

## EDITORIAL

# Declining Gastrointestinal Opportunistic Infections in HIV-Infected Persons: A Triumph of Science and a Challenge for Our HAARTs and Minds

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Gastrointestinal opportunistic infections, primarily oral and esophageal candidiasis, are common in persons infected with the human immunodeficiency virus (HIV) and contribute significantly to morbidity and mortality. Research early in the AIDS epidemic established a strong association between the presence of oral and esophageal candidiasis in patients complaining of odynophagia, demonstrated the diagnostic efficacy of a therapeutic trial with anti-fungal medicines, and defined the indications for endoscopy in HIV-infected persons with upper gastrointestinal complaints. Resulting diagnostic and treatment strategies with anti-fungal agents were very effective in preventing and treating mycotic infections of the gastrointestinal tract. Now, robust data from the United States and Europe indicate that recent advances in the development and use of highly active anti-retroviral therapy (HAART) are associated with a striking decline in the prevalence of oro-esophageal candidiasis in HIV-infected persons. In addition to developing more effective, safer antiviral agents, an HIV vaccine, and other novel approaches to combating this illness, a major challenge is to provide HAART to those without access to these life-saving drugs.

(Am J Gastroenterol 2005;100:1455–1458)

When the AIDS epidemic started, it was immediately apparent that gastrointestinal opportunistic infections, primarily oral and esophageal candidiasis, were common and contributed to the morbidity and mortality associated with this novel immunodeficiency disorder. Approximately 27 years later, in this issue of the *American Journal of Gastroenterology*, Mocroft *et al.* report a striking decline in oro-esophageal candidiasis in European HIV-infected patients treated with effective antiviral medicines (1). To understand the significance of these findings it is important to place them in historical context and to identify current challenges in preventing and managing fungal infections of the upper gastrointestinal tract in HIV-infected persons.

### THE PAST

In 1978, people in the United States, Sweden, Tanzania, and Haiti developed signs and symptoms of a novel immunodeficiency syndrome. Three years later, the first “official” report of this new disorder by the CDC indicated that mucosal, primarily oral and esophageal, candidiasis was a prominent feature. The report noted that in California between October 1980 and May 1981, five men who had sex with men were treated for biopsy-confirmed *Pneumocystis carinii* pneumonia (2). All five had laboratory-confirmed previous or current mucosal infection with *Candida albicans*. The authors concluded that “All the above observations suggest the possi-

bility of a cellular-immune dysfunction related to a common exposure that predisposes individuals to opportunistic infections such as pneumocystosis and candidiasis” (2). Time and intense investigation validated this hypothesis; the immunodeficiency disorder we now call AIDS is caused by infection with human immunodeficiency virus (HIV). HIV targets CD4 receptor-expressing T-lymphocytes (CD4<sup>+</sup> lymphocytes). In addition to the CD4 receptor, coreceptors, including CXCR4 and CCR5, assist binding of the HIV envelope glycoprotein gp120, thereby promoting infection. When the CD4<sup>+</sup> lymphocyte count decreases below 200/mm<sup>3</sup>, the characteristic opportunistic infections and neoplasms of AIDS appear. Early in the AIDS epidemic, before HIV and its mechanism of action were elucidated, unexplained oral candidiasis in at-risk persons was found to be highly predictive of reduced CD4<sup>+</sup> lymphocytes and the development of additional opportunistic infections (3).

By necessity, gastroenterologists working in large inner city hospitals with large numbers of AIDS patients, primarily in San Francisco and New York City, were quickly thrust into a prominent position. Gastrointestinal opportunistic infections associated with the AIDS epidemic of the early 1980’s posed complex clinical and logistical challenges. Was endoscopy necessary to diagnose esophageal candidiasis, the most common opportunistic infection of the esophagus? Were endoscopic personnel at increased risk for contracting AIDS? Were procedures to decontaminate endoscopes and accessories sufficient to prevent nosocomial transmission of

infectious agents? Survey data indicated that in many centers, fear of contracting AIDS resulted in costly, inefficient and possibly second-rate endoscopy practices, including equipment dedicated to AIDS cases, bedside procedures, and others (4). Endoscopes dedicated for AIDS cases were frequently older, worn fiberoptic instruments that were commonly gas sterilized after use, thereby further impairing their optical performance.

