush). Appearance of oral candidiasis is a good clinical correlate of advanced immunosuppression. Physical exam should always include the mouth.

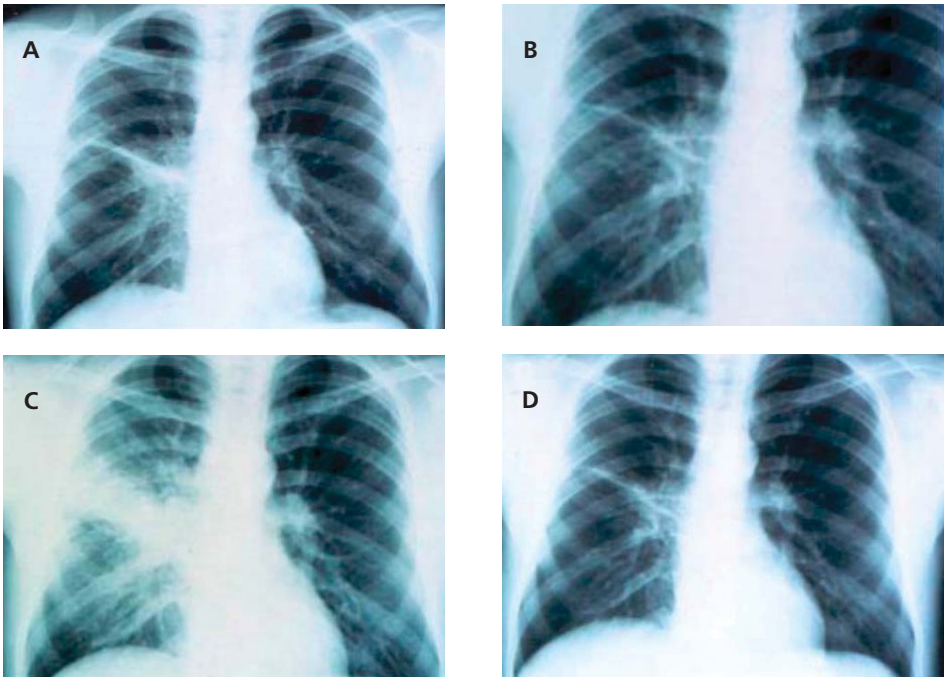


Figure **8.** (A) Initial chest x-ray of patient with tuberculosis shown in Figure 2. (B) Improvement after 1 month of 4-drug antituberculosis therapy. (C) After 1 month of potent antiretroviral therapy; apparent worsening of disease reflects increased inflammatory response associated with immune reconstitution under antiretroviral therapy. (D) One month later, after response to antiinflammatory medication.

and more readily available. High-dose fluconazole can be used to treat mild cases of infection. However, patients with mental status deterioration require amphotericin treatment for 2 weeks, followed by fluconazole for 8 to 10 weeks. It is ideal to combine amphotericin with flucytosine for the initial 2 weeks of treatment, since the combination treatment yields a lower relapse rate. However, flucytosine is variably available in many resource-limited areas. Chronic maintenance therapy consisting of fluconazole 200 mg/day must be given after successful treatment.

Toxoplasmosis

Figure 6 shows a CT scan of a patient presenting with fever and headache; the patient also had some motor weakness and a recent seizure, suggesting a focal neurologic lesion. The CT scan shows a typical toxoplasmosis lesion, with a ring-enhancing pale or blank area around the lesion. Although this area of edema is suggestive of toxoplasmosis, it is not diagnostic, since such edema may conceivably be present with other focal lesions (eg, lymphoma). The defining characteristic in imaging of toxoplasmosis is the presence of multiple focal lesions (not shown in Figure 6). As with the presentation of the current patient, findings in cerebral toxoplasmosis include headache, fever, confusion, and motor weakness, with focal neurologic signs on physical exam. Diagnosis is made by the finding of multiple mass lesions on CT or MRI. Treatment consists of pyrimethamine, sulfadiazine, and folinic acid for 8 weeks; chronic maintenance therapy is performed with the same regimen after successful treatment.

Oral Candidiasis

Practitioners in the Caribbean are likely very familiar with the appearance of oral candidiasis, or thrush (Figure 7). Diagnosis can be made visually; the white plaques can be lifted off with a tongue blade. Oral candidiasis is a reliable marker of advanced immunosuppression, emphasizing the importance of examining the mouth in all patients. There are many treatments for oral candidiasis, including clotrimazole troches (10 mg 5 times a day for 7 days), nystatin, and gentian violet, as well as fluconazole. For esophageal candidiasis, fluconazole should be given at 3 to 6 mg/kg/day for 2 weeks. It is suggested that maintenance therapy with fluconazole 200 mg/day be continued for several months after successful treatment.

Immune Reconstitution Syndromes

Figure 8 represents a phenomenon that is likely to be seen with increasing frequency as effective antiretroviral therapy becomes more widely available worldwide. Figure 8A shows the chest x-ray of the young man with TB previously discussed at presentation, and Figure 8B shows the changes after 1 month of 4-drug therapy for TB. At that point, the patient was clinically and radiologically improved, and the decision was made to start triple-drug antiretroviral therapy and to continue the TB regimen. After 1 month, the patient complained of fatigue and general malaise. Another chest x-ray was taken at that time (Figure 8C), showing changes that might reflect worsening of the TB due to nonadherence to medication, emergence of drug-resistant TB, or superinfection. However, the patient actually was experiencing an immune reconstitution reaction under antiretroviral therapy, characterized by increased immune system activation and inflammatory response to the tubercle bacilli in the lung, even though most of the organisms were probably dead at this time. The patient's clinical picture did not match the severity of illness suggested by the chest x-ray in that he was not complaining of much shortness of breath. He started antiinflammatory medication, to which he responded; 1 month later, the patient was doing quite well and the inflammatory response had resolved (Figure 8D).