Much has been written regarding the years of inertia of our elected leaders in recognizing and dealing with the challenges of this epidemic (5). However, for those willing to recognize and address these clinical challenges, they provided the opportunity to learn not only about this new disease, but also about gastrointestinal opportunistic infections in general, and to develop minimally invasive, safer, and cost-effective diagnostic and treatment strategies. For example, the recognition that, in patients with AIDS, oropharyngeal candidiasis (thrush) is a marker of esophageal candidiasis and that odynophagia is the most common clinical manifestation of esophageal involvement obviated the need for endoscopy in most patients (6, 7). A therapeutic trial with anti-fungal medication is frequently sufficient to establish the diagnosis and resolve symptoms, and became the standard of care. Endoscopy is reserved for patients who do not respond to anti-fungal therapy or who have other features suggestive of infection with opportunistic viruses (herpes or cytomegalovirus), idiopathic ulceration of the esophagus, or other esophageal disorders (8). Recognizing that, on occasion, focal esophageal candidiasis mimicked the radiological appearance of cancer also prevented unnecessary procedures (9). The discovery that some patients can be infected with strains of *C. albicans* or other fungi that are resistant to ketoconazole (10, 11) and, subsequently, with strains resistant to fluconazole, led to the use of newer, more effective agents, like itraconazole (12). These advances benefited not only patients with AIDS but also those with other conditions that predispose to esophageal candidiasis (e.g., post-transplant immunosuppression, diabetes mellitus, chemotherapy, thoracic radiation, and chronic corticosteroid and antibiotic therapy).

Nonetheless, despite the clear benefits of these treatment strategies, it was always evident that, based on the pathogenesis of the disease, the key to successful prevention and management of esophageal candidiasis and other opportunistic infections in the HIV-infected person was to prevent or reverse the primary immunodeficiency. In the industrialized world, this was accomplished in the 1990's for an increasing number of patients by the development of highly active anti-retroviral therapy (HAART).

## THE PRESENT

Recent animal studies, using T-cell deficient BALB/c and CBA/CaH *nu/nu* mice, confirmed the importance of CD4<sup>+</sup> lymphocytes in preventing progressive colonization and infection of oral mucosal surfaces (13). Not only did animals deficient in CD4<sup>+</sup> lymphocytes develop mucosal invasion

with *C. albicans* but mice reconstituted with CD4<sup>+</sup> lymphocytes cleared the infection (13). These findings predicted that antiviral approaches that maintain or replenish the CD4<sup>+</sup> lymphocyte pool would reduce the likelihood that HIV-infected persons would develop oro-esophageal candidiasis.

In this issue of the *American Journal of Gastroenterology*, the report by Mocroft *et al.* adds to a growing body of literature indicating that, in HIV-infected persons, HAART reduces the incidence of opportunistic infections of the gastrointestinal tract, including oro-esophageal candidiasis (1). A previous, much smaller study of 166 HIV-infected patients at one city in the United States (Birmingham, Alabama) demonstrated that over a 3-year interval there was an inverse correlation between the institution of HAART and the presence of opportunistic infections of the esophagus (14). Specifically, the prevalence of esophageal candidiasis declined from 10 cases during the first year of the study to only two cases during the last year of the study ( $p < 0.02$ ) (14). This change was attributed in large measure to a decrease in HIV viral load and an increase in CD4<sup>+</sup> lymphocyte counts in those on HAART (14). The authors acknowledged limitations of this study, including its localization to one geographic site, the predominance of homosexuality as the HIV risk factor (>80%), the failure to ascertain compliance with HAART, and the possibility of undetected changes in the study population during the 3-year course of investigation.

The convincing study reported by Mocroft *et al.* addresses many of these limitations (1). The multicenter study population of almost 10,000 HIV-infected persons was recruited in 82 centers that are primarily based throughout Europe, but also include sites in Israel and Argentina. The study population was comprised of persons with several HIV risk factors; homosexual encounters (~44%), intravenous drug use (~24%), heterosexual encounters (~25%), and others (~7%). Compliance with HAART and anti-fungal medication was carefully documented (1).

In this study population, the declining prevalence of esophageal candidiasis over time is striking. Over the 9-year course of the study, there was a 32% annual decline in the incidence of esophageal candidiasis. Concurrently, the proportion of the study population taking anti-fungal therapy declined from 18% at the start of the study to only 2% in January 2004! As would be expected from our understanding of the pathogenesis of opportunistic infections in this setting, low CD4<sup>+</sup> lymphocyte counts remained a risk factor for esophageal infection. Likewise, advanced age remained a risk factor for oro-esophageal candidiasis despite the use of HAART. Whether the latter observation is a consequence of detrimental effects of age on esophageal motility, immune function, or a combination of these and possibly other factors remains to be determined.