In addition to the so-called "paradoxical reaction" occurring under antiretroviral therapy in patients with TB, immune reconstitution syndromes have been observed with a number of other opportunistic conditions, whether previously diagnosed or not, usually within 2 to 6 weeks after starting potent antiretroviral therapy. Such syndromes have been observed for MAC disease, PCP, toxoplasmosis, hepatitis B virus infection, hepatitis C virus infection, cytomegalovirus infection, varicella-zoster virus infection, cryptococcosis, and progressive multifocal leukoencephalopathy. These immune reconstitution syndromes can be expected to occur with greater frequency as antiretroviral therapy becomes more

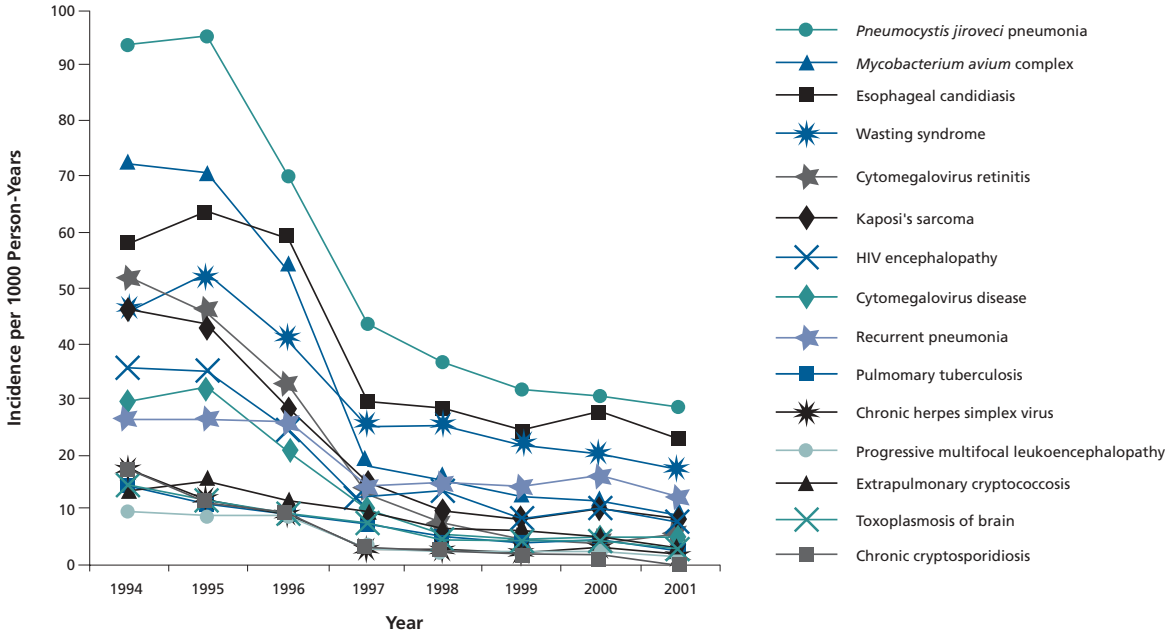


Figure **9.** Incidence of the 15 most common opportunistic illnesses from 1994 to 2001 in the Centers for Disease Control and Prevention's Adult and Adolescent Spectrum of HIV Disease Project. Adapted from Wolfe et al, Natl HIV Prev Conf, 2003.

widely available in resource-limited regions.

Prevention of OIs

Figure 9 shows the incidence of the 15 most common opportunistic illnesses in the United States between 1994 and 2001. The advent of triple-drug antiretroviral therapy in 1995 to 1996 brought sharp declines in the incidence of these illnesses, including both those for which there is effective prophylaxis and those for which there is not. The point to be gleaned in terms of prevention is that antiretroviral therapy is the most potent preventive regimen available against opportunistic illnesses. However, there are many specific interventions against OIs that are effective, that have been shown to reduce morbidity and mortality even in the setting of antiretroviral therapy, and that therefore remain important in the antiretroviral treatment era, particularly in those areas of the world that do not have access to antiretroviral drugs. Preventable illnesses include PCP, cerebral toxoplasmosis, TB, MAC disease, and disease caused by *S pneumoniae*.

The survival benefit of PCP prophylaxis was demonstrated in the late 1980s, and the recommendation for trimethoprim/sulfamethoxazole prophylaxis against PCP was made in 1989. In the early 1990s, it was often considered to be the single most important drug available in the HIV armamentarium because of its effectiveness in PCP prevention. The current eligibility criteria for PCP prophylaxis consist of CD4+ count below 200 cells/µL (or CD4+ cell percentage below 14%) or a history of oral candidiasis. In resource-limited areas where CD4+ cell count or percentage testing is not available, criteria may need to include other markers for advanced immunosuppression, such as WHO stage 4 clinical disease or total lymphocyte count below 1200/µL. The regimen of choice is trimethoprim/sulfamethoxazole 160/800 mg (1 double-strength tablet) once daily; if it is not tolerated, other drugs are available for prophylactic use. Trimethoprim/sulfamethoxazole prophylaxis is also recommended for HIV-exposed or –infected children aged 1 to 12 months and in older HIV-infected children with CD4+ cell percentage below 15%. There is a peak incidence of PCP in HIV-infected children at 3 to 6 months of age, prior to the age at which HIV infection may be diagnosed.

Trimethoprim/sulfamethoxazole is a powerful agent to have in the armamentarium. In addition to being an effective prophylaxis against PCP, it can also prevent cerebral toxoplasmosis, disease caused by *S pneumoniae*, disease caused by nontyphoid *Salmonella*, nocardiosis, isosporiasis, and malaria. This drug has a number of other advantages. It is inexpensive (US$1 per month) and easy to administer. The only contraindication to its use is history of sulfa allergy. The main adverse reaction is skin rash, and this has been found to be relatively uncommon in dark-skinned persons. Clinical rather than laboratory monitoring of therapy appears to be adequate. Adherence is not as critical as for antiretroviral therapy, as the missing of a dose or doses basically equals the loss of some efficacy. Finally, experience with taking a daily medication is good preparation and practice for taking daily antiretroviral therapy regimens.

Diagnosis, prevention, and treatment of TB was discussed more fully in the presentation by Jean William Pape, MD (also summarized in this issue of *Topics in HIV Medicine*). In brief, the WHO has formulated international "best practice" guidelines for use of isoniazid preventive therapy (IPT). If skin testing is available, IPT may be reserved for persons with a positive tuberculin skin test (≥5 mm induration in HIV-infected persons). Otherwise, it is suggested that all HIV-seropositive patients living in countries with a high prevalence of TB receive IPT. It is also suggested that HIV-seropositive persons exposed to a case of active TB receive IPT. Exclusion of active TB is imperative prior to initiating isoniazid prophylaxis, since administration of a

single drug to a person with active TB will likely result in antimicrobial resistance. The regimen for IPT is isoniazid 300 mg/day for 9 months. Isoniazid prophylaxis is also recommended for HIV-infected children exposed to a person with active TB.

Immune reconstitution under antiretroviral therapy can enable prophylaxis for OIs to be discontinued in some cases. In the absence of immune reconstitution, several forms of prophylaxis should be continued for life, including primary prophylaxis against PCP and secondary prophylaxis (chronic maintenance therapy) following successful treatment of PCP, cerebral toxoplasmosis, systemic (deep) fungal infections (eg, cryptococcosis, histoplasmosis), disseminated MAC infection, and cytomegalovirus disease.

Presented in June 2004. First draft prepared from transcripts by Matthew Stenger. Reviewed and updated by Dr Kaplan in November 2004.

Financial Disclosure: Dr Kaplan has no affiliations with commercial organizations that may have interests related to the content of this article.

Suggested Reading

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Results of Our E-mail Survey About IAS–USA Mission, Name, and Logo

In November 2004, a survey from the International AIDS Society–USA (IAS–USA) was sent to HIV professionals. The purpose of the survey was to better understand our target audience's perception of our mission and work, and to assess recognition of our name and logo. There has been long-standing confusion between the IAS–USA and the worldwide International AIDS Society (IAS) and one goal of the survey was to explore the extent of this confusion. Overall, the survey results and feedback were extremely positive and revealed valuable insights. The IAS–USA thanks those who took the time to complete the survey and share their objective comments. The following is a summary of the survey results.

Survey Participants

A cover letter with the details and a link to the survey was e-mailed to 5545 HIV professionals, who represented a cross-section of the IAS–USA audience, including clinicians who have attended 1 or 2 IAS–USA CME courses in the past 5 years, clinicians who have attended 3 or more IAS–USA CME courses in the past 5 years, and HIV professionals who have not attended any IAS–USA CME courses, but subscribe to *Topics in HIV Medicine*® (*THM*).

> "I recognize the logo and associate it with the IAS–USA, but it is not especially effective."

Familiarity, Recognition, and Identity

Of those who were sent the survey, 959 (17%) completed the survey. Of these, 87% (94% of the prior course attendees and 70% of *Topics in HIV Medicine* subscribers) answered that they were familiar with the IAS–USA. Further review of the responses and comments revealed that, as suspected, the majority of respondents were confused by the name, and its similarity and relationship to the International AIDS Society (IAS), which is a worldwide membership society that is a consortium of AIDS organizations.

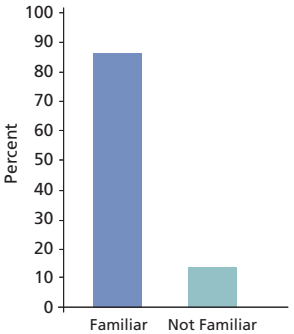
> "This organization has been for me a dependable beacon of light in an arena of an ever-moving target. Some good things should remain unchanged."

When asked, "What type of organization is the IAS–USA?" only about 25% correctly identified that the IAS–USA is a not-for-profit physician education organization with a similar name but not affiliated with the IAS. Of the 75% who were not familiar with the IAS–USA organization type, more than half thought it was a membership organization that was the US division of the worldwide International AIDS Society.

Of the 704 respondents who offered feedback on the IAS–USA name, 68% answered that there was confusion between the IAS–USA and the IAS and recommended that the IAS–USA change its name. One representative comment was "I have no contact with IAS but if there is confusion out there you should consider a new name with the same logo. I have loyalty to the IAS-USA organization and mission, not to a name." Another commented "I thought IAS-USA and IAS were the same organization. However, the reputation (and logo) for IAS-USA are well known and respected. I would consider a name change only if the (incorrect) association has negative impact. Consider, on one hand, we in HIV are very familiar with confusion! On the other hand, I guess Datsun successfully changed

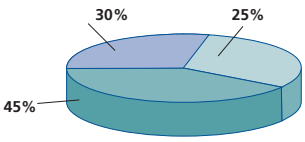
Who Are the 5545 Survey Participants?

- Clinicians who have attended 1 or 2 IAS–USA CME courses in the past 5 years
- Clinicians who have attended 3 or more IAS–USA CME courses in the past 5 years
- HIV professionals who have not attended IAS–USA CME courses, but subscribe to *Topics in HIV Medicine*



Familiarity With IAS–USA?

What Type of Organization Is the IAS–USA?



- Identified IAS–USA as a not-for-profit physician education organization not affiliated with IAS
- Incorrect identification: IAS–USA is a membership organization and the US division of IAS
- Another incorrect identification

its name..."

There were 756 who responded to the query about changing our logo. Of these, 52% recognized the logo and associated it with the IAS–USA, 14% suggested that the logo be updated or enhanced, and 14% indicated that they did not recognize the logo, noting that it did not fit the mission and needed to be changed. One respondent commented, "Organizations are often recognized by their acronyms (more so than logos), and I imagine that the similarity between your group and the International AIDS Society is where the confusion between the 2 organizations lies. I actually recognized the IAS–USA logo, but couldn't remember which organization it represented." Another mentioned, "The current logo looks like the logo for Target, a discount retailer." Interestingly, when clinicians were shown 5 logos (IAS, AMA, IAS–USA, USAID, and CHART) and asked to list the organization associated with each logo, the AMA logo was best recognized (ie, about two thirds correctly identified it), followed by the IAS–USA logo, with about half recognizing it.

> "I actually recognized the IAS–USA logo, but couldn't remember which organization it represented."

IAS–USA Programs Receive Positive Feedback

Many respondents took the time to comment on the organization and the programs. One respondent noted, "The programs are excellent. I think you need to focus on how to make resistance testing more concept-based." Another wrote, "The best one-day update available. Many of us service providers count on this to help us stay abreast of new information in the HIV field. Thank you for your efforts on our behalf and that of our patients."

Several respondents commented on how the language of the IAS–USA mission focuses on education for physicians' needs. They suggested that nonphysician health care practitioners who provide HIV primary care and attend IAS–USA activities be included in the mission. One such comment was, "I am grateful to the IAS–USA for bringing affordable HIV/AIDS education and updates to all medical providers who work with patients infected with HIV/AIDS.... I would suggest you make your focus on health care providers and not just physicians. There are many nonphysicians (PAs and NPs) providing HIV care."