Because of increased access to HIV education, testing, and other factors, HIV-infected persons commence HAART earlier in the course of their illness, when CD4<sup>+</sup> lymphocyte counts are higher (1). HAART is initiated before thrush progresses to esophageal candidiasis (1). Most likely, these

factors are responsible for the decline in esophageal candidiasis that is currently observed in HIV-infected persons even before HAART is commenced (1).

Collectively, the findings of the Monkemuller (14) and Mocroft (1) studies demonstrate a decline in oro-esophageal candidiasis in HIV-infected persons. Whereas it appears that, in HIV-infected persons, HAART is highly effective in reducing the incidence of gastrointestinal opportunistic infections, these data do not exclude the possibility that other factors contribute to this decline. These factors may include behavioral modifications that reduce the risk of fungal proliferation, changes in the virulence of fungal organisms, or others. Nonetheless, *Candida* colonization and infection is generally considered to be from endogenous organisms that are a normal component of the oral flora and not by transmission from exogenous sources. Moreover, there is good evidence that HAART is also associated with a reduction in the incidence of CMV and herpetic ulceration of the esophagus (14). Hence, we must conclude that, with regard to preventing gastrointestinal opportunistic infections, AIDS education and treatment with antiviral drugs works.

## THE FUTURE

Aside from the need for additional scientific advances to deal more effectively with AIDS, particularly the need for an effective vaccine, key issues are socio-economic. These relate primarily to access to the relatively costly medicines that comprise HAART. This is particularly true for those in the United States without access to health insurance and for persons living in less industrialized parts of Africa and Asia. In the United States, AIDS education, the promotion of condom use, clean needles, and other risk-reduction approaches, along with the implementation of HAART and other treatment strategies have been very effective. Although infection with HIV remains a serious concern for the infected individual, it is responsible for a relatively small reduction in overall life expectancy of the population. In contrast, in several African countries, AIDS has reduced overall life expectancy by over 30 years (15)! The increasing number of AIDS cases in parts of Asia is likely to have a similar devastating impact.

According to estimates from UNAIDS, an umbrella group representing the United Nations, the World Bank, and the World Health Organization, approximately 38 million people around the world currently have AIDS; 25 million of whom reside in sub-Saharan Africa. Of the nearly 19 million persons who have died from AIDS, 3.8 million were children under age 15 years. It is estimated that in Europe in the Middle Ages, bubonic plague resulted in 30 million deaths. For comparison, U.S. Census Bureau projections indicate that by 2010, the combination of AIDS deaths and the loss of future population resulting from the death of young women will reduce the expected population of sub-Saharan Africa by 71 million people. Most of these deaths will be attributable to opportunistic infection. In this population, oro-esophageal candidiasis will contribute to pre-existent nutritional defi-

ciencies, thereby resulting in life-threatening, severe weight loss that increases susceptibility to infection and hastening death from coexistent opportunistic infections or cancers. It is noteworthy that in parts of Africa, the eponym "slim disease," to describe the result of cachexia and wasting, is applied to infection with HIV.

Unfortunately, with reference to the historical overview for AIDS used in the present communication, for many regions of Africa, the present and the near future are no different than the past. Until very recently, the government of South Africa denied that HIV caused AIDS. HAART and other effective treatments for HIV and opportunistic infections are rarely available. In the United States, with a population approximating 274 million persons, about \$10 billion in public and private money is spent each year on AIDS education, research, treatment, and prevention (~\$37/person). African nations, total population approximately 543 million, spend only \$165 million/year (~\$0.3/person) on AIDS. As a consequence, currently in Africa, HAART is available only to a small number of relatively wealthy persons. Perhaps 93% of infected Africans, who are desperately poor, do not have access to these life-saving agents.

The immediate challenge for industrialized societies, that in a relatively short time made tremendous strides in understanding the cause and developing treatments for AIDS, is whether we have the heart to provide to AIDS patients in economically disadvantaged parts of the world the funds for HAART and other essential medicines. Moreover, do we as a society have the wisdom to understand the political and economic consequences of failing to provide these resources?

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*Received January 19, 2005; accepted January 24, 2005.*

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