When asked to select adjectives that best described the IAS–USA, the top responses were as follows: professional, informative, reliable, respected, well established, high quality, resourceful, organized, helpful, valuable, unbiased, trusted, balanced, and independent of commercial interests.

The Future for the IAS–USA Name and Logo

A number of respondents agreed that the logo needed enhancing and the name needed changing, but several commented that the IAS–USA should focus on its mission and not spend a lot of time or money on changes. Given that feedback, the IAS–USA and its board of directors have determined that the organization will, with guidance and minimal expense, revise our name to better describe the organization's mission; we will also somewhat update our logo but not change it entirely because of its recognition.

Conclusion

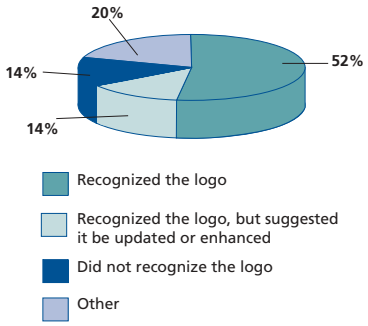
The IAS–USA recognizes the importance of the work that the HIV health care community does. The additional comments from the audience have reinforced our belief that we are privileged to be trusted by this devoted group of clinicians, and we will continue to work on your behalf to deliver the best educational programs possible.

We extend our sincere appreciation to the clinicians on the front lines of the epidemic taking care of people with HIV/AIDS and to the nationally and internationally respected experts in the science and treatment of HIV disease who contribute to the IAS–USA mission.

Top 10 adjectives that were noted to best describe IAS–USA:

1. professional
2. informative
3. reliable
4. respected
5. well established
6. high quality
7. resourceful
8. organized
9. helpful
10. valuable

How Recognizable Is the Logo?



Expect to see some changes for the IAS–USA in 2005. Based on the survey results we will:

- Change the organization name to better reflect our mission
- Update our current organization logo, but not change it substantially
- Broaden the mission to address needs of HIV experts other than physicians
- Continue to respond to the evolving educational needs of our audience and offer comprehensive, balanced, and unbiased treatment of material
- Maintain the high quality of the state-of-the-art, advanced-level course presentations

Perspective

Tuberculosis and HIV in the Caribbean: Approaches to Diagnosis, Treatment, and Prophylaxis

In the Caribbean region, the lifetime risk of active tuberculosis (TB) in purified protein derivative (PPD)-positive HIV-infected patients is 50%. Screening of individuals with cough who came to an HIV voluntary counseling and testing center in Haiti revealed active TB in 33% of patients. TB prophylaxis is effective in preventing active disease in HIV-infected individuals, and secondary prophylaxis has been shown to reduce recurrence in patients diagnosed with TB at more advanced stages of immunosuppression. Recommendations for anti-TB therapy differ according to whether antiretroviral therapy is available or not and according to whether the TB diagnosis is made while the patient is receiving antiretroviral therapy or not. This article summarizes a presentation by Jean William Pape, MD, at the first CHART Caribbean Conference on the Clinical Management of HIV/AIDS in Montego Bay, Jamaica in June 2004.

The populations in the developing world account for 95% of all cases of HIV-infection, more than 99% of HIV-related deaths, about 95% of all tuberculosis (TB) cases, and about 98% of TB-related deaths. In these areas, more than 85% of HIV deaths and 75% of TB deaths occur in the economically productive age group, ages 15 to 50 years. In the Caribbean region, some 40% to 90% of individuals are purified protein derivative (PPD)-positive. The lifetime risks of active TB are 5% to 10% among those without HIV infection and 50% in those with HIV infection.

Figure 1 shows a timeline of HIV disease in Haiti before the availability of antiretroviral therapy. The average time to AIDS (World Health Organization [WHO] HIV disease stage 4) was 6.5 years and average time to death was 7.4 years, representing disease progression in the absence of antiretroviral therapy approximately twice as rapid as that in developed countries. Similar findings have been made in Trinidad and Tobago. TB was the most common pre-AIDS manifestation in the Haitian cohort, occurring in 40% of patients prior to AIDS diagnosis. The most common AIDS-related illness was the wasting syndrome, which in many patients was associated with TB. The most common causes of death were wasting syndrome, TB, cryptococcal meningitis, and toxoplasmosis.

Diagnosis of TB

TB can occur at any time during the course of HIV infection. In a group of more than 1000 patients with HIV and TB seen at our site in Haiti, CD4+ cell count at TB diagnosis was above 350/µL in 56% of patients, between 200/µL and 350/µL in 23%, and below 200/µL in 21%. Pulmonary TB is still the most common form of the disease, with presentation depending on the degree of immunosuppression. Documented bacteriologic diagnosis is more difficult in HIV-infected patients than in those without HIV infection. In diagnosing TB, the disease manifestation in persons with early HIV infection closely resembles that in HIV-uninfected persons. Studies in Haiti have found that among patients with early HIV infection, chest x-ray often shows upper-lobe infiltrates and cavities, sputum smear is positive in 70% of patients, and 65% are PPD-positive. In contrast, in patients with late-stage HIV infection, chest x-ray may show lower-lobe infiltrates and no cavities, sputum smear is negative in 80% of patients, and PPD is negative in 80%. Blood culture may be helpful for diagnosis in HIV-infected patients who have lower concentrations of mycobacteria in sputum. Nucleic acid amplification assays can also be used in diagnosis; these assays are more reliable on positive smears from untreated patients (sensitivity of 95% and specificity of 98%) and least reliable in those receiving TB therapy.

Vigilance for TB must always be maintained in HIV-infected populations in the developing world. A high frequency of TB occurs among patients presenting with the wasting syndrome. Evaluation of 43 such patients via clinical assessment,

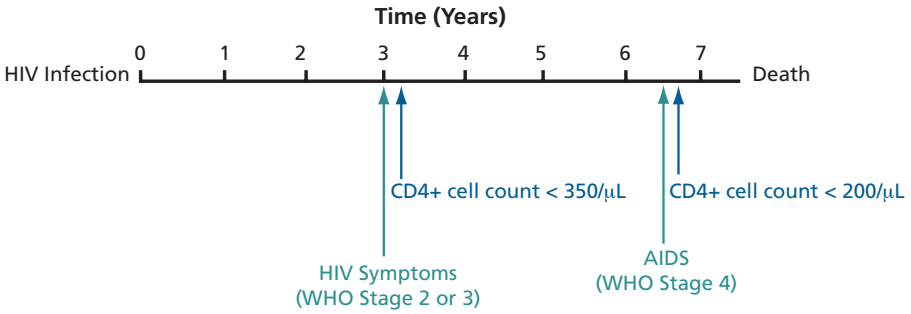


Figure **1**. Timeline of HIV infection in Haiti before the availability of antiretroviral therapy. WHO indicates World Health Organization.

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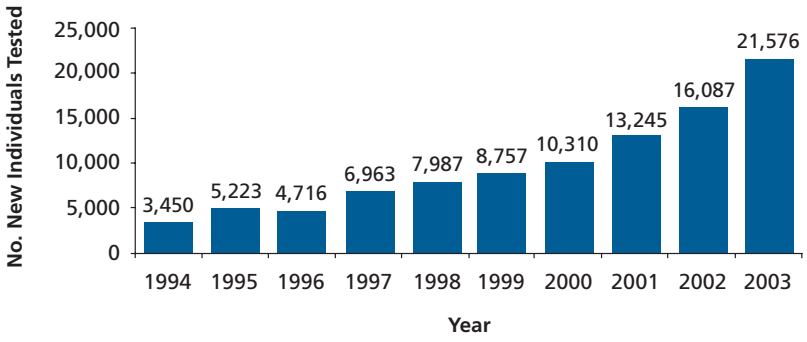

Figure **2**. Number of individuals newly tested for HIV at the Groupe Haitien d'Étude du Sarcome de Kaposi et des Infections Opportunistes (GHESKIO) voluntary counseling and testing center in Haiti from 1994 to 2003.

chest x-ray, sputum smear, TB culture, and blood culture found that 16 patients (37%) had bacteremia and that TB accounted for 50% of these cases. Screening for TB through HIV voluntary counseling and testing in Haiti has produced an astounding yield in TB diagnoses. Figure 2 shows the increase in numbers of individuals coming to the Groupe Haitien d'Étude du Sarcome de Kaposi et des Infections Opportunistes (GHESKIO) voluntary testing center in Haiti over the last 10 years; it is projected that more than 25,000 individuals will have presented during 2004. In a study conducted at the center, all persons coming for HIV testing who presented with cough underwent a work-up for TB with sputum smear, culture, and chest x-ray. Active TB was documented in 33% of all persons with cough and in 6% of all individuals who came to the center (Burgess et al, *AIDS*, 2001). More than 500 active TB cases per year are diagnosed this way and treated the same day, and more than 1000 persons per year coinfected with HIV and TB are put on isoniazid prophylaxis.

TB Prophylaxis

A number of studies in HIV-infected populations in the developing world have shown that isoniazid prophylaxis is effective in preventing active TB cases. In a study conducted by Pape and colleagues (*Lancet*, 1993), isoniazid prophylaxis for 1 year reduced the active TB rate from 10 cases to 1.7 cases per 100 person-years. Isoniazid prophylaxis had a beneficial impact on the natural history of HIV disease in PPD-positive patients, slowing progression to AIDS and to death; a similar effect was not observed in PPD-negative patients. In another study aimed at determining the appropriate length of isoniazid prophylaxis by the timing of TB recurrence in patients receiving primary isoniazid prophylaxis, time to diagnosis of active TB increased considerably with longer duration of prophylaxis. The median times to diagnosis of active TB from time of discontinuation of isoniazid prophylaxis were 8 months in those receiving 6 months of prophylaxis, 22 months in those receiving 12 to 24 months of prophylaxis, and 40 months in those receiving 24 to 36 months of prophylaxis (Fitzgerald et al, *Clin Infect Dis*, 2000).

The availability of potent antiretroviral therapy has a profound effect on rates of pulmonary and disseminated TB. Figure 3 shows rates of TB in Brazil prior to and after potent antiretroviral therapy became available around 1996.

TB Treatment

In general, the initial response to effective anti-TB treatment (absence of fever) occurs within 14 days even in patients with advanced AIDS. Persistent illness should raise concerns over drug-resistant TB, poor adherence, negative drug reactions involving TB medications, concomitant infections, or poor absorption of TB drugs, although the latter is infrequent in patients with AIDS.

Table 1 shows cure and recurrence rates in HIV-infected and HIV-uninfected patients with TB using different anti-TB regimens in developing countries. A study by Perriens and colleagues (*Am Rev Resp Dis*, 1991) showed an excessively high recurrence rate (14%) in patients receiving a regimen of isoniazid/streptomycin/thiacetazone for 2 months followed by isoniazid/thiacetazone for 10 months. In addition, many patients had Stevens-Johnson syndrome on this thiacetazone-containing regimen, with related fatalities occurring; thus, this regimen should not be used and thiacetazone avoided in HIV-infected patients. In another study by Perriens and colleagues (*N Engl J Med*, 1995), HIV-seropositive patients who received 12 months of treatment had an acceptable relapse rate of

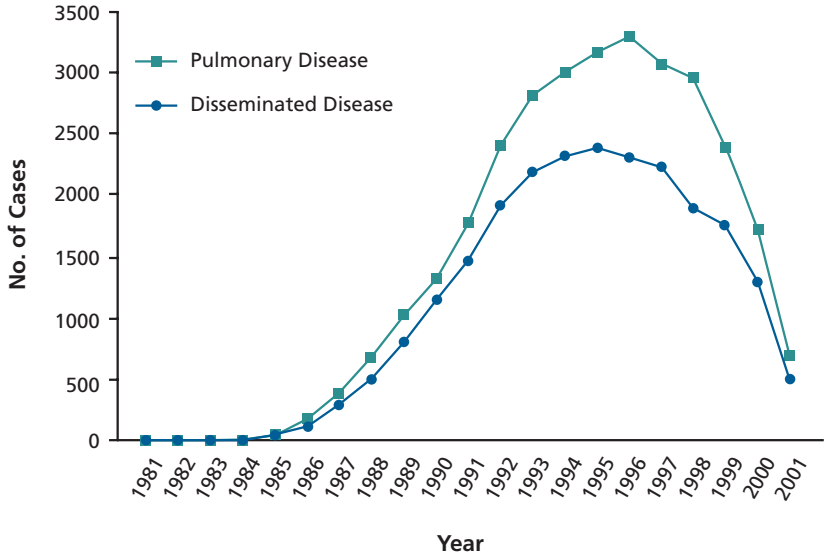

Figure **3**. Rates of pulmonary (green squares) and disseminated (blue circles) tuberculosis in patients with AIDS prior to and after availability of antiretroviral therapy in Brazil. Data from Brazilian Ministry of Health, 2002.

Table **1**. Anti-Tuberculosis Treatment Outcomes in HIV-Seropositive and HIV-Seronegative Patients

Study (location): Regimen	HIV-seropositive (%)		HIV-seronegative (%)	
	Cure	Relapse	Cure	Relapse
Perriens et al, *Am Rev Resp Dis*, 1991 (Zaire): 2 mo streptomycin, thiacetazone, isoniazid; 10 months thiacetazone/isoniazid[1]	84	14	87	5
Kassim et al, *AIDS*, 1995 (Ivory Coast): 2 mo isoniazid, rifampicin, pyrazinamide; 4 mo isoniazid, rifampicin	87	3	87	3
Perriens et al, *N Engl J Med*, 1995 (Zaire): 2 mo isoniazid, rifampicin/ pyrazinamide/ethambutol; 4-10 mo isoniazid, rifampicin	96	9, with 6 mo 1.9, with 12 mo	97	5.3
Ackah et al, *Lancet*, 1995 (Ivory Coast): 2 mo isoniazid, rifampicin, pyrazinamide; 4 mo isoniazid, rifampicin	93	—	92	—
Chaisson et al, *Am J Respir Crit Care Med*, 1996 (Haiti): 2 mo isoniazid, rifampicin, pyrazinamide, ethambutol; 4 mo isoniazid, rifampicin[2]	97	5.4	94	2.8
Desvarieux et al, *Am J PH,* 2001 (Haiti): 1 mo isoniazid, rifampicin, pyrazinamide; 4 mo isoniazid, rifampicin[3]	99	4	88	—

[1]Only regimen without rifampicin. [2]Directly observed therapy, thrice weekly regimen. [3]Modified directly observed therapy.

1.9%, compared with 9% among HIV-infected patients who only received 6 months of treatment. The Centers for Disease Control and Prevention (CDC) recommends treatment for 9 months in HIV-infected patients with a rifampicin-containing regimen.

In general, the highest initial cure rates are achieved in the setting of directly observed therapy. Initial cure rates are sometimes higher in HIV-infected patients than in HIV-uninfected patients. Survival in HIV-infected patients receiving anti-TB therapy is markedly better in those beginning treatment at higher CD4+ cell counts. One study in Abidjan showed that at 6 months after starting treatment, mortality rates were 10% in those with initial CD4+ cell counts below 200/µL, 4% in those with counts between 200/µL and 500/µL, and 3% in those with counts above 500/µL. A study in Kinshasa showed 18-month mortality rates of 67%, 22%, and 8%, respectively, in these CD4+ cell count categories.

Adverse reactions to anti-TB medications are common in HIV-infected patients, and serious adverse effects have been reported in 18% to 27% of patients in various studies (Small et al, *N Engl J Med*, 1991; Perriens et al, *N Engl J Med*, 1991; Perronne et al, *Tuber Lung Dis*, 1992; Nunn et al, *Lancet*, 1991). Common adverse reactions and the implicated drugs are shown in Table 2. Drug interactions are important to consider in treatment. For example, isoniazid and rifampicin decrease serum levels of ketoconazole and fluconazole, and that the latter 2 antimicrobials decrease absorption of rifampicin. As discussed below, the situation regarding drug interactions is especially complex when it comes to considering antiretroviral treatment, since some antiretroviral agents and anti-TB agents share metabolism via the cytochrome P450 (CYP450) enzyme pathways.

To determine the duration of response to anti-TB treatment and the potential benefit of secondary isoniazid prophylaxis, Fitzgerald and colleagues randomized 142 HIV-infected patients and 91 HIV-uninfected patients who had been treated for TB to placebo or secondary isoniazid prophylaxis (*Lancet*, 2000). All patients had normal chest x-ray findings and were culture-negative for TB after anti-TB treatment. Recurrence was statistically much higher in HIV-infected than in HIV seronegative patients. Among the HIV-infected patients, TB recurred in 12 of 74 placebo recipients and in 2 of 68 isoniazid recipients, rates (95% confidence interval) of 7.8 (4.1-13.3) and 1.4 (0.0-3.4) cases per 100 person-years, respectively. Among the HIV-uninfected patients, TB recurred in 0 of 40 placebo recipients and 1 of 51 isoniazid recipients, giving rates of 0.0 (0.0-4.0) and 0.7 (0.0-3.9) cases per 100 person-years, respectively. Further analysis showed that all cases of recurrence in the study were in patients with advanced HIV disease as indicated by CDC class B or C disease at the time of TB diagnosis. These findings

Table **2**. Adverse Reactions to Anti-Tuberculosis Therapy in HIV-Infected Patients

Reaction	Most frequently implicated drugs
Rash	thiacetazone, pyrazinamide, rifampicin, ethambutol
Stevens-Johnson syndrome	thiacetazone
Hepatitis	isoniazid, rifampicin, pyrazinamide
Gastrointestinal distress	rifampicin, pyrazinamide
Paresthesias	isoniazid
Optic neuritis	ethambutol
Arthralgias	pyrazinamide
Anaphylaxis	rifampicin

indicate that significant benefit may be achieved with secondary isoniazid prophylaxis after initial treatment in HIV-infected patients and that such prophylaxis should be provided following successful treatment for active TB in patients with advanced HIV disease at the time of TB diagnosis.

Santoro-Lopes and colleagues had similar findings from a study in a Brazilian cohort (*Clin Infect Dis*, 2002). As shown in Figure 4, the presence of TB is associated with decreased survival in patients with advanced HIV disease even in the context of antiretroviral therapy, indicating a role for such measures as secondary prophylaxis regardless of whether potent antiretroviral therapy is available. Survival was improved among patients with TB who received secondary TB prophylaxis.

TB relapse should be managed by reinstitution of the previous regimen if the organisms were susceptible to the regimen at the start of treatment. TB treatment failure (defined by persistence or worsening of TB-associated signs and symptoms, findings on chest radiograph, and/or smear-positive acid fast bacilli/positive culture for *M. tuberculosis*) should be managed by instituting a regimen with 3 drugs not previously used. In both cases, treatment should be conducted via directly observed therapy.

Antiretroviral Therapy in TB Patients

Should antiretroviral therapy be initiated in patients with active TB? In many cases, TB is the first opportunistic infection occurring in the HIV-infected patient, and may occur when CD4 + cell counts are relatively high—that is, before antiretroviral therapy needs to be initiated. Apart from this consideration, there are reasons to avoid initiating antiretroviral therapy in patients with active TB, including avoidance of potential drug interactions and toxicities and avoidance of the "paradoxical response" or "immune reconstitution inflammatory syndrome" to anti-TB therapy that can be caused by immune reconstitution under antiretroviral therapy. This response, which has been observed soon after initiation of antiretroviral therapy, is characterized by persistent or increasing fever, severe pulmonary inflammation, and lymphadenopathy. It may be associated with recovery of PPD-positivity and may respond to corticosteroid treatment. It is of interest that since antiretroviral therapy has become available in Haiti, few cases of TB immune reconstitution syndrome have been observed. The explanation for this phenomenon remains unclear.

Decisions to place patients on ART are often based on CD4 + cell count. However, TB in the absence of HIV can be associated with very low CD4 + cell counts that increase with anti-TB treatment. Thus, CD4 + cell count and response should be interpreted cautiously in HIV-infected patients undergoing anti-TB therapy. Concomitant therapy is also associated with a large pill burden that can threaten adherence to treatment regimens.

Drug interactions are a major consideration in decisions regarding concomitant antiretroviral therapy and anti-TB therapy. Rifampicin reduces blood levels of many antiretroviral agents, which can cause antiretroviral treatment failure and selection for antiviral drug resistance. Antiretroviral drugs metabolized by the liver, including nonnucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs), may cause liver toxicity, complicating patient management. Thus, antiretroviral drugs that should be avoided during anti-TB therapy include ones that undergo extensive CYP450 metabolism. These include the PIs nelfinavir, lopinavir/ritonavir, indinavir, amprenavir, and saquinavir, and the NNRTIs nevirapine, efavirenz, and delavirdine; however, nevirapine and efavirenz can be used with suitable dose adjustments. Interactions between anti-TB agents and antiretroviral agents are shown in Table 3. Antiretroviral drugs that can be safely

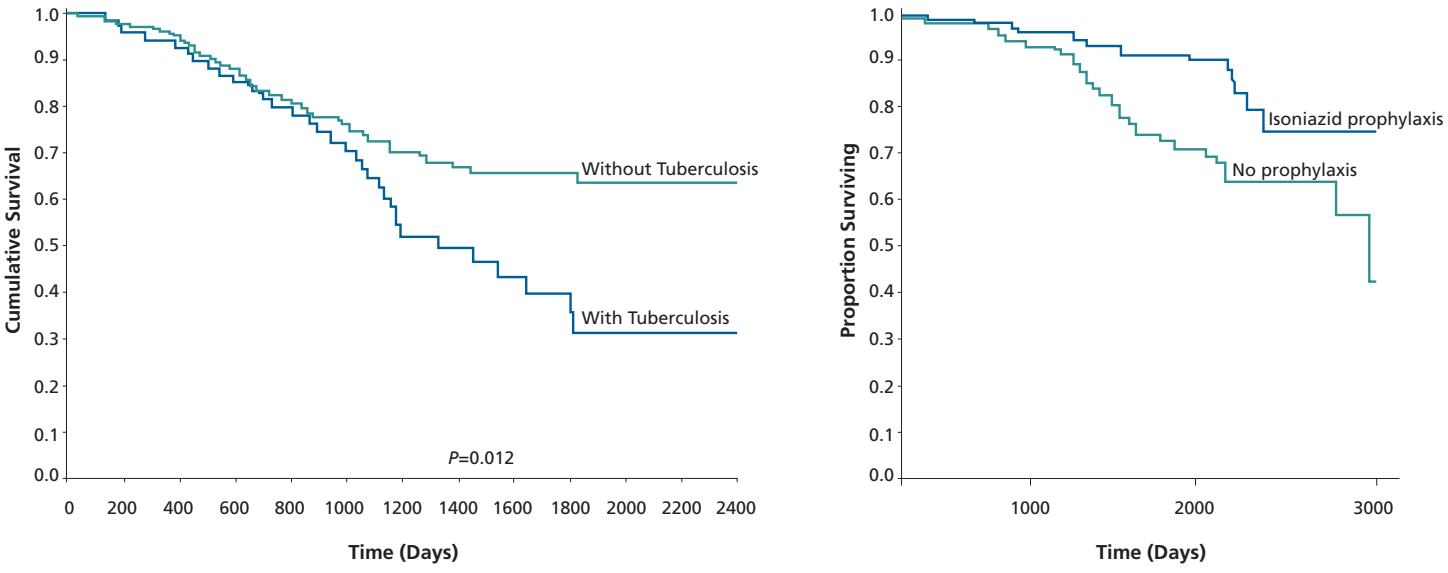

Figure **4**. Left: Survival among 312 patients in Brazil with advanced HIV disease (CD4+ cell percentage <15%) according to presence or absence of tuberculosis. Adapted from Santoro-Lopes et al, *Clin Infect Dis,* 2002. Right: Cumulative survival among those with tuberculosis according to use of isoniazid secondary prophylaxis or no prophylaxis. Adapted from Santoro-Lopes et al, *Clin Infect Dis*, 2002.

Table **3**. Drug Interactions Between Anti-Tuberculosis Agents and Nonnucleoside Reverse Transcriptase Inhibitors and Protease Inhibitors

Antimycobacterial	Nonnucleoside Reverse Transcriptase Inhibitor		
	Nevirapine	**Delavirdine**	**Efavirenz**
Rifampicin	Levels: nevirapine ↓ 37% Not recommended	Levels: delavirdine ↓ 96% Contraindicated	Levels: efavirenz ↓ 25% No dose adjustment
Rifabutin	Levels: nevirapine ↓ 16% No dose adjustment[1]	Levels: delavirdine ↓ 80% rifabutin ↑ 100% Not recommended	Levels: efavirenz unchanged; rifabutin ↓ 35% Dose: ↑ rifabutin dose to 450-600 mg qd or 600 mg 2-3x/week[1]; efavirenz: standard
Antimycobacterial	**Protease Inhibitor**		
	Indinavir	**Ritonavir**	**Saquinavir**
Rifampicin	Levels: indinavir ↓ 89% Contraindicated	Levels: ritonavir ↓ 35% Dose: No data Increased liver toxicity possible	Levels: saquinavir ↓ 84% Contraindicated, unless using ritonavir + saquinavir, then use rifampicin 600 mg qd or 2-3x/week
Rifabutin	Levels: indinavir ↓ 32%; rifabutin ↑ 2x Dose: ↓ rifabutin to 150 mg qd or 300 mg 2-3x/week Indinavir 1000 mg tid	Levels: rifabutin ↑ 4x Dose: ↓ rifabutin to 150 mg qd or dose 3x per week; Ritonavir: standard	Levels: saquinavir ↓ 40% No dose adjustment unless using ritonavir + saquinavir, then use rifabutin 150 mg 2-3x/week
Antimycobacterial	**Protease Inhibitor**		
	Nelfinavir	**Amprenavir**	**Lopinavir**
Rifampicin	Levels: ↓ 82% Contraindicated	Levels: amprenavir AUC ↓ 82% No change in rifampicin AUC Avoid concomitant use	Levels: Lopinavir AUC ↓ 75% Avoid concomitant use
Rifabutin	Levels: nelfinavir ↓ 32%; rifabutin ↑ 2x Dose: ↓ rifabutin to 150 mg qd or 300 mg 2-3x/week; ↑ nelfinavir dose to 1000 mg tid	Levels: amprenavir AUC ↓ 15%; rifabutin ↑ 193% Dose: no change in amprenavir dose; ↓ rifabutin to 150 mg qd or 300 mg 2-3x/week	Levels: rifabutin AUC ↑ 3-fold; 25-O-desacetyl metabolite ↑ 47.5-fold Dose: rifabutin dose to 150 mg qd; Lopinavir/ritonavir: standard

[1]Apply to regimens that do not include protease inhibitors. Adapted from Panel on Clinical Practices for Treatment of HIV Infection, US Department of Health and Human Services. *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents.* Oct. 29, 2004.
AUC indicates area-under-the-concentration curve.

used during anti-TB treatment in terms of drug interactions include zidovudine, lamivudine, stavudine, didanosine, abacavir, and tenofovir, all of which lack extensive CYP450 metabolism.

In general, recommendations for antiretroviral treatment in patients with active TB can be distinguished according to whether the patient is or is not receiving antiretroviral therapy when TB is diagnosed. For patients not receiving antiretroviral therapy, multidrug anti-TB therapy with isoniazid/rifampicin/ethambutol/pyrazinamide should be initiated, but antiretroviral therapy should be withheld initially. The clinical response to anti-TB therapy should be monitored—especially the fever curve over the initial 2 weeks—and indications for antiretroviral therapy should be evaluated after at least 2 to 4 weeks of anti-TB treatment. Initiation of antiretroviral therapy should be considered if the patient's condition worsens or if there is another indication to treat HIV infection. For patients already receiving antiretroviral therapy, such therapy generally may be continued during anti-TB treatment. If the patient is receiving PI treatment, consideration should be given to switching to a regimen consisting of all nucleoside reverse transcriptase inhibitors (NRTIs) or an NRTI plus NNRTI regimen. Alanine aminotransferase or aspartate aminotransferase level should be monitored every 2 to 4 weeks for signs of liver toxicity while the patient is receiving therapy, particularly if the patient is receiving an NNRTI or PI.

Summary

Management of TB in HIV-infected patients *without* access to antiretroviral therapy

1. HIV-infected patients can be effectively treated with rifampicin-containing, short-course regimens. The initial efficacy of treatment is comparable in HIV-infected and HIV-uninfected patients, but recurrence rates are higher in HIV-infected patients.
2. HIV-infected patients should receive a longer duration of therapy (9 months, as recommended by the CDC); another alternative for those with CDC class B or C disease at the time of TB diagnosis is to receive 6 months of therapy with 1 year of post-treatment isoniazid prophylaxis.
3. Treatment should be with at least 2 drugs to which the organism is sensitive, including rifampicin.
4. Adherence to treatment is the key to success. Directly observed therapy is the best choice; modified directly observed therapy protocols are acceptable with appropriate incentives.
5. Adverse drug reactions to anti-TB treatments are more common in HIV-infected patients than in patients not infected with HIV.
6. Drug interactions may interfere with blood levels of fluconazole, ketoconazole, rifampicin, and pyrazinamide.
7. The major determinant of TB mortality is the severity of immune deficiency at the time of TB diagnosis.

Management of TB in HIV-infected patients *with* access to antiretroviral therapy

1. If the patient is already receiving antiretroviral therapy, continue that therapy; if the patient is receiving a PI, consider switching to a less potentially toxic regimen.
2. If the patient is not receiving antiretroviral therapy, begin anti-TB therapy and delay antiretroviral therapy for at least 2 to 4 weeks if possible. Recommended antiretroviral regimens are nucleoside reverse transcriptase inhibitors (NRTIs) or an NRTI plus NNRTI regimen.
3. Monitor patients frequently for liver toxicity.

Presented in June 2004. First draft prepared from transcripts by Matthew Stenger. Reviewed and updated by Dr Pape in December 2004.

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HIV/AIDS Practitioners

We thank our audience—the participants in our continuing medical education (CME) courses and our readers—for actively participating in our programs and providing feedback on how we can improve the quality and relevance of our activities. In 2004, more than 3500 practitioners attended our live full-day or multiday CME courses, almost 2000 attended our interactive sessions at scientific conferences, and more than 12,000 received each issue of *Topics in HIV Medicine*.

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Antiretroviral Therapy Panel

The Antiretroviral Therapy Panel published its first set of recommendations in 1996. Subsequent updates were published in 1997, 1998, 2000, 2002, and, most recently, in July 2004 in the *Journal of the American Medical Association.*

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Resistance Testing Panel

The Resistance Testing Panel published its recommendations in 1998, 2000, and 2003.

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Drug Resistance Mutations Group

The Drug Resistance Mutations Group was convened in 2000 to maintain an ongoing, up-to-date database of HIV drug resistance mutations reflecting current research in the field. Each year, the group issues several updates to its list of mutations, the most recent of which appeared in the October/November 2004 issue of *Topics in HIV Medicine* and can also be found at www.iasusa.org/resistance_mutations.

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